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Title: Towards frailty biomarkers: Candidates from genes and pathways regulated in aging and age-related diseases

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Towards frailty biomarkers: Candidates from genes and pathways regulated in aging and age-related diseases

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Abstract

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Financial disclosure

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Highlights

- Frailty and frailty measurements are established, but complementary molecular biomarkers or biomarker panels are not available
- Genes modulated in aging, longevity and age-related diseases measurable in body fluids are highly valuable resources for frailty biomarkers
- Prioritization into core and expanded panel of frailty biomarkers for experimental validation in humans and animal models

Abstract

Objective: Use of the frailty index to measure an accumulation of deficits has been proven a valuable method for identifying elderly people at risk for increased vulnerability, disease, injury, and mortality. However, complementary molecular frailty biomarkers or ideally biomarker panels have not yet been identified. We conducted a systematic search to identify biomarker candidates for a frailty biomarker panel.

Methods: Gene expression databases were searched (<http://genomics.senescence.info/genes> including GenAge, AnAge, LongevityMap, CellAge, DrugAge, Digital Aging Atlas) to identify genes regulated in aging, longevity, and age-related diseases with a focus on secreted factors or molecules detectable in body fluids as potential frailty biomarkers. Factors broadly expressed, related to several “hallmark of aging” pathways as well as used or predicted as biomarkers in other disease settings, particularly age-related pathologies, were identified. This set of biomarkers was further expanded according to the expertise and experience of the authors. In the next step, biomarkers were assigned to six “hallmark of aging” pathways, namely (1) inflammation, (2) mitochondria and apoptosis, (3) calcium homeostasis, (4) fibrosis, (5) NMJ (neuromuscular junction) and neurons, (6) cytoskeleton and hormones, or (7) other principles and an extensive literature search was performed for each candidate to explore their potential and priority as frailty biomarkers.

Results: A total of 44 markers were evaluated in the seven categories listed above, and 19 were awarded a high priority score, 22 identified as medium priority and three were low priority. In each category high and medium priority markers were identified.

Conclusion: Biomarker panels for frailty would be of high value and better than single markers. Based on our search we would propose a **core** panel of frailty biomarkers consisting of (1) CXCL10 (C-X-C motif chemokine ligand 10), IL-6 (interleukin 6), CX3CL1 (C-X3-C motif chemokine ligand 1), (2) GDF15 (growth differentiation factor 15), FNDC5 (fibronectin type III domain containing 5), vimentin (VIM), (3) regucalcin (RGN/SMP30), calreticulin, (4) PLAU (plasminogen activator, urokinase), AGT (angiotensinogen), (5) BDNF (brain derived neurotrophic factor), progranulin (PGRN), (6) α -klotho (KL), FGF23 (fibroblast growth factor 23), FGF21, leptin (LEP), (7) miRNA (micro Ribonucleic acid) panel (to be further defined), AHCY (adenosylhomocysteinase) and KRT18 (keratin 18). An **expanded** panel would

also include (1) pentraxin (PTX3), sVCAM/ICAM (soluble vascular cell adhesion molecule 1/Intercellular adhesion molecule 1), defensin α , (2) APP (amyloid beta precursor protein), LDH (lactate dehydrogenase), (3) S100B (S100 calcium binding protein B), (4) TGF β (transforming growth factor beta), PAI-1 (plasminogen activator inhibitor 1), TGM2 (transglutaminase 2), (5) sRAGE (soluble receptor for advanced glycosylation end products), HMGB1 (high mobility group box 1), C3/C1Q (complement factor 3/1Q), ST2 (Interleukin 1 receptor like 1), agrin (AGRN), (6) IGF-1 (insulin-like growth factor 1), resistin (RETN), adiponectin (ADIPOQ), ghrelin (GHRL), growth hormone (GH), (7) microparticle panel (to be further defined), GpnmB (glycoprotein nonmetastatic melanoma protein B) and lactoferrin (LTF). We believe that these predicted panels need to be experimentally explored in animal models and frail cohorts in order to ascertain their diagnostic, prognostic and therapeutic potential.

1. Introduction

The term frailty was first mentioned in 1954 by Friend (Friend, 1954) but it was another three decades before Hays introduced the term “frail elderly” in context of health care (Hays, 1984). In the past 20 years, research on frailty has speeded up significantly with currently more than 2,000 publications per year (Fig. 1) and increasing interest shown in preclinical and clinical research. Frailty is a major phenotype of accelerated aging and describes multiorgan dysfunction or multimorbidity together with increased vulnerability to additional diseases in elderly people. Frailty can be easily measured in humans by assessing the accumulation of deficits through a tool known as the frailty index which can be used to predict response to therapies and progression of health status and mortality. The frailty index has recently been reverse translated to mice (Parks et al., 2012; Whitehead et al., 2014) to enable its use in preclinical aging and multimorbidity models. Since the concept of frailty has been reviewed previously (von Zglinicki et al., 2016) we will focus our current review on the frailty biomarker concept.

Biomarkers are generally accepted to be highly valuable tools in assessing the safety and efficacy of interventions in clinical and preclinical settings, but can also be used to diagnose conditions or stratify which patients would benefit most from interventions. The term biomarker was first mentioned in 1989 (Gallagher and Di Giulio, 1989; Masoro, 1989; Tunlid et al., 1989) and, interestingly, Masoro (Masoro, 1989) used the term in the context of aging research, reporting that the “lack of knowledge concerning the nature of the primary aging processes coupled to the lack of biomarkers of aging has made it difficult to devise fruitful approaches for the study of aging”. Since then, the understanding of the molecular and genetic pathways which are dysregulated in aging and age-related diseases has increased tremendously as has the interest in biomarkers (see Fig. 1) as a quick and quantitative measure in all areas of biomedical research.

Given there are many frailty phenotypic measures, molecular frailty biomarkers would be highly valuable and complementary. So far, biomarkers for frailty have not been extensively studied (see Fig. 1) although, interestingly, heart failure was the first predicted, albeit non-molecular marker for frailty (Rich et al., 1996). An early, rather global description of potential soluble biomarkers of frailty, including hormones, inflammatory markers, and nutrients, goes back to Ferrucci and colleagues in 2002 (Ferrucci et al., 2002) which was followed by a paper in which assessment of multiple markers was consecutively explored (Puts et al., 2005)). However, single predictive molecular markers have not been identified so far and proposed markers are often not reproduced across various frailty cohorts or do not correlate. Given that frailty is an age-related syndrome using the increased mechanistic understanding of aging seems an excellent tool to identify frailty markers. Additionally, since multiple molecular pathways are involved in the aging process and can all contribute to the various aspects of frailty, a panel of valid biomarkers in combination with measures of frailty would allow both diagnosis and follow up in preclinical and clinical settings.

2. Methods

2.1 Strategy

In this paper, we aim to review potential biomarkers for frailty, defined as a clinical syndrome of accelerated aging and multimorbidity. To this end, we focused our attention on a selection of markers found to be secreted and measurable in body fluids, and previously associated with the “hallmarks of aging” pathways (Lopez-Otin et al., 2013) and used or predicted as biomarkers in preclinical or clinical settings. We did not aim to generate an exhaustive list, but rather focus on promising candidates based on the consortium’s evaluation and expertise. For more details see Fig. 2 and Tables 1-8 and for concentration ranges of the selected biomarkers in body fluids see Fig. 5 and Table S1. As the frailty index is defined as an accumulation of deficits, we propose here that the accumulation of biomarker changes would be a promising, novel approach for identifying and monitoring frailty in both human and animal cohorts. In this context, this review aims to be the first step towards a better understanding of whether biomarkers, used in this way, might help to assess frailty on a molecular basis. We propose, as a logical second step in this process, the experimental validation of the markers in frail cohorts and animal models.

2.2 Approach

The knowledge of genes and pathways that are dysregulated in aging and age-related diseases has dramatically increased in recent years and has been made available in several databases (<http://genomics.senescence.info/genes> including GenAge, AnAge, LongevityMap, CellAge, DrugAge, Digital Aging Atlas). These databases are a great source for identifying potential markers of frailty, a clinical syndrome of accelerated aging and multimorbidity. Our search of these databases resulted in a

list of approximately 300 genes. Cross-referencing this extensive list with “frailty” we realised that less than 10% of the genes identified had been previously associated with frailty in the literature. Therefore, and as represented in Figure 2, we decided to broaden our search terms to focus our search on proteins that are known to be secreted and measurable in body fluids and that: a) had been previously used as markers in age-related diseases or b) had been linked to either “hallmark of aging pathways”, such as (1) inflammation, (2) mitochondria and apoptosis, (3) calcium homeostasis, (4) fibrosis, (5) NMJ and neurons, (6) cytoskeleton and hormones, or clearly linked to aging and age-related diseases (see Table 1-7). An intensive literature search was done and the most promising candidates were scored using the considerable expertise of consortium members, as well as looking at the broader or narrow relation of each gene with frailty, age-related disorders, and age-related pathways. Scores were given for further prioritisation (see Fig. 3-5 and Tables 1-8), with the highest scores being attributed to genes that were associated with frailty and with more than one hallmark of aging. Nevertheless, this scoring system is not designed to translate the direct relation of the gene with frailty but, instead, the amount of positive correlations and the broadness of its implication in the multimorbidity syndrome associated with frailty. Therefore, a high priority score means that there is a considerable amount of evidence to support the hypothesis that the marker is not equally expressed in frail versus non-frail individuals, even if the overall changes in the marker levels are relatively small. It is important to stress that, according to our scoring system, high priority markers do not always correspond to markers associated with large fold changes. Actually, one would expect generally smaller changes for individual markers than reported in fully manifested diseases. Instead, we support the notion that, even if small, the accumulation of changes in a set of markers with a broad coverage of aging-associated pathways and diseases, will better correlate with frailty than a single marker that presents large fold changes.

3. Results and discussion

The literature search resulted in the analysis of 44 biomarkers. Based on our scoring system, which takes into account connection to age-related pathways and dysfunction, as well as tissue distribution, we propose a core panel of 19 high priority markers and an expanded panel with 22 medium priority markers. In addition, three low priority markers are described. Most markers are proteins or genes, but we also included other emerging biomarker candidates such as miRNAs and microparticles.

3.1 Inflammation

Overall changes in the immune system, impacting both adaptive and innate immune responses, have emerged as one of the most relevant “hallmarks of aging” processes and immunological factors were among the first markers described for frailty (Fahey et al., 2000). The concept of inflammaging, first proposed by Franceschi and colleagues in 2000 (Franceschi et al., 2000) and recently revised (Monti et

al., 2017), is based on the hypothesis that the aging process is related to a systemic increase in pro-inflammatory mediators from various sources. This increase is either directly related to sustained exposure to infectious agents throughout life, or to age-related changes in gut microbiota, to metabolic dysfunction as seen in obesity or to secretion of antigens generated as a consequence of cell death and subsequent accumulation of cell debris. These so called danger signals vary depending on the tissue of origin and the cell death trigger, and include multiple metabolites, such as extracellular ATP (adenosine triphosphate), urate crystals, amyloids, ceramides, succinate, and the alarmin HMGB1. In addition, inflammaging is a dynamic process that can be propagated locally to neighbouring cells or systemically from organ to organ by circulating factors and microvesicles (Monti et al., 2017). Overall, inflammaging results in a chronic stimulation of immune cells that translate into a low-grade and long-lasting inflammation which influences both innate and adaptive immune responses.

In addition, aging results in marked changes in immune cell phenotypes and function. For example, a shift from lymphoid to myeloid differentiation was described for B and T cell populations. Similarly, monocytes, macrophages, dendritic cells, and neutrophils go through significant functional modifications, such as reduced phagocytic activity and changes in pattern recognition receptors (i.e. Toll-like receptors (TLRs) and RAGE), which are crucial for the detection of danger signals. Moreover, immune cells change their surface marker expression, are less efficient in the production of reactive oxygen species (ROS), show compromised migration capacity, and favour the production of pro-inflammatory over anti-inflammatory cytokines. Overall, this phenotype called “immunosenescence” contributes to the accumulation of cellular and molecular damage in aging tissues, potentiates many age-related disorders (e.g. atherosclerosis, diabetes, and neurodegenerative diseases), and most importantly diminish efficient response to infections, cancer and other tissue injury.

Accumulation of senescent cells is an additional driver of age-related phenotypes in many tissues and organs (Baker et al., 2011). Senescent cells are in growth arrest, but remain highly metabolically active and gradually acquire a secretory phenotype called senescence-associated secretory phenotype (SASP). SASP contains a variety of factors, including inflammatory proteins, cytokines, chemokines, growth factors, and matrix-remodelling enzymes which all negatively influence tissue homeostasis and regeneration. SASP is also responsible for spreading of senescence to neighbouring cells and tissues resulting in progressive damage of tissues and organs. The most prominent component of SASP is IL-6, whose elevated expression is associated with genotoxic stress in multiple cell types such as epithelial cells, fibroblasts, keratinocytes, and monocytes. In addition, serum IL-6 was shown to be a predictor for disability and frailty (Soysal et al., 2016). As previously mentioned, a big range of other bioactive molecules are also secreted from senescent cells, including CRP (C reactive protein), IL-1 α (interleukin 1 alpha), IL-1 β (interleukin 1 beta), TNF- α (tumour necrosis factor alpha), IL-8 (interleukin 8), several chemokines, such as CX3CL1, CXCL10 and CCL2 (C-C motif chemokine ligand 2), growth factors, such

as TGF β and BDNF, and various proteases. Thus, it is not surprising that molecules and SASP components involved in inflammaging and immunosenescence are highly valuable biomarker candidates for the chronic inflammatory phenotype seen in age-related diseases and frailty. We have selected seven “inflammation” biomarker candidates which are described below (see Tables 1, 8, S1 and Figs. 3-5).

CD14 antigen (also known as myeloid cell-specific leucine rich glycoprotein), is a surface antigen preferentially expressed by monocytes and macrophages. It binds exogenous danger signals such as bacterial LPS (lipopolysaccharide) and triggers innate immune responses mediated by TLRs and NF κ B (nuclear factor kappa B) signalling. Homozygous CD14 null mice present immunologic changes, such as impaired macrophage response to LPS or *E. coli* (Haziot et al., 1996) as well as impaired cytokine production (Jeyaseelan et al., 2005), accompanied by a favourable musculoskeletal phenotype with increased lean and body mass, reduced body fat, increased bone mineral density and decreased susceptibility to bone fracture (Johnson et al., 2004).

In monocytes CD14 is, together with CD16, an important marker to distinguish classical (CD14+/CD16-), intermediate (CD14+/CD16+), and non-classical (CD14 dim/CD16+) subsets. Interestingly, in frail individuals a shift of non-classical and classical towards intermediate monocytes has been observed (Lu et al., 2016). Similar subset shifts were found in coronary artery disease patients and shown to predict adverse cardiovascular outcomes (Cappellari et al., 2017; Yoshida et al., 2017). Moreover, in Alzheimer’s disease and rheumatoid arthritis patients, changes in total CD14 and increased intermediate monocytes were observed (Le Page et al., 2017; Smiljanovic et al., 2018), indicating an impaired innate immune response in these pathologies. The intermediate monocyte phenotype has also been employed as an intervention biomarker in coronary artery disease patients undergoing lipid-lowering therapy (Yoshida et al., 2017). Despite these observations, CD14 expression is restricted to innate immune cells and the criteria for distinguishing the different monocyte subsets are not completely clear, which hinders its use as an overall frailty biomarker.

CX3CL1, (C-X3-C motif chemokine ligand 1, aka fractalkine), is a unique chemokine, which exists as both membrane bound and soluble form, and actually the only member of the CX3C subgroup. Soluble CX3CL1 acts as chemo-attractant for T-cells, NK (natural killer) cells, and monocytes, while the membrane-bound form promotes adhesion of neutrophils to endothelial cells and contributes to the selective recruitment of monocytes to inflamed tissues (Jones et al., 2010; Kerfoot et al., 2003). In addition, CX3CL1 plays a role in angiogenesis and endothelial cell chemotaxis (Volin et al., 2010) as well as in different pathogenic conditions, including cancer, vasculitis, neuropathies, and atherosclerosis. The CX3CL1 gene is widely expressed in tissues and secreted into bio fluids such as plasma, saliva, synovial liquid, and cerebrospinal fluid.

CX3CL1 has a high potential as biomarker for frailty and aging-associated diseases and indeed, changes in CX3CL1 signalling were reported in frail elderly. Expression of CX3CL1 receptor (CX3CR1) in monocytes positively correlates with dementia and is negatively associated with anaemia and diabetes (Verschoor et al., 2014). Moreover, CX3CL1 expression is enhanced by TNF- α and IFN- γ (Interferon- γ) and in rheumatoid arthritis patients high levels are detected in synovial fluid which promotes the migration of monocytes, T-cells, and osteoclast precursors into joints (Ruth et al., 2001). Deletion of CX3CL1 significantly improved rheumatoid arthritis in animals (Nanki et al., 2017), and synovial and serum CX3CL1 were positively associated with self-reported pain and physical disability in osteoarthritis (Huo et al., 2015).

In brain disorders, CX3CL1 may have controversial functions. Generally, CX3CL1 is highly abundant in brains of young, but decreased in aged rodents. CX3CL1 signalling seems to increase amyloid pathology, but contrarily soluble CX3CL1 may prevent tauopathies (Merino et al., 2016). Similarly, CX3CR1 knockout resulted in neuroprotection in Parkinson's disease, and multiple sclerosis disease models, but had neurotoxic action in Alzheimer's disease models (Lauro et al., 2015), despite the fact that in human serum CX3CL1 was significantly greater in subjects with mild to moderate Alzheimer's disease than with severe disease (Kim et al., 2008b). In addition, there was a positive correlation between mini-mental status examination score and plasma CX3CL1 in the patients with Alzheimer's disease (Rogers et al., 2011).

CX3CL1 levels were positively associated in a cohort of about 4,000 patients with risk factors for several cardiovascular diseases and metabolic traits, lower estimated glomerular filtration rate, and higher levels of inflammatory cytokines (Shah et al., 2015). Actually, increased risk for death and/or myocardial infarction were observed in patients with high CX3CL1 levels. Plasma CX3CL1 also increased in various coronary artery disease populations (Damas et al., 2005) and here it was shown to exert cytotoxic effects on endothelium, as well as anti-apoptotic and proliferative effects on vascular cells affecting atherosclerotic plaques (Apostolakis and Spandidos, 2013). Moreover, serum CX3CL1 in patients with atherosclerotic carotid artery disease was significantly elevated when carotid stenosis was near occlusion (Stolla et al., 2012). In adipose tissue, CX3CL1 is considered a novel inflammatory adipokine that modulates monocyte adhesion to adipocytes and is associated with obesity, insulin resistance, and type 2 diabetes (Shah et al., 2011). In accordance, CX3CL1 together with secreted Frizzled-related protein 4 (SFRP4) is associated with low-grade inflammation in adipose tissue linking obesity to impaired insulin secretion and glucose metabolism (Bergmann and Sypniewska, 2014). Increased CX3CL1 is also correlated with better prognosis in some type of cancers, such as glioma, breast, and colon cancer (Andre et al., 2006; Locatelli et al., 2010; Park et al., 2012). While CX3CR1 usually contributes to tumour metastasis, CX3CL1 promotes aggregation of CX3CR1 and attracts cytotoxic effector T-cells or NK cells, decreasing the invasiveness of the cancer. Importantly, beside its general potential as inflammatory

biomarker, CX3CL1 can be used to monitor pharmacologic interventions with anti-inflammatory agents shown to alter CX3CL1 expression such as Etanercept, Rheumavax, Baicalin, Cyclophosphamide, and corticosteroids (Benham et al., 2015; Ding et al., 2016; Sato et al., 2011).

Pentraxin (PTX3) is a TNF- α induced protein involved in complement activation. It is induced by various inflammatory cytokines in peripheral blood leukocytes and myeloid dendritic cells, and acts as a component of humoral innate immunity (Moalli et al., 2011; Musilova et al., 2017). Pentraxin is also secreted by endothelial cells, vascular smooth muscle cells, fibroblasts, and adipocytes, promoting fibrocyte differentiation and playing a role in angiogenesis and tissue remodelling.

Pentraxin has a strong potential as biomarker for frailty, since its levels increase with age (Anuurad et al., 2011) and are also associated with leukocyte telomere length (Pavanello et al., 2017). Moreover, pentraxin expression has been reported to have prognostic value in different inflammatory conditions including sepsis (Liu et al., 2014a), prostate inflammation (Stallone et al., 2014), amnion inflammation (Musilova et al., 2017), appendicitis (Aygün et al., 2017), and hepatic cirrhosis (Narciso-Schiavon et al., 2017). In a population-based study of older men and women, pentraxin was associated with subclinical cardiovascular disease and mortality (Jenny et al., 2009), as well as with training-induced alteration of arterial stiffness in middle-aged and older adults (Zempo-Miyaki et al., 2016). Obese individuals have a lower pentraxin plasma concentration, whereas acute aerobic exercise increases plasma pentraxin levels compared with normal-weight individuals (Slusher et al., 2017). Pentraxin might also have an atheroprotective role (Nakamura et al., 2015). Studies performed in osteoporosis patients reported altered pentraxin expression in osteoblasts (Scimeca et al., 2017).

In the brain, pentraxin is a mediator of neurogenesis and involved in cerebral ischemia. Astrocyte-derived pentraxin supports blood-brain barrier integrity under the acute phase of stroke (Rodriguez-Grande et al., 2015; Shindo et al., 2016). In addition, pentraxin may predict tumour progression as low expression appears to facilitate tumour onset and progression (Giacomini et al., 2018). Accordingly, pentraxin is induced in the tumour stroma (cancer-associated *macrophages and fibroblasts*) after chemotherapy *in vitro* (Chi et al., 2015).

However, inhibition of pentraxin in glioma cells was shown to impair proliferation *in vitro* and *in vivo* (Tung et al., 2016) and suppression of pentraxin in lung adenocarcinoma was found to block growth and invasion (Hu et al., 2014) indicating a controversial role of pentraxin in cancer.

sVCAM/sICAM (soluble vascular cell adhesion molecule 1/ soluble Intercellular adhesion molecule 1) are immunoglobulin domain superfamily adhesion molecules expressed primarily on endothelial cells and activated leukocytes, where they mediate leukocyte-endothelium interaction and transendothelial

migration during inflammation. Actually, inflammatory mediators initially increase cell surface expression of these molecules, to promote protease-dependent shedding of the extracellular moieties in the form of soluble sVCAM and sICAM fragments. While this initial process has an anti-inflammatory action by inhibiting further leukocyte recruitment at the injury site, release of both sVCAM/sICAM into plasma results in rather detrimental effects such as endothelial injury, vascular inflammation, atherosclerosis, hypertension, and systemic endothelial dysfunction (Blankenberg et al., 2003; Tchalla et al., 2015). Thus not surprisingly, sVCAM/sICAM levels are used as risk predictors for cardiovascular events in healthy populations and various settings of disease, including type 2 diabetes (Moradi et al., 2018; Mulvihill et al., 2002).

A direct link between sVCAM/sICAM and frailty and aging has been reported. In frail elderly, elevated sVCAM-1 levels were associated with more severe cerebral blood flow dysregulation, mobility impairment and falls. Moreover, sICAM levels were increased stepwise in non-frail, pre-frail, and frail elderly people in a Taiwanese cohort, in a fashion that was independent of IL-6 levels. Conversely, an inverse relationship between plasma sVCAM/sICAM and the risk of cancer, another age-related condition mechanistically linked to inflammation and angiogenesis, has been observed (Tobias et al., 2017; Wang et al., 2015a). Finally, release of sICAM from senescent cells via microvesicles was also reported (Effenberger et al., 2014), further supporting a major role of sVCAM/sICAM in age and age-related diseases.

IL-6 (interleukin 6), one of the most prominent interleukins, is expressed in a variety of tissues including skeletal muscle, urinary bladder, gall bladder, appendix, oesophagus, bone marrow, lung, adrenal, prostate, and adipose tissues. It is primarily produced at inflammation sites, secreted into serum and induces a transcriptional inflammatory response through IL-6RA (IL-6 receptor, alpha). Roles of IL-6 have been confirmed in numerous pathophysiological conditions such as inflammation (Sindhu et al., 2015), mitochondrial myopathy (Rue et al., 2014), insulin resistance, cell proliferation (Chen et al., 2018), apoptosis, and cellular senescence (Zhuang et al., 2017).

Moreover, IL-6 serum levels were also positively correlated with aging (Carmeli et al., 2012; Tung et al., 2015) and many age-related diseases, including cardiovascular (Athilingam et al., 2013), neurological (Kim et al., 2017e; Kwan et al., 2013), musculoskeletal diseases, and cancer (Athilingam et al., 2013). Significantly higher levels of IL-6 in serum have been reported in almost every pathophysiological condition if patients are compared to control groups. In accordance, physical training and nutritional support, two of the best validated anti-aging factors, decrease or prevent increase in IL-6 levels in humans (Haider et al., 2017).

CXCL10 (C-X-C motif chemokine 10) is a IFN γ - inducible chemokine of the CXC subfamily and ligand for the receptor CXCR3, which is mainly expressed by activated T-lymphocytes (Luster et al., 1985), but also

in other cell types such as fibroblasts. Binding of CXCL10 to CXCR3 results in T-cell migration, but also in stimulation of monocytes and NK cells, as well as modulation of adhesion molecule expression and induction of apoptosis (Singh et al., 2010; Sui et al., 2006). CXCL10 is currently considered to be one of the most useful biomarkers for a range of infectious and inflammatory conditions (Ko et al., 2015; Otterdal et al., 2016; Zhang et al., 2014a), but was also shown to increase in human serum with age (Antonelli et al., 2006; Bonfante et al., 2017; Shurin et al., 2007). CXCL10 is elevated in the hippocampus of senescence-accelerated mice (Grinan-Ferre et al., 2016), as well as in the aorta during normal aging in mice (Trott et al., 2017). Thus, increased CXCL10 secretion may contribute to abnormal immune responses which are observed in the elderly.

Recently, CXCL10 was identified as a major component of SASP in human foetal lung fibroblasts. Since CXCL10 can stimulate its own transcription via CXCR3 and NF κ B signalling, it has a positive feedback on SASP and extensively promotes inflammation in surrounding tissues (Perrott et al., 2017), as well as tumour cell growth, motility, and metastasis (Wightman et al., 2015). The usefulness of CXCL10 as a secreted biomarker for aging and frailty-related conditions is further supported by the fact that its increase with age is counteracted by numerous interventions targeting aging, including caloric restriction (Trott et al., 2017), resveratrol (Palomera-Avalos et al., 2018), metformin (Bakhashab et al., 2016) and general suppression of the SASP by the flavone apigenin (Perrott et al., 2017).

Defensins are a large family of antimicrobial and cytotoxic peptides involved in host defence and in immunomodulation (Holly et al., 2017). They are small (18–45 residues), highly conserved cationic and amphipathic peptides that are distinguished by structure and conserved cysteine motifs. The defensin α family is divided into a) enteric, which are expressed in alimentary track, particularly in Paneth cells and epithelial cells, and b) myeloid, mostly expressed in peripheral blood cells, in particular neutrophils. Myeloid defensin α is the most promising biomarker for the accurate diagnosis of human periprosthetic joint infection in synovial fluid (Yuan et al., 2017), even though the gene is not active in laboratory mice. The defensin β family members are mostly expressed in endothelial cells of the skin and genitourinary, gastrointestinal, and respiratory tracts. Serum levels of defensin β have been explored as potential biomarkers for skin inflammation to monitor psoriasis treatment response and disease activity (Jin et al., 2017).

From these seven potential inflammatory biomarkers for frailty we identified three high priority (IL-6, CXCL10, CX3CL1), three medium priority (pentraxin, sVCAM/sICAM, defensin) and one low priority candidate (CD14).

IL-6 was by far the most convincing candidate with broad functional coverage and potential as a diagnostic, prognostic, and therapeutic biomarker, followed by CXCL10 and CX3CL1 which display

similar potential and all three are clear candidates for the core panel. The three medium priority markers were of similar value and overall had more limited or indirect functions than high priority markers. In particular, for defensins which are highly important for innate immune responses, more data are needed to define the specific isoforms that correlate to frailty. CD14 was assigned low priority because it is an indirect marker with rather narrow coverage compared to other candidates and its role is limited to the inflammatory response (see Tables 1, 8).

3.2. Mitochondria and apoptosis

Mitochondria play a central role in the production of ATP, and in the decline of basal metabolic rate and physical performance, and in energy-requiring tasks, which are characteristic of several age-related disorders. An age-dependent impairment of mitochondrial function includes decreased electron transfer rates, increased permeability to H^+ of the inner membrane, and impaired ATP synthesis. Both mitochondrial complex activities and enzyme activities of the tricarboxylic acid activities are reduced (Papa and Skulachev, 1997; Pollack and Leeuwenburgh, 2001). Moreover, mitochondrial DNA mutations accumulate in aging. In fact, the PolG mouse, a model mimicking increased mitochondrial mutations, displays a progeroid, multi-morbid, and frail phenotype (Li et al., 2017c; Safdar et al., 2011; Szczepanowska and Trifunovic, 2017).

Apoptosis, a process closely linked to mitochondrial dysfunction (Wang and Youle, 2009), is also elevated in the aging process (Pollack and Leeuwenburgh, 2001). Apoptotic proteins target mitochondria in various ways inducing membrane pores, caspase-activity, and mitochondrial swelling or changes in mitochondrial membrane permeability, thus ceasing mitochondrial respiration and leading to cell death. Similarly, autophagy, the most important process for mitochondrial turnover, also shows age-associated dysregulation (Carroll and Martin, 2013; Lee et al., 2012a). Recently, Patterson and colleagues revealed a mechanistic link between human aging and the risk of amyloidosis which may result from a dramatic slowing of amyloid- β turnover, which promotes protein misfolding and deposition (Patterson et al., 2015).

All cells, but in particular brain and muscle cells are particularly susceptible to mitochondrial dysfunction associated with oxidative damage, as large amounts of ATP are required to maintain neuronal processes and contractile function. As a consequence, a high O_2 and glucose consumption occurs, leading to a continuous production of ROS during the oxidative phosphorylation process. Aged cells show signs of increased oxidative stress, mitochondrial dysfunction, and accumulation of misfolded proteins, which are exacerbated in aged-related neurological and other disorders (Sas et al., 2018). We have selected five “mitochondrial and apoptosis” biomarker candidates which are described below (see Tables 2, 8, S1 and Figs. 3-5).

GDF15 (growth differentiation factor 15), also called myomitokine, is a pleiotropic cytokine ubiquitously secreted after stress response and injury which seems to activate GFRAL (GDNF family alpha like), a receptor linked to stress and apoptosis. In addition, GDF15 is extensively studied as biomarker for various diseases, including chronic inflammation, cancer, musculoskeletal, cardiovascular, kidney, liver, and neurological diseases (Corre et al., 2013).

In various studies, elevated GDF15 predicted mortality and disease progression. There are also studies directly assessing aging and age-related disorders showing that GDF15 can be used as a biomarker for mitochondrial dysfunction (Fujita et al., 2016b), for cognitive aging and dementia (Jiang et al., 2015a), for vascular pathologies (Eggers et al., 2012) and as independent predictor of mortality risk in the Rancho Bernardo community-dwelling older adult study (Daniels et al., 2011) and other causes of mortality (Wiklund et al., 2010). In addition, it predicts physical decline, diabetes, and insulin resistance, correlates negatively with muscle mass and many other age-related morbidities. GDF15 has been successfully used as an intervention biomarker, for example, for the use of metformin in people with dysglycemia (Gerstein et al., 2017) and for pyruvate therapy in mitochondrial diseases (Fujita et al., 2015).

FNDC5 (fibronectin type III domain containing 5), is a widely expressed transmembrane-protein which undergoes proteolytic processing to produce the secreted myokine irisin. It was only recently identified (Bostrom et al., 2012), shown to positively regulate brown fat differentiation, and proposed as a potential therapeutic target for metabolic and other disease. Since its identification, irisin has been extensively studied, originating in more than 500 publications. Irisin promotes mitochondrial biogenesis, preserves mitochondrial function in hypoxic conditions (Bostrom et al., 2012; Wang et al., 2017c; Xie et al., 2015; Zhang et al., 2014b), protects from apoptosis (Liu et al., 2017e; Natalicchio et al., 2017; Shao et al., 2017; Sugiyama et al., 2017), and has anti-inflammatory activity (Baran et al., 2017; Matsuo et al., 2015; Mazur-Bialy, 2017; Mazur-Bialy et al., 2017; Peng et al., 2017; Usluogullari et al., 2017).

Studies in aging showed that low irisin levels could predict sarcopenia (Chang et al., 2017a; Lee et al., 2015b), atherosclerosis (Icli et al., 2016; Lee et al., 2015b), and were associated with osteoporotic fractures (Anastasilakis et al., 2014). Irisin also correlated positively with global cognition and contributes to the neuroprotective effect of exercise (Kuster et al., 2017; Li et al., 2017a; Wrann et al., 2013). Prognostic and therapeutic effects were shown in metabolic and cardiovascular conditions (for review see (Perakakis et al., 2017)). For example, irisin seems to predict mortality in acute heart failure (Shen et al., 2017) and increased irisin improved obesity, glucose homeostasis, and ischemia-induced heart injury (Assyov et al., 2016; Chen et al., 2015a; Du et al., 2016; Jang et al., 2017; Tanisawa et al., 2014; Wang et al., 2017c). Similarly, irisin was associated with liver, kidney, and eye diseases (Hu et al., 2016b;

Polyzos et al., 2014; Wen et al., 2013). Interestingly, serum irisin levels are elevated in healthy centenarians and reduced in young patients with myocardial infarction (Aydin et al., 2014; Emanuele et al., 2014). In addition, plasma irisin levels were shown to be increased by exercise (Fox et al., 2018; Hew-Butler et al., 2015; Jedrychowski et al., 2015), following healthy diet (Crujeiras et al., 2014; Ko et al., 2016), by antihypertensive drugs (Celik et al., 2015), by a combination of isoprost and sildenafil used to reduce myocardial ischemia (Aydin et al., 2017), and with metformin treatment (Li et al., 2015b). Nevertheless, some of the irisin findings are controversial and need further evaluation.

Vimentin (VIM) is a ubiquitously expressed type III intermediate filament protein which is cleaved by caspases. Vimentin cleavage disrupts the cytoplasmic network of intermediate filaments and produces pro-apoptotic fragments (Byun et al., 2001). If vimentin is released from apoptotic cells it can be mutated and citrullinated, subsequently producing autoantigens and inducing antibodies against the mutated and citrullinated form (MCV). These autoantibodies are used as biomarkers in rheumatoid arthritis patients and maybe also useful for idiopathic pulmonary fibrosis patients (Reyes-Castillo et al., 2015; Zhu and Feng, 2013). Vimentin is also known as an epithelial to mesenchymal transition biomarker (Dong et al., 2017a) and, thus, used as a diagnostic, prognostic, and therapeutic marker in fibrotic diseases (Schiffers et al., 2000; Wolcott et al., 2017; Wu et al., 2017c). For example, vimentin was shown to be increased in the urine of chronic kidney disease patients (Cao et al., 2015). In accordance with its role in fibrosis, vimentin expression is also regulated by TGF β and pro-inflammatory cytokines.

We would like to note that in addition to vimentin there are several caspase-cleaved fragments described as disease biomarkers, such as, for example, Keratin 18 in liver disease (Lee et al., 2017), myosin-light chain (Petrasche et al., 2003) or myosin-heavy chain in cardiac diseases (Communal et al., 2002). These fragments also have potential as frailty biomarker candidates and Keratin18 is included in Section 3.4 on fibrosis.

APP (Amyloid precursor protein beta) is a precursor membrane protein, which matures in the Golgi complex, and is later cleaved and secreted in the extracellular space as soluble APP peptides.

In Alzheimer's disease and cerebroarterial amyloidosis patients, amyloid plaques are formed by insoluble peptides generated from alternative cleavage (e.g. A β 40 and A β 42) and various treatments targeting these plaques have been explored in patients (e.g. Lanabecestat, (Sakamoto et al., 2017)), or APP transgenic mice (NB-360, (Neumann et al., 2015), Liratuglide, (McClellan et al., 2015)). Secretion of APP peptides and plaque formation depend on autophagy (Cai et al., 2015; Nilsson et al., 2013) and APP turnover was shown to be significantly slowed with increased age (Patterson et al., 2015).

Similar accumulation of APP peptides has also been described in sporadic inclusion body myositis, the most common acquired muscle disease in patients over 50 years (Lunemann et al., 2007), as well as in metabolic and cardiovascular diseases, indicating a role of APP peptides outside the central nervous system (CNS). APPs can also be measured as biomarkers in circulation and were shown to predict the outcome in different diseases, including ischemic stroke (Liu et al., 2015) and heart failure (Bayes-Genis et al., 2017).

LDH (lactate dehydrogenase), catalyses the simultaneous conversion of pyruvate to lactate and NADH (nicotinamide adenine dinucleotide) to NAD⁺ and is needed in almost every single cell. LDH isoforms are expressed in a tissue-specific manner (e.g. LDHA in skeletal muscle, LDHB in the heart) and secreted during tissue damage and injury. Thus, elevated LDH levels reflect tissue breakdown and are used as a common marker for tissue injury and various age-related diseases including heart failure, cancer, neurodegeneration, lung, or liver disease. For example, plasma LDH is elevated in acute myocardial infarction (Wei et al., 2014) and amyloidosis and was shown to predict mortality in acute aortic syndrome and prognosis in patient with solid tumours (Agrawal et al., 2016; Petrelli et al., 2015; Yu et al., 2017c). In cancer LDH levels are associated with systemic inflammatory responses and predict survival and outcome in patients treated with anti-PD-1 therapy (Diem et al., 2016). Furthermore, LDH inhibitors were shown to reverse inflammation-induced effects in cancer cells indicating other possible roles.

In summary, from the five markers in the mitochondria and apoptosis category, the profile of GDF15, FNDC5 and vimentin – in predicting diagnostic, prognostic, and therapeutic potential - seems optimal enough to be included in the core biomarker panel for (see Table 8). Increased levels of GDF15 and vimentin, but reduced levels of FNDC5 would be expected in multi-morbid, frail people. Whereas FNDC5 and GDF15 represent biomarkers of mitochondrial dysfunction, vimentin, vimentin fragments, or MCV antibodies are more apoptotic and fibrotic (see also fibrosis) biomarkers of frailty. LDH reached medium priority as marker for the expanded panel being useful to monitor general tissue homeostasis and damage. In addition, the source of tissue damage could be further determined by measuring the levels of various isoforms. Similarly, APP is assigned to the expanded panel, mainly due to its more focused function and tissue distribution.

3.3 Calcium homeostasis

Calcium plays an important role in many physiologic and pathophysiologic processes both extracellularly and intracellularly. Intracellular calcium signalling, such as second messengers for GPCR (G-protein coupled receptors) and other receptors, is essential in any living cell as it allows efficient muscle contraction, hormone and neurotransmitter release, cell survival, and apoptosis. Dysregulation of calcium can include availability, intracellular translocation, and utilisation. Calcium levels have quite narrow limits

and small changes may cause tremendous dysfunction. Calcium is absorbed in the gut, excreted by the kidney and its levels are mainly regulated by the parathyroid hormone. Calcium is mainly stored in muscles, heart, and bone. Within the cell, the endoplasmic reticulum (ER) and mitochondria are the main storage and under homeostatic conditions relatively low concentrations of calcium occur in the cytoplasm. Cell contractility, cell viability and the activity of a large number of enzymes are calcium dependent. A big fraction of calcium is protein bound and calcium binding proteins have different cellular and tissue distribution and specific functions. So, it is not surprising that calcium homeostasis is dysregulated in many organ dysfunctions and diseases (for recent review see (Giorgi et al., 2018)). Measuring calcium levels is not an ideal method for detecting changes in calcium homeostasis due to the many influencing parameters and dependency of function on local availability. However, changes in calcium signalling and/or binding proteins have been proven to be effective markers of cellular and tissue dysfunction induced by disturbed calcium homeostasis. In the following section three “calcium homeostasis” biomarker candidates are described (see Tables 3, 8, S1 and Figs. 3-5).

S100B (S100 calcium binding protein B) is one of 24 members of the S100 calcium-binding protein family and exerts both intracellular and extracellular functions in calcium signalling. As a consequence, S100B is involved in the regulation of a number of cellular processes such as cell-cycle progression and differentiation. (for review see (Donato et al., 2013b)). This protein is ubiquitously expressed but enriched in brain and adipose tissue. S100B protein is involved in tissue development, repair and regeneration and many of its binding partners modulate pathways dysregulated in chronic and age-related diseases (e.g. p53, NF κ B).

Transgenic animals confirm a role of S100B in age-related diseases as S100B overexpressing animals display premature aging, whereas different S100B-deficient mice were generated with overall normal development and no severe impairment of motor function. Interestingly, one mouse strain showed allodynia (Bluhm et al., 2015). In addition, serum S100B is positively associated with better cognitive performance in healthy older adults (Lam et al., 2013). In inflammatory disorders, S100B plays a pathophysiologic role as shown for brain (Villarreal et al., 2014), obesity-related inflammation, (Buckman et al., 2014) and in the gut (Cirillo et al., 2011). For example, systemic inflammation is associated with high S100B in acute ischaemic stroke (Beer et al., 2010). In cancer, S100B-induced suppression of p53 contributes to cancer progression (Lin et al., 2010), whereas S100B protein levels are elevated in central nervous system disorders, Down Syndrome (Netto et al., 2005) and Alzheimer's disease (Ferguson et al., 2017).

S100B blood levels have been suggested as biomarker to predict the progress or the prognosis of subarachnoid haemorrhage (Chong, 2016). S100B can also be detected in exosomes from melanoma

patients and their quantification presents diagnostic and prognostic utility (Alegre et al., 2016). Moreover, pharmacologic inhibition of S100B (e.g. with the anti-microbial agent pentamidine) is being considered as a therapeutic option in brain injury (Cirillo et al., 2015), cerebral ischemia and Alzheimer's disease (Mori et al., 2010), acute colitis (Esposito et al., 2012), and malignant melanoma (Smith et al., 2010) (see Tables 3, 8, S1 and Figs. 3-5).

Regucalcin (RGN), also known as senescence-marker protein 30 (SMP30), is a gluconolactonase and one of the first described biomarkers shown to decrease with aging. It is widely studied as a biomarker or diagnostic tool (Kim et al., 2012; Vaz et al., 2015; Yamaguchi, 2014c; Zubiri et al., 2015). It has been shown to play a multifunctional role in many cell types, mainly as intracellular calcium signalling protein induced by oxidative stress that acts through membrane pumps located on the plasma membrane, ER, sarcoplasmic reticulum and mitochondria. For example, regucalcin increases Ca^{2+} -ATPase activity in heart, brain, and liver mitochondria (Akhter et al., 2006; Takahashi and Yamaguchi, 2000; Yamaguchi et al., 2008), but inhibits microsomal Ca^{2+} -ATPase activity in the brain and other tissues (Tobisawa et al., 2003). Consistent with its effects on calcium homeostasis regucalcin was shown to regulate the synthesis of DNA (Deoxyribonucleic acid), RNA, and proteins, chronic inflammatory processes, cell proliferation and cellular senescence (Fujisawa et al., 2011; Yamaguchi, 2013a, b). Overall, regucalcin seems to be a potent protective molecule against oxidative stress and chronic inflammation in a broad range of tissues.

Studies in transgenic animals further validated the role of regucalcin in aging and frailty. SMP30 knockouts have a shortened life-span, and elevated pro-inflammatory marker levels, and further increase Parkinson's disease and other age-related pathologies (Kim et al., 2012; Maruyama et al., 2004). Actually, regucalcin plays a pivotal role in vitamin C biosynthesis, and vitamin C deficiency induces shortened lifespan and accelerated aging in SMP30 knockouts (Ishigami, 2010). In contrast, overexpression of SMP30 protects against age-related disorders (Kim et al., 2012; Vaz et al., 2015), a number of stress-induced insults, as well as apoptosis and cell growth (Akhter et al., 2006; Correia et al., 2017; Maruyama et al., 2004). Regucalcin is significantly decreased with increasing age in various tissues such as the heart, brain, and prostate, and these reduced levels induce cellular senescence, frailty, fibrotic and other injuries in various organs including the liver, heart, kidney, and brain. For example, regucalcin is reduced in cirrhotic livers, particularly in fibrotic tissue, in various kidney diseases and also in heart failure where reduced regucalcin may play a key pathophysiologic role through the impaired activation of SOD (superoxide dismutase), an enzyme that under healthy conditions prevents cell death and apoptosis in the heart. Reduced regucalcin levels were also shown in various cancers (e.g. liver and pancreas) in association with worse survival (Tsurusaki and Yamaguchi, 2004; Yamaguchi and Murata, 2015; Yamaguchi et al., 2016).

As mentioned, regucalcin or serum autoantibodies against regucalcin are used as biomarker in various conditions, including many age-related diseases (Bystrom et al., 2017; Yamaguchi, 2014a). Besides being a diagnostic tool, regucalcin can also be used as prognostic and therapeutic marker. For example, in liver cirrhosis intervention with glutathione inosine increased regucalcin and in parallel significantly reduced fibrosis severity (Liu et al., 2014c). In addition, intervention with EUK4010, a natural compound which protects against A β 42-induced loss of neuronal cell viability, and intervention with the antihypertensive drug valsartan in settings of doxorubicin-induced cardiotoxicity (Park et al., 2016) similarly restored regucalcin. Interestingly, elevated regucalcin levels observed in Smad3 $^{-/-}$ mice were shown to protect against carbon tetrachloride-induced liver cirrhosis and improve glucose utilisation, lipid production, and insulin resistance in liver cells. In addition, the potential of regucalcin-based anticancer gene therapy is currently under investigation based on work showing reduced regucalcin levels in human tumours including kidney, lung, brain, breast, and prostate cancers.

Calreticulin (CALR) is a multifunctional protein initially identified as a Ca $^{2+}$ -storage protein in the ER. However, calreticulin is also expressed in mitochondria, at the surface of pre-apoptotic cells and in the ER, where it binds to misfolded proteins to prevent their export. Calreticulin has several functions in apoptosis and in the immune response. For example, calreticulin inhibits LPS-induced inflammatory osteoclastogenesis in the mouse calvarian bone (Fischer et al., 2017) and its presence at the surface of pre-apoptotic cells provides a signal recognised by antigen-presenting cells to initiate phagocytosis. Interestingly, calreticulin also interacts with APP at the γ -secretase cleavage site suggesting a role in neurodegenerative diseases (Stemmer et al., 2013).

Age-related levels of anti-Calreticulin antibodies were determined in three groups of cynomolgus monkeys and statistically significant differences were noted among the aged group. Calreticulin is increased in different fibrotic, chronic stress-induced or age-related diseases. For example, chronic stress activates calreticulin and mediates pathologic mechanisms in social defeat mice (Tomas-Roig et al., 2016). Circulating calreticulin is increased in myelofibrosis patients and highly correlates with symptoms (e.g. bone marrow fibrosis) and aggressiveness of the disease (Sollazzo et al., 2016). Moreover, calreticulin is upregulated in various cancers showing both prognostic and therapeutic use. Interestingly, calreticulin mutations were observed in Philadelphia-negative myeloproliferative neoplasm and these patients displayed a lower risk of splenomegaly and thrombosis and were favourably affected in overall survival. Increased levels are also observed in various inflammatory diseases, such as systemic lupus erythematosus, juvenile arthritis, bronchiectasis and rheumatoid arthritis where they are used as both a diagnostic and prognostic marker. In the heart, calreticulin is upregulated by cardiomyopathy inducers as well as angiotensin II (ATII) which causes mitochondrial injury and subsequently myocardial hypertrophy (Shan et al., 2014; Zhang et al., 2013); in addition, overexpression of calreticulin directly induces cardiac dysfunction. In the kidney, calreticulin is critically involved in the molecular mechanisms that drive renal

fibrosis progression and inhibition of calreticulin might be a therapeutic target for reduction of fibrosis and chronic kidney disease development (Bibi et al., 2011; Prakoura et al., 2013).

However, in the brain, calreticulin was described as neuroprotective factor and is downregulated in Alzheimer's disease cells and in the amyotrophic lateral sclerosis model SOD1(G93A). In the latter, background knockout of calreticulin further increased onset and degree of muscle weakness and denervation compared to control SOD1(G93A) (Bernard-Marissal et al., 2015). In accordance with this, calreticulin is down-regulated in cortical neurons of patients with Alzheimer's disease and is considered a potential biomarker for the diagnosis of Alzheimer's disease (Lin et al., 2014). Caloric restriction helped to maintain calreticulin expression in brains of 15-month old mice restricted for one year (Schafer et al., 2015).

Presently, calreticulin and auto-antibodies against calreticulin serve as biomarkers in various chronic and fibrotic conditions, including age-related diseases (Caira et al., 2017; Clarke et al., 2017; Ding et al., 2014; Guo et al., 2002; Lee et al., 2013; Ohadi et al., 2012). Besides representing a diagnostic and prognostic tool calreticulin may also be used as a direct therapeutic target or efficacy marker to monitor therapeutic interventions. For example, ZnCl₂ has the potential to enhance the therapeutic effects of anti-neoplastic agents partly by promoting calreticulin expression in cancer cells which activates dendritic cells and anti-tumour immune response (Cirone et al., 2013). Similarly, anthracyclines induce pre-apoptotic translocation of calreticulin to the cell surface to promote anti-cancer immune response and recombinant calreticulin increased cure rates of photodynamic therapy for squamous cell carcinoma in immunocompetent mice (Korbelik et al., 2015). Finally, treatment with the anti-viral bee toxin mellitin restored TNF α -induced calreticulin expression in smooth muscle cells (Cho et al., 2013).

Overall, the data available show that increased calreticulin levels were observed in most systemic pathologic conditions. However, in neurodegeneration calreticulin is reduced and its restoration induces neuroprotection.

In summary, from the three selected candidates involved in calcium homeostasis, both regucalcin and calreticulin reached high priority and are assigned to the core panel, whereas S100B will be included in the expanded panel.

3.4 Fibrosis

Fibrosis is the formation of fibrous tissue which can be part of the normal wound healing process after injury, later being replaced by newly formed healthy tissue. However, fibrotic tissue can also permanently replace functional tissue, for example, as a result of aging, when the healing process becomes sub-

optimal and fibrotic tissue builds up in organs such as the heart, lungs, kidneys, or liver and hampers normal tissue function. Improper tissue repair leads to hyperproliferation and enhanced inflammation due to the presence of a variety of inflammatory cells (neutrophils and macrophages). In addition, uncontrolled protease activity interferes with normal repair mechanisms and this may lead to increases in fibrotic tissue as some fibroblasts become senescent and may secrete SASP. In some cases, there is a reduction of angiogenesis accompanied by stem cell recruitment leading to aberrant extracellular matrix (ECM) remodelling (Eming et al., 2014). Cytokines, such as IL-13 (interleukin 13), IL-21 (interleukin 21), TGF β , BMPs (bone morphogenic proteins), chemokines such as MCP-1 (monocyte chemoattractant protein 1) and MIP-1 β (macrophage inflammatory protein-1 β) have been implicated in fibrosis. In addition, angiogenic factors (e.g. VEGF (vascular endothelial growth factor)), growth factors (e.g. PDGF (platelet derived growth factor)), and acute phase proteins, caspases and proteases, and components of the RAS (renin angiotensin aldosterone) system have been identified as important regulators of fibrosis and are being investigated as potential targets of anti-fibrotic drugs (Wynn, 2008). Fibrosis is seen in multiple organs, in particular the heart, lung, kidney, and liver (Zeisberg and Kalluri, 2013).

As mentioned above, the TGF β pathway, which is activated by a variety of molecules such as the three TGF β isoforms (TGF β 1, TGF β 2, and TGF β 3), BMPs, GDFs (growth and differentiation factors), AMH (anti-Müllerian hormone), activins, and nodal, plays a major role in fibrosis. These molecules regulate tissue regeneration, cell differentiation, embryonic development, and immune system differentiation and respond via TGF β , activin and BMP receptors and, mainly canonical SMAD signalling. The TGF β pathway is important for many processes starting early after embryonic development, but also later in life and is therefore an interesting source of biomarkers of aging and particularly frailty. So not surprisingly, several TGF β pathway molecules were identified as potential biomarkers for aging or frailty and our review includes seven “fibrosis” biomarker candidates discussed in this section (see Tables 4, 8, S1 and Figs. 3-5).

TGF- β (Transforming growth factor beta) is a pleiotropic cytokine belonging to the transforming growth factor superfamily and consists of three different isoforms (TGF β 1, TGF β 2, and TGF β 3). All TGF β isoforms are produced and secreted as latent proteins, and locally activated by various mechanisms to perform cellular functions, including the control of cell growth, cell proliferation, cell differentiation, and apoptosis. TGF β 1 is the main endocrine isoform (Zhao et al., 2017a), whereas TGF β 2 and TGF β 3 have mainly para- and autocrine function (Rodon et al., 2014; Van Themsche et al., 2010).

Higher concentrations of TGF β are found in the blood and cerebrospinal fluid of Alzheimer’s disease patients compared control subjects (Swardfager et al., 2010), suggesting a possible role in the neurodegenerative cascade leading to Alzheimer’s disease. Associations of TGF β s with various diseases have been newly discovered or elucidated in much more detail than before, including atherosclerosis,

acute and chronic liver and kidney disease, autoimmunity, osteoarthritis and neurodegenerative diseases and many of these disease are associated with aging and frailty (Krieglstein et al., 2012).

PAI-1 (Plasminogen activator inhibitor 1, also known as Serpine E1), is the principal inhibitor of tissue (PLAT) and PLAU, and acts as an inhibitor of fibrinolysis. PAI-1 is induced by the TGF β pathway and is a measurable SASP component (Eren et al., 2014; Ghosh et al., 2016).

Defects in this gene cause PAI-1 deficiency, and high PAI-1 concentrations are associated with thrombophilia. Alternatively spliced transcript variants have been found for this gene with different functions. Elevated PAI-1 levels are, in fact, a significant causative factor and circulating biomarker in the pathophysiology of many age-related diseases, including diabetes, vascular thrombosis, metabolic syndrome, septic coagulopathy, atherosclerosis, restenosis, and myocardial infarction, particularly in the context of increased tissue TGF β 1 levels. PAI-1 is also shown to be involved in many aging-associated disorders and considered as a direct therapeutic target (Edelmann et al., 2015; Eren et al., 2014; Ghosh et al., 2016; Huang et al., 2015b; Lee et al., 2014; Osada-Oka et al., 2017; Simone et al., 2014a). In accordance, a null mutation in PAI-1 protects against biological aging in humans (Arnoldussen et al., 2014; Fukami et al., 2014; Khan et al., 2017; Koh et al., 2005; Lassila et al., 2007; Srikanthan et al., 2016; Yamamoto et al., 2014a).

PLAU (urokinase plasminogen activator, also known as uPA), is a secreted serine protease that converts plasminogen to plasmin and a direct target of PAI-1 (discussed above). In addition, PLAU directly acts on the urokinase-type plasminogen activator receptor (uPAR) to induce intracellular signalling pathways. It is involved in a variety of physiologic and pathologic processes, including control of ECM turnover, cell migration, invasion, cell signalling, blood coagulation, inflammation, cell proliferation, apoptosis, and fibrosis. PLAU activity is directly controlled by PAI-1 and PAI-1 modulators such as TGF β family members, cortisol and growth factors all contribute to PLAU dysregulation in various age-related diseases showing impaired tissue regeneration, inflammation, and fibrosis (for review see (Sudol, 2011)).

Most importantly, PLAU was directly linked to aging processes and age-related disease (Miskin and Masos, 1997; Pinsky et al., 2017). It is expressed and secreted from senescent cells and controls cell proliferation and other processes (Connolly et al., 2010; Cunningham et al., 2009; Hildenbrand et al., 2008; Hodjat et al., 2013; Hohensinner et al., 2017; Kortlever and Bernards, 2006; Smith and Marshall, 2010; Wang et al., 2017f). Overexpression of PLAU in the brain reduces food consumption, causes growth and body weight retardation, accompanied by an increased lifespan (Miskin and Masos, 1997). PLAU signalling is also important for inflammatory responses. For example, it modulates innate brain inflammation (Cunningham et al., 2009), uPAR expression is elevated during inflammation in tissue remodelling and many human cancers and frequently indicates poor prognosis (Smith and Marshall, 2010). Moreover, inhibition of PLAU/uPAR interaction reveals a role in suppression of fibrin-associated

inflammation (Connolly et al., 2010) and genetic mouse models confirm the important role of PLAU in inflammation (Afoloniati et al., 2017; Carmeliet et al., 1993; Pinsky et al., 2017). PLAU also modulates the p53 pathway explaining its action on apoptotic, mitochondrial, cell proliferation, and senescence processes (Hohensinner et al., 2017; Kortlever and Bernards, 2006; Smith and Marshall, 2010; Wang et al., 2017f). Interestingly, it is highly expressed and induced by chemotherapy in cancer cells to promote mitochondrial-dependent apoptosis (Wang et al., 2017f), whereas in cardiomyocytes it protects from oxidative stress and apoptosis (Hohensinner et al., 2017). In cellular senescence, PLAU and PAI-1 are expressed and shown to mediate doxorubicin-induced senescence (Hodjat et al., 2013; Kortlever and Bernards, 2006).

In neurodegenerative diseases, genetic variants of PLAU are linked to the pathogenesis of late onset and sporadic Alzheimer's disease. Here, PLAU is involved in processing APP and degrades secreted and aggregated APP peptides (Ertekin-Taner et al., 2005; Finckh et al., 2003; Ji et al., 2012). Generally, PLAU is involved in CNS function and pathology (Cunningham et al., 2009) and, similar action was found in other organs and tissues. For example, PLAU and PAI-1 are induced in skeletal muscle injury and contribute to muscle repair (Novak et al., 2011) and are required for compensatory hypertrophy following synergistic ablation (DiPasquale et al., 2007; Suelves et al., 2005). Increased uPAR expression is associated with complication in diabetes patients and predicts outcome (Drechsler et al., 2017; Theilade et al., 2015). In contrast, PLAT has tissue protective effects and is used as anti-thromboembolic drug in cardiovascular diseases (Hohensinner et al., 2017; Kunamneni et al., 2008).

We would like to note that both PLAU and PAI-1 have high potential and are amongst the best validated prognostic biomarker tests for breast cancer (Duffy et al., 2016; Lampelj et al., 2015). They may be even interchangeable and it needs to be determined if these molecules are independently altered and both useful biomarkers for frailty. Nevertheless, in our scoring system PLAU reached high priority, whereas PAI-1 was medium priority.

MMP7 (matrix metalloproteinase 7, also known as matrilysin), is a member of MMP family of proteolytic enzymes which are also induced by the TGF β pathway. MMPs are involved in ECM remodelling and, thus, associated with processes such as morphogenesis, angiogenesis, and tissue repair. Dysregulation of ECM remodelling is associated with fibrosis, production of inflammatory cytokines, as well as endocrine and exocrine imbalances (Chaturvedi and Hass, 2011), and has been reported in pathologies such as liver cirrhosis, rheumatoid arthritis and cancer (Gong et al., 2014). As far as MMP7 is concerned, it is expressed in multiple organs and tissues, including the liver, lung, heart, breast, spleen, brain, spinal cord, and pituitary gland. It is detected in several biologic products, and mediates the cleavage of ECM and basement membrane proteins such as fibronectin, collagen type IV, and laminin (Gong et al., 2014). Increased MMP7 has been associated with extensive tissue remodelling and organ dysfunction, particularly in urinary and respiratory pathologies, with increased plasma and urine levels reported in renal fibrosis (Musial et al., 2015; Zhang et al., 2017a), and increased levels in plasma (Bauer et al.,

2017) and sputum (Guiot et al., 2017) of idiopathic pulmonary fibrosis patients. Elevated MMP7 expression has also been demonstrated in several tumours, and was again associated with ECM remodelling, epithelial-mesenchymal transition and malignant cells invasion and proliferation in cancers such as prostate and breast cancer (Chaturvedi and Hass, 2011; Gong et al., 2014). Furthermore, circulating MMP7 was elevated in individuals with distant metastases, suggesting a role of this MMP in their development (Gong et al., 2014).

TGM2 (transglutaminase 2, also known as C polypeptide) is the most widely distributed member of the transglutaminase family and catalyses cross-linking of proteins and is expressed in almost all cell types in the body to varying extents (Gundemir et al., 2012). TGM2 is a versatile protein, exhibiting multiple enzyme activities, also serving as a G protein for several transmembrane receptors, acting as a co-receptor for integrin $\beta 1$ and $\beta 3$ and acting as a protein scaffold or linker (Gundemir et al., 2012; Szondy et al., 2017). TGM2 is found in the ECM, plasma membrane, cytosol, mitochondria, recycling endosomes, and nucleus, and its subcellular localisation is an important determinant of its function (Gundemir et al., 2012; Tatsukawa et al., 2016). TGM2 is the most prevalent neuronal transglutaminase (Gundemir et al., 2012), playing a modulatory role in nervous system development as well as a regulatory effect on neuronal cell death (Ruan and Johnson, 2007).

The activities of TGM2 have been implicated in diverse pathophysiological processes such as wound healing, cell growth, cell survival, ECM modification, apoptosis, and autophagy (Agnihotri and Mehta, 2017), as well as inflammation and fibrosis (Szondy et al., 2017). TGM2 has been shown to contribute to fibrosis by ECM accumulation in some organs. It can promote fibrosis by crosslinking several matrix proteins making them more resistant to breakdown, and by contributing to TGF β formation which in turn has been associated with fibrosis in pathologies such as cardiac hypertrophy, liver cirrhosis, and renal fibrosis (Szondy et al., 2017). TGM2 is expressed by human lung fibroblasts, constituting a positive driver of idiopathic pulmonary fibrosis, a disease characterised by progressive fibrotic destruction of normal lung architecture, with TGM2 expression levels significantly higher in the fibroblasts from fibrotic patients compared with controls (Olsen et al., 2014). Moreover, TGM2 levels in sputum and plasma were elevated in patients with COPD (chronic obstructive pulmonary disease) and correlated with lung function, pointing to TGM2 as a novel potential diagnostic and therapeutic target for COPD (Ohlmeier et al., 2016).

THBS2 (thrombospondin 2), a member of the thrombospondin family, is a matricellular protein produced by multipotent mesenchymal progenitor cells in different tissues such as epithelium and endothelium, connective tissue, cartilage, and bone. It activates latent TGF β and plays an important role in the regulation of cell proliferation, apoptosis, and angiogenesis. THBS2 functions at the interface of the cell membrane and the ECM through its interactions with proteins and proteoglycans, such as collagens, integrins, and fibronectin, to regulate matrix structure and cellular behaviour.

Overexpression of THBS2 in rodent models and human hypertrophied heart causes hypertension and histologic features of interstitial fibrosis and cardiomyocyte hypertrophy. More recently, it was shown that heart failure patients with preserved ejection fraction present increased plasma levels of THBS2 and that circulating levels are correlated with disease severity, pointing to THBS2 as an independent predictor of cardiovascular events and risk of death (Kimura et al., 2016). THBS2 is also increased in serum of patients with chronic kidney disease, and was associated with fibrosis and endothelial-mesenchymal transition in cardiac tissue, placing THBS2, among other antiangiogenic inhibitors, as a player in the fibrosis-mediated cardiovascular disease associated with chronic kidney disease (Charytan et al., 2014). THBS2 is additionally involved in systemic sclerosis or scleroderma, an acquired disorder that typically results in fibrosis of the skin and internal organs. It was observed that increased THBS2 plasma levels deposited in systemic sclerosis fibroblasts contribute to tissue fibrosis by inducing collagen expression accompanied by down-regulation of intracellular THBS2 synthesis due to a negative feedback mechanism preventing increased extracellular THBS2 deposition and/or tissue fibrosis (Kajihara et al., 2012).

AGT (angiotensinogen, also known as *serpina8*), an angiotensin precursor, is produced by the liver and is converted into angiotensin I through the action of renin. Angiotensin I is further cleaved by angiotensin converting enzyme (ACE) into ATII, the main effector molecule of RAS. The classical RAS axis has been amplified with the discovery of novel enzymes, comprising the novel angiotensin-converting enzyme-related carboxypeptidase ACE2 and the MAS1 oncogene, which binds the ATII metabolite angiotensin (1-7), constituting an alternative pathway axis. The classical RAS axis is closely linked to TGF β signalling (Rosenkranz, 2004) and plays a key role in the regulation of systemic arterial blood pressure, vasoconstriction, water intake, and sodium retention, besides mediating pro-inflammatory, pro-thrombotic, and pro-fibrotic processes, whereas the alternative axis seems to play a protective role by opposing major ATII actions (Miranda and Simoes, 2017).

ATII (Chang and Wei, 2015), autoantibodies against ATII (Neuman and Danser, 2018) as well as ACE have been used as markers for various conditions including cardiovascular (Ikonomidis et al., 2017), liver (Noguchi et al., 2017) and kidney (Tan et al., 2016) diseases. Serum concentrations of ACE were associated with impaired myocardial deformation and torsion, likely by promoting abnormal collagen turnover and fibrosis, in never-treated patients with essential hypertension (Ikonomidis et al., 2017). The predictive value of serum ACE levels in detecting advanced stages of liver fibrosis as well as initial and intermediate fibrotic stages was also demonstrated, pointing to serum ACE as an accurate, non-invasive, widely available, and easy method to evaluate fibrosis related to chronic hepatitis B (Noguchi et al., 2017). Furthermore, RAS activation was shown to drive the progression of acute kidney injury and transition from acute to chronic disease stage as acute kidney injury patients with elevated urinary AGT have been shown to further progress and present higher mortality rates, suggesting that measurement of

urinary AGT could help with identifying acute kidney injury patients who are at risk of developing accelerated chronic kidney disease (Tan et al., 2016).

We would also like to note that a controlled balance between tissue turnover and fibrosis is key for proper tissue functioning. Most of the molecules mentioned above can be detected in blood or urine and may be used as biomarkers to determine the level of fibrosis inside the body. However, verification on tissue level needs further studies. Particularly interesting is the relationship between inflammation and fibrosis since both processes are required for physiological and pathological repair of tissue injury and are induced by tissue damage. Moreover, inflammation also induces wound healing and fibrosis by activating the wound healing cascade which leads to fibrosis (White and Mantovani, 2013). Thus, we believe the crosstalk between two main hallmarks of aging, namely inflammation and fibrosis, would make biomarkers that measure both, or combinations of biomarkers that measure either one of them, particularly attractive for diagnosis of frailty and age-related diseases

In summary, seven candidates, mainly from the TGF β pathway, were evaluated for their potential as fibrosis biomarkers for frailty. Two of the markers reached high priority (AGT, PLAU), and three markers medium priority (TGF β , PAI-1, TGM2) and are included in the core and expanded panel accordingly, whereas MMP7 and THBS2 were considered low priority.

3.5 NMJ and neurons

Neuronal loss occurs throughout life, particularly after the age of 60, and contributes to brain atrophy, neuroinflammation, cognitive decline in the CNS and loss motor units and impaired NMJ (neuromuscular junction) in the PNS (peripheral nervous system) in the elderly. In 2001, Paganini-Hill and colleagues (Paganini-Hill et al., 2001) employed for the first time the term cognitive frailty, which was later operationalised and proposed as an important part of the frailty syndrome, being included in the Frailty Index (Fried et al., 2001; Rockwood et al., 2005). Recently, several cross-sectional and longitudinal studies reported the association between physical frailty and cognitive outcomes in Alzheimer's disease, vascular dementia, and mild cognitive impairment (Avila-Funes et al., 2012). The reciprocal association has also been shown, with cognitive impairment being found at higher rates in frail individuals compared with age-matched controls (Avila-Funes et al., 2012). In fact, the presence of brain pathologies, including Alzheimer's disease, cerebrovascular disease, and Parkinson's disease has been associated with a more rapid decline in walking speed and a quicker progression of frailty (Buchman et al., 2013). The loss of MUNE was also directly connected to impaired physical function in old age (Gilmore et al., 2017; McKinnon et al., 2015; McNeil et al., 2005).

Several underlying mechanisms link physical and cognitive frailty, including cardiovascular and cerebrovascular disease, malnutrition and metabolic changes, hormonal and growth factor changes and inflammation. Cardiovascular risk factors and vascular diseases, such as myocardial infarction, congestive heart failure, atherosclerosis, and hypertension contribute simultaneously to physical frailty and to a higher degree of infarct-like brain lesions that are, in turn, representative of synaptic loss and neuronal death (Newman et al., 2001). Vascular comorbidities also impact the NMJ, decreasing the expression of C-terminal agrin fragment (CAF) and contributing to the age-related decline in muscle mass and function, also known as sarcopenia, which has been shown to worsen cognitive decline (Nourhashemi et al., 2002).

Nutritional choices and age-related hormone changes also influence late-life cognition (see also the section on hormones). Strong epidemiological evidence suggests that undernutrition, poor dietary patterns, low caloric intake and low intake of specific nutrients increase the risk to develop dementia (Bollwein et al., 2013; Morley, 2014). A similar effect is attributed to the age-related decrease in the production of testosterone (Maggio et al., 2012; Morley, 2014), BDNF (Gezen-Ak et al., 2013; Liang et al., 2015) and progranulin. These molecules are thought to be involved in the regulation of neuronal plasticity (Nikoletopoulou et al., 2017) and synaptic activity and have also been shown to interfere with A β deposition (Maggio et al., 2012; Nigam et al., 2017) and with the release of inflammatory mediators by microglia cells, the predominant immune cells of the brain. Throughout life microglia acquire a more reactive phenotype and this active/senescent phenotype (SASP phenotype) potentiates changes in the expression of surface receptors such as RAGE (Byun et al., 2012) and the release of pro-inflammatory mediators, including cytokines/cytokine receptors (IL-6, ST2) (Fu et al., 2016a; Montacute et al., 2017; Yang et al., 2017b), chemokines (CXCL10, CX3CL1) and complement proteins (C3, C1q) (Hong et al., 2016), while decreasing the expression of anti-inflammatory cytokines and growth factors such as BDNF and progranulin (Gezen-Ak et al., 2013; Lui et al., 2016). This shift compromises microglia's phagocytic activity and potentiates neuronal damage both directly, through the neurotoxic activity of inflammatory mediators, and indirectly, by perturbing microglia contribution to synaptic maintenance and neuronal homeostasis (Lui et al., 2016).

Taken together, age-related neuroinflammatory, vascular, and metabolic changes can have a tremendous impact in neuronal circuits, worsening cognitive performance and potentiating neurodegenerative diseases, such as age-related dementias, neuropsychiatric disorders, or depression (Lee et al., 2012b; Mezuk et al., 2012), which are considered both risk factors and consequences of frailty. In this context, several proteins have been recognised as potential biomarkers of neuronal and NMJ damage and cognitive impairment. We have focused on the seven "neuron and NMJ" proteins discussed below (see Tables 5, 8, S1 and Figs. 3-5).

BDNF (brain derived neurotrophic factor) is expressed in many tissues, including the nervous, musculoskeletal, respiratory, cardiovascular, urinary and reproductive systems and can be found in serum and plasma as well as in activated immune cells. This protein is known to regulate several aspects of neuronal development and function (Huang and Reichardt, 2001), such as survival and differentiation of different neuronal populations, synaptic transmission and plasticity and neuronal repair following injury. BDNF has also been described to contribute to glucose and energy homeostasis, food intake and body weight control (Willer et al., 2009) and exerts its roles mainly through the binding and activation of tyrosine kinase B receptor (Bartkowska et al., 2007) and consequent activation of three main pathways: PLC (phospholipase C), Akt (protein kinase B) and MAPKs (Mitogen-activated protein kinases). Downstream of these regulators, the main activities of BDNF are mediated by cAMP response element-binding (CREB) (Tao et al., 1998) and mammalian target of rapamycin (mTOR). There are several mouse models available for BDNF full or partial knockout. Homozygotes for targeted null alleles exhibit sensory neuronal loss that impact coordination, balance and hearing. These models present postnatal lethality, strengthening the important role of BDNF during neuronal development.

BDNF is also an important modulator of inflammation (Gezen-Ak et al., 2013; Liang et al., 2015) and autophagy (Nikoletopoulou et al., 2017; Wu et al., 2017a) and also presents important anti-oxidant properties (Wu et al., 2017a; Wu et al., 2016a), contributing to increase mitochondria performance and to mitigate neuronal metabolic defects following injury (Xu et al., 2017e). High BDNF plasma levels were also found to correlate positively with successful aging in a Malaysian cohort (Lau et al., 2017). On the other hand, BDNF expression is reduced in the brain of Alzheimer's disease, Parkinson's disease and Huntington's disease patients. A decrease in BDNF serum levels has also been reported in mild cognitive impairment (Shimada et al., 2014) and Alzheimer's disease patients (Siuda et al., 2017), correlating with lower cognitive test scores. In addition, BDNF has been identified in circulating vesicles with neuronal origin. Moreover, in the Baltimore Longitudinal study of Aging, participants with walking speed decline had higher levels of BDNF in neuron-derived vesicles than non-decliners, while no differences were observed BDNF levels in plasma or total extracellular vesicles (Suire et al., 2017).

In musculoskeletal diseases, with a strong inflammatory component, BDNF is increased in some tissues and decreased in others. While BDNF plasma levels were significant higher in knee osteoarthritis patients with respect to controls, the synovial fluid BDNF levels were lower than in controls (Pedard et al., 2018). In addition, in a rat model of adjuvant-induced arthritis, the animals presented lower brain BDNF levels, but an increase in BDNF serum levels (Simao et al., 2014).

Contradictory results have been found in type 2 diabetes patients. One study reports a decrease in plasma BDNF levels, which inversely correlates with fasting glucose levels and insulin resistance (Krabbe

et al., 2007), while two other studies reported an increase in BDNF levels, showing a positive correlation with percentage of body fat, triglyceride levels, fasting glucose levels and insulin resistance (Boyuk et al., 2014; Suwa et al., 2006). Despite this, BDNF has been consistently shown to be decreased in atherosclerosis (Casas et al., 2017) and stroke (Lasek-Bal et al., 2015). In particular, reduction in BDNF levels in the acute phase of stroke is related to poor outcomes. So far, several interventions have been shown to increase BDNF levels, including exercise (Gomes et al., 2014), cerebrolysin (Alvarez et al., 2016), estradiol (Numakawa et al., 2014), and metformin (Yoo et al., 2011).

Agrin (AGRN) is a secreted neuroprotein essential for the formation and stabilisation of synapses, in particular NMJ. Here, agrin activates clustering of nicotinic acetylcholine receptors via MusK/Lrp4 (Muscle-Specific Tyrosine-Protein Kinase Receptor/ LDL Receptor Related Protein 4) signalling to improve nerve-muscle connection (Bezakova and Ruegg, 2003; Burden, 1998; Campagna et al., 1997; Glass et al., 1996; Kim et al., 2008a; Zhang et al., 2008). The important role of agrin at the NMJ is further proven as genetic mutations or antibodies against agrin induce myasthenia gravis (MG) and agrin-deficient mice present with loss of synapses (Gautam et al., 1999; Gautam et al., 1996; Karakaya et al., 2017; Rimer, 1998; Yan et al., 2018). Cleavage by neurotrypsin or MMP3 inactivates agrin and the c-terminal fragment of agrin (CAF) indicates NMJ turnover and, thus, is explored as circulating biomarkers for neuromuscular diseases (VanSaun and Werle, 2000). Indeed, CAF levels are explored as frailty biomarker in humans.

Moreover, agrin is expressed in various tissues and also non-neuronal cell types such as brain, eye, heart, liver, kidney, lung, and Schwann cells. In accordance, non-synaptic actions have also been described, for example, on immune cells and by binding to TGF- β family members and β -amyloid (Banyai et al., 2010; Jury and Kabouridis, 2010; Reif et al., 2007; Trautmann and Vivier, 2001; Yang et al., 2001; Zhang et al., 2008). Actually, agrin was found to be regulated in a variety of disease conditions, such as diabetes, cardiovascular, kidney, muscle wasting, immunologic, lung, and neurodegenerative diseases as well as osteoarthritis, kidney, nerve, and brain injury and subsequently explored as biomarker (Donahue et al., 1999; Drey et al., 2013; Falo et al., 2008; Gros et al., 2014; Hettwer et al., 2013; Rauch et al., 2018; Steubl et al., 2016; Verbeek et al., 1999). Indeed, agrin seems to be a predictive marker in various degenerative diseases and is also being explored as a therapeutic intervention in neuromuscular diseases and muscular dystrophies (Hettwer et al., 2014; Li et al., 2018a; Rudolf et al., 2014).

Progranulin (PGRN) is a growth factor which is expressed in many tissues, including epithelia, bone marrow, immune cells and solid organs, where it plays multiple roles, from wound healing and tissue repair to cell proliferation (Kwack and Lee, 2017) and migration, tumorigenesis, cartilage development/degradation, and neuronal survival. Progranulin is mostly associated with the secretory pathway and can be found in plasma and cerebrospinal fluid and also in secreted exosomes. In fact, loss

of progranulin leads to a reduction in the number of exosomes and alters exosome composition (Benussi et al., 2016). Progranulin is cleaved by extracellular proteases into eight different granulin domains, which present distinct and sometimes contrary roles to progranulin. Several mouse strains modulating progranulin are available, including full knockout and heterozygous lines. Knockout display enhanced macrophage function, reproductive and behavioural abnormalities and premature death with increased cellular aging.

Progranulin has been considered to be an anti-inflammatory protein (Ma et al., 2017) and, in this context, its activity is thought to be mediated by TNF- α receptor and β -catenin. Progranulin loss has been observed in several dementias (Fardo et al., 2017), such as Alzheimer's disease and Frontotemporal lobar degeneration, as well as after acute brain injury, contributing to an increase in the expression of pro-inflammatory genes, to excessive microglia activation (Ma et al., 2017), and to autophagy impairment (Chang et al., 2017b; Xu et al., 2017a). On the other hand, plasma and cerebrospinal fluid progranulin levels are thought to increase during healthy aging (Ma et al., 2017; Nicholson et al., 2014) and have also been found to be increased in MS patients (Vercellino et al., 2011). The anti-inflammatory role of progranulin has been reported in cardiovascular diseases. Here, it augments vasorelaxation and reduces ischemia-reperfusion injury (Korolczuk and Beltowski, 2017). In addition, it protects against inflammatory reactions underlying atherosclerosis, being strongly expressed in foam cells of atherosclerosis plaques (Kawase et al., 2013). Progranulin is highly expressed in macrophages and loss in these cells leads to increased cholesterol levels and altered high-density lipoprotein-associated proteins (Yoo et al., 2013) which regulate insulin resistance (Zhou et al., 2015a). An increase in progranulin leads to insulin resistance and overall mitochondrial dysfunction and apoptosis in mice adipocytes (Guo et al., 2017). Circulating progranulin is increased in obesity (Zhou et al., 2015a), whereas progranulin deficiency protects from high fat diet-induced insulin resistance. There is a strong association between progranulin and type 2 diabetes and its complications, in particular microangiopathies (Xu et al., 2017a; Zhou et al., 2015a).

In osteoarthritis, progranulin plays a protective role by antagonising inflammatory mediators, protecting against cartilage defects and supporting osteoblast differentiation (Abella et al., 2016; Wang et al., 2016b; Zhao et al., 2015). In rheumatoid arthritis, the progranulin/TNF- α ratio was shown to correlate with the severity of disease, while the serum concentration of progranulin was found to be above healthy controls (Yamamoto et al., 2014b). Several compounds have been shown to revert the effects caused by progranulin loss and to modulate progranulin levels. The histone deacetylase inhibitor Vorinostat (also known as SAHA), the anti-malaria agent chloroquine, and the kinase inhibitors selumetinib and MEK162 are able to prevent TDP-43 (TAR DNA-binding protein 43) accumulation in progranulin-deficient lymphoblasts (Alquezar et al., 2015). Additionally, the natural disaccharide trehalose increases endogenous and extracellular progranulin levels and has multiple reported neuroprotective properties

(Holler et al., 2016). Despite being increased in some age-related conditions and decreased in others, its multiple cellular functions and dysregulation across several organs make progranulin a good biomarker, particularly in relation to inflammaging and neurodegeneration, where its decrease is consensual.

C3 and C1q (complement factor 3 and 1Q) belong to the complement cascade of immune system that orchestrates the recognition and elimination of pathogens and undesirable bodies, such as apoptotic cells and inefficient synapses (Dunkelberger and Song, 2010). C1q is the main protein of the classical complement cascade and is composed of three similar but distinct subunits, i.e., A, B, and C (Sellar et al., 1991). Following assembly, C1q attaches to the Fc chain of IgG and IgM antibodies which becomes activated by the binding to their respective antigen. C3 is the dominant protein of the alternative complement pathway, but also important in the classical cascade and lectin signalling. Following binding, either anaphylatoxins C1a/C3a which are potent pro-inflammatory molecules with immune cell functions or opsonins C1b/C3b which covalently bind to cell surface proteins, are produced by a series of cleavages. Ultimately, all these pathways culminate in the formation of the membrane attack complex (Dunkelberger and Song, 2010).

Both C1q and C3 have been observed to directly correlate with aging and cognitive decline. C1q levels are upregulated in plasma of aged individuals (Watanabe et al., 2015) and C3 levels are downregulated in the cerebrospinal fluid of subjects presenting fast cognitive decline (Toledo et al., 2014). In addition, the levels of both these proteins are increased in the brains of patients with neurodegenerative conditions, such as Alzheimer's disease, frontotemporal lobar degeneration and amyotrophic lateral sclerosis (Hong et al., 2016; Lui et al., 2016; Sta et al., 2011). In these diseases, C1q and C3 accumulate in synapses targeted for elimination (Hong et al., 2016; Lui et al., 2016) and in endothelial cells following cerebral ischemia-reperfusion injury (Lai et al., 2017).

C1q and C3 accumulation was also observed in other age-associated diseases unrelated to brain dysfunction. While C1qb is a clinical predictor (Peters et al., 2017) and C3 a risk factor for type 2 diabetes (Engstrom et al., 2005), these proteins were also found to be involved in atherosclerosis, although their role is still controversial. On the one hand, C1q promotes macrophage survival during ingestion of excess cholesterol (Pulanco et al., 2017) and, on the other hand, C3 activation in atherosclerotic lesions by cholesterol crystals induces release of potent inflammatory mediators (Niyonzima et al., 2017). Thus, the complement system activation is involved in several age-related pathologies and could be considered both a biomarker and a therapeutic target for age-related diseases.

sRAGE (soluble advanced glycosylation end product-specific receptor, aka AGER) binds macromolecules formed by glycation, called advanced glycation end-products (AGEs). AGEs may play a major role in aging and disease (Brownlee, 1995; Simm, 2013; Simm et al., 2015). It has been suggested

that activation of RAGE may be involved in diabetes mellitus (Schmidt, 2015), aging, neurological diseases and some forms of cancer (Ahmad et al., 2017). RAGE belongs to the family of immunoglobulins and has an extracellular ligand-binding domain and intracellular domain by which it initiates various age-related signalling pathways. RAGE activation is involved in inflammatory processes and DNA damage. sRAGE is a splice variant of RAGE, found in plasma that lacks the intracellular domain and does not initiate signalling. sRAGE is described as a decoy receptor which binds and functionally inactivates AGEs, reducing immuno-inflammatory responses (Wang et al., 2015b) and low sRAGE levels have been associated with increased arterial stiffness in hypertensive non-diabetic patients, while sRAGE has been found to be elevated in type I diabetes and associated with peripheral neuropathy in type II diabetes (Aubert et al., 2014; Bakker et al., 2015; Mayer et al., 2016). Moreover, sRAGE concentration is decreased in Alzheimer's disease patients compared with healthy controls (Xu et al., 2017d). Alternatively, sRAGE has been used as a biomarker for certain diseases such acute respiratory distress syndrome (Jabaudon et al., 2018)) and is also a prognostic biomarker in patients with sepsis (Brodska et al., 2013).

HMGB1 (high mobility group box 1), is an intracellular, DNA binding protein, ubiquitously expressed which regulates gene expression, but can also be released in the event of cellular damage. It is considered as damage-associated molecular pattern molecule that triggers inflammation and adaptive immune response (Bianchi et al., 2017) by binding in the extracellular space to an inflammatory receptor such as RAGE, TLR2, and TLR4 (Li et al., 2015a). In addition, HMGB1 is also a critical regulator of mitochondrial function and morphology (Tang et al., 2011), cell proliferation (particularly in cancer cells) (Angelopoulou et al., 2016; Ko et al., 2014) and autophagy. In this regard, it mediates autophagy in a p53-dependent manner to promote either tumour-cell survival or cellular senescence in various human cells (Davalos et al., 2013; Livesey et al., 2012).

Taking this into consideration, it is not surprising that an increase in HMGB1 levels is observed in neuroinflammation following brain injuries leading to epilepsy or cognitive dysfunction and can also trigger and amplify the inflammation cascade in ischemic injury (Qi et al., 2016; Ravizza et al., 2017; Wang et al., 2017a). HMGB1 orchestrates responses to tissue damage via inflammation, innate and adaptive immunity, tissue repair, and in sepsis. HMGB1 plasma levels were found to correlate with the disseminated intravascular coagulation and organ failure assessment (Bianchi et al., 2017; Hatada et al., 2005; Stevens et al., 2017). Other diseases with increased HMGB1 levels are fibrotic kidney disease (Chen et al., 2016a), diabetes (Wu et al., 2016b), various carcinomas, and gliomas (Angelopoulou et al., 2016; Ko et al., 2014; Nguyen et al., 2017), rheumatoid arthritis and myocardial infarction (Guo et al., 2011; Limana et al., 2005; Qi et al., 2016; Vezzoli et al., 2011). In heart failure, HMGB1 together with sRAGE are clinically used to assess prognosis and risk stratification (Marsh et al., 2017). Cerebrospinal fluid HMGB1 is associated with neuronal death in subarachnoid haemorrhage (Wang et al., 2017a).

Interestingly, serum levels of HMGB1 were shown to significantly decrease with age in humans (Fu et al., 2016b), which contrasts the detrimental effects of elevated HMGB1 in so many pathologic conditions. Moreover, studies with the senescence inhibitor metformin showed that it directly binds HMGB1 and inhibits its pro-inflammatory activity (Horiuchi et al., 2017). Inhibition of HMGB1 is also pursued as a therapeutic target in Sjogren's syndrome, experimental sepsis, gastric cancer, and epilepsy with attenuating and in some cases even disease-modifying activity (Chung and Lim, 2017; Kim et al., 2017b; Stevens et al., 2017; Zhao et al., 2017b).

ST2 (soluble suppression of tumorigenicity 2), is a member of the IL-1 receptor family also known as IL-33 receptor. It has been linked to inflammation potentiating the response of macrophages to LPS stimulus in a TLR4/MyD88-dependent pathway (Espinassous et al., 2009). In addition, following IL-33 binding, ST2 actively co-stimulates T-cell responses, enhancing the differentiation of diverse T-cell subsets, increasing clonal expansion and triggering antigen-independent cytokine production (Peine et al., 2016). Although no report has directly associated ST2 with aging, several studies implicated this molecule in age-related diseases such as type 2 diabetes or cardiovascular disorders (Griesenauer and Paczesny, 2017). Increased production of ST2 has been implicated in type 2 diabetes (Miller et al., 2012), as well as in cardiovascular injury (Wang et al., 2018a) with ST2 being considered a predictor of severity in ventricular cardiomyopathy (Broch et al., 2017) and of cardiovascular mortality in haemodialysis patients (Zhang et al., 2017c). Further, ST2 has also served as a prognostic biomarker following acute stroke (Wolcott et al., 2017) and associated with subclinical brain injury and cognitive impairment (Andersson et al., 2015). Interestingly, serum levels of ST2 are higher in rheumatoid arthritis patients than in healthy controls and are decreased following treatment with conventional disease-modifying antirheumatic drugs (Hong et al., 2011). Finally, increased levels of ST2 predict mortality risk in critically ill patients (Krychtiuk et al., 2018), making it a potential candidate as a frailty biomarker.

In summary, seven biomarker candidates with activity on NMJ and neurons were evaluated. We identified two high priority markers (progranulin, BDNF) which will be included in the core panel, and five medium priority markers (agrin, C3/C1q, sRAGE, HMGB1, and ST2) for the expanded panel. Many of the markers in this section are closely linked to inflammation and could be easily discussed in the inflammation section (3.1).

3.6 Cytoskeleton and hormones

Actin cytoskeleton is a cellular component whose role has been vastly underestimated for a long time and now is recognised as essential factor in various cellular functions, in particular for cell morphology. For instance, it is vital for the signalling networks that link cellular processes such as polarisation, organelle

movement, motility, and division to environmental signals. Also, oxidative stress can damage the actin cytoskeleton which may lead to apoptosis (Amberg et al., 2012). Thus, it is not surprising that cytoskeleton seems to have an important role in age-related diseases and aging (for review see (Rao and Cohen, 1990)).

The cytoskeleton is controlled by a variety of hormones which are regulated on their part in a complex manner such as production of pro-hormones in the hypothalamus, which induce the secretion of hormones from the pituitary gland, also called hypothalamus pituitary axis. Subsequently, pituitary hormones are circulating and affect the production of, adrenal, gonadal, thyroid, somatotropic, and prolactin hormones elsewhere in the body. These hormone cascades are regulated by positive and negative feedback loops and are, therefore, changing rapidly and affect each other's production and release. The dysregulation of hormones in aging is well established (for review see (Maggio et al., 2010)) and confirmed in many studies on caloric restriction (De Loof et al., 1996), an intervention that increases lifespan in organisms ranging from yeast to mammals. Indeed, in most organisms, the effect of caloric restriction correlates with alterations in insulin/IGF-1 pathways suggesting that hyperglycaemia and hyperinsulinemia are accelerating aging. GH/IGF-1 signalling molecules have been linked to longevity including their homologues in other species and IGF-I inhibition was shown to increase lifespan. Overall, the life-prolonging effects of caloric restriction correlated well with lowered IGF-1 levels. Not only hormones of the GH/IGF-1/Insulin pathways, but also members of other pathways such as mTOR, NAD⁺, Sirtuin, P53, α -klotho/FGF23, FGF21, and apolipoprotein (APOE) pathways have been linked to age-related diseases such as cancer, cardiovascular disease, diabetes, osteoporosis, and neurodegenerative diseases. Actually, it is now believed that hormones directly influence health during aging and represent key targets in anti-aging therapy such as α -klotho and ghrelin. For example, ghrelin or synthetic agonists are used as interventions to increase appetite and muscle mass in frailty and in frailty-associated disorders. Moreover, most hormones are easily detectable in serum and urine and may be good predictors of biological aging and subsequently frailty and here we nine "hormone" markers (see Tables 6, 8, S1 and Figs. 3-5). We would like to note that we intentionally did not include sex hormones in our frailty biomarker panels even though reduced levels are reported in aged and frail people and replacement therapy is pursued as therapeutic intervention. There are many reports and reviews in this area (see (Horstman et al., 2012; Samaras et al., 2014)) and our aim was to focus on sex-independent hormones and biomarkers.

GH (growth hormone also known as somatotropin) is a somatotropic peptide hormone that stimulates growth, cell reproduction, and cell regeneration in humans and laboratory animals. GH secretion is regulated by the hypothalamic hormone Gonadotropin-releasing hormone (GnRH) in a pulsatile profile with a strong dependence on sleep/waking and fasting. GH also stimulates, through the JAK-STAT signalling pathway, the production of IGF-1. It is therefore assumed that GH exerts its effects mainly through IGF-1 which will be discussed in more detail below. Actually, replacement therapy with GH in

frailty and other age-related conditions was first proposed a very long time ago (Hodes, 1994; Villareal and Morley, 1994). Moreover, there is a strong correlation between the levels of the hunger hormone ghrelin, also discussed below, GH, and IGF-1 (Arellanes-Licea Edel et al., 2014).

IGF-I (insulin-like growth factor 1) is a member of a peptide family that promotes growth and development during foetal and postnatal life. Although the IGF-1 gene is ubiquitously expressed in the body, it is mainly produced in the liver. Transgenic ablation and disruption of this gene results in reduced lifespan and severe growth retardation. In addition, absence of IGF-I in mice results in generalised organ hypoplasia, including underdevelopment of the CNS and defects in muscles, bones, and the reproductive system. Studies have shown that IGF-1 plays crucial roles at the molecular level in many processes such as nucleic-acid activation, carbohydrate, lipid and protein metabolism, cellular organisation and homeostasis, cell differentiation, cellular senescence, and apoptosis. Furthermore, IGF-I is also involved in variety of physiological and pathophysiological conditions such as immune system processes, inflammation, mitochondrial dysfunction, tumour development, frailty, aging, and age-related diseases. For example, it was reported that insulin/IGF-1 cross talk and IRS-1 (insulin receptor substrate 1) phosphorylation is responsible for longevity in Ames dwarf mice (Bartke and Darcy, 2017; Dogan et al., 2011; Handayaningsih et al., 2012; Jia et al., 2018; Lara-Diaz et al., 2017; Mathew et al., 2017; Olleros Santos-Ruiz et al., 2017; Papaconstantinou and Hsieh, 2015). Moreover, elevated serum IGF-I was reported in both humans and animals with increased body weight and adipose tissue. In addition, decreased IGF-I was reported after caloric restriction (Dogan et al., 2011; Dogan et al., 2017). Interestingly, while caloric restriction significantly decreased IGF-I levels detected in mice at 25, 37 and 55 weeks of age, no changes were found at earlier (week 13 or 14) or at later (week 74) age (Dogan et al., 2011). Various mouse models are available to study the IGF-I gene *in vivo*. While homozygote mutants are viable, fertile, and normal in size, homozygous null mutants are severely growth retarded and die perinatally due to immature organ systems. Moreover, partial knockout mice show growth retardation and abnormalities in selected organs.

α -Klotho (α -KL) is a transmembrane protein related to beta-glucosidases which controls organism sensitivity to insulin and plays a crucial role in cellular homeostasis (e.g. carbohydrate and protein metabolism). It interdependently works with FGF23 (discussed below) with α -klotho mainly functioning as a co-receptor for FGF23 signaling. Actually, α -klotho is one of the proteins with the most clear association with aging and was originally identified as putative aging-suppressor gene and significantly contributed to the advanced understanding of aging processes. In mice, overexpression of α -klotho significantly extends lifespan, whereas knockdown causes a progeroid phenotype with markedly shortened lifespan (Xu and Sun, 2015). Moreover, serum α -klotho declines with age and in patients with chronic renal failure, where it is suggested to be one of the factors underlying degenerative processes (e.g., atherosclerosis, osteoporosis, and skin atrophy) seen in the condition. Also, mutations within this protein have been

associated with aging and bone loss. α -klotho is expressed at the highest levels in kidney and brain. In the brain, expression is found in cerebellum and hippocampus, in microglia, oligodendrocytes, and neurons. α -Klotho can be detected in circulation after shedding of the amino-terminal extracellular domain (Abraham et al., 2016; Baldan et al., 2015; Bartali et al., 2013; Bian et al., 2015; Buendia et al., 2015; Fan and Sun, 2016; Guo et al., 2018; Hu et al., 2011; Kim et al., 2015a; Kim et al., 2017d; Lin and Sun, 2015; Saito et al., 1998; Sopjani et al., 2015; Xu and Sun, 2015; Zhou and Wang, 2015).

FGF23 (fibroblast growth factor 23, also known as phosphatonin) is a pleiotropic protein of the endocrine FGF sub-family secreted by osteocytes where it negatively regulates the plasma phosphate levels by acting on the kidneys. For its biologic actions, FGF23 requires α -klotho as co-receptor (see above). Secretion of FGF23 is tightly regulated by various factors, including α -klotho, PTH (parathyroid hormone), vitamin D, phosphate, and calcium and both genetically increased (autosomal dominant hypophosphatemic rickets) and decreased FGF23 activity (familial tumoural calcinosis) induce pathologies. Interestingly, α -klotho induces FGF23 causing increased FGF23 levels in conditions with low α -klotho which are believed to have mainly detrimental effects, such as in kidney and cardiovascular disease as well as aging, CNS disorders, osteoporosis, rheumatoid arthritis and diabetes. Indeed, increased FGF23 levels predict death and mortality in various diseases (Kuro, 2017; Langsford et al., 2017). Therefore, in contrast to α -klotho supplementation, inhibition of FGF23 is being explored as a therapeutic approach for kidney and other diseases with increased FGF23 levels. We would like to note that α -klotho or FGF23 are interchangeable as markers for the phosphate/vitamin D pathway and that they are often changed in opposite ways in age-related diseases as reduced α -klotho leads to a compensatory increase in FGF23 which seems to have mainly detrimental effects (Akhavue et al., 2018; Atta et al., 2016; Avtanski et al., 2016; Cavalli et al., 2012; Claramunt-Taberner et al., 2018; Clinkenbeard and White, 2017; Econs, 2017; Erben, 2017, 2018; Francis and David, 2016; Fukumoto, 2018; Hanudel et al., 2016; He et al., 2018; Hyun et al., 2018; Kanbay et al., 2017; Kutilek, 2017; Pastor-Arroyo et al., 2018; Rossaint et al., 2017; Ruppe et al., 2016).

FGF21 (fibroblast growth factor 21) is mainly known as an hepatokine regulating sugar intake via the central nervous system. However, it also has pleiotropic action as adipokine, mitokine, myokine, and neuroendocrine (Matuszek et al., 2010). FGF21 uses β -klotho as a co-receptor leading to distinct action from FGF23 even though both signal via FGF receptors. In contrast to α -klotho, β -klotho (Xu and Sun, 2015) is not extensively studied in the context of age-related diseases or frailty and, thus, is not considered a candidate for biomarkers of frailty. Moreover, FGF21 is also involved in many cellular activities, including mitosis and viability and is generally induced by mitochondrial-dependent mechanisms. Therefore, its role as potential biomarker of mitochondrial diseases together with GDF15 has been broadly explored and FGF21 could also be discussed in the mitochondria section.

Beside mitochondrial diseases it is modulated and used as potential biomarker in various diseases, such as metabolic syndrome, diabetes, sepsis, musculoskeletal, renal, cardiovascular, ocular, and liver disorders as well as osteoarthritis, rheumatoid arthritis and cancer. Interestingly, many pathologies are aggravated by FGF21 deletion as, for example, those induced by diabetes. There is also a link to premature aging and lifespan. In addition, FGF21 may predict mortality and protects against hepatotoxicity induced by acetaminophen. Actually, various long-acting and engineered FGF21 variants are explored in cardiovascular and metabolic diseases and FGF21 is induced by metformin, an agent also explored in age-related diseases, including frailty (Bartali et al., 2013; Davis et al., 2017; Davis et al., 2013; Davis et al., 2016; Domouzoglou et al., 2015; Dong et al., 2015; Dushay et al., 2010; Hsuchou et al., 2007; Hulejova et al., 2012; Itoh, 2014; Kohara et al., 2017; Lee et al., 2015a; Lee et al., 2016a; Lehtonen et al., 2016; Li et al., 2018c; Liu et al., 2014b; Lovadi et al., 2017; Mai et al., 2011; Morovat et al., 2017; Planavila et al., 2013; Scholle et al., 2018; Shi et al., 2018; Stein et al., 2010; Suomalainen et al., 2011; Talukdar et al., 2016; Woo et al., 2013; Ye et al., 2014; Ye et al., 2017a; Zagarskikh et al., 2018; Zhang et al., 2012).

Resistin (RETN) is a circulating factor, primarily secreted by white adipose tissue in mice and monocytes in humans (Al Hannan and Culligan, 2015). It has also been detected in human placenta, skeletal muscle, small intestine, spleen, stomach, thymus, thyroid gland, and uterus. Resistin plays a role in many pathways, such as inflammation (Demirci et al., 2017; Edwards et al., 2013; Meng et al., 2017; Shen et al., 2014; Zuniga et al., 2017), cell proliferation (Mohammadi et al., 2017; Singh et al., 2017), apoptosis (Lu et al., 2013; Zhu et al., 2017a) and mitochondrial function (Wen et al., 2018; Wen et al., 2015a; Zhou et al., 2013). Resistin also contributes to insulin and leptin resistance associated with reduced brown adipose tissue activity (Asterholm et al., 2014). Increased serum resistin levels were reported in adult and older persons with heart failure and cardiovascular diseases such as coronary artery disease, coronary syndrome, and peripheral arterial disease (Butler et al., 2009; Codoner-Franch et al., 2014; Gencer et al., 2016; Hsu et al., 2017a; Li et al., 2013; Wang et al., 2017e). Importantly, the adiponectin/resistin index is suggested to be even more strongly associated with atherosclerosis (Rubio-Guerra et al., 2013). Resistin has also been explored as a biomarker (for more details on adiponectin see below) in many other age-related diseases, including rheumatoid arthritis (Sato et al., 2017), osteoarthritis (Song et al., 2016a), neurological diseases (Dong et al., 2017b; Dong et al., 2010; Sawicka et al., 2017; Zanardini et al., 2018), metabolic diseases (Menzaghi et al., 2014; Solis-Cano et al., 2017; Wen et al., 2014), and various types of cancer (Georgiou et al., 2016; Hsieh et al., 2014; Kallio et al., 2017; Lee et al., 2016b; Vallega et al., 2016). In accordance, homozygous resistin null as well as mutant mice are available and present obesity, insulin resistance, as well as immunologic and inflammation phenotypes.

Adiponectin (ADIPOQ) is another adipokine secreted from adipose tissue and circulating as hormone in the blood. Adiponectin is decreased in various pathologic conditions such as obesity, diabetes, and coronary artery disease (Hotta et al., 2000; Kumada et al., 2003). In serum, three different adiponectin forms are distinguished: trimer, hexamer, and a high molecular weight high molecular weight adiponectin form (Ouchi et al., 2003) and these forms are differentially modulated in disease conditions

Adiponectin modulates various “hallmark of aging” mechanisms including inflammation, mitochondrial function, apoptosis, and cell proliferation. For example, It protects cells from inflammation, reduces cytokine secretion and inhibits NF κ B signalling and is being explored as inflammation biomarker (Awazawa et al., 2011; Cong et al., 2007; Dieudonne et al., 2006; Gong et al., 2016; Iwabu et al., 2010; Kang et al., 2005; Kim et al., 2011; Kobashi et al., 2005; Kobayashi et al., 2004; Liu et al., 2016b; Ma et al., 2002; Maeda et al., 2002; Ouchi et al., 2000; Zhao et al., 2017c). In accordance, adiponectin preserves insulin sensitivity via IL-6 signalling and adiponectin knockout mice show increased beta-oxidation and TNF- α levels in muscle and liver tissue (Berryman et al., 2004; Chen et al., 2017a; de Luis et al., 2016; Kubota et al., 2002; Ma et al., 2002; Maeda et al., 2002; Ohashi and Funahashi, 2006; Ortega Moreno et al., 2016; Ryo et al., 2004).

In various cancer cell lines adiponectin inhibits proliferation, ER stress, or induces apoptosis (Huang et al., 2015a; Karaduman et al., 2007; Korner et al., 2007; Mantzoros et al., 2004; Miyoshi et al., 2003). In aging, high molecular adiponectin form, but not total adiponectin is changed, and in long-lived animals plasma adiponectin are elevated (Bartke, 2016; Combs et al., 2004; Miller et al., 2017; Sun et al., 2013; Wang et al., 2007b). Moreover, high adiponectin levels are associated with decreased risk for myocardial infarction and exercise also has a positive effect on adiponectin, whereas low levels are associated with cancer and dysfunctions in various organs such as liver, ears, muscle, and many more (Ambroziak et al., 2018; Fujishima et al., 2017; Niinaga et al., 2016; Pischon et al., 2004; Sattar et al., 2006; von Eynatten et al., 2006a).

Thus, it is not surprising that adiponectin has been explored as a biomarker in various diseases including hepatitis C, various cancers, inflammation, renal disease, atherosclerosis, and migraine and is also being directly pursued as therapeutic intervention target (Chen et al., 2015b; Kelesidis et al., 2006; Liu et al., 2017a; Nawrocki et al., 2006; Otani et al., 2010). There is a tremendous amount of knowledge around adiponectin and it has great potential as diagnostic, prognostic and therapeutic biomarker for frailty.

Leptin (LEP) is another circulating adipokine mainly produced by adipocytes, but also expressed in various other tissues, such as cardiovascular, reproductive, liver, musculoskeletal and neurons. The major role of leptin is control of body weight and energy expenditure. In addition, leptin regulates different physiological and pathophysiological processes including apoptosis, angiogenesis, cell proliferation,

energy metabolism, inflammation, diabetes, reproduction, obesity, and different kinds of tumour development (Dogan et al., 2010; Ray and Cleary, 2017; Ryan et al., 2003; Silha et al., 2006; Xu et al., 2017c). There is also clear evidence for the role of leptin in aging and age-related diseases. For example, leptin was reported to contribute to worsening the prognosis of tumoral and neurodegenerative processes by increasing the susceptibility of cells to inflammatory mediators (Martin et al., 2017b). In animal studies serum leptin increased with aging (Dogan et al., 2017) and caloric restriction led to opposite effects. It should also be noted that there is some controversy as several studies reported no effects of caloric restriction on serum leptin levels both in human and animals (Ryan et al., 2003; Silha et al., 2006). Regarding mouse models, both leptin and leptin receptors knockout mouse models are available and used as models for obesity and diabetes as they gain weight rapidly. They also have potential as age-related disease and frailty models as they have a metabolic syndromes and more importantly shortened lifespan.

Leptin similar to adiponectin modulates various “hallmark of aging” mechanisms including inflammation, mitochondrial function, apoptosis, cellular senescence and cell proliferation and there is a lot of knowledge available around this ubiquitously expressed and modulated factor. In the following, only a few examples are given and we otherwise refer to previous reviews on the action of leptin and its potential as biomarker and therapeutic target (de Candia and Matarese, 2017; Mao et al., 2018; McGregor and Harvey, 2017; Pan and Myers, 2018; Ramos-Lobo and Donato, 2017; Ray and Cleary, 2017; Rehman et al., 2017; Tsai, 2017). For example, it is noteworthy that leptin exacerbates sepsis-mediated morbidity and mortality (Shapiro et al., 2010), mediates muscle- and liver-derived IGF-1 in aged mice (Hamrick et al., 2015), is important for musculoskeletal health (Philbrick et al., 2018; Philbrick et al., 2017; Yu et al., 2017a) and body composition (Denroche et al., 2011; Xiang et al., 2018). Moreover, leptin and analogues are used therapeutically in lipodystrophy (Muniyappa et al., 2017).

Ghrelin (GHRL) is a small peptide hormone, secreted mostly from the fundus of the stomach, intestines, pancreas, and hypothalamus, which plays a major role in the regulation of appetite and metabolism. The ghrelin peptide presents a carbon fatty acid linked through an ester bond to serine 3. Although, most ghrelin found in circulation is in the unacylated form (UnAG), only the acylated (AG) peptide is able to bind to the ghrelin receptor (also called growth-hormone-secretagogue receptor 1a), eliciting multiple biological effects, such as: 1) increase in appetite, 2) increase in food uptake, 3) modulation of glucose homeostasis and insulin sensitivity and 4) increase in GH release. Mice homozygous for most disruptions in the ghrelin gene display age-dependent changes in stimulated food intake and metabolism.

In addition to its orexigenic and GH releasing functions, AG-mediated signalling has been associated with an increase in gastric motility and an increase in lean body mass and has been shown to promote adipogenic and anti-inflammatory effects on monocytes and T-lymphocytes (Dixit et al., 2004). On the

other hand, UnAG is reported to also have important physiological roles that are independent from the ghrelin receptor and sometimes even oppose AG activity, such as: 1) enhancement of pancreatic β -cell survival and function and 2) improvement of cardiovascular activity and regulation of carbohydrate metabolism. UnAG has been shown to rescue mitochondria damage following ischemia/reperfusion injury in the liver (Rossetti et al., 2017), while treatment with AG normalised chronic heart failure-associated skeletal muscle mitochondrial dysfunction and pro-inflammatory changes, showing a potential positive impact in heart failure patients (Barazzoni et al., 2017). Ghrelin treatment was also shown to reduce intestinal mucosa injury and vascular calcification through stimulation of autophagy (Wan et al., 2016; Xu et al., 2017b), Ghrelin also mediates additional beneficial effects through stimulation of cell proliferation, inhibition of apoptosis (Liao et al., 2017) and a decrease in fibrosis (PMID: 46313288).

Concerning its direct action in aging, some controversy can be found in the literature. While several studies point to a relation between low ghrelin levels and higher weight loss and poorer hand grip strength in the elderly, longevity is not directly affected by ghrelin deletion. Despite this, treatment of wildtype and ghrelin knockout mice with ghrelin increases food intake, body weight, and muscle strength, which suggests that ghrelin can be used as an intervention to protect against some age-related disorders (Guillory et al., 2017). In this context, ghrelin levels and ghrelin administration were tested in three different models of accelerated or normal human aging. Elevated plasma ghrelin levels were observed in both α -klotho-deficient and senescence accelerated mice. Nevertheless, ghrelin administration failed to stimulate appetite and prolong survival in α -klotho-deficient mice, while ghrelin signalling potentiators were able to decrease microglial activation and prolong survival in all three animal models tested in this study (Fujitsuka et al., 2016). In humans, AG levels were shown to be increased in patients with mild cognitive impairment, in association with poorer language skills and defected long and short-term memory, in type II diabetes patients with visceral obesity and insulin resistance (Guillory et al., 2017; Mykhalchyshyn et al., 2015), and also in heart disease patients (Kilic et al., 2017). On the other hand, no correlation could be detected between ghrelin and sarcopenia (Serra-Prat et al., 2015), despite several studies showing a positive action of ghrelin in preventing decline in muscle strength and endurance (Guillory et al., 2017). Given these contradictory results, the potential of ghrelin as a frailty biomarker and therapeutic intervention, although promising, needs to be further explored before a final conclusion can be reached.

In summary, nine hormones capable of modulating the cytoskeleton were analysed. Since hormonal changes are key modulators of “hallmark of aging” pathways and hormones are often dysregulated in aging and age-related diseases they can be considered highly valuable biomarker candidates. Four candidates reached high priority scores (α -Klotho, FGF23, FGF21, Leptin) and the other five medium scores (GH, IGF-1, resistin, adiponectin, ghrelin).

3.7 Other principles

In this final section we are going to discuss six additional potential biomarkers for frailty which come from different principles and pathways not covered in the previous chapters. However, most of the markers have close relation to the hallmark of aging pathways and could even be shifted to other chapters (see Tables 7, 8, S1 and Figs. 3-5).

We would like to note again that we focused our review on key pathways and biomarkers measurable in bio fluids and used in other conditions. Of course, there are more pathways, factors, and markers which could be included, such as, for example, stem cell markers or pathways (e.g. Notch, Wnt), vitamins (e.g. vitamin D), or metabolites. We believe that many of such additional markers are indirectly covered as many of the markers have been shown to be interdependent and involved in various pathways. Moreover, if frailty biomarker panels are proven a valuable approach, optimising the power of the panel by expansion or exchanging of factors is an important next step.

miRNA (microRNA), are small non-coding RNA molecules that function in RNA silencing and play an important role in post-transcriptional regulation of gene expression. They are mostly intracellular and regulate multiple target genes. Thus, it is not surprising that miRNAs are key modulators of almost all physiologic processes including tissue homeostasis and, consequently miRNA dysregulation is seen in a variety of diseases. Actually, miRNAs specific to tissues (e.g. muscle, for a review see (Ludwig et al., 2016), cellular functions and dysfunction (e.g. mitochondria, apoptosis, fibrosis) as well as diseases (e.g. cancer, cardiovascular) have been identified. Moreover, with the discovery that miRNAs circulate in cell free blood (Hunter et al., 2008), a quest for finding miRNA based biomarkers in various body fluids including serum, plasma and even urine has begun (Razvi, 2013). miRNAs are secreted by specific cells and subsequently taken up by target cells to fine tune gene expression (Bayraktar et al., 2017). Due to high RNase activity in bio fluids, miRNAs are either packaged into extracellular vesicles or bound to proteins so that they can act as hormone-like molecules. Actually, packed miRNAs are surprisingly stable in body fluids and their use as biomarkers in clinical settings is an emerging, broadly explored field of research.

In fact, signatures of circulating miRNAs are generally explored as diagnostic, prognostic, and therapeutic markers for a large variety of diseases (Wang et al., 2016a; Witwer, 2015). This includes major age-related diseases contributing to frailty, such as cancer (Hatse et al., 2014), cardiovascular disease (Barwari et al., 2016), osteoporosis, cardiovascular disease (Barwari et al., 2016), osteoporosis (Hackl et al., 2016), osteoarthritis (Beyer et al., 2015), neurodegenerative diseases (Sheinerman and Umansky, 2013), or sarcopenia (Siracusa et al., 2018). Interestingly, miRNA signatures for predicting osteoporotic

fracture risk were even shown to have socio-economic benefits (Walter et al., 2018) and are hopefully entering clinical use in the near future.

miRNA panels seem to be especially valuable in the context of multifactorial conditions, for which frailty is a prime example, potentially complementary to single biomarker molecules in increasing detection sensitivity and specificity. Ideally, such miRNA panels for frailty should consist of tissue-, pathway- and disease-specific miRNAs (for review see (Baker et al., 2017)). For example, tissue-specific miRNAs are found in muscle (myomiRs) and bone (osteomiRs) and show age-related dysregulation. Similarly, a big variety of pathway-specific miRNAs exists for mitochondria (also known as mitomir), apoptosis, inflammation, and senescence, just to name a few, as well as for diseases such as cancer (also known as oncomir), cardiovascular, neurodegeneration, and many more. As for the other biomarkers discussed in this review, miRNAs with broader coverage of either “hallmark of aging” pathways or diseases would be ideal candidates such as, for example, miRNAs associated with cellular senescence (Schraml and Grillari, 2012; Weilner et al., 2013), inflammation (Olivieri et al., 2013), or mitochondrial dysfunction (Bedreag et al., 2016). Actually, systemic approaches to identify circulating miRNA based biomarkers for frailty are on the way such as the OMICs approach from the FRAILOMIC consortium (Erusalimsky et al., 2016; Lippi et al., 2015) and first results of these studies are expected to be published soon. During completion of this review there was a first publication available ahead of print in the Journal of Frailty and Aging reporting enrichment of miR-10a-3p, miR-92a-3p, miR-185-3p, miR-194-5p, miR-326, miR-532-5p, miR-576-5p, and miR-760 in frailty (Ipson et al. 2018, ahead of print).

To conclude, miRNA panels are emerging biomarkers in many different physiologic and pathophysiologic conditions and of great interest also for frailty. Studies are ongoing to identify frailty specific miRNA panels, already in print or discussed as scientific conferences and their outcome will open new possibilities. We would like to mention that the high priority score for miRNA in Table 8 is based on the broad potential of miRNAs as biomarkers but will depend on the identification of miRNA panels with high specificity and predictability of frailty.

AHCY (adenosylhomocysteinase) controls intracellular AHC (S-adenosylhomocystein) levels which are important for transmethylation reactions and metabolic functions. It converts (AHC) to HC (homocysteine) and adenosine, both molecules with broad biologic functions. In particular increased HC levels – due to increased AHCY activity – seem to be detrimental in many organs and were detected in neurodegenerative, inflammatory, and other diseases. For example, long-term elevation of HC may lead to mitochondrial dysfunction, ER stress and oxidation, apoptosis, and inflammation in a broad range of cell types (Abushik et al., 2015; Hu et al., 2017; Kalani et al., 2014b) and also accelerates senescence of endothelial cells via DNA hypomethylation of human telomerase reverse transcriptase (Zhang et al., 2018a). Pathologic conditions with high HC levels are rheumatoid arthritis, particularly patients with high

cardiovascular risk, Alzheimer's disease, Parkinson's disease, chronic kidney disease, atherosclerosis, and elderly patients (Derouiche et al., 2014; Haghdoost-Yazdi et al., 2014; Hu et al., 2017; Marino et al., 2014; Motzek et al., 2016; Sun et al., 2017a; Xia et al., 2014; Yang et al., 2015b; Ye et al., 2017b). In stroke patients, elevated HC independently predicted severe neurological impairment, poor functional outcome, and stroke recurrence (Shi et al., 2015b) and is associated with long-term mortality (Shi et al., 2015b).

Full body AHCY knockout mice with increased AHC are lethal and patients with AHCY deficiency also show markedly elevated plasma AHC and primarily neuromuscular symptoms including hypotonia, sluggishness, psychomotor delay, absent tendon reflexes, and delayed myelination (Baric et al., 2005; Motzek et al., 2016). In accordance, methionine metabolism was shown to change strikingly during aging. Accordingly, increased AHC and tissue-specific AHC down-regulation extended both health-span and lifespan in *Drosophila* (Parkhitko et al., 2016).

AHCY is also interesting as a therapeutic target and both direct and indirect inhibition is being pursued. For example, a few direct AHCY enzymatic inhibitors (e.g. eritadanine, 3-Deazaneplanocin A and 9-(2-deoxy-2-fluoro- β ,D-arabinofuranosyl) adenine)) or agents indirectly reducing AHCY (e.g. folate, vitamin Bs, inflammasome inhibitors, alpha-lipoic acid) exist and were shown to improve cognitive function in elderly people, reduce HC-induced inflammasome activation, glomerular sclerosis, cell dysfunction such as ER stress and oxidation, apoptosis and inflammation (Cheng et al., 2016b; Ctrnacta et al., 2010; Hu et al., 2017; Lee and Kim, 2013; Shokar et al., 2012; Zhu et al., 2017b).

The high priority score for AHCY is based on the fact that AHCY dysregulation in aging and age-related diseases seems highly evident and direct and indirect inhibition showed therapeutic effects. However, beside the enzymatic dysfunction there is evidence for accumulation of the substrate AHC with aging which may contribute to the observed deficits. Thus, measuring substrate AHC and the product HC or maybe building a ratio of the two measures would be the preferred way to include AHCY in frailty biomarkers.

Microparticles, also called circulating microvesicles, are small (0.1–1.0 μ m) plasma membrane-derived extracellular vesicles present in the bloodstream. Blood contains microparticles shed from different cell types, mainly platelets, but also red blood cells, granulocytes, monocytes, lymphocytes, and endothelial cells. They may be released during cell activation, cell injury, cell senescence, and apoptosis and contain immunologically active molecules affecting a variety of cellular processes such as inflammation, coagulation, antigen presentation, and apoptosis. Actually, microparticles can be characterised by cell surface antigens reflecting their origin and activation method. Therefore, determination of microparticles in plasma can be used as markers of cellular activation or damage (for review see (Cheng et al., 2016b).

Indeed, circulating microparticles have been detected in a variety of diseases and dysfunctions with proposed diagnostic and pathologic function. They promote endothelial cell senescence which may be important in vascular dysfunction in aging and acute coronary syndrome patients (Abbas et al., 2017; Burger et al., 2012). In inflammation, microparticles may contribute to the pathogenesis of systemic inflammation, autoimmune disease and sepsis (Bei et al., 2016; Blair et al., 2016; Liu et al., 2017c). In the latter endothelial microparticles induce an inflammatory response in endothelial cells, and both endothelial microparticles and endothelial cells can assist in early diagnosis of sepsis. Moreover, bacterial infection induces platelet microparticles which subsequently contribute to the inflammatory response. Moreover, in pulmonary arterial hypertension endothelial microparticles are involved in the vascular pathogenesis. Rheumatoid arthritis patients, even in early stages of disease, have increased levels of microparticles compared with healthy controls (Cunningham et al., 2014). Patients with active rheumatoid arthritis tended to have higher endothelial microparticles than nonactive patients. Similarly, microparticles are also detected in plasma of prediabetes, type 2 diabetes patients, in chronic kidney disease, in obesity, atherosclerosis, in idiopathic pulmonary fibrosis, various cancers and after exercise with pathogenic and diagnostic action (Bacha et al., 2017; Banz et al., 2016; Dimassi et al., 2016; Luna et al., 2016; Mege et al., 2016; Schwarz et al., 2018; Wekesa et al., 2014). Microparticle numbers are increased in some CNS diseases and can contribute to the onset and progression of neurodegenerative and neuroinflammatory diseases, including Alzheimer's disease, traumatic brain injury, and stroke (He et al., 2017b; Schindler et al., 2014).

Beside their potential as pathologic and diagnostic biomarkers, it has also been suggested to directly target microparticles, particularly their shedding and bioactivity, as a promising therapeutic strategy. Future research will show if this is feasible and also if they can be used as therapeutic biomarkers. To our knowledge microparticles have yet not been measured in therapeutic intervention studies. Moreover, specific panels need to be established for "frail" patients and like for miRNAs the score in Table 8 depends on our success in this endeavour.

KRT18 (keratin 18) is a type I cytokeratin and together with its partner KRT8, the major type 1 keratin in epithelia found in liver, pancreas, and intestine. Importantly, soluble fractions of KRT18 are secreted into the extracellular space and subsequently into the blood stream during cell death both in *vitro* and *in vivo* (Schutte et al., 2004).

In old mice, liver KRT18 is strongly upregulated and undergoes increased phosphorylation and lysine acetylation. In addition, KRT18 expression was shown to be associated with senescence and linked to anti-mitochondrial auto-antibody formation (Battaglia et al., 2017; Schallmoser et al., 2010; Toivola et al., 2015). The major pathologic action of KRT18 is on mitochondria as it modulates the shape and function

of hepatocyte mitochondria and mutation in KRT18 induces mitochondrial fragmentation in liver-derived epithelial cells. In accordance, knock-down of KRT18 leads to an abnormal clustering of mitochondria (Kumemura et al., 2008; Schwarz and Leube, 2016; Tao et al., 2009) as well as enhanced apoptosis and causes predisposition to liver injury and apoptosis (Ku et al., 1997; Mannery et al., 2011; Marceau et al., 2001; Tao et al., 2009). KRT18 is also a known marker of apoptosis and has been proposed as an indicator of progression in chronic liver diseases such as non-alcoholic fatty liver disease. As mentioned, keratins and their fragments are released into blood during liver and other epithelial tissue injury (Ku et al., 2016). In particular the caspase-cleaved fragment (cKRT18) is used to diagnose non-alcoholic fatty liver disease, especially non-alcoholic steatohepatitis, to predict development of type 2 Diabetes in non-alcoholic fatty liver disease patients, and as novel safety biomarkers for drug-induced liver injury as well as other liver disease and cancers. In accordance, mice with point-mutations in KRT18 develop chronic hepatitis and hepatocyte fragility in association with disruption of hepatocyte keratin filaments and have an increased susceptibility to drug-induced hepatotoxicity (Kullak-Ublick et al., 2017; Morling et al., 2014; Thulin et al., 2014). cKRT18 has potential as therapeutic biomarker and treatment with pan-caspase inhibitors reduces cKRT18 (Yang et al., 2014). In addition, serum KRT-18 levels are associated with 30-day mortality and could be used as a prognostic biomarker in patients with severe traumatic brain injury (Lorente et al., 2015).

Taken together, KRT18 and its fragment cKRT18 are highly validated biomarkers in diseases with mitochondrial and apoptotic defects for diagnostic, prognostic, and therapeutic purpose. Such defects are not only major “hallmarks of aging” and frailty but there is also evidence that KRT18 is indeed induced with increased age and may contribute to age-related diseases.

GpnmB (glycoprotein nonmetastatic melanoma B) is a membrane protein that can be secreted as a soluble form after cleavage. It is mainly expressed in melanocytes, osteoclasts, osteoblasts, dendritic cells, macrophages, and overexpressed in various cancer types. Its biologic action includes M2 macrophage polarisation, regulation of tissue remodelling, promoting cell migration, invasion, and metastasis. In addition, negative regulation of T-cell activation and proliferation as well as positive regulation of the MAPK cascade have been reported. Other biologic effects of GpnmB include modulation of osteoblast differentiation and bone mineralisation, protection from ER stress, and a role as a pathologic factor on mesenchymal stem cells in age-related skeletal diseases.

GpnmB has anti-inflammatory and regenerative functions. For example, in acute kidney and liver injury GpnmB promotes M2 macrophages polarisation and contributes to the balance between fibrosis and fibrolysis (Kumagai et al., 2015). Similarly, beneficial impact of GpnmB and its significance as a biomarker is described in non-alcoholic steatohepatitis (Katayama et al., 2015) and in wound repair where it regulates cross-talk between macrophages and mesenchymal stem cells. It has also been proposed as a

novel potential therapeutic target in cancer. Moreover, an emerging role of GpnmB is evident in neurodegenerative diseases. For example, GpnmB is neuroprotective in an animal model of amyotrophic lateral sclerosis, cerebral ischemia, and other disease models and increased brain expression is associated with risk for Parkinson's disease (Budge et al., 2017; Murthy et al., 2017; Noda et al., 2017).

Given these discoveries, GpnmB can be described as a macrophage marker with protective effects, as a prognostic marker for disease state determination, and as direct therapeutic option in neurodegenerative diseases and cancer (Rose et al., 2017). Since macrophages play a crucial role in age-associated chronic inflammation GpnmB is a highly valuable biomarker candidate for frailty. GpnmB has clear potential as a diagnostic frailty biomarker and further studies are needed to explore if it can also be used as a therapeutic biomarker to monitor drug intervention.

Lactoferrin (LTF, also known as lactotransferrin), a member of the transferrin family, is a major iron-binding protein in milk and other body fluids. It shows antimicrobial activity and is an important component of the non-specific immune system (Mayeur et al., 2016). It deprives pathogens from iron, or disrupts their plasma membranes (Drago-Serrano et al., 2017). It was also shown to reduce serum pro-inflammatory cytokines, such as TNF- α and IL-6, to inhibit Treg cells and to be involved in age-related biological processes. For example, lactoferrin protects human mesenchymal stem cells from oxidative stress-induced senescence and apoptosis (Park et al., 2017) and preserves mitochondrial calcium homeostasis in degenerating dopamine neurons (Rousseau et al., 2013).

Lactoferrin has potential as a biomarker for age-related neurodegenerative diseases and is, for example, upregulated in Alzheimer's disease. Interestingly saliva concentrations enable discrimination of mild cognitive impairment and Alzheimer's disease patients from a cognitively healthy control group (Carro et al., 2017). Accordingly, in APP-transgenic mice lactoferrin is localised in brain plaques and amyloid angiopathy and increased with age (Wang et al., 2010). Lactoferrin is also increased in cerebrospinal fluid of Parkinson's disease patients and serum TNF- α negatively correlated with both iron and lactoferrin (Yu et al., 2013).

Lactoferrin is also used as a relevant marker to monitor metabolic disorders. Actually, lactoferrin is inversely associated with fasting triglycerides, glucose, and body composition, but directly correlates with high density lipoprotein cholesterol (Moreno-Navarrete et al., 2008) In contrast, insulin resistance correlates positively and independently with plasma lactoferrin independent of adipositas (Mayeur et al., 2016). In cardiovascular disease, plasma lactoferrin predicts the risk for cardiovascular events. For example, increase lactoferrin is associated with ischemic stroke (Santos-Silva et al., 2002) and a predictor for fatal ischemic heart disease in diabetes mellitus type 2 patients (Vengen et al., 2010). Moreover, functional polymorphisms in lactoferrin are related to aortic plaques and coronary artery stenosis (Videm

et al., 2012). Interestingly, bovine milk-derived lactoferrin exerts proangiogenic effects in response to ischemia and reduces blood pressure (Ikeda et al., 2013).

With respect to age-related inflammatory disorders, rheumatoid arthritis patients have increased synovial lactoferrin which acts as chemoattractant for both neutrophils and lymphocytes (Stanczyk et al., 2005) and is a robust regulator of chondrocyte metabolism, comparable to TGF β 1. Furthermore, its dual catabolic and proliferative action in chondrocytes indicates a function as an early phase cytokine, enhancing MMPs which are necessary for degradation of damaged tissue and subsequent proliferation necessary for repair (Brandl et al., 2010). In inflammatory disease, faecal lactoferrin is useful in the diagnosis and management of inflammatory bowel diseases such as Crohn's disease (Langhorst and Boone, 2012).

Lactoferrin is also broadly explored as a therapeutic agent. For example, lactoferrin conjugates are tested as a new treatment for neurodegenerative disorders and lactoferrin is a component of new drug delivery systems to permeate the blood brain barrier (Meng et al., 2015) and rescue degenerative Alzheimer's disease neurons. A combination of Quercetin-encapsulated liposomes grafted with a bradykinin analogue and lactoferrin has been developed (Kuo and Tsao, 2017) and similarly, deferasirox, a high affinity iron chelator, has been conjugated to lactoferrin (Kamalinia et al., 2013). Lactoferrin also has potential as a therapeutic option for autoimmune and inflammatory diseases (Okubo et al., 2016), and as a protecting agent against certain type of cancers (Li et al., 2017d). For example, lactoferrin exerts anti-tumour effects by inhibiting angiogenesis and preventing migration and invasion of cancer cells. High doses of lactoferrin inhibited cell viability in a dose-dependent manner in a colon cancer model (Li et al., 2017d).

In summary, six biomarkers from other principles were evaluated and showed either high priority (miRNA panel, AHCY, KRT18) or medium priority scores (microparticle panel, lactoferrin, GpnmB). They are valuable and important additions to the panels of frailty biomarkers.

3.8. Published data for selected biomarker candidates in frailty

To close our analysis, we also searched for studies that tested at least part of our proposed markers in a frail cohort. We could not find data for the whole biomarker panel in any one study, but several of our selected markers appear in different studies measuring frail, older patients. The majority of data are around inflammatory factors as frailty markers and we found that changes reported for single markers across studies were not always consistent. In the following section, a few examples are described.

One relatively well characterised cohort is the Newcastle 85+ study and, indeed, various measures including circulating markers have been correlated to frail or non-frail participants. At first, inflammatory markers, including IL-6 from our list, were measured and correlated to different frailty indices (Collerton et al., 2012; Martin-Ruiz et al., 2011). Later on, a broader range of inflammation, immunosenescence and cellular aging markers were determined, including leptin, adiponectin, homocysteine and TGF- β , and cut-off points were used based on survival curves to compose a biomarker based frailty index (Mitnitski et al., 2015). This is a very interesting approach and similar to our proposal as a set of markers were tested. It would be interesting to see if the cut-offs may be generally applicable and if panels are expanded to additional “hallmark of aging” pathways. There are many other studies measuring a few of our markers and as mentioned results are not always consistent (Aguirre et al., 2014; Alvarez-Sanchez et al., 2018; Baylis et al., 2013; Compte et al., 2013; Darvin et al., 2014; Gunawardene et al., 2016; Hubbard et al., 2008a, b; Jorge-Ripper et al., 2017; Lai et al., 2014; Lana et al., 2017; Lee et al., 2016c; Leng et al., 2002; Lu et al., 2016; Nagasawa et al., 2018; Pacho et al., 2018; Qi et al., 2017; Qu et al., 2009; Shardell et al., 2017; Van Epps et al., 2016; Yeap et al., 2013).

To finally validate the usefulness of the proposed panels as well as the advantage over single measures, further studies including measurement of the whole panel of proposed markers in well-defined frailty cohorts are required.

4. Conclusion

Our search identified a variety of biomarker candidates from different “hallmark of aging” pathways. We propose to generate biomarker panels for frailty which should have higher value than single markers. A panel of biomarkers may be more sensitive to relatively small changes in individual markers, but collectively may reveal an overall decline in bodily functions that may contribute to the development of frailty and later on multimorbidity. The accumulation of small deficits may ultimately lead to a larger, more clinically relevant, malfunction. Based on our prioritisation score we suggest a core panel of frailty biomarkers consisting of the 19 high priority candidates: (1) IL-6, CXCL10, CX3CL1 (2) GDF15, FNDC5, VIM, (3) regucalcin, calreticulin, (4) PLA2, AGT, (5) agrin, BDNF, progranulin (6) α -klotho, FGF23, FGF21, leptin (7) miRNA panel (to be further defined), AHCY and KRT18. An expanded panel would include the 22 medium priority candidates (1) pentraxin, sVCAM/ICAM, defensin α (to be further defined), (2) APP, LDH, (3) S100B, (4) TGF β , PAI-1, TGM2 (5) sRAGE, HMGB1, C3/C1Q, ST2, (6) GH, IGF-1, resistin, adiponectin, ghrelin (7) microparticle panel (to be further defined), GpnmB, and lactoferrin. Three candidates were shown to have major limitations as frailty biomarkers and are only attributed low priority: (1) CD14, (4) MMP7, THBS. These predicted core and expanded panels need to be experimentally explored in animal models and frail cohorts for validation and assessing their diagnostic, prognostic, and therapeutic potential.

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Appendix**References**

- Abbas, M., Jesel, L., Auger, C., Amoura, L., Messas, N., Manin, G., Rumig, C., Leon-Gonzalez, A.J., Ribeiro, T.P., Silva, G.C., Abou-Merhi, R., Hamade, E., Hecker, M., Georg, Y., Chakfe, N., Ohlmann, P., Schini-Kerth, V.B., Toti, F., Morel, O., 2017. Endothelial Microparticles From Acute Coronary Syndrome Patients Induce Premature Coronary Artery Endothelial Cell Aging and Thrombogenicity: Role of the Ang II/AT1 Receptor/NADPH Oxidase-Mediated Activation of MAPKs and PI3-Kinase Pathways. *Circulation* 135, 280-296.
- Abella, V., Scotecce, M., Conde, J., Lopez, V., Pirozzi, C., Pino, J., Gomez, R., Lago, F., Gonzalez-Gay, M.A., Gualillo, O., 2016. The novel adipokine progranulin counteracts IL-1 and TLR4-driven inflammatory response in human and murine chondrocytes via TNFR1. *Scientific reports* 6, 20356.
- Abraham, C.R., Mullen, P.C., Tucker-Zhou, T., Chen, C.D., Zeldich, E., 2016. Klotho Is a Neuroprotective and Cognition-Enhancing Protein. *Vitamins and hormones* 101, 215-238.
- Abushik, P.A., Karelina, T.V., Sibarov, D.A., Stepanenko, J.D., Giniatullin, R., Antonov, S.M., 2015. [Homocysteine-Induced Membrane Currents, Calcium Responses and Changes of Mitochondrial Potential in Rat Cortical Neurons]. *Zhurnal evoliutsionnoi biokhimii i fiziologii* 51, 258-265.
- Adams, B.D., Arem, H., Hubal, M.J., Cartmel, B., Li, F., Harrigan, M., Sanft, T., Cheng, C.J., Pusztai, L., Irwin, M.L., 2018. Exercise and weight loss interventions and miRNA expression in women with breast cancer. *Breast cancer research and treatment*.
- Adriaensen, W., Mathei, C., Vaes, B., van Pottelbergh, G., Wallemacq, P., Degryse, J.M., 2014. Interleukin-6 predicts short-term global functional decline in the oldest old: results from the BELFRAIL study. *Age* 36, 9723.
- Adunsky, A., Chandler, J., Heyden, N., Lutkiewicz, J., Scott, B.B., Berd, Y., Liu, N., Papanicolaou, D.A., 2011. MK-0677 (ibutamoren mesylate) for the treatment of patients

- recovering from hip fracture: a multicenter, randomized, placebo-controlled phase IIb study. *Archives of gerontology and geriatrics* 53, 183-189.
- Afaloniati, H., Karagiannis, G.S., Hardas, A., Poutahidis, T., Angelopoulou, K., 2017. Inflammation-driven colon neoplasmatogenesis in uPA-deficient mice is associated with an increased expression of Runx transcriptional regulators. *Experimental cell research* 361, 257-264.
- Afzal, N., Zaman, S., Asghar, A., Javed, K., Shahzad, F., Zafar, A., Nagi, A.H., 2014. Negative association of serum IL-6 and IL-17 with type-II diabetes retinopathy. *Iranian journal of immunology : IJI* 11, 40-48.
- Agnihotri, N., Mehta, K., 2017. Transglutaminase-2: evolution from pedestrian protein to a promising therapeutic target. *Amino acids* 49, 425-439.
- Agoro, R., Montagna, A., Goetz, R., Aligbe, O., Singh, G., Coe, L.M., Mohammadi, M., Rivella, S., Sitara, D., 2018. Inhibition of fibroblast growth factor 23 (FGF23) signaling rescues renal anemia. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 32, 3752-3764.
- Agrawal, A., Gandhe, M.B., Gupta, D., Reddy, M.V., 2016. Preliminary Study on Serum Lactate Dehydrogenase (LDH)-Prognostic Biomarker in Carcinoma Breast. *Journal of clinical and diagnostic research : JCDR* 10, BC06-08.
- Aguirre, L.E., Jan, I.Z., Fowler, K., Waters, D.L., Villareal, D.T., Armamento-Villareal, R., 2014. Testosterone and Adipokines are Determinants of Physical Performance, Strength, and Aerobic Fitness in Frail, Obese, Older Adults. *International journal of endocrinology* 2014, 507395.
- Ahmad, S., Khan, H., Siddiqui, Z., Khan, M.Y., Rehman, S., Shahab, U., Godovikova, T., Silnikov, V., Moinuddin, 2017. AGEs, RAGEs and s-RAGE; friend or foe for cancer. *Seminars in cancer biology*.
- Akhabue, E., Montag, S., Reis, J.P., Pool, L.R., Mehta, R., Yancy, C.W., Zhao, L., Wolf, M., Gutierrez, O.M., Carnethon, M.R., Isakova, T., 2018. FGF23 (Fibroblast Growth Factor-23) and Incident Hypertension in Young and Middle-Aged Adults: The CARDIA Study. *Hypertension* 72, 70-76.
- Akhter, T., Nakagawa, T., Kobayashi, A., Yamaguchi, M., 2007. Suppression of regucalcin mRNA expression in the hearts of rats administered with free radical compound: the administration-induced death is accelerated in regucalcin transgenic rats. *International journal of molecular medicine* 19, 653-658.
- Akhter, T., Sawada, N., Yamaguchi, M., 2006. Regucalcin increases Ca²⁺-ATPase activity in the heart mitochondria of normal and regucalcin transgenic rats. *International journal of molecular medicine* 18, 171-176.
- Al Hannan, F., Culligan, K.G., 2015. Human resistin and the RELM of Inflammation in diabetes. *Diabetology & metabolic syndrome* 7, 54.
- Alegre, E., Zubiri, L., Perez-Gracia, J.L., Gonzalez-Cao, M., Soria, L., Martin-Algarra, S., Gonzalez, A., 2016. Circulating melanoma exosomes as diagnostic and prognosis biomarkers. *Clinica chimica acta; international journal of clinical chemistry* 454, 28-32.
- Allison, S.J., Knight, J.R., Granchi, C., Rani, R., Minutolo, F., Milner, J., Phillips, R.M., 2014. Identification of LDH-A as a therapeutic target for cancer cell killing via (i) p53/NAD(H)-dependent and (ii) p53-independent pathways. *Oncogenesis* 3, e102.
- Alquezar, C., Esteras, N., de la Encarnacion, A., Moreno, F., Lopez de Munain, A., Martin-Quero, A., 2015. Increasing progranulin levels and blockade of the ERK1/2 pathway: upstream and downstream strategies for the treatment of progranulin deficient frontotemporal dementia. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology* 25, 386-403.
- Alvarez-Sanchez, N., Alvarez-Rios, A.I., Guerrero, J.M., Garcia-Garcia, F.J., Rodriguez-Manas, L., Cruz-Chamorro, I., Lardone, P.J., Carrillo-Vico, A., 2018. Homocysteine levels are

- associated with bone resorption in pre-frail and frail Spanish women: The Toledo Study for Healthy Aging. *Experimental gerontology* 108, 201-208.
- Alvarez, X.A., Alvarez, I., Iglesias, O., Crespo, I., Figueroa, J., Aleixandre, M., Linares, C., Granizo, E., Garcia-Fantini, M., Marey, J., Masliah, E., Winter, S., Muresanu, D., Moessler, H., 2016. Synergistic Increase of Serum BDNF in Alzheimer Patients Treated with Cerebrolysin and Donepezil: Association with Cognitive Improvement in ApoE4 Cases. *The international journal of neuropsychopharmacology*.
- Amberg, D., Leadsham, J.E., Kotiadis, V., Gourlay, C.W., 2012. Cellular ageing and the actin cytoskeleton. *Sub-cellular biochemistry* 57, 331-352.
- Ambroziak, M., Kolanowska, M., Bartoszewicz, Z., Budaj, A., 2018. Adiponectin gene variants and decreased adiponectin plasma levels are associated with the risk of myocardial infarction in young age. *Gene* 642, 498-504.
- Anastasilakis, A.D., Polyzos, S.A., Makras, P., Gkiomisi, A., Bisbinas, I., Katsarou, A., Filippaios, A., Mantzoros, C.S., 2014. Circulating irisin is associated with osteoporotic fractures in postmenopausal women with low bone mass but is not affected by either teriparatide or denosumab treatment for 3 months. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA* 25, 1633-1642.
- Andersson, C., Enserro, D., Sullivan, L., Wang, T.J., Januzzi, J.L., Jr., Benjamin, E.J., Vita, J.A., Hamburg, N.M., Larson, M.G., Mitchell, G.F., Vasan, R.S., 2016. Relations of circulating GDF-15, soluble ST2, and troponin-I concentrations with vascular function in the community: The Framingham Heart Study. *Atherosclerosis* 248, 245-251.
- Andersson, C., Preis, S.R., Beiser, A., DeCarli, C., Wollert, K.C., Wang, T.J., Januzzi, J.L., Jr., Vasan, R.S., Seshadri, S., 2015. Associations of Circulating Growth Differentiation Factor-15 and ST2 Concentrations With Subclinical Vascular Brain Injury and Incident Stroke. *Stroke* 46, 2568-2575.
- Andre, F., Cabioglu, N., Assi, H., Sabourin, J.C., Delaloge, S., Sahin, A., Broglio, K., Spano, J.P., Combadiere, C., Bucana, C., Soria, J.C., Cristofanilli, M., 2006. Expression of chemokine receptors predicts the site of metastatic relapse in patients with axillary node positive primary breast cancer. *Annals of oncology : official journal of the European Society for Medical Oncology* 17, 945-951.
- Angelopoulou, E., Piperi, C., Adamopoulos, C., Papavassiliou, A.G., 2016. Pivotal role of high-mobility group box 1 (HMGB1) signaling pathways in glioma development and progression. *Journal of molecular medicine* 94, 867-874.
- Antonelli, A., Di Maggio, S., Rejman, J., Sanvito, F., Rossi, A., Catucci, A., Gorzanelli, A., Bragonzi, A., Bianchi, M.E., Raucci, A., 2017. The shedding-derived soluble receptor for advanced glycation endproducts sustains inflammation during acute *Pseudomonas aeruginosa* lung infection. *Biochimica et biophysica acta* 1861, 354-364.
- Antonelli, A., Rotondi, M., Fallahi, P., Ferrari, S.M., Paolicchi, A., Romagnani, P., Serio, M., Ferrannini, E., 2006. Increase of CXC chemokine CXCL10 and CC chemokine CCL2 serum levels in normal ageing. *Cytokine* 34, 32-38.
- Anuurad, E., Enkhmaa, B., Gungor, Z., Zhang, W., Tracy, R.P., Pearson, T.A., Kim, K., Berglund, L., 2011. Age as a modulator of inflammatory cardiovascular risk factors. *Arteriosclerosis, thrombosis, and vascular biology* 31, 2151-2156.
- Anuwatmatee, S., Allison, M.A., Shlipak, M.G., McClelland, R.L., Kramer, H., Tang, S., Hou, L., Rye, K.A., Ong, K.L., 2018. Relationship of fibroblast growth factor 21 with kidney function and albuminuria: multi-ethnic study of atherosclerosis. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*.
- Anuwatmatee, S., Tang, S., Wu, B.J., Rye, K.A., Ong, K.L., 2017. Fibroblast growth factor 21 in chronic kidney disease. *Clinica chimica acta; international journal of clinical chemistry*.

- Apostolakis, S., Spandidos, D., 2013. Chemokines and atherosclerosis: focus on the CX3CL1/CX3CR1 pathway. *Acta pharmacologica Sinica* 34, 1251-1256.
- Arampatzis, S., Chalikias, G., Devetzis, V., Konstantinides, S., Huynh-Do, U., Tziakas, D., 2017. C-terminal fragment of agrin (CAF) levels predict acute kidney injury after acute myocardial infarction. *BMC nephrology* 18, 202.
- Arellanes-Licea Edel, C., Baez-Ruiz, A., Carranza, M.E., Aramburo, C., Luna, M., Diaz-Munoz, M., 2014. Daily patterns and adaptation of the ghrelin, growth hormone and insulin-like growth factor-1 system under daytime food synchronisation in rats. *Journal of neuroendocrinology* 26, 282-295.
- Arnoldussen, I.A., Kiliaan, A.J., Gustafson, D.R., 2014. Obesity and dementia: adipokines interact with the brain. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology* 24, 1982-1999.
- Aronica, E., Boer, K., van Vliet, E.A., Redeker, S., Baayen, J.C., Spliet, W.G., van Rijen, P.C., Troost, D., da Silva, F.H., Wadman, W.J., Gorter, J.A., 2007. Complement activation in experimental and human temporal lobe epilepsy. *Neurobiology of disease* 26, 497-511.
- Arroba, A.I., Valverde, A.M., 2015. Inhibition of Protein Tyrosine Phosphatase 1B Improves IGF-I Receptor Signaling and Protects Against Inflammation-Induced Gliosis in the Retina. *Investigative ophthalmology & visual science* 56, 8031-8044.
- Arseneault, R., Chien, A., Newington, J.T., Rappon, T., Harris, R., Cumming, R.C., 2013. Attenuation of LDHA expression in cancer cells leads to redox-dependent alterations in cytoskeletal structure and cell migration. *Cancer letters* 338, 255-266.
- Assyov, Y., Gateva, A., Tsakova, A., Kamenov, Z., 2016. Irisin in the Glucose Continuum. *Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association* 124, 22-27.
- Asterholm, I.W., Rutkowski, J.M., Fujikawa, T., Cho, Y.R., Fukuda, M., Tao, C., Wang, Z.V., Gupta, R.K., Elmquist, J.K., Scherer, P.E., 2014. Elevated resistin levels induce central leptin resistance and increased atherosclerotic progression in mice. *Diabetologia* 57, 1209-1218.
- Athilingam, P., Moynihan, J., Chen, L., D'Aoust, R., Groer, M., Kip, K., 2013. Elevated levels of interleukin 6 and C-reactive protein associated with cognitive impairment in heart failure. *Congestive heart failure* 19, 92-98.
- Atta, M.G., Estrella, M.M., Fine, D.M., Zook, K., Monroy Trujillo, J.M., Stein, J.H., Lucas, G.M., 2016. Correlates and Longitudinal Renal and Cardiovascular Implications of FGF23 Levels in HIV-Positive Individuals. *PloS one* 11, e0155312.
- Aubert, C.E., Michel, P.L., Gillery, P., Jaisson, S., Fonfrede, M., Morel, F., Hartemann, A., Bourron, O., 2014. Association of peripheral neuropathy with circulating advanced glycation end products, soluble receptor for advanced glycation end products and other risk factors in patients with type 2 diabetes. *Diabetes/metabolism research and reviews* 30, 679-685.
- Avila-Funes, J.A., Carcaillon, L., Helmer, C., Carriere, I., Ritchie, K., Rouaud, O., Tzourio, C., Dartigues, J.F., Amieva, H., 2012. Is frailty a prodromal stage of vascular dementia? Results from the Three-City Study. *Journal of the American Geriatrics Society* 60, 1708-1712.
- Avtanski, D., Hirth, Y., Babushkin, N., Sy, V., Sharma, D., Poretsky, L., Seto-Young, D., 2016. In Vitro Effects of Pioglitazone on the Expression of Components of Wnt Signaling Pathway and Markers of Bone Mineralization. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme* 48, 468-475.
- Awazawa, M., Ueki, K., Inabe, K., Yamauchi, T., Kubota, N., Kaneko, K., Kobayashi, M., Iwane, A., Sasako, T., Okazaki, Y., Ohsugi, M., Takamoto, I., Yamashita, S., Asahara, H., Akira, S., Kasuga, M., Kadowaki, T., 2011. Adiponectin enhances insulin sensitivity by

- increasing hepatic IRS-2 expression via a macrophage-derived IL-6-dependent pathway. *Cell metabolism* 13, 401-412.
- Aydin, S., Aydin, S., Kobat, M.A., Kalayci, M., Eren, M.N., Yilmaz, M., Kuloglu, T., Gul, E., Secen, O., Alatas, O.D., Baydas, A., 2014. Decreased saliva/serum irisin concentrations in the acute myocardial infarction promising for being a new candidate biomarker for diagnosis of this pathology. *Peptides* 56, 141-145.
- Aydin, S., Kuloglu, T., Aydin, S., Yardim, M., Azboy, D., Temizturk, Z., Kalkan, A.K., Eren, M.N., 2017. The effect of iloprost and sildenafil, alone and in combination, on myocardial ischaemia and nitric oxide and irisin levels. *Cardiovascular journal of Africa* 28, 389-396.
- Aygun, A., Katipoglu, B., Imamoglu, M., Demir, S., Yadigaroglu, M., Tatli, O., Yurtsever, S., Usta, A., Mentese, A., Turkmen, S., 2017. Diagnostic Value of Plasma Pentraxin-3 in Acute Appendicitis. *Journal of investigative surgery : the official journal of the Academy of Surgical Research*, 1-6.
- Aygun, C., Senturk, O., Hulagu, S., Uraz, S., Celebi, A., Konduk, T., Mutlu, B., Canturk, Z., 2006. Serum levels of hepatoprotective peptide adiponectin in non-alcoholic fatty liver disease. *European journal of gastroenterology & hepatology* 18, 175-180.
- Bacha, N.C., Blandinieres, A., Rossi, E., Gendron, N., Nevo, N., Lecourt, S., Guerin, C.L., Renard, J.M., Gaussem, P., Angles-Cano, E., Boulanger, C.M., Israel-Biet, D., Smadja, D.M., 2017. Endothelial Microparticles are Associated to Pathogenesis of Idiopathic Pulmonary Fibrosis. *Stem cell reviews*.
- Badman, M.K., Koester, A., Flier, J.S., Kharitonov, A., Maratos-Flier, E., 2009. Fibroblast growth factor 21-deficient mice demonstrate impaired adaptation to ketosis. *Endocrinology* 150, 4931-4940.
- Bahrini, I., Song, J.H., Diez, D., Hanayama, R., 2015. Neuronal exosomes facilitate synaptic pruning by up-regulating complement factors in microglia. *Scientific reports* 5, 7989.
- Baines, K.J., Wright, T.K., Simpson, J.L., McDonald, V.M., Wood, L.G., Parsons, K.S., Wark, P.A., Gibson, P.G., 2015. Airway beta-Defensin-1 Protein Is Elevated in COPD and Severe Asthma. *Mediators of inflammation* 2015, 407271.
- Bains, W., 2013. Transglutaminase 2 and EGGL, the protein cross-link formed by transglutaminase 2, as therapeutic targets for disabilities of old age. *Rejuvenation research* 16, 495-517.
- Baker, D.J., Wijshake, T., Tchkonja, T., LeBrasseur, N.K., Childs, B.G., van de Sluis, B., Kirkland, J.L., van Deursen, J.M., 2011. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. *Nature* 479, 232-236.
- Baker, M.A., Davis, S.J., Liu, P., Pan, X., Williams, A.M., Iczkowski, K.A., Gallagher, S.T., Bishop, K., Regner, K.R., Liu, Y., Liang, M., 2017. Tissue-Specific MicroRNA Expression Patterns in Four Types of Kidney Disease. *Journal of the American Society of Nephrology : JASN* 28, 2985-2992.
- Bakhashab, S., Ahmed, F.W., Schulten, H.J., Bashir, A., Karim, S., Al-Malki, A.L., Gari, M.A., Abuzenadah, A.M., Chaudhary, A.G., Alqahtani, M.H., Lary, S., Ahmed, F., Weaver, J.U., 2016. Metformin improves the angiogenic potential of human CD34(+) cells coincident with downregulating CXCL10 and TIMP1 gene expression and increasing VEGFA under hyperglycemia and hypoxia within a therapeutic window for myocardial infarction. *Cardiovascular diabetology* 15, 27.
- Bakker, S.F., Tushuizen, M.E., Gozutok, E., Ciftci, A., Gelderman, K.A., Mulder, C.J., Simsek, S., 2015. Advanced glycation end products (AGEs) and the soluble receptor for AGE (sRAGE) in patients with type 1 diabetes and coeliac disease. *Nutrition, metabolism, and cardiovascular diseases : NMCD* 25, 230-235.
- Baldan, A., Giusti, A., Bosi, C., Malaventura, C., Musso, M., Forni, G.L., Volpato, S., Zuliani, G., Borgna-Pignatti, C., 2015. Klotho, a new marker for osteoporosis and muscle strength in beta-thalassemia major. *Blood cells, molecules & diseases* 55, 396-401.

- Banyai, L., Sonderegger, P., Patthy, L., 2010. Agrin binds BMP2, BMP4 and TGFbeta1. *PLoS one* 5, e10758.
- Banz, Y., Item, G.M., Vogt, A., Rieben, R., Candinas, D., Beldi, G., 2016. Endothelial- and Platelet-Derived Microparticles Are Generated During Liver Resection in Humans. *Journal of investigative surgery : the official journal of the Academy of Surgical Research* 29, 20-31.
- Bar, L., Feger, M., Fajol, A., Klotz, L.O., Zeng, S., Lang, F., Hocher, B., Foller, M., 2018. Insulin suppresses the production of fibroblast growth factor 23 (FGF23). *Proceedings of the National Academy of Sciences of the United States of America* 115, 5804-5809.
- Bar, L., Grossmann, C., Gekle, M., Foller, M., 2017. Calcineurin inhibitors regulate fibroblast growth factor 23 (FGF23) synthesis. *Naunyn-Schmiedeberg's archives of pharmacology* 390, 1117-1123.
- Baran, A., Mysliwiec, H., Kiluk, P., Swiderska, M., Flisiak, I., 2017. Serum irisin levels in patients with psoriasis. *The Journal of dermatological treatment* 28, 304-308.
- Barazzoni, R., Gortan Cappellari, G., Palus, S., Vinci, P., Ruozi, G., Zanetti, M., Semolic, A., Ebner, N., von Haehling, S., Sinagra, G., Giacca, M., Springer, J., 2017. Acylated ghrelin treatment normalizes skeletal muscle mitochondrial oxidative capacity and AKT phosphorylation in rat chronic heart failure. *Journal of cachexia, sarcopenia and muscle* 8, 991-998.
- Barber, A.J., Lieth, E., 1997. Agrin accumulates in the brain microvascular basal lamina during development of the blood-brain barrier. *Developmental dynamics : an official publication of the American Association of Anatomists* 208, 62-74.
- Baric, I., Cuk, M., Fumic, K., Vugrek, O., Allen, R.H., Glenn, B., Maradin, M., Pazanin, L., Pogribny, I., Rados, M., Sarnavka, V., Schulze, A., Stabler, S., Wagner, C., Zeisel, S.H., Mudd, S.H., 2005. S-Adenosylhomocysteine hydrolase deficiency: a second patient, the younger brother of the index patient, and outcomes during therapy. *Journal of inherited metabolic disease* 28, 885-902.
- Barma, M., Khan, F., Price, R.J.G., Donnan, P.T., Messow, C.M., Ford, I., McConnachie, A., Struthers, A.D., McMurdo, M.E.T., Witham, M.D., 2017. Association between GDF-15 levels and changes in vascular and physical function in older patients with hypertension. *Aging clinical and experimental research* 29, 1055-1059.
- Bartali, B., Semba, R.D., Araujo, A.B., 2013. Klotho, FGF21 and FGF23: Novel Pathways to Musculoskeletal Health? *The Journal of frailty & aging* 2, 179-183.
- Bartke, A., 2016. Healthspan and longevity can be extended by suppression of growth hormone signaling. *Mammalian genome : official journal of the International Mammalian Genome Society* 27, 289-299.
- Bartke, A., Darcy, J., 2017. GH and ageing: Pitfalls and new insights. *Best practice & research. Clinical endocrinology & metabolism* 31, 113-125.
- Bartke, A., Westbrook, R., Sun, L., Ratajczak, M., 2013. Links between growth hormone and aging. *Endokrynologia Polska* 64, 46-52.
- Bartkowska, K., Paquin, A., Gauthier, A.S., Kaplan, D.R., Miller, F.D., 2007. Trk signaling regulates neural precursor cell proliferation and differentiation during cortical development. *Development* 134, 4369-4380.
- Barwari, T., Joshi, A., Mayr, M., 2016. MicroRNAs in Cardiovascular Disease. *Journal of the American College of Cardiology* 68, 2577-2584.
- Battaglia, R.A., Kabiraj, P., Willcockson, H.H., Lian, M., Snider, N.T., 2017. Isolation of Intermediate Filament Proteins from Multiple Mouse Tissues to Study Aging-associated Post-translational Modifications. *Journal of visualized experiments : JoVE*.
- Baudino, L., Sardini, A., Ruseva, M.M., Fossati-Jimack, L., Cook, H.T., Scott, D., Simpson, E., Botto, M., 2014. C3 opsonization regulates endocytic handling of apoptotic cells resulting

- in enhanced T-cell responses to cargo-derived antigens. *Proceedings of the National Academy of Sciences of the United States of America* 111, 1503-1508.
- Bauer, Y., White, E.S., de Bernard, S., Cornelisse, P., Leconte, I., Morganti, A., Roux, S., Nayler, O., 2017. MMP-7 is a predictive biomarker of disease progression in patients with idiopathic pulmonary fibrosis. *ERJ open research* 3.
- Bayes-Genis, A., Barallat, J., de Antonio, M., Domingo, M., Zamora, E., Vila, J., Subirana, I., Gastelurrutia, P., Pastor, M.C., Januzzi, J.L., Lupon, J., 2017. Bloodstream Amyloid-beta (1-40) Peptide, Cognition, and Outcomes in Heart Failure. *Revista espanola de cardiologia* 70, 924-932.
- Baylis, D., Bartlett, D.B., Syddall, H.E., Ntani, G., Gale, C.R., Cooper, C., Lord, J.M., Sayer, A.A., 2013. Immune-endocrine biomarkers as predictors of frailty and mortality: a 10-year longitudinal study in community-dwelling older people. *Age* 35, 963-971.
- Bayraktar, R., Van Roosbroeck, K., Calin, G.A., 2017. Cell-to-cell communication: microRNAs as hormones. *Molecular oncology* 11, 1673-1686.
- Bedreag, O.H., Papurica, M., Rogobete, A.F., Sandesc, D., Dumache, R., Cradigati, C.A., Sarandan, M., Bratu, L.M., Popovici, S.E., Sima, L.V., 2016. Using Circulating miRNAs as Biomarkers for the Evaluation and Monitoring of the Mitochondrial Damage in the Critically Ill Polytrauma Patients. *Clinical laboratory* 62, 1397-1403.
- Beer, C., Blacker, D., Bynevelt, M., Hankey, G.J., Puddey, I.B., 2010. Systemic markers of inflammation are independently associated with S100B concentration: results of an observational study in subjects with acute ischaemic stroke. *Journal of neuroinflammation* 7, 71.
- Bei, J.J., Liu, C., Peng, S., Liu, C.H., Zhao, W.B., Qu, X.L., Chen, Q., Zhou, Z., Yu, Z.P., Peter, K., Hu, H.Y., 2016. Staphylococcal SSL5-induced platelet microparticles provoke proinflammatory responses via the CD40/TRAF6/NFkappaB signalling pathway in monocytes. *Thrombosis and haemostasis* 115, 632-645.
- Belviranli, M., Okudan, N., Celik, F., 2016. Association of Circulating Irisin with Insulin Resistance and Oxidative Stress in Obese Women. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme* 48, 653-657.
- Benham, H., Nel, H.J., Law, S.C., Mehdi, A.M., Street, S., Ramnoruth, N., Pahau, H., Lee, B.T., Ng, J., Brunck, M.E., Hyde, C., Trouw, L.A., Dudek, N.L., Purcell, A.W., O'Sullivan, B.J., Connolly, J.E., Paul, S.K., Le Cao, K.A., Thomas, R., 2015. Citrullinated peptide dendritic cell immunotherapy in HLA risk genotype-positive rheumatoid arthritis patients. *Science translational medicine* 7, 290ra287.
- Benigni, A., Cassis, P., Remuzzi, G., 2010. Angiotensin II revisited: new roles in inflammation, immunology and aging. *EMBO molecular medicine* 2, 247-257.
- Bentzinger, C.F., Barzaghi, P., Lin, S., Ruegg, M.A., 2005. Overexpression of mini-agrin in skeletal muscle increases muscle integrity and regenerative capacity in laminin-alpha2-deficient mice. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 19, 934-942.
- Benussi, L., Ciani, M., Tonoli, E., Morbin, M., Palamara, L., Albani, D., Fusco, F., Forloni, G., Glionna, M., Baco, M., Paterlini, A., Fostinelli, S., Santini, B., Galbiati, E., Gagni, P., Cretich, M., Binetti, G., Tagliavini, F., Prosperi, D., Chiari, M., Ghidoni, R., 2016. Loss of exosomes in progranulin-associated frontotemporal dementia. *Neurobiology of aging* 40, 41-49.
- Bergmann, K., Sypniewska, G., 2013. Diabetes as a complication of adipose tissue dysfunction. Is there a role for potential new biomarkers? *Clinical chemistry and laboratory medicine* 51, 177-185.
- Bergmann, K., Sypniewska, G., 2014. Secreted frizzled-related protein 4 (SFRP4) and fractalkine (CX3CL1) - Potential new biomarkers for beta-cell dysfunction and diabetes. *Clinical biochemistry* 47, 529-532.

- Bernard-Marissal, N., Sunyach, C., Marissal, T., Raoul, C., Pettmann, B., 2015. Calreticulin levels determine onset of early muscle denervation by fast motoneurons of ALS model mice. *Neurobiology of disease* 73, 130-136.
- Berryman, D.E., List, E.O., Coschigano, K.T., Behar, K., Kim, J.K., Kopchick, J.J., 2004. Comparing adiposity profiles in three mouse models with altered GH signaling. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society* 14, 309-318.
- Berzin, T.M., Zipser, B.D., Rafii, M.S., Kuo-Leblanc, V., Yancopoulos, G.D., Glass, D.J., Fallon, J.R., Stopa, E.G., 2000. Agrin and microvascular damage in Alzheimer's disease. *Neurobiology of aging* 21, 349-355.
- Beyer, C., Zampetaki, A., Lin, N.Y., Kleyer, A., Perricone, C., Iagnocco, A., Distler, A., Langley, S.R., Gelse, K., Sesselmann, S., Lorenzini, R., Niemeier, A., Swoboda, B., Distler, J.H., Santer, P., Egger, G., Willeit, J., Mayr, M., Schett, G., Kiechl, S., 2015. Signature of circulating microRNAs in osteoarthritis. *Annals of the rheumatic diseases* 74, e18.
- Bezakova, G., Helm, J.P., Francolini, M., Lomo, T., 2001. Effects of purified recombinant neural and muscle agrin on skeletal muscle fibers in vivo. *J Cell Biol* 153, 1441-1452.
- Bezakova, G., Ruegg, M.A., 2003. New insights into the roles of agrin. *Nature reviews. Molecular cell biology* 4, 295-308.
- Bhattacharya, R., Townley, R.A., Berry, K.L., Bulow, H.E., 2009. The PAPS transporter PST-1 is required for heparan sulfation and is essential for viability and neural development in *C. elegans*. *Journal of cell science* 122, 4492-4504.
- Bian, A., Neyra, J.A., Zhan, M., Hu, M.C., 2015. Klotho, stem cells, and aging. *Clinical interventions in aging* 10, 1233-1243.
- Bianchi, M.E., Crippa, M.P., Manfredi, A.A., Mezzapelle, R., Rovere Querini, P., Venereau, E., 2017. High-mobility group box 1 protein orchestrates responses to tissue damage via inflammation, innate and adaptive immunity, and tissue repair. *Immunological reviews* 280, 74-82.
- Bianchi, R., Kastrisianaki, E., Giambanco, I., Donato, R., 2011. S100B protein stimulates microglia migration via RAGE-dependent up-regulation of chemokine expression and release. *The Journal of biological chemistry* 286, 7214-7226.
- Bibi, A., Agarwal, N.K., Dihazi, G.H., Eltoweissy, M., Van Nguyen, P., Mueller, G.A., Dihazi, H., 2011. Calreticulin is crucial for calcium homeostasis mediated adaptation and survival of thick ascending limb of Henle's loop cells under osmotic stress. *The international journal of biochemistry & cell biology* 43, 1187-1197.
- Bidadkosh, A., Lambooy, S.P.H., Heerspink, H.J., Pena, M.J., Henning, R.H., Buikema, H., Deelman, L.E., 2017. Predictive Properties of Biomarkers GDF-15, NTproBNP, and hs-TnT for Morbidity and Mortality in Patients With Type 2 Diabetes With Nephropathy. *Diabetes care* 40, 784-792.
- Bixby, J.L., Baerwald-De la Torre, K., Wang, C., Rathjen, F.G., Ruegg, M.A., 2002. A neuronal inhibitory domain in the N-terminal half of agrin. *Journal of neurobiology* 50, 164-179.
- Blaber, E.A., Dvorochkin, N., Torres, M.L., Yousuf, R., Burns, B.P., Globus, R.K., Almeida, E.A., 2014. Mechanical unloading of bone in microgravity reduces mesenchymal and hematopoietic stem cell-mediated tissue regeneration. *Stem cell research* 13, 181-201.
- Blair, L.A., Haven, A.K., Bauer, N.N., 2016. Circulating microparticles in severe pulmonary arterial hypertension increase intercellular adhesion molecule-1 expression selectively in pulmonary artery endothelium. *Respiratory research* 17, 133.
- Blankenberg, S., Barboux, S., Tiret, L., 2003. Adhesion molecules and atherosclerosis. *Atherosclerosis* 170, 191-203.
- Bluhm, B., Laffer, B., Hirnet, D., Rothermundt, M., Ambree, O., Lohr, C., 2015. Normal cerebellar development in S100B-deficient mice. *Cerebellum* 14, 119-127.

- Bobbert, T., Schwarz, F., Fischer-Rosinsky, A., Pfeiffer, A.F., Mohlig, M., Mai, K., Spranger, J., 2013. Fibroblast growth factor 21 predicts the metabolic syndrome and type 2 diabetes in Caucasians. *Diabetes care* 36, 145-149.
- Bolliger, M.F., Zurlinden, A., Luscher, D., Butikofer, L., Shakhova, O., Francolini, M., Kozlov, S.V., Cinelli, P., Stephan, A., Kistler, A.D., Rulicke, T., Pelczar, P., Ledermann, B., Fumagalli, G., Gloor, S.M., Kunz, B., Sonderegger, P., 2010. Specific proteolytic cleavage of agrin regulates maturation of the neuromuscular junction. *Journal of cell science* 123, 3944-3955.
- Bollwein, J., Diekmann, R., Kaiser, M.J., Bauer, J.M., Uter, W., Sieber, C.C., Volkert, D., 2013. Dietary quality is related to frailty in community-dwelling older adults. *The journals of gerontology. Series A, Biological sciences and medical sciences* 68, 483-489.
- Bonfante, H.L., Almeida, C.S., Abramo, C., Grunewald, S.T.F., Levy, R.A., Teixeira, H.C., 2017. CCL2, CXCL8, CXCL9 and CXCL10 serum levels increase with age but are not altered by treatment with hydroxychloroquine in patients with osteoarthritis of the knees. *International journal of rheumatic diseases* 20, 1958-1964.
- Bonotti, A., Simonini, S., Pantani, E., Giusti, L., Donadio, E., Mazzoni, M.R., Chella, A., Marconi, L., Ambrosino, N., Lucchi, M., Mussi, A., Cristaudo, A., Foddìs, R., 2017. Serum mesothelin, osteopontin and vimentin: useful markers for clinical monitoring of malignant pleural mesothelioma. *The International journal of biological markers* 32, e126-e131.
- Bornheim, R., Muller, M., Reuter, U., Herrmann, H., Bussow, H., Magin, T.M., 2008. A dominant vimentin mutant upregulates Hsp70 and the activity of the ubiquitin-proteasome system, and causes posterior cataracts in transgenic mice. *Journal of cell science* 121, 3737-3746.
- Bose, C.M., Qiu, D., Bergamaschi, A., Gravante, B., Bossi, M., Villa, A., Rupp, F., Malgaroli, A., 2000. Agrin controls synaptic differentiation in hippocampal neurons. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 20, 9086-9095.
- Bosotti, R., Carpinelli, P., Healy, S., Locatelli, G., Cappella, P., Lanfrancone, L., Calogero, R., Moll, J., Isacchi, A., 2012. Transcriptional analysis of the Aurora inhibitor Danusertib leading to biomarker identification in TP53 wild type cells. *Gene* 494, 202-208.
- Bostrom, P., Wu, J., Jedrychowski, M.P., Korde, A., Ye, L., Lo, J.C., Rasbach, K.A., Bostrom, E.A., Choi, J.H., Long, J.Z., Kajimura, S., Zingaretti, M.C., Vind, B.F., Tu, H., Cinti, S., Hojlund, K., Gygi, S.P., Spiegelman, B.M., 2012. A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature* 481, 463-468.
- Boyuk, B., Degirmencioglu, S., Atalay, H., Guzel, S., Acar, A., Celebi, A., Ekizoglu, I., Simsek, C., 2014. Relationship between levels of brain-derived neurotrophic factor and metabolic parameters in patients with type 2 diabetes mellitus. *Journal of diabetes research* 2014, 978143.
- Brahma, M.K., Adam, R.C., Pollak, N.M., Jaeger, D., Zierler, K.A., Pocher, N., Schreiber, R., Romauch, M., Moustafa, T., Eder, S., Ruelicke, T., Preiss-Landl, K., Lass, A., Zechner, R., Haemmerle, G., 2014. Fibroblast growth factor 21 is induced upon cardiac stress and alters cardiac lipid homeostasis. *Journal of lipid research* 55, 2229-2241.
- Brandl, N., Zemmann, A., Kaupe, I., Marlovits, S., Huettinger, P., Goldenberg, H., Huettinger, M., 2010. Signal transduction and metabolism in chondrocytes is modulated by lactoferrin. *Osteoarthritis and cartilage* 18, 117-125.
- Breit, S.N., Johnen, H., Cook, A.D., Tsai, V.W., Mohammad, M.G., Kuffner, T., Zhang, H.P., Marquis, C.P., Jiang, L., Lockwood, G., Lee-Ng, M., Husaini, Y., Wu, L., Hamilton, J.A., Brown, D.A., 2011. The TGF-beta superfamily cytokine, MIC-1/GDF15: a pleiotropic cytokine with roles in inflammation, cancer and metabolism. *Growth factors* 29, 187-195.
- Briochè, T., Kireev, R.A., Cuesta, S., Gratas-Delamarche, A., Tresguerres, J.A., Gomez-Cabrera, M.C., Vina, J., 2014. Growth hormone replacement therapy prevents sarcopenia by a dual mechanism: improvement of protein balance and of antioxidant

- defenses. *The journals of gerontology. Series A, Biological sciences and medical sciences* 69, 1186-1198.
- Broch, K., Leren, I.S., Saberniak, J., Ueland, T., Edvardsen, T., Gullestad, L., Haugaa, K.H., 2017. Soluble ST2 is associated with disease severity in arrhythmogenic right ventricular cardiomyopathy. *Biomarkers : biochemical indicators of exposure, response, and susceptibility to chemicals* 22, 367-371.
- Brodská, H., Malicková, K., Valenta, J., Fabio, A., Drabek, T., 2013. Soluble receptor for advanced glycation end products predicts 28-day mortality in critically ill patients with sepsis. *Scandinavian journal of clinical and laboratory investigation* 73, 650-660.
- Brown, D.A., Moore, J., Johnen, H., Smeets, T.J., Bauskin, A.R., Kuffner, T., Weedon, H., Milliken, S.T., Tak, P.P., Smith, M.D., Breit, S.N., 2007. Serum macrophage inhibitory cytokine 1 in rheumatoid arthritis: a potential marker of erosive joint destruction. *Arthritis and rheumatism* 56, 753-764.
- Brownlee, M., 1995. Advanced protein glycosylation in diabetes and aging. *Annual review of medicine* 46, 223-234.
- Buchman, A.S., Yu, L., Wilson, R.S., Schneider, J.A., Bennett, D.A., 2013. Association of brain pathology with the progression of frailty in older adults. *Neurology* 80, 2055-2061.
- Buckman, L.B., Anderson-Baucum, E.K., Hasty, A.H., Ellacott, K., 2014. Regulation of S100B in white adipose tissue by obesity in mice. *Adipocyte* 3, 215-220.
- Budge, K.M., Neal, M.L., Richardson, J.R., Safadi, F.F., 2017. Glycoprotein NMB: an Emerging Role in Neurodegenerative Disease. *Molecular neurobiology*.
- Buendia, P., Carracedo, J., Soriano, S., Madueno, J.A., Ortiz, A., Martin-Malo, A., Aljama, P., Ramirez, R., 2015. Klotho Prevents NFkappaB Translocation and Protects Endothelial Cell From Senescence Induced by Uremia. *The journals of gerontology. Series A, Biological sciences and medical sciences* 70, 1198-1209.
- Burden, S.J., 1998. The formation of neuromuscular synapses. *Genes & development* 12, 133-148.
- Burger, D., Kwart, D.G., Montezano, A.C., Read, N.C., Kennedy, C.R., Thompson, C.S., Touyz, R.M., 2012. Microparticles induce cell cycle arrest through redox-sensitive processes in endothelial cells: implications in vascular senescence. *Journal of the American Heart Association* 1, e001842.
- Burgess, R.W., Nguyen, Q.T., Son, Y.J., Lichtman, J.W., Sanes, J.R., 1999. Alternatively spliced isoforms of nerve- and muscle-derived agrin: their roles at the neuromuscular junction. *Neuron* 23, 33-44.
- Burgess, R.W., Skarnes, W.C., Sanes, J.R., 2000. Agrin isoforms with distinct amino termini: differential expression, localization, and function. *J Cell Biol* 151, 41-52.
- Butler, J., Kalogeropoulos, A., Georgiopoulou, V., de Rekeneire, N., Rodondi, N., Smith, A.L., Hoffmann, U., Kanaya, A., Newman, A.B., Kritchevsky, S.B., Vasan, R.S., Wilson, P.W., Harris, T.B., Health, A.B.C.S., 2009. Serum resistin concentrations and risk of new onset heart failure in older persons: the health, aging, and body composition (Health ABC) study. *Arteriosclerosis, thrombosis, and vascular biology* 29, 1144-1149.
- Bystrom, S., Fredolini, C., Edqvist, P.H., Nyaiesh, E.N., Drobin, K., Uhlen, M., Bergqvist, M., Ponten, F., Schwenk, J.M., 2017. Affinity Proteomics Exploration of Melanoma Identifies Proteins in Serum with Associations to T-Stage and Recurrence. *Translational oncology* 10, 385-395.
- Byun, K., Bayarsaikhan, E., Kim, D., Kim, C.Y., Mook-Jung, I., Paek, S.H., Kim, S.U., Yamamoto, T., Won, M.H., Song, B.J., Park, Y.M., Lee, B., 2012. Induction of neuronal death by microglial AGE-albumin: implications for Alzheimer's disease. *PloS one* 7, e37917.

- Byun, Y., Chen, F., Chang, R., Trivedi, M., Green, K.J., Cryns, V.L., 2001. Caspase cleavage of vimentin disrupts intermediate filaments and promotes apoptosis. *Cell death and differentiation* 8, 443-450.
- Cai, Z., Zhou, Y., Liu, Z., Ke, Z., Zhao, B., 2015. Autophagy dysfunction upregulates beta-amyloid peptides via enhancing the activity of gamma-secretase complex. *Neuropsychiatric disease and treatment* 11, 2091-2099.
- Caira, S., Iannelli, A., Sciarrillo, R., Picariello, G., Renzone, G., Scaloni, A., Addeo, P., 2017. Differential representation of liver proteins in obese human subjects suggests novel biomarkers and promising targets for drug development in obesity. *Journal of enzyme inhibition and medicinal chemistry* 32, 672-682.
- Cambados, N., Walther, T., Nahmod, K., Tocci, J.M., Rubinstein, N., Bohme, I., Simian, M., Sampayo, R., Del Valle Suberbordes, M., Kordon, E.C., Schere-Levy, C., 2017. Angiotensin-(1-7) counteracts the transforming effects triggered by angiotensin II in breast cancer cells. *Oncotarget* 8, 88475-88487.
- Campagna, J.A., Ruegg, M.A., Bixby, J.L., 1997. Evidence that agrin directly influences presynaptic differentiation at neuromuscular junctions in vitro. *The European journal of neuroscience* 9, 2269-2283.
- Campagnolo, P., Hong, X., di Bernardini, E., Smyrniak, I., Hu, Y., Xu, Q., 2015. Resveratrol-Induced Vascular Progenitor Differentiation towards Endothelial Lineage via MiR-21/Akt/beta-Catenin Is Protective in Vessel Graft Models. *PLoS one* 10, e0125122.
- Canobbio, I., Visconte, C., Momi, S., Guidetti, G.F., Zara, M., Canino, J., Falcinelli, E., Gresele, P., Torti, M., 2017. Platelet amyloid precursor protein is a modulator of venous thromboembolism in mice. *Blood* 130, 527-536.
- Cao, T., Zhang, L., Yao, L.L., Zheng, F., Wang, L., Yang, J.Y., Guo, L.Y., Li, X.Y., Yan, Y.W., Pan, Y.M., Jiang, M., Chen, L., Tang, J.M., Chen, S.Y., Wang, J.N., 2017. S100B promotes injury-induced vascular remodeling through modulating smooth muscle phenotype. *Biochimica et biophysica acta* 1863, 2772-2782.
- Cao, W., Zhao, C., Shen, C., Wang, Y., 2013. Cytokeratin 18, alanine aminotransferase, platelets and triglycerides predict the presence of nonalcoholic steatohepatitis. *PLoS one* 8, e82092.
- Cao, X., Zhu, M., He, Y., Chu, W., Du, Y., Du, H., 2018. Increased Serum Acylated Ghrelin Levels in Patients with Mild Cognitive Impairment. *Journal of Alzheimer's disease : JAD* 61, 545-552.
- Cao, Y.H., Lv, L.L., Zhang, X., Hu, H., Ding, L.H., Yin, D., Zhang, Y.Z., Ni, H.F., Chen, P.S., Liu, B.C., 2015. Urinary vimentin mRNA as a potential novel biomarker of renal fibrosis. *American journal of physiology. Renal physiology* 309, F514-522.
- Capettini, L.S., Montecucco, F., Mach, F., Stergiopoulos, N., Santos, R.A., da Silva, R.F., 2012. Role of renin-angiotensin system in inflammation, immunity and aging. *Current pharmaceutical design* 18, 963-970.
- Cappellari, R., D'Anna, M., Bonora, B.M., Rigato, M., Cignarella, A., Avogaro, A., Fadini, G.P., 2017. Shift of monocyte subsets along their continuum predicts cardiovascular outcomes. *Atherosclerosis* 266, 95-102.
- Carino, A., De Rosa, S., Sorrentino, S., Polimeni, A., Sabatino, J., Caiazzo, G., Torella, D., Spaccarotella, C., Mongiardo, A., Strangio, A., Filippis, C., Indolfi, C., 2016. Modulation of Circulating MicroRNAs Levels during the Switch from Clopidogrel to Ticagrelor. *BioMed research international* 2016, 3968206.
- Carlomagno, N., Incollingo, P., Tammaro, V., Peluso, G., Rupealta, N., Chiacchio, G., Sandoval Sotelo, M.L., Minieri, G., Pisani, A., Riccio, E., Sabbatini, M., Bracale, U.M., Calogero, A., Dodaro, C.A., Santangelo, M., 2017. Diagnostic, Predictive, Prognostic, and Therapeutic Molecular Biomarkers in Third Millennium: A Breakthrough in Gastric Cancer. *BioMed research international* 2017, 7869802.

- Carmeli, E., Imam, B., Bachar, A., Merrick, J., 2012. Inflammation and oxidative stress as biomarkers of premature aging in persons with intellectual disability. *Research in developmental disabilities* 33, 369-375.
- Carmeliet, P., Kieckens, L., Schoonjans, L., Ream, B., van Nuffelen, A., Prendergast, G., Cole, M., Bronson, R., Collen, D., Mulligan, R.C., 1993. Plasminogen activator inhibitor-1 gene-deficient mice. I. Generation by homologous recombination and characterization. *The Journal of clinical investigation* 92, 2746-2755.
- Carro, E., Bartolome, F., Bermejo-Pareja, F., Villarejo-Galende, A., Molina, J.A., Ortiz, P., Calero, M., Rabano, A., Cantero, J.L., Orive, G., 2017. Early diagnosis of mild cognitive impairment and Alzheimer's disease based on salivary lactoferrin. *Alzheimer's & dementia* 8, 131-138.
- Carroll, R.G., Martin, S.J., 2013. Autophagy in multiple myeloma: what makes you stronger can also kill you. *Cancer cell* 23, 425-426.
- Casas, S., Perez, A.F., Mattiazzi, M., Lopez, J., Folgueira, A., Gargiulo-Monachelli, G.M., Gonzalez Deniselle, M.C., De Nicola, A.F., 2017. Potential Biomarkers with Plasma Cortisol, Brain-derived Neurotrophic Factor and Nitrites in Patients with Acute Ischemic Stroke. *Current neurovascular research* 14, 338-346.
- Cavalli, L., Mazzotta, C., Brandi, M.L., 2012. Phosphatonins: physiological role and pathological changes. *Clinical cases in mineral and bone metabolism : the official journal of the Italian Society of Osteoporosis, Mineral Metabolism, and Skeletal Diseases* 9, 9-12.
- Celik, H.T., Akkaya, N., Erdamar, H., Gok, S., Kazanci, F., Demircelik, B., Cakmak, M., Yigitoglu, R., 2015. The Effects of Valsartan and Amlodipine on the Levels of Irisin, Adropin, and Perilipin. *Clinical laboratory* 61, 1889-1895.
- Celikbilek, A., Akyol, L., Sabah, S., Tanik, N., Adam, M., Celikbilek, M., Korkmaz, M., Yilmaz, N., 2014. S100B as a glial cell marker in diabetic peripheral neuropathy. *Neuroscience letters* 558, 53-57.
- Chai, S., Wang, W., Liu, J., Guo, H., Zhang, Z., Wang, C., Wang, J., 2015. Leptin knockout attenuates hypoxia-induced pulmonary arterial hypertension by inhibiting proliferation of pulmonary arterial smooth muscle cells. *Translational research : the journal of laboratory and clinical medicine* 166, 772-782.
- Chaker, Z., Aid, S., Berry, H., Holzenberger, M., 2015. Suppression of IGF-I signals in neural stem cells enhances neurogenesis and olfactory function during aging. *Aging cell* 14, 847-856.
- Chakraborty, S., Hong, W., 2018. Linking Extracellular Matrix Agrin to the Hippo Pathway in Liver Cancer and Beyond. *Cancers* 10.
- Chang, J.S., Kim, T.H., Nguyen, T.T., Park, K.S., Kim, N., Kong, I.D., 2017a. Circulating irisin levels as a predictive biomarker for sarcopenia: A cross-sectional community-based study. *Geriatrics & gerontology international* 17, 2266-2273.
- Chang, M.C., Srinivasan, K., Friedman, B.A., Suto, E., Modrusan, Z., Lee, W.P., Kaminker, J.S., Hansen, D.V., Sheng, M., 2017b. Progranulin deficiency causes impairment of autophagy and TDP-43 accumulation. *The Journal of experimental medicine* 214, 2611-2628.
- Chang, Y., Wei, W., 2015. Angiotensin II in inflammation, immunity and rheumatoid arthritis. *Clinical and experimental immunology* 179, 137-145.
- Charytan, D.M., Padera, R., Helfand, A.M., Zeisberg, M., Xu, X., Liu, X., Himmelfarb, J., Cinelli, A., Kalluri, R., Zeisberg, E.M., 2014. Increased concentration of circulating angiogenesis and nitric oxide inhibitors induces endothelial to mesenchymal transition and myocardial fibrosis in patients with chronic kidney disease. *International journal of cardiology* 176, 99-109.

- Chaturvedi, S., Hass, R., 2011. Extracellular signals in young and aging breast epithelial cells and possible connections to age-associated breast cancer development. *Mechanisms of ageing and development* 132, 213-219.
- Chen, J.Q., Huang, Y.Y., Gusdon, A.M., Qu, S., 2015a. Irisin: a new molecular marker and target in metabolic disorder. *Lipids in health and disease* 14, 2.
- Chen, L.W., Chen, F.P., Hsieh, C.W., Kuo, S.F., Chien, R.N., 2017a. Analysis of the associations among *Helicobacter pylori* infection, adiponectin, leptin, and 10-year fracture risk using the fracture risk assessment tool: A cross-sectional community-based study. *PloS one* 12, e0175365.
- Chen, Q., Guan, X., Zuo, X., Wang, J., Yin, W., 2016a. The role of high mobility group box 1 (HMGB1) in the pathogenesis of kidney diseases. *Acta pharmaceutica Sinica. B* 6, 183-188.
- Chen, W., Ma, X., Zhang, P., Li, Q., Liang, X., Liu, J., 2017b. MiR-212-3p inhibits LPS-induced inflammatory response through targeting HMGB1 in murine macrophages. *Experimental cell research* 350, 318-326.
- Chen, X., Wei, J., Li, C., Pierson, C.R., Finlay, J.L., Lin, J., 2018. Blocking interleukin-6 signaling inhibits cell viability/proliferation, glycolysis, and colony forming activity of human medulloblastoma cells. *International journal of oncology* 52, 571-578.
- Chen, X., Zhang, H., Hill, M.A., Zhang, C., Park, Y., 2015b. Regulation of Coronary Endothelial Function by Interactions between TNF- α , LOX-1 and Adiponectin in Apolipoprotein E Knockout Mice. *Journal of vascular research* 52, 372-382.
- Chen, Y., Zhang, F., Tsai, Y., Yang, X., Yang, L., Duan, S., Wang, X., Keng, P., Lee, S.O., 2015c. IL-6 signaling promotes DNA repair and prevents apoptosis in CD133+ stem-like cells of lung cancer after radiation. *Radiation oncology* 10, 227.
- Chen, Y.J., Mahieu, N.G., Huang, X., Singh, M., Crawford, P.A., Johnson, S.L., Gross, R.W., Schaefer, J., Patti, G.J., 2016b. Lactate metabolism is associated with mammalian mitochondria. *Nature chemical biology* 12, 937-943.
- Cheng, C.W., Adams, G.B., Perin, L., Wei, M., Zhou, X., Lam, B.S., Da Sacco, S., Mirisola, M., Quinn, D.I., Dorff, T.B., Kopchick, J.J., Longo, V.D., 2014. Prolonged fasting reduces IGF-1/PKA to promote hematopoietic-stem-cell-based regeneration and reverse immunosuppression. *Cell stem cell* 14, 810-823.
- Cheng, D., Kong, H., Pang, W., Yang, H., Lu, H., Huang, C., Jiang, Y., 2016a. B vitamin supplementation improves cognitive function in the middle aged and elderly with hyperhomocysteinemia. *Nutritional neuroscience* 19, 461-466.
- Cheng, H., Lu, C., Tang, R., Pan, Y., Bao, S., Qiu, Y., Xie, M., 2017. Ellagic acid inhibits the proliferation of human pancreatic carcinoma PANC-1 cells in vitro and in vivo. *Oncotarget* 8, 12301-12310.
- Cheng, S.B., Lin, P.T., Liu, H.T., Peng, Y.S., Huang, S.C., Huang, Y.C., 2016b. Vitamin B-6 Supplementation Could Mediate Antioxidant Capacity by Reducing Plasma Homocysteine Concentration in Patients with Hepatocellular Carcinoma after Tumor Resection. *BioMed research international* 2016, 7658981.
- Chi, J.Y., Hsiao, Y.W., Li, C.F., Lo, Y.C., Lin, Z.Y., Hong, J.Y., Liu, Y.M., Han, X., Wang, S.M., Chen, B.K., Tsai, K.K., Wang, J.M., 2015. Targeting chemotherapy-induced PTX3 in tumor stroma to prevent the progression of drug-resistant cancers. *Oncotarget* 6, 23987-24001.
- Chien, S.J., Chen, T.C., Kuo, H.C., Chen, C.N., Chang, S.F., 2015. Fulvic acid attenuates homocysteine-induced cyclooxygenase-2 expression in human monocytes. *BMC complementary and alternative medicine* 15, 61.
- Cho, H.J., Kang, J.H., Park, K.K., Choe, J.Y., Park, Y.Y., Moon, Y.S., Chung, I.K., Chang, H.W., Kim, C.H., Choi, Y.H., Kim, W.J., Moon, S.K., Chang, Y.C., 2013. Comparative proteome

- analysis of Tumor necrosis factor alpha-stimulated human Vascular Smooth Muscle Cells in response to melittin. *Proteome science* 11, 20.
- Choi, H.M., Lee, Y.A., Yang, H.I., Yoo, M.C., Kim, K.S., 2011. Increased levels of thymosin beta4 in synovial fluid of patients with rheumatoid arthritis: association of thymosin beta4 with other factors that are involved in inflammation and bone erosion in joints. *International journal of rheumatic diseases* 14, 320-324.
- Chong, Z.Z., 2016. S100B raises the alert in subarachnoid hemorrhage. *Reviews in the neurosciences* 27, 745-759.
- Chong, Z.Z., Changyaleket, B., Xu, H., Dull, R.O., Schwartz, D.E., 2016. Identifying S100B as a Biomarker and a Therapeutic Target For Brain Injury and Multiple Diseases. *Current medicinal chemistry* 23, 1571-1596.
- Chow, W.S., Xu, A., Woo, Y.C., Tso, A.W., Cheung, S.C., Fong, C.H., Tse, H.F., Chau, M.T., Cheung, B.M., Lam, K.S., 2013. Serum fibroblast growth factor-21 levels are associated with carotid atherosclerosis independent of established cardiovascular risk factors. *Arteriosclerosis, thrombosis, and vascular biology* 33, 2454-2459.
- Chung, H.W., Lim, J.B., 2017. High-mobility group box-1 contributes tumor angiogenesis under interleukin-8 mediation during gastric cancer progression. *Cancer science* 108, 1594-1601.
- Cianciolo, G., Galassi, A., Capelli, I., Schillaci, R., La Manna, G., Cozzolino, M., 2018. Klotho-FGF23, Cardiovascular Disease, and Vascular Calcification: Black or White? *Current vascular pharmacology* 16, 143-156.
- Cirillo, C., Capoccia, E., Iuvone, T., Cuomo, R., Sarnelli, G., Steardo, L., Esposito, G., 2015. S100B Inhibitor Pentamidine Attenuates Reactive Gliosis and Reduces Neuronal Loss in a Mouse Model of Alzheimer's Disease. *BioMed research international* 2015, 508342.
- Cirillo, C., Sarnelli, G., Esposito, G., Turco, F., Steardo, L., Cuomo, R., 2011. S100B protein in the gut: the evidence for enteroglia-sustained intestinal inflammation. *World journal of gastroenterology* 17, 1261-1266.
- Cirone, M., Garufi, A., Di Renzo, L., Granato, M., Faggioni, A., D'Orazi, G., 2013. Zinc supplementation is required for the cytotoxic and immunogenic effects of chemotherapy in chemoresistant p53-functionally deficient cells. *Oncoimmunology* 2, e26198.
- Claramunt-Taberner, D., Bertholet-Thomas, A., Carlier, M.C., Dijoud, F., Chotel, F., Silve, C., Bacchetta, J., 2018. Hyperphosphatemic tumoral calcinosis caused by FGF23 compound heterozygous mutations: what are the therapeutic options for a better control of phosphatemia? *Pediatric nephrology* 33, 1263-1267.
- Clarke, A., Perry, E., Kelly, C., De Soya, A., Heesom, K., Gold, L.I., Ollier, W., Hutchinson, D., Eggleton, P., 2017. Heightened autoantibody immune response to citrullinated calreticulin in bronchiectasis: Implications for rheumatoid arthritis. *The international journal of biochemistry & cell biology* 89, 199-206.
- Clinkenbeard, E.L., White, K.E., 2017. Heritable and acquired disorders of phosphate metabolism: Etiologies involving FGF23 and current therapeutics. *Bone* 102, 31-39.
- Codoner-Franch, P., Tavaréz-Alonso, S., Porcar-Almela, M., Navarro-Solera, M., Arilla-Codoner, A., Alonso-Iglesias, E., 2014. Plasma resistin levels are associated with homocysteine, endothelial activation, and nitrosative stress in obese youths. *Clinical biochemistry* 47, 44-48.
- Collerton, J., Martin-Ruiz, C., Davies, K., Hilkens, C.M., Isaacs, J., Kolenda, C., Parker, C., Dunn, M., Catt, M., Jagger, C., von Zglinicki, T., Kirkwood, T.B., 2012. Frailty and the role of inflammation, immunosenescence and cellular ageing in the very old: cross-sectional findings from the Newcastle 85+ Study. *Mechanisms of ageing and development* 133, 456-466.
- Combs, T.P., Pajvani, U.B., Berg, A.H., Lin, Y., Jelicks, L.A., Laplante, M., Nawrocki, A.R., Rajala, M.W., Parlow, A.F., Cheeseboro, L., Ding, Y.Y., Russell, R.G., Lindemann, D.,

- Hartley, A., Baker, G.R., Obici, S., Deshaies, Y., Ludgate, M., Rossetti, L., Scherer, P.E., 2004. A transgenic mouse with a deletion in the collagenous domain of adiponectin displays elevated circulating adiponectin and improved insulin sensitivity. *Endocrinology* 145, 367-383.
- Communal, C., Sumandea, M., de Tombe, P., Narula, J., Solaro, R.J., Hajjar, R.J., 2002. Functional consequences of caspase activation in cardiac myocytes. *Proceedings of the National Academy of Sciences of the United States of America* 99, 6252-6256.
- Compte, N., Zouaoui Boudjeltia, K., Vanhaeverbeek, M., De Breucker, S., Tassignon, J., Trelcat, A., Pepersack, T., Goriely, S., 2013. Frailty in old age is associated with decreased interleukin-12/23 production in response to toll-like receptor ligation. *PloS one* 8, e65325.
- Cong, L., Gasser, J., Zhao, J., Yang, B., Li, F., Zhao, A.Z., 2007. Human adiponectin inhibits cell growth and induces apoptosis in human endometrial carcinoma cells, HEC-1-A and RL95 2. *Endocrine-related cancer* 14, 713-720.
- Connolly, B.M., Choi, E.Y., Gardsvoll, H., Bey, A.L., Currie, B.M., Chavakis, T., Liu, S., Molinolo, A., Ploug, M., Leppla, S.H., Bugge, T.H., 2010. Selective abrogation of the uPA-uPAR interaction in vivo reveals a novel role in suppression of fibrin-associated inflammation. *Blood* 116, 1593-1603.
- Constans, J., Conri, C., 2006. Circulating markers of endothelial function in cardiovascular disease. *Clinica chimica acta; international journal of clinical chemistry* 368, 33-47.
- Corigliano, A., Preiano, M., Terracciano, R., Savino, R., De Gori, M., Galasso, O., Gasparini, G., 2017. C3f is a potential tool for the staging of osteoarthritis. *Journal of biological regulators and homeostatic agents* 31, 29-35.
- Corre, J., Hebraud, B., Bourin, P., 2013. Concise review: growth differentiation factor 15 in pathology: a clinical role? *Stem cells translational medicine* 2, 946-952.
- Correia, S., Vaz, C.V., Silva, A.M., Cavaco, J.E., Socorro, S., 2017. Regucalcin counteracts tert-butyl hydroperoxide and cadmium-induced oxidative stress in rat testis. *Journal of applied toxicology : JAT* 37, 159-166.
- Cotman, S.L., Halfter, W., Cole, G.J., 2000. Agrin binds to beta-amyloid (Abeta), accelerates abeta fibril formation, and is localized to Abeta deposits in Alzheimer's disease brain. *Molecular and cellular neurosciences* 15, 183-198.
- Courbebaisse, M., Lanske, B., 2018. Biology of Fibroblast Growth Factor 23: From Physiology to Pathology. *Cold Spring Harbor perspectives in medicine* 8.
- Crujeiras, A.B., Gomez-Arbelaez, D., Zulet, M.A., Carreira, M.C., Sajoux, I., de Luis, D., Castro, A.I., Baltar, J., Baamonde, I., Sueiro, A., Macias-Gonzalez, M., Bellido, D., Tinahones, F.J., Martinez, J.A., Casanueva, F.F., 2017. Plasma FGF21 levels in obese patients undergoing energy-restricted diets or bariatric surgery: a marker of metabolic stress? *International journal of obesity* 41, 1570-1578.
- Crujeiras, A.B., Pardo, M., Arturo, R.R., Navas-Carretero, S., Zulet, M.A., Martinez, J.A., Casanueva, F.F., 2014. Longitudinal variation of circulating irisin after an energy restriction-induced weight loss and following weight regain in obese men and women. *American journal of human biology : the official journal of the Human Biology Council* 26, 198-207.
- Ctrnacta, V., Fritzler, J.M., Surinova, M., Hrdy, I., Zhu, G., Stejskal, F., 2010. Efficacy of S-adenosylhomocysteine hydrolase inhibitors, D-eritadenine and (S)-DHPA, against the growth of *Cryptosporidium parvum* in vitro. *Experimental parasitology* 126, 113-116.
- Cufi, S., Vazquez-Martin, A., Oliveras-Ferraros, C., Quirantes, R., Segura-Carretero, A., Micol, V., Joven, J., Bosch-Barrera, J., Del Barco, S., Martin-Castillo, B., Vellon, L., Menendez, J.A., 2012. Metformin lowers the threshold for stress-induced senescence: a role for the microRNA-200 family and miR-205. *Cell cycle* 11, 1235-1246.

- Cui, J.G., Bazan, N.G., 2010. Agrin downregulation induced by nerve injury contributes to neuropathic pain. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 30, 15286-15297.
- Cui, S., Li, W., Lv, X., Wang, P., Huang, G., Gao, Y., 2017. Folic acid attenuates homocysteine and enhances antioxidative capacity in atherosclerotic rats. *Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme* 42, 1015-1022.
- Cunningham, M., Marks, N., Barnado, A., Wirth, J.R., Gilkeson, G., Markiewicz, M., 2014. Are microparticles the missing link between thrombosis and autoimmune diseases? Involvement in selected rheumatologic diseases. *Seminars in thrombosis and hemostasis* 40, 675-681.
- Cunningham, O., Champion, S., Perry, V.H., Murray, C., Sidenius, N., Docagne, F., Cunningham, C., 2009. Microglia and the urokinase plasminogen activator receptor/uPA system in innate brain inflammation. *Glia* 57, 1802-1814.
- Cuppen, B.V., Rossato, M., Fritsch-Stork, R.D., Concepcion, A.N., Schenk, Y., Bijlsma, J.W., Radstake, T.R., Lafeber, F.P., all, S.R.U.i., 2016. Can baseline serum microRNAs predict response to TNF-alpha inhibitors in rheumatoid arthritis? *Arthritis research & therapy* 18, 189.
- Damas, J.K., Boullier, A., Waehre, T., Smith, C., Sandberg, W.J., Green, S., Aukrust, P., Quehenberger, O., 2005. Expression of fractalkine (CX3CL1) and its receptor, CX3CR1, is elevated in coronary artery disease and is reduced during statin therapy. *Arteriosclerosis, thrombosis, and vascular biology* 25, 2567-2572.
- Daniel, C., Amann, K., Hohenstein, B., Bornstein, P., Hugo, C., 2007. Thrombospondin 2 functions as an endogenous regulator of angiogenesis and inflammation in experimental glomerulonephritis in mice. *Journal of the American Society of Nephrology : JASN* 18, 788-798.
- Daniel, C., Wagner, A., Hohenstein, B., Hugo, C., 2009. Thrombospondin-2 therapy ameliorates experimental glomerulonephritis via inhibition of cell proliferation, inflammation, and TGF-beta activation. *American journal of physiology. Renal physiology* 297, F1299-1309.
- Daniels, L.B., Clopton, P., Laughlin, G.A., Maisel, A.S., Barrett-Connor, E., 2011. Growth-differentiation factor-15 is a robust, independent predictor of 11-year mortality risk in community-dwelling older adults: the Rancho Bernardo Study. *Circulation* 123, 2101-2110.
- Darvin, K., Randolph, A., Ovalles, S., Halade, D., Breeding, L., Richardson, A., Espinoza, S.E., 2014. Plasma protein biomarkers of the geriatric syndrome of frailty. *The journals of gerontology. Series A, Biological sciences and medical sciences* 69, 182-186.
- Daryadel, A., Haubitz, M., Figueiredo, M., Steubl, D., Roos, M., Mader, A., Hettwer, S., Wagner, C.A., 2016. The C-Terminal Fragment of Agrin (CAF), a Novel Marker of Renal Function, Is Filtered by the Kidney and Reabsorbed by the Proximal Tubule. *PloS one* 11, e0157905.
- Das, S.K., Gupta, I., Cho, Y.K., Zhang, X., Uehara, H., Muddana, S.K., Bernhisel, A.A., Archer, B., Ambati, B.K., 2014. Vimentin knockdown decreases corneal opacity. *Investigative ophthalmology & visual science* 55, 4030-4040.
- Davalos, A.R., Kawahara, M., Malhotra, G.K., Schaum, N., Huang, J., Ved, U., Beausejour, C.M., Coppe, J.P., Rodier, F., Campisi, J., 2013. p53-dependent release of Alarmin HMGB1 is a central mediator of senescent phenotypes. *J Cell Biol* 201, 613-629.
- Davis, G.R., Deville, T., Guillory, J., Bellar, D., Nelson, A.G., 2017. Relationship between family history of type 2 diabetes and serum FGF21. *European journal of clinical investigation* 47, 853-859.

- Davis, R.L., Liang, C., Edema-Hildebrand, F., Riley, C., Needham, M., Sue, C.M., 2013. Fibroblast growth factor 21 is a sensitive biomarker of mitochondrial disease. *Neurology* 81, 1819-1826.
- Davis, R.L., Liang, C., Sue, C.M., 2016. A comparison of current serum biomarkers as diagnostic indicators of mitochondrial diseases. *Neurology* 86, 2010-2015.
- Davis, R.L., Liang, C., Sue, C.M., 2018. Mitochondrial diseases. *Handbook of clinical neurology* 147, 125-141.
- de Candia, P., Matarese, G., 2017. Leptin and ghrelin: Sewing metabolism onto neurodegeneration. *Neuropharmacology*.
- De Haan, J.J., Haitjema, S., den Ruijter, H.M., Pasterkamp, G., de Borst, G.J., Teraa, M., Verhaar, M.C., Gremmels, H., de Jager, S.C.A., 2017. Growth Differentiation Factor 15 Is Associated With Major Amputation and Mortality in Patients With Peripheral Artery Disease. *Journal of the American Heart Association* 6.
- De Loof, A., Vanden, J., Janssen, I., 1996. Hormones and the cytoskeleton of animals and plants. *International review of cytology* 166, 1-58.
- de Luis, D.A., Izaola, O., de la Fuente, B., Primo, D., Fernandez Ovalle, H., Romero, E., 2016. rs1501299 Polymorphism in the Adiponectin Gene and Their Association with Total Adiponectin Levels, Insulin Resistance and Metabolic Syndrome in Obese Subjects. *Annals of nutrition & metabolism* 69, 226-231.
- Deak, F., Sonntag, W.E., 2012. Aging, synaptic dysfunction, and insulin-like growth factor (IGF)-1. *The journals of gerontology. Series A, Biological sciences and medical sciences* 67, 611-625.
- DeChiara, T.M., Bowen, D.C., Valenzuela, D.M., Simmons, M.V., Poueymirou, W.T., Thomas, S., Kinetz, E., Compton, D.L., Rojas, E., Park, J.S., Smith, C., DiStefano, P.S., Glass, D.J., Burden, S.J., Yancopoulos, G.D., 1996. The receptor tyrosine kinase MuSK is required for neuromuscular junction formation in vivo. *Cell* 85, 501-512.
- DeClercq, V., d'Eon, B., McLeod, R.S., 2015. Fatty acids increase adiponectin secretion through both classical and exosome pathways. *Biochimica et biophysica acta* 1851, 1123-1133.
- Del Campo Milan, M., Zuroff, L., Jimenez, C.R., Scheltens, P., Teunissen, C.E., 2015. Can agrin cerebrospinal fluid concentration be used as an early biomarker for Alzheimer's disease? *Alzheimer's & dementia* 1, 75-80.
- Demirci, S., Aynali, A., Demirci, K., Demirci, S., Aridogan, B.C., 2017. The Serum Levels of Resistin and Its Relationship with Other Proinflammatory Cytokines in Patients with Alzheimer's Disease. *Clinical psychopharmacology and neuroscience : the official scientific journal of the Korean College of Neuropsychopharmacology* 15, 59-63.
- Denroche, H.C., Levi, J., Wideman, R.D., Sequeira, R.M., Huynh, F.K., Covey, S.D., Kieffer, T.J., 2011. Leptin therapy reverses hyperglycemia in mice with streptozotocin-induced diabetes, independent of hepatic leptin signaling. *Diabetes* 60, 1414-1423.
- Derouiche, F., Bole-Feysot, C., Naimi, D., Coeffier, M., 2014. Hyperhomocysteinemia-induced oxidative stress differentially alters proteasome composition and activities in heart and aorta. *Biochemical and biophysical research communications* 452, 740-745.
- Deyst, K.A., McKechnie, B.A., Fallon, J.R., 1998. The role of alternative splicing in regulating agrin binding to muscle cells. *Brain research. Developmental brain research* 110, 185-191.
- Di Luigi, L., Corinaldesi, C., Colletti, M., Scolletta, S., Antinozzi, C., Vannelli, G.B., Giannetta, E., Gianfrilli, D., Isidori, A.M., Migliaccio, S., Poerio, N., Fraziano, M., Lenzi, A., Crescioli, C., 2016. Phosphodiesterase Type 5 Inhibitor Sildenafil Decreases the Proinflammatory Chemokine CXCL10 in Human Cardiomyocytes and in Subjects with Diabetic Cardiomyopathy. *Inflammation* 39, 1238-1252.

- Diem, S., Kasenda, B., Spain, L., Martin-Liberal, J., Marconcini, R., Gore, M., Larkin, J., 2016. Serum lactate dehydrogenase as an early marker for outcome in patients treated with anti-PD-1 therapy in metastatic melanoma. *British journal of cancer* 114, 256-261.
- Diener, S., Schorpp, K., Strom, T.M., Hadian, K., Lorenz-Depiereux, B., 2015. Development of A Cell-Based Assay to Identify Small Molecule Inhibitors of FGF23 Signaling. *Assay and drug development technologies* 13, 476-487.
- Dieudonne, M.N., Bussiere, M., Dos Santos, E., Leneuve, M.C., Giudicelli, Y., Pecquery, R., 2006. Adiponectin mediates antiproliferative and apoptotic responses in human MCF7 breast cancer cells. *Biochemical and biophysical research communications* 345, 271-279.
- Dilsizoglu Senol, A., Tagliafierro, L., Huguet, L., Gorisse-Hussonnois, L., Chasseigneaux, S., Allinquant, B., 2015. PAT1 inversely regulates the surface Amyloid Precursor Protein level in mouse primary neurons. *BMC neuroscience* 16, 10.
- Dimassi, S., Chahed, K., Boumiza, S., Canault, M., Tabka, Z., Laurant, P., Riva, C., 2016. Role of eNOS- and NOX-containing microparticles in endothelial dysfunction in patients with obesity. *Obesity* 24, 1305-1312.
- Dimitroulas, T., Sandoo, A., Hodson, J., Smith, J., Douglas, K.M., Kitas, G.D., 2016. Associations between asymmetric dimethylarginine, homocysteine, and the methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism (rs1801133) in rheumatoid arthritis. *Scandinavian journal of rheumatology* 45, 267-273.
- Ding, H., Hong, C., Wang, Y., Liu, J., Zhang, N., Shen, C., Wei, W., Zheng, F., 2014. Calreticulin promotes angiogenesis via activating nitric oxide signalling pathway in rheumatoid arthritis. *Clinical and experimental immunology* 178, 236-244.
- Ding, X.M., Pan, L., Wang, Y., Xu, Q.Z., 2016. Baicalin exerts protective effects against lipopolysaccharide-induced acute lung injury by regulating the crosstalk between the CX3CL1-CX3CR1 axis and NF-kappaB pathway in CX3CL1-knockout mice. *International journal of molecular medicine* 37, 703-715.
- DiPasquale, D.M., Cheng, M., Billich, W., Huang, S.A., van Rooijen, N., Hornberger, T.A., Koh, T.J., 2007. Urokinase-type plasminogen activator and macrophages are required for skeletal muscle hypertrophy in mice. *American journal of physiology. Cell physiology* 293, C1278-1285.
- Dixit, V.D., Schaffer, E.M., Pyle, R.S., Collins, G.D., Sakthivel, S.K., Palaniappan, R., Lillard, J.W., Jr., Taub, D.D., 2004. Ghrelin inhibits leptin- and activation-induced proinflammatory cytokine expression by human monocytes and T cells. *The Journal of clinical investigation* 114, 57-66.
- Dmello, C., Sawant, S., Alam, H., Gangadaran, P., Mogre, S., Tiwari, R., D'Souza, Z., Narkar, M., Thorat, R., Patil, K., Chaukar, D., Kane, S., Vaidya, M., 2017. Vimentin regulates differentiation switch via modulation of keratin 14 levels and their expression together correlates with poor prognosis in oral cancer patients. *PloS one* 12, e0172559.
- Dogan, S., Johannsen, A.C., Grande, J.P., Cleary, M.P., 2011. Effects of intermittent and chronic calorie restriction on mammalian target of rapamycin (mTOR) and IGF-I signaling pathways in mammary fat pad tissues and mammary tumors. *Nutrition and cancer* 63, 389-401.
- Dogan, S., Ray, A., Cleary, M.P., 2017. The influence of different calorie restriction protocols on serum pro-inflammatory cytokines, adipokines and IGF-I levels in female C57BL6 mice: short term and long term diet effects. *Meta gene* 12, 22-32.
- Dogan, S., Rogozina, O.P., Lokshin, A.E., Grande, J.P., Cleary, M.P., 2010. Effects of chronic vs. intermittent calorie restriction on mammary tumor incidence and serum adiponectin and leptin levels in MMTV-TGF-alpha mice at different ages. *Oncology letters* 1, 167-176.

- Domouzoglou, E.M., Naka, K.K., Vlahos, A.P., Papafaklis, M.I., Michalis, L.K., Tsatsoulis, A., Maratos-Flier, E., 2015. Fibroblast growth factors in cardiovascular disease: The emerging role of FGF21. *American journal of physiology. Heart and circulatory physiology* 309, H1029-1038.
- Donahue, J.E., Berzin, T.M., Rafii, M.S., Glass, D.J., Yancopoulos, G.D., Fallon, J.R., Stopa, E.G., 1999. Agrin in Alzheimer's disease: altered solubility and abnormal distribution within microvasculature and brain parenchyma. *Proceedings of the National Academy of Sciences of the United States of America* 96, 6468-6472.
- Donato, R., Cannon, B.R., Sorci, G., Riuzzi, F., Hsu, K., Weber, D.J., Geczy, C.L., 2013a. Functions of S100 proteins. *Current molecular medicine* 13, 24-57.
- Donato, R., Riuzzi, F., Sorci, G., 2013b. Causes of elevated serum levels of S100B protein in athletes. *European journal of applied physiology* 113, 819-820.
- Donato, R., Sorci, G., Riuzzi, F., Arcuri, C., Bianchi, R., Brozzi, F., Tubaro, C., Giambanco, I., 2009. S100B's double life: intracellular regulator and extracellular signal. *Biochimica et biophysica acta* 1793, 1008-1022.
- Dong, B.B., Yan, J.S., Yan, Y.Y., Xie, T.C., Xu, L., Hu, G.H., Xu, Y.F., Liu, M., 2017a. Downregulation of pigment epithelium-derived factor is associated with increased epithelial-mesenchymal transition in bladder cancer. *Panminerva medica* 59, 9-14.
- Dong, J.Q., Rossulek, M., Somayaji, V.R., Baltrukonis, D., Liang, Y., Hudson, K., Hernandez-Illas, M., Calle, R.A., 2015. Pharmacokinetics and pharmacodynamics of PF-05231023, a novel long-acting FGF21 mimetic, in a first-in-human study. *British journal of clinical pharmacology* 80, 1051-1063.
- Dong, Q., Zhu, X., Dai, C., Zhang, X., Gao, X., Wei, J., Sheng, Y., Zheng, Y., Yu, J., Xie, L., Qin, Y., Qiao, P., Zhou, C., Yu, X., Jia, H., Ren, N., Zhou, H., Ye, Q., Qin, L., 2016. Osteopontin promotes epithelial-mesenchymal transition of hepatocellular carcinoma through regulating vimentin. *Oncotarget* 7, 12997-13012.
- Dong, X.L., Xu, S.J., Zhang, L., Zhang, X.Q., Liu, T., Gao, Q.Y., Qian, Q.Q., Sun, B.L., Yang, M.F., 2017b. Serum Resistin Levels May Contribute to an Increased Risk of Acute Cerebral Infarction. *Molecular neurobiology* 54, 1919-1926.
- Dong, X.Q., Yang, S.B., Zhu, F.L., Lv, Q.W., Zhang, G.H., Huang, H.B., 2010. Resistin is associated with mortality in patients with traumatic brain injury. *Critical care* 14, R190.
- Drago-Serrano, M.E., Campos-Rodriguez, R., Carrero, J.C., de la Garza, M., 2017. Lactoferrin: Balancing Ups and Downs of Inflammation Due to Microbial Infections. *International journal of molecular sciences* 18.
- Drechsler, C., Hayek, S.S., Wei, C., Sever, S., Genser, B., Krane, V., Meinitzer, A., Marz, W., Wanner, C., Reiser, J., 2017. Soluble Urokinase Plasminogen Activator Receptor and Outcomes in Patients with Diabetes on Hemodialysis. *Clinical journal of the American Society of Nephrology : CJASN* 12, 1265-1273.
- Drey, M., Behnes, M., Kob, R., Lepiorz, D., Hettwer, S., Bollheimer, C., Sieber, C.C., Bertsch, T., Hoffmann, U., 2015. C-terminal agrin fragment (CAF) reflects renal function in patients suffering from severe sepsis or septic shock. *Clinical laboratory* 61, 69-76.
- Drey, M., Sieber, C.C., Bauer, J.M., Uter, W., Dahinden, P., Fariello, R.G., Vrijbloed, J.W., Fi, A.T.i.g., 2013. C-terminal Agrin Fragment as a potential marker for sarcopenia caused by degeneration of the neuromuscular junction. *Experimental gerontology* 48, 76-80.
- Du, X.L., Jiang, W.X., Lv, Z.T., 2016. Lower Circulating Irisin Level in Patients with Diabetes Mellitus: A Systematic Review and Meta-Analysis. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme* 48, 644-652.
- Dufek, M., Rektorova, I., Thon, V., Lokaj, J., Rektor, I., 2015. Interleukin-6 May Contribute to Mortality in Parkinson's Disease Patients: A 4-Year Prospective Study. *Parkinson's disease* 2015, 898192.

- Duffy, M.J., O'Donovan, N., McDermott, E., Crown, J., 2016. Validated biomarkers: The key to precision treatment in patients with breast cancer. *Breast* 29, 192-201.
- Dunkelberger, J.R., Song, W.C., 2010. Complement and its role in innate and adaptive immune responses. *Cell research* 20, 34-50.
- Dushay, J., Chui, P.C., Gopalakrishnan, G.S., Varela-Rey, M., Crawley, M., Fisher, F.M., Badman, M.K., Martinez-Chantar, M.L., Maratos-Flier, E., 2010. Increased fibroblast growth factor 21 in obesity and nonalcoholic fatty liver disease. *Gastroenterology* 139, 456-463.
- Eckes, B., Colucci-Guyon, E., Smola, H., Nodder, S., Babinet, C., Krieg, T., Martin, P., 2000. Impaired wound healing in embryonic and adult mice lacking vimentin. *Journal of cell science* 113 (Pt 13), 2455-2462.
- Econs, M.J., 2017. Genetic diseases resulting from disordered FGF23/klotho biology. *Bone* 100, 56-61.
- Edelmann, S., Fahrner, R., Malinka, T., Song, B.H., Stroka, D., Mermod, N., 2015. Nuclear Factor I-C acts as a regulator of hepatocyte proliferation at the onset of liver regeneration. *Liver international : official journal of the International Association for the Study of the Liver* 35, 1185-1194.
- Edwards, C.R., Hindle, A.K., Latham, P.S., Fu, S.W., Brody, F.J., 2013. Resistin expression correlates with steatohepatitis in morbidly obese patients. *Surgical endoscopy* 27, 1310-1314.
- Effenberger, T., von der Heyde, J., Bartsch, K., Garbers, C., Schulze-Osthoff, K., Chalaris, A., Murphy, G., Rose-John, S., Rabe, B., 2014. Senescence-associated release of transmembrane proteins involves proteolytic processing by ADAM17 and microvesicle shedding. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 28, 4847-4856.
- Eggers, K.M., Kempf, T., Lind, L., Sundstrom, J., Wallentin, L., Wollert, K.C., Siegbahn, A., 2012. Relations of growth-differentiation factor-15 to biomarkers reflecting vascular pathologies in a population-based sample of elderly subjects. *Scandinavian journal of clinical and laboratory investigation* 72, 45-51.
- El-Saeed, A.M., El-Mohasseb, G.F., 2017. Circulating Fibroblast Growth Factors 21 and 23 as Biomarkers of Progression in Diabetic Nephropathy in Type 2 Diabetes with Normoalbuminuria. *The Egyptian journal of immunology* 24, 93-99.
- El-Saeed, G.S., Fadel, F., Elshamaa, M.F., Galal, R.E., Elghoroury, E.A., Nasr, S.A., Thabet, E.H., Abdelrahman, S.M., 2015. Advanced glycation end products and soluble receptor as markers of oxidative stress in children on hemodialysis. *Renal failure* 37, 1452-1456.
- Eldridge, S., Nalesso, G., Ismail, H., Vicente-Greco, K., Kabouridis, P., Ramachandran, M., Niemeier, A., Herz, J., Pitzalis, C., Perretti, M., Dell'Accio, F., 2016. Agrin mediates chondrocyte homeostasis and requires both LRP4 and alpha-dystroglycan to enhance cartilage formation in vitro and in vivo. *Annals of the rheumatic diseases* 75, 1228-1235.
- Emanuele, E., Minoretta, P., Pareja-Galeano, H., Sanchis-Gomar, F., Garatachea, N., Lucia, A., 2014. Serum irisin levels, precocious myocardial infarction, and healthy exceptional longevity. *The American journal of medicine* 127, 888-890.
- Eming, S.A., Martin, P., Tomic-Canic, M., 2014. Wound repair and regeneration: mechanisms, signaling, and translation. *Science translational medicine* 6, 265sr266.
- Engstrom, G., Hedblad, B., Eriksson, K.F., Janzon, L., Lindgarde, F., 2005. Complement C3 is a risk factor for the development of diabetes: a population-based cohort study. *Diabetes* 54, 570-575.
- Erasso, D., Tender, G., Levitt, R.C., Cui, J.G., 2014. Agrin requires specific proteins to selectively activate gamma-aminobutyric acid neurons for pain suppression. *Experimental neurology* 261, 646-653.

- Erasso, D., Tender, G.C., Li, Q., Yan, J., Culicchia, F., Abdi, S., Cui, J., 2018. The Effects of Agrin Isoforms on Diabetic Neuropathic Pain in a Rat Streptozotocin Model. *Anesthesia and analgesia*.
- Erben, R.G., 2016. Update on FGF23 and Klotho signaling. *Molecular and cellular endocrinology* 432, 56-65.
- Erben, R.G., 2017. Pleiotropic Actions of FGF23. *Toxicologic pathology* 45, 904-910.
- Erben, R.G., 2018. alpha-Klotho's effects on mineral homeostasis are fibroblast growth factor-23 dependent. *Current opinion in nephrology and hypertension* 27, 229-235.
- Erben, R.G., Andrukhova, O., 2017. FGF23-Klotho signaling axis in the kidney. *Bone* 100, 62-68.
- Eren, M., Boe, A.E., Murphy, S.B., Place, A.T., Nagpal, V., Morales-Nebreda, L., Urich, D., Quaggin, S.E., Budinger, G.R., Mutlu, G.M., Miyata, T., Vaughan, D.E., 2014. PAI-1-regulated extracellular proteolysis governs senescence and survival in Klotho mice. *Proceedings of the National Academy of Sciences of the United States of America* 111, 7090-7095.
- Ertekin-Taner, N., Ronald, J., Feuk, L., Prince, J., Tucker, M., Younkin, L., Hella, M., Jain, S., Hackett, A., Scanlin, L., Kelly, J., Kihiko-Ehman, M., Neltner, M., Hersh, L., Kindy, M., Markesbery, W., Hutton, M., de Andrade, M., Petersen, R.C., Graff-Radford, N., Estus, S., Brookes, A.J., Younkin, S.G., 2005. Elevated amyloid beta protein (Abeta42) and late onset Alzheimer's disease are associated with single nucleotide polymorphisms in the urokinase-type plasminogen activator gene. *Human molecular genetics* 14, 447-460.
- Erusalimsky, J.D., Grillari, J., Grune, T., Jansen-Duerr, P., Lippi, G., Sinclair, A.J., Tegner, J., Vina, J., Durrance-Bagale, A., Minambres, R., Viegas, M., Rodriguez-Manas, L., Consortium, F., 2016. In Search of 'Omics'-Based Biomarkers to Predict Risk of Frailty and Its Consequences in Older Individuals: The FRAILOMIC Initiative. *Gerontology* 62, 182-190.
- Espinassous, Q., Garcia-de-Paco, E., Garcia-Verdugo, I., Synguelakis, M., von Aulock, S., Sallenave, J.M., McKenzie, A.N., Kanellopoulos, J., 2009. IL-33 enhances lipopolysaccharide-induced inflammatory cytokine production from mouse macrophages by regulating lipopolysaccharide receptor complex. *Journal of immunology* 183, 1446-1455.
- Esposito, G., Capoccia, E., Sarnelli, G., Scuderi, C., Cirillo, C., Cuomo, R., Steardo, L., 2012. The antiprotozoal drug pentamidine ameliorates experimentally induced acute colitis in mice. *Journal of neuroinflammation* 9, 277.
- Esteghamati, A., Khandan, A., Momeni, A., Behdadnia, A., Ghajar, A., Nikdad, M.S., Noshad, S., Nakhjavani, M., Afarideh, M., 2017. Circulating levels of fibroblast growth factor 21 in early-stage diabetic kidney disease. *Irish journal of medical science* 186, 785-794.
- Estep, M., Abawi, M., Jarrar, M., Wang, L., Stepanova, M., Elariny, H., Moazez, A., Goodman, Z., Chandhoke, V., Baranova, A., Younossi, Z.M., 2011. Association of obestatin, ghrelin, and inflammatory cytokines in obese patients with non-alcoholic fatty liver disease. *Obesity surgery* 21, 1750-1757.
- Fahey, J.L., Schnelle, J.F., Boscardin, J., Thomas, J.K., Gorre, M.E., Aziz, N., Sadeghi, H., Nishanian, P., 2000. Distinct categories of immunologic changes in frail elderly. *Mechanisms of ageing and development* 115, 1-20.
- Fallahi, P., Katz, R., Toma, I., Li, R., Reiner, J., VanHouten, K., Carpio, L., Marshall, L., Lian, Y., Bupp, S., Fu, S.W., Rickles, F., Leitenberg, D., Lai, Y., Weksler, B.B., Rebling, F., Yang, Z., McCaffrey, T.A., 2013. Aspirin insensitive thrombophilia: transcript profiling of blood identifies platelet abnormalities and HLA restriction. *Gene* 520, 131-138.
- Falo, M.C., Reeves, T.M., Phillips, L.L., 2008. Agrin expression during synaptogenesis induced by traumatic brain injury. *Journal of neurotrauma* 25, 769-783.

- Fan, J., Sun, Z., 2016. The Antiaging Gene Klotho Regulates Proliferation and Differentiation of Adipose-Derived Stem Cells. *Stem cells* 34, 1615-1625.
- Fang, Y.J., Pan, Z.Z., Li, L.R., Lu, Z.H., Zhang, L.Y., Wan, D.S., 2009. MMP7 expression regulated by endocrine therapy in ERbeta-positive colon cancer cells. *Journal of experimental & clinical cancer research : CR* 28, 132.
- Fardo, D.W., Katsumata, Y., Kauwe, J.S.K., Deming, Y., Harari, O., Cruchaga, C., Alzheimer's Disease Neuroimaging, I., Nelson, P.T., 2017. CSF protein changes associated with hippocampal sclerosis risk gene variants highlight impact of GRN/PGRN. *Experimental gerontology* 90, 83-89.
- Faul, C., 2017. Cardiac actions of fibroblast growth factor 23. *Bone* 100, 69-79.
- Feger, M., Hase, P., Zhang, B., Hirche, F., Glosse, P., Lang, F., Foller, M., 2017. The production of fibroblast growth factor 23 is controlled by TGF-beta2. *Scientific reports* 7, 4982.
- Ferguson, S.A., Panos, J.J., Sloper, D., Varma, V., 2017. Neurodegenerative Markers are Increased in Postmortem BA21 Tissue from African Americans with Alzheimer's Disease. *Journal of Alzheimer's disease : JAD* 59, 57-66.
- Ferraccioli, G., Carbonella, A., Gremese, E., Alivernini, S., 2012. Rheumatoid arthritis and Alzheimer's disease: genetic and epigenetic links in inflammatory regulation. *Discovery medicine* 14, 379-388.
- Ferrucci, L., Cavazzini, C., Corsi, A., Bartali, B., Russo, C.R., Lauretani, F., Ferrucci, L., Cavazzini, C., Corsi, A.M., Bartali, B., Russo, C.R., Lauretani, F., Bandinelli, S., Bandinelli, S., Guralnik, J.M., 2002. Biomarkers of frailty in older persons. *Journal of endocrinological investigation* 25, 10-15.
- Finckh, U., van Hadeln, K., Muller-Thomsen, T., Alberici, A., Binetti, G., Hock, C., Nitsch, R.M., Stoppe, G., Reiss, J., Gal, A., 2003. Association of late-onset Alzheimer disease with a genotype of PLAU, the gene encoding urokinase-type plasminogen activator on chromosome 10q22.2. *Neurogenetics* 4, 213-217.
- Fischer, C.R., Mikami, M., Minematsu, H., Nizami, S., Goo Lee, H., Stamer, D., Patel, N., Yu Soung, D., Back, J.H., Song, L., Drissi, H., Lee, F.Y., 2017. Calreticulin inhibits inflammation-induced osteoclastogenesis and bone resorption. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society* 35, 2658-2666.
- Fox, J., Rioux, B.V., Goulet, E.D.B., Johanssen, N.M., Swift, D.L., Bouchard, D.R., Loewen, H., Senechal, M., 2018. Effect of an acute exercise bout on immediate post-exercise irisin concentration in adults: A meta-analysis. *Scandinavian journal of medicine & science in sports* 28, 16-28.
- Fragala, M.S., Jajtner, A.R., Beyer, K.S., Townsend, J.R., Emerson, N.S., Scanlon, T.C., Oliveira, L.P., Hoffman, J.R., Stout, J.R., 2014. Biomarkers of muscle quality: N-terminal propeptide of type III procollagen and C-terminal agrin fragment responses to resistance exercise training in older adults. *Journal of cachexia, sarcopenia and muscle* 5, 139-148.
- Franceschi, C., Bonafe, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., De Benedictis, G., 2000. Inflamm-aging. An evolutionary perspective on immunosenescence. *Annals of the New York Academy of Sciences* 908, 244-254.
- Francis, C., David, V., 2016. Inflammation regulates fibroblast growth factor 23 production. *Current opinion in nephrology and hypertension* 25, 325-332.
- Franczyk, B., Gluba-Brzozka, A., Rysz, J., 2018. Biomarkers of Cardiovascular Risk in Haemodialysis Patients. *Current pharmaceutical design* 23, 6086-6095.
- Fried, L.P., Tangen, C.M., Walston, J., Newman, A.B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W.J., Burke, G., McBurnie, M.A., Cardiovascular Health Study Collaborative Research, G., 2001. Frailty in older adults: evidence for a phenotype. *The journals of gerontology. Series A, Biological sciences and medical sciences* 56, M146-156.

- Friend, J.H., 1954. Alas for Human Frailties! *Science* 119, 912.
- Fu, A.K., Hung, K.W., Yuen, M.Y., Zhou, X., Mak, D.S., Chan, I.C., Cheung, T.H., Zhang, B., Fu, W.Y., Liew, F.Y., Ip, N.Y., 2016a. IL-33 ameliorates Alzheimer's disease-like pathology and cognitive decline. *Proceedings of the National Academy of Sciences of the United States of America* 113, E2705-2713.
- Fu, G.X., Chen, A.F., Zhong, Y., Zhao, J., Gu, Y.J., 2016b. Decreased serum level of HMGB1 and MyD88 during human aging progress in healthy individuals. *Aging clinical and experimental research* 28, 175-180.
- Fu, Z., Wang, Z., Liu, C.H., Gong, Y., Cakir, B., Liegl, R., Sun, Y., Meng, S.S., Burnim, S.B., Arellano, I., Moran, E., Duran, R., Poblete, A., Cho, S.S., Talukdar, S., Akula, J.D., Hellstrom, A., Smith, L.E.H., 2018. Fibroblast Growth Factor 21 Protects Photoreceptor Function in Type 1 Diabetic Mice. *Diabetes* 67, 974-985.
- Fuentes-Santamaria, V., Alvarado, J.C., Rodriguez-de la Rosa, L., Murillo-Cuesta, S., Contreras, J., Juiz, J.M., Varela-Nieto, I., 2016. IGF-1 deficiency causes atrophic changes associated with upregulation of VGlut1 and downregulation of MEF2 transcription factors in the mouse cochlear nuclei. *Brain structure & function* 221, 709-734.
- Fuerst, P.G., Rauch, S.M., Burgess, R.W., 2007. Defects in eye development in transgenic mice overexpressing the heparan sulfate proteoglycan agrin. *Developmental biology* 303, 165-180.
- Fujisawa, K., Terai, S., Hirose, Y., Takami, T., Yamamoto, N., Sakaida, I., 2011. Senescence marker protein 30 (SMP30)/regucalcin (RGN) expression decreases with aging, acute liver injuries and tumors in zebrafish. *Biochemical and biophysical research communications* 414, 331-336.
- Fujishima, Y., Maeda, N., Matsuda, K., Masuda, S., Mori, T., Fukuda, S., Sekimoto, R., Yamaoka, M., Obata, Y., Kita, S., Nishizawa, H., Funahashi, T., Ranscht, B., Shimomura, I., 2017. Adiponectin association with T-cadherin protects against neointima proliferation and atherosclerosis. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 31, 1571-1583.
- Fujita, Y., Ito, M., Kojima, T., Yatsuga, S., Koga, Y., Tanaka, M., 2015. GDF15 is a novel biomarker to evaluate efficacy of pyruvate therapy for mitochondrial diseases. *Mitochondrion* 20, 34-42.
- Fujita, Y., Makishima, M., Bhawal, U.K., 2016a. Differentiated embryo chondrocyte 1 (DEC1) is a novel negative regulator of hepatic fibroblast growth factor 21 (FGF21) in aging mice. *Biochemical and biophysical research communications* 469, 477-482.
- Fujita, Y., Taniguchi, Y., Shinkai, S., Tanaka, M., Ito, M., 2016b. Secreted growth differentiation factor 15 as a potential biomarker for mitochondrial dysfunctions in aging and age-related disorders. *Geriatrics & gerontology international* 16 Suppl 1, 17-29.
- Fujitsuka, N., Asakawa, A., Morinaga, A., Amitani, M.S., Amitani, H., Katsuura, G., Sawada, Y., Sudo, Y., Uezono, Y., Mochiki, E., Sakata, I., Sakai, T., Hanazaki, K., Yada, T., Yakabi, K., Sakuma, E., Ueki, T., Nijima, A., Nakagawa, K., Okubo, N., Takeda, H., Asaka, M., Inui, A., 2016. Increased ghrelin signaling prolongs survival in mouse models of human aging through activation of sirtuin1. *Molecular psychiatry* 21, 1613-1623.
- Fukami, K., Yamagishi, S., Okuda, S., 2014. Role of AGEs-RAGE system in cardiovascular disease. *Current pharmaceutical design* 20, 2395-2402.
- Fukumoto, S., 2018. Targeting Fibroblast Growth Factor 23 Signaling with Antibodies and Inhibitors, Is There a Rationale? *Frontiers in endocrinology* 9, 48.
- Gallagher, E.P., Di Giulio, R.T., 1989. Effects of complex waste mixtures on hepatic monooxygenase activities in brown bullheads (*Ictalurus nebulosus*). *Environmental pollution* 62, 113-128.

- Gan, L., Liu, Z., Luo, D., Ren, Q., Wu, H., Li, C., Sun, C., 2017. Reduced Endoplasmic Reticulum Stress-Mediated Autophagy Is Required for Leptin Alleviating Inflammation in Adipose Tissue. *Frontiers in immunology* 8, 1507.
- Gao, J., Wu, L., Wang, Y., Cui, S., Duan, S., Dong, Z., Feng, Z., Chen, X., 2017. Knockdown of Cxcl10 Inhibits Mesangial Cell Proliferation in Murine Habu Nephritis Via ERK Signaling. *Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology* 42, 2118-2129.
- Garcia-Donas, J., Beuselinck, B., Inglada-Perez, L., Grana, O., Schoffski, P., Wozniak, A., Bechter, O., Apellaniz-Ruiz, M., Leandro-Garcia, L.J., Esteban, E., Castellano, D.E., Gonzalez Del Alba, A., Climent, M.A., Hernando, S., Arranz, J.A., Morente, M., Pisano, D.G., Robledo, M., Rodriguez-Antona, C., 2016. Deep sequencing reveals microRNAs predictive of antiangiogenic drug response. *JCI insight* 1, e86051.
- Garcia, J.M., Boccia, R.V., Graham, C.D., Yan, Y., Duus, E.M., Allen, S., Friend, J., 2015. Anamorelin for patients with cancer cachexia: an integrated analysis of two phase 2, randomised, placebo-controlled, double-blind trials. *The Lancet. Oncology* 16, 108-116.
- Gautam, M., DeChiara, T.M., Glass, D.J., Yancopoulos, G.D., Sanes, J.R., 1999. Distinct phenotypes of mutant mice lacking agrin, MuSK, or rapsyn. *Brain research. Developmental brain research* 114, 171-178.
- Gautam, M., Noakes, P.G., Moscoso, L., Rupp, F., Scheller, R.H., Merlie, J.P., Sanes, J.R., 1996. Defective neuromuscular synaptogenesis in agrin-deficient mutant mice. *Cell* 85, 525-535.
- Geiser, A.G., Letterio, J.J., Kulkarni, A.B., Karlsson, S., Roberts, A.B., Sporn, M.B., 1993. Transforming growth factor beta 1 (TGF-beta 1) controls expression of major histocompatibility genes in the postnatal mouse: aberrant histocompatibility antigen expression in the pathogenesis of the TGF-beta 1 null mouse phenotype. *Proceedings of the National Academy of Sciences of the United States of America* 90, 9944-9948.
- Gencer, B., Auer, R., de Rekeneire, N., Butler, J., Kalogeropoulos, A., Bauer, D.C., Kritchevsky, S.B., Miljkovic, I., Vittinghoff, E., Harris, T., Rodondi, N., 2016. Association between resistin levels and cardiovascular disease events in older adults: The health, aging and body composition study. *Atherosclerosis* 245, 181-186.
- Georgiou, G.P., Provatopoulou, X., Kalogera, E., Siasos, G., Menenakos, E., Zografos, G.C., Gounaris, A., 2016. Serum resistin is inversely related to breast cancer risk in premenopausal women. *Breast* 29, 163-169.
- Gerstein, H.C., Pare, G., Hess, S., Ford, R.J., Sjaarda, J., Raman, K., McQueen, M., Lee, S., Haenel, H., Steinberg, G.R., Investigators, O., 2017. Growth Differentiation Factor 15 as a Novel Biomarker for Metformin. *Diabetes care* 40, 280-283.
- Gertow, J., Ng, C.Z., Mamede Branca, R.M., Werngren, O., Du, L., Kjellqvist, S., Hemmingsson, P., Bruchfeld, A., MacLaughlin, H., Eriksson, P., Axelsson, J., Fisher, R.M., 2017. Altered Protein Composition of Subcutaneous Adipose Tissue in Chronic Kidney Disease. *Kidney international reports* 2, 1208-1218.
- Gezen-Ak, D., Dursun, E., Hanagasi, H., Bilgic, B., Lohman, E., Araz, O.S., Atasoy, I.L., Alaylioglu, M., Onal, B., Gurvit, H., Yilmazer, S., 2013. BDNF, TNFalpha, HSP90, CFH, and IL-10 serum levels in patients with early or late onset Alzheimer's disease or mild cognitive impairment. *Journal of Alzheimer's disease : JAD* 37, 185-195.
- Ghosh, A.K., Rai, R., Park, K.E., Eren, M., Miyata, T., Wilsbacher, L.D., Vaughan, D.E., 2016. A small molecule inhibitor of PAI-1 protects against doxorubicin-induced cellular senescence. *Oncotarget* 7, 72443-72457.
- Giacomini, A., Ghedini, G.C., Presta, M., Ronca, R., 2018. Long pentraxin 3: A novel multifaceted player in cancer. *Biochimica et biophysica acta* 1869, 53-63.
- Gillum, M.P., 2018. Parsing the Potential Neuroendocrine Actions of FGF21 in Primates. *Endocrinology* 159, 1966-1970.

- Gilmore, K.J., Kirk, E.A., Doherty, T.J., Rice, C.L., 2017. Effect of very old age on anconeus motor unit loss and compensatory remodelling. *Muscle & nerve*.
- Gingras, J., Rassadi, S., Cooper, E., Ferns, M., 2002. Agrin plays an organizing role in the formation of sympathetic synapses. *J Cell Biol* 158, 1109-1118.
- Gingras, J., Rassadi, S., Cooper, E., Ferns, M., 2007. Synaptic transmission is impaired at neuronal autonomic synapses in agrin-null mice. *Developmental neurobiology* 67, 521-534.
- Giorgi, C., Danese, A., Missiroli, S., Patergnani, S., Pinton, P., 2018. Calcium Dynamics as a Machine for Decoding Signals. *Trends in cell biology*.
- Glass, D.J., Bowen, D.C., Stitt, T.N., Radziejewski, C., Bruno, J., Ryan, T.E., Gies, D.R., Shah, S., Mattsson, K., Burden, S.J., DiStefano, P.S., Valenzuela, D.M., DeChiara, T.M., Yancopoulos, G.D., 1996. Agrin acts via a MuSK receptor complex. *Cell* 85, 513-523.
- Glosse, P., Fajol, A., Hirche, F., Feger, M., Voelkl, J., Lang, F., Stangl, G.I., Foller, M., 2018. A high-fat diet stimulates fibroblast growth factor 23 formation in mice through TNFalpha upregulation. *Nutrition & diabetes* 8, 36.
- Gohar, A., Goncalves, I., Vrijenhoek, J., Haitjema, S., van Koeverden, I., Nilsson, J., de Borst, G.J., de Vries, J.P., Pasterkamp, G., den Ruijter, H.M., Bjorkbacka, H., de Jager, S.C.A., 2017. Circulating GDF-15 levels predict future secondary manifestations of cardiovascular disease explicitly in women but not men with atherosclerosis. *International journal of cardiology* 241, 430-436.
- Goiran, T., Duplan, E., Chami, M., Bourgeois, A., El Manaa, W., Rouland, L., Dunys, J., Lauritzen, I., You, H., Stambolic, V., Biferi, M.G., Barkats, M., Pimplikar, S.W., Sergeant, N., Colin, M., Morais, V.A., Pardossi-Piquard, R., Checler, F., Alves da Costa, C., 2018. beta-Amyloid Precursor Protein Intracellular Domain Controls Mitochondrial Function by Modulating Phosphatase and Tensin Homolog-Induced Kinase 1 Transcription in Cells and in Alzheimer Mice Models. *Biological psychiatry* 83, 416-427.
- Gomes, W.F., Lacerda, A.C., Mendonca, V.A., Arrieiro, A.N., Fonseca, S.F., Amorim, M.R., Teixeira, A.L., Teixeira, M.M., Miranda, A.S., Coimbra, C.C., Brito-Melo, G.E., 2014. Effect of exercise on the plasma BDNF levels in elderly women with knee osteoarthritis. *Rheumatology international* 34, 841-846.
- Gomez, A.M., Froemke, R.C., Burden, S.J., 2014. Synaptic plasticity and cognitive function are disrupted in the absence of Lrp4. *eLife* 3, e04287.
- Gong, X., Liu, Y., Yao, S., Zheng, J.F., Wan, F., Xiang, X.D., Chai, X.P., 2016. Correlation between adiponectin and hemorrhagic shock in mice. *Genetics and molecular research : GMR* 15.
- Gong, Y., Chippada-Venkata, U.D., Oh, W.K., 2014. Roles of matrix metalloproteinases and their natural inhibitors in prostate cancer progression. *Cancers* 6, 1298-1327.
- Gonzalez-Guerra, J.L., Castilla-Cortazar, I., Aguirre, G.A., Munoz, U., Martin-Estal, I., Avila-Gallego, E., Granada, M., Puche, J.E., Garcia-Villalon, A.L., 2017. Partial IGF-1 deficiency is sufficient to reduce heart contractibility, angiotensin II sensibility, and alter gene expression of structural and functional cardiac proteins. *PloS one* 12, e0181760.
- Gouveia, M.C., Vella, J.P., Cafeo, F.R., Affonso Fonseca, F.L., Bacci, M.R., 2016. Association between irisin and major chronic diseases: a review. *European review for medical and pharmacological sciences* 20, 4072-4077.
- Griesenauer, B., Paczesny, S., 2017. The ST2/IL-33 Axis in Immune Cells during Inflammatory Diseases. *Frontiers in immunology* 8, 475.
- Grinan-Ferre, C., Palomera-Avalos, V., Puigoriol-Illamola, D., Camins, A., Porquet, D., Pla, V., Aguado, F., Pallas, M., 2016. Behaviour and cognitive changes correlated with hippocampal neuroinflammation and neuronal markers in female SAMP8, a model of accelerated senescence. *Experimental gerontology* 80, 57-69.

- Groenendyk, J., Lee, D., Jung, J., Dyck, J.R., Lopaschuk, G.D., Agellon, L.B., Michalak, M., 2016. Inhibition of the Unfolded Protein Response Mechanism Prevents Cardiac Fibrosis. *PloS one* 11, e0159682.
- Groffen, A.J., Buskens, C.A., van Kuppevelt, T.H., Veerkamp, J.H., Monnens, L.A., van den Heuvel, L.P., 1998. Primary structure and high expression of human agrin in basement membranes of adult lung and kidney. *European journal of biochemistry* 254, 123-128.
- Gros, K., Parato, G., Pirkmajer, S., Mis, K., Podbregar, M., Grubic, Z., Lorenzon, P., Mars, T., 2014. Non-synaptic roles of acetylcholinesterase and agrin. *Journal of molecular neuroscience : MN* 53, 454-460.
- Grow, W.A., Ferns, M., Gordon, H., 1999. Agrin-independent activation of the agrin signal transduction pathway. *Journal of neurobiology* 40, 356-365.
- Guillory, B., Chen, J.A., Patel, S., Luo, J., Splenser, A., Mody, A., Ding, M., Baghaie, S., Anderson, B., Iankova, B., Halder, T., Hernandez, Y., Garcia, J.M., 2017. Deletion of ghrelin prevents aging-associated obesity and muscle dysfunction without affecting longevity. *Aging cell* 16, 859-869.
- Guiot, J., Henket, M., Corhay, J.L., Moermans, C., Louis, R., 2017. Sputum biomarkers in IPF: Evidence for raised gene expression and protein level of IGFBP-2, IL-8 and MMP-7. *PloS one* 12, e0171344.
- Gunawardene, P., Bermeo, S., Vidal, C., Al-Saedi, A., Chung, P., Boersma, D., Phu, S., Pokorski, I., Suriyaarachchi, P., Demontiero, O., Duque, G., 2016. Association Between Circulating Osteogenic Progenitor Cells and Disability and Frailty in Older Persons: The Nepean Osteoporosis and Frailty Study. *The journals of gerontology. Series A, Biological sciences and medical sciences* 71, 1124-1130.
- Gundemir, S., Colak, G., Tucholski, J., Johnson, G.V., 2012. Transglutaminase 2: a molecular Swiss army knife. *Biochimica et biophysica acta* 1823, 406-419.
- Guo, C., Zeng, X., Song, J., Zhang, M., Wang, H., Xu, X., Du, F., Chen, B., 2012. A soluble receptor for advanced glycation end-products inhibits hypoxia/reoxygenation-induced apoptosis in rat cardiomyocytes via the mitochondrial pathway. *International journal of molecular sciences* 13, 11923-11940.
- Guo, C.X., Jiang, X., Zeng, X.J., Wang, H.X., Li, H.H., Du, F.H., Chen, B.X., 2016. Soluble receptor for advanced glycation end-products protects against ischemia/reperfusion-induced myocardial apoptosis via regulating the ubiquitin proteasome system. *Free radical biology & medicine* 94, 17-26.
- Guo, H.F., Liu, S.X., Zhang, Y.J., Liu, Q.J., Hao, J., Gao, L.X., 2011. High mobility group box 1 induces synoviocyte proliferation in rheumatoid arthritis by activating the signal transducer and activator transcription signal pathway. *Clinical and experimental medicine* 11, 65-74.
- Guo, L., Nakamura, K., Lynch, J., Opas, M., Olson, E.N., Agellon, L.B., Michalak, M., 2002. Cardiac-specific expression of calcineurin reverses embryonic lethality in calreticulin-deficient mouse. *The Journal of biological chemistry* 277, 50776-50779.
- Guo, Q., Xu, L., Li, H., Sun, H., Liu, J., Wu, S., Zhou, B., 2017. Progranulin causes adipose insulin resistance via increased autophagy resulting from activated oxidative stress and endoplasmic reticulum stress. *Lipids in health and disease* 16, 25.
- Guo, Y., Zhuang, X., Huang, Z., Zou, J., Yang, D., Hu, X., Du, Z., Wang, L., Liao, X., 2018. Klotho protects the heart from hyperglycemia-induced injury by inactivating ROS and NF-kappaB-mediated inflammation both in vitro and in vivo. *Biochimica et biophysica acta* 1864, 238-251.
- Hackl, M., Heilmeier, U., Weilner, S., Grillari, J., 2016. Circulating microRNAs as novel biomarkers for bone diseases - Complex signatures for multifactorial diseases? *Molecular and cellular endocrinology* 432, 83-95.

- Haddad, M., Knani, I., Bouzidi, H., Berriche, O., Hammami, M., Kerkeni, M., 2016. Plasma Levels of Pentosidine, Carboxymethyl-Lysine, Soluble Receptor for Advanced Glycation End Products, and Metabolic Syndrome: The Metformin Effect. *Disease markers* 2016, 6248264.
- Haffner, D., Leifheit-Nestler, M., 2017. Extrarenal effects of FGF23. *Pediatric nephrology* 32, 753-765.
- Haghdoust-Yazdi, H., Sarookhani, M., Faraj, A., Fraidouni, N., Dargahi, T., Yaghoobidoust, M.H., Azhdari-Zarmehri, H., 2014. Evaluation of the association between blood homocysteine concentration and the degree of behavioral symptoms in the 6-hydroxydopamine-induced Parkinsonism in rat. *Pharmacology, biochemistry, and behavior* 124, 297-304.
- Hagiwara, H., Fallon, J.R., 2001. Shaping membrane architecture: agrins in and out of the synapse. *J Cell Biol* 153, F39-42.
- Haider, S., Grabovac, I., Winzer, E., Kapan, A., Schindler, K.E., Lackinger, C., Titze, S., Dorner, T.E., 2017. Change in inflammatory parameters in prefrail and frail persons obtaining physical training and nutritional support provided by lay volunteers: A randomized controlled trial. *PloS one* 12, e0185879.
- Hallengren, E., Almgren, P., Engstrom, G., Hedblad, B., Persson, M., Suhr, J., Bergmann, A., Melander, O., 2014. Fasting levels of high-sensitivity growth hormone predict cardiovascular morbidity and mortality: the Malmo Diet and Cancer study. *Journal of the American College of Cardiology* 64, 1452-1460.
- Hamrick, M.W., Dukes, A., Arounleut, P., Davis, C., Periyasamy-Thandavan, S., Mork, S., Herberg, S., Johnson, M.H., Isales, C.M., Hill, W.D., Otvos, L., Jr., Belin de Chantemele, E.J., 2015. The adipokine leptin mediates muscle- and liver-derived IGF-1 in aged mice. *Experimental gerontology* 70, 92-96.
- Han, S.H., Choi, S.H., Cho, B.J., Lee, Y., Lim, S., Park, Y.J., Moon, M.K., Lee, H.K., Kang, S.W., Han, D.S., Kim, Y.B., Jang, H.C., Park, K.S., 2010. Serum fibroblast growth factor-21 concentration is associated with residual renal function and insulin resistance in end-stage renal disease patients receiving long-term peritoneal dialysis. *Metabolism: clinical and experimental* 59, 1656-1662.
- Handayaningsih, A.E., Takahashi, M., Fukuoka, H., Iguchi, G., Nishizawa, H., Yamamoto, M., Suda, K., Takahashi, Y., 2012. IGF-I enhances cellular senescence via the reactive oxygen species-p53 pathway. *Biochemical and biophysical research communications* 425, 478-484.
- Hanudel, M., Juppner, H., Salusky, I.B., 2016. Fibroblast growth factor 23: fueling the fire. *Kidney international* 90, 928-930.
- Happonen, K.E., Saxne, T., Aspberg, A., Morgelin, M., Heinigard, D., Blom, A.M., 2010. Regulation of complement by cartilage oligomeric matrix protein allows for a novel molecular diagnostic principle in rheumatoid arthritis. *Arthritis and rheumatism* 62, 3574-3583.
- Harry, G.J., 2013. Microglia during development and aging. *Pharmacology & therapeutics* 139, 313-326.
- Hartman, K.G., McKnight, L.E., Liriano, M.A., Weber, D.J., 2013. The evolution of S100B inhibitors for the treatment of malignant melanoma. *Future medicinal chemistry* 5, 97-109.
- Hatada, T., Wada, H., Nobori, T., Okabayashi, K., Maruyama, K., Abe, Y., Uemoto, S., Yamada, S., Maruyama, I., 2005. Plasma concentrations and importance of High Mobility Group Box protein in the prognosis of organ failure in patients with disseminated intravascular coagulation. *Thrombosis and haemostasis* 94, 975-979.
- Hatse, S., Brouwers, B., Dalmaso, B., Laenen, A., Kenis, C., Schoffski, P., Wildiers, H., 2014. Circulating MicroRNAs as easy-to-measure aging biomarkers in older breast cancer

- patients: correlation with chronological age but not with fitness/frailty status. *PLoS one* 9, e110644.
- Haudenschild, D.R., Chen, J., Pang, N., Steklov, N., Grogan, S.P., Lotz, M.K., D'Lima, D.D., 2011. Vimentin contributes to changes in chondrocyte stiffness in osteoarthritis. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society* 29, 20-25.
- Hausser, H.J., Ruegg, M.A., Brenner, R.E., Ksiazek, I., 2007. Agrin is highly expressed by chondrocytes and is required for normal growth. *Histochemistry and cell biology* 127, 363-374.
- Hays, H., 1984. Home care of the frail elderly and the terminally ill. *Canadian family physician Medecin de famille canadien* 30, 665-667.
- Haziot, A., Ferrero, E., Kontgen, F., Hijiya, N., Yamamoto, S., Silver, J., Stewart, C.L., Goyert, S.M., 1996. Resistance to endotoxin shock and reduced dissemination of gram-negative bacteria in CD14-deficient mice. *Immunity* 4, 407-414.
- He, L., Deng, L., Zhang, Q., Guo, J., Zhou, J., Song, W., Yuan, F., 2017a. Diagnostic Value of CK-18, FGF-21, and Related Biomarker Panel in Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. *BioMed research international* 2017, 9729107.
- He, X., Shen, Y., Ma, X., Ying, L., Peng, J., Pan, X., Bao, Y., Zhou, J., 2018. The association of serum FGF23 and non-alcoholic fatty liver disease is independent of vitamin D in type 2 diabetes patients. *Clinical and experimental pharmacology & physiology* 45, 668-674.
- He, Z., Tang, Y., Qin, C., 2017b. Increased circulating leukocyte-derived microparticles in ischemic cerebrovascular disease. *Thrombosis research* 154, 19-25.
- Hearps, A.C., Martin, G.E., Angelovich, T.A., Cheng, W.J., Maisa, A., Landay, A.L., Jaworowski, A., Crowe, S.M., 2012. Aging is associated with chronic innate immune activation and dysregulation of monocyte phenotype and function. *Aging cell* 11, 867-875.
- Heier, C.R., Fiorillo, A.A., Chaisson, E., Gordish-Dressman, H., Hathout, Y., Damsker, J.M., Hoffman, E.P., Conklin, L.S., 2016. Identification of Pathway-Specific Serum Biomarkers of Response to Glucocorticoid and Infliximab Treatment in Children with Inflammatory Bowel Disease. *Clinical and translational gastroenterology* 7, e192.
- Hensel, N., Schon, A., Konen, T., Lubben, V., Forthmann, B., Baron, O., Grothe, C., Leifheit-Nestler, M., Claus, P., Haffner, D., 2016. Fibroblast growth factor 23 signaling in hippocampal cells: impact on neuronal morphology and synaptic density. *Journal of neurochemistry* 137, 756-769.
- Heringlake, M., Charitos, E.I., Erber, K., Berggreen, A.E., Heinze, H., Paarmann, H., 2016. Preoperative plasma growth-differentiation factor-15 for prediction of acute kidney injury in patients undergoing cardiac surgery. *Critical care* 20, 317.
- Hettwer, S., Dahinden, P., Kucsera, S., Farina, C., Ahmed, S., Fariello, R., Drey, M., Sieber, C.C., Vrijbloed, J.W., 2013. Elevated levels of a C-terminal agrin fragment identifies a new subset of sarcopenia patients. *Experimental gerontology* 48, 69-75.
- Hettwer, S., Lin, S., Kucsera, S., Haubitz, M., Oliveri, F., Fariello, R.G., Ruegg, M.A., Vrijbloed, J.W., 2014. Injection of a soluble fragment of neural agrin (NT-1654) considerably improves the muscle pathology caused by the disassembly of the neuromuscular junction. *PLoS one* 9, e88739.
- Hew-Butler, T., Landis-Piwowar, K., Byrd, G., Seimer, M., Seigneurie, N., Byrd, B., Muzik, O., 2015. Plasma irisin in runners and nonrunners: no favorable metabolic associations in humans. *Physiological reports* 3.
- Hildenbrand, R., Gandhari, M., Stroebel, P., Marx, A., Allgayer, H., Arens, N., 2008. The urokinase-system--role of cell proliferation and apoptosis. *Histology and histopathology* 23, 227-236.

- Hilgenberg, L.G., Hoover, C.L., Smith, M.A., 1999. Evidence of an agrin receptor in cortical neurons. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 19, 7384-7393.
- Hoch, W., 1999. Formation of the neuromuscular junction. Agrin and its unusual receptors. *European journal of biochemistry* 265, 1-10.
- Hodes, R.J., 1994. Frailty and disability: can growth hormone or other trophic agents make a difference? *Journal of the American Geriatrics Society* 42, 1208-1211.
- Hodjat, M., Haller, H., Dumler, I., Kiyani, Y., 2013. Urokinase receptor mediates doxorubicin-induced vascular smooth muscle cell senescence via proteasomal degradation of TRF2. *Journal of vascular research* 50, 109-123.
- Hofmann, M., Halper, B., Oesen, S., Franzke, B., Stuparits, P., Tschan, H., Bachl, N., Strasser, E.M., Quittan, M., Ploder, M., Wagner, K.H., Wessner, B., 2015. Serum concentrations of insulin-like growth factor-1, members of the TGF-beta superfamily and follistatin do not reflect different stages of dynapenia and sarcopenia in elderly women. *Experimental gerontology* 64, 35-45.
- Hohensinner, P.J., Takacs, N., Kaun, C., Thaler, B., Krychtiuk, K.A., Pfaffenberger, S., Aliabadi, A., Zuckermann, A., Huber, K., Wojta, J., 2017. Urokinase plasminogen activator protects cardiac myocytes from oxidative damage and apoptosis via hOGG1 induction. *Apoptosis : an international journal on programmed cell death* 22, 1048-1055.
- Holler, C.J., Taylor, G., McEachin, Z.T., Deng, Q., Watkins, W.J., Hudson, K., Easley, C.A., Hu, W.T., Hales, C.M., Rossoll, W., Bassell, G.J., Kukar, T., 2016. Trehalose upregulates progranulin expression in human and mouse models of GRN haploinsufficiency: a novel therapeutic lead to treat frontotemporal dementia. *Molecular neurodegeneration* 11, 46.
- Holly, M.K., Diaz, K., Smith, J.G., 2017. Defensins in Viral Infection and Pathogenesis. *Annual review of virology* 4, 369-391.
- Hong, J.H., Chung, H.K., Park, H.Y., Joung, K.H., Lee, J.H., Jung, J.G., Kim, K.S., Kim, H.J., Ku, B.J., Shong, M., 2014. GDF15 Is a Novel Biomarker for Impaired Fasting Glucose. *Diabetes & metabolism journal* 38, 472-479.
- Hong, S., Beja-Glasser, V.F., Nfonoyim, B.M., Frouin, A., Li, S., Ramakrishnan, S., Merry, K.M., Shi, Q., Rosenthal, A., Barres, B.A., Lemere, C.A., Selkoe, D.J., Stevens, B., 2016. Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science* 352, 712-716.
- Hong, Y.S., Moon, S.J., Joo, Y.B., Jeon, C.H., Cho, M.L., Ju, J.H., Oh, H.J., Heo, Y.J., Park, S.H., Kim, H.Y., Min, J.K., 2011. Measurement of interleukin-33 (IL-33) and IL-33 receptors (sST2 and ST2L) in patients with rheumatoid arthritis. *Journal of Korean medical science* 26, 1132-1139.
- Horiuchi, T., Sakata, N., Narumi, Y., Kimura, T., Hayashi, T., Nagano, K., Liu, K., Nishibori, M., Tsukita, S., Yamada, T., Katagiri, H., Shirakawa, R., Horiuchi, H., 2017. Metformin directly binds the alarmin HMGB1 and inhibits its proinflammatory activity. *The Journal of biological chemistry* 292, 8436-8446.
- Horstman, A.M., Dillon, E.L., Urban, R.J., Sheffield-Moore, M., 2012. The role of androgens and estrogens on healthy aging and longevity. *The journals of gerontology. Series A, Biological sciences and medical sciences* 67, 1140-1152.
- Hotta, K., Funahashi, T., Arita, Y., Takahashi, M., Matsuda, M., Okamoto, Y., Iwahashi, H., Kuriyama, H., Ouchi, N., Maeda, K., Nishida, M., Kihara, S., Sakai, N., Nakajima, T., Hasegawa, K., Muraguchi, M., Ohmoto, Y., Nakamura, T., Yamashita, S., Hanafusa, T., Matsuzawa, Y., 2000. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arteriosclerosis, thrombosis, and vascular biology* 20, 1595-1599.
- Hsieh, Y.Y., Shen, C.H., Huang, W.S., Chin, C.C., Kuo, Y.H., Hsieh, M.C., Yu, H.R., Chang, T.S., Lin, T.H., Chiu, Y.W., Chen, C.N., Kuo, H.C., Tung, S.Y., 2014. Resistin-induced

- stromal cell-derived factor-1 expression through Toll-like receptor 4 and activation of p38 MAPK/ NFkappaB signaling pathway in gastric cancer cells. *Journal of biomedical science* 21, 59.
- Hsu, B.G., Lee, C.J., Yang, C.F., Chen, Y.C., Wang, J.H., 2017a. High serum resistin levels are associated with peripheral artery disease in the hypertensive patients. *BMC cardiovascular disorders* 17, 80.
- Hsu, L.A., Wu, S., Juang, J.J., Chiang, F.T., Teng, M.S., Lin, J.F., Huang, H.L., Ko, Y.L., 2017b. Growth Differentiation Factor 15 May Predict Mortality of Peripheral and Coronary Artery Diseases and Correlate with Their Risk Factors. *Mediators of inflammation* 2017, 9398401.
- Hsuchou, H., Pan, W., Kastin, A.J., 2007. The fasting polypeptide FGF21 can enter brain from blood. *Peptides* 28, 2382-2386.
- Hu, F.Q., Qiao, T., Xie, X., Hu, R., Xiao, H.B., 2014. Knockdown of the inflammatory factor pentraxin-3 suppresses growth and invasion of lung adenocarcinoma through the AKT and NF-kappa B pathways. *Journal of biological regulators and homeostatic agents* 28, 649-657.
- Hu, G.X., Zhang, J., Tian, Y.G., Li, Y.H., Mou, L., Qiao, L.J., 2017. Diagnostic value of joint detection of homocysteine and RDW CV on acute myocardial infarction. *European review for medical and pharmacological sciences* 21, 4472.
- Hu, H., Wang, C., Jin, Y., Meng, Q., Liu, Q., Liu, K., Sun, H., 2016a. Alpha-lipoic acid defends homocysteine-induced endoplasmic reticulum and oxidative stress in HAECs. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie* 80, 63-72.
- Hu, M.C., Shi, M., Zhang, J., Quinones, H., Griffith, C., Kuro-o, M., Moe, O.W., 2011. Klotho deficiency causes vascular calcification in chronic kidney disease. *Journal of the American Society of Nephrology : JASN* 22, 124-136.
- Hu, W., Wang, R., Li, J., Zhang, J., Wang, W., 2016b. Association of irisin concentrations with the presence of diabetic nephropathy and retinopathy. *Annals of clinical biochemistry* 53, 67-74.
- Huang, D., Wang, Z., Tong, J., Wang, M., Wang, J., Xu, J., Bai, X., Li, H., Huang, Y., Wu, Y., Ma, Y., Yu, M., Huang, F., 2018. Long-term Changes in the Nigrostriatal Pathway in the MPTP Mouse Model of Parkinson's Disease. *Neuroscience* 369, 303-313.
- Huang, E.J., Reichardt, L.F., 2001. Neurotrophins: roles in neuronal development and function. *Annual review of neuroscience* 24, 677-736.
- Huang, T., Larsen, K.T., Moller, N.C., Ried-Larsen, M., Frandsen, U., Andersen, L.B., 2015a. Effects of a multi-component camp-based intervention on inflammatory markers and adipokines in children: A randomized controlled trial. *Preventive medicine* 81, 367-372.
- Huang, W.T., Akhter, H., Jiang, C., MacEwen, M., Ding, Q., Antony, V., Thannickal, V.J., Liu, R.M., 2015b. Plasminogen activator inhibitor 1, fibroblast apoptosis resistance, and aging-related susceptibility to lung fibrosis. *Experimental gerontology* 61, 62-75.
- Hubbard, R.E., O'Mahony, M.S., Calver, B.L., Woodhouse, K.W., 2008a. Nutrition, inflammation, and leptin levels in aging and frailty. *Journal of the American Geriatrics Society* 56, 279-284.
- Hubbard, R.E., O'Mahony, M.S., Calver, B.L., Woodhouse, K.W., 2008b. Plasma esterases and inflammation in ageing and frailty. *European journal of clinical pharmacology* 64, 895-900.
- Huh, J.H., Ahn, S.V., Choi, J.H., Koh, S.B., Chung, C.H., 2016. High Serum Irisin Level as an Independent Predictor of Diabetes Mellitus: A Longitudinal Population-Based Study. *Medicine* 95, e3742.
- Hui, T.H., McClelland, R.L., Allison, M.A., Rodriguez, C.J., Kronmal, R.A., Heckbert, S.R., Michos, E.D., Barter, P.J., Rye, K.A., Ong, K.L., 2018. The relationship of circulating

- fibroblast growth factor 21 levels with incident atrial fibrillation: The Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis* 269, 86-91.
- Hulejova, H., Andres Cerezo, L., Kuklova, M., Pecha, O., Vondracek, T., Pavelka, K., Vencovsky, J., Haluzik, M., Senolt, L., 2012. Novel adipokine fibroblast growth factor 21 is increased in rheumatoid arthritis. *Physiological research* 61, 489-494.
- Hunter, M.P., Ismail, N., Zhang, X., Aguda, B.D., Lee, E.J., Yu, L., Xiao, T., Schafer, J., Lee, M.L., Schmittgen, T.D., Nana-Sinkam, S.P., Jarjoura, D., Marsh, C.B., 2008. Detection of microRNA expression in human peripheral blood microvesicles. *PLoS one* 3, e3694.
- Huo, L.W., Ye, Y.L., Wang, G.W., Ye, Y.G., 2015. Fractalkine (CX3CL1): a biomarker reflecting symptomatic severity in patients with knee osteoarthritis. *Journal of investigative medicine : the official publication of the American Federation for Clinical Research* 63, 626-631.
- Hur, K.Y., 2014. Is GDF15 a Novel Biomarker to Predict the Development of Prediabetes or Diabetes? *Diabetes & metabolism journal* 38, 437-438.
- Husain, K., Hernandez, W., Ansari, R.A., Ferder, L., 2015. Inflammation, oxidative stress and renin angiotensin system in atherosclerosis. *World journal of biological chemistry* 6, 209-217.
- Hwang, N., Kwon, M.Y., Cha, J.B., Chung, S.W., Woo, J.M., 2016a. Tunicamycin-induced Endoplasmic Reticulum Stress Upregulates the Expression of Pentraxin 3 in Human Retinal Pigment Epithelial Cells. *Korean journal of ophthalmology : KJO* 30, 468-478.
- Hwang, Y.C., Jeon, W.S., Park, C.Y., Youn, B.S., 2016b. The ratio of skeletal muscle mass to visceral fat area is a main determinant linking circulating irisin to metabolic phenotype. *Cardiovascular diabetology* 15, 9.
- Hyun, Y.Y., Kim, H., Oh, Y.K., Oh, K.H., Ahn, C., Sung, S.A., Choi, K.H., Kim, S.W., Lee, K.B., Group, K.-C.S., 2018. High fibroblast growth factor 23 is associated with coronary calcification in patients with high adiponectin: analysis from the Korean Cohort Study for Outcome in Patients with Chronic Kidney Disease study. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*.
- Icli, A., Cure, E., Cumhuri Cure, M., Uslu, A.U., Balta, S., Arslan, S., Sakiz, D., Kucuk, A., 2016. Novel myokine: irisin may be an independent predictor for subclinical atherosclerosis in Behcet's disease. *Journal of investigative medicine : the official publication of the American Federation for Clinical Research* 64, 875-881.
- Ikeda, Y., Tajima, S., Izawa-Ishizawa, Y., Kihira, Y., Ishizawa, K., Yoshida, S., Aihara, K., Tsuchiya, K., Tamaki, T., 2013. Bovine milk-derived lactoferrin exerts proangiogenic effects in an Src-Akt-eNOS-dependent manner in response to ischemia. *Journal of cardiovascular pharmacology* 61, 423-429.
- Ikonomidis, I., Tzortzis, S., Tsantes, A., Ntai, K., Triantafyllidi, H., Trivilou, P., Katsimaglis, G., Dima, K., Parisis, J., Lekakis, J., 2017. The interplay between renin-angiotensin system activation, abnormal myocardial deformation and neurohumoral activation in hypertensive heart disease: a speckle tracking echocardiography study. *The international journal of cardiovascular imaging* 33, 323-329.
- lordache, F., Constantinescu, A., Andrei, E., Amuzescu, B., Halitzchi, F., Savu, L., Maniu, H., 2016. Electrophysiology, immunophenotype, and gene expression characterization of senescent and cryopreserved human amniotic fluid stem cells. *The journal of physiological sciences : JPS* 66, 463-476.
- Iram, T., Ramirez-Ortiz, Z., Byrne, M.H., Coleman, U.A., Kingery, N.D., Means, T.K., Frenkel, D., El Khoury, J., 2016. Megf10 Is a Receptor for C1Q That Mediates Clearance of Apoptotic Cells by Astrocytes. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 36, 5185-5192.

- Iroz, A., Couty, J.P., Postic, C., 2015. Hepatokines: unlocking the multi-organ network in metabolic diseases. *Diabetologia* 58, 1699-1703.
- Isakova, T., Cai, X., Lee, J., Xie, D., Wang, X., Mehta, R., Allen, N.B., Scialla, J.J., Pencina, M.J., Anderson, A.H., Talierco, J., Chen, J., Fischer, M.J., Steigerwalt, S.P., Leonard, M.B., Hsu, C.Y., de Boer, I.H., Kusek, J.W., Feldman, H.I., Wolf, M., Chronic Renal Insufficiency Cohort Study, I., 2018. Longitudinal FGF23 Trajectories and Mortality in Patients with CKD. *Journal of the American Society of Nephrology : JASN* 29, 579-590.
- Ishigami, A., 2010. [Anti-aging research using SMP30/GNL knockout mice]. *Yakugaku zasshi : Journal of the Pharmaceutical Society of Japan* 130, 25-28.
- Isogai, M., Oishi, K., Shimokawa, N., Yamaguchi, M., 1994. Expression of hepatic calcium-binding protein regucalcin mRNA is decreased by phenobarbital administration in rats. *Molecular and cellular biochemistry* 141, 15-19.
- Itoh, N., 2014. FGF21 as a Hepatokine, Adipokine, and Myokine in Metabolism and Diseases. *Frontiers in endocrinology* 5, 107.
- Itoh, N., Ohta, H., Nakayama, Y., Konishi, M., 2016. Roles of FGF Signals in Heart Development, Health, and Disease. *Frontiers in cell and developmental biology* 4, 110.
- Iwabu, M., Yamauchi, T., Okada-Iwabu, M., Sato, K., Nakagawa, T., Funata, M., Yamaguchi, M., Namiki, S., Nakayama, R., Tabata, M., Ogata, H., Kubota, N., Takamoto, I., Hayashi, Y.K., Yamauchi, N., Waki, H., Fukayama, M., Nishino, I., Tokuyama, K., Ueki, K., Oike, Y., Ishii, S., Hirose, K., Shimizu, T., Touhara, K., Kadowaki, T., 2010. Adiponectin and AdipoR1 regulate PGC-1alpha and mitochondria by Ca(2+) and AMPK/SIRT1. *Nature* 464, 1313-1319.
- Jabaudon, M., Berthelin, P., Pranal, T., Roszyk, L., Godet, T., Faure, J.S., Chabanne, R., Eisenmann, N., Lautrette, A., Belville, C., Blondonnet, R., Cayot, S., Gillart, T., Pascal, J., Skrzypczak, Y., Souweine, B., Blanchon, L., Sapin, V., Pereira, B., Constantin, J.M., 2018. Receptor for advanced glycation end-products and ARDS prediction: a multicentre observational study. *Scientific reports* 8, 2603.
- Jalali, S., Aghasi, M., Yeganeh, B., Mesaeli, N., 2008. Calreticulin regulates insulin receptor expression and its downstream PI3 Kinase/Akt signalling pathway. *Biochimica et biophysica acta* 1783, 2344-2351.
- Jang, H.B., Kim, H.J., Kang, J.H., Park, S.I., Park, K.H., Lee, H.J., 2017. Association of circulating irisin levels with metabolic and metabolite profiles of Korean adolescents. *Metabolism: clinical and experimental* 73, 100-108.
- Jedrychowski, M.P., Wrann, C.D., Paulo, J.A., Gerber, K.K., Szpyt, J., Robinson, M.M., Nair, K.S., Gygi, S.P., Spiegelman, B.M., 2015. Detection and Quantitation of Circulating Human Irisin by Tandem Mass Spectrometry. *Cell metabolism* 22, 734-740.
- Jenny, N.S., Arnold, A.M., Kuller, L.H., Tracy, R.P., Psaty, B.M., 2009. Associations of pentraxin 3 with cardiovascular disease and all-cause death: the Cardiovascular Health Study. *Arteriosclerosis, thrombosis, and vascular biology* 29, 594-599.
- Jeon, B., Kim, H.R., Kim, H., Chung, D.K., 2016. In vitro and in vivo downregulation of C3 by lipoteichoic acid isolated from *Lactobacillus plantarum* K8 suppressed cytokine-mediated complement system activation. *FEMS microbiology letters* 363.
- Jeyaseelan, S., Chu, H.W., Young, S.K., Freeman, M.W., Worthen, G.S., 2005. Distinct roles of pattern recognition receptors CD14 and Toll-like receptor 4 in acute lung injury. *Infection and immunity* 73, 1754-1763.
- Ji, X., Jia, L., Jia, J., Qi, L., 2012. Genetic association of urokinase-type plasminogen activator gene rs2227564 site polymorphism with sporadic Alzheimer's disease in the Han Chinese population. *Neural regeneration research* 7, 2377-2383.
- Jia, T., Choi, J., Ciccione, J., Henry, M., Mehdi, A., Martinez, J., Eymin, B., Subra, G., Coll, J.L., 2018. Heteromultivalent targeting of integrin alphavbeta3 and neuropilin 1 promotes cell survival via the activation of the IGF-1/insulin receptors. *Biomaterials* 155, 64-79.

- Jialal, I., Camacho, F., Nathoo, B., Tam, P., Pahwa, R., Wu, G.G., 2017. Fibroblast Growth Factor 23 Predicts Mortality and End-Stage Renal Disease in a Canadian Asian Population with Chronic Kidney Disease. *Nephron* 137, 190-196.
- Jiang, J., Trollor, J.N., Brown, D.A., Crawford, J.D., Thalamuthu, A., Smith, E., Breit, S.N., Liu, T., Brodaty, H., Baune, B.T., Sachdev, P.S., Wen, W., 2015a. An inverse relationship between serum macrophage inhibitory cytokine-1 levels and brain white matter integrity in community-dwelling older individuals. *Psychoneuroendocrinology* 62, 80-88.
- Jiang, J., Wen, W., Sachdev, P.S., 2016. Macrophage inhibitory cytokine-1/growth differentiation factor 15 as a marker of cognitive ageing and dementia. *Current opinion in psychiatry* 29, 181-186.
- Jiang, S.S., Chen, C.H., Tseng, K.Y., Tsai, F.Y., Wang, M.J., Chang, I.S., Lin, J.L., Lin, S., 2011. Gene expression profiling suggests a pathological role of human bone marrow-derived mesenchymal stem cells in aging-related skeletal diseases. *Aging* 3, 672-684.
- Jiang, X., Guo, C.X., Zeng, X.J., Li, H.H., Chen, B.X., Du, F.H., 2015b. A soluble receptor for advanced glycation end-products inhibits myocardial apoptosis induced by ischemia/reperfusion via the JAK2/STAT3 pathway. *Apoptosis : an international journal on programmed cell death* 20, 1033-1047.
- Jimenez-Sousa, M.A., Gomez-Moreno, A.Z., Pineda-Tenor, D., Medrano, L.M., Sanchez-Ruano, J.J., Fernandez-Rodriguez, A., Artaza-Varasa, T., Saura-Montalban, J., Vazquez-Moron, S., Ryan, P., Resino, S., 2017. CXCL9-11 polymorphisms are associated with liver fibrosis in patients with chronic hepatitis C: a cross-sectional study. *Clinical and translational medicine* 6, 26.
- Jin, T., Sun, Z., Chen, X., Wang, Y., Li, R., Ji, S., Zhao, Y., 2017. Serum Human Beta-Defensin-2 Is a Possible Biomarker for Monitoring Response to JAK Inhibitor in Psoriasis Patients. *Dermatology* 233, 164-169.
- Johnson, G.B., Riggs, B.L., Platt, J.L., 2004. A genetic basis for the "Adonis" phenotype of low adiposity and strong bones. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 18, 1282-1284.
- Jones, B.A., Beamer, M., Ahmed, S., 2010. Fractalkine/CX3CL1: a potential new target for inflammatory diseases. *Molecular interventions* 10, 263-270.
- Jorge-Ripper, C., Aleman, M.R., Ros, R., Aguilera, S., Gonzalez-Reimers, E., Espelosin, E., Santolaria, F., 2017. Prognostic value of acute delirium recovery in older adults. *Geriatrics & gerontology international* 17, 1161-1167.
- Jung, K.J., Lee, E.K., Kim, S.J., Song, C.W., Maruyama, N., Ishigami, A., Kim, N.D., Im, D.S., Yu, B.P., Chung, H.Y., 2015a. Anti-inflammatory activity of SMP30 modulates NF-kappaB through protein tyrosine kinase/phosphatase balance. *Journal of molecular medicine* 93, 343-356.
- Jung, S.H., Yang, D.H., Ahn, J.S., Kim, Y.K., Kim, H.J., Lee, J.J., 2015b. Serum lactate dehydrogenase with a systemic inflammation score is useful for predicting response and survival in patients with newly diagnosed diffuse large B-cell lymphoma. *Acta haematologica* 133, 10-17.
- Juranek, J.K., Daffu, G.K., Geddis, M.S., Li, H., Rosario, R., Kaplan, B.J., Kelly, L., Schmidt, A.M., 2016. Soluble RAGE Treatment Delays Progression of Amyotrophic Lateral Sclerosis in SOD1 Mice. *Frontiers in cellular neuroscience* 10, 117.
- Jury, E.C., Eldridge, J., Isenberg, D.A., Kabouridis, P.S., 2007. Agrin signalling contributes to cell activation and is overexpressed in T lymphocytes from lupus patients. *Journal of immunology* 179, 7975-7983.
- Jury, E.C., Kabouridis, P.S., 2010. New role for Agrin in T cells and its potential importance in immune system regulation. *Arthritis research & therapy* 12, 205.
- Kabadi, S.V., Stoica, B.A., Zimmer, D.B., Afanador, L., Duffy, K.B., Loane, D.J., Faden, A.I., 2015. S100B inhibition reduces behavioral and pathologic changes in experimental

- traumatic brain injury. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism* 35, 2010-2020.
- Kajihara, I., Jinnin, M., Yamane, K., Makino, T., Honda, N., Igata, T., Masuguchi, S., Fukushima, S., Okamoto, Y., Hasegawa, M., Fujimoto, M., Ihn, H., 2012. Increased accumulation of extracellular thrombospondin-2 due to low degradation activity stimulates type I collagen expression in scleroderma fibroblasts. *The American journal of pathology* 180, 703-714.
- Kalani, A., Kamat, P.K., Chaturvedi, P., Tyagi, S.C., Tyagi, N., 2014a. Curcumin-primed exosomes mitigate endothelial cell dysfunction during hyperhomocysteinemia. *Life sciences* 107, 1-7.
- Kalani, A., Kamat, P.K., Voor, M.J., Tyagi, S.C., Tyagi, N., 2014b. Mitochondrial epigenetics in bone remodeling during hyperhomocysteinemia. *Molecular and cellular biochemistry* 395, 89-98.
- Kalinkovich, A., Livshits, G., 2015. Sarcopenia--The search for emerging biomarkers. *Ageing research reviews* 22, 58-71.
- Kallio, J., Hamalainen, M., Luukkaala, T., Moilanen, E., Tammela, T.L., Kellokumpu-Lehtinen, P.L., 2017. Resistin and interleukin 6 as predictive factors for recurrence and long-term prognosis in renal cell cancer. *Urologic oncology* 35, 544 e525-544 e531.
- Kamalinia, G., Khodaghali, F., Atyabi, F., Amini, M., Shaerzadeh, F., Sharifzadeh, M., Dinarvand, R., 2013. Enhanced brain delivery of deferasirox-lactoferrin conjugates for iron chelation therapy in neurodegenerative disorders: in vitro and in vivo studies. *Molecular pharmaceutics* 10, 4418-4431.
- Kanbay, M., Vervloet, M., Cozzolino, M., Siriopol, D., Covic, A., Goldsmith, D., Solak, Y., 2017. Novel Faces of Fibroblast Growth Factor 23 (FGF23): Iron Deficiency, Inflammation, Insulin Resistance, Left Ventricular Hypertrophy, Proteinuria and Acute Kidney Injury. *Calcified tissue international* 100, 217-228.
- Kang, J.H., Lee, Y.Y., Yu, B.Y., Yang, B.S., Cho, K.H., Yoon, D.K., Roh, Y.K., 2005. Adiponectin induces growth arrest and apoptosis of MDA-MB-231 breast cancer cell. *Archives of pharmacal research* 28, 1263-1269.
- Karaduman, M., Bilici, A., Ozet, A., Sengul, A., Musabak, U., Alomeroglu, M., 2007. Tissue levels of adiponectin in breast cancer patients. *Medical oncology* 24, 361-366.
- Karakaya, M., Ceyhan-Birsoy, O., Beggs, A.H., Topaloglu, H., 2017. A Novel Missense Variant in the AGRN Gene; Congenital Myasthenic Syndrome Presenting With Head Drop. *Journal of clinical neuromuscular disease* 18, 147-151.
- Katayama, A., Nakatsuka, A., Eguchi, J., Murakami, K., Teshigawara, S., Kanzaki, M., Nunoue, T., Hida, K., Wada, N., Yasunaka, T., Ikeda, F., Takaki, A., Yamamoto, K., Kiyonari, H., Makino, H., Wada, J., 2015. Beneficial impact of Gpnmb and its significance as a biomarker in nonalcoholic steatohepatitis. *Scientific reports* 5, 16920.
- Katurabayashi, S., Kawano, H., Li, M., Nakano, S., Tatsumi, C., Kubota, K., Takasaki, K., Mishima, K., Fujiwara, M., Iwasaki, K., 2016. Overexpression of Swedish mutant APP in aged astrocytes attenuates excitatory synaptic transmission. *Physiological reports* 4.
- Kawase, R., Ohama, T., Matsuyama, A., Matsuwaki, T., Okada, T., Yamashita, T., Yuasa-Kawase, M., Nakaoka, H., Nakatani, K., Inagaki, M., Tsubakio-Yamamoto, K., Masuda, D., Nakagawa-Toyama, Y., Nishida, M., Ohmoto, Y., Nishihara, M., Komuro, I., Yamashita, S., 2013. Deletion of progranulin exacerbates atherosclerosis in ApoE knockout mice. *Cardiovascular research* 100, 125-133.
- Keeley, R.J., Hong, N.S., Fisher, A., McDonald, R.J., 2015. Co-morbid beta-amyloid toxicity and stroke produce impairments in an ambiguous context task in rats without any impairment in spatial working memory. *Neurobiology of learning and memory* 119, 42-51.
- Keipert, S., Ost, M., Johann, K., Imber, F., Jastroch, M., van Schothorst, E.M., Keijer, J., Klaus, S., 2014. Skeletal muscle mitochondrial uncoupling drives endocrine cross-talk through

- the induction of FGF21 as a myokine. *American journal of physiology. Endocrinology and metabolism* 306, E469-482.
- Kelesidis, I., Kelesidis, T., Mantzoros, C.S., 2006. Adiponectin and cancer: a systematic review. *British journal of cancer* 94, 1221-1225.
- Kelley, S.L., Lukk, T., Nair, S.K., Tapping, R.I., 2013. The crystal structure of human soluble CD14 reveals a bent solenoid with a hydrophobic amino-terminal pocket. *Journal of immunology* 190, 1304-1311.
- Kempf, T., Guba-Quint, A., Torgerson, J., Magnone, M.C., Haefliger, C., Bobadilla, M., Wollert, K.C., 2012. Growth differentiation factor 15 predicts future insulin resistance and impaired glucose control in obese nondiabetic individuals: results from the XENDOS trial. *European journal of endocrinology* 167, 671-678.
- Kerfoot, S.M., Lord, S.E., Bell, R.B., Gill, V., Robbins, S.M., Kubes, P., 2003. Human fractalkine mediates leukocyte adhesion but not capture under physiological shear conditions; a mechanism for selective monocyte recruitment. *European journal of immunology* 33, 729-739.
- Khairalla, A.S., Omer, S.A., Mahdavi, J., Aslam, A., Dufailu, O.A., Self, T., Jonsson, A.B., Georg, M., Sjolinder, H., Royer, P.J., Martinez-Pomares, L., Ghaemmaghami, A.M., Wooldridge, K.G., Oldfield, N.J., Ala'Aldeen, D.A., 2015. Nuclear trafficking, histone cleavage and induction of apoptosis by the meningococcal App and MspA autotransporters. *Cellular microbiology* 17, 1008-1020.
- Khan, A.A., Bose, C., Yam, L.S., Soloski, M.J., Rupp, F., 2001. Physiological regulation of the immunological synapse by agrin. *Science* 292, 1681-1686.
- Khan, S.S., Shah, S.J., Klyachko, E., Baldridge, A.S., Eren, M., Place, A.T., Aviv, A., Puterman, E., Lloyd-Jones, D.M., Heiman, M., Miyata, T., Gupta, S., Shapiro, A.D., Vaughan, D.E., 2017. A null mutation in SERPINE1 protects against biological aging in humans. *Science advances* 3, eaao1617.
- Kilic, N., Dagli, N., Aydin, S., Erman, F., Bek, Y., Akin, O., Kilic, S.S., Erdemli, H.K., Alacam, H., 2017. Saliva/serum ghrelin, obestatin and homocysteine levels in patients with ischaemic heart disease. *Cardiovascular journal of Africa* 28, 159-164.
- Kim, A.M., Somayaji, V.R., Dong, J.Q., Rolph, T.P., Weng, Y., Chabot, J.R., Gropp, K.E., Talukdar, S., Calle, R.A., 2017a. Once-weekly administration of a long-acting fibroblast growth factor 21 analogue modulates lipids, bone turnover markers, blood pressure and body weight differently in obese people with hypertriglyceridaemia and in non-human primates. *Diabetes, obesity & metabolism* 19, 1762-1772.
- Kim, E.K., Lee, S.H., Jhun, J.Y., Byun, J.K., Jeong, J.H., Lee, S.Y., Kim, J.K., Choi, J.Y., Cho, M.L., 2016a. Metformin Prevents Fatty Liver and Improves Balance of White/Brown Adipose in an Obesity Mouse Model by Inducing FGF21. *Mediators of inflammation* 2016, 5813030.
- Kim, J.H., Hwang, K.H., Park, K.S., Kong, I.D., Cha, S.K., 2015a. Biological Role of Anti-aging Protein Klotho. *Journal of lifestyle medicine* 5, 1-6.
- Kim, J.S., Baek, S.J., Sali, T., Eling, T.E., 2005. The conventional nonsteroidal anti-inflammatory drug sulindac sulfide arrests ovarian cancer cell growth via the expression of NAG-1/MIC-1/GDF-15. *Molecular cancer therapeutics* 4, 487-493.
- Kim, K.H., Kim, D.H., Jeong, H.J., Ryu, J.S., Kim, Y.J., Oh, J.Y., Kim, M.K., Wee, W.R., 2017b. Effects of subconjunctival administration of anti-high mobility group box 1 on dry eye in a mouse model of Sjgren's syndrome. *PloS one* 12, e0183678.
- Kim, M.H., Park, J.S., Jung, J.W., Byun, K.W., Kang, K.S., Lee, Y.S., 2011. Daidzein supplementation prevents non-alcoholic fatty liver disease through alternation of hepatic gene expression profiles and adipocyte metabolism. *International journal of obesity* 35, 1019-1030.

- Kim, M.S., Lee, G.H., Kim, Y.M., Lee, B.W., Nam, H.Y., Sim, U.C., Choo, S.J., Yu, S.W., Kim, J.J., Kim Kwon, Y., Who Kim, S., 2017c. Angiotensin II Causes Apoptosis of Adult Hippocampal Neural Stem Cells and Memory Impairment Through the Action on AMPK-PGC1alpha Signaling in Heart Failure. *Stem cells translational medicine* 6, 1491-1503.
- Kim, N., Stiegler, A.L., Cameron, T.O., Hallock, P.T., Gomez, A.M., Huang, J.H., Hubbard, S.R., Dustin, M.L., Burden, S.J., 2008a. Lrp4 is a receptor for Agrin and forms a complex with MuSK. *Cell* 135, 334-342.
- Kim, S.H., Kim, K.H., Kim, H.K., Kim, M.J., Back, S.H., Konishi, M., Itoh, N., Lee, M.S., 2015b. Fibroblast growth factor 21 participates in adaptation to endoplasmic reticulum stress and attenuates obesity-induced hepatic metabolic stress. *Diabetologia* 58, 809-818.
- Kim, S.H., Park, H.S., Hong, M.J., Yoo, J.Y., Lee, H., Lee, J.A., Hur, J., Kwon, D.Y., Kim, M.S., 2016b. Tongqiaohuoxue decoction ameliorates obesity-induced inflammation and the prothrombotic state by regulating adiponectin and plasminogen activator inhibitor-1. *Journal of ethnopharmacology* 192, 201-209.
- Kim, S.J., Cheresh, P., Eren, M., Jablonski, R.P., Yeldandi, A., Ridge, K.M., Budinger, G.R.S., Kim, D.H., Wolf, M., Vaughan, D.E., Kamp, D.W., 2017d. Klotho, an antiaging molecule, attenuates oxidant-induced alveolar epithelial cell mtDNA damage and apoptosis. *American journal of physiology. Lung cellular and molecular physiology* 313, L16-L26.
- Kim, T.S., Lim, H.K., Lee, J.Y., Kim, D.J., Park, S., Lee, C., Lee, C.U., 2008b. Changes in the levels of plasma soluble fractalkine in patients with mild cognitive impairment and Alzheimer's disease. *Neuroscience letters* 436, 196-200.
- Kim, Y.H., Lee, E.K., Park, S.A., Kim, N.H., Kim, C.W., 2012. Proteomic analysis of plasma from a Tau transgenic mouse. *International journal of developmental neuroscience : the official journal of the International Society for Developmental Neuroscience* 30, 277-283.
- Kim, Y.S., Lee, K.J., Kim, H., 2017e. Serum tumour necrosis factor-alpha and interleukin-6 levels in Alzheimer's disease and mild cognitive impairment. *Psychogeriatrics : the official journal of the Japanese Psychogeriatric Society* 17, 224-230.
- Kimura, Y., Izumiya, Y., Hanatani, S., Yamamoto, E., Kusaka, H., Tokitsu, T., Takashio, S., Sakamoto, K., Tsujita, K., Tanaka, T., Yamamuro, M., Kojima, S., Tayama, S., Kaikita, K., Hokimoto, S., Ogawa, H., 2016. High serum levels of thrombospondin-2 correlate with poor prognosis of patients with heart failure with preserved ejection fraction. *Heart and vessels* 31, 52-59.
- Kinoshita, S., Kawai, M., 2016. The FGF23/KLOTHO Regulatory Network and Its Roles in Human Disorders. *Vitamins and hormones* 101, 151-174.
- Kireev, R.A., Vara, E., Tresguerres, J.A., 2013. Growth hormone and melatonin prevent age-related alteration in apoptosis processes in the dentate gyrus of male rats. *Biogerontology* 14, 431-442.
- Knott, M.E., Minatta, J.N., Roulet, L., Gueglio, G., Pasik, L., Ranuncolo, S.M., Nunez, M., Puricelli, L., De Lorenzo, M.S., 2016. Circulating Fibroblast Growth Factor 21 (Fgf21) as Diagnostic and Prognostic Biomarker in Renal Cancer. *Journal of molecular biomarkers & diagnosis* 1.
- Ko, B.J., Park, K.H., Shin, S., Zaichenko, L., Davis, C.R., Crowell, J.A., Joung, H., Mantzoros, C.S., 2016. Diet quality and diet patterns in relation to circulating cardiometabolic biomarkers. *Clinical nutrition* 35, 484-490.
- Ko, T.M., Kuo, H.C., Chang, J.S., Chen, S.P., Liu, Y.M., Chen, H.W., Tsai, F.J., Lee, Y.C., Chen, C.H., Wu, J.Y., Chen, Y.T., 2015. CXCL10/IP-10 is a biomarker and mediator for Kawasaki disease. *Circulation research* 116, 876-883.
- Ko, Y.B., Kim, B.R., Nam, S.L., Yang, J.B., Park, S.Y., Rho, S.B., 2014. High-mobility group box 1 (HMGB1) protein regulates tumor-associated cell migration through the interaction with BTB domain. *Cellular signalling* 26, 777-783.

- Kobashi, C., Urakaze, M., Kishida, M., Kibayashi, E., Kobayashi, H., Kihara, S., Funahashi, T., Takata, M., Temaru, R., Sato, A., Yamazaki, K., Nakamura, N., Kobayashi, M., 2005. Adiponectin inhibits endothelial synthesis of interleukin-8. *Circulation research* 97, 1245-1252.
- Kobayashi, H., Ouchi, N., Kihara, S., Walsh, K., Kumada, M., Abe, Y., Funahashi, T., Matsuzawa, Y., 2004. Selective suppression of endothelial cell apoptosis by the high molecular weight form of adiponectin. *Circulation research* 94, e27-31.
- Koene, S., de Laat, P., van Tienoven, D.H., Weijers, G., Vriens, D., Sweep, F.C., Timmermans, J., Kapusta, L., Janssen, M.C., Smeitink, J.A., 2015. Serum GDF15 Levels Correlate to Mitochondrial Disease Severity and Myocardial Strain, but Not to Disease Progression in Adult m.3243A>G Carriers. *JIMD reports* 24, 69-81.
- Koh, T.J., Bryer, S.C., Pucci, A.M., Sisson, T.H., 2005. Mice deficient in plasminogen activator inhibitor-1 have improved skeletal muscle regeneration. *American journal of physiology. Cell physiology* 289, C217-223.
- Kohara, M., Masuda, T., Shiizaki, K., Akimoto, T., Watanabe, Y., Honma, S., Sekiguchi, C., Miyazawa, Y., Kusano, E., Kanda, Y., Asano, Y., Kuro, O.M., Nagata, D., 2017. Association between circulating fibroblast growth factor 21 and mortality in end-stage renal disease. *PLoS one* 12, e0178971.
- Kokkinos, J., Tang, S., Rye, K.A., Ong, K.L., 2017. The role of fibroblast growth factor 21 in atherosclerosis. *Atherosclerosis* 257, 259-265.
- Kolbinger, F., Loesche, C., Valentin, M.A., Jiang, X., Cheng, Y., Jarvis, P., Peters, T., Calonder, C., Bruin, G., Polus, F., Aigner, B., Lee, D.M., Bodenlenz, M., Sinner, F., Pieber, T.R., Patel, D.D., 2017. beta-Defensin 2 is a responsive biomarker of IL-17A-driven skin pathology in patients with psoriasis. *The Journal of allergy and clinical immunology* 139, 923-932 e928.
- Koot, B.G., van der Baan-Slootweg, O.H., Bohte, A.E., Nederveen, A.J., van Werven, J.R., Tamminga-Smeulders, C.L., Merkus, M.P., Schaap, F.G., Jansen, P.L., Stoker, J., Benninga, M.A., 2013. Accuracy of prediction scores and novel biomarkers for predicting nonalcoholic fatty liver disease in obese children. *Obesity* 21, 583-590.
- Korbelik, M., Banath, J., Saw, K.M., Zhang, W., Ciplys, E., 2015. Calreticulin as cancer treatment adjuvant: combination with photodynamic therapy and photodynamic therapy-generated vaccines. *Frontiers in oncology* 5, 15.
- Korner, A., Kratzsch, J., Gausche, R., Schaab, M., Erbs, S., Kiess, W., 2007. New predictors of the metabolic syndrome in children--role of adipocytokines. *Pediatric research* 61, 640-645.
- Korolczuk, A., Beltowski, J., 2017. Progranulin, a New Adipokine at the Crossroads of Metabolic Syndrome, Diabetes, Dyslipidemia and Hypertension. *Current pharmaceutical design* 23, 1533-1539.
- Kortlever, R.M., Bernards, R., 2006. Senescence, wound healing and cancer: the PAI-1 connection. *Cell cycle* 5, 2697-2703.
- Kosi-Trebotic, L., Thomas, A., Harreiter, J., Chmelik, M., Trattnig, S., Kautzky-Willer, A., 2017. Gliptin therapy reduces hepatic and myocardial fat in type 2 diabetic patients. *European journal of clinical investigation* 47, 829-838.
- Kovesdy, C.P., Quarles, L.D., 2016. FGF23 from bench to bedside. *American journal of physiology. Renal physiology* 310, F1168-1174.
- Krabbe, K.S., Nielsen, A.R., Krogh-Madsen, R., Plomgaard, P., Rasmussen, P., Erikstrup, C., Fischer, C.P., Lindegaard, B., Petersen, A.M., Taudorf, S., Secher, N.H., Pilegaard, H., Bruunsgaard, H., Pedersen, B.K., 2007. Brain-derived neurotrophic factor (BDNF) and type 2 diabetes. *Diabetologia* 50, 431-438.
- Kraemer, R.R., Goldfarb, A.H., Reeves, G.V., Meachum, W.A., Castracane, V.D., 2016. Effects of partial vascular occlusion on irisin responses to loaded muscle contractions. *Applied*

- physiology, nutrition, and metabolism = *Physiologie appliquee, nutrition et metabolisme* 41, 332-334.
- Krautbauer, S., Rein-Fischboeck, L., Haberl, E.M., Pohl, R., Wiest, R., Buechler, C., 2018. Circulating fibroblast growth factor 21 in patients with liver cirrhosis. *Clinical and experimental medicine* 18, 63-69.
- Krawczyk, M., Zimmermann, S., Hess, G., Holz, R., Dauer, M., Raedle, J., Lammert, F., Grunhage, F., 2017. Panel of three novel serum markers predicts liver stiffness and fibrosis stages in patients with chronic liver disease. *PLoS one* 12, e0173506.
- Kreis, S., Schonfeld, H.J., Melchior, C., Steiner, B., Kieffer, N., 2005. The intermediate filament protein vimentin binds specifically to a recombinant integrin $\alpha 2/\beta 1$ cytoplasmic tail complex and co-localizes with native $\alpha 2/\beta 1$ in endothelial cell focal adhesions. *Experimental cell research* 305, 110-121.
- Kriegelstein, K., Miyazono, K., ten Dijke, P., Unsicker, K., 2012. TGF- β in aging and disease. *Cell and tissue research* 347, 5-9.
- Krychtiuk, K.A., Stojkovic, S., Lenz, M., Brekalo, M., Huber, K., Wojta, J., Heinz, G., Demyanets, S., Speidl, W.S., 2018. Predictive value of low interleukin-33 in critically ill patients. *Cytokine* 103, 109-113.
- Ksiazek, I., Burkhardt, C., Lin, S., Seddik, R., Maj, M., Bezakova, G., Jucker, M., Arber, S., Caroni, P., Sanes, J.R., Bettler, B., Ruegg, M.A., 2007. Synapse loss in cortex of agrin-deficient mice after genetic rescue of perinatal death. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 27, 7183-7195.
- Ku, N.O., Liao, J., Omary, M.B., 1997. Apoptosis generates stable fragments of human type I keratins. *The Journal of biological chemistry* 272, 33197-33203.
- Ku, N.O., Strnad, P., Bantel, H., Omary, M.B., 2016. Keratins: Biomarkers and modulators of apoptotic and necrotic cell death in the liver. *Hepatology* 64, 966-976.
- Kubota, N., Terauchi, Y., Yamauchi, T., Kubota, T., Moroi, M., Matsui, J., Eto, K., Yamashita, T., Kamon, J., Satoh, H., Yano, W., Froguel, P., Nagai, R., Kimura, S., Kadowaki, T., Noda, T., 2002. Disruption of adiponectin causes insulin resistance and neointimal formation. *The Journal of biological chemistry* 277, 25863-25866.
- Kullak-Ublick, G.A., Andrade, R.J., Merz, M., End, P., Benesic, A., Gerbes, A.L., Aithal, G.P., 2017. Drug-induced liver injury: recent advances in diagnosis and risk assessment. *Gut* 66, 1154-1164.
- Kumada, M., Kihara, S., Sumitsuji, S., Kawamoto, T., Matsumoto, S., Ouchi, N., Arita, Y., Okamoto, Y., Shimomura, I., Hiraoka, H., Nakamura, T., Funahashi, T., Matsuzawa, Y., Osaka, C.A.D.S.G.C.a.d., 2003. Association of hypoalbuminemia with coronary artery disease in men. *Arteriosclerosis, thrombosis, and vascular biology* 23, 85-89.
- Kumagai, K., Tabu, K., Sasaki, F., Takami, Y., Morinaga, Y., Mawatari, S., Hashimoto, S., Tanoue, S., Kanmura, S., Tamai, T., Moriuchi, A., Uto, H., Tsubouchi, H., Ido, A., 2015. Glycoprotein Nonmetastatic Melanoma B (Gpnmb)-Positive Macrophages Contribute to the Balance between Fibrosis and Fibrolysis during the Repair of Acute Liver Injury in Mice. *PLoS one* 10, e0143413.
- Kumar, P., Millischer, V., Villaescusa, J.C., Nilsson, I.A.K., Ostenson, C.G., Schalling, M., Osby, U., Lavebratt, C., 2017. Plasma GDF15 level is elevated in psychosis and inversely correlated with severity. *Scientific reports* 7, 7906.
- Kumemura, H., Harada, M., Yanagimoto, C., Koga, H., Kawaguchi, T., Hanada, S., Taniguchi, E., Ueno, T., Sata, M., 2008. Mutation in keratin 18 induces mitochondrial fragmentation in liver-derived epithelial cells. *Biochemical and biophysical research communications* 367, 33-40.
- Kunamneni, A., Ravuri, B.D., Saisha, V., Ellaiah, P., Prabhakar, T., 2008. Urokinase-a very popular cardiovascular agent. *Recent patents on cardiovascular drug discovery* 3, 45-58.

- Kuo, Y.C., Tsao, C.W., 2017. Neuroprotection against apoptosis of SK-N-MC cells using RMP-7- and lactoferrin-grafted liposomes carrying quercetin. *International journal of nanomedicine* 12, 2857-2869.
- Kuro-o, M., Matsumura, Y., Aizawa, H., Kawaguchi, H., Suga, T., Utsugi, T., Ohyama, Y., Kurabayashi, M., Kaname, T., Kume, E., Iwasaki, H., Iida, A., Shiraki-Iida, T., Nishikawa, S., Nagai, R., Nabeshima, Y.I., 1997. Mutation of the mouse *klotho* gene leads to a syndrome resembling ageing. *Nature* 390, 45-51.
- Kuro, O.M., 2017. The FGF23 and *Klotho* system beyond mineral metabolism. *Clinical and experimental nephrology* 21, 64-69.
- Kuro, O.M., 2018. *Klotho* and endocrine fibroblast growth factors: marker of chronic kidney disease progression and cardiovascular complications? *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*.
- Kuster, O.C., Laptinskaya, D., Fissler, P., Schnack, C., Zugel, M., Nold, V., Thurm, F., Pleiner, S., Karabatsiakakis, A., von Einem, B., Weydt, P., Liesener, A., Borta, A., Woll, A., Hengerer, B., Kolassa, I.T., von Arnim, C.A.F., 2017. Novel Blood-Based Biomarkers of Cognition, Stress, and Physical or Cognitive Training in Older Adults at Risk of Dementia: Preliminary Evidence for a Role of BDNF, Irisin, and the Kynurenine Pathway. *Journal of Alzheimer's disease : JAD* 59, 1097-1111.
- Kutilek, S., 2017. Burosumab: A new drug to treat hypophosphatemic rickets. *Sudanese journal of paediatrics* 17, 71-73.
- Kwack, K.H., Lee, H.W., 2017. Progranulin Inhibits Human T Lymphocyte Proliferation by Inducing the Formation of Regulatory T Lymphocytes. *Mediators of inflammation* 2017, 7682083.
- Kwak, H.I., Kang, H., Dave, J.M., Mendoza, E.A., Su, S.C., Maxwell, S.A., Bayless, K.J., 2012. Calpain-mediated vimentin cleavage occurs upstream of MT1-MMP membrane translocation to facilitate endothelial sprout initiation. *Angiogenesis* 15, 287-303.
- Kwan, J., Horsfield, G., Bryant, T., Gawne-Cain, M., Durward, G., Byrne, C.D., Englyst, N.A., 2013. IL-6 is a predictive biomarker for stroke associated infection and future mortality in the elderly after an ischemic stroke. *Experimental gerontology* 48, 960-965.
- Lai, H.Y., Chang, H.T., Lee, Y.L., Hwang, S.J., 2014. Association between inflammatory markers and frailty in institutionalized older men. *Maturitas* 79, 329-333.
- Lai, W., Xie, X., Zhang, X., Wang, Y., Chu, K., Brown, J., Chen, L., Hong, G., 2017. Inhibition of Complement Drives Increase in Early Growth Response Proteins and Neuroprotection Mediated by Salidroside After Cerebral Ischemia. *Inflammation*.
- Lam, V., Albrecht, M.A., Takechi, R., Giles, C., James, A.P., Foster, J.K., Mamo, J.C., 2013. The Serum Concentration of the Calcium Binding Protein S100B is Positively Associated with Cognitive Performance in Older Adults. *Frontiers in aging neuroscience* 5, 61.
- Lamb, Y.N., 2018. Burosumab: First Global Approval. *Drugs* 78, 707-714.
- Lampelj, M., Arko, D., Cas-Sikosek, N., Kavalari, R., Ravnik, M., Jezersek-Novakovic, B., Dobnik, S., Dovnik, N.F., Takac, I., 2015. Urokinase plasminogen activator (uPA) and plasminogen activator inhibitor type-1 (PAI-1) in breast cancer - correlation with traditional prognostic factors. *Radiology and oncology* 49, 357-364.
- Lamy, L., Foussat, A., Brown, E.J., Bornstein, P., Ticchioni, M., Bernard, A., 2007. Interactions between CD47 and thrombospondin reduce inflammation. *Journal of immunology* 178, 5930-5939.
- Lana, A., Valdes-Becares, A., Buno, A., Rodriguez-Artalejo, F., Lopez-Garcia, E., 2017. Serum Leptin Concentration is Associated with Incident Frailty in Older Adults. *Aging and disease* 8, 240-249.
- Langhorst, J., Boone, J., 2012. Fecal lactoferrin as a noninvasive biomarker in inflammatory bowel diseases. *Drugs of today* 48, 149-161.

- Langlois, B., Belozertseva, E., Parlakian, A., Bourhim, M., Gao-Li, J., Blanc, J., Tian, L., Coletti, D., Labat, C., Ramdame-Cherif, Z., Challande, P., Regnault, V., Lacolley, P., Li, Z., 2017. Vimentin knockout results in increased expression of sub-endothelial basement membrane components and carotid stiffness in mice. *Scientific reports* 7, 11628.
- Langsford, D., Tang, M., Cheikh Hassan, H.I., Djurdjev, O., Sood, M.M., Levin, A., 2017. The Association between Biomarker Profiles, Etiology of Chronic Kidney Disease, and Mortality. *American journal of nephrology* 45, 226-234.
- Lara-Diaz, V.J., Castilla-Cortazar, I., Martin-Estal, I., Garcia-Magarino, M., Aguirre, G.A., Puche, J.E., de la Garza, R.G., Morales, L.A., Munoz, U., 2017. IGF-1 modulates gene expression of proteins involved in inflammation, cytoskeleton, and liver architecture. *Journal of physiology and biochemistry* 73, 245-258.
- Lasek-Bal, A., Jedrzejowska-Szypulka, H., Rozycka, J., Bal, W., Holecki, M., Dulawa, J., Lewin-Kowalik, J., 2015. Low Concentration of BDNF in the Acute Phase of Ischemic Stroke as a Factor in Poor Prognosis in Terms of Functional Status of Patients. *Medical science monitor : international medical journal of experimental and clinical research* 21, 3900-3905.
- Lassila, M., Fukami, K., Jandeleit-Dahm, K., Semple, T., Carmeliet, P., Cooper, M.E., Kitching, A.R., 2007. Plasminogen activator inhibitor-1 production is pathogenetic in experimental murine diabetic renal disease. *Diabetologia* 50, 1315-1326.
- Lau, H., Mat Ludin, A.F., Rajab, N.F., Shahar, S., 2017. Identification of Neuroprotective Factors Associated with Successful Ageing and Risk of Cognitive Impairment among Malaysia Older Adults. *Current gerontology and geriatrics research* 2017, 4218756.
- Lauro, C., Catalano, M., Trettel, F., Limatola, C., 2015. Fractalkine in the nervous system: neuroprotective or neurotoxic molecule? *Annals of the New York Academy of Sciences* 1351, 141-148.
- Lauzier, A., Charbonneau, M., Paquette, M., Harper, K., Dubois, C.M., 2012. Transglutaminase 2 cross-linking activity is linked to invadopodia formation and cartilage breakdown in arthritis. *Arthritis research & therapy* 14, R159.
- Le Page, A., Lamoureux, J., Bourgade, K., Frost, E.H., Pawelec, G., Witkowski, J.M., Larbi, A., Dupuis, G., Fulop, T., 2017. Polymorphonuclear Neutrophil Functions are Differentially Altered in Amnesic Mild Cognitive Impairment and Mild Alzheimer's Disease Patients. *Journal of Alzheimer's disease : JAD* 60, 23-42.
- Leaf, D.E., Siew, E.D., Eisenga, M.F., Singh, K., Mc Causland, F.R., Srivastava, A., Ikizler, T.A., Ware, L.B., Ginde, A.A., Kellum, J.A., Palevsky, P.M., Wolf, M., Waikar, S.S., 2018. Fibroblast Growth Factor 23 Associates with Death in Critically Ill Patients. *Clinical journal of the American Society of Nephrology : CJASN* 13, 531-541.
- Leao, R., van Agthoven, T., Figueiredo, A., Jewett, M.A.S., Fadaak, K., Sweet, J., Ahmad, A.E., Anson-Cartwright, L., Chung, P., Hansen, A., Warde, P., Castelo-Branco, P., O'Malley, M., Bedard, P.L., Looijenga, L.H.J., Hamilton, R.J., 2018. Serum miRNA predicts viable disease post-chemotherapy in testicular non-seminoma germ cell tumor patients. *The Journal of urology*.
- Lechner, J., Chen, M., Hogg, R.E., Toth, L., Silvestri, G., Chakravarthy, U., Xu, H., 2016. Higher plasma levels of complement C3a, C4a and C5a increase the risk of subretinal fibrosis in neovascular age-related macular degeneration: Complement activation in AMD. *Immunity & ageing : I & A* 13, 4.
- Lee, C.H., Hui, E.Y., Woo, Y.C., Yeung, C.Y., Chow, W.S., Yuen, M.M., Fong, C.H., Xu, A., Lam, K.S., 2015a. Circulating fibroblast growth factor 21 levels predict progressive kidney disease in subjects with type 2 diabetes and normoalbuminuria. *The Journal of clinical endocrinology and metabolism* 100, 1368-1375.

- Lee, D., Oka, T., Hunter, B., Robinson, A., Papp, S., Nakamura, K., Srisakuldee, W., Nickel, B.E., Light, P.E., Dyck, J.R., Lopaschuk, G.D., Kardami, E., Opas, M., Michalak, M., 2013. Calreticulin induces dilated cardiomyopathy. *PloS one* 8, e56387.
- Lee, E.K., Jeong, H.O., Bang, E.J., Kim, C.H., Mun, J.Y., Noh, S., Gim, J.A., Kim, D.H., Chung, K.W., Yu, B.P., Chung, H.Y., 2018a. The involvement of serum exosomal miR-500-3p and miR-770-3p in aging: modulation by calorie restriction. *Oncotarget* 9, 5578-5587.
- Lee, J., Giordano, S., Zhang, J., 2012a. Autophagy, mitochondria and oxidative stress: cross-talk and redox signalling. *The Biochemical journal* 441, 523-540.
- Lee, J.H., Kang, Y.E., Chang, J.Y., Park, K.C., Kim, H.W., Kim, J.T., Kim, H.J., Yi, H.S., Shong, M., Chung, H.K., Kim, K.S., 2016a. An engineered FGF21 variant, LY2405319, can prevent non-alcoholic steatohepatitis by enhancing hepatic mitochondrial function. *American journal of translational research* 8, 4750-4763.
- Lee, J.K., Kim, K.C., 2013. DZNep, inhibitor of S-adenosylhomocysteine hydrolase, down-regulates expression of SETDB1 H3K9me3 HMTase in human lung cancer cells. *Biochemical and biophysical research communications* 438, 647-652.
- Lee, J.S., Xiao, J., Patel, P., Schade, J., Wang, J., Deneen, B., Erdreich-Epstein, A., Song, H.R., 2014. A novel tumor-promoting role for nuclear factor IA in glioblastomas is mediated through negative regulation of p53, p21, and PAI1. *Neuro-oncology* 16, 191-203.
- Lee, K., Lee, K.B., Jung, H.Y., Yi, N.J., Lee, K.W., Suh, K.S., Jang, J.J., 2017. The correlation between poor prognosis and increased yes-associated protein 1 expression in keratin 19 expressing hepatocellular carcinomas and cholangiocarcinomas. *BMC cancer* 17, 441.
- Lee, K.J., Jang, Y.O., Cha, S.K., Kim, M.Y., Park, K.S., Eom, Y.W., Baik, S.K., 2018b. Expression of Fibroblast Growth Factor 21 and beta-Klotho Regulates Hepatic Fibrosis through the Nuclear Factor-kappaB and c-Jun N-Terminal Kinase Pathways. *Gut and liver* 12, 449-456.
- Lee, M.J., Lee, S.A., Nam, B.Y., Park, S., Lee, S.H., Ryu, H.J., Kwon, Y.E., Kim, Y.L., Park, K.S., Oh, H.J., Park, J.T., Han, S.H., Ryu, D.R., Kang, S.W., Yoo, T.H., 2015b. Irisin, a novel myokine is an independent predictor for sarcopenia and carotid atherosclerosis in dialysis patients. *Atherosclerosis* 242, 476-482.
- Lee, R.S., Hermens, D.F., Porter, M.A., Redoblado-Hodge, M.A., 2012b. A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. *Journal of affective disorders* 140, 113-124.
- Lee, T.M., Chen, W.T., Chang, N.C., 2016b. Sitagliptin decreases ventricular arrhythmias by attenuated glucose-dependent insulinotropic polypeptide (GIP)-dependent resistin signalling in infarcted rats. *Bioscience reports* 36.
- Lee, W.J., Chen, L.K., Liang, C.K., Peng, L.N., Chiou, S.T., Chou, P., 2016c. Soluble ICAM-1, Independent of IL-6, Is Associated with Prevalent Frailty in Community-Dwelling Elderly Taiwanese People. *PloS one* 11, e0157877.
- Lee, Y.T., Gong, M., Chau, A., Wong, W.T., Bazoukis, G., Wong, S.H., Lampropoulos, K., Xia, Y., Li, G., Wong, M.C.S., Liu, T., Wu, W.K.K., Tse, G., International Health Informatics Study, N., 2018c. Pentraxin-3 as a marker of sepsis severity and predictor of mortality outcomes: A systematic review and meta-analysis. *The Journal of infection* 76, 1-10.
- Lehtonen, J.M., Forsstrom, S., Bottani, E., Viscomi, C., Baris, O.R., Isoniemi, H., Hockerstedt, K., Osterlund, P., Hurme, M., Jylhava, J., Leppa, S., Markkula, R., Helio, T., Mombelli, G., Uusimaa, J., Laaksonen, R., Laaksovirta, H., Auranen, M., Zeviani, M., Smeitink, J., Wiesner, R.J., Nakada, K., Isohanni, P., Suomalainen, A., 2016. FGF21 is a biomarker for mitochondrial translation and mtDNA maintenance disorders. *Neurology* 87, 2290-2299.
- Leifheit-Nestler, M., Kirchhoff, F., Nespore, J., Richter, B., Soetje, B., Klintschar, M., Heineke, J., Haffner, D., 2018. Fibroblast growth factor 23 is induced by an activated renin-

- angiotensin-aldosterone system in cardiac myocytes and promotes the pro-fibrotic crosstalk between cardiac myocytes and fibroblasts. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*.
- Leng, S., Chaves, P., Koenig, K., Walston, J., 2002. Serum interleukin-6 and hemoglobin as physiological correlates in the geriatric syndrome of frailty: a pilot study. *Journal of the American Geriatrics Society* 50, 1268-1271.
- Leon-Mateos, L., Casas, H., Abalo, A., Vieito, M., Abreu, M., Anido, U., Gomez-Tato, A., Lopez, R., Abal, M., Muinelo-Romay, L., 2017. Improving circulating tumor cells enumeration and characterization to predict outcome in first line chemotherapy mCRPC patients. *Oncotarget* 8, 54708-54721.
- Lerner, L., Gyuris, J., Nicoletti, R., Gifford, J., Krieger, B., Jatoi, A., 2016. Growth differentiating factor-15 (GDF-15): A potential biomarker and therapeutic target for cancer-associated weight loss. *Oncology letters* 12, 4219-4223.
- Li, D., Lei, C., Zhang, S., Zhang, S., Liu, M., Wu, B., 2015a. Blockade of high mobility group box-1 signaling via the receptor for advanced glycation end-products ameliorates inflammatory damage after acute intracerebral hemorrhage. *Neuroscience letters* 609, 109-119.
- Li, D.J., Fu, H., Zhao, T., Ni, M., Shen, F.M., 2016a. Exercise-stimulated FGF23 promotes exercise performance via controlling the excess reactive oxygen species production and enhancing mitochondrial function in skeletal muscle. *Metabolism: clinical and experimental* 65, 747-756.
- Li, D.J., Li, Y.H., Yuan, H.B., Qu, L.F., Wang, P., 2017a. The novel exercise-induced hormone irisin protects against neuronal injury via activation of the Akt and ERK1/2 signaling pathways and contributes to the neuroprotection of physical exercise in cerebral ischemia. *Metabolism: clinical and experimental* 68, 31-42.
- Li, G., Li, Y., Tan, X.Q., Jia, P., Zhao, J., Liu, D., Wang, T., Liu, B., 2017b. Plasma Growth Differentiation Factor-15 is a Potential Biomarker for Pediatric Pulmonary Arterial Hypertension Associated with Congenital Heart Disease. *Pediatric cardiology* 38, 1620-1626.
- Li, H., Cao, Z., Xu, J., Wang, F., Xiong, R., Xu, Z., Luo, X., Li, G., Tan, X., Liu, Z., Gao, Z., Kang, Y., Xiao, J., Liu, Y., Li, X., 2018a. Cerebrospinal fluid FGF23 levels correlate with a measure of impulsivity. *Psychiatry research* 264, 394-397.
- Li, H., Fang, Q., Gao, F., Fan, J., Zhou, J., Wang, X., Zhang, H., Pan, X., Bao, Y., Xiang, K., Xu, A., Jia, W., 2010. Fibroblast growth factor 21 levels are increased in nonalcoholic fatty liver disease patients and are correlated with hepatic triglyceride. *Journal of hepatology* 53, 934-940.
- Li, H., Shen, L., Hu, P., Huang, R., Cao, Y., Deng, J., Yuan, W., Liu, D., Yang, J., Gu, H., Bai, Y., 2017c. Aging-associated mitochondrial DNA mutations alter oxidative phosphorylation machinery and cause mitochondrial dysfunctions. *Biochimica et biophysica acta* 1863, 2266-2273.
- Li, H.Y., Li, M., Luo, C.C., Wang, J.Q., Zheng, N., 2017d. Lactoferrin Exerts Antitumor Effects by Inhibiting Angiogenesis in a HT29 Human Colon Tumor Model. *Journal of agricultural and food chemistry* 65, 10464-10472.
- Li, J., Zhang, H., Shi, M., Yan, L., Xie, M., 2014. Homocysteine is linked to macular edema in type 2 diabetes. *Current eye research* 39, 730-735.
- Li, J., Zhu, S., Tong, J., Hao, H., Yang, J., Liu, Z., Wang, Y., 2016b. Suppression of lactate dehydrogenase A compromises tumor progression by downregulation of the Warburg effect in glioblastoma. *Neuroreport* 27, 110-115.

- Li, J.J., Kwak, S.J., Jung, D.S., Kim, J.J., Yoo, T.H., Ryu, D.R., Han, S.H., Choi, H.Y., Lee, J.E., Moon, S.J., Kim, D.K., Han, D.S., Kang, S.W., 2007. Podocyte biology in diabetic nephropathy. *Kidney international. Supplement*, S36-42.
- Li, L., Han, J.L., Mao, J.M., Guo, L.J., Gao, W., 2013. Association between serum resistin level and cardiovascular events in postmenopausal women with acute coronary syndrome undergoing percutaneous coronary intervention. *Chinese medical journal* 126, 1058-1062.
- Li, L., Kang, L., Zhao, W., Feng, Y., Liu, W., Wang, T., Mai, H., Huang, J., Chen, S., Liang, Y., Han, J., Xu, X., Ye, Q., 2017e. miR-30a-5p suppresses breast tumor growth and metastasis through inhibition of LDHA-mediated Warburg effect. *Cancer letters* 400, 89-98.
- Li, L., Xiao, T., Li, F., Li, Y., Zeng, O., Liu, M., Liang, B., Li, Z., Chu, C., Yang, J., 2017f. Hydrogen sulfide reduced renal tissue fibrosis by regulating autophagy in diabetic rats. *Molecular medicine reports* 16, 1715-1722.
- Li, L., Xiong, W.C., Mei, L., 2018b. Neuromuscular Junction Formation, Aging, and Disorders. *Annual review of physiology* 80, 159-188.
- Li, M., Yang, M., Zhou, X., Fang, X., Hu, W., Zhu, W., Wang, C., Liu, D., Li, S., Liu, H., Yang, G., Li, L., 2015b. Elevated circulating levels of irisin and the effect of metformin treatment in women with polycystic ovary syndrome. *The Journal of clinical endocrinology and metabolism* 100, 1485-1493.
- Li, S., Zhang, Q.Z., Zhang, D.Q., Feng, J.B., Luo, Q., Lu, X., Wang, X.R., Li, K.P., Chen, D.Q., Mu, X.F., Gao, L., Liu, Q.J., 2017g. GDF-15 gene expression alterations in human lymphoblastoid cells and peripheral blood lymphocytes following exposure to ionizing radiation. *Molecular medicine reports* 15, 3599-3606.
- Li, X., Zhu, Z., Zhou, T., Cao, X., Lu, T., Liang, Y., He, J., Liu, C., Dou, Z., Shen, B., 2018c. Early increases in serum FGF21 levels predict mortality of septic patients. *Cytokine*.
- Li, Z., Hilgenberg, L.G., O'Dowd, D.K., Smith, M.A., 1999. Formation of functional synaptic connections between cultured cortical neurons from agrin-deficient mice. *Journal of neurobiology* 39, 547-557.
- Li, Z., Li, M., Wood, K., Hettwer, S., Muley, S.A., Shi, F.D., Liu, Q., Ladha, S.S., 2018d. Engineered agrin attenuates the severity of experimental autoimmune myasthenia gravis. *Muscle & nerve* 57, 814-820.
- Li, Z.C., Xiao, J., Wang, G., Li, M.Q., Hu, K.Z., Ma, T., Wang, W.L., Liu, Z.D., Zhang, J.D., 2015c. Fibroblast growth factor-21 concentration in serum and synovial fluid is associated with radiographic bone loss of knee osteoarthritis. *Scandinavian journal of clinical and laboratory investigation* 75, 121-125.
- Liang, C., Tan, S., Huang, Q., Lin, J., Lu, Z., Lin, X., 2015. Pratensein ameliorates beta-amyloid-induced cognitive impairment in rats via reducing oxidative damage and restoring synapse and BDNF levels. *Neuroscience letters* 592, 48-53.
- Liang, X., Liu, L., Fu, T., Zhou, Q., Zhou, D., Xiao, L., Liu, J., Kong, Y., Xie, H., Yi, F., Lai, L., Vega, R.B., Kelly, D.P., Smith, S.R., Gan, Z., 2016. Exercise Inducible Lactate Dehydrogenase B Regulates Mitochondrial Function in Skeletal Muscle. *The Journal of biological chemistry* 291, 25306-25318.
- Liao, P., Yang, D., Liu, D., Zheng, Y., 2017. GLP-1 and Ghrelin Attenuate High Glucose/High Lipid-Induced Apoptosis and Senescence of Human Microvascular Endothelial Cells. *Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology* 44, 1842-1855.
- Liebner, S., Czupalla, C.J., Wolburg, H., 2011. Current concepts of blood-brain barrier development. *The International journal of developmental biology* 55, 467-476.
- Limana, F., Germani, A., Zacheo, A., Kajstura, J., Di Carlo, A., Borsellino, G., Leoni, O., Palumbo, R., Battistini, L., Rastaldo, R., Muller, S., Pompilio, G., Anversa, P., Bianchi,

- M.E., Capogrossi, M.C., 2005. Exogenous high-mobility group box 1 protein induces myocardial regeneration after infarction via enhanced cardiac C-kit⁺ cell proliferation and differentiation. *Circulation research* 97, e73-83.
- Lin, H., Muramatsu, R., Maedera, N., Tsunematsu, H., Hamaguchi, M., Koyama, Y., Kuroda, M., Ono, K., Sawada, M., Yamashita, T., 2018. Extracellular Lactate Dehydrogenase A Release From Damaged Neurons Drives Central Nervous System Angiogenesis. *EBioMedicine* 27, 71-85.
- Lin, J., Yang, Q., Wilder, P.T., Carrier, F., Weber, D.J., 2010. The calcium-binding protein S100B down-regulates p53 and apoptosis in malignant melanoma. *The Journal of biological chemistry* 285, 27487-27498.
- Lin, Q., Cao, Y., Gao, J., 2014. Serum calreticulin is a negative biomarker in patients with Alzheimer's disease. *International journal of molecular sciences* 15, 21740-21753.
- Lin, T.N., Kim, G.M., Chen, J.J., Cheung, W.M., He, Y.Y., Hsu, C.Y., 2003. Differential regulation of thrombospondin-1 and thrombospondin-2 after focal cerebral ischemia/reperfusion. *Stroke* 34, 177-186.
- Lin, Y., Sun, Z., 2015. Antiaging Gene Klotho Attenuates Pancreatic beta-Cell Apoptosis in Type 1 Diabetes. *Diabetes* 64, 4298-4311.
- Lippi, G., Jansen-Duerr, P., Vina, J., Durrance-Bagale, A., Abugessaisa, I., Gomez-Cabrero, D., Tegner, J., Grillari, J., Erusalimsky, J., Sinclair, A., Rodriguez-Manas, L., consortium, F., 2015. Laboratory biomarkers and frailty: presentation of the FRAILOMIC initiative. *Clinical chemistry and laboratory medicine* 53, e253-255.
- Liu, D., Li, S., Li, Z., 2017a. Adiponectin: A biomarker for chronic hepatitis C? *Cytokine* 89, 27-33.
- Liu, F., Zhang, Y., Men, T., Jiang, X., Yang, C., Li, H., Wei, X., Yan, D., Feng, G., Yang, J., Bergquist, J., Wang, B., Jiang, W., Mi, J., Tian, G., 2017b. Quantitative proteomic analysis of gastric cancer tissue reveals novel proteins in platelet-derived growth factor b signaling pathway. *Oncotarget* 8, 22059-22075.
- Liu, J., Ma, J., Tang, K., Huang, B., 2017c. Therapeutic Use of Tumor Cell-Derived Extracellular Vesicles. *Methods in molecular biology* 1660, 433-440.
- Liu, P.F., Kang, B.H., Wu, Y.M., Sun, J.H., Yen, L.M., Fu, T.Y., Lin, Y.C., Liou, H.H., Lin, Y.S., Sie, H.C., Hsieh, I.C., Tseng, Y.K., Shu, C.W., Hsieh, Y.D., Ger, L.P., 2017d. Vimentin is a potential prognostic factor for tongue squamous cell carcinoma among five epithelial-mesenchymal transition-related proteins. *PloS one* 12, e0178581.
- Liu, S., Du, F., Li, X., Wang, M., Duan, R., Zhang, J., Wu, Y., Zhang, Q., 2017e. Effects and underlying mechanisms of irisin on the proliferation and apoptosis of pancreatic beta cells. *PloS one* 12, e0175498.
- Liu, S., Qu, X., Liu, F., Wang, C., 2014a. Pentraxin 3 as a prognostic biomarker in patients with systemic inflammation or infection. *Mediators of inflammation* 2014, 421429.
- Liu, W.Y., Huang, S., Shi, K.Q., Zhao, C.C., Chen, L.L., Braddock, M., Chen, Y.P., Feng, W.K., Zheng, M.H., 2014b. The role of fibroblast growth factor 21 in the pathogenesis of liver disease: a novel predictor and therapeutic target. *Expert opinion on therapeutic targets* 18, 1305-1313.
- Liu, X., Gao, R.W., Li, M., Si, C.F., He, Y.P., Wang, M., Yang, Y., Zheng, Q.Y., Wang, C.Y., 2016a. The ROS derived mitochondrial respiration not from NADPH oxidase plays key role in Celastrol against angiotensin II-mediated HepG2 cell proliferation. *Apoptosis: an international journal on programmed cell death* 21, 1315-1326.
- Liu, Y., Wu, J., Liang, Y.D., Lu, S., Cheng, M.L., Liu, J.Y., 2014c. [Gene expression changes of regucalcin and prohibitin in cirrhotic rat liver and the related effects of compound glutathione inosine injection intervention]. *Zhonghua gan zang bing za zhi = Zhonghua ganzangbing zazhi = Chinese journal of hepatology* 22, 826-830.

- Liu, Y., Zhang, R., Qu, H., Wu, J., Li, L., Tang, Y., 2017f. Endothelial microparticles activate endothelial cells to facilitate the inflammatory response. *Molecular medicine reports* 15, 1291-1296.
- Liu, Y.H., Cao, H.Y., Wang, Y.R., Jiao, S.S., Bu, X.L., Zeng, F., Wang, Q.H., Li, J., Deng, J., Zhou, H.D., Wang, Y.J., 2015. Serum Abeta is predictive for short-term neurological deficits after acute ischemic stroke. *Neurotoxicity research* 27, 292-299.
- Liu, Z., Gan, L., Wu, T., Feng, F., Luo, D., Gu, H., Liu, S., Sun, C., 2016b. Adiponectin reduces ER stress-induced apoptosis through PPARalpha transcriptional regulation of ATF2 in mouse adipose. *Cell death & disease* 7, e2487.
- Livesey, K.M., Kang, R., Vernon, P., Buchser, W., Loughran, P., Watkins, S.C., Zhang, L., Manfredi, J.J., Zeh, H.J., 3rd, Li, L., Lotze, M.T., Tang, D., 2012. p53/HMGB1 complexes regulate autophagy and apoptosis. *Cancer research* 72, 1996-2005.
- Lobsiger, C.S., Boillee, S., Cleveland, D.W., 2007. Toxicity from different SOD1 mutants dysregulates the complement system and the neuronal regenerative response in ALS motor neurons. *Proceedings of the National Academy of Sciences of the United States of America* 104, 7319-7326.
- Locatelli, M., Boiocchi, L., Ferrero, S., Martinelli Boneschi, F., Zavanone, M., Pesce, S., Allavena, P., Maria Gaini, S., Bello, L., Mantovani, A., 2010. Human glioma tumors express high levels of the chemokine receptor CX3CR1. *European cytokine network* 21, 27-33.
- Lok, S.I., Winkens, B., Goldschmeding, R., van Geffen, A.J., Nous, F.M., van Kuik, J., van der Weide, P., Klopping, C., Kirkels, J.H., Lahpor, J.R., Doevendans, P.A., de Jonge, N., de Weger, R.A., 2012. Circulating growth differentiation factor-15 correlates with myocardial fibrosis in patients with non-ischaemic dilated cardiomyopathy and decreases rapidly after left ventricular assist device support. *European journal of heart failure* 14, 1249-1256.
- Lopez-Otin, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of aging. *Cell* 153, 1194-1217.
- Lorente, L., Martin, M.M., Gonzalez-Rivero, A.F., Argueso, M., Ramos, L., Sole-Violan, J., Caceres, J.J., Jimenez, A., Borreguero-Leon, J.M., 2015. Serum levels of caspase-cleaved cytokeratin-18 in patients with severe traumatic brain injury are associated with mortality: a pilot study. *PLoS one* 10, e0121739.
- Lovadi, E., Csereklyei, M., Merkli, H., FuLop, K., Sebok, A., Karcagi, V., Komoly, S., Pal, E., 2017. Elevated FGF 21 in myotonic dystrophy type 1 and mitochondrial diseases. *Muscle & nerve* 55, 564-569.
- Lu, D.Y., Chen, J.H., Tan, T.W., Huang, C.Y., Yeh, W.L., Hsu, H.C., 2013. Resistin protects against 6-hydroxydopamine-induced cell death in dopaminergic-like MES23.5 cells. *Journal of cellular physiology* 228, 563-571.
- Lu, Q.Y., Zhang, L., Yee, J.K., Go, V.W., Lee, W.N., 2015. Metabolic Consequences of LDHA inhibition by Epigallocatechin Gallate and Oxamate in MIA PaCa-2 Pancreatic Cancer Cells. *Metabolomics : Official journal of the Metabolomic Society* 11, 71-80.
- Lu, X., Hu, M.C., 2017. Klotho/FGF23 Axis in Chronic Kidney Disease and Cardiovascular Disease. *Kidney diseases* 3, 15-23.
- Lu, Y., Tan, C.T., Nyunt, M.S., Mok, E.W., Camous, X., Kared, H., Fulop, T., Feng, L., Ng, T.P., Larbi, A., 2016. Inflammatory and immune markers associated with physical frailty syndrome: findings from Singapore longitudinal aging studies. *Oncotarget* 7, 28783-28795.
- Ludwig, N., Leidinger, P., Becker, K., Backes, C., Fehlmann, T., Pallasch, C., Rheinheimer, S., Meder, B., Stahler, C., Meese, E., Keller, A., 2016. Distribution of miRNA expression across human tissues. *Nucleic acids research* 44, 3865-3877.

- Lui, H., Zhang, J., Makinson, S.R., Cahill, M.K., Kelley, K.W., Huang, H.Y., Shang, Y., Oldham, M.C., Martens, L.H., Gao, F., Coppola, G., Sloan, S.A., Hsieh, C.L., Kim, C.C., Bigio, E.H., Weintraub, S., Mesulam, M.M., Rademakers, R., Mackenzie, I.R., Seeley, W.W., Karydas, A., Miller, B.L., Borroni, B., Ghidoni, R., Farese, R.V., Jr., Paz, J.T., Barres, B.A., Huang, E.J., 2016. Progranulin Deficiency Promotes Circuit-Specific Synaptic Pruning by Microglia via Complement Activation. *Cell* 165, 921-935.
- Luna, C., Alique, M., Naval Moral, E., Noci, M.V., Bohorquez-Magro, L., Carracedo, J., Ramirez, R., 2016. Aging-associated oxidized albumin promotes cellular senescence and endothelial damage. *Clinical interventions in aging* 11, 225-236.
- Lunemann, J.D., Schmidt, J., Schmid, D., Barthel, K., Wrede, A., Dalakas, M.C., Munz, C., 2007. Beta-amyloid is a substrate of autophagy in sporadic inclusion body myositis. *Annals of neurology* 61, 476-483.
- Luster, A.D., Unkeless, J.C., Ravetch, J.V., 1985. Gamma-interferon transcriptionally regulates an early-response gene containing homology to platelet proteins. *Nature* 315, 672-676.
- Ma, K., Cabrero, A., Saha, P.K., Kojima, H., Li, L., Chang, B.H., Paul, A., Chan, L., 2002. Increased beta -oxidation but no insulin resistance or glucose intolerance in mice lacking adiponectin. *The Journal of biological chemistry* 277, 34658-34661.
- Ma, L., Shao, Z., Wang, R., Zhao, Z., Zhang, X., Ji, Z., Sheng, S., Xu, B., Dong, W., Zhang, J., 2015. The beta-amyloid precursor protein analog P165 improves impaired insulin signal transduction in type 2 diabetic rats. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology* 36, 593-598.
- Ma, Y., Matsuwaki, T., Yamanouchi, K., Nishihara, M., 2017. Involvement of progranulin in modulating neuroinflammatory responses but not neurogenesis in the hippocampus of aged mice. *Experimental gerontology* 95, 1-8.
- Mack, N., Mazzi, E.A., Bauer, D., Flores-Rozas, H., Soliman, K.F., 2017. Stable shRNA Silencing of Lactate Dehydrogenase A (LDHA) in Human MDA-MB-231 Breast Cancer Cells Fails to Alter Lactic Acid Production, Glycolytic Activity, ATP or Survival. *Anticancer research* 37, 1205-1212.
- Maeda, N., Shimomura, I., Kishida, K., Nishizawa, H., Matsuda, M., Nagaretani, H., Furuyama, N., Kondo, H., Takahashi, M., Arita, Y., Komuro, R., Ouchi, N., Kihara, S., Tochino, Y., Okutomi, K., Horie, M., Takeda, S., Aoyama, T., Funahashi, T., Matsuzawa, Y., 2002. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. *Nature medicine* 8, 731-737.
- Maekawa, Y., Sugiyama, A., Takeuchi, T., 2017. Lactoferrin ameliorates corticosterone-related acute stress and hyperglycemia in rats. *The Journal of veterinary medical science* 79, 412-417.
- Maetzler, W., Deleersnijder, W., Hanssens, V., Bernard, A., Brockmann, K., Marquetand, J., Wurster, I., Rattay, T.W., Roncoroni, L., Schaeffer, E., Lerche, S., Apel, A., Deuschle, C., Berg, D., 2016. GDF15/MIC1 and MMP9 Cerebrospinal Fluid Levels in Parkinson's Disease and Lewy Body Dementia. *PloS one* 11, e0149349.
- Maggio, M., Cattabiani, C., Lauretani, F., Ferrucci, L., Luci, M., Valenti, G., Ceda, G., 2010. The concept of multiple hormonal dysregulation. *Acta bio-medica : Atenei Parmensis* 81 Suppl 1, 19-29.
- Maggio, M., Dall'Aglio, E., Lauretani, F., Cattabiani, C., Ceresini, G., Caffarra, P., Valenti, G., Volpi, R., Vignali, A., Schiavi, G., Ceda, G.P., 2012. The hormonal pathway to cognitive impairment in older men. *The journal of nutrition, health & aging* 16, 40-54.
- Mai, K., Schwarz, F., Bobbert, T., Andres, J., Assmann, A., Pfeiffer, A.F., Spranger, J., 2011. Relation between fibroblast growth factor-21, adiposity, metabolism, and weight reduction. *Metabolism: clinical and experimental* 60, 306-311.

- Maia, C.J., Santos, C.R., Schmitt, F., Socorro, S., 2008. Regucalcin is expressed in rat mammary gland and prostate and down-regulated by 17beta-estradiol. *Molecular and cellular biochemistry* 311, 81-86.
- Malicka, B., Skoskiewicz-Malinowska, K., Kaczmarek, U., 2016. Salivary lactate dehydrogenase and aminotransferases in diabetic patients. *Medicine* 95, e5211.
- Maneerat, Y., Prasongsukarn, K., Benjathummarak, S., Dechkhajorn, W., 2017. PPBP and DEFA1/DEFA3 genes in hyperlipidaemia as feasible synergistic inflammatory biomarkers for coronary heart disease. *Lipids in health and disease* 16, 80.
- Manek, R., Moghieb, A., Yang, Z., Kumar, D., Kobessiy, F., Sarkis, G.A., Raghavan, V., Wang, K.K.W., 2017. Protein Biomarkers and Neuroproteomics Characterization of Microvesicles/Exosomes from Human Cerebrospinal Fluid Following Traumatic Brain Injury. *Molecular neurobiology*.
- Manerba, M., Di Ianni, L., Govoni, M., Roberti, M., Recanatini, M., Di Stefano, G., 2017. LDH inhibition impacts on heat shock response and induces senescence of hepatocellular carcinoma cells. *European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences* 105, 91-98.
- Mann, S., Kroger, S., 1996. Agrin is synthesized by retinal cells and colocalizes with gephyrin [corrected]. *Molecular and cellular neurosciences* 8, 1-13.
- Mannery, Y.O., McClain, C.J., Vos, M.B., 2011. Keratin 18, Apoptosis, and Liver Disease in Children. *Current pediatric reviews* 7, 310-315.
- Mans, S., Banz, Y., Mueller, B.U., Pabst, T., 2012. The angiogenesis inhibitor vasostatin is regulated by neutrophil elastase-dependent cleavage of calreticulin in AML patients. *Blood* 120, 2690-2699.
- Mantzoros, C., Petridou, E., Dessypris, N., Chavelas, C., Dalamaga, M., Alexe, D.M., Papadiamantis, Y., Markopoulos, C., Spanos, E., Chrousos, G., Trichopoulos, D., 2004. Adiponectin and breast cancer risk. *The Journal of clinical endocrinology and metabolism* 89, 1102-1107.
- Mao, S., Fang, L., Liu, F., Jiang, S., Wu, L., Zhang, J., 2018. Leptin and chronic kidney diseases. *Journal of receptor and signal transduction research*, 1-6.
- Marceau, N., Loranger, A., Gilbert, S., Daigle, N., Champetier, S., 2001. Keratin-mediated resistance to stress and apoptosis in simple epithelial cells in relation to health and disease. *Biochemistry and cell biology = Biochimie et biologie cellulaire* 79, 543-555.
- Maric, G., Rose, A.A., Annis, M.G., Siegel, P.M., 2013. Glycoprotein non-metastatic b (GPNMB): A metastatic mediator and emerging therapeutic target in cancer. *OncoTargets and therapy* 6, 839-852.
- Marino, A., Menghini, R., Fabrizi, M., Casagrande, V., Mavilio, M., Stoehr, R., Candi, E., Mauriello, A., Moreno-Navarrete, J.M., Gomez-Serrano, M., Peral, B., Melino, G., Lauro, R., Fernandez Real, J.M., Federici, M., 2014. ITCH deficiency protects from diet-induced obesity. *Diabetes* 63, 550-561.
- Marmary, Y., Adar, R., Gaska, S., Wygoda, A., Maly, A., Cohen, J., Eliashar, R., Mizrachi, L., Orfaig-Geva, C., Baum, B.J., Rose-John, S., Galun, E., Axelrod, J.H., 2016. Radiation-Induced Loss of Salivary Gland Function Is Driven by Cellular Senescence and Prevented by IL6 Modulation. *Cancer research* 76, 1170-1180.
- Marques, R., Maia, C.J., Vaz, C., Correia, S., Socorro, S., 2014. The diverse roles of calcium-binding protein regucalcin in cell biology: from tissue expression and signalling to disease. *Cellular and molecular life sciences : CMLS* 71, 93-111.
- Marsh, A.M., Nguyen, A.H., Parker, T.M., Agrawal, D.K., 2017. Clinical use of high mobility group box 1 and the receptor for advanced glycation end products in the prognosis and risk stratification of heart failure: a literature review. *Canadian journal of physiology and pharmacology* 95, 253-259.

- Marshall, D.D., Sadykov, M.R., Thomas, V.C., Bayles, K.W., Powers, R., 2016. Redox Imbalance Underlies the Fitness Defect Associated with Inactivation of the Pta-AckA Pathway in *Staphylococcus aureus*. *Journal of proteome research* 15, 1205-1212.
- Martin-Ruiz, C., Jagger, C., Kingston, A., Collerton, J., Catt, M., Davies, K., Dunn, M., Hilkens, C., Keavney, B., Pearce, S.H., den Elzen, W.P., Talbot, D., Wiley, L., Bond, J., Mathers, J.C., Eccles, M.P., Robinson, L., James, O., Kirkwood, T.B., von Zglinicki, T., 2011. Assessment of a large panel of candidate biomarkers of ageing in the Newcastle 85+ study. *Mechanisms of ageing and development* 132, 496-502.
- Martin, E., Boucher, C., Fontaine, B., Delarasse, C., 2017a. Distinct inflammatory phenotypes of microglia and monocyte-derived macrophages in Alzheimer's disease models: effects of aging and amyloid pathology. *Aging cell* 16, 27-38.
- Martin, M., Blom, A.M., 2016. Complement in removal of the dead - balancing inflammation. *Immunological reviews* 274, 218-232.
- Martin, R., Cordova, C., Gutierrez, B., Hernandez, M., Nieto, M.L., 2017b. A dangerous liaison: Leptin and sPLA2-IIA join forces to induce proliferation and migration of astrocytoma cells. *PLoS one* 12, e0170675.
- Maruyama, N., Ishigami, A., Kondo, Y., 2005. [Molecular abnormality in aging: its contribution to clinical pathology]. *Rinsho byori. The Japanese journal of clinical pathology* 53, 728-734.
- Maruyama, N., Ishigami, A., Kuramoto, M., Handa, S., Kubo, S., Imasawa, T., Seyama, K., Shimosawa, T., Kasahara, Y., 2004. Senescence marker protein-30 knockout mouse as an aging model. *Annals of the New York Academy of Sciences* 1019, 383-387.
- Marzetti, E., Calvani, R., Lorenzi, M., Marini, F., D'Angelo, E., Martone, A.M., Celi, M., Tosato, M., Bernabei, R., Landi, F., 2014. Serum levels of C-terminal agrin fragment (CAF) are associated with sarcopenia in older hip fractured patients. *Experimental gerontology* 60, 79-82.
- Masoro, E.J., 1989. Food restriction research: Its significance for human aging. *American journal of human biology : the official journal of the Human Biology Council* 1, 339-345.
- Mathew, R., Pal Bhadra, M., Bhadra, U., 2017. Insulin/insulin-like growth factor-1 signalling (IIS) based regulation of lifespan across species. *Biogerontology* 18, 35-53.
- Matoba, K., Muramatsu, R., Yamashita, T., 2017. Leptin sustains spontaneous remyelination in the adult central nervous system. *Scientific reports* 7, 40397.
- Matsuo, Y., Gleitsmann, K., Mangner, N., Werner, S., Fischer, T., Bowen, T.S., Kricke, A., Matsumoto, Y., Kurabayashi, M., Schuler, G., Linke, A., Adams, V., 2015. Fibronectin type III domain containing 5 expression in skeletal muscle in chronic heart failure-relevance of inflammatory cytokines. *Journal of cachexia, sarcopenia and muscle* 6, 62-72.
- Matuszek, B., Lenart-Lipinska, M., Duma, D., Solski, J., Nowakowski, A., 2010. Evaluation of concentrations of FGF-21 - a new adipocytokine in type 2 diabetes. *Endokrynologia Polska* 61, 50-54.
- Mayer, O., Seidlerova, J., Filipovsky, J., Vagovicova, P., Wohlfahrt, P., Cifkova, R., Windrichova, J., Topolcan, O., 2016. Soluble receptor for advanced glycation end products and increased aortic stiffness in the general population. *Hypertension research : official journal of the Japanese Society of Hypertension* 39, 266-271.
- Mayeur, S., Spahis, S., Pouliot, Y., Levy, E., 2016. Lactoferrin, a Pleiotropic Protein in Health and Disease. *Antioxidants & redox signaling* 24, 813-836.
- Mazagova, M., Buikema, H., van Buiten, A., Duin, M., Goris, M., Sandovici, M., Henning, R.H., Deelman, L.E., 2013. Genetic deletion of growth differentiation factor 15 augments renal damage in both type 1 and type 2 models of diabetes. *American journal of physiology. Renal physiology* 305, F1249-1264.
- Mazur-Bialy, A.I., 2017. Irisin acts as a regulator of macrophages host defense. *Life sciences* 176, 21-25.

- Mazur-Bialy, A.I., Pochee, E., Zarawski, M., 2017. Anti-Inflammatory Properties of Irisin, Mediator of Physical Activity, Are Connected with TLR4/MyD88 Signaling Pathway Activation. *International journal of molecular sciences* 18.
- Mazzon, C., Anselmo, A., Soldani, C., Cibella, J., Ploia, C., Moalli, F., Burden, S.J., Dustin, M.L., Sarukhan, A., Viola, A., 2012. Agrin is required for survival and function of monocytic cells. *Blood* 119, 5502-5511.
- McClellan, P.L., Jalewa, J., Holscher, C., 2015. Prophylactic liraglutide treatment prevents amyloid plaque deposition, chronic inflammation and memory impairment in APP/PS1 mice. *Behavioural brain research* 293, 96-106.
- McGregor, G., Harvey, J., 2017. Food for thought: Leptin regulation of hippocampal function and its role in Alzheimer's disease. *Neuropharmacology*.
- McKinnon, N.B., Montero-Odasso, M., Doherty, T.J., 2015. Motor unit loss is accompanied by decreased peak muscle power in the lower limb of older adults. *Experimental gerontology* 70, 111-118.
- McNeil, C.J., Doherty, T.J., Stashuk, D.W., Rice, C.L., 2005. Motor unit number estimates in the tibialis anterior muscle of young, old, and very old men. *Muscle & nerve* 31, 461-467.
- Mege, D., Mezouar, S., Dignat-George, F., Panicot-Dubois, L., Dubois, C., 2016. Microparticles and cancer thrombosis in animal models. *Thrombosis research* 140 Suppl 1, S21-26.
- Meier, T., Hauser, D.M., Chiquet, M., Landmann, L., Ruegg, M.A., Brenner, H.R., 1997. Neural agrin induces ectopic postsynaptic specializations in innervated muscle fibers. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 17, 6534-6544.
- Meng, F., Asghar, S., Gao, S., Su, Z., Song, J., Huo, M., Meng, W., Ping, Q., Xiao, Y., 2015. A novel LDL-mimic nanocarrier for the targeted delivery of curcumin into the brain to treat Alzheimer's disease. *Colloids and surfaces. B, Biointerfaces* 134, 88-97.
- Meng, X., Ezzati, P., Wilkins, J.A., 2011. Requirement of podocalyxin in TGF-beta induced epithelial mesenchymal transition. *PLoS one* 6, e18715.
- Meng, Z., Zhang, Y., Wei, Z., Liu, P., Kang, J., Zhang, Y., Ma, D., Ke, C., Chen, Y., Luo, J., Gong, Z., 2017. High serum resistin associates with intrahepatic inflammation and necrosis: an index of disease severity for patients with chronic HBV infection. *BMC gastroenterology* 17, 6.
- Menzaghi, C., Bacci, S., Salvemini, L., Mendonca, C., Palladino, G., Fontana, A., De Bonis, C., Marucci, A., Goheen, E., Prudente, S., Morini, E., Rizza, S., Kanagaki, A., Fini, G., Mangiacotti, D., Federici, M., De Cosmo, S., Pellegrini, F., Doria, A., Trischitta, V., 2014. Serum resistin, cardiovascular disease and all-cause mortality in patients with type 2 diabetes. *PLoS one* 8, e64729.
- Merino, J.J., Muneton-Gomez, V., Alvarez, M.I., Toledano-Diaz, A., 2016. Effects of CX3CR1 and Fractalkine Chemokines in Amyloid Beta Clearance and p-Tau Accumulation in Alzheimer's Disease (AD) Rodent Models: Is Fractalkine a Systemic Biomarker for AD? *Current Alzheimer research* 13, 403-412.
- Mezuk, B., Edwards, L., Lohman, M., Choi, M., Lapane, K., 2012. Depression and frailty in later life: a synthetic review. *International journal of geriatric psychiatry* 27, 879-892.
- Milanesi, E., Zanardini, R., Rosso, G., Maina, G., Barbon, A., Mora, C., Minelli, A., Gennarelli, M., Bocchio-Chiavetto, L., 2017. Insulin-like growth factor binding protein 2 in bipolar disorder: An expression study in peripheral tissues. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry*, 1-9.
- Miller, A.M., Purves, D., McConnachie, A., Asquith, D.L., Batty, G.D., Burns, H., Cavanagh, J., Ford, I., McLean, J.S., Packard, C.J., Shiels, P.G., Turner, H., Velupillai, Y.N., Deans, K.A., Welsh, P., McInnes, I.B., Sattar, N., 2012. Soluble ST2 associates with diabetes

- but not established cardiovascular risk factors: a new inflammatory pathway of relevance to diabetes? *PloS one* 7, e47830.
- Miller, K.N., Burhans, M.S., Clark, J.P., Howell, P.R., Polewski, M.A., DeMuth, T.M., Eliceiri, K.W., Lindstrom, M.J., Ntambi, J.M., Anderson, R.M., 2017. Aging and caloric restriction impact adipose tissue, adiponectin, and circulating lipids. *Aging cell* 16, 497-507.
- Mionnet, C., Buatois, V., Kanda, A., Milcent, V., Fleury, S., Lair, D., Langelot, M., Lacoeyille, Y., Hessel, E., Coffman, R., Magnan, A., Dombrowicz, D., Glaichenhaus, N., Julia, V., 2010. CX3CR1 is required for airway inflammation by promoting T helper cell survival and maintenance in inflamed lung. *Nature medicine* 16, 1305-1312.
- Miranda, A.S., Simoes, E.S.A.C., 2017. Serum levels of angiotensin converting enzyme as a biomarker of liver fibrosis. *World journal of gastroenterology* 23, 8439-8442.
- Miskimins, W.K., Ahn, H.J., Kim, J.Y., Ryu, S., Jung, Y.S., Choi, J.Y., 2014. Synergistic anti-cancer effect of phenformin and oxamate. *PloS one* 9, e85576.
- Miskin, R., Masos, T., 1997. Transgenic mice overexpressing urokinase-type plasminogen activator in the brain exhibit reduced food consumption, body weight and size, and increased longevity. *The journals of gerontology. Series A, Biological sciences and medical sciences* 52, B118-124.
- Miskin, R., Tirosh, O., Pardo, M., Zusman, I., Schwartz, B., Yahav, S., Dubnov, G., Kohen, R., 2005. AlphaMUPA mice: a transgenic model for longevity induced by caloric restriction. *Mechanisms of ageing and development* 126, 255-261.
- Mitnitski, A., Collerton, J., Martin-Ruiz, C., Jagger, C., von Zglinicki, T., Rockwood, K., Kirkwood, T.B., 2015. Age-related frailty and its association with biological markers of ageing. *BMC medicine* 13, 161.
- Mittaud, P., Camilleri, A.A., Willmann, R., Erb-Vogtli, S., Burden, S.J., Fuhrer, C., 2004. A single pulse of agrin triggers a pathway that acts to cluster acetylcholine receptors. *Molecular and cellular biology* 24, 7841-7854.
- Miyoshi, Y., Funahashi, T., Kihara, S., Taguchi, T., Tamaki, Y., Matsuzawa, Y., Noguchi, S., 2003. Association of serum adiponectin levels with breast cancer risk. *Clinical cancer research : an official journal of the American Association for Cancer Research* 9, 5699-5704.
- Moalli, F., Jaillon, S., Inforzato, A., Sironi, M., Bottazzi, B., Mantovani, A., Garlanda, C., 2011. Pathogen recognition by the long pentraxin PTX3. *Journal of biomedicine & biotechnology* 2011, 830421.
- Mohammadi, M., Zarghami, N., Hedayati, M., Ghaemmaghami, S., 2017. Synergistic Effects of Resistin and Visfatin as Adipocyte Derived Hormones on Telomerase Gene Expression in AGS Gastric Cancer Cell Line. *Acta medica Iranica* 55, 621-627.
- Mohle, L., Israel, N., Paarmann, K., Krohn, M., Pietkiewicz, S., Muller, A., Lavrik, I.N., Buguliskis, J.S., Schott, B.H., Schluter, D., Gundelfinger, E.D., Montag, D., Seifert, U., Pahnke, J., Dunay, I.R., 2016. Chronic *Toxoplasma gondii* infection enhances beta-amyloid phagocytosis and clearance by recruited monocytes. *Acta neuropathologica communications* 4, 25.
- Montacute, R., Foley, K., Forman, R., Else, K.J., Cruickshank, S.M., Allan, S.M., 2017. Enhanced susceptibility of triple transgenic Alzheimer's disease (3xTg-AD) mice to acute infection. *Journal of neuroinflammation* 14, 50.
- Monti, D., Ostan, R., Borelli, V., Castellani, G., Franceschi, C., 2017. Inflammaging and human longevity in the omics era. *Mechanisms of ageing and development* 165, 129-138.
- Montoro-Garcia, S., Hernandez-Romero, D., Jover, E., Garcia-Honrubia, A., Vilchez, J.A., Casas, T., Martinez, P., Climent, V., Caballero, L., Valdes, M., Marin, F., 2012. Growth differentiation factor-15, a novel biomarker related with disease severity in patients with hypertrophic cardiomyopathy. *European journal of internal medicine* 23, 169-174.

- Moradi, N., Fadaei, R., Emamgholipour, S., Kazemian, E., Panahi, G., Vahedi, S., Saed, L., Fallah, S., 2018. Association of circulating CTRP9 with soluble adhesion molecules and inflammatory markers in patients with type 2 diabetes mellitus and coronary artery disease. *PloS one* 13, e0192159.
- Morello, F., Ravetti, A., Nazerian, P., Liedl, G., Veglio, M.G., Battista, S., Vanni, S., Pivetta, E., Montrucchio, G., Mengozzi, G., Rinaldi, M., Moiraghi, C., Lupia, E., 2016. Plasma Lactate Dehydrogenase Levels Predict Mortality in Acute Aortic Syndromes: A Diagnostic Accuracy and Observational Outcome Study. *Medicine* 95, e2776.
- Moreno-Navarrete, J.M., Ortega, F.J., Bassols, J., Castro, A., Ricart, W., Fernandez-Real, J.M., 2008. Association of circulating lactoferrin concentration and 2 nonsynonymous LTF gene polymorphisms with dyslipidemia in men depends on glucose-tolerance status. *Clinical chemistry* 54, 301-309.
- Mori, T., Asano, T., Town, T., 2010. Targeting S100B in Cerebral Ischemia and in Alzheimer's Disease. *Cardiovascular psychiatry and neurology* 2010.
- Morishita, S., Kawaguchi, H., Ono, T., Miura, N., Murakoshi, M., Sugiyama, K., Kato, H., Tanimoto, A., Nishino, H., 2016. Enteric lactoferrin attenuates the development of high-fat and high-cholesterol diet-induced hypercholesterolemia and atherosclerosis in Micromini pigs. *Bioscience, biotechnology, and biochemistry* 80, 295-303.
- Morley, J.E., 2014. Cognition and nutrition. *Current opinion in clinical nutrition and metabolic care* 17, 1-4.
- Morling, J.R., Fallowfield, J.A., Williamson, R.M., Nee, L.D., Jackson, A.P., Glancy, S., Reynolds, R.M., Hayes, P.C., Guha, I.N., Strachan, M.W., Price, J.F., 2014. Non-invasive hepatic biomarkers (ELF and CK18) in people with type 2 diabetes: the Edinburgh type 2 diabetes study. *Liver international : official journal of the International Association for the Study of the Liver* 34, 1267-1277.
- Moro-Garcia, M.A., Echeverria, A., Galan-Artimez, M.C., Suarez-Garcia, F.M., Solano-Jaurrieta, J.J., Avanzas-Fernandez, P., Diaz-Molina, B., Lambert, J.L., Lopez-Larrea, C., Moris de la Tassa, C., Alonso-Arias, R., 2014. Immunosenescence and inflammation characterize chronic heart failure patients with more advanced disease. *International journal of cardiology* 174, 590-599.
- Morovat, A., Weerasinghe, G., Nesbitt, V., Hofer, M., Agnew, T., Quaghebeur, G., Sergeant, K., Fatter, C., Guha, N., Mirzazadeh, M., Poulton, J., 2017. Use of FGF-21 as a Biomarker of Mitochondrial Disease in Clinical Practice. *Journal of clinical medicine* 6.
- Motzek, A., Knezevic, J., Switzeny, O.J., Cooper, A., Baric, I., Beluzic, R., Strauss, K.A., Puffenberger, E.G., Mudd, S.H., Vugrek, O., Zechner, U., 2016. Abnormal Hypermethylation at Imprinting Control Regions in Patients with S-Adenosylhomocysteine Hydrolase (AHCY) Deficiency. *PloS one* 11, e0151261.
- Muchtar, E., Dispenzieri, A., Lacy, M.Q., Buadi, F.K., Kapoor, P., Hayman, S.R., Gonsalves, W., Warsame, R., Kourelis, T.V., Chakraborty, R., Russell, S., Lust, J.A., Lin, Y., Go, R.S., Zeldenrust, S., Dingli, D., Leung, N., Rajkumar, S.V., Kyle, R.A., Kumar, S.K., Gertz, M.A., 2017. Elevation of serum lactate dehydrogenase in AL amyloidosis reflects tissue damage and is an adverse prognostic marker in patients not eligible for stem cell transplantation. *British journal of haematology* 178, 888-895.
- Muller, S., Ronfani, L., Bianchi, M.E., 2004. Regulated expression and subcellular localization of HMGB1, a chromatin protein with a cytokine function. *Journal of internal medicine* 255, 332-343.
- Mulvihill, N.T., Foley, J.B., Crean, P., Walsh, M., 2002. Prediction of cardiovascular risk using soluble cell adhesion molecules. *European heart journal* 23, 1569-1574.
- Muniyappa, R., Abel, B.S., Asthana, A., Walter, M.F., Cochran, E.K., Remaley, A.T., Skarulis, M.C., Gorden, P., Brown, R.J., 2017. Metreleptin therapy lowers plasma angiopoietin-

- like protein 3 in patients with generalized lipodystrophy. *Journal of clinical lipidology* 11, 543-550.
- Murata, Y., Konishi, M., Itoh, N., 2011. FGF21 as an Endocrine Regulator in Lipid Metabolism: From Molecular Evolution to Physiology and Pathophysiology. *Journal of nutrition and metabolism* 2011, 981315.
- Murthy, M.N., Blauwendraat, C., Ukbec, Guelfi, S., Ipdgc, Hardy, J., Lewis, P.A., Trabzuni, D., 2017. Increased brain expression of GPNMB is associated with genome wide significant risk for Parkinson's disease on chromosome 7p15.3. *Neurogenetics* 18, 121-133.
- Musial, K., Bargenda, A., Zwolinska, D., 2015. Urine matrix metalloproteinases and their extracellular inducer EMMPRIN in children with chronic kidney disease. *Renal failure* 37, 980-984.
- Musilova, I., Andrys, C., Krejsek, J., Drahosova, M., Zednikova, B., Pliskova, L., Zemlickova, H., Jacobsson, B., Kacerovsky, M., 2017. Amniotic fluid pentraxins: Potential early markers for identifying intra-amniotic inflammatory complications in preterm pre-labor rupture of membranes. *American journal of reproductive immunology*.
- Mykhalchyshyn, G., Kobylak, N., Bodnar, P., 2015. Diagnostic accuracy of acyl-ghrelin and its association with non-alcoholic fatty liver disease in type 2 diabetic patients. *Journal of diabetes and metabolic disorders* 14, 44.
- Na, K.R., Kim, Y.H., Chung, H.K., Yeo, M.K., Ham, Y.R., Jeong, J.Y., Kim, K.S., Lee, K.W., Choi, D.E., 2017. Growth differentiation factor 15 as a predictor of adverse renal outcomes in patients with immunoglobulin A nephropathy. *Internal medicine journal* 47, 1393-1399.
- Nagasawa, M., Takami, Y., Akasaka, H., Kabayama, M., Maeda, S., Yokoyama, S., Fujimoto, T., Nozato, Y., Imaizumi, Y., Takeda, M., Itoh, N., Takeya, Y., Yamamoto, K., Sugimoto, K., Nakagawa, T., Masui, Y., Arai, Y., Ishizaki, T., Ikebe, K., Gondo, Y., Kamide, K., Rakugi, H., 2018. High plasma adiponectin levels are associated with frailty in a general old-old population: The Septuagenarians, Octogenarians, Nonagenarians Investigation with Centenarians study. *Geriatrics & gerontology international* 18, 839-846.
- Nagaya, N., Moriya, J., Yasumura, Y., Uematsu, M., Ono, F., Shimizu, W., Ueno, K., Kitakaze, M., Miyatake, K., Kangawa, K., 2004. Effects of ghrelin administration on left ventricular function, exercise capacity, and muscle wasting in patients with chronic heart failure. *Circulation* 110, 3674-3679.
- Nagpal, S.J., Lopez, R., Feldstein, A.E., Alkhoury, N., 2015. Serum cytokeratin-18 fragment levels predict development of type 2 diabetes mellitus in adult patients with NAFLD. *Liver international : official journal of the International Association for the Study of the Liver* 35, 2621.
- Nair, V., Robinson-Cohen, C., Smith, M.R., Bellovich, K.A., Bhat, Z.Y., Bobadilla, M., Brosius, F., de Boer, I.H., Essioux, L., Formentini, I., Gadegbeku, C.A., Gipson, D., Hawkins, J., Himmelfarb, J., Kestenbaum, B., Kretzler, M., Magnone, M.C., Perumal, K., Steigerwalt, S., Ju, W., Bansal, N., 2017. Growth Differentiation Factor-15 and Risk of CKD Progression. *Journal of the American Society of Nephrology : JASN* 28, 2233-2240.
- Naito, A.T., Sumida, T., Nomura, S., Liu, M.L., Higo, T., Nakagawa, A., Okada, K., Sakai, T., Hashimoto, A., Hara, Y., Shimizu, I., Zhu, W., Toko, H., Katada, A., Akazawa, H., Oka, T., Lee, J.K., Minamino, T., Nagai, T., Walsh, K., Kikuchi, A., Matsumoto, M., Botto, M., Shiojima, I., Komuro, I., 2012. Complement C1q activates canonical Wnt signaling and promotes aging-related phenotypes. *Cell* 149, 1298-1313.
- Nakamura, A., Miura, S., Shiga, Y., Norimatsu, K., Miyase, Y., Suematsu, Y., Mitsutake, R., Saku, K., 2015. Is pentraxin 3 a biomarker, a player, or both in the context of coronary atherosclerosis and metabolic factors? *Heart and vessels* 30, 752-761.
- Nakatsuji, H., Kishida, K., Kobayashi, H., Funahashi, T., Shimomura, I., Senri Study, I.I.G., 2013. Three-month treatment with pioglitazone reduces circulating C1q-binding

- adiponectin complex to total-adiponectin ratio, without changes in body mass index, in people with type 2 diabetes. *Diabetes research and clinical practice* 99, e14-17.
- Nanki, T., Imai, T., Kawai, S., 2017. Fractalkine/CX3CL1 in rheumatoid arthritis. *Modern rheumatology* 27, 392-397.
- Narciso-Schiavon, J.L., Pereira, J.G., Silva, T.E., Bansho, E.T.O., Morato, E.F., Pinheiro, J.T., Muraro-Wildner, L., Bazzo, M.L., Dantas-Correa, E.B., Schiavon, L.L., 2017. Circulating levels of pentraxin-3 (PTX3) in patients with liver cirrhosis. *Annals of hepatology* 16, 780-787.
- Nass, R., 2013. Growth hormone axis and aging. *Endocrinology and metabolism clinics of North America* 42, 187-199.
- Natalicchio, A., Marrano, N., Biondi, G., Spagnuolo, R., Labarbuta, R., Porreca, I., Cignarelli, A., Bugliani, M., Marchetti, P., Perrini, S., Laviola, L., Giorgino, F., 2017. The Myokine Irisin Is Released in Response to Saturated Fatty Acids and Promotes Pancreatic beta-Cell Survival and Insulin Secretion. *Diabetes* 66, 2849-2856.
- Navratilova, Z., Kolek, V., Petrek, M., 2016. Matrix Metalloproteinases and Their Inhibitors in Chronic Obstructive Pulmonary Disease. *Archivum immunologiae et therapiae experimentalis* 64, 177-193.
- Nawrocki, A.R., Rajala, M.W., Tomas, E., Pajvani, U.B., Saha, A.K., Trumbauer, M.E., Pang, Z., Chen, A.S., Ruderman, N.B., Chen, H., Rossetti, L., Scherer, P.E., 2006. Mice lacking adiponectin show decreased hepatic insulin sensitivity and reduced responsiveness to peroxisome proliferator-activated receptor gamma agonists. *The Journal of biological chemistry* 281, 2654-2660.
- Netto, C.B., Portela, L.V., Ferreira, C.T., Kieling, C., Matte, U., Felix, T., da Silveira, T.R., Souza, D.O., Goncalves, C.A., Giugliani, R., 2005. Ontogenetic changes in serum S100B in Down syndrome patients. *Clinical biochemistry* 38, 433-435.
- Neuman, R., Danser, A.H.J., 2018. Autoantibodies against angiotensin and adrenergic receptors: more than a biomarker? *Clinical science* 132, 127-130.
- Neumann, F.R., Bittcher, G., Annies, M., Schumacher, B., Kroger, S., Ruegg, M.A., 2001. An alternative amino-terminus expressed in the central nervous system converts agrin to a type II transmembrane protein. *Molecular and cellular neurosciences* 17, 208-225.
- Neumann, U., Rueeger, H., Machauer, R., Veenstra, S.J., Lueoend, R.M., Tintelnot-Blomley, M., Laue, G., Beltz, K., Vogg, B., Schmid, P., Friauff, W., Shimshek, D.R., Staufenbiel, M., Jacobson, L.H., 2015. A novel BACE inhibitor NB-360 shows a superior pharmacological profile and robust reduction of amyloid-beta and neuroinflammation in APP transgenic mice. *Molecular neurodegeneration* 10, 44.
- Newington, J.T., Rappon, T., Albers, S., Wong, D.Y., Rylett, R.J., Cumming, R.C., 2012. Overexpression of pyruvate dehydrogenase kinase 1 and lactate dehydrogenase A in nerve cells confers resistance to amyloid beta and other toxins by decreasing mitochondrial respiration and reactive oxygen species production. *The Journal of biological chemistry* 287, 37245-37258.
- Newman, A.B., Gottdiener, J.S., McBurnie, M.A., Hirsch, C.H., Kop, W.J., Tracy, R., Walston, J.D., Fried, L.P., Cardiovascular Health Study Research, G., 2001. Associations of subclinical cardiovascular disease with frailty. *The journals of gerontology. Series A, Biological sciences and medical sciences* 56, M158-166.
- Nguyen, A.H., Detty, S.Q., Agrawal, D.K., 2017. Clinical Implications of High-mobility Group Box-1 (HMGB1) and the Receptor for Advanced Glycation End-products (RAGE) in Cutaneous Malignancy: A Systematic Review. *Anticancer research* 37, 1-7.
- Ni, M., Wei, W., Wang, Y., Zhang, N., Ding, H., Shen, C., Zheng, F., 2013. Serum levels of calreticulin in correlation with disease activity in patients with rheumatoid arthritis. *Journal of clinical immunology* 33, 947-953.

- Nicholson, A.M., Finch, N.A., Thomas, C.S., Wojtas, A., Rutherford, N.J., Mielke, M.M., Roberts, R.O., Boeve, B.F., Knopman, D.S., Petersen, R.C., Rademakers, R., 2014. Progranulin protein levels are differently regulated in plasma and CSF. *Neurology* 82, 1871-1878.
- Niculescu, F., Rus, H., 2004. The role of complement activation in atherosclerosis. *Immunologic research* 30, 73-80.
- Nigam, S.M., Xu, S., Kritikou, J.S., Marosi, K., Brodin, L., Mattson, M.P., 2017. Exercise and BDNF reduce Abeta production by enhancing alpha-secretase processing of APP. *Journal of neurochemistry* 142, 286-296.
- Niinaga, R., Yamamoto, H., Yoshii, M., Uekita, H., Yamane, N., Kochi, I., Matsumoto, A., Matsuoka, T., Kihara, S., 2016. Marked elevation of serum M2BP-adiponectin complex in men with coronary artery disease. *Atherosclerosis* 253, 70-74.
- Nikoletopoulou, V., Sidiropoulou, K., Kallergi, E., Dalezios, Y., Tavernarakis, N., 2017. Modulation of Autophagy by BDNF Underlies Synaptic Plasticity. *Cell metabolism* 26, 230-242 e235.
- Nilsson, P., Loganathan, K., Sekiguchi, M., Matsuba, Y., Hui, K., Tsubuki, S., Tanaka, M., Iwata, N., Saito, T., Saido, T.C., 2013. Abeta secretion and plaque formation depend on autophagy. *Cell reports* 5, 61-69.
- Nishimura, M., Umehara, H., Nakayama, T., Yoneda, O., Hieshima, K., Kakizaki, M., Dohmae, N., Yoshie, O., Imai, T., 2002. Dual functions of fractalkine/CX3C ligand 1 in trafficking of perforin+/granzyme B+ cytotoxic effector lymphocytes that are defined by CX3CR1 expression. *Journal of immunology* 168, 6173-6180.
- Niyonzima, N., Halvorsen, B., Sporsheim, B., Garred, P., Aukrust, P., Mollnes, T.E., Espevik, T., 2017. Complement activation by cholesterol crystals triggers a subsequent cytokine response. *Molecular immunology* 84, 43-50.
- Noda, Y., Tsuruma, K., Takata, M., Ishisaka, M., Tanaka, H., Nakano, Y., Nagahara, Y., Shimazawa, M., Hara, H., 2017. GPNMB Induces BiP Expression by Enhancing Splicing of BiP Pre-mRNA during the Endoplasmic Reticulum Stress Response. *Scientific reports* 7, 12160.
- Noguchi, R., Kaji, K., Namisaki, T., Moriya, K., Kitade, M., Takeda, K., Kawaratani, H., Okura, Y., Aihara, Y., Furukawa, M., Mitoro, A., Yoshiji, H., 2017. Serum angiotensin-converting enzyme level for evaluating significant fibrosis in chronic hepatitis B. *World journal of gastroenterology* 23, 6705-6714.
- Nourhashemi, F., Andrieu, S., Gillette-Guyonnet, S., Reynish, E., Albarede, J.L., Grandjean, H., Vellas, B., 2002. Is there a relationship between fat-free soft tissue mass and low cognitive function? Results from a study of 7,105 women. *Journal of the American Geriatrics Society* 50, 1796-1801.
- Novak, M.L., Bryer, S.C., Cheng, M., Nguyen, M.H., Conley, K.L., Cunningham, A.K., Xue, B., Sisson, T.H., You, J.S., Hornberger, T.A., Koh, T.J., 2011. Macrophage-specific expression of urokinase-type plasminogen activator promotes skeletal muscle regeneration. *Journal of immunology* 187, 1448-1457.
- Numakawa, T., Richards, M., Nakajima, S., Adachi, N., Furuta, M., Odaka, H., Kunugi, H., 2014. The role of brain-derived neurotrophic factor in comorbid depression: possible linkage with steroid hormones, cytokines, and nutrition. *Frontiers in psychiatry* 5, 136.
- Nunez Lopez, Y.O., Pittas, A.G., Pratley, R.E., Seyhan, A.A., 2017. Circulating levels of miR-7, miR-152 and miR-192 respond to vitamin D supplementation in adults with prediabetes and correlate with improvements in glycemic control. *The Journal of nutritional biochemistry* 49, 117-122.
- Obeid, M., Tesniere, A., Ghiringhelli, F., Fimia, G.M., Apetoh, L., Perfettini, J.L., Castedo, M., Mignot, G., Panaretakis, T., Casares, N., Metivier, D., Larochette, N., van Endert, P., Ciccocanti, F., Piacentini, M., Zitvogel, L., Kroemer, G., 2007. Calreticulin exposure dictates the immunogenicity of cancer cell death. *Nature medicine* 13, 54-61.

- Oh, S.M., Pyo, C.W., Kim, Y., Choi, S.Y., 2004. Neutrophil lactoferrin upregulates the human p53 gene through induction of NF-kappaB activation cascade. *Oncogene* 23, 8282-8291.
- Ohadi, M., Mirabzadeh, A., Esmailzadeh-Gharehdaghi, E., Rezazadeh, M., Hosseinkhanni, S., Oladnabi, M., Firouzabadi, S.G., Darvish, H., 2012. Novel evidence of the involvement of calreticulin in major psychiatric disorders. *Progress in neuro-psychopharmacology & biological psychiatry* 37, 276-281.
- Ohashi, K., Funahashi, T., 2006. [Mutations and polymorphisms in adiponectin gene]. *Nihon rinsho. Japanese journal of clinical medicine Suppl* 3, 264-268.
- Ohlmeier, S., Nieminen, P., Gao, J., Kanerva, T., Ronty, M., Toljamo, T., Bergmann, U., Mazur, W., Pulkkinen, V., 2016. Lung tissue proteomics identifies elevated transglutaminase 2 levels in stable chronic obstructive pulmonary disease. *American journal of physiology. Lung cellular and molecular physiology* 310, L1155-1165.
- Okubo, K., Kamiya, M., Urano, Y., Nishi, H., Herter, J.M., Mayadas, T., Hirohama, D., Suzuki, K., Kawakami, H., Tanaka, M., Kurosawa, M., Kagaya, S., Hishikawa, K., Nangaku, M., Fujita, T., Hayashi, M., Hirahashi, J., 2016. Lactoferrin Suppresses Neutrophil Extracellular Traps Release in Inflammation. *EBioMedicine* 10, 204-215.
- Okugawa, Y., Yao, L., Toiyama, Y., Yamamoto, A., Shigemori, T., Yin, C., Omura, Y., Ide, S., Kitajima, T., Shimura, T., Fujikawa, H., Yasuda, H., Hiro, J., Yoshiyama, S., Kobayashi, M., Tanaka, K., Inoue, Y., Araki, T., Miki, C., Kusunoki, M., 2018. Prognostic impact of sarcopenia and its correlation with circulating miR-21 in colorectal cancer patients. *Oncology reports* 39, 1555-1564.
- Olivera Santa-Catalina, M., Redondo, P.C., Cantonero, C., Granados, M.P., Sanchez-Collado, J., Albarran, L., Lopez, J.J., 2017. New insights into adipokines as potential biomarkers for type-2 diabetes mellitus. *Current medicinal chemistry*.
- Olivieri, F., Rippo, M.R., Procopio, A.D., Fazioli, F., 2013. Circulating inflamma-miRs in aging and age-related diseases. *Frontiers in genetics* 4, 121.
- Olleros Santos-Ruiz, M., Sadaba, M.C., Martin-Estal, I., Munoz, U., Sebal Neira, C., Castilla-Cortazar, I., 2017. The single IGF-1 partial deficiency is responsible for mitochondrial dysfunction and is restored by IGF-1 replacement therapy. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society* 35, 21-32.
- Olsen, K.C., Epa, A.P., Kulkarni, A.A., Kottmann, R.M., McCarthy, C.E., Johnson, G.V., Thatcher, T.H., Phipps, R.P., Sime, P.J., 2014. Inhibition of transglutaminase 2, a novel target for pulmonary fibrosis, by two small electrophilic molecules. *American journal of respiratory cell and molecular biology* 50, 737-747.
- Ong, K.L., Rye, K.A., O'Connell, R., Jenkins, A.J., Brown, C., Xu, A., Sullivan, D.R., Barter, P.J., Keech, A.C., investigators, F.s., 2012. Long-term fenofibrate therapy increases fibroblast growth factor 21 and retinol-binding protein 4 in subjects with type 2 diabetes. *The Journal of clinical endocrinology and metabolism* 97, 4701-4708.
- Ortega Moreno, L., Copetti, M., Fontana, A., De Bonis, C., Salvemini, L., Trischitta, V., Menzaghi, C., 2016. Evidence of a causal relationship between high serum adiponectin levels and increased cardiovascular mortality rate in patients with type 2 diabetes. *Cardiovascular diabetology* 15, 17.
- Osada-Oka, M., Shiota, M., Izumi, Y., Nishiyama, M., Tanaka, M., Yamaguchi, T., Sakurai, E., Miura, K., Iwao, H., 2017. Macrophage-derived exosomes induce inflammatory factors in endothelial cells under hypertensive conditions. *Hypertension research : official journal of the Japanese Society of Hypertension* 40, 353-360.
- Otani, K., Kitayama, J., Yasuda, K., Nio, Y., Iwabu, M., Okudaira, S., Aoki, J., Yamauchi, T., Kadowaki, T., Nagawa, H., 2010. Adiponectin suppresses tumorigenesis in Apc(Min)(/+) mice. *Cancer letters* 288, 177-182.

- Otterdal, K., Portillo, A., Astrup, E., Ludviksen, J., Davi, G., Holm, S., Santilli, F., Vitale, G., Raoult, D., Olano, J.P., Schjalm, C., Halvorsen, B., Oteo, J.A., Mollnes, T.E., Aukrust, P., Nilsson, P.H., 2016. High serum CXCL10 in *Rickettsia conorii* infection is endothelial cell mediated subsequent to whole blood activation. *Cytokine* 83, 269-274.
- Ouchi, N., Kihara, S., Arita, Y., Okamoto, Y., Maeda, K., Kuriyama, H., Hotta, K., Nishida, M., Takahashi, M., Muraguchi, M., Ohmoto, Y., Nakamura, T., Yamashita, S., Funahashi, T., Matsuzawa, Y., 2000. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. *Circulation* 102, 1296-1301.
- Ouchi, N., Kihara, S., Funahashi, T., Matsuzawa, Y., Walsh, K., 2003. Obesity, adiponectin and vascular inflammatory disease. *Current opinion in lipidology* 14, 561-566.
- Pacho, C., Domingo, M., Nunez, R., Lupon, J., Nunez, J., Barallat, J., Moliner, P., de Antonio, M., Santesmases, J., Cediell, G., Roura, S., Pastor, M.C., Tor, J., Bayes-Genis, A., 2018. Predictive biomarkers for death and rehospitalization in comorbid frail elderly heart failure patients. *BMC geriatrics* 18, 109.
- Paganini-Hill, A., Clark, L.J., Henderson, V.W., Birge, S.J., 2001. Clock drawing: analysis in a retirement community. *Journal of the American Geriatrics Society* 49, 941-947.
- Palomera-Avalos, V., Grinan-Ferre, C., Izquierdo, V., Camins, A., Sanfeliu, C., Canudas, A.M., Pallas, M., 2018. Resveratrol modulates response against acute inflammatory stimuli in aged mouse brain. *Experimental gerontology* 102, 3-11.
- Pan, W.W., Myers, M.G., Jr., 2018. Leptin and the maintenance of elevated body weight. *Nature reviews. Neuroscience* 19, 95-105.
- Panati, K., Suneetha, Y., Narala, V.R., 2016. Irisin/FNDC5--An updated review. *European review for medical and pharmacological sciences* 20, 689-697.
- Pandya, J.M., Lundell, A.C., Andersson, K., Nordstrom, I., Theander, E., Rudin, A., 2017. Blood chemokine profile in untreated early rheumatoid arthritis: CXCL10 as a disease activity marker. *Arthritis research & therapy* 19, 20.
- Papa, S., Skulachev, V.P., 1997. Reactive oxygen species, mitochondria, apoptosis and aging. *Molecular and cellular biochemistry* 174, 305-319.
- Papaconstantinou, J., Hsieh, C.C., 2015. IGF-1 mediated phosphorylation of specific IRS-1 serines in Ames dwarf fibroblasts is associated with longevity. *Oncotarget* 6, 35315-35323.
- Park, J.H., Choi, S.H., Kim, H., Ji, S.T., Jang, W.B., Kim, J.H., Baek, S.H., Kwon, S.M., 2016. Doxorubicin Regulates Autophagy Signals via Accumulation of Cytosolic Ca(2+) in Human Cardiac Progenitor Cells. *International journal of molecular sciences* 17.
- Park, M.H., Lee, J.S., Yoon, J.H., 2012. High expression of CX3CL1 by tumor cells correlates with a good prognosis and increased tumor-infiltrating CD8+ T cells, natural killer cells, and dendritic cells in breast carcinoma. *Journal of surgical oncology* 106, 386-392.
- Park, S.J., Kong, H.K., Kim, Y.S., Lee, Y.S., Park, J.H., 2015. Inhibition of S-adenosylhomocysteine hydrolase decreases cell mobility and cell proliferation through cell cycle arrest. *American journal of cancer research* 5, 2127-2138.
- Park, S.W., Kim, J.H., Mook-Jung, I., Kim, K.W., Park, W.J., Park, K.H., Kim, J.H., 2014. Intracellular amyloid beta alters the tight junction of retinal pigment epithelium in 5XFAD mice. *Neurobiology of aging* 35, 2013-2020.
- Park, S.Y., Jeong, A.J., Kim, G.Y., Jo, A., Lee, J.E., Leem, S.H., Yoon, J.H., Ye, S.K., Chung, J.W., 2017. Lactoferrin Protects Human Mesenchymal Stem Cells from Oxidative Stress-Induced Senescence and Apoptosis. *Journal of microbiology and biotechnology* 27, 1877-1884.
- Park, Y.G., Jeong, J.K., Lee, J.H., Lee, Y.J., Seol, J.W., Kim, S.J., Hur, T.Y., Jung, Y.H., Kang, S.J., Park, S.Y., 2013. Lactoferrin protects against prion protein-induced cell death in

- neuronal cells by preventing mitochondrial dysfunction. *International journal of molecular medicine* 31, 325-330.
- Park, Y.W., Kang, Y.M., Butterfield, J., Detmar, M., Goronzy, J.J., Weyand, C.M., 2004. Thrombospondin 2 functions as an endogenous regulator of angiogenesis and inflammation in rheumatoid arthritis. *The American journal of pathology* 165, 2087-2098.
- Parkhitko, A.A., Binari, R., Zhang, N., Asara, J.M., Demontis, F., Perrimon, N., 2016. Tissue-specific down-regulation of S-adenosyl-homocysteine via suppression of dAhcyL1/dAhcyL2 extends health span and life span in *Drosophila*. *Genes & development* 30, 1409-1422.
- Parks, R.J., Fares, E., Macdonald, J.K., Ernst, M.C., Sinal, C.J., Rockwood, K., Howlett, S.E., 2012. A procedure for creating a frailty index based on deficit accumulation in aging mice. *The journals of gerontology. Series A, Biological sciences and medical sciences* 67, 217-227.
- Pastor-Arroyo, E.M., Gehring, N., Krudewig, C., Costantino, S., Bettoni, C., Knopfel, T., Sabrautzki, S., Lorenz-Depiereux, B., Pastor, J., Strom, T.M., Hrabe de Angelis, M., Camici, G.G., Paneni, F., Wagner, C.A., Rubio-Aliaga, I., 2018. The elevation of circulating fibroblast growth factor 23 without kidney disease does not increase cardiovascular disease risk. *Kidney international* 94, 49-59.
- Patel, C.G., Yee, A.J., Scullen, T.A., Nemani, N., Santo, L., Richardson, P.G., Laubach, J.P., Ghobrial, I.M., Schlossman, R.L., Munshi, N.C., Anderson, K.C., Raje, N.S., 2014. Biomarkers of bone remodeling in multiple myeloma patients to tailor bisphosphonate therapy. *Clinical cancer research : an official journal of the American Association for Cancer Research* 20, 3955-3961.
- Patel, T.R., Butler, G., McFarlane, A., Xie, I., Overall, C.M., Stetefeld, J., 2012. Site specific cleavage mediated by MMPs regulates function of agrin. *PloS one* 7, e43669.
- Patterson, B.W., Elbert, D.L., Mawuenyega, K.G., Kasten, T., Ovod, V., Ma, S., Xiong, C., Chott, R., Yarasheski, K., Sigurdson, W., Zhang, L., Goate, A., Benzinger, T., Morris, J.C., Holtzman, D., Bateman, R.J., 2015. Age and amyloid effects on human central nervous system amyloid-beta kinetics. *Annals of neurology* 78, 439-453.
- Pavanello, S., Stendardo, M., Mastrangelo, G., Bonci, M., Bottazzi, B., Campisi, M., Nardini, M., Leone, R., Mantovani, A., Boschetto, P., 2017. Inflammatory Long Pentraxin 3 is Associated with Leukocyte Telomere Length in Night-Shift Workers. *Frontiers in immunology* 8, 516.
- Pedard, M., Demougeot, C., Prati, C., Marie, C., 2018. Brain-derived neurotrophic factor in adjuvant-induced arthritis in rats. Relationship with inflammation and endothelial dysfunction. *Progress in neuro-psychopharmacology & biological psychiatry* 82, 249-254.
- Peine, M., Marek, R.M., Lohning, M., 2016. IL-33 in T Cell Differentiation, Function, and Immune Homeostasis. *Trends in immunology* 37, 321-333.
- Peng, J., Deng, X., Huang, W., Yu, J.H., Wang, J.X., Wang, J.P., Yang, S.B., Liu, X., Wang, L., Zhang, Y., Zhou, X.Y., Yang, H., He, Y.Z., Xu, F.Y., 2017. Irisin protects against neuronal injury induced by oxygen-glucose deprivation in part depends on the inhibition of ROS-NLRP3 inflammatory signaling pathway. *Molecular immunology* 91, 185-194.
- Peng, Y., Kim, M.J., Hullinger, R., O'Riordan, K.J., Burger, C., Pehar, M., Puglielli, L., 2016. Improved proteostasis in the secretory pathway rescues Alzheimer's disease in the mouse. *Brain : a journal of neurology* 139, 937-952.
- Perakakis, N., Triantafyllou, G.A., Fernandez-Real, J.M., Huh, J.Y., Park, K.H., Seufert, J., Mantzoros, C.S., 2017. Physiology and role of irisin in glucose homeostasis. *Nature reviews. Endocrinology* 13, 324-337.

- Perfield, J.W., 2nd, Ortinau, L.C., Pickering, R.T., Ruebel, M.L., Meers, G.M., Rector, R.S., 2013. Altered hepatic lipid metabolism contributes to nonalcoholic fatty liver disease in leptin-deficient Ob/Ob mice. *Journal of obesity* 2013, 296537.
- Perrott, K.M., Wiley, C.D., Desprez, P.Y., Campisi, J., 2017. Apigenin suppresses the senescence-associated secretory phenotype and paracrine effects on breast cancer cells. *GeroScience* 39, 161-173.
- Peters, K.E., Davis, W.A., Ito, J., Winfield, K., Stoll, T., Bringans, S.D., Lipscombe, R.J., Davis, T.M.E., 2017. Identification of Novel Circulating Biomarkers Predicting Rapid Decline in Renal Function in Type 2 Diabetes: The Fremantle Diabetes Study Phase II. *Diabetes care* 40, 1548-1555.
- Petrache, I., Birukov, K., Zaiman, A.L., Crow, M.T., Deng, H., Wadgaonkar, R., Romer, L.H., Garcia, J.G., 2003. Caspase-dependent cleavage of myosin light chain kinase (MLCK) is involved in TNF-alpha-mediated bovine pulmonary endothelial cell apoptosis. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 17, 407-416.
- Petrelli, F., Cabiddu, M., Coinu, A., Borgonovo, K., Ghilardi, M., Lonati, V., Barni, S., 2015. Prognostic role of lactate dehydrogenase in solid tumors: a systematic review and meta-analysis of 76 studies. *Acta oncologica* 54, 961-970.
- Petta, S., Valenti, L., Svegliati-Baroni, G., Ruscica, M., Pipitone, R.M., Dongiovanni, P., Rychlicki, C., Ferri, N., Camma, C., Fracanzani, A.L., Pierantonelli, I., Di Marco, V., Meroni, M., Giordano, D., Grimaudo, S., Maggioni, M., Cabibi, D., Fargion, S., Craxi, A., 2017. Fibronectin Type III Domain-Containing Protein 5 rs3480 A>G Polymorphism, Irisin, and Liver Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. *The Journal of clinical endocrinology and metabolism* 102, 2660-2669.
- Philbrick, K.A., Martin, S.A., Colagiovanni, A.R., Branscum, A.J., Turner, R.T., Iwaniec, U.T., 2018. Effects of hypothalamic leptin gene therapy on osteopetrosis in leptin-deficient mice. *The Journal of endocrinology* 236, 57-68.
- Philbrick, K.A., Wong, C.P., Branscum, A.J., Turner, R.T., Iwaniec, U.T., 2017. Leptin stimulates bone formation in ob/ob mice at doses having minimal impact on energy metabolism. *The Journal of endocrinology* 232, 461-474.
- Phoonsawat, W., Aoki-Yoshida, A., Tsuruta, T., Sonoyama, K., 2014. Adiponectin is partially associated with exosomes in mouse serum. *Biochemical and biophysical research communications* 448, 261-266.
- Pilely, K., Fumagalli, S., Rosbjerg, A., Genster, N., Skjoedt, M.O., Perego, C., Ferrante, A.M.R., De Simoni, M.G., Garred, P., 2017. C-Reactive Protein Binds to Cholesterol Crystals and Co-Localizes with the Terminal Complement Complex in Human Atherosclerotic Plaques. *Frontiers in immunology* 8, 1040.
- Pinsky, M., Rauch, M., Abbas, A., Sharabi-Nov, A., Tamir, S., Gutman, R., 2017. Long-lived weight-reduced alphaMUPA mice show higher and longer maternal-dependent postnatal leptin surge. *PloS one* 12, e0188658.
- Pischon, T., Gorman, C.J., Hotamisligil, G.S., Rifai, N., Hu, F.B., Rimm, E.B., 2004. Plasma adiponectin levels and risk of myocardial infarction in men. *Jama* 291, 1730-1737.
- Planavila, A., Redondo, I., Hondares, E., Vinciguerra, M., Munts, C., Iglesias, R., Gabrielli, L.A., Sitges, M., Giral, M., van Bilsen, M., Villarroya, F., 2013. Fibroblast growth factor 21 protects against cardiac hypertrophy in mice. *Nature communications* 4, 2019.
- Pollack, M., Leeuwenburgh, C., 2001. Apoptosis and aging: role of the mitochondria. *The journals of gerontology. Series A, Biological sciences and medical sciences* 56, B475-482.
- Polyzos, S.A., Kountouras, J., Anastasilakis, A.D., Geladari, E.V., Mantzoros, C.S., 2014. Irisin in patients with nonalcoholic fatty liver disease. *Metabolism: clinical and experimental* 63, 207-217.

- Prakoura, N., Politis, P.K., Ihara, Y., Michalak, M., Charonis, A.S., 2013. Epithelial calreticulin up-regulation promotes profibrotic responses and tubulointerstitial fibrosis development. *The American journal of pathology* 183, 1474-1487.
- Puche, J.E., Munoz, U., Garcia-Magarino, M., Sadaba, M.C., Castilla-Cortazar, I., 2016. Partial IGF-1 deficiency induces brain oxidative damage and edema, which are ameliorated by replacement therapy. *BioFactors* 42, 60-79.
- Puig, K.L., Brose, S.A., Zhou, X., Sens, M.A., Combs, G.F., Jensen, M.D., Golovko, M.Y., Combs, C.K., 2017. Amyloid precursor protein modulates macrophage phenotype and diet-dependent weight gain. *Scientific reports* 7, 43725.
- Pulanco, M.C., Cosman, J., Ho, M.M., Huynh, J., Fing, K., Turcu, J., Fraser, D.A., 2017. Complement Protein C1q Enhances Macrophage Foam Cell Survival and Efferocytosis. *Journal of immunology* 198, 472-480.
- Pulliero, A., Izzotti, A., 2016. Preface: MicroRNA as Disease Biomarkers. *MicroRNA* 5, 2-4.
- Pun, S., Tsim, K.W., 1997. Antisense agrin cDNA transfection blocks neuroblastoma cell-induced acetylcholine receptor aggregation when co-cultured with myotubes. *Molecular and cellular neurosciences* 10, 87-99.
- Puts, M.T., Visser, M., Twisk, J.W., Deeg, D.J., Lips, P., 2005. Endocrine and inflammatory markers as predictors of frailty. *Clinical endocrinology* 63, 403-411.
- Putt, M., Hahn, V.S., Januzzi, J.L., Sawaya, H., Sebag, I.A., Plana, J.C., Picard, M.H., Carver, J.R., Halpern, E.F., Kuter, I., Passeri, J., Cohen, V., Banchs, J., Martin, R.P., Gerszten, R.E., Scherrer-Crosbie, M., Ky, B., 2015. Longitudinal Changes in Multiple Biomarkers Are Associated with Cardiotoxicity in Breast Cancer Patients Treated with Doxorubicin, Taxanes, and Trastuzumab. *Clinical chemistry* 61, 1164-1172.
- Qi, Y., Goel, R., Kim, S., Richards, E.M., Carter, C.S., Pepine, C.J., Raizada, M.K., Buford, T.W., 2017. Intestinal Permeability Biomarker Zonulin is Elevated in Healthy Aging. *Journal of the American Medical Directors Association* 18, 810 e811-810 e814.
- Qi, Y.F., Zhang, J., Wang, L., Shenoy, V., Krause, E., Oh, S.P., Pepine, C.J., Katovich, M.J., Raizada, M.K., 2016. Angiotensin-converting enzyme 2 inhibits high-mobility group box 1 and attenuates cardiac dysfunction post-myocardial ischemia. *Journal of molecular medicine* 94, 37-49.
- Qin, C.Y., Zhang, H.W., Gu, J., Xu, F., Liang, H.M., Fan, K.J., Shen, J.Y., Xiao, Z.H., Zhang, E.Y., Hu, J., 2017a. Mitochondrial DNA-induced inflammatory damage contributes to myocardial ischemia reperfusion injury in rats: Cardioprotective role of epigallocatechin. *Molecular medicine reports* 16, 7569-7576.
- Qin, S., Chen, X., Gao, M., Zhou, J., Li, X., 2017b. Prenatal Exposure to Lipopolysaccharide Induces PTX3 Expression and Results in Obesity in Mouse Offspring. *Inflammation* 40, 1847-1861.
- Qin, W., Li, Z., Luo, S., Wu, R., Pei, Z., Huang, R., 2014. Exogenous fractalkine enhances proliferation of endothelial cells, promotes migration of endothelial progenitor cells and improves neurological deficits in a rat model of ischemic stroke. *Neuroscience letters* 569, 80-84.
- Qu, T., Yang, H., Walston, J.D., Fedarko, N.S., Leng, S.X., 2009. Upregulated monocytic expression of CXC chemokine ligand 10 (CXCL-10) and its relationship with serum interleukin-6 levels in the syndrome of frailty. *Cytokine* 46, 319-324.
- Ramos-Lobo, A.M., Donato, J., Jr., 2017. The role of leptin in health and disease. *Temperature* 4, 258-291.
- Rana, K.S., Arif, M., Hill, E.J., Aldred, S., Nagel, D.A., Nevill, A., Randeva, H.S., Bailey, C.J., Bellary, S., Brown, J.E., 2014. Plasma irisin levels predict telomere length in healthy adults. *Age* 36, 995-1001.
- Rao, K.M., Cohen, H.J., 1990. The role of the cytoskeleton in aging. *Experimental gerontology* 25, 7-22.

- Rasheed, N., Alghasham, A., Rasheed, Z., 2016. Lactoferrin from *Camelus dromedarius* Inhibits Nuclear Transcription Factor-kappa B Activation, Cyclooxygenase-2 Expression and Prostaglandin E2 Production in Stimulated Human Chondrocytes. *Pharmacognosy research* 8, 135-141.
- Rauch, U., Bengtsson, E., Goncalves, I., Hultgardh-Nilsson, A., 2018. Distinctive peri-luminal presence of agrin in murine and human carotid atherosclerotic plaques. *Histology and histopathology*, 11970.
- Ravizza, T., Terrone, G., Salamone, A., Frigerio, F., Balosso, S., Antoine, D.J., Vezzani, A., 2017. High Mobility Group Box 1 is a novel pathogenic factor and a mechanistic biomarker for epilepsy. *Brain, behavior, and immunity*.
- Ray, A., Cleary, M.P., 2017. The potential role of leptin in tumor invasion and metastasis. *Cytokine & growth factor reviews* 38, 80-97.
- Razvi, E., 2013. Epigenetic and circulating biomarkers: future analytes for liquid biopsies. *Epigenomics* 5, 615-617.
- Rege, T.A., Fears, C.Y., Gladson, C.L., 2005. Endogenous inhibitors of angiogenesis in malignant gliomas: nature's antiangiogenic therapy. *Neuro-oncology* 7, 106-121.
- Rehman, K., Akash, M.S.H., Alina, Z., 2017. Leptin: A new therapeutic target for treatment of diabetes mellitus. *Journal of cellular biochemistry*.
- Reif, R., Sales, S., Hettwer, S., Dreier, B., Gisler, C., Wolfel, J., Luscher, D., Zurlinden, A., Stephan, A., Ahmed, S., Baici, A., Ledermann, B., Kunz, B., Sonderegger, P., 2007. Specific cleavage of agrin by neurotrypsin, a synaptic protease linked to mental retardation. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 21, 3468-3478.
- Reyes-Castillo, Z., Palafox-Sanchez, C.A., Parra-Rojas, I., Martinez-Bonilla, G.E., del Toro-Arreola, S., Ramirez-Duenas, M.G., Ocampo-Bermudes, G., Munoz-Valle, J.F., 2015. Comparative analysis of autoantibodies targeting peptidylarginine deiminase type 4, mutated citrullinated vimentin and cyclic citrullinated peptides in rheumatoid arthritis: associations with cytokine profiles, clinical and genetic features. *Clinical and experimental immunology* 182, 119-131.
- Rich, M.W., Shah, A.S., Vinson, J.M., Freedland, K.E., Kuru, T., Sperry, J.C., 1996. Iatrogenic congestive heart failure in older adults: clinical course and prognosis. *Journal of the American Geriatrics Society* 44, 638-643.
- Rimer, M., 1998. Agrin-induced aggregation of acetylcholine receptors in muscles of rats with experimental autoimmune myasthenia gravis. *Annals of the New York Academy of Sciences* 841, 546-549.
- Rockwood, K., Song, X., MacKnight, C., Bergman, H., Hogan, D.B., McDowell, I., Mitnitski, A., 2005. A global clinical measure of fitness and frailty in elderly people. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 173, 489-495.
- Rodon, L., Gonzalez-Junca, A., Inda Mdel, M., Sala-Hojman, A., Martinez-Saez, E., Seoane, J., 2014. Active CREB1 promotes a malignant TGFbeta2 autocrine loop in glioblastoma. *Cancer discovery* 4, 1230-1241.
- Rodrigues, K.F., Pietrani, N.T., Fernandes, A.P., Bosco, A.A., de Sousa, M.C.R., de Fatima Oliveira Silva, I., Silveira, J.N., Campos, F.M.F., Gomes, K.B., 2018. Circulating microparticles levels are increased in patients with diabetic kidney disease: A case-control research. *Clinica chimica acta; international journal of clinical chemistry* 479, 48-55.
- Rodriguez-Grande, B., Varghese, L., Molina-Holgado, F., Rajkovic, O., Garlanda, C., Denes, A., Pinteaux, E., 2015. Pentraxin 3 mediates neurogenesis and angiogenesis after cerebral ischaemia. *Journal of neuroinflammation* 12, 15.

- Rodriguez-Ortiz, M.E., Rodriguez, M., 2015. FGF23 as a calciotropic hormone. *F1000Research* 4.
- Roefs, M.M., Carlotti, F., Jones, K., Wills, H., Hamilton, A., Verschoor, M., Durkin, J.M.W., Garcia-Perez, L., Brereton, M.F., McCulloch, L., Engelse, M.A., Johnson, P.R.V., Hansen, B.C., Docherty, K., de Koning, E.J.P., Clark, A., 2017. Increased vimentin in human alpha- and beta-cells in type 2 diabetes. *The Journal of endocrinology* 233, 217-227.
- Rogers, J.T., Morganti, J.M., Bachstetter, A.D., Hudson, C.E., Peters, M.M., Grimmig, B.A., Weeber, E.J., Bickford, P.C., Gemma, C., 2011. CX3CR1 deficiency leads to impairment of hippocampal cognitive function and synaptic plasticity. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 31, 16241-16250.
- Romi, F.R., Gilhus, N.E., Luckman, S.P., 2008. Serum matrix metalloproteinase-3 levels are elevated in myasthenia gravis. *Journal of neuroimmunology* 195, 96-99.
- Ronquist, K.G., Ek, B., Morrell, J., Stavreus-Evers, A., Strom Holst, B., Humblot, P., Ronquist, G., Larsson, A., 2013. Prostatomes from four different species are able to produce extracellular adenosine triphosphate (ATP). *Biochimica et biophysica acta* 1830, 4604-4610.
- Rose, A.A.N., Biondini, M., Curiel, R., Siegel, P.M., 2017. Targeting GPNMB with glembatumumab vedotin: Current developments and future opportunities for the treatment of cancer. *Pharmacology & therapeutics* 179, 127-141.
- Rosenkranz, S., 2004. TGF-beta1 and angiotensin networking in cardiac remodeling. *Cardiovascular research* 63, 423-432.
- Rossaint, J., Unruh, M., Zarbock, A., 2017. Fibroblast growth factor 23 actions in inflammation: a key factor in CKD outcomes. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 32, 1448-1453.
- Rossetti, A., Togliatto, G., Rolo, A.P., Teodoro, J.S., Granata, R., Ghigo, E., Columbano, A., Palmeira, C.M., Brizzi, M.F., 2017. Unacylated ghrelin prevents mitochondrial dysfunction in a model of ischemia/reperfusion liver injury. *Cell death discovery* 3, 17077.
- Rousseau, E., Michel, P.P., Hirsch, E.C., 2013. The iron-binding protein lactoferrin protects vulnerable dopamine neurons from degeneration by preserving mitochondrial calcium homeostasis. *Molecular pharmacology* 84, 888-898.
- Ruan, Q., Johnson, G.V., 2007. Transglutaminase 2 in neurodegenerative disorders. *Frontiers in bioscience : a journal and virtual library* 12, 891-904.
- Rubio-Guerra, A.F., Cabrera-Miranda, L.J., Vargas-Robles, H., Maceda-Serrano, A., Lozano-Nuevo, J.J., Escalante-Acosta, B.A., 2013. Correlation between levels of circulating adipokines and adiponectin/resistin index with carotid intima-media thickness in hypertensive type 2 diabetic patients. *Cardiology* 125, 150-153.
- Rudolf, R., Khan, M.M., Labeit, S., Deschenes, M.R., 2014. Degeneration of neuromuscular junction in age and dystrophy. *Frontiers in aging neuroscience* 6, 99.
- Rue, N., Vissing, J., Galbo, H., 2014. Insulin resistance and increased muscle cytokine levels in patients with mitochondrial myopathy. *The Journal of clinical endocrinology and metabolism* 99, 3757-3765.
- Ruegg, M.A., Bixby, J.L., 1998. Agrin orchestrates synaptic differentiation at the vertebrate neuromuscular junction. *Trends in neurosciences* 21, 22-27.
- Ruiz-Margain, A., Pohlmann, A., Ryan, P., Schierwagen, R., Chi-Cervera, L.A., Jansen, C., Mendez-Guerrero, O., Flores-Garcia, N.C., Lehmann, J., Torre, A., Macias-Rodriguez, R.U., Trebicka, J., 2018. Fibroblast growth factor 21 is an early predictor of acute-on-chronic liver failure in critically ill patients with cirrhosis. *Liver transplantation : official*

- publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 24, 595-605.
- Ruppe, M.D., Zhang, X., Imel, E.A., Weber, T.J., Klausner, M.A., Ito, T., Vergeire, M., Humphrey, J.S., Glorieux, F.H., Portale, A.A., Insogna, K., Peacock, M., Carpenter, T.O., 2016. Effect of four monthly doses of a human monoclonal anti-FGF23 antibody (KRN23) on quality of life in X-linked hypophosphatemia. *Bone reports* 5, 158-162.
- Rusu, C.C., Racasan, S., Kacso, I.M., Moldovan, D., Potra, A., Tirinescu, D., Budurea, C., Orasan, R., Patiu, I.M., Bondor, C.I., Vladutiu, D., Caprioara, M.G., 2017. The metabolic hormone FGF21 is associated with endothelial dysfunction in hemodialysis patients. *International urology and nephrology* 49, 517-523.
- Ruth, J.H., Volin, M.V., Haines, G.K., 3rd, Woodruff, D.C., Katschke, K.J., Jr., Woods, J.M., Park, C.C., Morel, J.C., Koch, A.E., 2001. Fractalkine, a novel chemokine in rheumatoid arthritis and in rat adjuvant-induced arthritis. *Arthritis and rheumatism* 44, 1568-1581.
- Ryan, A.S., Berman, D.M., Nicklas, B.J., Sinha, M., Gingerich, R.L., Meneilly, G.S., Egan, J.M., Elahi, D., 2003. Plasma adiponectin and leptin levels, body composition, and glucose utilization in adult women with wide ranges of age and obesity. *Diabetes care* 26, 2383-2388.
- Ryan, K.K., Packard, A.E.B., Larson, K.R., Stout, J., Fourman, S.M., Thompson, A.M.K., Ludwick, K., Habegger, K.M., Stemmer, K., Itoh, N., Perez-Tilve, D., Tschop, M.H., Seeley, R.J., Ulrich-Lai, Y.M., 2018. Dietary Manipulations That Induce Ketosis Activate the HPA Axis in Male Rats and Mice: A Potential Role for Fibroblast Growth Factor-21. *Endocrinology* 159, 400-413.
- Rygasiewicz, K., Hryszko, T., Siemiatkowski, A., Brzosko, S., Rydzewska-Rosolowska, A., Naumnik, B., 2018. C-terminal and intact FGF23 in critical illness and their associations with acute kidney injury and in-hospital mortality. *Cytokine* 103, 15-19.
- Ryo, M., Nakamura, T., Kihara, S., Kumada, M., Shibazaki, S., Takahashi, M., Nagai, M., Matsuzawa, Y., Funahashi, T., 2004. Adiponectin as a biomarker of the metabolic syndrome. *Circulation journal : official journal of the Japanese Circulation Society* 68, 975-981.
- Sabbagh, M.N., Agro, A., Bell, J., Aisen, P.S., Schweizer, E., Galasko, D., 2011. PF-04494700, an oral inhibitor of receptor for advanced glycation end products (RAGE), in Alzheimer disease. *Alzheimer disease and associated disorders* 25, 206-212.
- Sada, N., Lee, S., Katsu, T., Otsuki, T., Inoue, T., 2015. Epilepsy treatment. Targeting LDH enzymes with a stiripentol analog to treat epilepsy. *Science* 347, 1362-1367.
- Sadoun, E., Reed, M.J., 2003. Impaired angiogenesis in aging is associated with alterations in vessel density, matrix composition, inflammatory response, and growth factor expression. *The journal of histochemistry and cytochemistry : official journal of the Histochemistry Society* 51, 1119-1130.
- Saeed, H., Qiu, W., Li, C., Flyvbjerg, A., Abdallah, B.M., Kassem, M., 2015. Telomerase activity promotes osteoblast differentiation by modulating IGF-signaling pathway. *Biogerontology* 16, 733-745.
- Safdar, A., Bourgeois, J.M., Ogborn, D.I., Little, J.P., Hettinga, B.P., Akhtar, M., Thompson, J.E., Melov, S., Mocellin, N.J., Kujoth, G.C., Prolla, T.A., Tarnopolsky, M.A., 2011. Endurance exercise rescues progeroid aging and induces systemic mitochondrial rejuvenation in mtDNA mutator mice. *Proceedings of the National Academy of Sciences of the United States of America* 108, 4135-4140.
- Saito, Y., Yamagishi, T., Nakamura, T., Ohyama, Y., Aizawa, H., Suga, T., Matsumura, Y., Masuda, H., Kurabayashi, M., Kuro-o, M., Nabeshima, Y., Nagai, R., 1998. Klotho protein protects against endothelial dysfunction. *Biochemical and biophysical research communications* 248, 324-329.

- Sakamoto, K., Matsuki, S., Matsuguma, K., Yoshihara, T., Uchida, N., Azuma, F., Russell, M., Hughes, G., Haeberlein, S.B., Alexander, R.C., Eketjall, S., Kugler, A.R., 2017. BACE1 Inhibitor Lanabecestat (AZD3293) in a Phase 1 Study of Healthy Japanese Subjects: Pharmacokinetics and Effects on Plasma and Cerebrospinal Fluid Abeta Peptides. *Journal of clinical pharmacology* 57, 1460-1471.
- Salanova Villanueva, L., Sanchez Gonzalez, C., Sanchez Tomero, J.A., Aguilera, A., Ortega Junco, E., 2016. Bone mineral disorder in chronic kidney disease: Klotho and FGF23; cardiovascular implications. *Nefrologia : publicacion oficial de la Sociedad Espanola Nefrologia* 36, 368-375.
- Samaras, N., Papadopoulou, M.A., Samaras, D., Ongaro, F., 2014. Off-label use of hormones as an antiaging strategy: a review. *Clinical interventions in aging* 9, 1175-1186.
- Sanchis-Gomar, F., Pareja-Galeano, H., Santos-Lozano, A., Garatachea, N., Fiuza-Luces, C., Venturini, L., Ricevuti, G., Lucia, A., Emanuele, E., 2015. A preliminary candidate approach identifies the combination of chemerin, fetuin-A, and fibroblast growth factors 19 and 21 as a potential biomarker panel of successful aging. *Age* 37, 9776.
- Sandor, N., Schilling-Toth, B., Kis, E., Benedek, A., Lumniczky, K., Safrany, G., Hegyesi, H., 2015. Growth Differentiation Factor-15 (GDF-15) is a potential marker of radiation response and radiation sensitivity. *Mutation research. Genetic toxicology and environmental mutagenesis* 793, 142-149.
- Sanes, J.R., Apel, E.D., Burgess, R.W., Emerson, R.B., Feng, G., Gautam, M., Glass, D., Grady, R.M., Krejci, E., Lichtman, J.W., Lu, J.T., Massoulié, J., Miner, J.H., Moscoso, L.M., Nguyen, Q., Nichol, M., Noakes, P.G., Patton, B.L., Son, Y.J., Yancopoulos, G.D., Zhou, H., 1998a. Development of the neuromuscular junction: genetic analysis in mice. *Journal of physiology, Paris* 92, 167-172.
- Sanes, J.R., Apel, E.D., Gautam, M., Glass, D., Grady, R.M., Martin, P.T., Nichol, M.C., Yancopoulos, G.D., 1998b. Agrin receptors at the skeletal neuromuscular junction. *Annals of the New York Academy of Sciences* 841, 1-13.
- Sanes, J.R., Lichtman, J.W., 2001. Induction, assembly, maturation and maintenance of a postsynaptic apparatus. *Nature reviews. Neuroscience* 2, 791-805.
- Santos-Silva, A., Rebelo, I., Castro, E., Belo, L., Catarino, C., Monteiro, I., Almeida, M.D., Quintanilha, A., 2002. Erythrocyte damage and leukocyte activation in ischemic stroke. *Clinica chimica acta; international journal of clinical chemistry* 320, 29-35.
- Sas, K., Szabo, E., Vecsei, L., 2018. Mitochondria, Oxidative Stress and the Kynurenine System, with a Focus on Ageing and Neuroprotection. *Molecules* 23.
- Sato, H., Kazama, J.J., Murasawa, A., Otani, H., Abe, A., Ito, S., Ishikawa, H., Nakazono, K., Kuroda, T., Nakano, M., Narita, I., 2016. Serum Fibroblast Growth Factor 23 (FGF23) in Patients with Rheumatoid Arthritis. *Internal medicine* 55, 121-126.
- Sato, H., Muraoka, S., Kusunoki, N., Masuoka, S., Yamada, S., Ogasawara, H., Imai, T., Akasaka, Y., Tochigi, N., Takahashi, H., Tsuchiya, K., Kawai, S., Nanki, T., 2017. Resistin upregulates chemokine production by fibroblast-like synoviocytes from patients with rheumatoid arthritis. *Arthritis research & therapy* 19, 263.
- Sato, M., Ohtsuka, K., Takahashi, R., Wakabayashi, K., Odai, T., Isozaki, T., Yajima, N., Miwa, Y., Kasama, T., 2011. Involvement of CX3CL1/CX3CR1 axis in etanercept therapy for patients with active rheumatoid arthritis. *Open access rheumatology : research and reviews* 3, 1-7.
- Sattar, N., Wannamethee, G., Sarwar, N., Tchernova, J., Cherry, L., Wallace, A.M., Danesh, J., Whincup, P.H., 2006. Adiponectin and coronary heart disease: a prospective study and meta-analysis. *Circulation* 114, 623-629.
- Sawicka, K., Michalska-Jakubus, M., Kowal, M., Potembska, E., Krasowska, D., 2017. Resistin: a possible biomarker of organ involvement in systemic sclerosis patients? *Clinical and experimental rheumatology* 35 Suppl 106, 144-150.

- Schafer, M.J., Dolgalev, I., Alldred, M.J., Heguy, A., Ginsberg, S.D., 2015. Calorie Restriction Suppresses Age-Dependent Hippocampal Transcriptional Signatures. *PloS one* 10, e0133923.
- Schallmoser, K., Bartmann, C., Rohde, E., Bork, S., Guelly, C., Obenauf, A.C., Reinisch, A., Horn, P., Ho, A.D., Strunk, D., Wagner, W., 2010. Replicative senescence-associated gene expression changes in mesenchymal stromal cells are similar under different culture conditions. *Haematologica* 95, 867-874.
- Scherthaner, C., Lichtenauer, M., Wernly, B., Paar, V., Pistulli, R., Rohm, I., Jung, C., Figulla, H.R., Yilmaz, A., Cadamuro, J., Haschke-Becher, E., Pernow, J., Schulze, P.C., Hoppe, U.C., Kretzschmar, D., 2017. Multibiomarker analysis in patients with acute myocardial infarction. *European journal of clinical investigation* 47, 638-648.
- Schiegnitz, E., Kammerer, P.W., Rode, K., Schorn, T., Brieger, J., Al-Nawas, B., 2016. Growth differentiation factor 15 as a radiation-induced marker in oral carcinoma increasing radiation resistance. *Journal of oral pathology & medicine : official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology* 45, 63-69.
- Schiffers, P.M., Henrion, D., Boulanger, C.M., Colucci-Guyon, E., Langa-Vuves, F., van Essen, H., Fazzi, G.E., Levy, B.I., De Mey, J.G., 2000. Altered flow-induced arterial remodeling in vimentin-deficient mice. *Arteriosclerosis, thrombosis, and vascular biology* 20, 611-616.
- Schindler, S.M., Little, J.P., Klegeris, A., 2014. Microparticles: a new perspective in central nervous system disorders. *BioMed research international* 2014, 756327.
- Schmidt, A.M., 2015. Soluble RAGEs - Prospects for treating & tracking metabolic and inflammatory disease. *Vascular pharmacology* 72, 1-8.
- Scholle, L.M., Lehmann, D., Deschauer, M., Kraya, T., Zierz, S., 2018. FGF-21 as a Potential Biomarker for Mitochondrial Diseases. *Current medicinal chemistry* 25, 2070-2081.
- Schraml, E., Grillari, J., 2012. From cellular senescence to age-associated diseases: the miRNA connection. *Longevity & healthspan* 1, 10.
- Schreiner, B., Hedskog, L., Wiehager, B., Ankarcrona, M., 2015. Amyloid-beta peptides are generated in mitochondria-associated endoplasmic reticulum membranes. *Journal of Alzheimer's disease : JAD* 43, 369-374.
- Schutte, B., Henfling, M., Kolgen, W., Bouman, M., Meex, S., Leers, M.P., Nap, M., Bjorklund, V., Bjorklund, P., Bjorklund, B., Lane, E.B., Omary, M.B., Jornvall, H., Ramaekers, F.C., 2004. Keratin 8/18 breakdown and reorganization during apoptosis. *Experimental cell research* 297, 11-26.
- Schwarz, N., Leube, R.E., 2016. Intermediate Filaments as Organizers of Cellular Space: How They Affect Mitochondrial Structure and Function. *Cells* 5.
- Schwarz, V., Dusing, P., Liman, T., Werner, C., Herm, J., Bachelier, K., Krull, M., Brechtel, L., Jungehulsing, G.J., Haverkamp, W., Bohm, M., Endres, M., Haeusler, K.G., Laufs, U., 2018. Marathon running increases circulating endothelial- and thrombocyte-derived microparticles. *European journal of preventive cardiology* 25, 317-324.
- Scimeca, M., Salustri, A., Bonanno, E., Nardozi, D., Rao, C., Piccirilli, E., Feola, M., Tancredi, V., Rinaldi, A., Iolascon, G., Orlandi, A., Gasbarra, E., Maffulli, N., Brandi, M.L., Tarantino, U., 2017. Impairment of PTX3 expression in osteoblasts: a key element for osteoporosis. *Cell death & disease* 8, e3125.
- Secemsky, E.A., Scherzer, R., Nitta, E., Wu, A.H., Lange, D.C., Deeks, S.G., Martin, J.N., Snider, J., Ganz, P., Hsue, P.Y., 2015. Novel Biomarkers of Cardiac Stress, Cardiovascular Dysfunction, and Outcomes in HIV-Infected Individuals. *JACC. Heart failure* 3, 591-599.
- Seddon, J.M., Yu, Y., Miller, E.C., Reynolds, R., Tan, P.L., Gowrisankar, S., Goldstein, J.I., Triebwasser, M., Anderson, H.E., Zerbib, J., Kavanagh, D., Souied, E., Katsanis, N.,

- Daly, M.J., Atkinson, J.P., Raychaudhuri, S., 2013. Rare variants in CFI, C3 and C9 are associated with high risk of advanced age-related macular degeneration. *Nature genetics* 45, 1366-1370.
- Sellar, G.C., Blake, D.J., Reid, K.B., 1991. Characterization and organization of the genes encoding the A-, B- and C-chains of human complement subcomponent C1q. The complete derived amino acid sequence of human C1q. *The Biochemical journal* 274 (Pt 2), 481-490.
- Serpinskaya, A.S., Feng, G., Sanes, J.R., Craig, A.M., 1999. Synapse formation by hippocampal neurons from agrin-deficient mice. *Developmental biology* 205, 65-78.
- Serra-Prat, M., Palomera, E., Roca, M., Puig-Domingo, M., Mataro Ageing Study, G., 2010. Long-term effect of ghrelin on nutritional status and functional capacity in the elderly: a population-based cohort study. *Clinical endocrinology* 73, 41-47.
- Serra-Prat, M., Papiol, M., Monteis, R., Palomera, E., Cabre, M., 2015. Relationship between Plasma Ghrelin Levels and Sarcopenia in Elderly Subjects: A Cross-Sectional Study. *The journal of nutrition, health & aging* 19, 669-672.
- Shah, R., Hinkle, C.C., Ferguson, J.F., Mehta, N.N., Li, M., Qu, L., Lu, Y., Putt, M.E., Ahima, R.S., Reilly, M.P., 2011. Fractalkine is a novel human adipochemokine associated with type 2 diabetes. *Diabetes* 60, 1512-1518.
- Shah, R., Matthews, G.J., Shah, R.Y., McLaughlin, C., Chen, J., Wolman, M., Master, S.R., Chai, B., Xie, D., Rader, D.J., Raj, D.S., Mehta, N.N., Budoff, M., Fischer, M.J., Go, A.S., Townsend, R.R., He, J., Kusek, J.W., Feldman, H.I., Foulkes, A.S., Reilly, M.P., Investigators, C.S., 2015. Serum Fractalkine (CX3CL1) and Cardiovascular Outcomes and Diabetes: Findings From the Chronic Renal Insufficiency Cohort (CRIC) Study. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 66, 266-273.
- Shan, H., Wei, J., Zhang, M., Lin, L., Yan, R., Zhu, Y., Zhang, R., 2014. Calreticulin is localized at mitochondria of rat cardiomyocytes and affected by furazolidone. *Molecular and cellular biochemistry* 397, 125-130.
- Shao, L., Meng, D., Yang, F., Song, H., Tang, D., 2017. Irisin-mediated protective effect on LPS-induced acute lung injury via suppressing inflammation and apoptosis of alveolar epithelial cells. *Biochemical and biophysical research communications* 487, 194-200.
- Shapiro, N.I., Khankin, E.V., Van Meurs, M., Shih, S.C., Lu, S., Yano, M., Castro, P.R., Maratos-Flier, E., Parikh, S.M., Karumanchi, S.A., Yano, K., 2010. Leptin exacerbates sepsis-mediated morbidity and mortality. *Journal of immunology* 185, 517-524.
- Sharaf El Din, U.A., Salem, M.M., Abdulazim, D.O., 2017. FGF23 and inflammation. *World journal of nephrology* 6, 57-58.
- Shardell, M., Semba, R.D., Kalyani, R.R., Bandinelli, S., Prather, A.A., Chia, C.W., Ferrucci, L., 2017. Plasma klotho and frailty in older adults: Findings from the InCHIANTI Study. *The journals of gerontology. Series A, Biological sciences and medical sciences*.
- Sheinerman, K.S., Umansky, S.R., 2013. Early detection of neurodegenerative diseases: circulating brain-enriched microRNA. *Cell cycle* 12, 1-2.
- Shen, C., Zhao, C.Y., Wang, W., Wang, Y.D., Sun, H., Cao, W., Yu, W.Y., Zhang, L., Ji, R., Li, M., Gao, J., 2014. The relationship between hepatic resistin overexpression and inflammation in patients with nonalcoholic steatohepatitis. *BMC gastroenterology* 14, 39.
- Shen, J., Chan, H.L., Wong, G.L., Choi, P.C., Chan, A.W., Chan, H.Y., Chim, A.M., Yeung, D.K., Chan, F.K., Woo, J., Yu, J., Chu, W.C., Wong, V.W., 2012. Non-invasive diagnosis of non-alcoholic steatohepatitis by combined serum biomarkers. *Journal of hepatology* 56, 1363-1370.
- Shen, S., Gao, R., Bei, Y., Li, J., Zhang, H., Zhou, Y., Yao, W., Xu, D., Zhou, F., Jin, M., Wei, S., Wang, K., Xu, X., Li, Y., Xiao, J., Li, X., 2017. Serum Irisin Predicts Mortality Risk in

- Acute Heart Failure Patients. *Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology* 42, 615-622.
- Sheng, W., Chen, C., Dong, M., Zhou, J., Liu, Q., Dong, Q., Li, F., 2014. Overexpression of calreticulin contributes to the development and progression of pancreatic cancer. *Journal of cellular physiology* 229, 887-897.
- Shi, Q., Chowdhury, S., Ma, R., Le, K.X., Hong, S., Caldarone, B.J., Stevens, B., Lemere, C.A., 2017. Complement C3 deficiency protects against neurodegeneration in aged plaque-rich APP/PS1 mice. *Science translational medicine* 9.
- Shi, Q., Colodner, K.J., Matousek, S.B., Merry, K., Hong, S., Kenison, J.E., Frost, J.L., Le, K.X., Li, S., Dodart, J.C., Caldarone, B.J., Stevens, B., Lemere, C.A., 2015a. Complement C3-Deficient Mice Fail to Display Age-Related Hippocampal Decline. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 35, 13029-13042.
- Shi, Y.C., Lu, W.W., Hou, Y.L., Fu, K., Gan, F., Cheng, S.J., Wang, S.P., Qi, Y.F., Liu, J.H., 2018. Protection Effect of Exogenous Fibroblast Growth Factor 21 on the Kidney Injury in Vascular Calcification Rats. *Chinese medical journal* 131, 532-538.
- Shi, Z., Guan, Y., Huo, Y.R., Liu, S., Zhang, M., Lu, H., Yue, W., Wang, J., Ji, Y., 2015b. Elevated Total Homocysteine Levels in Acute Ischemic Stroke Are Associated With Long-Term Mortality. *Stroke* 46, 2419-2425.
- Shimada, H., Makizako, H., Doi, T., Yoshida, D., Tsutsumimoto, K., Anan, Y., Uemura, K., Lee, S., Park, H., Suzuki, T., 2014. A large, cross-sectional observational study of serum BDNF, cognitive function, and mild cognitive impairment in the elderly. *Frontiers in aging neuroscience* 6, 69.
- Shindo, A., Maki, T., Mandeville, E.T., Liang, A.C., Egawa, N., Itoh, K., Itoh, N., Borlongan, M., Holder, J.C., Chuang, T.T., McNeish, J.D., Tomimoto, H., Lok, J., Lo, E.H., Arai, K., 2016. Astrocyte-Derived Pentraxin 3 Supports Blood-Brain Barrier Integrity Under Acute Phase of Stroke. *Stroke* 47, 1094-1100.
- Shiraishi, K., Fukuda, S., Mori, T., Matsuda, K., Yamaguchi, T., Tanikawa, C., Ogawa, M., Nakamura, Y., Arakawa, H., 2000. Identification of fractalkine, a CX3C-type chemokine, as a direct target of p53. *Cancer research* 60, 3722-3726.
- Shokar, A., Au, A., An, S.H., Tong, E., Garza, G., Zayas, J., Wnuk, S.F., Land, K.M., 2012. S-Adenosylhomocysteine hydrolase of the protozoan parasite *Trichomonas vaginalis*: potent inhibitory activity of 9-(2-deoxy-2-fluoro-beta,D-arabinofuranosyl)adenine. *Bioorganic & medicinal chemistry letters* 22, 4203-4205.
- Shuang, T., Fu, M., Yang, G., Wu, L., Wang, R., 2017. The interaction of IGF-1/IGF-1R and hydrogen sulfide on the proliferation of mouse primary vascular smooth muscle cells. *Biochemical pharmacology*.
- Shurin, G.V., Yurkovetsky, Z.R., Chatta, G.S., Tourkova, I.L., Shurin, M.R., Lokshin, A.E., 2007. Dynamic alteration of soluble serum biomarkers in healthy aging. *Cytokine* 39, 123-129.
- Silha, J.V., Weiler, H.A., Murphy, L.J., 2006. Plasma adipokines and body composition in response to modest dietary manipulations in the mouse. *Obesity* 14, 1320-1329.
- Silverman, S.M., Kim, B.J., Howell, G.R., Miller, J., John, S.W., Wordinger, R.J., Clark, A.F., 2016. C1q propagates microglial activation and neurodegeneration in the visual axis following retinal ischemia/reperfusion injury. *Molecular neurodegeneration* 11, 24.
- Simao, A.P., Mendonca, V.A., de Oliveira Almeida, T.M., Santos, S.A., Gomes, W.F., Coimbra, C.C., Lacerda, A.C., 2014. Involvement of BDNF in knee osteoarthritis: the relationship with inflammation and clinical parameters. *Rheumatology international* 34, 1153-1157.
- Simm, A., 2013. Protein glycation during aging and in cardiovascular disease. *Journal of proteomics* 92, 248-259.
- Simm, A., Muller, B., Nass, N., Hofmann, B., Bushnaq, H., Silber, R.E., Bartling, B., 2015. Protein glycation - Between tissue aging and protection. *Experimental gerontology* 68, 71-75.

- Simone, T.M., Higgins, C.E., Czekay, R.P., Law, B.K., Higgins, S.P., Archambeault, J., Kutz, S.M., Higgins, P.J., 2014a. SERPINE1: A Molecular Switch in the Proliferation-Migration Dichotomy in Wound-"Activated" Keratinocytes. *Advances in wound care* 3, 281-290.
- Simone, T.M., Higgins, S.P., Higgins, C.E., Lennartz, M.R., Higgins, P.J., 2014b. Chemical Antagonists of Plasminogen Activator Inhibitor-1: Mechanisms of Action and Therapeutic Potential in Vascular Disease. *Journal of molecular and genetic medicine : an international journal of biomedical research* 8.
- Sindhu, S., Thomas, R., Shihab, P., Sriraman, D., Behbehani, K., Ahmad, R., 2015. Obesity Is a Positive Modulator of IL-6R and IL-6 Expression in the Subcutaneous Adipose Tissue: Significance for Metabolic Inflammation. *PLoS one* 10, e0133494.
- Singh, L., Arora, S.K., Bakshi, D.K., Majumdar, S., Wig, J.D., 2010. Potential role of CXCL10 in the induction of cell injury and mitochondrial dysfunction. *International journal of experimental pathology* 91, 210-223.
- Singh, S., Chouhan, S., Mohammad, N., Bhat, M.K., 2017. Resistin causes G1 arrest in colon cancer cells through upregulation of SOCS3. *FEBS letters* 591, 1371-1382.
- Siracusa, J., Koulmann, N., Banzet, S., 2018. Circulating myomiRs: a new class of biomarkers to monitor skeletal muscle in physiology and medicine. *Journal of cachexia, sarcopenia and muscle* 9, 20-27.
- Siuda, J., Patalong-Ogiewa, M., Zmuda, W., Targosz-Gajniak, M., Niewiadomska, E., Matuszek, I., Jedrzejowska-Szypulka, H., Lewin-Kowalik, J., Rudzinska-Bar, M., 2017. Cognitive impairment and BDNF serum levels. *Neurologia i neurochirurgia polska* 51, 24-32.
- Slusher, A.L., Shibata, Y., Whitehurst, M., Maharaj, A., Quiles, J.M., Huang, C.J., 2017. Exercise reduced pentraxin 3 levels produced by endotoxin-stimulated human peripheral blood mononuclear cells in obese individuals. *Experimental biology and medicine*, 1535370217706963.
- Smiljanovic, B., Radzikowska, A., Kuca-Warnawin, E., Kurowska, W., Grun, J.R., Stuhlmuller, B., Bonin, M., Schulte-Wrede, U., Sorensen, T., Kyogoku, C., Bruns, A., Hermann, S., Ohrndorf, S., Aupperle, K., Backhaus, M., Burmester, G.R., Radbruch, A., Grutzkau, A., Maslinski, W., Haupl, T., 2018. Monocyte alterations in rheumatoid arthritis are dominated by preterm release from bone marrow and prominent triggering in the joint. *Annals of the rheumatic diseases* 77, 300-308.
- Smith, H.W., Marshall, C.J., 2010. Regulation of cell signalling by uPAR. *Nature reviews. Molecular cell biology* 11, 23-36.
- Smith, J., Stewart, B.J., Glaysher, S., Peregrin, K., Knight, L.A., Weber, D.J., Cree, I.A., 2010. The effect of pentamidine on melanoma ex vivo. *Anti-cancer drugs* 21, 181-185.
- Soberg, S., Andersen, E.S., Dalgaard, N.B., Jarlhelt, I., Hansen, N.L., Hoffmann, N., Vilsboll, T., Chenchar, A., Jensen, M., Grevengoed, T.J., Trammell, S.A.J., Knop, F.K., Gillum, M.P., 2018. FGF21, a liver hormone that inhibits alcohol intake in mice, increases in human circulation after acute alcohol ingestion and sustained binge drinking at Oktoberfest. *Molecular metabolism* 11, 96-103.
- Sobol, A., Galluzzo, P., Weber, M.J., Alani, S., Bocchetta, M., 2015. Depletion of Amyloid Precursor Protein (APP) causes G0 arrest in non-small cell lung cancer (NSCLC) cells. *Journal of cellular physiology* 230, 1332-1341.
- Sodhi, K., Bracero, L., Feyh, A., Nichols, A., Srikanthan, K., Latif, T., Preston, D., Shapiro, J.I., Elitsur, Y., 2016. Role of Serum Biomarkers in Early Detection of Non-Alcoholic Steatohepatitis and Fibrosis in West Virginian Children. *Journal of clinical & cellular immunology* 7.
- Sole, S., Petegnief, V., Gorina, R., Chamorro, A., Planas, A.M., 2004. Activation of matrix metalloproteinase-3 and agrin cleavage in cerebral ischemia/reperfusion. *Journal of neuropathology and experimental neurology* 63, 338-349.

- Solis-Cano, D.G., Porchia, L.M., Gonzalez-Mejia, M.E., Perez-Fuentes, R., Ruiz-Vivanco, G., Nieva-Vazquez, A., Torres-Rasgado, E., 2017. Serum resistin levels inversely associated with cardiovascular risk indices in type 2 diabetics from central Mexico. *Diabetes & metabolic syndrome* 11 Suppl 2, S1053-S1057.
- Sollazzo, D., Forte, D., Polverelli, N., Perricone, M., Romano, M., Luatti, S., Vianelli, N., Cavo, M., Palandri, F., Catani, L., 2016. Circulating Calreticulin Is Increased in Myelofibrosis: Correlation with Interleukin-6 Plasma Levels, Bone Marrow Fibrosis, and Splenomegaly. *Mediators of inflammation* 2016, 5860657.
- Song, Y., Gao, J., Qu, Y., Wang, S., Wang, X., Liu, J., 2016a. Serum levels of leptin, adiponectin and resistin in relation to clinical characteristics in normal pregnancy and preeclampsia. *Clinica chimica acta; international journal of clinical chemistry* 458, 133-137.
- Song, Y.Z., Guan, J., Wang, H.J., Ma, W., Li, F., Xu, F., Ding, L.B., Xie, L., Liu, B., Liu, K., Lv, Z., 2016b. Possible Involvement of Serum and Synovial Fluid Resistin in Knee Osteoarthritis: Cartilage Damage, Clinical, and Radiological Links. *Journal of clinical laboratory analysis* 30, 437-443.
- Sopjani, M., Rinnerthaler, M., Kruja, J., Dermaku-Sopjani, M., 2015. Intracellular signaling of the aging suppressor protein Klotho. *Current molecular medicine* 15, 27-37.
- Sorci, G., Riuizzi, F., Arcuri, C., Tubaro, C., Bianchi, R., Giambanco, I., Donato, R., 2013. S100B protein in tissue development, repair and regeneration. *World journal of biological chemistry* 4, 1-12.
- Souma, N., Isakova, T., Lipiszko, D., Sacco, R.L., Elkind, M.S., DeRosa, J.T., Silverberg, S.J., Mendez, A.J., Dong, C., Wright, C.B., Wolf, M., 2016. Fibroblast Growth Factor 23 and Cause-Specific Mortality in the General Population: The Northern Manhattan Study. *The Journal of clinical endocrinology and metabolism* 101, 3779-3786.
- Soysal, P., Stubbs, B., Lucato, P., Luchini, C., Solmi, M., Peluso, R., Sergi, G., Isik, A.T., Manzato, E., Maggi, S., Maggio, M., Prina, A.M., Cosco, T.D., Wu, Y.T., Veronese, N., 2016. Inflammation and frailty in the elderly: A systematic review and meta-analysis. *Ageing research reviews* 31, 1-8.
- Sperling, M.A., 2016. Traditional and novel aspects of the metabolic actions of growth hormone. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society* 28, 69-75.
- Spurna, J., Karasek, D., Kubickova, V., Goldmannova, D., Krystynik, O., Schovanek, J., Zadrazil, J., 2018. Relationship of Selected Adipokines with Markers of Vascular Damage in Patients with Type 2 Diabetes. *Metabolic syndrome and related disorders* 16, 246-253.
- Srikanthan, K., Feyh, A., Visweshwar, H., Shapiro, J.I., Sodhi, K., 2016. Systematic Review of Metabolic Syndrome Biomarkers: A Panel for Early Detection, Management, and Risk Stratification in the West Virginian Population. *International journal of medical sciences* 13, 25-38.
- Sta, M., Sylva-Steenland, R.M., Casula, M., de Jong, J.M., Troost, D., Aronica, E., Baas, F., 2011. Innate and adaptive immunity in amyotrophic lateral sclerosis: evidence of complement activation. *Neurobiology of disease* 42, 211-220.
- Stallone, G., Cormio, L., Netti, G.S., Infante, B., Selvaggio, O., Fino, G.D., Ranieri, E., Bruno, F., Prattichizzo, C., Sanguedolce, F., Tortorella, S., Bufo, P., Grandaliano, G., Carrieri, G., 2014. Pentraxin 3: a novel biomarker for predicting progression from prostatic inflammation to prostate cancer. *Cancer research* 74, 4230-4238.
- Stanczyk, J., Kowalski, M.L., Grzegorzczak, J., Szkudlinska, B., Jarzebska, M., Marciniak, M., Synder, M., 2005. RANTES and chemotactic activity in synovial fluids from patients with rheumatoid arthritis and osteoarthritis. *Mediators of inflammation* 2005, 343-348.

- Stein, S., Bachmann, A., Lossner, U., Kratzsch, J., Bluher, M., Stumvoll, M., Fasshauer, M., 2009. Serum levels of the adipokine FGF21 depend on renal function. *Diabetes care* 32, 126-128.
- Stein, S., Stepan, H., Kratzsch, J., Verlohren, M., Verlohren, H.J., Drynda, K., Lossner, U., Bluher, M., Stumvoll, M., Fasshauer, M., 2010. Serum fibroblast growth factor 21 levels in gestational diabetes mellitus in relation to insulin resistance and dyslipidemia. *Metabolism: clinical and experimental* 59, 33-37.
- Steinbeck, L., Ebner, N., Valentova, M., Bekfani, T., Elsner, S., Dahinden, P., Hettwer, S., Scherbakov, N., Schefold, J.C., Sandek, A., Springer, J., Doehner, W., Anker, S.D., von Haehling, S., 2015. Detection of muscle wasting in patients with chronic heart failure using C-terminal agrin fragment: results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). *European journal of heart failure* 17, 1283-1293.
- Stemmer, N., Strelakova, E., Djogo, N., Ploger, F., Loers, G., Lutz, D., Buck, F., Michalak, M., Schachner, M., Kleene, R., 2013. Generation of amyloid-beta is reduced by the interaction of calreticulin with amyloid precursor protein, presenilin and nicastrin. *PLoS one* 8, e61299.
- Stephan, A., Mateos, J.M., Kozlov, S.V., Cinelli, P., Kistler, A.D., Hettwer, S., Rulicke, T., Streit, P., Kunz, B., Sonderegger, P., 2008. Neurotrypsin cleaves agrin locally at the synapse. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 22, 1861-1873.
- Stephan, A.H., Madison, D.V., Mateos, J.M., Fraser, D.A., Lovelett, E.A., Coutellier, L., Kim, L., Tsai, H.H., Huang, E.J., Rowitch, D.H., Berns, D.S., Tenner, A.J., Shamloo, M., Barres, B.A., 2013. A dramatic increase of C1q protein in the CNS during normal aging. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 33, 13460-13474.
- Stetefeld, J., Alexandrescu, A.T., Maciejewski, M.W., Jenny, M., Rathgeb-Szabo, K., Schulthess, T., Landwehr, R., Frank, S., Ruegg, M.A., Kammerer, R.A., 2004. Modulation of agrin function by alternative splicing and Ca²⁺ binding. *Structure* 12, 503-515.
- Steubl, D., Hettwer, S., Vrijbloed, W., Dahinden, P., Wolf, P., Luppa, P., Wagner, C.A., Renders, L., Heemann, U., Roos, M., 2013. C-terminal agrin fragment--a new fast biomarker for kidney function in renal transplant recipients. *American journal of nephrology* 38, 501-508.
- Steubl, D., Roos, M., Hettwer, S., Angermann, S., Wen, M., Schmaderer, C., Luppa, P., Heemann, U., Renders, L., 2016. Comparison of Peritoneal Low-Molecular-Weight-Protein-Removal in CCPD and CAPD Patients Based on C-Terminal Agrin Fragment Clearance. *Kidney & blood pressure research* 41, 175-185.
- Stevens, N.E., Chapman, M.J., Fraser, C.K., Kuchel, T.R., Hayball, J.D., Diener, K.R., 2017. Therapeutic targeting of HMGB1 during experimental sepsis modulates the inflammatory cytokine profile to one associated with improved clinical outcomes. *Scientific reports* 7, 5850.
- Stolla, M., Pelisek, J., von Bruhl, M.L., Schafer, A., Barocke, V., Heider, P., Lorenz, M., Tirniceriu, A., Steinhart, A., Bauersachs, J., Bray, P.F., Massberg, S., Schulz, C., 2012. Fractalkine is expressed in early and advanced atherosclerotic lesions and supports monocyte recruitment via CX3CR1. *PLoS one* 7, e43572.
- Stout, J.R., Fragala, M.S., Hoffman, J.R., Robinson, E.H.t., McCormack, W.P., Townsend, J.R., Jatjner, A.R., Emerson, N.S., Oliveira, L.P., Fukuda, D.H., 2015. C-terminal agrin fragment is inversely related to neuromuscular fatigue in older men. *Muscle & nerve* 51, 132-133.
- Streit, M., Riccardi, L., Velasco, P., Brown, L.F., Hawighorst, T., Bornstein, P., Detmar, M., 1999. Thrombospondin-2: a potent endogenous inhibitor of tumor growth and

- angiogenesis. *Proceedings of the National Academy of Sciences of the United States of America* 96, 14888-14893.
- Su, S.L., Wang, W.F., Wu, S.L., Wu, H.M., Chang, J.C., Huang, C.S., Cheng, W.L., Soong, B.W., Lee, Y.C., Li, J.Y., Kuo, S.J., Chen, M., Huang, C.N., Liu, C.S., 2012. FGF21 in ataxia patients with spinocerebellar atrophy and mitochondrial disease. *Clinica chimica acta; international journal of clinical chemistry* 414, 225-227.
- Sudol, M., 2011. From Rous sarcoma virus to plasminogen activator, src oncogene and cancer management. *Oncogene* 30, 3003-3010.
- Suelves, M., Vidal, B., Ruiz, V., Baeza-Raja, B., Diaz-Ramos, A., Cuartas, I., Lluís, F., Parra, M., Jardi, M., Lopez-Aleman, R., Serrano, A.L., Munoz-Canoves, P., 2005. The plasminogen activation system in skeletal muscle regeneration: antagonistic roles of urokinase-type plasminogen activator (uPA) and its inhibitor (PAI-1). *Frontiers in bioscience : a journal and virtual library* 10, 2978-2985.
- Sugiyama, Y., Asai, K., Yamada, K., Kureya, Y., Ijiri, N., Watanabe, T., Kanazawa, H., Hirata, K., 2017. Decreased levels of irisin, a skeletal muscle cell-derived myokine, are related to emphysema associated with chronic obstructive pulmonary disease. *International journal of chronic obstructive pulmonary disease* 12, 765-772.
- Sui, Y., Stehno-Bittel, L., Li, S., Loganathan, R., Dhillon, N.K., Pinson, D., Nath, A., Kolson, D., Narayan, O., Buch, S., 2006. CXCL10-induced cell death in neurons: role of calcium dysregulation. *The European journal of neuroscience* 23, 957-964.
- Suire, C.N., Eitan, E., Shaffer, N.C., Tian, Q., Studenski, S., Mattson, M.P., Kapogiannis, D., 2017. Walking speed decline in older adults is associated with elevated pro-BDNF in plasma extracellular vesicles. *Experimental gerontology* 98, 209-216.
- Sun, F., Qian, W., Zhang, C., Fan, J.X., Huang, H.F., 2017a. Correlation of Maternal Serum Homocysteine in the First Trimester with the Development of Gestational Hypertension and Preeclampsia. *Medical science monitor : international medical journal of experimental and clinical research* 23, 5396-5401.
- Sun, H., Yang, Y., Shao, H., Sun, W., Gu, M., Wang, H., Jiang, L., Qu, L., Sun, D., Gao, Y., 2017b. Sodium Arsenite-Induced Learning and Memory Impairment Is Associated with Endoplasmic Reticulum Stress-Mediated Apoptosis in Rat Hippocampus. *Frontiers in molecular neuroscience* 10, 286.
- Sun, L., Wang, L., Sun, Y., Tang, S.W., Hu, Y., 2006. Protective effects of EUK4010 on beta-amyloid(1-42) induced degeneration of neuronal cells. *The European journal of neuroscience* 24, 1011-1019.
- Sun, L.Y., Spong, A., Swindell, W.R., Fang, Y., Hill, C., Huber, J.A., Boehm, J.D., Westbrook, R., Salvatori, R., Bartke, A., 2013. Growth hormone-releasing hormone disruption extends lifespan and regulates response to caloric restriction in mice. *eLife* 2, e01098.
- Suomalainen, A., Elo, J.M., Pietilainen, K.H., Hakonen, A.H., Sevastianova, K., Korpela, M., Isohanni, P., Marjavaara, S.K., Tyni, T., Kiuru-Enari, S., Pihko, H., Darin, N., Ounap, K., Kluijtmans, L.A., Paetau, A., Buzkova, J., Bindoff, L.A., Annunen-Rasila, J., Uusimaa, J., Rissanen, A., Yki-Jarvinen, H., Hirano, M., Tulinius, M., Smeitink, J., Tynismaa, H., 2011. FGF-21 as a biomarker for muscle-manifesting mitochondrial respiratory chain deficiencies: a diagnostic study. *The Lancet. Neurology* 10, 806-818.
- Suwa, M., Kishimoto, H., Nofuji, Y., Nakano, H., Sasaki, H., Radak, Z., Kumagai, S., 2006. Serum brain-derived neurotrophic factor level is increased and associated with obesity in newly diagnosed female patients with type 2 diabetes mellitus. *Metabolism: clinical and experimental* 55, 852-857.
- Swardfager, W., Lanctot, K., Rothenburg, L., Wong, A., Cappell, J., Herrmann, N., 2010. A meta-analysis of cytokines in Alzheimer's disease. *Biological psychiatry* 68, 930-941.
- Swinnen, M., Vanhoutte, D., Van Almen, G.C., Hamdani, N., Schellings, M.W., D'Hooge, J., Van der Velden, J., Weaver, M.S., Sage, E.H., Bornstein, P., Verheyen, F.K.,

- VandenDriessche, T., Chuah, M.K., Westermann, D., Paulus, W.J., Van de Werf, F., Schroen, B., Carmeliet, P., Pinto, Y.M., Heymans, S., 2009. Absence of thrombospondin-2 causes age-related dilated cardiomyopathy. *Circulation* 120, 1585-1597.
- Szczepanowska, K., Trifunovic, A., 2017. Origins of mtDNA mutations in ageing. *Essays in biochemistry* 61, 325-337.
- Szondy, Z., Korponay-Szabo, I., Kiraly, R., Sarang, Z., Tsay, G.J., 2017. Transglutaminase 2 in human diseases. *BioMedicine* 7, 15.
- Takahashi, H., Ozeki, M., Fujisaka, T., Morita, H., Fujita, S.I., Takeda, Y., Shibata, K., Sohmiya, K., Hoshiga, M., Tamaki, J., Ishizaka, N., 2018. Changes in Serum Fibroblast Growth Factor 23 in Patients With Acute Myocardial Infarction. *Circulation journal : official journal of the Japanese Circulation Society* 82, 767-774.
- Takahashi, H., Yamaguchi, M., 2000. Stimulatory effect of regucalcin on ATP-dependent Ca(2+) uptake activity in rat liver mitochondria. *Journal of cellular biochemistry* 78, 121-130.
- Talukdar, S., Zhou, Y., Li, D., Rossulek, M., Dong, J., Somayaji, V., Weng, Y., Clark, R., Lanba, A., Owen, B.M., Brenner, M.B., Trimmer, J.K., Gropp, K.E., Chabot, J.R., Erion, D.M., Rolph, T.P., Goodwin, B., Calle, R.A., 2016. A Long-Acting FGF21 Molecule, PF-05231023, Decreases Body Weight and Improves Lipid Profile in Non-human Primates and Type 2 Diabetic Subjects. *Cell metabolism* 23, 427-440.
- Tammineni, P., Ye, X., Feng, T., Aikal, D., Cai, Q., 2017. Impaired retrograde transport of axonal autophagosomes contributes to autophagic stress in Alzheimer's disease neurons. *eLife* 6.
- Tan, H.L., Yap, J.Q., Qian, Q., 2016. Acute Kidney Injury: Tubular Markers and Risk for Chronic Kidney Disease and End-Stage Kidney Failure. *Blood purification* 41, 144-150.
- Tanajak, P., Pongkan, W., Chattipakorn, S.C., Chattipakorn, N., 2018. Increased plasma FGF21 level as an early biomarker for insulin resistance and metabolic disturbance in obese insulin-resistant rats. *Diabetes & vascular disease research* 15, 263-269.
- Tanaka, H., Goto, H., Inoko, A., Makihara, H., Enomoto, A., Horimoto, K., Matsuyama, M., Kurita, K., Izawa, I., Inagaki, M., 2015. Cytokinetic Failure-induced Tetraploidy Develops into Aneuploidy, Triggering Skin Aging in Phosphovimentin-deficient Mice. *The Journal of biological chemistry* 290, 12984-12998.
- Tanaka, T., Narazaki, M., Kishimoto, T., 2014. IL-6 in inflammation, immunity, and disease. *Cold Spring Harbor perspectives in biology* 6, a016295.
- Tang, C.Z., Zhang, Y.L., Wang, W.S., Li, W.G., Shi, J.P., 2016. Serum Levels of High-sensitivity C-Reactive Protein at Admission Are More Strongly Associated with Poststroke Depression in Acute Ischemic Stroke than Homocysteine Levels. *Molecular neurobiology* 53, 2152-2160.
- Tang, D., Kang, R., Livesey, K.M., Kroemer, G., Billiar, T.R., Van Houten, B., Zeh, H.J., 3rd, Lotze, M.T., 2011. High-mobility group box 1 is essential for mitochondrial quality control. *Cell metabolism* 13, 701-711.
- Tanisawa, K., Taniguchi, H., Sun, X., Ito, T., Cao, Z.B., Sakamoto, S., Higuchi, M., 2014. Common single nucleotide polymorphisms in the FNDC5 gene are associated with glucose metabolism but do not affect serum irisin levels in Japanese men with low fitness levels. *Metabolism: clinical and experimental* 63, 574-583.
- Tao, G.Z., Looi, K.S., Toivola, D.M., Strnad, P., Zhou, Q., Liao, J., Wei, Y., Habtezion, A., Omary, M.B., 2009. Keratins modulate the shape and function of hepatocyte mitochondria: a mechanism for protection from apoptosis. *Journal of cell science* 122, 3851-3855.
- Tao, X., Finkbeiner, S., Arnold, D.B., Shaywitz, A.J., Greenberg, M.E., 1998. Ca²⁺ influx regulates BDNF transcription by a CREB family transcription factor-dependent mechanism. *Neuron* 20, 709-726.

- Tatrai, P., Dudas, J., Batmunkh, E., Mathe, M., Zalatnai, A., Schaff, Z., Ramadori, G., Kovalszky, I., 2006. Agrin, a novel basement membrane component in human and rat liver, accumulates in cirrhosis and hepatocellular carcinoma. *Laboratory investigation; a journal of technical methods and pathology* 86, 1149-1160.
- Tatsukawa, H., Furutani, Y., Hitomi, K., Kojima, S., 2016. Transglutaminase 2 has opposing roles in the regulation of cellular functions as well as cell growth and death. *Cell death & disease* 7, e2244.
- Taya, M., Hammes, S.R., 2018. Glycoprotein Non-Metastatic Melanoma Protein B (GPNMB) and Cancer: A Novel Potential Therapeutic Target. *Steroids* 133, 102-107.
- Tchalla, A.E., Wellenius, G.A., Trivison, T.G., Gagnon, M., Iloputaife, I., Dantoine, T., Sorond, F.A., Lipsitz, L.A., 2015. Circulating vascular cell adhesion molecule-1 is associated with cerebral blood flow dysregulation, mobility impairment, and falls in older adults. *Hypertension* 66, 340-346.
- Terrado, J., Burgess, R.W., DeChiara, T., Yancopoulos, G., Sanes, J.R., Kato, A.C., 2001. Motoneuron survival is enhanced in the absence of neuromuscular junction formation in embryos. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 21, 3144-3150.
- Theilade, S., Lyngbaek, S., Hansen, T.W., Eugen-Olsen, J., Fenger, M., Rossing, P., Jeppesen, J.L., 2015. Soluble urokinase plasminogen activator receptor levels are elevated and associated with complications in patients with type 1 diabetes. *Journal of internal medicine* 277, 362-371.
- Theret, M., Gsaier, L., Schaffer, B., Juban, G., Ben Larbi, S., Weiss-Gayet, M., Bultot, L., Collodet, C., Foretz, M., Desplanches, D., Sanz, P., Zang, Z., Yang, L., Vial, G., Viollet, B., Sakamoto, K., Brunet, A., Chazaud, B., Mounier, R., 2017. AMPKalpha1-LDH pathway regulates muscle stem cell self-renewal by controlling metabolic homeostasis. *The EMBO journal* 36, 1946-1962.
- Thiessen, S.E., Vanhorebeek, I., Derese, I., Gunst, J., Van den Berghe, G., 2015. FGF21 Response to Critical Illness: Effect of Blood Glucose Control and Relation With Cellular Stress and Survival. *The Journal of clinical endocrinology and metabolism* 100, E1319-1327.
- Thomas, M.R., Lip, G.Y., 2017. Novel Risk Markers and Risk Assessments for Cardiovascular Disease. *Circulation research* 120, 133-149.
- Thulin, P., Nordahl, G., Gry, M., Yimer, G., Aklillu, E., Makonnen, E., Aderaye, G., Lindquist, L., Mattsson, C.M., Ekblom, B., Antoine, D.J., Park, B.K., Linder, S., Harrill, A.H., Watkins, P.B., Glinghammar, B., Schuppe-Koistinen, I., 2014. Keratin-18 and microRNA-122 complement alanine aminotransferase as novel safety biomarkers for drug-induced liver injury in two human cohorts. *Liver international : official journal of the International Association for the Study of the Liver* 34, 367-378.
- Tobias, D.K., Akinkuolie, A.O., Chandler, P.D., Lawler, P.R., Manson, J.E., Buring, J.E., Ridker, P.M., Wang, L., Lee, I.M., Mora, S., 2017. Markers of Inflammation and Incident Breast Cancer Risk in the Women's Health Study. *American journal of epidemiology*.
- Tobisawa, M., Tsurusaki, Y., Yamaguchi, M., 2003. Decrease in regucalcin level and enhancement of protein tyrosine phosphatase activity in rat brain microsomes with increasing age. *International journal of molecular medicine* 12, 577-580.
- Toivola, D.M., Habtezion, A., Misiorek, J.O., Zhang, L., Nystrom, J.H., Sharpe, O., Robinson, W.H., Kwan, R., Omary, M.B., 2015. Absence of keratin 8 or 18 promotes antimitochondrial autoantibody formation in aging male mice. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 29, 5081-5089.

- Toledo, J.B., Korff, A., Shaw, L.M., Trojanowski, J.Q., Zhang, J., 2014. Low levels of cerebrospinal fluid complement 3 and factor H predict faster cognitive decline in mild cognitive impairment. *Alzheimer's research & therapy* 6, 36.
- Tomas-Roig, J., Piscitelli, F., Gil, V., Del Rio, J.A., Moore, T.P., Agbemeyah, H., Salinas-Riester, G., Pommerenke, C., Lorenzen, S., Beissbarth, T., Hoyer-Fender, S., Di Marzo, V., Havemann-Reinecke, U., 2016. Social defeat leads to changes in the endocannabinoid system: An overexpression of calreticulin and motor impairment in mice. *Behavioural brain research* 303, 34-43.
- Tomaschitz, A., Pilz, S., Marz, W., 2016. GDF-15, soluble ST2 and Troponin-I: Biomarkers of Subclinical Vascular Disease? *Atherosclerosis* 248, 255-256.
- Toutouzas, K., Stathogiannis, K., Latsios, G., Synetos, A., Drakopoulou, M., Penesopoulou, V., Michelongona, A., Tsiamis, E., Tousoulis, D., 2017. Biomarkers in aortic valve stenosis and their clinical significance in transcatheter aortic valve implantation. *Current medicinal chemistry*.
- Tran, C.L., Sethi, S., Murray, D., Cramer, C.H., Sas, D.J., Willrich, M., Smith, R.J., Fervenza, F.C., 2016. Discontinuation of dialysis with eculizumab therapy in a pediatric patient with dense deposit disease. *Pediatric nephrology* 31, 683-687.
- Trautmann, A., Vivier, E., 2001. Immunology. Agrin--a bridge between the nervous and immune systems. *Science* 292, 1667-1668.
- Troncone, L., Luciani, M., Coggins, M., Wilker, E.H., Ho, C.Y., Codispoti, K.E., Frosch, M.P., Kaye, R., Del Monte, F., 2016. Abeta Amyloid Pathology Affects the Hearts of Patients With Alzheimer's Disease: Mind the Heart. *Journal of the American College of Cardiology* 68, 2395-2407.
- Trott, D.W., Lesniewski, L.A., Donato, A.J., 2017. Selected life-extending interventions reduce arterial CXCL10 and macrophage colony-stimulating factor in aged mouse arteries. *Cytokine* 96, 102-106.
- Trueba-Saiz, A., Cavada, C., Fernandez, A.M., Leon, T., Gonzalez, D.A., Fortea Ormaechea, J., Lleo, A., Del Ser, T., Nunez, A., Torres-Aleman, I., 2013. Loss of serum IGF-I input to the brain as an early biomarker of disease onset in Alzheimer mice. *Translational psychiatry* 3, e330.
- Tsai, J.P., 2017. The association of serum leptin levels with metabolic diseases. *Ci ji yi xue za zhi = Tzu-chi medical journal* 29, 192-196.
- Tsai, V.W., Lin, S., Brown, D.A., Salis, A., Breit, S.N., 2016. Anorexia-cachexia and obesity treatment may be two sides of the same coin: role of the TGF- β superfamily cytokine MIC-1/GDF15. *International journal of obesity* 40, 193-197.
- Tsurusaki, Y., Yamaguchi, M., 2004. Role of regucalcin in liver nuclear function: binding of regucalcin to nuclear protein or DNA and modulation of tumor-related gene expression. *International journal of molecular medicine* 14, 277-281.
- Tung, B.T., Rodriguez-Bies, E., Talero, E., Gamero-Estevez, E., Motilva, V., Navas, P., Lopez-Lluch, G., 2015. Anti-inflammatory effect of resveratrol in old mice liver. *Experimental gerontology* 64, 1-7.
- Tung, J.N., Ko, C.P., Yang, S.F., Cheng, C.W., Chen, P.N., Chang, C.Y., Lin, C.L., Yang, T.F., Hsieh, Y.H., Chen, K.C., 2016. Inhibition of pentraxin 3 in glioma cells impairs proliferation and invasion in vitro and in vivo. *Journal of neuro-oncology* 129, 201-209.
- Tunlid, A., Hoitink, H.A., Low, C., White, D.C., 1989. Characterization of bacteria that suppress rhizoctonia damping-off in bark compost media by analysis of Fatty Acid biomarkers. *Applied and environmental microbiology* 55, 1368-1374.
- Tzikas, S., Palapies, L., Bakogiannis, C., Zeller, T., Sinning, C., Baldus, S., Bickel, C., Vassilikos, V., Lackner, K.J., Zeiher, A., Munzel, T., Blankenberg, S., Keller, T., 2017. GDF-15 predicts cardiovascular events in acute chest pain patients. *PloS one* 12, e0182314.

- Ueta, R., Yamanashi, Y., 2018. [Homeostasis and Disorder of Musculoskeletal System. Molecular signaling and its pathogenic alterations in neuromuscular junction formation.]. *Clinical calcium* 28, 360-366.
- Ulu, S.M., Yuksel, S., Altuntas, A., Kacar, E., Ahsen, A., Altug, A., Celik, S., Sezer, M.T., 2014. Associations between serum hepcidin level, FGF-21 level and oxidative stress with arterial stiffness in CAPD patients. *International urology and nephrology* 46, 2409-2414.
- Ursini, F., Abenavoli, L., 2018. The Emerging Role of Complement C3 as A Biomarker of Insulin Resistance and Cardiometabolic Diseases: Preclinical and Clinical Evidence. *Reviews on recent clinical trials* 13, 61-68.
- Usluogullari, B., Usluogullari, C.A., Balkan, F., Orkmez, M., 2017. Role of serum levels of irisin and oxidative stress markers in pregnant women with and without gestational diabetes. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology* 33, 405-407.
- Vallega, K.A., Liu, N., Myers, J.S., Yu, K., Sang, Q.X., 2016. Elevated Resistin Gene Expression in African American Estrogen and Progesterone Receptor Negative Breast Cancer. *PLoS one* 11, e0157741.
- Valvona, C.J., Fillmore, H.L., Nunn, P.B., Pilkington, G.J., 2016. The Regulation and Function of Lactate Dehydrogenase A: Therapeutic Potential in Brain Tumor. *Brain pathology* 26, 3-17.
- van Dijk, K.D., Berendse, H.W., Drukarch, B., Fratantoni, S.A., Pham, T.V., Piersma, S.R., Huisman, E., Breve, J.J., Groenewegen, H.J., Jimenez, C.R., van de Berg, W.D., 2012. The proteome of the locus ceruleus in Parkinson's disease: relevance to pathogenesis. *Brain pathology* 22, 485-498.
- Van Epps, P., Oswald, D., Higgins, P.A., Hornick, T.R., Aung, H., Banks, R.E., Wilson, B.M., Burant, C., Graventstein, S., Canaday, D.H., 2016. Frailty has a stronger association with inflammation than age in older veterans. *Immunity & ageing : I & A* 13, 27.
- Van Themsche, C., Chaudhry, P., Leblanc, V., Parent, S., Asselin, E., 2010. XIAP gene expression and function is regulated by autocrine and paracrine TGF-beta signaling. *Molecular cancer* 9, 216.
- VanSaun, M., Herrera, A.A., Werle, M.J., 2003. Structural alterations at the neuromuscular junctions of matrix metalloproteinase 3 null mutant mice. *Journal of neurocytology* 32, 1129-1142.
- VanSaun, M., Werle, M.J., 2000. Matrix metalloproteinase-3 removes agrin from synaptic basal lamina. *Journal of neurobiology* 43, 140-149.
- Vaz, C.V., Rodrigues, D.B., Socorro, S., Maia, C.J., 2015. Effect of extracellular calcium on regucalcin expression and cell viability in neoplastic and non-neoplastic human prostate cells. *Biochimica et biophysica acta* 1853, 2621-2628.
- Vengen, I.T., Dale, A.C., Wiseth, R., Midthjell, K., Videm, V., 2010. Lactoferrin is a novel predictor of fatal ischemic heart disease in diabetes mellitus type 2: long-term follow-up of the HUNT 1 study. *Atherosclerosis* 212, 614-620.
- Verbeek, M.M., Otte-Holler, I., van den Born, J., van den Heuvel, L.P., David, G., Wesseling, P., de Waal, R.M., 1999. Agrin is a major heparan sulfate proteoglycan accumulating in Alzheimer's disease brain. *The American journal of pathology* 155, 2115-2125.
- Vercellino, M., Grifoni, S., Romagnolo, A., Masera, S., Mattioda, A., Trebini, C., Chiavazza, C., Caligiana, L., Capello, E., Mancardi, G.L., Giobbe, D., Mutani, R., Giordana, M.T., Cavalla, P., 2011. Progranulin expression in brain tissue and cerebrospinal fluid levels in multiple sclerosis. *Multiple sclerosis* 17, 1194-1201.
- Verschoor, C.P., Johnstone, J., Millar, J., Parsons, R., Lelic, A., Loeb, M., Bramson, J.L., Bowdish, D.M., 2014. Alterations to the frequency and function of peripheral blood monocytes and associations with chronic disease in the advanced-age, frail elderly. *PLoS one* 9, e104522.

- Vezzoli, M., Castellani, P., Corna, G., Castiglioni, A., Bosurgi, L., Monno, A., Brunelli, S., Manfredi, A.A., Rubartelli, A., Rovere-Querini, P., 2011. High-mobility group box 1 release and redox regulation accompany regeneration and remodeling of skeletal muscle. *Antioxidants & redox signaling* 15, 2161-2174.
- Videm, V., Dahl, H., Walberg, L.E., Wiseth, R., 2012. Functional polymorphisms in the LTF gene and risk of coronary artery stenosis. *Human immunology* 73, 554-559.
- Villareal, D.T., Morley, J.E., 1994. Trophic factors in aging. Should older people receive hormonal replacement therapy? *Drugs & aging* 4, 492-509.
- Villarreal, A., Seoane, R., Gonzalez Torres, A., Rosciszewski, G., Angelo, M.F., Rossi, A., Barker, P.A., Ramos, A.J., 2014. S100B protein activates a RAGE-dependent autocrine loop in astrocytes: implications for its role in the propagation of reactive gliosis. *Journal of neurochemistry* 131, 190-205.
- Volin, M.V., Huynh, N., Klosowska, K., Reyes, R.D., Woods, J.M., 2010. Fractalkine-induced endothelial cell migration requires MAP kinase signaling. *Pathobiology : journal of immunopathology, molecular and cellular biology* 77, 7-16.
- von Eynatten, M., Hamann, A., Twardella, D., Nawroth, P.P., Brenner, H., Rothenbacher, D., 2006a. Relationship of adiponectin with markers of systemic inflammation, atherogenic dyslipidemia, and heart failure in patients with coronary heart disease. *Clinical chemistry* 52, 853-859.
- von Eynatten, M., Schneider, J.G., Humpert, P.M., Kreuzer, J., Kuecherer, H., Katus, H.A., Nawroth, P.P., Dugi, K.A., 2006b. Serum adiponectin levels are an independent predictor of the extent of coronary artery disease in men. *Journal of the American College of Cardiology* 47, 2124-2126.
- von Zglinicki, T., Varela Nieto, I., Brites, D., Karagianni, N., Ortolano, S., Georgopoulos, S., Cardoso, A.L., Novella, S., Lepperdinger, G., Trendelenburg, A.U., van Os, R., 2016. Frailty in mouse ageing: A conceptual approach. *Mechanisms of ageing and development* 160, 34-40.
- Vuppalanchi, R., Marri, S., Kolwankar, D., Considine, R.V., Chalasani, N., 2005. Is adiponectin involved in the pathogenesis of nonalcoholic steatohepatitis? A preliminary human study. *Journal of clinical gastroenterology* 39, 237-242.
- Walter, E., Dellago, H., Grillari, J., Dimai, H.P., Hackl, M., 2018. Cost-utility analysis of fracture risk assessment using microRNAs compared with standard tools and no monitoring in the Austrian female population. *Bone* 108, 44-54.
- Wan, S.X., Shi, B., Lou, X.L., Liu, J.Q., Ma, G.G., Liang, D.Y., Ma, S., 2016. Ghrelin protects small intestinal epithelium against sepsis-induced injury by enhancing the autophagy of intestinal epithelial cells. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie* 83, 1315-1320.
- Wang, B., Lian, Y.J., Su, W.J., Peng, W., Dong, X., Liu, L.L., Gong, H., Zhang, T., Jiang, C.L., Wang, Y.X., 2017a. HMGB1 mediates depressive behavior induced by chronic stress through activating the kynurenine pathway. *Brain, behavior, and immunity*.
- Wang, C., Youle, R.J., 2009. The role of mitochondria in apoptosis*. *Annual review of genetics* 43, 95-118.
- Wang, H., Chen, Q., Li, Y., Jing, X., Yang, J., 2017b. Prognostic value of growth differentiation factor-15 in Chinese patients with heart failure: A prospective observational study. *Cardiology journal*.
- Wang, H., Zhao, Y.T., Zhang, S., Dubielecka, P.M., Du, J., Yano, N., Chin, Y.E., Zhuang, S., Qin, G., Zhao, T.C., 2017c. Irisin plays a pivotal role to protect the heart against ischemia and reperfusion injury. *Journal of cellular physiology* 232, 3775-3785.
- Wang, J., Chen, J., Sen, S., 2016a. MicroRNA as Biomarkers and Diagnostics. *Journal of cellular physiology* 231, 25-30.

- Wang, J., Gao, Z.P., Qin, S., Liu, C.B., Zou, L.L., 2017d. Calreticulin is an effective immunologic adjuvant to tumor-associated antigens. *Experimental and therapeutic medicine* 14, 3399-3406.
- Wang, J., Ma, R., Sharma, A., He, M., Xue, J., Wu, J., Dun, B., Li, G., Wang, X., Ji, M., She, J.X., Tang, J., 2015a. Inflammatory serum proteins are severely altered in metastatic gastric adenocarcinoma patients from the Chinese population. *PloS one* 10, e0123985.
- Wang, J., Wang, H., Shi, J., Ding, Y., 2015b. Effects of bone marrow MSCs transfected with sRAGE on the intervention of HMGB1 induced immuno-inflammatory reaction. *International journal of clinical and experimental pathology* 8, 12028-12040.
- Wang, J.H., Lee, C.J., Yang, C.F., Chen, Y.C., Hsu, B.G., 2017e. Serum resistin as an independent marker of aortic stiffness in patients with coronary artery disease. *PloS one* 12, e0183123.
- Wang, L., Sato, H., Zhao, S., Tooyama, I., 2010. Deposition of lactoferrin in fibrillar-type senile plaques in the brains of transgenic mouse models of Alzheimer's disease. *Neuroscience letters* 481, 164-167.
- Wang, L., Zhang, Y., Wang, W., Zhu, Y., Chen, Y., Tian, B., 2017f. Gemcitabine treatment induces endoplasmic reticular (ER) stress and subsequently upregulates urokinase plasminogen activator (uPA) to block mitochondrial-dependent apoptosis in Panc-1 cancer stem-like cells (CSCs). *PloS one* 12, e0184110.
- Wang, N., Zhang, J., Yang, J.X., 2016b. Growth factor progranulin blocks tumor necrosis factor- α -mediated inhibition of osteoblast differentiation. *Genetics and molecular research : GMR* 15.
- Wang, R., Li, Q.F., Anfinogenova, Y., Tang, D.D., 2007a. Dissociation of Crk-associated substrate from the vimentin network is regulated by p21-activated kinase on ACh activation of airway smooth muscle. *American journal of physiology. Lung cellular and molecular physiology* 292, L240-248.
- Wang, X., Hattori, Y., Satoh, H., Iwata, C., Banba, N., Monden, T., Uchida, K., Kamikawa, Y., Kasai, K., 2007b. Tetrahydrobiopterin prevents endothelial dysfunction and restores adiponectin levels in rats. *European journal of pharmacology* 555, 48-53.
- Wang, X., Zhu, L., Wu, Y., Sun, K., Su, M., Yu, L., Chen, J., Li, W., Yang, J., Yuan, Z., Hui, R., 2016c. Plasma growth differentiation factor 15 predicts first-ever stroke in hypertensive patients. *Medicine* 95, e4342.
- Wang, X.L., Liu, Q., Chen, G.J., Li, M.L., Ding, Y.H., 2017g. Overexpression of MTERF4 promotes the amyloidogenic processing of APP by inhibiting ADAM10. *Biochemical and biophysical research communications* 482, 928-934.
- Wang, Y., Tan, X., Gao, H., Yuan, H., Hu, R., Jia, L., Zhu, J., Sun, L., Zhang, H., Huang, L., Zhao, D., Gao, P., Du, J., 2018a. Magnitude of Soluble ST2 as a Novel Biomarker for Acute Aortic Dissection. *Circulation* 137, 259-269.
- Wang, Y., Xie, J., Liu, Z., Fu, H., Huo, Q., Gu, Y., Liu, Y., 2017h. Association of calreticulin expression with disease activity and organ damage in systemic lupus erythematosus patients. *Experimental and therapeutic medicine* 13, 2577-2583.
- Wang, Z., Li, X., Shen, J., Tian, D., Ji, Q., Xia, L., Lv, Q., 2018b. Plasma microRNAs reflecting cardiac and inflammatory injury in coronary artery bypass grafting surgery. *The Journal of surgical research* 224, 58-63.
- Wang, Z.G., Zhu, B., 2016. Is FGF23 or FGF21 a Promising Biomarker to Indicate the Aging Process in COPD? *Chest* 150, 467-468.
- Washington, T.A., Healey, J.M., Thompson, R.W., Lowe, L.L., Carson, J.A., 2014. Lactate dehydrogenase regulation in aged skeletal muscle: Regulation by anabolic steroids and functional overload. *Experimental gerontology* 57, 66-74.
- Watanabe, S., Sato, K., Hasegawa, N., Kurihara, T., Matsutani, K., Sanada, K., Hamaoka, T., Fujita, S., Iemitsu, M., 2015. Serum C1q as a novel biomarker of sarcopenia in older

- adults. *FASEB journal* : official publication of the Federation of American Societies for Experimental Biology 29, 1003-1010.
- Waters, M.J., Brooks, A.J., 2012. Growth hormone and cell growth. *Endocrine development* 23, 86-95.
- Watt, A.D., Perez, K.A., Ang, C.S., O'Donnell, P., Rembach, A., Pertile, K.K., Rumble, R.L., Trounson, B.O., Fowler, C.J., Faux, N.G., Masters, C.L., Villemagne, V.L., Barnham, K.J., 2015. Peripheral alpha-defensins 1 and 2 are elevated in Alzheimer's disease. *Journal of Alzheimer's disease* : JAD 44, 1131-1143.
- Waxman, A.B., Kolliputi, N., 2009. IL-6 protects against hyperoxia-induced mitochondrial damage via Bcl-2-induced Bak interactions with mitofusins. *American journal of respiratory cell and molecular biology* 41, 385-396.
- Wei, N., Lin, C.Q., Modafferi, E.F., Gomes, W.A., Black, D.L., 1997. A unique intronic splicing enhancer controls the inclusion of the agrin Y exon. *Rna* 3, 1275-1288.
- Wei, W., An, X.R., Jin, S.J., Li, X.X., Xu, M., 2018. Inhibition of insulin resistance by PGE1 via autophagy-dependent FGF21 pathway in diabetic nephropathy. *Scientific reports* 8, 9.
- Wei, Z., Zeng, X., Xu, J., Duan, X., Xie, Y., 2014. Prognostic value of pretreatment serum levels of lactate dehydrogenase in nonmetastatic nasopharyngeal carcinoma: single-site analysis of 601 patients in a highly endemic area. *OncoTargets and therapy* 7, 739-749.
- Weilner, S., Schraml, E., Redl, H., Grillari-Voglauer, R., Grillari, J., 2013. Secretion of microvesicular miRNAs in cellular and organismal aging. *Experimental gerontology* 48, 626-633.
- Wekesa, A.L., Cross, K.S., O'Donovan, O., Dowdall, J.F., O'Brien, O., Doyle, M., Byrne, L., Phelan, J.P., Ross, M.D., Landers, R., Harrison, M., 2014. Predicting carotid artery disease and plaque instability from cell-derived microparticles. *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery* 48, 489-495.
- Wen, F., An, C., Wu, X., Yang, Y., Xu, J., Liu, Y., Wang, C., Nie, L., Fang, H., Yang, Z., 2018. MiR-34a regulates mitochondrial content and fat ectopic deposition induced by resistin through the AMPK/PPARalpha pathway in HepG2 cells. *The international journal of biochemistry & cell biology* 94, 133-145.
- Wen, F., Li, B., Huang, C., Wei, Z., Zhou, Y., Liu, J., Zhang, H., 2015a. MiR-34a is Involved in the Decrease of ATP Contents Induced by Resistin Through Target on ATP5S in HepG2 Cells. *Biochemical genetics* 53, 301-309.
- Wen, F., Yang, Y., Jin, D., Sun, J., Yu, X., Yang, Z., 2014. MiRNA-145 is involved in the development of resistin-induced insulin resistance in HepG2 cells. *Biochemical and biophysical research communications* 445, 517-523.
- Wen, F., Zhang, H., Bao, C., Yang, M., Wang, N., Zhang, J., Hu, Y., Yang, X., Geng, J., Yang, Z., 2015b. Resistin Increases Ectopic Deposition of Lipids Through miR-696 in C2C12 Cells. *Biochemical genetics* 53, 63-71.
- Wen, M.S., Wang, C.Y., Lin, S.L., Hung, K.C., 2013. Decrease in irisin in patients with chronic kidney disease. *PLoS one* 8, e64025.
- White, E.S., Mantovani, A.R., 2013. Inflammation, wound repair, and fibrosis: reassessing the spectrum of tissue injury and resolution. *The Journal of pathology* 229, 141-144.
- White, H.K., Petrie, C.D., Landschulz, W., MacLean, D., Taylor, A., Lyles, K., Wei, J.Y., Hoffman, A.R., Salvatori, R., Ettinger, M.P., Morey, M.C., Blackman, M.R., Merriam, G.R., Capromorelin Study, G., 2009. Effects of an oral growth hormone secretagogue in older adults. *The Journal of clinical endocrinology and metabolism* 94, 1198-1206.
- Whitehead, J.C., Hildebrand, B.A., Sun, M., Rockwood, M.R., Rose, R.A., Rockwood, K., Howlett, S.E., 2014. A clinical frailty index in aging mice: comparisons with frailty index data in humans. *The journals of gerontology. Series A, Biological sciences and medical sciences* 69, 621-632.

- Wightman, S.C., Uppal, A., Pitroda, S.P., Ganai, S., Burnette, B., Stack, M., Oshima, G., Khan, S., Huang, X., Posner, M.C., Weichselbaum, R.R., Khodarev, N.N., 2015. Oncogenic CXCL10 signalling drives metastasis development and poor clinical outcome. *British journal of cancer* 113, 327-335.
- Wiklund, F.E., Bennet, A.M., Magnusson, P.K., Eriksson, U.K., Lindmark, F., Wu, L., Yaghoutyfam, N., Marquis, C.P., Stattin, P., Pedersen, N.L., Adami, H.O., Gronberg, H., Breit, S.N., Brown, D.A., 2010. Macrophage inhibitory cytokine-1 (MIC-1/GDF15): a new marker of all-cause mortality. *Aging cell* 9, 1057-1064.
- Willer, C.J., Speliotes, E.K., Loos, R.J., Li, S., Lindgren, C.M., Heid, I.M., Berndt, S.I., Elliott, A.L., Jackson, A.U., Lamina, C., Lettre, G., Lim, N., Lyon, H.N., McCarroll, S.A., Papadakis, K., Qi, L., Randall, J.C., Ruccasecca, R.M., Sanna, S., Scheet, P., Weedon, M.N., Wheeler, E., Zhao, J.H., Jacobs, L.C., Prokopenko, I., Soranzo, N., Tanaka, T., Timpson, N.J., Almgren, P., Bennett, A., Bergman, R.N., Bingham, S.A., Bonnycastle, L.L., Brown, M., Burtt, N.P., Chines, P., Coin, L., Collins, F.S., Connell, J.M., Cooper, C., Smith, G.D., Dennison, E.M., Deodhar, P., Elliott, P., Erdos, M.R., Estrada, K., Evans, D.M., Gianniny, L., Gieger, C., Gillson, C.J., Guiducci, C., Hackett, R., Hadley, D., Hall, A.S., Havulinna, A.S., Hebebrand, J., Hofman, A., Isomaa, B., Jacobs, K.B., Johnson, T., Jousilahti, P., Jovanovic, Z., Khaw, K.T., Kraft, P., Kuokkanen, M., Kuusisto, J., Laitinen, J., Lakatta, E.G., Luan, J., Luben, R.N., Mangino, M., McArdle, W.L., Meitinger, T., Mulas, A., Munroe, P.B., Narisu, N., Ness, A.R., Northstone, K., O'Rahilly, S., Purmann, C., Rees, M.G., Ridderstrale, M., Ring, S.M., Rivadeneira, F., Ruokonen, A., Sandhu, M.S., Saramies, J., Scott, L.J., Scuteri, A., Silander, K., Sims, M.A., Song, K., Stephens, J., Stevens, S., Stringham, H.M., Tung, Y.C., Valle, T.T., Van Duijn, C.M., Vimalaswaran, K.S., Vollenweider, P., Waeber, G., Wallace, C., Watanabe, R.M., Waterworth, D.M., Watkins, N., Wellcome Trust Case Control, C., Witteman, J.C., Zeggini, E., Zhai, G., Zillikens, M.C., Altshuler, D., Caulfield, M.J., Chanock, S.J., Farooqi, I.S., Ferrucci, L., Guralnik, J.M., Hattersley, A.T., Hu, F.B., Jarvelin, M.R., Laakso, M., Mooser, V., Ong, K.K., Ouwehand, W.H., Salomaa, V., Samani, N.J., Spector, T.D., Tuomi, T., Tuomilehto, J., Uda, M., Uitterlinden, A.G., Wareham, N.J., Deloukas, P., Frayling, T.M., Groop, L.C., Hayes, R.B., Hunter, D.J., Mohlke, K.L., Peltonen, L., Schlessinger, D., Strachan, D.P., Wichmann, H.E., McCarthy, M.I., Boehnke, M., Barroso, I., Abecasis, G.R., Hirschhorn, J.N., Genetic Investigation of, A.T.C., 2009. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nature genetics* 41, 25-34.
- Williams, S., Ryan, C., Jacobson, C., 2008. Agrin and neuregulin, expanding roles and implications for therapeutics. *Biotechnology advances* 26, 187-201.
- Windrichova, J., Fuchsova, R., Kucera, R., Topolcan, O., Fiala, O., Finek, J., Slipkova, D., 2017. MIC1/GDF15 as a Bone Metastatic Disease Biomarker. *Anticancer research* 37, 1501-1505.
- Witwer, K.W., 2015. Circulating microRNA biomarker studies: pitfalls and potential solutions. *Clinical chemistry* 61, 56-63.
- Wolcott, Z., Batra, A., Bevers, M.B., Sastre, C., Khoury, J., Sperling, M., Meyer, B.C., Walsh, K.B., Adeoye, O., Broderick, J.P., Kimberly, W.T., 2017. Soluble ST2 predicts outcome and hemorrhagic transformation after acute stroke. *Annals of clinical and translational neurology* 4, 553-563.
- Woo, Y.C., Lee, C.H., Fong, C.H., Xu, A., Tso, A.W., Cheung, B.M., Lam, K.S., 2017. Serum fibroblast growth factor 21 is a superior biomarker to other adipokines in predicting incident diabetes. *Clinical endocrinology* 86, 37-43.
- Woo, Y.C., Xu, A., Wang, Y., Lam, K.S., 2013. Fibroblast growth factor 21 as an emerging metabolic regulator: clinical perspectives. *Clinical endocrinology* 78, 489-496.

- Woolbright, B.L., Ding, W.X., Jaeschke, H., 2017. Caspase inhibitors for the treatment of liver disease: friend or foe? *Expert review of gastroenterology & hepatology* 11, 397-399.
- Wrann, C.D., White, J.P., Salogiannis, J., Laznik-Bogoslavski, D., Wu, J., Ma, D., Lin, J.D., Greenberg, M.E., Spiegelman, B.M., 2013. Exercise induces hippocampal BDNF through a PGC-1alpha/FNDC5 pathway. *Cell metabolism* 18, 649-659.
- Wright, S.D., Ramos, R.A., Tobias, P.S., Ulevitch, R.J., Mathison, J.C., 1990. CD14, a receptor for complexes of lipopolysaccharide (LPS) and LPS binding protein. *Science* 249, 1431-1433.
- Wu, C.L., Chen, C.H., Hwang, C.S., Chen, S.D., Hwang, W.C., Yang, D.I., 2017a. Roles of p62 in BDNF-dependent autophagy suppression and neuroprotection against mitochondrial dysfunction in rat cortical neurons. *Journal of neurochemistry* 140, 845-861.
- Wu, C.L., Chen, S.D., Yin, J.H., Hwang, C.S., Yang, D.I., 2016a. Nuclear Factor-kappaB-Dependent Sestrin2 Induction Mediates the Antioxidant Effects of BDNF Against Mitochondrial Inhibition in Rat Cortical Neurons. *Molecular neurobiology* 53, 4126-4142.
- Wu, C.L., Yin, J.H., Hwang, C.S., Chen, S.D., Yang, D.Y., Yang, D.I., 2012. c-Jun-dependent sulfiredoxin induction mediates BDNF protection against mitochondrial inhibition in rat cortical neurons. *Neurobiology of disease* 46, 450-462.
- Wu, G., Li, H., Fang, Q., Zhang, J., Zhang, M., Zhang, L., Wu, L., Hou, X., Lu, J., Bao, Y., Jia, W., 2017b. Complementary Role of Fibroblast Growth Factor 21 and Cytokeratin 18 in Monitoring the Different Stages of Nonalcoholic Fatty Liver Disease. *Scientific reports* 7, 5095.
- Wu, H., Chen, Z., Xie, J., Kang, L.N., Wang, L., Xu, B., 2016b. High Mobility Group Box-1: A Missing Link between Diabetes and Its Complications. *Mediators of inflammation* 2016, 3896147.
- Wu, Q., Jiang, D., Matsuda, J.L., Ternyak, K., Zhang, B., Chu, H.W., 2016c. Cigarette Smoke Induces Human Airway Epithelial Senescence via Growth Differentiation Factor 15 Production. *American journal of respiratory cell and molecular biology* 55, 429-438.
- Wu, S.W., Chen, P.N., Lin, C.Y., Hsieh, Y.S., Chang, H.R., 2017c. Everolimus suppresses invasion and migration of renal cell carcinoma by inhibiting FAK activity and reversing epithelial to mesenchymal transition in vitro and in vivo. *Environmental toxicology* 32, 1888-1898.
- Wu, X., Gu, W., Lu, H., Liu, C., Yu, B., Xu, H., Tang, Y., Li, S., Zhou, J., Shao, C., 2016d. Soluble Receptor for Advanced Glycation End Product Ameliorates Chronic Intermittent Hypoxia Induced Renal Injury, Inflammation, and Apoptosis via P38/JNK Signaling Pathways. *Oxidative medicine and cellular longevity* 2016, 1015390.
- Wu, X., Qi, Y.F., Chang, J.R., Lu, W.W., Zhang, J.S., Wang, S.P., Cheng, S.J., Zhang, M., Fan, Q., Lv, Y., Zhu, H., Xin, M.K., Lv, Y., Liu, J.H., 2015. Possible role of fibroblast growth factor 21 on atherosclerosis via amelioration of endoplasmic reticulum stress-mediated apoptosis in apoE(-/-) mice. *Heart and vessels* 30, 657-668.
- Wu, Y., Zhang, S., Xu, Q., Zou, H., Zhou, W., Cai, F., Li, T., Song, W., 2016e. Regulation of global gene expression and cell proliferation by APP. *Scientific reports* 6, 22460.
- Wyatt, A.R., Zammit, N.W., Wilson, M.R., 2013. Acute phase proteins are major clients for the chaperone action of alpha(2)-macroglobulin in human plasma. *Cell stress & chaperones* 18, 161-170.
- Wynn, T.A., 2008. Cellular and molecular mechanisms of fibrosis. *The Journal of pathology* 214, 199-210.
- Xi, J., Yan, C., Liu, W.W., Qiao, K., Lin, J., Tian, X., Wu, H., Lu, J., Wong, L.J., Beeson, D., Zhao, C., 2017. Novel SEA and LG2 Agrin mutations causing congenital Myasthenic syndrome. *Orphanet journal of rare diseases* 12, 182.
- Xia, M., Conley, S.M., Li, G., Li, P.L., Boini, K.M., 2014. Inhibition of hyperhomocysteinemia-induced inflammasome activation and glomerular sclerosis by NLRP3 gene deletion.

- Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology 34, 829-841.
- Xiang, L., Li, J., Wang, Q., Tang, R., Qi, J., 2018. Leptin Gene Transfer Improves Symptoms of Type 2 Diabetic Mice by Regulating Leptin Signaling Pathway and Insulin Resistance of Peripheral Tissues. *Human gene therapy* 29, 68-76.
- Xiao, Y., Xu, A., Law, L.S., Chen, C., Li, H., Li, X., Yang, L., Liu, S., Zhou, Z., Lam, K.S., 2012. Distinct changes in serum fibroblast growth factor 21 levels in different subtypes of diabetes. *The Journal of clinical endocrinology and metabolism* 97, E54-58.
- Xiao, Y., Yang, N., Zhang, Q., Wang, Y., Yang, S., Liu, Z., 2014. Pentraxin 3 inhibits acute renal injury-induced interstitial fibrosis through suppression of IL-6/Stat3 pathway. *Inflammation* 37, 1895-1901.
- Xiao, Z., Shu, J., Zhou, F., Han, Y., 2018. JQ1 is a potential therapeutic option for COPD patients with agrin overexpression. *American journal of physiology. Lung cellular and molecular physiology* 314, L690-L694.
- Xie, C., Zhang, Y., Tran, T.D., Wang, H., Li, S., George, E.V., Zhuang, H., Zhang, P., Kandel, A., Lai, Y., Tang, D., Reeves, W.H., Cheng, H., Ding, Y., Yang, L.J., 2015. Irisin Controls Growth, Intracellular Ca²⁺ Signals, and Mitochondrial Thermogenesis in Cardiomyoblasts. *PLoS one* 10, e0136816.
- Xu, A., Wang, Y., Keshaw, H., Xu, L.Y., Lam, K.S., Cooper, G.J., 2003. The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver diseases in mice. *The Journal of clinical investigation* 112, 91-100.
- Xu, H.M., Tan, L., Wan, Y., Tan, M.S., Zhang, W., Zheng, Z.J., Kong, L.L., Wang, Z.X., Jiang, T., Tan, L., Yu, J.T., 2017a. PGRN Is Associated with Late-Onset Alzheimer's Disease: a Case-Control Replication Study and Meta-analysis. *Molecular neurobiology* 54, 1187-1195.
- Xu, L., Zhang, L., Zhang, H., Yang, Z., Qi, L., Wang, Y., Ren, S., 2018. The participation of fibroblast growth factor 23 (FGF23) in the progression of osteoporosis via JAK/STAT pathway. *Journal of cellular biochemistry* 119, 3819-3828.
- Xu, M., Liu, L., Song, C., Chen, W., Gui, S., 2017b. Ghrelin improves vascular autophagy in rats with vascular calcification. *Life sciences* 179, 23-29.
- Xu, M.D., Wu, X.Z., Zhou, Y., Xue, Y., Zhang, K.Q., 2016. Proteomic characteristics of circulating microparticles in patients with newly-diagnosed type 2 diabetes. *American journal of translational research* 8, 209-220.
- Xu, T., Xie, W., Ma, Y., Zhou, S., Zhang, L., Chen, J., Cai, M., Sun, R., Zhang, P., Yu, S., Xu, Z., Jiang, W., Wu, M., 2017c. Leptin/OB-R pathway promotes IL-4 secretion from B lymphocytes and induces salivary gland epithelial cell apoptosis in Sjogren's syndrome. *Oncotarget* 8, 63417-63429.
- Xu, X.Y., Deng, C.Q., Wang, J., Deng, X.J., Xiao, Q., Li, Y., He, Q., Fan, W.H., Quan, F.Y., Zhu, Y.P., Cheng, P., Chen, G.J., 2017d. Plasma levels of soluble receptor for advanced glycation end products in Alzheimer's disease. *The International journal of neuroscience* 127, 454-458.
- Xu, Y., Sun, Z., 2015. Molecular basis of Klotho: from gene to function in aging. *Endocrine reviews* 36, 174-193.
- Xu, Z., Lv, X.A., Dai, Q., Lu, M., Jin, Z., 2017e. Exogenous BDNF Increases Mitochondrial pCREB and Alleviates Neuronal Metabolic Defects Following Mechanical Injury in a MPTP-Dependent Way. *Molecular neurobiology*.
- Yamaguchi, M., 2010. Regucalcin and metabolic disorders: osteoporosis and hyperlipidemia are induced in regucalcin transgenic rats. *Molecular and cellular biochemistry* 341, 119-133.
- Yamaguchi, M., 2013a. The anti-apoptotic effect of regucalcin is mediated through multisignaling pathways. *Apoptosis : an international journal on programmed cell death* 18, 1145-1153.

- Yamaguchi, M., 2013b. Suppressive role of regucalcin in liver cell proliferation: involvement in carcinogenesis. *Cell proliferation* 46, 243-253.
- Yamaguchi, M., 2014a. Regucalcin as a potential biomarker for metabolic and neuronal diseases. *Molecular and cellular biochemistry* 391, 157-166.
- Yamaguchi, M., 2014b. Regulatory role of regucalcin in heart calcium signaling: Insight into cardiac failure (Review). *Biomedical reports* 2, 303-308.
- Yamaguchi, M., 2014c. The role of regucalcin in bone homeostasis: involvement as a novel cytokine. *Integrative biology : quantitative biosciences from nano to macro* 6, 258-266.
- Yamaguchi, M., Goto, M., Uchiyama, S., Nakagawa, T., 2008. Effect of zinc on gene expression in osteoblastic MC3T3-E1 cells: enhancement of Runx2, OPG, and regucalcin mRNA expressions. *Molecular and cellular biochemistry* 312, 157-166.
- Yamaguchi, M., Murata, T., 2015. Suppressive effects of exogenous regucalcin on the proliferation of human pancreatic cancer MIA PaCa-2 cells in vitro. *International journal of molecular medicine* 35, 1773-1778.
- Yamaguchi, M., Osuka, S., Weitzmann, M.N., Shoji, M., Murata, T., 2016. Increased regucalcin gene expression extends survival in breast cancer patients: Overexpression of regucalcin suppresses the proliferation and metastatic bone activity in MDA-MB-231 human breast cancer cells in vitro. *International journal of oncology* 49, 812-822.
- Yamamoto, K., Takeshita, K., Saito, H., 2014a. Plasminogen activator inhibitor-1 in aging. *Seminars in thrombosis and hemostasis* 40, 652-659.
- Yamamoto, Y., Takemura, M., Serrero, G., Hayashi, J., Yue, B., Tsuboi, A., Kubo, H., Mitsuhashi, T., Mannami, K., Sato, M., Matsunami, H., Matuo, Y., Saito, K., 2014b. Increased serum GP88 (Progranulin) concentrations in rheumatoid arthritis. *Inflammation* 37, 1806-1813.
- Yamashita, E.K., Teixeira, B.M., Yoshihara, R.N., Kuniyoshi, R.K., Alves, B.C., Gehrke, F.S., Vilas-Boas, V.A., Correia, J.A., Azzalis, L.A., Junqueira, V.B., Pereira, E.C., Fonseca, F.L., 2014. Systemic chemotherapy interferes in homocysteine metabolism in breast cancer patients. *Journal of clinical laboratory analysis* 28, 157-162.
- Yan, H., Xia, M., Chang, X., Xu, Q., Bian, H., Zeng, M., Rao, S., Yao, X., Tu, Y., Jia, W., Gao, X., 2011. Circulating fibroblast growth factor 21 levels are closely associated with hepatic fat content: a cross-sectional study. *PloS one* 6, e24895.
- Yan, M., Liu, Z., Fei, E., Chen, W., Lai, X., Luo, B., Chen, P., Jing, H., Pan, J.X., Rivner, M.H., Xiong, W.C., Mei, L., 2018. Induction of Anti-agrin Antibodies Causes Myasthenia Gravis in Mice. *Neuroscience* 373, 113-121.
- Yan, X., Chen, J., Zhang, C., Zeng, J., Zhou, S., Zhang, Z., Lu, X., Chen, J., Feng, W., Li, X., Tan, Y., 2015. Fibroblast growth factor 21 deletion aggravates diabetes-induced pathogenic changes in the aorta in type 1 diabetic mice. *Cardiovascular diabetology* 14, 77.
- Yang, H., Filipovic, Z., Brown, D., Breit, S.N., Vassilev, L.T., 2003. Macrophage inhibitory cytokine-1: a novel biomarker for p53 pathway activation. *Molecular cancer therapeutics* 2, 1023-1029.
- Yang, H., Park, S.H., Choi, H.J., Moon, Y., 2010. The integrated stress response-associated signals modulates intestinal tumor cell growth by NSAID-activated gene 1 (NAG-1/MIC-1/PTGF-beta). *Carcinogenesis* 31, 703-711.
- Yang, J.F., Cao, G., Koirala, S., Reddy, L.V., Ko, C.P., 2001. Schwann cells express active agrin and enhance aggregation of acetylcholine receptors on muscle fibers. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 21, 9572-9584.
- Yang, L., Tang, L., Dai, F., Meng, G., Yin, R., Xu, X., Yao, W., 2017a. Raf-1/CK2 and RhoA/ROCK signaling promote TNF-alpha-mediated endothelial apoptosis via regulating vimentin cytoskeleton. *Toxicology* 389, 74-84.

- Yang, M., Antoine, D.J., Weemhoff, J.L., Jenkins, R.E., Farhood, A., Park, B.K., Jaeschke, H., 2014. Biomarkers distinguish apoptotic and necrotic cell death during hepatic ischemia/reperfusion injury in mice. *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society* 20, 1372-1382.
- Yang, S.P., Yang, X.Z., Cao, G.P., 2015a. Acetyl-L-carnitine prevents homocysteine-induced suppression of Nrf2/Keap1 mediated antioxidant in human lens epithelial cells. *Molecular medicine reports* 12, 1145-1150.
- Yang, X., Gao, F., Liu, Y., 2015b. Association of homocysteine with immunological-inflammatory and metabolic laboratory markers and factors in relation to hyperhomocysteinaemia in rheumatoid arthritis. *Clinical and experimental rheumatology* 33, 900-903.
- Yang, X.Y., Zheng, K.D., Lin, K., Zheng, G., Zou, H., Wang, J.M., Lin, Y.Y., Chuka, C.M., Ge, R.S., Zhai, W., Wang, J.G., 2015c. Energy Metabolism Disorder as a Contributing Factor of Rheumatoid Arthritis: A Comparative Proteomic and Metabolomic Study. *PLoS one* 10, e0132695.
- Yang, Y., Liu, H., Zhang, H., Ye, Q., Wang, J., Yang, B., Mao, L., Zhu, W., Leak, R.K., Xiao, B., Lu, B., Chen, J., Hu, X., 2017b. ST2/IL-33-Dependent Microglial Response Limits Acute Ischemic Brain Injury. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 37, 4692-4704.
- Yao, W., Fan, W., Huang, C., Zhong, H., Chen, X., Zhang, W., 2013. Proteomic analysis for anti-atherosclerotic effect of tetrahydroxystilbene glucoside in rats. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie* 67, 140-145.
- Yao, X., Wang, D., Zhang, L., Wang, L., Zhao, Z., Chen, S., Wang, X., Yue, T., Liu, Y., 2017. Serum Growth Differentiation Factor 15 in Parkinson Disease. *Neuro-degenerative diseases* 17, 251-260.
- Yard, B.A., Kahlert, S., Engelleiter, R., Resch, S., Waldherr, R., Groffen, A.J., van den Heuvel, L.P., van der Born, J., Berden, J.H., Kroger, S., Hafner, M., van der Woude, F.J., 2001. Decreased glomerular expression of agrin in diabetic nephropathy and podocytes, cultured in high glucose medium. *Experimental nephrology* 9, 214-222.
- Yardley, D.A., Weaver, R., Melisko, M.E., Saleh, M.N., Arena, F.P., Forero, A., Cigler, T., Stopeck, A., Citrin, D., Oliff, I., Bechhold, R., Loutfi, R., Garcia, A.A., Cruickshank, S., Crowley, E., Green, J., Hawthorne, T., Yellin, M.J., Davis, T.A., Vahdat, L.T., 2015. EMERGE: A Randomized Phase II Study of the Antibody-Drug Conjugate Glembatumumab Vedotin in Advanced Glycoprotein NMB-Expressing Breast Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 33, 1609-1619.
- Ye, D., Li, H., Wang, Y., Jia, W., Zhou, J., Fan, J., Man, K., Lo, C., Wong, C., Wang, Y., Lam, K.S., Xu, A., 2016a. Circulating Fibroblast Growth Factor 21 Is A Sensitive Biomarker for Severe Ischemia/reperfusion Injury in Patients with Liver Transplantation. *Scientific reports* 6, 19776.
- Ye, D., Wang, Y., Li, H., Jia, W., Man, K., Lo, C.M., Wang, Y., Lam, K.S., Xu, A., 2014. Fibroblast growth factor 21 protects against acetaminophen-induced hepatotoxicity by potentiating peroxisome proliferator-activated receptor coactivator protein-1 α -mediated antioxidant capacity in mice. *Hepatology* 60, 977-989.
- Ye, S., 2006. Influence of matrix metalloproteinase genotype on cardiovascular disease susceptibility and outcome. *Cardiovascular research* 69, 636-645.
- Ye, X., Qi, J., Yu, D., Wu, Y., Zhu, S., Li, S., Wu, Q., Ren, G., Li, D., 2017a. Pharmacological efficacy of FGF21 analogue, liraglutide and insulin glargine in treatment of type 2 diabetes. *Journal of diabetes and its complications* 31, 726-734.

- Ye, Z., Zhang, Q., Li, Y., Wang, C., Zhang, J., Ma, X., Peng, H., Lou, T., 2016b. High Prevalence of Hyperhomocysteinemia and Its Association with Target Organ Damage in Chinese Patients with Chronic Kidney Disease. *Nutrients* 8.
- Ye, Z., Zhang, Z., Zhang, H., Hao, Y., Zhang, J., Liu, W., Xu, G., Liu, X., 2017b. Prognostic Value of C-Reactive Protein and Homocysteine in Large-Artery Atherosclerotic Stroke: a Prospective Observational Study. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association* 26, 618-626.
- Yeap, B.B., Paul Chubb, S.A., Lopez, D., Ho, K.K., Hankey, G.J., Flicker, L., 2013. Associations of insulin-like growth factor-I and its binding proteins and testosterone with frailty in older men. *Clinical endocrinology* 78, 752-759.
- Yoo, D.Y., Kim, W., Nam, S.M., Yoo, K.Y., Lee, C.H., Choi, J.H., Won, M.H., Hwang, I.K., Yoon, Y.S., 2011. Reduced cell proliferation and neuroblast differentiation in the dentate gyrus of high fat diet-fed mice are ameliorated by metformin and glimepiride treatment. *Neurochemical research* 36, 2401-2408.
- Yoo, H.J., Hwang, S.Y., Hong, H.C., Choi, H.Y., Yang, S.J., Choi, D.S., Baik, S.H., Blüher, M., Youn, B.S., Choi, K.M., 2013. Implication of progranulin and C1q/TNF-related protein-3 (CTRP3) on inflammation and atherosclerosis in subjects with or without metabolic syndrome. *PLoS one* 8, e55744.
- Yoshida, N., Yamamoto, H., Shinke, T., Otake, H., Kuroda, M., Terashita, D., Takahashi, H., Sakaguchi, K., Hirota, Y., Emoto, T., Amin, H.Z., Mizoguchi, T., Hayashi, T., Sasaki, N., Yamashita, T., Ogawa, W., Hirata, K.I., 2017. Impact of CD14(++)CD16(+) monocytes on plaque vulnerability in diabetic and non-diabetic patients with asymptomatic coronary artery disease: a cross-sectional study. *Cardiovascular diabetology* 16, 96.
- You, A.S., Kalantar-Zadeh, K., Lerner, L., Nakata, T., Lopez, N., Lou, L., Veliz, M., Soohoo, M., Jing, J., Zaldivar, F., Gyuris, J., Nguyen, D.V., Rhee, C.M., 2017. Association of Growth Differentiation Factor 15 with Mortality in a Prospective Hemodialysis Cohort. *Cardiorenal medicine* 7, 158-168.
- Yu, B., Alboslemy, T., Safadi, F., Kim, M.H., 2018. Glycoprotein Nonmelanoma Clone B Regulates the Crosstalk between Macrophages and Mesenchymal Stem Cells toward Wound Repair. *The Journal of investigative dermatology* 138, 219-227.
- Yu, B., Jiang, K., Chen, B., Wang, H., Li, X., Liu, Z., 2017a. Leptin differentially regulates chondrogenesis in mouse vertebral and tibial growth plates. *BMC musculoskeletal disorders* 18, 235.
- Yu, D., Li, H.X., Liu, Y., Ying, Z.W., Guo, J.J., Cao, C.Y., Wang, J., Li, Y.F., Yang, H.R., 2017b. The Reference Intervals for Serum C-Terminal Agrin Fragment in Healthy Individuals and as a Biomarker for Renal Function in Kidney Transplant Recipients. *Journal of clinical laboratory analysis* 31.
- Yu, S.L., Xu, L.T., Qi, Q., Geng, Y.W., Chen, H., Meng, Z.Q., Wang, P., Chen, Z., 2017c. Serum lactate dehydrogenase predicts prognosis and correlates with systemic inflammatory response in patients with advanced pancreatic cancer after gemcitabine-based chemotherapy. *Scientific reports* 7, 45194.
- Yu, S.Y., Sun, L., Liu, Z., Huang, X.Y., Zuo, L.J., Cao, C.J., Zhang, W., Wang, X.M., 2013. Sleep disorders in Parkinson's disease: clinical features, iron metabolism and related mechanism. *PLoS one* 8, e82924.
- Yu, Z., Ono, C., Aiba, S., Kikuchi, Y., Sora, I., Matsuoka, H., Tomita, H., 2015. Therapeutic concentration of lithium stimulates complement C3 production in dendritic cells and microglia via GSK-3 inhibition. *Glia* 63, 257-270.
- Yuan, J., Yan, Y., Zhang, J., Wang, B., Feng, J., 2017. Diagnostic accuracy of alpha-defensin in periprosthetic joint infection: a systematic review and meta-analysis. *International orthopaedics* 41, 2447-2455.

- Yuen, K.C., Chong, L.E., Riddle, M.C., 2013. Influence of glucocorticoids and growth hormone on insulin sensitivity in humans. *Diabetic medicine : a journal of the British Diabetic Association* 30, 651-663.
- Zagarskikh, E.Y., Proshchai, G.A., Vorokhobina, N.V., 2018. [Fibroblast growth factor-21 as a marker of premature aging in young and middle-aged men with type 2 diabetes]. *Urologiia*, 92-95.
- Zamanian, M., Qader Hamadneh, L.A., Veerakumarasivam, A., Abdul Rahman, S., Shohaimi, S., Rosli, R., 2016. Calreticulin mediates an invasive breast cancer phenotype through the transcriptional dysregulation of p53 and MAPK pathways. *Cancer cell international* 16, 56.
- Zanardini, R., Benussi, L., Fostinelli, S., Saraceno, C., Ciani, M., Borroni, B., Padovani, A., Binetti, G., Ghidoni, R., 2018. Serum C-Peptide, Visfatin, Resistin, and Ghrelin are Altered in Sporadic and GRN-Associated Frontotemporal Lobar Degeneration. *Journal of Alzheimer's disease : JAD* 61, 1053-1060.
- Zeisberg, M., Kalluri, R., 2013. Cellular mechanisms of tissue fibrosis. 1. Common and organ-specific mechanisms associated with tissue fibrosis. *American journal of physiology. Cell physiology* 304, C216-225.
- Zempo-Miyaki, A., Fujie, S., Sato, K., Hasegawa, N., Sanada, K., Maeda, S., Hamaoka, T., Iemitsu, M., 2016. Elevated pentraxin 3 level at the early stage of exercise training is associated with reduction of arterial stiffness in middle-aged and older adults. *Journal of human hypertension* 30, 521-526.
- Zhan, K., Ning, M., Wang, C., Tang, Y., Gu, H., Yan, C., Tang, X., 2016. Formaldehyde accelerates cellular senescence in HT22 cells: possible involvement of the leptin pathway. *Acta biochimica et biophysica Sinica* 48, 771-773.
- Zhang, B., Luo, S., Wang, Q., Suzuki, T., Xiong, W.C., Mei, L., 2008. LRP4 serves as a coreceptor of agrin. *Neuron* 60, 285-297.
- Zhang, B., Qi, X., Zhao, Y., Li, R., Zhang, C., Chang, H.M., Pang, Y., Qiao, J., 2018a. Elevated CD14(++)CD16(+) Monocytes in Hyperhomocysteinemia-Associated Insulin Resistance in Polycystic Ovary Syndrome. *Reproductive sciences*, 1933719118756772.
- Zhang, B., Yan, J., Umbach, A.T., Fakhri, H., Fajol, A., Schmidt, S., Salker, M.S., Chen, H., Alexander, D., Spichtig, D., Daryadel, A., Wagner, C.A., Foller, M., Lang, F., 2016. NFkappaB-sensitive Orai1 expression in the regulation of FGF23 release. *Journal of molecular medicine* 94, 557-566.
- Zhang, D., Sun, X., Liu, J., Xie, X., Cui, W., Zhu, Y., 2015a. Homocysteine accelerates senescence of endothelial cells via DNA hypomethylation of human telomerase reverse transcriptase. *Arteriosclerosis, thrombosis, and vascular biology* 35, 71-78.
- Zhang, J., Ren, J.Y., Chen, H., Han, G.P., 2015b. [Statins decreases expression of five inflammation-associated microRNAs in the plasma of patients with unstable angina]. *Beijing da xue xue bao. Yi xue ban = Journal of Peking University. Health sciences* 47, 761-768.
- Zhang, J., Ren, P., Wang, Y., Feng, S., Wang, C., Shen, X., Weng, C., Lang, X., Chen, Z., Jiang, H., Chen, J., 2017a. Serum Matrix Metalloproteinase-7 Level is Associated with Fibrosis and Renal Survival in Patients with IgA Nephropathy. *Kidney & blood pressure research* 42, 541-552.
- Zhang, M., Wei, J., Shan, H., Wang, H., Zhu, Y., Xue, J., Lin, L., Yan, R., 2013. Calreticulin-STAT3 signaling pathway modulates mitochondrial function in a rat model of furazolidone-induced dilated cardiomyopathy. *PloS one* 8, e66779.
- Zhang, W., Chu, S., Ding, W., Wang, F., 2015c. Serum Level of Fibroblast Growth Factor 21 Is Independently Associated with Acute Myocardial Infarction. *PloS one* 10, e0129791.
- Zhang, X., Guo, K., Xia, F., Zhao, X., Huang, Z., Niu, J., 2018b. FGF23(C-tail) improves diabetic nephropathy by attenuating renal fibrosis and inflammation. *BMC biotechnology* 18, 33.

- Zhang, X., Lawler, J., 2007. Thrombospondin-based antiangiogenic therapy. *Microvascular research* 74, 90-99.
- Zhang, X., Shen, J., Man, K., Chu, E.S., Yau, T.O., Sung, J.C., Go, M.Y., Deng, J., Lu, L., Wong, V.W., Sung, J.J., Farrell, G., Yu, J., 2014a. CXCL10 plays a key role as an inflammatory mediator and a non-invasive biomarker of non-alcoholic steatohepatitis. *Journal of hepatology* 61, 1365-1375.
- Zhang, Y., Huang, B., Wang, H.Y., Chang, A., Zheng, X.F.S., 2017b. Emerging Role of MicroRNAs in mTOR Signaling. *Cellular and molecular life sciences : CMLS* 74, 2613-2625.
- Zhang, Y., Li, R., Meng, Y., Li, S., Donelan, W., Zhao, Y., Qi, L., Zhang, M., Wang, X., Cui, T., Yang, L.J., Tang, D., 2014b. Irisin stimulates browning of white adipocytes through mitogen-activated protein kinase p38 MAP kinase and ERK MAP kinase signaling. *Diabetes* 63, 514-525.
- Zhang, Y., Xie, Y., Berglund, E.D., Coate, K.C., He, T.T., Katafuchi, T., Xiao, G., Potthoff, M.J., Wei, W., Wan, Y., Yu, R.T., Evans, R.M., Kliewer, S.A., Mangelsdorf, D.J., 2012. The starvation hormone, fibroblast growth factor-21, extends lifespan in mice. *eLife* 1, e00065.
- Zhang, Z., Shen, B., Cao, X., Liu, Z., Chen, X., Nie, Y., Yu, J., Zou, J., Ding, X., 2017c. Increased Soluble Suppression of Tumorigenicity 2 Level Predicts All-Cause and Cardiovascular Mortality in Maintenance Hemodialysis Patients: A Prospective Cohort Study. *Blood purification* 43, 37-45.
- Zhao, H., Zhang, H., Qin, X., 2017a. Agerelated differences in serum MFGE8, TGFbeta1 and correlation to the severity of atherosclerosis determined by ultrasound. *Molecular medicine reports* 16, 9741-9748.
- Zhao, J., Wang, Y., Xu, C., Liu, K., Wang, Y., Chen, L., Wu, X., Gao, F., Guo, Y., Zhu, J., Wang, S., Nishibori, M., Chen, Z., 2017b. Therapeutic potential of an anti-high mobility group box-1 monoclonal antibody in epilepsy. *Brain, behavior, and immunity* 64, 308-319.
- Zhao, L., Zhang, P., Su, X.J., Zhang, B., 2018. The ubiquitin ligase TRIM56 inhibits ovarian cancer progression by targeting vimentin. *Journal of cellular physiology* 233, 2420-2425.
- Zhao, Y.L., Li, F., Liu, Y.W., Shi, Y.J., Li, Z.H., Cao, G.K., Zhu, W., 2017c. Adiponectin attenuates endoplasmic reticulum stress and alveolar epithelial apoptosis in COPD rats. *European review for medical and pharmacological sciences* 21, 4999-5007.
- Zhao, Y.P., Liu, B., Tian, Q.Y., Wei, J.L., Richbourgh, B., Liu, C.J., 2015. Progranulin protects against osteoarthritis through interacting with TNF-alpha and beta-Catenin signalling. *Annals of the rheumatic diseases* 74, 2244-2253.
- Zhou, B., Li, H., Liu, J., Xu, L., Guo, Q., Sun, H., Wu, S., 2015a. Progranulin induces adipose insulin resistance and autophagic imbalance via TNFR1 in mice. *Journal of molecular endocrinology* 55, 231-243.
- Zhou, J.Y., Xu, B., Li, L., 2015b. A New Role for an Old Drug: Metformin Targets MicroRNAs in Treating Diabetes and Cancer. *Drug development research* 76, 263-269.
- Zhou, L., Yu, X., Meng, Q., Li, H., Niu, C., Jiang, Y., Cai, Y., Li, M., Li, Q., An, C., Shu, L., Chen, A., Su, H., Tang, Y., Yin, S., Raschke, S., Eckardt, K., Eckel, J., Yang, Z., 2013. Resistin reduces mitochondria and induces hepatic steatosis in mice by the protein kinase C/protein kinase G/p65/PPAR gamma coactivator 1 alpha pathway. *Hepatology* 57, 1384-1393.
- Zhou, L., Zhuo, H., Ouyang, H., Liu, Y., Yuan, F., Sun, L., Liu, F., Liu, H., 2017. Glycoprotein non-metastatic melanoma protein b (Gpnmb) is highly expressed in macrophages of acute injured kidney and promotes M2 macrophages polarization. *Cellular immunology* 316, 53-60.

- Zhou, M., Xu, A., Tam, P.K., Lam, K.S., Chan, L., Hoo, R.L., Liu, J., Chow, K.H., Wang, Y., 2008. Mitochondrial dysfunction contributes to the increased vulnerabilities of adiponectin knockout mice to liver injury. *Hepatology* 48, 1087-1096.
- Zhou, X., Wang, X., 2015. Klotho: a novel biomarker for cancer. *Journal of cancer research and clinical oncology* 141, 961-969.
- Zhou, Y.M., Li, M.J., Zhou, Y.L., Ma, L.L., Yi, X., 2015c. Growth differentiation factor-15 (GDF-15), novel biomarker for assessing atrial fibrosis in patients with atrial fibrillation and rheumatic heart disease. *International journal of clinical and experimental medicine* 8, 21201-21207.
- Zhu, D., Wang, H., Zhang, J., Zhang, X., Xin, C., Zhang, F., Lee, Y., Zhang, L., Lian, K., Yan, W., Ma, X., Liu, Y., Tao, L., 2015. Irisin improves endothelial function in type 2 diabetes through reducing oxidative/nitrative stresses. *Journal of molecular and cellular cardiology* 87, 138-147.
- Zhu, J., Wu, D., Zhao, C., Luo, M., Hamdy, R.C., Chua, B.H.L., Xu, X., Miao, Z., 2017a. Exogenous Adipokine Peptide Resistin Protects Against Focal Cerebral Ischemia/Reperfusion Injury in Mice. *Neurochemical research* 42, 2949-2957.
- Zhu, L., Jia, F., Wei, J., Yu, Y., Yu, T., Wang, Y., Sun, J., Luo, G., 2017b. Salidroside protects against homocysteine-induced injury in human umbilical vein endothelial cells via the regulation of endoplasmic reticulum stress. *Cardiovascular therapeutics* 35, 33-39.
- Zhu, T., Feng, L., 2013. Comparison of anti-mutated citrullinated vimentin, anti-cyclic citrullinated peptides, anti-glucose-6-phosphate isomerase and anti-keratin antibodies and rheumatoid factor in the diagnosis of rheumatoid arthritis in Chinese patients. *International journal of rheumatic diseases* 16, 157-161.
- Zhuang, P.Y., Zhang, K.W., Wang, J.D., Zhou, X.P., Liu, Y.B., Quan, Z.W., Shen, J., 2017. Effect of TALEN-mediated IL-6 knockout on cell proliferation, apoptosis, invasion and anti-cancer therapy in hepatocellular carcinoma (HCC-LM3) cells. *Oncotarget* 8, 77915-77927.
- Zubiri, I., Posada-Ayala, M., Benito-Martin, A., Maroto, A.S., Martin-Lorenzo, M., Cannata-Ortiz, P., de la Cuesta, F., Gonzalez-Calero, L., Barderas, M.G., Fernandez-Fernandez, B., Ortiz, A., Vivanco, F., Alvarez-Llamas, G., 2015. Kidney tissue proteomics reveals regucalcin downregulation in response to diabetic nephropathy with reflection in urinary exosomes. *Translational research : the journal of laboratory and clinical medicine* 166, 474-484 e474.
- Zuniga, M.C., Raghuraman, G., Hitchner, E., Weyand, C., Robinson, W., Zhou, W., 2017. PKC-epsilon and TLR4 synergistically regulate resistin-mediated inflammation in human macrophages. *Atherosclerosis* 259, 51-59.

Table 1 Inflammation

Summary of selected marker characteristics and testing in intervention studies based on literature

Markers	Hallmark of aging pathways	Age/ Age-related Diseases	Genetics	Intervention	Literature
Defensins	<ul style="list-style-type: none"> • Markers of inflammation 	<ul style="list-style-type: none"> • Defensin α are markers of periprosthetic joint infections • Defensin α elevated in Alzheimer's disease patients • Defensin α are potential coronary artery disease markers in some Asian populations • Defensin β are potential biomarkers for psoriasis activity • Defensin β are elevated in COPD and severe asthma 	<ul style="list-style-type: none"> • In contrast to humans, mice lack myeloid defensin α. Mice lacking the MMP7 gene are functionally deficient in enteric defensin α. • Partial knockout of nine defensin β genes is available, however, redundancy in function may be a confounding factor 	<ul style="list-style-type: none"> • Secukinumab 	<ul style="list-style-type: none"> • (Baines et al., 2015; Holly et al., 2017; Jin et al., 2017; Kolbinger et al., 2017; Maneerat et al., 2017; Watt et al., 2015; Yuan et al., 2017)
CXCL10	<ul style="list-style-type: none"> • Induced by IFN-γ and infections • SASP component • Decreases mitochondrial activity • Induction of apoptosis • Decreases cell proliferation 	<ul style="list-style-type: none"> • Increased serum levels in various aging cohorts • Increased in rheumatoid arthritis patients • Increased in hippocampus of senescence accelerate mice and neurodegenerative diseases • Increased in aged mouse aorta • Increased in CYP-induced cystitis • Increased in cancer, promoting tumour growth 	<ul style="list-style-type: none"> • Knockout animals have defective T cell response, impaired proliferation and IFNγ secretion following antigenic challenge • CXCL10 polymorphism are related to increased liver fibrosis risk in Hepatitis C virus patients 	<ul style="list-style-type: none"> • Caloric restriction • Resveratrol • Apigenin • Sildenafil • Metformin 	<ul style="list-style-type: none"> • (Antonelli et al., 2006; Bakhshab et al., 2016; Bonfante et al., 2017; Di Luigi et al., 2016; Gao et al., 2017; Grinan-Ferre et al., 2016; Hearps et al., 2012; Jimenez-Sousa et al., 2017; Ko et al., 2015; Luster et al., 1985; Otterdal et al., 2016; Palomera-Avalos et al., 2018; Pandya et al., 2017; Perrott et al., 2017; Shurin et al., 2007; Singh et al., 2010; Sui et al., 2006; Trott et al., 2017; Wightman et al., 2015; Zhang et al., 2014a)

CD14	<ul style="list-style-type: none"> • Surface antigen preferentially expressed in phagocytes • Mediates innate immune responses to bacterial lipopeptides 	<ul style="list-style-type: none"> • Increased CD14+/CD16+ monocytes (intermediate phenotype) in frail individuals • Decreased levels of CD14 and CD16 in mild AD patients • Reduced terminal differentiation of CD14+/CD16+ monocytes in RA • Shift towards the CD14+/CD16+ phenotype in diabetic patients with coronary artery disease • CD14+/CD16+ levels are associated with coronary plaque vulnerability 	<ul style="list-style-type: none"> • Homozygous null mice display impaired response to bacteria and decrease in cytokine production • Homozygous null mice present increased lean body mass, reduced total body fat, increased bone mineral density and decreased susceptibility to bone fracture 	<ul style="list-style-type: none"> • (Cappellari et al., 2017; Haziot et al., 1996; Johnson et al., 2004; Kelley et al., 2013; Le Page et al., 2017; Lu et al., 2016; Smiljanovic et al., 2018; Wright et al., 1990; Yoshida et al., 2017)
sVCAM/ sICAM	<ul style="list-style-type: none"> • sVCAM1 and sICAM1 are markers for endothelial inflammation • sICAM1 is released from senescent cells by microvesicles. 	<ul style="list-style-type: none"> • Both associated with increased odds of injurious falls, and frailty • sVCAM associated with cognitive impairment and increased cerebrovascular resistance • sVCAM1 associated with hypertension, vascular inflammation, and systemic endothelial dysfunction. • Both used as risk predictors of cardiovascular events • Variably associated with malignancy 	<ul style="list-style-type: none"> • Full and conditional knockout mice available • Full VCAM1 knockout is embryonically lethal • sICAM1, but not sVCAM1 levels elevated in young healthy adult offspring of parents with type 2 diabetes compared to controls. 	<ul style="list-style-type: none"> • sVCAM1↓ with exercise (aerobic and anaerobic) in overweight women • sICAM1↓ with 4-week dark chocolate in overweight men • (Constans and Conri, 2006)
CX3CL1	<ul style="list-style-type: none"> • Soluble form responsible for chemo-attracting T-cells, NK cells and monocytes • Membrane-bound form promotes adhesion of neutrophils to endothelial cells and recruitment to tissues • CX3CR1 defines peripheral 	<ul style="list-style-type: none"> • High concentrations detected in synovial fluid of patients with rheumatoid arthritis and osteoarthritis • CX3CL1 levels were associated positively with several cardiovascular disease risk factors and metabolic traits 	<ul style="list-style-type: none"> • Mice homozygous for a knockout allele show a specific reduction in Gr1(low) monocyte levels and increased neuronal cell loss in Parkinson disease models • Mice homozygous for a different knockout allele are 	<ul style="list-style-type: none"> • Rheumavax • Baicalin • Cyclophosphamide • Remifentanyl • AMD3100 • Glucocorticoids • Aspirin • Resveratrol • (Andre et al., 2006; Harry, 2013; Huo et al., 2015; Locatelli et al., 2010; Merino et al., 2016; Mionnet et al., 2010; Nishimura et al., 2002; Park et al., 2012; Qin et al., 2014; Ruth et al., 2001; Shah et al.,

	<p>blood cytotoxic effector lymphocytes and is a direct target of p53</p> <ul style="list-style-type: none"> Increases proliferation of endothelial cells and enhances the migration of endothelial progenitor cells in ischemic penumbra CX3CL1/CX3CR1 expression is decreased in the aged brain. 	<ul style="list-style-type: none"> Promotes aggregation of the receptor and attracts cytotoxic effector T-cells or NK killer cells, decreasing cancer invasiveness May increase amyloid pathology while soluble CX3CL1 levels could prevent tauopathies 	<p>less susceptible to cerebral ischemia-reperfusion injury.</p>	<ul style="list-style-type: none"> Vincristine Etanercept 	<p>2015; Shiraiishi et al., 2000)</p>
Pentraxin	<ul style="list-style-type: none"> Promotes fibrocyte differentiation and is regulates inflammation and complement activation. Plays a role in angiogenesis and tissue remodelling. Pentraxin levels are associated with leukocyte telomere length. Inhibits the IL-6/Stat3 pathway in acute renal injury. Pentraxin inhibits acute renal injury-induced interstitial fibrosis through suppression of IL-6/Stat3 pathway. 	<ul style="list-style-type: none"> Pentraxin blood levels increase with age. Pentraxin is an important biomarker for different inflammatory processes in the body, including sepsis, prostate inflammation, amnion inflammation and appendicitis. Astrocyte-Derived Pentraxin Supports blood brain barrier integrity under acute phase of Stroke. Involved in osteoblast proliferation, differentiation and function and is reduced in osteoporosis patients. Pentraxin and adiponectin showed similar associations with metabolic factors. Pentraxin might have an atheroprotective role. Associated with subclinical cardiovascular disease and mortality, both cardiovascular-related and other causes. Induced in the tumour stroma after chemotherapy in vitro. Significantly predicts disease severity and mortality in sepsis 	<ul style="list-style-type: none"> Homozygous mutant mice display female subfertility and are susceptible to invasive pulmonary aspergillosis and impaired induction of adaptive type 2 responses. 	<ul style="list-style-type: none"> Tunicamycin Exercise LPS 	<ul style="list-style-type: none"> (Anuurad et al., 2011; Giacomini et al., 2018; Hwang et al., 2016a; Jenny et al., 2009; Lee et al., 2018c; Liu et al., 2014a; Musilova et al., 2017; Pavanello et al., 2017; Qin et al., 2017b; Rodriguez-Grande et al., 2015; Scimeca et al., 2017; Slusher et al., 2017; Stallone et al., 2014; Xiao et al., 2014)

IL-6

- Produced at the inflammatory sites.
- Oxidative stress
- Increase cell proliferation
- Cellular senescence
- Promotes cell apoptosis in cancer
- Increase glycolysis
- Promote DNA damage repair in cancer cells
- IL-6 also plays an important role on acquired immune response by stimulation of antibody production and of effector T-cell development.
- Related to aging
- IL-6 levels increase with age
- Myocardial ischemia/reperfusion injury
- Induced by obesity
- Increased in Cancer
- Increased in Stroke
- Alzheimer Disease
- Increased in Parkinson Disease
- Diabetes
- Increased in Chronic heart failure and cardiovascular disease
- IL-6 mutant mice develop spontaneous Type 1 diabetes. They may show defects in responses to various viruses and in inflammatory responses to tissue damage or infection.
- Homozygous null mutants show impaired immune response to pathogens, decreased T cell numbers and resistance to plasma cell neoplasia.
- Knockouts are defective in wound healing and liver regeneration and show increased emotionality and high bone turnover rate.
- **Caloric restriction decreases**
- **Physical activity decreases**
- **Epigallocatechin- 3-gallate (EGCG)**
- **Bazedoxifine**
- **Tocilizumab**
- **Sylvant (siltuximab)**
- **Sarilumab**
- (Adriaensen et al., 2014; Afzal et al., 2014; Chen et al., 2018; Chen et al., 2015c; Dogan et al., 2017; Dufek et al., 2015; Haider et al., 2017; Kim et al., 2017e; Kwan et al., 2013; Marmay et al., 2016; Moro-Garcia et al., 2014; Qin et al., 2017a; Tanaka et al., 2014; Waxman and Kolliputi, 2009)

Table 2 Mitochondria and apoptosis

Summary of selected marker characteristics and testing in intervention studies based on literature

Markers	Hallmark of aging Pathways	Age/ Age-related Diseases	Genetics	Intervention	Literature
<ul style="list-style-type: none"> • GDF15 	<ul style="list-style-type: none"> • Pleiotropic cytokine • Predictive marker in chronic inflammation • Marker for mitochondrial function and diseases • Altered expression after radiation and senescence • Marker for p53 pathway activation. • Mediator of stress signals • Novel biomarker for assessing atrial and liver fibrosis 	<ul style="list-style-type: none"> • Potential biomarker in aging and a big variety of age-related disorders including cognitive aging, Parkinson disease, dementia, muscle loss, declining physical function, vascular pathologies, heart diseases, bone remodelling, osteoarthritis, insulin diabetes, stroke, rheumatoid arthritis, chronic kidney disease and many more • Marker of all-cause mortality including myocardial infarction • Correlated positively with age and negatively with muscle mass • Predicts future risk for many age-related disease including insulin resistance, cardiovascular risk in type 2 diabetes and haemodialysis patients, first-ever stroke in hypertensive patients. • Biomarker and therapeutic target for cancer-associated weight loss. • Shows diverse roles in cancer 	<ul style="list-style-type: none"> • Genetic deletion of GDF15 augments renal damage in both type 1 and type 2 models of diabetes 	<ul style="list-style-type: none"> • Monoclonal GDF15 antibody and therapeutic protein • Metformin • Sulidnac (NSAIDS) • Pyruvate • Biphosphonate • Danusertib 	<ul style="list-style-type: none"> • (Andersson et al., 2016; Andersson et al., 2015; Barma et al., 2017; Bidarkosh et al., 2017; Blaber et al., 2014; Bosotti et al., 2012; Breit et al., 2011; Brown et al., 2007; Corre et al., 2013; Daniels et al., 2011; De Haan et al., 2017; Eggers et al., 2012; Franczyk et al., 2018; Fujita et al., 2015; Fujita et al., 2016b; Gerstein et al., 2017; Gohar et al., 2017; Heringlake et al., 2016; Hofmann et al., 2015; Hong et al., 2014; Hsu et al., 2017b; Hur, 2014; Jiang et al., 2016; Kalinkovich and Livshits, 2015; Kempf et al., 2012; Kim et al., 2005; Koene et al., 2015; Kosi-Trebotic et al., 2017; Krawczyk et al., 2017; Kumar et al., 2017; Lehtonen et al., 2016; Leon-Mateos et al., 2017; Lerner et al., 2016; Li et al., 2017b; Li et al., 2017g; Lok et al., 2012; Maetzler et al., 2016; Mazagova et al.,

				<p>2013; Montoro-Garcia et al., 2012; Na et al., 2017; Nair et al., 2017; Patel et al., 2014; Putt et al., 2015; Sandor et al., 2015; Scherthner et al., 2017; Schiegnitz et al., 2016; Secemsky et al., 2015; Tomaschitz et al., 2016; Toutouzas et al., 2017; Tsai et al., 2016; Tzikas et al., 2017; Wang et al., 2017b; Wang et al., 2016c; Wiklund et al., 2010; Windrichova et al., 2017; Wu et al., 2016c; Yang et al., 2003; Yang et al., 2010; Yao et al., 2017; You et al., 2017; Zhou et al., 2015c)</p>
<p>FNDC5</p> <ul style="list-style-type: none"> • General anti-inflammatory action • Promotes mitochondrial biogenesis and mitochondrial function under hypoxia • Predicts telomere length in healthy adults • Inhibits apoptosis 	<ul style="list-style-type: none"> • Increased in healthy centenarians; decreased with age and inversely related with osteoporotic fractures in post-menopausal women • Independently predicts sarcopenia in dialyzed patients • Decreased in patients with type 2, but not type 1 diabetes • Low serum irisin level is an independent predictor of cardiovascular disease, Alzheimer Disease and tissue AGE accumulation • Positively correlated with body mass index but overexpression in mice reduces obesity 	<ul style="list-style-type: none"> • The FNDC5 3480A-G variant is associated with protection from fibrosis in patients with non-alcoholic fatty liver disease • No association of the FNDC5 genetic variants rs16835198 and rs726344 with exceptional longevity • Liver steatosis and impaired autophagy/FAO in starved FNDC5 knockout mice 	<ul style="list-style-type: none"> • Physical exercise • Healthy diet • Antihypertensive drugs & Sildenafil • Metformin 	<ul style="list-style-type: none"> • (Anastasialakis et al., 2014; Aydin et al., 2017; Baran et al., 2017; Belviranli et al., 2016; Bostrom et al., 2012; Celik et al., 2015; Chang et al., 2017a; Chen et al., 2015a; Du et al., 2016; Emanuele et al., 2014; Fox et al., 2018; Gouveia et al., 2016; Huh et al., 2016; Hwang et al., 2016b; Icli et al., 2016; Jang et al., 2017; Jedrychowski et al., 2015; Ko et al., 2016; Kraemer et al., 2016; Lee et

				<p>al., 2015b; Li et al., 2017a; Li et al., 2015b; Matsuo et al., 2015; Mazur-Bialy, 2017; Mazur-Bialy et al., 2017; Natalicchio et al., 2017; Panati et al., 2016; Peng et al., 2017; Perakakis et al., 2017; Petta et al., 2017; Polyzos et al., 2014; Rana et al., 2014; Shen et al., 2017; Tanisawa et al., 2014; Usluogullari et al., 2017; Wang et al., 2017c; Wen et al., 2013; Wrann et al., 2013; Xie et al., 2015; Zhang et al., 2014b; Zhu et al., 2015)</p>
<p>Vimentin</p> <ul style="list-style-type: none"> • Induced by TGFβ1 and TNFα • Cleaved and activated by calpain • Osteopontin increases vimentin stability • Vimentin is a component of focal adhesions and binds to integrin α2/β1 • Vimentin regulates actin dynamics • Vimentin filaments play a role in active force development and contraction 	<ul style="list-style-type: none"> • Marker for prognosis and diagnosis for idiopathic pulmonary fibrosis • Anti-mutated citrullinated vimentin is detected rheumatoid arthritis patients. • Vimentin contributes to chondrocyte stiffness • May contribute to α- and β-cell dysfunction in type 2 diabetes • Altered expression in chronic kidney disease • Altered expression in various cancers • Predicts survival in various cancers • Marker for epithelial to mesenchymal transition 	<ul style="list-style-type: none"> • Vimentin null mice have altered cell migration, angiogenesis and expression of adhesion molecules • Vimentin null mice show altered arterial remodelling • Phosphovimentin deficient mice develops premature skin aging 	<ul style="list-style-type: none"> • Ellagic acid (EA) • Certican and Neoral 	<ul style="list-style-type: none"> • (Bhattacharya et al., 2009; Bonotti et al., 2017; Bornheim et al., 2008; Cao et al., 2015; Cheng et al., 2017; Das et al., 2014; Dmello et al., 2017; Dong et al., 2016; Eckes et al., 2000; Gertow et al., 2017; Haudenschild et al., 2011; Kreis et al., 2005; Kwak et al., 2012; Langlois et al., 2017; Lin et al., 2018; Liu et al., 2017d; Meng et al., 2011; Reyes-Castillo et al., 2015; Roefs et al., 2017; Schiffers et al., 2000; Tanaka et al., 2015; Wang et al., 2007a; Wolcott et al.,

					2017; Yang et al., 2017a; Zhao et al., 2018; Zhu and Feng, 2013)
APP	<ul style="list-style-type: none"> • MTERF4 (Mitochondrial Transcription Termination Factor 4) promotes the amyloidogenic processing of APP • Nuclear trafficking, histone cleavage and induction of apoptosis by the meningococcal APP and MspA autotransporters. • Overexpression of Swedish mutant APP in aged astrocytes attenuates excitatory synaptic transmission. • APP modulates macrophage phenotype 	<ul style="list-style-type: none"> • Microglia and monocyte-derived macrophages display distinct phenotypes in Alzheimer Disease models and there are specific effects of normal aging vs Aβ peptides on inflammatory processes that occur during the disease progression. • Highly significant correlation between increasing age and slowed Aβ turnover rates specifically in participants with amyloid deposition • Co-morbid APP toxicity and stroke produce impairments in an ambiguous context task in rats 	<ul style="list-style-type: none"> • Depletion of APP causes G0 arrest in non-small cell lung cancer cells. 	<ul style="list-style-type: none"> • Liraglutide • NB-360 • Lanabecestat 	<ul style="list-style-type: none"> • (Canobbio et al., 2017; Dilsizoglu Senol et al., 2015; Ferraccioli et al., 2012; Goiran et al., 2018; Katsurabayashi et al., 2016; Keeley et al., 2015; Khairalla et al., 2015; Ma et al., 2015; Martin et al., 2017a; McClean et al., 2015; Mohle et al., 2016; Neumann et al., 2015; Park et al., 2014; Patterson et al., 2015; Peng et al., 2016; Puig et al., 2017; Sakamoto et al., 2017; Schreiner et al., 2015; Sobol et al., 2015; Tammineni et al., 2017; Troncone et al., 2016; Wang et al., 2017g; Wu et al., 2016e)
LDH	<ul style="list-style-type: none"> • LDH inhibition impacts heat shock response • Induces senescence of hepatocellular carcinoma cells • AMPKα1/LDH pathway regulates muscle stem cell self-renewal by controlling metabolic homeostasis • Serum LDH levels are associated with the systemic inflammatory response • During overflow metabolism the Pta-AckA pathway plays a 	<ul style="list-style-type: none"> • Plasma LDH Levels predict mortality in acute aortic syndrome • Potential biomarker of RA • The LDH response to functional overload and nandrolone decanoate administration in aged muscle is opposite to the response observed in young muscle. 	<ul style="list-style-type: none"> • LDH-A silencing by RNAi, or its inhibition using a small-molecule inhibitor, resulted in a p53-dependent increase in the cancer cell ratio of NADH:NAD$^{+}$. • miR-30a-5p suppresses breast tumour growth and metastasis through inhibition of LDHA-mediated Warburg effect • Stable shRNA silencing of LDHA in Human MDA-MB-231 Breast Cancer Cells Fails to 	<ul style="list-style-type: none"> • Oxamate • Stripentol and analogues 	<ul style="list-style-type: none"> • (Allison et al., 2014; Arseneault et al., 2013; Chen et al., 2016b; Jung et al., 2015b; Li et al., 2016b; Li et al., 2017e; Liang et al., 2016; Lu et al., 2015; Mack et al., 2017; Malicka et al., 2016; Manerba et al., 2017; Marshall et al., 2016; Miskimins et al., 2014; Morello et al., 2016;

critical role in preventing cell viability defects by promoting intracellular redox homeostasis.

alter lactic acid production, glycolytic activity, ATP or survival.

- Suppression of LDHA compromises tumour progression

Muchtar et al., 2017; Newington et al., 2012; Petrelli et al., 2015; Ronquist et al., 2013; Sada et al., 2015; Theret et al., 2017; Valvona et al., 2016; Washington et al., 2014; Yang et al., 2015c; Yu et al., 2017c)

Table 3 Calcium homeostasis

Summary of selected marker characteristics and testing in intervention studies based on literature

Markers	Hallmark of aging Pathways	Age/ Age-related Diseases	Genetics	Intervention	Literature
S100B	<ul style="list-style-type: none"> Increased in inflammation Contributes to cancer progression by downregulating p53 Involved in survival and cell proliferation 	<ul style="list-style-type: none"> Premature aging in transgenic S100B overexpressing animals Increased in Alzheimer disease Biomarker to predict subarachnoid haemorrhage prognosis Increased in melanoma patients Decreased in diabetic patients 	<ul style="list-style-type: none"> S100B-deficient mice have normal development of the cerebellum and no severe impairment of motor function 	<ul style="list-style-type: none"> Pentamidine Arundic acid Anti-S100B 	<ul style="list-style-type: none"> (Alegre et al., 2016; Beer et al., 2010; Bianchi et al., 2011; Bluhm et al., 2015; Buckman et al., 2014; Cao et al., 2017; Celikbilek et al., 2014; Chong et al., 2016; Cirillo et al., 2015; Cirillo et al., 2011; Donato et al., 2013a; Donato et al., 2009; Esposito et al., 2012; Ferguson et al., 2017; Hartman et al., 2013; Kabadi et al., 2015; Lam et al., 2013; Lin et al., 2010; Mori et al., 2010; Smith et al., 2010; Sorci et al., 2013; Villarreal et al., 2014)
Regucalcin	<ul style="list-style-type: none"> Suppressive effect on calcium signalling in proliferative cells. Overexpression prevented oxidative stress insults. Increases Ca²⁺-ATPase activity in the heart mitochondria Expression decreases with aging, acute liver injuries and tumours in zebrafish. Overexpression suppresses apoptosis Regucalcin expression decreased with aging Regucalcin mRNA and protein levels are decreased in 	<ul style="list-style-type: none"> Overexpression of regucalcin induces bone loss in transgenic rats and deficiency causes osteomalacia . Up-regulated in coeruleus tissue of Parkinson disease patients Suppress Ca²⁺-dependent protein tyrosine phosphatase, calcineurin and nitric oxide synthase activity in the heart cytoplasm and may play a role in heart failure Biomarker in pronephric tubules, and the ureteric bud and metanephric 	<ul style="list-style-type: none"> Regucalcin-deficient mice induced a shorter lifespan and redox changes. Transgenic rats have been found to induce hyperlipidaemia with increasing age 	<ul style="list-style-type: none"> 1,1-diphenyl-2-picrylhydrazyl Tert-butyl hydroperoxide and cadmium chloride 17β-Estradiol Doxorubicin Exogenous Ca²⁺ Phenobarbital EUK4010 	<ul style="list-style-type: none"> (Akhter et al., 2007; Akhter et al., 2006; Correia et al., 2017; Fujisawa et al., 2011; Isogai et al., 1994; Jung et al., 2015a; Maia et al., 2008; Marques et al., 2014; Maruyama et al., 2005; Maruyama et al., 2004; Park et al., 2016; Sun et al., 2006; van Dijk et al., 2012; Vaz et al., 2015; Yamaguchi, 2010, 2013a, b, 2014a, b, c; Yamaguchi and Murata, 2015)

the hearts of rats with increasing age.

mesenchyme.

- Regulates intracellular Ca²⁺ homeostasis in kidney proximal tubule epithelial cells.
- Down-regulated in development of carcinogenesis in rat liver.
- Depression of regucalcin expression may be associated with activity progression of carcinogens.
- Potential biomarker for metabolic and neuronal diseases.

Calreticulin

- Calcium-binding chaperone participating in immune response.
- Modulator of the regulation of gene transcription by nuclear hormone receptors.
- Inhibit LPS- induced inflammatory osteoclastogenesis
- Induced by unfolded protein in the ER
- Expressed at the surface of pre-apoptotic cells is recognized by antigen presenting cells and results in phagocytosis
- Reduced expression in senescent amniotic fluid stem cells.
- Activated by chronic stress, may cause motor coordination and motor learning dysfunctions of social defeat mice.

- Calreticulin is overexpressed in stromal compartments of malignant breast cancer tissues and invasion is a calreticulin-dependent.
- Biomarker for diagnosis and prognosis of systemic lupus erythematosus
- Calreticulin expression was significantly higher in serum and synovial fluids of rheumatoid arthritis patients compared to that of osteoarthritis and healthy controls
- Calreticulin is down-regulated in the cortical neurons of Alzheimer Disease patients
- Calreticulin is over expressed in liver biopsies from human obese
- High expression of calreticulin was positively associated with tumour stage and lymph nodes

- Homozygotes for targeted null mutations exhibit decreased cardiac cell mass, increased apoptosis of cardiac myocytes, neural tube defects
- Rescued calreticulin null mice develop severe hypoglycaemia. In addition, ventricular cardiomyocytes have increased glycogen deposits.
- Transgenic mice overexpressing calreticulin in the heart revealed impaired left ventricular systolic and diastolic function and impaired mitral valve function.
- Somatic insertions/deletions in the calreticulin gene have recently been discovered to be causative alterations in myeloproliferative neoplasms.

- **2,3,5,4'-tetrahydroxystilbene-2-O-β-D-glucoside (TSG)**
- **Anthracyclins**
- **Mellitin**
- **Vasostatin**
- **Tauroursodeoxycholic acid**
- **Furazolidone**

- (Bernard-Marissal et al., 2015; Caira et al., 2017; Cho et al., 2013; Ding et al., 2014; Fischer et al., 2017; Groenendyk et al., 2016; Iordache et al., 2016; Jalali et al., 2008; Lee et al., 2013; Liu et al., 2017b; Mans et al., 2012; Ni et al., 2013; Obeid et al., 2007; Schafer et al., 2015; Shan et al., 2014; Sheng et al., 2014; Stemmer et al., 2013; Tomas-Roig et al., 2016; Wang et al., 2017d; Wang et al., 2017h; Yao et al., 2013; Zamanian et al., 2016)

- Caloric restriction helps to maintain expression of neuroprotective factor calreticulin in hippocampal CA1 region of older-adult mice.
- metastasis and was an independent adverse prognostic indicator in patients with pancreatic or lung cancer.

Table 4 Fibrosis

Summary of selected marker characteristics and testing in intervention studies based on literature

Markers	Hallmark of aging Pathways	Age/ Age-related Diseases	Genetics	Intervention	Literature
PAI-1	<ul style="list-style-type: none"> Elevated PAI-1 levels are, in fact, a significant causative factor in the pathophysiology of diabetes, vascular thrombosis, metabolic syndrome, septic coagulopathy, atherosclerosis, restenosis and myocardial infarction, particularly in the context of increased tissue TGFβ1 levels 	<ul style="list-style-type: none"> PAI-1 may play a critical role in the development of aging-associated pathological changes. In addition, PAI-1 is recognized as a marker of senescence and a key member of a group of proteins collectively known as the senescence-messaging secretome. In the extended Amish kindred, carriers of the null PAI-1 allele had a longer life span. Data indicates a causal effect of PAI-1 on human longevity, which may be mediated by alterations in metabolism 	<ul style="list-style-type: none"> Although mice homozygous for disruptions in this gene display an essentially normal phenotype, a mild blood clotting defect does exist. Mice homozygous for an allele with amino acid substitutions exhibit decreased sensitivity to LPS-induced lethality. PAI-1^{-/-} mice demonstrated increased expression of MyoD and developmental myosin after injury as well as accelerated recovery of muscle morphology. 	<ul style="list-style-type: none"> TM5441, a potent small molecule inhibitor of PAI-1, effectively prevents Doxorubicin-induced senescence in cardiomyocytes, fibroblasts and endothelial cells. 	<ul style="list-style-type: none"> (Ghosh et al., 2016; Khan et al., 2017; Koh et al., 2005; Simone et al., 2014b; Yamamoto et al., 2014a)
TGFβ	<ul style="list-style-type: none"> TGFβ1 is a secreted protein that performs many cellular functions, including the control of cell growth, cell proliferation, cell differentiation and apoptosis. 	<ul style="list-style-type: none"> Numerous associations of TGFβs with various diseases have been newly discovered or elucidated in much more detail than before, including atherosclerosis, acute and chronic liver and kidney disease, immunity osteoarthritis and neurodegenerative diseases. Many of these are associated with aging. 	<ul style="list-style-type: none"> TGFβ1 knockout mice are able to survive only until 3–4 weeks of age. They are characterized by inflammatory infiltrates in multiple organs leading to a wasting syndrome and death as early as 3 weeks after birth. 	<ul style="list-style-type: none"> LY2109761 is an inhibitor of TGFβs but has not been tested for aging – related diseases 	<ul style="list-style-type: none"> (Geiser et al., 1993; Kriegstein et al., 2012)
MMP7	<ul style="list-style-type: none"> Mediates the cleavage of ECM and basement membrane proteins such as fibronectin, collagen type IV, and laminin Increased MMP7 associated with extensive tissue 	<ul style="list-style-type: none"> Increased plasma and urine levels in renal fibrosis Increased levels in plasma and sputum of idiopathic pulmonary fibrosis patients. Elevated MMP7 expression in 	<ul style="list-style-type: none"> MMP7 knockout have impaired innate host defense response, are more susceptible to bacterial infection of the small intestine mucosal epithelium, defective wound repair 	<ul style="list-style-type: none"> Tamoxifen alone and/or 5-FU downregulate MMP7 expression in colon cancer cells with high metastatic 	<ul style="list-style-type: none"> (Bauer et al., 2017; Chaturvedi and Hass, 2011; Fang et al., 2009; Gong et al., 2014; Guiot et al., 2017; Li et al., 2017f; Musial et al.,

	remodelling and organ dysfunction, particularly in urinary and respiratory pathologies	tumours and metastasis, associated with ECM remodelling, epithelial-mesenchymal transition, and invasion and proliferation. <ul style="list-style-type: none"> • Increased in the kidney of streptozotocin (STZ)-induced diabetes mellitus • Increased in coronary artery disease, arterial stiffness, and/or abdominal aortic aneurysm. • No references found about age-associated diseases like Alzheimer and Parkinson Disease. 	(reepithelialisation) and reduced apoptosis in prostate and pancreatic tissue.	potential	2015; Ye, 2006; Zhang et al., 2017a)
PLAU	<ul style="list-style-type: none"> • Expressed and secreted from senescent cells and controls cell proliferation • Overproduction of uPA in brain reduced food consumption and increased longevity 	<ul style="list-style-type: none"> • Linked to the pathogenesis of late onset Alzheimer Disease • Increased by complication in diabetes patients 	<ul style="list-style-type: none"> • Genetic association with sporadic Alzheimer's Diseases. • Transgenic model for longevity induced by caloric restriction. 	<ul style="list-style-type: none"> • induced by chemotherapy in cancer cells↑ • Biomarker for breast cancer. • Tissue injury ↑ 	• (Lampelj et al., 2015; Miskin et al., 2005)
TGM2	<ul style="list-style-type: none"> • Induced by pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) and NFκB, as well as by high glucose, insulin, and AGEs • Catalyses protein cross-linking in the heart after ischemia and reperfusion • Accumulates in atherosclerotic plaques and participates in the atherosclerotic process by NFκB activation, TNF-α and nitric oxide synthase expression • Promotes survival, by promoting the anchorage to ECM, protecting from anoikis. 	<ul style="list-style-type: none"> • Increase with age and age-related diseases • Associated with fibrosis in pathologies such as cardiac hypertrophy, liver cirrhosis, renal fibrosis, and idiopathic pulmonary fibrosis • Significant levels of TGM2 activity and cross-links are reported in human osteoarthritis and arthritic joints. • Dysregulation of TGM2 found in many neurodegenerative disorders, including Huntington's disease, 	<ul style="list-style-type: none"> • TGM2 knockout show defects in glucose tolerance, on phagocytosis-associated crosstalk between macrophages and apoptotic cells and in function of mitochondrial respiratory complex I. 	<ul style="list-style-type: none"> • Cystamine reduces blood pressure in spontaneously hypertensive rats • ZED1227, a small pyridinon derivative, for the treatment of coeliac disease through blocking the TGM2-mediated deamidation of gliadin peptides is the only one TGM2 inhibitor in clinical trial (phase1b). 	• (Bains, 2013; Gundemir et al., 2012; Lauzier et al., 2012; Ruan and Johnson, 2007; Szondy et al., 2017)

	Alzheimer disease, Parkinson disease and amyotrophic lateral sclerosis, as well as in stroke.				
THBS2	<ul style="list-style-type: none"> • THBS2 is a potent endogenous inhibitor of tumour growth and angiogenesis. • THBS2 antiangiogenic effect is mediated, at least in part, through CD36. • THBS2 represents a protective mechanism in chronic inflammation in RA regulating angiogenesis and inflammation in the synovium • Lack of THBS2 accelerates and enhances responses to renal injury. • THBS2 inhibits the glomerular proliferative and inflammatory response as well as TGFβ activation and ECM accumulation 	<ul style="list-style-type: none"> • Increased expression in aging, associated with impaired angiogenesis, and lack of expression of TGFβ1 and VEGF. • Increased plasma levels in patients with heart failure, correlated with disease severity. • Increased in the serum of patients with cardiovascular disease associated with chronic kidney disease. • Increased expression of THBS2 (together with that of THBS1), in the ischemic brain, likely contributing to the spontaneous resolution of postischemic angiogenesis. 	<ul style="list-style-type: none"> • THBS2-deficient mice suffer prolonged cutaneous inflammation. • Old THBS2 knockout mice showed severe heart alterations, accompanied by an inflammatory response, increased MMP-2, and fibrosis. 	<ul style="list-style-type: none"> • Cyclophosphamide increases the circulating levels of THBS1, but not THBS2 	<ul style="list-style-type: none"> • (Charytan et al., 2014; Daniel et al., 2007; Daniel et al., 2009; Kimura et al., 2016; Lamy et al., 2007; Lin et al., 2003; Park et al., 2004; Rege et al., 2005; Sadoun and Reed, 2003; Streit et al., 1999; Swinnen et al., 2009; Zhang and Lawler, 2007)
AGT	<ul style="list-style-type: none"> • Activation of the classic RAS down regulates pro-survival genes, increases ROS production and pro-inflammatory cytokines and chemokines release, leading to cell senescence, inflammation and development of autoimmune dysfunctions. • ATII stimulates the production of ROS that trigger mitochondrial dysfunction and cellular injury. • ATII leads to activation of NAD(P)H oxidase and ROS production, resulting in 	<ul style="list-style-type: none"> • ATII contributes to inflammatory responses and activation of the immune system in autoimmune diseases like rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis. • The RAS plays an important role in atherosclerosis by inflammatory reactions, thrombosis, and oxidant injury of the endothelium. • Serum concentrations of ACE, a marker of an over active RAS, were associated with 	<ul style="list-style-type: none"> • AGT-knockout present low systolic blood pressure and low survivability • AGT duplication is characterized by elevated blood pressure 	<ul style="list-style-type: none"> • Captopril • Enalapril • Perindopril • Losartan • Xanthenone • Diminazene aceturate • And several others 	<ul style="list-style-type: none"> • (Benigni et al., 2010; Cambados et al., 2017; Capettini et al., 2012; Chang and Wei, 2015; Husain et al., 2015; Ikonomidis et al., 2017; Kim et al., 2017c; Liu et al., 2016a; Noguchi et al., 2017; Tan et al., 2016)

oxidative stress and vascular senescence that contribute to age-related vascular diseases.

- ATII promotes the proliferation of cancer cells.
- ATII caused hippocampal neural stem cells apoptosis through mitochondrial ROS formation and subsequent AMPK-PGC1 α signalling.

heart dysfunction and fibrosis in patients with hypertension.

- AGT is elevated in kidney injury patients.
- ACE levels are increased in fibrosis related to chronic hepatitis B
- Brain RAS activation is involved in the pathogenesis and progression of Alzheimer and Parkinson disease.

Table 5 NMJ and neurons

Summary of selected marker characteristics and testing in intervention studies based on literature

Markers	Hallmark of aging Pathways	Age/ Age-related Diseases	Genetics	Intervention	Literature
ST2	<ul style="list-style-type: none"> Induced in inflammation Potentiates macrophage response to LPS Modulates T cell function and differentiation 	<ul style="list-style-type: none"> Increased in various aging conditions Increased in type 2 diabetes Increased in cardiovascular injury Increased in stroke and associated with brain injury and cognitive impairment Associated with advanced and metastatic gastric cancer 	<ul style="list-style-type: none"> Knockout animals display an abnormal Th2 type inflammatory response and abnormal response to infection. 	<ul style="list-style-type: none"> Corticosteroids Disease-modifying antirheumatic drugs 	<ul style="list-style-type: none"> (Espinassous et al., 2009; Griesenauer and Paczesny, 2017; Peine et al., 2016) (Andersson et al., 2015; Broch et al., 2017; Hong et al., 2011; Krychtiuk et al., 2018; Miller et al., 2012; Wang et al., 2018a; Wolcott et al., 2017; Zhang et al., 2017c)
BDNF	<ul style="list-style-type: none"> Regulates neuronal survival and synaptic plasticity Is involved in glucose and energy homeostasis and body weight control BDNF signalling via TrkB suppresses autophagy Presents anti-oxidant effects, suppressing ROS and protecting mitochondria Promotes non-amyloidogenic APP processing 	<ul style="list-style-type: none"> Plasma levels correlate positively with successful aging Low serum BDNF was associated with lower cognitive scores, mild cognitive impairment and Alzheimer disease Plasma BDNF levels were higher in osteoarthritis patients and correlated with self-reported pain BDNF is decreased in atherosclerosis Reduction in BDNF indicates poor functional prognosis after stroke 	<ul style="list-style-type: none"> Knockout animals present postnatal lethality, sensory neuron losses, cerebellar abnormalities and increased sympathetic neuron number 	<ul style="list-style-type: none"> Exercise Cerebrolysin Estradiol Metformin 	<ul style="list-style-type: none"> (Alvarez et al., 2016; Casas et al., 2017; Gomes et al., 2014; Huang and Reichardt, 2001; Lasek-Bal et al., 2015; Lau et al., 2017; Nigam et al., 2017; Nikolettou et al., 2017; Numakawa et al., 2014; Shimada et al., 2014; Simao et al., 2014; Siuda et al., 2017; Willer et al., 2009; Wu et al., 2017a; Wu et al., 2016a; Wu et al., 2012; Yoo et al., 2011)
Agrin	<ul style="list-style-type: none"> Secreted neuroprotein that stabilizes neuromuscular junction via MusK/Lrp4 by clustering acetylcholine 	<ul style="list-style-type: none"> Associated with neuromuscular disorders, diabetes, cardiovascular diseases, kidney function and 	<ul style="list-style-type: none"> Mutations and antibodies cause myasthenia gravis (MG) Loss of synapses in agrin-deficient mice 	<ul style="list-style-type: none"> Engineered agrin for neuromuscular diseases such as MG (e.g. NT-1654) 	<ul style="list-style-type: none"> (Arampatzis et al., 2017; Banyai et al., 2010; Barber and Lieth, 1997; Bentzinger et al., 2005; Berzin et al.,

receptors

- Involved in formation of blood brain barrier
- Also secreted by Schwann cells, kidney, eye and lung
- Cleaved by neurotrypsin into c-terminal fragment (CAF) and MMP3
- Non-synaptic actions, for example in immune cells, binding to TGF β family proteins and beta-amyloids

diseases, sarcopenia, dystrophies and other muscle wasting conditions, liver cancer and diseases, cognitive functions and neurodegenerative disorders, OA, nerve and brain injury, immunologic disorder and lung dysfunction

- Predictive biomarker in various degenerative diseases
- Linked to frailty, aging

- Defective eye development in agrin-overexpressing mice

• **Overexpression of mini-agrin in congenital muscular dystrophy**

2000; Bezakova et al., 2001; Bezakova and Ruegg, 2003; Bixby et al., 2002; Bolliger et al., 2010; Bose et al., 2000; Burden, 1998; Burgess et al., 1999; Burgess et al., 2000; Campagna et al., 1997; Chakraborty and Hong, 2018; Cotman et al., 2000; Cui and Bazan, 2010; Daryadel et al., 2016; DeChiara et al., 1996; Del Campo Milan et al., 2015; Deyst et al., 1998; Donahue et al., 1999; Drey et al., 2015; Drey et al., 2013; Eldridge et al., 2016; Erasso et al., 2014; Erasso et al., 2018; Falo et al., 2008; Fragala et al., 2014; Fuerst et al., 2007; Gautam et al., 1999; Gautam et al., 1996; Gingras et al., 2002, 2007; Glass et al., 1996; Gomez et al., 2014; Groffen et al., 1998; Gros et al., 2014; Grow et al., 1999; Hagiwara and Fallon, 2001; Hausser et al., 2007; Hettwer et al., 2013; Hettwer et al., 2014; Hilgenberg et al., 1999; Hoch, 1999; Jury et al., 2007;

Jury and Kabouridis, 2010; Kalinkovich and Livshits, 2015; Karakaya et al., 2017; Khan et al., 2001; Kim et al., 2008a; Ksiazek et al., 2007; Li et al., 2007; Li et al., 2018b; Li et al., 1999; Li et al., 2018d; Liebner et al., 2011; Mann and Kroger, 1996; Marzetti et al., 2014; Mazzon et al., 2012; Meier et al., 1997; Mittaud et al., 2004; Neumann et al., 2001; Patel et al., 2012; Pun and Tsim, 1997; Rauch et al., 2018; Reif et al., 2007; Rimer, 1998; Romi et al., 2008; Rudolf et al., 2014; Ruegg and Bixby, 1998; Sanes et al., 1998a; Sanes et al., 1998b; Sanes and Lichtman, 2001; Serpinskaya et al., 1999; Sole et al., 2004; Steinbeck et al., 2015; Stephan et al., 2008; Stetefeld et al., 2004; Steubl et al., 2013; Steubl et al., 2016; Stout et al., 2015; Tatrai et al., 2006; Terrado et al., 2001; Trautmann and Vivier, 2001; Ueta and Yamanashi, 2018; VanSaun et

					al., 2003; VanSaun and Werle, 2000; Verbeek et al., 1999; Wei et al., 1997; Williams et al., 2008; Xi et al., 2017; Xiao et al., 2018; Yan et al., 2018; Yang et al., 2001; Yard et al., 2017b; Zhang et al., 2008)
Progranulin	<ul style="list-style-type: none"> • Progranulin is involved in wound healing, cell migration, tissue repair and cell proliferation • Progranulin loss decreases the number of EVs and changes their composition • Mediates anti-inflammatory activity through TNFR and β-catenin • Progranulin loss impair autophagy 	<ul style="list-style-type: none"> • Progranulin loss occurs in several dementias and acute brain injury, triggering microglia activation • Progranulin levels increase during healthy aging • Augments vasorelaxation and reduces ischemia-reperfusion injury • Protects against inflammation in atherosclerosis and is strongly expressed in foam cells • Progranulin deficiency protects from insulin resistance resulting from high-fat diet • Circulating progranulin levels increase in obesity and type II diabetes • Plays a protective role in osteoarthritis • Progranulin/TNFα ratio correlates with stage of the disease in rheumatoid arthritis 	<ul style="list-style-type: none"> • Progranulin knockouts present enhanced macrophage function, reproductive and behavioural abnormalities and premature death with increased cellular aging • SNPs in the progranulin gene are associated with frontotemporal lobar degeneration, ceroid lipofuscinosis-11 (CLN11) and other neurodegenerative diseases 	<ul style="list-style-type: none"> • SAHA • Chloroquine • Selumetinib • MEK162 • trehalose 	<ul style="list-style-type: none"> • (Abella et al., 2016; Alquezar et al., 2015; Benussi et al., 2016; Chang et al., 2017b; Fardo et al., 2017; Holler et al., 2016; Kawase et al., 2013; Korolczuk and Beltowski, 2017; Kwack and Lee, 2017; Ma et al., 2017; Nicholson et al., 2014; Vercellino et al., 2011; Wang et al., 2016b; Xu et al., 2017a; Yamamoto et al., 2014b; Zhao et al., 2015; Zhou et al., 2015a)
C3/C1q	<ul style="list-style-type: none"> • Are involved in the recognition and tagging for degradation of designated antigens • C1q activation induces the production of C3 and 	<ul style="list-style-type: none"> • C1q plasma and brain levels increased in aging • Brain C1q increased in Alzheimer disease, Frontotemporal lobar 	<ul style="list-style-type: none"> • C1qa knockout exhibit behaviour and neurological abnormalities with phenotypes linked to epilepsy, glomerulonephritis, increased 	<ul style="list-style-type: none"> • C1 – Pioglitazone • C3 – Eculizumab • C3 – pLTA • C3 - Lithium 	<ul style="list-style-type: none"> • (Aronica et al., 2007; Bahrini et al., 2015; Baudino et al., 2014; Corigliano et al., 2017;

<p>consequent enhancement of anaphylatoxin, which are potent pro-inflammatory mediators</p> <ul style="list-style-type: none"> • Balance inflammation by recognition of apoptotic and necrotic cells • Deficiency in an C1q receptor decreases apoptotic cell uptake • C3 is a chaperone of apoptotic cargo and misfolded proteins • C1qb can be released in exosomes following brain injury and C3 is increased in microglia following uptake of exosomes 	<p>degeneration, temporal lobe dementia and, amyotrophic lateral sclerosis</p> <ul style="list-style-type: none"> • C1q is inhibited in rheumatoid arthritis • C1q is a clinical predictor of type 2 diabetes • C1q is increased in retinal and brain ischemia • C1q is protective in atherosclerosis • C3 protects aging decline and its levels are decreased in the cerebrospinal fluid of mild cognitive impairment patients • C3 is increased in Alzheimer disease, Parkinson disease, temporal lobe epilepsy and amyotrophic lateral sclerosis • Cleavage products of C3 are a marker of osteoarthritis • Increased deposition of C3b in rheumatoid arthritis • C3 levels are a risk factor for diabetes • C3 deposits in brain ischemia • C3 is retained in atherosclerotic lesions • High plasma levels of C3 in age-related macular degeneration 	<p>numbers of glomerular apoptotic bodies, high antibody titres and increased mortality</p> <ul style="list-style-type: none"> • C3 knockout exhibit behaviour abnormalities regarding memory and anxiety, immune alterations related to neutrophil morphology and aberrant inflammatory responses; • C3 knockouts also present increased neuron number and synaptic puncta in the hippocampus 	<p>Dunkelberger and Song, 2010; Engstrom et al., 2005; Happonen et al., 2010; Hong et al., 2016; Huang et al., 2018; Iram et al., 2016; Jeon et al., 2016; Lai et al., 2017; Lechner et al., 2016; Lobsiger et al., 2007; Lui et al., 2016; Manek et al., 2017; Martin and Blom, 2016; Naito et al., 2012; Nakatsuji et al., 2013; Niculescu and Rus, 2004; Peters et al., 2017; Pilely et al., 2017; Pulanco et al., 2017; Seddon et al., 2013; Shi et al., 2017; Shi et al., 2015a; Silverman et al., 2016; Sta et al., 2011; Stephan et al., 2013; Toledo et al., 2014; Tran et al., 2016; Ursini and Abenavoli, 2018; Watanabe et al., 2015; Wyatt et al., 2013; Yu et al., 2015)</p>
<p>sRAGE</p> <ul style="list-style-type: none"> • Belongs to family of immunoglobulins • Activates several pathways including PI3K, NFκB, ERK, ROS and Ras/Jak/Stat • Recognizes AGE • RAGE activation can result in inflammation and DNA 	<ul style="list-style-type: none"> • sRAGE is expressed during development, downregulated during adult life and up-regulated with increased age • RAGE activation is involved in diabetes mellitus, neurological diseases and some types of cancer 	<ul style="list-style-type: none"> • Homozygotes for null allele show increased bone mass strength, reduced osteoblast number, abnormal blood vessel healing, altered pain perception in induced diabetes • Homozygotes for another null allele show restored diabetes- 	<ul style="list-style-type: none"> • Metformin • 4,6-bis(4-chlorophenyl)pyrimidine analogue • PF-04494700 <p>(Antonelli et al., 2017; Aubert et al., 2014; Bakker et al., 2015; El-Saeed et al., 2015; Guo et al., 2012; Guo et al., 2016; Haddad et al., 2016; Jiang et al., 2015b; Juranek et al.,</p>

	<p>damage</p> <ul style="list-style-type: none"> • sRAGE is produced by alternative splicing or proteolytic cleavage and is found in plasma. • sRAGE does not initiate signalling but can act as a decoy receptor, binding RAGE ligands 	<ul style="list-style-type: none"> • sRAGE has been used as biomarker in acute respiratory distress syndrome • sRAGE can be an earlier prognosis biomarker in sepsis • Low circulating sRAGE has been associated with increased arterial stiffness in hypertensive diabetic patients • sRAGE concentration is decreased in Alzheimer disease versus healthy controls 	<p>induced angiogenic responses</p>	<p>2016; Mayer et al., 2016; Sabbagh et al., 2011; Wang et al., 2015b; Wu et al., 2016d; Xu et al., 2017d)</p>
HMGB1	<ul style="list-style-type: none"> • Triggers and amplifies inflammatory cascade • Critical regulator of mitochondrial function • Activates the FAK/PI3K/mTOR signalling cascade to promote cancer cell proliferation/migration 	<ul style="list-style-type: none"> • Decreased serum levels with age • Increased in RA • Mediates depressive behaviour induced by chronic stress • Progression of diabetes, and initiation and development of diabetic complications • Prognostic marker in melanoma 	<ul style="list-style-type: none"> • Knockout mice die within 24 h because of the inability to use the glycogen stored in the liver 	<ul style="list-style-type: none"> • Metformin • Anti-HMGB1 <p>(Angelopoulou et al., 2016; Chen et al., 2016a; Chung and Lim, 2017; Davalos et al., 2013; Guo et al., 2011; Horiuchi et al., 2017; Kim et al., 2017b; Ko et al., 2014; Limana et al., 2005; Livesey et al., 2012; Muller et al., 2004; Nguyen et al., 2017; Qi et al., 2016; Ravizza et al., 2017; Stevens et al., 2017; Tang et al., 2011; Vezzoli et al., 2011; Wang et al., 2017a; Wu et al., 2016b; Zhao et al., 2017b)</p>

Table 6 Cytoskeleton and hormones

Summary of selected marker characteristics and testing in intervention studies based on literature

Markers	Hallmark of aging Pathways	Age/ Age-related Diseases	Genetics	Intervention	Literature
GH	<ul style="list-style-type: none"> • GH promotes stem cell activation, cell proliferation, differentiation and survival, either directly or through the induction of IGF-1. • GH and melatonin prevent age-related alteration in apoptosis processes in the dentate gyrus of male rats. • GH replacement therapy resulted in an increase in the skeletal muscle protein synthesis and mitochondrial biogenesis pathways. • GH also suppressed the accumulation of oxidative stress markers and the gene expression of anti-oxidant enzymes. • GH treatment antagonized diet-induced changes in the gene expression of adiponectin, leptin, and monocyte chemoattractant protein-1 	<ul style="list-style-type: none"> • The intact GH/IGF-1 axis is essential to maintain health span and that elevated GH, even late in life, associates with increased pathology. • Circulating GH levels show a significant decline with aging. • GH-resistant and GH-deficient animals live much longer than their normal siblings, while transgenic mice overexpressing GH are short lived • GH induces insulin resistance in muscle and fat while at the same time facilitating nitrogen retention in the muscle and lipolysis in the fat tissue • GH excess and deficiency are both associated with increased insulin resistance related to differing aetiologies in these two distinct clinical syndromes. • Higher values of GH were associated with an increased risk of cardiovascular morbidity and mortality 	<ul style="list-style-type: none"> • In transgenic mice expressing various GH genes under control of metallothionein or phosphoenolpyruvate carboxykinase promoters, massive overproduction of GH leads to drastically reduced lifespan and many symptoms of accelerated aging. • GH deficiency in hypopituitary mutants and GH resistance in mice with targeted deletion of GH receptors are associated with approximately 30%–60% lifespan extension, depending on the mutation involved, genetic background, sex and diet composition. • GH-deficient and GH-resistant mice exhibit many symptoms of delayed aging and have extended “health span” that is a period of life free from major disease or functional impairments. 	<ul style="list-style-type: none"> • CR • Exercise • Diet • GH replacement • Somatropin, Clonidine, L-Arginin-Hydrochloride, Estradiol valerate • Omega-3 • recombinant human IGF-1 	<ul style="list-style-type: none"> • (Bartke et al., 2013; Briocche et al., 2014; Hallengren et al., 2014; Kireev et al., 2013; Nass, 2013; Sperling, 2016; Trueba-Saiz et al., 2013; Waters and Brooks, 2012; Yuen et al., 2013)
IGF-I	<ul style="list-style-type: none"> • Cell proliferation, • Cell differentiation • Cell death • Cellular Senescence • Immune system process, • Inflammation 	<ul style="list-style-type: none"> • The intact GH/IGF-1 axis is essential to maintain health span and that elevated GH, even late in life, associates with increased pathology. • Decreased IGF-I level by fasting play crucial role in 	<ul style="list-style-type: none"> • 16 strains and lines available including B6.129(FVB)-Igf1tm1Dlr/J mice (also known as Igf1flox). These homozygote mutants are viable, fertile, and normal in size. 	<ul style="list-style-type: none"> • CR • Exercise • Diet • Growth Hormone • Somatropin, Clonidine, L-Arginin-Hydrochloride, 	<ul style="list-style-type: none"> • (Arroba and Valverde, 2015; Chaker et al., 2015; Cheng et al., 2014; Deak and Sonntag, 2012; Dogan et al., 2011; Fuentes-Santamaria et al., 2016; Gonzalez-

<ul style="list-style-type: none"> • Mitochondrial dysfunction • Lipid metabolic process, • Protein metabolic process, 	<p>regulating hematopoietic stem cell protection, self-renewal, and regeneration.</p> <ul style="list-style-type: none"> • Lacking of encoded protein in mice shows generalized organ hypoplasia that includes underdevelopment of CNS and developmental defects in muscle, bone and reproductive systems • Brain diseases (neurogenesis); IGF-1 deficiency is responsible for increased brain oxidative damage, oedema, and impaired learning and memory capabilities. • Elevated IGF-I is associated with cancer • Impaired IGF/AKT signalling contributes to decreased bone mass and bone formation exhibited by telomerase deficient osteoblastic cells. 	<ul style="list-style-type: none"> • Homozygous null mutants which are severely growth retarded, die perinatally due to the immature organ systems. • Mice lacking the IGF-I gene exhibit profound deafness and multiple anomalies in the inner ear and spiral ganglion. • Partial knockout mice show growth retardation and abnormalities in selected organs e .g. heart 	<p>Estradiol valerate</p> <ul style="list-style-type: none"> • Omega-3 • Nutropin [Somatropin (rDNA origin) for injection] • recombinant human IGF-1 • Orlistat 	<p>Guerra et al., 2017; Handayaningsih et al., 2012; Lara-Diaz et al., 2017; Olleros Santos-Ruiz et al., 2017; Puche et al., 2016; Saeed et al., 2015; Shuang et al., 2017; Trueba-Saiz et al., 2013)</p>
<p>α-klotho</p> <ul style="list-style-type: none"> • α-Klotho is a transmembrane protein that controls the sensitivity of the organism to insulin and appears to be involved in aging. • α-Klotho plays a role in cellular homeostasis (e.g. carbohydrate and protein metabolism) and is involved in cell signalling. α-Klotho functions as a co-receptor for FGF23 and enhances signalling of other fibroblast growth factors. 	<ul style="list-style-type: none"> • α-Klotho protein has been shown to be a circulating factor detectable in serum that declines with age. • The α-Klotho gene was originally identified as a putative aging-suppressor gene, has generated tremendous interest and has advanced understanding of the aging process. In mice, the overexpression of the KL gene extends the life span, whereas mutations to the KL gene shorten the life span. • α-Klotho is a neuroprotective and cognition-enhancing 	<ul style="list-style-type: none"> • Mutations within this protein have been associated with aging and bone loss. • Homozygous mutant mice have a short lifespan and growth retardation with one allele homeostatic imbalances and soft tissue calcification are also seen. With a second allele abnormal cancellous bone and femur morphology are seen. 	<ul style="list-style-type: none"> • The small molecule Tioconazole did not inhibit the activation of MAPK signalling after bFGF induction, while FGF23-mediated phosphorylation of ERK1/2 was clearly reduced. Effect on α-Klotho induced anti-aging needs to be further studied 	<ul style="list-style-type: none"> • (Bartali et al., 2013; Diener et al., 2015; Kuro-o et al., 1997; Xu and Sun, 2015)

Protein.				
FGF23	<ul style="list-style-type: none"> • FGF23 has pleiotropic action with a main function in phosphate, mineral and iron homeostasis • FGF23 acts with α-klotho as co-receptor • FGF23 is regulated by α-klotho inflammation, fibrotic inducers, phosphate, calcineurin, IGF-I, vitamin D, anaemia 	<ul style="list-style-type: none"> • Elevated in various kidney and cardiovascular diseases • Also associated with aging, liver diseases, CNS disorders, osteoporosis, RA, diabetes, • Can predict death and mortality 	<ul style="list-style-type: none"> • Human FGF23 mutations linked to Tumoral Calcinosis (loss of function) and hypophosphataemic rickets (gain of function) 	<ul style="list-style-type: none"> • Inhibition of FGF23 using neutralizing antibodies (e.g. burosumab), the c-tail antagonist fragment or receptor blockers in kidney diseases and hypophosphatemia • (Agoro et al., 2018; Akhabue et al., 2018; Atta et al., 2016; Bar et al., 2018; Bar et al., 2017; Cavalli et al., 2012; Cianciolo et al., 2018; Claramunt-Taberner et al., 2018; Clinkenbeard and White, 2017; Courbebaisse and Lanske, 2018; Econs, 2017; Erben, 2016, 2017, 2018; Erben and Andrukhova, 2017; Faul, 2017; Feger et al., 2017; Francis and David, 2016; Fukumoto, 2018; Glosse et al., 2018; Haffner and Leifheit-Nestler, 2017; Hanudel et al., 2016; He et al., 2018; Hensel et al., 2016; Hyun et al., 2018; Isakova et al., 2018; Jialal et al., 2017; Kanbay et al., 2017; Kinoshita and Kawai, 2016; Kovesdy and Quarles, 2016; Kuro, 2017; Kutilek, 2017; Lamb, 2018; Langsford et al., 2017; Leaf et al., 2018; Leifheit-Nestler et al., 2018; Li et al., 2016a; Li et al., 2018a; Lu

				<p>and Hu, 2017; Pastor-Arroyo et al., 2018; Rodriguez-Ortiz and Rodriguez, 2015; Rossaint et al., 2017; Ruppe et al., 2016; Rygasiewicz et al., 2018; Salanova Villanueva et al., 2016; Sato et al., 2016; Sharaf El Din et al., 2017; Souma et al., 2016; Takahashi et al., 2018; Wang and Zhu, 2016; Xu et al., 2018; Zhang et al., 2016; Zhang et al., 2018b)</p>
<p>FGF21</p>	<ul style="list-style-type: none"> • Pleiotropic action as hepatokine, adipokine, mitokine, myokine and neuroendocrine • Regulated by Inflammation, fibrosis, alcohol, vitamin D, glucose, ER, starvation or fasting 	<ul style="list-style-type: none"> • Increased and potential biomarker in mitochondrial diseases, metabolic disorders and diabetes, musculoskeletal diseases, sepsis, renal disorders, cardiovascular disorders, liver diseases, cancer, eye disorders, osteoarthritis, rheumatoid arthritis • Linked to aging, pre-mature aging and lifespan • Predicts mortality • Protects against hepatotoxicity induced by acetaminophen on 	<ul style="list-style-type: none"> • FGF21-deletion aggregates diabetes-induced and other diseases • Long-acting and engineered variants as therapeutics in heart and metabolic diseases • Induced by metformin intervention 	<ul style="list-style-type: none"> • (Anuwatmatee et al., 2018; Anuwatmatee et al., 2017; Badman et al., 2009; Bartali et al., 2013; Bergmann and Sypniewska, 2013; Bobbert et al., 2013; Brahma et al., 2014; Chow et al., 2013; Crujeiras et al., 2017; Davis et al., 2017; Davis et al., 2013; Davis et al., 2016, 2018; Domouzoglou et al., 2015; Dong et al., 2015; Dushay et al., 2010; El-Saeed and El-Mohasseb, 2017; Esteghamati et al., 2017; Fu et al., 2018; Fujita et al., 2016a; Gillum, 2018; Han et al., 2010; Hsuchou et al., 2007; Hui et al., 2018; Hulejova et al., 2012; Iroz et al.,

2015; Itoh, 2014;
Itoh et al., 2016;
Keipert et al., 2014;
Kim et al., 2017a;
Kim et al., 2016a;
Kim et al., 2015b;
Knott et al., 2016;
Kohara et al., 2017;
Kokkinos et al., 2017;
Koot et al., 2013;
Krautbauer et al.,
2018; Kuro, 2018;
Lee et al., 2015a; Lee
et al., 2016a; Lee et
al., 2018b; Lehtonen
et al., 2016; Li et al.,
2010; Li et al., 2018c;
Li et al., 2015c; Liu et
al., 2014b; Lovadi et
al., 2017; Mai et al.,
2011; Matuszek et
al., 2010; Morovat et
al., 2017; Murata et
al., 2011; Olivera
Santa-Catalina et al.,
2017; Ong et al.,
2012; Planavila et al.,
2013; Ruiz-Margain
et al., 2018; Rusu et
al., 2017; Ryan et al.,
2018; Sanchis-Gomar
et al., 2015; Scholle
et al., 2018; Shen et
al., 2012; Shi et al.,
2018; Soberg et al.,
2018; Sodhi et al.,
2016; Spurna et al.,
2018; Stein et al.,
2009; Stein et al.,
2010; Su et al., 2012;
Suomalainen et al.,
2011; Talukdar et al.,
2016; Tanajak et al.,
2018; Thiessen et al.,
2015; Ulu et al.,
2014; Wei et al.,
2018; Woo et al.,

					2017; Woo et al., 2013; Wu et al., 2017b; Wu et al., 2015; Xiao et al., 2012; Yan et al., 2011; Yan et al., 2015; Ye et al., 2016a; Ye et al., 2014; Ye et al., 2017a; Zagarskikh et al., 2018; Zhang et al., 2015c; Zhang et al., 2012)
Resistin	<ul style="list-style-type: none"> • Inflammation • Cell proliferation • Apoptosis • Reduced mitochondrial content reduced brown adipose tissue activity 	<ul style="list-style-type: none"> • Increased in coronary artery disease, coronary syndrome and peripheral arterial disease; adiponectin/resistin index is an indicator for atherosclerosis • Resistin contributes to the pathogenesis of RA. • Resistin level are associated with increased risk of acute cerebral infarction • Serum resistin level is elevated in subjects with metabolic syndrome, may be related to severity of it. 	<ul style="list-style-type: none"> • Homozygous null mice display impaired gluconeogenesis, lower fasting blood glucose levels, and a weaker positive correlation between body weight and blood glucose. 	<ul style="list-style-type: none"> • No interventions known 	<ul style="list-style-type: none"> • (Asterholm et al., 2014; Butler et al., 2009; Codoner-Franch et al., 2014; Demirci et al., 2017; Dong et al., 2017b; Dong et al., 2010; Gencer et al., 2016; Hsu et al., 2017a; Li et al., 2013; Meng et al., 2017; Menzaghi et al., 2014; Milanesi et al., 2017; Mohammadi et al., 2017; Sato et al., 2017; Sawicka et al., 2017; Shen et al., 2014; Singh et al., 2017; Solis-Cano et al., 2017; Song et al., 2016b; Wang et al., 2017e; Wen et al., 2018; Wen et al., 2014; Wen et al., 2015b; Zhou et al., 2013; Zuniga et al., 2017)
Adiponectin	<ul style="list-style-type: none"> • Biomarker of inflammation • Reduces inflammation • Reduces MMP-9 levels, eNOS, IL-10, gene expression of TNF-α, IL-6, sVCAM1 and inhibited the activation of 	<ul style="list-style-type: none"> • Total adiponectin levels were not changed with aging • Osteoarthritis/rheumatoid arthritis • Low plasma adiponectin levels are biomarker for metabolic 	<ul style="list-style-type: none"> • Adiponectin knockout mice showed hepatic steatosis and mitochondrial dysfunction • Adiponectin knockout mice developed hearing impairment • Adiponectin knockout had 	<ul style="list-style-type: none"> • ApoE(-/-) mice • Thiazolidinediones: PPARγ agonists upregulates Circulating adiponectin levels 	<ul style="list-style-type: none"> • (Ambroziak et al., 2018; Aygun et al., 2006; Chen et al., 2015b; Cong et al., 2007; de Luis et al., 2016; DeClercq et al., 2015; Dieudonne et al.,

<p>NFκB pathway and the expression of NFκB nuclear protein p65</p> <ul style="list-style-type: none"> • Insulin resistance • Apoptosis of different cancer cells • Exosome marker 	<p>syndrome</p> <ul style="list-style-type: none"> • High serum levels of adiponectin was associated with mortality in patients with type 2 diabetes • High plasma adiponectin levels are associated with a decreased risk of myocardial infarction in healthy men • Low circulating adiponectin levels is a biomarker for coronary artery disease in men • Low adiponectin levels were correlated with age-related hearing impairment • Low adiponectin level is a risk factor for non-alcoholic fatty liver disease and non-alcoholic steatohepatitis • Leptin/adiponectin (L/A) ratio is a reliable biomarker of breast cancer 	<p>increased beta-oxidation in muscle and liver tissue</p>	<ul style="list-style-type: none"> • Adiponectin administration improved endothelium-dependent vasodilation of coronary arterioles in ApoE knockout atherosclerotic mice and can be suggested as vasoprotective. • Pioglitazone, Rosiglitazone and Tongqiaohuoxue decoction increases adiponectin levels 	<p>2006; Fujishima et al., 2017; Kang et al., 2005; Kim et al., 2016b; Nawrocki et al., 2006; Niinaga et al., 2016; Phoonsawat et al., 2014; Pischon et al., 2004; Ryo et al., 2004; Sattar et al., 2006; von Eynatten et al., 2006b; Vuppalanchi et al., 2005; Xu et al., 2003; Zhou et al., 2008)</p>
<p>Leptin</p> <ul style="list-style-type: none"> • Can inhibit food intake and/or regulate energy expend • Apoptosis, • Angiogenesis, • Cell proliferation, • Cellular senescence • Inflammatory action • Autophagy • Mitochondria. reduced hepatic mitochondrial content and function in leptin deficient mice • IGF-I signalling pathway. Attenuates IGF-I in aging mice 	<ul style="list-style-type: none"> • Controls body weight and regulates energy balance • Obesity • Inflammation • Diabetes • Obesity • Different kinds of tumour development • Promote cancer cell proliferation • Tumour development • Worsen the prognosis of tumoral and neurodegenerative processes by increasing the susceptibility of cells to inflammatory mediators 	<ul style="list-style-type: none"> • 18 strains and lines available including B6.Cg-Lepob/J mice (also known as B6 ob). This mice strain is homozygous for the obese spontaneous mutation. This homozygous mutant mice gain weight rapidly and might reach three times the normal weight of wild type ones. • Homozygous mutants exhibit obesity, hyperphagia, glucose intolerance, a diabetes-like syndrome of hyperglycemia, an increase in hormone production, subfertility, have low activity, high metabolic 	<ul style="list-style-type: none"> • Leptin • Aripiprazole • Irbesartan • Amlodipine • Leuprolide Acetate • Sandostatin LAR • Metformin • CR/Diet • Aging • Exercise 	<ul style="list-style-type: none"> • (Chai et al., 2015; Dogan et al., 2017; Dogan et al., 2010; Gan et al., 2017; Hamrick et al., 2015; Martin et al., 2017b; Matoba et al., 2017; Perfield et al., 2013; Philbrick et al., 2017; Ray and Cleary, 2017; Ryan et al., 2003; Silha et al., 2006; Xu et al., 2017c; Zhan et al., 2016)

	<ul style="list-style-type: none"> • Serum leptin level increases with aging • Leptin stimulates bone formation in leptin deficient mice • Brain diseases with different effect • Cardiovascular diseases 	<p>efficiency, impaired thermogenesis, infertility and</p> <ul style="list-style-type: none"> • Homozygous mutants exhibit short lifespan, impaired wound healing and elevated plasma insulin. • Hypometabolic and hypothermic. Obesity in these mice characterized by an increase in both adipocyte size and number. • Strain background affects severity and course of diabetes. 		
Ghrelin	<ul style="list-style-type: none"> • Ghrelin plays a role in the stimulation of GH secretion and regulation of energy homeostasis. • Reduces the production of pro-inflammatory cytokines in monocytes and T-lymphocytes. • Unacylated ghrelin improves mitochondria function through Opa1, a modulator of mitochondrial morphology. • Induces autophagy by increasing the expression of several autophagy-related proteins, such as LC3, Atg7 and Beclin1. • Increases the expression of cell cycle proteins cyclins D1 and E and CDK2. 	<ul style="list-style-type: none"> • Lower ghrelin levels were associated with higher weight loss and poorer hand grip in men. • Lower ghrelin levels were observed in the plasma of two different animal models of accelerated aging. • No differences were found between ghrelin in young and old men or women. • Levels of acylated ghrelin were increased in mild cognitive impairment patients and were associated with Alzheimer disease risk factors: age, hypertension and hyperlipidaemia. • Acylated ghrelin is increased in type 2 diabetes patients with insulin resistance and visceral obesity. • Serum ghrelin levels are increased in heart disease patients and patients with non- 	<ul style="list-style-type: none"> • Longevity is not affected by ghrelin deletion, but ghrelin administration to WT or Ghrelin KO mice increases food intake, body weight and strength. 	<ul style="list-style-type: none"> • Anamorelin • Capromorelin • MK-677 • Ghrelin <p>(Adunsky et al., 2011; Barazzoni et al., 2017; Cao et al., 2018; Dixit et al., 2004; Estep et al., 2011; Garcia et al., 2015; Guillory et al., 2017; Kilic et al., 2017; Liao et al., 2017; Mykhalchyshyn et al., 2015; Nagaya et al., 2004; Rossetti et al., 2017; Serra-Prat et al., 2010; Wan et al., 2016; White et al., 2009; Xu et al., 2017b)</p>

alcoholic fat-liver disease

Table 7 Other principles

Summary of selected marker characteristics and testing in intervention studies based on literature

Markers	Hallmark of aging Pathways	Age/ Age-related Diseases	Genetics	Intervention	Literature
miRNA	<ul style="list-style-type: none"> • Tissue- and pathway specific as well as disease-specific miRNAs described including myomirs, mitomirs and oncomirs • Hallmark of aging pathways miRNAs for senescence, inflammation, apoptosis, fibrosis, mitochondrial dysfunction, • For many of the proposed biomarkers of frailty interacting or modulating miRNAs have been described. 	<ul style="list-style-type: none"> • Signatures of circulating miRNAs have been explored in aging and a variety of age-related disease: e.g. cancer, cardiovascular, osteoporosis, osteoarthritis, COPD, neurodegeneration and sarcopenia • Search for frailty miRNA panel on the way (e.g. Frailomics) • First publication reporting enrichment of the following eight miRNAs in frailty: miR-10a-3p, miR-92a-3p, miR-185-3p, miR-194-5p, miR-326, miR-532-5p, miR-576-5p, and miR-760 	<ul style="list-style-type: none"> • n/a 	<ul style="list-style-type: none"> • Exercise • Rapamycin, doxorubicin and other chemotherapeutics • Antiangiogenic • Metformin • Surgery • HGMB1 • Corticoids and anti-TNFα • Vitamin D • Clopidogrel • MMP inhibitors • Statins • Resveratrol 	<ul style="list-style-type: none"> • (Adams et al., 2018; Baker et al., 2017; Barwari et al., 2016; Bedreag et al., 2016; Beyer et al., 2015; Campagnolo et al., 2015; Carino et al., 2016; Carlomagno et al., 2017; Chen et al., 2017b; Cufi et al., 2012; Cuppen et al., 2016; Erusalimsky et al., 2016; Garcia-Donas et al., 2016; Heier et al., 2016; Hunter et al., 2008; Leao et al., 2018; Lee et al., 2018a; Lippi et al., 2015; Ludwig et al., 2016; Navratilova et al., 2016; Nunez Lopez et al., 2017; Okugawa et al., 2018; Pulliero and Izzotti, 2016; Schraml and Grillari, 2012; Sheinerman and Umansky, 2013; Siracusa et al., 2018; Thomas and Lip, 2017; Wang et al., 2016a; Wang et al., 2018b; Weilner et al., 2013; Witwer, 2015; Zhang et al., 2015b; Zhang et al., 2017b; Zhou et al., 2015b); Ipson

AHCY	<ul style="list-style-type: none"> • HC activates inflammasome and inflammatory pathways including NFκB • HC induces oxidative, ER stress, mitochondrial dysfunction and apoptosis • HC accelerates senescence 	<ul style="list-style-type: none"> • Clinical marker to evaluate rheumatoid arthritis patients with high cardiovascular risk. • AHCY levels relate to Alzheimer Disease, Parkinson Disease, neurologic impairment after stroke and impaired cognitive function • HC is linked to macular oedema in type 2 diabetes. • Serum HC levels were associated with impaired renal function in patients with chronic kidney disease • HC is associated with long-term mortality in acute ischemic stroke 	<ul style="list-style-type: none"> • Tissue-specific down-regulation of AHC via suppression of dAHCYL1/dAHCYL2 extends health span and life span in Drosophila • AHCY deficiency protects from diet-induced obesity. 	<ul style="list-style-type: none"> • Alpha-lipoic acid • Salidroside • Folate, vitamin B6, vitamin B12 • Eritadenine • 3-Deazaneplanocin A • 9-(2-deoxy-2-fluoro-β,D-arabinofuranosyl)adenine <p>(Abushik et al., 2015; Cheng et al., 2016a; Chien et al., 2015; Ctrnacta et al., 2010; Cui et al., 2017; Derouiche et al., 2014; Dimitroulas et al., 2016; Haghdoost-Yazdi et al., 2014; Hu et al., 2016a; Kalani et al., 2014a; Lee and Kim, 2013; Li et al., 2014; Marino et al., 2014; Motzek et al., 2016; Park et al., 2015; Parkhitko et al., 2016; Shi et al., 2015b; Shokar et al., 2012; Sun et al., 2017b; Tang et al., 2016; Xia et al., 2014; Yamashita et al., 2014; Yang et al., 2015a; Ye et al., 2016b; Zhang et al., 2015a; Zhu et al., 2017b)</p>
Microparticles	<ul style="list-style-type: none"> • Endothelial microparticles are released from TNF-α-stimulated endothelial cells. • Endothelial microparticles from acute coronary syndrome patients induce premature endothelial senescence through ATII-mediated activation of MAPK and PI3K/Akt. • Blood MPs from type 2 diabetes patients are enriched in proteins involved in platelet 	<ul style="list-style-type: none"> • Microparticles promote endothelial cell senescence through oxidative processes that may be important in vascular dysfunction in aging. • With aging, there is an increase in endothelial senescence, with release of endothelial microparticles, which contribute to the increase of cardiovascular disease. • Microparticles are increased 	<ul style="list-style-type: none"> • N/A 	<ul style="list-style-type: none"> • (Abbas et al., 2017; Burger et al., 2012; Cunningham et al., 2014; Liu et al., 2017f; Luna et al., 2016; Rodrigues et al., 2018; Schindler et al., 2014; Xu et al., 2016)

	<p>activation, cell adhesion, and inflammation.</p> <ul style="list-style-type: none"> • Increased levels of microparticles were observed in rheumatoid arthritis patients and can transfer molecules to target cells, which amplify inflammation, apoptosis, and cell proliferation, impacting immune responses. 	<p>and can contribute to the onset and progression of neurodegenerative and neuroinflammatory diseases, by mediating the transfer of inflammatory mediators and other molecules, such as A??.</p> <ul style="list-style-type: none"> • Higher levels of microparticles derived from platelets, leukocytes or endothelium were detected in the plasma of type 2 diabetes patients. 		
KRT18	<ul style="list-style-type: none"> • Keratins modulate the shape and function of mitochondria • Mutation in KRT18 induces mitochondrial fragmentation • Marker for apoptosis and proposed as an indicator of progression in chronic liver diseases • Absence or mutation cause predisposition to liver injury and apoptosis • KRT18 mediates resistance to stress and apoptosis • KRT18 is senescence-associated gene 	<ul style="list-style-type: none"> • KRT18 linked to antimitochondrial autoantibody formation in aging • Liver KRT18 is upregulated and undergo increased phosphorylation and acetylation in livers from old mice • Serum levels are associated with 30-day mortality and could be used as a prognostic biomarker in patients with severe traumatic brain injury. • cKRT18 predicts non-alcoholic fatty liver disease • Biomarker to diagnose non-alcoholic fatty liver disease • Association with a number of metabolic risk factors. • Safety and diagnosis biomarker for Idiosyncratic drug-induced liver injury diagnosis 	<ul style="list-style-type: none"> • Mice with point-mutant KRT18 develop chronic hepatitis and hepatocyte fragility. and have an increased susceptibility to drug-induced hepatotoxicity • Knockdown of either KRT18 leads to altered clustering of mitochondria and enhanced apoptosis 	<ul style="list-style-type: none"> • Caspase inhibitors • (Battaglia et al., 2017; Cao et al., 2013; He et al., 2017a; Ku et al., 1997; Kullak-Ublick et al., 2017; Kumemura et al., 2008; Lorente et al., 2015; Mannery et al., 2011; Marceau et al., 2001; Morling et al., 2014; Nagpal et al., 2015; Schallmoser et al., 2010; Schwarz and Leube, 2016; Tao et al., 2009; Thulin et al., 2014; Toivola et al., 2015; Woolbright et al., 2017)
GpnmB	<ul style="list-style-type: none"> • GpnmB has anti-inflammatory and reparative functions, and was shown to be 	<ul style="list-style-type: none"> • Emerging role in neurodegenerative disease. • Neuroprotective in animal 	<ul style="list-style-type: none"> • Homozygous mutants exhibit dispersed pigmentation of the iris, deterioration of the 	<ul style="list-style-type: none"> • Glembatumumab • (Budge et al., 2017; Jiang et al., 2011; Maric et al., 2013; Murthy et al., 2017;

<p>neuroprotective</p> <ul style="list-style-type: none"> • Highly expressed in macrophages of acute injured kidney and promotes M2 macrophages polarization. • Regulates the crosstalk between Macrophages and mesenchymal stem cells toward Wound Repair. • Induced in ER stress 	<p>model of amyotrophic lateral sclerosis, cerebral ischemia, and other disease models.</p> <ul style="list-style-type: none"> • Potential therapeutic target for multiple neurodegenerative diseases. • Altered expression is associated with risk for Parkinson disease • Pathological role in aging-related skeletal diseases • A novel potential therapeutic target for cancer • Biomarker and drug target for cardiac and Gaucher Disease 	<p>posterior iris epithelium and s transillumination defects and contributes to glaucoma</p>	<p>Noda et al., 2017; Taya and Hammes, 2018; Yardley et al., 2015; Yu et al., 2018; Zhou et al., 2017)</p>
<p>Lactoferrin</p> <ul style="list-style-type: none"> • Component of non-specific immune system • Regulates cellular growth and differentiation • Protects Human mesenchymal stem cells from Oxidative Stress-Induced Senescence and Apoptosis. • Inhibited the production of hydrogen peroxide-induced intracellular ROS • Neutrophil lactoferrin up-regulates p53 gene • Lactoferrin protects against prion protein-induced cell death in neurons 	<ul style="list-style-type: none"> • Anti-arthritis activity in IL-1β stimulated primary human chondrocytes. • Rheumatoid arthritis synovial fluids express increased lactoferrin level. • Lactoferrin salivary levels allow to discriminate diagnosed mild cognitive impairment and Alzheimer disease patients from cognitively healthy control group • Cerebrospinal fluid lactoferrin levels increase in Parkinson disease patients with sleep disorders • Lactoferrin is a novel predictor of fatal ischemic heart disease in type 2 diabetes • Lactoferrin levels are strongly associated with insulin resistance independently of total adiposity. • Lactoferrin exerts anti-tumour 	<ul style="list-style-type: none"> • Individuals heterozygotes for rs1126477 (AG) have decreased fasting triglyceride concentrations than AA homozygotes. Individuals who are G carriers for rs1126478 had lower fasting triglyceride concentrations and higher high density lipoprotein cholesterol • Lactoferrin localizes in brain senile plaques of APP-transgenic mice and its concentration increase with age • Homozygous mice show increased susceptibility to inflammation-induced colorectal dysplasia along with increased cell proliferation and decreased apoptosis in colonic tissues. • Enteric lactoferrin inhibit 	<ul style="list-style-type: none"> • (Carro et al., 2017; Choi et al., 2011; Fallahi et al., 2013; Li et al., 2017d; Maekawa et al., 2017; Mayeur et al., 2016; Moreno-Navarrete et al., 2008; Morishita et al., 2016; Oh et al., 2004; Park et al., 2017; Park et al., 2013; Rasheed et al., 2016; Santos-Silva et al., 2002; Stanczyk et al., 2005; Vengen et al., 2010; Wang et al., 2010; Yu et al., 2013)

effects by inhibiting
angiogenesis in a colon
tumour model.

the hypercholesterolemia and
atherosclerosis in
microminipigs with a high-
fat and high-cholesterol diet.

Table 8 Biomarker prioritization

Scoring of selected biomarkers based on links to inflammation (Infl), mitochondria (Mito), apoptosis (Apop), fibrosis (Fibr), proliferation (Prolif), stress response (Stre), cellular senescence (Senes), proteasome signaling (Prot) and tissue distribution (Tiss). Each score represents the the sum of the “+”. “++”: strong evidence, “+”: ome evidence, “-”: no evidence. A total of 18 points could be reached and the following priorities were assigned: ≥ 12 (high: priority 1), 6-12 (medium: priority 2), < 6 (low: priority 3).

Pathway	Marker	INFL	MITO	APOP	FIBR	PROLIF	STRESS	SENES	PROT	TISS	Score	Priority
Inflammation	IL-6	++	++	++	++	++	-	++	-	++	14	1
	CXCL10	++	+	++	+	++	-	++	+	+	12	1
	CX3CL1	++	++	++	++	++	-	+	-	+	12	1
	Pentraxin	++	-	-	++	++	-	-	-	++	8	2
	sVCAM/sICAM	++	-	-	-	+	+	++	-	++	8	2
	Defensin	++	-	++	-	-	+	-	+	++	8	2
	CD14	++	+	-	-	-	-	-	-	+	4	3
Mitochondria & Apoptosis	GDF15	++	++	++	++	-	++	+	-	++	13	1
	FNDC5	++	++	++	+	-	++	+	-	++	12	1
	Vimentin	++	++	+	+	+	+	+	+	++	12	1
	LDH	+	++	+	+	+	+	+	-	++	10	2
	APP	++	++	+	-	+	-	+	+	+	9	2
Calcium homeostasis	Regucalcin	+	++	++	++	+	+	++	-	++	13	1
	Calreticulin	+	+	++	+	++	++	++	-	++	13	1
	S100B	+	+	+	+	+	+	+	+	++	10	2
Fibrosis	AGT	++	++	++	+	+	+	+	-	++	12	1
	PLAU	++	++	++	+	+	-	+	++	+	12	1
	TGF β	+	+	-	++	+	+	++	-	++	10	2
	PAI-1	-	-	++	++	+	+	++	-	++	10	2
	TGM2	++	-	-	++	+	-	-	-	++	7	2
	MMP7	+	-	-	++	-	-	-	-	++	5	3
	THBS	-	-	-	++	-	-	-	-	++	4	3
	NMJ & Neurons	Progranulin	++	++	+	+	++	+	-	++	++	13
BDNF		++	+	++	-	+	++	+	++	+	12	1
Agrin		++	+	+	++	+	-	-	+	++	10	2
C3/C1q		++	+	++	-	+	-	+	-	++	9	2
sRAGE		++	+	+	-	+	+	-	+	-	7	2
HMGB1		++	+	+	-	-	-	++	-	+	7	2
ST2		++	-	-	++	++	-	-	-	+	7	2
Cytoskeleton		FGF21	++	++	++	++	+	++	+	-	++	14
	α -Klotho	++	+	++	++	++	-	++	-	++	13	1

& hormones	FGF23	++	+	++	++	++	-	++	-	++	13	1
	Leptin	++	++	++	+	++	+	+	-	+	12	1
	Ghrelin	+	++	++	+	++	-	-	++	+	11	2
	IGF-1	++	++	-	-	+	-	++	+	++	10	2
	GH	+	+	+	-	++	+	-	-	++	8	2
	Resistin	++	++	++	-	+	-	-	-	+	8	2
	Adiponectin	++	+	++	-	+	-	-	+	+	8	2
Other principles	miRNA panel*	++	++	++	++	++	++	++	++	++	18	1
	AHCY	++	++	+	++	+	+	+	+	++	13	1
	KRT18	+	++	++	++	-	++	+	-	++	12	1
	Microparticle panel*	++	+	++	++	-	+	+	-	++	11	2
	Lactoferrin	++	++	+	+	+	+	+	+	+	11	2
	GpnMB	++	-	+	++	+	+	+	-	++	10	2

* Panel needs further definition

Figure Legends

Figure 1 – Literature overview for the terms frailty and biomarkers. Timeline of publication mentioning biomarkers, frailty or biomarkers and frailty together. The graph presents the first publication(s) for each term and for both terms together, the number of publications (Y axis) per year (X axis) and the total number of publications until 2017.

Figure 2 - Research strategy and approach. (1) The Initial step of this research was a database search for genes regulated in aging or age-related diseases. (2) Genes were then limited to secreted factors, factors measurable in body fluids and factors previously used as biomarkers.(3) Selected markers were assigned to “hallmark of aging” pathways or other principles and (4) an extensive literature search was performed for each selected marker.

Figure 3 - Biomarker stratification according to pathway and priority. Following extensive literature search, we propose a **core** panel of 19 frailty biomarkers (priority 1, inner circle), as well as an **expanded** panel of 22 biomarkers (priority 2, middle circle). Markers that were not found to correlate significantly with frailty were considered priority 3 biomarkers (outer circle).

Figure 4 - Tissue distribution of priority 1 frailty biomarkers. Biomarker tissue distribution is shown for the **core** panel of markers (adapted from Petryszak , PMID 26481351). Markers are shown in bold in the organ with highest marker expression.

Figure 5 - Concentration ranges for frailty biomarkers in serum/plasma. The graph shows the expected concentration range of the proposed frailty biomarkers in human plasma or serum, according to the literature.











