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Review

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

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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

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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) TGFβ (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 2000 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

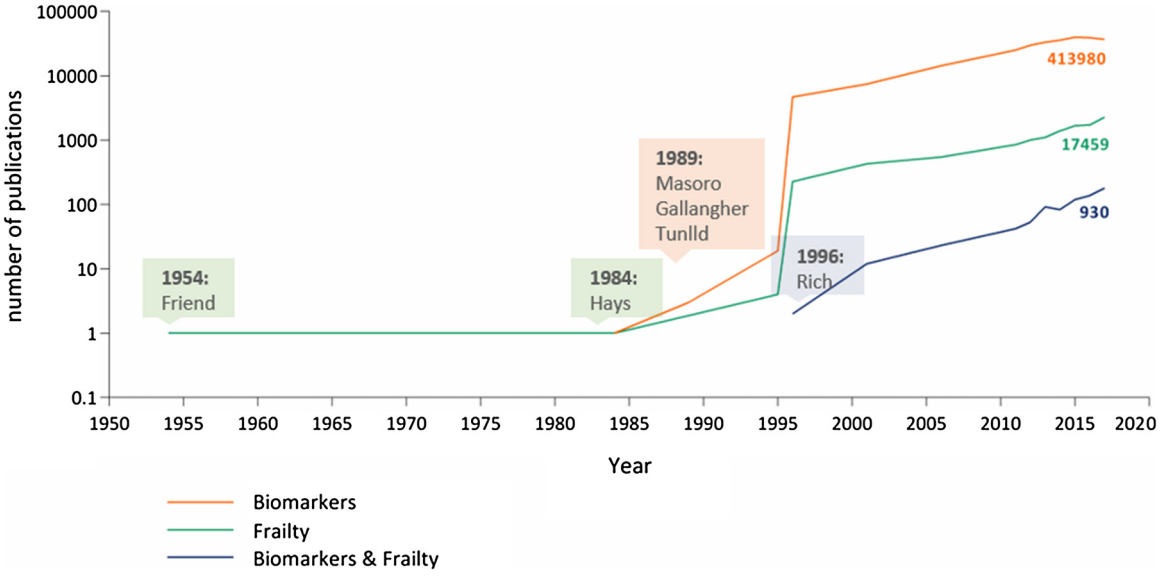

Fig. 1. Literature overview for the terms frailty and biomarkers. Timeline of publication mentioning biomarkers, frailty or biomarkers and frailty together. The graph presents the first publication(s) for each term and for both terms together, the number of publications (Y axis) per year (X axis) and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

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 Fig. 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

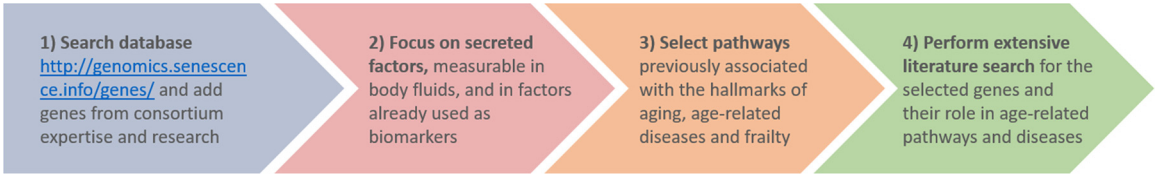

Fig. 2. Research strategy and approach. (1) The Initial step of this research was a database search for genes regulated in aging or age-related diseases. (2) Genes were then limited to secreted factors, factors measurable in body fluids and factors previously used as biomarkers.(3) Selected markers were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

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	• Markers of inflammation	• 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	• 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	• Secukinumab	• (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	• Induced by IFN-γ and infections • SASP component • Decreases mitochondrial activity • Induction of apoptosis • Decreases cell proliferation	• 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	• 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	• Caloric restriction • Resveratrol • Apigenin • Sildenafil • Metformin	• (Antonelli et al., 2006; Bakhashab 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	• Surface antigen preferentially expressed in phagocytes • Mediates innate immune responses to bacterial lipopeptides	• 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	• 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		• (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	• sVCAM1 and sICAM1 are markers for endothelial inflammation • sICAM1 is released from senescent cells by microvesicles.	• 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	• 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.	• sVCAM1↓ with exercise (aerobic and anaerobic) in overweight women • sICAM1↓ with 4-week dark chocolate in overweight men	• (Constans and Conri, 2006)
CX3CL1	• 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	• 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	• 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 less susceptible to cerebral ischemia-reperfusion injury.	• Rheumavax • Baicalin • Cyclophosphamide • Remifentanil • AMD3100 • Glucocorticoids • Aspirin	• (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., 2015; Shiraishi et al., 2000)

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Table 1 (*continued*)

Markers	Hallmark of aging pathways	Age/ Age-related Diseases	Genetics	Intervention	Literature
	• CX3CR1 defines peripheral blood cytotoxic effector lymphocytes and is a direct target of p53 • 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.	• 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 taupathies		• Resveratrol • Vincristine • Etanercept	
Pentraxin	• 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.	• 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	• Homozygous mutant mice display female subfertility and are susceptible to invasive pulmonary aspergillosis and impaired induction of adaptive type 2 responses.	• Tunicamycin • Exercise • LPS	• (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, 2015c; Dogan et al., 2017; Dufek et al., 2015; Haider et al., 2017; Kim et al., 2017e; Kwan et al., 2013; Marmary 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
• GDF15	• 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	• 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	• Genetic deletion of GDF15 augments renal damage in both type 1 and type 2 models of diabetes	• Monoclonal GDF15 antibody and therapeutic protein • Metformin • Sulidinac (NSAIDS) • Pyruvate • Biphosphonate • Danusertib	• (Andersson et al., 2016, 2015; Barma et al., 2017; Bidadkosh 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, 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, g; Lok et al., 2012; Maetzler et al., 2016; Mazagova et al., 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; Schernthaner 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, c; Wiklund et al., 2010; Windrichova et al., 2017; Wu et al., 2016c; Yang et al., 2003, 2010; Yao et al., 2017; You et al., 2017; Zhou et al., 2015c)
FNDC5	• General anti-inflammatory action • Promotes mitochondrial biogenesis and mitochondrial function under hypoxia • Predicts telomere length in healthy adults • Inhibits apoptosis	• 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	• 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	• Physical exercise • Healthy diet • Antihypertensive drugs & Sindenafil • Metformin	• (Anastasilakis 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 al., 2015b; Li et al., 2017a, b; 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)
Vimentin	• Induced by TGFβ1 and TNFα • Cleaved and activated by calpain • Osteopontin increases vimentin stability	• Marker for prognosis and diagnosis for idiopathic pulmonary fibrosis • Anti-mutated citrullinated vimentin is detected rheumatoid arthritis patients.	• Vimentin null mice have altered cell migration, angiogenesis and expression of adhesion molecules	• Ellagic aicd (EA) • Certican and Neoral	• (Bhattacharya et al., 2009, Bonotti et2017; 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.,

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Table 2 (*continued*)

Markers	Hallmark of aging Pathways	Age/ Age-related Diseases	Genetics	Intervention	Literature
	• 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	• 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	• Vimentin null mice show altered arterial remodelling • Phosphovimentin deficient mice develops premature skin aging		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	• 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	• 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	• Depletion of APP causes G0 arrest in non-small cell lung cancer cells.	• **Liraglutide** • **NB-360** • **Lanabecestat**	• (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	• 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 critical role in preventing cell viability defects by promoting intracellular redox homeostasis.	• 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.	• 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 alter lactic acid production, glycolytic activity, ATP or survival. • Suppression of LDHA compromises tumour progression	• **Oxamate** • **Stripentol and analogues**	• (Allison et al., 2014; Arseneault et al., 2013; Chen et al., 2016b; Jung et al., 2015b; Li et al., 2016b, e; 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; 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	• Increased in inflammation • Contributes to cancer progression by downregulating p53 • Involved in survival and cell proliferation	• 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	• S100B-deficient mice have normal development of the cerebellum and no severe impairment of motor function	• **Pentamidine** • **Arundic acid** • **Anti-S100B**	• (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, 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	• 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 the hearts of rats with increasing age.	• 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 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.	• Regucalcin-deficient mice induced a shorter lifespan and redox changes. • Transgenic rats have been found to induce hyperlipidaemia with increasing age	• **1,1-diphenyl-2-picryl-hydrazyl** • **Tert-butyl hydroperoxide and cadmium chloride** • **17β-Estradiol** • **Doxorubicin** • **Exogenous Ca2+** • **Phenobarbital** • **EUK4010**	• (Akhter et al., 2007, 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, 2013b, 2014a, 2014b, 2014c; Yamaguchi and Murata, 2015)
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 recognised 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 metastasis and was an	• 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, h; Yao et al., 2013; Zamanian et al., 2016)

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Markers	Hallmark of aging Pathways	Age/ Age-related Diseases	Genetics	Intervention	Literature
	• Caloric restriction helps to maintain expression of neuroprotective factor calreticulin in hippocampal CA1 region of older-adult mice.	independent adverse prognostic indicator in patients with pancreatic or lung cancer.			

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-1α (interleukin 1 alpha), IL-1β (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 TGFβ 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 NFκB (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

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	• 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	• PAI-1 may play a critical role in the development of aging-associated pathological changes. In addition, PAI-1 is recognised 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	• 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.	• **TM5441, a potent small molecule inhibitor of PAI-1, effectively prevents Doxorubicin-induced senescence in cardiomyocytes, fibroblasts and endothelial cells.**	• (Ghosh et al., 2016; Khan et al., 2017; Koh et al., 2005; Simone et al., 2014b; Yamamoto et al., 2014a)
TGFβ	• TGFβ1 is a secreted protein that performs many cellular functions, including the control of cell growth, cell proliferation, cell differentiation and apoptosis.	• 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.	• TGFβ1 knockout mice are able to survive only until 3–4 weeks of age. They are characterised by inflammatory infiltrates in multiple organs leading to a wasting syndrome and death as early as 3 weeks after birth.	• **LY2109761 is an inhibitor of TGFβs but has not been tested for aging –related diseases**	• (Geiser et al., 1993; Krieglstein et al., 2012)
MMP7	• Mediates the cleavage of ECM and basement membrane proteins such as fibronectin, collagen type IV, and laminin • Increased MMP7 associated with extensive tissue remodelling and organ dysfunction, particularly in urinary and respiratory pathologies	• Increased plasma and urine levels in renal fibrosis • Increased levels in plasma and sputum of idiopathic pulmonary fibrosis patients. • Elevated MMP7 expression in tumours and metastasis, associated with ECM remodelling, epithelial-mesenchymal transition, and invasion and proliferation. • 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.	• MMP7 knockout have impaired innate host defence response, are more susceptible to bacterial infection of the small intestine mucosal epithelium, defective wound repair (reepithelialisation) and reduced apoptosis in prostrate and pancreatic tissue.	• **Tamoxifen alone and/or 5-FU downregulate MMP7 expression in colon cancer cells with high metastatic potential**	• (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., 2015; Ye, 2006; Zhang et al., 2017a)
PLAU	• Expressed and secreted from senescent cells and controls cell proliferation • Overproduction of uPA in brain reduced food consumption and increased longevity	• Linked to the pathogenesis of late onset Alzheimer Disease • Increased by complication in diabetes patients	• Genetic association with sporadic Alzheimer´s Diseases. • Transgenic model for longevity induced by caloric restriction.	• **induced by chemotherapy in cancer cells↑** • **Biomarker for breast cancer.** • **Tissue injury ↑**	• (Lampelj et al., 2015; Miskin et al., 2005)
TGM2	• 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	• 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.	• TGM2 knockout show defects in glucose tolerance, on phagocytosis-associated crosstalk between macrophages and apoptotic cells and in function of mitochondrial respiratory complex I.	• **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)

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Markers	Hallmark of aging Pathways	Age/ Age-related Diseases	Genetics	Intervention	Literature
	• Promotes survival, by promoting the anchorage to ECM, protecting from anoikis.	• Dysregulation of TGM2 found in many neurodegenerative disorders, including Huntington's disease, Alzheimer disease, Parkinson disease and amyotrophic lateral sclerosis, as well as in stroke.			
THBS2	• 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	• 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.	• 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.	• **Cyclophosphamide increases the circulating levels of THBS1, but not THBS2**	• (Charytan et al., 2014; Daniel et al., 2007, 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	• 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 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-PGC1α signalling.	• 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 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.	• AGT-knockout present low systolic blood pressure and low survivability • AGT duplication is characterised by elevated blood pressure	• **Captopril** • **Enalapril** • **Perindopril** • **Losartan** • **Xanthenone** • **Diminazene aceturate** • **And several others**	• (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)

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	• Induced in inflammation • Potentiates macrophage response to LPS • Modulates T cell function and differentiation	• 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	• Knockout animals display an abnormal Th2 type inflammatory response and abnormal response to infection.	• **Corticosteroids** • **Disease-modifying antirheumatic drugs**	• (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	• 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	• 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	• Knockout animals present postnatal lethality, sensory neuron losses, cerebellar abnormalities and increased sympathetic neuron number	• **Exercise** • **Cerebrolysin** • **Estradiol** • **Metformin**	• (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; Nikoletopoulou 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, a; Wu et al., 2012; Yoo et al., 2011)
Agrin	• Secreted neuroprotein that stabilizes neuromuscular junction via MusK/Lrp4 by clustering acetylcholine 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 TGFβ family proteins and beta-amyloids	• Associated with neuromuscular disorders, diabetes, cardiovascular diseases, kidney function and 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	• Mutations and antibodies cause myasthenia gravis (MG) • Loss of synapses in agrin-deficient mice • Defective eye development in agrin-overexpressing mice	• **Engineered agrin for neuromuscular diseases such as MG (e.g. NT-1654)** • **Overexpression of mini-agrin in congenital muscular dystrophy**	• (Arampatzis et al., 2017; Banyai et al., 2010; Barber and Lieth, 1997; Bentzinger et al., 2005; Berzin et al., 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, 2018; Falo et al., 2008; Fragala et al., 2014; Fuerst et al., 2007; Gautam et al., 1999, 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, 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, 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.,

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Markers	Hallmark of aging Pathways	Age/ Age-related Diseases	Genetics	Intervention	Literature
					2007; Rimer, 1998; Romi et al., 2008; Rudolf et al., 2014; Ruegg and Bixby, 1998; Sanes et al., 1998a, b; 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, 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., 2001; Yu et al., 2017b; Zhang et al., 2008)
Progranulin	• 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	• 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	• 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	• **SAHA** • **Chloroquine** • **Selumetinib** • **MEK162** • **trehalose**	• (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	• Are involved in the recognition and tagging for degradation of designated antigens • C1q activation induces the production of C3 and consequent enhancement of anaphylatoxin, which are potent pro-inflammatory mediators • 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	• C1q plasma and brain levels increased in aging • Brain C1q increased in Alzheimer disease, Frontotemporal lobar degeneration, temporal lobe dementia and, amyotrophic lateral sclerosis • 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	• C1qa knockout exhibit behaviour and neurological abnormalities with phenotypes linked to epilepsy, glomerulonephritis, increased numbers of glomerular apoptotic bodies, high antibody titres and increased mortality • 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	• **C1 – Pioglitazone** • **C3 – Eculizumab** • **C3 – pLTA** • **C3 - Lithium**	• (Aronica et al., 2007; Bahrini et al., 2015; Baudino et al., 2014; Corigliano et al., 2017; 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, 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.,

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Markers	Hallmark of aging Pathways	Age/ Age-related Diseases	Genetics	Intervention	Literature
		• 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			2015; Wyatt et al., 2013; Yu et al., 2015)
sRAGE	• 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 damage • 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	• 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 • 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	• 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-induced angiogenic responses	• **Metformin** • **4,6-bis(4-chlorophenyl) pyrimidine analogue** • **PF-04494700**	• (Antonelli et al., 2017; Aubert et al., 2014; Bakker et al., 2015; El-Saeed et al., 2015; Guo et al., 2012, 2016; Haddad et al., 2016; Jiang et al., 2015b; Juranek et al., 2016; Mayer et al., 2016; Sabbagh et al., 2011; Wang et al., 2015b; Wu et al., 2016d; Xu et al., 2017d)
HMGB1	• Triggers and amplifies inflammatory cascade • Critical regulator of mitochondrial function • Activates the FAK/PI3K/mTOR signalling cascade to promote cancer cell proliferation/migration	• 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	• Knockout mice die within 24 h because of the inability to use the glycogen stored in the liver	• **Metformin** • **Anti-HMGB1**	• (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)

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	• 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	• 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	• 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.	• **CR** • **Exercise** • **Diet** • **GH replacement** • **Somatropin, Clonidine, L-Arginin-Hydrochloride, Estradiol valerate** • **Omega-3** • **recombinant human IGF-1**	• (Bartke et al., 2013; Brioche 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	• Cell proliferation, • Cell differentiation • Cell death • Cellular Senescence • Immune system process, • Inflammation • Mitochondrial dysfunction • Lipid metabolic process, • Protein metabolic process,	• 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 regulating hematopoietic stem cell protection, self-renewal, and regeneration. • Lacking of encoded protein in mice shows generalised 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.	• 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. • 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	• **CR** • **Exercise** • **Diet** • **Growth Hormone** • **Somatropin, Clonidine, L-Arginin-Hydrochloride, Estradiol valerate** • **Omega-3** • **Nutropin [Somatropin (rDNA origin) for injection]** • **recombinant human IGF-1** • **Orlistat**	• (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-Guerra et al., 2017; Handayaningsih et al., 2012; Lara-Díaz 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)
α-klotho	• 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	• 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	• 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	• **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**	• (Bartali et al., 2013; Diener et al., 2015; Kuro-o et al., 1997; Xu and Sun, 2015)

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Markers	Hallmark of aging Pathways	Age/ Age-related Diseases	Genetics	Intervention	Literature
	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.	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 Protein.	second allele abnormal cancellous bone and femur morphology are seen.	**α-Klotho induced anti-aging needs to be further studied**	
FGF23	• 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	• Elevated in various kidney and cardiovascular diseases • Also associated with aging, liver diseases, CNS disorders, osteoporosis, RA, diabetes, • Can predict death and mortality	• Human FGF23 mutations linked to Tumoral Calcinosis (loss of function) and hypophosphataemic rickets (gain of function)	• **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, 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, a; Lu 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)
FGF21	• Pleiotropic action as hepatokine, adipokine, mitokine, myokine and neuroendocrine • Regulated by Inflammation, fibrosis, alcohol, vitamin D, glucose, ER, starvation or fasting	• 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	• FGF21-deletion aggregates diabetes-induced and other diseases	• **Long-acting and engineered variants as therapeutics in heart and metabolic diseases** • **Induced by metformin intervention**	• (Anuwatmatee et al., 2018, 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, 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;

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Markers	Hallmark of aging Pathways	Age/ Age-related Diseases	Genetics	Intervention	Literature
					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, a; 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, 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, 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, 2013; Wu et al., 2017b, 2015; Xiao et al., 2012; Yan et al., 2011, 2015; Ye et al., 2016a, 2014; Ye et al., 2017a; Zagarskikh et al., 2018; Zhang et al., 2015c, 2012)
Resistin	• Inflammation • Cell proliferation • Apoptosis • Reduced mitochondrial content • reduced brown adipose tissue activity	• 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.	• Homozygous null mice display impaired gluconeogenesis, lower fasting blood glucose levels, and a weaker positive correlation between body weight and blood glucose.	• **No interventions known**	• (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, 2014; Wen et al., 2015b; Zhou et al., 2013; Zuniga et al., 2017)
Adiponectin	• Biomarker of inflammation • Reduces inflammation • Reduces MMP-9 levels, eNOS, IL-10, gene expression of TNF-α, IL-6, sVCAM1 and inhibited the	• Total adiponectin levels were not changed with aging • Osteoarthritis/rheumatoid arthritis • Low plasma adiponectin levels are biomarker for metabolic syndrome	• Adiponectin knockout mice showed hepatic steatosis and mitochondrial dysfunction • Adiponectin knockout mice developed hearing impairment	• **ApoE(-/-) mice** • **Thiazolidinediones: PPARgamma agonists upregulates Circulating adiponectin levels**	• (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., 2006; Fujishima

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Markers	Hallmark of aging Pathways	Age/ Age-related Diseases	Genetics	Intervention	Literature
	activation of NFκB pathway and the expression of NFκB nuclear protein p65 • Insulin resistance • Apoptosis of different cancer cells • Exosome marker	• 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	• Adiponectin knockout had increased beta-oxidation in muscle and liver tissue	• **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**	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)
Leptin	• 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	• 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 • Serum leptin level increases with aging • Leptin stimulates bone formation in leptin deficient mice • Brain diseases with different effect • Cardiovascular diseases	• 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 efficiency, impaired thermogenesis, infertility and • Homozygous mutants exhibit short lifespan, impaired wound healing and elevated plasma insulin. • Hypometabolic and hypothermic. Obesity in these mice characterised by an increase in both adipocyte size and number. • Strain background affects severity and course of diabetes.	• **Leptin** • **Aripiprazole** • **Irbesartan** • **Amlodipine** • **Leuprolide Acetate** • **Sandostatin LAR** • **Metformin** • **CR/Diet** • **Aging** • **Exercise**	• (Chai et al., 2015; Dogan et al., 2017, 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)
Ghrelin	• 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.	• 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.	• Longevity is not affected by ghrelin deletion, but ghrelin administration to WT or Ghrelin KO mice increases food intake, body weight and strength.	• **Anamorelin** • **Capromorelin** • **MK-677** • **Ghrelin**	(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)

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Markers	Hallmark of aging Pathways	Age/ Age-related Diseases	Genetics	Intervention	Literature
	• Increases the expression of cell cycle proteins cyclins D1 and E and CDK2.	• 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-alcoholic fat-liver disease			

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 taupathies (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 4000 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

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	• 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.	• 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	• n/a	• **Exercise** • **Rapamycin, doxorubicin and other chemotherapeutics** • **Antiangiogenic** • **Metformin** • **Surgery** • **HGMB1** • **Corticoids and anti-TNFα** • **Vitamin D** • **Clopidogrel** • **MMP inhibitors** • **Statins** • **Resveratrol**	• (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, b; Weilner et al., 2013; Witwer, 2015; Zhang et al., 2015b, b; Zhou et al., 2015b); Ipson et al. 2018, ahead of print in JFA
AHCY	• HC activates inflammasome and inflammatory pathways including NFκB • HC induces oxidative, ER stress, mitochondrial dysfunction and apoptosis • HC accelerates senescence	• 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	• 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.	• **Alpha-lipoic acid** • **Salidroside** • **Folate, vitamin B6, vitamin B12** • **Eritadenine** • **3-Deazaneplanocin A** • **9-(2-deoxy-2-fluoro-β,D-arabinofuranosyl) adenine**	• (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.,

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Markers	Hallmark of aging Pathways	Age/ Age-related Diseases	Genetics	Intervention	Literature
					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)
Microparticles	• 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 activation, cell adhesion, and inflammation. • 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.	• 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 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??. • Higher levels of microparticles derived from platelets, leukocytes or endothelium were detected in the plasma of type 2 diabetes patients.	• N/A		• (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)
KRT18	• 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	• 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	• 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	• **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	• GpnmB has anti-inflammatory and reparative functions, and was shown to be neuroprotective • Highly expressed in macrophages of acute injured kidney and	• Emerging role in neurodegenerative disease. • Neuroprotective in animal model of amyotrophic lateral sclerosis, cerebral ischemia, and other disease models.	• Homozygous mutants exhibit dispersed pigmentation of the iris, deterioration of the posterior iris epithelium and s transillumination defects and contributes to glaucoma	• **Glembatumumab**	• (Budge et al., 2017; Jiang et al., 2011; Maric et al., 2013; Murthy et al., 2017; Noda et al., 2017; Taya

(*continued on next page*)

Table 7 (*continued*)

Markers	Hallmark of aging Pathways	Age/ Age-related Diseases	Genetics	Intervention	Literature
	promotes M2 macrophages polarization. • Regulates the crosstalk between Macrophages and mesenchymal stem cells toward Wound Repair. • Induced in ER stress	• 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			and Hammes, 2018; Yardley et al., 2015; Yu et al., 2018; Zhou et al., 2017)
Lactoferrin	• 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	• Anti-arthritic 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 effects by inhibiting angiogenesis in a colon tumour model.	• 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 the hypercholesterolemia and atherosclerosis in microminipigs with a high-fat and high-cholesterol diet.	• **Aspirin** • **RMP-7-Lf-QU-LS** • **Lf-mNLC** • **LF-derived peptides** • **AEC-CP-Fe-bLf-NC**	• (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)

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 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
	TGFβ	+	+	–	++	+	+	++	–	++	10	2
	PAI-1	–	–	++	++	+	+	++	–	++	10	2
	TGM2	++	–	–	++	+	–	–	–	++	7	2
	MMP7	+	–	–	++	–	–	–	–	++	5	3
	THBS	–	–	–	++	–	–	–	–	++	4	3
NMJ & Neurons	Progranulin	++	++	+	+	++	+	–	++	++	13	1
	BDNF	++	+	++	–	+	++	+	++	+	12	1
	Agrin	++	+	+	++	+	–	–	+	++	10	2
	C3/C1q	++	+	++	–	+	–	+	–	++	9	2
	sRAGE	++	+	+	–	+	+	–	+	–	7	2
	HMGB1	++	+	+	–	–	–	++	–	+	7	2
	ST2	++	–	–	++	++	–	–	–	+	7	2
Cytoskeleton & hormones	FGF21	++	++	++	++	+	++	+	–	++	14	1
	α-Klotho	++	+	++	++	++	–	++	–	++	13	1
	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[a]	++	++	++	++	++	++	++	++	++	18	1
	AHCY	++	++	+	++	+	+	+	+	++	13	1
	KRT18	+	++	++	++	–	++	+	–	++	12	1
	Microparticle panel[a]	++	+	++	++	–	+	+	–	++	11	2
	Lactoferrin	++	++	+	+	+	+	+	+	+	11	2
	GpnmB	++	–	+	++	+	+	+	–	++	10	2

[a] Panel needs further definition.

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 (Aygun 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

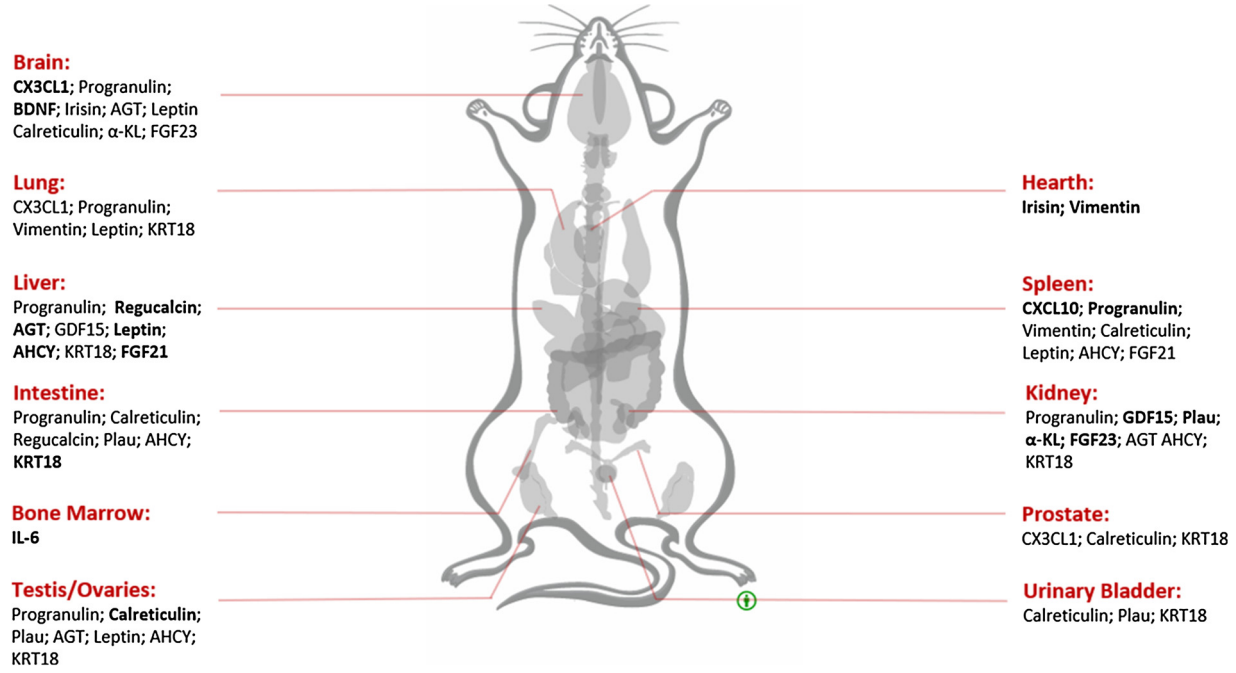

Fig. 3. Biomarker stratification according to pathway and priority. Following extensive literature search, we propose a ***core*** panel of 19 frailty biomarkers (priority 1, inner circle), as well as an ***expanded*** panel of 22 biomarkers (priority 2, middle circle). Markers that were not found to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

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 IFNγ- 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 NFκB 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

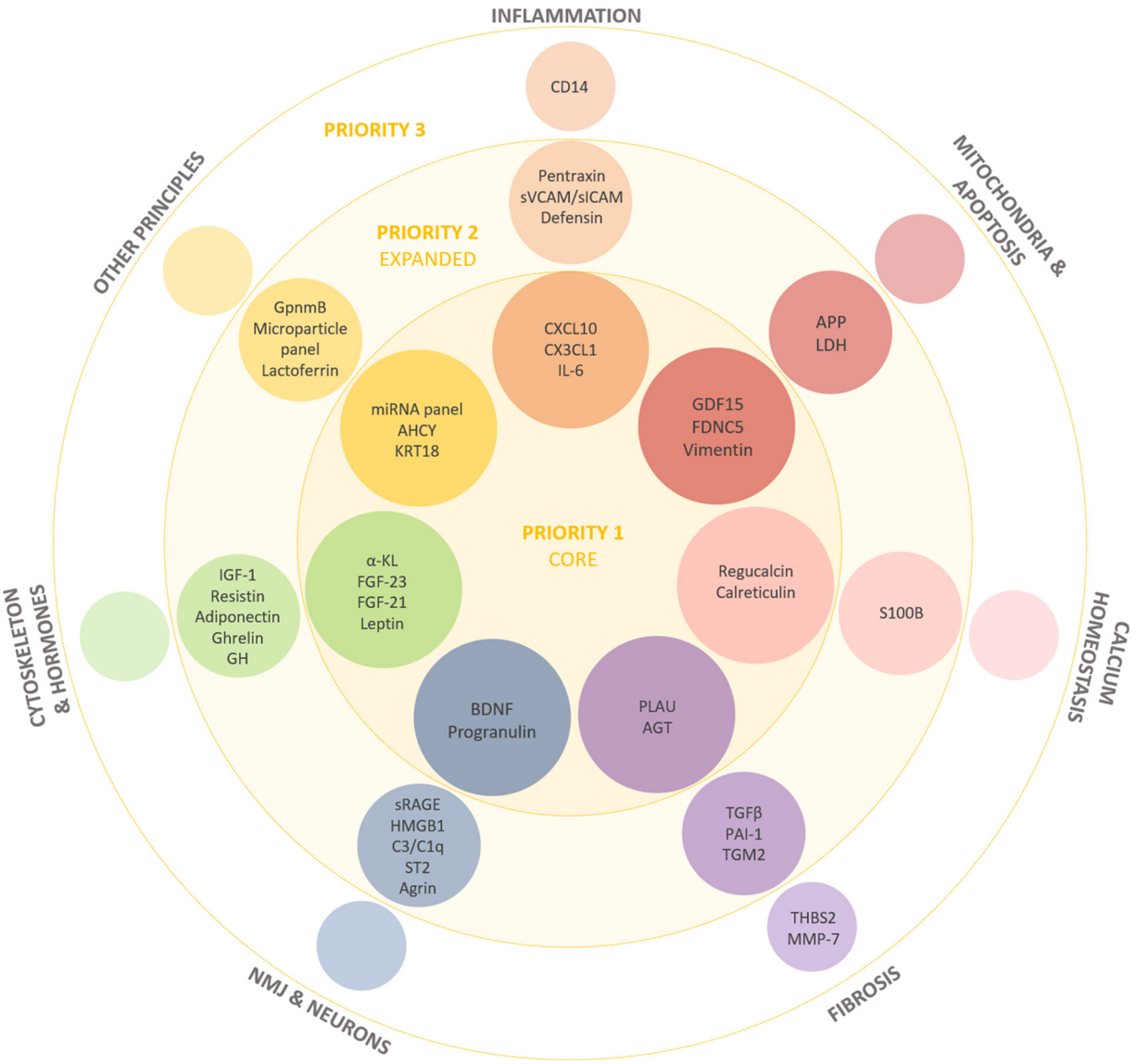

Fig. 4. Tissue distribution of priority 1 frailty biomarkers. Biomarker tissue distribution is shown for the ***core*** panel of markers (adapted from Petryszak, PMID 26481351). Markers are shown in bold in the organ with highest marker expression.

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;

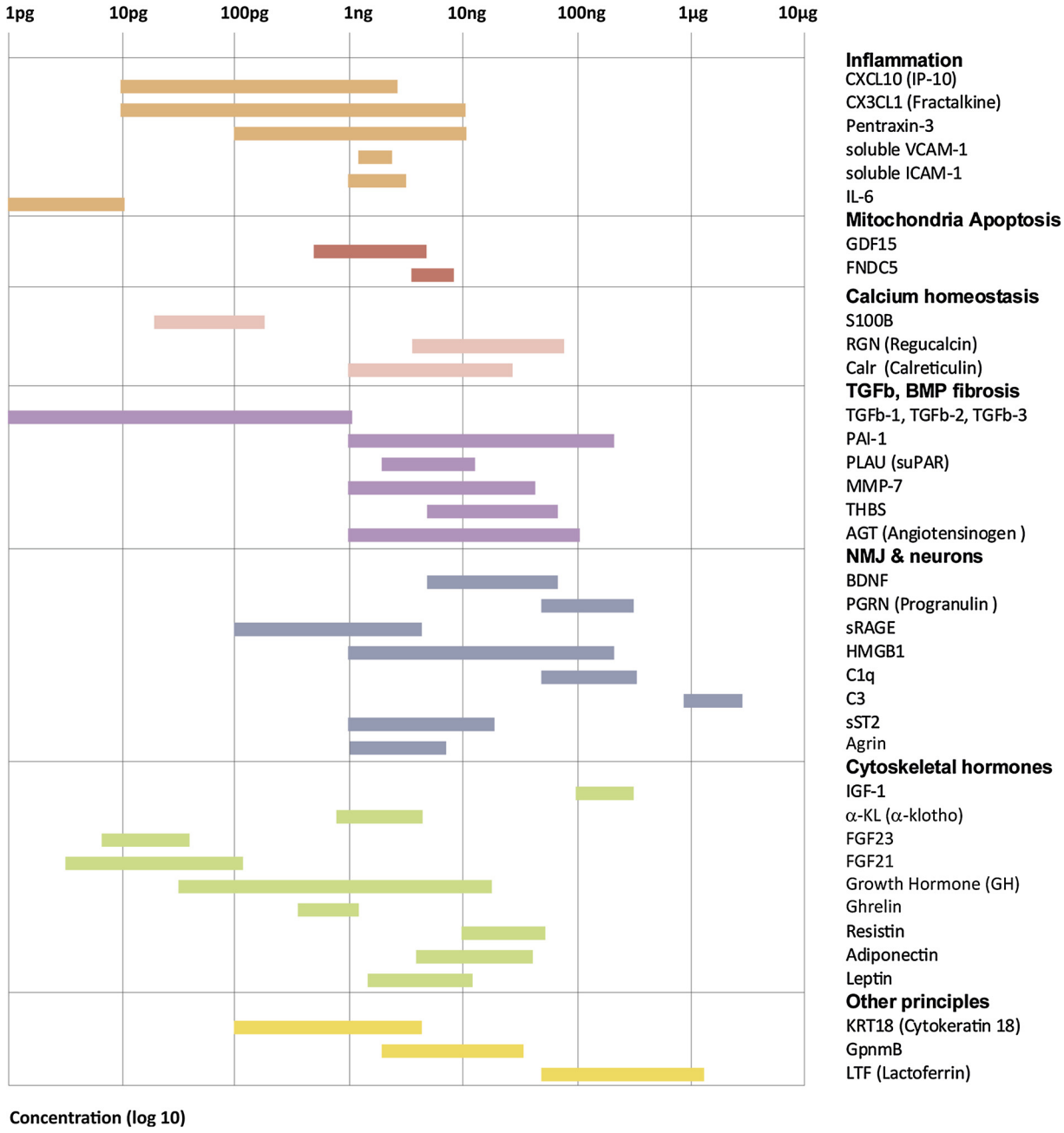

Fig. 5. Concentration ranges for frailty biomarkers in serum/plasma. The graph shows the expected concentration range of the proposed frailty biomarkers in human plasma or serum, according to the literature.

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 O2 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 TGFβ 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 (Petrache 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. Aβ40 and Aβ42) 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, (McClean 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, NFκB).

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 Ca2+-ATPase activity in heart, brain, and liver mitochondria (Akhter et al., 2006; Takahashi and Yamaguchi, 2000; Yamaguchi et al., 2008), but inhibits microsomal Ca2+-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,b). 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 Aβ42-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 Ca2+-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 inhibit 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(G93 A). In the latter, background knockout of calreticulin further increased onset and degree of muscle weakness and denervation compared to control SOD1(G93 A) (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 TNFα-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), TGFβ, BMPs (bone morphogenic proteins), chemokines such as MCP-1 (monocyte chemoattractant protein 1) and MIP-1β (macrophage inflammatory protein-1β) 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 TGFβ pathway, which is activated by a variety of molecules such as the three TGFβ isoforms (TGFβ1, TGFβ2, and TGFβ3), 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 TGFβ, activin and BMP receptors and, mainly canonical SMAD signalling. The TGFβ pathway is important for many processes starting early after embryonic development, but also later in life and is therefore an interesting source for biomarkers of aging and particularly frailty. So not surprisingly, several TGFβ 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 (TGFβ1, TGFβ2, and TGFβ3). All TGFβ 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. TGFβ1 is the main endocrine isoform (Zhao et al., 2017a), whereas TGFβ2 and TGFβ3 have mainly para- and autocrine function (Rodon et al., 2014; Van Themsche et al., 2010).

Higher concentrations of TGFβ 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 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, 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 TGFβ 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 TGFβ1 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 TGFβ 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 (Afaloniati 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 antithromboembolic 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 among 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 TGFβ 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 β1 and β3 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 TGFβ 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 TGFβ 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 TGFβ 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 profibrotic 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 TGFβ 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 (TGFβ, 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 show to interfere with Aβ 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, 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).

Proganulin (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, HMBG1 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 Sjoergren'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 prohormones 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, 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 domaine (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, d; 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 supplemention, 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 (Akhabue 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 mechanims. 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, cardioavascular, ocular, and liver disorders as well as osteoarthritis, rheumatoid arthritis and cancer. Interestingly, many pathologies are aggrevated 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, 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, a; 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, 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, 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, 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 NFκB 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, 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 μm) 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 TGFβ1. 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) PLAU, 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) TGFβ, 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 A. Supplementary data

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