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PERSPECTIVE

Pathway to Independence: a forecast for the future of developmental biology

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ABSTRACT

In 2022, Development launched its Pathway to Independence (PI) programme, aimed at supporting postdocs as they transition to their first independent position. In 2025, we welcome our third cohort of eight talented PI fellows. In this article, each fellow discusses their perspective on the future of their field and how their work will contribute to this exciting new era.

Small but mighty: how small RNAs shape phenotypic plasticity

Chee Kiang Ewe

Caterpillars of the moth *Nemoria arizonaria* hatching in spring look like young oak flowers, whereas those that hatch in summer resemble fresh twigs, allowing them to blend seamlessly into their environments and evade predators; the water flea (*Daphnia spp.*) develops a protective helmet in response to predator kairomones; the Mexican cavefish lacks eyes and pigmentation, along with exhibiting metabolic changes compared to its river-dwelling relatives, enabling adaptation to life in darkness. These are only a few of the countless examples of developmental plasticity. How do organisms sense, respond and ultimately adapt to their environments to survive? Non-coding small RNAs (sRNAs) involved in RNA interference (RNAi) are excellent candidates for environmentally induced developmental switches that drive phenotypic plasticity.

At the heart of RNAi are Argonaute proteins (AGOs), which are highly conserved across all domains of life. Non-coding sRNAs, coupled with AGOs, form the RNAi-induced silencing complex, which can drive rapid and precise gene expression change. In many cases, sRNAs guide AGOs to complementary mRNAs, targeting them for post-transcriptional gene silencing (Swarts et al., 2014; Wu et al., 2020). Despite intense efforts to understand the mechanisms of RNAi since its discovery in plants and *Caenorhabditis elegans* in the 1990s, we seem to have only glimpsed the tip of a very large RNAi iceberg. How do AGOs select their targets, and how does this selection change across different cellular contexts? How do sRNA/AGO regulatory outputs change in response to environmental triggers? What are the roles of sRNA/AGO in environmental adaptation and evolution?

AGOs target different genetic elements, such as transposons, pseudogenes and protein-coding genes, and exhibit distinct target repertoires (Seroussi et al., 2023). How different sRNAs are selectively loaded onto the AGOs is not well understood, although the spatial-temporal expression of the AGOs is clearly important (e.g. Chen and Phillips, 2025). Interestingly, in our recent study, we found that the *C. elegans*-specific AGO, SAGO-2, can perform opposing functions, either silencing or activating gene expression, depending on its expression levels. This is regulated by an immunological switch that controls infection by intracellular pathogens such as viruses (Ewe et al., 2025a). How SAGO-2 activates gene expression is currently unknown. One possibility is that SAGO-2 recruits different protein binding partners depending on its abundance, expanding the variety of RNAi gene regulatory outcomes.

Since the discovery of RNAi, it has become clear that regulatory sRNAs can cross cell boundaries and regulate genes through specific base-pairing (Jose, 2015). We recently demonstrated that neuronal sensory inputs can influence the expression and activity of AGOs in a cell-non-autonomous manner, suggesting that the small RNA pathway integrates environmental information via the nervous system. Importantly, these effects appear to be independent of the direct transfer of mobile RNAs and, instead, act through a neuroendocrine-like signalling mechanism (Ewe et al., 2025b preprint; Teichman et al., 2024 preprint). Future studies in my lab will elucidate how the sRNA machinery integrates intrinsic and extrinsic information across tissues to orchestrate complex, systemic gene regulation, thereby advancing our understanding of the molecular basis of genotype-by-environment interactions that give rise to developmental plasticity.

Leveraging the nature of insect neural lineages to explore neural circuit evolution

Max S. Farnworth

Brains are complex structures made up of thousands to billions of cells (Azevedo et al., 2009; Polilov, 2012). Even ∼140,000 neurons in a small brain of the fruit fly *Drosophila melanogaster* form 50 million synaptic connections (Dorkenwald et al., 2024). Neurons construct circuits that interconnect functionally related neurons to facilitate a particular behavioural outcome. Often, generalizable patterns of connected neurons, or motifs, emerge (Braganza and Beck, 2018) that permit us to make sense of the complexity of many of these connections.

However, in insects, another dimension helps organize this complexity into more manageable elements: their brains develop

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through neural lineages. We currently assume that there is a conserved number of ∼100 neural stem cells, or neuroblasts, per hemisphere (Urbach and Technau, 2003). The complete progeny of one of those neuroblasts is a neural lineage (Spindler and Hartenstein, 2010).

Intriguingly, the cell somata of a neuroblast's progeny tend to stay tightly clustered (Spindler and Hartenstein, 2010). I hypothesize that this is because insects have predominantly unipolar neurons (Spindler and Hartenstein, 2010), which potentially evolved out of size constraints – push all the neuronal nuclei to the outside of the brain, and have input and output sites in the centre. Therefore, cell body location, in part, harbours information about genetic and developmental relatedness (Lacin and Truman, 2016; Spindler and Hartenstein, 2010). Moreover, if cell somata form clusters, neurites projecting out from these somata during neurogenesis also start off in proximity and tend to fasciculate into bundles, or lineage-associated tracts (Farnworth et al., 2022; Hartenstein et al., 2015; Ito et al., 2013; Lee, 2017; Schlegel et al., 2024). The DALv2 lineage, for example, forms many neurons, with tightly clustered cell bodies, and distinct neuron types in this lineage with distinct functions (Farnworth et al., 2025; Kandimalla et al., 2023). Consequently, anatomical proximity of neuronal somata and parts of their neurites partially indicates genetic, developmental and functional relatedness (Kandimalla et al., 2023; Schlegel et al., 2024).

Despite its importance, neural lineage identity is underused in neural circuit studies. We now have synapse-level maps of all neuronal connections, or connectomes, in *Drosophila* (Dorkenwald et al., 2024; Scheffer et al., 2020). However, we have only now started to piece together how the information of the *Drosophila* connectome relates to the maps of neural lineages produced years before, with many elements remaining unclear (Kandimalla et al., 2023; Schlegel et al., 2024).

I am ultimately fascinated by how neural circuits evolve. Due to the nature of neural lineages, insects are a very intriguing model system. Widespread and cost-effective single-cell sequencing (Cicconardi et al., 2025; Vandereyken et al., 2023), advances in gene editing (Ahmed et al., 2025; Matsuoka et al., 2025) and accessible ways of creating precise anatomical maps (Sayre et al., 2021; Tavakoli et al., 2025) create permissible technical pathways into many non-model organisms. By determining the genetic and developmental underpinnings of neural circuits and their precise anatomical structure across species, it is time to delve into how neural circuits develop and evolve.

Beyond steady state: why protein expression dynamics matter for development

Anzy Miller

Proteins are not always steadily expressed. Instead, many demonstrate dynamic expression patterns, with repeated peaks and troughs in protein levels over time (oscillations). Perhaps the best-known example are circadian clock proteins, where rhythmic expression creates periodic 24-h cycles (Hastings et al., 2019). Another example is p53 dynamics in response to stresses: γ-irradiation leads to p53 expression oscillations and cell cycle arrest, while UV radiation results in a single, broader pulse of p53 expression, causing apoptosis (Batchelor et al., 2011; Purvis et al., 2012).

Does oscillatory protein expression occur during development? Yes – several research labs have found that many key developmental regulators have dynamic expression observed across tissues and species. For example, NOTCH signalling pathway effectors oscillate during neurogenesis, pancreas development, somitogenesis, myogenesis and intestinal cell differentiation in organisms ranging from mice and humans to zebrafish and chick (Delaune et al., 2012; Diaz-Cuadros et al., 2020; Imayoshi et al., 2013; Manning et al., 2019; Marinopoulou et al., 2021; Matsuda et al., 2020; Miller et al., 2025; Palmeirim et al., 1997; Seymour et al., 2020; Shimojo et al., 2011; Soto et al., 2020; Takashima et al., 2011; Weterings et al., 2024 preprint; Zhang et al., 2021). Beyond NOTCH signalling components, effectors part of the FGF, WNT, HIPPO and TGFβ signalling pathways are also oscillatory in their expression (Aulehla et al., 2003; Matsuda et al., 2020; Niwa et al., 2011). Even transcription factors (TFs) that integrate signals from multiple signalling pathways, such as SOX2 (Fu et al., 2024), have oscillatory expression, illustrating how widespread and pervasive oscillatory expression is in developmental biology.

Why should we care about protein expression dynamics in development? Organ development relies on generating the right cell types at the right time, guided by successive cell-fate decisions, which are controlled by the expression of unique sets of TFs. Therefore, our understanding of development is incomplete without studying TF expression dynamics. Importantly, TF dynamics are functional: I recently showed that NGN3 oscillations control the timing of pancreatic endocrine cell differentiation (Miller et al., 2025), and oscillations can also balance proliferation with differentiation (Imayoshi et al., 2013; Seymour et al., 2020; Shimojo et al., 2008; Zhang et al., 2021) and control stem cell exit from quiescence (Marinopoulou et al., 2021). However, we know little about how these dynamics are decoded and read by the cells to control these functions. Furthermore, oscillations might encode multiple layers of information within a single signal (Levine et al., 2013). We know that the fold-change/amplitude, period and phase of oscillation are functionally important (Dean et al., 2024 preprint; Goentoro and Kirschner, 2009; Miller et al., 2025; Sabherwal et al., 2021; Schröter and Oates, 2010; Sonnen et al., 2018; Weterings et al., 2024 preprint). But what mechanisms allow downstream targets to read these different parts of an oscillation? I have recently shown that the gene regulatory network downstream of NGN3 is important to decode fold-change variation from NGN3 noisy oscillations (Miller et al., 2025). I am excited to explore these mechanisms further to understand how protein expression dynamics impact cell-fate decisions and timing. The future is dynamic!

The future is here: developmental neuroscience in the -omics era

Joaquín Navajas Acedo

How the embryo robustly generates its many cell types remains a fundamental question in biology. This is particularly relevant during nervous system development, where some animals, such as the invertebrates *C. elegans* or *Drosophila*, create cells deterministically using fixed lineages. Others, such as vertebrates, use a non-deterministic way of generating a highly heterogeneous and elaborate cellular architecture with hundreds of cell types with distinct molecular, morphological and physiological properties (Lodato and Arlotta, 2015; Sharma et al., 2020; Holguera and Desplan, 2018; Pollington et al., 2023; Hobert, 2016).

The complex phenotypical diversity observed in vertebrates is a product of an intricate combination of spatial, local and temporal signals, and a hierarchy of transcription factors in progenitors and postmitotic neurons (Di Bella et al., 2024; Sagner and Briscoe, 2019; Lodato and Arlotta, 2015; Roome and Levine, 2023). However, we still lack an integrated and comprehensive single-cell-level view of this process. This is, in part, due to nervous system accessibility in space and time, as well as its size; even the smallest vertebrate brain, in *Danionella cerebrum*, has thousands of neurons

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(Schulze et al., 2018). Furthermore, some biological systems use stochasticity as a feature – not a bug – to generate diversity (Nerli et al., 2023; Miller et al., 2021; He et al., 2012). The problem thus possesses many layers of intricacy: (1) producing diversity at the cellular level; (2) producing diversity at the populational level; and (3) producing diversity robustly at the interindividual level. How does the genome integrate information spatiotemporally to generate the phenotype of a given neuron? How do cell division and morphogenesis modulate this process? What are the cellular mechanisms behind developmental robustness within and across populations of neurons?

Achieving a detailed cellular-level, high-definition understanding of the mechanisms generating robust neuron diversity in the vertebrate nervous system requires studying simple, tractable models that still possess neuron complexity. My system of choice is the Rohon-Beard (RB) neurons of zebrafish. RBs are somatosensory neurons in the dorsal spinal cord of anamniotes that are born early and remain throughout juvenile stages, which I showed counter to a ∼150-year-old assumption of total disappearance by programmed cell death (Navajas Acedo, 2024; Liu and Kucenas, 2024). Due to the fast development of RB neurons, their direct accessibility to manipulations and imaging, and their small number, they represent an ideal model to study nervous system development. My current work describes the different layers of RB neuron diversity – transcriptional, spatial and between individuals – during development, by tracking their simple cell lineages and dissecting the transcription factors necessary for their diversification. Interestingly, RB neuron molecular diversification process follows a stepwise logic, and even if some of the steps seem to rely on stochastic events, it is remarkably robust across individuals.

It is an exciting time to be a developmental neurobiologist because of the recent innovations in lineage tracing *ex vivo* and *in vivo*, temporospatial analysis of RNA and chromatin architecture during development, and precise genome manipulations. Such techniques are allowing me to comprehensively disentangle when and how cell behaviours and molecular cascades contribute to neuron diversification. We will be able to systematically link molecular and genomic events across the totality of differentiation trajectories. Ultimately, we will mechanistically explain each of the phenotypical characteristics of the neuron, and how these are produced in a robust way within a population.

Jumping through evolution: deciphering the roles and rules of transposable elements in mammalian development

Marlies E. Oomen

How does a selfish element become useful to its host? Transposable elements (TEs) are mobile genetic units that, once inserted, multiply throughout the genome (Wells and Feschotte, 2020). To maintain the ability to transpose, TEs hijack the host cell transcription machinery. Consequently, successful TEs typically contain transcription factor motifs and other sequences that enhance their transcription (Hermant and Torres-Padilla, 2021). TEs have been prolific at this genomic colonization; around half of the mouse and human genomes originates from TE sequences (Rodriguez-Terrones and Torres-Padilla, 2018). As transposition activity of TEs can cause genome instability, activity of TEs is controlled to maintain host cell fitness (Oomen and Torres-Padilla, 2024). In addition to epigenetic silencing (Almeida et al., 2022), many TEs become domesticated and lose sequence integrity over evolutionary time, leaving remnants of their sequences that can no longer transpose. Interestingly, these remnants can be beneficial to the host and often contain sequence substructures that allow them to be transcribed, bind transcription factors, act as cis-regulatory sequences and function as a sequence repository for genome innovation (Fueyo et al., 2022; Modzelewski et al., 2022).

Since their discovery in maize by Barbara McClintock (McClintock, 1950), TEs have remained long understudied in the age of genomic sequencing – not through lack of interest, but lack of tools to study them. Their repetitive nature makes it challenging to accurately map genomic and transcriptomic reads to an individual insertion (Lanciano and Cristofari, 2020). However, TEs have become more broadly studied, thanks to the rise of long-read sequencing methods (Berrens et al., 2022), improved genome assemblies and annotations (Storer et al., 2021), and software tools for accurate quantification (Jin et al., 2015; Oliveira et al., 2023). Furthermore, large language models and machine learning approaches will enable further analysis of TE sequence characteristics and the prediction of their cis-regulatory roles (Eraslan et al., 2019).

The evolutionary balance between selfish elements, which jeopardize genome integrity, and the co-option of beneficial regulatory elements is at the heart of TE research. One enticing hypothesis proposes that TEs can act as sequence-encoded switches that regulate transcriptional programmes genome-wide (Friedli and Trono, 2015). This is particularly interesting in the context of development, when transcriptional programmes rapidly transition. Several examples of TE co-option are known, primarily in the mouse embryo and embryonic stem cells (Modzelewski et al., 2021; Hermant et al., 2025; De Iaco et al., 2017; Macfarlan et al., 2012). However, TEs, and their co-option, are present in all lifeforms (Matsushima et al., 2024; Osmanski et al., 2023; Oomen et al., 2025). Moreover, some TEs are shared across species; once inserted in a common ancestor, they co-evolved with their hosts as species diversified and remained transcriptionally active, despite losing transposition activity many million years ago (Oomen et al., 2025). Understanding the interactions between the host genome and TEs requires studying the regulation of and by TEs by comparing different species, highlighting conserved regulatory pathways and species-specific diversification. Embracing recent technological advances and an evolutionary perspective will lead to a better understanding of the roles and rules of TEs in mammalian genome regulation.

Thriving in a noisy world: towards an integrated view of developmental robustness

Giulia Paci

Development unfolds under the continuous action of fluctuating mechanical forces, originating from the environment or within the developing organism. For example, plants exhibit the fascinating phenomenon of thigmorphogenesis (Braam and Chehab, 2017), in which growth and development are altered dramatically by stimuli such as touch and wind. Even in organisms we typically consider ‘shielded’ from the environment, such as humans, development can be affected by mechanical inputs. Recent studies of foetal movements in the womb have found that kicking forces are significantly reduced in the case of breech position, which correlates with an increased risk of developmental hip defects (Verbruggen et al., 2018). Organs themselves often develop while generating mechanical forces: in the heart, fluid shear stress and stretching forces generated by heartbeats are important for valve morphogenesis (Fukui et al., 2021) and cardiac contraction affects extracellular matrix remodelling (Gentile et al., 2024). The presence of ‘mechanical noise’ permeates to the cellular scale, where stochastic expression and assembly of cytoskeletal elements and motor proteins generate fluctuating tension levels. In the *Drosophila* developing leg, Myosin II planar polarity buffers these fluctuations to ensure precise tissue folding (Martin et al., 2021). Robust development in these ‘noisy’ conditions is even more striking

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if we consider that mechanical forces impact key cellular functions such as fate specification, division and apoptosis (Paci and Mao, 2021).

Mechanical forces also determine cell shapes, which in turn can affect signalling, particularly when membrane-bound receptor/ligand pairs are involved (Dullweber and Erzberger, 2023). We recently demonstrated that 3D cell shapes can tune the effective range of Notch-Delta signalling and directly impact developmental patterning in the *Drosophila* wing (Paci et al., 2025 preprint). Wing disc cells have an elongated, tortuous 3D shape and exchange neighbours multiple times along their apico-basal axis. Experimentally 'straightening' the cells by perturbing cortical stiffness resulted in an altered pattern of wing margin sensory organ precursors. Since similar complex 3D shapes (Gomez-Galvez et al., 2018) are widespread in developing tissues, it will be exciting to explore whether dynamic modulation of cell shapes represents a universal mechanism by which tissues fine-tune signalling distance to coordinate cell growth and fate specification with morphogenesis.

Importantly, this relationship is not one-directional, but signalling can feed back directly into cell mechanics and control cell shape. For example, in the developing zebrafish heart, Notch-mediated actomyosin dampening enables compact layer cells to stretch, supporting tissue growth (Andrews et al., 2025). These observations reveal multiple feedback loops between mechanics, cell geometry and signalling, which collectively contribute to robust development.

Looking ahead, it will be exciting to explore how mechanical forces interact with other environmental stressors, which never act in isolation in nature. Temperature, for example, alters cytoskeletal dynamics, membrane fluidity and enzymatic activity, affecting both mechanical properties and signalling. Metabolism is deeply intertwined with tissue mechanics, cell proliferation and growth. These factors are tightly interwoven with developmental processes and may modulate how cells interpret mechanical cues. Robustness in development is a multidimensional problem requiring an interdisciplinary cross-cutting approach. Bringing together researchers working across scales, from molecular aspects to organism-level physiology, will advance a more holistic understanding of how robust development is achieved amid fluctuating environments.

One genome's 'junk' is another genome's treasure

Sonya A. Widen

In his wonderfully titled 1972 paper, "So Much 'Junk' DNA In Our Genomes", Susumu Ohno argued that the majority of non-coding DNA in the human genome was highly repetitive 'junk DNA' with no clear contribution to any phenotype (Ohno, 1972). He was the first to coin this term that became widely used for decades, labelling transposable elements (TEs) and other highly repetitive sequences as largely useless – an idea that persisted for long enough that, in 2007, it was taught to me in introductory genetics as a bachelor's student.

The era of genomics and the combined efforts of many talented scientists have changed the narrative of TEs and endogenous retroviruses from genomic parasites to powerful evolutionary forces shaping development, diversity and disease (Gasparotto et al., 2023; Oomen and Torres-Padilla, 2024; Li et al., 2025). If TEs are 'junk', then evolution has gone antiquing. For example, TEs and retroviral sequences have shaped our placentas (Shiura et al., 2023) and taken our tails (Xia et al., 2024). Across eukaryotes, most unexpectedly, some TE families can mobilize not only within a genome, but between them, laterally colonizing new species through horizontal transposon transfer (HTT; Gilbert and Feschotte, 2018). We recently discovered that ancient eukaryotic virus-like transposons called *Mavericks* (or Polintons) have been repeatedly transferred between diverse nematode species on a global scale (Widen et al., 2023; Jeong et al., 2023). In fact, *Mavericks* have systematically picked up two novel nematode gene families as 'cargo' and transferred them between species, identifying *Mavericks* as a long-sought vector of horizontal gene transfer (HGT) in animals (Widen et al., 2023).

Although viruses and related TEs have been proposed to mediate HGT (Gilbert and Cordaux, 2017), the first implication of *Mavericks* as vectors of HGT adds another layer of complexity. The impacts of HGT on evolution and development are now well documented (Gabaldón, 2020; Keeling, 2024), and examples of HGT both within and between eukaryotic kingdoms are accumulating rapidly, but the vectors underlying these transfers remain unknown. Do *Mavericks* and analogous TEs with viral properties mediate HGT beyond nematodes? How can they bypass both physical and genetic barriers to integrate into the germline of a new species? Are some genes or sequences more likely to be horizontally transferred than others? How do vectors overcome phylogenetic and geographical distance? Our ability to answer these questions hinges upon: (1) wider sampling of genomes from more diverse organisms; and (2) the development of models where we can test evolutionary questions at a mechanistic level. The discovery of widespread *Maverick*-mediated HGT in nematodes is just the beginning (the first recurrent system where both vector and cargo are known in an organism amenable to lab study) but in the age of genomics, it will not be the last. The coming years will move researchers from describing HGT events of the past, into understanding at a functional level how TEs and viruses are able to escape the 'vertical' confines of their home species. This will undoubtedly open a new understanding of how eukaryotes evolved, changing our tree of life into a more interconnected web of life.

Engineering development in the era of stem cell models

Toshimichi Yamada

How a single cell, a zygote, grows into a whole baby is a central question in developmental biology. While significant advances have been made in understanding mammalian development, particularly in mice, the *in utero* environment presents a unique technical challenge as embryogenesis is largely inaccessible. This has made model organisms, such as *Xenopus* and zebrafish, valuable to understand the fundamental principles governing early development (Choi et al., 2021; Kostiuk and Khokha, 2021).

Recent advances in stem cell biology and bioengineering have opened this developmental black box. We can now guide pluripotent stem cells into structures that resemble natural embryos (Shahbazi et al., 2019; Zernicka-Goetz, 2023), such as blastoids (Kagawa et al., 2022) and gastruloids (Moris et al., 2020) that recapitulate pre-implantation and gastrulation, respectively, and stem cell-based embryo models that reconstruct the entire early embryo (Oldak et al., 2023; Weatherbee et al., 2023).

This technological milestone raises a deeper question: what should we do with these models? Much of the field has focused on perfecting the technology, trying to make accurate models of natural embryos. While essential, if we only focus on copying what happens in nature, we might overlook the true potential of these *in vitro* models. Instead of recapitulating native development, can we learn deeper by actively redesigning it?

To find the path forward, we can look back to one of the landmarks in the history of developmental biology: the Spemann-Mangold organizer (Spemann and Mangold, 1924). They transplanted a piece from the dorsal lip of an amphibian embryo to the opposite side of another embryo. This small graft organized the surrounding

host tissue to form a second, complete body axis, generating conjoined twin tadpoles. The organizer concept fundamentally transformed developmental biology, shifting the field from descriptive embryology toward experimental, hypothesis-driven science. Using the organizer, researchers could actively manipulate embryos to understand the molecular logic underlying development (De Robertis, 2006).

What if we applied these organizing principles to stem cell-based embryo models, but with a synthetic biological approach? Instead of transplanting cells between embryos, I tried to engineer an organizer from scratch to control signal types, amplitude and timing (Yamada et al., 2025). Starting from a mouse fibroblast cell line, we constructed a 'synthetic organizer', a user-defined signalling centre that secretes specific morphogens, which allows us to directly test the sufficiency of specific signals in directing cell fate and tissue morphology, deconstructing the complex process of development into its causal relationships.

This synthetic approach to development has the potential to unlock fundamental design principles (Trentesaux et al., 2023). By building development from the bottom up, we can ask questions that would be impossible with natural embryos: what are the minimal requirements for organizing a body axis? How do cells integrate multiple signalling inputs to make cell fate decisions? Can we engineer entirely new developmental programmes that do not exist in nature? The implications extend beyond basic science. Understanding the modular logic of development will revolutionize our approach to regenerative medicine and the treatment of developmental disorders.

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References

Ahmed, H. M. M., Zheng, L. and Hunnekuhl, V. S. (2025). Transferable approaches to CRISPR-Cas9 induced genome editing in non-model insects: a brief guide. *Front. Zool.* **22**, 13. doi:10.1186/s12983-025-00566-2

Almeida, M. V., Vernaz, G., Putman, A. L. K. and Miska, E. A. (2022). Taming transposable elements in vertebrates: from epigenetic silencing to domestication. *Trends Genet.* **38**, 529-553. doi:10.1016/j.tig.2022.02.009

Andrews, T. G. R., Cornwall-Scoones, J., Ramel, M. C., Gupta, K., Briscoe, J. and Priya, R. (2025). Mechanochemical coupling of cell shape and organ function optimizes heart size and contractile efficiency in zebrafish. *Dev. Cell* [Epub ahead of print]. doi:10.1016/j.devcel.2025.07.011

Aulehla, A., Wehrle, C., Brand-Saberi, B., Kemler, R., Gossler, A., Kanzler, B. and Herrmann, B. G. (2003). Wnt3a plays a major role in the segmentation clock controlling somitogenesis. *Dev. Cell* **4**, 395-406. doi:10.1016/s1534-5807(03)00055-8

Azevedo, F. A. C., Carvalho, L. R. B., Grinberg, L. T., Farfel, J. M., Ferretti, R. E. L., Leite, R. E. P., Filho, W. J., Lent, R. and Herculano-Houzel, S. (2009). Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. *J. Comp. Neurol.* **513**, 532-541. doi:10.1002/cne.21974

Batchelor, E., Loewer, A., Mock, C. and Lahav, G. (2011). Stimulus-dependent dynamics of p53 in single cells. *Mol. Syst. Biol.* **7**, 488. doi:10.1038/msb.2011.20

Berrens, R. V., Yang, A., Laumer, C. E., Lun, A. T. L., Bieberich, F., Law, C.-T., Lan, G., Imaz, M., Bowness, J. S., Brockdorff, N. et al. (2022). Locus-specific expression of transposable elements in single cells with CELLO-seq. *Nat. Biotechnol.* **40**, 546-554. doi:10.1038/s41587-021-01093-1

Braam, J. and Chehab, E. W. (2017). Thigmomorphogenesis. *Curr. Biol.* **27**, R863-RR64. doi:10.1016/j.cub.2017.07.008

Braganza, O. and Beck, H. (2018). The circuit motif as a conceptual tool for multilevel neuroscience. *Trends Neurosci.* **41**, 128-136. doi:10.1016/j.tins.2018.01.002

Chen, S. and Phillips, C. M. (2025). Nuclear Argonaute protein NRDE-3 switches small RNA partners during embryogenesis to mediate temporal-specific gene regulatory activity. *eLife* **13**, RP102226. doi:10.7554/eLife.102226.3

Choi, T.-Y., Choi, T.-I., Lee, Y.-R., Choe, S.-K. and Kim, C.-H. (2021). Zebrafish as an animal model for biomedical research. *Exp. Mol. Med.* **53**, 310-317. doi:10.1038/s12276-021-00571-5

Cicconardi, F., Farnworth, M. S., Grob, R., Shodja, D. N., Bacquet, C., el Jundi, B., Martin, A. and Montgomery, S. H. (2025). Emerging tools to advance neuroethology in butterflies and moths. *EcoEvoRxiv*. doi:10.32942/X2K92R

De Iaco, A., Planet, E., Coluccio, A., Verp, S., Duc, J. and Trono, D. (2017). DUX-family transcription factors regulate zygotic genome activation in placental mammals. *Nat. Genet.* **49**, 941-945. doi:10.1038/ng.3858

De Robertis, M.,E. (2006). Spemann's organizer and self-regulation in amphibian embryos. *Nat. Rev. Mol. Cell Biol.* **7**, 296-302. doi:10.1038/nrm1855

Dean, J. A., Reyes, J., Tsabar, M., Jambhekar, A., Lahav, G. and Michor, F. (2024). Functional consequences of a p53-MDM2-p21 incoherent feedforward loop. *bioRxiv*. doi:10.1101/2024.06.25.600070

Delaune, E. A., François, P., Shih, N. P. and Amacher, S. L. (2012). Single-cell-resolution imaging of the impact of Notch signaling and mitosis on segmentation clock dynamics. *Dev. Cell* **23**, 995-1005. doi:10.1016/j.devcel.2012.09.009

Di Bella, D. J., Domínguez-Iturza, N., Brown, J. R. and Arlotta, P. (2024). Making Ramón y Cajal proud: development of cell identity and diversity in the cerebral cortex. *Neuron* **112**, 2091-2111. doi:10.1016/j.neuron.2024.04.021

Diaz-Cuadros, M., Wagner, D. E., Budjan, C., Hubaud, A., Tarazona, O. A., Donelly, S., Michaut, A., Al Tanoury, Z., Yoshioka-Kobayashi, K., Niino, Y. et al. (2020). In vitro characterization of the human segmentation clock. *Nature* **580**, 113-118. doi:10.1038/s41586-019-1885-9

Dorkenwald, S., Matsliah, A., Sterling, A. R., Schlegel, P., Yu, S., McKellar, C. E., Lin, A., Costa, M., Eichler, K., Yin, Y. et al. (2024). Neuronal wiring diagram of an adult brain. *Nature* **634**, 124-138. doi:10.1038/s41586-024-07558-y

Dullweber, T. and Erzberger, A. (2023). Mechanochemical feedback loops in contact-dependent fate patterning. *Curr. Opin. Syst. Biol.* **32-33**, 100445. doi:10.1016/j.coisb.2023.100445

Eraslan, G., Avsec, Ž, Gagneur, J. and Theis, F. J. (2019). Deep learning: new computational modelling techniques for genomics. *Nat. Rev. Genet.* **20**, 389-403. doi:10.1038/s41576-019-0122-6

Ewe, C. K., Teichman, G., Weiss, S., Knott, M. M. L., Anava, S., Gingold, H., Sarmiento, M. B., Troemel, E. and Rechavi, O. (2025a). Dynamic control of Argonautes by a rapidly evolving immunological switch. *Curr. Biol.* **35**, 3076-3089.e5. doi:10.1016/j.cub.2025.05.039

Ewe, C. K., Achache, H., Weiss, S., Mogilevskaya, A., Valenski, M., Teichman, G., Anava, S., Gingold, H., Posner, R., Antonova, O. et al. (2025b). Neuronal oversight of germline small RNAs prevents heat-induced sterility in lab-domesticated Caenorhabditis elegans. *bioRxiv*, 2025.08.07.669182. doi:10.1101/2025.08.07.669182

Farnworth, M. S., Bucher, G. and Hartenstein, V. (2022). An atlas of the developing Tribolium castaneum brain reveals conservation in anatomy and divergence in timing to Drosophila melanogaster. *J. Comp. Neurol.* **530**, 2335-2371. doi:10.1002/cne.25335

Farnworth, M. S., Toh, Y. P., Loupasaki, T., Hodge, E. A., el Jundi, B. and Montgomery, S. H. (2025). Distinct evolutionary trajectories of two integration centres, the central complex and mushroom bodies, across Heliconiini butterflies. *eLife* **14**, RP107589. doi:10.7554/eLife.107589.1

Friedli, M. and Trono, D. (2015). The developmental control of transposable elements and the evolution of higher species. *Annu. Rev. Cell Dev. Biol.* **31**, 429-451. doi:10.1146/annurev-cellbio-100814-125514

Fu, R. Z., Cottrell, O., Cutillo, L., Rowntree, A., Zador, Z., Wurdak, H., Papalopulu, N. and Marinopoulou, E. (2024). Identification of genes with oscillatory expression in glioblastoma: The paradigm of SOX2. *Sci. Rep.* **14**, 2123. doi:10.1038/s41598-024-51340-z

Fueyo, R., Judd, J., Feschotte, C. and Wysocka, J. (2022). Roles of transposable elements in the regulation of mammalian transcription. *Nat. Rev. Mol. Cell Biol.* **23**, 481-497. doi:10.1038/s41580-022-00457-y

Fukui, H., Chow, R. W., Xie, J., Foo, Y. Y., Yap, C. H., Minc, N., Mochizuki, N. and Vermot, J. (2021). Bioelectric signaling and the control of cardiac cell identity in response to mechanical forces. *Science* **374**, 351-354. doi:10.1126/science.abc6229

Gabaldón, T. (2020). Patterns and impacts of nonvertical evolution in eukaryotes: a paradigm shift. *Ann. N. Y. Acad. Sci.* **1476**, 78-92. doi:10.1111/nyas.14471

Gasparotto, E., Burattin, F. V., Di Gioia, V., Panepuccia, M., Ranzani, V., Marasca, F. and Bodega, B. (2023). Transposable Elements Co-Option in Genome Evolution and Gene Regulation. *Int. J. Mol. Sci.* **24**, 2610. doi:10.3390/ijms24032610

Gentile, A., Albu, M., Xu, Y., Mortazavi, N., Ribeiro da Silva, A., Stainier, D. Y. R. and Gunawan, F. (2024). Mechanical forces remodel the cardiac extracellular matrix during zebrafish development. *Development* **151**, dev202310. doi:10.1242/dev.202310

Gilbert, C. and Cordaux, R. (2017). Viruses as vectors of horizontal transfer of genetic material in eukaryotes. *Curr. Opin. Virol.* **25**, 16-22. doi:10.1016/j.coviro.2017.06.005
Gilbert, C. and Feschotte, C. (2018). Horizontal acquisition of transposable elements and viral sequences: patterns and consequences. *Curr. Opin. Genet. Dev.* **49**, 15-24. doi:10.1016/j.gde.2018.02.007
Goentoro, L. and Kirschner, M. W. (2009). Evidence that fold-change, and not absolute level, of beta-catenin dictates Wnt signaling. *Mol. Cell* **36**, 872-884. doi:10.1016/j.molcel.2009.11.017
Gomez-Galvez, P., Vicente-Munuera, P., Tagua, A., Forja, C., Castro, A. M., Letran, M., Valencia-Exposito, A., Grima, C., Bermudez-Gallardo, M., Serrano-Perez-Higueras, O. et al. (2018). Scutoids are a geometrical solution to three-dimensional packing of epithelia. *Nat. Commun.* **9**, 2960. doi:10.1038/s41467-018-05376-1
Hartenstein, V., Younossi-Hartenstein, A., Lovick, J. K., Kong, A., Omoto, J. J., Ngo, K. T. and Viktorin, G. (2015). Lineage-associated tracts defining the anatomy of the Drosophila first instar larval brain. *Dev. Biol.* **406**, 14-39. doi:10.1016/j.ydbio.2015.06.021
Hastings, M. H., Maywood, E. S. and Brancaccio, M. (2019). The Mammalian circadian timing system and the suprachiasmatic nucleus as its pacemaker. *Biology* **8**, 13. doi:10.3390/biology8010013
He, J., Zhang, G., Almeida, A. D., Cayouette, M., Simons, B. D. and Harris, W. A. (2012). How variable clones build an invariant retina. *Neuron* **75**, 786-798. doi:10.1016/j.neuron.2012.06.033
Hermant, C. and Torres-Padilla, M.-E. (2021). TFs for TEs: the transcription factor repertoire of mammalian transposable elements. *Genes Dev.* **35**, 22-39. doi:10.1101/gad.344473.120
Hermant, C., Mourra-Díaz, C. M., Oomen, M. E., Altamirano-Pacheco, L., Pal, M., Nakatani, T. and Torres-Padilla, M.-E. (2025). The transcription factor SRF regulates MERVL retrotransposons and gene expression during zygotic genome activation. *Genes Dev.* **39**, 490-509. doi:10.1101/gad.352270.124
Hobert, O. (2016). A map of terminal regulators of neuronal identity in Caenorhabditis elegans. *WIREs Dev. Biol.* **5**, 474-498. doi:10.1002/wdev.233
Holguera, I. and Desplan, C. (2018). Neuronal specification in space and time. *Science* **362**, 176-180. doi:10.1126/science.aas9435
Imayoshi, I., Isomura, A., Harima, Y., Kawaguchi, K., Kori, H., Miyachi, H., Fujiwara, T., Ishidate, F. and Kageyama, R. (2013). Oscillatory control of factors determining multipotency and fate in mouse neural progenitors. *Science* **342**, 1203-1208. doi:10.1126/science.1242366
Ito, M., Masuda, N., Shinomiya, K., Endo, K. and Ito, K. (2013). Systematic analysis of neural projections reveals clonal composition of the Drosophila brain. *Curr. Biol.* **23**, 644-655. doi:10.1016/j.cub.2013.03.015
Jeong, D.-E., Sundrani, S., Hall, R. N., Krupovic, M., Koonin, E. V. and Fire, A. Z. (2023). DNA polymerase diversity reveals multiple incursions of polintons during nematode evolution. *Mol. Biol. Evol.* **40**, msad274. doi:10.1093/molbev/msad274
Jin, Y., Tam, O. H., Paniagua, E. and Hammell, M. (2015). TEtranscripts: a package for including transposable elements in differential expression analysis of RNA-seq datasets. *Bioinformatics* **31**, 3593-3599. doi:10.1093/bioinformatics/btv422
Jose, A. M. (2015). Movement of regulatory RNA between animal cells. *Genesis* **53**, 395-416. doi:10.1002/dvg.22871
Kagawa, H., Javali, A., Khoei, H. H., Sommer, T. M., Sestini, G., Novatchkova, M., Scholte op Reimer, Y., Castel, G., Bruneau, A., Maenhoudt, N. et al. (2022). Human blastoids model blastocyst development and implantation. *Nature* **601**, 600-605. doi:10.1038/s41586-021-04267-8
Kandimalla, P., Omoto, J. J., Hong, E. J. and Hartenstein, V. (2023). Lineages to circuits: the developmental and evolutionary architecture of information channels into the central complex. *J. Comp. Physiol. A Neuroethol. Sens. Neural Behav. Physiol.* **209**, 679-720. doi:10.1007/s00359-023-01616-y
Keeling, P. J. (2024). Horizontal gene transfer in eukaryotes: aligning theory with data. *Nat. Rev. Genet.* **25**, 416-430. doi:10.1038/s41576-023-00688-5
Kostiuk, V. and Khokha, M. K. (2021). *Xenopus* as a platform for discovery of genes relevant to human disease. In *Current Topics in Developmental Biology, Amphibian Models of Development and Disease* (ed. S. Y. Sokol), pp. 277-312. Academic Press. doi:10.1016/bs.ctdb.2021.03.005
Lacin, H. and Truman, J. W. (2016). Lineage mapping identifies molecular and architectural similarities between the larval and adult Drosophila central nervous system. *eLife* **5**, e13399. doi:10.7554/eLife.13399
Lanciano, S. and Cristofari, G. (2020). Measuring and interpreting transposable element expression. *Nat. Rev. Genet.* **21**, 721-736. doi:10.1038/s41576-020-0251-y
Lee, T. (2017). Wiring the Drosophila brain with individually tailored neural lineages. *Curr. Biol.* **27**, R77-R82. doi:10.1016/j.cub.2016.12.026
Levine, J. H., Lin, Y. and Elowitz, M. B. (2013). Functional roles of pulsing in genetic circuits. *Science* **342**, 1193-1200. doi:10.1126/science.1239999
Li, T. D., Toohill, K. and Modzelewski, A. J. (2025). From junk DNA to genomic treasure: impacts of transposable element DNA, RNA, and protein in mammalian development and disease. *WIREs RNA* **16**, e70022. doi:10.1002/wrna.70022
Liu, K. E. and Kucenas, S. (2024). Rohon-beard neurons do not succumb to programmed cell death during zebrafish development. *Dev. Biol.* **515**, 186-198. doi:10.1016/j.ydbio.2024.06.020
Lodato, S. and Arlotta, P. (2015). Generating neuronal diversity in the mammalian cerebral cortex. *Annu. Rev. Cell Dev. Biol.* **31**, 699-720. doi:10.1146/annurev-cellbio-100814-125353
Macfarlan, T. S., Gifford, W. D., Driscoll, S., Lettieri, K., Rowe, H. M., Bonanomi, D., Firth, A., Singer, O., Trono, D. and Pfaff, S. L. (2012). Embryonic stem cell potency fluctuates with endogenous retrovirus activity. *Nature* **487**, 57-63. doi:10.1038/nature11244
Manning, C. S., Biga, V., Boyd, J., Kursawe, J., Ymisson, B., Spiller, D. G., Sanderson, C. M., Galla, T., Rattray, M. and Papalopulu, N. (2019). Quantitative single-cell live imaging links HES5 dynamics with cell-state and fate in murine neurogenesis. *Nat. Commun.* **10**, 2835. doi:10.1038/s41467-019-10734-8
Marinopoulou, E., Biga, V., Sabherwal, N., Miller, A., Desai, J., Adamson, A. D. and Papalopulu, N. (2021). HES1 protein oscillations are necessary for neural stem cells to exit from quiescence. *iScience* **24**, 103198. doi:10.1016/J.ISCI.2021.103198
Martin, E., Theis, S., Gay, G., Monier, B., Rouviere, C. and Suzanne, M. (2021). Arp2/3-dependent mechanical control of morphogenetic robustness in an inherently challenging environment. *Dev. Cell* **56**, 687-701 e7. doi:10.1016/j.devcel.2021.01.005
Matsuda, M., Yamanaka, Y., Uemura, M., Osawa, M., Saito, M. K., Nagahashi, A., Nishio, M., Guo, L., Ikegawa, S., Sakurai, S. et al. (2020). Recapitulating the human segmentation clock with pluripotent stem cells. *Nature* **580**, 124-129. doi:10.1038/s41586-020-2144-9
Matsuoka, Y., Nakamura, T., Watanabe, T., Barnett, A. A., Tomonari, S., Ylla, G., Whittle, C. A., Noji, S., Mito, T. and Extavour, C. G. (2025). Establishment of CRISPR/Cas9-based knock-in in a hemimetabolous insect: targeted gene tagging in the cricket Gryllus bimaculatus. *Development* **152**, dev199746. doi:10.1242/dev.199746
Matsushima, W., Planet, E. and Trono, D. (2024). Ancestral genome reconstruction enhances transposable element annotation by identifying degenerate integrants. *Cell Genomics* **4**, 100497. doi:10.1016/j.xgen.2024.100497
McClintock, B. (1950). The origin and behavior of mutable loci in maize. *Proc. Natl Acad. Sci. USA* **36**, 344-355. doi:10.1073/pnas.36.6.344
Miller, A. C., Urban, E. A., Lyons, E. L., Herman, T. G. and Johnston, R. J. (2021). Interdependent regulation of stereotyped and stochastic photoreceptor fates in the fly eye. *Dev. Biol.* **471**, 89-96. doi:10.1016/j.ydbio.2020.12.008
Miller, A., Biga, V., Rowntree, A., Chhatriwala, M., Woods, F., Noble, B., Marinopoulou, E., Kamath, A., Vallier, L. and Papalopulu, N. (2025). NGN3 oscillatory expression controls the timing of human pancreatic endocrine differentiation. *Dev. Cell* [Epub ahead of print]. doi:10.1016/j.devcel.2025.06.004
Modzelewski, A. J., Shao, W., Chen, J., Lee, A., Qi, X., Noon, M., Tjokro, K., Sales, G., Biton, A., Anand, A. et al. (2021). A mouse-specific retrotransposon drives a conserved Cdk2ap1 isoform essential for development. *Cell* **184**, 5541-5558.e22. doi:10.1016/j.cell.2021.09.021
Modzelewski, A. J., Gan Chong, J., Wang, T. and He, L. (2022). Mammalian genome innovation through transposon domestication. *Nat. Cell Biol.* **24**, 1332-1340. doi:10.1038/s41556-022-00970-4
Moris, N., Anlas, K., van den Brink, S. C., Alemany, A., Schröder, J., Ghimire, S., Balayo, T., van Oudenaarden, A. and Martinez Arias, A. (2020). An in vitro model of early anteroposterior organization during human development. *Nature* **582**, 410-415. doi:10.1038/s41586-020-2383-9
Navajas Acedo, J. (2024). Complete persistence of the primary somatosensory system in zebrafish. *Dev. Biol.* **515**, 178-185. doi:10.1016/j.ydbio.2024.05.004
Nerli, E., Kretzschmar, J., Bianucci, T., Rocha-Martins, M., Zechner, C. and Norden, C. (2023). Deterministic and probabilistic fate decisions co-exist in a single retinal lineage. *EMBO J.* **42**, e112657. doi:10.15252/embj.2022112657
Niwa, Y., Shimojo, H., Isomura, A., González, A., Miyachi, H. and Kageyama, R. (2011). Different types of oscillations in Notch and Fgf signaling regulate the spatiotemporal periodicity of somitogenesis. *Genes Dev.* **25**, 1115-1120. doi:10.1101/gad.2035311
Ohno, S. (1972). So much "junk" DNA in our genome. *Brookhaven Symp. Biol.* **23**, 366-370.
Oldak, B., Wildschutz, E., Bondarenko, V., Comar, M.-Y., Zhao, C., Aguilera-Castrejon, A., Tarazi, S., Viukov, S., Pham, T. X. A., Ashouokhi, S. et al. (2023). Complete human day 14 post-implantation embryo models from naive ES cells. *Nature* **622**, 562-573. doi:10.1038/s41586-023-06604-5
Oliveira, D. S., Fablet, M., Larue, A., Vallier, A., Carareto, C. M. A., Rebollo, R. and Vieira, C. (2023). ChimeraTE: a pipeline to detect chimeric transcripts derived from genes and transposable elements. *Nucleic Acids Res.* **51**, 9764-9784. doi:10.1093/nar/gkad671
Oomen, M. E. and Torres-Padilla, M. E. (2024). Jump-starting life: balancing transposable element co-option and genome integrity in the developing mammalian embryo. *EMBO Rep.* **25**, 1721-1733. doi:10.1038/s44319-024-00118-5
Oomen, M. E., Rodriguez-Terrones, D., Kurome, M., Zakhartchenko, V., Mottes, L., Simmet, K., Noll, C., Nakatani, T., Mourra-Diaz, C. M., Aksoy, I. et al. (2025). An atlas of transcription initiation reveals regulatory principles of gene and

transposable element expression in early mammalian development. *Cell* **188**, 1156-1174.e20. doi:10.1016/j.cell.2024.12.013

Osmanski, A. B., Paulat, N. S., Korstian, J., Grimshaw, J. R., Halsey, M., Sullivan, K. A. M., Moreno-Santillán, D. D., Crookshanks, C., Roberts, J., Garcia, C. et al. (2023). Insights into mammalian TE diversity through the curation of 248 genome assemblies. *Science* **380**, eabn1430. doi:10.1126/science.abn1430

Paci, G. and Mao, Y. (2021). Forced into shape: mechanical forces in Drosophila development and homeostasis. *Semin. Cell Dev. Biol.* **120**, 160-170. doi:10.1016/j.semcdb.2021.05.026

Paci, G., Berkemeier, F., Baum, B., Page, K. M. and Mao, Y. (2025). 3D epithelial cell topology tunes signalling range to promote precise patterning. *bioRxiv* 2025.08.08.668674. doi:10.1101/2025.08.08.668674

Palmeirim, I., Henrique, D., Ish-Horowicz, D. and Pourquié, O. (1997). Avian hairy gene expression identifies a molecular clock linked to vertebrate segmentation and somitogenesis. *Cell* **91**, 639-648. doi:10.1016/S0092-8674(00)80451-1

Polilov, A. A. (2012). The smallest insects evolve anucleate neurons. *Arthropod. Struct. Dev.* **41**, 29-34. doi:10.1016/j.asd.2011.09.001

Pollington, H. Q., Seroka, A. Q. and Doe, C. Q. (2023). From temporal patterning to neuronal connectivity in Drosophila type I neuroblast lineages. *Semin. Cell Dev. Biol.* **142**, 4-12. doi:10.1016/j.semcdb.2022.05.022

Purvis, J. E., Karhohs, K. W., Mock, C., Batchelor, E., Loewer, A. and Lahav, G. (2012). p53 dynamics control cell fate. *Science* **336**, 1440-1444. doi:10.1126/science.1218351

Rodriguez-Terrones, D. and Torres-Padilla, M.-E. (2018). Nimble and ready to mingle: transposon outbursts of early development. *Trends Genet.* **34**, 806-820. doi:10.1016/j.tig.2018.06.006

Roome, R. B. and Levine, A. J. (2023). The organization of spinal neurons: insights from single cell sequencing. *Curr. Opin. Neurobiol.* **82**, 102762. doi:10.1016/j.conb.2023.102762

Sabherwal, N., Rowntree, A., Marinopoulou, E., Pettini, T., Hourihane, S., Thomas, R., Soto, X., Kursawe, J. and Papalopulu, N. (2021). Differential phase register of Hes1 oscillations with mitoses underlies cell-cycle heterogeneity in ER(+) breast cancer cells. *Proc. Natl. Acad. Sci. USA* **118**, 45. doi:10.1073/pnas.2113527118

Sagner, A. and Briscoe, J. (2019). Establishing neuronal diversity in the spinal cord: a time and a place. *Development* **146**, dev182154. doi:10.1242/dev.182154

Sayre, M. E., Templin, R., Chavez, J., Kempenaers, J. and Heinze, S. (2021). A projectome of the bumblebee central complex. *eLife* **10**, e68911. doi:10.7554/eLife.68911

Scheffer, L. K., Xu, C. S., Januszewski, M., Lu, Z., Takemura, S., Hayworth, K. J., Huang, G. B., Shinomiya, K., Maitlin-Shepard, J., Berg, S. et al. (2020). A connectome and analysis of the adult Drosophila central brain. *eLife* **9**, e57443. doi:10.7554/eLife.57443

Schlegel, P., Yin, Y., Bates, A. S., Dorkenwald, S., Eichler, K., Brooks, P., Han, D. S., Gkantia, M., dos Santos, M., Munnelly, E. J. et al. (2024). Whole-brain annotation and multi-connectome cell typing of Drosophila. *Nature* **634**, 139-152. doi:10.1038/s41586-024-07686-5

Schröter, C. and Oates, A. C. (2010). Segment number and axial identity in a segmentation clock period mutant. *Curr. Biol.* **20**, 1254-1258. doi:10.1016/j.cub.2010.05.071

Schulze, L., Henninger, J., Kadobianskyi, M., Chaigne, T., Faustino, A. I., Hakiy, N., Albadri, S., Schuelke, M., Maler, L., Del Bene, F. et al. (2018). Transparent Danionella translucida as a genetically tractable vertebrate brain model. *Nat. Methods* **15**, 977-983. doi:10.1038/s41592-018-0144-6

Seroussi, U., Lugowski, A., Wadi, L., Lao, R. X., Willis, A. R., Zhao, W., Sundby, A. E., Charlesworth, A. G., Reinke, A. W. and Claycomb, J. M. (2023). A comprehensive survey of C. elegans argonaute proteins reveals organism-wide gene regulatory networks and functions. *eLife* **12**, e83853. doi:10.7554/eLife.83853

Seymour, P. A., Collin, C. A., Egeskov-Madsen, A. . R., Jørgensen, M. C., Shimojo, H., Imayoshi, I., de Lichtenberg, K. H., Kopan, R., Kageyama, R. and Serup, P. (2020). Jag1 modulates an oscillatory Dll1-Notch-Hes1 signaling module to coordinate growth and fate of pancreatic progenitors. *Dev. Cell* **52**, 731-747.e738. doi:10.1016/J.DEVCEL.2020.01.015

Shahbazi, M. N., Siggia, E. D. and Zernicka-Goetz, M. (2019). Self-organization of stem cells into embryos: a window on early mammalian development. *Science* **364**, 948-951. doi:10.1126/science.aax0164

Sharma, N., Flaherty, K., Lezgiyeva, K., Wagner, D. E., Klein, A. M. and Ginty, D. D. (2020). The emergence of transcriptional identity in somatosensory neurons. *Nature* **577**, 392-398. doi:10.1038/s41586-019-1900-1

Shimojo, H., Ohtsuka, T. and Kageyama, R. (2008). Oscillations in notch signaling regulate maintenance of neural progenitors. *Neuron* **58**, 52-64. doi:10.1016/j.neuron.2008.02.014

Shimojo, H., Ohtsuka, T. and Kageyama, R. (2011). Dynamic expression of notch signaling genes in neural stem/progenitor cells. *Front. Neurosci.* **5**, 78-78. doi:10.3389/fnins.2011.00078

Shiura, H., Kitazawa, M., Ishino, F. and Kaneko-Ishino, T. (2023). Roles of retrovirus-derived *PEG10* and *PEG11*/*RTL1* in mammalian development and evolution and their involvement in human disease. *Front. Cell Dev. Biol.* **11**, 1273638. doi:10.3389/fcell.2023.1273638

Sonnen, K. F., Lauschke, V. M., Uraji, J., Falk, H. J., Petersen, Y., Funk, M. C., Beaupeux, M., François, P., Merten, C. A. and Aulehla, A. (2018). Modulation of phase shift between Wnt and Notch signaling oscillations controls mesoderm segmentation. *Cell* **172**, 1079-1090.e1012. doi:10.1016/j.cell.2018.01.026

Soto, X., Biga, V., Kursawe, J., Lea, R., Doostdar, P., Thomas, R. and Papalopulu, N. (2020). Dynamic properties of noise and Her6 levels are optimized by miR-9, allowing the decoding of the Her6 oscillator. *EMBO J.* **39**, e103558. doi:10.15252/embj.2019103558

Spemann, H. and Mangold, H. (1924). über Induktion von Embryonalanlagen durch Implantation artfremder Organisatoren. *Arch. Für Mikrosk. Anat. Entwicklungsmechanik* **100**, 599-638. doi:10.1007/BF02108133

Spindler, S. R. and Hartenstein, V. (2010). The Drosophila neural lineages: a model system to study brain development and circuitry. *Dev. Genes Evol.* **220**, 1-10. doi:10.1007/s00427-010-0323-7

Storer, J., Hubley, R., Rosen, J., Wheeler, T. J. and Smit, A. F. (2021). The Dfam community resource of transposable element families, sequence models, and genome annotations. *Mob. DNA* **12**, 2. doi:10.1186/s13100-020-00230-y

Swarts, D. C., Makarova, K., Wang, Y., Nakanishi, K., Ketting, R. F., Koonin, E. V., Patel, D. J. and van der Oost, J. (2014). The evolutionary journey of Argonaute proteins. *Nat. Struct. Mol. Biol.* **21**, 743-753. doi:10.1038/nsmb.2879

Takashima, Y., Ohtsuka, T., González, A., Miyachi, H. and Kageyama, R. (2011). Intronic delay is essential for oscillatory expression in the segmentation clock. *Proc. Natl. Acad. Sci. USA* **108**, 3300-3305. doi:10.1073/pnas.1014418108

Tavakoli, M. R., Lyudchik, J., Januszewski, M., Vistunou, V., Agudelo Dueñas, N., Vorlaufer, J., Sommer, C., Kreuzinger, C., Oliveira, B., Cenameri, A. et al. (2025). Light-microscopy-based connectomic reconstruction of mammalian brain tissue. *Nature* **642**, 398-410. doi:10.1038/s41586-025-08985-1

Teichman, G., Sela, M., Ewe, C. K., Rieger, I., Anava, S., Mor, Y., Szántó, P., Meyer, D. H., Doron, H., Shachar, O. et al. (2024). Perception of temperature even in the absence of actual change is sufficient to drive transgenerational epigenetic inheritance. *bioRxiv* 2024.12.02.626416. doi:10.1101/2024.12.02.626416

Trentesaux, C., Yamada, T., Klein, O. D. and Lim, W. A. (2023). Harnessing synthetic biology to engineer organoids and tissues. *Cell Stem Cell* **30**, 10-19. doi:10.1016/j.stem.2022.12.013

Urbach, R. and Technau, G. M. (2003). Early steps in building the insect brain: neuroblast formation and segmental patterning in the developing brain of different insect species. *Arthropod. Struct. Dev.* **32**, 103-123. doi:10.1016/S1467-8039(03)00042-2

Vandereyken, K., Sifrim, A., Thienpont, B. and Voet, T. (2023). Methods and applications for single-cell and spatial multi-omics. *Nat. Rev. Genet.* **24**, 494-515. doi:10.1038/s41576-023-00580-2

Verbruggen, S. W., Kainz, B., Shelmerdine, S. C., Arthurs, O. J., Hajnal, J. V., Rutherford, M. A., Phillips, A. T. M. and Nowlan, N. C. (2018). Altered biomechanical stimulation of the developing hip joint in presence of hip dysplasia risk factors. *J. Biomech.* **78**, 1-9. doi:10.1016/j.jbiomech.2018.07.016

Weatherbee, B. A. T., Gantner, C. W., Iwamoto-Stohl, L. K., Daza, R. M., Hamazaki, N., Shendure, J. and Zernicka-Goetz, M. (2023). Pluripotent stem cell-derived model of the post-implantation human embryo. *Nature* **622**, 584-593. doi:10.1038/s41586-023-06368-y

Wells, J. N. and Feschotte, C. (2020). A field guide to eukaryotic transposable elements. *Annu. Rev. Genet.* **54**, 539-561. doi:10.1146/annurev-genet-040620-022145

Weterings, S. D. C., Eto, H., de Leede, J.-D., Giladi, A., Hoekstra, M. E., Beijk, W. F., Liefting, E. J. M., van den Anker, K. B., van Rheenen, J., van Oudenaarden, A. et al. (2024). NOTCH-driven oscillations control cell fate decisions during intestinal homeostasis. *bioRxiv* 2024.2008.2026.609553. doi:10.1101/2024.08.26.609553

Widen, S. A., Campo Bes, I., Koreshova, A., Pliota, P., Krogull, D. and Burga, A. (2023). Virus-like transposons cross the species barrier and drive the evolution of genetic incompatibilities. *Science* **380**, eade0705. doi:10.1126/science.ade0705

Wu, J., Yang, J., Cho, W. C. and Zheng, Y. (2020). Argonaute proteins: structural features, functions and emerging roles. *J. Adv. Res.* **24**, 317-324. doi:10.1016/j.jare.2020.04.017

Xia, B., Zhang, W., Zhao, G., Zhang, X., Bai, J., Brosh, R., Wudzinska, A., Huang, E., Ashe, H., Ellis, G. et al. (2024). On the genetic basis of tail-loss evolution in humans and apes. *Nature* **626**, 1042-1048. doi:10.1038/s41586-024-07095-8

Yamada, T., Trentesaux, C., Brunger, J. M., Xiao, Y., Stevens, A. J., Martyn, I., Kasparek, P., Shroff, N. P., Aguilar, A., Bruneau, B. G. et al. (2025). Synthetic organizer cells guide development via spatial and biochemical instructions. *Cell* **188**, 778-795.e18. doi:10.1016/j.cell.2024.11.017

Zernicka-Goetz, M. (2023). The evolution of embryo models. *Nat. Methods* **20**, 1844-1848. doi:10.1038/s41592-023-02077-6

Zhang, Y., Lahmann, I., Baum, K., Shimojo, H., Mourikis, P., Wolf, J., Kageyama, R. and Birchmeier, C. (2021). Oscillations of Delta-like1 regulate the balance between differentiation and maintenance of muscle stem cells. *Nat. Commun.* **12**, 1318. doi:10.1038/s41467-021-21631-4