

EDITORIAL

Development's Inaugural Outstanding Paper Prize

James Briscoe*, Katherine Brown^{‡,§} and Steve Wilson[¶]

Last year, the editors of Development decided to initiate an 'Outstanding paper prize' to recognise some of the most exciting work published in the journal in each calendar year. To select the winner(s), we agreed that each editor would look over all the published papers they handled over the year and choose their favourite; based on these choices, we (J.B., K.B. and S.W.) would then select a handful of finalists and an overall winner, the first author(s) of which would be awarded a £1000 prize.

This has not been an easy task – in 2022, we published 350 research papers across the whole breadth of developmental and stem cell biology, and selecting the 'best' is always going to be a somewhat subjective process. So before announcing the finalists and winner, we'd like to take the opportunity to acknowledge the authors of all our 2022 papers for their valuable contributions to the journal, and particularly to congratulate all those shortlisted by our editors – these papers are listed at the end of this editorial, along with a brief summary from the relevant editor as to why they chose that paper. These 21 papers include experimental, theoretical and technical papers, feature well-loved model organisms like *Drosophila*, zebrafish and *Arabidopsis*, as well as non-traditional models such as the silkworm and the dunnart, and address a wide range of developmental topics – from the evolution of chromatin landscapes to the mechanical control of tissue growth. Many of these papers make use of cutting-edge techniques like single-cell sequencing, high-resolution imaging or *in vitro* organoid culture, while others have used more classical approaches to uncover exciting new biology.

And so, on to the winners. After much deliberation, we chose four finalists:

Divergent evolution of developmental timing in the neocortex revealed by marsupial and eutherian transcriptomes by Peter Kozulin, Rodrigo Suárez, Qiong-Yi Zhao, Annalisa Paolino, Linda J. Richards and Laura R. Fenlon (doi:10.1242/dev.200212)

PILS proteins provide a homeostatic feedback on auxin signaling output by Elena Feraru, Mugurel I. Feraru, Jeanette Moulinier-Anzola, Maximilian Schwihla, Jonathan Ferreira Da Silva Santos, Lin Sun, Sascha Waidmann, Barbara Korbei and Jurgen Kleine-Vehn (doi:10.1242/dev.200929)

Hypoxia induces an early primitive streak signature, enhancing spontaneous elongation and lineage representation in gastruloids by Natalia López-Anguita, Seher Ipek Gassaloglu, Maximilian Stötzl, Adriano Bolondi, Deniz Conkar, Marina Typou, René Buschow, Jesse V. Veenvliet and Aydan Bulut-Karslioglu (doi:10.1242/dev.200679)

The GATA factor ELT-3 specifies endoderm in *Caenorhabditis angaria* in an ancestral gene network by Gina Broitman-Maduro, Simo Sun, Taisei Kikuchi and Morris F. Maduro (doi:10.1242/dev.200984)

Of these, we selected the study by Natalia Lopez-Anguita and colleagues as our overall winner – many congratulations to all the authors of this outstanding piece of work. For more on the motivation behind this paper and how it came about, see Box 1.

So what made these papers stand out? The study by Peter Kozulin, Rodrigo Suárez and colleagues addresses a fundamental question – what are the developmental mechanisms underlying brain evolution? – and uncovers differences in the timing of neurogenesis between eutherian and marsupial mammals. This paper fits into a growing body of work investigating the relevance of developmental heterochrony in evolutionary diversification. As one of the referees commented, this paper is 'a real tour de force given the very limited existing genomic resources on this species [the dunnart]', allowing the authors to reach 'the fascinating conclusion that cortical development is heterochronous between these two species [dunnart and mouse]'.

The paper from Elena Feraru and colleagues investigates how auxin signalling output, which is crucial for so many aspects of plant development, is buffered against variability in auxin levels. One of the things we liked about this paper was that it uses a classical developmental biology approach – forward genetic screening – to identify a tightly controlled feedback mechanism and provide insights in to the 'bigger picture' question of how developmental robustness is achieved. This paper came to us from Review Commons, the journal-independent peer-review platform, and met with enthusiastic feedback from referees, who said that the paper would 'deepen our understanding of auxin regulatory loops' and make 'a significant contribution to the auxin community'.

In their work, Natalia Lopez-Anguita and colleagues tackle the question of environmental and metabolic regulation of development (a topic close to Development's heart at the moment, as this is the focus of our upcoming Special Issue). In mammals, we know that early embryogenesis occurs in a hypoxic environment, but what is the significance of this for development? Using embryonic stem cells and gastruloid culture systems, the authors show that hypoxia promotes symmetry breaking and regulates lineage commitment. As well as advancing our understanding of the influence of the hypoxic environment, this work has, as one of the referees noted, 'the potential to change how *in vitro* models of early development are generated'.


Finally, Gina Broitman-Maduro and colleagues used the well-characterised gene regulatory network controlling endoderm development in *C. elegans* to ask the question of how such networks evolve over time. Using divergent *Caenorhabditis* species, the authors identify an ancestral network and explain how this simplified system for endoderm specification may have evolved to the more complex network found in *C. elegans*. One referee told us: '[This work provides] a textbook case of gene regulatory

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Box 1. The story behind the paper

We asked the authors of the winning paper to tell us about the background to this work and what the future holds.

What was the motivation behind this study?

During development, the embryo has to coordinate intrinsic regulators with a continuously changing microenvironment. In mammals, the placenta provides oxygen to the embryo, but it is not fully functional until mid-gestation in the mouse, so early embryogenesis takes place in a hypoxic environment. Most research on hypoxia has focussed on acute effects, but we wanted to look into the impact of prolonged hypoxia on cellular differentiation programmes.

How did the collaboration between the Bulut-Karsioglu and Veenvliet labs come about?

The project was initiated in the Bulut-Karsioglu lab, but once we realised that hypoxia induced the expression of primitive streak genes, we wanted to investigate its effects in 3D aggregates. Fortunately, Jesse Veenvliet was in the same institute as us at the time – developing and working with gastruloid models. This allowed us to test some of the predictions from our stem cell work in the gastruloid system. Our collaboration continued after Jesse moved to Dresden to set up his own lab, and in the end we learned a huge amount from the gastruloid model.

Where are you taking this work next?

Both labs are continuing to work in this area, looking at the impact of hypoxia on early development. The big goal is to understand how the same effector (hypoxia) can lead to cell type-specific outcomes.

Natalia: as the first author of this paper, can you tell us a bit about your career history and future plans?

I completed my Bachelor's degree in Biochemistry in Cordoba, Spain, and my Master's in Omics Data Analysis in Barcelona. During my studies, it became clear to me that I wanted to study stem cells and apply next generation sequencing to answer biological questions. Moving to Aydan's lab for my PhD provided me with an excellent scientific atmosphere to develop both my experimental and computational skills. Recently, I have started a postdoc at the Max-Delbruck Center in Berlin, diving into single cell biology to understand cellular heterogeneity in the adult human heart. Going forwards, I would like to keep learning and to be a mentor to a new generation of talented students.

network evolution. I predict this paper will become a classic.' More generally, this paper exemplifies the fact that, even in such a well-studied system as *C. elegans* endoderm specification, there is much to learn about how developmental programs are implemented and evolve.

We are delighted that these four papers span such a wide range of model systems and topics, and employ such a diverse range of approaches. Just looking at these papers – as well as the others on the shortlist – demonstrates what a vibrant and varied field we work in. To celebrate our paper prize finalists, we are organising a special 'Development presents' webinar, at which three of our finalists will speak (Natalia Lopez-Anguita already presented her work at an earlier edition of Development presents – you can watch her talk here: <https://thenode.biologists.com/development-presents-december-videos-2/development-presents/>). We will be announcing the date and time of this webinar shortly, and hope many of you will be able to join us.

To close, we'd like to congratulate our winning research team again, as well as our three other finalists and all those papers shortlisted by our editors. It was tough selecting just one winner from the hundreds of papers we published last year, but also rewarding to revisit some of the exciting work we've featured in the journal. We plan to make this an annual award, and look forward to selecting next year's finalists and winners – if you'd like to be in with a chance, please send your next great paper our way!

Shortlisted papers

ECM-integrin signalling instructs cellular position sensing to pattern the early mouse embryo by Esther Jeong Yoon Kim, Lydia Sorokin and Takashi Hiiragi (doi:10.1242/dev.200140)

Selected by Patrick Tam: 'This study demonstrated that extracellular matrix-integrin interaction enables the cells in the embryo to perceive their position in the cellular cluster and thereby acquire the appropriate cellular phenotype. This work is of clear interest to developmental biologists, especially those studying pre-implantation mammalian development.'

The Hox gene *Antennapedia* is essential for wing development in insects by Chunyan Fang, Yaqun Xin, Tao Sun, Antónia Monteiro, Zhanfeng Ye, Fangyin Dai, Cheng Lu and Xiaoling Tong (doi:10.1242/dev.199841)

Selected by Cassandra Extavour: 'Our understanding of the genetic control of development is usually most heavily influenced by the results obtained in the most well-studied laboratory model organisms. As time passes, even if gene function has only been studied in one organism, the generalized view that "gene X is/is not required for process Y" becomes more and more entrenched. This paper provides a beautiful example of how important it is to remain open to the possibility that gene X may actually be required for process Y, but simply in an organism not yet examined. The authors examine the case of the Hox gene *Antennapedia*. The long-standing consensus in the field has been that because neither overexpression nor loss of function appear to impact wing development in the fruit fly, this gene, and indeed all Hox genes, are dispensable for insect forewing development. Here, the authors examine multiple insects and provide strong evidence that *Antennapedia* is indeed required for wing development in multiple species. The study highlights the eternal importance of diversity in taxon sampling, and shows that even in a well-studied model organism, hidden mysteries remain in our understanding of the mechanisms of development.'

Pthlha and mechanical force control early patterning of growth zones in the zebrafish craniofacial skeleton by Diego J. Hoyle, Daniel B. Dranow and Thomas F. Schilling (doi:10.1242/dev.199826)

Selected by Steve Wilson: 'I enjoyed this paper for many reasons, not least because it started with a fortuitous observation by well-trained eyes. Unexpectedly, early transgene labelling of a cell population enabled the authors to perform incisive and informative experiments to elegantly resolve how genetically encoded signals interact with mechanical forces to shape skeletal elements.'

Regulation of stem cell identity by miR-200a during spinal cord regeneration by Sarah E. Walker, Keith Z. Sabin, Micah D. Gearhart, Kenta Yamamoto and Karen Echeverri (doi:10.1242/dev.200033)

Selected by Ken Poss: 'The authors find that neural stem cells in axolotls respond with different programs in response to transection of spinal cord tissue versus amputation of the tail, of which they highlight differential regulation of the microRNA miR-200a. They report that miR-200a-mediated control of its targets plays a key role in promoting the neurogenic fate of neural stem cells during spinal cord regeneration. As one referee commented: "The hypothesis that neural stem cells respond differently to spinal cord injury or tail amputation and that miR-200a tunes the potency of spinal cord stem cells as part of this differential response is an exciting and significant concept in tissue regeneration."'

Divergent evolution of developmental timing in the neocortex revealed by marsupial and eutherian transcriptomes by Peter Kozulin, Rodrigo Suárez, Qiong-Yi Zhao, Annalisa Paolino, Linda J. Richards and Laura R. Fenlon (doi:10.1242/dev.200212)

Selected by Paola Arlotta and Debby Silver: ‘In this study, the authors perform elegant and careful characterization of gene expression across stage-matched brains of different species. The similarities and differences they find highlight important and interesting new observations valuable for understanding cortical evolution.’

Selective requirement for polycomb repressor complex 2 in the generation of specific hypothalamic neuronal subtypes by Behzad Yaghmaeian Salmani, Brad Balderson, Susanne Bauer, Helen Ekman, Annika Starkenberg, Thomas Perlmann, Michael Piper, Mikael Bodén and Stefan Thor (doi:10.1242/dev.200076)

Selected by François Guillemot: ‘The importance of epigenetic mechanisms for the generation of cellular diversity is not well understood. This question is addressed in this paper by investigating how the complete elimination of H3K27me3 marks affects the development of the hypothalamus. Interestingly, although the loss of H3K27me3 results in the deregulation of a substantial number of genes, only a few neuronal subtypes fail to be generated, indicating that different neuronal lineages are differentially dependent on histone methylation for their specification.’

In vitro culture of ovine embryos up to early gastrulating stages by Priscila Ramos-Ibeas, Leopoldo González-Brusi, Maria Torres Used, Maria Jesús Cocero, Pilar Marigorta, Ramiro Alberio and Pablo Bermejo-Álvarez (doi:10.1242/dev.199743)

Selected by Maria Elena Torres-Padilla: ‘This timely technical paper describes a robust protocol for *in vitro* culture of sheep embryos through to gastrulation stages. Extending the time period through which mammalian embryos can be maintained in culture is an important goal, and the use of an alternative model system (beyond mouse and human) provides a valuable resource for the community.’

Blood-progenitor redox homeostasis through olfaction-derived systemic GABA in hematopoietic growth control in *Drosophila* by Manisha Goyal, Ajay Tomar, Sukanya Madhwal and Tina Mukherjee (doi:10.1242/dev.199550)

Selected by Irene Miguel-Aliaga: ‘This is a nice study that sheds new mechanistic light on the unexpected coupling between a peripheral sense and the growth of a hematopoietic organ. The authors convincingly show that, in *Drosophila*, a systemic and olfaction-dependent neurotransmitter (GABA) supports lymph gland growth by blunting TCA activity and ROS levels in blood progenitors.’

The immune environment of the mammary gland fluctuates during post-lactational regression and correlates with tumour growth rate by Jessica Hitchcock, Katherine Hughes, Sara Pensa, Bethan Lloyd-Lewis and Christine J. Watson (doi:10.1242/dev.200162)

Selected by Florent Ginhoux and Paul Martin: ‘This paper uses the mouse model to address an important question – how the tissue environment and its immune cell composition influence the capacity for tumour growth – and provides some potential insights into why the post-pregnancy risk of breast cancer is particularly exacerbated in older mothers.’

The extra-embryonic space and the local contour are crucial geometric constraints regulating cell arrangement by Sungrim Seirin-Lee, Kazunori Yamamoto and Akatsuki Kimura (doi:10.1242/dev.200401)

Selected by Thomas Lecuit: ‘Addressing the role of geometric constraints on development is really important and this is a great system. As one of the referees wrote, “This work is an important advance both methodological and conceptual to understand cell positions during early embryo development.”’

‘Neighbourhood watch’ model: embryonic epiblast cells assess positional information in relation to their neighbours by Hyung Chul Lee, Cato Hastings, Nidia M. M. Oliveira, Ruben Perez-Carrasco, Karen M. Page, Lewis Wolpert and Claudio D. Stern (doi:10.1242/dev.200295)

Selected by Paul François: ‘I liked this paper because it comes from a nice theoretical perspective first (the idea that cells ‘compute’ their positional information in a relative way), and the authors then proceeded by formalizing their ideas using theory, and then tested them with success. I think it is a nice illustration of how conceptual thinking can lead to experiments via mathematical modelling, with direct application to important developmental problems.’

Identification of fibroblast progenitors in the developing thymus by Pedro Ferreirinha, Ruben G. R. Pinheiro, Jonathan J. M. Landry and Nuno L. Alves (doi:10.1242/dev.200513)

Selected by Hanna Mikkola: ‘In this paper, the authors characterise the thymic fibroblast population and provide insights into how these cells differentiate – revealing a key role for thymic crosstalk in their maturation. This is an understudied but important area of thymus development. As referee 2 commented, “this work is highly timely and reveals new insights into how different stromal cells differentiate and are maintained”.’

Daw1 regulates the timely onset of cilia motility during development by Elizabeth A. Bearce, Zoe H. Irons, Samuel B. Craig, Colin J. Kuhns, Cynthia Sabazali, Dylan R. Farnsworth, Adam C. Miller and Daniel T. Grimes (doi:10.1242/dev.200017)

Selected by Elizabeth Robertson: ‘This brief report shows that mutations in Daw1, a protein involved in intraflagellar transport, causes a very pronounced early onset phenotype affecting curvature of the body axis due to highly reduced ciliary motion, but that this is rescued with time as the cilia regain close to wild-type beating frequencies. Overall, the study helps explain why Daw1 mutations in human lead to pronounced laterality defects (presumably due to defects in the embryonic node cilia) but that other adult phenotypes normally associated with ciliary defects (e.g. lung defects) are not observed.’

Dissecting mechanisms of chamber-specific cardiac differentiation and its perturbation following retinoic acid exposure by David M. Gonzalez, Nadine Schrode, Tasneem A. M. Ebrahim, Nicolas Broguiere, Giuliana Rossi, Lika Drakhlis, Robert Zweigerdt, Matthias P. Lutolf, Kristin G. Beaumont, Robert Sebra and Nicole C. Dubois (doi:10.1242/dev.200557)

Selected by Benoit Bruneau: ‘A carefully designed and well-analysed atlas of mouse early heart development uncovered new transcriptional paths towards chamber formation. The manipulation of retinoic acid levels uncovers interesting new details in the response of chamber-specific programs to this teratogen.’

An integrated atlas of human placental development delineates essential regulators of trophoblast stem cells by Yutong Chen, Dylan Siriwardena, Christopher Penfold, Adam Pavlinek and Thorsten E. Boroviak (doi:10.1242/dev.200171)

Selected by Samantha Morris: ‘This study presents a unified atlas of human trophoblast development, spanning zygote formation through to mid-gestation. The authors demonstrate the value of this resource, using it to reveal new cell fate regulators and signalling pathways controlling trophoblast development.’

PILS proteins provide a homeostatic feedback on auxin signaling output by Elena Feraru, Mugurel I. Feraru, Jeanette Moulinier-Anzola, Maximilian Schwihla, Jonathan Ferreira Da Silva Santos, Lin Sun, Sascha Waidmann, Barbara Korbei and Jurgen Kleine-Vehn (doi:10.1242/dev.200929)

Selected by Ykä Helariutta: ‘This paper starts from a mutant screen to identify a novel gene that appears to control the abundance of two PILS proteins that control auxin responsiveness. While the authors don’t unravel all the mechanistic links, the paper makes a valuable contribution to the auxin field and will be of significant interest to the community.’

Retrovirus-derived *RTL5* and *RTL6* genes are novel constituents of the innate immune system in the eutherian brain by Masahito Irie, Johbu Itoh, Ayumi Matsuzawa, Masahito Ikawa, Hiroshi Kiyonari, Miho Kihara, Toru Suzuki, Yuichi Hiraoka, Fumitoshi Ishino and Tomoko Kaneko-Ishino (doi:10.1242/dev.200976)

Selected by Haruhiko Koseki: ‘The paper by Kaneko-Ishino and colleagues shows the contribution of a retrotransposon-derived genetic element that accepts genomic imprinting in extra-embryonic tissues to mediate innate immunity in the brain of eutherian animal. This paper will be a milestone towards understanding how retrotransposal elements could be internalized into the genome as functional genetic elements.’

Hypoxia induces an early primitive streak signature, enhancing spontaneous elongation and lineage representation in gastruloids by Natalia López-Anguita, Seher Ipek Gassaloglu, Maximilian Stötzel, Adriano Bolondi, Deniz Conkar, Marina Typou, René Buschow, Jesse V. Veenvliet and Aydan Bulut-Karslioglu (doi:10.1242/dev.200679)

Selected by James Briscoe: ‘This study exemplifies the potential of *in vitro* models to provide insight into developmental processes. The authors show that hypoxia induces embryonic stem cells to express primitive streak genes, initiate morphological elongation and symmetry breaking, even in the absence of WNT signalling usually used to initiate these events *in vitro*. The result links physiological environment to key events in embryogenesis and it will prompt further investigation of the underlying mechanism.’

Rapid and robust directed differentiation of mouse epiblast stem cells into definitive endoderm and forebrain organoids by Daniel Medina-Cano, Emily K. Corrigan, Rachel A. Glenn, Mohammed T. Islam, Yuan Lin, Juliet Kim, Hyunwoo Cho and Thomas Vierbuchen (doi:10.1242/dev.200561)

Selected by James Wells: ‘While the differentiation of human pluripotent stem cells into definitive endoderm has been widely used, the robust and efficient differentiation of mouse embryonic stem cells into definitive endoderm (DE) has been more challenging. This new method to generate mouse DE will open the door for new studies of mouse endoderm development using the many previously generated genetically modified embryonic stem cell lines.’

Pendulum of induction between the epiblast and extra-embryonic endoderm supports post-implantation progression by Erik J. Vrij, Yvonne S. Sholte Op Reimer, Laury Roa Fuentes, Isabel Misteli Guerreiro, Viktoria Holzmann, Javier Frias Aldeguer, Giovanni Sestini, Bon-Kyoung Koo, Jop Kind, Clemens A. van Blitterswijk and Nicolas C. Rivron (doi:10.1242/dev.192310)

Selected by Matthias Lutolf: ‘Nicolas Rivron and colleagues have pioneered the development of “blastoids”, self-organizing 3D tissues derived from embryonic stem cells (ESCs) and trophoblast stem cells (TSCs) that mimic key morphological and transcriptional features of the blastocyst, and can be used as a model for the preimplantation stage and integrated development of the conceptus. This work represents a further improvement of the original protocol, with the introduction of chemically defined culture conditions for both ESCs and TSCs, and provides interesting mechanistic insights into the crosstalk between the two cell compartments.’

The GATA factor ELT-3 specifies endoderm in *Caenorhabditis angaria* in an ancestral gene network by Gina Broitman-Maduro, Simo Sun, Taisei Kikuchi and Morris F. Maduro (doi:10.1242/dev.200984)

Selected by Swathi Arur: ‘This is a nice experimental example of evolution of a gene regulatory network that leads to endoderm specification in two distant yet related species, wherein the authors identify a basic gene regulatory network which drove endoderm specification in nematodes. I will quote one of the reviewers, since they say it so well: “Endoderm specification is fundamental to animal development and its specification is at the heart of developmental gene networks. As such, it provides a superb opportunity to study the evolution of development, including of gene regulatory networks. This is textbook stuff!”’