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EDITORIAL

Development's 2023 Outstanding Paper Prize

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We are delighted to announce the winners of Development's Outstanding Paper Prize for papers published in 2023. Initiated last year (Briscoe et al., 2023), this prize highlights some of the best research published in the journal each calendar year, with the first author(s) of the winning paper(s) being awarded a cash prize and being featured in a special edition of our Development presents... webinar on Tuesday 21 May at 15:00 BST (https://thenode.biologists.com/devpres).

Last year, almost 290 papers were eligible for this prize and the editor team whittled this down to a shortlist of 16 (listed below); from these, we selected two joint winners and a runner-up. We felt these best exemplified the kinds of papers we aim to publish: studies that make strong conceptual and technical contributions to an area of developmental or stem cell biology, and that will drive the field forwards. Before announcing the chosen papers though, we'd like to take the opportunity to thank all our authors for submitting to the journal – without you, there wouldn't be a journal! – and to congratulate in particular all those who made the shortlist.

And so to the winners… Coincidentally, both our winning papers (between which we could not choose) feature members of the Frizzled family of Wnt receptors as the star (in both cases named Frizzled 2 but, given historic naming conventions in flies and mammals, members of different subfamilies), but otherwise they sit, in terms of scope, at opposite ends of the spectrum of papers published in the journal. The first paper, 'Successful therapeutic intervention in new mouse models of frizzled 2-associated congenital malformations' (Liegel et al., 2023), uses state-of-the-art genome engineering techniques in mouse to model a human congenital anomaly, autosomal dominant Robinow syndrome, associated with heterozygosity for specific C-terminal *FZD2* variants. Although loss-of-function *fzd2* mice have previously been found to partially recapitulate the human syndrome – characterised by craniofacial dysmorphism and shortened limbs – this collaborative study, spearheaded by co-first authors Ryan Liegel, Megan Michalski and Sanika Vaidya, not only generated a set of mouse models that more completely reflect the Robinow syndrome phenotype, but also demonstrated that this phenotype can be partially alleviated through pharmacological upregulation of the Wnt signalling pathway. As one of the referees commented: 'This is an excellent study demonstrating the power of mouse models for defining protein functions linked to pathological genetic variants.'

The second winner, 'Frizzled2 receives WntA signaling during butterfly wing pattern formation' (Hanly et al. 2023), addresses the question of how members of ancient signalling pathways can evolve to regulate highly diverse phenotypes in distinct organisms. A technical tour-de-force (one referee stated that the paper 'seriously raises the bar for butterfly wing pattern evo-devo research'), the paper again uses gene editing approaches to analyse the consequences of *Fz2* disruption – but this time in a range of butterfly species. Building on decades of research on Wnt signalling pathways and functions in *Drosophila*, the authors of this paper (another multi-team effort, led by Joe Hanly and Ling Loh) demonstrate how shifts in the expression patterns of *Fz2* and its ligand *WntA* can direct colour patterning variation across evolution. The paper also explores the distinct roles of other frizzled receptors in the butterfly wing, building up a more complete picture of the complexity of signalling in this system.

Although these two papers ask very different scientific questions, common themes emerge. The first is the power of CRISPR-based genomic editing technologies to open up new avenues to explore old questions. Both in well-studied (the mouse) and less conventional (butterflies) experimental organisms, we now have the ability to manipulate the genome to generate precise lesions (e.g. to recapitulate human variants) and to explore gene function in previously intractable organisms. Secondly, these two studies demonstrate how much there is left to learn about even one of the most well-studied developmental signalling molecules. Research over several decades has uncovered many of the details of Wnt pathway mechanisms and functions in development, but we still have an incomplete understanding of how a limited repertoire of signalling pathways can be deployed across space and time to orchestrate such a diverse array of outputs, and how specific genetic variants can differentially impact on the functions of signalling proteins.

In addition to these two outstanding papers, we also wanted to highlight a third study that we felt demonstrated how new stem cell technologies can be used to advance our understanding of developmental processes. 'Gastruloid-derived primordial germ cell-like cells develop dynamically within integrated tissues' (Cooke et al., 2023) builds on the earlier observation that primordial germ cell-like cells (PGCLCs) can be found within mouse gastruloids (self-organising 3D stem cell structures that recapitulate *in vitro* many of the events of early embryogenesis) and characterises their specification and differentiation. Importantly, PGCLCs that form within gastruloids can mature to a greater extent than those derived through other *in vitro* methods. As the referees noted, this study was 'very well controlled and executed' and the resulting paper 'a joyful read'.

Many congratulations to the authors of all three of these papers, and to the others who made our shortlist. We are excited by the quality, depth and diversity of research on show in this list – choosing just a handful of winners from among all the papers we published last year was not an easy task, but having the opportunity to revisit these studies certainly made it an enjoyable one. We have already published some promising candidates for next year's prize, but it's not too late for your paper to be among them, so please do consider submitting your next study to Development to be in with a chance of winning!

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Box 1. The story behind 'Successful therapeutic intervention in new mouse models of frizzled 2-associated congenital malformations'

A brief interview with Ryan Liegel, Megan Michalski, Bart Williams and Rolf Stottmann.

What was the motivation behind this study?

RS: The human FZD2 variant was one of the first we identified in the Stottmann lab as we moved into human genetics studies. As we studied the literature, we recognized there were several open questions for which we thought this variant could be used as an entry point. The most pressing of these was whether canonical and/or non-canonical WNT signalling pathways were affected in the presence of this variant.

How did the collaboration between the Stottmann and Williams labs come about?

BW: For almost 25 years, the Williams lab has worked to understand the role of Wnt signalling in normal development and how it is dysregulated in human disease. We recently turned our attention to trying to understand how Frizzled receptors signal in more detail and became more familiar with the Stottmann lab's work identifying FZD2 variants as being linked to autosomal dominant omodysplasia. We contacted Dr Stottmann and started conversations about Frizzled receptor function, which eventually led to this very productive collaboration.

One of the exciting findings of this work is that pharmacological intervention can partially rescue the FZD2 mutant phenotype. To what extent do you think this might be translatable therapeutically?

RS: I think this is very much something that might be taken into clinical applications and this is what has me the most excited. Of course, we need to think about delivery and potential toxicity to the mother, among other concerns, but this is a very exciting direction for us to pursue.

Where are you taking this work next?

RS: Exactly because of the clinical promise, I am preparing a grant proposal to take this forward. We did get partial rescue of the phenotypes with our treatment, but we only tried one dosing regimen. I want to see whether tweaking this and/or using other related compounds might be as (or more) effective. In an ideal scenario, we might identify a WNT agonist that is already FDA-approved for another use and has been deemed safe. We also want to dive deeper into the molecular mechanism of the rescue – it's a puzzle as we think the phenotypes are most likely due to non-canonical WNT activity, but the small molecule is thought to stimulate the canonical pathway. Finally, and perhaps most exciting, there are reasons to think the treatment might act just as well on other genes already known to cause autosomal-dominant Robinow-like omodysplasia and several mouse models exist for some of these genes. Can we extend our treatment paradigm to these models as well?

Ryan and Megan – can you each tell us a little about your career history and future plans?

RL: During my doctoral work at the Medical College of Wisconsin under the guidance of DJ Sidjanin, I became interested in genetic approaches to modelling disease. This led me to Rolf's lab for a postdoc, where I worked on a number of projects leveraging the great clinical genetic collaborations we had at the Cincinnati Children's Hospital Medical Center to model patient variants of craniofacial anomalies, including this one. I then moved back to Wisconsin, where I worked for a time in Phil Newmark's lab developing transgenic techniques for flatworms. I'm now a full-time dad to my two young children, and while I would like to get back into science some day, family is my focus for now.

MM: I completed a dual DDS (Doctor of Dental Surgery)/PhD programme at the University of Michigan School of Dentistry, focussing on the immune system's regulation of bone turnover and healing. My dental background sparked an interest in craniofacial development, and I joined Bart William's lab at the Van Andel Institute as a postdoc in 2017 to work on how Wnt signalling regulates the developing structures of the face, with a particular focus on developing mouse models to study the role of the Wnt pathway in congenital anomalies. I have recently transitioned into a Research Scientist role in Bart's lab and would like to continue working at the bench on these projects.

RS: The third co-first author, Sanika, performed this work as an undergraduate scholar in my lab and has since matriculated into the Wake Forest University School of Medicine; she was not available to contribute to this interview.

Shortlisted papers

***NANOGP1*, a tandem duplicate of *NANOG*, exhibits partial functional conservation in human naive pluripotent stem cells** by Katsiaryna Maskalenka, Gökberk Alagöz, Felix Krueger, Joshua Wright, Maria Rostovskaya, Asif Nakhuda, Adam Bendall, Christel Krueger, Simon Walker, Aylwyn Scally and Peter J. Rugg-Gunn (doi:10.1242/dev.201155)

'The paper by Rugg-Gunn and colleagues demonstrates a function for a duplicate of the *NANOG* gene in pluripotency. Often such duplications and pseudogenes are understudied or ignored and are overall very poorly understood. This paper is important as it systematically studies the function of a duplication of one of the key regulators of the gene regulatory network of pluripotency, which the authors also document is conserved across species.' Maria Elena Torres-Padilla

Successful therapeutic intervention in new mouse models of frizzled 2-associated congenital malformations by Ryan P. Liegel, Megan N. Michalski, Sanika Vaidya, Elizabeth Bittermann, Erin Finnerty, Chelsea A. Menke, Cassandra R. Diegel, Zhendong A. Zhong, Bart O. Williams and Rolf W. Stottmann (doi:10.1242/dev.201038)

'This is a nice example of state-of-the-art genome engineering *in vivo* using i-GONAD-based CRISPR/Cas9 to generate dysfunctional alleles of a disease relevant gene. They relate the phenotypic description of these alleles to human syndromes, provide evidence of a molecular mechanism and proof of concept for a therapeutic intervention. It exemplifies the use of gene editing in mice to investigate rare developmental disorders and their suitability for establishing potential therapeutic approaches.' James Briscoe

Hox11-expressing interstitial cells contribute to adult skeletal muscle at homeostasis by Corey G. K. Flynn, Paul R. Van Ginkel, Katharine A. Hubert, Qingyuan Guo, Steven M. Hrycaj, Aubrey E. McDermott, Angelo Madruga, Anna P. Miller and Deneen M. Wellik (doi:10.1242/dev201026)

'Skeletal muscle homeostasis and regeneration is historically attributed to a rare population of stem cells called satellite cells. Using genetic fate-mapping approaches in mice, Flynn and colleagues identify a population of interstitial cells that contribute nuclei to myofibers during muscle homeostasis *in vivo*. These strong and unexpected myogenic functions of this cell subpopulation highlight how interstitial cells help regulate myonuclear number in mammalian skeletal muscle.' Ken Poss

An ancient testis-specific IQ motif-containing H gene regulates specific transcript isoform expression during spermatogenesis by Paula Navarrete-López, Marta Lombó, Maria Maroto, Eva Pericuesta, Raúl Fernández-González, Priscila Ramos-Ibeas, María Teresa Parra, Alberto Viera, José Ángel Suja and Alfonso Gutiérrez-Adán (doi:10.1242/dev.201334)

'The authors took a classical gene knockout approach and came up with a novel implication of IQCH gene products in the regulation of alternative splicing during spermiogenesis. This manuscript,

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Box 2. The story behind 'Frizzled2 receives WntA signaling during butterfly wing pattern formation'

A brief interview with Joe Hanly, Ling Loh and Arnaud Martin

What was the motivation behind this study?

We had been racking our brains over how WntA, a highly versatile ligand repeatedly employed across lepidoptera in colour patterning, functions on a molecular level. Given that the known receptors of Wnt ligands are members of the Frizzled (Fz) family, we systematically identified and tested the roles of four lepidopteran Fz family members in six different species of butterflies by amassing over 12,000 embryo injections by many Martin lab members.

The paper is the result of an international, multi-team collaboration. How did this come about?

When we started this project back in late 2017, it was still the very early days of butterfly CRISPR, and so we were actively communicating with a bunch of other teams who were trying to get the method going in their own hands. Because we'd found that *Fz2* knockout worked really well, we suggested it as a good positive control gene for people who were making their first CRISPR attempts, so this helped the project become a big multi-team collaboration.

Can you say a little about some of the challenges of working with butterflies?

We can pose so many interesting questions with butterfly wing patterns in terms of phenotypic and genotypic diversity: we have a 'simple' system of an essentially 2D groundplan, but with myriad colour patterns, and both within- and between-species variation. But in terms of rearing in the lab, they aren't *Drosophila*, to put it mildly! This was the first big project we embarked on after Arnaud opened his lab, so a really big part of the process was figuring out how to successfully rear (making good artificial diets, optimising temperature and humidity for different species, stopping caterpillars from eating each other and so on) and inject them. This was one of the ways that the amazing team of undergrad researchers were absolutely critical in making this project happen. There were some major bumps along the way: Joe vividly recalls a morning in the summer of 2018 when he arrived in the greenhouse to find several hundred final-instar *Agraulis* caterpillars literally melting, due to an outbreak of Nuclear Polyhedrosis Virus (the infection is easily identifiable by the smell of rotting meat). A pretty devastating moment!

Where are you taking this work next?

Is WntA 'canonical', is it a long-range acting secreted morphogen, and what is the transcriptional effector of WntA? Many questions remain, and we indeed hope to keep using butterfly colour patterns as a study system to investigate signalling and spatial patterning. Anyi Mazo-Vargas is starting her lab at Duke and will be exploring the transcriptional response to WntA signals using single-cell RNA-seq, which may give us an entry point on the type of transduction mechanism at play. Arnaud is interested in developing transgenic assays, which may allow us to overexpress the ligand and better characterize the generation of pattern boundaries.

Joe and Ling – can you each tell us a little about your career history and future plans?

LL: I started working with butterflies during my undergraduate studies in Singapore, and joined Arnaud's lab for my PhD, from which I gained a more developmental perspective in thinking about how butterflies use wing patterns to solve problems of finding a mate, escaping from predators and even just surviving. I have always been intrigued by how conserved mechanisms can be manipulated to produce the extensive diversity in nature. With that, I am moving to work on other insect systems, using development to understand how different strategies are employed during multispecies interactions, with the aim of delving into the role of sensory systems at the organism–environment interface.

JH: After finishing my PhD in late 2017, I joined Arnaud's lab at The George Washington University as an NSF-funded postdoc. Since then, I've been a Biodiversity Genomics fellow with the Smithsonian Institution and now am a postdoc with Greg Wray at Duke University, though I still spend most of my time in DC or at the Smithsonian Tropical Research Institute in Panama. I'm now working on a project where we're studying how gene regulatory networks evolve in closely-related species of mimetic butterflies. Looking forward, I'm hoping to be able to start my own research group, where I'll use population and functional genomics to study how the genome produces phenotypic diversity through development. I'm on the market, call me!

though still quite descriptive, represents an entry point towards a mechanistic understanding of tissue-specific alternative splicing.' Haruhiko Koseki

Craniofacial dysmorphology in Down syndrome is caused by increased dosage of Dyrk1a and at least three other genes by Yushi Redhead, Dorota Gibbins, Eva Lana-Elola, Sheona Watson-Scales, Lisa Dobson, Matthias Krause, Karen J. Liu, Elizabeth M. C. Fisher, Jeremy B. A. Green and Victor L. J. Tybulewicz (doi:10.1242/dev.201077)

'This paper exploits novel mouse models of Down syndrome to identify the subset of genes causally associated with the craniofacial dysmorphology phenotype seen in the majority of individuals with Down syndrome. The study enabled the identification of a minimal syntenic region that contains the *Dyrk1a* serine/threonine kinase gene in addition to three other genes. When present in three copies, inheritance of this minimal region results in decreased neural crest proliferation and a marked decrease in the size of the frontal bone primordial of the developing skull. An important conclusion is that overexpression of *Dyrk1a* may in part contribute to the craniofacial defects in individuals with Down syndrome.' Liz Robertson

Dysfunction of programmed embryo senescence is linked to genetic developmental defects by Cristina de Lope, Rebeca García-Lucena, Marta Magariños, Yolanda León, Nuria Casa-Rodríguez, Nuria Contreras, Carmen Escudero-Iriarte, Isabel Varela-Nieto, Pascal Maire and Ignacio Palmero (doi:10.1242/dev.200903)

'This study highlights the impact of dysregulation of programmed cellular senescence in a disease model of the human Branchio-Oto-Renal syndrome. Importantly, the findings of this study point to the causality of regulation of cellular senescence for genetic developmental disease.' Patrick Tam

Female reproductive dormancy in *Drosophila* is regulated by DH31-producing neurons projecting into the corpus allatum by Yoshitomo Kurogi, Eisuke Imura, Yosuke Mizuno, Ryo Hoshino, Marcela Nouzova, Shigeru Matsuyama, Akira Mizoguchi, Shu Kondo, Hiromu Tanimoto, Fernando G. Noriega and Ryusuke Niwa (doi:10.1242/dev.201186)

'I chose this paper because it sheds mechanistic light on a fascinating physiological adaptation of insects: reproductive dormancy (or diapause), whereby female insects arrest egg development in unfavourable conditions. Through a series of carefully executed anatomical and functional experiments, the authors demonstrate a causal role for a neuroendocrine mechanism in this context.' Irene Miguel-Aliaga

A dynamical systems treatment of transcriptomic trajectories in hematopoiesis by Simon L. Freedman, Bingxian Xu, Sidhartha Goyal and Madhav Mani (doi:101242/dev.201280)

'We are living in the age of big data acquisition. In parallel, we have classical, abstract models of development (such as Waddington's landscape), now connected to dynamical systems theory, and it is important to make a connection between such higher-level, theoretical descriptions and data (to confirm or falsify them). This paper shows practically how one can take single-cell

RNA-seq data and look for signatures of bifurcations, allowing us to rigorously define and track cellular decisions.' Paul Francois

Developmental emergence of cortical neurogliaform cell diversity by Lucia Gomez, Christelle Cadilhac, Julien Prados, Nandkishor Mule, Denis Jabaudon and Alexandre Dayer (doi:10.1242/dev.201830)

'This study defines the specification and maturation of a unique GABAergic interneuron population born from the preoptic area, which are distinct from most cortical interneurons. The study stands out for the use of a vast array of technical tools (fate mapping, single cell analysis, electrophysiology and functional manipulations in mice). Importantly it adds to an understanding of the vast diversity of neuroglia and their embryonic origins.' Debra Silver

Frizzled2 receives WntA signaling during butterfly wing pattern formation by Joseph J. Hanly, Ling S. Loh, Anyi Mazo-Vargas, Teomie S. Rivera-Miranda, Luca Livraghi, Amruta Tendolkar, Christopher R. Day, Neringa Liutikaite, Emily A. Earls, Olaf B. W. H. Corning, Natalie D'Souza, José J. Hermina-Perez, Caroline Mehta, Julia A. Ainsworth, Matteo Rossi, Riccardo Papa, W. Owen McMillan, Michael W. Perry and Arnaud Martin (doi:10.1242/dev.201868)

'This paper addresses an important question about how members of ancient signalling pathways can evolve to regulate highly diverse phenotypes in distinct organisms. The work is outstanding both for its intellectual contributions, illuminating the evolutionary roles of this highly pleiotropic pathway in diversifying fitness-relevant pattern phenotypes, and also for its technical contributions, raising the bar for rigor and depth of analysis using CRISPR-mediated genome editing across multiple understudied model species.' Cassandra Extavour

Gastruloid-derived primordial germ cell-like cells develop dynamically within integrated tissues by Christopher B. Cooke, Christopher Barrington, Peter Baillie-Benson, Jennifer Nichols and Naomi Moris (doi:10.1242/dev.201790)

'This is a compelling example of the power of *in vitro* embryoid models, to capture complex three-dimensional developmental processes in early embryogenesis and organogenesis. The authors show that gastruloids contain a population of primordial germ cell-like cells that resemble early primordial germ cells *in vivo*. Strikingly, these cells appear in a spatially and temporally coordinated manner with respect to surrounding somatic cells, demonstrating the importance of tissue–tissue interactions for the coordinated specification and maturation of key cell types.' Matthias Lutolf

The translation initiation factor homolog *eif4e1c* regulates cardiomyocyte metabolism and proliferation during heart regeneration by Anupama Rao, Baken Lyu, Ishrat Jahan, Anna Lubertozzi, Gao Zhou, Frank Tedeschi, Eckhard Jankowsky, Junsu Kang, Bryan Carstens, Kenneth D. Poss, Kedryn Baskin and Joseph Aaron Goldman (10.1242/dev.201376)

'This work combines evolutionary biology, structure-function analysis, zebrafish developmental biology and regeneration, and ribosome profiling to discover the function of a translation initiator conserved in aquatic species but absent in terrestrial vertebrates. It is a deep and interesting exploration of a new protein that modulates translation in heart development and regeneration.' Benoit Bruneau

Adipose triglyceride lipase promotes prostaglandin-dependent actin remodeling by regulating substrate release from lipid droplets by Michelle S. Giedt, Jonathon M. Thomalla, Roger P. White, Matthew R. Johnson, Zon Weng Lai, Tina L. Tootle and Michael A. Welte (doi:10.1242/dev.201516)

'This innovative paper uses a range of elegant approaches and addresses a problem that I expect should be of broader significance in other organisms.' Thomas Lecuit

Dihydrofolate reductase activity controls neurogenic transitions in the developing neocortex by Sulov Saha, Thomas Jungas, David Ohayon, Christophe Audouard, Tao Ye, Mohamad-Ali Fawal and Alice Davy (doi:10.1242/dev.201696)

'We selected this paper because it showed strikingly specific expression and neurodevelopmental roles for a key enzyme in one-carbon/folate metabolism, underscoring the instructive roles of metabolism in controlling developmental transitions.' Irene Miguel-Aliaga and Lydia Finley

Calcium signals tune AMPK activity and mitochondrial homeostasis in dendrites of developing neurons by Akane Hatsuda, Junko Kurisu, Kazuto Fujishima, Ayano Kawaguchi, Nobuhiko Ohno and Mineko Kengaku (doi:10.1242/dev.201930)

'I like this paper because it reveals a mechanistic link between two seemingly unrelated aspects of neuronal biology: dendritic morphogenesis and mitochondria metabolism. The study is very thorough and compelling and the finding that mitochondria homeostasis is controlled by neuronal activity and calcium signalling and is required for dendritic outgrowth was unexpected.' Francois Guillemot

A chemo-mechanical model of endoderm movements driving elongation of the amniote hindgut by Panagiotis Oikonomou, Helena C. Cirne and Nandan L. Nerurkar (doi:10.1242/dev.202010)

'I chose this paper because it combines classic embryonic approaches with a systems biological approach to explore a poorly understood area of developmental biology, namely morphogenetic movements during gut tube formation. It links FGF signalling to endoderm cell behaviours in a way that was not previously appreciated, making a new model employing a chemo-mechanical model for hindgut endoderm morphogenesis.' James Wells

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