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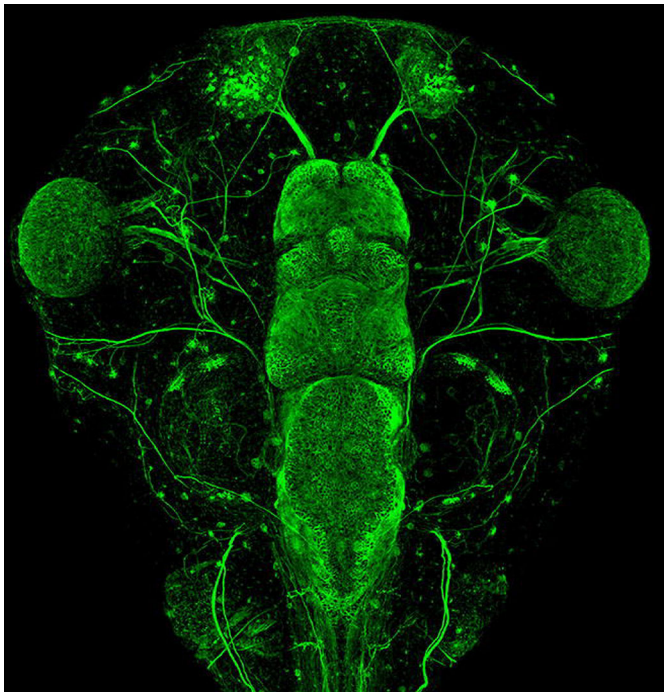
EDITORIAL

Developmental disorders Journal Meeting: a collaboration between Development and Disease Models & Mechanisms

Kirsty M. Hooper[1], Monica J. Justice[2] and E. Elizabeth Patton[3,*]



Developmental disorders present at birth or arise during childhood, leading to physical or intellectual disabilities with long-term effects on morbidity. According to a study from the Centers for Disease Control and Prevention, one in six children in the USA has a developmental disability that affects their education and lifestyle (Zablotsky et al., 2019). These disorders encompass a wide range of conditions, and are caused by genetic and/or environmental factors. Expanding research in this area is fundamental to improving diagnosis, preventing progression and treating these conditions. At Disease Models & Mechanisms (DMM), we have a strong interest in research that delineates the mechanisms that underlie developmental disorders, with a dedicated collection of Reviews, Perspectives and Research articles. We pursue pre-clinical modelling to discover new mechanistic insights with a view towards how this can support children and their families, and inform their care.

This year, DMM has joined with sister journal Development to bring together developmental biologists, disease modellers, human geneticists and clinicians to address the most-pressing issues within this field. The Company of Biologists Journal Meeting 'Developmental Disorders: From Mechanism to Treatment' will be held on 14–17 September 2021 (Box 1). This virtual Meeting, organised by Phil Beales (University College London, UK), Development Editor-in-Chief James Briscoe (The Francis Crick Institute, London, UK), DMM Editor Monica J. Justice (The Hospital for Sick Children, Toronto, Canada) and Lee Niswander (University of Colorado, Boulder, CO), will build and strengthen connections between disciplines, and encourage researchers and clinicians to share their perspectives to drive progress. Patients will also share their journeys living with these disorders. We believe that the patient's perspective is crucial for a holistic understanding of the disease and can help to unify the unmet needs of this research.

Genetics play a pivotal role in the causation of many developmental disorders including rare diseases. This years' Meeting will address how advances in genetic technology can be applied to the discovery of causative genetic variants for rare developmental diseases. Animal models of rare developmental disorders are key to understanding the mechanisms and whole-body physiological effects of mutations, especially given the challenges of the small patient cohorts. Research published by DMM exploring this and other genetic mechanisms that underlie rare disease can be found in the collection 'Rare Disease Translational Research Using Model Systems'. In one study, understanding the genetic cause of the rare neurodevelopmental disorder Rett syndrome identified a novel treatment in which a small neurotrophin receptor-targeting molecule can reduce respiratory and motor control deficiencies in a pre-clinical mouse model (Adams et al., 2020).

Unlike monogenic disorders, in which mutations within a single gene cause the particular disease, certain developmental disorders can be caused by variants of multiple genes that can converge to affect a singular organelle (Abdelhamed et al., 2020; Falkenberg et al., 2021; Lange et al., 2021). Ciliopathies, which will be discussed at the Meeting, are caused by defects in motile and non-motile cilia that act as signalling organelles extending from the surface of most eukaryotic cells. As cilia are found in most cells, mutations in cilia components can lead to developmental defects in multiple organs and tissues, including the brain, bones, kidneys and sensory organs. Genes associated with ciliopathies often have high variability in their phenotypic effects; therefore, it is particularly important to study the effects of missense variations – rather than gene depletion – on a disease phenotype to accurately mirror the genetic presentation in patients. Joubert syndrome is a ciliopathy that primarily affects brain development and devastatingly reduces life expectancy to under 10 years of age. This disease is associated

[1]The Company of Biologists, Station Road, Histon, Cambridge CB24 9LF, UK. [2]Program in Genetics and Genome Biology, The Hospital for Sick Children, and Department of Molecular Genetics, The University of Toronto, Toronto, Ontario M5G 0A4, Canada. [3]MRC Human Genetics Unit and Cancer Research UK Edinburgh Centre, MRC Institute of Genetics and Cancer, The University of Edinburgh, Western General Hospital, Crewe Road South, Edinburgh EH4 2XU, UK.

*Author for correspondence (e.patton@ed.ac.uk)

Kirsty Hooper is the DMM Features & Reviews Editor, Monica Justice is a DMM Monitoring Editor and Elizabeth Patton is the DMM Editor-in-Chief.

K.M.H., 0000-0003-2900-3849; M.J.J., 0000-0003-3562-2099; E.E.P., 0000-0002-2570-0834

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Box 1. The Company of Biologists Journal Meetings.

Journal Meetings are at the heart of The Company of Biologists. These events draw focus to some of the most intrinsic research areas in our community, and foster scientific progress through sharing knowledge and discussing pressing challenges in the fields covered by our journals (Development, Journal of Cell Science, Journal of Experimental Biology, DMM and Biology Open). DMM Meetings gather leading scientists and clinicians that work in a particular field, and aim to progress research from bench to bedside. The inaugural DMM Meeting 'Blood Disorders: Models, Mechanisms and Therapies' showcased the power of model systems for the discovery of basic pathogenic mechanisms and for the identification of potential treatments for diseases related to haematopoiesis (Justice et al., 2020).

The Company of Biologists international Journal Meetings vary in size but all have a strong focus on networking. Small, focused Workshops allow for in-depth discussion of a particular topic and larger Journal Meetings explore a broader scope of research. All are accessible to students and postdocs. This year, owing to coronavirus restrictions, we will adopt a virtual setting. Although we will miss the in-person interactions, we aim to retain the communicative and collaborative spirit of previous Meetings by using software that facilitates more-intuitive face-to-face conversation through video chats. One way in which the online format can benefit the Meeting – and one we hope to carry forward even after COVID-19 restrictions have lifted – is that it is more accessible to international participants. We, therefore, look forward to welcoming colleagues from around the world who might otherwise not be able to join us.

With the stark reality of the global climate crisis at the forefront of our minds, another benefit of the virtual conferences is their drastically reduced carbon footprint. The Company of Biologists Sustainable Conferencing Initiative supports organisers in lowering the environmental footprint of their events. On its dedicated website, relevant resources are available together with information about our Sustainable Conferencing Grants. We know that meeting in person has unique and inherent values that are not easily duplicated online. However, hub or hybrid conferences are a good alternative as they minimise travel and, when the sustainability of the in-person aspect is carefully considered, these events can have a significantly lower environmental footprint while being more inclusive. Our Initiative is also looking into these alternative types of conferencing and the new technologies that surround them. The Company of Biologists aims to create more environmentally friendly and socially responsible Meetings, and provide the necessary support to our community though this Initiative.

with different missense variations in *B9D2*, a gene that controls the entry of molecules into the cilia as well as its formation. As described by Lange et al. (2021), two of these pathogenic variants were modelled in *Caenorhabditis elegans*, resulting in defective cilia function and recapitulation of patient phenotype. This study exemplified the complex nature of genotype–phenotype correlations in ciliopathies and the power of using tractable model systems, such as *C. elegans*, to dissect them.

Congenital disorders can specifically affect single-organ systems, such as the heart (reviewed by Rufaihah et al., 2021), kidneys (reviewed by Blackburn and Miller, 2019), as well as skeleton and muscles (Liu et al., 2019; Rios et al., 2021; Wong et al., 2020). Patients with congenital bicuspid aortic valve have two instead of three flaps in this valve, which can lead to disease of this major artery. Peterson et al. (2020) used a mouse model with disrupted nitric oxide signalling to recapitulate features of this congenital heart disease. This study provides an alternative insight into the mechanism of congenital bicuspid aortic valve development compared with genetically modified models and, importantly, these mice mirror the altered gene expression of patients. Abnormalities in muscular and skeletal development can cause conditions affecting the spine, such as scoliosis. Rios et al. (2021) used saturation mutagenesis and radiographic screening to identify mice with severe spine malformations due to developmental disruptions. Making an important link to the clinic, they identified a mutation in one of the mouse models that led to the diagnosis of a patient with a previously undiagnosed skeletal disease. These articles highlight that congenital disorders require well-suited model systems that effectively recapitulate human physiology and have the potential to improve clinical practice.

The developing foetus is sensitive to signals, nutrients and pollutants from the environment, and these factors can combine with genetic risk factors to cause developmental disorders that vary in severity. This is especially true of neurocristopathies (Baddam et al., 2021; Wang et al., 2019), i.e. disorders caused by anomalies in the development of the neural crest, a transient embryonic migratory cell population in vertebrates. Cleft palate is a common congenital disorder characterised by craniofacial anomalies and its incidence can be increased by excessive vitamin A intake during pregnancy. To help delineate the mechanism of the vitamin A metabolite retinoic acid in cleft palate pathogenesis, Wang et al. (2019) administered retinoic acid to pregnant mice during embryogenesis. This results in increased apoptosis of cranial neural crest cells, underscoring the importance of neural crest cells in craniofacial development. Another common developmental disorder partially caused by altered nutrient demand during pregnancy is spina bifida, which is characterised by incomplete closure of the spinal neural tube during embryonic development (Rolo et al., 2019; Sudiwala et al., 2019). The study by Sudiwala et al. (2019) explored the mechanism of neural tube defects in a mouse model expressing a mutated version of the transcription factor *Pax3*. They found that Pax3 is important for the proliferation of the neuroepithelium, allowing fusion of the neural tube during development. The loss of Pax3 could be compensated for by folic acid supplementation during pregnancy. These studies highlight the importance of diet and nutrition during development, and provide a framework for understanding how underlying interactions between genes and environmental affect disease outcome.

The complex clinical manifestation of cognitive impairment associated with neurodevelopmental disorders presents a significant challenge to disease modellers. Coll-Tané et al. (2019) have reviewed the well-established use of *Drosophila* to research intellectual disability and autism spectrum disorders. The fruit fly can be used to study associated phenotypes at molecular, cellular, brain and behavioural level with easy genetic manipulation, and there is an expanding array of techniques that allow in-depth and high-throughput research with this organism. These flies were utilised by Tamberg et al. (2020), who show that silencing the fruit fly orthologue of the transcription factor TCF4 – that has been linked to intellectual disability and schizophrenia – can impair larval memory and locomotive function, and causes loss of synaptic proteins. Behavioural anomalies have also been explored in mouse models of Down syndrome (Shaw et al., 2020) and of diseases related to the dysregulation of gap junction protein connexin 3, which more frequently affect the skin (Novielli-Kuntz et al., 2021). Impaired cognitive development is a common outcome of many developmental disorders. Identifying and understanding the underlying cause of this impairment would enable accurate diagnosis and treatment of patients, and will be highlighted at the Journal Meeting.

Developmental disorders can have devastating effects on patients during childhood and throughout their lives. As they are challenging

to diagnose and challenging to treat, an array of model systems and techniques will be required to expand research into these disorders, and to drive forward translation to the clinic. We welcome scientists at all career stages, clinicians, patients and their advocates to our first joint Journal Meeting 'Developmental Disorders: From Mechanism to Treatment', to address many of the continued challenges in this field and to help progress research in order to improve the clinical prognosis of patients with developmental disorders.

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