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EDITORIAL

Celebrating FocalPlane and microscopy in Disease Models & Mechanisms

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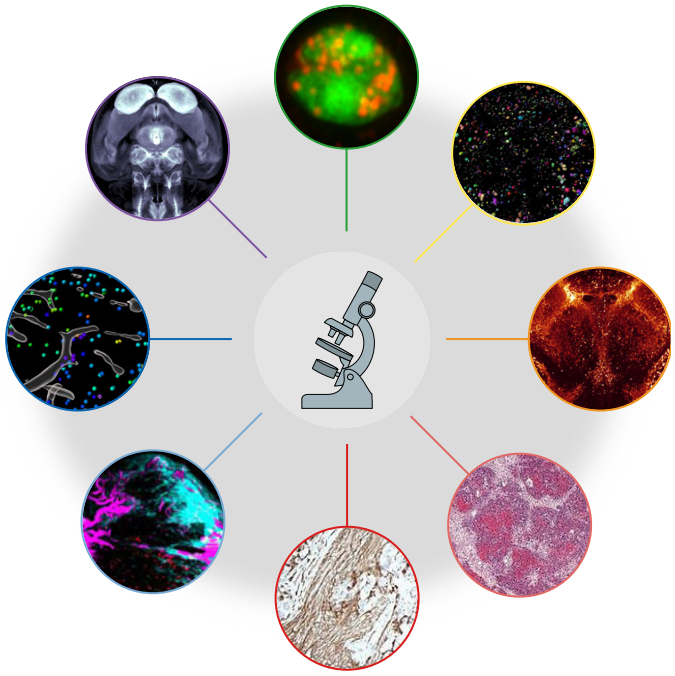
From the use of fabric dyes in early histopathology to today's fluorophores and advanced imaging techniques, researchers have relied on the optical microscope to discover and visualise disease-related processes. These approaches are instrumental in diagnosing and studying disease in patients, and are just as important for preclinical and translational research in model systems, from cell lines and organoids to animals. This Editorial celebrates the first anniversary of FocalPlane, the community site for microscopy, and highlights the importance of microscopy to research published in *Disease Models & Mechanisms* (DMM).

One of the key aims of DMM is to foster the translation of basic mechanistic and preclinical research to the clinic. Microscopy and imaging play pivotal roles in driving this research forwards. Here, we highlight some of the contributions these tools have made to recent research published in our journal and celebrate the first anniversary of the launch of the microscopy community site FocalPlane (Box 1), supported by our not-for-profit publisher The Company of Biologists and hosted by our sister journal *Journal of Cell Science* (JCS). FocalPlane launched a year ago with the goal to provide biologists with resources, best practices and technical know-how. Crucially, it is a community hub where experts and newcomers alike can exchange ideas and experience or simply marvel at the gallery of stunning images.

Nearly all research articles published in DMM feature microscopy images, illustrating the importance of imaging-based data for inferring disease mechanisms. Classic bright-field microscopy is, probably, the most accessible and, thus, most frequently used approach. When combined with chromophores, it allows researchers to study the histology of tumours that arise in newly developed mouse models of rare cancers, such as the novel angiosarcoma model described by Valerie Brunton's team (Salter et al., 2019). The broad accessibility and flexibility of bright-field microscopes mean that the set-ups can be adapted for live imaging of optically transparent model systems, such as organoids (Yoshimoto et al., 2020) and zebrafish embryos (Kuil et al., 2019), across a range of time points and experimental conditions. Importantly, the captured images are amenable for computational analyses, including machine-learning tools.

The development of fluorescence microscopy, together with the advent of fluorophores and fluorescent proteins, has opened up new avenues for biomedical research. These approaches have enabled the labelling and detection of multiple (endogenous) molecules in the same sample, and can be used for imaging live cells or organisms. For example, the groups of Ruth Muschel and Marc Vooijs combined transgenic fluorescent labelling of cancer cells with the use of multi-photon intravital microscopy to track the fate of hypoxic cells within murine tumours at a single-cell resolution (Vermeer et al., 2020). Moreover, fluorescence microscopy approaches have been adapted for high-throughput screening in disease models. Girish Ratnaparkhi and colleagues developed a kinetic fluorescence microscopy-based assay to functionally screen genes involved in the regulation of pathogenic SOD1 aggregates in a *Drosophila* model of amyotrophic lateral sclerosis (Chaplot et al., 2019). Like *Drosophila*, zebrafish models are also amenable to high-throughput screening that relies on fluorescence microscopy, as described in a recent study by the groups of Catherina and Thomas Becker, who developed an automated drug screening platform to identify synapse-stabilising compounds in juvenile zebrafish models of spinal muscular atrophy (Oprişoreanu et al., 2021). These examples show how integrating microscopy has benefited our understanding of rare neuromuscular disease biology and treatment opportunities, and provide a blueprint for future studies of rare disease.



Advanced microscopy techniques offer unprecedented opportunities to visualise disease-causing cellular and molecular processes with improved spatial and temporal resolution. For example, Serge Mostowy and Eva Maria Frickel's groups used correlative light-electron microscopy (CLEM) to visualise the proliferation of the obligate intracellular parasite *Toxoplasma gondii*

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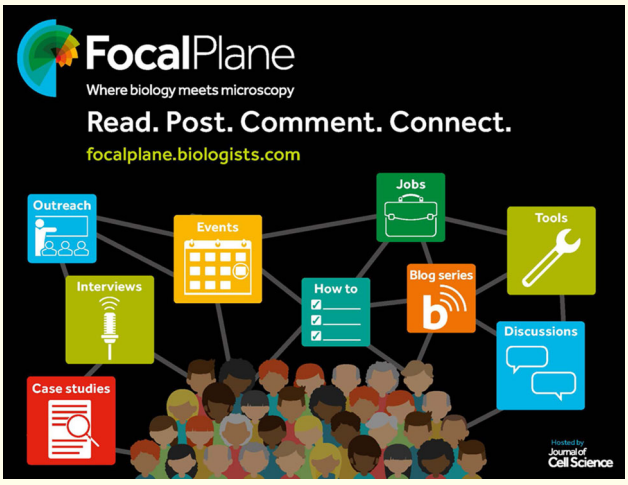
Box 1. FocalPlane

FocalPlane is the new microscopy community site, hosted by Journal of Cell Science. The site encompasses all fields in the biological sciences where they meet microscopy.

The ability to tackle ever-more-refined biological questions is improving as microscopy and image analysis become increasingly more complex and sophisticated. However, this has made it more and more difficult for non-experts to access user-friendly resources or tools tailored to their questions. Thus, there is a need for a platform for both microscope/software developers and researchers to exchange ideas and information in order for the field to develop and progress. To encourage these interactions, FocalPlane provides the opportunity for researchers to contribute primers on new techniques, interviews and case studies, validate a technique and share it with the community or even post their own short video tutorials.

FocalPlane is run by a dedicated Community Manager, who is supported by a distinguished Scientific Advisory Board.



Featuring news, interviews, blog series, tools, job listings, an events calendar, a regular journal club and a monthly webinar series called ‘FocalPlane features…’, the community site is free to access and users can register for a free account to post their own contributions.

We encourage you to make FocalPlane part of your online routine. Read, post, comment and get involved.

at high resolution in a newly developed zebrafish model (Yoshida et al., 2020); and research by Jacob Hecksher-Sørensen’s group relied on light-sheet fluorescence microscopy (LSFM) to image whole-brain samples and study neuron architecture in a murine model of Parkinson’s disease (Roostalu et al., 2019), and to track the changes in pancreatic islet cells of murine models of type I and II diabetes (Roostalu et al., 2020). LSFM images can be analysed computationally to allow automated measurement of disease-related phenotypes. For example, the group of Christopher Nguyen developed a deep-learning-based approach that automates capture and analysis of volumetric cardiac function data on the basis of microscopy images of embryonic zebrafish hearts (Akerberg et al., 2019). Moreover, techniques, such as Förster resonance energy transfer (FRET) (Wen et al., 2020) and super-resolution microscopy (SRM) (Jacquemet et al., 2020), allow researchers to study molecule dynamics, stoichiometry or localisation at nanometer resolution. These methods are particularly relevant in relation to transcription factors and other proteins with dose-dependent functions under homeostatic and pathological conditions (reviewed by Auer et al., 2021).

Of course, optical microscopy is not the only imaging methodology available to translational researchers. Other imaging modalities allow preclinical researchers to track the development and progression of a disease phenotype, and the response to therapeutic interventions in model systems. For example, imaging based on ultrasound and photoacoustics (Brown et al., 2019), and on magnetic resonance (Resaz et al., 2019) enable the *in vivo* visualisation of disease processes that affect soft tissues, particularly tumours, whereas X-ray-based imaging has been successfully used in *in utero* studies of developmental disorders in animal models (Friedl et al., 2019; Desgrange et al., 2019). These techniques reveal *in vivo* processes that provide new hypotheses and highlight the potential of disease model-based research.

These and other studies highlight how strongly the preclinical research community relies on microscopy to understand and treat disease. As emphasised in the JCS Editorial that marks FocalPlane’s launch, microscopy has reached a golden era – but finding relevant information in one place has been a challenge (Ahmad et al., 2020). Providing such a resource to serve and inspire the biological community was the key motivation behind the inception of FocalPlane. The site offers a wealth of information, but it was designed to provide a smooth user experience and interactivity. We encourage our authors and readers to join and contribute.

“We want to create a common language, a common place where we [microscopy developers and biologists] can talk in an easier way… and have a resource that actually stimulates this conversation.”

Dr Ricardo Henriques, group leader at Instituto Gulbenkian de Ciência in Oeiras, Portugal, and member of FocalPlane’s Scientific Advisory Board

Integrating microscopy and other imaging approaches into mechanistic research allows scientists to visualise processes that drive disease at molecular, cellular, tissue and whole-organism levels. In turn, this provides the required information to tackle the open challenges in disease research, from gaps in mechanistic understanding to evaluating the efficacy of novel treatment approaches. However, as with other aspects of biomedical research, obtaining robust and reproducible data is key to ensure the microscopy-based results are valid. As discussed by Teng-Leong Chew and colleagues, this should also extend to accurate reporting of imaging experiments and analyses – from describing the light source, optics, lenses and detectors to clarifying denoising, deconvolution, thresholding and segmentation parameters (Heddleston et al., 2021; Aaron and Chew, 2021). Furthermore, since reproducible preclinical data are a requisite for their successful translation, DMM, as an open-access biomedical journal, remains committed to supporting these efforts, and supports the initiative and guidance outlined by FocalPlane for accurate reporting of microscopy results.

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