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EDITORIAL

Bridging the gap between basic and applied biology: towards preclinical translation

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Summary

To better translate basic research findings into the clinic, we are moving away from the traditional one-gene–one-phenotype model towards the discovery of complex mechanisms. In this Editorial, the new Editor-in-Chief and Senior Editors of *Disease Models & Mechanisms* (DMM) discuss the role that the journal will play in this transition. DMM will continue to provide a platform for studies that bridge basic and applied science, and, by demanding the rigorous assessment of animal models of disease, will help drive the establishment of robust standards of preclinical testing for drug development.

The 'Great Merger' of basic and applied biology

Historically, biology disciplines have experienced periods of isolation followed by Great Mergers. For example, embryology and genetics were once seen as separate disciplines, divided by their respective goals and emphases and even by geographical location. Eventually, the two fields merged as the goals of embryologists and geneticists aligned and their knowledge deepened sufficiently to enable them to speak the same language. Cell biology and neurophysiology, and developmental biology and evolutionary biology have undergone similar mergers. When we look back on our current times we will recognize the early 21st century as the Great Merger of basic and applied biology. Of course, basic researchers have always understood that their work informs patient treatments as they explore the mechanisms of development and homeostasis: this box always needed to be checked on grant applications. But a confluence of forces is now accelerating this merger.

As our understanding of biological processes deepens, it will aid the development of rational approaches to disease. This enhanced understanding of biological processes must also be applied to animal models of disease. In the past, model organisms were used exclusively for understanding the cellular and molecular basis for disease; increasingly, they are being used directly to discover new therapies. Yet for most major diseases, clinical trials based on preclinical models show a very low success rate. At a time when the non-science public is more involved in funding decisions for science than ever before, we are under pressure to provide cures. Fast.

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This is a challenging but also an exciting time for science. We were graduate students in the era of the one-gene–one-thesis: isolate and explore the function of a gene and you had a PhD. Today, we can achieve nanometer resolution in our investigations, for example by imaging individual proteins, but we can also apply a holistic approach, as seen with systems biology. Stem cells have taken cell culture to an unprecedented level of sophistication. Whole genome sequencing is possible and cheap. Our tools are not only more powerful, their level of improvement itself is accelerating. Not surprisingly, we are now trying to imagine how these tools can be applied to disease. What we find remarkable is that the founders of DMM understood these trends years ago. These are developmental biologists, cell biologists, geneticists and other non-clinical scientists who anticipated that their favorite tools would be used to model diseases and search for therapeutics. This seems an obvious point now, but an amazing insight in 2008.

The story so far

DMM was arguably the first journal devoted to merging basic and clinical research, and it has established itself as a flagship journal in translational medicine. With its specific focus on the use of model systems to study disease, the journal occupies a unique niche.

As predicted by Matthew Freeman and Daniel St Johnston in their inaugural editorial entitled *Wherefore DMM?* (Freeman and St Johnston, 2008), the application of basic discoveries in model organisms has accelerated the study of human disease in recent years. This rapid growth is reflected in the number of research articles published in DMM since its launch, and in the breadth of these studies, which encompass a wide range of diseases and model systems. The journal has reported many milestones, including: the discovery of mitochondrial proteases with a role in Parkinson's disease (in *Drosophila*) (Whitworth et al., 2008); insights into the role of the serotonin transporter in depression (in mice) (Bartolomucci et al., 2010); evidence that melanoma progression can be halted using a PI3K inhibitor (in zebrafish) (Michailidou et al., 2009); the identification of small-molecule compounds with a protective role in neurodegenerative disease (in yeast, and *C. elegans*) (Su et al., 2010); and several patient-derived cell models for disease (Abrahamsen et al., 2013; Hick et al., 2013; Matigian et al., 2010). DMM has also published papers reporting on a number of important databases and resources, such as the generation of the Dre-*rox* system in mice (Anastassiadis et al., 2009). The quality of the primary articles, together with the diversity of its review content, helped DMM achieve a respectable impact factor (4.94 in 2011), despite its status as a new journal.

Undeniably, founding Editor-in-Chief Vivian Siegel has played a major part in the success of the journal. With her editorial experience and strong scientific background, Vivian provided the initial, critical push that brought the journal to the attention of the research community. She was also involved in establishing the editorial practice that ensured a steady stream of high-quality

research papers, and in introducing the journal's open-access policy. The decision to adopt an open-access model was an important step forward in the journal's development. This move facilitated faster publication and wider dissemination of research, maximizing the impact of the work published in DMM. Under Vivian's guidance, the scope was also expanded to include a broader range of experimental approaches, so that any papers offering insight into disease mechanisms, diagnostics or therapeutics are now considered, regardless of the approach used.

In her farewell Editorial (Siegel, 2013), Vivian likens her relationship with DMM to that of a mother and child. No longer a child, we aim to provide a maturing DMM with the nourishment it needs to continue to flourish.

Moving forward: challenges and opportunities

So, where do we go from here? What is the place of DMM in the Great Merger? Crucially, DMM is focused not only on utilizing disease models to translate basic biology to the clinic but also on examining and improving those models at the most basic level. Many of the failures we have seen in translating novel basic biological discoveries to useful medicines are a result of the inadequacies of the animal models we use at the critical juncture between bench and bedside. Oncology stands out as a field in which animal models have proven to be exceptionally poor at predicting clinical success, but other disease areas also suffer from a lack of robust and selective preclinical models. Why do these models fail? Reasons include physiological differences between the model and humans, a lack of proper model validation and/or a lack of thorough analysis. DMM will provide a dedicated journalistic platform through which scientists can communicate about disease models in order to improve the translation of basic science to the clinic. Only through improving translational research can we effectively bring to patients the fruits of the astonishing biological discoveries that our new tools have provided.

Our goals

What is great about stepping into this role is that we can play a part in helping DMM reach its full potential – we can dream big, and then make those dreams happen. Our primary goal is to be the 'go to' journal for research on disease models. But, more than continuing to publish excellent scientific papers, we will work *to bridge the gap between basic and applied sciences*. To accomplish this, we will strive to educate each side of the divide to speak the same language. We will establish a dialog on the type of science that is needed to push forward disease research and therapeutics. What sorts of model systems are useful and how do we decide if a model is predictive of human disease? What is the role of genetic background on the phenotype? How many genetic backgrounds need to be checked? How can we determine if a drug that is successfully metabolized in a model is similarly metabolized in humans? How can a model be optimally used to determine the systemic effects of a mutation, a drug or a gene therapy treatment? What types of drug leads are truly 'druggable', sit in 'patented chemical space' and can be pushed towards clinical trials? Which intellectual property issues should be considered before beginning a drug screen? For that matter, what is intellectual property exactly, and why should we care? As basic researchers (Monica and Ross) and a biotechnology industry executive (George), we are already debating these issues and are planning a series of columns to bring them into the public domain.

We will also introduce new standards to encourage work on, and publication of, disease models and mechanisms that can be reliably used for the selection of drug candidates to be entered into the expensive and time-consuming next phase of drug development. The pharmaceutical biotechnology industry relies heavily upon the integrity of basic academic research in order to make the large investment in clinical trials necessary to translate these breakthroughs to verified therapeutics. Almost without exception, industry bears the burdens (and the fruits) of navigating the minefield of clinical development through to marketing approval. Typical toxicology testing prior to entering clinical trials can cost up to US$5 million, excluding the scale-up involved in manufacturing the clinical grade drug product. Early clinical trials are designed solely to measure safety, with efficacy being assessed only with the onset of Phase 2 trials. Effectively, this means that, prior to any substantial data on efficacy, an investment well in excess of US$10 million is required. Therefore, robust and determinative preclinical animal testing is an extremely important focus of the drug development industry.

Recently, two major pharmaceutical companies, Bayer and Amgen, reported on the lack of reproducibility of published preclinical research (Begley and Ellis, 2012; Prinz et al., 2011). The basic scientific community has also noted the increasing presence of ascertainment (sampling) and publication biases in scientific reports, with data being dismissed or even omitted to promote the findings that are perceived as the most impressive (Ioannidis, 2005). Yet disciplines such as therapeutic oncology benefit from the publication of negative data; such negative data can be as informative as positive data when exploring therapeutics, particularly when reported in conjunction with other findings. To support this, we will help promote – through our publications – a change in the scientific culture responsible for the asymmetric publication of positive results. We believe that DMM can play a crucial role in helping the scientific community improve the process for screening appropriate candidates for clinical development by establishing and promoting standards for the preclinical analysis of animal models, and by demanding their rigorous assessment. We are also holding discussions with the pharmaceutical world to determine their publication needs and standards for following up on disease-focused papers.

Finally, we are thinking of ways for DMM to connect young trainees to new avenues of science. The journal already provides Travelling Fellowships to help graduate students and postdoctoral researchers travel on collaborative visits to other laboratories. But what about young scientists who wish to explore non-academic routes? We will open a dialogue with students and early stage researchers to help them to search for positions in academia and beyond. Most of us train in universities or medical centers: how does one become a pharmaceutical researcher, and is it a good fit for our needs? What about consulting? Wall Street? In these difficult economic times, we want to help connect trainees to dream positions in the world of biomedical science. In doing so, we hope to help the next generation of scientists pick up the baton and push forward the Great Merger, moving basic scientific understanding into the realm of cures and medicines. This is work worth doing, a goal worth pursuing, and we want to be your choice when you are ready to share your contributions with the community.

REFERENCES

Abrahamsen, G., Fan, Y., Matigian, N., Wali, G., Bellette, B., Sutharsan, R., Raju, J., Wood, S. A., Veivers, D., Sue, C. M. et al. (2013). A patient-derived stem cell model of hereditary spastic paraplegia with SPAST mutations. *Dis. Model. Mech.* **6**, 489-502.

Anastassiadis, K., Fu, J., Patsch, C., Hu, S., Weidlich, S., Duerschke, K., Buchholz, F., Edenhofer, F. and Stewart, A. F. (2009). Dre recombinase, like Cre, is a highly efficient site-specific recombinase in E. coli, mammalian cells and mice. *Dis. Model. Mech.* **2**, 508-515.

Bartolomucci, A., Carola, V., Pascucci, T., Puglisi-Allegra, S., Cabib, S., Lesch, K.-P., Parmigiani, S., Palanza, P. and Gross, C. (2010). Increased vulnerability to psychosocial stress in heterozygous serotonin transporter knockout mice. *Dis. Model. Mech.* **3,** 459-470.

Begley, C. G. and Ellis, L. M. (2012). Drug development: Raise standards for preclinical cancer research. *Nature* **483**, 531-533.

Freeman, M. and St Johnston, D. (2008). Wherefore DMM? *Dis. Model. Mech.* **1**, 6-7.

Hick, A., Wattenhofer-Donzé, M., Chintawar, S., Tropel, P., Simard, J. P., Vaucamps, N., Gall, D., Lambot, L., André, C., Reutenauer, L. et al. (2013). Neurons and cardiomyocytes derived from induced pluripotent stem cells as a model for mitochondrial defects in Friedreich's ataxia. *Dis. Model. Mech.* **6**, 608-621.

Ioannidis, J. P. A. (2005). Why most published research findings are false. *PLoS Med.* **2**, e124.

Matigian, N., Abrahamsen, G., Sutharsan, R., Cook, A. L., Vitale, A. M., Nouwens, A., Bellette, B., An, J., Anderson, M., Beckhouse, A. G. et al. (2010). Disease-specific, neurosphere-derived cells as models for brain disorders. *Dis. Model. Mech.* **3**, 785-798.

Michailidou, C., Jones, M., Walker, P., Kamarashev, J., Kelly, A. and Hurlstone, A. F. L. (2009). Dissecting the roles of Raf- and PI3K-signalling pathways in melanoma formation and progression in a zebrafish model. *Dis. Model. Mech.* **2**, 399-411.

Prinz, F., Schlange, T. and Asadullah, K. (2011). Believe it or not: how much can we rely on published data on potential drug targets? *Nat. Rev. Drug Discov.* **10**, 712-712.

Siegel, V. (2013). Provoking progress: a new chapter. *Dis. Model. Mech.* **6**, 557-558.

Su, L. J., Auluck, P. K., Outeiro, T. F., Yeger-Lotem, E., Kritzer, J. A., Tardiff, D. F., Strathearn, K. E., Liu, F., Cao, S., Hamamichi, S. et al. (2010). Compounds from an unbiased chemical screen reverse both ER-to-Golgi trafficking defects and mitochondrial dysfunction in Parkinson's disease models. *Dis. Model. Mech.* **3**, 194-208.

Whitworth, A. J., Lee, J. R., Ho, V. M.-W., Flick, R., Chowdhury, R. and McQuibban, G. A. (2008). Rhomboid-7 and HtrA2/Omi act in a common pathway with the Parkinson's disease factors Pink1 and Parkin. *Dis. Model. Mech.* **1**, 168-174.