› RESEARCH IN BRIEF

A new batch of rare disease models

The International Mouse Phenotyping Consortium (IMPC) has been working to systematically create mutant embryonic stem cells for every gene in the mouse genome and catalogue the resulting genotype-phenotype relationships. Version 5.0, released in August 2016, is up to over 3300 different gene knock-outs and includes more than 28,000 phenotypes. New research, published in *Nature Genetics*, reports on efforts to link those phenotypes to particular diseases with Mendelian inheritance (2017; doi:10.1038/ng.3901).

The team compared phenotype annotations in the IMPC database to descriptions in the Online Mendelian Inheritance in Man and Orphanet databases, which describe the 7000 thousand different rare diseases in humans. They were able to link 889 murine phenotypes to rare diseases, and identified 360 mutant mice variants that could serve as a disease model in future research.

A little sound goes a long way

Every year, 100,000 bone fractures in the United States are unable to heal properly. The go-to treatment, grafts, don't always take, and recombinant bone morphogenetic protein (BMP) therapies can be expensive and carry high incidences of side effects. Targeted gene therapies are promising, and getting those therapies where they need to be might be as simple as adding a little sound (*Sci. Transl. Med.* **9**, eeal3128; 2017).

Working with mini-pigs, researchers at Cedars-Sinai implanted a biodegradable collagen scaffold into tibial bone fractures. Two weeks later, they injected the bones with microbubbles loaded with the *BMP-6* gene; one group of pigs also received ultrasound therapy. Bones in the ultrasound-treated animals healed with better mechanical properties than those that received the gene therapy alone, and with no adverse effects observed. The results suggest a noninvasive way to improve gene therapy delivery.

Light-powered heart repair

During cardiac ischemia, a patient does not receive adequate blood flow to the heart. Restoring blood flow—and thus oxygen delivery—is critical, but new research suggests a little photosynthesis could also do the trick (*Sci. Adv.* **3**, e1603078; 2017). Mammals may not be able to generate their own oxygen, but a photosynthetic cyanobacteria called *Synechococcus elongatus* can. Rats modeling acute myocardial infarction that received injections of the microorganisms while their hearts were exposed to laboratory light had improved oxygenation and outcomes compared to controls and animals treated in the dark. Though adapting the idea to human hearts will take some work, the study shines light on a novel way to treat ischemia.

Killing cells, without collateral damage

Understanding processes that involve cell death involves killing cells, but existing techniques often result in collateral damage. To kill specific cells with precision, researchers at Yale have developed a method they call 2Phatal, for two-photon chemical apoptotic targeted ablation (*Nat. Commun.* **8**, 15837; 2017). Cells to be killed are marked with a special dye that binds closely to nuclear DNA. Firing a two-photon, femtosecond-pulsed laser bleaches the dye, causing a reactive oxygen species cascade that kills the cell targeted without spilling over into neighbors. The dye itself, known as H33342, was non-toxic and could be administered directly onto the brain or intravenously. They successfully tested 2Phatal against neurons, astrocytes, and other specific cells in live mice, and against neuromast lateral line hair cells in zebrafish.

FISHing in the fly brain

There are several methods for quantifying gene expression levels in the brain, but most require extracting cells from their native environment. RNA fluorescence *in situ* hybridization (or FISH) is a useful tool for neuroscientists to visualize and quantify mRNA expression with subcellular resolution while preserving the spatial relationships between neurons.

Using a combination of tissue clearing methods and Bessel beam optics, Long *et al.* describe a new FISH method that allows imaging and quantification of mRNA throughout an entire whole-mount adult *Drosophila* brain, opening up gene expression studies in the fly nervous system with unprecedented resolution and scale (*Nat. Methods* **14**, 703–706; 2017).

Patching up poor blood flow

Ischemia is a leading cause of mortality worldwide, but treatment options are often inadequate (or contraindicated) for certain patients. Using 3D printing of endothelial cells, organized into pre-designed fibrin patches, Mirabella *et al.* provide a novel method to induce therapeutic levels of angiogenesis in a variety of ischemic conditions (*Nat. Biomed. Eng.* **1**. 0083; 2017).

Using a mouse hindlimb ischemia model, as well as a mouse model for myocardial infarction, the group demonstrate that their implanted 3D patches can significantly improve blood flow in ischemic limbs, as well as rescue cardiac function in damaged hearts. The paper provides an important proof-of-principle for the technology, which could help improve how life-threatening ischemia is treated in humans.

Neonatal drug exposure influences hippocampal development

Evidence is accumulating that early postnatal exposure to anesthetics can have detrimental effects on brain development. In new work published in *PLoS Biology*, a group led by C. David Mintz at the Johns Hopkins University School of Medicine studied this issue in more detail, to try and extract a mechanistic basis for anesthetic-induced changes to young brains (*PLoS Biol.* **15**, e2001246; 2017).

Using *in vivo* imaging of developing dendrites in dentate gyrus granule cells (DGCs) of the hippocampus, the team found that exposure to clinically relevant levels of the gas anesthetic isoflurane in neonatal mice generated abnormal dendritic arbors and spines in DGCs, and that inhibition of the mTOR signalling pathway could reverse these changes. Further, using learning paradigms, they demonstrate that the changes in dendrites were accompanied by behavioral deficits, which could also be reversed by inhibiting the mTOR pathway.

Early stressors impact worm sperm

The sperm of *C. elegans* typically has no problem finding an oocyte to fuse with in the hermaphrodite reproductive tract, but new research from Michael Miller's lab at the University of Alabama School of Medicine shows that early stressors can cause specific circuits to activate and negatively impact sperm's navigation (*PLoS Biol* **15**, e2002047; 2017).

Using an imaging platform that allowed them to directly visualize sperm movement *in vivo*, the team discovered a chemosensory pathway that counteracts the negative impact of hyperoxic environmental conditions on sperm navigation. The authors suggest the mechanism may serve as a systemic response to challenging environmental conditions that could impact male worm fertility.