
Steve Brown



# Straight talk with… Steve Brown

For decades, the study of gene function has relied heavily on the creation of 'knockout' mice, bioengineered to lack certain genes. But making a rodent without a specific gene is a chore—so much so that doctoral students sometimes dedicate their entire PhD work to generating a single mouse strain. The International Knockout Mouse Consortium (IKMC), launched in 2006, plans to change all that. The consortium, involving scientists from 33 research centers in nine countries, is creating a library of every gene knockout in embryonic stem cell lines, which can be used to produce mouse strains.

In June, the group passed 10,000 embryonic stem cell lines generated in a targeted fashion, and, as they approach their goal of around 21,000 mouse gene knockouts, the project is moving onto its next step: phenotypes. The offshoot collaboration, the International Mouse Phenotyping Consortium (IMPC), plans to document disease-related phenotypes for each generated mouse strain including metabolic, neurological and behavioral data. The effort received support on 29 September, when the US National Institutes of Health (NIH) awarded $110 million to three US centers over five years to phenotype 833 strains each. **Hannah Waters** spoke with Steve Brown, chairman of the IMPC and director of the UK Medical Research Council's Mammalian Genetics Unit in Harwell to learn more about the plans for the project.

**Before we look ahead, how is the effort to create new knockout mouse strains going?**

It's going very well. The expectation is that the project will have knockouts for most, if not all, of the 21,000 or so mouse genes in the next few years, maybe in about three or four years' time. What the IMPC will be doing is taking each of the embryonic stem cell lines and injecting them into mouse blastocysts, where they colonize the developing embryo to create chimeras. And those chimeras can be bred to produce a mouse mutant that carries the knocked-out gene. I think the IKMC has really delivered some exceptional resources that are going to be fundamental to uncovering the function of genes in the mammalian genome in a comprehensive and systematic way.

**How can phenotyping mice help elucidate human disease?**

We're effectively putting our mice through a series of clinical tests to find out what's going wrong with your mouse when you change a particular gene. And I think that's fundamentally what we're trying to do: to bridge that relationship between gene and changes in phenotypes. And changes in phenotypes often manifest themselves as disease.

**What attributes will you phenotype?**

We do a whole variety of tests, including the very simple and straightforward, like looking at the morphology of the mice as a clinician might do: their claws and teeth and coats, and so on. We're doing neurological tests and looking at blood glucose levels and metabolic rates. We're doing tests to look at body composition: the amount of fat in the mouse, the composition of bones. We also test the mice in an open-field arena, which looks at behavioral parameters such as anxiety. We're looking at the eyes of the mouse to see if there is any degeneration that might be associated with common diseases like macular degeneration. So, as you can see, across all these major organ systems and associated disease areas, we're doing quite a broad range of tests.

**How long will it take to phenotype a mouse strain?**

We start when the mouse is nine weeks of age, and we finish at 16 weeks of age. And, for each mutant [strain], we follow a cohort of seven males and seven females. So a considerable effort is put into looking into each particular line, and this is why it's such a big endeavor, costing a considerable amount of money. Over the next five years, we're aiming to do 5,000 mutants, at 1,000 mutants a year across the whole of the consortium. And in the second phase of the project, we plan to ramp that up to three times that number and do 15,000 in five years.

**Some people have been calling for the use of other model organisms such as rats or pigs that perhaps better represent human physiology. Do you think the mouse is still relevant?**

My own personal opinion is very much 'yes'. Of course, when we're looking at the function of a gene in a mouse, it doesn't mean that we're exactly replicating what's happening in humans. What we're looking at are the genetic systems involved: we're trying to understand what genes do, what is the interplay between genes. That's not to say that we shouldn't be looking at the function of these genes in other model organisms, all the way from yeast to rat. But here [with the mouse], we have a chance to look at the function of all the genes in the genome in a mammal in a relatively cost-efficient and comprehensive way.

**How do researchers get their hands on these mice?**

Once the mice are created, we can freeze sperm and embryos to create a very readily available resource of mice, which can be distributed anywhere in the world to any researcher to look at the phenotypes in more detail. Europe has a coordinated European archive, the European Mouse Mutant Archive [based in Munich, Germany]. North America has a major archive [the Knockout Mouse Project Repository at the University of California in Davis], as does Japan, for example, at RIKEN. So not every research center will be the hub for distribution of these resources, but rather we see a global network of a few centers that will be responsible for distributing many of these resources.