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Still much to learn about mice

A project that aims to mutate every gene in the mouse genome to improve our knowledge of mouse biology should help to avoid irreproducible results and costly failures in drug development.

The mouse is the undisputed king of laboratory science. It achieved its royal status after it was chosen as the first mammal — after the human — to have its genome sequenced. Understanding the genome made it possible to develop new molecular technologies to make mutant mice, and scientists have made them by the thousand. They have also used these mutant mice to illuminate how genes and the molecular pathways they control operate in health and disease. This has also cast some welcome, if indirect, light on human diseases.

Specialized repositories have sprung up around the world to accommodate these mutant mice and to allow them to be shared. Everybody benefits: researchers, who can have the latest mouse mutants sent to them; and science more broadly, as the repositories guarantee the quality of the genetics and the health of each strain, which is crucial for comparing the results of different experiments.

That quality must be defended. At a meeting in Munich, Germany, earlier this month, representatives of repositories from China, the United States, Europe, Japan, Canada and elsewhere expressed a concern: new technology renders it so easy to make a knockout mouse that more scientists may start to use it, without being aware of the general genetics expertise needed. It is a concern that deserves broader discussion.

At present, the ability to make a high-quality knockout of a gene in a mouse requires considerable skill in genetics and breeding techniques. But new and disruptive technologies — gene-editing methods such as CRISPR — have entered the scene, making mouse engineering considerably less challenging. But will this mean a series of strains produced with inadequate quality control? If so, experiments will be harder to reproduce, and medical research could suffer.

Since 2010, those involved with the mouse repositories, together with other geneticists, have been coordinating the International Mouse Phenotyping Consortium (IMPC). The consortium aims to make a conditional mouse mutant — in which the targeted gene can be switched off to order — for every gene in the mouse genome in a defined genetic background. Each mutant mouse will be examined in detail to find out exactly what changes occur in the animal's physiology, anatomy or behaviour when the gene is removed. It is a colossal task, with a colossal estimated price tag of US$900 million to be shared by participating nations.

The first thousand of these phenotyped mutants will be available in a couple of months. Fifteen thousand will be available by 2021 if all goes to plan. But that plan assumes that the requisite funding will continue to flow. And like all those with power, the mouse has enemies, whose views may shake the confidence of funding agencies, already notoriously averse to large, long-term investments such as repositories. Mouse mutants are invaluable in understanding biological processes and what can go wrong in biochemical or cellular pathways in diseases such as cancer or Alzheimer's. Too often, however, scientists consider them models of human disease, as if a manipulated gene or two could actually recapitulate a disease in a different species. Therapies that 'cure' a mutant mouse but then fail in the clinic, bring the mouse into disrepute — as recently lamented by Steven Perrin, of the Amyotrophic Lateral Sclerosis Therapy Development Institute in Cambridge, Massachusetts, who has witnessed the phenomenon too many times in relation to this disease (*Nature* **507,** 423–425; 2014).

"Therapies that 'cure' a mutant mouse but then fail in the clinic, bring the mouse into disrepute."

Some scientists complain that the phenotyping approach is unreliable because when different laboratories knock out the same gene, they may see different consequences — adding to the current crisis in the reproducibility of biomedical results. But the discrepancies are usually because mice in different labs are of different genetic strains; this makes a big difference to whether the function of a missing gene will be compensated for. Another cause of discrepancies can be viruses in the mice, which can change the way that genes are expressed. In fact, 12% of the strains submitted to one of the main mouse repositories, the Jackson Laboratory in Bar Harbor, Maine, are contaminated by pathogens.

This is why it is so desirable to have repositories that guard the health and genetic quality of the deposited mice. It is also why the IMPC is so important — by detailing the function of each gene in a standard genetic background, it will provide a necessary source of information for researchers for many decades, and help in the effort to ensure that biological results are reproducible. ■

Not on the label

A US push to flag foods as genetically engineered is hard to swallow.

The tiny US state of Vermont is no stranger to gourmands, particularly those with a fondness for its maple syrup and ice cream. On 8 May, Vermont carved out a new position in the national food scene when its governor, Peter Shumlin, signed into law a bill that requires foods on sale in the state that were made with genetically engineered ingredients to be labelled as such. It is the first such law in the country.

The law's fate is unclear: food-industry groups immediately vowed to challenge it in court. Vermont's attorney-general is readying the state's legal defence — the bill Shumlin signed included provisions to

fund these courtroom battles. It is tempting to see Vermont's move as the first success in a larger US movement that aims to limit the spread of genetically modified foods.

The Center for Food Safety, a consumer activist group in Washington DC, says that there are 35 similar food-labelling bills in the works across 16 states. That is not to say that all will follow in Vermont's footsteps. In 2012 and 2013, voters in California and Washington state defeated similar ballot measures. Vermont — the only state to boast a self-described socialist as a senator — is something of an outlier on the US political spectrum. But the interest in laws on labelling is a striking trend in a country that is the world's leading producer of genetically engineered crops.

There is plenty of precedent for such laws: more than 60 countries require genetically engineered foods to be labelled. Many of those countries grow few, if any, genetically engineered crops. The US labelling movement poses a number of logistical challenges. Navigating a patchwork nation in which labelling requirements vary from state to state is one obvious problem for the food industry. The sheer pervasiveness of genetically engineered crops in all manner of foods is another.

In 2013, such crops populated about half of US farmland. That included more than 400,000 hectares of sugar beets modified to withstand the herbicide glyphosate. By 2010, some 95% of the US sugar-beet crop was genetically engineered, and more than half of the processed sugar made in the country derives from sugar beets. Although neither the genetically engineered DNA nor protein remains in the finished product, laws proposed in some states would require that foods containing this sugar be labelled as 'genetically modified'.

And so it would go for most genetically engineered crops, which make their way onto the dinner table largely by way of processed foods. Herbicide-tolerant corn (maize) appears as the sweetener high-fructose corn syrup, and engineered soya beans are used to make the common food additive soy lecithin. Corn oil made from engineered corn is chemically no different from that made with conventionally bred corn. Yet some proposed laws would require a frozen pizza drizzled with corn oil made from genetically engineered corn to be labelled as 'genetically modified'.

The definition of that term is set to become even fuzzier as new technologies widen the array of genetic modifications available to crop breeders. Some are experimenting with 'cisgenics' — the science of modifying a crop by expressing genes plucked from related species. Methods that alter gene expression using RNA molecules are also in vogue. And advances in genetic engineering have yielded ways to precisely edit the genome, inserting genes at specific locations. These methods allow just a few letters of the DNA sequence to be changed.

"Determining the provenance of some engineered crops may be impossible."

It is a far cry from the days when genes that conferred insect resistance or herbicide tolerance were taken from a bacterium and shot near-randomly into crop genomes. Yet while regulators are deep in discussions about how to handle the new varieties of genetically engineered foods, popular conceptions of such foods seem largely unchanged. Vermont's labelling law and many of the other proposals make no distinction: products of a crop engineered using recombinant DNA techniques to make heritable changes to the genome are to be labelled, regardless of whether that change was one that could have been produced through conventional methods such as breeding with relatives or exposing seeds to mutagens. It is also not clear whether the labelling laws could be enforced: determining the provenance of some of these engineered crops may be impossible, because the products will be indistinguishable from those made using conventional crops.

The issue of genetically engineered foods is a muddled one, and the debate surrounding them is heated. Some oppose the technology because they oppose industrialized agriculture; others worry that engineered crops could pose environmental hazards. And many consumers believe, despite evidence to the contrary, that the foods pose more health risks than those grown through conventional breeding and mutagenesis.

Researchers may understandably be hesitant to plunge into these turbulent waters. But the popular discourse around genetically engineered crops is in dire need of a scientific update. Without it, public discussion and political legislation will continue to drift away from reality. ■

Out with a bang

The discovery of a Wolf–Rayet supernova rebuts the idea that the biggest stars go quietly.

A long time ago, a faraway star threw up its insides and ended its days in a colossal explosion. The first light to hold the record of this supernova reached Earth about this time last year. Just a few hours later, quick-thinking astronomers were able to point a telescope at the hole in the sky where the star had been. The resulting images help to resolve a key question in stellar physics. And they might raise more questions about the fate of Earth.

Supernovae are one of the most stunning events in the night sky; the explosions are so well known for their violence that the term has even entered common parlance. Yet supernovae are rare, and so, therefore, are direct observations of the circumstances immediately before and after them.

As astronomers describe on page 471 of this issue, being able to focus on the immediate aftermath of a supernova has shed new light on why some stars go bang with such force. In this case, the emissions spectra sent out by the dying star show that it was a Wolf–Rayet star, massive bodies that shed their mass rapidly in strong stellar winds.

The finding is significant because, although astronomers assumed that Wolf–Rayet stars would go supernova, there was no direct evidence that they did. In fact, in the absence of observations of such supernovae, a rival theory was gaining ground: that they might end their lives not in a bang but with a whimper. As John Eldridge explains in an accompanying News & Views article on page 431: "Until this event, there was growing evidence that such stars were likely to have dim or unobservable deaths."

Wolf–Rayet stars are more than 20 times more massive than our Sun and are very breezy places: their fierce stellar winds can reach more than 1,000 kilometres per second. They are also rare, so if the name rings a bell then it could be because you have heard of a particular specimen: WR 104, a binary star about 2,450 parsecs (8,000 light years) from Earth that shot to fame in 2008 when astronomers warned that we could be in the firing line if it exploded. If you are concerned by this (and you probably needn't be), then the finding that Wolf-Rayet stars do go supernova will do little to ease your anxiety.

A mere supernova would not threaten us at that distance, but some very massive stars explode as two powerful beams of lethal radiation known as γ-ray bursts. Depending on which way WR 104 is pointing — and the jury remains out on that — one of those bursts could head our way.

There are plenty of ifs and buts there — evidence suggests, for instance, that WR 104 has the wrong environment for γ-ray bursts — but, technically, the odds of such an event just shortened, very slightly. All Wolf–Rayet stars will go bang, the paper proposes, WR 104 included. The question is when — it could be next week, or thousands of years hence. Or it may already have happened. ■

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