TYLER JACKS

SPEEDY MODELER

IT'S ALREADY SOMETHING OF A machine for scientific discovery. But now Tyler Jacks' laboratory at Ludwig MIT is stepping up production.

The laboratory is renowned for its mice, which Jacks and his team engineer to carry mutant versions of genes involved in cancer. Their engineered mice have provided great insight into how cancer develops and spreads, but generating such models is painstaking work that can take years. In 2014, however, they showed that things don't have to be that way. Jacks and his colleagues applied an emerging gene editing technology dubbed CRISPR/Cas9 to rapidly alter cancer genes in adult mice and study the consequences.

"This technology is huge," says Jacks. "It has overtaken my laboratory in a remarkably short period of time." Mouse models that once took years to make, he notes, are now being turned out within months.

Traditional methods of engineering mice involve generating changes to DNA in embryos and breeding the mice for a few generations. By contrast, the new CRISPR/Cas9 technology is direct and efficient, and can be used on adult mice with relative ease. Cas9 is a DNA-snipping enzyme from bacteria. It is directed to specific sequences in the DNA by small, complementary RNA molecules. The RNA shows where to cut and the enzyme snips the DNA. In addition to knocking out genes, the technology can be adapted to replace or add genes, or to change them subtly.

The technique was first used to engineer mammalian genes barely two years ago. Since then, laboratories across the world have quickly adapted it to their particular investigations. Jacks was eager to put it to the test in cancer research.

Snipping genes

His first task was to test whether CRISPR/Cas9 worked just as well as traditional methods for making modified mice.

To examine this, his team knocked out two familiar genes in the liver. CRISPR/Cas9 mice lacking these genes resembled the corresponding mouse models they had made using traditional techniques.

The researchers next used CRISPR/Cas9 to generate mice with novel combinations of altered genes in the lung to recapitulate lung cancer. To do so, they injected the lungs of mice with viruses that produced Cas9 and RNA guides corresponding to the genes they wished to perturb.

Jacks and his colleagues knocked out three genes—NKX2-a, PTEN and APC—that act as tumor suppressors in mice that had already been engineered to express a cancer gene called KRAS. The study accurately reproduced the effects of the first two mutations, and showed for the first time that APC might play a role in lung cancer as well.

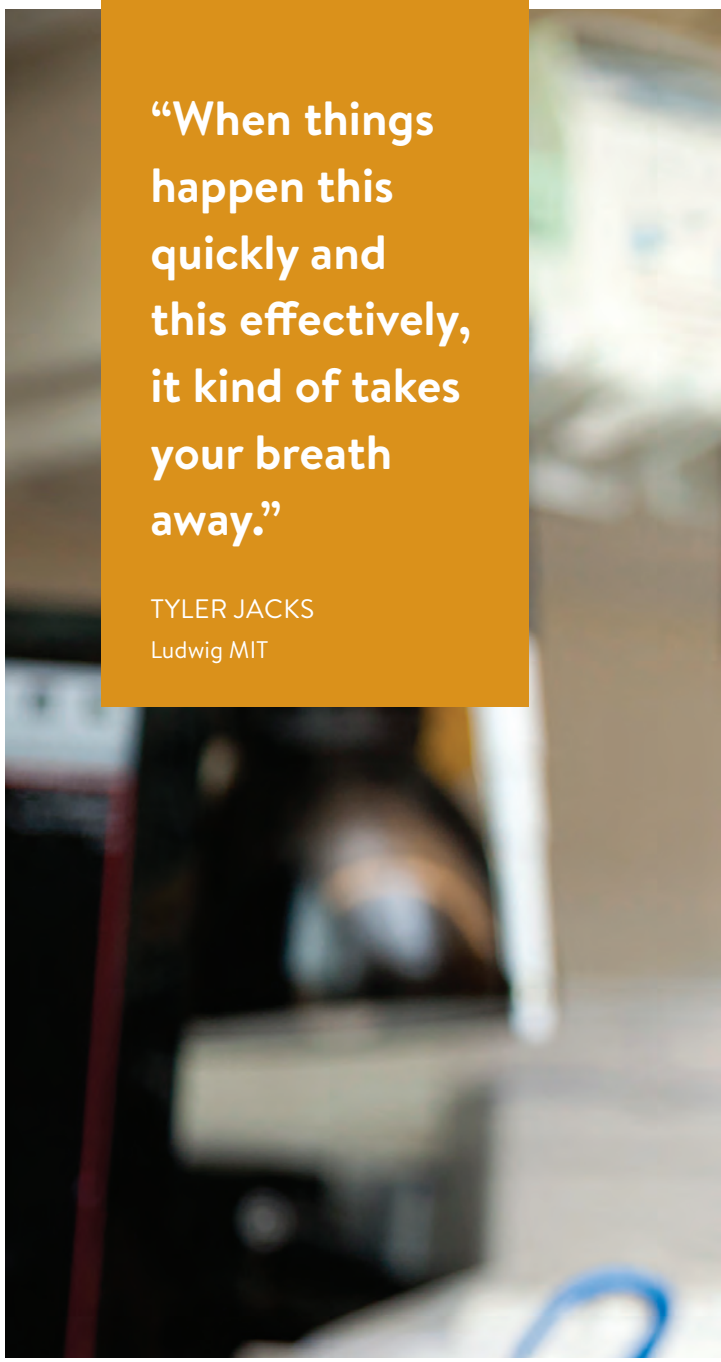
Jacks and his colleagues showed that they could also use CRISPR/Cas9 to knock out more than one gene simultaneously. And they could generate mice with genes altered to gain functions similar to those seen in human cancers.

Fast forward

The technique is unleashing a flurry of new projects in the Jacks lab. "Until now, the field has been kind of stuck," says Jacks, who is gearing up to test panels of genes implicated in human cancers by generating mice with the same defects seen in human tumors. "Now we can get through lists of genes of interest much more rapidly and cost effectively than we ever could have before." Such an approach has the potential to lead to subtler biological insights and significantly improve the identification of new drug targets.

Jacks and his colleagues are also now mutating various genes thought to be involved in metastasis, a focus of Ludwig MIT. "We have an extremely cohesive group of Ludwig investigators here," says Jacks. "We all are sharing ideas, strategies and reagents." Jacks will soon pass along some new CRISPR/Cas9 mice to his Ludwig colleagues so they can take a close look at how tumors spread and establish themselves at new sites in the mouse body.

"I am used to things taking their time and having to slog through it," says Jacks.



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