New gene editing tool helps zero in on small cancer-linked mutations

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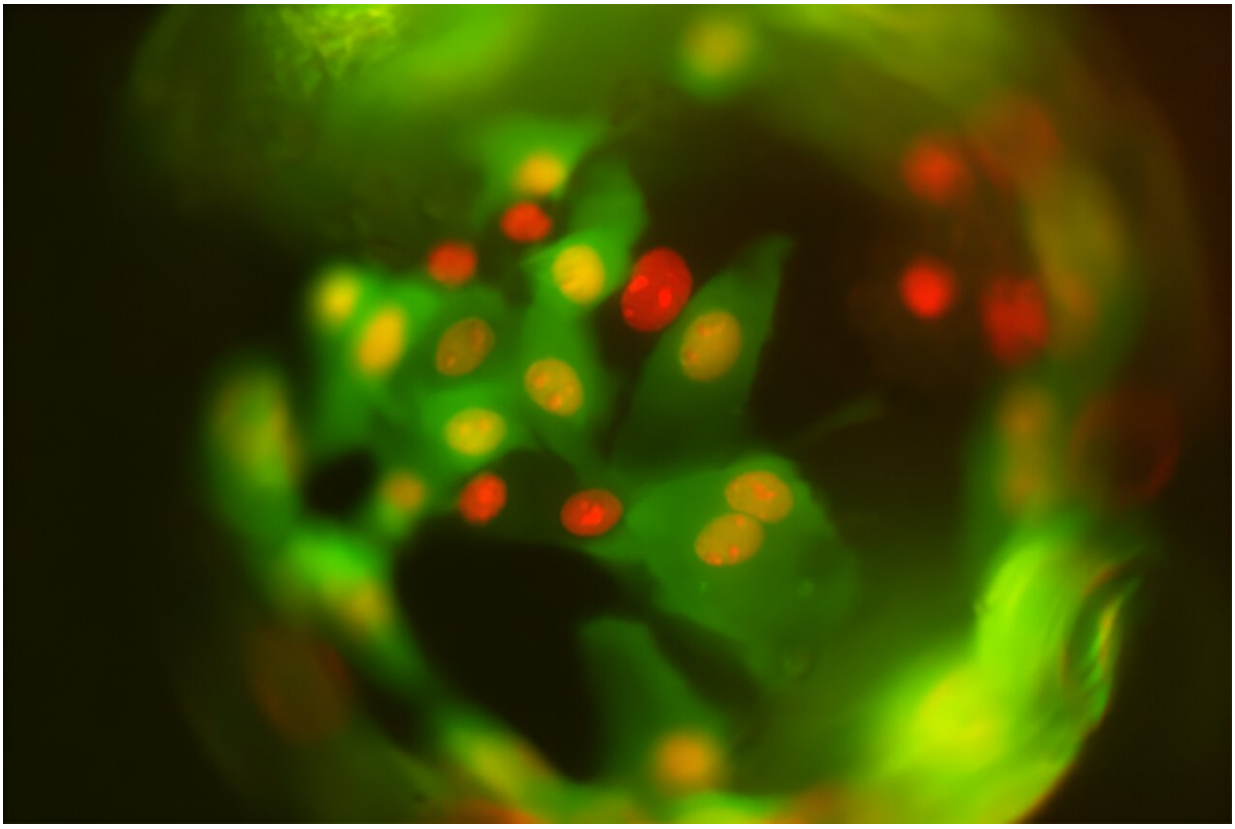

The image shows a 3D pancreatic organoid derived from the in vivo base editing (iBE) model. A red nucleus highlights individual cells that carry a base-editing reporter. When the base editor is activated by the drug doxycycline to create a single base change, the cells turn fluorescent green. Credit: Dow lab

A change in just one letter in the code that makes up a cancer-causing

gene can significantly affect how aggressive a tumor is or how well a patient with cancer responds to a particular therapy. A new, very precise gene-editing tool created by Weill Cornell Medicine investigators will enable scientists to study the impact of these specific genetic changes in preclinical models rather than being limited to more broadly targeted tactics, such as deleting the entire gene.

The tool was described in a study published Aug. 10 in *Nature Biotechnology*. Dr. Lukas Dow, an associate professor of biochemistry in medicine at Weill Cornell Medicine, and his colleagues genetically engineered mice to carry an enzyme that allows the scientists to change a single base or "letter" in the mouse's genetic code. The enzyme can be turned on or off by feeding the mice an antibiotic called doxycycline, reducing the prospect of unintended genetic changes occurring over time. The tool can also grow miniature versions of intestine, lung, and pancreas tissue called organoids from the mice, enabling even more molecular and biochemical studies of the impact of these precise genetic changes.

"We are excited about using this technology to try and understand the genetic changes that influence a patient's response to cancer therapies," said Dr. Dow, who is also a member of the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine.

Dr. Dow noted that differences in a single base in a gene can have functional consequences. But most gene-editing tools currently available aim at larger targets like whole genes. Scientists can also use viruses to deliver genes with specific mutations, but this technique is limited to targeting specific tissues like the brain and liver, he said.

"We've had good tools for a long time now to knock genes out or overexpress genes," Dr. Dow said. "But we have not had good ways to create the single-base mutations that we see in patient's tumors."

The mouse model allows them to study the effects of the changes on tumors and determine which therapies work best for those with a particular mutation. Organoids derived from the mice enable detailed experiments in tissues that scientists could not easily target with virus-based approaches.

"One mouse model allows you to do two things: test the effects of a mutation in cancer initiation, progression, or treatment response in mice; and take a closer look at the associated molecular or biochemical changes using organoids," Dr. Dow said.

Dr. Dow and his team, including co-first authors Dr. Alyna Katti, a former graduate student, and Dr. Adrián Vega-Pérez, a postdoctoral associate, are currently using this new technology to identify the effects of
single-base mutations in lung, colon, and pancreatic cancer. Their genetically engineered mice will be available to other researchers to use, which may help accelerate progress toward personalized cancer treatment.

"We are making the technology available to other people in the field so they can use it to study their mutations of interest," Dr. Dow said. "If we can learn the genetic underpinnings of what causes tumor formation and why patients have different outcomes, that may help us develop new drugs or select the best drugs for a particular patient."

More information: Alyna Katti et al, Generation of precision preclinical cancer models using regulated in vivo base editing, *Nature Biotechnology* (2023). DOI: 10.1038/s41587-023-01900-x

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