

## **The Good, the Bad, and the Ugly**

By Lena Huang

Our daily life is unnerving. Think ISIS, Sandy Hook, Ferguson, Ebola. But it is also exciting. A ninth planet, global child mortality on the decline, legalization of gay marriage.

So when SXSW asked to identify one thing that is unnerving or exciting, I thought tackle both. As the editorial director of *Genome* magazine for the past year and as a science writer and editor for many more, I can think of one technology that fits the bill, and that is CRISPR, a powerful gene-editing tool that has made it easy and cheap to make precise changes to a gene.

As we reported in *Genome*, CRISPR has already been used to edit out a genetic eye condition in mice, to modify genetic changes in a set of twin monkeys, and to edit out HIV in an infected cell in culture. Since our article, the applications of CRISPR have skyrocketed, and many scientific research papers using the technique have been published or submitted. More recently, one research group claimed to use CRISPR to correct a genetic defect that causes blindness, while three different research groups announced success in using CRISPR to excise genes associated with Duchenne muscular dystrophy in mice. This technology has the amazing potential to eliminate disease in our lifetimes.

### **More Good**

My mother died of a rare disease — appendix cancer. The tumor was a signet-ring cell adenocarcinoma, rarer than the more common carcinoid tumor found in most cases of appendix cancer. After her doctor surgically removed as much of the tumor as possible, we turned to chemotherapy. But as with many rare cancers, there was no standard of care, so we tried chemotherapies designed for the next closest cancer — colorectal. Shots in the dark. We consulted with experts at MD Anderson but after the chemo didn't work and the cancer continued to metastasize, we tried experimental therapies through clinical trial. She didn't last a year after that as the chemotherapies destroyed her body until she had little strength to go on.

Since her death, gene editing technologies have blossomed and more targeted treatments for cancer, even rare cancers, have emerged. Last November, doctors successfully used another genome editing tool called TALEN to alter a donor's immune system T cells to seek out and kill leukemia cells in a baby girl that saved her life. At the National Cancer Institute and in other research programs, CRISPR is being used to identify the gene targets that allow cancer cells to survive and proliferate.

Knowing the potential of this technology, it is hard for my mind not to wander. What if we knew my mother's cancer was caused by a genetic mutation? Could that mutation be altered or edited in some way that would rid her body of the cancer? Or

what if we created a T cell therapy that targeted and stopped her cancer from metastasizing just like in the baby girl with leukemia? Mom might be here with us today.

Researchers are already creating cancer therapies that treat specific mutations and many more are in the pipeline. And while it's still hard to know what will happen to that baby girl in the future, the treatment has made her live for now.

### **Some Bad**

Did you ever want to look different? Have a characteristic that you don't have? I think most people at some point in their lives wish to change some aspect about themselves, trade in curly hair for straight, brown eyes for blue. When I was young I wished for curly blond hair and blue eyes to look like the images around me: my Barbie doll, Farrah Fawcett, the Brady Bunch.

With gene editing, it may be possible someday to deliver a made-to-order, designer baby. You want blue eyes? Edit here. You want blond hair? Modify there. Chinese scientists have already used CRISPR to edit genes that inhibit hair and muscle growth in a goat. They have also disabled a growth hormone receptor in pigs to develop a minipig pet.

So, while CRISPR is being used to edit out the bad genes, it's also being used to change characteristics. This use is troubling to researchers and clinicians who called an International Summit on Human Gene Editing in December 2015 to discuss this topic for three days. At the end of the conference, the U.S. National Academy of Science, the U.S. National Academy of Medicine, the Royal Society, and the Chinese Academy of Sciences agreed that it would be "irresponsible" to use gene-editing tools to modify human embryos or gametes. However, they did not rule out that usage in the future if international communities could come to a consensus on the benefit to human health and welfare.

But while these international powers agree that this type of gene editing is "irresponsible," who is stopping someone in his or her lab from doing it?

### **Some Ugly**

In Mary Shelley's *Frankenstein*, Victor Frankenstein becomes obsessed with discovering the secret of life, produces a living being, but then is horrified by the monster he created. After the monster kills his brother, Frankenstein is pressured by the monster to create a companion for him and he promises that they will seclude themselves from the world. While working on the companion, Frankenstein realizes they might breed, "creating a race of devils" that will plague mankind, and he destroys the female creature. The monster responds by killing everyone Frankenstein loves.

An issue in editing embryos or gametes (germline editing) is that the resulting genetic alterations will be passed on from generation to generation. A conclusion of the International Summit was “once introduced into the human population, genetic alterations would be difficult to remove.” Another concern voiced was in editing a gene that we think causes a disease actually may result in causing another disease or some unexpected change, since we still do not fully understand the functions of all genes. For example, could curing blindness result in hearing loss?

And what about inaccurate editing? This actually happened in China when scientists attempted to edit the genes that cause a blood disorder in non-viable embryos. The result was imprecise with the DNA cut in unintended points. The scientists concluded that editing for human embryos “may be premature at this stage.”

Right now, this gene-editing world is bit like the Wild West. It’s being used in so many different applications; it’s difficult to keep up. It’s potential is great but the results unknown. Responsible scientists are harnessing this potential while being careful not to introduce the unexpected. Last November, scientists announced they discovered a way to use CRISPR to edit out the malaria parasite in mosquitos with the promising hope this would extinguish malaria in humans. However, these mosquitos have not been released into the world because we do not fully understand how their existence might affect evolution.

So, after we eliminate malaria, Duchenne muscular dystrophy, acute lymphoblastic leukemia, blindness, what will edit out next? If we edit the gene that might cause a serious disease in an embryo, is it also okay to decide if that embryo is a boy or girl? And then what is next? Eye color? Hair color? Skin color? Race?

My friends in the scientific world think this is ridiculous, and I hope they are right. I hope that gene editing will only be used for the greater good, to eliminate devastating diseases and to cure painful conditions. But again, my mind wanders. Is there a Dr. Frankenstein out there? Will someone use this technology for the wrong reasons? And if so, will a new generation of super humans lack some of the finer human qualities, such as compassion and humility?

This gene-editing technology has introduced so many questions. Until we find the answers, I’ll be happy with what I have and be thankful for a future that’s both exciting and unnerving.