

Navigating the Future in a Sea of CRISPR Uncertainty: Contemplating Map Essentials

June 27, 2019

When is it time to act?

Opening Words

Ecclesiastes

Time for Everything,

There is a time for everything,
and a season for every activity under the heavens:

a time to be born and a time to die,
a time to plant and a time to uproot,

a time to kill and a time to heal,
a time to tear down and a time to build,

a time to weep and a time to laugh,
a time to mourn and a time to dance,

a time to scatter stones and a time to gather them,
a time to embrace and a time to refrain from embracing,

a time to search and a time to give up,
a time to keep and a time to throw away,

a time to tear and a time to mend,
a time to be silent and a time to speak,

a time to love and a time to hate,
a time for war and a time for peace.

When I first thought about this morning's question, "When is it time to act?" I did so in the context of thinking about when would be the right time, the "okay" or, the "green light" time to use CRISPR to edit human germlines? There are many other

applications of CRISPR technology, but the possibility that grabs the most headlines is the one about editing the human germline. *We know that at least one individual, on their own, already made a decision about when to act on that possibility.* In November 2018 Chinese scientist He Jiankui announced to the world that he had created the first genetically edited human babies using CRISPR, despite the recommendation from the First International Summit on Human Genome Editing in 2015 that stated: “It would be irresponsible to proceed with any clinical use of human germline editing unless and until (i) the relevant safety and efficacy issues have been resolved, based on appropriate understanding and balancing of risks, potential benefits, and alternatives, and (ii) there is broad societal consensus about the appropriateness of the proposed application.” The first international summit was Co-hosted by the US National Academy of Sciences and the National Academy of Medicine’s Human Gene-Editing Initiative, the Chinese Academy of Sciences and the U.K.’s Royal Society, *but their statement didn’t stop He from performing his experiment.* In March of this year scientists and ethicists from seven nations called for a moratorium on gene-editing experiments designed to alter heritable traits in human babies and they called for an international governing body to oversee the technology.

He Jiankui was reprimanded by the Chinese government (exactly what shape this reprimand is going to take for the rest of his life isn’t clear) and he was fired from the University he worked at in China. The jury is still out, I think, on just how involved his former Ph.D. advisor, a professor at Rice University was in the work and what this will mean for the rest of his professional career. Statements

condemning the experiment poured in from around the world, and in early June of this year research was published in *Nature Medicine* that was a point blank reminder of just how premature He's experiment was; the gene he knocked out of the three human embryos to render them immune to HIV *also gives them a 21% chance of being more likely to die before reaching the average life expectancy, and will also leave them more vulnerable to dangerous flus and the West Nile virus.*

He Jiankui claims he was trying to prevent disease, and in particular one that carries a heavy social stigma in China, HIV-AIDS. Let's imagine reaching a "broad societal consensus in the U.S. about the appropriateness of altering the human germline for preventing a particular disease, and that research communities worked in tandem with bioethicists and public stakeholders to determine that "the relevant safety and efficacy issues had been resolved" and the time was right to take action to alter the human germline. All good, but the human germline is blind to national borders. *Could an international governing body reach an agreement about when the time is right to alter the human germline, and how do they deal with individuals working outside of and in disregard of their regulations?* Setting aside the latter concern, judging from what we know about the gene editing of somatic cells, or germline cells of non-human animals, timing will not be something that is easy to reach an agreement on.

Genetic editing using CRISPR technology is proceeding at different rates in different countries. The story here is what is happening in China compared to the US and Europe. In April of this year scientists at the University of Pennsylvania, after being given the green light for a clinical trial ultimately involving 18 patients,

began their first CRISPR treatments with two of those patients. The treatments are medical interventions used to address the diseases of the individual patients and not an alteration of their germline cells. Immune system cells were removed from the patients, genetically edited in the lab to target and destroy cancer cells and then infused back into the patients' bodies. Meanwhile in Europe and Canada numerous clinical trials are also launching that use CRISPR to treat genetic blood disorders and perhaps soon cancerous tumors. According to one gene-editing scientist from the Altius Institute for Biomedical Sciences "2019 is the year when the training wheels come off and the world gets to see what CRISPR can really do for the world in the most positive sense."

But in this bike race the Chinese have already been zipping around on a two-wheeler for sometime. The first clinical applications took place there as early as 2015 and have involved dozens of people. While the University of Pennsylvania experiment had to pass two federal review boards and the review of two hospital committees, in China review by a single hospital committee was all that was needed to move forward. China has made this type of research a priority and since 2012 China's annual investment in science overall has dramatically risen (71%). When it comes to CRISPR China has been all about firsts; the first use of CRISPR edited cells to treat cancer, the first CRISPR editing of a human embryo and the first CRISPR editing of monkeys all occurred in Chinese labs. The challenge any international governing body will face setting guidelines to oversee this technology is the very real difference in societal values from one country to another.

Now in the interest of full disclosure, and before I say anything about contrasting values using China and the US as examples, I will tell you that my interest in China is more than academic. I am married to one of the very first Chinese students sent to the U.S. by the Chinese government in the 80s to attend graduate school in the sciences. We have been married for 27 years and have two daughters (they taught me a new word, Wasians). Since 1992 I have traveled to China almost yearly with my daughters to spend a few weeks visiting the in-laws and/or traveling in the country. One of my daughters is currently in Beijing for the summer participating in an intensive language program. The other will be leaving soon to spend three weeks shuttling between uncles, aunts and cousins in China who will all try and out do each other in showing her a fun time. I have always felt, from the very first time I visited China, warmly welcomed and loved. When I hear or read news reports about China my personal experiences certainly impact my impressions. But that doesn't mean I view China with rose-colored glasses, I don't.

My father-in-law joined the Communist party because he believed they were working to help the people, later during the cultural revolution he was publically ridiculed and sent for re-education, his oldest son was sent to the country side to work. That same son is now a communist party member himself. All of my Chinese relatives know what happened in Tiananmen square 30 years ago and they are aware of what is happening with the Uyghur community in northwestern China today and of the growing concerns of Chinese living in Hong Kong and Tawain. *They have also experienced first hand an increase in the quality of life for themselves and many rural Chinese over the last 30 years.* I will suggest that stability is what matters

to most Chinese people on the mainland and they will work to find a way to hang onto it no matter what their government is doing. *We need to understand that Nationalism is alive and well in China, just as it is in the US. And one of the ways that nationalism is currently being expressed in China is an increased investment in science and technology.*

The US is no longer by default the first or only place Chinese graduate students or early career Chinese scientists consider pursuing their work. The Chinese government and people value science, no worries about teaching evolution or climate change in China. They also place a higher value on social relations, and what is good for society at large, often at the expense of the individual. It is not hard to see how those values combine to result in their bioengineering field advancing and continuing to advance at a rate that can be unsettling for Westerners. We won't all answer the question "When is it time to act?" the same way, whether it is gene editing of the human germ line or somatic cells. *This challenge is made more difficult if we view bio-engineering as a national competition, thereby making international scientific collaboration and exchange also more difficult.*

There is agreement among international research communities, whether the public realizes it or not, that CRISPR is a fantastic lab tool. CRISPR is changing the landscape of research in biomedicine. It is being used to create laboratory animals and cell lines with specific genetic characteristics that help researchers better study human diseases. What once took years of research can now be accomplished in months. No longer do researchers need to wait years to breed generations of mice with different genes knocked out, they can do so in months with no breeding.

Another popular animal for gene editing research is the marmoset, a small monkey native to South America. Their physiology, including their brain, reflects human physiology and disease processes more closely than rodents. The National Academies Press recently released a workshop report about the *Care, Use and Welfare of Marmosets as Animal Models for Gene-Editing Based Biomedical Research* in which they explain:

“They [*marmosets*] may be particularly useful for the development of new disease models using genetic engineering and assisted reproductive technologies. However, concerns have been voiced with respect to the development of new marmoset-based models of disease, ethical considerations for their use, the supply of marmosets available for research, and gaps in guidance for their care and management.”

It's a scary time to be a marmoset. Their popularity as laboratory animals began in the 1960s but since their genome was sequenced, in the 1990's I think, they are in high demand including for gene therapy and aging studies. Their reproductive characteristics make them very attractive for research, they can gestate up to four embryos at once, have two pregnancies a year, and become physically mature in only 18 months. The demand for the animals is outstripping their limited supply and there is no standard of practice for their use and care, - hence the workshop organized by the U.S. Roundtable on Science and Welfare in Laboratory Animal Use to explore and address these concerns.

The workshop is good news for marmosets, in the U.S. there is a recognition of concern for the ethical care of the research animals. Maybe you would rather not

know this, but among monkeys, marmosets are known for cooperative social behavior: They call to each other in back-and-forth conversations, and mated pairs share responsibility for rearing young. In the U.S. using non-human primates as laboratory animals is facing a growing backlash from a public concerned about animal rights. This is not an issue in China. *The Atlantic* did a story on monkey research in China a year ago and had this to say:

“American scientists worry that the United States is falling behind China on primate research. ‘I have two big concerns,’ says Michael Platt, a brain scientist at the University of Pennsylvania who studies primates. ‘The United States is not investing heavily in these [primate] models. Therefore we won’t have the access that scientists have in China.’ The second, he says, is that ‘we might lose the talent base and expertise for actually doing primate neuroscience.’

It’s all about the competition...

If the research you are pursuing relies on using monkeys then working with a collaborator in China will give you an edge in access to a large supply of non-human primates and while the Chinese public is increasingly concerned about the welfare of dogs they keep as pets, this concern does not extend to animal models used to potentially advance human medicine. The Chinese public does not question the use of the animals in research and their government provides support for monkey breeding facilities. This is not to say there are no ethical concerns about the treatment of the laboratory animals in China. In fact, according to the author of *The Atlantic* article, many of the Chinese scientists performing the research were trained

in the U.S. and brought back to China a western appreciation of the ethical care that should be afforded these animals. I think non-human primates would be all for international scientific collaboration and exchange.

When is it time to act? While there seems to be international agreement to hold off on editing the human germline, as for plant, and non-human animal and primate germlines the research community is moving forward as they are able, within the constraints applied by their respective governments. Action is already happening, whether you will applaud it or not, especially if it involves research with non-human primates, might depend on whether you or someone you love is suffering, for example, from autism or Alzheimer's, just two of the diseases that researchers are using CRISPR and non-human primates to study. Our dilemma is that inaction has a cost too. There is a time for everything. But I don't believe now is the best time to focus on scientific competition and nationalism; in fact it may be the worst time. The human germline is blind to national borders. Thankfully, love can be too.

Closing Words

Chinese proverbs

A journey of a thousand miles begins with a single step.

Do not believe you will reach your destination without leaving the shore.

So let it be. Amen.