[Existential Risk / Opportunity] Singularity Management

January 2017

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CRISPR: A Job for us?

by James Blodgett

CRISPR-CAS9 is a new method of gene editing. From a distance it looks like an existential risk/opportunity singularity right out of this publication's title, and therefore a job for our SIG.

Both CRISPR and CAS are acronyms. You can Google them, but it takes biology that is a distraction right now to explain what they mean. Together they constitute a system of gene editing that is much faster and more accurate than previous methods. Their potential and the speed of their development look like a singularity to me. Emmanuelle Charpentier saw the first hints in 2011. She partnered with Jennifer Doudna to study the system. Feng Zhang discovered other parts. All three have filed separate patents and started separate companies. Charpentier and Doudna won prizes for their work. It is thought that they have not yet won a Nobel because of the patent dispute. Meanwhile the process is being used in many projects in almost all genetics labs, investors are lining up to put money into it, and demo kits are available for a few hundred dollars. The potential is huge. The Gates foundation and others hope to use it to eradicate malaria-carrying mosquitoes, it might cure genetic diseases and cancer in humans, and several agricultural companies have already used it to put beneficial genes into food plants on a test basis. Most researchers also speak of dangers, and most are following protocols that address those dangers. However, those protocols could use thought

regarding the tradeoffs between risks and benefits. Some of the risks are risks to single individuals and families who might receive or inherit genetic modifications with unforeseen problems, some are risks to ecosystems that may be disorganized by the absence of eradicated pests. Other risks may be existential risks. A technology that can eradicate mosquitoes might also misfire and eradicate humans.

The technology has two parts. One part is a guide RNA that locates a specific sequence of DNA, with high but not perfect accuracy, and provides a template for new DNA that will be inserted. The other is a set of molecular scissors that cuts the DNA at that point. Normal DNA repair functions tie the pieces together. This much of the technology is adequate to edit genes. However, the system can also be built into what is called a "gene drive," which is DNA edited into the genome, DNA that codes for and remakes the CRISPR and CAS components that insert the gene in the first place. A gene drive coded into a gametocyte will be passed on to descendents. Most normal traits passed on to descendents follow the rules of Mendelian inheritance. One set of genes comes from the father, another from the mother. If only one parent has the trait, an offspring that inherits the trait via a dominant gene has the gene for it on only one of two matching chromosomes. If the offspring's mate does not have the trait, the offspring's offspring has a 50% chance of getting that chromosome and inheriting that trait. However, if a gene drive is involved, it can edit the gene into the other chromosome, so the probability of inheritance approaches 100%. This means that the gene will spread faster, and it also means that a gene that reduces the chances of an organism's survival less than it increases the chances of its own reproduction will not be eliminated by evolution. Mosquitoes might be eradicated by a gene drive that cuts a gene required to make functioning females. That would eliminate most functioning females, leaving males who can spread the drive to fertilize those functioning females that remain. Since mosquitoes reproduce rapidly, gene drives can spread through their entire population rapidly.

This technique might save millions of lives. However, there seem to be several ways this might go wrong and take millions of lives, or even make us extinct. This seems to be a time when we need the existential risk/opportunity singularity management in our title to balance the risks and the benefits.

Biologists already know that CRISPR is potentially dangerous, and they have developed safety protocols. Biologists have a history of addressing such issues that is better than the history of some other fields. Google "Asilomar Conference 1975." Despite that history, they like all scientists have somewhat of a conflict of interest that tilts towards being able to conduct their experiments, a tilt that could benefit from outside comment. We have a specialty too, a specialty that can make a contribution. We have a better appreciation than most of the enormous negative expected value of human

extinction, and of the value of balancing risks and benefits. We can contribute to the discussion by thinking about and critiquing biologists' protocols.

EROSM is a quarterly publication. I had other ideas for a January article, but they haven't come together yet. I have also been wanting to consider potential dangers of the CRISPR technology. Therefore I decided to write an article about CRISPR, pointing out potential problems and inviting readers to help me study the issue and advocate for effective protocols.

Some safety protocols are already being followed. One scientific paper about using this technique with mosquitoes describes containment protocols. One protocol is the fact that the research is being done by a northern university in an area where the test mosquitoes do not live naturally, so even if one escapes from the lab, it will not find mates. This seems to be a nice thought that should work most of the time. However, it is easy to imagine an improbable failure. An escaped mosquito flies to a nearby airport, bites a sweating baggage handler, and gets trapped in the baggage compartment of an airplane that flies to Venezuela where it finds mates. Once in the environment, the gene drive has unexpected effects. I could conceptualize many other failure scenarios.

However, I tried to do this too quickly. I was able to think of several potential problems with CRISPR, but some may have been based on misunderstanding of the technique.

As an example of my misunderstanding, the spread of a gene drive has some aspects of a gene and some aspects of a virus. When it is written into the genome it will spread when that genome is reproduced. When it is expressed as a protein it floats around the cell like a virus, and I thought it might spread to other cells and even other species, especially if mosquitoes carried the drive and bit other species. Because cancer had been mentioned as something that CRISPR could help, I assumed that CRISPR would have to float through the blood to reach many cancer cells. However, when I read about a proposed cancer treatment, that was not how it worked. Rather, it was proposed that gene editing be used to fix immune system cells so that they would attack the cancer. Presumably the gene drive will spread to many immune cells as they reproduce. If gene drives do not spread like viruses but only by spreading to child organisms, then their spread though the human population would be slow since we have children infrequently. If necessary it would seem that we could stop their spread via genetic testing. However, do we know for sure that gene drives cannot spread like viruses? They must be introduced into a cell by scientists. Could something like the mechanism of that introduction occur in nature?

Other problems I think I see may also be due to misunderstanding. If all potential problems have adequate resolutions, we may have no need for advocacy. I am not yet

convinced that all problems are solved, so I hope to study the technique. Perhaps we can organize an informal seminar group via email, with participants summarizing articles they have read and things they have learned, and brainstorming safety protocols. Perhaps we can get geneticists who are using the technique to lecture and answer questions. If readers are interested in participating, send an email to our SIG's contact page at http://global-risk-sig.org/contacts.htm .

Upcoming Topics: Space Industrialization & Runaway Global Warming

by James Blodgett

Space Industrialization

I have mentioned space industrialization before. I hope to introduce some of the people working on it, and some of their ideas. Meanwhile, here is a link to an article that might be of interest: http://spacefaringamerica.net/?p=992 .

Runaway Global Warming

The standard model of global warming suggests that it will be inconvenient in some fairly large ways, but does not make it out to be an existential risk that will make us all extinct. Agriculture and cities may have to move, with much inconvenience and some tragedy, but agriculture and cities do not become impossible. However, there are other models. Some serious scientists, and some others whose motivation may be political rather than scientific, question whether global warming will happen at all, and even if it happens, whether it is caused by human activity. Another speculative model has global warming running away until it does kill us all. We hope to discuss this in more detail. Meanwhile, consider the following article: http://www.werbos.com/Atacama.pdf . It starts with a proposal for solar power in Chile, but read to (or skip to) the last few pages; its motivation is the idea that global warming will kill us all, and that solar power on a large scale can prevent that. It suggests some good reasons why both might be true. Its author, Paul Werbos, (Google him) is knowledgeable in many fields.