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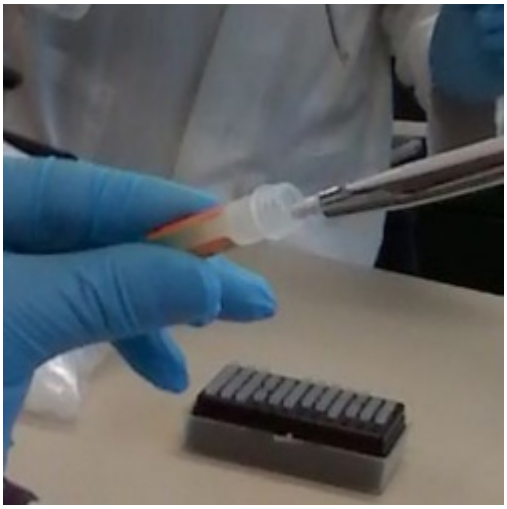
Genetically Modified People: Gene Editing Arrives in the Clinic

By Christopher Gerry — August 6, 2019



Credit: Alana Escoto/Wikipedia [1]

Genetically modified organisms may soon be walking among us. But don't worry—it won't be due to some horrible tomato-based [2] experiment gone awry.

Pop culture often depicts laboratory research as a frenetic rush filled with exploding test tubes, plumes of greenish smoke, and hair-singeing breakthroughs. In reality [3], science is a methodical, incremental process that more closely resembles an oil tanker than a jet ski. Drug discovery tends to be particularly sluggish because we must be absolutely sure that a new medicine is both safe and effective before we let patients both pay for it and put it in their bodies.

True "eureka" moments are rare, and rarer still are findings that change how entire branches of medicine attack diseases. But they do happen. Alexander Fleming's serendipitous discovery of penicillin sparked the "dawn of the antibiotic age [4]." Genentech's laboratory-based production of human insulin [5] launched the modern biotechnology industry. And now, less than a decade after it was first disclosed, a gene-altering technology called CRISPR is facing its first real clinical tests.

The scientific details behind CRISPR have been discussed on this site [6] and others [7], but I'll provide a brief overview here. CRISPR allows scientists to make changes at specific locations in the genome by tethering a pair of molecular scissors (a protein called Cas9) to a homing beacon for a defined DNA sequence (a molecule called a "guide RNA"). Cas9-mediated cuts in a gene are a great way to "break" that gene and render it permanently non-functional, but they can also enable precision editing of the genome to "correct" harmful mutations. Therefore, for diseases in which pathology is linked to a single faulty gene, such as Duchenne muscular dystrophy [8] or Huntington's disease [9], a single dose of a CRISPR-based drug could prove curative.

After seven white-knuckle years of research in both academia and the biotech industry, CRISPR therapies have started to shift from the buoyant realm of hypothesis to the unforgiving arena of experiment. The first US-based clinical trial involving CRISPR—sponsored by the University of Pennsylvania and Tmunity Therapeutics—started less than a year ago [10]. The candidate therapy comprises CRISPR-edited T cells that are primed to kill cancer. Though the trial doesn't involve CRISPR breaking or correcting a faulty gene directly, broadly raising the destructive power of the immune system has already been shown to be an effective anti-cancer strategy [11].

Tests of CRISPR's ability to treat genetic diseases are also in full swing. Earlier this year, a joint venture between CRISPR Therapeutics and Vertex Pharmaceuticals reported progress [12] on CRISPR-based trials targeting two crippling blood disorders. This unconventional treatment uses CRISPR to edit the DNA of hematopoietic stem cells—the cells living in your bone marrow that give rise to all other blood cells—such that they produce higher levels of a protein called fetal hemoglobin. The hope is that introducing fetal hemoglobin can cure patients with beta thalassemia [13] or sickle cell disease [14], both of which are caused by defects in the hemoglobin protein. Patients with beta thalassemia [12] and sickle cell [15] have already been treated with this therapy in Germany and the United States, respectively, and the early results are promising.

One complicating factor of the Vertex/CRISPR Therapeutics trial is that the editing actually takes place outside of the patient's body; hematopoietic stem cells are extracted from bone marrow, edited, and then replaced. In contrast, Allergan and Editas Medicine are currently developing a CRISPR therapy that performs genetic editing inside the body. The clinical candidate is designed to treat an inherited form of blindness called Leber congenital amaurosis 10 (LCA10), and the first patient is scheduled for dosing later this year [16].

So far, almost all clinical uses of CRISPR have been in somatic cells, which cannot transfer genetic information to future generations. So-called "germline" editing of sperm, eggs, or viable embryos has been largely avoided because the permanent nature of the changes combined with their unknown long-term consequences present a bevy of ethical and safety concerns. As a result, experts in the field have repeatedly called for a moratorium [17] on germline editing. Late last year, however, a Chinese scientist reportedly used CRISPR to edit the DNA of embryos [18] that were eventually brought to term. The birth of the first "CRISPR babies" prompted not only boatloads of press [18], but also swift and severe condemnation [19] from the scientific community.

Separating fact from fiction in this controversial, rapidly evolving field will take many years, but scientists have already taken a handful of important first steps. And though the words "revolution," "breakthrough," and "game-changer" are embarrassingly common in write-ups of biomedical

research, precision gene editing has the potential to meet the hype. Will we be prepared if it does?

Links

[1] https://en.wikipedia.org/wiki/Genetic_engineering#/media/File:Master_Mix_with_Primers_form_PCR.jpg
[2] https://www.imdb.com/title/tt0080391/
[3] https://xkcd.com/683/
[4] https://www.acs.org/content/acs/en/education/whatischemistry/landmarks/flemingpenicillin.html
[5] https://www.gene.com/media/press-releases/4160/1978-09-06/first-successful-laboratory-production-o
[6] https://www.acsh.org/news/2016/05/25/what-is-crispr-cas9-and-why-do-we-need-to-know-about-it
[7] https://time.com/4379503/crispr-scientists-edit-dna/?iid=toc_062316
[8] https://www.technologynetworks.com/genomics/news/one-year-later-crispr-success-in-duchenne-muscular-dystrophy-model-315586
[9] https://www.nature.com/articles/d41586-018-05177-y
[10] https://singularityhub.com/2019/05/02/crispr-used-in-human-trials-for-the-first-time-in-the-us/
[11] https://medicalxpress.com/news/2019-06-immunotherapy-five-year-survival-people-advanced.html
[12] http://ir.crisprtx.com/news-releases/news-release-details/crispr-therapeutics-and-vertex-announce-progress-clinical
[13] https://ghr.nlm.nih.gov/condition/beta-thalassemia
[14] https://ghr.nlm.nih.gov/condition/sickle-cell-disease
[15] https://www.npr.org/sections/health-shots/2019/07/29/744826505/sickle-cell-patient-reveals-why-she-is-volunteering-for-landmark-gene-editing-st
[16] http://ir.editasmedicine.com/news-releases/news-release-details/allergan-and-editas-medicine-initiate-brilliance-phase-12
[17] https://www.nature.com/articles/d41586-019-00726-5
[18] https://www.statnews.com/2018/11/25/china-first-gene-edited-babies-born/
[19] https://www.npr.org/sections/health-shots/2018/11/28/671375070/facing-backlash-chinese-scientist-defends-gene-editing-research-on-babies