
Thu, 2018/07/26 - 10:31am

UC San Francisco graduate student Theo Roth is first-author on a paper that appeared in *Nature* [1] this month. Around the same time, alongside stories about investigations into election tampering by the Russians, the weather, and other news of the day, news of Roth’s research also appeared in the *New York Times* [2]. The story hailed the discovery of a revolutionary new technique in gene editing, one that holds great promise in fighting cancer, infections, and autoimmune diseases.

Roth is a member of UCSF’s highly selective Medical Scientist Training Program [2] (MSTP), which comprises a group of seemingly insatiable and indefatigable learners. Students in the 8-year program start out in medical school, then switch to a PhD program, then return to medical school to finish up their dual MD/PhD degree. Right now, Roth is in the second year of the PhD part in the Biomedical Sciences program [3].

Roth and his co-authors, under the mentorship of their PI, Alexander Marson [4], MD, PhD, found a way to skirt the more routine, somewhat haphazard, way of editing genes, employing viruses to get inside cells. Instead, they use electrical fields to make the surface of cells more porous, facilitating the introduction of new DNA sequences and proteins through the cell membrane.

Marson Lab [5] had previously shown that this process, called electroporation, was a viable
way to introduce genetic components into T cells, a key element of the body's immune system, but they had trouble inserting long DNA sequences in just the right place without killing the host cells. Roth expanded on that work, finding a way to introduce large stretches of new DNA sequences, enabling the insertion of new DNA at well-defined sites in the genomes of human T cells without using a viral vector.

In other words, now they can take genes out of the white blood cells in the immune system and replace them with new-and-improved, engineered versions. They can also do it in a highly targeted way, more quickly and neatly than ever before - time and precision both counting for a lot in treating cancer and many other diseases.

Marson told the Times that Roth "tested thousands of conditions," before hitting on just the right mix of variables. The Times even described the effort as "herculean," but to hear Roth explain it, that kind of tenacious effort is par for the course in research. Great discoveries seldom result from a "single, perfect, elegant experiment," he says, rather "it's figuring out how to do many experiments and test many possibilities in an efficient way."

Using the new method, Roth was able to test 100 different permutations in a single experimental process that didn't require a lot of hands-on attention. "It took time and effort to get that pipeline up and running, but once it was, we could rapidly iterate through conditions, and focus in on the protocol alterations that were yielding greater numbers of live, correctly edited cells," Roth said.

"It's always exciting to see a graduate student like Theo Roth recognized for their research, and I commend him, his PI, and his research group on their groundbreaking discovery. It's also immensely satisfying to know that everyone at UCSF contributes to the collaborative scientific culture here, which enables students like Theo to do their best work. I look forward to seeing many more breakthroughs driven by graduate research, skillfully guided along by our outstanding mentors like Alex Marson," said Elizabeth Watkins, dean of the Graduate Division and vice chancellor of Student Academic Affairs.

Roth describes eloquently the interplay of the PI, graduate students, and other trainees in an academic lab. "Principle investigators lead and acquire funding for research programs that are quite expansive and beyond the scope of any one individual's work. A trainee, whether it is a graduate student or postdoc, has responsibility for a single project, a single story that will be told in one unit, as opposed to the PI's focus on how each of those projects/stories is part of a bigger picture. The design and organization of individual experiments, the physical process of actually doing them, the analysis of that data and initial ideas of what to do next, those are all the responsibility of the trainees. This cycle of experimentation is the process that is probably the most important, single thing for graduate students to learn."

For further reading:

- Feature in Sports Illustrated about Roth's earlier research in traumatic brain injury
- UCSF News coverage of breakthrough in Marson Lab (story by Pete Farley)
- "Reprogramming human T cell function and specificity with non-viral genome targeting," in Nature