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# Impossible? Can researchers develop 100 drugs in ten years?

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Develop 100 drugs in 10 years. That's the ambitious goal set by a group of scientists and engineers at the University of Utah, founders of Recursion Pharmaceuticals, a start-up company that is able to quickly and affordably identify unexpected ways a drug could be used by testing it on diseased cells.

The disruptive approach to drug development, aided by custom-designed software capable of tracking changes, or signs of healing, in cells, could speed discovery of therapies for so-called "orphan" diseases.

Scientists at Recursion have already identified two possible therapies for cerebral cavernous malformation (CCM), a rare hereditary vascular disease that leads to hemorrhagic strokes—including an over-the-counter, vitamin D supplement (cholecalciferol). A study showing that the compounds successfully reduced lesions by 50 percent in a mouse model of human CCM disease will be published Monday in the American Heart Association's journal, *Circulation*.

In addition, Recursion has applied for a $1.4 million National Institutes of Health grant to fund the screening of hundreds more drugs for use with 2,000 rare diseases. "By partnering with pharmaceutical companies, we can identify new uses for their drug candidates at a fraction of the cost to get more treatments to more patients more safely and quickly," said Recursion CEO, Christopher Gibson, an M.D./Ph.D. student at the University of Utah who has taken a leave of absence from his studies after finishing his Ph.D. dissertation under Dean Li, Vice-Dean of

research at University of Utah Health Sciences and Chief Scientific Officer at University of Utah Health Care.

It was in Li's lab that Recursion was born. The conventional path to drug discovery is to identify, through years of study, the biological mechanism behind a given a disease and then target it with a drug, testing it first in the lab, then in animals and finally on humans. The entire process can take 10 to 15 years on average and $1 billion, or more. And often, despite the best science, the drug fails to work as promised, by which time the manufacturer has wasted hundreds of millions of dollars. Ninety-five percent of drugs that are being prepared for clinical trials don't make it to market—a rate-limiting factor that determines how many medicines are invented, which diseases they treat and the prices patients pay, said Gibson. "It's not a viable business model in the long-term. Drug companies can't afford it and neither can we as a society."

The problem is especially acute for patients with rare diseases. In the U.S., a rare disease is defined by the Orphan Drug Act of 1983 as one that afflicts fewer than 200,000 people nationwide. There are about 7,000 different rare diseases, which together affect about 30 million Americans, according to the Institute of Medicine. Less than 5 percent of those diseases have therapies, and the therapies that exist come at a premium price because drug makers have to recoup their costs. The U.S. Food and Drug Administration is doing its part to remove regulatory hurdles to orphan drug development. Scientists at the University of Utah, meanwhile, are reengineering the discovery pipeline.

Recursion's strategy is two-fold. Instead of targeting specific molecular targets for a disease, Recursion makes a human cellular model of the disease and then targets the resulting phenotype (its observable characteristics of the cell) by testing the ability of compounds to restore misshapen and diseased human cells to their normal appearance and function. Doing so is a good predictor of a drug's success or failure. And

instead of starting from scratch with a new compound, their business model is to partner with manufacturers to salvage and repurpose drugs that passed early safety trials but never made it to market. They also intend to identify new uses for retired drugs or formulas available only in Europe and Asia. "These drugs are just sitting in freezers. We're saying, 'Give us your drugs and we'll monetize them,'" Gibson said.

Modeling disease in cells is a not a new technique, nor is repurposing drugs.

"But most drug-repurposing successes happen serendipitously, or with an educated guess based on deep biological understanding of a given disease. And while that may work for well-studied diseases, we don't have that same level of understanding with rare disorders," said Li, Recursion's co-founder. "With disease modeling and computational algorithms we developed, we're able to make drug repurposing scalable for use with rare diseases."

Li's team seized on the idea after a decade of studying CCM, a hemorrhagic stroke syndrome characterized by vascular malformations, or lesions, in the central nervous system. CCM lesions are unstable and leak, causing stroke. Currently the only treatment is surgical removal of the lesions. While studying the disease, scientists were struck by the phenotype, or how obviously the disease manifested in cellular changes. "We thought, 'Let's bathe them with different compounds and see if we can rescue them,'" Li said.

Gibson used software developed at the Broad Institute by Dr. Anne Carpenter, now a Scientific Advisor to Recursion, to quickly and accurately analyze cellular changes by tracking hundreds of parameters on 10,000 cells at once. "We compared doing this process by hand and using a computer, and the computer performed better. It was seeing things that people weren't seeing," Gibson said.

Two compounds proved most effective at rescuing the cells, including vitamin D and another drug currently in pre-clinical trials. Recursion is now working with a CCM specialist at the Mayo Clinic to test vitamin D in humans, and is negotiating with the maker of the second drug to co-develop or out-license it. "The two compounds work differently, but we think, synergistically," Gibson said.

He believes Recursion's discovery model is replicable and scalable to other diseases—an estimated 4,500 caused by "loss of function mutations" that halt or diminish the normal function of proteins. "Not all those diseases will be amenable to the platform we've built, but a good portion, maybe 25 to 50 percent will be," he said.

The idea of a pharmaceutical company tackling hundreds of diseases in a year is unthinkable for even the largest drug makers, which may be working on a dozen diseases at a time. "There will be doubters, those who say we're naïve to think we can accomplish that. But that's where science is taking is us," Gibson said. "It's exciting to think of the difference we'll make for people in desperate need of solutions, the lives we can save and health we can restore."

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