Novartis hire applies Darwinian mindset to drug discovery [1]

Discovery [2]

As a newly minted MD-PhD in 1984, Gerald Joyce faced two choices: stay in medicine or return to the lab. He was working as an intern at Mercy Hospital in San Diego, struggling with the decision, when a patient in the step-down unit went into cardiac arrest. Contrary to portrayals in medical dramas, most patients in full cardiac arrest die, even when this occurs in a hospital. Despite the odds, medical teams treat every patient and hope for the best. That night at Mercy Hospital the patient survived. Joyce was relieved, even happy, but the experience ultimately drove him back to research.

“I realized that we just got lucky,” says Joyce, the new Director of the Genomics Institute of the Novartis Research Foundation (GNF), who was surprised to hear some of his colleagues make self-congratulatory remarks. “We knew the odds, and we followed a standard protocol, so it seemed strange to make it about our egos.”

In that moment, Joyce missed being in the lab, where nothing felt rote and most challenges could be met with energy and intellect. Opting for a postdoc rather than a residency, he spent the next 30 years exploring the interface of biology and chemistry, first at The Salk Institute and then as a faculty member at The Scripps Research Institute. Joyce was recently recognized for his achievements through election to the Institute of Medicine [3]. He is perhaps best known for being one of the inventors of directed evolution technology and, more recently, for creating the first self-replicating RNA enzyme.

But Joyce never lost sight of patients. Although he stepped away from the clinic, he consistently applied discoveries made in the lab to real world problems. Now he will take that commitment to the next level at GNF.

As a part of the Novartis Institutes for BioMedical Research, GNF has always embraced the complexity of biological systems. GNF researchers use cutting-edge technology—including automation and robotics developed at the institute—to take advantage of emerging large-scale, data-rich fields for drug discovery. They collaborate with the academic groups shaping fields such as proteomics and metabolomics to understand the latest advances and apply them to pharmaceutical research.

“We have to maintain close connectivity with academic labs and feed what we learn forward to the rest of the research organization,” says Joyce.

Gerald Joyce,
Director of the Genomics Institute of the Novartis Research Foundation

He plans to strengthen collaborations with outside groups and forge new ones, beginning with scientists at Scripps, which is located adjacent to GNF in La Jolla, California. Joyce will continue to maintain a small lab at the academic research institute to encourage connectivity. But he also understands the expectations for his new role across the street.

“GNF has an obligation to maintain its steady output of clinical candidates,” says Joyce. “It’s not an academic institute in sheep’s clothing.”

Following is an excerpt from a conversation with Joyce about his scientific journey and vision for GNF.

Were you initially drawn to science or medicine?

Joyce: When I started as an undergrad at the University of Chicago, I wanted to be an ichthyologist, that’s a person who studies fish. It was 1974, and it was the beginning of the molecular genetics revolution. There’s incredible diversity of fish, which is the main reason evolutionary biologists are interested in them. I wanted to study them through the lens of molecular genetics, but the ichthyology field wasn’t yet ready for the revolution, so I spent most of my time cataloguing variation. For example, I would count the number of scales between the lateral line and the dorsal fin. I’m not a collector type, so I was bored. I wanted to watch evolution in motion and think about the biochemistry behind it.

When you grew tired of fish, did you shift to straight molecular genetics?

Joyce: I wanted to, but you have to put yourself in the mindset of that time. The Iranian

hostage crisis was underway, there was chaos in Central and South America, and there was a lot of malaise in the country. I worried that our borders would be overrun and federal support for basic, curiosity-driven science would evaporate. I decided that I needed a more durable skill. Medicine seemed like a good way to connect my basic science interests to the real world while deepening my knowledge base.

Have you continued to make connections between disciplines?

Joyce: My wife says I always play both sides against the middle. In fact, I was part of a movement in the 90s to create a new discipline called chemical biology, which is a phrase you didn't hear before 1991 or 1992. Before that point, you had to pick a tribe, either chemistry or biology. The first chemical biology groups included chemists who wanted to apply their wares to complex systems that matter and biologists who weren't afraid to synthesize molecules and use them to interrogate and perturb biology. So chemical biology isn't just between the two disciplines; it's where they intersect. There is so much opportunity in that space. That's where my lab plays.

What's the focus of your research program at Scripps?

Joyce: If you Google me, the pages that pop up first pertain to the origins of life. My name is often associated with the scientific definition of life. But that's not the bull's eye for me. I'm most interested in the evolutionary process, which is remarkably powerful and inventive. Life sustains itself through Darwinian evolution, discovers new things through Darwinian evolution and optimizes through Darwinian evolution. All the crazy little gadgets that biology has fashioned—enzymes that catalyze reactions, pheromones that help organisms attract mates, toxins to ward off predators—are the product of Darwinian evolution. My lab focuses on understanding how the process works and capturing it as a technology. We use the same principles that nature uses to invent molecules that have functions we find interesting, useful, marketable, curative; all of these.

Can you describe a recent research success?

Joyce: We generated a synthetic system that self-replicates and evolves on its own. It's a functional RNA molecule—an enzyme—that produces new copies of itself. The enzyme joins pieces of RNA together to produce more of itself, and as it produces copy after copy, genetic information is transferred from parent to progeny molecules. There are occasional mutations, so the enzyme actually evolves right before your eyes. But it's not alive. It doesn't display the inventiveness of a living system, at least not yet.

Why are you moving from academia to industry?

Joyce: I love my lab, but it's a boutique operation. It's never been larger than 13 or 14 people and is currently half that size. I'm at a point in my career where I'm ready for more action. I want to play at scale. Drug discovery is something that really matters to society, and I want to be involved. GNF is the perfect fit for me because it's one of the most academic-facing parts

of Novartis. We are the eyes and ears for the company at the interface between basic science and preclinical drug discovery. And we have the technological infrastructure to take advantage of emerging, data-rich fields like genomics and proteomics, which are just now unfolding in academia. GNF researchers are used to playing the big numbers game. We can help the company leverage a deluge of information on genes, proteins and pathways to make drugs.

How would you like to see GNF evolve over the next few years?

Joyce: I don't expect to make radical changes. It's important to play off of our strengths and be very honest with ourselves about our weaknesses. I genuinely think that we have the best high-throughput screening center in the world. There's a spirit at GNF to seize upon cutting-edge technologies, adopt them and integrate them into the drug discovery process, and we should continue in that vein.

One weakness that I've identified is that there aren't enough medical scientists at GNF. You have to stay focused on the end game as you progress through the drug discovery process. People often refer to the "pipeline" in this industry. If you look at the attrition rate for drug candidates, it's actually a funnel. The later something gets funneled out, the more money it costs and the greater the opportunity costs. I think we need to involve MDs earlier so that we better recognize when there is no viable path forward to the clinic and redirect our resources.

It sounds like you want to apply more selective pressure to the drug discovery process. Has evolution informed your thinking on this front?

Joyce: Darwinian evolution is a great paradigm for success. Initially, we should throw diversity at a problem and try a lot of different things. Then we need to pause and take a critical look at the results. We should assign each project a fitness value before starting the next round of discovery. If certain projects keep diminishing in fitness value, round after round, then we should sundown them. This mentality will help us prioritize and ultimately succeed in delivering new medicines to patients.

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