

Wendell Lim: Exploring the path not chosen

Lim is creating new biological systems from the parts evolution provided.

Have you ever played with LEGO®? Using the same set of colorful plastic bricks and a little imagination, it's possible to build anything from fairy castles to spaceships. Now, instead of plastic pieces, imagine getting to play with the modules that make up proteins: a tool kit of binding, regulatory, and catalytic domains. Arranging these functional modules in different ways would create proteins with very different functions—like the best LEGO® set ever.

Wendell Lim loves tinkering with proteins' functional domains, creating new arrangements that nature hasn't come up with yet. Not only is this fun, he says, but in the process he can learn a lot about protein function (1, 2), signaling pathway operation (3, 4), and evolution (5). We called him at his lab at the University of California, San Francisco, to hear how he constructed his career and what cool toys he's playing with now.

BUILDING BLOCKS

You began your research career with an interest in structural biology...

Sometime in early college, I realized that what you read in textbooks does not necessarily tell the whole story of how biological systems work. I distinctly remember the first time I thought, "This is all amazing stuff, but there has to be more to it." For example, I had all these textbooks saying that enzymes accelerate reactions and that this is one of the keys to how life works, but none of the books I had explained how enzymes really work. So as an undergrad, I became interested in enzyme mechanisms, which then led to working on protein structure and how that's linked to function.

I did my graduate work at MIT with Bob Sauer. Bob was one of the first people to really combine biophysical, structural, and genetic methods to look at protein structure.

We used classic methodologies from phage genetics to screen randomized variants of the λ repressor sequence and ask which variations would still allow the molecule to function. It was a revelation to me to discover that by studying a protein's structure you can describe what it looks like, but, in order to intimately relate that information to a protein's function, you have to combine structural studies with something like genetics.

What shaped your interest in the kinds of questions you work on now?

I wanted to learn more about quantitative structural methods, like crystallography, and at that time Yale was the top place to study structural biology; it was undergoing a kind of renaissance there. I did my postdoc with Fred Richards, who was actually retired at the time, and he gave me a lot of freedom to start exploring how I could take the tools of structural biology, genetics, and biochemistry and apply them to different sorts of problems.

Before that, I really hadn't thought much about biological problems; I was more interested in the fundamentals of protein structure and evolution. But as a postdoc I had to start thinking, "What are some of the big questions out there now?" I really didn't know anything about stuff like signal transduction, but I

became very interested in the question of how cells use systems of molecules to detect what's going on in their environment and to make decisions accordingly.

About that time, more and more protein sequence information started appearing, and it was becoming apparent that many signaling proteins are built from ensembles of smaller, independently folding modules. It seemed that evolution was shuffling these modules around to make new signaling or regulatory circuits. I started to think about

"Many signaling proteins are built from ensembles of smaller, independently folding modules."



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what the structure and function of these modules were and how they were used as components to build higher orders of biological function.

ALTERNATE ARRANGEMENTS

Your work has also focused on creating novel systems and proteins from existing modules...

I think that, from the very beginning, when I first read about these domains as a postdoc, it was clear to me that these were essentially like words that evolution could use as a vocabulary to build different sentences and paragraphs of higher-order complex function. One of the big problems that lay ahead was to understand how evolution has used these components, but the obvious corollary to that is: Can we use them to modify function in ways that evolution hasn't yet explored or that we don't know about? It probably took a good ten years for me to get around to that problem.

The late 1990s and early 2000s was a really exciting time. A lot of structures of signaling proteins were solved. We started getting insight into their mechanisms and how multiple domains worked together. Although they all had a lot of complexity to them, at their core, many signaling proteins had just a few mechanisms that were almost universal: catalytic domains combined with different regulatory domains that determined where these molecules would go and become activated within the cell. This is true for kinases, phosphatases, guanine nucleotide exchange factors (GEFs), etc.

It's not trivial to redesign or reengineer pathways, but it's doable. Evolution has certainly done it. So we had a number of papers during that period where we looked at different signaling proteins and asked: Can we take some canonical output, such as a GEF that regulates one of the small GTPases that controls cellular morphology, and then put different regulatory domains on it to change the cellular function it encodes? Can we change the inputs that drive a morphological response? We showed that, in fact, it was really quite easy to get these kinds of new behaviors.

Did you have some practical outcome in mind that you were working toward?

It's one thing to say, "Okay, we want to understand how the modern pathways we see in ourselves or other organisms could have evolved." A lot of our effort has been devoted to that question, and we've gotten some insights into that for some pathways.

But if, in fact, modular protein organization means that there's a huge range of decision-making or information-processing behaviors that could exist, then the obvious question is: What could you do with this?



A light-drawn cell alludes to our ability to resculpt cell shape and responses using engineered inputs such as light.

Could you design cells that make new decisions or carry out new, useful functions? There are a lot of things one could imagine.

One of the areas that we've focused on is the idea of therapeutic cells, for example in adoptive immunotherapy. We're exploring the idea of redesigning T cells with new artificial receptors that allow them to detect cancer antigens and kill cancer cells but whose activity we can modulate using small molecules. People in this area of synthetic biology are also thinking about things like replacing β cells in diabetes with more robust versions that we can control or interface with and that aren't susceptible to the underlying autoimmune disorder associated with type 1 diabetes.

Don't you have to understand how a system normally works before you alter it?

I would politely disagree with the idea that we have to completely understand a biological system before we can do something with it. Trying to make some new function that's biologic-like, but different, ends up informing us about the fundamentals of the biological system and the design rules governing how it works. It's an iterative process.

CREATIVE PURSUITS

You make it sound almost like making art...

I think over the last couple decades I've gained an appreciation of just how much science allows you to almost take a blank canvas and create something new. I feel very lucky, in that this career has been much more of a creative process than I might have expected when I started out.



Lim and his daughter prepare for a meditative moment.

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Of course, I have other creative outlets as well. I have a wonderful wife and three kids, and we love to explore creative things together. We do a lot of art, including painting and printmaking.

What other hobbies do you enjoy?

I play basketball and, in the last five years, have started to surf. I like being in the water. It is both meditative and chaotic. The waves are crashing on you, but you have to just deal with it and work with what the ocean throws at you. It's exhausting and harrowing, but it's also relaxing at the same time.

Do you think about science when you surf?

Not really. I just try to stay alive, I think. [Laughs]

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