UCI biologist shares quest for malady's cause

Arthur Lander explains how he found a gene that causes birth defects, and its ramifications.

By PAT BRENNAN / ORANGE COUNTY REGISTER

How do the cells in our bodies talk to each other? Why do birth defects and cancer happen? For that matter, why don't they happen more often? And what is the molecular basis of evolution?

The questions fly fast and thick in a conversation with UC Irvine systems biologist Arthur Lander, including an obvious one: What is a systems biologist?

Arthur Lander is the new Donald Bren Professor of Developmental and Cell Biology at UC Irvine, a chair created to encourage innovative research. He studies how cells communicate with each other, explaining the mechanisms behind birth defects, cancer and genetic disease.
SAM GANGWER, ORANGE COUNTY REGISTER

Lander has been answering some questions and asking far more for two decades, the last eight years at UCI. Systems biology – the holistic study of groups of molecules, genes, cells or entire organisms, and how they work together – led him to help zero in on a gene that causes a variety of birth defects.

His searching and probing for possible genetic candidates, which helped another biologist locate the gene itself, came too late for his first daughter, who died only a month after she was born.

But the discovery helped give Lander and other researchers a genetic target in their fight to defeat the malady she suffered from, Cornelia de Lange syndrome. Now the disease, which used to have only a name and a suite of debilitating symptoms, has a cause as well.

Lander also is the brother of Eric Lander, a genetic researcher known for his work on the Human Genome Project.

Arthur Lander was recently named UCI's new Donald Bren Professor of Developmental and Cell Biology. He took some time recently to let the questions fly.

Q. Are you targeting, research-wise, a particular topic?

A. The meaning of systems biology is very broad. It's not a niche within biology. It's more like a movement, almost like a philosophical change in biology, that's aimed at resolving a lot of issues in areas where we know a lot, but still don't understand very much. It's frustrating, because we've spent the last century getting to the point where we know a whole lot – really, really fast. Yet it's surprising: The more we know, it almost seems like the less we understand. So systems biology directly targets that problem. How do you actually get to understanding? It can be applied to almost any corner of biology, though it tends to work best on the molecular and the cellular end.

We focus on the problems of how cells are talking to each other, which makes possible things like development – accurate development – where we, more or less, come out OK when we're born. It's an amazing thing that that happens at all. (The research extends) to other specific things, like cancer – how it is that cancer cells are able to wage a battle against the rest of your body, and win?

Q. So systems biology is what it sounds like, the study of whole systems?

A. One big point of it is holistics, studying biological systems as a whole. But the main reason why it's focused at that holistic level is because it's trying to kind of close the loop between evolution and molecular biology. We tend to think of it as sort of a linear pathway; you start with molecules, they make proteins, the proteins make cells, the cells make tissues, the tissues make organisms, the organisms make populations that then evolve and do stuff. (But) it's not really linear. It's really a loop, because when evolution does stuff, it does stuff by changing the molecules. So really, it's one big feedback.

If you want to understand molecules, it's not enough to understand what they do. You have to understand why they're there, why we have the genes we have, as opposed to what the genes cause. You can only pose that question in a holistic way.

It sounds like this work could yield insights into evolution, as well as some of the more medically oriented research.

A. Yes, that's right. One of the things that makes evolutionary biology so interdisciplinary, so team-oriented, is that in order to close that loop you not only need to have different flavors of biologists. People who understand evolution have typically been a very different group from the people who understand molecules. You not only have to have those people working together, but rules that explain how particular arrangements at the molecular level give rise to functions useful at a higher level. Those rules are the rules of engineering, physics and mathematics. And in order to use data measurements to get at those rules – well, you need computer scientists, because you can't manage data and make inferences without computers. At the end of the day, you have to have biologists, mathematicians, computer scientists and physicists, all working together.

Q. You helped identify the gene that causes Cornelia de Lange syndrome. Are you still working on that?

A. My daughter had that syndrome. She survived for a month, and passed away. So my wife (Professor Anne Calof in the department of anatomy and neurobiology) and I became two of a small number of people in the world working on it. Now we've kind of roped in, like, five other investigators. Now we have this great interdisciplinary team at UCI; now we're pushing forward on that frontier. This particular disorder, it's a birth defect syndrome. That means children potentially have birth defects in almost every organ system. It turns out to be a systems biology problem, too. The cause of the syndrome is that that there is one particular gene that produces a certain protein at too low a level. And that protein controls the expression of an enormous number of genes. So as a result, the transcription – the product of genes throughout the genome – is slightly disregulated everywhere. So it's like there are just slight maladjustments all over your genome. It gives rise to these very specific defects in the body. It becomes a very interesting question: How do lots of little errors combine to form some very big problems? It turns out that this may be a better model of just normal human variability. Why are people different? Why are some long-lived, some not? Some are tall, some are short. Some are smart, some are less smart. It may not be the kind of classical model – find one gene which, when altered, is responsible for each different observable variation – but in fact a collective effect, a lot of tiny alterations in a lot of different places throughout the genome. It might be a good model for our diversity.

And you are also the brother of Eric Lander. Does his research intersect with yours?

A. We haven't officially collaborated. He runs the Broad Institute at Harvard and MIT. They're probably the leading genomics institute in the world. They played a major role in the Human Genome Project. Now he is one of three co-chairs of the President's Council of Advisors (on Science and Technology). I guess you would call him a human genomicist, so that overlaps with systems biology.

Q. Did you both take the same road in science?

A. No, we went down very different roads. He got a Ph.D. in math at Oxford. He was a Rhodes scholar. He came back to the states and got a job at the Harvard Business School, so he could kind of figure out what to do with the rest of his life. And at that point I kind of challenged him to apply himself in biology. I told him I thought we desperately needed people who could handle math within biology.

Biology is changing dramatically quickly toward the more mathematical, molecular end of things. This is really a revolutionary period in biology. The last time we had a period like this was in the '40s and '50s, when the biological revolution got started. This is like that revolution, but dramatically different. Currently the NIH (National Institutes of Health) fund these 15 national centers for systems biology. That was their attempt to put a stamp on this kind of revolution – here is where we think it should be, here is where the battle lines are. So we have one of those 15 centers. That's what the Center for Complex Biological Systems is. If you look at all 15 centers in this program, that is a really good way to see what the community at large feels what the heart of this change is.

Contact the writer: 714-796-7865 or pbrennan@ocregister.com.