

The Slope of Biology: An Interview with Eric Lander

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Dr. Eric Lander, a principal leader of the Human Genome Project who is widely regarded as one of the world's leaders in genomics, recently took some time out of his busy schedule to sit down with two MURJ staff writers for a brief interview. What followed was a valuable, thought-provoking discussion about some of the most important topics in biological research today.

Melis: First, we wanted to hear your thoughts on how the biology department has changed since you first arrived at MIT.

Dr. Eric Lander: My goodness, wow. Well, my perspective is that the biology department hasn't changed. The central feature of the MIT biology department is that it has always had very creative young faculty exploring the edge of biology, and it's always been a lively department ever since the days of Salvador Luria [Director of the Center for Cancer Research at MIT and 1969 Nobel Laureate]. The biology department has always been one of the best in the world. It has stayed that way by having a steady stream of young scientists joining the faculty and having older faculty keep reinventing themselves, working on new things. One of the wonderful things about the department is that it's so lively. Nobody gets stuck in their ways, everybody is challenging paradigms, inventing new approaches. I think that aspect of the culture is a constant.

The other constant of the culture is teaching. Undergraduate and graduate teaching have been signatures of the biology department since I've been here and long before, certainly going back to the 60's. MIT has always felt that great researchers should be in classes, even teaching introductory courses. The teaching enterprise and the research enterprise are inextricably linked at MIT, as compared to some other universities where the research faculty don't teach the introductory classes. MIT has always had that as part of its culture. Same for the graduate program. MIT is famous for inventing a graduate class called "Methods and Logic," a paper-reading course, for graduate students to read biology papers and discuss and debate them. This course have been copied at many other universities.

So in that sense I would say that MIT hasn't really changed much because of its two central pillars: that it's all about change and reinvention, staying on the cutting edge, never being satisfied, always being curious, bringing in new people; and that it's all about teaching. Those pillars have been there all along.

Paul: Previously, you were one of the leading collaborators on the Human Genome Project. We were just wondering if you could tell us, on a personal level, what that experience was like.

EL: It varied depending on what day you ask! It was exhilarating, just exhilarating. It is one the most remarkable scientific projects of our generation, perhaps the signature project of our generation. It was an effort larger than any of us, so we all felt that we were contributing to something that we would be very proud to tell our grandchildren we had done. We felt that it would change the face of biology in medicine, and I think it has. On any given day it could be frustrating because machines would blow up on us—metaphorically, they wouldn't be working—or strategies wouldn't work. You'd have reporters calling, you'd have never-ending wars with the private company that was competing to sequence the human genome, or whatever. But I had the pleasure of being part from the very beginning, all the way to its successful completion. The overarching feeling is a sense of purpose and satisfaction. We all felt we knew why we were doing this.

There were challenges at every step of the way—nothing was easy. When the project was laid out, it involved trying to do something 10,000 times larger than had been done before. It wasn't just scale-up, it was solving a zillion problems, but it was exhilarating to solve those problems every day and to work with a community of people. As for MIT, we had an extraordinary community of hundreds of people involved in multiple disciplines—from biology, from engineering, from computer science, from chemistry—all working together for a common goal. And we were part of an international network. There were groups in twenty different centers in six different countries. The largest group in the world was here at MIT, but it was just wonderful to feel like we had a community that stretched to my friend Yang Huangming in Beijing, Henry as he's called, who runs the genome center in Beijing; or our colleagues in the Sanger Institute in England, or in St. Louis or in Japan. And so we felt that we were all part of the same goal. There was great pride that the data was released at the end of every day freely on the web. There were, I still remember,

meetings every Friday at 11 A.M., international conference calls for six years. I'll probably never get over that.

It was a great experience, a tremendous challenge. It was very different than my own research lab. I did still have a regular research lab, I still had graduate students and post-docs, though it was a small lab, but on the side, I had about 500 people working together. So it was an interesting balance and it was a tremendous privilege, I have to say.

Paul: Now that the human genome has been sequenced, what keeps you busy now?

EL: So what's the to-do list? [laughs] Here's the to-do list. We sequenced the human genome, but we need to know everything that's encoded in it. 1) We need to know all the functional elements encoded in the genome. All the genes, regulatory elements and structural elements 2) We need to know all the genomic variants and how they correlates with the risk of disease. 3) We need to know all the mutations that can occur that can give rise to cancer. 4) We need to be able to recognize all the cellular circuits and how they're read out. So when a cell is doing something, we need to recognize that a certain pathway is turned on. And 5) we need to be able to manipulate or modulate genes in situ. That's pretty much the to-do list. And it's not something for the 21st century, but just for the next ten years, because there's enormous progress being made towards it already.

How do we identify functional elements? We can use evolution—compare the human genome to other species and see what bits evolve slowly, which elements are conserved, in other words. Well, the human genome was finished in 2003, the draft in 2001, and as of now, we have 24 more mammalian genomes sequenced—dogs, mice, rats, elephants, armadillos, etc. We have projects here at MIT to line up all those sequences and figure out what's conserved. We have projects to do large-scale chromatin analysis. Chromatin are proteins that wrap up DNA and are modified in different ways to control genes. In the last 6 months, it's become possible to do large-scale analysis of chromatin structure, build whole maps of the chromatin regulatory states of cells. With regard to human genetic variation, in 1998, there were only a couple well-documented human genetic variants, single nucleotide changes, in the human population. We started a project here to generate some, about 4,000, as a pilot project for a larger project that in two years grew into about a million, which grew into 10 million. And that's actually the majority of human genetic variation. So, most human genetic variation has already been identified, and it's pretty cool.

Correlation with disease: we can look at the genetic variants and see which ones are enriched in people with diabetes or early heart disease or asthma. That only just became possible last summer, with tools that we had been working on. And over this past twelve months, there has just been a huge explosion. For the first time we have genes being discovered all over the world, every week, as risk factors for common disease -- for diabetes, for inflammatory bowel disease, for early myocardial infarction. It's just fantastic. It's something we've been aiming at for ten years and it's finally come to pass.

With regard to cellular circuits and signatures, it's possible to study all the RNAs in a cell and build inventories, catalogues of expression of genes. There are projects here to try to do that. Also there are projects to use RNAi, inhibitory RNAs, to modulate genes. It is sort of like Human Genome Project 2. Human Genome 1 was getting the sequences, Human Genome 2 was breathing meaning into that sequence.

Paul: Apart from what you just mentioned, what do you feel are some of the unsolved problems or “hot topics” within biology?

EL: [sighs] So those weren't impressive enough? Just teasing!

Oh, there are huge, huge problems. They range from the very fundamental problems, like that we still don't really understand development—how it is that a single cell develops into an organism and cells adopt fates in persistent ways. They make career decisions, but we don't really know what that means. What does it mean at the molecular level that a precursor cell is committed to becoming a liver cell? You can buy whole books on development, and read them, and there isn't a meaningful answer to that question at the molecular level. That's a major problem that still is being worked out.

That's a very fundamental question, and at the extreme opposite of the spectrum is an applied question. We still don't really know how to make vaccines. HIV is our most embarrassing case, we can't make a vaccine against HIV. We don't have the deep science of how to make vaccines.

So, the unsolved problems are anywhere from what does it mean for a cell to make a commitment, to how do you actually design and make a vaccine, and many questions in between. But we have tools, and biology is at an amazing time where we can actually begin to take on these huge questions.

Melis: Since this is an undergraduate research journal, what role do you think undergraduates should play in tackling these huge biological problems?

EL: Get involved. The most important thing for an undergraduate to know is that science is changing rapidly. As an undergraduate, you're learning biology for the first time. Maybe you're scrambling just to learn the facts. What you learn in class is: Here are the facts of biology, here are the point estimates of where biology is now. That's useful, I suppose, but it's far more interesting to look at not the point estimate but the derivative. What is the slope of biology? Undergraduates sometimes feel like they should learn just what's in the textbook. But really, what they should do is read the textbook from ten years ago, then read the textbook from today, see how rapidly things are changing and then project forward to what the textbook is going to be twenty years from now when you'll be in the middle of your research career. The best thing to do is work in a laboratory, and see how fast this stuff is changing.

What's the reason to go to a university like MIT? Why not go to a place that is only about teaching? A school that is primarily devoted to teaching can teach you the current state of biology. They can have fabulous teachers. But what they

can't do as well is to teach you how rapidly the field is changing, because only by actually doing the research can you really feel how it's changing. I don't really care if students learn the current state of biology, I care that they're going to develop the next stage of biology. You have to learn the current stage to reinvent it, but I don't want you to take the stuff as received wisdom, I want you to look at it and say, "Well, that's nice, but it's pretty imperfect. There are all sorts of questions can't be answered." Or, there are all sorts questions developed in the last ten years. Think about what can be developed in the next ten years. Edginess, impatience, possibility.

Most undergraduates aren't going to make huge discoveries as an undergraduate: you have a too much classwork to have the time necessary to do it. But what you can do is get the feeling deep in your bones of the exhilaration of being part of such a vast intellectual enterprise. It is addictive, it is an extraordinarily addictive experience to know things that nobody else in the world knows. To know, "Wow, we are the only people who know this so far. The rest of the world will know in a month but right now we're the only ones who know this." Once you do that, then you want to do it again, and again.

Melis: Since you've had many UROP students, you know that we have time constraints, but what are the main qualities you look for in a UROP?

EL: Self-reliance. Often a good UROP is just dropped into the middle of an environment and everyone is busy working, they're busy with their classes, and you know, you learn by encounters with other people. You've got to be flexible, you've got to talk to people. So when I look for a UROP I look for somebody who's curious, gregarious, who will seek others out and ask questions. Flexible—and, in some sense driven—driven to do something, driven to know something. But, of course, most MIT students are like that. And of course, you can only take a handful of UROPs, so it's always tough.

The most legendary UROP that I ever took is Mark Daly. I took him when he was a freshman in 1986. He stayed and continued his UROP all four years, and then came and took a job here, and basically stayed forever. He became known as the most extraordinary genetic analyst in the world. People began writing to him to collaborate with him on different projects. He took up a job as staff scientist at the genome center, and people just began assuming he was a professor. He began writing papers on all sorts of different subjects, and became the world expert and made some very important discoveries, just by basically continuing his UROP for 15 years. And, at some point, it became apparent that he had made such extraordinary contributions to science, people were asking, "Do you want to go to graduate school?" and he would say, "I don't have time to go to graduate school, I'm doing too much science." He was just too productive to want to go to graduate school. So what was arranged was this: the University of Leiden in the Netherlands has an old tradition, going back to the Middle Ages, of being able to award Ph.D.'s to people for work that they have already completed, if they write it up as a thesis. So it was arranged that Mark would write up all his work as a thesis to Leiden and defend it there.

He was awarded his Ph.D. from Leiden for the work that he completed, and now has had a faculty position as a professor at the Massachusetts General Hospital for the past couple of years.

But, it was just amazing, it was just a UROP project! And you never know what UROP project will grow into.

Melis: Could you describe some of the projects that UROPs in your lab have undertaken?

EL: Well, Mark was one, whose job was to make a genetic linkage map using DNA polymorphisms and do the analysis of that. Other UROPs have worked on cloning genes in mice, or writing computer programs to analyze gene expression in diabetes, or all sorts of projects.

Paul: Did your UROPs come into your lab already knowing how to do those things?

EL: No, they learned on the job. You come in with some things, you learn some things.

Melis: Graduate schools seem to place a great deal of emphasis on publications. Do you have any publication tips for undergraduates?

EL: Write clearly. I'm serious. The ability to write clearly helps your papers get published far more than you might realize. There are tens of thousands of people doing biology. The ability to get people to stop and pay attention to your work depends on clear communication. You have to know how to give a clear talk, write a clear paper, otherwise people don't have the time to find the gem.

Find papers you love and use them as a model. Emulate writers just as a novelist would emulate some novels as a model. Good scientists should know of some papers that they say, "Wow, that's a model on how to write a paper. It's so crisp, so clear. The sentences flow, the ideas flow. There's a voice."

I hate the traditional way of writing a paper. The usual way they teach in school is tremendously repetitive: give an introduction, give the materials and methods, then give us the results, and only then give a discussion. That's boring, that's incredibly boring. First of all, I don't want to see your materials and methods before I've read your results to see if I'm interested, so put materials and methods at the end. Cell and Nature and a few other journals do that. I don't want to hear the same thing three times, just get to the point. I want to know what the point is. The idea of separating your results from your interpretation is nuts, life doesn't go that way, you don't get a whole bunch of results and then do your interpretations. You say, we got this result, we think it means this, we therefore did something else, we think it means that, we therefore did something else, and so on.

It's a story—writing a paper is telling a story. It's an intellectual story, it's a scientific story, it's a rigorous story, but humans are set up to hear stories. A great scientific paper is a story. Look at "The General Nature of the Genetic Code" by Crick, Brenner, Barnett, and Watts-Tobin, a paper on the fact that the genetic code is in triplet letters. It's a beautiful

paper, it's written in the first person and it's gorgeous, it's really nice.

The passive voice should be killed, there's no excuse for writing in the passive voice. Please write "we"! Science was done by a "we" or an "I," there needs to be a subject to sentences in most cases. Because we thought that it would be a good idea to do this, or we reasoned that. I want to hear that personal voice in there, because I can believe it or disbelieve it, but I want an actor in that story. I don't want some passive hands-off description of things. I want flesh and blood in the paper. Anyway, I have a lot of feelings on how to write a great paper.

Paul: You've done some of your greatest work in the field of genomics. How do you feel your accomplishments are going to affect the lives of everyday people in the near future?

EL: Well, my work has been devoted to making the tools to find the basis of disease. In the 20th century we didn't know the molecular basis of most diseases—diabetes, most kinds of cancer. Pretty much everything I've done, from the beginning of building genetic linkage maps, and physical maps, and sequencing the genome, and determining genetic variation, has been building the tools for finding the cause of disease. How will that affect people? Well, while occasionally it's possible to create therapies for a disease without knowing the cause, it's a pretty shaky business. The most effective approach we have for finding therapies is to start with the cause. So I hope that at some point, in my lifetime or not, there will be hundreds of diseases for which we have more effective diagnostics and therapeutics because the human genome got laid out. That's why we focused on the tools. We apply the tools ourselves to particular problems—I've worked on cancer and other diseases, but I've always had my mind that the real goal is to create the tools that will enable 10,000 people to work on these things, because the multiplier is so much greater than what we can do in our own lab. We work on some such problems ourselves, because that's how we know we're building the right tools, and it's good feedback, but we can't possibly do all that has to be done. But, we can enable the world. That's why feel so strongly about getting the tools out, the information out, freely.

Paul: Finally, what are your thoughts on the growing field of bioengineering?

EL: I think the more we understand cellular circuitry, the more we can try to design cellular circuits. Systems biology is kind of the analysis of circuits, but there's a design component just like there is in electrical engineering. Could we design a new circuit that would make a cell do something for us. It's a challenge, we're nowhere near the point where we have all the parts on the shelf and we just can pull them down say, "Now let's put together a circuit that will do something." I think bioengineering is pretty exciting as a long-term discipline.

Dr. Eric Lander is the Founding Director of the Broad Institute of MIT and Harvard. A mathematics genius turned geneticist, Dr. Lander applied his mathematical prowess to crack the world's most complicated code—the sequence of DNA carried by all human beings. In addition to his extraordinary contributions to the Human Genome Project, Dr. Lander has won the Woodrow Wilson Prize from Princeton University, the City of Medicine Prize, and the Gairdner International Prize. A former MacArthur fellow, Dr. Lander was elected as a member of the U.S. National Academy of Sciences and the U.S. Institute of Medicine. He has served as chair of the Joint Steering Committee for Public Policy. In addition to his work at the Broad Institute, Dr. Lander is a member of the Whitehead Institute and a professor of biology at MIT, where he has won the prestigious Baker Memorial Award for Undergraduate Teaching. He has taught MIT's Introductory Biology course (7.012) for sixteen years.

