AN AUDIENCE WITH...

Eric S. Lander

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Eric S. Lander is a geneticist, molecular biologist and mathematician, and was one of the principal leaders of the Human Genome Project. He earned his B.A. in mathematics from Princeton University in 1978 and his Ph.D., as a Rhodes Scholar, in mathematics from Oxford University in 1981. After assistant and associate professorships in managerial economics at Harvard Business School, Lander founded the Whitehead Institute/Massachusetts Institute of Technology (MIT) Center for Genome Research in 1990, which then became part of the Broad Institute — a research collaboration of MIT, Harvard and its hospitals, and Whitehead, founded in 2003 with Lander as Founding Director. Lander is also professor of biology at MIT, professor of systems biology at Harvard Medical School and a member of the Whitehead Institute, where, in addition to his research, he is an enthusiastic undergraduate teacher. His many awards include the MacArthur Foundation Prize Fellowship in 1987, the City of Medicine Award in 2001 and the Baker Memorial Award for Undergraduate Teaching at MIT in 1992. Lander was elected a Member of the US National Academy of Sciences in 1997 and the US Institute of Medicine in 1999, and in 2000 delivered a special Millennium Lecture at the White House.

There seems a huge gap between identifying a gene implicated in a disease and actually finding a way to prevent or treat that disease. Is this an efficient model for drug discovery?
Absolutely — but, it's not enough to simply identify individual genes associated with disease. We need to identify the physiological states associated with diseases and then identify molecules that can modulate these physiological states. We need large-scale databases that show the effects on cells of thousands of small molecules and other perturbations. In this way, we can identify molecules that modulate physiological pathways of interest. These aren't immediately going to be drugs that we can use in patients, but they will represent important leads. In the past, drug development has typically employed rather limited phenotypic read-outs. We need to use much broader read-outs. What we really want is to search for drugs by looking at their effect on the entire readout of the cell.

Do you believe that only a portion of the genome is druggable?
What is 'druggable'? I remember when protein kinases were not considered druggable! So, I don't take much stock in 'druggable' as being a definition of nature. Druggable is merely a description of the current state of our abilities.

Some diseases with a genetic basis, such as sickle cell anaemia, are genetically well defined but still poorly treated. Is this the exception or the rule?
I think it's neither exception nor rule. There will certainly be diseases that 50 years from now we still won't know how to treat. On the other hand, there are many for which treatments have been developed based on genetic information, such as HIV and chronic myeloid leukaemia. For sickle cell anaemia, there are some treatments available based on our knowledge of the disease, but their benefit is not as dramatic as one would like. Some diseases will yield to molecular understanding but some won't; it's hard to predict with precision. But understanding trumps ignorance, and it's a no-brainer to predict that understanding diseases will often have a large impact on treatment.

History suggests that it's perhaps not necessary to understand entire biological networks to discover effective drugs. Do you agree?
I don't think one can draw that conclusion. We've succeeded at making drugs in some cases where we don't understand the pathways — showing that it is sometimes possible. But, we've done poorly in many cases and it is likely that we'd have done better with better understanding.

What do you think of systems biology, and is it important for drug development?
Well, I'm not entirely sure what 'systems biology' means! People use it in many different ways. If you're asking whether it is important to understand the molecular mechanism of disease in order to treat it, you bet it is. Alternatively you could be asking whether it is essential to have a precisely predictive mathematical model for the physiology of the cell in order to do effective drug development. Well, it's going to be a while before we have any such thing, and I think we can make a lot of progress without it. As with most scientific activities, drug development is the art of the soluble. Increased understanding of mechanism is turning out to be crucial, and it is making drug discovery much more efficient. I don't think that a precise, mathematical, quantitative model of the cell is the key missing ingredient right now — it's not where I would put my energy.

Do you think that we will ever be able to design drugs in a similar way to designing planes, by using only models and simulation?
One can only look foolish by predicting that something will never happen, but I don't think it will happen in the next ten years. I don't think we should count on it for the next major improvement in drug development. All that each generation can do is to make drug development better than it was before. The next generation will then come up with a better way to do it. It's progress — what more can you hope for?

How will you measure the Broad's success?
There are many projects today that require a collaborative team approach that are fundamentally academic science and are not appropriate for the commercial sector, but which also don't fit in to the usual model of the single graduate sitting alone working at the bench. The Broad Institute is meant to be a nucleus for those types of projects across Harvard and the MIT community. So, it's success will be measured in ideas and projects that enable our understanding and treatment of disease, and in smart young scientists taking on problems that they couldn't have done without the benefit of this scientific community.