Interview with Edison Liu M.D. by Ute Deichmann, New York City, 17 October 2022

Edison Liu is former president and CEO of The Jackson Laboratory, and the former director of its NCI-designated Cancer Center. His scientific research has focused on the functional genomics of human cancers, particularly breast cancer (identifying the tandem duplicator phenotype genomic configuration), discovering new oncogenes (AXL family of receptor tyrosine kinases), and deciphering the dynamics of gene regulation on a genomic scale that modulates cancer biology. His work has spanned basic sciences to population sciences to translation to the clinic. He has authored over 340 scientific papers and reviews and co-authored two books.

Ute

I would like to talk to you about your research, your move to CEO of the Jackson Laboratory and reasons for your success, your thoughts about the interface of science and society, and other things that come to our minds. Let's start with your research.

I Research

1. From medical practitioner to researcher in genomics

You received an MD from Stanford University and later had postdoc fellowships in microbiology, hematology, and oncology. Your main interest is in genetics or genomics.

Edison

Molecular genetics and genomics.

Ute

When and how did you become interested in genomics?

Edison

It is a long story. I'll just tell you most of my life is a series of very fortunate accidents and experiments. I was, I am an immigrant child from China, from Hong Kong. Both my parents are physicians, and then most of my family are and were physicians. So, I was going to go into practice. But I was always curious, and I did research in chemistry and psychology - I actually did research in social psychology and in pharmacology. And then I went and did my training in hematology and oncology because of Saul Rosenberg, a Jewish gentleman who was a remarkable human being. At that time, I was actually seriously going to go into cardiovascular surgery, but he taught me a physician, as a person, can be a therapeutic entity. Through example, he showed that by being a physician - with the demeanor of a compassionate doctor - you could heal beyond the knife or beyond a drug and I wanted to aspire to that.

But after my medical school - I completed all my clinical training before I did any research, not like some of the colleagues who knew they were going to be researchers. However, I was dissatisfied with what I was doing as a physician in those days. I mean it was like alchemy, you know, you're mixing things together and seeing if you get gold. And in chemotherapy, we were trying one combination after the other. And that was uncomfortable to me. So, I decided to take a detour, and it was simply a detour, to try what was at that time a new discipline, that of recombinant engineering and molecular genetics.

I went into the laboratory of J. Michael Bishop, who subsequently won the Nobel Prize for the discovery of oncogenes. And that experience literally changed my life. My focus has always been on the impact of medicine on my patients, and now for the very first time, I was seeing science not as a tool to get to that point, but I saw the beauty of the scientific questions. Though, I'm not a trained geneticist, over the years, because of the work that I did, because it was DNA- and gene-based, I became more and more involved in genetic questions. As an oncologist I was primarily interested in somatic genetics and less so in errors in the germline. I started to run a breast cancer research program at the University of North Carolina at Chapel Hill about the same time as BRCA1 was identified and cloned; so, there was a need for people in oncology to start programs in cancer genetics.

Ute

What is BRCA?

Edison

BRCA1 was the first germline cancer-susceptibility gene discovered in breast cancer. Some of my friends were deep in the middle of that cloning project and once that happened, it became imperative for me as a clinician that we started incorporating that into the practice. But because I was also an epidemiologist, I ran the laboratory of Molecular Epidemiology, which set up a program, among the first of its kind in epidemiology, doing genetic tests on preserved samples to assess mutations in various cancer genes, which was totally new. And it's that confluence of molecular biology and epidemiology that then got me interested in what became the discipline of genomics. At that time, the genomics field was focused heavily on sequencing the human genome. However, when I was at the National Cancer Institute, I pivoted to go into what was to be called expression genomics. This approach focused on interrogating the transcriptome - the RNA output of the genome - using the newly devised expression array technology.

Early on, we would assess RNA transcripts one gene at a time using northern blot technology. But with these arrays, now we could investigate 2,000 genes at a time. However, before companies took over, we had to then create our own arrays by printing them with crude robots. We did our own printing and did our own analysis. As the head of the intramural clinical-translational program at the National Cancer Institute I had the resources to establish this for the institute. That was how all my molecular genetics and clinical genetics interests converged to guide my entry into the field of genomics.

But the second break came when I was asked by the country of Singapore to start the whole genomics program for the country. In 2000, Singapore announced that it would go into the life sciences as a pillar of its economy and understood that they could not accomplish this without some genomic capabilities. At that time, they had no such capabilities and understood they had to import talent to get it started. They approached me for my interest to pioneer such a program. I already knew that as a practicing clinician, I would never get a position in the United States to run a genomics program, which was completely focused on whole genome sequencing

and sequencing technologies. This was clearly not my skill set, but also not my interest. But the people in Singapore wanted somebody who could actually take genomics into something more applied rather than as a theoretical construct. In fact, they were interested in using genomics to study cancer, which was perfect for me. So, they invited me in 2001 to establish the genomic capabilities for Singapore, to recruit genomic scientists, and to train Singaporeans to one day take over. It was, you know, a blank slate, which was a remarkable opportunity which I could not pass up. That's when I quit all clinical medicine, and I started the Genome Institute of Singapore. This, then, became my deep dive into genomics and is the fundamental story of how I got into genomics.

2. Science and society in Singapore - genomics and health science policies

The 11 years I was in Singapore were truly a profound educational experience for me. It was an immersion into how science can shape a society. The country of Singapore is a little rock of 20 miles by 40 miles that doesn’t even have their own water supply. Yet by sheer will and intellect they made it into one of the economic tigers of Asia. Its success was all predicated on intelligent organization, logistics, and science and engineering. It's just those factors. So, for 11 years I was involved in every aspect of the biomedical initiative in that country, especially in integrating biomedical research into the economic, academic, and health functions of the country. I was part of their first bioethics initiative; I participated in changing their secondary school system to incorporate more life sciences; I helped reconstruct the university system into research universities; I took part in modulating the healthcare system to become a more investigative structure as opposed to simply delivery of care; I also played a role with the Economic Development Board in enticing life sciences companies to set up shop in Singapore. One of the most fun I had was being the chairman of Singapore’s Health Sciences Authority, which was the amalgamation of blood bank, FDA, and the investigative forensics groups.

In that role, I worked with the authority’s leadership to undertake a series of regulatory reforms to streamline product regulation. Therefore, not only did I have a front row seat to observe the impact of science on society and the essentiality of that for this nation, but I also participated in the execution of it, with all the successes and failures that took place. For example, I was the senior scientific officer for Singapore

during the SARS crisis in 2003, where our institute was pivotal in the sequencing of the virus and the construction of the first diagnostic. Then subsequently, I was party to how Singapore acted with each successive pandemic. The impact on me was profound because it moved me directly out of my pure science shell into one of being a responsible policy maker, you know, who helped incorporate science into the fabric of governmental functions and societal aspirations.

Ute

So, your work has left a big mark in Singapore, right?

Edison

There were many people in Singapore who had an impact during these critical years, but certainly I participated in it. I was very proud when, at the fiftieth anniversary of the founding of Singapore as a nation, I was named as one of the fifty most important foreigners who shaped the nation.

I think however, my thinking about the interface between society and science began when I was at the National Cancer Institute. At the NCI, I wasn't focused on the general role of science in society but started by being engaged in how the cancer research on the national level affected public opinion and the public's sense of well being. That was my first exposure into the absolute importance of the dialogue between academic researchers and the public including legislators. It was at a time when that relationship between legislators and scientists in the US was good. You know, unfortunately, it's very different now.

3. Big data and experiments in genomics research

Ute

My next question concerns genomics and sequencing, but also the expression array. Do you think that the revolution of big data medicine, like in genomics, with its promises of more precise and personal diagnosis and treatment, will supersede or complement the practices resulting from the previous revolution, that is, the molecular revolution?

Edison

I think it's a natural progression. The kind of genomics we're talking about is conceptually no different than what we were doing before, except it's being done in a massive scale.

Ute

But you usually don't use experiments anymore to decipher the molecules, I mean the particular molecules involved in some of the diseases. That's why I asked whether it supersedes or complements molecular medicine.

Edison

What is your assumption, that the data will allow us to forgo testing? I don't understand.

Ute

Some people claim that data is enough, and we don’t need experimental testing anymore.

Edison

That is totally false.

Ute

I also think it is false. I just wanted to hear what you think …

Edison

Let me tell you that this is actual wishful thinking but wrong. The economists showed us that already. When several Nobel laureates in economics got together and started

Long Term Capital Management hedge fund that used big data processed by sophisticated algorithms. Everybody joined in. It completely crashed – lost everything. It's no longer existing. People lost billions of dollars. They tried to sell the idea, which I know they believed in, that big data was going to predict the market. Big data is good for predicting what happened in the past. It is not good for predicting the unusual events of the future. It never is, especially for highly complex systems.

Ute

That is an interesting statement. What, do you think, is needed to predict events in the future?

Edison

It is fallacious to believe, especially in the complexity of the human body and disease, that you can make consistent predictions simply on data. The term big data is relative and too liberally used – how big is big, and when is data big enough to have confidence in the predictions? In biology, there's usually not enough data. Sometimes this erroneous thinking approaches absurdity. I have heard people say “oh, I'm using artificial intelligence on lots of data from 150 people”. That’s the kiss of death because - can you actually take the realities of 150 people and predict the actions of the other seven billion human beings in the world? The answer is: absolutely not. Using a limited dataset to predict the range of outcomes for a much larger population gives rise to overfitting errors.

The other aspect is that we know only what we know. If you had talked to us 25-30 years ago, the argument was, if I knew every single gene element and promoter, I would be able to predict you as a human being. Well, I'm sorry that doesn't happen. It doesn't happen because what we thought of as the universe of known information is only a small fraction of reality. We now know that the complexity of splice variance, the complexity of alternative promoters, the complexity of post translational modification, the complexity of gene-gene interactions, the complexity of eQTLs (genomic loci that explain variation in expression levels of mRNAs), where distant enhancer sites affect a gene megabases away. This is all new information. So, if we were simply to model on old data that we considered was the totality of the biological

universe, our predictions would have been mainly wrong. This is why I think the idea that big data in medicine is going to supplant experimentation is not only unreal, it's absolutely dangerous. In fact, I'm really fearful that we're going to fall into the trap of the Dark Ages. What happened to the Dark Ages? You know, the Hellenistic view of empiricism was supplanted by absolutism: that all knowledge had been described in the Bible and there is no need to seek new discoveries.

Ute

By the bible?

Edison

By the Bible. It was blasphemy for one to ask questions that challenged what was written in the Bible.

Ute

Asking questions was always dangerous in the history of Christianity but …

Edison

That’s what I am trying to say, OK, so if we are to adopt the belief that big data will supplant experimentation in biology and medicine, we will strangely move into an intellectual dark age.

Ute

What I heard, and this makes it even more dangerous, is that many young people are somehow reluctant to work the hard way of doing experiments and finding out about mechanisms. They prefer to do discovery science and data mining and come up with a PhD, which is much easier and much faster than if they complemented it with experimental testing. At a conference on personalized medicine, Aaron Ciechanover said that all progress in the future is based on molecules. Genomic and

other data are very important, and you can do a lot of things with them, but you also need molecules.

Edison

And we don't know what we don't know, and the danger is the assumption that we know it all. That is the greatest conceptual danger, more than anything else. That is the most fearful for me.

Ute

I completely agree.

Is it correct that your work is based on the one hand on whole genome sequencing in humans, and on the other, on experimental research in animals, e.g., mice?

Edison

Yes. In fact, our mantra is that you can only fathom the complexity of the human organism if you can work in the parallel universes of model systems, like the mouse. And the mouse-human intersection is going to be one of the most critical intersections for us to learn what we don't know, especially as we move into more and more of an understanding that biology is no longer based solely on the knowledge of individual genes. It really is about complex gene-gene, gene-environment, and epigenetic interactions.

Just as an aside, when I was going up in the ranks, there were many professors who studied p53 all their lives and the only molecule they knew was p53. That was how you made your way up the academic ladder. Nowadays you can't do that because we know that p53 is a member of a much larger and more complex group of pleiotropic genes, meaning it has many functions and have many forms, consequently, when you start moving into this kind of complexity, you can no longer focus on an individual component part.

The engineers already told us this. At one point, the electrical engineers worried about how you made a transistor. You know you can have transistors with different ohms - different resistances - and it came as a concrete piece. Now it is all about the

integrated motherboard of a computer that is etched by photolithography. They no longer worry about what that component, and the electrical resistance on that one electrical path. They are concerned about how the profile of switches is actually integrated with the motherboard itself. We're exactly at that stage in biology where the individual components are important, but by themselves, can never explain the function of the whole.

4. AI, hypotheses, and computational modeling

Ute

Molecular embryologist and systems biologist Eric Davidson was of the opinion that despite the revolutionary novelty provided by whole genome sequencing for systems wide approaches, "what still lies uniquely at the heart of real science, including basic science done at the system level, is the inductive use of predictive hypothesis." Other biologists seem to think that they can dispense with hypothesis and experiment. What is your opinion?

Edison

I think one of the challenges is that there's a lure of big data, you know, being able to explain everything. I firmly assert that you cannot dispense with hypothesis testing and direct experimentation.

Ute

There are people like the journalist of WIRED magazine, Anderson, who claimed not only that you don't need experiments, but also that you don't need hypotheses anymore, because it's all done by algorithms.

Edison

That is just absurd. And as I have stated, it's downright dangerous. But there is a lure to that, and what I think is really necessary is for people to show where this has gone astray, where it really doesn't work. I mean all you have to do is to take a look at the airline crash of the Boeing Max. They used AI, but then what seemed to have

happened was that the computational decision mechanisms overrode the human control. The machine did not know what it doesn't know. When faced with an unknown, the machine took over and actually pushed the plane to its death. Right? Here again I think this kind of danger has to be exposed. I really think there's no question, like all technologies, that the power of big data and the power of the genomics is extraordinary, it's truly extraordinary, but, simply, it does not follow, that we're at a point now that we don't need human intervention, thoughtful experimentation, and hypothesis testing. In fact, I would argue that in the world of big data, one needs hypotheses to frame rational outcomes. With big enough datasets, you need something that actually constrains what you are looking for, because the possible outcomes of complex systems can be near infinite. In clinical trials, one must have a hypothesis to test. The idea of accepting any serendipitous discovery outside the central hypothesis is verboten. It doesn't mean you can't explore for new ideas – new hypotheses, but you simply cannot assume that what you have uncovered is real. You may not know this.

What I mean is that the rate of false discovery is high. OK. A study should be constructed with sufficient statistical power to test the central hypothesis but will not have the power to ascertain the validity of ten other ancillary ideas. It got extreme in the past when in phase three clinical trials, the data gatekeepers would basically say, "no, we will not let you look at the data to generate hypotheses." Now that is wrong. So there needs to be a balance and the balance is, we need to know when we are looking at data to generate hypotheses to be tested in the future, and we need to know when the data actually tells you the truth based on the central hypothesis that you're examining. It's all about statistically avoiding false positives and understanding the probability of the false negative.

Ute

I'm just wondering - in two days I will speak at a conference on Turing ...

Edison

Turing machines?

Ute

No, not Turing machines. It is commemorating the 70th anniversary of Turing's paper on morphogenesis in 1952. There are many researchers who use Turing mechanisms to predict or simulate morphogenesis of certain features of animals or humans, and one of them pointed to the problem that with the Turing mechanism or Turing theory, you have many, many possibilities. In order to find out which of them is used in the organism, you need to do perturbation experiments.

Is this related to what you said?

Edison

Yes, it's precisely what I said. The bigger the data set, the larger the possibilities of any outcome. And most of those outcomes are false. Therefore, it is helpful to do perturbation analyses. You need to perturb the system in order to help filter out what is junk and what is real. Part of that is parameter setting. The early people who were doing phage biology used sort of a Turing algorithm.

Ute

Max Delbrück?

Edison

Max Delbrück for example, and Mark Ptashne, they actually were able to create control diagrams early on, but that's because the organism they studied, phage, is a very simple organism that uses primarily binary controls. We now know in Mendelian systems and most higher organisms, that these controls are no longer binary, and have complex feed forward and feedback loops. Therefore, there may be a multitude of possible outcomes from a single input. So, one has to really narrow down – to limit - the parameters in order to have realistic outputs. Importantly, perturbation analysis allows us to derive the constants within the equation that can predict outcome.

Edison

Francis Crick, Max Delbrück, Wally Gilbert all were physicists who brought, I believe, a very important quantitative rigor to analyze complex biological system. Classical biologists were more than happy to wave their hands and say, “Well that's the way life is.”

Ute

Freeman Dyson is reported to have said, “Biologists love to leave the world a little bit more complicated than they found it."

Edison

That is so true, but mathematical rigor in biology created other challenges. There is a term “mathematical biology”, and as a discipline it attempted to render biological systems into mathematical constructs. Well, it turned out that the mathematicians who tried to model biology failed primarily because they assumed what we knew at the time was the universal truth that they can compute on, when in reality, we, as a field, were so far from that state of data completeness. Then they compensated by simplifying complex biological processes to a point that the outcomes were not helpful.

Ute

Yes, I know about this. For a long time, most biologists did not take the models seriously because the simulations did not reflect reality. The stripes of Drosophila are not generated by Turing mechanisms. It is easy to simulate them using Turing equations, but in the organism, they are generated by gene networks.

Edison

Eric Davidson's major contribution was developmental biology - I still remember with awe his early papers.

Ute

With Roy Britten in 1969?

Edison

Of the sea urchin and ...

Ute

Yes, that was what he was working on.

Edison

And how he actually drew a gene-based control map of the early development of sea urchins. As I started to work in the field of computational modeling, I realized that there is a real difference between developmental biology and cancer, the field that I am in, and the major difference is a mathematical one. Eric Davidson very wisely chose a system that was unidirectional. A cell that was undifferentiated became differentiated, and there was no way to get back. That unidirectionality is irreversible.

Once you move into homeostatic systems, then the equations get infinitely more complex. When you have multiple homeostatic mechanisms, simultaneously working on a biological output, then it becomes, I would argue, a system that cannot be computed. Unless you make assumptions to simplify this complexity – sometimes called heuristics. It's all about the assumptions that you make that will shape the predictive output. This brings us again to this whole crazy idea that, “OK, I could just get enough data and compute a certain outcome.” One has to either significantly temper the claim of certainty of such a computed outcome, or artificially limit the predictive space with assumptions or previously determined parameters. These computational actions already violate that assertion that hypothesis setting and experimentation can be dispensed with in predictive medicine.

5. Work on oncogenes

Ute

Coming back to your own work: One of your major achievements was the discovery of a special genome-wide instability configuration (TDP) and of new oncogenes. Is it correct that your work is based on the one hand on whole genome sequencing in humans, on the other, on experimental research in animals, e.g., mice? I wonder, how, for example, can you deduce a causal relationship like driving of TDP induction from correlations?

Edison

What you said is most critical. If you take a look at that paper in Cancer Cell, the most important figure was describing the work in the mouse. The reason is that, in the first instance, we made the association between BRCA1 deficiency and TDP with big data. It was pretty good, but it was simply association. What moved it from a very good paper to a paper that had impact, was the fact that we had our mouse experiment where we recapitulated the exact, precise human event. Literally with genomic precision. We used a mouse model that was engineered to have BRCA1 and TP53 mutations in their mammary cells and found the resultant mammary tumors had precisely the same genomic marks. So, in essence, we took a correlation and experimentally tested the hypothesis by reconstructing it in a model organism.

Ute

And then you could demonstrate the causality.

Edison

Completely proved the causality.

Ute

And with correlations alone you could not?

Edison

Exactly. This is why in the genomics world, people are progressively asking: the correlations are cool, but can you show that these associations are real? Big data helps because it tells us the possibilities. I think the danger comes when both editors and authors collude to say this is reality.

Ute

I think this would be one aspect of science and society where people should engage.

Edison

Yes. It is very interesting to me that, more and more, there is a genre in literature of science for the layman, for the lay public. You have Michael Pollan, you have Jared Diamond, you have a whole bunch of these authors who are quite smart. They are really good; some of them are obviously not scientists but they interpret the science in a way that an intelligent public could truly understand and grasp. It moves them away from trying to explain, you know, the details of the Krebs cycle, to the impact of this knowledge on a societal basis.

By the way, I am expressing this partly because I wasn't trained as a scientist. I was trained as a physician; I never got a PhD. My intentions getting an MD was to take care of patients and being able to talk to them was part of that responsibility. But when I became a basic scientist, I took care of graduate students, and the overwhelming assumption for the training for the PhD, is to get them to be a scientific specialist. The key was for them to communicate with other specialists because their career is dependent on it. In that context, you get into a communications quandary because talking to other scientists require a technical precision as you talk about the experiment. But then when you interpret it to the public, you've got to shed all that and come up with metaphors that are easily understandable, narratives that are compelling, and even philosophical discussions, which we are poorly trained to do.

Ute

I would like to ask one more question about your research. I assume that in your paper on chromatin interaction, this demonstration of genome-wide chromatin

interactions is also not done alone by sequencing, but you also conducted some experiments to show that, right?

Edison

Yes, it's embedded in the experimental discussion. Proving chromatin interactions, is really an experimental challenge, because how do you go about doing it on a genome wide scale? What my colleagues did - I didn't do the primary work - was to use markers, the fluorescent probes that hybridize to specific segments of the genome proposed to interact in 3D. They then showed that these two dots actually came together in nuclear space while highly separated in linear genomic space. This confirmed our predictions.

Ute

You used electron microscopy?

Edison

No, it’s just standard fluorescence microscopy. You don't need electron microscopy. In fact, I don't know if using electron microscopy, you're going to be able to, because the way you process electronic microscopic samples, you got to do a lot of various fixations that might change the associations itself. Here is another very interesting thing about the perturbation analysis. Stefan Mundlos in Berlin actually took that concept and used human disease and genetic mutations as the perturbation. He looked at families that had a congenital limb developmental disorder, and by genome sequencing they knew that the associated germline mutations were deletions, duplications, or inversions, something that's structural, but far away from the critical gene. What he found was that these structural mutations disrupted three-dimensional interactions and caused an abnormal rewiring of gene expression important in limb development. Consistent with our earlier conversation, he proved causation by recapitulating this abnormality in engineered mice.

It was a single structural rearrangement in a non-coding region that changed the whole structure of the three-dimensional interaction. It was this kind of perturbation

analysis, dependent on an unfortunately genetic error, that literally showed the importance of this three-dimensional chromatin structure in human biology.

Ute

That is very interesting because when I read this article, I thought you would say in some diseases the three-dimensional direction is perhaps more important than transcription factors and gene regulation.

Edison

I would be the last person to say that statement.

Ute

But something like that was written, and I wanted to ask you because I thought you would not say it.

Edison

You know there's a little bit of salesmanship that you have to have sometimes.

Ute

I also think the three-dimensional arrangement would not be so specific.

Edison

This is interesting. Transcription factors can also sometimes target many genes.

Ute

Yes, I know. Let me cite geneticist and epigeneticist Adrian Bird. He said that making switches in the liquid state like the cell is not easy. He compared the biological and genomic regulation in the cell to bureaucracy. Bureaucracies are clumsy but they

work and that means that things are not related to one, let’s say, transcription factor, but you have to have several regulatory factors that can cause a proper response. Of course, they are more or less specific. But we should not expect a one-to-one relationship.

Edison

That's exactly right. I published about that earlier in the 2000s when we first described transcription factor binding and were able to map them. What really was very surprising was how our earlier concept of a one-to-one enhancer promoter interaction was completely thrown out of the window. There are certain genes where that is the case, but the majority has multiple enhancers interacting to control a promoter, and the question was why. I actually made a statement that, listen, this actually provides tremendous robustness to the system, So that, if you have an error in one of the enhancers, it causes maybe a problem, a subtle change, but is not going to kill the organism. In fact, these subtle changes may assist in providing phenotypic diversity useful for evolutionary robustness of a species.

The biggest surprise we saw was when we started to look at the evolution of enhancers in their position and their sequence across related organisms. We were surprised to find how poorly conserved these enhancers were despite the fact that in the protein coding regions they were very close, and we also found that enhancers were created and destroyed throughout evolution, created by internal expression and then reintegration of endogenous retroviruses. And now it’s written frequently that enhancer remodeling is a major part of the evolutionary process. It is also a very important mechanism for an organism to generate the kind of variability that is necessary for environmental changes. In other words, these subtle changes do not change the organism’s baseline viability but give them enough variation within the population so that if there's a drought, you know, a portion will survive because there is variability in terms of how certain systems of genes are controlled.

II CEO of the Jackson Laboratory; reasons for success

Ute

I would now like to ask a few questions about your move to accept the position of the president and CEO of the laboratory.

Edison

The Jackson Laboratory.

Ute

Yes, the Jackson Laboratory and its Cancer Center. That is what you did for many years and what you told us before about your work in Singapore, explained it in part: you obviously have a motivation and capability of run institutions on that high level.

Edison

You know that is sort of a personal decision. I like to run organizations, but I like to do so in a way that would have an impact.

Ute

Right, but to like is certainly not enough. So, what made you so especially successful in Singapore and also in the Jackson lab that grew significantly in revenue, number of employees, and international presence under your leadership?

Edison

That's a very good question. To start with, in Singapore, I really learned that I enjoy building - building as opposed to sustaining institutions. I also enjoy organizations where there is a clear sense that the constituents, the people who work in the institution, not just believe in the science they are doing, but believe in the values of their community. That's very important. Science for community is something that I found exhilarating in Singapore, which I never had the opportunity to experience in the United States in my other jobs. When I say “science for community” I mean the fact that science isn't just simply to make a professor famous and one day get the

Nobel Prize. That's great but what I was really excited about was how a high level scientific organization can contribute to the community on the ground.

This is why Singapore and the Jackson Labs (JAX) are very unusual places. JAX has 2,700 individuals, about 1,600 in Maine itself, a rural state, but because it's there, it's probably the most important academic organization in that entire state. We also are the 14th largest employer in the state, therefore how we conduct ourselves as an employer actually changes the employer-employee interactions for an entire community. And the other aspect is that it was an institution where, as CEO, I had a lot of authority, and I know for a fact that if I went to university, I'd be tied up with all sorts of bureaucracy and hierarchies. You really can't make tremendous headway in the university system if you want to change society.

Additionally, academia is very conservative; academics want to keep the system exactly the same as what they had before. I don't mean political, but organizationally. So, the success of the Jackson Labs is because I could actually move the wheels and gears in different directions and reconstruct the framework of the operations - often to make it more efficient so we can have greater scientific and social impact. To do so, we had to be constantly viewing metrics. In my experience academics are lousy managers. And a lot of it is because they believe so deeply in their own capabilities and in what they do, they actually don't like contrary data when it comes to how they manage. I'm often astonished at that. You know, they could be the most hard-nosed scientist but when you put in front of them the fact that the spreadsheet shows that their revenues are collapsing, they either say, “I don't believe it” or they blame someone else – like the government. It's true, isn't it?

Ute

I think you are right. But it is different in different countries. For example, German academia is quite conservative.

Edison

And that is why I chose Jackson Labs. The scientific reason was that I wanted to advance systems biology and for this, I knew that we could no longer rely on simple experiments in human cells in cell culture. We needed to reconstruct them in whole

organisms and so when Jackson Labs asked me to look at the job on a scientific level, I was actually intrigued because JAX—The Jackson Labs—is the premier place for mouse genetics in the world. I can do the genomics, and the translation, but I wanted to better master biology at the organismal level.

Ute

So, it was this experimental aspect that …

Edison

It was really this experimental aspect. However, they were stuck in this academic bubble where they were content with playing around with mice and not worrying about what it means to the human. What was needed was to make the bridge to human biology, and I thought that’s what would make JAX’s approach so much more powerful.

Ute

One reason for me to learn more about business success is Daniel Kahneman's book "Thinking, fast and slow," where he claims that luck, and he especially wrote about Google, played a very large role in the success of that company and others and that personalities or special abilities can be downplayed. This made me angry.

Edison

I totally agree.

Ute

You agree? I don't agree. I mean what you said is just the opposite.

Edison

No, here's the thing, to be honest with you, I didn't interpret him as saying that expertise and personality don't make a difference. It has to. In fact, I would argue that is necessary but not sufficient. To have quality people is necessary but not sufficient for success.

Ute

I agree. Of course, luck and opportunities et cetera are playing a role, but the same luck applies to many; there are many shop owners, but only few succeed to build giant companies.

Edison

That's totally true. I think that luck plays a big role but luck as an independent stochastic event will never produce fame or glory. It is actually the unusual individual, who had one lucky break and then capitalized on that lucky break. Perhaps a second lucky break and then a third, but it's an issue how you capitalize on those opportunities. That is the function of the individual or the team.

Ute

Yes, luck will also not explain why you have been successful for so many years.

Edison

But let me just say that I've seen a lot of people who were given the opportunity for something decide not to take it. So, when I say “luck” I believe that everybody is given a lucky chance at some point. But do you take it? Do you not? That's number one. The second is when you take it and it turns out that it was good, do you then exploit that to your next, because there are people who after the first lucky thing, either jump to something else or say, “I'm retiring.” Right? Now the third aspect of it, which I kind of agree with Kahneman, is that sheer intelligence doesn't do it.

Ute

I agree.

Edison

There is a unique quality about people who are successful in anything.

Ute

Einstein would not have been a good businessman.

Edison

He would not have been a good businessman. Zero. But then, science, especially physics, is one of the few places where being a pure intellect might allow you to be famous. But I think that in most cases, in business in particular, let's say in administration, like what I do, that pure intellect doesn't make it. It's necessary but it's clearly not sufficient. There's something else, such as your ability to communicate, your ability to lead your community, your ability to think of systems as a whole and how these parts can integrate.

I love reading biographies because I see more and more that these great people that you read about, are not so great per se, I mean they are not Einsteins but there's something about them - sometimes it is ruthlessness, but almost always it's this combination of taking the chances and then capitalizing on them. A classic example, Stalin, was in Siberia for five or seven years. He could have languished there but somehow, he got back in. He's not my hero, but how is it that a Georgia communist rises to the head of the USSR? It isn't simply by ruthlessness. It's by capitalizing on luck and then superimposing on that with hard work and cunning.

Ute

I agree. Do you have a few minutes more?

Edison

I have all morning.

III Science and society

Ute

I don’t want to impose myself on you. We already talked about science and society at the beginning, but we didn't record anything about that here. I remember that at the conference in Tel Aviv you stated in response to my lecture that eugenics on the one hand, and Lysenkoism on the other, were examples where science impacted very, very strongly and very, very badly on society. And, you also said that in your opinion, both tendencies still exist in society. What exactly were you thinking about? Are you more thinking about right-wing activists who try to use the existence of genetic inequality to make value judgements, or left-wing activists who downplay the relevance of genes and genetics, recently in the name of epigenetics? What is your major concern?

Edison

It is both, you know, it's the same argument; who do you like better, Hitler or Stalin?

I just hate both of them. Their genetic principles were really false, and these were the biological basis of their political beliefs: in one corner, the sanctity of racial purity, in the other, the complete malleability of the human cog in society. Now here is the very interesting thing that just emerged. When it comes to genetic modification, I see is that the right-wing people are progressively for germline genetic modification.

Ute

Modification of crops or of humans?

Edison

Of humans.

Ute

Really?

Edison

Oh yes. I mean, look, it's back to eugenics again, that you can actually craft the superhuman by genetic modification. It's a little bit with tangential discussions, this fascination with the science fiction lore of the super soldier.

OK, let me just say that my left-wing friends don't like those movies. My right-wing - I wouldn't call them friends but some people I know that are in the right, actually love those movies. These seem to be the cultural proclivities that they have.

Now at the same token, it is a fascinating thing on the left, that there is an attempt to erode the importance of genetics. Very recently, in the Atlantic magazine, Karen Wu wrote a big article about one piece of evidence that the genetics of dogs don't predict behavior of dogs. She was trying to debunk the determinism of genes. By the way, that also goes hand-in-hand with the anti-GMO framework – the fear of genetics - which is prevalent in the left. Both sides, the left and the right, are irrational.

Ute

Irrational because if the genes have no impact, why be afraid of the genome?

Edison

That's exactly right. In terms of the biases, where one side believes in genetic determinism, the other side is vociferous against any kind of genetic determinism believing the primacy of environmental influences.

Ute

The interesting thing about the Nazis is that, on the one hand, ideologues cited human geneticists in their political pamphlets. On the other, the even stronger ideological element of the Nazis was anti-reductionist, holistic.

Edison

I think they're basically saying, I can identify genetic perfection, but some people are just sullied or “dirtied” by bad environmental influences.

Ute

There were not many geneticists who did animal or plant genetics in Germany at the time. Of course, there were anthropologists, and medical scientists who conducted what was later called human genetics. Interestingly, the (non-human) geneticists joined the Nazi party at lower percentages than the rest of the biologists. They were less politically committed except for occasional statements in favour of eugenics.

Edison

I think that's also true in the US. I personally don't know of any current geneticist who is a right-wing ideologue. What I mean by the importance of genetics in politics is not what the geneticists do but how the politicians interpret genetics. As we have stated, some of the most egregious crimes against humanity have been perpetrated because of misinterpretation of genetic principles. In truth, geneticists have been involved in propagating race-based policies in the US such as forced sterilization and anti-miscegenation laws. But scientists were “expert witnesses” in the court of public opinion where the “jury” who would be the populace were already biased.

Ute

That is true. And many human geneticists supported Nazi race policy. On the other hand, some Nazis ideologues said, we don't need science in order to know that certain races are inferior. They knew it long before the Nazis came to power. I mean, racism existed long before there was the science of race.

Edison

Jonathan Haidt is a well-known experimental psychologist who studies how people formulate their moral positions. He's quite evenly balanced, but his general premise is that as human beings, we basically function on biases. And if we're lucky, our minds allow us to be more precise and modify our biases. But on the whole, you have a set of biases and then you use your intellect to justify those biases. Racism

was prevalent, and the public sought scientific justifications for their deeply held biases. If you get a chance, I'd suggest that you might want to just glance at his work. I think Daniel Kahneman and Amos Tversky fundamentally have said the same things.

Ute

Yes, I certainly will.

Edison

His point is that we come with biases, and we then justify them with our intellect as human beings and in fact, it's my experience that the smarter the individual, the harder it is to change their minds simply because they are so good at justifying.

Ute

Let's look at the strong tradition of being anti-genetic of the left. One of the scientists was Richard Lewontin, according to whom the concept of race has no genetic basis because all human beings have nearly identical genomes. There is also Craig Venter - of course, he is not anti-genetic - who said something similar to Lewontin, namely that the only small differences in human genomes show that the concept of race has no genetic basis. What do you think of this view?

Edison

I think this is a bit of an exaggeration but there's a lot of truth to it, because on the statistical basis, in any population except in the artificially inbred populations, there's always diversity. Just by the nature of mutations there will be diversity if you give time. If you look at the human species and our evolution compared to our nearest neighbor, let's say the chimpanzee, there is a lot more variability, theoretically, in West African chimpanzees than there is in the entire human race. In that context, race is an artificial construct.

Ute

Yes, it is.

Edison

And so, it is akin to this dog analogy, you know, there are big dogs and small dogs, and how different are dogs from wolves? Dogs and wolves are immensely different. Even though the phenotypic variability in domesticated dogs is huge, dogs are much more different than wolves. I think the interpretation of diversity becomes challenging depending on what you compare.

Ute

I would like to talk about David Reich ...

Edison

I know David.

Ute

who said that geographical populations were separated long enough to develop significant genetic differences. This does, of course, not mean race as it was conceived 100 years ago, but differences in human populations. And he said that we should not deny this fact, but as you sure know, that we should never use these differences as a pretext for discrimination.

Edison

I completely agree with him. But what if there are differences? I mean, when populations are segregated, they will form, over time, genetically distinct groups. The bigger question is, does that segregation give one group a greater advantage over the other?

Ute

It depends on the context.

Edison

It depends, extremely, on the context.

Ute

But it is important to know it in order to take action, e.g. in the education system to counteract genetic (and of course also other) disadvantages in learning. In my opinion, it is dangerous to deny the existence of differences.

Edison

Well, I think so, but here's another thing. My view is that genetic diversity actually is the salvation of humanity of any population because that diversity, which is frequently a random event, basically reshuffles the cards so that in case the next disaster comes in, that the species will not die. This is because some individuals with reshuffled genetics will be more resilient to a particular challenge. So, the political statement that we are all alike is not helpful. Equally wrong is asserting that we can easily define genetic inferiority. The term inferior is a phenotype that is very context specific. For example, is a weed inferior to a colorful tulip? To humans that might be the case, but in terms of survival in the wild, weeds outperform tulips any day.

Ute

But this is the species level.

Edison

That's exactly right. Diversity is essential for the preservation of any species at the population level. This is a fact. Defining superiority or inferiority is an assignment of a value based on biases and is highly dependent on context. Unfortunately, the two are conflated in the minds of the lay public. There’s further confusion because of the

fact that genetics is statistical and probabilistic, whereas human decision making seeks absolutes. Human biases toggle between genetic determinism and environmental absolutism. These ambiguities in the popular mind may have been philosophical discussions early on, but in the twentieth century, they were the cause of immeasurable societal pain. In the twenty-first century, the power and speed of our genetic technologies are such that many major governmental and policy decisions will have to be made based on these genetic realities with all their uncertainties. GMOs to feed the growing population in the midst of climate change; and medical interventions that can change germline genetics both have profound effects on the sustainability of this earth and the future of our species. The limited knowledge of a public that still is uncomfortable with basic genetic principles is of great concern to me.

Ute

Thank you so much for sharing with me your deep thoughts about your biography, research, work as CEO of the Jackson laboratory, and on pertinent questions of today's genomic research, ethics, and the interaction of science and politics.