Episode 47—Xin Jin: Building a telescope for the brain

Lauren (00:08):

Welcome to Science Changing Life. I'm your host Lauren Fish. Back in the early 16 hundreds, Galileo built a telescope that transformed our modern understanding of the cosmos. But what if we could construct a tool today that enabled scientists to appear into something just as mysterious as the universe, the human brain? That's exactly what neuroscientist and Assistant Professor Shinji has been working on. In this episode, shin will explain how she's building a telescope for the brain to illuminate the main genetic and cellular drivers of neurological diseases. She starts off by sharing her first inspiration for her scientific research, her grandfather, I've

Xin (00:45):

Always been fascinated by molecules that started when I was an undergrad studying chemistry. But little by little, I was more intrigued by how these molecules, they interact with each other. They act in a coordinated fashion, and a lot of these more complex organisms at a level of cells or multicellular organism. And from there, I become interested in using molecules and this chemistry as an entry point to understand organ level actions such as the brain. But even before that, as you mentioned, my grandfather, I grew up in the Botanic Research Institute that he worked at, and he's a researcher and really interesting classifying plants. The so-called the name Taxonomy. And that is where I first found the process of research a fascinating job because it's really, as a child for me to imagine what does it really mean when you are a scientist or when you're in a lab, what you're doing day to day. And what I realized is that, oh, you can play with plants and you can actually join pictures about these beautiful plans and starting to sort them into bins and buckets and being, oh, this is the tree and how tall it is, and based on the morphology. And I just found that entire process extremely satisfying and also interesting. So I guess that's sort of how everything started.

Lauren (02:06):

And I remember in the past you've told me about some of his sketches that he's done. Do you still have any of this?

Xin (02:11):

I do. And it was really interesting because from a child just looking at these extremely sophisticated drawings, as well as all these labeling use a lot of Latin and non-Chinese characters. So for me, I was just like, wow, that is cool. But little by little, you start to really appreciate the morphology carry a lot of meanings. And that's how, again, a lot of times that we classify plants or even cells based on the shape. And to a certain degree, I think a lot of the forms do inform function in the biological system, but oftentimes it's also not. So I think this kind of, I guess ideological tension between how do we classify things, how do we classify cell types? And to the degree, how do we describe disease and disorder, how much of it can be just descriptive and how much of it is at a different latent space in the level that your bare eye or my bare eye or our micr microscopic views cannot reveal, but at a deeper level. So I think that's something that is still going on in my life, in my academic pursuit of how do we really

Lauren (03:24):

Classify, classify things. Yeah, that's so interesting. I think both at a scientific level as well as more of a philosophical level, how do we classify anything as a style description as a bi function? How do we make that distinction?

Xin (03:37):

And that is important when you start thinking about some of the questions that we're thinking about in the lab in terms of approaching complex disorders, right? Many sort of psychiatric disorders. And then I think one of the biggest challenges among many challenges we're facing is the heterogeneity. And we know that when we call out the disorder, no matter schizophrenia or aging or neuro degeneration, we start to appreciate that it's not just, yes, you have it, or no, you don't. The manifestation is different. The factors contributing to the manifestation is definitely different. Even let's just taking this isolating picture of the genetic contribution, which is a small picture amongst all the environmental and plasticity, but the genetics are also complex and not just one gene. Once the genetic variants occur, give rise the disease, there are many, many contributing factors and it is a confluence of many things. So that really is a way to help us to shape our thinking, to approach these questions.

Lauren (04:33):

So let's talk about that more kind of what your work at Scripps Research is doing, how you're uncovering these genetic variants, how you're determining all of these confounding factors that lead to these diseases.

Xin (04:47):

Yeah, yeah. We're really taking a genetic approach just because leveraging on the research and the progress the field has made in the past decade or two, now we know these devastating brain disease or disorder have strong genetic roots. And I think that itself is already a very conceptual differences than what we had 30 years ago. We really do not know these manifestation in the brain and also because this is the mind. So there's a lot

Lauren (05:12):

Of unique challenges associated with

Xin (05:14):

Study challenges and also just social norms that people impose and complications in certain degree biases and inclusivity. And now we know that there are, in the case of schizophrenia, bipolar and autism disorders, these are very heterogeneous disorders. They are strong genetic contributions, but we're not talking about one or two genes. We're talking about collectively these 5,200 genes are causally associated, that very, very strong genetic data suggested that there are long lists of genes, that they are loss of function or there are alteration of the functions associated with the manifestation. And the question is, okay, so it's not a one gene disorder, but how do we approach the disorder instead of studying one gene at a time? Because it would take a long time. And I will also argue that when you're looking only one piece of the big puzzle, when you're looking at only one gene, it's harder to appreciate what is the disease or disorder really is, rather than just the single gene.

(06:09):

So what we're really hoping to build is to take a holistic approach to take not just one or two, but the complete long list of the genes and start taking a functional approach. Also start going to the cells and in the brain and perturb these genes and ask purely observe well after perturbation what the cells react to it. And it's not surprising that we know that these gene function are very, very sensitive to the cell types that a mutation in your, let's say skin cell may not do anything but the mutation, same mutation in the brain cells might kill the neurons, for example, because the cellular context are very different. I think fundamentally that's a fascinating biological question,

and it's also important for us to think about how to interpret these disease risk regimes that they simply do different jobs in different cell type. They are simply interpreted differently in different cell type. So that's sort of the whole genetic screening platform that we're building called in vivo perturb that is really set out to

Lauren (07:06):

Understand. And I remember you used this metaphor where you kind of likened it to a fruit salad where beforehand we would just investigate one component of the said fruit salad, but now with your technologies, we're really able to view it in this holistic way. That's right. It's kind of all interacting together, all the different cell types, just all in one piece where beforehand we didn't really have the technologies to do something like that, and now we're really at this new frontier at neuroscience because of that.

Xin (07:36):

Yeah. No, no, no. I think that's a really big breakthrough for the field collectively in neuroscience, but also not all the other field that we started to appreciate individual pieces of the fruit cell, rather than taking a chunk of it blended into a smoothie, which is still very, very meaningful. Because if you have a very detectable, or very drastic, we call it large effect size changes in the fruit salad, even if you blend it into a smoothie, you can be like, Ooh, it tastes like this. Time has more pineapple. That's how it did it. But when you start appreciating at a single cell level, you will be able to say, Hey, this fruit salad has 25 grapes and 10 pineapple, whereas this one pineapple seems to be absent or a few pieces of oranges, or I added the apple that come from California instead of somewhere else in the country.

(08:25):

So all these kind of subtlety, which I think is really thanks to technology, we can do this experiment rapidly, accurately, robustly, but also reasonably cheaply compared to a decade ago that really the scalability kicked in, but also argue that this level of sophistication and resolution is probably required to interpret something like a brain disorder because it's not a lethal disorder. We're not expecting fruit salad suddenly become, I dunno, a Caesar salad. That kind of changes is something that you may be able to detect using very sort of blonde hammer. Whereas for disorder, we are kind of expecting more and more evidence suggesting a very rare cell type or a very specific brain regions engage, but the rest of the brain is okay, but then starting at a seed to propagate and therefore you do need to know on your plate, are the grapes, are the pineapples alright? Because those are likely the culprit

Lauren (09:20):

And you need that depth, not just that scalability, but also that ability to go really deep

Xin (09:27):

Specific. I agree. Yeah, so I think that's a very interesting concept. In the biology, there are two things. I feel like we are constantly making choices and one as you said is the depth and the other is the scale. You can study one or two genes really, really deeply. You can remove the gene and do everything you can with this, but then you probably can't afford to do this with hundreds of genes. Just so much effort and time consuming and also just complicated. But at the same time, you may be able to do these genome wide screen and for a genetic screen that people have been doing in the past, but you usually want to focus on one or two things that you put your money on. I bet the cell cycle has changed, or I bet this particular protein abundance changes. It's very hard to say I want to stay a thousands of genes with a scale, but also looking

at everything that I, without a priority assumption, just really to look for what has changed. But we are really hoping to combine the scale and the resolution. We call it high throughput, but also high content analysis.

Lauren (10:26):

That's amazing. And I feel like especially obviously there is so much still unknown about the brain, so to be able to, I don't know, combine both of those entities is just amazing. Yeah, no, we're very excited. Yeah, totally new forefront. So I was hoping we could also talk about, we touched a little bit on your background and experience and I was hoping you could tell me your career path schooling, what eventually led you to Scripps research?

Xin (10:55):

Yeah, that's a long conversation.

(10:59):

So I think I may have a very sort of relatively different career path starting as a chemist and then drift away, become a neuroscientist. And still when I was working with my PhD thesis is focused on the nervous system of a nematode species. But I still was very excited about bringing new tools or taking existing tools and tweak them a little bit to answer a question. It's like, how can you be Galileo without the telescope? So I think that kind of tool making, but not just make the tool but also use the tool to solve a question has always been early in my research ethos and genomics really is the last piece that came in into my training. As I moved to Harvard as a junior fellow, I really thought at that time the scalable version of the single cell NA sequencing, the technology of the fruit s sorting that we talked about would just become the paper is published.

(11:53):

And you knew this is a complicated experiment, not by all means, but you can start seeing other people using it and making progress and you're like, oh, this is a good time. Without that, that wouldn't have been possible. And CRISPR of course also happen the tool to really programmable quickly, quickly introduce genetic perturbation in a way that we want. So these two pieces of technology really helped me to build the platform throughout my time. So I become sort of still using brain as a system just because I'm very just interested and by the organ and how much we can do with this system, how much function it did really in Dallas, but at the same time going back to a little bit chemistry and technology building to integrate them together, which I think it really is something that scripts attracted me back in 2021 when I was on the job market and still making me feel that was one of the best choice I've made.

Lauren (12:51):

Yeah, amazing. I love that metaphor that you use Galileo without the telescope, right? It is specifically what you want to do, but you have to build the actual tools and technologies to get there. So what are some of the discoveries that you've been able to make since being at Scripps and really using these technologies and uncovering these parts of your brain?

Xin (13:13):

So the lab has two focus, and I would say it's not a division of the lab person. Now everyone touch upon the two parts. It's just like maybe 80%, one 20% of the other kind of stuff, which is really the ethos of improving, integrating, troubleshooting, and bringing new technology, but then use that to solve a very specific biological question we care about. And at a sort of technology front for perturb seeking, especially, we're doing these in the brain in vivo where the cell type diversity is just daunting. I think now we know this number about 200 to 300 different

cell types across the brain region. And we're talking about in the adult stuff like mature brain. And if you imagine during development in this dynamical process when things are coming in and now the picture, there's more diversity over there. So we are really trying to figure out, okay, we know it's a heart problem.

(14:09):

We have thousands of genes, we probably have hundreds of cell types and one step all a time using the traditional approaches to label these extremely fragile cell types in nivo was just too slow. So a graduate student, one of the first cohort, the student that joined my lab, then she really took a heroic approach to improve the viral vector engineering. Again, this is something that's driven by the need of like, oh, we do need to be able to harvest this many cells and the traditional labeling is too inefficient. And she performed really heroic amount of work to engineer both the vector engineering side as well as the booster of the amplification of the expression of the vector. But long story short, her net outcome is that she can achieve a labor efficiency that usually takes people weeks two to three weeks. That's accelerated to two days.

(15:02):

Wow. So that's efficient vector that now we're sharing, we had the preprint out right now and we're sharing this vector with many, many groups who are interested in doing the kind of research we do, but some are taking a completely different approach. They just want a good vector. So it's a very broadly impacting approach. And now we're finally ready taking this vector and to tackle the question that Shing and many other people in the lab are very excited about, which is what is the cell type specific effect across these different risk genes implicated in psychiatric disorders? And I'll share maybe a little bit biological discovery that we found. So we take some of these risking and perturb them and just observe across all these 15 different cell types that we harvested in the cortex at that time of the development, who has changed it's fruit salad with or without a perturbation?

(15:56):

What are the differences? And when we found out, I think we knew this sort of as a textbook notion, but when we first see the data, we were still just very shocked that these context specific action, for example, a particular risking important for the intellectual disability, we we're just very, very surprised that its impact is very restricted in this particular layer of neuron called cortical thalamic neuron that is sitting in the deep, deep layers of your cortex in the brain. And it basically shifted the fate of this particular cell type to acquire alternative cell fate. But if you look at another cell type in the same layer, basically it's the neighbor you imagine on a fruit salad, this is right next to this pile of oranges or whatnot. It does not change at all with the perturbation. So it's just telling us that our brain cells, just like all these different pieces of fruits in our food salad when mutation comes in or when even you can think about it, and when physiological change or environmental changes come in, they have completely different action and some don't really care. They're very resilient to some degree. And it's interesting to think about why you're so resilient, but some of them are extremely sensitive, and those may be the one that we can sort of really focus on and see what has changed and is that a cell type and a time window that the therapy should occur, whereas all these other cell types, they're not changing anyways and they shouldn't by this kind of logic, it may not be the primary sites of action for these diseases.

Lauren (17:29):

Yeah, that's so incredible. That's so fascinating. On one hand, one thing I did want to say is how is that scene, your technology that you use continue to evolve both within your own lab as well as with other people? What is that experience like?

Xin (17:43):

Yeah, no, we're really happy that as a tool builder, we build tools because we have a question and we really want to solve. So we build the tools and we publish it, but then we just take it and then to the next level and do our own experiments. But what I found really, really rewarding is that once the preprint is out and many people reach out and some of them want to do the similar experiments we're doing, so we're helping them. And that's very rewarding because it's always good that you build a telescope and other people can use it, look at different planets. Right, exactly. So it become a really community

Lauren (18:15):

That's form the whole environment too, as you're trying to build this better framework for looking at the brain and understanding it. So

Xin (18:21):

I've been in touch with, actually many investigator reached out to me and usually in their first email I'm like, why are you touching me? Because the size is very different and many of them are doing very different approaches. But on the one hand, it's just intellectually really satisfying to start making friends in from fields and from people that I just wouldn't usually even go to a same conference with. But then they explain their challenges and their question, I'll be like, oh, our vector can help and we can start doing that. And I think that really the powerful parts about molecular biology is that nowadays you can literally print out a sequence of the D-N-A-A-T-C-G-C-C, and you can send it out to companies, and next day you have this DNA sequences in a tube synthesized, send it to you with the exact molecular, it's a 3D printer, but printing life these other things that we just didn't have 20, 30 years ago. And I think this sort of very modular nature of molecular biology and also with a lot of the tools that we are building make it probably much easier for anyone in the field to quickly, reasonably relatively quickly adopt and taking the tools and make them useful in their own

Lauren (19:37):

Lab. Things are just possible that just weren't even imaginable come decades ago. So I do want to talk about this interdisciplinary nature of your work and some of the other scientists that you might work with that maybe traditionally in neuroscience you wouldn't work with or collaborate with or

Xin (19:57):

Yeah, yeah. No, we work very collaboratively across many disciplines and starting from the geneticists without talking to the geneticist and understand these genes that come from all human huge consortia efforts and research. And I think learning from them was obviously intellectually stimulating and super important to, without understanding which genes to pick from our experiment would not be meaningful. But at the same time, I think these huge consortia we're talking about in code and starting from human genome projects and these multi sites and international collaboration really gave us, at least for me as a junior investigative of like, whoa, science can be done like that. It is really a big effort and nobody should own, I don't know the entire Pacific Ocean to themselves, but you can contribute to it. So I think that the genome field has been just really fascinating also to observe how much progress being made by these extremely talented group of people working together.

(21:02):

And I would say the same with a lot of the genomic computational tools. Now we can generate these, so-called perturb seek data, but you look at it and be like, oh, half a million cells, you're facing this huge matrix of you can measure 20,000 genes and half a million cells. This is a matrix that I couldn't even open on my own computer. How do we make sense out of it? We can say, Hey, we can actually do this high content, high throughput experiment we talked about earlier, but then what do we do with the data? So I think that's also a huge challenge, and we work very closely with mathematicians and computer scientists, and it is important to understand the structure of the data, but also how to even just at a software engineering front to be able to efficiently not running analysis takes two years, right? So there are really strong collaboration across institutes and also the relationship we've been fostering for years. And it's really fun to talk to these people because it's kind of like we all come in and we sort of have our own takes of the data and what we think is exciting and interesting, but aligning each other's language and expertise. And it's really, really fun because we learn from each other constantly. Yeah,

Lauren (22:20):

Absolutely. I can imagine even your vocabulary for discussing certain things might be different and kind of speaking the same language and making sure you have the same objective with that.

Xin (22:30):

Yeah, right. So those are all very long-term collaborators. We are very fortunate to have, and we're continuing working together. Once you have that relationship, it just make the science better, more

Lauren (22:42):

Rigor and more fun. Well kind of seeing it at a different angle. So one might have a different perspective if they're viewing it from Absolutely. Yeah, slightly different outlook. One thing I also wanted to touch on was, so Scripts research is celebrating it centennial this year. So I was hoping from your standpoint, I could get what your favorite thing about Scripps is or what you enjoy most about working here. Yeah,

Xin (23:05):

I think it's the science and the collaboration. And from the science from Ray, it is crazy to think about how much biomedical advancements we have had collectively in the field, but also here at Scripps. How many Nobel rates do we have as a very simple way of calculating this. But what I can imagine is that in the next 100 years, we're almost certainly going to do more, not less than what we have already accomplished collectively in the last 100 years, which was absolutely fascinating. And in terms of the people and the collaboration, I think Scripps is also just so unique. We are small, we are lean and petite, and we move very fast and that kind of energy and very, very focused and this sort of clean vision of going for scientific excellence is very unique. And then I think the scale allow us to talk to each other and I can sit here, have a conversation relatively quickly. And I think the direct communication, collaboration, bringing people working on different fields from chemistry and neuroscience, immunology and structure and so on, is really the fundamental creativity juice. And I think that's going to continue to brew in then next

Lauren (24:18):

Hundred years, just exponential growth. Okay. One final roundup question. If you could give any piece of advice or wisdom to an up and coming scientist, what would it be and why? I

Xin (24:30):

Think we are very, at least I am very fortunate to be in this industry where we talked about when I was a child and watching what is it like being a scientist, being a biologist, what is the day-to-day like? And now looking back, I felt I was just very lucky. This is such a privileged job that we get to work on exciting questions almost up to your choosing, right? It's really just like the only limitations, your own creativity you can work on question you're excited about, and you can work with a group of people who are absolutely amazing. And I'm talking about both from collaborator, coming from computer science and mathematicians and thinking in ways that's like a hundred miles different from your ways and collaborate, but also working with the young generation and every day coming to my lab, I think the young trainees in my lab across different career stages and their passion is really that sort of drive me and inspire me.

(25:27):

And I think that's just such a privileged position to be that my lab, young people might come in and go, but I'll be here. I'm always welcoming the first year of graduate student. What kind of job allow you to do this? So for young, sorry, young trainees and I think just like me, maybe when I was young and just mildly curious about what this job really is. And I think the fun part about the science really is this is kind of an endless feast that you'll have endless questions to work on. You will have almost endless, not absolute terms, but almost endless flow of talents coming in out of the lab and these kind of scientific intellectual growth as well as these personal bonds that we've been able to make and to work with young people at their most exciting formative years. I really consider this a huge privilege and a really, really cool thing. And I really hope that more trainees will come and join us for this endless feast.

Lauren (26:30):

Well, that's amazing. I mean, you're even talking about your graduate student that was able to expedite the technology so much, and I mean that's just from her working with you and kind of seeing your process and really being able to understand it and make it even better. So yeah, what an inspiration.

Xin (26:50):

It is really, really fun and very, very unique position and industry that we're in.

Lauren (26:59):

And that's a wrap on this episode of Science Changing Life. Many thanks to Shin for joining today and sharing how our research is helping usher in a new era in neuroscience. Be sure to check out the show notes for more information on our work and other behind the scenes scripts research content. If you liked what you heard today, please subscribe, rate or leave us a comment. We always love to hear feedback. Stay curious out there and we'll see you next time on Science Changing Life.