Episode 46—Hugh Rosen: A physician-scientist's guide to developing medicines

Lauren (00:08):

This is science changing life, and I'm your host Lauren Fish. It's a known fact that most drugs fail somewhere along the way from the lab bench to approval. Only 10% of drugs make it once they reach phase one testing, and that doesn't even include the initial discovery component. Science is inherently risky and drug development is even riskier. But then you meet someone like Hugh Rosen, the physician scientist who co-invented the drug ozanimod, approved for both MS and ulcerative colitis, as well as navacaprant, a precision therapy in phase three trials for major depressive disorder. Listen in is Rosen, who's the chair of cellular and molecular biology at Scripps Research, shares how he found success and how these treatments came into being. We started where it all began.

Hugh (00:52):

I grew up in South Africa and we didn't have television. I mean, there was no television in the country until 1977. So I was forced to read and while I was in middle school and high school, I became interested in the evolution of medicine and particularly in the 19th century, great advances in medicine, particularly those of the German pathologists and in the search for bacteria, viruses and the pathogens, the understanding of which changed 19th century medicine in a fundamental way. And I became really interested in that. So it became logical based on those interests to train initially as a physician, while I was a pre-med student, I had a teacher of cell biology and medical biochemistry v givers who had trained with Hans Krebs in Oxford and then subsequently Fritz Lipman at Rockefeller and was a really talented Israeli talented scientist and a wonderful human being. And he opened up the world of molecular approaches to physiology and pathology in a way that's just inspired me then to spend every free moment as a medical student working in the lab and acquiring improved scientific skills.

Lauren (02:37):

Got it. Wow. Okay. So you were really interested in the 19th century era particularly because it was this kind of paradigm shifting time in science and medicine. How did you uncover that initially?

Hugh (02:52):

It's sort of the random inquiry of a curious mind. I had access to a public library and I needed to read three or four books a week just to keep myself sane. No TV in a culturally deprived environment that was not only culturally deprived, but human rights is deprived, so you find refuge where you can. And for me, it was in books and one book in particular, I remember catalyzing it, the Virus Hunters. And funnily enough, this was something that was shared between myself and the late Michael Oldstein, one of our

Lauren (03:35):

Familiar.

Hugh (03:36):

He also was inspired by the very same book in high school, and it was one of the things that drew us into a similar intellectual orbit and of course a wonderful collaboration over many years in 17 publications.

Lauren (03:55):

That's amazing. I actually think I have one of his books on my desk, Michael, old

Hugh (03:59):

Stones, A Viruses Plagues in History,

Lauren (04:01):

I think that is on my desk right now as we speak. What is the pathway from that time at Oxford and then eventually kind of making your way into Scripps Research?

Hugh (04:11):

So I completed my PhD in Oxford in about two and a half years, quite accelerated, and then had a research fellowship at one of the old Oxford Colleges. Jesus and I became interested in the application of science in therapeutics and really wanted to bring Merck Chemical tools to play in the way I thought about biological processes and their modulation. And so I sort of electively moved from the University of Oxford to Merck in Rollway in New Jersey where I spent 11 years learning my craft.

Lauren (04:56):

Got it. Okay. And then what eventually caused you to come from Merck back to more of the academic research setting?

Hugh (05:05):

So the interesting thing was that in those intervening years, people like Pete Schultz had changed the face of chemical biology. They had invented tools that allowed the possibility of unique chemical discovery to take place not only in the pharmaceutical and biotech sector, but also on a very focused scale in the academic setting. And so this was actually fundamental in scripts. Not only that, but there is the opportunity in academia to persevere with deep and big problems for as long as it may take to solve them. You're not held hostage to quarterly sales or to short term financial maneuverings that are the currency of large and small corporations. And so it's that buffer. So the attractiveness to me was the change in chemical infrastructure that had become apparent in a very small number of institutions like Scripps. And that was the attraction. A colleague of mine was living in San Diego and he'd heard that Richard Lerner was recruiting. And so he introduced me to Richard. I came to Scripps to give a talk, and after about 30 minutes with Richard, he said, you have to come to Scripps. And I thought about it and I said, absolutely

Lauren (07:00):

Easy decision.

Hugh (07:02):

And it turned out that really for me, Scripps has been the ideal environment. Why? It's a combination of things. It's a combination of infrastructure, great minds and the colleagues and collaborations that allow us to do really big things in science and therapeutics.

Lauren (07:29):

And I'm even thinking about Pete's front row talk where we're really trying to bridge this huge divide that's perpetuated the industry and academia for so long. And Scripps really does seem to have all of those core components and that secret sauce, and one of which you touch on collaboration where so many entities will say that they are inherently collaborative, but Scripps seems to actually embody that among its faculty, which I do feel like is particularly unique.

Hugh (07:57):

There's no question that the interactions between colleagues at Scripps is remarkable and it's close. And one of the wonderful things about Scripps is that we have a set of tremendously accomplished colleagues. We have sort of three current Nobel Prize winners on the faculty. We have almost 30 members of the national academies on the faculty. People, however, seem to be happy to celebrate the wonderful accomplishments of their colleagues. And that's what makes Scripps really a very different scientific and collegial environment. And I really give a lot of credit to our leadership, especially Pete, for really doing this by example and by doing it by example. It creates an environment where this becomes the norm. And I think that's been one of the wonderful things to participate in.

Lauren (09:10):

Right, absolutely. So let's talk about some of those collaborations specifically. I'd love to learn more about how you've worked with Edward Roberts. Edward Roberts is a professor of chemistry here at Scripps Research. Beforehand, he'd had a distinguished career as a medicinal chemist and was the head of chemical discovery at Roche. Ed is the co-inventor of the drug ozanimod in Navi Print, one of which as he will shortly describe. First began as a drawing on a napkin

Hugh (09:36):

Ed and I first met at the Scripps Desert meeting, and we had a chat and got to know each other a little bit. But in 2006, after I'd got the Scripps Molecular Screening Center funded as one of the large national centers at the time by the NIHI really wanted to engage with Ed in bringing his wonderful expertise at medicinal chemistry into collaboration in an area of joint interest. By chance. We were both in Tel-Aviv at different meetings. And on the same day we met by complete random chance in the lobby of the David Intercontinental in Tel Aviv. And we sat down and it was literally one of these amazing moments. We sat down and we sketched out the program that became ozanimod. Wow. And we sort of laid it out essentially. It's literally one of those sort of coffee shop napkin conversations. And we've been the closest and best of colleagues and friends ever since. It's now at least 17 years that we've been working together. We've put three compounds into man, one of which Ozanimod is approved for the treatment of patients with multiple sclerosis and ulcerative colitis, one of which Nvac caprin is in phase three for major depressive disease. And then we have NMRA five 11, which is entering phase two for agitation in dementia. And this has been an incredible journey and odyssey, and from my perspective, at least the most wonderful fun. I

Lauren (11:40):

Was going to say, how do you even sketch that concept on a napkin? How can you even transfer that?

Hugh (11:48):

It evolves, and the wonderful thing about ED is that he is a very intuitive person. Ed really is a chemical savant. He's someone who can look at molecules and he can actually rotate them in his head. I mean, he really is the most remarkable medicinal chemist that I've ever had the joy of knowing. He understands in the most intuitive and brilliant way, the trade-offs that you need to make in a molecule between the random properties that you need to deal with, the rational properties that you choose to deal with, and the physical chemical properties that turns something into a drug that reaches the right compartments and does exactly what you need to do without excessive adverse effects. Wow. It is an absolute gift, and we are incredibly lucky as an institution to have faculty like this.

Lauren (13:04):

That is absolutely amazing. I'm thinking back to my organic chemistry courses with my molecular building kit and trying to piece everything together. So the fact that he's able to really envision this mentally is just insane to think about.

Hugh (13:19):

He has a tremendous gift. And the other thing that I will say, just to exemplify what this means to me is that when we first began collaborating, we had that discussion in Tel Aviv, and we said at the time that if anything useful and productive emerges from it, this was the way we were going to deal with the patents and any royalties and so on that would flow from that. And we shook hands and our entire collaboration, whether there was something coming out of it or not, turned on that handshake. And we have been true to our word these past 17 years. And that I think is a tribute to Ed, an attributes to scripts as well.

Lauren (14:23):

And your collaboration, I think your intent behind it, right? If you are developing these or thinking about these molecules and developing them, you ultimately want to get them into the hands of patients. That's what ultimately matters. At the end of the day,

Hugh (14:36):

As a physician scientist, there's no question that to me, impacting on the human element of disease is really what has driven my entire adult life. Disease is personal, and I always look on it as personal as a teenager, one of our family friends was diagnosed with rapidly progressive multiple sclerosis, and I saw firsthand in that respect at a very young age, the depredations that these debilitating diseases have are not only the patient themselves, but on the families that surrounds them. And the cost is awful.

(15:25):

And so it sort of has always reminded me that what we try to do at Scripps is define mechanisms of disease that are tractable, that we can usefully intervene with in an intelligent way to provide benefit to the patient and to those that care for them, whether it's the immediate family or in fact, it's also those that give care to the patient. Because in so doing by defining mechanisms of disease modification, we improve the lives and dignity of the patient themselves and of their family and the people that give them care. We do all of those things.

Lauren (16:15):

Yeah. So have you, since Ozanimod approval specifically, have you gotten to hear any specific patient stories in the MS community? I know that there was just some of the later data that resulted from the longer term phase three trial.

Hugh (16:30):

I do hear things anecdotally, and it obviously gladdens my heart, but when I see something like the recent release from Bristol Myers who now have the right to sell Ozanimod, where the trial data that they're collecting shows that there is a long-term improvement in the cognitive functioning. In other words, there's enhanced retention of cognitive function in patients with multiple sclerosis that we're actually bending the curve. We're saving patients from the depredations of the disease on their cognitive functioning in the long term. It just brings the lump to my throat.

Lauren (17:20):

That's absolutely

Hugh (17:21):

Insane because it's just a wonderful, wonderful outcome. These molecules teach us about mechanism. They teach us about the way the body is wired. They teach us about the way the immune system is regulated and dysregulated under conditions of disease. And it teaches us, again, in the words of Louis Thomas in his wonderful essay, the Medusa and the snail, that the more we learn about these things, the more they become open to intelligent intervention. And intelligent intervention is what Scripps is all about.

Lauren (18:00):

Right? Well, and especially because ozanimod, given its immune modulating properties, is also able to be applied to ulcerative colitis too. So being able to extrapolate, you know how its affects, be like, oh, I might also be able to work in these other indications because of the mechanism underlying it.

Hugh (18:18):

Absolutely. And this is it. Our mantra of science changing life is exactly that intelligent inquiry, delineation of mechanism if relevant, the application of those mechanisms to therapeutics. And then changing life. We change life by building this process of scientific understanding where it's like the construction of the gothic cathedral, brick by brick, the stone masons put in the structure over hundreds of years, some of them building walls, some of them building flying buttresses, some of them putting in the keystone to those remarkable arches. We don't know necessarily where our data fits in, but it fits into that overall structure. And as the structure builds, the applications to the world become more clear. Absolutely. And science changes life,

Lauren (19:21):

Right? In terms of scientific progress, where would you say that cathedral stands now? How clear of a picture, I guess, should we have of what that looks like in your opinion? Or is that impossible to answer?

Hugh (19:36):

Structures always evolve, and the way I try to think about it is in a way where we think about resolution of structure. The key advantage that we have in modern chemistry and biology is that

of higher resolution. And we hope that with succeeding generations of scientists, that resolution continues to get finer and finer. So

Lauren (20:03):

As Scripp's Research is celebrating, its a hundred years, and as it looks forward to the next a hundred years and the new department that you're chair of Molecular and cellular biology, what excites you the most about all of these changes to come?

Hugh (20:17):

What excites me the most is that day in, day out, we have new groups of young scientists coming into the Scripps ecosystem, whether it's our graduate students and I, right now I'm participating in the cell biology teaching for our graduate students. And it's a joy because these are bright, highly intelligent, questioning people who are going to make their mark on the world. They come into our ecosystem. We're recruiting new young faculty to the institution. And the institution is what I call sort of in the German sense tno. It's old and new. It's old in the sense that we have a hundred year tradition. We've got a tradition of tremendous accomplishment. We've got faculty who through their accomplishments and their recognition, give the institute institution a stature and a visibility and a notion of really impacting in science in a substantial way. And I think of our colleague Pu as just a wonderful exemplar of really the best of who we can be. So we've got all of those, and then we are recruiting young scientists into our ecosystem to make their own mark on these next inflection points. And I think creating an environment for the training and the growth of the next generation of scientists is such an important thing. And there's nothing more rejuvenating for, how shall I put it, the grizzled veterans of decades in discovery science than to be rejuvenated by the enthusiasm, the ideas, and the insights of our colleagues.

Lauren (22:47):

What is some of the advice that you give to up and coming scientists who are just entering this world and have all of these new ideas?

Hugh (22:57):

One of the things to me that exemplifies scripts is that element of risk taking that is so essential. You need a basis of rigor and then the ability to take a risk. And that's the essence, really of a soft money institution. People are self-sustaining, and they need to take a level of risk in order to sustain themselves and sustain our institution. And so what I tell them is there are a mixture of activities and choices that you will face. There are the things that are predictable, and that might be sort of bread and butter that sustain you, but never lose sight of the riskier big idea that is going to make the transforming difference. And so what we, I think love at Scripps are people who know how to balance and manage that risk. We look for people who have that sort of fearless nature, that self-confidence, that vision in their science that allows them to manage the basics and manage risk at the same time, and therefore do something that is big and unexpected. So what do I tell them? Never be afraid.

Lauren (24:41):

Well, I love that you balance that too with kind of having the basics as well, right? It's not just risk without calculation. It is calculated and it's able to sit on that foundation of rigor as you put it.

Hugh (24:55):

That's exactly right.

Lauren (24:55):

Right. Yeah. It's the balance of both things.

Hugh (24:58):

I learned while training in medicine that the ability to do something to a patient, for instance, isn't an indication to do it. You have to understand outcomes. I also did some rock climbing as a student, and you have to understand something about risk in order to survive.

Lauren (25:16):

Absolutely. Yeah. Especially with rock climbing where it is so methodical and yeah, you want to make sure your hands and feet are all in the proper places and let you have a path, a path below

Hugh (25:26):

You, and protection, right?

Lauren (25:28):

Oh, yeah, absolutely.

Hugh (25:29):

Absolutely. The importance of the belay. So that applies in science too. You need the protection, which is the basics, but you also need to know when to make the move to the crux. And the skillful scientists who expand our horizons will know when to make the move on the crux when they've got things in place to make

Lauren (25:57):

That move. Yeah, it's a clear path where that is the way to go.

Hugh (26:00):

Exactly. So it does, it requires vision. It requires risk-taking, it requires self-belief and requires multiple orthogonal experiments to validate what is true.

Lauren (26:16):

So you mentioned rock climbing. What are some things in reading, I know you're a voracious reader. What are some other hobbies that you are up to when you're not thinking about science?

Hugh (26:27):

I like to have something to switch off in the evenings, certainly. So I used to play classical guitar, and then I had a long multi-decade hiatus, but I've gone back to it. That's amazing. And taking lessons once a week to I it. But it gives me a lot of joy.

Lauren (26:45):

And as you said, don't be afraid. Right.

Hugh (26:47):

That's exactly right. I also love outdoor sports, and particularly fly fishing. I tie all my own flies, and so when I get the chance to do that, I get very excited.

Lauren (27:03):

Where's the best place to do that around here?

Hugh (27:08):

I usually like to go to the mountains because I really like trout. And I've been very lucky over the years in having a number of colleagues at Scripps who've taken me fishing.

Lauren (27:20):

Okay, very cool.

Hugh (27:21):

So the lake professor, old Stone, would love to arrange talks for us to give at the Rocky Mountain National Labs in Hamilton.

Lauren (27:31):

Oh,

Hugh (27:31):

Convenient Location, Montana. And so he would say, yes, this is the time we're going. You're going to talk at the following times. I will talk in the following times. The rest of the time you can fish. I said, thank you, Michael.

Lauren (27:40):

Amazing. Thank you. This is exactly what I needed. That's wonderful. Okay, and as a personal question, I'd love to ask, what have been some of the most impactful books that you've read? I know that there's probably a huge long list that you have, but if you had to choose a couple titles,

Hugh (27:58):

If I had to choose a couple of titles, this is like Desert Island disc, right? I know there's

Lauren (28:04):

Probably so many categories. They're

Hugh (28:06):

Not even,

(28:06):

So let's take off the two items that you were given on your desert island, which is the Bible in Shakespeare. Okay. So there's no question that I would take my Hebrew Bible and my Shakespeare. There's just no question about that. I do have a voracious appetite for books. I share that with the members of my family. My wife has a background in history and particularly the Dead Sea Scrolls. And so it is very, very learned. She's currently writing something on the retail Holocaust that was perpetrated in the Ukraine by the Nazis after Operation Barbara. And I think it's just wonderful work. I'm very interested in military history. I like poetry. I have a first

edition of Robert Graves World War I memoir and goodbye to all that on my bookshelf. First edition of Siegfried Tao's, memoirs of an Infantry Officer. Okay, I got it. I'm looking for a first edition of Tennyson's Ulysses at the moment, so eclectic in my taste.

Lauren (29:27):

But I feel like if you have spent so much of your life reading, then of course it's going to be eclectic because you just have a passion for,

Hugh (29:34):

It's an intellectual journey, right? Over many, many years. And I've been lucky enough to be able to hang on to most of these books over the years. That's amazing. That's

Lauren (29:46):

Wonderful. I think we could all benefit from Hugh's advice, take more risks, and read more books. Many thanks to Hugh for joining us today in reiterating how scientific discovery can fundamentally transform a patient's life. Be sure to check out the show notes where we'll have more information on Hughes research and the other exciting work being done at the Institute. Thanks for tuning in with us today, and we'll catch you next time on Science Changing Life.