IbD_Ep2_Tim_Jenkins_Final.mp3

Transcript

Hashem

Welcome to Immunity by Design, where we bring together scientists, biotech innovators, and policymakers to explore how emerging technologies are shaping the way we understand immunology. My name is Hashem Koohy, and I am delighted to be hosting this sales. Today, I'm delighted to be joined by Dr. Timothy Jenkins, who is the head of Center for Translational Protein Design at the Technical University of Denmark. Tim leads a highly successful research group working at the interface of immunology and data science, and his work sits right at the heart of what this podcast is about. So in a very recent publication, Tim and his team present an integrated pipeline to discover nanobodies that combine multiple snake neurotoxins simultaneously. This matters enormously for snakebite antivenom, where single antibody needs to neutralize toxins across many snake species, a problem that has claimed around 100,000 lives every year and remain unresolved for more than a century. So welcome on board, Tim.

Tim

Thank you very much. Glad to be here.

Hashem

Yeah, to get started, could you please tell us a little bit about who you are, the group you lead, and the mission you are on?

Tim

Of course. So yeah, thanks. You already introduced me really well. I run a group called the Digital Biotechnology Lab. It's a group of 20 or so scientists right now striving to innovate the field of protein design. That means both developing machine models that can help us create proteins with desired functions, but also scientists who are able to translate these AI tools into real-world molecules and go into the wet lab and make sure that across many different applications, they have the functions we desire. And that means we're covering primarily therapeutic applications such as snakebite, cancer immunotherapy, migraine treatments and others, but also non-therapeutic applications, for instance, bio-industrials. And as such, it's very much a technology-centric group and with a lot of biology to be explored.

Hashem

Fantastic, Tim. Now we want to actually put one step back and look into the knowledge in gap that led you to this study. So here, as we discussed, snake bite kills around 100,000 people a year, yet antivenom hasn't fundamentally changed for nearly a century. From your perspective, what has kept the field stuck and why is antibody-based antivenom so hard to crack compared to, say, conventional therapeutic antibody progress?

Tim

Yeah, great question, Hashem. But I think that there's a lot of nuances to the answer. I'll try and keep it simple. The reason why snakebite still is such an unresolved burden, very short, is that it's a disease of poverty. It's mostly impoverished regions across the globe that are affected, people living in tropical and subtropical areas where healthcare as such is not as well funded as in other areas across the globe. And therefore, there has not been a huge incentive, commercial incentive, to solve this problem. which is very sad since the humanitarian challenge is massive. I mean, we've got, yeah, roughly 100,000 people dying every year. But beyond that, we've got 300,000 people permanently disabled every year. And amongst them are many children, working men, which doesn't just have obviously social and humanitarian impact, but also further socioeconomic impact on the societies, meaning the working people can no longer provide for their families, driving this devastating circle of poverty even further. Now, the other question you mentioned was regarding the complexity of the problem from a more technological challenge. Why is it so hard to make antibodies or therapeutics for snake bite? Well, the answer lies within evolution. Snakes have evolved to subdue prey in many different ways. and also protect themselves from different predators in many different ways. And they've created this molecular arsenal of many, many hundreds of different toxins that serve different purposes. And in many cases, a single venom has 10s of different potentially lethal toxins that you need to neutralize. So unlike in cancer, where maybe one or two or three targets are sufficient to be targeted by a therapeutic, we have to target 10s of different targets for a single snake bite. And then again, you have many snakes in our region. And so in reality, we want to neutralize more than one single snake bite. And so this complexity in terms of the amount of different molecules, toxins, that we need to neutralize is very, very hard to overcome and very hard to engineer using traditional antibody technology solutions.

Hashem

Yeah, thank you so much, Tim, because you also answered my second question that I was going to ask about the importance of this so-called polyspecificity. Yeah, thank you for that. Then one of the technologies that you use is structured prediction tools. The question

I'm going to ask here is that structured prediction tools like AlphaFold have been around some form since 2020, And another technology that you use, Yeast Display, has been around for more than perhaps a decade. So the question is, what was missing that prevented someone from combining them the way you did and what made right now the right time to do this?

Tim

I mean, we're trying to tackle this problem from many different angles. We've had three different publications now in Snakebite over the last year or so, and we've tried different technological approaches. Actually, one of the recent ones that was also published in Nature, we used, I'd say, more traditional, still cutting edge, but more traditional antibody discovery technologies where we immunized alpacas because they generate really interesting types of antibodies called nanobodies with snake venoms. Don't worry, the alpacas are fine. They just got basically a vaccine shot. And then we took their antibody repertoire and used phage display to actually figure out which antibodies, or nanobodies in this case, could be used. And that worked really well. It's the furthest we've gotten in terms of making something that's close to product ready. We're able to demonstrate that we can neutralize most snake venoms from sub-Saharan Africa using a cocktail of these nanobodies. But it took us many, many years to do this. Another paper that we worked on together with David Baker that was published earlier last year was a complete AI-guided design of proteins. So instead of discovering from an immune repertoire, we wanted to craft a therapeutic solution. The main advantage here is that we can use computational power to do the work of the immune system. We're designing all of these molecules, and we were able to demonstrate for the first time ever that these AI-created molecules work as well in terms of protecting mice, in this case, from dying as traditional antibodies. Now, the last paper that you're also referring to, we try to kind of merge these two worlds a bit. There's a lot of advantages of using more natural antibodies. But you also want the power of machine learning to aid you in that discovery. And so what we try to do here is use the same antibodies or nanobodies that we got from the alpacas, but we wanted to be a bit smarter on how we select the right ones. And so here we could use tools such as AlphaFold to select ones that we would recognize as likely being more polyspecific, meaning they're able to neutralize more similar toxins. So instead of needing 10 nanobodies for one toxin group, we maybe only need one. So there we try to merge these two worlds.

Hashem

So before this work, how were researchers typically trying to identify broadly neutralizing antibodies against neurotoxins? And what were the practical bottlenecks? Was it, you know, for example, in time, cost, or scientific insights that those approaches hit?

Tim

So I mean, it depends on which field we're talking about. In snake bite, again, the lack of resources has meant that there has been a lack of technological innovation. There's been some very hardworking people who've done some important work in actually making antivenoms that are saving lives right now. But the way that this polyspecificity challenge was tackled was by relying on an animal immune system. In this case, they were injecting horses with snake venoms, hoping the horse venom would develop antibodies against every single toxin in that venom. They would then take blood from the horse, purify the plasma, and use this to be the final therapeutic compound to inject. The main difference is, you might have heard me mentioning, we were injecting some alpacas, like how's that different from horses? We only do this once, right? We only do this as a discovery part, but then we use bio-industrial production pipelines, the same day where we're making insulin nowadays, for instance. to grow the same type of antibody every single time. So we know exactly what the different antibodies are. We have quality control, product control, and every single antibody in our mix is defined and useful. When you're just relying on the host immune system and extracting the pool, you'll get antibodies against viruses, against parasites, against other things, and maybe also not all of the antibodies you need against all of the toxins. So that's how this technology was explored in snakebite traditionally. But the idea of using what are called monoclonal antibodies, these defined antibodies and discovering them, that has been already explored in the field of HIV, for instance, where you also have several targets that you want to have antibodies towards where you go and selectively search for these antibodies. The.

Hashem

Study is really an elegant study. And my understanding from the study is that you guys combine phage display, yeast display, deep sequencing, and AlphaFold all in one go. So the question I'm going to ask is that what was the key design decision that made these pieces to fit together rather than just being, four separate individual experiments?

Tim

Yeah, great question, Hashem. So, well, each of these technologies has their own advantage that is very synergistic with each other. Phage display has the power of being able to screen very large size libraries. way larger than yeast display, for instance. So if we want to take diversity of library, we want as big a pool as possible, and phage display can

theoretically go up to 10 over 10 or so. And so billions of variants, 10s of billions of variants. And with yeast display, we're more limited. We can only screen millions or so of different potential antibodies. And so what we did is we used this face display as a first filter, basically. Screen as many different options, shots on goal that we have as possible, and then take the best ones that we find most interesting into yeast display. Now why use yeast display if it's not as high throughput as face display? Well, yeast display has a, I'd say, the main advantage of having a functional readout directly related to this antibody. And what I mean by this, in phage display, you are selecting by 1 antibody being presented on the surface and you have one target that's interacting. Yeast display, you have millions of copies of that same antibody on the surface. And if you have something that is fluorescently tagged, you can detect it using a microscope. So you can actually visibly see what's happening with your nanobodies in this case. And so what we used yeast display for was not to select a given nanobody against a given toxin, but select for polyspecificity, because we could have different toxins with different color labels, lights, that we could then see in the microscope. And if we would see a green light, we know it bind toxin A. If we saw a red light, toxin B. If we saw red and green, we saw that they bound both. And so we could use this to already select antibodies or nanobodies in this case that are poly-specific. That was the main reason why we used yeast display. Now, why AlphaFold 3? Well, AlphaFold 3 has the power of giving us an understanding on where does this nanobody interact with the toxin? Where does it physically actually bind? And that's gives us the power to also come in with our brains and rationally think about, is it likely going to be blocking that toxin from targeting a receptor? So it gives us an idea on, is it just tagging along going for a joyride with the toxin, or is it functionally going to inhibit it from blocking the receptor that is then causing paralysis? And so that gave us this visual cue. And it also allowed us to use some of the more sophisticated machine learning tools out there that take the structure as an input to then generate improved variants of these original nanobodies. So we could combine it with a very, I'd say, state-of-the-art machine learning workflow to further improve our nanobodies to being better drugs, better therapeutics going forward.

Hashem

Yeah, that is really fascinating. What I liked about, use of AlphaFold that, led you guys to identify or, point you to receptor binding sites to minimize the, perhaps, the heart. I'll come back to this. But speaking of AlphaFold 3, again, my understanding from the study is that It performs impressively well for poly-specific binders. You guys report precision of about 94%, but rather struggle more with mono-specific ones. So if my understanding from this is correct, what do you think is actually happening there mechanistically? What does that

asymmetry Tell us about the central limits of a structure prediction for antibody-antigen complexes.

Tim

Yeah, great question. I wish I had an elegant answer for you. My honest answer is I'm not entirely sure why it's struggling more with these monospecific binders. We've got some hypothesis and that's kind of related to this consensus seeking approach. If you have a better idea, an overlap of predictions across multiple targets, you'll get a better consensus output of accuracy or how likely is it to interact. I think the more honest answer is that AlphaFold just isn't perfect. It isn't able to always give you an accurate prediction of two molecules interacting or not. And especially if we have flexible molecules like nanobodies that use this flexible loop to interact with our targets, the accuracy can drop. I mean, we were actually quite positively surprised as to how accurate it was in the polyspecific case. We expected it actually to perform more as we saw it performing for, let's say, this monospecific case. So long story short here, AlphaFold isn't perfect and you have to thoroughly test what you can use it for. And that's why we tried to be quite thorough in validating our AlphaFold 3 predictions. And then we were encouraged by the data that we're seeing, but also obviously some room for improvement for the Google DeepMind team to get it even better.

Hashem

Yeah, I agree. I think we also see similar situations when it comes to TCR peptide MHC complex predictions. And as you pointed, one of the most striking results in this study, again, from my point of view, is that AlphaFold3's high confidence predictions pointed directly at the receptor binding sites of the toxin that, in a sense, means these antibodies would likely block the toxin from doing HARK. So question here is that how much of that was by design and how much of that was, computational or modeling guided discovery?

Tim

So, I mean, we didn't design the nanobodies as such. We used it as a filtering tool. So we looked at which of the nanobodies that seem to be polyspecific are actually binding epitopes that are driving this polyspecificity, but are also located in a way where we know it will lead to blocking. We've luckily got some good mechanistic understanding of the interaction of these toxins and the nicotinic ascholine receptor that they block. And so we could use AlphaFold to really visually see. if that interaction would block or not. With obviously a certain level of uncertainty, but it allowed us to filter out things that we were pretty sure weren't going to block, but just hang on for a joyride.

Hashem

Sure. And another thing here is that you used two distinct optimization strategy in this study. One was a structured-informed language model for affinity. And the other one, something you mentioned, a council for solubility. So firstly, what is this council? And then this strategy basically yielded improved variance without disrupting fully specificity. So the question here is, how did you think about that constraints and what did it cost you in terms of how many candidates survived or a little bit more elaboration about on this?

Tim

Yeah, great question. So multi-objective optimization is obviously a big topic in the field of therapeutic design. You want to optimize as many parameters as you can in parallel. Here we tried with two that we thought were quite important. We have affinity that will dictate how strongly we bind and hopefully how well we neutralize our toxins. We've seen in previous study that affinity is a very good measure of functional efficacy. The higher your affinity, the better the outcomes we've seen in mice. Now, solubility is very important, more from a formulation perspective. When you are going to deliver a drug, it has to be in a very highly concentrated formulation. And if your protein isn't soluble, it will aggregate, it will clog up, which will be a big issue in terms of injectables and these types of things. Also on the manufacturing side, it will limit the protein. Your question was alluding to, are there any costs towards the protein's fitness in a way? Do we lose many candidates by trying to optimize both parameters? And quite interestingly, I mean, it's not completely unexpected, but they don't come at a cost of each other, really, from what we saw. But it also logically makes sense because affinity is very much driven by the epitope and paratope, the binding regions of your binder, your nanobody to the target. And so that has to be optimized primarily for the affinity gain. Solubility actually is more looking at the global properties of the proteins. So there's different biophysical and biochemical properties of proteins that make them more or less soluble. So things like hydrophobicity, having a lot of hydrophobic patches on your protein, meaning that it doesn't like water, it attracts water, usually leads to a higher chance of things aggregating. So you don't necessarily need to optimize your protein in two entirely different ways. Just focus the solubility of the protein on everything that isn't really related to the binding region. and vice versa. But affinity is primarily focused on that. Now, also, I should add, we use machine learning driven tools. So we didn't really put these rational decisions into this. We just prayed that the tools would do what they should do. And luckily enough, we came out on top because these tools have also learned using evolutionary data, how to make these molecules very soluble and how to drive towards increased affinity. And so long story short, it didn't come at a big fitness cost and we didn't lose many candidates in trying to do this multi-parameter optimization. But there

might be other parameters that you want to combine where you have to rank the priority and say, this is more important than this because they will come at a cost of each other.

Hashem

Thank you so much. Very clear. Perhaps my last question about the study is rather a bit technical and that is about the threshold score of note.8 IEPTM score that I believe is a confidence score. So the question is that why note.8 rather than something more permissive and also for some of our audience coming from other disciplines, would you be able to intuitively explain what is this IPTM scores are.

Tim

Sure, I'll do my best. So let's start with IPTM. So IPTM is in essence a confidence metrics, a metric that AlphaFold 3 spits out. It's one of the metrics that it tells you or uses to tell you how confident it is in its prediction of a certain setting. And the I stands for interaction. So it's the confidence in the interaction between these two molecules interacting, being your nanobody and your target. So that is the rough idea of IPTM. And it's been used and been demonstrated by us and many other groups that it is one of the more predictive scores for binding interaction. So it is something that doesn't give you an affinity or anything like that. It just gives you with a certain level of confidence a estimate on will your protein actually bind if you take it into the lab or not. And it is one of the more predictive scores. Now, why 0.8 is a good question. The whole idea on how you filter out computation using these AI models, what will work, what will not work in the wet lab is a bit of a, I'd say, esoteric art right now. Everybody's got their own set of filters, own way of doing things, own way of combining different metrics. 0.8 actually is, let's say, the... It's a factorial recommended cutoff. It is on the more stringent level because it will penalize flexibility. And as I mentioned earlier, there is quite a bit of flexibility in these nanobodies via the interaction of these loops. But we really want it to be stringent. I mentioned that we were screening a lot of different candidates in this paper, a lot of different nanobodies. We wanted to filter things out that we didn't have high confidence in. So We were happy to maybe get rid of things that were still good at the cost or with the benefit of then having to screen less in the wet lab and knowing that the things we're taking there, the chances of them being really good being higher. So we accepted some, I'd say, false negatives, but we really didn't want any false positives ideally.

Hashem

Yeah, thank you. And now I want to move towards, what this study mean in terms of future potential applications. So if this pipeline were adapted more broadly, where do you think

the biggest gain would be? Is it speed? Is it cost, the ability to tackle targeted spaces that were previously intractable or something else?

Tim

Yeah, great question. Hopefully a bit of all of them. It's hard to say where it will have the biggest impact. It depends a bit on who's using it. If we say in a pharma context, right, one of the bigger impacts is it's one of the first demonstrations on how you effectively use AlphaFold. in the context of, I'd say, existing discovery pipelines. So we didn't present new yeast display technology, new phage display technology. People are using this in industry to discover antibodies. And we wanted to present the value that AlphaFold or similar tools can bring in these existing pipelines without having to shift majorly technologies as we do in, for instance, de novo design, where we AI create these binders from scratch. So I think it should speed up the process a bit. But what I mean by speeding up the process is that this element of being able to understand how your antibody, how your nanobody in this case, interacts with the target will help you select things that are in the right place. So they are functionally doing what you want them to do. Normally, when people do antibody discovery, you have no idea where you bind your target. You have to do x-ray crystallography or cryon electron microscopy, which takes quite a lot of time. We're talking weeks, if not many months, to resolve a single structure of a complex of your antibody and your target. So here we can do this in the 10s of thousands, right? So you know what's going on. So you can go a lot more rationally about what you want to do. Now, the other thing that it allows us to do, as I mentioned, is use these structural complexes with machine learning tools. Many of these machine learning tools need an input structure to work. And again, you don't really want to take your best candidate to require an electron microscopy and then go into machine learning tools. You want to do it for as many as possible. So you have as many shots on goals, so you're hopefully going to score many goals and not just one that gets saved maybe. So that's the main idea that you can know what you're doing, you're not flying in the dark, and then you can use state-of-the-art machine learning tools to help optimize your antibody to not just be a good binder, but be a good therapeutic and optimize it across many different parameters.

Hashem

Thank you, Tim. You mentioned that AlphaFold 3 axis is still limited, but other similar open source alternatives like BOLS2 or CHI1 are closing the gap. So the question here is that how important is democratization of these tools for fields with limited resources such as rare diseases?

Tim

Critical, absolutely critical. I think democratization of these tools is really, really essential. And yes, we used AlphaFold 3 here. It is the most accurate tool right now. We've tested quite a lot of different tools. But Actually, what we've seen come closest to beating AlphaFold 3 is Rosetta Fold 3 out of David Baker's in Seattle. That's free to use, also commercially free to use. It's way faster, which means you have to spend less money on compute, which is very valuable and it also speeds up the process. So the study uses AlphaFold 3, but you can easily replace it with some other tools. And they're obviously very much evolving. It's a very hot community. There's a lot of activity. Some of the tools are not free, but most of the tools are actually being made available, which is a very nice drive within the community to drive innovation and particularly help tackle challenges that have been overlooked, such as rare diseases and neglected diseases out there.

Hashem

Sure, thank you. So although previously you basically mentioned some other diseases that, you know, the same strategy can be applied, but Now that our audience hopefully have a bigger picture of this study, I'm going to ask this question again. This paper is explicitly about a snake bite, but you know that the pipeline is antigen agnostic. So where else do you see polyspecificity being a therapeutic design goal? And are there immunological settings where targeting conserved epitopes across a family of antigens is similarly critical?

Tim

Yeah, great question again. Yes, I mean, we designed this pipeline to be target agnostic. It doesn't matter what your objective is within biology, you can use this pipeline. And a couple of examples to give you here are within the virus space, for instance, we sadly had to all live through the COVID pandemic. Initial diagnostics were good, initial therapeutics were good, and suddenly we had escape mutations. and our drugs and diagnostics weren't working anymore. And so in this case, we really want to have therapeutics that are poly-specific. They're able to find one version of the virus, but also the other versions of the virus. And we've got more and more machine learning tools out there that help us also predict before it has happened, where viruses might evolve. So you can even use prediction to try and preemptively design solutions. And it's one of the projects we've got running in the group. Another project, which is, I'd say, also not a happy thing to talk about, but sadly, we are in a state now where defense is becoming increasingly important also in Europe, the context of NATO. And we're looking at using these types of technologies also to protect from potential biothreats, where again, you want to design not just against one toxin, but also potential derivatives or whole clusters of potential toxins. But beyond that, there's many other applications, and you also don't have to use it for polyspecificity. You

can also use it for monospecificity, where you specifically select your binder to be ultra-specific to your target. And that's very important in the context of cancer or autoimmunity, where you might want to guide your immune system to kill a cancer cell, but not healthy cells. So it's hopefully a very easily applicable technology to many different disease settings and also non-disease settings.

Hashem

Amazing. And then the next question is about data. data set you generated here, positive binders, negative binders, mono-specific, poly-specific, is also described as a training data for future machine learning models. So very generally speaking, is there a vision here where the experimental and computational sides enter a self-improving loop and how far away is that in practice?

Tim

Yeah, definitely. I think we're not the first ones to want to build closed loop experiments. There's a lot of efforts across the globe trying to see how we can use data in an interactive way to learn or teach machine learning models to improve. We've got a big project together with a pharma company called Northern Nordisk where we're doing this on a large scale where we're building a closed loop platform. where the data that's being generated is feeding the models and helping us continuously improve across many different parameters. So yes, it's very much part of the strategy, part of the plan. How far are we? I mean, we've already started using data to improve things in the loop. It's a big part also of one of my startup companies. called Affinity AI, where that is a big, big thing that we're trying to do is use these data, upgrade the machine learning model, and we've demonstrated that it works and improves performance quite significantly. So it's already happening in the public space. It's also not very far away from happening. We're talking a year or two, and we'll see major improvements in this space.

Hashem

Thank you. That actually, you know, the way you answer set the scene for my next question, which is more general question, looking into a bigger picture, and that is, this paper is essentially an argument that antibody discovery can become more predictive and less empirical. So how far do you think that shift can go and what do you think will remain stubbornly in the hands of wet lab?

Tim

I think it's an important question to ask. So we will always need the wet lab, but I'm hoping we're going to see the same innovation that AlphaFold brought to protein structure

prediction, where initially we would use to do a lot of X-ray crystallography for exploration, for discovery. And then AlphaFold came out, and now we're just using it for validation. I'm hoping the same thing will happen across the board in antibody discovery, that we'll have these AI-first models. They'll spit out molecules that are already optimized across many different parameters, but we will always need the wet lab to prove that they are doing their job. And the accuracy will improve and improve, but that they'll be always perfect, I think, is very far away. That we'll have big utility from it is not far away at all. We're already seeing that now. So that's how I see the future. And I think it's quite exciting because we should be able to solve many diseases a lot faster than we have in the past decades.

Hashem

Yeah, thank you so much for your very insightful and clear, responses and discussion. So, for the last few minutes of this podcast, I would like to basically talk a little bit about positive research culture and also multidisciplinary. A reason why is that, from the outcome of your research group, I can see that all the research is very multidisciplinary. And also you are a champion of multidisciplinary research in Denmark and in Europe. So for that reason, I want to basically, you know, discuss a little bit difficulties and potentials of disciplinary, multidisciplinary research. So to start with, building a multidisciplinary team, what actually makes it work, what values and what difficulties you see in that?

Tim

Yeah, first I want to say I love that you make this a focus also in this podcast. I think it's often overlooked. It's always about science and I'm excited about science, but the science only can happen if you have a positive research culture. I mean, good science can also come out of negative research culture, sadly, but it's not sustainable. So Let me answer your question. How do you build a multidisciplinary team? I think, well, first off, you need to be a good communicator. And you need to teach the people in your team to be good communicators. You need to be able to elevate the way that you talk about your science. from super technical to super basic and start building these bridges early on. And you need to be patient with each other, right? So if people have all of these different expertise and they're in the same space, that brings a ton of value. That drives innovation in my opinion. And that's why I've built my career around interdisciplinary science. But you have to have the patience of people to come to this common knowledge, common understanding, common language. And that takes some time and goodwill. But again, this positivity around it and the excitement about the potential of what you can do by levering each other's skills, that buys you that patience because you really get a vision and you can share that vision with your team and that team can be excited about it and be driven by that.

Hashem

I completely agree. Really, that is the key for multidiscipline research. And actually, you answered my second question, because as you see, second question in that part was that how to speak each other language, but you very nicely basically spoke about that. So therefore, the next question, what do you wish someone had told you at the start of this multidisciplinary journey?

Tim

Great question. Maybe I can quote a very nice movie called Galaxy Quest, which is never give up, never surrender. It's a tough journey. I did my PhD in Cambridge, you know, your arch rival here at Oxford. But when I was there, I was quite happy with my research output, my outcomes. But I wanted to switch scientific domains a bit. I was working on microbiome work, next generation sequencing, a lot of computational work as well. But I wanted to go more translational. I wanted to go more in a therapeutic in an applied space. And so I had job offers to stay in Cambridge as a postdoc. But when I proposed a change of research career, I got a lot of no's. I had many, many rejections from positions I thought I should have a pretty good shot at. I wasn't even invited for interview for many of them because I was put into this pile of people who are doing some microbiome work and not antibody work. And so I think the message I also have for people out there who are interested in shifting careers a bit is just never give up, never surrender. I kept applying and I finally got a fellowship funded by Marie Curie to come to Denmark to do what I really was passionate about doing. And it was tough. When I started my postdoctoral journey here, some of the master's students knew more about antibody discovery, and I did because I came from a different space. Very quickly, I caught up, I spent the time, I learned, and then I could add the research knowledge that I had, my background, into a new ecosystem and inject that and really drive innovation through it. So I think it's a long-winded answer, but it's also a very important question.

Hashem

Yeah, thank you. know, as a person who at least I like to think that I actually lead a multidisciplinary team, I need to make sure that the multidisciplinary culture is placed. And for that, sometimes I think about some metrics. What does a good multidisciplinary culture look like? What kills it?

Tim

so I think the first answer to this is collaboration. What I love to see, and one of the things that I'm most happy about seeing when I walk past my offices, when I see my PhD

students, my postdocs, my students talking to each other, explaining each other things, and coming up with new creative ideas where they utilize each other's skill set. And that happens quite frequently. And then they come into my office, pitch me ideas, and many times they have pretty brilliant ideas. And that for me is a very good sign of having a multidisciplinary culture where you have this shared language and people are using it to drive innovation. Now, a very measurable output of it is how many authors do you have on papers, right? Like if you have a lot of people involved in these projects, then you're going to have a lot of authors on papers. And a lot of our articles have a lot of names on them because they are so multidisciplinary. You need all of these different people to contribute. And so that is a good way to keep track on if you're actually achieving your goals. But the more important one actually is the soft metric here for me is seeing, visibly seeing the team work well with each other. You also had the point of kind of what kills that culture. And that is, I think, internal competition. I always preach to my team that I am very happy to be competitive. I want to be competitive. I want our science to be amongst the best on this planet. And for that, you need to but never with each other and never in a negative way and you never treat people poorly, you never put other people down, you treat collaborators well, you treat competitors well. You need to be a nice person while being competitive. And if you're not, that starts killing it. And that's probably the only time people will see me angry in my group is if I ever see it. Luckily, I haven't had to. My message has been clear so far, I guess. But that is, I think, the biggest threat to a research group is when you have competition in a very negative fashion.

Hashem

I love it, Tim. I love it, really. If you happen to give some seminars about positive research culture, please let me know. I'll bring all my group members and, yeah, happily listen to your advice. So I'll tell you again, you had a very nice advice that never give up. But I've written here as my next question specifically for PhD students, that what advice you have for PhD students sitting at the interface today? And perhaps, you know, to make it a little bit different from what you advised already. One key issue that we see with PhD students is that we know that PhD program is not a linear A to B path. There is quite a lot of ups and downs and in fact quite a lot of failure and just sometimes success comes along. This is what we used to, but PhD students not. So what's your advice would be for PhD students from that perspective?

Tim

I have a lot of advice if it's useful or not. Let's see. But I mean, one is, again, talk to each other. If you've got a good team around you, if you've got nice peers, it could be, I mean, we have a luxury in the Oxbridge collegiate system that you have colleges, you have people

around you who are not directly working with you, but they're probably sharing some of the same experiences as you. And you'll quickly find out that you're not alone. I also always tell my students, The lows are low in science and the highs are high. You have to just accept that both are part of your life. And the best way to overcome them is friendship, community, family, also taking a break sometimes. I think it's very much undervalued. We are in competitive research cultures. Luckily, I'm in Scandinavia where there's a bit more of a focus on it, but take care of yourself. It's okay to take a break. It's okay to say, I'm going to take a holiday. I just need to refocus and refind my joy. But that's, I think, the most important way to overcome hardship in a PhD. Another piece of advice I would like to add, which is more focused on this whole interdisciplinary approach towards science, and I mentioned communication is key. And at least personally, the way I've trained my communication was, and it's a very, non-linear ways. It was not very typical for my career. I was actually a tour guide in Cambridge. I was doing walking tours where I had to explain all kinds of concepts to kids on the tour, to historians who were on the tour. It was a big range of people, but it really taught me how to communicate at very different levels very quickly. And I did the same when I was in Australia. I did crocodile shows at a zoo in Australia where you had to talk about ecology, sustainability, wildlife, again, to a very broad audience. So whatever you can do, I'm not saying go and run croc shows, but whatever you can do to train yourself to talk in different audiences. And it can be also popular science writing. It can be running podcasts or participating in podcasts. A pint of science was a really cool thing that I attended a lot in the UK. There's a lot of other opportunities to really train that. And even if you don't want to do it in such a public space to begin with, do it with your family. I mean, I know that I still struggle the most explaining what I'm doing to my own family sometimes. Use them as a good practice ground because that skill is critical to talking to each other and very quickly boiling down, what is it that you can do that's super valuable to me? And what is it that I can do what's super valuable to you? That's what it boils down to in terms of creating great interdisciplinary science.

Hashem

Thank you. put it very nicely. And Tim, believe it or not, I mean to add what you said. One reason that actually I set up this podcast is along the line of your advice to improve your communication and try to communicate, you know, at a different level, to different audience from different people about different things. So the podcast was to put me under pressure to talk to people with different disciplines, about things that are not in my comfort zone. So I think that's a great advice. And I'm afraid with this, we are reaching to the end of this podcast that I really enjoyed. So my final question is, any final thought or any word of wisdom?

Tim

No, I think people had already too much time to suffer from my wisdom. So I'll leave them in peace. But I would like to thank you, Yashim, for very nice questions and a very nice discussion. I think your ethos for starting the podcast and running the podcast is right on point. And thanks for having me. It's been a lot of fun.

Hashem

Thank you so much, Tim. It was really brilliant. Thank you for your time and your insightful thoughts. Thank you for listening. I hope you enjoyed this episode as much as I did. If you did, please stay tuned and I look forward to seeing you in the next one.