Audio file

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Transcript

Hashem

Welcome back to Immunity by Design, where we bring together leading scientists, biotech innovators, and representatives of policymakers or funding bodies to explore how emerging technologies and AI are reshaping our understanding of immunology. I'm Hashem Koohy, an Associate Professor of Systems Immunology at the University of Oxford, and I am delighted to be hosting this service. Today, I'm truly honored to be joined by Dr. Agne and Antanaviciute, one of the corresponding authors of a seminal paper published in Nature titled Spatial Fibroblast Niches Define Crohn's Fistula. Crohn's disease is a chronic inflammatory condition of the gut, affecting roughly one in every 650 people. In around 30 to 40% of patients, The disease takes a particularly destructive turn. Ulcers eat through the wall thickness of the bowel wall and burrow outward, creating abnormal tunnels, called fistula, that can connect the intestine to the skin, bladder, vagina, or other organs. These are particularly painful, frequently infected, and profoundly damaging the quality of life. In this paper, Agne and her colleagues set out to investigate the molecular and cellular basis of this devastating complication. And by doing so, they have produced the largest and most detailed cellular and molecular atlas of human intestinal fistula ever constructed. Welcome on board, Agni.

Agne

Hi, Hashim, and thank you very much for having me.

Hashem

Thank you. It's a pleasure to have you on board. Perhaps to start with, would you like to introduce yourself? Tell us about your interest and the mission you are on.

Agne

So I'm primarily a computational biologist. I say primarily. I think I like to keep my toes in the wet lab. So I I would describe myself maybe as a damp biologist, not a trial or a wet lab one. So I'm really interested both in the biology of the intestine and in particular in development and inflammatory diseases. But at the same time, I think my passion really is big data and really looking at large multimodal data sets and trying to put together pieces of the puzzle and see what we can learn about various diseases or development or how really cells come together and form tissues or how these processes go wrong in disease.

Hashem

Awesome. With this introduction, let's put one step back and look into the gap in the knowledge that made you towards this study. You and the team have sent a good number of years gathering data and studying this devastating disease. In the light of this, can you describe what a fistula actually is, what it feels like to be a patient living with one, and why it represents such a distinct and serious complication of Crohn's disease.

Agne

I think you've already done a really good job introducing what fistulae are. So I mean, really just to repeat what you said, so a fistula is really an abnormal tunnel that connects different body surfaces that normally wouldn't be connected and normally wouldn't supposed to connect. And so in Crohn's disease, during long-term ongoing chronic inflammation, fistula can form between intestine and other parts of the body. So it can form between two different parts of the intestine, small and large intestine, for example. It can connect the intestine to the skin. This often happens perianally, or it can connect the intestine to other organs, such as bladder or vagina. And really what this means is that you end up with this, often non-healing tunnel, which causes pain, recurrent absences, cycles of infection, obviously, you know, repeat hospital visits for the patients and sometimes major surgery because they don't or often don't heal on their own. And as you can imagine, you know, it affects a patient's daily life from some basic comfort to the ability to work and move and I think a large part of the disease really is also the sort of the social aspects of living with Crohn's disease, because you constantly have to be on the lookout for a bathroom. It's not something that is comfortable to talk about. You know, often people can feel embarrassed by it. And so it's something that quite often people don't really hear about because just because of, you know, the stigma that can be associated with it as well, which I think is very, very unfair and maybe why we also don't put enough resources towards studying these aspects of the disease.

Hashem

I completely agree. It's a very awful disease. So as we spoke, fistula affect up to 40% of Chrons patients and can be utterly life-changing. Yet for decades, the field had a limited idea of what was actually happening at the cellular and molecular level inside the tunnels. What made them so difficult to study and why had no one built this kind of atlas before?

Agne

So fistula are obviously really complicated structures and no 2 fistula are really the same. Because they happen between different parts of the body, they can form really complicated branching structures and they're very heterogeneous in general. Actually, having sufficient access to tissue samples that would power a large study is #1 challenge. Obviously, samples can really come from patients undergoing surgery and they have to be donated. And there needs to be very close clinical collaboration between scientists and clinicians and data analysts to actually achieve a study like this. And all of these are really strong barriers. We also don't have very good models for the disease. So for a lot of diseases and slightly less complicated forms of IPD. We do have very good animal models, for example, mouse models. We also have in vitro tissue models. But for fistula, these don't really exist, which make any functional studies of a disease really, really hard. And so in combination with with difficult to access tissue, a very complicated disease and very, very poor animal and in vitro models. I think really this combines to make it a very, very understudied disease. And I think in our study, we've really come together. And at least on looking at the human side, we really managed to take advantage of close collaborations between clinicians and basic scientists and computational biologists to really overcome some of these barriers and actually, you know, look at the pathology at slightly larger scales than before.

Hashem

Greate, quite a lot of barriers to overcome that makes perfect sense. So before this paper, what was the leading hypothesis about how fistula is for? My shallow understanding is that there were some older work on epithelial to mesenchymal transition. Were those ideas on the right track or partially right or there was something else in place?

Agne

So yeah, so there's a substantial body of older literature that alludes to epithelial to mesenchymal transition. So the idea was that you would have damage in the epithelial barrier and epithelial cells in attempting to repair the barrier would acquire these almost, you know, cancer-like properties which would then enable them to migrate and abnormally create fistula. This was something that we started with initially at the outset and actually we spent a very, very long time looking for any evidence of EMT in our own data before eventually stepping back from that idea because we couldn't really find anything in our data that would support that. For example, we couldn't really see any epithelial cells at the leading edge of the fistula where the barrier was damaged, that would look like they might be undergoing EMT. But what's interesting is that many of the genes that we did see that would be linked to, for example, invasiveness and migration and tissue remodelling, which do strongly overlap these programmes. We saw them in our fibroblast populations. And so We think, those initial ideas were not completely wrong because similar pathways are activated. I think just the cellular source of them was probably misinterpreted slightly. And, you know, the hypothesis that fish to themselves start from the intestinal lesions that fail to heal is also not entirely, you know, it's not entirely new. What we found in a work that fistula might actually start from the basis of intestinal ulcers, it makes sense with our data. And this hypothesis also previously existed in literature. So I think we just found some further evidence to really prop it up.

Hashem

That's interesting. The way you described actually leads very nicely to my next question. That is, For those unfamiliar with gut cellular composition, firstly, what is fibroblasts normally doing in a healthy intestinal tissue? And then the question is that why would anyone have suspected these quiet structural cells of being the central players in fistula formation?

Agne

Fibroblasts are fascinating and actually really multifunctional. So you think of a fibroblast, especially in a gut, as having the main function would be to form the extracellular matrix and contribute to the structure formation. Obviously, different parts of your gut need different types of extracellular matrix with different mechanical properties. You know, it needs sponginess and so on. So different specialized type of fibroblasts exist in different parts of the intestine that support that. But beyond that, fibroblasts do loads of different things. So there's a special type of fibroblast near epithelial barrier that actually provides morphogens to epithelium that really supports epithelial cell differentiation and regeneration. And another really exciting type of fibroblast exists that organizes immune follicles, for example. So these cells help recruit T cells, for instance. So they tell them exactly where to come and hang out. So you can mount really robust, adapt immune responses in your gut. So obviously, fibroblasts do loads of really important functions just in a healthy environment. And when we think about it in terms of what goes wrong in disease, obviously, if you think about a fibroblast that naturally supports healthy immune function, you can see how that can become overactive and start encouraging, you know, too much inflammation and lead to a really an unchecked inflammatory response. You can see how a fibroblast that would normally support epithelial regeneration, for example, can now start supporting abnormal epithelial regeneration in the fistula tract. And we see that there are parallels, you know, a lot of the same molecules are involved. So a lot of the processes that would be part of the normal gut function. If you repurpose them in the wrong context, in the wrong way, That's how you end up with disease pathology.

Hashem

So with this background, now I want to move on to the results and the observations that you report. Obviously, this is a very rich paper, and if we want to talk about all the findings, it would take ages. But here I have highlighted a few questions that I believe are at the intersection of immunology and data science. To begin with, The paper combines single cell RNA-Seq, Visium, Xenium, multiplex immunofluorescence and collagen imaging. That is actually a genuinely daunting multimodal data set. Walk us through the core logic, why you needed each of these data sets and how did they come together.

Agne

So I think that's actually been probably the most fun part of the study. Having the ability to combine different types of modalities to really look at the pathology of a disease for different angles. I really don't think we would have arrived at the conclusions that we did if we just looked at each data set individually. So obviously single cell sequencing is great because it gives us really an unbiased look at what each individual cell is doing. But we end up losing all of the structural information. We don't know where each cell has come from. And when you're trying to study a very, you know, very abnormal structural pathology. It's really, really important to know where individual cells come from to really understand, you know, what might just be a normal part of the tissue and the cell might be coming from a normal part of the tissue and what might actually be pathological. So really this is where spatial transcriptomics came into its own. So Using spatial transcriptomics, what we could really do is sit down with histopathologists, and I'm incredibly grateful for doctors, Fryer and Dr. Beef, who really helped us with this. Yeah, so we could really sit down together, look at the histology of the fistula and say, you know, What's going on in this part of the tissue? What's going on in that part of the tissue? Where's the leading edge of the fistula tract? What exactly should we target? And this was really helpful because we could really, you know, look in the tissue and look where the action was and map out, you know, what was happening at the modicellular molecular level precisely at those lesion edges. So on the other hand, transcriptomic technologies like that are really, really powerful and really lets us see what's happening in cells. In fistula, what's happening outside of cells, i.e. in the extracellular matrix at protein level, is probably equally important in helping us understand pathology. So, you know, adding a layer of multiplexed immunofluorescence and looking at protein expression, looking at collagen imaging of the extracellular matrix and putting all of that together really enabled us to look at the environment of these pathogenic cells. So, you know, we could see how these cells actually sort of reshape their environment as well. For example, we could see sort of borders in tissue where cells would secrete enzymes that would break down extracellular matrix and we could see the corresponding regions where this matrix was broken down as these pathogenic fibroblasts were really carving the way through the tissue. You know, we could see the precise areas where they are tunnelling through the muscle wall of the bowel We could see where in other areas where these cells would switch off all of these remodeling programs and instead switch on. matrix deposition programs, and then that corresponded with a lot more fibrosis and stiffening of the matrix. So really that, almost gave you like a local microenvironment functional readout of what a cell is doing and how it's actively reshaping the tissue that it's sitting in.

Hashem

My next question is about the, what you have called the fast fibroblasts. Firstly, what is fast fibroblasts? And then the question is that is fast fibroblasts are organized in concentric rings around the fistula tract, each zone doing something different, perhaps proliferating and tunneling or modeling, remodeling. or laying down the fibrotic scalp. So how did you discover that spatial architecture and what does it tell us biologically about the life cycle of fistula?

Agne

So yeah, so fast fibroblasts, we call them fast as a shorthand for just fistula associated stroma. We think they're really a several types or other states of inflammatory fibroblasts that we see in other contexts in inflammation, but have really, really specialized to drive changes in the local microenvironment. So for example, we see a particular state of these cells right at the lesion edge of the fistula. And here these cells are the most active So, they make a lot of, for example, factors that would break down the matrix. They express a lot of genes that would be associated with migration and proliferation. So we know that they're probably helping propagate the fistula at the leading edges. they also express a lot of molecules that would recruit immune cells to the edge of the lesion. And so probably actually help propagate inflammation in this area. And as we sort of move away from the lesion edge, these cells start acquiring phenotypes which enable them to deposit additional collagen instead of actually chewing up the collagen in the microenvironment. And so what we think is happening is that just a little bit away from the lesion edge, these cells are then trying to reinforce the fistula tract by depositing, you know, almost like a fibrotic scar. And what this means is that the fistula tract gets reinforced and this doesn't really, it really stabilizes the tract and doesn't help it heal. If you think about it, in the process that we describe is really, it's really the cycle of normal wound healing that you would have in different parts of the body. It's just that it's wound healing gone wrong. It's, you know, it's wound healing fibroblasts which have gone on a march in the wrong direction instead of closing the wound, the breaking up tissue and creating the, you know, the wound and perpetuating it.

Hashem

It's a very nice analogy for that. And speaking of triggers of the fistula, One of the interesting observations that you report is that fibroblasts have switched on transcription factors, things such as TWIST1 or OSR2 or PRRX1 or RANX2 that normally shouldn't be active. So the question is that, how do you think that switch gets triggered in the 1st place? And what is it about the inflammatory environment of Crohn's lesion that permits this developmental reprogramming?

Agne

This transcription factors do a lot of different things. So for example, we know that some of them control more pro-inflammatory signalling that these fibroblasts are doing. So checking out chemokines that would attract immune cells, for example. And others, for example, like TWIST-1, appear to control a lot more pro-fibrotic actions of these cells. It's difficult to say how they get switched on. Our favorite hypothesis, and it's probably not too far off, is that because Crohn's disease really is multiple cycles of chronic inflammation, And that potentially leads to the same fibroblasts getting activated and reactivated and reactivated during multiple bouts of inflammation. They're exposed to, you know, to signals from their environment that signal stress, injury, inflammation. And so probably over multiple bouts, of chronic inflammation. They potentially acquire epigenetic memory that, you know, sort of makes them dysregulated and makes them respond to, you know, to intestinal injury in the way that a normal fibroblast wouldn't. But exactly what the precise mechanisms behind that is something that we'd really like to explore.

Hashem

Another striking findings that you report in the paper is the interaction between fast fibroblasts and other immune cells, including macrophages, macrophage population that are SPP1 positive, creating what sounds like a self-reinforcing loop. Can you crosstalk? What are fibroblasts telling to macrophages and vice versa? And why does that loop matter therapeutically?

Agne

So if you think about a fistula tract, In many cases, you can have a fistula tract that is covered by epithelium or a fistula tract that is potentially in its earlier stages where it's not covered by epithelium yet and is really exposed to the intestinal environment. And that means, you know, that means a lot of bacteria, a lot of foreign antigens. And at the edge of the lesion where we have fistula fibroblasts, It obviously makes sense that we also have a lot of immune cells to defend against these pathogens. Obviously, you need macrophages play a really, really big role in wound healing, not only to act as innate defense cells, but also to really, you know, clean up debris in the area. And macrophages also help, can also help remodel matrix. So it's really interesting, this dynamics, this crosstalk between these populations, because we can see the fast fibroblasts at the edges of fistula actually upregulate a lot of chemokines that would recruit these macrophages to the area. And then on the other hand, you see these macrophages actually expressing a lot of molecules that would then further activate fibroblasts in the region and encourage them to deposit matrix or remodel matrix. And so you can almost end up with this pathological loop where in a healthy tissue, the sleep would eventually resolve. And if you're trying to, sorry, when I say in a healthy tissue, I mean, in a normal case where the sleep would help wound repair, it would eventually resolve. But because you're trying to repair a wound in the wrong direction of the fistula, generally doesn't very easily resolve. And so you can end up with this sort of self-reinforcing loop of the cells telling, yeah, with your cells basically encouraging each other. But it's really interesting because, you know, these macrophage populations have been reported across other organs and other diseases, especially in fibrotic diseases as well. So it's quite interesting to see actually that potentially you have the same processes going wrong. causing multiple different pathologies in different parts of the organs. And I think it would be really, really nice if, rather than studying these diseases in isolation, to really pay a little bit more attention what is happening in other organ systems, because I think some people have had great ideas. For example, you know, in the lung, people have studied these macrophages for a lot longer than we have in the gut, even though, and they know a lot more about them than we do. So I think it's a sort of, I think we would really benefit from collaborating with people working on different organs and diseases to, and not to really silo ourselves a little bit so we don't end up repeating other people's work just in a different organ system.

Hashem

Sure, yeah, it's fascinating. And along the line of what you said, you also report traces of FAS-like fibroblasts at the base of ulcers in patients who haven't yet developed fistula. So the question here is that how confident are you that these cells are genuinely precursor for to fistula rather than by a standard responses? And what would it take to prove it clinically?

Agne

It's a reasonable hypothesis, isn't it? I think it would be quite hard to prove beyond a doubt. You'd obviously need, you know, lineage tracing, and you could never do that in humans, and we'd need advanced tissue or animal models. I think our data genuinely does support this particular hypothesis because while we see these cells in the basis of ulcers, we're also extremely fortunate to capture some very, very rare samples of fistula where basically where you can capture a really early stage fistula, what we call a fishing ulcer. So basically where You have a lesion that has penetrated a little bit into the bowel wall, already past your sort of muscularis mucosa layer, but hasn't really made a full fistula tunnel, and so... that gives us a little bit of a context as to how you go from an early stage lesion to a full-blown fistula. And when we look at these early lesions and when we look at ulcers, which may or may not heal, we can see that actually the main common thing between them is these fibroblasts lining precisely this really small early lesion. And we can see that there are actually quite a few differences. even though they're very similar, there are quite a few differences between these cells and ulcers and in full-blown fistula. So we think that, somewhere along the way, again, potentially from multiple bouts of inflammation, these cells probably, become maybe a little bit more ambitious in how they tackle wound healing, maybe a bit more migratory, or maybe just lose their direction and start attempting to repair these lesions in the wrong direction. And this is probably where, you know, fistula, or at least some fistula, likely come from. But, you know, as I said previously, to really prove that, one would really need much more advanced models. And this is actually maybe one of our more blue sky ambitions to can we build a model of a fistula in a dish? And then you can play with it. Then you can, you know, overexpress various pathogenic fibroblast factors and see what happens.

Hashem

Well, I'm sure that they will come and that will be fascinating. So as I said, this is a very rich study and we can talk overs about findings and discoveries of this. But if it's okay with you, I would like to switch the gear and talk a little bit about implications of this study and what does it mean to patients' care. And in that regard, my first question is that if fast fibroblasts are the drivers of fistula forbation, The obvious clinical ambition is to target them. But these cells also seem to have regenerative properties. How do you think about therapeutic challenges of switching off the destructive behaviors without destroying their repair functions? Is it a solvable problem?

Agne

It's really tricky. I think because they do so many different things in different contexts, and some of them we want to keep and some of them we want to switch off. The first step is obviously understanding what they do. And I think we've come, we've come some way towards that. But you say regenerative properties, and I'd like to say that actually in the context of Fischler, the regenerative properties is a bit of a double-edged sword. this is something that you don't want. So if you'd normally say, hey, should we have some molecules that would encourage barrier repair and inflammation? You'd think, great, that's fantastic, that's what I want. But in the case of fistula, that's actually quite harmful and can really jeopardize fistula healing because, for example, if you if you encourage re-epithelialization of the tract, i.e. barrier repair, in a fistula tract, you know, it actually stabilizes A fistula and prevents them from closing. And this is what you don't want. Whereas if you have, for example, just a lesion in your normal intestinal mucosa, yes, you want those regenerative signals to help repair that. So really, it's important where you have the regenerative signal. So, to answer that question, perhaps local drug delivery methods, for example, topical applications could really work here because you could actually target these pathways where you want to target them and spare the parts of the gut where you don't want them.

Hashem

Transcription factors you have identified Twist1 and OSR2, for example, are developmental regulators express across many tissue. Do you think this can be targeted specifically in the gut without causing any problem?

Agne

Not easily. They, as you mentioned, they do a lot of different things in the body. In fact, they're not even not entirely fibroblast specific. So, for example, we know that TWIST one can be active in some regulatory T-cells as well. And if you indiscriminately target it in fibroblasts in the guts, you might have, you know, you might actually harm some cell populations that would, for example, like regulatory T-cells dampen inflammation. And that could be a very, very double-edged sword. For us, these transcription factors are really interesting from maybe from understanding the basic biology of these cells and how the, you know, the broader regulation of these functions and programs in these cells are happening. But in terms of targeting them, I do think it would be quite difficult to do so specifically.

Hashem

Thank you. Thinking of broader applications and transfer knowledge about this study, So this study is restricted to Crohn's disease fistula. And if my understanding is correct, the biology you are describing that fibroblasts reverting to embryonic programs forming biological niches with immune cells sounds like it could be relevant far beyond IBD. Where else do you think this framework might apply?

Agne

So that's a great question, actually, because I mean, the obvious sort of parallels that you can draw here is between other fibrotic diseases and really, you know, how the process of collagen deposition and remodeling can happen. We know from previous studies, for example, that the fibroblasts in the gut and other organs have a lot of parallels. And so if you, really, if we think about the molecules that we've discovered, they have also been described in other, in fibrosis in other organs, for example, in kidney. So I think really, I mentioned before that there are a lot of parallels between different diseases. Beyond that, I think it's actually, quite a fascinating insight into how wound healing in the intestine really happens. Because I think normally we, sort of think about it with a really big focus on barrier repair and how one would close a bigger, lesion is really fascinating. So I think one thing that, we found from this is the ability of these fibroblasts to encourage sort of very focal and local epithelial regeneration. So, in the fish will attract. as you go along the tract, these fibroblasts start secreting molecules which would encourage epithelial regeneration. And so you see, you know, that these fibroblasts can almost be dragging this, you know, re-epithelialization, like just a little bit behind them to close the tract. And I think that's really interesting when, you know, we think about how the processes of wound healing happen in the gut. but also in other diseases. So when we initially looked at these fibroblasts and thought, hey, is this just wound healing gone wrong? We thought, you know, what other examples of wound healing are there in literature that we can draw on? And so we went and looked in skin in people who have diabetic ulcers. And what's quite fascinating there is that there are a lot of parallels between healing and non-healing ulcers in skin and these fibroblast populations that we see in fistula. And so I think, you know, a lot of biology in different areas is really, you know, sort of quite copy paste, really. You know, it's not efficient to invent something new. You wouldn't have a very different repair process in one part of the body and in another one unless you really needed something different. So I think, you know, what we've learned here, I think is very, very transferable to a lot of other areas.

Hashem

Very fascinating. And the last question of this section, You have made the entire data set publicly available. What are you hoping other scientists and perhaps computational biologists or AI researchers will do with it that your own group hasn't done it yet?

Agne

Hopefully a lot of things. The data is enormous. We focused on fibroblasts because, to us, that seemed quite interesting. I'm a big fan of fibroblasts in general, and we've done quite a bit of work and understand them reasonably well. And so that seemed, you know, quite a natural area to gravitate towards. But, you know, this is not probably the only cell that's contributing to the pathogenesis of fistula. I mean, naturally, of course, immune cells play a huge role. But you can even think about things like, you know, how do fistula attracts vascularized, for example, you know, how do you support this growth and remodelling? You know, how the muscle cells actually, you know, responding to these fiberblasts as, they start breaking down the matrix and carving the path. these are all really interesting areas to explore. And, we really hope other people can use our data and their own research and hopefully come up with insights we haven't. And, in terms of AI, I think we're at the really, really fascinating point right now, where, as a research community, especially when it comes to omics data, we are at the point where we actually have, just about sufficient volume of data to start doing some really, really interesting things. Yeah, so in terms of AI, I think... As a research community, we're now at the point where, in terms of omics data, we have sufficient data sets to really start doing really, really interesting things with it. And, although our data set is large, it probably still... isn't large enough for a lot of applications. So we really hope that, other people can also come along and undertake similar studies and really, refute to validate some of our results and, really use some of these emerging technologies to be able to to generate new insights to, maybe reason through this enormous data, a much larger scale in a less biased way, not just through the lens of basically what, a team of a few humans thinks, but, in a much more agnostic way.

Hashem

Yeah, absolutely. It's really difficult for me to think how the future, even short-term future, will look like under the light of AI and its application to multi-omics. data and how we will be doing research. So for the last few minutes of this podcast, I would like to switch to positive research culture and the importance of multidisciplinary research because I believe this study was really a great example of a collaborative project. And in that regard, my first question is that from your point of view, what makes multidisciplinary research a success and what kills it?

Agne

I think the most critical thing is a lot of goodwill and a lot of excitement from everybody involved and actually collaborating. not just involving other people tangentially because they might know X technique or they might have a resource you need, but, everybody fully buying into a particular problem and everybody acting in a way such that, everybody is included and has a stake as much as possible. So, this particular project, has really been started because of the very close collaboration we had with the clinic. So, Dr. Kalima Gregor, who's, you know, one of the first authors, she regularly sees patients with specializing Crohn's disease in the clinic. And, you know, she was, you can see how frustrated she was by how little research had been done onto something that is so life altering for her patients. And, but to really sort of change that, you really need, and to make a study like ours happen, you really need to have buy-in and know-how, not just from, the clinical side, but from molecular biologists, computational scientists, clinicians, histopathologists, and so on. So, I think, I think environment is really, really important to make it happen because you generally need a place where multiple people can, come together and generally give it their best as opposed to just feeling tangentially involved.

Hashem

Interesting. And along the line of what you said, one is that to, truly everyone playing their role and the second one is, the culture is very important. So that brings me to my next question. And that is, how do you measure success in a multidisciplinary research culture and make sure everyone is playing their role and getting credit accordingly.

Agne

I think success is, you know, is obviously achieving something. that everybody is proud of, whether that's a publication or, developing a tool. I think to me, success is having something that everybody involved can be genuinely proud of, whether that means a publication or developing a tool or, actually getting some insights towards, how we can potentially tackle a disease. Or, at the end of the day, even if even if things that you do might not be a success, I think having had fun and having built collaborations and friendships and partnerships, even when things fail, actually being able to take it forward to the next thing and so on. But I get the point of your question because, as an interdisciplinary researcher yourself, you probably know that this, it's a difficult scientific culture question as to how do you make sure that nobody is overlooked? And for example, traditionally, wet lab biologists always, you know, carry the leadership flag in projects. I think the current scientific environment is changing a little bit. Shared authorships are becoming a lot more common. And I think everybody's recognizing that if you really want to bring together a large scale project, it cannot be one person doing it. And I think we really, really need to think about how we can, you know, sort of cement these changes into our culture going forward because And if we move away from that notion that one person has to be the project, then we will have a lot more projects that actually, proper teamwork. And therefore, I think we'll have a lot more successful projects.

Hashem

Fantastic. The next few questions is more kind of your own experience with this project. What did you like or disliked about this project the most?

Agne

I think, as I said before, the best part is really being in a place where I'm at and working with the people that I get to work with every day. I think, where I am in my scientific career has been entirely due to the people who have been around me, both, peers and mentors. And It makes me really sad, to hear that sometimes people don't have such a positive experience because I think that really, makes or breaks how you view science. And so, I think for me, the most exciting part has just been the people I'm working with and how we tackle problems together. The part that I disliked the most, the early days were really hard. I think this is This is quite normal, but for example, we spent about two years trying to optimize spatial transcriptomics to work for our tissues with very, very little success, a lot of repeated failures, and it took… it took a long time to actually have a breakthrough. So, obviously this is quite normal as part of a scientific process that sometimes things just didn't work. And I think for one's own sanity, you always have to have multiple things on the go because you can't just fail and fail and fail. So I wouldn't like to repeat that part, but I'm happy that we persevered.

Hashem

Okay. So I mean, in the light of that, what do you wish someone had told you at the start?

Agne

Well, obviously, I wish somebody had told me all the things that wouldn't work and not to try them and to try the things that did work. But maybe not. You know, it's character building. I think it's good for you to struggle sometimes.

Hashem

Fair enough. What advice would you have for PhD students sitting at the interface today?

Agne

Do you mean interdisciplinary PhD students?

Hashem

Mostly, yes, yeah.

Agne

Oh, that's very hard to advise right now. I mean, we're on the verge of such change, especially in the eye that, I don't know. I guess it's a really exciting time to do science because I think we'll have to rethink a lot about how we approach things in general. just the loop of a project. I think a lot of things will become much quicker to do, but I think we'll also face a lot of challenges. So, Yeah, I wish I could foresee the future, but I think it's a strange time to be filled with both excitement and trepidation at what's to come.

Hashem

Yeah, okay. So let me rephrase my question a little bit and link it to what you said earlier that, you know, the first two years you tried quite a lot of different things and they all failed. So now you know that failure is part of research and actually it's a educational part of the research. But for PhD students, this is very depressing. And the fact that, a PhD path is not a linear path from A to B, they quickly become depressed and disappointed and they feel that, their life goes nowhere. So what your advice would be in that regard?

Agne

I think you can train yourself out of that way of thinking. I think it's really, really beneficial to start viewing, failure and to some extent also criticism that you receive as part of the process and not really a reflection on your own self-worth or your own abilities as a scientist because those, are not necessarily related. And if you view it as part of the process, then I think, then you're not, you're not so, emotionally attached to, when do your experiments when they don't work, for example, or, when somebody criticizes your work, you're less likely to take it as an attack on you, but rather as, as direction towards how you can improve. And so, I think working on that and really not tying it to, how you see yourself as a person, this is really, really important and possibly one of the best skills you can have. I won't say that I have that mastered because I think this is really difficult sometimes, but it's worth reminding yourself that it's a process and it's nothing to do with you.

Hashem

That is very true indeed. Yes, and we all, experience that, but just the level is different, I guess. And the very last question, any final thought you wish to finish off this episode with?

Agne

No, I think I just want to say thank you for having me on this podcast, Hashem. It's really been a pleasure talking to you. And again, I'd really like to thank all of the collaborators who made the study a success and all of the people who I've worked with over the years. You're awesome.

Hashem

Thank you so much, Agni. It was a great conversation. Well done to you and congratulations to the whole team for this fantastic a study with a great future for friskiller patients. Thank you.