Episode 5 - Lloyd Steele

[00:00:00]

Hashem (3): /

/

/

Hello, welcome back to Immunity by Design, where we bring together leading scientists, biotech innovators, and policy representatives to explore how emerging technologies and AI are reshaping our understanding of immunology. I'm Hashem Kooy, an associate professor of systems immunology at University of Oxford, and I am delighted to be hosting this series

Hashem: And today, I'm truly honored to be joined by Dr. Lloyd Steele, a lead author of a fascinating study at the interface of immunology and data science, by which they reveal hidden immune memory niches in inflammatory skin diseases. The central provocation of this work is really striking. The tissue architecture of inflammatory skin disease [00:01:00] is far richer and more therapeutically relevant than a century of H&E histopathology has ever revealed.

In this study, Steele and colleagues present an atlas-scale integration of genomics, high-plexity spatial transcriptomics, and AI-based niche discovery to systematically uncover immune memory structure that are clinically consequential and yet completely invisible to our standard diagnostic toolbox.

Welcome on board, Lloyd, and it's wonderful to have you with us today.

Lloyd: thanks for the introduction, and thanks for inviting me

Hashem: ~~Uh, Yeah, it's a pleasure. And~~ what about if, we start this episode by introducing yourself? What are the missions you are on, and what is it that you enjoy in science and the immunology?

Lloyd: Yeah, sure. So I'm Lloyd. I'm doing a clinical PhD at the Sanger in [00:02:00] Cambridge and then I'm also a final year dermatology resident. I guess I'm very interested in disease, so specifically skin disease and then using, say, computational methods and the current technologies we have for generating

data at scale to try understand these diseases in more detail to be able to offer new therapies and yeah, I guess bring things to clinic.

Hashem: ~~Uh, great. And, uh, yeah. So now~~ let's put one step back and look into the gaps in the knowledge that led you to this study. So why was human skin a great tissue for this type of a study, and why you are interested in actually skin and skin diseases in the first place?

Lloyd: Ah, yeah, why choose skin? I think one thing is that the diseases are very common. So the diseases we looked at were eczema and psoriasis, and I feel like most people know those or know someone with those conditions they're very common. So it's quite interesting to investigate something that's so common that can help lots of people from the understanding.

Yeah, and I think skin is a really [00:03:00] interesting tissue to understand all the processes that we see in disease. So things like scarring, fibrosis, inflammatory diseases, cancer, like they all occur in skin, and it's something that we can access with like low morbidity, or it's not as invasive as accessing other tissues.

And then I think we can apply that knowledge more broadly

Hashem: ~~Yeah.~~

Lloyd: ~~for when you... Yeah~~

Hashem: Okay. The studies mainly focus on histopathology data. So histopathology has shaped dermatology for decades, but what did you feel ~~it is~~ it was fundamentally missing when trying to understand inflammatory skin diseases?

Lloyd: Yeah, so I really like histopathology and in clinic it's really useful, if you see something and you're not sure exactly like the diagnosis and you get this extra information from you biopsy the tissue and then look at it under the microscope. And then each disease has its own sort of spatial pattern, so you can see these patterns and they can tell you, is it...

Or point you towards the diagnosis. So I think that's really nice, and it's something we use a lot in clinical practice. I think what is [00:04:00] missing is it doesn't give you the detailed cell types, like exactly which cells are there which chemicals or chemokines they're secreting to attract different cells.

It can't tell you that sort of level of molecular information. So we were interested in trying to understand the spatial patterns that we see in these different diseases and try to get more information than what we can see from the microscope

Hashem: ~~Yeah. Okay. So~~ then speaking of cellular composition of skin, before this study, we had rich single cell catalogs of skin cells, but less understanding of how those cells organize spatially . What was the key conceptual gap you wanted to address in this study?

Lloyd: Yeah, so it's bridging those catalogs of cells that you see. So in recent years, we made these catalogs of more detailed cell types of human tissues. We don't exactly know where they are in the tissue. And then there's different older branches, there's histopathology that we still use in clinic.

So I guess conceptually what we [00:05:00] were interested in was mapping these detailed cell types onto the H&E, so that when you look at the H&E image, instead of just the current appearance we have of these dyes that they use for the tissue, we could actually see these really detailed cell types. And that in the end ended up giving us new insights into eczema and psoriasis that we didn't know before

Hashem: Excellent. The two diseases that you study ~~two~~ inflammatory diseases, one atopic dermatitis ~~and~~ AD, and the other one psoriasis, PS, frequently recur at previously affected anatomical sites even after apparent clinical resolution. So what observation or experimental evidence convinced you that this reflects tissue-embedded inflammatory memory rather than simply repeated recruitment from systematic immune compartment?

Lloyd: Yeah, so it's probably a combination of experiments and clinical observation. So for clinical observations, [00:06:00] definitely with psoriasis, it does seem to occur very specifically at sites it's occurred before. If you stop the treatment, you often get reactivation in exactly the same sites. So that sort of suggests that it's something in the tissue, otherwise it would also...

You'd expect it to affect other sites or sites nearby. And then there have been experiments done as well that have pointed to that. So say taking psoriasis skin and then grafting that onto a mouse without an immune system, you The '90s, early 2000s, these sort of experiments. And then they showed that actually in that grafted skin, the psoriasis would reoccur, which would suggest it was in the tissue that was transplanted.

And there were other similar experiments like blocking T cells or immune cells exi- exiting the blood vessels, and it would still reoccur. So the, sort of these clinical observations and these experimental studies pointed towards the tissue having the memory, but before we've only really been able to look with a H&E level resolution, so it's been quite unclear which cells exactly are mediating that memory.

And that memory is also relevant across [00:07:00] all immune-mediated diseases~~ so~~

Hashem: ~~Yeah.~~ Okay.~~ Now with these gaps in in mind, let's move on to the findings of this study. And to start with is the experimental design of the study.~~ A study at this scale of multidisciplinary and multimodal data integration, it requires quite a lot of planning and experimental design and so on and so forth.

So the question I have is that once you identify this conceptual gap between classical histopathology and the underlying molecular organization of tissue, how did you design a framework capable of systematically resolving these hidden spatial structures? Was it, a planned a priori, everything planned or ~~you— it—~~ did the study just evolve along the way?

Lloyd: Yeah, a convergence of the data we were collecting and then the tools that were being made in the institute as well. So in terms of data, we used a lot of public data to get the detailed cell types that you mentioned, like these catalogs of cell types. But then, and also helped by the Sanger being very good at data generation [00:08:00] at scale, like generating these spatial maps of the tissue.

So measuring sort of thousands of genes in the tissue that enable you to then map on this reference to it. And then I guess the second was the tools. So there's, I partly in the Moula Fallahi's lab at the Sanger too, where they're developing lots of AI tools to try and understand this data.

And then one element there was trying to capture not just the cell types, but the neighborhood. So say a nerve structure doesn't just have the nerve, but there'd be the Schwann cells wrapped around it. There'd be some perineural macrophages and other things. So we wanted to capture these structures as separate niches to try then see what was new in disease.

So it's this combination of the data we generated, the tools being made at the same time, and then Sanger helping like the scale of what you could generate.

And so I think putting those together enabled us to then, yeah, answer this question.

Hashem: In this study, you profiled over five million cells, combined single-cell RNA, spatial transcriptomic, [00:09:00] H&E imaging, and deep learning to identify 26 niches in health and disease. Of everything you found, which single discovery most changed what you think about inflammatory skin diseases, and why?

Lloyd: Yeah, it's a good question, 'cause I don't know exactly where each finding will go, 'cause I think we describe a lot of findings to them. I think each one will probably be understood further in time. I think what I quite like, 'cause it's very simple, was like I was saying, we make these maps of these detailed cell types in the tissue, and so then you look at it and you just see these like new cell types that you weren't aware of being there before.

And so I think just seeing these memory T cells in the outer layer of the skin, along with this sort of different T cell are linked with deciding whether you interact or react to the microbiome, like the bacteria and other things on the skin as well. I think seeing those two cells, like in this outer [00:10:00] layer of skin in eczema, for me was, yeah, quite interesting, 'cause you don't really, in eczema, the resident memory T cells weren't well defined. But then also seeing this slightly unusual like innate lymphoid or T cell nearby that has this role in the intestine of interacting with microbiome, I think for me was really, yeah, interesting. And it'd be interesting to see like how we can build upon that to try understand exactly what these cells do

Hashem: Interesting. So as we spoke earlier, this study was possible partly because skin is accessible, well-funded, and clinically well-characterized. But most tissues and disease don't have this luxury. Which elements of your framework do you think are transferable to other diseases or tissues, and which ones are not?

Lloyd: And so I think the core concept of a spatial map of tissue like this really amazing detail, I think that, that is possible. So they have recent papers in Nature [00:11:00] on intestine and kidney, like making these spatial maps. I think it was a previous episode of this, of some... Using that in intestine.

But I think what's quite unique to skin, and so I think we're looking at, is using time or getting multiple tissue biopsies over time. So it's quite interesting to know if you start a treatment, then what's the skin like one day later, three days

later, seven days later. And I think with skin, we can do that and take these multiple biopsies, and it's not a problem.

But say, in like heart tissue or lung tissue, or say intestine tissue in IBD, getting samples like one day later, three days later, seven days later isn't really feasible. So yeah, I'm quite interested in understanding how these cells change over time in skin, and then hopefully those can translate to other tissues.

So things like recent drugs approved in psoriasis, but then approved in IBD. The recent drugs in eczema, like later approved in asthma. So I think using skin as this way of looking at human tissue, like a actual tissue, how it changes over time, I think is really exciting for us [00:12:00] specifically.

But definitely the spatial maps I think can be applied to other tissue and, for example, I'm really interested in seeing what joints are like in like rheumatoid arthritis and psoriatic arthritis in this sort of spatial resolution, which I think should be coming soon

Hashem: yeah. One of the most striking findings in, in this study is that the sebaceous and sweat glands structures we thought we understood turn out to be active immune sanctuaries hiding in plain sight. What does it mean that something this immunologically significant was sitting in every skin biopsy ever taken but completely overlooked?

Lloyd: Yeah, I think it probably depends on its structure. So the sebaceous gland is what produces sebum, that's linked to, say, acne and what causes a greasy nature of skin sometimes. And so if you look at it under the microscope, it's just packed with cells, and it's quite hard to see exactly which cell is which.

But then when you put this sort of spatial map onto [00:13:00] it, then you see it has lots of these resident memory T cells, and I think that's really hard to detect by microscopy alone. But it does make sense in that sebum has lots of lipids which are thought to be needed for skin resident memory T cells, and there's retinoic acid gradient, which is like this really common acne treatment of modulating retinoic acid.

So it, it makes sense to have them enriched in that area. I think before we just couldn't see it. And then I think for the sweat gland, so this was seeing these antibody-producing cells near the sweat gland. People had seen before, I think nineteen eighty-nine, nineteen ninety-one there were antibodies in the sweat and also on the sort of bacteria living, or, and yeast as well, living on the skin.

They saw them coated in these antibodies. So the thought was, like, there must be antibody-producing cells nearby. But the studies looking at where these antibody-producing cells are in skin recently like one they just said it was around the blood vessels, and then there was another recent one in mice.

But then mice they only have sweat glands or these specific type of sweat gland on the bottom of [00:14:00] the feet. So whereas humans have these sweat glands everywhere, so there's also this species-specific difference. And I think g-going forward, I think it'd be interesting there are obviously these classical histopathological observations, like seeing antibodies in sweat, but now we have these spatial maps of the tissue, and then we can start to understand more about these specific diseases and what's unique to each one.

Hashem: ~~Thank you.~~ Another interesting observation is that the sebaceous gland-associated niche is enriched in resident memory T cells and carries the molecular machinery to sustain them. But then the question is that do you see this niche as a passive reservoir or a- an active organizer of inflammatory memory or something even more dynamic?

What experiments do you think is needed to settle questions like this?

Lloyd: Yeah, it's a good question. I would be open to suggestions that you have, like how you do this. But we did do one cool experiment, or I thought it was quite good [00:15:00] thanks to St John's Dermatology in London and the patients there, of... We found a cohort of patients on an eczema treatment called dupilumab, where they'd had clear skin for more than a year.

The skin was clear, no eczema. But the problem in these patients is you just have to keep carrying on the drug. If you stop it, it will come back. So then you have this, The drug's obviously very expensive. So we're kinda interested in ideally how you modulate that in the future.

But then the experiment we did was if you take a biopsy of the clear skin and then you stop the drug, and then wait for the eczema to come back, and then do the biopsy, and that was a way of looking in human eczema, like actually how do these environments change. And so then what we saw in the clear skin was there were resident memory T cells in the sebaceous structure still, and it had the most in the outer layer of the skin.

But then when you had the disease coming back after about eight weeks, then suddenly you saw much more of them. So we were suggesting both there's a reservoir of them within this structure, but also that it is a site where cells

[00:16:00] enter into the outer layer of the skin. So normally there are no blood vessels there, and so it suggests that's where they come through and then move out.

So yeah, we looked at it in human, which I thought was quite nice

Hashem: I also found it interesting where you report a plasma cell-rich niche near sweat glands as an analog to a lung's GAIL . The, that brings the question to me that what does this tell us about B-cell memory in AD, a disease we have always considered a T-cell-driven disease?

Lloyd: Yeah, so the lung gain is like this reported relatively recently in the human lung, like around the glandular structures. They saw like antibody secreting cells, and that yeah, they would get transported and then secreted out with the, like glandular secretions. So then we saw a similar structure in the human skin.

And then eczema is like a classically, yeah, like you say, T-cell mediated disease. I think the link I guess [00:17:00] we've not fully understood it yet, is that unlike psoriasis, patients with eczema have a much higher risk of food allergies and other allergies, especially children. If you have very early onset eczema, so two to three months old, like they almost always have food allergies, or it's just very common to have allergies at that time.

So there's clearly this association of eczema and this more like antibody-associated immunity. I guess more recent times, there's this idea of you get exposure through this leaky barrier, and then that triggers it. But yeah, I think it's something we're interested looking at in the future, like exactly why do these patients have food allergies?

Why does that seem to become less common over time? And relating that to eczema, where in eczema, the skin's classically like leakier, I would say, whereas in psoriasis it's thought to have a better barrier. So in psoriasis, you don't see the same effect. So then it was quite nice to see yeah, only this plasma cell niche in eczema really.

So yeah, I guess we need to do more work on it, but there is this, like idea of linking it to the [00:18:00] allergies

Hashem: Speaking of plasma cell-rich niche, does this suggest a shared immune architecture in barrier tissue, do you think?

Lloyd: Yeah, so we were suggesting it was shared. So these barrier tissues have this shared role, so that would be stuff like skin, lung, intestine, but they have to interface with the external environment. There's lots of microbes living on the skin, there's lots in the intestine there's an outer layer of your respiratory tract too, like nasal kind of mucosa, you have these as well.

So they have to interface with it. And yeah, I, I guess I probably didn't know this at the start, like they're all coated in antibodies, or not all lots are coated in antibodies. So we seem to find that these three different places, like nasal mucosa, lung and skin, I guess intestine's known for a longer time.

You have these sort of three elements of antibody-secreting cells next to the gland. You have gland cells that secrete the protein that transports the antibody out, so how cells like transport it through. And then the glandular cells themselves seem to secrete the chemicals or chemokines [00:19:00] that attract the plasma cells.

And so that was unknown for the human sweat gland. It secretes the cells, the chemokines that attract them. So they have these three shared features. And I think that's... I think the interesting area is how that relates to like vaccination. So in the nasal mucosa, they're relating this plasma cell niche to nasal vaccination and looking at these, yeah, different modalities for giving vaccinations.

Hashem: thank you. For sure this study is very rich and we can actually talk for a long time about that. But let's switch gear and talk a little bit about implications and limitations of the study. We have spoken quite a lot about niches, but let's actually zoom in a little bit and see what ~~are~~ really these niches are.

So the question here is that, are niches biologically discrete entities or are they computational abstractions imposed on continuous tissue gradients?

Lloyd: Yeah, interesting question. [00:20:00] Yeah, so when we talk about niches, because we have these cells, like the spatial map, essentially we want to group the cells, not just into their individual cell, but like the neighborhood or structure it forms. I would argue biologically discrete because we can map them to functional structures that we see on the H&E.

So when I say skin niches, we're talking about things like the sweat gland duct the sebaceous gland the outer layer of the hair follicle, inner layer of the hair

follicle. You do get these interesting ones that maybe we wouldn't call a niche before what we call a T-zone.

So it's like this area in the lymph node that has lots of T-cells that we see in human skin which we don't seem to see in mouse skin, like in the mouse models of eczema it doesn't seem to have the same effect. So lots of them we could map onto functional structures that we know from H&E, and nerve would be another one, like the nerve and the perineural structure would be another niche.

But then we were interested in what would be new that you see in disease that you don't see or not recognized as a H&E feature. But definitely there is this element of [00:21:00] because of how we're detecting them computationally, could it be an artifact of that? So for that reason, like we always try relate it to the H&E, but then looking exactly which cell types make it up.

So yeah, for me, and I'm a bit biased, like being very interested in histopathology I think they're biologically discrete

Hashem: Now, having established the definition of niches, if these hidden niches contribute to relapse, as my understanding is that you report they are, could future ~~therapeutic,~~ therapeutics aim not just to suppress inflammation, but erase or reprogram inflammatory memory?

Lloyd: Yeah, that would be the dream, right? And I think that applies across different tissues too. So I guess just to explain to everyone there's a lot of immune-mediated diseases, so things like eczema, psoriasis, inflammatory bowel disease where for some patients the treatments are very effective and essentially the disease is in remission.

But you have to typically continue them for a very [00:22:00] long time, otherwise their disease comes back. So with psoriasis, there's some patients who have been on these drugs for more than twenty years now and still come back to clinic every year. And that has problems from potential side effects of drugs and the cost of them.

So ideally what we would like to do would be to erase a memory to stop it coming back. A classic challenge has been understanding exactly which cell types do it. I think in psoriasis it was known more that it was these resident memory T cells. In eczema that was less well understood, so it's quite good to define that.

And yeah, people have started to do studies in psoriasis to see what happens to these resident memory T cells under this drug treatment including this study, and they do seem to stick around. So yeah, I guess a future avenue is how do you erase those or remove those cells? At the moment, we don't know.

But I think defining exactly what cell types, especially which we do here with eczema, I think gives us a potential avenue, but that is the dream and that would apply across

Hashem: Yeah, y-y-you partly pointed to my next question, and that [00:23:00] was, one, how difficult that is. That would be basically either erasing or reprogramming this inflammatory memory. And also are there potentials to any side effects? The angle I look into this is that, for instance, imagine there are some transcription factors that play a role and, for instance, you need to switch off those transcription factors.

But if those transcription factors have some other, say, developmental roles in other tissues or in other context, then you will be running into a problem

Lloyd: Yeah, that's a good point. Yeah, so you do see that effect to a degree with the targeted treatment. So for example, in psoriasis, one... there are different pathways you can target, but like one of them targeting like IL-17, there is a risk, an increased risk of fungal type infections because you're...

that's what that cell defends from really. These cells aren't have this evolutionary history of defend against different [00:24:00] effects. And also with the eczema one, like there's a theoretic risk of worsened parasite or decreased parasite defense. So yeah, there is always that consequence.

I guess definitely with the very targeted treatments in eczema and psoriasis, like they, they do seem very safe. But it's probably a bit out of my expertise. But yeah, I guess when you're thinking about targeting these cells or raising them, I guess you have to remember that they also have a defense role and it's like a local tissue immunity, right?

These cells are... In the vaccine world, I think people are interested, how do you get these resident memory T cells to come up to give you protection? Whereas coming from the inflammatory disease angle is a bit different and you're "We want to get rid of them." But yeah, definitely you have to remember that sort of these cells are built to protect you against different responses.

And I think we probably need to understand more about their specificity, I think

Hashem: Absolutely, yeah. And I agree with you, that's a, a dream, and it will be hugely impactful in the field. But that's for future. But talking about the study and the observations you [00:25:00] report there. And one thing, as we said, the sebaceous and plasma cell niche are compelling candidates for inflammatory memory.

So do you think these niches are drivers, consequences, or a transient ecological status?

Lloyd: Yeah, maybe I probably have a different answer for each one. So like the sebaceous starts having these memory T cells, that seems to be especially doing that experiment I mentioned before of stopping the drug, seeing does it come back. That seems to support having a disease effect role.

We also looked at like genetic variants linked to eczema, and they seem to be enriched in this area specifically. But I think the plasma cell one, so this antibody secreting cells around the gland, that probably I feel is more transient 'cause we didn't see that when you stop the drug and it get this very early disease.

Like maybe it's a response to prolonged inflammation, like in eczema, the barrier is leakier. So if you imagine all these sort of microbiomes or [00:26:00] antigens leaking into the skin, does that trigger this responsive antibody generating cells turning up? And that seems to be more transient. So it really depends on the specific niche that you talk about

Hashem: Yeah. As we spoke briefly, your Atlas enables transfer learning and mapping of new datasets, ~~a and~~ also the concept that you introduce in this study. So how do you imagine this improving the study of rare or under-profiled skin diseases or its application in other

Lloyd: They are the better thing to scale this yeah. So yeah, the transfer learning part is probably one of my favorite parts of the study. And then using the data we show here to help inform future studies and future diseases. I envisioned it being like a jigsaw puzzle, right?

Our goal was to get five million cells and the goal is like you map out the whole jigsaw puzzle. Like you have all the pieces and you put them together and then you understand the picture in much more detail. So then if someone gives you ten [00:27:00] random jigsaw pieces, you can which would be like a small study or a rare disease. It's actually much easier then to know where those pieces go and to understand how they fit into the picture. Because if you don't have the

reference, like the completed puzzle, it would be really hard with just ten pieces in a big puzzle to understand what was going on.

And so our goal was like making this reference so that when you have future studies, you can get much more detail. And the detail in this sort of context is just much more detailed cell types to then try understand what's going on. So I think it's helpful and we show in the paper how you can use that for these previous studies to get this newer detail

Hashem: Yeah. And my understanding is that actually your study somehow suggests a paradigm shift. And to put it in the context the histopathology has historically been morphology first, human interpretable, and relatively low dimensional. But your work argues that biologically meaningful disease [00:28:00] organization might exist below the resolution of what the human eye can recognize on H&E sections, and that AI-derived spatial representations may, in some contexts, become more biologically informative than classical structures pathology has relied on for over a century.

So do you see this really as a paradigm shift, and what are the challenges and mindset here going forward?

Lloyd: Yeah, I think it's definitely this idea of just more resolution and getting more detail, and that gives you new insight. So you could have said the same before, historically, like when you couldn't do histopathology. People would still see these diseases and they would want to know what's going on, but they had like a limited view.

So then people learned like how you can take these biopsies and look at them under a microscope, and then there was a new like wave of reporting about these diseases and separating them out. And that has proven to be [00:29:00] very useful and really key to dermatology and other medical specialties too.

So I guess what we're now saying is that instead of just the H&E from the microscope, you can map on these detailed molecular profiles, and that's starting to give new insights. So we show eczema and psoriasis, but the idea would be you can take any of these diseases from skin, like the sort of hundreds hey, vitiligo or acne would be these common ones people know, or alopecia areata and then start to understand in new detail what's going on.

And I think that's really exciting for, yeah, getting new insights into these diseases, what cells can we target going forward, like this new approach to histopathology.

Hashem: Okay. What would you describe as the key limitations of your study?

Lloyd: I think our limitation is that we're very descriptive. Our aim is we describe these spatial maps of skin. We say these are new structures, these are new cells, but we don't [00:30:00] go into detail in exactly what these cells do. So I think an interesting question is these innate lymphoid cells in the outer layer of the skin that can attest in a link to modulating how you respond to the microbiome.

We don't look into that in detail. So I guess we're like a descriptive spatial map, and I think going forward these functional validation studies would be particularly valuable for that. And then I guess also the scale, like the scale of our study is quite big in the relatively, like more than a hundred and twenty sections of this high-resolution spatial.

But still between patients, eczema can look very different. And so trying to understand those patient-specific differences, I think needs even more patients and yeah, to try and understand why some patients respond to drugs, why some patients don't. So I'd say those are the key two

Hashem: ~~Sure.~~ This study at this scale of data use and model development was unimaginable five or even three years ago. How do you see the landscape of research at the interface of [00:31:00] immunology and data science and AI in five or even three years time from now?

Lloyd: Yeah, I think, yeah, the field of immunology generally is very exciting. Like previously, I guess over a slightly longer timeframe of that, we've seen how like clinical care would shift from immunological advances. So immunotherapy and melanoma then applies to lots of other different tissues means that, there's patients living with metastatic melanoma like more than five years, which was just unthinkable before.

And now we have like new treatments for eczema that are like much better than what we had before. So yeah, I guess historically it's really nice to see how advances in immunology have translated into clinical care. I guess in the next three to five years it's quite hard to predict because AI and immunology is like a really broad field.

So there's people doing things totally distinct to what I'm talking about here. So things like which antigens are T cells actually recognizing or designing protein, proteins to target specific antigens or specific targets. [00:32:00] So there are

like lots of different avenues within that. I think it's hard to predict like exactly what it will be.

I think in this specific field that I'm talking about, I think we'll see more of these spatial maps and you get this like digital histopathological interpretation of them. I think that's like an immediate one, but obviously there's lots of different branches and it's quite exciting to see actually, like what will happen.

I don't know.

Hashem: is indeed. And, the speed by which everything moves forward, it's unimaginable for me to say even, what we will have in next couple of years and how we will be doing science. And that was actually one reason, I set up this podcast to boost the communications on where we are heading.

So I would like to end on a methodological challenge that I think deserve more attention in the field. This study chains together multiple computational models. For example ambient RNA correction, batch integration, label transfer, niche embedding gene program ~~interfa~~ [00:33:00] inference and et cetera with its own assumptions and error rates for each.

When you integrate them sequentially, there is a risk that errors don't add up linearly but grow combinatorially, potentially amplifying artifacts that look like biology but really are just artifacts. So was this a problem in your case? And if so, how you basically mitigate the risk?

And do you think this reflects a broader issue in the community that it needs to be taken seriously?

Lloyd: Yeah. So who, the, I guess this is common problem in biology of there being lots of noise. So I guess the data we're talking about is just measuring thousands of genes within a cell that happens in different labs from different patients. So there's inherently like this very noisy data that we [00:34:00] collect.

I think a positive about the single-cell field or this general field of research that I'm talking about is that it's a very big community, and so there are a lot of people working on it, and some people just purely work on methodology within the field. So there are lots of people trying to optimize these steps.

So yeah, the things you mentioned like ambient RNA, batch correction, like there are people working specifically on those problems. With the spatial maps,

like a big ongoing challenge is that you need to decide the genes you measure, which cell exactly are they in, which is a bit harder than it sounds, but you don't exactly know the boundary.

So there's a lot of people working on trying to improve that so you get cleaner data. I would say we, yeah, we definitely take it seriously and there's lots of people working on it. But also it, I think it reflects a bit how abstract you go if you start talking about like gene modules and scoring these patterns of selected genes, it can go a bit more abstract.

But I guess here we try to be very descriptive and just focus on quite simple [00:35:00] things really. If you look at this cell in the outer layer of the skin, does it have these classical markers of a innate lymphoid cell three, for example. And so showing that in the single-cell data where it's, the tissue's broken apart and then showing it spatially, you're pretty sure it's the same cell.

So I think it does depend a bit how abstract you get, but I think a nice thing is that, yeah, as a community, there's lots of people working on trying to optimize it. And here we've, we're very descriptive and quite simple. So yeah, I don't think there's anything else to work. Yeah

Hashem: ~~Yeah, sure.~~ And also, I guess it basically highlights the importance of a validation at each step to make sure that at least you are mitigating the errors ~~or you are-- you know what you're doing.~~ For the final part of this episode, I would like to discuss a little bit importance of multidisciplinary research and collaborations.

This study sits at the intersection of dermatology, immunology, spatial genomics and AI. What were the biggest challenges and perhaps [00:36:00] advantages of bringing together such a multidisciplinary team around a single biological question and to implement it and deliver it?

Lloyd: Yeah, I would say for me in this project fortunately weren't too many challenges of that regard. I think because of the institute, so the Sanger Institute, I'm sure it's true of other institutes. Just having lots of people with different expertise, like co-located. So for example, I could never run or generate the spatial data myself.

It's a challenging task for me. So being able to work with a spatial genomics team here was like very useful. There's also people with expertise in AI, im- immunology. So I found like having these teams in the institute to be really helpful and fortunately there weren't any challenges o- of that.

But there are definitely there are advantages. You rely on these people's expertise. Like we could... I could never do this project alone 'cause there's so many different aspects to it. And so having this multidisciplinary team of people with expertise in immunology, [00:37:00] spatial genomics, AI, allowed us to do this project.

I guess you see this more and more in this type of research, like having multidisciplinary teams. So I think it's yeah, really important

Hashem: Yeah, perhaps not in your study, but, some challenges may be like the people from different disciplines to understand the language of other disciplines to be able to communicate with each other. Or how they are playing their parts and also getting credit for what they do.

Yeah, making a culture and environment that people feel shared and feel rewarded. It's something that needs to be considered in order to make a project at this scale very successful and deliver effectively. The work combines cutting-edge experimental platforms with generative AI and graph neural networks.

How important do you think it [00:38:00] is that future immunologists become computationally fluent, and conversely, that AI scientists deeply understand biology? Or at least, to a good level they understand biology to be able to communicate with each other well.

Lloyd: Yeah, I think this is a good question, and I guess relevant to how you train the next generation of scientists, right? Because you have this technology that's increasingly being used at a broader scale. So then, yeah, what's the exact skill set that you encourage people to have? I've definitely found being in two labs at the Sanger, so Mazana for Mulofalat yeah, like what you said earlier about having the language to communicate or being able to understand.

I think that's a really valuable skill, and I think that requires learning some degree of the other field. I guess the more the better, but I don't think you could be successful working with these different teams if you were purely in your area and you never made an effort to understand the language.

Yeah, I guess for me the language is a key point. Can you [00:39:00] formulate a problem in a language that both people understand? I think showing enthusiasm to learn, people always respect that whichever way it is. And those people I find it really easy to work with. Yeah

Hashem: So ~~a study,~~ studies like this generate an enormous amount of highly complex data. In your view, what is currently the biggest bottleneck for the field and for the community? Is it data generation, computational integration and interpretation, or functional validation or something else?

Lloyd: Yeah, I think probably data generation, although I guess you could argue each of these points. So here we consider it like a large scale representation of human scale, like 5 million cells. But actually maybe like to truly understand the result of these very rare cell types, maybe you need 500 million, 5 billion.

Like you don't really know where the cap is. I guess it's quite very commonly said, but AlphaFold being this very good example of how [00:40:00] data generation was key, of collecting the data over decades that cost billions roughly to generate. But you could never make the model without that data. So I think for me, like the data generation is a big aspect to it.

And definitely yeah, in the AI side as well. So I think I recently came back from like a AI conference and like the scale of the data they use is just so different to what we even in like single cell field use. So I think in terms of biology, I think that's our big area

Hashem: Okay. Based on your experience at this, at the heart of this multidisciplinary research, do you think the biologists and healthcare researchers are embracing AI the power it offers at a speed to keep pace with rapidly transforming AI and data science developments?

Lloyd: Yeah, I think it probably varies based on the lab, right? Like the engagement you have or how you want to do it. I definitely think the, there is quite good engagement for biology. [00:41:00] I think also it's worth noting, like there is this like hype around AI, like justified, but still there's this hype of if you start putting AI in your work me- especially if like people aren't like experts in that field it could be received very well when you propose it because of impacts people have seen of AI in different domains.

So I would say the engagement is quite good. But also there's this about being realistic about currently what AI can deliver in biology and single cell biology. I think that's also important because maybe you get too much engagement and everyone's doing AI and then being able to understand how you use it

Hashem (3) (2): But looking ahead, where do you see the greatest opportunities for a spatial AI and Atlas scale biology to transform medicine, not only in

inflammatory skin diseases, but more broadly, for example, chronic diseases or human immunology?

Hashem: ~~Sure. But looking ahead, where do you see the greatest opportunities for spatial AI and atlas scale biology to transform medicine? Not only in inflammatory skin diseases, but more broadly ac-across human immunology and perhaps chronic diseases~~

Lloyd: Yeah, I think I guess maybe biased by my own like background, but I think disease and [00:42:00] drug discovery is a big one. Like just seeing how these drugs have changed practice, like this idea of being able to develop drugs more quickly, understand diseases in more detail. Yeah, I guess cancer is a big one, right?

Like just getting greater insights into human immunology in cancer, being able to modulate that. I think it's a great opportunity for these sort of spatial maps and atlas biology because I think they do show these new insights into exactly what's happening that you couldn't get before. And I don't know exactly where it will go, but I think quite broadly there is this recognition of how powerful it is.

And so there are big initiatives that generating this data that help to tackle these problems. So yeah, I don't know exactly where it'll go, but it's definitely exciting

Hashem: Okay. You partly pointed to my next question, but I'm going to ask more specifically. In the field you work on, what do you think is the next AI breakthrough, and what do you want or like to be the next AI [00:43:00] breakthrough?

Lloyd: Yeah, I get it. I think it could go so many ways. I think an interesting one is robotics. Like being able to automate these lab procedures that can help generate data in a different way. So I've been talking a lot about just human disease and then profiling that and trying to understand it, but obviously there's a lot of interest in being able to understand how do certain cells react to certain chemicals or stimulation.

And then you can get a, an idea of predicting future targets, changing cell states between them. And I guess in, in Maz's, Mazanaffar's lab there's a lot of people doing skin organoid work, so like growing human skin from stem cells, and you get the, almost the entire structure without immune cells.

But obviously it's very labor intensive and I'm in awe of what they do. But this idea of having robotics to automate these sort of pipelines to then make data generation easier in a more sort of interventional way or causing these perturbations, measuring the response, I think that will probably allow us to go from...

Will be [00:44:00] important in going from this sort of observational work that I've been talking about to then causal work and understanding exactly what elements of the pathway do. So I think robotics, but I think the exciting thing is there's so many other arguments you could put forward

Hashem: Yeah it's surely it's a lovely study. It's very rich, and we can actually speak for ages, but I'm afraid because of the time, we have to end it here. So is there anything in this study that you think I haven't covered and you'd like to finish off with that?

Lloyd: No, I think you've covered everything really. I think I'm, was key, as keen as possible to just try to keep the study quite simple. Just take the human tissue and then look at it in much more detail than you could before, like a spatial map of this. I think you put it quite nicely earlier, like this molecular detail that you couldn't see before.

I think that's quite like a simple concept. It doesn't make it too strange, and I think it, yeah, I think it does give you new insights into how these diseases [00:45:00] are-

Hashem: Yeah. ~~I,~~ the the final question is that is there anything in this study that I haven't covered and you would like to finish off with that?

Lloyd: Yeah, no, I can't think of anything really. I think you, you covered it pretty well in that we try to keep... I try to keep this concept very simple of just going from a tissue that we see on H&E and then mapping this new molecular detail to it, and how that gives us new understanding. Like seeing these new cell types, how they interact in different diseases.

Yeah, I... If anyone had any questions, I'm happy to answer them. But yeah I quite like it as a simple concept.

Hashem (4): Thank you so much, Lloyd. It has been a real pleasure having you on board and discussing this fascinating study with you. Congratulations to you and to the team again on this excellent work, and we wish you every success

with your future research. And thank you for listening. I hope you [00:46:00] enjoyed this episode and found it both informative and thought-provoking.

If you did, please consider sharing it with colleagues, students, and anyone who may be interested. And if you would like to stay connected, please join ImmunoIntelligence community, where we share open access webinars, podcasts, educational resources, and discussions at the intersection of immunology, data science, and AI.

Until next time, thank you so much and have a good time

/