Treating Inflammatory Diseases by Blocking Neutrophils Moving from Bone Marrow with James Mackay Aristea Therapeutics
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Karen Jagoda: Welcome to the EmpoweredPatientPodcast.com Show. I'm Karen Jagoda, and my guest today is James Mackay. He's the Founder, President, and CEO of Aristea Therapeutics, aristeatx.com. James, I want to welcome you to the show today. I appreciate you taking a few minutes to be with us.

James Mackay: Karen, thanks very much for having me on the show. I'm looking forward to talking with you.

Karen Jagoda: Thank you. Let's start with a bit of a discussion about the mission there at Aristea and what your area of focus really is.

James Mackay: Yes, we founded Aristea Therapeutics four years ago in August 2018. We're a clinical stage immunology focused drug development company with a specific focus on developing treatments for serious inflammatory diseases.

Karen Jagoda: I've been talking to a lot of people recently about inflammation. And it seems to me that one of the entry points that you all are using is the neutrophils cytokine receptor that's kind of at play here when it comes to inflammation. So can you tell us what neutrophils are and what role they really play?

James Mackay: Yes, sure. So neutrophils are cells that are part of the immune system. They sit in the bone marrow, and then when there's either an infection or an inflammatory response in the body, the neutrophils are attracted out of the bone marrow to the site of infection or inflammation. In inflammatory diseases, what you often see is extremely large numbers of neutrophils accumulating at the site of the inflammation, which obviously causes some challenges for the patients.

James Mackay: And in our particular case, we have a drug, it's called RIST4721, which is a CXCR2 antagonist which actually blocks the neutrophils moving from the bone marrow to the site of inflammation. And we believe that this is potentially a way to treat a whole range of serious inflammatory diseases.

Karen Jagoda: And one of the first diseases you're looking at is a rare skin condition. Can you tell us a little bit about PPP?

James Mackay: So PPP is the much easier abbreviation for the full name, which is palmoplantar pustulosis. It is a relatively rare inflammatory skin condition. The patients get what are called multiple flares every year. And when a patient gets a flare, they get these outbreaks of sterile, neutrophil-filled pustules on the palms of the hands and the soles of the feet. Doesn't affect any other part of the body. And these pustules will appear on the palms of the hands and the soles of the feet. It's an extremely painful condition.

James Mackay: Eventually, the pustules dry out, and the skin cracks open. And then, normally, before the skin has had a chance to fully re-heal, the patient will then have another flare. They will get another outbreak of pustules. So you basically get flare upon flare upon flare, and the skin gets worse and worse over time.

James Mackay: And it's extremely debilitating, obviously. If it's on your hands, it's very difficult to do just normal everyday things. If it's on your feet, many of these patients struggle to even walk. So a very debilitating condition. There are no approved treatments for this in either the US or Europe. There are about 175,000 PPP patients in the US, so although a rare disease, it's one of the larger rare diseases. And we believe that our treatment, which stops the neutrophils from moving from the bone marrow to the epidermis on the palms of the hands and the soles of the feet, is a potentially good way to try to treat this disease

Karen Jagoda: Who is most likely to be affected by this condition?

James Mackay: So it's very interesting as 85%+ of the people who get this disease are females, mostly postmenopausal females. And then also very interesting, 90%+ of the patients either are current cigarette smokers or have got a history of cigarette smoking. So there's definitely a direct link to cigarette smoking. There's not much basic research been done on PPP, so the exact reason for that is not clear, but we believe, based on some of the research, that it's due to the nicotine receptor in the sweat ducts on the palms of the hands and the soles of the feet. And the sweat ducts on the hands and the feet are different structures from those elsewhere in the body, which is why this disease probably just affects the palms of the hands and the soles of the feet.

Karen Jagoda: I was going to ask you why it would just affect those parts of the body, so thank you for clarifying that. Tell us a little bit more about how your molecule is thinking about the problem in a new way.

James Mackay: So this is a unique mechanism of action for this disease. Most of the potential treatments that have been tested in PPP have already been approved for more generalized psoriasis treatments. And most of those are biologics, so they're targeting single, individual cytokines, whether it be IL-1, IL-17, IL-23, or IL-36. And what we find with those drugs, in general, is that they don't work consistently across a large group of patients. Some patients may receive some relief for some time, but in general, that relief either doesn't last or is inconsistent across the patients.

James Mackay: We believe that's probably because of the redundancy in the immune system. So, if you target any one of these individual cytokines and block that immune pathway, because of the redundancy in the immune system, it's likely that another pathway will be activated and ultimately result in the inflammation that's the basis of these diseases. And that's why we believe that our approach, which is moving upstream, so in a sense becoming less specific than targeting those individual cytokines. If we move upstream and actually target the neutrophil as the key mediating cell in these diseases, we believe that we stand a better chance of getting some relief for these patients of these rather difficult-to-treat diseases.

Karen Jagoda: And based on your current clinical trials, what is the method of treatment? Is this a one-shot deal? Is this a continuous, everyday kind of approach?

James Mackay: Conditions like PPP are chronic conditions, so once the patient has the condition, they've basically got it for life. Any treatment that's going to be effective in treating these diseases is going to have to be dosed chronically, so the subjects are going to have to take it every day. The treatment that we are developing is an oral small molecule, so it will be delivered as a tablet once a day to these patients. And basically, if they start taking the drug and the drug works, then they'll continue to take the treatment for the rest of their lives.

Karen Jagoda: And do you think there are any genetic biomarkers that would indicate who might benefit most from this kind of treatment?

James Mackay: As I indicated earlier, not much basic research has been done on PPP. We are actually sponsoring some research with one of the leading PPP researchers, Dr. Murakami in Japan, which we hope will generate some information that will help that. What we're also doing in our clinical trial is that we are collecting blood samples all the way through the clinical trial, and we will analyze those for biomarkers at the end and try to correlate those with the results of this study.

James Mackay: Then, in addition to that, we're also utilizing a technology called tape stripping from a company called DermTech, actually also based here in San Diego, where we are, and that allows us an alternative to biopsies. Biopsies, of course, are pretty impossible to do on these patients because they're in so much pain already. But the tape stripping actually allows you basically to strip off multiple layers of the cells, and then you can analyze those tape-stripped cells in order to look for a genetic signature or biomarkers in the skin. And we'll do that as well as doing all the blood analysis. We're doing a fairly large Phase 2b study right now, so I hope that with the number of patients that we're looking at, we'll be able to develop a pretty rich collection of biomarker data that will really inform us and put us in a better position to answer a question like that going forward.

Karen Jagoda: Thanks for that explanation. I'm wondering, are there other neutrophil-mediated inflammatory indications that you're also looking at or that your current work will lead to more understanding about?

James Mackay: Yes. So PPP is our lead indication. First of all, we licensed this molecule from AstraZeneca. I was a long-term AstraZeneca executive and was with the company for nearly 30 years. And our molecule, RIST4721, I'd always liked that molecule. And when AstraZeneca decided to stop the development of that for a completely different indication, respiratory indications, a number of years ago, I kept my eye on that molecule, and we licensed that. And we knew exactly how the molecule operated. As I said earlier, it stops the neutrophils from moving from the bone marrow to the site of inflammation.

James Mackay: So once we'd licensed the molecule, we basically started searching through the scientific literature for diseases where there was really strong evidence that the neutrophil was the key cell in terms of the inflammatory response. And we identified a group of diseases called neutrophilic dermatoses, which affect the skin, and then narrowed that down to palmoplantar pustulosis, or PPP. But if we continue to see good evidence in PPP, then the probability of the drug working across a range of neutrophil-mediated skin diseases increases.

James Mackay: And we are actually doing a Phase 2a study in another inflammatory skin condition called hidradenitis suppurativa, or HS. And that study is underway already. And then basically, going through the literature, we also identified a couple of rheumatology diseases, familial Mediterranean fever, or FMF and Behcet's disease. Again, both with strong evidence that neutrophils play a key role. And we're in the process of setting up Phase 2a studies for both of those diseases. So we are looking across a range of four diseases right now, but there's certainly utility far beyond that if we continue to see good efficacy in these studies.

Karen Jagoda: How well are neutrophils really understood, do you think?

James Mackay: Neutrophil biology is very well understood. So we understand exactly how the neutrophils are attracted to the inflammation. We know exactly how they're activated. And one of the nice things about our molecule is that, as I said earlier, it blocks CXCR2. And CXCR2 plays a key role in attracting the neutrophils to the site of inflammation. Our molecule does not, however, block CXCR1, which is required for activation of the neutrophils if there's an infection, for example, that needs to be fought.

James Mackay: So although we reduce the number of neutrophils that are circulating in the body, those neutrophils are still active. If for some reason a patient experiences an infection, then those neutrophils that are there can still be activated by CXCR1. And we see that as a safety advantage compared to molecules that block both CX1 and CXCR2. So I think neutrophil biology is extremely well understood and provides us with a solid platform to move forward and try and treat some of these neutrophil-mediated diseases.

Karen Jagoda: Thanks for that great background. I'm wondering if we could just talk for a minute about the San Diego community for biotech and drug development, and where do you see the growth really coming from in this community?

James Mackay: I've been in San Diego for nearly ten years now, and it has one of the most amazing life science innovation ecosystems. I think the last report I saw indicated that there are over 500 small biotech companies in San Diego. And combine that with the incredible universities and research institutes that we have and the very collaborative nature of the San Diego environment, and I think it creates a great opportunity for there to be continued development in the life science space. I mean, I think we're number three, behind Boston and San Francisco. And that innovation ecosystem, together with an equally impressive tech innovation ecosystem, continues to develop.

James Mackay: And I've been involved for a number of years with an innovation accelerator here in San Diego called CONNECT that really helps to mentor entrepreneurs who are setting up either tech or life science companies. I'm currently Chairman of the Board of Directors of that. Back in April, we held San Diego's biggest ever innovation event, celebrating all the innovation that's taking place in San Diego. And we plan to do that on an annual basis. We continue to see significant numbers of venture capital dollars being invested in San Diego companies. In the last five or six years, that's gone up from $1 billion to $9 billion a year. So we are seeing tremendous growth here, and I think that is just going to continue.

Karen Jagoda: My last question before I let you go. I'm just wondering, given your background in big pharma, what's changed the most in drug development and commercialization?

James Mackay: I think it's interesting over time. Big pharmas used to have their own discovery organizations. You see more and more that big pharma is relying on small biotechs to do that innovation. Then they are either licensing those products or buying those companies and then taking those potential medicines into the big pharma for the final stages of the development process. Of course, big pharma is extremely well set up to conduct these very large, global clinical trials.

James Mackay: And then, of course, they're very well set up to ensure that the manufacturing is done properly and that they've got a strong commercial platform in order to launch the product and get those to patients. So I think that we'll continue to see big pharma look for innovation from small biotechs, and certainly, having moved and created my own small biotech. We are a small company. There are only nine of us in the company, all very experienced drug developers. But you can do things extremely fast in a small company, and I think it really allows the innovation to thrive.

Karen Jagoda: Thanks to my guest today, James Mackay, Founder, President, and CEO of Aristea Therapeutics, aristeatx.com. Follow them on Twitter @aristeatx. I'm Karen Jagoda, and you've been listening to the EmpoweredPatientPodcast.com Show. Follow me on Twitter @karenjagoda. Like us on Facebook at Empowered Patient Radio. Thanks for listening, and we'll see you next time.