

**Voiceover:** The *BioWorld Insider Podcast*.

**Lynn Yoffee:** This is the *BioWorld Insider Podcast*. I'm Lynn Yoffee, BioWorld's publisher. When the CEO of Cambrian Biopharma watched his grandfather fail every cancer treatment and eventually pass away, he came to a realization that now forms the backbone of his company. James Peyer said, the more he learned about cancer, the more convinced he became that approaching cancer as a disease was wrong. He said we shouldn't wait until people become sick to do something. Peyer has described his own company as focused 15% on moonshots and 85% on longevity innovation.

The firm is developing multiple anti-ageing therapies, all of which are at the preclinical stage, very early. He built Cambrian with a unique business model, one that fits the new field of geroscience. Today, Lee Landenberger, a staff writer for BioWorld, is speaking to him about the company and how it fits into the new field. Over to you, Lee.

**Lee Landenberger:** Thanks, Lynn. James, thanks for joining me. I remember talking to you in October of 2021 when you got your Series C and it's good to chat with you again.

**James Peyer:** Hi, Lee. Great to be here in, nice to talk to you again.

**Lee:** I think this story about the death of your grandfather's instructive and you talked about the approach that medicine has taken and that it's done a disservice, you told me, by the conflation of two things. What drugs could actually do for patients and then there's the philosophical science fiction-like obsession that mankind has with slow ageing. That's a long way of saying you built this company to fit this new field, that of longevity. Could you talk to me about geroscience and what Cambrian's mission is?

**James:** Absolutely. I think that the distinction that you made between the way that this new field of science can actually turn into drugs and help patients versus this philosophical and sociological fascination that we have as a society around extending human life is the right place to start here. Cambrian takes that second piece around what would it mean to dramatically extend human life? We basically pushed that into the, maybe science will figure that out someday, but that has nothing to do with what science is telling us right now.

My fascination in the way that we built this company is around this deeper understanding that the academic study of what at the cellular and molecular level goes wrong with our bodies as we age, that presage disease. How can we turn that new knowledge into medicines today? I think that's the animating thesis behind Cambrian and the whole pipeline that we've put together. The fascinating thing from my perspective is that many of these discoveries, at least when they start in mice, begin with an observation that you can make a single tweak.

Change one gene give one pharmaceutical intervention and dramatically extend the healthy lifespan of an animal model through the mechanism of preventing the onset of all sorts of diseases. Not just cancer and heart disease at the same time, which in itself is quite impressive, but also muscle frailty and bone weakness and memory

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and these sorts of things can all be delayed using some of these same shared biological mechanisms that become dysfunctional as we age.

The strategy that Cambrian is using to push forward these new discoveries and make them into real human medicines is to say, let's find at a molecular level what's going wrong and create a new tool that can fix those molecular changes that happen with ageing, that presage disease.

**Lee:** I'm curious, so you would take somebody when they're younger, but before they're sick and they don't have any symptoms or anything, so you would run tests on them to find out what could be wrong.

**James:** This is where we get then into the strategy of how we do this. There's been a lot of hay made or discussions had about this idea that ageing is not a disease and you'll get people actually on both sides of this debate. Some who say it is some who say it isn't. I'm strongly on the it isn't side. We can talk a little bit about what that would mean from a regulatory perspective, but the most important thing to understand about this whole field of possible preventative medicines. Doing what you were talking about.

Saying, let's try to find a healthy person and give them some type of medicine that could prevent them from getting sick, is that you would never want to start a drug development program there. The bar for safety for a preventative medicine has to be extremely high. At Cambrian, the way we've constructed our strategy is by looking to a few examples from the past. My favourite example here are actually statins because that's actually the closest thing we have to something that would be a geroscience science or a primary preventative drug for multiple diseases.

What is a statin? It's a drug that you would take to prevent strokes and heart attacks as complications of cardiovascular disease but statins didn't start going for primary prevention as their initial approval indication. They started going for familial hypercholesterolemia, a rare disease that caused a dramatic dysfunction of high LDL cholesterol that had some of these same complications come out of it. Cambrian is structured the same way. For each discovery that we make, each drug that we start moving into the clinic, those drugs will initially undergo safety and efficacy testing.

Eventually reach the market for specific disease indications that make sense within the standard biotech and regulatory box that we have today. Then once we have safety and efficacy data, we can start asking the question that you're talking about, how can we identify high-risk people for whom these sorts of medicines could be used as primary or secondary preventatives to prevent them from getting a disease instead of just reacting to it? Does that make sense?

**Lee:** Yes, it does. It's a whole new way of approaching this and so you design the company to fit this unique model. It's a bunch of things. It's a company that's a biotech. It's also a venture cap fund which you have a background in and it also is an incubator so could you talk to me about how all that comes together?

**James:** Sure. I would say at the high-level Cambrian is just a biopharmaceutical company. The way that we're structured is as a biotech, but we've made a number of, let's call it business organization decisions to create something that is a little bit

different than a standard biotech. Like you said, we have elements of what's working well in the VC company building world elements that are working well, even in the big pharma context of creating deep expertise around specific indication areas, investing in drugs for a very long term and elements of a scrappy entrepreneurial biotech.

We've taken the best elements of each of those three worlds that live within our industry and pulled those pieces together to create what we call a distributed development company, which is what Cambrian is. There's a single, we call it the Nexus, which is Cambrian, which holds majority but not 100% stakes in a bunch of different subsidiary companies. We call them pipeline companies that are partnerships usually with universities and scientists who have made fantastic discoveries related to the biology of ageing.

Then we keep those scientists involved with a company as we deploy expert drug development personnel to come in and pair with them to build a specific biotech going after a specific disease indication and ultimately after prevention. This allows us to get the diversification of venture capital fund, but also the deep expertise and flexibility of an entrepreneurial biotech with the long-term vision of a big pharma company.

**Lee:** Talk to me about your pipeline. I want to make sure I understand because it sounds like, if I understand correctly that each pipeline candidate would have its own company..?

**James:** That's right. We have 15 different drugs under development at Cambrian currently held across 10 different pipeline companies. Some even have more than one and it's more based around a group of shared mechanisms. For example, we have two rapamycin analogs that are in development entering IND-enabling work now and both of those assets live in our pipeline company, Tornado Therapeutics. It's not one-to-one, but our 10 subsidiary companies are developing 15 drugs.

**Lee:** Got it. So are the rapamycin candidates the most advanced ones?

**James:** As far as we've announced, yes. One of the advantages of our system is that we don't need a very early-stage biotech.

We don't need to be broadcasting everything that we're doing out into the wider world at all times because so many early-stage biotechs have to spend so much of their time and energy on just worried about raising funds all the time. A big part of our thesis is let's put money to work, go produce science and not worry about the PR or making a big announcement every time a program moves forward. At the start, Lynn mentioned that we're preclinical stage. That's actually not even true anymore. We actually have some clinical-stage programs, we just haven't announced them yet.

That may be coming by the time this comes out or a little bit later but yes. The short version is it's one of our more advanced, but Cambrian is on track to have six clinical-stage programs that will all be announced by the end of 2024. That's right. That one we started talking about but it's only of the 10 that live under Cambrian-

**Lee:** And you just launched a new company – Isterian, is that right? Can you give me some details on that or you're keeping mum on that one too?

**James:** That one we've started talking about but it's only...of the ten that live underneath Cambrian we've actually only announced four and Isterian was the 4<sup>th</sup> one. So, Isterian is a really very cool project. It's a partnership with a group at the University of Aston in Birmingham in the UK. A group there led by Martin Griffin who is a professor that has been spending the majority of his career interested in the cross-linking of the extracellular matrix. What we found is that there is this enzyme called transglutaminase 2 or TG2. TG2 is responsible for the majority of what are called enzymatic cross-links that happen during the onset of fibrosis.

When we try to create a scar, the body wants to patch up an abrasion or some injury to a tissue as fast as possible and they just lay down a bunch of collagens and other extracellular matrix components and then an enzyme like TG2 will bind them all together covalently through this process called cross-linking. Then once you have that fibrosis set in or that scar set in, the way it transitions to a pathological fibrosis is by continually taking this disordered extracellular matrix and patching on more disordered ECM components to that already disordered bunch.

What we found is that if you push the pause button on this enzymatic cross-linking by inhibiting TG2, it actually gives the body time and space to disassemble the disordered extracellular matrix scar and rebuild it much more slowly now that there's no longer an active wound with healthy well-ordered ECM. We've now worked in four different preclinical animal models of disease where we've been able to show that we can repair established fibrosis by inhibiting enzymatic cross-linking.

It's a great story tying back to this geroscience or science of ageing hypothesis because one of the things that was early on our radar is one of the changes that happens in all of our bodies as we age. We begin to shift away from producing new young ECM components and more towards trying to cross-link older extracellular matrix proteins which causes stiffness and brittleness in our ECM. We got interested in this mechanistic hypothesis around the biology of ageing and that helped us find a new drug candidate that's useful in fibrotic diseases.

**Lee:** I'll put you on the spot. When do you expect to get into the clinic? It's okay to say, "I can't tell you."

**James:** I think there's a number of variables here, still. We've got a few--

I don't think I'm revealing too much here but we've got a few different lead series now. We've got great in vivo animal data but this is again one of the strengths that I think of the model at Cambrian is that whereas a traditional biotech would probably push to overpromise and underdeliver. Like we could move into the clinic next year if we wanted to but that might involve taking a lot of risk on, is this actually the right candidate that will serve patients best or could we take another six months and do more medicinal chemistry and a little bit more pre-clinical de-risking and then structure a better trial.

I'm not going to make a promise, but it's not this year for sure. I think one of the strengths of Cambrian is thinking about all of this IP generation and each drug as

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asking how do we do the most cost-effective de-risking of an asset as opposed to just saying, how can we get into the clinic as fast as humanly possible so that we can raise money as a clinical-stage biotech. I think those types of incentives are destructive.

**Lee:** Right. Hey, I wanted to ask you about that about fundraising. I'm guessing that the fundraising process for this company is different than that of a traditional biotech. Can you tell me about some of the differences that you make encounter? I also was curious about are there particular things that investors have real questions about because they're probably not used to coming up across this kind of a model.

**James:** It is pretty different. Let me take those two separately and if there's kind of a more wide-ranging conversation we have there, we'd be happy to have it. On the how we go about fundraising side, the key element for me on this is that we have 10 different programs developing 15 different drugs that live underneath Cambrian, but we only really need one person running around talking to investors about raising capital and all of that capital with only a few exceptions goes into Cambrian. We can just raise as a single monolithic biotech company, which is what I was saying before that the way that we're structured in the way that we're run is that we're just one company.

That saves so much time, energy and distraction because as you mentioned a bit earlier on my background was actually in starting and running a company-building VC firm before I created Cambrian. One of the things that really got under my skin was how much time executives of early-stage companies have to spend wringing their hands and greying their hair around worrying about fundraising for the next tranche, the next milestone, et cetera. As they're wringing their hands how much incentive there is to design poor experiments.

This is the thing that gets me the most is if you want science to be appropriately de-risked, then an investor and an entrepreneur or a scientific founder and an operational team in our case have to be able to sit together and say, "Here's our clear hypothesis. Here's the experiment that we're going to design in order to make a go or a no-go decision on that hypothesis. Here's how much money it's going to take to get us there. Let's just give a thumbs up on that money and go run that experiment."

As opposed to needing to construct a narrative of why this is going to be the biggest drug on the market and why this phase one trial or this preclinical thing has no real risk attached to it and sell that whole bill of goods or that potential. Then later with some investors, the good ones then later sit with those folks and say, "Now let's design the right experiment." I felt that that set of incentives is so pernicious to the industry.

It's one of the reasons that I felt a new business model like the one we have in Cambrian was needed to improve the efficiency of early-stage drug development in a way that VC company-building is doing better than pharma companies, but it's still really messy with a bunch of room for improvement. I think that's the how we go about fundraising part. I don't know if you want to double-click on anything there. I'm

also happy to touch on the second piece around what's different as we talked to investors.

**Lee:** I'm curious. You probably get some raised eyebrows and I'm curious what kind of questions that a potential investor might be asking you.

**James:** I would say similar to how we started this conversation, with these two different worlds of people who look at longevity from the very practical, technical problem of 'how do we take these discoveries about the biology of ageing and get them to patients in some way' on hand number one. Then on hand number two, should we extend human lifespan and how would we do that? I think that when I talk to investors, I see people coming from those two camps towards this center point that is Cambrian and as a society, I think we've become more and more interested in this topic of longevity.

I know you guys have done another podcast on this, I've talked with Annette from your team at BioWorld, a couple of times before, as so many groups within the industry and also outside of the industry are just fascinated by this idea of, could we do something about slowing ageing? I think for people coming to me from that world of like, "Hey, we heard that Cambrian is the leading company working on building drugs that can slow ageing, how do you do that?"

The main thing that I have to do to those groups of people is say, "Okay, well, look, here's how we take this big idea of building a drug that could prevent multiple diseases, and then turn that into a business model that makes sense to invest across VC timelines today. That can make sense in the existing regulatory environment and doesn't take absolutely gigantic pile of risk of trying to develop some preventative medicine or some "anti-ageing" drug and just throw it into the ether."

I think that's probably the first piece of talking some really visionary type investors away from saying, "Oh, yes, this is just an easy thing that some big company's going to be able to come in and achieve this moonshot." The second kind of group of investors that are the more technical and practical folks that are used to looking at therapeutics companies today, the conversation that I have to have with those folks is oftentimes why it's worth it to focus on the long term.

Let me explain a little bit of what by that, because, again, it gets to one of my reasons for creating Cambrian the way that we did and a discomfort around how the existing model works. Is that in a standard biotech plus investor relationship, you have an expectation of saying, "All right, well, we're going to take this drug, or we're going to take this hypothesis, and we're going to move it forward hit milestone X, milestone Y, get into the clinic, produce some nice data."

Then either you go public, or you sell to a pharma company, but in both cases, the investors that supported you through X and Y, are basically selling their shares, returning that to their investors, and then recycling that capital into new early-stage programs. One of the things that gets under my skin about that model is it becomes extremely hard to invest in long-term goals with that early-stage capital.

Because by the time that you've passed that risk off to public market investors, or to a pharma company, the small investments that you might have been doing at the early stage to say, enable a second set of trials and expand your indication into something like primary prevention, that's not going to get realized for any value by that point. One of this other side of conversation is why we need a platform like Cambrian's in order to enable these kinds of investments and even stuff like biomarkers and observational studies, at the early stage.

To enable these prevention studies that can happen 5 or even 10 years down the line. If we wait to do this early stage discovery work, early stage enabling work to look at these as preventative medicines, we can save ourselves five years later down the line, once we actually know that this drug is going to be successful for its first little what we call a stepping stone indication, it's first safety and efficacy data. I just don't see that happening elsewhere in the industry.

**Lee:** James, when you are looking ahead, a unique business model, and you've got pipeline candidates and you're in the clinic and you're looking at the space, what is it that you see in the relatively near future?

**James:** I think the milestones for this field are first and foremost the demonstration of robust safety infancy data in existing, understandable, clearly regulated disease areas like fibrosis that we talked about before, cardiometabolic disease, oncology, muscle wasting. These sorts of things that are real indications that will come out of basic biology and academic discoveries around how our bodies have changed or how our bodies degrade as we age. I think that's the first set of near-term milestones that this field is delivering on right now.

That we see, and are pretty excited about underneath the hood at Cambrian. As you move forward not in the 2 to 3-year timeframe, but in the 5 to 10-year timeframe, that's where this fascinating shift will start happening that we are talking about a little bit today, which is all right, now you've got a drug that is number one, safe, and effective at treating a specific disease. Number two, has the potential to be a multi-disease preventative, like a statin, but something that could prevent cancer, heart disease, Alzheimer's disease, and age-related frailty, all at the same time.

Now, how do you design and start a trial, going after a drug with a potential like that, that you could then start giving to healthy or elderly at-risk people in order to, again, be proactive instead of reactive to these diseases of ageing? That's the timeline that these trials will get underway, but the only way that they will get underway in that second half of the 2020s timeline is if we put the thought, money, and time into planning for that potential today, which is what Cambrian is all about.

**Lee:** We want to wish you the best of luck and thank you very much for your insights, and your time. I look forward to seeing what else comes out of the company.

**James:** Thanks, Lee. I appreciate it. This is a fun conversation.

**Lee:** Lynn, back to you.

**Lynn:** Thank you, James and Lee, for these insights. James, the business model is extremely compelling. We've certainly seen a lot of companies over the years with

terrific science that have failed in the long run, but Cambrian's business model is truly compelling. For our listeners who would like to learn more about this topic, check out BioWorld's multi-part series, called Extending the Human Lifespan. The team examined the latest science, the key biological drivers that can be targeted pharmacologically, and the company's developing potential fountain of youth candidate drugs.

We'll include a link to that special report alongside the podcast. As always, BioWorld will continue to keep you informed of all the most important scientific, clinical, and business updates. That's our show for today. If you need to track the development of drugs turn to [bioworld.com](http://bioworld.com). Follow us on Twitter, and you can e-mail us at [newsdesk@bioworld.com](mailto:newsdesk@bioworld.com). If you're enjoying our podcast, remember to subscribe. Thanks for joining us.

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