

# Denali Therapeutics: defeating degenerative diseases

**Ryan Watts (RW):** I imagine a future where our health span is increased. We are able to die with dignity. We're able to comfortably live in our own homes until our last days.

**Tom Slater (TS):** And it's rare to have that academic and scientific track record, but combine it with that drive, that execution ability, to turn that into a company and to grow that business.

**RW:** A large number of big pharmaceutical companies completely exited neuroscience. And we founded Denali, basically, already swimming upstream.

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**Claire Shaw (CS):** Hello, and welcome to Invest in Progress, a podcast brought to you by the Scottish Mortgage Team. I'm Claire Shaw, a director and investment specialist. This podcast is designed to give you a behind-the-scenes look at the conversations that take place between our managers and the visionary founders, entrepreneurs and business leaders of the world's most exceptional growth companies.

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As we are a UK investment trust, we can only market Scottish Mortgage to certain audiences and in certain jurisdictions. Check out the podcast description to ensure this content is suitable for you. Also, please bear in mind that as with any investment, your capital is at risk. Today, we're looking at Denali, a company tackling one of the greatest medical challenges of our time, neurodegenerative diseases like dementia.

One in three people born today will develop dementia and that's a condition far too familiar for families all over the country who have to witness its heart-breaking effects. For Alzheimer's disease, the most common form of dementia, there is currently no cure or ability to slow the disease. Finding a treatment is paramount. Denali is aiming to do just this and tackle other diseases of the brain, such as Parkinson's and motor neurone disease.

To discuss this potentially game-changing company, I am joined today by Scottish Mortgage manager, Tom Slater. Welcome, Tom.

**TS:** Thank you.

**CS:** This is something that's extraordinarily hard to do. Big pharma has spent billions and failed in this area. Why has it been so difficult?

**TS:** It's been difficult for a combination of reasons. Firstly, our understanding of the genetic and molecular basis of the disease has been lacking. Second of all, it's been very

difficult when you've developed a drug to actually get it into the human brain, because there is a mechanism called the blood-brain barrier which prevents unwanted substances for getting into the brain. And then the third piece is that it's been very hard to test if a drug was working, because you can't biopsy the brain in the way you might biopsy a tumour.

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CS: Must take a pretty exceptional individual to lead a company, who's trying to address this massive problem. Which brings me to our guest today, who's the co-founder and CEO, Ryan Watts. Tom, tell us a little bit about Ryan. When did you meet him? What were your first impressions of him?

TS: We first met Ryan in 2015, 2016. And I think what will come across is he's a really driven individual. But the other thing that was immediately clear from his scientific credentials is just how important the work he had done as a scientist was in this area. And not just him, but some of his co-founders as well. It's the combination of the drive and the scientific understanding.

CS: I'm sure we'll see his passion and motivation come through in your discussion with him. But as usual, we'll catch up after. But until then, I will leave it to you and Ryan.

TS: Thank you very much for doing this.

RW: It's fantastic to be here, Tom. Thank you for the invitation.

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TS: We start by asking all of our guests the same question. What is the problem that Denali is trying to solve?

RW: The problem we're trying to solve is neurodegenerative diseases, Alzheimer's disease, Parkinson's, ALS and rare neurodegenerative disorders. My guess is that most listeners hear, at least one in three have someone they know and love that has dementia. If they have dementia, there's an 80% chance that that dementia is Alzheimer's dementia, an incredibly prevalent disease.

When we founded the company, we decided to think even bigger and not just focus on Alzheimer's, which is an enormous unmet need, but also on Parkinson's and ALS and other diseases in which the nervous system degenerates, in which the communicating cells in your brain start to die. And that spans a large number of diseases and a massive unmet need.

TS: I almost hesitated about inviting you on the podcast because the problems that you're trying to address are so important for the world that I'd hate using your time for anything else.

RW: I appreciate that. I should mention that I was hoping we would have done it on December 25th. That day, I know I have off, for sure.

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TS: Scottish Mortgage first invested back in 2016. But take us back before that time. What is it that motivated you to start a company to address this huge problem?

RW: There are a lot of motivators. And frankly, there are a lot of founders of a company like Denali. There are founding investors. There's founding scientists. I happen to be one of the, obviously, founders of the company, and both scientist, investor and employee and all the above. And for me, it was deeply personal. I had started my academic career working on the nervous system. I was very interested in the brain, how it works, how it functions.

But what happened is a couple personal experiences. I think the first, probably most compelling experience, is that my wife's family has a family history of Alzheimer's disease. And I remember her grandfather developing Alzheimer's disease. And it took me back and I thought, maybe there's an area I should start focussing on. And I was really lucky because at the time, I was working at Genentech and had focussed initially on cancer.

That transitioned into neurodegenerative diseases, which I worked on for a number of years. But the driving force for me personally, basically seeing my own mother start to develop dementia. And I knew exactly what was happening. I know my genetic risk. I know her genetic risk. It's imputed from mine. And I was like, I know what path that we're on. I think that that personal motivation allowed me to leave a place like Genentech that I think most people should never leave.

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It's such an incredible place. And actually, founded Denali in 2015. But you guys have been with us almost from the beginning. 2016 is just a year later. We were still in the early days.

TS: I think even at that stage, it was just clear how big the problem was that you're going after and also what an opportunity that was for a company that was able to make progress with this. But I think it's fair to say you've taken quite a different approach as compared to a traditional biotech start-up company. Could you outline how you've thought differently about it? And I guess, feeding on from that, how do you think that impacts the chances of success?

RW: I think one of the other co-founders, Alex Schuth, one of the things that he and I did is, for over ten years, we looked at every neuro company that had been formed during that ten-year period, looking for partnerships for Genentech. And we started to assess patterns and patterns of success. By the way, very hard to look at patterns of success in neuro companies because it's such an incredibly difficult space.

But one of the things we noticed is that, especially at the time of founding of Denali, you can't be focussed on a single idea or a single hypothesis. You can't found a company based on one molecule. The chances of that succeeding are extremely low. And we knew at the beginning, there are two things we needed. We needed a pipeline, which is basically multiple medicines. And we needed a platform, that if successful, would open up all of the nervous system, not just for neurodegenerative diseases.

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And that allowed us to go after, for example, some rare, even childhood diseases that have a neurological or a neurodegenerative component, where you know exactly what's causing the disease. And that has a much higher probability of success to prove your platform. And then you can go in parallel after Parkinson's and Alzheimer's and ALS. And the pipeline and platform concept, it was unique among the neuro companies that we had seen.

In fact, nothing at this scale of what Denali was trying to achieve. Obviously, we want to defeat degeneration. We want to solve Alzheimer's and Parkinson's. But if you look at success stories in biotech, it's a winding road and you have to follow the biology. And having a platform really is the, I think, way to success.

TS: And I think it explains how we got to know each other so early in Denali's journey. Because actually, part of being able to take forward multiple drugs or potential medicines at the same time and have that flexibility to follow the science means you have to have a big balance sheet. You have to have a big pile of cash in the bank, right from the start.

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RW: That's exactly right. And I think what that allows you to do, it allows you to fail, to iterate and to accelerate. It's a really interesting principle. You need the capital in order to get data really quickly and understand the direction. And we have had at least a dozen programmes that we stopped developing. Any one of those programmes would be a single biotech company. But because we had that capital, allowed us to really invest in the underlying science and the platform.

And I think, in addition to that, personal motivation, which it's not just me at Denali. We actually recently, interestingly, asked everyone at Denali how many of them have a personal connection to neurodegenerative disease. And I don't want to be exact, but it was 63%. It was an enormous number that had someone they love with Alzheimer's or Parkinson's... Majority of them were Alzheimer's dementia, really.

But the other piece to this, having that balance sheet, having that firepower, as we could build this platform. And I'll tell you the one area that I'm obsessed with is solving the blood-brain barrier. And the brain has been such a hard place to develop medicines for because medicines don't get into the brain very well. And that was the thing. It's like, if we could solve the blood-brain barrier and we could be passionate about neurodegenerative diseases, we would create a unique purpose, which is organised as a company to really solve these big questions.

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TS: Can you just explain exactly what the blood-brain barrier is?

RW: Absolutely. The blood-brain barrier, it comes down to what the blood vessels are like in your brain. The human brain has 400 miles of blood vessels. I probably should do this in kilometres, but I'll just tell you. Let me give you a perspective. It's basically San Francisco to Los Angeles. Again, I should pick European cities, but we're based in San Francisco. The blood vessels are everywhere inside the brain, but they're unique.

They evolved to basically exclude molecules from entering the brain. Anything that you need in the brain is actually physically actively transported across these blood vessels.

A good example is even sugar. In order to get into the brain, it actually has to be actively transported. Iron, we get iron from our diet and the iron is actively transported. In fact, we utilise some of these natural transport mechanisms like iron to cross the blood-brain barrier with our transport vehicle technology.

And this blood-brain barrier is established to protect the brain, but it also, unfortunately, limits the uptake of medicines across the blood-brain barrier. And hence the reason we needed to invent a platform or technology to cross the blood-brain barrier.

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TS: The blood-brain barrier is just that linking factor in all of these different conditions, the limiting factor for so much of what has been done previously?

RW: That's exactly right. And I think no one in science is trained to necessarily study the blood-brain barrier. It's not neuroscience and it's not vascular biology. It's actually the mix of the two. And I think that's where a lot of questions still lie in sciences when you're at the interface of two areas of biology or two areas of technology. And that's where the blood-brain barrier is.

TS: Talk about then how the company has evolved. Because there's a number of candidates that have fallen by the wayside as you've continued to follow the science and prioritise based on what you think is the most promising route. Talk through how you've got from that starting point to where you are today.

RW: When you joined us in 2016, we had our first medicine enter clinical trials. We now have seven medicines in clinical development. And notably, we have three that are in late-stage development, which is basically the last stages before a medicine will get approved. It's the big experiment. It's testing, will the drug actually work? And what we decided to do... And I think, Tom, this is probably a reflection of Denali.

We've actually done everything in parallel, in part because we're just super impatient. We have a Parkinson's disease programme that's now in a Phase Three clinical trial. It's actually in two large studies. We also have an ALS programme that's in a large study. We'll have a second ALS programme starting a large study in this coming year. And then we have our most advanced programme, which is in Hunter syndrome, which is essentially a Phase Two, Three trial in that disease.

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This broad portfolio, approaching in parallel. But the way we've managed the risk is actually quite interesting. It's hard to go into a global clinical study across the world in something like Parkinson's disease. We actually selected larger partners for some of those bigger disease areas. That was part of the strategy, is to have these broader partnerships to increase our probability of success. But certainly, the most advanced programme is the Hunter programme, in which we're using our blood-brain barrier technology to get an enzyme across the blood-brain barrier.

TS: I agree, it's just astonishing their progress since 2016. And it's so exciting to see some of what we talked about back then being in the clinic today and on its way to helping patients.

Could we just take a step back now from what Denali is doing and just talk about the context in which you're doing this and the pharma industry's inability to develop effective drugs for Alzheimer's, for other forms of neuro degeneration. That just wasn't through want of trying. Just talk us through the background and the industry's staggering failure rate in this area.

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RW: And it's good to have some perspective on drug development and how challenging it is broadly. I think people don't appreciate that the failure rate for developing cancer medicines is about 93 or 94%. It's a very high failure rate. The challenge, though, in Alzheimer's disease, it's 99.7%. It's an enormous rate. And as you've said, it's not for a lack of trying. There was a huge effort placed in this area. And I think we just didn't know enough about the disease.

And we certainly didn't spend time looking at biomarkers or ways of showing that the medicine is actually getting into the brain. There are so many studies. And I'll tell you this actually interesting perspective, Tom. In founding Denali, it was in 2015, either a year before or a year after, a large number of big pharmaceutical companies completely exited neuroscience. We were going against the trend. Everyone was leaving neuroscience.

Everyone was going to cancer and to rare disease. That was the main focus. And some immunology indications. But broadly, cancer was the way to go. And we founded Denali basically already swimming upstream. As everyone's exiting, that's where we're going to. Because guess what? The unmet need is only getting larger. We're living longer. We have better cardiovascular medicines. We have better cancer medicines.

What do we have? Neurodegeneration. We have age-related diseases. And the question we get all the time is, what makes you think you can succeed? And that's a fair question. And I think the way that we have to approach that is we need, again, tractable questions, solve technological challenges and then in parallel, take the bigger biology risk. And I think that's what the portfolio allows us to do at Denali.

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It allows us to go after diseases that there are already approved medicines. They just need to get into the brain. It's a very simple equation. And then as we've proven that, we then take the bigger risk in diseases like Alzheimer's and Parkinson's. But Tom, it's great to have this podcast right now because even the Alzheimer's space has massively evolved in the last year. I think we will have our first approved, potentially disease-modifying medicine coming from Eisai, which is an antibody targeting an Alzheimer's protein known as Abeta.

It's now shown, pretty definitively in a clinical trial, that it's slowing disease. There's a lot of room for improvement. And I think not a lot of that drug gets across the blood-brain barrier into the brain. That may be one area that we can improve upon. But this is exactly what the field needs, Tom. And what you're going to see is that suddenly, what was an outflow of interest in neurodegeneration is going to be a massive inflow.

And maybe we were five, six, seven years ahead, but it's such an exciting time. We see so much... And even the FDA in the US is viewing, we need medicines for ALS. We

need medicines for Alzheimer's disease. And it's much more collaborative to try to solve this, which is, frankly, a pandemic over the last three or four decades, now that the average lifespan is 80, 90 years old.

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TS: This point about actually seeing a disease-modifying drug get through the approval process is such a watershed moment, given that stunning failure rate you've seen historically. Just pulling apart why that's happening now, is it about deeper understanding of the biology of what's happening or is it what you refer to about biomarkers and actually being able to more accurately test whether a medicine is having an impact? What's changing?

RW: It's really in 1991 that amyloid precursor protein known as APP was discovered as the major contributor to Alzheimer's disease. And the idea of targeting amyloid beta with antibodies have been around for a long time. But there have been a number of limitations. And I think that probably the area that was most important is patient selection based on biomarkers. How do you run the right clinical trial in the right patients?

Those technologies have evolved rapidly in the last ten years. And then a lot of discipline around clinical endpoints. And as I said, there's a lot of room to improve on what appears to be a clinical benefit. And I actually think probably the most important factor for success is when we intervene. And this is the vision. I think we'll have some way of detecting disease before you have cognitive deficits and then you remove the amyloid.

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Now that's probably going to give them the biggest benefit. But I do think the biomarkers, the improvement on the antibody properties. But we have a long way to go to have even better medicines and better diagnostics.

TS: To overcome these huge challenges and actually get a drug into the right patients, cross the blood-brain barrier, see if it works, I think you just need a pretty unique way of working, differentiated teams with creative ways of approaching these challenges. Let's talk a little bit about that. What do you think is different about the culture at Denali? And maybe, I guess, having worked at some other really successful organisations, what is it that's unique to the way that you're going after the challenge at Denali?

RW: I love that question because, as a scientist, you realise very, very quickly the environment with which you work in is such a driver for invention and collaboration. And I'm fortunate, again, because I had worked at Genentech for a number of years and has a long history of doing incredible science. But there are many things that are uniquely Denali. And I think the first one is that we don't talk about culture because culture is actually the product of an equation.

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And I'll just share this equation with you, my theory about culture, which is there are additives, there are subtractors and there's multipliers. For us, probably the multipliers are where we focus most of our effort. And the number one multiplier is purpose. And if you have an organisation that's driven by purpose and in fact, if purpose is more

important than the organisation, it's a driving force for everything. You can deal with setbacks.

You can deal with working enormously long hours. In fact, people don't even count how long they work. You can deal with challenges along the way. And certainly, the successes are so much more meaningful. They just have this incredible meaning because you see... I'll give you an example. We had invented this medicine to cross the blood-brain barrier to treat Hunter syndrome. We have gotten to know several of the families that have children that have Hunter syndrome and the devastation.

These are boys. It's an X-linked disease. And some will develop very normally. And by ages three, four or five, learn to walk and talk and then they'll start to lose their ability to talk and lose their ability to walk. It's just unbelievably devastating. Fast-forward, we get our medicine into the clinic. We get our very first data. And I'll remember this day forever because I had just spent three hours, actually, collecting a video history with my mother who had Alzheimer's disease.

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And I didn't realise it was basically a year before she would pass away. And I asked her questions about her childhood. Anyway, I walk out of my childhood home and I get a text message from our chief medical officer that says, we need to chat. She called me and she says, Ryan, four out of the five patients have completely normal levels of the substrate in the brain. And it was unbelievable, Tom. As you're driven by...

That is a multiplier. I will work endlessly to try to solve these diseases. You get to know the families. I think that that is probably the number one driver for culture. The second one, which is totally related to that, is having an impact. I often get the question, why did you leave a place like Genentech? I was one of 80,000 employees. You come to a small company like Denali, which has now grown, you're going to have an impact.

It's going to be positive or it's going to be negative, but whatever you do is going to be impactful. And I think that's also a big part of culture, is knowing your purpose and that what you do is going to be impactful.

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TS: It's just such an inspiring story, just seeing the success that you're having in Hunter syndrome, where these families have had no hope, basically. And I guess it speaks a little bit to the strategy that you've pursued of going after these big, really difficult, multi-decade problems to solve. But also, making sure you have wins along the way in some of these other areas that really bring the point home about just how important it is what you're doing.

RW: I love that. I'm going to use your terminology going forward. It's wins along the way. If you set out and the only thing you are going to do is solve Alzheimer's, it's a 15-year development programme and very low probability of success. And you want to build an organisation that can weather failures.



TW: Could you just talk a little bit about some of the challenges you faced? I'm really interested in this because one of the things I've noted about Denali is that you've embraced failures. You've said, this is inevitable, as you mentioned, the programmes that you haven't taken forward and the stress you've put on learning from those moments. Have the difficult points on Denali's journey been about individual programmes getting pulled or is it something else that you would pull out as the difficult?

RW: I could recite for you every time we decided to stop a... I remember all of them and felt them very deeply. But rather than that, I'd like to share a different challenge, which is interesting, in retrospect. And it was, essentially, right at the beginning of the pandemic, we had just presented the first data ever in Parkinson's patients treated with a LRRK2 inhibitor. And we were very excited about that and we were planning to start our Hunter programme and then the pandemic hit.

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And being CEO of a company at the beginning of a pandemic, just an enormous amount of uncertainty. Extremely challenging. And I just remember feeling overwhelmed. What are we going to do? We have obligation to patients. We run clinical trials at medical institutes. And it was these two months of planning. And I have a very simple equation. It's, uncertainty without a plan equals anxiety. And uncertainty with a plan equals opportunity.

And I think we learnt very quickly to always seek out the opportunity with the uncertainty. And I have never been more impressed with a group of people than the people I worked with during those first three months of the pandemic and the planning. We ended up, in June, dosing our first Hunter patient in 2020. Don't ask me how it happened. And that is now stuck with us. That, I don't want to call it a failure.

It's definitely a challenge. The challenge created a new way of working, a new way of prioritising, a new way of planning. And I never wondered if people were working. It was nights, weekends. And no matter where they were, there was this singular focus on hitting our revised goals for that year. And it was an amazing year. It was an amazing year for Denali.

TS: And I appreciate this is asking you to simplify or speculate. Go as far as or hold back as you wish. But how far away are we? How long away are we for finding an effective treatment for the diseases of the brain?

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RW: Generalising is very difficult because each one of these diseases has its own set of genes, its own set of development timelines. But let's start first with the rare degenerative diseases. I think we're there. We're on that. Basically, it's now just designing the right clinical trial and showing definitively that you're improving patients' lives. And then frankly, getting the medicine as early as possible. I think with Alzheimer's disease...

I'll go to the other end of the spectrum. I think with the recent successes, the way I would do this... And I'm going to wildly speculate. I hope that's okay. But I think what we have to be doing is we have to be imaging to ask, does someone have plaque in the brain

in their 60s? And if they do, remove the plaque. And I think that if we were to do that, we would see a substantial delay in the onset of Alzheimer's disease.

The genetics is super compelling. The most recent clinical data is compelling. I think it's, we have to move towards a prevention setting. We actually have all of those tools and we actually will soon have the medicine to allow us to do that. And then we need to improve upon that. Those are the two ends of the spectrum. Actually, Tom, it's a fantastic time, with the hope that I wouldn't have told you that three years ago or four years ago.

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And, look, I think where we're positioned, where Denali is positioned is, in some cases, at the forefront, bringing the very first medicine, and in some cases, bringing a better medicine that has better exposure in the brain. And that in both cases, it's still a very important advance.

TS: A final question. I think what you've talked about there hints at it and I think you made a comment earlier. But what does the world look like if Denali succeeds?

RW: I think about that often. Frankly, I think mostly about the singular benefit to the patient and their family. And I can tell you, from personal experience, that the thing that was the hardest for me in losing my mother is that the last two years of her life were terrible. And it's someone I... I'm the youngest of seven children. I'm very close to my mother. I in fact would call her every day on the way to work when I was at Genentech before she started to develop dementia.

And loved hearing about her life. And what I really regret is that we all die. We know that. That's the inevitable. But how we die and with what dignity and what experiences... Because she lived an amazing life, I feel like. She raised seven children and she was incredibly generous and loving, especially during the holiday season. It was her favourite time of year. And yet those last years were not the way to end.

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And I imagine a future where our health span is increased. We're able to die with dignity. We're able to comfortably live in our own homes until our last days. And yet the way we get there is we need to predict a little bit what the future is going to be like for each of us from a medical perspective. We need to be able to predict early cancer, early Alzheimer's, early Parkinson's, even before we have any symptoms.

And then take medicines that were invented that we show slow disease, actually completely halt disease or cure disease if they're taken ten years before you actually get the medicine. And that is totally doable, Tom. I think with the biomarkers, when Denali is successful, our medicines that are engineered to cross the blood-brain barrier will be the ideal medicines to be able to take to prevent these diseases.

They'll act fast. They'll be able to cross the blood-brain barrier. We'll be able to have biomarkers to show they're working. That's the vision. And then from a company perspective, I'd love to see Denali 40 or 50 years from now iterating on the next medicines in each of these areas. And as we solve one disease... Let's face it, 100 years ago,

Alzheimer's and Parkinson's, these diseases didn't matter. We lived to 50. They're new diseases.

But I think it's about having incredible life up to the point when it's time to move on.

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TS: It's just been really inspiring to hear you talk about both what you've done at Denali, but also just how personal a mission it is for you. And thank you so much for sharing that.

RW: Tom, fantastic being with you. Thank you.

CS: Tom, it's hard not to be blown away by the conversation that you've just had there with Ryan. This is a company with a deep sense of mission.

TS: It is. I think that having a purpose beyond just making money is really important in terms of increasing the chances of success. And this is a company with a mission which affects the vast majority of us, given the prevalence of the diseases that they're trying to address.

CS: And you can tell that when he was talking with the people that also work at Denali. I read somewhere the turnover rate was between 8 and 9%, which is quite remarkable in the biotech Bay Area. But then when you hear that, what? It was over 60% of the people that work at Denali have a personal connection to the disease, it really shows you that that sense of mission is not just Ryan and his own experiences. It penetrates the whole organisation.

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TS: I think that it's about... Our interest in companies and technologies is about the problems that they solve. And you've seen these fundamental technologies, whether it's our understanding of genomics, it's our computational capacity, it's deeper understanding of the molecular basis of disease. All of these things are contributing to progress in solving some of the really big problems out there. And it's companies that are able to harness that that get us really excited.

CS: And I think as a founder, we got a real sense of him as well. He talked about going against the tide. I think he used the phrase swimming upstream. When all of his competitors were moving away from neuroscience, he was being attracted to that space. It really gives you a sense of what drives him. It says a lot about him as a person.

TS: And what he didn't say, and one of the things that initially attracted us to the company, is the amazing academic track record of himself and some of the other founders. These were the leading scientists in the field who have just done an enormous amount to push it forward. And it's rare to have that incredible academic and scientific track record, but combine it with that drive, that execution ability, to turn that into a company and to grow that business and actually take that science and make it impactful.

CS: And he alluded to this during the podcast, we've been on quite a long journey with Denali. We first met them in 2015, I think it was, not long after it was founded. We invested

for Scottish Mortgage about six months later. And it's really been fascinating to follow the evolution of the company. For you, I'm really curious to know, what moments have stood out for you on Scottish Mortgage's journey with Denali?

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TS: If you go back to that starting point, first of all it's, can we use our scale and capital resources to actually increase the chances of success here? And when you think about impact investing, forget the box-ticking exercises. But actually, by investing in something, can you increase the chances of a good outcome? And that combined with the scale of the opportunity, we talk about the fact that this set of diseases impacts most of us.

The other way of talking about that is, there is a huge end market for anybody that can develop effective medicines. What I would also note is it's not traditional biotech investing where you have a company with a molecule that may or may not succeed. It's a binary outcome. From the start, this is about, can you build a platform for treating this set of diseases? That's partly, we have various medicines under development and we don't tie the fortunes of the company to any one of them.

And we fail and fail over to the second molecule that we're working on in this area, to the third molecule. It's having that redundancy in the pipeline. And that's happened. If you go back to the notes I have from those early years, some of the drug candidates that they were most excited at that point have fallen by the wayside, but the company's progress has not been impacted. It's both that pursuit of that big opportunity, the long-term goal, and then approaching it in a way that is resilient.

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And then the milestones along the way. Ryan talked about the Hunter syndrome. It's just these increasing data points that, this is actually going to work.

CS: And I think if I could add in one more, I think that it's also the patience. Patience is key in this field. I think Ryan alluded to it. You can't solve these problems overnight. For us having the patience to support Denali while they are trying to defeat what is a huge problem.

TS: I think that it takes a long time for the science to mature. It takes a long time, for good reasons, to go through the clinical trials of these drugs to check that they're safe, to check their effectiveness. You have to approach this with a long time horizon. And what you see is that the market sometimes gets excited about this. Sometimes it gets really pessimistic. But generally, particularly in this area, that's not on the basis of data. And you have to wait years to accumulate that data.

CS: I guess, Tom, if I could play devil's advocate for a minute, you say, by your own admission, we're not healthcare experts. And in the same way, we're not experts in lots of other fields. How do you think you can effectively assess the company and its prospects?

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TS: I think that specialism can be dangerous in many areas. Because if you're dealing with companies that are the cutting-edge of what they're doing, then even specialism in a very adjacent area may not be enough. And I think it's very hard to have an edge in

investing by thinking you understand the detail better than others. Our approach is much more about trying to understand the problem, trying to understand why a given company may have an edge in going after that problem.

Maybe because of the structure, maybe because of the people, maybe because of the culture of the organisation. And none of those things are specific to a given industry. And then it's partly about establishing long-term relationships with people who are experts in the area whose views trust and helping to benefit from their insights. Ryan talked about having Jay Flatley, the former CEO of Illumina, on the board.

He is somebody that we got to know through our very long-term ownership of Illumina shares. And his views, the fact that he is on the board of this company, I think adds more credibility to their ability to execute.

00:38:59

CS: And I guess from here, Tom, when you're listening to Ryan, what do you think is the biggest challenge for Denali to achieve that outlier status that you look for? We talk a lot about, in Scottish Mortgage, we're trying to find those companies that can be those outliers. First of all, how could Denali become one of those outliers? But what are the challenges for it to go and be one of them?

TS: I think the answer to, how could it become one of the outliers? The answer is really simple. If it's medicines, work in these huge diseases with huge unmet clinical need. And it's as simple as that. But to get there, I don't think you can rate the probabilities of success. You have to look at the inputs, not at those outputs. Firstly, it's the core scientific development and their progress in bringing new medicines into the trial process.

And seeing those go through the different hurdles and having that process ongoing. It's also the commercial strategy. What do you do yourself? What do you partner with others on? Ryan talked about some of the big disease categories where actually crossing the blood-brain barrier is really important, but they aren't the core focus of Denali. You're looking for that endorsement that comes from big medical companies paying to partner with Denali to bring these medicines to market.

And it's all of these different factors that are the ingredients. And what would ultimately drive the value is the drugs coming out the other side.

00:40:29

CS: It's certainly a remarkable company, led by a pretty incredible founder. And I think, like many others listening, have a real personal passion for what Denali is trying to do. They're trying to address one of the largest medical challenges of our time. And I think we're deeply committed, obviously, to helping Denali in their mission, I guess, to defeating these diseases of the brain. With that, Tom, thank you very much for your time.

I've really loved listening to that discussion. And I'm sure many of our shareholders and listeners will as well.

TS: Thanks, Claire.

CS: Many thanks to our guests in this episode, Ryan Watts from Denali, and also to our investment manager, Tom Slater. In the next episode, we will be talking to Tim Steiner, the CEO of the online grocery and technology business, Ocado, a company recently described by one of their partners as probably one of the most innovative companies in the world. You can subscribe to our podcast to be kept informed of what's coming up.

And you can learn more about Scottish Mortgage by visiting our website at [scottishmortgage.com](http://scottishmortgage.com). You've been listening to Invest in Progress. Thank you for joining us.

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