Podcast - Speaking of Mol Bio - Season 1 Episode 1

Dr. Gabriel Alves 00:10
Welcome to Speaking of Mol Bio, a new podcast series about molecular biology and its trending applications in life sciences. I'm Dr. Gabriel Alves.

Steve Lewis 00:19
And I'm Steve Lewis. Since this is our first ever episode, we thought we'd start by telling you a bit more about us and what you can expect from this podcast series. Let's start with Gabriel.

Dr. Gabriel Alves 00:30
I am native of Brazil. I worked in nursing there until moving to the United States almost 10 years ago. I earned my PhD in neuroscience from Western Michigan University, and nowadays I teach part time at my alma mater, and work as a global market development manager for Thermo Fisher Scientific. I'm really excited to be co-hosting this podcast series with Steve.

Steve Lewis 00:54
I'm really excited about this too. I started my academic career at Virginia Tech and then earned a master's degree in biotechnology from Johns Hopkins University. I began work in product management almost immediately after I entered the industry, and I joined Thermo Fisher Scientific in 2020. I'm currently a Senior Global Product Manager for PCR plastics within our molecular biology business.

Dr. Gabriel Alves 01:19
In our first season of Speaking of Mol Bio, we are going to focus our conversations in four exciting application areas: CRISPR cell engineering, multiomics, exosomes, and single cell analysis. We will have multiple episodes on each topic. We hope that through listening to our podcast, you gain appreciation for the role that molecular biology techniques play in enabling these higher-level applications.

Steve Lewis 01:46
Today, we'll be talking about CRISPR cell engineering with Travis Hardcastle. Travis is currently a product manager at Synthego working with their engineered cells portfolio. He has extensive experience working in microbiology as well. We hope you enjoy our conversation.

Dr. Gabriel Alves 02:05
Travis, for people who don't know, or do not work with CRISPR, how do you explain this technique?

Travis Hardcastle 02:13
I think I heard it best explained when I was at a conference and I saw Dr. Jennifer Doudna talk about CRISPR Cas9 and, obviously, as the pioneer in the research and, the way she equated it was it's like the search, find, and replace function on a Word document right. So you can go into the genome, you can search for any sequence that you want. And then you can use the tools of CRISPR Cas9 to go in and cut out or edit any part of that genome and replace it with whatever you want. So I think that's the best, simplest way from a non-scientific way of explaining what CRISPR Cas9 is. It's really like going

into the genome and finding the exact sequence you want to edit and being able to edit, cut it out, edit it and do whatever you need to do with it.

Dr. Gabriel Alves 02:52
How did you get involved with CRISPR?

Travis Hardcastle 02:54
I didn't really stumble across CRISPR Cas9 until moving to Colorado and starting to work it with Dharmacon and you know GE Healthcare, the Dharmacon brand there, where were they were just coming out with their products, right? I think I was one of the first hires whenever Dharmacon became a part of GE Healthcare from the scientific team, for the R&D team. And it was really there where I got, you know, got my knowledge, and got my start into understanding CRISPR Cas9, and digging into the details about it, because obviously, they had just launched the new portfolio, their new products, and it was really coming up to speed so I can help contribute to the development of other products along those lines.

Dr. Gabriel Alves 03:32
So in the current position, you work as a product manager for engineered cells. What kind of cell lines do you work with? And your customers that are purchasing? What are they doing with those cell lines?

Travis Hardcastle 03:46
We can pretty much work with just about any cell lines. Tjere's, you know, you think of a lot of the common and immortalized cancer types of cell lines A549s, HeLa cells, HEK-293Ts or any of those comps, any of those cell lines. I think at this point, the last time I checked, we've worked with well over you know, I think 700 different cell lines at this point. So anything that a customer can provide us with we can pretty much work with. From an editing standpoint, right, we do at all. We do knock outs, right? You tell us a gene you want to knockout, we knock that gene out. And you tell us you know, if there's a particular polymorphism you want us to knock in, we can do that. Or we can you know introduce tags such as D tags or fluorescent proteins if you want to, you know, do some sort of reporting system, right? If you if you're going to knock it down and look at what happens to that protein over time. We can do any of those things in both these immortalized cell lines or these IPSC cell lines.

Steve Lewis 04:39
And in that explanation, we had IPSC's, we had knockouts, we had cell lines even. Do you mind going into just like the high-level overview of you know what Synthego is, from a business platform perspective. And what do you hope to achieve with this cell line engineering, phenotypic results, what have you?

Travis Hardcastle 05:05
Yes, Synthego was very interesting, in a great I think pioneering company when it comes to this, this gene editing this CRISPR Cas9, this gene editing space, right? As a company in general, they have two really different main business units, right? One of those, the one of that being the reagent side of the business. So, the single guide RNA, which customers can do a lot of the cell engineering in their own lab, right, so they need the reagents from the Cas9 nuclease or the guides to guide that Cas9 to

the particular spot in the genome to do the editing. You know, we can provide that to a customer from that perspective. So they can tell us a gene they want to target and we can provide them with, you know, guides to target to knock out or knock in anything in that particular gene. And so that's more the do it yourselfers. The researchers who don't want to outsource those opportunities to a company, like Synthego, to create that cell line for them, they can do that themselves, right? It is a lot of work, from a cell line engineering perspective to generate these edits, you know, whether it be a knockout or a knock in, it is very time consuming, it takes a lot of work, which is where the other side of Synthego comes in, which is the side of the portfolio of the I manage, which is the cell line engineering business. Where Synthego's value proposition comes in is we've created this very high throughput highly automated platform, that we can take lots of cells and do lots of edits with them side by side. And so we can provide, you know, oftentimes, if you're looking at a disease, or if you're looking at a particular drug discovery platform, and you're wanting to look at multiple targets side by side, you as you can see, as you can think of it as that scales, it's hard to do from an individual lab perspective. But that's where we come in and we can do that from our automated platform to allow those types of things.

Dr. Gabriel Alves 06:47
Let's shift a little bit of gears here. The first CRISPR gene editing drug is coming soon, possibly, next year 2023, the drug will treat beta thalassemia, which is characterized for damaging or missing genes that caused the body to produce less hemoglobin, and essential protein to transport oxygen. And also, that drug would treat sickle cell anemia as well, which has a defective gene as well, that causes malformed hemoglobin that are stiff, sticky, and disturbs the blood movement in the body. So my question is, with these drugs coming in new therapies coming in into the market, where do you see the market the CRISPR, especially in the next five years?

Travis Hardcastle 07:41
Yeah, I think that as you see these clinical trials, and these therapies start to be involved and become accepted and pass through the FDA and get approvals and those things, I think you're going to see a huge shift in the market to more of the therapies coming out, right? Once you get those that one through, once you break through that first layer of, of approvals, right, I think that just opens the door for being able to do this with more diseases. Where can we make these, you know, these improvements with the therapies by using CRISPR Cas9, and the types of technology that's the spinoff of that. I think in the next five years, you're going to see a multitude of therapies that are a result of CRISPR Cas9, and I think we're just breaking the ground of what that could be and where that's going to be eventually.

Steve Lewis 08:24
What role does data analysis play with your overall approach to building out these CRISPR platforms?

Travis Hardcastle 08:32
As far as where data that comes in and how does data play into what we do from our perspective? Right? I mean, we take a lot from, from publications, from what is being researched by, you know, academic institutes, and those bigger sorts of broader analyses. You know, big things that come into consideration, originally, right, when you move CRISPR, probably first came out was, you know, what are the off-target effects? Are you sure that you're only editing that specific gene that you're wanting to edit? Is it editing anything else downstream? Right, I mean, that's, that's a huge concern, particularly as

we talked to you just recently about moving to the clinic, right? You want to make sure that whatever you're editing in somebody's, you know, stem cells that the that is specifically associated with that, and you're not editing anything else in the genome. And so you want to take those things into consideration. I think, much of the algorithms now that have been developed by different companies, and different academic institutes take all those things into consideration, I think we have a pretty good view of, okay, the data saying that we're not producing any other off target effects with a lot of the guides that we're generating these days, because we've gotten so well with this particular technology. So that's where machine learning comes in. That's where, you know, from, from our perspective we've done, so many edits, at this point that we have, we can rely on that data from us to say, “Okay, this is a good guide, this is a bad guide.” We targeted this gene with one cell line, and we know that we don't see any downstream or do linear, deleterious effects, right. So we can say, “Okay, that's a good guide to move forward with different projects.” And this is that feedback constant we commonly sometimes call internally, it's like this CRISPR feedback loop, right? So we're saying, Okay, we understand, we can use success stories of being able to successfully edit one cell line to feed that back into, like this machines machine learning pathway to say, “Okay, this is what makes a good design, right?” So it's just, it's using that internal data and their internal know-how what's been successful and not successful to keep on being successful and generate more successful projects for customers.

Steve Lewis 10:30
From a continuing, like quality thread, I know that automation is not just a big thing for Synthego but across the industry. Particularly in drug discovery, it's becoming more important. From a technology gap perspective, what do you think the big gaps in automation are right now to truly making an efficient automation workflow?

Travis Hardcastle 11:01
Yeah, I mean, you're never going to fully automate everything, right? I think that, obviously, somebody has to enter the cells in the system, and somebody has to enter that into the reagents in the system, right. So once, once you get to that point, it can somewhat be automated, but then you can't automate cell growth, right? You can't make cells grow faster, right? A lot of times I have said our projects are 10 weeks long and a lot of that is not from us doing anything with them, it's just like, hey, they have to grow. With this, you can only start with so many cell lines, or so many cells in a dish. And, and hopefully get that edit you want. But for a pure automation standpoint, right, I think that I don't see very many gaps other than like, you know, you can't, we haven't found a way to specifically automate the transfection process from being able to get all the reagents, you know, we have to enter reagents into the system but after that. it's semi-automatable. We still have to move some plates around here in there, right. But from the growth standpoint, a lot of the growth aspects are automated. They're sitting in incubators, we're imaging cells every three or four days, in that, and that's a lot of automation that goes with that, to make sure that they're growing well, and those types of things. But the next the next phase would be figuring out a way to automate, automate the QC aspect of it from a Sanger sequencing or from a sequencing standpoint, how do you how do you automate harvesting the cells and running this through these NGS, you know, these NGS platforms and those types of things? I think once you can do that, you know, what's new and automate everything from, from my perspective,

Dr. Gabriel Alves 12:29

Especially for diseases that are high prevalence in our society, such as hypertension, high blood pressure, type two diabetes, certain autoimmune diseases. I think CRISPR technology will be a revolution, especially in the next five years, as Travis said. Do you see CRISPR also helping with these diseases that are high prevalence in our society?

Travis Hardcastle 12:59
So I think it's going to just, it's going to take off over time. Again, I think it's going to be exponential. I think once the first, you know, first few go through, and you and you see there's no long-term side effects,so there's no sort of issues that persist over time that they are safe, and they're, they're not going to have any malice does not mean the sort of malice effects from them. It'll just allow for that research to just explode. And you know, there's already so many research that's going into using CRISPR as a therapeutic that, you know, I can't, I don't know how many different companies you have. Now they're in that space, that it's just going to allow each one of those to develop new, new drugs to the market to help patients that they really need this really a personalized medicine at that point.

Dr. Gabriel Alves 13:48
We hope you're enjoying this episode of Speaking of Mol Bio. We want to take a quick moment to tell you about the Invitrogen School of Molecular Biology. It is a great educational hub for molecular biology with rich and reliable content designed for new and experienced molecular biologists alike. Check it out today at thermofisher.com/ISMB. And now, back to our conversation.

Steve Lewis 14:17
From a product management perspective, this isn't particularly science based, but seems like you manage both custom products and commoditized products and that having that experiences, you know, it gives you different perspectives, right? You're building something bespoke for customers versus you're building, you know, higher volume of products that gets sold at a faster rate, for example. I guess my question is, I'm curious, do you hit a point where you when you've managed those two kinds of products, do you feel like you can kind of jump into any product category or portfolio where you can, you know, you come in you learn a bit about the product and you're almost technology agnostic, in a way?

Travis Hardcastle 15:07
They each have their own, you know, pitfalls, right? I mean, from a bespoke standpoint, bespoke custom/customer standpoint is, you probably know, it makes it, the unknowns make it a lot hard like you don't know what projects are going to come up and what's going to go wrong with those projects, right? A lot of times like you try to take into account like all possible solutions, and what those are going to look like. But there's always, there's always those situations that you didn't think about that come up and like how do you solve this situation? How do you, how do you create an offering for even a customer base that you never thought of before? Because now you're seeing more customers come to you to ask you for this project you never even thought of. And so there's those pitfalls and there's the things that come up with that. But again, the off the shelf stuff has its own problems as well, right? It's very, as you said, commoditized. It's a race to the bottom at that point with pricing. It's a race to the bottom with how can I just, how can I differentiate myself in this market where everybody else is playing in, right? What makes my product not a me-too product everybody else is sitting with? So that's

oftentimes a pitfall as well, like, were you going to distinguish yourself from everybody else in the commoditized market? They're both exciting. I guess I haven't gotten the instrument space at this point. So that might be a little bit different with you, if I, if I want to go into, I mean, I was just at ASHG last week and PacBio, you know, brought in Maroon Five and introduced their two new systems. I mean, I would love to be a product manager who was introducing the newest one like that that's going to maybe what they're hoping to change the game with how sequencing is done with these long read sequencing, or sequencing technology. Right? That's, that's a groundbreaking technology that maybe I'm not going to get to introduce from a product standpoint, within, you know, these bespoke services or an off the shelf product, right? That's a whole other space in general, that maybe is I don't know how it fit into that. But it would be interesting, I would love to get that opportunity, maybe at one point later on in my career, and after I'm done here at Synthego.

Dr. Gabriel Alves 17:00
Coming from those early days in CRISPR and nowadays with the development of new Cas9 proteins, higher fidelity. How do you see kind of going back to the product, a question, again, how you see these, the quality of these products, impacting the outcome of your work with the engineering cells, and maybe also for the clinical side of it?

Travis Hardcastle 17:29
I mean, I think just the higher fidelities that we've seen, I think there's no, there's been companies that worked on the high fidelity Cas9 stuff that we've talked about, if you one thing as you move closer to clinic, you have to be 100% positive, you're not seeing the sort of off target effects, you're not seeing any sort of deleterious effects elsewhere in the genome, other than that specific site that you want to have the edit in. And so I think, you know, as technologies are evolving to be higher fidelity, to have them be able to do specifically what you wanted to do and have the precision right, I think that's a great word, I think the precision you're able to develop, versus probably what it was, in the early days that area. And if and if it wasn't, you didn't know how precise it was because technology was still evolving. How do you analyze all this? I mean, minus whole genome sequencing, which, at the time, is super expensive, right? I mean, you look at the whole genome sequencing back many, many, many years ago was an expensive thing to do. How do you make sure that you're not having to resort to that? So I think the development of precise proteins, precise methods of editing the genome have played a huge impact on getting us closer to the clinic, and making this higher quality therapeutics over time.

Dr. Gabriel Alves 18:40
One of the things that I see coming out in the market are new medications, and their costs are always pretty high. With CRISPR technology, CRISPR Cas9, do you see the possibility of this methodology lowering the cost of medications that may come from this technology?

Travis Hardcastle 19:08
That's a tough question. I mean, I don't know enough about the political nature, the market dynamics of how pharmaceuticals work, and what not. A part of me wants to say like this, does that increase the price for it because you're driving demand down for those particular therapeutics at that point that for that are sold by the pharmaceutical companies. So if you're replacing that technology, or those therapies with another form of therapy, that's not from the pharma company, obviously they want to

make their money back so the demand side they're going to the prices are going to go up at that point, right. But you're also if you can replace it with a cheaper alternative such as and I don't know the price of the therapy for CRISPR. I don't know that I don't have a grasp of that market or the market dynamics for CRISPR therapeutics and, and what those costs but as we get better at developing them as we get better at producing the components to go part of that is obviously the price is going to go down. So I can see where those. If you can get those prices down to a point to where many, many people can afford them or your insurance companies to pay for them, I can see the prices of other therapies going up at the same time. Right? So, it's I think it's a half one way or half the other, how that can play into the market.

Dr. Gabriel Alves 20:23
Yeah, I remember seeing some news, back in the day, when the first gene therapy came out. It was to treat muscle dystrophy, muscular dystrophy. And the cost per treatment for that particular medication a year was $1.2 million cash. So it doesn't fit in anybody's budget. So yeah, having the ability to produce these medications that may cure or treat diseases to a different level than the regular medications. But also, having those medications, medications, and technologies accessible to people will be the ideal.

Travis Hardcastle 21:05
Actually, yeah, I have ever actually another question for you, Steve. And now I think you mentioned you're in bioproduction. And this is where on a previous company I worked at had a bioproduction business unit, right, and a lot of the stuff that they did was use CRISPR to knock out particular in cell lines and things like that, to knock out certain genes and make this cell lines grow more, better. And then I probably don't understand the bioproduction market as well as you do. But how does CRISPR, how do you find CRISPR plays into a bioproduction marketplace and then things like that? Can CRISPR be used from, from your perspective, to make better bioproduction cell lines and make more and better proteins or therapeutics?

Steve Lewis 21:45
Absolutely. From a from a cell line development perspective, I think the goal in bioproduction is that you can make a competent cell line that you can ultimately scale up. Scale is always the big challenge there. But I think on the pure research level, even early-stage development level, CRISPR is going to be and I'm sure already is in the laboratory and absolutely critical, paradigm shifting technology. Right? Anything from expression levels of a potential cell line all the way to like you said knocking in and out single mutations. What was interesting about that question to me that Gabriel just asked is I was looking at this, for folks who are listening, this is our very first podcast and I started Googling a supply chain graphic that I had seen for CAR-T therapy. And then I realized that's probably bad radio to pull up a picture and start sharing it. So hopefully, for people listening to us, you can forgive me, but I'll try to describe. It essentially showing this pathway where you know, for CAR-T therapy, you have to start with the patient's own cell, right? And then you can edit it, but then you have to go to the level that you actually can manufacture it. And so, picture almost like a like a board game maze, like Candyland, if people are familiar, even Chutes and Ladders have all these different points for manufacturing in the process where you have a CRO, maybe engineering a cell line who then passes it up to like a CDMO, who tries to scale it up to like one liter, maybe even 5,10 liters of product. And then for the for there right, you have to worry about cold chain shipping, getting it to a customer making sure that transfusion

is done correctly, making sure you have people educated along the way with how to, you know use all of this new technology. Right now, it's almost like the infrastructure is a limiting factor and which I think most people, at least in the biotech space, are aware of that. But I also think to Gabriel's question about the cost, I think it'll be interesting figuring out as we can truly develop more personalized medicines that start with the patient. Finding in a cost-effective pathway to getting through the R&D all the way back to the patient in the clinic, in a fast amount of time is going to be you know, really interesting, impact, I think, to both the insurance market as well as to of course, any clinical organization. And there's a lot of opportunities right that I think everybody sees to a degree in this space. I read that Thermo Fisher a few months ago partnered with UCSF to basically make a space that is dedicated to gene therapy. So it's essentially you can picture it almost like a shipping container lab where it's attached to the UCSF hospital, and patients coming in needing that particular therapy, that that can be driven by cell line engineering can be done all within a very, very close space. Does that model get copied at academic centers or teaching hospitals, things like that? I'd be curious to know both of your perspectives on that, because I think that's a really interesting concept. And scales up is always, always the big challenge here. and I think that these emerging technologies are no exception to that.

Travis Hardcastle 25:57
One thing that came to mind when you're talking about that, is we're talking about personalized medicine, but it's autologous versus allogeneic. Right. So that's the big debate to give you. Maybe I don't have to have my own cells, but could I have is there some sort of, you know, T-cell bank, right, that you can start from and you started that editing processes without having to harvest like my T-cells cells? Or my, my stem cells, right? And if you could do that, I think there's many, many, many companies who are working on that from a supply chain, as you're talking about, from a supply chain standpoint, at least you have that common base and that common stock to start with, where it's like, okay, I know which, I know what your mutation is, I know what I need to do to you have a personalized medicine for you. And you bypass that, that initial phase at least of having to harvest those the cells from the patient at least, and you can view jumpstart that process. And I think that's, that's a huge area. And I know, there's many, many companies who are working in that space. And so that would be my sort of my thing with that.

Dr. Gabriel Alves 26:52
Yeah, my view of having personalized medicine and technologies that could facilitate that there will be, it will transform and revolutionize the medicine and how we practice medicine. And speaking from my personal experience, I have multiple sclerosis, which is an autoimmune disease. I initially started treating with medication A, for six months, it didn't work out. I had an increase in number of lesions. And then I switched to a medication B, which is was one of the first oral medications developed for MS and, and it’s been working since then. You know, in, you know, having this luck, and finding a medication that worked for me, doesn't happen with everybody with a MS. Some people will fall into a progressive state of that disease that will make things a little bit more complicated there. But if you have a medication or therapy that will work across the board that's personalized, and will work for that individual, it will be amazing. Yes, and if I before we finish, if I could maybe just come up with a question here for Travis. As we come to the end of our episode, let's conclude with a final question that we would like to ask Travis, which is, what would you say that has been the most important ingredient of success as far as in your career currently?

Travis Hardcastle 28:33
Yeah, great question. I think I've been surrounded by a mountain of amazing mentors who have, in R&D labs and right into products, and by all means, like, somebody had to take a chance on me. And so I think it's just being surrounded by people who put trust in me to be able to take on new positions I've taken on and who have had the faith that was going to go on and do good things. And so those mentorships were probably the biggest thing that allowed me to succeed in anything I've ever done. And I'm always grateful for everybody who's ever taken a chance on me to get to where I'm at right now.

Steve Lewis 29:13
That was Travis Hardcastle, product manager at Synthego. We're grateful to him for being our first guest and to you for giving our podcast a listen. If you're interested in hearing even more of today's conversation, you can view the extended video version of this interview by visiting the URL in the Episode Notes. And while you're there, make sure to subscribe to our series to get notifications as future episodes drop. We're excited about what's to come. This episode was produced by Matt Ferris, Sarah Briganti, and Matthew Stock. Thanks for listening.