Podcast - Speaking of Mol Bio - Season 1 Episode 4

Dr. Gabriel Alves 00:09
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.

Dr. Gabriel Alves 00:21
In our first season of Speaking of Mol Bio, we are focusing our conversations on four exciting application areas: CRISPR cell engineering, multi-omics, exosomes, and single cell analysis. And after exploring multi-omics with our last two guests, we are going to dive into exosomes today with Jim West.

Steve Lewis 00:41
Jim is the CEO of Clara Biotech, an exosome innovation startup in Kansas City. Since 2018, they have been working to bring new diagnostic and therapeutic exosome uses to the market. And Jim is excited to share his perspective on the massive potential he sees in this area, we hope you enjoy our conversation.

Jim West 01:06
Exosomes are kind of the body's cellular FedEx delivery system. Cells create these little packages, and these packages have cargo, and they have an address. And the address allows them to basically perform cellular communication. And each one's different. You know, they're very unique and diverse, they're heterogeneous. But these exosomes are exciting because if you look at their genetic cargo, you can actually tell the origin of the exosome to the cell. And so you could envision a future with liquid biopsy, kind of the third leg of liquid biopsy, next to circulating tumor cells, cell free DNA, you've got exosomes that are containing proteomic information, micro RNAs, mRNAs, DNA. And all of these things give your insight into the cells of the body. So, you've already got companies developing cancer diagnostics, using these technologies. And then the ability to deliver to cells really opens up a huge, exciting paradigm in precision medicine. We're talking about natural targeted drug delivery. You know, a huge step up from lipid nanoparticles where targeting is hard and too much of it becomes very toxic, exosomes seem to be a really nice modality for sort of this next generation of gene therapy delivery. And then one last thing that I think about exosomes, it's really exciting, is exosomes that come from certain cell types have properties that are really interesting. So for example, cancer releases exosomes, and those exosomes actually help shut down local cells and help the cancer spread with signaling. And conversely, exosomes from stem cells seem to maintain a lot of the active properties of the stem cell kind of the active ingredient, but without the stem cell. And so there's a new opportunity to maybe create some regenerative therapies based on exosomes that are acellular, which is really exciting. Now going back to an exosome itself, they're only about 100 nanometers in diameter, there's a lot of variability there, they get up to 200, maybe even 300. But they're about 100 nanometers in diameter. And that means that that scale, they kind of can get confused with a lot of other things at that scale. And so that's one of the difficulties of the field is how do you actually know you have and are working with an extracellular vesicle as opposed to something else?

Steve Lewis 03:41
How does one with a diagnostic differentiate between an extracellular vesicle or material contained within?

Jim West 03:49
So think of it this way, you've got a cell, and the cell internally is budding, these little exosomes. And the way that happens is it's actually capturing a small part of that cell's genetic material. And so that means when these exosomes are collected, you can you know, lyse them, you can dissolve the membranes, and it releases the genetic content. And then if you know the biomarkers that you're looking for, you can actually get a signal to exactly what you're, you know, the cell of origin. So, for example, one of our early customers is a cancer center, they were really excited because they were able to analyze patient samples in a clinical trial. And they knew the biomarkers they were looking for, and they said, you know, using Clara's technology, we were able to identify three things about this these cancer patients. One, this is head and neck cancer, and sort of like one we could tell whether the patient had HPV human papilloma virus, which is really important because that's going to affect the type of chemotherapy you get. Second, we could detect the presence of the cancer. And third, we believe we can detect the stage of the cancer. Now, these aren't claims I'm not saying this is, this is one customer's story to us. But, you know, the potential is there, and there's no companies doing this currently. But there's a lot of really fascinating information within these exosomes that I think is going to open up really new neat possibilities in diagnostics and prognostics in the future.

Dr. Gabriel Alves 05:30
Awesome. And in terms of treatment and cure for diseases, how does exosome come into play?

Jim West 05:38
Right now, you know, the thinking is there's kind of two exosome therapeutic opportunities. And the difference is really based on a regulatory strategy. And so you have, like I mentioned at the beginning, you know, you have these stem cells that create exosomes, and they kind of have two properties. They act as an anti-inflammatory. And they promote, they seem to promote local tissue regeneration. And so you can envision the benefits of that. And the nice thing is, it's an unadulterated exosome. It's an unadulterated biological product. And so it actually goes through the Office of Tissue and Advanced Therapies at the FDA. And it's a different regulatory pathway than a drug. And you don't have to do as much safety toxicity type work in this pathway as you do in a modified or a drug pathway. So it's as a natural sort of product it has a much easier regulatory pathway. So, there's a few companies pursuing those, those options. And then the other hand, you have the exosome, which could be modified, where you could load drugs into or onto the exosome, you can modify or change the surface proteins, which will affect the targeting. There exosomes are so small, they you know, we believe that they can cross the blood-brain barrier without any problems, so they can kind of cross all the tissues in your body. And I guess there's actually a third category, which isn't really drugs as much, but it's vaccines. These exosomes can be kind of turned into immunotherapies, cancer immunotherapies, kind of like next generation CAR T cell type things, but again, more from a allogeneic perspective as opposed to an autologous perspective.

Dr. Gabriel Alves 07:37
And I imagine for each one of those applications, purification of the exosome will be very important. And I would like to know from you like what are the steps for purifying an exosome, what molecular biology technology is used to purify these exosomes, so if you could walk us by the technique, that will be awesome.

Jim West 07:58
The whole field was started around ultra-centrifugation. It's the gold standard. And when I talked to researchers, it's like the worst gold standard in the world. Nobody likes it. It's difficult. It's long, it's time consuming. One thing to note about exosomes is they're actually really sensitive to shear stresses. They're fairly robust biologically, but they're very sensitive to shear stresses. And so when you put them in that, that sort of that density gradient, it really transforms, modifies, and damages those exosomes in significant ways. But, that's the gold standard. The second sort of major way people will isolate exomes is through kits. There's a number of them. But you know, no matter how pure your starting material is, you're still going to have unwanted and unquantified noise and contaminants at these levels. That's a challenge in the field today.

Steve Lewis 08:54
I can imagine there's a tremendous amount of prep work that would go into ultimately isolating that as the end product. Along the way, I'm curious if you could just chat about some of the molecular biology tools that you might use, whether on a specific patient or even in an allogenic way, like you were mentioning.

Jim West 09:20
Yeah. So I mentioned NTA (nanoparticle tracking analysis) before, so quantifying and counting the nanoparticles based on size and distribution, it's a very common one. But again, in a sample, you don't actually know how much of those correlate to exosomes, although it is it is a pretty easy and robust test. The other things that people will do is they'll look at the content and so you know, mass spectrometry, proteomics, looking at looking at what's in and on the exosome is a another very common method it generally gives very high quality insightful data. But it can also be difficult because you have to have a large amount of material. So, I guess let's step back within an exosome, you've got proteins, you've got RNAs, and you've got DNA. And so each of these can be analyzed in their own ways. So with the mass spec, you also have western blotting. Moving on to RNA, you know, there's all the different you know, all the different types of RNA you can look at. And there's different types of micro-RNA, messenger RNA, silent RNA. Each of these has their own methods to be honest, I'm not, I'm not deeply nuanced in this area. So, I can only say that they do them. But um, we're working on being able to quantify micro-RNA quantification, but it's just a bulk measurement method, not a not a sequencing. And then DNA, so you can sequence the DNA, PCR, and digital PCR, things like that. Again, it's changing all the time. So, some of the new stuff coming out, you know, there's, there's some very interesting companies out there, there's one, they have a little chip that they put antibodies on the surface of the chip, and the exosomes bind, and they have a sort of a digital western blot on these chips, that can quantify what binds to the surface of the chip. There are other companies like NanoFCM, they've got a very neat product that's coming out, it's out, but it's getting talked about a lot. And it gives you very deep, insightful data into the exosome. And I think they can get down to almost

single exosome analysis, which is, is crazy. And even flow cytometry, you know, all the flow cytometry companies, a lot of them are from the top down, they're moving into this space, too. So, it's, it's changing all the time. But there's a lot of, it's still a wild West away in a bit of how you how you characterize these.

Dr. Gabriel Alves 11:54
And talking about companies, and this world of new companies coming to the market. And with these new applications, it leads me to the startup world, which is a bit unique, a little bit crazy too. Tell me about your experience, leading, being the head of a startup, and what have you learned from it, and the pros and cons of having a startup?

Jim West 12:20
The pros and cons of a startup? Well, there's a lot of cons. It's very hard. But I think that my personality, if it's not hard, it wouldn't be worth doing. And I really enjoy it. For me, it's very well suited. But you know, thinking through, like, if I was giving advice to others wanting to follow this type of path, there's definitely a couple things you want to do. And keep it in mind. So, you know, the first thing I did when I joined the company, is we talked to at least 100 customers, prospective customers. And that's actually how I learned about and kind of came into the field, learning the nomenclature, understanding state of the art, understanding, most importantly, the customer problems and needs, firsthand. And then using that insight to help kind of drive the business and the strategy. And the story around what we're trying to do is really, I think, very critical. And then, you know, the next part is how you get funding. So, we've had a few SBIRs (small business innovation research grants), so we've worked with the National Cancer Institute at the NIH. And then we've gotten some other grants as well. But, you know, early on, especially with an emerging technology like this, the grants are fantastic and important way to kind of give you the capital to get it to the point where you can, you know, then start presenting it to investors, and bringing in kind of the traditional angel and venture funds. So, we've, we've been mostly funded by grants and angel investors to date. We've participated in a number of accelerators that have helped us in numerous ways. And last year, we were, we were actually listed as one of the top five bio tool innovators in the world through another platform we did. So, things like that just kind of getting the word out, building your story, getting to the point you can get people to give you money and then you know being come off on it, you can turn that into a product. Those are all part of the startup journey.

Steve Lewis 14:21
Zooming out a little bit, where does exosome research fall within the cancer world? You mentioned it as a potential drug delivery system, and one thing that came to mind was can extracellular vesicles pass through the fluid membrane of cells freely or are there extracellular membrane receptors specific to extracellular vesicles?

Jim West 14:49
I need to be a little careful here because I'm not a scientist. I'm the CEO so speaking too much on science I could get in trouble. But I'll give you my layman's understanding. As an exosome buds from a cell, it gets a little bit of those proteins that wrap around it from the cell. So, I don't think that there are specific proteins to the exosome that aren't in the cell. But I say that I don't think we have data we don't know. But I don't think there's much reason to believe that an exosome would have unique proteins a

cell doesn't. There's no functional genetic material in an exosome. It's really just like pieces of hard drives. Right? It, there's information there, but there's no CPU, there's no graphics card, there's no memory, there's no, you know, there's nothing else. It's just a little bit of data. As they go into cells, this is also an area we don't really know a lot about, but I believe, when they enter a cell, I don't think they enter intact. I think that the proteins, you know, act kind of like a key on the cell, that's how they recept. And then I think the exosome gets pulled into the cell, maybe it's endocytosed. I don't, I don't actually know that part. I should not answer this because I don't know the answer to that. But to be honest, I don't think anybody really knows the answer. And so, I think this is an area where we really need more research and insight. Because we don't, we don't know what happens once it enters the cell.

Dr. Gabriel Alves 16:27
We hope you're enjoying this episode of Speaking of Mol Bio, we wanted 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 technical content designed for new and experienced molecular biologists alike. Check it out today at thermofisher.com/ismb. And now, back to our conversation.

This is a question that I asked all of our guests. It is a question more personal, what would you say that has been the most important ingredient for your success so far in your career?

Jim West 17:12
So, I think the number one asset to me, as you mentioned, I'm very persistent. I don't really give up. And I'm kind of weird that way. Like, I've only had a few hobbies in my life, I have friends invite me to play golf. And I'm like, I'm not going to play golf with you because if I pick it up and like it, I'm not going to stop for 10 years, and it's going to take too much time. I usually am very focused, and I go very deep on my hobbies and interests. So, I think that that sort of tenacity that just, you know, focus and direction is very critical and important. But that being said, you know, there's obviously a lot of different factors that come into play. You know, I think communication is very important, I think as CEO of an emerging company, you know, honestly, one of my most important jobs is storytelling. You know, the story of the company, the story of what we're doing, that's almost you know, that storytelling ability, I think, is very critical. And important, because you got to you got to tell your story to customers, you got to tell your story to investors, you got to tell your story to your team, so people know where you're going and what you're doing. So that's I think a very important skill that's often overlooked. And then I have a background in, you know, life science medical devices. And I think that that's part of what allows me to kind of be successful here. Because I know where we're going from a manufacturing perspective, and I know how to get there and what's going to be needed. So, kind of having that that regulatory quality manufacturing framework, I think is also very important.

Steve Lewis 18:48
Now for maybe an aspiring entrepreneur out there who is working in the life sciences space, what would you say to them if they're considering getting into exosomes research, versus any other area of the life sciences?

Jim West 19:05

When you're starting a new company, especially from scratch, you look around. You know, there's a few things that you want to have to be able to like, call out for success, or at least increasing optimization for success. And one of them is this a growing or shrinking market? Exosomes are definitely growing. There's a company called Capricor. And their CEO Linda Marban she few years ago, she was giving a quarterly update and she said something really interesting. She said, you know, I've been around for 20, 30 years in this field and 30 years ago, we saw monoclonal antibodies kind of coming onto the scene, this little research toy and you fast forward 20 years and the top 11 drug candidates are all monoclonal antibody based. They have transformed and kind of you know, pushed forward and matured. And in the same way, I see exosomes following the same trajectory but that accelerated. And so, I think that the risks are there because we still don't know a lot. But I think that the opportunity is so huge and there's so many different applications and ways to win and learn. The investors and the community are learning about it, it's forward looking, it's growing, there's still a lot to do. I think it's a great place to be. And we need more companies and people coming into this field to help grow and learn and engage, because we've got to get drugs and products to market so that a pathway is developed so that we can keep it going. And I would absolutely encourage it as a great place to be. Just because there is so much, I think, untapped opportunity, and potential at this stage.

Steve Lewis 20:47
That's great. That's a really exciting analogy, comparing to monoclonal antibodies. And especially when you take it in scope of even over the past five years, we're already talking about bi-specifics and tri-specifics. You can imagine how quickly something like this can accelerate. It's really, really exciting.

Dr. Gabriel Alves 21:08
Question out of curiosity, in your opinion, what will come out to the market first? Would it be an exosome-based diagnosis tool or a therapy-based, exosome-based therapy for any disease?

Jim West 21:26
Well, that one's easy to answer, because there already is a diagnostics company. And so they they're doing a lab developed test for lung and a prostate cancer. Their company is Exosome Diagnostics, they were acquired by Bio-Techne. But they they've been around as much. And I think that's still the right answer. Because in the world of bringing a diagnostic medical product or a therapeutic pharmaceutical to market, a diagnostic is way easier. I mean, the risks to health are so much more minimal. It's very straightforward, right? You know, you got to do your trials, you got to get the data, but it's just a lot cheaper, easier overall, it's a much lower lift. So, I think the answer would always be diagnostics are easier to get to market than therapeutics, but going to look at the payoff, I think that the opportunity in therapeutics is much larger.

Dr. Gabriel Alves 22:20
Makes sense.

Steve Lewis 22:21
In terms of growth, you've mentioned a couple of times, of course, about this being a growth market. Are you seeing also growth in terms of labs. You mentioned 25% growth in the number of papers that are published. I'm curious, are you also noticing academic environments that are taking up this area of

research? And is that 25% going to grow, maybe even exponentially, over the coming years in your view?

Jim West 22:52
Yeah. You know, even to academics, in life sciences, a lot of them still don't really know about exosomes. It's still an area that there's not a lot of broad knowledge about. And I think as this field evolves, and the again, the research continues to come out, it's going to attract more and more. And when I look at the research field, I really see two kinds of segments in the market. I see exosome biologists, you know, researchers looking at exosomes and their biogenesis, their life cycle, what they are, where they come from, what they do, everything about the exosome and its life cycle. And then there's another set, which is more application focused, right? So you look at a research clinical hospital, and they're looking for, to solve specific problems, but they don't really care about how they got there, it's just exosomes might be the path to get to what they want to do. So, exosomes are kind of the path they need to go to get what they want. And these are two I think they're fundamentally very different views of, of the world and this research field. But I think that that field, the application side, where people see about the potential and the function and everything else going on with exosomes, they're looking at, they're saying, "I want to get into that. I want to do some stuff there. I want to account for that. I want to see what's going on." As the field matures, and again, more people get trained in the field, it will continue to grow exponentially, and especially if we can get tools that that really lower that barrier of entry. I think it'll really expand very fast.

Dr. Gabriel Alves 24:46
You mentioned about the reproducibility of exosome research, and you mentioned that some tools that will come into the market will lower the bar or increase reproducibility of experiments. In terms of reproducibility, is it technique-based? Is it product based? Is it technology? What is the main focus on that?

Jim West 25:16
It's just a broad challenge in the field. You do an experiment one day, you do it a second day, and you can get different results with the same sample. The reproducibility is really a huge challenge, because I mentioned the sort of the standards, they're trying to kind of wrap their arms around this problem and say, well, if we're going to attempt reproducibility between labs and things like that, we need to know so many things about how they're doing it, what they're, you know, what materials, chemicals, processes, procedures they are using, so that we can replicate it in the same way. Because if we do a different step differently, a step differently than what they did, it might not reproduce the result the way that we expect. And so, the answer is, it's just, it's hard. None of the tools today really seem to account for this. And it's an area where, especially when you get into, you know, clinical applications, reproducibility is going to be crucial to making an exosome diagnostic actually work. I think that it has to be solved. And I think that there's a number of ways that can be done. But I don't think it's solved yet. And I think it's a combination of having the tools on hand, and the skills of a person. And right now they're both high. You need good tools, and you need good skills, and you still get variable results. And we want to get it so you got you know, simple tools and low skills, and you get pretty similar results. That's the that's the goal. Whether we can do it, you know, I think we can, but you know, time will tell.

Steve Lewis 26:57
Yeah, I'm especially intrigued, I've just been considering application areas. And I really think that throughout this conversation, one thing that stuck out is just the idea of exploring further tumor microenvironments around perhaps solid-state tumors, which is a really fascinating area. And I'll be interested to see development over time.

Jim West 27:23
There are actually different techniques people have developed for trying to get exosomes out of solid tissues. There's a ton of exosomes in solid tissues. And so, yeah, you should be able to, if you desire, to develop a protocol to take a biopsy or a solid tumor, and then you could get a lot of exosomes out of it.

Dr. Gabriel Alves 27:46
You also mentioned earlier in the interview that exosomes, because they're so small, can possibly cross the blood brain barrier. I'm also very interested to see where this field is going to go in the future, especially for therapies. As I mentioned, in previous episodes, I have multiple sclerosis. It's a neurodegenerative disease, but there are plenty of others out there. ALS, Alzheimer's, Parkinson's. So, I'm very curious and excited to see where this field is going to take. And I hope the best comes along.

Jim West 28:21
There is actually a lot of research looking at things like traumatic brain injury, MS, ALS, Alzheimer's Disease. There's a variety of, of neural signals that if you can get specific enough should be in the blood, right? So, you don't have to do a spinal tap, you don't have to do some of these very invasive procedures. For example, this doesn't really answer your question here, but you know, we have we have a paper that my co-founder Mei did a few years ago, and she was actually taking urine samples from bladder cancer patients. And we were able to identify through DNA, bladder cancer mutations in the urine. Yeah, if you can get to the right signal, and there's enough of it, then you very well should be able to really open up a new world again in kind of liquid biopsy applications.

Steve Lewis 29:19
Very interesting. Across this conversation, have there been any areas or topics that you might want to discuss or come across to our listeners that we might not have touched on?

Jim West 29:34
As I've said before, there's a lot of people very interested in reading about these this field, but it's very difficult to get into. It doesn't have to be as hard as it appears. It does take good skills and techniques. And it also takes a little bit of an investment to get the right tooling and equipment and chemicals and training and everything else. But I do think that there is a lot of opportunity here. And I think that, you know, I meet so many brilliant people every day doing totally different applications, and I'm learning every single day talking to different people in this field. And I'm continually blown away by people saying, oh, you know, I'm studying exosomes and the effect on this, and it's just like, oh, wow, like, I never thought of that. That's fascinating. You know, there's, there's one lady I know, she's looking at HIV, and how HIV and exosomes interact, and how you can maybe build a vaccine or a treatment

based on exosomes to the HIV virus. There are other ones. We have a paper that a collaborator published. And I think we have a record for maybe the smallest isolation of exosomes from a sample ever. It was inner ear fluid from mice. And they were actually able to identify genetic and molecular biomarkers to detect hearing loss.

Dr. Gabriel Alves 31:14
This is nuts.

Steve Lewis 31:16
Wow. That's incredible.

Jim West 31:19
So, yeah, it's so much opportunity and so much to do, and I would encourage people to do it, and I hope that I hope that we can help them get there faster.

Steve Lewis 31:32
That was Jim West, CEO of Clara Biotech. 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 if you'd like, consider sharing something you learned on today's episode with a colleague who might enjoy the show. This episode was produced by Matt Ferris, Sarah Briganti, and Matthew Stock.