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TRANSCRIPT - GR 09 08 23 Molecular Imaging of Pulmonary Fibrosis" guest speaker Sydney Montesi, MD from Harvard Medical School

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- It is my absolute pleasure, and he is our speaker, Massachusetts general in Boston. She stayed on faculty as a position, finances and an assistant professor at Harvard Medical School. Her emphasis is primarily on clinical and translational. She focuses on profession and treatment. She has a prolific publication history, and has all many roles and educational mentorship and leadership roles, including Foundation and the American Graphics Society. So we're looking forward to learning from Donald Tesi today. He's joining
- Yup. Yup.
- great! And thank you, everyone. Thank you. I think, for that highlights. I don't for the technology here. And the development can be applicable to people setting a multitude of diseases across word and processes. So I do have several disclosures about point on. Here we receive some industry findings related to the work. I will talk about what I'd like to do today is talk about the challenges and unmet needs, and then transition there to talk about molecular targets for fibrosis energy. And while we'll do this, we'll talk about the concept of molecular energy which is probably very familiar for relevant people as well as transition to the areas.
- So clinical challenges and fibrotic diseases. Well, there are many, notably imaging tools are generally limited for early on basic depression, they work better for advanced disease and one limitation that we have. Is it the imaging tools, for the most part, really are limited in their ability to distinguish active disease from which is particularly standard in many cases especially early. But Riff, maybe in particular, there seems to be a shift in the field in terms of less biopsy. and then again challenges this challenges. We have clinical we have challenges in drug development for fibrosis. So for some available treatments, only work. That's a slow progression disease. This is what we have in terms of limited ability, activity or assessment. That's just regularly halfway, and then because of this, their concerns over target engagement. And I think, you know, a lot of these issues are have started to be addressed in in the recent decade in terms of quality, in terms of stratifying that's so much based on disease activities, but based on its regular mutation size.
- So we don't always have that in terms of might not be as readily available.
- So in terms of progress, progress, progress, progress, progress, progress progression for an individual patient, and then our current monitoring measures of Ct or pulmonary function tests.
- They provide disease severity, but they don't give you any information in terms of change over time. Unless you have a multiple measurements, and there's really a limited ability or inability to determine individual treatment response. If you have the patient that has more inflammatory on disease where you can document their benefit or improvement with suppression. That's one thing. But in terms of tree patients.
- And so this just highlights kind of national history of disease, progression over time, pulmonary function. Over time. They'll see. This whole is a progressive disease.
- However, what we know is that progress should be can be quite variable, will have progressive disease until death. Some patients will have a more force. Some people will

have rapid progression over a short period of time and their fortune locations that might come location in terms of care, plan, treatment.

- And then, from a clinical trial standpoint, you can imagine that you want to clinical trials.
- And then if we think about the IP treatment, we have 2 treatments. This is showing here. There's similar data to support a similar effect in terms of and other types of progression and medication. This slow down the rate of progression it in the rate progression, variable patient. It's literally impossible to determine treatment, location, and these medications come with considerable side effects. So you'd like to know a certain view whether or not your patient is receiving a benefit. And again, these have implications not only for patient care, but also clinical trials.
- And then, if you think about the field of idea. There's been a multitude of trials. And highlighted in red are the 2 they had for which the primary endpoint was multiple trials. But with a few. Your escrow.
- Okay? half way. Because I can't.
- These are important questions. In the current time. We have no real ability to be able to do this.
- So I kind of went over this already measurement term response treatment. It'd be only possible. And then there's a major difficulty determine early efficacy for the current time, the main standard this user and usually uses the primary endpoint for terminating efficacy for treatment is for side capacity.
- Well, what we've known recently is that early changes at 12 weeks don't always equate to a long term effect of 12 months. So we have difficulty determined early advocacy. We think about progression, and at the current time we think that 5 roses is not reversible. Like 5 years from now we might be thinking differently. Time, as long, so to speak.
- So I look at this and kind of convince you that kind of we really need a a marker of the activity that also can help participate, but also have potential use in terms of clinical trials. By allowing individual treatment response, and then in such, maybe utilize this clinical trial to try have an early answer in terms of broad effects.
- So this is
- But we think about fibrosis is is apparently are there ways that we can assess these biologic processes nonvasively. And if so, this is what kind of the the wheel of packages in terms of activity. If we could kind of quantify how active, let's say, matrix accumulation of cross linking is at any one time. Could that give us a window in terms of Cpx. Would be.
- So I'd like to introduce the concept of molecular energy which you're probably all familiar with. If we think about Ftg for for oncological reasons. But think about in terms of molecular energy for vibrations, and I think it has a lot of advantages. One. Because the last non invasive assessment of cellular processes.
- And then you can think about it as a way to not only monitor but also quantify, just regulated molecular. You can replace that with any type of process of interest, because there are multiple different. Whatever can have multiple different indications that can. What disease process we have, it, might have any kind of need to fibrosis and then thinking about opportunities to advance clinical care and development comes from areas that I think are important about, how can we use this for early infection saving and on the clinical trial the early phase front think about, can we look and see? The drug is engaging in target.
- And so if there are any effects in terms of treatment, and then any kind of moving ahead, you can think about molecular. What happened in terms of lung cancer treatment in the past decade in terms of, you know, treatment not showing in the back when treating small cell lung cancer. But then, if you feed it, type of molecular and you can start to in terms of

so we've now rolled out into the disease. Angry eyes cancer. Whatnot. Okay? So this is just a schematic showing the potential applications. And then other people gone and work that we're doing to try and address some different issues. But this is so. For example, if you had a pet imaging mining and it competes with your drug of interest. You could you could use that and be able to determine, like what your drug concentration is and how much drug you use to you know, to block that. And then if you wanted to try to understand, like whether or not your target is expressed, and with what frequency? That is something you could do. It adds value to other types of conventional imaging licenses. And then some work that I'm particularly interested in. We'll talk about. In this case we use something like this for early.

- So this is just a snapshot of a multitude of different pet probes that have been developed. And again, this is something that was published a couple of years ago. So the list that's really expanded and it should be noted that a lot of these pros are developed for indications other than vibrations within imaging they might have been developed to image Macro pages. What not? But again, there could be a lot of these pros can be leveraged for different indications of interest.
- And then, in terms of going through kind of going through some examples meeting in terms of exactly expression. So you know that that's not insignificant.
- And we have limited ability to capitalism ability to a activate latency and just showing if you look over here to the right. You have the Ct scan showing evidence process, and then you can see on the pet imaging where there was increase signal with a higher scgan, showing that target itself is engaged and then use the development in an early base therape in terms of being able to turn in not only was it targeted express but how much investigational drug kind of engage the target. So as an example of having confirmation before you move on late face. Development, to know that. Yes, your target is there. You have a therapy that can change your target.
- This is another example of accepting engagement. So this was a big one. Study brandy, basic small number of patients gave ipf, and then had with this specific 30 min after dose and 24 h after dose vacant. The numbers are really tiny but what you're looking for is, you're looking for change. And this might be beneficial.
- And then then doing a step further and they see it. And they're the evidence of any pharmacogenomic effect. Right?
- You can see here and again the numbers are. And then, after several days of treatment, it went down slightly.
- So kind of getting a little bit of confidence that perhaps starting to get raises to me to try and very, very competitive landscape with multiple local targets.
- And so here's that again, that yellow patent genesis, and in terms of different models, and those I highlighted in red, corresponding the kind of the pathways they might be targeting and then in yellow. Or if I agree and actually are in different pros that have been human studies.
- And I'll switch for a second talk about some work you've done with that foxes it, and then spend most of time talking about work we're doing with a technical college and pro.
- okay. So as I mentioned before, relationship fiber of it.
- And the lab where I was working is located. in the same building as at large in my center. That's it. Ng, and one of the one of the Phd there.
- MRI, and about the role of adequate. That's it's clearance. Of. A radio label, Mac or molecule. So this is a large molecule that's available. And then thought, being that the greater breakdown of the album or capillary barrier the faster the clearance rate is gonna

be. And so what they show here, is it? The room number 4 that had the fastest clearance of this relabel macro molecule. Those had the worst survival.

- And then there's another study that measured the amount of amount of protein and be all fluid, and they did it as a ratio to the protein in the blood to get a protein permeability index, and they show that if you looked at ipf patients overall. The protein permeability at index was higher and ipf patients compared to normal. And then, if you further stratify that based on those 2, 5, or survive over a 3 year period, you'll see that those who died within 3 years of follow up have high protein, permeability index.
- And so this kind of you know, to consider who we do molecular to try to understand it, whether or not we can even measure any type of so is a Galenian based algorithm molecular pro.
- And the time it was FDA approved some blood pool reagents for more as geography. And there is evidence and pre clinical models that it can affect increase faster permeability. And now it's modeled in vivo. And so these are apoe deficient minds diet and they had developed accelerate sclerosis, and they were there was increase MRI signal in areas where there was and kind of supporting its ability to kind of pick out faster permeability.
- So we did our first study really exciting. We enrolled like 6 patients and 4 healthy volunteers, and then they pulled on market, not for safety reasons, but that was a bad day for me, but nonetheless. This is what we found which really surprised us.
- This is a healthy volunteer. And so basically, this is like the app and your brand. You can see the high signal, and these images are contracted images. So I did post injection minus pre injection MRI, and then superimpose on pre injection. And so this is the healthy volunteer here. And this is a patient with Pomeroy roses. You can see that this amount of signal is, I thought, was quite impressive. And it's just a corresponding Ct, that was signed within 3 months of the MRI. And this is a patient.
- You can visualize that that the amount, the visual burden of hybrid changes, the overall model. This is someone who's who's diagnosis that I get was confirmed via
- and so visually installed. There was a market increase. And then we actually, we quantified strategy and index. And basically, we just looked at the difference of a signal intensity. After before administration contracts and along. And we normalize that for the change and move, that's all. And then again, I know certain numbers are incredibly tiny. But one thing that was interesting to us is it out in that strategy was increased throughout the long, and maybe we had 100 people there? We might, we might determine there was some type of mild regional effect, but if we just look at it visually and tiny numbers, it seems to be visually similar.
- So and but sadly, was open the market. So we started doing something else. So as I mentioned the center where the research lab was they had done a lot of advancements in our development. One thing that they had done is they develop functional MRI, and they did a lot of work in developing different ways to analyze dynamic contracts in Uri. So the thought was, Well, can we then use any like contract a little, you know. But I'll get back some more molecular in a minute in terms of a way to measure. popular permeability. And so some advantages to MRI is you get functional information as well as atomic information, and then you've got there'd be more improvements in in
- the ability to see what's the long in, in terms of trying to overcome some of the signal limitations, to be able to initialize higher resolution.
- So basically, what you see inrias is a dynamic. 2, one way imaging, and it looks at the extradition of an intravascular contraction and then depending on. And I'll show you in a second. You can use this information and to really determine what calculator fusion with microbes and ability. And let's actually get space and then kind of and so what happens is

you have someone in our Icm, you do a continuous acquisition like really, really fast on the order of several seconds. So it's repeating, you get that, and then roll the baseline images you inject with the power injector. Galen and then you. So we think about using cardiac

- and over I'm I don't know. I don't get any calls in the room. But multiple times a day. Multiple places around the world is when they when people have got to breast in our eyes, and so you can map out the signals. You can see over economy and in the breast module, and you can see this one side will rapid, uptake or wrap it down. If one is, take a little slower up and it doesn't really wash out. And so in in the press, on top of the world, or the world, you can classify different type one type, 2 or type 3. And based on that contract comes in. How quickly it washes out. It gives you the for webinars.
- So bottom line on this, I think I just wanted to kind of show you that there are some changes, maybe and there's always also political usage of this. And so we did this in patient with you package. And again we get continuous imaging here, and we inject the signal.
- And then it washes that over time, and these are average healthy controls and Ips. There are 17 and 15 respectively, and you can see that in the group patients with ipf the peak enhancement, slower, slightly slower washing, but the tissue doesn't wash out as fast
- so visually you can notice a difference between the 2 groups and to try to see what we were trying to understand what we saw before we think about peak enhancement. So that's gonna be a maximum amount of signal. When a when the contrast first goes in again. We saw that peak enhancement was different. Not, and not just send the lower regions, but alone again supporting there might be microvascular changes that are important, how we get in our regional.
- And then we go for regional changes. We think about walkout. So we think about the rate at which contract watches out, and then that kind of be slow with where fibrosis is greater. Not surprisingly. Where do we detect our difference in the lower region of a month.
- And these are these are just showing the curves on the left. And when you start doing well, this one, this one out at the bottom doesn't look good, right? Because the contract keeps going positive. It's not even washing out and then, if you look over the parametric maps. Here you can see that the contracts the washout time is really slow. And so you see, there's more red, and this is a patient with rapid progression. And rapid progression is determined by either that or Fpc. And 10% in the the subsequent 12 months. And this is the patient that had stable slow progression. You can see visually the colors are different, and then we go right here to the pointer. Doesn't fully cover everything. If you were to visually look at you say, well, it's not as if the personal graph progression coming everywhere, and you visually similar in our parents, and then the following, 12 months much more.
- And just to show that these techniques may be applicable to other types of a long addition. This is more. We did. That we published earlier this year, and and the Blue Journal, and what we initially had prior COVID-19 when we compared them to A similar volunteers, and notably most notable about these reduce the and peak enhancement in patients with prior covid infection compared to healthy. And this should show some examples here. Healthy. So it helped me that higher peak enhancement. So more contracts coming into tissue injury, red and compared to Prior Covid. So it didn't question, what's going on right now?
- Okay, so moving to work reviewing on college, and which has a lot of people.
- So The affinity is moderate. That's so pretty work to bind in States. English. There's more positive and the other thing based on the degree of how you know, collagen is well established there. There are less binding sites that are available to the pro and technology on our first human studies, which I'll show you in a second. We see, very minimal any

increase uptake in the skin or the phone, or for patients for whom we've had Ct over time and areas in which the different areas have been present for several years.

- Okay. And I maybe skip this for the sake of time to show animal data. In terms of model and the integrator.
- And then this should show that I just want to point out here. This image here. So these are. I'm looking at how well CD buying human ipf lump tissue. And this is the person injected program. And then person here is a very nice correlation here you can tell alright. So we've done our first and human studies. Using this pro we found those well tolerated billing to say adverse effects which you would expect and then we publish several years ago. So this is kind of our first use of it. And humans and then he is a participant with Ipf and see is a corresponding Ct region. But some things that are interesting. You look at the corresponding Ct not all areas are hot, and if you look at the area, the arrows that are white, you see some. So again it raises the question, are we seeing something before? There's no structural damage. And there's and we did quantify this very simply looking at. And I guess the point of this, which was kind of reassuring to us it. It makes sense. We saw the highest update in in the in the lower region of the Long and IP subjects, and especially in the suburbs. So again, we're kind of seeing what we would do with stack based on distribution.
- And this is an image showing. Then, again, this is very preliminary, but it seems like our signal may be increased in areas of recent progression. So this is the MRI that we do with the padden arm, which is not very good. You can tell that it's not very clear. But if you look over to the right on Dean, this is a clinical Ct that was performed approximately one year before the and you can see that. Yeah, there's areas of fibrosis and basic. But it does look like there's fibrosis progress a little bit right above the liver. But the majority of fibrosis progression is been around middle port from along. And that's really what we're seeing, where it's hot on this side. We're not seeing much. I'll take it all on the left, which visually
- doesn't look dramatically change, and we have not been like algorithms. But it does suggest that we're visually on TV, and where there's a great progression. That's where we're seeing our hottest areas on and then our number probably then, about 30 participants. Today with ips here is a healthy volunteering, a and patient who has and see, the patient has less than 5% over 12 months progression kind of how it's going to
- from oncology, where you have mass and volume right? And then you have a process very heterogeneous, and you don't want it in in a small amount. It's incredibly hot, might be actually more problematic than a larger amount. That's just above what you would need to be normal. So we still have a lot of work to do in terms of quantification whatnot, but I think that this is going to perhaps give us encouragement, perhaps might be on to something that might be kind of more related to active disease. And so if we need to kind of my area that I'm particularly interested in, well, it is something that is detecting response.
- And then we have done test to test imaging, and a very small number of patients. Ipf, where we repeated their pet imaging within 2 weeks. And we found that the repeatability is actually quite good. Repeatability, for Sg is on the order of 20 and this is looking at Maggie. Now, client activity for a lower loan region from the first year in the second hand there, there is a deep overlap, because if you, if you the better the better. Your pet probe is in terms of the minimal, less variability, the more sensitive small amount of changes. And so you know the for it to be for this technology to be helpful in that clinical trial setting. We really need something that we can have other institutions be able to use. One advantage of doing this with gallium is readily available, and I see that gallium is that you can, Jack, and even within an hour so and then walk. That is really expensive. You can at some point document that it can help guide treatment, or, you know, guide a clinical trial program

again. That's something, provide information, and perhaps it could be cost effective. And so this gets me to some work that we're important. And I'm particularly excited about so, as I mentioned before, and probably and that's he published a research letter in the English Journal and which patients there will have undergoing lung diagnosis, and that resulted in rejections and extract full collision one as well. Biomarkers all number of patients. So with how and right now we put in an age, grant to be able to do a relative level over.

- So we think that our hopefully, we'll have full time.
- The first time in which change in a pet marker will be the primary outcome of an IP clinical trial.
- So there's a lot of applications in for other reason you can imagine we have active processes, active protocols in place to look at systemic services, progressive home America at Eagleheim, to look at patients early in their schedule and disease, and see if this can help us understand what patients may be which the most active TV are undergoing calls and head, and there we follow that imaging one year later. Try to help understand what's the? And also does it correspond with cardio card and then we're working on developing other pros. So one pro we're working on developing is one is more specific genesis. So fiber Genesis is really the active process of formation. And then, as part of that our product of blocks active on, on collagen and so the hypothesis, we develop a contract agency MRI, here's a cham pro and this is a there's a lot of activities you can see here and be and then it goes down in 4 weeks. And then Rachel, my colleague, and she working on a translating pet imaging pet version indication and it could be purpose for viruses imaging and and it could be helpful for people. So you know. So I hope and conclusion. And I hope I kind of tried to convince you all of them feasible? Is there opportunities here in conformance to biology and disease, activity for the goal of non-negative phenotyping? And I think we have great opportunities and therapy monitoring drive, enrichment, early termination treatment funds. And again, I'm on the clinical side. But I think there's a lot of opportunities here for people that component
- I should acknowledge here caravan, who is the inventor of the call and pro and all the work with. They've been very helpful in terms of assistance with the sequences and data analysis. And of course, and then volunteers on their studies are costly. And so there's been a significant amount of investment by governmental funding and and foundation support, which we've been very grateful.
- And so thank you very much for your time. It's really an honor to be here. If anyone has any questions, I'd be glad to try to answer them.
- Be for an excellent talk, and for your patience there's people difficulties at the beginning. I will be monitoring the chat, but I can get the questions in the room. Sorry. So
- passing that with the Gallium Cpe, CD, 8 pro, you can target active fibrosis in different areas. So long do you see that any potential clinical utility to seeing where that active or is it more just activity?
- And that's a great question. I think. I think they're recording uniform every and then you can maybe try to understand where fibrosis progression might be going and maybe back in terms of you know, basic all of these.
- I think. Yes, it. It is both ways, both in terms of our understanding, and then maybe uses some more understanding. Maybe we can develop kind of different targets for understanding. So. I think that's one thing that we're hoping to do by II couldn't agree with that. But we have, Mr.
- And then what base biomarkers. And hopefully, this will be helpful for people that are much more than to try to understand Ohman's work. So we can try to kind of see what

these changes are regionally and how that may correspond to other changes in in blood or or Ct or whatnot, for reasons that aren't clear, and we still don't know why the fibrosis tend to be lower, low, and peripheral, right like. And also, you know, for the reasons we see that are might be more central based. Well, I know once that the body can kill itself, or and then we're not gonna see that fibrotic area 6 months from now.

- So I think these are things that we don't know. And it's a really under explored area, which is probably why I like it.
- Be honest, thank you hey, Sydney? Great talk! You know I really enjoyed your discussion of vascular permeability and the role of micro vascular. I think that's really under appreciated in the disease, and maybe think about how clinically. When we see IP patients, some of them have micro vascular features like renounce phenomenon, they can have changes as well, and we think about them as like a sub category. It's called ipad, but they don't need criteria for a full and connected tissue disease. So I was wondering if your imaging could help us understand that clinical phenotype better. If you've done any imaging in. I get patients that have those kind of features as a different yeah, no, I think great question. We've done an idea. And we in terms of the like microbasket type. And we started doing it split numbers so we could try to understand. So I think right now, that's been our. Our limitation is just our smaller numbers. But I mean, I think that one thing I want focus, limited, but and is there a way you can kind of tie in this multi-system. That's
- where problem which is, I think, what you're going with And then one nice thing about the pen mark. If you can extend your acquisition or your billing you and try to get you know, more organ.
- So cool. Thank you.
- Thanks. So my question was, when it comes to like a pro development or finding appropriate pros and a lot of medicine, I think we often start with what's available like you talk about in oncology. Other. What's your efforts are being made to like maybe from intelligence about our view, but intelligently discover probes. Because you can imagine with that wonderful picture of Albuolus, all these processes are happening that contribute to scarring. So how do we figure out what to look for.
- Yeah, it is great question. All those new development.
- So I think there are opportunities. With the spir grants, because there, there seems to be a lot of growing interest from industry. II get, I get emails. I can't make anything. But I can have a discussion, right? So I think that. Ii think that we once this technology becomes more out there, I think there, there'll be a lot of opportunities from industry, academic collaboration to try to develop these. And one thing I should say about Pet, because you just need a tiny, tiny amount of those. It's a lot easier to get that through development under an id. And if you're gonna make you know pro so II think in terms of your idea of like, what's up? What's a important target? And then perhaps find either an industry or a small business collaborator? I think that that could be least, and my experience that has been very helpful. Because then you can also, I shouldn't say leverages the right word. But then you can also kind of do more development as well cause these things are expensive. But take your point right. Ftg a It's so much. It's even say that the rudimentary in the sense that they, you know, they target metabolism like, how do you be more specific than that? And I think of it. You know my hope is in 10 years, you know, combining it with like Emory's work, we might have like something like, so what we call idea. That's now, you know, Abcd, ivf wonderful talk. I know we're reaching the end of the hour. So I have about 1,000 questions. I actually just have one pretty direct one. Make one comment.
- We had a paper a couple of years ago. It's demonstrated that the healthy part of the lungs will not help you at all. Looking at the privacy of the tissue in comparison. The second is

David Wilkes. Here was our previous team work looking at Call 5, and I was curious. If you have any pros, call on because one of the real limitations of that work was those who don't have a type, one call and wraps around the type 5. Like of his role.

- And it's for call 5 system.
- And who to select for treatment was limited by who I supposed?
- Yeah right? Well, target, because there like that was a really exciting talk. I'm not actually a radiology. So I was thinking, but you're talking context with things I've seen at recent conferences that look at cell specific pet pro targets. I was curious if you could deliver multiple pros at once, and then leverage that to look at, maybe sales of interest in conjunction with looking at college. And yeah, I think I think probably answers yet on the yes, the other thing that on the on the human side there have been some developments in terms of like pet scanners in terms of the sensitivity to sensitivity. Per dose such that you could give a really small amount of radiation, and you could get more than one pro at the same time, so you could try to understand. And okay, alphabet 6 is here collagen here, or that sort of thing. So I think that based on that. And then I think that's also one advantage of radiation with Ct, but you could have ways that you could play dose in these really high scanners be able to do that. But on the pre clinical side you definitely go because we've had talks about doing, you know, running multiple pros through like precision. One cut sizes to try to really understand more kind of where it is sells all areas are most affected.
- Thank you. Again. we'll conclude. Thank you.