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TRANSCRIPT - GR 09 27 24 ***"The Broken Wall in Idiopathic Pulmonary Fibrosis (IPF): Ectopic Epithelial Cells Drive Fibroblast Activation"*** guest speaker James Kass MD, Univesity of Pittsburgh Medical Center

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**Internal Medicine Grand Rounds**

- So good afternoon, everyone. It's my pleasure. Looking into today's speaker, Dr. James Pass. University of Pittsburgh Medical Center in 2010, where he is now an associate professor of medicine, clinical and Translational science as well as the Director of the North Ep. And Richard P. Simmons Center for interstitial Lung disease. The Nih Funded research has focused on diverse areas of Iops, including fibroblast biology as well as public trials with the ultimate goal of developing novel therapeutic strategies to treat type work.
- The clinical practice is primarily devoted to patients to finish.
- Hi, can you hear me. Okay, okay, well, I'm so thankful to be here. I got in last night. My suitcase was soaked, and I got into a hotel at 1130, and I everything dry, in hopes that everything would be ready. So thank you. Thank you. To Dr. Emory knows who's a president and colleague. Thank you so much for the invitation and all of you for coming to to hear me today.
- So we're gonna talk today about idea. And this is kind of what gets me up in the morning. That's good.
- So okay, just get to the disclosure. So I've been a consultant most recently for caldes therapeutics.
- And today, what I want to talk about is to understand really the latest theories in the pathogenesis of Ipf, and to really understand the impact of biomarkers. And it's hard for me to be in the presence of Dr. To really talk about biomarkers, since he has really innovated in this field. And there's yet more to come, so I'm looking forward to hearing about. In days, my heck! So we'll talk about Jack. And again I'm please. I hope you'll ask questions. Jack is a 67 year old man. He's a former smoker, and he works for us steel.
- Okay, so this is, these are my patients. These are the patients of Western Pennsylvania, and he's had progressive shortness of breath over the last year he saw his Pcp. And he diagnosed Copd.
- Not a bad thought. He's a smoker. He's from Western Pennsylvania, and epidemiologically, it's probably a pretty good, but there's a subset of group of people for whom this is not the right diagnosis, and as he progressed, rockodilator therapy provided no relief, which is typical.
- And then Jack was sent for cardiac testing, and many patients with Ipf will tell you that they've had significant delays in their diagnosis. And so he went for a stress test. He had reversible ischemia, and he went to for path, and he got a stent, and lo and behold, he remained shorter which is probably not again not surprising to this audience. So here's the chest X-ray. And so the chest X-ray, as my grandmother would have called it, is Schwarzenegger. It's busy, and there's there's a lot of extra

lines around and this is clearly not the X-ray of somebody who has chronic, obstructive, pulmonary lysis.

- And so you probably get Jack to a pulmonologist again, nothing against the cardiologist. But again, this is a lung disease. Jack gets pulmonary function tests, and Jack's pulmonary function test. He has a restrictive, ventilatory defect which is defined by low total lung capacity or Tlc. And impaired Gas Exchange. So he has a low Dlco and you send him for a high resolution. Ct. Scan, and you see some very characteristic things here. So you see something called traction bronchiectasis, which, again, are these kind of large dilated airways which look like bronchiectasis. But it's not real bronchiectasis. So the airways are being pulled distally by the fibrosis caused by the sublural honeycomb.
- And so again, this disease is characterized by fibrosis and shrinklery, and it pulls the airways distally when we see this thing called traction brochures.
- And so you see, Traction bronchiectasis and your trusted radiologist reads the Ct as a probable Uip pattern. Okay? And we'll talk a little bit about what you likely fits.
- And so what's the diagnosis? Jack has a probable Uip pattern on Ct, and you can diagnose Uip. And I'm going to get to that Uip, either by biopsy or by a very suggestive Ct scan. So in many people you can avoid a biopsy and you, as the pulmonologist, have excluded any other known cause of interstitial lung disease. I'll just tell you there's nothing to suggest autoimmunity, no really significant organic exposures. And so in a patient, after all, clauses are excluded. Somebody with Uip you can make the diagnosis of idiopathic pulmonary fibrosis so just to kind of give you a sense of the scope of the problem. Copd, according to the World Health Organization several years ago, was the 3rd leading cause of death in the world, and that's not ipf. However, ipf does have a significant mortality burden, so the death rate for Copd can be anywhere from 0 point 3 to 3 per 100,000 person years and it's almost 20 fold higher in Ipf. And this is something that many of the pulmonologists see, which you can have somebody with a terrible Fev. One, and they can live for 10 years. But the Median survival for a patient with idiopathic pulmonary fibrosis is 3 to 4 years from the time of diagnosis.
- So we asked, what you are, what is Uip?
- And so to get at Uip? Let's go back to what the lung looks like. So here's the lung, and you remember it from histology. It's a beautiful, fine, lacy structure that's methylized for gas exchange, and when, if you laid it out end to end, it would have a surface area of the size of a tennis court and so in the box are are the is an airway, and right next to it a pulmonary artery. And so the again, what's lining these structures? Okay? Again, the airway is the specialized airway epithelium, which, if anyone can remember from histology, what's the kind of epithelium in the airway columnar? Okay, palumar epithelium. But then and then there's a separate alveolar epithelium. Again we see the very finely structure of of the alveolar septum one cell layer thick, and it's and is specialized for gas exchange. And so when we think of the embryonic development of the lung again, the epithelium is highly specialized, and there was always there's there was the airway epithelium here with these columnar epithelial cells. Some of them have cilia. Some of them are secretory cells, so they think mucus or different things.
- There are neuroendocrine cells. But as you progress down the airway, and I'm sure you probably remember this from studying for lung histology at a certain point, you hit the bronchoalvular duct junction and you transitioned from the airway epithelium to the alveolar epithelium. And so the alveolar epithelium again, remember type one

cells which are flat epithelial cells specialized for gas exchange, and the type 2 cell which is called the defender of the Alveolus more on that a little while. So, again, looking at higher power, you see ciliated epithelial cells. Cilia. You can see there's this triangular cell that sits along the basement membrane called a basal cell. A basal cell is very hot in the Ipo field, and it's largely considered to be kind of an airway stem cell and then mucus cells, where you can see kind of this kind of white clearing like inside the cells.

- Then we have alveolar epithelium. Again, type 2 cells make.
- Thank you and type one cells again specialized for gas exchange and lots of lineage. Tracing experiments have verified what we've always thought, which is that the type 2 cell is the stem cell of the alveolar space.
- And so, Uip when we get back to it, it's a histologic pattern characterized by something the pathologists call temporal heterogeneity and fibroblastic foci. And so I'll show you an example. So low power, diagnosis, high power pathologist. The saying goes on the left here is normal lung again, the fine lacy structure. But then you look at the right and then at a low power. This is usual interstitial pneumonia and so the temporal heterogeneity is the fact that you do have what looks like kind of spared lung here in the center, and some pathologists call this the Donut sign, where there's again a rim of fibrosis sparing in the center. And then, when you look more closely can you see these structures, which are called fibroblastic foci and fibroblastic foci were defined as these type 2 cells that overlay atop the fibroblasts. And again, fibrosis is the deposition of collagen, and really the destruction of the Gas exchange surface a long time ago embry probably knows this literature. The number of fibroblastic foci in the lung was really proportional to the prognosis of the patient. So there were analyses that showed that the number of fibroblastic coci and the amount of collagen that one could see histologically was proportional to a patient's risk of mortality and again, these these cells here, we're always kind of very interesting. They're called type 2 cell type, 2 cell hyperplasia.
- And but very early on, you know, and really accurate pathologic descriptions.
- Pathologists really understood that these cells really weren't type 2 cells. They kind of looked like type 2 cells because they were cuboidal. But these were these cells were different. The classic histological studies identified that the lung in Ipf has a transitional epithelium.
- I don't know. I didn't come up with it, and I'm sure maybe Emory knows I've pulled a couple of people, but I've heard some people refer to it as like a height, one and a half, so it seems to be kind of somewhat arrested in you know, in its differentiation.
- But again, these these classical studies describe the appearance of a cuboidal cell population derived from the bronchiolar epithelium. These are studies which go back to 1982 also fibrosis associated with transitional phantoms between type one and type 2 cells, 1996. So these were all classical histologic descriptions.
- But you know, the 21st century came along, and single cell Rna sequencing came along, and this is an article by one of my mentors, Naftali Kavinsky, and this showed that in the Ipf Lung there were some sort of dramatic changes when you looked at this level. So in red is Ipf looked at, the control is blue, and you can look at type 2 cells. So the cells that met the rigorous criteria for type. 2 cells were significantly lost in patients. With Ipf, however, there seemed to be a tremendous enrichment of these ciliated cells of club cells which used to be called Clara cells. And then there are these cells that they define transcriptomic excuse me,

transcriptomically called like aberrant basaloid cells, and there are cells that have the features of basal cells.

- And and so this was kind of really led us to a new thought about pulmonary fibrosis, which is, that is, that there there was always a really a wall. There was a wall between the airway epithelium, and there was, and the alveolar epithelium and the lines never crossed and there was always a very hard stop. But in this disease that wall seems to break down, and it leads to new paradigms to thought about what this disease is caused by. And so the current paradigm for the pathogenesis of Ipf is that there's normal epithelium up here on the left here you don't see the mask. Okay. On the left there is a normal epithelium. It experiences injury and then type 2 cells which are supposed to proliferate on the bottom left begin to proliferate, and sometimes they successfully differentiate back into type one cells and so again specialized for gas exchange. But then there's a transitional epithelial cell which is which is in that middle. There it says, transitional, and a k 8 stands for keratin. 8. Because this is the marker of this kind of transitional epithelium, and then they they wind up kind of becoming these aberrant basaloid cells. Now, the author of this article because suggested that one of the things that leads to the activation of fibroblasts, because at the end of the day fibrosis you got to lead to activation of fibroblasts. Somehow the fibroblasts need to be active in order to produce collagen.
- And so the transitional epithelial cell somehow leads to expression of chemokines. I'll talk about that in a second. That activate the macrophages and then leads to tgf beta, which the sine qua non of pulmonary fibrosis. I want to suggest to you actually that the chemokines may have a direct role on the fibroblastic part.
- And and so we sort of asked ourselves why chemokines, so chemokines are inflammatory mediators. The airway epithelium is the primary site of lung host defense and these and the and the and this epithelium is enriched in lots of inflammatory mediators, including plutotins. And the reason why I, as a fibroblast biologist, became interested in chemokines, is that chemokines typically signal through G protein coupled receptors. Now, we're getting into some basic biology and G protein coupled receptors have a lot of heterogeneity, and they're signaling
- Gs signaling is typically anti fibroide.
- So one example is a hormone called relaxin. Relaxin is a hormone which was thrown about years ago as a cure for pulmonary fibrosis because it relaxed fibroblasts. You put relaxin on fibroblasts and they calm down.
- But in contrast to relaxin chemokines signal through G Alpha I and G alpha I signaling is typically profibrotic. And so our idea was that you would have all of a sudden these ectopic epithelial cells and then these ectopic epithelial cells are now in the wrong place in pulmonary fibrosis, and then being elaborate different chemokines to illicit fibrosis.
- And so I was just talking to my esteemed colleagues here who have who discussed with me the importance of research on fresh biopsied lung as opposed to most of the lung that I investigate, which is excellent.
- And and so I got this table here from this is from the Lung Genomics Research consortium, which you participated in. Well false citation to Dr. But this was a large consortium of tissue, where we actually had 137 ipf. Lung biopsies that were sent for the early transcriptomic experiments in my children.
- And so we looked at this sample and we compared it to a hundred 8 donor controls.
- And so what was the donor control at that time the donor control lungs were was often histologically normal lung that was distant from a tumor.

- And so if somebody went for a resection of a lung cancer they got resection of the whole lobe. There was a tumor, and then, far away from it, seemed to have some normal lump.
- And so that was the that was the normal one, and that was probably quite normal.
- But it served as our analysis, and we collected really the chemokine, the differentially expressed Chemokines in the gene set here, and we found this gene called Cxcl. 6, and Cxcl. 6, was important for us, because we knew from precedent literature that it was expressed in the Bronchiolar epithelium on the right. Here is the is actually the hybridization signal. You can see that the the signal and ipf is much higher.
- So what is cxcl. 6, cxcl. 6 is a member of the Il. 8. Family, il. 8 is the chemotactic signal for neutrophils, and it signals through the receptors. Cxcr. One and Cxcr. 2.
- And what you may not know about Ilh is that Ilh is frequently elevated in lots of different disease processes. It's elevated in Ipf and has been associated with prognosis, but no one's ever looked at Cxcl. 6 before.
- And so our 1st foray into this was to look at Cxcl. 6 gene expression by single cell, Rna-seq. And so this is a single cell, Rna-seq violin plot from my colleagues at Pittsburgh, and what you can see here is that there's enrichment of Cfcl 6 in. Goblet cells in club cells. Again, club cells were what we used to call Clara cells and basal cells. So again, this lends evidence to the idea that there is enrichment of this chemokine, particularly in these different kinds of cells. It is, however, in multiple different cell types. You can see it in macrophages. But again, the primary enrichment seems to be in these airway epitheliums.
- And so we we did immunostaining. And again I'm starting trying to look at some.
- It's good to look at a picture. Low power that's right in front of you, maybe hard to see it projected, but project out the yellow sign. So on the left, here in the yellow box you can see a fibroblastic focus. So again, that's the Cardinal Lesion of Ipf. And overlying it, you can see the brown staining for for Cx. For an antibody that marks both Cxcl. 5 and Cxcl. 6, and that this is present over the thyroblastic boci and again across the lung you can see it really scanning epithelial cell surfaces as well as cells in the airspace. We think that the cells in the airspace are probably macrophages, and this is probably picking up cxcl. 5. In those cells look more closely at immunofluorescence, and we can see that Cxcl. 6 is expressed in airway positive cells. So muc 5 B has been known in the Ipf world as a risk factor for the development of Ipf in the promoter region of Muc. 5 B. Cxcl. 5 cxcl. 6. These are honeycomb cysts that the nuclei and then you overlay, and you can see that again. Cxcl. 6. Expression is localized through these airway epigenes.
- And so many of the pulmonologists know in the audience that I said that Cxcl. 6 promotes the accumulation of neutrophils in different tissue but they would tell me that they were studying for the board, and they looked at Uip sample. They don't see a lot of new proposals in the in the IP ipf, one. And that's because I don't think cxl 6 is signaling through those cells.
- In fact, I think Cxcl. 6 directly stimulates the fibroblast compartment. So our idea was, again, if they're expressed, if Cxcl 6 is expressed in the fibroblastic focus, and there are fibroblasts beneath it. We think this is a power frame expression of Cxcl. 6.
- And it's directly stimulating these fibroblasts. And so this is Hari in my lab, and Hari has stimulated Cxcl. 6 fibroblasts derived from patients with idiopathic pulmonary fibrosis, and we've wanted for collagen and so they take you through the Western

plot in the unstimulated transition on the first.st That's baseline collagen level in an Ipf fibroblast. But then you give it Txcl. 6 in the second column and the collagen kind of explodes.

- But then you knock down the receptors, both Cxcr. One and Cxcr. 2, and you can see that the collagen goes away. So we think that there's a very important role played by Cxcl. 6 in stimulating the collagen expression in these cells. And then it goes through the receptors. Cx. 0, 1, and cx. 0 2.
- Well, it's all very nice to have, you know, nice Western blots and nice immunostaining, but I think it's very important that we have to relate it to actual patients. And so we next ask the question, is there a clinical relevance to high? Cxcl. 6. Expression in an ipot.
- And so we looked at the blood. So we have a large plasma collection from patients with Ipf roughly, 274 patients. And we looked at it and actually applied the man Whitney test. It was actually favorable. So there's a there's a significant increase. Okay, that significant increase is 5 picograms per mil.
- And that's that significant increase we really thought was really not quite all that biologically.
- Then we thought about well, where is it expressed. It's expressed in the airway and if something's expressed in the airway we might be able to get it in the bronchial alveolar lavage. But where are we going to find bronchoalveolar lavage from patients with Ipf. And Emory may know the punchline to the joke is that we're not going to find it in the United States.
- Okay? And and so the diagnosis of idiopathic pulmonary fibrosis outside the United States often requires a negative bronchoscopy. We never bronchoscope patients. For ipf but in Europe they have an extensive collection of bronchoalveolar lavage from patients with Ivf. And so I collaborated with a friend and colleague, Ankiaprase. She's now at the University of Basel and I'm waiting for that invitation because I'm here to you're going to go visit. She has really done an extraordinary amount of work on the airway epithelium and its role in pulmonary fibrosis. So one of the things she does is that she's done bronchoscopies on patients with Ipf and she's done brushes, and she's brushed the epithelium. And then she's taken that epithelium and brought it into the lab and cultured it air liquid interface. Okay? Air liquid interfaces Ali, which is on the Y axis there, and she compared the epithelium derived from healthy volunteers. Some people volunteer for bronchoscopy and from patients with Ipf and when she cultured these cells she found a higher level of Cxcl. 6. Expression, those from from the epithelial cells derived from patients with ipf. And so this really gave us the reason to look further, and so, if she has brushings, she probably has lavage. And so when you look in lavage, you actually see a much stronger sale is that the the expression of Cx. The levels of of Cxcl protein in the bronchoarveolar vise is significantly higher and when we look at different cohorts of patients. High Cxcl. 6 levels in bronchial ravage associate with a risk of mortality and the other measure of progression in our disease is death or progression.
- So again, in the upper left hand corner is a cohort from 2018, with 120 patients, the patients were segregated by above Median and below Median levels of Cxcl. 6. The patients with above Median levels of Cxcl 6 had a 3.5 4 risk of death in that cohort. And then we replicated the cohort with a smaller group of 59, and in that group it was even higher, so an increased risk of 5 to sixfold increased risk of death in that group.

- And so we know we found really some clinical relevance. We published it this past year, and we were very pleased to get an accompanying opinion piece, and they invested a lot of effort into building a figure for us. And so, really, from this this figure. This is kind of what we think, that again, ectopic epithelial cells elaborate a lot of stuff. And amongst the stuff that they that they elaborate include chemokines like Cxcl. 6. And this function is to drive up collagen synthesis in the fibroblasts next door. Now it turns out again that fibroblasts themselves make ila fibroblasts make cxcl. 6. So fibroblasts stimulate each other so there seems to be a layering effect.
- The cells sort of vary deeper, and that we think that there's a synchronized way of Cxcl. 6. Signaling in. Or 6 Cxcl. 6. Family signaling in Ipf.
- So this gets us back to Jack. So what are we going to do for poor Jack? And Jack asks you if he needs oxygen? He asks, is there a medicine? And do I need a lung transplant.
- And so one question about oxygen is something that we're going to talk about tomorrow. I want to thank Tessie and Emery for inviting me to speak to their patient support group. Tomorrow we're going to talk about another research program I have, which is on oxygen.
- And this was we just published this review of oxygen therapy in the annals of the American Thoracic Society. This was with Clark, who was a graduating fellow Pittsburgh. He's now in Buffalo, and he has summarize the role of oxygen in patients with with Ipf. What we'll talk about tomorrow is the fact that Ipf patients need a lot more oxygen than patients with Copd.
- And unfortunately, we test patients for oxygen the same way. So we walk patients in the hall with Copd, and we walk patients with ipf in the hall, and Copd patients need a little bit of oxygen. They don't need a lot of oxygen, but when you look at ipf patients, especially when you exert them, their oxygen needs can go as high as 15 liters per minute and that's what we can deliver at home. So again, I've always thought that you know oxygen is the pulmonologist special power.
- We have been able to take people and make them feel infinitely better by providing them oxygen. So this is a gentleman who's 1 of my patients who he has some resources at his disposal, and what he's carrying is a liquid oxygen reservoir and some of. You can see the high flow green tubing, you know, dangling between his legs. But this this oxygen reservoir allows him to do, the things that he likes to do and so he's able to go to the beach. And this was not possible before we met, and and that he relied on the small delivery systems that he was 1st prescribed.
- So again, the oxygen gets as high as 15 liters per minute. We'll talk quickly if I want to get to to questions. But
- October 15, th 2014, was the release of the 2 Ipf medications as this, just this past week there was a press release that phase, 3 trial met its primary endpoints, and we might have a new drug within the next year. But this is these were the 1st drugs out of the games.
- Okay and quickly. Profenadone and Tetanib are the 2 drops. We consider them equally efficacious, and both in all the the trials that we've seen in this one.
- Oh, this is propane. So the readouts in our trials are change in force, vital capacity, or change in Fpc. And in all these trials everyone deteriorates. I think it's important to know that everybody in Ipf is going to deteriorate over time. But the people who take the drug deteriorate more slowly.
- And and so that's in the in the top line of propenadone, and that the the change in Fbc was worse in patients on Placebo.

- And this is from diagnosis trials which include inteminib. And again, this shows the same thing. Probably easiest on the left is that the change in Fpc. Was worse in the placebo compared to the patients who got the drug.
- Okay? So the adverse effects you have to think about are propenadone cramping photosensitivity is what we always think about. We tell patients really make sure you wear a floppy hat, and you wear like Spf 100, because this can happen even in wintertime, and Tennib is diarrhoic anywhere from upwards of 60 to 75% of patients experience diarrhea with the tentative from the from the studies. And so it comes with a in many circumstances. So, and it's often a reason for discontinuing.
- So really kind of like rushed through some of my research. And but I just wanted to say again, thank you for having me. The current theory suggests that there's a breakdown of the wall between the airway and the alveolar epithelium, and we really think that there are functional consequences to the transitional epithelium that exists now in the Ipf lung that's not able to resolve injury and repair the lung in order to facilitate improvements in gas exchange and one example of it, it's Cxcl. 6 is associated with an increased risk of mortality in patients with pulmonary disease.
- So I really again, I want to thank you very, very much for inviting me. Actually, the picture goes all the way down. You see their feet. But I want to thank my collaborators at the University of Pittsburgh. I need to change that slide because I moved from Hanover in Germany to to Basel the Yale collaborators and my funding. And the reason why we do this is, you know, we do this for our patients. These are our bosses and one of I feel very privileged to take care of this group of people. I would say that most of the people on this slide are deceased at this point, and this is a disease with a high burden of suffering. Some patients will come in and after a biopsy. And they'll say, Doc, is it cancer? And I say no, and they wipe their brow, and they say and what they don't know is that it's probably worse.
- And so we try. We. This is pictured outside the gateway clipper. The gateway clipper is a riverboat in Pittsburgh, and we take our patients out on the rivers of Pittsburgh. You know, to facilitate our our support of them and and their caregivers.
- So with that, I will conclude. Thank you very much for your time.
- Thank you so much for your talk. I really appreciate it.
- One question I had is with cxcl. 6. If there's any potential use for prognostication. Off of the Als and then on that. Is there any potential therapeutics?
- So I think we would, you know, in the because we barely detected it in the plasma. I don't think there's there's use for it, plasma.
- And then, if we're gonna get it from Bal, we've got to dramatically change practice in this country and start rocking people.
- I don't think it's necessary, but I think it highlights the importance of what that research tool can help us learn about, which is again the role of the airway epithelium in this disease. And so therapeutics. So there is an agent that blocks these receptors. Now, one risk about blocking a receptor that's chemotactin for neutrophils is going to be infected.
- And so it's it has come to like phase, 2 trials in different diseases, because Ioa signaling is important in cancer. And so the agent is available.
- And if there's anybody here who wants to help me get the clinical trial off the ground, I would be very interested because you could consider. Well, maybe maybe we can do this in an inhaled version that still runs the risk of infection, because again, 50% of the body's neutrophil components are all ready to be evaluated within the lock.

- We're ready to pounce on potential infections. And so I think it's something we have to be a little bit careful of. But a lot of my research, again, is focused on, maybe some downstream events that might be more amenable to targeting.
- This is hybrid because it showed that in the region. I just wonder if this impact on the conscious faces depending on the concentration.
- Oh, it's collagen synthesis depending on the computation different don't know. I don't know that we in the lab when we- we generally have a dose response for that chemokine. So. But I think what I didn't show is that there's another chemokine, Cxcl. One which is also a member of the family. Cxcl. One is actually minor curve for survival is even stronger for Cxcl. One, again signals through the same components and also stimulates firewall. So I think Cxcl. 6 is not the only member of family. I think there's really a way of this entire family. 1, 2, 3, 1, 2, 3, 4, 5, 7, and 8, that all signal through these receptors so excuse me. Shut down.
- Hi! Thanks for being here. My name is Andrew. I'm a simple country pulmonologist, and so he's a liar. I had 2 questions for you. Number one, do house staff still get free tickets to the ballet and pirates games? I believe they do.
- Okay? And the second question, so when I was a fellow and we were being forced into research projects right? So bone, marrow transformation of fibroblasts was the hot ticket. My understanding that theory has been since debunked, and it's not exactly in vogue. So I guess the question I would have is, what is our thoughts about where fibroblasts for this whole process I get. They're being recruited. But from where and so what are our thoughts about that?
- So that's a that's a good question. So what what Andrew is talking about is that there was a theory at 1 point is that the collagen producing cells were recruited from the bone marrow and so inflammatory signals in the lung were stimulating the bone marrow to send these cells along, and I will tell you that I believe that they exist in mice.
- And because we've in the mice that we've used, we've labeled
- Polygen, producing cells. And we've also found that they've expressed bone marrow blockers when we injure on the mouse, much harder to prove in, certainly in situ, in idea forms. But there has been a lot of literature that you can find a circulation and whether or not they they contribute to the org or something.
- A couple of years ago the idea of epithelial methral transition, so that epithelial cells turning into fibroblasts you know, is probably not true. However, lots of these single cell experiments have suggested that epithelial cells in this transitional state start to express.
- Monitors of fibroblasts where we think fibroblasts originate is I think they're they're in the lung already. They're in the interstitium, and that they are simulated by the different forces in the lung to expand.
- And when you think about
- lung development, it's a very intimate relationship between the mesenchymal compartment and the epithelial compartment.
- The reason why we have airways is because the because the fiberglasts development stimulate the airways to delivery. And then then the airways say, Okay, enough, and they stimulate those fibroblasts to to turn off.
- So I think, though, those cells do exist in the lung. And and I'm currently of a belief that I think this is local residential accumulation.
- Thank you. Good afternoon.

- Thank you again for joining us and for tomorrow as well. A little off topic here. Can you comment on oxygen use in your population? We don't commonly use it here, and it's always a challenge to get appropriate access to patients for supplemental oxygen, whether it's Poc or otherwise. And also in the context of the soar act that's happening in terms of advocacy or access. Yeah again, I'm making the point that patients with pulmonary fibrosis need a lot of oxygen, and they need a. This is in contrast to cov mutation, and we've always found that the best way to deliver oxygen to this population is through liquid and so liquid oxygen. So there are a couple of forces that are kind of working against them. The thing we like about liquid is that you can put it in a smaller container, and it lasts longer because it's a concentrated sample.
- But If you've ever looked at a liquid oxygen reservoir, you can see that they haven't been updated in 30 years, and the fact is that the Ipf market, a tiny market or durable neck equipment providers, and so they lose money on our patients. And so when I got to Pittsburgh 14 years ago, we were able to give lots of people liquid oxygen and allow them to do lots of different things. But gradually the market has really contracted, and, in fact, there's no provider in Western Pennsylvania providing liquid anymore and which is a problem for us because we want oxygen to be liberating. We want people to use oxygen, but they're not going to use oxygen, because if they have to bring an e-tank with them, they take the e-tank with them, and they're panicked when they go to the grocery store. They want to make sure that they have enough oxygen to get themselves home because if they're if they're they don't have enough oxygen to get the cell phone. They'll be hypoxemic on the road hey? You know. And so it's a problem. And so, you know, we're planning an uphill battle in terms of advocacy, because it's a small part of the market.
- And there, of course, again, that Patience
- Dmes make a lot more money on portable oxygen concentrators, which again, don't satisfy our patients.
- Yeah, I'm I'm from the clinic department, and what we find is that after acute kidney injury, we can. Some kidneys will transition to chronic kidney seisma, while others will nicely repair.
- And you know, Jack, factor, normal function. And the research that has been done shows that there might be a problem during the repair phase, especially after severe or recurrent injury, and that some of these normal cells during repair might transition, might transition to a malaductive cell which then produce these various chemokines and cytokines that that allowed the fibroblasts to do this thing do them question I have for you is that you? You have indicated. You're mostly showing that there is an association between Icl systems and this. You're not really shown that this is the real.
- This is what turns on my progress and the other thing. So I'm trying to figure out if there is some kind of specificity like, do you see? High Cs Cxclc in, for example, fibrosis of the sarcoidosis, for example, pulmonary sarcoidosis. Okay? And secondly, and and I know you don't believe in mouse models. But but and are there mouse models of of hemphatic pulmonary fibrosis?
- And have they done it in Cxcl? 6 deficiencies. Okay, so that's a great bunch of questions. Maybe I'll take the sort of last 1 first.st The most commonly employed model of pulmonary fibrosis is bleomycin injury. So we take advantage of bleomycin's well-known side effect of causing pulmonary fibrosis. It's a much maligned model, because it doesn't resemble a solid video.

- But if you want to get fibroblasts, into the lungs and and have them express collagen. It's a great model and so the other. So it's been done. So we've we've Cxcl 6 is not made in mice. So they're they're they're closest homologic. Cxt 5.
- We've put Cxcl 5 in the lock. We get more collagen.
- I mean, the experiment has been done by a selective knockout of Cxcr. 2, which is the signal, and after tax from fibrosis I'm sorry the whole animal, the aftertex from collagen accumulation in bluemycin injury, and another group has taken a Cxcl. 6 neutralizing antibody and has increased collagen accumulation in nature. So again, there's a lot of there is a lot of supportive information from mice and so the link between between epithelial cells again are it's I. We think it's a strong link, but I think you're right. Saying causality is is perhaps not there. I think we still think that tgf, beta is is the sine qua non of fibrosis. And currently, we think that there's kind of a perfect storm of circumstances where there's a Tgf beta stimulated fibroblast compartment, and then signaling from along the family from Cxcl. 6 and il. 8, stimulate collagen synthesis. Now, what I didn't tell you is that the pathways are independent. So when we stimulate a fibroblast in the lab of Tgf beta it makes collagen. We make more collagen while we took out Cxcl. 6, and that when use when you knock out the pathways for strategic Beta, cxl. 6 still makes has the cells still make a lot of collagen.
- So the link is, you know, sort of not quite. Now we're talking, and I think you also talked about chronic kidney disease and the transition that some, some resolve, some some don't.
- And yes, I had. Somebody's your in return you know, 4 months later, and they're which they're very excited, reasonable that you know that. one of the biggest risk factors for Ipf are shortened calendars and that's you know. We think that you know, with short telomeres who have an Epis have a vulnerable epithelium that can't repair it.
- And so I think they're probably genetic risk factors that are probably discoverable in the feeling of which will tell us who's going to resolve
- people help on?
- I don't know.
- There's there's data on a series of the April health
- in a couple of them.
- Thank you.
- Oh, regarding we don't. This is this is not a lot of information.
- Yeah, yeah, we see a lot of inflammation and and sarcoid, I think for the most part doesn't kill people.
- It causes a high burden of suffering, but you know, but it's got a pretty long on one hand.
- Actually, the number of people transplanted for sarcoid and otherwise fortune years of the story. So we don't see this. We see inflammation if you get the whole big other black box. So if there's any enterprising residents or fellows who want to do some research, sarcoid is an open book.
- Anything else?
- Alright? Well, thanks thanks for inviting me.
- Thank you.