A rare and fatal lung disease, IPF has met its match

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Ken: September is pulmonary fibrosis awareness month and we're honored to have one of the world’s leading experts on idiopathic pulmonary fibrosis, or IPF, and other respiratory diseases. Today on CU on the Air we're speaking with Dr. David Schwartz about IPF, a rare but fatal lung disease, and breakthroughs he and his team at the CU Anschutz Medical Campus have discovered. Dr. Schwartz is a professor of medicine in immunology and the Robert W Scarier chair of medicine at the CU Anschutz Medical Campus. Welcome Dr. Schwartz. Thank you for being here today.
Dr. Schwartz: It's very good to be here. Thank you.

Ken: Tell our listeners what exactly is IPF?

Dr. Schwartz: It's a form of pulmonary fibrosis where the disease is completely localized to the lung, and it's a progressive disease that gets worse over time and is associated with a very high mortality. So basically what happens in IPF, is you get scarring of normal lung tissue and that scarring results in progressive loss of lung tissue that prevents the lung from expanding and prevents the lung from exchanging gas, and is associated with a very high mortality.

Ken: So by the time it's diagnosed, it's often fatal.

Dr. Schwartz: By the time idiopathic pulmonary fibrosis is diagnosed, there's a three to five year survival in individuals with the disease unless they undergo lung transplantation or unless they happen to be one of the very fortunate people where the disease doesn't progress rapidly.

Ken: And you and your team found a variant that causes IPF, what is that?

Dr. Schwartz: Well, for many years, for about 25 years we've been studying the genetics of IPF, the causes of this disease. And what we found is that there are a number of gene variants changes in the genome that are associated with the risk of developing pulmonary fibrosis. And in particular we've discovered the main cause of pulmonary fibrosis, a gene change in a mucin gene, a gene that produces mucus in the lung that we know causes pulmonary fibrosis.

Ken: And people in certain populations are at risk, who are they?

Dr. Schwartz: These are people that are mainly European descent who have-

Ken: Not Irish though, right?

Dr. Schwartz: ... Irish for sure.

Ken: Darn it?

Dr. Schwartz: Yeah. Irish for sure, European descent, but in general, these are individuals that have a gene variant that causes an increased expression of mucus in the lung, especially in the very distal portion of the lung where the airway meets the breathing sacs of the lung.
Ken: And how prevalent is this disease?

Dr. Schwartz: The disease is infrequent. Established idiopathic pulmonary fibrosis occurs about maybe 50 in 100,000 individuals, so it’s uncommon. But we found that if you look at individuals that have this genetic change, these early forms of the disease may occur in 2% to 3% of individuals greater than 50 years of age. Even though the established form, the progressive form of this disease is infrequent, we found that we can make the diagnosis much earlier in a wide range of individuals that are older than 50 years of age.

Ken: And is this a disease that runs in families?

Dr. Schwartz: It does. In fact, we discovered the MUC-5B or the mucin gene by collecting families with two or more cases of pulmonary fibrosis. What we have found is that many people who present with sporadic forms of pulmonary fibrosis, you find that there are early forms of the disease in first degree relatives. So it is a familial disease, and it is a disease that progresses and can cause fatal death in individuals with pulmonary fibrosis.

Ken: And it's often been misdiagnosed. Some people diagnose it as emphysema or frequent pneumonia or other lung diseases. Why is that?

Dr. Schwartz: Unfortunately this disease is, as I mentioned before, a really rare disease. And being a rare disease, even experienced lung doctors have a hard time diagnosing the condition. So it’s oftentimes confused with emphysema, chronic obstructive lung disease, or other forms of pulmonary fibrosis. This disease affects individuals in ways that it limit their life and sometimes the disease is so progressive that by the time the disease causes these individuals to have progressive lung injury and progressive limitation of their lung function, they die before the diseases even diagnosed.

Ken: What are the symptoms?

Dr. Schwartz: The main symptom is progressive shortness of breath where someone realizes that they can’t go up steps the way they used to before, or they develop shortness of breath with a little bit of exertion, or they develop a dry cough where they can’t seem to bring up their sputum. The sputum collects in the very small airways of the lung, and sometimes the small airways end up getting obstructed and you can’t bring up the sputum in those areas of the lung.
Ken: And you’ve made some incredible progress understanding the disease, does that make the diagnoses easier?

Dr. Schwartz: We can make the diagnosis a lot better by performing genetic studies on family members of those who have pulmonary fibrosis. So in other words, individuals that have pulmonary fibrosis, if we check out their first degree family relatives, their brothers, sisters, children and parents, and we use the genetics that we know puts people at high risk, we can diagnose the disease earlier in these individuals and we could begin to apply treatment to those individuals in the early stages of disease to hopefully prevent them from developing progressive pulmonary fibrosis.

Ken: There is a connection between IPF and rheumatoid arthritis, what is that?

Dr. Schwartz: Well, we know that pulmonary fibrosis presents in a number of different conditions and rheumatoid arthritis is one of those conditions. Now, what’s absolutely fascinating about pulmonary fibrosis associated with rheumatoid arthritis is, other than the rheumatoid arthritis, it looks identical to idiopathic pulmonary fibrosis. So, what we did is we tested whether the MUC-5B gene, the mucin gene that we know that’s important in idiopathic pulmonary fibrosis is also important in pulmonary fibrosis associated with rheumatoid arthritis, and we found that it has an identical risk associated with the development of pulmonary fibrosis associated with rheumatoid arthritis. In other words, individuals with rheumatoid arthritis, we can use the genetics of pulmonary fibrosis to tell those patients whether or not they happen to be at risk of developing pulmonary fibrosis in addition to their rheumatoid arthritis. And we think that this will identify potential individuals that could be reversed with the same treatments that we plan on using with those with idiopathic pulmonary fibrosis.

Ken: That’s an incredible connection between two seemingly unconnected things.

Dr. Schwartz: It is a very amazing connection. However, if you look at the lung disease and you forget about the rheumatoid arthritis, the presence or absence of rheumatoid arthritis, the lung disease looks identical in terms of the way it presents, the symptoms that someone has, their shortness of breath and cough, the development of lung function abnormalities, and the development of abnormalities on the high resolution CT scan and also on
pathologic specimens, they're absolutely identical. And what we have found is that the genetic risks are absolutely identical as well.

**Ken:** So, how do genetic abnormalities arise and is there any benefit?

**Dr. Schwartz:** Oftentimes genetic abnormalities have adverse effects and when they get invaded in a human population they also have beneficial effects. And we think that the overproduction of mucus in the lung associated with the MUC-5B variant probably has beneficial effects early in childhood or young adulthood. However, as this overexpression of mucus continues into the older population, it places them at risk of pulmonary fibrosis. In fact, we know that among Europeans, about one in five individuals have at least one copy of the variant, and that copy of the variant was recently introduced into the genome and appears to have a very positive effect in the European genome.

**Ken:** And you mentioned Europeans, are there other ethnicities at risk?

**Dr. Schwartz:** Other ethnicities are at risk of developing pulmonary fibrosis, but they clearly have a different genetic variant that puts them at risk. In other words, although Europeans have, one in five Europeans have at least one copy of the variant, far less than 5% of Asians have at least one copy of the variant, and less than 1% of Africans have at least one copy of the variant. So, this is a variant in MUC-5B that was introduced into the European genome maybe a couple of thousand years ago, and may have been in response to some sort of respiratory pandemic that enhanced the ability of these individuals to do well with a respiratory infection. However, resulted in long-term complications in those who live beyond 50 years of age.

**Ken:** And what are the treatments?

**Dr. Schwartz:** Currently the treatments are standard treatments. There are two anti-fibrotic treatments that are on the market for pulmonary fibrosis. The problem is that these treatments come with a lot of side effects, and over half the people who take the treatment can't tolerate the side effects. Another problem with the current treatments that are available is that these treatments end up having very little effect on the course of the disease. So we're working with other groups to direct our treatment at the mucus that's being overproduced in the lung. In other words, our approach is a completely different approach to treating the disease by focusing on the cause of the disease and focusing on mucus in the airways.
Ken: You've had collaborations with pulmonologists around the globe on this, how does that work?

Dr. Schwartz: We do. We have what is called a Global Idiopathic Pulmonary Fibrosis Network. And we've created this network about three years ago, and we have about 60 investigators around the world participating in this network. And basically other investigators around the world make the diagnosis of pulmonary fibrosis by chest CT scan or by lung biopsy. They make the diagnosis, they collect a DNA specimen and they send the DNA specimen to us. And we've been using those DNA specimens to understand the genetics of the disease much more carefully, much more accurately. And what we have found is that the MUC-5B, the mucin gene is largely responsible for the risk of developing pulmonary fibrosis. There are other genetic changes that are associated with pulmonary fibrosis, but that accounts for much less of the disease than the MUC-5B variant.

Ken: Sounds like you've made great progress in your work thus far, what do you see as the next steps? What's ahead?

Dr. Schwartz: Well, what we have a been able to do is focus in on individuals of European descent. What we would like to do is to understand the genetics of other ancestries like Asians or Africans, because those individuals develop pulmonary fibrosis also. And we suspect that, although the same genes are involved, it's probably very different gene variants in those populations. So, one thing is we'd like to identify the other genetic risks in other ancestries.

The second thing that we'd like to do is to identify the proteins that work with the genetic changes to put people at higher risk of developing pulmonary fibrosis so that we can use that to diagnose the disease earlier. So, early diagnosis is a focus of what we're trying to do. And the last aspect of what we're trying to do is to develop treatments that are focused specifically on the mucin genes that we know are important in terms of developing pulmonary fibrosis. So if we can decrease the expression of these mucus genes, and decrease the expression of mucus in the lungs, especially the terminal airways of the lungs, we think we can begin to control the development of disease.

Ken: And there's a lot obviously of genetics involved here and you have been involved in the development of personalized medicine here at CU Anschutz Medical Campus, which as I understand it was driven in large measure by the human genome project. Can you tell our listeners a little bit about personalized medicine, which is
probably something that many people hadn't heard of 10, 15 years ago?

Dr. Schwartz: From my perspective, the most exciting thing about personalized medicine is to move diagnosis and treatment from established disease to early forms of the disease. So idiopathic pulmonary fibrosis is a good example of moving individuals from established disease to very early forms of the disease so that we can begin to prevent the development of disease progression and we could prevent the limitations that fibrotic lung presents for individuals with established disease. That applies to all forms of chronic diseases. Emphysema, diabetes, high blood pressure, heart disease, and you name it, preventative medicine or personalized medicine aims at using the genetics to identify individuals at risk to either prevent the development of early disease or to identify individuals with early disease and begin to focus on the causes that prevent the development of established forms of disease that unfortunately still limit life.

Ken: How prevalent right now is the use of some of the things you're describing genetics and as a prevention tool?

Dr. Schwartz: I think it's becoming more and more prevalent. It's becoming more and more possible. While we can use genetics to identify people at risk, we haven't yet sufficiently used genetics to prevent people from developing progressive disease. It's beginning to become helpful in women who are at risk of developing breast cancer. It's beginning to become relevant in people who are at risk of developing pulmonary fibrosis. It's beginning to become relevant in terms of people who are at risk of developing either high blood pressure or diabetes, but we're in the very early stages. What we're trying to do is to focus in on identifying the risk factors so that we can move these diseases from a disease where we end up palliating a condition to a disease where we can prevent the condition from occurring.

Ken: And how does that look practically? I mean, say I'm a patient who walks in, have diabetes, how would this manifest itself for someone like me?

Dr. Schwartz: Well, first of all, it would tell us if we understood your condition and your type of diabetes. We would begin to then pick apart the genetics and the early markers of diabetes in terms of your particular subtype of diabetes. We'd be able to apply that hopefully to your family, identify your kids or your siblings who might be at risk of developing diabetes and treat them before they
develop the condition, before their diabetes results in end stage disease in their heart, in their development of skin lesions, in the development of visual problems. So the idea is that if we can use genetics and if we can use early markers of disease to identify disease before it's had secondary outcomes, we'll be able to reduce the impact of a particular disease not only on the patient, but on the patient's family.

Ken: So the old saying is true, an ounce of prevention is worth a pound of cure.

Dr. Schwartz: That's the way we think we can make a lot of headway in pulmonary fibrosis. And that's the way we think we can make headway in a lot of chronic conditions that in turn is take care of every day of the week.

Ken: So, again, this is something that is relatively new in the field of medicine, where would you say we are on the continuum of what's possible with personalized medicine?

Dr. Schwartz: In terms of personalized medicine, we're pretty good at identifying individuals at risk. Unfortunately, we haven't yet began to explore how the treatments are different in people at risk versus people with established disease. And so, it's very likely that the therapeutic approach to disease prevention in those at risk individuals is different than the therapeutic approach to establish disease. So we're just beginning to identify individuals at risk, and now we have to begin to think about therapies that prevent people from developing progressive disease on all levels.

Ken: Big data is a driver in the work you're doing, how does data fit in with personalized medicine?

Dr. Schwartz: It creates a very expensive and complex approach to understanding personalized medicine. First of all, you have to establish large populations. These are not simple populations that are easy to collect. You have to do this on a collaborative basis, and you have to involve investigators from lots of different communities and academic settings. In terms of the approaches, they have to be more than genetic, they have to involve the pathogenesis of the disease, and they have to begin to involve very early markers of what the disease looks like. And if you can identify disease before some of them become symptomatic, that's where you can have the biggest effect in terms of reversing the disease process or preventing the disease process from resulting in end organ damage.
Ken: You’ve been at this type of work for a number of years now. Where would you say the CU Anschutz Medical Campus is as far as other academic medical centers around the world?

Dr. Schwartz: Well, we’ve established a great program in personalized medicine. And that program is being led by Kathleen Barnes who has developed both a division that involves a number of investigators and she’s also developed a database that involves a lot of DNA samples in patients that are seen throughout the University of Colorado hospitals and systems. That comprehensive program will allow not only her group but individuals across the entire spectrum of investigators of both basic and applied investigators to begin to discover the genetic causes of a variety of different chronic conditions, and to begin to identify those at early risk of disease that could be studied for effective interventions that would prevent the progression of disease processes.

Ken: A big part of what happens out here on the campus is preparing the next generation of physicians and health care providers. So, how does your work both with IPF and personalized medicine affect the training of the health care workforce of the future?

Dr. Schwartz: Well, that's a complex question. There are so many people that are excited about this type of research. There are basic geneticists that are involved in my group that are trying to understand the specific gene-gene interactions that occur on a very basic level and those that are trying to understand how the genetics are affecting the biological manifestations and also the clinical manifestations of disease.

Then there are those that are trying to take those early markers of disease and begin to see how you can reverse them biologically, or how you can reverse them therapeutically by targeting specifically molecules that are being expressed either being over expressed or being under expressed in individuals who are at risk of developing disease. I think it’s going to take a very comprehensive approach, quite honestly. I think that it will involve a number of individuals from lots of different backgrounds, whether they be basic genetic backgrounds or very applied clinical backgrounds coming together and interacting across the research spectrum, not only at universities but across universities and also with pharmaceutical companies that are now focusing their attention on who’s at risk and how can we prevent the disease from developing into an end stage process.
Ken: And are those kinds of collaborations happening or do they need to be developed?

Dr. Schwartz: They're happening. So, yes, within my group they are happening. We have a lot of very basic PhD students and post-doctoral candidates. We also have clinicians and individuals that are expert at taking care of patients. We've developed a company that serves as the interface between the university and pharmaceutical companies, and we're in the process of trying to figure out how we can diagnose the disease early, how we can develop drugs that change the biology of those early manifestations of disease, and then whether those can prevent the progression of disease processes in individuals who are at risk.

Ken: One of the big initiatives here on the campus is really to attract some of the top talent from around the country around the world, how would you describe the talent level that is working on these issues now at CU Anschutz?

Dr. Schwartz: Well, I think in general in terms of personalized medicine, we have established a very broad based talent pool, a talent pool that understands the importance of genetic risk, that understands the populations who are at risk, that is beginning to identify ways to communicate with those at risk individuals. And most importantly is developing the kinds of connections that will allow us to treat the disease earlier in experiments and figure out how we can prevent disease. So we're moving from palliating disease to preventing disease.

Ken: As we came out here we passed by the crane that is going to be building the Anschutz personalized medicine building, what will that facility mean for your efforts?

Dr. Schwartz: I think it's a tremendous step forward, and I think that Kathleen Barnes has done a great job in developing the program in personalized medicine here on the Anschutz campus, in working with those at the University of Colorado hospitals and systems, and in working with new faculty in the school of Medicine. She's recruited a number of people from the outside who have the capability of defining who's at risk, and maybe even equally importantly she's developed relationships with clinicians across the spectrum that allow her to expand way beyond her areas of expertise, which are asthma and allergic diseases, and begin to collaborate with individuals interested in heart, lung and different forms of cancer.
Ken: You've been at CU now for how long?

Dr. Schwartz: For nine years.

Ken: Nine years. And in that time things have moved at a rapid clip, what do you see ahead for you and your teams and the work out here?

Dr. Schwartz: Well, I think what we need to do at the University of Colorado is to develop a seamless interface between what research and clinical work is going on at the university with what opportunities we can partner with in industry. I think that that's happening across the spectrum of different diseases. I think that many of the pharmaceutical and biotech industry are very interested in developing partnerships with faculty who have developed research programs that identify individuals at much earlier stages of disease and reversible stages of disease.

Ken: Well, Dr. David Schwartz, chair Robert W Schrier chair of medicine at CU Anschutz Medical Campus. Congratulations on the great work you're doing. I know there's more to come, but thank you for being with us today.

Dr. Schwartz: Thank you very much. It's a great opportunity to talk with you.