[MUSIC PLAYING]

[APPLAUSE]

MICHAEL MYERBURG: Thank you for the kind introduction. I think it was prone to hyperbole, but I'll take it. I'll take it.

So it's crazy. The last time I gave this talk was in 2012, which is crazy to think it's been that long. And when I was putting the slides together, what's great about giving this talk is every year I have to add another year to the median survival. So that's a good little tidbit. And I also added tattoos this year because everyone seemed to like the tattoos that I showed last year. So I figured I'd put it in the title.

So today what I'm going to talk about is some background about the disease, the history of the disease, and some milestones in cystic fibrosis science and care. Then I'll talk about the basic pathophysiology from the ion transport defect and how that leaves to airways disease.

I tried to shrink those sections and expand a little bit on the clinical manifestations and overall the treatment strategies now that our patients are coming here, as you may have figured out by now. So you're going to be exposed to more of these. And I just want to just go over the basic therapeutic strategies. And then I really wanted to leave room at the end to talk about these new CFTR modulators and ion channel modulators that are really exciting and likely to completely transform the disease.

So as the obligatory first slide, it's the most common life-shortening genetic disease in Caucasians. People could argue that and say, well, diabetes has some genetic component. But it's widely quoted as being the most common fatal disease among white people.

It affects 30,000 individuals in America and about 70,000 worldwide. And actually, carrying one mutation to CFTR is quite common. So one in 25 people have a CFTR mutation. It's autosomal recessive, so you have to have two mutated copies of the gene called Cystic Fibrosis Transmembrane Conductance regulator, which is a mouthful and we just say CFTR.

And now the median age of survival is 44 years. That was from the statistics in 2017, so it's probably about 46 ow. And I think that-- well, anyways.

So it's believed that this mutation arose in Europe 52,000. This is from genetic studies, haplotype data. It's actually remarkable if you think about a fatal mutation persisting in the population for 52,000 years.

And people have asked me, how did this happen? And it winds up that being a carrier or having mild mutations is semi-protective against dehydration from profuse watery diarrhea. So if you knock CFTR out of a mouse and then give it cholera, it doesn't die, whereas the mice with wild type CFTR would. And back 52,000 years ago, people were dying of dysentery quite commonly and they hadn't figured how to knock themselves off with opioids like we have in the current era.

And so then the first reference in the literature comes from about the 1700s where in German folklore there was a statement that woe to the child which when kissed on the forehead tastes salty. He is bewitched and soon will die. And we think that that was a reference to people with cystic fibrosis way back then.

And it wasn't really until the 1930s where the whole syndrome was described by Dorothy Andersen. She's this lady up here. And she described the whole phenotype with involvement of the lung, the pancreas, and the gut.

And really I think that's where progress really started. So for 52,000 years people died before they reached a year of age. And then she described the disorder in the late 1930s. And around that time we got some therapies, the big ones being pancreatic enzymes and a realization that this disease is caused by tons of mucus in the airway. So we came up with strategies to clear that out just by physical chest PT. And then some antibiotics came around for staph first and then pseudomonas. And as you can see, the survival just jumps up with that breakthrough.

And I guess the point I'm trying to make is that survival has increased with new scientific discovery and new therapies. And it's not just a linear thing. It happens in response to these new therapies coming about.

So next came a whole plethora of therapies around the 1980s. Pulmozyme, or recombinant human DNase, inhaled tobramycin or TOBI, chronic azithromycin, 7% hypertonic saline later around 2000. And then now we also have inhaled aztreonam, which was called AZLI in two trials. I wish they would have kept that name because Cayston doesn't really reflect what it is. I think AZLI is a much better name.

And in 1989 they identified the CFTR gene. And I think that that initiated a whole series of research that led to what I think is the next big breakthrough, which happened in 2012 when the first highly efficacious CFTR modulator therapy became available and approved by the FDA. And we'll talk about that at length at the end of the talk.

And so over the last several decades you can see that the adult population with CF has grown, which is just a reflection of increased survival. In 2015 our clinic here the adult side got larger than the pediatric side, which was just an exciting fact. And this is just across the country looking at people who are adults.

So what causes the disease? So it's all about dehydration of the Airway Surface Liquid. And I figured I talk about this soon because pretty soon I'll start saying ASL. And if I don't define what that means, no one will-- I'll lose you. So the ASL or the Airway Service Liquid is actually a fairly complicated layer of fluid and mucus on top of the airway surface or in the luminal surface of the airway.

Traditionally, it was just thought that there was just mucus and then liquid that bathed the cilia. It winds up being a little bit more complicated than that. But I think just as a generalization so you can understand the concept, you have this periciliary liquid fluid and mucus on top of that. And then what happens is that that liquid acts as a low viscosity medium that allows the cilia to beat freely. It prevents the mucus from sticking to the airway so it can glide from your distal airways up to where you can cough it up. And so you can see that's how the normal mucus area clearance works.

There's an electron micrograph on the side there from UNC just focusing on the cilia. And you can see that the cilia are outstretched and have room to move around. But conversely, in cystic fibrosis that fluid is absent. The cilia can't beat effectively. The mucus sticks to the airway, becomes desiccated, and over time you get problems.

So how does that happen? So this is just a simple image to show that airway epithelium is relatively permeable the water. So this is one of those parts in the body where water is going to follow salt. So salt moves, water follows.

And the main ion channels are believed to be ENaC, which absorbs sodium and water; and that's counterbalanced by CFTR, which secretes chloride. And water follows either of those.

So in cystic fibrosis, CFTR doesn't work. You can't secrete or you have an impaired ability to secrete chloride. And for a multitude of reasons, ENaCs or sodium channels are upregulated and excessively absorb sodium. So those two factors just rapidly desiccate the airway.

And so that sets up this cascade of events where you have defective CFTR that leads to altered ion transport. The net result of that is that you get airway dehydration, impaired mucus clearance, mucus stasis, mucus accumulation, obstruction of the airways. And then there's a vicious cycle of obstruction, bacterial colonization, inflammation, and airway destruction. I think most bad diseases have some sort of a vicious cycle somewhere in them, as does CF.

So I want to talk about just the basic clinical manifestations and how we treat them, as I talked about before. So in general, CF will affect the entire body wherever CFTR is expressed. So there's a lot of CFTR in the airways. So you're going to get severe sinus disease, and severe airway disease, and chronic infection-- like we'll talk about at length.

There's also a lot of CFTR in the hepatobiliary tree and the pancreatic duct. So that leads to liver disease. Frequently that's just a cholestatic problem. We put people on Urso and it's usually not a problem. But about 5% of people will go on to develop cirrhosis and need a liver transplant.

In my experience, usually that's coupled with somebody who has a second hit of some sort, be it alcohol usually or NASH in a couple of instances.

Our patients are frequently pancreatic insufficient. So they can't produce enzymes to help them digest fat and fat-soluble vitamins. So they frequently will have bowel problems, bowel obstructions, constipation, malnutrition, and problems such as that.

And they also have destruction of their pancreas over time. So in later disease they get a form of diabetes known as Cystic Fibrosis Related Diabetes, or CFRD as we call it.

And of it's tricky because most endocrinologists, if you go there, they'll tell you to limit your calories. And these people's BMIs-- 16, 17, and they're telling them not to eat carbohydrates. That's not what we want them to do. We want them to be on insulin. And so we're always fighting with our endocrine colleagues to put people on insulin.

And I think our approach is pretty much well-supported in the literature that that's what they need. And it makes sense. If you have pancreatic insufficiency, putting somebody on oral agent doesn't make any sense.

Like I said, they have lots of bowel problems. So you meconium ileus is the classic one that we learn about in med school. But there is an adult manifestation of that or version of that called DIOS, or Distal Intestinal Obstructive Syndrome, that happens in adults.

There's CFTR in the sweat ducts, and so people have elevated sweat chloride. That leads to people getting frequently dehydrated in the summer. But it's really not a big deal. It's one of these things that just is used diagnostically. People will tell you that they go through a lot of hats on a hot summer because they stain them with salt. But it's not a major deal.

And there's a lot of CFTR in the vas deferens. So males are frequently-- almost universally-- infertile. And so that's the typical disease where everything is labeled as severe.

There's also a mild atypical form of CF where generally these patients have less severe mutations. And it's kind of like semi-CF, I guess, is a way to talk about it. And they have similar problems but just not as severe.

And since the last time I gave this talk actually, we've come up with a few terms for these people with mild disease, the first one being CFTR-related metabolic syndrome. And basically that came from-- now we're doing newborn screening. So this is somebody who screens positive but has non-diagnostic sweat chloride and doesn't have two CF-causing mutations. So that's where that term came about.

And I use CFTR-related disorder-- I guess I never really learned the difference until looking through these. But that just is a grab bag term for somebody who doesn't meet the criteria for CF but has lots of CF manifestations. And they typically have CFTR mutations that haven't really been associated with severe disease.

And we have a growing number of people like this in our clinic. And it's probably just because we're looking harder.

And so with these sorts of individuals we still will follow them in our CF clinic. But over time we just try to see them less. So we see all of our people every three months and we'll see these people maybe once or twice a year and just make sure that we keep tabs on them. Because these are the kinds of people that are going to respond really well to modulators. And so if they start having problems, we can start adding therapies. And we just like to keep tabs on them to make sure they don't start slipping.

AUDIENCE: What's the mortality [INAUDIBLE]?

MICHAEL MYERBURG: Gosh. Well, we have people who are in their 60s and stuff like that. So it's kind of hard to say.

AUDIENCE: [INAUDIBLE]

MICHAEL MYERBURG: They tend to live much longer than people. And I think a lot of these people are going to start passing away from non-CF-related complications.

So when I said sinusitis, it's not just like, oh yeah, my nose is running a little bit. This is severe sinusitis. I like this image because it's unilateral and you can see the kind of pressure that's developing in the sinus such that it's pushing everything over. Typically it's bilateral and it's not as impressive as a CT scan. But if you look at our patients, oftentimes you'll notice that their nasal brow is red, sticks out. These people get headaches and literally facial pain from all the pressure that's going on in there.

And the mainstay of our treatment-- what we do is we try to have them-- or encourage them to do nasal irrigation with large volumes of saline. So we use the NeilMed device or some device like that where you're basically using quarter of a liter of physiologic fluid that you're putting in one nose and rinsing out the sinuses.

One of my patients calls it a brain douche, you know.

[LAUGHTER]

It's a large volume of fluid and so it's not always such an easy sell. But more recently, depending on what kind of compounding pharmacies are actually funded, we can get them to sometimes mix up antibiotics and steroids in that solution, which is really nice. Because then they're just doing one treatment and they're lavaging everything with appropriate antibiotics based on their cultures. And I think it helps. We also use a lot of nasal steroids, especially for people who have nasal polyps.

And then surgical therapy. And we're really fortunate here. We have Stella Lee, who's been here for several years now. And she's an expert in sinus surgery and has been really accommodating to our population. So she has a CF clinic on Wednesdays, which is our clinic day. And so we can frequently one-stop shopping-- come in, get your sinuses cleaned up, get checked out, and then see us all in one day. And we're really thankful to have her here.

But the surgical approach is really we do polypectomies on people who have polyps. And they frequently reoccur. And usually what they're doing is they're going in there endoscopically, cleaning out the sinuses, and opening up the ostia so that they can drain better.

They can put balloons across these things and pop them open and they can also do it surgically. But the idea is that we're trying to marsupialize the sinuses so that these rinses have access to wash all the junk out.

So a lot of our patients have recurrent-- have had multiple sinus surgeries. It's a big deal. And as we're learning now, we think that a lot of the bacterial progression starts in the sinus and then works its way down. And that's an evolving field.

So as I mentioned, these patients frequently get bowel obstructions. And as a child it's called a meconium ileus and as an adult it's Distal Intestinal Obstruction Syndrome.

What this is is the intestinal contents get desiccated. And basically a piece of dried-up stool blocks the ileocecal valve. And you get a fairly high grade small bowel obstruction. And so as you can see on these images, it's pretty nasty. It's no joke.

So typically these people-- as opposed to constipation, which we frequently see, which will be semi-acute, they'll have vague abdominal complaints-- this, they call you, they're sick. It's usually acute. They usually have pain around the belly button or in the right lower quadrant and sometimes vomiting.

When you see these patients, it's very common for them to come in through the ER or somehow get through the hospital before were involved. And oftentimes surgery gets involved. And we've had several cases where people have had surgeries that they probably didn't need. And you've got somebody who's had perhaps gut surgery in the past, and you're going in there again, and then you get adhesions. And it's really morbid for these people to have to go through these procedures. And so just call us before you call in surgery, please.

And usually these obstructions are incomplete. So these people will not be vomiting. When you look at them, they don't look toxic. And usually for those people we'll just hydrate them and we'll give them GoLytely from above, some MiraLAX, and usually they'll get going in a couple of days.

But sometimes you'll see these people who come in with a complete obstruction. They're vomiting. And when you look at them, they look scared, they look toxic. It's no joke. You just look in their eyes and they're like, oh man, this isn't good.

For those people, we usually will decompress them with an NG tube, make them NPO, IV hydrate them. And really what we try to do is use gastrografin enemas.

And I don't know that everybody knows what that really means. We've had cases where people have come into the hospital, and been on our services, and get a nurse-delivered gastrografin enema. And what we're talking about-- when I say gastrografin enema, what I'm talking about is IR, down in the IR suite, pumping the rectum and the colon filled with gastrografin. And what we want to see is that retroflex through the ileocecal valve and get into the distal small bowel. Because that basically knocks the fecalith out. And then usually once that happens, they open up and they feel a lot better really quickly.

Some people need that a few times. And there's some evidence that sometimes giving it from above is also helpful. And it's basically just acting as an osmotic agent at that point.

AUDIENCE: So can CT [INAUDIBLE]?

MICHAEL MYERBURG: One can identify the location. So if it's at the ileocecal valve-- but it's oftentimes-- at least for me it's difficult to say that's the ileocecal valve. I think Joe's probably a little bit better at it. And a gut radiologist I'll call in if that's what they're thinking.

But most of the time that's what it is. Every now and then, someone will have a volvulus or something. But usually it's something that a gastrografin enema will fix. So call us, not surgery.

And then the lung disease. It causes a severe bronchiectasis. It looks pretty nasty here on this X-ray. And you can see this horrible bronchiectasis in this individual.

So typically how we manage these people is they're on a chest regimen of some sort. We ask them to exercise at least three times a week. We're big on exercise in this center. I think it's a great form of clearance.

Then we ask these people to generally do chest clearance 30 minutes twice a day with or without albuterol to open them up. And then we typically will use hypersonic saline twice a day, a pulmozyme once a day. And then for most of our patients they're doing nebulized antibiotics two to three times a day.

So if you add that all up, we're asking people to do hours of chest therapy every day. I can't find time to exercise, so it's a huge treatment burden. And unfortunately, it doesn't always work and our patients frequently get exacerbations.

As opposed to like a lot of other pulmonary infections, these people rarely have radiographic change. And so we oftentimes won't even get an X-ray. It doesn't influence our decision about how we're going to treat them. It's really mostly based on their symptoms and their spirometry.

But they'll come in with increased cough, more frequent cough, more sputum, or a change in the appearance of the sputum. Some people will say that they taste differently. And change in hemoptysis, just symptomatic change more than anything.

Oftentimes they'll be losing weight. They might have a fever. Their FEV1 drops, they might have a new oxygen requirement, that kind of thing.

But like I said, chest X-ray doesn't influence our decision. And when you ID involved, they'll be like, well, there's no infiltrate. But their lungs are filled with pus and they're drowning so you've got to give them antibiotics.

So we treat a lot of our patients that we see as outpatients just with stepping up their clearance, encouraging them to do their junk, plus or minus oral antibiotics and nebulized antibiotics.

In the standard exacerbation, people will go on IV therapy for two, three weeks. The duration of that's unclear. There's actually a trial going on right now. But really I think this is a person to person type of decision.

Usually we'll pick two antibiotics based on their recent culture. So we have so much culture data on these people-- we get sputum on them every three months. And we have just information going back years, and years, and years, plus what we've treated them with in the past.

So we treat based on what we know about them. And it's fairly uncommon for their exacerbations to be caused by a new acquisition of some pathogen. So really, these people sometimes come to the hospital and they get a BAL when they wind up on a ventilator. And I think it's kind of a knee jerk response-- these guys are infected, got to get a sample.

But I would just encourage you not to do that. Because you're taking an infection that's localized to the airway and then you're pushing it into the distal lung. And these people will frequently get really sick after that.

And occasionally we need to do a BAL-- we can't find what pathogen is causing their problem and so we'll go searching. But in general, it really bothers us when our patients wind up coming into the hospital and getting a BAL.

I work in the ICU. And you may intubate somebody and you think you're going to need a sample so you might as well just get one. But for our patients, it's rare that it would be a new pathogen and it's rare that we would find something in that instance.

So we usually start antibiotics in the hospital. But a lot of our patients have been doing this for so long we just get a PIC and have them start at home. And I'll skip the stuff about recurring exacerbations.

And so the other thing I want to talk about-- I like this picture from Dr. [INAUDIBLE] of this patient. I think it shows a lot of different features of the disease.

One, this person's malnourished. You can see the digital clubbing. And I really like talking about the tattoos, not to make fun or to poke fun at these people. It says a lot about their disease. They've got no struggle, no progress. These people, they're fighting. And as I'll talk more, it's a big psychological burden to have a disease like this.

You'll see a lot of 65 roses. And I made the mistake when I was a fellow working in the CF clinic of asking someone, well, what's that. And I blew it with them. They're like, you don't know the first thing about CF.

And it winds up that "65 roses" is a trademark term from the CF foundation. And the story goes that in the 1970s, a boy-- a young boy-- with CF overheard his mom on the phone trying to raise money for CF. And he could tell that she was nervous and trying to hide this from him. And he's like, mom, you don't have to hide from me. I know what you're talking about. You're talking about my 65 roses.

And that resonated with a lot of people just because it shows the innocence of these people affected by the disease. And that's how it came to be. But you'll see lots of tattoos with roses like this one. And you'll also see lots of tattoos with clocks and things referring to time-- I wish time was on our side.

And we have a whole population-- the people who are probably frequently coming into the hospital now are in their 30s, maybe 40s. And these people have literally been at the end of their life expectancy since they were in high school. And it's hard to imagine what that would do to a developing mind. You're trying to figure out what you want to do with yourself and you don't think you're going to be around. So I try to be really more understanding than usual.

[LAUGHTER]

So I think we talked a little bit--

AUDIENCE: [INAUDIBLE] talking about something Wednesday after [INAUDIBLE].

MICHAEL MYERBURG: I don't know. That's when I need a drink.

[LAUGHTER]

But yeah. So I'll just go through the overall strategies. Last time I went through all the data for all these. And I think people started nodding off. And so I'm going to just try to get through this because I think people have seen the data.

So anyways, for the inflammation and the airways obstruction we've been using azithromycin. Some macrolide antibiotics are going to be ineffective for most of the pathogens that our patients have so we're not using it as an antibiotic. But macrolides have this side effect that modulates inflammation in the airways in such a way that it delays the progression of lung disease and it reduces exacerbation frequency. So the vast majority our patients are on azithromycin.

There's also a lot of our patients on steroids, these chronic steroids. Most of these people have ABPA or some allergic airways disease. But a lot of our patients just have such intense inflammation and they just do better when they're on it. And so they just wind up hanging-- it hangs on for years, and years, and years.

And it's not a good practice. We recognize that. These people have diabetes. And we have young people breaking ribs from coughing and 20-year-old males with osteoporosis. So it's not a sustainable practice. But I think it's probably better than the alternative. We can't manage them with anything else.

And there's been a lot of other research looking at anti-inflammatories. We've used oral NAC. Our patients really like that. And I don't know what the data showed. A lot of these trials that we do, you never see what the result was. I assume that it probably was ineffective, but for a lot of our patients they really swore by it.

But right now we're studying a new anti-inflammatory by a company Corbis. It's a synthetic cannabinoid that interacts with CB2 receptors and purportedly has anti-inflammatory effects. It's important to tell your patients that it's not in the natural occurring plant and it's a synthetic one.

[LAUGHTER]

But yeah, that's in trials as we speak. We also use a lot of inhaled antibiotics for the bacterial colonization.

And I put this slide up. Sometimes we show this, and it's one person's over time, and there's a well-described succession. It's almost like an ecology experiment.

But this is just over time for the general population. And I think it's really interesting. You can see how our practice is influencing the prevalence of these different bugs. So as we've came up with anti-pseudomonal nebulized therapy, the prevalence of people having pseudomonas has dropped. And along with that we have this increase in staph.

And it's kind of interesting. We have people who will have staph and pseudomonas but they seem like there will all staph for a while, and then we try to treat their staph, and then the pseudomonas will pop back up. It seems like the two are a yin and a yang. And I think it'll be interesting when someone figures that one out.

And you can also see that aside from the H. flu down here, these people have a lot of nasty pathogens. So B cepacia is well-associated with bad outcomes. And I think we've all had experiences with this organism just being nasty. So about 5% of our patients have that. We also have lots of really resistant achromobacter and maltophilia. And these things are just really tough to treat.

And so right now the available antibiotics that we have for nebulization, the ones that are approved are TOBI and aztreonam-- or Cayston. So those are the ones that we use most frequently.

And typically these people will be on one every other month. And if they continue to have exacerbations, we'll do continuous alternating therapy. So we'll be on one and then the next month they'll be on another.

And our center uses a lot of Fortaz colistin. And we've been using that for a long time. I think we use more than a lot of other centers. They are generally well-tolerated except for the smell of Fortaz, which is pretty gross.

We've also been using much more inhaled vancomycin, which has never been known as a really clean antibiotic. And it's really rough on the airways. So typically what we'll do is we'll bring people over to a short stay, take PFTs, nebulize the antibiotic and repeat the PFTs, and see if it drops. And probably 70% of our patients will pass that test and will try it. And probably about 50% of them overall will stay on it. Because after a while, some people, it's just too rough for them. But for the people it works for, it seems to really help, especially these people.

We've also been using more meropenem, which seems to be pretty well-tolerated. And we use inhaled amikacin. There's a form of dry powder Levaquin that's been kicking around for about 10 years. And we've done trials here. And I haven't really seen too much results, so I assume it's not working as you'd anticipate.

And for all these antibiotics the data looks pretty much like the ones from the Tobi study where when you start the antibiotic you get a modest improvement in your FEV1 while you're on it. And over time when you're going on and off it, over time it leads to a slowing of your rate of lung function decline and reduced exacerbation frequency.

Moving up a little bit further, we've got clearance in using recombinants human dnase or pulmozyme as well as osmotic agents. I'll talk a little bit about clearance.

But osmotic agents, the idea is hypertonic saline. It's more salty than the fluid in your airway, so it's drawing moisture into the airway. And it's also inducing cough. So it's actually a really effective way of improving clearance. And pulmozyme we'll talk about in a second.

For clearance, really it starts at the beginning. We really encourage our patients to cough. You know a lot of our patients are embarrassed by their cough because they're sick of being the kid who's always coughing. And a lot of adults suppress it. And they'll suppress it. And so we encourage them to cough, get it out. And that's the first step.

We do chest PT or using the vest-- depending on patient's preference-- or a Flutter, whatever. And we've been big on exercise in our center. And I'll show you some of the data for that in a second.

I like this picture just because it shows a young person banging it all out at once. So for a while when the Wii came out people consider that exercise. So they'd tell you that they're doing their exercise, their vest, taking some [INAUDIBLE], getting it done.

But exercise is really kind of interesting. So there's old data here showing that people who have a higher exercise capacity live longer with cystic fibrosis. That's not surprising. And then they say they correct for all the other things that one would correct for statistically. I don't know how you do that. But someone who can run farther is probably going to live longer.

But more recently there's been some really cool data about why that might be. So this is a figure from a German study where they took people with and without cystic fibrosis, and they put them on a bicycle, and they did a nasal potential difference. So this would be difficult to do on a bike.

But what you do-- basically, you put a reference electrode in the skin in the arm. And then you profuse the nose with a physiologic solution that can carry electrical current. And then you put an electrode right on the nasal epithelium. And you can measure the potential difference across that epithelium.

And so people with cystic fibrosis are hyperpolarized because their excessive sodium absorption and not enough CFTR activity. And you can see that right at baseline. But then when these people start riding the bike, they become depolarized towards normal-- and you can see that here-- which is really kind of cool. This is in humans. And a couple of years ago the group at UNC figured out a little bit what that might be caused by.

So what they did is they took cultures of primary human airway cells. And they put them on this device that caused phase phasic shear stress. So a--

[CLICKING]

And that's meant to mimic tidal breathing and the shear that would be cause on the airway from the air flowing across it. And what they found when they did that is that mucus transport in these cultures of cystic fibrosis tissue went up back to normal. It was kind of neat.

And in this paper what they showed is that the shear stress causes ATP release from the airway. And that binds to purinergic receptors-- P2Y2 receptors. Lead to an increase in intracellular calcium, which does many things that would be purported to be beneficial and CF1. It increased ciliary beat frequency. And it activates CAC, which stands for Calcium Activated Chloride transporter.

Now we know that is TMEM16A, if you've ever seen papers about that. For a long time we didn't know what the calcium-activated chloride channel is. Now we do. And so it activates that.

And that's a chloride secretory pathway that still works in CF. So you increase chloride secretion and you also inhibit ENaC. So it's like a perfect therapy in essence, doing exercise.

And so this whole pathway that normally works falls apart when there's a viral infection. So when there's a viral infection, it's been shown-- whoa-- that there is an increase in these ectonucleotidases that'll break down the ATP and cause it to no longer be effective.

And I threw this in here not to talk about pulmozyme or make sure that there's leftover pizza for me after the talk. But you can see here that these airways are just filled with pus and bacteria and just tenacious, tenacious mucus.

But the real reason why I show this now in the talk was just to show you this is what all the data looks like from all the prior studies that I've talked about is that there's a modest increase in FEV1 for these therapies and there is a delay in the exacerbation frequency. And that's going to change when we start getting to the exciting stuff. So now we're working on ion channel modulators. So now we're going right at the source.

So there's a couple different ways-- a couple of different targets-- outside of CFTR. And I'll talk about them briefly first.

So the first being ENaC. If you can inhibit ENaC, you ought to prevent absorption. So unfortunately, there hasn't been a trial that's really shown any benefit from any of these therapies.

The first one we were using was amiloride, which is your prototypical ENaC inhibitor. The problem with that is that it had such a short half life in the airway that by the time there was any efficacy people were hyperkalemic. So that's not good.

So now there have been airway-specific amiloride analogs and other ENaC inhibitors that have been tried. And we've done all these trials. And our patients, they say it's like doing hypertonic saline.

And none of them have been published yet so I'm assuming that they haven't been very efficacious. And there are several that are in the pipeline. And so it's not looking it's not looking good for that.

There's also this TMEM or CAC that I was talking about. And so exercise, ATP-- well, what if we just had people inhaled UTP or ATP analogs and see what happens there? So there was a medicine called denufosol that was developed with the idea being that it's going to do the same thing. It's going to activate chloride secretion, inhibitor ENaC, it's going to be great.

But what happened was that when you chronically increase intracellular calcium, you're also chronically increasing mucus secretion. And so at the end of the day, you had more mucus and the two effects kind of balance one another out and it wasn't beneficial. So that got tossed out of the way.

And now there's companies working on direct TMEM agonists. And the preclinical stuff that I've seen looks pretty cool, but we'll see where that goes.

And so that brings us to CFTR. And I'm going to spend the rest of the talk talking about CFTR biogenesis and efforts that have been made to try to fix this problem.

So to fix this problem, you've first got to understand how complicated the problem is. So CFTR gets transcribed and then it gets translated in the ER, transported through the golgi where it goes through extensive modification. It gets glycosylated and folded correctly. And it also goes under quality control. After it passes all that, it will transport up to the cell surface.

This is a western blot. And you can see that there's these two bands when you do a blot for CFTR. We call this band B. And that's immature CFTR that doesn't have mature glycan. So that's intracellular CFTR. Whereas the fully glycosylated, we call that band C, is the mature protein that can actually do something. All right. And then once it gets there, it has to gate open.

And so it winds up that there's over 1,000 mutations that have been described. And so how are you going to fix this problem? It gets really complicated.

Fortunately, these mutations fall into classes that have allowed us to develop therapies for specific types of mutations. So the first class of mutations, or class 1 mutations, are mutations that end in x. So those are nonsense mutations. So there's an early stop codon, and you get a truncated protein, and it doesn't work at all in general. They're pretty severe mutations.

There's been some efforts to fix that. There was these ribosomal readthrough agents that we tested a while back. And they didn't do anything. And it just fundamentally doesn't seem like a good idea to do ribosomal readthrough.

But anyways, class 2 mutations are delta F508. So that's the most common mutation. About 70% of CF individuals have at least one delta F508 allele. And that that protein as it's passed in through the golgi gets recognized as being misfolded and gets degraded before it ever gets anywhere. So there's essentially no CFTR on the cell surface. It's a bad mutation.

Class 3 mutations are G551D mutations. So these are gating mutations. The protein gets to the right place but it doesn't open up.

And then class 4, 5, and 6 mutations, basically either you'll have some protein in the membrane that will open infrequently, or there'll be a reduced number of channels in the cell surface due to inefficient transcription, or a reduced membrane half life. So what can we do about this?

The first thing is, well, what about potentiating the channel. So when we say potentiating, we mean taking these channels that are there and making them work more. That's what potentiator therapies-- that's what we're trying to do. That's the mechanism.

Correctors, we're correcting the biosynthetic defect, the biosynthetic defect being that it doesn't pass quality control. So we're trying to correct that. OK.

And then amplifiers are a new class that I'm not really going to talk about because there's really nothing published about them yet. But the ideas that they just make more substrate. So you have more band B. And the idea is, well, you just have more shots on goal, essentially. You've got more chances of correction.

And when you work with these companies who are developing these drugs, you come across amplifiers all the time. They're relatively easy compounds to find.

So the first one we'll talk about is potentiators. And as Dr. [INAUDIBLE] used to call it, he was like, this is the low hanging fruit. Because the protein is in the right place. All you've got to do is make it work.

So about 15 years ago the CF Foundation partnered with academics and industry and made a large investment in doing basically high throughput screening trying to find compounds. And the first thing that came out was VX-770. And that's Ivacaftor or Kalydeco now.

So 770 was the first one that came out of these screens. And it potentiates the channel. So this is a single channel recording. The C or the dashed line is the close date. And when the channel opens, it deflects down.

And so they add agonists for CFTR, it doesn't really open. But if you add this compound with the agonist, boom, the thing starts opening. So you can see this really large increase in the open probability of delta F or G551D, wild type CFTR. It increases the open probability of the channel.

So this is a very useful compound. It actually works in primary human cells. So these are cells that Joe sent to Vertex. So these are G551D delta F cells. And this is the benchmark for something that's going to work in people as if it works in human cells. And you can see as more 770 was added, CFTR becomes active.

So then first clinical trials, second clinical trials. And basically it got approved in 2012. These trials were really cool to be a part of. I was just starting out of fellowship. And it was just remarkable.

It's one of these trials that you can't be blinded to. These people come to clinic, and you've followed them, and all of a sudden three weeks later their FEV1 has gone up dramatically in an unprecedented way. And they'll tell you, I feel amazing. It's just been really, really cool.

And the reason why I picked this one figure out of all of them was that now on the Y you're looking at sweat chlorides. You're fixing the problem. You're causing a 50 milliequivalent reduction in the sweat chloride. That's huge. That's crazy, right? Very clean.

And I think these images from Tim really sum it up. I love showing these.

We took patients, had them inhale radioactive particles, and then imaged them serially with a gamma counter. And if you do that to somebody with cystic fibrosis who is not on Ivacaftor, you can see that the particles deposit in the lung and they don't really move anywhere. Down here is going to be-- that's your stomach. There's really not a whole lot of clearance.

So then you take that same person 90 days later on Ivacaftor and watch this. See all those particles clearing from the lung, and getting swallowed, and winding up in the stomach? It works. It works really well. You want to see that again, don't you?

[LAUGHTER]

That's awesome.

So anyways, now we have a highly efficacious modulator that was initially approved for 5%-- less than 5%-- of individuals with CF. And over the last several years the FDA has kept expanding the indication. So now about 10% to 15% of people are available for this therapy. And it works really well.

The other thing that's really important about Ivacaftor is that we learned a lot about how much CFTR do we have to fix to cause a real meaningful impact. And so there is this sweat chloride CFTR activity chart. And you can see with 770 you're getting about 30% of wild type CFTR. That's associated with significant reduction in your sweat chloride. It brings you down into this mild non-classic CF range. And there was a huge clinical benefit.

And so this is good news, right? We don't have to fix it entirely. We just need to fix it a little bit-- 30%.

And that 30% number keeps coming up. So in our lab-- most labs who study this kind of stuff have similar data.

This one was a silly experiment. We just took CF cells, and we added increasing proportions of wild type CF cells, and looked at the airway surface hydration as well as chloride secretion. And you can see when we get about 30%, we restore the volume and you add more, it doesn't work any better. And same with the chloride transporter, which is really kind of surprising. You'd think that more is better.

So that's good, right? We only need to get 30%. And so that's informed all of the preclinical work. You can get about that kind of correction, it's probably going to work.

So 15%, how are we going to get more patients? Well, it's like Sutton's law-- 70% of people have one delta F, let's go after delta F. And it winds up that this is a tough nut to crack.

So again, remember that this is wild type CFTR that's functional. But with delta F508 it gets degraded and it's just in the cell-- it's not on the surface.

And so this quality control is pretty baked into a cell. Yeast has quality control mechanisms. The vast majority of the protein that your cell makes is degraded.

This is pretty important. How are we going to get that to not matter and get the channel to get through, get to the cell surface, and function? It's not an easy challenge.

And so what these companies did-- along with academics-- is they just did industrial strength high throughput screening just basically looking for a needle in a haystack. And so this is a picture of this setup that they have in Vertex.

And these guys aren't playing around. They've got robots up in here. They're doing 10,000 primary assays a day.

And I can tell you that from working with these guys is like only less than 1 in 100 of these primary hits actually translates to working in human cells. So it's a huge amount of work that went into finding these things. And it's really amazing.

So they find something that on a cell-based assay does something beneficial. And then they group them together-- are they additive, are they not additive? They're trying to find different mechanisms that they can fix this. And then these guys can just look at the structure, and tweak it-- change it-- and see if it works better or doesn't work at all. Or if it's toxic, can we engineer out the toxicity? Until after a lot of work you come up with something that looks like a drug.

So the first one that came out of this was VX-809. That's Lumacaftor. It's what's in or can be along with Ivacaftor. And so here you can see that when you take delta F508 cells and you add increasing amounts of 809, you get some band C.

And this is quantitation of these bots you can see. And unfortunately, this is not what you want to see in a really nice drug. You want to see a sigmoidal relationship where this keeps going like this and then toxicity is way over here so you have a nice wide therapeutic. This isn't really the kind of pharmacology that excites you.

But anyways, it works. It works in primary cells. And if you take these cells, and incubate them in 809, and then hit them with 770 when they're in the chamber, you get up to this 30%. So we were all super psyched. The CF community was super psyched for this to be the next big thing.

And it works. There's a signal. But it doesn't do much. And it wasn't nearly as much of a response as we all anticipated.

It was approved by the FDA in 2015. But you can see here that the change in lung function is really nominal. And this is probably what drove the FDA to approve it. There's a reduction in the exacerbation frequency. But it's not anything that you're going to be jumping up and down about.

And it was interesting. We were so optimistic. We were starting people on these medicine. And they'd tell you they feel awful. And we'd say, well, stick with it, that's a good thing. What's happening now is all your mucus is starting to move. And it's going to be tough. This is the failure before the success. It's going to work.

But they found another compound. It was 661 in trial. It's very similar, same mechanism of action as Lumacaftor. And that's now what's in Symdeko. And that's a little cleaner of a compound and it has less drug-drug interactions. It works a little bit better, but people don't feel awful when you start it. So that's what's now being used.

But you can see that it's really not dramatic. There's a reduction in the exacerbation frequency. There's really not much weight gain. There's a subtle improvement in symptom score.

Now this is 100 point scale, so 6? I mean, come on, you know. And there's a reduction in sweat chloride.

And what's exciting about this is that it's proof of concept. We're doing something. And some of our patients really do seem to benefit from it. But overall it hasn't been a big thing.

And if you look at overall-- so we're saying that now we've got about half of our patients on a modulator. I put it in gray because I don't really view it as being highly efficacious. And after the fact, we've learned that the reason why it didn't work as well as we thought had to do with how we were doing our experiments in vitro.

And if you incubate the cells in 809 alone, you get a nice degree of CFTR correction. But if you incubate it with the corrector and the potentiator, you really knock down that. And so we all observed this after the fact.

And it winds up that when you correct delta F508 and potentiated it, it puts it in an unstable state so it gets degraded more rapidly. So that's why it work as well as we think it should have.

But all the while there is this effort going on and on finding new compounds. And this is where it gets really exciting. Here we go.

So recently they've found two more compounds-- it's 445 and 659. They're related. They seem to be doing the same thing. They're additive to tezacaftor, so they're presumably a new mechanism of action.

And as you can see here, they work so well that now they'll work in people who only have one copy of delta F50. So Symdeko does nothing for somebody who has one copy of delta F508. This works really well, actually, for people with just one copy. So these minimal functions, this is going to be someone with delta F508 and a stop, something that's not going to potentate with a potentiator. So they've got one allele that they're working with.

And you can see that when they add this new compound you get an increase in band C. OK. And same in the heterozygous.

And interestingly, if you look at the protein, it looks like when you add the Ivacaftor to the mix it actually goes down a little bit. So we think that that has to do with what I just showed you, when you potentiate. But when you look at the current, you need that Ivacaftor to really crank that thing open. And now you're seeing just massive chloride secretion, which is pretty exciting.

So this is the phase II trials. And this is legit. So in 30 days you've got a huge improvement in your FEV1 for people with just one copy and with two copies of delta F508. So this is causing a huge impact.

There is a ginormous decrease in your sweat chloride. And this is on top of people who are already on Symdeko. So this was the best corrector available. And now we drop them down again way further than they got from their original drug. And so this is a significant improvement in sweat chloride. This is huge.

And then I think this tells it all. So now you're looking at an improvement on 100 point scale going up about 20. And the baseline for these people was 70, and now they're going up to about 90. So these people are nearly asymptomatic.

And I can just tell you from these people who are on these trials that I've interacted with, they'll say things like, I've never felt this good, I don't remember feeling this good. One guy told me he used to sleep nine hours a night and generally felt fatigued. Now he's sleeping seven hours and he feels like he's got tons of energy. One guy set the burpee record in his Crossfit gym. One guy said my son asked me in the car why I don't cough anymore.

It's transformative. It's changing people's lives. And we're really excited.

And so now we're bracing ourselves for one of these two drugs going to the FDA and hopefully being approved in the next year. And that's going to put 90 plus percent of our patients on a highly efficacious drug, which is going to make this a new disease in my opinion altogether.

There's going to be people with stop mutations and there's going to be people who can't tolerate these drugs. But we think the vast majority of people are going to be on therapy that's going to profoundly impact their disease.

AUDIENCE: Do you have symptomatic control in terms of bowel function, and digestive function, and all that that comes with these as well over time?

MICHAEL MYERBURG: Yeah. Yeah. It works throughout their entire body. So it's an oral medicine twice a day that affects the gut. So alkalinization of the duodenum goes back to normal.

A problem we're having is a lot of people are gaining tons of weight, like too much weight. Because they're used to eating like we all wish we could. And now they're digesting their food like we all do. So we have a lot of people don't want to start these therapies because they're worried about their weight.

AUDIENCE: So you're going to have to start talking about birth control?

MICHAEL MYERBURG: What's that?

AUDIENCE: You have to start talking about birth control with them?

MICHAEL MYERBURG: Yeah, we do.

So anyways, there's still a lot of other next steps, I think. One of them is what are we going to do with these people who aren't covered by it. The Foundation is investing heavily in gene editing, what they're calling the one time cure kind of stuff. That's a ways off. And then there's all these alternative ion channels that we might be able to modulate that will work regardless of what CFTR mutations you have.

I think we really need new antimicrobial therapies. I could have talked the whole time about the whole infection antimicrobial thing.

But we need phage. We need things other than antibiotics. Because these bugs are just getting nasty. And as people live longer, and longer, and longer, they're going to be ridiculous.

We need to figure out when and who to start these modulators on. They're wicked expensive. They're like $300,000 a year. And so at what point should we start this is in the disease and how can we make this more affordable?

And then the next question is, well, can we start peeling off some of these therapies that we're asking our patients to do. We hope that we will be able to.

So I think this disease has come a long way. I don't think people really think of CF as as much of a success story as it's really been. It's been remarkable, I think, that we found these compounds given how difficult-- it's not traditional drug design. You're fishing and we got lucky.

And I think it's going to dramatically improve survival. And I think that it's only possible when you have a foundation that's facilitating collaboration between industry, academics, clinical providers, and then all of our patients and families who are just game to try all this stuff and made it all happen. So thanks.

[APPLAUSE]