# Targeting the Toughest Diseases

## Episode 3 – Targeting Genetic Kidney Disease

**Miami Arena. March 29th, 1996.**

**The Miami Heat are facing the Washington Bullets.**

**All night long, Alonzo Mourning of the Heat has been guarded by a giant of a man named Gheorghe Muresan.**

**At seven-foot-seven, Muresan is one of the fiercest players in the league… the tallest player in NBA history… an impenetrable wall… with a non-stop motor.**

**But Alonzo Mourning is one of the greatest ever to step on the court.**

**When the final buzzer goes, the Heat have won 112 to 93 and Mourning has scored an incredible 50 points.**

**That game was a career high for Mourning. He would go on to be a seven-time All-Star, and a gold medalist in the 2000 Olympics.**

**But little did he know – his toughest opponent was yet to come.**

**After returning from the Olympics in Sydney, Mourning started into his usual off-season training.**

**But he noticed something was wrong.**

***Alonzo Mourning:*** *I was experiencing lethargy, edema in my legs, swelling in my lower extremities, extremely tired, worn out.*

**He thought it was jet lag. Maybe the flu. He figured he'd just take a couple days off, then resume his training.**

**His doctor had a different idea. He suggested they run some tests.**

***Alonzo Mourning:*** *I answered the phone next to the bed. And he said, 'You know, I got your results back.' He said that 'You've got this rare genetic disorder called focal segmental glomerulosclerosis.' And I said, 'Doc, what is that?' He said, 'It's a disease that scars the filters in the kidney.'*

**Focal segmental glomerulosclerosis – or FSGS – causes scar tissue to develop on the small parts of the kidneys that filter waste from the blood.**

***Alonzo Mourning:*** *I asked him three questions. I said, 'Is there a cure for this?' He said, 'No.' I said, 'Can I play basketball again?' He said, 'I don't know,' And then I said, 'Well, am I gonna die?'*

**Hi. I'm Jordan Gass-Pooré, I'm a member of the University of Southern California's Center for Health Journalism.**

**This is *Targeting the Toughest Diseases*, a podcast produced by Bloomberg Media Studios and Vertex Pharmaceuticals.**

**In this series, we look at some of humanity's most challenging diseases, and how Vertex – a Boston-based biotech company – is using innovative tools, methods and a unique philosophy to search for treatments and cures.**

**Today, we're looking at APOL1-mediated kidney disease. A disease caused by a genetic abnormality. One that 13% of African Americans carry.**

**This abnormality can cause a number of types of kidney diseases, one of which is FSGS, the condition Alonzo Mourning was diagnosed with.**

***Alonzo Mourning:*** *I thought to myself, not 'Why me', but 'Why right now God, why am I dealing with this right now, of all times?' I had just come back from the Sydney, Australia Olympics winning the gold medal. I had just come off an amazing basketball season where I had first team, all NBA, all-star team the list goes on, you know, all the accolades. And then all of a sudden, bam, this happens.*

**Lots of young professional athletes view themselves as invincible. Alonzo suddenly found out, he wasn't.**

***Alonzo Mourning:*** *I hung up the phone and my face fell in my hands.*

***Alonzo Mourning:*** *I felt like I was gonna play until I was in my forties because I was in such great shape. Just hearing it from somebody saying, 'Hey, you got to stop playing.' It was humbling. And it was deflating, you know, and I just was just sitting there just trying to figure out, okay, how is this all gonna materialize?*

**We can't survive without our kidneys. They play a vital role.**

- **They help our bodies maintain just the right balance of electrolytes – like potassium**
- **They control blood pressure**
- **They clean our blood**
- **And they even help maintain our hormone levels**

**Each kidney is made up of a million or so tiny filters called glomeruli.**

**They're like little coffee filters. The filtered liquid becomes urine. And the protein left behind stays in our blood.**

**But when the glomeruli become damaged – those proteins start leaking into the urine.**

**The scary thing is – it's estimated 37 million adults in the United States have kidney disease, and 90 percent of them don't even know they have it.**

**And in the case of APOL1-mediated kidney disease, the prime causal factor is invisible. It's genetic… caused by mutations in the *APOL1* gene.**

**Back in the early 1990s, Dr. David Friedman – a doctor, researcher and an associate professor with Harvard Medical School who currently works with Vertex on its clinical trials – first started to notice something unusual. He was seeing African American families where multiple members all had kidney disease.**

***Dr. David Friedman:*** *When there's an important inherited component of a disease, it tends to cluster in families.*

**Understanding there was a genetic cause was just the beginning. Next, they had to find the exact gene.**

***Dr. David Friedman:*** *I think a real breakthrough in our understanding came in 2008 when some teams at Johns Hopkins and the NIH were the first to find a location in the genome on chromosome 22, where it became apparent that there was something strong that was impacting kidney disease in people of African ancestry.*

**Then in 2010, Dr. Friedman and his colleagues identified the specific mutations that led to this type of kidney disease.**

***Dr. David Friedman:*** *There were two important advances in technology which really helped us to pinpoint these two genetic variants in APOL1.*

*The first was related to tools for identifying positive selection in the genome. And these mathematical tools helped us envision the genome in a slightly different way.*

*And the second major technological advance was a database of genetic variance in people of widely diverse ancestries called the 1000 Genomes Project. Up until that time, most of what we knew about genetic variation came from people of European ancestry. And this new, very powerful tool was really the equivalent of an encyclopedia of genetic variation around the world.*

**From there – our understanding of APOL1 has continued to increase – including why the risk variants in this gene only affect people of recent African descent, including African American, LatinX, and Afro-Caribbean communities.**

**Thousands of years ago, a genetic mutation in the *APOL1* gene developed in Sub-Saharan Africa as a protective mechanism.**

***Dr. David Friedman:*** *We all have a gene that encodes for the APOL1 protein. But the version which causes kidney disease contains some very slight changes in the instructions for building that protein that turn out to make it very effective for killing the trypanosomes that cause African sleeping sickness in humans.*

**"Sleeping sickness" is a disease spread by the bite of an infected fly… and it can cause death within a matter of weeks. But this genetic mutation stops it in its tracks.**

***Dr. David Friedman:*** *Because it was so effective, it spread very quickly in the population. But it's these proteins with a slightly different version of APOL1 that's very, very effective for killing trypanosomes and preventing African sleeping sickness, which is the same version of the protein which makes the kidneys of people sick who have this genetic variant.*

**We now understand that having one APOL1 risk variant could protect you from many forms of sleeping sickness. But if you were unlucky enough to inherit two – one from your mother and one from your father – your chances of getting kidney disease goes up 10-fold.**

**Once your kidneys start to fail, there really are only a few ways to stay alive.**
**One is dialysis. It replaces the function of the kidney.**

**Dr. Janice Lea studies kidney disorders at Emory University School of Medicine in Atlanta, Georgia.**

***Dr. Janice Lea:*** *Kidneys excrete waste products, and they get rid of excess fluid from our bodies. So, that's what the dialysis machine does.*

**Two needles are inserted into a patient's arm. One draws blood out and sends it through the machine to be cleaned. The other needle returns the clean blood back into the patient. Which is pretty much exactly the way our kidneys work.**

**Except, while your kidneys work slowly, 24 hours a day, seven days a week… dialysis means sitting in a chair, plugged into a machine for two to three hours at a time, three times a week.**

**It works, but it's not ideal.**

***Dr. Janice Lea:*** *If you really think about it, we go to the bathroom, excrete our urine, two or three, four times or more a day. So, when patients are on dialysis, they're really getting their blood cleansed just three days a week for a few hours. And so, patients can feel washed out when they get off of dialysis, because they've had all this fluid from two days' worth of not excreting any waste products or fluid.*

**There's no cure available for chronic kidney disease. The medications currently on the market focus on making sure a person's kidneys don't deteriorate further.**

**The current options include:**

- **Medications that suppress the immune system**
- **Diuretics**
- **ACE inhibitors or ARB medications to control blood pressure or lower urine protein**
- **Anticoagulants to prevent blood clots**
- **And then there's the option Alonzo Mourning had done for his FSGS: a kidney transplant**

**That approach requires you to be fortunate enough to find a suitable donor. On average, it also only lasts 10 to 12 years.**

**Vertex Pharmaceuticals is a company that is researching APOL1-mediated kidney disease and other tough diseases where there is a huge unmet need. They are targeting conditions where:**

- **The human biology is understood**
- **The technology already exists, or Vertex thinks it can develop it**
- **And where Vertex has an approach they think may be transformative**

**They have several programs in their investigational research, including APOL1-mediated kidney disease.**

**Dr. Ogo Egbuna leads clinical development for the team researching kidney disease at Vertex.**

*Dr. Ogo Egbuna: As we speak here in the U.S., there are probably more than a hundred thousand people waiting for a kidney. And, not everyone is fortunate to be able to get one. Many people will die waiting for a kidney.*

**The staggering number of people living with and dying from kidney disease is one of the main reasons why Dr. Egbuna joined Vertex's efforts.**

*Dr. Ogo Egbuna: It was really heartbreaking. You know, at the beginning of the year, I'd have a whole host of patients on dialysis. And at the end of the year, one or two out of every three would have, you know, passed on. That was just too depressing for me.*

*Jordan Gass-Pooré: Why did Vertex choose to focus on APOL1 versus other types of kidney disease?*

*Dr. Ogo Egbuna: This is actually one of the most difficult kidney diseases that have plagued a minority population and underserved population for so long. And for the longest time we have attributed this to either by a bad diet or lack of exercise or nutrition. But we do know now that there is a genetic basis for a lot of this disparity. And I think in typical Vertex fashion, we go after diseases that have a serious unmet need. And in addition to that, we go after diseases where the underlying cause is well understood and for which we apply the best science available to try and address it.*

*Jordan Gass-Pooré: What can we look forward to?*

**Dr. Ogo Egbuna:** *Part of the reason why I'm actually so excited about what we're doing here at Vertex is because we have found small molecule therapies that are investigational to the underlying cause of what I've described as APOL1-mediated kidney disease. We have evaluated these potential therapies in experimental settings and first-in-human studies, as well as a preliminary proof-of-concept study in patients.*

**Developing a potential small molecule therapy is no easy feat. Dr. Egbuna says scientists at Vertex have gone through hundreds of thousands of candidate molecules in their kidney disease research.**

**Dr. Ogo Egbuna:** *Nothing good or great comes easy. Therein lies the promise and the excitement.*

**While their research continues, Dr. Egbuna says he and his team at Vertex will do everything they can to raise awareness for the disease. That includes educating on preventative measures like "genotyping," which can help determine whether a patient carries the *APOL1* genetic variant.**

**Dr. Ogo Egbuna:** *So, in addition to supporting the clinical community and patients, and increasing the rates of diagnosis of kidney disease, we also want an increase in the awareness and of genotyping so that precise diagnosis can be made so that the right therapy can be brought to the patient.*

**Dr. Ogo Egbuna:** *Alonzo Mourning is one of those great examples of people that went through, the signs, symptoms, the worries, the challenges of end-stage advanced kidney disease, got a transplant and he got back on his feet.*

**Alonzo Mourning underwent a kidney transplant three years after his initial diagnosis.**

**Alonzo Mourning:** *So, the recovery process was grueling, and it was extremely painful at times, and it was difficult. But if you think about anything in life worth having… it's very difficult to get it. And I was trying to get my health back and I was trying to get back on the court. So, I was trying to get back to some sense of normalcy, but it challenged me tremendously. It really, truly challenged me.*

**Mourning talks about his struggle to get and then adapt to living with a new kidney, knowing full well that he had a lot of advantages.**

**Alonzo Mourning:** *I was in optimal condition, excellent health, you know, but that was the benefit of my recovery so fast because the doctors told me like, 'Hey, you know, if you wasn't this high-performance athlete then you probably wouldn't have bounced back as fast after the transplant.'*

**And bounce back he did. Just three years after his transplant Alonzo Mourning would go on and win a championship with the Miami Heat in 2006.**

**And today, he's partnering with Vertex as a spokesperson, using his profile and his experience to advocate and educate.**

**Alonzo Mourning:** *You know, a big part of it is to try to inspire and provide hope and encouragement for those who are going through the same ordeal.*

**And Mourning says he's hoping Vertex will be able to help kidney patients by raising awareness of the disease, encouraging people to visit their doctor, and continuing to search for a potential treatment.**

**Alonzo Mourning:** *So, if this can happen, then all of what I've gone through is so much more worthwhile because I'm able to help save other people's lives.*

**This is *Targeting the Toughest Diseases*, a podcast from Bloomberg Media Studios and Vertex Pharmaceuticals.**

**If you like what you hear, subscribe and leave us a review.**

**I'm Jordan Gass-Pooré, thanks for listening.**