Santa J. Ono: Broadcasting from the University of British Columbia. This is *Blue and Goldcast*. I'm Santa Ono, the president and vice-chancellor of UBC. On this season of the *Blue and Goldcast*, I'm speaking with the people who are leading some of the most innovative and creative work coming out of our campuses.

Santa: My guest today is Julio Montaner. Dr. Montaner is the director of the British Columbia Center for Excellence in HIV/AIDS, the chair in the AIDS research, and head of the division of AIDS in the faculty of medicine at the University of British Columbia. He's a global leader in HIV and AIDS research and his work on antiretroviral therapy and advocating for treatment as prevention, has had deep and lasting impacts on the field.

He's authored hundreds of publications on HIV/AIDS and he has received numerous awards and accolades for his work including the Knowledge Translation Award from the Canadian Institutes of Health and the Queen Elizabeth II Diamond Jubilee Medal. He was inducted into the Canadian Medical Hall of Fame in 2015.

It is an honor to have him on the show today. Julio, welcome to *Blue and Goldcast*. Can you tell us a little bit about how your career began? How'd you end up in Vancouver?

Dr. Julio Montaner: I'm originally from Buenos Aires, Argentina. My dad was a prominent physician back there. He had a prominent academic career in respiratory medicine and my desire was to work with him and hopefully be a force for transformation.

Very early on, although I did reasonably well in medical school, I felt that in order for me to be able to have the authority to do stuff, I needed to validate my credentials elsewhere. I discussed it with my dad so, I interviewed a number of places, I went to Europe, I went to North America. Although I had fairly good receptions, getting a job like that is very difficult, particularly when you're a medical student.

Anyways, as it happens, I went to a medical conference in Uruguay**,** it was an international conference. As I was walking around, I went to a symposium that I was interested on. A difficult topic at the time, other respiratory stress syndromes, something that I was very interested but it was technically complicated. At least, I could never quite wrap my head around some of those physiopathological issues.

I walked into this room and I started to listen to a lecture and there was this guy speaking a language that I didn't quite was comfortable with at the time. My children would argue that I'm still not comfortable, that's another story. I started to listen to him and I was fascinated because, even though he was giving his lecture in English, which I was not particularly proficient at the time, I understood everything. Stuff that I never quite crystallized in my mind became perfectly clear to me, to the point that I was starting to ask myself questions. "What about you use this? If you do that and if you change this?" to the many experiments that he was discussing.

He finished his talk. Being young and not really conscious about the implications. I decided I was going to approach him. I reached out and I said, "Dr. Hogg, I hope you don't mind. My name is Julio Montaner. I enjoyed your lecture. I wanted to ask you a couple of questions." He was talking to a guy there from Nashville by the way.

Thanks God, he didn't join us because I would understand nothing [chuckles] that he was talking about.

We sat down. I engaged in a conversation and I asked him a bunch of questions. We discussed various experiments. By the end of the brief conversation, to be honest with you, he said, "Dr. Montaner, the experiments that you're discussing are quite of interest. If you're interested, I'll be happy to entertain an opportunity for you to come and do those experiments in my laboratory back in Vancouver in Canada."

I didn't know where Vancouver was, I didn't know who he was. I was just interested because I was fascinated, to be honest. I talked to my dad second-in-command, so to speak at the time. My dad was, as I said, very prominent in the field. I said "Look, this is what happened to me." He said, "Julio, do you know who you really engaged with?" I said, "I have no idea." He said, "But this guy is a genius. He discovered the side of the lesion, people who smoke, in terms of COPD," dah, dah, dah. He went on and on and on. I had no idea what he was talking about. He said, "Julio, you had to go." He grabbed a couple of his friends, he said, "Tell them what happened to you." They were all so excited. That night, I couldn't sleep.

The next morning I approached Jim Hogg during breakfast and I said, "Dr. Hogg, I hope you don't mind." "Oh no, Julio, yes, so nice to see you." Very engaging, very friendly. I said, "I'd like to reconsider." He said, "Yes, of course. Send me a letter and we'll keep in touch." Within a bunch of months, eventually, I received a letter from him about an opportunity to do research with him.

That was the beginning of the end, or the end of the beginning, [chuckles] whatever you going to call it. He totally transformed my life. It was the best thing I ever did.

Santa: It's an amazing story. You ended up in Vancouver, a place you hadn't even heard of. Where did you land? What part of Vancouver did you land in terms of-- Where was your research carried out?

Dr. Montaner: Jim was at that time a couple of years into-- Since he moved his laboratory from Montreal to Vancouver. He was just starting to build his research enterprise, so he introduced me to John Ruedy. At that time, John Ruedy was the chairman of the department of medicine at St. Paul's. It's also based at UBC. Between John and Jim, they took me under their wing. They mentor me and I started my clinical training.

Again, I was still beginning to understand the system and the language, and everything else. I have a great deal of admiration for all of the patients. Not just the two of them but many others had with me in those early days. Eventually, it was the early '80s and I made it into the respiratory fellowship. As I was the respiratory fellow, the HIV epidemic just started.

It had been described by the Americans in '81 but it didn't really hit Vancouver until a couple of years later. It really took off in the mid-'80s, so to speak, '83, '84, '85. By those days the numbers were atrocious, things were really out of control. Being the youngest member of the group, I would be sent down to emergency to deal with-- Which was the critical, potentially lethal infection for people with HIV. The more I saw

it the more I drew parallels between other respiratory distress syndromes which is what brought me down to work with Jim, and what we were seeing in the clinic.

Eventually, one day, as I was doing a bronchoscopy in the ICU with a patient that was very severely ill, we dragged out a material that was basically suffocating this patient. They were bronchiolar casts that were perfectly resembling the respiratory tree. We looked at each other and we said, "No wonder this person cannot breathe." Basically her lungs-- It was a woman, are totally clouded with this very viscous and almost solidified material.

I had an idea. I took it to Jody Wright, who was senior to me in the pulmonary respiratory lab back in the day when I started. I took it to her in the pathology lab and I said, "Jody, I want you to help me figure out what's in these casts."

We looked at it under the microscope and we figured out that they were immunoglobulins. We concluded that this was an inflammatory exudate. I hypothesized that dealing with inflammation, aside from dealing with the infection, while we were trying to deal with infection within the **[unintelligible 00:09:01]** could ameliorate the respiratory distress in these patients.

We tried that by using corticosteroid which was **[unintelligible 00:09:10]** the time because people with HIV were felt to be immunosuppressed. If you give them more immunosuppressants, people would say "You're going to make it worse." We said, "Well, let's try this and see what happens." They were dying.

We tried it on a clinical basis and within a matter of a dozen patients that we did out of desperation in the ICU, people that were supposed to be dying 100% of the time, all of a sudden were making it out of the ICU. Of course, the more I work in HIV, the more I became interested. It became clear to us that even though we were successful at treating and preventing opportunistic infections, we needed to do more.

That's when I decided to basically abandon the rest of my work and dedicate myself to find an antiretroviral therapy strategy in my work.

Santa: Isn't it true that **[unintelligible 00:10:00]** of AIDS that there were different phases of the public reaction? One was almost a denial that there was a situation because of the way gay men were actually viewed by the establishment, by governments. It really took quite a bit of advocacy for there to be appropriate levels of funding and resource not only in Canada but even in the US, where it was a much bigger problem. What was it like in the early '80s with HIV/AIDS?

Dr. Montaner: Let me say a couple of things. First, we were inundated by HIV cases in the early phase of the epidemic. Although everything that you're saying is true. We didn't have time to do advocacy and to go and lobby because it was really overwhelming.

When you look at COVID today, yes, COVID is bad but this actually, was uniformly lethal. Not only that but there was a concern that we didn't know how it was transmitted early on. We didn't know about **[unintelligible 00:11:07]** precautions. I was doing bronchoscopies without precautions when we started all of this. Thanks God, I don't know how we made it through the whole thing.

The stigma and the discrimination related to HIV, not just the MSN, the men having sex with men population but every group that was most affected, because at the end of the day, it became a serious problem for us. For example, in the injection drug-using community or in the commercial sex worker, areas that we were not really familiar with before all of this happened.

The stigma and the discrimination were powerful. People often say, "Oh, well, St. Paul's stepped up at the time and did the right thing and embraced the population." I, privately, like to describe these as saying, "Everybody walked backward so fast that St. Paul's was left there, and it was left alone." It's true. Eventually, the Sisters rallied behind the cause because they identified the fact that our patients were the people that needed the care the most but that didn't happen until years into it.

Oftentimes, people forget that if we got a separate unit to care for people with HIV at the time, it was not because it was better for them. It was because they were not allowed in the other units. If I was receiving patients in the middle of the night, more often than not, I was receiving because the person that was on call at the other hospital, whatever hospital that would be, gave them a taxi voucher and said, "You go to St. Paul's." It was tough.

Santa: Now, I want to get to this huge transformative contribution that you made. You talked about how you got interested in AIDS. Tell me a little bit about antiretroviral therapy and HAART. What exactly does that mean and why was it important as a prevention strategy?

Dr. Montaner: We were in the middle of dealing with all of the opportunistic infections and we were very successful at treating, preventing them, but our patients were going on to die, regardless. This became a huge frustration for us.

Talking to John Ruedy and the like, we felt that it was imperative that now at the time '84, '85 that the virus had been identified, that we start paying attention to what could we do to deal with the underlying virus, which was a reason why the immunity was basically gone, and people were susceptible to all of these infections like cancer.

When the first drug became available, AZT, we were lucky enough that because of the prominence of the work that we had done together, the government was looking for some way to start getting people aware of this new molecule. John was invited to be the PI of the first antiretroviral therapy trial in Canada. That was a multicenter Canadian AZT trial and that I never forget about it. I was the research fellow if you want to put it that way. My job was to look after the patients and coordinate staff.

I got to know Mark Wainberg, Michael **[unintelligible 00:14:08]**, a number of senior people, biologists, clinicians. I was soaking up all this knowledge in every possible way I could. The early experience with AZT was mixed. Clinical trials had shown that AZT could prolong survival but the side effects, the tolerability issues, and the quantitative improvement related to it no matter how you measure it at the time was very limited. It became very controversial.

I was fortunate enough that I was doing work with the late Mark Wainberg. I was doing correlates of resistance in our patients. Because my dad had expertise in tuberculosis, I was drawing parallels with the TB experience. I became interested in

the fact that when exposed to AZT, a large number of these people would eventually select full resistant variants. I started to ponder whether we could add treatment to this.

We started to try alternating drugs, adding drugs. Being young and a bit more aggressive than many, I was shopping around the world for a third candidate drug that we could combine with these two **[unintelligible 00:15:22]** at the time, AZT and DDI. I ran into a person that I knew, Maureen Meyers, formerly from the NIH, and now working as a research lead for Boehringer Ingelheim. They had a new drug, it was called nevirapine. It was a non-nucleoside analog, the first non-nucleoside reverse transcriptase that became available.

I made my pitch about trying this triple-drug therapy in previously untreated individuals. What happened was that if you treat sequentially and people become resistant to one drug, and then resistant to the other drug, and then resistant to the other drug, the benefit of the treatment becomes very short-lasting. I hypothesized that if we were to use a TB approach and give the three drugs at once so that we could have a maximal effect at once, we may render the ability of the virus incompetent in its ability to generate resistance, except that they were testing the drug predominantly in inexperienced patients.

Maureen Meyers was very fond of my work and my passion and the energy that I was bringing to the table.

She said, "Look, I'm going to convince the German family--" It was a family-owned company, "To do a one pilot study to look at this." Lo and behold, it was my first international collaborative trial. We call it the INCAS trial because it embodied Italy, Netherlands, Canada, Australia, and the States. That was my biggest contribution at the time-- [chuckles] Came up with the acronym.

We randomized volunteers to get two drugs or two other drugs, or a combination of the three drugs. We had basically all of the variables. We treated people for a period of time. They were all not previously treated. Within a year, we had blinded data, six months to complete follow-up. We sent it to the laboratory. Mark Wainberg was measuring what in those days we used to call time to viral culture positivity as a surrogate marker of the antiviral potency of the regimen. The better your regimen, the longer it will take for the virus to grow. That gives you the signal how pessimistic we were in our thinking around these drugs because we were basically expecting that everybody would eventually overcome the effects of the drugs.

I go to a meeting in **[unintelligible 00:17:51]** in late 1995. Mark Wainberg calls me aside and he says, "Julio, I need a moment with you privately. We have issues with the INCAS trial." I said, "Mark, what are you talking about?" He says, "I'm not able to grow virus in the proportion of the patients in the trial." I said, "Well, Mark, why is that a problem?" He says, "Well because we always grow the virus in everybody no matter what." I said, "Mark, have you thought maybe the drugs are working?" He said, "No, that's not possible." I said, "Oh, my God, what are we going to do?" He said, "Are you sure, Julio, that you're not messing up with the methodology or the protocols?" I said, "No, Mark, we're doing it the same way that we always did it. No, that's not the case." He said, "Well, look, if we cannot measure the virus, I don't know what we're going to measure. What are we going to do?" I said, "Mark, look,

give me a little bit of time. I'm going to go back to Vancouver. I'm going to revisit all of the protocols to be sure that everything is fine. Let me see what happens."

I came back home and I called the team. We looked at everything. Everything is fine. As it happens, John **[unintelligible 00:19:00]** who was a scientist working with Roche, and a good friend of ours had actually sent me a bunch of kits of a new test that they were prototype to see what it could mean, what we could do with that. He said, "Julio, look if you find a group of patients that you find these may be of interest, just give it a try and see if you can tell me what you think about it."

Lo and behold, this was a PCR assay, the first generation of a quantitative **[unintelligible 00:19:31]**. We got the PCR machine with them and the kit. We got all of that because we were going to be a better testing site in a protocol yet to be defined because we had access to a lot of samples, a lot of **[unintelligible 00:19:43]**. They said, "If anybody can help us to figure out what it means, you guys can do it." I said, "You know what? I'm going to run all of these samples and see what happens."

The PCR even though in those days it took longer, it was done very quickly. We ran all those samples in our laboratory. Within a matter of a couple of weeks, I got a plot that shows two lines going down and bouncing up, and one line coming down and staying down. Correct?

Santa: Right, the triple treated, okay?

Dr. Montaner: Yes. [chuckles] You got it. I looked at this and I said, "Oh my God, the triple therapy works." Let me remind you, these were unblinded data because it was six months. I was not authorized to un-blind the study but the facto, it was the only explanation. I shared it with everybody, I shared it with a bunch of colleagues.

As it happens, a **[unintelligible 00:20:38]** an American colleague are working with **[unintelligible 00:20:41]** at the same time was doing a clinical trial on an AZT-3TC and antiretroviral protease inhibitor and basically, coming up with the same results even though we had never shared notes or anything like that.

By early 1996, we had two separate clinical trials using two different modalities. We're adding more antiretroviral power. You could crash down the virus and if you continue to take the medicines, you keep it there.

Now, what did it mean? We didn't know, but in my troubles, I had run to John Millers, an excellent biologist. He's based at Hopkins. I talked to John and I said, "Tell me about your experience with a quantitative PCR." What he had done is he applied the quantitative PCR to a cohort of individuals who were not treated. He measured the viral load and he established that the cross-sectional viral load was the best possible predictor of clinical outcome over a three-year period.

In other words, if you had a high viral load, the likelihood of death was very high. If you have a low viral load, the likelihood of survival was very high. We hypothesized then that in artificially decreased antiretroviral therapy mediated, viral load if kept that way, would allow the immune system to come back, which we saw in our trials.

Furthermore, it could replicate the cross-sectional ulceration of **[unintelligible 00:22:12]**. We put **[unintelligible 00:22:14]**, Montaner and Millers together. We crafted that story and in 1996, we came out at the Vancouver international conference, which I happened to be one of the organizers. We reshaped the program, we made it about HAART and it was the big coming-out party for HAART. It was absolutely incredible.

We got tremendous opposition from the community, from everybody, scientists, all kinds of people, "Oh, this is premature," and so on and so forth but our position was "People are dying and this is the best data that we have."

There is no harm on accelerating the development and moving on to the next phase. We put all of the data together and within months the clinical status of my patients, who now were accessing free because the government of British Columbia was the first jurisdiction that made it available for free to anybody. The health status of my patients dramatically changed and the mortality started to decrease immediately.

Santa: What advice do you have for young researchers, especially clinician-scientists, who are doing something very innovative, especially before you're fully established and you face that criticism? What advice do you have for them? Because you stood up to it.

Dr. Montaner: Santa, I had to be very careful here. My advice to young scientists is, "Be careful" because I made it to the other side but I have a lot of scars to show for it. Some of those are very deep and some of those were potential life or career-ending.

Santa: Career-limiting moments. [chuckles]

Dr. Montaner: All right. Career-ending moments. I'm not going to spill my guts here with all [chuckles] of that but suffice to say that these are difficult situations. What I would advise young scientists or people that are beginning a career are a couple of things that you can learn from what we discussed so far.

First is that I find lots of people that are incredibly motivated to pursue an academic career and they walk into it with a defined idea of what they want to do and I did that. I wanted to do ARDS, acute respiratory distress syndrome, pulmonary medicine, public health, blah, blah, blah, and guess what? I changed my mind and I moved in the other direction. Why? Because it was the opportunity, it was the important issue. It was a relevant issue and it was where I needed to be to make a difference.

The first one is to keep your eye options open and be smart because at the end of the day all of this is highly gratifying. What you want is to do good science and if you're lucky, science that you can then implement and change people's life and societal outcomes and the like. I find myself in this position and I am incredibly delighted but if I would've been too stubbornly fixed on doing what I originally intended, I would've find myself in a corner and without anywhere to go.

Next, as you progress with this approach, you may find controversy. Be sure that you have a mentor that will have the cloud and the understanding and the ability to support your work, without throwing you under the bus.

I was fortunate that Jim Hogg and John Ruedy, in particular, played that role for me at a time in which I was young and naive. I was doing the best I could and I could have hurt myself but they were very incredibly helpful in guiding me how to do this.

It is critically important that we, as an institution, collectively understand that success has a price but for us to reach that success which is important for our academic progression, for our students, for our patients, for our public health program, we need to be able to have a protective environment beyond what people out there realize.

Santa: Well, we're very proud of you for all of your seminal contributions, for your mentoring of other people who have gone on to their own eminent careers. I don't know how many listeners know this but there has been a commemorative stamp recognizing your achievements. I have it framed in my office, I'm very proud of it. Thank you so much for giving this much of your very valuable time to have a conversation. It's really an honor to have you as a member of our faculty.

Dr. Montaner: Thank you, Santa. I thank you for your support, and for your encouragement. That it's very much appreciated.

Santa: Dr. Julio Montaner. Thanks so much for being on *Blue and Goldcast* today. Dr. Julio Montaner is the director of the British Columbia Center for Excellence in HIV/AIDS, the chair in AIDS research and head of the division of AIDS in the faculty of medicine at the University of British Columbia.

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