cure hht
The Cornerstone of the HHT Community

CHRIS HUGHES

On the Cutting Edge

On the current state of HHT innovation

Q: Can you tell us about your professional background and how you first got interested in HHT research?

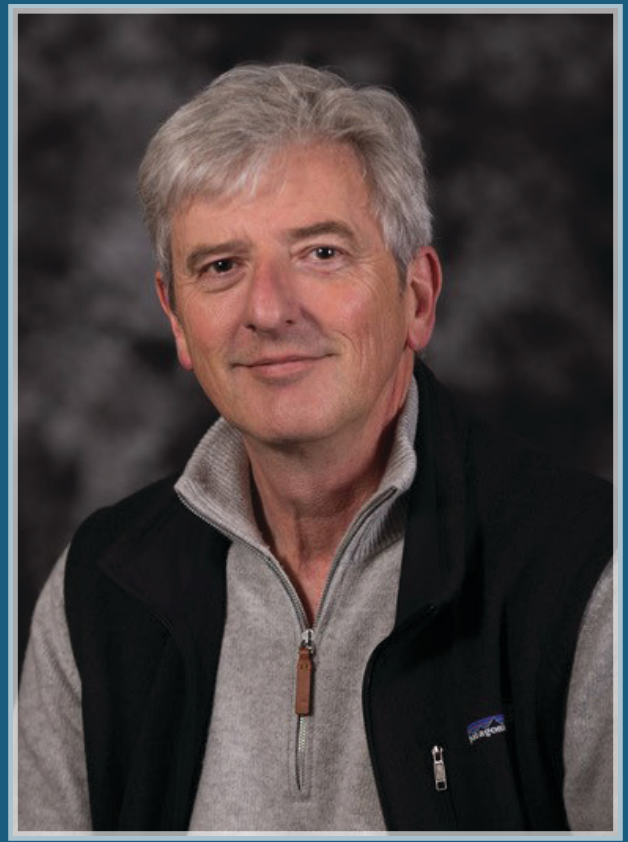
A: I have my Ph.D. in vascular biology from the University of London. When I first moved to the U.S. in 1988, I started working at Harvard and then Yale in vascular biology. I ended up starting my own lab in 1996 at University of California – Irvine and worked on various aspects of blood vessel development. At some point – probably 15 to 20 years ago by now – I saw a call that Cure HHT had a request for applications for a grant. At the time, I had a particular theory about what might be going wrong in HHT, so I applied and got funding. Part of the deal with the funding is you do the work, and then you go to the following year's annual meeting – the patient and physician conference -- and present your findings. So, I went to the meeting in St. Louis around 2007. They had a GRMAB (Global Research and Medical Advisory Board) meeting afterwards and Marianne asked me if I wanted to sit in. I said, "Yeah sure." At one point, I put up my hand and asked if were OK if I spoke. They said absolutely. I guess I said some stuff that seemed to have an impact. The next thing I know, I'm chairing the committee to come up with research directions for HHT. And that's very much what happens with Marianne. She has a very strong gravitational field. If you get too close, you just can't get away! She's just so wonderful. So, that's what happened. I started working with Cure HHT and I just haven't left. There are such wonderful people involved here – the staff, Marianne, and I'm always meeting patients which is great. That's how it started.

Q: From when you first started getting involved in HHT research in 2007 to today, how have you seen the field change?

A: Well, for one, there's a lot more work being done in HHT. And a lot of that is thanks to Marianne and the foundation and the work they've done to create that -- and get funding from bodies like the National Institutes of Health. The annual meetings have really brought in a lot of researchers over the years to focus on this disease. Cure HHT has been a big part of growing the community and generating interesting research. In recent years, we've had a lot of important model systems developed that have really helped – such as genetic studies with Zebrafish, mouse models and more – that have really helped our knowledge. We're just so much farther along today.

Q: Can you tell the HHT community more about your work in developing AVMs on chips, and how this can help with future drug development?

A: Sure. But first, a quick step back. It's important to know that what happens in HHT is improper connections between arteries and veins. The arteries are the ones carrying oxygenated blood around your body and the vein carries deoxygenated blood back to your lungs. In your tissues, the oxygen is given up to the tissues that use it through small vessels called the



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capillaries, which connect the arteries and veins. What happens in HHT is you get malformations and improper connections between arteries and veins. That's basically what HHT is. So, what we have we're doing in our lab is creating arteries and veins on a chip. We can either connect them with normal vessels or connect them with AVMs. So basically, we can recreate an HHT patient on a chip. This device is the size of an iPhone, and we can put 16 AVMs – living, real AVMs – on this plate. We can then use that for drug screening and trying to find drugs that will turn the AVMs back to normal vessels or to stop the AVMs from forming in the first place. It gives us a way to test new drugs without patient involvement. If they work, we can move on to patients. The PAZ trial – we've shown that that drug works on our platform. We can block AVM formations with PAZ, and we're seeing that drug is working for patients. Now, we're looking for other drugs that can work on our platform that will also work for patients. So, we're using it as a way to screen drugs.

Q: That's truly incredible work. What are some of the next steps?

A: Two areas. A senior post-doc in my lab currently – Jennifer Fang – is about to start her own lab at Tulane. She's been doing the work in our lab, but we're going to be going in two directions with this; One is to use these AVMs to develop a mechanistic understanding of what happens in these regions and asking: "Why do these blood vessels go wrong?" So, we have some data on that and some ideas on that. Jennifer is going to follow up on that. I'm going to focus more on drug discovery and how to fix these vessels. Those are the two direction our labs are going to go in.

Q: What do you find rewarding, whether personally or professionally, about focusing on HHT.

A: It's the patients. Marianne often has me come to patient conferences and help explain the science to the patients, and I love the chance to interact with patients and try to answer their questions. That's the rewarding part. But I tell this story: several years ago, I came home from work and my young daughter is 9 or 10 at the time. She says hello and asks me how was my day. I tell her; "Oh, it was great". She then asks: "Did you cure anyone?" She knows I do lab research and so I said: "Well, no that's not what I do, right? I do basic research. The work I do, in 20 years' time may help patients." I could see the disappointment on her face that I wasn't actually helping patients. That made me think I wanted to do more translational research and get closer to the "pointy end". That actually coincided with when I first started getting involved with HHT. So, my whole research program now is much more translational than it used to be. I like the idea of coming home and telling my daughter; Yes, I did help patients today. We did get to that point, actually. The first clinical trial of PAZ, I was one of the people who helped design that and was an author on the paper that showed yes, this could help patients. Now lots of patients get PAZ and love it. I was able to say to my daughter, actually yes. I did do a study that helped patients.

Q: What would your message be to patients about the state of research today?

A: For many years, we've been fumbling around in the dark trying to figure out ways to help patients. In the last 10 years, the pace of discovery and understanding has just accelerated so much that we've entered the phase of having new treatments to help patients. PAZ is a great example. We're not all the way there. We don't know if we can target large AVMS, but we're certainly helping pervasive bleeding. We're going to have new drugs coming along faster and faster. I'm really optimistic that we're making major strides right now.

Q: If I gave you a crystal ball, what do you hope you'd see in 5-10 years' time in HHT research or treatment?

A: We'll, what everyone wants is a cure. What I imagine a lot of patients don't know is that we know exactly how to do that. We do. HHT is relatively simple disease, we think. It's a lack of a cell surface receptor – ALK1 or endoglin. And we know how to put those genes back in to cells by gene therapy. What's holding us back is the availability of a safe delivery system. We know if we put in a good copy of ALK 1 into endothelial cells of patients, they will not get HHT. The problem is, how do you get that gene into the cell reliably and safely? That's not what HHT researchers do. That's what gene therapists do. We are all waiting for the gene therapy people to figure out how to safely deliver genes to cells. We're getting there. There are some examples of people who have done that successfully in trials in other diseases. So, I would think there's a reasonable chance that in 10 years, there could be a form of gene therapy for patients. That would be my hope. Whether it happens, unfortunately, that's outside my scope.

A: Community is the first thing. Cure HHT gives us a place to collaborate with everyone who is working on this disease. We get together and share ideas on a regular basis, and that's really important – and it happens because of Cure HHT. I've said to people many times: I don't think I've ever had a good idea sitting in a room alone. But I've had a lot of good ideas sitting in a room talking to people about science. That back and forth is what gets creative juices flowing. Science moves forward that way. A big issue with basic science is access to clinicians and talking through what they and patients need. I've got the science down. But what's the clinical side say? Cure HHT bridges that gap. And they also help with sources of funding and bringing new people into focusing on this disease.

But also, here's a great example; there was a time where I wanted to create stem cells. That would usually take months and months and months to get samples from patients. Not with Cure HHT. I called up Marianne, told her what I needed. She asked me how many patient samples I needed and when? Two days later, she got me the samples and we're off to the races. It was unbelievable. Just having a resource like that is unbelievable.

Q: Thank you so much for the time, Chris. Is there anything else you'd want to share with the patient community?

A: I would just want them to know that everyone I've met who focuses on this diseases feels a strong sense of commitment to helping the patient. We've met so many of them. And that's the coolest thing about Cure HHT is they bring together researchers, clinicians and patients. We all feel very called to help. For example, I do a lot of work on cancer as well – but I'm hardly ever meeting cancer patients. I meet HHT patients all the time. We all feel a strong level of commitment to help patients. I want them to know that. Oh, and that you need to wrap Marianne in bubble wrap and keep her safe! We couldn't do any of this without her.