JCI The Journal of Clinical Investigation

A conversation with Michael Hall

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J Clin Invest. 2017;127(11):3916-3917. https://doi.org/10.1172/JCI97760.

Conversations with Giants in Medicine

The control of cell growth was once thought to be passive when there were cellular building blocks in nutrients; a cell would grow and ultimately divide. But I'm joined today by Dr. Michael Hall (Figure 1) from the University of Basel in Switzerland who upended this simple assumption and, instead, elucidated the very complex and elegant signaling pathways that result in cell growth. At the core is TOR, the target of rapamycin. Watch the full interview at www.jci.org/videos/cgms to find out how many times a day he says "rapamycin" and whether or not he's ever been to Rapa Nui. JCI: You have international roots. Hall: I have a rather complicated life history. I was born in Puerto Rico, and my family moved when I was three to South America, to Peru, where we lived for several years, and then eventually we moved to Venezuela, where we lived several more years. I left South America as a teenager to go to boarding school in the United States. My father was an executive for a multinational company. My mother had studied Spanish in college and had a degree in Spanish. They liked the culture of Latin America, and they decided to make their lives there. JCI: Where did an interest in science come from? Hall: It was a very gradual process for […]

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JCI: Where did an interest in science come from?

Hall: It was a very gradual process for me. What set the foundation was my parents instilling in me the importance of knowledge. I think that came through most clearly when they sent me away to boarding school when I was 13. That was a huge sacrifice for my mother because it was a breaking apart of the family, but she understood the importance of education. Had I stayed in South America, I would not have received a very good education.

Boarding school in Massachusetts was one of the defining experiences in my life. It was a huge cultural shock. I had a carefree life in South America; everything was open and free. Then I went to this boarding school that was at the other end of the spectrum, very disciplined, very rigid, and the weather was not the same, I had to wear a coat and tie every day instead of a T-shirt, shorts, and sandals. It was a radical change for me in every way. It was also an academic awakening.

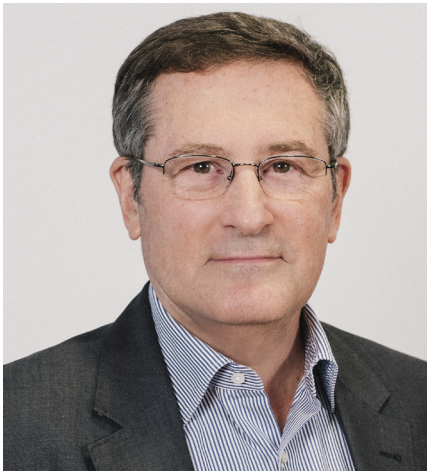

Figure 1. Michael Hall on September 14, 2017, in New York. Image credit: Alexey Levchenko.

JCI: Why did you decide to pursue undergraduate studies in zoology?

Hall: Well, that was not a very direct path either. Growing up in Venezuela, I had chemistry sets, electronics, art, and sports. I was always interested in different things, with no particular focus. When I went to university, I began as an art major and then decided I needed something that provided a more structured framework. I decided to study medicine and that's why I was doing zoology, as part of a premed major. I worked in the emergency room at the local hospital and realized medicine was not very appealing to me. At the same time, I was doing an undergraduate honors thesis in a laboratory. When I started doing actual experiments at the bench, I found it incredibly exciting. I was working in a lab that did molecular genetics, and I became completely fascinated by François Jacob and Jacques Monod; my fascination with their very elegant bacterial genetics is what took me to Harvard, where I did my PhD studies.

JCI: You did a short postdoc at the Institut Pasteur and then headed to UCSF. What brought you to Paris? Was it Jacob and Monod?

Hall: Yes, I felt I had to go to... it was mecca for me. There was also a practical aspect because my real postdoc advisor, Ira Herskowitz, was in Oregon at the time, and after he accepted me into his lab, he said he was moving to San Francisco. I didn't want to move twice in a few months, so I decided I would just meet him in San Francisco and thus had about eight months to kill. I contacted Maxime Schwartz, with whom I'd already been collaborating as a PhD student, and asked if I could come to work in his lab.

When I finally joined the Herskowitz lab, I made a transition from bacterial to eukaryotic genetics — in this case, yeast genetics. I studied nuclear protein localization, which was different from what the lab was working on; they were working on a signal transduction and mating-type control. This is also something that marked my pathway. I've always been a bit of a contrarian. I'm attracted to a problem, but once there, I do something else.

JCI: What made you consider Switzerland for your academic career?

Hall: I was looking for assistant professor positions in the US and in French-speaking Europe. I'd had a wonderful stint in France, including meeting my Parisian wife, and this made it attractive to go back to at least French-speaking Europe.

It's a funny story how I got to Switzerland, because Basel is not French-speaking Europe. When I was looking, a future colleague asked me if I'd be interested in looking at a position in Basel. Nothing was further from my mind, but he invited me to come and take a look anyway. I fell in love immediately with the institute, the Biozentrum. I've stayed there because the funding and the science are extremely stable, well supported by both local and federal governments, and Basel is a wonderful place to raise a family. Maybe I was a little tired of moving around so much.

JCI: What projects did you decide to take on at first?

Hall: We were studying nuclear localization signals, which was a bit of a revolution because before then, it was thought that proteins passively diffused into the nucleus where they might bind a substrate. If they bound, they were retained in the

Reference information: *J Clin Invest*. 2017;127(11):3916–3917. https://doi.org/10.1172/JCI97760.

nucleus, and if not, they just diffused back out. That seemed rather naive to me as a mechanism for nuclear protein localization, so I reasoned that there must be a localization signal that actively mediates the transport of proteins into the nucleus. It was such a signal that I discovered as a postdoc.

We were interested in identifying the machinery with which a nuclear localization signal interacts. We made certain assumptions at that time; we thought the machinery would be in the nuclear pore complex, but we were looking in the wrong place, and as a result, the work was not going very well. What then set us on a good path, not the right path in terms of nuclear localization, but a good path, was Joe Heitman, a postdoc who got interested in immunosuppressive drugs.

JCI: But why choose your lab to study immunosuppressive drugs?

Hall: He came with a similar background to mine: bacterial genetics. His wife was a postdoc in Lausanne, and that was another reason for him to come to Switzerland. He started by working on the problem of nuclear localization. His project, like everybody else's in the lab at that time, seemed to be failing because of the faulty assumption we made.

Coincidentally and fortunately, the company that then had the blockbuster immunosuppressive drug on the market was Sandoz, headquartered in Basel. I had a colleague at Sandoz [Rao Movva], and we got together to start working on immunosuppressive drugs. It was known that these drugs blocked intermediate steps in signal transduction, in T cells in particular — why they're immunosuppressive. In other words, they blocked the step between a receptor being activated on the surface of the cell and the transcription factors that are then activated in the nucleus — nobody understood the in-between step, how a signal is transmitted from the receptor into the nucleus. So studying the drugs fit in a very broad context of what we were already doing.

JCI: How did you justify doing this work in yeast instead of in T cells?

Hall: Well, this is actually what I found very exciting. Cyclosporine was already on the market. Two other drugs, FK506 and rapamycin, were still being developed for clinical use. Nobody knew how any of the drugs worked at the molecular level, and everybody was naturally working on this problem in mammalian cells. Joe and Rao had the idea to use yeast genetics. It seemed like an outlandish idea to many, but these drugs are natural compounds that evolved as weapons in microbiological warfare; they evolved to act on other microbes, such as yeast. Joe and Rao decided to use these drugs for what they had evolved. If you look at it from that perspective, the notion of giving these drugs to humans is somewhat outlandish.

These new drugs were responsible for medical breakthroughs. Transplantation surgery became a clinical procedure where before it was only experimental. There was a lot of excitement about the drugs, and understanding how they worked and what they bound was viewed as an important step. We were able to win the race with regard to rapamycin because we worked with yeast.

JCI: Your lab went on to isolate the two different TOR complexes and proposed that TOR was essential for cell division. Was it then a gradual understanding that it was more about cell growth?

Hall: To tell the truth, the project almost died early on because we'd answered the initial question we set out to answer, Joe left, and the TOR mutants that he'd isolated were just sitting in the freezer. Then another student's project fell through, so she picked up the mutants and started cloning and sequencing the TOR genes. When she knocked out TOR1 and TOR2, the cells arrested in the G1 phase of the cell cycle. That's the same effect rapamycin had on T cells.

That was the single most important phenotype we had: cell cycle arrest. In the context of those days, this is what you read about everywhere — the cell cycle was a very active area of research. We thought we had discovered a new control mechanism for the cell cycle. It was actually a rather dark phase in the lab because all our experiments were based on that assumption, but our experiments were not giving the answers that we hoped for or expected.

I would say our discovery that TOR controls cell growth was a gradual understanding with a few mini aha moments sprinkled throughout. One of the first important mini aha moments came during a seminar I gave in Vienna. Kim Nasmyth, who was a cell cycle expert, had invited me. I presented our data from the perspective that what we had was a system to control the cell cycle. My hosts were experts in cell division, and what I described did not fit with what they thought and what they were working on, so they were very skeptical.

We started wondering, if it's not cell division, what could it be? We eventually came to the possibility that TOR might be controlling cell growth: increase in cell mass or size as opposed to increase in cell number. This was a revolution in itself because cell growth was not thought to be a regulated process; it was thought to be passively controlled. We had to challenge our assumptions and the existing paradigm. Maybe cell growth is controlled, and if it's controlled, maybe then that is what TOR is doing. Once the switch was flicked in this direction, we started looking at our data in a different light. Everything fell into place immediately.

JCI: How did you come up with the name TOR?

Hall: We went back to look at Joe's lab notebook and there's a page, December 2, 1990, where he wrote "Name?" and then listed several possibilities. In yeast, names for genes and proteins follow a specific nomenclature convention of 3-letter acronyms. He made a list of 3-letter names based on rapamycin or FKBP, which is a protein that rapamycin binds to that then binds and inhibits TOR. He had PIF, PAF, RAT, TFR, and TOR was somewhat down the list. I liked TOR. It was a natural name.

Joe liked TOR because he lived near one of the medieval gates that opened into Basel called Spalentor. In German, *Tor* means "gate." This was still the time we thought TOR controlled the cell cycle. He thought very romantically that TOR was the entry into the cell cycle much like Spalen Gate was the entry into the formerly fortified city of Basel. But *Tor* has two different meanings depending on gender. Gate is *das Tor*, but the masculine form of *Tor* in German, *der Tor*, means "the fool." But Joe wasn't deterred.

JCI: If you weren't a scientist, what else do you think that you would have done?

Hall: It certainly would've been something where there's a creative element, much like science. Maybe I would've been an artist. Although I don't think I have the courage to be an artist because it's too free form. Science allows this creative element, but in a more structured environment.

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