People & Ideas

Graham Warren: Gaining ground on the Golgi

Warren's studies of the Golgi have yielded a rich trove of insights.

The elegantly stacked cisternae of the Golgi are central to secretory protein maturation and trafficking. Graham Warren has made it his life's work to demystify the biology of this essential organelle.

Trained as a classical biochemist in England, Warren took a position as group leader at the then newly established European Molecular Biology Laboratory (EMBL). There, he studied protein trafficking through the Golgi (1) and pioneered the use of cell-free methods to study other membrane trafficking processes. Later professorships in Scotland (2), England (3), and the United States (4) saw Warren applying these methods to how the Golgi fragments and disperses between daughter cells during mitosis.

Warren is now serving as Director of the Max F. Perutz Laboratories in Vienna, Austria. Meanwhile, his research continues to focus on Golgi inheritance, but he now uses the parasitic protozoan *Trypanosoma brucei* as a model system to probe this process (5, 6). We called him up to have him break down his career for us.

> "I believe everything should be quantitated."

THE RIGHT CHEMISTRY

You were born in postwar England, is that right?

Yes, I was born and brought up in London. I came from a working class part of the city. My father was a carpenter, and because we were quite poor, my mother worked various factory jobs to help support the family. I was actually the first person in my family ever to go to college. During those postwar days, places like Oxford and Cambridge were opening up and becoming more meritocratic rather than class based, so I went to Cambridge, where I won a scholarship. That was an important opportunity for me. Being born at the right time always helps.

What else was special about growing up at that time?

Oh, it was a very different time. In chemistry classes, I remember gathering around a desk with my classmates to watch the teacher drop a lump of sodium into a bowl of water—and see it skimming across the surface of the water. But I imagine that this might not be done as much in schools these days because it's potentially dangerous. And I had interests that I suspect not many children are able to pursue these days: growing up, I had my own chemistry laboratory, and I loved to make things like transistor radios. Of course, it's not really possible to make a radio with off-the-shelf components these days; things are far too miniaturized and complicated.

You had your own chemistry laboratory as a child?

My chemistry teacher had an incentive for us, which was that if you were one of the top three students in the class, he would sign orders that you could take to a big chemical supplier and buy chemicals and equipment to experiment with at home. You'd make a list of the items you wanted to buy, which the teacher would have to approve. Then you'd save up your pocket money and take your signed order to the tradesmen's entrance at the supplier's. Of course, it was always a kind of game to try to sneak in things that you knew would explode if you mixed them together. But the teacher would always catch us and cut those off the list.

I think things like this have been lost, largely because of safety issues. That's a shame in my view, because this was how I personally got interested in science, and I don't know how many children have opportunities like that anymore.

Graham Warren

BIOCHEMIST'S APPROACH

How did your initial interest in chemistry affect your later choices?

Well, I always knew I wanted to be a scientist, and it so happened that Cambridge was a great place to pursue that. Several of my undergraduate lectures, for example, were given by Fred Sanger on protein sequencing. Having the person who invented the method give you the lecture on it was really quite amazing, I have to say. Enzyme kinetics at that time was considered the subject to do, and it was a very exciting time to do it. That's why I was a biochemist initially. Later I became more of a molecular cell biologist, but coming from a biochemical angle, which means I believe everything should be quantitated.

You stayed on at Cambridge for your PhD and postdoc?

Yes, but I hadn't planned it that way. I'd actually gone to London for my postdoc, but then ended up back in Cambridge when my supervisor got a position there. So I was there for another two years before heading off to EMBL at Heidelberg, which was exciting because the institute was just getting started then.

Text and Interview by Caitlin Sedwick
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As a new investigator at EMBL, did you have any training in how to run your own laboratory?

At EMBL, Kai Simons was the program coordinator in the cell biology program, which turned out to be crucial for me. He was my mentor. He was the one who taught me how to focus on problems, and he generally guided and encouraged me, but also let me go my own direction. I had this great feeling of being independent, but also of being looked after. This is something I've tried to pass on to those who've worked with me: I like to foster a sense of scientific independence early on.

What do you mean by "scientific independence"?

I think it's important for people to take ownership of their work. For instance, one thing I am rather strict about is the authorship of papers. I strongly feel that the person who did the work should be the one who gets credit for it. I shouldn't be on a paper if I only contributed reagents or grant money. A pragmatic test of this is whether I understand it well enough to present it at a major meeting.

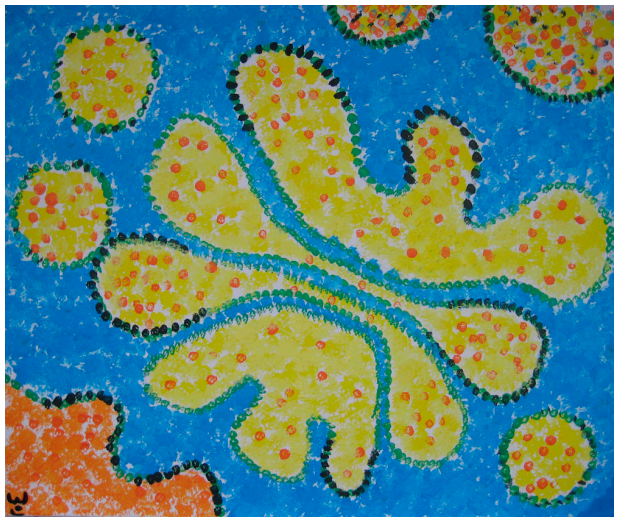
How did you get interested in trying to understand the Golgi?

My postdoctoral work was on membranes. I'd always been interested in the Golgi—it's such a beautiful, elegant looking thing, really. But it was actually at EMBL, on Kai's suggestion, that I got into looking at the passage of viral membrane proteins through the cell. These proteins are made in the ER and end up on the plasma membrane, but at the time we didn't know how they got there—for all we knew, they might skip the Golgi altogether. One of the first things we did in my own laboratory was to actually look at this process and show that membrane proteins go from the ER to the Golgi to the plasma membrane. It sounds trivial now, but at that time it was quite an important step to show that membrane proteins all followed the same pathway as did soluble secretory proteins.

BREAKING IT DOWN

But eventually you became interested in what happens to the Golgi in mitosis?

Our EMBL colleagues had made an antibody against mannosidase II, which visualizes whole Golgi, and we saw that if you looked at the Golgi of most interphase cells, you'd see the nucleus and this nice Golgi ribbon next to it. But if you looked at cells undergoing mitosis, the Golgi would virtually disappear—it completely fragments—and is later reassembled in each daughter cell after mitosis. I saw there was essentially no literature on this, so I decided to look into it. At this time, no one knew about COPI vesicles and things like that, but we eventually came up with the idea that what happens during mitosis is that vesicles keep budding off the Golgi as part of the normal process of protein transport, but they can no longer fuse, leading to the Golgi's disintegration.



The Golgi has captured Warren's imagination, inspiring an artistic rendition.

> "I strongly feel that the person who did the work should be the one who gets credit for it."

Why did you recently move to studying Golgi duplication in trypanosomes?

Much of my work has been done in mammalian cells. But the trouble with a mammalian cell is that it has 100 copies of the Golgi that become 200 copies during mitosis. All of them are stitched together into one huge ribbon, so you really can't follow what's going on. In trypanosomes, you just have one Golgi and you can actually watch it duplicate using GFP-tagged proteins. And, because the organism is genetically tractable and the genome completely sequenced, you can also do all the normal experiments like mutating candidate genes, RNAi, and so on.

We recently discovered this new structure that we call a bilobe. It seems to be a scaffold that designates where the new Golgi grows during the cell cycle. We're now trying to explore its composition, and what function it has in cells. We're taking the biochemist's approach, again: pick it apart and see how it works.

Let's pick apart your career: you've moved around a lot, haven't you?

I always try to tell people it's good to move every ten years or so, because you just don't realize how comfortable you become where you are. When you're suddenly thrown into a new environment it can jog your thinking out of any rut you might have been in. But perhaps I am done with moving now. I'm Director here at the Max Perutz, and the two universities here have set me up with a very nice package of funding for junior group leaders. We're bringing in new people with great ideas. It's very exciting.

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