Vivek Malhotra: Gaga for the Golgi

Vivek Malhotra has issues with the Golgi complex.

Vivek Malhotra first began studying protein secretion in the late 1980s, and he has spent most of his career since then trying to unlock the secrets of secretion and in particular the organization of the Golgi complex. In doing so, Malhotra has developed a true passion for the scientific process.

As a postdoc at Stanford, Malhotra made some significant discoveries—he found that a protein called NSF was essential for fusion of transport vesicles with target membranes (1), and he purified a class of transport vesicles, now known as COPI (2). His research into the Golgi complex then took off after he moved to the University of California, San Diego, as an assistant professor in the biology department. In the two decades that he spent there, Malhotra tackled difficult questions such as how the Golgi is organized (3, 4), how transport vesicles that are targeted to the cell surface form at the Golgi (5), what role the Golgi plays in mitosis (6, 7), and whether it's involved in unconventional protein secretion (8).

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His recent move to the Center for Genomic Regulation in Barcelona will no doubt lead him to new questions. And as long as it stays fun for him, he says, he's ready for more.

KNOWING WHAT YOU'RE NOT

How did you first get interested in science?

I was not one of those people who knew at the age of seven that they wanted to do science. I got into science because I knew the things that I was not very good at. I was not very good with numbers, and I was not particularly good at remembering facts.

When I was young, the fashion was that children of Indian families went to either medical school or engineering school, or became chartered accountants. These were considered safe and privileged professions, but I knew that I didn't care for any of those.

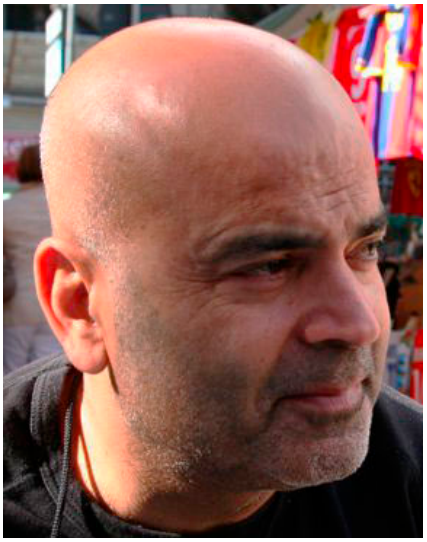
My first summer job was at the life science department at the University of Botswana. As a technician, my job was to set up the laboratory for students who took biology and chemistry and organize their laboratory classes. Then I would sit through the classes taught by a group of Dutch scientists working at the university. Most of the talks were quite boring, but some of the talks on the modern science of that time were interesting. I realized that this was something one could do without having to rely heavily on mathematics and without having to remember facts. As long as you had the concepts clear and you knew the questions, I thought you could do a wonderful job.

The job got me excited about doing a BS in biochemistry. So in 1978 I enrolled in the biochemistry department at the University of Stirling in Scotland. The professors there were outstanding. The graduating class had only about 17 students, so you had a direct interaction with the professors. They were really imaginative people who taught in an imaginative style.

I was lucky enough to do a project in my final year—I purified an enzyme from slime molds. That got me thinking that the scientific process is really interesting. You have a problem, you think about how to address the problem, and you get results, which make you think about the problem even more. So it's an unending situation. I basically decided, "Hm, this is fun."

And now you're hooked.

It's like a drug. The more you do it, the more you want to do it. And if you do it right, you make progress, that keeps you going. To be perfectly honest, I really don't think of it as a profession. I think the day science becomes my job, I would quit.



Vivek Malhotra

DISCOVERING HIS PASSION

After your time at Stirling, you went to Oxford?

Yes. I got a fellowship to study for my PhD at Oxford's biochemistry department. There, I worked on a class of proteins called the complement receptors, which are involved in the immune system. But, I was not particularly excited with what I was doing.

Why was that?

I was trying to characterize the cell surface proteins that have binding affinities for complement proteins. But it wasn't clear to me where we were going with the kinds of questions we were addressing.

So, although I was able to finish my PhD in three years, I wasn't very excited about the science. But during the last year of my stay at Oxford, I met John Singer, and it was during a seminar of his that I learned about a mechanism by which the cells secrete proteins in a directional manner. I remember asking John,

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"So how is it that proteins move from one place to another within a cell, and how are these proteins secreted from the cell?" He said, "Literally nothing is known about this process." This caught my interest.

He told me that Jim Rothman at Stanford and Randy Schekman at UC Berkeley were trying to address this issue, so I wrote to them for a postdoc. Schekman wrote back to say that there was no room for the next two years, so I joined Rothman's laboratory.

This time in Jim's laboratory is when my interest in research really took off. I found the problem of protein trafficking very interesting, and I found the issues relating to the Golgi apparatus even more interesting. It has a remarkable structure. No other structure in the cell has that shape or organization.

During this time, one thing I did of significance, was to purify a class of carriers, now called COPI transport vesicles, that transport proteins between the Golgi membranes.

So after four and a half years at Stanford, you moved to San Diego?
Yes. I realized that if I was going to stay in the US, I had to be in California. I thought that if I had to leave California, I might as well go back to Europe.

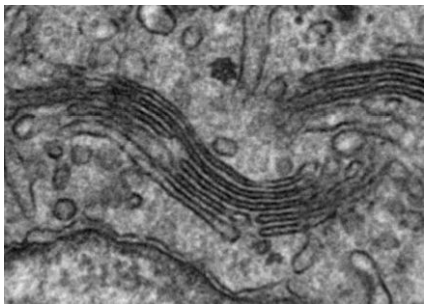
I was very lucky that George Palade decided to move his laboratory from Yale to UC San Diego to start a new department in the medical school. And I was also lucky that he made me an offer of assistant professor, a position that came with funding from the Howard Hughes Medical Institute.

I knew that I did not want to continue with the research I was doing as a postdoc. I thought that lots of laboratories would be working on COPI coated vesicles, and I would be competing with everyone. So I wanted to work on a completely different aspect of transport-related issues. My interest at that time, and it remains to date, was to try to understand how the organization of the Golgi is maintained during protein transport, and how this compartment is partitioned into daughter cells during cell division.

But when this offer came from George Palade, I got a little scared because I thought the Hughes position came with a lot of expectations. Fortunately, I was also offered an assistant professor position in the biology department at UCSD. And so, call it my naiveté or chutzpah: I turned down George Palade's position, and I accepted the other one.

Was he surprised you turned him down?
Oh, he was very surprised. In fact, he didn't speak with me for the first six months of my stay at UCSD. I was quite concerned since one of the greatest cell biologists of our time, and absolutely the hero of the field, had decided not to communicate with me.

But after six months we met, and we talked. He was very kind. In fact, we were going to write a book together about protein transport and the organization of the Golgi apparatus. But the field was changing so rapidly that after a few meetings, we decided that it was probably not a useful exercise. I feel bad about that because it would've been great to have written a book with one of the greats in cell biology.



An electron micrograph of a Golgi stack (top). A stack of pancakes (bottom) depicts the unusual structure of the Golgi, which has fascinated Malhotra for two decades.

HEADING BACK TO EUROPE

After 18 years in San Diego, what prompted you to move last year to Barcelona?
There was nothing wrong with San Diego. I was just beginning to get a little bored. I'd been there too long.

Barcelona, I don't need to tell anyone, is a spectacular city. I'm the chair of cell and developmental biology at the Center for Genomic Regulation. It's a brand new institute. It's not linked to any university, and its sole purpose is to do creative science. We have all the facilities, all the money, all the help that one can think of that would be necessary to do creative science. I couldn't think of a reason why I should not take this opportunity.

"To be perfectly honest, I really don't think of it as a profession. I think the day science becomes my job, I would quit."

Sounds like a perfect place to work. So what is it about protein secretion that has held your interest for so long?
I just find that every time we do something, we find there is so much that we don't know, and it just keeps you going. You don't seem to reach an endpoint. If you really think about it, all of my science has to do with some aspect of the Golgi, whether it's the structural organization of the Golgi, its location, or the mechanism by which proteins enter and/or leave the Golgi.

There is so much that we don't understand about the Golgi, that I can easily see myself working on this topic for the next 25 years. JCB

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