Ira Mellman: from endosomes to industry

Disease-related research requires a different kind of teamwork, says Ira Mellman. He hopes to find that team at his new home at Genentech.

Directed trafficking is how the cell patterns itself, and Ira Mellman has been a leader in efforts to understand this feat of self-organization. He started with the discovery, naming, and characterization of endosomes (1), moved to study pathways (2), sorting determinants (3), and sorting adapters (4) in polarized epithelial cells, and has more recently revealed how dendritic cells reorganize themselves to present antigens (5, 6). Now, however, he is ready for a new challenge. In April 2007, he started as Director of Research Oncology at Genentech in South San Francisco, CA. He joins Genentech's other recent converts from academia such as Richard Scheller, Marc Tessier-Lavigne, Vishva Dixit, and Eric Brown. As Mellman rushed to get ready for the move, he discussed both his past work and future hopes.

> "At the time I entered the field, it was exploding at the conceptual level."

TRAFFICKING

How did you connect first with Zanvil Cohn and Ralph Steinman at Rockefeller and then with Ari Helenius at Yale?

In the late 1970s, Cohn and Steinman published a series of absolutely spectacular papers on endocytosis and membrane dynamics. So I went to learn cell biology, and was a bit horrified when I got there to find that they were really immunologists.

As for Yale, I was being recruited by George Palade, who proceeded to tell me that he had just hired Ari Helenius from EMBL in Heidelberg. Apparently, he had also told Ari that I was going. Neither of us had actually agreed to go, but we both decided, "Well, if this other guy's going, I might as well also." Finally, we met and realized that we'd kind of been snookered. I believe John Huston used much the same technique to get both Humphrey Bogart and Katharine Hepburn to star in "The African Queen."

But it worked out really for the best. We met several times and decided basically to merge our laboratories from the moment we arrived in 1981. We shared a lab, a desk, and a phone. Our kids basically grew up together, and science and family ruled our lives. It was a magical time in many ways.

Why trafficking?

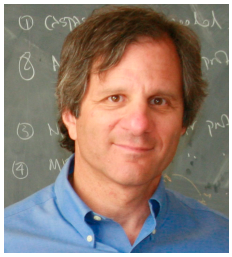
At the time I entered the field, it was exploding at the conceptual level. The idea was that, "Gee, this is really what controls overall cell organization."

George had basically laid out for us what his generation had done: they had defined all of the working components of the cell, all the organelles, and what must happen. Our responsibility was to figure out the mechanisms by which all of this fits together: what the pathways were; how membranes knew to form vesicles; and how those vesicles contained the right cargos that knew where to go. The entire field took that on as the charge, and for the next decade and a half this effort yielded one terrific new principle after the next.

And dendritic cells?

In the early 1990s, Ari and I began to get a little squirrelly looking for more challenges rather than just continuing to beat up on endocytosis. We were getting the feeling that these efforts were becoming repetitive with less conceptual content. Many of our colleagues were starting to do the same things again and again, working incrementally on the same genes or their binding partners.

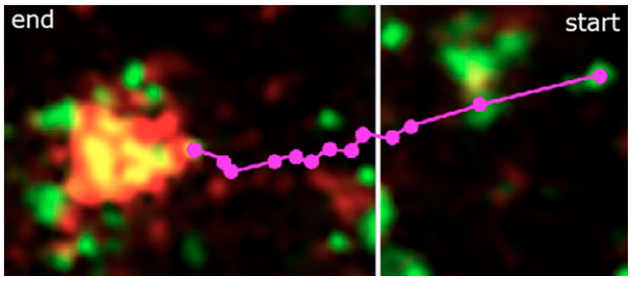
Around that time, we had adapted our technology for characterizing endosomes to isolate antigen-processing compartments from B cells. Ralph's response was, "Don't waste your time with B cells; dendritic cells are much more important." But there were no cell lines. Ralph actually sent us cells on the train from New York. All the shaking on Metro-North caused the cells to switch their organization and function overnight, which we noticed also happened after stimulating them with various immune agonists. There was an awful lot of cell biology involved in that, not the least of which involved some terrific alterations in membrane traffic. It also had an increasing relevance to understanding how immunity is generated and to human biology and disease.



Ira Mellman

How would you describe your current philosophy about biological research?

We're at a bifurcation point. You can take problems into extraordinary molecular or even atomic-level detail, which is I think the natural course for most scientists. You grab onto a problem and you wring its neck until it yields all of its secrets. But for me, the true conceptual excitement is learning how to apply molecular information to understand more complex, systems-level phenomena. You have to follow the most profound and most exciting problems wherever they lead you regardless of the techniques, cell types, genes or systems



MELLMAN

New proteins in polarized cells travel from trans-Golgi to recycling endosomes before reaching the cell surface.

Text and Interview by William A. Wells
wellsw@rockefeller.edu

involved. Pick your problem and go after it and don't let your problem pick you.

Why the move to Genentech?

Applying reductionist approaches to solving complex problems in humans is extraordinarily difficult to approach in academia. Academia does a great job with tissue culture cells or flies or mice, but it doesn't easily accommodate the types of broad-based interdisciplinary teams that you really need in order to organize experiments using human beings as a biological system.

"The only model for human cancer is human cancer."

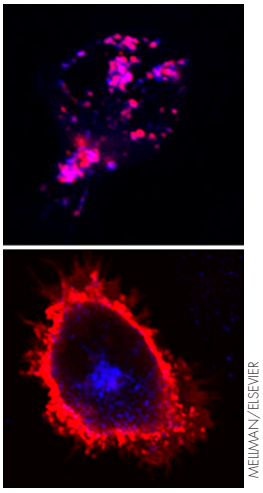
I've been grappling with this problem at the Ludwig Institute and the Yale Comprehensive Cancer Center. But now people with exactly the same background as myself have offered me the possibility of coming and playing in a completely different sandbox.

Why does Genentech often recruit from academia rather than pharma?

They believe that drug discovery begins as a valid problem of basic science. If that's the case, then you have to get the best scientists, the people with the broadest understanding of fundamental aspects of biology and biomedicine, to manage the process.

The brilliance of Genentech is that it melds the rigor and deep commitment to fundamental science that one finds from excellent people coming from the academic world with the discipline, insight, and creativity characteristic of the best of the biotech and pharmaceutical industry. These two groups come together with a terrific amount of mutual respect.

In my view, Genentech has turned drug development into a scientific problem of the first order. The people who have moved there were all at the tops of their games career-wise; they certainly didn't need to find jobs. They aren't doing this for the money, yet they go.



MELLMAN/ELSEVIER

A switch in ubiquitination status sends MHC II (red) to the surface in mature dendritic cells (bottom).

What challenges come with a switch from an academic to biotech environment?

In academia, the basic process is cyclical. We develop a project, write a paper, get it published, get a grant, and turn the crank again. In biotech you still want to publish but that's not the only end point. You want to get something into humans. So you have to have a high level of intellectual and scientific discipline to keep yourself on message.

That's going to be a challenge, but a really welcome challenge. After 25 years or more of doing science, I could say I'm getting a bit tired of turning the crank. It's very satisfying, but it's iterative. This new task is much more vectorial and linear.

In my case, another reason I went to Genentech is that my oldest son, Peter, has Crohn's Disease. When he was crashing with the disease and became unresponsive to all the conventional therapies, they were basically considering removing his entire gastrointestinal tract. He lost half his body weight and was in continuous pain.

Then they treated him with a monoclonal antibody to TNFα, a drug called Remicade (not a Genentech product, by the way). Within 36 hours, Peter and I were playing basketball in the front driveway, and it was a realization that hey, you know, this biotech stuff can really do it. This is a miracle.

Knowing something about this pathway, we established a company in New Haven called CGI Pharmaceuticals that targeted immune cells involved in this disease. Genentech ended up buying the rights to that particular agent. Now, I can help oversee the development of that agent, which might eventually be used as a more effective maintenance therapy for my own son. At the risk of sounding melodramatic, there can be nothing, absolutely nothing, that would be more satisfying to me as a scientist.

Genentech's marketing of drugs such as TPA, growth hormone, and Avastin has sometimes been controversial. How does a for-profit drug company fit with your liberal family background, which emphasized social justice?

It's worse: I come from a long line of socialists and labor organizers. Nevertheless, the only way to turn science into realistic, utilitarian products that can be used to benefit individuals and society is to make use of the capitalist system. I have come to grips with that.

Companies and people who run them are going to make money out of pharmaceuticals. And because money is involved, not everyone is going to, at all times, be scrupulously moral or honest. Having met a number of people at various levels at Genentech, however, I feel that the current management and leadership structure is about as trustworthy as any group of individuals I've seen anywhere. They all seem to be liberal, open-minded people who are deeply concerned with the interface between science and society, and indeed troubled by the fact that pricing structures can wind up creating drugs that are hugely expensive. They try very hard to mitigate that.

As a future Director of Research Oncology, what is your vision of human cancer research?

I have come to dislike the term "translational research." It incorrectly evokes a process whereby basic discoveries made in the laboratory using mice can simply be translated to humans. In reality, this is rarely the case. What we need is clinical discovery research with a rigorous, reductionist scientific approach to human cancer using human patients as subjects. The only model for human cancer is human cancer. JCB

1. Helenius, A., et al. 1983. *Trends Biochem. Sci.* 78:245–250.
2. Schmid, S., et al. 1988. *Cell.* 52:73–83.
3. Matter, K., et al. 1994. *J. Cell Biol.* 126:991–1004.
4. Fölsch, H., et al. 1999. *Cell.* 99:189–198.
5. Trombetta, E.S., and I. Mellman. 2005. *Annu. Rev. Immunol.* 23:975–1028.
6. Shin, J.-S., et al. 2006. *Nature.* 444:115–118.