People & Ideas

Rick Horwitz: Words do not suffice

Horwitz is leading the Allen Institute for Cell Science in its quest to comprehend the cell.

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Rick Horwitz

Around the turn of the century, the advent of large-scale, collaborative genomic sequencing efforts greatly accelerated the pace of biomedical research. Genomic data allowed biologists to single out genes and proteins and probe their functional and structural activities. However, scientists still don't have a very good understanding of how different proteins work together in functional complexes and how these complexes interact with others to affect the overall behavior of a cell.

Rick Horwitz's lab at the University of Virginia is well known for its contributions to the fields of adhesion (1, 2), cell migration (3, 4), and neuroscience (5), and he's always loved studying how these topics interconnect and overlap (5, 6). Although recent advances in microscopy and automation make it possible to uncover how well-studied systems interact to affect cellular behavior—for example, by exhaustively describing and cataloging the organization and functions of these systems in living cells—such a project wouldn't fit into the mission or budget of a single government-funded research lab. That's why Horwitz jumped at the chance to head up the newly created Allen Institute for Cell Science in Seattle, which is poised to take on exactly this task.

> "We had to get back to studying a problem rather than a molecule."

FINDING AN ENTRY

How did you go from a PhD in biophysics to studying cell adhesion and migration?

In college and high school I really enjoyed chemistry, physics, and math. I was always interested in biomedical research, particularly neuroscience; but I never had much biology in school because I'm very squeamish.

The big transformation for me was when I learned about cell culture. When I found out you could get cell lines and grow them in a dish like a bacterium, I saw my entry point. By that time I had already started a postdoc studying magnetic resonance, but when I learned about cell culture, I asked a biologist if I could serve as a tech in his lab at night to learn how to culture cells.

Around that same time, there was this feeling in the air that adhesion was really important, explaining morphogenesis, cancer, immunology, and neuronal specificity. But again, I didn't have an entrée to that field because the biochemistry and fractionation assays used at that time seemed so difficult and tedious. Then, the hybridoma and monoclonal antibody technology emerged. I thought it would be relatively easy to make an antibody that blocked cell adhesion and use it to purify an adhesion molecule. So, my lab developed a monoclonal antibody that blocked adhesion and targeted a matrix adhesion receptor. We then collaborated with Clayton Buck on its characterization, and Richard Hynes used it to clone the first matrix adhesion receptor, the β1 integrin subunit. That was a major advance and very exciting. We all knew that this was important.

Your lab studied integrins, adhesion, migration…

We had a biological problem, and we'd found a molecule involved in it. At that point, a project can take on a life of its own. You can lose your way a little bit—at least, I did.

Many people had proposed that there was a transmembrane linkage between fibronectin and the cell cytoskeleton, and integrins were now obvious candidates for this. So we collaborated with Keith Burridge and showed biochemically that fibronectin bound to integrin, which bound to talin, which bound to vinculin, which bound to actin. Then we became interested in the integrin cytoplasmic domain because it was short, yet very functional, so we mapped its activities and binding partners.

But eventually, it struck me that we had to get back to studying a problem rather than a molecule. We knew that integrins are important for migration, and migrating cells are asymmetric. So, could adhesions be asymmetric, doing different things and being regulated differently at the front versus at the rear of the cell? This was a problem that had to be approached using a microscope.

But even though we knew we had to do these studies under the microscope, it was not easy because neither the technology nor the available probes were very good. It was also clear there were many more molecules involved in adhesion and migration than we had originally thought. All of these things pointed to the realization that we needed a collaborative effort to solve the problem of adhesion in migration. So when the National Institute of General Medical Sciences announced a new large, collaborative grant initiative, it seemed to me that this was perfectly matched to what the field needed at the time. My colleague Tom Parsons was thinking along the same lines, and we brought together an interdisciplinary group of colleagues and generated the Cell Migration Consortium.

COLLECTIVE EFFORT

What was your group's contribution to the consortium's effort?

We were involved in phospho-proteomics and in moving correlation microscopy

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Text and Interview by Caitlin Sedwick
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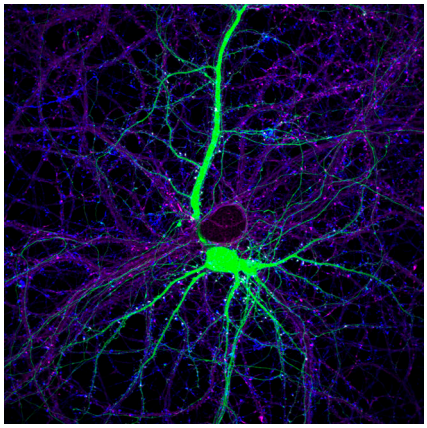

IMAGE COURTESY OF KAREN LITWA

Synapses as adhesions: a rat hippocampal neuron expressing GFP (green), stained for actin (magenta) and the presynaptic protein synaptophysin (blue).

from looking at specific places in a cell, one at a time, to making cellular maps that could inform us about local protein concentrations, dynamics, and associations. When the consortium reached its sunset after ten years, we had a tremendous amount of data and technology to work with—both on migration and the other projects we had been studying. For example, I've always been interested in looking at the neuronal synapse as an adhesion, rather than simply as a site of neurotransmitter release. Our view of the synapse is that it's a specialized kind of adhesion, and that many of the molecules that we've studied in the context of fibroblast adhesion are probably doing analogous things in the neuron.

So you'd planned to keep studying these topics…

Yes, but then last year I was contacted about Microsoft cofounder and philanthropist Paul Allen's interest in launching a new cell biology institute in Seattle. Paul is amazingly well informed about science and has a sincere and deep interest in understanding the cell.

This was so unexpected—a once-in-a-lifetime opportunity, if you're lucky! And as a logical extension of the Cell Migration Consortium, it was a chance to do interdisciplinary team science outside of the constraints of an academic institution or the NIH. Not that there are many constraints at the NIH, but in NIH-sponsored research, many scientists study a particular process. We stumble upon a small number of molecules and study them in depth. But the cell contains myriad of these molecules organized into complexes, "molecular machines," and organelles, and nobody studies how these entities function as complex systems and how they interact to determine cellular behaviors. Instead, people focus on just a small, manageable part.

At the Allen Institute for Cell Science, we will study the cell and its components as complex systems, using systematic approaches. We'll ask questions such as, How do perturbations in a particular protein affect both the complex or molecular machine in which it resides and the other complexes and organelles in the cell? And because many of these effects will be transient and localized, we'll use microscope-based assays to assess them.

> **"The institute would like to create an 'animated cell' that contains all the information we collect."**

IMAGE OF SHARING

What types of cells will you be studying?

We'll start by studying human induced pluripotent stem cells. Our goal is to assemble a library of gene-edited stem cells expressing fluorescently tagged proteins. We'll need the help of the research community to generate our library; they can tell us which proteins are the most useful and which GFP fusions work well.

Once we've made the cells, we'll make them freely available. But in the institute, we'll start characterizing the fusion proteins and making movies of them in cells. We'll gather data on how the proteins behave as the cell divides, migrates, differentiates, or executes other activities, as well as under conditions such as oxidative stress, mutation, natural variation, and environmental perturbation.

How will you make that data available to the community?

In my view, a big problem in cell biology is that most of the things that we study and then write about originate from visual information. Our papers can be hard to read because we're trying to describe dynamic visual phenomena in words. So for our final output, the institute would like to create an "animated cell" that contains all the information we collect—where things are, how they change—in an integrated visual format. We would also like to include structural data that is already out there, so users would be able to zoom in and see the supramolecular structure of an organelle or the atomic structure of a protein. The goal is to bring it all together in an interactive, queryable format. Obviously, we can't do this all by ourselves in a short time frame, but we can start.

We're beginning to hire now, and we're looking for cell biologists, biophysicists, engineers, computer scientists, and mathematical modelers who want to work as a group, in a team. The institute won't be composed of principal investigators each doing their own thing. This project is going to take a team approach with shared challenges, successes, and rewards.

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Horwitz and his wife enjoy the outdoors. They're excited to explore their new environs in the Pacific Northwest, if Rick gets any time to unwind from work.

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