People & Ideas

Kenneth Yamada: Exploring the paths of cell migration

The intrepid Yamada has made many discoveries while mapping out cell adhesion and motility.

Kenneth Yamada's interest in cell movements began as a PhD student with Norman Wessells at Stanford University in the late 1960s, where he studied the contribution of actin filaments and microtubules to axon growth (1). As a postdoc with James Weston at the University of Oregon and then with Ira Pastan at the National Cancer Institute in Bethesda, MD, Yamada characterized fibronectin (2)—a key component of the extracellular matrix with roles in cell adhesion, migration, and morphogenesis.

Yamada has maintained an interest in all three of these fields during his 30 years as an investigator at the National Institutes of Health. In that time, he's taken his research into new dimensions—studying adhesion and migration in 3D (3) and, more recently, 1D models (4). He has also used different systems to investigate branching morphogenesis (5), a developmental process that can be recapitulated in vitro with isolated salivary gland cells (6). When asked to name his favorite publication, Yamada demurs, saying that it would be like having to choose his favorite child. That sense of fairness is reflected in Yamada's service on the NIH's scientific conduct and ethics committee, where he educates researchers on the dangers of image manipulation (7).

In a recent interview, Yamada explained how curiosity and luck have guided him through a long and successful research career.

EARLY EXPLORATIONS

What were your earliest experiences in science?

My father was a research technician who became a physician. We actually kept my father's lab's guinea pigs in a large bank of cages at our house. Those were the days before animal care committees, so those lab animals were my first exposure to science.

But I've always been very curious—I tend to plunge immediately into a topic because it intrigues me, without figuring out an endpoint. For example, when I was a preschooler I wanted to understand how door locks worked. I carefully took apart our house locks, but then couldn't reassemble them, to the disapproval of my parents!

What would you be if not a scientist?

Maybe I was born in the wrong century, but I think I should have been an explorer. I guess the equivalent now might be a wildlife photographer. I really like photography, so that might've been it.

You did an MD-PhD. Did you intend to practice medicine at one point?

It was a very difficult choice between medicine and basic research. I did all my graduate work first, and then I went to the clinics. It was like a forced sabbatical for three years and I discovered that I really missed designing experiments and discovering new things. I think I actually had withdrawal symptoms. So that's when I figured out that I had to do basic research. But I don't regret the medical training at all. It gives you a broad exposure to all kinds of different knowledge, a viewpoint relevant to human health, and it teaches you the importance of time management.

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How did you end up working with Norman Wessells?

I'd worked with him as an undergrad, and I really loved the way he mentored. It was a sink-or-swim approach in which he gave an exceptional level of autonomy to his students, and yet was always available for discussion.

I could make up my own experiments, or change projects completely. It was a great time because we were trying to understand roles of actin microfilaments—using the wonder drug at that time, cytochalasin—and comparing them with microtubules in axon extension and cell migration.

Kenneth Yamada

Were there times when you thought you might sink rather than swim?

Not really. Nowadays, people panic sooner, but things were different then. We had time to do whatever we thought was interesting, without worrying about a career. We could do what we loved to do and hope it would all work out in the end.

DRAFTED INTO SERVICE

After completing your MD, you went to Oregon for a postdoc with James Weston.

That was actually one of the luckiest accidents of my life. During the Vietnam War, everyone with medical training was drafted. I was strongly opposed to the war, and so, like a number of other now-senior researchers, I was able to fulfill my military obligation by serving in the US Public Health Service at the NIH. But I actually miscalculated and missed the application deadline, so I had to fill in one year.

I hooked up with Weston because I thought the field of cell surface biology was going to be important. He had been working on a factor that suppressed contact inhibition of migration. I joined his lab to purify and characterize that mystery protein.

I set up a reliable bioassay, extracting material with low concentrations of urea from fibroblasts, but I kept running into this major contaminant that actually looked quite pure on SDS gels. It ran at about 220 kD. I decided that I might as well study a

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purified protein that nature had given me as a gift. We characterized it, and wrote *PNAS* and *Cell* papers on that contaminant protein that turned out to be fibronectin.

Did you think that you'd still be working on the same protein 30 years later?

I thought that it would open up interesting new areas, though at the time I thought fibronectin would be involved in growth regulation rather than cell adhesion. It's remarkable though—when we have meetings, we have many of the original people in the field who are still working on fibronectin or related molecules. It's a protein that's been very good to a lot of us.

Young researchers should always try to study a new protein if they can, because there are going to be really interesting surprises. It gives you tremendous opportunities and it's a lot of fun. Of course, it all depends on having a good mentor. I've been lucky in that sense too: I had another mentor at the NIH, Ira Pastan, who gave me a lot of creative freedom, even as a postdoc.

Do you take a sink-or-swim approach in your own mentoring?

The ultimate goal is still to have my postdocs become completely independent. They're responsible for making the key decisions, but I'm always happy to give lots of advice.

Also, I feel strongly that postdocs should be allowed to take their project with them, to start their own lab. And that actually has a positive effect on our own research, because it forces us to go in new research directions. We stay in the same general area of extracellular matrix, cell dynamics, and so forth, but we don't take a linear, focused approach to research, which actually fits with my personal preferences, too.

MIGRATION AND MORPHOGENESIS

As a result, you use many different model systems in your research. When did it become clear to you that 2D models of migration weren't sufficient?

We were interested in cell adhesion and migration in fibroblasts, and had started to worry that what we were looking at wasn't entirely correct, so we developed 3D models. I've published a lot in 2D, and I think we actually missed quite a bit. However, it's also clear that different extracellular matrices have different properties. So you can't just say, "I'm working in 3D." You also have to define whether it matches your physiological model.

Recently, we published a paper using micropatterning to study 1D migration, which seems to mimic 3D migration closely. When Andrew Doyle was doing those studies in our lab, I would say, "We've got to find something where 2D is closer to 3D than 1D, otherwise nobody will believe us." We don't want to appear as if we're attacking people who use regular 2D tissue culture. But so far, we haven't found anything in 2D studies closer to 3D than 1D. It's pretty surprising that there are so many differences in 2D.

One of Yamada's favorite photos, taken in the Masai Mara, Kenya.

How do these different models of migration compare?

First of all, overall cell morphology is uniaxial in 1D and 3D. Whereas in 2D, fibroblasts have lamellae going off in multiple directions. The migration rate is significantly faster in 1D—cells seem to love straight lines. It's a dogma in the cell adhesion field that there's an optimal concentration for the adhesive surface: if you have too little adhesion, the cells have poor traction; if there's a lot, then the cells form strong attachments and won't migrate fast. But in 3D you have almost pure protein and proteoglycan fibers. So that's a very high local concentration. It turns out that in 1D you can have extremely high levels and the cells still migrate fast. So that's another difference compared to 2D, which does show the classic biphasic behavior.

There are other differences, too. Myosin II contractility doesn't seem to be essential for 2D migration, but you get slower migration in 3D and 1D if you inhibit myosin II. And the centrosome leads the way for cells migrating in 2D, whereas in 3D and 1D, the centrosome's at the rear. We're now trying to identify differences in the signaling systems between 2D and 3D—we're going to look at Rho family GTPase functions next. The overall question is whether there really are fundamental differences in the mechanism and regulation of migration in 2D versus 3D or 1D. We don't really know.

You're also interested in salivary gland branching morphogenesis. What is it that fascinates you about the process?

I think it's the dynamics—I'm a very visual person, so this dramatic remodeling is really intriguing. What kind of physical and signaling cues allow cells to assemble a complete and functional organ? Remarkably, it turns out that fibronectin is required for branching morphogenesis, so things have come full circle. We can now reconstitute the process with dissociated salivary epithelial cells. They can reassemble and self-organize into a tissue. It's just astonishing when you watch how incredibly motile these cells are.

We're learning that there's no preordained map of where branches should occur, and cells seem to readjust very quickly. So in the reconstituted system, a duct cell can become a bud cell. And we're helping to construct a developmental gene atlas of salivary gland development using laser micro-dissection that will look at differences in gene expression in all the different cell types. We hope to identify the genes and mechanisms involved in morphogenesis, but it will be complicated.

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