People & Ideas

Jeffrey Fredberg: Flow under pressure

Fredberg takes a physical approach to model mechanical properties of cells and tissues.

PHOTO COURTESY OF JEFF FREDBERG

Jeff Fredberg

While most people are largely unaware of the flow of air through their lungs, an asthmatic suffering an attack battles for every breath. After years of study, scientists still aren't sure what lies at the root of this problem. Jeffrey Fredberg has pursued this question for much of his career, seeking to understand it at every level. It's a chase that's spanned his 15 years running his own nonprofit research institute, and—after the institute was folded into the Harvard School of Public Health—all the years since.

With his focus on physics and early training in fluid mechanics, Fredberg has taken a different road than most cell biologists. Along the way, he's made some startling observations about the mechanical properties of connective tissues (1), epithelial sheets (2, 3), and individual cells (4, 5). We called him at his lab and learned what cells have in common with ketchup and coffee beans.

NOT AFRAID TO FAIL

Do you remember any formative events from your childhood?

I was a great failure as a student early on. Probably I had learning disabilities, but these were unknown at the time. By the time I'd learned to compensate for whatever problems I had, I was a discouraged student, and in my sophomore year of high school I actually flunked out.

That was a pivotal event, of course, but it turned out to be one of the best things to ever happen to me because I went to a new high school. The first class on my first day happened to be Latin, which I had already had at my old school. So when the teacher, Mr. McCarthy, asked an elementary question of the class and no one else volunteered, I raised my hand and answered it correctly. And this teacher pointed to me and said, "Good. What's your name?"

That was the first positive thing that had happened to me in school, maybe ever. It was kind of a watershed moment. For the first time in memory, I went home and did my homework, and from there it was straight up. I graduated top of the class. Just those few words from a kind teacher made all the difference.

In what way has that experience impacted you down the road?

I've used it to try to encourage people who are having their own troubles. You can overcome them. You can be resilient. I'm always pushing my trainees to take chances because young people often want to play it safe. They're afraid to fail. But if you're not afraid to fail, you can dream bigger, and maybe discover something bigger. I think being comfortable with failure and using it to motivate you is key.

> "If you're not afraid to fail, you can dream bigger, and maybe discover something bigger."

FINDING THE FLOW

Once you discovered you were good at school, what interested you?

I found I had a real talent for math, science, and physics. The math book we used in my freshman and sophomore years at Tufts University had chapters on vector calculus at the back of the book, and I just thought those equations were beautiful. All the examples in the book were from fluid flow so I decided I wanted to study fluid flow and mechanical engineering, and that what I most wanted to do was to understand disease processes and biology through the lens of physics and engineering.

Early on, you were focused on airway biomechanics…

I've always had an interest in airway narrowing in asthma but the level at which we've looked at the problem has kept evolving. The first decade of my career, we were interested in resistance to airflow. But after about 10 years, I realized that we still didn't understand asthma any better, and the real problems in asthma weren't in the gas flow but in the behavior of lung tissues. So I decided to move over into the tissue side, and we made a lot of really basic discoveries about the mechanical properties of lung connective tissues. But we still didn't understand what was going on in asthma, and I began to realize that it wasn't just about the connective tissue in the lung; the smooth muscle that wraps around the individual air tubes in the lung was also important. When those muscles constrict, the airways narrow and you can't breathe. I decided to make yet another leap.

When I went into that area, the field was very heavy in biochemistry. I'm not a chemical thinker; I'm a mechanical thinker, and I decided that if we were going to understand asthma, we had to understand more about the contractility and mechanical properties of smooth muscle. Years before, Andrew Huxley had proposed the sliding filament model of muscle contraction. But this was focused on striated muscle, not on smooth muscle, which lacks the crystalline structure of striated muscle. I saw that the mathematics of Huxley's model resembled the equations for fluid mechanics, so we were able to come up with by far the best computational model of smooth muscle dynamics.

Text and Interview by Caitlin Sedwick
csedwick@gmail.com

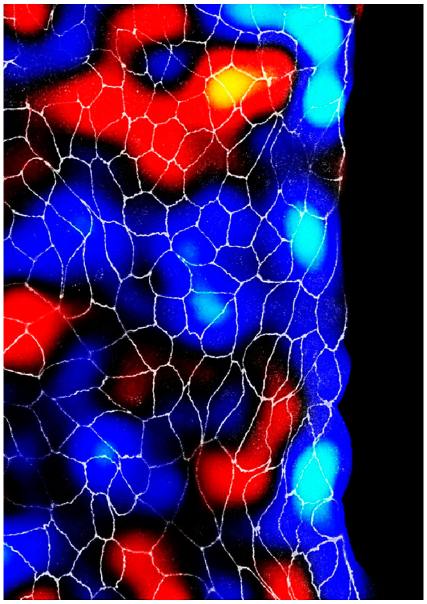
IMAGE COURTESY OF DR. JAE HUN KIM

The distribution of mechanical tension (indicated by color) in an advancing cell sheet.

GLASSES AND JAMS

You've made some surprising discoveries about cells' mechanical properties…

To measure the mechanical properties of single cells, we used magnetic microbeads coated with molecules that bind to integrins on the cell surface. We could apply magnetic fields to twist these beads and then infer the mechanical properties of the cell. We knew the on- and off-rates of the actin–myosin interaction, so we expected this would dictate the molecular time scales for relaxation from a twist. But when Ben Fabry, a fellow in my lab, did these experiments, we were totally shocked because instead we found that the rheology of smooth muscle cells—and actually many other cell types—varies according to what's called a weak power law. The faster a cell is deformed, the stiffer it becomes, smoothly, slowly, and without limit.

Ben marched himself over to the physics department with a graph of this power law rheology to ask if anyone had seen anything like it before. Eventually, he stumbled into the office of David Weitz, who took one look at it and said, "Oh yeah, sure, that's a universal behavior of all soft matter: pastes, foams, colloid suspensions, slurries, and emulsions like mayonnaise and ketchup. If that's how a cell behaves mechanically, then it must be in the same class of materials as a soft glass."

So Ben and I started reading about soft glasses and we saw that, indeed, Weitz was right. The cytoskeleton, like these materials, is malleable: If you put forces on it, you can change its shape. If you remove the forces, it retains that shape, but if you put the forces back on, it will flow again.

Another recent focus in your group has been on collective migration…

A group at Boston University invented a technique called traction microscopy, where a single cell is placed on an elastic substrate with fluorescent markers embedded into it. When a cell contracts it deforms the gel, and if you know enough about how the gel deforms, you can map the distribution of forces that cause the deformation. The problem was that the computations required a supercomputer. When I showed this to my colleague, Jim Butler, who's a mathematical physicist, he came back the next day saying, "I can compute this much more easily."

> "I'm not a chemical thinker; I'm a mechanical thinker."

Jim showed he could use a Fourier transformation approach to do the same calculation in milliseconds on a desktop computer. Then a fellow named Xavier Trepat joined my lab, and we applied Jim's approach to study a peculiar behavior of airway smooth muscle. In normal people a deep breath wipes out contractile tone in constricted airways. In fact, a deep breath is the most effective bronchodilator we know of. But in asthmatics during a spontaneous, severe asthma attack, bronchoconstriction gets even worse after taking a deep breath, so we decided to look at the behavior of smooth muscle when it's stretched.

Xavier showed that when smooth muscle or any kind of adherent cell is stretched it goes from a solid-like state to a fluid-like state. It turns out that's another feature of soft glasses. But when he was all done, Xavier told me he wanted to look at mechanical properties of lung epithelium, and the forces cells exert during wound closure. I didn't think he'd be able to extend the single cell measurements to an extended monolayer, but he tried anyway. Working with Jim Butler, Xavier developed a whole new theory of traction microscopy that allowed them to measure the forces that the cells of a cellular collective exert on their substrate, and on their immediate neighbors. We've recently shown that the epithelial cells taken from normal and asthmatic owners behave in very different ways, although we don't know yet if this is a cause or an effect of asthma.

So where are you going now with this work?

We're now totally switched over into collective cellular migration, and an interesting phenomenon we discovered called cell jamming. It's analogous to what happens when coffee beans jam together in the dispenser chute at a supermarket. It turns out jamming is a very hot but poorly understood topic in condensed matter physics. We've shown that confluent layers of pseudostratified epithelial cells can jam and also un-jam. There can be lots of routes to unjamming; for example, wounding. I think this could have very interesting implications for processes like development, pattern formation, and cancer.

1. Fredberg, J.J., and D. Stamenovic. 1989. *J. Appl. Physiol.* 67:2408–2419.
2. Kim, J.H., et al. 2013. *Nat. Mater.* 12:856–863.
3. Park, J.-A., et al. 2015. *Nat. Mater.* http://dx.doi.org/10.1038/nmat4357
4. Fabry, B., et al. 2001. *Phys. Rev. Lett.* 87:148102.
5. Trepat, X., et al. 2007. *Nature*. 447:592–595.


PHOTO COURTESY OF JEFF FREDBERG

Fredberg with his wife, without whom, he says, he'd never have succeeded.