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People & Ideas

Cliff Brangwynne: All the right materials

Brangwynne's work centers on the phase transitions that underlie various aspects of cell biology.

Growing up in the Boston area, Cliff Brangwynne was a kid with distinct interests. He recalls performing one of his first experiments after watching a TV program on quantum mechanics: spending an afternoon bouncing a tennis ball off a wall in an attempt to observe quantum tunneling. Through high school, he read pop-science books about the weirdness of the quantum world. Fritjof Capra's *The Tao of Physics* especially captivated him; the atomic world seemed so different, with interconnected energies that were in a sense mystical. It was this mystical aura about the scientific world that ultimately drew him in.

Today, Brangwynne explores the mystical realms of materials physics and cell biology in his own lab at Princeton University, where he studies the phase transitions that underlie the formation and function of membraneless organelles and other cellular processes. We contacted him to learn more.

Where did you study before starting your own lab?

I was an undergraduate at Carnegie Mellon University. I almost majored in biology but decided to study materials science and physics. The intro biology course was all memorization, which I wasn't any good at, while the intro materials science course had a lab component where we got to pour lava hot copper and watch it crystallize. That department knew how to hook undergraduates! However, I was still very interested in biology, and I took a year off in the middle of college (though it was mostly because I wanted to travel around Central America) and spent time in Don Ingber's lab at Harvard Medical School working on the cytoskeleton, cell shape, and migration (1). I then went on to do a PhD, working with Dave Weitz at Harvard, who is a pioneer in the field of "soft matter physics," which concerns squishy materials like gels and colloidal suspensions. In his lab I worked on the biophysics of the microtubule cytoskeleton (2). I then went on to do a postdoc with Tony Hyman in Dresden, where I became interested in membraneless organelles in cells (3).

What was it that first drew your interest to membraneless organelles and phase transitions in cell biology?

I'm very passionate about this area of research because it is the marriage of two things that I really love: materials physics and cell biology. I feel like my path has been about trying to reconcile my different interests, and this is an area where the part of my brain that gets jazzed up about physics can get its fix, while the part of my brain that wants to know how cells work can also be happy.

What is your lab actively working on?

I'm pretty excited about how phase transitions are controlling the flow of information in the cell (4). We are thinking a lot about how the cell organizes the different states of biological matter and how this organization can go awry. I think the problem that cells are trying to deal with—keeping the dense collection of cytoplasmic proteins stable over decades—is only going to get harder as humans live longer.

> "Bringing in [a] playful child-like aspect to scientific inquiry is important."

What kind of approach do you bring to your work?

For me it is all curiosity driven, and I think that bringing in that playful child-like aspect to scientific inquiry is important. Kids are so uninhibited and wildly creative because they haven't internalized all of our grown-up constraints and conventions about how things should be. I've noticed that it can be very useful to not have read all the same books that other people working in a field have read. Of course you need to know what experiments have been done and how the experts in a field understand a particular phenomena, but having a certain "beginner's mind" is useful for cultivating new ideas. I like to ponder the fact that if we were to fast-forward 100 years from now, probably 90% of our concepts will prove to be mistaken or just plain wrong. Being skeptical about what is "known" is important, and I think that can open up the creative process.

PHOTO COURTESY OF CLIFF BRANGWYNNE

Cliff Brangwynne

What did you learn during your PhD and postdoc that helped prepare you for being a group leader?

I learned how to engage with problems and how to turn them over and over in my mind. I also think that I learned the importance of failure, which is critical. It's of course difficult in the moment, but it's important to remind yourself that failing is a key part of the process. It's good to get experience failing, figuring out the lesson from your mistake, and then moving on.

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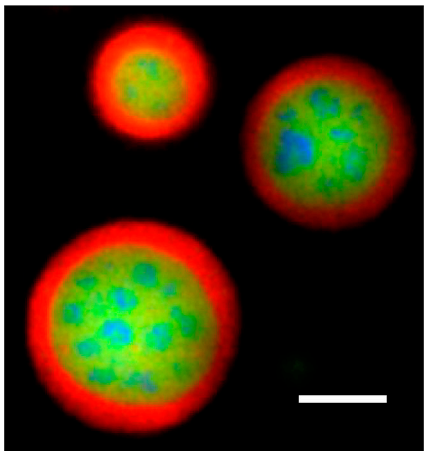

IMAGE COURTESY OF MARINA FERIC

Nucleoli within the germinal vesicle of a *Xenopus laevis* oocyte. The granular component is visualized with NPM1 (red), dense fibrillar component with FIB1 (green), and fibrillar center with POLR1E (blue). Scale Bar, 10 µm.

Was there anything you were unprepared for?
I was probably least prepared for managing people in my lab. When you set up a lab you're creating a little intellectual ecosystem. Especially for the kind of work we do, it's important to have the "right mix" of people, and to encourage synergistic interactions where each person can develop and flourish. But this is something that you have zero experience with before you become a PI, so there is a lot of on the job training. I try to give grad students and postdocs in my lab mentoring opportunities because this is something that takes years to master. It's both the most thrilling and at times frustrating part of the job.

Congratulations on being awarded the Gibco Emerging Leader Prize at the American Society of Cell Biology 2015 Conference. How does it feel having your research recognized and applauded?
It is certainly nice to have people recognize my work. But hopefully no one invites me to cocktail parties hoping that I will say smart sounding things.

What have been the biggest accomplishment and challenge in your career so far?
Helping ignite the field of intracellular phase transitions is my biggest accomplishment (3, 4, 5, 6). Starting as a new PI has definitely been an adventure—probably the hardest thing I've done.

What has been your biggest accomplishment outside of the lab?
Convincing my wife to marry me.

Who were the key influences early in your career?
Kit Parker at Harvard has been a key mentor for many years now. I met him when I was an undergraduate in Don Ingber's lab. He and Don had a strong influence on me early on—they helped me see what scientific creativity and innovation were all about. Dave Weitz taught me how to be fearless in choosing problems to work on. More recently, from Tony Hyman I internalized the idea that life is short so you ought to only tackle big problems. Tim Mitchison is also someone who has had a big influence on me. I'm incredibly fortunate to have spent quality time with so many truly visionary scientists over the years.

"Being skeptical about what is 'known'... can open up the creative process."

What hobbies do you have?
I like to read broadly—history books especially. I've played ice hockey since I was eight, and I still play pickup hockey once or twice a week on campus with Princeton students and faculty. I've also started playing the ukulele, though not well. I've made progress on "Creep" by Radiohead, and there's a good imposter syndrome line there: "what the hell am I doing here..."

What is the best advice you have been given?
Find your passion and the rest will sort itself out.

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Members of the Brangwynne lab hiking on one of their annual retreats.

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