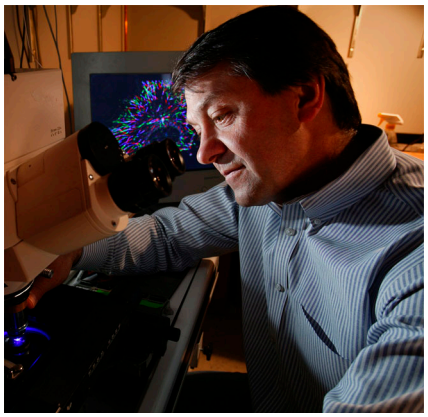
People & Ideas

Stephen Doxsey: At the (peri)center of things

Doxsey studies how centrosomes and pericentriolar material affect cell function.

Centrosomes—organelles composed of two centrioles surrounded by a halo of pericentriolar material—organize the microtubule cytoskeleton. During the division of most eukaryotic cells, the mitotic spindle is organized by centrosomes that sit at either end of the oblong mitotic apparatus. Curiously, however, some types of cells can dispense with centrioles and still assemble a functional spindle—but only so long as they retain their pericentriolar material.

As a postdoc, Stephen Doxsey cloned pericentrin (1), a key component of the pericentriolar material. Through his work on the protein, he's shown how it contributes to centrosome function (2), to mitosis (3), and to processes that, in turn, depend on carefully regulated mitotic divisions (4). But like a trekker out on safari, Doxsey also keeps a sharp eye out for the interesting and unexpected, and he isn't afraid to veer off the beaten path. He has recently stepped into exciting new fields (5), as he told us when we called him at his lab at the University of Massachusetts.



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Stephen Doxsey

OUT OF DOORS

Were you interested in science as a child?

Well, I was always interested in running around outside. My brothers and I were all pretty athletic. We especially liked to build forts and then wreck each other's creations. [Laughs] But I remember the three of us with our heads together, looking at a frog that was in the process of laying eggs and being fascinated by it. We were always interested in and enamored by the outdoors and wildlife. And it's still the same for me, even today.

I feel like I never really made hard decisions about my career. I loved biology, so I became a biology major. Then I decided to go to Africa, and then graduate school, and all the rest. But I always felt like I was on a path.

> "We both got excited about this protein—which turned out to be pericentrin."

A trip to Africa sounds like a pretty big detour…

Well, as an undergraduate I went to the University of Connecticut. At the time, they didn't really have much in the way of research, so I didn't get involved in too many laboratory courses, even though that would have helped me formulate a plan for the future. In fact, that's why I am now such an advocate for exposing kids to laboratory science early on—I co-started an outreach program that invites local Advanced Placement high school students into actual research labs to gain hands-on research experience, and it's been very successful. But in spite of not having had any research experience of my own in college, I still wanted to stay in biology, and I eventually took a job as a research tech at Harvard.

I didn't spend too much time there, though, because Don Fawcett, who was the chair of the department at the time, was stepping down to take a position in Kenya doing electron microscopy for an agency called ILRAD—International Laboratory for Research on Animal Diseases—based in Nairobi. He and I had developed a kind of rapport based on our mutual interest in wildlife. And I had gotten pretty good at what I was doing, things like preparing thin sections for electron microscopy. I guess that's why he invited me along.

It was really only then—in Kenya, when I started working with Fawcett—that I understood what discovery was. We studied a tick that has seven to eight different cells in its salivary gland, each of which performs a different function to ensure a successful blood meal. For me, it was incredibly interesting to see how each cell type was specifically designed for a particular and essential process.

And I loved being in Africa. Before I really got used to it, I would write things in my journal like, "Today, I saw a giraffe walking up my driveway." I went to a Maasai boma for a week, lived with them, and drank blood/milk mixtures. It was amazing, and Fawcett and I were doing great work and publishing a lot. But, I eventually realized that I wanted to get on with the business of my career, so I reluctantly went back to the US to begin graduate school. I went to Yale, where I worked on endocytosis with Ari Helenius and Ira Mellman, whose labs were well integrated. It was fantastic, except for the problem I had in completing my thesis.

THE IMPORTANCE OF BACKUPS

What was the problem?

Toward the end of graduate school, as I was writing up my thesis, I unwisely kept my only copy of it on a floppy disc in my backpack. And on my way home one day, I'd just gotten out of my car when I got mugged by three guys. One of them had a gun. As they grabbed me from behind, I tossed my house and car keys in the brush. They were after my car but were unable to find the keys, so they just took off—but then I realized that one of them had my backpack! The next thing I know, I'm running after them. This was probably not the best idea, but there I was, yelling, "There's nothing of value in the backpack. Please just leave it." The guy had already opened it up a little bit, and he confirmed that that was the case, so he stepped toward me and waved his gun at me, then

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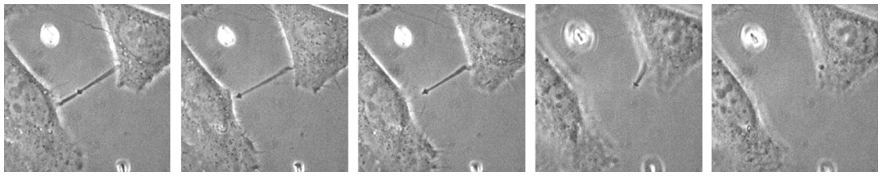

IMAGES COURTESY OF CHUN-TING CHEN

A phase-contrast image sequence shows a midbody (dark dot) being delivered to one daughter cell after division.

dropped the bag and ran away. Later, when I gave my thesis defense, Ari said, "This is the most challenging thesis ever, because Doxsey had to face a gun in order to get it done."

While a postdoc, you encountered the protein you work on now…

When I interviewed with Marc Kirschner for a postdoc position, he asked what I wanted to work on. I had been talking to Tim Mitchison, who was just finishing up in Marc's lab, so I said, "Centrosomes." Marc's eyes just lit up.

We both got excited about this protein—which turned out to be pericentrin—that is present around centrosomes in most cells. It is also present in cells that don't have centrioles and therefore lack bona fide centrosomes. We showed that pericentrin is involved in mitosis and spindle organization. It's a universal protein for organizing centrosomal material, with or without centrioles, to coordinate spindle assembly.

> "We're always looking for the unexpected."

EXPECT THE UNEXPECTED

Is its universality reflected in functional importance?

When you compromise pericentrin, you compromise the pericentriolar material that surrounds the centrioles. When this happens, you lose some microtubule-nucleating capacity, and we believe that leads to a loss of microtubules, especially during mitosis. We've looked at this in my lab, and it appears that astral microtubules are functionally compromised. Astral microtubules are involved in orienting the spindle within the cell, which could explain why our pericentrin knockout mouse is unable to orient its mitotic spindles properly.

We believe this affects stem cell self-renewal and creates havoc during organ development. We have data showing that stem cells in the ventricle of the brain undergo fewer self-renewing divisions than they should, and this may be why these mice have microcephaly.

It's known that mutations in pericentrin cause a type of primordial dwarfism called MOPD II. People with this disorder are very tiny, and we think this might be caused by decreased self-renewing cell divisions, leading to fewer stem cells. These people also have cardiac defects, and we're working on a paper with Cecilia Lo that shows that defects in asymmetric cell division cause misorientation of the septum in the heart ventricle.

Is your lab totally centered on pericentrin?

Actually, no. We're always looking for the unexpected, and that's been really exciting for us. For example, a little while ago we started exploring the role of centrosomes in vesicle transport, because Rab11-positive recycling endosomes are brought to centrosomes before they are recycled out of the cell. We recently identified molecules on the centrosome that interact with these vesicles to control recycling. Surprisingly, we found that some of the vesicle proteins are also on the centrosome and that they have important functions there as well. We weren't looking for this when we started.

We also recently published a paper where we found out that a cilia protein, IFT88, has mitotic functions. Following up on that work, we've found several other cilia proteins that have mitotic phenotypes when they're knocked down. The centrosome is important both for the spindle pole at mitosis and as the structural basis of the cilium. This raises a question: Are ciliopathies really "centrosomopathies"? We'll have to use separation-of-function mutants to dissect the functions of these cilia proteins in mitosis versus cilia, which will be an exciting challenge.

And then, last year, we published a paper about midbodies. These are structures that are important for cell division but then are thought to be lost after cytokinesis. However, they are actually retained by some cells, such as cancer cells and stem cells. We did some experiments showing that these postmitotic midbodies are required for cancer tumorigenesis phenotypes, so we asked how this is happening. We identified what may be an autophagy pathway that degrades midbodies in normal cells but not cancer or stem cells. We're now testing how midbodies contribute to stem and cancer cell activities.

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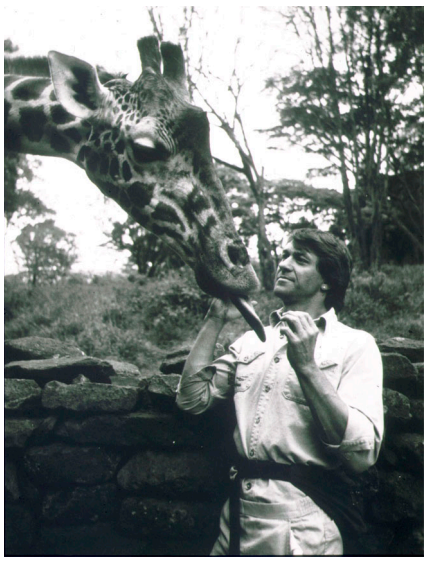

PHOTO COURTESY OF STEPHEN DOXSEY

Doxsey has long harbored a passion for wildlife and for discovery.