W. Zacheus Cande: Evolutionary biologist in cell biologist's clothing

Zac Cande wants to get to the roots of cell division and cytoskeletal mechanics.

How eukaryotic cells achieve the mammoth task of dividing into daughter cells is a question many cell biologists—including Cande—spend their careers trying to answer. While most cell biologists look for answers in one or two cell systems, however, Cande has a nearly insatiable appetite for diversity.

"It was seeing the chromosomes move that really got me fired up—it's just a thrill. It still is."

His self-professed penchant for weird and wonderful organisms ("there's always these oddball things that do really fascinating stuff, which I've always loved," he says) has led him to work on spindle dynamics in unicellular algae (1), spindle pole body formation and telomere clustering in yeast (2, 3), meiotic chromosome pairing (4, 5) and telomere clustering (6) in maize, and, most recently, the mechanisms of mitosis in the protozoan, *Giardia* (7). Oh, and just for the record, he's also studied mammalian cells.

In a recent interview, Cande explained that studying *Giardia,* an intestinal parasite, has allowed him to return to his first love: evolutionary biology. To understand how fundamental cellular processes such as division have evolved, says Cande, it's essential to look further back along the taxonomic tree than the relatively recent divergence of yeast and man.

SCHOOL DAYS

What was it that sparked your enthusiasm for science?

I had really good science teachers in high school. I took biology and chemistry, and I got really excited by that. Between my junior and senior years of high school, I took a botany course sponsored by the National Science Foundation, and that gave me a lot of confidence.

If I'd had wonderful English teachers instead, I might be quite different. My parents weren't scientists or anything like that. My father has an engineering background, my mother was a musician.

What did you study at university?

I went to Yale, and originally I tried out chemistry, but I switched to biology. I really loved biology, and so I stuck with it. I liked just about everything I studied but particularly evolutionary biology. I never wanted to go to medical school or any of that stuff, like all my friends, just cutting up another corpse.

How did you choose your Ph.D.?

I was studying ecology and evolution, and I was very much influenced by a guy named Charles Remington; he worked on butterfly evolution. I love this stuff. I thought I could do something like that in plants. So I got excited, and I went to work with Peter Ray at Stanford—an exceedingly good plant physiologist—but the project was way ahead of its time. There weren't the necessary molecular tools. It was clear as soon as I started that none of that was going to work. So I did a much more conventional developmental biology/plant hormone Ph.D. thesis.

ALTERNATIVE LABSTYLE

Was there any particular reason you chose plants?

I like unusual organisms. I've always liked plants, I've always liked microbial organisms. Different types of organisms that aren't mammalian/metazoan tissue culture cells can give you an edge on certain problems. I don't think I would've thought of it that way back then, but I just liked being a little bit different. This was '67. It was the hippy era!

What about the post-doc years?

There was a small element of cell biology in my Ph.D. thesis, which was to think about whether cytoplasmic streaming was involved in hormone movement, and so I got interested in cell motility, streaming, and cellular architecture. At that time, it wasn't even clear that things like actin and myosin were important for plants. People were thinking that things like actin were much more muscle-based and metazoan and not present in every single eukaryotic cell.

Zac Cande

So I was going to work on cytoplasmic streaming with Dick McIntosh in Boulder (Colorado). But instead we thought we would work on mitosis. This all makes sense in hindsight, but none of it was predictable. It's one of these things where you wander to the top of a mountain, and you can look down when you're there, but you would never imagine that was going to be your path.

Is that how you got hooked on cell division?

Most of the things cells do are in interphase, not at cell division, but visually, that's their most dramatic time. So I suspect that it was seeing the chromosomes move that really got me fired up —it's just a thrill. It still is.

After Boulder you moved to Berkeley?

Yeah, to my surprise, I got hired as an assistant professor! I arrived at Berkeley in January '76, right on my 30th birthday. This is my only job. I've never moved. I've been here for 30 years.

Much of your cell division work has been performed in maize. Why did you choose that system?

I've worked on a variety of model organisms. But the thing that was really wonderful about maize is that it has the most beautiful chromosomes. The cytology is unbelievable.

Getting into this was really the product

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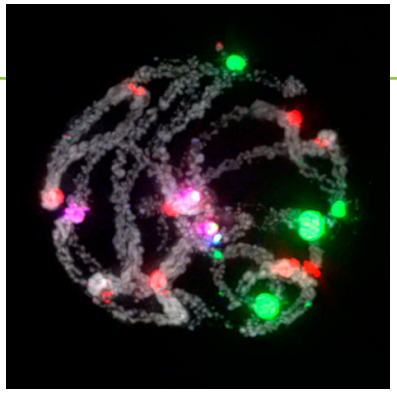


Cande studies the movement of maize chromosomes through cell division.

of three people. One was Mike Freeling, a really excellent maize geneticist here at Berkeley who convinced me to start looking at maize. Another was Inna Golubovskaya, a wonderful Russian scientist, now at Berkeley with me, who's one of the foremost geneticists working on maize meiosis. She had this incredible mutant collection. And the third was John Sedat at UCSF, who was into advanced light microscopy. He had developed deconvolution methods, so we applied this imaging technology to maize and looked at the mutants and chromosome behavior.

It was serendipity. A lot of my life has been that way. You meet somebody interesting, and they tell you a great story, and you get fired up.

A RETURN TO ROOTS

More recently, you've returned to your early passion for evolution. Tell me about that.

I've always been interested in evolution, and in the last five or six years my lab has gone back to thinking about how the cytoskeleton and cell division evolved in eukaryotes. I guess the thing that fascinates me is you've got to go from one to two, and how do you do it faithfully?

It's one of the most amazing things that cells do. It's clear that forming the spindle in mitosis is a dramatic and elegant event. It involves sorting and movement and this and that. In meiosis, it's even more difficult, because first the homologous chromosomes have to find each other. Evolution has made it all work!

It's fun to get back to this after 30 years.

For these evolution studies you've turned to the microorganism* Giardia*?

Yeah, in most of my studies I picked the organisms not because of the evolutionary twist, but because they had some aspect of their biology that made it much easier to look at, for example, chromosome structure.

In fission yeast, cytology of the chromosomes is easy because they're big and there are 3, as opposed to 16, in budding yeast. Plus you have all the molecular biology tools for yeast. Maize is incredible for cytogenetics, and it also has a wonderful mutant collection. I started working in diatoms because they have highly ordered spindles. I've worked with mammalian cells. You have to take what the systems will give you.

> **"The basic problem for most cell biologists now is they're not using microbial diversity."**

But *Giardia*, that's a real attempt to pick an organism not because it's a little different, but because it really might illuminate evolution. Ultimately, plants, animals, and yeast may be very different in how they do certain things, but the underlying mechanism is going to be very similar. Whereas *Giardia*, who knows? It is so divergent.

Evolutionarily, plants, animals, and yeast shared a common ancestor maybe three-quarters of a billion years ago. *Giardia* last shared a common ancestor with man or yeast maybe two billion years ago.

What have you discovered about cell division and spindles from* Giardia*?

The logic of the spindle is similar to that of metazoans. Many aspects of its architecture are similar. Scott Dawson, a former postdoc, started this project and has been investigating the various motors at the kinetochore that are involved in chromosome movement. He found that many of the motors in metazoans are also in *Giardia*, and most seem to be playing similar roles.

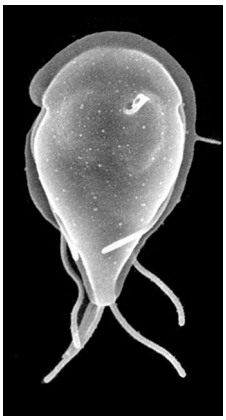
Some of the motors are absent from yeast but are present in metazoans and in *Giardia*. It's not that yeast never had them, they just threw them away. Also, *Giardia* has flagella and basal bodies, just like humans. Yeast doesn't have any of that.

If you compare yeast and man, without an out group, it's hard to know what's happening. Are you really adding on or are you losing? *Giardia* tells you that, for example, the complexity of spindle motors is very ancient. Not that it evolved subsequent to the divergence of yeast and man.

Do you think more cell biologists should study* Giardia*?

What I'm going to argue for the future is that more of these very divergent eukaryotic microbes should be looked at, because it's here that you're going to begin to understand the impact of the evolution of these very basic processes.

I think the cell biology community recognizes the importance of evolution. But their idea of evolution and thinking about evolution with respect to fundamental cellular processes is to compare, let's say, yeast and man. And maybe they throw in plants. This is sort of like comparing houses in the same neighborhood with similar building codes. Some of them have a garage, some of them don't, some of them have two stories, some have one. But these are not profound differences compared with, let's say, housing in Africa or India.



Studying divergent microorganisms like *Giardia*, says Cande, could reveal the evolutionary secrets of eukaryotic cellular processes.

The basic problem for most cell biologists now is they're not using microbial diversity. We've started to, and we hope others will as well. JCB

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