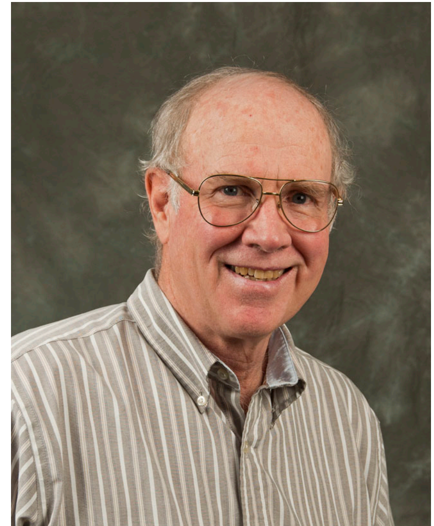
People & Ideas

Ted Salmon: Kinetochores at the core of it all

Salmon uses cutting-edge microscopy to dissect kinetochore structure and function.



Ted Salmon

Mitosis is tightly regulated to ensure the faithful segregation of chromosomes to daughter cells. For instance, anaphase (when chromosomes aligned at the metaphase plate start moving toward opposite spindle poles) should only commence once all the chromosomes' kinetochores are accurately attached to spindle microtubules from opposing poles. The kinetochores signal their attachment status to the cell to satisfy a checkpoint in the mitotic process. How they do this—and how they then generate force to segregate the chromosomes—isn't yet clear, but Ted Salmon is determined to bring these mechanisms into focus.

Salmon is a prominent figure in the mitosis and cytoskeletal biology fields. In the course of his career, he's been involved in everything from the early studies of microtubule dynamic instability (1) to the mechanisms that govern chromosome movements during prometaphase and anaphase (2, 3) and, most recently, the protein function and architecture of kinetochores (4–6). Along the way, his lab at the University of North Carolina at Chapel Hill has worked at the leading edge of microscopy, pioneering new techniques for assaying protein function in living cells (7). We called him up to get a closer look at his career and his work.

"At the time I started working on mitosis, there were more ideas and theories than there were hard facts."

UNDER THE MICROSCOPE

Why did you pursue an engineering degree in college?

As a child, I was interested in ham radio, and I would buy electronics with my paper route money from a store in downtown Syracuse, New York that sold surplus electronics from the Korean War. They had excellent manuals from the army about electricity and electronics, and I learned lots of things from them. My interest in science really started with my interest in electronics and the things you could do with that.

In part, I got into Brown University because I played pretty good high school football, but I only lasted on the football team through my freshman year. After that I decided I was too small. There were people just as smart as me that weighed 50 pounds more—it hurt. Also, the engineering courses at Brown were a lot of work, but I really loved them. So, I gave up on football.

How has your engineering background influenced your career?

My ability to build electronic stuff was important in my life, particularly before I became a real cell biologist. In the 1970s, it turned out to be important for something unexpected: My wife Nancy and I were going to have a baby, but postdoctoral salaries weren't great back then and Nancy wasn't working, so I wasn't sure how I could make ends meet. One day I ran into David DeRosier at Brandeis, who asked me if I could build him an optical diffractometer, which is a device that structural biologists use to scan negatives to see which ones will be good for diffractional analysis. I don't remember how much they paid me for that, but it was enough to provide for our baby boy. I gather they used that device up until five years ago, when they finally retired it.

A CLOSER LOOK

At what point did you first encounter the biological sciences?

I did an honors thesis while at Brown, and for that I decided to build some sort of electronic gadget because that was easy for me to do. One of my professors told me about a friend of his in the biology department who needed a device that would be able to discriminate different amplitude action potentials in cockroach leg neurons. I thought, "Wow, that sounds fun, I can do that." So I met with this fellow in the biology department, and he taught me a bit about neurons and muscles and so on. I'd never had much biology, but I got this idea that there was a whole new area of biology opening up at that time, in which people with talents like mine would be able to work on instrumentation development. So when I went to graduate school, I decided to go into the area of biomedical engineering.

You did your PhD with Shinya Inoué…

I decided to go to Penn for my graduate work, and while I was there I took a cell biology course from Inoué. His colleague, Hidemi Sato, taught a lab to go with this course, in which they explained how to use microscopes to extract interesting information from living cells. There was a group of young graduate students in biology during that time that sort of clicked together: David Begg, Mark Mooseker, Kip Sluder, Doug Murphy, John Fuseler, and Dan Kiehart. This period of time turned out to be the beginning of what we now call the cytoskeletal field, and I was there to watch it happen and be a part of it.

Shinya Inoué is a remarkable man. He is probably the person who has been the most influential in my career. He taught me how to think about problems, how to find the crucial things that I could

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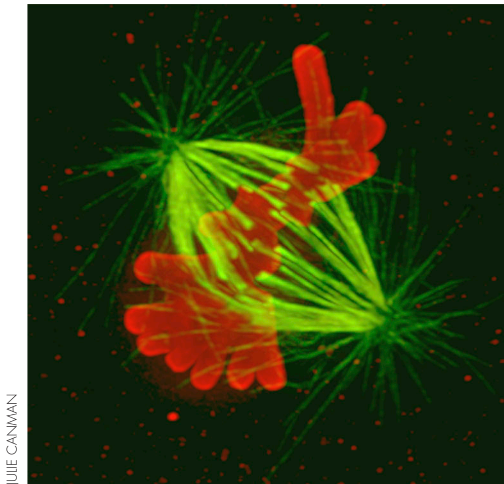

JULIE CANMAN

A mitotic metaphase spindle with chromosomes (red) attached via their kinetochores to microtubules (green).

attack with my own capabilities. Through him, I've had the opportunity to meet and to interact with the best people in the field. He also introduced me to the Marine Biological Laboratory (MBL) at Woods Hole, which is my second scientific home. He would go there each summer, and after my first year, he asked me to come and work with him. I've been going back to the MBL most summers since then. For the past 15 years, Tim Mitchison and I have organized an informal Cell Division Group during summers at MBL that has included many young scientists who are now major contributors to the mitosis field.

"I feel like the last ten years have been really busy in my lab, with lots of really bright people."

NEW FOCUS

What have you been working on recently?

At the time I started working on mitosis, there were more ideas and theories than there were hard facts. People didn't know anything about what kinetochores are made out of. We were just trying to understand what a microtubule consisted of. But by the turn of the century it was clear to me that significant progress in the mitosis field depended on identifying the key proteins for kinetochore–microtubule attachment in mammalian cells.

By that time, it was apparent that the Ndc80 protein complex is critical for both attachment and controlling the spindle assembly checkpoint in yeast. In the last ten years, our lab has shown that the human homologue of the Ndc80 complex is part of the core kinetochore–microtubule attachment site and has important functions in force generation, attachment error correction, and the spindle assembly checkpoint.

More recently I have been interested in how the Ndc80 complex fits within the protein architecture of the kinetochore: where is it located and oriented relative to the chromatin, microtubule ends, and the other major protein complexes of the kinetochore. With Kerry Bloom's lab we developed a method for measuring protein copy numbers in budding yeast kinetochores and found that a single microtubule attachment site has eight Ndc80 complexes. We've also shown, in collaboration with Tatsuo Fukagawa's lab, that this number is conserved between yeast and vertebrates.

How do you study the kinetochore's structure?

To get at the protein architecture, we developed a two-color fluorescence microscopy method for measuring the average separation between two different protein epitopes. Using this technique, we were able to obtain the first nanometer scale maps of protein organization within budding yeast and human kinetochores. We've also recently found in both humans and in *Drosophila* that upon microtubule attachment there is an increase in the distance of the Ndc80 complex from the inner kinetochore that correlates with changes in protein phosphorylation and with inactivation of the signal that prevents anaphase from starting. We're still pursuing how that switch mechanism might be generated and which proteins might be changing interactions or conformation.

What are you focusing on next?

I should say that I feel like the last ten years have been really busy in my lab, with lots of really bright people. But I'm now 66, so I'm kind of slowing down a little bit and picking specific things to focus on. Right now I'm looking for a way that I can study the dynamics of an individual Ndc80 complex within a kinetochore of a human cell, instead of studying ensemble averages. My lab has also been working with Arshad Desai on more protein mapping within human kinetochores to find out where other spindle checkpoint proteins are located relative to the Ndc80 complex within the core microtubule attachment site. I believe that when postdocs leave my lab they should be able to take their projects with them, which forces me to keep looking for new directions.

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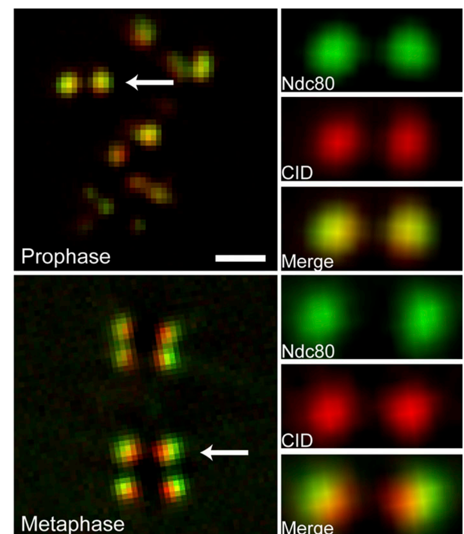

MARESCA AND SALMON, 2009

The outer kinetochore's Ndc80 complex (green) is stretched away from the inner kinetochore's CENP-A protein (red) during metaphase.