David S. Roos

Considering the company it keeps, the apicoplast was not easy to peg. That company is the notorious phylum Apicomplexa, protozoan parasites that range from the malaria parasite *Plasmodium* to lesser known but still potent human threats such as *Toxoplasma* and to *Eimeria,* a scourge of the poultry industry. Apicomplexans are named for a distinctive apical complex of secretory organelles used to invade host cells.

But apicomplexans also harbor mysteries. Forty years ago, researchers spotted a mysterious object, wrapped in multiple membranes, floating in the cytosol of these parasites. Was this an imaging artifact, a bizarre manifestation of the endoplasmic reticulum, an adjunct to the Golgi apparatus, or a discrete organelle? Later, episomal DNA was identified in apicomplexan cells. But whether it was from a mitochondrial genome or from something else entirely was unclear. Apicomplexan parasites were bona fide eukaryotes, yet certain antibiotics killed them. Was their metabolism akin to that of prokaryotic bacteria?

Investigating the mechanism of drug action against *Toxoplasma gondii* at the University of Pennsylvania (Penn), David Roos sampled the 35-kilobase episomal DNA and found similarities to chloroplast DNA. An algal origin for this mystery DNA had been suggested, but Roos and his colleagues localized the 35-kilobase circular genome inside an organelle bounded by four membranes and sequenced the organellar genome. They also used well conserved genes to build a phylogenetic tree linking *Toxoplasma*, *Plasmodium*, and *Eimeria* to a common algal ancestor. The mysterious object in the cytoplasm had become the "apicomplexan plastid," which along the way the researchers shortened to "apicoplast."

"David nailed the apicoplast," according to University of Vermont cell biologist and ASCB Treasurer Gary Ward. "He did some really beautiful work in identifying its origin. That's what was important—synthesizing information from disparate sources to get to the realization of where the apicoplast came from." It is now well accepted that an ancient ancestor of these parasites "ate" a eukaryotic alga, retaining the algal chloroplast as an essential parasite organelle.

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The Internationalization of Bioscience

The apicoplast was an important discovery for many reasons. The identification of a plantlike ancestor for the *Plasmodium* plastid suggested that malaria parasites might be vulnerable to herbicides. Follow-up studies with Geoff McFadden at the University of Melbourne, among others, have identified a wealth of candidate drug targets. But beyond any single discovery, the career of David Roos shows the increasingly interdisciplinary nature of research and the increasing internationalization of bioscience, according to Keith Gull, a microbiologist at Oxford University.

Gull, who studies trypanosome parasites, is working with Roos and other members of the ASCB International Affairs Committee on a new program underwritten by the Carnegie Corporation of New York to develop workshops on cutting-edge bioscience in collaboration with African universities (see page 7). Roos will be a featured speaker this July at the first workshop, to be held at Sokoine University in Tanzania. (The workshop is also in partnership with Paul Gwakisa of Sokoine and Patrick Duffy of the Seattle Biomedical Research Institute.)

Gull says that Roos has long been a leader in international outreach. He has taught bioinformatics on behalf of the World Health Organization (WHO). "David has been a stalwart in teaching these workshops in Africa and throughout the world," says Gull.

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Postgenomic Skill Set

Gull believes that the eclectic mix of disciplines and techniques exemplified by Roos's approach illustrates where research will go in this new century. According to Gull, "David underscores what many of us feel about modern cell and molecular biology: It's now full-scale. You go from the genome right the way through. It's not just hypothesis-driven individual work on individual genes but a full-scale systems approach." Gull continues, "There are still too many people in biology who don't understand that this is really a postgenomic century. We'll need additional skill sets, and David covers many of these areas in considerable depth."

Roos was born in Boston, carried off to Wisconsin almost immediately, and brought back to New England at age 3. That's when his father, endocrinologist Thomas Roos, joined the biology faculty at Dartmouth. Looking back, Roos says that he had fairly typical interests growing up in rural New Hampshire—hiking, cycling, kayaking, and skiing—but also advanced math courses at Dartmouth and early exposure to computer programming. Roos wrote his first program in the third grade.

Roos was so enthusiastic about computers that he took a job, straight out of high school, running Honeywell's computer exhibits at the Boston Museum of Science and the Boston Children's Museum. A year later, he decided to go to college after all, entering Harvard with interests in the arts, English, and a great deal else. Only as a junior did the biology bug bite him in earnest. He was driven by exposure to cell biology through classes taught by Ken Miller, now at Brown, and Daniel Branton, still at Harvard. Reports on actin polymerization written by Lewis Tilney at Penn also fascinated him. "Tilney was always my idol in cell biology. It was a tremendous treat ultimately to wind up teaching an advanced cell biology class with him, as we did for 10 years before Lew's retirement," says Roos.

Last Possible Moment

For graduate studies at the Rockefeller University, Roos joined the lab of virologist Purnell Choppin (later president of the Howard Hughes Medical Institute). Working on the biochemistry of viral membranes gave Roos a feeling for what he now calls "the pathogen's side of things." He received his doctorate in 1984. "That was the last possible moment when one could get a doctorate without knowing any molecular genetics," Roos recalls. "I'd never purified a plasmid or run a nucleic acid gel."

For remediation, he joined Robert Schimke's lab at Stanford as a Whitney Fellow, working on the mechanics of drug resistance in human cells. The excitement of molecular genetics, and Schimke's tolerance for eclectic approaches, provided a stimulating research environment. However, Roos took himself to the library to consider career options. An interest in host–pathogen interactions drew him to consider parasitology. *Plasmodium* seemed the worthiest target, but at the time, Roos remembers, "it was relatively inaccessible in experimental terms. You couldn't even grow many of these bugs." There was little genetics and virtually no molecular genetics—even engineering *Plasmodium* DNA into stable clones was difficult.

Further reading led him to Elmer Pfefferkorn, a Dartmouth microbiologist who was making breakthroughs in the culture and genetic manipulation of a related human parasite, *T. gondii*. With the blessing of Schimke and Stanford parasitologist John Boothroyd, Roos went home to Hanover to do "a two-week postdoc" with Pfefferkorn. That was the start of years of work that led Roos to develop a robust genetic transfection system for *Toxoplasma.* This would be a model later adapted by others for *Plasmodium*. Today *Plasmodium* remains Roos's primary interest, but "Toxo" provides an experimental model, he says, much as *Drosophila* is used in development biology research.

His Great Good Fortune

In 1989, Roos took up his first and so far only faculty appointment at Penn. He didn't publish a major report on *Toxoplasma* until 1993. "In retrospect, I can see that I was tremendously lucky to find colleagues willing to give me a job," Roos believes. Then he was fortunate to persuade the National Institutes of Health to provide funding for work that was still very much in its early stages. "I'm not sure that would be possible now, and it certainly wasn't a good idea then. Fortunately, things worked out okay."

"The great thing about science," adds Roos, "is that it is probably more tolerant of people who 'think different' than almost any other discipline." Today his lab is known for taking a variety of approaches to a wide range of problems. There, molecular cell biology, biochemistry, genetics, immunology, evolutionary genomics, and computational biology are brought to bear on projects ranging from the origin of eukaryotic organelles to the molecular dissection of parasite differentiation.

Roos's success in running such a diverse laboratory does not surprise David Sibley, who

studies *Toxoplasma* at Washington University in St. Louis. "David is one of those people who can move seamlessly between disciplines, contributing to all of them. I have a great deal of respect for his work." Sibley first met Roos when both were postdocs at Stanford. "My first impression was that he's very creative, very spontaneous, but a bit unstructured. I think David would agree with that," says Sibley. "I remember thinking, 'This guy is extremely bright, but how's he ever going to settle on one thing?' That's the remarkable thing about David. He hasn't settled on one thing, but he's had an important impact on many scientific areas." Nearly 20 years later, Roos remains grateful and a bit surprised to have made a career at Penn by never settling on any one thing.

Roos and his wife, Anurag Sagar, met as graduate students at Rockefeller. Seeking a career with more immediate impact on people's lives, Sagar eventually left science for work with Philadelphia's Center for Literacy, where she tries to stay in the classroom and out of administration. Their daughter, Ambika, has just started at Brown, where her passion for art, architecture, and design competes with interests in international affairs—and maybe even science.

An international perspective comes naturally to the family. Roos vividly remembers living in The Netherlands as a child, while his father was on sabbatical. Sagar is originally from India. When family schedules coincide, they have been able to combine trips on behalf of WHO and other international organizations with travel in Mexico, Cameroon, Uganda, India, Japan, Australia, and elsewhere. In July, Roos and his family hope to sneak in some sightseeing amid Roos's commitments to the ASCB workshop in Tanzania.

Roos's willingness to take his expertise on the road should qualify him as a world science hero, according to Rob Ridley. Ridley is director of the WHO's Special Program for Research and Training in Tropical Diseases based in Geneva. Roos has tirelessly promoted online databases, distributed software tools, and run workshops to engage scientists from the underdeveloped world in global biomedical research, says Ridley. "But David doesn't overreach himself," Ridley adds. "He knows where his expertise lies. He's happy to pass things on. He's not one of those people who keeps hold of things and doesn't let go. He's a facilitator as well as an educator and a researcher." ■

—John Fleischman

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