All Systems Go

Alan Aderem earned his PhD while under house arrest for protesting apartheid in South Africa. His early political involvement has guided his scientific focus, encouraging fellow systems biologists to study immunology and infectious diseases.

By Anna Azvolinsky | December 1, 2014

ALAN ADEREM
President, Seattle BioMed
Professor of immunology and medicine, University of Washington Cofounder, Institute for Systems Biology, Seattle, Washington
COURTESY OF SEATTLE BIOMED

Born and raised in South Africa during the apartheid era (1948–1994), Alan Aderem became increasingly politically active—an underground involvement that put his science career in jeopardy. "I didn't know what the future would hold. I was regularly being arrested. There was conscription for white males, and I knew I was going to refuse to go, so all that uncertainty made me not really think ahead too far about my science."

Aderem experienced apartheid firsthand. "I remember very well that there could be 100 blacks waiting in line and as a little white kid walking into a store, they would serve me first. I had a black woman who looked after me that I considered a second mother, and I couldn't figure out why she was a second-class citizen. That stuff bothered me and drove me to politics," he says. By the end of high school, Aderem was participating in student protests—and getting arrested for it. At university, together with friends, Aderem started a workers' advice program that evolved into a black trade union. Aderem also edited a community newspaper called *Phambili*, which was circulated within Cape Town's black townships.

At age 23, Aderem was banned from leaving his district and placed under five-year house arrest for his antiapartheid activities. "I decided to pursue a PhD in biophysics, since I could do the computational analyses at home. It took me two and a half years total to finish because I had real motivation to get it done—I didn't know what

went on to study the immune system's response to pathogens, and later, as director of the Institute for Systems Biology in Seattle, Washington, to drive the merger between computational science and biology.

Here, Aderem discusses how exile from South Africa led him to study diseases such as malaria, tuberculosis, and HIV; why all of his experiments in graduate school were on the millisecond time scale; and how he helped launch the world's first systems-biology institute.

repressive measures would come next." Aderem

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Aderem's Affinities

Family inspiration. Aderem shadowed his mother, a physician who served the black community in the countryside of apartheid South Africa. "She was very engaged, and I understood the issues of global health at an early age through direct experience, thanks to her. I remember going with her to attend to someone with tuberculosis. The person was coughing up volumes blood and that was very impressive to a young kid."

Rigor required. Inspired by his surfing and diving hobbies, Aderem pursued a degree in marine biology at the University of Cape Town, but soon found that his project on kelp beds, which included measuring their growth, was not scientifically rigorous enough for him. After three years, Aderem switched to biochemistry and microbiology.

House arrest–inspired research. "It was ultimately the community organization—the newspaper editing and being a trade unionist—that led to my banning and house arrest. The police didn't really care about students running around with placards, but the last thing they wanted was an organization of the black labor force. I was not allowed to leave my house except between 9 a.m. and 4 p.m. on a few weekdays and not at all on weekends. I also couldn't communicate with anyone else who was under house arrest, teach, publish, or enter educational institutions."

Having few options for continuing his scientific education, Aderem decided a PhD in biophysics would be most practical, since experiments did not take much time, and data analysis could be done at home. He chose an advisor, Mervyn Berman, who was open-minded and who had a broad interest in biology, medicine, and technology. Amnesty International spotlighted Aderem as a prisoner of conscience, which resulted in pressure from an international group of scientists to allow him to pursue his PhD. This resulted in Aderem's gaining permission to access his university laboratory between 10 a.m. and 3 p.m. on some weekdays; while there he was permitted to interact only with one senior postdoc and his advisor.

Fourteen seconds of experiments. Because of the time restrictions, Aderem studied energy transduction in the sarcoplasmic reticulum—physiological events with millisecond time courses. He examined the mechanism of ATP hydrolysis and synthesis, driven by calcium transport. "Adding up all of the time courses I did, it was a total of about 14 seconds!" he says. His results contradicted some aspects of the chemiosmotic theory, and the paper was initially rejected by a number of journals. Aderem approached Paul Boyer, a prominent researcher in the energy transduction field and a future Nobel laureate, who agreed with Aderem's findings. Boyer sent the paper to *PNAS* and subsequently became Aderem's external PhD advisor.

Aderem Abounds

Science in exile. After he received his PhD in 1979, politics still occupied most of Aderem's time. "I had been recruited to the African National Congress and was active in the underground. A close friend and colleague, who was also a union activist, died in police custody, and I was advised to leave South Africa. I had no money or resources, but decided that I wanted congruence in my life, to balance my politics and

science.” Influenced by the diseases of poverty he witnessed in Africa, Aderem decided to study the immune response to infectious diseases. He was accepted into Zanvil Cohn’s laboratory at Rockefeller University in New York City and left South Africa illegally, traveling to London, where he spent almost a year waiting for the United Nations to grant him refugee travel papers. “My passport had been confiscated very early on.”

New (York) opportunity. Aderem arrived at Rockefeller in 1982 wanting to study parasitic protozoans, but Cohn’s lab did not work on malaria at that time. “Zan gave me a really great piece of advice from the start. He said, ‘Pathogens come and go—don’t focus on a specific pathogen, rather, study the host response.’ I agreed, and the immune response to infectious diseases has been my focus ever since.”

Host defenses. Aderem studied signal transduction in macro-phages, working out how bacterial lipopolysaccharides (LPSs)—the major surface component of gram-negative bacteria—regulate the production of arachidonic acid metabolites in these cells. These bioactive lipids play a critical role in the activation and resolution of inflammatory responses. The discoveries led to additional findings, including the mechanism by which LPSs prime macrophages for enhanced responses, setting up a cascade that allows innate immune cells to react more quickly and effectively when subsequently confronted with a pathogen.

A lab of his own. In 1985, Aderem became a faculty member at Rockefeller. With a growing group of postdocs and students, he was able to expand his exploration of signal transduction in macrophages. This led to the discovery of the importance of protein kinase C (PKC) pathways in phagocytosis and inflammation; the identification and characterization of a number of PKC substrates, including the MARCKS and MacMARCKS family of proteins; and protein myristoylation, a novel posttranslational modification. His lab showed that the MARCKS family of proteins regulates actin structure in a PKC- and calmodulin-dependent manner, and gene-deletion studies demonstrated a role for these proteins in adhesion, motility, membrane traffic, and the formation of the neural tube. The Aderem laboratory also characterized phagocytosis mediated by a variety of different phagocytic receptors at a molecular, cell biological, and immunological level. By 1991 Aderem was head of the Laboratory of Signal Transduction at Rockefeller, and he was beginning to think about the large-scale characterization of phagocytosis. This led his lab to generate 800 monoclonal antibodies to phagosomal proteins and to set the stage for his plunge into systems biology.

Going West. Aderem ran into Lee Hood in 1995, and the two realized that they had both been thinking about a similar concept—one that would become the field of systems biology. “The genome had been sequenced, and the question was, ‘What were we going to do with that information?’ Coming from biophysics, I wanted to marry biology, technology, and computation to do large-scale science.” Hood was already at the University of Washington in Seattle, and Aderem moved to the school’s department of immunology in 1996, seeing the change as a springboard to starting a systems-biology institute. “Seattle felt like a place where people felt as if they could change the world, with lots of experts in computation and informatics. Everything made sense.”

Aderem Accelerates

All systems go. Aderem and Hood, along with Ruedi Aebersold, wanted to establish the institute at the University of Washington, but there were too many complications, according to Aderem. So, in 2000, the three founded the Institute for Systems Biology (ISB)—the first such institution anywhere in the world. “The goal of the institute for me was to move from the single-gene paradigm to a holistic view of cells and organisms,” says Aderem. He also wanted to move toward vaccine design for devastating diseases such as tuberculosis, malaria, and HIV/AIDS. “I thought the predictive power of systems biology would enable rational vaccine design.” All three ISB founders kept their affiliations with the University of Washington, and Aderem continues to teach there.

Toward systems biology of the innate immune system. Aderem’s lab at the University of Washington had demonstrated that Toll-like receptors on macrophages are able to sample the contents of a phagosome, distinguishing between engulfed pathogens. The lab then identified some of the substrates of these receptors, including flagellin—the main component of bacterial flagella. It turned out

that flagellin was also detected by NLRC4, an intracellular pattern recognition receptor. "We were beginning to elucidate the barcodes on these bugs that are recognized by the immune cells, and there are lots of them, and cocktails of them. This was a systems-biology problem—to uncover the crosstalk among these receptors and ligands." In 2006, Aderem and colleagues demonstrated the utility of this approach, identifying a transcription factor that regulates Toll-like receptor inflammatory responses.

Another move. "When we started the ISB I had always intended to use systems biology to understand diseases that plague the developing world and to develop drugs, diagnostics, and vaccines, while Lee wanted to do preventive, personalized medicine. We could not do both under one roof because the institute would get too big. Seattle BioMed is a global infectious-disease research institute, founded in 1976 by Ken Stuart, that studies malaria, HIV, and neglected diseases. It had a terrific faculty, biocontainment labs, and the infrastructure required for cutting-edge global infectious-disease research. It is one of four places in the world that does live-malaria vaccination challenges." Aderem's lab, along with about 50 other scientists, moved to Seattle BioMed in 2011, while the ISB moved to a nearby building, allowing for continued collaborations.

Back to his roots. Aderem has maintained his connections to South Africa. When the Mandela government was elected, he was asked to chair a parliamentary commission on the transformation of the South African Medical Research Council. In 2009, the Howard Hughes Medical Institute, together with the University of KwaZulu-Natal, established K-RITH, a basic-science research institute in Durban, South Africa. According to Aderem, its goal is to make discoveries in the heart of the tuberculosis and HIV epidemics that will drive innovation to control these deadly diseases. Aderem has served as chairman of the board of directors of K-RITH since its inception.

Aderem Articulates

No boundaries. Despite the restrictions imposed on him as a young activist by the South African government, Aderem says that in his formative years as a young scientist, there were no boundaries. "Because the scientific community [in South Africa] was so small, everyone interacted with each other. Everyone was forced out of his or her comfort zone. You were trained to follow the question, and if you needed a technology, you built it. If you didn't understand a concept, you learned it. This broad training was very helpful for my thinking about systems biology."

The detritus of biology. "What fascinated me when we started the ISB was that I thought that biologists would have a difficult time with computation, and that mathematicians and physicists would have an easy time with biology. The opposite was true. The physicists had a difficult time dealing with the detritus of evolution."

To each his own. Aderem's oldest daughter is a playwright and works for an NGO that constructs wells to provide clean drinking water in resource-poor countries. His son is studying psychology, and his youngest daughter is working as an au pair in London. All are politically active. Aderem says that he never had expectations for his children to follow him and his wife, Kathy Barker—also a scientist—into science. "I want them to be happy. I really believe that everyone should do what makes them happy, if they are lucky enough."

Greatest Hits

- Identified protein myristoylation as a critical posttranslational modification in regulating inflammation; also identified the molecular mechanisms underlying reversible membrane association of myristoylated proteins.
- Identified and characterized the MARCKS family of protein kinase C substrates and demonstrated their involvement in phagocytosis, motility, membrane traffic, cell polarization, and development.
- Demonstrated how Toll-like receptors in the mammalian immune system distinguish between different pathogens.
- Identified TLR5 as the extracellular flagellin receptor.
- Used systems-biology approaches to identify signaling and transcriptional regulatory networks underlying inflammation.

- Analyzed genes that underlie the immune response in humans.
- Identified lipid networks that mediate the induction and resolution of inflammation during mouse and human influenza infection.
- Cofounder and director of ISB, the first systems biology–focused institute in the world.
- President of Seattle BioMed, the largest freestanding infectious disease research institute in the U.S.

Editor's Note: Alan Aderem would like to clarify that while the millisecond energy-transduction time courses he measured for his thesis totaled only about 14 seconds, "ultimately all the experiments in my thesis took a few hours!"

Tags

tuberculosis, systems biology, profile, phagocytosis, myristoylation, MARKS proteins, malaria, MacMARKS, innate immune system, infectious disease, immunology, HIV and bacterial lipopolysaccharides

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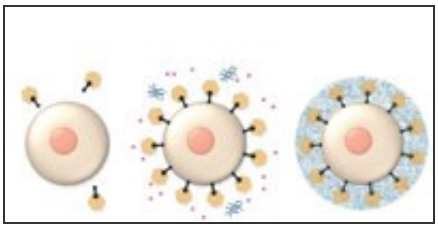

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