Ron Vale

Then a new Japanese postdoc, Gohta Goshima, arrived at the University of California, San Francisco (UCSF), lab of Ron Vale in 2002, expecting to join a motor protein outfit. After all, Vale was known for his role in the discovery of kinesin, the plus-end-oriented molecular motor that strolls along microtubules, towing intracellular cargoes to their destinations. Goshima had been drawn to Vale after hearing him lecture in Japan (and in Japanese) on motor proteins, including the growing superfamily of kinesins. In San Francisco, Goshima joined Vale's ambitious biophysical group exploring molecular motors, microtubules, and actin in the cell cycle. But others in the Vale lab group were looking at mRNA localization, and another small cluster was investigating signal transduction in the immune system. Goshima found all this "wide view" science under one lab roof exciting if a little bewildering. The link, of course, was Vale, who was able to follow it all. Goshima grew to enjoy the lab's experimental diversity, even as his own work homed in on augmin. Augmin is a protein complex Goshima discovered that beefs up microtubule nucleation sites in the mitotic spindle.

Vale's research lab was only part of his wide interests. There was Micro-Manager, the open source software that Vale developed together with Nico Stuurman and Nenad Amodaj to control modern robotic microscopes and cameras. There was the Microscopy4Kids website that Vale started to show teachers how a low-cost digital microscope could bring excitement for science into elementary and middle school classrooms. There was Vale's involvement with the biotech company that he co-founded and still advises, Cytokinetics. And after a sabbatical in Bangalore, Vale returned determined to stoke the bioscience revolution in India. How? By founding and organizing an international course in microscopy (the Bangalore Microscopy Course) and meetings devoted to mentoring Indian postdocs and junior faculty (the Young Investigator Meeting), and by setting up a website that serves as a central portal for information and networking on Indian biology (IndiaBioscience.org).

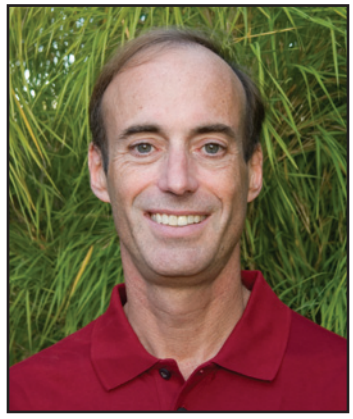
Then there were the summers when Vale, along with family and a rotating cast of UCSF lab members, decamped for the Marine Biology Laboratory (MBL) in Woods Hole, MA. Vale—ASCB President-Elect—and ASCB Past President Tim Mitchison from Harvard Medical School completely revamped the MBL's venerable Physiology Course. They turned it into an innovative training group and research center that combined cell biology with physical science and computational approaches.

Vale was known for his role in the discovery of kinesin, the plus-end-oriented molecular motor that strolls along microtubules, towing intracellular cargoes to their destinations.

Green Screen Science

Goshima saw the start of Vale's iBioSeminars before he returned to Japan in 2007 to join the faculty at Nagoya University. The seminars grew out of a Vale plan to put world-class talks on the Web by filming them in a standardized "green screen" video format. That's what weather forecasters use. Working with the Howard Hughes Medical Institute (HHMI), ASCB, and UCSF, Vale has since expanded his video efforts, adding iBioMagazine. The educational outreach channel features shorter video pieces on the human side of being a scientist.

Goshima notes Vale's unwavering commitment to family—his wife, cell biologist Karen Dell, and children, Christopher, 16, and Sophie, 14. Dell was Reviews Editor at the *Journal of Cell Biology* for a decade and now edits talks for iBioSeminars. Goshima mentions Vale's love for sabbaticals—he spent a year sabbatical with Toshio Yanagida in Japan, eight months with Satyajit Mayor in India, and three months with Ari Helenius in Switzerland. His family often travels with him for work or vacation. (Vale's children currently report that their passports have been stamped in 25 countries.)



Ron Vale

Finally Goshima recalls Vale's other great passion—the San Francisco Giants. Family, lab, and baseball seemed to collide on the afternoon that a major paper they'd submitted to a major journal came back rejected. Goshima was distraught. Vale had tickets and kids. "Why don't you come with us?" Vale suggested. At the ballpark, Vale waited for lulls in the action to glance over the rejected paper and toss out suggestions. "I don't even remember how the game went, but somehow by the end I had got rid of the bad feelings," Goshima says.

"I remember someone asking Ron, 'How are you managing so many things?' His answer was, 'I'm not. They manage themselves.'"Goshima reports.

Vale has a different take on his managerial style. "I just juggle, keep my eye on the ball, and hope for the best."

Chaos Theory

Still, the sheer scale of Vale's scientific portfolio long ago convinced Dyche Mullins, a UCSF colleague and Vale's successor as a co-director of the MBL Physiology Course, that Ron Vale was one of the "half a dozen people in each generation without whom the world would descend into utter chaos." Mullins mentions Vale's ever-lengthening publications list, his manifold international activities, and his election as President of the ASCB as proof. "He has organizational skills that I've never seen in anyone else," says Mullins. "Ron is never content to run his lab and create great science. He's always creating some new infrastructure and some new creative enterprise. And now he's taking over as ASCB President."

"He has organizational skills that I've never seen in anyone else," says Dyche Mullins. "Ron is never content to run his lab and create great science. He's always creating some new infrastructure and some new creative enterprise."

Ron Vale is from Hollywood, being both a graduate of Hollywood High School and the son of the Hollywood screenwriter and novelist Eugene Vale. His mother, Evelyn Wahle, had been an actress with Broadway credits, yet his parents never pushed a show business career for their only child. "They wanted to expose me to lots of things," Vale recalls, "and they were always fans of science. My parents, neither of whom finished college, were completely self-taught. My father knew more about history, literature, and religion than virtually anyone I have known. My mother was similar. She liked to take me to museums, and when my dad enrolled in an astronomy class at UCLA, he took me along. He thought I might be interested."

Vale was interested in many things, but biology moved to the fore in high school when he interned in a University of California, Los Angeles, lab. He chose the University of California, Santa Barbara (UCSB), over Stanford for the chance to work in UCSB's College of Creative Studies with Beatrice Sweeney, a pioneer in studying circadian rhythms using dinoflagellates. "She was an amazing scientist and a dynamic woman who was a real ball of fire in the laboratory," Vale remembers.

Vale took some of that spirit to Stanford Medical School when he started in the MD/PhD program there. For his PhD research, he was drawn to the neuroscience lab of Eric Shooter and experiments on nerve growth factor and its receptor ligands. On the floor below the Shooter lab, Stanford's Jim Spudich, an ASCB past president, and his sabbatical visitor from the University of Connecticut Health Center, Mike Sheetz, had just made an experimental breakthrough on one of the oldest logistics problems in muscle motility. Vale thought the work on muscle might be applied to neurons. Neurons are the longest cells in the human body, yet no one in 1983 had any idea of how neurons handled the internal transport of proteins and organelles over such distances. Motor proteins seemed the likely answer and myosin, the best-known candidate. Sheetz and Spudich reconstructed in vitro the movement on purified actin of myosin-coated plastic beads. Vale wondered if the beads could track non-muscle myosin movement inside intact neurons. Sheetz encouraged him to try.

Squid to Go

The first step was to order squid, *Loligo pealei*, a creature beloved in neuroscience because of its outsize axon. Vale filed a squid request with Stanford's Hopkins Marine Station but the squid were just not running that spring. (It would turn out to be an El Niño year in the eastern Pacific.) Hurriedly, Vale and Sheetz transferred their experiment eastward to MBL, where fishing reports were more favorable. Vale flew east, loaded up a rusty Volkswagen Beetle with lab supplies from the Sheetz lab at Storrs, and drove to Woods Hole with a windsurfing board lashed to the roof.

They set up operations in cooperation with Tom Reese and Bruce Schnapp, who had an established electron microscopy (EM) laboratory at MBL. Schnapp also had an early version of a video enhanced-contrast microscope developed from the independent work at Woods Hole by Bob Allen and Shinya Inoue. The squid neuron was the star of many of these early microscope videos. One by Allen, S.J. Lasek, and Scott Brady showed small membrane

organelles moving at fast speeds inside the cell. Hypothesizing that actin might be involved, Sheetz and Vale hoped to reconstitute that system with myosin-coated beads injected into a squid axon. Nothing happened. In the videos, the myosin-coated beads sat there inert. More perplexingly, in one control experiment a few beads without the myosin coating were seen moving about. It was a back-to-square-one moment. Indeed, later that summer, Schnapp, Reese, Sheetz, and Vale found that the filaments supporting long-distance transport in the axon were microtubules, not actin.

Vale returned to Woods Hole the following summer with a new strategy to take apart the squid axon biochemically. Vale assembled an in vitro test system, mixing microtubules extracted from cow brain with membrane organelles and purified cytosol from squid neurons. With added ATP, the system sprang to life, the organelles chugging along the microtubules like freight cars on a model railroad track. As a control, Vale ran the system without the organelle cargoes—just cow microtubules, squid neuron cytosol, and ATP. To his astonishment, the microtubule segments became the cargo, being shunted across the bare glass substrate by some kind of engine that was stuck to the surface of the glass coverslip. It was two o'clock in the morning when Vale witnessed this result and suddenly realized that here was an abundant, free-floating motor protein with an affinity for microtubules and ability to attach itself to surfaces.

Such a motor would explain the baffling result in his first experiment where only the bare plastic beads moved along the axons. Indeed, the movement of plastic beads repeated beautifully when tested with neuronal cytosol. Something other than myosin moved those beads, something that could anchor itself to bare plastic, to glass, and to organelles. But what was the factor? Vale asked Stanford to defer his year of medical "clerkships" needed for his MD so that he could spend the winter of 1985 in Woods Hole.

The Winter of Content

The village in winter was another planet. The summer crowds were gone, the smart restaurants and boutiques closed, the village bar reclaimed by commercial fishermen. The weather closed in. Most of the MBL campus was boarded up, but working alone in a corner of the Reese lab Vale made steady progress. "It was the scientific experience of a lifetime to be chasing down this problem in this almost 19th-century setting of Woods Hole in winter," Vale recalls. "You could just dig into the problem, waking up every morning and deciding what's the next thing to do, without any type of distraction."

It was two o'clock in the morning when Vale witnessed this result and suddenly realized that here was an abundant, free-floating motor protein with an affinity for microtubules and ability to attach itself to surfaces.

The protein was kinesin, the unidirectional molecular motor that walks step-wise toward the plus ends of microtubules. Today we know of 45 varieties of kinesins in humans alone, says Vale. They perform specialized functions in all realms of cellular behavior. Vale has remained at the forefront of motor protein biophysics, developing the first single molecule assay, solving the first crystal structure, and building an increasingly detailed structural picture of kinesin motility. Now, most of his lab's biophysical effort has shifted toward dynein, another microtubule motor protein.

The discovery of a whole new class of motor proteins launched Vale's academic career. He joined UCSF in 1986, became a full professor in 1994, and was named an HHMI investigator in 1999. But Vale says that hoping for a Eureka moment is not enough to sustain a research career. "You have to enjoy science and celebrate the small victories. Otherwise, the profession is just not tenable. You have to enjoy going into the lab every day with the hope of just getting the problem you're working on that one step forward."

The next step forward for Vale is the presidency of the ASCB in 2012. ■

—John Fleischman

"You have to enjoy science and celebrate the small victories. Otherwise, the profession is just not tenable. You have to enjoy going into the lab every day with the hope of just getting the problem you're working on that one step forward."