Amy L. Davidson
1958–2013

Jue Chen

On 2 April 2013, Amy L. Davidson lost her battle against thyroid cancer. The membrane transport field has lost one of its best biochemists and a superb mechanistic thinker. Amy devoted her career to uncovering the secrets of the maltose transporter, a prototype of a large protein family called ATP-binding cassette (ABC) transporters.

Amy was an unusual scientist. She was always ahead of the pack. With a PhD in nutritional biochemistry from Cornell University, Amy joined Hiroshi Nikaido's laboratory at the University of California–Berkeley in 1986 to study how *Escherichia coli* takes up nutrients. At that time, the field of ABC transporters—a membrane protein family of 2,000 members—was in its infancy. It was known that maltose is imported into *E. coli* by an active transport system. Based on the sequence of the transporter, ATP hydrolysis was suspected to be the energy source for this process, but experimental evidence was lacking. Amy took a daring approach to obtain the answer; she simultaneously overproduced the three protein components (MalF, MalG and MalK), purified the transporter complex and reconstituted the transport activity in proteoliposomes. Using this system, she demonstrated unambiguously that ATP hydrolysis was responsible for energizing the system. The presence of two ATPase subunits is now recognized as a defining feature of ABC transporters, and it was Amy who first determined the subunit stoichiometry. She also discovered that the periplasmic maltose-binding protein (MBP) regulates the transporter's ATPase activity. This was a remarkable discovery because the ATPase component is located inside the cell membrane, but MBP is located outside. Amy's result meant that MBP binding must transmit a signal across the membrane to stimulate ATPase activity. It is now established that the presence of substrate or substrate-binding protein is the 'on switch' for ABC transporters, a fundamental mechanism for cells to avoid futile ATP hydrolysis in the absence of the substrate.

In 1992, Amy moved to the Baylor College of Medicine, where, as a junior faculty member with a small laboratory, she undertook the ambitious goal of elucidating precisely how ATP hydrolysis catalyzes active transport. Her grant application was criticized as "attempting to seek details of mechanism that are most likely unattainable." Undeterred, Amy pressed toward her goal. She discovered that ATP is hydrolyzed with positive cooperativity, which led her to believe that the two ATP-binding sites must interact with each other. She then unmasked the nature of this interaction using a clever chemical trick of vanadate to show that the γ-phosphate of ATP lies along the MalK interface, bound by the Walker A motif of one subunit and the ABC signature motif of the second subunit. This work settled a long-standing controversy over the correct architecture of the ATPase subunits.

It was clear to Amy early on that crystal structures would be essential to obtaining a more complete understanding of mechanism. Having already established methods to produce large quantities of functional transporter, she convinced Florante Quiocho, my postdoctoral mentor at Baylor, to pursue crystallographic studies of the maltose transporter. That was the beginning of my collaboration with Amy, one of the most fortunate events of my scientific career. I knew very little about membrane proteins at the time, so I studied Amy's publications carefully and thought it would be a good idea for crystallization to stabilize the transporter in the vanadate-inhibited state. But I soon ran into a problem: after incubation with vanadate, a 'contaminating' protein always purified together with the transporter. Upon explaining this observation to Amy, she immediately asked whether the contaminant was MBP. Amy was correct. Based on the biochemical properties of the trapped complex, Amy deduced a conceptual model for how binding protein–dependent ABC transporters function as molecular pumps. This early model, published in 2001, turned out to be amazingly accurate.

In 2002, I began my own laboratory at Purdue University, with the aim of determining crystal structures of the maltose transporter. Happily for our collaboration, Amy and her family also moved to Indiana, where she joined the Purdue faculty. Amy and I shared the greatest joy, working side-by-side to put the pieces of the puzzle together. Ideas, reagents, students and postdoctoral fellows constantly flew between our laboratories. One step at a time, we built an atomic-level description of the entire transport cycle. The results have been illustrated in multiple textbooks as an example of how nature so elegantly uses the chemical energy of ATP hydrolysis to perform work—solute transport against a chemical gradient. Our 14 years of collaboration were a period of joy on both intellectual and emotional levels. I have been privileged to work with such an intelligent scientist, a sincere friend and a truly kind human being.

Amy was a mentor not only to her own students and postdoctoral fellows but also to the larger scientific community. She helped to organize several international meetings and served on the editorial board of the *Journal of Biological Chemistry* for years. Through collaborations and personal contacts and by acting as an anonymous reviewer and editor, Amy helped numerous scientists in the field. Her influence in science goes well beyond her own laboratory and beyond her own lifetime. Her scientific contributions will be honored in June 2013 at a Gordon Research Conference in South Hadley, Massachusetts, and in March 2014 at the ABC Proteins meeting in Innsbruck, Austria. We will miss all of the warmth, kindness and wisdom of Amy Davidson. ■

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