Profile of Mark E. Davis

In 1995, California Institute of Technology (Pasadena, CA) chemical engineering Professor Mark E. Davis faced an issue that would dramatically alter his primary area of research. His response to that challenge is sure to have lasting effects on drug design and the field of nanomedicine.

"Unfortunately, my wife had breast cancer," he says somberly. An accomplished flautist, Mary Davis was only 36 when doctors diagnosed the disease and put her on aggressive chemotherapy. The painful drug regimen caused weakness, hair loss, nausea, and wrecked her immune system. The cure, it seemed, was almost worse than the disease. "I lived in the hospital with her for several months," says Davis. "She was in isolation for a long time."

From this ordeal, Davis and his wife knew that someone had to develop better treatments. She urged him to use the wealth of resources and the talents at California Institute of Technology to create specific therapeutics with fewer side effects. "I really got to see this whole cancer area: the issues, everything," he says. During the days he spent in his wife's hospital room at the City of Hope Cancer Center (Duarte, CA), Davis read literature on carcinogenesis and cancer therapies, analyzing how he could best apply his engineering expertise to help with cancer treatment. "I was never afraid to go out of my area to learn new stuff, even as an undergraduate," he reveals.

Davis' background as a chemical engineer with a history of designing catalytic materials, which are substances that speed up chemical reactions without being consumed in the process, gave him the necessary tools. Drug discovery and development is "in a classical sense, a big systems problem, and that's part of what engineering does," he says. "A therapeutic, when you're going to stick it in someone's body, has to find the right spot; it has to get into the cell, recognize that it's in the cell, and perform a function on the target. You also have to be able to manufacture it and make it [of suitable] quality to go into humans."

After nearly a year, his wife's cancer went into remission. She is fine today and continues to play the flute with a number of groups in California. This personal encounter with the disease, however, propelled Davis into the field of nanotherapeutics. "There's been a long history of people designing molecules for therapies, but the idea of building materials from a molecular perspective was not the norm in medicine when we began," he explains.

Mark E. Davis enjoying one of his favorite hobbies. Image courtesy of Jane Zanes.

In his Inaugural Article in the April 3, 2007 issue of PNAS (1), Davis, who was elected to the National Academy of Sciences (NAS) in 2006, demonstrates the safety of using targeted nanoparticles to deliver silencing RNA (siRNA)—short, double-stranded RNA molecules that interfere with the expression of specific genes, into non-human primates. The technology is so promising that one of Davis' companies, Calando Pharmaceuticals (Pasadena, CA), is about to begin the first clinical trial in humans, using this technique for cancer. The company is named after a musical notation that tells a performer to slowly fade into silence, analogous to the way that siRNA shuts off a cancerous gene.

From Pennsylvania to Kentucky

For nearly 30 years, Davis has been exploring core questions of the physical and biological sciences using the tools of synthetic chemistry and analytical engineering. He now resides in Pasadena, CA, but Davis was born in 1955 in a far less sunny climate—Ellwood City, PA—on the Ohio border. He was raised a few hours north in industrial Erie, PA.

Although his parents were teachers of history and English, the sciences held special interest for Davis from a young age. He credits the instruction he received at McDowell High School in Erie with setting the foundation for his career as a chemical engineer. "My high school was pretty advanced, and the teachers I had in both chemistry and calculus were fantastic and made the subjects enjoyable."

An avid runner from middle school on, Davis strode to the University of Kentucky (Lexington, KY) on a track and field scholarship and would letter in the sport. Of the many awards that he has received, one of the first was from the university for being the top scholar-athlete among all students in varsity sports. Today, the Warren and Katharine Schlinger Professor of Chemical Engineering at California Institute of Technology continues to run, competing in 100- and 200-meter events in master's track meets. Living close to the Pacific Ocean, he also scuba dives and travels around the world photographing sharks, rays, and whatever else he encounters underwater.

Odd One Out

Davis first discovered chemical engineering at Kentucky. "When I got onto campus, I heard that chemical engineering was a combination of both chemistry and mathematics, and I thought, 'Hey, this is really pretty interesting.'"

In college, however, Davis was also captivated by the biological sciences and briefly considered a career in medicine. "The good news was that at Kentucky, people in the [chemical engineering] department were very helpful and gave me a lot of flexibility to try other things. They said 'if this is what you want to explore—then go do it.'" He would trek halfway across campus to the medical school to take classes. "I was always the only one in the class not in the mainstream. When I'd take these classes, I'd be the odd one out, especially since I was an undergraduate."

Davis undertook a research project in neurophysiology before deciding to get his masters in chemical engineering. With William L. Conger, currently a professor emeritus of chemical engineering at Kentucky, he studied the entropy and efficiency of a thermochemical cycle that produces hydrogen. The relevance of this research continues today, as the generation of hydrogen from water is finding a renewed interest in the development of alternative energy sources. This work led to the completion of Davis' masters degree, also in chemical engineering, and to the publication of his first paper.

During his time in Lexington, Davis began to take note of the fields within chemical engineering that truly interested him. Influenced by his stint in the biological sciences, catalysis caught his eye. "I became intrigued by enzymes and how they can accomplish chemical reactions so efficiently, what chemical engineers would classically call 'the reac-

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This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 5715 in issue 14 of volume 104.

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tion engineering' side of things." For his doctorate, Davis chose to work with John Yamanis, who he describes as "a very good young faculty member whose area was kinetics and catalysis." Davis was Yamanis' first doctoral student, and they collaborated on six papers. The first came from Davis' dissertation and described a new reactor configuration, the annular bed reactor. This configuration allows extremely hot, exothermic reactions, such as the methanation of carbon dioxide, to take place efficiently.

Molecular Engineering of Materials

Upon completing his doctorate in 1981, after eight years in Kentucky, Davis moved east to take a position as assistant professor of chemical engineering at Virginia Polytechnic Institute and State University (Blacksburg, VA). There, he met his wife Mary, who received her undergraduate degree and a master's of business administration from Virginia Tech.

In the shadow of the Blue Ridge Mountains, Davis began research that would change the field of catalysis and the direction of chemical engineering. "I was very interested in the chemical side [of engineering]," he emphasizes. "My thought was to bring the synthesis of highly functional materials from a molecular design perspective, the so-called molecular engineering of materials, into mainstream chemical engineering. Back when I started, it was a pretty radical change to go and do that."

The future of the field, Davis felt, was at the molecular level, and naturally occurring minerals called zeolites offered an attractive medium. Natural zeolites form from the confluence of volcanic rock, ash, and brackish water. Their crystallization can take many thousands of years and result in multicolored stones riddled with tiny, highly uniform, sieve-like pores. These pores allow for the precise and consistent filtration of impure materials such as crude oil or noxious gasses. Natural and manufactured zeolites are deployed widely in industrial and domestic processes, including catalytic cracking used in separating hydrocarbons in oil refineries, purifying water, and producing medical grade oxygen.

"When you look at zeolites, they are one of the most uniform materials we know of," Davis says. "I thought that they gave me the best shot at being able to manipulate at the molecular level and then have a macro-scale expression of that manipulation."

Throughout the 1980s and 1990s, Davis began numerous programs in materials synthesis and created several new classes of catalysts and molecular sieves. His group modified zeolites in every conceivable way, and in some ways that weren't conceivable before they did them. His first major success was stretching the standard zeolite pore size, which varied from 0.2 to 0.8 nanometers, to more than a nanometer. "People had predicted that this could exist, but no one had ever made one before. In fact, the barrier in this pore size had been around for centuries," Davis explains. A larger zeolite pore meant that larger molecules could be run through the sieves. Catalytic cracking, for example, could be done on heavier hydrocarbons, producing more gasoline per barrel of oil.

At a time when zeolites were commonly used as solid acids—materials that, as they sound, have acidic properties like liquid acids, but exist in solid states—Davis' group at Virginia Tech turned them into solid bases. "We always try to go the opposite direction of everybody else," he says contently. The group also immobilized organometallic complexes, chemical compounds containing bonds between carbon and metal ions, in thin liquid films onto solids. This technique, called supported aqueous phase catalysis, can be used for chiral drug synthesis on solid supports, a boon for the pharmaceutical industry. Chirality refers to the asymmetry of a molecule with respect to its mirror image. Certain drugs, like naproxen used to treat back pain, only have therapeutic effects in a specific configuration and must be precisely manufactured. The stakes are high; the ineffective configuration of naproxen has no analgesic effect and can cause liver damage.

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An Elite Group

Recognition for Davis' accomplishments began to quickly accumulate while he was teaching at Virginia Tech. In 1985, just four years after earning his doctorate, the National Science Foundation (NSF) awarded him the Presidential Young Investigator Award. That same year, the American Society of Engineering Education gave him the Dow Outstanding Young Faculty Award. Like his parents, Davis is a teacher at heart and feels that his most important contribution is "the people who I have had the pleasure of mentoring. Many of them have gone on to be highly successful professionals."

In 1990, Davis received the Alan T. Waterman Award, the federal government's preeminent scientific award that recognizes an outstanding researcher 35 years old or younger in any field of science or engineering supported by the NSF. The award citation acknowledged his pioneering work in the development of catalytic materials and in reaction engineering, stating that "each of these accomplishments opens up a new and potentially important area in catalytic science and technology and also has implications for separations technology and environmental control." Davis was the first engineer to receive the award.

He has also received what is perhaps the most prestigious honor for an engineer: induction into the National Academy of Engineering (NAE). In fact, Davis is in an elite group of distinguished engineers and scientists who have memberships in both the NAE and the National Academy of Sciences.

Caltech Catalysis

After a brief stint as a visiting professor at Stanford University (Palo Alto, CA) in 1990, Davis joined the California Institute of Technology faculty in 1991 and continued his work on catalysis and inorganic materials. His group gave zeolites the ability to function like organic substances by synthesizing organosilanes in the mineral's internal pore surfaces. Organosilanes are carbon-based molecules that have silicon atoms incorporated into the zeolite structure.

Returning to his initial intrigue with enzymatic catalysis, Davis began positioning organic functional groups in three-dimensional space on porous solids. "This goes all the way back to the early thinking of what an enzyme does," says Davis. "An enzyme has different chemical groups positioned in space in the active site. This research was our first movement into that area, and today we're still working on this positioning. We're just now getting spectacular catalytic behavior out of these types of materials."

The group has been working on a synthetic material that can mimic the ability of enzymes to orchestrate what chemists call a cooperative acid-base reaction. "If you take an acid and a base," Davis explains, "and put them into solution, the two neutralize each other and you get no reaction. An enzyme can put an acid and a base next to each other in the active site, far enough away that they can't touch each other, but not too far away that they can't work in concert. That's

really where we're focusing our catalytic efforts. [We're] getting to the point where we can make these functional groups cooperate with each other like you see in an enzymatic reaction."

Zeolites to Nanomedicines

While at Caltech, Davis' interests began to broaden. Colleagues encouraged him to give biomaterials a try because of his strong background in materials synthesis. He approached this field as in the past: he started at the molecular level. "Materials in medicine have [typically] been known materials created for other uses and then applied to medicine, what I call the bandage approach," explains Davis. "That is, one keeps adding more bandages to something to finally get it to work to some degree. Our approach was to start from the beginning and build new materials with the features and functions that you want for the desired medical application."

At the time, however, Davis wasn't sure what materials to study. Then, his wife was diagnosed with breast cancer. "I finally figured out where I wanted to go," he says.

Davis' group had little experience in rational drug design, which, unlike traditional design methods, relies on a knowledge of specific chemical responses in the body, not on trial and error. "We just started from zero," he remarks. With the assistance of California Institute of Technology faculty who helped with cell culture, they decided to work on finding a new way to deliver therapeutic drugs to specific sites.

They started with molecules called cyclodextrin-containing polymers. Cyclodextrins, cyclic chains of simple sugars derived from starch, offer a number of advantages from a therapeutic standpoint. "They are very biocompatible molecules, with a low toxicity," says Davis. "If you put them in humans, there's no immune response." Cyclodextrin polymers can also encapsulate anticancer agents like siRNA molecules, in effect caging them until the therapeutic enters a tumor. "The cyclodextrin part of it is very critical to making these things assemble and disassemble correctly to perform the kinds of functions we need."

Davis' team surmised that, ideally, they had to create particles that were ≈50 nanometers in size—large enough to carry a payload and not be filtered out by the kidneys like many drugs, but small enough to be swept through the bloodstream and penetrate tumors.

Davis' first success was loading a cyclodextrin-based nanoparticle with the anticancer drug camptothecin. He and his collaborators injected the compound into groups of mice, each with a different type of cancer: colorectal cancer, non-small-cell and small-cell lung cancers, pancreatic cancer, and breast cancer. The treatment worked. Cyclodextrin protected the cancer drug from the slightly alkaline environment of the animals' blood and prevented it from being secreted as waste. In addition, once inside cancer cells, which hungrily absorb nutrients and other materials from their surroundings and, therefore, take up drugs at higher rates than do healthy cells, the oligosaccharide dissolved, releasing its toxic payload and destroying the tumor. Davis helped bring this nanomedicine into phase I clinical trials with his company Insert Therapeutics (Pasadena, CA). This trial is currently proceeding, and one patient broke confidentiality to reveal that the only side effect was that some of his food tasted slightly funny—a far cry from losing one's appetite, hair, or immune system as with standard chemotherapies. Insert's phase I trial is almost over, and the company is preparing for phase II.

Davis' success with small molecule therapeutics encouraged him to load his cyclodextrin nanoparticles with other anticancer agents. In particular, he decided to work with substances that interfere with cancer cells' gene expression. "We heard about silencing RNA right at the beginning. The good fortune for us was that we had a lot of experience with nucleic acids already, and the system that we had worked with siRNA."

In a mouse model of metastatic Ewing's sarcoma, a rare cancer that afflicts bone and soft tissues, Davis and coworkers directed a siRNA-containing nanoparticle to cancer cells using a transferrin protein to target the therapeutic. The therapy effectively treated the disease with minimal side effects for the mice. His Inaugural Article takes these results one step further, demonstrating that the system is safe and effective in cynomolgus monkeys with an siRNA that is applicable to a wide range of cancers. Calando plans to use a similar siRNA nanoparticle in their phase I trial in humans.

Davis is optimistic that some of the therapeutics his companies are developing could be ready for the public within approximately five years, assuming the clinical trials continue to progress. Ultimately, he has his sights on an even more ambitious goal: "I would like to be able to create therapeutics that could be administered without affecting the day-to-day lives of patients, ones so safe that they could be given prophylactically. That is my dream."

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1. Heidel JD, Yu Z, Liu JY, Rele SM, Liang Y, Zeidan RK, Kornbrust DJ, Davis ME (2007) *Proc Natl Acad Sci USA* 104:5715–5721.
2. Davis ME, Conger WL (1980) *Int J Hydrogen Energy* **5**:475–485.
3. Davis ME, Fairweather G, Yamanis J (1981) *Can J Chem Eng* 59:497–500.
4. Davis ME, Saldarriaga C, Montes C, Garces J, Crowder C (1988) *Nature* 331:698.
5. Hathaway PE, Davis ME (1989) *J Catal* 116:263–278.
6. Arhancet JP, Davis ME, Merola JS, Hanson BE (1989) *Nature* 339:454–455.
7. Wan KT, Davis ME (1994) *Nature* 370:449–450.
8. Jones CW, Tsuji K, Davis ME (1998) *Nature* 393:52–54.
9. Katz A, Davis ME (2000) *Nature* 403:286–289.
10. Schluep T, Hwang SJ, Cheng J, Heidel JD, Bartlett DW, Davis ME (2006) *Clin Cancer Res* 12:1606–1614.
11. Hu-Lieskovan S, Heidel JD, Bartlett DW, Davis ME, Triche TJ (2005) *Cancer Res* 65:8984–8982.