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The Overman Influence

An accidental discovery in UCI Distinguished Professor Larry Overman’s lab in the 1970s helped define his research direction and legacy.

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Top: Professor Larry Overman stands in what used to be one of his labs in the UCI Department of Chemistry. Overman's labs closed their doors for good last August.

Bottom: A legacy in a photograph. Professor Larry Overman (left) poses with two of his former students: Professor Vy Dong (middle), who worked in Overman's lab as an undergraduate and is now a faculty member in the UCI Department of Chemistry, and Professor David MacMillan (right) of Princeton University, who was a Ph.D. student of Overman's in the 1990s, and who later was Dong's graduate advisor at UC Berkeley. Last year, MacMillan won the Nobel Prize in Chemistry, and this year came to UCI on May 24th to give a talk about his career and life in the wake of his

prize.

Picture Credit:
Lucas Van Wyk Joel

It was 1974, and Professor Larry Overman of the UCI Department of Chemistry was in his Rowland Hall lab on a Saturday when the accidental discovery happened. Overman was a new professor at UCI — the 13th professor hired in his department. He was so new that he was only mentoring two graduate student researchers at the time, and he knew that his own laboratory efforts would be essential to get his career up and running.

He was in his lab on a weekend, too, because he was simply curious about his experiment and what he might find, and he was excited to have what he describes as one of the best jobs on the planet.

“I think the job I have is the most fantastic job imaginable,” said Overman while sitting in his office on the fourth floor of Frederick Reines Hall at the UCI School of Physical Sciences. “You get to follow your interests and work with smart, interesting people.”

Overman’s lab closed its doors last August after fifty years. It’s a lab that started in Rowland Hall in what was originally a teaching lab, and it grew until it occupied the entire north wing of the fourth floor of Reines. The lab saw legions of chemists pass through its doors, many of whom went on to work in positions across the field of chemistry, from industry to academia and beyond.

It’s a story that started in northern Indiana in an industrial town called Hammond, which is where Overman grew up, and which is where he worked in the steel mills in the summertime to help pay for his tuition at Earlham College — a small liberal arts college in Richmond, Indiana. It was at Earlham that Overman first discovered his interest in chemistry, and it’s where he met his wife, Joanne. He went on to study at the University of Wisconsin, Madison for his Ph.D., and, after working as a postdoctoral researcher at Columbia University, he came to UCI in 1971.

Then, on that Saturday in 1974, the discovery happened.

“The first major discovery in my lab, which has become known as the Overman rearrangement, I made myself,” said Overman. “I remember the eureka moment

that Saturday morning. It was so obvious — we had a unique signature from one bit of data, and I knew immediately what had happened and realized the implications. That set in motion everything I've done subsequently."

The Overman rearrangement is a reaction that exchanges atoms in a molecule; it removes an oxygen atom and replaces it at a different site with a nitrogen atom.

It's a discovery perhaps best showcased by a poster hanging in the hallway right outside Overman's office. The poster shows the molecules used most in prescribed pharmaceutical drugs, and most are what chemists call "small molecule drugs." Almost all of them carry a nitrogen atom, so being able to easily replace an oxygen atom in a molecule with a nitrogen atom is, if you want to develop new drugs, a key tool.

The Overman rearrangement changes molecules, and it also changed the course of history for the people who came to work with Overman.

Many years later, in 1990, with his lab's reputation as a place where chemists worked to discover new chemical reactions and catalysts set, a young student from Glasgow, Scotland came to work with him as his Ph.D. student. That student was David MacMillan, who's now a professor at Princeton University and who last year won the Nobel Prize in Chemistry for developing reactions that promise to help make things like the development of pharmaceuticals much cheaper and, in the process, more affordable and sustainable.

"I'm from Scotland. So, Larry assumed I could play golf. So he said 'alright, let's go play golf,'" MacMillan said with a chuckle as he remembered what was like when he first got to UCI.

Out on the fairways MacMillan hit a ball where he didn't want it to go, so he pulled out another ball to try again from the same spot, a move golfers call a mulligan.

Overman wasn't amused.

"'What's the difference between a mulligan and just cheating? Why not just cheat, then?'" A grinning MacMillan recalled Overman saying.

That moment, MacMillan believes, captures Overman's essence. "Everything he does he does the correct way, and he holds himself to a great standard. And even when he plays golf, you have to do it, you have to do it right, you just have to do it

the right way.”

MacMillan’s old fume hood is in a lab in Reines that looks out on Rowland Hall. The hood is where MacMillan did a bulk of the work that earned him his Ph.D., and nowadays a printed picture of a Nobel Prize medal hangs above the hood. Back in 1990, though, all that hung over the hood were questions about how to start his career, and, true to form, Overman did things the right way; he encouraged MacMillan and told him that, sometimes, you just have to be “really, really determined” to get research success, MacMillan explained.

“He’s one of the most selfless, generous, professional human beings that you’ll ever meet in your life,” MacMillan said. “He is just so incredibly knowledgeable, and he brought out the best in people. He cared about getting everyone up to speed, and he did it because it was the right thing to do, which is who Larry Overman is.”

“There’s two types of groups,” MacMillan added. “There’s the one where everyone loves the boss, but the people don’t like each other. They fight amongst themselves. Or they really don’t like the boss, and the group loves each other because they’re all in the trenches together. Larry’s group is the only group I’ve ever seen in my life where they all love the boss, but they all loved each other. And I thought that was remarkable how he did that. I still don’t know how he did that.”

Another chemist to come out of Overman’s group is Vy Dong, who today is a professor in the UCI Department of Chemistry. Back in the late 90s, though, she was an undergraduate chemistry major at UCI working in Overman’s lab. Dong wanted to go to graduate school, and Overman suggested she go work with MacMillan, who at the time had just started as an assistant professor at UC Berkeley.

Overman had a good feeling about MacMillan’s prospects, but going to work with him would be a leap of faith for Dong because he was still a new, unproven professor. “You don’t know if they are going to get tenure,” Dong said. “But Larry really encouraged me to work with Dave.”

So she took the leap, and what she found along the way still defines her lab today. “One thing about Dave, he has this contagious optimism. He knew what we were working on would be important,” Dong said.

In a more recent leap, one fueled by MacMillan-grade, Overman-inspired optimism, Dong is collaborating with Xiaoyu Shi, an expert in cell biology and flourescent

microscopy and an assistant professor in the UCI Department of Developmental and Cell Biology and the UCI Department of Chemistry. Their students, Alexander Jiu and Kirsten Ruud, are making molecules that could shed light on how the brain works.

“What are all the proteins in a single neuron?” Dong asked. No one knows, and to find out her lab is designing molecules that can target proteins in the brain and, Dong said, “light up” along the way.

The work has the promise to help researchers see the difference between the proteins that comprise healthy brain cells from those in diseased brain cells. “It’s incredibly exciting, and I wouldn’t be here today if it weren’t for Larry,” said Dong, whose students have already used the tools of organic chemistry to build a prototype of the protein-detecting molecules.

In a way, one can trace the cutting-edge science happening in Dong’s lab back to Overman’s 1974 accidental discovery, which itself is just one link in a chain of other discoveries that happened in Overman’s lab that today help chemists synthesize new molecules. The names of those discoveries include things like the intramolecular Heck reaction, the Prins-pinacol reaction and the aza-Cope-Mannich reaction. “He showed, quite masterfully, that one could build intricate natural products using these transformations,” said Neil Garg, who was a National Institutes of Health Postdoctoral Fellow in Overman’s lab from 2005 to 2007 and who today is a distinguished professor of chemistry and the Kenneth N. Trueblood Endowed Chair in the Department of Chemistry and Biochemistry at UCLA. “Understanding how and why these reactions work is another key component of Overman’s legacy, driven by his background and command of physical organic chemistry.”

And Garg, like other lab alumni, recalls Overman’s deft hand as a mentor.

“I made mistakes regularly, and Larry never scolded or embarrassed me,” said Garg, who recounted a moment in the lab when he thanked Overman for being patient with him. “‘I am still learning,’” Garg recalled saying once. “He looked back at me, smiled and nodded, and said ‘Neil, so am I.’ I will never forget that moment, and I regularly recount this anecdote to the researchers I advise today.”

“What sticks out in my mind, is that Larry allowed people time to grow scientifically,” said Javier Read de Alaniz, who was a UC President’s Postdoctoral Fellow in Overman’s lab and who’s now a professor in the Department of Chemistry and Biochemistry at UC Santa Barbara. “He had the unique ability to allow people to

find their own way through challenging problems.”

Now, with his lab’s doors closed, Overman’s days of seeding the world with expert chemists are over. “It was time,” said Overman, who’s fine with the new arrangement because it means he now has more time to spend helping raise his grandchildren and to travel with Joanne.

Had it been someone else in the lab in 1974 aside from Overman, that first discovery might have never happened, and the history that grew from his lab like some kind of grand rearrangement of its own might never have flourished, either.

The lesson? “Don’t be afraid to try new things,” said Overman.

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