Perec wants to build his own version of aquaporin—a channel whose architecture can be tweaked to filter water, one molecule at a time. “No one has done it yet, but I think maybe we are close,” he says.
Virgil Percec is one of the world’s greatest polymer chemists, but this morning, over dark and smoky espresso, he’s telling me about a time when he wasn’t.

“You’ll like this,” he says. In 1982, when he was a new assistant professor at Case Western Reserve University, the physicist Aaron Klug came to campus to give a lecture. “I was invited to have dinner with Klug that evening. The dinner was to be at the most expensive French restaurant in town, so I felt obliged to go to the lecture.”

The name Klug doesn’t register, so I lean in to catch the details of Percec’s story. He speaks softly, with a thick accent from his native Romania.

“I thought the lecture was very boring,” Percec continues. “He was giving it to the physics community, and it didn’t seem connected to what I was doing. I was very naive.”

A few days later, Percec was reading The New York Times on a plane. On the front page was a picture of Klug. “I thought he must have done something wrong. You don’t get on the front page of the paper in this country unless you do something wrong. Well, Aaron Klug had received the Nobel Prize. And the shock was not that he had received the Nobel Prize, but that he received it for chemistry as a physicist. So I figured he must have said something important in that lecture.”

Klug’s message was deceptively simple: “Structure determines function.” It was the lesson passed down by the scientific generation before him, by DNA mavericks like Watson and Crick. By the time Klug got his Ph.D., says Percec, “he had decided that DNA was over, so he moved on to the next challenge,” understanding the interactions of really big molecules and proteins – work that earned him the Nobel. And more than 20 years later, Percec, now the P. Roy Vagelos Professor in Chemistry at Penn, is applying Klug’s dictum to a new and decidedly modern pursuit: building designer molecules that work like the real thing.

“Now here’s an interesting problem,” says Percec, showing me a computer image of a tangled structure nicknamed “the hourglass.” Within its curvy silhouette, red spheres parade single file through a hollow column of coiled and colorful ribbons. We’re looking at a model of aquaporin, a protein channel that transports pure water into cells at a rate of a billion molecules a second. “It’s an amazing structure,” he says. “It makes manmade methods of water purification look like something out of the Stone Age.”

Peter Agre of Johns Hopkins University won the Nobel Prize for his 1991 discovery of aquaporin. Years later, researchers at the Berkeley Lab uncovered its structure. Percec wants to go a step further and build his own version of aquaporin – a channel whose architecture can be tweaked to yield a host of possible functions that include filtering water, one molecule at a time.

“No one has done it yet, but I think maybe we are close,” he says, a smile playing on his lips.

Laying the foundation

“I didn’t intend to become a chemist,” Percec tells me. We’re sitting in his fourth floor office in the Vagelos Labs, surrounded by stacks of papers and books. On the wall above his desk hangs a bright orange, yellow and red painting that, at first glance, looks like a bouquet of fiery flowers. Actually, says Percec, it’s a spherical molecule he built in the lab. The painting was an award from the Royal Netherlands Chemical Society.

“I loved art when I was a boy,” he continues. His father was a painter and musician who encouraged his son in both areas. “Although I became addicted to art, I did not want to be second to my father, and therefore I decided to study architecture,” he told Chemical and Engineering News in 2004. But two organic chemistry courses during his last semester of high school
changed everything, and he decided to switch to chemistry.

That decision made his parents very unhappy. “The Romanian system, you see, was more complicated than the American system. Usually it’s quite a dangerous experiment to change direction like that.” Because university programs were limited and specialized, Percec risked not getting a position in any program. That was the last thing his parents wanted. He was the first in the family with a chance to go to college. His grandfather had been a teacher and politician, “but when the Communists took over, he was thrown into prison and his seven kids were kicked out of school.”

Percec’s experiment paid off. In 1976, he earned a Ph.D. at the Institute of Macromolecular Chemistry in Jassy, Romania, specializing in polymer chemistry, the science of large molecules made of simple repeating units. As a young researcher at the institute, he got off to an auspicious start. His work on the synthesis and structural analysis of a certain type of polymer is still used by scientists today as a blueprint for the design of large helical-shaped molecules.

But one day in the late 1970s, Percec returned from an international conference to discover that a KGB officer had reported him to the government. “I don’t remember why exactly. I probably said something about the freedom in the West compared to the East,” he speculates. As a consequence, his traveling privileges were curtailed, and he had to turn down all invitations to do research and give lectures around the world. “For a combination of reasons,” he says, including his family history, Percec imagined a limited future in his homeland.

Several years later, the Romanian government granted permission to travel to conferences in Russia and Italy. However, his requests for a passport to attend a meeting of the International Union of Pure and Applied Chemistry in France were repeatedly denied. “The government probably thought, ‘this guy Percec cannot be trusted,’” he surmises. Finally, a colleague who was close to the entourage of Nicolae Ceausescu, the Romanian president, intervened and helped him get a passport. Percec decided that if he got out of the country, he would not return. “That night I rode the train from Bucharest. You can never be sure if they’ll let you across the border. Even with a passport, they can turn you away.”

He made it to the conference, where he told colleagues he was defecting. The next step was to get his wife, who is also a chemist, and young daughter out of Romania. Dozens of prominent scientists, including Nobel laureate Paul Flory, wrote letters to the Romanian embassy in Washington, D.C., on Percec’s behalf. Only when the scientific community threatened to boycott a major conference in Bucharest and embarrass Elena Ceausescu, the president’s wife and host of the conference, were Percec’s wife and daughter allowed to join him.

With his family by his side and the constraints of the Romanian government behind him, Percec’s scientific career took off. By 1986, he was a full professor at Case Western, and in 1999, he joined the Penn faculty. The move seems to have accelerated his already distinguished career. An ambitious and prolific scientist, Percec has more than 500 papers, 32 patents and 700 invited lectures to his name. In the last few years, he has won several major awards, including the 2004 American Chemical Society Award for Polymer Chemistry. He is widely recognized as one of the most creative and innovative polymer chemists working today.

Building blocks
Creating a synthetic version of a protein channel isn’t an easy task, explains Percec, pointing to the image aquaporin on his 12-inch Macintosh laptop. The pleasing and colorful picture gives no hint of the multi-leveled, step-by-step building process.
“Mother Nature has spent billions of years working this out. We, most likely, will not be able to understand it in less time. So, therefore, am I going to give up? Say that it is not possible because I won’t be around for billions of years?”

Instead, he and his research team have developed techniques in the lab that mimic what happens in nature. They start by choosing chemical building blocks that come together much like the components of proteins do.

“Proteins have multiple levels of structure,” Percec explains. The first level is a polypeptide chain, a string of tightly bonded amino acids spaced evenly along a chemical backbone. The second level of structure is caused by “local” chemical attractions, the twisting of the polypeptide chain along its backbone. The next level is the overall three-dimensional shape of the molecule – the way it bunches and turns in on itself so that the “water-hating” parts of the molecule are grouped together on the inside and the “water-loving” parts are on the outside. Sometimes several polypeptide chains come together to form an even larger structure. It is this final three-dimensional shape that gives the protein its biological function.

“The primary structure is the driving force for the higher-level structures,” Percec says. The chemistry of the initial polypeptide chain – the type of amino acids and side chains, its size, whether it is “right-handed or left-handed” – determines how the structure will “self-assemble” into the desired three-dimensional shape.

In the lab, the process is similar. Andres Dulcey, one of Percec’s research assistants, explains it this way: “We choose the bricks, but we don’t build the house. The house builds itself depending on the properties of the bricks.”

Percec’s choice of “brick” makes his work unique. He and his team are using dendritic peptides, tree-like polymers that can be altered in countless ways. If the research group is trying to build a sphere (like the one in the painting in Percec’s office), they start with cone-shaped dendritic peptides that cluster together with the tapered ends touching at a single point. Building blocks shaped like pie slices come together to form disks that can stack into columns. “Small changes in the dendritic peptides can give you big changes in structure,” Percec explains.

**Molecular cathedrals**

Last summer, Percec reported in *Nature* the creation of a helical structure that looks and works like protein pores in a cell – the holes through which “all the materials that make life possible” pass into and out of the micro-organism. Percec’s creation is the first successful attempt at a synthetic pore that is stable, functional and flexible. He and his team are now modifying the size and shape of the minuscule structure to make it selective like aquaporin, allowing only certain molecules to pass through it. *Structure determines function.*

Percec likes to compare his protein pore mimic to the Rose Window on the west facade of Chartres Cathedral in France. He shows me a computer image of the pore superimposed on an image of the window. The resemblance is uncanny. The dendritic peptides have branching tendrils that radiate from a central core, and the cathedral window has a series of tear-shaped stained-glass panels that radiate from a central window.

**Tweaking those architectural motifs to yield new structures with new properties is part of the art and science of Percec’s work.**

“What do you think? Twins, maybe?”

He’s being playful, of course, but the comparison gets at one of the fundamental aspects of his work: developing architectural motifs – wedges and cones, for example – that assemble into structures that are “beautiful” in both a functional and aesthetic sense.

Tweaking those architectural motifs to yield new structures with new properties is part of the art and science of Percec’s work. That’s where the creativity comes in.

“When I was young, I had a dream of creating art with molecules,” he says. “I still have that dream.”

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