

PROFILE

Profile of Jonathan L. Sessler

Sandeep Ravindran, *Science Writer*

Jonathan Sessler's foray into chemistry began with a deafening blast. As a teenager, he scoured old chemistry abstracts from the University of California, Berkeley, library until he figured out how to make—and explode—a few drops of nitroglycerin using his childhood chemistry set. Luckily, he had his safety goggles on, but the blast was substantial enough to deafen him temporarily and shower him with porcelain fragments from the crucible in which he heated the nitroglycerin.

Sessler's childhood explorations would eventually lead him to a long and distinguished career as a chemist. He is known for his work on synthetic analogs of blood pigments, called porphyrins, and his research on expanded versions of porphyrins has enriched scientific understanding of the compounds' applications and formed the basis of two biotechnology startup companies. Now the Doherty–Welch Regents Chair in Chemistry at The University of Texas at Austin, Sessler was elected to the National Academy of Sciences in 2021.

Sessler's interest in science was a natural outgrowth of his family environment. His father was a former director of the Lawrence Berkeley National Laboratory and a winner of the Enrico Fermi Award, and his mother was one of the first women to receive a master's degree in physics from Columbia University. Childhood dinner conversations would often revolve around the latest issue of *Science*, with his father asking Sessler and his siblings for thoughts on an article's hypothesis and controls.

Sessler's father helped him set up a home chemistry laboratory. "I took to that like fish to water," says Sessler. "The nice thing about explosives is you know whether or not your experiment worked without needing fancy mass spectrometers," he says without a hint of irony. Sessler also received encouragement from his teachers. "I knew I wanted to be a chemistry professor since seventh grade, and I was blessed to have wonderful high school and college instructors, so it was just a lot of fun along the way," he says.

Bigger Molecules in Texas

Sessler attended Berkeley for an undergraduate degree in chemistry, but while at Berkeley, he was



Jonathan L. Sessler. Image credit: Michael Krische (photographer).

diagnosed with Hodgkin's lymphoma, a cancer of the lymphatic system. Much of his senior year was spent in treatment, and the diagnosis influenced his choice of graduate school.

In 1977, Sessler chose Stanford University for graduate studies, motivated not only by the renown of its chemistry department but also by its proximity to the Stanford Medical Center, where he could receive cancer treatment.

During his doctoral studies, Sessler worked on naturally occurring porphyrins with chemist James P. Collman. "That was a wonderful environment, and many of the people who were mentored and taught by Professor Collman went on to become household names in chemistry," says Sessler. Unfortunately,

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during his third year of graduate school, Sessler's cancer returned, putting him through a year of chemotherapy. "This was a tough time for my chemistry education," he says.

Despite this setback, Sessler completed his doctorate in 1982, and received an NSF-NATO and NSF-National Center for Scientific Research (France) postdoctoral fellowship to join Jean-Marie Lehn's group at the University of Strasbourg in France. He also spent 5 months with Iwao Tabushi's group at Kyoto University in Japan. Toward the end of his doctorate, Sessler became interested in the relatively new field of supramolecular chemistry, which deals with molecular assemblies and intermolecular bonds, and he delved into this field for his postdoctoral research.

When Sessler became an assistant professor at the University of Texas at Austin in 1984, he decided to combine themes of supramolecular chemistry and porphyrins. "I quickly learned that in Texas, everything should be bigger, so I had the inspiration to make a bigger version of a porphyrin," says Sessler. He named this expanded porphyrin "texaphyrin" and characterized the molecule using crystallography in 1988 (1).

Expanded porphyrins have since remained a major theme of Sessler's research. "The number of papers total in the thousands now for expanded porphyrins and other porphyrin analogs, and much of this can be traced back to our idea to try to make these things Texas-sized," says Sessler. "Bigger molecules give you new possibilities, and it worked really well and turned out to be really fun," he says.

Nonbinary Molecular Switch

In 2010, one of Sessler's postdoctoral researchers, Han-Yuan Gong, created a larger version of so-called "blue-box" pyridinium macrocycles developed by the Nobel laureate Sir Fraser Stoddart. "We realized this was an expanded, or a Texas-sized, version of Sir Fraser's box, and so, of course, we had to call it a Texas box," says Sessler (2). "It's pretty big, so it would capture all kinds of anions, and we've had a lot of fun with that, which brings us to my PNAS Inaugural Article," he says.

In the Inaugural Article (3), Sessler and Gong describe a Texas box that, in conjunction with dibasic photo-isomerizable acids, can act as a nonbinary molecular switch. Depending on the pH, the guest molecules for the Texas box can be neutral, mono-negative, or dinegative, with a correspondingly different degree of binding. "To a first approximation, if you double the charge, you're going to double the binding," says Sessler. "So, one way of regulating it is by the degree of protonation," he adds.

However, Sessler and Gong also found that photoirradiation could switch some of the charged guests between their *cis* and *trans* conformations. "The idea is that the *cis* form doesn't bind that well, so now you have two kinds of control," says Sessler.

In addition to showing multiple modes of control, Sessler and Gong also found that the system could

be regulated under nonequilibrium conditions. They used trichloroacetic acid to change the degree of protonation and, thus, the binding of the compound. However, heating or irradiation would decompose the trichloroacetic acid and reset the system so it could bind again. "So, you can switch this back-and-forth off equilibrium," says Sessler.

The Texas box described in the article (3) can move through multiple switching events under nonequilibrium conditions. "It's like instead of just turning your light on and off, you can turn your light on, off, and sideways, which, of course, is key to logic devices, such as transistors," says Sessler. "The ability to do logic and then interface it to downstream processes is tremendously exciting to me, and you can imagine using this for drug release inside or outside of a cell as a function of pH," he says. The advance is hardly the first time Sessler's compounds have had real-world applications.

Introduction to Biotech

When Sessler was considering potential applications for texaphyrins, he was inspired by an interaction he had while receiving chemotherapy from a Stanford doctor named Richard A. Miller. "This is one of the most remarkable and smart people I've ever had the pleasure of interacting with," Sessler says. "Here I was, a third-year graduate student, getting chemotherapy and feeling sick, and he kept asking me what I was researching," says Sessler. When Sessler mentioned he was working on porphyrins, Miller asked him why he was not using these compounds to cure cancer.

Motivated by his memory of Miller's question, Sessler applied for a grant to test whether texaphyrins could be used to treat cancer. Unfortunately, the NIH reviewers were unconvinced by his proposal. "It was probably the worst grade I had ever gotten in my life," says Sessler.

A downcast Sessler mentioned his grant rejection to Miller during his next check-up. Miller immediately asked if he could take a look at the proposal. "Of course, I had hoped he would say that, and I whipped out from my bag [a] proposal the size of a small phone book," says Sessler. "A few days later, Miller goes, 'I read your proposal, and we have got to start a company,'" says Sessler.

Within days, Sessler squeezed into his *bar mitzvah* suit for his first meeting with venture capitalists. "I knew nothing about biotech company culture, and they showed up in their flip-flops and sweatshirts," he recalls. "It took us a couple years to raise money, and we cofounded [a] company called Pharmacyclics and tried to make texaphyrins into drugs," says Sessler.

Pharmacyclics entered two texaphyrins into advanced clinical trials, including one to phase 3 clinical trials. "For a variety of reasons, the statistics weren't quite good enough to proceed further, but getting a drug from your lab to phase 3 is still a pretty big deal," he says. "This is something I'm

terribly proud of, and it really shows that this whole class of bigger porphyrins have utility,” he adds.

Although texaphyrins eventually failed to pan out for Pharmacylics, the company developed ibrutinib, one of the first successful covalent anticancer drugs. “Ibrutinib emerged as [a] blockbuster drug, and it’s been a tremendous success,” says Sessler.

Exciting Developments

After a few years, Miller and Sessler moved on from Pharmacylics, but Sessler continues to develop drugs based on texaphyrins at a company called OncoTEX. “We’re now using these [compounds] as carriers, we think it’s a whole platform, and we’re currently optimistic that we’re going to be able to make another run at bringing out a drug,” says Sessler (4). Along these lines, he and OncoTEX are also pursuing gold carbenes as immunogenic cell death agents.

In early 2020, Sessler and Jonathan Arambula—now CEO of OncoTEX—discovered that adding redox-active components to an N-heterocyclic gold carbene helped promote the cellular levels of reactive oxygen species, which are deleterious to cells. Gold carbenes had previously been shown to interfere with the enzyme thioredoxin reductase, which helps protect against oxidative stress. “So, on the

one hand, we’re making reactive oxygen species and, on the other hand, we’re blocking the cell’s ability to deactivate them,” says Sessler. “And, of course, cancer cells are very susceptible to oxidative stress, and if you generate enough stress you trigger a new mechanism of cell death called immunogenic cell death.”

With collaborators, including Arambula, Zhengrong Cui, and Esther Maier, Sessler found that administering gold carbenes into mice and challenging the mice with an injection of cancer cells resulted in 80% of the mice being protected from the cancer (5). Shortly after this finding, the experiments were temporarily shelved due to the COVID-19 pandemic. “When Maier came back and found some of the mice still alive, she reinjected them with fresh cancer cells and found that none of them developed tumors,” says Sessler. “That’s probably the most exciting recent development from our group, so stay tuned.”

Even as he reflects on his scientific achievements, Sessler remains hopeful that texaphyrins and gold carbenes will enable him to fulfill a longstanding dream. “My one outstanding remaining professional goal is to try and bring at least one of these drug candidates across the chemist’s finish line to clinical trials,” he says.

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