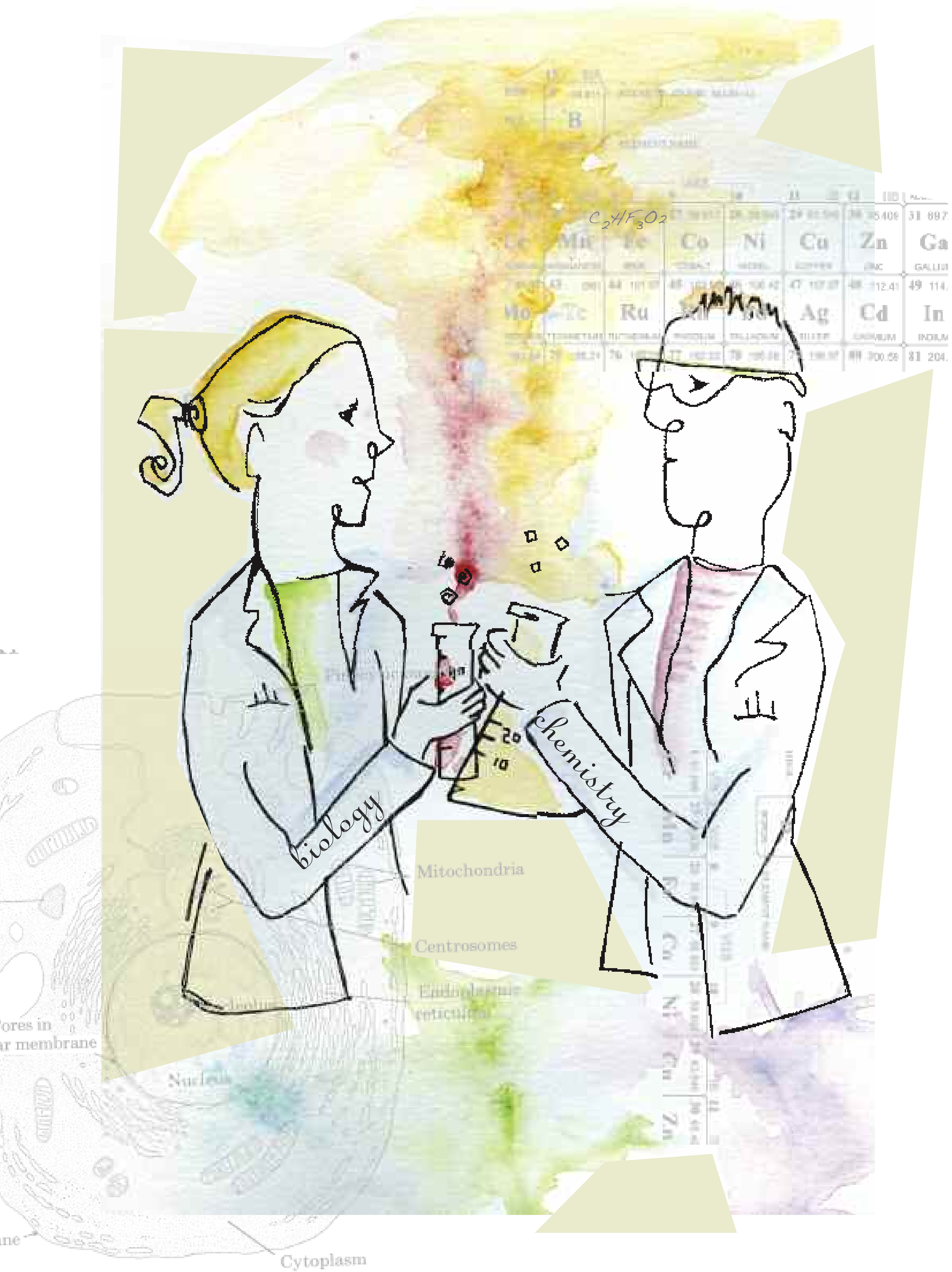


Chemical Attraction

By Aline McKenzie

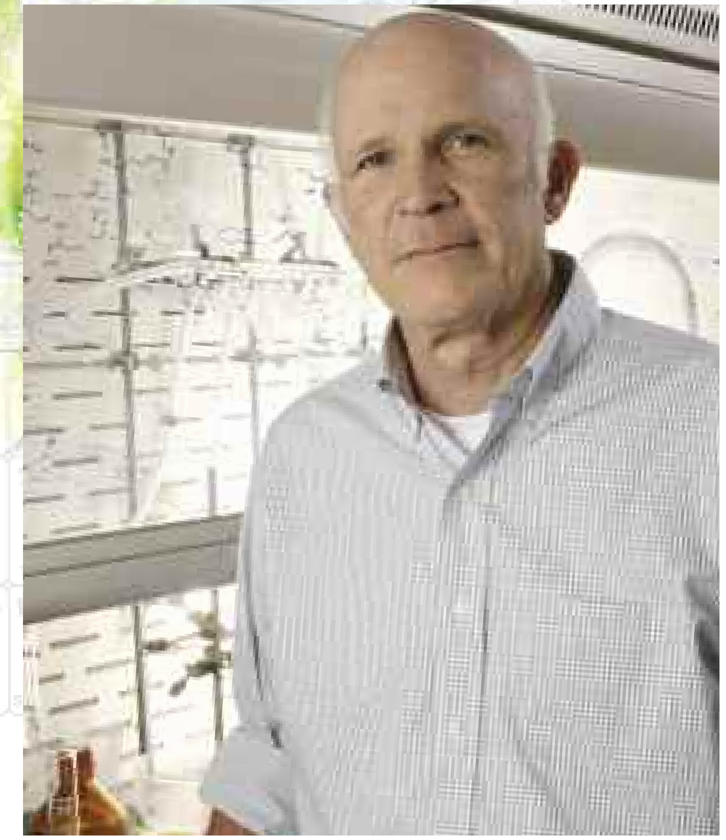
On the fourth floor of a building on UT Southwestern Medical Center's South Campus, a strange vinegary smell permeates the air. It's an odor found almost nowhere else at the medical center.

The acrid odor, caused by acid used in chemical reactions, stems from a unique program at UT Southwestern – full-time faculty chemists working side by side with biologists.

UT Southwestern was the first academic biomedical center to create a "pure" chemistry program, which focuses on analyzing, synthesizing and modifying molecules that might have promise for the future treatment of human diseases.

"It's unusual to have research capabilities in hard-core chemistry in a medical center, and yet I think the opportunity for chemistry to impact medicine is tremendous," said Dr. Steven McKnight, chairman of biochemistry and the driving force behind the program.

The difference between UT Southwestern and a more traditional chemistry department is that the chemical compounds discovered and studied here are prioritized for biological activity – one may show promise in killing cancer cells, another may be a potential antibiotic.



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In a traditional program, chemical reactions might be so exotic as to be studied only by mathematicians and physical chemists. At UT Southwestern, after a chemist's work is done, a biologist applies the discoveries to real-life situations.

Chemists and biologists work next door to each other, so exchanging ideas means walking a few yards. Sometimes a chemist discovers an interesting molecule from, say, a marine bacterium, and wants to know how it affects cells. Sometimes a biologist has an active molecule that doesn't dissolve well in water or is weak and needs to be modified so it's more usable or more potent.

"Without the chemists, it would be folly for us to pursue new drug leads," said Dr. McKnight, holder of the Distinguished Chair in Basic Biomedical Research and the Sam G. Winstead and F. Andrew Bell Distinguished Chair in Biochemistry. "It would never work.

"The chemists don't come here solely to give us additional ways of studying biology. They themselves have their own fields."

Dr. Alfred Gilman, executive vice president for academic affairs, provost, and dean of UT Southwestern Medical School, said, "Steven McKnight has been able to attract a group of really exciting young chemists who appreciate being here. It can be like being in a candy store, rather than being in a traditional department of chemistry.

"Putting chemists next door to biologists is particularly important," said Dr. Gilman, holder of the Nadine and Tom Craddick Distinguished Chair in Medical Science; the Atticus James Gill, M.D., Chair in Medical Science; and the Raymond Willie and Ellen Willie Distinguished Chair in Molecular Neuropharmacology, in Honor of Harold B. Crasilneck, Ph.D.

"If they're not rubbing elbows, they don't have the opportunity to say, 'Hey, I can help you with that; I can see a way to do that,'" said Dr. Gilman, who also directs the Cecil H. and Ida Green Comprehensive Center for Molecular, Computational and Systems Biology.

Dr. Jef De Brabander, one of the first chemists to join the program, said the communication and talent of the two groups of scientists was what appealed to him, as he made a risky career jump into an untried program 10 years ago. He is a professor of biochemistry and a member of the Harold C. Simmons Comprehensive Cancer Center.

"Dr. McKnight calls it bringing chemistry back into biochemistry," Dr. De Brabander said. "It comes down to how things function – that's a chemical problem."

Dr. De Brabander's work focuses on re-creating molecules found in marine sponges, soil bacteria and other species.

"Our passion is 'How do I make this?'" he said.

There are several reasons to try to synthesize a biologically active molecule, rather than just purify it from its source. Primarily, the original organism may be too rare or difficult to gather to provide enough of the compound.

This was the case of two molecules with possible actions against cancer and osteoporosis that Dr. De Brabander was studying. His laboratory was the first to create the molecules in the lab from scratch.

In addition to their rarity, one of the compounds came from animals in Antarctica called sea squirts. International treaties forbid harvesting for profit in Antarctica, so the compound *must* be created in the lab.

"You can take a sponge, grind it up, isolate the compounds, but then you have no more source," said Dr. Chuo Chen, assistant professor of biochemistry, who works primarily with marine organisms.

The researchers' interest in the sea squirts was rooted in previous work on a compound from sponges that killed cancer cells. Biologists from UT Southwestern found that the substance acted on a molecule that pumps protons out of solid tumors, presumably to prevent them from building up acid. Unfortunately, the compound from sponges proved to have toxic side effects in the brain.

The compound from the sea squirts acts on the same pump, but so far, no side effects have been noted.

"We know now we have a new lead," Dr. De Brabander said. "We were working with some of the best biologists around to see how it really functioned. You can only do that if there's really a back-and-forth of people addressing problems together."

Dr. Omid Soltani, now a chemist at a pharmaceutical company, was one of the first graduate students to join the program. Having grown up in the Dallas-Fort Worth area, he was familiar with UT Southwestern and was eager to join the new program.

"I knew the quality of the research in general at UT Southwestern was quite high, so if chemistry was going to be done, it was going to be quite high as well," Dr. Soltani said. "Knowing this, I didn't feel it was a great risk joining a nontraditional chemistry program."

"Being able to walk down the hall and talk to someone is different than at other universities."

— Dr. Jennifer Kohler

Dr. Soltani worked several years to synthesize a compound found in yeast. Then, working with researchers in internal medicine, physiology and cell biology, he was able to study its properties as a carrier of protons and metal ions and as a promotor of cholesterol uptake.

Working in a brand-new program "was very intense and fast-paced," he said. "We wanted to make our presence felt among chemistry researchers elsewhere and to establish ourselves as excellent students within UT Southwestern."

Dr. Jennifer Kohler, assistant professor of internal medicine and biochemistry, studies how carbohydrates on cell surfaces interact during immune reactions and other processes.

These interactions are fleeting and chemically weak, so her work involves variations of the molecules that can lock onto each other, so the researchers can then analyze them.

But while she understands and can make the variations needed, the biology requires input – where exactly in the cell are these molecules? What controls the molecules to which the cell binds?

"Being able to walk down the hall and talk to someone is different than at other universities," Dr. Kohler said. "We don't know all the biology techniques."

The collaboration between the chemists and the biologists allows them to take two different approaches, Dr. McKnight said.

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“Novel bacteria will yield novel molecules. That's when the chemistry begins. We have to determine the structure of these molecules – that's what we spend our time doing.”

— Dr. John MacMillan

In some cases, the researchers already know what cell system they're interested in – for example, they might want to look for compounds that affect the brain receptors involved in sleep. A chemist might help them develop variations of existing compounds in this case.

Several times, UT Southwestern chemists have studied a compound whose structure was believed to have been known and found that previous reports had been incorrect. Correcting this information provides a base for better chemistry and modification of the compounds.

In other situations, the scientists might take a novel compound, perhaps harvested from marine bacteria, and find what cellular process it affects, Dr. McKnight said.

“At the outset of almost every project, we don't know how the compound's working,” he said. “It's a black box.

“Very rarely, a compound could be medically useful,” Dr. McKnight said, but that's not the department's only goal. Several current and former faculty members have, however, formed companies to further develop compounds they've created. In some instances, department members have formed associations with companies to carry out complex, expensive clinical trials that are beyond the reach of the Department of Biochemistry.

Dr. John MacMillan, assistant professor of biochemistry and the Chilton/Bell Scholar in Biochemistry Research points out that studying compounds made naturally by living organisms follows a centuries-old tradition. Many folk cures, some of which led to modern treatments, came from plants. In addition, bacteria or molds have proven a reliable source of many antibiotics, such as penicillin.

“Scientists would go out and collect dirt to find new organisms to study,” he said.

Now he continues that tradition, except he goes out to sea to hunt organisms.

“Until recently, the microbial environment of the ocean was not well understood,” Dr. MacMillan said. “We can now collect sediments in a biologically friendly way. There's no reason to think that microbial natural products won't continue to play a role in antibiotic development.

“Novel bacteria will yield novel molecules. That's when the chemistry begins. We have to determine the structure of these molecules – that's what we spend our time doing.”

Once a year Dr. MacMillan goes out on a research vessel funded by the National Science Foundation, which carries 27 researchers from a variety of fields and from 10 nations.

He uses a device called a “mud missile,” which can go down 3,000 meters and collect sediment using remote-controlled jaws. A plain electric fishing reel then pulls it up.

Once back at the lab, part of his work is figuring out how to keep the bacteria alive in culture – a very different thing than culturing bacteria that live on the land. “So far, we've been pretty lucky,” he said.

Dr. McKnight said, “John is like an oil prospector. He goes out; he collects all these samples. He comes back here to UT Southwestern; he cultures them. He extracts; he looks for a new activity that perhaps might be a new molecule that would stop bacteria from growing. It might be an antibiotic, or it might be a new molecule that would stop cancer cells from growing.”

Part of the chemist's work is to find ways to make biologically active compounds easier to make. It's one thing to make one-half milligram of something, using expensive ingredients and possibly risky steps.

“It's another thing to try to make it in bulk quantities,” Dr. De Brabander said. The chemists sometimes must find a new way to synthesize the compound using less expensive and more environmentally friendly ingredients, perhaps even discovering a way that uses far fewer steps.

“We call that ‘more elegant,’” he said.

Dr. McKnight said, “If you have a very complex molecule, it's not trivial to say, ‘How do I put this together from its basic components?’ It might take 20 or 30 or 40 steps.

“The foundation of being able to use chemistry at UT Southwestern rests on having world-class chemists on our faculty.”

Several core support programs work with both chemists and biologists on campus: the Small Molecule Library, the High Throughput Screening System and the Synthetic Chemistry Core Facility.

The Small Molecule Library consists of more than 200,000 commercially available compounds, carefully selected for their possible biological actions.

Researchers can select which ones they'd like to test in an experiment, or all 200,000 compounds can be tested, using the technique of High Throughput Screening (HTS).

In a typical HTS experiment, cells are put into each of 384 small wells in a plate, and an automated system delivers a single compound to each well. The system can then look for signs of a reaction between a compound and a cell, such as the activation of a green fluorescent molecule implanted in the cells.

“Experiments can be as specialized as detecting a change in a single molecule, or as general as a change in a cell's behavior,” said Dr. Michael Roth, professor of biochemistry and head of the High Throughput Screening System. Once the screen is completed, chemists then step in, because typically the compounds found in the screen are not active enough.

“These small molecules may become the first-ever drugs specifically designed to enhance the human heart's natural repair mechanism, helping the heart rebuild muscle after a heart attack.”

— Dr. Jay Schneider, with Dr. Jenny Hsieh

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Sometimes an initial screening of the full 200,000-compound library can be narrowed down quickly to just a handful of compounds to pursue for further study.

The Synthetic Chemistry Core Facility assists other researchers in creating variations of promising lead compounds that have shown biological activity.

The facility also provides researchers at UT Southwestern with the latest in synthetic, medicinal and analytical chemistry as an in-house service that is unique among medical centers in the United States, Dr. McKnight said. This service means that researchers can work where biology and chemistry intersect without having to outsource.

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Collaborations already have been established with researchers from internal medicine, cardiology and developmental biology.

The researchers can also draw on a device called a LC-SPE-NMR, a mouthful but one that combines three types of analytical methods – liquid chromatography, solid phase extraction, and nuclear magnetic resonance – into one device, providing a powerful tool for unraveling the structure of a molecule. UT Southwestern is one of only two U.S. universities that have this device, Dr. MacMillan said. "It's going to be extremely powerful for us."

Dr. Jenny Hsieh, assistant professor of molecular biology and in the Cecil H. and Ida Green Center for Reproductive Biology Sciences, was an early beneficiary of the core resources available at UT Southwestern. She and Dr. Jay Schneider, assistant professor of internal medicine, found by accident that a substance called isoxazole-9 nudged immature stem cells into becoming more mature nerve cells. This discovery came as they were looking for compounds that would prompt stem cells into becoming heart cells.

"Isoxazole small molecules were safe and well tolerated by mice and have great potential as drugs for humans," Dr. Schneider said. "These small molecules may become the first-ever drugs specifically designed to enhance the human heart's natural repair mechanism, helping the heart rebuild muscle after a heart attack.

"This is very exciting, and chemistry was the key."

Dr. Hsieh said the chemists were fully engaged from the start.

"If certain molecules were more potent in triggering neurogenesis [creation of nerve cells], the chemists would use it as a guide to make further modifications and additional variations," she said. "They'd make 10 molecules at a time. It would take us two weeks to test them; then we'd meet again."

Isoxazole-9 was not the original compound that triggered their interest. Instead, it's a variation that is more potent and dissolves more easily in water.

> "The real hope and dream is that it will lead to candidates for therapeutic compounds, going beyond the initial step of getting hits in high-throughput screening that show preliminary effects on a cell."
>
> — Dr. Alfred Gilman

In the original study, Dr. Schneider and his colleagues screened hundreds of thousands of molecules to see whether any could transform pluripotent embryonic stem cells into a form resembling immature heart cells. Again, the original promising molecules were modified into more active and useful forms.

When the researchers implanted blood stem cells activated by this compound into injured rodent hearts, the cells took root and improved the animals' heart function.

"This is exactly what this program is designed to do," Dr. Gilman said. "The real hope and dream is that it will lead to candidates for therapeutic compounds, going beyond the initial step of getting hits in high-throughput screening that show preliminary effects on a cell." ✳