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Catalyst

Brandeis University Research

**Brandeis develops
21st-century
chips that shrink
the chemistry
lab and reduce
cholesterol**

**Nobel Prize winner
Roderick MacKinnon '78
on science and Brandeis**

Research

LCD technology
University's fifth HHMI investigator
Neuroscience awards



Lab-on-a- chip

By Laura Gardner

**“Faster, cheaper, better”
is the mantra of lab-on-a-
chip technology,
which promises to revolutionize
how chemistry is done and drugs
are developed.**



Take a cat whisker. Stroke the parent crystal to pick up invisible seeds. Now, draw a streak line across a new drop....” Though it may seem like it, these are not instructions from a sixteenth century alchemist’s handbook revealing the secrets of transforming lead into gold. These are a leading scientist’s standard crystallography methods to nudge proteins—large and complex molecules containing thousands of atoms—to grow into tidy crystals whose structures can be determined through x-ray diffraction. X-ray crystallography is the vehicle that transports scientists to the protein’s structure itself. Once scientists have a protein’s structure in hand, they can work on understanding its function—the holy grail of targeted drug development.

The human body is comprised of about 30,000 proteins; 10,000 of these are membrane proteins—the macromolecules that provide communication between and within cells. Sixty percent of drugs are based on an important class of membrane proteins known as G coupled-protein receptors (GPCRs), representing some \$47 billion in annual drug sales. To date, only one structure in this class of membrane proteins has been solved, and it has no therapeutic value.

The confluence of these factors has created a classic scientific challenge, replete with enormous frustration (conventional crystallography), extreme intractability (the membrane proteins), and incalculable dividends (better drugs, for starters).

All told, it’s a situation that excites physicist Seth Fraden. The maverick scientist is leading an ambitious, perhaps even risky, multidisciplinary research project to radically change the

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course of conventional protein crystallography. His goal: to enable scientists to quickly, predictably, and accurately access the gold mine of information locked inside the structure of proteins—a process that presently can take years before a usable crystal is made, if it can be made at all.

“We’re trying to transform protein crystallography from an art into a science by applying the tools of physics and chemistry to a problem of biology,” says Fraden, who is using microfluidic technology to bring protein crystallization into the twenty-first century.





Popularly known as lab-on-a-chip technology, microfluidics reduces the volume of chemicals used in common laboratory practices, such as mixing and purifying solutions, by factors of thousands or more, while simultaneously improving the precision

Fraden's prototype is singularly designed to overcome the barriers to protein crystallization that scientists face every day.

with which chemicals can be manipulated. This technology exploits the same processes developed by the semiconductor industry in making the electronics (chips) found inside computers. Lab-on-a-chip technology is developing at an astounding speed, with improvements coming faster than Moore's Law, which describes how computer power has doubled every two years in the last three decades.

With funding from the National Institutes of Health, Fraden is developing and manufacturing a novel microfluidic device in a small facility on campus that keeps three undergraduates, three graduate students, and two postdocs busy creating and testing silicone rubber "chips" that fit easily into a cupped palm. Although just a rough-edged rectangular piece of clear plastic at first glance, inspection of the chip under a microscope reveals an intricate system



of wells and passages that enables multiple experiments to be carried out on the microscale. This is a development Fraden believes will revolutionize the way chemistry is done over the next decade and direct billions of dollars into microscale drug research.

Fraden's prototype is singularly designed to overcome the barriers to protein crystallization that scientists face every day. First, human membrane proteins don't grow well in bacteria, so there's very little to be had—a huge advantage for microfluidics, which uses 10,000 times less protein than standard crystallography. Second, screening thousands of conditions for the ones that make crystallization possible is equivalent to finding the proverbial needle in a haystack. Fraden's chip can store thousands of subnanoliter drops in individual wells and prepare 1,000 screening trials in minutes. Testing for the same conditions using conventional crystallography requires loading protein solutions in trays, stacking them floor to ceiling in cold rooms, and waiting months while more or less praying for the crystals to grow.

Finally, and most crucially, Fraden's technology separates the two processes that typically make protein crystallization an "empirical slog," as biochemist Chris Miller puts it. Essentially, giving birth to a new crystal requires conditions that are antithetical to those needed to nurture

growth. The result is that, in standard crystallization, a compromise must be reached in which crystals often grow quickly and sloppily with too many defects, or not at all. Fraden's technology separates these opposing conditions, making it possible to independently optimize the two processes of crystal nucleation and growth.

"What we have now are trial-and-error methods that don't directly confront the underlying physics," Fraden notes. "Our chip simply promises to be faster, cheaper, and better for the production of protein crystals."

Three Brandeis biochemists, experts on the personalities of the proteins they study, are collaborating with Fraden by supplying key membrane proteins for crystallization. The prospect of an exponentially better way to obtain crystals seems to engender a state of near exhilaration in all of them.

"Seth's project is terrific, it's wonderful. It provides us with a whole new geometry with which to grow crystals, and gives us the possibility of testing more conditions," exclaims Dagmar Ringe, professor of biochemistry and chemistry and a leading crystallographer who has worked on crystallizing several dozen proteins over a long career.

Miller, who has spent the last few decades of his career researching a subclass of membrane proteins called ion channels, most famously known for generating electrical signals in the cell, has equally high hopes for Fraden's research. "You need to know

something about the soul of a protein to navigate these tough waters of crystallography, so I'm thrilled that Seth's technique gives us the possibility of getting through 10,000 conditions in a couple of days, using a very small amount of protein."

Daniel Oprian, the Louis and Bessie Rosenfield Professor of Biochemistry,

"Our chip simply promises to be faster, cheaper, and better for the production of protein crystals."

researches GPCRs and arguably stands to benefit the most from Fraden's chip, as these are the proteins notoriously resistant to protein crystallization, while their importance to human health is monumental. "The prospect of obtaining diffracting crystals is vanishingly small using standard methods," says Oprian, "so we're relying on Seth to make us famous."

Whether fame is in their future is still uncertain. But one thing is crystal clear: this project is signature Brandeis science—bold in scope and impact, highly collaborative, cross-disciplinary and agile, and involving a handful of people, all with big ideas. This microscale project has potential to make a mega impact. ■

