Esselen Award Lecture

Microwell Arrays: From Genetic Analysis to Ultra-High Sensitivity Diagnostics

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It is a great honor to be the recipient of the 2014 Gustavus John Esselen Award for Chemistry in the Public Interest. The list of previous recipients is both humbling and inspiring.

When I started my academic position many years ago, I was interested in doing what virtually every academic scientist strives for—build a successful and well-funded research program by identifying interesting problems, carry out appropriate experiments to solve the problems and publish in the top journals. While these goals have been met, there were a few unexpected detours that have shaped both my research direction and my outlook.

Shortly after starting a faculty position at Tufts, I became interested in the field of chemical sensors. The lab made numerous contributions in developing some useful chemistries for making chemical sensors and biosensors and had established a reputation in the optical sensing area. In 1995, a highly industrious postdoctoral associate, Paul Pantano (now an Associate Professor at the University of Texas- Dallas), was working on a project involving near field microscopy. Paul was trying to develop a rapid ultra-high resolution optical imaging method. The approach involved etching optical fiber bundles to create an array of near field scanning probe tips. Every time he tried to etch the fiber arrays, he obtained the opposite result from what he was trying to accomplish. Instead of an array of sharp tips, divots appeared—tiny wells arrayed in a regular pattern with highly reproducible and predictable depths. These microwell arrays, as well as nanowell arrays prepared using the same technique, were orders of magnitude smaller than anything reported previously. Although Paul eventually succeeded in preparing the near field arrays, the microwells have been a sig- nature platform of the laboratory ever since. After the initial demonstration of the microwell preparation, Karri Michael, a graduate student working at the lab bench across from Paul, carried out an interesting experiment in which she assembled microspheres (also called beads) into the wells. The size of the beads was matched to the size of the wells such that only one bead would be able to fit into each well. She created the first "Bead Arrays."

The microwell array and bead array technology have been used in my laboratory as a platform for performing bioanalytical measurements. We have successfully implemented the microwell array platform for a multitude of applications including genetic and protein analysis. The microwells serve as miniature reaction vessels and confine reaction mixtures to ultra-small volumes. In the bead array scheme, microwells are filled with size-matched beads containing receptors for performing high-throughput genetic and protein analysis. The ability to randomly assemble these microarrays using beads that were size matched to the well sizes provides access to incredibly high density and easily reconfigurable microarrays.

In another scheme, the microwells are used as miniature reactor chambers to confine single molecules. Digital measurements, based on counting single molecules, enable extremely high sensitivity because low background signals can be readily distinguished, making for a much lower limit of detection. We have used the microwell arrays to develop methods to measure the concentration of proteins more than a thousand times lower than ELISAs— the standard for immunoassays. My laboratory is presently pursuing several clinical applications of the technology including early detection of both breast cancer and infectious disease. Our goal is to detect these diseases much earlier than is now possible, with the expectation that early diagnosis will lead to superior clinical outcomes. We are also using the microwell arrays to investigate fundamental aspects of enzymes by observing single enzyme molecules in action.

As a consequence of the technological innovations that have been developed in my laboratory, there have been some unexpected but fulfilling deviations from the traditional academic path. Both of these applications of microwell arrays have been commercialized. In 1997 I was approached to commercialize the bead array technology. The technology portfolio was licensed from Tufts University and a company, Illumina Inc., was founded in San Diego, CA. After five years, Illumina became the leader in microarrays for genetic analysis and is now the leader in DNA sequencing. The microwell technology still powers the company's microarray products and is also incorporated into its sequencing products. It is important to note that there are countless other creative technologies responsible for the company's products. Many highly talented individuals have been involved in making Illumina the huge commercial success it is today—technicians, scientists, engineers, the sales force, financial experts, manufacturing specialists, and business executives. Seven years ago, the single molecule technology was licensed and another company was founded—Quanterix Corporation, based in Lexington, MA. The company recently launched its first platform that enables researchers to discover new protein biomarkers of potential clinical utility and a large commercial partner has licensed the rights to the clinical diagnostics market.

These commercial successes have enabled the discoveries in my laboratory to be translated into the market- place. Illumina employs over 3000 people and Quanterix employs nearly 60. The products are responsible for advances in clinical medicine and agriculture, and have enabled thousands of important research findings. These societal benefits would not be possible outcomes for the typical academic laboratory. I and the students and post-docs in my laboratory feel tremendous pride in having played a role in both job creation and bettering the human condition.

The trajectory of my lab's research program relied on some serendipitous discoveries (aka mistakes), perceptive recognition of important but unexpected results, and luck. My focus has shifted to areas of research that we believe will lead to important out- comes. Publications are still necessary for researchers to disseminate knowledge and to demonstrate that they can bring a project to fruition, but another motivator is whether the research has the potential to eventually lead to outcomes with societal impact. This path is not for everyone and the scientific enterprise would soon fall apart without the basic fundamental research that is the lifeblood for tomorrow's technologies.

I am immensely grateful to the many talented graduate students and postdoctoral associates who have contributed to the culture of creativity and invention that has characterized the laboratory. The productivity of the laboratory is a direct result of their tremendous dedication and incredible work ethic. I conclude with special thanks to my wonderful and supportive family, without whom none of these accomplishments would have been possible.