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Prognostic Medical Devices — The Wave of the Future

Imagine a world where disease could be predicted before it happens, instead of diagnosed and cured by drugs or surgery. Where doctors could change a patient's life style, diet and exercise, and prevent the disease.

A Bishop once told me, long ago before the advent of the diagnostics revolution, that God designed the human body to produce very small amounts of antigens to signal the advent of diseases, and was just waiting for man to rise to the level of intelligence to create devices that would be able to detect these.

Flashback to 1989, when I met Kary Mullis, who won the Nobel Prize in Chemistry in 1993 for a technology called Polymerase Chain Reaction, and he said: "I want you to design a tube that is so thin and so uniform in thickness, it has never been done before in plastic!" And we asked, why plastic?

Because we will produce millions and millions of these "thermocycler tubes", and it has to be manufacturable and cheap, robust and accessible to ordinary folks. It blew our minds, because the concept of amplifying (making copies) of DNA was not only foreign to us young plastics engineers but mind-boggling in its concept.

The way he explained PCR to our "primitive" minds was like this: Imagine our DNA chain as a railroad track twisted like a helix. Under heat, this railroad track unravels into a straight track. The polymerase enzyme takes base pairs from other sections of this railroad track and puts it in the same sequence as the DNA sequence you want to copy. And it can do this hundreds, millions, even billions of times.

He said the thermocycler tube wall thickness must be incredibly uniform, so uniform in fact that it was well nigh impossible to produce with the state of plastics technology at the time.

As I said, it blew our minds! Fast forward 3 years later, and the first GeneAmp PCR System was developed and the ultra-thin, ultra-uniform PCR thermocycler tube was a reality. I certified the polypropylene material that is still used today in all your labs.

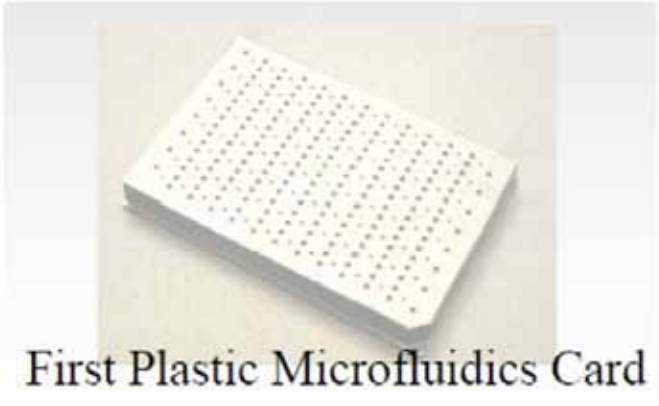
I have a Polaroid photo of myself and the Perkin-Elmer guys kicking the first box of PCR tubes out the door. One of its first applications, even before it was ever mass-produced, came about from a very tragic incident in Petaluma in 1993.

First PCR Thermocylcer Tube
(Perkin-Elmer/Applied BioSystems)

The FBI approached Perkin-Elmer and said: "We heard you have a new method for making copies of DNA. We have a very small spec of blood on the scene where a little girl by the name of Polly Klaas was abducted and subsequently murdered, and which we believe was of the perpetrator. The

spec is so minute, we can't identify it."

I have to tell that when the District Attorney held up that tube on TV and said: "This is Polly's blood!", I ran up and down my neighborhood and yelled, "That's my tube! That's my tube!" When I recount this story today, it still gives me goose bumps almost 25 years later.


First Plastic Microfluidics Card

Fast forward to 2000, when we made the very first microfluidics chip in plastic at Aclara Biosciences. Seventeen years ago, advances in materials, machinery, equipment, and software were still in their early stages to enable replication of micron plastic features. It was a struggle.

Fast forward some more to 2010, when we were using injection-compression molding technology, borne out of the CD/DVD industry and morphed by Sony DADC Biosciences for biotech applications, to mold at Illumina a credit-card sized PCR chip with 2.8 million wells, each well 30 microns in diameter. Who would have thought this was possible 25 years ago!

I tell this story about PCR because as the engine that revolutionized research to sprout new fields in DNA sequencing, genomics, bioinformatics and the like, this surging wave spurred the plastics industry to develop new techniques, new machinery, new tools, and new polymers to meet the demanding challenges of replicating increasingly smaller and smaller features.

The result was the plastic microfluidic chip embedded in almost every diagnostic medical device today.

Polymer-Based Microfluidic Chips: The Engine That Is Driving a New Generation of Medical Devices Called Prognostic Point-Of-Care Devices

The impact of the microfluidic chip in the Life Sciences is similar in magnitude to the impact of the microchip in the Information Sciences. If the microchip reduced building-size computers to the size of your hand, the microfluidic chip is reducing building-size laboratories and hospitals to the size of your thumb.

Why plastic? Consider this: It costs around $0.30 cents per sq cm for a silicon-glass chip and $0.03 per sq cm for the same chip molded in Cyclic Olefin Polymer. As Kary Mullis said, it must "manufacturable and cheap, robust and accessible" to the masses.

The push over the last 15 years is transitioning from glass to polymer substrates, because of the latter's scalability, manufacturability, lower cost and biocompatibility. Microfluidics means smaller reagent volumes (some of which can cost several hundred or thousand $ per liter), but also shorter reaction times and faster analyses results (from days in a lab, to hours or even minutes), on-site delivery of test results, smaller sample sizes (blood, cells, etc.), and greater number of iterations (from tens to several millions) – all of these translating to less cost, portability and disposability.

Hence, the development of exciting new devices such the ubiquitous Lab-on-a-Chip, the more recent Organ-on-a-Chip and Body-on-a-Chip, each about the size of your thumb or palm. All of these devices take advantage of the unique fluidic flow properties at the microfluidic level, and most if not all powered by micro pumps and valves without external power sources except capillary pressure, all integrated into the plastic design. Did I say moldable? Yes!

How these are accomplished in fact is due to a convergence of teams of researchers with inventions for advanced immunoassay devices and dense arrays (from sample prep, to amplification, to detection, to immunoassays, to sequencing) with teams of plastics engineers who have developed these new techniques

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to make their scale-up a reality.

As Healthcare moves away from curing diseases to predicting diseases via handheld POC (point-of-care) devices, the advent of the polymer-based microfluidic chip is the enabling technology that is making this happen. These new devices are called Prognostic Devices.

At the heart of these disease-predicting devices are novel developments in nano-biosensors and ultra-sensitive DNA detection.

One Example: Imagine a microfluidics-based POC device that can detect BNP, a cardiac marker antigen that is produced by the heart in very minute quantities before the advent of Arrhythmia in a patient. Then the doctor can prevent the disease by changing the patient's life style, diet and exercise.

There is such a device right now, in production by a China-based company, Micropoint Bioscience (http://www.micropointbio.cn), and was initially funded by the Chinese government, because there are 100 million people with incipient arrhythmia-risk in the Chinese mainland, many without direct access to government hospitals.

The device is called mLabs® Precision POC Testing, which is an immunoassay diagnostic platform, based on their patented microfluidic technologies and advanced fluorescence detection.

According to Micropoint's CEO, Nan Zhang, the device currently tests for D Dimer (a protein released by blood clots), but more cardiac markers are coming soon, including Troponin I (a marker for heart muscle damage), hs-Troponin I (a marker for acute thrombosis syndrome), and the aforementioned BNP.

Why polymer-based microfluidics chips? Over the last 25 years, microfluidics has been largely silicon-glass based, due to their micron-size features, which was difficult to replicate using conventional molding methods and materials.

The state of the art has finally caught up with the exacting demands of the microfluidics field. There are exciting breakthroughs in the following technologies that are enabling microfluidic chip injection molding:

(1) Conformal cooling, microstructure and microfluidic tooling
(2) Microchannel molding, dense micro-array and replication processes
(3) Surface modification and surface treatment techniques
(4) Advanced polymers and plastic materials

There are exciting developments in automation, simulation software, molding equipment, and 3D printing that have advanced in lock-step with the growth of the microfluidic chip field.

Succeeding articles will touch on these breath-taking developments and more examples of Prognostic Devices that are breaking new ground.

About the Author

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