The Little Things That Kill

Jeff Reinke

A look inside the design of cancer detection and imaging technology offers insight on the time, footprint and specification challenges inherent to medical product development.

Cancer cells in a blood sample

Thom Haubert is, by all accounts, a pretty sharp guy. The medical device engineer from Battelle's Health and Life Science Global Business has been honored as Battelle's Inventor of the Year, contributed to and led numerous projects, holds 20 patents and has another 42 applications pending. He manages a group of engineers, designers and technicians and was even recognized for his volunteer work with the OneLab Initiative to develop a manual pearl millet thresher that increases harvest yields to combat world hunger.

Like all design engineers, Thom Haubert is also a problem solver. However, one of his latest projects offered the ultimate challenge in solving a puzzle with literally billions of pieces. The mission for Haubert and his team was to develop new ways of tracking and detecting cancer and other “rare event” cells. So not only was he tasked with helping to create new weapons against a seemingly invincible army, he had to do it what can modestly be described as a challenging operational environment.

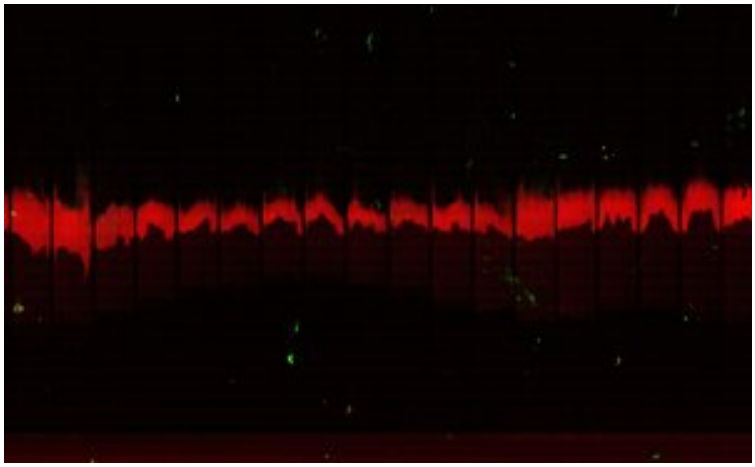
The methodology behind the design of this early detection system focused on the ability to sort out and identify free-floating cancerous cells from amongst the healthy cells in the blood stream. The standard that had to be met was detecting a single cancer cell in10 mL of blood. There are roughly 50 billion red blood cells and 100 million white blood cells in that amount of blood.

“Although flow cytometry (cell counting) is one way to potentially perform this analysis, it is costly and time consuming,” states Haubert. “So the goal of this program was to develop a low-cost, disposable device that could relatively quickly scan for as little as one cell of interest.”

Haubert and his team learned that one possible route would be to focus on what is referred to as the ‘buffy coat’, a fraction of an anti-coagulated blood sample after exposure to a density gradient centrifugation (spinning it really fast in order to create a separation of the different blood components), which contains the white blood cells and platelets. It accounts for only about one-half percent of the total volume. “We learned about cancer cells in buffy coat from our collaborators and partners, Drs. Robert Levine and Stephen Wardlaw (along with two others, Drs. Paul Fiedler and David Rimm),” states Haubert.

Now that they had a reasonable sample to work with, Haubert and his team needed a way to prepare the buffy coat layer so that all the cells could be imaged and analyzed in finding the cancer cells. “Initially, we looked at using some precision glass tubing, which would need to be scaled up from a previous application, and a float device that provided 50 microns of clearance (approximately half the diameter of a human hair.) The trick here was that the float needed to be the same density as the buffy coat in order to spread this substance out along the length of the tube,” explains Haubert. These dynamics would allow for simplified viewing of the sample and a way to ideally pinpoint cancer cells.

Change Of Plans

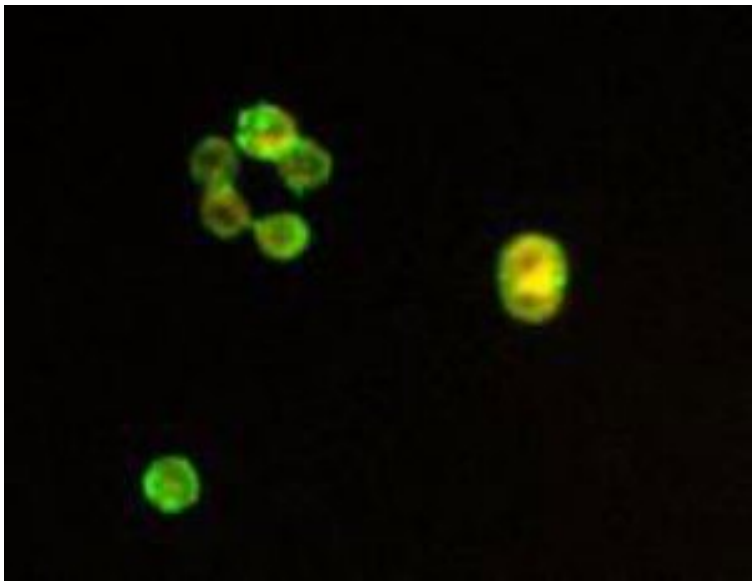


CD45 (red); EpCAM (green)

“Unfortunately, neither the glass tube nor float was available in the size we needed,” recalls Haubert. “And, they were cost-prohibitive to make, so we used a

slightly undersized plastic tube that would expand under centrifugation and a plastic float with precision ridges to create the gap. Once we were able to get the tube and float system to repeatedly capture and display the buffy coat (where the white cells, tumor cells and other cells of interest are located), the team began recovery tests by spiking a number of cancer cells into whole blood samples, and seeing how many could be recovered.

“In order for the device to be successful, we needed to be able to accurately locate and enumerate the cancer cells within the blood sample.” The project would be a success, with the technology licensed by RareCyte, a high-end imaging company serving research labs.



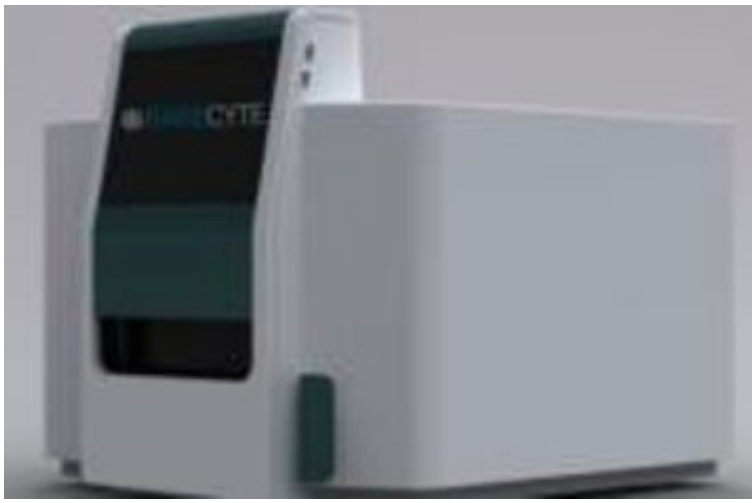
EpCAM (green); CK (yellow)

“Right now, the initial application the company is focusing on is to help cancer physicians and scientists advance their understanding of diseases like cancer and evaluate appropriate treatment methods by enumerating circulating tumor cells in patients,” states Haubert. “Eventually, the hope it that this device will become part of an annual physical, working as an early screening procedure for cancer.”

Building on the work of Haubert and his team, RareCyte has developed their AccuCyte platform which images the displaced buffy coat, which is turned into a thin layer along the inside of the tube wall, with an automated scanning microscope. The images are analyzed for the presence of cancer cells and the data is displayed for the user to review. Cells can be viewed individually, or in the context of the whole sample.

After the composite sample, or individual cell, is imaged, the cell or cells of interest can be isolated through immuno-magnetic separation. This is where all cells are magnetically held in the tube while subsequent washing removes unwanted white and red blood cells. The entire process can be integrated into an existing lab and takes approximately four hours to complete.

The company has also used this technology to develop a custom automated microscope that can collect over 12,000 images per sample, and draws from proprietary software to automatically detect and display the cells in question. Testing with the AccuCyte platform has led to the validation of over 25 disease biomarkers, with studies confirming a consistent recovery of over 90 percent in detecting prostate, breast, colon and lung cancer.



The CyteFinder™ scanner is a custom automated microscope that acquires over 12,000 images per sample (3040 individual fields of view; 4 fluorescent channels each).

Although this particular project doesn't offer a great deal of component-specific best practices, Haubert and his team's insight on medical design does offer some take-away for any design engineer. "The desire to have things smaller, faster and cheaper continues to grow in the medical marketplace," he states. Haubert also sees more medical technology being developed with a focus on getting these devices into emerging markets – primarily third world countries.

This offers a number of challenges, including the need for a simplified, easy-to-use product that may need to be disposable and, of course, less expensive to produce and buy. Electronic components in such products also need to be able to withstand rugged environments, something not always synonymous with the elegance of many medical products.

All of the challenges, however, do have their rewards. "Working on a device that has the potential to positively impact millions of lives was exciting, and I felt privileged to be able to work on it," states Haubert. "The other item to note is that as developers of medical products, we are often working with devices that, if they were to fail, could seriously injure a patient. For this reason, our design and development process always includes Safety Risk Management process. In the same way that if a device fails and either its contents or components pose a risk to a person, a diagnostic device that creates a misdiagnosis can be equally as hazardous."

Jeff is the editorial director of Advantage Business Media's Design Group and MDT. He has worked with print and electronic media properties covering industrial operations, OEM product design, processing and transportation, as well as the medical marketplace. He has a B.A. in communications from UW-Whitewater.

Source URL (retrieved on *12/13/2013 - 3:38pm*):
http://www.mdtmag.com/articles/2012/07/little-things-kill?qt-recent_content=0&qt-video_of_the_day=0