Partners for Life

By Melissa Kinsey, The Blue Waters Group

Some the most successful inventions in history were launched by a smart alliance between an inventor and a partner with good business chops.

Alfred Nobel, best known as the inventor of dynamite and the philanthropist who endowed the Nobel Prize, had respectable business instincts himself, but he also had enough sense not to rely on them. Instead, he enlisted partners around the world to help promote his invention to railroad and canal builders.

The same might be said of the brilliant Notre Dame scientist Hsueh-Chia "Chia" Chang. He's joined forces with entrepreneur and former R&D executive Leslie "Les" Ivie, founder of the biotech firm F3, pronounced "F Cubed."

Chang, the company's chief scientific advisor, is developing a portable device that can rapidly pinpoint pathogens, toxins, and other harmful substances in body fluids, such as blood and saliva. The device can also analyze water samples from lakes and streams. This tool may revolutionize or even supplant certain conventional technologies in the areas of homeland security, environmental safety, and medical diagnostics. In short, it promises to make the world a better place.

"There are so many ways to help people because the technology has so many applications," says Ivie. Ivie and Chang have assembled an elite team of researchers and other professionals to perfect Chang's brainchild and bring it to market.

"I just like to see my ideas and inventions realized," says Chang, who has been granted three patents and six provisional patents. "Writing another paper at my age isn't all that rewarding anymore."

Chang is the Bayer Professor of Engineering at the University of Notre Dame and editor of the prestigious journal *Biomicrofluidics.* Ivie discovered Chang's research during a stint as chief technology officer at Honeywell. After some soul-searching and with the encouragement of his wife, Ivie decided to wager the American dream for a shot at saving the planet.

He left Honeywell, trading in his Corinthian leather executive chair and corner office for the opportunity to start F3, which has licensed the patent for the novel technology that is the basis of Chang's handheld diagnostic device.

Taking advantage of Notre Dame connections

Although Ivie is based in Chicago, F3's research and development activities take place at Innovation Park at Notre Dame, where Ivie has leased customized laboratory space fitted out with the latest high-tech equipment.

"Innovation Park is one of the most state-of-the-art facilities available in the U.S.," Ivie says. "It had the right lab and technology infrastructure already in place for us. The Park team has been so helpful and accommodating to us through this critical stage … There's simply nothing like it in Chicago."

But make no mistake: the principles underlying F3's remarkable technology are a product of Chang's groundbreaking work as a member of the University of Notre Dame's Advanced Diagnostics and Therapeutics initiative. The AD&T initiative is an interdisciplinary effort to create diagnostic and therapeutic systems that address some of the most pressing health and environmental needs in the world.

The Notre Dame connection doesn't stop there, either. F3 also is a key customer of the University of Notre Dame's Nanofabrication Facility, where researchers develop nanostructures and microelectronics for sectors ranging from communications and computing to energy and healthcare. It fabricates the biochips used in Chang's device.

A device that can make a big difference in the world

Simply put, Chang's prototype is a portable tool that employs microfluidics technology for real-time detection of the DNA of various disease-causing organisms, such as hepatitis, E. coli, and even anthrax, in any liquid sample—blood, urine, lung secretions, or just water. And the device can be used to detect unsafe levels of bacteria or other contaminants in public water supplies, lakes, and rivers.

Now, you might conclude that Chang's clever little appliance is unlikely to be comprehensible, much less interesting, to anyone who hasn't, say, sequenced the human genome or synthesized a wrinkle cream that actually works. But as sophisticated as the instrument may be, it's also elegantly simple.

"This portable device integrates existing and new technologies into a platform that can rapidly and selectively identify target proteins and nucleic acids," says Chang. "Antibodies and oligo probes are coupled to nanotubes in the device, in order to create functionalized sensors that can detect protein and DNA molecules in very small concentrations."

Essentially, a matrix of these hollow nanotubes, each only a few billionths of a meter wide, serves as a high-tech net to catch target molecules associated with specific pathogens. Then a biochip emits an electronic signal that pushes, or “flows,” the liquid sample across the nanotubes.

“This open-flow trapping technology fishes the target molecules out of the liquid,” Chang continues. “A change in impedance—that is, opposition to the electrical current—not only tells us that a target has been identified, but also measures its concentration in the sample. It works like a charm.”

Chang’s lab-on-a-chip technology has an astonishing range of conceivable applications. Point-of-care diagnostics is perhaps the most intriguing, both in terms of its financial promise and its potential to save lives. The device may prove commercially lucrative as a means of instantly diagnosing garden-variety ailments, such as strep throat, and more serious maladies, such as HIV and hepatitis C. The only limitation of the technology is that, for the moment, each biochip can be fabricated to target only a single pathogen. In other words, the device can confirm or rule out only one suspected pathogen at a time. Chang's group is actively working to develop a biochip capable of probing for multiple targets, an attribute known as “multiplex pathogen detection.”

An effective tool to detect TB in low-income countries

The so-called point of care at which Chang’s device could be used might be a doctor’s office, a patient’s bedside in a skilled nursing facility, or even a walk-in clinic at a pharmacy. But for researchers like Jeffrey Schorey, a Notre Dame biology professor who collaborates with the F Cubed team, there’s a more urgent need for the technology at a point of care 8,000 miles away. The entire continent of Africa has been devastated by pulmonary tuberculosis, a lung infection spread by airborne droplets released when a person with an active TB infection coughs, sneezes, or talks.

“More than 2 billion people — about one third of the world’s population — carry the bacterium that causes TB,” says Schorey. “But only about 5 percent of them have active disease, which means that they have symptoms of illness and can transmit the bacterium to others.”

TB, explains Schorey, is the most common opportunistic infection among people with AIDS. Thus, the fatality rate among people with TB in some African countries is double the fatality rate elsewhere in the world, because the prevalence of HIV/AIDS in those countries is as high as 26 percent among adults ages 15 to 49. Between 1.5 and 2 million deaths are attributed to TB each year, but Schorey believes the real figure to be much higher, given that TB deaths among people with AIDS are recorded as AIDS fatalities.

Tests used to diagnose TB are notoriously inaccurate because they lack sensitivity and specificity. Low specificity means that certain non-TB bacteria can trigger a false-positive result in people who are not infected. Low sensitivity means that the test often fails to identify those who have the disease. Chang's instrument yields better predictive value compared with other methods because it can detect the TB antigen with 10 to 100 times less of the target molecule present in the sample than is required by the most commonly used conventional tests for TB diagnosis.

Throughout much of Africa, reaching even rudimentary healthcare services may mean trekking or being carried for miles across a landscape that's so challenging to traverse, it makes the Amazing Race look like a stroll down the Champs-Élysées.

Shrinking the distance from patient to point of care is just good horse sense, yet practical problems seem to conspire against anyone who tries. Equipment transported to rural outposts can be damaged en route, for example. Biological samples taken to a lab for analysis tend to be unstable without refrigeration, rendering them diagnostically useless. Chang's device overcomes these and other challenges. Schorey ticks off the advantages of the technology over current diagnostic methods.

"It's relatively inexpensive," he says. "It's simple to use, so people don't have to be trained. The antigen we're looking for is found in the urine of people infected with TB, so we have a readily accessible sample. There's no need for transport or refrigeration. And the results are available immediately."

TB is difficult to treat because the TB bacillus has become resistant to the potent antibiotics that used to guarantee a swift cure. So what's the point of an accurate, efficient diagnosis if a nation's healthcare infrastructure consists of little more than a network of field hospitals and mobile clinics?

"These countries have limited resources, not *no* resources," Schorey explains. "They need to know which population to treat in order to curb the spread of TB and prevent latent or dormant disease from progressing to active disease. If we could cut the death rate by even 10 percent, that would be huge."

A weapon against bioterrorism and environmental threats

As a leader in the global community, the U.S. government offers grant funding and other support to buoy such public health efforts. The federal government is equally enthusiastic, however, about the possible national security applications of Chang's technology.

Detection of pathogens in the drinking-water supply after a natural disaster or mass-casualty incident could prevent the spread of water-borne disease. Quick diagnosis of diseases caused by weaponized biologic agents, such as anthrax, could help health officials isolate a bioterrorist attack quickly and zero in on the source of the agent before the general populace could be infected. It would also allow law enforcement agencies to begin immediately pursuing the person or group responsible for the incident.

The Environmental Protection Agency is also keenly interested in F3's technology. Chang's device can detect the DNA not just of viruses and bacteria, but also of invasive species like the Quagga mussel, a small bivalve native to Eastern Europe that has colonized Lake Michigan. This freshwater mussel has a destructive propensity to multiply quickly and attach itself to almost any surface, causing Midwestern business and industry hundreds of millions of dollars every year. Clusters of mussels choke off water intake pumps at power plants and water treatment facilities. A crusty rind of mussels can form on boat hulls, docks, and even beaches, the sharp shells posing a hazard to beachgoers. The Quagga mussel and other nuisance species, as the federal government calls them, disturb ecosystems by competing with, physically displacing, or killing native species. Instant detection using Chang's device could allow a ship's ballast water to be tested before it enters the lake. Any vessel found to be contaminated could be denied passage.

Earlier this year, the EPA embarked on a Cooperative Research and Development Agreement study with F3 to explore related ideas, such as the placement of remote sensors in rivers to warn of contamination before it reaches recreational areas or municipal water supplies. "To some, that may not seem like the sexiest application," Ivie admits, "but it gave us an area to focus on right out of the gate."

The study offers no direct funding, but it gives F3 priceless access to the EPA's extensive collection of water samples, permits F3 personnel to train at EPA labs, and complements F3's own capitalization efforts. "They've written some pretty powerful recommendations for us," says Ivie. "Two letters they wrote on our behalf allowed us to raise $1.5 million from other sources."

Ivie's attention to funding brings us around full circle to the importance of good entrepreneurship skills. Financial support for F3 has been supplied by a variety of agencies and investors, including the National Institute of Allergy and Infectious Diseases and the Academic Model Providing Access to Healthcare, an offshoot of the United States Agency for International Development.

But Ivie no longer assumes he knows where the next dollar will come from. "My mother-in-law talked to someone who was interested in what we were doing," he recalls. "My wife kept pestering me to call this guy, so one day I finally did it, just to show her that it was a wild goose chase. Turns out the guy really *was* interested, and he really *did* want to invest. Boy, was I wrong!"

It seems Ivie isn't the only one with a head for business.