First Light Biosciences Developing Rapid Syndromic ID/AST System Using Digital Imaging

Apr 11, 2018 | Madeleine Johnson

NEW YORK (GenomeWeb) – First Light Biosciences is developing a diagnostic system to identify pathogens and perform antibiotic susceptibility testing directly from patient samples using inexpensive labeling and non-magnified digital imaging technologies. The Massachusetts-based startup expects to have a product submitted to the US Food and Drug Administration some time next year.

Getting a patient on the right antibiotic at the onset of infection is "the holy grail of clinical microbiology," Don Straus, founder and CEO of First Light, said in an interview. Advantages include more focused use of limited resources, improved medical outcomes, and, potentially, staving off superbugs.

But good antimicrobial stewards can find themselves stymied by commonly used rapid diagnostic tests that miss low levels of target, as well as by nucleic acid amplification tests that are so sensitive that they can detect contamination and asymptomatic carriage.

Straus, who previously worked on microbial contamination in pharmaceutical manufacturing, or "bugs in drugs," with his first company, Rapid Micro Biosystems, came at the ID/AST field with a determination to make the technology simple. The result has been a digital imaging system with genetic, phenotypic, and protein detection components capable of counting single molecules and determining antibiotic susceptibility, Straus said.

The instrument, called MultiPath, can be used to count labeled bacterial cells or single molecules tagged with antibody-coated fluorescent nanoparticles.

"The core technology is non-magnified digital imaging of microscopic things," he said.

Taking pictures of microscopic things without magnification allows single molecule counting because fluorescent labeling enables counting targets that are about the size of a single pixel in a standard million-pixel digital camera.

Importantly, the fluorescence-based method can be used to count individual targets in large areas, so it can detect "a small number of small things in a big volume," Straus said. And, it is very inexpensive since it uses standard CMOS technologies found in cell phone digital cameras.

Another key to First Light's technology involves magnetic particles, which are tagged to a different site on the target molecules than the florescent label and are used to pull labeled targets down to the camera surface, thus eliminating background signal and making for a "wash-free" assay.

"The pictures look like stars in the sky, so it is really trivial just to count the spots," Straus said.

The technology grew out of a finger-stick anthrax detection test Straus began developing with a company, Genomic Profiling Systems, that has since become First Light using funding from the NIH and the Biomedical Advanced Research and Development Authority.

For BARDA, the firm is also developing the same MultiPath technology for point-of-care use outside of the hospital, Straus said, including rapid AST testing.

First Light's MultiPath platform now boasts a 20-sample capacity with throughput of 200 multiplexed pathogen ID tests or 40 AST tests in one eight-hour shift on a random access, fully automated benchtop instrument. Assays are cartridge based and can be run directly from samples, including urine, whole blood or plasma, stool, and swabs.

The system recently was one of 10 semifinalists for the National Institutes of Health antibiotic resistance diagnostics competition, and the technology has broad patent claims in the US and Europe, Straus said.

The first test on the platform will be a highly accurate test for *Clostridium difficile* toxin. The market problem with *C. diff* testing is that immunoassays are not sensitive enough to detect low levels, Straus said, while nucleic acid tests detect *C. diff* carriage.

The MultiPath *C. diff* test is direct from stool,and detects toxin at 60 times lower levels than common on-market immunoassays, Straus said.

First Light Biosciences has also been awarded more than $4 million in funding from the National Institute of Allergy and Infectious Diseases since 2015 to develop the syndromic ID/AST test system, with the most recent funding renewal describing a diagnostic test for catheter-acquired urinary tract infections directly from patient samples.

"About 25 percent of sepsis cases are urosepsis that come from these complicated infections, so they are really dangerous," Straus noted. The firm is also developing a POC test for UTIs to "get patients on the right empiric therapy at the onset of infection," he said, adding that it chose UTI tests among its first to market because urine testing is the highest volume test in hospital labs.

The firm is also interested in the sepsis market, as competitive as it may be becoming. "The crowded part [of the market] is the positive blood culture tests," Straus said, since blood cultures have a high density of targets that most any technology can tackle. First Light plans to develop blood infection AST using whole blood samples, he said, which might provide a competitive advantage.

Straus compared the firm's rapid, direct-from-sample ID/AST in development to the only platform currently clearedby the US Food and Drug Administration for rapid ID/AST, the PhenoTest BC Kit bloodstream infection test from Accelerate Diagnostics.

Accelerate's test can identify bacteria or yeast from a positive blood culture in about 1.5 hours using fluorescent *in situ* hybridization, with phenotypic AST determination incorporating imaging and morphometric analysis in about 6.5 hours after the organisms are detected from blood cultures. While the First Light platform may process 40 positive blood culture tests in a shift, Romney Humphries, Accelerate's CSO said in a recent interview that most labs are unlikely to have more than five or so positive blood cultures per day and thus the Accelerate test may be better tailored to a typical labs' needs.

The First Light test will determine phenotypic susceptibility in non-sterile samples, Straus said, as well as in polymicrobial samples. Accelerate's test, as well as most other tests in development, use FISH for ID and then time-lapse darkfield microscopy to measure growth, "which is not specific for any particular bug," Straus said. The MultiPath cartridge on the

other hand enable looking at growth using FISH for multiple targets and perform a differential growth test for AST analogous to the method used to determine minimum inhibitory concentration.

The company envisions its system could also be used as a reflex phenotypic AST test for other syndromic panels for molecular ID on the market.

Whether labs will soon be ready to give up their current ID/AST methods – such as automated *in vitro* ID-AST tests like BioMérieux's Vitek 2, Becton Dickinson's Phoenix, Beckman Coulter's MicroScan, and Thermo Fisher Scientific's Sensititre, or molecular tests that can detect a handful or resistance genes, like Luminex's Verigene and BioMerieux's FilmArray – remains to be seen, as previously reported.

But First Light counts former CEO of Nanosphere William Moffit, Qiagen's senior VP of molecular diagnostics Thierry Bernard, and former senior VP of research and development at Orasure Technologies Sal Salamone among its board members. In terms of throughput and capability to do rapid polymicrobial ID/AST direct from sample, "My board understands we have something that is potentially really big," Straus said.