PROBE-MONOCLONAL COMPETITION HEATING UP

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Left: Genetic Systems' monoclonal-based *Legionella* test. The red counterstain makes it easier to see the (green) fluorescent bacteria.
Right: Gen-Probe's nucleic acid probe-based test kit.

SAN FRANCISCO—Monoclonal antibodies and nucleic acid probes are two revolutionary—and sometimes competing—technologies. According to J. Kay Noel, an El Cerrito, CA-based healthcare consultant, monoclonals will be used to replace polyclonal antibodies in existing analyte tests, and they will dominate in therapeutic drug monitoring and cell typing. Nucleic acid probes, however, are the only answer for genetic testing, detecting latent viral infections, and determining disease susceptibility and antibiotic resistance in bacteria. Most interestingly, the techniques will go head-to-head in diagnosing infectious disease (in humans, animals, and plants), detecting cancer, and testing food.

Voicing her views at the Annual Meeting of the Society for Industrial Microbiology here, Noel noted that over 100 monoclonal-based kits are on the market in the U.S. today. But, she said, the application of antibodies to infectious disease has been more difficult than expected due to specificity and sensitivity problems. Probes, on the other hand, have the potential for excellent specificity and sensitivity, but she called this technology "commercially unproven." Only a handful of probe-based tests have reached the market so far.

Noel pointed out that antibodies recognize only a 4–5 amino acid sequence on a protein, while probes can detect much longer nucleic acid sequences. This is what gives probes their exquisite specificity, and it means that probes could be better in cases where genetic drift is a problem and antigenic determinants tend to change. Monoclonals, however, have an edge in ease-of-use, she said, and

antibodies will continue to be cheaper than probes for at least the next several years.

According to David E. Kohne, chief scientist at Gen-Probe (San Diego, CA), soon it will be possible to develop probe technology to detect as few as 1–10 organisms in a sample. In addition, it is easier to vary the specificity of probes than that of monoclonals. For example, Gen-Probe has developed probes that detect all cellular life, all eubacteria, all species in a genus, a complex of species, or just a single species. Another advantage of probes, Kohne said, is that the hybridization complexes formed when a probe binds to complementary single-stranded RNA or DNA are stable; antigen-antibody complexes tend to disassociate under harsh conditions or temperature. Finally, Kohne stressed that Gen-Probe is designing its tests to fit current clinical laboratory procedures, so they should be no harder to run than serological tests.

Probes and antibodies are already competing directly in the marketplace in a few instances. Genetic Systems (Seattle WA) uses a fluorescein-labeled monoclonal to detect *Legionella* infection, while Gen-Probe takes advantage of a DNA probe to *Legionella* ribosomal RNA. In another instance, Bionetics Research (Rockville, MD) uses a pair of monoclonals to detect *Salmonella* contamination in food, while Integrated Genetics (Framingham, MA) markets a DNA probe kit for the same purpose. Jerome A. Mattingly, associate director of product R&D at Bionetics, said that his company's test, which uses monoclonals designated M467 and 6H4, detects all of the 500–600 *Salmonella* strains the company has test-

ed. Although the test, which sells for \$3.85, also reacts with about 10 percent of the (non-dangerous) *Citrobacter*, Mattingly does not view these rare false-positives as a serious problem. Most importantly, the assay gives results in 44–54 hours, quite an improvement over the four days required by conventional culture methods. The Integrated Genetics test costs between \$7 and \$8, and it gives results in 46 hours. Integrated senior scientist Michael Curiale stressed, however, that probes do not have the same history of cost-reduction as antibodies, so he expects that probe prices will decline greatly.

Speed is the crucial factor for *Salmonella* tests because food companies must store their product while the safety tests are performed. Conventional *Salmonella* testing takes 4–5 days, while other tests on food take a maximum of two. Curiale said that probes could cut the time of *Salmonella* detection down to 24–36 hours within two years. This could represent big savings to food companies if the time for the other tests can also be trimmed to one day. Mattingly, however, doesn't look for monoclonal assays to take less than two days, but he does not foresee this as a problem as long as tests for other infections still take that long.

One problem that both technologies are running into is the finding of positive readings in samples that test negative using traditional culturing methods. Mattingly pointed out that at least some of these "false positives" may actually be unculturable *Salmonella* species. "The culture method," he complained, "is the Bible to which we have to be compared."

—Arthur Klausner