



Miraculins Preparing Prostate Dx for FDA Review in 2008, Seeks Development Partners

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By Tony Fong

Five years after it first began developing its mass spec-based prostate cancer diagnostic, Miraculins said this week it is getting ready to begin testing it in order to submit it to the US Food and Drug Administration.

Last month, the Winnipeg, Manitoba-based company said a validation study confirmed the ability of its pre-prostate-cancer biomarker diagnostic to weed out 23 percent of unnecessary biopsies and identify 93 percent of patients positive for prostate cancer.

The next step is to perform tests for FDA approval, expected to begin in early 2008, Miraculins CEO Christopher Moreau told *ProteoMonitor* this week. In the meanwhile, it has begun talking with potential commercialization partners for the diagnostic, and has also contracted with outside firms to develop the test, currently mass spectrometry-based, into an ELISA test format.

In addition to its prostate diagnostic, Miraculins' lead product, the company is developing tests for colorectal, stomach, and pancreatic cancers. If it performs as anticipated, and the company is successful in bringing it to market, it would address an issue that has long plagued the prostate-specific antigen screening test: a high rate of false positives. By some estimates as many as 70 percent of all PSA tests that show elevated levels turn out to be false positives.

While these tests can detect elevated levels of PSAs, they cannot correlate higher levels of the protein with cancer because high PSA levels can also indicate benign growths. The result is that some men have been wrongly diagnosed, leading to unnecessary treatments such as surgery or radiation.

Indeed, the National Cancer Institute says on its website that the test is not known to save lives and cites a 1994 study published in *The Journal of Urology* that found that only 25 percent to 30 percent of men who have biopsies due to elevated PSA levels actually have the cancer.

Miraculins' test is not intended as a replacement for PSA tests, Moreau said, but as a complement. After a PSA test weeds out those patients who aren't indicated for cancer, Miraculins' test would help doctors determine who might be candidates for additional tests and treatments.

"The focus is on giving urologists an additional tool for biopsy diagnosis," Moreau said.

Miraculin's diagnostic is based on a panel of three protein biomarkers discovered and identified by the company as being closely associated with prostate cancer. The markers were found via Surface Enhancement Laser Desorption Ionization-Time-of-Flight mass spec analysis.

The most recent study, initiated in November 2006, was conducted as a follow-on "to demonstrate the utility of the Miraculins biomarkers in identifying men who underwent an unnecessary prostate biopsy ... without compromising the correct diagnosis of men who do have prostate cancer," the company said in a summary of its test results.

For this study, the company recruited 198 men from 20 sites in Canada. The study included three separate urine collection methods, including prior-to-digital-rectal examination, or DRE; post-DRE; and 24-hour collection, to eliminate artifacts.

Of the 198 participants, 106 were subsequently diagnosed with prostate cancer. According to the company, its biomarker panel performed with a sensitivity of about 93 percent and a specificity of about 23 percent, meaning that in its test 21 men would have been spared unnecessary biopsies, and five men with prostate cancer would not have had their diagnosis confirmed by prostate biopsies, according to Miraculins.

The company added that further analysis of the data indicated that its diagnostic had even better results when trying to differentiate patients with aggressive prostate cancer — those with a Gleason Grade of 7 or more — from those with non-aggressive cancer. Those findings showed the test to have a sensitivity of approximately 92 percent and a specificity of about 50 percent, depending on the classification model used.

The Gleason Grade, represented as a range from a low of two to a high of 10, is a measurement of the aggressiveness of a tumor.

Chance for Missed Diagnoses?

But while the company is trumpeting the potential of its diagnostic to reduce the number of false positive PSA results, one expert in the cancer community expressed concern that in doing so, some true positives may be missed.

"The bottom line here is that any way to reduce the rate of false positives is a good thing and it's worth pursuing. But you have to ask yourself, 'At what cost?'"

Robert Smith, director of cancer screening for the American Cancer Society, said that prostate cancer progresses relatively slowly, and the goal is to identify those cases that truly have lethal potential and to avoid unnecessarily treating cases that may not become lethal for years, or ever. Over-treatment, he said, often leads to irreversible side effects such as incontinence and impotence.

But Smith added that attempts to weed out false positives carry their own dangers. What concerns him about Miraculins' diagnostic is that "it's not 100 percent

sensitive, which means that you've got somebody who's scheduled for a biopsy that the test would say doesn't need one, [when in fact] they do have cancer," he said. "The bottom line here is that any way to reduce the rate of false positives is a good thing and it's worth pursuing. But you have to ask yourself, 'At what cost?'"

"There are screening programs around the world that place a higher priority on reducing the number of false positives, and it is at some cost due to missed cancers," he said.

Moreau said that the company is continuing to fine-tune the test, and that once it is moved to an ELISA-based format both the sensitivity and specificity will increase. But trying to develop a test that can detect true positives while reducing false positives is a balancing act, he said.

"You want to eliminate men who don't have to go for a biopsy, but at the same time you don't want to miss men who have [cancer]," he said. Calling the test "an adjunct to the toolbox that a urologist has," Moreau said he is "comfortable with 93 percent sensitivity."

Miraculins is now preparing to go into full testing for FDA approval and has employed the services of Washington, DC, law firm Hogan & Hartson to help it design the study.

It has also begun talking to potential partners to eventually commercialize the test, though Moreau declined to elaborate. He estimated the market for the diagnostic to be \$300 million to \$500 million annually.

Miraculins has diagnostics for other cancers in development. After its prostate test, its colorectal cancer test is furthest along in development. The company acquired the colorectal cancer biomarkers as part of its purchase of Europroteome two years ago [See [PM 06/24/05](#)]. It and the Fox Chase Cancer Center in Philadelphia began validating them last summer [See [PM 06/15/06](#)].

Six analytes have been validated at 90 percent sensitivity and 40 percent specificity, Moreau said. Two of the six have been purified and sequenced. The test is meant as an alternative to a colonoscopy and fecal occult blood test.

The company has also validated an undisclosed number of biomarkers for stomach and pancreatic cancers and is currently studying the results.

It has delayed further work on its breast cancer diagnostic due to limited financial and human resources. Depending on how its other diagnostics proceed, work may pick up again on its breast cancer test sometime next year.