

**DNA SEQUENCING**

## BAYLOR'S METZKER STRIVES FOR FOUR-LASER 'SUITCASE SEQUENCER'

In one of the most anticipated talks at February's Advances in Genome Biology and Technology conference in Marco Island, Fla., **Baylor's** Mike Metzker unveiled a new concept for what he says could be the first portable DNA sequencer.

The germ of the idea has been in the works for several years. "Graham Scott and I were brainstorming one afternoon in my office about three years ago about new ways to sequence DNA," says Metzker, an assistant professor at Baylor and adjunct at **Rice University** as well as a member of Baylor's Human Genome Sequencing Center. One goal in particular was to be able to sequence genomic DNA directly to eliminate the need for cloning and PCR, which represent "a bigger part of the sequencing process than sequencing itself," he says. The concept that emerged was a four-laser machine

that would give superior sensitivity and specificity in base calls, thereby enabling direct-DNA sequencing.

But reducing that to practice has been quite a challenge, Metzker says — and one that's still very much in the works. It took "a lot of optical engineering" and the efforts of four people — in addition to himself and Scott, Rice faculty Robert Curl and Carter Kittrell contributed to the design of the pulse-multiline excitation device. By the time Metzker gave his talk in February, he says, the instrument was far enough along in development that the pieces are operating together as a functioning bread board detector.

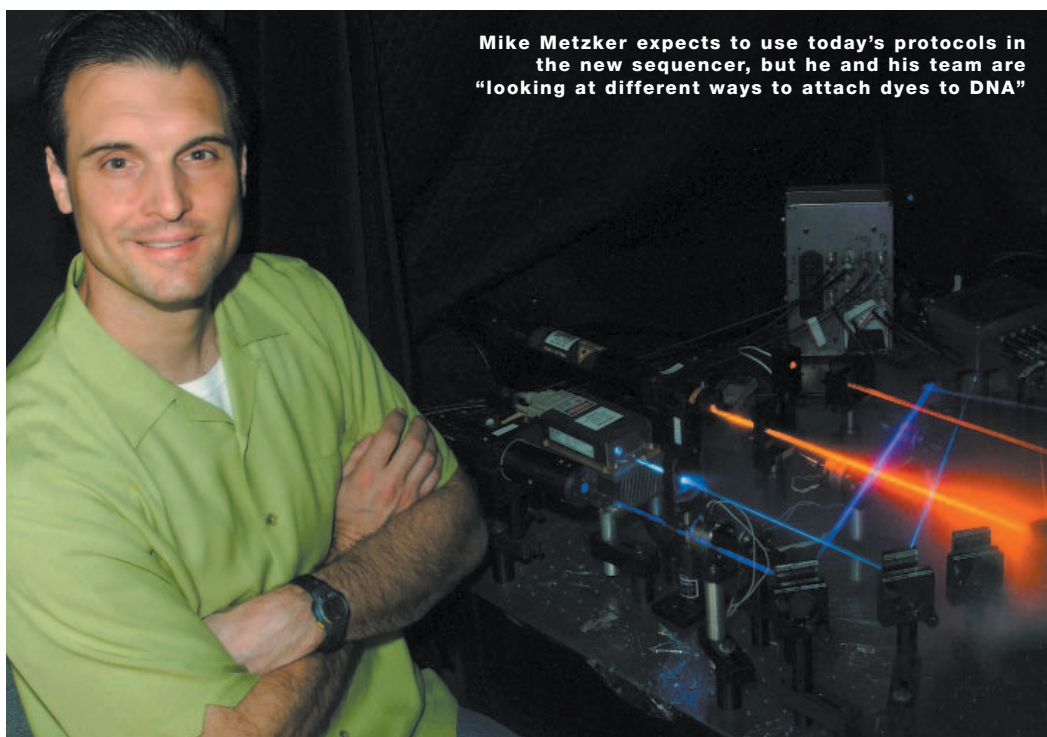
In spite of the complex optics, the sequencer design itself is fairly simple. Four lasers, their beams focused through a kind of reverse prism into a single coaxial beam, fire sequentially at a target molecule, exciting only the particular dye

each is tuned for. The fluorescence emitted is measured by a detector, and that data is combined with time correlation data that monitors which laser fired when. It's all done in what Metzker calls "a color-blind manner" — measuring the dye only by its photon emission rather than reducing it to a color, a method that makes the instrument more sensitive to weak fluorescent signals such as those from genomic DNA.

So far, the system has simulated base calling in tests that involved four test tubes holding four different dye-labeled primers, presented in random order. "The order of the fluorescent traces allowed us to determine the dye sequence," Metzker says. "We then compared that to the sequence of dyes given and it was perfect."

Those early tests have been sufficient to apply for a patent on the instrument (held by Baylor), and they've also given Metzker grounds to win **NHGRI** funding. He's started up his own company, **LaserGen**, with the eventual goal of manufacturing and selling the sequencer. Metzker says, "We are forecasting very aggressively the product hitting the market in 2007."

Next up, Metzker is working to couple the instrument to a single capillary to prove that the system works for DNA sequencing — there's still a long way to go, he acknowledges. In the meantime, Metzker is also pursuing design tweaks such as smaller, lighter lasers that would make the sequencer portable — small enough, in fact, that he calls it the "suitcase sequencer" — for any kind of application requiring field experiments.



Mike Metzker expects to use today's protocols in the new sequencer, but he and his team are "looking at different ways to attach dyes to DNA"