Rade Drmanac

Launching the world's first commercial human genome sequencing center is currently the 'unreasonable' career ambition of sequencing-by-hybridization pioneer Rade Drmanac.

Of all the technologies being developed for large-scale genome studies, sequencing by hybridization (SBH) may be the one you hear about the least. There's a simple reason for that. According to Charles Cantor, chief scientific officer at San Diego–based Sequenom, "it hasn't delivered."

But don't tell that to Rade Drmanac, serial entrepreneur and founder of HySeq (now Nuvelo, of Sunnyvale, California), who is on the verge of launching his fourth company. Drmanac got on board with SBH early on—he described it first in a paper he wrote as a graduate student in 1987 back in his homeland, the former Yugoslavia. The reason, Drmanac will tell you, is also quite simple. He hated acrylamide gels. "I've never run a sequencing gel in my life," he says—quite an admission from someone who has made a career out of genomics.

Drmanac recalls reading about PCR and brainstorming with friends about the possibilities of using primers for mapping and sequencing. "Wow. If we use two primers, four, eight…I was so excited just thinking there was another way to approach sequencing." That was the birth of sequencing by hybridization. And with a little help from the US Department of Energy (DOE), Drmanac and his mentors in Belgrade worked out the details of SBH, which can be found in a 1989 paper (*Genomics* **4**, 114). The grant, a mere $150,000 a year, is a pittance by today's standards, but at that time and in that place, those "real US dollars" went a long way.

SBH works by hybridizing a series of probes to an unknown sequence and reading 'words', unlike its competing technology, sequencing by synthesis, which reads one base at a time. That's only one of its advantages, according to Drmanac. No molecular separation is involved, which in conventional DNA sequencing is the slowest, as well as the most difficult to miniaturize, step. In addition, each successive reaction is independent from the previous one, which is to say, the reaction doesn't lose efficiency as it goes along. The same can't be said for sequencing by synthesis: you miss incorporating one base, and it's game over for that strand.

Following the early work on SBH, the DOE grant ran out and the agency, though interested in having the work continue, balked at providing more funding to Yugoslavia. Solution: Drmanac, along with nine colleagues, came to the United States to set up shop at Argonne National Laboratories near Chicago. At Argonne, his group initiated mapping studies and, rather quickly, unearthed novel genes, which Drmanac realized had value. From this effort followed patents as well as a commercial venture, HySeq. According to William Bains, a fellow entrepreneur currently at the University of Cambridge UK, none of this was easy. Drmanac admits that raising money was difficult, at least not without giving away the company—70% is what investors wanted at that time, according to Drmanac. Instead, another federal program, the Advanced Technology Program (ATP) of the National Institute of Standards and Technology of Gaithersburg, Maryland, came to the rescue, and with a $1.5 million ATP award and a few million from small investors, Drmanac founded HySeq, which in less than three years went public.

Like many of the genomics-based companies in the 1980s, HySeq found it challenging to transition from genomics to pharmaceuticals, and the collapse of the market didn't help. "What one learns is that market forces are stronger than any good company. No matter how good the company, if the market is bad, you have no choices," says Drmanac. This bump in the road led him back to one of his earlier ideas—doing SBH on high density spotted arrays, which had technically become possible, owing to work by people like Ed Southern and Steve Fodor.

And with the launch of his latest venture, Complete Genomics, Drmanac is expecting to take SBH to new levels, although it is SBH that has been through many iterations. Complete Genomics calls its sequencing technology combinatorial probe-anchor ligation (cPAL), and at its core is an array of DNA 'nanoballs', which are arranged in a precise, high-density grid (350 million spots per slide now; Drmanac suggests up to a billion in the next iteration). The system retains the main advantages but resolves several limitations of SBH, using a set of 40 probes and eight adapter-specific anchors. It reads off 2×35 base paired–end sequences in an independent, unchained base reading.

Drmanac has been singularly, one might say doggedly, focused on one goal most of his scientific career: to provide complete, high-quality human genome sequences for medical and clinical use. And according to Harvard's Church, he has tried every possible way to do it—short primers or universal arrays—and has taken SBH technology farther than anyone else in the field. Now, with his new company, Drmanac may get to realize his goal, assuming he gets help from improvements in both arraying technology and detection technology. His claims for the platform are ambitious: Complete Genomics will deliver a complete human genome for almost 100 times lower than the next lowest one (the only similar service has a price tag of $350,000—see p. 1109). It will be set up as a service company, with plans to sequence 1,000 human genomes in 2009, scaling up to 20,000 in 2010 (10% of them for a single client, Seattle's Institute for Systems Biology), and to ultimately create a string of nine genomics centers in collaboration with countries, companies or academic institutes.

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One secret to Drmanac's success is his boundless enthusiasm. Bains, who like Church, has known him since the early days of SBH, says, "He radiates enthusiasm. He dared to say 'Let's do this.'" Church conjures up a quote by George Bernard Shaw when talking about his longtime friend and colleague. "Reasonable people adapt themselves to the world. Unreasonable people attempt to adapt the world to themselves. All progress, therefore, depends on unreasonable people." "Drmanac," says Church, "is unreasonable."

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