

## GONE FISHING

**TROLLING FOR TRANSCRIPTION FACTORS**

NEW YORK—"Why transcription factors?" The question echoed through academia's ivy-covered halls and ricocheted off the glass-and-steel bastions of corporate biotechnology. The speculation centered as much on the validity of focusing a biotech company on transcription factors—enzymes that control transcription—as the motivations behind the principles involved. Had venture-capitalist dad forced talented—but impoverished—academics into shotgun-wedded bliss so they might benefit from their future research? Or, could it be that scientists at the pinnacle of their careers had lost faith in the altruistic pursuit of knowledge—and cashed in on their marquee value?

Clearly the fact that Robert Tjian of the University of California (Berkeley) and Steve McKnight of Carnegie Institution (Baltimore, MD) had joined forces with Genentech's (So. San Francisco, CA) David Goeddel to form Tularik (Menlo Park, CA) caused a minor tremor felt by neighbors on both sides of the biotech faultline. The truth appears simpler than expected (or hoped for): outstanding scientists united to seize what they see as biotech's challenge of the 1990s—controlling disease at the level of gene expression. What makes Tularik unusual is its single mindedness. While other companies like Oncogene Science (Manhasset, NY) include transcription-factor inhibition in their potential arsenal, Tularik sees it as its only weapon.

**New frontier**

The lure hit the water out in the Alaskan frontier—on the namesake Tularik River—reputedly one of the world's richest trout-fishing estuaries. Tjian and Goeddel had fished the river for a dozen years or so, talking over their respective worlds. Two years ago the discussions turned to forming a company, but at that time Tjian wasn't sure. "I needed a clear scientific reason for doing it," he says.

Results during the last year, combined with a survey of industrial approaches, "encouraged me that no one had tried to apply transcription factors in a directed way," Tjian says. Still he needed "someone to bounce ideas off," he says, so he went to McKnight.

"What appealed to me," says McKnight, "are both the number and specificity of transcription factors. Ten years ago when we started to break into it, we didn't know how many transcription factors there were—one, ten, or 100. Now I'd guess 10,000. Ten percent of the entire human genome appears dedi-

cated to expressing transcription factors." Tjian agrees, "We now know enough about transcription factors that we can entertain ideas of finding or designing molecules that could interfere with activity."

**Providing a rudder**

Both McKnight and Tjian credit Goeddel with steering their ship into what's for them the uncharted waters of business. Goeddel navigated them to Mayfield (Menlo Park, CA), one of three or four venture capital companies he would consider working with. "He knew the pitfalls for a scientist trying to get into an entrepreneurial field," says Tjian. "They didn't just give us money," says McKnight. "They helped us focus on issues, realize what the difficulties will be, and confront our problems from the start." Mayfield's Mark Levin will initially skipper Tularik as chief execu-

*Three outstanding scientists have united to control disease at the level of gene expression.*

tive officer, overseeing his company's majority investment in the \$3.8 million start-up. Genentech, for its part, kicked in an undisclosed amount.

Tularik plans to emulate its academic past in establishing the business. It will take just what it needs to hire the best people and grow gradually. Neither Tjian nor Goeddel will give up their day jobs at this point, though McKnight will dive into the project head first in August. A core of five scientists, with one technician each, will get the company up and running in temporary digs, while a permanent lab is built somewhere near Genentech.

But casting into a rich stream doesn't guarantee success. "The fundamental problem that separates this company from the rest of biotech," says McKnight, "is that we can't just go clone and inject." After isolating a transcription factor, Tularik must make and deliver an inhibitor that consistently forces the factor to strike it.

The group has a clear idea of how to attack the problem from their intimate knowledge of how transcription factors work. They see this as their advantage in beating out the competition. "Other companies can think about it, but wouldn't go after it in the same way," says Tjian. "We are going after it from the biochemical angle, not just transient transfection assays."

**Emerging strategy**

The emerging strategy sets up assays that allow Tularik to screen small-molecule libraries, netting potential inhibitors. As a model the company wants to emulate, McKnight points to Merck's (Rahway, NJ) success in inhibiting the steroid-synthesizing HMG coA Reductase pathway. But becoming a "mini-Merck" implies access to libraries that Tularik doesn't have. Goeddel admits that negotiating these libraries is a major next step for the company. Tularik must convince pharmaceutical firms that they offer more than a contractual service.

Much of that convincing will come from the way the company picks its initial targets. Despite their preeminence as scientists, the founders lacked a sophisticated understanding of what was clinically relevant. Again, this is where Mayfield came in. "They helped get us educated," says McKnight, "bringing in lots of physicians to talk about important disease states where no cure exists."

While targets remain unspecified, immediate possibilities include a virus like herpes, where delivery isn't as big a problem since the virus appears on the skin. Many of the herpes reagents, in fact, are already in the founders' freezers, as they've worked with the virus before. For mid-range goals, Tularik will attempt inhibition of known disease-mediating cellular transcription factors. Clearing cholesterol and reducing inflammation through endothelial cell biology are all areas Tularik's principles mention. The long-term program will include discovery of new transcription factors, their inhibitors, and novel means of delivery.

The bottom line for Tularik's founders is that this was just too tempting a challenge to pass up. "I can understand how people might think McKnight and Tjian are selling out," says McKnight, "but this isn't a 'gimmie.' It's a personal challenge—can I make a contribution to human health." Whether transcription factors will rise for Tularik's dangled lines remains a fish story waiting to be told.

—Stephen M. Edgington