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Fc Regions: Next Advance In Antibody Drug Research

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SAN FRANCISCO – Bassil Dahiyat, Xencor Inc.'s president and CEO, livened the first day of Biotechnology Industry Organization's InvestorForum conference at the Palace Hotel here with news of \$20 million raised for protein optimization, and a few words about what could be a hot new antibody approach.

"We've tapped into a new way to inhibit TNF-alpha," Dahiyat told *BioWorld Today*, adding that privately held Xencor's cash now on hand is enough to last "through the first part of the Phase I trial" with the drug, called DN-TNF.

"To be perfectly blunt, we're going to have to raise more investor money [to move beyond that point]," he said. "We're looking to do another round in 2006."

Dahiyat described the compound as "a human protein engineered as a mutated form of TNF-alpha that mixes with the TNF-alpha in your body and essentially deactivates it. We don't inhibit the TNF-alpha still stuck on immune cell surfaces," he said, only that which is released and circulating.

Infection is one well-known side effect that "occurs in a small but meaningful sector" of patients treated with the TNF blocker Enbrel (etanercept), from Thousand Oaks, Calif.-based Amgen Inc., Dahiyat noted, because the drug is holding back the immune system.

"Our agent is not immunosuppressive at all," he said, and DN-TNF has proved "very active in mouse and rat models of arthritis." He expects the Phase I trial to last "a little over a year," with Phase II likely in late 2007 or early 2008.

Dahiyat is a co-founder (in 1997) of Moravia, Calif.-based Xencor, and co-inventor of the firm's Protein Design Automation technology, which has many licensees and will continue to add them as the company develops its own pipeline.

"We feel that there is so much to be mined from protein and antibody therapeutics, it would be silly to shut our

research capability down," he said. "Research for us means engineering of proteins, and how many of those we can carry forward into development is a matter of how much money we've got."

Also gaining significant notice is Xencor's suite of XmAb Fc's – monoclonals with engineered fragment-crystallizable (Fc) domains, which are said to enhance the potency of cytotoxic drugs.

"People have been hammering on the variable regions of antibodies for 15 years," Dahiyat said. "It's absolutely swamped. But the constant region [where Xencor is focused] is, relatively speaking, a green field."

Quietly making forays into that field as well, it turns out, is antibody specialist Medarex Inc., of Princeton, N.J., whose scientific director Nils Lonberg spoke Wednesday on an antibody panel with Dahiyat.

"We have spent a lot of time on [Fc domains], but we haven't talked a lot about it," Lonberg said. The company has been "rather stealthy," he said, "waiting for all of [Xencor's] patents to publish so we can see what the intellectual property landscape is. In the meantime, I'm not going to give anything away."

Thirty-five monoclonal antibodies that are derived from transgenic mice are in clinical development. Of those, 25 involve Medarex deals, "so we've been pretty good about getting our technology out there," he said.

Jason Kantor, managing director and biotechnology analyst with New York-based RBC Capital Markets moderated the panel. Five to 10 years ago, he pointed out, "we'd be here talking about humanization and human antibodies, and now it's not even a topic" because most that go into the clinic fall into those categories.

"Will every antibody be in some way Fc-optimized in the future?" Kantor asked.

Lonberg was not certain, calling the research “still a clinical experiment” and saying he awaits Xencor’s investigational new drug application eagerly.

“Me, too,” Dahiyat said. “We pose all of our work here as a hypothesis we’re going to be testing in the clinic.” The IND is expected by the end of next year, and “we’re also going to run that Phase I ourselves,” he said.

Dahiyat predicted that the question in 10 years will have to do with how Fc regions might be engineered not only for the currently envisioned uses but “to improve a whole variety of immune-mediated activities.”

Another panel member, Clay Siegall, president and CEO of Seattle Genetics Inc., of Bothell, Wash., said the Fc approach “may work tremendously well for some targets and not for others, and we’ll just have to see. But the preclinical data is too compelling and exciting for it not to work in some settings.” Mixed success ultimately with such drugs, he added, would only make them “like almost everything else that is developed.”

Not surprisingly, potency was seen as the likely key to making the Fc-engineering method fight disease in the wide genetic range of patients.

“Obviously, we can’t go in and change the Fc receptor sequence of the patient, but perhaps we can modify the ligand so that it will bind to the Fc receptor at very high affinity and overcome a polymorphism,” Lonberg said.

That’s the goal, Dahiyat said. “You can bet every single patient going forward in a clinical trial is going to be genotyped quite thoroughly, and then we’ll see,” he said.

The BIO conference, with about 1,100 registrants, continues through today. ■