MacroGenics

A fresh perspective on monoclonal antibodies.

The beauty of monoclonal antibodies as therapeutics is that they can be generated against a limitless variety of protein targets. To date, it has been this flexibility and specificity—conferred by the antibodies' "variable region"—that has generated the most interest within the industry. However, MacroGenics believes that the "stem" or constant (Fc) region of the antibody plays an equally important role and one that has, to date, been overlooked.

One of MacroGenics' cofounders, Jeffrey Ravetch of the Rockefeller University (New York), was the first to show that the biological outcome of an antigen–antibody reaction *in vivo* depended on the way in which the Fc region interacted with effector cells, such as macrophages, mast cells, and neutrophils. Effector cells possess stimulatory and inhibitory Fc receptors, both of which are engaged by the antibody–antigen complex, and the balance between these opposing signals determines the strength of the immune response evoked. It's a new concept, and offers MacroGenics a unique and distinctive position within what is currently a crowded antibody arena. Ravetch explains that most of its competitors are still focused on the "front end" of the antibody, and are modulating antigen-binding sites.

Jeffrey Ravetch, cofounder of MacroGenics.

Recent data from Ravetch's laboratory has brought home the importance of the Fc region. In collaboration with Genentech (S. San Francisco, CA), Ravetch and his team revealed the role of effector Fc receptors in the efficacy of two therapeutic antibodies—Rituxan and Herceptin. Mice lacking inhibitory Fc receptors were 10 times more sensitive to the antitumor effects of Herceptin than wild-type animals, whereas animals lacking stimulatory Fc receptors were relatively resistant to the drug's effects (*Nat. Med.* 6, 373, 2000).

"Companies are now approaching us about the technology … always a good sign," says Ravetch. In theory, the clinical activity of many therapeutic antibodies is influenced by effector receptors, and so MacroGenics technology could be applied widely throughout the industry. Another key advantage of the technology is that it offers a means to both upregulate and downregulate the activation of the immune system, providing novel routes to control inflammatory and autoimmune diseases.

However, Macrogenics' primary goal is to develop its own antibodies using its understanding of the function of the Fc effector receptor. The most advanced product is a blocking antibody for an activation Fc receptor for the treatment of inflammatory disorders, which could offer competition for the market for gamma globulins. The company will also develop antibodies for prostate and lung cancers, drawing on its close links with the Institute for Systems Biology (Seattle, WA), which was set up last year by local University of Washington scientists and MacroGenics' cofounders Leroy Hood, Ruedi Aebersold, and Alan Aderem, for integrating genomics, proteomics, and bioinformatics for identifying disease targets. *LF*

Founded: August 2000
Founders: Jeffrey Ravetch, Leroy Hood, Alan Aderem, and Ruedi Aebersold
Employees: 5
Financing to date: $11.5 million
Location: Rockville, MA and Seattle, WA

ExonHit Therapeutics

Capitalizing on the human spliceosome.

Recent estimates from the Human Genome Project suggest there could be around 30,000 human genes in the genome, yet these may encode more than 100,000 different proteins. The disparity arises through the process of "alternative splicing", when the mRNA encoding one gene is cut and "spliced" together in different combinations, generating multiple protein isoforms. ExonHit Therapeutics is exploiting its understanding of mRNA splicing to enable it to identify promising diagnostic and therapeutic targets—without the need for raw DNA sequence.

Alterations in mRNA splicing are known to be tightly associated with various disease pathologies. For example, mRNA splicing is altered by drugs, environmental toxins, and viral infections, and can change as we age. Cancers and neurodegenerative conditions (such as Alzheimer's disease) also result from changes in the protein variants expressed. ExonHit therefore developed a technology platform—so-called DATAS (for differential analysis of transcripts with alternative splicing)—to analyze the changes in mRNA splicing accompanying pathological changes.

In DATAS, samples from diseased and healthy tissue are collected and the mRNA population in each sample isolated. The two populations are then compared, enabling ExonHit to identify which protein variants are involved—those specific mRNA variants that are upregulated, downregulated, or newly expressed. Libraries of cDNA sequences, encoding the expressed RNA splice variants, are then produced and displayed on chips.

DATAS can be used to identify which functional subunits of the encoded proteins are involved in the pathology/drug action, and therefore their function. The whole process takes only about six weeks, primarily because extensive DNA sequencing is not required—only coding regions (rather than both coding- and noncoding regions) are sequenced.

The company's mission is to create drugs

Founded: 1997
Founders: Bruno Tocque; Laurent Bracco; and Fabien Schweighoffer (all formerly at Rhone-Poulenc)
Employees: 45
Financing to date: E17.4 million
Location: Paris, France and Gaithersburg, MD
http://www.exonhit.com