PREPUBLICATION RESULTS

MIXED RESULTS FOR TARGETED TOXINS

GENOA, Italy—Prepublication results from two clinical trials show that targeted toxin molecules are well tolerated by bladder-cancer patients, though similar compounds directed against HIV caused toxicity problems. The trials were discussed at a conference entitled "Biotech RIA '92: New Generation of Monoclonal Antibodies in Diagnosis and Therapy" held in Genoa in mid-April.

For the bladder-cancer trial, sponsored by Merck (Rahway, NJ), David Fitzgerald and Ira Pastam of the National Cancer Institute (NCI, Bethesda, MD) constructed TGF-PE40, a chimera of transforming growth factor and forty amino acids of the *Pseudomonas* exotoxin. Cells of bladder tumors frequently display elevated levels of epidermal-growth-factor receptor to which TGF binds. The chimeric toxin was injected directly into the bladder of 20 patients suffering from bladder cancer. After two hours, toxin in the bladder had been reduced to undetectable levels, having been eliminated in the urine. The trial continues, and though Merck has not yet published preliminary results, Fitzgerald commented that early results were "good," with no evidence of toxicity. Yet lack of toxicity may be due less to the toxins and more to the fact that it was rapidly excreted.

Early results from a second trial conducted with a similar reagent by the NCI investigators and sponsored by Upjohn (Kalamazoo, MI) have been less satisfactory. The reagent, CD4-PE40, was directed against gp120 of HIV, since CD4 binds gp120. It was injected intraveneously into 40 patients. Most, however, are facing some toxicity problems.

Preclinical trial results reported at the conference supported the idea that humanizing monoclonal antibodies may reduce toxicity problems. Thomas Waldmann of the National Institutes of Health (NIH, Bethesda, MD) intends to use humanized anti-Tac monoclonals armed with toxins or radionucleotides to treat adult T-cell leukemia patients. The monoclonals—which bind to the CD25 subunit of interleukin-2 receptors on T-cell tumors—contain mouse complementary determining regions in a human IgG1-kappa framework. In a Cynomologous monkey model, the humanized antibody was less immunogenic than its wholly murine counterpart, although the significance of this in cross-species preclinicals is unclear. Furthermore, the humanized antibody appeared to retain its activity: there was evidence of antibody-dependent cellular cytotoxicity with human mononuclear cells.

The preclinical results from NIH have been encouraging enough to take the humanized antibody into the clinic. The first phase of trials in human cancer patients began in May and are expected to be complete in about two months.

To develop wholly human antibodies, Carl Borrebaeck of Lund University in Sweden used an approach that he said "combines cell biology and molecular biology." By transplanting the human humoral immune system into SCID-mice, Borrebaeck restored both primary and secondary immune activity in the mice. And the immune cells the mice subsequently produced in response to antigenic stimulation generated high-affinity human antibodies.

—**Angiola Bono**