KIDNEY REJECTION REVERSAL

ORTHO AWAITS NOD ON THERAPEUTIC MONOCLONAL

RARITAN, N.J.—“We believe it will be the first approved therapeutic monoclonal antibody ever,” says Gideon Goldstein, referring to Orthoclone OKT3™. Goldstein is vice president of immunobiology at Ortho Pharmaceutical Corp., Johnson & Johnson's wholly owned subsidiary here. Murine OKT3 has been used in clinical trials on over 800 patients to reverse acute renal-allograft rejection. In recent tests (*New England Journal of Medicine* 313:337-342, 1985), the Ortho Multicenter Transplant Study Group reported 97 percent reversal of rejections as compared to 75 percent reversals with standard steroid treatment. The monoclonal antibody did not, however, reduce the recurrence of rejection episodes.

Goldstein reports that Ortho submitted information on OKT3's safety and efficacy to the U.S. Food and Drug Administration (FDA) last year, and that he hopes to receive approval “before too long.”

OKT3 counteracts organ rejection by reacting with the antigen-recognition structures of T cells. In this way it acts like a drug: if the T cells can no longer recognize foreign molecules, then rejection is effectively reversed. Side effects do occur following the first administration of the OKT3. These flu-like symptoms, counters Goldstein, “are certainly a minor load to bear to save a kidney.”

The biggest problem with OKT3 therapy (and other treatments using monoclonal antibodies) is that patients build up their own antibodies that bind to and disable OKT3. Goldstein says this complication can be overcome in three ways: doctors can inhibit a patient's antibody response with drugs, they can administer increasing levels of OKT3, or they can evade the immune response by using different monoclonals that all have the same effect of binding to T-cell receptor sites. Once these problems are alleviated, Goldstein says, doctors will be able to use OKT3 earlier to prevent rejections, or later to reverse subsequent rejections.

Although the current FDA application covers only renal transplants,

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Goldstein says, Ortho has promising data for heart and liver transplants as well. Further in the future, OKT3 (when applied in tandem with Orthoclone OKT11, another monoclonal that recognizes T cells) could be used to prevent graft-versus-host reactions in patients with autoimmune diseases like multiple sclerosis and systemic lupus erythematosus. In this case, the monoclonal mixture will be used to eliminate T cells in donor bone marrow *in vitro*, before the marrow is transplanted into the patient.

A variety of other research groups, including Britain's Wellcome Biotechnology Ltd. (see *BioTechnology* 3:686, Aug. '85), are developing monoclonals that affect T-cell function. One potential U.S. competitor

with Ortho could be a two-year-old company called T Cell Sciences (Cambridge, MA). T Cell's vice president and scientific director, Patrick C. Kung, previously worked at Ortho with Goldstein. (In fact, he is the inventor listed on Ortho's original patent for OKT3.) Says Kung, “T Cell Sciences is actively developing more specific second-generation anti-T-cell monoclonal antibodies, which we feel will have applications in the treatment of juvenile-onset diabetes, rheumatoid arthritis, multiple sclerosis, as well as organ transplant rejections.” He refuses, however, to elaborate on T Cell Sciences' strategy.

Goldstein reports that 90 percent of Ortho's work on therapeutic monoclonals concentrates on OKT3. The company is also looking at an antibody it calls Orthoclone OKT4, which blocks helper T cells. He says that researchers have achieved “interesting” results using this monoclonal to reverse and block models of autoimmune diseases in animals. Eventually, he adds, Ortho will work on developing anti-cancer monoclonals.

On the diagnostic front, Ortho is already marketing monoclonals from the OKT series for determining the levels of T cells or the ratio of T cells to helper T cells in patients. Currently, the company is suing Becton Dickinson (Paramus, NJ) for infringing on its patent rights by marketing equivalent monoclonal diagnostics.

Better known to most than the Orthoclone OKT series is Ortho's home pregnancy test called Advance™. According to Monoclonal Antibodies Inc. (Mountain View, CA), which designed and still manufactures the test, Advance is the fastest growing home pregnancy kit on the market. Ortho's Advanced Care Products Division recently signed an agreement with Monoclonal Antibodies for additional collaboration on future home diagnostic tests using monoclonal antibodies.

Even with all of its monoclonal antibody R&D, Ortho remains best known as a gynecological company. As one of its slogans reads, however, “We're a lot more than you think.”

—Arthur Klausner