Mabs: A new lease on life for transplant patients?

"We are killing patients with overimmunosuppression and there is a need for a better combination [of therapies]." So said Lucienne Chatenoud of the Hôpital Necker (Paris) at the 16th International Congress of the Transplantation Society (Barcelona, Spain, August 25–30). Immunosuppression regimens that work have lifted transplant physicians and surgeons over the acute graft rejection hurdle as 90% of kidney and liver graft patients now survive at least a year. But in each year of extended life, the morbidity of transplant patients increases. In order to keep patients alive long term, physicians need to maintain the survival of the graft without handicapping the immune system to the extent that it can not effectively fend off infection.

The need for a more effective chronic immunosuppressive regimen has prompted many companies to turn back to monoclonal antibodies (Mabs) to help block graft rejection. Chatenoud's group at Hôpital Necker, for instance, had shown that Mabs can optimize graft survival in conjunction with other immunosuppressants (such as cyclosporin A) by specifically obstructing T-cell receptor mediated antibody pathways and receptor molecules that cause T-cell proliferation. Jean Paul Squifflet of the University of Louvain Medical School (Brussels) presented results at the Barcelona meeting from a small clinical trial on Biotransplant's (Charlestown, MA) BTI-322, an antiCD2 Mab. Of 20 patients in the group that received BTI-322 (with the routine immunosuppression regimen), only 1 exhibited delayed graft function; 6 of 20 in the control group did.

The need for a more effective chronic immunosuppressive regimen has prompted many companies to turn back to monoclonal antibodies to help block graft rejection.

The potential effectiveness of Mabs for immunosuppression was established in animal experiments in the early 1980s. Several research teams identified and engineered Mabs to obstruct different parts of the graft rejection pathway in rodents. However, molecules blocking the equivalent steps in pigs and primates were not as numerous. Because the human Mab preparations for clinical use are very expensive and very difficult to manufacture, pharmaceutical companies had previously leaned more heavily toward developing chemical immunosuppressants. Consequently, only one antibody product is currently on the transplant market, the Mab against CD-3, OKT3 (Ortho Novum, Raritan, NJ).

But that seems to be changing. Several companies have transplant-related human Mabs in development. In addition to Biotransplant's BTI-322, Sandoz's (Basel, Switzerland) antiCD25 monoclonal is in phase III trials in Europe and the United States. IMTIX (Lyon, France) has developed an antiLFA (leukocyte function associated antigen) that blocks the adhesion of polymorphonuclear leukocytes to endothelial cells. Ortho Novum is developing an antiCD4 antibody, OKT4. Bristol Myers Squibb's (Syracuse, NY) CTLA-4, an immunoligand, has demonstrated antiCD28 activity, and Medimmune's (Gaithersburg, MD) T10B9 blocks T-cell receptors.

According to Chatenoud, investing in the development and production of human Mabs is the key to identifying effective cellular domains. But, it is perhaps only the start of the process. Companies will construct antibody fragments, peptides, or develop mimetic drugs to act upon these specific domains. The reduction in the size of the interacting moiety will be desirable—if not essential—because Mabs are too large to infiltrate the lymph nodes where the cells that reject transplant organs reside.

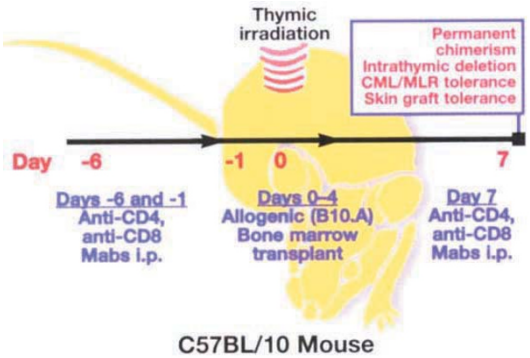
Barbara Nasto

Barbara Nasto is a science and medical writer for Nature Publishing Co. in New York.

Making tolerance permanent

Transplant recipients are notorious for not taking their medicine, nasty cocktails of immunosuppressant drugs—a problem that can only get worse as xenotransplantation moves closer to the clinic. The success of xenotransplantation will require immunosuppressive measures much more severe than those used for allografts. Consequently, investigators are exploring ways to induce permanent organ tolerance, as recent presentations indicated at the 16th International Congress of the Transplantation Society (Barcelona, August 25–30).

Researchers at the University of Pittsburgh Medical Center (Pittsburgh, PA) have found tolerance can be induced in patients if they are treated with immunosuppressants for sufficient periods and then weaned while under careful monitoring. Thomas Starzl and colleagues at the University of Pittsburgh have successfully weaned 23 of 91 long-term (greater than 5 years) liver graft recipients from immunosuppressants. They decreased the dosages (cyclosporin, 60% of the standard dose; azathioprine, 35%; and prednisone, 57%) and then treated rejection with pulsed steroids. The technique did not work for everyone (27 patients rejected the organ), but the fact that it can work warrants further investigation.



Induction of macrochimerism and tolerance without whole body irradiation

Megan Sykes of Harvard Medical School (Boston, MA) is taking a different approach. She aims to return the immune system to a more primordial state before the organ is grafted, so that newly developing hematopoietic cells in the patient can identify a new graft as self. So far she has induced graft tolerance in mice by irradiating the thymus and infusing a large dose of donor bone marrow. The fact that Sykes was able to induce tolerance without whole body irradiation makes this strategy clinically more acceptable. The rationale behind her approach and Starzl's approach lies with a phenomenon known as chimerism: In long-term allograft survivors, immune cells from both donor and recipient tissues coexist in the recipient. "Chimerism in the thymus can educate immune cells to think the donor is self," she explains.

Barbara Nasto