SOUTHWESTERN NEWS

Contact: Susan A. Steeves
(214) 648-3404
or E-mail: ssteev@mednet.swmed.edu

GENETICALLY ENGINEERING LONGER-LASTING ANTIBODIES COULD LEAD TO BETTER THERAPEUTIC DRUGS

DALLAS — July 25, 1997 — Delivering drugs to fetuses and fighting such diseases as cancer and autoimmunity may be greatly enhanced by altering a common antibody so that it stays in the blood stream longer, according to researchers at UT Southwestern Medical Center at Dallas.

By taking a portion of the natural antibody IgG and using protein engineering techniques, the scientists found they could isolate fragments that bound with higher affinity or force to the Fc receptor, FcRn. This receptor is involved in regulating the level of gamma globulin, the part of the blood containing most antibodies, in many mammals. In rodents and humans, it also is believed to be part of the pathway that transfers antibodies across the placenta from mother to child. The research, published in a recent issue of *Nature Biotechnology,* showed that manipulating the antibody extended its half-life in the circulation of mice.

"We thought if we could increase the binding affinity of an IgG fragment for FcRn, then it would have a longer serum half-life than the endogenous (naturally occurring) IgGs," said Dr. E. Sally Ward, associate professor of microbiology and Cancer Immunobiology Center researcher. "We mutated antibody fragments called Fc fragments and selected ones that bound better to FcRn."

Antibodies are Y-shaped proteins with IgG being the most common type. The long arm of IgG is the Fc fragment, which is the non-antigen binding portion of the molecule and carries out tasks called effector functions.

Because a very similar Fc receptor is found in humans, Ward said their research could be applicable to people. Since the altered antibodies are more persistent in the blood, smaller amounts of therapeutic antibodies made with this technology would be needed.

(MORE)

Therefore, the necessity for repeated doses would be reduced. This approach also could be used to isolate smaller molecules that have high affinity for bonding to FcRn. These molecules could then be used to tag drugs.

"If the drugs have a longer serum persistence, then it will be cheaper and more economically attractive for patients," Ward said. "We also believe this tighter binding of the IgG fragment to FcRn will transfer antibody across the placenta more efficiently."

This means it may be possible to deliver therapeutic antibodies or drugs to fetuses in cases where the mothers have a disease such as AIDS, she said.

The UT Southwestern investigators found that the mutant antibody fragment had a binding affinity for FcRn that is 3.5 times higher than the unaltered Fc fragment from which it was derived. In one strain of laboratory mouse, the amount of mutated antibody still effectively circulating in the blood 20 days after injection of IgG was four times greater than with the parent antibody. It was twice as much in another strain.

Other researchers involved in this study were Dr. Victor Ghetie, associate professor of microbiology; Dr. Sergei Popov, assistant instructor of pharmacology; research fellows, Jozef Borvak and Dr. Corneliu Medesan; former UT Southwestern research fellows Caius Radu and Diana Matesoi; and Dr. Raimund Ober, a collaborator from The University of Texas at Dallas.

The study was funded by grants from the National Institutes of Health, the Welch Foundation and the Texas Advanced Research Program.

###