Targeted immuno-suppression with T_{regs}

By Kai-Jye Lou, Staff Writer

Researchers at **University College London** and **The Netherlands Cancer Institute** have engineered a population of T_{regs} that recognize a single antigen and can locally suppress an immune response *in vivo*.¹ The approach could lead to cell therapies that block harmful autoimmune disease—causing immune responses without compromising broad host immune surveillance against infections and cancer.

T_{regs} are a subset of immunosuppressive T cells that recognize antigens, home to tissues in which the antigen is present and then disarm immune-promoting effector T cells in the vicinity. A handful of companies are evaluating antibodies and small molecules that activate or expand the T_{reg} population to treat diseases like type 1 diabetes and graft-versus-host disease (GvHD).

However, multiple studies have reported that an overabundance of T_{regs} can compromise immune responses to antigens from tumors and pathogens.^{2–4}

To mitigate the risk of broadly compromising the immune system, a team of European researchers used retroviral gene transfer to program an entire population of T_{regs} to recognize a single antigen. As proof of concept, they engineered mouse T_{regs} that expressed a T cell receptor (TCR) that recognized the test antigen ovalbumin, a protein in egg whites.

In a mouse model of arthritis, the engineered T_{regs} decreased joint swelling in knees that had been injected with ovalbumin but not in knees in which ovalbumin was absent.

“Our work demonstrates for the first time the practical feasibility of administering immune suppression in a targeted manner *in vivo*,” said Hans Stauss, professor of immunology at University College London and senior author of the paper in the *Proceedings of the National Academy of Sciences* that described the results. “The engineered T_{regs} we use are specific for an antigen so they don’t interfere with protective immunity against other conditions like viral infections and cancer.”

“One could envision using this type of approach to direct regulatory T cell activity to prevent damage in any organ-specific autoimmune disease and potentially in situations involving tissue transplantation where antigen-specific tolerance would be beneficial,” said Todd Brusko, a postdoctoral fellow at the **University of California, San Francisco**.

Brusko’s lab is already using the approach described in *PNAS* to engineer T_{regs} for treating type 1 diabetes. “Perhaps the most exciting point conveyed by the work of Stauss and colleagues is the implication that immune responses can be suppressed in an antigen-specific fash-

ion, without the need for broad and nonspecific immune suppression,” he told *SciBX*.

“The study significantly adds to our understanding of how regulatory T cells function *in vivo* and therefore provides us with additional clues as to how they can be therapeutically manipulated,” said Douglas Ringler, CEO of **Tolerx Inc.** “However, whether adoptive transfer of redirected or manipulated regulatory T cells can be further translated to man safely is a question that will take significant time and effort to resolve.”

Tolerx’s otelexizumab, a mAb against CD3, is in Phase III trials for type 1 diabetes. The mAb is thought to induce T_{regs} and to block the function of T effector cells that attack the body’s tissues and cause autoimmune disease. The compound is partnered with **BTG plc** and **GlaxoSmithKline plc**.

Benefit claims

Although the engineered T_{regs} described in *PNAS* are able to suppress immune responses in a localized and antigen-specific manner, it remains to be seen whether the increased specificity will produce benefit.

“The question that needs to be answered is, do we need to make these regulatory T cells more specific? At this point, it is just not known whether increasing the specificity of regulatory T cells will improve their clinical application,” said Robert Negrin, a professor of medicine in the Division of Blood and Marrow Transplantation at the **Stanford University School of Medicine**. “Improving the specificity could potentially increase the specificity of immunosuppression, but the jury is still out as to how important this would be. Right now, there isn’t any clinical data out there with respect to modulating the specificity of regulatory T cells.”

Reiko Namikawa, SVP of research and strategy at **Regimmune Corp.**, said it will be necessary to identify antigens that can safely and efficiently draw the engineered T_{regs} to disease sites in humans.

Namikawa said a candidate antigen needs to have selectivity for the disease site and not result in any adverse effects. “The availability of such antigens will determine the target organs and hence the target indications,” she said.

It also will be necessary to evaluate the safety of the engineered T_{regs} themselves and show that their tolerance-promoting effects persist inside the body following infusion. “One thing we learned about regulatory T cells is that specific immune environments can cause their function to change,” Negrin told *SciBX*. “There is some data out there suggesting that hyperstimulated regulatory T cells can convert into proinflammatory T cells.”

Regimmune’s lead compound is RGI-2001, a liposomal formulation of a small molecule that induces antigen-specific immune tolerance via induction of T_{regs}. The compound is in preclinical testing for GvHD, and the company expects to submit an IND and begin a Phase I trial in 1Q10.

Stauss said the next step is to show that the engineered T_{regs} can be targeted to a tissue-specific antigen. “We also need to demonstrate that

these injected T_{regs} do not convert to inflammatory cells,” he said. “Once we get this information from animal models, I believe we would be able to move into studies using human cells.”

University College London has two issued patents covering genetic engineering approaches to redirect T cell activity. The licensing status is undisclosed.

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Contact: Hans Stauss, University College London, London, U.K.
e-mail: h.stauss@medsch.ucl.ac.uk

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COMPANIES AND INSTITUTIONS MENTIONED

BTG plc (LSE:BGC), London, U.K.

GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.

The Netherlands Cancer Institute, Amsterdam, the Netherlands

Regimmune Corp., Tokyo, Japan

Stanford University School of Medicine, Palo Alto, Calif.

Tolerx Inc., Cambridge, Mass.

University College London, London, U.K.

University of California, San Francisco, Calif.