



- Home
- Search
- Back Issues
- RSS Feed
- Events Calendar
- Contact Us

F O C U S

News from Harvard Medical, Dental, and Public Health Schools

Contents
June 25, 2010

- Enough Time to Change the World
- World Class
- Grads Called to Action
- Global Oral Health
- We Have Met the Enemy, and He Is Us
- Alumni Without Borders
- Doing Right
- Delivering in Haiti
- Caring for Survivors
- Renovating Care
- Medicare Payment Cuts Increase Cancer Treatments
- Color-coded Mouse Sheds Light on Transplant Tolerance

COMMUNITY

News

In Memoriam

Bert Vallee

FORUM

Getting More

UPCOMING

Event Listing
Wednesday, June 30
– Tuesday, August 3

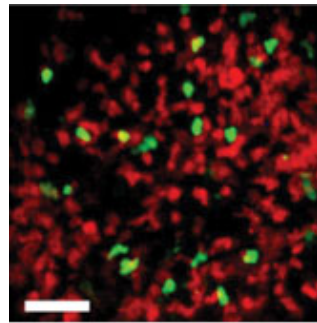
RESEARCH

Color-coded Mouse Sheds Light on Transplant Tolerance

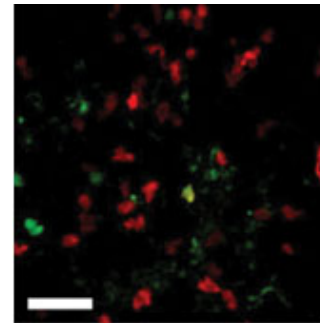
Organ transplants do not always work, despite accompanying treatment with immunosuppressive drugs. Sometimes the immune system accepts the foreign tissue, and other times it launches a full-fledged attack.

To better differentiate the chain of events underlying the body’s tolerance of transplanted tissue versus the events leading up to rejection, researchers have to monitor the complex behavior of T cells—a class of immune cell comprising both protective and destructive groups.

Control Mice (transplant rejected)



Treated Mice (transplant tolerated)



Window on T cell behavior. Islet transplants in control mice (left) versus mice given a treatment that promotes tolerance (right) appear 12 days after transplantation. Red-colored cells are destructive T cells (Teffs), and green cells are protective T cells (Tregs). While the number of protective cells does not appear to be significantly different, the number of destructive cells infiltrating transplants is much higher in the transplant-rejecting (control) mice than in the transplant-tolerating (treated) mice.

In a study with broad implications for the capacity to analyze immune responses, a team led by investigators at HMS presents a mouse model with T cell subsets that are distinctively color-coded. The different fluorescent labels allow tracking of T cell behavior in a living animal at the level of the individual cell. So researchers can see what the T cells are actually doing.

Using these mice, the team transplanted pancreatic islets (which are damaged in type 1 diabetes) beneath tissue that surrounds the kidneys. Then the researchers performed endoscopic microscopy at the transplant site and noninvasive imaging of the labeled immune cells circulating in the bloodstream. This strategy revealed new and somewhat surprising information about T cell dynamics, which could guide development of techniques for greater transplant tolerance. In the future, the strategy might be extended beyond transplant studies, perhaps to visualize T cell behavior in mouse models of diseases such as type 1 diabetes or cancer, in which the immune response is central to the pathology.

Prior to this study, it had not been possible to track immune cell subsets within living animals with single-cell resolution, said senior coauthor **Terry Strom**, HMS professor of medicine and director of the Transplant Research Center at Beth Israel Deaconess Medical Center. The technology that made such imaging possible was an innovation from a group led by Charles Lin, an HMS associate professor of dermatology at the Wellman Center for Photomedicine at Massachusetts General Hospital.

“The immune response to foreign proteins usually involves a mixture of various cytotoxic and at least two cytoprotective T cell subsets,” said senior coauthor **Maria Koulmanda**, HMS associate professor of surgery and director of nonhuman primate research in the Beth Israel Transplant Center. “The vigor and nature of the response can be fully understood only by identifying the number, frequency and molecular phenotype of the T cell subsets engaged in the immune response.”

The study appears in the June issue of *Nature Medicine*, with co-first authors Zhigang Fan, a research fellow at BID, and Joel Spencer of Massachusetts General Hospital.

Flying Colors

In order to create the color-coded immune mouse that received islet transplants, the team started with a mouse genetically designed to lack T cells. Then the researchers populated its immune system with green fluorescent protein-expressing protective T cells called regulatory T cells (Tregs) and red fluorescent protein-expressing destructive T cells called effector T cells (Teffs).

“The immune response to foreign proteins usually involves a mixture of various cytotoxic and at least two cytoprotective T cell subsets.”

—*Maria Koulmanda*

In addition to identifying these two basic types of T cells, the fluorescent proteins enabled researchers to distinguish between two subcategories of Tregs that before had been nearly impossible to distinguish in living animals: natural Tregs and induced Tregs. While natural Tregs acquire their protective identity during T cell maturation in the thymus, induced Tregs are T cells that have become protective due to environmental conditions. Under certain conditions, for example, Teffs can become induced Tregs, transforming from destructors to protectors. When the red Teffs become induced Tregs, they begin to produce green in addition to red fluorescent protein. The combination of colors makes them appear yellow, distinguishing them from both red

Teffs and green natural Tregs.

Population Behavior

Having labeled these three different varieties of T cells, the team proceeded to investigate each variety’s role in the transplant response. As Strom put the question: “What is the tempo and magnitude at which these different cell types home to the transplant or appear in the circulation in mice that undergo vigorous rejection versus those that don’t undergo rejection at all?”

While the control group of color-coded mice rejected islet transplants after 14 days, the mice given rapamycin plus CD154 antibody—a tolerance-promoting treatment—did not. The team had expected to see a large increase in protective T cells at the graft site in these transplant-tolerating mice, since a general hypothesis in the field is that tolerance is supported by increased Treg-mediated protection. To the researchers’ surprise, however, there was no appreciable change in the number of green or yellow cells. Instead, they noted a dramatic reduction in the number of infiltrating red cells in the transplant-tolerating mice. One reasonable interpretation is that Tregs do a better job of protecting transplants when they have fewer destructive Teffs to contend with.

In addition to probing the T cell response to transplantation at a molecular level, the team expects in the future to use the color-coded mouse model to study T cell dynamics in disorders whose pathology is based on the immune response. These include autoimmune diseases and

cancer. The team has already begun to study autoimmunity by applying their color-coded in vivo imaging strategy to a widely accepted mouse model of type 1 diabetes.

How will this approach guide the development of therapeutics?

“It doesn’t give you a magic treatment,” said Strom, “but it gives you a basis for determining the necessities of creating a vigorous immune response or to create tolerance.”

—Parizad Bilimoria

For more information, students may contact Terry Strom at tstrom@bidmc.harvard.edu or Maria Koulmanda at mkoulman@bidmc.harvard.edu.

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[top](#)