IN THE NEWS

Diabetes cure?

A 61-year-old man has become the first person in the UK to be cured of type 1 diabetes, thanks to a ground-breaking cell-transplant procedure. Richard Lane of Bromley in Kent, who has been dependent on multiple daily injections of insulin and has suffered frequent hypoglycaemic attacks for 30 years, received three islet-cell transplants from donors who had died. These were injected into his liver, and he now no longer needs insulin injections. He told *The Guardian* newspaper: "I haven't felt better in myself for 30 years. I have to pinch myself to ensure I am not dreaming".

Surgeon James Shapiro, in Edmonton, Canada, pioneered the technique and was the first to achieve insulin independence, in 2001. Previously, two other patients in the UK have undergone the procedure, but both still require small doses of insulin. In light of the recent success, Annwen Jones, Chief Executive Officer of Juvenile Diabetes Research Foundation International, said that "Great improvements have been made since the first procedure of this type in 2001 and we are delighted that we now have the expertise to achieve insulin independence in the UK." (*BBC News*).

However, there remain several drawbacks. First, patients who receive islet-cell transplants spend the rest of their lives on immunosuppressive drugs to prevent rejection, and second, there is a severe shortage of donor pancreases from which to extract islet cells. Acknowledging these shortcomings, Professor Stephanie Amiel, a consultant on diabetes at King's College London said that "more research needs to be done to perfect the islet isolation procedures and the drugs we use to prevent rejection of the islets and recurrence of the diabetes" (*The Guardian*).

Lucy Bird

TECHNIQUE

A new approach to studying tolerance

Antigen-receptor-transgenic mice are commonly used to study lymphocyte responses because they increase the frequency of antigen-specific cells to easily detectable levels. However, such systems are designed to distort lymphocyte development and generate quasi-monoclonal immune systems. These non-physiological changes mean that results from receptor-transgenic mice require verification in normal, polyclonal immune systems. Nemazee and colleagues have developed a new approach using single-chain antibodies that allows them to do just that, by creating a superantigen that binds a high frequency of polyclonal B-cell receptors (BCRs).

They generated a single-chain antibody consisting of an Fv domain specific for the constant region of mouse Igκ light chain, hinge regions and the Fc portion from rat IgG1, and transmembrane and cytoplasmic regions from H–2K^b. Cells transfected with the chimeric gene expressed a stable cell-surface protein with the desired specificity for mouse Igκ. Transgenic mice were then created that have uniform and ubiquitous expression of this protein under control of the ubiquitin C promoter. This 'macro-self' antigen can bind the BCRs of a high proportion of polyclonal B cells (those that are Igκ$^+$) without requiring skewing of the lymphocyte repertoire.

Almost all of the B cells in these transgenic mice expressed Igλ light chains rather than Igκ, indicating that the antigen can induce B-cell tolerance. One potential mechanism for such tolerance is receptor editing involving secondary light-chain

T-CELL RESPONSES

Too fat to respond

During the lifetime of a 'successful' T cell, it must migrate in the following way: out of the thymus, where it develops; into the peripheral blood, where it circulates through lymph nodes searching for its cognate antigen for activation; and eventually, into the target organ, where it mediates its effector functions. These migration patterns are carefully controlled by the expression of specific chemokines and adhesion molecules. The lipid mediator sphingosine 1-phosphate (S1P) was recently recognized to be a new type of chemotactic signal for T cells, acting through sphingosine 1-phosphate receptor 1 ($S1P_1$), which is expressed by developing T cells, to promote egress from the thymus. Hongbo Chi and Richard Flavell now show that the regulation of $S1P_1$ signals is also important for the effector responses of mature T cells.

The role of $S1P_1$ in mature T-cell responses has been difficult to address so far because $S1P_1$-deficient mice lack peripheral T cells, owing to a block in egress from the thymus. On the basis of the observation that $S1P_1$ is highly expressed by naive T cells but is downregulated after T-cell activation, the authors created transgenic mice that constitutively express $S1P_1$ under control of the human *CD2* promoter in all T cells to analyse the biological relevance of this downregulation of $S1P_1$.

The transgenic mice had slightly fewer T cells in peripheral lymph nodes, but they had 70% more splenocytes than wild-type mice and an increased number of CD4$^+$ and CD8$^+$ T cells in the peripheral blood. As expected, the transgenic T cells underwent significantly greater chemotaxis in response to S1P *in vitro* than did wild-type T cells. Adoptive transfer of CD4$^+$ wild-type or transgenic T cells was then used to show that $S1P_1$ also regulates mature T-cell migration *in vivo* and can account for the increased distribution to the blood. Five hours after transfer to wild-type mice, there were 60% more transgenic CD4$^+$ T cells than transferred wild-type T cells in the blood of recipients. Given that the concentration of S1P is higher in the blood than in other tissues, it is probable that this results from increased egress of the transgenic T cells into the blood, rather than from reduced entry to secondary lymphoid organs.

Chi and Flavell then analysed the effects of altered T-cell migration owing to enforced $S1P_1$ expression in three models: contact hypersensitivity, autoimmunity and immunization of T-cell-receptor-transgenic mice with cognate antigen. In all cases, the *S1p1*-transgenic mice had a