'Given the restricted therapeutic window after injury, and the fact that the effect is T-cell mediated, we thought that active vaccination (which induces speedy production of T cells) would be quicker than raising T cells *in vitro* and then injecting them into the body,' says Eti Yoles, formerly a research associate in Schwartz's laboratory at the Weizmann Institute, and now Vice-President of Research at Proneuron (Rehovot, Israel; a biotechnology company that is developing the vaccine).

For its animal studies the team is currently using rats and mice with spinal cord and optic nerve injuries to compare the effects of vaccination either with Copaxone (glatiramer acetate) or non-pathogenic synthetic derivatives of peptides derived from myelin antigens. Copaxone is a synthetic copolymer consisting of four amino-acids (alanine, lysine, tyrosine and glutamate), which has already been approved by the FDA as being safe and having no adverse side-effects. It is hoped that T cells that react against Copaxone will also work against MBP.

Clinical trials are planned in which patients with glaucoma or spinal cord injury will be vaccinated with either Copaxone or with modified peptides in an attempt to prevent the progressive loss of retinal ganglion cells. 'Because we are dealing with the body's own mechanism of repair, we hope the vaccine will cause fewer safety problems', says Schwartz.

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New hope for sickle cell anaemia

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Two recent studies have suggested new approaches to the treatment of sickle cell anaemia. Robert Iannone and colleagues (Johns Hopkins Hospital and Oncology Center, Baltimore, MD, USA) have developed a chimaeric stem-cell transplant technique[1] in mice that might reduce anaemia in those with sickle-cell disease (SCD), while minimizing the risk of a traditional bone-marrow transplant. More fundamental research by Leslie Parise's group at the University of North Carolina (Chapel Hill, NC, USA) has identified a novel synergy between the signalling of integrin-associated protein (IAP) and shear stress, which might explain why sickled erythrocytes adhere to the inner wall of blood vessels[2]. Blocking this pathway could be a future strategy for preventing the vaso-occlusive crises and degenerative organ damage that is typical of SCD.

A 'mini-transplant': getting the correct balance

Conventional bone-marrow transplantation is the only therapy for SCD that has curative potential but it carries the risks of disease recurrence, long-term adverse effects caused by transplant conditioning or graft-versus-host disease, and death. However, SCD patients who have serendipitously developed mixed chimaerism, after their own bone marrow has been only partially ablated, remain symptom free and have a much lower complication rate. These observations led Iannone and colleagues to use a mouse model to investigate the 'optimum' balance between self and donor cells after a bone marrow transplant, and to examine whether a chimaeric transplant resulted in increased organ pathology. Lethally irradiated mice were given varying rations of T-cell depleted marrow from normal and transgenic 'sickle-cell' mice, producing different ratios of myeloid chimaerism. Mice that had 25:75% normal:sickle stem-cells had >90% normal haemoglobin in their blood, but this was insufficient to reduce

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their SCD symptoms or to prevent histologically observed abnormalities in organs such as the liver. A myeloid chimaerism of 40% was required to eliminate sickled red blood cells (RBCs) completely, and a chimaerism of 70% was needed to obviate the symptoms of anaemia.

'Although these results, together with clinical observations of chimaeric patients, suggest that mixed myeloid chimaeric transplants may significantly ameliorate SCD, a relatively high degree of normal donor haematopoiesis is necessary,' warns Iannone. He also stresses that analysis of the mice results shows that low ratios of donor stem-cells that cause a minimal or modest reduction in abnormal haemoglobin might actually exacerbate the associated organ damage. 'This is important for developing the mini-transplant technique, but it also means that if a patient develops a low-level donor-haematopoiesis after a traditional bone-marrow transplant, their donor haematopoiesis must be boosted to avoid long-term problems,' adds Iannone.

Mark Walters, Director of the Blood and Marrow Transplant Program at the Children's Hospital in Oakland (Oakland, CA, USA), has recently launched a multicentre clinical investigation of 'mini-transplants' for SCD supported by the National Institutes of Health (Bethesda, MD, USA). He finds the results of the new study encouraging: 'Non-ablative allogenic transplantation for SCD could revolutionize how we do transplants,' he says. If successful, Walters thinks that 'mini-transplants' would permit a safer and less costly method that could also be used in patients with health problems that currently exclude them from having a traditional bone-marrow transplant. However, he does add a note of caution: 'There are significant differences between mice and humans, and it would be extremely useful to develop other animal models of SCD to investigate donor chimaerism further before promoting their use in patients,' he suggests.

Why are sickle RBCs 'sticky'?

Many of the complications of SCD that a transplant seeks to prevent could be treated using drugs, if appropriate targets could be identified. Julia Brittain's study at the University of North Carolina reveals that the adhesiveness of sickle RBCs is increased when they become activated in response to cell signalling. When sickle RBCs pass through narrow blood-vessels and are exposed to a certain level of shear stress, IAP on the surface membrane of the erythrocyte binds soluble thrombospondin (a protein present in plasma) and becomes activated via a signal-transduction pathway that involves large G-proteins and tyrosine kinases. This mediates binding of the sickle RBCs via IAP to immobilized thrombospondin molecules that act as receptors on the inside of blood vessels. 'Until recently, peripheral human RBCs were thought to be passive and unable to control their fate by cell signalling. This now turns out not to be the case, and sickle RBCs are particularly responsive to thrombospondin-induced IAP activation,' explains Brittain.

New therapeutic targets

Eric Brown (University of California, San Francisco, CA, USA) comments that this study suggests for the first time that IAP might play an important role in SCD. 'This work has implications for the pathophysiology and treatment of SCD but it also raises important fundamental questions about the mechanisms of IAP signal-transduction that could be useful for other fields of research,' he points out. Parise reports that the group has since identified two enzyme inhibitors: one that blocks G-protein activation and another that inhibits tyrosine kinases. 'These are commercially available for laboratory use, rather than drugs in development, but they both prevented sickle RBCs sticking to thrombospondin in our experimental model,' she explains. Any component of the new pathway could provide a potential target for drug development and, although a future collaboration with a pharmaceutical partner is a possibility, Parise stresses that the group is currently trying to identify a second receptor on sickle RBCs that, in addition to IAP, mediates increased adhesion. 'Once we have identified this receptor, we would like to pursue a therapeutic strategy that potentially involves both IAP and this currently unknown target,' she says.

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