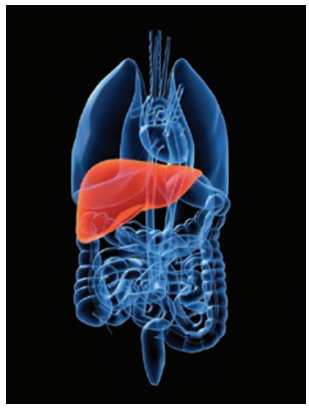
Successful treatment for liver failure

Using a new approach to immunomodulation, researchers at Massachusetts General Hospital (Boston) have developed two practical methods for treating acute liver failure in rats.

Fulminant hepatic failure is associated with a local and systemic immune response that interferes with the liver's ability to repair itself. Attenuating this immune response could enable patients with liver failure to survive until a donor organ is available, and may even provide enough support to allow the liver to regenerate, eliminating the need for a transplant. In previous studies, Martin L. Yarmush and colleagues successfully used immunomodulation to treat rats with liver failure but sought a clinically viable approach. Now they achieve a similar effect using human bone marrow mesenchymal stem cells (MSCs), which have been shown to inhibit immune cell function.

The researchers induced liver failure in rats using a hepatotoxin and assessed various MSC treatment modalities (*PLoS ONE* **9**, e941; 2007). Though direct transplantation of MSCs was not effective, intravenous



Sebastian Kaulitzki

injections of MSC cellular lysates had a distinct survival benefit, as did injection of a conditioned medium of MSC-derived molecules. Reduction in mortality was dependent on cell mass and had an optimum: benefit diminished when the number of cells was raised beyond a certain point, indicating a therapeutic window of efficacy.

Cycling rats' blood through an extracorporeal bioreactor containing MSCs was also effective: 71% of rats treated with the MSC-seeded bioreactor were still alive a week later, whereas only 14% of those in control groups survived. Such external liver assist devices have previously shown promising results but are so far not practical for routine use because they require a supply of functionally stable human liver cells, which are difficult to acquire and maintain outside the body. Using MSCs in these devices may eliminate the need for human hepatocytes. Moreover, the observation that human MSCs were effective in rats suggests that the treatments can cross species barriers.

More investigation is needed to establish whether MSC treatment is applicable to humans. "Ideally, we have developed two clinically relevant treatment strategies that could be employed individually or in tandem," Yarmush tells *Lab Animal*. "In the acute setting, a patient presenting with [fulminant hepatic failure] could be treated with injections of MSC molecules as an 'off-the-shelf' product. If the damage is too extensive, a patient can be supported by an extracorporeal bioreactor as a curative treatment or as a bridge to transplantation."

Karen Marron

ADVANCES IN UVEITIS TREATMENT

Recent experiments in rats have elucidated the mechanism of action underlying uveitis, one of the world's leading causes of blindness in humans, and have identified a new avenue for its treatment. Uveitis, inflammation of the tissue layer below the outer surface of the eye (uvea), which includes the iris, can be caused by autoimmune disease, infection or toxin exposure. It is the primary cause of severe visual impairment in humans, accounting for 5–15% of cases of total blindness in the US and a higher proportion of those cases in developing countries.

Current treatment for uveitis is immune suppression via steroids or other drugs, which can have unwanted side effects and should not be used long-term. This is a particular concern for uveitis associated with autoimmune disorders, because these cases require long-term treatment.

Kota V. Ramana and colleagues at the University of Texas Medical Branch (Galveston) searched for non-steroidal means of reducing the inflammation in uveitis. They worked with a rat model of uveitis called endotoxin-induced uveitis (EIU), which is thought to represent certain types of human uveitis. EIU is induced in rats by subcutaneous injection of lipopolysaccharide. Ramana and his group targeted the inflammation signaling pathway and found that inhibition of aldose reductase (AR), an enzyme involved in producing inflammatory signaling molecules, suppressed ocular inflammation in EIU rats (*Invest. Ophthalmol. Vis. Sci.*, **48**, 4634–4642; 2007). Leukocyte infiltration, protein leakage into the aqueous humor and expression of several markers of inflammation in eye tissues were all reduced in EIU rats treated with an AR inhibitor compared with EIU rats not given the inhibitor.

These results suggest that inhibition of AR might hold promise for reducing ocular inflammation in human disorders such as uveitis. This potential represents a new treatment approach, and Ramana and his colleagues hope their research will progress to clinical trials.

They used an AR inhibitor called zopolrestat, which is currently undergoing phase 3 clinical trials as a treatment for diabetic complications and has shown no major side effects so far. Other AR inhibitors would probably have similar effects on ocular inflammation. If clinical trials for uveitis do take place and have positive results, Ramana's group intends to develop an eye-drop formulation of zopolrestat to deliver the treatment directly to the tissues of the eye.

Monica Harrington