Research presented at the American Heart Association's Scientific Sessions 2008 explains how team of researchers from the University Hospital of Munich build human heart valves from umbilical cord blood.

Umbilical cord blood used to build human heart valves in the lab

A recent study showed that it is possible to create human heart valve tissue, in a laboratory, from umbilical chord blood. The results of the study were presented at the American Heart Association's Scientific Sessions 2008.

Infants with heart valve malfunction that cannot be fixed by surgery are reliant upon replacement valves. Currently, these replacements are animal tissue valves, valves made from artificial materials or compatible human donations. The replacements save the lives of many infants; however, they are a short-term solution. They cannot grow or change shape, and as the child matures, further surgery is often required to replace the outgrown valves. Each type of replacement valve also presents its own problems. Compatible donor valves are not always available, and animal tissue valves are less durable than their human counterparts and may stiffen with time, and children who receive artificial valves must be treated with blood-thinning agents.

"In our concept, if prenatal testing shows a heart defect, you could collect blood from the umbilical cord at birth, harvest the stem cells, and fabricate a heart valve that is ready when the baby needs it," hypothesized Ralf Sodian, a cardiac surgeon at the University Hospital of Munich, Germany, and lead author of the study.

Tissue engineering of heart valves is still unexplored territory, and researchers are currently investigating the potential of using cells from various sources including blood, bone marrow and amniotic fluid. Ralf Sodian and his team of researchers used stem cells ($CD133^+$ cells) from umbilical cord blood. The blood was preserved by freezing, and after 12 weeks the cells were seeded on eight heart valve scaffolds made from biodegradable material. After being left to grow on the scaffold in a laboratory, the structures were examined with electron microscopes. The cells were found to have grown into pores on the scaffolding and had formed a tissue layer. Not only had the cell layer expanded, but biochemical analysis revealed that extracellular matrix proteins, essential for proper tissue function and structure had been produced.

Compared with human tissue from pulmonary heart valves, the engineered tissue was composed of 77.9% as much collagen, 85% as much glycosaminoglycan, and 67% as much elastin (a protein in connective tissue). In addition, desmin, lamin, α-actin and the endothelial wall components, CD31, VWF and VE-adherin, were contained in the engineered valves. These markers indicate the team had managed to grow actual human cardiovascular tissue in their laboratory.

There is still much to learn regarding the creation of functional heart valves from umbilical cord blood, including how to optimize the scaffold material and the conditioning of valves in the laboratory so that they function correctly after being implanted. Although it is still early days, Ralf Sodian believes that tissue engineering shows great promise and may save children with heart valve defects from successive valve replacement surgery, "Tissue engineering provides the prospect of an ideal heart valve substitute that lasts throughout the patient's lifetime and has the potential to grow with the recipient and to change shape as needed."

Source: Sodian R, Schaefermeier P, Abegg-Zips S et al.*: Presented at:* American Heart Association's Scientific Sessions 2008. *New Orleans, Louisiana. 8–12 November, 2008*

future medicine part of fsg

Novel therapeutic target shows promise for the treatment of a hard-to-beat childhood leukemia

A team of researchers from Children's Hospital Boston and the Dana-Farber Cancer Institute (both MA, USA) have demonstrated how a hard-to-treat leukemia activates cancer-causing genes, and in doing so have isolated a new potential therapeutic target.

With modern therapies, the cure rates for the major types of childhood leukemia stand at around 80%. However, the outcome for those with MLL-AF4, a subtype of acute lymphoblastic leukemia (ALL), is not as promising. Although the disease is rare among adults, it accounts for 70% of all ALLs that cause infants to fall sick. With chemotherapy achieving a cure rate of below 50%, MLL-AF4 is a disease in need of much attention.

In a study reported recently in *Cancer Cell*, Scott Armstrong of Children's Hospital Boston and Dana-Farber and his team developed a mouse model of MLL-AF4, and discovered that the fusion protein that characterizes the disease, also called MLL-AF4, acts by entering the nucleus of a cell and modifying histone H3. Histones give chromosomes their shape and aid with the process of gene activation, so when MLL-AF4 modifies histone H3, chromosome structure is altered and this leads to the activation of genes that initiate leukemia. Using gene-expression profiles, the team found that mouse model ALL cells display significant similarities to those from human subjects, highlighting the mechanism as a potential drug target. "If you could inhibit that abnormal histone modification, you might be able to reverse the tumorigenic properties of the fusion protein," suggests Armstrong.

The authors also managed to demonstrate that the MLL-AF4 protein modifies histone H3 by recruiting the DOT1L enzyme, which methylates the amino acid K79 of histone H3. The group predict that DOT1L would be a relatively easy target for a small molecule inhibitor given that there are already drugs in the clinic that target histone-modifying drugs, namely histone deacetylase inhibitors.

By inhibiting DOT1L, the genes that contribute to malignancy in MLL-AF4 could potentially be switched off. Although such an inhibitor has not yet been found, Armstrong and his colleagues suggested that the theory could work by suppressing DOT1L using RNA interference. As expected, the cancer-causing genes were switched off.

Armstrong believes that, "Reversal of histone modifications could be an important therapeutic approach for this and potentially other cancers."

Source : Krivtsov AV, Feng Z, Lemieux ME et al.*: H3K79 methylation profiles define murine and human MLL-AF4 leukemias.* Cancer Cell *14(5), 355–368(2008).*

Brain injury reduced by early phototherapy in jaundiced pre-term infants

The authors of a recent study conducted by researchers in the National Research Network of NIH's Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), MD, USA, show that early phototherapy can reduce the chance of neurodevelopmental disorders in preterm infants.

Jaundice is common in newborns, and usually its characteristic yellow colour fades without leaving damaging effects. However, sometimes the liver cannot remove bilirubin quickly enough, and it builds to dangerously high levels that are toxic, causing severe brain injury.

Treatment for newborns with hyperbilirubinemia is phototherapy, which converts bilirubin to a less toxic substance excreted in the urine. Previously, little information has been available regarding the treatment of preterm infants.

In the study, led by Brenda H Morris from the University of Texas Medical School, 1974 infants (12–36 h old) were assigned to either aggressive (early) or conservative phototherapy treatment groups. Those in the aggressive, group received therapy if their bilirubin levels reached 5 mg/dl, and those in the conservative group reveived therapy after levels reached 8 mg/dl. Evaluation of 'neurodevelopmental impairment' was made between 18 and 22 months, defined by a range of conditions including blindness, hearing loss and cerebral palsy.

Aggressive phototherapy significantly reduced the number of infants with neurodevelopmental impairment compared with the conservative treatment group. However, the authors found that, although not statistically significant, there was a higher proportion of death in smaller infants (501–750 g) in the aggressive treatment group.

"The study results provide important information for treatment options in extremely low birth weight infants with neonatal jaundice," said NICHD Director Duane Alexander.

The authors concluded that infants weighing above 1000 g should be considered for aggressive treatment but for those of lower birth weights, the potential to decrease brain injury must be weighed against the possibility of an increased risk of death.

Source: Morris BH, Oh W, Tyson JE et al.*: Aggressive vs. conservative phototherapy for infants with extremely low birth weight.* N. Engl. J. Med. *359, 1885–1896 (2008).*

Drug Watch

Colesevelam is safe and effective at lowering LDL cholesterol in children with familial hypercholesterolemia

During the American Heart Association Scientific Sessions in November 2008, Evan Stein from the Metabolic and Atherosclerosis Research Center in Ohio, OH, USA, presented data on the use of colesevelam, a bile-acid sequestrant, to treat children with heterozygous hypercholesterolemia. The drug acts to lower LDL cholesterol in children with the disease, and was well tolerated by patients.

A total of 191 patients aged 10–17 years with familial hypercholesterolemia were assigned to three groups; placebo, 1.875 g/day colesevelam and 3.75g/day colesevelam in a randomized, double-blind study.

After the eighth week, the 3.75 g/day group showed a 13% reduction in LDL cholesterol that was maintained throughout an 18-week period. Children in this group also achieved a HDL increase of 6% compared with placebo.

"Treatment with colesevelam HCl in pediatric patients with inherited high cholesterol significantly reduced their LDL or 'bad' cholesterol and increased the HDL or 'good' cholesterol. This was seen in children who received colesevelam HCl alone or combined with a statin, demonstrating the additive effect on LDL cholesterol reduction that is offered by colesevelam therapy," Dr Stein commented.

Source: Stein E: Efficacy and safety of colesevelam HCl in pediatric patients with heterozygous familial hypercholesterolemia. Presented at: American Heart Association's Scientific Sessions 2008. *New Orleans, LO. 8–12 November, 2008.*

Omalizumab added to optimized treatment improves asthma control in children with inadequately controlled allergic asthma

The results of a recent study investigating the use of omalizumab, a recombinant, DNA-derived, humanized anti-IgE monoclonal antibody, for the treatment of children with inadequately controlled allergic asthma, was the topic of a poster presentation by Bobby Q Lanier from the University of North Texas Health Science Center, TX, USA. Lanier's presentation was given at the American College of Allergy, Asthma and Immunology Annual Scientific Meeting and described data from his study of 628 children aged 6–11 years with moderate to severe asthma, which is inadequately controlled by inhaled corticosteroids (ICS).

During the randomized, double-blind study, the children had their ICS doses optimized and baseline measurements established. Those who were still symptomatic were assigned to either the omalizumab group or the placebo group for 52 weeks, along with ICS.

Omalizumab was found to reduce the rate of clinically significant asthma exacerbations by 43% over the 52-week treatment phase. Adverse effects included nasopharyngitis, sinusitis and upper respiratory infections and were similar between the two groups. No anaphylaxis due to omalizumab were seen, and no malignances or thrombocytopenia were reported. Dr Lanier and colleagues concluded that the drug added to optimized treatment can improve asthma control in children and is well tolerated.

Source : Lanier RQ. Efficacy and safety of omalizumab added to optimized asthma care in children with inadequately controlled allergic asthma. Presented at: American College of Allergy, Asthma & Immunology Annual Meeting. *Seattle, WA. November, 2008.*