MANCHESTER 1824
The University of Manchester

MPS Stem Cell Research Newsletter

Lady Shauna Gosling Trust | Norah Al-Ballaa Foundation | NHS | Department of Health | Lois Gosling | Irish MPS Society | The Canadian Society for Mucopolysaccharide & Related Diseases Inc. | bbsrc

Issue 2, June 2010

What are Mucopolysaccharide diseases?

Mucopolysaccharide (MPS) diseases such as Hurler and Sanfilippo are genetic disorders mainly affecting children. There are several disease types, each lacking a specific enzyme needed to break down glycosaminoglycans (GAGs). These GAGs build up in all cells of the body usually causing severe progressive mental decline, heart and other organ problems as well as bone and joint disease in some cases. Severe forms of MPS, which are the main disease type, often result in death in early childhood.

Manchester MPS Stem Cell Research

Our group was established in Spring 2006 at the Royal Manchester Children's Hospital in Manchester by Drs Rob Wynn, Ed Wraith and Brian Bigger, with funding from the UK MPS Society and other national MPS and children's charities. Last year we moved into new laboratories at the University of Manchester and we also have laboratories in the recently built children's hospital alongside the Willink Biochemical Genetics Centre for MPS disease diagnosis and treatment.

New laboratories in the University of Manchester

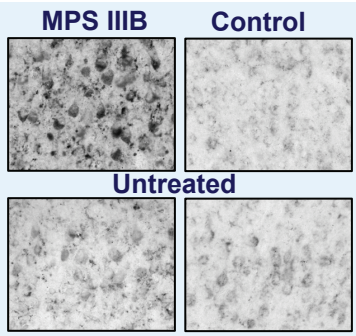
Therapies in development at Manchester

Milder forms of MPS can be treated by weekly injection of the missing enzyme (MPS IS (Sheie/HurlerScheie), II (Hunter), VI (Maroteaux-Lamy) to date). Most severe forms of MPS are untreatable as enzyme supplied in the blood is unable to cross into the brain or correct bone defects. MPS IH (Hurler) can be treated using bone marrow transplantation (BMT) where donor cells cross into the brain to supply the missing enzyme in the transplanted recipient and halt the mental decline.

Our goal is to improve these available therapies and to develop novel therapies for MPS and related diseases. There is no treatment available at the moment for MPS III, however, we have two therapies in development.

Genistein treatment for MPS IIIB

We have investigated a drug called genistein in a disease model of MPS IIIB to see if it can reduce GAG production and improve the disease. In short term experiments, very high doses of genistein reduced GAG levels in liver to near normal levels. We have now completed long term experiments in collaboration with the University of Gdansk and have found a significant reduction in GAG storage and inflammation in the brain as well as improvements in behavioural outcomes. We are hoping to move into clinical trial in the near future.



Reduction in storage in genistein treated brain

Marcela Malinowska of Gdansk University

Stem cell gene therapy for MPS IIIA

This approach aims to increase the level of the missing enzyme produced in blood cells after bone marrow transplant. The gene for the missing enzyme is delivered to bone marrow cells using a lentiviral vector and these cells are used for transplant. The cells repopulate the recipient's immune system and start to produce active enzyme in the blood that can be taken up by all cells in the body, reducing the amount of GAGs stored.

The enzyme cannot cross the blood brain barrier, but some cells from the bone marrow are able to move into the brain and release enzyme. This is then taken up by brain cells. In an MPS IIIA disease model, we have found that we can reduce GAG storage, inflammation and produce 10% of normal enzyme levels in the brain. We are now working on vector improvements to boost enzyme production further.

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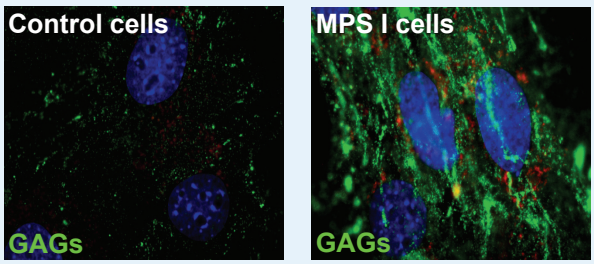
Ongoing research in the MPS laboratory

Bone marrow transplant is a risky procedure which requires a harsh conditioning regimen to prevent rejection of the donor cells. This means that BMT is not used to treat milder forms of MPS.

We are using a model of BMT to investigate reduced intensity conditioning regimens using lower doses of chemotherapy and immune blocking antibodies to create the same level of tolerance to donor cells without the need for such harsh chemotherapy.

We are also looking at how heparan sulphate, one of the GAGs stored in MPS, is involved in movement of the freshly transplanted cells to the bone marrow.



Storage in control and MPS I stromal cells

Once the cells have engrafted we need to find out if the cells traffic correctly to the brain. Therefore we are comparing this in models of MPS I and MPS III.

Early diagnosis and an early start to therapy are essential to ensure good treatment outcomes in MPS diseases. Therefore we are evaluating the use of heparin cofactor II-thrombin complex (HCII-T), which can be measured in blood samples, as a biomarker for diagnosis of MPS. HCII-T can be used for monitoring treatment outcomes in patients receiving BMT and/or enzyme replacement therapy.

Amongst other innovations we are developing a test for measuring neutralising antibodies in patients receiving enzyme replacement. This will help predict treatment failure in patients who may benefit from early BMT.

The MPS Stem Cell Group enjoying the Christmas Party

Publications

Archer LD, Langford K, Bigger B, Fildes JE. **Immune activation or immunomodulation in the brains of MPS IIIB mice?** *J Neurosci Res*. 2010 Feb 1;88(2):233.

Maria M Canal, Fiona L Wilkinson, Jonathan D Cooper, J Ed Wraith, Rob Wynn, Brian W Bigger. **Circadian rhythm and suprachiasmatic nucleus alterations in the mouse model of mucopolysaccharidosis IIIB.** *Behavioural Brain Research*. 2010 209:212–220.

Malinowska M, Wilkinson FL, Bennett W, Langford-Smith KJ, O'Leary HA, Jakobkiewicz-Banecka J, Wynn R, Wraith JE, Wegrzyn G, Bigger BW. **Genistein reduces lysosomal storage in peripheral tissues of MPS IIIB mice**. *Mol Genet Metab*. 2009 Nov;98(3):235-42.

Wynn RF, Wraith JE, Mercer J, O'Meara A, Tylee K, Thornley M, Church HJ, Bigger BW. **Improved metabolic correction in patients with lysosomal storage disease treated with hematopoietic stem cell transplant compared with enzyme replacement therapy.** *J Pediatr*. 2009 Apr;154 (4):609-11.

Wynn RF, Stubbs M, Ozyilmaz N, Wraith JE, Bigger B, **Cellular therapy of lysosomal storage disorders: Current status and future prospects.** *Curr Ped Reviews. 2009 Aug;5(3): 147-159.*

Invited presentations 2009-10

Team Sanfilippo Conference, Kenilworth, NJ, USA
European Society for Blood and Marrow Transplantation, Cambridge, UK
MPS Society biannual conference, Northampton, UK
Brains for Brain conference, Frankfurt, Germany
British Society for Gene Therapy, London, UK
All Ireland MPS conference, Belfast, N Ireland
11th International Symposium on MPS and related Disease, Adelaide, Australia
Gordon Research Conference, Proctor Academy, USA

Poster prizes

Congratulations to our PhD students who have both won prizes for their poster presentations:-
Angharad O'Leary (Harden Conference, Cambridge, UK) and Ana Sergijenko (NHS R&D Conference, Manchester, UK).

Grants

Our group has several current grants from the MPS Society UK, Norah Al-Ballaa Foundation, SCRF, Canadian MPS society, National MPS society, Manchester BRC, Irish MPS society, BBSRC, UK Dept. of Health and various other charitable donations, which is all used for research into MPS and related diseases.

Up and coming events

We will be recruiting a new post-doctoral research associate this summer. Please check our website for more information on this and the latest news and events.
http://www.medicine.manchester.ac.uk/staff/BrianBigger
http://www.mpssociety.co.uk/events.htm