MPS Stem Cell Research Newsletter

Issue 1, May 08

A new group working on MPS

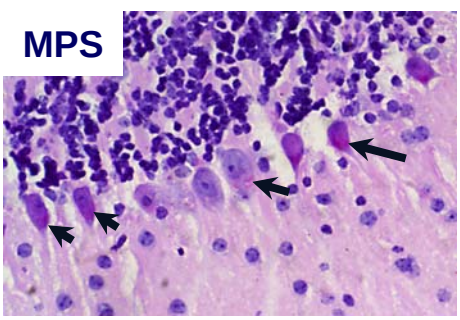
A new Mucopolysaccharide disease (MPS) stem cell research laboratory has been established at the Royal Manchester Children's Hospital in Manchester by Drs Rob Wynn, Ed Wraith and Brian Bigger, with funding from the UK MPS Society and other national MPS and children's charities.

Our goal is to use a multidisciplinary approach to investigate stem cell and gene therapies to improve bone marrow transplantation in MPS and related diseases.

The MPS Stem Cell Research Laboratory. From left to right; Dr Ed Wraith, Kia Langford, Dr Rob Wynn, Angharad O'Leary, Alex Smith, Marcelina Malinowska, Dr Fiona Wilkinson, Dr Brian Bigger and Dr Omar Pathmanaban.

What is Mucopolysaccharide disease?

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 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 form, usually result in death in early childhood.



Stained MPS I mouse brain. Arrows show GAGs (bright pink) stored in the Purkinjie neurons.

Ongoing research to improve treatment of MPS

Over the past two years our research group has grown and we now have a team of scientists working on different aspects of the disease. The group is made up of a clinical arm; Dr Ed Wraith, a consultant paediatrician and Dr Rob Wynn, a consultant haematologist. Dr Brian Bigger heads the lab-based research team comprising a post doctoral research scientist, a research technician and three PhD students.

Dr Fiona Wilkinson, a postdoctoral associate, is currently examining the potential of defined stem cell subsets from bone marrow to repopulate organs that are difficult to treat in MPS such as the brain and bones.

Current treatments for MPS

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 currently untreatable as enzyme supplied in the blood is not able to cross into the brain or to correct bone defects. The exception is MPS IH (Hurler), which 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.

BMT carries some risk, as with any treatment, because it requires intensive chemotherapy prior to transplant to ensure that donor cells engraft successfully in the patient. Although BMT can partly cure MPS IH, it is ineffective in MPS III (Sanfilippo) and MPS II (Hunter), and the reason for this is currently under investigation.

The risks of BMT to the MPS patient are high due to the immune responses between the donor and patient cells. Kia Langford (research technician and part-time PhD student) is developing immunomodulators and T regulatory cells to achieve transplant tolerance using less severe chemotherapy.

The MPS Stem Cell Group at the MPS Society's 25th anniversary afternoon tea at the Houses of Parliament

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In MPSIH, BMTs are not always successful first time. Angharad O'Leary (PhD student) is investigating the mechanisms of cell engraftment in MPS and how we can improve stem cell homing and engraftment.

Alex Smith (PhD student) is developing a combined stem cell and gene therapy approach for MPS IIIA. This involves improving the delivery of the missing enzyme by modifying stem cells in the bone marrow to produce a large quantity of enzyme to correct the disease.

Marcelina Malinowska, a visiting PhD student from our collaborators in Poland, is investigating the use of substrate or GAG reducing agents to improve the symptoms of MPS III subtypes.

Dr Omar N Pathmanaban, a clinical research fellow and trainee neurosurgeon is studying the role of stem cells in brain tumour formation. These techniques are very similar to those that we are using to develop stem cell therapies for MPS.

The combined expertise in the group brings together clinicians with expertise in metabolic disease, transplantation and neuroscience, the Willink Biochemical Genetics Centre for MPS disease diagnosis and a strong group of basic research scientists working towards new therapies for MPS diseases and insights into how the diseases progress.

Focus on: Stem cell subsets for MPS I

With a substantial amount of funding from the Lady Shauna Gosling Trust, we were able to buy a flow cytometer to characterise new stem cell subsets that could be used to improve bone marrow transplants in MPS I.

So far Fiona has isolated and expanded mesenchymal and endothelial stem cell subsets in tissue culture and is currently testing these in disease models of MPS I. We have also found that these stem cell subsets can successfully engraft in the liver as scar tissue and hope that they can be used to provide enzyme to organs such as the bones and joints of MPS I patients, which at present are the main areas that are not well corrected by bone marrow transplants.

Fiona characterises MPS bone marrow using the flow cytometer from the Lady Shauna Gosling Trust

Presentations

Over the past 2 years the research from the MPS stem cell research laboratory has been presented at several national and international conferences including 10 invited presentations or lectures, 2 oral presentations and 12 posters. The most notable are:
MPS conference, Venice, Italy, 2006
MPS conference, Northampton, UK, 2007
BSBMT, UK, 2007
Brains for Brain conference, Frankfurt, 2008
WORLD lysosomal conference, Las Vegas, 2008
Keystone Transplant tolerance, Keystone, USA, 2008
MPS conference, Vancouver, Canada, 2008

Scientists in one of the MPS Stem Cell Laboratories

Awards

The group has gratefully received grant funding of more than £850,000 to date from the MPS Society UK, The Lady Shauna Gosling Trust, The Ollie G ball, The Children's Bone Marrow Trust fund, the BBSRC, Lois Gosling and various other charitable donations, which is all used for research into MPS and related diseases.

In addition, Dr Fiona Wilkinson received a travel award fellowship from the British Society of Gene Therapy. This award funded a visit to the Lysosomal Diseases Research Unit run by Prof John Hopwood at the Women's and Children's Hospital in Adelaide, Australia. The aim of this visit was to gain expertise in MPS mouse model behavioural analysis and characterisation. Dr Bigger also received a travel fellowship from The Samantha Dickinson trust to visit this group in late 2008 to consolidate our existing collaboration and exchange ideas.

Up and coming events

The MPS Stem Cell Research Group hopes to hold an open day for the members of the public in collaboration with the MPS Society UK in late 2008. All are very welcome. Watch this space for details.

http://www.medicine.manchester.ac.uk/staff/BrianBigger
http://www.mpssociety.co.uk/events.htm