Update on MS research

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Plan

• Where do we do MS research in Edinburgh?

• What is missing in MS therapy?

• 2 ways to improve brain repair in MS using our own stem cells

• Making stem cells from MS patients
Project Base - Edinburgh

MRC Scottish Centre for Regenerative Medicine
230 Researchers

No 9, Bioincubator

MRC hub for Stem cell niche - £5.6 million

Medical School
250 Researchers

Anne Rowling Regenerative Neurology Clinic – 1700 MS patients. 1/500 in Scotland

Royal Infirmary
870 beds

Clinical Research Facility
MHRA Accredited Phase 1 Unit

Queen’s Medical Research Institute
650 Researchers
Drug Discovery Core

Clinical Research Imaging Centre
What is MS?

Immune attack

Oligodendrocyte precursor cells to remyelinate
Neural protection
MS therapy

Anti-inflammatory drugs: βIFN, Fingolimod, Natalizumab, Teriflunomide, fumarate, Alemtuzumab

Neuroprotective therapies: 

- Inflammation
- Neurodegeneration
- Relapses
- Progression
- Disability

Time
Neuroprotective strategies

- Demyelination
- Axon degeneration
- Promote axon survival as in MND, AD, stroke etc.
- Remyelination (inefficient)
What is required for remyelination?

Demyelination  Remyelination

Oligodendrocyte Precursor Cell

Recruitment  Maturation
Causes of remyelination failure in MS

- Failure of OPC recruitment: 40%
- Successful OPC recruitment: 60%
- Failure of OPC maturation
- Remyelination failure
Semaphorin action on OPCs in MS?

Chronic demyelination

Sema 3A
Repulsive
Some human MS lesions have few OPCs and more Sema3A

Boyd A, Zhang H, Williams A. 2013
Experimental plan

Day 1
Stereotaxic injection of LPC into corpus callosum

Day 4
MR scan

Day 6
Stereotaxic injection of NaCl, Sema3A or into corpus callosum

Look at remyelination after 2 and 3 weeks
Evidence that manipulation of Sema3A alters remyelination

More Sema3A
Less OPCs
Less remyelinated fibres

Less Sema3A
More OPCs
More remyelinated fibres

(data from 3 independent labs)
Target

Block OPC response to Sema3A through receptor Neuropilin1 to improve recruitment and remyelination
Causes of remyelination failure in MS

Failure of OPC recruitment (40%)

Successful OPC recruitment (60%)

Remyelination failure

Remyelination success

Failure of OPC maturation
Remyelination is improved by 9cRA

Huang, Jarjour.....Williams....ffrench-Constant, Franklin. 2011 Nature Neuroscience
Other molecules involved

Recruitment (negative)
- Sema3A PMID: 23595275
- Netrin-1 PMID: 24942777, PMID: 23831296

Maturation (negative)
- LINGO-1 PMID: 19334062
- Endothelin-1 PMID: 24507193
- Notch signalling PMID: 12357247
- Wnt signalling PMID: 19515974, PMID: 21706018
- Hyaluronan PMID: 16086023
- BMP signalling PMID: 17872503, PMID: 21430151

Recruitment (positive)
- Sema3F PMID: 23595275
- PDGF PMID: 17984680

Maturation (positive)
- RXRg signalling PMID: 21131950
- CXCL12 PMID: 20534485
- Endothelin-2 PMID: 23518706
- Olesoxime PMID: 22367994
- Diosgenin PMID: 22461009
- Benztropine PMID: 24107995
- Phosphodiesterase 7 PMID: 23661015

Myelinating oligodendrocyte
Timelines

Discovery of LINGO Inhibiting O maturation 2004
blocking antibodies promoting rodent CNS remyelination 2007
Phase 1 trial 2012
Phase 2 trial 2014

RXRg agonists aid remyelination 2011
Grant to develop drugs 2015

Sema3A/NP1 inhibits remyelination 2013
Grant to develop drug inhibitors 2015
A stem cell can self-renew or differentiate

SELF-RENEWAL
(copying) stem cell

DIFFERENTIATION
(specialising)
specialised cell
e.g. muscle cell, nerve cell

grow
repair
renew
Different types of stem cells

Tissue stem cells
Throughout life

Embryonic stem cells
Blastocyst
Inner cell mass

Induced pluripotent stem cells
Cell from the body
Genetically reprogrammed
Pluripotent cell

Different types of stem cells
What is a stem cell?

Induced pluripotent stem cell

- Neural stem cell
  - Nerve
  - Oligodendrocyte
- Gut stem cell
- Blood stem cell
- Cardiac stem cell
- Mesenchymal stem cell
  - Bone
  - Cartilage
  - Fat
- Skin cell
- Immune cell
How to make an iPS cell?

ES cells → Skin fibroblasts

Oct4, c-Myc, Klf4, Sox2 → iPS cells

iPS cells

• In theory, from any cell, to make any cell

• Person specific – compatibility/disease lines (drug testing, understanding biology)

• Ethically easier
Regrowing the brain?

Myelin repair
Nerve replacement

Can grow human nerves and myelin in culture dish

Not feasible at present in people
Problems

Multiple lesions
How do we get stem cells in?

New lesions
Can they migrate?

Some lesions repair themselves
Where do we get them from?

Danger – operations, drugs, infection, tumours
How will they know what connections to make?
Spinal cord injury

How do we get stem cells in?

One lesion

Can they migrate?

No new lesions

Where do we get them from?

Very little repair

How will they know what connections to make?

Danger – operations, drugs, infection, tumours
I want stem cells for my MS

I will take any risks

Why won’t the NHS give me stem cells?

We have collected thousands of pounds to get stem cell treatment

It is a conspiracy to keep Drs and drug companies in a job

I want to be a guinea pig for stem cells
Stem cell tourism
Put ‘stem cell’ and ‘MS’ into Google – get over 1 million hits
Researchers Highlight Warning Signs On Adult Stem Cell Treatments

STEM CELL TOURISM: SEEKING TREATMENT ON THE INTERNET AND PAYING FOR IT WITH YOUR LIFE

“While there are some very promising results ... the ‘treatments’ being advertised by these clinics are dubious, mostly ineffective, and sometimes positively harmful.” Alta Charo

Panel decries overseas clinics that provide treatments devoid of scientific validity

Desperate patients warned to avoid stem cell tourism abroad over unproven 'miracle' claims

Stem cell hype and the dangers of stem cell “tourism”

‘Stem cell tourism’ growing trend

Stem Cell Fraud: A 60 Minutes investigation

Stem cells in Texas: Cowboy culture
How do we compete?

“In short... I’ve got my life back... my kids have their dad back... and my wife has the man she knew before this terrible disease changed our lives.”

"We decided... through endless hours of discussion that this is the best investment we can make to improve both our lives... We're always just waiting in hope."

“Stem cells have become a magic word. Often new areas of science get that reputation; in the 19th century .... everything with electricity or magnetism was magic. Today it's stem cells and nanotechnology. It is time to lose the hype without losing the hope."
It’s nothing a few stem cells and another 75 years of research won’t fix
What causes MS?

Young
2F:1M

1 in 500 in Scotland

Genetic

- Twin studies – 30% MZ
- GWAS – HLA DR2, others in immune system

Immune

- Position of plaques
- Latitude and vitamin D

Infective

- EBV, chlamydia, coxsackie, canine distemper virus, HHV6, Clostridium

Others in immune system