MS Research—Your Questions Answered

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Overview

1. Multiple Sclerosis 401
2. Key advances MS research
3. What the Society is doing to find solutions for people living with all forms of MS?
Why Aren’t There More Treatments for Progressive MS?

• **Short answer:** We still don’t fully understand the cause of progressive MS

• Lack of animal models for progressive disease

• Progression is not well defined and it is hard to measure

• Lack of accepted endpoint for clinical trials

• Lack of effectiveness of DMT’s for RRMS is a clue

• **Reason to be optimistic:** 57 ongoing interventional trials in progressive forms of MS
Possible Mechanisms of Neurodegeneration in MS

- **Dysfunction in myelin repair**
  - May deny the neurons survival signals
  - Leaves the neurons vulnerable

- **Neuronal cell damage induced by:**
  - Excitotoxicity
  - Oxidative stress
  - Loss of nerve cell support factors/receptors
  - Energy failure

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Cells with the Ability to Repair Myelin are Present in the Brain

- Oligodendrocyte Progenitor Cells (OPC’s)
- 5-8% of all the cells in the nervous system
- Tremendous ability to induce “natural repair”

*Mouse embryonic-stem-cell-derived oligodendrocyte precursor cells (mESC-OPCs).*
Normal White Matter
Remyelinated Lesion
- Shadow Plaque
Chronic Inactive Lesion
Promoting Natural Myelin Repair with Anti-LINGO

- LINGO-1 inhibits remyelination
- Anti-LINGO-1 promotes remyelination in an MS-like disease in mice
- Shown to be safe in early human trials
- Early evidence for efficacy in optic neuritis
- Currently in a phase II trials in RRMS

Mi, et al., Nature Medicine, 2007; 13(10):1228
Repurposing FDA Approved Drug-Benztropine to Promote Repair

A regenerative approach to the treatment of multiple sclerosis

Yashali D. Deshmukh1, Virginia Tardiff2, Costas A. Lyssiotis1, Chelsea C. Green1, Bilal Kerman1, Hyung Soon Kim2, Krishnan Padmanabhan3, Jonathan C. Erskine4, Ismail Almam5, Saera Kand6, Fred H. Gage1, Angqvist N. Theodorpoulos5, Brian R. Lawson7, Peter G. Schulte7 & Luke L. Litson7,8

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Transplantation of Skin Derived OPC is Another Promising Approach for MS Repair Therapy

How iPS cells are made:
- Take skin cells
- Introduce genes
- Culture
- Differentiation
  - Nerve cells
  - Cardiac muscle cells
  - Fat cells
  - Cartilage
- Can be the base for various tissues
### Agents of Interest for Neuroprotection in MS

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Agents</th>
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</thead>
<tbody>
<tr>
<td>Sodium channel blockers</td>
<td>Lamotrigine, <strong>amiloride</strong>, phenytoin, flecainide, carbamazepine</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Nimodipine, nifedipine, ryanodine, CYLA, bepridil</td>
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<tr>
<td>Glutamate antagonists</td>
<td><strong>Riluzole</strong>, NBQX, talampanel, memantine</td>
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<tr>
<td>Growth factors</td>
<td>Erythropoietin, rhIGF</td>
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<tr>
<td>NO blockers</td>
<td>Furoxan</td>
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<tr>
<td>Sex hormones</td>
<td>Estriol, testosterone</td>
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<tr>
<td>Phenols</td>
<td>Resveratrol, epigallocatechin-3-gallate</td>
</tr>
<tr>
<td>Statins</td>
<td><strong>Simvastatin</strong>, atorvastatin</td>
</tr>
<tr>
<td>Immunophilin ligands</td>
<td>Cyclosporin A, FK506, rapamycin</td>
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<tr>
<td>PPARg agonists</td>
<td>Pioglitazone</td>
</tr>
<tr>
<td>Agents with pleiotropic</td>
<td><strong>Ibudilast</strong>, minocyclin, co-Q10, galectine-1, vitamin D</td>
</tr>
</tbody>
</table>

*Note: Bolded agents indicate potential neuroprotective effects.*
Simvastatin (Zocor) Trial (MS-STAT)

- Jeremy Chataway-University College London
- High dose simvastatin (80 mg)
- 140 people with established SPMS
- 50% decrease in brain atrophy
- Significant Improvement in disability
Society Sponsored Trials of Neuroprotective Agents for Progressive MS

- US-based Phase II trial in SPMS/PPMS (n = 250)
  - Uses NIH-sponsored Phase II trial network
  - 2 arms: ibudilast, placebo
  - Outcomes: atrophy @ 96 weeks, DTI, MTR, OCT

- UK-based Phase II trial in SPMS (n = 440)
  - 4 arms: riluzole, amiloride, ibudilast, placebo
  - Outcomes: atrophy @ 96 weeks, advanced imaging and CSF biomarkers (subset)
Finding solutions for people with MS is the Society’s Highest Priority - **Research is essential to that goal**

- The Society has invested nearly **$870 million** in research, contributing to many of the FDA-approved therapies
- Fueling research through increased investment
  - 2014: **$50.6 million** for 380 new/ongoing projects
  - 2015: **$52+ million**
- The Society now leads the way, funding more research and impacting more lives than any other MS organization in the world
Research Principles

• **Comprehensive and Collaborative**
  • Pursue all promising paths
  • Remain nimble, seize promising new opportunities
  • Act with urgency!

• **Strategic**
  • identify gaps and opportunities that will catalyze advances

• **Centralized peer review:**
  • perform rigorous due diligence

• **Fund worldwide**
  • no boundaries
An expanding alliance of MS organizations from around the world

Mission
To expedite the development of therapies for effective disease modification and symptom management in progressive MS

www.endprogressivems.org
Key Priorities

• Leverage and coordinate the Global MS movement to focus on Progressive MS

• Expand the global commitment to progressive MS research by €22 million ($30 million) over the next 6 years

• For the first time ever, MS Societies are funding research together without considering geography

• Funding the best science anywhere in the world
INTERNATIONAL
PROGRESSIVE MS ALLIANCE

CONNECT TO END PROGRESSIVE MS

• Managing Members
  • United States
  • Australia
  • Italy
  • United Kingdom
  • Canada
  • Multiple Sclerosis International Federation

• Contributing Members
  • Denmark
  • Spain
  • Germany
  • Netherlands
  • France
Key Milestones

• **Convened** global scientific leaders in progressive MS research to develop a research strategy
• **Awarded** 22 pilot research grants to researchers from 11 different countries
• **Issued** a request for grant proposals focused on establishing global collaborative networks
• Subscribe to the monthly National eNEWS: www.nationalmssociety.org/MyProfile

• Visit: www.nationalmssociety.org/research for full coverage on everything from research breakthroughs to clinical trials near you.
Text your questions in the chat box at the bottom left hand side of your screen OR the operator will assist you with asking your questions.

“Mr. Osborne, may I be excused? My brain is full.”