Making Progress with Progressive MS?

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Disclosures:

I have received personal consulting fees from Actelion, Biogen, EMD Serono, Genentech, Novartis, and Teva. I have served on advisory committees for Actelion, Biogen, Novartis, and received clinical trial contract and research grant funding from Biogen and Novartis.
Why so important?

- Large worldwide impact: about half of all MS patients (2.3 million)
- Onset of progression is the main determinant of disability
- Currently limited treatments for progressive MS
- Finding treatments for progressive MS is one of the top priorities for patients
Making Progress with Progressive MS

- What is progressive MS?
- How is progressive MS measured?
- How can we treat progressive MS?
- What about stem cells?
- What’s next for progressive MS?
Making Progress with Progressive MS

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- How is progressive MS measured?
- How can we treat progressive MS?
- What about stem cells?
- What’s next for progressive MS?
Defining the clinical course of multiple sclerosis
The 2013 revisions

Fred D. Lublin, MD
Stephen C. Reingold, PhD
Jeffrey A. Cohen, MD
Gary R. Cutter, PhD
Per Soelberg Sørensen,
    MD, DMSc
Alan J. Thompson, MD

Neurology® 2014;83:278-286
Two Types of Progressive MS

• Secondary Progressive
  – An estimated 65% of individuals with relapsing remitting MS will convert to SPMS within 20 years

• Primary Progressive
  – 15% of PwMS
  – Older age at onset
  – 1:1 ratio of women to men
  – Prominent spinal cord involvement - impairs mobility
  – Less often cerebellar with tremor and imbalance

• They are much more similar than different
Onset of progressive phase determines disability

Scalfari et al Neurology 2011
New insights into the burden and costs of multiple sclerosis in Europe

Gisela Kobelt, Alan Thompson, Jenny Berg, Mia Gannedahl and Jennifer Eriksson; the MSCOI Study Group* and the European Multiple Sclerosis Platform

Costs related to disability
16 European countries, N = 16,808
Promote recovery and prevent disability progression.

To prevent disability progression:
- Prevent tissue damage
- Promote recovery
- Neuroprotection
- Remyelination

Axonal loss and tissue damage.
Protective mechanisms become exhausted with time

- Initially, structural damage leads to functional reorganization, resulting in low disability
- After functional reorganization is exhausted, disability progressively develops
Possible causes of progression

- Slowly expanding pre-existing lesions
- Compartmentalized inflammation
- B cell/antibody involvement
- Persistent microglial activation
- Remyelination failure
- Metabolic derangement (i.e. mitochondrial failure)
- Exhaustion of neuroplasticity

We don’t really understand what is driving progressive MS
Will the real multiple sclerosis please stand up?

Peter K. Stys, Gerald W. Zamponi, Jan van Minnen and Jeroen J. G. Geurts

Nat Rev Neurosci 2012
Making Progress with Progressive MS

- What is progressive MS?
- How is progressive MS measured?
- How can we treat progressive MS?
- What about stem cells?
- What’s next for progressive MS?
How is progressive MS measured?

- Clinically:
  - Disability scale
  - Walking speed
  - Arm function
  - Cognitive testing
Multiple Sclerosis Performance Test (MSPT) – Developed at Cleveland Clinic
Multiple Sclerosis Performance Test (MSPT)

- Cognition
- Vision
- Dexterity
- Walking speed
MSPT measures Neurological “Vital Signs”
Phenotyping patients in the clinic, integrating clinical care with research
Imaging Measures of Progressive MS

Progressive atrophy over 14 years

Atrophy continues, even when there are no new lesions
Imaging Measures of Progressive MS

- Magnetization transfer ratio
- Diffusion tensor imaging
- Brain atrophy
- Optical coherence tomography
- Cortical atrophy
Fluid Biomarkers – Neurofilaments

Scaffolding protein in neurons/axons

- Neurofilament Heavy (NfH): 200 kDa
- Neurofilament Medium (NfM): 150 kDa
- Neurofilament Light (NfL): 68 kDa

- Highly specific neuronal proteins,
  - Very stable in vitro
- Important structural proteins (13% of overall protein)
  - Determines axon diameter
- NfL in CSF reflects axonal damage
  - MS, Alz Dz, ALS, Parkinson’s Dz, and trauma)
- Blood levels are 50-100 fold less than CSF
sNfL in MS

NfL_{Se} is higher in MS than healthy controls

NfL_{Se} is associated with disability

Disanto, G. et al, Ann Neurol, 2017
Making Progress with Progressive MS

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Treating Progressive MS

- Disease modifying therapies
- Symptom therapies
- Therapy / Rehabilitation
- Lifestyle choices
Fingolimod in PPMS

Graph showing the percent of patients with 3-month confirmed disability progression over study weeks for Fingolimod 0.5 mg and Placebo groups. Cox regression: HR 0.95 (95% CI 0.80, 1.12); p=0.544. Log-rank test: p=0.689.

Bar chart comparing the number of lesions for New/newly enlarging T2, Gd-enhancing T1, and Brain Volume Loss. Placebo vs Fingolimod 0.5 mg with significant reductions in lesion counts (−73%, p<0.001; −78%, p<0.001).

Rituximab in PPMS

Hazard Ratio: 0.77 (95% CI: 0.55, 1.09)
P=0.1442

Rituximab in PPMS

**Age ≥51 Gd Lesion=0**

N=187

HR: 127
(95% CI: 0.71-2.27)

P=0.4256

**Age ≥51 Gd Lesion ≥1**

N=37

HR: 0.52
(95% CI: 0.18-1.52)

P=0.2243

**Age <51 Gd Lesion=0**

N=143

HR: 0.63
(95% CI: 0.34-1.18)

P=0.1427

**Age <51 Gd Lesion ≥1**

N=72

HR: 0.33
(95% CI: 0.14-0.79)

P=0.0088

Ocrelizumab reduced the risk of disability progression by 24%

24% reduction in risk of CDP
HR (95% CI): 0.76 (0.59–0.98); P=0.0321

Caveats: trial only enrolled patients ≤ 50 yrs with MS duration <10-15 years
Benefit all but disappeared in patients without active MRI at start
Ocrelizumab PPMS sub-group analysis

Figure 2. 12W-CDP analyzed by prespecified subgroups

<table>
<thead>
<tr>
<th>Baseline risk factors</th>
<th>PBO (n=244)</th>
<th>OCR (n=488)</th>
<th>Favours OCR</th>
<th>Favours PBO</th>
<th>HR (95% CI)</th>
<th>p interact.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td>244 (90)</td>
<td>487 (160)</td>
<td></td>
<td></td>
<td>0.76 (0.59, 0.98)</td>
<td>NA</td>
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<tr>
<td><strong>Baseline weight, &lt;75 kg</strong></td>
<td>142 (53)</td>
<td>200 (93)</td>
<td></td>
<td></td>
<td>0.76 (0.54, 1.07)</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Baseline weight, ≥75 kg</strong></td>
<td>101 (43)</td>
<td>195 (67)</td>
<td></td>
<td></td>
<td>0.76 (0.52, 1.12)</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Duration since MS symptom onset</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.88</td>
</tr>
<tr>
<td>≤3 years</td>
<td>53 (24)</td>
<td>79 (25)</td>
<td></td>
<td></td>
<td>0.63 (0.36, 1.12)</td>
<td></td>
</tr>
<tr>
<td>&gt;3 to ≤5 years</td>
<td>82 (20)</td>
<td>111 (39)</td>
<td></td>
<td></td>
<td>0.92 (0.63, 1.58)</td>
<td></td>
</tr>
<tr>
<td>&gt;5 to ≤10 years</td>
<td>96 (34)</td>
<td>202 (80)</td>
<td></td>
<td></td>
<td>0.83 (0.54, 1.28)</td>
<td></td>
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<tr>
<td>&gt;10 years</td>
<td>36 (15)</td>
<td>81 (30)</td>
<td></td>
<td></td>
<td>0.63 (0.33, 1.19)</td>
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<tr>
<td><strong>Baseline EDSS score, ≤5.5</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.86</td>
</tr>
<tr>
<td>Baseline EDSS score, &gt;5.5</td>
<td>163 (61)</td>
<td>348 (100)</td>
<td></td>
<td></td>
<td>0.73 (0.53, 1.00)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>81 (35)</td>
<td>139 (80)</td>
<td></td>
<td></td>
<td>0.84 (0.55, 1.28)</td>
<td></td>
</tr>
<tr>
<td><strong>Age group, ≤45 years</strong></td>
<td>118 (49)</td>
<td>230 (71)</td>
<td></td>
<td></td>
<td>0.64 (0.45, 0.92)</td>
<td>0.23</td>
</tr>
<tr>
<td>Age group, &gt;45 years</td>
<td>126 (47)</td>
<td>257 (89)</td>
<td></td>
<td></td>
<td>0.88 (0.62, 1.26)</td>
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</tr>
<tr>
<td><strong>Baseline T1 Gd+ lesions, yes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>Baseline T1 Gd+ lesions, no</td>
<td>60 (27)</td>
<td>133 (43)</td>
<td></td>
<td></td>
<td>0.65 (0.40, 1.06)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>183 (88)</td>
<td>350 (115)</td>
<td></td>
<td></td>
<td>0.84 (0.62, 1.13)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex, Female</strong></td>
<td>124 (44)</td>
<td>236 (85)</td>
<td></td>
<td></td>
<td>0.04 (0.66, 1.36)</td>
<td>0.10</td>
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<tr>
<td>Sex, Male</td>
<td>120 (52)</td>
<td>251 (75)</td>
<td></td>
<td></td>
<td>0.61 (0.43, 0.88)</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Wolinsky et al, CMSC 2018
Ocrelizumab PPMS sub-group analysis

Adapted from Wolinsky et al, CMSC 2018
Siponimod SPMS sub-group analysis

Adapted from Wolinsky et al, CMSC 2018
Rituximab in PPMS

Treating Progressive MS

- Disease modifying therapies
  - Currently, therapies to modify the disease course are very limited

- Symptom therapies
  - Multitude of symptoms – most of which are managable

- Therapy / Rehabilitation
  - PT / OT / Speech / Swallowing / Physical Medicine can be very helpful and is sometimes forgotten

- Diet
  - Many dietary approaches, none with compelling evidence of benefit

- Comorbidities
  - Diabetes, heart disease, hypertension, obesity
Future of MS

- Neuroprotection
- Repair/Remyelination
- Lifestyle modifications
- Rehabilitation
Making Progress with Progressive MS

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What about Stem Cells?

Cancun Stem Cell Clinic

How it works?
When a stem cell divides, each new cell has the potential to either remain a stem cell or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a brain cell.

STEM CELL CENTER
OF NORTH AMERICA

Serving the Whole World

"Among the Top Seven Stem Cell Treatment Centers in the World"
Offering Unique Blend of Stem Cell Therapy with Complementary and Alternative Medicine

CELL MEDICINE
DEDICATED TO THE ADVANCEMENT OF ADULT STEM CELLS FOR THE TREATMENT OF HUMAN DISEASES.
What about Stem Cells?

Cell-Based Strategies to Treat MS

• Anti-inflammatory therapy
  – Immunoablation and autologous hematopoietic stem cell transplantation

• Remyelination/repair
  – Direct cell replacement
  – Utilization of stem cells to deliver trophic factors to endogenous stem cells
  – Pharmacological modulation of endogenous stem cells

Courtesy Jeff Cohen, MD
What about Stem Cells?

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Courtesy Jeff Cohen, MD
• In aggregate, the available data suggest I/AHSCT has potent, durable efficacy against MS inflammation
• Patients most likely to benefit: young, relatively recent disease onset, still walking, recent clinical relapses and MRI lesion activity
  – Continued activity despite 1st and 2nd line agents
• There are risks, and financial costs are significant
What about Stem Cells?

Cell-Based Strategies to Treat MS

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• Remyelination/repair
  – Direct cell replacement
  – Utilization of stem cells to deliver trophic factors to endogenous stem cells
  – Pharmacological modulation of endogenous stem cells

Courtesy Jeff Cohen, MD
Intrinsic Repair Mechanisms Are Present in Chronic MS Lesions

Abundant myelin-making cells – they just don’t myelinate the axons

Lack of myelinating stem cells is not the main problem. Rather, we need to promote better function of the cells already there.
What about Stem Cells?

Cell-Based Strategies to Treat MS

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• Remyelination/repair
  — Direct cell replacement
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  — Pharmacological modulation of endogenous stem cells

Courtesy Jeff Cohen, MD
Mesenchymal Stem Cells Promote Repair by Providing Support for Remyelination

- Adult stem cells that can be isolated from bone marrow and fat tissue and then grown in a laboratory to large numbers
- Potential ability to prevent and reverse damage from MS through a range of immune, brain-protective, and repair-promoting functions
- However, none have been shown effective yet
What about Stem Cells?

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Courtesy Jeff Cohen, MD
Clinical Testing

Primary Screening in vitro

Secondary Screening in vitro

Brain Tissue Assay

Remyelination Assays in vivo

Focused Decision Gates

High Throughput
100,000 drugs feasible
Low cost

Medium Throughput
100 drugs feasible
Medium Cost

Low Throughput
5-10 drugs feasible
High Cost
Stem Cells Have Risks

Multiple spinal cord tumors after stem cell injection

Berkowitz AL et al.  NEJM 2016;375:196-8
Cell-Based Therapy: Conclusions

• Several types of cell-based treatment are under study in MS, with different risks, benefits, and goals

• Some of these strategies show promise, but many significant questions remain

• Stem cell transplantation is not yet appropriate for general use to treat MS
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Challenges of Progressive MS

• Understand what is driving the progression in progressive MS
• Identify new therapeutic targets
  – Probably not inflammation
• Validate a outcomes for clinical trials
  – Clinical measures
  – Biomarkers
• Drive symptomatic treatments and rehabilitation
• Coordinate efforts globally
Mission: To expedite the development of effective disease modifying and symptom management therapies for progressive forms of multiple sclerosis
• **Mission:** To expedite development of effective disease modifying and symptom management therapies for progressive forms of MS

• **Action:** Collaborate to END Progressive MS

• **Research Priorities:**
  – Understand Progression
  – Develop More Responsive Outcome Measures and Shorter, Faster Clinical Trial Designs
  – Enhance Well-Being through Rehabilitation and Symptom Management
Alliance Milestones

2010 – Progressive MS Think Tank (Boston)

2011 – London Organizing Meeting

2012 – Action Plan Drafted/Framework Paper Published (MSJ)

2013 – First Scientific Congress; Alliance Formalized

2014 – Challenge Awards Funded

2015 – Industry Forum Formed; Network Planning Awards Funded

2016 – Network Second Scientific Congress
Progressive MS Treatments In Development: 2012

- 3 Immune Therapies
- 1 Neuroprotection
Progressive MS Treatments In Development: 2018

- **29** Immune Therapies
- **18** Neuroprotection
- **22** Symptom Management
- **9** Myelin Repair
- **10** Rehabilitation
- **2** Stem Cells
NN102 / SPRINT-MS Trial of Ibudilast

- 96-week, 28-site, phase II trial utilizing NIH-sponsored NeuroNEXT network
- Inclusion:
  - Age 18-65 years
  - Primary or secondary progressive MS
  - Typical MS lesions on brain MRI
  - Expanded Disability Status Scale 3.0-6.5
  - Disability progression in the preceding 2 years (EDSS, 25FW, 9HPT)
  - Concurrent treatment with IFN or GA allowed
- Imaging:
  - 3T MRIs – GE, Siemens
  - Spectral domain optical coherence tomography
- 1:1 Randomization to ibudilast or matching placebo
  - Stratified by disease (PPMS/SPMS) and DMT (untreated or IFN/GA)

Fox et al, Contemporary Clin Trials, 2016
NN102 / SPRINT-MS Study Endpoints

• Primary:
  • Whole brain atrophy – Brain Parenchymal Fraction (BPF)
  • Safety – Adverse events, Serious adverse events
  • Tolerability – early discontinuation

• Secondary
  • Diffusion Tensor Imaging in pyramidal tracts
  • Magnetization Transfer Ratio in normal appearing brain tissue
  • Retinal Nerve Fiber Layer Thickness - Optical Coherence Tomography
  • Cortical atrophy - Cortical Longitudinal Atrophy Detection Algorithm

Fox et al, Contemporary Clin Trials, 2016
### Current state of MS Drug Candidates by Stage

* Compounds are counted twice if tested in more than 1 indication

#### All MS Indications (under active development)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Preclinical</td>
<td>39</td>
</tr>
<tr>
<td>Phase I</td>
<td>29</td>
</tr>
<tr>
<td>Phase II</td>
<td>39</td>
</tr>
<tr>
<td>Phase III</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>118</td>
</tr>
</tbody>
</table>

#### Progressive MS

<table>
<thead>
<tr>
<th>Stage</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Preclinical</td>
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</tr>
<tr>
<td>Phase I</td>
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</tr>
<tr>
<td>Phase II</td>
<td>9</td>
</tr>
<tr>
<td>Phase III</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
</tr>
</tbody>
</table>

(very early are not counted)

Source: Thomson Reuters: Clarivate Analytics Integrity drug discovery and development portal
Where we are now?

• **Successful studies**
  - ORATORIO
  - Biotin (II)
  - Simvastatin (II)
  - Siponimod
  - Ibudilast (II)

• **Reasonable pipeline**
  - MS Smart (Amiloride, Riluzole, Fluoxetine)
  - Simvastatin (III)
  - Biotin (III)
  - Mastinib
  - GZ402668
Progressive MS remains a significant unmet need
We lack a fundamental understanding of the drivers of progression
There are sensitive ways to measure clinical progression, but the optimal biomarker remains unknown
Treatments modifying the disease course remain limited, but many potential therapies are in development, and there are many symptom-targeted management options
Stem cells are intriguing, but not yet appropriate for treating progressive MS
A multi-faceted approach has been organized to overcome the bottlenecks in developing treatments for progressive MS
The future for progressive MS looks bright!