International Progressive Multiple Sclerosis Collaborative: Update on Research Strategy
Progressive Forms of MS

- Many MS patients begin with a relapsing form and convert to a progressive form.
- A small percentage of MS patients have nearly continuous progression of disability with no distinct relapses.
Development of secondary progression is the dominant determinant of long-term prognosis, independent of disease duration and early relapse frequency.
Onset of progressive phase determines disability

Scalfari et al Neurology 2011
Goals of treatment

1. Reduce relapse disability
2. Reduce relapse rate
3. Reduce rate of progression
4. Stop progression
5. Reverse progression

Time in years

Relapsing remitting
(onset: 85% remains: 30%)

Clinically isolated syndrome
Clinically definite MS

Secondary progressive (60%)

Primary progressive (15%)

Progressive relapsing (rare)
Many new drugs available/coming very soon

• Prevention of T cell circulation and transmigration
  – Natalizumab
  – Fingolimod

• Anti-metabolities - Teriflunomide

• Leukocyte depletion
  - Alemtuzumab
  - Daclizumab [Phase III]

• B-cell directed therapies - Ocreluzimab [Phase III]
  – Laquinomod, Fumarate
Do you think we are doing enough to address the needs of MSers with progressive disease?

- Yes (0%)
- No (86%)
- Not sure (14%)
WHAT ARE YOUR EXPECTATIONS OF A THERAPY FOR PROGRESSIVE MS?

- Recovery: 18%
- Improvement: 18%
- Stable: 44%
- Slowed: 20%
1. Delayed Progression

2. Stabilised Progression

3. Improved Function

4. Recovered Function
MAJOR UNMET NEED
Background to the IPMSC

• Think-tank - Boston December 2010
• Societies convened to explore possibility of an international consortium - July 2011
• Kick off Steering committee - January 2012
• Presentation to MSIF Board - October 2012
• Working group meeting in London
• Followed by Steering committee - November 2012
International Progressive MS Collaborative

Mission

to expedite the development of therapies for effective disease modification and symptom management in progressive MS
What Do We Hope to Achieve?

- To build on existing research investments to create an integrated, multidisciplinary, collaborative research effort.

- To rally the research community and bring additional worldwide resources to propel this effort forward.
Setting a research agenda for progressive multiple sclerosis: The International Collaborative on Progressive MS

Robert J. Fox¹, Alan Thompson², David Baker³, Peer Baneke⁴, Doug Brown⁵, Paul Browne⁶, Dhia Chandraratna⁷, Olga Ciccarelli², Timothy Coetzee⁶, Giancarlo Comi⁷, Anthony Feinstein⁸, Raj Kapoor⁹, Karen Lee¹⁰, Marco Salvetti¹¹, Kersten Sharrock¹², Ahmed Toosy², Paola Zaratin¹³ and Kim Zuidwijk¹⁴
International Progressive MS Collaborative

Initial discussions identified 5 priority areas:

- Experimental Models
- Target pathways and drug repurposing
- Proof of concept trials
- Phase III clinical outcome measures
- Symptom management and rehabilitation
# Previous trials

## Table 2 A: Trials in MS

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Follow Up in Yrs</th>
<th>Entry EDSS</th>
<th>Active Treatment</th>
<th>Primary outcome measure</th>
<th>Primary Result</th>
<th>Comments</th>
<th>Publication Yr &amp; Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine-MSSG</td>
<td>547</td>
<td>1.5</td>
<td>3.0-7.0</td>
<td>Cyclosporine</td>
<td>Time to confirmed EDSS worsening</td>
<td>-ve</td>
<td>Two other co-primary endpoints were also used: time to wheelchair bound (+ve); activities of daily living (-ve)</td>
<td>1990</td>
</tr>
<tr>
<td>CCMSSG</td>
<td>168</td>
<td>2 (mean)</td>
<td>4.0-6.5</td>
<td>Cyclophosphamid or plasma exchange</td>
<td>Comparison of rates of EDSS worsening</td>
<td>-ve</td>
<td>Enrollment allowed if pre-study deterioration due to incomplete relapse recovery (more of RRMS cohort)</td>
<td>1991</td>
</tr>
<tr>
<td>EUSPMS</td>
<td>718</td>
<td>3</td>
<td>3.0-6.5</td>
<td>Betaseron 8MU/alternate days vs placebo</td>
<td>Time to confirmed EDSS worsening</td>
<td>-/+ve</td>
<td></td>
<td>1998</td>
</tr>
<tr>
<td>SPECTRIMS</td>
<td>618</td>
<td>3</td>
<td>3.0-6.5</td>
<td>Rebif (22 or 44mcg 3/week)</td>
<td>Time to confirmed EDSS worsening</td>
<td>-ve</td>
<td></td>
<td>2001</td>
</tr>
<tr>
<td>IMPACT</td>
<td>436</td>
<td>2</td>
<td>3.5-6.5</td>
<td>Avonex (60mcg/week)</td>
<td>MSFC</td>
<td>-/+ve</td>
<td>Positive outcome on MSFC (upper limb but not walking component), but not EDSS</td>
<td>2002</td>
</tr>
<tr>
<td>MIMS</td>
<td>188</td>
<td>2</td>
<td>3.0-6.0</td>
<td>Mitoxantrone 5 or 12 mg/m2 every 3 months</td>
<td>Composite measure (EDSS/ambulation index/relapses)</td>
<td>-/+ve</td>
<td>50% of cohort RRMS; 5 domain outcome measure not validated; cardiotoxicity/leukaemia risk</td>
<td>2002</td>
</tr>
<tr>
<td>NASG</td>
<td>939</td>
<td>3</td>
<td>3.0-6.5</td>
<td>Betasercen 8MU or 5MU/m2 alternate days</td>
<td>Time to confirmed EDSS worsening</td>
<td>-ve</td>
<td></td>
<td>2004</td>
</tr>
<tr>
<td>ESIMS</td>
<td>318</td>
<td>2</td>
<td>3.0-6.5</td>
<td>Immunoglobulin 1g/kg/month (27 months)</td>
<td>Time to confirmed EDSS worsening</td>
<td>-ve</td>
<td></td>
<td>2004</td>
</tr>
<tr>
<td>MAESTRO</td>
<td>612</td>
<td>2</td>
<td>3.0-6.5</td>
<td>MBP8298</td>
<td>Time to confirmed EDSS worsening</td>
<td>-ve</td>
<td></td>
<td>2011</td>
</tr>
</tbody>
</table>

## Table 2 B: Current UK Trials in SPMS

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Follow up Yrs</th>
<th>Entry EDSS</th>
<th>Active Treatment</th>
<th>Primary outcome measure</th>
<th>Reporting Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUPID (Phase III)</td>
<td>493</td>
<td>3</td>
<td>4.0-6.5</td>
<td>Tetra-hydrocannabinol</td>
<td>Time to confirmed EDSS worsening; MSIS29 mean change</td>
<td>2012</td>
</tr>
<tr>
<td>MS-STAT (Phase IIb)</td>
<td>140</td>
<td>2</td>
<td>4.0-6.5</td>
<td>Simvastatin</td>
<td>MRI brain atrophy</td>
<td>2012</td>
</tr>
</tbody>
</table>
Challenges in drug development for progressive MS

Animal Model

Phase I Safety

Phase II Proof of Concept

Phase III Efficacy

Market Approval

Needed:
1. Experimental models
2. Imaging metrics
3. Sensitive clinical metrics
COMMUNITY ENGAGEMENT TO IDENTIFY RESEARCH GAPS TO PROPOSE FUNDING STRATEGIES AND COLLABORATIVE MODELS
Why These Five Priority Areas?

➤ Addresses gaps in understanding about progressive MS

➤ Creates the tools and resources needed to accelerate research

➤ Builds on existing research investments
Adaptive Trial Design

- 4 test treatments and 1 control (placebo)

**Stage 1 cohort**

- **Control**: $n_1$
- **A**: $n_1$
- **B**: $n_1$
- **C**: $n_1$
- **D**: $n_1$

**Stage 2**

- **1** Stage 2 cohort
- **2** 4 Phase 2 Trials
- **3** 2 Phase 3 Trials

**Interim Analysis**

- based on early outcome(s); e.g. MRI and/or disability
- Purpose:
  - treatment selection
  - futility stopping
  - no early stopping for rejection of $H_0$

**Patients to extension study**

- Randomised to treatments A and C

**Final Analysis**

- including data from stages 1 & 2
- disability outcome; e.g. EDSS
MS-STAT trial

High dose oral Simvastatin in Secondary Progressive Multiple Sclerosis
Five working groups develop ideas in each priority area
80+ scientific leaders engaged to develop priorities

Research Strategy paper developed and endorsed by
member societies

- Priority research areas
- Logistics, budget and timeline for first RFAs
- Criteria for funding and management of projects

First Annual IPMSC Meeting – Milan, Feb 2013

- More than 170 MS researchers, clinicians, and PwMS.
- Academics & Industry partners
- Recommendations for each priority area presented by
  working group chairs
Countries represented: Argentina, Austria, Australia, Belgium, Canada, Denmark, Finland, France, Germany, Israel, Italy, Netherlands, Norway, Spain, Switzerland, United Kingdom, United States
First Annual IPMSC Meeting - 2013

• Overall attendees rated the meeting highly

• Reinforced the importance of the initiative

• Attendees initiated collaborations as a result of the meeting (e.g. Fox / Chataway Trials)

• Great momentum, now need to keep it moving

• Need for clear goals/priorities to focus community
Alignment with Other Initiatives

- The Multiple Sclerosis Outcome Assessments Consortium (MSOAC)
- The International Advisory Committee on Clinical Trials in MS Committee (ICTC)
- UK MS Society Clinical Trials network
- SUMMIT Risk Factors for Progression study
- CENTERS (Centro Neurologico Terapie Sperimentali, Rome): repurposing of existing drugs
A New MS Consortium for
A New MS Clinical Outcome Measure

Nicholas G. LaRocca, Ph.D.
Richard Rudick, M.D.
Lynn Hudson, Ph.D.
Co-Directors, MSOAC

U.S. Food and Drug Administration
April 1st, 2013
The Mission of MSOAC

The Multiple Sclerosis Outcome Assessments Consortium (MSOAC), funded by the NMSS, aims to:

Evaluate existing clinical trial data to qualify a new primary clinical outcome measure for disability in MS clinical trials.
MSOAC Members

- **MSOAC Leadership**
  - Lynn Hudson, PhD; Nick LaRocca, PhD; Richard Rudick, MD

- **Academic Investigators**

- **Industry**

- **Patient Advocacy Groups**
  - NMSS, Italian MS Society, MS Society of UK
  - Alberta MS Research Foundation
  - Consortium of MS Centers

- **Regulators and Government Funding Agencies**
  - FDA
  - EMA
  - NINDS
Organizational Activities to support Research Strategy

- Steering committee guides overall scientific activity – staff and volunteers

- NMSS acting as project manager for science - support provided by AISM, MSSC, & MSIF

- Infrastructure available through NMSS for first call for proposals
Next Steps

• Steering Committee meets May 20
  - to decide on priorities
  - issue call for proposals

• Additional scientific community and industry engagement
  - workshops
  - focused initiatives.
Progressive MS

• Greatest challenge for patients and researchers

• Improved understanding which will provide greater potential to identify new targets

• More innovative trial design & encouraging recent data

• Greater international collaboration essential to raise profile and accelerate progress
People with progressive MS still lack effective disease modifying treatments. MS Societies, academia, industry and other stakeholders have to identify a new operative model to collaborate to revitalize innovation and help to introduce disease modifying treatments for progressive MS.
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