Hope in MS
Recovery of Function

John R. Corboy, MD
Professor, University of Colorado School of Medicine
Co-Director, RMMSC at AMC
Director, RMMSC Tissue Bank

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• NIH
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• JDRF
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• Novartis
• Lilly
• Celgene
• Teva
• Multiple Slides courtesy of John Sladek, PhD
Recovery and Repair in MS?

Limitations of Present Therapy

- Only “partial”, i.e., people still have attacks, more scan lesions, and disability progression
- No treatments proven for PPMS, ?SPMS
- Expensive
- Side effects
- Difficult to “see or feel” benefit of therapy, thus adherence is challenging (“shot burnout”)
- All address immunology
  - Minimal effect on reversing disability, recovery of function
  - Persistent symptoms, i.e., incomplete remission
  - Need more clearly “neuroprotective” or “regenerative” approaches
Symptomatic Therapy in MS

- Fatigue
- Spasticity
- Gait Dysfunction, Imbalance and Falls
- Bowel/Bladder/Sexual Dysfunction
- Mood Issues
- Cognitive Issues
- Pain
  - Spasticity
  - Neuralgia

Effects of Exercise in MS

- Exercise studies have demonstrated benefits in
  - Fitness level
  - Quality of life
  - Balance
  - Walking capacity
  - Variable effects on fatigue
- Trouble showing effects on disease progression
  - Studies are small, short, observational (not interventional), uncontrolled, and we need better outcome measures (see Ther Adv Neurol Dis 2012 Mar;5(2):81-95.
- Exercise and disease progression in multiple sclerosis: can exercise slow down the progression of multiple sclerosis? Dalgaard U and Stenager E.)
Fatigue and Gait Immobility

- 50-85% of MS patients have one or both
- Multiple sclerosis–related fatigue is strongly linked to impaired physical activity and quality of life
- Fatigue Treatment in MS
  - Medications – amantadine, modafanil, stimulants
  - Exercise - variable effects on fatigue
  - Energy Conservation Techniques and Equipment
- Role of Postural Control in MS Fatigue?
  - Can Vestibular Rehabilitation Help both Postural Control AND fatigue?

Prospective participant and study participant flow diagram.

Hebert J R et al. PHYS THER 2011;91:1166-1183
Fatigue, Upright Postural Control, Disability Due to Dizziness or Disequilibrium, Walking Capacity, and Depression: Baseline to End of Intervention Phase (10 Weeks).

### Table 2

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Exercised Group (n=127)</th>
<th>Exercising Control Group (n=132)</th>
<th>Multivariate Analysis Compared With Exercise Control Group</th>
<th>Exercised Group Compared With Multivariate Control Group</th>
<th>Exercised Group Compared With Multivariate Control Group</th>
<th>Exercised Control Group Compared With Multivariate Control Group</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>31.0 (4.6)</td>
<td>32.0 (6.0)</td>
<td>33.9 (5.3)</td>
<td>31.6 (4.5)</td>
<td>32.7 (6.0)</td>
<td>34.3 (5.0)</td>
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<td>Fatigue</td>
<td>29.3 (13.5)</td>
<td>32.0 (15.4)</td>
<td>34.2 (17.1)</td>
<td>29.8 (13.6)</td>
<td>31.5 (15.4)</td>
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<td>Change in SRT</td>
<td>-3.7 (5.7)</td>
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<td>-4.4 (6.2)</td>
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<td>-4.0 (6.2)</td>
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<tr>
<td>P (&lt;0.05)</td>
<td>0.002</td>
<td>0.004</td>
<td>0.002</td>
<td>0.004</td>
<td>0.002</td>
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<tr>
<td>Baseline</td>
<td>46.3 (15.6)</td>
<td>49.0 (17.5)</td>
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<tr>
<td>Fatigue</td>
<td>53.1 (14.6)</td>
<td>55.1 (16.5)</td>
<td>58.1 (15.2)</td>
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<td>58.9 (15.8)</td>
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<td>-7.7 (9.8)</td>
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<tr>
<td>P (&lt;0.05)</td>
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<td>0.006</td>
<td>0.009</td>
<td>0.007</td>
<td>0.006</td>
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<td>Baseline</td>
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<td>Fatigue</td>
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<td>46.5 (15.8)</td>
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<td>49.9 (15.4)</td>
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<td>Change in SRT</td>
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<td>-9.7 (9.9)</td>
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<tr>
<td>P (&lt;0.05)</td>
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<td>0.008</td>
<td>0.010</td>
<td>0.007</td>
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</tbody>
</table>

Hebert J R et al. PHYS THER 2011;91:1166-1183

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Conclusions

- Vestibular Rehabilitation is feasible
- Vestibular Rehabilitation has Significant Impact on Fatigue, Upright Postural Control, and Disability
  — And all these Improvements Correlate with One Another
- Effects of this Approach Last at least 4 weeks
- Longer “maintenance” approaches need to be studied
- ? Does this Approach Lead to Enhanced Myelin and Neural Repair?
4-Aminopyridine = Dalfampridine

• Potassium channel blocker
  – Enhances electrical conduction of nerves
• Studies for many years in MS, equivocal outcomes
• Can get via “compounding” pharmacy
• Ampyra-SR® is a long-acting, proprietary form of dalfampridine (Acorda Therapeutics)
  – Completed two Phase III trials looking at gait function
  – Approved by FDA and available since early 2010

Patients were defined as responders or non-responders. A timed walk responder was defined as a patient with a faster walking speed for at least three of the four visits during the double-blind treatment period than the maximum speed for any of the first five off-drug visits (four before double-blind treatment and one at 2 weeks after discontinuation of treatment—ie, screening and visits 0, 1, 2, and 7).
4/16/2012

Figure 3. Percent change in walking speed at each visit after randomisation. The fampridine-treated timed walk responders showed a sustained improvement during the treatment period that was completely reversed at 2-week and 4-week follow-up visits. The fampridine-treated timed walk non-responders showed a significant improvement compared with the placebo group only for visit 3 (2 weeks after randomisation). TW=timed walk. *Means fampridine TW responders are greater than placebo and fampridine TW non-responders (p<0·001). †Means fampridine TW non-responders are greater than placebo only (p<0·001).

Dalfampridine Side Effects

- Headache
- Nausea
- Insomnia
- “Jitteriness”
- Urinary tract infections
  - Check urinalysis at baseline
- Seizures rarely
  - Need to check kidney function (drug is cleared by kidney)
- Insurance issues

35% of treated group defined as responders
Long Term Dalfampridine Use

• As of 12/31/11
  – 59,000 prescriptions written, by 8600 practitioners
  – 70% refill at one month, 40% at 6 months
  – 90% compliance rates, average of 1.8 pills per day
  – No new safety concerns
  – Patients continue to progress with MS

Suggestions for Patients

• Everyone with MS should
  – NOT Smoke Cigarettes
  – Take Vitamin D
  – Participate in Some Form of Exercise on a Regular Basis
    • Consider Vestibular Rehabilitation for Fatigue and Balance
• Aggressively Treat Spasticity and Related Symptoms
• Consider Use of Ampyra if Gait-Impaired
• Treat Other Symptoms Aggressively as Well
  – Avoid “Overtreatment”, and Drug Side Effects or Drug Interactions
Neural Protection and Repair/Replacement

To Protect, Repair, or Replace?

- Neuroprotection
- Enhanced Myelin Repair
- Enhanced Neural Repair
- Neural Replacement

- Some approaches may utilize multiple processes, including immunoregulation
Neuroprotection

• Avoid initial insult +/or prevent consequences of processes damaging axons, neurons, synapses and dendrites
• Interferons sustain neuronal cell growth in vitro, stimulate NGF by astrocytes in vitro and vivo, and decrease progression of brain atrophy
• Interferons and GA reduce T1 hole production

Neuroprotective Strategies

• Anti-excitotoxics, eg, glutamate receptor
• NO and iNOS inhibitors, ? Statins – recent study neg
• Calpain inhibitors
• Anti-oxidants and free radical scavengers
• COX-2 inhibitors
• Anti-apoptotic therapies, eg caspase inhibitors
• Na+ channel, Na+/Ca++ exchange inhibitors, eg diphenylhydantoin
• Ca++ channel blockers
• Neurotrophic factors, eg CNTF
• ?Laquinimod – small effect on relapse rate, but larger effect on progression of disability
Stem Cells

Enhance Repair, Replace damaged Cells?

Neural Cells - Old Notions

- Neurons/other cells in adult brain do not regenerate
- Maximum number available at birth
- Cells committed to a certain phenotype by virtue of residence in a mature organ cannot change destiny, cannot be re-programmed
- These are FALSE
  - Progenitor cells required to regenerate neural cells are present in CNS, but are inhibited, eg Oligodendrocyte Precursor Cells (OPCs)
  - Oligodendrocytes make Myelin
- Cells from other lineages can be re-programmed
Main Entry: stem cells

Part of Speech: noun

Definition: all-embracing, universal diversified, multiform.

Stem Cells

- Defined by functional capacity to:
  - Self-renew
  - Generate large numbers of differentiated progeny
  - Totipotent = can generate ALL cells → Complete organism, eg, a fertilized egg
  - Pluripotent = can generate many cells, eg placental
  - Multipotent = are committed to one type, eg nervous system
  - Throughout development, there are residual, quiescent, uncommitted cells ensuring self-renewal of stem cell population
Stem Cells

Precursor Cells

Fully Differentiated Cells
>>> Become Specific Organs, eg skin, liver, blood, nervous system

Some definitions:

Totipotent: A fertilized egg is considered totipotent, meaning that its potential is total; it gives rise to all the different types of cells in the body. "master cells"

Pluripotent: Stem cells can give rise to any type of cell in the body except those needed to develop a fetus; those of the placenta

Multipotent: Stem cells that can give rise to a small number of different cell types are generally called multipotent, but cannot switch and are committed to one type
Sources of Stem/Precursor Cells

- Embryonic – best source, most ethically challenging and least available
- Placental – easily available, no ethical issues, are inducible
- Adult – Already present in the body
  - Bone Marrow - easily available, no ethical issues, are inducible >> other cell types
  - May also be able to induce already differentiated cells to “go backwards” and become stem cells of a different lineage

Bone Marrow Stromal Cells

- Hematopoietic Stem Cells (HSC)
- Non-HSC Precursors = Mesenchymal Stem Cells
- Bone
- Cartilage
- Tendon
- Muscle
- Liver
- Fat

Neurons/Glia under conditions that cAMP or Noggin
Inducible Pluripotent Stem Cells - IPCs

Repair – Does it occur in MS?

• YES!
  – 40% of lesions show evidence of remyelination
• Can see in MS brains and EAE
• Remyelination likely due to oligodendrocyte precursor cells (OPCs) as well as Neural Precursor Cells (NPCs)
Neural Repair

- **Inflammation** – Some inflammation is GOOD
- **Brain plasticity** – the recruitment of alternative “non-damaged” functioning neuronal pathways (cortical maps) mainly via axonal branching and synaptogenesis, occurs as a consequence of brain damage.
- **Endogenous adult neural stem/precursor cells** – if these cells survive the inflammatory and/or degenerative insult, they may be capable of migrating within damaged areas and promoting repair via several mechanisms of action, such as cell replacement, remyelination, and/or neuroprotection.


Good Inflammation

  - Lysolecithin model of demyelination
  - Remyelination is enhanced in “old” mice exposed to a youthful systemic milieu through heterochronic parabiosis, i.e. circulatory system of two mice are joined
  - Macrophages from “young” mice help stimulate increased numbers of resident OPCs in demyelinated, “old” mice
The future of brain repair: methods of delivery

- **Intracerebral injections** of stem/progenitor cells, growth factors, regeneration-support factors
- “Neuropoietins”
- **Systemic injections** “homing”

STIMULATING NEURAL REPAIR
Hormonal Effects on Remyelination

- Third trimester pregnancy protective in MS
- Exclusive breastfeeding appears to be more protective in MS than partial breastfeeding

Effect of pregnancy (C) or prolactin (D) on remyelination in lysolecithin model

Pregnancy (C) and Prolactin (D) Reduce area of demyelination

Pregnancy (C) and Prolactin (D) Increase # of new oligodendrocytes

Copaxone + Estriol trial now open at RRMSC at AMC
Estriol in MS Study Continues Recruitment Completed

Potential Inhibitors of OPC Differentiation

• Notch-Jagged
• PSA-NCAM
• Hyaluronan
• Myelin Debris
• LINGO-1
LINIGO-1
Leucine rich repeat and Ig domain containing NOGO receptor interacting protein 1

- LINGO-1 enhances OPC differentiation and myelination *in vitro*
- LINGO-1 knockout mice show early myelination *in vivo*
- LINGO-1 Mab 1A7 enhances functional recovery in MOG-induced EAE
Treatment with an antibody antagonist to LINGO-1 function leads to functional recovery and increased integrity of axons in MOG-induced EAE rats.

Mi et al., 2007
MOG Rat Model of EAE, Treated with anti-LINGO 1A7

Figure 1. 1A7 enhanced optic nerve remyelination in the experimental autoimmune encephalomyelitis (EAE) optical neuritis demyelination model. (A) Direct visualization of the rat optic nerve. (B) Electron microscopic visualization of myelinated axon fibers. Scale bar = 5 μm. (C) Quantification of myelination in normal, control, and 1A7-treated optic nerve after toluidine blue staining of 1 μm sections. p values were determined using one-way analysis of variance analysis.


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Anti-LINGO Antibody

Phase I study about to end
Small number of sites
A Biogen product
Neural Replacement

Adult Neural Stem Cells in EAE

  - MOG model of chronic EAE in mice, iv or ic
  - Neurospheres derived from syngeneic mice brains
    - Capacity to develop into neurons, astroglia, oligodendroglia
  - Pretreat with LPS, or TNF-α and IL-1β (open BBB)
  - Inject
    - Cells enter CNS, home to damaged areas, differentiate
    - OPCs increased, demyelination/astrogliosis decreased, remyelination increased, EAE scores markedly improved

a-c Less gliosis (brown) and more intact myelin (blue) in ic(a) or iv(b) injection v control(c); spinal cords

d-f Significant reduction in FGF-II mRNA v controls

e-g Increase in PDGFα receptor expressing OPCs in ic(e) and iv(f) treated mice v controls(g)

EAE scores
a ic v controls
b iv v controls
c whole BM cells v controls
d fibroblasts v controls
e dead neural cells v controls
f improved conduction velocity
Subsequent Animal Studies

- NPCs
- NPCs stimulated to become oligodendrocytes
- Astrocytes
- Mesenchymal Stem Cells

Mesenchymal Stem Cells

Neuroprotective +/- Repair +/- Replacement?
Bone Marrow Stromal Cells

Hematopoietic Stem Cells (HSC) → RBC, WBC, Platelet

Non-HSC Precursors → Mesenchymal Stem Cells → Bone, Cartilage, Tendon, Muscle, Liver

Neurons/Glia → under conditions that cAMP or Noggin

Mesenchymal Stem Cells

• Potent immunomodulatory effects
  – Prolong skin allograft in baboons
  – Prevent rejection of allogeneic tumor in mice
  – Alleviate steroid-resistant GVH in human
  – Alleviate EAE
Fig. 1. The neurological response of EAE mice treated with BMSCs or PBS. Results show that the average clinical scores in the BMSC treatment group were significantly or marginally decreased over a total duration of 49 days out of the total 90 day disease course.

Bone marrow stromal cell therapy reduces proNGF and p75 expression in mice with experimental autoimmune encephalomyelitis. Zhang et al. *J Neurol Sci* 279; 15 April 2009, Pages 30-38

**Figure 2.** Staining by Luxol fast blue and Bielschowsky silver (LFB + B) showed the myelin (yellow, arrowheads) and axons (red, arrows) in the striatum (A) and the corpus callosum (B) of EAE mice treated with PBS and hBMSCs. Quantitative data (C) showed that the axonal density was significantly increased in the white matter of the brain of the hBMSC treatment group compared with that of the PBS treatment group at 1, 10, 34, and 45 weeks after clinical onset. Scale bars = 50 m.

STEM CELLS IN MS

Mesenchymal Stem Cells
Human Studies Soon? NOW

• McGill
• Hadassah – early data starting to come out
• Cleveland Clinic
Other Stem Cell Studies

- Whole Bone Marrow Stem Cells – English Study
  - Six MS patients reported
  - Safe over one year, too early for effectiveness data
- Placental/Cord Stem Cells – Celgene
  - Started in small number of sites with MS patients, including U of Colorado/RMMSC
  - Cultured placental cell lines, act very similarly to mesenchymal stem cells
  - Phase I Completed – some infusion reactions
  - Phase II trials planned
- ESCs in ALS, Parkinson’s, not in MS (as yet)