"I can walk down the hall just fine, but I'd trade that for a wheelchair if I could have my mind back"
Treating cognitive impairment in MS:
from clinical problem to research question to treatment

- Pathophysiology
- Disease models
- Identifying therapeutic targets
- Screening candidate treatments
- Preclinical testing
  - Safety, efficacy
- Investigational New Drug application
- Clinical trials
  - Early phase, late phase
- Clinical practice

Phase 1: safety, dosing
Phase 2: efficacy
Phase 3: effectiveness
Phase 4: post-marketing
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Pathological basis for cognitive impairment in MS?

Lesion effect - amnesia in a patient with hippocampal demyelination

Cognitive impairment in a patient with minimal lesion burden
Cognitive impairment in MS correlates with gray matter injury


MS gray matter pathology - hippocampus

Neuronal injury associated with activated microglia in MS cortex


Do activated microglia trigger neuronal injury in MS gray matter?
EAE hippocampus: a mouse model of MS gray matter degeneration

Control

25 day

EAE

55 day

Synapses (PSD95)

10 µm

Sham EAE

25 d

1.0

0.72

Sham EAE

55 d

1.0

0.68

* *

EAE hippocampus: a mouse model of MS gray matter degeneration

Control

EAE

Microglia / Synapses

(lba1) (PSD95)

5 µm
Attenuation of microglial activation protects against hippocampal synapse loss in EAE mice

Identifying targets for neuroprotection: an *in vitro* model of microglial activation and neuronal injury
Synaptic injury in neuron-microglia co-cultures

Activated microglia promote excitotoxic injury
Activated microglia promote excitotoxic injury

Excitatory activity
Activated microglia promote excitotoxic injury
Activated microglia promote excitotoxic injury
Activated microglia promote excitotoxic injury

[Image of neuron-like structures and bar graph showing % neurons beaded]
Blocking platelet-activating factor (PAF) receptor prevents activity-dependent injury

Excess PAF disrupts hippocampal synaptic plasticity
Excess PAF disrupts hippocampal synaptic plasticity

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UNIVERSITY of ROCHESTER MEDICAL CENTER

MEDICINE of the HIGHEST ORDER