Capitalizing on the Molecular Revolution:

Progress toward Neuroprotection and More Effective Treatments for Neuropathic Pain

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Harnessing the molecular revolution to preserve and restore function after injury to the brain and spinal cord
M.C. Previously healthy female accountant

22 y.o.: Optic neuritis. VA 20/20 → 20/200
Remission p 4 wks. VA → 20/20

24 y.o.: Diplopia, slurred speech, facial numbness
Remission: nearly full recovery p 5 wks

25 y.o.: Numbness, weakness of legs
Numbness resolves. Weakness persists

26 y.o.: Persistent, unpleasant paraesthesia in legs

29 y.o.: Trigeminal neuralgia. Rx: Carbamazepine

31 y.o.: Intention tremor, cerebellar ataxia
Multiple Sclerosis

i) Demyelination w/o remyelination >> Remitting Deficits
   ii) Axonal degeneration >> Permanent Deficits

- Can we induce remissions in MS and SCI?
- Can we prevent axonal degeneration?
- Can we develop better treatments for pain and spasticity, etc?
T.B. 18 y.o. college freshman. Motor vehicle accident.

C5 - C6 fracture - dislocation.
SCI: C6, clinically complete.
Spastic quadriplegia.
Sensory loss below C6.
Intermittent severe pain.
No recovery.
Demyelinated axons can insert new sodium channels in their membrane, and this can restore impulse conduction.
We are unraveling the genetic code and understanding molecules that are key players in SCI, MS, and Neuropathic Pain.
Inducing Remissions:
We will harness the genes involved in remissions, to restore impulse conduction in demyelinated brain and spinal cord axons in MS and SCI
Targeting Sodium Channels for Neuroprotection and as Therapeutic Targets for Neuropathic Pain.

Diagram showing sodium channel properties and effects of depolarization (Depol).
There are 9 different subtypes of sodium channels (Nav1.1 – Nav1.9).

They share a common overall architecture, each consisting of ~1800 amino acids, like beads on a necklace.

The 9 different sodium channel subtypes have different amino acid sequences.

They can be targeted in a specific manner.
Different Na channel isoforms: Different functional properties

**Current-voltage relationship**

- Fast TTX-S
- Slow TTX-R
- Persistent TTX-R

**Steady-state inactivation**

- Fast TTX-S
- Slow TTX-R
- Persistent TTX-R
Predominant Na channel in spinal cord axons: $\text{Na}_V1.6$
Neuroprotection: Can we prevent the degeneration of At-Risk axons in MS and SCI?