Transverse Myelitis Update at the Walton Centre FT

Anu Jacob

The Walton Centre, Liverpool,

United Kingdom NMO Service

Plan of talk

1. About the Walton Centre
2. Research at the Walton
   - Published
   - Ongoing
3. Bit of immunology
4. TM research
5. Stem cells
6.. Trials what you need to know, before you believe

The Walton Centre FT

- The UK's only stand-alone Neurosciences Centre
- 30 neurologists
- Neurosurgeons, Neuroradiologists , Neuroanaesthesia, Pain , Neurorehabilitation
- Channel 5 series

Neurology

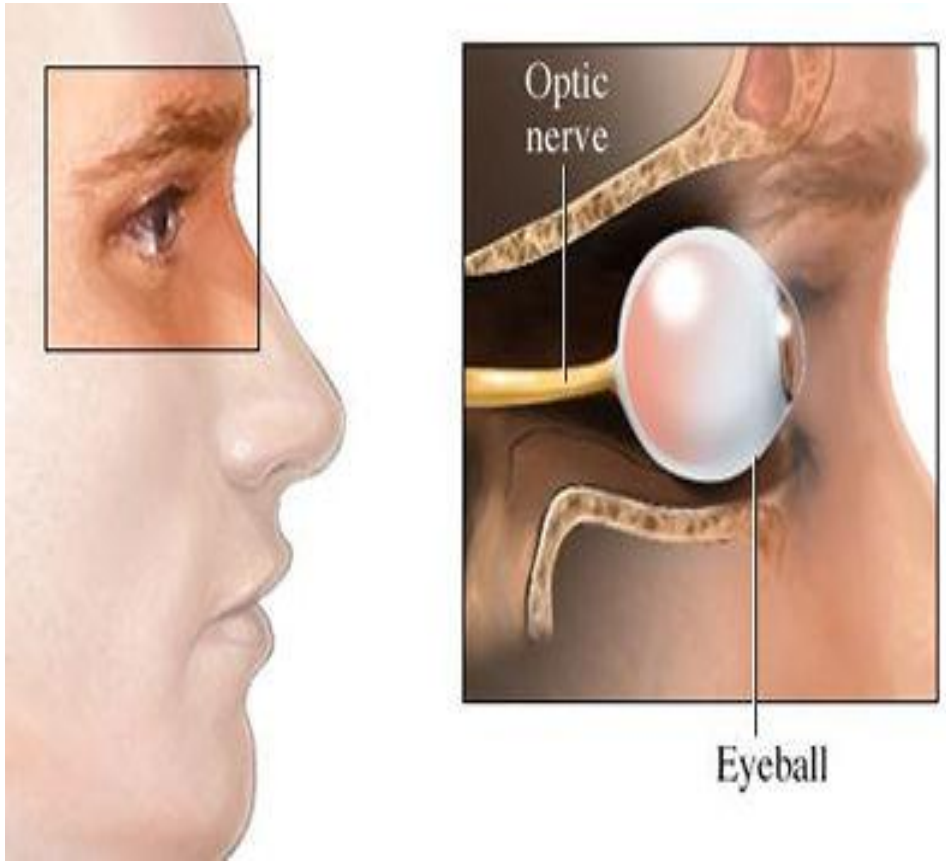
- All specialties
- Multiple Sclerosis -5 Consultants

- Neuromyelitis optica Service :
  - NMO
  - Transverse Myelitis
  - ADEM

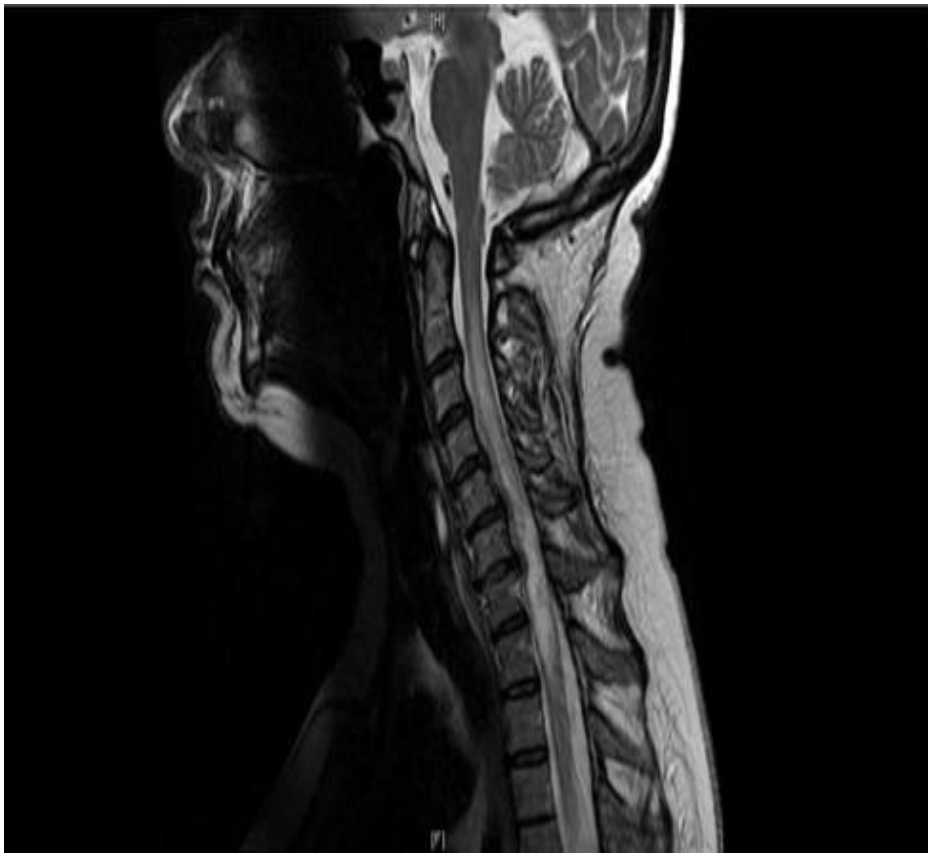
Research in WCFT

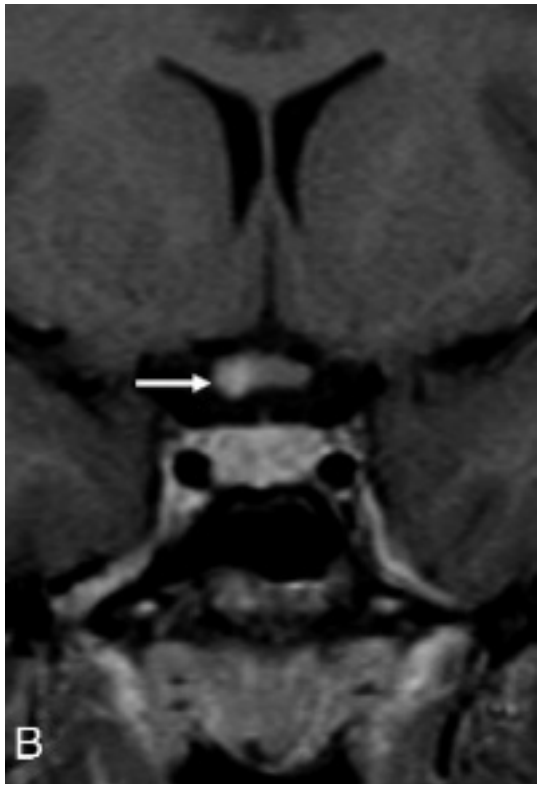
- 20 Publications 2012- 2014
- 15 research projects
- Association of British Neurologist Meeting
  Next week – 6 abstracts

Optic Nerve



Radiology

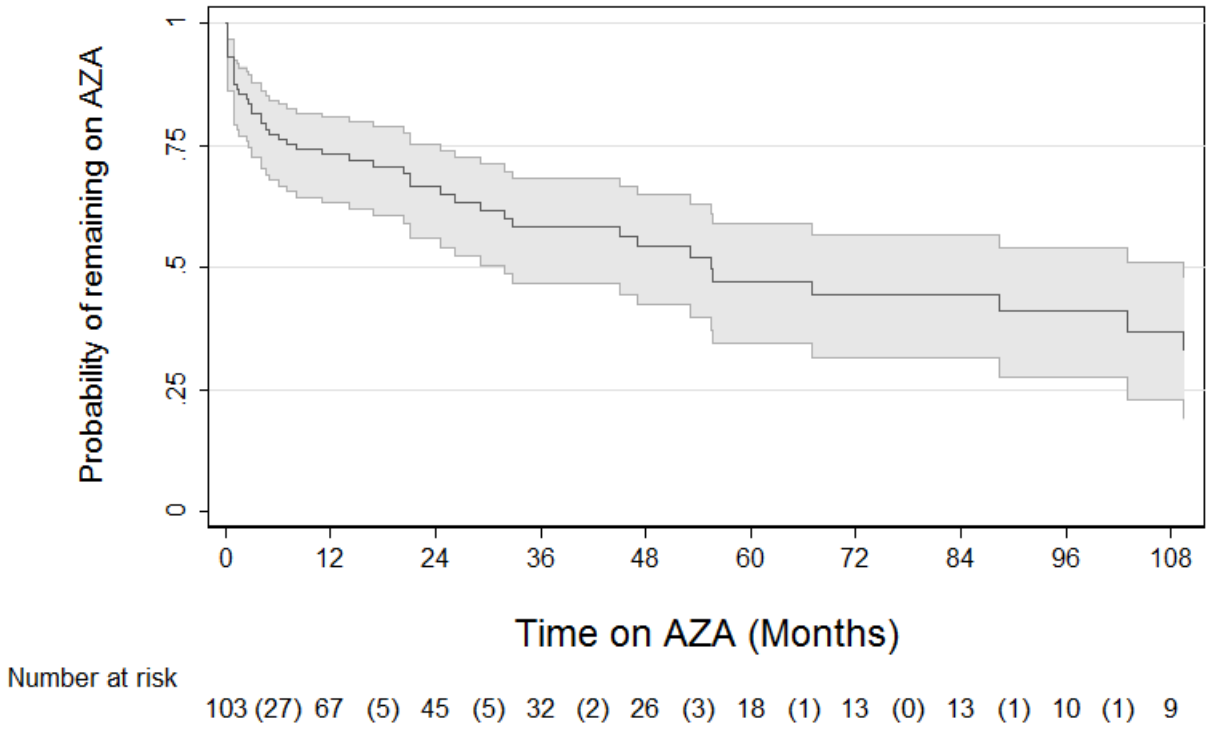




AQP4 density highest in Optic Nerve and Spinal cord Matiello etal JAMA 2013

Azathioprine in NMO

Probability of remaining on AZA over time



Probability of remaining on AZA at:
1 year was 73% (95% CI: 63, 81),
3 years was 58% (95% CI: 47, 68),
5 years was 47% (95%CI: 34, 59)
10 years was 33 % (95% CI: 19, 48).

If 100 patients went on AZA ,
-89 will have a reduction of relapses
-61 will achieve remission

Elsone, Jacob Multiple Sclerosis, 2014

IVIG in acute attacks of NMO?

Short Report

MULTIPLE SCLEROSIS JOURNAL | MSJ

Multiple Sclerosis Journal
0(0) 1–4

DOI: 10.1177/1352458513495938
msj.sagepub.com
SAGE

Role of intravenous immunoglobulin in the treatment of acute relapses of neuromyelitis optica: experience in 10 patients

Liene Elsone[1], Jay Panicker[1], Kerry Mutch[1], Mike Boggild[2], Richard Appleton[3] and Anu Jacob[1]

- 5/11 (45% of attacks) had a modest beneficial effect

Pain in NMO

Short Report

MULTIPLE SCLEROSIS JOURNAL | MSJ

Neuropathic pain in neuromyelitis optica affects activities of daily living and quality of life

Multiple Sclerosis Journal
1–4

DOI: 10.1177/1352458514522103
msj.sagepub.com
SAGE

Sizheng Zhao, Kerry Mutch, Liene Elsone, Turo Nurmikko, and Anu Jacob

- 50 patients of NMO with myelitis (39F, 11 male)
- 82% +ve for Aqp4-IgG
- Douleur neuropathique(DN4) questionnaire, >4/10)
- Brief Pain Inventory
- Structured interview
- QOL: SF36

Results

- DN: 31/50 (62%) had neuropathic pain*
- BPI : 28 completed
  - (3 had no pain in last 24 hours, on analgesics)
- 30 were on analgesics (24/30 were on neuropathic pain drugs)
  - Amitryptiline(6) Gabapentin/Pregabalin(19)
  - Duloxetine(1) LTG (1), CBZ(1) baclofen (1) Sativex (1) opiates (6)
  - 7 took no analgesics because of side effects / lack of effect
- Constant pain (68%), intermittent (25%), constant with exacerbations (7%)

*Prevalence of pain in advanced metastatic cancer is 65% Annals of Oncology 2007

- Pain intensity was more in females (72% vs 27%)
- No effect of age, antibody status
- Pain as first sign of relapse- 57%
- 25% reported pain as their worst symptom
  - Despite needing one cane to walk/bladder bowel symptoms
  - resting /sleep improved pain

Pain : NMO Versus MS

	MS (n=66)	NMO (n=29)
Frequency	41%	86%
Severity on 10 point scale	1.85	5.38
% free of pain	48	0
% on medications	38	76
>1 medication	15	66

Qian Archives of neurology 2012

Tonic spasm associated pain

- Paroxysmal
- Brief <1 minute
- Associated with muscle spasm
- 10/10 severity
- Usually in recovery phase from myelitis

“Itch” as a neurologic symptom in spinal cord inflammation

Itch (pruritus) is a new symptom

Research Paper

MULTIPLE SCLEROSIS JOURNAL | MSJ

Multiple Sclerosis Journal
0(0) 1–5

DOI: 10.1177/1352458512457720
msj.sagepub.com
SAGE

Neuropathic pruritus (itch) in neuromyelitis optica

Liene Elsone[1], Tristan Townsend[1], Kerry Mutch[1], Kumar Das[1], Mike Boggild[1], Turo Nurmikko[1,2] and Anu Jacob[1]

25% patients mention itch as a prominent symptom

Often heralds relapse

What is in the pipeline?

Clinical Trials

IVIG as acute treatment in TM

Is there a role for IVIG in acute Rx of relapses?

- PLEX considered only in week 2/3 only if recovery/scope of recovery is poor
- Difficult to organise , particularly in smaller hospitals
- IVIG works in other antibody mediated illnesses
- Anecdotal data in relapse prevention in NMO

Trial approved

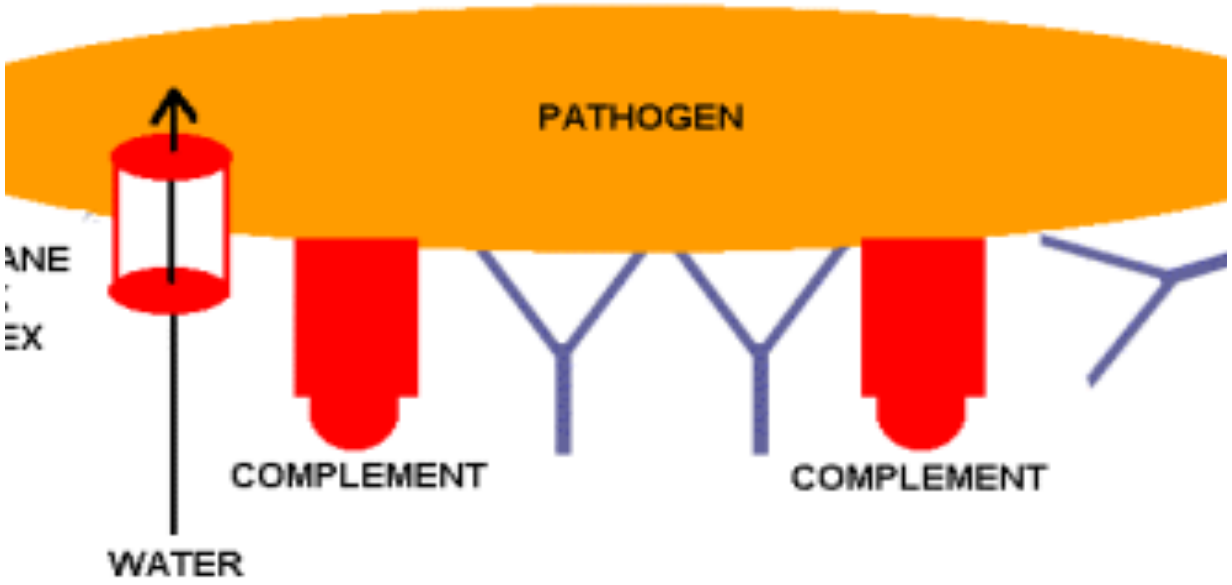
- NIHR approved £1.5 million
- Compare IVIG + steroids Vs Steroids alone
- If beneficial compare PLEX with IVIG

Trials in NMO

Preventing relapses in NMO

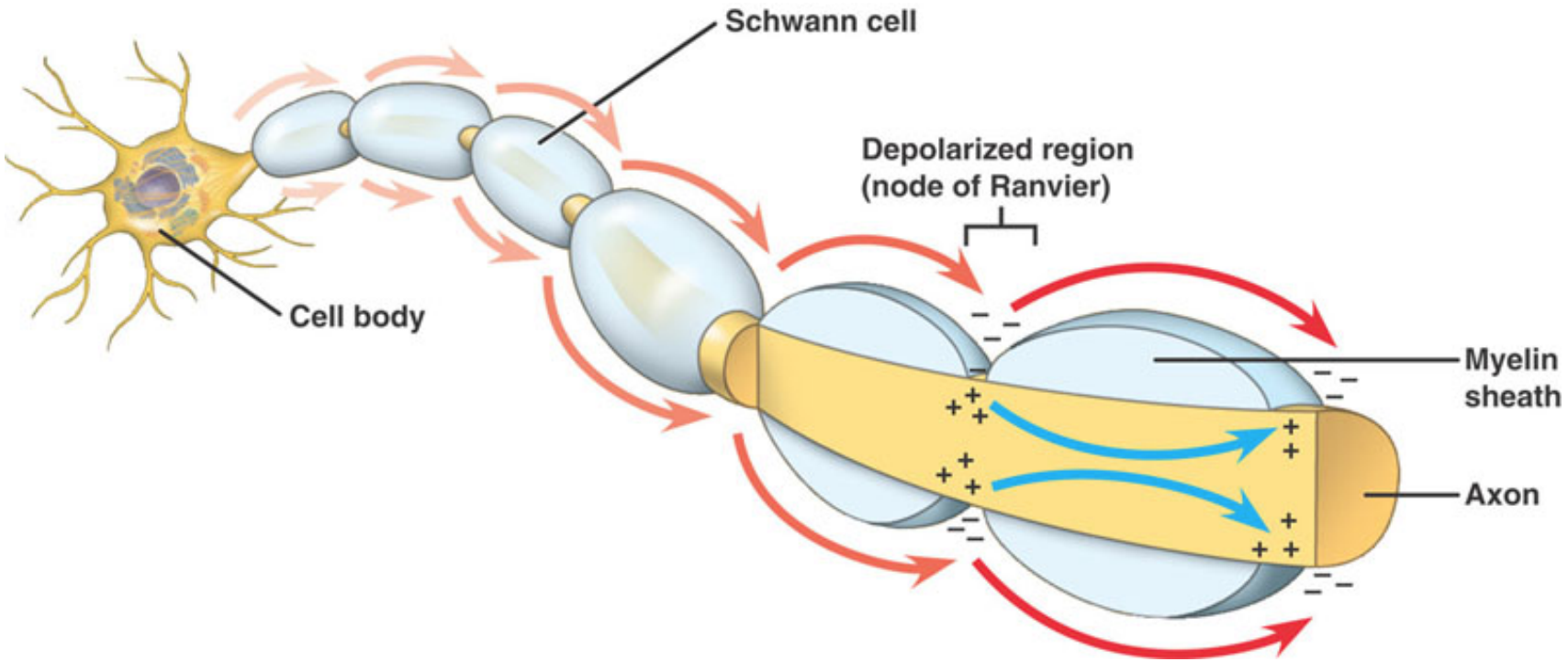
- SA 237 (anti IL-6) trial

Eculizumab – a Complement inhibitor



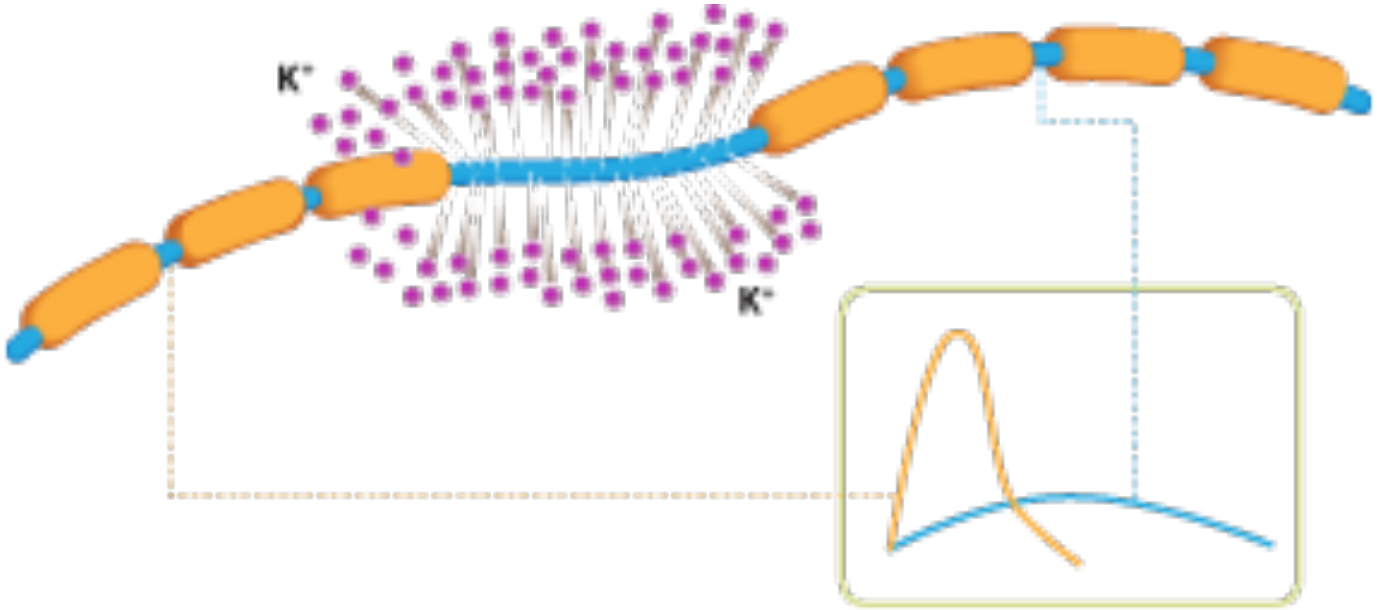
Fampridine in TM associated NMO

Electrical conduction in nerves



Slide courtesy of Michael Levy Johns Hopkins

Electrical conduction in nerves



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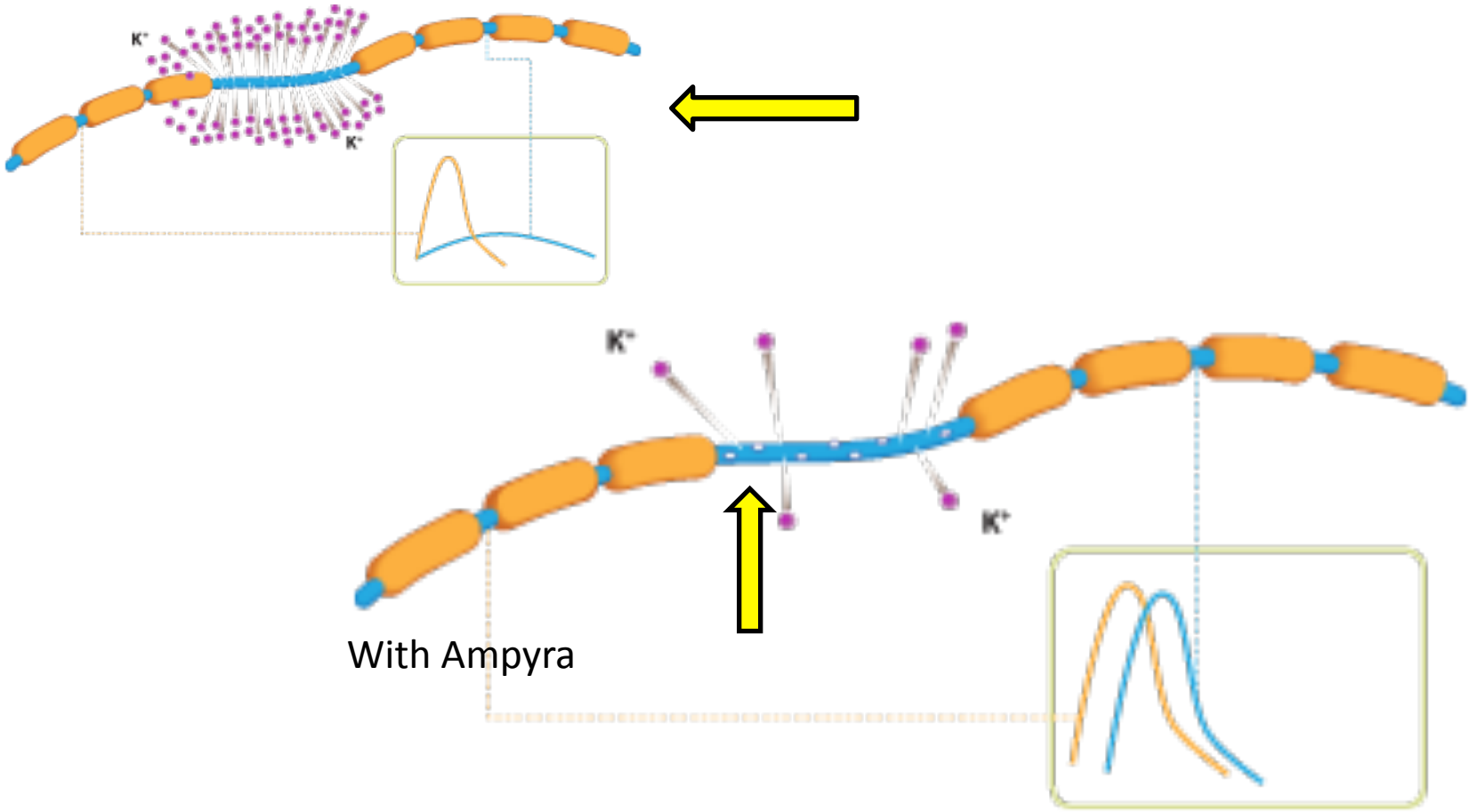
Electrical conduction in nerves



Slide courtesy of Michael Levy Johns Hopkins

Multiple Sclerosis Trials

Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial

Andrew D Goodman, Theodore R Brown, Lauren B Krupp, Randall T Schapiro, Steven R Schwid, Ron Cohen, Lawrence N Marinucci, Andrew R Blight, on behalf of the Fampridine MS-F203 Investigators†*

Lancet 2009; 373: 732–38

A Phase 3 Trial of Extended Release Oral Dalfampridine in Multiple Sclerosis

Andrew D. Goodman, MD,[1] Theodore R. Brown, MD, MPH,[2] Keith R. Edwards, MD,[3] Lauren B. Krupp, MD,[4] Randall T Schapiro, MD,[5] Ron Cohen, MD,[6] Lawrence N. Marinucci, MS,[6] and Andrew R. Blight, PhD[6] on behalf of the MSF204 Investigators

ANN NEUROL 2010;68:494–502

Just one lesion

TM patients have only
1 lesion to overcome

Slide courtesy of Michael Levy Johns Hopkins

- What is Fampridine ?

- Fampridine increases walking speed in MS
- JH study on Fampridine
- Can Fampridine improve Walking speed in NMO myelitis ?
- 20 patient study starting in May

Stem cells

Why don’t humans regrow ?

What parts of humans regrow ?

Does spinal cord regrow ?

How to repair ?

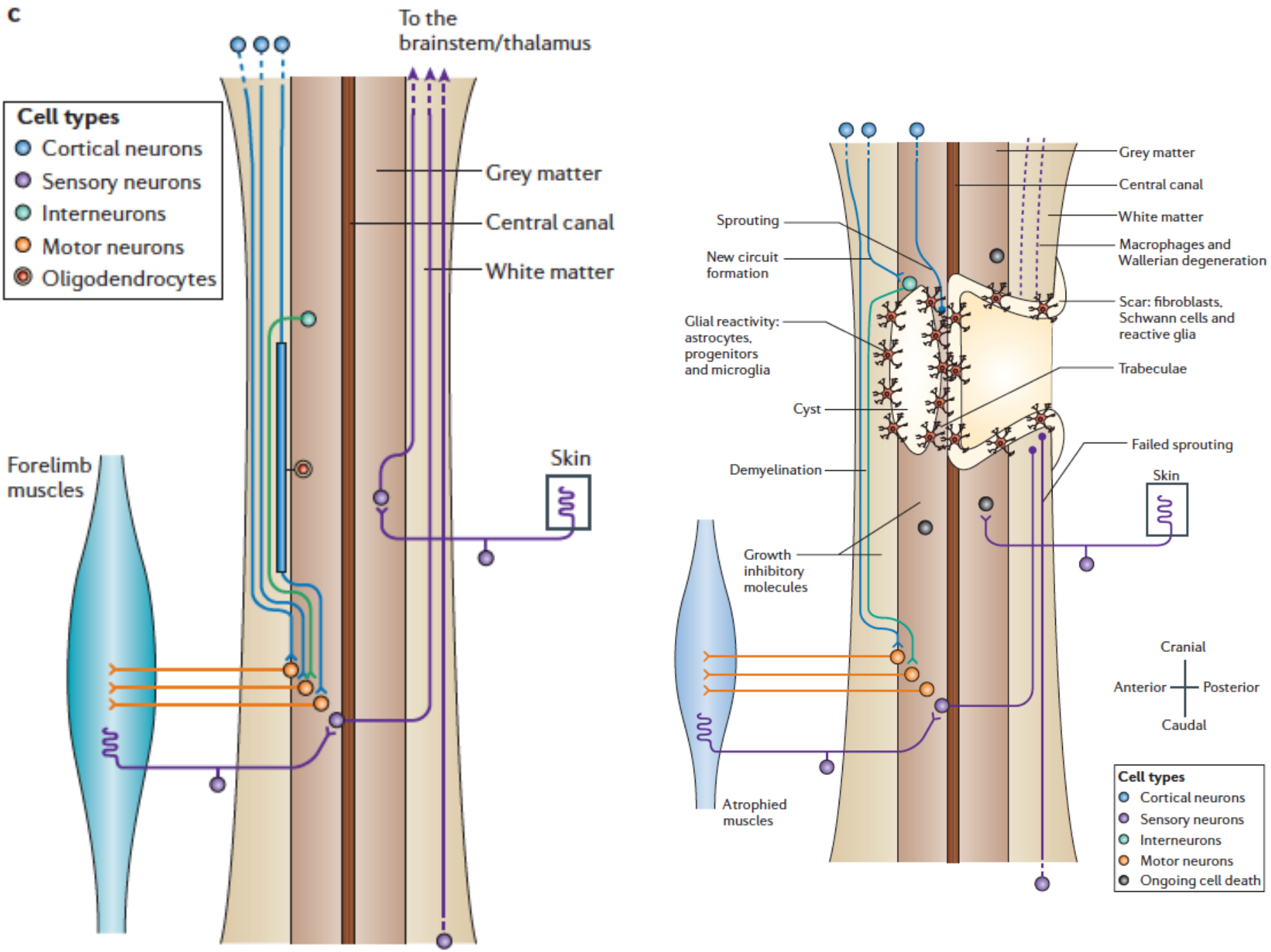


Figure 1 | **Intact spinal cord. a** | Schematic showing a

QJM

Central nervous system regeneration—where are we?

A. WILLIAMS

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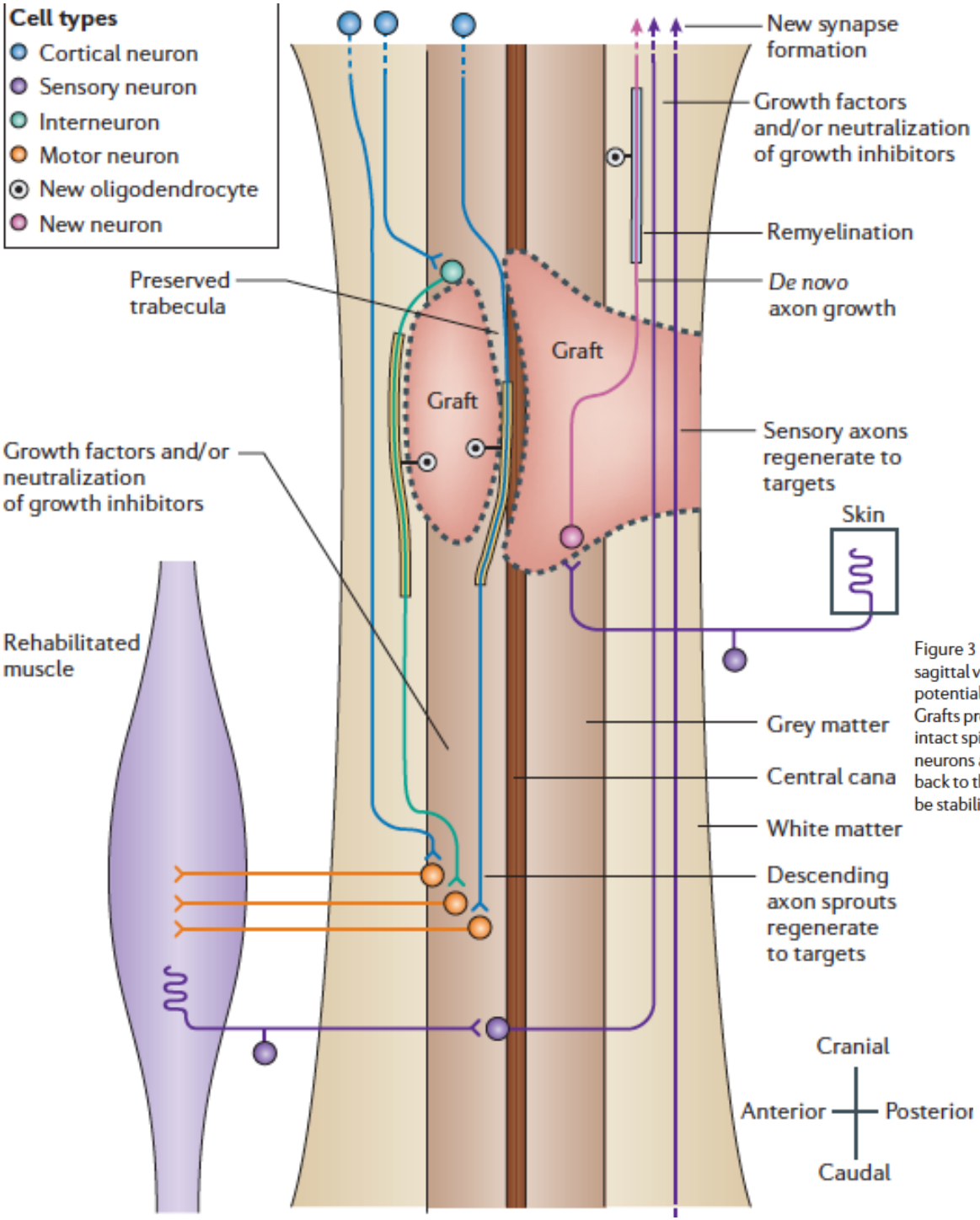


Figure 3 | **Injured spinal cord after combination treatments.** Schematic showing a sagittal view through injured cervical spinal cord after a hypothetical combination of potential therapies. Cysts are filled by vascularized grafts and trabeculae are spared. Grafts provide remyelinating cells, and inhibitory molecules in the scar regions and in intact spinal cord are neutralized using antibodies, peptides or enzymes. Grafted neurons allow the formation of new relay circuits or the regeneration of injured axons back to their original targets. Furthermore, rehabilitation may allow correct synapses to be stabilized and reverses muscle atrophy.

- Put in cells – stem cells
- Support growth
- Suppress inhibitory factors

- What cells ?
- Own nerves and nerve cells
- Other Regenerating cells
- Embryonic cells
- Adult stem cells

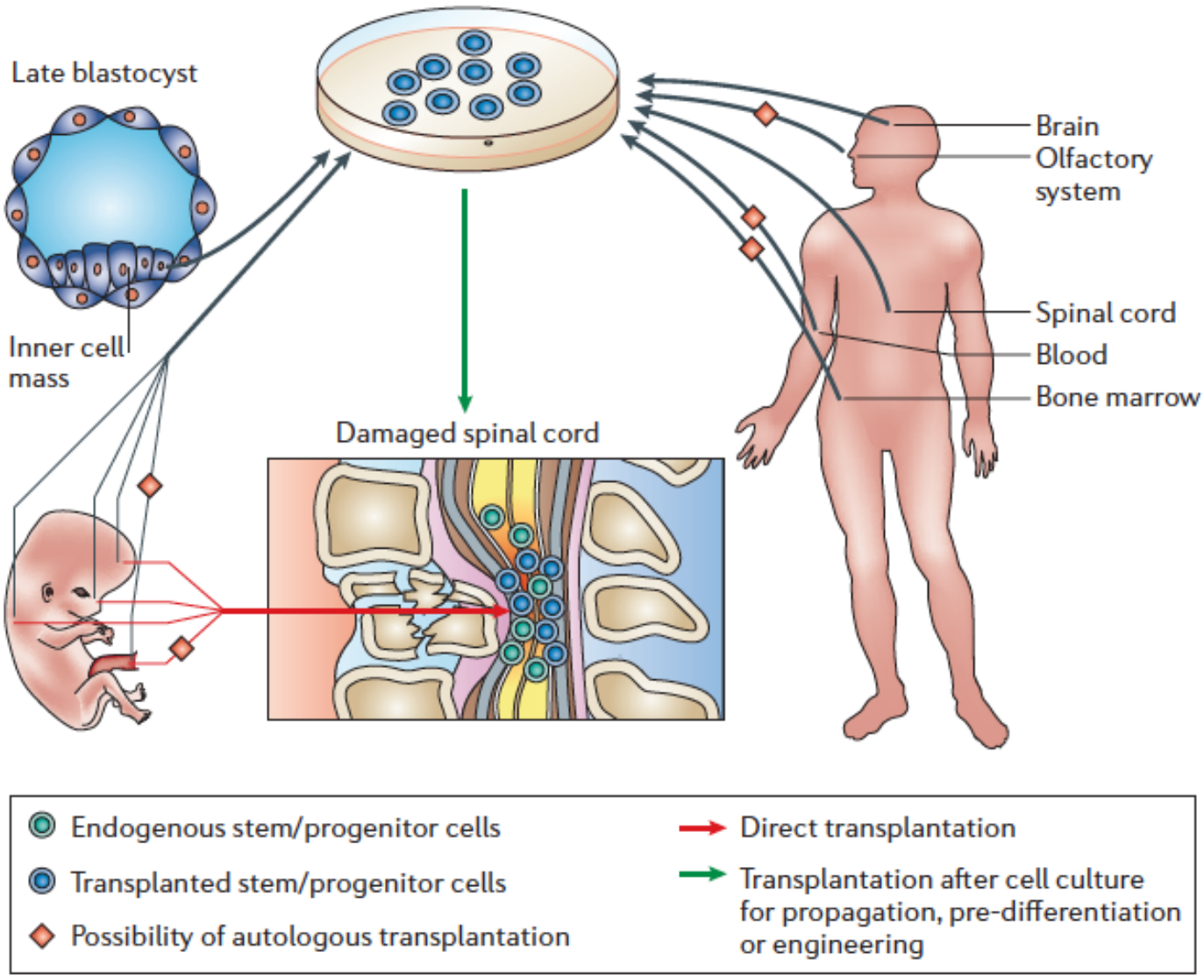


Figure 5 | **Potential sources of stem/progenitor cells for transplantation into the injured spinal cord.** Stem/progenitor cells can be collected at three different stages of development: from the inner cell mass layer of the mature blastocyst; from the brain

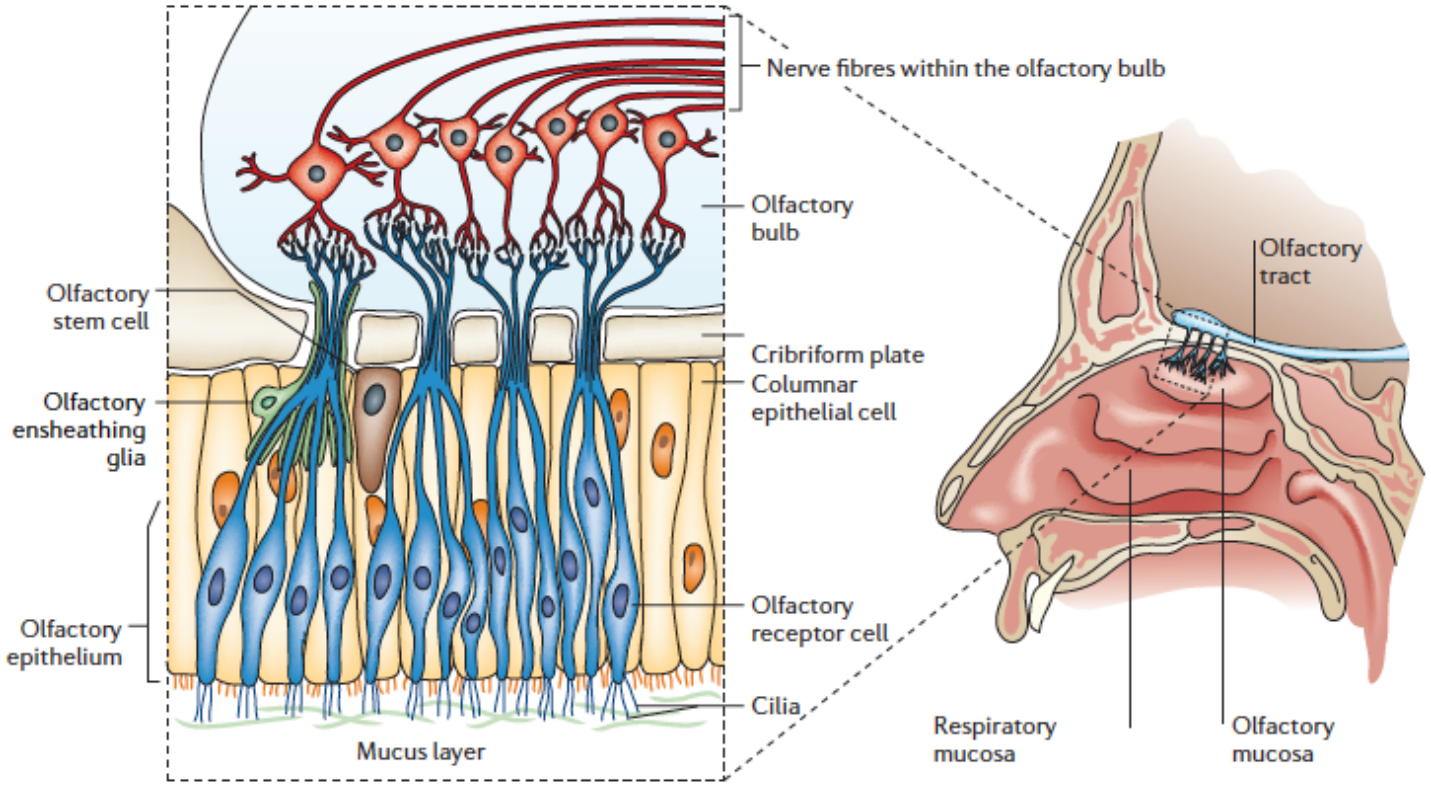


Figure 4 | **The olfactory nervous system.** Schematic of a sagittal section through the human head, showing the olfactory nervous system (right), with a section of the olfactory nervous system depicted in greater detail (inset). Stem cells at the base of the olfactory epithelium generate new olfactory receptor neurons throughout life, which extend axons

Human induced pluripotent stem cells

- Takahashi and Yamanaka 2006
- Adult mouse fibroblasts could be sent back in time to an embryonic-like state
- By adding pluripotency transcription factors.

Remyelination

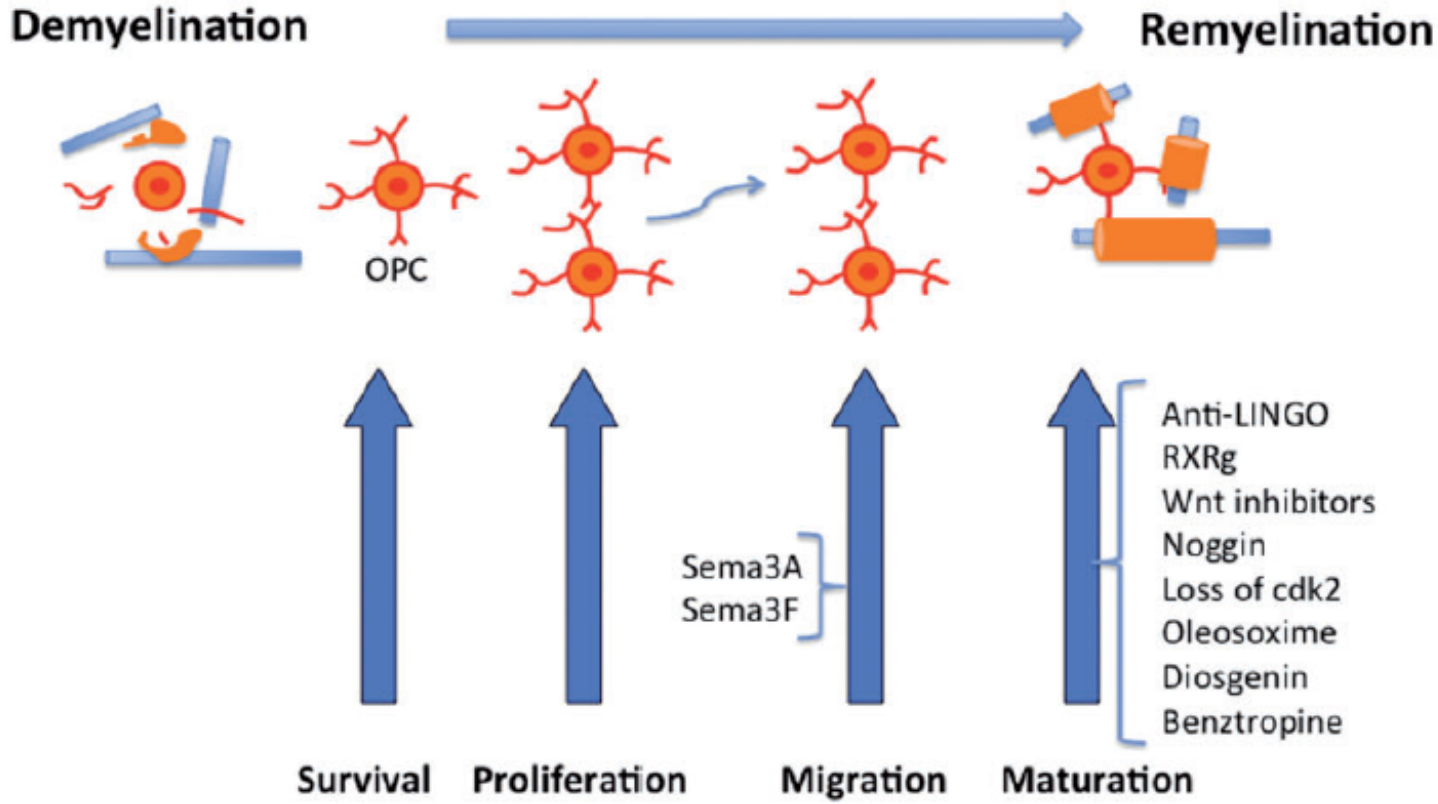


Figure 2. For remyelination to succeed, OPCs must survive the demyelinating attack, proliferate, migrate to the area of damage and mature into myelinating oligodendrocytes. Remyelination failure may happen at each of these steps, and molecule targets aimed at altering migration or maturation are shown here.

The Role of Exercise

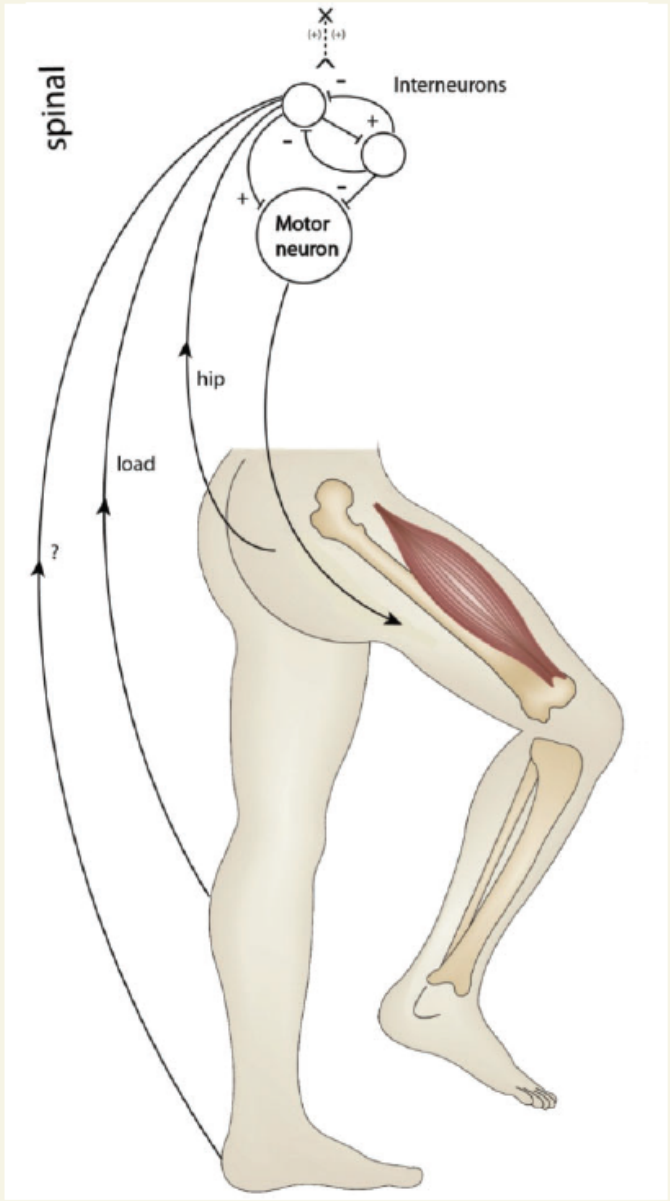


Figure 2 Neuroplasticity after spinal cord injury. Schematic drawings showing the mechanisms underlying neuroplasticity after spinal cord injury. The spinal neuronal circuits become activated by an appropriate afferent input leading to the gen-

Section 5
Understanding the approach to new drugs and treatment

How does my doctor know how to treat me?

- Which drug is good ?
- Which is bad?
- How are medicines made?
- Who makes them? Why?
- Who regulates them?
- Government licences?
- What's a doctor's role?

Evidence based Medicine and Evidence free Medicine

Placebo Effect and Bias

Randomisation

Publication

The Placebo Effect

- **Placebo** is a substance or procedure a patient accepts as medicine or therapy, but which has no specific therapeutic activity
- Power of suggestion.

- Latin: ‘I will please’


ROBERT
CABE
chardonnay
2000

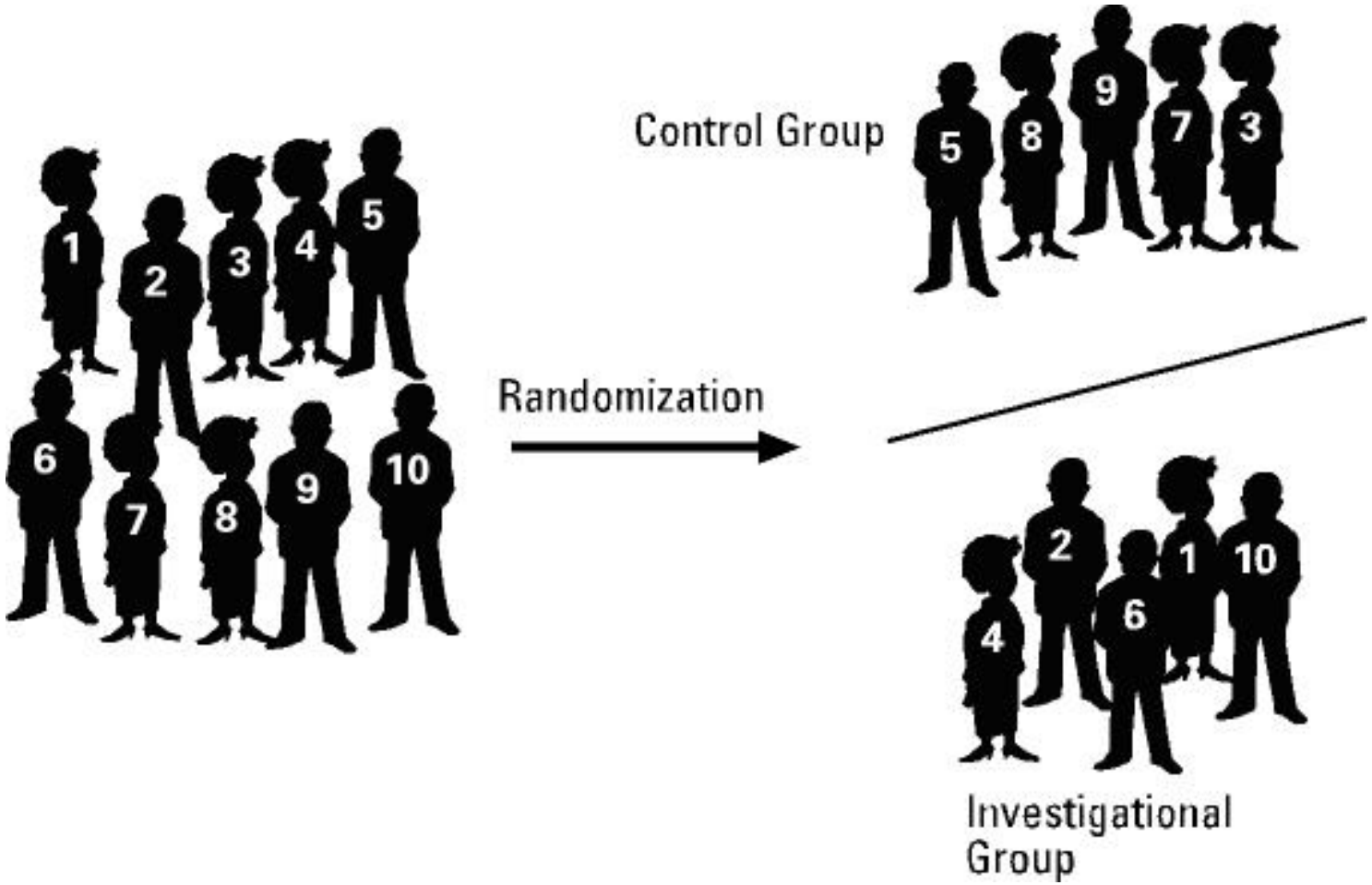
Bias

- Would you let the politician count his own votes?

- Isn’t my baby the ‘cutest’?

- How do we avoid bias and placebo?

Randomisation



Blinding

- Single blinded

  -Only patients

- Double blinded

  -Patients and doctors (both treating doctor and assessing doctor)

Results

- Peer-reviewed journals
- Public announcements
  - Results not made public until end of trial

Checklist before you believe..

- **What kind of study was done?**
- **Who were the researchers?**
- **Where was the research done?**
- **Who (or what) were the subjects in the study?**
- **How many people were in the study?**
- **What elements were controlled in the study?**

- **How do the results compare with other research on the topic?**
- **Has the study been published in a reputable scientific journal?**
- **What is the statistical / clinical significance?**

Vitamin D

- How many on Vit. D supplements ?
- How many think we are insufficient ?

- In a fair skinned person:
  - 20 minutes to 30 minutes of sunlight exposure on the face and forearms at midday is = 2000 IU of vitamin D.
  - Two or three such sunlight exposures a week sufficient in summer
- In pigmented skin :
  - exposure time or frequency need to be 2 -10X fold to get the same level of vitamin D

But …..

- Six months of the year (October to April), insufficient UV B in
  - all of Scandinavia,
  - much of western Europe (including 90% of the UK),
  - and 50% of the North American landmass

- 50% UK population insufficient in Spring
- 77% Americans

- 9/10 Asians !!

What to do ?

- Get out more
- Sun Screen ?
- Eat Vit. D rich food

- SUPPLEMENTS !!

My Practice and Thoughts

- All MS patients recommended Vit D 800-2000/day
  - Helps bone
  - likely to be deficient anyway

- I take Vit. D 2000 u/day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