

# PUBLIC LECTURE

## *Series*

### 2015-2016



THE UNIVERSITY  
of EDINBURGH

MRC

Medical  
Research  
Council



“Let's talk about health”

**Multiple Sclerosis – Success, challenges and Hope**

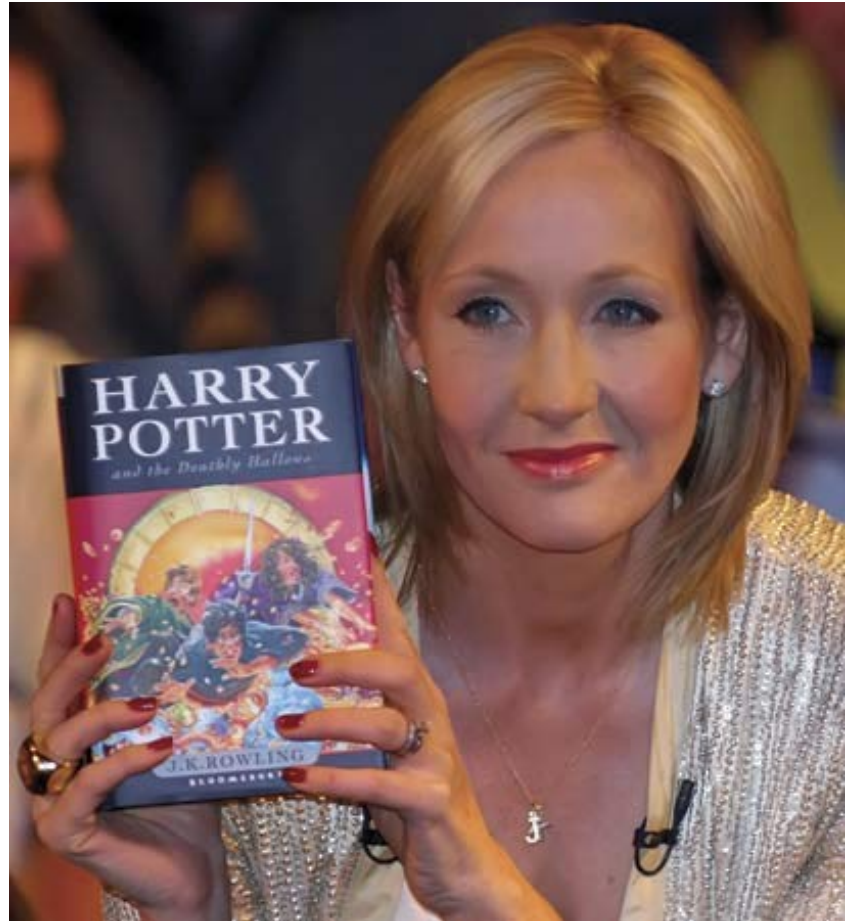
# Multiple Sclerosis

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- How common is multiple sclerosis in Scotland?
  - A) 1 in 10
  - B) 1 in 500
  - C) 1 in 2000

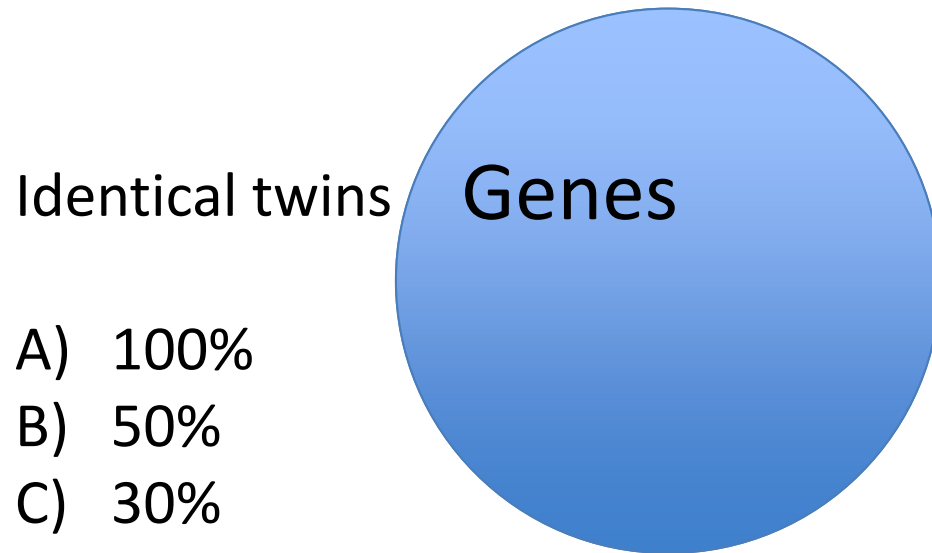
# Multiple Sclerosis

- Young
- 2F:1M

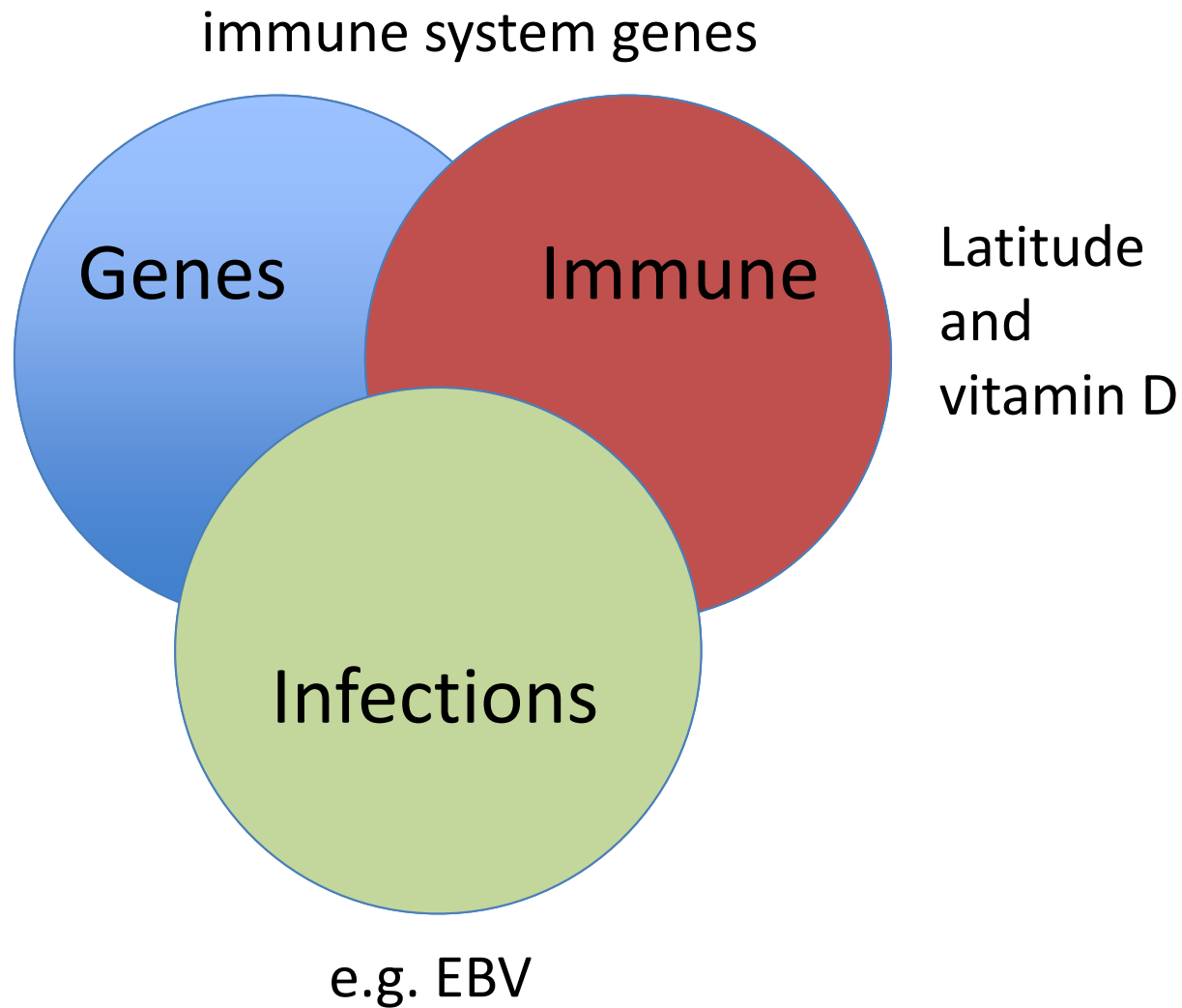


# What causes MS?

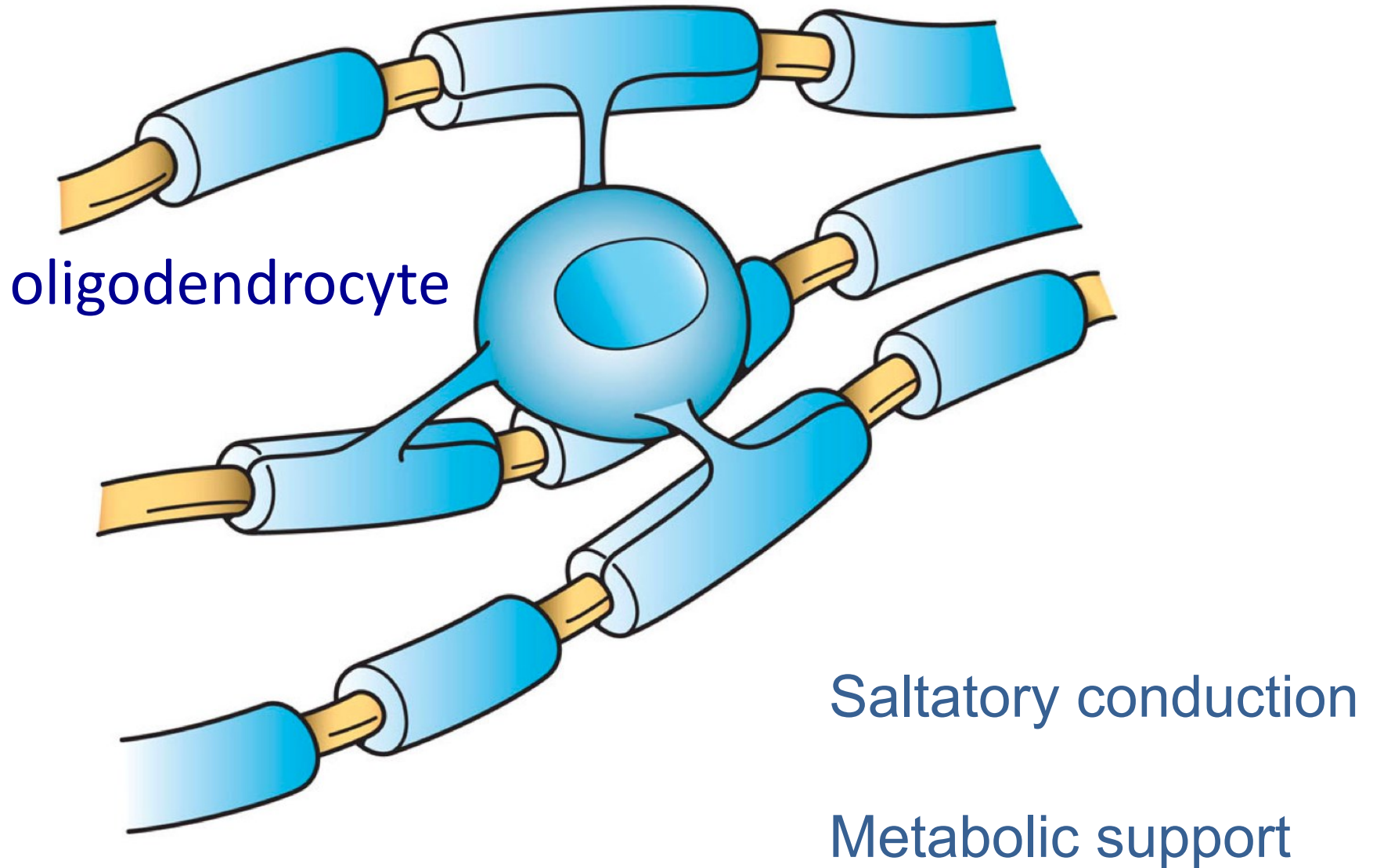
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# What causes MS?

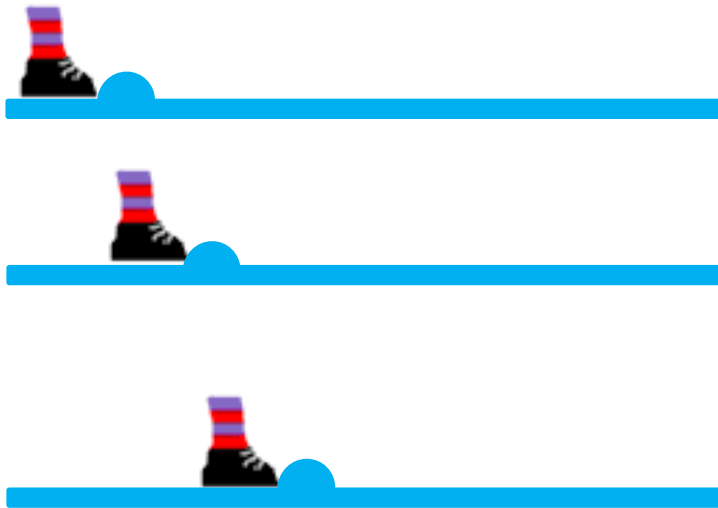


# MS is a disease of brain and spinal cord myelin

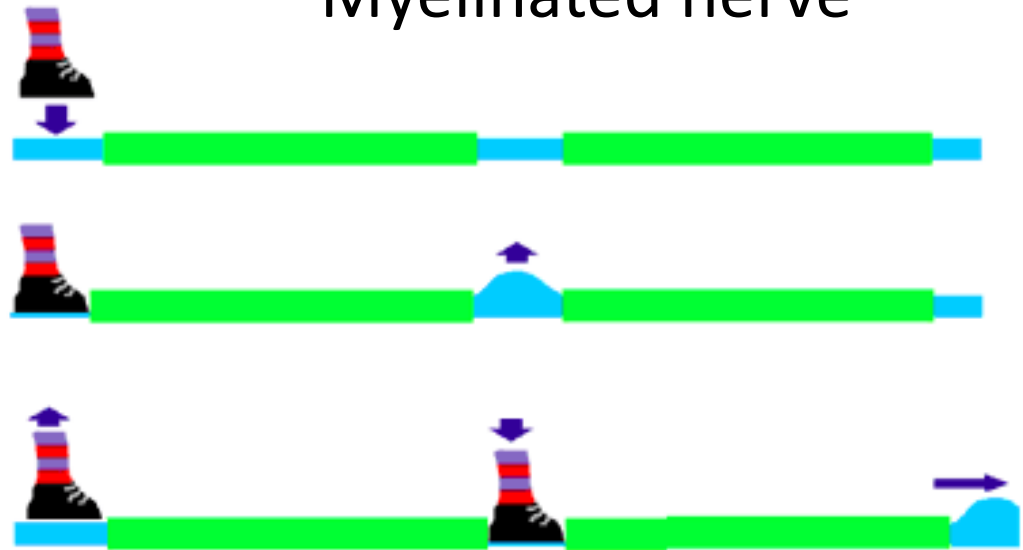


# Continuous conduction v saltatory conduction

Unmyelinated nerve

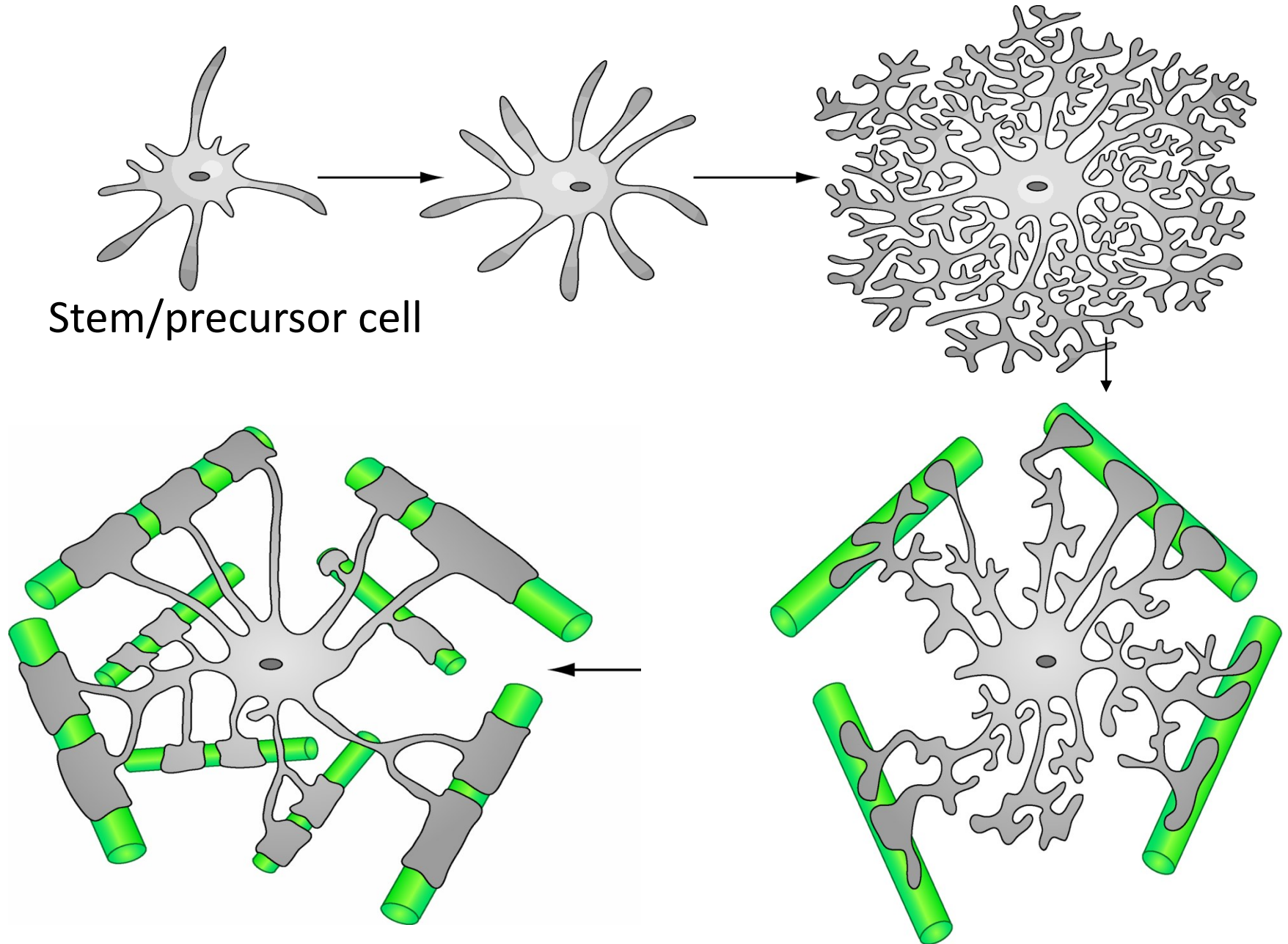


Myelinated nerve



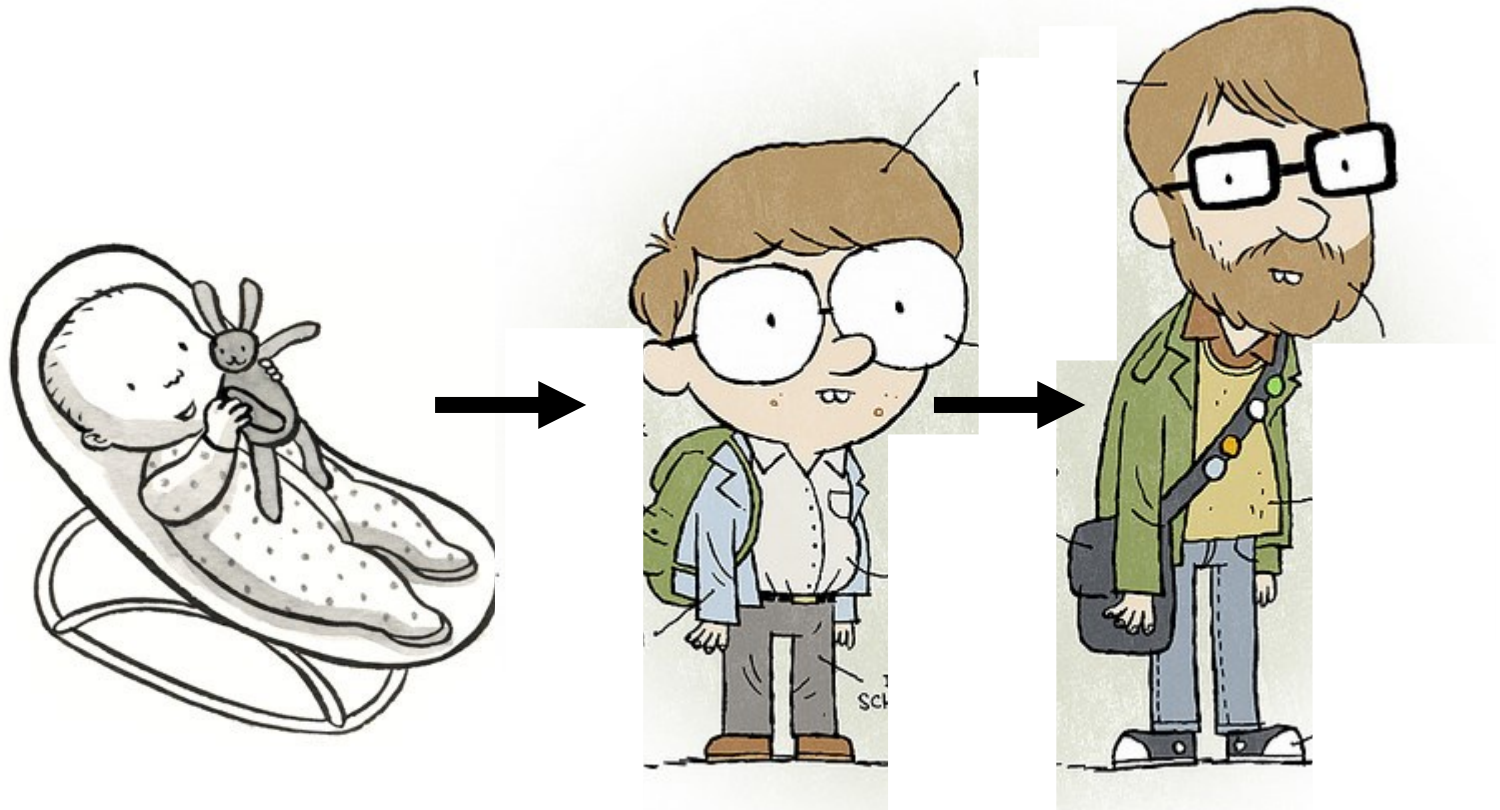


# Oligodendrocytes myelinate the brain





# Myelin is important in development

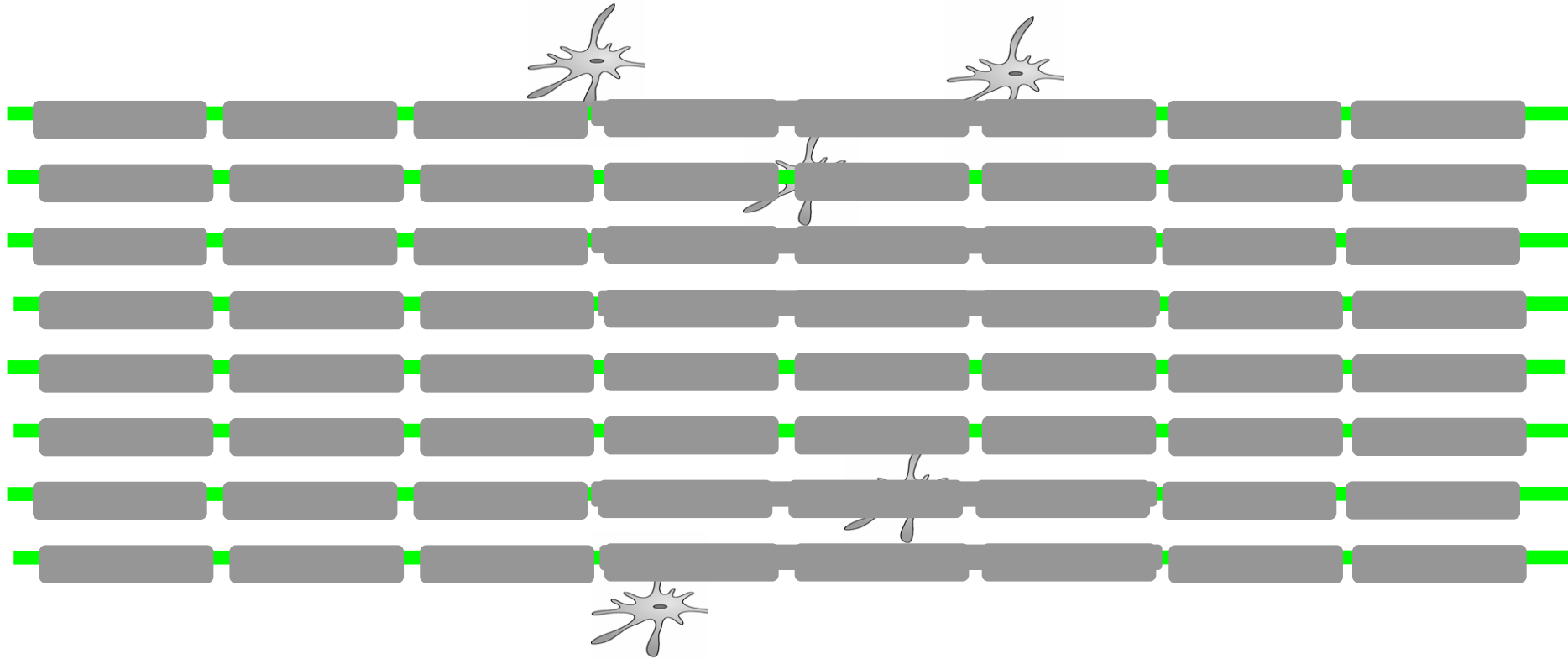


Increasing physical and mental skills



# What happens in MS?

## Immune attack

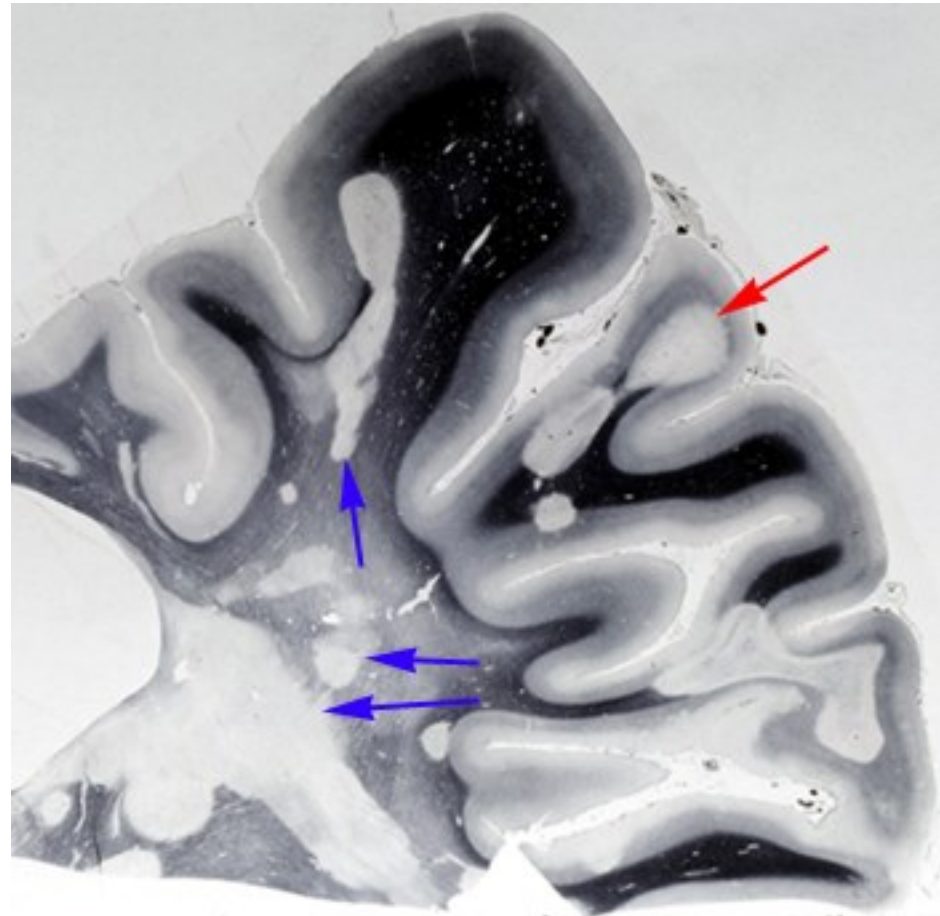


Oligodendrocyte precursor cells to remyelinate  
Nerve protection

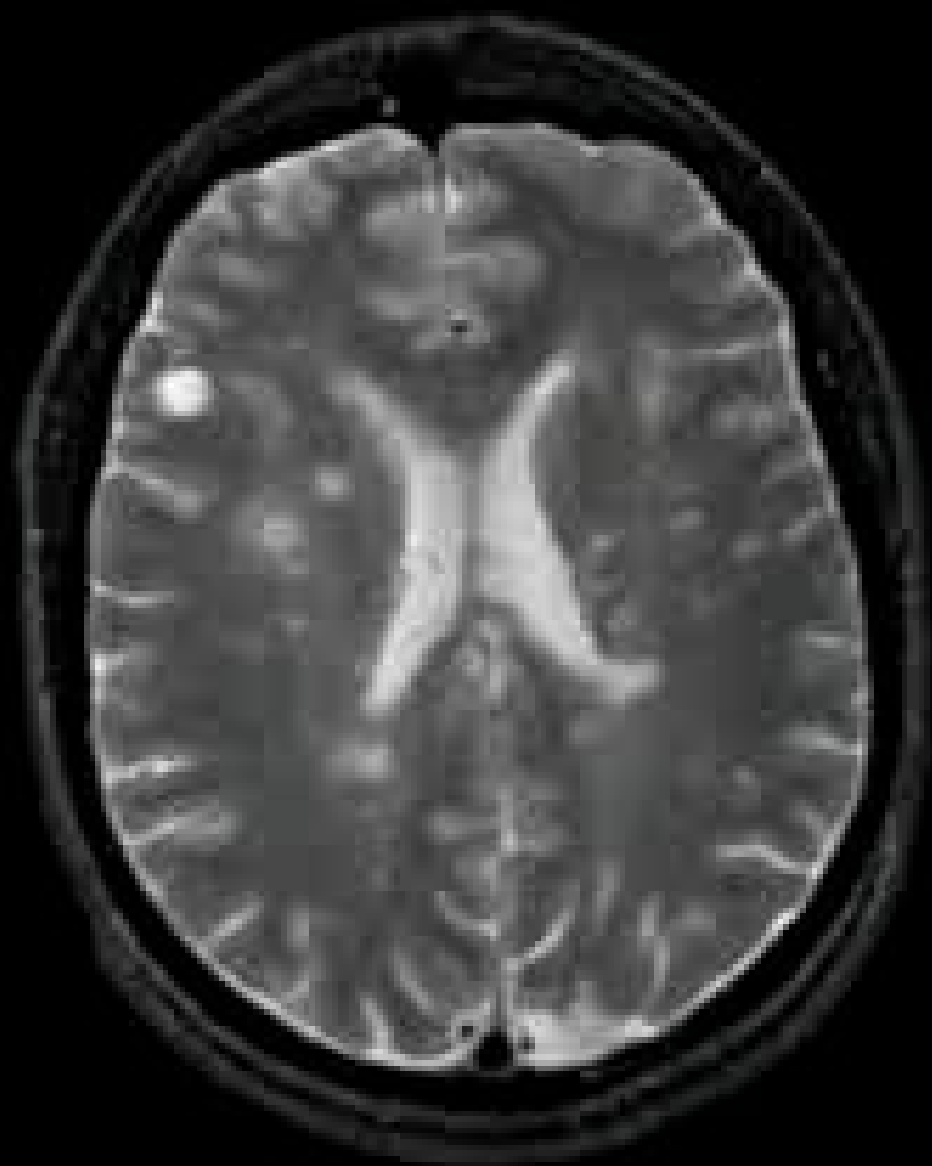
# Pathology of myelin – multiple sclerosis brain



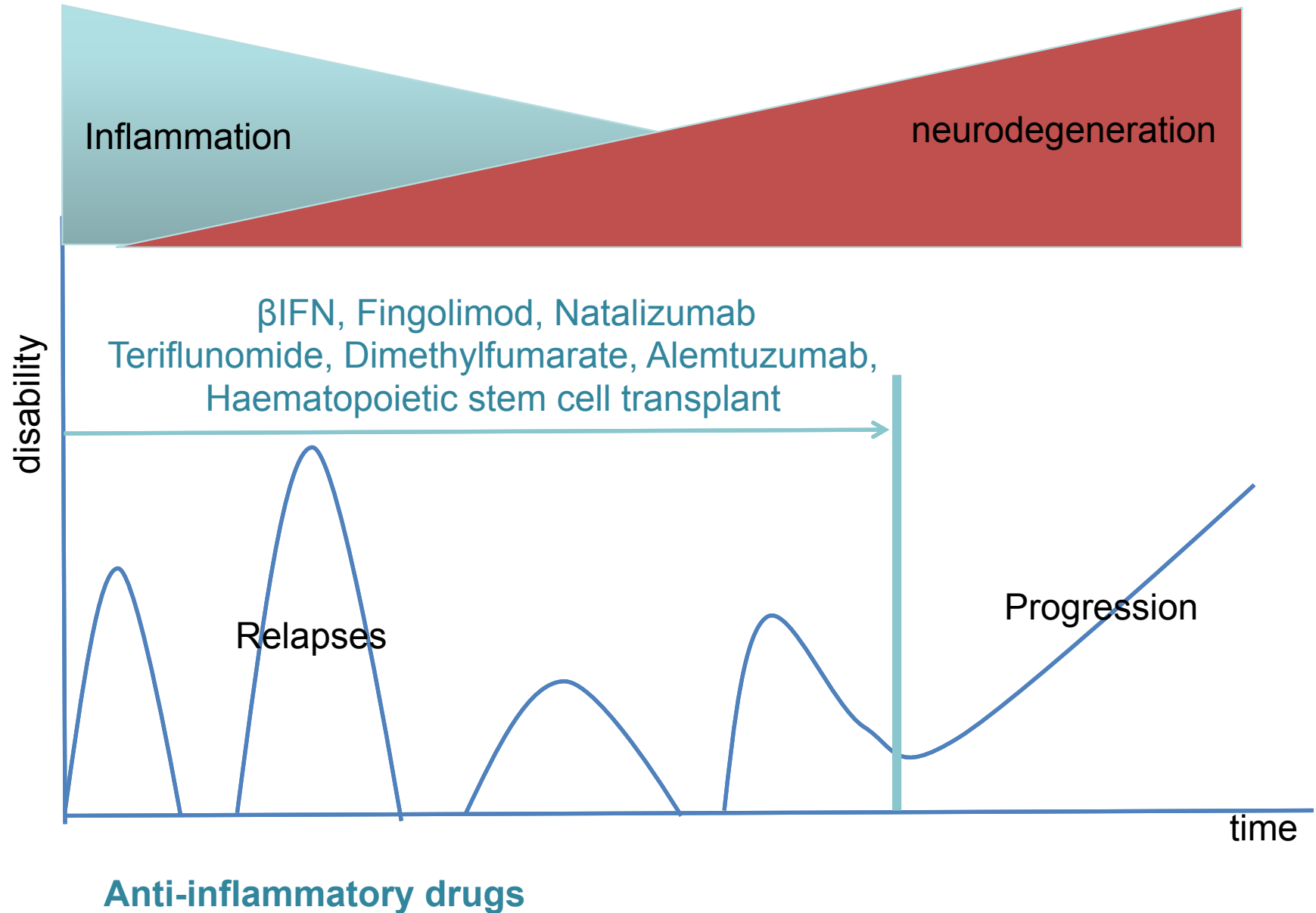
Normal



Multiple sclerosis



# MS disease course



# Success: treatments for relapsing-remitting MS

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Beta-interferon

Glatiramer acetate

Teriflunomide

↓ relapses by 30%

Dimethylfumarate

Fingolimod

↓ relapses by 50%

Natalizumab

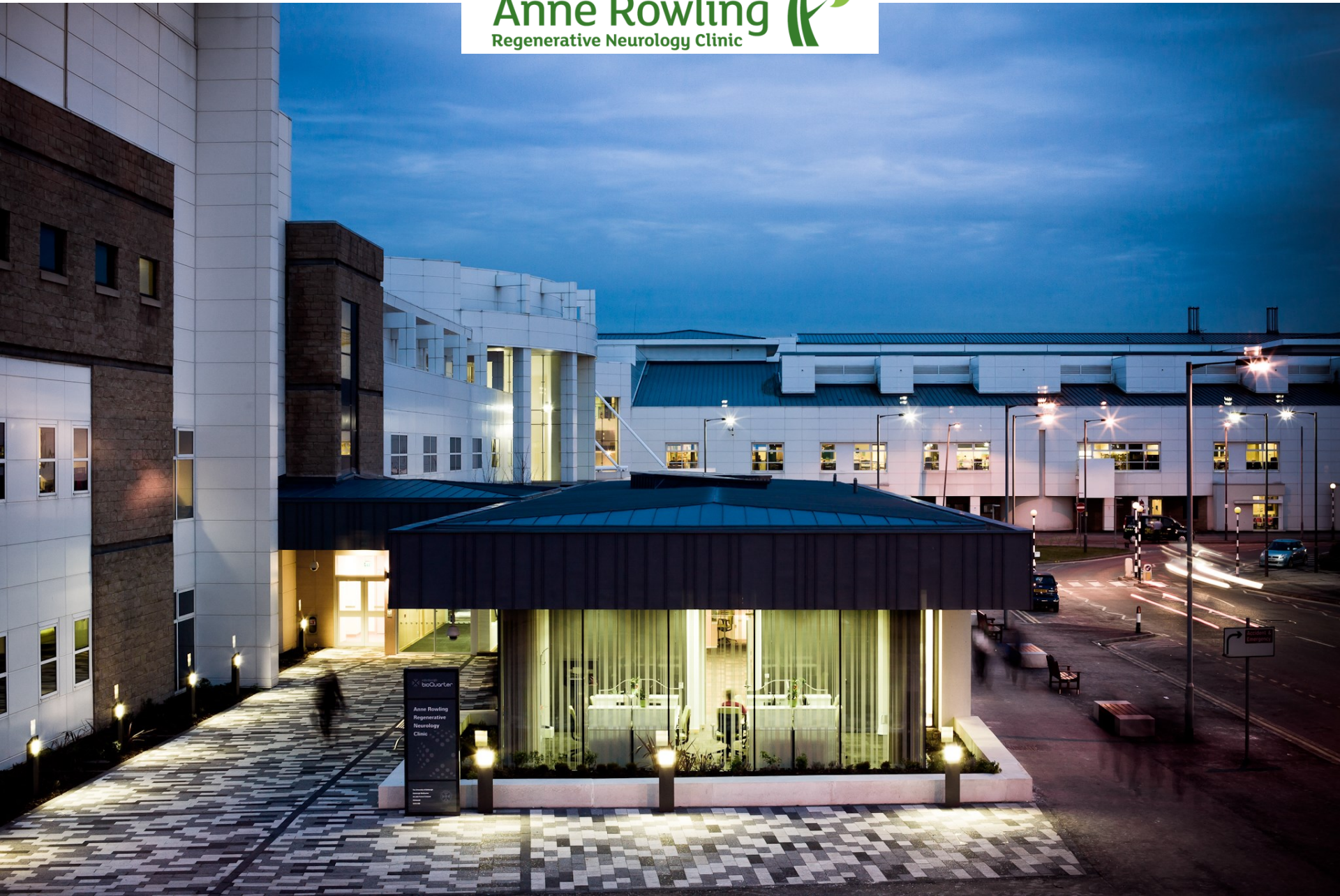
Alemtuzumab

Haematopoietic stem cell transplant

↓ relapses by >70%



# Success:



# Success: MS Tissue Bank

## MS Donor Card



"I want to help MS research by donating my brain"

Name:

Tel. Number to ring for donation and information:

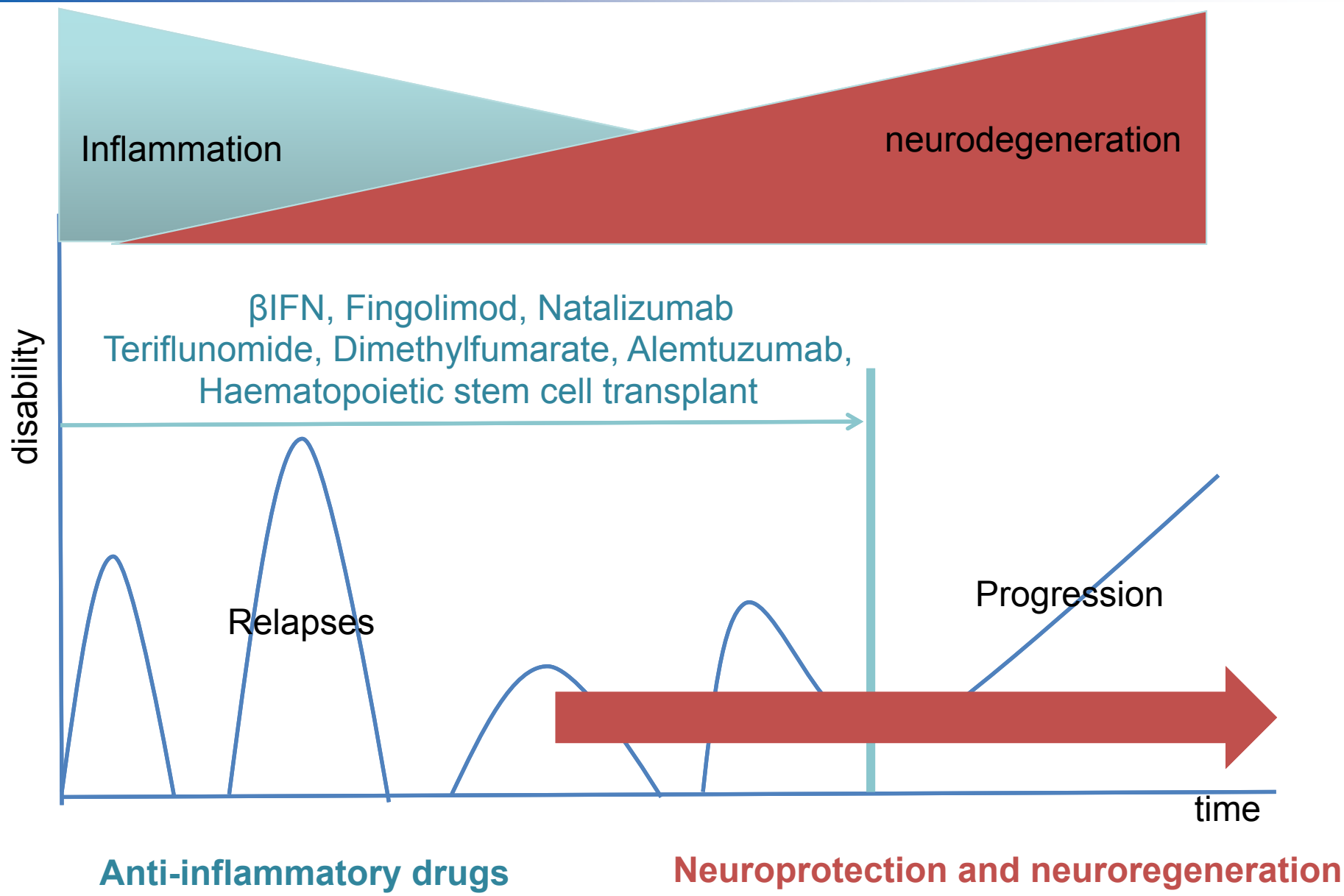
0131 465 9522 or 07913 296845

"I want to help MS research by donating my brain"



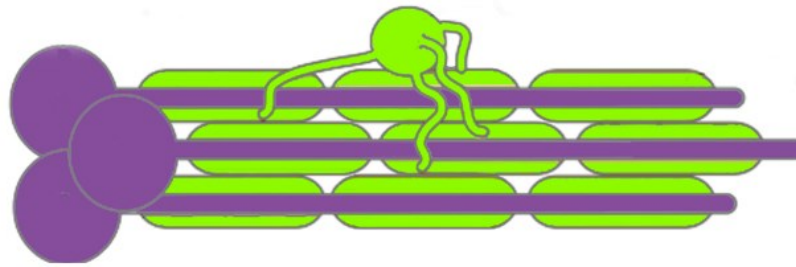
Multiple Sclerosis Society

# Challenge

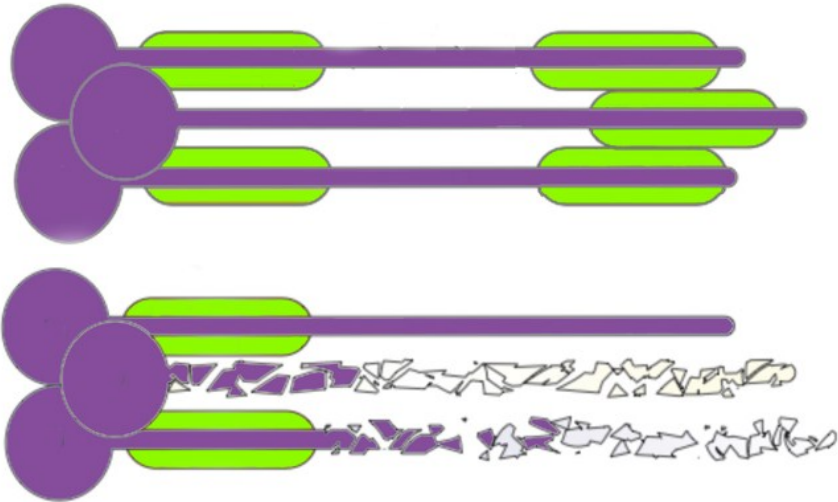
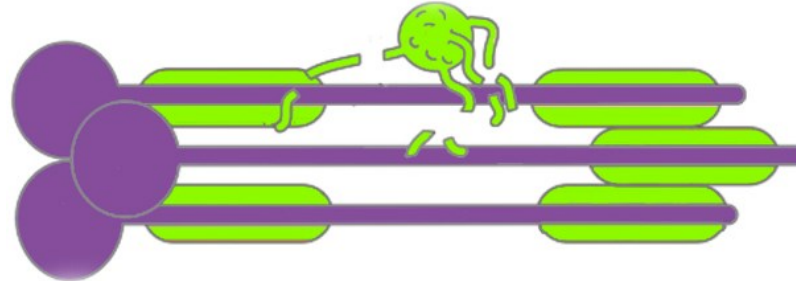




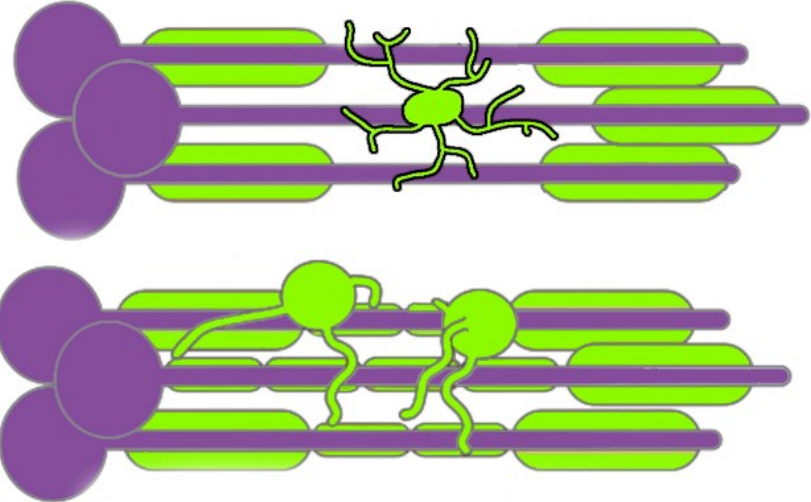
Healthy Brain



Myelin Damage (MS)

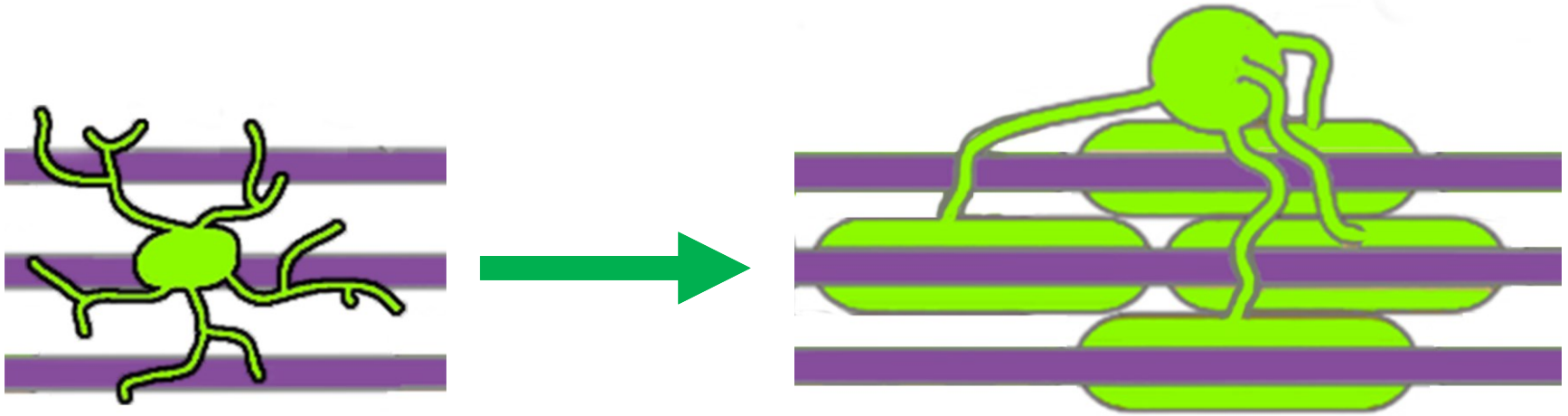


No regeneration of myelin  
Nerves degenerate



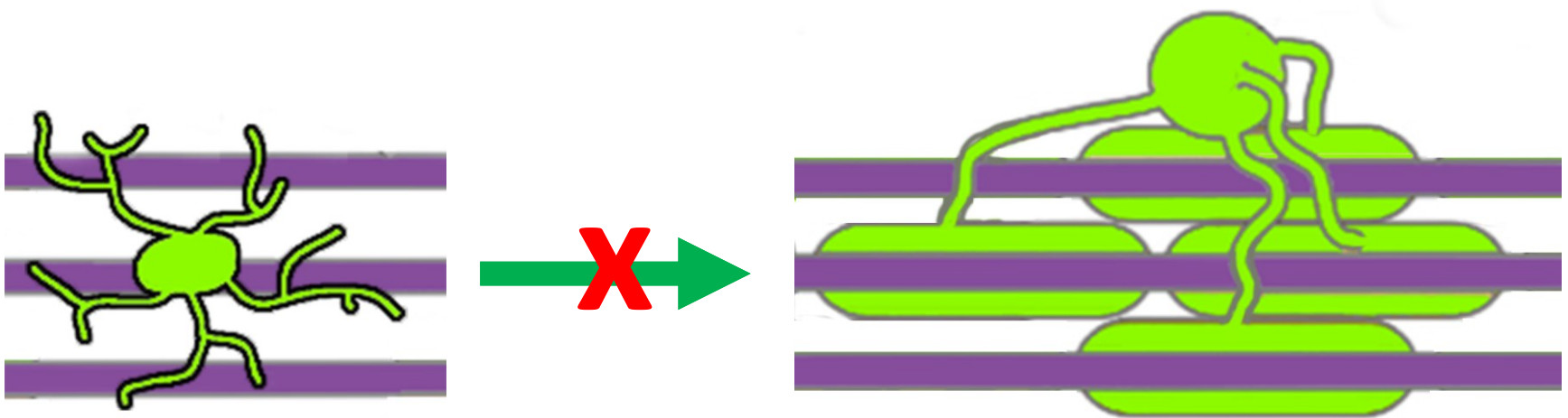
Myelin regeneration by  
Oligodendrocyte stem cells  
For Neuroprotection

About 5% of our brain cells are oligodendrocyte stem cells



**These cells generate myelin  
throughout life and during regeneration**

## Ability of stem cells to make myelin impaired in MS

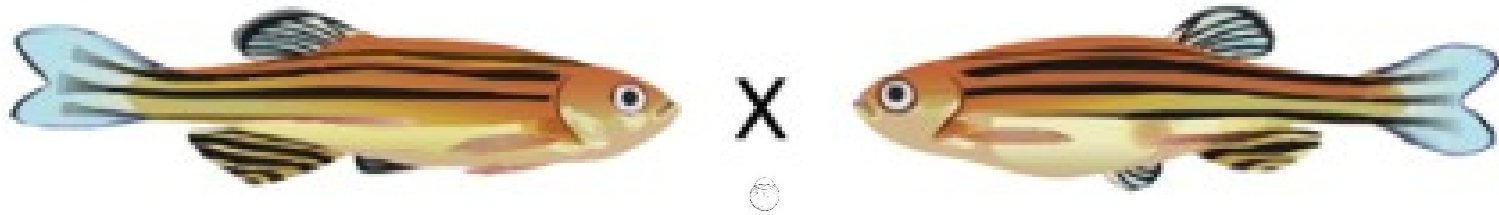


We need coax stem cells to make myelin

How do we do this?



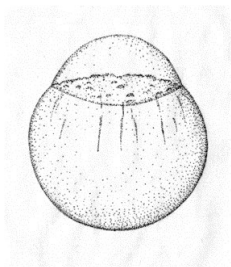
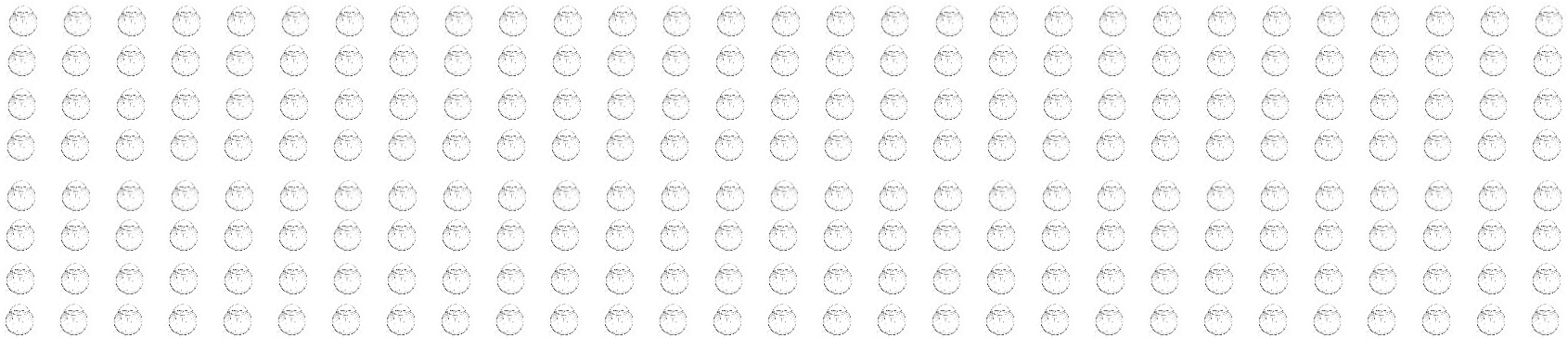
# We can use zebrafish to identify drugs that promote myelination



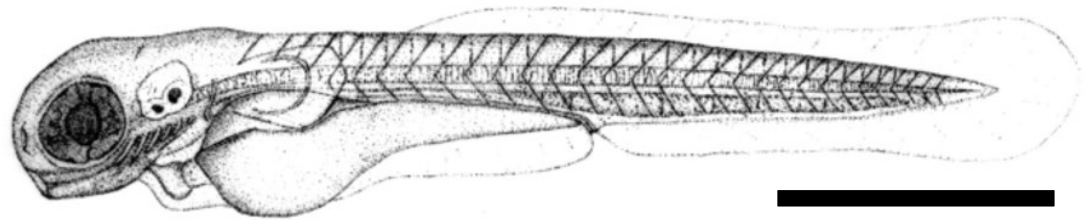
1-5 embryos?

10-50 embryos?

100-500 embryos?



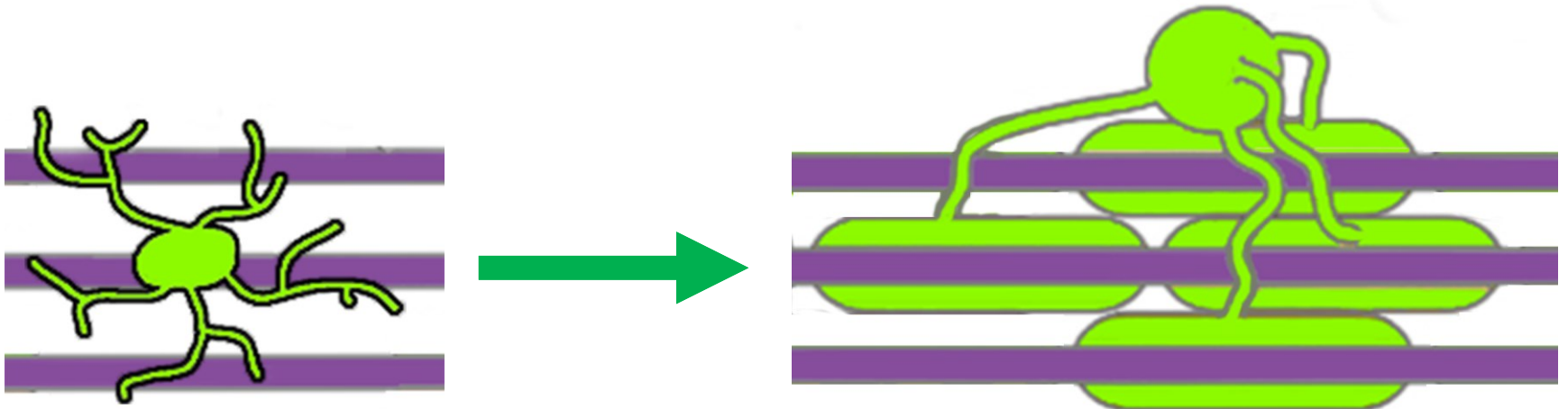
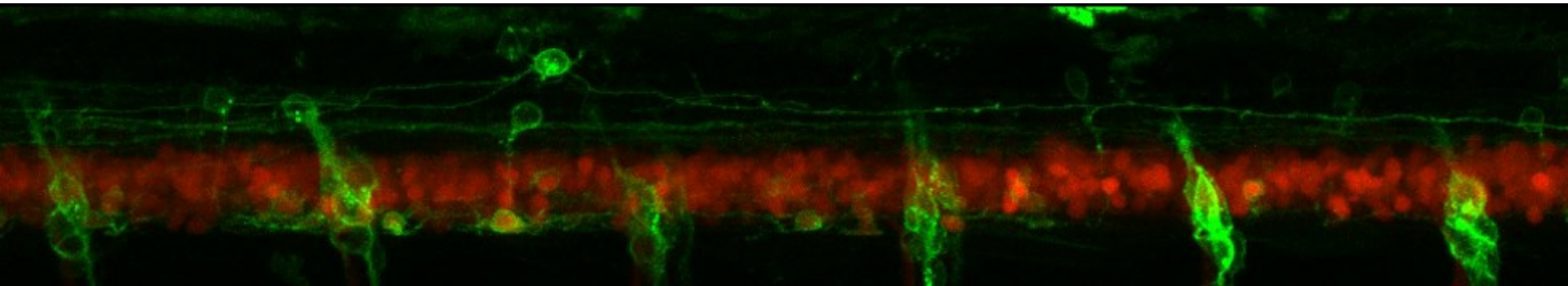
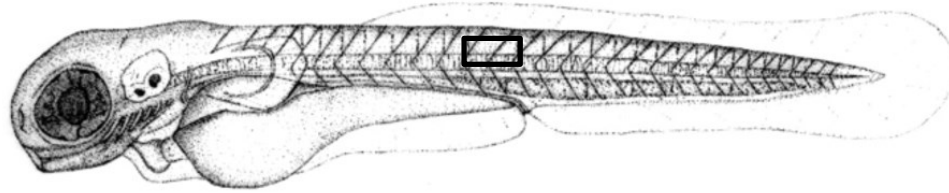
3 days!



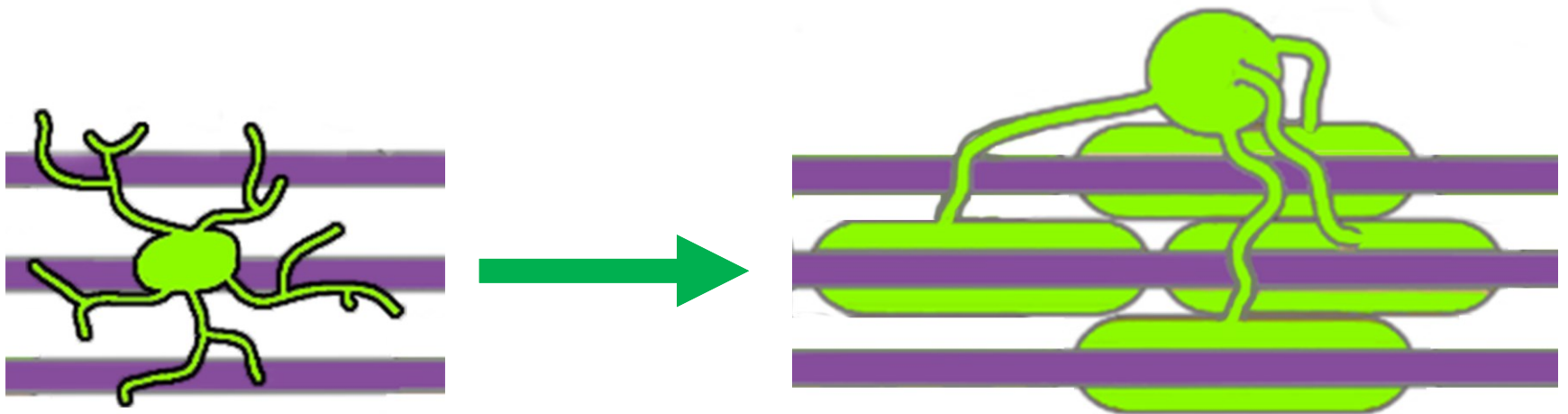
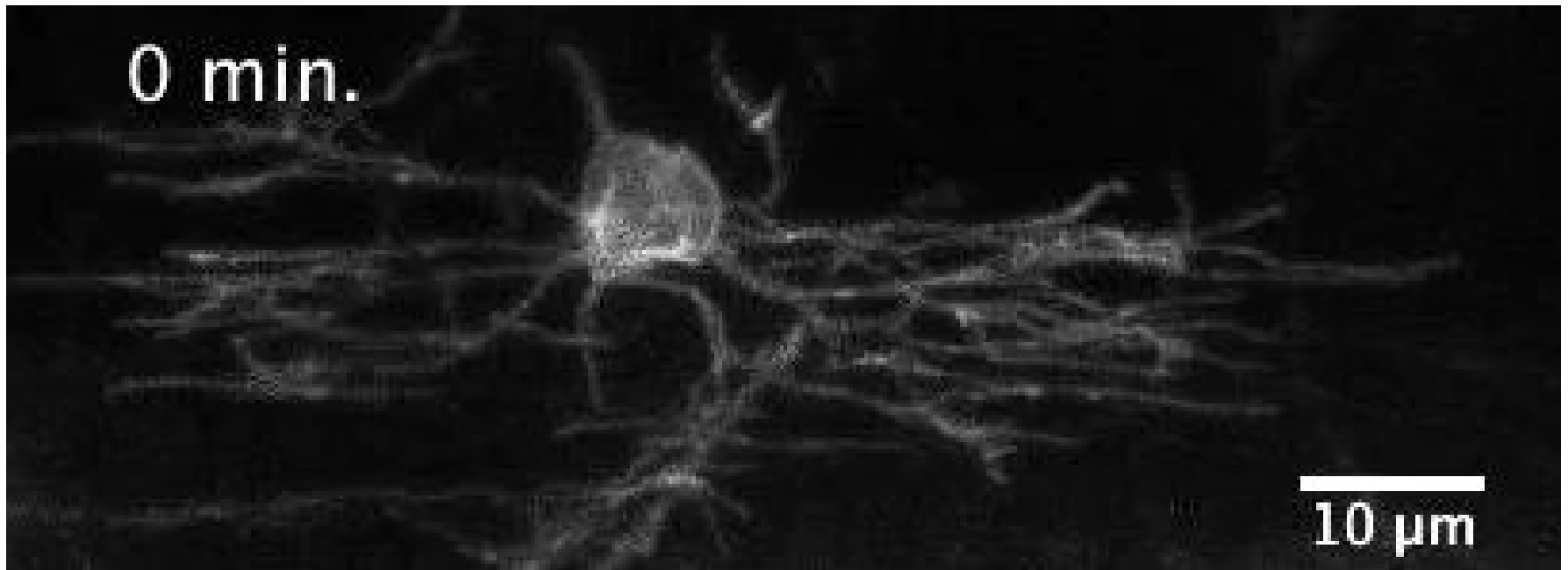
1 mm

**Zebrafish share many similarities with us**  
**Clinical trials (cancer) following studies in zebrafish**

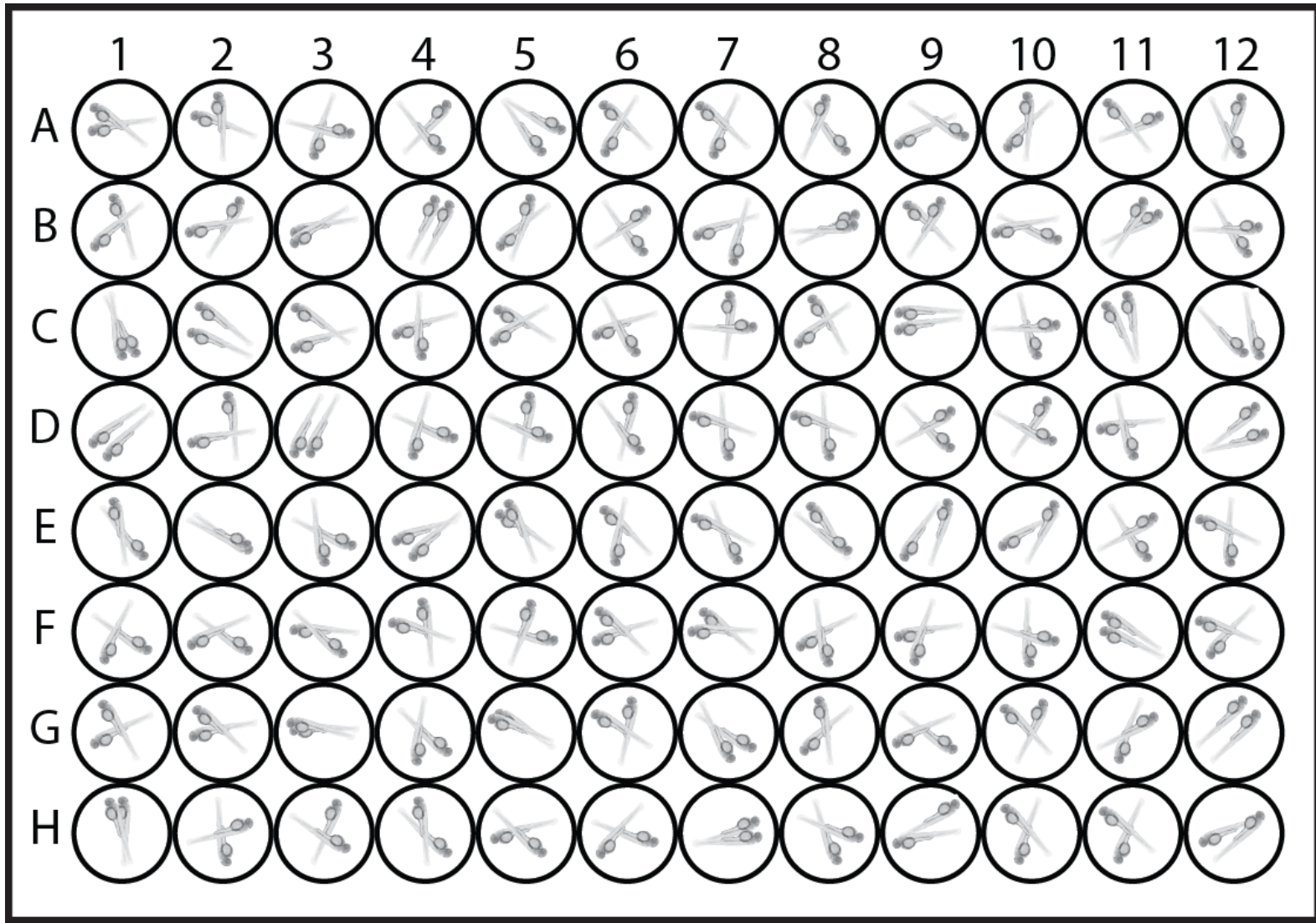
**We can watch stem cells make myelinating oligodendrocytes**



## We can watch myelination

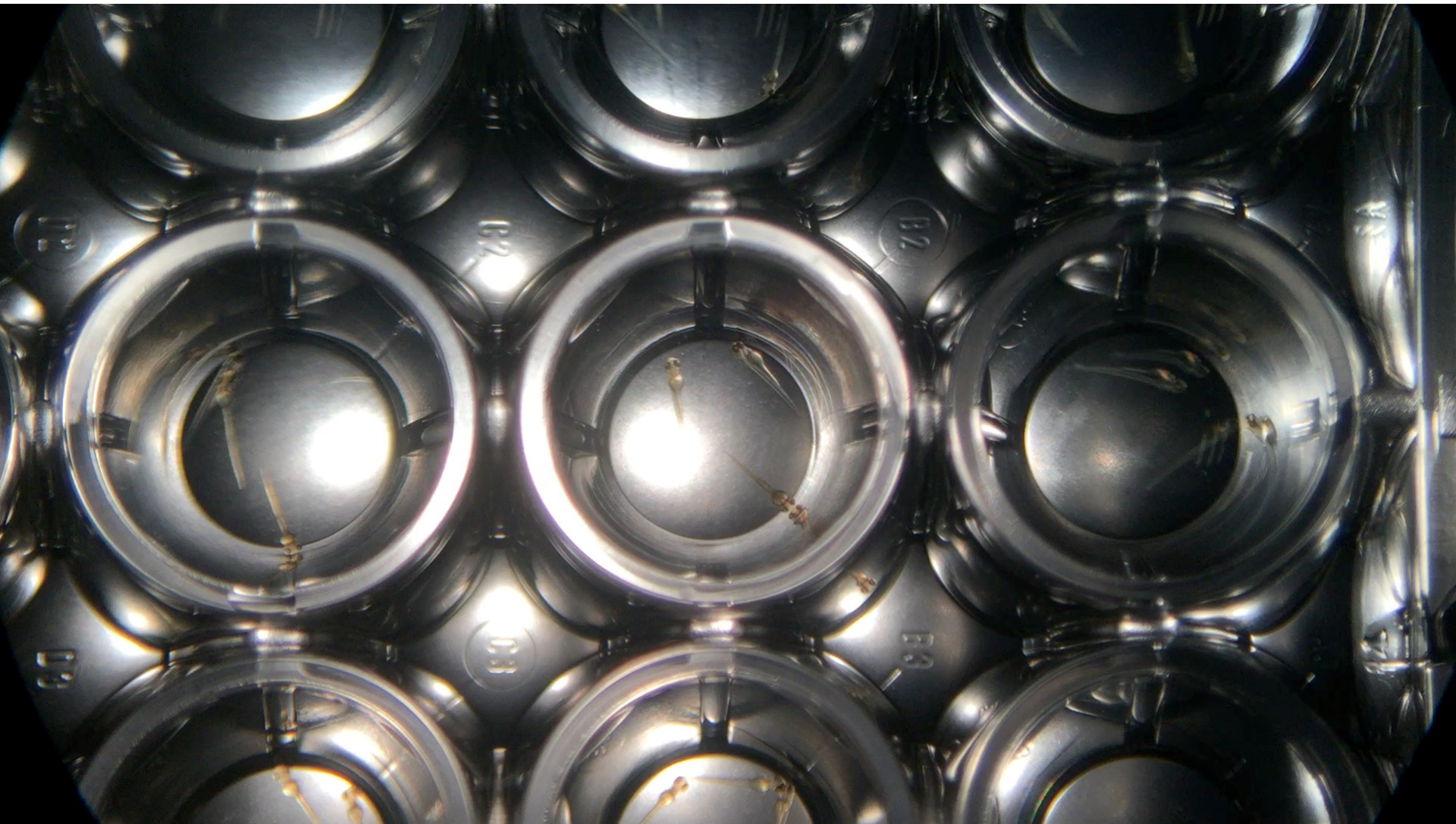


**Embryos can be put into small “wells” in plate**

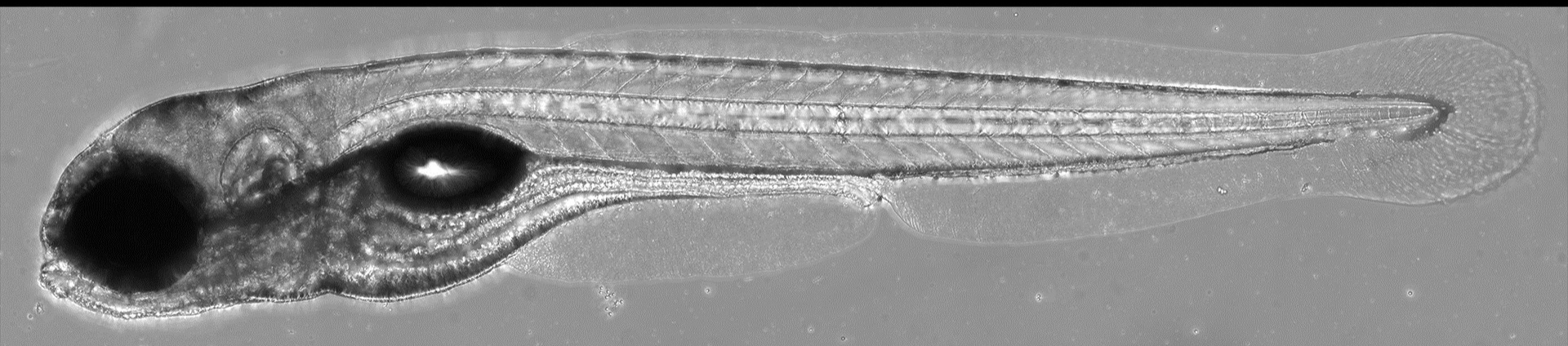


**Drugs dissolved in water and can be taken up by fish**





**How do we look at how drugs regulate production of myelinating OLs?**



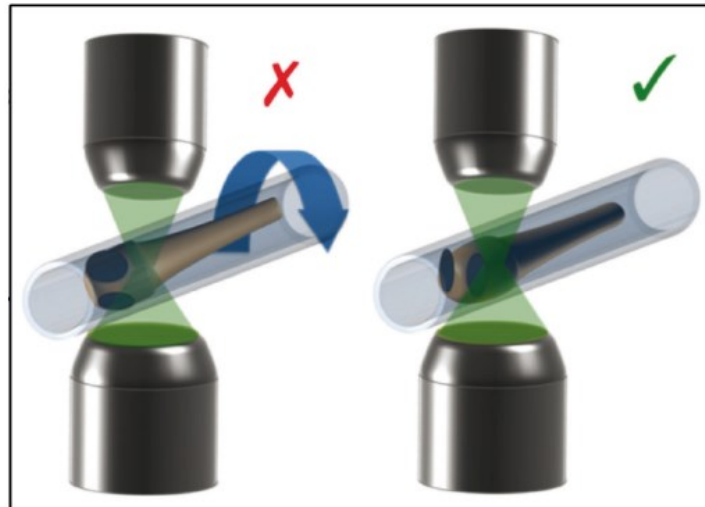
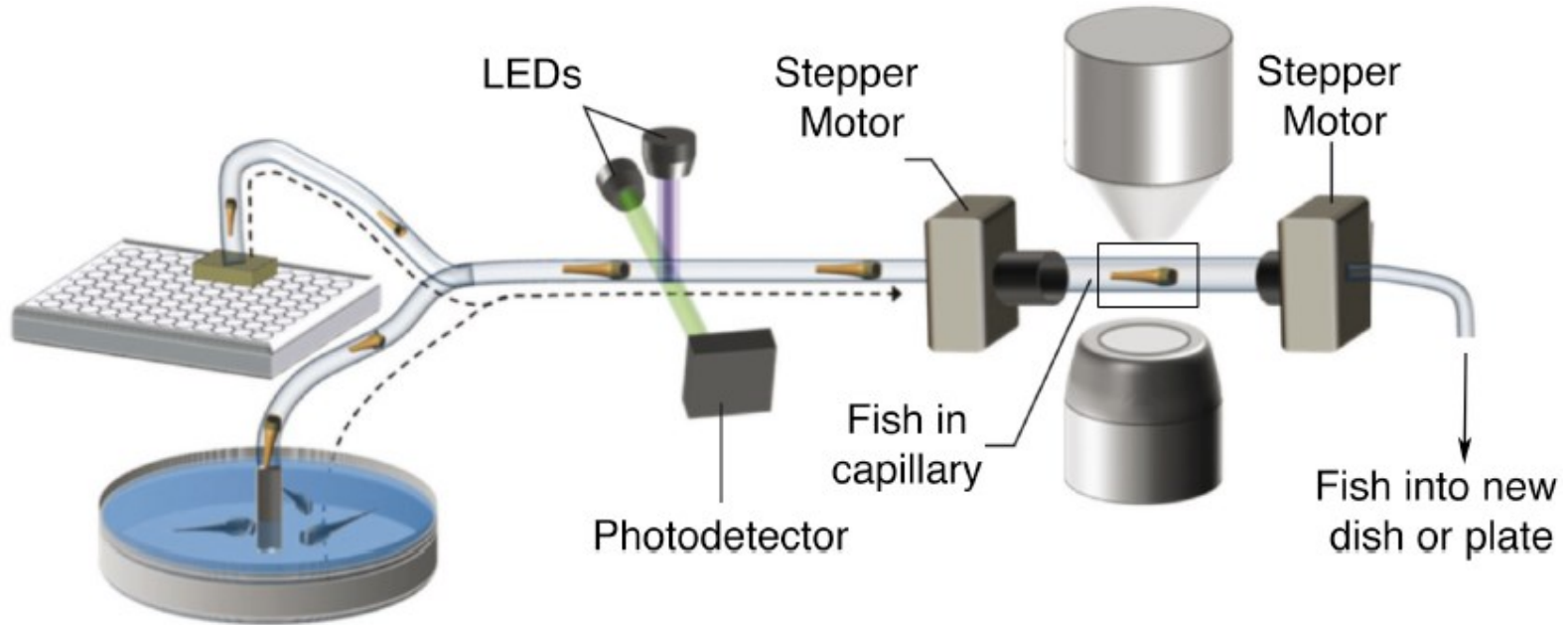
**All oligodendrocytes in entire brain and spinal cord imaged in 30 secs**

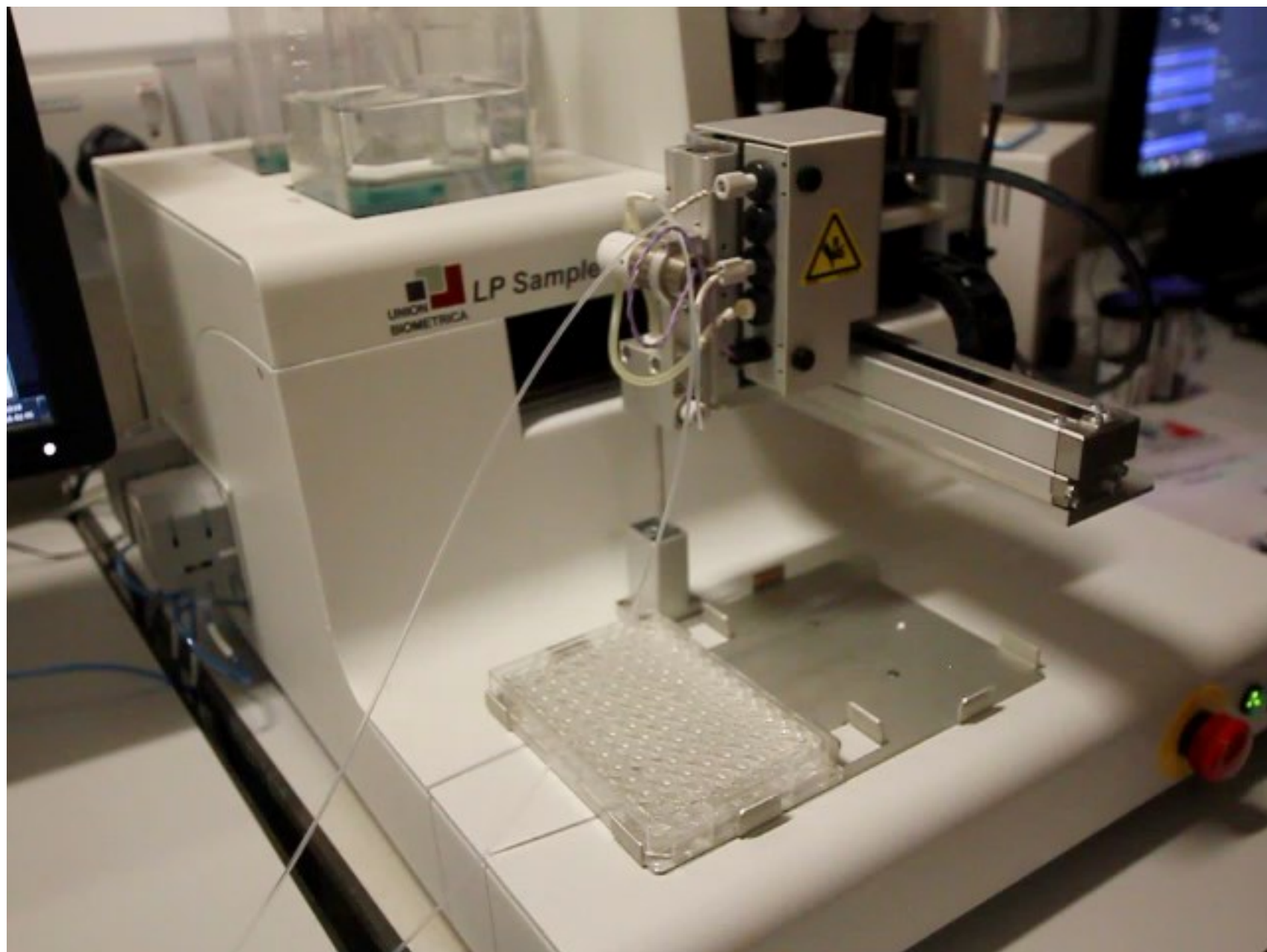


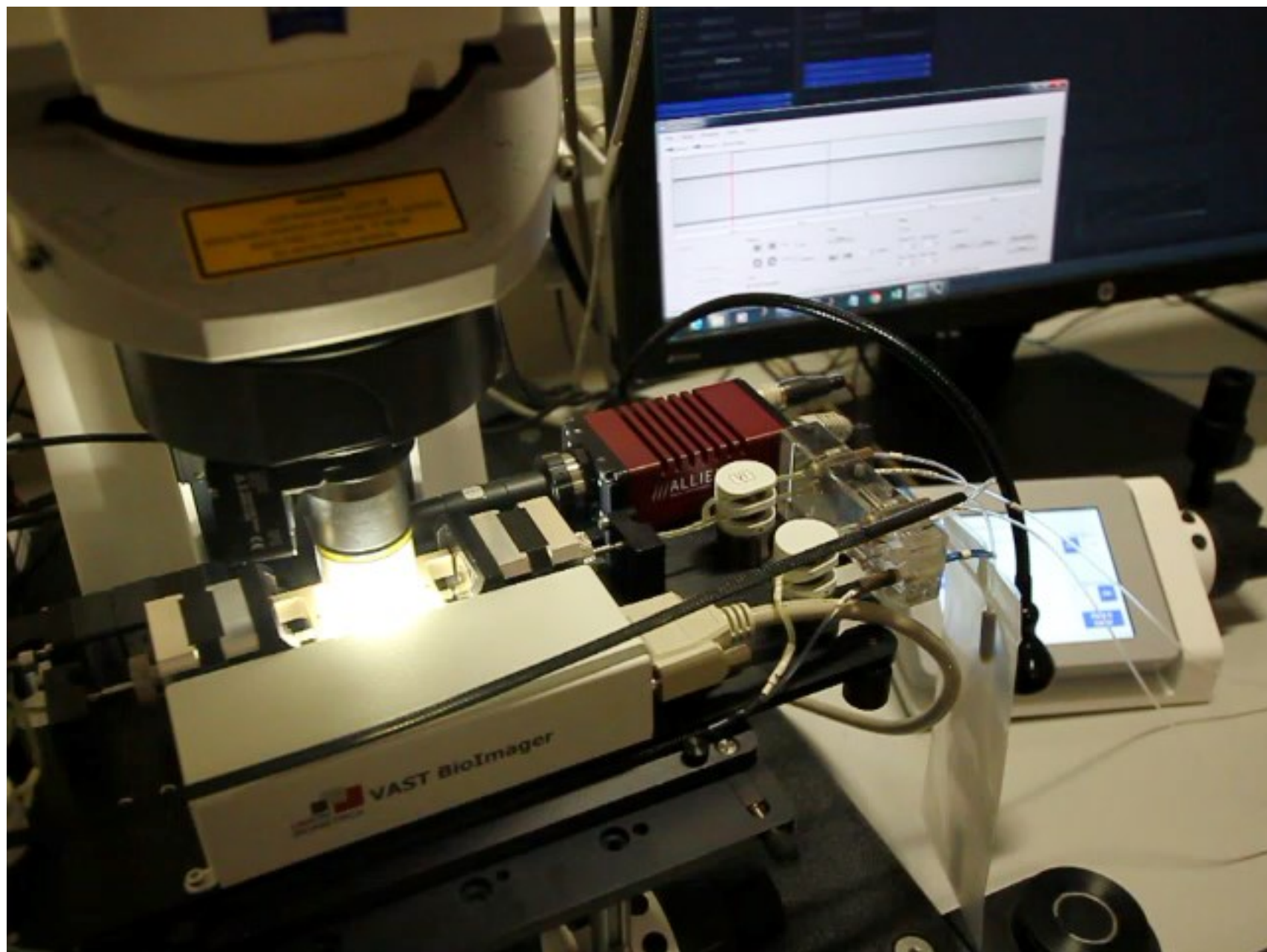


**All oligodendrocytes in entire brain and spinal cord imaged in 30 secs**

# How do we get fish from plate to microscope?











2015-11-12...



2015-11-12...

File type

File suffix: .tif

Z-Stack Prefix

Z-MIP Prefix

X-MIP Prefix

Start from file# 2

Threshold for posterior maxima 100

☐ Use X-MIPs?

☐ Bounding crop?

☐ 3D crop?

☐ Re-use ROIs from another folder?

☒ Manual selection adjustment?

☐ Heart Marker Present?

Start of Spinal cord? 500

☒ Count Dorsal?

☐ Count Ventral?

☒ Manual count adjustment?

OK Cancel

\*2015-11-13\_Assisted-Counting\_JE1.ijm (Running)

File Edit Language Templates Run Tools Tabs

Macro.ijm:ijm | 2015-11-07\_Batch-MAX\_JE.ijm | \*2015-11-13\_Assisted-Counting\_JE1.ijm (Running)

```
7 //Set location of corresponding XY XZ MIPs.
8 //Set output location.
9 //Set input file extension.
10
11 //Other settings:
12 //X Start = X Location (pixels) to start analysing fish (~where spinal cord begins)
13 //X Interval = Distance between sampling points.
14 //ROI Width####
15
16 var suffix, zPrefix, zMipPrefix, xMipPrefix, MIPZ, MIPX, useX-MIP, output, zInput;
17
18 macro "Assisted Counting" {
19
20   setBatchMode(false);
21
22   input = getDirectory("Folder containing \"Z-Stacks\", \"Z-MIPs\", \"X-MIPs\" and
23   zInput = input+"Z-Stacks"+File.separator;
24   MIPZ = input+"Z-MIPs"+File.separator;
25   MIPX = input+"X-MIPs"+File.separator;
26   output = input+"Output"+File.separator;
27   //zInput = getDirectory("ZStack directory");
28   //MIPZ = getDirectory("Z-MIP directory");
29   //MIPX = getDirectory("X-MIP directory");
30   //output = getDirectory("Output directory");
31
32   Dialog.create("File type");
33   Dialog.addString("File suffix: ", ".tif", 10);
34   Dialog.addString("Z-Stack Prefix", "Stitched_", 15);
35   Dialog.addString("Z-MIP Prefix", "Stitched_MAX_", 15);
36   Dialog.addString("X-MIP Prefix", "XZ-MAX_Stitched_", 15);
37   Dialog.addNumber("Start from file#", 2);
38   Dialog.addNumber("Threshold for posterior maxima", 500);
39   Dialog.addCheckbox("Use X-MIPs?", false);
40   Dialog.addCheckbox("Bounding crop?", false);
41   Dialog.addCheckbox("3D crop?", false);
42   Dialog.addCheckbox("Re-use ROIs from another folder?", true);
43   Dialog.addCheckbox("Manual selection adjustment?", false);
44   Dialog.addCheckbox("Heart Marker Present?", false);
45   Dialog.addNumber("Start of Spinal cord?", 500);
46   Dialog.addCheckbox("Count Dorsal?", true);
47   Dialog.addCheckbox("Count Ventral?", false);
48   Dialog.addCheckbox("Manual count adjustment?", false);
49   Dialog.show();
50   suffix = Dialog.getString();
51   zPrefix = Dialog.getString();
```

Run Kill Show Errors Clear

Started 2015-11-13\_Assisted-Counting\_JE1.ijm at Fri Nov 13 13:27:17 GMT 2015  
Started 2015-11-13\_Assisted-Counting\_JE1.ijm at Fri Nov 13 13:28:09 GMT 2015  
Started 2015-11-13\_Assisted-Counting\_JE1.ijm at Fri Nov 13 13:28:55 GMT 2015  
Started 2015-11-13\_Assisted-Counting\_JE1.ijm at Fri Nov 13 13:29:33 GMT 2015  
Started 2015-11-13\_Assisted-Counting\_JE1.ijm at Fri Nov 13 13:30:10 GMT 2015  
Started 2015-11-13\_Assisted-Counting\_JE1.ijm at Fri Nov 13 13:30:45 GMT 2015  
Started 2015-11-13\_Assisted-Counting\_JE1.ijm at Fri Nov 13 13:31:23 GMT 2015  
Started 2015-11-13\_Assisted-Counting\_JE1.ijm at Fri Nov 13 13:32:02 GMT 2015  
Started 2015-11-13\_Assisted-Counting\_JE1.ijm at Fri Nov 13 13:34:18 GMT 2015  
Started 2015-11-13\_Assisted-Counting\_JE1.ijm at Fri Nov 13 13:44:25 GMT 2015

(Fiji Is Just) ImageJ

File Edit Image Process Analyze Plugins Window Help

Running command: script:C:\Users\Jason\Google Drive\ImageJ\Macros\WA...



**What kind of “drugs” do we test?**

**Drugs already approved to treat other diseases in humans**

Well defined safety profiles

Cuts out time from concept to clinic

**Drugs that affect **genes/ proteins** implicated in myelin repair**

**nature  
neuroscience**

## **Retinoid X receptor gamma signaling accelerates CNS remyelination**

Jeffrey K Huang<sup>1,7</sup>, Andrew A Jarjour<sup>2,7</sup>, Brahim Nait Oumesmar<sup>3</sup>, Christophe Kerninon<sup>3</sup>, Anna Williams<sup>2</sup>, Wojciech Krezel<sup>4</sup>, Hiroyuki Kagechika<sup>5</sup>, Julien Bauer<sup>6</sup>, Chao Zhao<sup>1</sup>, Anne Baron-Van Evercooren<sup>3</sup>, Pierre Chambon<sup>4</sup>, Charles ffrench-Constant<sup>2</sup> & Robin J M Franklin<sup>1</sup>



**9-cis-Retinoic acid binds to RXR protein and promotes myelin formation and regeneration?**

Associated with severe side effects

Unsuitable long-term e.g. for progressive MS

**We want a drug that SPECIFICALLY PROMOTES RXR activity**

How could we do this?

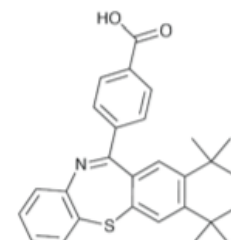
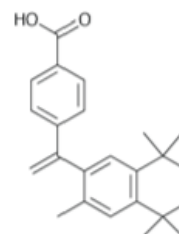
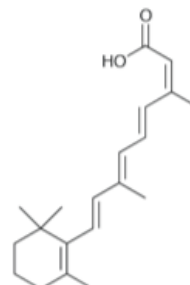
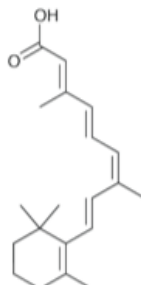
## ATOMIC STRUCTURE OF RXR



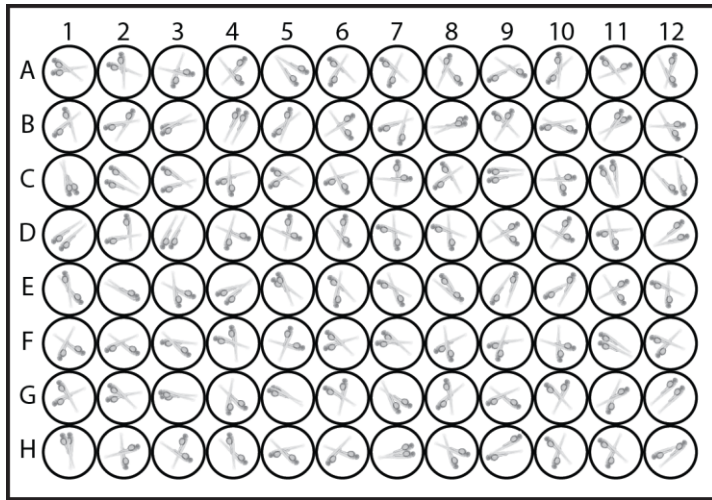
Computer matches RXR structure to all known drug-like chemicals



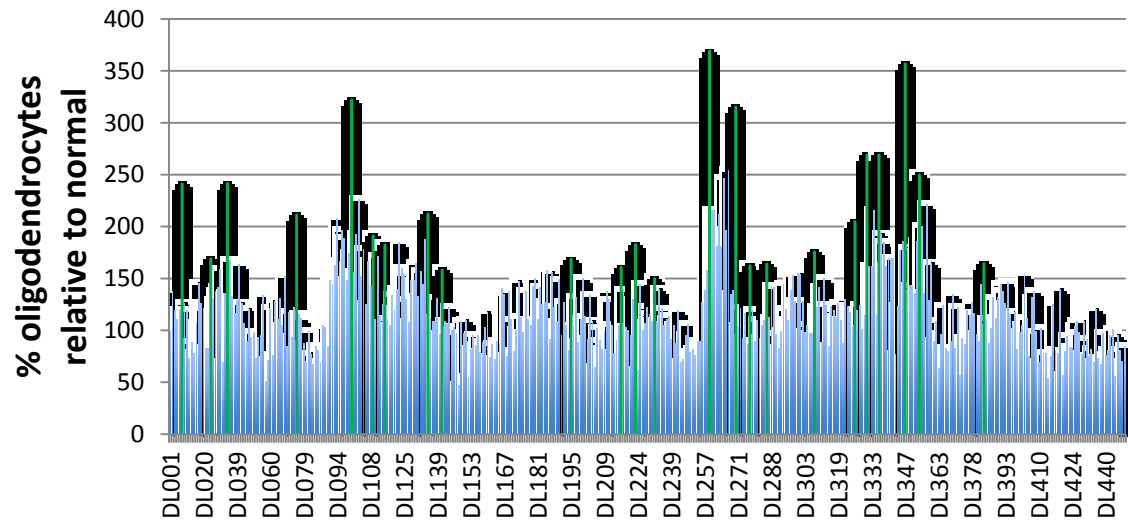
We get lists of “drugs” to try on promote myelination?



# Tested 450 “RXR” compounds for ability to promote myelination



**9 consistently increase myelination**



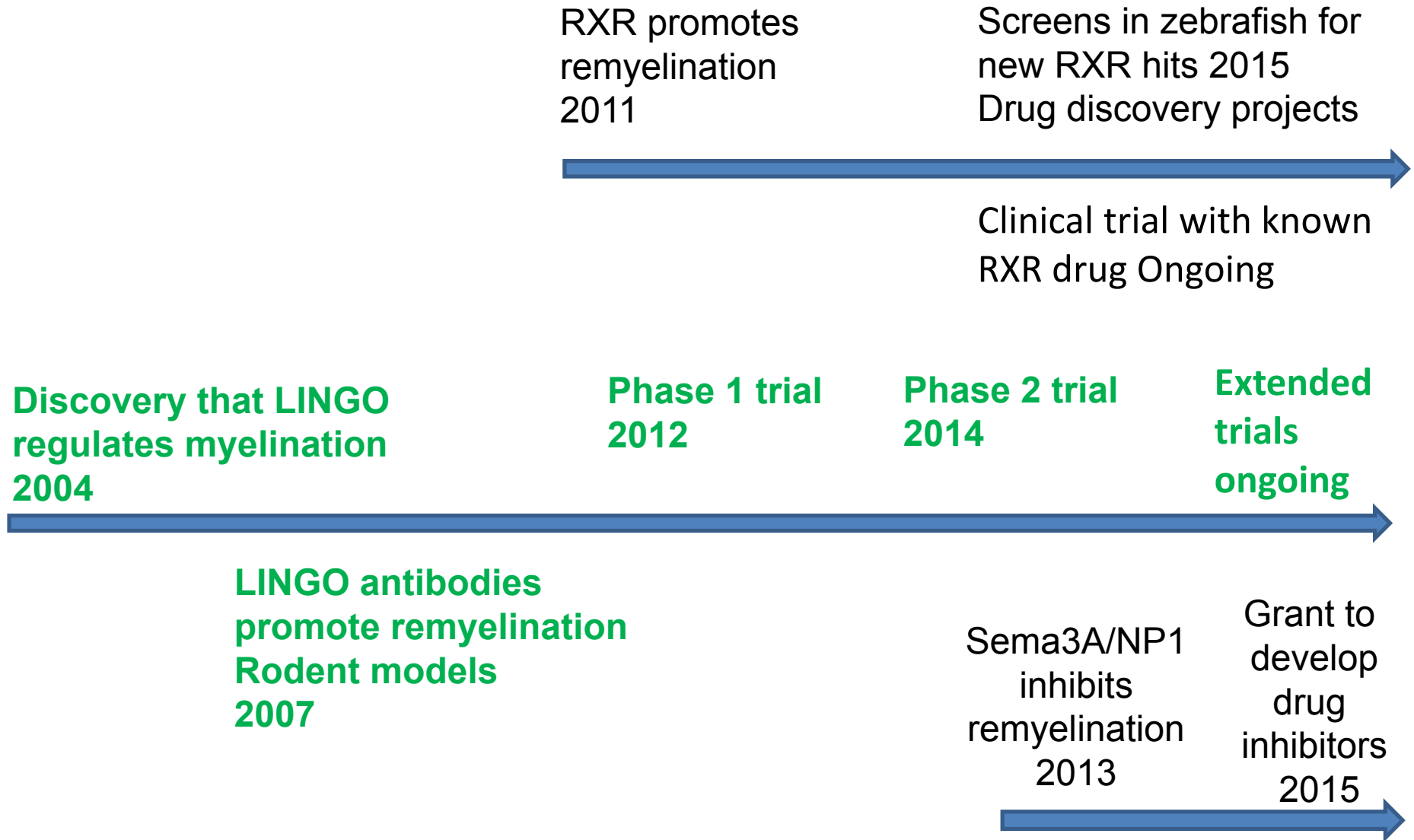
## Ongoing work

How do drugs promote myelination?

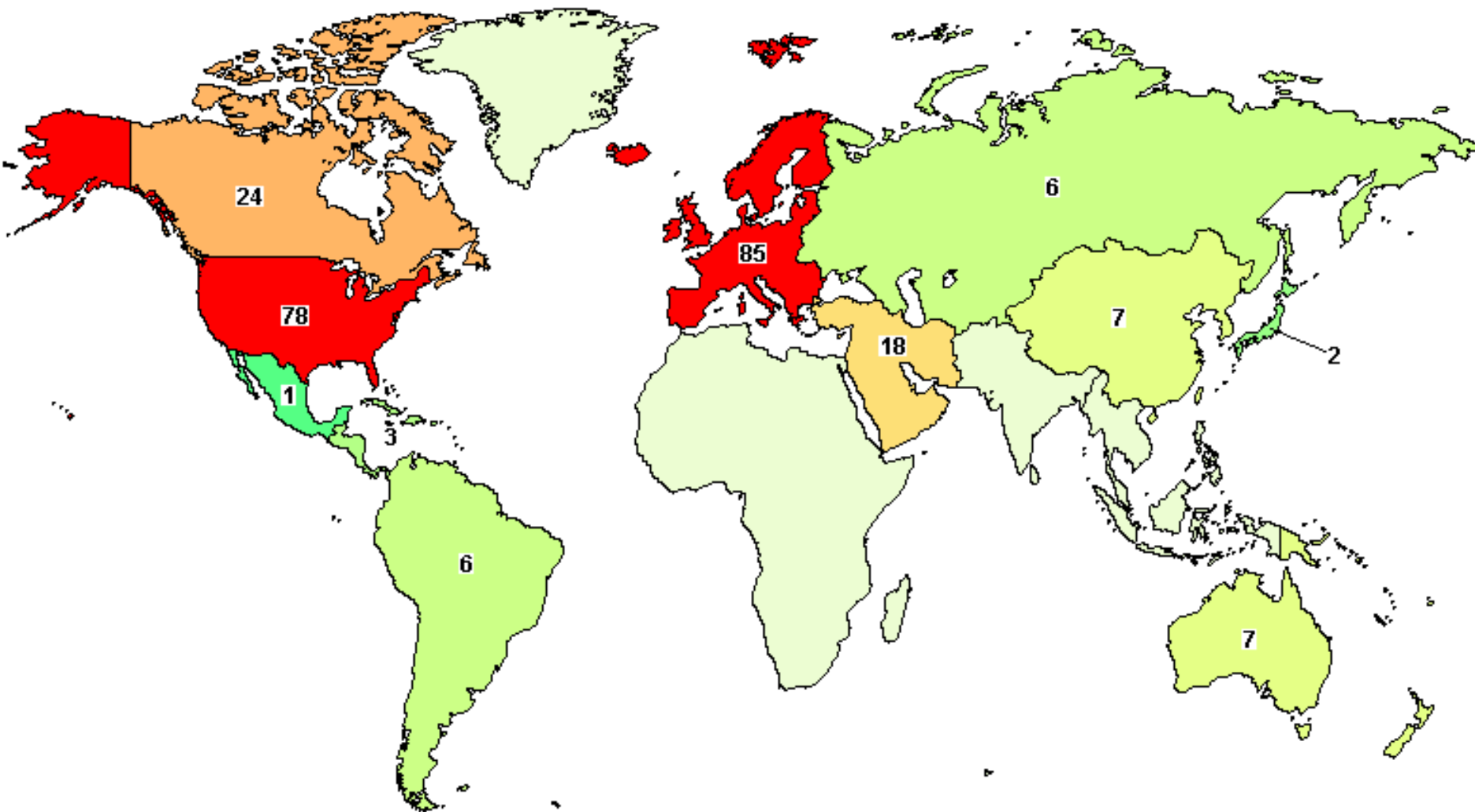
Can drugs promote myelin regeneration?

Do drugs work in mammals and on human cells?

# HOPE!



## Targetting progressive MS is a global research priority



**194 trials to date on Progressive MS- Of those 75 actively recruiting!**

(Information from [clinicaltrials.gov](https://clinicaltrials.gov))

# Thank you – any questions?

Supported by  
**wellcome**trust

**MS**  
Multiple Sclerosis Society

 **BBSRC**  
bioscience for the future

 **The Lister Institute**  
of Preventive Medicine

 Centre for  
Neuroregeneration

 Edinburgh Centre for  
Multiple Sclerosis Research

 **Biogen.**



**MRC** | Centre for  
Regenerative  
Medicine

 **Centre for  
Regenerative  
Medicine**

 **Shift.ms**