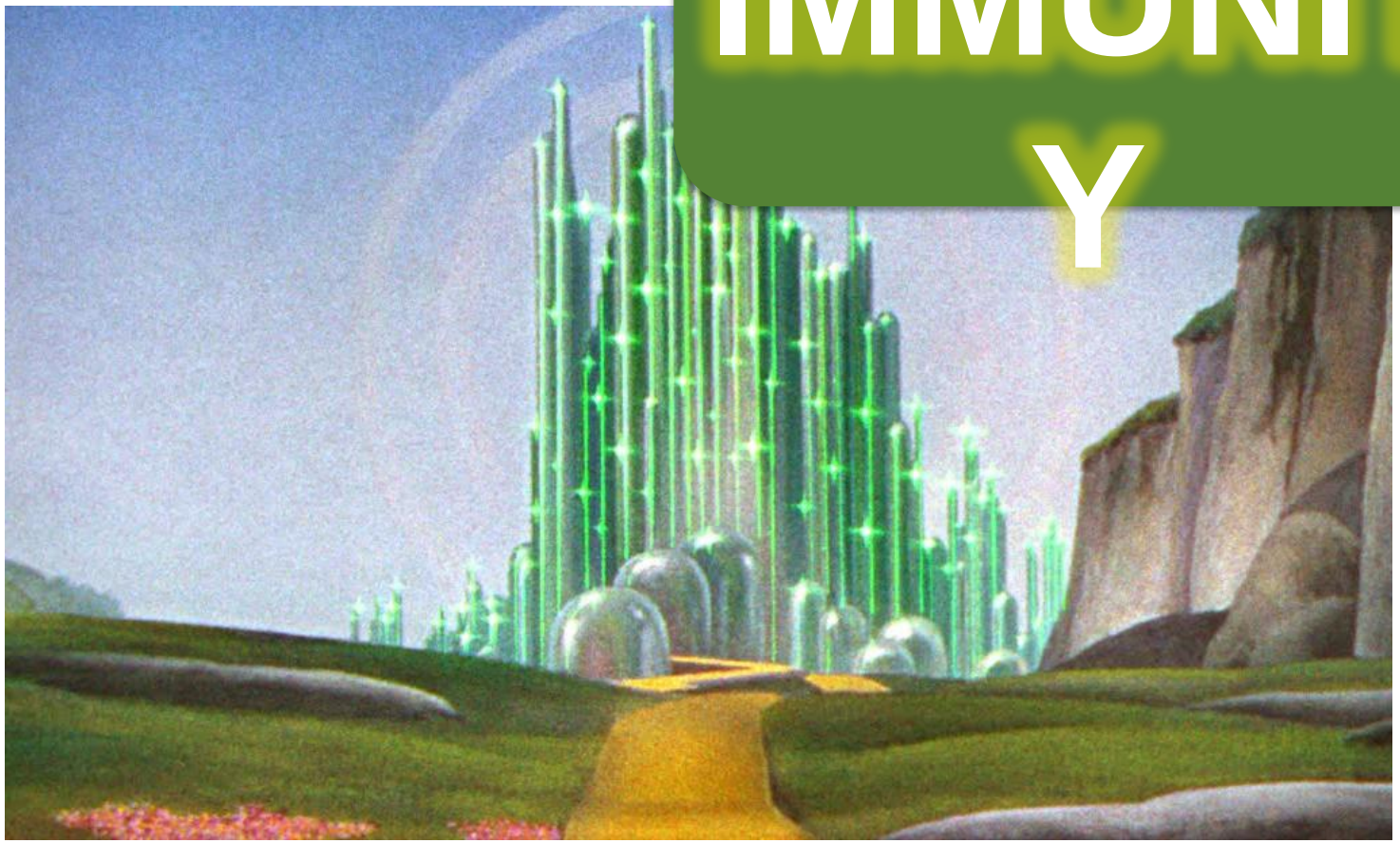
BALANCE

immune

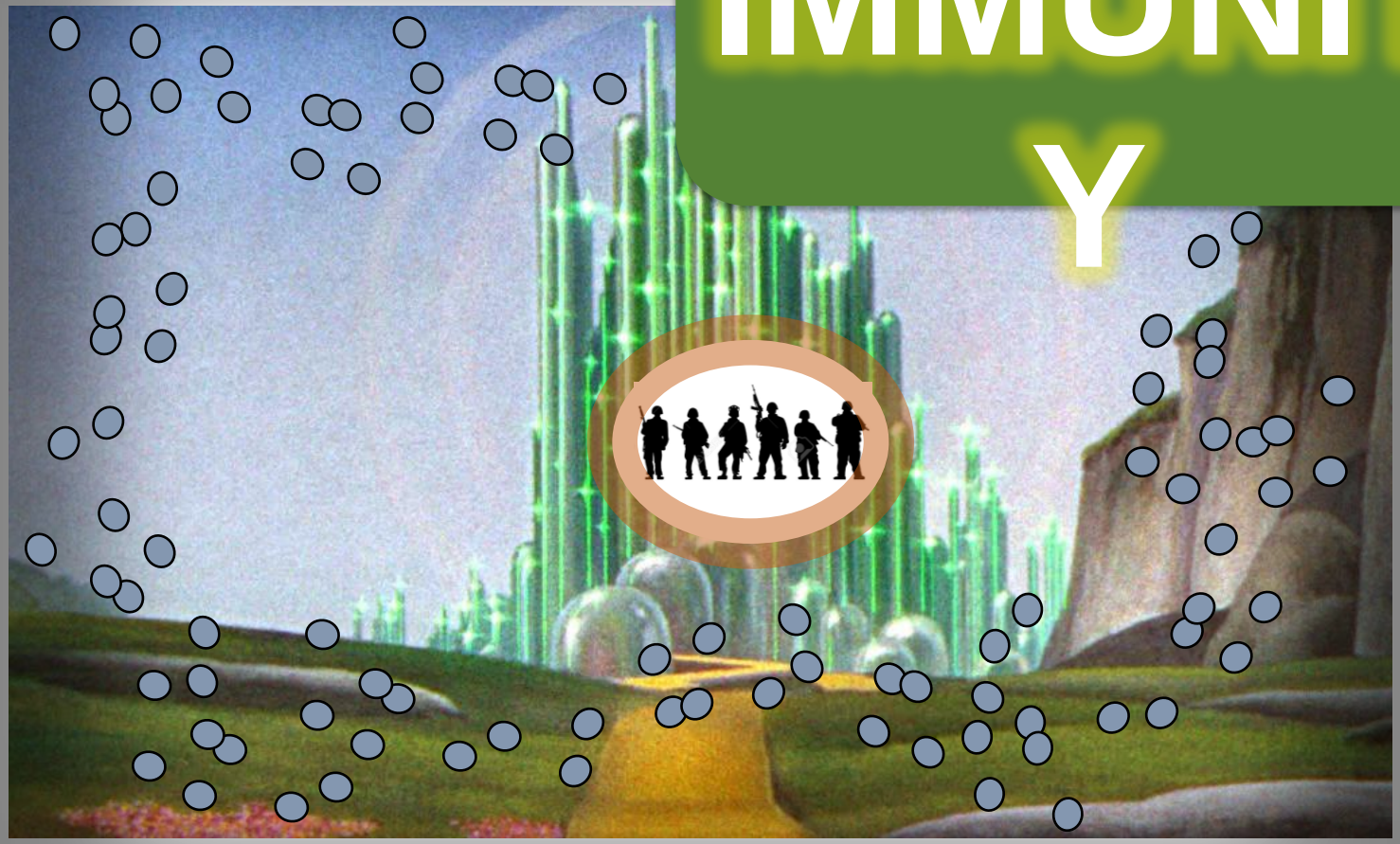
"The consequences of losing your balance"

Prof Anne La Flamme
School of Biological Sciences
Malaghan Institute of Medical Research

IMMUNITY

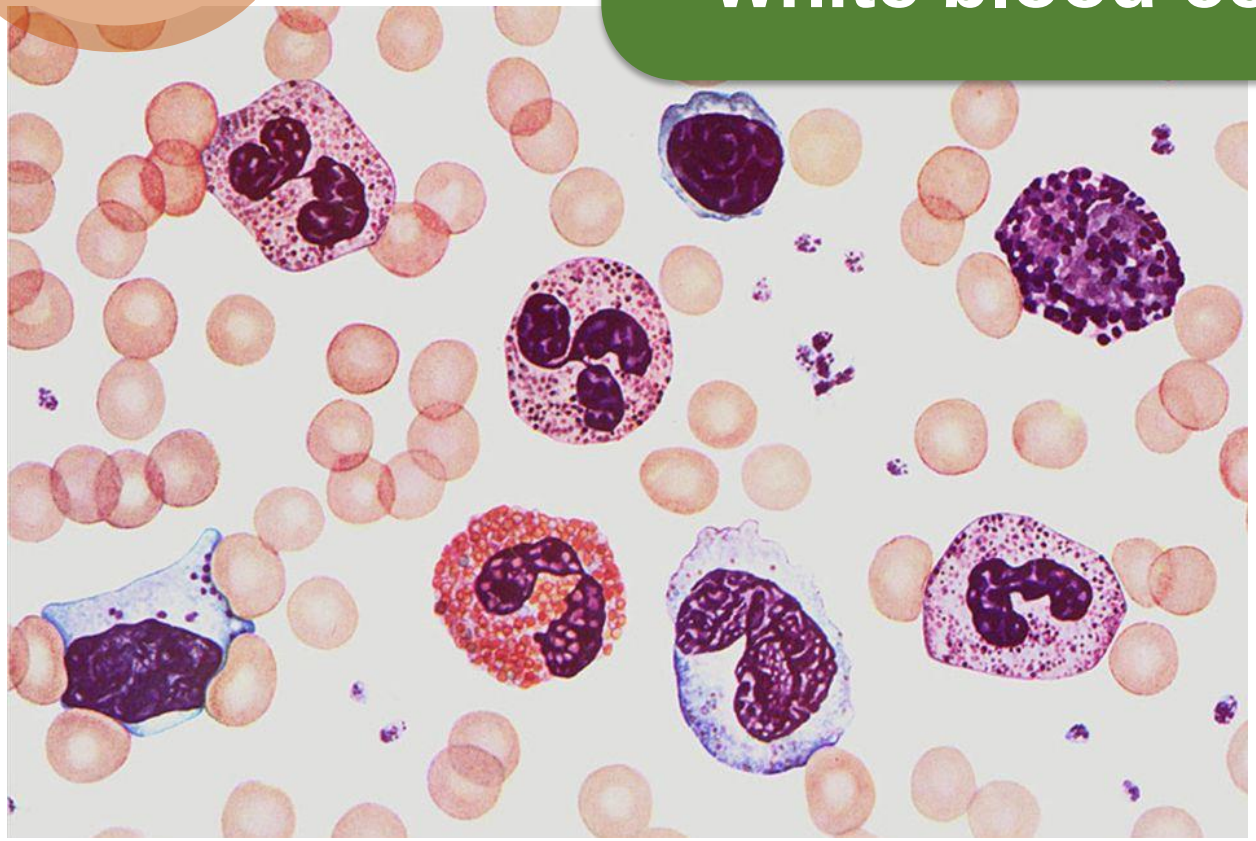


IMMUNITY



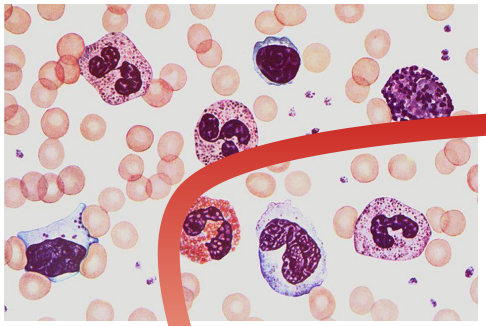
WBC

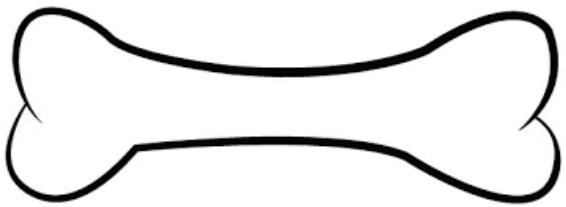
white blood cells



What is immunity and how good is it?

immunity

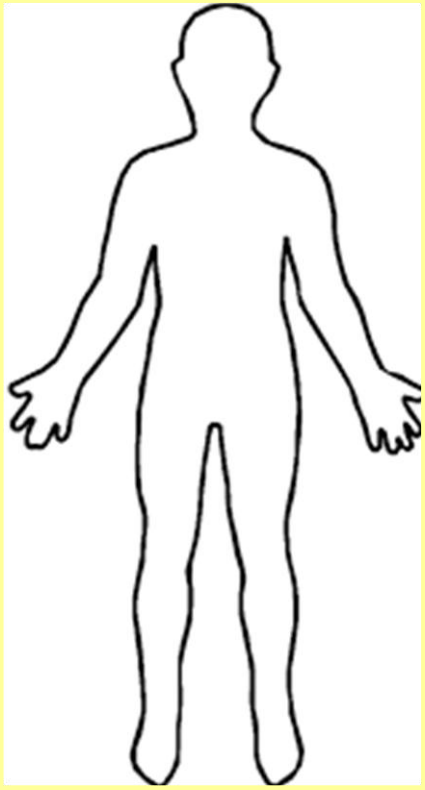




- Recognize the enemy
- Act fast
- Neutralize the enemy
- Minimize damage
- Rebuild damaged areas
- Clean up afterwards
- Remember the enemy

immunity

What is immunity and how good is it?



What is immunity and how good is it?

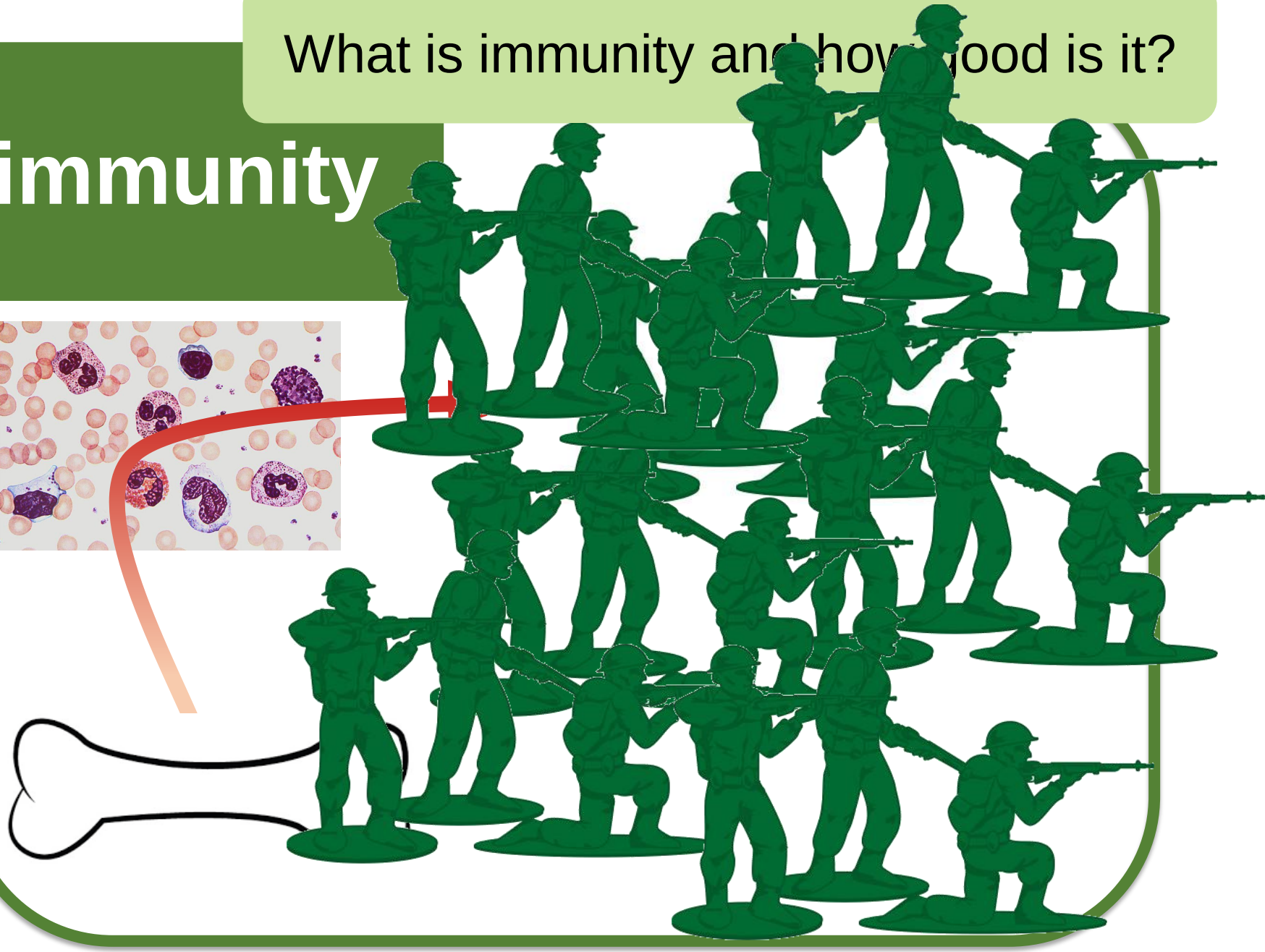
immunity

disease

fail

immunity

What is immunity and how good is it?



What is immunity and how good is it?

immunity

control

- numbers
- location

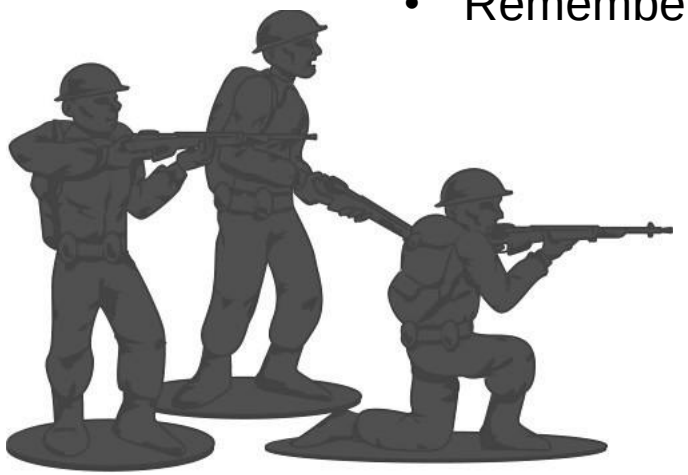
provide

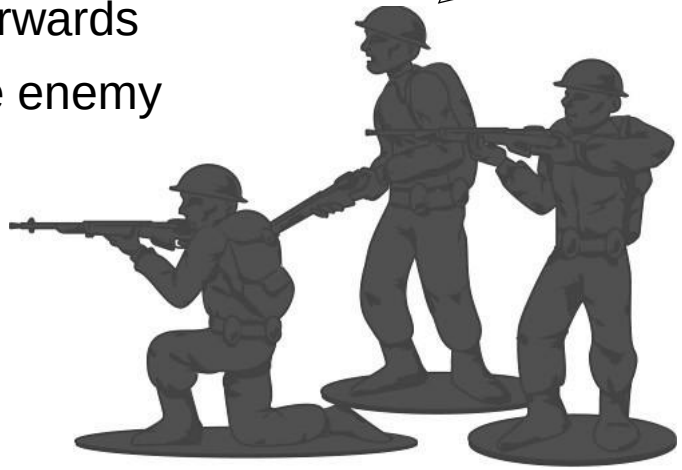
- resources
- training

- Recognize the enemy
- Act fast
- Neutralize the enemy
- Minimize damage
- Rebuild damaged areas
- Clean up afterwards
- Remember the enemy

Is that me?

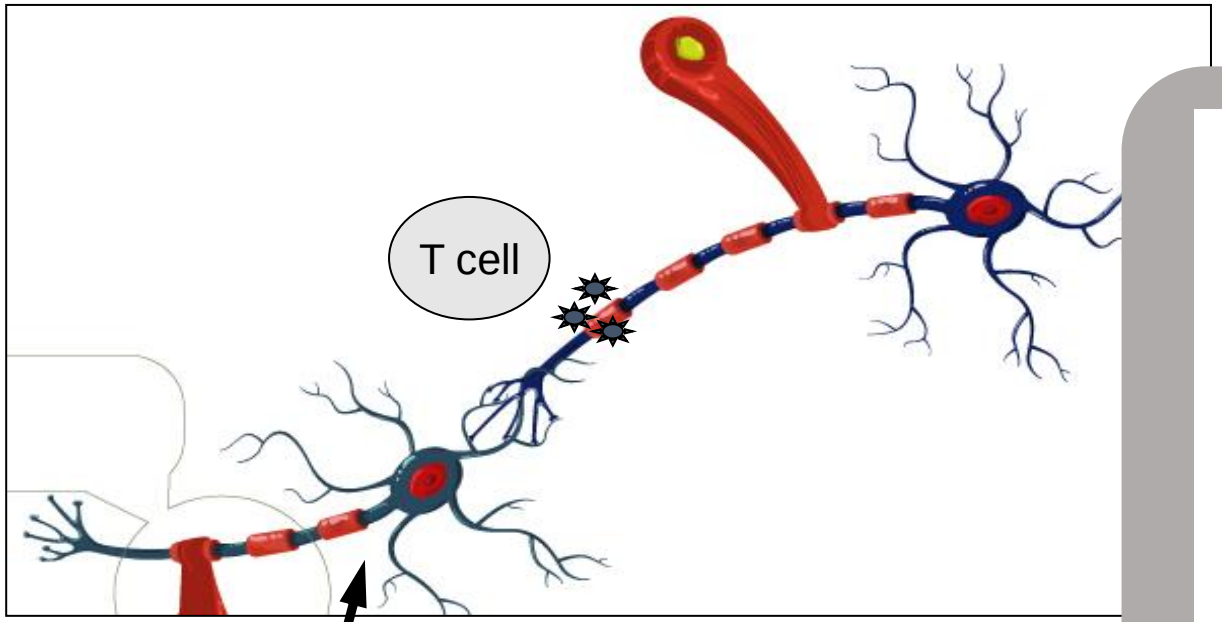
Do those guys look familiar?

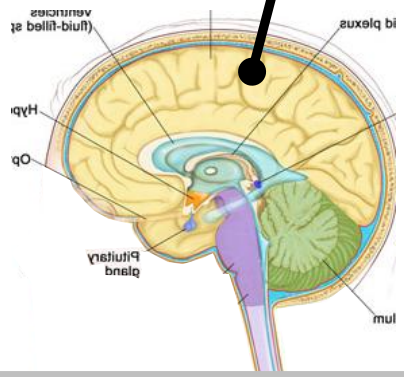




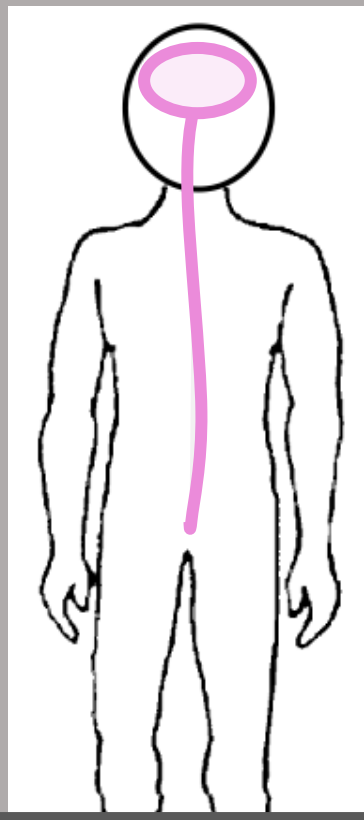
autoimmunity

What is autoimmunity and why does it develop?





immune-driven neurological damage



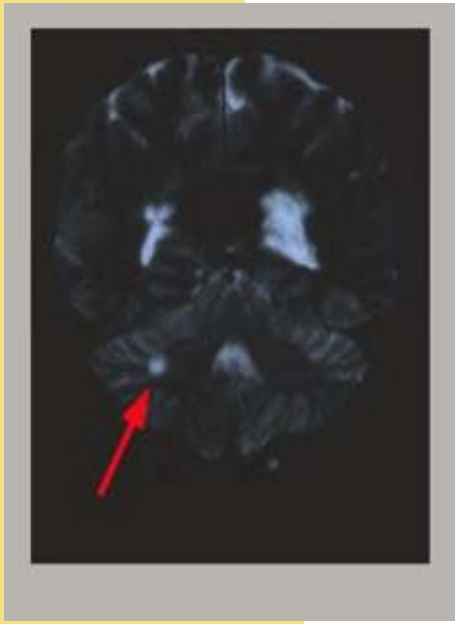
autoimmunity

multiple sclerosis

Outside in?
Only inside?

Multiple Sclerosis (MS)

- ~2.5 million people worldwide.
- In New Zealand: 1 in 1100 (2896 confirmed; 1220 possible)
- Progressive disability affecting vision, coordination, mobility, and cognition. There is no cure.
- Treatments are available for ~50% of patients.



MRI showing a lesion in the brain

neurodegenerative

no cure

urgent need for new therapies

Multiple Sclerosis

Who gets the disease?

- Diagnosis generally occurs between 20 and 40 years of age (rarely <12 or >55 years).
- One of the most common central nervous system diseases in young adults.
- Females are at least 3 times more likely than males to get MS.
- Most prevalent in people from a European background.

young

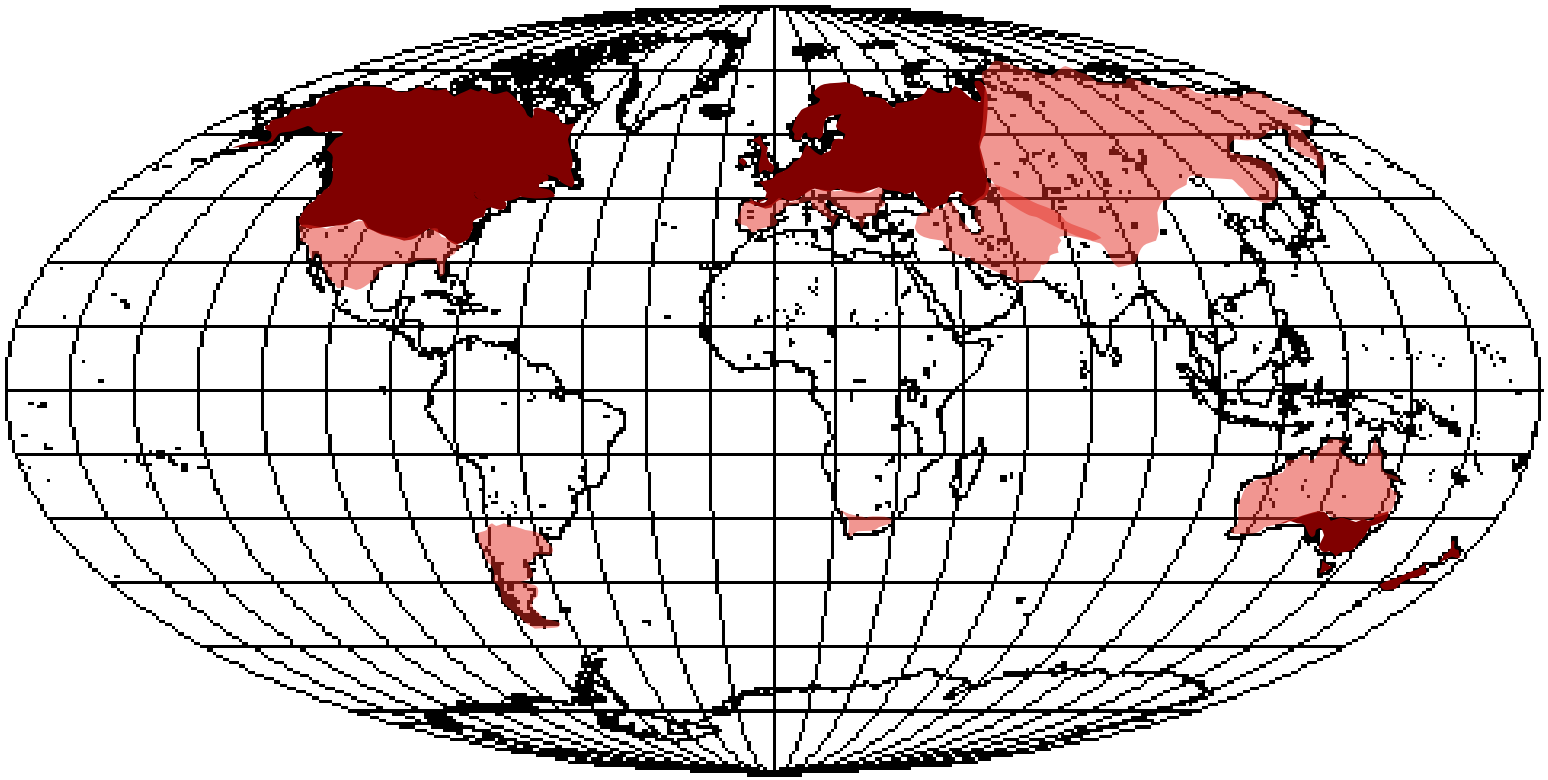
female

Caucasian

Global Distribution of Multiple Sclerosis

High Frequency Zone (30+ per 100,000)

Medium Frequency Zone (5-30 per 100,000)



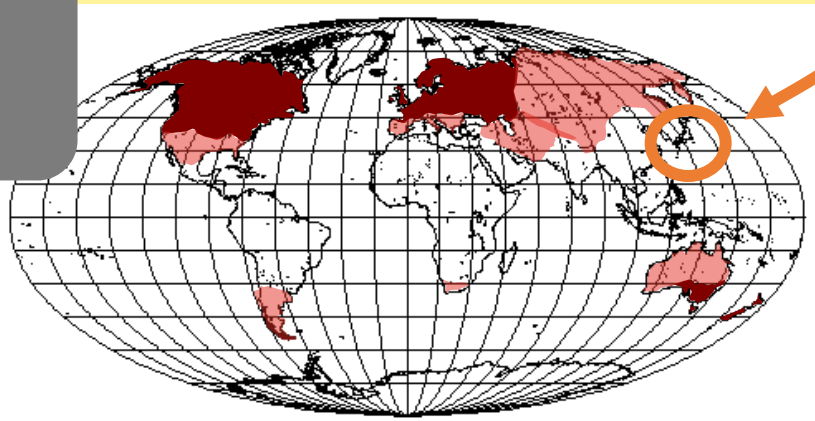
* New Zealand = 71.9 per 100,000

Multiple Sclerosis

On the rise

- New Zealand: In 1986 the frequency of MS in Wellington was 69 per 100,000 and in 2008 the frequency was 86 per 100,000.
- Japan: In 1974 there were ~500 cases of MS in Japan. Today there are more than 12,000.

diet?



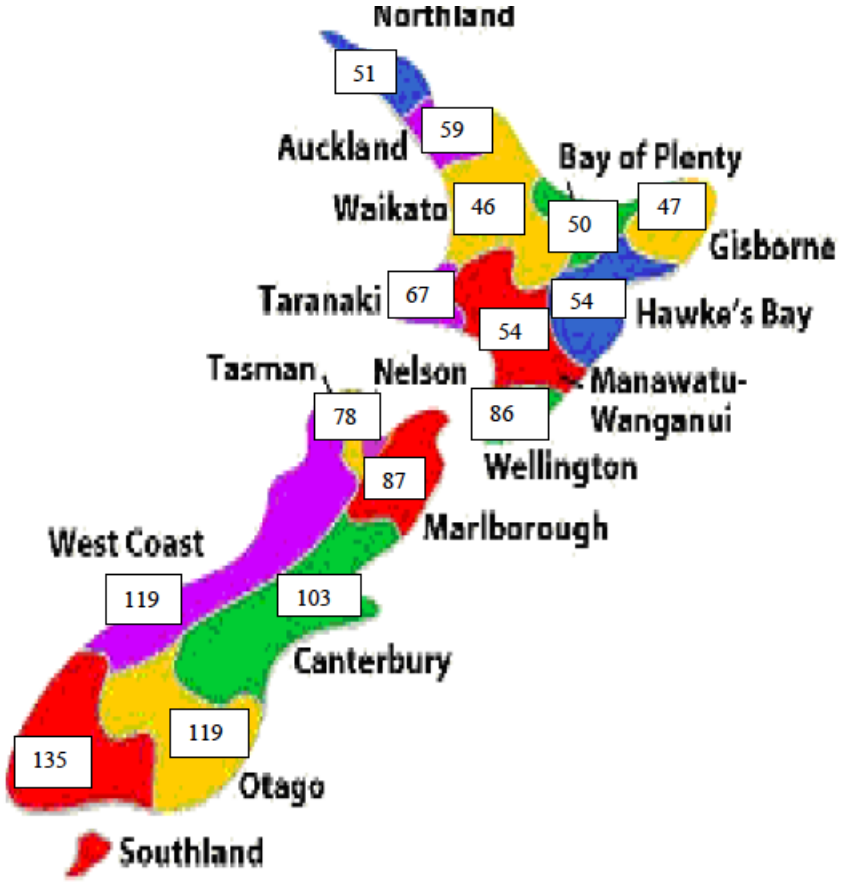
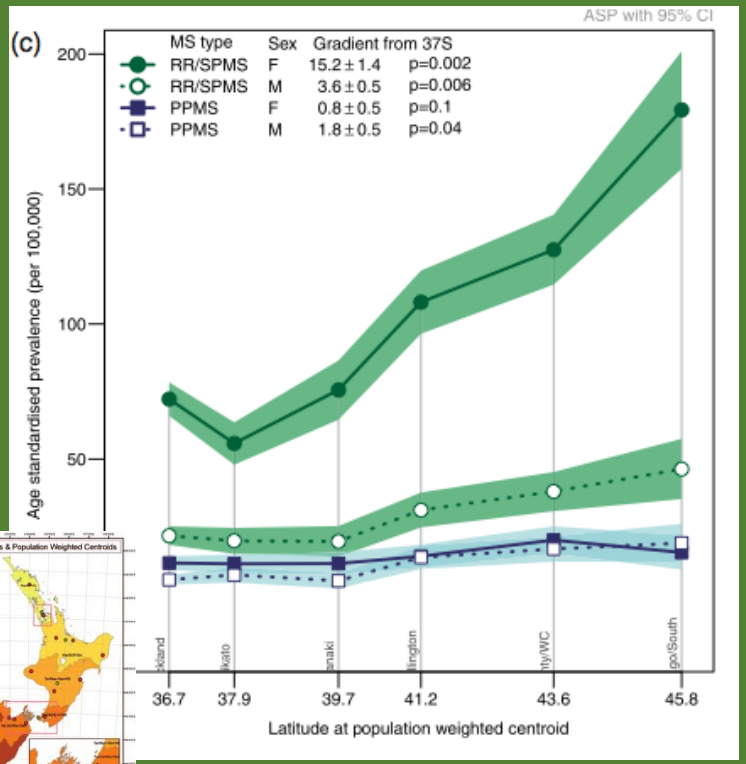


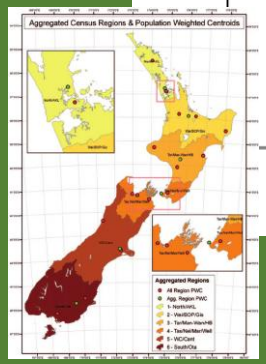
Figure 1.

These results confirm a latitudinal gradient in prevalence, with the age-standardised prevalence increasing from North to South. The latitudinal gradient is shown below (Figure 2).

Ref: Taylor. MSSoNZ. 2008 Prevalence study

MS in New Zealand





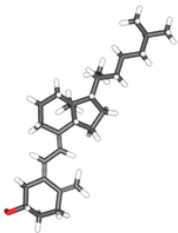
Taylor. 2010. *MSJ*. 16:1422.

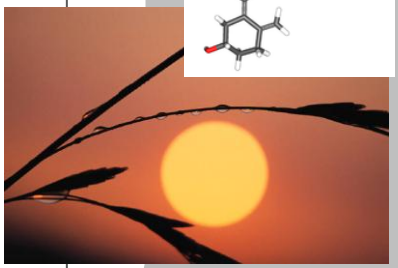
What causes MS?

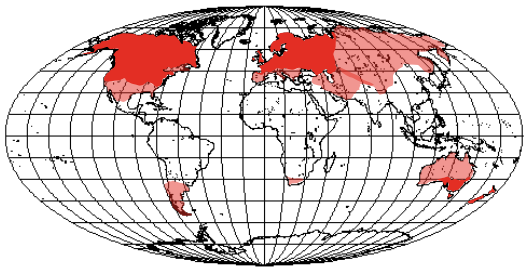
Nobody knows.

genetics
infections
sunlight
vitamin D
sex

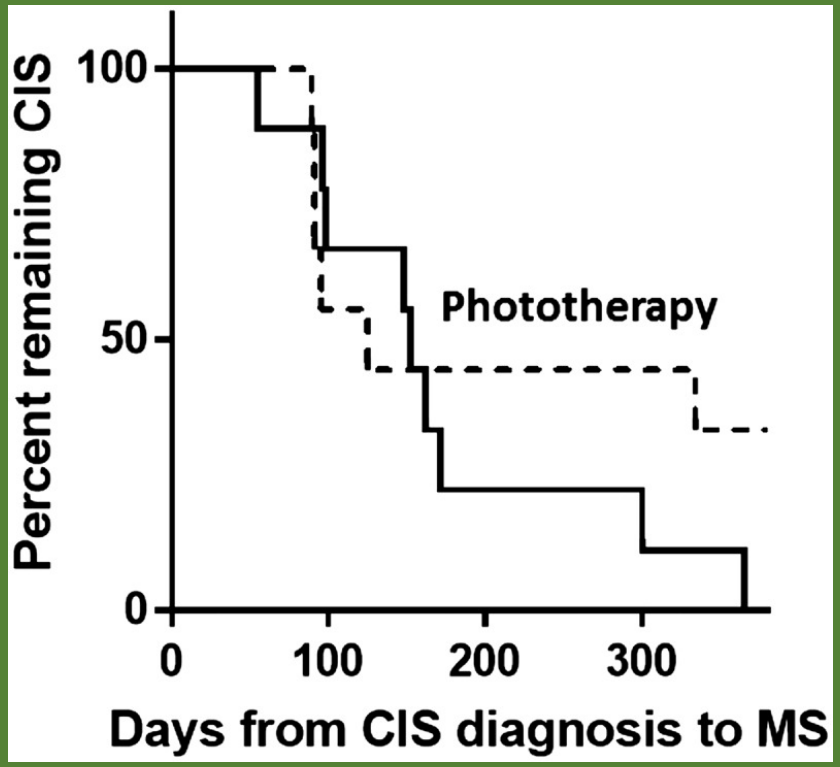
vitamin D







MS in New Zealand



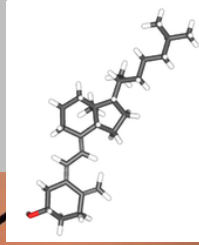
Hart. 2018. MS J Exp Transl Clin.4(2): 2055217318773112.

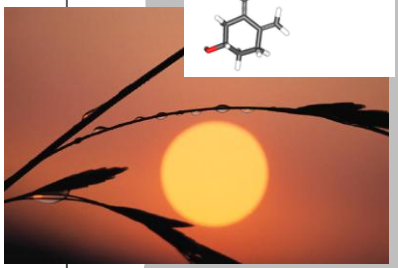
What causes MS?

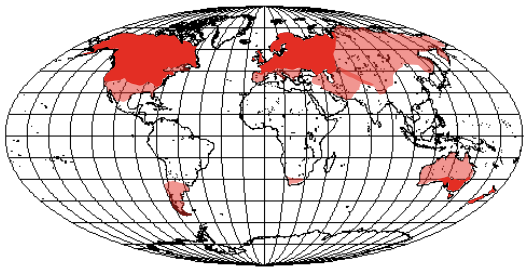
Nobody knows.

genetics
infections
sunlight
vitamin D
sex

vitamin D

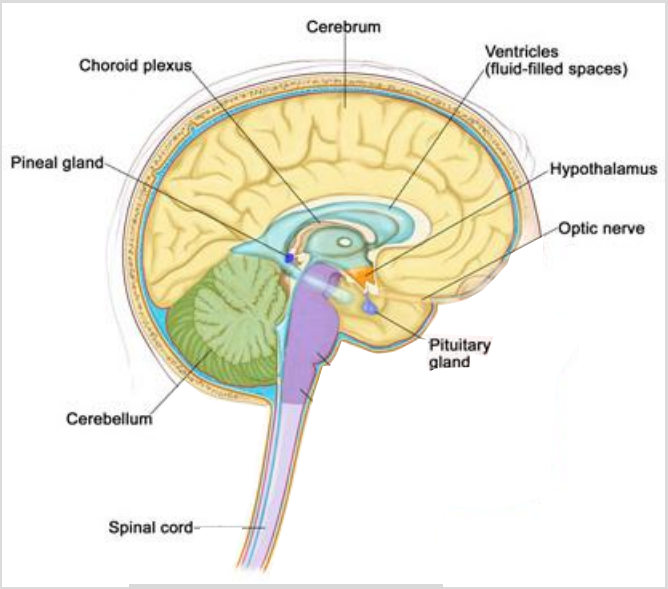


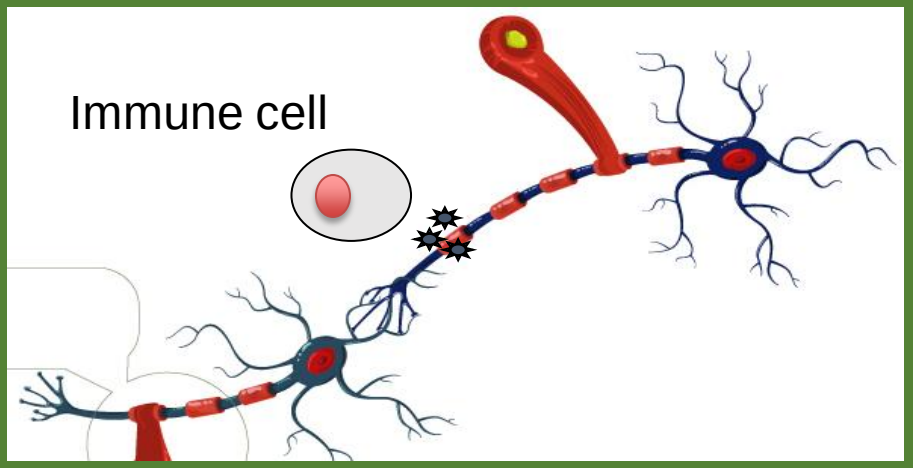


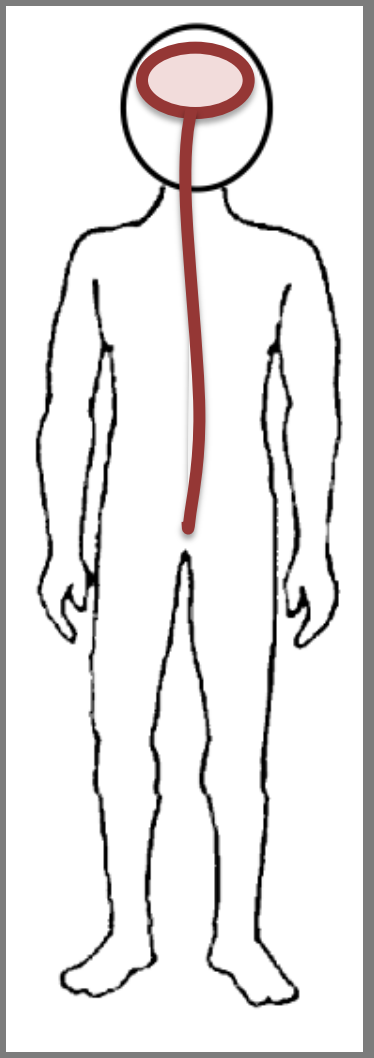


Multiple Sclerosis

Immune-mediated neurological damage

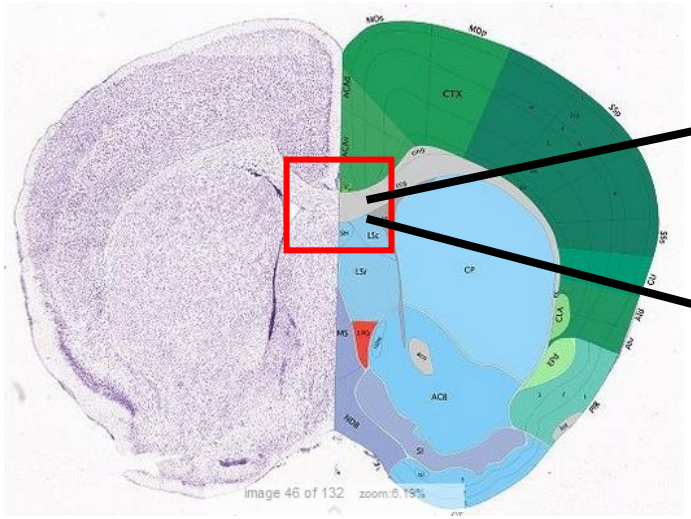


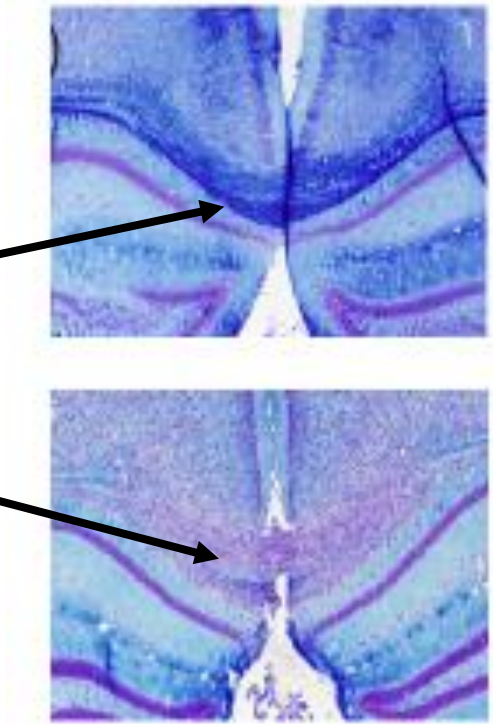




Outside in?
Inside out?

Demyelination during progressive MS





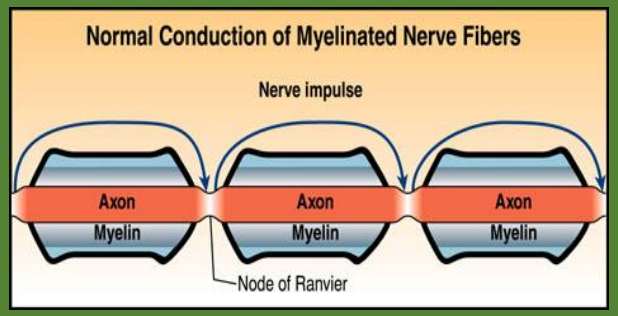
normal myelination

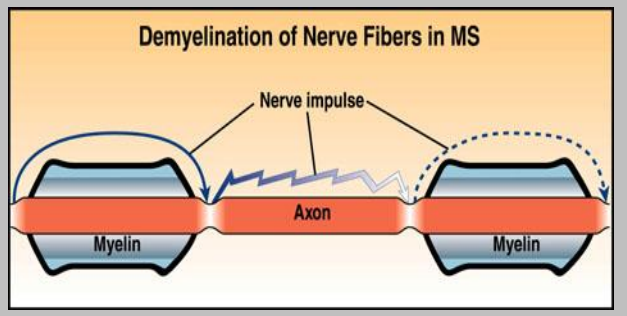
induced demyelination

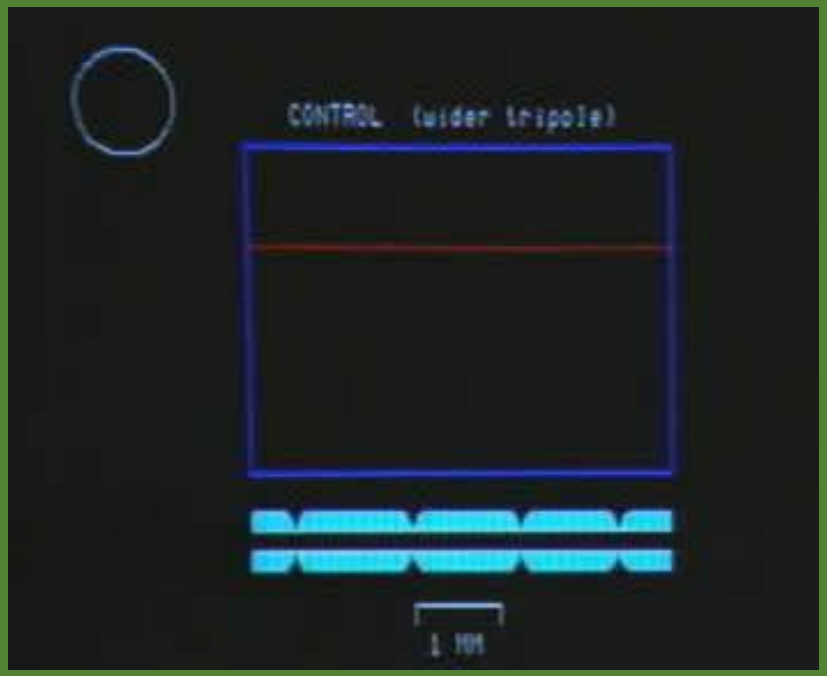
A representative coronal section of a mouse brain showing the region of interest for demyelination indicated by the red box- the **corpus callosum**.

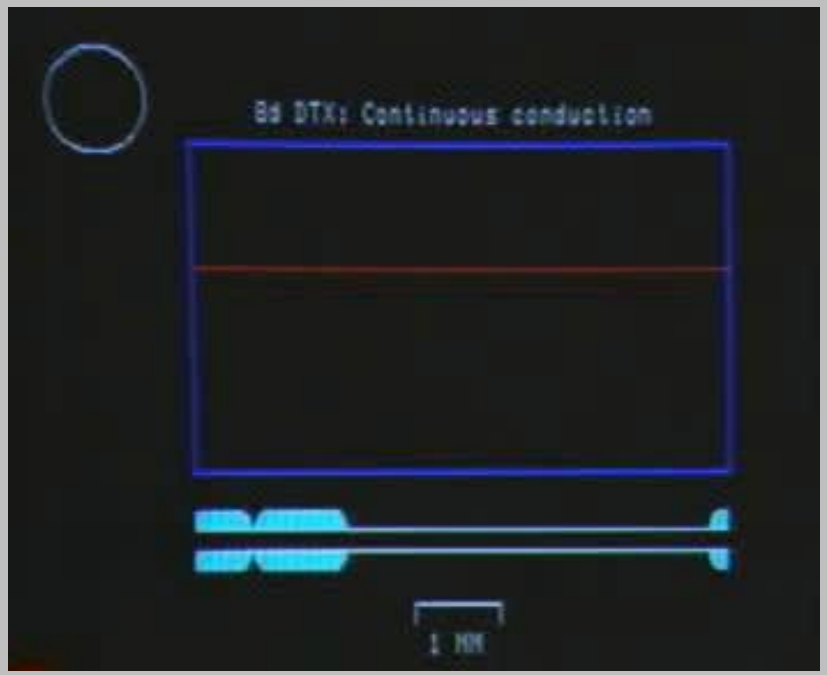
Myelination (dark blue staining) in the corpus callosum in healthy mouse and after inducing oligodendrocyte loss and demyelination with cuprizone.

What is “demyelination”?









Kindly provided by Prof Gavin Giovannoni

Multiple sclerosis

Symptoms and Diagnosis

- There is no simple blood test nor one common symptom.
- >50 different symptoms, which vary in duration and intensity.
- Common symptoms include: tingling, numbness, vision disturbance, vertigo, bladder dysfunction, and **fatigue**.
- Diagnosis relies on medical history, neurological tests, and imaging to identify lesions.

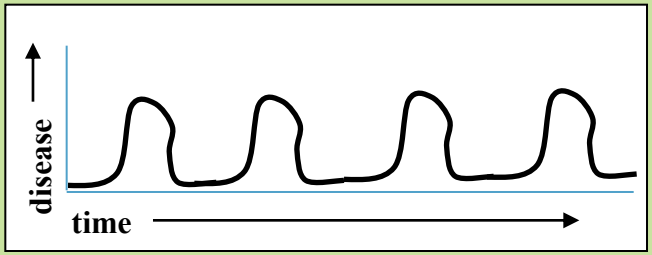
MAURICIO LIMA/ AFP/Getty Image

Ron Levine/The Image Bank/Getty Images

Multiple Sclerosis

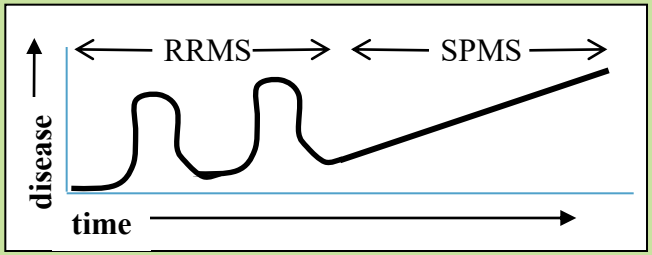
Main Clinical Forms

Relapsing-remitting
(85%)



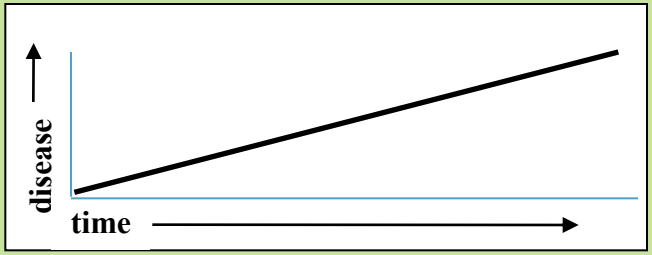
~50%

Secondary progressive
(~50% of RRMS)



~30%

Primary progressive
(~10%)

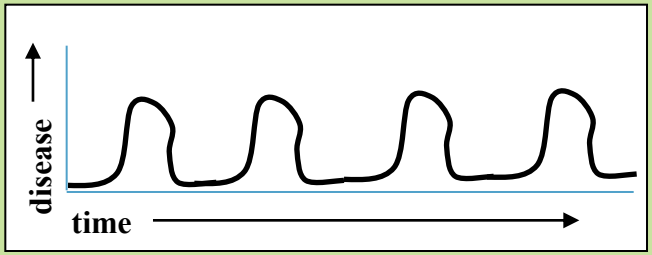


15-20%

Multiple Sclerosis

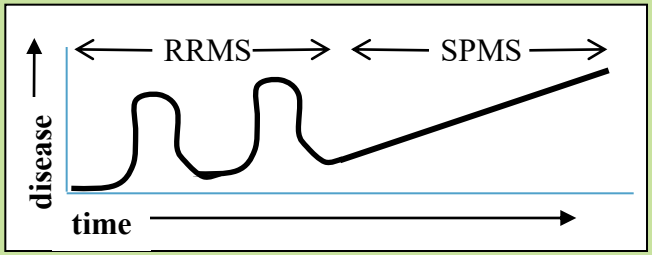
Main Clinical Forms

Relapsing-remitting
(85%)



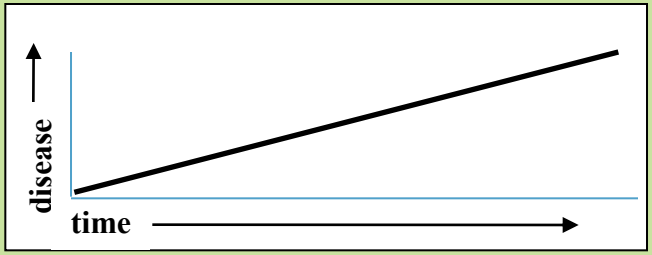
Outside in

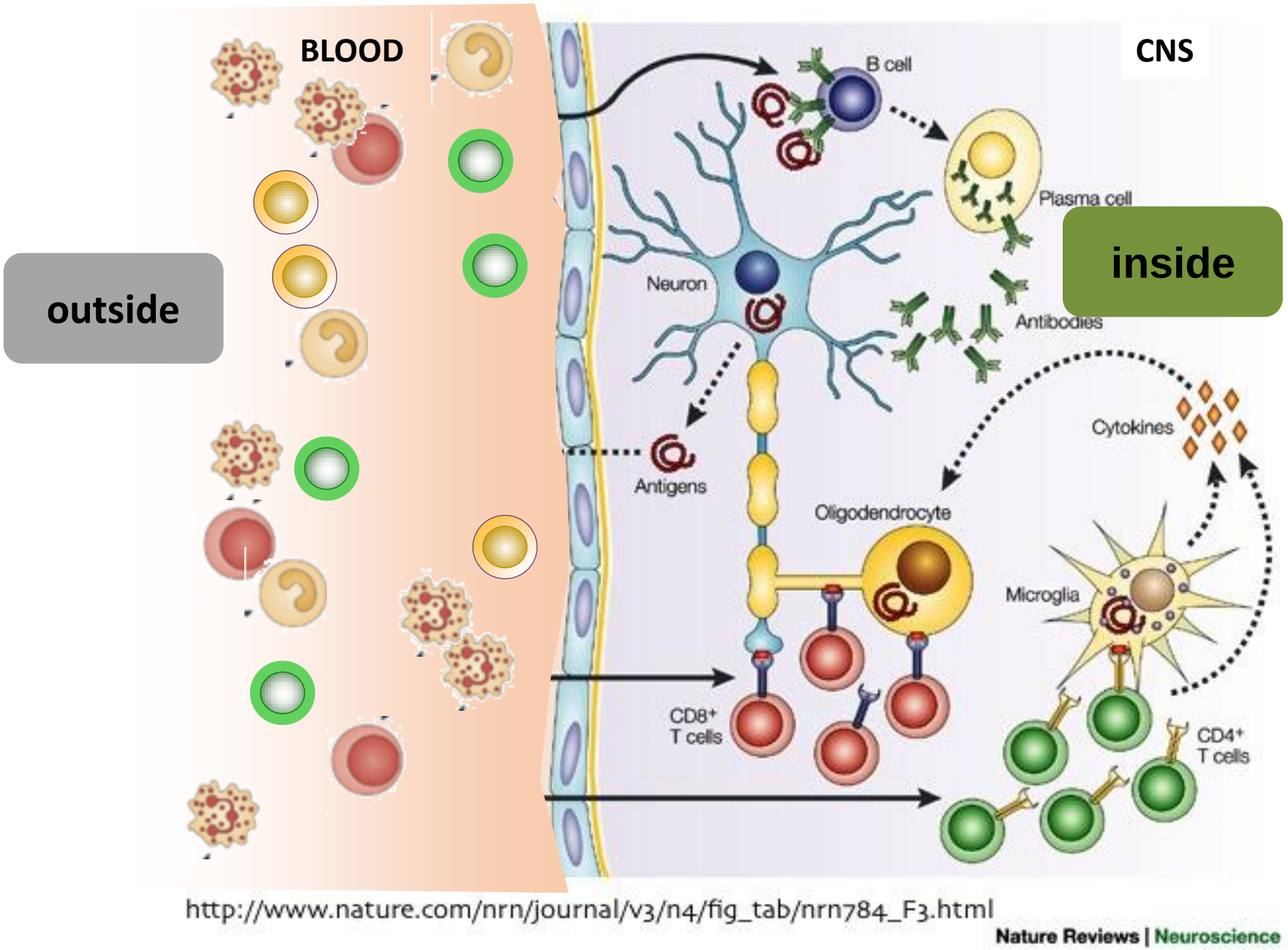
Secondary progressive
(~50% of RRMS)



Inside only

Primary progressive
(~10%)




outside
BLOOD
CNS
inside
B cell
Plasma cell
Neuron
Antibodies
Antigens
Cytokines
Oligodendrocyte
Microglia
CD8+
T cells
CD4+
T cells
http://www.nature.com/nrn/journal/v3/n4/fig_tab/nrn784_F3.html
Nature Reviews | Neuroscience

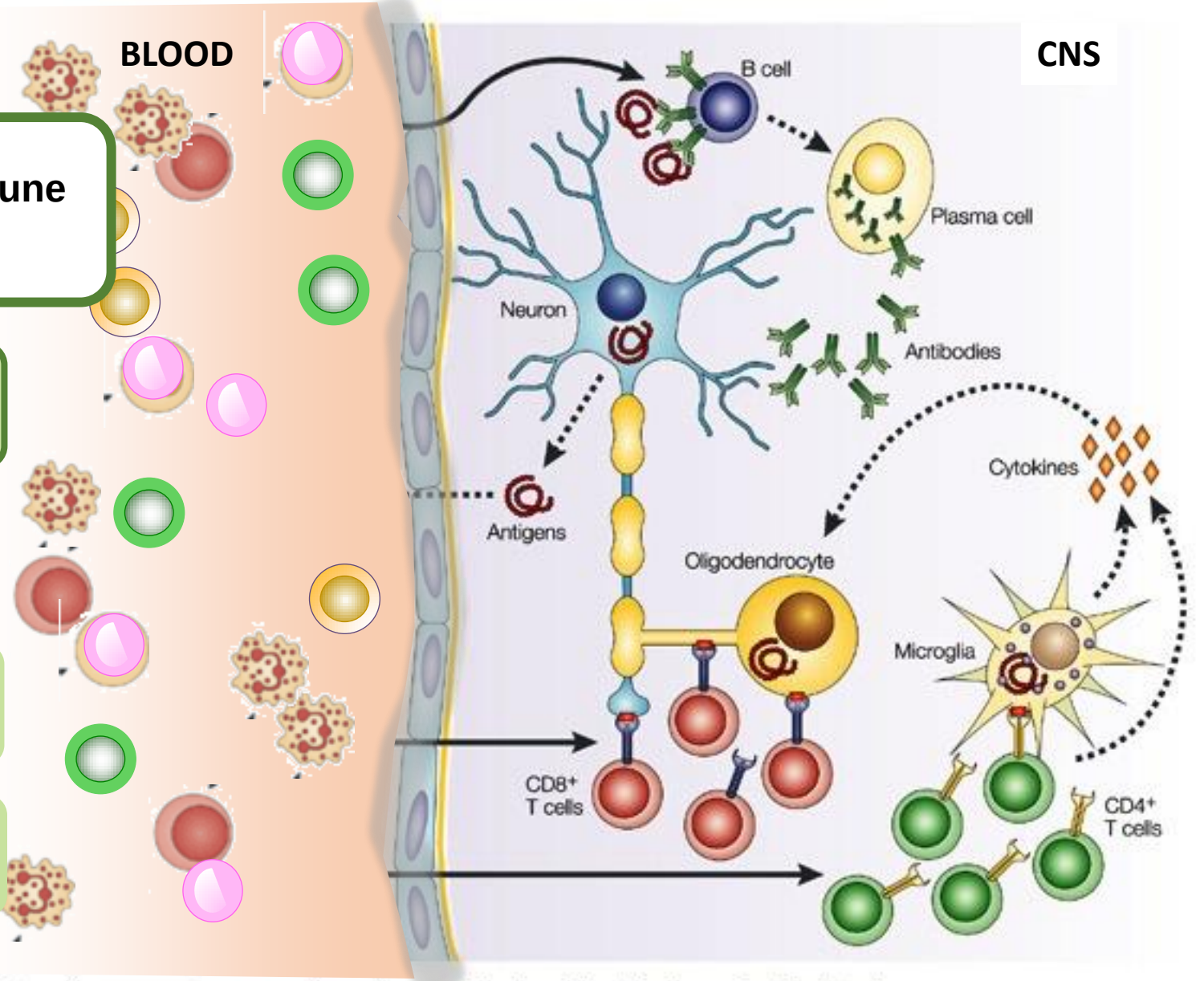
modify immune cells

Copaxone
(glatiramer acetate)

Avonex/Betaseron
(β interferon)

Tecfidera
(fumerate)

Aubagio
(teriflunomide)



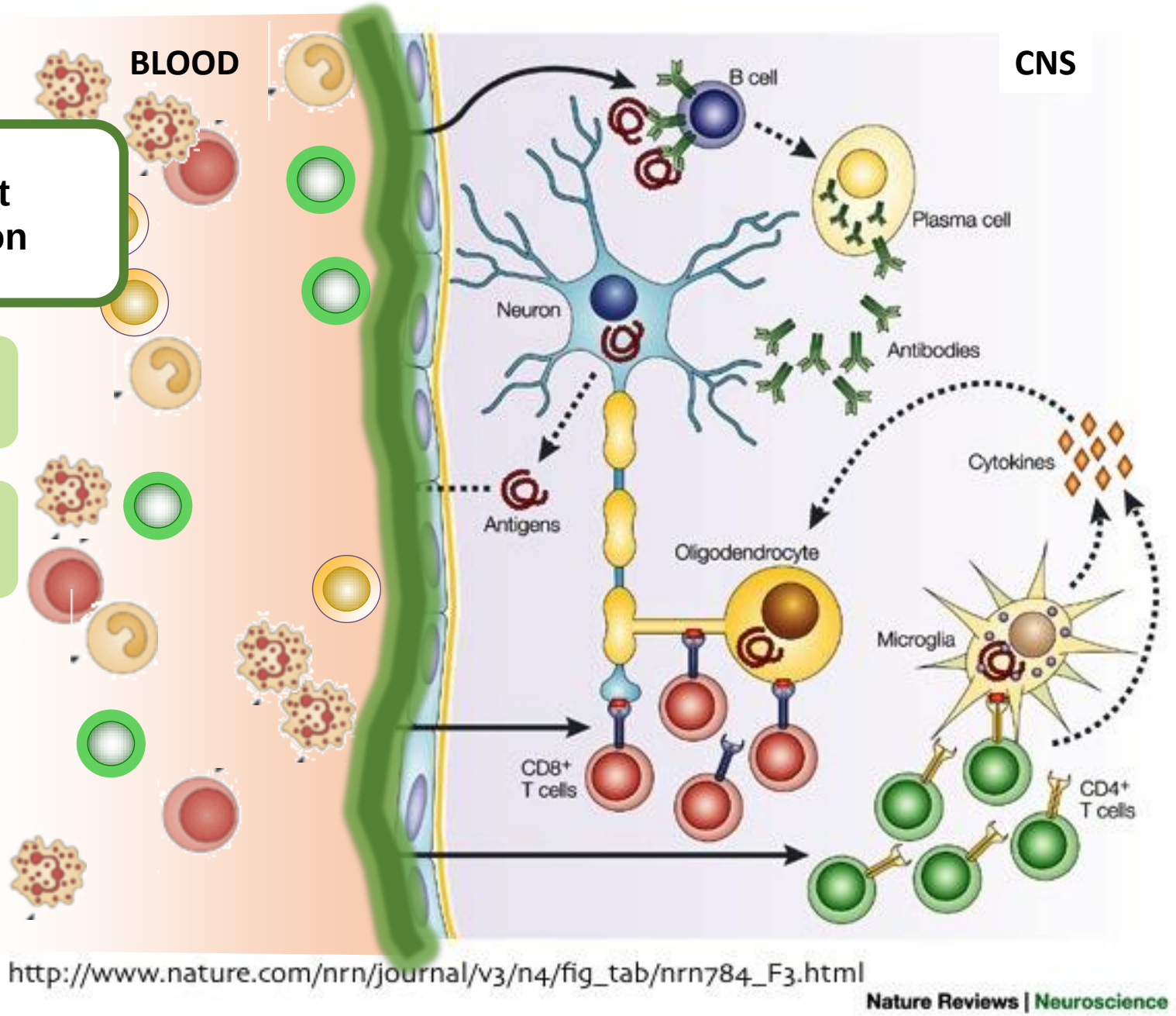
http://www.nature.com/nrn/journal/v3/n4/fig_tab/nrn784_F3.html

Nature Reviews | Neuroscience

prevent migration

Tysrabi
(natalizumab)

Gilenya
(fingolimod)

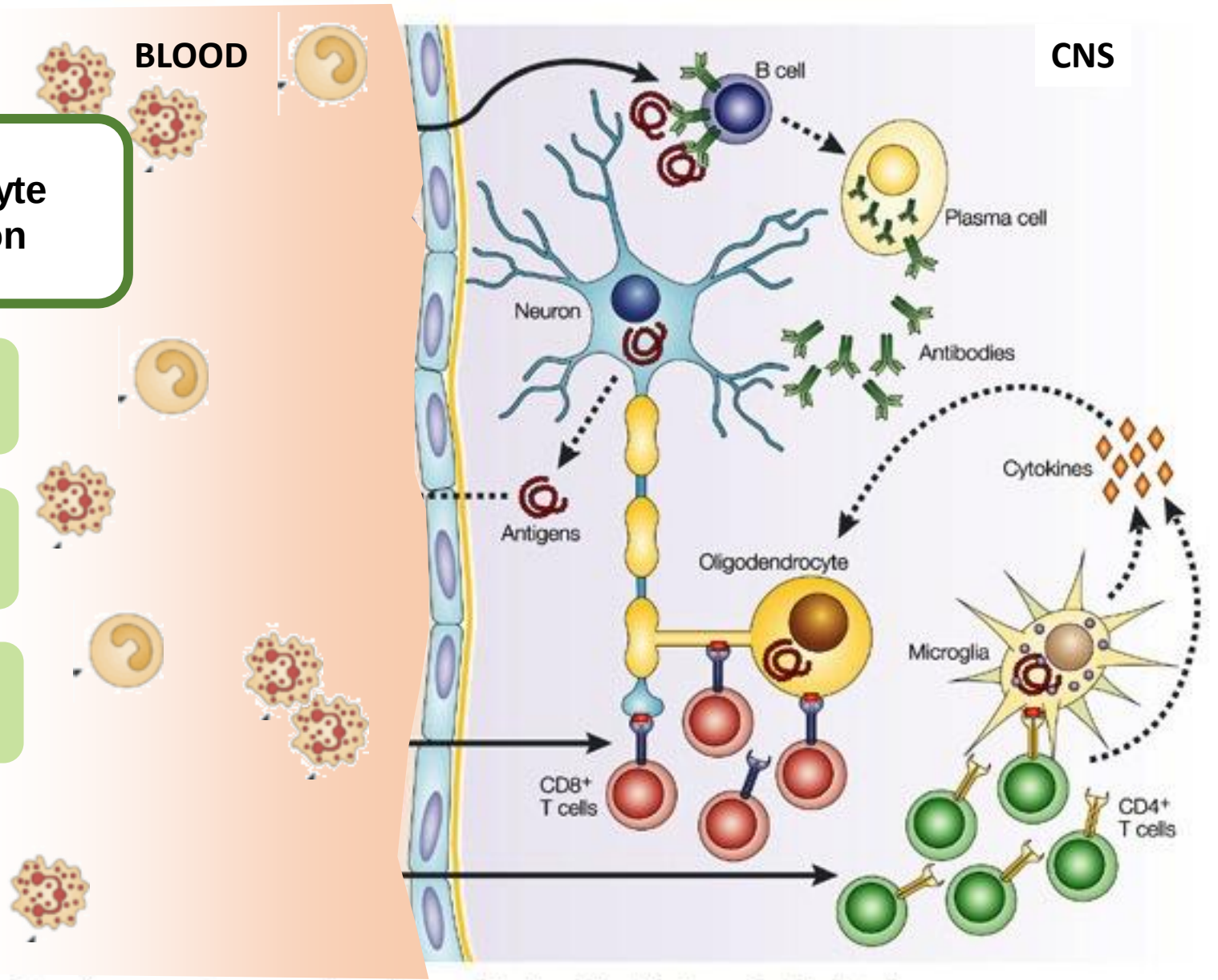


lymphocyte depletion

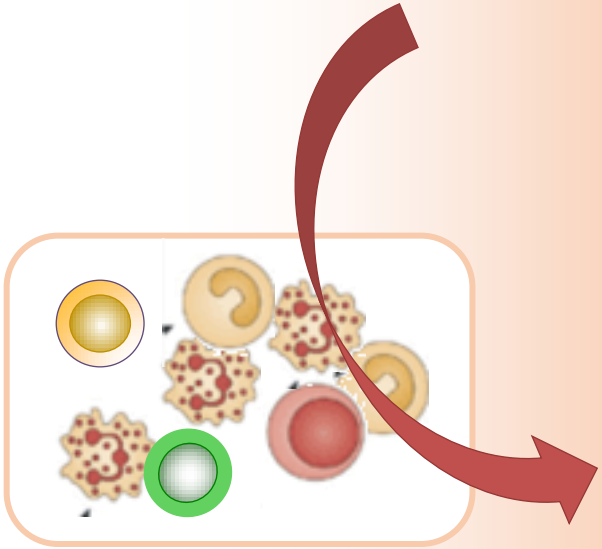
Ocrelizumab
(ocrevus)

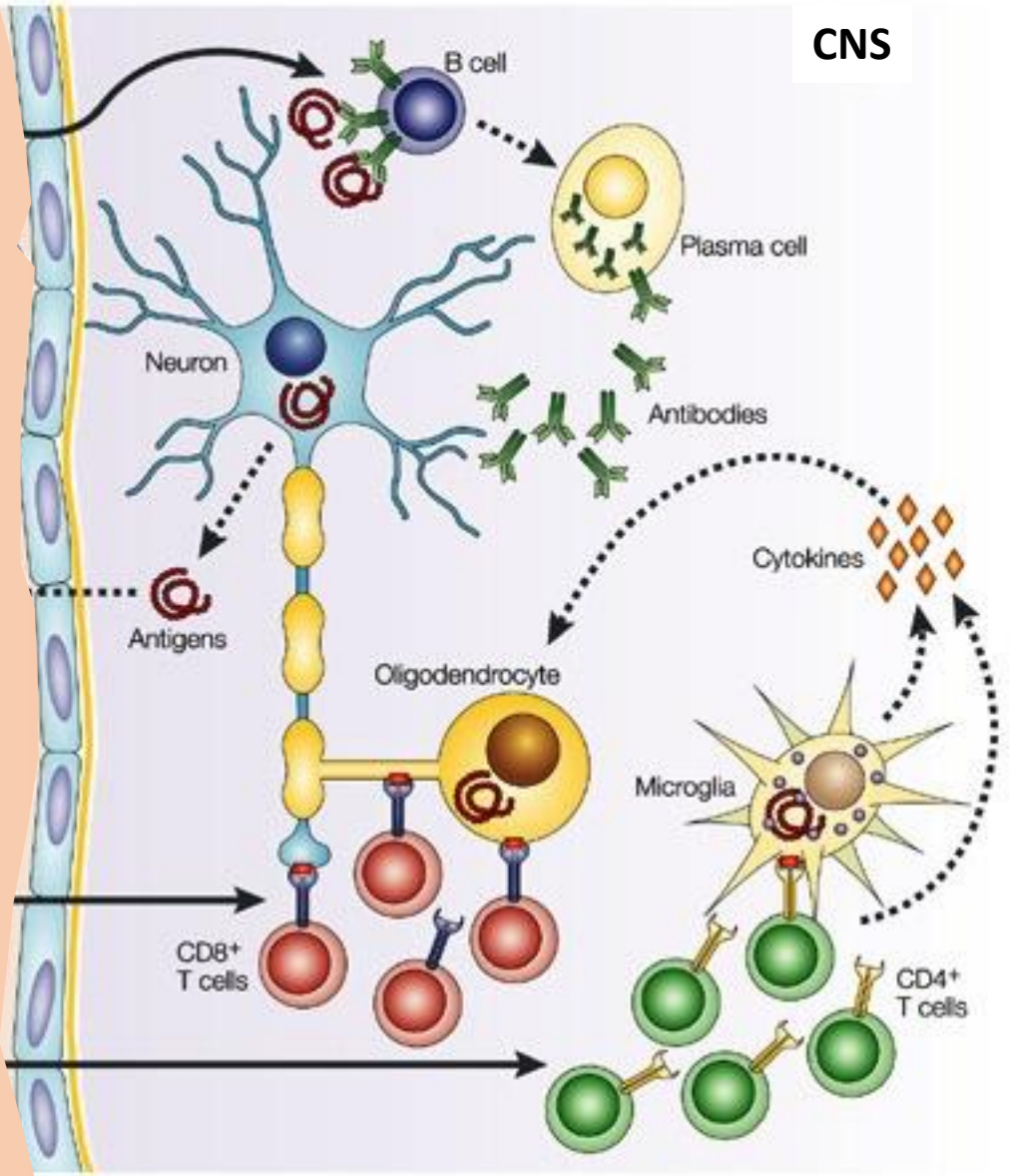
Lemtrada
(alemtuzumab)

Aubagio
(teriflunomide)



autologous hematpoietic stem cell transplantation

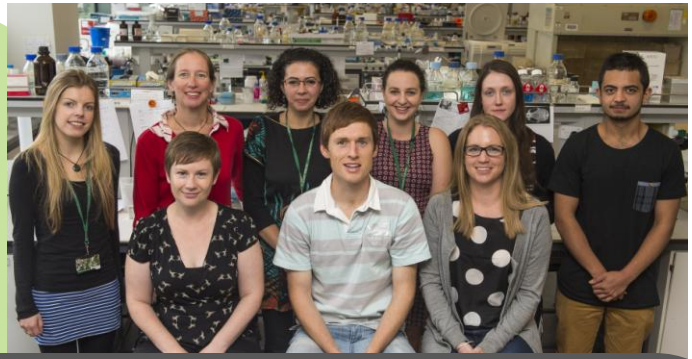




http://www.nature.com/nrn/journal/v3/n4/fig_tab/nrn784_F3.html

Nature Reviews | Neuroscience

Finding new treatments for multiple sclerosis



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CCDHB: David Abernethy

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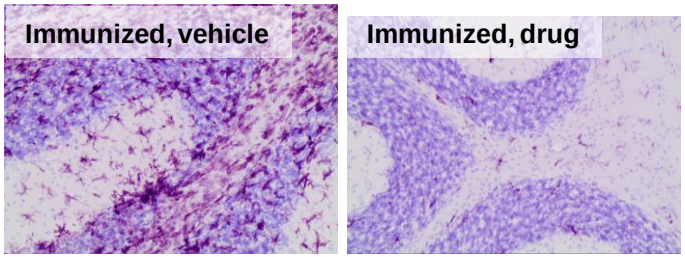
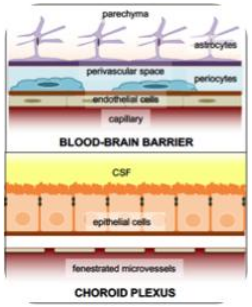
Anti-psychotic drugs: Mode of action and clinical efficacy

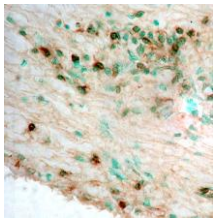


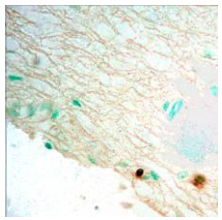
MIS416: harnessing the immuno-modulatory effects of innate cell activation

Blocking invasion with heparan sulphate mimetics



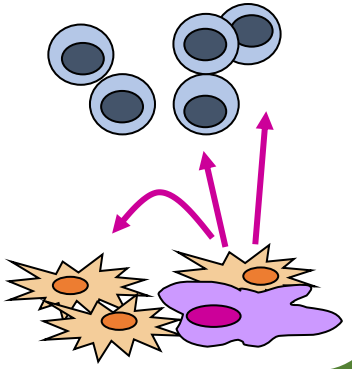
Immunoregulation of MS



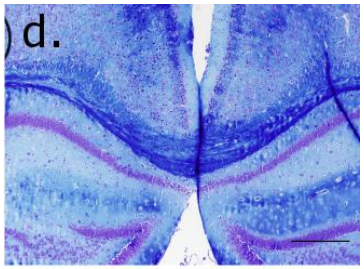


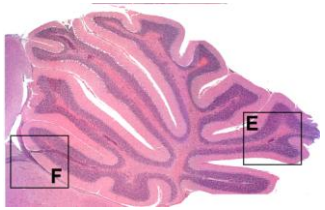
Th2 response regulation of MS

Shaping macrophage and monocyte responses during MS



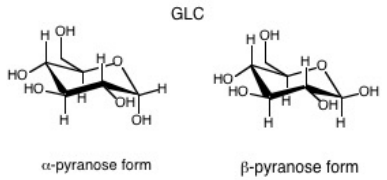
Targeting immune resolution during MS – enhancing repair





Modeling MS pathology: BALB/c model of EAE

Anti-carbohydrate antibodies in MS



Collaborators

VUW - Bronwyn Kivell, Bridget Stocker, Mattie Timmer

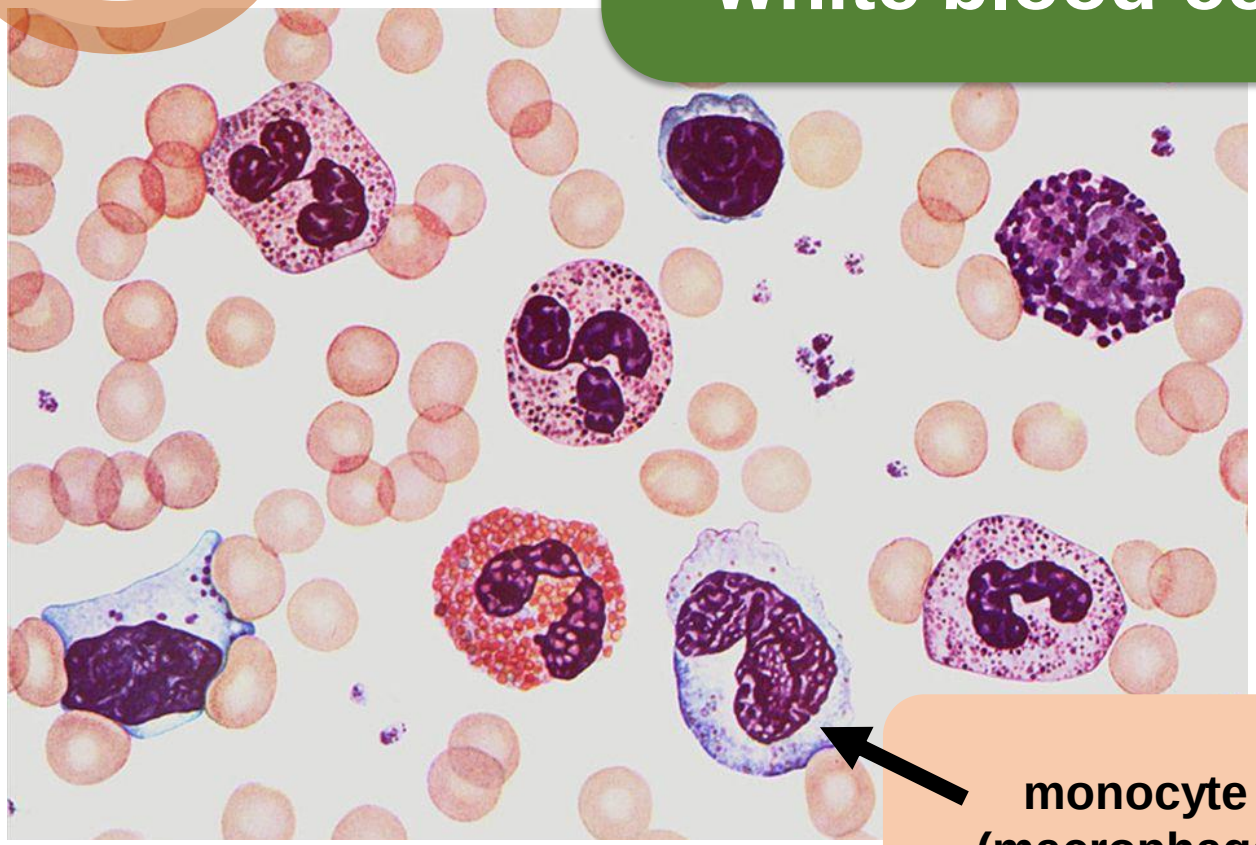
UoA - Bronwen Connor

La Trobe - Jacqueline Orian

CCDHB - David Abernethy

WBC

white blood cells

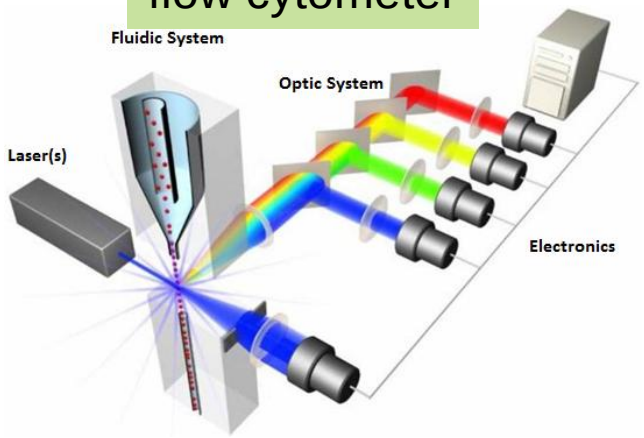


monocyte
(macrophage)

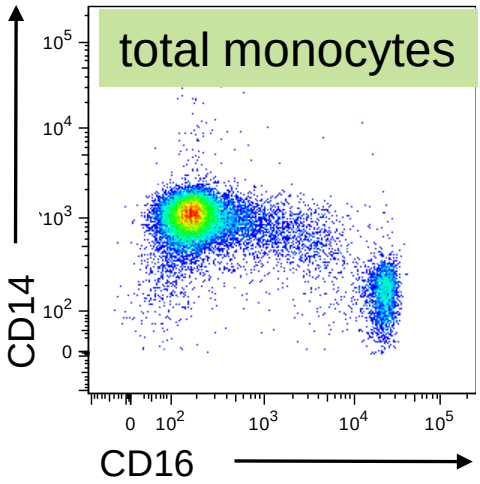
Why macrophages?

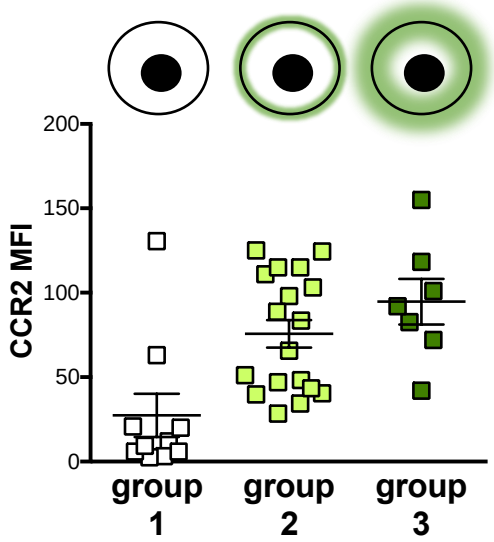
Assessing immune phenotype

flow cytometer



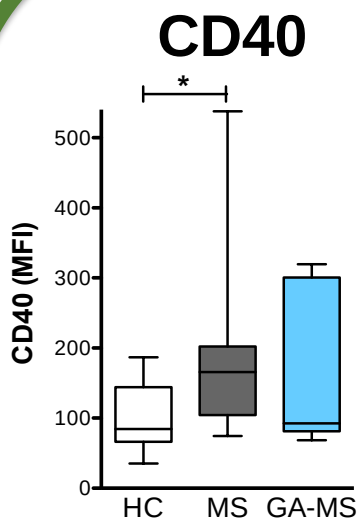
total monocytes

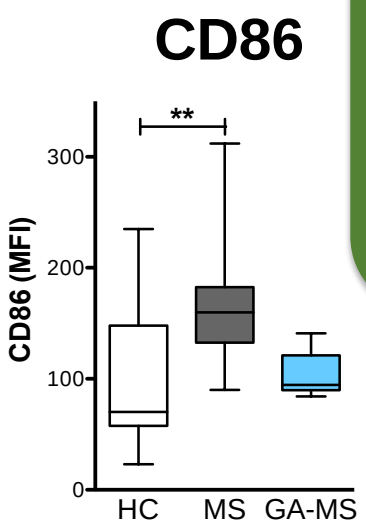


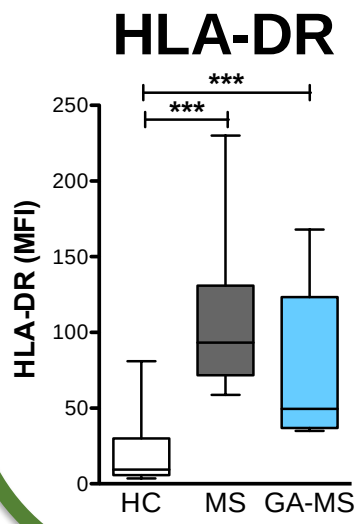


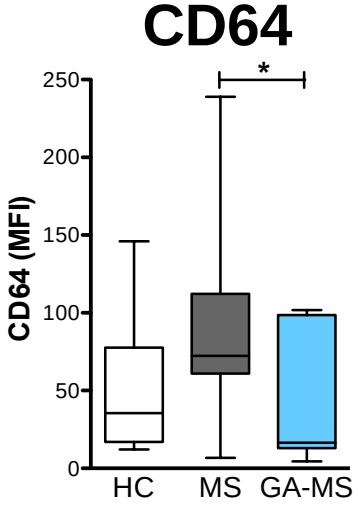
activation marker

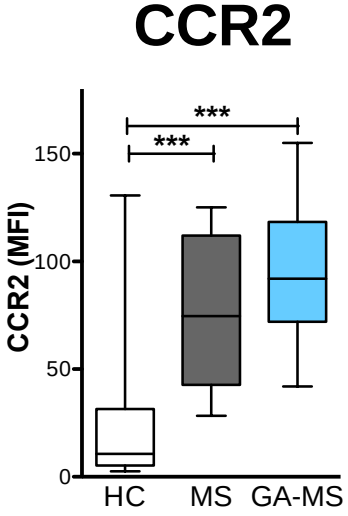
Assessing individual changes







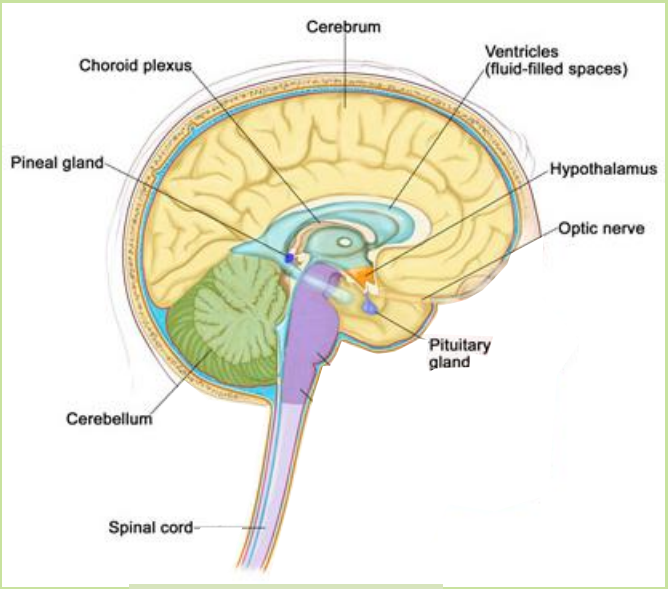


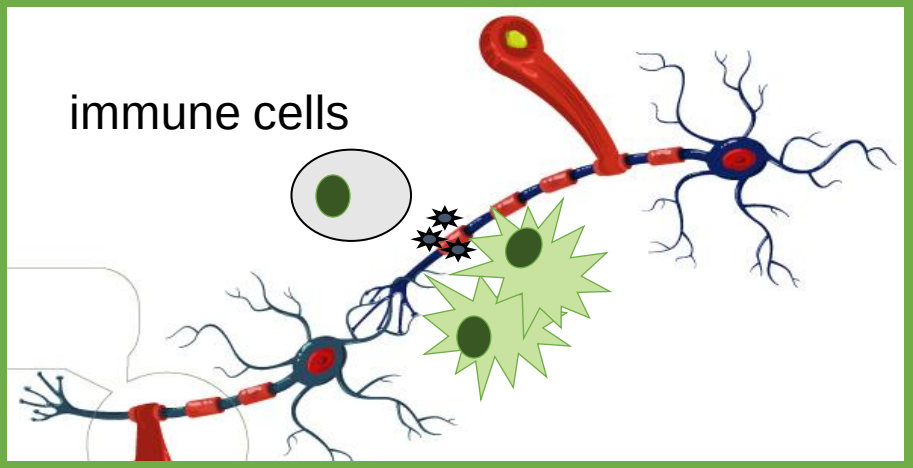


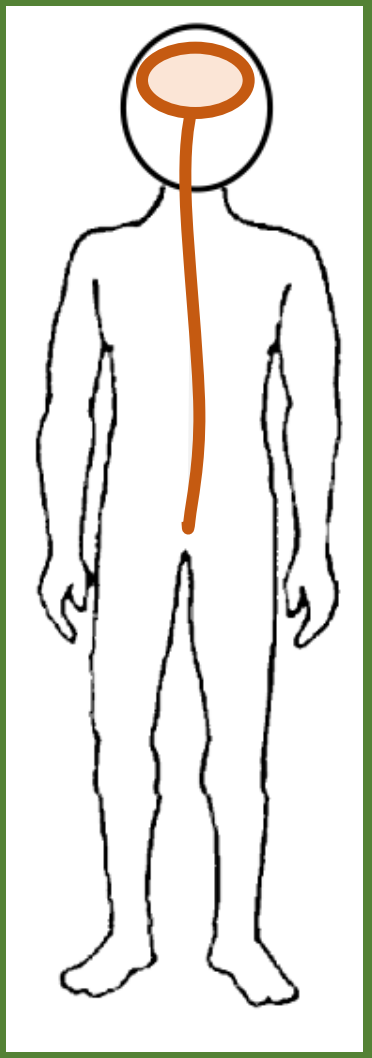
study population → blood → monocytes → flow cytometry

Multiple Sclerosis

immune-mediated neurological damage



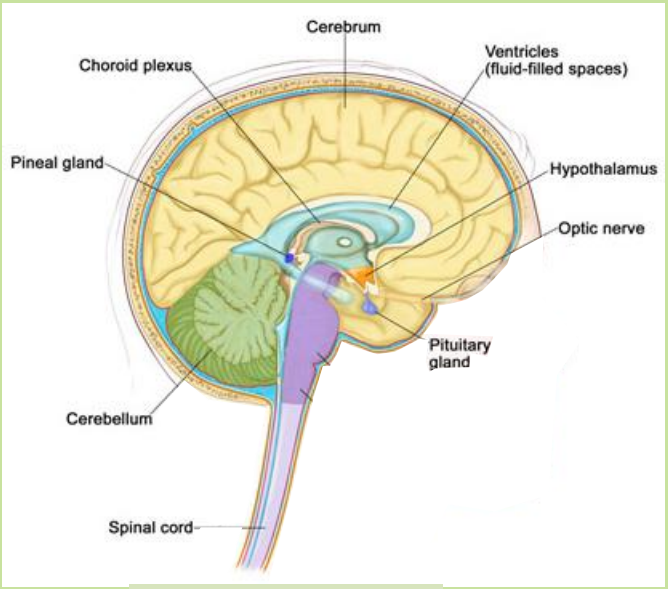


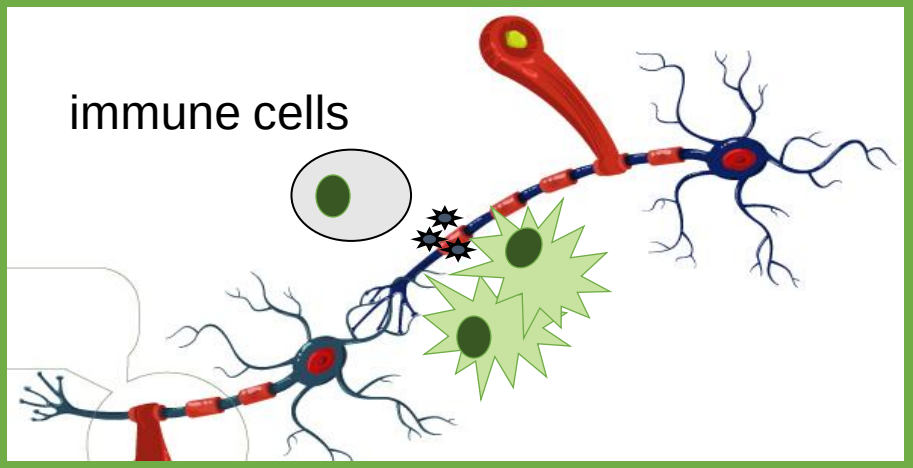


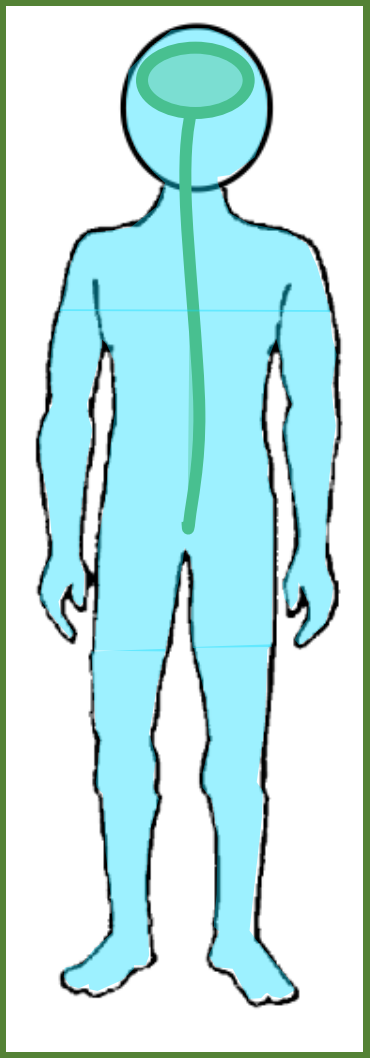
Outside in?
Inside out?

Multiple Sclerosis

immune-mediated neurological damage

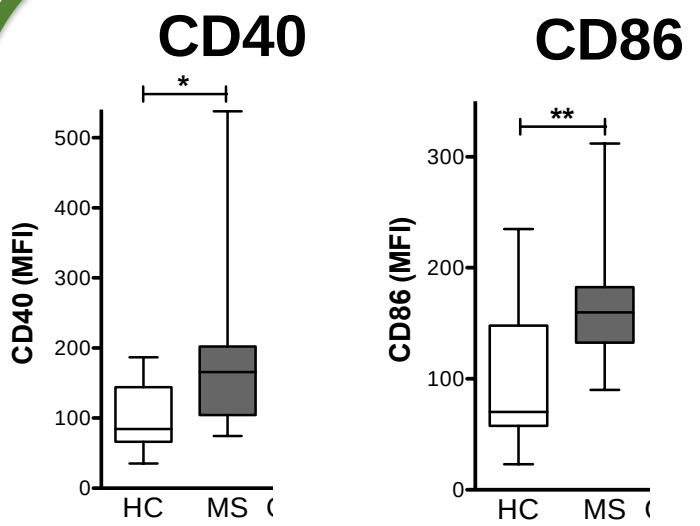






glatiramer acetate

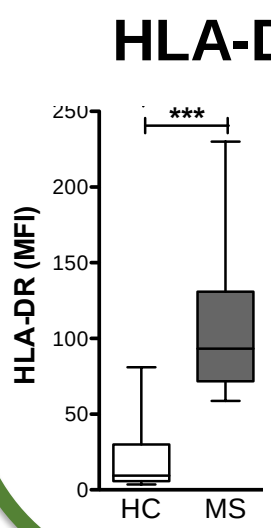
Assessing changes in MS patients

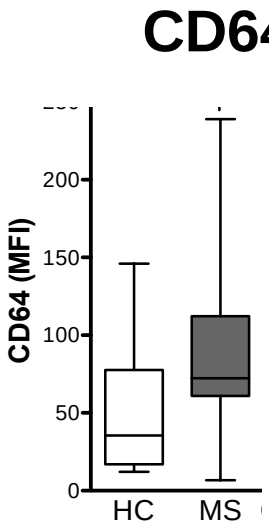


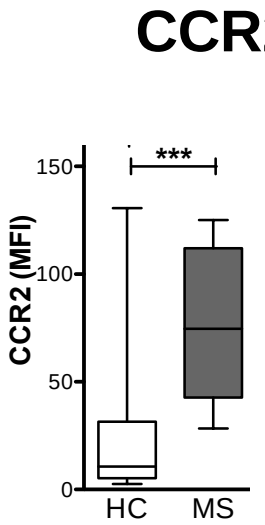
study population

healthy subjects

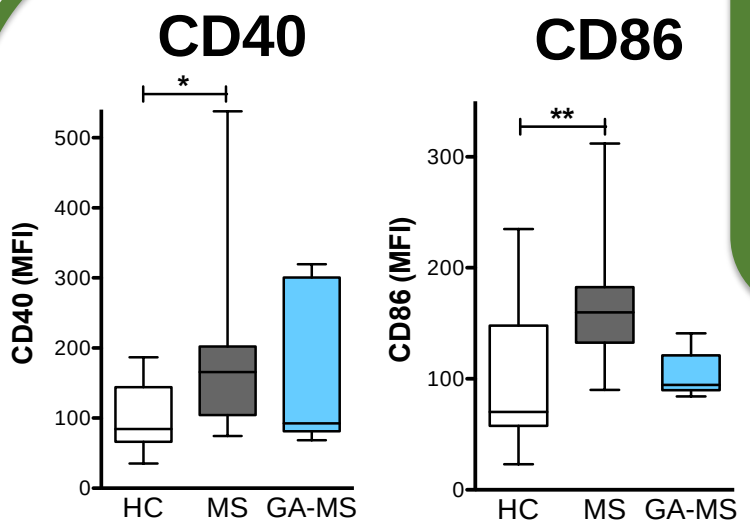
untreated MS patients

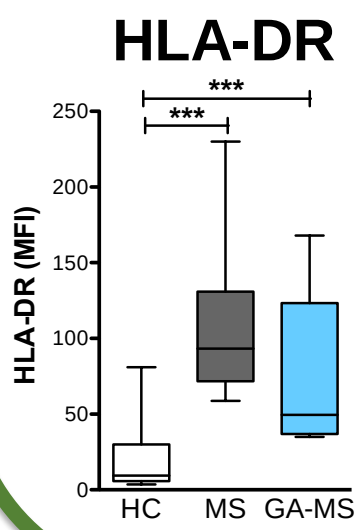


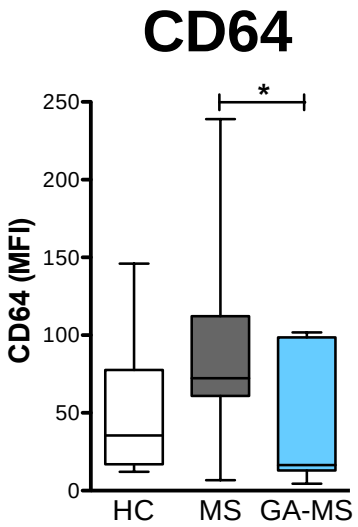


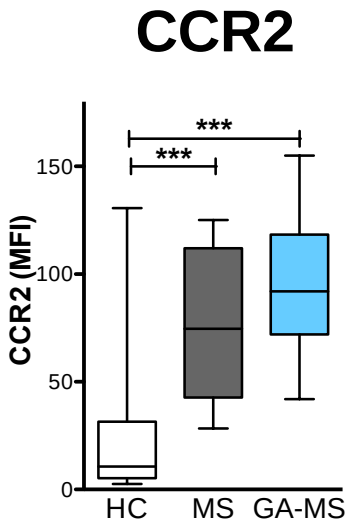


Assessing changes in MS patients









study population

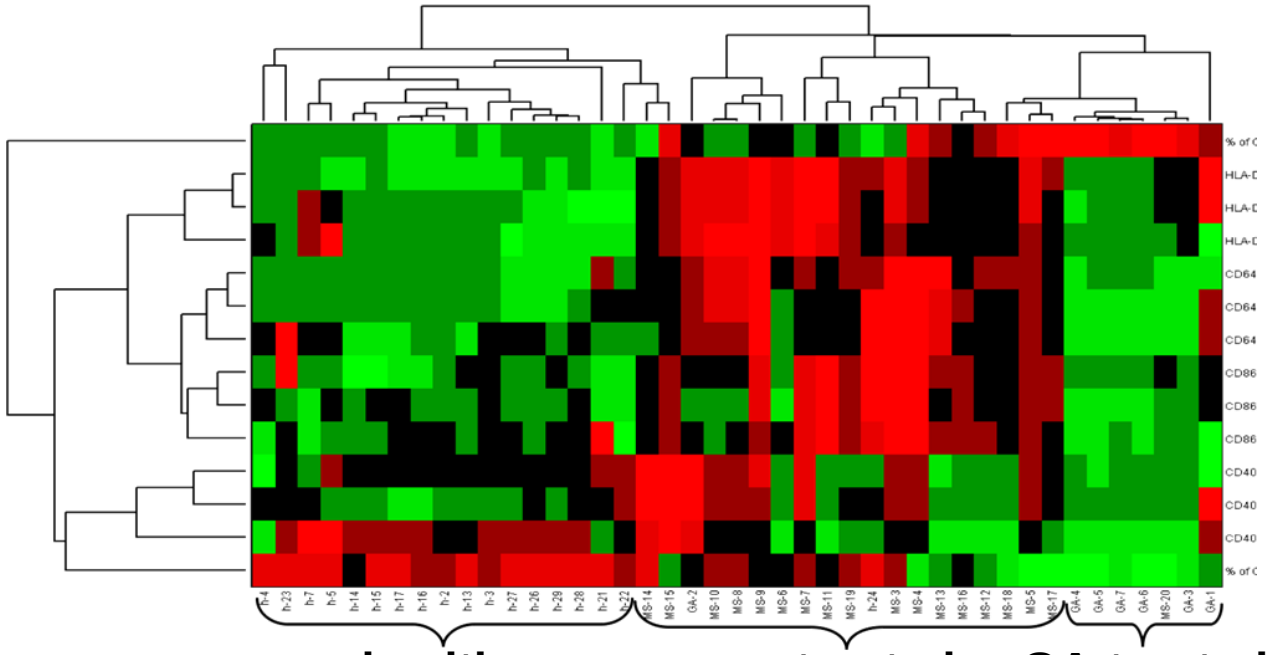
healthy subjects

untreated MS patients

GA-treated MS patients

Balancing the immune environment

Unbiased analysis of ALL immune parameters

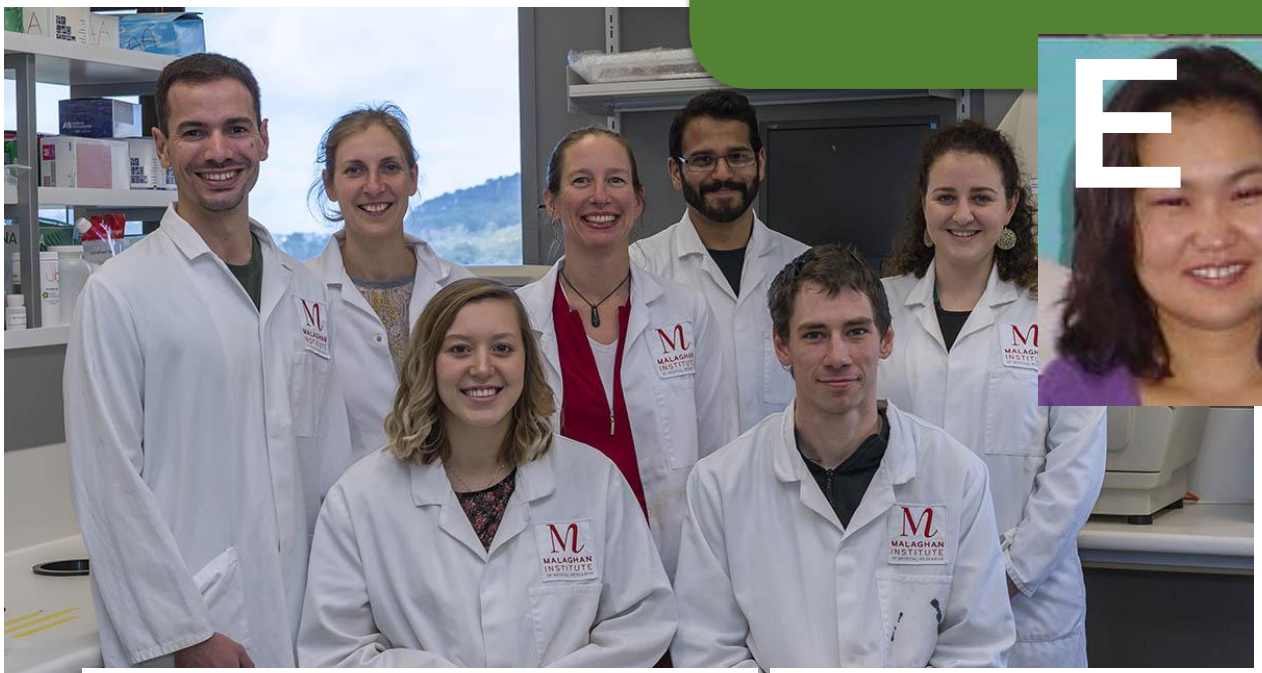


healthy subjects

untreated MS patients

GA-treated MS patients

BALANCE



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OF MEDICAL RESEARCH

and a huge thank you to all of our trial volunteers!