

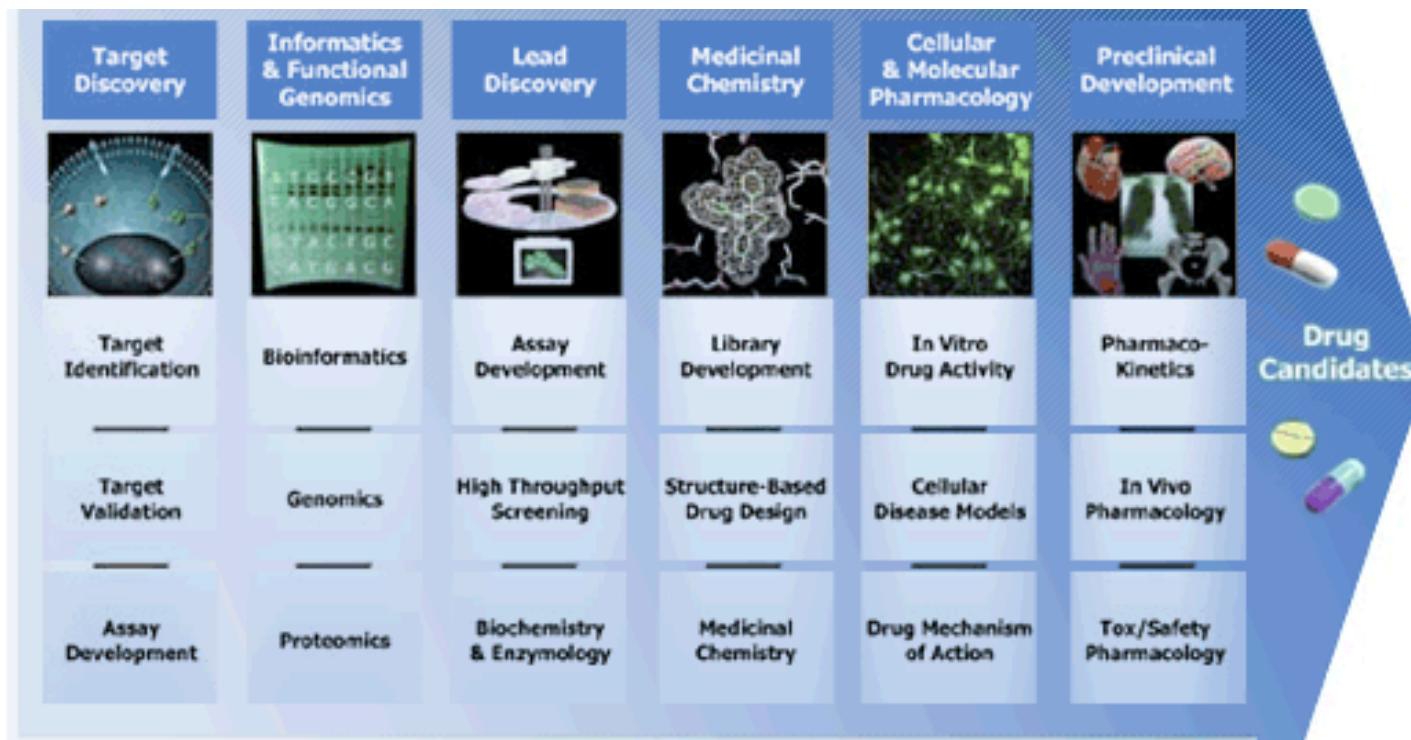
# Drug Discovery

**Amna Hyder, Myles Marin,  
Adelle Strobel**

# Organic Chemistry

- Majority of drugs out there are **organic chemicals**
- Organic
  - Carbon, hydrogen oxygen

# Drug discovery Overview



# Identify Target

Key macromolecules that are linked to disease

## Target

Insulin receptor

HMG-CoA reductase

H+ pump

Angiotensin Converting Enzyme

$\beta$ 2-Adrenergic receptor

ADP Receptor

cGMP-dependent phosphodiesterase 5

Peptidoglycan biosynthesis

Microtubule polymerization

Cholesterol in membranes

DNA

## Disease

Diabetes

Hypercholesterolemia

Dyspepsia etc

Hypertension

Asthma

Coronary Disease

Erectile Dysfunction

Bacterial Infection

Cancer

Fungal infection

Cancer

## Drug

Insulin

Lipitor

Nexium

Captopril

Advair

Plavix

Viagra

Penicillin

Taxol

Amphotericin

Adriamycin

# Identify Targets

Biochemistry

- Affinity chromatography and labeling

Biology

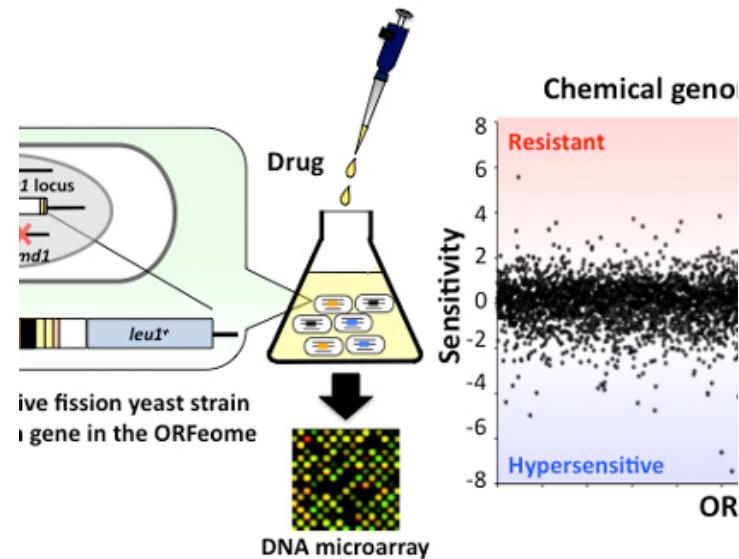
- Genetics (mutants, knock-outs)

# Verify targets

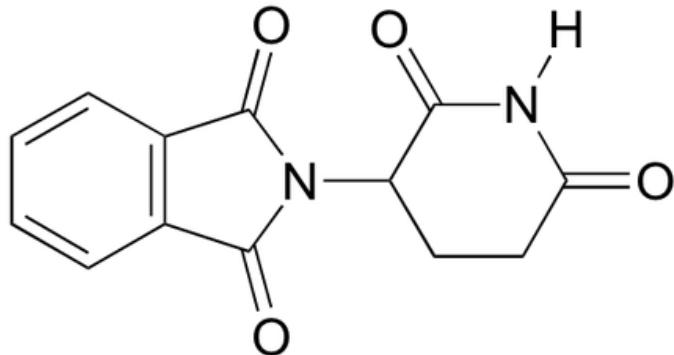
In silico (on a computer)



Microarrays

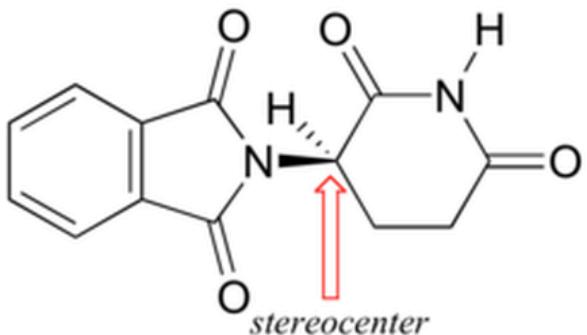


# Thalidomide

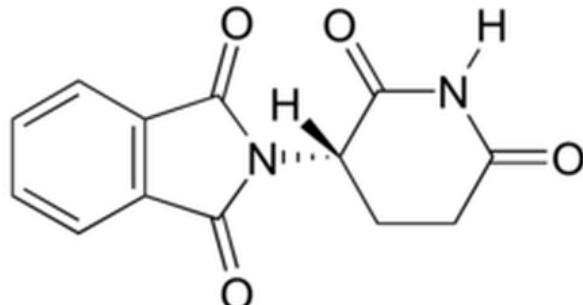


- <https://www.youtube.com/watch?v=41n3mDoVbvk>

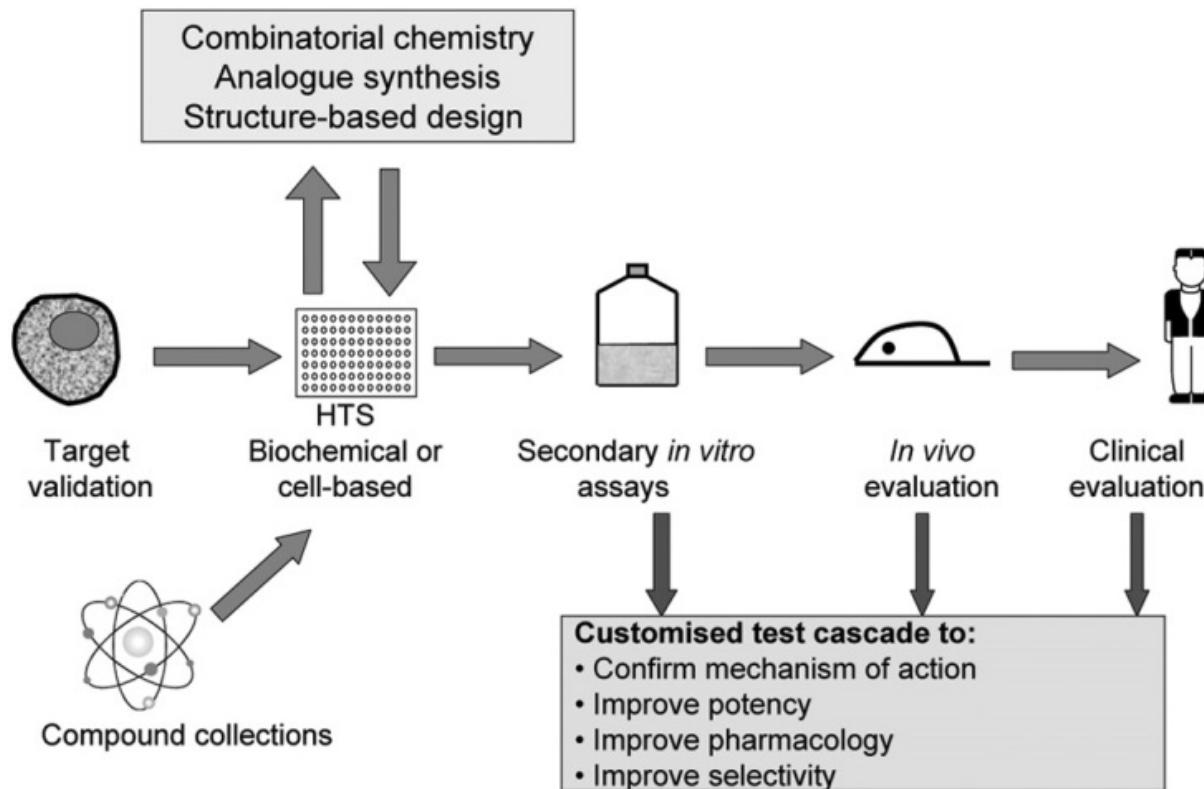
effective isomer



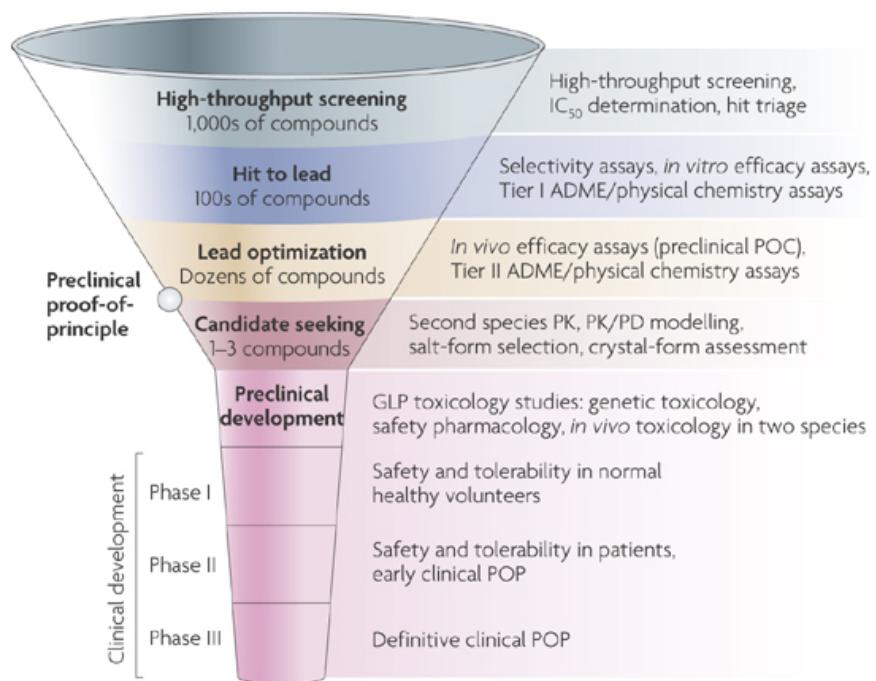
mutagenic isomer



# High Throughput screening



# High Throughput screening



# Raw Materials

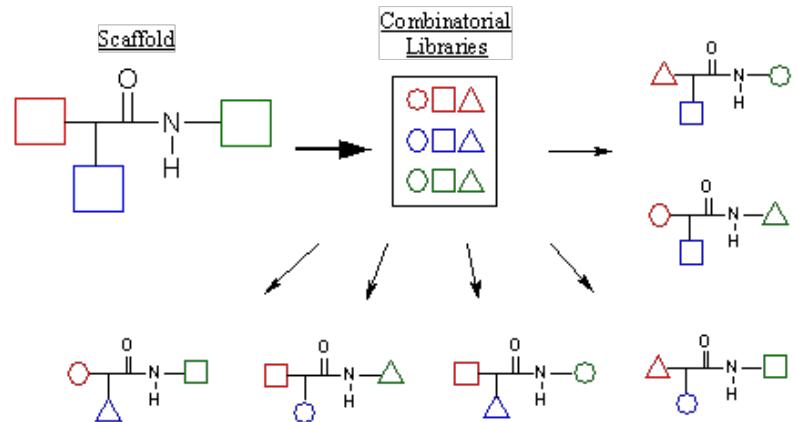
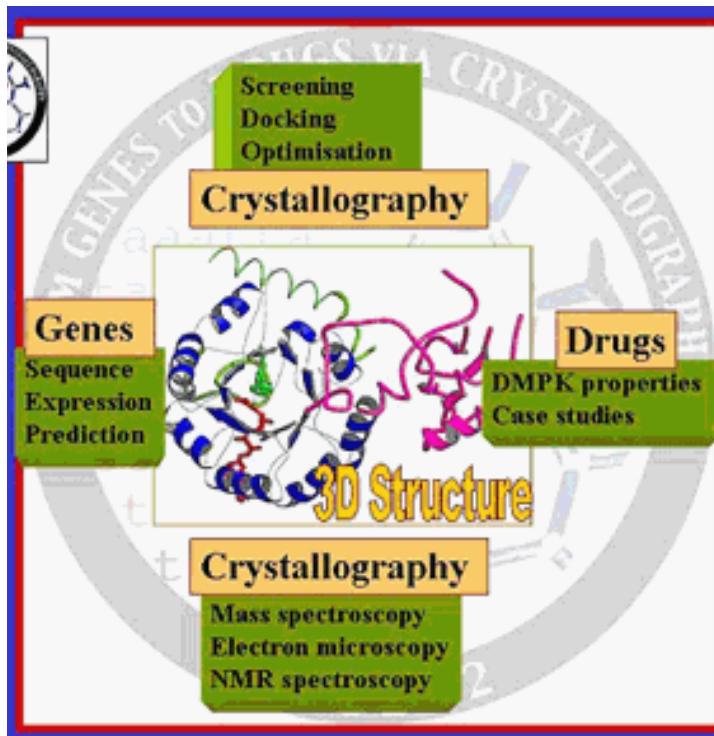
## Natural Product

- Many stereocenters
- Purification process
- Ex. aloe products for after sunburns, aspirin, taxol,

## Synthetic Compounds

- May be based on *in Silico* work
- Combinational chemistry

# Structure-based vs combinatorial biochemistry



# Why drugs fail?

Top two reasons why 4 out of 5 drugs fail:

- Lack of efficacy
- Pharmokinetics

# Drug Properties

- **Structure**

- H-bonding; pKa
- Shape
- MW
- Lipophilicity & polar surface area

- **Physiochemical**

- Solubility
- Permeability
- Stability

- **Biochemical**

- Metabolism
- Protein/tissue binding
- Transport (uptake/efflux)

- **Pharmacokinetics**

- Clearance
- $t_{1/2}$
- Bioavailability
- LD50
- Drug-Drug interactions

# Fate of a Drug

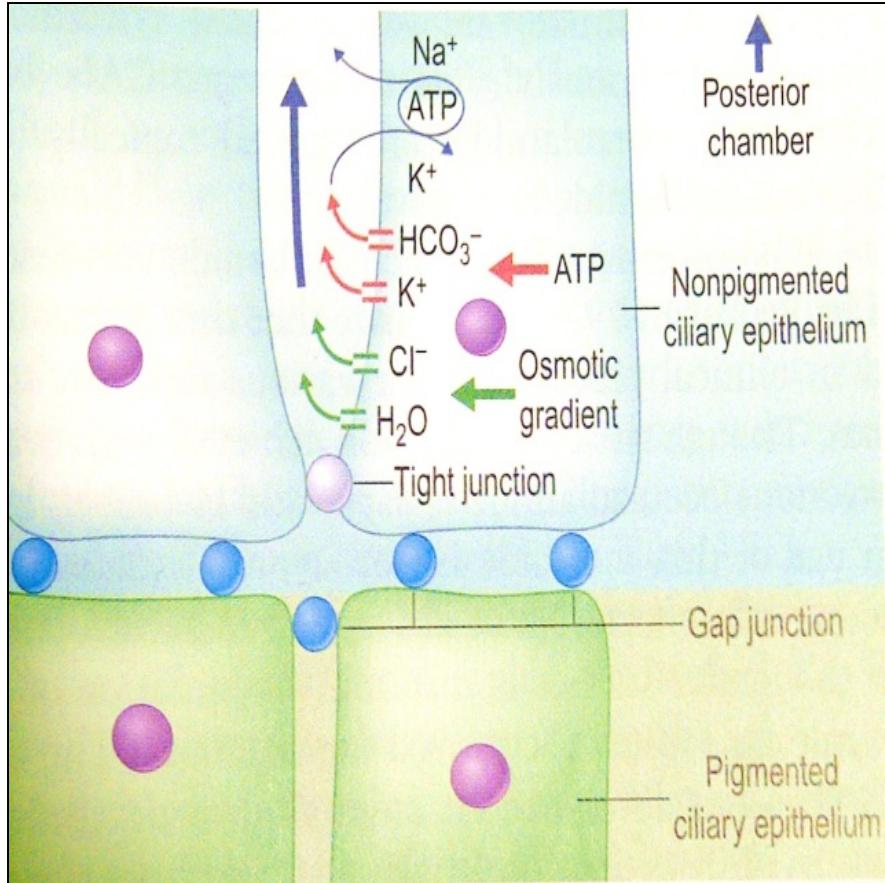
- Absorption
- Distribution
- Metabolism (liver)
- Excretion
- Toxicity (does the drug kill cells)

# Patents – Solution to DD Financing?

- What are the costs associated with DD?
- A patent: A legal document that grants property rights to the inventor



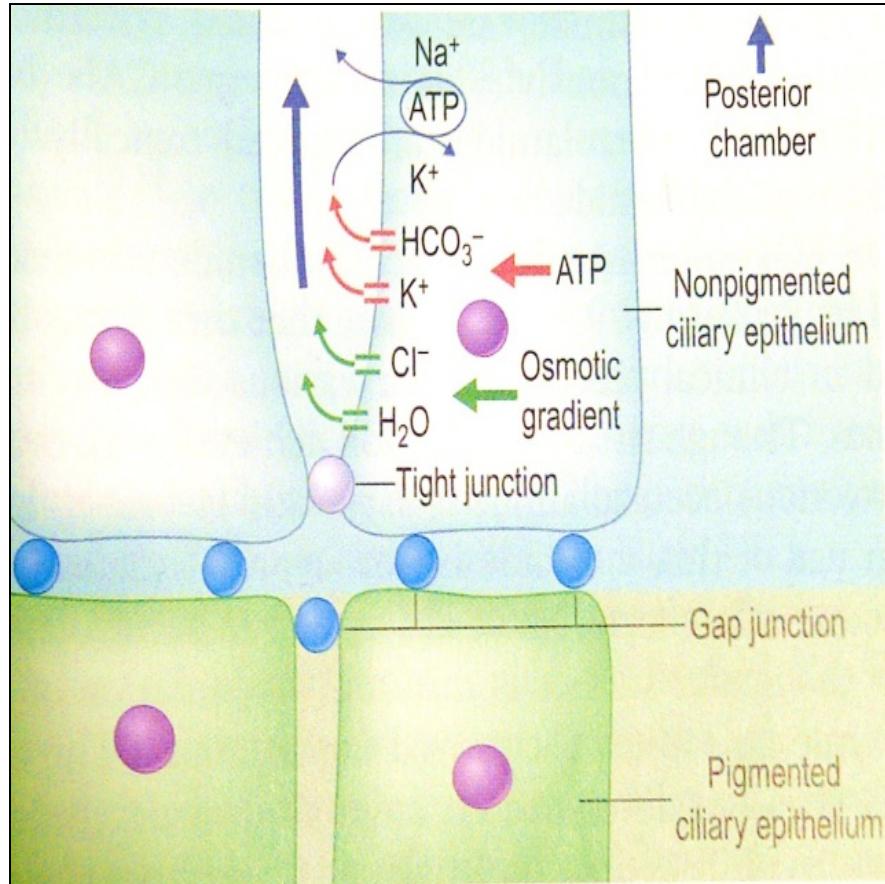
# Function of CAs in glaucoma



- **Glaucoma:**
- Family of eye diseases characterized by increased pressure on the intraocular nerve, leading to damage

Image taken from: *Glaucoma: Medical Diagnosis and Therapy* Vol. 1 [1]

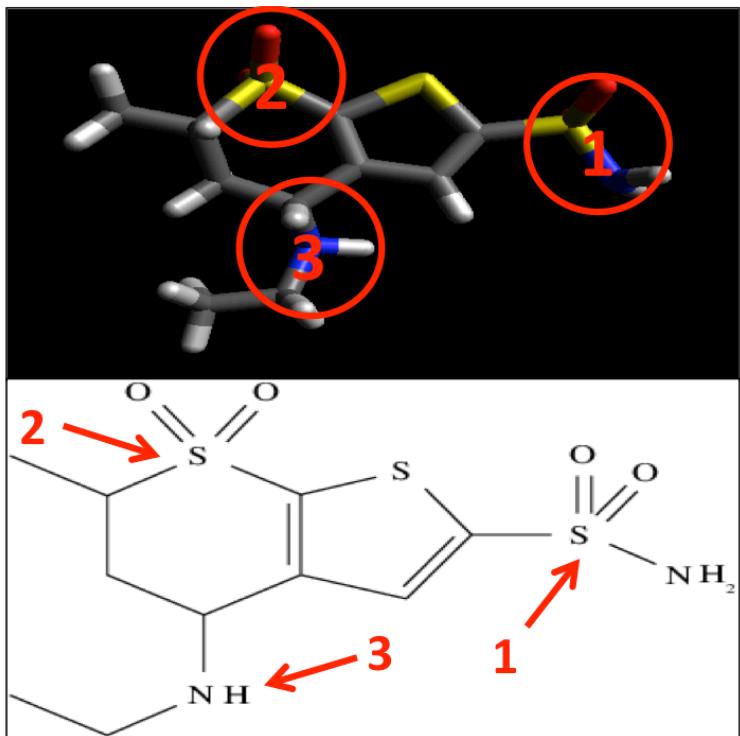
# Function of CAs in glaucoma



- Commonly treated by the inhibition of CA IV
- Catalyzes interconversion between  $\text{CO}_2$  and  $\text{HCO}_3^-$
- Highly efficient mechanism:  $10^4$ - $10^6$  reactions per second

Image taken from: *Glaucoma: Medical Diagnosis and Therapy* Vol. 1 [1]

# Dorzolamide: A CA IV inhibitor used in the treatment of glaucoma



Images created using Avogadro (a) [2] and ChemTool (b) [3]

- Topical treatment for glaucoma
- A sulfonamide CA inhibitor
- Interacts with Zn metal and displaces the catalytic OH<sup>-</sup>
- Functional groups:
  1. Sulfonamide
  2. Sulfoxide
  3. Amine

# Objective: A better dorzolamide

Dorzolamide has **greater affinity for CA II ( $K_i = 9 \text{ nM}$ ) than CA IV ( $K_i = 8530 \text{ nM}$ )** and so disrupts systemic CA II function, leading to undesired side-effects.<sup>4</sup>

## GOAL:

- Generate modified dorzolamide that displays **INCREASED** affinity for CA IV and **DECREASED** affinity for CA II

# Methodology

1. Identify structural differences between CAIV and CAII
2. Determine functional groups on dorzolamide that interact differentially with CA IV and CA II
3. Modify previous identified groups and analyse ligand-receptor interaction energies to determine relative affinities of the new drug for CA IV and CA II

# hCAs share significant sequence similarities

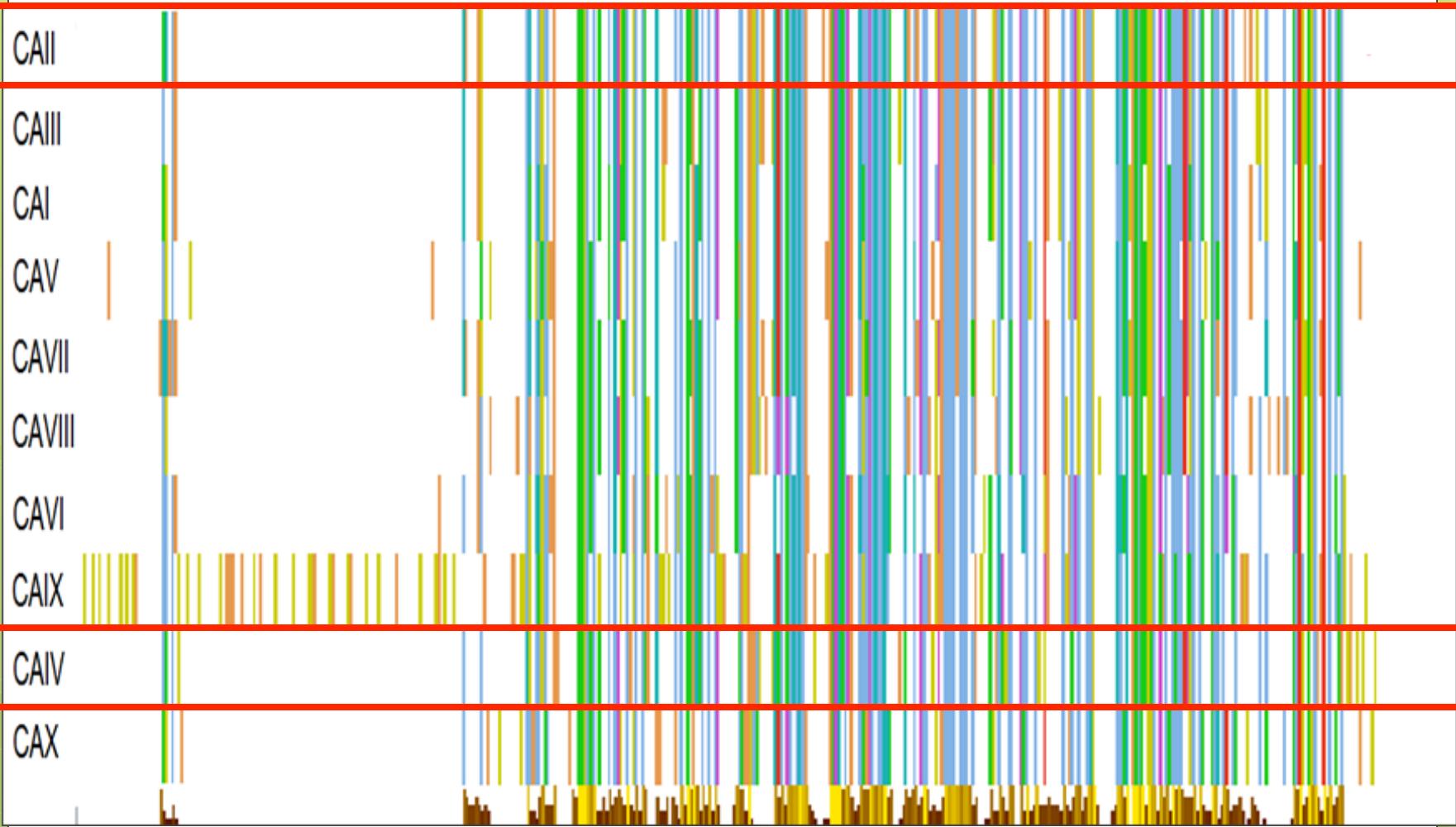
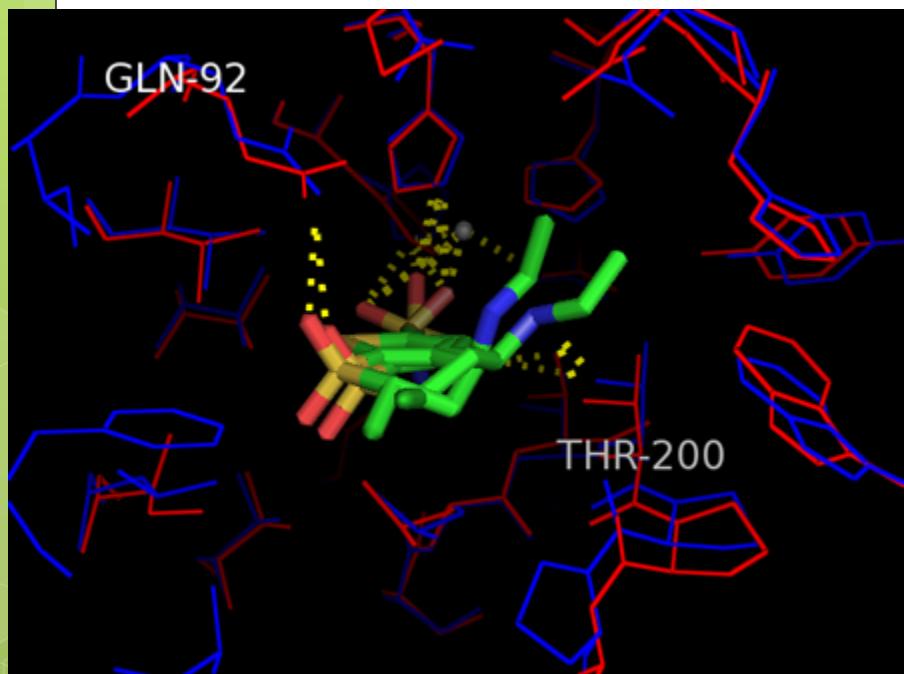


Image created using Clustal W [5]

# Alignment of CA IV and CA II active sites

**BACK**



**FRONT**

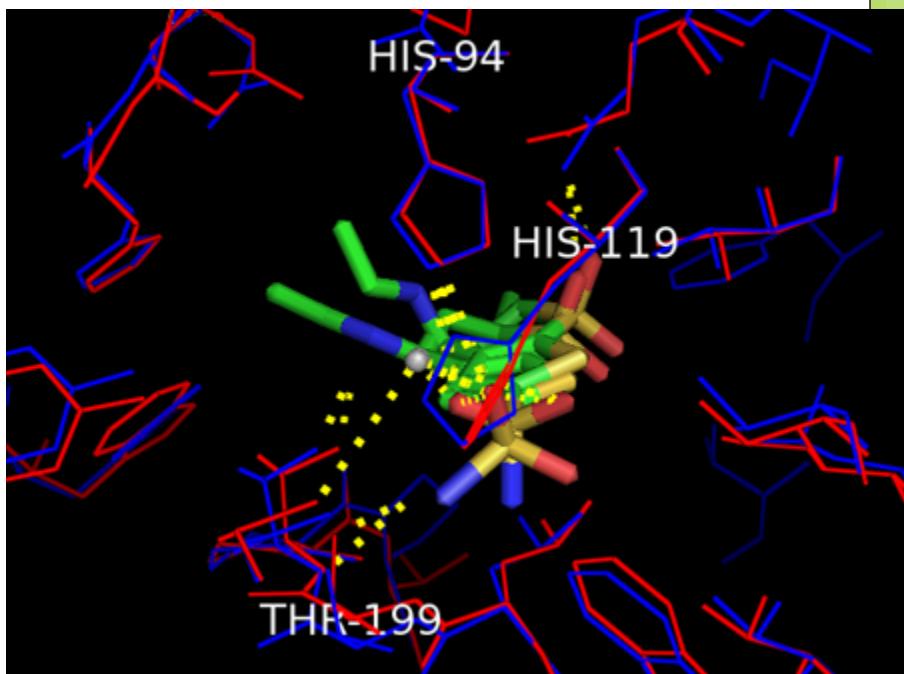
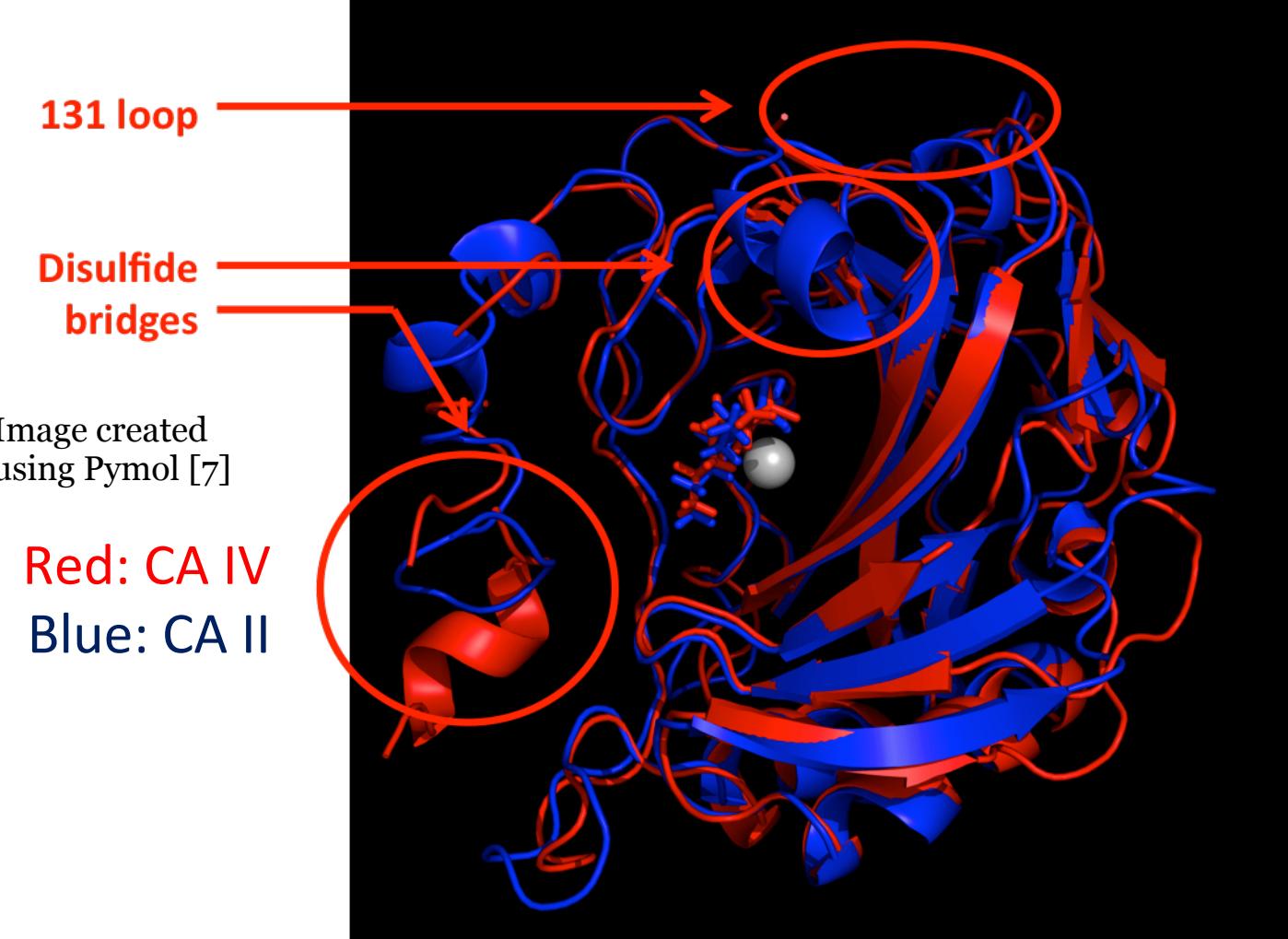


Image created using Pymol [7]

Red: CA IV

Blue: CA II

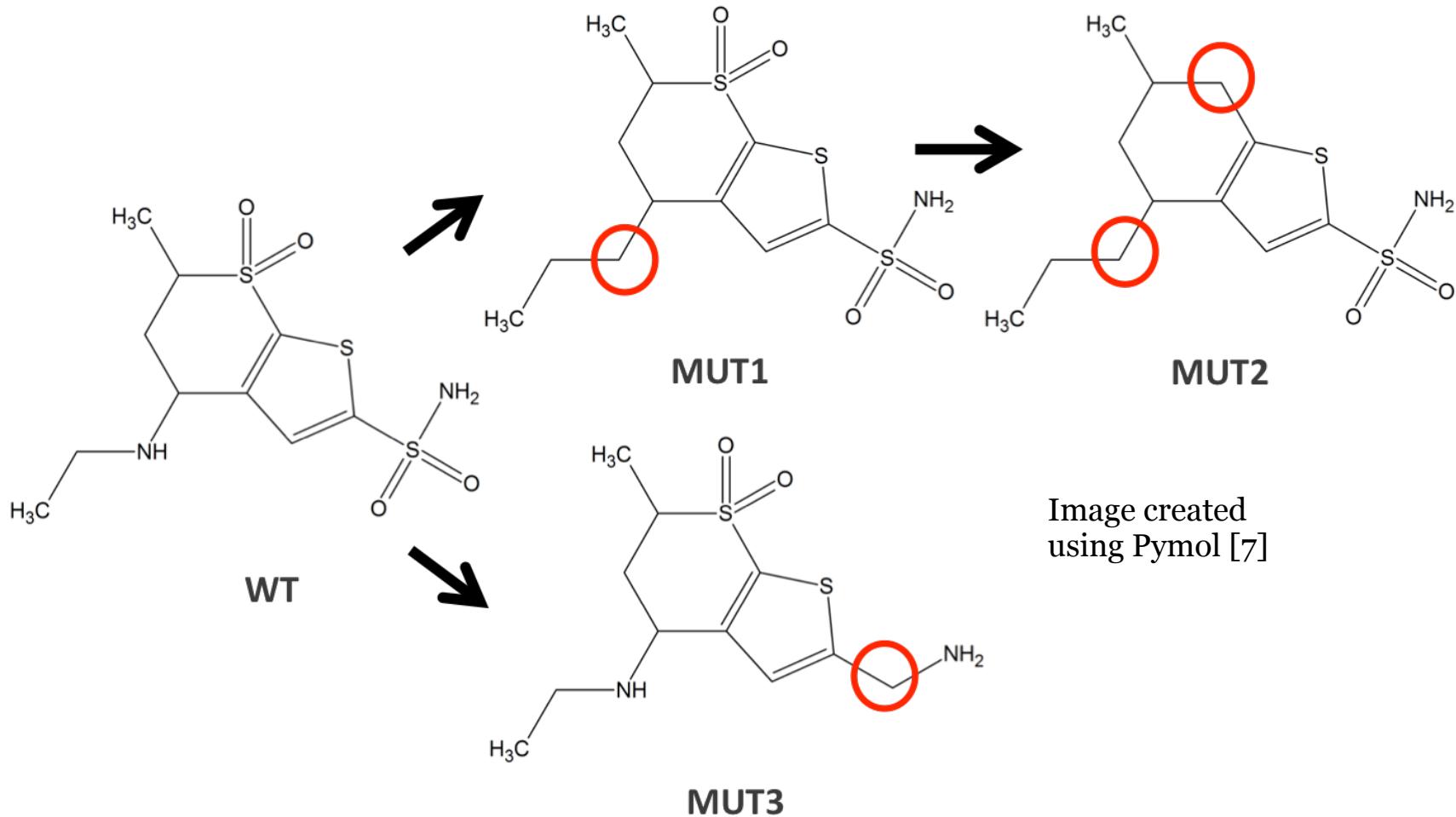
# Alignment of CA IV and CA II crystal structures



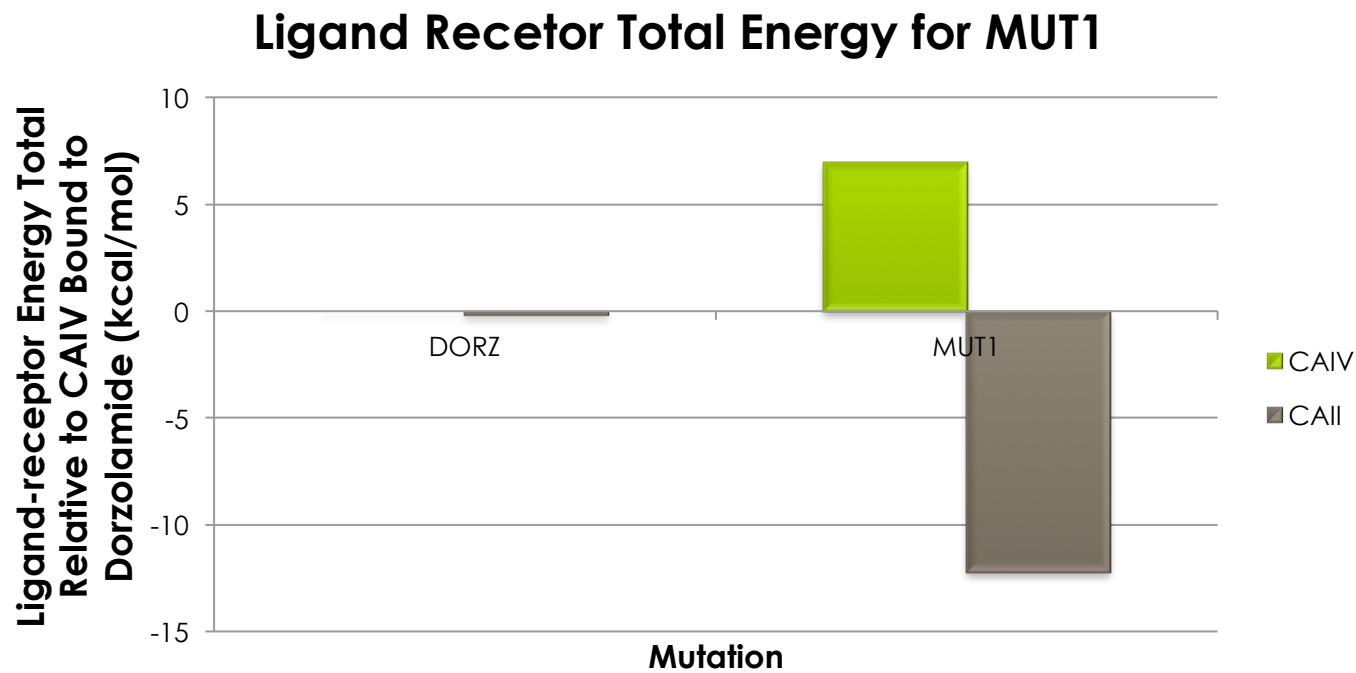
# Construction of mutant CA IV (mCA II) and CAII (mCA IV)

- 2 major structural difference between CA IV and CA II:
  1. 131 loop
  2. **disulfide bridges**
- To examine effect on receptor-ligand binding and interaction energies:
  - A. **mCA IV:** Removal of disulfide bridge from CA IV
  - B. **mCA II:** Addition of disulfide bridge to CA II

# Ligand modifications

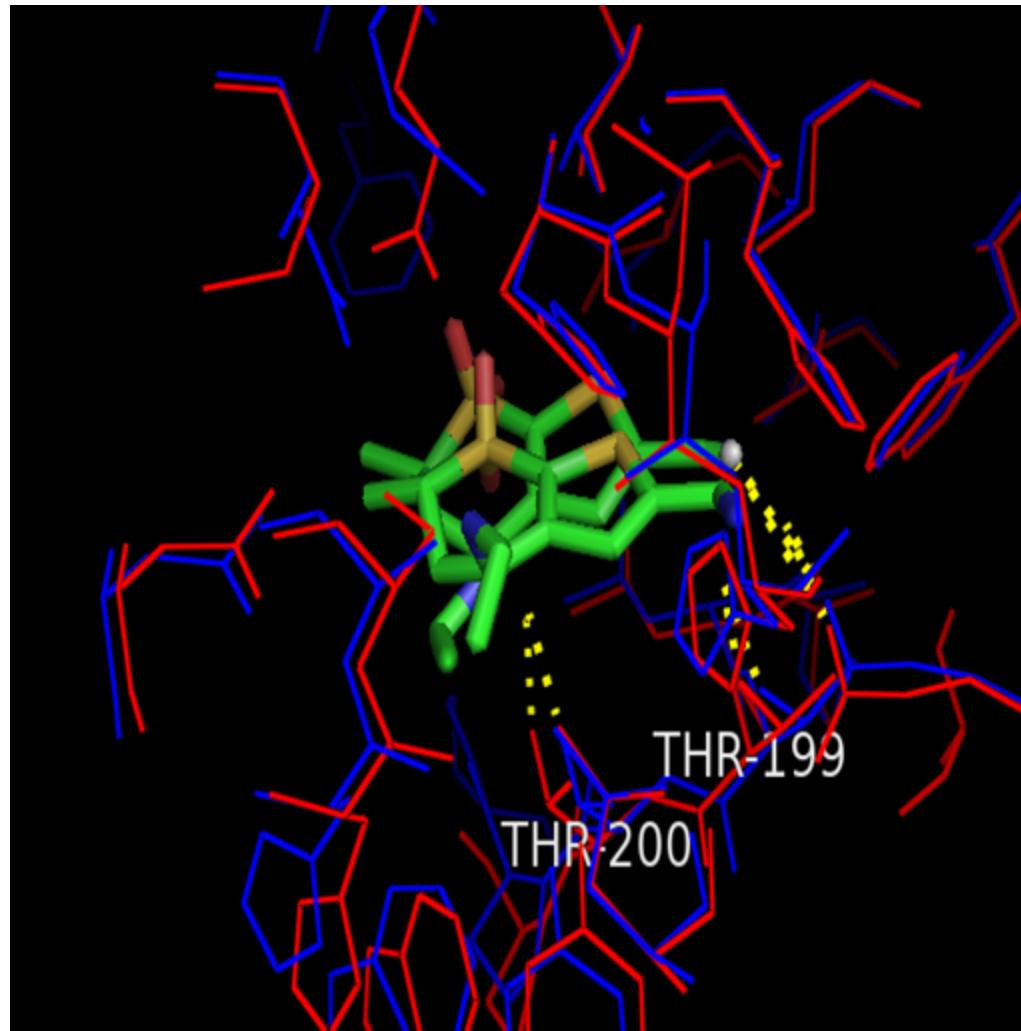


# MUT1 demonstrated decreased affinity for CA IV and increased affinity for CA II



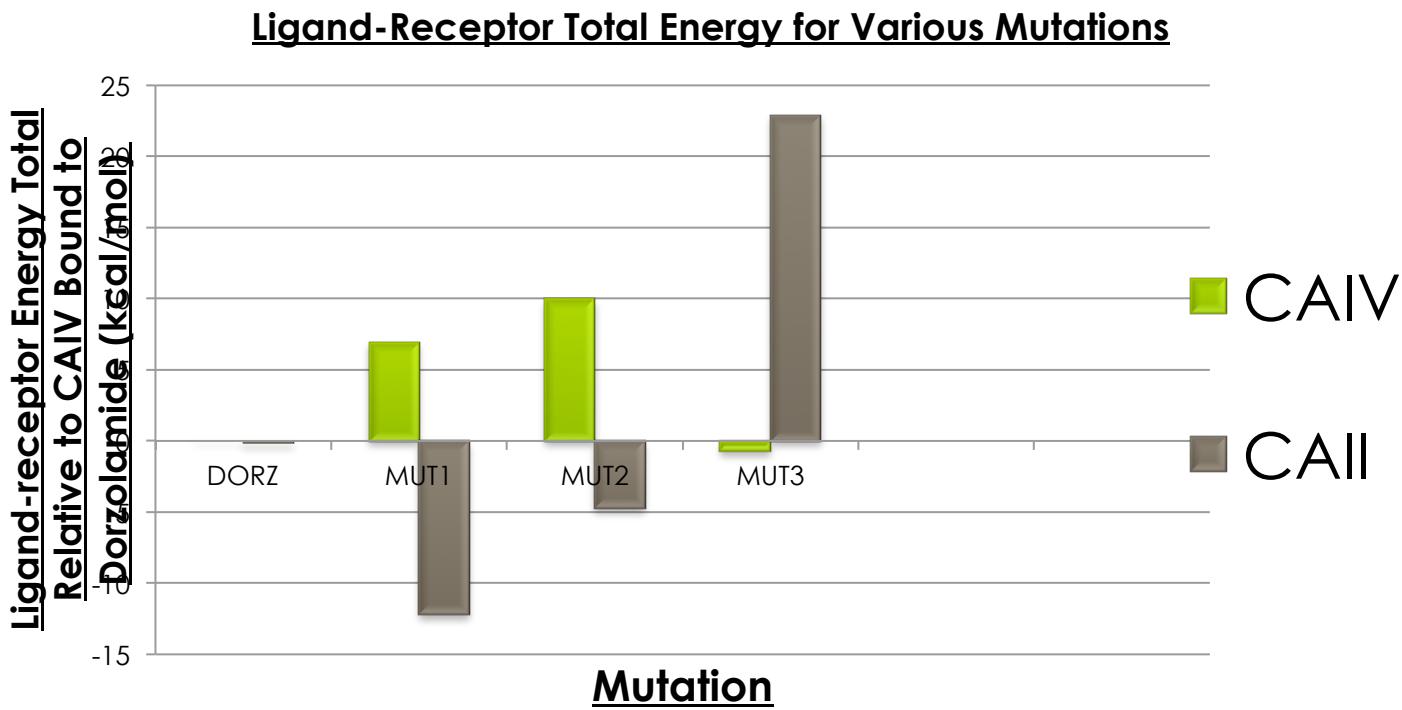
# MUT3 binding to CA IV and CAII

Image created  
using Pymol [7]



Red: CA IV  
Blue: CA II

# MUT3 demonstrates significantly improved binding to CA IV



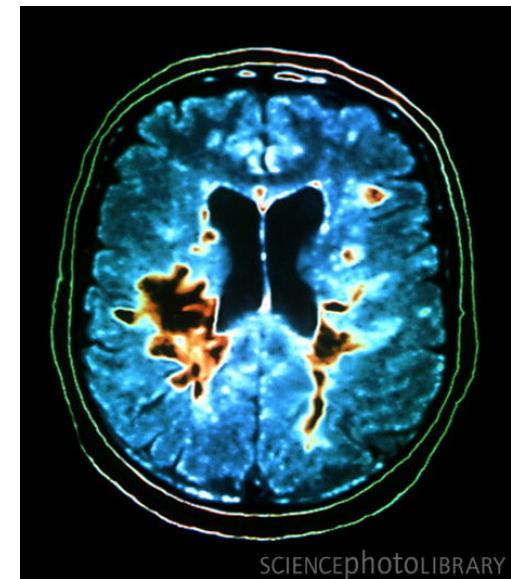
# Discussion

- Constructed 3 mutant dorzolamide-like drugs *in silico* in an attempt to strengthen CA IV binding whilst simultaneously weakening CA II binding
- **MUT3 resulted in much improved differential binding to CA IV versus CA II**

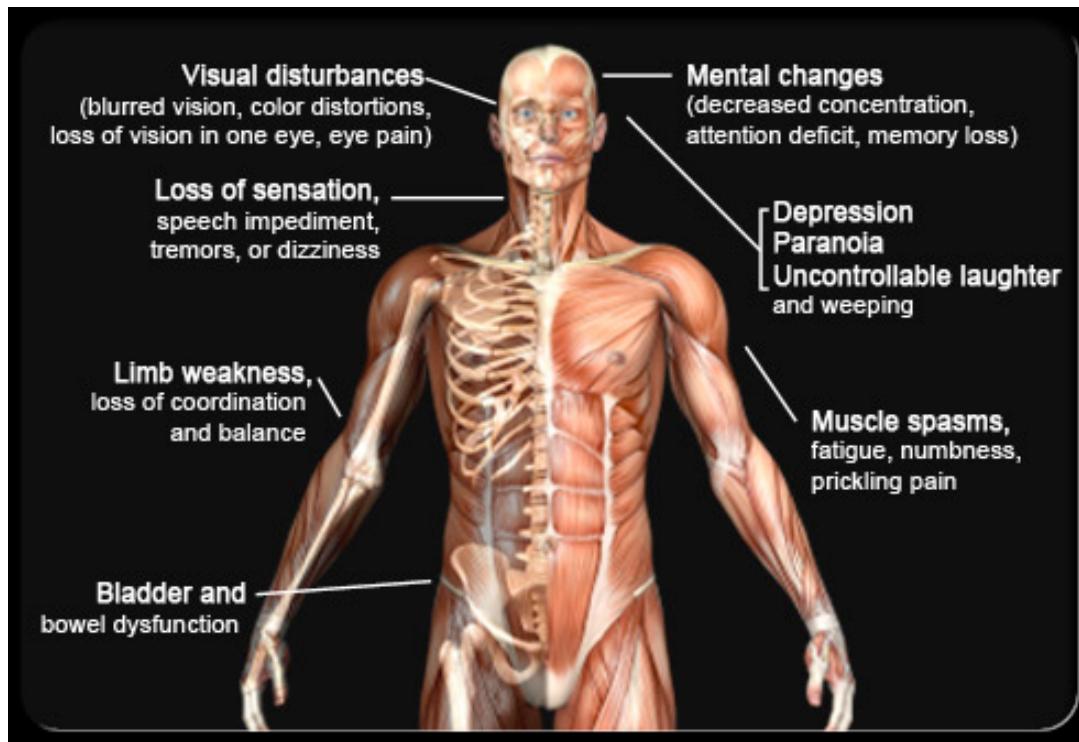
# Case Study

-get into groups of 3 or 4

# Multiple Sclerosis: A Neuroscientific Paradigm on Drug Development



# Multiple Sclerosis



# Types of Neurons

Afferent

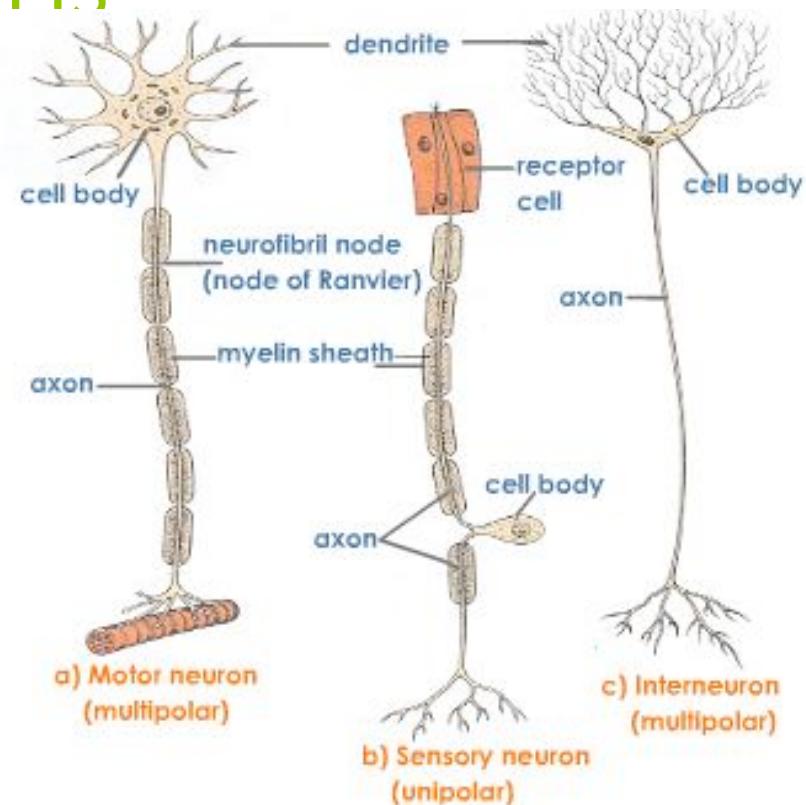
Motor Neurons

Efferent

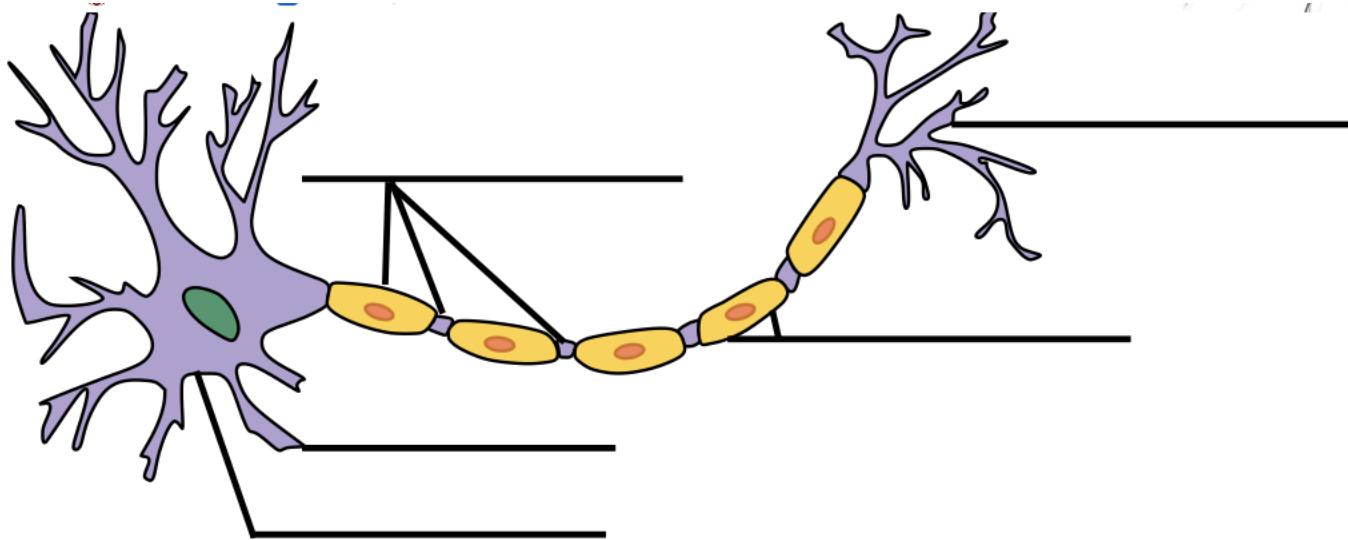
Sensory Neurons

In the CNS

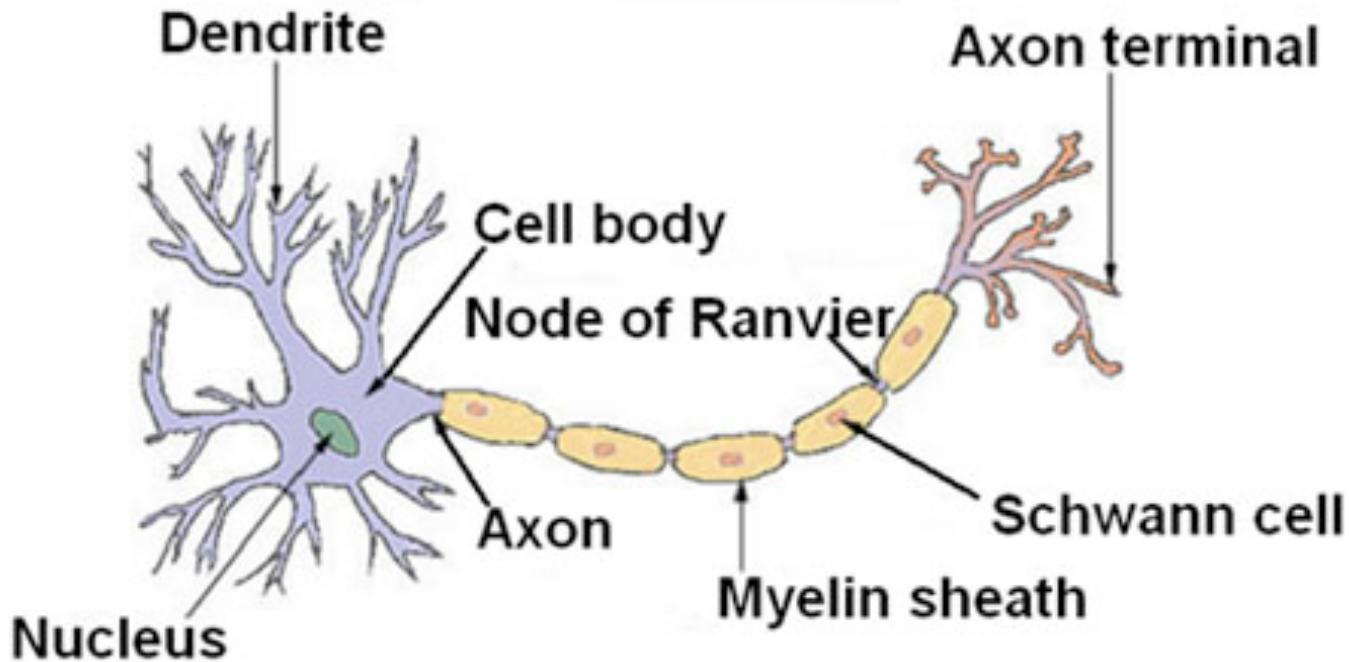
Interneurons



# Structure of a Typical Neuron



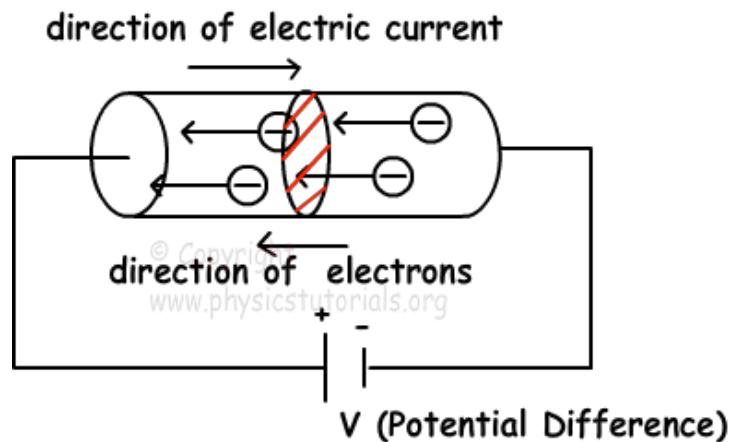
# Structure of a Typical Neuron



# Electrodiffusion

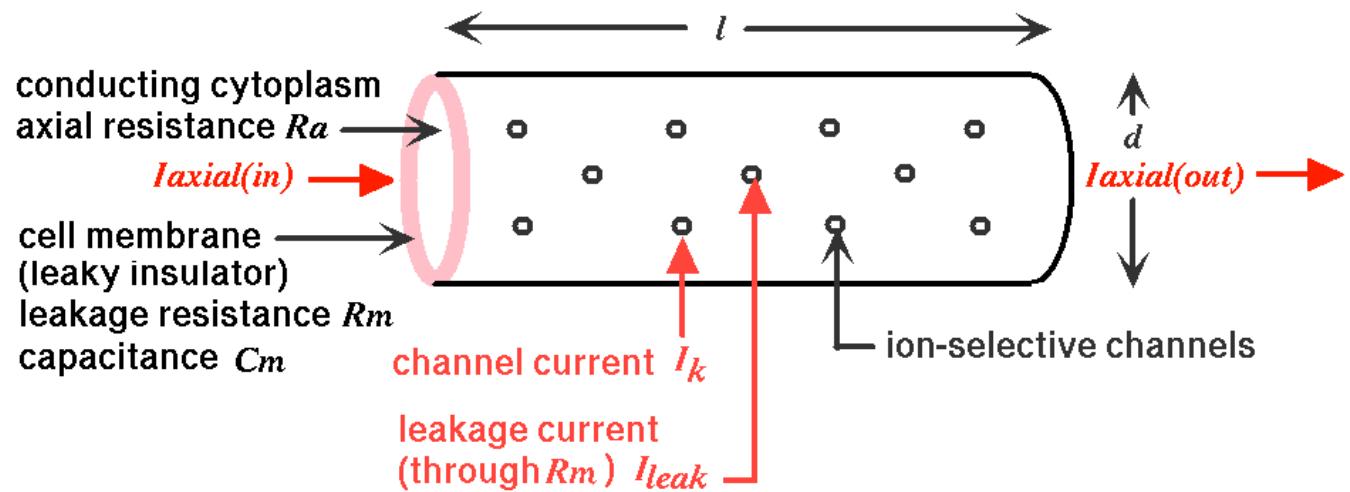


Library of Congress

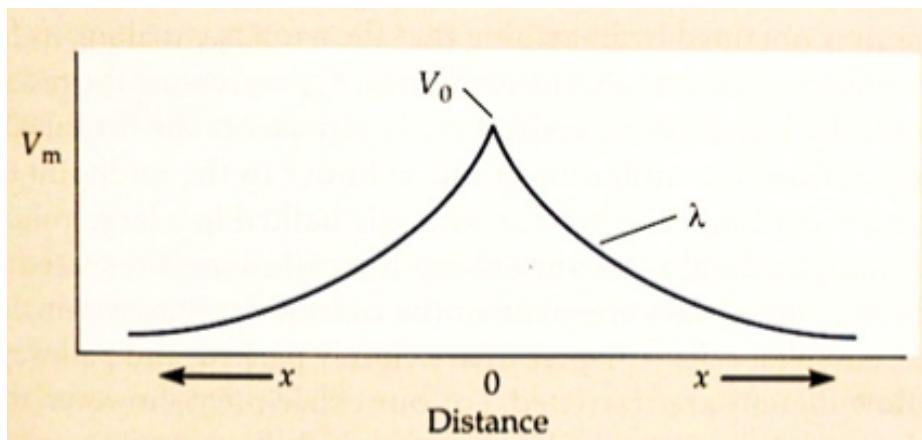


# Circuits

# Dendrite



# Potential and Current – exponential decay



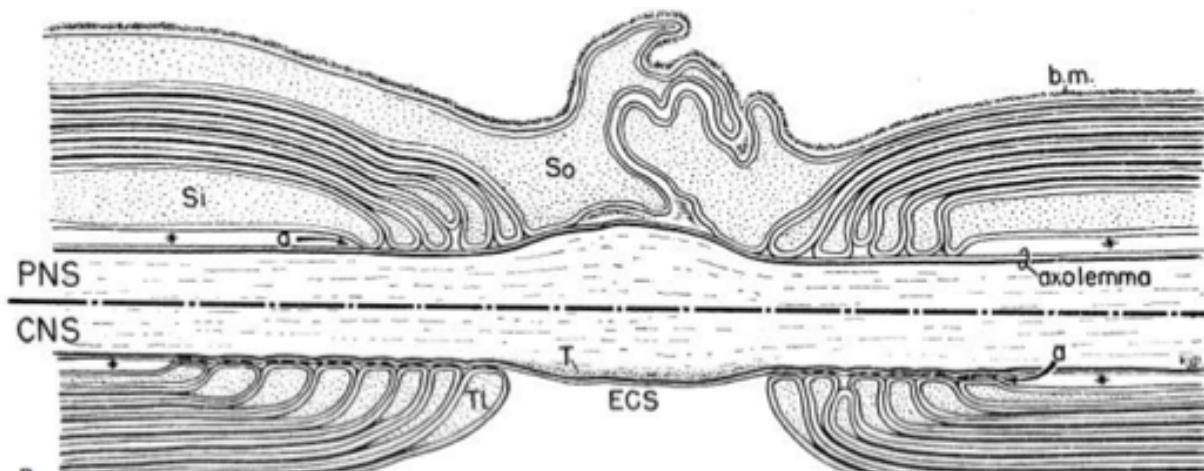
$$V_x = V_0 e^{\frac{-x}{\lambda}}$$

$$\lambda = \left(\frac{r_m}{r_a}\right)^{\frac{1}{2}}$$

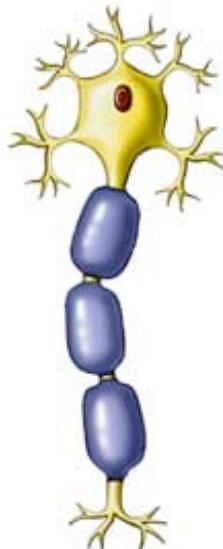
# Capacitance

$$C_{membrane} = \left( \frac{1}{c_1} + \frac{1}{c_2} + \frac{1}{c_3} + \dots + \frac{1}{c_n} \right)^{-1}$$

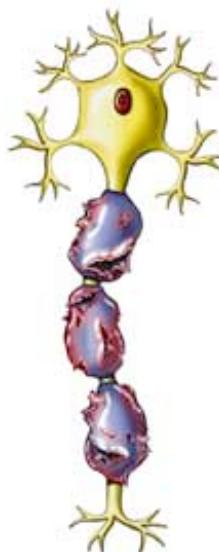
- $C = (\text{Charge}) / (\text{Voltage}) = Q/V$
- HIGH capacitance:
  - More ions are required to charge the membrane
  - Reduces the distance at which the current propagates
- Want LOWER capacitance!



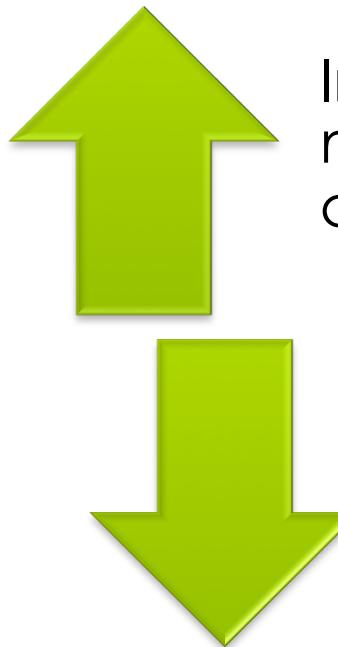
# Myelination – Multiple Sclerosis



Neuron with myelin sheath



Neuron with damaged myelin sheath



Increased  
membrane  
capacitance

Lower  
membrane  
resistance

# MS Symptoms



## Main symptoms of Multiple sclerosis

### Central:

- Fatigue
- Cognitive impairment
- Depression
- Unstable mood

### Visual:

- Nystagmus
- Optic neuritis
- Diplopia

### Speech:

- Dysarthria

### Throat:

- Dysphagia

### Musculoskeletal:

- Weakness
- Spasms
- Ataxia

### Sensation:

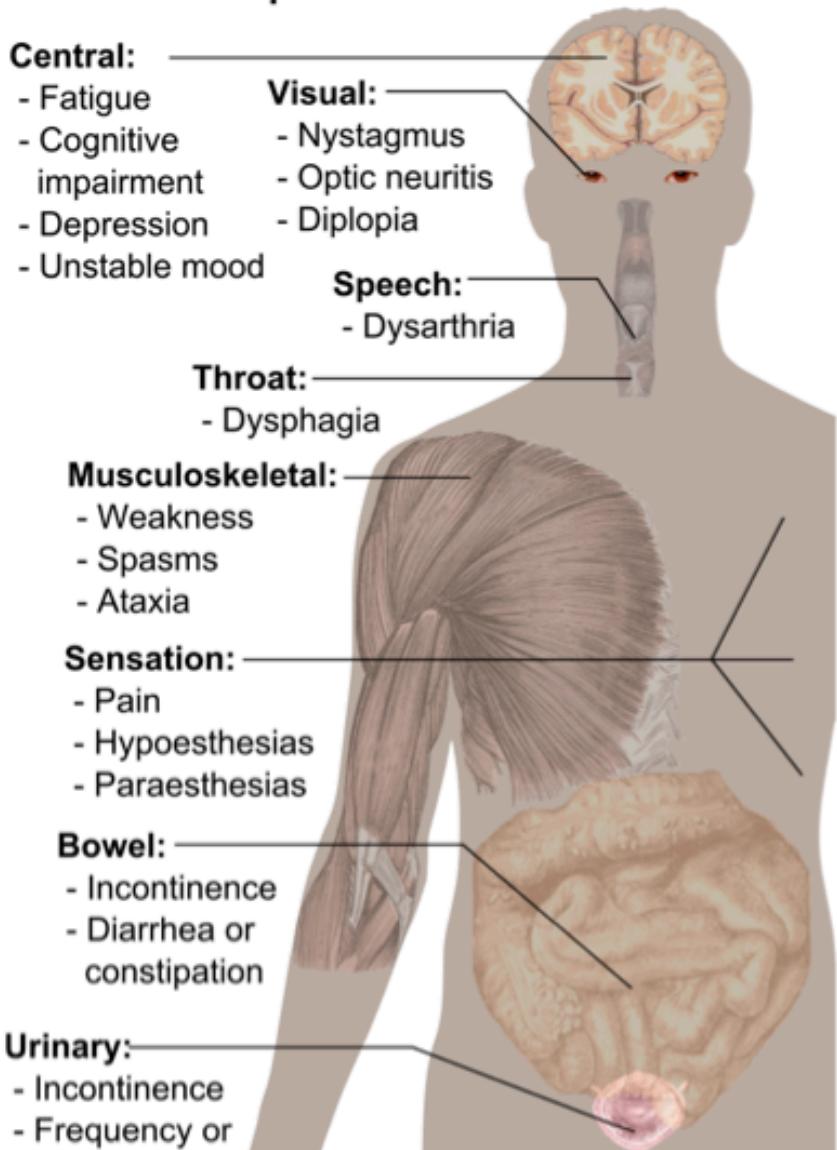
- Pain
- Hypoesthesia
- Paraesthesia

### Bowel:

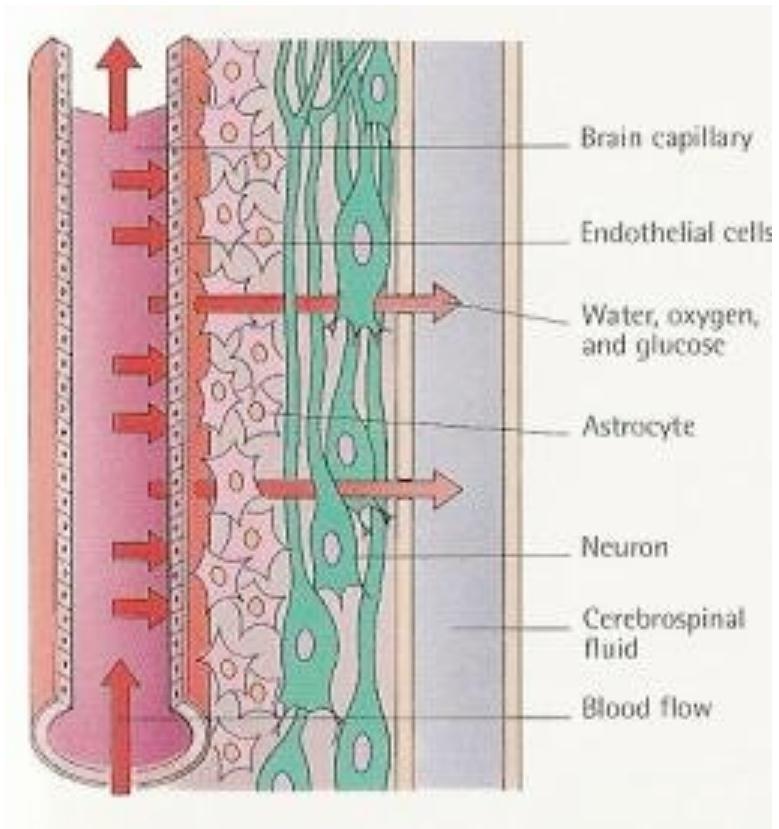
- Incontinence
- Diarrhea or constipation

### Urinary:

- Incontinence
- Frequency or



# Normal Immune system

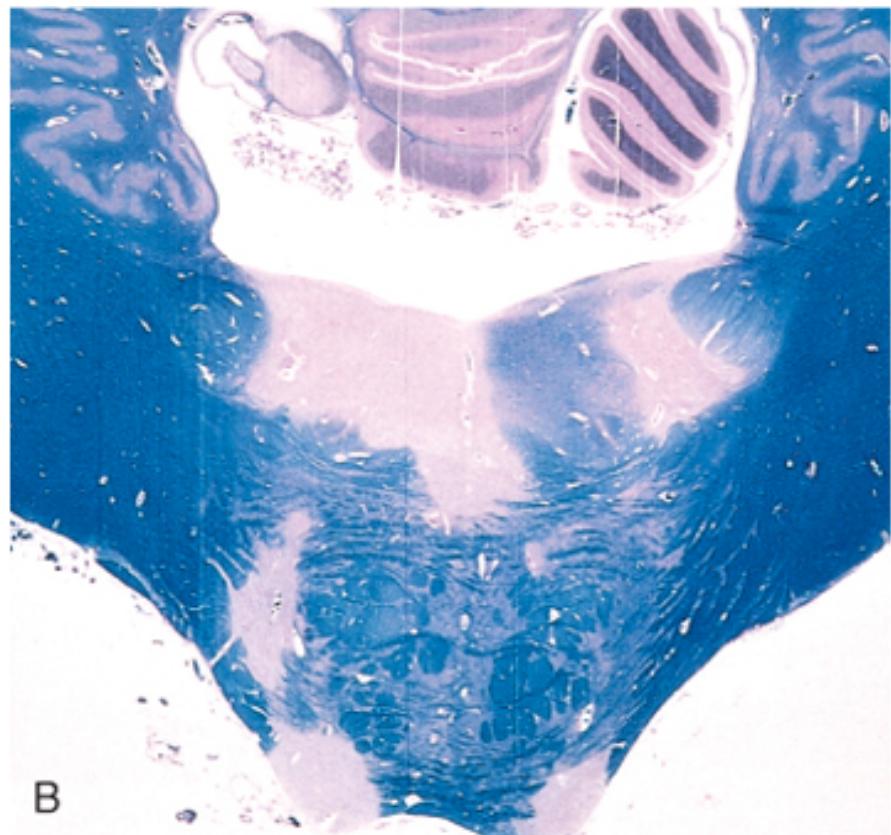
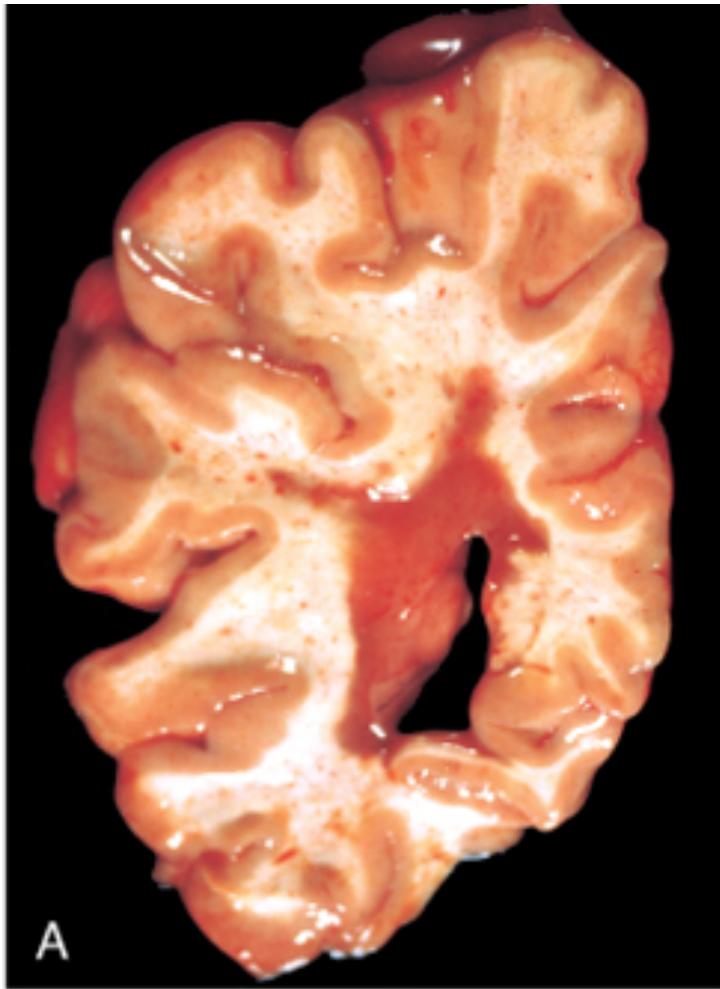


# Blood brain barrier break down

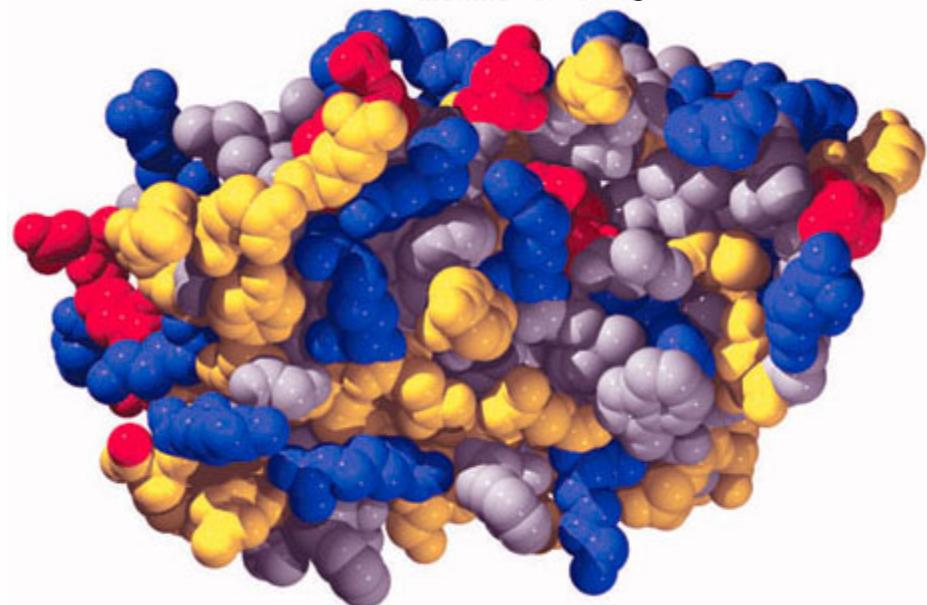
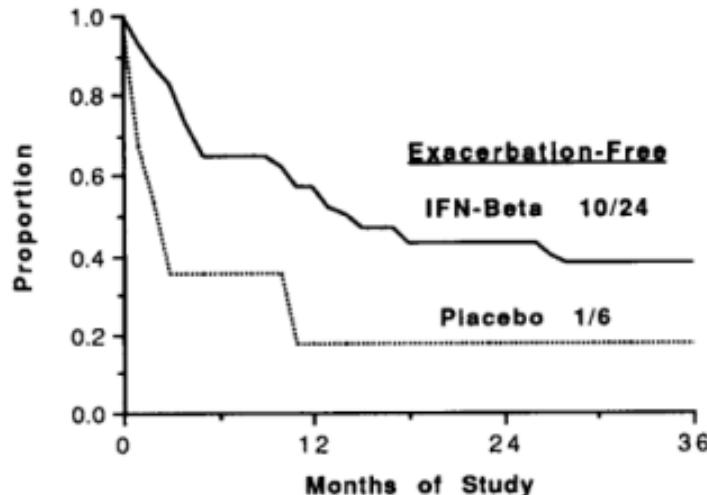
- biomarkers
- T-cell attack
- molecular mimicry
- virus cause?



# Scleroses (Plaques)



# Treatment



## Common:

- Corticosteroids
- Interferon- $\beta$

## Emerging Treatments:

- Remyelination
- CCSVI Surgery

# Assessment

Rules:

- Groups of 4 to 5
- 5 minutes to design project
- You have a paper in front of you with reaction mechanisms for

