UCSF Weill Institute for Neurosciences

Memory and Aging Center

Staying Sharp:
Current and Future Approaches to Brain Health and Alzheimer's Therapeutics

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Dept. of Neurology
University of California, San Francisco
2019.10.24

Dementia: “The graveyard of therapeutics”

- 2002 - 2012: 244 compounds, 413 clinical trials
- 0.4% success rate--lowest of any therapeutic area
- Since 2002, only memantine approved
- Trials: symptomatic (37%), disease-modifying small molecules (35%) and immunotx (18%)
- Other drugs approved for AD pre-2002:
  - donepezil (1997)
  - rivastigmine (2000)
  - galantamine (2001)

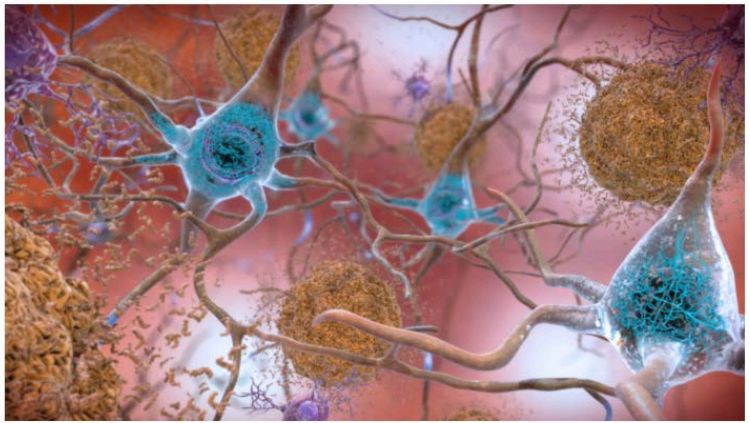
Cummings et al, 2014

Recent news in AD therapeutics: Anti-amyloid antibodies reanimated?

BREAKING NEWS

In shocking reversal, Biogen to submit experimental Alzheimer's drug for approval

By MATTHEW HERPER @matthewherper / OCTOBER 22, 2019



NATIONAL INSTITUTE ON AGING, NIH

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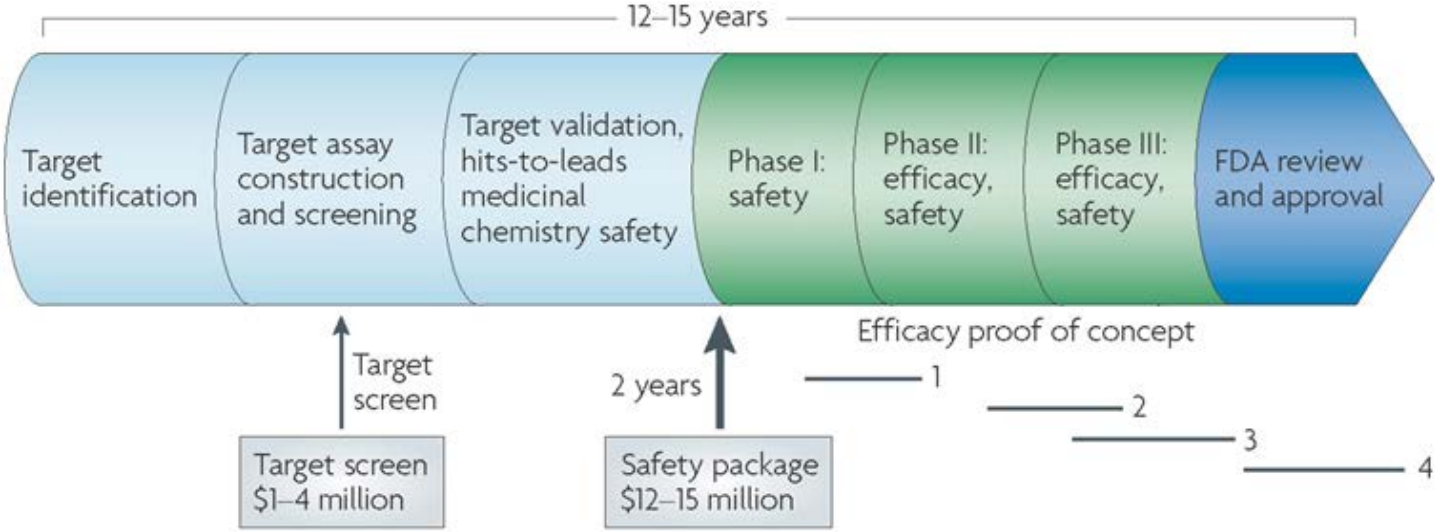
The Long and Expensive Drug Development Pipeline



Nature Reviews | Drug Discovery

A. Roses, 2008

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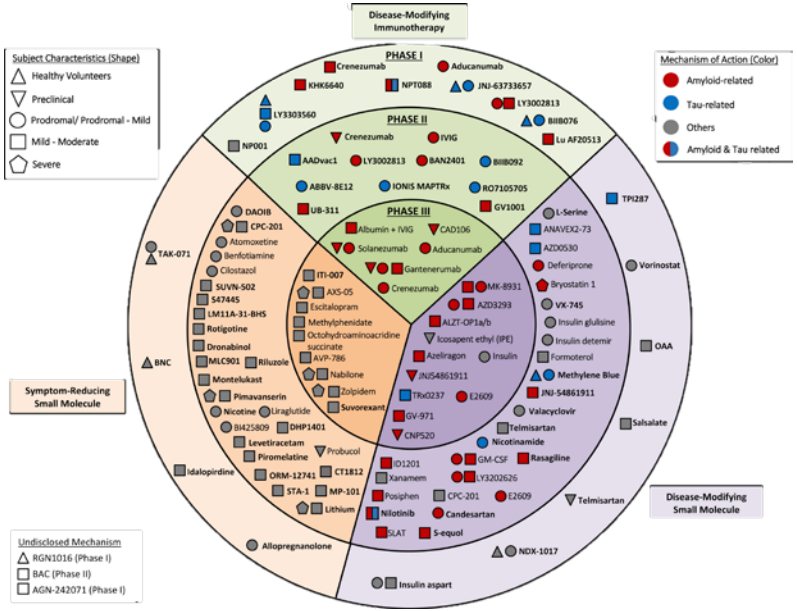
More drugs in the pipeline for neurodegeneration

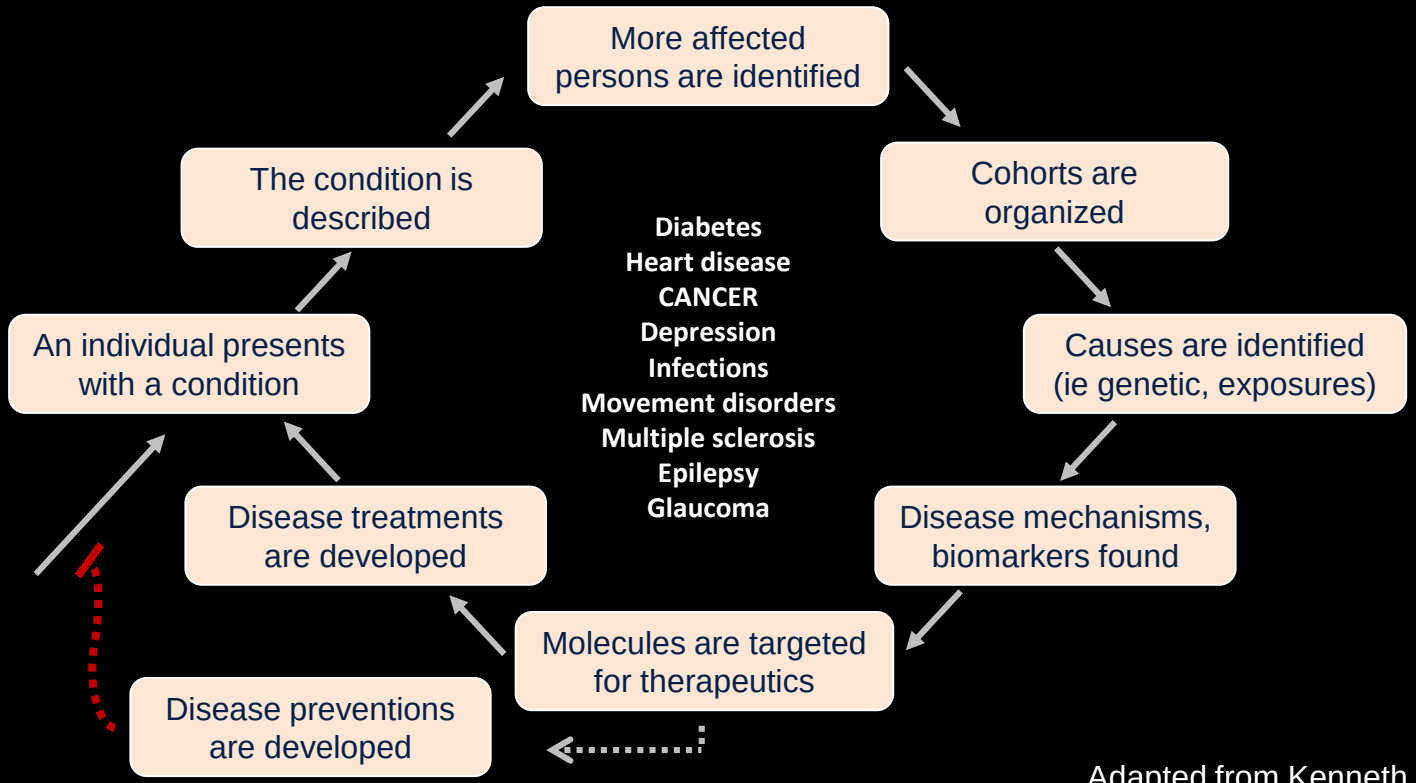
Overview of Targets

- Plaques/amyloid
- Tangles/tau
- Microtubule stabilization
- Prevent neuron death
  - Oxidative stress
  - Inflammation
  - Neuroprotection



Cummings, Lee, Ritter, Zhong 2018

The benevolent cycle of human disease research



Adapted from Kenneth Fishbeck, MD

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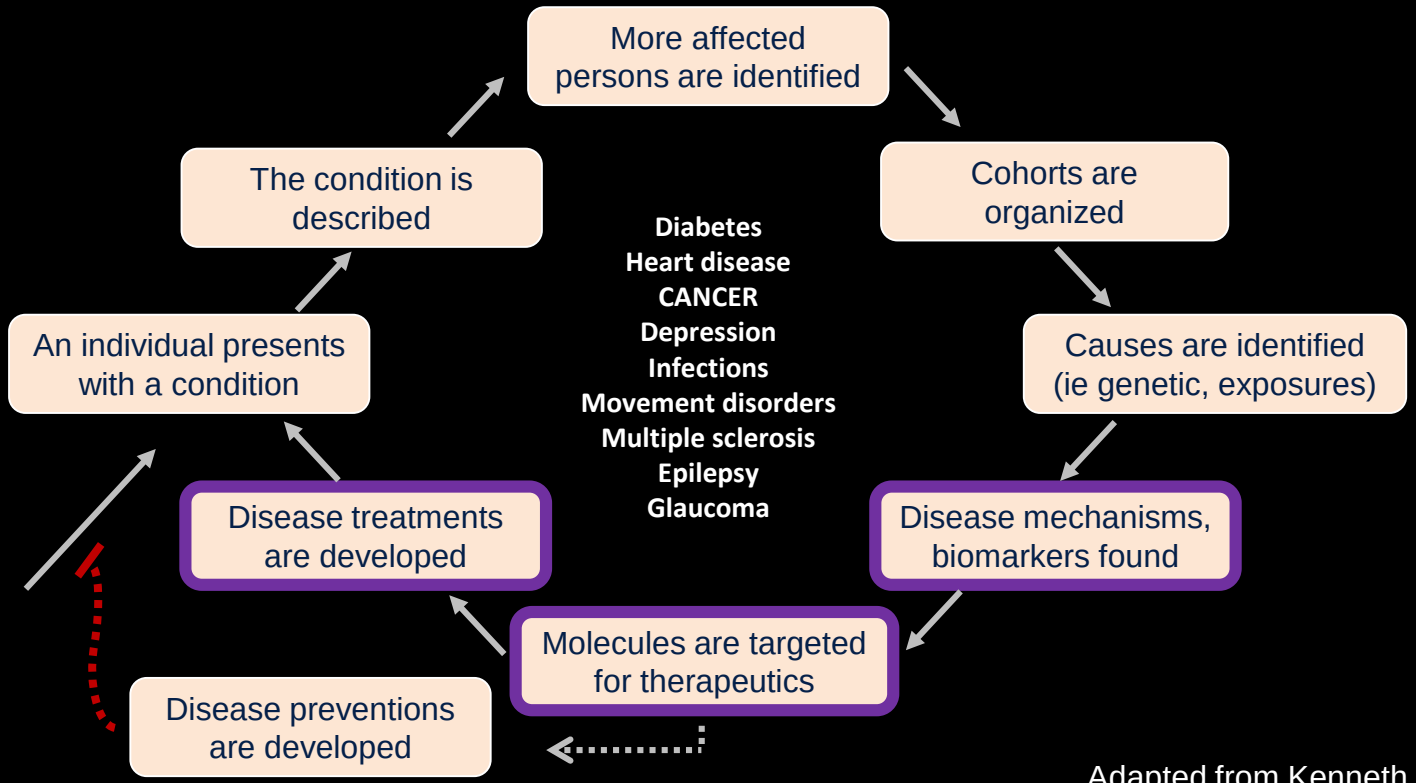
The benevolent cycle of human disease research



Adapted from Kenneth Fishbeck, MD

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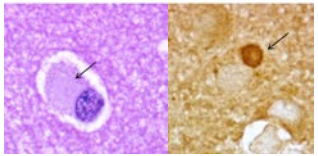
Neuronal protein aggregates are the “pathognomonic” feature of neurodegenerative diseases

Arnold Pick

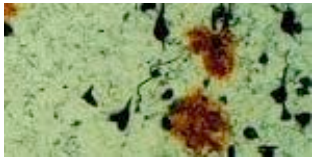


Pick Bodies (1892)

Frontotemporal dementia

Behavior

Alois Alzheimer

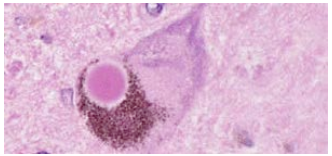


Plaques/tangles (1906)

Alzheimer’s Disease

Memory

Frederic Lewy



Lewy Bodies (1912)

Parkinson’s Disease

Movement

Developing therapeutics: Can we learn from other fields?

- ***Perspective:*** ~20 years behind cancer
- ***Needed:***

  - Better genetic and molecular characterization of neurodegenerative disease
  - Personalized approaches
  - Understanding of the basic science!

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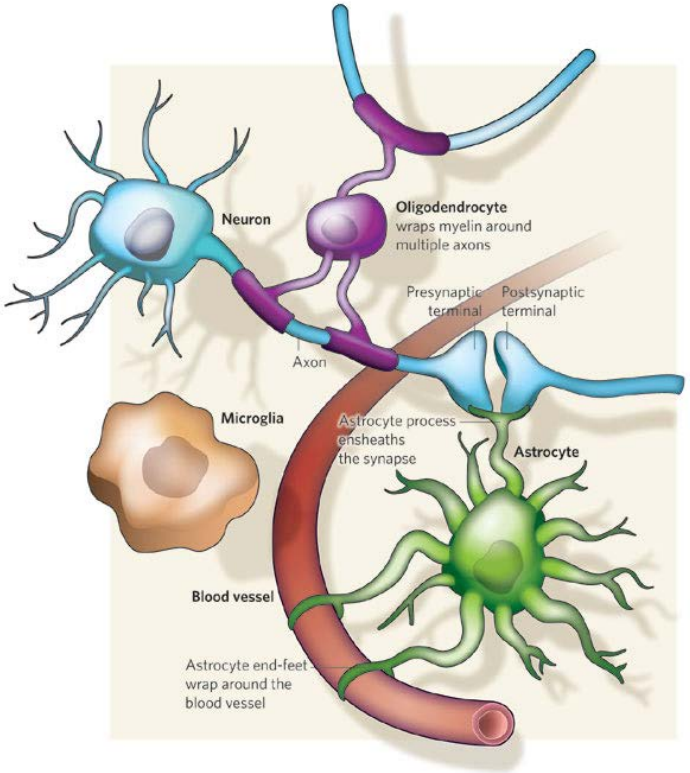
A laundry list of potential mechanisms for neurodegeneration

Genetics
Gene mutation
Gene dosage
SNPs
Epigenetics
Molecules

RNA
RNA BP
miRNA
RNA foci
Stress granules
RNA structure

Proteostasis
Lysosome/Autophagy
Proteosome
ER stress
Chaperones
Prion/aggregation
PTM

Trafficking
Nuclear pore
Endo/lysosome
Axonal
Dendritic



www.wiki.brown.edu

Synapses/activity
Excitotoxicity
Selective vulnerability
Synaptic dysfunction
Excessive pruning
Microtubule stability

Aging
Oxidative stress
Mitochondrial dysfxn
Gene expression
Cell senescence

Injury/Environment
Traumatic Brain Injury
Auto-immunity
Complement
Lipid Homeostasis
Metabolism
Heavy metals

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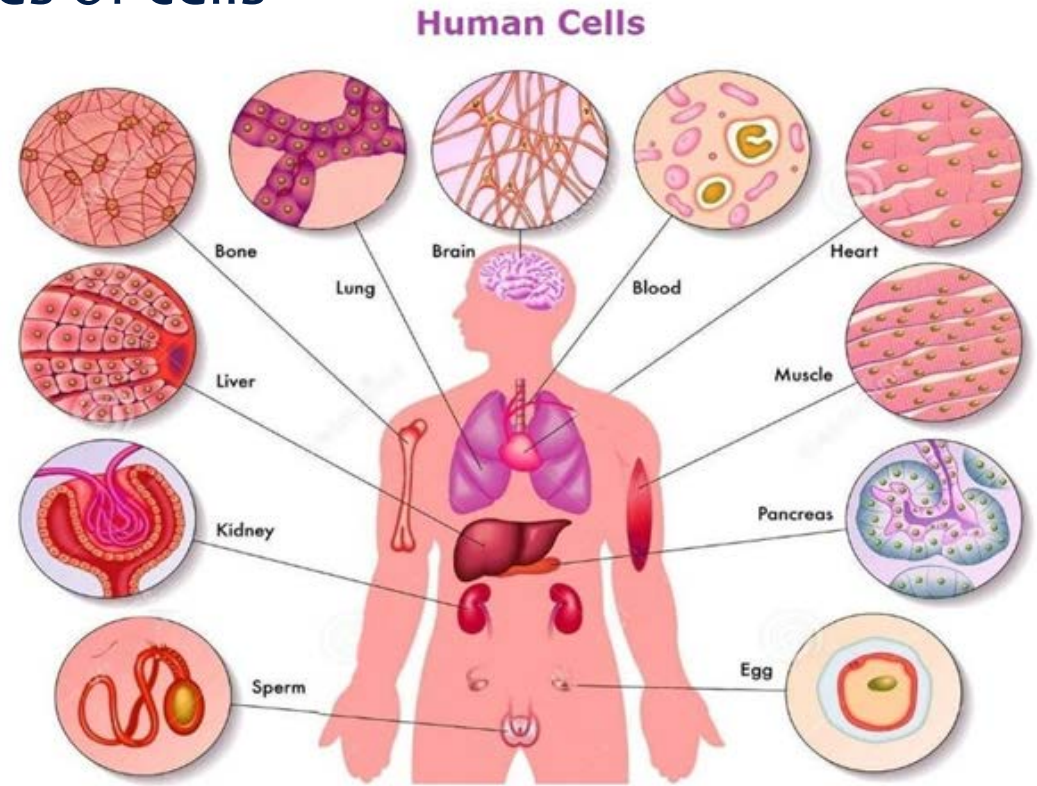
So, why more basic science?

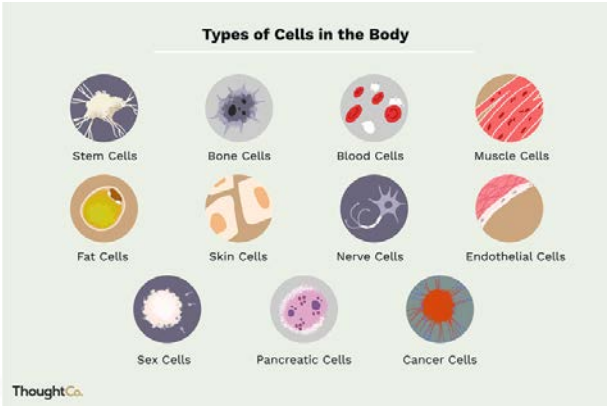
- Hard to solve a problem if you don't know the cause
- The fundamental biology surrounding the problem needs to be in places as well
  - ie Cell cycle studies and apoptosis→checkpoint inhibitors
  - ie Single cell DNA sequencing→Anti-tumor neo-antigens
- Dramatic shift towards more, different, humanized models

Two basic science stories…

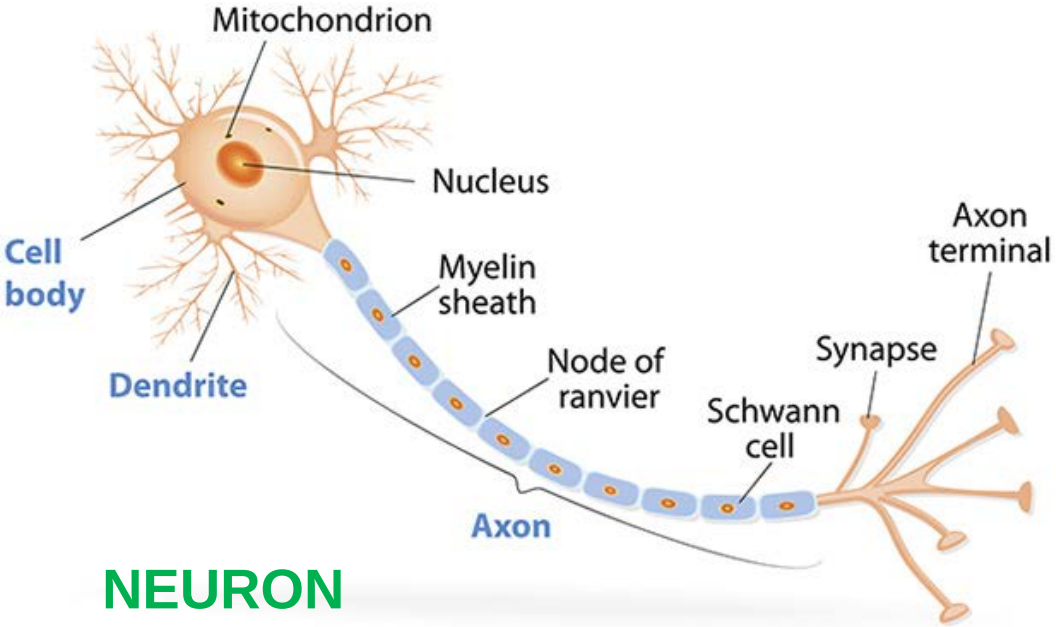
- Stem cells and genome editing
- Better custodial services in neurons

Humans and other organisms are made of many different types of cells

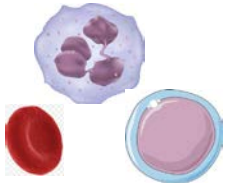




Stem cells are cells that can become any other cell type



NEURON



Blood Cells

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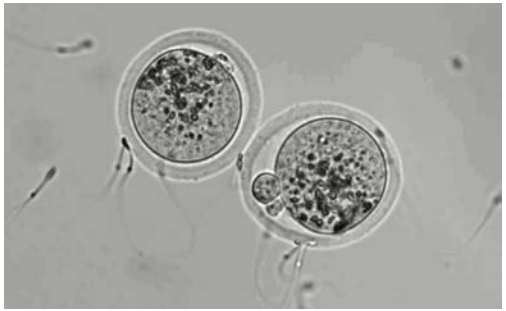
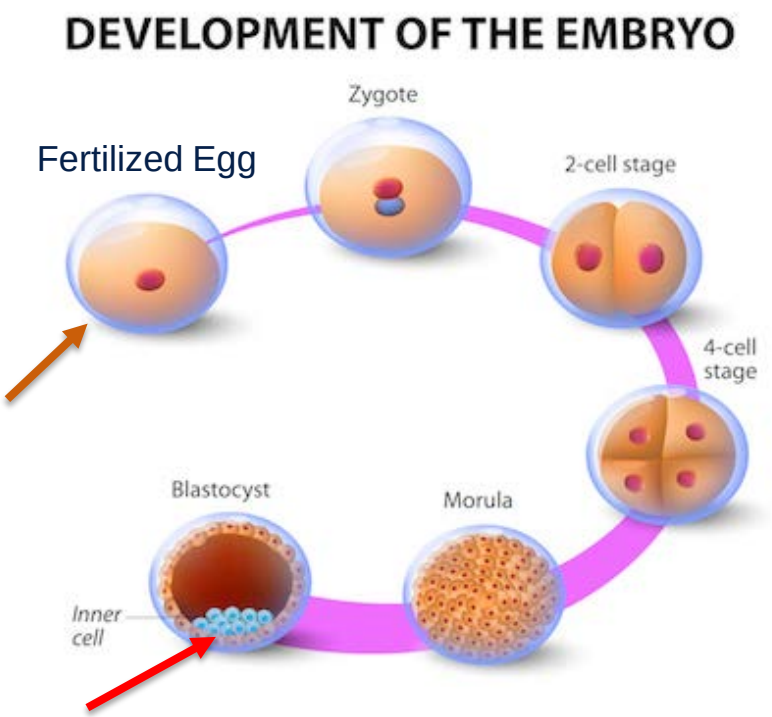
Where do stem cells come from?





Stem cells!

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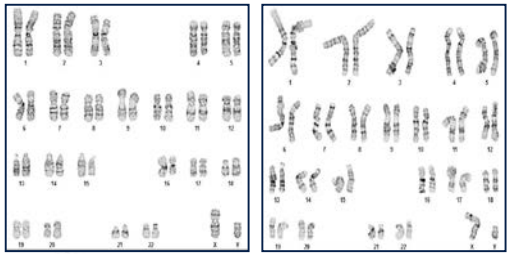
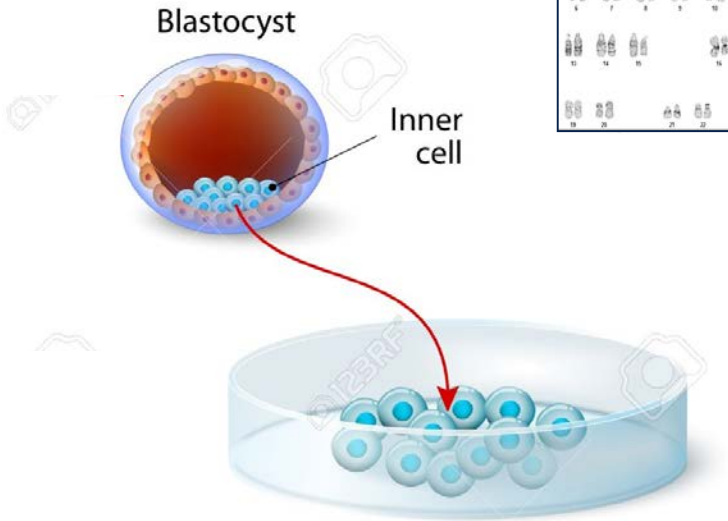
What are characteristics of stem cells?

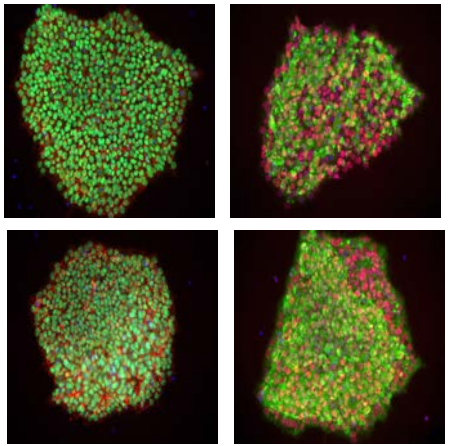
Karyotype: 46 chromosomes





Special markers

SSEA4 Oct4 NANOG Tra-1-60



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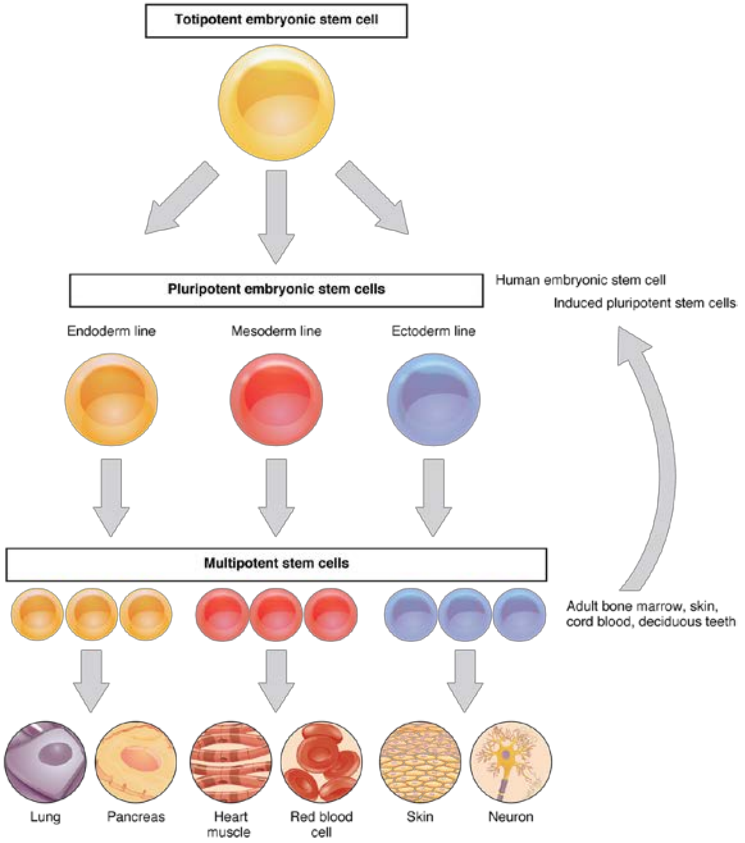
Stem cells come in 3 varieties

- Totipotent
- Pluripotent
- Multipotent



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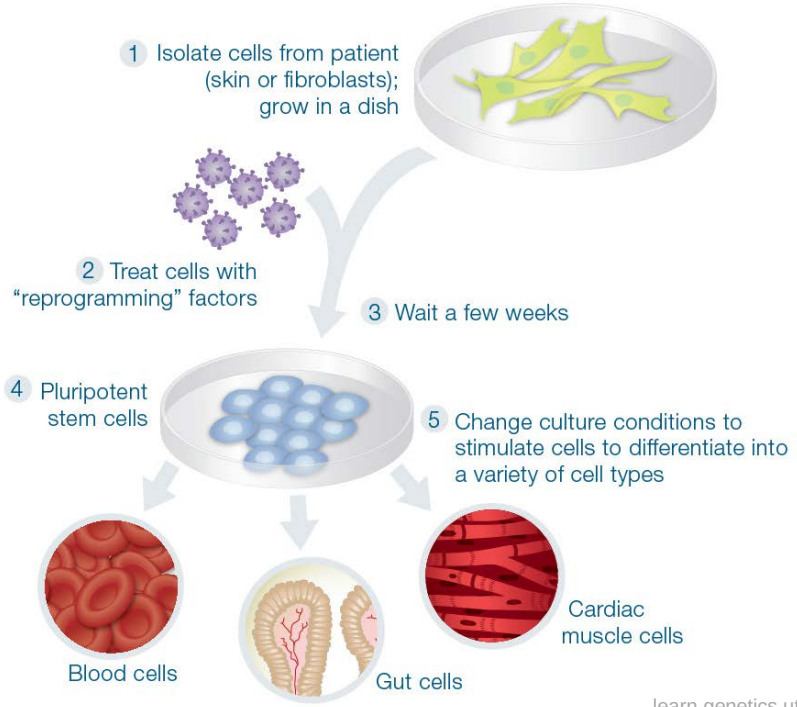
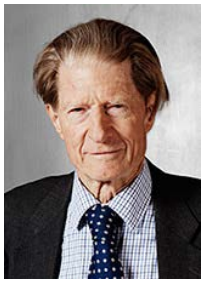
“Reprogramming” skin cells into induced Pluripotent Stem Cells (iPSCs)



learn.genetics.utah.edu



Gurdon

Yamanaka

Thomson

2012 Nobel Prize in Physiology or Medicine

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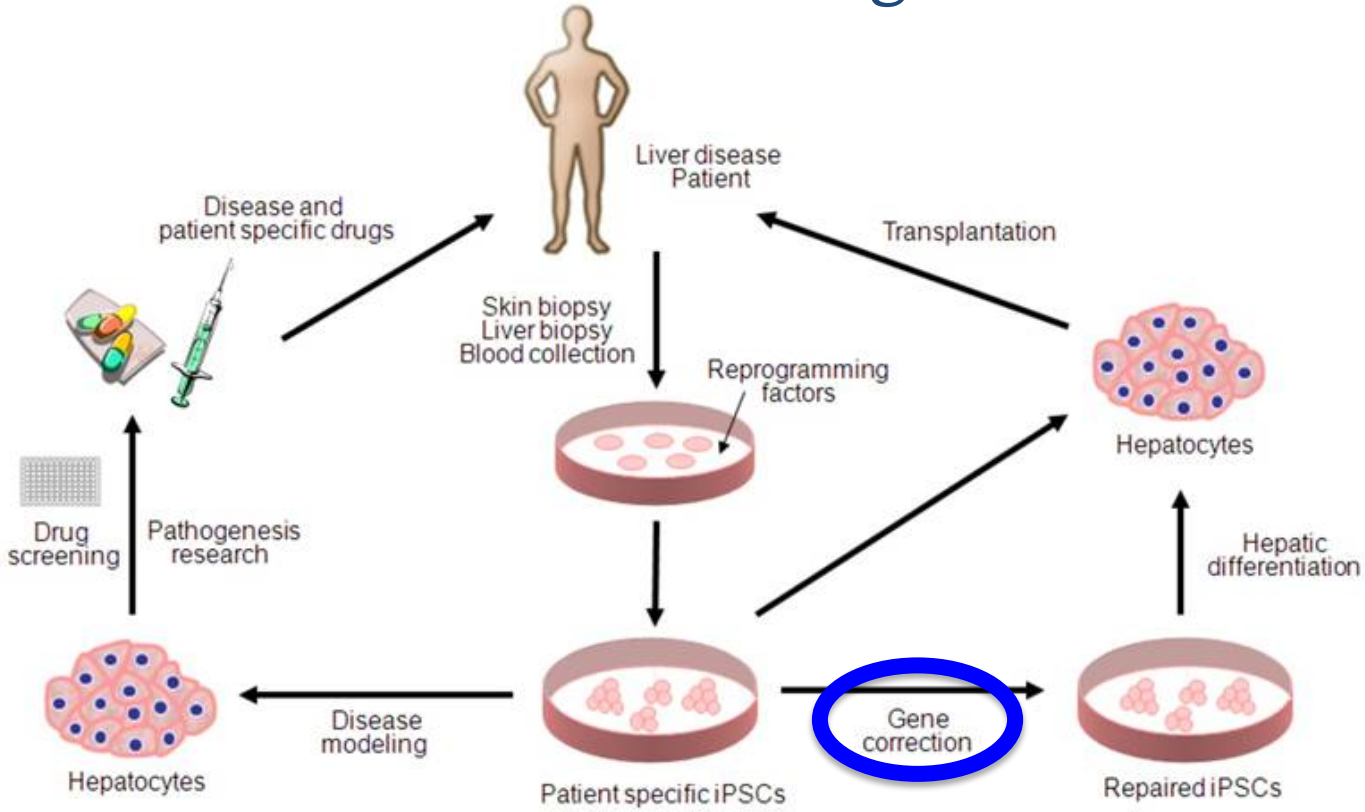
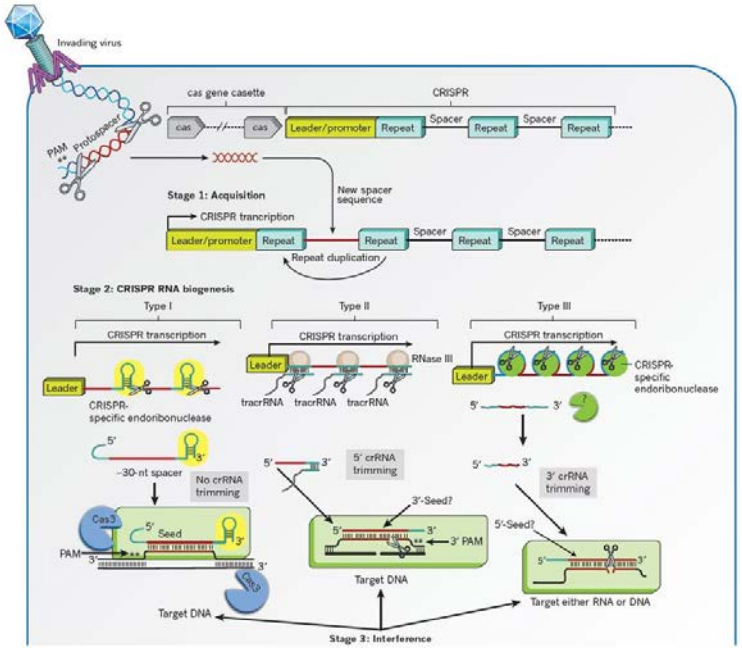
iPSCs are revolutionizing medicine



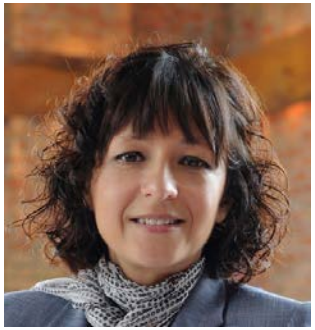
CRISPR-Cas 9 genome editing

Bacterial have to fight viruses, too!

- Doudna, Charpentier and others studied bacterial adaptive immunity



Jennifer Doudna, PhD



Emmanuelle Charpentier, PhD

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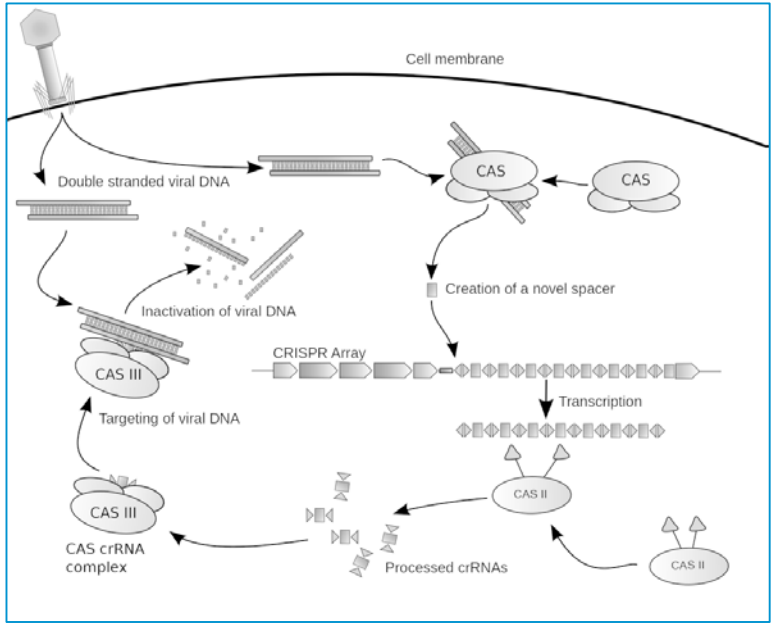
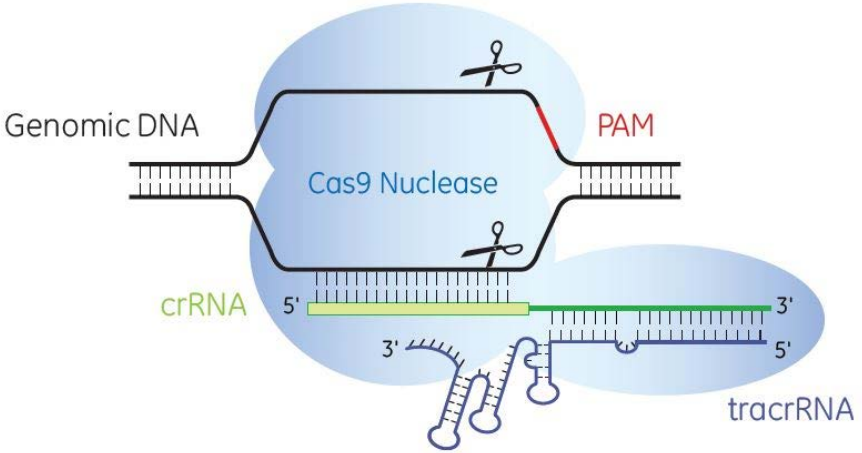
So, what is a “CRISPR-Cas 9 System”?

- **C**lustered **R**egularly **I**nterspaced **S**hort **P**alindromic **R**epeats
- A way that bacteria can fight viruses they have been exposed to before
- Cas9 cuts the RNA



How did bacterial immunity turn into genome editing?

Doudna Charpentier Zhang



A minimal CRISPR/Cas9 system

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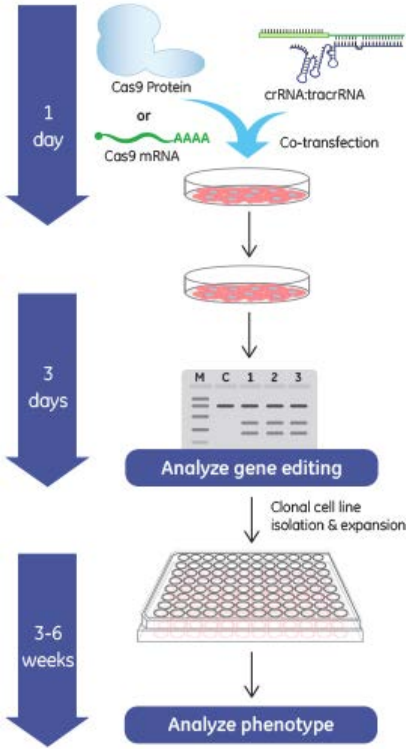
Uses for CRISPR/Cas9 gene editing



- Knock out a gene
- Mutate a gene
- Repair a gene
- Inhibit or overexpress specific genes (CRISPRi and CRISPRa)

- In cells and model organisms
- What about humans?

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Nonetheless, CRISPR gene editing may have already been performed in humans

The New York Times

Nov. 26, 2018

Chinese Scientist Claims to Use Crispr to Make First Genetically Edited Babies

The researcher, He Jiankui, offered no evidence or data to back up his assertions. If true, some fear the feat could open the door to "designer babies."

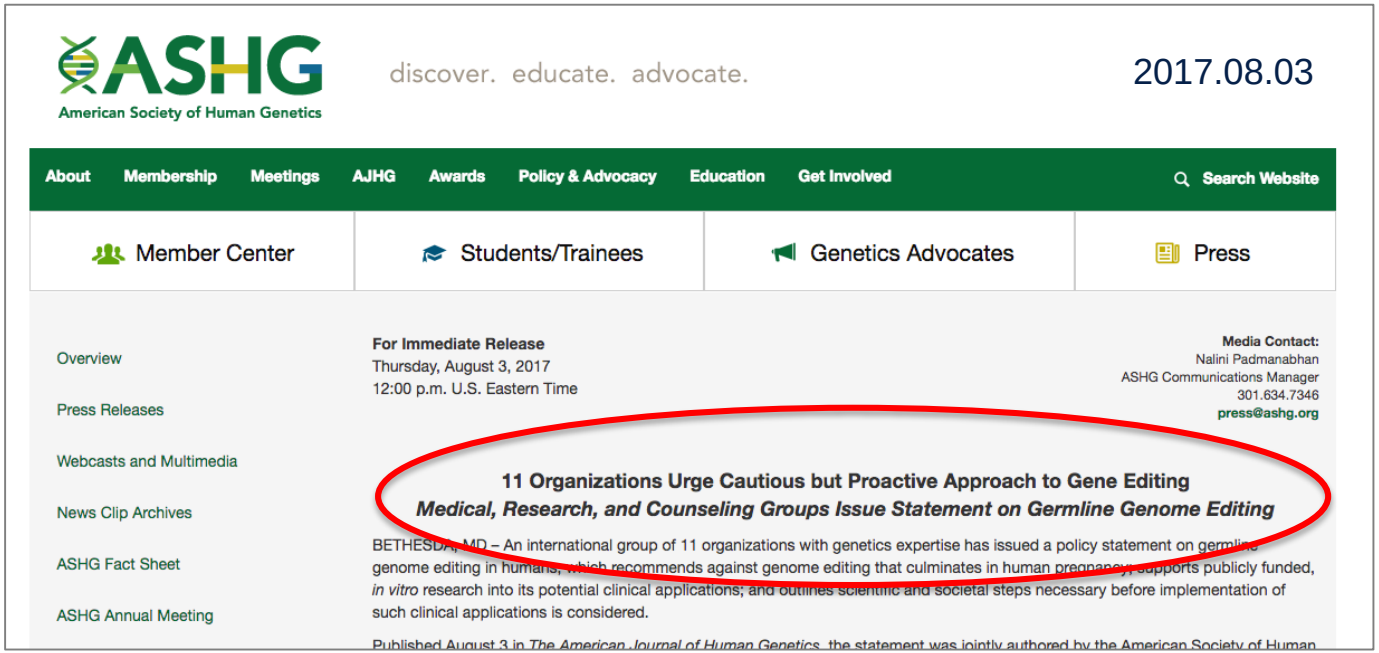
New gene editing technology could correct 89% of genetic defects

CNN

By Jessie Yeung, CNN

Updated 4:36 AM ET, Tue October 22, 2019

Geneticists don't think CRISPR is ready for humans…



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American Society of Human Genetics

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For Immediate Release
Thursday, August 3, 2017
12:00 p.m. U.S. Eastern Time

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11 Organizations Urge Cautious but Proactive Approach to Gene Editing

Medical, Research, and Counseling Groups Issue Statement on Germline Genome Editing

BETHESDA, MD – An international group of 11 organizations with genetics expertise has issued a policy statement on germline genome editing in humans, which recommends against genome editing that culminates in human pregnancy; supports publicly funded, *in vitro* research into its potential clinical applications; and outlines scientific and societal steps necessary before implementation of such clinical applications is considered.

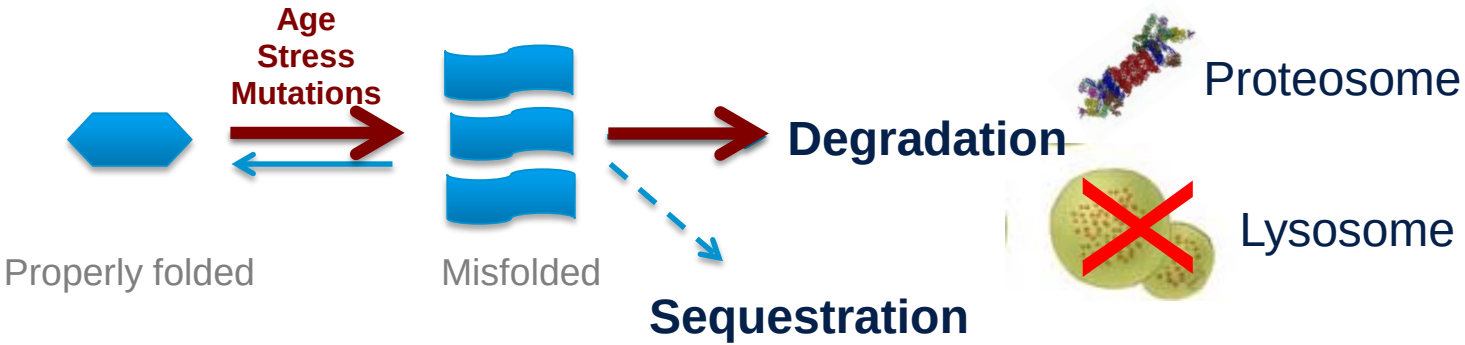
Published August 3 in *The American Journal of Human Genetics*, the statement was jointly authored by the American Society of Human

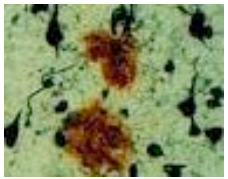
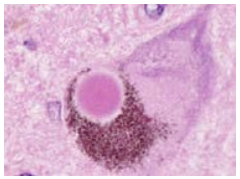
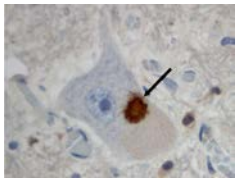
Due to scientific, ethical and policy questions

Two basic science stories…

- Stem cells and genome editing
- Better custodial services in neurons

Neurodegenerative diseases: Age-related disorders of selectively impaired “protein homeostasis”



	Alzheimer’s	Parkinson’s	FTD/ALS
			
Protein inclusion:	Aβ and tau	α-synuclein	TDP-43
Cell type of origin:	Ent Crtx	LC/SNpc	VEN/Motor N.
Genes:	*APP, PSEN*	*Pink, Parkin*	*Pgrn, CHMP2B*

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Lysosomes are responsible for breaking down misfolded proteins

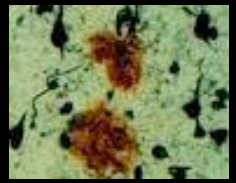
Properly folded

Misfolded

Degradation

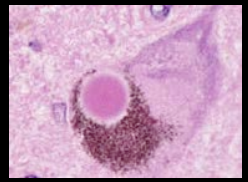
Lysosomes

Alzheimer's Disease



Amyloid plaques
Tau tangles

Parkinson's Disease



α-synuclein
Lewy Body

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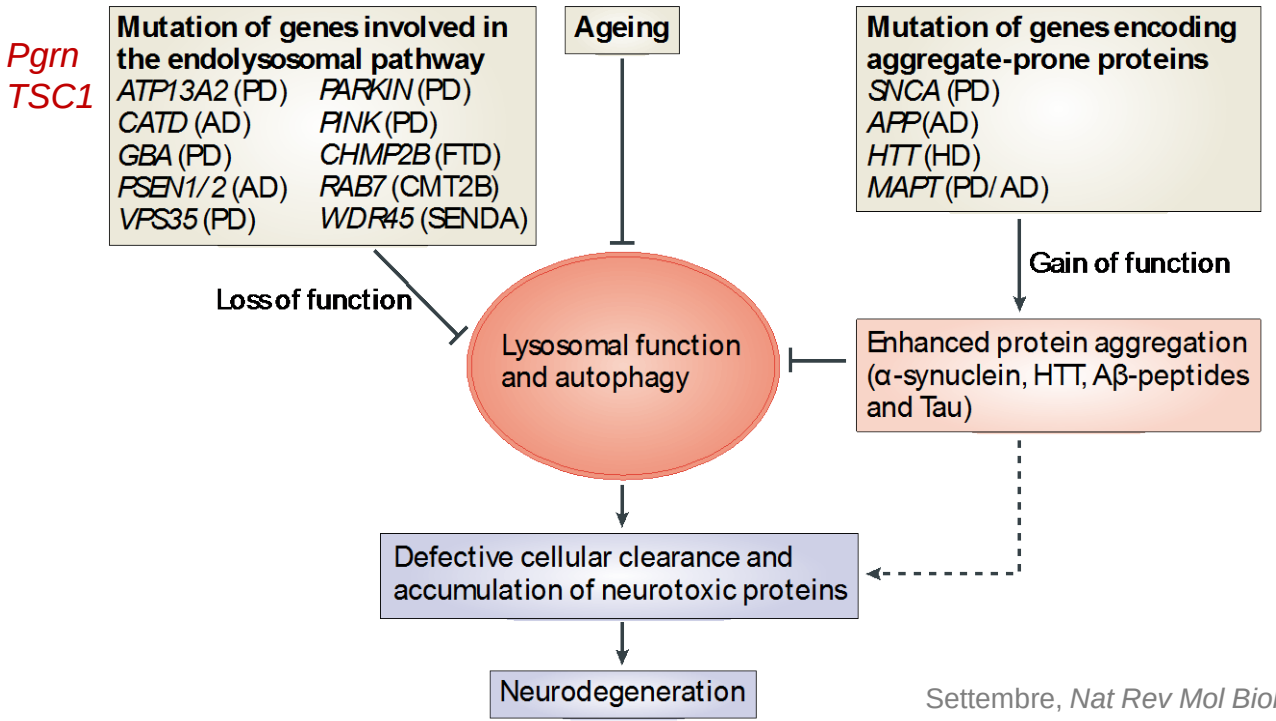
Genetic clues from neurodegenerative diseases from point to the importance of the lysosome



Settembre, *Nat Rev Mol Biol* 2013

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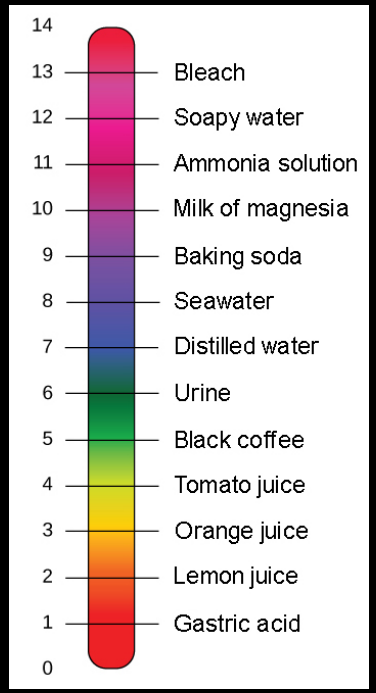
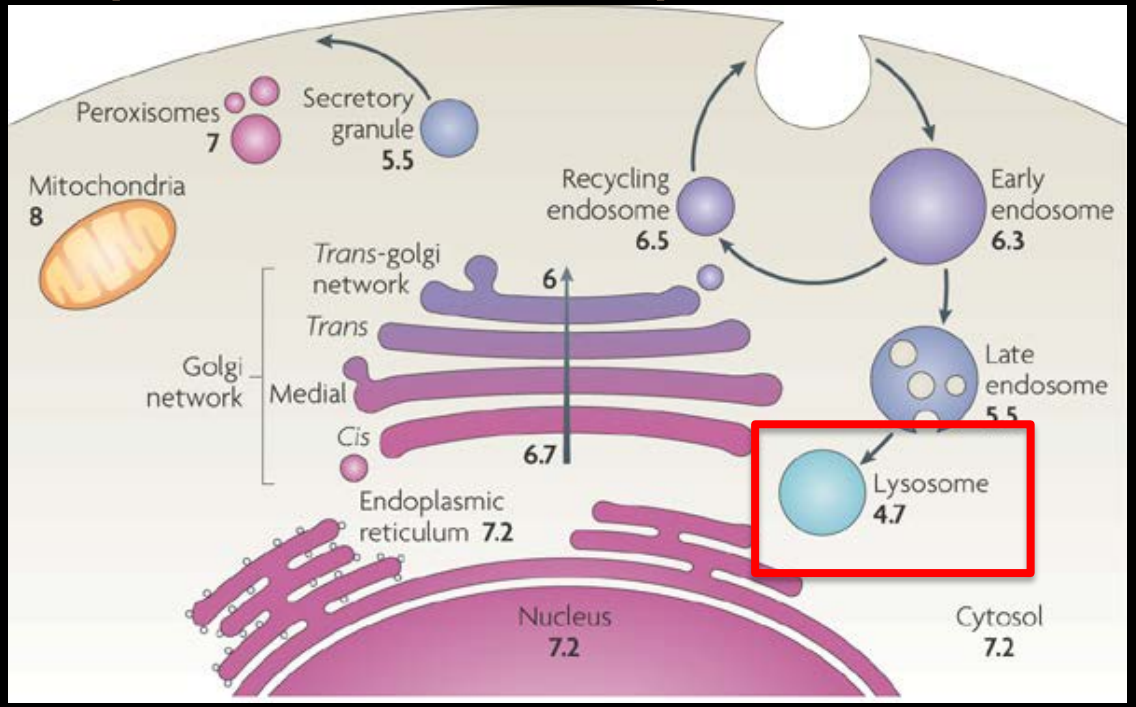
Like lemons, lysosomes are acidic

pH scale



pH varies in different part of the cell



Casey *et al.*, Nat Rev Mol Cell Biol 2010

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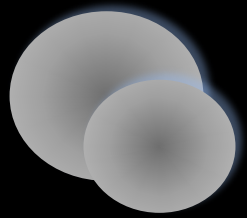
How is lysosome function controlled?

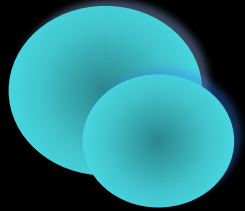


Impairs Function

Mutations

AD: *CATD, PSEN/2*
PD: *GBA, Pink, Parkin*
FTD: *PGRN, TSC1*

Aging



Improve function

?

1) **Sharpen the blades**
2) **Soup up the motor**

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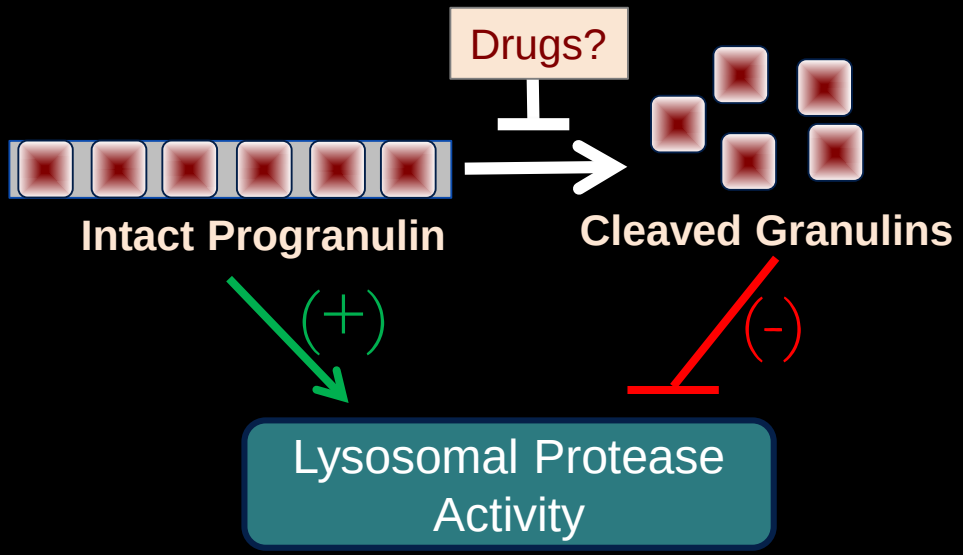
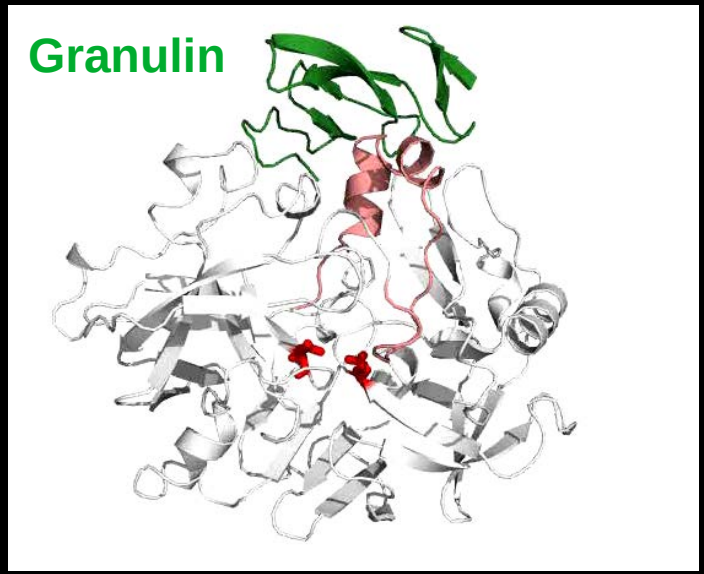
Supercharge the lysosome by sharpening the shredder blades

Lysosomal proteases = Shredder blades





Lysosomal Protease

Soup up the motor by hyper-acidifying the lysosomes

Acidity = horsepower

Other drugs?

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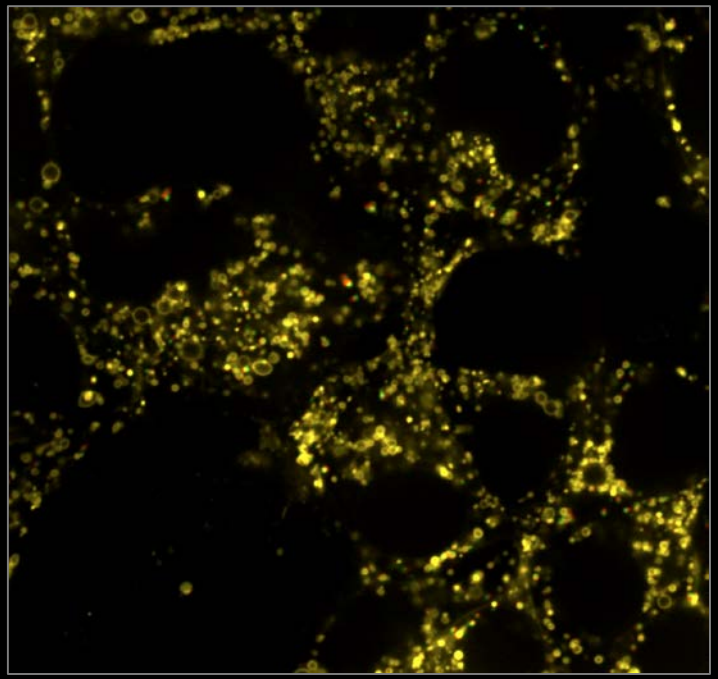
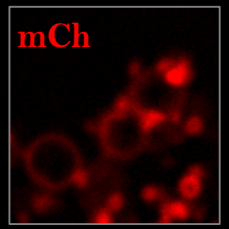
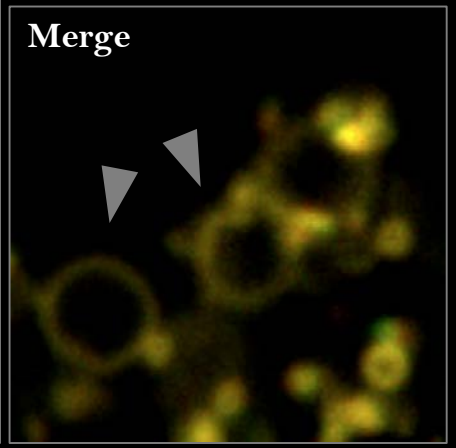
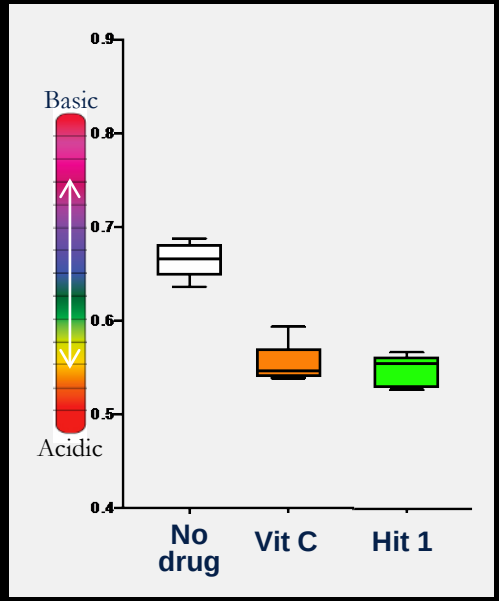
A novel tool to visualize pH in live lysosomes

pHLIP = **pH** of the **L**ysosome **I**ndicator **P**rotein









Triple pHLIP: Basic science, study disease, drug discovery

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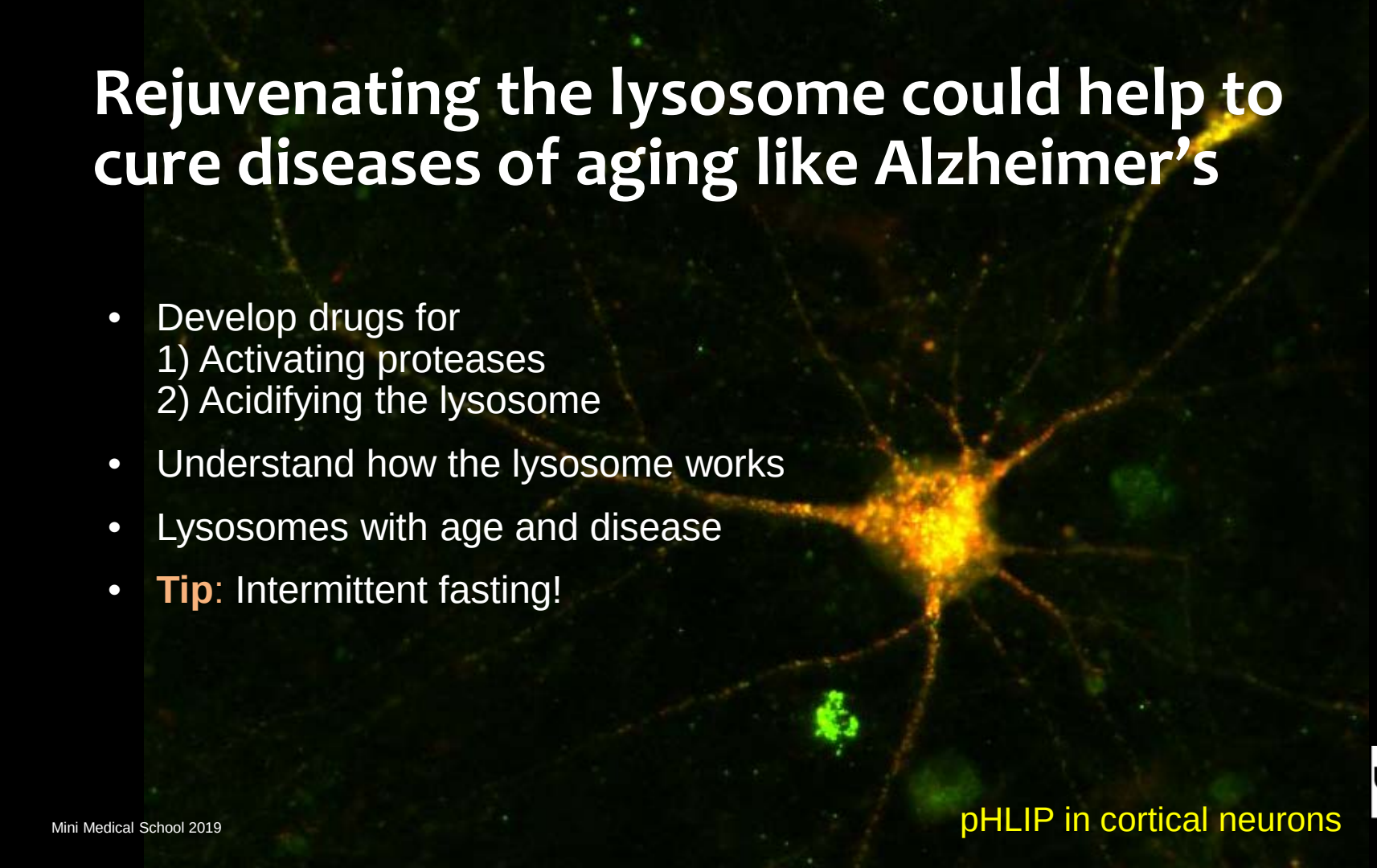
Rejuvenating the lysosome could help to cure diseases of aging like Alzheimer's

- Develop drugs for
  1) Activating proteases
  2) Acidifying the lysosome
- Understand how the lysosome works
- Lysosomes with age and disease
- **Tip**: Intermittent fasting!



pHLIP in cortical neurons

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Thank you!

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