Dr Aubrey de Grey PhD

Repairing the aging brain:

challenging, but not so futile as some say

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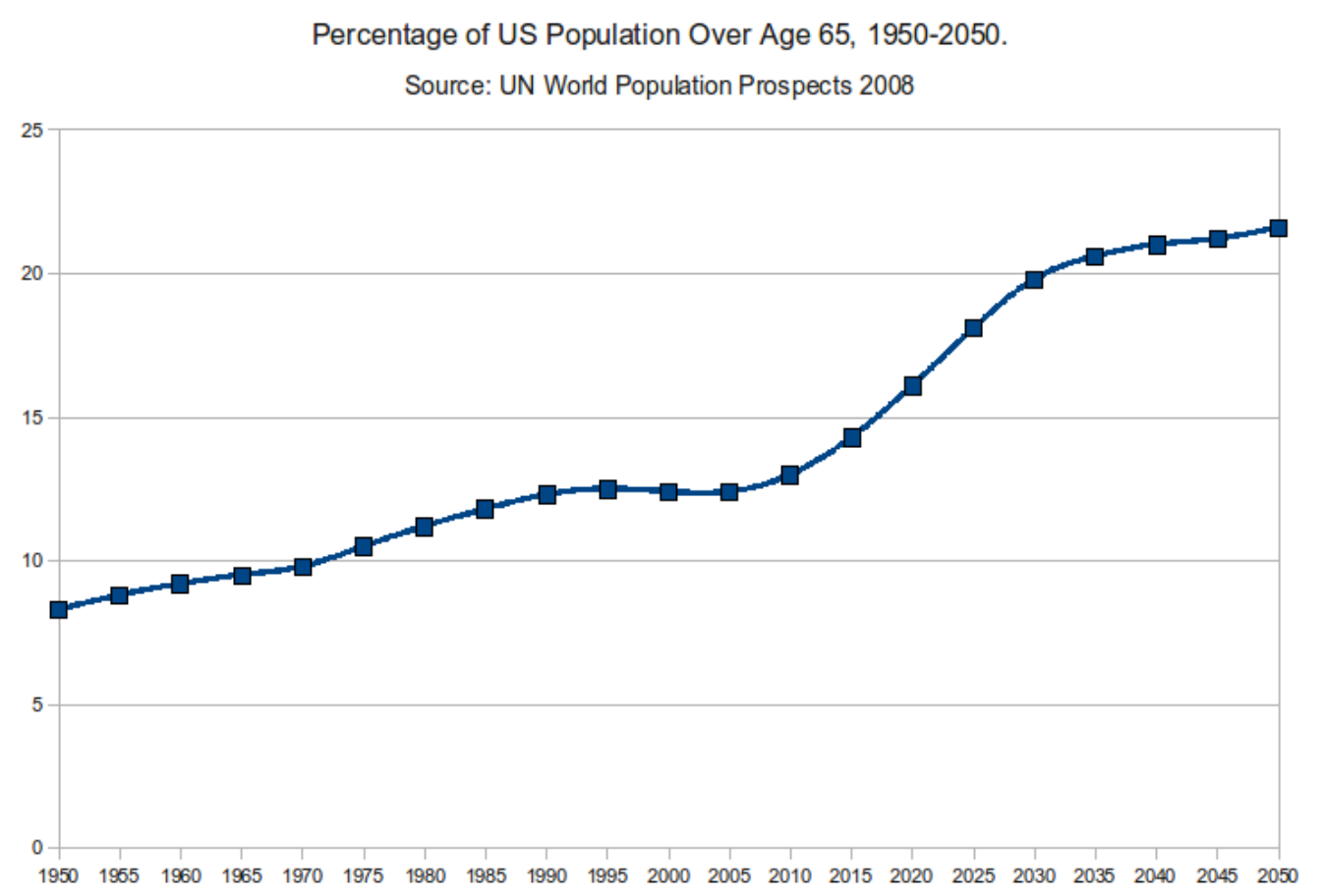
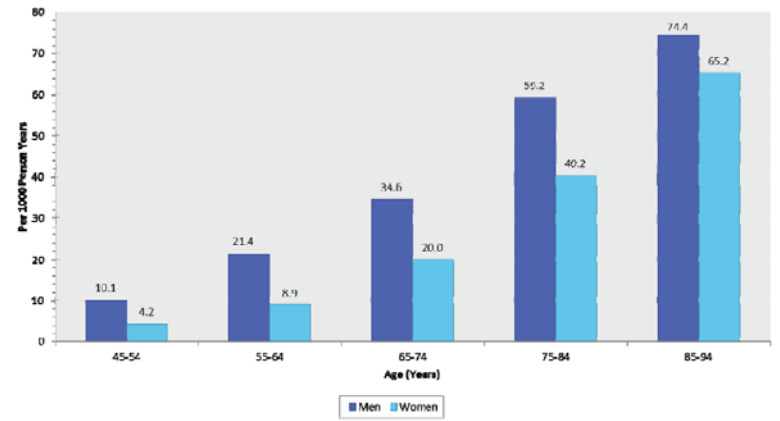
The aging population



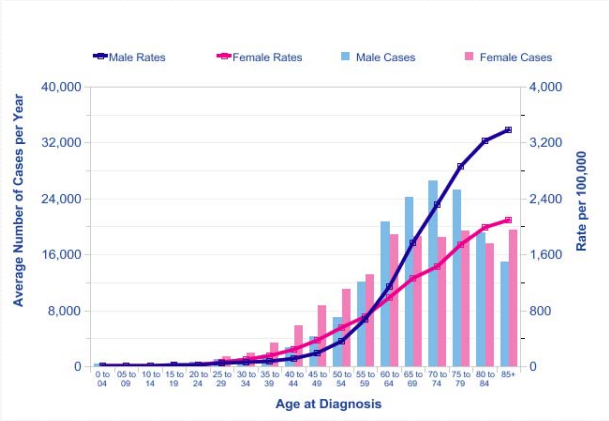
* Source: http://esa.un.org/wpp/unpp/panel_population.htm

Disease prevalence by age

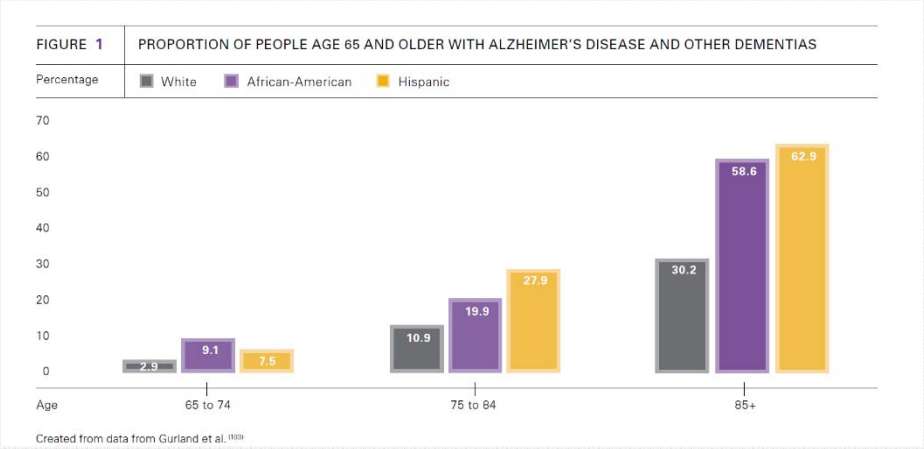
Heart Disease



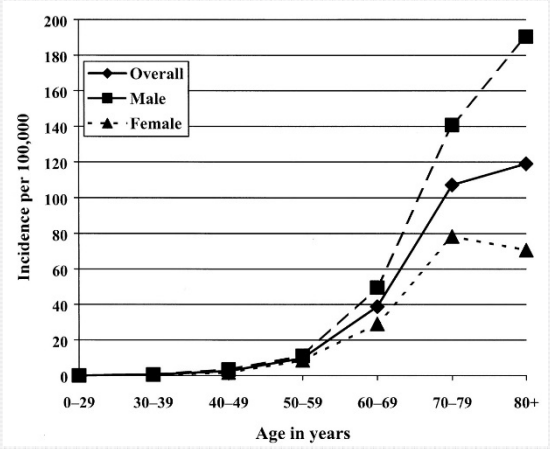
All Cancers



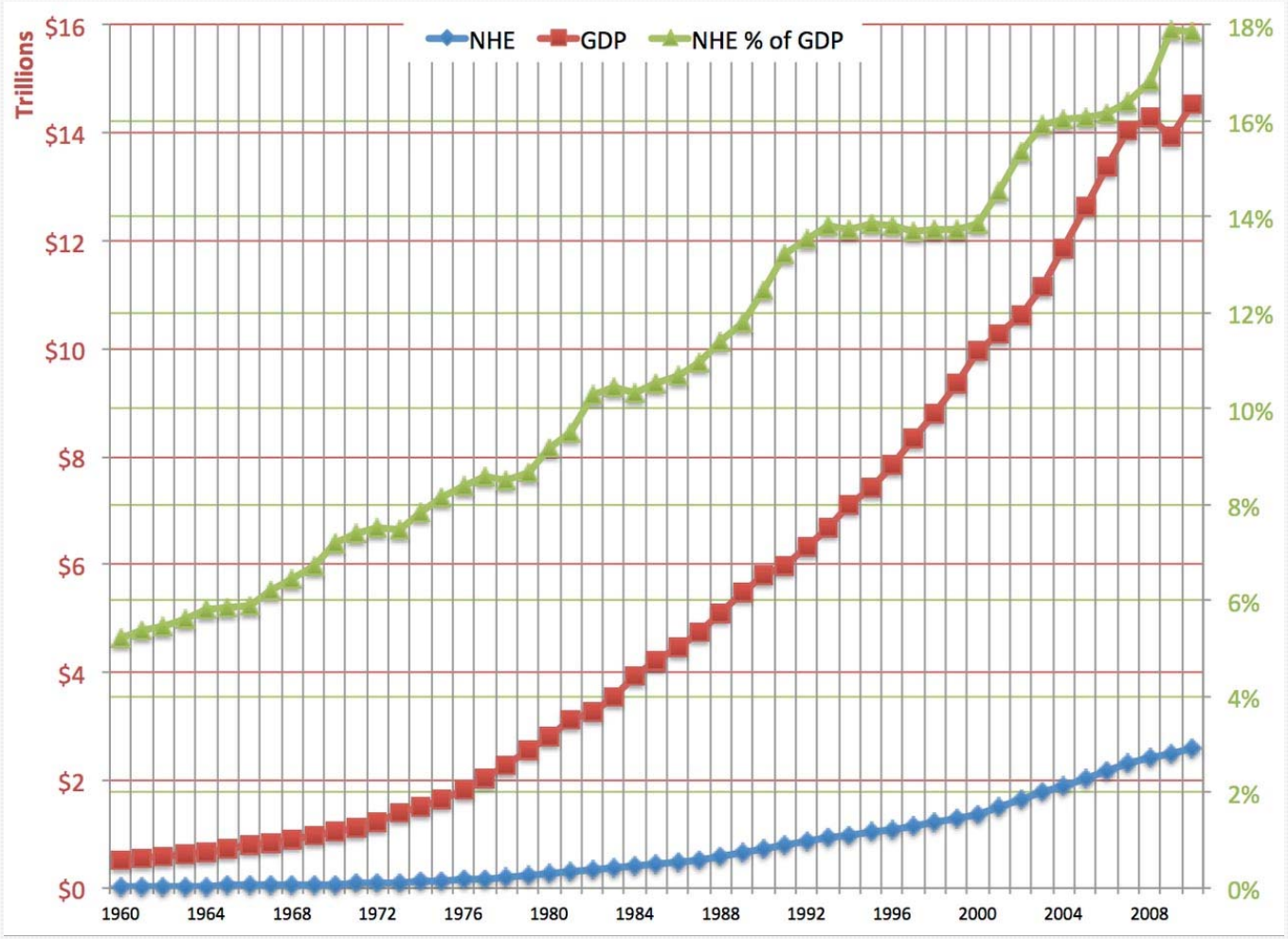
Alzheimer's Disease



Parkinson's Disease



The economics of aging



Source: http://sambaker.com/econ/classes/nhe10/

If historical rates continue, US healthcare spending will be 34% of GDP by 2040. *Source:* http://www.whitehouse.gov/administration/eop/cea/TheEconomicCaseforHealthCareReform

In 2010, the US spent $1.186 trillion on healthcare for people 65+

Source: http://www.deloitte.com/assets/Dcom-UnitedStates/Local%20Assets/Documents/us_dchs_2012_hidden_costs112712.pdf

Age-related vs. infectious diseases

- Most infectious diseases have been easily prevented
  - Sanitation
  - Vaccines
  - Antibiotics
  - Carrier control
- Age-related diseases have not. Why not?

So… what is ‘aging’, exactly?

Aging is:

The life-long accumulation of damage to the tissues, cells, and molecules of the body that occurs as an intrinsic side-effect of the body’s normal operation.

The body can tolerate some damage, but too much of it causes disease and disability.

A bizarrely underappreciated truth

Age-related diseases are caused by aging!

Thus, they are:

- widespread now that infections are “rare”
- staggeringly costly
- universal if you live long enough
- not medically curable, in the strict sense

But they, and aging itself, are nonetheless:

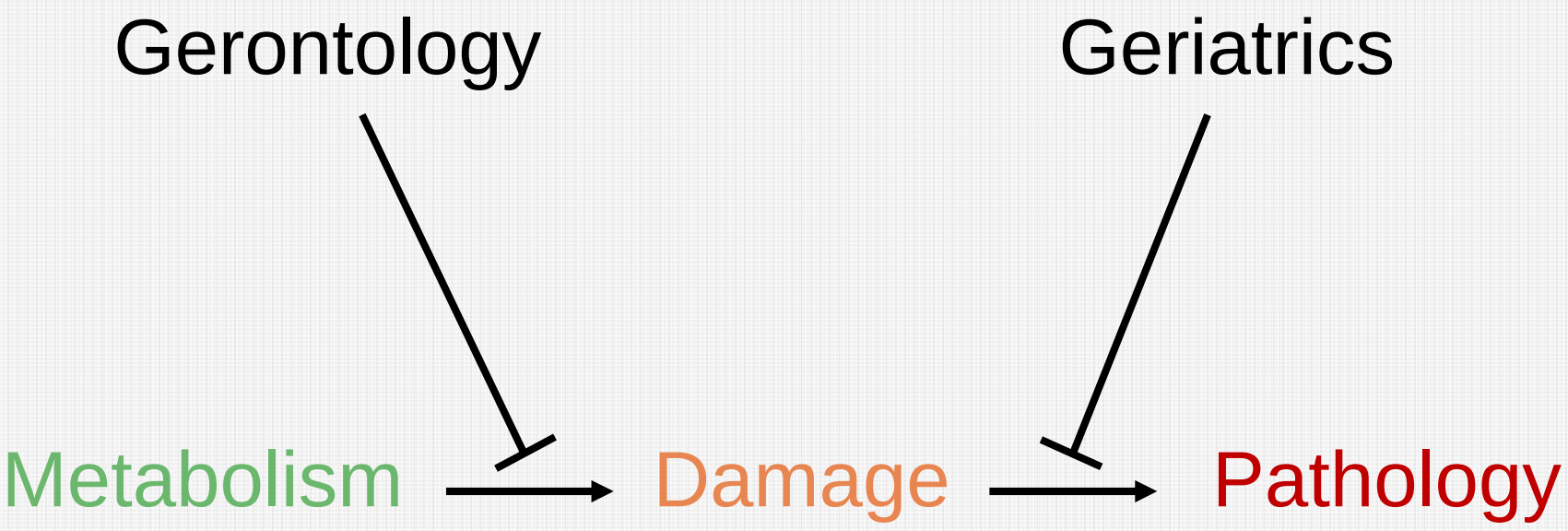
- medical problems
- medically preventable in principle

What this misguidedness means in $$

Even though 90% of US deaths and at least 80% of US medical costs are caused by aging:

National Institutes of Health budget ($M)	~30,000
National Institute of Aging budget	~1,000
Division of Aging Biology budget	~150
Spent on translational research (max)	~10
SENS Research Foundation budget	~5

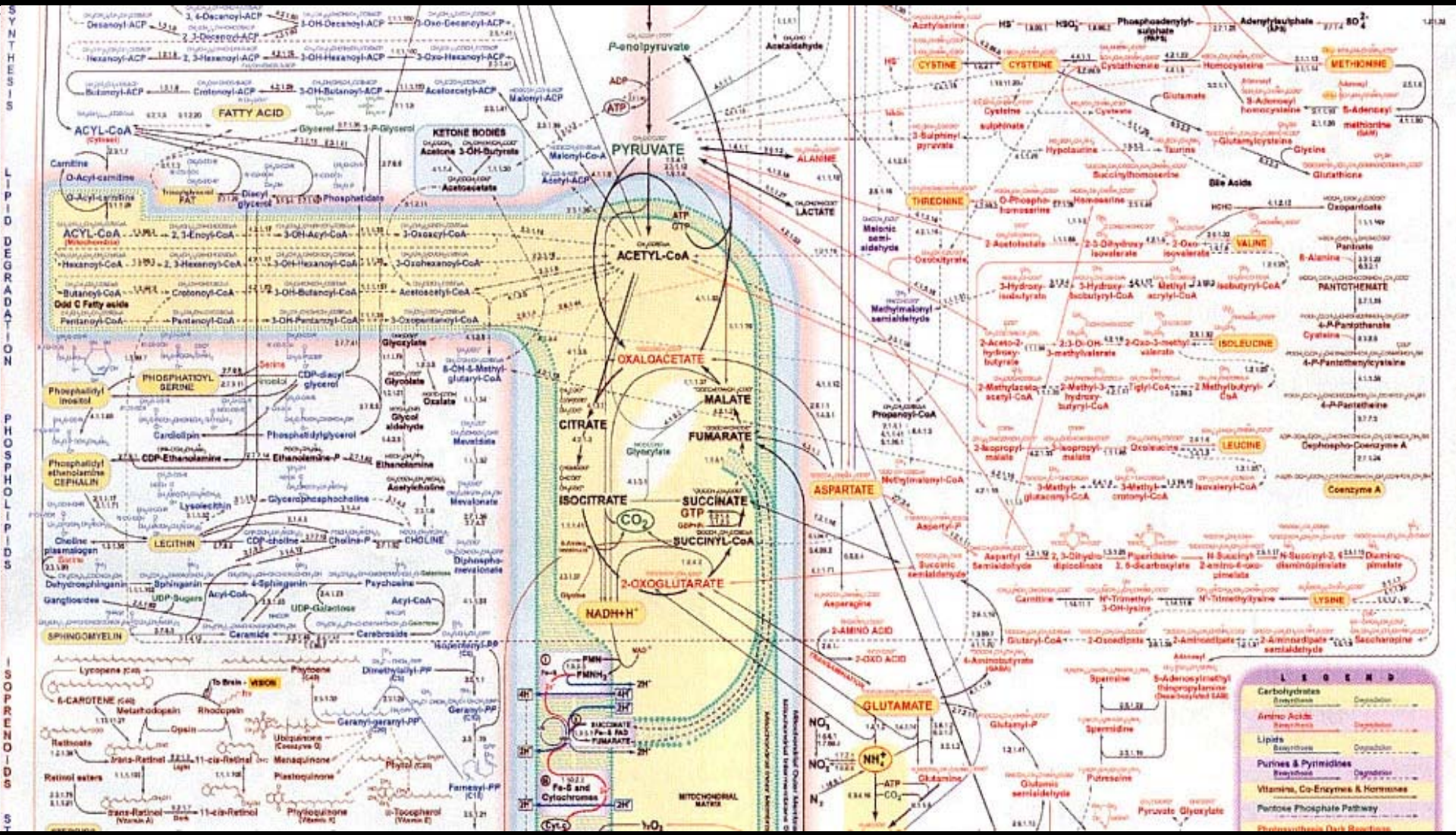
How age-related disease is addressed today



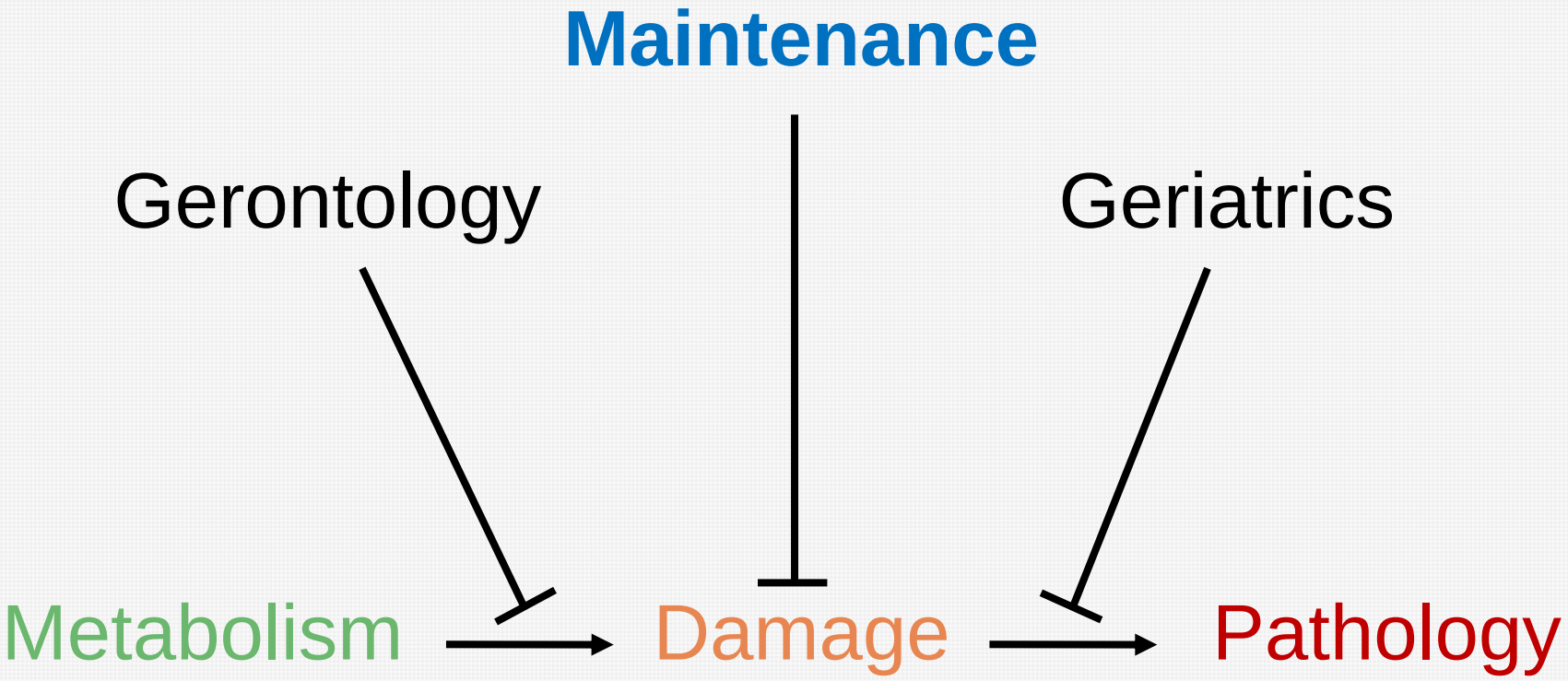
Targeting pathology: tricky

presbycusis
osteoporosis
osteoarthritis
autoimmunity
greying hair
presbyopia
cataract
glaucoma
temporal arteritis
polymyalgia rheumatica
wrinkling
Alzheimer's disease
Pick's disease
corticobasal degeneration
progressive supranuclear palsy
Parkinson's disease
multiple system atrophy
dementia with Lewy bodies
sarcopenia
glomerulonephritis
senile cardiac amyloidosis
atherosclerosis
arteriosclerosis
age-related macular degeneration
cardiomyopathy
diastolic heart failure
cancer
systemic inflammation
oxidative stress
reduced coronary blood flow
loss of cardiac reserve
andropause
thymic involution
reduced plasma renin activity
reduced aldosterone
reduced melatonin diurnal rhythm
reduced light adaptation
reduced ethanol metabolism
altered drug pharmacokinetics
somatopause
loss of cardiac adaptability
incontinence
impaired wound healing
idiopathic axonal polyneuropathy
autonomic neuropathy
arrhythmia
chronic obstructive pulmonary disorder
benign prostatic hypertrophy
menopause
leukoaraiosis
stroke
vascular dementia
frontotemporal dementia
immunosenescence
anosmia
cachexia
anorexia of aging
systolic hypertension
ageusia
erectile dysfunction
orthostatic hypotension
impaired adaptive beta-cell proliferation
fibroblast collapse
anergic T-cell clones
cellular senescence
vascular calcification
impaired transdermal absorption
impaired thermoregulation
reduced tactile acuity
impaired vasoconstriction
loss of neuromuscular junctions
delayed withdrawal reflex
impaired pH maintenance
reduced chemical clearance
altered dermal immune cell residence and function
aberrant allergic and irritant reactions
loss of skin elasticity
impaired vitamin D synthesis
reduced renal reserve
renal cortex atrophy
gut dysbiosis
loss of jejunal villus height
impaired response to vaccination
impaired thirst
lentigo senilis
thinning hair
impaired proprioception
impaired balance
reduced vital capacity
reduced cardiorespiratory endurance
impaired sweat response
impaired blood distribution
nutrient malabsorption
diverticular disease
presbyphagia
increased reflux
alveolar loss
neuronal loss
senile emphysema
degenerative disc disease
joint calcification
pineal calcification
aberrant differentiation
gait instability
frontal demyelination
axonal atrophy
impaired functional connectivity
impaired working memory

Targeting metabolism: also tricky



Maintenance: targeting damage



Claim: unlike the others, the maintenance approach can deliver a big extension of human healthy lifespan quite soon

Advantages of damage repair

- Claim: damage repair can increase healthspan….
  - *more quickly*
  - *more safely*
  - *more thoroughly*
  - *more economically*

  than the gerontology or geriatrics options. Why?
- ***Prevents*** disease, addressing causes not symptoms
- But ***avoids*** interfering in metabolism

Analogy: car maintenance

Categorizing damage

Damage Types

- Cell loss, cell atrophy
- Division-obsessed cells
- Death-resistant cells
- Mitochondrial mutations
- Intracellular junk
- Extracellular junk
- Extracellular matrix stiffening

No new type of damage confirmed since 1982

And, I've said so without challenge since 2002

Diseases by damage type

Damage Types

- Cell loss, cell atrophy
- Division-obsessed cells
- Death-resistant cells
- Mitochondrial mutations
- Intracellular junk
- Extracellular junk
- Extracellular matrix stiffening

Cancer

Diseases by damage type

Damage Types

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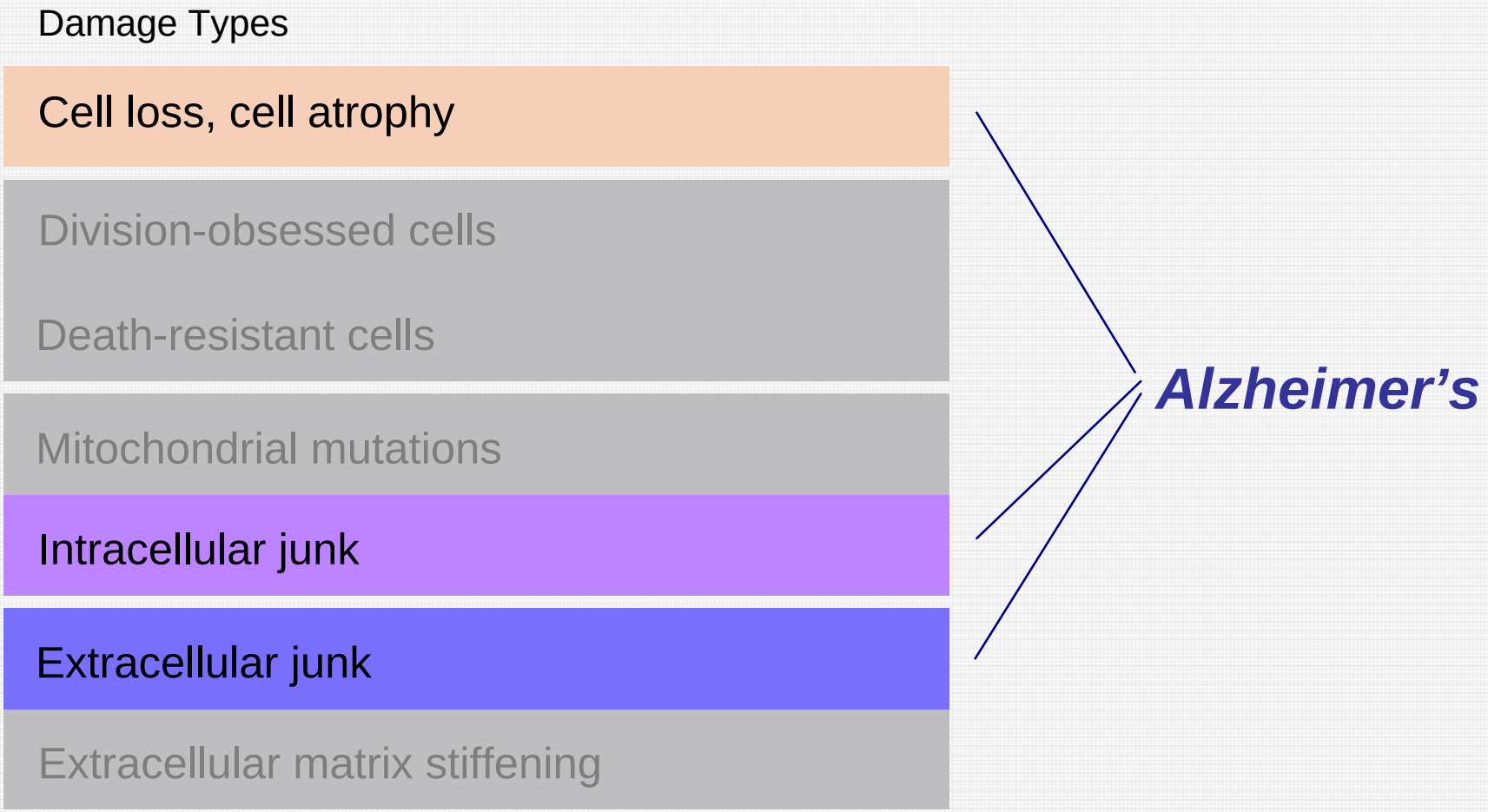
Parkinson's

Diseases by damage type



The “how” of preventative maintenance

- Replace
- Remove
- Repair
- Reinforce

Addressing each category

Damage type	The maintenance approach
Cell loss, cell atrophy	Replace
Division-obsessed cells	Reinforce
Death-resistant cells	Remove
Mitochondrial mutations	Reinforce
Intracellular junk	Remove
Extracellular junk	Remove
Extracellular matrix stiffening	Repair

Addressing each category

Damage type	The maintenance approach
Cell loss, cell atrophy	Cell therapy, mainly
Division-obsessed cells	Telomerase/ALT gene deletion plus periodic stem cell reseeding
Death-resistant cells	Suicide genes, immune stimulation
Mitochondrial mutations	Allotopic expression of 13 proteins
Intracellular junk	Transgenic microbial hydrolases
Extracellular junk	Phagocytosis by immune stimulation
Extracellular matrix stiffening	AGE-breaking molecules/enzymes

Clinical trials for brain aging diseases

Damage type	The maintenance approach
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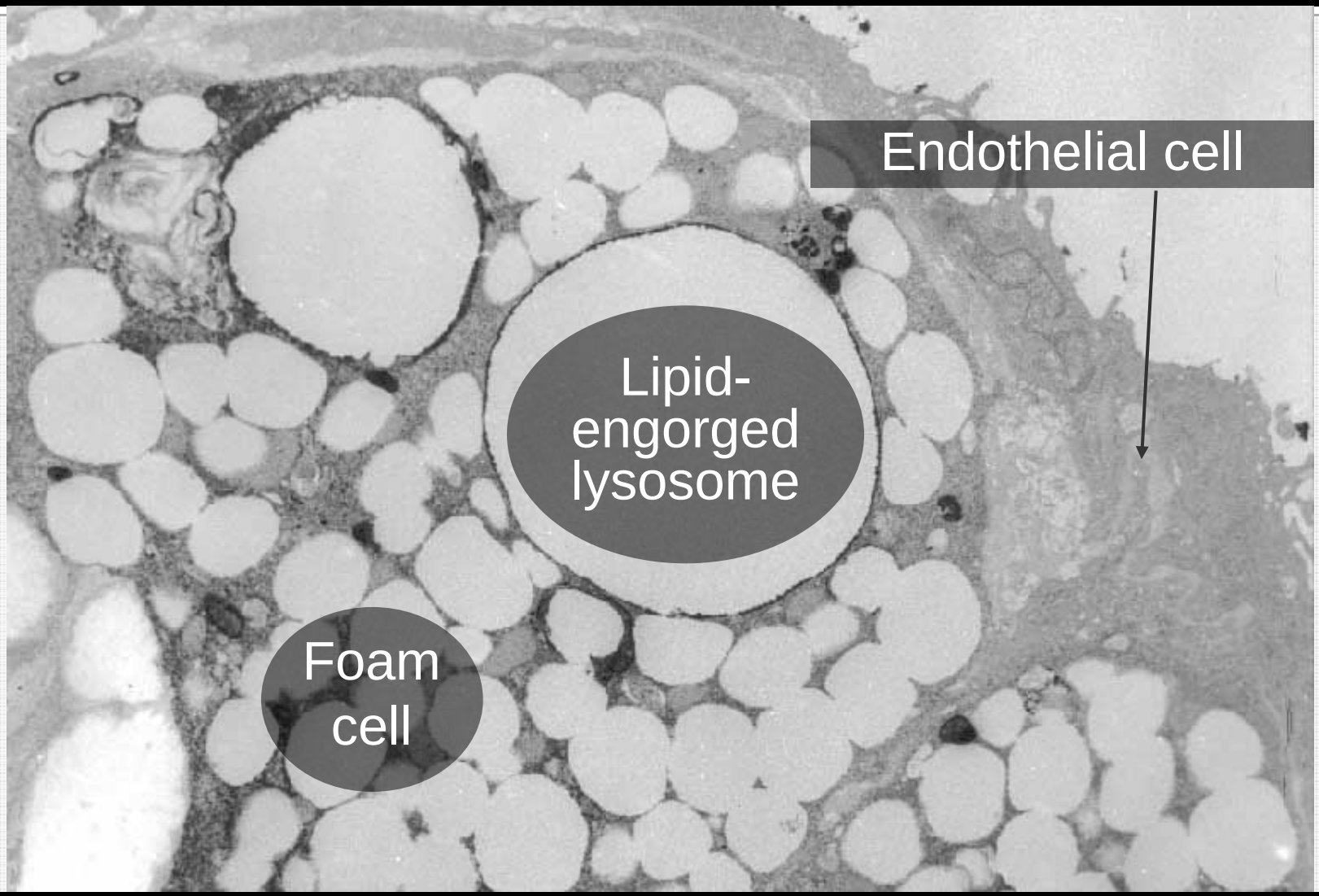
A huge flaw in medical research today

- Two big Phase III trials of amyloid vaccines were recently concluded
- Clinical endpoints were not achieved
- Amyloid ***was*** robustly removed
- Tangles were not (not targeted), cells not replaced
- AD has no clear chain of causation!

Another flaw in medical research today

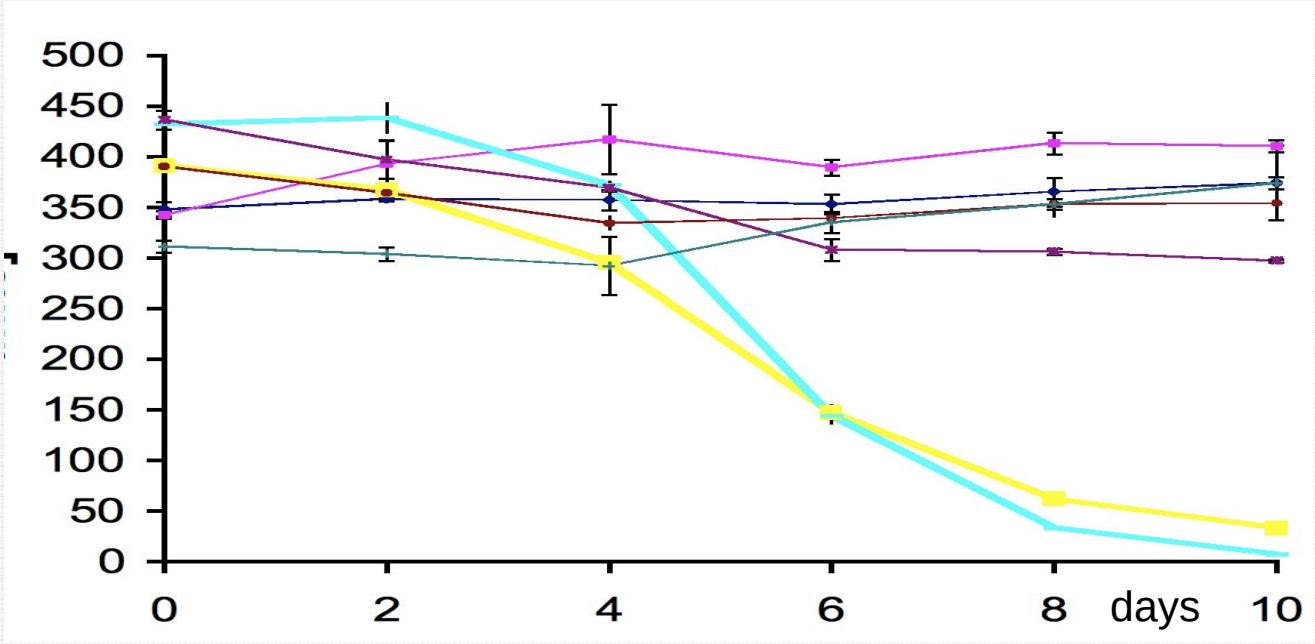
- Fetal stem cells were used to treat Parkinson's
- Success was patchy but massive when good
- Subsequent trials with other stem cells failed
- Nearly all researchers abandoned this approach
- Turns out the stem cells didn't make DA neurons!

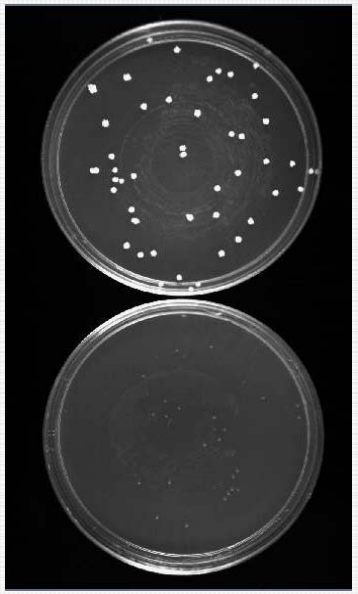
Intracellular junk in the artery



We found bacteria that eat 7KC

7KC over time in enrichment cultures





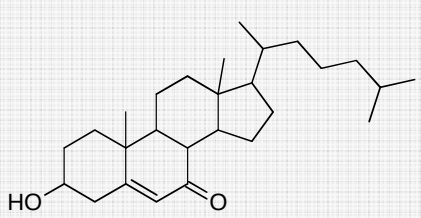
Mathieu et al, Biodegradation 2008; 19(6):807-813

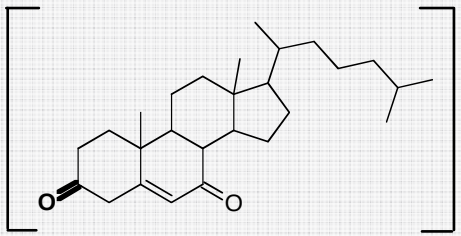
We found out what enzyme they use

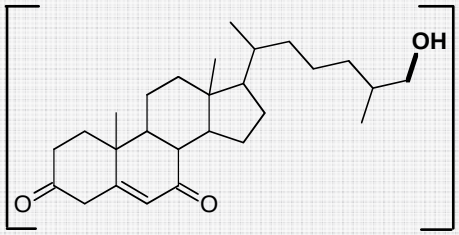
7-ketocholesterol
M = 400, M_{13C} = 401

Dione metabolite ?
M = 398, M_{13C} = 399

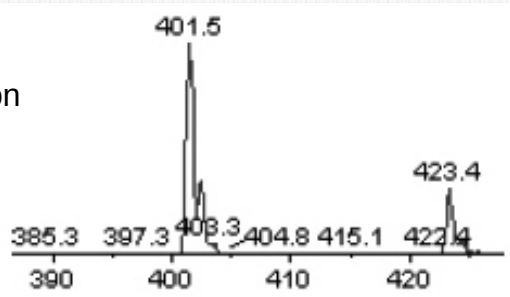
Hydroxylated dione ?
M = 414, M_{13C} = 415

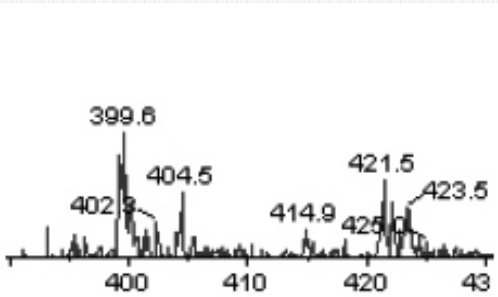


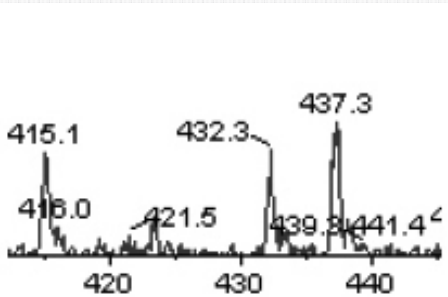




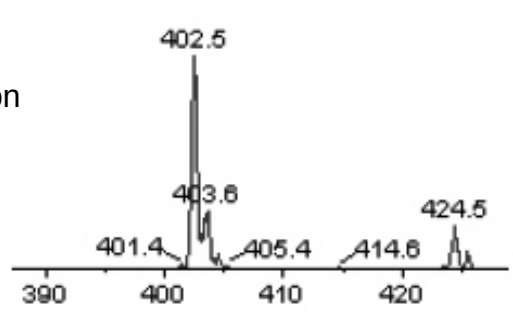
Culture growing on
7-ketocholesterol

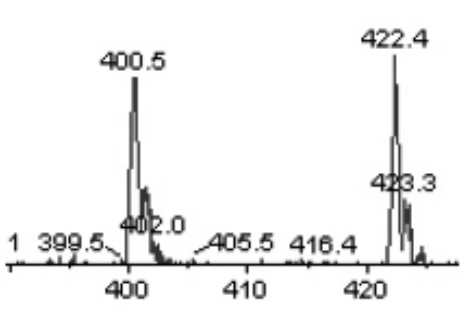


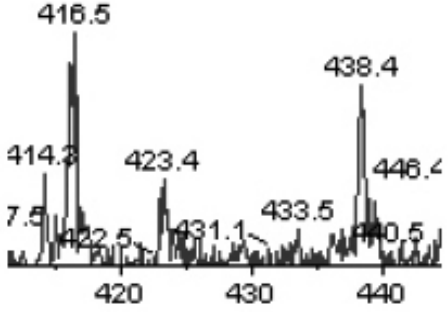




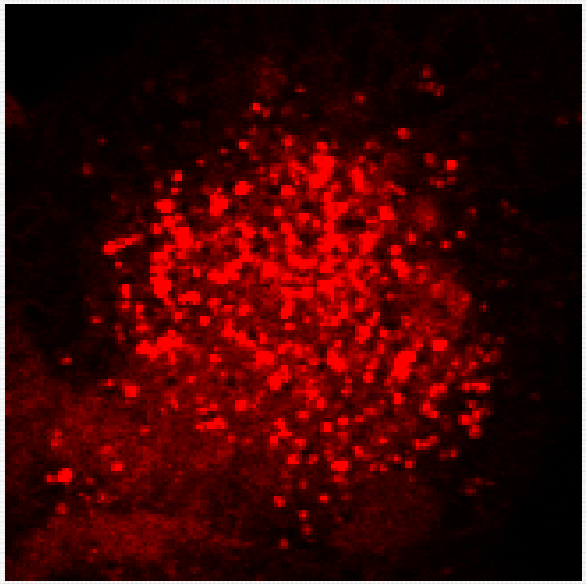
Culture growing on
^{13}C-labeled
7-ketocholesterol



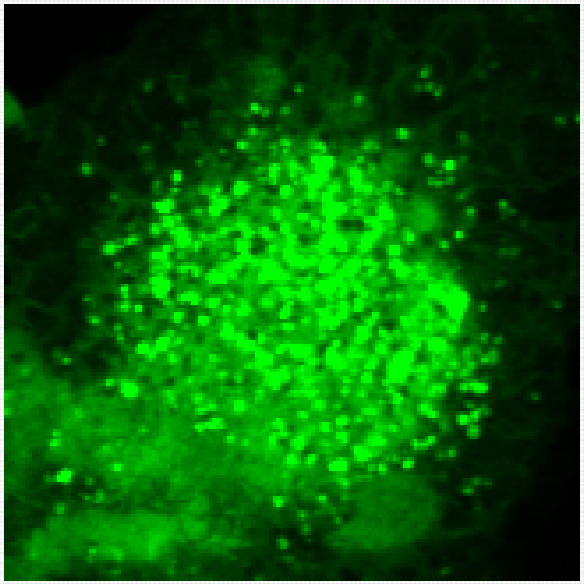




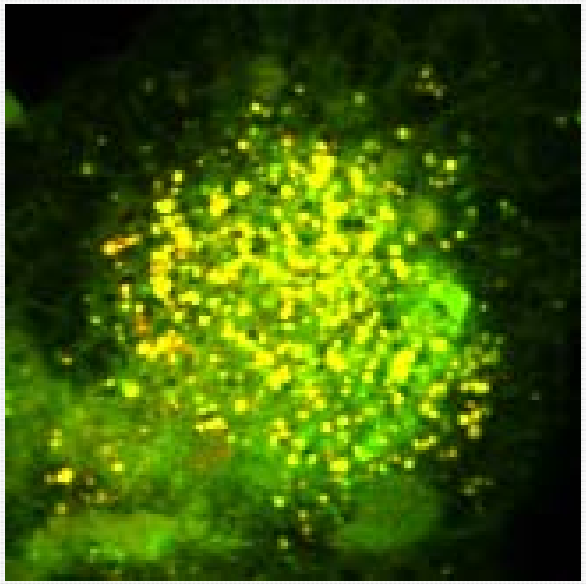
We modified it to go to the lysosome



Acridine Orange

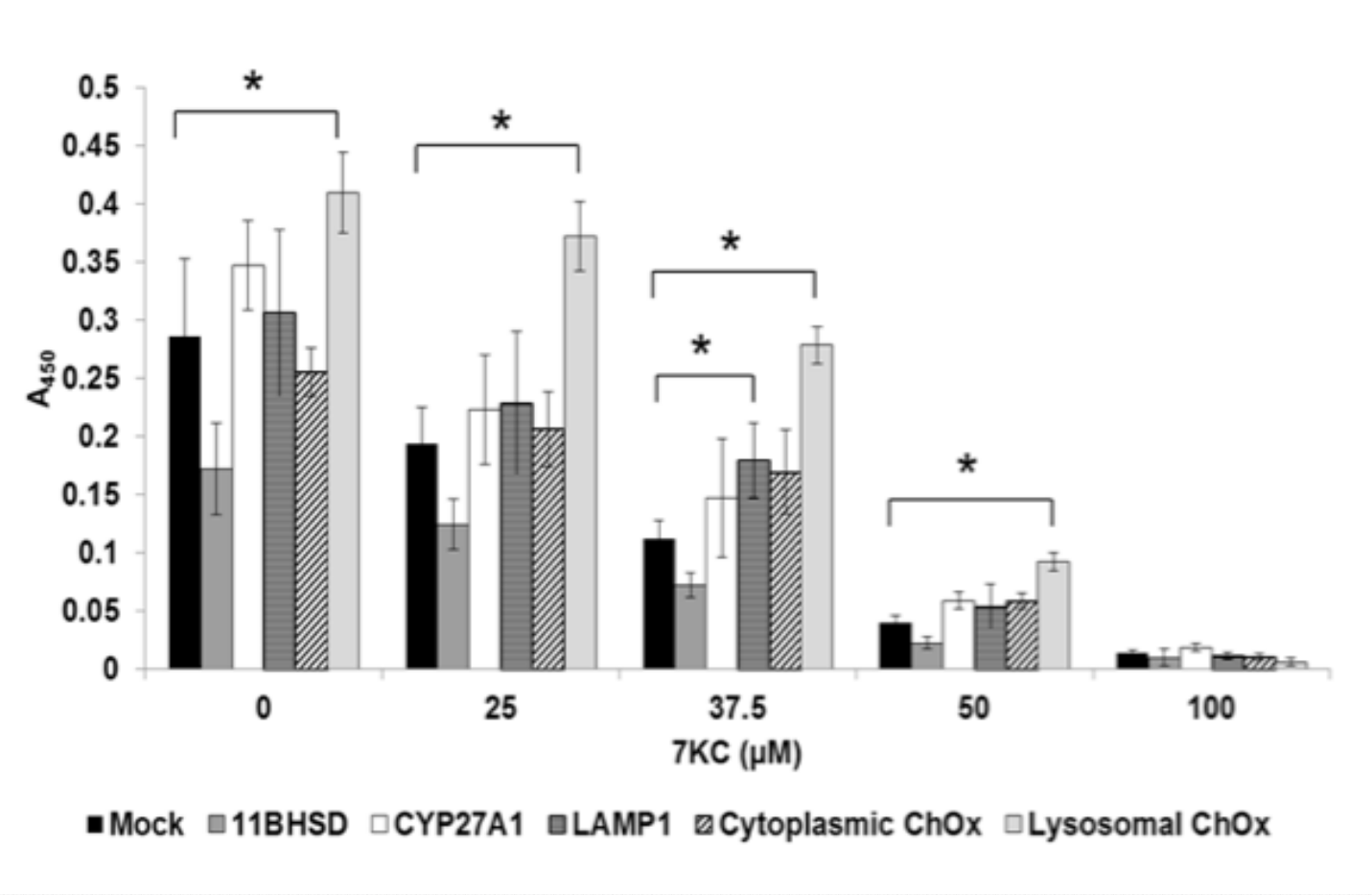


EGFP



Merge

Our enzyme protects cells from 7KC



Mathieu et al., Biotechnol. Bioeng. 2012; 109(9):2409-2415

And there's so much more

- We pursue three major in-house projects at our Mountain View HQ
- We sponsor over a dozen other projects at top academic institutions
- Our educational program currently places interns both in our own lab and extramurally at the Buck Institute for Research on Aging and four prestigious universities worldwide

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