



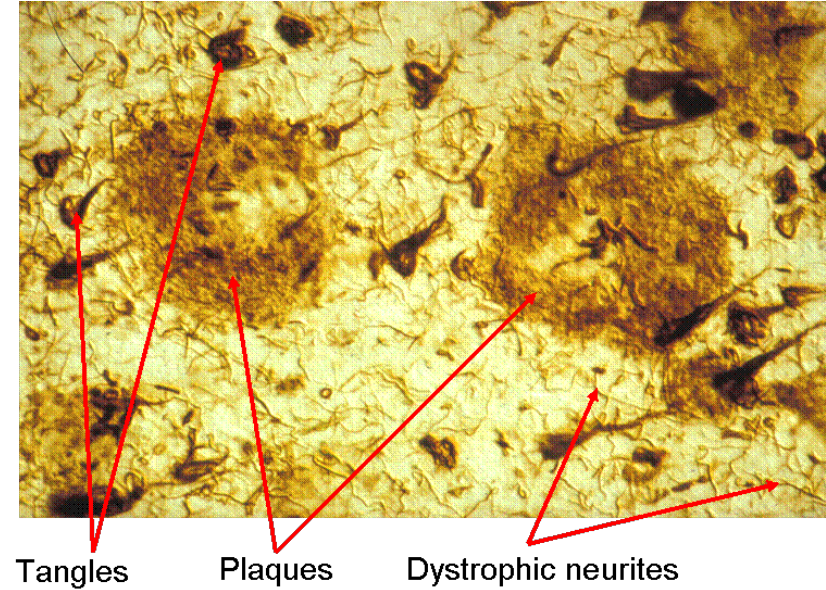
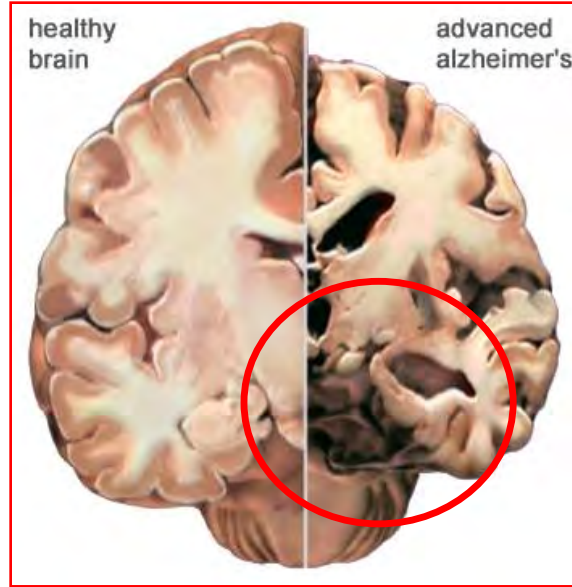
Alzheimer's
Drug Discovery
Foundation

AGING

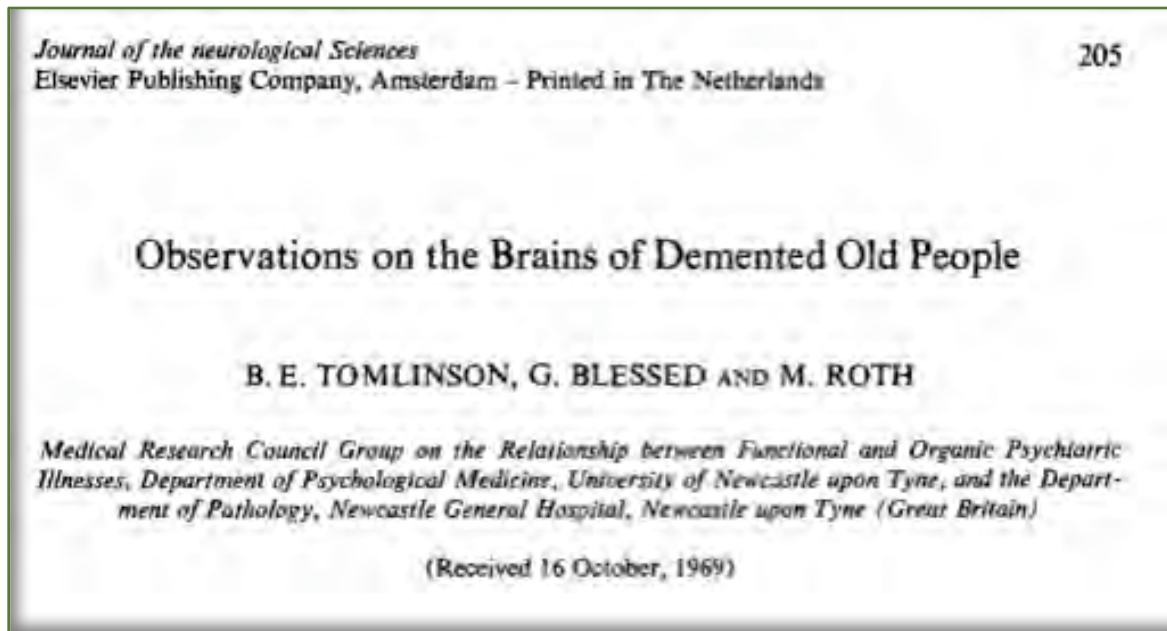
Translating Biological Gerontology to Alzheimer's Therapy

Thank you to the Yulgilbar Foundation!

What Dr. Alzheimer Observed: *Clues to Therapy?*



No Progress on Alzheimer's Disease Until ~1970

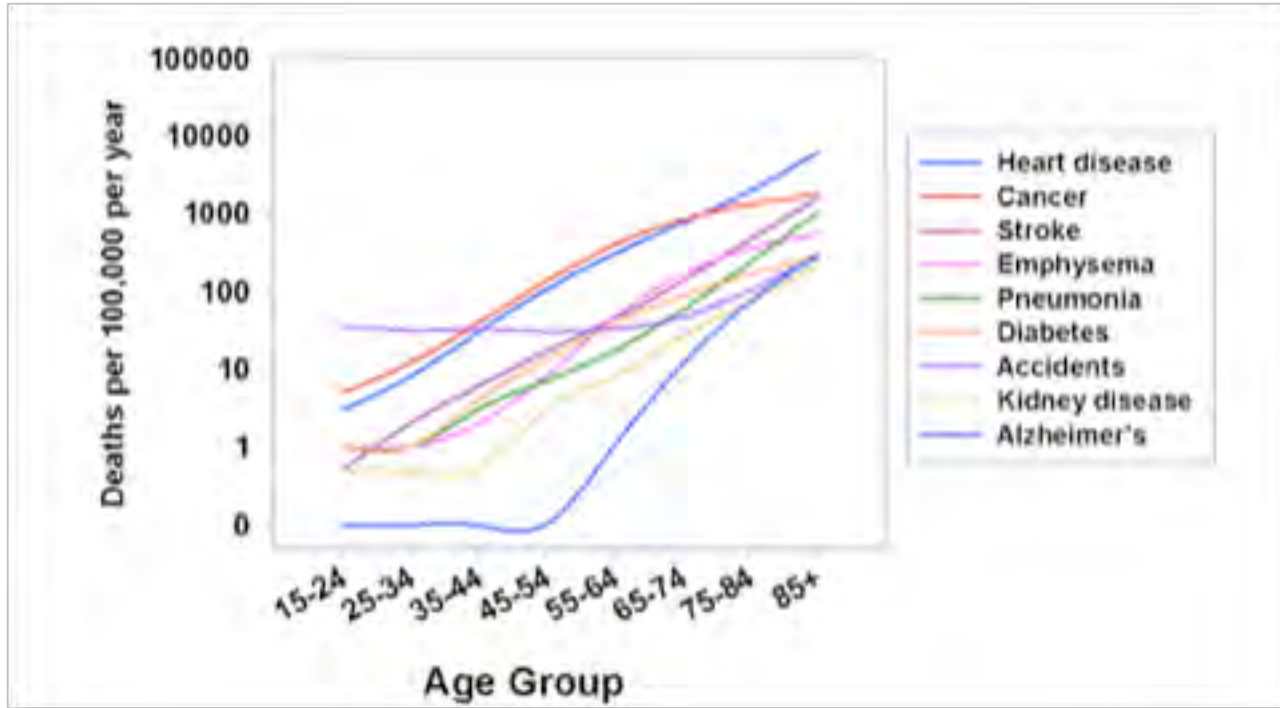


AGING

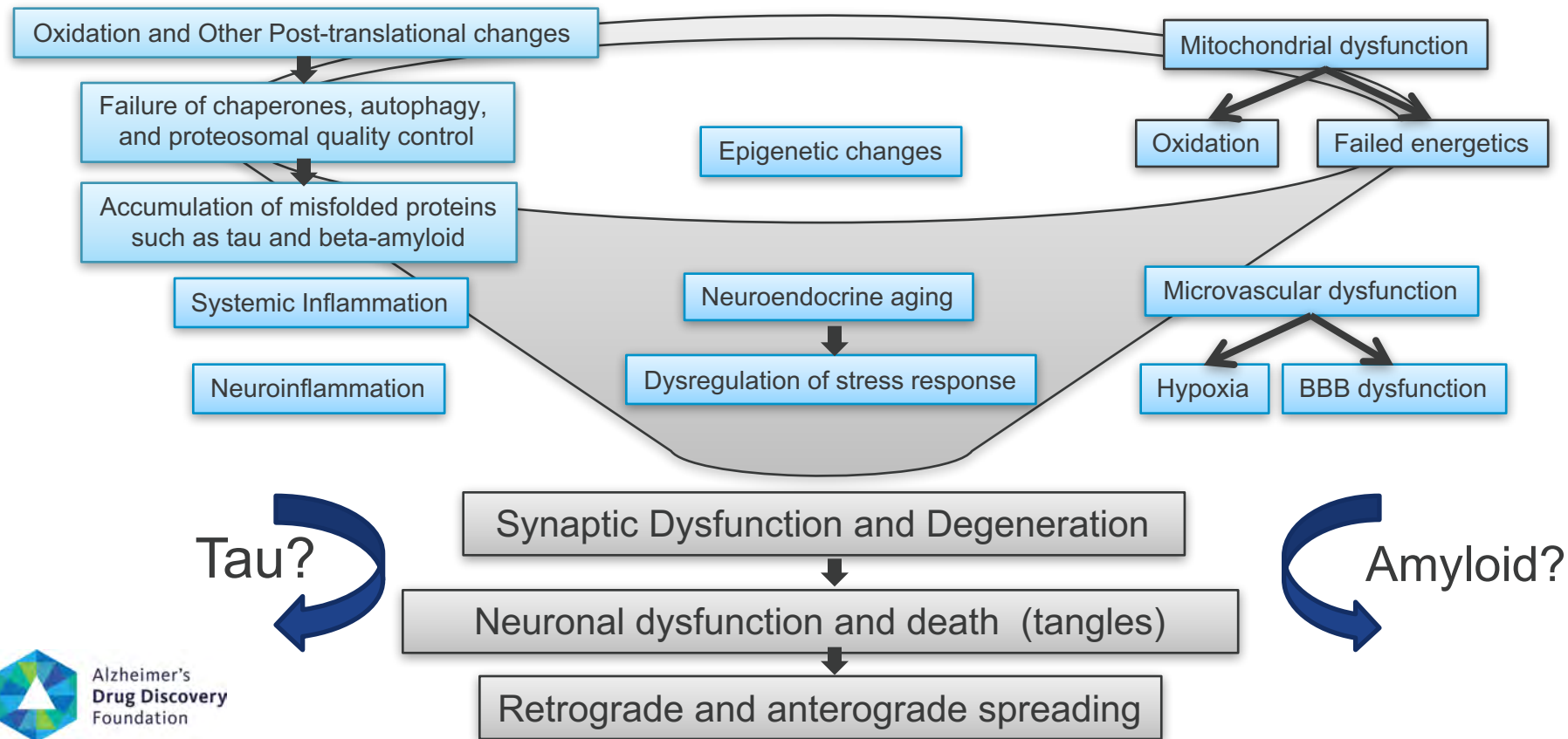


IS THE LEADING
RISK FACTOR FOR
ALZHEIMER'S
DISEASE

BIOLOGICAL GERONTOLOGY: ACCUMULATION OF DAMAGE & DISEASE



The “Accumulation of Damage” View of Brain Aging and Alzheimers: Novel Therapeutic Targets





DEVELOPING NOVEL DRUGS FOR ALZHEIMERS

12⁺
YEARS

>\$2 BILLION

**BASIC
SCIENCE**
*Understanding the
Underlying Causes
of the disease*



**DRUG
DISCOVERY**
*Translating
Knowledge into
Drugs*



**IND
ENABLING**
*Preparing Drugs
for Testing in
Humans*



**CLINICAL
TRIALS**
*Human Trials of
Potential New
Drugs*



Drug Discovery: A Vital Stage in Drug Development When Innovation is Created

BASIC SCIENCE

*Understanding the
Underlying Causes
of the disease*

DRUG DISCOVERY

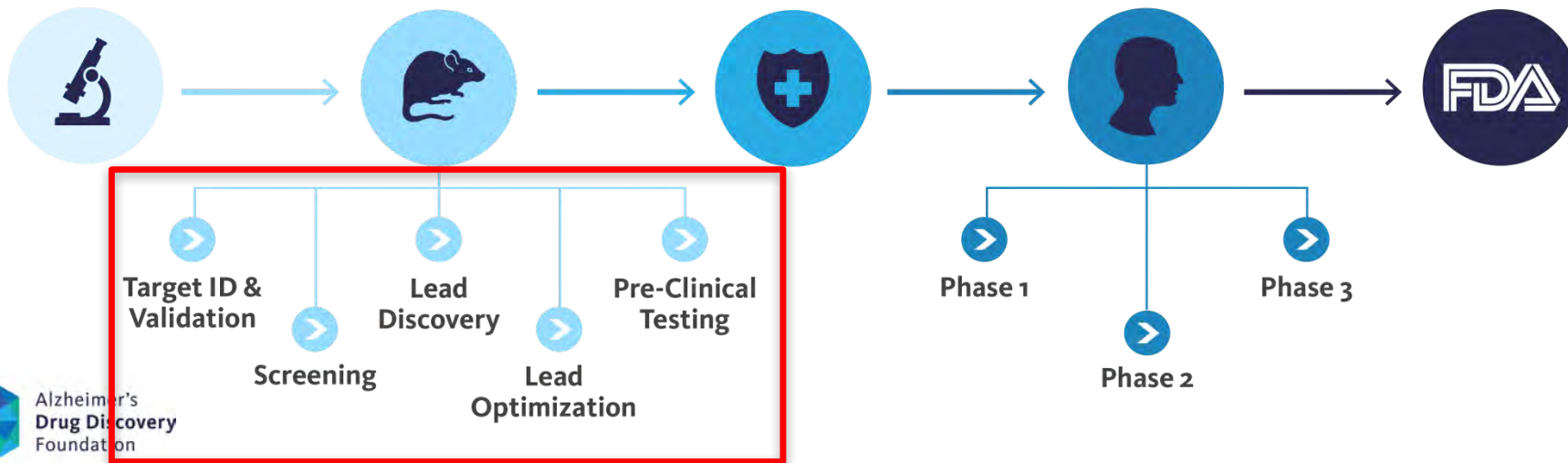
*Translating
Knowledge into
Drugs*

IND ENABLING

*Preparing Drugs
for Testing in
Humans*

CLINICAL TRIALS

*Human Trials of
Potential New
Drugs*



Challenges: *How a Chemist Thinks About Targets for Drug Discovery*

Success Rates of Target Types

GPCR
Enzyme
Ion channel
Nuclear receptor
Protease
Protein kinase
Protein-protein

“RELATIVELY”HIGH SUCCESS RATE

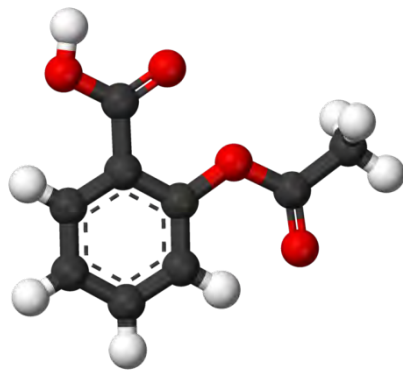


“RELATIVELY”LOW SUCCESS RATE



The Origins of FDA-Approved Drugs: Chemical Space is Relatively “Unlimited”

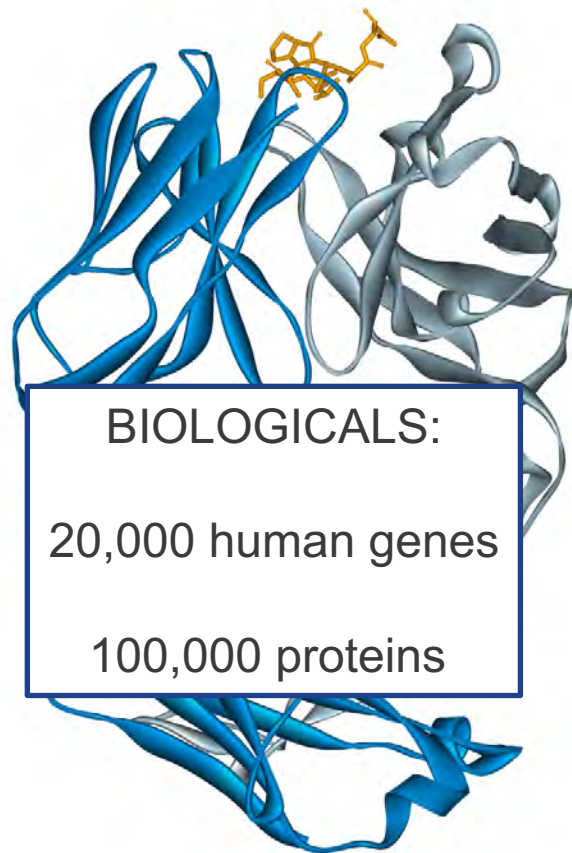
ASPIRIN



The Universe of SMALL MOLECULES:

~50M compounds in Chem Abstracts

10^{40} - 10^{100} possible small molecules



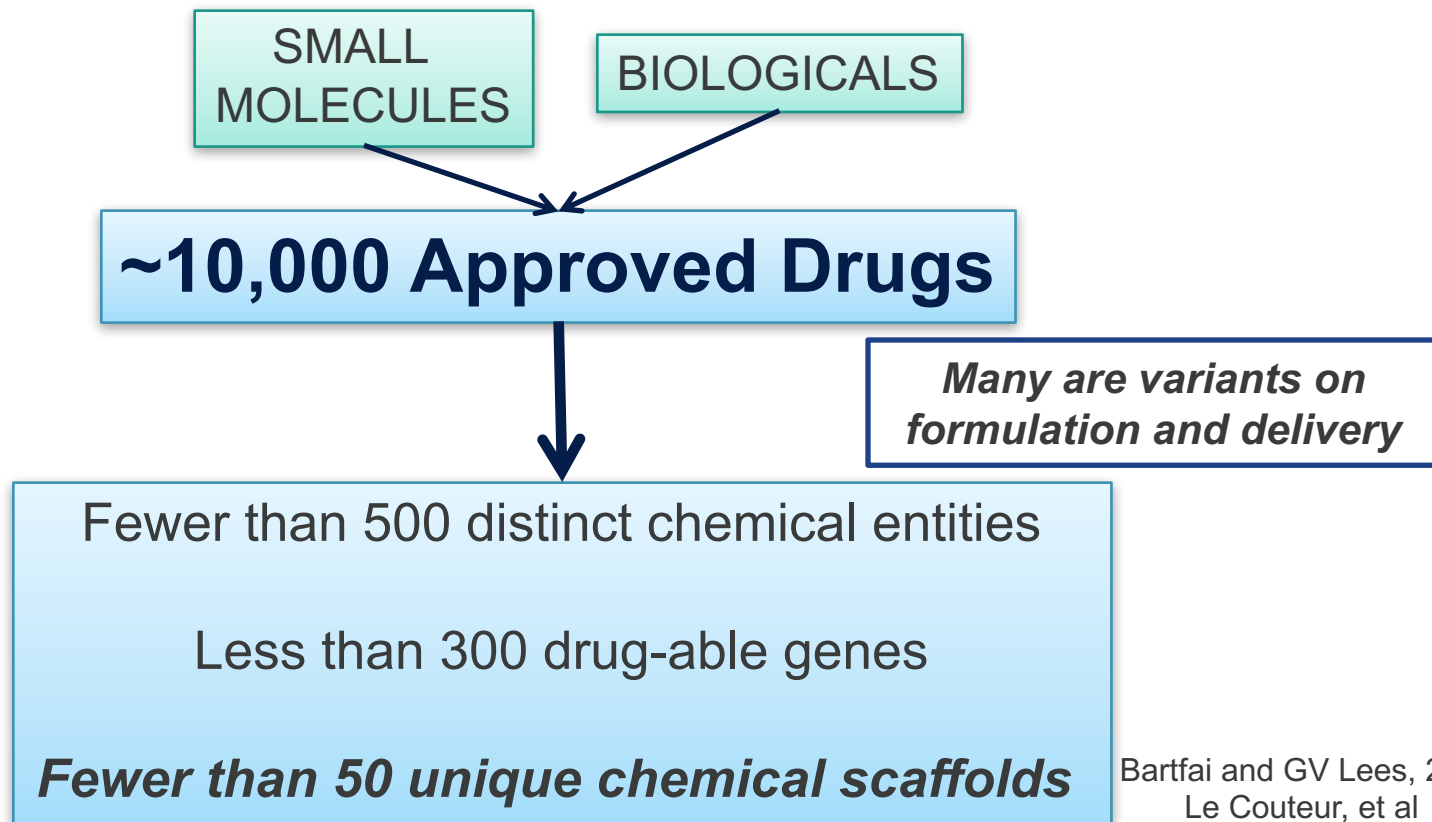
BIOLOGICALS:

20,000 human genes

100,000 proteins



But “Drug-able” Chemical Space is Very Limited



Bartfai and GV Lees, 2006;
Le Couteur, et al 2011



Challenges: Improving the Predictive Value of Animal Trials

- Animal models have contributed to our understanding of the *mechanisms* of disease, but are generally poorly predictive of clinical trial outcomes
- Lack of standards in design, conduct and analysis of animal trials persist
- ***Apply the scientific and procedural rigor of clinical trials to animal trials***

Shine et al. *Alzheimer's Research & Therapy* 2011, 3:28
<http://alzres.com/content/3/5/28>

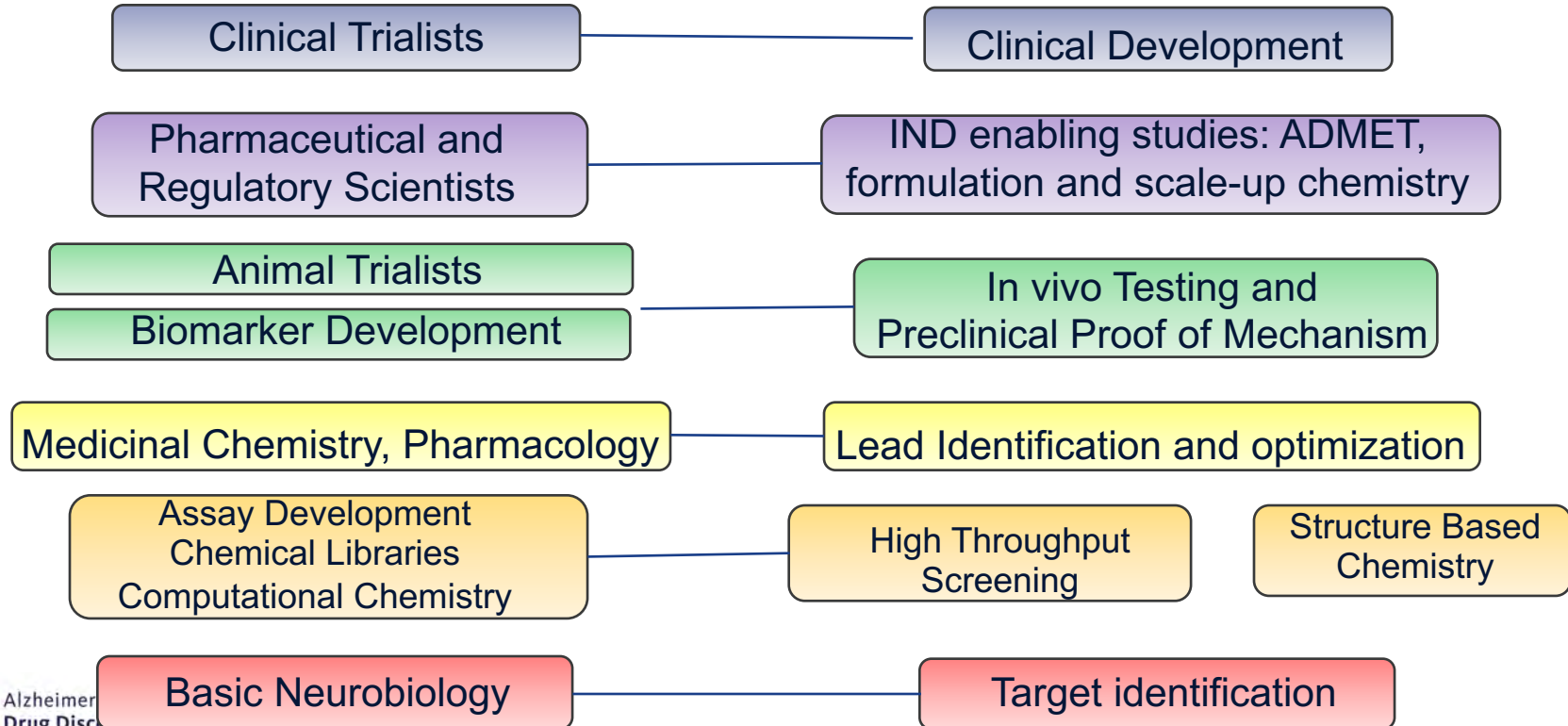


REVIEW

Accelerating drug discovery for Alzheimer's disease: best practices for preclinical animal studies

Diana W. Shineman^{1*}, Gurqbal S. Bas², Jennifer L. Bizon³, Carol A. Colton⁴, Barry D. Greenberg⁵, Beth A. Hollister⁶, John Lincecum⁷, Gabrielle G. LeBlanc⁸, Linda (Bobbi) H. Lee^{2,9}, Feng Luo¹⁰, Dave Morgan¹¹, Iva Morse¹², Lorenzo M. Refolo¹³, David R. Riddell¹⁴, Kimberly Searce-Levie¹⁵, Patrick Sweeney¹⁶, Juha Yrjanheikki¹⁷ and Howard M. Fillie¹

Challenges: Drug Discovery and Development Requires Multidisciplinary Teams of Scientists



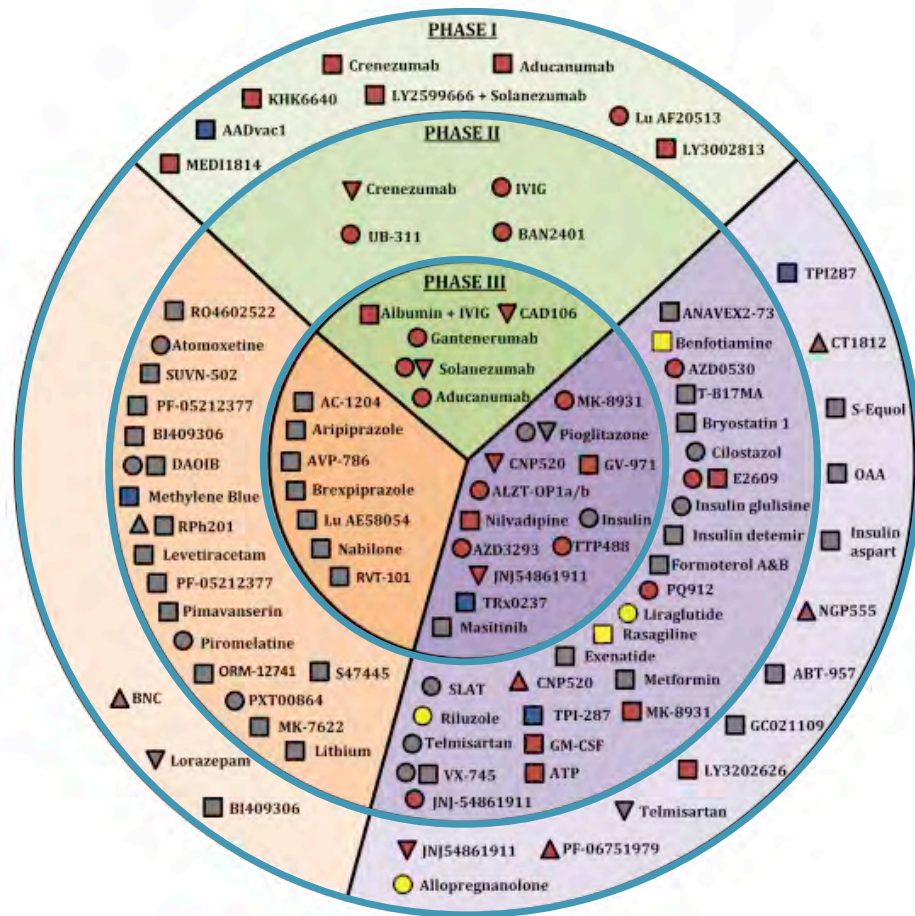
93

Therapies in Active Clinical Trials

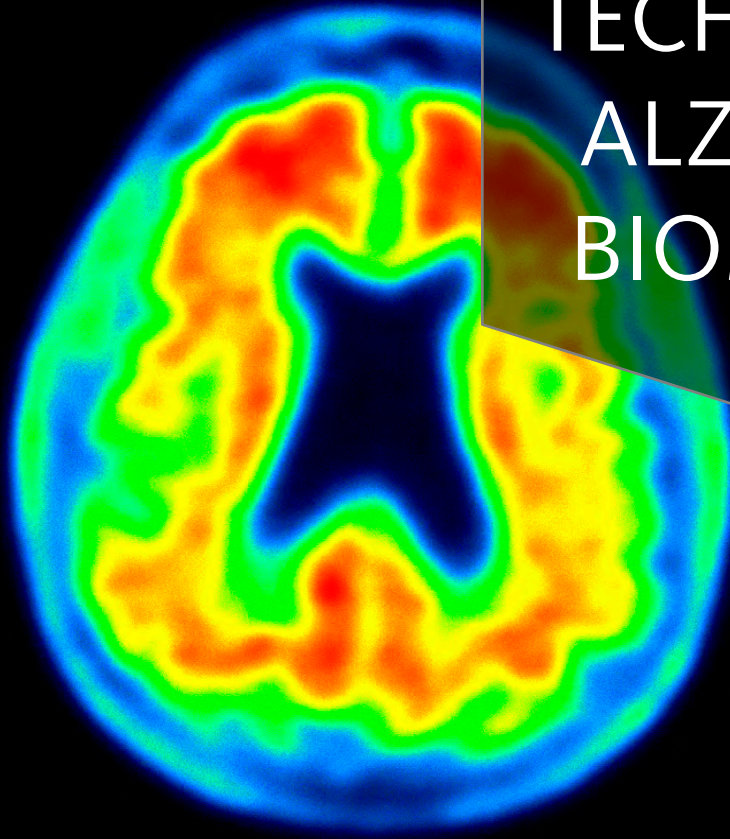
24 in Phase 3

45 in Phase 2

24 in Phase 1

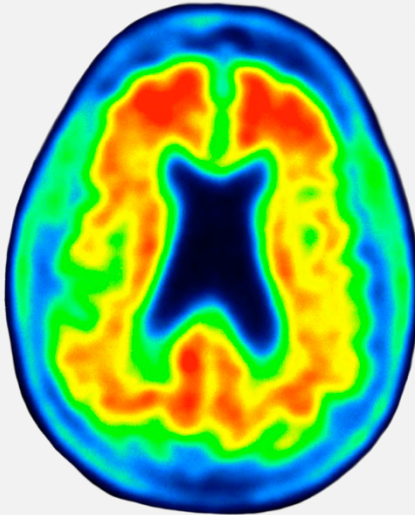


ENABLING TECHNOLOGY: ALZHEIMERS BIOMARKERS

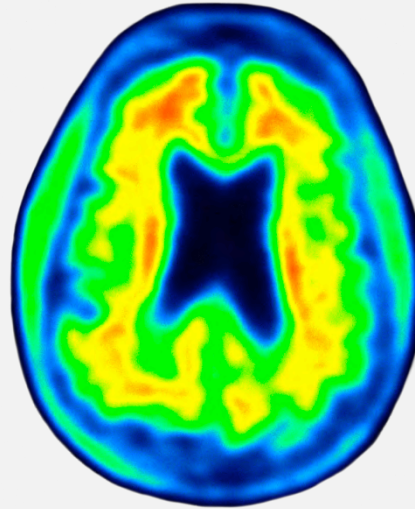


AMYLOID PET SCANNING And CSF Testing

PLACEBO
TREATMENT



VACCINE
TREATMENT



- Earlier and more accurate diagnosis
- More scientifically rigorous and efficient clinical trials
- Enabled prevention:
 - Disease starts ~20 years before symptoms begin
 - Anti-amyloid prevention clinical trials are underway

The antibody aducanumab reduces A β plaques in Alzheimer's disease

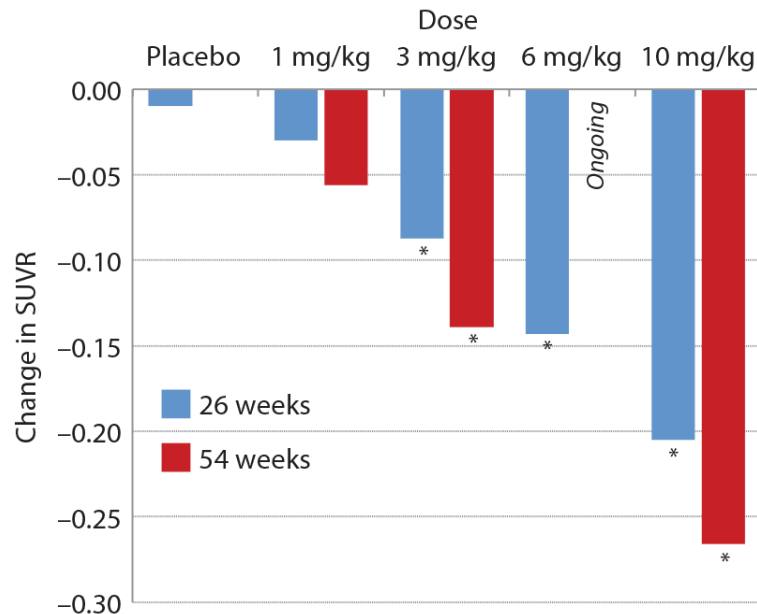
Jeff seigny₁*, ping chiao₁*, Thierry bussière₁*, paul H. Weinreb₁*, Leslie Williams₁, marcel maier₂, Robert Dunstan₁, stephen salloway₃, Tianle chen₁, Yan Ling₁, John O'Gorman₁, Fang Qian₁, mahin Arastu₁, mingwei Li₁, sowmya chollate₁, melanie s. brennan₁, Omar Quintero-monzon₁, Robert H. scannevin₁, H. moore Arnold₁, Thomas Engber₁, Kenneth Rhodes₁, James Ferrero₁, Yaming Hang₁, Alvydas mikulskis₁, Jan Grimm₂, christoph Hock_{2,4}, Roger m. Nitsch_{2,4}§ & Alfred sandrock₁§

Nature, September 2016

Aducanumab: N-terminal Anti-beta amyloid antibody

From Biogen Phase 1b Clinical Trial

- Reduces Amyloid Plaques
- Effects on cognition and function?



Aducanumab: N-terminal Anti-beta amyloid antibody

From Biogen Phase 1b Clinical Trial

- Reduces Amyloid Plaques
- Some effects on cognition

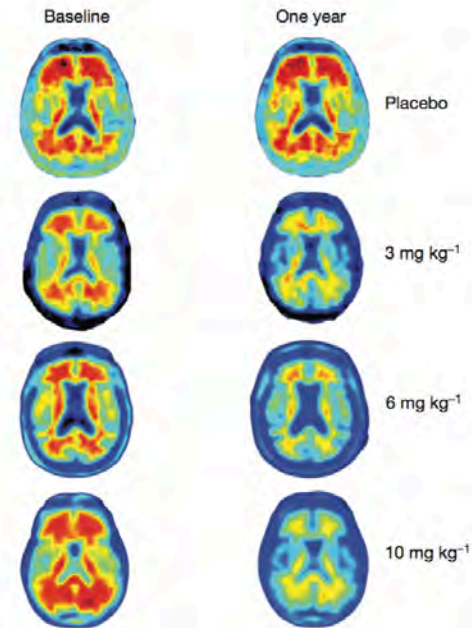
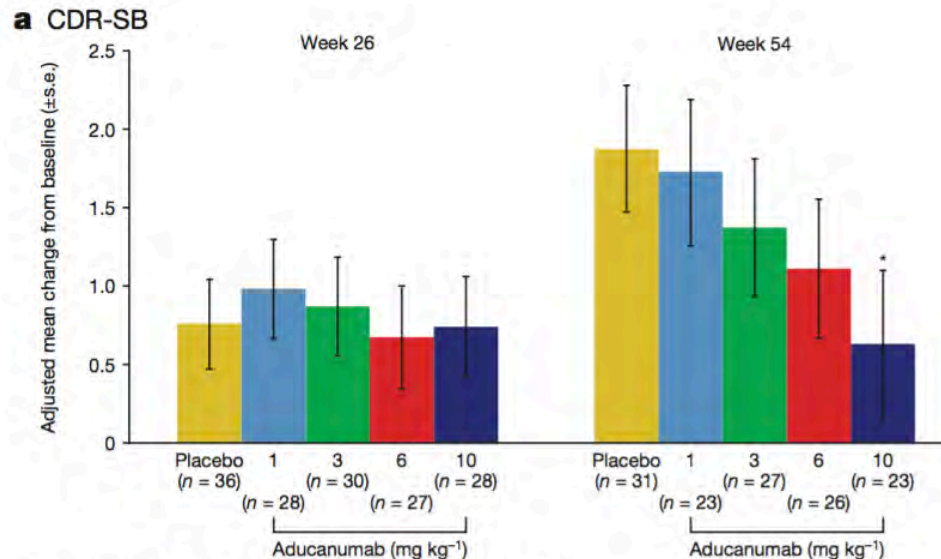


Figure 1 | Amyloid plaque reduction with aducanumab: example amyloid PET images at baseline and week 54. Individuals were chosen based on visual impression and SUVR change relative to average one-year response for each treatment group ($n = 40, 32, 30$ and 32 , respectively). Axial slice shows anatomical regions in posterior brain putatively related to AD pathology. SUVR, standard uptake value ratio.

Aducanumab: N-terminal Anti-beta amyloid antibody

From Biogen Phase 1b Clinical Trial

- Reduces Amyloid Plaques
- Some effects on cognition



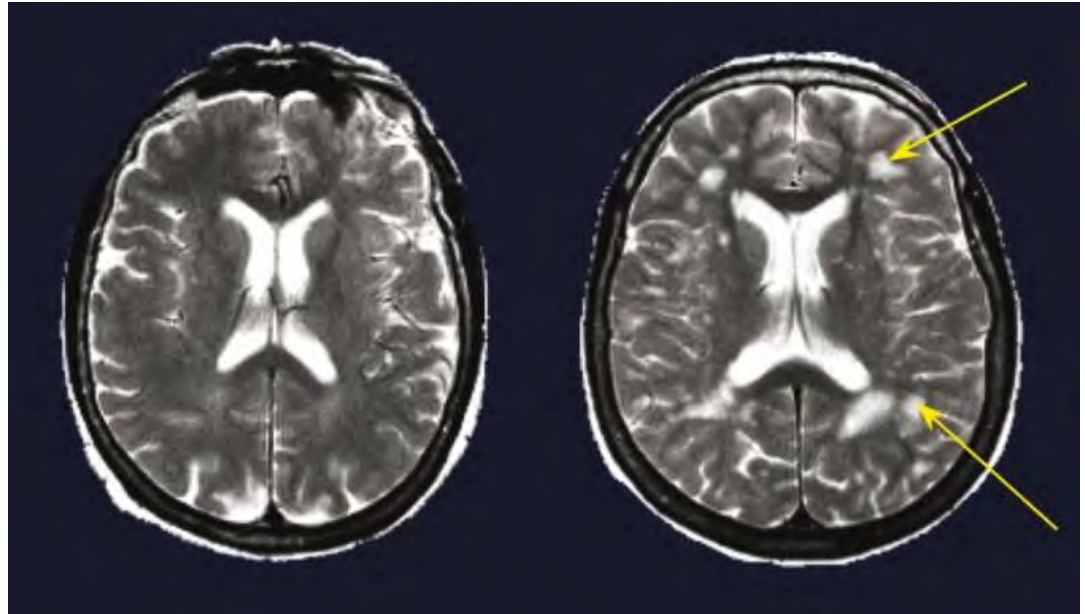
Dose-response $P < 0.05$ at week 54 based on a linear contrast test



ADVANCES IN MRI NEUROIMAGING

MRI Brain

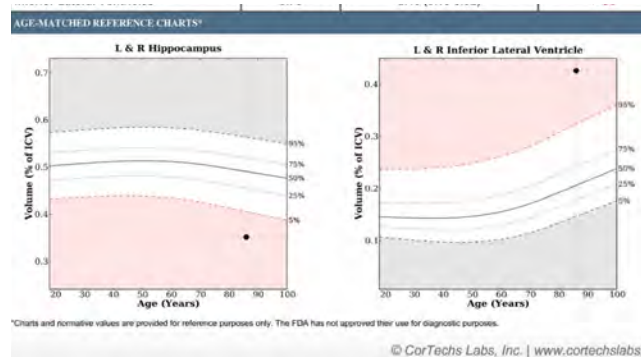
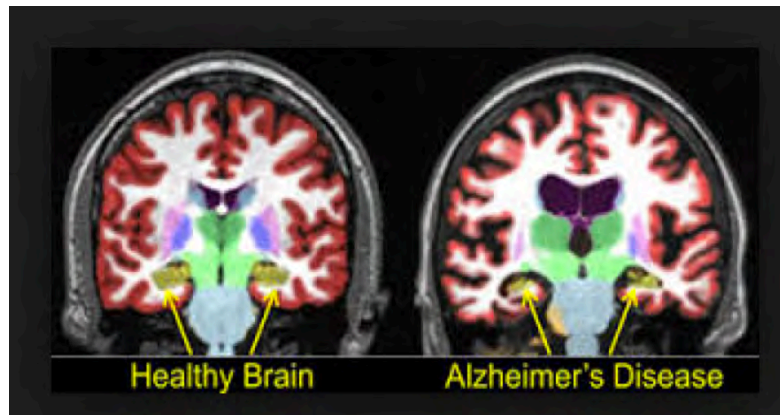
Detect white matter disease,
microvascular disease



STRUCTURAL NEUROIMAGING to DETECT NEURODEGENERATION

Volumetric analysis (NeuroQuant®)

Clinically measures hippocampal and ventricular volume



Recent Advances in Neuroimaging Alzheimers: Seeing the Plaques *and* Tangles

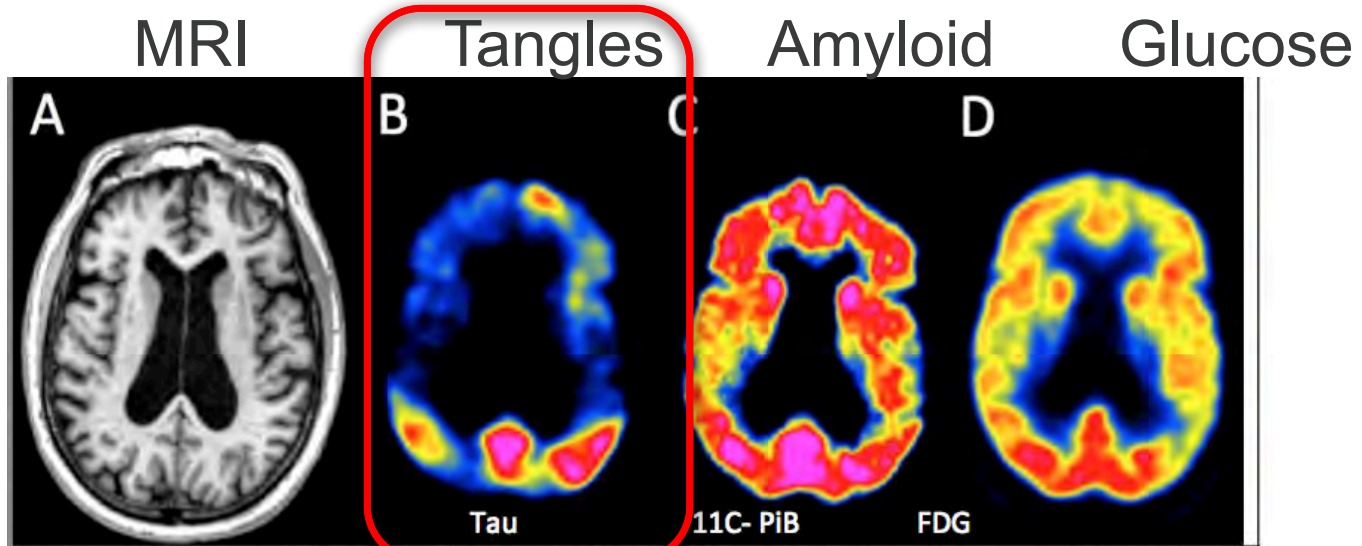
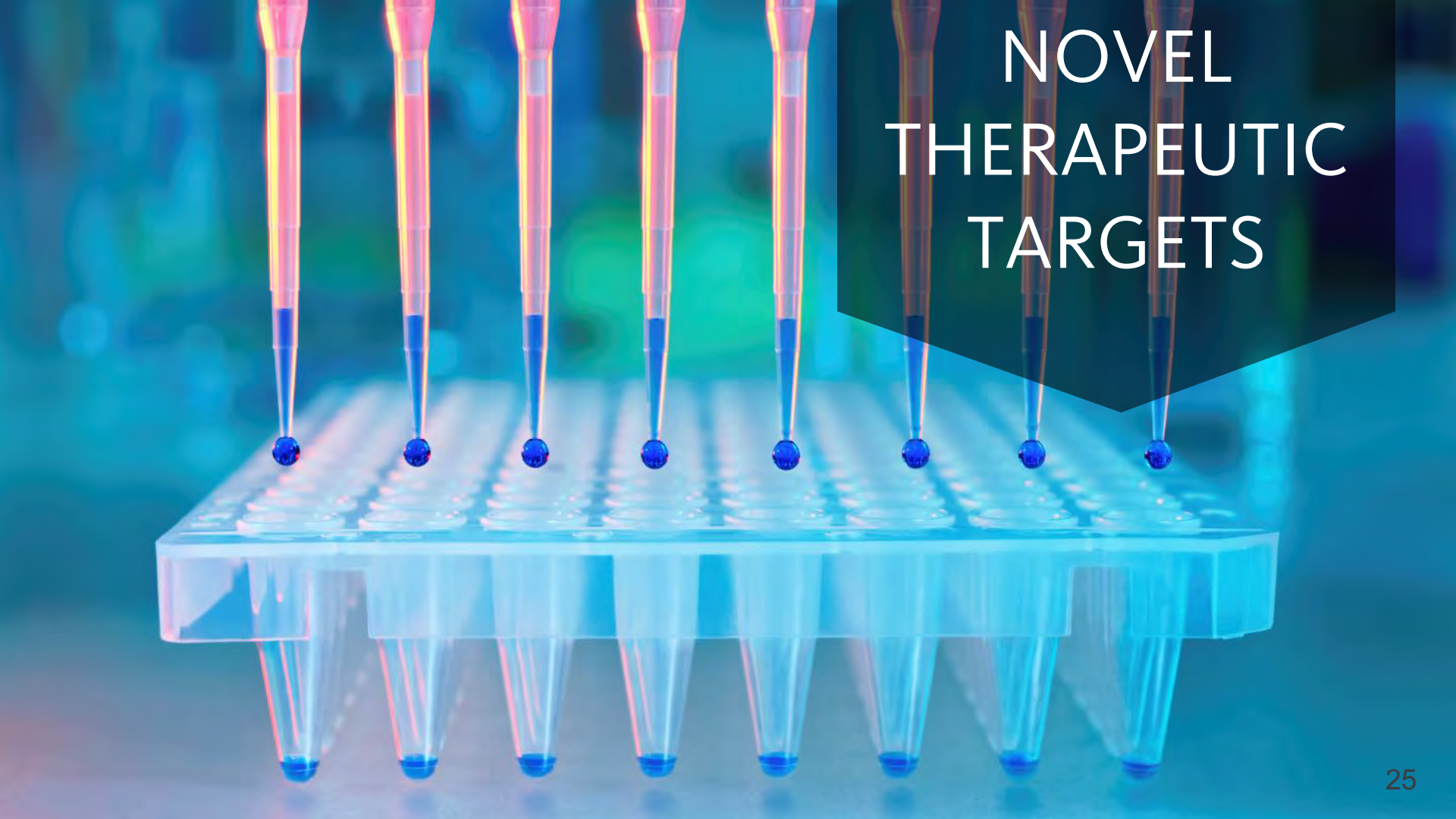


Figure 1. Transaxial slices from a 68 year-old man with Alzheimer's disease of





NOVEL THERAPEUTIC TARGETS

“Tau” Targets for Alzheimer’s Disease

TAU PATHWAY	
Phosphorylation inhibitors	
CDK5	Low
GSK3 β	Low
MARK/par1	Low
PKC	Low
MAPK	Low
PKA	Low
p70S6K	Low
Antiaggregants (TRx0237)	Low
Microtubule stabilizing agents (BMS 241027)	Low
Reduction of tau levels (Tau antibodies and antisense oligonucleotides)	Low



FROM THE NOVEMBER 2006 ISSUE

DNA Is Not Destiny: The New Science of Epigenetics

Discoveries in epigenetics are rewriting the rules of disease, heredity, and identity.

By Ethan Watters | Wednesday, November 22, 2006

Lifelong risk factors cause cellular stress, resulting in the chemical modification of genes *and their expression*



Audrey Hepburn, who spent her childhood in the Netherlands during the Dutch Hongerwinter, attributed her clinical depression later in life to the malnutrition in her formative years (Credit: Hulton Archive)



Alzheimer's
Drug Discovery
Foundation

With Aging, Epigenetic Changes May Cause Neurodegeneration

doi:10.1038/nature10849

An epigenetic blockade of cognitive functions in the neurodegenerating brain

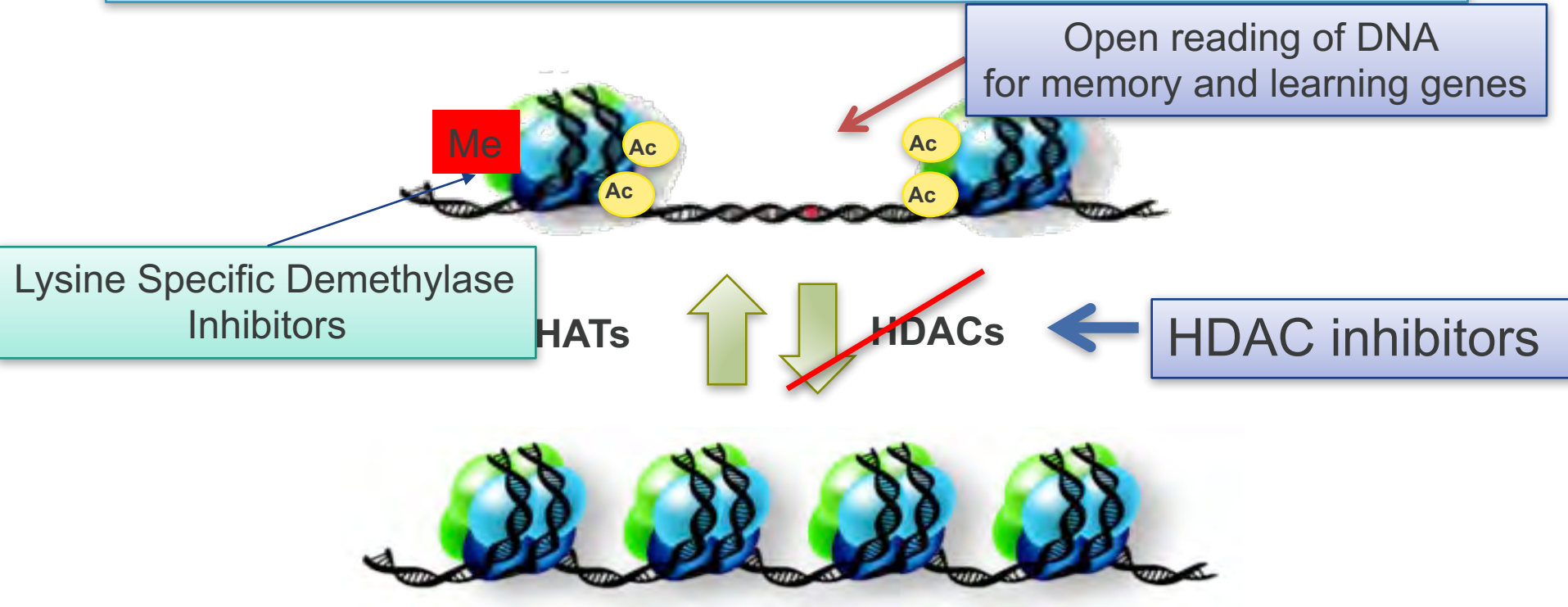
Johannes Gräff^{1,2,3}, Damien Rei^{1,2}, Ji-Song Guan^{1,2,3}, Wen-Yuan Wang^{1,2,3}, Jinsoo Seo^{1,2}, Krista M. Hennig^{3,4}, Thomas J. F. Nieland³, Daniel M. Fass^{3,4}, Patricia F. Kao⁵, Martin Kahn¹, Susan C. Su^{1,2}, Alireza Samiei¹, Nadine Joseph^{1,2,3}, Stephen J. Haggarty^{3,4}, Ivana Delalle⁵ & Li-Huei Tsai^{1,2,3}

NATURE | VOL 483 | 8 MARCH 2012



Alzheimer's
Drug Discovery
Foundation

Drugs Are In Development To Treat Alzheimers Based on Epigenetics



Epigenetic Drugs in Development

The logo for ORYZON, featuring the word "ORYZON" in white, uppercase, sans-serif font, centered within a black rectangular box.

Tamara Maes, PhD
Barcelona, Spain

DRUG: ORY-2001; Lysine Specific
Demethylase 1/ MAO-B Inhibitor

STAGE: Phase 1 Clinical Trial

The logo for rodin THERAPEUTICS, with "rodin" in a blue, lowercase, sans-serif font and "THERAPEUTICS" in a smaller, blue, uppercase, sans-serif font below it. To the right is an orange stylized graphic of a person with arms raised.

Berkley Lynch, PhD
Boston, USA

DRUG: HDAC2 Inhibitor

STAGE: Preclinical

ADDF is Helping Rodin to Develop Specific HDAC Inhibitors for Alzheimers Through *Venture Philanthropy*



DDF 2016 FiercePharma Jobs Resources Ev

FierceBiotech

BIOTECH RESEARCH IT CRO MEDICAL DEVICES

Biogen backs Rodin's Alzheimer's efforts in a \$500M deal

by *Damian Garde* | Jan 6, 2016 7:01am

FREE I

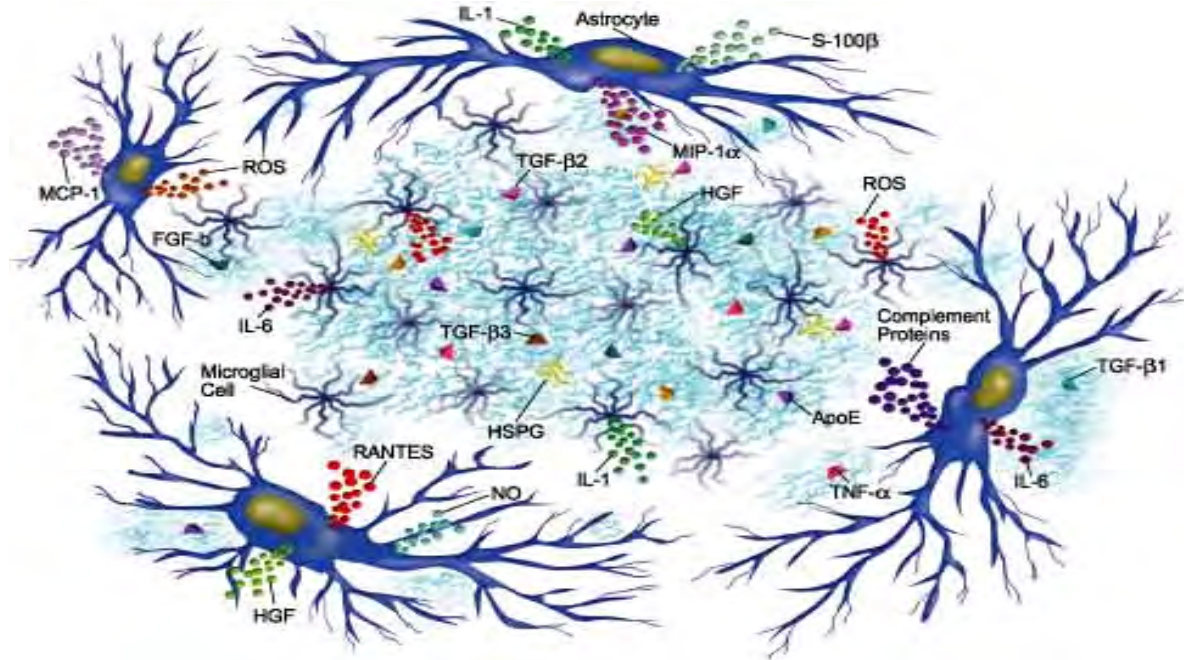
Join over
from Fier
topics as
clinical tr



Alzheimer's
Drug Discovery
Foundation

Neuroinflammation

Chronic systemic and central neuroinflammation can accelerate Alzheimer's and may be a trigger of the disease.



Repurposing to Reduce Systemic Neuroinflammation

UNIVERSITY OF
Southampton



Clive Holmes, PhD
University of Southampton, UK
Drug: Etanercept
Phase 2 Clinical Trial

Neuroinflammation: Microglial Purinergic Receptors



Philip Haydon, PhD
GliaCure, Boston

Drug: GCo21109
Phase 1 Clinical Trial
Target: P2Y6



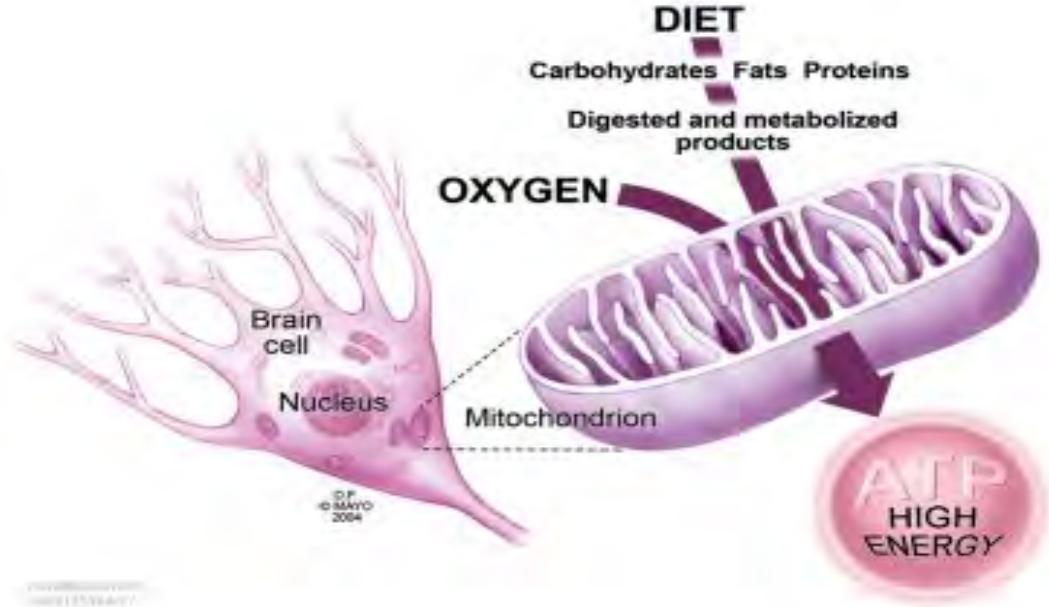
Paolo Pevarello, PhD
Axxam SpA, Milan

Drug: AXXoo179871
Preclinical
Target: P2X7

Mitochondrial Dysfunction With Aging

Brain is 3% of body weight, uses 25% of available energy

The most metabolically active organ, dependent on glucose and oxygen



Repurposing to Improve Neuronal Energy Failure



Imperial College
London

Paul Edison, MD, PhD
Imperial College London

Drug: Liraglutide
Phase 2 Clinical Trial



 Cleveland Clinic

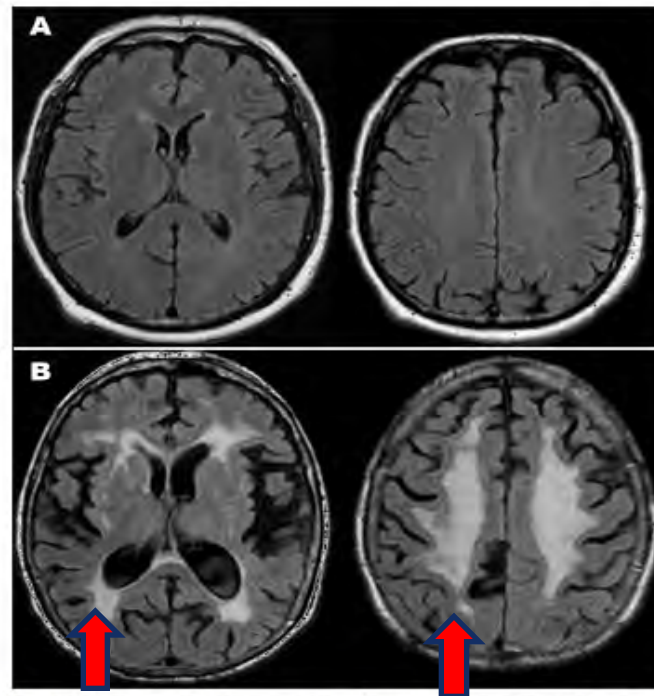
Jeffrey L. Cummings, MD
The Cleveland Clinic

Drug: Rasagiline
Phase 2 Clinical Trial

Hypertension, the White Matter and Alzheimer's Disease

Clinical trials of *neuroprotective anti-hypertensives* for Alzheimer's disease

- Clinical trials of angiotensin receptor blockers in patients with MCI
- NILVAD: clinical trial supported by the European Commission of a calcium channel blocker

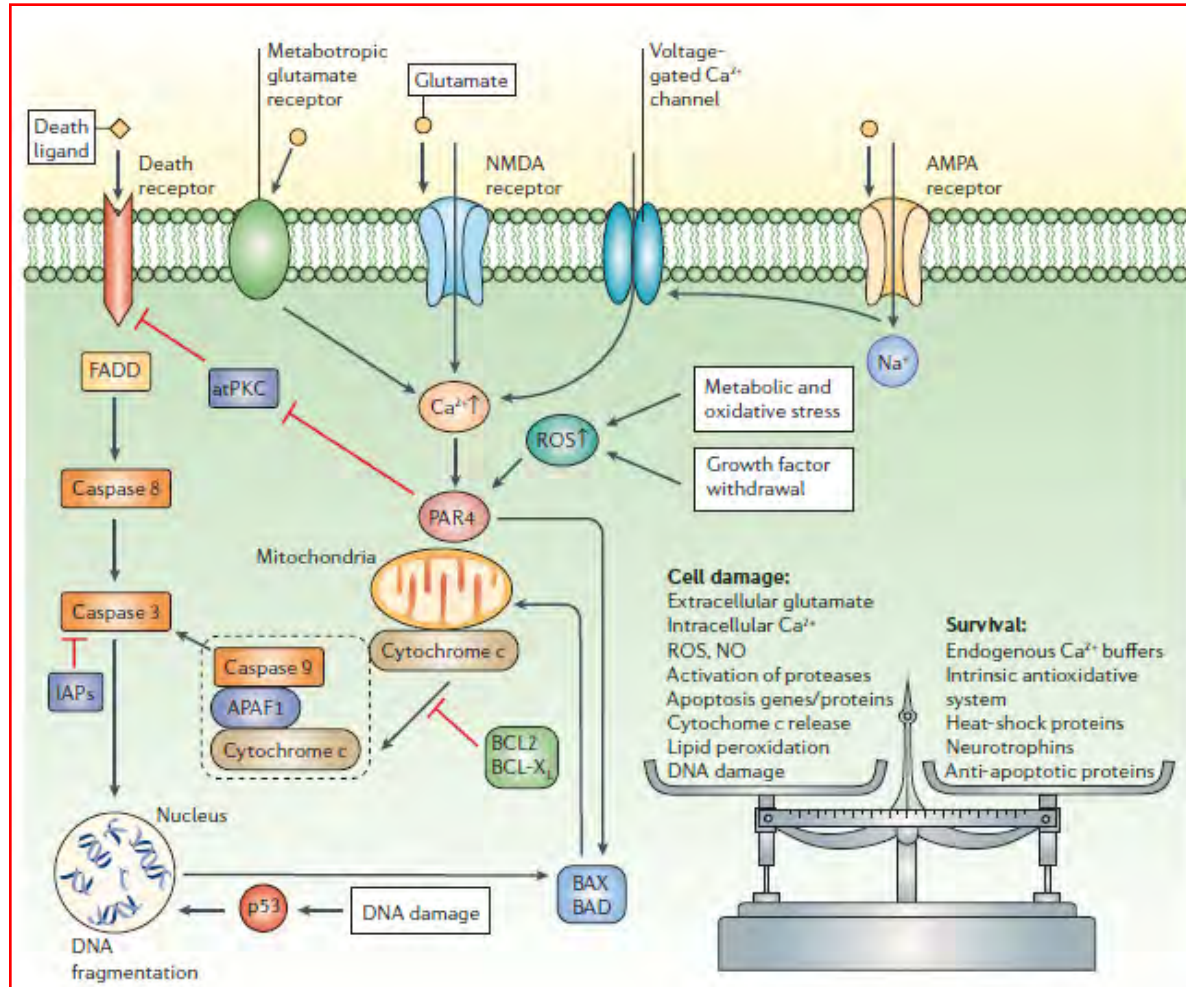


White Matter Lesions



Neuroprotection

Neuroprotective treatment strategies seek to shield nerve cells from degeneration and death



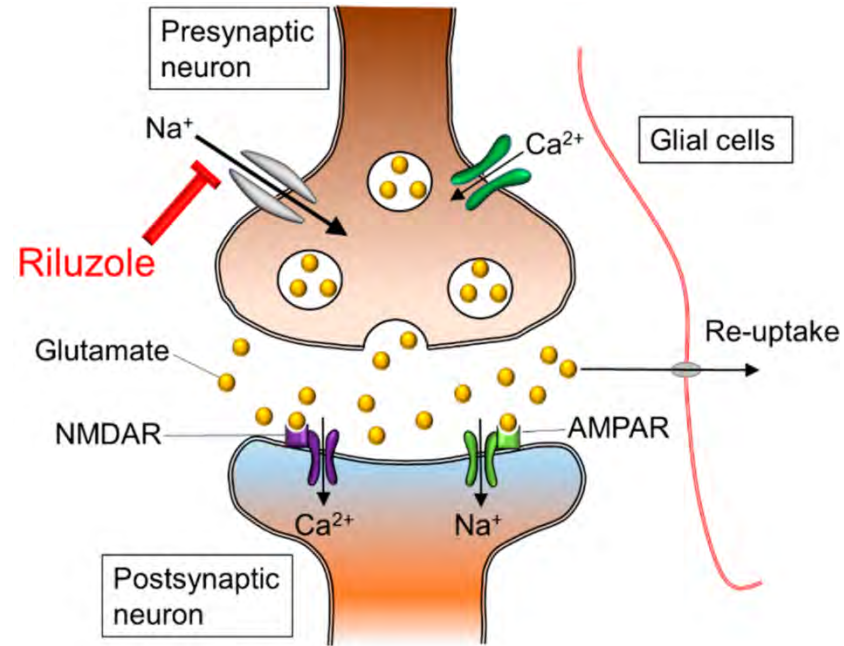
Neuroprotection



Ana Pereira, MD

The Rockefeller University

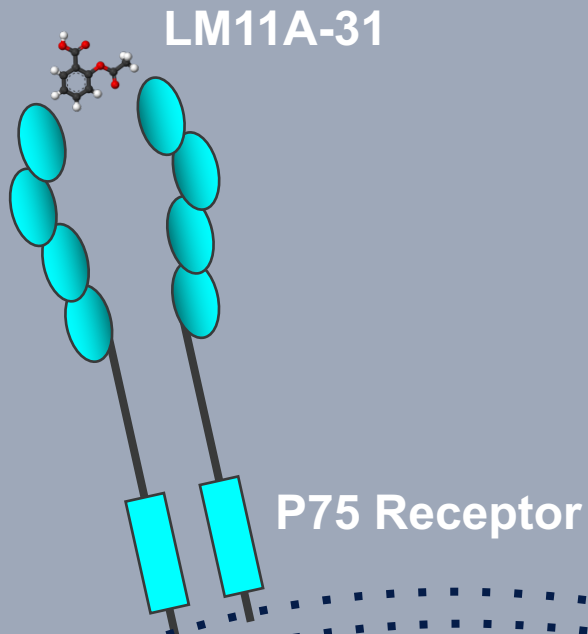
Drug: Riluzole
Phase 2 Clinical Trial



Neuroprotection



Frank Longo, MD, PhD
*Stanford University
School of Medicine &
Pharmatrophix*



Drug
LM11A-31

Stage
Phase 2 Clinical Trial

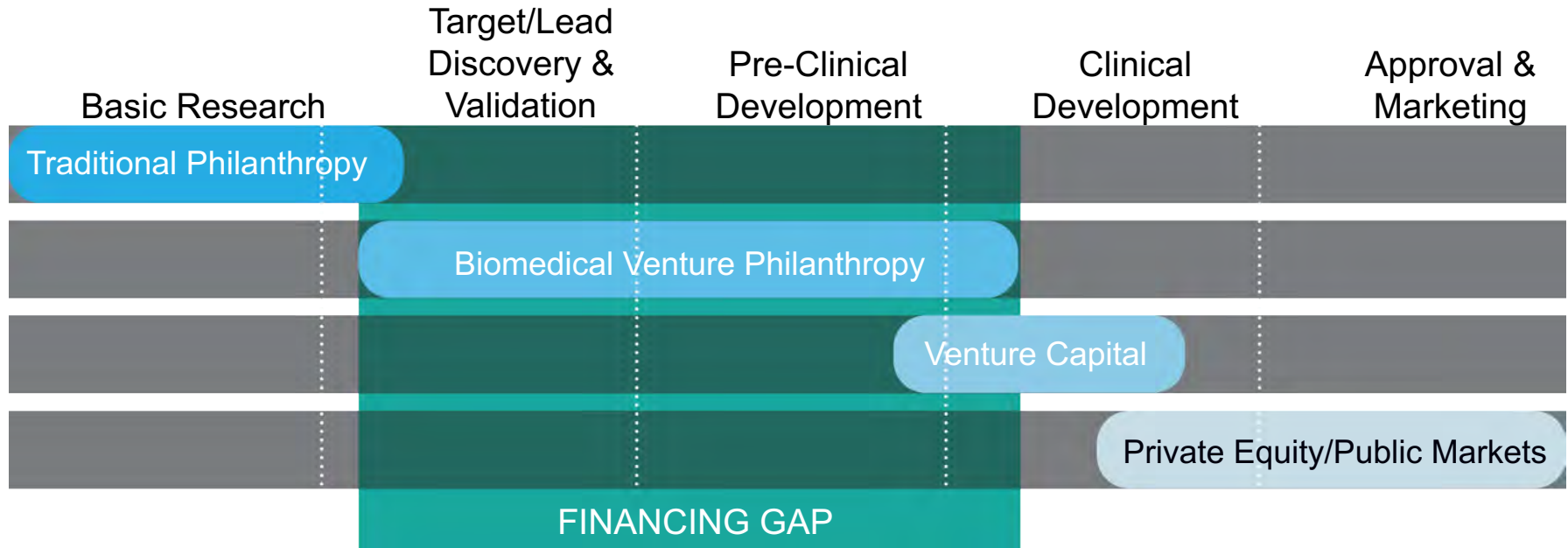
Neuroprotection



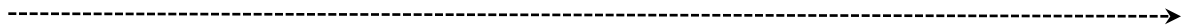
Frank Longo, MD, PhD
Pharmatrophix



VENTURE PHILANTHROPY IN DRUG DISCOVERY



HIGH RISK



LOW RISK



Alzheimer's
Drug Discovery
Foundation

OVER 100 ACTIVE PROGRAMS,
INCLUDING 17 CLINICAL TRIALS

Funded 500+
PROGRAMS IN
18 COUNTRIES



Alzheimer's
Drug Discovery
Foundation

\$92+
MILLION
INVESTED

85+
BIOTECHS

ADDF PARTNERSHIPS



Today, Conquering Alzheimer's is an Achievable Goal

- *Early diagnosis* of Alzheimer's disease is possible
- *Disease modifying drugs* to prevent and treat Alzheimer's disease are in human clinical trials
- *Prevention* of Alzheimer's disease by mid-life strategies is possible





AlzDiscovery.org

**THANK
YOU!**



Thank you to the Yulgilbar Foundation!



HFillit@AlzDiscovery.org



212.901.8000