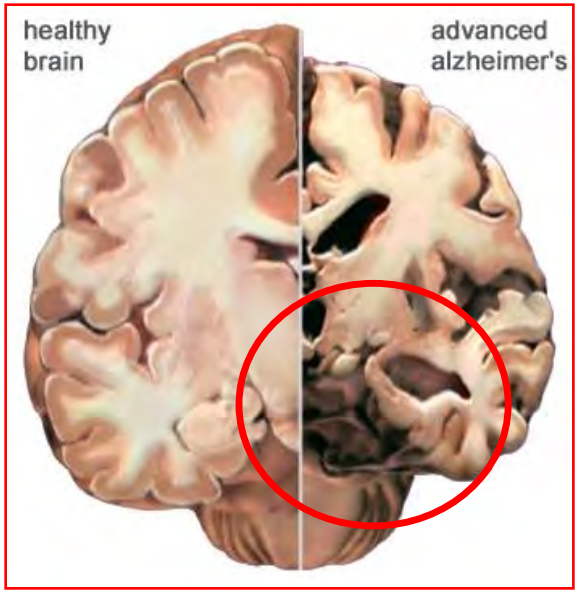
Alzheimer's
Drug Discovery
Foundation

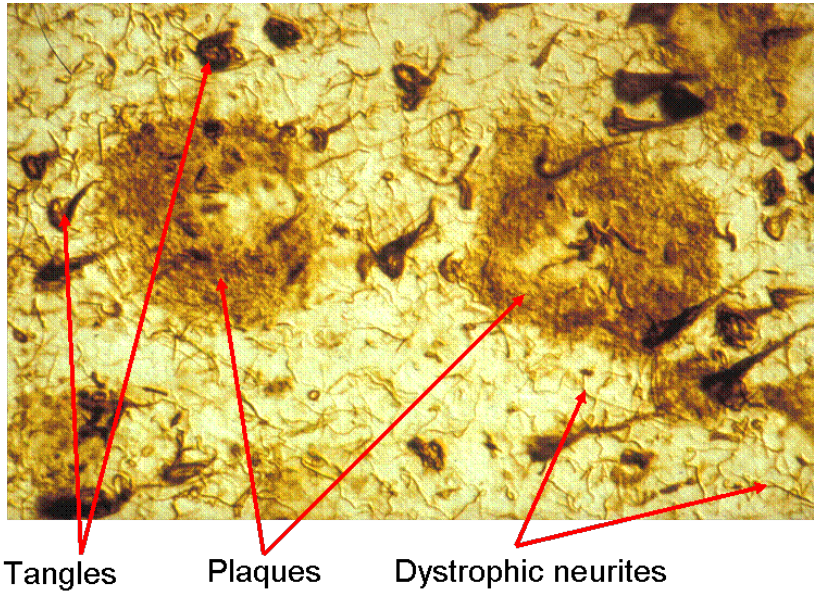
AGING

Translating Biological Gerontology to Alzheimer's Therapy

Thank you to the Yulgilbar Foundation!

What Dr. Alzheimer Observed:
Clues to Therapy?





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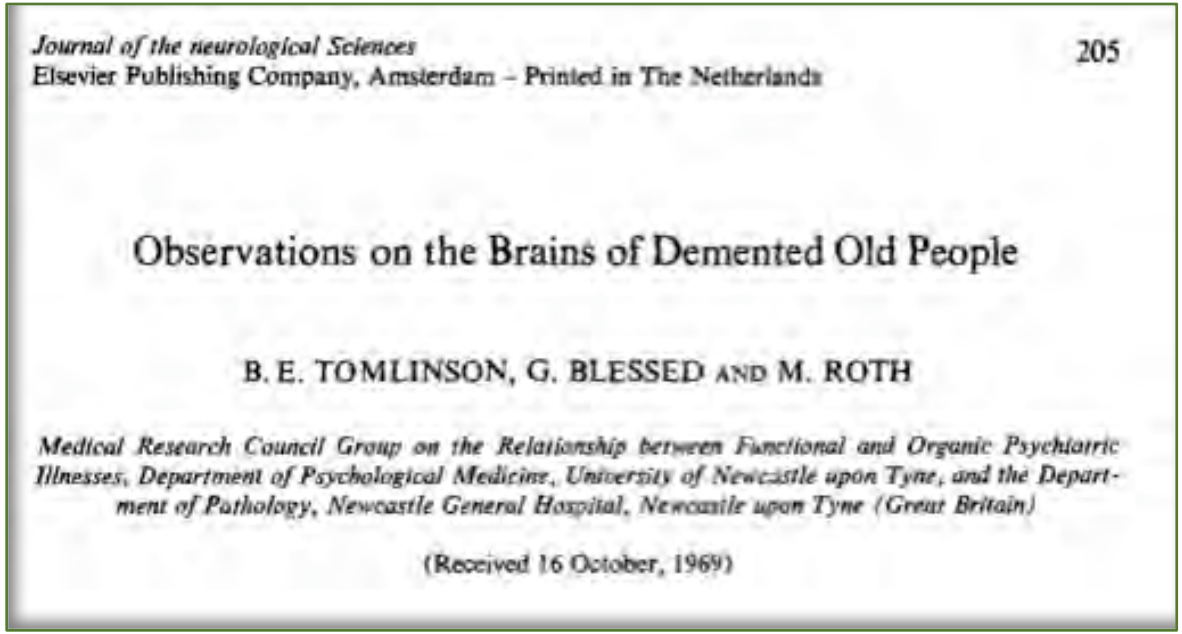
No Progress on Alzheimer's Disease Until ~1970



Journal of the neurological Sciences
Elsevier Publishing Company, Amsterdam – Printed in The Netherlands

205

Observations on the Brains of Demented Old People

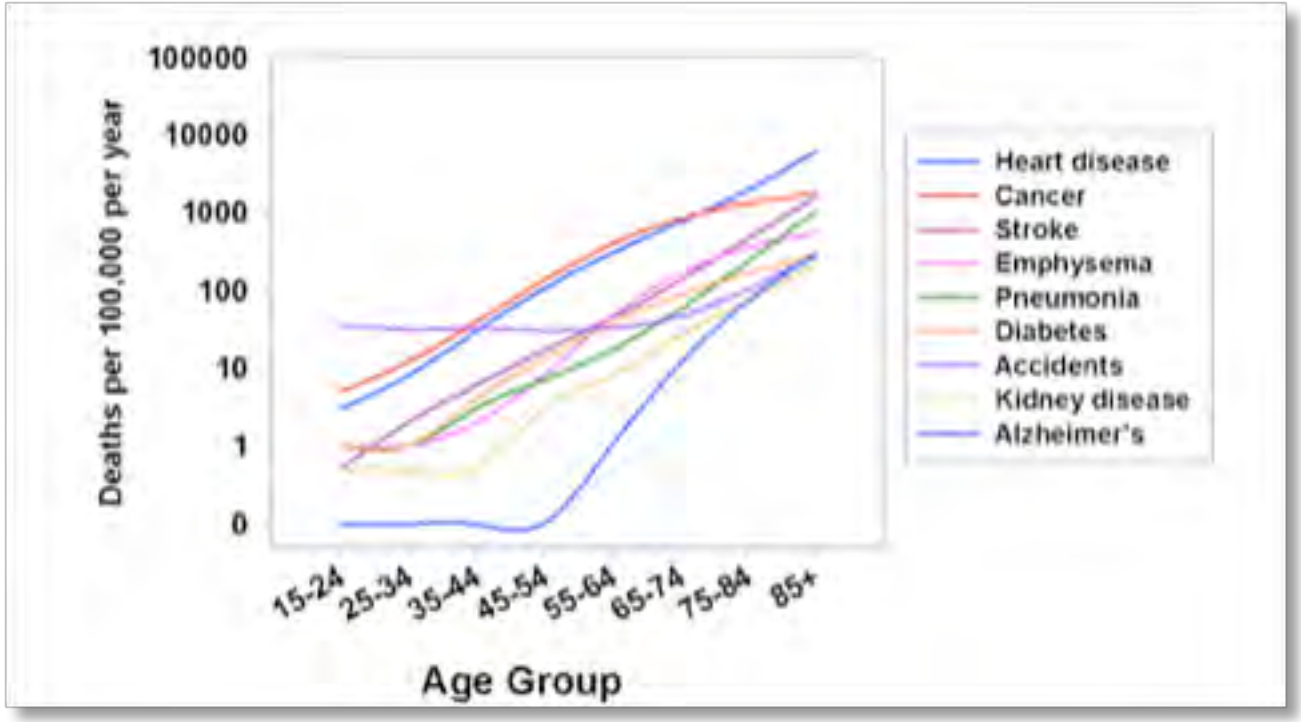
B. E. TOMLINSON, G. BLESSED AND M. ROTH

Medical Research Council Group on the Relationship between Functional and Organic Psychiatric Illnesses, Department of Psychological Medicine, University of Newcastle upon Tyne, and the Department of Pathology, Newcastle General Hospital, Newcastle upon Tyne (Great Britain)

(Received 16 October, 1969)


AGING
IS THE LEADING RISK FACTOR FOR ALZHEIMER'S DISEASE

BIOLOGICAL GERONTOLOGY: ACCUMULATION OF DAMAGE & DISEASE



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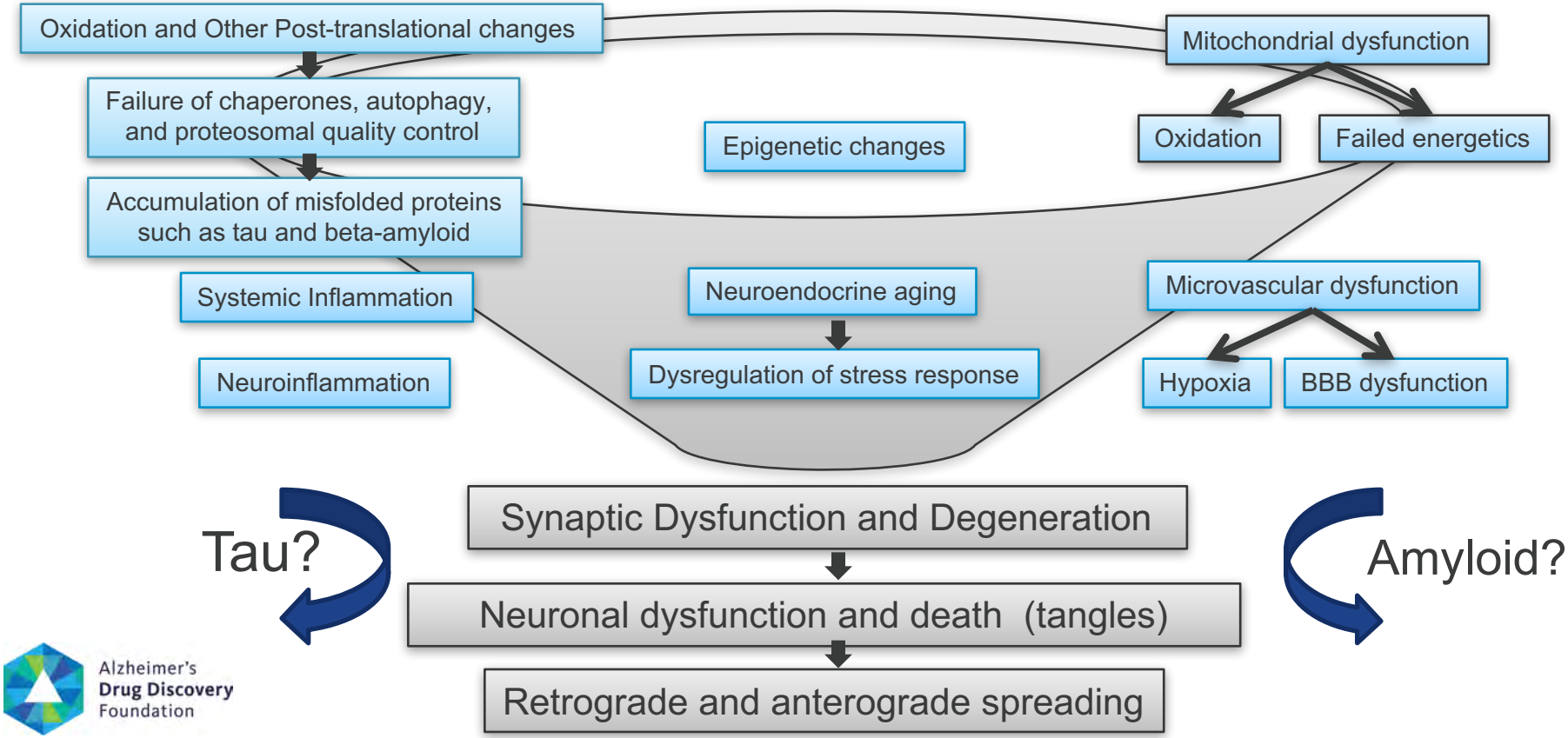
The “Accumulation of Damage” View of Brain Aging and Alzheimers: Novel Therapeutic Targets



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DEVELOPING NOVEL DRUGS FOR ALZHEIMERS

12+ YEARS

>$2 BILLION

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

BASIC SCIENCE

Understanding the Underlying Causes of the disease

DRUG DISCOVERY

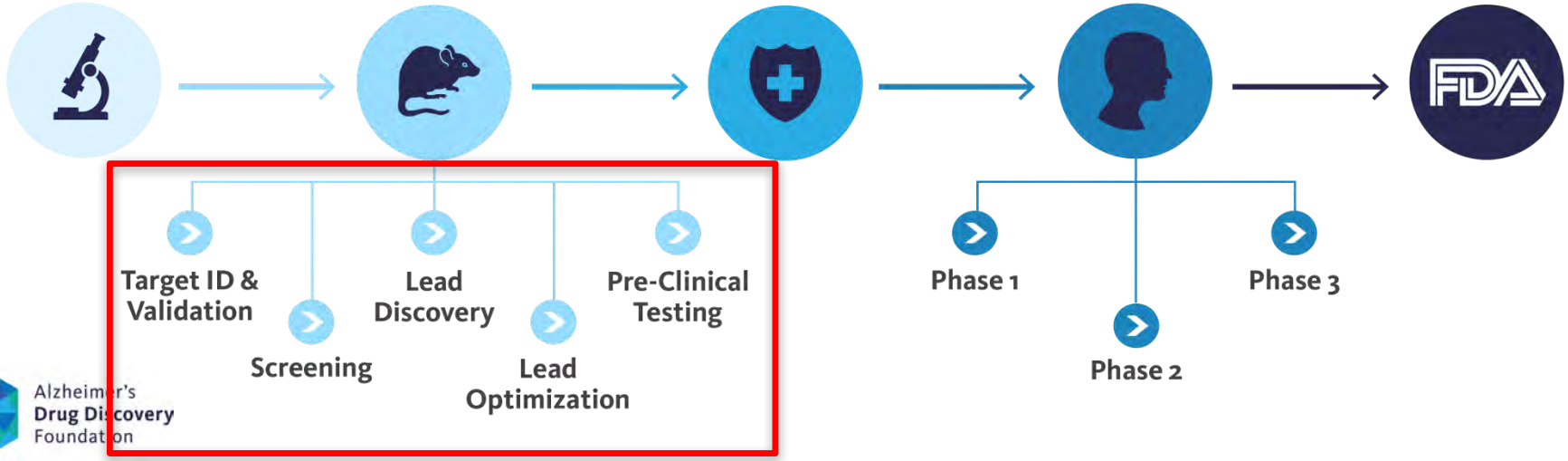
Translating Knowledge into Drugs

IND ENABLING

Preparing Drugs for Testing in Humans

CLINICAL TRIALS

Human Trials of Potential New Drugs



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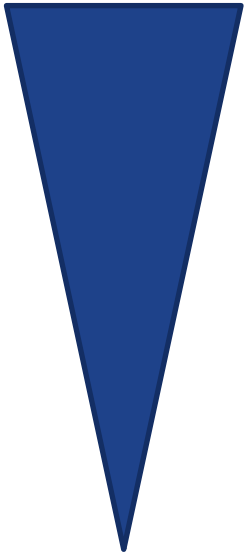
Challenges: *How a Chemist Thinks About Targets for Drug Discovery*
Success Rates of Target Types

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

"RELATIVELY"HIGH SUCCESS RATE



"RELATIVELY"LOW SUCCESS RATE

From: T. Bartfai and GV Lees,, 2006

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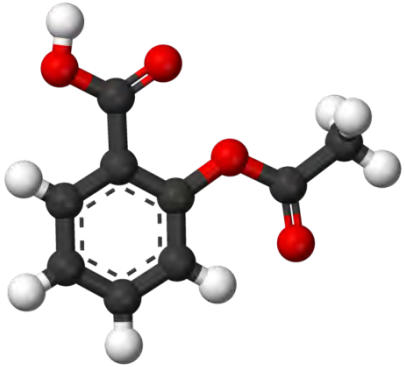
The Origins of FDA-Approved Drugs: Chemical Space is Relatively "Unlimited"

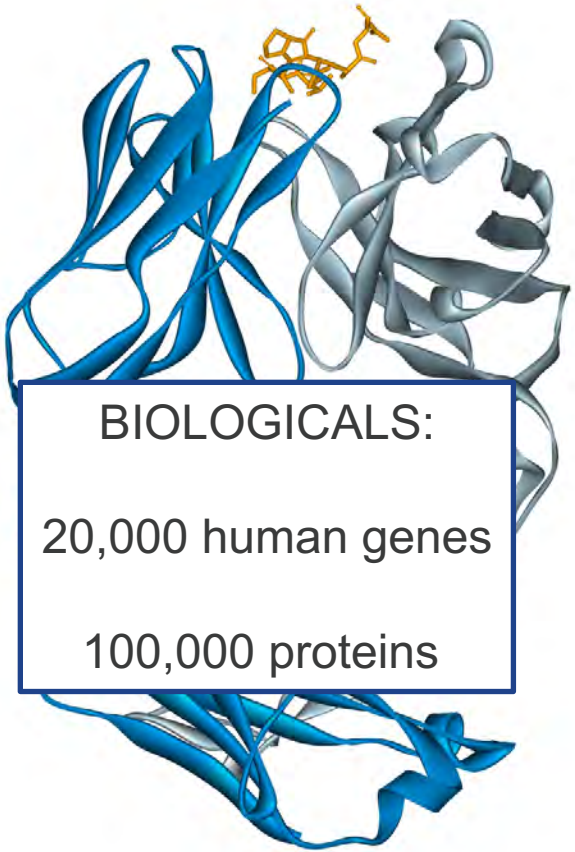
ASPIRIN



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

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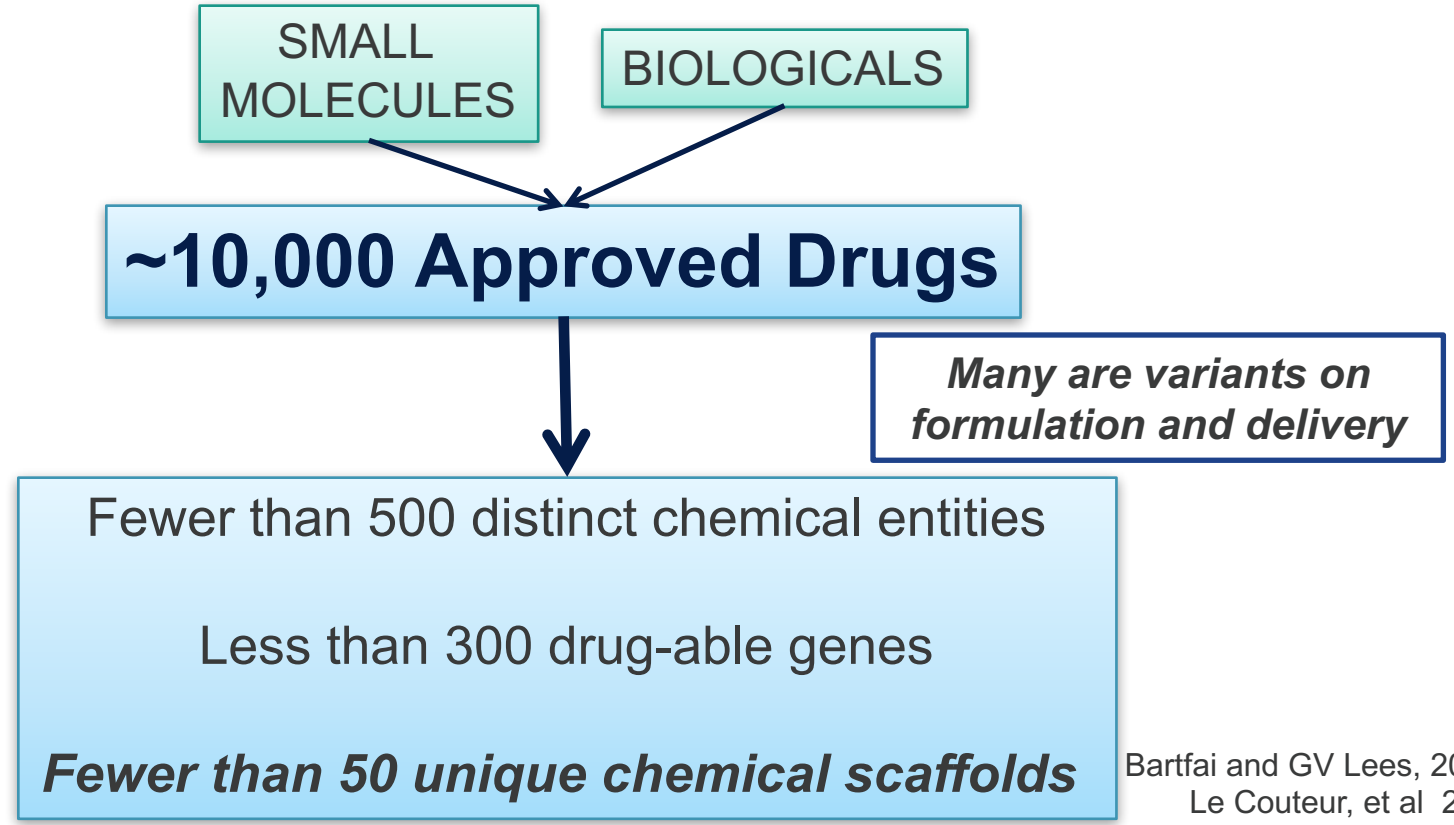
But “Drug-able” Chemical Space is Very Limited



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

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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***

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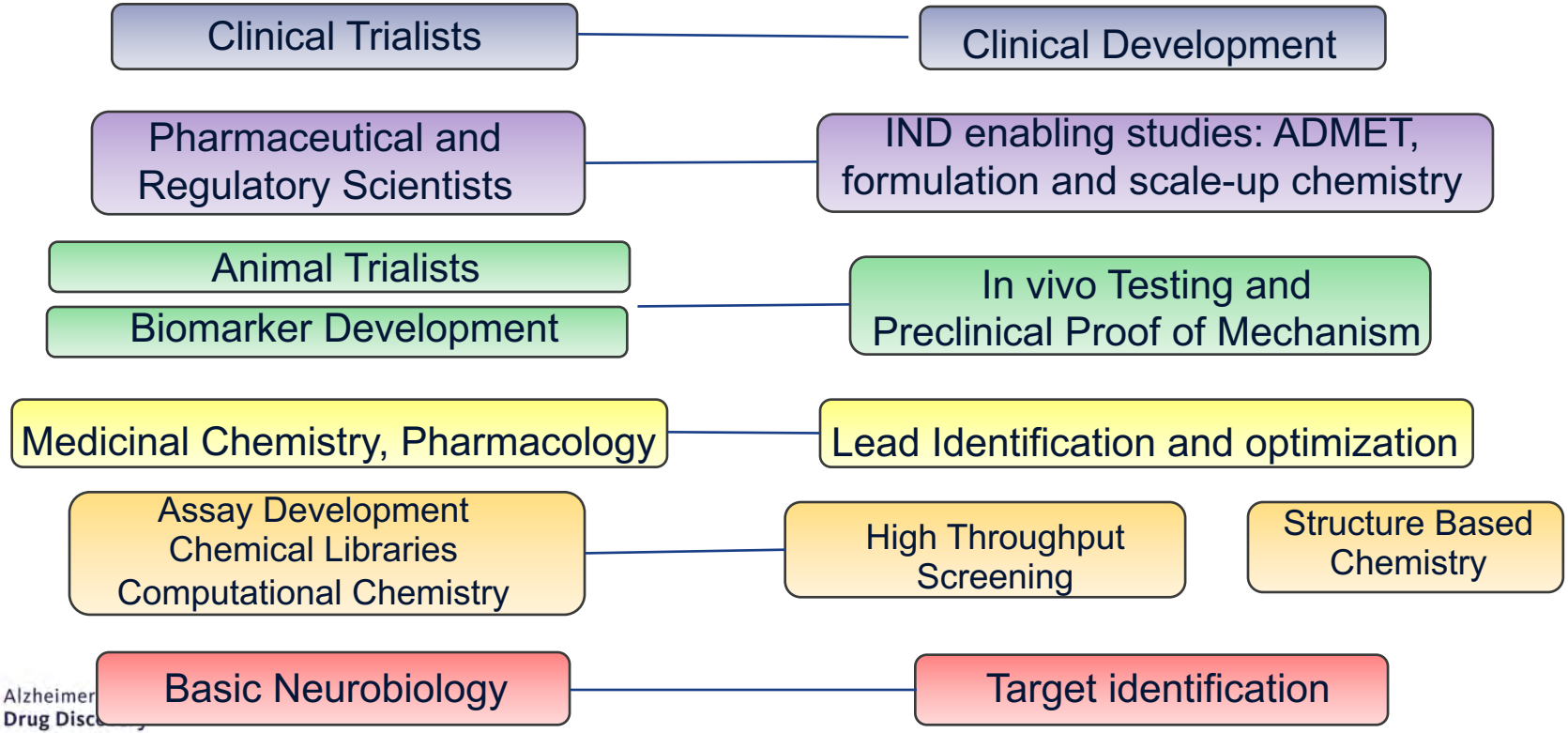
Challenges: Drug Discovery and Development Requires Multidisciplinary Teams of Scientists



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Foundation

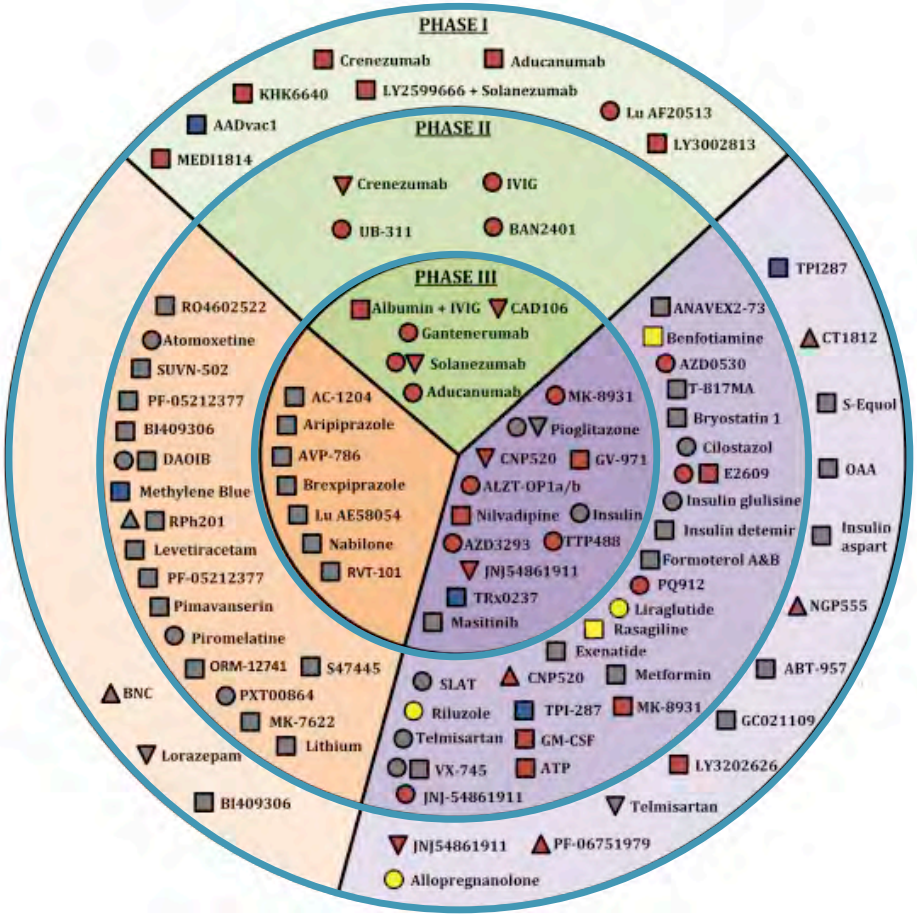
93

Therapies in Active Clinical Trials

24 in Phase 3

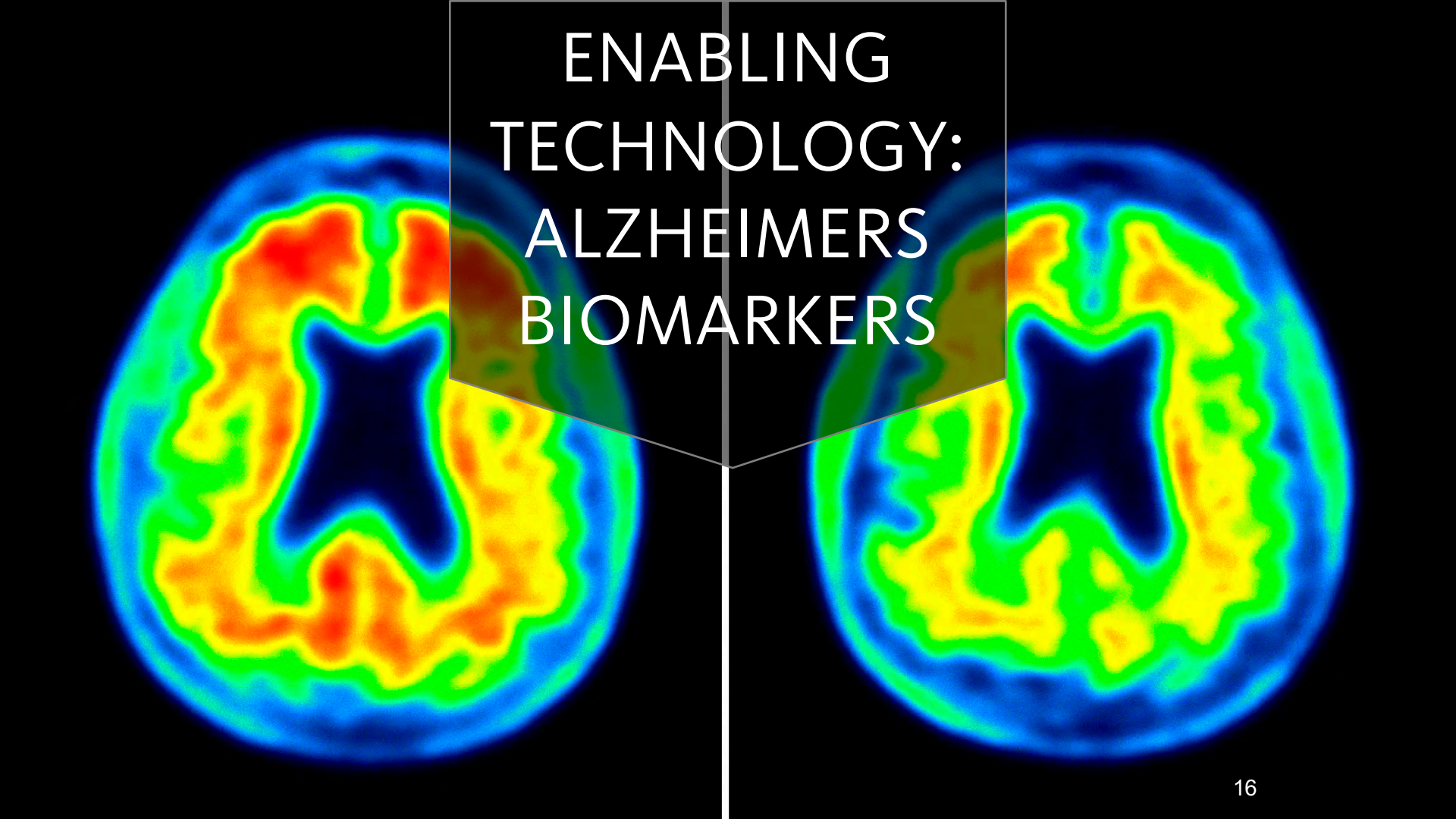
45 in Phase 2

24 in Phase 1



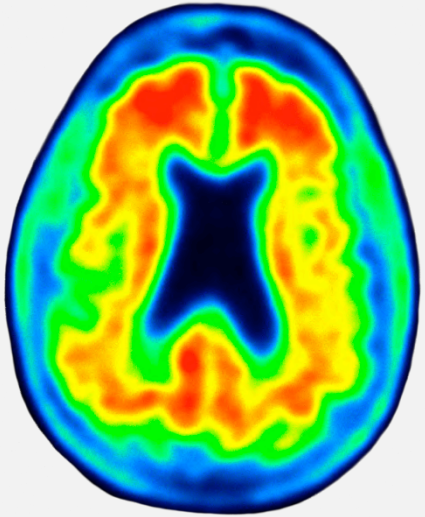
Cummings et al, Alz & Dem 2016

ENABLING TECHNOLOGY: ALZHEIMERS BIOMARKERS

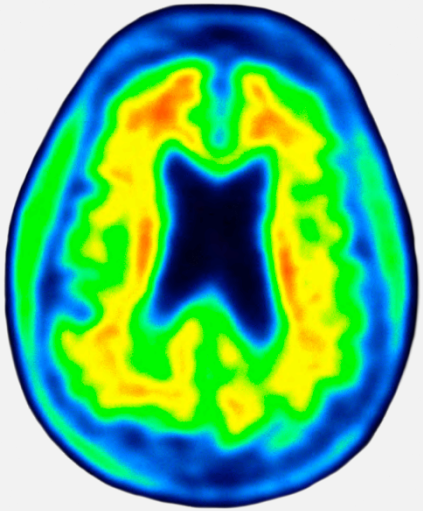


AMYLOID PET SCANNING And CSF Testing

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

Aducanumab: N-terminal Anti-beta amyloid antibody

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff sevigny[1]*, ping chiao[1]*, Thierry bussière[1]*, paul H. Weinreb[1]*, Leslie Williams[1], marcel maier[2], Robert Dunstan[1], stephen salloway[3], Tianle chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], mahin Arastu[1], mingwei Li[1], sowmya chollate[1], melanie s. brennan[1], Omar Quintero-monzon[1], Robert H. scannevin[1], H. moore Arnold[1], Thomas Engber[1], Kenneth Rhodes[1], James Ferrero[1], Yaming Hang[1], Alvydas mikulskis[1], Jan Grimm[2], christoph Hock[2,4], Roger m. Nitsch[2,4]§ & Alfred sandrock[1]§

Nature, September 2016

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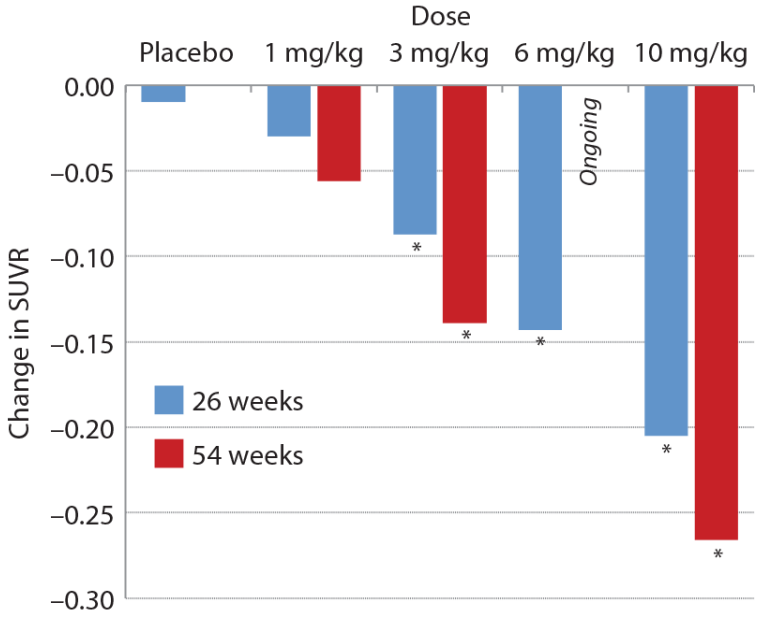
Aducanumab: N-terminal Anti-beta amyloid antibody

From Biogen Phase 1b Clinical Trial

- Reduces Amyloid Plaques
- Effects on cognition and function?



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Aducanumab: N-terminal Anti-beta amyloid antibody

From Biogen Phase 1b Clinical Trial

- Reduces Amyloid Plaques
- Some effects on cognition

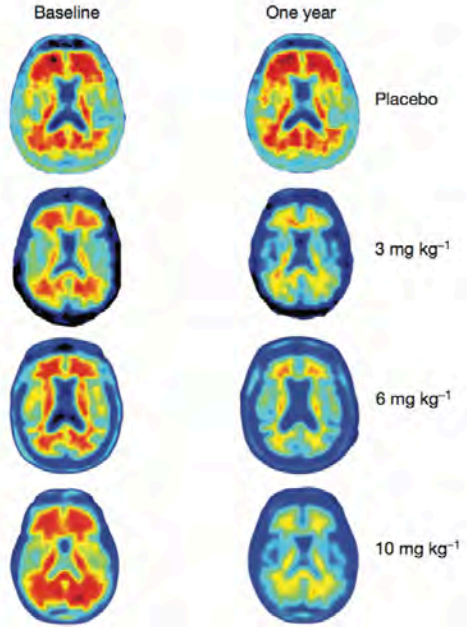

Figure 1 | Amyloid plaque reduction with aducanumab: example amyloid PET images at baseline and week 54. Individuals were chosen based on visual impression and SUVR change relative to average one-year response for each treatment group ($n = 40, 32, 30$ and 32, respectively). Axial slice shows anatomical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

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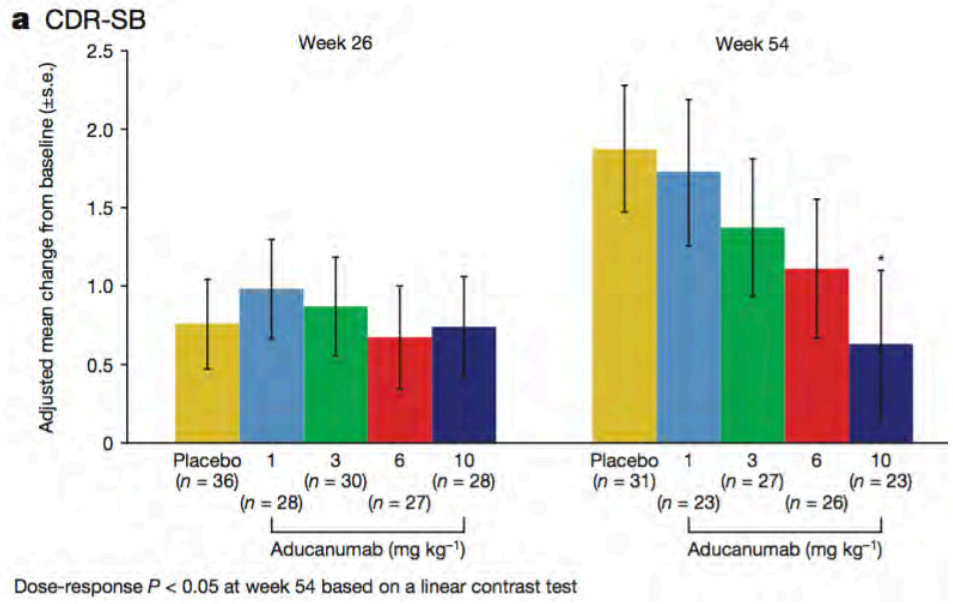
Aducanumab: N-terminal Anti-beta amyloid antibody

From Biogen Phase 1b Clinical Trial

- Reduces Amyloid Plaques
- Some effects on cognition



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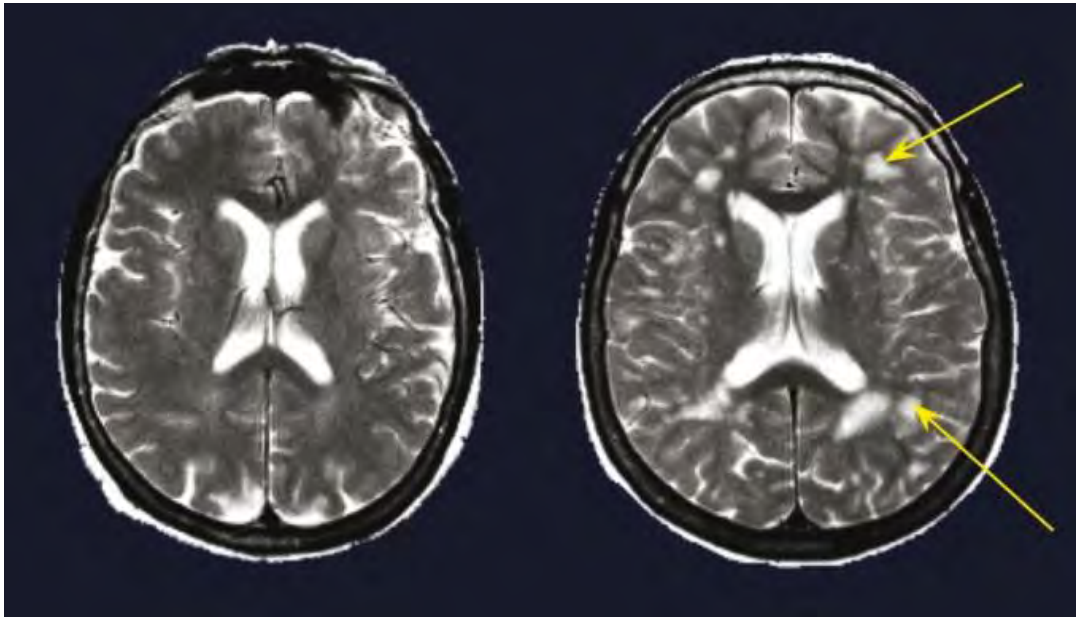
ADVANCES IN MRI NEUROIMAGING

MRI Brain

Detect white matter disease, microvascular disease



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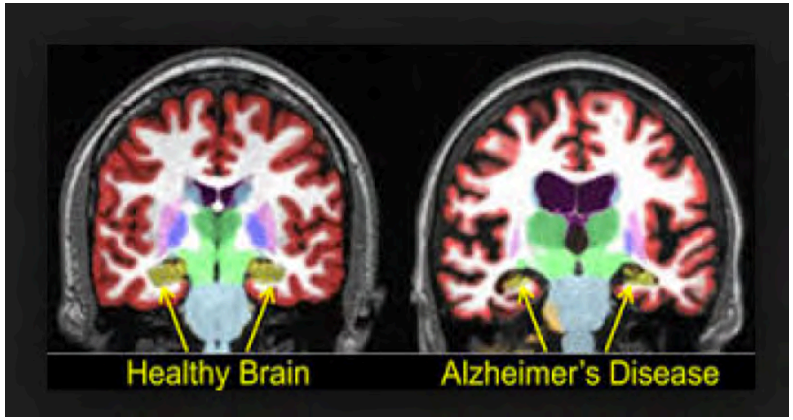
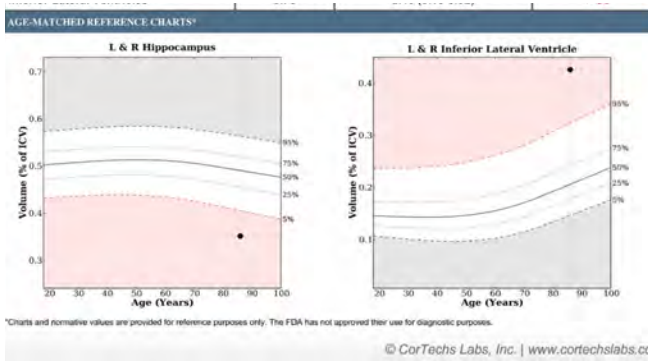
STRUCTURAL NEUROIMAGING to DETECT NEURODEGENERATION

Volumetric analysis (NeuroQuant®)

Clinically measures hippocampal and ventricular volume





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

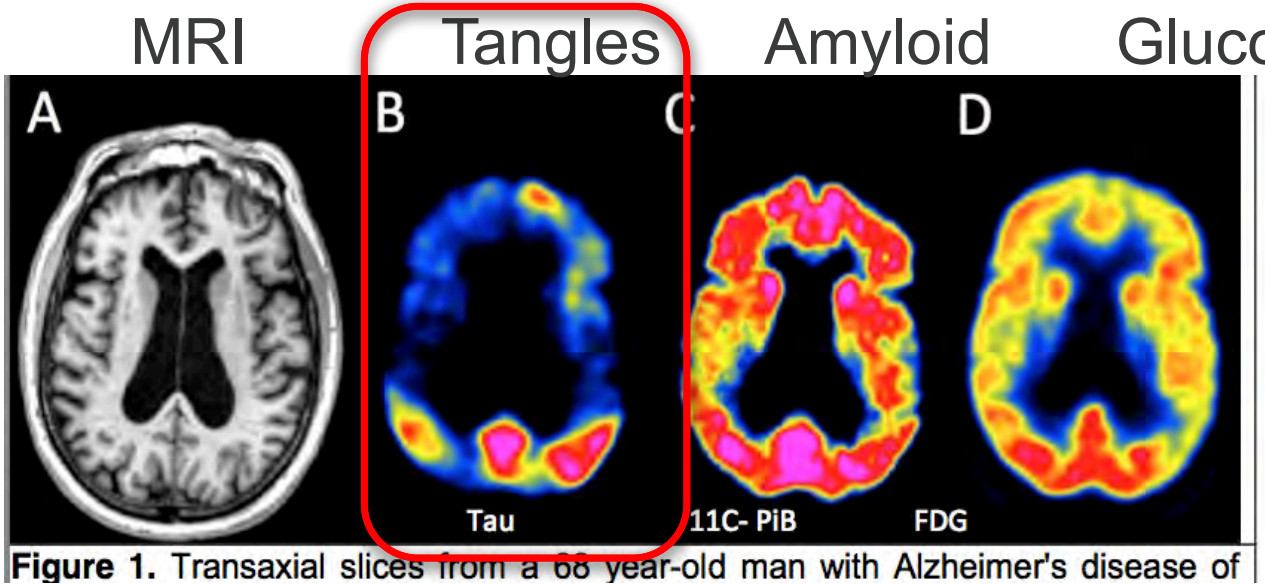

Figure 1. Transaxial slices from a 68 year-old man with Alzheimer's disease of

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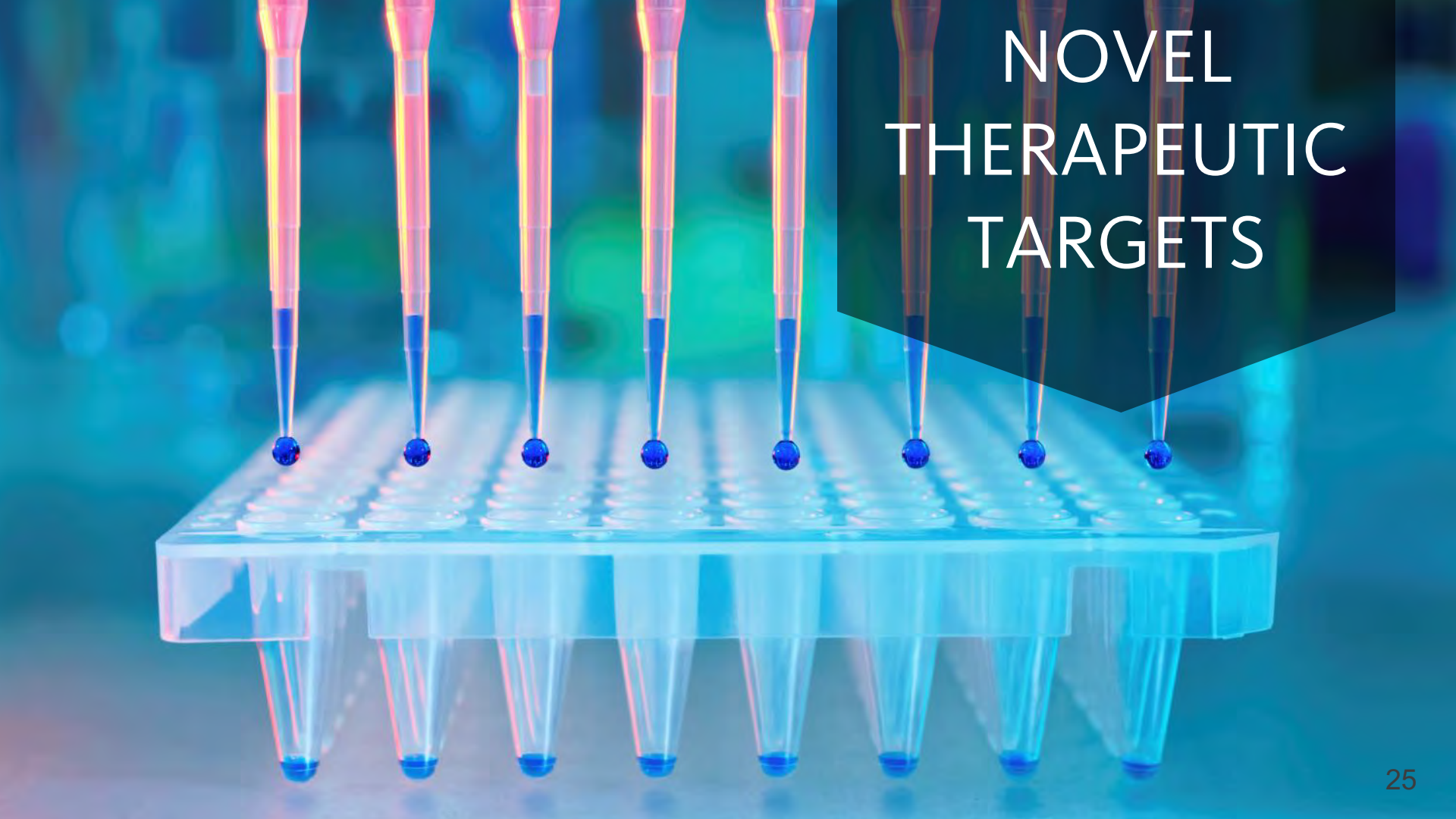

NOVEL THERAPEUTIC TARGETS

“Tau” Targets for Alzheimer’s Disease

TAU PATHWAY	
Phosphorlyation inhibitors	
CDK5	Low
GSK3β	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

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Lo et al, *Sci Transl Med* 2014

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)

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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. Nieland[3], Daniel M. Fass[3,4], Patricia F. Kao[5], Martin Kahn[1], Susan C. Su[1,2], Alireza Samiei[1], Nadine Joseph[1,2,3], Stephen J. Haggarty[3,4], Ivana Delalle[5] & Li-Huei Tsai[1,2,3]

NATURE | VOL 483 | 8 MARCH 2012

Drugs Are In Development To Treat Alzheimers Based on Epigenetics

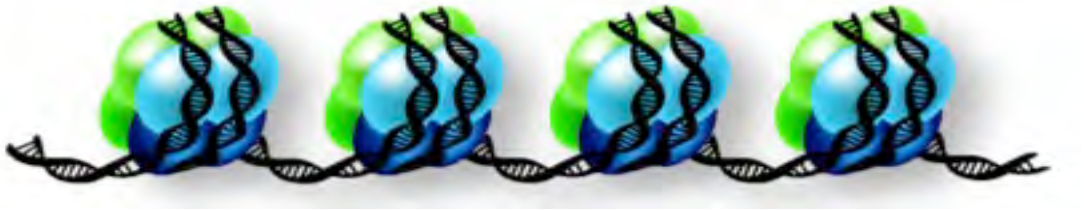
Open reading of DNA for memory and learning genes

Lysine Specific Demethylase Inhibitors

HATs

HDACs

HDAC inhibitors



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Epigenetic Drugs in Development

ORYZON

Tamara Maes, PhD
Barcelona, Spain
DRUG: ORY-2001; Lysine Specific Demethylase 1/ MAO-B Inhibitor
STAGE: Phase 1 Clinical Trial

rodin THERAPEUTICS

Berkley Lynch, PhD
Boston, USA
DRUG: HDAC2 Inhibitor
STAGE: Preclinical

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

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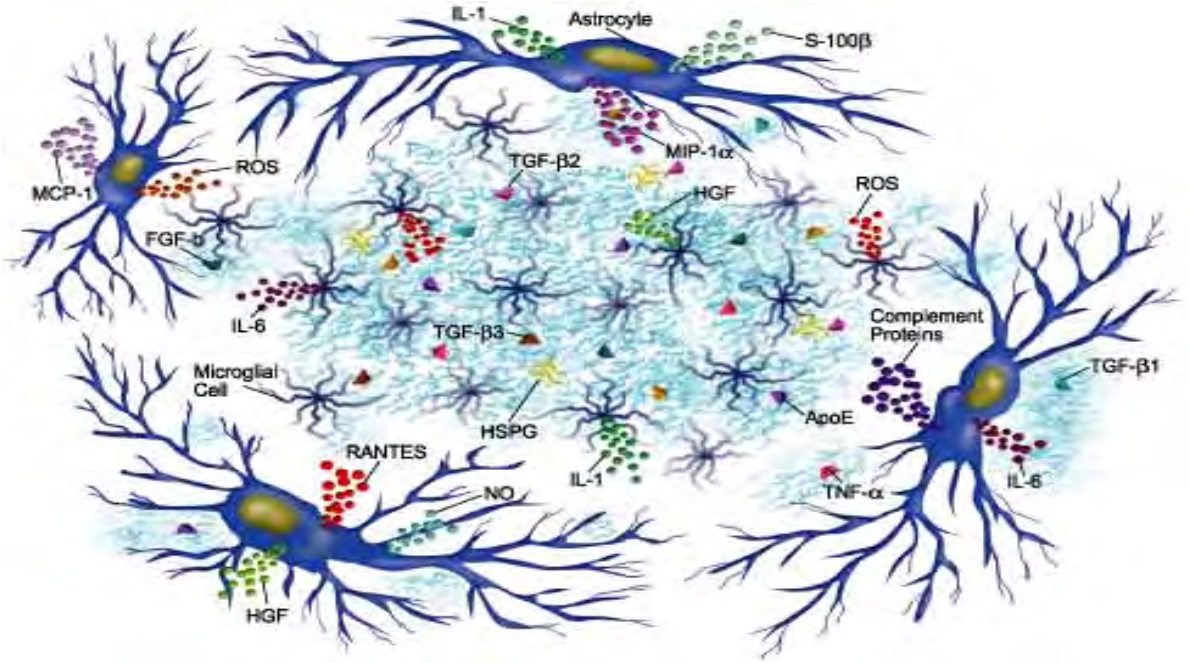
Neuroinflammation

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



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Repurposing to Reduce Systemic Neuroinflammation

Clive Holmes, PhD

University of Southampton, UK

Drug: Etanercept

Phase 2 Clinical Trial

Neuroinflammation: Microglial Purinergic Receptors

GliaCure

Philip Haydon, PhD

GliaCure, Boston

Drug: GC021109
Phase 1 Clinical Trial
Target: P2Y6

AXXAM

Paolo Pevarello, PhD

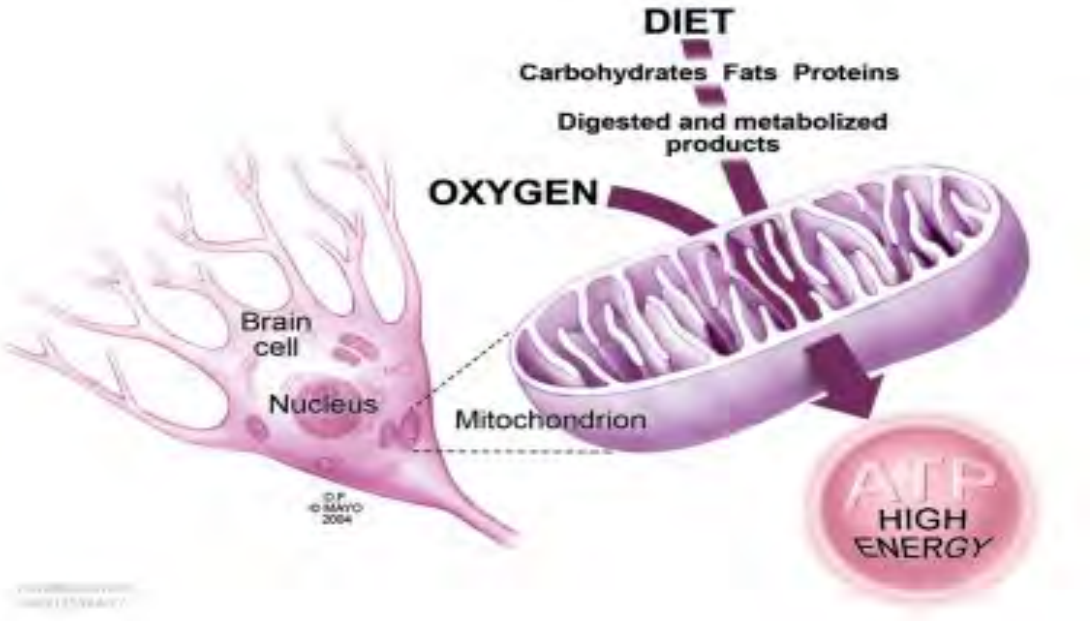
Axxam SpA, Milan

Drug: AXX00179871
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



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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

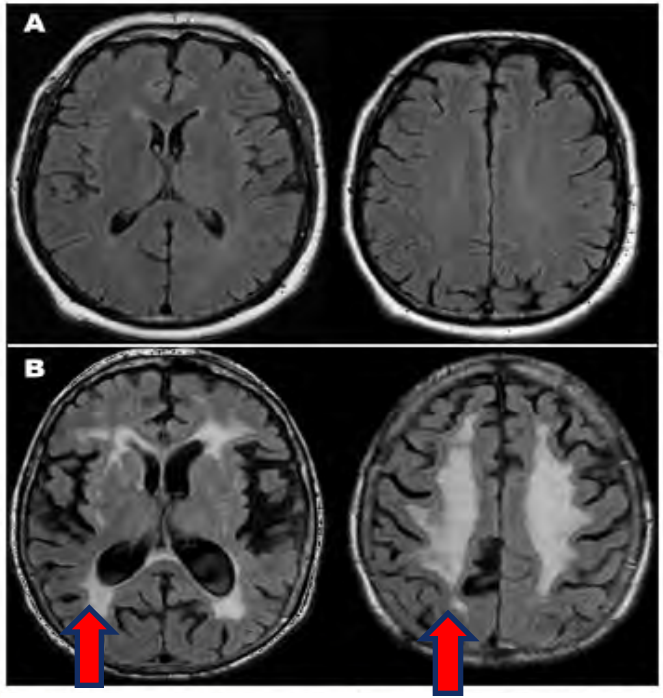
The Cleveland Clinic

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

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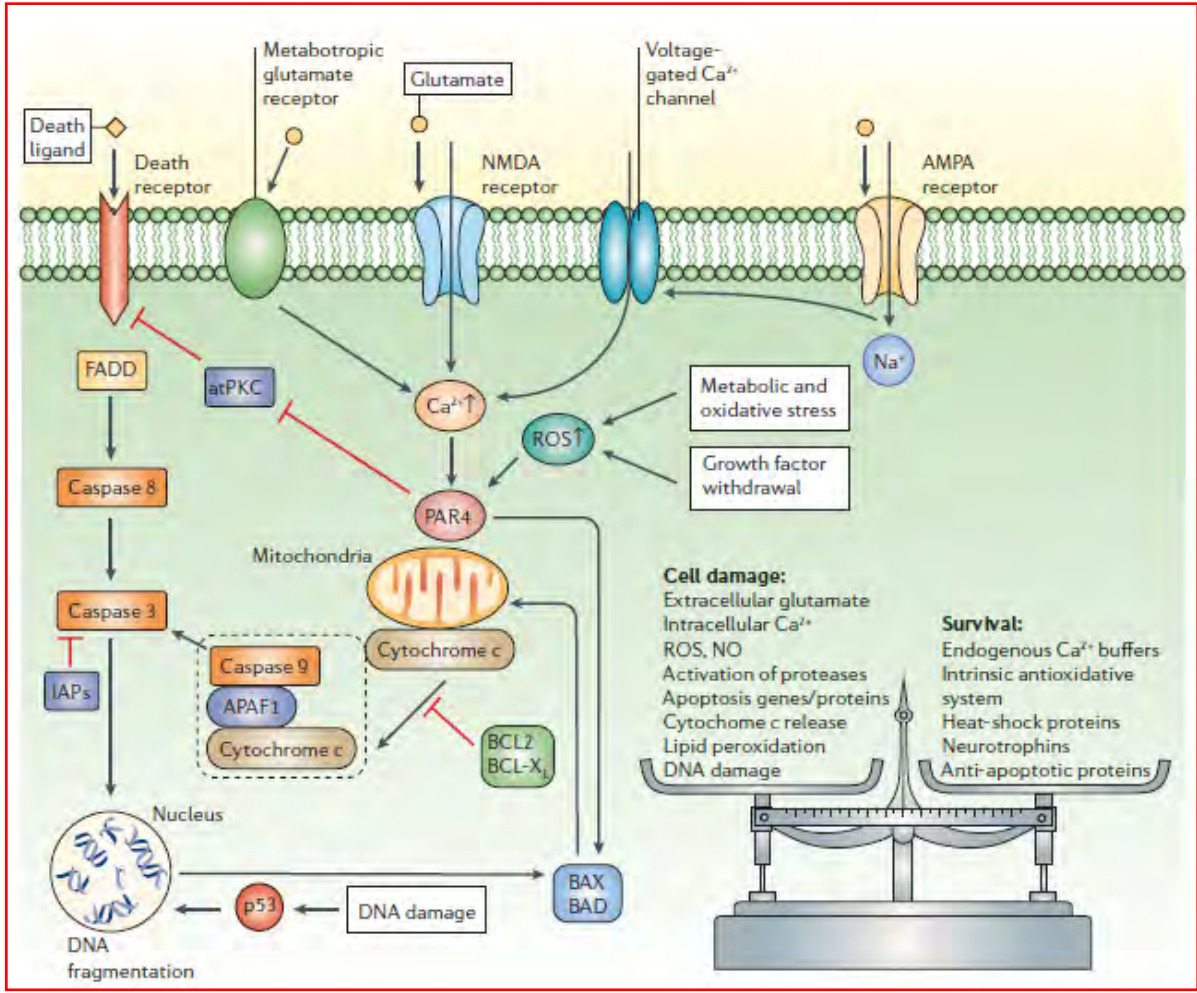
Neuroprotection

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



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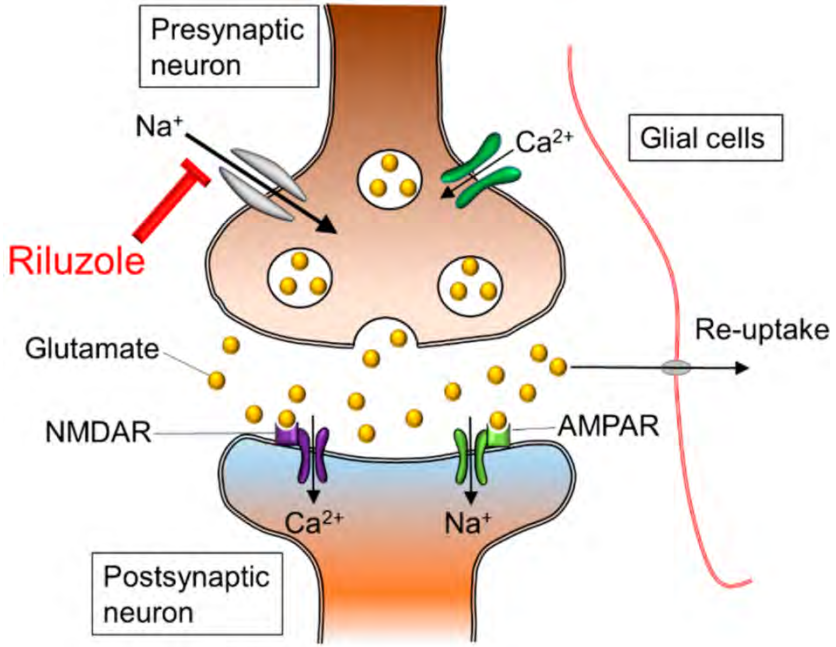
Neuroprotection

Ana Pereira, MD

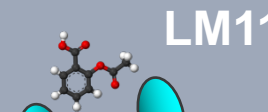
The Rockefeller University

Drug: Riluzole
Phase 2 Clinical Trial



Neuroprotection

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



LM11A-31

P75 Receptor

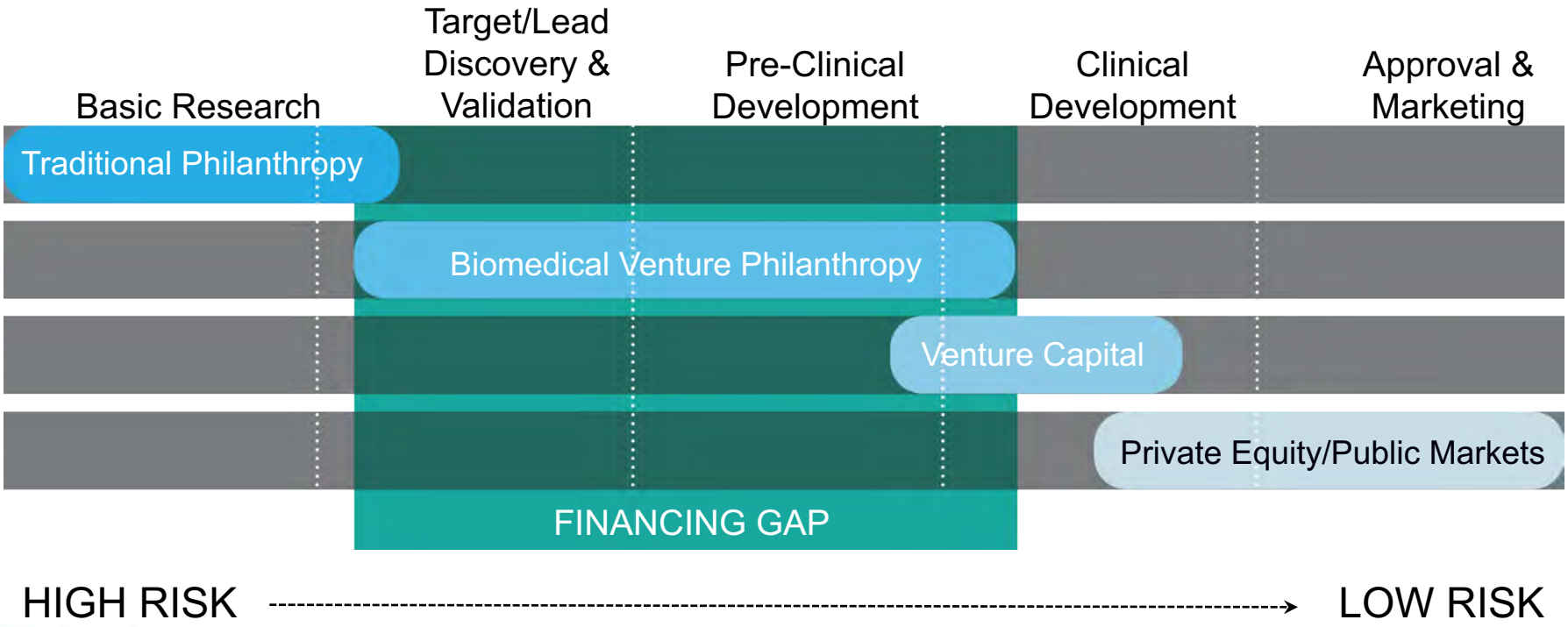
Drug
LM11A-31

Stage
Phase 2 Clinical Trial

Neuroprotection

Frank Longo, MD, PhD
Pharmatrophix

VENTURE PHILANTHROPY IN DRUG DISCOVERY



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Alzheimer's
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OVER 100 ACTIVE PROGRAMS,
INCLUDING 17 CLINICAL TRIALS

Funded 500+

PROGRAMS IN
18 COUNTRIES

$92+
MILLION
INVESTED

85+
BIOTECHS

Alzheimer's
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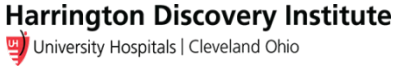
Foundation

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

Alzheimer's Drug Discovery Foundation

AlzDiscovery.org

THANK YOU!

Thank you to the Yulgilbar Foundation!

HFillit@AlzDiscovery.org

212.901.8000

Alzheimer's Drug Discovery Foundation