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 Alzheimer’s: Novel Therapeutic Targets

- Systemic Inflammation
- Neuroinflammation
- Neuroendocrine aging
- Dysregulation of stress response
- Microvascular dysfunction
- Hypoxia
- BBB dysfunction
- Oxidation
- Failed energetics
- Mitochondrial dysfunction
- Epigenetic changes
- Accumulation of misfolded proteins such as tau and beta-amyloid
- Failure of chaperones, autophagy, and proteosomal quality control
- Oxidation and Other Post-translational changes

Synaptic Dysfunction and Degeneration
- Neuronal dysfunction and death (tangles)
- Retrograde and anterograde spreading
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

“RELATIVELY” HIGH SUCCESS RATE

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

“RELATIVELY” LOW SUCCESS RATE

From: T. Bartfai and GV Lees, 2006
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

The Origins of FDA-Approved Drugs: Chemical Space is Relatively “Unlimited”
But “Drug-able” Chemical Space is Very Limited

~10,000 Approved Drugs

Fewer than 500 distinct chemical entities
Less than 300 drug-able genes

Fewer than 50 unique chemical scaffolds

Many are variants on formulation and delivery

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

Challenges: Improving the Predictive Value of Animal Trials

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

Challenges: Drug Discovery and Development Requires Multidisciplinary Teams of Scientists

- Clinical Trialists
- Clinical Development
- IND enabling studies: ADMET, formulation and scale-up chemistry
- In vivo Testing and Preclinical Proof of Mechanism
- Biomarker Development
- Animal Trialists
- Pharmaceutical and Regulatory Scientists
- Medicinal Chemistry, Pharmacology
- Base Neurobiology
- Lead Identification and optimization
- High Throughput Screening
- Structure Based Chemistry
- Assay Development
- Chemical Libraries
- Computational Chemistry
- Target identification
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
• 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 Aβ plaques in Alzheimer’s disease

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
Aducanumab: N-terminal Anti-beta amyloid antibody

From Biogen Phase 1b Clinical Trial

• Reduces Amyloid Plaques
• Some effects on cognition
ADVANCES IN MRI NEUROIMAGING

MRI Brain

Detect white matter disease, microvascular disease
Volumetric analysis (NeuroQuant®)

Clinically measures hippocampal and ventricular volume
Recent Advances in Neuroimaging Alzheimer's: Seeing the Plaques and Tangles

*Figure 1.* Transaxial slices from a 66 year-old man with Alzheimer's disease of...
NOVEL THERAPEUTIC TARGETS
### TAU PATHWAY

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphorlyation inhibitors</td>
<td>Low</td>
</tr>
<tr>
<td>CDK5</td>
<td>Low</td>
</tr>
<tr>
<td>GSK3β</td>
<td>Low</td>
</tr>
<tr>
<td>MARK/par1</td>
<td>Low</td>
</tr>
<tr>
<td>PKC</td>
<td>Low</td>
</tr>
<tr>
<td>MAPK</td>
<td>Low</td>
</tr>
<tr>
<td>PKA</td>
<td>Low</td>
</tr>
<tr>
<td>p70S6K</td>
<td>Low</td>
</tr>
<tr>
<td>Antiaggregants (TRx0237)</td>
<td>Low</td>
</tr>
<tr>
<td>Microtubule stabilizing agents (BMS 241027)</td>
<td>Low</td>
</tr>
<tr>
<td>Reduction of tau levels (Tau antibodies and antisense oligonucleotides)</td>
<td>Low</td>
</tr>
</tbody>
</table>
Lifelong risk factors cause cellular stress, resulting in the chemical modification of genes and their expression.
With Aging, Epigenetic Changes May Cause Neurodegeneration

An epigenetic blockade of cognitive functions in the neurodegenerating brain

Johannes Gräff¹,²,³, Damien Rei¹,², Ji-Song Guan¹,²,³, Wen-Yuan Wang¹,²,³, Jinsoo Seo¹,², Krista M. Hennig³,⁴, Thomas J. F. Nieland⁵, Daniel M. Fass³,⁴, Patricia F. Kao⁵, Martin Kahn⁶, Susan C. Su¹,², Alireza Samiei⁷, Nadine Joseph¹,²,³, Stephen J. Haggarty³,⁸, Ivana Delalle⁹ & Li-Huei Tsai¹,²,³

NATURE | VOL 483 | 8 MARCH 2012
Drugs Are In Development To Treat Alzheimers Based on Epigenetics

Lysine Specific Demethylase Inhibitors

HDACs

Open reading of DNA for memory and learning genes

HDAC inhibitors

HATs
Epigenetic Drugs in Development

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

Berkley Lynch, PhD
Boston, USA
**DRUG:** HDAC2 Inhibitor
**STAGE:** Preclinical
ADDf is helping Rodin to develop specific HDAC inhibitors for Alzheimers through *Venture Philanthropy*.

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

by Damian Garde | Jan 6, 2016 7:01am
Chronic systemic and central neuroinflammation can accelerate Alzheimer’s and may be a trigger of the disease.
Repurposing to Reduce Systemic Neuroinflammation

Clive Holmes, PhD
University of Southampton, UK

**Drug:** Etanercept
Phase 2 Clinical Trial
Neuroinflammation: Microglial Purinergic Receptors

Philip Haydon, PhD
_GliaCure, Boston_
**Drug:** GC021109
Phase 1 Clinical Trial
Target: P2Y6

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
Repurposing to Improve Neuronal Energy Failure

Paul Edison, MD, PhD
Imperial College London
Drug: Liraglutide
Phase 2 Clinical Trial

Jeffrey L. Cummings, MD
The Cleveland Clinic
Drug: Rasagiline
Phase 2 Clinical Trial
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
Neuroprotective treatment strategies seek to shield nerve cells from degeneration and death.
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

Basic Research

Target/Lead Discovery & Validation

Pre-Clinical Development

Clinical Development

Approval & Marketing

Traditional Philanthropy

Biomedical Venture Philanthropy

Venture Capital

Private Equity/Public Markets

FINANCING GAP

HIGH RISK ———————————————— LOW RISK
OVER 100 ACTIVE PROGRAMS, INCLUDING 17 CLINICAL TRIALS

Funded 500+ PROGRAMS IN 18 COUNTRIES

$92+ MILLION INVESTED

85+ BIOTECHS
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
THANK YOU!

Thank you to the Yulgilbar Foundation!

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