Pharmaceutical Research & Development for Alzheimer’s Disease

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Alzheimer’s Disease – A Health Crisis

- About 35 million people living with dementia in the world; the majority with Alzheimer’s disease
  - > 5 million people with Alzheimer’s disease in the USA

- Alzheimer’s disease is growing rapidly
  - Major patient, caregiver and health care burden

- We need better treatments
  - Current medicines provide modest symptomatic improvement
  - There are no “disease modifying therapies” available
Alzheimer’s Medicines – Many Attempts, Few Successes so Far….

4 Approved Medicines
123 Unsuccessful Drug Programs for Alzheimer’s

Memantine
Namzaric (memantine & donepezil)
Galantamine (2001)
Rivastigmine (2000)
Donepezil (1996)

Finding a New Drug is Complex & Risky

- On average 12% of drug molecules entering clinical studies reach the market
  - Many more do not even make it past preclinical studies
- On average > 10 years for one medicine to make it through the R&D process
- Average costs $2.6 billion / developed medicine
- Failure is an inherent part of drug R&D
  - As science grows, so does the complexity of developing new medicines
Drug Research & Development Process

**Preclinical studies**
- **Target & Drug Discovery**
  - Understand drug target biology
  - Search for active substances on target
- **Preclinical Development**
  - Toxicology on various types of animals
  - Regulatory review
  - Investigational New Drug Application for permission to administer a new drug to humans

**Clinical studies**
- **Phase I**
  - Safety studies on healthy volunteers
  - 50–250 persons
- **Phase II**
  - Clinical studies on a limited scale
  - Safety & Proof of Concept
  - 100–800 patients
- **Phase III**
  - Comparative studies on a large number of patients
  - Confirm effect & doses
  - 500–5,000 patients

**Commercialization**
- **Regulatory filing & review**
- **Registration**
- **Launch**
  - Market introduction
- **Phase IV**
  - Continued comparative studies

**At least 15 years from idea to marketable drug**

- **3–10 yrs.**
- **0.5–1 yr**
- **4–10 yrs.**
- **1–2 yrs.**
Understanding & Studying Alzheimer’s Disease

Progressive deficits in cognition (memory), activities of daily living with behavioral changes

- Extracellular amyloid plaques
- Intracellular neurofibrillary tangles
- Neurodegeneration
- Neuroinflammation

“Biomarkers”

- Decreased brain metabolism
- Brain atrophy

Alois Alzheimer
1864 -1915

Auguste Deter
1850 –1906
(Mutation in the PSEN1 gene)
Unraveling Very Complex Biology

Many additional associated molecular processes
Fatty acid transporters & metabolism – e.g. ApoE
Immunological reactions & Inflammation
Critical Understanding Through Studies on Alzheimer’s Causing Mutations

Swedish mutation KM670/671NL: More Aβ40/42

~ 60 gene variants found along the APP gene
  • Most gene variants pathogenic (AD, PD Cerebral Amyloid Angiopathy)

Dutch mutation: Peptides more prone to form fibrils
Hereditary Cerebral Hemorrhage

Flemish mutation: N-terminal heterogeneity

Italian mutation

Arctic mutation Peptides more prone to form protofibrils

\(\beta\)-secretase BACE1/2

\(\alpha\)-secretase ADAM10

\(\gamma\)-secretase Complex; PS1


C-terminal
Drugs Work on Biological "Targets"

- "Novel Targets" Linked to Human Disease
- "Emerging" Targets Signs of Human Effect Established
- "Novel" Targets

~2200 “druggable” targets are expressed in the Central Nervous System

~2-3 Opportunities in Alzheimer’s

~10-15 Opportunities In Alzheimer’s
Finding Inhibitors of the BACE Enzyme Was a Major Industry Effort

- Difficult brain target for a small molecule inhibitors
  - Membrane bound intracellular protease
  - Requires potent enzyme inhibition plus brain “penetration”
How to Evaluate “Disease Modification” in Alzheimer’s

- Pre-symptomatic
- Prodromal phase
- Clinically manifest phase
- Stop progression
- Slow progression

Disease progression

Time

Degree of disability

Treatment Effect “Efficacy”

Treatments usually 18-24 months
Challenges With Alzheimer’s Drug Development

- Only possible to determine that drug works late in the development process
- Effects measured on “rating scales”
- Very long trials
- Very expensive trials
- Very complex infrastructure for AD trials
- Very difficult getting patients to the trials
- Very difficult getting the “right” patients to the trials
Alzheimer’s Disease is a Continuum

Pre-Dementia ➔ Dementia

Pre-Symptomatic ➔ Cognitive Impairment ➔ Cognitive, Functional & Behavioral deficits

Memory complaints ➔ MCI / Prodromal AD ➔ Mild ➔ Moderate ➔ Severe

No apparent symptoms ➔ Symptoms ➔ Current diagnosis & treatment

• Risk factors; family history, old age, ApoE4 genotype, TBI, mutations
• No symptoms, or subtle cognitive deficits (memory complaints)
• Emerging biomarker evidence of AD pathology

• Mild cognitive impairment (MCI)
• Amnestic Mild Cognitive Impairment (aMCI) - episodic memory deficits
• aMCI combined with biomarker evidence of AD pathology = Prodromal AD

• AD diagnosis based on clinical symptoms; cognitive deficits & dementia of the AD type
• Biomarker evidence of AD pathology may increase specificity of diagnosis
Amyloid PET For Amyloid Detection

Amyloid Negative Example

Amyloid Positive Example: Diffuse

Amyloid Positive Example: Diffuse + Focal
A Typical Alzheimer’s Drug Trial

Pre-Screening → Screening → MRI → Baseline → amyloid PET →

~ 2 Months

Randomize → Treatment → “Data lock” & “Unblinding” & Analysis

~ 1-3 Years

< 75% subjects screen fail on inclusion criteria
(35-50% fail on amyloid PET)
20-30% “drop out” during the treatment period
Web-Based Tools for Patient Enrollment
Online Cognitive Assessment

Self-assessments using a web-based online computer based cognitive test
What Do We Do to Further Improve?

- More research – basic & clinical
- Developing even better diagnostics
  - Earlier detection
  - More precise definition of patients
- Evaluating further medicines hypotheses
  - Better symptomatic management (cognition and beyond)
  - Disease modification – delaying disease progression
  - Disease prevention
Many Ongoing Drug Trials…….
Broad Spectrum of Public Private Partnerships in Dementia R&D

Disease Understanding

Targets

New Medicines

Translational Tools & Clinical Trials

Real World Evidence

Regulators & Payers

Slide concept kindly provided by Luc Truyen, VP Neuroscience External Affairs, Janssen
Declaration of Conflict of Interest

I am a full time employee Eisai Inc.

I own shares in AstraZeneca and Merck Inc.
These young women had a:

- Great-grandmother with Alzheimer’s
- Great-grandmother’s sister with Alzheimer’s
- Paternal grandmother with Alzheimer’s
- Paternal grandmother’s sister with Alzheimer’s

and

- Maternal grandmother has currently MCI
Most Critical Factor for the Alzheimer’s Medicine Efforts

- **Patient & caregiver engagement to participate in trials**
  - Increased interest to enter trials
  - Increased willingness to remain in trials