Animal research for Alzheimer disease: failures of science and ethics

Francesca Pistollato
European Commission, Joint Research Centre, Ispra, Italy
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John J. Pippin: Physicians Committee for Responsible Medicine, Washington, DC, USA
Sarah E. Cavanaugh: Rockville, Maryland, USA
Francesca Pistollato: European Commission, Joint Research Centre, Ispra, Italy
“This is a uniquely human disease, with impairments in abstract reasoning and judgment. We’ve cured mice engineered with this disease over 500 times. The mouse models don’t translate into humans...”

(Howard Fillit, Chief Science Officer, Alzheimer’s Drug Discovery Foundation, in Shakoor et al., 2017)
Alzheimer's disease
Epidemiology and current status

- 50-75% of all dementia cases

- The number of people living with dementia worldwide 47.5 million, projected to increase to 75.6 million by 2030 and more than triple by 2050 (World Health Organization, 2015).

- The estimated global cost of AD in 2015 was US 818 billion (McDade and Bateman, 2017).

- In the last 10 years no new drugs have been developed

- Existing drugs only stabilize symptoms temporarily, do not slow disease
Alzheimer's disease research

Amyloids

- Aβ plaques tend to accumulate in AD brains

- However, studies have shown that 14%–21% of clinically diagnosed patients have zero or minimal brain Aβ plaques on postmortem examination (Beach et al., 2012; Beekly et al., 2007; Serrano-Pozo et al., 2014)

- Real causation or rather correlation and/or adaptation?
We and others have demonstrated that AD pathology is a manifestation of cellular adaptation, specifically as a defense against oxidative injury. As such, AD pathology is therefore a host response rather than a manifestation of cytotoxic protein injury, and is unlikely to be a fruitful target for therapeutic intervention. An “expansionist” view of the disease, we believe, with oxidative stress as a pleiotropic and upstream process, more aptly describes the relationship between various and numerous molecular alterations and clinical disease.
Are the AD animal models reliable?
Gene-disease links have been associated predominantly with autosomal dominant, early-onset familial AD (< 5% of cases)

↓

transgenic animal models have been based on early-onset disease

↓

results have been extrapolated to relate to the much more common, late-onset sporadic AD
Animal Models of Alzheimer Disease: Historical Pitfalls and a Path Forward

Sarah E. Cavanaugh\textsuperscript{1}, John J. Pippin\textsuperscript{1} and Neal D. Barnard\textsuperscript{1,2}

\textsuperscript{1}Physicians Committee for Responsible Medicine, Washington, D.C., USA; \textsuperscript{2}Department of Medicine, George Washington University School of Medicine and Health Sciences, Washington, D.C., USA
### Common mouse models of Alzheimer disease, relevant transgenes and mutations (if applicable), and the promoter under which transgenes are expressed

<table>
<thead>
<tr>
<th>Model</th>
<th>Transgene(s)</th>
<th>Mutation(s)</th>
<th>Promoter</th>
<th>Reference</th>
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<tr>
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<td>PDGF</td>
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<td>Chin et al., 2005</td>
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<td>hAPP</td>
<td>K670N, M671L</td>
<td>Hamster prion protein</td>
<td>Hsiao et al., 1996</td>
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<tr>
<td>APP23</td>
<td>hAPP</td>
<td>K670N, M671L</td>
<td>Thy-1.2</td>
<td>Sturchler-Pierrat et al., 1987</td>
</tr>
</tbody>
</table>

**Familial/genetically driven AD**
- <5%

**Late-onset/sporadic AD**
- >95%

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**European Commission**

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Animal models of AD

- AD research → animal models (Tg & inbred mice) → to recapitulate genetic & pathological traits of human AD

- Tg animals:
  - Aβ formation
  - neuritic plaques
  - NFTs
  - Gliosis
  - Synaptic alterations
  - Some signs of cognitive impairment
Animal models of AD

Tg animals:

- NO clinico-pathological complexity of AD (Dodart et al., 2002; Duyckaerts, Potier and Delatour, 2008).

- Translational research failure

- Generate false negative data → exclusion of potentially effective compounds from clinical studies
Animal models have provided some partial insights into the cellular & molecular mechanisms of brain amyloidosis or tauopathy,

but there are immutable differences in gene function, gene expression, protein production, and phenotypic or physiological results that render translation unpredictable and unreliable...
AD animal models for drug development

- **in AD**: overall failure rate for 244 drugs in 413 trials from 2002-2012 is reported to be **99.6%**! (Alzheimers Res Ther 2014 6, 37)
- Only a single drug was approved from these trials (memantine in 2003)
- An analysis of subsequent AD clinical drug trials reported from Jan 2004, (after memantine approval) through July 2017, reveals 1273 completed or closed trials and no approved drugs

https://www.clinicaltrials.gov/ct2/results?term=alzheimer&recrs=g&recrs=h&recrs=e&recrs=i&age_v=&gndr=&type=&rslt=&Search=Apply
Only 5 drugs have been approved for treating the various stages of AD:

- produce very small changes, of dubious clinical relevance, on cognitive and behavioral measurement scales (Delrieu et al., 2011)
- mild impact on symptoms in only a minority of patients
- no effect on disease progression or mortality
- often lose any effectiveness within several months
- may produce serious adverse effects
An alternative interpretation is that the timing of Aß-targeted therapies may be key—once Aß plaques have formed, it may be too late to reverse the pathological consequences!

Stop Alzheimer’s before it starts

Success in the hunt for drugs to halt Alzheimer’s disease has remained elusive; it’s time to stop the disease before it gets started, urge Eric McDade and Randall J. Bateman.

In 2015, the global cost of Alzheimer’s disease was US$818 billion. That’s similar to the gross domestic product of the world’s 18th-largest economy. By 2030, the number of people with the disease is expected to rise to more than 70 million worldwide (see ‘Staying ahead’).

Unless there is a breakthrough in treatment, nearly one in every 2–3 people over 85 will have Alzheimer’s. Even those who escape the disease will have at least one close friend or relative who can no longer converse with them, has no recollection of what happened minutes before and is reliant on round-the-clock care.

Clinical trials have predominantly focused on therapies aimed at treating people who have developed symptoms (memory loss, confusion and difficulties communicating) and begun to lose independence. In the past five years, investigative drugs targeted at an early or ab-path have been halted trials at an early stage when it became clear that the clinical loss is mild, if any, the hallmark of Alzheimer’s being the presence of amyloid plaques.

How should this be translated to the clinic? Should the treatment be given when the signature pathology appears? The search for an Alzheimer’s ‘primary prevention’ is statins. In the early 1980s, these now-widespread medications were shown to lower blood cholesterol in people with a rare genetic disorder that severely elevates it. People with the condition (around 0.005% of the population) typically develop cardiovascular symptoms as adolescents or young adults. Without treatment, they typically die in their 30s. But when statins are given to such people in childhood, the onset of heart disease and stroke is delayed by decades, and lifespan prolonged by between 15 and 30 years.

“The best way to test the role of amyloid β pathology is to stop it from taking hold in the first place.”
Frustrated Alzheimer’s researchers seek better lab mice

Several projects are trying to develop animal models that more closely mimic how the brain disease affects people.

Sara Reardon

Bart de Strooper (KU Leuven): “The biggest mistake you can make is to think you can ever have a mouse with Alzheimer’s disease.”
Need to reconsider etiopathology of AD

- Advancing age
- Diet
- Low levels of physical activity
- Reduced cognitive stimulation
- Low socioeconomic status
- Low educational attainment
  - Poor sleep quality
  - Air pollution
  - Smoking
- Intake of metals, pesticides & insecticides
  - Metabolic-related dysfunctions
  - Cardiovascular-related dysfunctions

These have strong relevance for late-onset AD (> 95% total AD cases)
reductionist holistic
A new roadmap for AD research?
A Human-based framework covering multiple levels of biological complexity to get a broader overview of AD causation

Towards a 21st-century roadmap for biomedical research and drug discovery: consensus report and recommendations

Gillian R. Langley1, Ian M. Adcock2, François Busquet3, Kevin M. Crofton3, Elena Csernov4, Christoph Giese5, Tuula Heinonen6, Kathrin Herrmann7, Martin Hoffmann-Apitius8, Brigitte Landesmann9,10, Lindsay J. Marshall11, Emily McVor1, Alysson R. Muotri1, Fozia Noor1,11, Katrin Schute12, Troy Seidell13, Anja van de Stolpe14, Hilde Van Esch15,16, Catherine Willett17 and Grzegorz Woszczek18

1Research & Technology Department, Humane Society International, London, UK
2Manchester Institute for Biotechnology, Imperial College, London, UK
3Center for Alternatives to Animal Testing (CART), Brussels, Belgium
4National Center for Research on Computational Toxicology/US Environmental Protection Agency, Research Triangle Park, NC, USA
5Department of Experimental Medicine – Rhenologis, Zentrum für Klinische Forschung GmbH, Schlosspark, Wiesbaden, Germany
6ProteinGum, Berlin, Germany
7Forschungszentrum Jülich, Jülich, Germany
8Université de Lorraine, Nancy, France
9National Institute of Environmental Health Sciences, NC, USA
10Center for Toxicogenomics, University of North Carolina Chapel Hill, USA
11National Institute of Child Health and Human Development, NIH, USA
12Research & Technology Department, Humane Society International, Washington, DC, USA
13Department of Pediatrics, College of Medicine, University of Illinois at Chicago, Chicago, USA
14Department of Biomedical Engineering, University of Pennsylvania, Philadelphia, PA, USA
15Department of Chemical Engineering, University of California, San Diego, CA, USA
16Department of Chemistry, University of British Columbia, Vancouver, BC, Canada
17Department of Pediatrics, University of Oxford, Oxford, UK
18Department of Chemistry, King’s College London, London, UK

Introduction

Despite the investment of billions of dollars, development of new drugs and other potential disease interventions remain elusive and immensely expensive. The average preapproval cost of research and development for a new drug is estimated to be US$2.6 billion (1) and the number of drugs that have been approved per billion US dollars spent has remained approximately constant each year since 1950 (2). More than 90% of drug candidates entering clinical trials fail to gain regulatory approval, usually as a result of insufficient efficacy and/or unacceptable toxicity, based on limited predictive value of preclinical studies (3). One analysis of attrition between 1991 and 2000, using data from ten big pharma companies in the EU and US, found Phase 2 and 3 trials of 62% and 44%, respectively (4). Although there is widespread acknowledgment that the likelihood of success varies with therapeutic area (oncology has particularly low success rates (5)), it is clear that drug candidates are failing between Phase 2 and submission.

References

Advantages of a human AOP-based approach

- A systems-based understanding of human diseases
- Cost-effective and predictive data
- Discovery of novel and multiple drug targets
- Human-relevant information earlier in drug development
- Possible reduction of late-stage drug attrition
Need to reconsider AD research priorities

Alzheimer disease research in the 21st century: past and current failures, new perspectives and funding priorities

Francesca Pistollato¹, Elan L. Ohayon², Ann Lam¹,², Gillian R. Langley³, Thomas J. Novalk⁴, David Pamies⁵, George Perry⁶, Eugenia Trushina⁷, Robin S.B. Williams⁸, Alex E. Roher⁹,¹⁰, Thomas Hartung⁵, Stevan Harnad¹¹, Neal Barnard¹, Martha Clare Morris¹², Mei-Chun Lai¹, Ryan Merkley¹ and P. Charukhesi Chandrasekera¹

Some possible recommendations

✓ Implement funding for the production and centralized distribution of patient-derived cells (e.g. iPSCs)
✓ Allocate funding on centres conducting omics research in human-based settings
✓ Foster the design of preventive strategies (e.g., definition of early biomarkers of human diseases for early diagnosis)
✓ Encourage the creation of ‘pathways to disease’ framework(s), following the AOP approach
✓ Allocate funding on projects focused on integrated multi-disciplinary approaches, covering multiple levels of biological complexity

PRIORITIZE HUMAN RELEVANT RESEARCH AND EXPLORE ALTERNATIVE RESEARCH AVENUES
The need to address human relevance and measure return on investment in biomedical research

Pirotta Francesca, Ivana Campi, Camille Bernasconi, Clements Wittwer and Maurice Wheeler
European Commission, Joint Research Centre, Ispra, Italy

Abstract
Animal models have been traditionally used in biomedical research to recapitulate human disease features and develop new drugs, as they are generally purported to resemble some of the major hallmarks of human diseases. However, these animals do not develop the disease as it occurs in humans, and their use has not paved the way to the development of drugs effective in human patients. Indeed, despite enormous research and economical endeavours, the clinical failure rate in drug development still remains very high, with an overall likelihood of approval from Phase I of about 9.4%. On the other hand, the expanding toolbox of non-animal methods, accounting for e.g., induced pluripotent stem cells derived from patients, next-generation sequencing, omics and integrated computer modelling can be used to study human diseases in human-based settings, identify new potential drugable targets, and evaluate treatment effects. Research proposals based on the use of both animal and/or non-animal approaches have been extensively funded at European level. Notwithstanding, defining indicators to measure return on investment of research funding strategies is necessary to retrospectively assess public health trends, and readiness funding strategies when needed. Here we discuss these aspects, presenting a list of indicators that could be suitable to measure return on investment in biomedical research.

Why
- Prevalence of chronic degenerative diseases is increasing in European countries
- Traditional research has focused on the creation of animal models of human diseases for basic research and drug development
- About 10% of drugs tested in animals fail in human trials
- Need to retrospectively assess "return on investment" of EU-funded projects

What
Move beyond 3Rs and consider the role of "human-relevant" approaches to reply to real societal needs and:

How

Ultimate goals
- Monitor over-time success rate of research funding strategies (i.e., are they contributing to improving public health?)
- Assess whether and at what extent human-relevant approaches are applied in biomedical research
- Define new strategies and drive public health policy changes (if needed)
Thanks for your attention!

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francesca.pistollato@ec.europa.eu