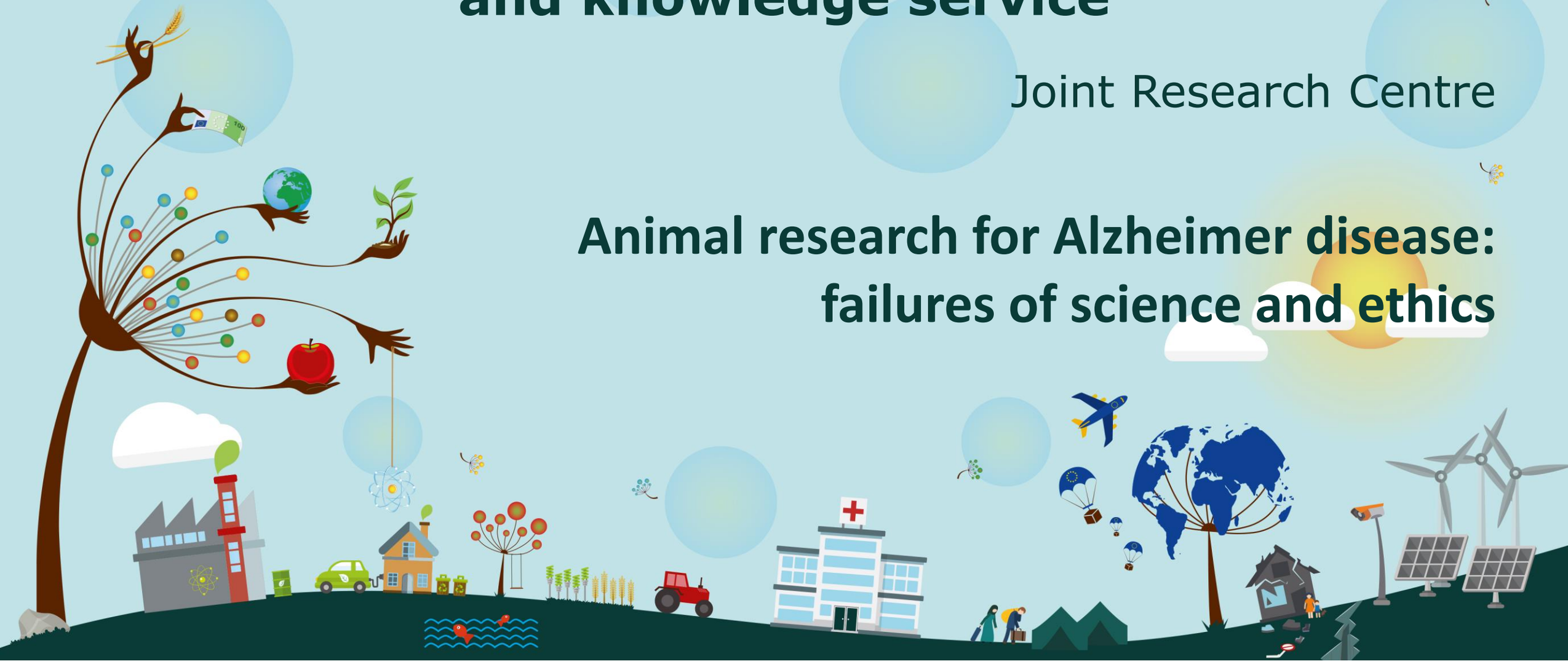
The European Commission's science and knowledge service

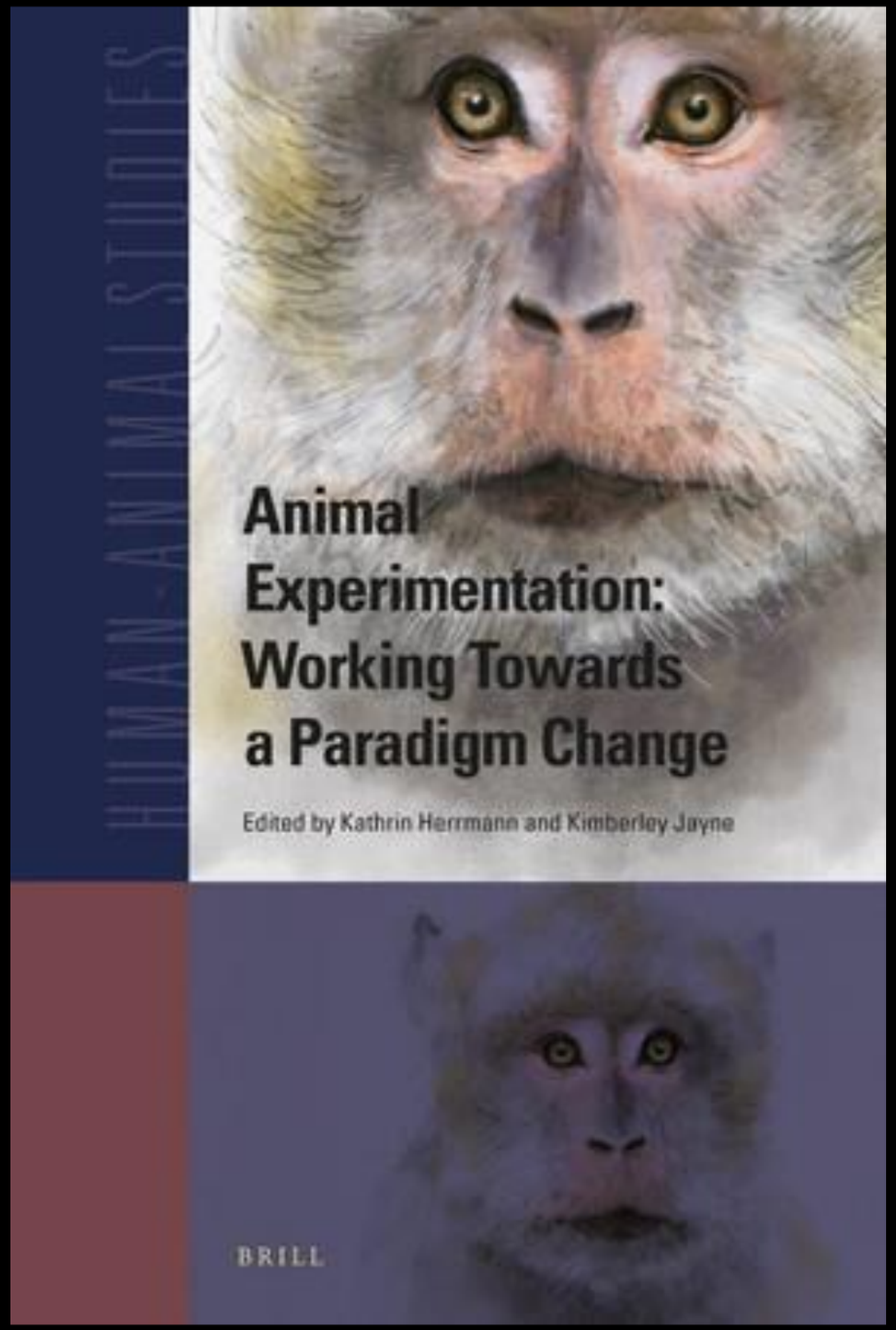
Joint Research Centre



Animal research for Alzheimer disease: failures of science and ethics

Francesca Pistollato
European Commission, Joint Research Centre, Ispra, Italy

European Commission



https://brill.com/view/title/35072

Animal research for Alzheimer disease: failures of science and ethics

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

PCRM Physicians Committee for Responsible Medicine

European Commission

“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

- Aß plaques tend to accumulate in AD brains

- However, studies have shown that 14%–21% of clinically diagnosed patients have zero or minimal brain Aß 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?

Int. J. Mol. Sci. **2009**, *10*, 1386-1406; doi:10.3390/ijms10031386

OPEN ACCESS

International Journal of
Molecular Sciences
ISSN 1422-0067
www.mdpi.com/journal/ijms

Review

Molecular Pathogenesis of Alzheimer's Disease: Reductionist *versus* Expansionist Approaches

Rudy J. Castellani [1,*], Xiongwei Zhu [2], Hyoung-Gon Lee [2], Mark A. Smith [2] and George Perry [2,3]

[1] Division of Neuropathology, University of Maryland, Baltimore, Maryland, USA
[2] Department of Pathology,
[3] College of Sciences, Unive

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?

Mellor B. Nature 2008

European Commission

Animal models of AD

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

European Commission

Animal models of AD

(ALTEX. 2014;31(3):279-302.)

Animal Models of Alzheimer Disease: Historical Pitfalls and a Path Forward

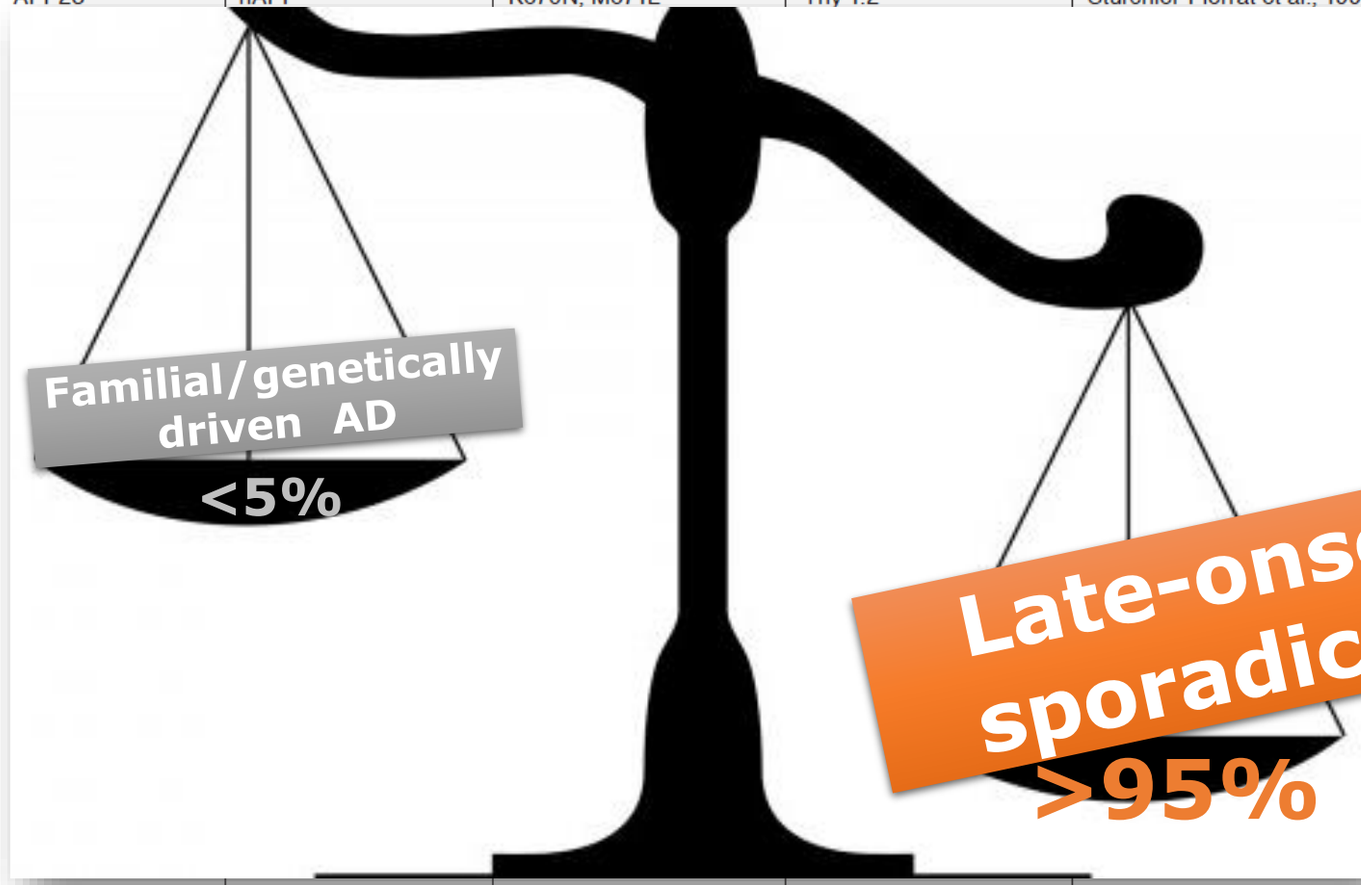
Sarah E. Cavanaugh[1], *John J. Pippin*[1] *and Neal D. Barnard*[1,2]

[1]Physicians Committee for Responsible Medicine, Washington, D.C., USA; [2]Department of Medicine, George Washington University School of Medicine and Health Sciences, Washington, D.C., USA

European Commission

Tab. 1: Common mouse models of Alzheimer disease, relevant transgenes and mutations (if applicable), and the promoter under which transgenes are expressed

Model	Transgene(s)	Mutation(s)	Promoter	Reference
PDAPP	hAPP	V717F	PDGF	Games et al., 1995
H6	hAPP	N/A	PDGF	Wyss-Coray et al., 1997
J9	hAPP	N/A	PDGF	Chin et al., 2005
J20	hAPP	N/A	PDGF	Chin et al., 2005
Tg2576	hAPP	K670N, M671L	Hamster prion protein	Hsiao et al., 1996
APP23	hAPP	K670N, M671L	Thy-1.2	Sturchler-Pierrat et al., 1997
Tau P301S	hTau	P301S	Thy1.2	Allen et al., 2002
Tau G272V, P301S	hTau	G272V, P301S	Thy1.2	Schindowski et al., 2006
3xTg-AD	hAPP, hPSEN1, hTau	APP K670N, M671L; PSEN1 M146V; tau P301L	Thy1.2 (APP, Tau)	Oddo et al., 2003



European Commission

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

European Commission

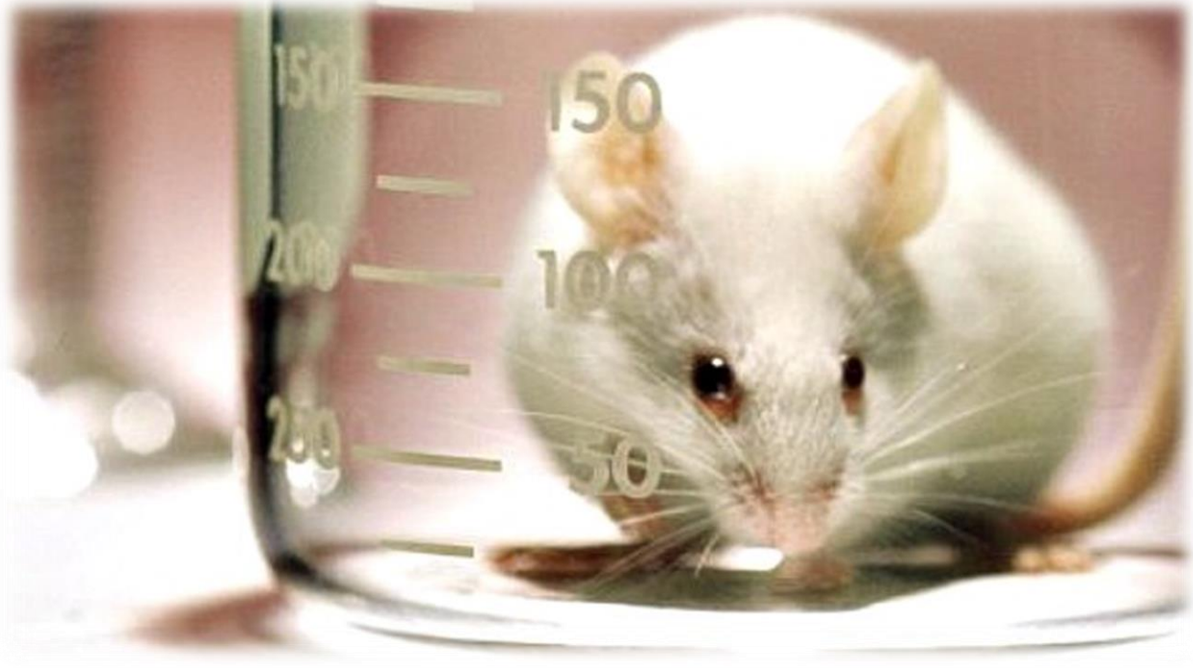
Animal models of AD

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 <u>immutable differences</u> 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

AD animal models for drug development

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

European Commission

AD animal models for drug development

An alternative interpretation is that **<u>the timing of Aß-targeted therapies may be key</u>**

→ 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, investigators have started trials at an ea… y loss is mild or ab… the hallmark path… in plaques. How… k should be turne… when the sig- natu… t appeared. An… t for such '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[1]. 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 search for an Alzheimer's 'statin' is ▶

"The best way to test the role of amyloid-ß pathology is to stop it from taking hold in the first place."

meanwhile…

NEWS · 21 NOVEMBER 2018

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."

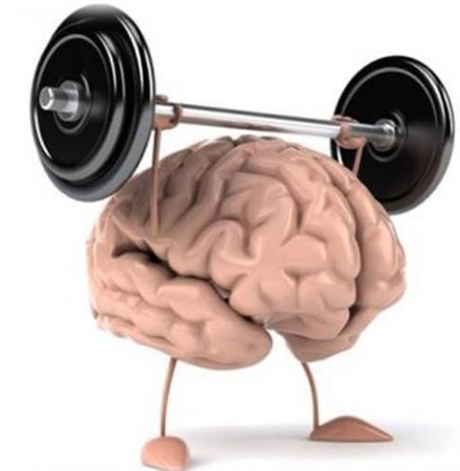
https://www.nature.com/articles/d41586-018-07484-w

European Commission

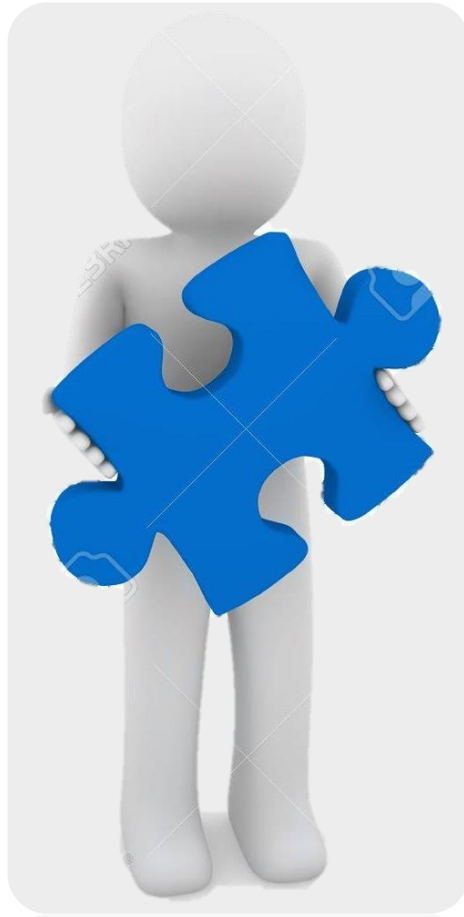
Need to reconsider etiopathology of AD

- ✓ 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

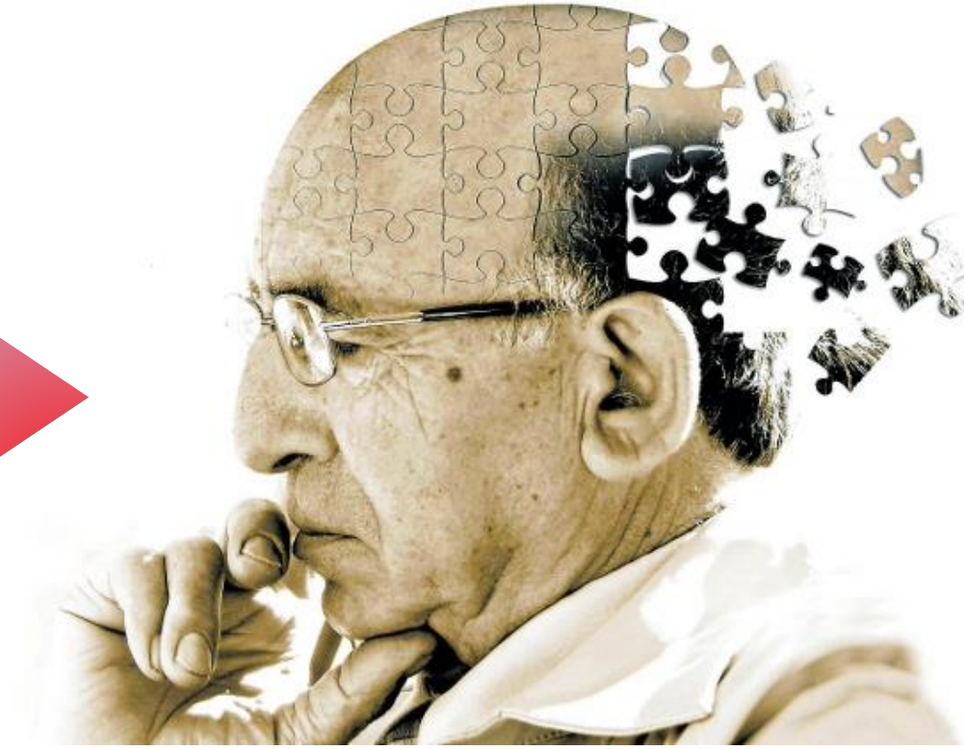
These have strong relevance for late-onset AD (> 95% total AD cases)



reductionist



holistic

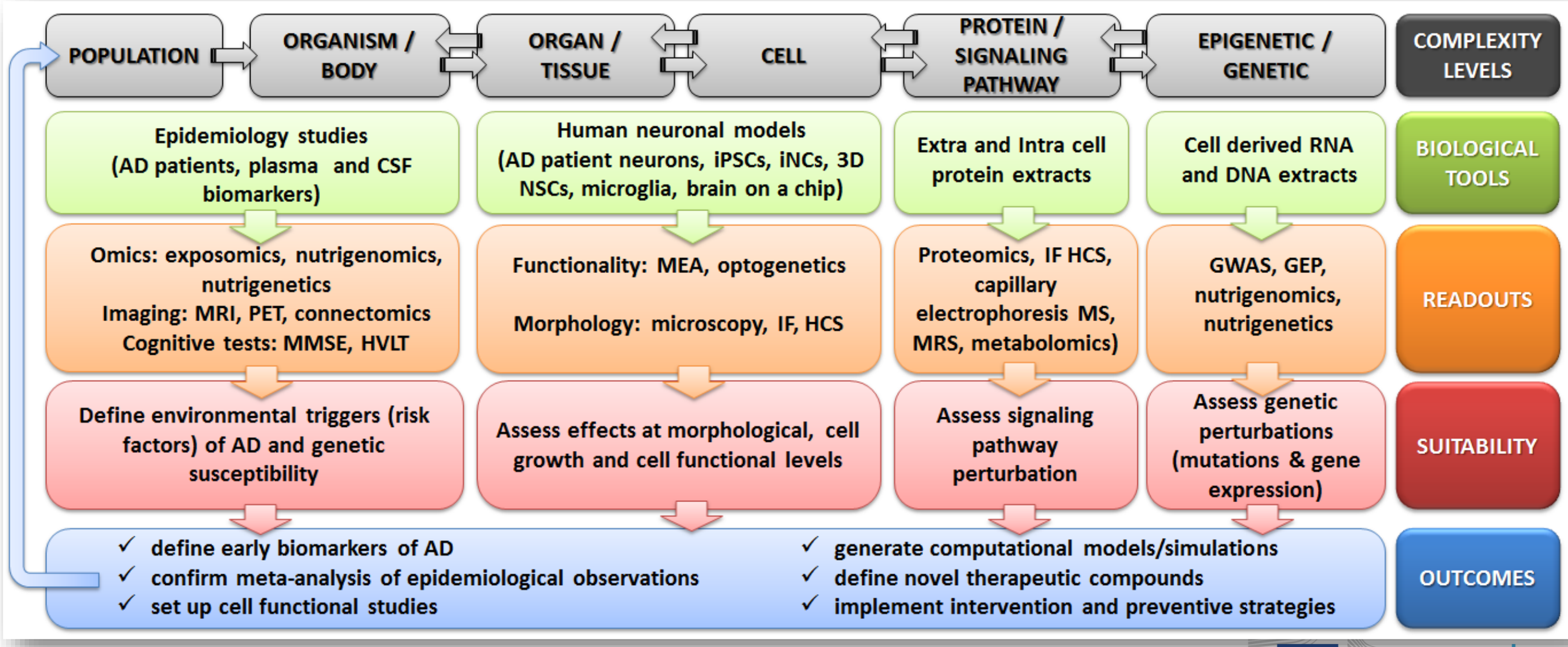


European Commission

A new roadmap for AD research ?

New priorities

A Human-based framework covering multiple levels of biological complexity to get a broader overview of AD causation



(Pistollato F. et al. JAD, vol. 47, no. 4, pp. 857-868, 2015)

Teaser To discover and develop new therapies, we need 21st-century roadmaps for biomedical research based on multiscale human disease pathways, and supported by policy and funding strategies that prioritise human relevance.

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

Gillian R. Langley[1], Ian M. Adcock[2], François Busquet[3], Kevin M. Crofton[4], Elena Csernok[5], Christoph Giese[6], Tuula Heinonen[7], Kathrin Herrmann[8], Martin Hofmann-Apitius[9], Brigitte Landesmann[10], Lindsay J. Marshall[11], Emily McIvor[12], Alysson R. Muotri[13], Fozia Noor[14], Katrin Schutte[15], Troy Seidle[16], Anja van de Stolpe[17], Hilde Van Esch[18], Catherine Willett[19] and Grzegorz Woszczek[20]

[1] Research & Toxicology Department, Humane Society International, London, UK
[2] Respiratory Cell & Molecular Biology, National Heart & Lung Institute, Imperial College, London, UK
[3] Center for Alternatives to Animal Testing (CAAT) Europe, Brussels, Belgium
[4] National Center for Computational Toxicology, US Environmental Protection Agency, Research Triangle Park, NC, USA
[5] Department of Internal Medicine – Rheumatology, Esslingen District Clinics GmbH, Kirchheim Clinic, Academic Teaching Hospital, University of Tübingen, Kirchheim unter Teck, Germany
[6] ProBioGen AG, Berlin, Germany
[7] Finnish Centre for Alternative Methods, School of Medicine, University of Tampere, Tampere, Finland
[8] Dahlem Research School, Free University Berlin, Berlin, Germany
[9] Department of Bioinformatics, Fraunhofer Institute for Algorithms and Scientific Computing (SCAI), Institutszentrum Birlinghoven, Sankt Augustin, Germany
[10] European Commission, DG Joint Research Centre, Directorate F – Health, Consumers and Reference Materials, F3 Chemical Safety and Alternative Methods Unit, Ispra (VA), Italy
[11] School of Life and Health Sciences, Aston University, Aston Triangle, Birmingham, UK
[12] Humane Society International, London, UK
[13] Department of Pediatrics & Cellular & Molecular Medicine, UCSD School of Medicine, Rady Children's Hospital, Sanford Consortium, La Jolla, CA, USA
[14] Biochemical Engineering Institute, Saarland University, Saarbrücken, Germany
[15] European Commission, DG ENVIRONMENT, Directorate A – Green Economy, Unit A.3 – Chemicals, Brussels, Belgium
[16] Research & Toxicology Department, Humane Society International, Toronto, Canada
[17] Philips Research (Philips Group Innovation), Eindhoven, The Netherlands
[18] Center for Human Genetics, University Hospitals Leuven, Leuven, Belgium
[19] Animal Research Issues, The Humane Society of the United States, Boston, MA, USA
[20] MRC/Asthma UK Centre in Allergic Mechanisms of Asthma, Division of Asthma, Allergy & Lung Biology, King's College London, Guy's Hospital, London, UK

Corresponding author: Langley, G.R. (sciencesources@btinternet.com)

Gillian Langley is currently a scientific consultant to Humane Society International. Her academic career focussed on neurochemistry at Cambridge University, while at Nottingham University, she specialised in studying signalling pathways in human neural cells *in vitro*. Subsequently, she led science programmes at the Dr Hadwen Trust for Humane Research, a medical charity developing human-specific disease models and research techniques. Gill has been a member of the British Government's advisory committee on animal experiments, and was an adviser on non-animal safety tests during the development of the European chemicals legislation (REACH) and a member of European Commission expert subgroups on non-animal testing.

Alysson Muotri is a professor at the University of California San Diego and director of the UCSD Stem Cell Program. His research focuses on human brain development and evolution, and utilises a range of advanced models and molecular tools to study neurological diseases, such as autism spectrum disorders. Using human induced pluripotent stem cells, Alysson's team has developed several techniques to culture human neurons and glia for basic research and drug screening. He is a recipient of numerous awards, including the NIH Director's New Innovator Award.

Martin Hofmann-Apitius is head of Department of Bioinformatics at the Fraunhofer Institute for Algorithms and Scientific Computing, and professor of Applied Life Science Informatics at Bonn-Aachen International Center for Information Technology. Martin's current research focuses on automated methods for extracting relevant information from unstructured information sources, such as journal publications, patents, and web-based sources, as well as knowledge-based, mechanistic modelling of neurodegenerative diseases (including the first comprehensive, computable model of Alzheimer's disease), and mining in real-world data (social networks, patient fora, and electronic patient records). He is the initiator and academic co-ordinator of the Innovative Medicines Initiative project 'AETIONOMY'.

Teaser Improved translation of research is needed to inform safe and effective drug development. This will require a broad collaborative effort, open data sharing, and prioritized funding for human-relevant research.

Recommendations toward a human pathway-based approach to disease research

Lindsay J. Marshall[1], Christopher P. Austin[2], Warren Casey[3,4], Suzanne C. Fitzpatrick[5] and Catherine Willett[1]

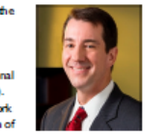
[1] Humane Society International, The Humane Society of the United States, 700 Professional Drive, Gaithersburg, MD 20879, USA
[2] Office of the Director, National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, MD 20817, USA
[3] National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods, USA
[4] National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709, USA
[5] Center for Food Safety and Applied Nutrition, FDA, Harvey W. Wiley Building, 5100 Paint Branch Parkway, College Park, MD 20740, USA

Failures in the current paradigm for drug development have resulted in soaring research and development costs and reduced numbers of new drug approvals. Over 90% of new drug programs fail, the majority terminated at the level of Phase 2/3 clinical trials, largely because of efficacy failures or unexplained toxicity. A recent workshop brought together members from research institutions, regulatory agencies, industry, academia, and nongovernmental organizations to discuss how existing programs could be better applied to understanding human biology and improving drug discovery. Recommendations include increased emphasis on human relevance, better access and curation of data, and improved interdisciplinary and international collaboration.

Introduction

Despite the investment of billions of dollars, development of new drugs and other potential disease interventions remain elusive and immensely expensive. The average pre-approval cost of research and development for a successful drug is estimated to be US$2.6 billion [1] and the number of new drugs approved per billion US dollars spent has halved approximately every 9 years since 1950 [2]. More than 90% of drug candidates entering clinical trials fail to gain regulatory approval, mainly as a result of insufficient efficacy and/or unacceptable toxicity, because of the limited predictive value of preclinical studies [3]. One analysis of attrition rates between 1991 and 2000, using data from ten big pharma companies in the EU and USA, found Phase 2 and 3 failures of 62% and 45%, respectively [4]. Although there is widespread acknowledgement 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,

Corresponding author: Marshall, L.J. (lmarshall@hsi.org)



Christopher Austin is the director of the National Center for Advancing Translational Sciences (NCATS) at the US National Institutes of Health (NIH). He leads the Center's work to improve the translation of observations in the laboratory, clinic, and community into interventions that reach and benefit patients, from diagnostics and therapeutics to medical procedures and behavioral changes. Under his direction, NCATS researchers and collaborators are developing new technologies, resources, and collaborative research models; demonstrating their usefulness; and disseminating the data, analysis, and methodologies for use by the worldwide research community.

Warren Casey is the director of National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and Executive Director of the US Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). These groups work together to facilitate the development, validation, regulatory acceptance, and industry adoption of non-animal test methods. He has been a diplomate of the American Board of Toxicology (DABT) since 2007, received the 2016 Society of Toxicology Animal Welfare Award, currently serves as the vice president of the SOT *In vitro* and Alternative Methods Specialty Section, and co-chairs the OECD Validation Management Group – Non Animal.

Catherine Willett is the director of Regulatory Toxicology, Risk Assessment and Alternatives at Humane Society International and the Humane Society of the United States. She coordinates the Human Toxicology Project Consortium, a multistakeholder group focusing on pathway-based toxicology. She is an active member of the OECD Adverse Outcome Pathway (AOP) training group as well as the Society for the Advancement of AOPs. Dr Willett is a member of SOT, serves on the US National Toxicology Program Scientific Advisory Committee on Alternative Toxicological Methods, and is on the Scientific Advisory Board of the Institute of *In vitro* Sciences and Shell's Animal Testing Review Panel.

https://doi.org/10.1016/j.drudis.2018.05.038

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

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 26

Research Paper: Gerotarget (Focus on Aging)

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

Francesca Pistollato[1], Elan L. Ohayon[2], Ann Lam[1,2], Gillian R. Langley[3], Thomas J. Novak[4], David Pamies[5], George Perry[6], Eugenia Trushina[7], Robin S.B. Williams[8], Alex E. Roher[9,10], Thomas Hartung[5], Stevan Harnad[11], Neal Barnard[1], Martha Clare Morris[12], Mei-Chun Lai[1], Ryan Merkley[1] and P. Charukeshi Chandrasekera[1]

(Pistollato F et al. Oncotarget. 2016 Jun 28;7(26):38999-39016.)

PCRM Physicians Committee for Responsible Medicine

European Commission

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

Poster # 33

The need to address human relevance and measure return on investment in biomedical research

Pistollato Francesca, Ivana Campia, Camilla Bernasconi, Clemens Wittwehr and Maurice Whelan

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 conspicuous 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 9.6%. 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 druggable 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 readdress 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.

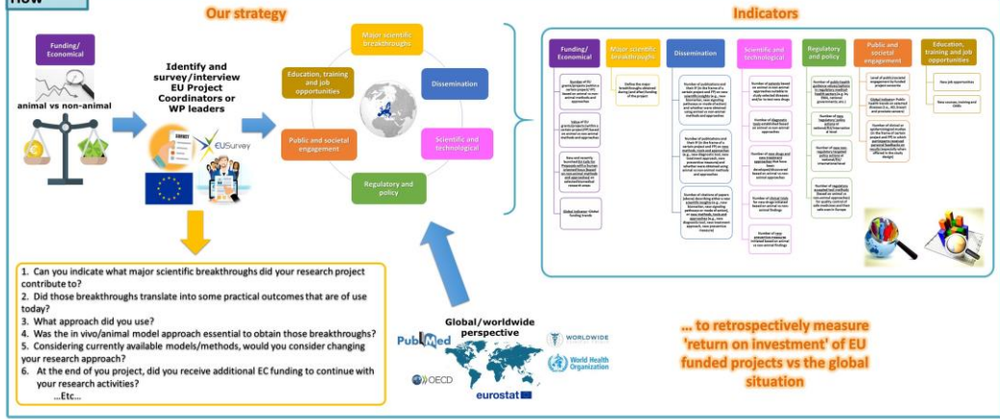
Why

- 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 90% of drugs tested in animals fail in human trials
- Need to retrospectively assess 'return on investment' of EU funded projects

What

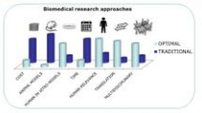
Move beyond 3Rs and consider the role of 'human-relevant' approaches to reply to real societal needs and:

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)



Contact information:

Francesca Pistollato, PhD francesca.pistollato@ec.europa.eu

Joint Research Centre

European Commission

Thanks for your attention!

ec.europa.eu/jrc

@EU_ScienceHub

EU Science Hub - Joint Research Centre

Joint Research Centre

EU Science Hub

francesca.pistollato@ec.europa.eu

European Commission