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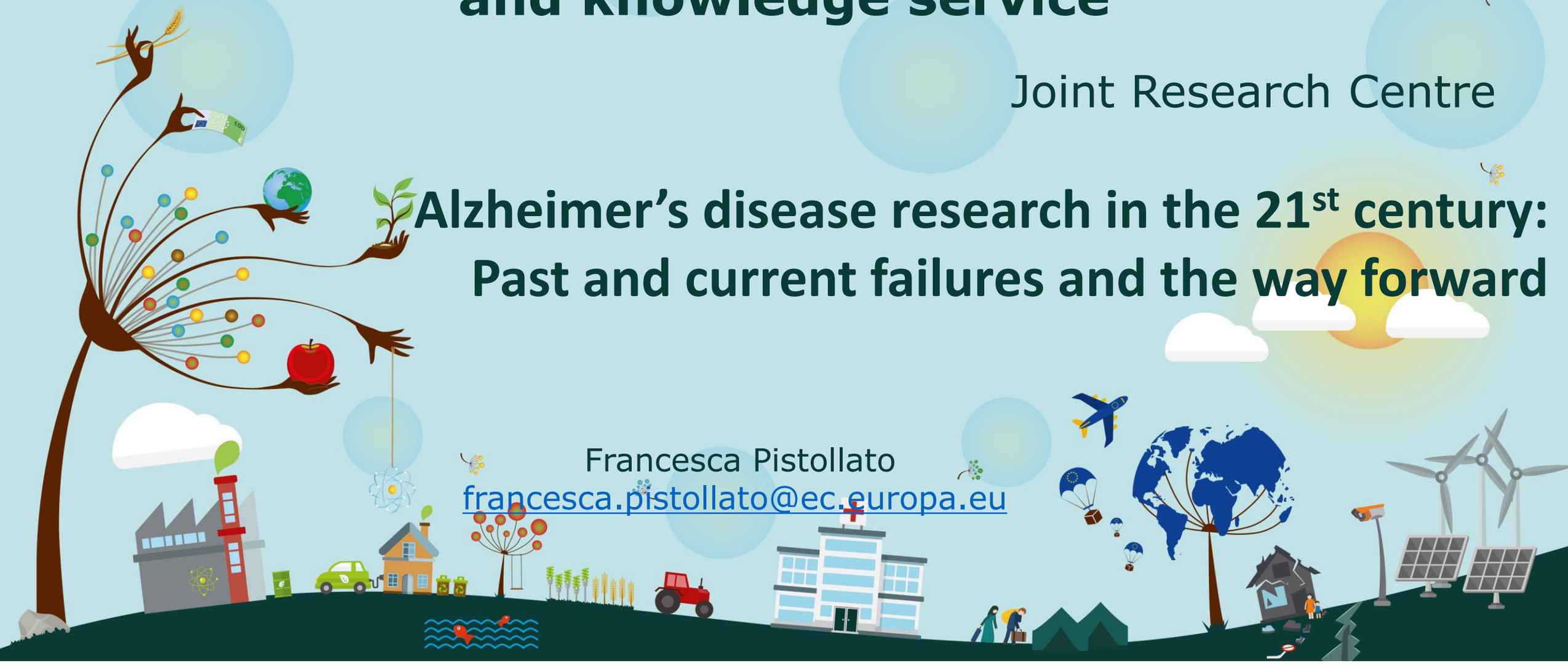


Alzheimer's disease research in the 21st century: Past and current failures and the way forward

Francesca Pistollato
francesca.pistollato@ec.europa.eu

European Commission

The Joint Research Centre (JRC)

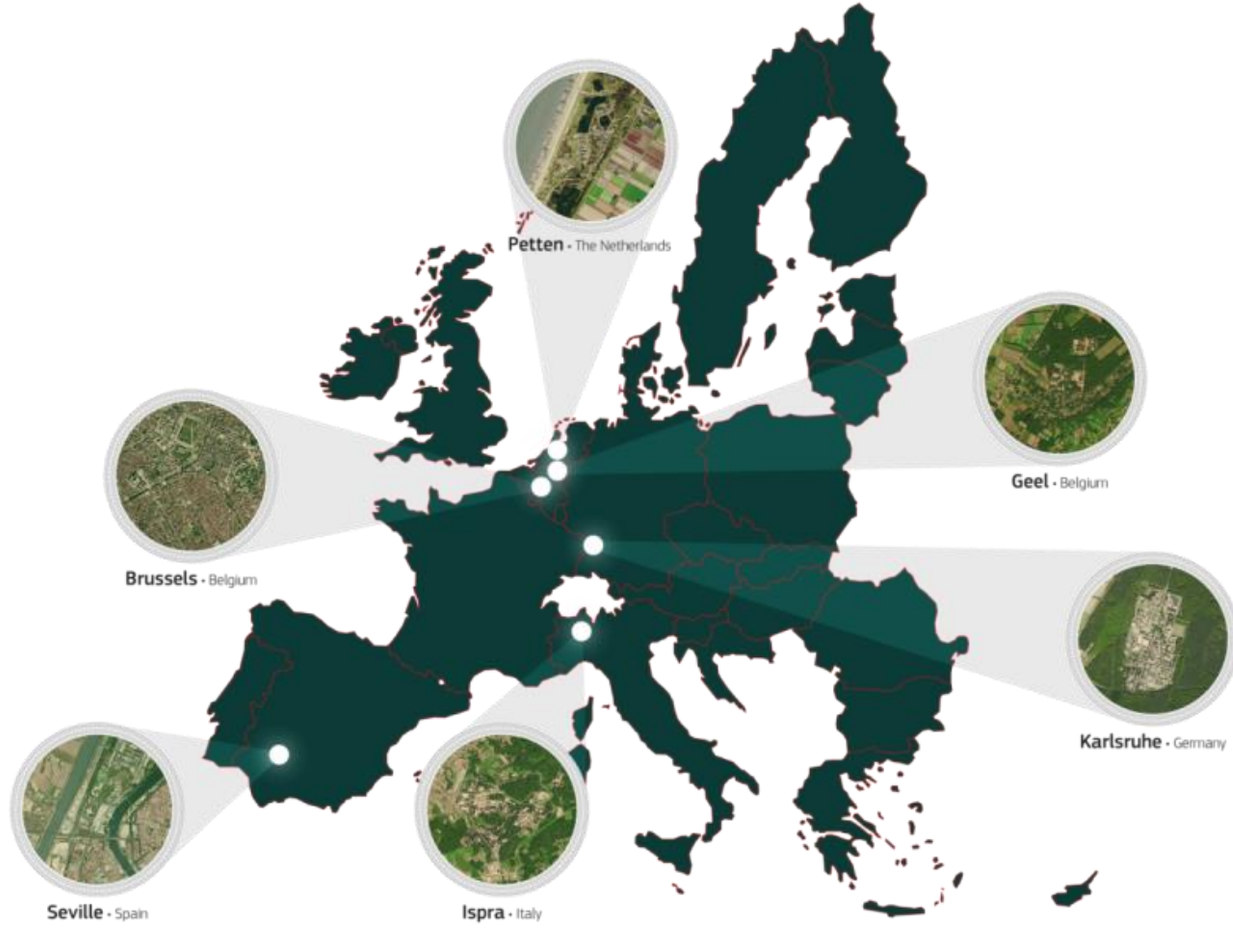
As the science and knowledge service of the Commission **our mission** is to support EU policies with independent evidence throughout the whole policy cycle.

~ 3000 staff

Almost 75% are scientists.

Headquarters in Brussels.

Research facilities located in 5 Member States.



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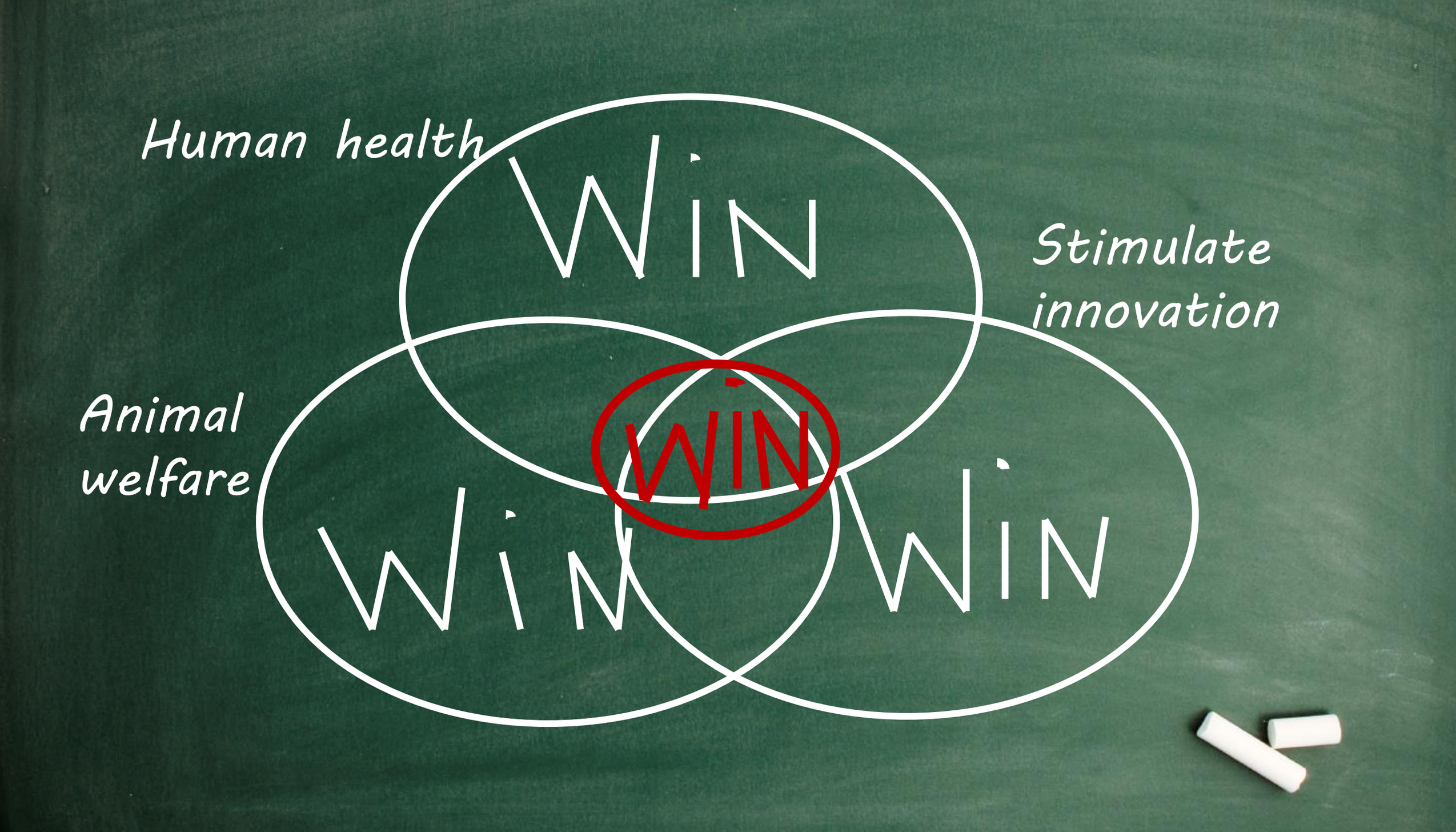
Directive 2010/63/EU on the protection of animals used for scientific purposes

- **Stimulate development**
- **Coordinate validation**
- **Provide information**
- **Promote dialogue**

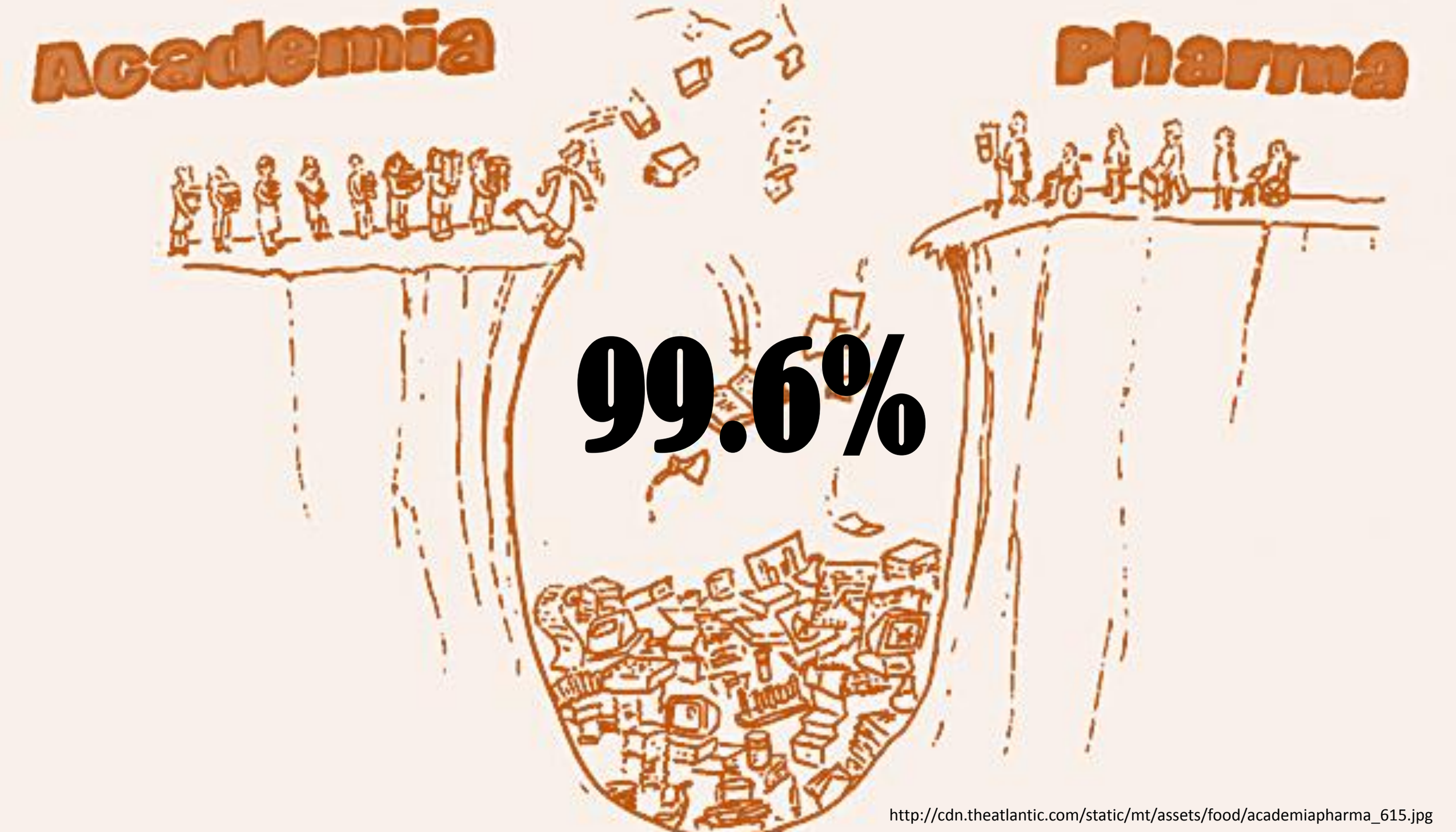
EURL ECVAM

European Commission


Human health
WIN
Stimulate innovation
Animal welfare
WIN
WIN
WIN

Alzheimer's disease research
Some facts:

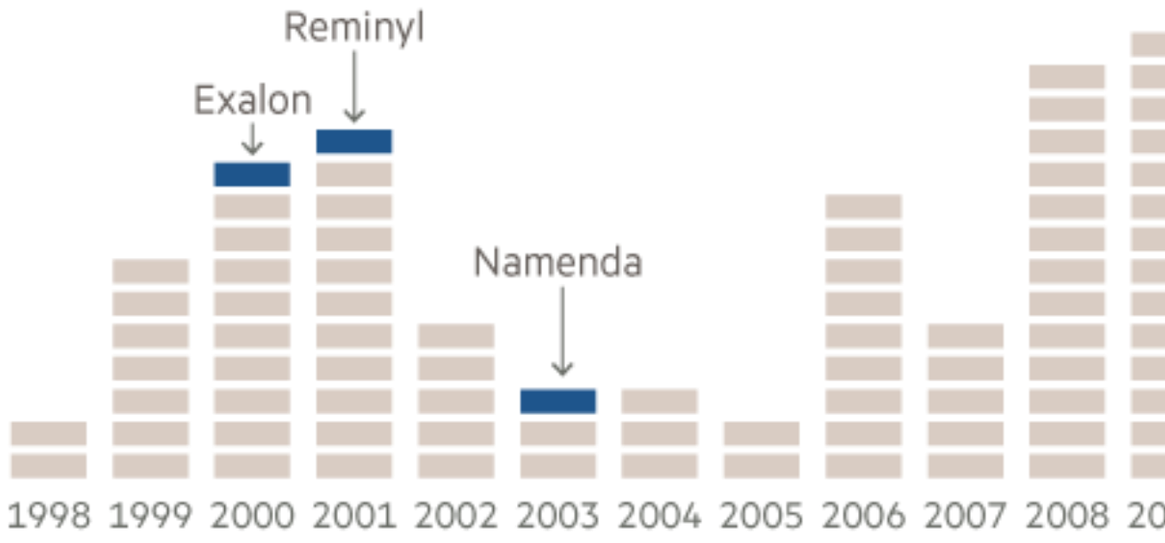
- AD: 50-75% of all dementia cases
- affects 10.5 million people, 177 billion euros/year (World Alzheimer's report 2016)
- In the last 10 years → no new drugs
- Existing drugs only stabilize symptoms temporarily, do not slow disease
- 244 drugs in 413 trials (2002-2012) → failure rate 99.6%!
  (Alzheimers Res Ther 2014 6, 37)



http://cdn.theatlantic.com/static/mt/assets/food/academiapharma_615.jpg

There is a 30-to-1 failure-to-approval ratio for new Alzheimer's medicines

None of the approved drugs cure, prevent or slow the progression of the disease



Graphic: Alan Smith Source: PhRMA analysis of Adis R&D Insight Database, 17 June 20

https://www.ft.com/content/c4e1241e-f731-11e7-88f7-5465a6ce1a00

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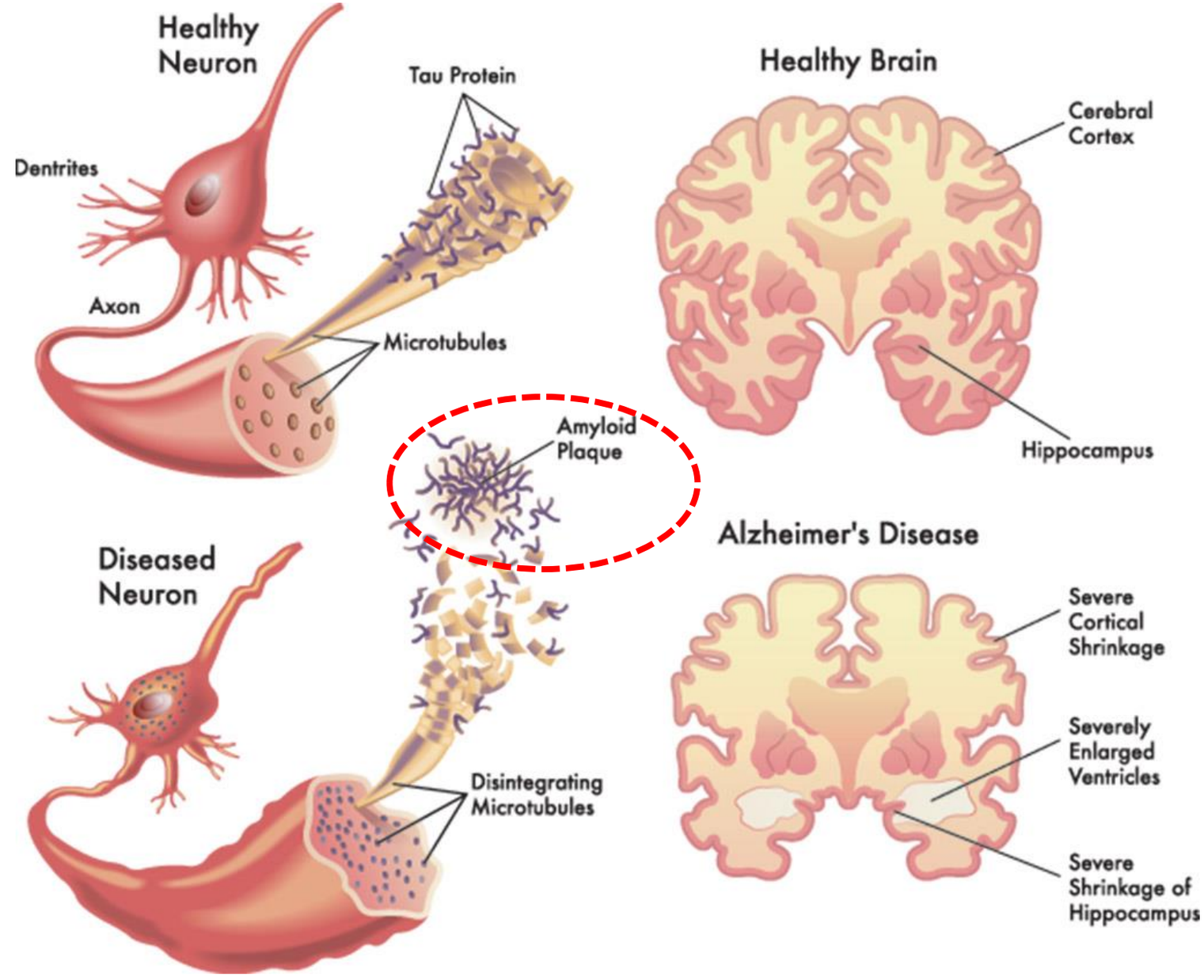
Time to question some hypotheses:

correlation vs adaptation vs causation?



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

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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.

A: estimated relative amounts of *unsuccessful investment* based on 37 of the 59 drugs that *have been discontinued…*

BIOBUSINESS BRIEFS

TRIAL WATCH

Tracing investment in drug development for Alzheimer disease

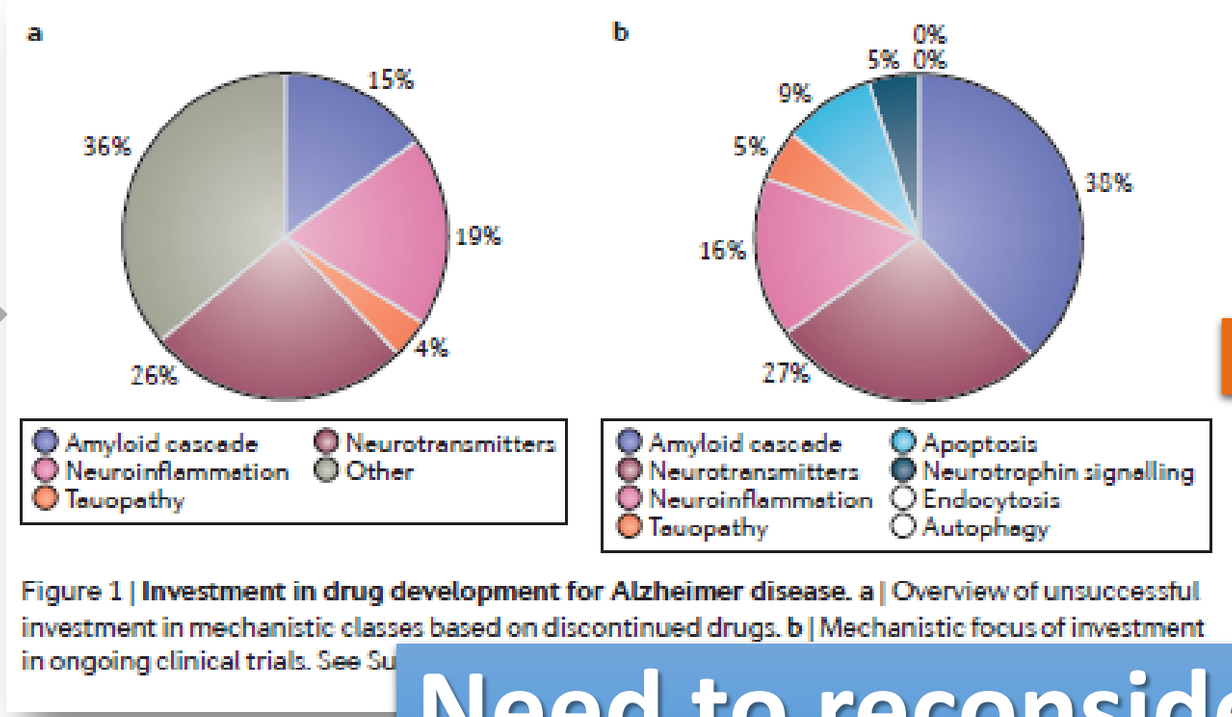

Figure 1 | **Investment in drug development for Alzheimer disease. a** | Overview of unsuccessful investment in mechanistic classes based on discontinued drugs. **b** | Mechanistic focus of investment in ongoing clinical trials. See Su

B: current investment in different mechanisms based on 61 of the 88 drugs in ongoing clinical trials

→ *little or no investment in some promising novel mechanisms* (e.g. targeting endocytosis or autophagy)

Need to reconsider strategies in drug development…

Nat Rev Drug Discov. 2017 Dec;16(12):819.

Business and Society Review

Journal of the Center for Business Ethics
Bentley University

Business and Society Review **123:1** 3–58

Human Stakeholders and the Use of Animals in Drug Development

LISA A. KRAMER AND RAY GREEK

We contend that by using animal models to predict human outcomes, the drug development industry is behaving like the proverbial drunk looking for his lost keys under a streetlamp rather than where he dropped them, in the dark. This is especially tragic given more promising methods are readily available. Personalized medicine is a more modern approach to delivering healthcare that is customized to an individual patient, taking account of her unique biological makeup.[12] To this end, instead of seeking druggable targets from animal tissues, scientists are using human tissue. Scientists are also

Volume123, Issue1 Spring 2018 Pages 3-58

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."

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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**.

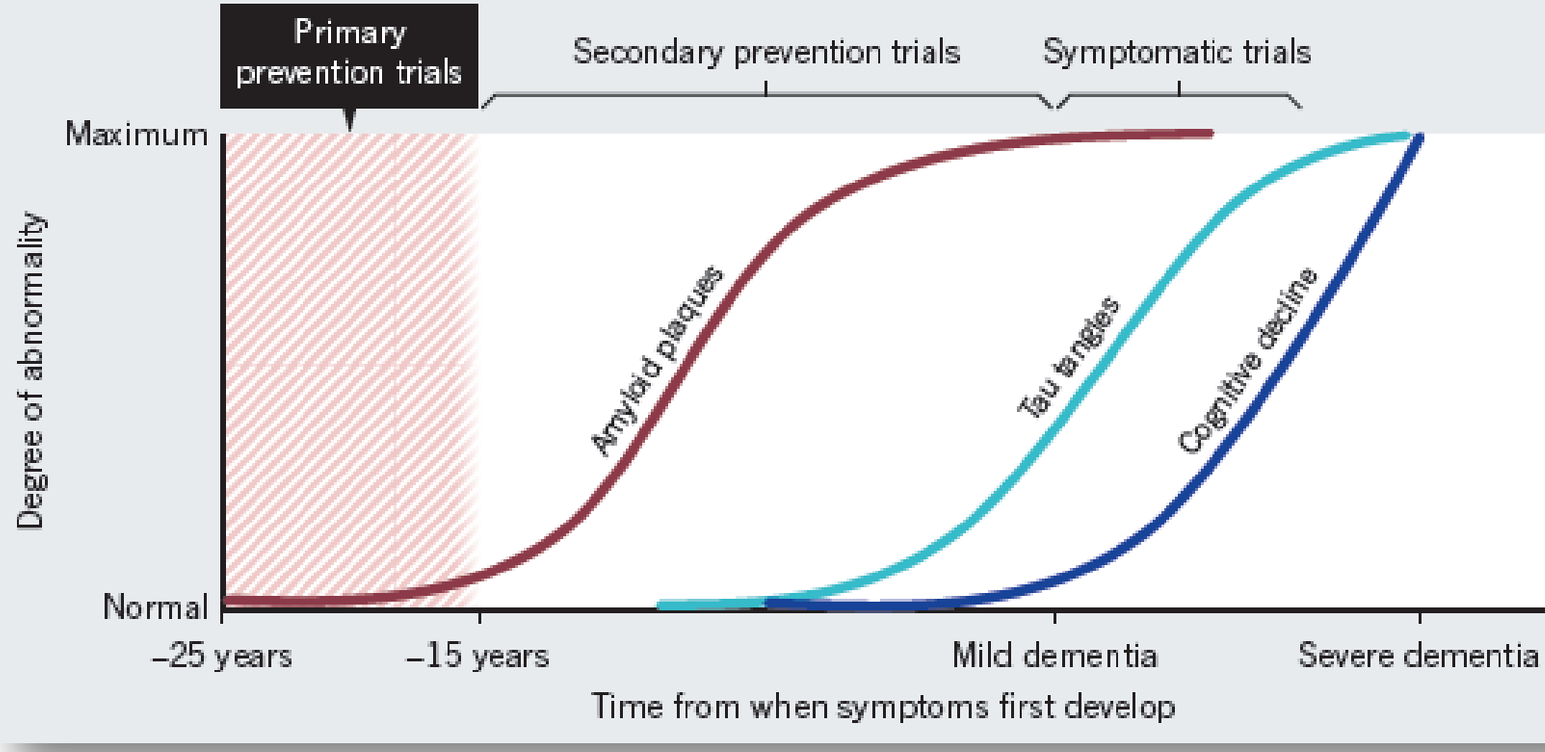
In 2015, the global cost of Alzheimer's disease was US$818 billion. That's similar to the gross domestic product of the world's 18th-largest economy. By 2030, the number of people with the disease is expected to rise to more than 70 million worldwide (see 'Staying ahead').

Unless there is a breakthrough in treatment, nearly one in every 2–3 people over 85 will have Alz… escape the dise… close friend or r… converse with t… of what happen…

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

STAYING AHEAD

Primary prevention trials would investigate drugs designed to treat Alzheimer's disease before brain pathology, such as amyloid-β plaques and tau tangles, or cognitive symptoms develop.



Nature. 2017 Jul 12;54

Are we looking at the right models?

Mellor B. Nature 2008

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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

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Animal models of AD

Tg animals:

- ✘ **NO clinico-pathological complexity of AD**
- ✘ **Translational research failure**
- ✘ **Generate false negative data → exclusion of potentially effective compounds from clinical studies**

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

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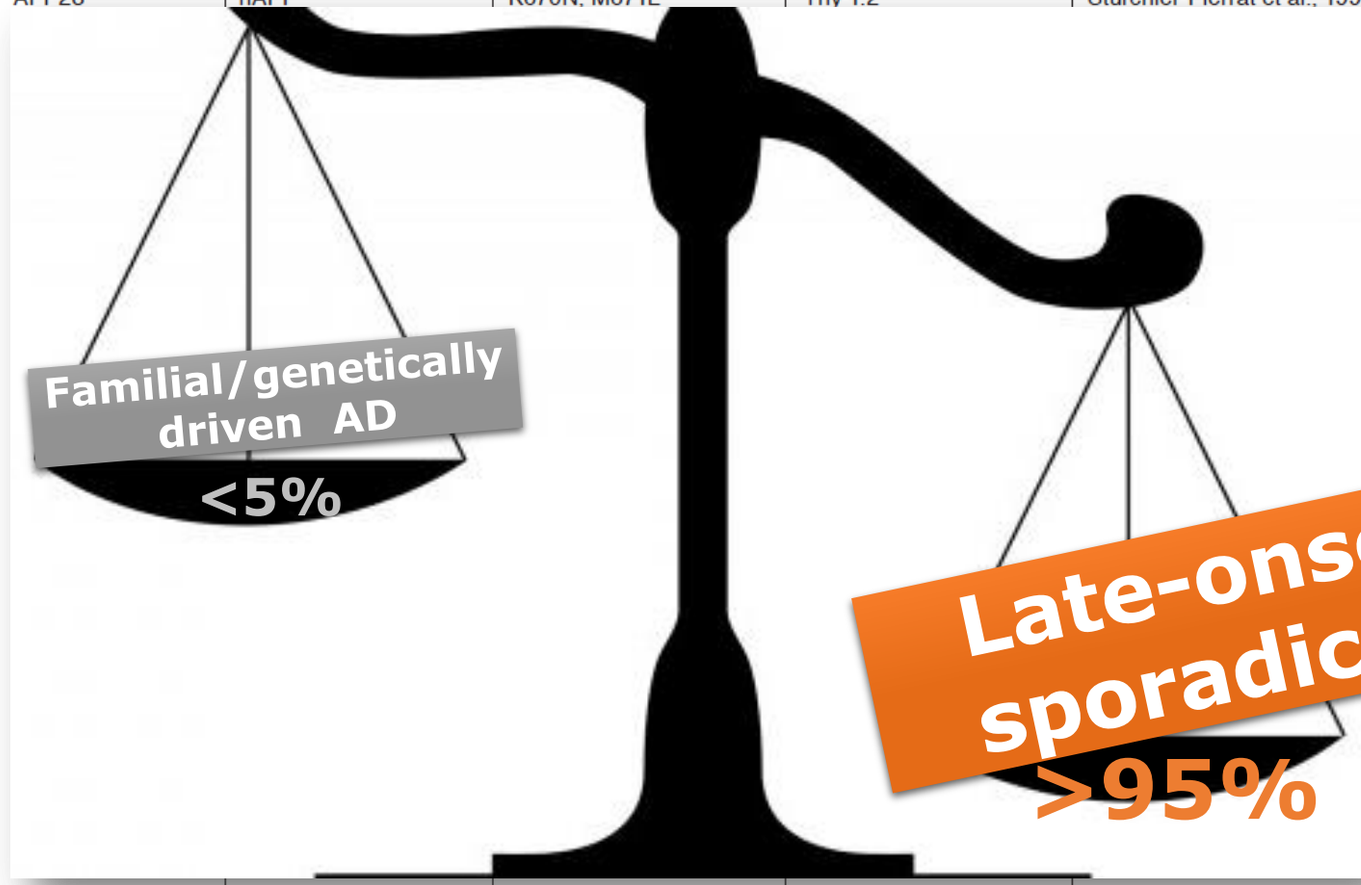
Tab. 1: Common mouse models of Alzheimer disease, relevant transgenes and mutations (if applicable), and the promoter under which transgenes are expressed

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



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Animal models of AD

SAMP8 & SAMP8-APP/PS1 models (senescence-accelerated)
→ to investigate late-onset AD

<u>However:</u>

- **genes responsible for senescence and observed pathologic traits are largely unknown**

  (http://www.alzforum.org/research-models/senescence-accelerated-mouse-samp8)

- **no studies have reported on the efficacy of current available AD drugs in SAMP8 mice**

  (Ageing Res Rev, 2014. 13: p. 13-37)

- **pathological granules found in the hippocampus do not seem to contain either Aβ peptides or tau, but rather <u>a glycosidic neo-epitope (IgM)</u>**

(Age (Dordr), 2014. 36(1): p. 151-65.)

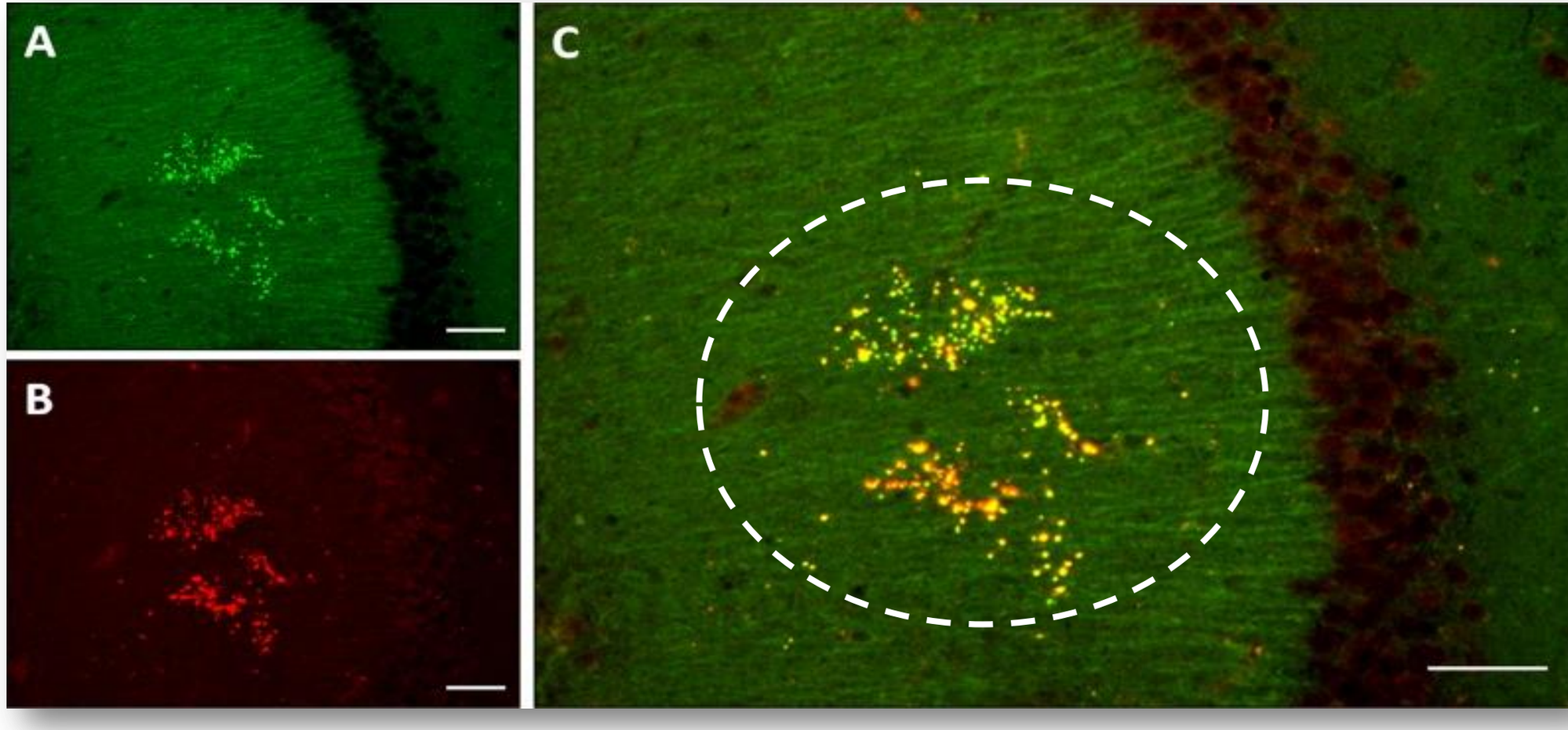

Fig. 4: Immunohistochemical staining of the brain sections from SAMP8 mice with Tau5A antibody. a Secondary antibody against IgG. b Secondary antibody against IgM. c Merging of a and b. *Yellow* corresponds to colocalisation of both stainings. *Scale bar* 100 µm

(Age (Dordr), 2014. 36(1): p. 151-65.)

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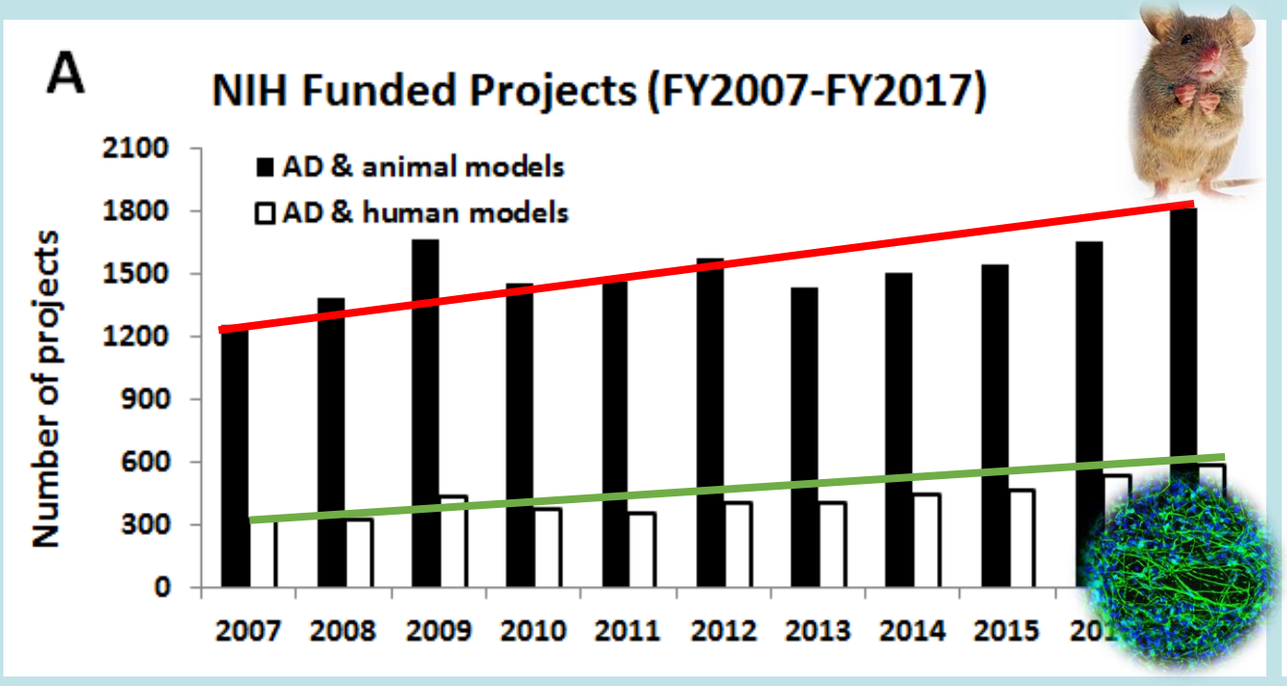
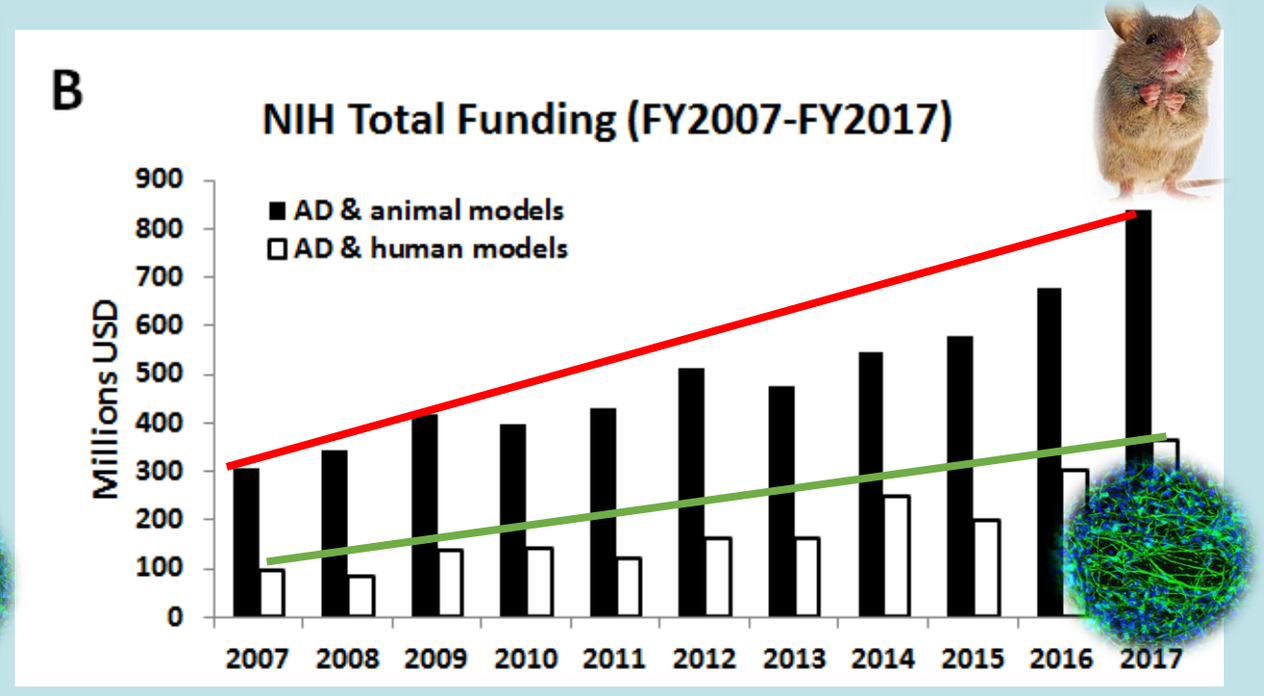
Funding for AD research

→ bias in the peer-review process ?





http://projectreporter.nih.gov/reporter.cfm

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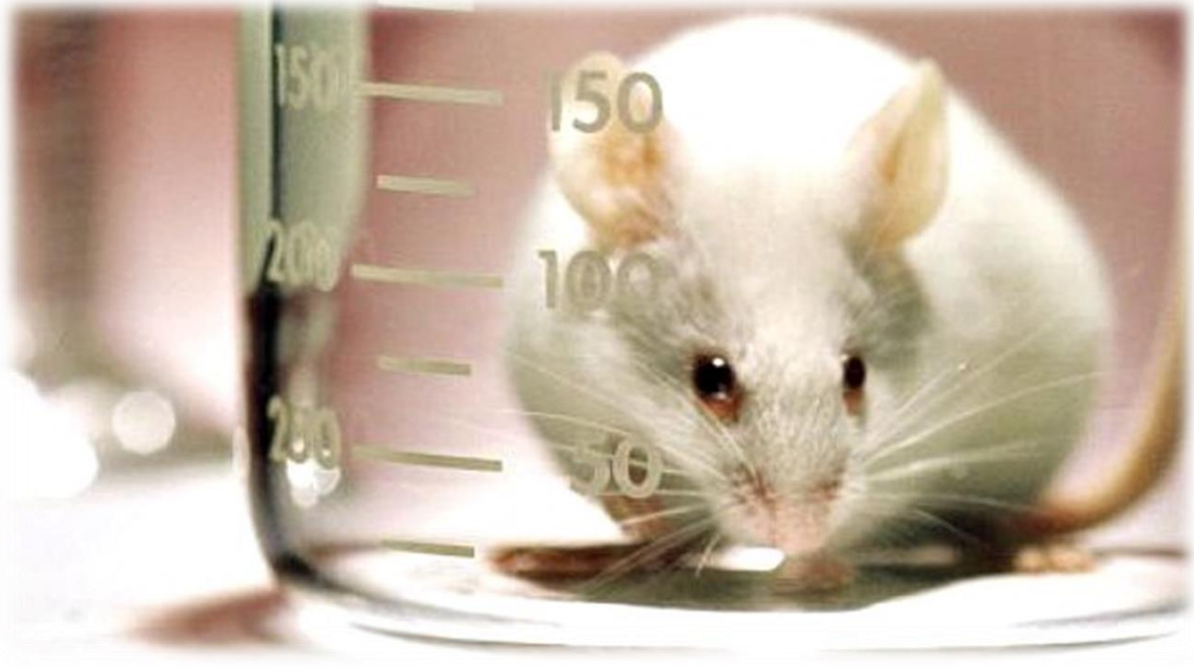
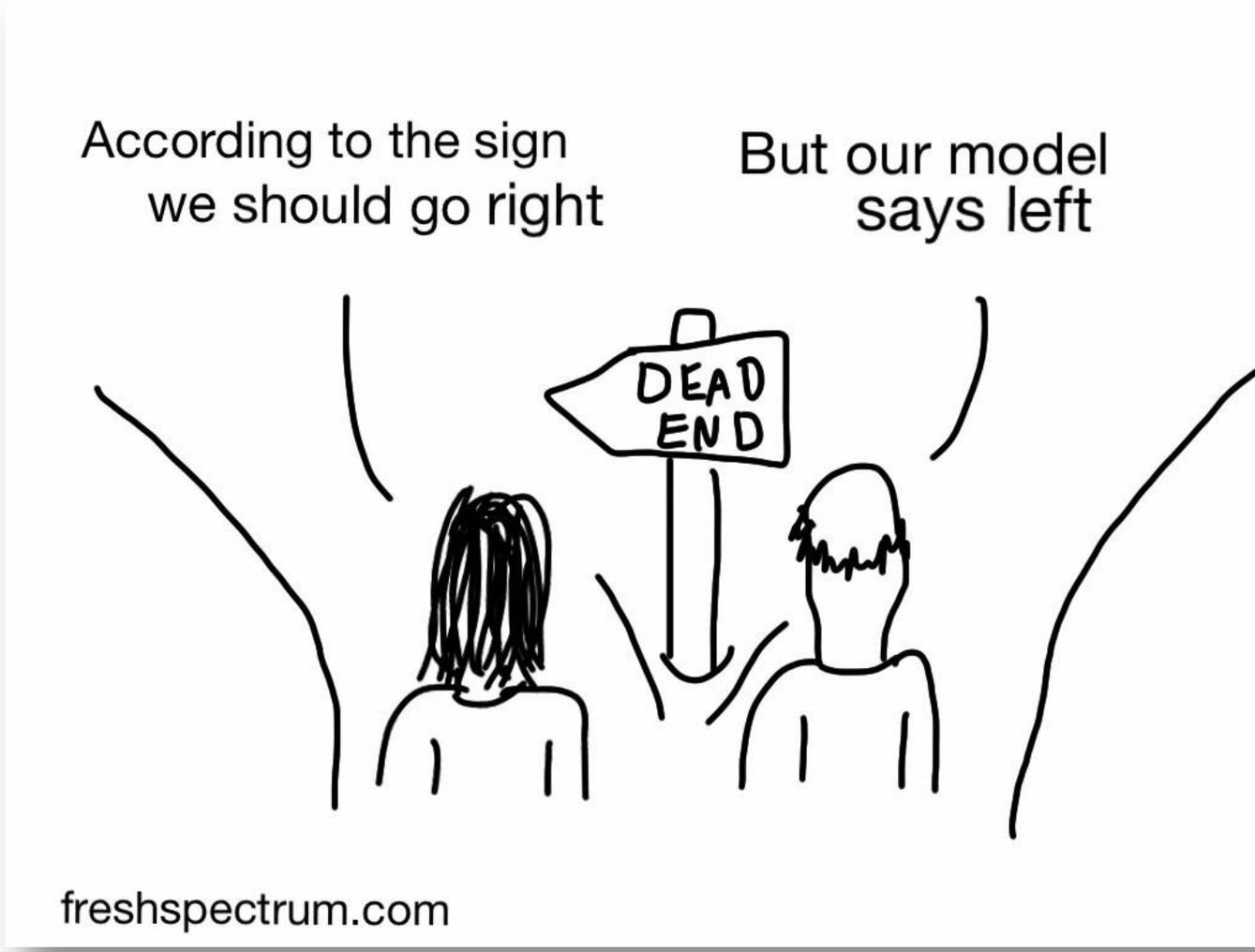
Animal models have provided some partial insights into the cellular & molecular mechanisms of brain amyloidosis or tauopathy,

but they are <u>not</u> suitable to develop drugs and predict their effects in AD patients…



A new roadmap for AD research ?



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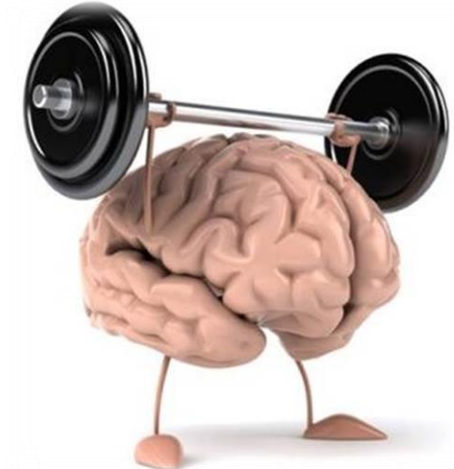
Need to reconsider etiopathology of AD

- ✓ 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)



Dementia in western Europe: epidemiological evidence and implications for policy making

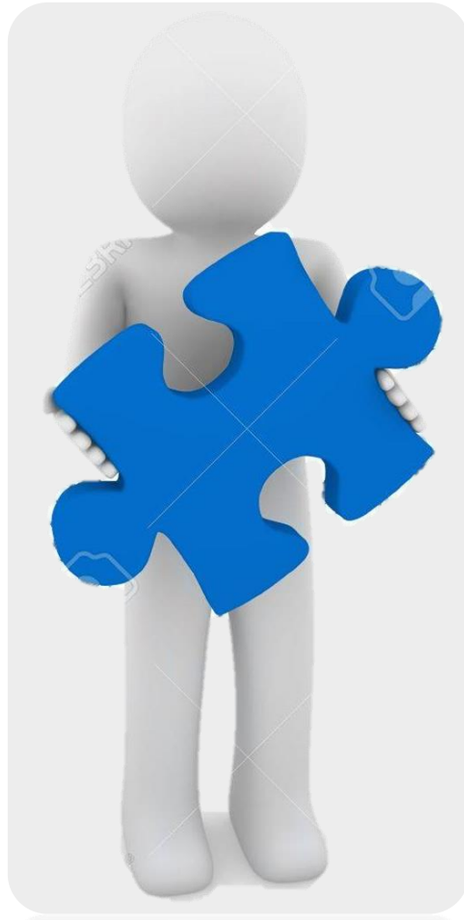
(Lancet Neurol. 2015 Aug 20. pii: S1474-4422(15)00092-7.)

Yu-Tzu Wu, Laura Fratiglioni, Fiona E Matthews, Antonio Lobo, Monique M B Breteler, Ingmar Skoog, Carol Brayne

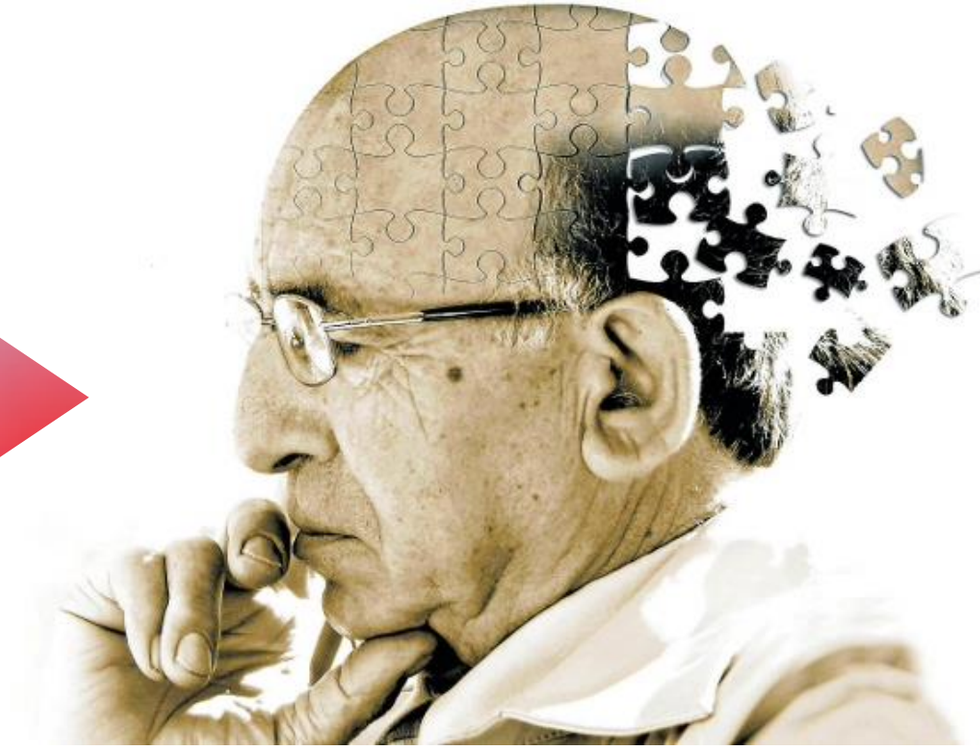
Dementia is receiving increasing attention from governments and politicians. Epidemiological research based on western European populations done 20 years ago provided key initial evidence for dementia policy making, but these estimates are now out of date because of changes in life expectancy, living conditions, and health profiles. To assess whether dementia occurrence has changed during the past 20–30 years, investigators of five different studies done in western Europe (Sweden [Stockholm and Gothenburg], the Netherlands [Rotterdam], the UK [England], and Spain [Zaragoza]) have compared dementia occurrence using consistent research methods between two timepoints in well-defined geographical areas. Findings from four of the five studies showed non-significant changes in overall dementia occurrence. The only significant reduction in overall prevalence was found in the study done in the UK, powered and designed explicitly from its outset to detect change across generations (decrease in prevalence of 22%; p=0·003). Findings from the study done in Zaragoza (Spain) showed a significant reduction in dementia prevalence in men (43%; p=0·0002). The studies estimating incidence done in Stockholm and Rotterdam reported non-significant reductions. Such reductions could be the outcomes from earlier population-level investments such as improved education and living conditions, and better prevention and treatment of vascular and chronic conditions. This evidence suggests that attention to optimum health early in life might benefit cognitive health late in life. Policy planning and future research should be balanced across primary (policies reducing risk and increasing cognitive reserve), secondary (early detection and screening), and tertiary (once dementia is present) prevention. Each has their place, but upstream primary prevention has the largest effect on reduction of later dementia occurrence and disability.

Reduction of cardiovascular risk factors → reduced risk of AD

reductionist



holistic



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Neurosci Bull April 1, 2014, 30(2): 253–270. http://www.neurosci.cn
DOI: 10.1007/s12264-013-1425-9

Environmental factors in the develc late-onset Alzheimer's disease

Moses N. Wainaina[1,3], Zhichun Chen[1], Chunjiu Zhong[1,2]

[1]*Department of Neurology, Zhongshan Hospital; State Key Laboratory 200032, China*

[2]*Institutes of Brain Science; Fudan University, Shanghai 200032, Chin*

[3]*Pwani University, Kilifi, Kenya*

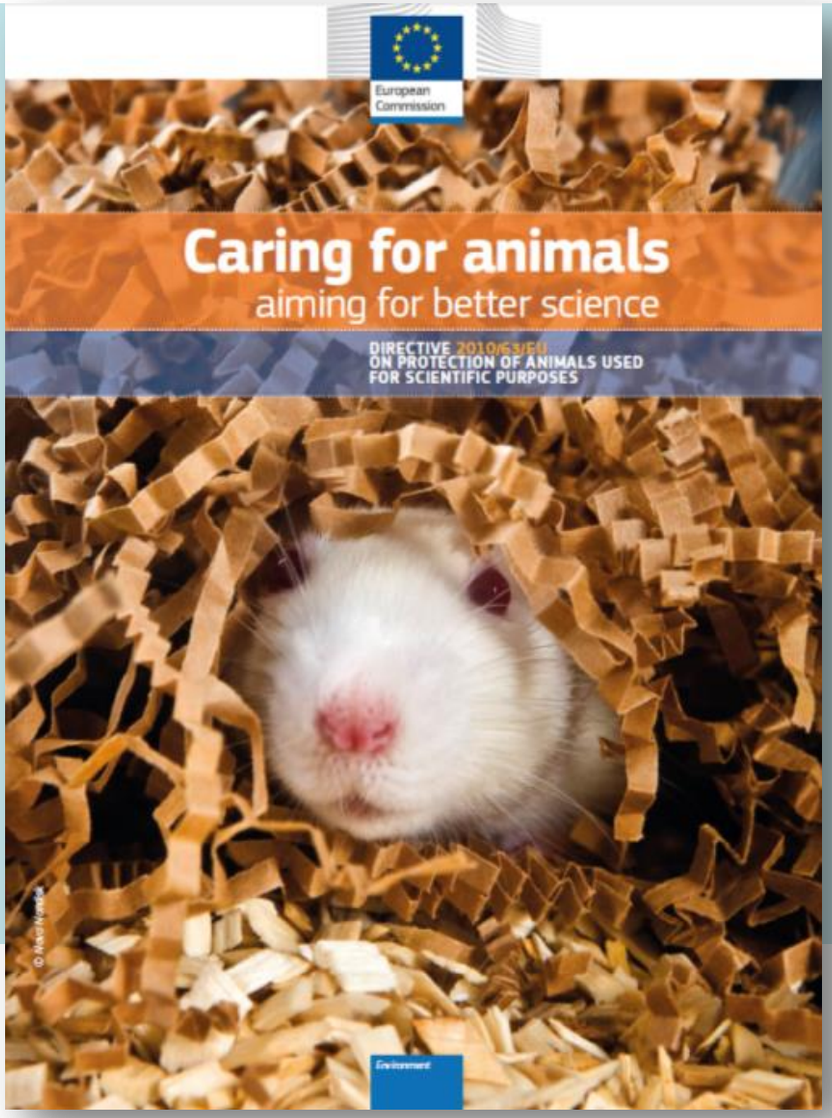
Corresponding author: Chunjiu Zhong. E-mail: Zhongcj@163.com

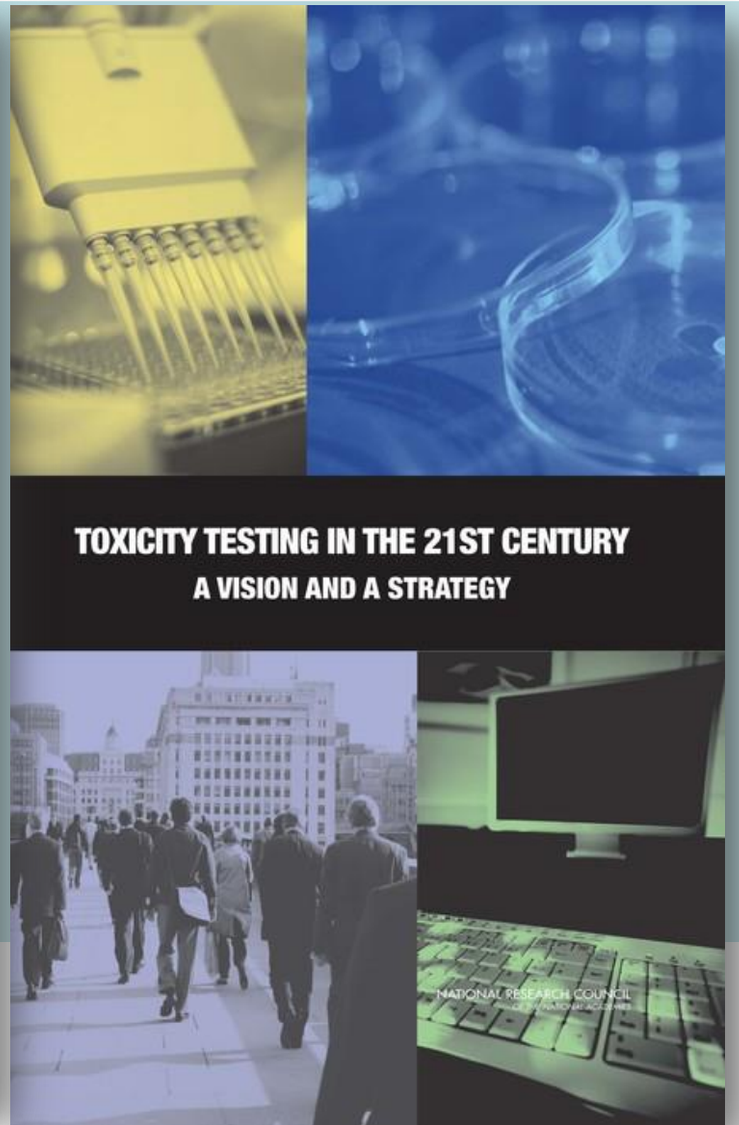
As described in our review of glucose metabolism in LOAD[58], previous studies seem to have led to a frustrating impasse in LOAD research. Considering that most studies have long been focused on the two pathological hallmarks, their related mechanisms and consequences, we argue that it is time to understand the disease from an ecological perspective, using the concept of environmental stress. In this review, we admit that the typical pathological changes play a significant role in understanding LOAD; however, we tend to focus on the precedents of the pathology, and emphasize environmental risk factors and their pathological pathways in LOAD. This new orientation changes the concepts underlying LOAD management, such that early prevention of environmental risk factors and blocking the intermediate pathological pathways induced by environmental stress are the most attractive treatment. Based on this concept, we argue that avoidance or reduction of exposure to environmental factors is the first step in LOAD prevention and treatment. Metals, nutrients, air pollution, pesticides, and chronic psychological stress can all be controlled by individual or social measures.

How can we tackle these issues?

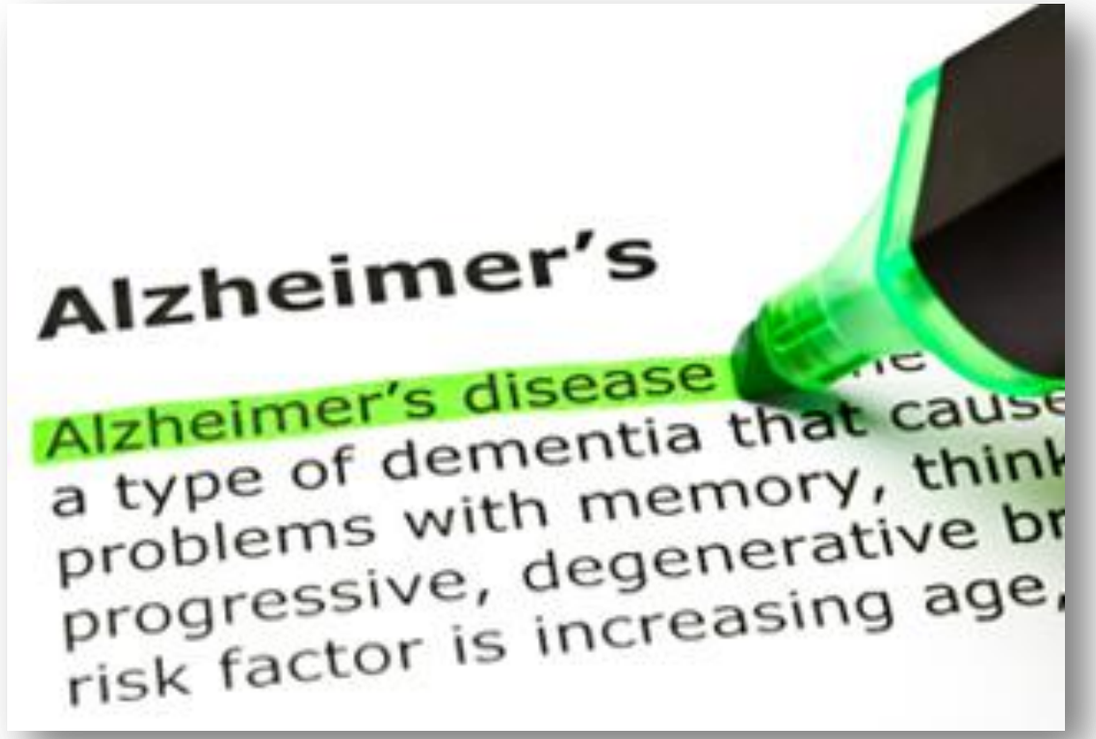
New priorities

Can we learn from the transition in toxicology? The need to improve human relevance



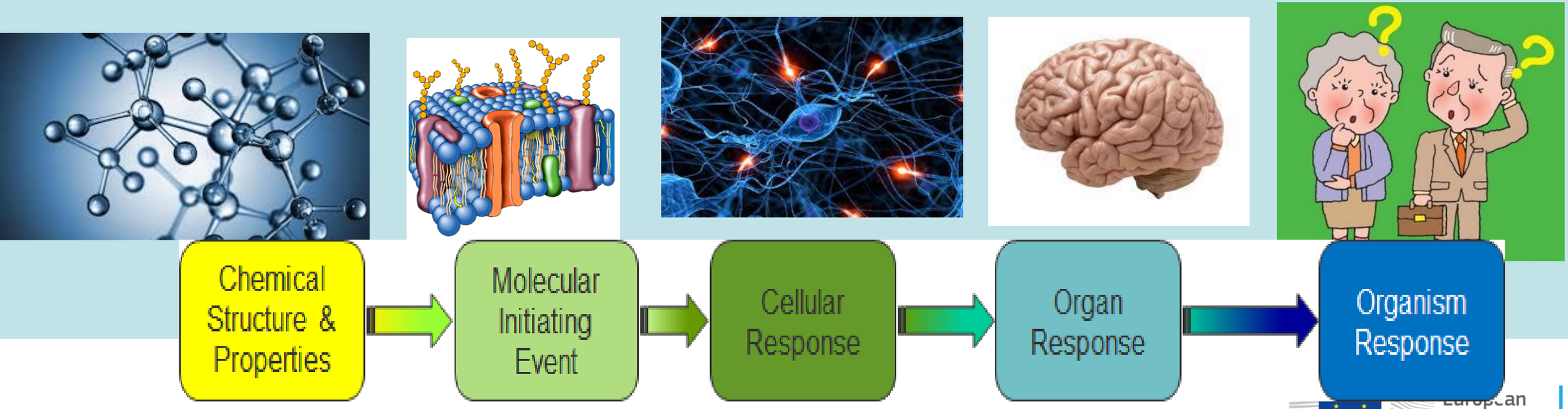


Can we apply the same transition also in AD research?

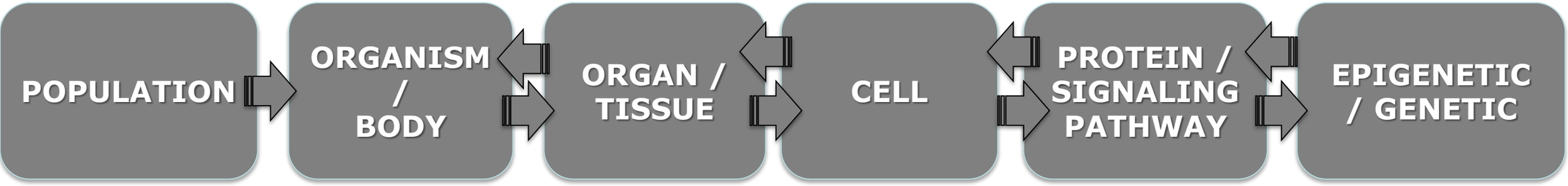


The ‘adverse outcome pathway’ (AOP) concept in AD research

- **What signaling pathways get perturbed at the onset of AD?**
- **Can we link environmental & genetic causes with whole-person outcomes, via multiscale AOPs?**



(Langley GR. Drug Discov Today. 2014 Aug;19(8):1114-24.)



What are the tools & models available to cover the different levels of biological complexity ?

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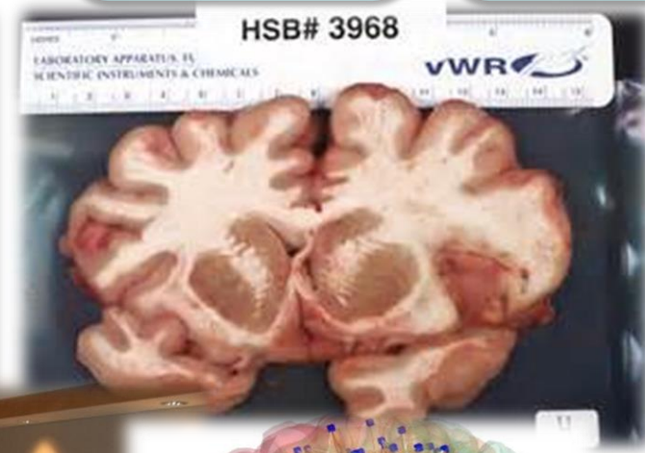
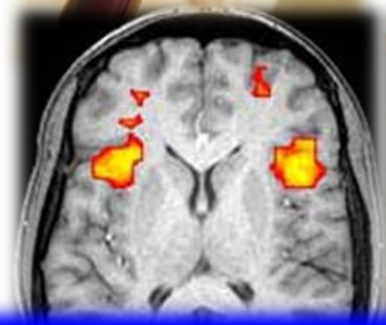
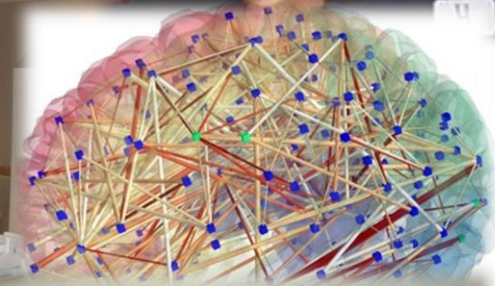
POPULATION → ORGANISM / BODY → ORGAN / TISSUE → CELL → PROTEIN / SIGNALING PATHWAY → EPIGENETIC / GENETIC

Observational, epidemiological, intervention studies on humans (e.g., Phase 0, microdosing)

POPULATION → ORGANISM / BODY ↔ ORGAN / TISSUE ↔ CELL ↔ PROTEIN / SIGNALING PATHWAY ↔ EPIGENETIC / GENETIC







Alzheimer Disease Assessment Scale—Cognitive Subscale (ADAS-cog) 11-Item

	Score range
Memory and new learning	**0 - 35**
Word recall *(mean number of words not recalled)*	0 - 10
Orientation *(one point for each incorrect response)*	0 - 8
Word recognition *(mean number of incorrect responses)*	0 - 12
Remembering test instructions	0 - 5
Language	**0 - 25**
Commands	0 - 5
Spoken language ability	0 - 5
Naming objects/fingers	0 - 5
Word-finding difficulty	0 - 5
Comprehension	0 - 5
Praxis	**0 - 10**
Constructional praxis	0 - 5
Ideational praxis	0 - 5
Total	**0 - 70**

Increasing scores indicate worsening cognitive function.

Human ex vivo tissue (healthy & diseased, e.g. brain, CSF, blood)

Imaging: MRI, PET, connectomics

Cognitive tests: MMSE, HVLT

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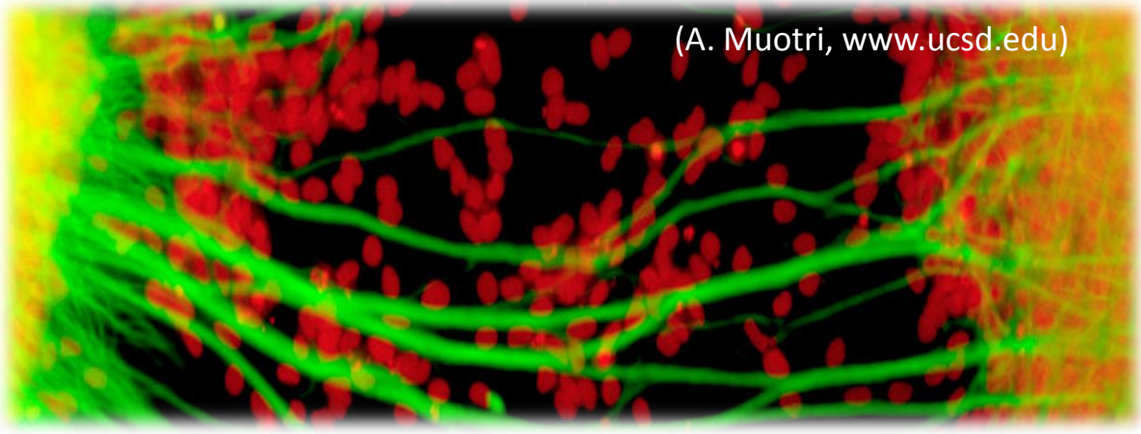
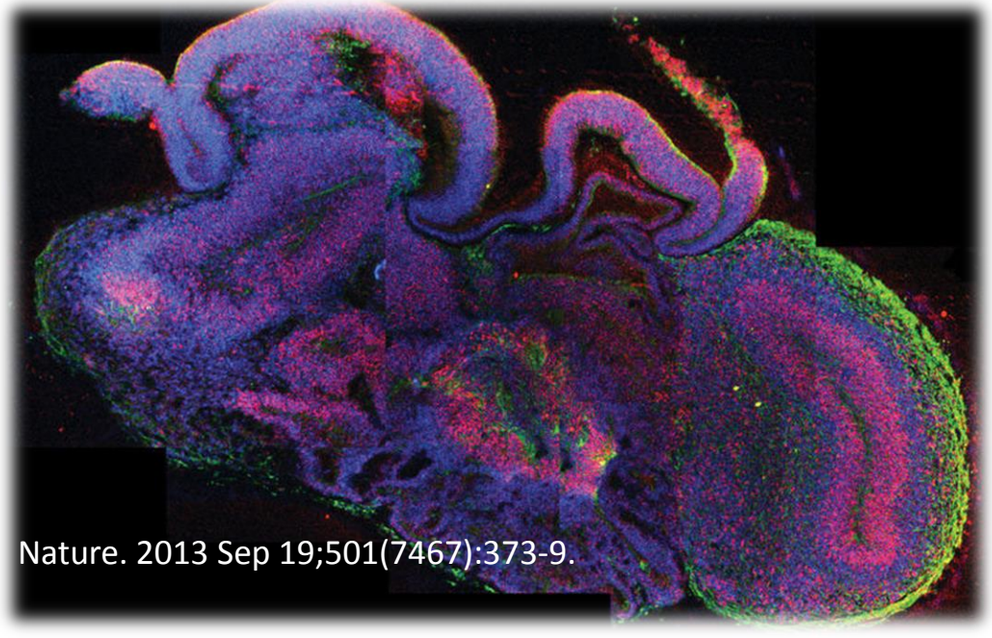
POPULATION → ORGANISM / BODY → ORGAN / TISSUE → CELL → PROTEIN / SIGNALING PATHWAY → EPIGENETIC / GENETIC



(A. Muotri, www.ucsd.edu)

Human induced pluripotent stem cells (hiPSCs) & neuronal derivatives (normal & patient)



Nature. 2013 Sep 19;501(7467):373-9.

3D cell models: improved viability, cellular & tissue properties retained *in vitro*

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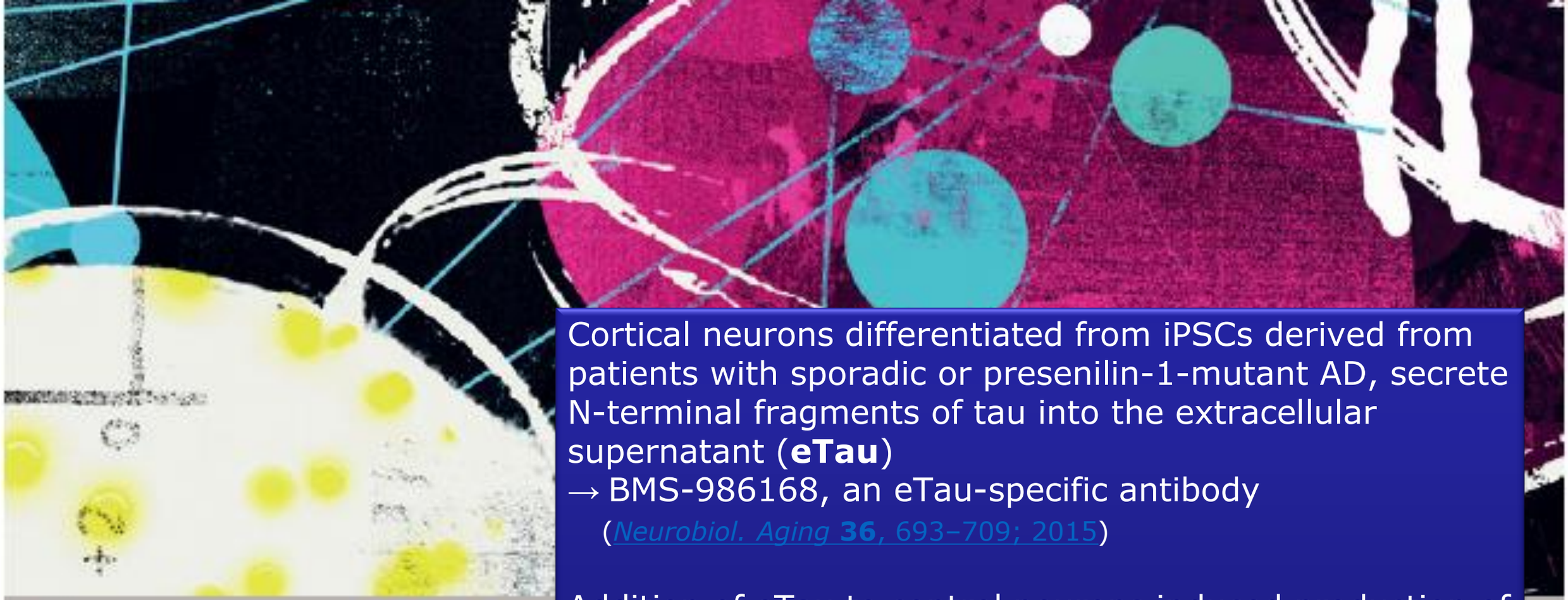


Cortical neurons differentiated from iPSCs derived from patients with sporadic or presenilin-1-mutant AD, secrete N-terminal fragments of tau into the extracellular supernatant (**eTau**)
→ BMS-986168, an eTau-specific antibody
(*Neurobiol. Aging* **36**, 693–709; 2015)

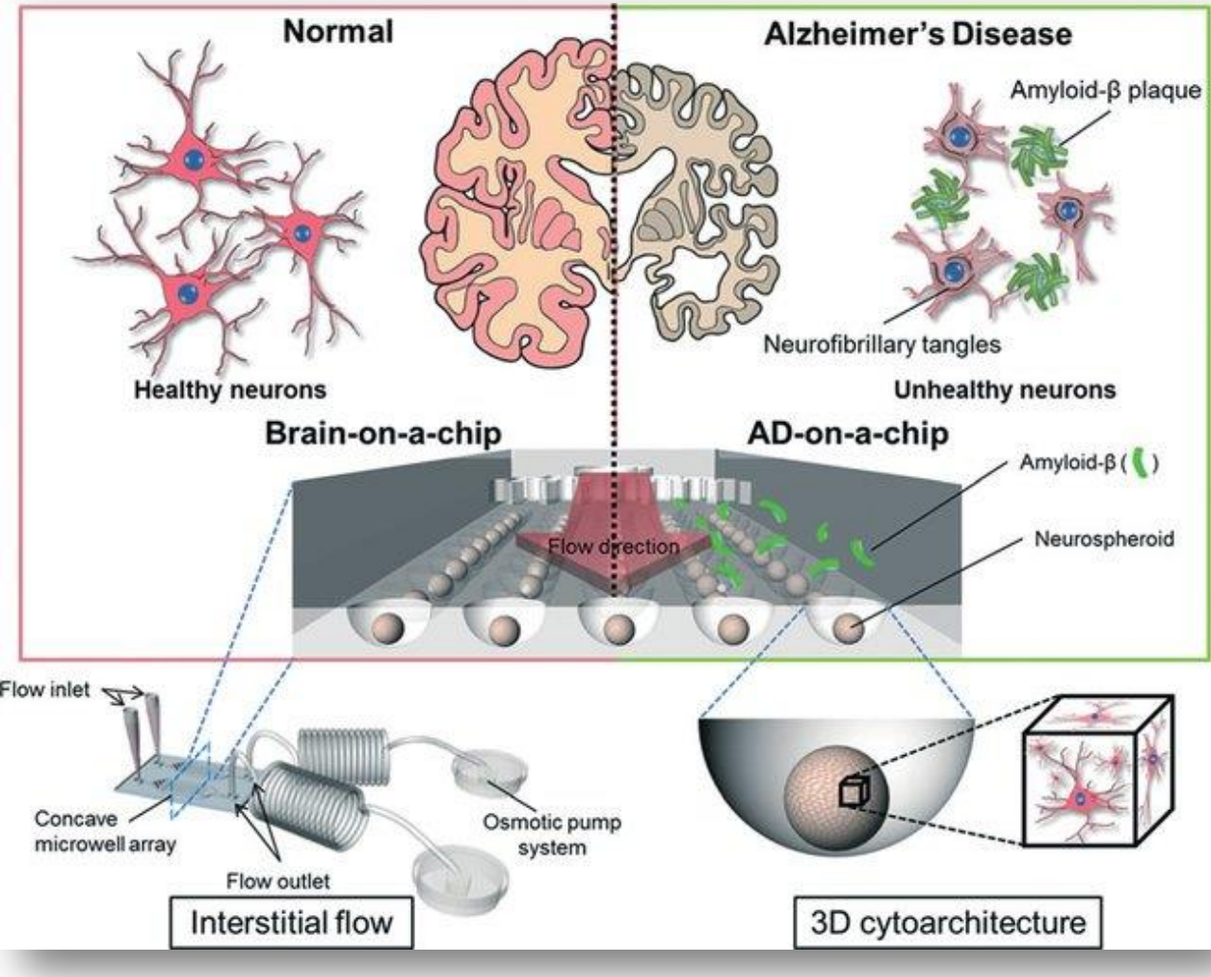
Addition of eTau to control neurons induced production of amyloid-β and induced neuronal hyper-excitability.

The application of the anti-eTau antibody reversed these effects.

Stem-cell disc
first clinical c

Induced pluripotent stem cell-derived 'disease-in-a-dish' models have propelled neurological drugs from Bristol-Myers Squibb, GlaxoSmithKline and Roche into clinical trials.

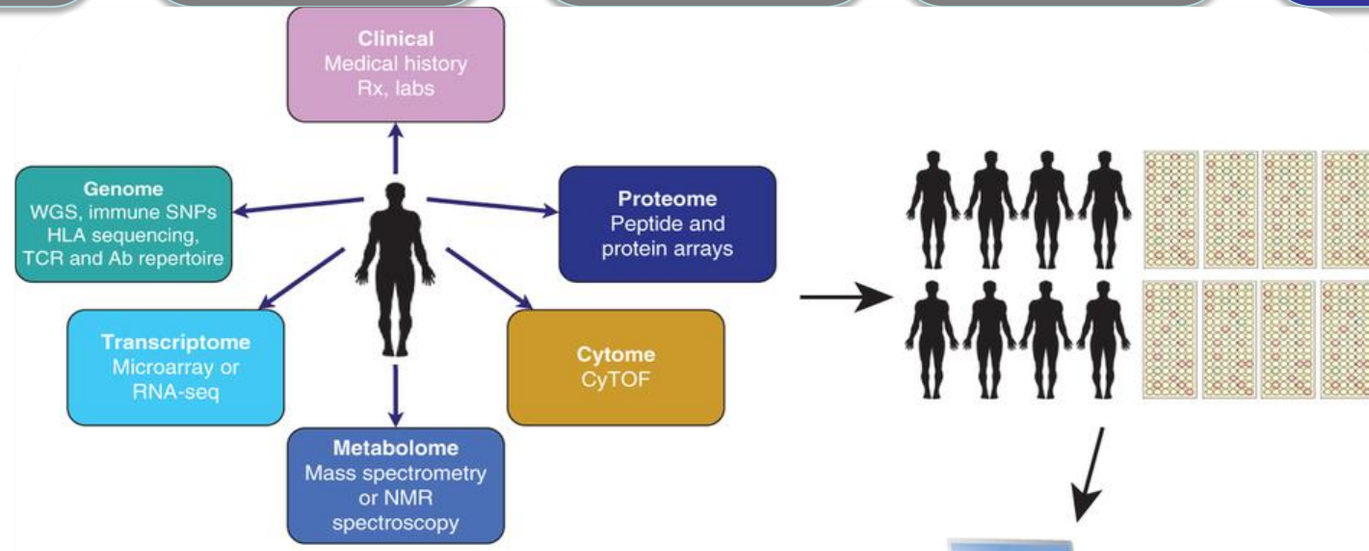
POPULATION → ORGANISM / BODY ↔ ORGAN / TISSUE ↔ CELL ↔ PROTEIN / SIGNALING PATHWAY → EPIGENETIC / GENETIC

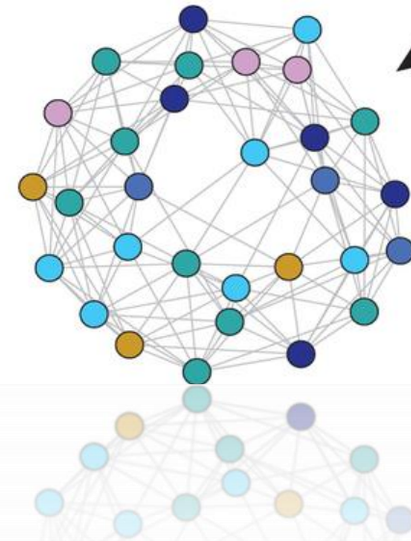


Microfluidics, brain-on-chip: Rapid, reproducible, sensitive

Park et al., Lab Chip. 2015 Jan 7;15(1):141-50.

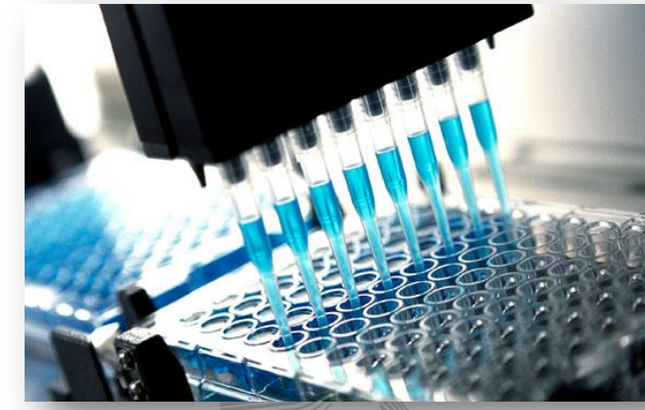
POPULATION → ORGANISM / BODY ↔ ORGAN / TISSUE ↔ CELL ↔ PROTEIN / SIGNALING PATHWAY ↔ EPIGENETIC / GENETIC





Next-generation sequencing ('omics')

Integrated computer modeling Systems biology & pharmacology



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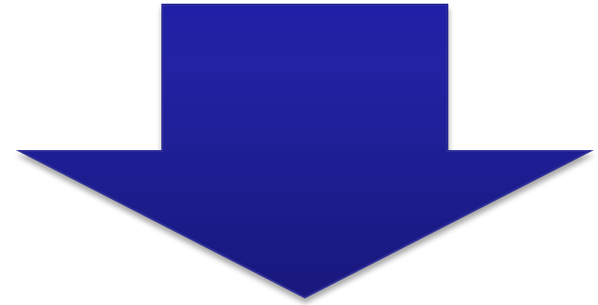
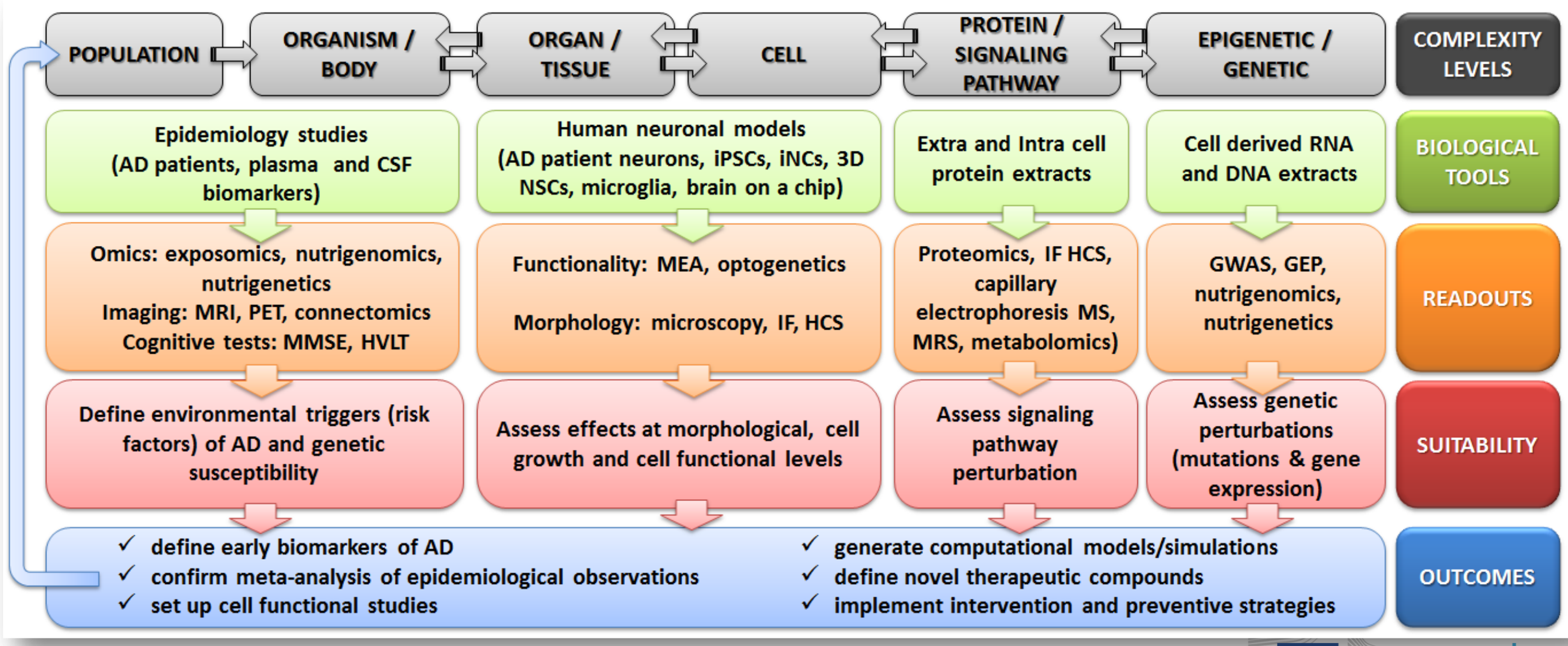


- ✓ **AD-related pathways (onset & progression)**
- ✓ **drug targets, efficacy & toxicity**
- ✓ **Human-relevant information earlier in drug development**
- ✓ **Possible reduction of late-stage drug attrition**
- ✓ **multi-scale data integration:**
  e.g., Omics data ↔ patients' cognitive scores ↔ neuroimaging

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)

A Section 508–conformant HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1510345.

Lessons from Toxicology: Developing a 21st-Century Paradigm for Medical Research

http://dx.doi.org/10.1289/ehp.1510345

SUMMARY: Biomedical developments in the 21st century provide an unprecedented opportunity to gain a dynamic systems-level and human-specific understanding of the causes and pathophysiologies of disease. This understanding is a vital need, in view of continuing failures in health research, drug discovery, and clinical translation. The full potential of advanced approaches may not be achieved within a 20th-century conceptual framework dominated by animal models. Novel technologies are being integrated into environmental health research and are also applicable to disease research, but these advances need a new medical research and drug discovery paradigm to gain maximal benefits. We suggest a new conceptual framework that repurposes the 21st-century transition underway in toxicology. Human disease should be conceived as resulting from integrated extrinsic and intrinsic causes, with research focused on modern human-specific models to understand disease pathways at multiple biological levels that are analogous to adverse outcome pathways in toxicology. Systems biology tools should be used to integrate and interpret data about disease causation and pathophysiology. Such an approach promises progress in overcoming the current roadblocks to understanding human disease and successful drug discovery and translation. A discourse should begin now to identify and consider the many challenges and questions that need to be solved.

Introduction

The genomics era opened a door to understanding genetic changes in susceptibility to diseases, such as single nucleotide polymorphisms, gene copy number variations, and gene deletions and insertions (Zerhouni 2014). The subsequent explosion of related "omics" approaches, including transcriptomics, metabolomics, and proteomics, have provided more details of how gene regulation and protein production are implicated in human disease mechanisms.

However, many human illnesses such as cancers, diabetes, immune system and neurodegenerative disorders, and respiratory and cardiovascular diseases are caused by a complicated interplay between multiple genetic and environmental factors (Lango and Weedon 2008). The environmental counterpart to genomics is exposomics, which aims to capture an individual's lifetime exposure to external factors (e.g., infections, environmental chemicals, drugs, radiation) measured via biomarkers in blood, urine, feces, or breath samples. It provides an opportunity to develop an environmental analog of genome-wide association studies, similarly top down and hypothesis free (Lioy and Rappaport 2011).

Another emerging omics tool is epigenomics—the study of changes in gene activity not attributable to DNA sequence alterations (e.g., DNA methylation and chromatin remodeling). Epigenetic changes including inherited effects and environmentally induced alterations are implicated in disease causation, and epigenomics is being developed in disease research. The U.S. National Institutes of Health (NIH) Roadmap Epigenomics Consortium has provided detailed human epigenomic maps to enhance studies of human disease and development (NIH Roadmap Epigenomics Consortium 2015). Epigenomics is also being explored in environmental health research with many exposures being associated with adverse health effects (Shenderov and Midtvedt 2014). These developments provide an unprecedented opportunity to add a new dimension to the study of human diseases.

The 21st century has seen these and many other pivotal advances in science and technology: Together, they offer, for the first time, the possibility of gaining a dynamic systems-level and human-specific understanding of the causes and pathophysiologies of disease (van de Stolpe and Kauffmann 2015). This understanding is a vital need, in view of current failures (Scannell et al. 2012; Kaitin and DiMasi 2011) in health research, drug discovery, and clinical translation (Collins 2011). But these developments in human-specific models and tools require a new research paradigm to unlock their full potential. We suggest it is time for a novel, overarching paradigm for medical research based on adapting and applying the transitional process underway in toxicology that includes reducing reliance on animal models, and instead emphasizing human biology and approaches based on multiscale pathways.

Discussion

In future health research and drug discovery, diseases can be envisaged as the combined outcome of extrinsic causes that include many types of exposures, not just chemical exposures, and intrinsic genetic and epigenetic changes (e.g., Gohlke et al. 2009) that interact at multiple levels (Figure 1). This combined approach would provide a more coherent "big picture" by linking environmental sciences with medical research.

Some of the thinking required to develop a more comprehensive framework for understanding disease causation has already begun. Toxicologists and environmental health scientists are already devising new models that explore synergies between toxic exposures and infectious pathogens in complex diseases, exemplified by interactions between the hepatitis B virus and aflatoxin in liver cancer (Birnbaum and Jung 2010).

A new medical research paradigm. To maximize the value of advanced models and technologies, we believe that a new paradigm is needed for fundamental research into human diseases and for drug discovery. The focus should move decisively away from preclinical animal studies and overly simplistic cell models toward a systems biology framework to integrate new types of scientific data, such as from omics, novel human-specific *in vitro* models, and clinical studies. Such a framework would help enable a comprehensive and dynamic understanding of disease causation and pathophysiology.

A concept that systematically describes links between causes of disease and outcomes could be repurposed from 21st-century toxicology. Since the publication of the U.S. National Research Council (NRC) report calling for a new paradigm (NRC 2007), a transition in toxicology has been underway, actively supported by U.S. regulatory and research agencies both from environmental and medical arenas (Collins 2011), as well as by the European Union [Scientific Committees on Health and Environmental Risks (SCHER) et al. 2013]. The focus in toxicological research turned first to understanding toxicity pathways—the normal cellular processes involving genes, proteins, and small molecules that lead to adverse human health effects when significantly perturbed by chemical toxicants (NRC 2007).

The notion of the cell-level toxicity pathways described in the NRC report (2007) has already been extended to the broader concept of adverse outcome pathways (AOPs), thereby addressing the sequence of changes between the molecular initiating event (e.g., a chemical binds to a cell receptor) and adverse outcomes at the molecular, cellular, organ, organism, and population levels. An AOP is a standardized way to describe concisely the critical mechanisms of toxic effects

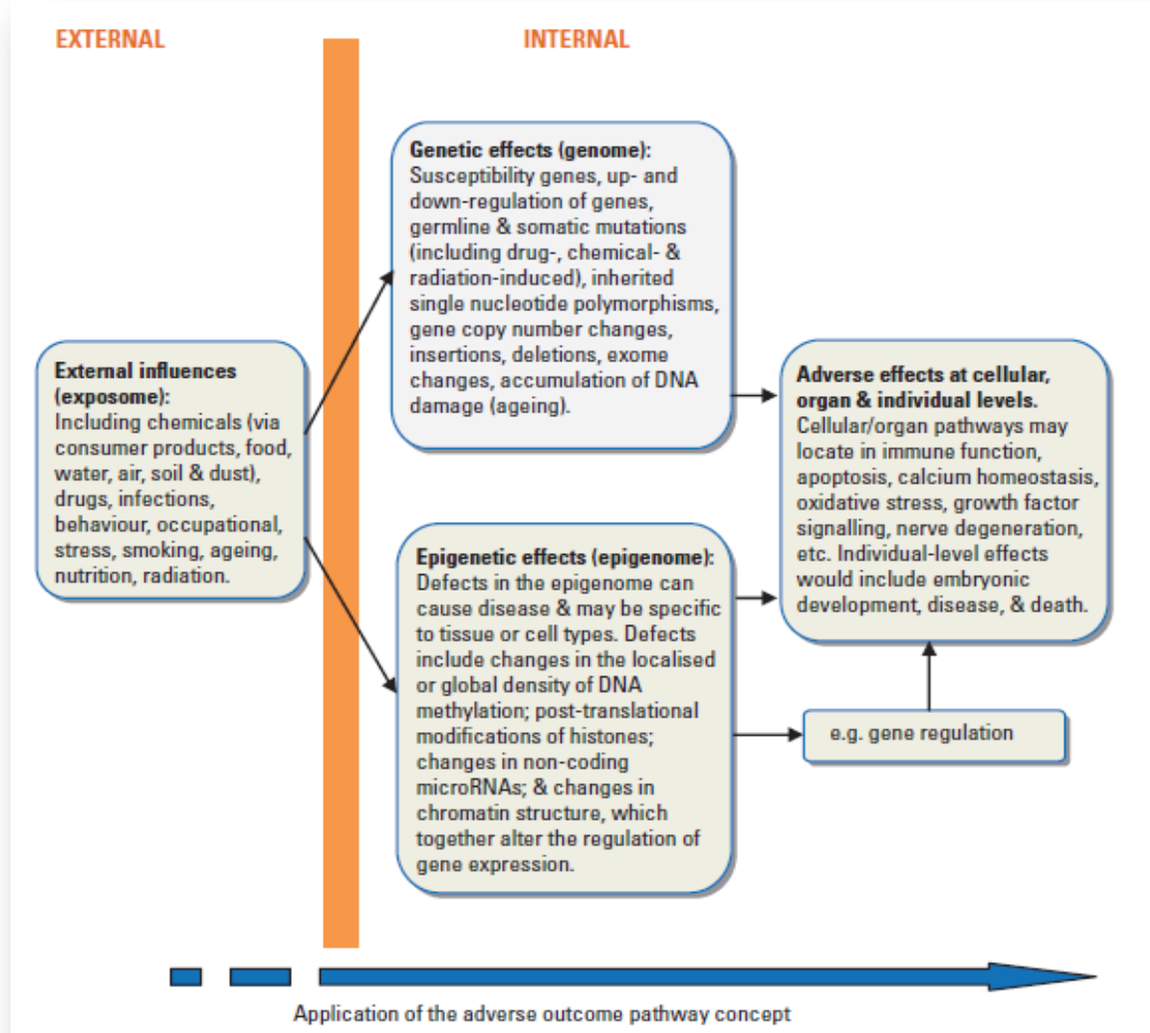


Figure 1. Integrating data on extrinsic and intrinsic causes of disease using systems biology provides a more comprehensive understanding of human illnesses. The adverse outcome pathway (AOP) concept links exposure, via chemical structure (or structures), the molecular initiating event, and key events, to an adverse outcome.

Drug Discovery Today • Volume 00, Number 00 • November 2016 REVIEWS

ELSEVIER

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 an… discovery: consensus re… recommendations

Gillian R. Langley[1], Ian M. Adcock[2], François B…, Kevin M. Crofton[4], Elena Csernok[5], Christoph …, Tuula Heinonen[7], Kathrin Herrmann[8], Martin Hofmann-Apitius[9], Brigitte Landesmann…, Lindsay J. Marshall[11], Emily McIvor[12], Alysson …, 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]

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

BOX 1

Summary of major recommendations

A true shift in paradigm will require greater emphasis to be placed on human relevance, from top-down funding decisions to data generation, to building of databases and/or knowledge management tools.

International and interagency collaboration is critical: formal collaboration between major organizational and funding bodies should be established.

Funding should be prioritized for researching human-based biology (versus 'improved' animal models) and promoting open access data.

Human data should be collected in collaborative, open-access high-quality databases.

Common reporting formats and common ontologies should be established for collecting and collating human biology information, from different 'omics technologies to human clinical data.

There is a need to establish formal processes for cross-sector communication.

There is an immediate need for the creation of case studies to demonstrate applications and benefits of predictive, mechanism-based approaches in the context of translation and human disease biology, and for the identification of new therapeutics.

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'.

Drug Discovery Today • Volume 00, Number 00 • June 2018 REVIEWS

ELSEVIER

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.

…ons toward a human … approach to disease

…er P. Austin[2], Warren Casey[3,4], …atherine Willett[1]

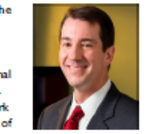
…he United States, 700 Professional Drive, Gaithersburg, …

…anslational Sciences, National Institutes of Health, …

…e Evaluation of Alternative Toxicological Methods, USA …). Box 12233, Research Triangle Park, NC 27709, USA …vey W. Wiley Building, 5100 Paint Branch Parkway, …

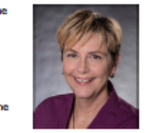
…drug development have resulted in …ts and reduced numbers of new drug …rams fail, the majority terminated at …argely because of efficacy failures or …iop brought together members from …icies, industry, academia, and …iscuss how existing programs could …uman biology and improving drug …increased emphasis on human …of data, and improved …ollaboration.

…evelopment of new drugs and other potential …ely expensive. The average pre-approval cost of …is estimated to be US$2.6 billion [1] and the …ollars spent has halved approximately every 9 …candidates entering clinical trials fail to gain …fficient efficacy and/or unacceptable toxicity, …nical studies [3]. One analysis of attrition rates …pharma companies in the EU and USA, found …ely [4]. Although there is widespread acknowl… …ith therapeutic area (oncology has particularly low success rates [5]), it is clear that drug candidates are failing between Phase 2 and submission,



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.

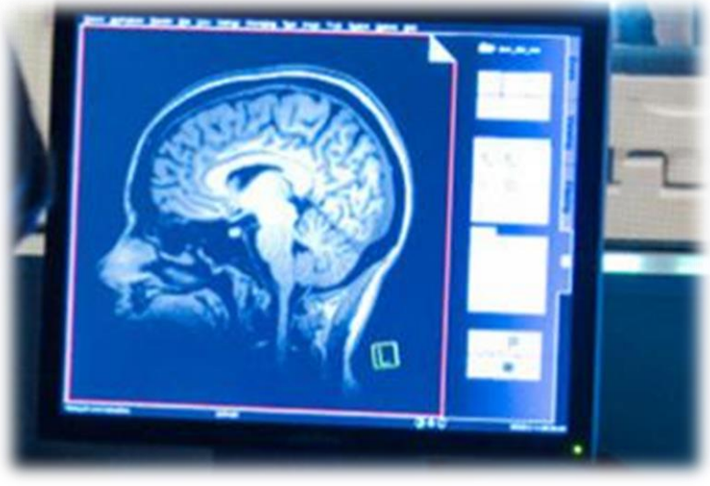
Corresponding author: Marshall, L.J. (lmarshall@hsi.org)

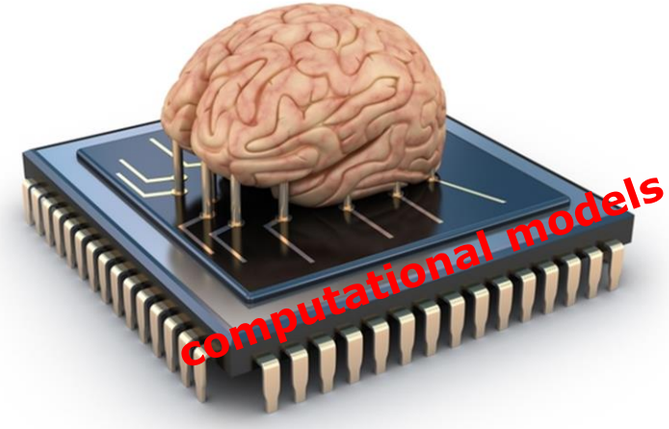
https://doi.org/10.1016/j.drudis.2018.05.038

Advantages of a human AOP-based approach

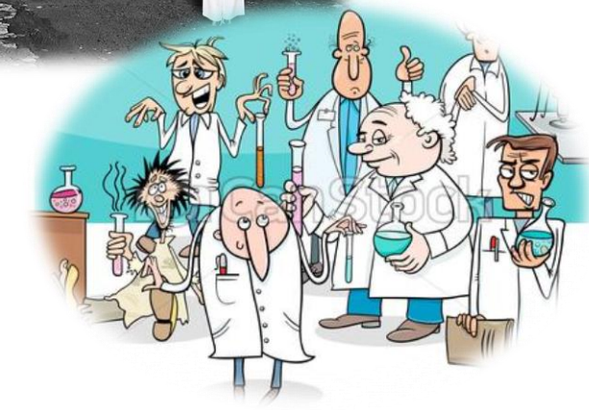
- A systems-based understanding of human diseases
- Cost-effective and predictive data
- Discovery of novel and multiple drug targets
- Human-relevant information earlier in drug development
- Possible reduction of late-stage drug attrition

Technical challenges





Knowledge challenges



European Commission

Need to reconsider AD research in the 21st century

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

www.herinneringen.eu

European Commission

Other European initiatives to tackle AD research

The Human Brain Project (HBP)

→ Human Brain Project (launched in 2013, H2020 FET Flagship Project) aims to provide researchers worldwide with Information & Communication Technology (ICT) tools and mathematical models for sharing and analysing large brain data they need for understanding how the human brain works and for emulating its computational capabilities.

112 partner organisations (mostly from Europe, but also from the USA, Japan, and China);

multidisciplinary: experts in computer science, neuroscience, robotics, micro-electronics, innovation and exploitation, ethics, education, programme management and communication

https://www.humanbrainproject.eu/en/

European Commission

Other European initiatives to tackle AD research

Boosting translational research on AD in Europe: The Innovative Medicine Initiative –IMI- *(€3.3 billion budget, 2014-2024, the world's biggest public-private partnership in the life sciences)* ***AD research platform:***

→ a dedicated research program of 3 highly complementary projects:

EMIF

European Medical Information Framework (EMIF) facilitates the use of data from research cohorts and population studies and routine care data

Aetionomy

generates a “mechanism-based taxonomy of AD and Parkinson's Disease”.
A “Big Data” approach in neurodegenerative disease research, aimed at identifying disease candidate mechanisms

EPAD

European Prevention of Alzheimer's Dementia (EPAD) cohort; responds to the need to early identify the high risk population with accurate risk models, and measure the success of a drug (or combination of drugs) against clinically meaningful endpoints

Alzheimers Dement. 2015 Sep;11(9):1121-2.

Thanks for your attention!

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