# Considering a new paradigm for Alzheimer's disease research

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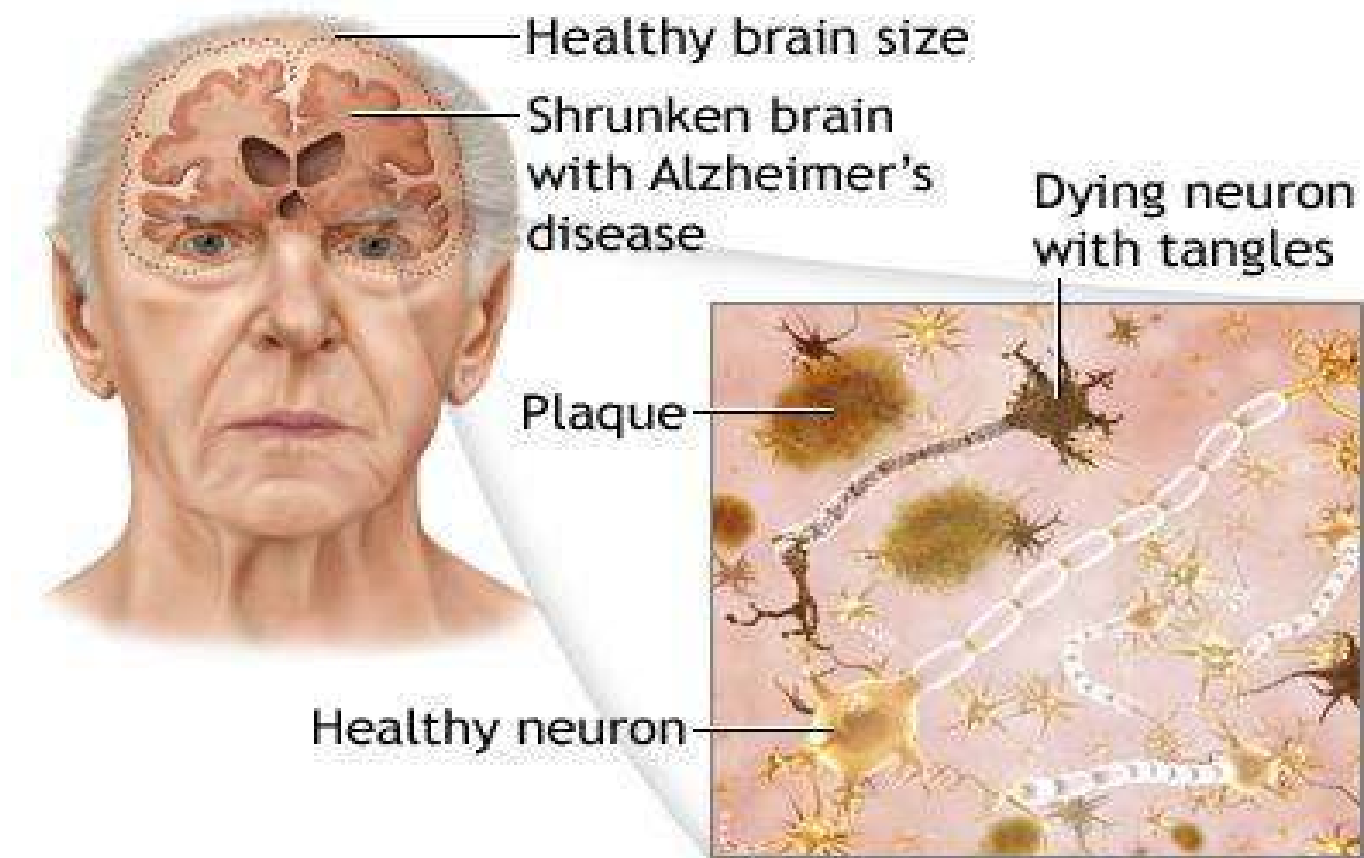
Langley, G.R. Considering a new paradigm for Alzheimer's disease research. Drug Discov. Today (2014) 19(8): 1114-1124.

Langley, G.R. et al. Lessons from toxicology: Developing a 21st-century paradigm for medical research. Env. Health Perspect. (2015). http://dx.doi.org/10.1289/ehp.1510345.

# Characteristics of Alzheimer's disease

BIOMED²¹



Healthy brain size

Shrunken brain with Alzheimer's disease

Dying neuron with tangles

Plaque

Healthy neuron

www.premedhq.com/alzheimers-disease

**Alzheimer's disease:**
**A failing research paradigm [1]**

BIOMED<sup>21</sup>

➢ 100s of compounds have failed in clinical trials despite encouraging results in animal models: no new drugs for ten years

➢ Existing drugs only stabilise symptoms temporarily, in some patients, but do not slow progression

➢ Current research paradigms are too dependent on transgenic mice

**Alzheimer's disease:**
**A failing research paradigm [2]**

➤ Species and strain differences tend to be overlooked or underplayed

➤ *Patients are being failed by research*

# Learning from the transition in toxicology

For similar reasons, toxicology is transitioning towards a new paradigm:

➢ Strategically implementing 21st-century scientific tools including systems biology

➢ Applied to advanced human-specific molecular & *in vitro* models

➢ Based on the 'adverse outcome pathways' (AOP) concept

➢ Moving away from animal use

**Alzheimer's research
and drug discovery – a new paradigm**

➢ Research into Alzheimer's disease may benefit from a similar transition

➢ The new paradigm would implement next-generation tools

➢ Applied to advanced **human** *in vitro, ex vivo* and *in vivo* models, with the aid of systems biology

# Pathways-based research

➢ Multiscale human disease pathways would be the core of the new paradigm, based on the AOP concept in toxicology

➢ Linking environmental and genetic/epigenetic causes with whole-person outcomes

# A broader overview of disease causation

BIOMED²¹

➢ Genetic effects (genome)

➢ Epigenetic effects (epigenome)

➢ External influences (exposome)

*Lead to*

➢ Adverse outcomes via disease pathways ("disease AOPs") at the molecular, cellular, organ & individual levels
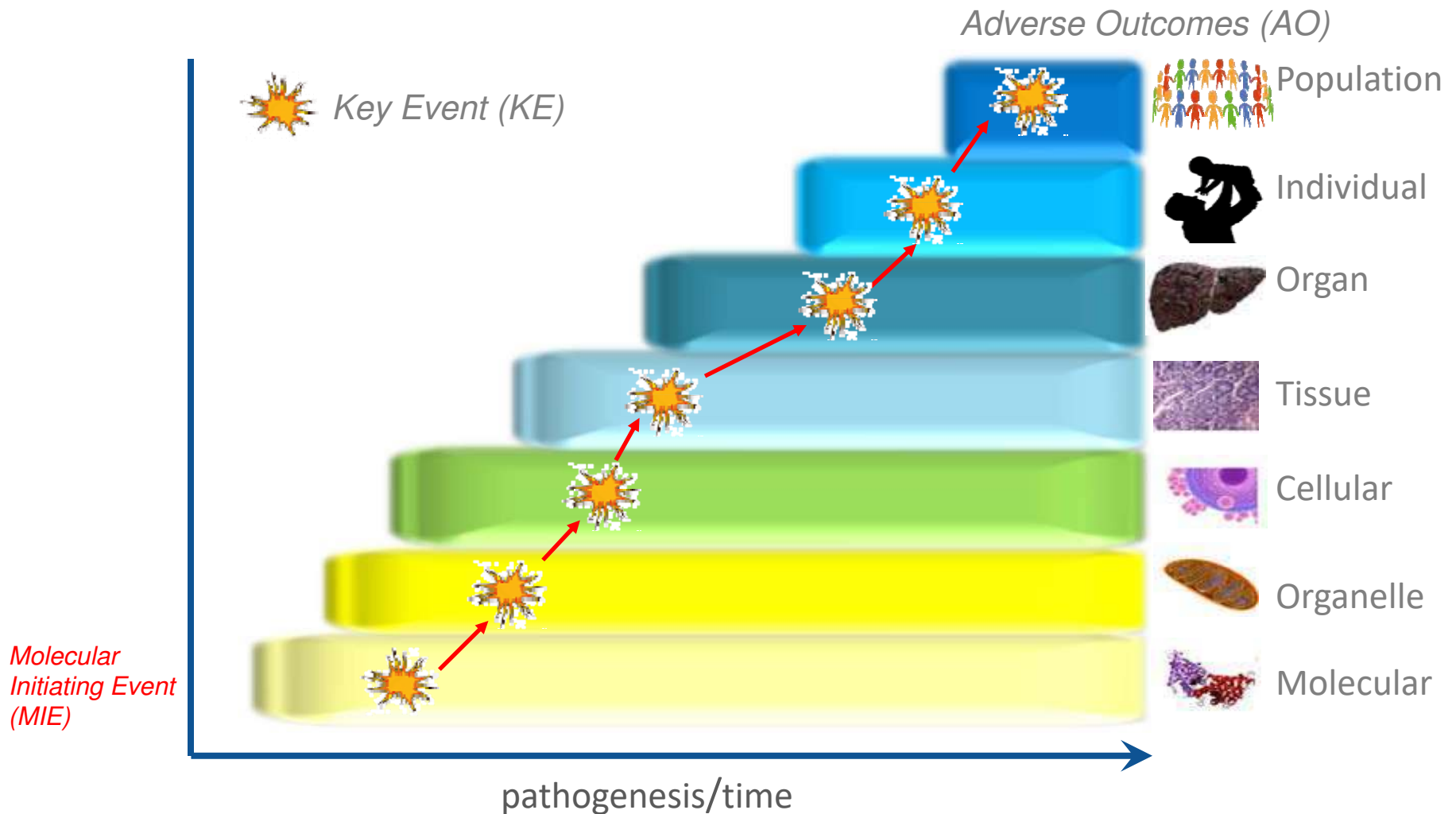
# In Alzheimer's research

**Can we get from this...**          **...to this?**

# AOPs are multiscale pathways

Adapted from presentation by OECD's Environment Directorate

BIOMED²¹

Adverse Outcomes (AO)

Key Event (KE)

Population

Individual

Organ

Tissue

Cellular

Organelle

*Molecular Initiating Event (MIE)*

Molecular

pathogenesis/time

# 21st-century human-specific models & techniques



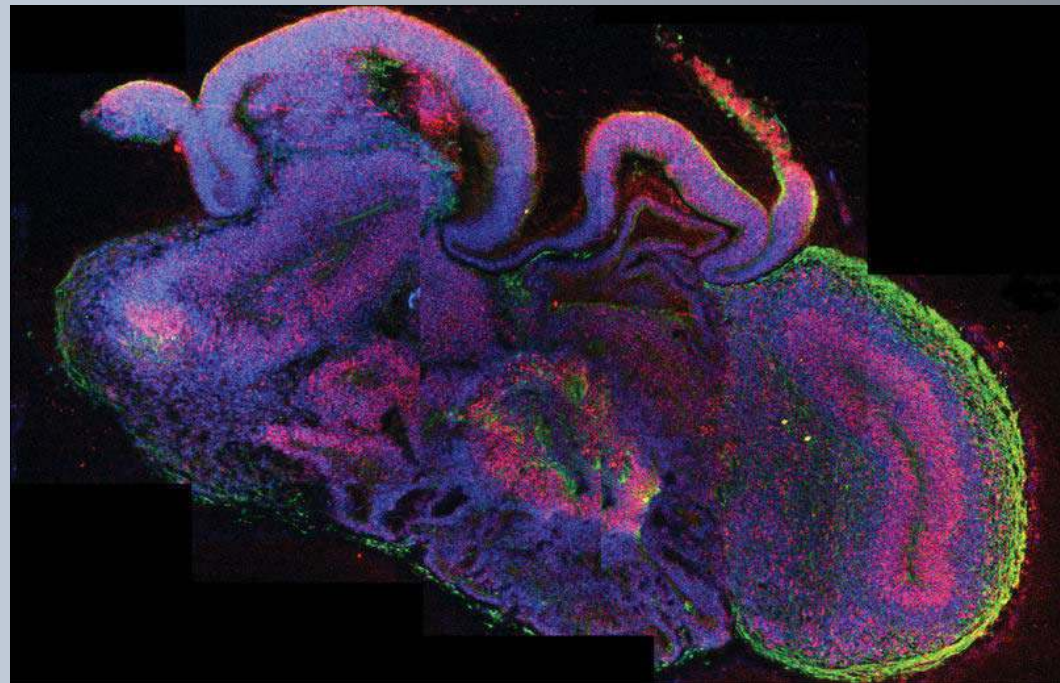1. **Brain cells derived from human induced pluripotent stem cells** (normal & patient-specific)



Alysson Muotri, Univ. California, San Diego

# 21st-century human-specific models & techniques


BIOMED 21
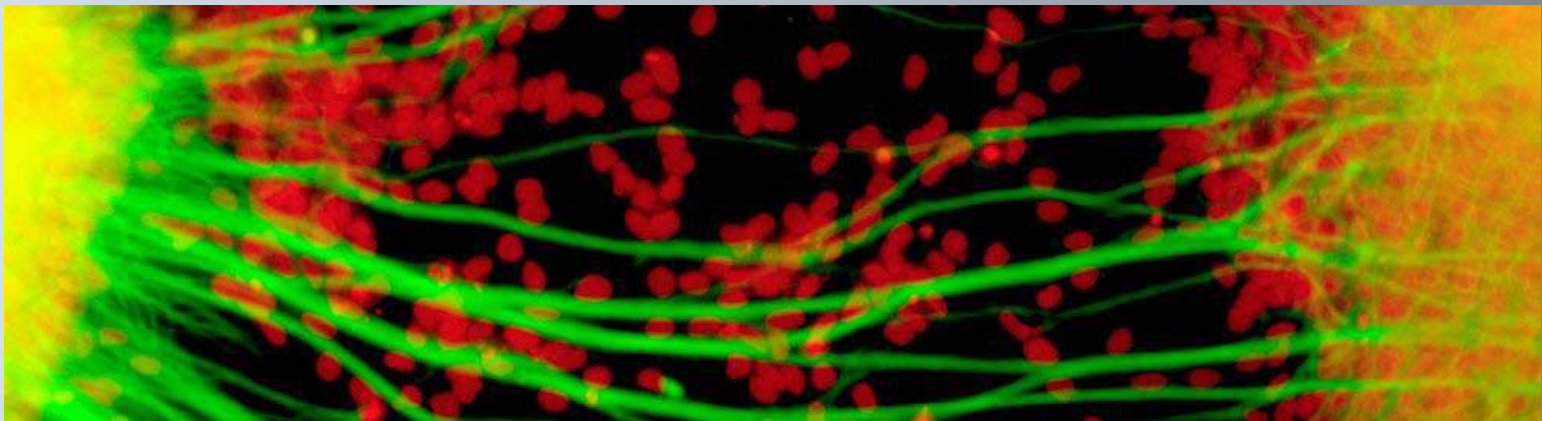
## 2. 3D human cell models:

Robust, controllable, improved viability, retain cellular/tissue properties *in vitro.*



Human pluripotent stem cells developed into cerebral organoids
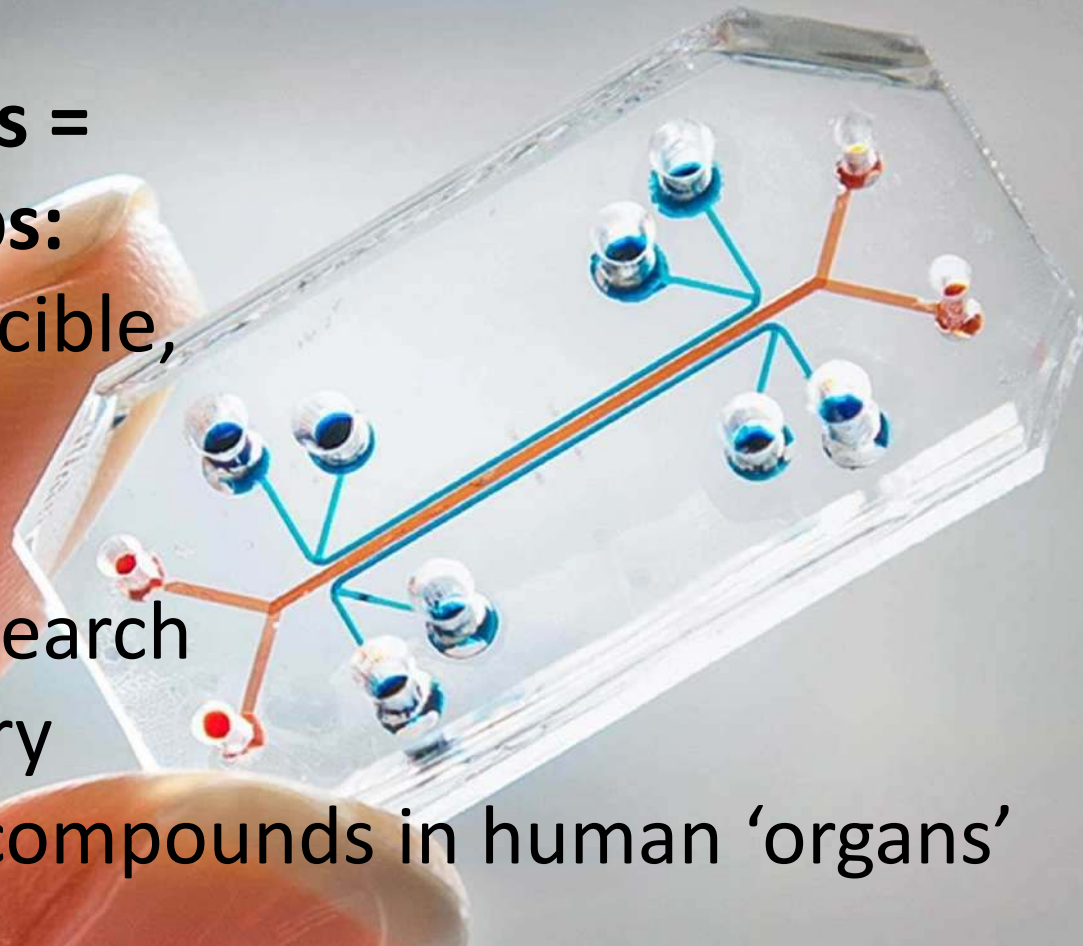M.A. Lancaster et al. Nature (2013). doi:10.1038/nature12517

**21st-century human-specific models & techniques**


BIOMED²¹

**3. Microfluidics = organs-on-chips:**
Rapid, reproducible, sensitive
platforms for:
➤ pathways research
➤ drug discovery
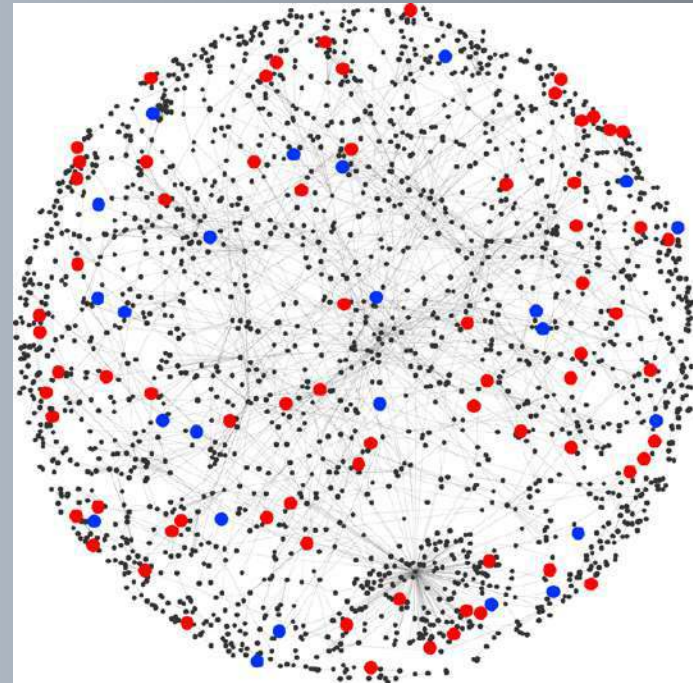➤ testing lead compounds in human 'organs'

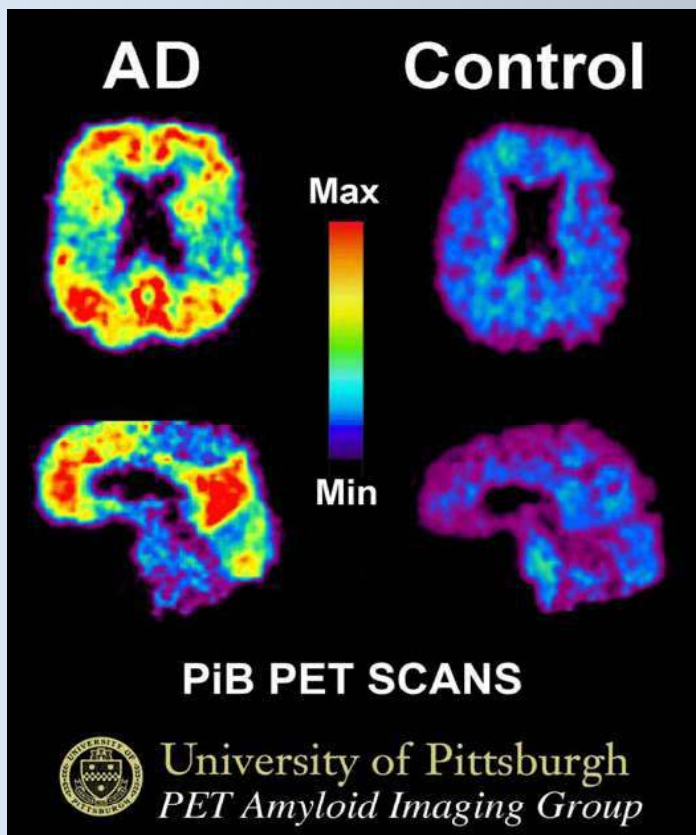# 21st-century human-specific models & techniques



## 4. Human *ex vivo* tissues

➤ Next-generation sequencing

(all the 'omics, multiplexed

fluorescent *in situ* visualisation of

DNA, RNA, proteins)

➤ disease pathways research

➤ status & dynamics of regulatory gene networks

➤ drug targets, efficacy & toxicity

# The 'omics



Not just genomics, also transcriptomics, proteomics, metabolomics, epigenomics, exposomics, connectomics…

# 21st-century human-specific models & techniques

## 5. Advanced clinical studies e.g. neuroimaging



AD    Control

Max

Min

PiB PET SCANS

University of Pittsburgh
PET Amyloid Imaging Group

# 21st-century human-specific models & techniques



## 6. Computational modelling & systems biology/systems pharmacology

# 21st-century human-specific models & techniques

## 6. Computational modelling & systems biology/systems pharmacology:

➢ Multi-scale modelling e.g. protein signalling pathways suggest new therapeutic concepts or clinical trial simulations

➢ Multiple source data integration

➢ Integrate & interpret big data from 'omics e.g. with patients' memory scores, for new drug targets

➢ Elucidate disease pathways & progression

# 21st-century human-specific models & techniques



## 6. Computational modelling & systems biology/systems pharmacology
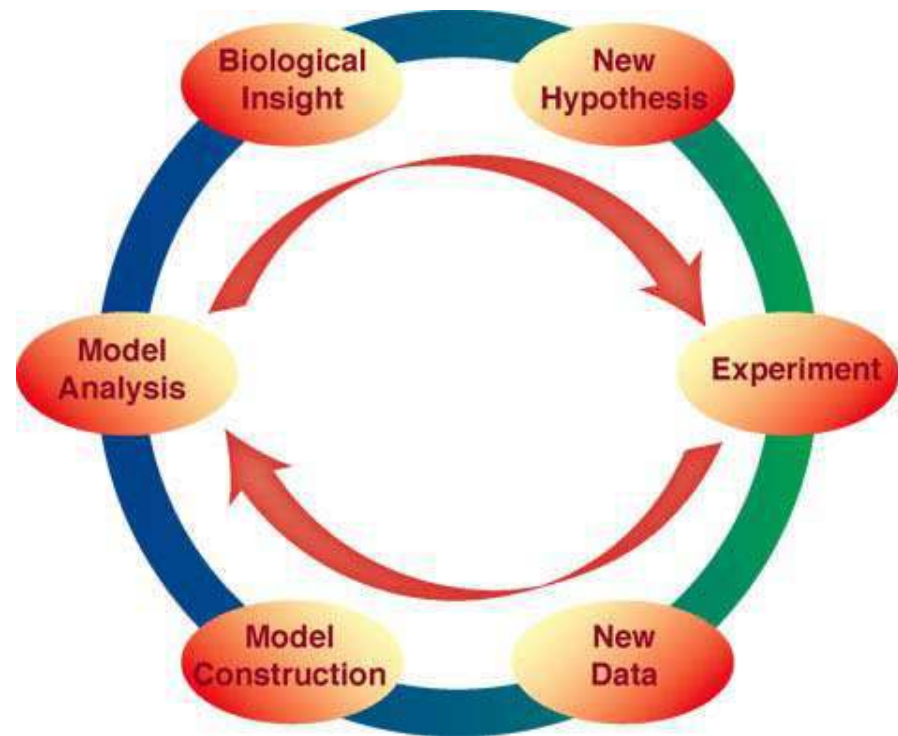
CISBIC, Imperial College

**Advantages of a new research paradigm**

➢ Offers a systems-based understanding of Alzheimer's disease

➢ May yield more cost-effective and predictive data

➢ Should help discover novel and multiple drug targets

➢ Could enable personalised and/or stratified data

➢ Would provide human-relevant information earlier in drug development

➢ Is likely to reduce late-stage drug attrition

# Some challenges...

**Technical & scientific challenges include**

➢ Improved selection, characterisation & validation of new cell models (incl. hiPSC)

➢ Optimisation of novel platforms for cell models

➢ Better quality post-mortem human tissue

➢ Further development of imaging technologies

➢ Synthesis of data to develop & validate computational models

➢ Improved *in vitro/in vivo* extrapolation

# Some challenges...

**BIOMED**²¹

**Knowledge and cultural challenges include:**

➤ *Moving out of the 'comfort zone' of animal studies*
➤ Interpretation & analysis of Big Data from 'omics
➤ Developing tools for open knowledge growth and collaboration, for describing & assessing 'AD AOPs'
➤ Constructing a detailed roadmap for AD research in the 21st century
➤ Changing science would require a new regulatory approach
➤ Persuading industry, funders, regulators and health scientists of the need for change
➤ Developing infrastructure to translate 21st-century tools into real-world use

# A roadmap for Alzheimer's disease research in the 21st century

**BIOMED**²¹

**????**
**Human-specific paradigm**

**2018**

**2017**

**2016**

**2015**
**Mouse-based paradigm**

# A Human Pathways Approach to Alzheimer's Disease Research

# Thank you!