European Commission

Advanced Non-animal Models in Biomedical Research

Neurodegenerative Diseases

Executive Summary

Joint Research Centre

EUR 30334/2 EN

This Executive Summary describes a study conducted by the JRC's EU Reference Laboratory for alternatives to animal testing (*EURL ECVAM*) to identify current and emerging non-animal models and methods used for biomedical research related to neurodegeneratove diseases.

The resulting collection of non-animal models have been analysed in a JRC Technical Report (Witters, H., Verstraelen, S., Liesbeth, A., Miccoli, B., Delahanty, A., Gribaldo, L., *Advanced Non-animal Models in Biomedical Research – Neurodegenerative Diseases*, EUR 30334 EN, Publications Office of the European Union, Luxembourg, 2021, ISBN 978-92-76-35944-9, doi:10.2760/386, JRC124723) and made publicly available from the *JRC Data Catalogue*.

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Neurodegenerative diseases such as Alzheimer's and Parkinson's are incurable and debilitating conditions that result in progressive loss of cognitive and motor functions.

Dementia is the most burdensome symptom and affects over 8 million people in Europe — a figure expected to double in the next 30 years[1]. Apart from the devastating impact on sufferers and their families, approximately €160 billion are spent each year to care for people with dementia across Europe[2].

Existing therapies for neurodegenerative diseases are limited and typically only treat the symptoms rather than offer any form of cure.

The failure rate of drug development for Alzheimer's disease is 99%[3] and the last new medicine was approved in 2003. One reason for this high failure rate is the poor translation of research results obtained using animal models to the human situation.

Recent scientific developments in the biomedical research field have resulted in a new generation of advanced models that better address the human-specific features of these diseases. In order to evaluate and communicate this progress, the JRC's EU Reference Laboratory for alternatives to animal testing (EURL ECVAM) launched a study to catalogue and review advanced non-animal models used in the field of neurodegenerative diseases, specifically for Alzheimer (AD) and Parkinson (PD) diseases.

The study covers approaches that use cells and tissues cultured in the laboratory (*in vitro* methods), computer modelling and simulation

1 Alzheimer Europe (2019), Dementia in Europe Yearbook 2019 – Estimating the prevalence of dementia in Europe.

2 Cost of illness and burden of dementia – The base option. *https://www.alzheimer-europe.org/Research/European-Collaboration-on-Dementia/Cost-of-dementia/Cost-of-illness-and-burden-of-dementia*

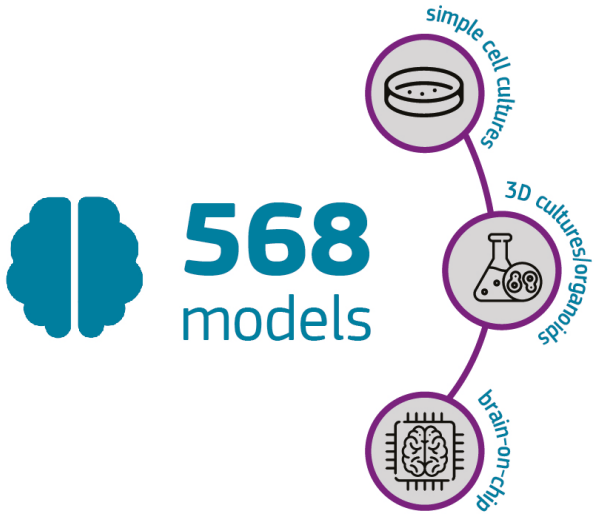
3 Cummings, J.L., Morstorf, T., and Zhong, K., Alzheimer's disease drug-development pipeline: few candidates, frequent failures. *Alzheimers Res Ther.*, 2014, 6, 37–43, doi:*10.1186/alzrt269*.

(*in silico* methods) or cells and tissues explanted from a patient (*ex vivo* methods).

Advanced models for human relevant research

The EURL ECVAM review comprises 568 different models, compiled from peer-review publications between 2013 and 2018.

The majority of the models identified are based on induced pluripotent stem cells (iPSCs) (see Box 1), with an important difference in terms of application between the AD and PD fields. While the majority of primary or stem cell models are used for mechanistic studies in AD research, there is a larger focus on treatment and therapy (e.g. dopaminergic cell replacement) when it comes to PD.



Models based on *ex-vivo* human material are primarily being used to evaluate aspects of protein aggregation in the case of PD, and amyloid β and tau accumulation in the case of AD (see Box 2).

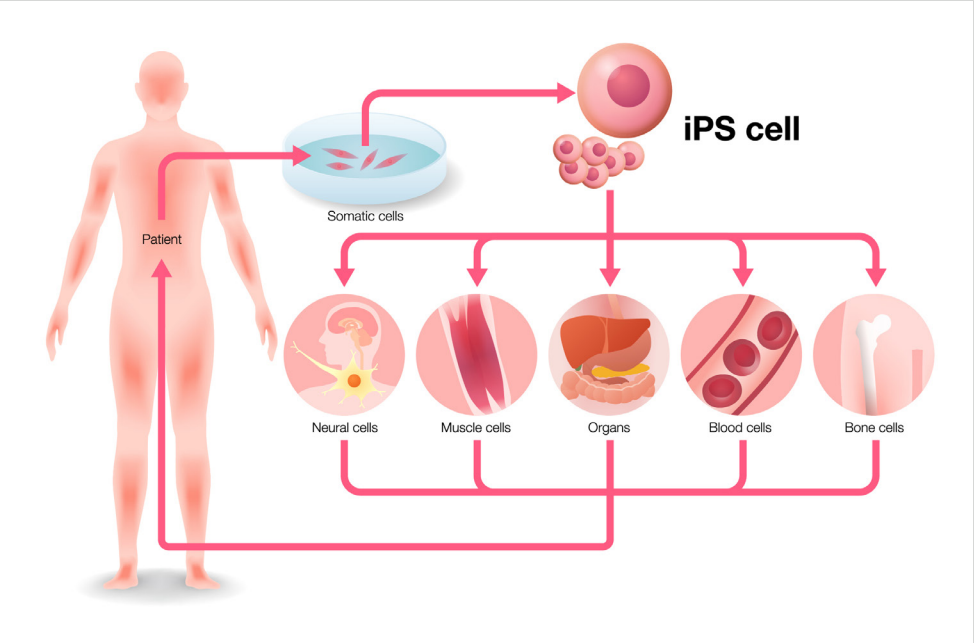
The study highlights promising areas of model and method development. For example, future advances include the optimisation of microfluidic devices for the identification of biomarkers in clinical settings and as tools to monitor disease progression.

The emerging trend is to exploit the human relevance of advanced non-animal models to provide strong mechanistic rationale for diagnostic, preventative and therapeutic interventions, thus representing an important step towards precision medicine tailored to the patient.

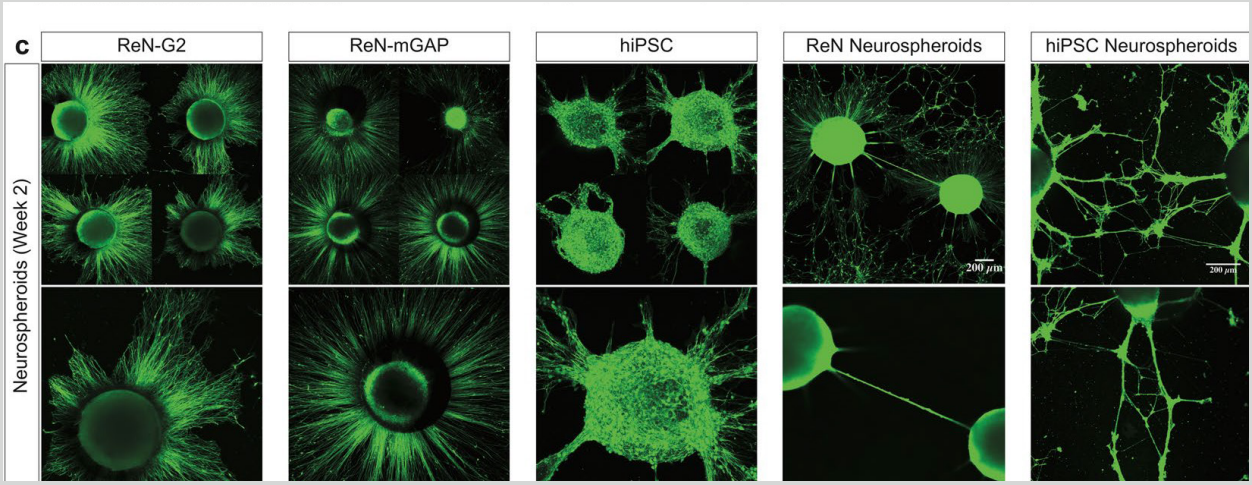
Box 1. Induced pluripotent stem cells (iPSC)

Stem cells are termed 'pluripotent' because they can transform themselves into different types of cells in the human body. This process of 'differentiation' is crucial for the development of an embryo into a mature organism and continues in some organs during adulthood.

Induced pluripotent stem cells (iPSC) are produced by biochemically reprogramming mature cells to reverse the differentiation process. They can replicate themselves almost indefinitely and can be differentiated again into any cell type such as neurons. They are more convenient for *in vitro* biomedical research than embryonic stem cells for both practical and ethical reasons.



Scientists can grow iPSC in three-dimensions as brain organoids and neurospheroids to better reproduce some aspects of AD in the laboratory. A research group from the Harvard Medical School successfully generated neurospheroids from human iPSC that showed two types of protein aggregation — amyloid plaques and neurofibrillary tangles — both distinctive features of the disease in humans (Jorfi *et. al.*, 2018).



Neurospheroids grown from human iPSC. ©Jorfi, M., D'Avanzo, C., Tanzi, R.E., Kim, D.Y, and Irimia D. (2018), Human Neurospheroid Arrays for In Vitro Studies of Alzheimer's Disease. *Scientific Reports,* 8, 2450, doi:10.1038/s41598-018-20436-8 under CC BY 4.0.

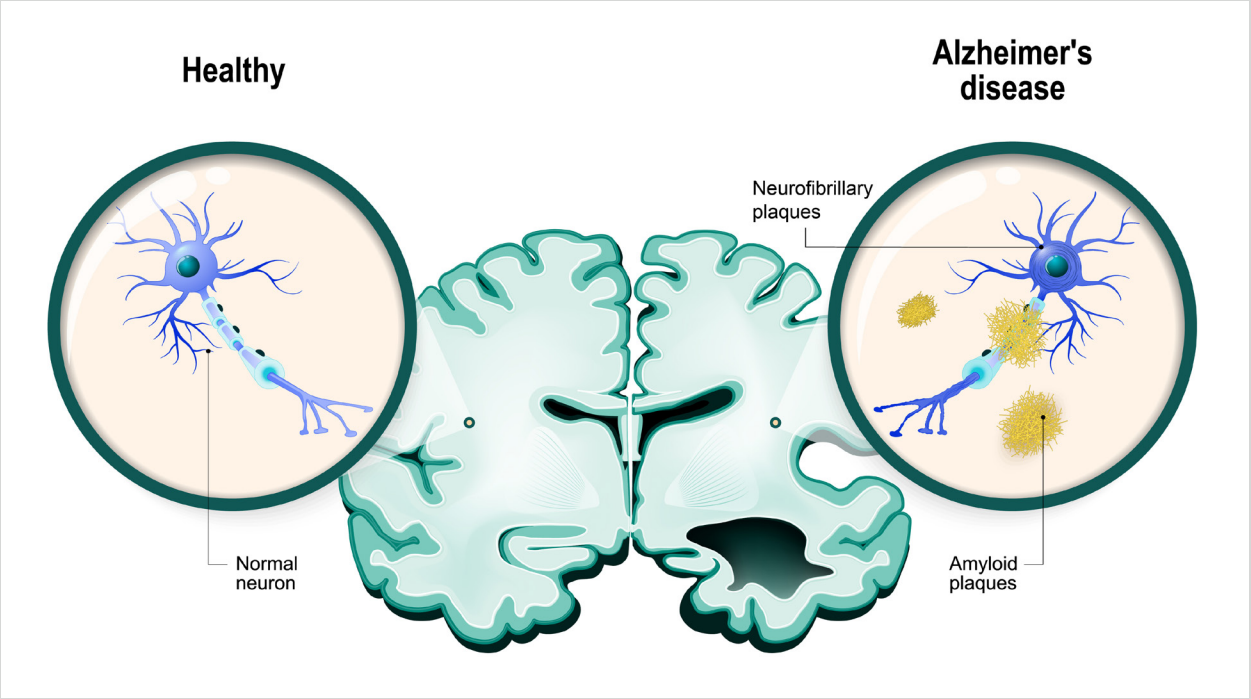
Box 2. Protein aggregation in Alzheimer's disease

Alzheimer's diseases is characterised by two major kinds of protein aggregation: amyloid plaques and neurofibrillary tangles.

Amyloid plaques are clumps formed in the spaces between nerve cells in brain tissue. They are made up of β-amyloid, which is a protein with toxic effects on the function of the surrounding brain cells. The role of amyloid plaques in the pathogenesis of AD is still not fully understood. They are more prevalent in AD patients but it is unclear if they are actually a casual factor or just a by-product of the disease.

Neurofibrillary tangles are intracellular aggregates that involve the twisting of tau protein threads of the nerve cells in the brain tissue. Individuals with AD typically present tau protein with a larger number of phosphate molecules than normal. This can lead to the formation of tau threads that become entangled inside cells. This in turn affects neurons and reduces their ability to function and work together in a network.

Rodents, especially transgenic mice, are used to study AD development and progression. They are usually genetically modified to produce high levels of human amyloid protein to cause plaques to develop in their brains. However, they do not display the loss of memory observed in humans. In addition, mouse models showing deposition of amyloid-β plaques lack the neurofibrillary tangles that are a distinctive feature of AD in humans.



The knowledge base

This study has produced a unique and highly curated knowledge base that contains detailed descriptions of 568 advanced non-animal models being used for research on neurodegenerative diseases.

It is freely available to download from the EURL ECVAM Collection in the JRC Data Catalogue[4], together with a JRC Technical Report[5] that describes the review methodology and presents the main findings (see Box 3).

This unique knowledge base can serve the needs of multiple stakeholders:

- **researchers** can identify models and methods that can be adapted and applied to tackle their own research questions;
- **educators** can provide the latest information on the state-of-the-art to their students;
- **funding bodies** can consider trends, identify impactful research avenues and target promising areas for investment;
- **project evaluation committees** can ensure that project proposers have adequately considered the use of non-animal models and methods in their research proposals;
- **National Contact Points** and **National Committees**[6] can support knowledge sharing on non-animal methods within Member State networks and organisations involved in biomedical research using animals.

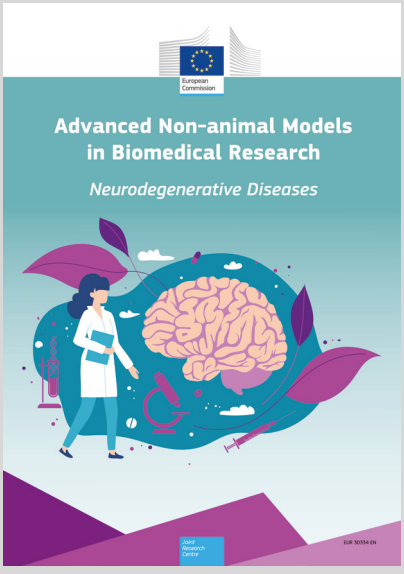
4 *https://europa.eu/!kq67JR*

5 Witters, H., Verstraelen, S., Aerts, L., Miccoli, B., Delahanty, A., Gribaldo L., *Advanced Non-animal Models in Biomedical Research – Neurodegenerative Diseases*, EUR 30334 EN, Publications Office of the European Union, Luxembourg, 2020, ISBN 978-92-76-35944-9, doi:*10.2760/618741*, JRC124723.

6 As referred to in Directive 2010/63/EU for the protection of animals used for scientific purposes.

Box 3. Knowledge base of advanced non-animal models

This study is a part of a series that EURL ECVAM is carrying out to review available and emerging non-animal models used for research in seven disease areas. Details on the published studies are available on the *EURL ECVAM website*.



In this study, around 13,000 peer-reviewed publications on neurodegenerative diseases were initially retrieved and screened for representative papers describing innovative and promising advanced non-animal models.

An important outcome of this study is a highly curated knowledge base containing detailed descriptions of 568 non-animal models used for neurodegenerative disease research. It is easily downloadable as a spreadsheet file from the EURL ECVAM collection in the *JRC Data Catalogue*.

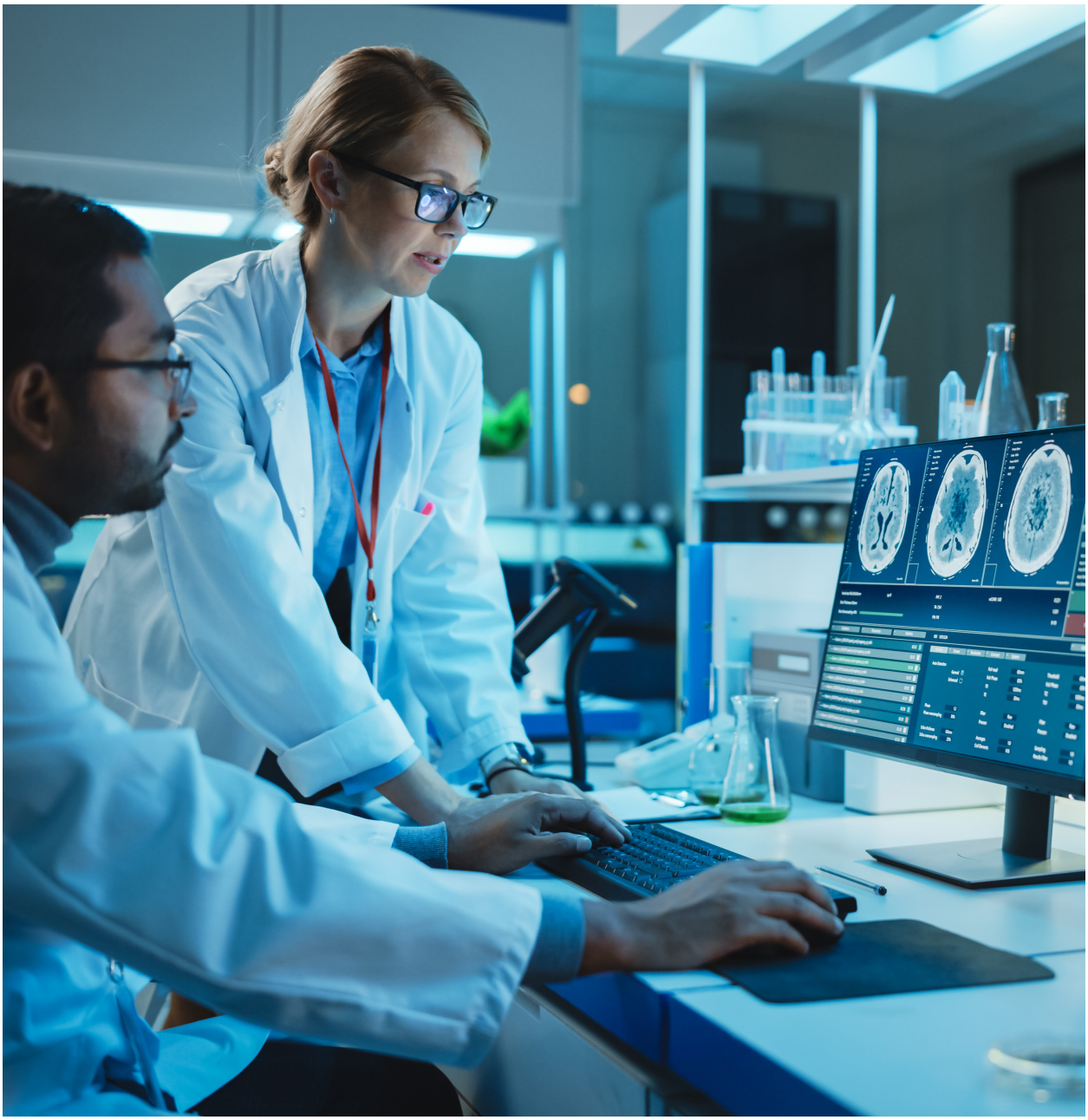
This knowledge base is complemented with a *Technical Report* that provides an in-depth analysis of the models identified and a description of the review methodology employed.

Findings of this study can also inform aspects of **policy making** regarding the protection of animals used for scientific purposes, setting of research priorities to progress the development and uptake of non-animal methods, and the promotion of modern human-relevant scientific approaches to combat diseases such as cancer.

Finally, this knowledge base can serve as a means to explore the strengths and limitations of both animal and non-animal models used in biomedical research, to stimulate healthy scientific debate, to challenge mind-sets, and to pave the way for doing better and more predictive science.

Thus the knowledge base can act as a bridge across methods and disciplines in the biosciences[7] to improve biomedical research for the ultimate benefit of patients and society.

7 Carusi A., Whelan M. and Wittwehr C., *Bridging Across Methods in the Biosciences – BeAMS*, EUR 29852 EN, Publications Office of the European Union, Luxembourg, 2019, ISBN 978-92-76-11181-8, doi:*10.2760/190697*, JRC116305.



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