



# Innovative models in biomedical research

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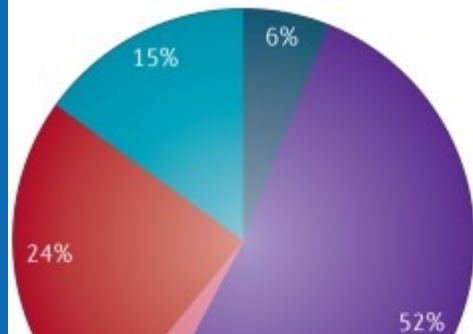
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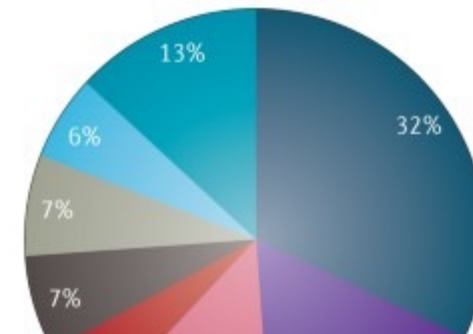


**95% rats & mice**

a Reason for failure 2013–2015



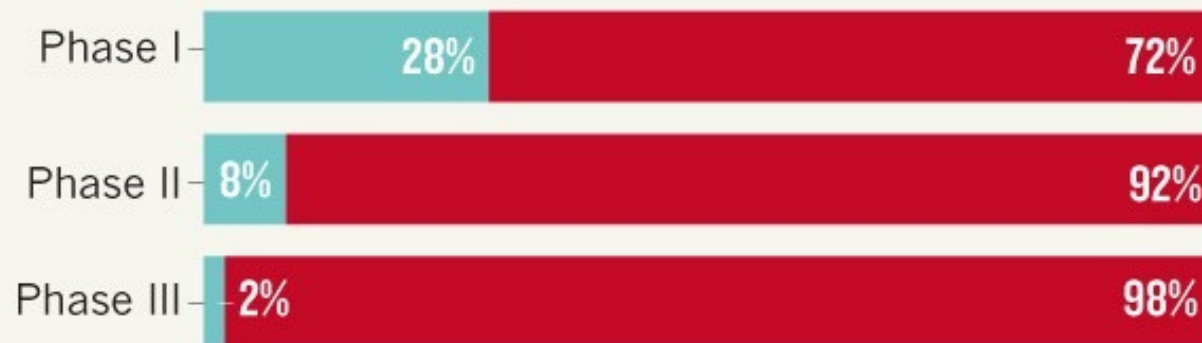
b Percentage failure by therapeutic area



## ALZHEIMER'S DRUG ATTRITION

A decade's worth of clinical trials identified only one approved drug.

■ Moved to next phase ■ Dropped

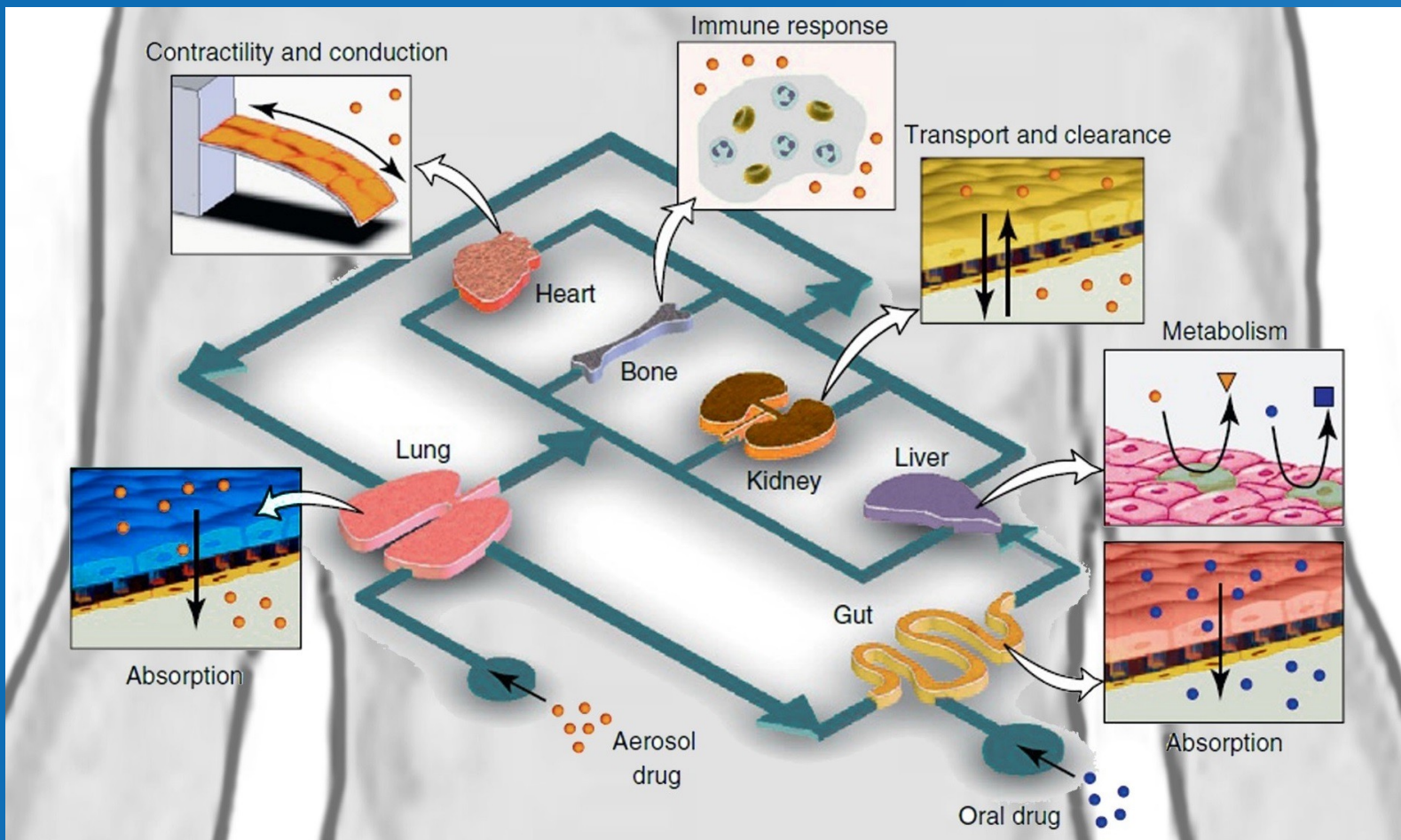


**99.6%** of **413** trials (testing a total of **244** compounds from 2002 to 2012) failed to produce a drug.

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# Innovative NAMs





# Non-animal methods used in research

- **Knowledge-base** of models
- **Meta-analyses** to understand strategies and approaches



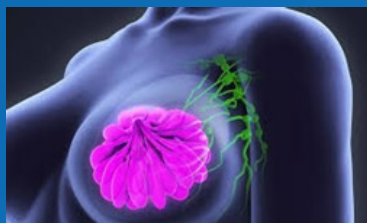
**Respiratory tract diseases**



**Neurodegenerative diseases**



**Cardiovascular diseases**



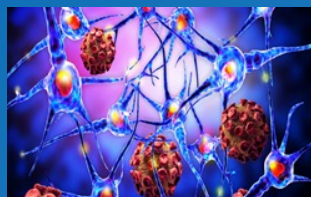
**Breast Cancer**



**Immunogenicity testing for ATMPs**

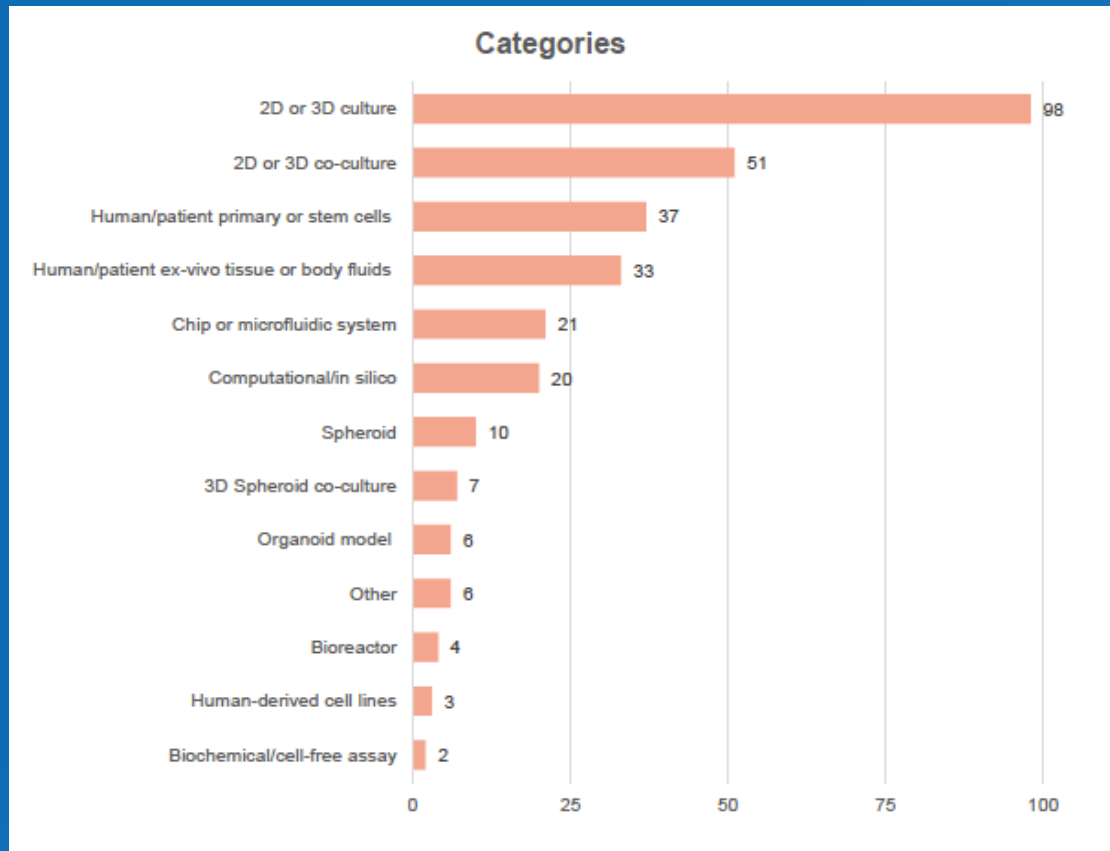


**Immuno-oncology**

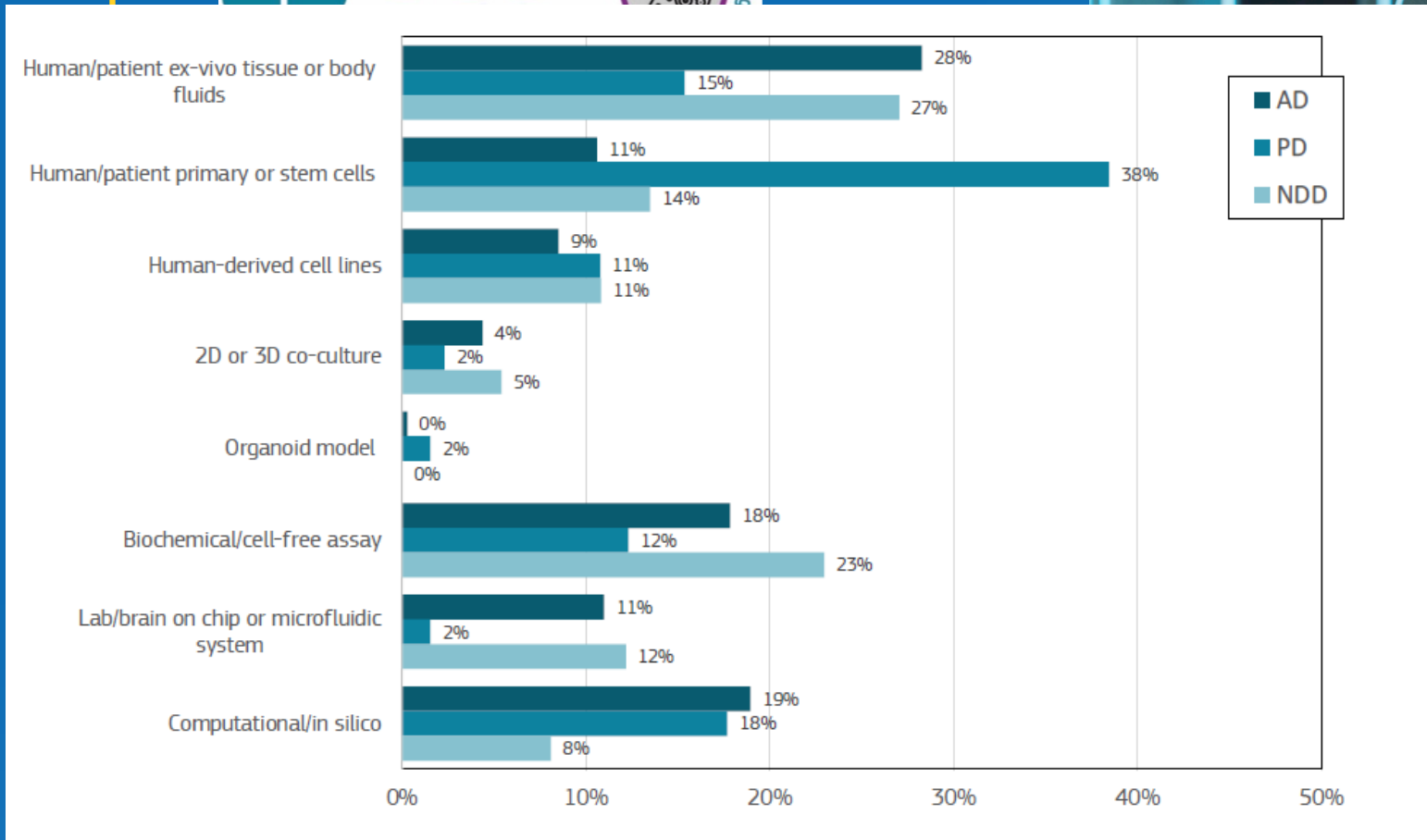
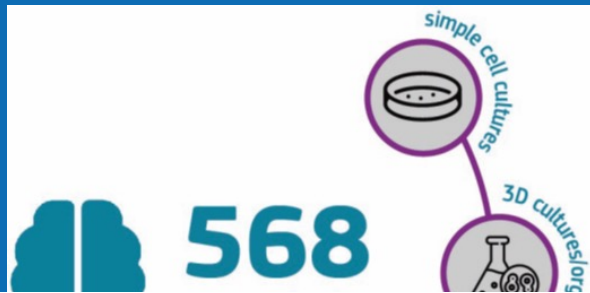


**Autoimmune diseases**

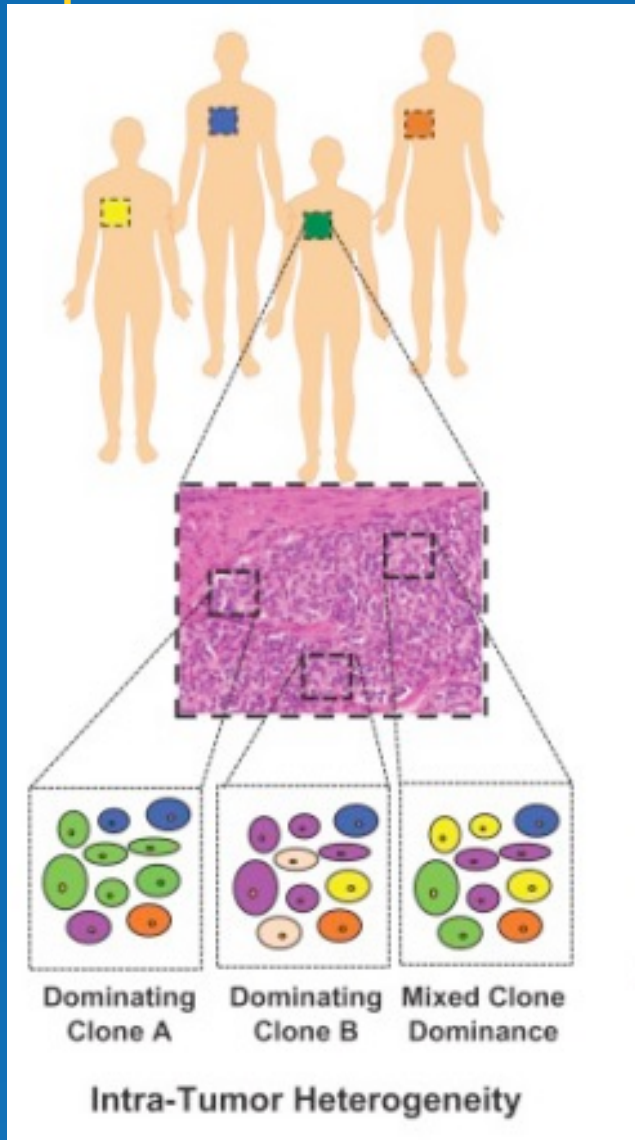
# Respiratory Tract Diseases



# Neurodegenerative disease

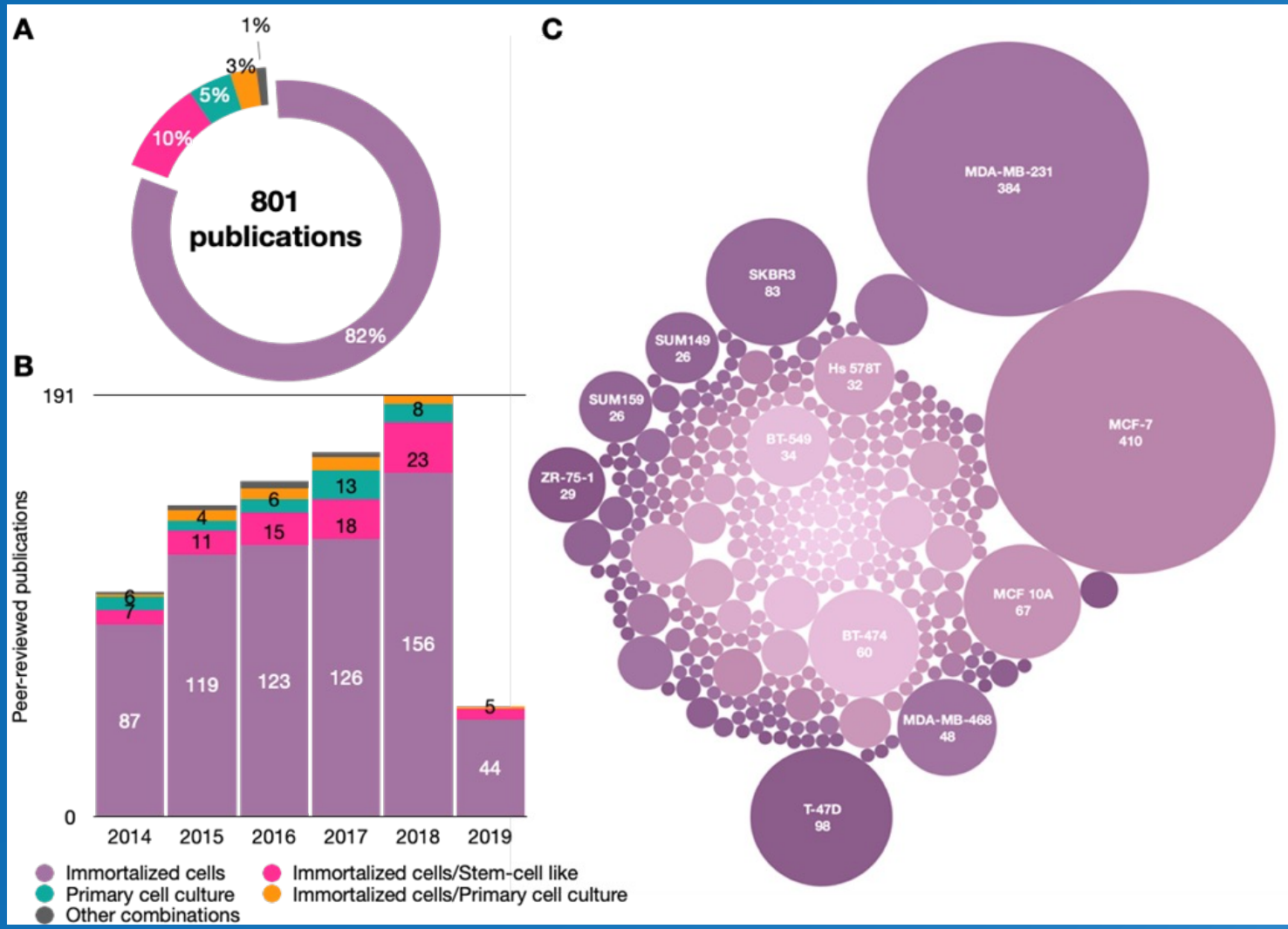


# Breast Ca

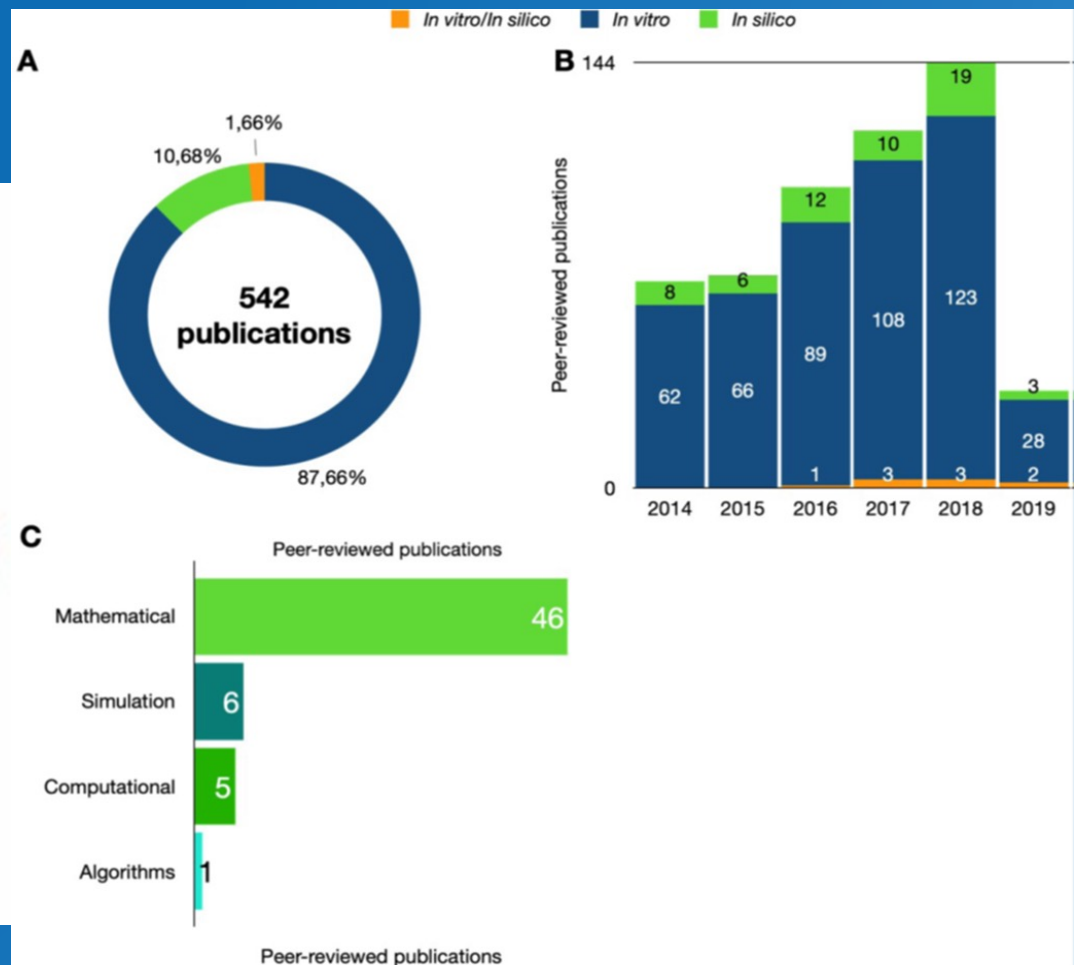
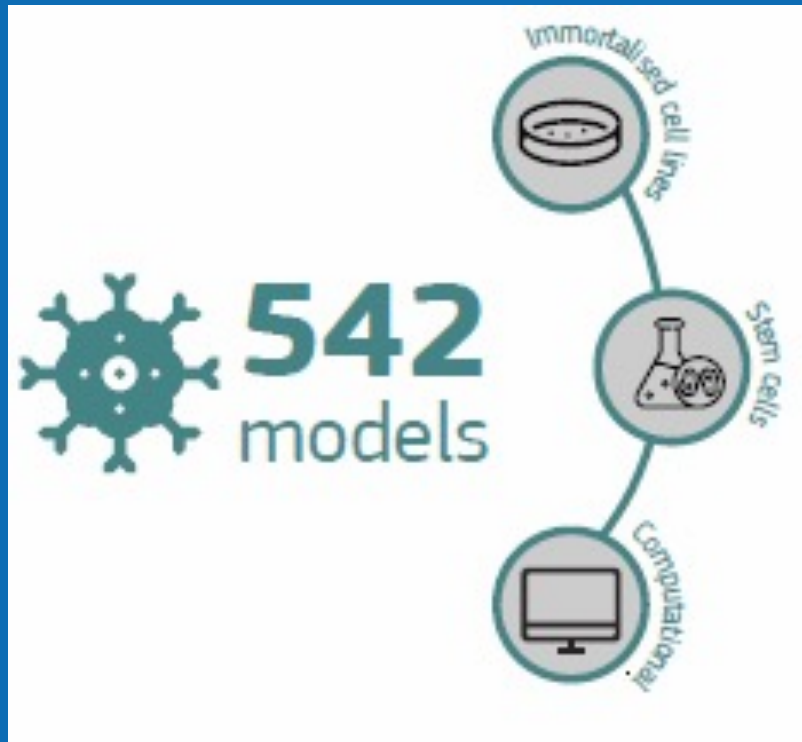


**In EU over 355,000 women diagnosed with breast cancer in 2020 (source: ECIS)**

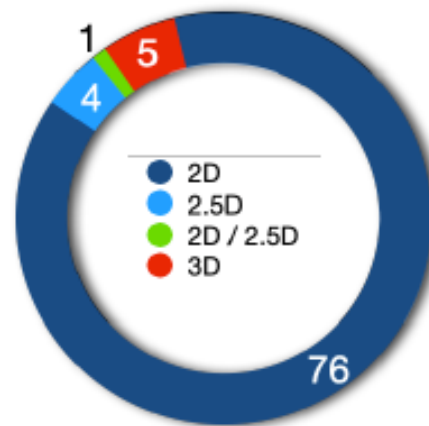
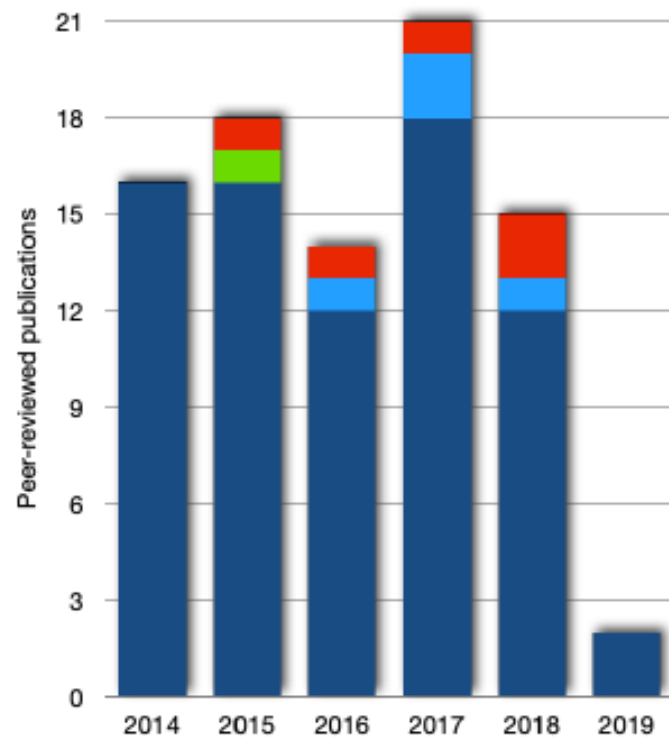




# Immuno-oncology



# Immunogenicity for ATMP testing



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A



# Advanced Non-animal Models in Biomedical Research

## Immunogenicity testing for advanced therapy medicinal products



Joint Research Centre

EUR 30354-4 EN



### Advanced Non-animal Models in Biomedical Research:



### Advanced Non-animal Models in Biomedical Research: Breast Cancer



**Breast cancer** is the most common cancer among women in the European Union and worldwide. Preclinical breast cancer research currently relies on animal models, mostly rodents. However, animal models mimic **limited aspects** of human breast cancer. The European Commission's Joint Research Centre JRC has carried out an extensive review of the state-of-the-art of advanced non-animal models used for basic and applied research on breast cancer. Researchers characterised and catalogued about **900 models** to make them more accessible for human relevant studies that avoid the use of animals.

"Before reaching the age of 75, 1 in 22 women will be diagnosed with breast cancer and 1 in 73 women will die from breast cancer, worldwide"

IARC Handbooks of Cancer Prevention Volume 15

#### BREAST CANCER AND ITS HETEROGENEITY

Breast cancer is the **most commonly occurring cancer in women** in the European Union and worldwide. The European Cancer Information System (ECIS) estimates that in 2020 over 355,000 women were diagnosed with breast cancer in the EU, accounting for 13.3% of all cancers diagnosed.

Despite advances in early detection and understanding of breast cancer biology, relapse and subsequent metastasis often occurs in bone, lung, liver and brain.

Human breast cancer is **highly heterogeneous**, even within the same tumour. To offer better treatment with increased efficacy, it is necessary to use therapies that match patient profiles and the clinical and molecular characteristics of the tumour.

Breast cancer research currently relies heavily on animal models, which, however, have limitations in capturing important cancer traits.

For this reason, research is gradually moving towards the use of advanced non-animal models that more faithfully represent the characteristic heterogeneity peculiar to human breast cancer.

#### LEGISLATIVE FRAMEWORK

**Directive 2010/63/EU** on the protection of animals used for scientific purposes sets out clear legal

requirements for the implementation of the 'Three Rs' principles of **Replacement**, **Reduction** and **Refinement** of animal procedures. The final goal is the phasing out of animal testing when scientifically valid non-animal alternatives are available.

To aid this transition, the JRC's EU Reference Laboratory for alternatives to animal testing (EURL, EC/AM) produced a unique **knowledge base** of detailed descriptions of non-animal models used for breast cancer research.

#### KNOWLEDGE BASE OF NON-ANIMAL MODELS

About 120,000 scientific papers were reviewed to identify relevant human-based models of breast cancer. From those, a total of **935 models** were selected as being the most representative and promising.

**935 models**



Joint Research Centre

- Technical Report
- Executive Summary
- Leaflets
- JRC Data catalogue



A	B	C	D	E	F	G	H	I	J	K	L	M
Model no.	Disease area	Disease feature	Category	Type	Application/ aim	Biological or disease-specific endpoint	Assay Throughput/ Content	Relevance	Potential/Future developments	DOI	Author name	Year
1	AD	Protein aggregation	Lab/brain on chip or microfluidic system	Proteins	Disease mechanism (exp/theor)	Protein dysfunction: amyloid peptide (any version)	Low-medium/medium	Medium - Attempting to recapitulate fluid-	A more complete in vitro microfluidic system for studying	<a href="http://dx.doi.org/10.1021/acscchemneuro.7b00285">http://dx.doi.org/10.1021/acscchemneuro.7b00285</a>	Gospodarczyk	2017
2	AD	Protein aggregation	Lab/brain on chip or microfluidic system	Proteins	Drug developm/ testing	Protein dysfunction: BACE1	High (automatic)/low	Low - Method of screening therapeutics, BACE1	Could be applied to additional small molecule libraries	<a href="http://dx.doi.org/10.1007/s00216-017-0617-y">http://dx.doi.org/10.1007/s00216-017-0617-y</a>	Liu	2017
3	AD	Protein aggregation	Lab/brain on chip or microfluidic system	Proteins	Diagnosis of disease	Protein dysfunction: amyloid peptide (any version)	High (automatic)/low	Low - Diagnosis of disease by detection of	The high sensitivity of the device suggests that it may	<a href="http://dx.doi.org/10.1038/s41598-017-14338-4">http://dx.doi.org/10.1038/s41598-017-14338-4</a>	Yoo	2017
4	AD	Protein aggregation	Lab/brain on chip or microfluidic system	Proteins	Drug developm/ testing	Protein dysfunction: BACE1	High (automatic)/low	Low - Method of screening therapeutics, BACE1	Could be integrated into fully automated system	<a href="http://dx.doi.org/10.1016/j.chroma.2017.08.065">http://dx.doi.org/10.1016/j.chroma.2017.08.065</a>	Roman	2017
5	AD	Protein aggregation	Lab/brain on chip or microfluidic system	Proteins	Diagnosis of disease	Protein dysfunction: amyloid peptide (any version)	High (automatic)/low	Low - Diagnosis of disease by detection of Amyloid Beta,	May be adapted to detection of other biomarkers	<a href="http://dx.doi.org/10.3390/bios7030029">http://dx.doi.org/10.3390/bios7030029</a>	Dai	2017
6	AD	Neuroinflammation	2D or 3D co-culture	Neurospheres/3D model	Drug developm/ testing	Changed protein expression	High (automatic)/medium	High - throughput of 96well compatible format >1000	Model likely to be used for high throughput drug	<a href="http://dx.doi.org/10.1038/s41598-018-20436-8">http://dx.doi.org/10.1038/s41598-018-20436-8</a>	Jorfi	2018
7	AD	Protein aggregation	Lab/brain on chip or microfluidic system	Proteins	Diagnosis of disease	Protein dysfunction: amyloid peptide (any version)	High (automatic)/low	Low - Diagnosis of disease by detection of	Magnetic Bead assay could be automated for high	<a href="http://dx.doi.org/10.1016/j.snb.2017.09.003">http://dx.doi.org/10.1016/j.snb.2017.09.003</a>	Mai	2018
8	AD	Protein aggregation	Lab/brain on chip or microfluidic system	Proteins	Diagnosis of disease	Protein dysfunction: amyloid peptide (any version)	High (automatic)/low	Low - Diagnosis of disease by detection of	Magnetic Bead assay could be automated for high	<a href="http://dx.doi.org/10.1016/j.bios.2014.10.042">http://dx.doi.org/10.1016/j.bios.2014.10.042</a>	Kim	2015
9	AD	Protein aggregation	Lab/brain on chip or microfluidic system	Proteins	Disease mechanism (exp/theor)	Protein dysfunction: amyloid peptide (any version)	High (automatic)/medium	Medium - Platform for studying in vitro protein-protein	Can be used for a variety of proteins and determination	<a href="http://dx.doi.org/10.1016/j.bios.2014.11.025">http://dx.doi.org/10.1016/j.bios.2014.11.025</a>	Wang	2015
10	Several NDD	Exploratory/ no specific feature	Biochemical/cell-free assay	Fibrils	Disease mechanism (exp/theor)	Protein dysfunction: a-synuclein	Low-medium/low	Medium - Platform for fibril growth (PD-related)	Could be used for identification of compounds that	<a href="http://dx.doi.org/10.1016/j.jmb.2015.01.020">http://dx.doi.org/10.1016/j.jmb.2015.01.020</a>	Woerdhoff	2015
11	PD	Neuroinflammation	Lab/brain on chip or microfluidic system	Co-culture model (multiple cells)	Disease mechanism (exp/theor)	Oxidative/nitrosative stress	High (automatic)/medium	Medium - In vitro platform for investigation of	Could be used to study generation of chemotaxis	<a href="http://dx.doi.org/10.3389/fnins.2016.00511">http://dx.doi.org/10.3389/fnins.2016.00511</a>	Fernandes	2016
12	PD	Protein aggregation	Lab/brain on chip or microfluidic system	Co-culture model (multiple cells)	Disease mechanism (exp/theor)	Protein dysfunction: a-synuclein	High (automatic)/medium	Medium - In vitro platform for investigation of a-	Could be used to study generation of chemotaxis	<a href="http://dx.doi.org/10.3389/fnins.2016.00512">http://dx.doi.org/10.3389/fnins.2016.00512</a>	Fernandes	2017
13	Several NDD	Exploratory/ no specific feature	Lab/brain on chip or microfluidic system	Other	Disease mechanism (exp/theor)	Mitochondrial dysfunction	High (automatic)/medium	Medium - In vitro platform for measuring	Could be applied to specific disease-state models as a	<a href="http://dx.doi.org/10.1007/s13238-016-0268-3">http://dx.doi.org/10.1007/s13238-016-0268-3</a>	Chen	2016
14	AD	Protein aggregation	Lab/brain on chip or microfluidic system	Proteins	Diagnosis of disease	Protein dysfunction: amyloid peptide (any version)	High (automatic)/low	Low - SPR platform used for measuring amyloid beta	High sensitivity suggests could be used for clinical	<a href="http://dx.doi.org/10.3938/kps.69.793">http://dx.doi.org/10.3938/kps.69.793</a>	Kim	2016
15	AD	Protein aggregation	Lab/brain on chip or microfluidic system	Peptides	Disease mechanism (exp/theor)	Protein dysfunction: amyloid peptide (any version)	High (automatic)/low	Medium - In vitro platform for measuring APP	Could be used to investigate neurite specific response to	<a href="http://dx.doi.org/10.1002/adhm.201600895">http://dx.doi.org/10.1002/adhm.201600895</a>	Li	2017

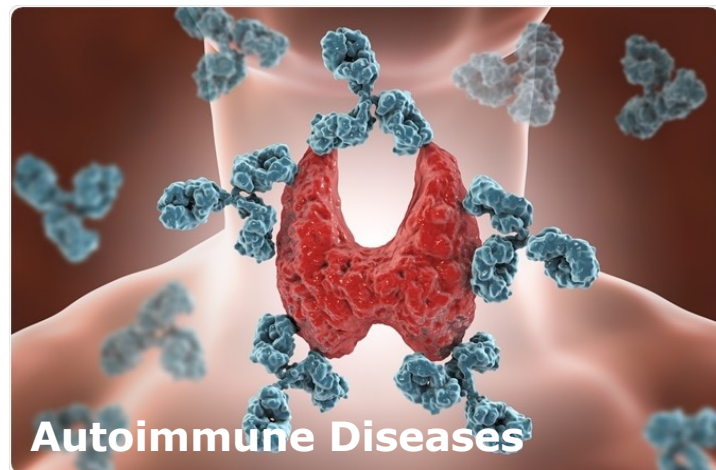
# Main Conclusions

- Extensive use of NAMs (esp. *in vitro*) but clear need for more complex ones.
- Standard operating procedures (SOP) for model generation and testing will be essential and should be encouraged.
- Promote more effective cross-talk and multidisciplinary between different fields - essential for further development of organoid, OoC etc models.

# Dissemination Plan

- **Research groups** submitting a project proposal which makes use of living animals;
- **Animal Welfare Bodies** advising research groups on project proposals;
- **Competent Authorities** who are responsible for project evaluation;
- **National Committees** that facilitate a coherent approach to project evaluation, dissemination of information and sharing of best practice within each Member State;
- **National Contact Points**, who are responsible for the implementation of the Directive in the Member States

# Coming Soon



## Life science research

According to the last [report on the use of animals for scientific purposes in EU Member States](#), in 2019 about 70% of animals were used in basic and in applied and translational research in the fields of human and veterinary medicine.

## Review of advanced non-animal models in biomedical research

EURL ECVAM has launched a series of studies to review available and emerging non-animal models being used for research in seven disease areas:

- respiratory tract diseases
- breast cancer
- neurodegenerative disorders
- immuno-oncology
- immunogenicity testing for advanced medicinal therapy products
- cardiovascular disease
- autoimmunity

### Aim

The aim is to identify and describe specific research contexts where animal models have been put aside in favour of novel non-animal techniques that use, for example, in vitro methods based on human cells and engineered tissues or in silico approaches employing computer modelling and simulation.

### Transition towards non-animal approaches

The expectation is that by understanding and sharing information on successful use-cases of alternative models in biomedical research, the transition towards non-animal approaches can be better facilitated and potentially accelerated.

### Tackling human diseases

Encouraging the uptake of alternative methods is important to tackle such considerable reliance on animal experiments for carrying out research.

Moreover, since alternative methods offer the promise of recapitulating human physiology more effectively than many animal models, shifting to new animal-free methodologies and research strategies can in fact enhance the understanding of human-specific biology and disease.

### The series of studies



#### Respiratory tract diseases

A total of 284 publications were identified as the most representative and innovative models according to a set of inclusion/exclusion criteria.



#### Breast cancer

Around 120,000 peer-reviewed publications were retrieved and screened for innovative and promising advanced non-animal models of breast cancer.



#### Neurodegenerative diseases

We created an inventory of 567 models, ranging from biochemical and computational approaches to different types of cell cultures and procedures using ex vivo human material.



#### Immuno-oncology

542 scientific peer-reviewed articles were selected for a deeper analysis of the non-animal models used.



#### Immunogenicity testing for advanced therapy medicinal products

88 advanced non-animal models were selected as being promising for testing immunogenicity of ATMPs.



# Work in progress



- This year, the EP funded a Pilot Project to develop an **automated database** to collect and structure NAMs for use in biomed research.
- Based on this dataset for training **machine learning** algorithms or **AI**.
- We are launching the project with the aim to complete it by 2024 when a consolidated version of the dataset should be published.

# Thank you!



**EURL**  
**ECVAM**

Views expressed in this presentation are the ones of the presenter and do not necessarily reflect the official views of the European Commission.

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