European Commission

Advanced Non-animal Models in Biomedical Research

Immuno-oncology

Executive Summary

Joint Research Centre

EUR 30334/3 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 being used for biomedical research related to immuno-oncology.

The resulting collection of non-animal models are analysed in a JRC Technical Report (Romania, P., Folgiero, V., Nic, M., Dibusz, K., Novotny, T., Busquet, F., Rossi, F., Straccia, M., Daskalopoulos, E. P., and Gribaldo, L., *Advanced Non-animal Models in Biomedical Research – Immuno-oncology*, EUR 30334/3 EN, Publications Office of the European Union, Luxembourg, 2021, ISBN 978-92-76-39986-5, doi:10.2760/393670, JRC125256) and publicly available from the *JRC Data Catalogue*.

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Immuno-oncology is the study of the immunological mechanisms behind cancer initiation and development with the aim of developing treatments (immunotherapy) that use the body's immune system to fight cancer (see Box 1).

The significant progress made in the immuno-oncology field has clearly demonstrated the feasibility of manipulating immune cells to selectively target cancerous cells and tumours. This approach often achieves better clinical outcomes and improved quality of life in comparison to conventional therapies.

However, the percentage of patients responding positively to immunotherapeutic treatments varies from 20 to 40%[1]. This depends on a variety of factors including the type of cancer and the biomarkers expressed by tumour.

Development of new therapies

A deep understanding of the interaction between the immune system and cancer cells is fundamental to the development of advanced therapies that can effectively activate our immune system to identify and kill tumour cells.

The rapid pace in the science behind immuno-oncology has been pushing the rate of translation of research results into new treatments. In the period 2017 to 2020 alone, the number of immuno-oncology therapies in development increased by 233% at all preclinical and clinical phases of trials[2].

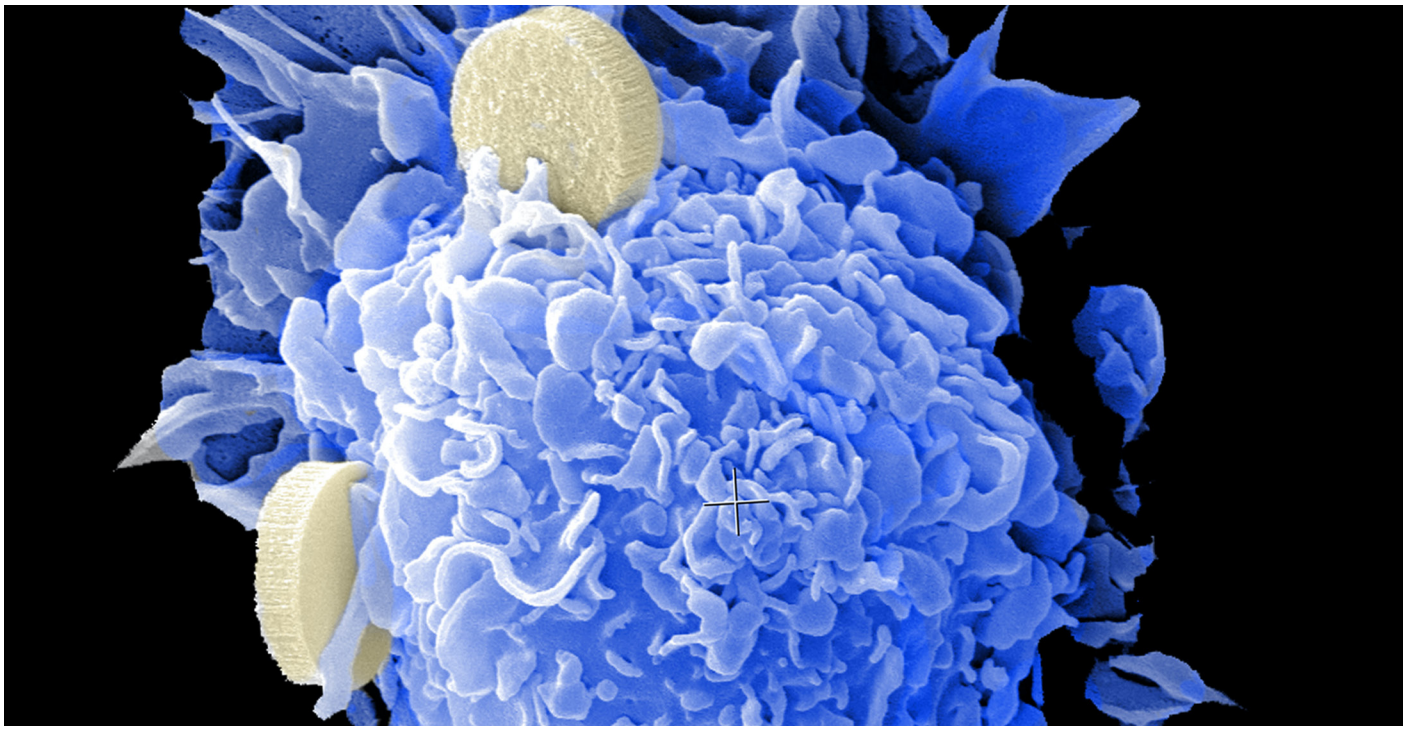
For all main types of immunotherapy (see Box 2) the number of preclinical trials had doubled, with cell therapy representing the greatest increase of advanced therapies being registered.

Trends in immuno-oncology research

Although it is widely recognised that immuno-oncology has the potential to revolutionise

1 Boucherit, N., Gorvel, L., and Olive, D. (2020), 3D Tumor Models and Their Use for the Testing of Immunotherapies, *Frontiers in Immunology*, 11, doi:*10.3389/fimmu.2020.603640*.

2 Upadhaya, S., Hubbard-Lucey, V. M., and Yu, J. X. (2020), Immuno-oncology drug development forges on despite COVID-19, *Nature Reviews Drug Discovery*, 19, 751-752, doi:*10.1038/d41573-020-00166-1*.



cancer treatment, there are nevertheless some major scientific hurdles to overcome to achieve significant clinical impact.

One of these is the need of experimental models for use in preclinical research that capture all the biological intricacies of the human immune system and which demonstrate the array of complex patient responses that can be expected with new therapies.

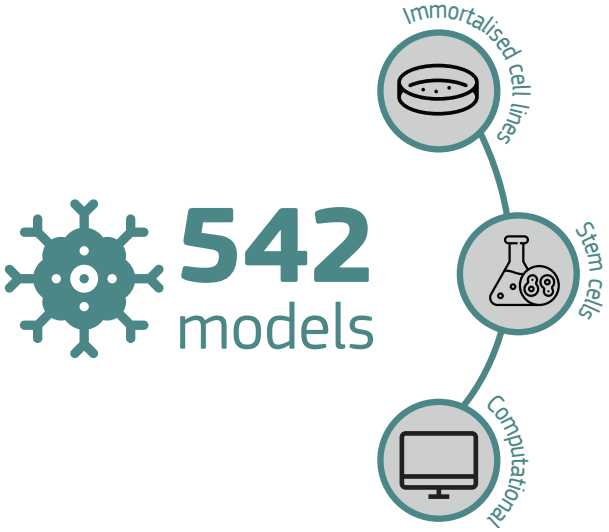
Mouse models are widely used in cancer research. However, human cancer artificially developed in mice leads to species-specific responses that often misrepresent human tumour biology and thus limit the applicability of these tools, resulting in poor translation of research results into the clinic.

One very promising avenue to address this critical research need is the development and application of non-animal models and methods that are more human relevant than conventional animal models.

The JRC's EU Reference Laboratory for alternatives to animal testing (EURL ECVAM) therefore conducted a study to review the state-of-the-art of advanced non-animal models in use for immuno-oncology research.

Categories of advanced models and their applications

The EURL ECVAM study draws on a detailed review of scientific literature published from January 2014 to March 2019 that identified 542 peer-reviewed articles as being the most relevant according to defined criteria.



The review found that six particular types of cancers are most frequently studied with advanced non-animal models, namely, colorectal, breast, melanoma, pancreatic, ovarian and non-small-cell-lung cancers (Figure 1).

The majority of these advanced models were used to study biological mechanisms responsible for cancer initiation and progression, and for research towards the development of better and safer immunotherapies.

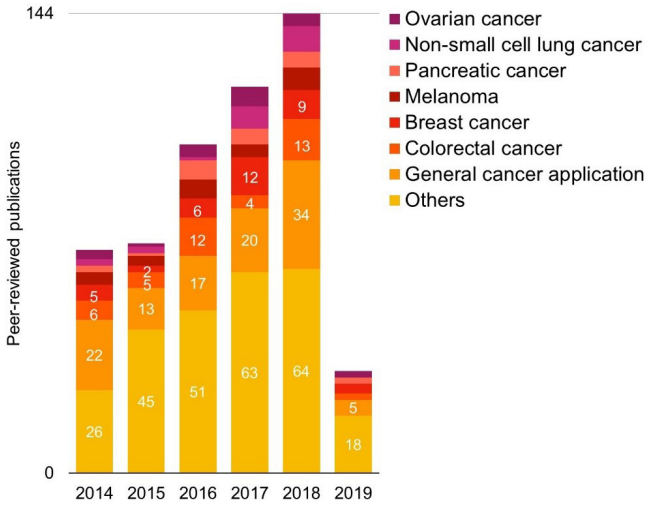


Figure 1: Distribution (cancer type and year of publication) of peer-reviewed articles using non-animal models.

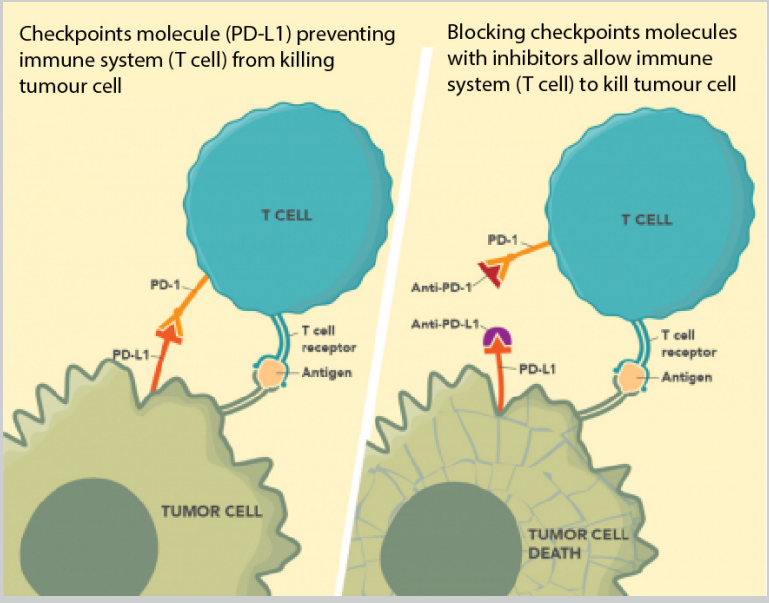
Box 1. Immuno-oncology in a nutshell

The immune system is able to recognise external threats, such as viruses, bacteria or allergens, and distinguish these from normal cells in our body.

As a consequence of normal function and lifecycle, there are always cells in our body that have the potential to turn cancerous. These typically develop a particular biochemical signature that makes them discoverable by the immune system that ultimately destroys them. However, sometimes cancerous cells manage to avoid detection by our immune system and thus become a threat to our health.

Immuno-oncology is the study of the mechanisms behind cancer initiation and development with the aim of discovering potential therapies to prevent or stop cancer evading the immune system.

One such potential therapy targets cancerous cells that evade our immune system by producing immune "checkpoint molecules" on their surface. These molecules are also present on normal cells since they act as normal modulators of immune response. Thus in this way, diseased cells can appear normal and avoid triggering any protective response from the immune system.



Immunotherapy drugs called immune checkpoint inhibitors (see Box 2) work by neutralising the checkpoint molecules that stop the immune system from attacking the cancer cells.

Almost 10% of the publications analysed highlighted the importance of better models and research approaches to assess potential therapeutic strategies.

Although the study found that use of in vitro human-based models in immuno-oncology research is extensive, there is still a clear need for even more advanced models that capture complex human physiology.

High-throughput methods based on non-animal models and 'omics, for example, can deliver big datasets rich with biological information. Such approaches have significant potential both to accelerate translation of relevant research results to the clinic and to support the move towards precision medicine tailored to patients.

The knowledge base

This study has produced a unique and highly curated knowledge base that contains detailed descriptions of 542 advanced non-animal models used for immuno-oncology research. It is freely available to download from the EURL

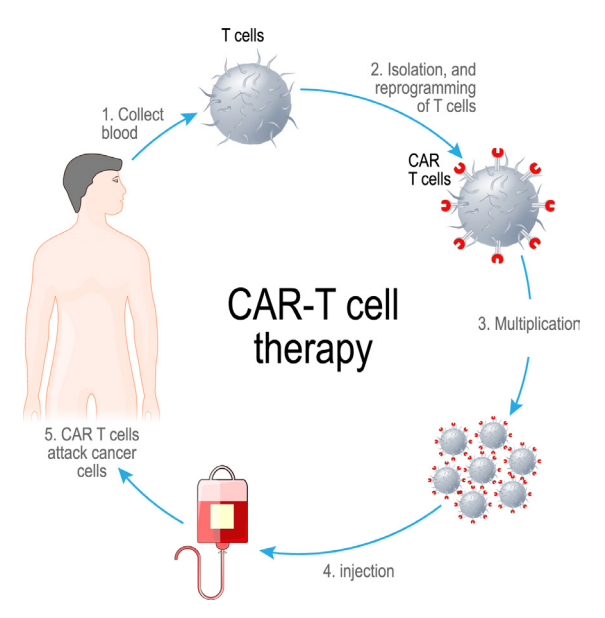
Box 2. Types of immunotherapy

Advanced immuno-oncology therapies use different strategies to augment or re-establish the immune system's ability to prevent and fight cancer, such as:

- Reintroduction of a patient's own immune cells harvested from tissue extracted from their tumour(s), also known as **cell therapy**. These include CAR-T cells or natural killer (NK) cells of the immune system, and can be modified or left unmodified before being administered.

- **Targeted antibodies**, which are proteins created in the lab that are designed to bind to specific targets on cancer cells and thereby trigger an immune response, e.g. monoclonal antibodies.

- **Cancer vaccines** that prevent the onset of cancer by stimulating an immune response against cancer cells. A prominent example of this is the human papillomavirus (HPV) vaccine to prevent cervical cancer.



- **Immuno-modulators** that stimulate or suppress the immune system to help fight cancer such as checkpoint inhibitors or cytokines involved in cellular signalling.

- **Oncolytic viruses** which are modified viruses that can infect and destroy tumour cells. An example is Imlygic (*Talimogene laherparepvec*) for the treatment of adults with melanoma.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ECVAM Collection in the JRC Data Catalogue[3], together with a JRC Technical report[4] 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 properly considered the use of non-animal models and methods in their research proposals;
- **National Contact Points** and **National Committees**[5] can ensure proper knowledge sharing on non-animal methods within Member State networks and organisations involved in biomedical research using animals.

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

3 *https://europa.eu/!6PXVf8*

4 Romania, P., Folgiero, V., Nic, M., Dibusz, K., Novotny, T., Busquet, F., Rossi, F., Straccia, M., Daskalopoulos, E. P., and Gribaldo, L., Advanced Non-animal Models in Biomedical Research – Immuno-oncology, EUR 30334/3 EN, Publications Office of the European Union, Luxembourg, 2021, ISBN 978-92-76-39986-5, doi:*10.2760/393670*, JRC125256.

5 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 being used for research in seven disease areas. Details on the published studies are available on the *EURL ECVAM website*.

In this study around 130,000 peer-reviewed publications on immuno-oncology 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 542 non-animal models being used for immuno-oncology 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 of the review methodology used.

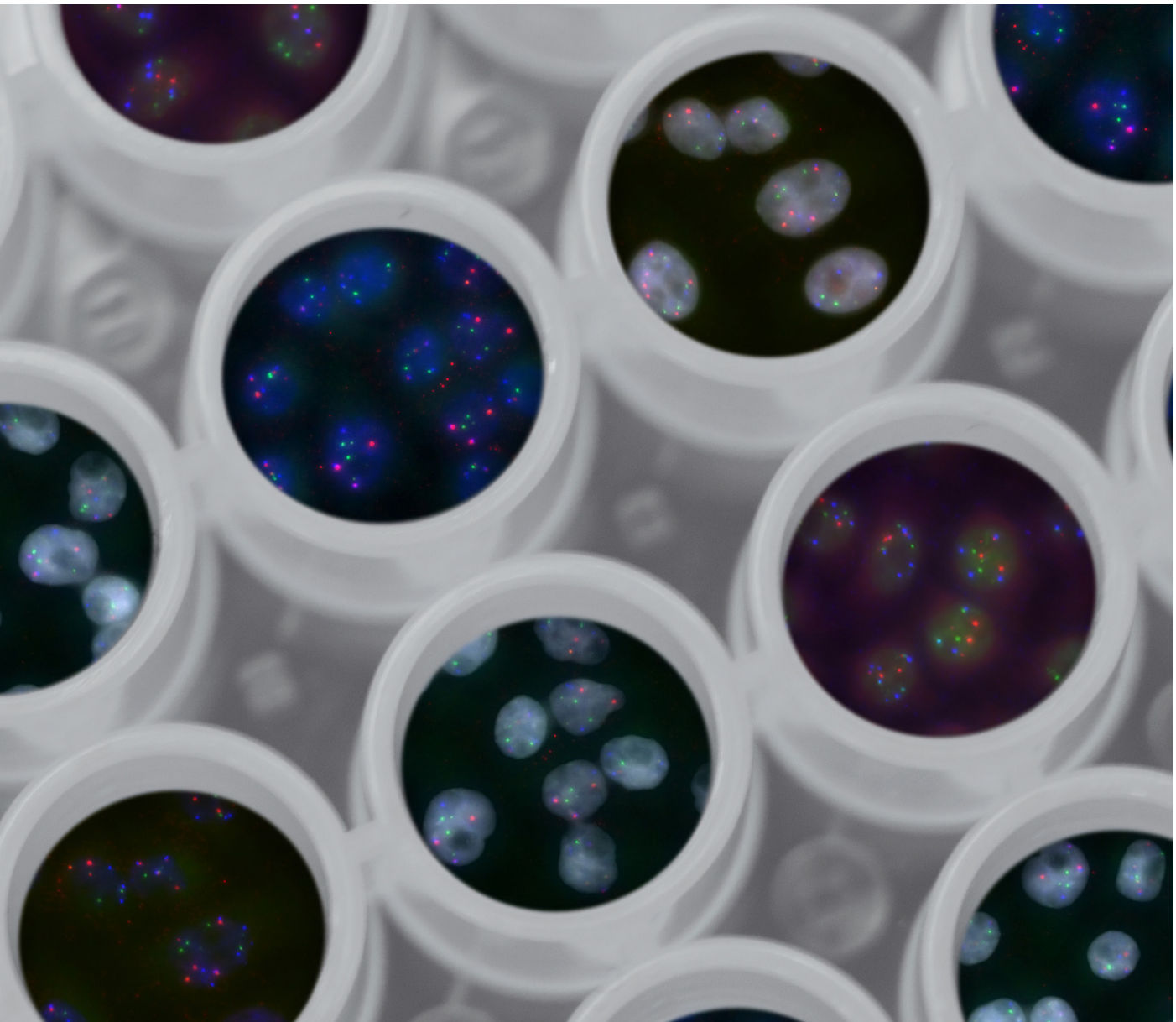
scientific approaches to support Europe's Beating Cancer Plan[6] and Cancer Mission[7].

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[8] to improve biomedical research for the ultimate benefit of patients and society.

6 *https://europa.eu/!xCTWu3*

7 *https://europa.eu/!wt73cr*

8 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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