Science Advancement & Outreach
A DIVISION OF PETA

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Response to Request for Information (RFI): Seeking Input for the National Cancer Institute (NCI) on Advancing Research in Immuno-oncology, Immunoprevention, and/or Immunotherapy (**NOT-CA-22-072**)

People for the Ethical Treatment of Animals
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Cancer has been the second leading cause of death in the U.S. for more than half a century, despite the billions of dollars spent and decades of research conducted. One major roadblock to meaningful progress in immuno-oncology, immunoprevention, and immunotherapy research has been the continued allocation of resources toward research methods using other animals, even though these methods have never been formally validated as relevant to humans,[1] and despite the well-documented low translatability and reliability of this line of research.

As PETA scientists detailed in a November white paper on cancer research, which was sent to NCI along with a joint letter signed by the National Hispanic Medical Association and more than 100 physicians and other health professionals, the National Cancer Institute (NCI) should avoid funding projects using animal models.

The above white paper detailed the many scientific issues with xenograft rodent models, including that the model uses immune-compromised animals, and so are especially poorly suited for research involving immuno-oncology, immunoprevention, and immunotherapy.[2] NCI Director Norman E. Sharpless and former MD Anderson Cancer Center President Ronald DePinho noted many of the problems with these models more than 15 year ago, stating "many agents that show consistent and potent anticancer activity in specific xenograft models prove to be of limited use in the therapy of human cancer. This single fact is a major contributor to the low success rate of novel therapeutics when first tested in humans."[3]

The white paper also noted similar fundamental problems with genetically-engineered animal models, environmentally-induced cancer models in animals, and humanized mice. In a report on the need for more human-relevant models for immuno-oncology research, the European Commission's Joint Research Centre (JRC) noted that even if humanized mouse models were to be improved, they would still be lacking because of the "sub-optimal development of specific human immune cell types … or the residual mouse immune components."[4]

The JRC concluded, "Recent advances in immuno-oncology research highlight the limitations of commonly used animal models in developing new approaches for cancer therapy. These models have failed to recapitulate the variable responses and potential toxicity seen in clinical settings."[5]

The report authors highlighted important publications that describe promising advanced, non-animal models. These studies used human-based, non-animal methods for developing immunotherapies, studying cancer initiation and development, exploring anti-cancer therapies, studying immunomodulation of cancer physiology or potentially effective strategies for enhancing the anti-tumor immune response, determining molecular features that can represent biomarkers in specific cancer pathogenesis, exploring adoptive cell therapies and virotherapies, and more.[6]

In addition, the JRC's report noted the many advantages of tumor-on-chip (ToC) models. According to the JRC, "They are immunocompetent, in that they recapitulate the interplay between immune and cancer cells. They can be personalised by introducing patient-derived autologous primary cells, and they can be treated with drugs and visualised in real time by video microscopy. ToC is a disruptive approach to investigate the drug-dependent plasticity of tumor ecosystems and the mechanisms underlying immunotherapy resistance."[7]

Clearly, there are significant advantages to preferentially funding non-animal methods, instead of experiments on animals. Importantly, scientists using non-animal methods for cancer research are faced with a smaller translational hurdle, because all human-relevant methods are grounded in human—instead of rodent—biology.

To facilitate more productive and relevant immuno-oncology research and protect humans from cancer, the following steps should be taken:

- Reallocate NCI funding to animal-free, human-relevant models and cancer prevention
- Commission an unbiased, multi-stakeholder committee in order to systematically review the translatability of immuno-oncology research in animals to human patients
- Provide regulators and researchers with opportunities to receive free training and information about the use of human-relevant immune-oncology models.

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[1] Matthews RAJ. Medical progress depends on animal models--doesn't it? *J R Soc Med*. 2008;101(2):95-98.
[2] Jackson SJ, Thomas GJ. Human tissue models in cancer research: looking beyond the mouse. *Dis Model Mech*. 2017;10(8):939-942.; Cekanova M, Rathore K. Animal models and therapeutic molecular targets of cancer: utility and limitations. *Drug Des Devel Ther*. 2014;8:1911-1922.
[3] Sharpless NE, Depinho RA. The mighty mouse: genetically engineered mouse models in cancer drug development. *Nat Rev Drug Discov*. 2006;5(9):741-754.
[4] Romania P, Folgiero V, Nic M, et al. *Advanced Non-Animal Models in Biomedical Research: Immuno-Oncology*. Luxembourg; 2021.
[5] *Ibid.*
[6] *Ibid.*
[7] *Ibid.*