EUROGROUP FOR ANIMALS

# Genetically altered animals used in biomedical research

Position Paper

**December 2023**

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## Background

The use of genetically altered animals has become routine within biomedical and pharmaceutical research. Genetic modifications include transgenic, knockout and other forms of genetic alteration, and naturally occurring or induced mutations (European Commission 2020a). Emerging gene editing technologies, notably Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9, have made it possible to remove many technical and economic barriers which, so far, hindered the development of genetically altered animals. Scientists are now able to alter targeted DNA sequences through the adding, replacing, or deleting of one or more DNA base pairs of almost any cell or organism in a simple, fast, and relatively cheap way (Bortesi et al. 2016). For instance, the development of genetically altered mouse models can cost up to 81% less (Liu et al. 2017), and can take less than a month, while previous methods required months or even years to establish such models (Xiao et al. 2021). However, a number of serious ethical, welfare and safety concerns arise from the creation and use of genetically altered animals.

**First, the development of modern gene editing technologies has significantly increased the number of genetically altered animals and species used in research** to understand gene function; create models of human disease; study drug metabolism, chemical toxicity and carcinogenicity; produce organs (Lu et al. 2021; European Commission 2020b; Reardon 2016); and improve the health of companion animals (Sohal et al. 2020). In particular, with the availability of CRISPR-Cas9 technology, the number of genetically altered non-human primates is increasing, with a number of researchers arguing for their necessity in biomedical research (Kang et al. 2019; Luo, Li, and Su 2016). Since the

breeding of genetically altered animals is subject to the laws of genetics, the offspring do not always carry the genetic alteration of interest, and large numbers of animals are killed without being used in a study (the Netherlands National Committee for the protection of animals used for scientific purposes 2015).

Furthermore, millions of animals are killed every year for the sole purpose of 'producing' a modest number of genetically altered animals for scientific procedures. According to the latest EU statistical data on the use of animals for scientific purposes, of the 10 million animals involved in genetically altered research, 2.65 million were used for research purposes, 1.21 million were used for the creation and maintenance of genetically altered lines, while more than 6.1 million animals were bred and killed for the creation and maintenance of genetically altered lines, but not used in scientific procedures (European Commission 2020b; European Commission 2022). The large number of animals required to produce viable offspring carrying the desired genetic alteration is best illustrated in non-human primates. A recent study has shown that the percentage of embryos that are transferred and result in a live, gene-edited non-human primate offspring ranges from 0 to 16.28%, despite the transfer of a large number of embryos to many surrogate mothers (Schmidt et al. 2022). While suggestions have been made that modern gene editing technologies can help reduce the number of animals needed for research (eBioMedicine 2022; Kim, Moon, and Kim 2019; Greenfield 2017), it is more likely that the number of genetically altered animals will further increase as researchers look to apply genetic technologies involving animals to more and more areas of scientific research .

**Second, the impact of gene editing on animal welfare is a major concern.** The creation of genetically altered animals involves procedures that may cause pain, suffering and distress at every step (Bailey 2019), and gives rise to animals that can exhibit a variety of phenotypes, some causing no adverse effects, and some causing adverse outcomes and lasting harm (European Commission 2021a). In addition, unintended DNA alterations adjacent to, or away from the target site are persistent and often more significant than expected (Höijer et al. 2021; Ono et al. 2019; Kosicki, Tomberg, and Bradley 2018), and can lead to the loss of function of non-targeted genes, causing adverse outcomes and fatal abnormalities (Bailey 2019; Komor, Badran, and Liu 2017). Despite the many efforts to detect and reduce these on- and off-target effects, they still remain incredibly high, and may never be completely removed. Moreover, CRISPR-Cas9 technology can alter genes at different stages of embryonic development resulting in organisms carrying altered and unaltered cells (Mehravar et al. 2019), a condition that can cause severe health problems

(Ishii 2017).

**Third, the generation of humanised, transgenic and chimeric animals raises serious questions about the boundaries between animals and humans.** These animals are used to produce organs, tissues and pharmaceuticals for human benefit (Koloskova et al. 2020; Hryhorowicz et al. 2017; Wu et al. 2017; Bourret et al. 2016), or in basic research dissociated from any direct, tangible societal benefit (Shi et al. 2019; Mansour et al. 2018). Ethical concerns related to the breeding and use of these particular genetically altered animals include the generation of traits in animals that are considered to be exclusively or typically human, and the exploitation of animals by using them as research tools or organ donors for uncertain human benefit.

Finally, while it is widely claimed that modern gene editing techniques, notably CRISPR-Cas9, can make a major contribution to improving our knowledge of human diseases, and advancing research by developing efficient treatments (Wong et al. 2021; Alagoz and Kherad 2020; Lee, Yoon, and Kim 2020; Birling, Herault, and Pavlovic 2017), **the failure of many genetically altered animal models to accurately predict human response to drugs and disease is increasingly acknowledged in scientific literature** (van der Velden et al. 2022; Bailey 2019; Wagar et al. 2018; Akhtar 2015; Garner 2014; Greek and Hansen 2013). Animal-human species differences, the inability to recreate complex human diseases in other animals, the poor applicability of animal-based models to clinical settings, and adverse effects of laboratory procedures and conditions on animals' physiology and behaviours are some examples of key factors that contribute to the poor rates of translation of findings from genetically altered animals to humans. Furthermore, safety issues related to CRISPR-Cas9 technology are being addressed at multiple levels as the high frequency of undesired DNA alterations caused by the gene editing process raises serious concerns for therapeutic and clinical applications (Teboul et al. 2020; Kanchiswamy et al. 2016; Fu et al. 2013).

**Genetically altered human-based cell lines and organoids have already shown potential for enhancing our understanding of human diseases and accelerating the discovery of effective treatments** (Hendriks, Clevers, and Artegiani 2020; Bassett 2017; Brookhouser et al. 2017; Driehuis and Clevers 2017). The genetic alteration of human-based models has many advantages as it adds another level of sophistication that allows the study of genes and mutations in different human genetic backgrounds, as well as the establishment of cellular models of disease from individual patients, offering therefore exciting possibilities

for precision medicine (Tang et al. 2022; Wang, Ye, and Jang 2021). The combination of gene editing technologies and human-based models also provides a unique opportunity to study human disease-associated mutations that cannot be investigated in other animals due to a low degree of conservation of these mutations between species (Bassett 2017). Additionally, while unintended DNA alterations are a serious ethical and welfare concern in animals, they can be thoroughly studied in human cell lines without raising such concerns.

Transitioning to non-animal models can reduce the failure rate during drug development and significantly improve our understanding of human diseases by producing data based on human biology, leading to effective and personalised therapies (Ewart et al. 2021; Hutchinson, Owen, and Bailey 2022). The toolbox of non-animal models has considerably grown in recent years and includes, for instance, organ-on-chip technology, sophisticated computer simulations, and 3D cultures of human cells (Madden et al. 2020; Clevers 2016; Adcock et al. 2020; Romania et al. 2021; Rossi et al. 2020; Witters et al. 2021; Wilkinson 2019; Merkes 2019).

Furthermore, growing complex artificial organs on demand *in vitro* will be a game-changer in the field of organ transplantation that might become reality within the next decades. For instance, human organoids and human tissue and organ engineering using 3D bioprinting technologies are examples of promising human-based solutions to meet the demands for human organ and tissue transplantation (Tang et al. 2022; Hsia et al. 2021; Klak et al. 2020; Noor et al. 2019). In the meantime, possible alternative approaches to the use of genetically altered animals as organ donors exist, and could be further enhanced, including for example facilitating wider support for the deployment of public health policies that presume consent (or default 'opt-in') for organ donation.

**Large sums of money are flowing towards animal-based research methods, whereas investment in non-animal based research is still very limited.** In Horizon 2020, approximately 48 million Euros have been committed annually to research projects directly aimed at developing non-animal methods, but this amount represents only 0.5% of the total annual budget of this EU framework programme. With regard to gene editing, a recent study published by the European Commission revealed that, from 2007 to 2020, EU research and innovation funding for new genomics techniques in health and medical-oriented research amounted to €2.5 billion, of which €1.2 billion was dedicated to animal studies using whole organisms, and €1.8 billion to basic research projects focus-

ing on changes to the genetic material of cells *in vitro* (European Commission 2021b). However, the report does not specify the species from which these cells were collected. With CRISPR-Cas9 becoming the gene editing tool of choice in biomedical and pharmaceutical research, increased financial support for animal-based research to develop novel gene editing techniques can be expected under the 2021-2027 EU framework programme (Horizon Europe).

## Eurogroup for Animals' position

Eurogroup for Animals is opposed to the use of animals in science, testing and education which causes animals pain, suffering, distress or lasting harm. This includes the use of genetically altered animals in biomedical research given the serious ethical and animal welfare concerns that it raises. We strive for a paradigm shift in society, policy and academia towards humane, innovative, and animal-free science that can offer more effective and accurate humane solutions for biomedical research. Until full replacement of animal experiments is achieved, all projects involving the use of genetically altered animals for scientific purposes must be subject to a rigorous, transparent and publicly accountable system of regulation, oversight and inspection. This should include a critical, independent review of the justification for, and the scientific or wider societal benefits or impacts of, the development or use of genetically altered animals, as well as a rigorous assessment of how well the 3Rs principles (replacement, reduction and refinement) have been applied.

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