ANIMAL-HUMAN CHIMERAS : *State of play and bioethical questions*

European Institute of Bioethics

Introduction

The recent development of experiments with chimeras (i.e. an individual carrying cells with different DNA) could stir our imagination by the spectre of fabulous and frightening creatures. Above all, it raises fundamental ethical questions. Although this research is still in its infancy and is currently limited to fairly isolated experiments, it arouses the interest of the international scientific community and challenging legislators. In February 2018, at the congress of the *American Association for the Promotion of Science* (AAAS) in Austin (Texas), the first results of an experiment with human-sheep chimera embryo were presented.

For many scientists, the creation of chimeras would be one of the most promising medical advances of the 21st century which would lead to a better understanding of the development of the human embryo and to the production of human organs in animals in order to meet a growing need for transplants. Note that in 2017, 24,000 people were waiting for an organ transplant in France[1] and 1,300 in Belgium.[2]

It has been found that the latest scientific publications and the articles in the general press on the subject tend to present chimerism as the only solution to the shortage of organs. Some argue for a relaxation of the legislation relating to these experiments. Cautiously stating a '*science fiction scenario*' some scientists want to temporarily put the ethical questions about the ongoing research on hold and in any case not regulate it too strictly. However, the questions are not minor: under what conditions is the mixing of human organs or cells in animals permissible? Is the breeding of animals for the sole purpose of reconciling the supply of human organs compatible with human dignity or with animal welfare?[3]

The *European Institute of Bioethics* wishes to contribute to this ethical reflexion with the present dossier.

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1 According to the Activity report 2017 of the *French Agence de biomédecine*, published 2018

2 Aude Quinet in the Belgian newspaper La Libre *On manque toujours de donneurs d'organes*, of 13/02/2017

3 Florence Rosier in the French newspaper Le Monde *Des premiers embryons chimériques homme-singe ont été créés* of 18/04/2021

I. The current state of science

a. What preceded

In genetics, a chimera is **an organism or tissue whose cells simultaneously** have the characteristics from two or more individuals of the same species (intr**a**specific chimeras) or of different species (int**er**specific chimeras).[4] However, the common language associates chimeras with beings from **two different species**.

First of all, we must distinguish between **artificial chimeras** (created by human intervention) and **natural chimeras or hybrid beings** (which are present in nature).

The **natural chimeras** have always existed and are the product of hybridisation between two animal species through natural reproduction. The best known are the mule (cross between a mare and a donkey), the wolfhound, the wild pig (cross between a pig sow and a male wild boar), the zebroid (crossing of a donkey and a zebra) and the liger (crossing of a lion and a tigress). In fact, *'hybridisation mainly occurs in closely related animal species, and those hybrids do not even have a name*.' These crossings are often dysfunctional, leading to varying degrees of infertility and even sterility.[5]

Experiments with **artificial chimeras** began in the early 20th Century with attempts to give a living (animal) species the genetic characteristics of an extinct species (e.g. the mammouphant project: crossing a mammoth with an elephant).[6]

In that period (1924), the Russian biologist Ilya Ivanovich Ivanov ventures into a controversial **human-animal experiment**: he artificially inseminated a female monkey with human sperm. Although the two species are very close, if not the closest, in terms of gene structure, it failed to induce a pregnancy.[7]

From the sixties onwards, the complexity of experiments with animals increased. In Warsaw and Yale, André Tarkowski and Béatrice Mintz managed to '*merge*' two mouse *embryos*[8]. The resulting chimeric embryo bore the genetic characteristics of all four parents.

In **1969** in France, Nicole Le Douarin created the **first interspecies chimera embryo** by transplanting a fragment at the site of quail spinal cord where chicken wings are formed. In **1984**, the first viable goat-sheep chimeras were born at the Cambridge Institute of Animal Physiology coated with a mosaic of hard hair and wool.[9]

In **2007**, three teams of British biologists succeeded in creating human-rabbit and a human-cow chimera embryo by placing the nucleus of a human cell in the animal's pre-denuclearized oocyte, embryos that were destroyed after 14 days in accordance with the law.[10]

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4 Nicole Le Douarin *Des chimères, des clones et des gènes*, Paris, Odile Jacob, 2000.

5 Read on this topic: the Wikipedia keyword Hybrid (06/08/2022)

6 Read about this '*resurrection experiment*': the Wikipedia keyword *De-extinction 4.1. the woolly mammoth* (17/05/2021)

7 Wikipedia keyword: Ilia Ivanovs (19/05/2021)

8 Jean-Yves Nau in the French newspaper Le Monde: *La chèvre-brebis de Cambridge. Une prouesse technique des chercheurs anglais*, 05/03/1984

9 Jean-Yves Nau *La chèvre-brebis de Cambridyou* (cited in footnote 8)

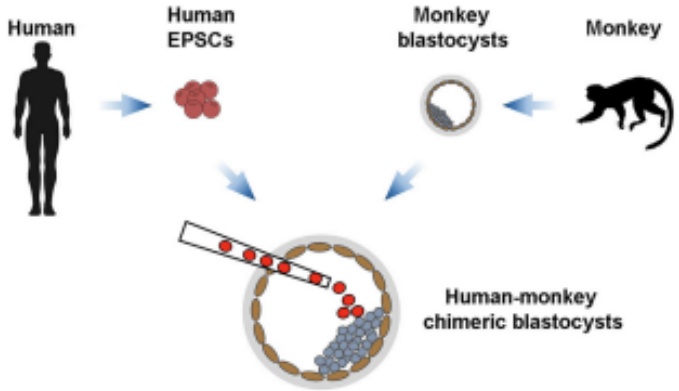
10 Jean-Yves Nau reported on this British human-animal experiment in Le Monde: Des équipes britanniques vont créer des embryons mêlant l'humain à l'animal of 06/10/2006

In **2010**, Hiromitsu Nakauchi's team conceived the birth of mice with a rat pancreas. These animals led an almost normal life for two or three years. They were the first team to breed interspecies chimeras.

In **2013**, researchers at the State University of New York at Buffalo teamed up with *Roswell Park Comprehensive Cancer Center* created the first chimeric mouse-human embryos; these contained 4% human DNA and survived for 17 days of embryonic maturation.[11] **These results revived hopes for a better understanding of human pathology**: if we manage to maintain human cells in animals, once contaminated, we can study how these cells behave in order to better understand and treat the pathology.

For several decades, researchers introduced human cancer cells into adult animals to observe their multiplication and metastasis. and then to find out which therapeutic molecules can be used to eliminate them. This adult-stage chimerisation process is also used to study how *'stem cells promote the repair of damaged organs in certain degenerative diseases*.'[12]

There are two types of chimeras mixing man and animal at the embryonic stage: the first results of the insertion of animal cells into a human embryo; the second from the introduction of human cells into an animal embryo. In the second case, the researcher places in the animal embryo (which has about ten stem cells at that stage) between 5 and 10 human stem cells derived from human embryos either conceived in vitro or from somatic cells that have been reprogrammed into pluripotent stem cells.[13] This intervention at an early stage (blastocyst) is intended to allow the inserted human cells to contribute significantly to the development of the (animal) embryo. During cell division, if the embryo survives, these cells compete with the animal cells. Division and differentiation then takes place without the DNA of the two species mixing. Nevertheless, different types of human and animal cells may be found in the same organ. When cells interact with their developmental environment, cell mutations cannot be ruled out.



Graphic of an animal-human chimerisation process[14]

[11] Read: Grégoire Ryckmans' article on the website of the Belgian Radio RTBF: *Des scientifiques créent un embryon de souris contenant 4% de cellules humaines, ouvrant une voie à la fabrication d'organes humains*, article of 25/05/2020. Also: Zhixing Hu, Hankin Li, Houbo Jiang, et al. *Transient inhibition of mTOR in human pluripotent stem cells enables robust formation of mouse-human chimeric embryos* in the journal Science Advances of May 2020

[12] Press article published on 09/03/2021 in the French journal Le Monde: Les chimères homme-animal sont une alternative à l'expérimentation humaine

[13] Also called: induced pluripotent stem cells

[14] Chart taken from Tao Tan et al., *Chimeric contribution of human extended pluripotent stem cells to monkey embryos ex vivo*, Cell Press Journal, 15/04/2021

In 2014, the team of the Spanish Juan Carlos Izpisua Belmonte produce mouse-rat and mouse-pig embryos of 28 days thanks to a special authorisation of experimentation from his university.

However, in order to succeed in **developing human organs in animals** – a goal that has gradually become the most prominent when talking about chimeras – it is necessary to experiment on larger animals whose organ functions are more similar to humans. In 2017, an experiment conducted on human-pig embryos showed[15] that human cells contribute little to the development of the embryo. In February 2018, researchers at Stanford University created sheep-human chimera embryos.[16] When destroyed after 28 days, they were able to establish that less than 1% of the cells found in these embryos were human.

The year 2021 was particularly productive in chimerical experiments. On 12 January 2021, the INSERM France team published the results of a study with monkey-human chimeras in the journal *Stem Cell Reports*[17]. In an attempt to colonize rabbit embryos (rabbits are at the same evolutionary distance from humans as mice), the team first observed the respective chimeric ability of the induced pluripotent cells of mice and humans. Then, they focused on improving the colonizing ability of human cells in more suitable environments, such as monkey embryos, which are at a shorter evolutionary distance. The study concludes that the chimeric capacity of human cells (i.e. the ability to contribute to embryonic growth) is very low, potentially improving, if there is a greater (evolutionary) proximity between species.

On 15 April 2021, a Chinese team associated with the Belmonte team enthusiastically announced that human-ape proximity would open the way to promising chimeric experiments. However, the results were in line with those of the French INSERM team. Specifically, the team, per macaque embryo, inserted 25 human stem cells into a total of 132 embryos. Only three survived for as long as 19 days, and human cells accounted to only 5 to 7% of the embryo's cells.[18]

b. The technical limits of xenotransplantation

If today chimeras are the subject of so much attention from the scientific world but also from public opinion, it is because the promise of xenotransplantation is associated with them.

In xenotransplantation, cells, tissues or organs are transferred from one species to another. Most often animal organs (e.g. pigs) are transplanted in humans.

Today, in addition to mechanical prostheses, biological prostheses are very common. They are made of animal tissue, such as heart valves made from pig, bovine or horse tissue [19] The xenotransplantation of a complete organ is still in the experimental phase and the chance that it succeeds is still uncertain. In order to improve this, a human organ that is perfectly compatible with the recipient should be able to develop in the animal. However, the complexity of human genetics makes the chances of a viable animal-human chimera uncertain. As we have seen, the human cells are characterized by a low

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15 Jun Wu et al., *Interspecies Chimerism with Mammalian Pluripotent Stem Cells*, Cell Press Journal, part 168, no. 3, January 2017, pp. 473-486

16 Michael Greshko, *Sheep human hybrids chimeras crispr organ transplant health science* in the National Geographic, 18/02/2018

17 I. Aksoy et al., Apoptosis, G1 Phase Stall, and Premature Differentiation Account for Low Chimeric Competence of Human and Rhesus Monkey Naive Pluripotent Stem Cells, in: Stem Cell Reports, Vol. 16, number 1, p. 56-74, 12/01/2021.

18 Belmonte et al., *Chimeric contribution* (cited in footnote 14)

19 According to the report of the French Agency for National Security for Medicines and health products (ANSM): *Surveillances des dispositifs médicaux implantables*, Report 2018

chimeric capacity, witch means that they contribute only to a limited extent to the organic cell structure. In addition, a relatively large number of aborted (human) embryos are needed. All this casts doubt on the feasibility of xenotransplantation.

The human gene structure is very different from the other living species. If cells or organs are mixed between species, the risk of graft rejection increases. Incidentally, the development of human organs in an animal body is not self-evident because the animal vascular system works very different from that of humans and has a significantly lower blood flow. It is questionable whether such organs can perform the same functions in the human body. In organ transplants onto an animal body, rejection appearances can occur, which also limits the chances of success of a normally developed chimera. The question of the advisability of chimeric research has thus been raised, which leads a well-known bioethicist to conclude that '*the uncertain success of the experiments and the high risk of rejection are probably sufficient to oppose them*'.[20]

b. Health risks

Mixing species, especially in animal-human chimeras, is not without serious health risks at the local population or even worldwide. In a study adopted by the French Council of State as reference for the revision of the bioethics law, it concluded that experiments with chimera embryos can entail a high risk of **new zoonoses** (i.e. infection or infestation which can naturally transmit from vertebrate animals to humans and vice versa).[21] For example, endogenous retroviruses of one species (which is adapted to them) may infect other species not immune to them. George Church's team at Harvard University (Boston USA) succeeded in inactivating the DNA sequences encoding endogenous porcine retroviruses. However, there are still other factors in pigs that cause rejection by the human immune system or can harm humans.[22]

The Covid-19 pandemic has demonstrated the extent that a viral contamination can take, compared to previous pandemics such as H1N1 flu or mad cow disease. Viruses to which the immune systems of humans and animals react differently can spread rapidly in a globalized world and can mutate regularly in close contacts.

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[20] Elio Sgreccia, chapter Le cas de la xénotransplantation of his Manuel de Bioéthique. Les fondements et l'éthique biomédicale, , éd. Mame EDIFA, 2004

[21] Conseil d'État Français: Révision de la loi de bioéthique: quelles options pour demain?, Report of 28/07/2018, p. 186

[22] Celine Deluzarche, *Record: plus the 13,000 CRISPR modifications effectuées dans une seule cellule!*, article in Futura Santé, 01/04/2019

II. The legal framework around chimeras

The scientific reality of animal-human chimeras is not unambiguous and therefore difficult to grasp in a **legal framework**. 'Human-animal crosses disrupt the existing legal categories: the question arises whether a 'humanised' animal is always subject to property law or does it become a person' [23] Scientists often retort that so far only human cells are inserted into animals and are not otherwise. They suggest that a legislative framework takes a positive approach to the therapeutical, scientific and xenotransplantation promises of current chimeric techniques.[24]

In any case, the international scientific community today **unanimously rejects** the **insertion of animal cells into the human embryo**.[25] However, it cannot be ruled out that this position will evolve if more flexible legislation is established in countries (such as e.g. Japan) which play a leading role in this field. We note that the International Society for Stem Cell Research (ISSCR) in its most recent guidelines of May 2022 no longer prescribes a legal limit of 14 days for keeping in vitro conceived human embryos alive.[26]

a. Belgium

The law allows the creation of embryos specifically for research.[27] Nevertheless, the **implantation of human embryos in animals or the creation of chimeras or hybrid creatures** is legally prohibited. The law also prohibits the implantation of embryos intended for research in humans, unless this research for therapeutic purpose (e.g. to detect a genetic or sex-related disease of the child) or for observations that does not affect the integrity of the embryo. Chimerism is therefore basically forbidden in both directions.

b. France

In **France**, Article L. 2151-2 of the Code of Public Health prohibits the insertion into a human embryo of cells of another species. The bioethics law (amended in 2021) allows the **input of human** (embryonic or induced pluripotent) **stem cells into an animal embryo and their transfer to the female on simple declaration** at the Agence of biomédecine.[28]

c. The United Kingdom

In the **United Kingdom**, the **Human Fertilisation and Embryology Act 1990** permits **chimerisation**, in particular the insertion of human cells into animal embryos and their transfer to an animal uterus,

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[23] Jean-Rene Binet, Fasc. 5: *Présentation générale de la loi relative à la bioéthique*, in: Juris-Classeur du Code civil, art. 16 until 16-14, 2012, no. 47 a.f.

[24] Jean-Paul Soulilou *Xénotransplantation, une chimère nous rattrape*, Médecine/Sciences, 13, 1997, p. 295-298

[25] See Prof. Pierre Savatier's Reporting to the French Parliament: *Compte-rendu n°24 de la Commission spéciale chargée d'examiner le projet de loi relatif à la bioéthique*, 04/09/2019

[26] Read about a possible extension of the 14-day period: the news item from Constance du Bus *The International Society for Stem Cell Research (ISSCR) drops the 14-day limit on human embryo research*, European Institute of Bioethics, 30/06/2021

[27] Art 5 1° of the Law of 11/05/2003 *on in vitro embryo research*; see also: Art. 10 of the Law of 06/07/2007 *on medically assisted reproduction and the destination of supernumerary embryos and gametes*.

[28] French Law No. 2021-1017 Loi *relative à la bioéthique* of 02/08/2021; *Article L. 2151-6 & 7 of the French Code de La Santé publique*.

provided that the animal DNA remains '*predominant*' over human DNA.[29] However, the definition of *'human predominance*' is not legally established and remains subject to the appreciation by researchers.[30] In any case, embryo chimeras that do not meet the condition cannot be implanted and must be systematically **destroyed after 14 days** (e.g. embryo's containing animal cells or animal embryos with predominantly human DNA…).

d. Germany

In **Germany**, the addition of animal cells to a human embryo is **prohibited by law**, but the reverse is possible.[31] In its 2011 opinion, the German Ethics Council (*Deutscher Ethikrat*[32]*)* calls for amendments to the Animal Welfare and Embryo Protection Act to strike a balance between the expected medical benefits of chimeras and respect for animal welfare. It also calls for a ban on the addition of human **nerve cells** to the brains of great apes, the transfer of animal embryos to humans, the insertion of animal material into human germ cells and the creation of chimeras capable of producing human gametes. Today, the questions raised by this opinion have not yet been subject of legislation.

e. The United States

In the **United States** no federal law regulates experiments with chimeras containing human organic matter. In 2005, the National Research Council and the Institute of Medicine recommended imposing limits on this research and, among other things, a ban on the insertion of human stem cells into primate embryos and the creation of human-animal chimeras.[33] In 2015, the National Institute of Health (NIH) imposed a moratorium on federal funding of human-animal chimeric research pending its ethical content being investigated. This issue was only opened in 2021.[34]

f. Japan

Since 2019, Japan has allowed the creation of animal embryos with human cells and their implantation in an animal uterus.[35] Until then, there was a ban on keeping these embryos alive for more than 14 days after fertilisation.[36]

g. International recommendations[37]

The World Health Organization (WHO) has published a report on the risk of inter-species infection (zoonosis) contained in chimerism. It calls on the national health authorities to give their opinion on

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[29] About the so-called '*human admixed embryos*': see Article 31, Part I, Section IV of the *Human Fertilisation and Embryology Act 1990*, changed in 2008

[30] Antonio Regalado, *Human-Animal Chimeras Are Gestating on U.S. Research Farms* in Technology review of 06/01/2016

[31] German *Gesetz zum Schutz von Embryonen* of 13/12/1990 (Embryonenschutzgesetz - ESchG)

[32] Advice the German Ethikrat: *Mensch-Tier-Mischwesen*, 2011, p. 123

[33] Gretchen Bird, *Major grant in limbo, NIH revisits ethics of animal-human chimeras*, 2015, pp. 1–6

[34] U.S. National Institutes of Health (NIH): *Report on human neural organoids, transplants, and chimeras*, 2021

[35] Loup Besmond de Senneville, *Le Japon ouvre la voie aux embryons chimères*, article in the daily newspaper La Croix of 02/08/2019

[36] Sophie Bécherel, *Le Japon autorise la création d'embryons humains-animaux pour permettre la production d'organes dans l'animal*, article on the website of Radio France Inter published on 01/08/2019

[37] This overview is inspired by the table contained in the memorandum for the French Senate published 08/06/2021 in view of de the amendment of Article 17 of the '*Projet de loi relatif à la bioéthique'*

this health risk. In this context, the U.S. *Food and Drugs Administration* and several national authorities consider that for the moment the potential benefits of these techniques warrant their further development if due care is taken and more knowledge about the health risk of experiments with chimeras is gained.[38]

At the European Union level, a 1998 directive prohibits any industrial and commercial use of human embryos, without, however, mentioning research on embryos (chimeras or not). [39] In addition, a project funded by the European Union must comply with the laws of the country where the research is carried out.[40] Although the European Commission no longer funds research that destroys embryos and isolates new human embryonic stem cell lines, it nevertheless allows the funding of experiments on human embryonic stem cells resulting from these techniques. In itself, therefore, a research project in which these cells are inserted into animal embryos is not prohibited.[41]

The **International Society for Stem Cell Research** (ISSCR) recommends a ban on the transfer of chimeric embryos to humans or monkeys, as well as research involving the reproduction of chimeras or the formation of human gametes.[42]

III. Ethical considerations in chimeric research

a. The importance of ethical reflection on chimeric techniques

For researcher Frank Yates, **three essential points** call for rapid regulation of the issue of chimeras.[43] **If legislating delays too much**, the ethical issues and the many open questions will only complicate the **debate on chimeric experiments**. It is indeed difficult to **prohibit** posteriori practices that already take place openly in some countries and are even the subject of international publications. So we need to establish a clear moral and legal framework now that determines the fate of animal-human chimeras in case they come into the world. Finally, legislating also means taking into account the '*sensitivity to these topics in **public opinion***', while for the researcher 'an ***open debate*** is *essential*'.

In the research on chimeras, the **principle of prudence** should be the rule. It 'encourages policy makers to take protective measures if there is insufficient scientific evidence of the effects on the environment or health and of the major challenges that the research poses'[44]. In addition, the research must **observe** the **proportionality test** as elaborated by the Swedish philosopher Göran Hermerén[45] and more specifically:

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[38] J.A. Fishman, L. Scobie, Y. Takeuchi, *Xenotransplantation-associated infectious risk: a WHO consultation*. Xenotransplantation, 2012, No 19, p. 72–81.

[39] European Union: Directive 98/44/EC of the European Parliament and of the Council of 06/07/1998 *on the legal protection of biotechnological inventions*

[40] European Union: Horizon 2020, the EU framework program for research and innovation funding.

[41] Flash Expert of the European Institute of Bioethics: *La Commission européenne et la recherche sur les cellules souches embryonnaires humaines*, 11/2021.

[42] ISSCR, Guidelines on Chimeras, 2021

[43] Florence Rosier, *De premiers embryons chimériques homme-singe ont été créés* (cited in footnote 3)

[44] Thus the report of the Research Service for members of the European Parliament (EPRS), *Le principe de précaution. Définitions et gouvernance*, 2015

[45] Göran Hermerén, The principle of proportionality revisited: interpretations and applications, Medical Health Care, Philos, 2012, no. 15, p. 373-382

a. make clear the **importance of the research** for science and/or society
b. to have a **sufficient resource budget** to enable research to be carried out successfully
c. to choose **the most favourable option** rather than more controversial or risky ones
d. **not excessive** use of the available resources in relation to the desired goal, taking into account the strictly necessary costs of the project and the costs for society.

In an opinion article in the French newspaper Le Monde, a Collective of Scientists argued that chimeras were essential to **better understand the mechanisms of embryonic development** (possibly with an improvement in medically controlled reproductive techniques) and offer new possibilities for **better treatment of cancers and degenerative diseases** (e.g. Parkinson).[46] In the longer term, chimeras could be used to produce grafts. The chimera would be an alternative to experimentation on humans, more reliable than animals, to test the effectiveness of therapeutic treatments and their side effects. These researchers believe that the expected scientific and medical benefits outweigh the risks involved.[47]

The number of ethical think tanks has increased significantly in recent years. Some of the teams working on chimeras have set up their own ethics committees to resolve moral questions that inevitably arise. However, the true independence of these bodies, hosted by the same research centres and including researchers directly involved, is questionable.

At the same time, scientists often temper the turmoil caused by their research on chimeras by retorting that the production of human organs in animals at this initial stage *is* '*a scenario that is science fiction*'.[48] This would justify not yet strictly regulating research. But then collective reflection comes up against factual answers, such as *'very few human cells* enter *the animal's body and so no human characteristics can develop*'.[49] And if such answers are based on the current state of science, **they should not stand in the way of ethical reflection on future developments**.

Although only a limited number of scientific teams are working on chimeras for the moment, they are internationally recognized, are attached to the world's leading universities and are publishing their results in reputable journals. This shows that, even if ethical questions remain, this very expensive research finds the necessary funding. In this context, ethical discussion is limited, legislators subject to the rhythm of scientists, and, in a way, bioethics seems to follow in the footsteps of science instead of directing them.

b. Are there limits to experiments with animals?

The question is perhaps surprising, but rightly so: is working with laboratory animals acceptable for the sole purpose of obtaining organs from them and thus meeting the urgent need for human organs? Fundamentally, the question arises: should we subordinate '***the own finality***' of animals to the

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[46] Thus the Collective of scientists published a Free Tribune in the French diary Le Monde of 09/03/2021: *Les chimères homme-animal sont une alternative à l'expérimentation humaine.* (This Free Tribune was placed after the French Senate rejects the modificatin of Article 17 of the '*Projet de loi relatif à la bioéthique(*. Later, on the 08/06/2021 (cited in footnote 37), the Senate approved a new proposal.

[47] In this way: Jean-Yves Nau, *Des équipes britanniques vont créer des embryons mêlant l'humain à l'animal* (cited in footnote 10)

[48] Florence Rosier, cited in footnote 3

[49] Article in the African edition of the BBC News *Que sont les "chimères homme-animal" et comment le Japon est-il devenu le premier pays à permettre aux scientifiques de les élever ?*, 12/08/2019

necessities of xenotransplantation and consider them as real '*reserves of organs*'?[50] '*Considering animals as bodies, often leads to treating them as machines*', warns philosopher Pascal Ide.[51]

When Aristotle states that every living being is born for a purpose, he is implying that nothing happens in vain in nature. The question is therefore whether we do not treat animals in an undignified way if we consciously **remove them from their natural environment**? In addition, chimeras have a significantly reduced life expectancy compared to their purely animal counterpart. Indeed, in vitro fertilization reduces the quality of embryos which in turn grow in less optimal conditions and compromises their survival. And due to the incompatibilities of two organisms in one, those embryos are at greater risk of developing diseases.

Are these experiments compatible with animal welfare in the light of the **increasing number of laws regulating it**? Do they cause **them unnecessary suffering**? How many '*failures*' are to be allowed in the name of results that are still so inconclusive? The shortage of organs for transplantation, coupled with the lucrative potential of xenotransplantation and the rapid biological development of organs in animals, could result in farming just as intensive as that associated with meat production today.

c. Are there any acceptable alternatives?

Whether organs from chimeras are a real alternative to human grafts is not obvious. This objective has not been achieved today and there is no guarantee that chimeras will ever be of sufficient quality to function properly in a human body. Social and cultural barriers must also be taken into account: will patients accept having an entire animal organ transplanted?

For years various alternatives have existed to overcome the shortage of organs in a simple and safe way. Firstly, there is **human-to-human organ donation**, which is **medically** most appropriate due to the excellent species compatibility between donor and recipient. **Socially**, it is an important trigger to human solidarity. This donation is **fully compatible with human dignity**, for both the donor and the recipient. The donor is aware of the recipient's suffering and of his contribution to alleviating it.[52] Especially when the donor agrees to it during his lifetime, the donation is **a free, selfless and above all generous** gesture. It is a **self-gift** in which the whole person is involved and that participates in social life. Of course the chimera can do none of this. Public policy should provide greater incentives for donorship in order to meet the shortage of grafts.[53]

Another alternative that has been gaining acceptance for some time is the production of **synthetic organs or prostheses**. These artificial organs made of plastic and metal (e.g. external bladder prostheses) are in full development. Nowadays they are created with 3D printing, a fast and cheap option.[54] For example, prostheses have already been developed for parts of the heart, kidney, liver, bladder and vascular structures. In addition, portable dialysis and oxygen devices have been developed that, in the absence of specific donors, still provide patients with sufficient ventilation that enables them to live more comfortably. Prostheses have their limits, but their ethical angle is fundamentally different from that of the instrumentalization of animals whose vital organs can be '*used*' at will.

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[50] Aristotle (343 BC), *History of animals,* cited by Pierre Pellegrin, *Un finalisme tempéré* in the magazine *Pour la Science*, 01/11/2005

[51] Pascal Ide *L'homme et l'animal, une altérité corporelle significative* in *L'humain et la personne*, Dir. François-Xavier Putallaz and Bernard N. Schumacher, ed. Le Cerf, Paris, 2008.

[52] Alain De Broca, *Comment penser l'homme*, ed. de l'Atelier, Paris, 2009

[53] IEB Dossier *(FR) Is an organ donation after euthanasia ethical?*, 03/10/2020

[54] Wikipedia keyword *3D bioprinting* from 01/11/2022

Since there are fully-fledged alternatives available, it is questionable whether the creation of chimeras is really intended as a solution to the shortage of donors. Some studies focus on the chimeric capacity of humans and animals. But how far can scientific curiosity legitimately venture? And isn't there a danger that they are willing to push the natural boundaries by feeding their own fantasy through a far-reaching chimerization between man and animal?

d. Are animal-human chimeras compatible with human dignity?

The use of chimeras for purposes of xenotransplantation invites us think about the risks of introducing animal organs into humans. Isn't there a risk of alteration of the personality of man.[55] Contrary to what a mechanistic vision may suggest, man transcends the idea of an assembly of replaceable parts.

Beyond organ production, the spectre of chimeras raises the question of human dignity. We cannot answer that question of definition and the limits of humanity simply by looking at the structures of the human genome. Even if he agrees, no human being is permitted to violate his intrinsic human dignity.[56] It entails a moral obligation of which he cannot arbitrarily dispose; his body can never be a commodity, either in whole or in part, and it is not permissible to take his own life.

Although *the deep ecology movement* rather trivializes the boundary between humans and animals, '*man* is *not an improved ape species*, *he has become something else, a different species*'.[57] The human-animal distinction is a **universal anthropological invariant** never denied until now: man has a specificity that not simply lies in his physical and psychological characteristics. According to the French philosopher Pascal Ide, the otherness of humans and animals should never be considered as a difference between two **animal** species.[58]

For the time being, the insertion of animal cells into human embryos is generally rejected. If we observe the golden rule that '*prevention is better than cure*', we can no longer avoid the questions about these experiments: they need a preventive and proactive answer.

e. Is there a real risk of interference between species?

When do chimeras become ethically problematic? From the moment the number of human cells exceeds that of animal cells? As soon as those animals develop human traits and '*humanizes*'? How far can we go in the human-animal mix?

The production of chimeras is in principle not problematic if it were free of ambiguity about his status. Especially at an early stage, chimeras are '*beings*' whose moral status is uncertain and we don't know if they have reached the threshold of human dignity, in which case it would be immoral to manipulate or destroy them. Thus, in this strong moral confusion it seems obvious that *'science requires clear*

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55 Elio Sgreccia, Elio, chapter '*Le cas de la xenotransplantation*' of his *Manuel de bioéthique* (cited in footnote 20)

56 Bertrand Mathieu, *Manuel de bioéthique*, ed. Dalloz, coll. *Connaissance du droit*, 2009, p. 41.

57 According to the French paleontologist and anthropologist André Leroi-Gourhan in *Le geste et la parole, Technique et langage*, Paris, Albin Michel, 1965, p. 165

58 Pascal Ide, *L'homme et l'animal, une altérité corporelle significative* (cited in footnote 51)

ethical boundaries if it aims to maintain public trust and an essential moral boundary between what is human and what is not.'[59]

The French biologist Pierre Savatier describes **three red lines** that should not be crossed: 'human cells should never contribute to the formation of an animal **brain**, of animal **gametes** or of a **human appearance**'.[60]

1. the risk of human features in animals

Human features or a human appearance can, in a deceptive or ambiguous way, blur the line between man and animal. Human features are not only limited to appearances. Language is certainly a specific (human) attribute, but our moral intuition tends to be influenced by identity attributes; this is called '*intuitive ontological classification*'.[61] When human cells are introduced into animal embryos, the presence of external human features can blur the human-animal boundary and question the specificity of the human species.

However, the principle of representation is limited and should be considered in conjunction with the **principle of proportion.** Indeed, a **majority of human cells in an animal body** will not necessarily give this animal a human appearance. We would thus obtain an almost human chimera, which we would take illusory for an animal.

According to Elio Sgreccia, the inherent animal or human qualities of chimeras should neither alter nor contradict the extraordinary character that distinguishes man from other creatures.[62] There is no problem as long as animal cells are added to their vital organs *(e.g. kidney or liver)* for **purely functional applications** that are not specific to the human species. It becomes problematic if those cells were to control parts of the body or develop a certain intelligence. This risk is obvious in organs with **neural cells** as building blocks, such as the brain (100 billion neurons), the intestinal system (500 million) or the heart (40,000).[63]

2. the use of human gametes

Should we allow human cells to colonize all parts of the whole body? The insertion, without further precautions, of human germ cells into an animal embryo is particularly problematic as it could lead to the formation of exclusively human gametes suitable for reproduction. The prospect of a deceitful and indeterminate animal lineage of a human being is a risk that no one wants to take. Sterilization is considered against this risk.

3. the risk of conscience

In case of migration of human cells to the developing animal brain, there is a risk of disruption of the behaviour and mental abilities of the animal, since its nervous system is not yet fully constituted.[64]

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[59] David Albert Jones, Director of the Anscombe Bioethics Centre, Oxford, in the Radio program on France Culture of 12/05/2021: *Chimères homme-animal: la fin d'une frontière? La méthode scientifique de Nicolas Martin.*

[60] Pierre Savatier at the INSERM (Institut National de la Santé) et de la Recherche Médicale) in the radio program *Chimères homme-animal : la fin d'une frontière?* (cited in footnote 59)

[61] Matthew H. Haber & Bryan Benham, *Reframing the Ethical Issues in Part-Human Animal Research: The Unbearable Ontology of Inexorable Moral Confusion*, The American Journal of Bioethics (AJOB), vol. 12, Issue 9, 2012, p. 17-25

[62] Elio Sgreccia, chapter '*Le chimérisme génétique*', of his *Manuel de bioéthique* (cited in footnote 20), ed. Mame EDIFA, 2004

[63] Wikipedia keyword Neuron consulted on 31/10/2022

[64] According to the 2021 study from the U.S. National Academy of Sciences: *The Emerging Field of Human Neural Organoids, Transplants, and Chimeras: Science, Ethics, and Governance*

However, some scientists already stress the need for chimeras containing human neural cells to treat neurodegenerative diseases (Alzheimer's, Parkinson's).[65]

Chimera cells are unevenly distributed throughout its body, and researchers sometimes have difficulty determining the degree of colonization by human cells.[66] Therefore, Estrella Nunez recommends not to cross the red line of 14 days for keeping embryonic chimeras alive corresponding to the formation of their central nervous system.

Currently, the human cells in chimeras are characterized by a limited ability to compete with the other cells. Some scientists label an ethical review as '*not premature, but still unfounded*', including that the neural cells would destroy themselves if they migrated to the brain.[67] Still, we may wonder if, at the brain level and given their complexity and quantity, human cells are no more competitive than animal ones. Researchers recommend the implementation of genetic scissors to overcome this problem: they could disable differentiation into neural cells, or activate the '*suicide*' genes of neural division or the MIXL1 gene that forces cells to become visceral fat.

Conclusion

The ethical problems in experiments with chimeras are not so much in determining the therapeutic objectives (such as the better understanding of certain diseases, an improvement in treatment or the production of organs, etc.), but in their implementation and in the possible risks.

Although a few countries frame experiments with chimeras, they remain too few. Moreover, these frames are neither aligned between the different countries nor precise enough, thus favouring relocation of the projects to countries with the most permissive framework. This leads to personal and very relative limits that researchers set for themselves as to the degree of chimerism they allow themselves to achieve.

Human genius has developed many alternatives more respectful of human dignity to compensate for the lack of grafts, if this is however the main reason for these experiments. These solutions include encouraging the altruistic donation of grafts between human beings, the creation of synthetic organs, the making of prostheses. If they are relatively little exploited currently, the promises of biomedical 3D-printing and the systematic solicitation of families in case of potential donor would already make it possible to respond more favourably to the demand.

As for the hopes of better understanding certain human diseases or the development of the human embryo through chimeras, a balancing of risks and benefits at the ethical level –including the protection of the human embryo– and public health is absolutely necessary, as well as the prohibition of mixing certain types of cells that participate in what makes human identity.

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[65] Sebastian Porsdam Mann, Rosa Sun & Göran Hermerén, *A framework for the ethical assessment of chimeric animal research involving human neural tissue*, in BMC Medical Ethics, 20(1): 10; 25/01/2019

[66] Juste Aznar, *Problèmes éthiques dans la production de chimères humaines et singes dans les enquêtes d'Izpisua*, 2021, Observatoire de bioéthique à l'Institut des sciences de la vie à l'Université catholique de Valence

[67] Estrella Nunez (collaborating biologist in the Chinese project, vice-rector from the Universidad Católica San Antonio de Murcia (UCAM) in: Sebastian Porsdam Mann, Rosa Sun & Göran Hermerén: *A framework for the ethical assessment* (cited in footnote 65): this article lays the basics for the use of chimera nerve cells that, according to these researchers, will become indispensable in the near future.