Irina DELAMARE

The unfulfilled promises of Transgenic Monkey

Genetically modified animal models that exhibit human diseases symptoms are a powerful and efficient way to study sicknesses and to produce therapeutic treatments. [25, 24] A genetically modified animal, or a transgenic animal, is an organism whose genetic material has been altered using genetic engineering techniques like ZFN, TALEN or CRISPR. [1] Those genome editing techniques used engineered nucleases[1], and are just starting to develop. It is a quick and efficient way to select desirable traits.

Usually, mice or rats are used as models. However, because they are not our closest relative, it is pretty clear that using an animal that shares a higher percentage of our DNA like monkeys would help better understand and treat human pathology (especially neurological and neurodegenerative diseases). [1, 11] So generating genetically engineered monkey models of Human diseases for a study purpose could help produce therapeutic treatments and cure people.

The most common non-human primates used for lab study are marmosets, macaque monkeys, rhesus monkey, baboons, tamarins, spider monkeys, owl monkeys, vervet monkeys, and squirrel monkeys. [13]

First of all, we will describe the reasons to experiments on monkeys and how it is relevant in our society. Second of all, we will focus on the teams working on this research subject, who finances them, in which country they are located, what are there plan in the near future, etc … Third of all, we will look at the legal status of non-human primates and apes, and the jurisdiction and control of their use for scientific purpose. Fourth of all, we will talk about the link between the controversies and the ethical issues to use monkeys in experiments. And last but not least, we will talk about the openings of this subject, what if we genetically engineered humans?

This is an interesting subject because it allows to cover a much more general problem : the relation between human being and animals, whether in consumption or experimentation. Being a vegetarian, I already knew a bit about farm animal treatments and welfare. So I wanted to extend my knowledge on animal experimentation. Monkeys are genetically close to humans, and were recently in the center of many controversies about the modification of their genome in scientific studies that I was able to read in the newspaper. So primates were the obvious choice of model animal for scientific experimentation. Making transgenic monkey is kind of extreme and open the discussion to genetically engineering humans. It also reveal social issues around animal experimentation, with ethical problems.

To study brain development and disorders, using a transgenic monkey model of human diseases would be more reliable than using transgenic rodents. Indeed, “it has been difficult to identify autism-like behaviors in the mouse model of MeCP2 overexpression” states Liu Zhen and Xiao Li in the article “Autism-like Behaviours and Germline Transmission in Transgenic Monkeys Overexpressing MeCP2.” published in 2016 in Nature magazine. [5] However, the references used in this article to support the use of monkey states the opposite. Indeed, Rodney C Samaco and Caleigh Mandel-Brehm “report that doubling MECP2 levels causes heightened anxiety and autism-like features in mice [...].” in 2012 articles called “Crh and Oprm1 mediate anxiety-related behavior and social approach in a mouse model of MECP2 duplication syndrome”. [12] The reason to use transgenic non-human primates rather than mice is that primates can “provide more accurate models for human (neurological) disease”. [1] Even with the opposition find in the two previous papers, other articles states that mice are “less reliable as models of human disease, because the networks linking genes to disease are likely to differ between the two species”. [49] Developing genetically engineered non-human primates models of human diseases is a relevant topic in our society to better understand the illness functionment and helping find a cure.

Acknowledging this contradiction, what are the real reasons to experiment on monkey rather than rodents?

An article from the Philosophical Transactions of the Royal Society in Biological Sciences identifies goals for non-human animals genome editing : human health, efficiency, risks and uncertainty, animal welfare, animal dignity, environmental considerations, and public acceptability reasons. [1] This article also brings a particular focus on monkeys : it settles that in most papers relating transgenic animal experimentation, “although the moral status and interests of non-human primates were brought up, the moral status of other animals was rarely mentioned.”[1] So those ethical issues mainly exist in primates experimenting. Other reasons supporting non-human primate genome editing is that even if it “could be considered ethically problematic, it is much more ethically problematic to watch people die who could be saved.”[1]

On the other hand, the “moral permissibility of this approach is questionable given available alternatives” [1] such as using organoids or stem cell models of disease [26] or using animal models of smaller animals such as mice [12].

We can also note that no study has yet used transgenic monkeys to develop clinically applicable therapies for diseases so we can wonder on the real utility of genetically engineering primates. Furthermore, monkey models are still not as easy to study than rats. Indeed, because of the greater life span of Simians, of their longer reproduction cycle, and of the big enclosure needed to house them, they are trickier to study. [11]

Most studies claiming to have generated transgenic monkey models of Human diseases were made in China, in Chinese University, by Chinese researcher's (except for one Japanese team that we will focus further in the reading). We count multiple teams that work on that research subject. Though, in most of the papers, the researcher that contributed to the article came from the same university, and generally even from the same team. This is particularly true for a team from the State Key Laboratory of Neuroscience, Key Laboratory of Primate Neurobiology (from the Institute of Neuroscience, CAS Center for Excellence in Brain Science and Intelligence Technology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai 200031, China). Zhen Liu and Peiyuan Qiu are part of this team and have participated in the publication of the following articles. [4, 5, 6, 7, 11] This team made no collaboration but is one of the most active in terms of publications. On the opposite, the Yunnan Key Laboratory of Primate Biomedical Research (from the Institute of Primate Translation Medicine, Kunming University of Science and Technology, Kunming, 650500, China) co-operated with laboratories from the same University like the State Key Laboratory of Genetic Resources and Evolution, Primate Research Center, Center for Excellence in Animal Evolution and Genetics (from the Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming 650223, China). Yongchang Chen and Lei Shi are part of these teams and have participated in the publication of the following articles. [2, 8] Another team working on developing transgenic non-human primates is the Guangdong-Hongkong-Macau Institute of CNS Regeneration (Ministry of Education CNS Regeneration Collaborative Joint Laboratory, Jinan University, 510632, Guangzhou, Guangdong, China). Weili Yang is part of this team and has participated in the publication of the following articles. [9, 10] The only laboratory working on this research subject out of China is the Laboratory for Marmoset Neural Architecture (from the RIKEN Brain Science Institute, Wako-shi, Saitama 351-0198, Japan). Hideyuki Okano is part of this team and has participated in the publication of the following articles. [21, 22] He even created the Brain/MINDS project, a Japanese national brain project for marmoset neuroscience. [22]

All of Chineses' studies were financed by the universities and the Chinese government. What are the stakes that lead China to finance and encourage such projects ? We could identify obvious political reasons : the thirst of producing knowledge, the hunger for more power, the desire to be an influential technological and scientific pole… In 2011, China five-year plan set "primate disease models as a national goal." [34] Moreover, in 2014, the science ministry of China invested 25 million yuan (US$3.9 million) into the endeavor. [34] This stands in contrast to Europe and the US where "non-human-primate research increasingly faces regulatory hurdles, costs and bioethical opposition" [34]. [27, 34]

All those teams produced multiple scientific articles. We encounter little or no researchers from other nationalities in the papers. We can wonder why they are no collaborations between Universities and countries ? One hypothesis lies in the difference in the legislation of countries about developing transgenic animals for scientific purpose. Even though, China's teams plan to work with international researchers allowing the scientists to experiment on in China over the next few years. [34]

Experimenting with non-human primates is legal in many countries because of the lack of legislation concerning their legal status. [15] Homo sapiens are considered as persons and protected in law by the United Nations Universal Declaration of Human Rights. [16] Because monkeys are not classified as persons in most countries, experimenting and testing drugs on them is allowed. [17] They are considered as furniture and their individual interests do not have any protections.

However, projects like the Great Ape Project (GAP) are trying to change those legislation to give a legal status to great apes to help protect their basic interests like the right to live, the protection of individual liberty, and the prohibition of torture (this includes the right not to be used in experiments). [14] The GAP is an international movement that aims to defend the rights of the non-human primates. However, I couldn't find any reference of their position concerning transgenic monkeys.

Thanks to the GAP project, Great apes have been given basic right in some countries like Spain, Austria, New Zealand, the Netherlands, Sweden, and the UK. [18]

A British group comprising animal researchers, philosophers, primatologists, and animal advocates called The Boyd Group even advice a global prohibition on the use of non-human primates. [19] They are many groups and associations trying to defend Simians right and prohibit their use for scientific purpose.

In France, current legislation (articles R214-87 to R214-137 of the rural code) regulates experimentations on vertebrates. [42] However, primates use is restricted and apes use is prohibited. [42] Actually apes are not used in Europe since a few years. [42] Monkey use in the laboratory for experimentation is restricted by [42]:

- Animals origin (they need to come from a breeding center with an governmental authorization),
- Experiment necessity (primates use is only allowed for human health and environmental research, and only if the other possibilities are dismissed),
- Laboratory governmental authorization (the authorization is granted for 6 years, a veterinary and a structure for animal welfare must be created. Regular inspection are made),

- Ethics committee (ethical evaluation will give the authorization for the research project to start).

Even if non-human primates experimenting is not prohibited in most countries, there are obvious ethical issues, and controversies around this subject have a great amplitude. [26] But why is that ? Why is it so taboo to experiment on apes ? Why does the creation of a transgenic monkey create such an interest in newspapers all around the world? [32, 33, 34, 35, 36, 37, 38, 39, 40, 41] What is this new craze all about ?

First of all, the discussion of apes and monkey conscience remains ongoing. Answering this question could give a final resolution to the debates on primates legal status. [27] Lori Marino, Senior Lecturer in Neuroscience at Emory University and the Science Director for the Nonhuman Rights Project, believe that “many nonhuman animals are smarter and more aware than previously thought — what will certainly upset our notions of their legal and moral standing” [43].

Non-human primates are capable of high levels of cognition. [31] They can make and use tools. [31] “They are status conscious, manipulative and capable of deception, they can recognize kin and conspecifics, they can learn to use symbols and understand aspects of human language including some relational syntax, concepts of number and numerical sequence.” [31] Moreover, some apes are even capable to learn sign language which allowed them to communicate with humans that raised them. [28, 29] Because tests on persons have strict legislation and control, defining non-human primates as persons would result in a final prohibition of Simian’s lab test and exploitation. [27]

Second of all, because primates are closely related to humans, we easily identify ourselves to them. Indeed, empathy is correlated with phylogenetic relatedness to humans and communicative abilities states Harrison Marissa in “Anthropomorphism, Empathy, and Perceived Communicative Ability Vary with Phylogenetic Relatedness to Humans.” published in 2010 in the Journal of Social, Evolutionary, and Cultural Psychology. [20] On the opposite, human beings have a harder time recognizing themselves in mice or lab rats. When experiments on monkeys are made, we can easily emphasize them and develop empathy for the primate. The attribution of human traits, emotions or intentions to non-human beings like apes is called anthropomorphism. This behavior only amplifies our understanding and compassion for primates, which inevitably leads to putting ourselves in their shoes.

Chinese and Japanese researcher already genetically engineer monkeys! What prevents the next step to be genetically engineered *Homo sapiens*?

Genetically engineering humans being would raise so many ethical issues about health risk. Using genetically engineering tools like CRISPR on human germinal cells

would imply a definitive modification of the human genome. [44] This means creating or removing genes, alleles, mutations. Modifying germinal cells is different from modifying stem cells genome because in the first case the mutation will be passed on to the next generation. [44]

Apart from ethical issues that human experimenting can generate, they are important juridical risks linked to people filing a complaint because human beings are recognized as natural and legal persons. (A natural person is a person of the species *Homo sapiens*, a legal person or legal entity is a human or non-human entity that is recognized as having legal capacities such as companies and corporations.)

We can explain the controversies about creating transgenic monkeys because genetically engineered human is a taboo subject at the center of ethical debates, and because of the way we emphasize and transpose ourselves to monkeys. This explains why so many papers in the press recall to ethics when reviewing genetically engineered primates. [32, 33, 34, 35, 36, 37, 38, 39, 41] On 9 papers reviewing experiments on transgenic monkeys, 8 of them speak, at one term of the article, about the ethical questions raise by those experiments. Papers reviewing these experiments are from well known journals like “Le Monde” [35], “Science et avenir” [32], “New Scientist” [39, 40], “Nature” [34], “FranceInfo” [33], “The Scientist Magazine” [37].

Press article have a big impact on the controverse evolution. Since journals reviewed “Transgenic Rhesus Monkeys Carrying the Human MCPH1 Gene Copies Show Human-like Neoteny of Brain Development.” article by Shi Lei [8], “the work provokes a profoundly moral and visceral uneasiness”. [41] One of the collaborators, Martin Styner, a computer scientist, even consider removing his name from the paper. [41]

Despite that this research subject is quite recent, controversies and fear of this leading to transhumanism is not. Transhumanism is the belief that humanity can evolve beyond its current physical and mental limitations, especially by means of science (with genetic engineering for example) and technology. Books like “Brave New World” by Aldous Huxley published in 1931 and movies like “Gattaca” by Andrew Niccol in 1997 were already discussing the risk of yielding to the desire to transform men for better. Both masterpieces are dystopia were transhumanism lead to a world full of dread. “In popular belief, we are in Planet of Apes”, says the bioethics researcher Jacqueline Glover about the implementation of a gene responsible for human brain development on rhesus monkeys. [35] Humans fear a world where “best traits” are selected, or implemented to their genome. This is called eugenics, which is the practices to improve the genetic quality of a human population by “excluding certain genetic groups judged to be inferior, and promoting other genetic groups judged to be superior”. [45] So genetically engineering human would be eugenics, which inspires fear because it was the goal of some dictatorships (the Nazi regime for example).

A Chinese researcher, He Jiankui, already genetically modified twin girls using CRISPR to enable the offspring to be resistant to HIV, smallpox, and cholera. [46] This claim, that hasn't yet be reported in a scientific article, provoked a huge polemic around the world. [47] It initiated a "firestorm of criticism, with some scientists and bioethicists calling the work "premature," "ethically problematic," and even "monstrous." [47] The Chinese Society for Cell Biology states the experiment as "a serious violation of the Chinese government's laws and regulations and the consensus of the Chinese scientific community." [47]

As far as I am concerned, after discussing the reasons to experiments on monkeys, the scientific community involved by this research subject, the legal status of non-human primates, the control of their use for scientific purpose, and the ethical issues to use monkeys in experiments, the real benefice and utility of this research subject don't seem clear.

The promise offered by transgenic monkey to produce therapeutic treatments isn't yet fulfilled. The use of non-human primates raise many ethical issues that limits scientific experiments on Simians. Many of those experiments are also avoided by using other model organism like mice, even if they are not as closely related to us than primates.

A movement to adopt a global moratorium on heritable genome editing was even created by specialists from seven countries. They call for the "establishment of an international government framework in which nations would commit to not approve any use of clinical germline editing unless certain conditions are met". [48]

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