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THE CHIMAERAS OF NATURE AND THEIR PROMISE TO GROW HUMAN ORGANS

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In a recent landmark study, scientists have reported successfully producing a live infant chimeric monkey of the species Macaca fascicularis. Representative individual shown above, April 23, 2022. | Photo Credit: Sharp Photography (CC BY-SA 4.0)

At present, more than 3 lakh people are waiting for an organ transplant in India alone; the global number is far higher, with no respite in sight. There is an alarming disparity in the number of organ donors and the number of recipients – and animals have played an important part in filling this gap.

The successful application of animal insulin and the more recent use of animal heart valves in human surgeries have saved human lives. Researchers have also made attempts to grow full human organs inside the bodies of animals using advancements in induced pluripotent stem cells (iPSCs) technology.

At the same time, controversy continues to beset this field, most of it centred on the use of human iPSCs in animal embryos and the creation of chimeric animals, the results of which we are yet to fully comprehend. However, humans are not new to the concept of chimaeras. Mythology abounds with a rich collection of these beguiling beings.

A genetic chimaera is a single organism composed of cells of more than one distinct genotype (or genetic makeup). The animal kingdom has several examples of varying degrees of chimerism. The half-sider budgerigar, a type of common parakeet widely adopted as pets, has different colours on either side of its body due to chimerism. The anglerfish displays an extreme degree of symbiotic chimerism in which the male fish fuses with and is eventually absorbed into the female fish, mixing their genetic makeups into a single animal. Marine sponges are known to have up to four distinct genotypes in a single organism.

A photograph of a half-sider budgerigar. | Photo Credit: Susan Dennis, public domain

Natural chimaeras among humans are well documented in the medical literature. They occur when the genetic material in one cell changes and gives rise to a clonal population of cells different from all the other cells. The fusion of two fertilised zygotes early in the embryonic stage can also lead to a condition in which two genetic makeups coexist in a single individual. Chimerism can also result from twin or multiple pregnancies evolving into a single foetus or a

twin foetus being absorbed into a singleton.

Researchers have also documented individuals living with two blood types. In fact, blood-group chimerism during multiple births is relatively common. Most chimaeras are detected during routine blood tests in hospitals or when family members undergo tests ahead of an organ transplant. Pregnant women have been known to harbour the genetic material of her foetus in the bloodstream during the pregnancy. (Such foetal DNA can be used to screen for genetic defects and congenital abnormalities using non-invasive prenatal testing.)

Studies have also recorded a phenomenon called microchimerism, in which traces of the foetus's genetic material are observed in mothers' tissues many years after childbirth, resulting in two different genetic materials in a single person.

Individuals undergoing treatments like bone marrow transplants usually have their bone marrow destroyed and replaced by that from a suitable donor. Since the donor's bone marrow contains stem cells, they will produce blood cells that will subsequently repopulate the recipient's blood-cell repertoire. Eventually, the recipient will have blood cells that resemble the donor's and will be different from the genetic makeup of the recipient's other tissues – resulting in a chimeric individual.

Solid organ transplants in humans are bound to produce individuals with two unique genetic makeups as well. The makeup of the donor's organs will be significantly different from that of the recipient's other tissues, also resulting in chimerism.

Previously, chimaeras have been induced in laboratory settings, of rat-mouse, human-pig, and human-cow. These were in a bid to develop model systems that could 'generate' human organs of a suitable size, anatomy, and physiology. While rat-mouse chimerics had a near-normal lifespan, human-pig chimaeras had to be terminated in three to four weeks.

While such studies have shown promise for growing organs destined for transplant, they are also limited by the fact that rats, mice, pigs and cows are evolutionarily distant from humans, and will pose biological and technical challenges when being used to grow human organs.

In a recent landmark study published in the journal *Cell*, scientists reported the successful generation of a live chimaera in non-human primates – species that are actually evolutionarily close to humans. This is the first time scientists have succeeded in producing a live infant chimeric monkey.

In studies with Cynomolgus monkeys, a.k.a. long-tailed macaques (*Macaca fascicularis*), researchers extracted embryonic stem cells from one-week-old embryos. They modified the DNA in these cells to include a green fluorescent protein (GFP).

These GFP-marked embryonic stem cells were then injected into recipient embryos that were implanted into surrogate female monkeys, which delivered six full-term offspring. Using detectors, the researchers located the GFP signal in the tissues of one aborted male foetus and in one live-birth male. The latter signal originated from the donor cells that had been injected into the recipient's embryo.

The chimeric monkey had to be euthanised after ten days for health reasons. Extensive genome-sequencing investigations conducted with its cells showed a high degree of chimerism in its tissues, including eyes, fingernails, brain, heart, kidney, liver, gonads, and placenta.

As such, this study opens new doors for scientists to use non-human primates to create

chimaeras that could become models for basic and translational biomedical applications in the near future. Just like other advances in science, this study wasn't without limitations and ethical quandaries – and which we must address before thinking about the human biomedical applications.

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