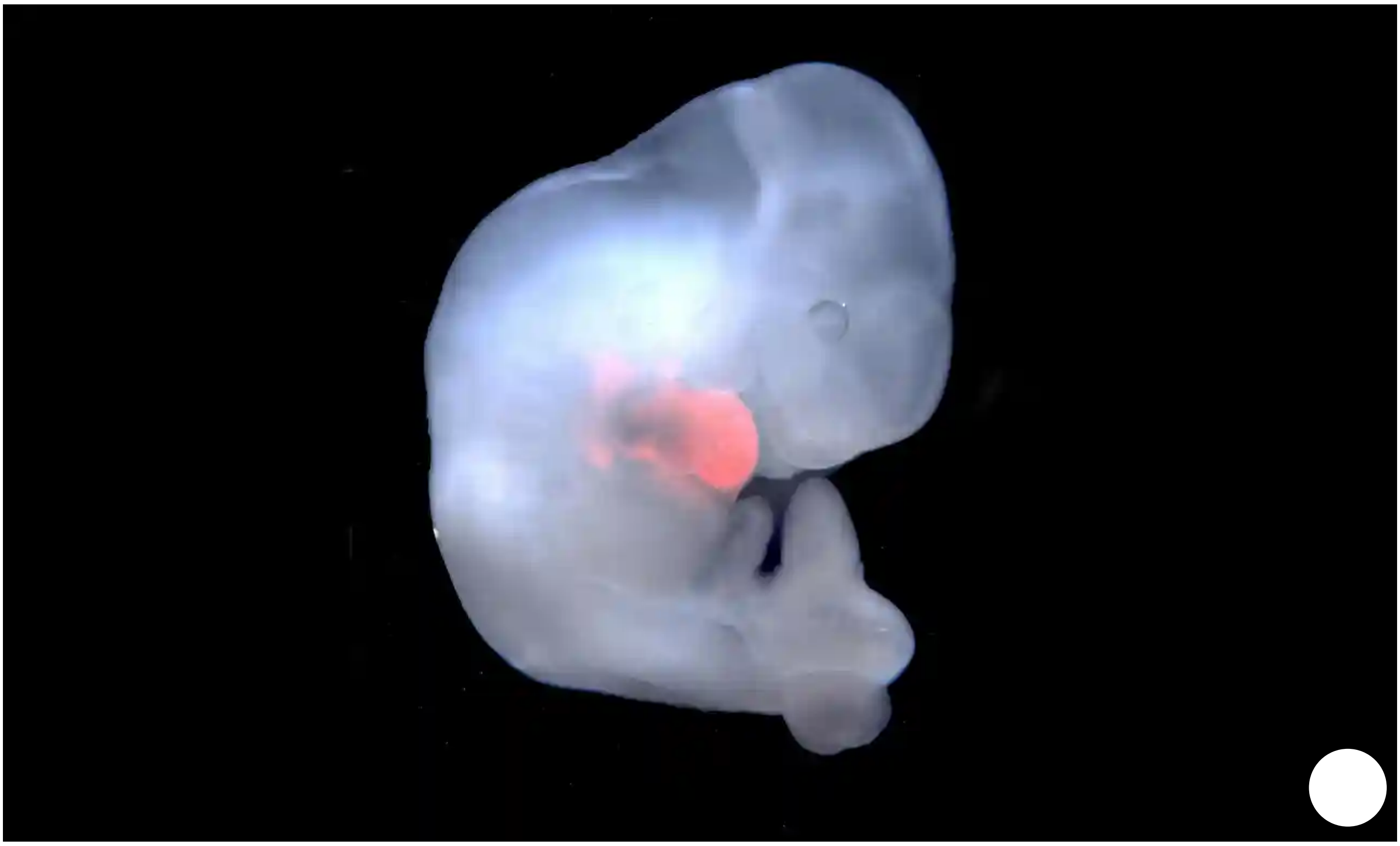

The Observer

Mixed messages: is research into human-monkey embryos ethical?

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Sat 15 May 2021 16.00 BST

When King Minos of Crete was given a magnificent bull by the sea god Poseidon for a sacrifice, he could not bring himself to kill it. In anger, Poseidon enchanted Minos's wife Pasiphaë to be filled with lust for the creature. The result of their trans-species mating was the bull-headed monster the Minotaur.

Hybrids of humans and animals throng within myth and legend: centaurs, mermaids, goat-footed Pan. We're both fascinated and uneasy about the boundary that separates us from other animals - and whether it is leaky.

So the recent report by a team in the US and China of embryos that contain a mixture of human and monkey cells mines an ancient seam of anxiety. What strange hybrids are we creating, and why?

Living entities containing the cells or tissues of more than one species are technically called chimeras - the name of a legendary monster that Homer described in *The Iliad* as "lion-fronted and snake behind, a goat in the middle".

We've long known that these mosaic-style animals are possible. A chimera with a mixture of goat and sheep tissues, called a geep and having a goat's head but a sheep's woolly body, was reported in 1984. Chimeras are generally made by transferring stem cells, capable of growing into a range of tissue types, from one species into the embryo of another. In some circumstances, the foreign cells can keep growing and thriving in their new host.

The unease provoked by such biological patchworks is considerably stronger when the chimeras contain human cells. But these have been known for years too. Human embryonic stem cells have previously been inserted into sheep foetuses and mouse, rabbit and pig embryos. Some of these cells can survive for days.

Such experiments might evoke grotesque echoes of HG Wells' maverick mad scientist Doctor Moreau, who "humanised" animals by surgery. But there are good reasons for them. In particular, the shortage of human organs such as kidneys for transplantation - which leads to many potentially preventable deaths from organ failure - could be solved by growing "human" organs in animals.

Several years ago, Japanese biologists Hiromitsu Nakauchi and Toshihiro Kobayashi pioneered a trick for getting cells injected into an embryo from another species to develop into just the organ you want. They created a "niche" for the foreign cells by genetically modifying the animal embryos so that they can't grow the target organ - a liver, say - on their own. The embryo will then use the guest stem cells to make it instead.

The technique has been shown to work for growing rat organs, such as pancreases, in mice, and vice versa. But rodents obviously can't be the hosts for full-grown human organs; for that you need a larger animal. In 2017 a team led by Juan Carlos Izpisua Belmonte at the Salk Institute in La Jolla, California, showed that human stem cells added to pig embryos could survive for up to four weeks.

But in contrast to rat-mouse chimeras, the human cells grew in only small and dwindling proportions: not enough to generate human tissues and organs. "It was a disappointing outcome," says Jun Wu, who was a postdoctoral researcher in the Salk team and is now at the University of Texas Southwestern Medical Center in Dallas. "Why is it so difficult for the human cells to survive?"

The Chimera of Arezzo, a 5th century BC bronze sculpture, depicts the chimera of Greek mythology, part lion, part goat and part snake. Photograph: Science History Images/Alamy

Izpisua Belmonte suspects it is because we're too distantly related to pigs: our branch of the evolutionary tree diverged from theirs 90m years ago. That's why he and his colleagues, collaborating with Weizhi Ji's group at the Kunming University of Science and Technology in Yunnan, China, have now made human-monkey chimeras. Because our evolutionary relationship to monkeys (the researchers used macaques) is closer - we diverged around 20-30 million years ago - the researchers figured the two cell types might get along better, and hoped to discover more about what promotes their compatibility. "If we can learn about the crosstalk between the cells," says Wu, "we might be able to improve on the pig work."

Of the 132 chimeric embryos the researchers made and cultured in a dish, most died before day 17 after fertilisation. Just three were still alive at day 19. But the researchers say that, in general, the human cells seemed to integrate better with the monkey cells than they had in pig embryos. Several embryos still had around 4-7% of human cells by day 15.

This means that human-monkey chimeras might be able to support more intimate and extensive mixtures of the two types of cell, with less predictability about where they might end up growing. Nakauchi, now at Stanford University in California, says that the ethics of such experiments are most fraught if they generate "ambiguous animals, such as a pig with a human face or human brain". That might be impossible even in principle, given the evolutionary distance between pigs and humans - but for monkeys it's less clear. So we should avoid making human-animal chimeras with a large human component, he says - and perhaps use genetically modified human stem cells that can't make brain cells. Wu agrees, but stresses that they never intended to implant any of their chimeric embryos for further growth anyway - the aim is not to grow human organs in monkeys. He doesn't think that should be contemplated if we don't know where the human cells might end up.

"What matters to me is where the human cells go and how many there are," says biologist Marta Shahbazi, who works on embryo development at the University of Cambridge. "If we confine them exclusively to an organ of interest, like a pancreas, that's OK: a mouse with a pancreas made of human cells is in no meaningful sense 'human'. But for a mouse with human stem cells spread throughout all the tissues, the answer is not so clear. And for a monkey, things get even more blurry."

Alfonso Martinez Arias, a developmental biologist at Pompeu Fabra University in Barcelona thinks the claims of Izpisua Belmonte and colleagues are completely overblown anyway. He thinks all they have really shown is that when some human cells are added to monkey embryos, they become moribund. "If you add some extraneous cells that make it more difficult for the embryo to survive, what have you learned from what is a rather sick biological entity?" he asks.

"Human-monkey chimeras are not coming soon, and may never come," he says. "In any case, we don't need them - not to answer biological questions, nor to solve problems associated with organ donors."

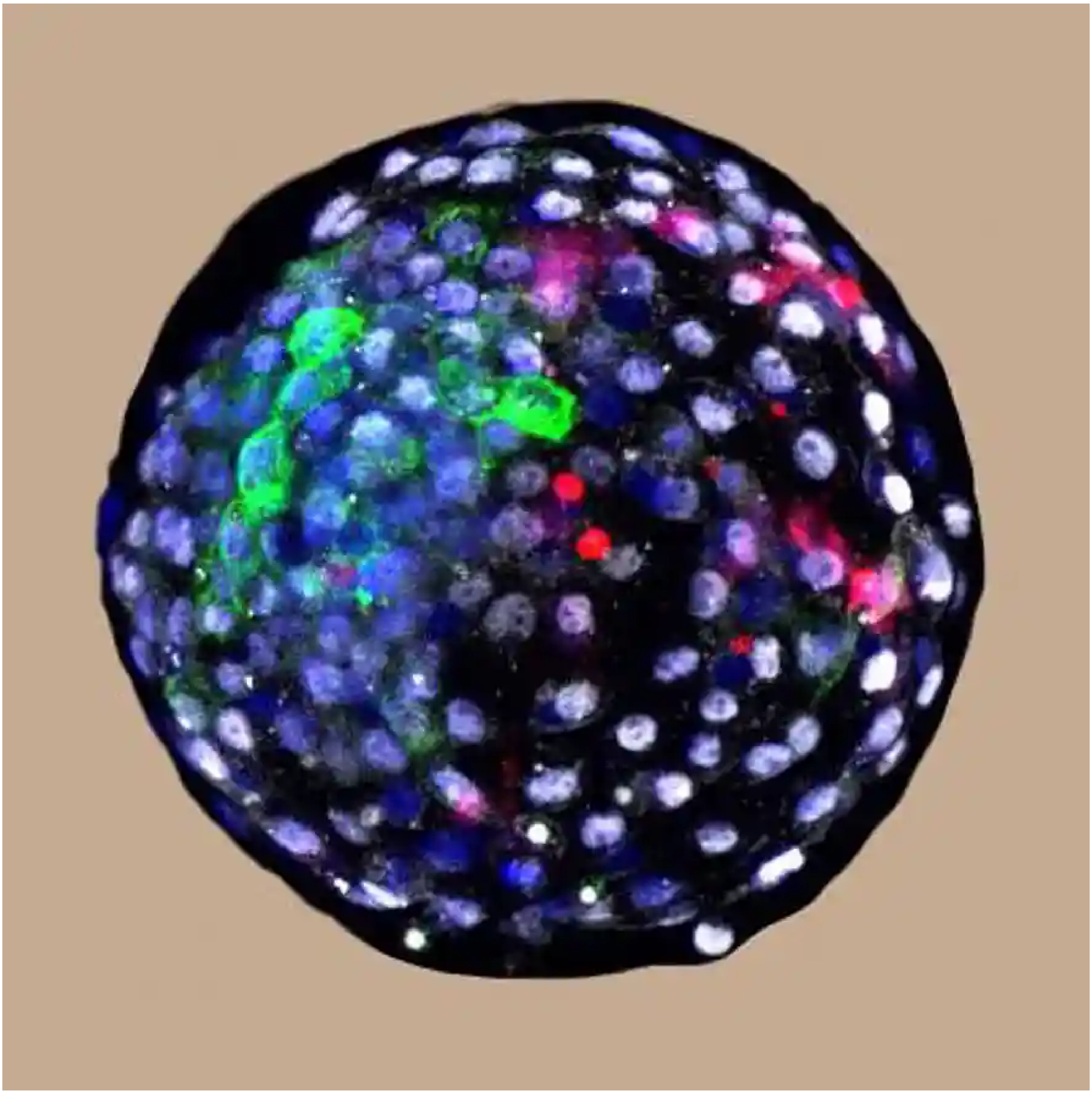
A mouse, a rat-mouse chimera, a mouse-rat chimera, and a rat. Photograph: Tomoyuki Yamaguchi / NAKAUCHI ET AL./THE UNIVERSITY OF TOKYO

Even if so, other human-animal chimeras surely are coming. Yet they are banned in many countries. Nakauchi moved from Japan to the US to escape such restrictions, ironically only to encounter a moratorium on federal funding of this kind of research in 2015. The ban in Japan was lifted in 2019, but even so Nakauchi says that the new guidelines make it "practically very difficult to get approval". This reticence frustrates him: "Animal-grown organs could transform the lives of thousands of people facing organ failure. I just don't understand why there continues to be resistance." Izpisua Belmonte insists that his work on monkey-human chimeras paid "utmost attention to ethical considerations".

Some of the issues are covered by existing regulations, for example on animal welfare: it would not be ethical to use pigs to grow human organs if the animal suffered as a result. And because human embryonic stem cells are generally taken from excess IVF embryos donated for research, donors should be told if the cells were to be used for such a controversial purpose. "This particular use of human tissue might be one that donors would find particularly icky," says Hank Greely, a specialist in bioethics and law at Stanford.

It's not easy, though, to know who should regulate this research, or what rules they should apply. In the UK, the Human Fertilisation and Embryology Authority, created in 1990 in the wake of IVF, regulates work on human embryos, but has no jurisdiction for work involving human stem cells transferred to animal embryos. That, says Shahbazi, would instead require approval from the UK Stem Cell Bank steering committee.

These frameworks don't pay any heed to how "humanised" a chimera is; Shahbazi says that an animal embryo with 80% human cells is a very different entity from one with 5%. What's more, it is possible in principle to make chimeras in which the animal embryo becomes just a housing for a developing organism made only from human cells. Could such a thing be implanted in the womb of a cow or a gorilla? It's not obviously impossible.



▲ Human cells (red) stud a lab-grown monkey embryo. Photograph: Weizhi Ji/Kunming University of Science and Technology

Maybe a uterus won't even be needed. Recently, a team in Israel reported mouse embryos gestated in glass containers filled with a nutrient medium for up to half the full gestation period – the heart was pumping and the limbs were starting to form. "In theory one could apply that method to culture chimeric human-mouse embryos and get to foetal stages," says Shahbazi.

She sees this potential for development as an ethical Rubicon. As long as chimeric embryos can't develop beyond a relatively early stage, she sees no problem. "Would I be comfortable if the mouse-human chimeric embryo was transferred to a recipient mouse female and allowed to develop to term? No. For me there is a limit."

While it is possible to imagine sci-fi horrors like pigs with human brains, there is no obvious motivation for attempting such an experiment. And when the research has a wellmotivated, humanitarian goal, like producing human organs for transplants or getting better understanding of embryo development to address fertility problems or the causes of miscarriage, bans based purely on an instinctive aversion need to consider what potential benefits are lost. “Growing human organs in pigs would, if it works, save lots of lives,” says Greely. Ultimately, says Izpisua Belmonte, “we conduct these studies to understand and improve human health”.

All the same, we can’t simply hope all scientists will have the best motives. Some might want simply to make a self-aggrandising splash. Take the maverick Greek Cypriot biologist who claimed in 2003 to have made a human-cow chimeric embryo that could in theory have been implanted into a woman’s womb. Or the Chinese researcher He Jiankui, who shocked the world in 2018 by using gene editing - with unknown consequences and risks - on human embryos implanted for IVF.

At this point, says Shahbazi, it’s not hard to imagine a situation where the ethical and legal guidelines “do not reflect the complexity of the biology”. The International Society for Stem Cell Research will present revised guidelines for stem-cell research, including human-animal chimeras, this month. Wu welcomes that prospect - he says it’s easier to do this work when it is clear what is and isn’t permitted. “The public should also know that there are guidelines, and that this sort of work is not out of control,” he says.

Until recently, human-animal chimeras were simply the stuff of legend and folklore: hardly a good basis for making ethical judgements. Yet the history of deliberations in assisted conception shows that such stories have a dangerous tendency to sway our perceptions when nothing better is on offer. The issues need far-reaching societal discussions, says Greely. But will they be able to keep up with the science?

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