

## Animal-human chimera, the mixing and matching

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The mixing up and merging of species is not new to science. A multitude of creatures straddling the line between animal and human already exist in laboratories around the world. Technology allowed inserting one or two genes at a time into the germ line or genetic inheritance. More recently, artificial chromosome technology has allowed insertion of hundreds of genes at a time. Both techniques create what is called a "transgenic". For 20 years now, transgenic mice containing human genes in their genetic inheritance have been scurrying about in laboratory cages.

Scientists believe that the creation of part-human part-animal creatures can help to study disease, advance areas such as fertility, and boost understanding of our basic biology.

These creatures are called chimeras, and are defined as organisms that contain at least two genetically different groups of cells originating from different organisms.

Different from hybrids, which are formed when one species' egg is fertilized with another species' sperm, such as the horse-donkey-cross mule, chimeras can occur between the same species or between different species and exist in nature or be created in the laboratory.

Although fairly rare, chimeras made of two humans do exist, most commonly formed when non-identical twins fuse in the womb to create a single person. If a male embryo fuses with a female embryo, this can result in hermaphroditism, where a person has a mixture of male and female sexual organs. But, if the embryos are of the same sex, then there may be no obvious differences apparent at all.

### **Interspecies chimeras**

It is the chimeras made from different species that are currently proving of most interest to scientists.

Irving Weissman of Stanford University and his colleagues pioneered these chimera experiments in 1988 when they created mice with fully human immune systems for the study of AIDS. Later, the Stanford group and StemCells Inc., which Weissman co-founded, also transplanted human stem cells into the brains of newborn mice as preliminary models for neural research. And working with foetal sheep, Esmail Zanjani of the University of Nevada at Reno has created adult animals with human cells integrated throughout their body.

Chinese scientists at the Shanghai Second Medical University in 2003 successfully fused human cells with rabbit eggs. The embryos were reportedly the first human-animal chimeras successfully created. They were allowed to develop for several days in a laboratory dish before the scientists destroyed the embryos to harvest their stem cells.

The creation of the oddly named Geep in 1984, a creature formed by merging the embryos of a sheep and goat, opened the floodgates into an unprecedented area of research. And these interspecies chimeras can be created in a variety of ways.

In the proposed stem cell research, although the animal egg has been emptied of its nuclei, tiny amounts of mitochondrial DNA would mix with the human nuclei and the resulting stems cells would be about 99.9 percent human and 0.1 percent animal--on the cusp of being chimeric.

Other methods for creating chimeras include:

- Fusing embryos of different species
- together;
- Transplanted genes, cells, tissues or organs from one species into another;
- Or injecting stem cells from one species into a developing embryo or an adult of another species.

Scientists say these interspecies creatures could help science in a number of ways--from making human stem cells and improving animal models to study disease, to one day, perhaps, creating organ or tissue factories for transplants into humans. And using chimeras also helps scientists to carry out experiments, such as those using developing embryos, which would be ethically difficult to perform on human beings.

For 20 years, transgenic mice containing human genes in their genomes have been scurrying about in laboratory cages. These human genes were placed into the mouse genome and passed on to subsequent mice generations. However, several technical obstacles have limited the amount of human genes that are expressed in a mouse. Only a few human genes could be successfully inserted into the mouse genome at a time without interrupting essential mouse gene functions or creating a fatal combination. This may not be the end of the story, though, as the wedding of human embryonic stem cell biology and mouse developmental biology may allow for the creation of even more fascinating--and more mixed--human-mouse chimeras. Human stem cells could potentially be placed in a mouse embryo with the result that human genetic material alone would drive developing "human" tissues and organs in a mouse.

### **Major research works**

In China, there are 29 goats running around on a farm with human cells coursing through their organs, a result of scientists dropping human blood cells into goat embryos.

In Boston, US, scientists have transplanted human breast tissue onto mice to study the development of breast cancer.

Esmail Zanjani at the University of Nevada, Reno is trying to grow a wide range of other tissues, such as insulin-producing islet cells for treating diabetes.

St Kitts, Yale University researchers are injecting millions of human brain cells into the heads of monkeys afflicted with Parkinson's disease.

While another American team recently showed it was able to grow immature human testicular tissue in mice. The researchers wanted to see if it would be possible to harvest sperm, for example from boys who had contracted cancer in childhood, from this tissue which could then be frozen and stored for later use. And whole organ research is also underway. Researchers have shown that it is possible to create a mouse with 95 percent of human liver cells, and other teams have created a mouse with a human immune system--both groups hope they can use the animal-human models to better understand the origins of disease.

One of the latest chimeras to hit the headlines was created by scientists in Korea. They sparked controversy when they injected human embryonic stem cells into developing mouse embryos. The finding that these the cells were then distributed throughout the mouse's body, including the brain, caused public outrage, and the scientists later abandoned the experiments as the protests increased.

### **New trends**

Until recently, most of these animals were created by inserting just one or two genes from one species into an animal of another species. However, the current trend is to insert more and more human DNA into an animal of another species. Newer techniques using yeast artificial chromosomes (YACs) and bacterial artificial chromosomes (BACs) allow insertions of up to 1/3 of a chromosome to create a transgenic animal. This YAC transgenic technology is currently being employed to create transgenic pigs for the purpose of developing organs for human transplantation (a technique known as "xenotransplantation").

If perfected, the technique could overcome some of the big stumbling blocks facing researchers who want to make tissues and organs for implants. It might yield significant quantities of just about any kind of cell or tissue, for instance, with no need to fiddle about with different culture conditions or growth factors.

Instead, the host animal's own developmental program guides the injected human stem cells into their final roles. It would also allow doctors to obtain immune-compatible cells without having to create human embryos by therapeutic cloning. Human cells could be separated from the animal ones simply by modifying existing cell-sorting machines.

Providing the method really does produce normal human cells, they would not be rejected. And any stray animal cells would be killed off by the recipient's immune system.

The chimeric models would allow the effects of various factors on a gene's function to be tested in a whole animal rather than merely in a test tube or cell. By inserting human DNA into an animal such as a mouse, medical researchers are provided with important information, which may help them in their efforts to conquer human disease.

The formation of these hybrids is a relatively recent phenomenon with some scientists say the more humanlike the animal, the better research model for testing drugs or possibly growing "spare parts," such as livers, to transplant into humans. Watching how human cells mature and interact in a living creature may also lead to the discoveries of new medical treatments.

The successful application of these techniques has raised important ethical questions. For example, should there be a limit to the amount of human DNA inserted into an animal? Should such limits be enforced for transgenic research, which has great therapeutic benefit for human beings? How would such "therapeutic benefit" be determined?

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