Does ‘humanizing’ mice for drug experiments pose ethical challenges for researchers?

Biomedical research has discovered the value of humanizing rodents and using genetics to better predict the after-effects of many drugs and procedures. And, while we might feel sorry for the little lab mice, these little creatures are helping us better understand disease so we can cure serious illnesses.

For years, scientists relied on animals as models for human disease. Initially, we used fruit flies and roundworms as models because they’re genetically similar to humans. But, mice were more so — sharing 97.5 percent of their working DNA with human beings. The mouse was also the first non-human creature to have its genome fully mapped.

Researchers found that there were only 21 genes that humans had that mice didn’t. In mice, there were only 14 genes unique to them.

Some companies are attempting to ‘humanize’ mice — that is to say — to make them more like us on the genetic level. As explained here, with the advances that have come from genetic modification, scientists are now able to alter the DNA of mice. For example, they have created mice with small amounts of human brain cells in an effort to make realistic models of neurological disorders such as Parkinson’s disease. By doing so they can mimic the human physiology at least for certain functions. For instance, if they want to measure the response of a drug on liver function, they can make attempt to make the liver of lab mice more closely match the characteristics of the human liver. This way the scientists can monitor the results of such tests and more accurately predict what the human implications would be.

This could revolutionize how drugs are studied. Instead of using human beings as test subjects in clinical trials, mice could be used to test drugs with near-perfect accuracy.

Researchers hope to alter mouse genes to express human proteins, for example, or to carry human cells or other tissues — even organs.

In this way, mice could stand in as proxies for humans. We could test drugs on mice with two-year natural lifespans and see both lifetime and generational effects on those mice. This kind of alteration would also allow scientists to do preclinical *in vivo* tests where there are currently no good models to use for humans.

In fact, in recent years, this type of technology has already helped scientists study the effects of various pathogens and viruses on mice implanted with human livers, tumors, pancreatic cells, and various types of immune cells. Some research has also been carried out on mice with glial cells from a human nervous system.

Special mice with modified immune systems have also been used to test various diseases, like HIV/AIDS and hepatitis C — diseases that normal mice cannot get.

What fialuridine can teach us about testing

The “humanized mice” idea started after a catastrophic failure of the drug fialuridine. The infamous phase 2 clinical trial in 1993 saw five human subjects die a terrible death. The drug, which was meant to treat Hepatitis B viral infections, instead built up to toxic levels in human subjects and killed them. The drug never affected mice, rats, dogs, and primates in this way, however. Scientists, at the time, didn’t realize that a nucleoside transporter in human beings works very differently than in all of the previous test subjects.

Researchers later wanted to see if genetically altered mice could experience the same toxic effects as the humans in the 1993 study. So, they replaced 90 percent of the mice’s liver cells with human liver cells. Researchers found that chimeric mice developed the same toxicity symptoms as the humans in the 1993 study did.

Going forward, drugs like fialuridine can be stopped in the research stage before they cause harm to human beings.

Non-animal testing

Still, there’s an ongoing debate in scientific circles. How ethical is it to use animals as test subjects? Many scientists are split on the issue, with vocal opponents and proponents making a case against and for animal testing, respectively.

And, it’s not just mice scientists are worried about. Some test subjects include higher-level animals, like chimpanzees. Chimps are used because they share 99 percent of our DNA, making them excellent proxies for humans.

At the same time, many people believe chimpanzees deserve to be treated with dignity and respect, and that precludes using them as test subjects for potentially dangerous drugs. If chimps can’t be used, where will new treatments come from? This is where proponents have a strong argument: “which is better — testing on chimps or humans?”

It’s a tricky issue. But the debate may never be clearly resolved because medical technology is advancing to a point where animals may be unnecessary in the future. By growing entire living organs, and tissues, scientists can test treatments directly on live human organs without the need for animal models. So-called “human avatars” could replace test animals altogether.

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