Introduction

I'm Jarrod Bailey, a geneticist, a research associate at Newcastle University in England for the last 13 years, and a scientific consultant to the New England Anti-Vivisection Society (or NEAVS). I'd like to thank the IOM for inviting me to speak today.

Given the ethical and economic concerns surrounding invasive chimpanzee research, we all agree that it is imperative that science critically assesses claims that it is useful or necessary. Part of my work over the last 6 years has been to critically assess the contributions of chimpanzee research to some of the biggest killer diseases affecting humanity, and I'd like to present some of this to you now, and draw your attention to the summaries of this work that I've provided you all with.

HIV/AIDS

The first disease examined was AIDS—the reason why so many chimpanzees were bred for research in the U.S. and why we have had a 'surplus' of lab chimpanzees for so long. I assessed the contribution of chimpanzees to AIDS vaccine development, by comparing the results of HIV vaccine trials in chimpanzees and humans, to determine to what degree the chimpanzee trials were predictive of human vaccine responses. This showed that:

Vaccine responses in chimpanzees are not predictive of responses in humans.

At the time of this work in 2008, 85 different HIV vaccines had been tested in almost 200 clinical trials: protection and/or significant therapeutic effects had not been shown by any of the vaccines in humans, in spite of many 'successful' trials of most vaccine types in chimpanzees.

Claims that chimpanzees are still important for testing HIV/AIDS vaccines therefore have no scientific foundation, illustrated further by:

- AIDS-related chimpanzee studies falling by around 90% in the last decade.

- The fact that chimps don't get AIDS, with just one seriously flawed exception.

- VaxGen's AIDSVAX vaccines failed to protect almost 8000 trial participants from HIV infection, despite being perhaps the most promising vaccines ever.

Cancer

A study of cancer research showed that chimpanzees have scarcely been used in cancer research at all. Chimpanzees actually have a very low incidence of cancer, especially epithelial cancers that kill many human patients, and chimp tumours are biologically different from human cancers. There are differences in the causes and initiation of tumours, and in apoptosis and metastasis, for instance.

Available evidence also indicates chimpanzees are not essential in the development of therapeutic monoclonal antibodies for cancer. No publications were found describing chimpanzee use in the development or testing of these drugs.

The few papers that did describe potential new cancer therapies tested in chimpanzees included warnings concerning species differences, acknowledged that the chimpanzee model performed no better than other animal models, and/or described interventions that had not been pursued clinically.

Nutritional and ecological differences contribute to differences in cancer incidence between the species, but cannot coherently explain an order of magnitude increase in cancers of the breast, ovary, lung, stomach, colon and rectum in humans. Rather, research implicates some of the estimated 40 million various genetic differences between humans and chimpanzees. For instance, around 500 genes involved in apoptosis and DNA repair are differentially spliced, regulated, expressed and post-translationally modified.

HepC

Human-based research features heavily in historical accounts of the discovery and early characterisation of hepatitis C.

Chimpanzees were useful in the generation of serum samples with high titers of the infectious agent, which aided identification of HCV. But: many advanced molecular techniques that now exist were not available then; and in retrospect, it is likely that the use of uncharacterized ('standard' titer) samples not screened in chimpanzees would have been equally useful for cDNA library construction, and to the eventual identification of HCV clones and the virus itself.

Chimpanzee Hep C research has declined by around 50-60% over the past 30 years and is at an historic low—while the use of non-animal hep C research methods has increased 80 times over the same period.

There are now many robust *in vitro* methods for hep C research. It is possible to investigate the entire HCV life cycle and to identify and test new therapies and vaccines, and many more things – in vitro, and all in a human context. While full life-cycle infectious cellular clones represent the long awaited and most comprehensive system for many aspects of HCV study, all the *in vitro* methods employed, including primary and immortalized cell cultures, infectious molecular clones, replicons, and virus-like particles and pseudoparticles, have added greatly to the body of hepatitis C knowledge and progress toward treatments, especially when supported by clinical, epidemiological, *ex vivo* and *in silico* methods.

Finally, chimpanzees are used infrequently in the development of HCV antiviral drugs. Regulatory requirements have been fulfilled in the majority of cases without recourse to chimpanzee use. GlaxoSmithKline recently decided that they could do without chimpanzees in their research, including for HepC drugs and vaccines. Where chimpanzee experiments have been performed, it can be argued that they were redundant. The role of the target molecule in HCV replication of the drug SPC3649, and of the therapeutic potential of it and other related agents, were recently reported from chimp studies, but have been described over the last four years via human tissue culture and other *in vitro* experiments.

Genetics

Genetic differences underpin all of this evidence for the chimpanzee as a poor model for human disease research. It is often claimed that humans and chimpanzees are 98-99% genetically identical, and that it *must* therefore follow that they are very similar biologically – in the diseases that they suffer, and in their responses to infectious agents and drugs, and so on.

But it is facile and even dishonest to do this. Humans and chimps are actually about 94% genetically similar—a big difference—and when account is taken of genomic rearrangements, mobile DNA elements such as long and short interspersed elements (LINEs and SINEs), duplications and gene deletions, copy number variation, differences in transcription factors and their binding sites, DNA methylation, miRNAs and their binding sites, gene editing and splicing, protein phosphorylation, and more, we see a bigger and truer picture.

Such differences are present in genes involved in: tumour formation; the immune system; in cancer, schizophrenia and other cognitive disorders, migraine, and autoimmune diseases like lupus and rheumatoid arthritis; in HIV infection; in Alzheimer's, Parkinson's and Huntington's diseases.

Differences in gene expression occur throughout the body: 1/3 to 2/3 of genes differ in expression in human and chimpanzee liver, kidney, brain, heart and testes, for instance.

80% of orthologous proteins differ to some degree in their amino acid sequences. Dozens of human proteins that interact with HIV have no orthologue in chimpanzees, and thousands of HIV-interacting proteins have hundreds of species-specific phosphorylation sites, affecting protein stabilities, interactions, and enzyme activities.

In short, there are many and fundamental genetic reasons why chimpanzees, however closely related they are to humans, are not and cannot be good models in research.

Efficacy

This all brings us back to the very first investigation I did for NEAVS, which asked, 'How are chimps actually being used? And how important is that use?'

Of the 1000 or so chimpanzees in U.S. labs today, only about 10-20% are in active research protocols at any one time. And their use is decreasing dramatically: chimpanzee AIDS studies down nearly 90% in recent years; and chimp hepatitis C research down 50-60% and at a historic low.

But it also appears that when chimps *are* used, that use isn't considered important by science. Our citation analysis showed:

…that greater than 85% of a large, randomised and representative sample of chimpanzee studies are not cited at all, or not cited with any relevance to human medicine. Just 15% *had* been cited in human medical papers …

And in all cases – that 15% of chimpanzee experiments that had been cited in human medical papers had contributed little, if anything, to the outcome of those studies reporting an advance in human clinical practice.

The actual contributors to those studies' overall findings were a wide array of *in vitro* research methods, human clinical and epidemiological

investigations, molecular assays and methods, and genomic studies and so on.

Trauma Studies

Finally, psychological studies on research chimpanzees show that chimps in labs suffer from PTSD as defined by human criteria. This has scientific, as well as ethical consequences, because stress causes significant increases in cortisol—and cortisol affects the immune system and has been associated with many human diseases. In humans, stress affects 49 different genetic pathways including pathways and genes associated with the immune system—crucial for the study of infectious diseases such as hepatitis C and HIV/AIDS—and many of their vital organs such as the liver—important for the metabolism of drugs being tested and central to the study of the effects of hepatitis C virus—the brain, in neuroscience research—and so on. Lab chimps are stressed chimps—and stressed chimps show biological consequences of this, such as different gene expression affecting all major organs and the immune system. Even if they were a 'good' research model, the inherent stress of their lab life renders data from their experiments confounding.

Summary

So in summary, after careful review of over thirty years of chimpanzee use in many areas of human disease research, the following conclusions can be drawn and supported scientifically: the use of chimpanzees in research has declined massively, both in the long-term and short term; they're rarely used today; they have proven to be poor models in many areas, including HIV/AIDS, and hepatitis C; chimpanzee use in cancer and heart disease research has been almost non-existent because they either don't get the disease, or they get a very different disease; there is burgeoning evidence of major, important and widespread genetic differences showing *why* chimpanzees are poor models for human research….and why they can *never* be good models.

None of these points would be true if chimpanzees really were a crucial and indispensable research model, without which we can't hope to treat or cure human diseases.

Thank you very much for your attention, and I'd like to emphasize my eagerness, willingness and ability to serve on this committee and be a strong asset to its task at hand.