NAS/IOM Committee Meeting on

The Use of Chimpanzees in Biomedical and Behavioral Research

Presentation by

Jarrod Bailey, PhD
Science Director/Consultant
New England Anti-Vivisection Society

May 26, 2011

New England Anti-Vivisection Society | 333 Washington Street, Suite 850 | Boston, MA 02108

PAPERS AVAILABLE ON REQUEST

An Assessment of the Role of Chimpanzees in AIDS Vaccine Research

Bailey, J. (2008). Alternatives to Laboratory Animals (ATLA), 36(4), 381-428.

Abstract

Prior to Simian Immunodeficiency Virus (SIV)-infected macaques becoming the 'model of choice' in the 1990s, chimpanzees were widely used in AIDS vaccine research and testing. Faced with the continued failure to develop an effective human vaccine, some scientists are calling for a return to their widespread use. To assess the past and potential future contribution of chimpanzees to AIDS vaccine development, databases and published literature were systematically searched to compare the results of AIDS vaccine trials in chimpanzees with those of human clinical trials, and to determine whether the chimpanzee trials were predictive of the human response. Protective and/or therapeutic responses have been elicited in chimpanzees, via: passive antibody transfer; CD4 analogues; attenuated virus; many types and combinations of recombinant HIV proteins; DNA vaccines; recombinant adenovirus and canarypox vaccines; and many multi-component vaccines using more than one of these approaches. Immunogenicity has also been shown in chimpanzees for vaccinia-based and peptide vaccines. Protection and/or significant therapeutic effects have not been demonstrated by any vaccine to date in humans. Vaccine responses in chimpanzees and humans are highly discordant. Claims of the importance of chimpanzees in AIDS vaccine development are without foundation, and a return to the use of chimpanzees in AIDS research/vaccine development is scientifically unjustifiable.

Points of Interest from Study:

- Despite 85 different vaccines having been tested in 197 clinical trials, protection and/or significant therapeutic effects had not been demonstrated by any of those vaccines in humans, in spite of prior successful trials for most vaccines and vaccine types in chimpanzees.
- AIDS-related chimpanzee studies fell by nearly 90% from 1998 to 2005.
- VaxGen's AIDSVAX B/B and AIDSVAX B/E vaccines were the first to complete Phase III clinical trials. Comprising HIV gp120 proteins from different strains, AIDSVAX B/B failed to protect more than 5000 trial participants at high risk of HIV infection, and AIDSVAX B/E failed to provide protection against HIV infection for over 2500 users of injected drugs, despite repeated booster immunizations.

An Examination of Chimpanzee Use in Human Cancer Research

Bailey, J. (2009). Alternatives to Laboratory Animals (ATLA), 37(4), 399-416.

Abstract

Advocates of chimpanzee research claim the genetic similarity of humans and chimpanzees make them an indispensable research tool to combat human diseases. Given that cancer is a leading cause of human death worldwide, one might expect that if chimpanzees were needed for, or were productive in, cancer research, then they would have been widely used. This comprehensive literature analysis reveals that chimpanzees have scarcely been used in any form of cancer research, and that chimpanzee tumors are extremely rare and biologically different from human cancers. Often, chimpanzee citations described peripheral use of chimpanzee cells and genetic material in predominantly human genomic studies. Papers describing potential new cancer therapies noted significant concerns regarding the chimpanzee model. Other studies described interventions that have not been pursued clinically. Finally, available evidence indicates that chimpanzees are not essential in the development of therapeutic monoclonal antibodies. It would therefore be unscientific to claim that chimpanzees are vital to cancer research. On the contrary, it is reasonable to conclude that cancer research would not suffer, if the use of chimpanzees for this purpose were prohibited in the US. Genetic differences between humans and chimpanzees make them an unsuitable model for cancer, as well as other human diseases.

Points of Interest from Study:

- No publications were identified that described chimpanzee use in the development or testing of mAb cancer therapies.
- Papers describing potential new cancer therapies tested in chimpanzees included significant caveats concerning species differences, and acknowledged that the chimpanzee model performed no better than other animal models.
- At least twenty genes implicated in human cancers, some of which are definitively involved in tumor formation, are significantly different in chimpanzees.
- Significant differences have been identified in protease genes, many of which affect the immune system and that therefore have a potential bearing on tumor establishment and growth.
- 80% of orthologous proteins differ between humans and chimpanzees, including proteins linked to breast cancer. 6-8% of orthologous exons display pronounced differences in splicing, which affect diverse functions including gene expression, signal transduction, cell death, immune defense, and susceptibility to certain diseases, including cancers.

An Assessment of the Use of Chimpanzees in Hepatitis C Research Past, Present and Future: 1. Validity of the Chimpanzee Model

Bailey, J. (2010). Alternatives to Laboratory Animals (ATLA), 38(5), 387-418.

Abstract

The USA is the only significant user of chimpanzees in biomedical research in the world, since many countries have banned or limited the practice due to substantial ethical, economic and scientific concerns. Advocates of chimpanzee use cite hepatitis C research as a major reason for its necessity and continuation, in spite of supporting evidence that is scant and often anecdotal. This paper examines the scientific and ethical issues surrounding chimpanzee hepatitis C research, and concludes that claims of the necessity of chimpanzees in historical and future hepatitis C research are exaggerated and unjustifiable, respectively. The chimpanzee model has several major scientific, ethical, economic and practical caveats. It has made a relatively negligible contribution to knowledge of, and tangible progress against, the hepatitis C virus compared to non-chimpanzee research, and must be considered scientifically redundant, given the array of alternative methods of inquiry now available. The continuation of chimpanzee use in hepatitis C research adversely affects scientific progress, as well as chimpanzees and humans in need of treatment. Unfounded claims of its necessity should not discourage changes in public policy regarding the use of chimpanzees in U.S. laboratories.

Points of Interest from Study:

- Human-based research features heavily in the discovery of hepatitis C and its causative agent.
- The acknowledged human-based contributions include: demonstrating that non-A non-B hepatitis (NANBH) was the salient complication of transfusion therapy; defining NANBH's natural history; identifying surrogate markers of the disease, such as alanine aminotransferase; and lowering the incidence of transfusion-associated NANBH, even prior to the identification of the virus itself.
- Chimpanzees were useful in the generation of serum samples with high titers of the infectious agent, which aided identification of HCV. Many advanced molecular techniques that now exist were not available then, however;
- …and in retrospect, it is likely that the use of uncharacterized ('standard' titer) samples would have been equally useful for cDNA library construction, and to the eventual identification of HCV clones and the virus itself.
- Chimpanzees are infrequently used in the development of HCV antiviral drugs.
- Regulatory requirements for preclinical PK and toxicological data from two animal species have been fulfilled in the majority of cases—as is the case for HCV vaccine development—without recourse to chimpanzee use.
- GlaxoSmithKline recently decided that they could do without chimpanzees in their research, including their hepatitis C research.
- Where chimpanzee experiments have been performed, it can be argued that they were redundant. Chimpanzee use was recently reported in the development of the miRNA drug, SPC3649. However, the role of the target molecule of the drug, miRNA-122, in HCV replication was described four years prior via tissue culture experiments with human liver cells. Subsequent *in vitro* experiments demonstrated the therapeutic potential of other agents very similar to SPC3649, in decreasing the level of HCV during infection.

An Assessment of the Use of Chimpanzees in Hepatitis C Research Past, Present and Future: 2. Alternative Replacement Methods

Bailey, J. (2010). Alternatives to Laboratory Animals (ATLA), 38(6), 471-494.

Abstract

The use of chimpanzees in hepatitis C virus (HCV) research was examined in the report associated with this paper (*1: Validity of the Chimpanzee Model*), in which it was concluded that claims of past necessity of chimpanzee use were exaggerated, and that claims of current and future indispensability were unjustifiable. Furthermore, given the serious scientific and ethical issues surrounding chimpanzee experimentation, it was proposed that it must now be considered redundant—particularly in light of the demonstrable contribution of alternative methods to past and current scientific progress, and the future promise that these methods hold. This paper builds on this evidence, by examining the development of alternative approaches to the investigation of HCV, and by reviewing examples of how these methods have contributed, and are continuing to contribute substantially, to progress in this field. It augments the argument against chimpanzee use by demonstrating the comprehensive nature of these methods and the valuable data they deliver. The entire life-cycle of HCV can now be investigated in a human (and much more relevant) context, without recourse to chimpanzee use. This also includes the testing of new therapies and vaccines. Consequently, there is no sound argument against the changes in public policy that propose a move away from chimpanzee use in U.S. laboratories.

Points of Interest from Study:

- While full life-cycle infectious cellular clones represent the long awaited comprehensive *in vitro* system for many aspects of HCV study, all the *in vitro* methods employed, including HCV-infected cultured primary and immortalized cells, infectious molecular clones, subgenomic and genomic replicons, and virus-like particles and pseudoparticles, have added greatly to the body of knowledge on the hepatitis C virus, pathology, and treatments.

- Full life- cycle infectious clones (HCVcc), which were urgently called for by the research community for decades, can provide all the necessary data to facilitate the development and testing of HCV therapies, when supported by clinical, epidemiological, *ex vivo* and *in silico* methods.

- It is now possible to investigate the complete HCV life-cycle, from host-cell attachment to release of progeny, immune responses to infection, the roles of host factors, identification of therapeutic targets, testing of new therapies and vaccines, and so on, in a human, and therefore completely relevant, context.

- While chimpanzee hepatitis C research has declined by 50-60% over the last three decades, the use of non-animal alternatives has increased 80-fold.

Lessons from Chimpanzee-based Human Disease Research: the Implications of Genetic Differences

Bailey, J. (2011). In Review.

Abstract

The validity of using chimpanzees to investigate human diseases is frequently asserted via claims of the 98 – 99% genetic similarity between humans and chimpanzees. Critical analyses of the relevance of chimpanzee studies to human biology, however, indicate that this genetic similarity does not result in sufficient physiological similarity for the chimpanzee to constitute a good model for research, and that there is a lack of translation of chimpanzee data to clinical practice and progress. Examples include: the minimal citation of chimpanzee research relevant to human medicine; highly different pathology of HIV/AIDS and hepatitis C virus infection and lack of correlation of vaccine and treatment efficacy for these diseases; lack of usefulness in cancer research; and others. The major molecular differences underlying these interspecies phenotypic disparities have been revealed by comparative genomics and molecular biology: namely, key differences in all aspects of gene expression, from chromosome structure through to post-translational modifications. The collective effects of these differences are striking, extensive and widespread, and show the *superficial* similarity between human and chimpanzee genetic sequences to be of little consequence for biomedical research. The extrapolation of biomedical data from the chimpanzee to the human is therefore highly unreliable, and the chimpanzee model must be considered of little value, particularly given the breadth and potential of alternative methods of scientific enquiry currently available to science.

Points of Interest from Study:

- The following phenomena all contribute to human/chimpanzee biological differences, above and beyond simple nucleotide substitutions: genomic rearrangements, mobile DNA elements such as 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.

- Many genes are present in humans but entirely absent in chimpanzees, or vice versa, largely due to the duplication and deletion of large genomic regions already noted. Since the evolutionary split of humans and chimpanzees, humans have gained 689 genes and lost 86, while chimpanzees have gained 26 genes and lost 729 that are still present in humans. This means that humans differ by 6.4% in terms of their gene complement *alone* (1,418 genes out of 22,000).

- One study analyzed an average of approximately 10,500 genes in various organs and found that a striking 34% showed differential expression between humans and chimpanzees in the brain, 25% differed in the liver, 33% in the kidney, 35% in the heart, and 62% in the testes. Another study, which analyzed even more genes (17,231), identified 16.3% of genes in the liver, 19.5% in the kidney, and 18.5% in the heart that were expressed to different levels.

- 80% of orthologous proteins were found to differ to some degree in their amino acid sequences, by an average of two amino acids per protein. A comparative analysis of proteins that interact with HIV-1 revealed that, of 1,447 such human proteins, 77 had no ortholog in nonhumans, including chimpanzees. For 1,370 human and chimpanzee orthologous proteins that were compared, each species had more than 600 species-specific phosphorylation sites, potentially affecting thousands of protein-protein interactions, enzyme activities, and protein stabilities.

Chimpanzee Research: An Examination of Its Contribution to Biomedical Knowledge and Efficacy in Combating Human Diseases

Bailey, J., Balcombe, J. & Capaldo, T. (2007). Project R&R.

Abstract

Research on captive chimpanzees (*Pan troglodytes*) incurs considerable animal welfare, ethical and financial costs. Advocates of such research claim these costs are outweighed by substantial advancements in biomedical knowledge, and that the genetic similarity of chimpanzees to humans enables the former to make critical contributions to preventing, diagnosing and combating human diseases. To assess these claims, we examined the disciplines investigated in 749 studies of captive chimpanzees published from 1995 – 2004 inclusive, and subjected 95 randomly selected papers to a detailed citation analysis: 49.5% (47/95) of papers had not been cited at the time of this study; 38.5% (34/95) were cited by 116 papers that did not describe well-developed methods for combating human diseases; 14.7% (14/95) of these chimpanzee studies were cited by (a total of 27) papers describing well-developed prophylactic, diagnostic or therapeutic methods for combating human diseases. Close examination of these 27 human medical papers revealed that *in vitro* research, human clinical and epidemiological investigations, molecular assays and methods, and genomic studies, contributed most to their development. Duplication of human outcomes, inconsistency with other human or primate data, and other causes resulted in the absence of any chimpanzee study demonstrating an essential contribution, or, in most cases, even a significant contribution of any kind, towards the development of the described human treatment.

Points of Interest from Study:

- The chimpanzee studies cited in each of the 27 citing human medical papers did not contribute to the findings of those papers for various reasons. These may be summarized as follows:

Reason for lack of contribution of chimpanzee study to human prophylactic, diagnostic or therapeutic method	**Total number of reviews in category (of 27)**
Redundant (concurrent human experiments/"confirmations" of human data)	14
Method not developed further (possibly due to chimpanzee/human differences)	7
Chimpanzee study peripheral to human method described	7
Historical citation with no direct relevance	3
Inconsistent with data from other NHP studies	3
Inconsistent with human data	2
Purely speculative in nature	2
May have helped establish need for new diagnostic method but did not contribute further to its development.	1

Building an Inner Sanctuary: Complex PTSD in Chimpanzees

Bradshaw, G.A., Capaldo, T., Lindner, L., & Grow, G. (2008). Journal of Trauma & Dissociation, 9(1), 9-34.

Abstract

Through the analysis of case studies of chimpanzees *(Pan troglodytes)* in residence at a sanctuary, who previously sustained prolonged captivity and biomedical experimentation, we illustrate how human psychological models of diagnosis and treatment might be approached in great apes. This study reflects growing attention to ethical, scientific, and practical problems associated with psychological well-being of animals. The analysis concludes that a diagnosis of Complex PTSD in chimpanzees is consistent with descriptions of trauma-induced symptoms as described by the DSM-IV and human trauma research. We report on how these findings contribute to diagnosis and treatment of chimpanzees in captivity and elucidate discussion concerning their continued laboratory use. This clinical study contributes toward theory and therapeutic practices of an emergent trans-species psychology inclusive of both humans and other species. Such an ability to extend what we know about models of human trauma opens deeper understanding and insights into ourselves as well as individuals from other species.

Developmental Context Effects on Bicultural Posttrauma Self Repair in Chimpanzees

Bradshaw, G.A., Capaldo, T., Lindner, L., & Grow, G. (2009). Developmental Psychology, 45(5), 1376-1388.

Abstract

Longitudinal studies have shown how early developmental contexts contribute significantly to self-development; their influence extends through adulthood, informs sociality, and affects resilience under severe stress. While the importance of sociality in trauma recovery is recognized, the relationship between developmental and posttrauma contexts and recovery effects is less appreciated, particularly in cases in which recovery contexts differ widely from the culture of origin. Using an attachment-based model of bicultural (competence in two cultures) development, the authors examined the role of self in posttrauma repair of chimpanzees (*Pan troglodytes*) who had been differentially reared by humans during neuroethologically formative periods and subsequently used as biomedical subjects. Results show that variations in posttrauma schema correlate with early socialization patterns. Self-resilience supports, but also may constrain, recovery depending on the compatibility of internal self models with recovery resources. Trauma severity notwithstanding, the cultural context of origin emerges as a critical factor in designing effective therapeutic intervention and assessments in primates, humans inclusive. Finally, the results underscore the ethical implications for the practices of cross-fostering nonhuman primates and their use in research.

Points of Interest from these Studies:

- The chimpanzees' symptoms of hypervigilance, dissociation, violent self-attacks, insomnia, ritualistic behaviors, inability to tolerate touch and limited social skills are representative of human trauma survivors as well as other chimpanzees from research.

- Based on these findings, there is a strong argument that the Animal Welfare Act's requirement that the psychological well-being of primates is met is not possible for chimpanzees.

- Chimpanzees subjected to laboratory confinement and biomedical research and testing exhibit trauma-induced psychological symptoms, and those cross-fostered must contend with an identity crisis and the enhanced vulnerability and compounded trauma this presents.

- Cross-fostered chimpanzees show a compromised ability to socialize with other chimpanzees, and symptoms consistent with a diagnosis of depression.

- There is a great deal of evidence that laboratory animals are also inherently stressed animals. Significant increases in cortisol—a measurable indicator of stress—occur in chimpanzees following anesthesia (a known stressor) that may be measured in their urine and feces for up to two days. Cortisol affects the immune system, and has been associated with human diseases including obesity, Alzheimer's disease, AIDS dementia, and depression. It affects glucose metabolism, inflammation and various components of the immune system that are associated with type 2 diabetes; and in humans, 49 different genetic pathways including genes associated with the immune system. It must be accepted that experiments using chimpanzees produce data from *stressed* chimpanzees. Stress-associated differences in gene expression must therefore be taken into account, which affect chimpanzees' immune systems—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.