Author's response to reviews

Title: Human-animal Chimeras for Vaccine Development: An Endangered Species or Opportunity for the Developing World?

Authors:

Anant Bhan (anant.bhan@mrcglobal.org)  
Peter A. Singer (peter.singer@mrcglobal.org)  
Abdallah S. Daar (a.daar@utoronto.ca)

Version: 3 Date: 25 March 2010

Author's response to reviews: see over
Author's response to reviews

Title: Human-animal Chimeras for Vaccine Development: An Endangered Species or Opportunity for the Developing World

Manuscript ID: 7372073393194490

Authors:
Anant Bhan (anant.bhan@mrcglobal.org)
Peter A. Singer (peter.singer@mrcglobal.org)
Abdallah S. Daar (a.daar@utoronto.ca)

Version: 2 Date: 23 March 2010

Author's response to reviews: see over
To,         23 March 2010
The Editor-in-Chief,
BMC International Health and Human Rights

Subject: Re-Submission of commentary titled “Human-animal Chimeras for Vaccine Development: An Endangered Species or Opportunity for the Developing World”; commentary id number MS: 7372073393194490

Dear Dr. Morton,

Thank you for your email dated 5th February 2010 and for providing us the reviewer comments for the manuscript.

We found the comments of the reviewers very useful in revising our manuscript and we have taken all comments into consideration while modifying our manuscript.

A revised version of the manuscript is being submitted, and we are also listing in detail in the following section our response to the reviewers and highlighting the relevant modifications made. We hope these revisions will adequately address the reviewer comments we have received. We would be happy to respond to any further queries.

Thank you.

Best wishes,
Abdallah S. Daar
Peter A. Singer
Anant Bhan
Response to reviewer Laurie Zoloth

We thank Dr. Zoloth for her comments on our manuscript.

Dr. Zoloth feels that we are giving an impression in the manuscript that chimeras in western cultural and folk traditions are only seen as monsters, and that hence this is linked to the negative impressions in parts of the west at present. She feels it would be problematic to give such an impression, since there are instances of human shape-changers and werewolves in western traditions which are not necessarily evil, but rather could be forces of good.

We would like to clarify that we do not want through the manuscript to give any such impression of chimeras historically in the west being evil and in the east being looked upon as good. What we would like to focus in on is the fact that there have been historical and folk depictions of chimeras in the west and east, both positive and negative, but the opposition to the use of chimeras (especially on moral and political grounds) is much more stark currently in the west. On the contrary, the perspectives towards chimeras in the developing world could be considered generally more welcoming. This includes the fact that chimeras remain part of contemporary folk and religious identity and practice in countries such as India (as mentioned in the article through the examples). We link this to the need for encouraging more research using human-animal chimeras in the developing world.

We have modified the content of the section titled ‘Developing World Perspectives on Chimeras Welcoming’ accordingly: “Human-animal chimeras have been part of the cultural traditions in most parts of the world. This includes the west, where descriptions of human shape-changers, who changed shape yet remained human, were part of folklore in both Christian and Jewish traditions. An example is the description of the ‘Proteus legend’ by Homer as a prophet who could change shape to various forms including animals, if captured [20]. However, in current debates in the west, opposition to human-animal chimeras based on conservative political viewpoints and ‘moral taboo argument(s)’ [21] is quite vocal, and influences policy making in this area.”
Response to reviewer Zdenek Hel

We thank Dr. Zdenek Hel for his feedback on our manuscript.

a. Dr. Hel has requested that we clarify that human-animal chimeras are not a new concept, various forms of hybrids have been used for many years, and there are instances of mammalian cultures, genes expressed in rodent models etc.

We have put in an additional line “Human-animal chimeras have been used in research for the past few years, and have been crucial to study diseases and developing therapies for them” in the manuscript in the background section. Also we would like to clarify that the focus of the paper is on human-animal chimeras specifically produced for vaccine development (as specified in the title of the paper).

b. Dr Hel is concerned that we seem to be advocating shifting the moral responsibility of conducting research for global health problems from the west to the scientists and administrators in the developing world. It’s not our intention to stress on the need for the onus of the research for important global health problems to be shifted to the developing world. Rather, what we are suggesting is that given the more liberal viewpoints about chimeras, and increasing scientific capacity in countries such as India and China, research in these countries in developing human-animal chimeras for testing vaccines should be encouraged. We have put in a line in the way forward section clarifying this “This would be a way to move the scientific field forward, and to address the development of solutions to important global health problems; this would supplement the excellent work happening in the west in this area, which is sometimes held up because of conservative attitudes to human-animal chimeras”.

c. Dr. Hel also points out that we should make sure that the message which goes out includes a caution for the need for the research with the chimeras to be carried out ethically, respectfully and without causing undue pain to the animals. We agree with Dr. Hel and have put in a caveat in our concluding sentence about ensuring that research funded in the developing world includes respectful treatment of the chimeras and also is properly carried out: “Researchers in developing countries with relevant scientific capacity such as China and India should develop research projects with this perspective in mind, knowing that, so long as they fulfill scientific and ethical criteria (including humane treatment of the human-animal chimeras, careful planning and conduct of experiments as well as regulation through mechanisms such as Animal Care and Use Committees and Stem cell Research Oversight Committees) for funding, they are likely to be successful.” It’s also important to point out that in most developing countries, animal research guidelines are well established and there is regulation carried out through mechanisms such as establishment of animal care and use committees.
Response to reviewer Alexander Ploss

We thank Dr. Ploss for his extensive comments and useful feedback on the article.

Dr. Ploss has encouraged us to be more specific in the article and argue on the basis of solid scientific facts. We have kept this in mind while revising the article.

In the section on growing interest in chimeras, we have included the following additions or modified the content as suggested by Dr. Ploss to reiterate the crucial role of human-animal chimeras in the conduct of vaccine candidate research:

1. ‘Vaccine candidate testing in large non-human primates like chimps is very costly, the number of animals available is usually small and there are concerns about inter-animal variability which effects data interpretation; also most jurisdictions discourage research on large non-human primates due to ethical concerns.’;
2. ‘Conducting testing in humans directly could be hazardous and expensive, scientifically improbable and also not allowed under current ethics guidelines’;
3. ‘Human-animal chimeras are particularly key because they can be made to resemble the human immune system for early, efficient and fast testing for efficacy of new vaccines; this is crucial because of the unique human tropism of these diseases’.

We have clarified the kind of human-animal chimeras we are focused in the article by mentioning: “In this article, we focus especially on human-animal chimeras which are xeno-transplantation models, and involve engraftment of human cells (such as blood forming progenitor cells, hepatocytes etc.) into specially conditioned mice. “ Also in the same section, we have expanded on the role of these chimeras to say: “Human-animal chimeras are particularly key because they can be made to have components which resemble the human immune system or human liver for early, efficient and fast testing for efficacy of new vaccines; this is crucial because of the unique human tropism of these diseases”

Dr. Ploss points out that the kind of human chimeras classified in the Human Chimera Prohibition Act would not cover the human-animal chimeras being developed for research with infectious diseases (and development of vaccines) which we are focused on in the article. We agree that this is true; we have mentioned the Act to discuss the prevailing atmosphere of general distrust in some sections of the American political landscape about research on chimeras, which could directly or indirectly delay use of human-animal chimeras in research. To clarify, we have qualified the mention of the act with the statement” to oppose of the use of certain kinds of human-animal chimeras”.
Dr Ploss points out that there is a lot of research currently ongoing for refining the protocols to differentiate human embryonic stem (ES) cells or induced pluripotent stem (iPS) cells in cell culture into various tissue specific cells, including liver cells and these will produce better human-animal chimeric mice, and hence the chances of human cells translocating to the nervous system of mice are very remote. We agree with Dr. Ploss about the robustness of the protocols, and the progress achieved which make the possibility of neural graftment of human cells (in the case of human-animal chimeras being developed with a humanized immune system or liver); we have hence added the following qualifier to the mention of possibility of transport of human cells to the mouse nervous system: “(though this is a very remote possibility given the advances in science and the refinement made in the protocols used)”.

The example of neural chimeras used in the context of ethical reservations about chimeras deals specifically with human-animal neural chimeras which could involve use of human fetal brain cells implanted in mice, and the extensive discussion in science policy and bioethics literature opposing development of human-animal neural chimeras. We use this as an illustration about the opposition to (specific kinds of) human-animal chimeras which is quite widespread in the west.

While we acknowledge the important point that Dr. Ploss makes that research with human-animal chimeras is crucial, but its costly and time-consuming and hence the need to call for more funding in the article, we have chosen to not focus in the article on the issue of need for more funding in the area. While its important for the progress of the science, we feel that the focus of the commentary needs to be focused on encouraging research with human-animal chimeras in the developing world, and not be expanded to look at larger issues around (the need for more) funding for research with human-animal chimeras at a global level.

In his comments about outlook, Dr. Ploss requests that we consider discussing scenarios to bring the opposite viewpoints together. We have attempted to do that by arguing for greater collaborations between developed and developing countries, but also stressed that important research should continue to be funded and encouraged especially in the developing world given the paucity of time to address the global health challenges. We have also stressed that such research in the developing world needs to be carried out in an environment of strong regulation and oversight to ensure that the quality of science and ethical propriety is maintained.

Also, we acknowledge that pharma companies will not make decisions to go ahead with specific vaccine candidates specifically on moral concerns, but rather on the basis of risk-benefit ratios and hard scientific facts. The focus of our article
is encouragement of more basic research with human-animal chimeras in the
developing world to speed up vaccine development. We believe that any vaccine
models developed either in the developing or developed world would of course
need to satisfy ethical and regulatory criteria about the risk-benefit ratio and also
have strong scientific data to support advancing to future human trials.

Again in this article, we do not focus on the issue of public engagement in
science which as Dr. Ploss mentions is important to address some of the
challenges associated with rigid views about areas such as research with
chimeras as we do not want to move away from the central argument of this
commentary. In the context of the developing world, we have published on public
engagement strategies for global health problems (Cohen et al, BMC Public
Health 2008, 8:168). Also in the context of regenerative medicine, work has been
done to inform and educate the public through the The Regenerative Medicine
Ethics Network (http://www.mrcglobal.org/projects/rmethnet)

Also Dr. Ploss has raised other specific concerns which we have responded to:

a) Our wording on Page 2: "...on human-animal chimera like beings…”
suggesting some level of consciousness in the animal due to the
humanization, which is not the case in immune and/or liver chimeras: this
mention has been made as when we have looked at instances of mentions of
chimeras in mythology, we have cast a wide compass to look at any
depictions of beings which have human-animal chimera characteristics. We
have not restricted ourselves to immune and/or liver chimeras as our focus is
on mythological and folk depictions.

b) We have changed the information about Hepatitis-C to include the statistics
about prevalence: “Recent research has raised hopes that better chimeric
mouse models of infection with Hepatitis- C virus, which infects 3 to 4 million
people worldwide annually (including a significant proportion in developing
countries) adding to the existing global burden of approximately 170 million
(or 3% of the world’s population) people who are chronically infected with
Hepatitis-C and at risk of progressing to severe and potentially fatal liver
disease, can be produced”.

c) We have changed reference 7 to reflect the discussion in the recent Cell Host
Microbe article by Legrand et al which is more relevant to the discussion
about human-animal chimeric mice model for Hepatitis-C as pointed out by
Dr. Ploss.

d) We have included information about the fact that there has been progress
after the work on the SCID-hu model through referencing the review
published in 2007: “Further work carried out in recent years on human-animal
chimeras has led to the development of specific and improved strains with
applications for translational research, as well encapsulated in a review
published in 2007”. 
e) Page 8: “..., for example in the literature on xenotransplantation”. The reference for this statement has now been provided as reference number 26.

f) We are cognizant that there are two other consortia funded to develop human-animal chimeras for vaccine development which are based in the west, we only used the specific case of the funding for the project based at Peking University, Beijing as an example of a project based in the developing world (in this case China) which has been funded. We have added a line in the text to point out that two other consortia based in the west are working on the same scientific challenge: “This is in addition to the funding granted to two consortia based in the west (Europe and the U.S.A.) as part of the same initiative for addressing the same scientific challenge of developing (humanized chimeric mice) model systems to evaluate live attenuated vaccine candidates”