Frequently Asked Questions on Chimera Proposal

1) What are the potential benefits of this research?

Research using animal models containing human cells is certainly not new. For example, the introduction of human stem cells into mice has been used to validate and characterize different types of stem cells. Some scientists hope the human cells will develop into specific tissues or organs for potential transplant purposes, or for drug testing. Other researchers are exploring the developmental nature of particular types of human cells, which may yield important insight into human biology and disease development. Animal models with human cells in the brain can be used to study many human brain diseases, including Parkinson's, Alzheimer's, and schizophrenia, and may be useful models for testing new drugs. Furthermore, these animal models could be used to study whether introduction of therapeutic human cells can improve outcomes for diseases that are caused by the death or dysfunction of neural or other brain cells, prior to testing the cells in people.

2) What kind of research does NIH anticipate funding in the future?

This will depend on the ideas of the research community, but if researchers are successful in the development of animal models with human tissues or organs, those animal models could have many research applications for studying disease development and testing new therapeutics, as well as a possible source of tissues or organs for transplant.

3) Does NIH currently have any policy in this research area?

Yes. The NIH Guidelines for Human Stem Cell Research prohibit the introduction of human pluripotent cells into non-human primate blastocyst-stage embryos, and prohibit the breeding of animals where the introduction of human pluripotent cells may have led to human sperm or human eggs being produced in the animal.

NIH proposed to revise the Guidelines to expand the existing prohibitions to include the introduction of human pluripotent stem cells in pre-blastocyst stage non-human primate embryos; and to expand the prohibition on research involving the breeding of animals to include the introduction of any type of human cell that may contribute to the germ line.

4) For what aspect of the chimera policy did NIH seek public comment?

NIH sought comment on the scope of the research to be considered by the steering committee, which we proposed to be: 1) research in which human pluripotent cells are introduced into non-human vertebrate embryos, up through the end of gastrulation stage, with the exception of non-human primates, which would only be considered after the blastocyst stage, or 2) research in which human cells are introduced into other mammals (excluding rodents), later in development, such that there could be either a substantial contribution or a substantial functional modification to the animal brain.

NIH also sought public comment on two modifications to the NIH Guidelines for Human Stem Cell Research. NIH proposed to revise the Guidelines to expand the existing prohibition on introducing human pluripotent stem cells (including human embryonic stem cells and induced pluripotent stem cells) into blastocyst stage non-human primate embryos to include the pre-blastocyst stage; and to expand the prohibition on research involving the breeding of animals where the introduction of any type of human cell may contribute to the germ line (egg or sperm cells).

5) How has NIH engaged stakeholders during this policy development?

During our consideration of potential policy modifications, NIH held a publically webcast workshop in November 2015 with leading experts to discuss the latest technical advances, future research plans, ethical and welfare issues, and strategies to promote progress and mitigate concerns. Dr. Carrie Wolinetz, NIH Associate Director for Science Policy also posted a blog about the moratorium and workshop.

NIH invited the public to provide input to our proposed policy changes, which were published on August 5, 2016, in the Federal Register and as an NIH Guide Notice. Dr. Wolinetz posted an accompanying blog and has been interviewed by multiple reporters.

6) When will NIH issue a final policy?

The public comment period closed on September 6, 2016, with the NIH receiving over 21,000 public comments. NIH is in the process of considering all of the public comments and developing a final policy. After NIH reaches a final decision, the policy will be announced in the Federal Register and the NIH Guide to Grants and Contracts. Until that time, the moratorium will remain in effect.

7) What sparked the moratorium?

A number of researchers are beginning to grow human tissues and organs in animals by introducing human pluripotent cells into early animal embryos. Various types of chimeric animals have been used in research for a long time, but this new approach raises the question of whether human cells could contribute to or affect off-target organs. That outcome could be problematic from ethical and animal welfare perspectives, particularly if there are significant alterations of the animal's cognitive state. NIH instituted a funding pause in September 2015 so the agency could consider whether new policy was needed to guide this area of research.

8) What is the purpose of the NIH steering committee's work?

The NIH steering committee will consider proposed research projects using certain types of human-animal chimeras, and provide programmatic input to the director of the relevant NIH Institute(s) or Center(s) (or equivalent NIH official responsible for funding decisions). The steering committee will not replace IACUC or IRB review.

9) Will this steering committee consideration affect peer review of grant applications?

No. The internal programmatic work by the steering committee will be conducted independent of, and in addition to, the usual peer review procedures for research at the NIH. The relevant IC director(s) will consider the input from the steering committee, in addition to other NIH programmatic input, as well as the funding recommendations and evaluations of the initial Scientific Review Group and the relevant Institute or Center's Advisory Council or Board.

10) Will the steering committee make funding recommendations or decisions?

No. Funding decisions will continue to be made by the same NIH officials who are currently making funding decisions.

11) What will be the composition of and duration of the steering committee?

The steering committee will be a new committee and composed of government employees only, with expertise in relevant scientific areas and animal welfare. NIH anticipates that the committee will be in existence for as long as NIH thinks that its consideration of proposed research is appropriate, which at this time is difficult to predict.

12) What criteria will the steering committee use in its considerations?

The steering committee consideration is expected to include these sorts of factors:

- the characteristics of the human cells to be introduced (including potency and any modifications of those cells);
- characteristics of the recipient animal (e.g., species, stage of development, and any modifications that affect location or function of human cells);
- other data relevant to the likely effects on the animal (e.g., changes in cognition, behavior, or physical appearance);
- planned monitoring (including animal welfare assessments); and
- any staging of proposed research (e.g. assessing outcome of particular experiment before conducting further experimentation).

13) What will be the process for reviewing these two specific types of chimera research projects outlined in the Federal Register?

a) All applications go through the NIH peer review process. Peer reviewers score the application for scientific and technical merit. No changes are being made to the peer review process.
b) Grant applicants who receive fundable scores will be asked to answer a short set of questions to be considered by an internal NIH steering committee. The questions will ask about the characteristics of the human cells, characteristics of the recipient animals, other data relevant to the likely effects on the animal, planned monitoring, and staging of the research.

c) The NIH Institute and Center Directors will make the final funding decision. The Director will consider the input from the steering committee, in addition to other NIH programmatic input, as well as the funding recommendations and evaluations of the initial Scientific Review Group and the relevant Institute or Center's Advisory Council or Board.

14) Will researchers need to put additional information into their grant applications?

Grant applicants who receive fundable scores will be asked to answer a short set of questions to be considered by the steering committee. The questions will ask about the characteristics of the human cells, characteristics of the recipient animals, other data relevant to the likely effects on the animal, planned monitoring, and staging of the research.

15) Will the form with instructions to applicants be revised?

Yes. Changes to the instructions to grant applicants require approval by the White House Office of Management and Budget.

16) Will this additional work by NIH slow down the grant review?

The steering committee will meet on a regular basis and consider research proposals as quickly as possible. As emphasized by the International Society for Stem Cell Research's 2016 guidelines, this is an area of science that could be extremely valuable for medicine, but deserves careful consideration.