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Lift NIH restrictions on chimera research

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## LETTERS

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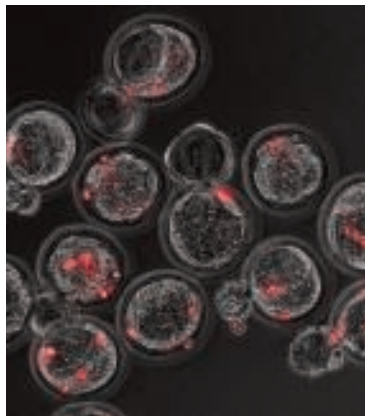
## Lift NIH restrictions on chimera research

MANY OVERSIGHT MECHANISMS exist for research involving human subjects and cells, as well as the transfer of materials into other vertebrates, partly to reassure the public that biomedical research is ethically conducted. In the recently posted notice NOT-OD-15-158, the NIH stated that it “will not fund research in which human pluripotent cells are introduced into non-human vertebrate animal pre-gastrulation-stage embryos while the agency considers a possible policy revision in this area” (1). This notice encompasses human pluripotent stem cells (hPSCs), including human induced pluripotent stem cell (hiPSC)-based human/non-human chimera studies. We believe that this notice poses a threat to progress in stem cell biology, developmental biology, and regenerative medicine. We hope the guideline recommendations that emerge from the NIH Workshop on 6 November will accelerate the decision to reinstate NIH funding for this research area, which has tremendous promise. We strongly believe that a continued dialogue between scientists and bioethicists regarding human/non-human chimera studies is critical for advancing human health through basic science.

Much of the bioethical concern in regard to human/non-human chimerism arises from the possibility of chimeric animals harboring human neurons and germ cells. Can human neural cells coexist with those from animals and establish “humanized” cerebral anatomy and circuitries? Furthermore, would such chimeras be elevated to a higher metaphysical state and “think” more like us (2)? Current scientific data have not supported such possibilities, despite hundreds of xenotransplant studies introducing human neurons into the mouse brain (3–5). With regard to germline transmission, the National Academy of Medicine and the National Research Council have stated in

the Guidelines for Human Embryonic Stem Cell Research that animals in which human pluripotent stem cells (hPSCs) have been introduced during development should not breed and that hPSC chimerism with non-human primates is restricted (6).

Research involving hPSC complementation in non-human, pre-gastrulation-stage vertebrate embryos represents a special topic with tremendous potential to elucidate early human development. Development of stem and progenitor cells from pre-gastrulation embryos occurs over the weeks following blastocyst implantation into appropriate hosts. Currently, it is impossible to accurately recapitulate human development in vitro, and there is no ethical



Engraftment of hiPSC (red) into mouse blastocyst-stage embryo

method to obtain post-implantation-stage human fetal tissue for isolating tissue and organ stem cells for regenerative medicine. Although early chimera studies involving hESCs/iPSCs and non-human vertebrate animal blastocysts have shown some capacity for contribution to host tissues (7–9), much work remains to unravel key differences in early development between humans and other vertebrates. If we

succeed in inducing significant chimerism between hPSCs and pre-gastrulation-stage embryos from non-human vertebrates, tremendous potential exists to develop humanized disease models for studying drug pharmacology. Similarly, implantation of hPSCs derived from patients with heritable diseases could illuminate genetic disease pathogenesis in an appropriate in vivo context. It may even be possible to generate an unlimited supply of therapeutic replacement organs using porcine or sheep models, an effort that we (H.N.) have undertaken with support from the California Institute for Regenerative Medicine. By eliminating federal funding for this research, the NIH casts a shadow of negativity towards all chimerism studies regardless of whether human cells are involved.

Ultimately, we believe that human/non-human chimerism studies in pre-gastrulation embryos hold tremendous potential to improve our understanding of early development, enhance disease modeling, and promote therapeutic discovery. Given that the objective of the NIH is to enable discoveries that advance human health, the restrictions presented

in NOT-OD-15-158 serve to impede scientific progress in regenerative medicine and should be lifted.

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## Making sense of the troubles at NEON

IN HIS 25 September News Feature “Ecology’s tough climb” (p. 1436), J. Mervis detailed the problems that have plagued the National Science Foundation’s (NSF’s) National Ecological Observatory Network (NEON). The severity of NEON’s troubles recently led to a congressional hearing in which James Olds, head of NSF’s Biological Sciences Directorate, said that NEON Inc. would be replaced as NEON’s contractor

if it didn't get its act together. I served as NEON's lead scientist and observatory director in 2013–2014, and Mervis summarized my own frustrations at NEON as an example of how poorly the project has been managed.

I agree with Mervis's assessment of what has gone wrong at NEON, but some additional clarification might help understand why. Thus far, the spotlight has primarily been on mismanagement by NEON Inc., which prompted the recent removal of its CEO as well as the congressional hearing. But NEON program directors at NSF also bear considerable responsibility for how the project has been run. The authority they hold extends to nearly all levels of the organization, as well as how it can and cannot interact with the external community. To date, their philosophy has been that the Observatory can be most efficiently built by project managers with minimal interference from scientists or members of the community. Applying this approach to a distributed ecological observatory that lacked a detailed blueprint was a mistake that has put NEON under a chronic strain. This

underlies a number of NEON Inc.'s present difficulties, its own management failures notwithstanding.

At the 18 September congressional hearing on NEON, Olds told panel members that "NSF is going to be sitting on NEON Inc. over the next three months...and we will know very quickly whether this organization is going to be successful under new leadership" (1). Sound management by whatever organization builds NEON is clearly needed to get the project back on track. But NEON's success will equally depend on improvements within NSF and a shift in perspective that puts stewardship of NEON science back in the hands of scientists.

**Scott V. Ollinger**

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1. Committee on Science, Space, and Technology, "Subcommittee on Research and Technology and Subcommittee on Oversight Hearing: NEON Warning Signs: Examining the Management of the National Ecological Observatory Network" (<https://science.house.gov/legislation/hearings/subcommittee-research-and-technology-and-subcommittee-oversight-hearing-neon>).

#### ONLINE BUZZ

## Disaster Preparedness

In her Editorial "Preparing for the next Katrina" (28 August, p. 905), M. McNutt discussed how far disaster preparedness has come in the past 10 years and how we should continue to move forward. Readers added their warnings and encouragement in the comments section. Excerpts from their comments are below. See the full comments, and add your own, at <http://comments.sciencemag.org/content/10.1126/science.aad2209>.

#### A selection of your thoughts:

...We would like to caution against an endorsement of the unqualified benefits of social media in all phases of a disaster. A recent report showed that people who used social media following Hurricane Sandy were more likely to exhibit higher levels of post-traumatic stress reactions when compared to survivors who opted for more traditional information providers [R. Goodwin *et al.*, *J. Psychiatr. Res.* **47**, 1099 (2013)]. A similar pattern of results was observed after the Super Typhoon Haiyan with regard to acute stress reactions and psychological distress [R. Goodwin *et al.*, *Psychother. Psychosom.* **84**, 253 (2015)]. Even informed social media can result in "stress contagion," wherein psychological difficulties experienced by some may augment the adverse effects of the event. Social media, in its sheer immediacy and volume, can rapidly overload the user, making it more difficult to coordinate effective behaviors.... Every asset has its liabilities....

**Menachem Ben-Ezra, Krzysztof Kaniasty, Robin Goodwin**

...The importance of communities being aware of...what they themselves might be able to do is essential. When the seawall cracks or the tsunami strikes, it is an absolute duty of authorities and aid agencies to establish a meaningful engagement with populations so that people are respected....[I]f there truly is a listening process, populations are empowered....

**Martin Dawes**