

Summary of the symposium on ‘Non-Human Primate ART to ES Cells’

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One of the things I wanted to do before we end this symposium is to express our appreciation again to Barry and Carol for their organisational efforts. Thank you.

If I recall correctly, ‘non-human primate’ was featured in the title of this symposium yet it seems that this afternoon, the presentations focused on studies conducted in other species from sheep to humans. This exemplifies the unique problem faced by scientists using non-human primate models. Specifically regarding embryonic stem (ES) cell efforts, the bandwagon for human ES cell work is clearly moving and is well funded, in contrast to non-human primate work. This is entirely appropriate perhaps but we need to recognise the point and restrict our focus to studies that cannot readily be conducted in lower mammals or in humans. What are the specific applications in non-human primates that are justifiable in the minds of our presenters? From my perspective, areas that would be most appropriately researched with human ES cells include the development of feeder-free culture systems, the characterisation of signalling pathways and the molecular correlates of self-renewal or differentiation. The development of *in vitro*-directed differentiation protocols is another area that is appropriate with human ES cells. Steve Stice discussed the propagation and isolation of specific desirable phenotypes from human ES cells of potential interest to reproductive medicine as well as the need to isolate and define populations that are epigenetically normal and free of pluripotent cell contamination.

A second general comment that derives from our symposium today is that only a few non-human primate ES cell lines are available for distribution. The parthenote-derived, cynomolgus macaque line described by Jose Cibelli carries limitations because of its known epigenetic abnormalities. There are at the present time no restrictions, apart from funding, on the development of additional lines and so I hope we will see that in other macaque species. Third, and as a reiteration of what I’ve all ready said, non-human primate researchers must focus on studies that can’t be done in other species. An appropriate example might be the development of cell- or tissue-based treatments for neurodegenerative diseases where most animal models are inappropriate and efforts in patients are impacted by ethical concerns. A recent

report by Takagi and co-workers (2005) on the transplantation of ES cell-derived dopaminergic neuronal phenotypes into chemically lesioned monkeys with modest, but somewhat encouraging, results typifies how the monkey might be appropriately used in translational research.

Finally, we could itemize tools that are available or are needed to support our research efforts. We have a few existing lines, we have Keith Latham’s PREGER resource, and we now have a rhesus monkey Affychip, so we can begin characterisations of gene expression profiles, and we have lenti-viral-mediated introduction of reporter genes.

As to needs of the non-human primate research community, this could be a long list, for example, additional ES cell lines and training programs. The NIH has specifically targeted training programs for human embryonic stem cell research yet non-human primate ES cells are, if anything, more difficult to culture or maintain than are human ES cells. Another problem is animal access, which is inherent in working with valuable non-human primates. We need disease models in non-human primates and it might be noted that genetic screening for spontaneously occurring diseases is not yet operative throughout the Primate Center System. Rob Norgren told us about progress in creating disease models using a combination of gene targeting and somatic cell nuclear transfer. This is an exciting prospect but it might be well to remember that the monkey is not a mouse. Perhaps it is a somewhat trivial issue, but we need karyotyping services for non-human primates. In Shoukhrat Mitalipov’s presentation, loss of imprinting in ES cells would suggest that epigenetic evaluations should become a routine component of defining an ES cell line.

Regarding future directions for us to consider based on the presentations that we heard today, intra- and inter-line variability continues to be important. This is relevant to all ES cell lines, including those from the human, and might include differences based on embryo origin, epigenetic status, passage number, differentiation potential and cryopreservation history, to name just a few parameters. To reiterate, we need development of ES cell lines from new, under-represented non-human primates as unique applications in biomedical research exist for each species.

Finally, I would like to solicit input from the audience on how the non-human primate can best be used in translational research. Thank you for your participation in this symposium. I think it has been a profitable and an enjoyable day and I hope you agree. Would anybody like to comment on the appropriate uses of non-human primates or non-human primate ES cells?

Reference

- Takagi, Y., Takahashi, J., Saiki, H., Morizane, A., Hayashi, T., *et al.* (2005). Dopaminergic neurons generated from monkey embryonic stem cells function in a Parkinson primate model. *J. Clin. Invest.* **115**, 102–119. doi:10.1172/JCI200521137