

NATIONAL INSTITUTES OF HEALTH (NIH)  
RECOMBINANT DNA ADVISORY COMMITTEE (RAC)

140<sup>TH</sup> MEETING

RAC BIOETHICS DISCUSSION

BETHESDA, MD

BUILDING 45, CONFERENCE ROOM E1/E2

DECEMBER 11, 2014

Agenda

11:00 AM Welcome and Introductions

*Session I(a): Balancing Access to Clinical Research for Pediatric Patients with Ethical Standards in Early Phase Gene Transfer Trials*

11:10 AM **Regulations Governing Enrollment of Pediatric Patients into Research Trials that pose “Greater than Minimal Risk”**

**Speaker:** Kristina Borrer, Ph.D., Office for Human Research Protections, Rockville, MD

11:25 AM **FDA Perspective on Enrollment of Pediatric Patients in Early Phase Gene Transfer Trials**

**Speaker:** Wilson Bryan, M.D., Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, MD

11:35 PM **A Bioethicist and IRB’s Chair Perspective**

**Speaker:** Norman Fost, M.D., M.P.H., University of Wisconsin, Madison, WI

11:45 PM **Case Study 1:**

Several phase I, T cell immunotherapy protocols have shown significant efficacy (>50% response) in children with advanced cancer who have no other therapeutic options. Children at this stage of their disease have a very limited life expectancy. This approach has been less successful in adults with the same disease, and more toxicity was seen in adults than in children. Nonetheless, there have been serious toxicities in both children and adults. A new protocol will target the same hematologic cancer for which previous T cell immunotherapy protocols have

demonstrated significant clinical benefit for children; however, the target antigen for the gene modified T cells was changed. The design of the trial, including dosing, draws on the experience of previous protocols. Additionally, the preclinical data is as strong as what was seen in these other trials. The investigators propose to enroll children in this trial.

- Is it necessary to enroll adults first? Why or why not?
- Should older children be preferentially enrolled over younger children?
- How should assent be obtained if older children are enrolled?

**Panelists:** Crystal Mackall, M.D., National Cancer Center (NCI) National Institutes of Health (NIH), Bethesda, MD

David Maloney, M.D. Fred Hutchinson Cancer Center, Seattle, WA  
Melinda Merchant, M.D., NCI, NIH, Bethesda, MD

Catherine Bollard, M.D., MBChB, Children’s National Health System, Washington DC

**12:15 PM RAC Discussion**

**12:45 PM LUNCH**

*Session II: Communicating about Risks and Benefits in  
Early Gene Transfer Trials*

**1:20 PM Communication about Risk and Benefit in First in Human Trials**

Early phase studies are primarily designed to assess safety. While an individual participant may experience some clinical benefit, data across trials indicate that individual benefit is unlikely in early phase trials. One review of non-pediatric oncology trials from 1991- 2002, found that for studies testing a single investigational agent, a complete or partial response was seen in < 5% of participants, although a much higher number had stable disease or “less-than-partial” response (Hortstmann, E. *et al.* NEJM 2005; 353:895-904). It is estimated that more than 90% of investigational agents that enter clinical trials will fail to become a licensed product.

- While each trial is unique, how does one best communicate about the benefits of enrolling in a first-in human clinical trial?
- Does one need to communicate about the prospect of direct benefit in early phase pediatric trials?
- In addition, as gene transfer agents may persist and have long-term effects, should research participants be advised that enrollment in one trial could preclude enrollment in other investigational studies?

Review of sample language

**Lead Discussants:** Norm Fost, M.D., M.P.H.  
Michael Atkins, M.D., Georgetown Medical Center,  
Washington DC

*Session I(b): Balancing Access to Clinical Research for Pediatric Patients with Ethical Standards in Early Phase Gene Transfer Trials*

**2:20 PM**

**Case Study 2:**

A gene transfer agent is being developed for a severe progressive neurological disease. Some individuals live into young adulthood but at that time the disease is so advanced that it is not clear its course can be modified and many have diminished mental capacity to consent. Similarly, adolescents are often fairly far advanced but might be able to assent. This is a rare disease with limited population and it is anticipated that if one receives this gene transfer agent the expected immune response will preclude redosing. This first in human trial is using a vector that has been used before by the same delivery route (intravenous).

- Would it be appropriate to enroll children before adults?
- Would it be appropriate to enroll younger children (e.g. age 2 years) rather than older more advanced children, assuming those older children would be able to assent?
- If the study is to have the prospect of direct benefit, how should the initial dose be selected? Should a dose that shows clinical activity in animals be chosen over a more conservative dose that is less likely to lead to clinical benefit but may be safer?
- How would the analysis change if the delivery of the vector was a first in human use, e.g. intrathecal?

**Panelists:**

Victor Santana, M.D., St Jude Cancer Center, Memphis, TN

Ron Crystal, M.D., Weil Cornell Medical Center, New York, NY

Eric Kodish, MD, Cleveland Clinic, Cleveland, OH (teleconference)

Steven Hirshfield, M.D., Ph.D., National Institute of Child Health and Development, NIH

**3:00 PM**

**RAC Discussion**

**3:20 PM**

**Public Comment**

*Session III: Review of Selected Language from the  
NIH Informed Consent Guidance for Human Gene Transfer Trials*

**3:30 PM      Communication about Withdrawal from Gene Transfer Trials**

Many gene transfer agents can persist for long periods of time or even indefinitely if the modified cells are stem cells. Research participants are told that they can withdraw at any time but one cannot “undo” the gene transfer. What is the best way to communicate this to potential research participants?

Review of Sample Language

**Lead Discussant:** Rebecca Dresser, J.D., Washington University, St. Louis, MI

**4:10 PM      Avoiding Therapeutic Misconception when Communicating about Long-Term Follow-up and Reproductive Issues**

Gene transfer agents are unique in that long-term follow-up is often required because of the persistence of the agent can be years. Long term follow-up may range up to 15 years. In trials where the expected life expectancy may be less than a year, how can one communicate about long-term follow-up without leading to therapeutic misconception?

As in many other areas of investigational medicines, the effect of gene transfer agents on reproduction is not known. In trials involving individuals with terminal illness, where the likelihood of pregnancy is highly unlikely does the possibility of pregnancy need to be discussed and if so how can it be done in a sensitive manner that will not inadvertently foster therapeutic misconception?

Review of sample language

**Lead Discussant:** Laurie Zoloth, Ph.D., Northwestern University, Evanston, IL

**4:45 PM      Wrap Up**

**5:00 PM      ADJOURN**