Background:

I am here today in my capacity as an independent investigator and also as Director of the University of Florida Powell Gene Therapy Center. Our Center has a long history of gene therapy research and the founding members have all made seminal contributions to the field, especially in the area of AAV biology and clinical application of AAV vectors. My own research focuses on the use of AAV vectors in neuromuscular disease. My role in this research area is both as a clinician and principal investigator of gene therapy studies in a variety of diseases. In 1996, our group made the first observation that AAV vectors delivered to skeletal muscle could lead to sustained expression of a therapeutic gene (1). This work has lead to a variety of studies in the now very active area of gene therapy for various forms of muscular dystrophy as well as inherited storage diseases. I have served as both an ad hoc member of the RAC and also as an investigator with studies under review by the RAC.

The AAV technology we have developed is owned by both Johns Hopkins University and the University of Florida and has been licensed by several biotechnology companies, where I have served as an advisory board member without payment. I am a member of the Board of Directors of the American Society of Cell and Gene Therapy as well as Chair of the Regulatory Affairs Committee of the ASGCT.

Gene Transfer Research – Renaissance:

The field of gene therapy is certainly vastly different today from when I started in the area 15 years ago. Early phase proof-of-concept studies using local vector dosing have now led to systemic dosing studies aimed at product registration. In fact, just this year a product has been approved by the European Medicines Association for use in the treatment of hyperlipidemia (2). This approach is based on work by Xiao and Samulski (3) along with our 1996 report (1) of AAV delivered to skeletal muscle. Undoubtedly, similar programs will be presented to the FDA for approval in the coming years (4) based on the recent reauthorization of the Prescription Drug User Fee Act (PDUFA) and the Food and Drug Administration Safety and Innovation Act (FDASIA) where there is increased focus on rare and orphan conditions. The work in the field has been substantially supported by NIH investment in this area, beginning with NCRR support for vector production methods, establishing best practices in toxicology studies, and currently by NIH NHLBI Gene Therapy Resources Program (5). In the past few years there has been substantial interest in the field both from the biotechnology community as well as large pharmaceutical companies. The progression to
commercialization was first established as a central tenant of the NIH Roadmap as described by Director Elias Zerhouni in 2002 (6). The Roadmap also provided strategies to streamline the clinical research enterprise and speed discovery of novel therapies. Regulatory approval of an AAV vector for use by intramuscular delivery required 16 years of basic and clinical research from the time the concept was first described. Clearly, in order to make progress in the field, we need to find approaches that will accelerate this process and speed delivery of promising therapeutic options to patients, especially where no treatment alternatives exist. Over this time period, the RAC has fulfilled an important role in providing public information and oversight, however the current state of the field mandates a different approach to maintain the momentum that exists in the field today.

Pathway Forward:

In our groups experience with study submission to the Intitutitional Review Board, Institutional Biosafety Committee and FDA review, we have found the most expert reviewers are embedded in the FDA. The FDA review team can serve as an important collaborator to establish that clinical studies will be safe and address the fundamental question related to the disease process. Among the review agencies, there is not harmonization of the documentation required by these agencies and therefore an IND submission is cumbersome. The role of the IRB at the home institution is well established. The IBC documentation is also straightforward and therefore has not been an impediment to speedy approval. The RAC submission however does lead to double jeopardy in that specific protocol review can be at odds with prior discussion with the FDA. In these circumstances the investigator can be put in the difficult position of reconciling these differences to keep the protocol on track. Since the RAC only serves in an advisory capacity, the final authority for approval rests with the FDA and therefore the RAC comments only influence the further interactions with the NIH agency that may be supporting the study directly or indirectly.

Specific points to consider in enhancing the role of the RAC going forward:

1) Build on the public information mission activity through consensus meetings.
   The RAC has held several informative meetings addressing critical topics in the field. Sponsors could volunteer to use specific protocol information for in depth discussion on issues that will facilitate expediting gene therapy clinical research. The FDA would benefit from the ability to have public discussions on critical topics that would otherwise be an issue of confidentiality between sponsors.

2) Enhance to functionality of GeMCRIS and ClinicalTrials.gov:
   Current requirements for long-term outcome reporting could be enhanced by establishing a portal within GeMCRIS for patient reported outcomes. By establishing a richer data set on patient reported outcomes, it may be possible to determine outcomes of participation in a gene therapy study that go past adverse event reporting and also captures the positive events related to participation.
Efforts to report clinical study results in via clinicaltrials.gov should be enhanced and therefore lead to better public information in the field.

3) Discontinue specific protocol review.
Specific protocol review has not in my experience contributed to improving the protocol design or enhancing the safety of the study. We have found that consistent expertise from RAC members either related in the disease process or the drug development pathway has been difficult to obtain.

4) Foster sharing of pre-clinical data to avoid cost and duplication of effort:
The scientific journals Human Gene Therapy – Clinical Devolvement and Molecular Therapy allow for publication of pre-clinical data, and both are now facilitating the sharing of preclinical data in a way which would streamline the IND process via sponsor letters of cross reference. There may be other new mechanisms for such data sharing that could be facilitated by the RAC and NIH. For example, sharing of such data should be an explicitly stated requirement of all federally funded programs. Since many industry sponsors work closely with academic investigators, hopefully, cooperation in this pre-competitive area will be of overall benefit to the mission and growth of the field.

Citations: