In Vivo Gene Therapy with DNA Vectors

ASGCT-FDA/CBER Liaison Meeting

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Advancing knowledge, awareness, and education of gene and cell therapy
Disclosures

Dr. Crystal has equity in and/or is a consultant to the following companies with gene therapy programs:

- Adverum
- ReGenX
- BioMarin
- XyloCor
- Jannu
- LEXEO
**In Vivo Gene Therapy with DNA Vectors**

Adenovirus

Modify or prevent disease

Modify gene expression
Risks to *In Vivo* Gene Therapy with DNA Vectors

- Germline gene transfer
- Recombination
- Contamination of the environment
- Persistent and/or overexpression
- Systemic or organ-specific anti-vector and/or transgene product immunity
- Off-target effects
Vector Toxicology Guidelines

Issue

- There is extensive experimental animal and human safety data relating to *in vivo* administration of DNA vectors
- Toxicology-related studies are often repetitive, and provide little additional information than what is already known

Recommendation

- Significant effort and cost could be eliminated by having periodic guidance documents that state common concepts/guidelines that could eliminate some of the repetitive toxicology work

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Communication

Issue

● The FDA knows what all companies and academics are doing and the data they have generated, while the individual investigator groups know only their own data, what is public and gossip

● This is particularly relevant in toxicity/safety issues relating to vectors, including manufacturing, e.g., acceptable cell lines, quality of plasmids, quality of final products

Recommendation

● When serious issues arise that the agency is aware of that may alter protocol design and manufacturing practices, it would be of significant help to provide information to the community of the FDA’s concerns that can have major implications to programs based on long term commitments

● For consideration – a symposium at the annual ASGCT meeting organized jointly by the ASGCT and the FDA to discuss these issues
Reporting

Issue

- There is now a 25 year experience with *in vivo* administration of DNA vectors, and the 15 year reporting requirement for many gene therapy applications is no longer relevant to many *in vivo* DNA vector applications

Recommendation

- As articulated in the July 2018 Draft guidance document, it is rational to have reporting requirements that are vector and disease-specific, with some requiring long-term observation and others short-term or no observation at the end of the clinical protocol
- It would be very useful for the FDA to publish a data-driven document of the 15 year monitoring data generated over the past 25 years
Control Groups

**Issue**
- For many of the rare diseases, placebo studies are not feasible
- This is not specific to *in vivo* use of DNA vectors

**Recommendation**
- For many rare, fatal disorders, natural history studies are the only way to demonstrate efficacy
- An FDA guidance document focused on control groups would be useful, and might also be a topic for an ASGCT joint symposium
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Adenovirus

Adeno-associated virus

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