Gene Therapy: Nonclinical and Regulatory Strategy

Module 1 Abstract: All Gene Therapies Are Not Created Equal

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It has been almost 50 years since Friedmann and Roblin's seminal article in *Science*, "Gene Therapy for Human Genetic Disease?", advocated for the continuation of research while opposing attempts in patients until sufficiently ready. They highlighted in part the lack of knowledge of short-range and long-term side effects (1). The field has evolved over the past five decades, despite occasional setbacks, to a better understanding of safety resulting in the initiation of large numbers of early-phase clinical trials and subsequent trials which have led to recent product approvals. The excitement in gene-based therapies continues to be fueled by the potential to not only improve treatment outcomes and/or regimens but possibly even provided "cures "both rare and more common diseases. The principal therapeutic modalities are based on either *in vivo* gene delivery to target cells or tissues or *ex-vivo* gene delivery into autologous or allogeneic cells followed by adoptive transfer to the patient. The translational imperative is to design preclinical programs that support the delivery of not only safe, but also active doses in the first subjects. "It's All About the Dose" (2).

The preclinical safety evaluation of gene-based therapies supporting the successful translation into the clinic incorporates the *basic principles* used in the preclinical safety evaluation of small molecule (drugs) and large molecule (biologics). But like biologics, the *practice,* by necessity, is based upon a "case-by-case" approach to program design, which takes into consideration not only the indication but also specific attributes of the product. Importantly, constant innovations have been encouraged by new learnings resulting in variations on the theme not only across modalities but also within a specific modality. As such, all gene therapies are not created equal.

This seminar is meant to be an orientation on "How to Think" about the preclinical development of gene-based therapies. The first part of the seminar will provide an overview of general and specific product attributes which direct which questions to ask and how best to answer to make the case. Product considerations will include non-viral vectors and various genetically modified organisms used as vectors including dual vectors; different types of promoters; use of single and multiple transgenes including regulators of transgene expression as well as surrogate constructs. Additional considerations will include both *in vivo* and *ex-vivo* gene modified cells and combination drug or device gene therapy strategies. The second part of the seminar will address considerations for dose extrapolation particularly for novel routes of administration. Case studies will be presented to emphasize key concepts.

1. Friedmann T and Roblin R (1972) *Science* 175: 949-955. doi: 10.1126/science.175.4025.949
2. Cavagnaro JÁ (2021) - Hum Gene Ther 32: 335-340. doi: 10.1089/hum.2021.29154.jac.