Molecular Therapy
Editorial

# The Pharmacology of Gene Therapy

The objective for human gene therapy is to express DNA or RNA constructs at a desired site in vivo for long enough and to reach sufficient levels to produce a therapeutic effect. However, several challenges have been identified during the past two decades in the translation of promising preclinical results to the clinics. An important component of these problems has been a poor optimization of pharmacological characteristics that uniquely apply to gene therapy products as compared to traditional small molecule drugs.

Classical well-known ADME parameters are usually used to characterize pharmaceutical products. ADME stands for absorption, distribution, metabolism, and excretion. However, for gene therapy products, pharmacological evaluation should be extended beyond the classical ADME parameters because they only apply to the therapeutic product (expressed as a consequence of a successful gene transfer), whereas they do not apply very well to the gene transfer vector, even though the safety and efficacy of gene therapy greatly depends on the delivery methods and properties of the vector.[1] Too often a suboptimal dose or inefficient delivery to the target cells has caused failures in clinical trials. To exemplify this, injection of $1 \times 10^{11}$ viral particles, or a volume of 3 mL containing 200 mg plasmid, into mouse tail vein would correspond to $3 \times 10^{14}$ viral particles or 9 l and 600 mg in man. Also, a 28G needle causes an approximately 500 μm-wide track in mouse myocardium, where damaged cardiomyocytes and inflammatory cells act as a confounding source of cytokines and growth factors. The needle track can easily be $\approx$ 1/8 of the total thickness of the left ventrical wall in mouse hearts, but only 1/200 of the thickness of the human myocardium. Therefore, additional parameters to ADME are needed to optimize therapeutic approaches in humans.

It has been proposed that a set of so-called STED parameters should be used in optimizing gene therapy product pharmacology in addition to the ADME parameters.[2] STED stands for Spreading through and reaching appropriate cells in the target tissue, Transduction efficiency, Expression strength in the transduced cells, and Duration of gene expression. For gene transfer vectors, absorption and metabolism are usually not applicable, whereas getting the vector into the desired tissue with efficient spreading throughout the target tissue are of significant importance. These parameters should be carefully optimized and characterized in preclinical studies. If the vector cannot reach and penetrate the target tissue and transduce a sufficient number of desired cells, the therapy will not be successful.

Transduction efficiency is obviously a crucial parameter for gene therapy. Even the best vectors currently available for clinical use are still quite inefficient in large human tissues, a fact that is in sharp contrast to the relatively high transduction efficiencies obtained in rodents. Successful transduction involves several steps: binding to cell membrane receptors, uptake into the cells, escape from the endocytic pathway, and transport to the nucleus. At present, efficient transduction and production of enough therapeutic protein or RNA still represent the Achilles' heel of current in vivo gene therapy approaches.[3]

The strength of gene expression in the transduced cells is another important parameter that needs to be optimized. The type of the vector and promoter obviously influence this factor, but the transgene (including codon usage) and its associated regulatory sequences also affect gene expression, post-translational processing, trafficking, and secretion of the therapeutic compound. It is not clear whether strong expression in a few cells produces a similar therapeutic effect as low level expression in a greater number of target cells.

Duration of gene expression is yet another key determinant of the kinetics and total amount of the expressed therapeutic product. Some applications require long-term gene expression, whereas others require only a transient, but very strong, gene expression. The duration of gene expression is obviously determined by the choice of the vector, promoter, and immunological reactions to the transduced cells and the gene product. However, before these factors can play their role, steps according to the STED parameters need to be successful. These parameters also crucially affect determination of the optimal dose of the gene drug. It appears that a proper dose-finding is one of the most often neglected areas in preclinical and early clinical development.[2] Thus, the total amount of the therapeutic product and its pharmacokinetics can be greatly influenced by the STED parameters in addition to the classical ADME parameters.

Recognizing the need to develop more standardized approaches to gene therapy pharmacology, *Molecular Therapy - Methods & Clinical Development* (MTMCD) will devote an upcoming special issue to the topic of optimizing preclinical and early clinical work so as to achieve successful clinical translation of gene therapy products that are currently in development. The special issue will appear in 2018, and those interested in contributing either a review article or primary research for this issue should contact MTMCD Editor-in-Chief, Roland Herzog (methods@molther.org). The special issue will highlight pharmacological aspects of gene therapy that are of broad interest to our field.

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http://dx.doi.org/10.1016/j.ymthe.2017.07.007

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