Recombinant Adeno-Associated Virus–Based Gene Therapy for Disorders Detected by Newborn Screening: Inherent Limitations of This Approach

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For more than 50 years, newborn screening (NBS) in the United States has been used for early detection of potentially lethal single gene disorders, such as phenylketonuria and congenital adrenal hyperplasia. Recent clinical successes with recombinant adeno-associated virus (rAAV)–based gene therapy for single gene disorders, such as RPE-65 inherited retinal dystrophy and spinal muscular atrophy, have led investigators and geneticists to consider the possibility of gene therapy for NBS-detected disorders. Among the NBS-detected disorders, enzymatic defects leading to failure of synthesis of adrenal cortical steroids, known collectively as congenital adrenal hyperplasia, are among the most significant, in that they can be fatal if untreated, but they can be readily treated with oral corticosteroid replacement if detected promptly. Specifically, in 21-hydroxylase (21-OH) deficiency, deficits in both glucocorticoid and mineralocorticoid functions may lead to hypoglycemia, hyperkalemia, and hyponatremia, any one of which may be life threatening.

In this issue, Markmann et al., present proof-of-concept studies directed at gene therapy for 21-OH deficiency using rAAVrh10 and rAAV9 vectors in 21-OH-deficient mice. Their results demonstrate that robust transduction of adrenal cortical cells is feasible, albeit more efficient with rAAVrh10 than rAAV9 vectors. This transduction results in correction of the hormonal deficiencies characteristic of this disorder. However, the duration of correction is limited to approximately 8 weeks. The authors further demonstrate that this limitation is due to turnover of adrenal cortical cells rather than to immunologic responses to the vector. These data are consistent with the prior finding that rAAV vector DNA exists primarily in episomal forms, which are lost when target cells are proliferating.

This study demonstrates an important concept for future prospects to broaden the application of human gene therapy to all single gene disorders. One of the early decisions to be made in the product development path is the choice of which vector system to use. The rAAV system is highly attractive for targeting many different cell types, and the ever-broadening availability of new AAV capsid variants with different tissue tropisms holds great promise for even broader dissemination of this approach. However, the issue of persistence with rAAV remains dependent in the nonproliferating characteristics of the target cell population. In diseases due to defects in secreted proteins, there may be some choice of which cell types to target, such that one might choose a nonproliferating target cell matched with an appropriate rAAV vector type. However, for gene products that function as enzymes in complex pathways, such as those involved in corticosteroid synthesis, there may be only one appropriate target cell type. If that cell type is in an active state of proliferation, another vector choice, such as a lentivirus vector, may be required. This example also points out how crucial it is that the design of therapeutic vectors be guided by a thorough understanding of both the normal biology of the cells and tissues in question and of the pathogenesis of the specific disease to be treated.
REFERENCES


