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Molecular Therapy
Commentary

In Utero Gene Therapy Consensus Statement from the IFeTIS

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In utero gene therapy (IUGT) holds great promise for treating/curing many inherited genetic diseases. At present, IUGT stands at a critical juncture and has vast potential for dramatically improving the standard of care for many patients with genetic disorders. Considering the remarkable progress in gene therapy over the past two decades, the International Fetal Transplantation and Immunology Society (IFeTIS) facilitated a panel discussion of international experts at its 2018 annual meeting to consider scientific, clinical, and ethical issues related to prenatal gene transfer for the treatment of genetic diseases. The goals of the session were to revisit the 1999 NIH Recombinant DNA Advisory Committee (RAC) policy conference recommendations,[1] examine the current status of IUGT, identify gaps in knowledge in need of resolution, achieve an agreement among the members of the international scientific community regarding target diseases, review procedural- and vector-related safety considerations, and define a roadmap for developing clinically translatable IUGT therapeutic approaches.

The NIH RAC policy conference was held in 1999 after the submission of two prenatal gene transfer preliminary trial protocols by Drs. Zanjani and Anderson to the RAC based on work by Porada et al.,[2] describing the successful gene transfer into fetal sheep by direct intraperitoneal injection of retroviral vectors.

The RAC working group and *ad hoc* participants acknowledged that prenatal gene transfer has the remarkable potential of preventing or treating serious and life-threatening genetic diseases. Nevertheless, the overall conclusion was that there was insufficient preclinical data at that time to safely pursue the initiation of clinical trials. Their overall recommendations included the requirements for accurate prenatal diagnosis, provision of comprehensive information to assist the mother with the decision-making process, the minimization of risks to both the mother and the fetus, with proven maximized direct benefit to the latter, and negligible risk of fetal germline modification. The RAC advised that the ideal candidate diseases should be those associated with serious morbidity or mortality, prior to or after birth, in the absence of other serious abnormalities not corrected by gene delivery.[1] The RAC also determined that the need existed for further technical advances that would enable the development of novel gene delivery approaches that could provide disease-specific transgenes with high and durable, but regulated, levels of gene expression. Safety aspects, such as insertional mutagenesis, fetal immune response to gene products, and detection of alterations in fetal development, were also points of discussion.

Since this 1999 RAC meeting, considerable advances in gene-transfer efficiency, safety, and delivery have resulted in several clinically approved cell and/or gene therapy products, which have been successful when used in adult patient populations.[3] Further attesting to this leap in technological progress is the recent joint statement from the NIH and US Food & Drug Administration (FDA), which reports more than 700 active investigational new drug (IND) applications for gene therapy.[4]

IUGT has also evolved at a rapid pace and, for the last 20 years, studies using mouse, sheep, and non-human primate models have demonstrated the safety and efficacy of IUGT (reviewed in Almeida-Porada et al.[5] and Wit et al.[6]). For example, a recent study[7] demonstrated the first successful application of prenatal gene therapy in a mouse model of acute neuronopathic Gaucher disease (nGD). nGD is a human genetic disease in which marked irreversible neurological pathology already manifests *in utero*. The acute childhood form of nGD is lethal and untreatable since enzymes cannot cross the blood-brain barrier. In this remarkable study, Massaro et al.[7] showed that IUGT with an adeno-associated virus (AAV) vector encoding glucocerebrosidase (GC) reconstituted neuronal GC expression, abolished neurodegeneration and neuroinflammation, and enabled the mice to be fertile, fully mobile, and live for up to at least 18 weeks.

In a ground-breaking clinical study, Schneider et al.[8] demonstrated that the intra-amniotic administration of recombinant ectodysplasin A (EDA) protein to three X-linked hypohidrotic ectodermal dysplasia (XLHED)-affected human fetuses at the end of the 2nd trimester led to the birth of infants who were able to sweat normally and exhibited no signs of XLHED-related illness during their 14 to 22 months of follow-up.

In another recent landmark study, Chan et al.[9] reported that *in utero* delivery of AAV5 or -8 vectors encoding human coagulation factor

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IX (hFIX) or hFX under the control of a liver-specific promoter into nonhuman primate fetuses at 40% gestation, which is equivalent to 12 to 14 weeks gestation in the human pregnancy, resulted in sustained curative levels of hFIX and hFX and induced durable immune tolerance to the coagulation factors in the absence of clinical toxicity, supporting IUGT's therapeutic potential for early-onset monogenic disorders.

In light of these remarkable advances in the field of gene therapy, it is only appropriate to revisit the RAC's nearly two decade-old recommendations concerning fetal gene therapy, examine the current knowledge and technological capabilities, and determine the hurdles that must still be overcome for the clinical application of this promising treatment.

After extensive deliberation, the 2018 IFeTIS panel members agreed that IUGT, using an *ex vivo* or *in vivo* direct approach, remains the best therapeutic strategy for treating, and ideally curing a wide range of genetic disorders early in gestation, such as lysosomal storage disorders and spinal muscle atrophy, and even for diseases such as the hemophilias for which postnatal treatment options current exist but are cost-prohibitive, carry the risk of complications/treatment failure, or are limited to a selective group of patients.

Despite this great promise, however, it was acknowledged that IUGT should only be considered when reliable prenatal enzymatic[10] or genetic diagnosis exists and genotype and phenotype correlates strongly with clinical prognosis. Moreover, it was agreed that the decision to use IUGT would have to be driven by the need to intervene during development to prevent damage caused by the disease or by compelling evidence that the unique physiologic and/or immunological characteristics of the fetus would offer marked advantages and/or benefits over treatments that could be offered after birth. The panelists also recommended that, for diseases to be considered for treatment with IUGT, the disease should result in severe fetal morbidity and/or mortality either *in utero* or postnatally and should not be associated with other serious abnormalities or disorders that are not corrected by the therapeutic gene. However, they also agreed that the application of IUGT should not be limited to diseases with severe fetal morbidity, but it should also include those for which available postnatal therapies produce a poor outcome, are limited by huge economic burden, or are hindered by immunologic responses and/or rejection.

Prior to initiating human IUGT trials, the group emphasized the importance of obtaining and compiling relevant, rigorous, and reproducible data through *in utero* studies in an appropriate animal model of the disease in question, recognizing that large animal models will not be available for most diseases. The group also noted, however, that for many candidate diseases, such as lysosomal storage disorders and the hemophilias, these preclinical studies already exist.

The remainder of the panel's time was spent considering the ethical issues and addressing concerns regarding diagnosis and treatment decisions and the safety of both the procedure and the therapeutic to be administered.

Some of the key conclusions reached were that prenatal testing should be based on a personal choice and that fetal therapy must hinge on the concept of non-directive counseling in which the options of no therapy and experimental therapy—with all possible risks and benefits—are explained without any personal bias from the physician, ensuring that the mother fully appreciates the experimental nature of the procedure. The panel also spent a good deal of time carefully considering the difficult situation raised by diseases that are usually fatal *in utero* and for which partial correction may result in the survival of a severely disabled child with long-term morbidity.

With respect to safety, the panel members acknowledged that, as with any fetal intervention, maternal safety is a critical consideration for IUGT and noted that infection, preterm labor, and fetal loss are all theoretically possible. They felt it important to make the public aware, however, that a considerable amount of clinical data exist that provide unassailable proof that the human fetus can be accessed multiple times with an extremely low procedure-related risk, assuming that a minimally invasive, ultrasound-guided approach is employed,[5] and they stressed that the technical aspects of injections using fetal umbilical vein access or intraperitoneal injection are safe and straightforward mainstream procedures.

The panel members felt it was particularly important to consider maternal safety with respect to possible exposure to the viral vectors or gene products infused into the fetus that could theoretically result in a maternal immune response to the vector and/or the protein. They noted that, in cases where the mother is tolerant to the missing protein, this risk should be exceedingly low. They also stressed the need to consider infection and impairment of the future ability of the mother to reproduce, even though the procedure itself poses minimal risk to the mother. While data thus far in animals have not indicated significant germline integration, the panelists felt there was still concern for integration of the viral vector and/or off-target effects for the fetus when using an *in vivo* direct approach. They then pointed out that some of these limitations may be solved in the future with new technologies that allow non-viral delivery and/or specific cell targeting and gene-editing to minimize the risk of off-target events or by the use of an *ex vivo* approach to IUGT.

In conclusion, the panel stressed that IUGT holds great promise for treating and/or curing many inherited genetic diseases. Gene delivery and therapy technologies have evolved significantly in the last decade, such that many of the most daunting obstacles have now better been identified and this exciting field has been reinvigorated. There is no doubt that surpassing the few remaining hurdles to allow clinical implementation of these therapies is urgently needed and that IUGT will dramatically change the whole paradigm for the way we perceive and treat many genetic disorders.

SUPPLEMENTAL INFORMATION

Supplemental information can be found with this article online at https://doi.org/10.1016/j.ymthe.2019.02.015.

CONFLICT OF INTEREST

The authors declare that the consensus agreement was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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