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Gene Therapy Continues to Make Progress: Clinical and Regulatory Perspectives

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Current Gene Therapy

“This Special Issue is dedicated to Beatriz Castro who is bravely battling cancer from the other side of the trenches”

Gene therapy, defined as the use of genetic elements to treat diseases, is increasingly being used, with more than 1,300 clinical trials approved during the last decade [1]. These trials involve direct gene transfer into the target affected tissues, or the use of *in vitro* genetically engineered and expanded bone marrow stem cells. Deadly diseases such as adenosine deaminase deficiency (ADA) [2, 3], chronic granulomatous disease [4], and X-linked severe combined immunodeficiency (X-SCID) [5-7] have been successfully treated using autologous bone marrow cells transduced with retroviral vectors encoding the mutated genes.

In spite of the biochemical, immunological, and clinical improvements in patient's lives, the development of leukemia in 5 out of 20 treated patients in the SCID-X1 gene therapy trials, involving the use of CD34+ autologous bone marrow cells transduced with retrovirus encoding the common γ -chain of cytokine receptors, called into question the overall safety of this therapeutic approach [8, 9]. It was later demonstrated that the development of leukemia in these patients was due to the insertion of the therapeutic gene in the vicinity of the LMO2 oncogene, and the unopposed growth advantage of transduced cells [10]. Importantly, out of the 5 patients who developed leukemia, one died in spite of treatment for leukemia, and 4 were in remission following chemotherapy, with a reconstituted immune system as a result of gene therapy. Thus, out of 20 patients who would have otherwise been restricted to life in a sterile bubble, 19 are able to have a normal life or a 95% success rate in an otherwise incurable disease.

Since in the overall majority of the treated patients, the leukemia was successfully treated with chemotherapy, this highlights the tremendous success of gene therapy in treating a deadly disease, albeit at the expense of putative serious but treatable side effects. The events described above highlight the critical importance of very carefully assessing the possible risk vs. benefit ratios before attempting the clinical implementation of a novel therapeutic strategy, and the importance of learning lessons from clinical trials that will surely lead to improved genetic therapies.

Another recently very highly publicized trial involved a Phase I-II gene therapy trial for rheumatoid arthritis [11] utilizing tgAAC94, adeno-associated vector (AAV), in which one of the patients enrolled in the trial died. Although the death was initially suspected to be potentially related to gene therapy, detailed investigations concluded that the most likely

cause of death was disseminated, recrudescence fungal infection with *Histoplasma capsulatum* [12]. As these investigations regarding the details surrounding this patient's death unraveled, a number of questions were posed, i.e., should this patient have been enrolled in this trial given the substantial immunosuppressive treatment this patient was receiving to control her disease, were the inclusion-exclusion criteria sufficiently stringent, was the risk vs. benefit ratio properly evaluated, were the channels of communication between all parties involved appropriate? Curiously however, the fact that the gene therapy was being developed to selectively treat the affected joints, without having to expose patients to the very high incidence of serious adverse events caused by the systemic immune suppressants needed, was mostly missed by all reports.

Evaluation of the available literature linking the clinical benefits to the potential side effects which have arisen or could potentially arise from the use of gene therapy indicates a somewhat unrealistic expectation that gene therapy should be completely free of potential risks and side effects. This expectation is not a viable option, not only for gene therapy, but for all other currently available forms of therapy; it is well known that every treatment comes hand in hand with many possible side effects, some more serious than others. One only needs to take a closer look at the history of bone marrow, heart, lung or liver transplantation; how many adverse events and failures it took to get to where we are today. Of note, it has been reported that even after excluding errors in drug administration, adverse drug reactions (ADRs) could account for as much as the fourth to sixth leading causes of death in the USA, further, drug-related adverse side effects occur in ~6.7% of hospitalized patients [13, 14]. These are staggering statistics which should call for caution when evaluating benefits vs. adverse events and also any biological side effects reported from the utilization of gene therapy. In conclusion, with gene therapy as with classical drugs, the key issue is to very carefully consider whether the benefits outweigh the risks and also take into account which are these potential risks so the informed consent can accurately portray them. It is important to remind ourselves however, that, without gene therapy, the boys successfully treated for SCID-X1, would never ever in their lives have been able to leave their sterile bubble.

In closing, we would like to conclude by conveying our tremendous gratitude to all the authors who have so generously contributed their data, time and ideas to put together this very exciting collection of reviews. These highlight, from diverse perspectives the status of the clinical phase of gene therapy, including the hurdles and challenges which still need to be overcome to make this exciting and novel therapeutic approach into a clinical reality widely available to treat a vast array of devastating diseases, from cancer to neurological, metabolic and genetic diseases. It is the expectation of the gene therapy scientific, clinical and regulatory communities that more and more successful gene therapy clinical trials will be implemented and will prove to be safe and highly efficacious. The reviews portrayed in the Special Issue highlight some of the most exciting approaches currently under development. It is our sincere hope that after reading this issue, efforts will continue to intensify in this exciting biomedical basic and translational research field.

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