Running Interference: Evading Host Immune Response in Gene Transfer

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Over the past two decades, gene therapy has offered hope for patients with serious congenital and acquired diseases. With new advances, such as the development of inhibitory RNA therapies that offer a more robust delivery of gene therapy, this approach may soon be applied in many diseases and malignancies.

Yesterday, the Education Session on gene therapy, chaired by Dr. Cynthia Dunbar, updated gene therapy and the role of inhibitory RNA therapies. Dr. Dunbar discussed clues to the cause of genotoxic complications in clinical trials using gene therapy in patients and suggested possible avenues to harness the great potential of hematopoietic stem cell gene therapy with decreased genotoxic risk.

Dr. Katherine High discussed the current status of genetic therapies for hemophilia. Long-term cure of hemophilia has been achieved using AAV-gene transfer strategies in the hemophilic dog model. However, translation of these strategies to the clinic has not yet resulted in long-term expression of the donated gene at therapeutic levels. Dr. High described problems uncovered in the course of clinical trials, the underlying pathophysiology of these problems, and potential solutions and alternative approaches.

The use of RNAi or RNA interference to inhibit gene expression sequence specificity is a revolutionary concept in gene transfer, as well as in cancer and viral infections, according to Dr. Mark Kay in the last talk of the session. Although the efficacy of RNAi suppression is far greater than gene-knockdown approaches, there is concern that monotherapy with RNAi might allow viral escape. Thus, it might be advantageous to combine RNAi suppression with gene expression inhibitors, or combine several RNAi effectors. The results of such concepts, in early clinical trials, are eagerly awaited. Some of the potential risks of RNAi technology might include the development of an immune response or oversaturation of endogenous pathways.

In this year's annual meeting program, there are more than 400 abstracts on gene transfer. The oral sessions on gene transfer will be presented tomorrow, including clinical trials and lessons learned in gene transfer for chronic granolomatous diseases, and hematopoeitic stem cell gene therapy for Wiskott-Alrich syndrome. With new approaches using RNA interference, the future of gene transfer is showing exciting promise in the treatment of genetic, acquired, and infectious diseases, and in the successful future development of safer and more efficacious gene transfer approaches.