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The Case for Immunosuppression in Clinical Gene Transfer

Thanks to recent press coverage, when addressing lay audiences I seem to be getting more questions asking whether gene therapy will truly ever fulfill its promise. The answers are not difficult to formulate. Since the idea was first put on paper in the early 70s, many of the technical challenges of therapeutic gene transfer have been met. We can now easily identify a therapeutic gene, isolate it from the genome and insert it into a variety of gene transfer vectors. We have made significant improvements to all vectors by blocking the capacity of the parent viruses to replicate, by removing pathogenic genes, and even by replacing entire genomes with engineered sequences. And, especially for cancer applications, we have successfully harnessed natural virus replication for therapeutic intent.

Nevertheless, the challenger retorts, the expected “magic bullets” have failed to materialize. Although surprising when one considers that “bubble boys” have recently been playing outside their sterile bubbles and that the lives of cancer patients have been significantly extended by gene therapy, the challenger is aware that unexpected side effects have halted some of the more promising clinical trials. In a number of these, the culprit has been the immune system.

The challenge imposed by the immune system is neither new nor unexpected. As Jonathan Yewdell once remarked, the immune system has had close to a 450 million-year head start over gene therapists. Inflammatory responses are triggered when viral vectors are administered into the liver, muscle, or even the “immune privileged” brain. Subsequent adaptive immunity can abolish transgene expression. These responses can render the therapy ineffective, can lead to serious tissue inflammation if the immune response kills the transduced cells, and even to worsening of disease if cell loss occurs in populations of non-dividing neurons.

Experience with immunosuppressive agents, however, reveals that immune responses can be blocked to a degree that can have a significant effect on patients' lives. For example, transplantation patients receive lifelong treatment with immunosuppressive agents, providing a high quality of life to patients with terminal liver, heart, and kidney disease, despite important side effects. Gene therapy vectors are effective in small and large animal models of human disease, and immunosuppressive agents are effective in blocking most inflammatory and immune responses against viral vectors. However, immunosuppression is not being used in clinical gene therapy. So, why not?

The fact that the need for immunosuppression in most cases will only be transient provides a strong argument in favor of the use of immunosuppressive agents as adjuvants for gene therapy requiring long-term transgene expression, such as for the treatment of inherited or neurodegenerative disorders. The enormous advances in the development of viral vectors during the past five years has resulted in lentivirus, AAV, adenovirus, and HSV-1 derived vectors that are completely devoid of wild-type viral genes. Thus, the only potential antigens that could be recognized by the immune system are the viral envelope and capsid proteins of the input virions. In the case of patients with no pre-existing immunity to the vector, immunosuppression should only be necessary during the phase of vector uncoating, when virion proteins can potentially be presented to the immune system. The length of the uncoating phase is currently being assessed for most vectors.

Once the genomes of these vectors have made their way to the cells' nuclei, they literally become invisible to the immune system, since they do not encode any potentially antigenic proteins. Therefore, transient immunosuppression during the early phase of viral vector administration (and uncoating) should be sufficient. Once in the nucleus, the vector could express the therapeutic transgene long term despite the presence of a fully active immune system. Thus, the immunocompetence of the patients would be only minimally and transiently affected, which should provide greater safety than in organ transplantation where patients need to be immunosuppressed chronically.

A criticism of this idea is that many patients may have been exposed to the parent viruses, or to cross-reacting viruses, and they therefore may mount an immune response to the input virions. However, even in this case, transient immunosuppression could still be effective for the reasons discussed above. And even if chronic immunosuppression were ever necessary, if it works so well for organ transplantation, why should it not be equally effective for gene therapy? Of course, there are potential risks involved in transient and chronic immunosuppression—risks that all transplant patients are willing to accept.

I believe that the intrinsic clarity and simplicity of the original gene therapy proposals precluded our consideration of the use of immunosuppression in a clinical setting. The early idea that gene therapy could be a “magic bullet” in some ways may have made the need for immunosuppression tantamount to failure of the therapy. However, the time has come to consider immunosuppression as an adjuvant in clinical gene therapy, as discussed and proposed at the recent ASGT Stakeholders’ Meeting and Annual Meeting by Kathy High and Dan Salomon. Far from signaling failure, the use of immunosuppression would signal the entry of gene therapy into the realm of real clinical options—much as organ transplantation only gained widespread clinical acceptance following the discovery and use of cyclosporin A.

Even if gene therapy’s bullets lose some of their magic in the process, the combination with immunosuppressive agents may provide a better quality of life for many patients. We must not forget that even the “bubble boys” treated successfully with gene therapy, but who sadly developed leukemia, were afforded many years of normal interactions with the outside world—experiences they would have never had without gene therapy. With due consideration to the thorny ethical issues at stake, most of us would choose quality of life over quantity if given the choice.

PEDRO R. LOWENSTEIN

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