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Editorial Open Access

# Gene Therapy and Transplantation - A Symbiosis for the Future?

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## Editorial

In many ways, Organ transplantation was really the first gene therapy. Bone-marrow transplantation to treat SCID or liver transplants to treat life-threatening metabolic disorders is good examples. Mark A. Kay, Nature Reviews

Many of my colleagues might be surprised to learn that I spent the past 25 years in the field of gene therapy. My academic career seemed to focus on pancreas transplantation and development of immunosuppressants. So why the change to gene therapy? First of all, my direct interest was the application of gene therapy toward a cure for diabetes. Second, the field of transplantation has not taken advantage of the potential applications of gene therapy. In fact, there is a possibility that gene therapy could cure diseases so a transplant will not be required. A good example is oxalosis, which in severe cases requires replacement of the liver and kidney. Successful transduction of hepatocytes with the gene coding for oxalase would solve the problem without further intervention. Eduardo Salido from Tenerife has performed groundbreaking work which could make Phase I trials imminent.

Gene therapy could also have a direct effect in transplantation. Technically, it seems rather straightforward to design vectors with specific affinity to a plasma cell producing a donor-specific antibody. The vector would transduce the plasma cell with a suicide gene, and as a result, make transplantation possible. This approach would be far superior to generalized immunosuppression with its substantial side effects. Similarly, cytotoxic T-cells could be specifically eliminated [1].

One of the major advances in gene therapy is the recent demonstration that the most popular vector, Adeno-Associated-Virus (AAV), is not only safe, but also can provide long-term expression of the transgene. In several hundred trials reported to the Federal Drug Administration, not a single mutagenic event was reported.

Conditioning of the donor organ with gene therapy seems to be a particularly attractive possibility. Specific elimination of antigen presenting cells or using vectors suppressing the expression of co-stimulatory molecules are certainly in the realm of already available technologies. This approach is becoming increasingly attractive with the success of warm liver preservation championed by Peter Friend. In a normothermic environment, transduction of hepatocytes is likely to be very effective. One could also take advantage of the tolerogenic effect of the liver. Vectors with liver-specific promoters carrying transgenes coding for donor-specific MHC under rapamycin coverage could lead to allograft tolerance. A similar approach has already been shown to be successful in inducing unresponsiveness to viral capsid surface structures.

In our own laboratory, we have made attempts to use a kidney-specific vector to deliver anti-fibrotic molecules.

As in all investigations, the devil is in the details, and it will require years and millions of dollars to realize these concepts. However, the tools are available, and when it comes to my own field of interest-iabetes-convincing long-term insulin-free survival has already been reported in rodents and dogs by at least four groups from three different continents.

In summary, gene therapy will be symbiotic with transplantation, but will certainly also replace transplantation in certain circumstances. In the end, the patients will win.

### Reference

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