Journal of Cellular Biochemistry 45:317–318 (1991)

VIEWPOINT

Past Progress and Future Trends in Cell Transplantation

The history of cell transplantation has its origins in the field of organ transplantation, which has had a long and varied past. Organ transplantation was dreamed about from antiquity. People hoped it would work, based on successful plant grafts since the Roman era. Numerous attempts throughout the Middle Ages were made using human organs, but results were always fatal. It was not until the early 1920s, when there was a better understanding of the ABO blood groups, that the first cases of cell transplantation were achieved in humans. This gave rise to the blood transfusion centers we have today.

Serious experimental work began with other cell types in the 1930s with animal skin transplantation model systems. However, it really was not until a decade later that real advances were made in the field. At that point there was a clearer understanding of the delayed type hypersensitivity pioneered by Landstein and Chase and a knowledge of the immunological nature of skin homograft rejection by Medawar. The identification and understanding of the significance of the HLA antigens by Dorsett, Payne, and Amos and their colleagues in the early 1950s provided a framework for the first successful renal transplantations. An understanding of graft venous host reactions (Simonsen) and the use of whole body irradiation (Hamburger) rapidly followed. This opened up the whole field of organ transplantation. It consolidated the concept in the medical community as a viable alternative approach to treating serious human diseases.

The use in the early 1960s of the drug 6-mercaptopurine by Schwartz provided the first significant method of immunosuppression and allowed reasonably mismatched tissues to be transplanted. In the 1970s all was in place. There was essentially an explosion in the whole field of organ transplantation. The HLA Locus in man was defined biochemically. The first human pancreas, liver, and cardiac transplantations took place. A clearer understanding of the class II antigens evolved, as well as an identification of suppressor T-cells. This really enhanced the viability of the organ transplantation concept. The identification of cyclosporin and its clinical use broadly opened the possibility for mismatched tissue transplantation. The first artificial heart—an alternative to tissue transplantation—really illustrated the limitations of medical devices at that time. It, in effect, encouraged much more effort on the approach of using cadaver tissue to treat disease. This, combined with new advances in the area of immunosuppression utilizing a triple therapy of cyclosporin, prednisone, and azathorprine, as well as other newer drugs, has encouraged investigators to explore new frontiers for organ transplantation.

However, there are some serious limitations to organ transplantation. Obtaining fresh, biologically functional cadaver organs continues to be a very major limitation. While dramatic progress has been made in the field of immunosuppression, there are still issues concerning long-term survival of the organs. The surgery involved, including follow-up, is often enormously expensive and complicated. Furthermore, some procedures can only be done in relatively few locations. There clearly will be further progress made in the field of organ transplantation, but cell transplantation may now become more widespread as an alternative method to treat some diseases.

In the past, many diseases have traditionally been treated with chemistry-based therapeutic drugs. More recently, thanks to the biotech industry, the treatments have included recombinant biological molecules. In many cases these treatments are adequate for a short term. However, they often do not treat the fundamental cause of the disease. A better solution is to attack the fundamental problem, a cell deficiency. This may be done by supplementing the defective cells in an organ of the individual with cells that are biologically intact and responsive to the natural feedback systems that exist in a normal healthy individual. This is the fundamental concept of cell transplantation. This new therapeutic approach is accomplished by placing

biologically functional cells back into the body of an individual to treat their disease. There are significant potential benefits in this approach. In many cases, the surgery is relatively simple. It can often be done with local anesthetic in an outpatient setting. The supply of cells should not be limiting, because many of the cells can be frozen and stored indefinitely. Also, there should *not* be the tremendous difficulty in the logistics of getting tissues in a timely manner. Cell types could be better matched with patient immunological needs or autologous cells could be used.

In all of these cases the concept is to use cells in much the same way that we would use biological molecules to treat the disease. We are, in essence, using the biological molecules that the cells themselves produce in a regulated manner, rather than biologics, to treat disease. Examples would be islet cells to produce insulin, hepatocyte or endothelial cells that produce blood clotting factors, and neural cells to produce dopamine for Parkinson's disease. While these approaches have been thought of and talked about for many years, it is only recently, with our understanding of molecular biology, cell biology, immunology, and biomaterials, that we have progressed to the point in the science where the concept is now viable. It involves the bringing together of a number of very specialized fields of research and medical technology. I believe that we are on the verge of an explosion in this new therapeutic approach.

There are many directions in which the cell transplantation technology will evolve, not only in terms of identifying cells with useful clinical potential, but also in finding ways to place these cells in the body to be fully functional. An area of great potential is the combination of cell transplantation with biocompatible materials. This may allow the placement of cells in synthetic organ-like devices, such that immunosuppression would not be required. Another area is the field of gene transfer therapy where cells will be genetically augmented before transplantation. A number of academic groups have provided a theoretical framework and have done considerable research in these areas. However, only now has the biotech community realized the potential. We should expect to see heightened interest in cell transplantation in the near future.

John J. Monahan
Research and Development
Hana Biologics, Inc.
Alameda, California 94501-1034