Polymers, Encapsulation, and Artificial Organs (Report on Session 26.0) Washington D.C., July 15, 1992

Paul R. Sanberg, Thomas B. Freeman and David W. Cahill

*Division of Neurological Surgery, Departments of Surgery, Psychiatry, Pharmacology and Therapeutics
University of South Florida College of Medicine
12901 Bruce B. Downs Blvd., MDC Box 16, Tampa, FL 33612-4799, USA*

The session "Polymers, Encapsulation, and Artificial Organs" at the Fourth International Symposium on Neurotransplantation consisted of five presentations examining the possibility that polymer capsules with or without cells could have therapeutic application for various neurological diseases. Dr. Robert Langer of the Massachusetts Institute of Technology provided an introduction to the use of polymers as systems for controlled release, long-term drug delivery /4/. Some of these systems are currently in use for the treatment of ophthalmic diseases, tobacco addiction, and birth control, and can continuously release drugs for over one year.

Of interest is the use of these slow releasing polymers for delivering drugs and chemicals directly into the brain, bypassing the blood-brain barrier. Polyanhydride-containing bio-erodible polymers were discussed as a way to introduce both large and small molecules into the brain. Dr. Langer suggested that polymers which release drugs by surface erosion, thereby leading to nearly constant release rates, may be the most appropriate delivery system for CNS applications. The polymers are now used clinically in over 56 medical centers in an FDA-approved study examining delivery of BCNU in post-operative patients with primary cerebral malignancy. These polyanhydride polymer wafers are placed in the resection cavity and provide a sustained release of the chemotherapeutic agent. Dr. Langer reported preliminary data demonstrating increased efficacy of the localized BCNU polymer implants over intravenous systemic administration /4/.

In another possible application it was shown that polymers impregnated with dopamine could release the compound steadily for over a year.

Studies examining dopamine releasing polymers in Parkinson's disease models are currently underway in several laboratories.

Dr. Patrick Aebischer from Brown University presented an overview of data showing the use of polymer membranes to encapsulate cells for transplantation into the nervous system /1/. While the previous presentation described polymers impregnated with dopamine for transplantation into parkinsonian brains, Dr. Aebischer described data demonstrating that dopamine secreting cells can be encapsulated by thermoplastic polymer membranes and virtually made into a living dopamine mini-pump. These polymer membranes with maximum molecular porosity at about 50,000 MW impair host rejection via either antibody or cellular responses. This allows the use of xenogeneic or allogeneic transplants without the need for pharmacological immunosuppression. The subsequent presentation by Dr. Meg Palmatier from CytoTherapeutics, Inc. gave further details of the basic science and potential clinical application of these encapsulated dopamine implants for Parkinson's disease /2/. The commercial utilization of these implants involves the use of PC12 cells in PAN/PVC membranes which will be implanted directly into the striata of Parkinson's disease animal models and humans. These implants were shown to release dopamine continuously and to improve behavioral recovery in rodent and primate models. This product was noted to be undergoing safety and toxicology studies in preparation for commercial marketing. Of interest were additional data which demonstrated that implanting these dopamine sources into aged rodents seemed to improve some of the abnormal motor behavior seen in aged animals.

In regard to applications of this technology in other models, Dr. Aebischer provided data showing that encapsulated fibroblasts genetically engineered to release NGF could improve an animal model of Alzheimer's disease based on medial septal cholinergic lesions /1/. Finally, Dr. Aebischer described the use of polymer capsules and tubes to produce a regenerative environment for the nervous system. By loading the polymers with cells and/or impregnating them with bioactive molecules, such as growth or trophic factors, he suggested that these tubular conduits can induce or enhance regeneration, and guide regenerating neural elements to their appropriate targets. Similarly, in a subsequent presentation by Dr. Larry Kromer of Georgetown University /3/, data were presented that compared the amount of regeneration of the septal hippocampal cholinergic system within a three dimensional organization of extracellular matrix cables seeded with or without Schwann cells. Using selectively permeable polymer channels similar to those used by Dr. Aebischer's group, he demonstrated that specimens survived for months and promoted regeneration of axons through these cables from the septum to the hippocampus. Their observations support the hypothesis that Schwann cells produce a more favorable environment than do endogenous CNS glia for axonal regeneration, probably by producing growth factors and cell adhesion molecules necessary for such regeneration to occur.

The application of these polymer channel technologies goes beyond the experiments on cholinergic system regeneration presented by the groups of Aebischer and Kromer. Clearly there is future use for these channels in spinal cord injury and other sensory/motor system regeneration. The presentation by Dr. Woerly of the Czechoslovakian Academy of Sciences discussed the use of another type of polymer matrix for neural transplantation /5/. Hydrogels were shown to form porous matrices, which, when coated with collagen, could serve as artificial bridge substrates and regeneration templates for CNS lesions. Cells attached to the polymers could be maintained *in vitro*, where they were shown to differentiate and extend axons throughout the hydrogel's surface. Such hydrogels may have application in

transplantation of neural tissue in which axons are required to extend into the host brain. Immunoprotective thermoplastic membranes, as discussed above, do not allow for anatomical connections between the transplanted and host cells because of their small pore size. Hydrogels may serve as a potentially important matrix for implantation of cells within the brain that need to make functional connections. If these hydrogels are impregnated with surface active molecules, such as basement membrane proteins, glucosamine or various peptides, they can provide substrates that influence cell adhesion, differentiation and axonal growth of the transplanted cells, thereby facilitating restoration of function compared to transplantation of the cells alone. This strategy may also facilitate the survival of the transplanted cells prior to transplantation since various growth promoting substances can be used with the hydrogel matrix.

Interestingly, the scientists from CytoTherapeutics, Inc. /2/ and Dr. Aebischer's lab /1/ discussed data combining hydrogel and other types of matrices within the immunoprotective outer thermoplastic polymer membranes used in these encapsulated cell implants. The matrices were shown to provide a substrate for enhanced growth and survival of cells within the thermoplastic membranes in both *in vitro* and *in vivo* animal studies.

In summary, the session on "polymers, encapsulation and artificial organs" provided important data demonstrating the unique nature of intracerebral application of polymers of different types with and without cells and their potential clinical application. In the periphery, some prosthetic implants have been noted to produce tissue scarring and poor biocompatibility over time. Interestingly, polymer implants into the brain seemed significantly biocompatible, with little inflammatory scarring, edema or immune response. Nevertheless, before polymer implants are used in humans, additional long-term data will be needed on their biocompatibility and sustained function.

REFERENCES

1. Aebischer P. Biomaterials as an aid for the reconstruction of lesioned nervous system structures. *Rest Neurol Neurosci* 1992; 4: 190.
2. Emerich DF, Flanagan TR, Frydel BR, Gentile FT, Palmatier MA, Winn SR. Transplantation of encapsulated dopamine-secreting cells as a treatment for Parkinson's disease. *Rest Neurol Neurosci* 1992; 4: 190.
3. Kromer LF, Goodglick T. Characterization of CNS axonal regeneration through transplants of extracellular matrix and Schwann cell/matrix terrains within semipermeable polymer channels. *Rest Neurol Neurosci* 1992; 4: 191.
4. Langer R. Polymer drug delivery systems for the brain. *Rest Neurol Neurosci* 1992; 4: 190.
5. Woerly S, Morassutti D. Polymeric matrices for neural transplantation. *Rest Neurol Neurosci* 1992; 4: 190.