IMMUNOSUPRESSION, TOLERANCE AND CELL TRANSPLANTATION

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Abstract. This paper gives a brief overview of part of a life's work in the field of transplantation science, that formed the basis of a lecture on the occasion of the Prince Mahidol Award in Bangkok in January 2003.

I will try to outline the developments of immunosuppression, especially drug-induced immunosuppression and how this has influenced the practise of organ transplantation. In particular, I will discuss our work with the powerful lympholytic antibody Campath 1H originally prepared in Cambridge by Waldmann and his group. This has been used in a series of renal transplants as a pre-emptive strike as the sole immunosuppressant for the first three days, to 'wipe the slate clean' as it were, of lymphocytes and monocytes and leave the field clear for minimal maintenance immunosuppression which I have called "*prope* or almost tolerance". The five year results of the initial trial of 31 recipients of cadaveric renal transplants have been encouraging and a number of further trials have been initiated, with varying maintenance immunosuppression (Moore *et al*, 1960; Starzl *et al*, 1960).

The current expectations in organ transplantation have improved steadily, particularly in the last five years. The first immunosuppression was x-irradiation which proved to be very unsatisfactory with a high toxicity and a poor therapeutic index. The only long survivors were two recipients of kidneys from non-identical twins. The introduction of chemical immunosuppression with aziothioprine made transplantation possible between people who are not identical twins and the addition of steroids improved the clinical results so that kidney transplantation became a reasonable therapeutic option.

The introduction of cyclosporine in the early 1980s was, however, a watershed in immunosuppression. Instead of a one year functional survival expected to be around 50%, the figure rose to over 80% and this encouraged many new centers to embark on organ transplantation (Garnier *et al*, 1965). A disappointing long-term observation of patients treated with cyclosporine was that the organ graft survival at 10 years did not differ significantly from the 10 year survival of patients treated with aziothioprine and steroids. However, the early improved results with cyclosporine were a spur to look for better immunosuppression. Anti-lymphocyte antibody preparations became more refined, both poly and monoclonal. The macrolide, FK506 developed originally in Japan, was shown by Starzl and his colleagues in Pittsburgh to be a powerful immunosuppressant and it proved to have substantially the same mode of action as cyclosporine without some of the side effects, particularly the troublesome hirsutism and gum hypertophy that occurred in some patients taking cyclosporine. However, both cyclosporine and FK506 can be nephrotoxic and diabetegenic. Rapamycin, a macrolide with a chemical structure in part similar to FK506, has proved to be an interesting immunosuppressant as it has a different mode of action to cyclosporine and FK506 which are calcinurin-inhibitors. Rapamycin acts at a later stage and is not nephrotoxic on its own although it can potentiate the nephrotoxicity of cyclosporine.

The most effective immunosuppression so far described with a low toxicity has been a combination of FK506 and rapamycin in an important series of clinical investigations performed by McAslister in Halifax, Nova Scotia (McAlister *et al*, 2000). It was this combination, together

with an anti-Il 2 receptor antibody that led to a complete change of attitude of the transplant community to islet transplantation in the treatment of type 1 diabetes. The series of patients treated by Shapiro and colleagues in Edmonton has now reached more than 40 with a one year success rate in terms of insulin independence of 80% and a two year success rate of 75% (Shapiro *et al*, 2000). The procedure usually requires at least two cadaver pancreas donors in order to get sufficient islets and this highlights the fact that cadaveric islet transplantation can never be a main-stream therapy for type 1 diabetes. Another disadvantage is that the patients require life-long immunosuppression so they substitute immunosuppression for insulin, but this can be a good trade-off if the patient is a brittle diabetic and it is hoped that the islet transplants will prevent secondary complications of diabetes.

With the progress in islet transplants together with important advances in bone marrow transplantation, especially using myelodepleting plated techniques, the stage is set for a major advance in transplantation. Hopefully non-myelodepleting bone transplantation to produce macrochimerism will result in true tolerance as has been observed in bone marrow and renal transplants between close blood relatives treated at the Massachusetts General Hospital in Boston, where the recipients had suffered from myeloma and renal failure (Buhler *et al*, 2002). The move from closely-matched donor to an unmatched donor will be a big step. Therefore, there is great interest in the possibility of engineering stem cells to provide large numbers of suitably differentiated cells to treat diseases such as diabetes, Parkinson's disease and in-born errors of metabolism. Currently, it is uncertain whether adult stem cells from bone marrow or other sources will be suitable for this task or whether it will be necessary to use fully totipotent embryonic stem cells which, of course, can differentiate into any tissue. With any stem cells therapy, there is a potential danger of tumor formation and also the possibility of virus disease if a virus is used to engineer cells to produce specific proteins. Since the cloning of Dolly, the possibility of nuclear transfer to produce bespoke stem cells or differentiated cells with the unique HLA configuration of the sick recipient is another area that is being explored.

So for young investigators interested in transplantation the field continues to be exciting, particularly the possibility of producing tolerance for transplantation of whole organs on the one hand, and the development of non-immunogenic surrogate specialized cells to treat patients with diseases requiring specific cell protein synthesis.

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