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Coping with rejection: immunosuppressants and organ transplantation

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'Discovery consists of seeing what everybody has seen and thinking what nobody has thought'
Albert Szent-Gyorgyi
(Biochemist who first isolated vitamin C)

December 2004 marked the 50th anniversary of the first successful organ transplant, which was performed in Boston (MA, USA) by Joseph Murray between identical twins Richard and Ronald Herrick. Half a century on, organ transplantation is much more commonplace, with thousands of people receiving organ transplants every year – and along with the transplant, a more optimistic prognosis. However, surgery is not the final encumbrance that transplantation patients face in their endeavour for survival: they must also overcome the attempts of their own immune system to reject their new chance of life. This necessitates the use of immunosuppressive drugs. Since 1995, there has been a steady increase in the number of immunosuppressants in active development (Figure 1). A plateau from 1999 to 2002 was followed by subsequent increases in 2003 and 2004.

The foundations of immunosuppression

The origins of immunosuppressive drugs are found many years earlier, in the late 1950s. At that time, transplant recipients would be given cell-division inhibitors, such as the dihydrofolate reductase inhibitor methotrexate, which was developed by American Home Products (now part of the pharmaceutical giant Wyeth); this agent is still widely used in the treatment of rheumatoid arthritis. Subsequently, alkylating agents and purine analogues, such as Imuran® (azathioprine; GlaxoSmithKline), which was discovered in 1957 by Nobel Prize winners George Hitchings and Gertrude Elion, were added to the immunosuppressant arsenal. Thanks to these discoveries, by 1963, the rate of related donor transplants surviving for one year had reached 80%.

Unfortunately, the first-generation drugs had substantial flaws. Their non-specific action resulted in 'blanket' immunosuppression, rendering patients highly susceptible to serious infections and increasing their risk of developing cancer.

The elucidation of the precise mechanisms involved in organ rejection heralded the advent of second-generation compounds – predominantly corticosteroids – that exerted their toxic effect mainly on lymphocytes through the inhibition of interleukin-2 (IL-2) and other inflammatory mediators. However, it took the evolution of a subsequent generation of immunosuppressant medicines to enable the success of organ transplantation.

Ciclosporin is a molecule isolated from the fungus *Tolypocladium inflatum*. It had previously failed preclinical tests as an antifungal, but the discovery of its potent immunosuppressive activity in mice rescued it from a dismal future and marked the emergence of the third generation of immunosuppressants that selectively act on T-cells. Because it inhibits calcineurin, ciclosporin – now marketed as Sandimmun®

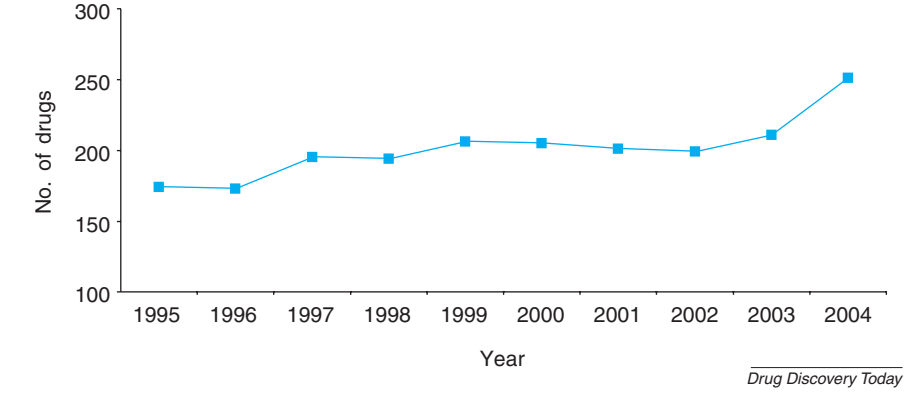

FIGURE 1
Immunosuppressants in active development 1995–2004.

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and Neoral® – prohibits the formation of a factor that is essential for transcription of the IL-2 gene. Although the absorption of ciclosporin initially hinged on the presence of bile salts, the recent development of a microemulsion formulation has overcome this problem. Ciclosporin was first launched in 1983, and remains the front-line immunosuppressant treatment more than 20 years later.

Today, transplant recipients are typically given a cocktail of three or four different drugs. Even so, they might experience graft rejection, sometimes months or years after transplantation. A second compound derived from a fungus, Prograf® (tacrolimus; Fujisawa), that was introduced a few years after ciclosporin unfortunately causes the same major side-effect – nephrotoxicity. Clearly, a significant need for safe and effective treatments remains to be addressed.

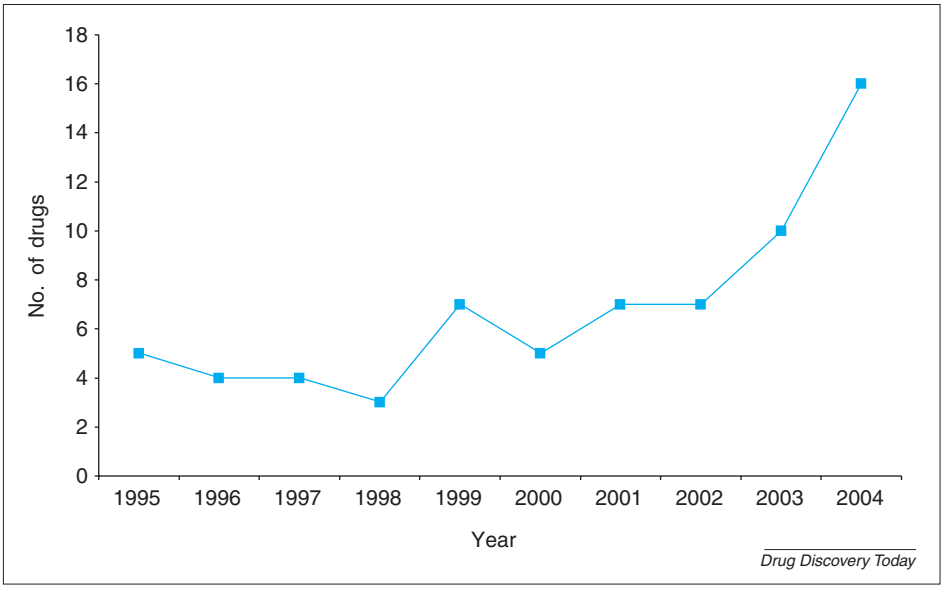

FIGURE 2

Immunosuppressant formulations in active development 1995–2004.

Reformulating the success

Several pharmaceutical companies are using drugs such as ciclosporin and tacrolimus as the foundation of their rationale for the development of immunosuppressants. Reformulation of these drugs to improve their pharmacokinetic and pharmacodynamic properties is a popular strategy, as highlighted by the 60% increase in the number of immunosuppressant formulations in active development from 2003 to 2004 (Figure 2). IVAX is developing a formulation of ciclosporin in a microemulsion of polyglycerol esters and fatty acids as Equoral®, which is currently in preclinical trials. An inhaled formulation of ciclosporin is licensed by Chiron for use in lung transplant patients, and is currently in late clinical development; a new drug application filing is expected this year. Furthermore, Fujisawa is currently conducting a three-arm Phase III trial in *de novo* kidney transplant recipients of a modified-release formulation of tacrolimus, intended for once-daily administration.

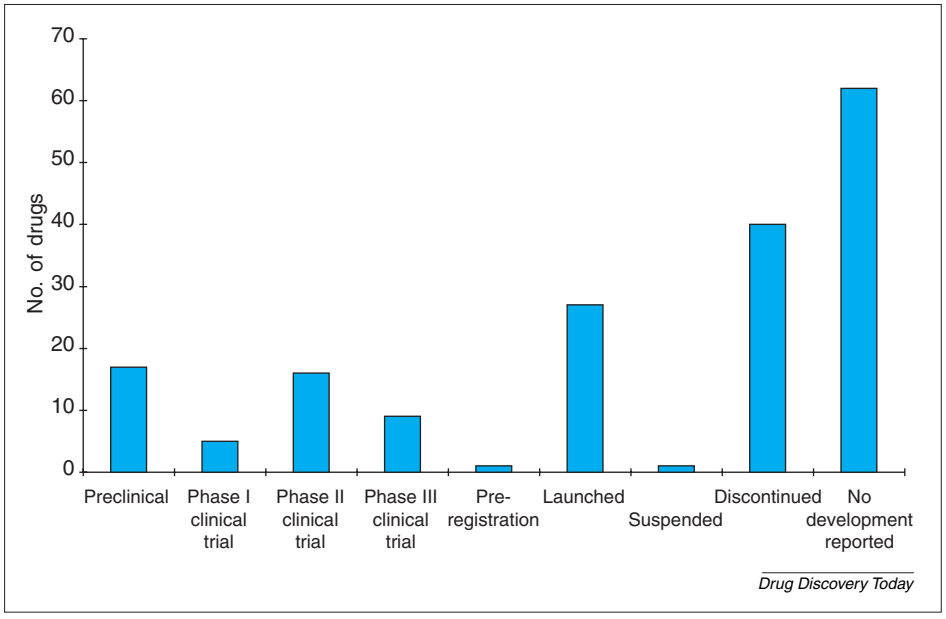

FIGURE 3

Stages of development of drugs used to abate transplant rejection (by world status).

Beyond ciclosporin

The most recent addition to the range of 27 launched immunosuppressives (Figure 3) is everolimus (Novartis), which was introduced in Germany as Certican® in March 2004. Everolimus is an orally active analogue of sirolimus (Wyeth), also known as rapamycin and marketed as Rapamune®, which is named after Rapa Nui (the native name for Easter Island) – the source of the rare actinomycete from which sirolimus was first isolated. Everolimus and sirolimus inhibit the mTOR (mammalian target of rapamycin) kinase – for once the target is named after the drug – the action of which enables the translation of a family of proteins that is essential for cell-cycle progression.

Data presented at the *Transplantation Society Congress*, which was held in Vienna, Austria, on 5–10 September 2004, suggested that mTOR kinase inhibitors (e.g. everolimus) could rival the success of ciclosporin. A retrospective study indicated that transplant patients receiving mTOR kinase inhibitor therapy were 47% less likely to develop malignancies when compared with those receiving calcineurin-based therapies. These data are reinforced by animal studies that

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suggest calcineurin-modulating immunosuppressants induce formation of tumour cells by increasing levels of transforming growth factor (TGF)-β. However, mTOR inhibitors reduce levels of TGF-β and vascular endothelial growth factor, and thus inhibit tumour angiogenesis. This is an alluring prospect – immunosuppressants with anticancer properties. The determination of pharmaceutical firms to exploit this possibility is represented by a massive upsurge in the number of mTOR kinase inhibitors in development as immunosuppressants over the past year (Figure 4).

Another pharmacological strategy prominent in this area is inhibition of inosine monophosphate dehydrogenase (IMPH)-1. CellCept® (mycophenolate mofetil), which was introduced by Roche in the mid-1990s, acts by depleting guanosine nucleotides. Novartis recently launched an enteric-coated version of mycophenolate mofetil (Myfortic®). Vertex Pharmaceuticals is evaluating another IMPH inhibitor, VX944, in Phase I trials.

Reflecting the current trend for the use of biologically derived medicines in immune-mediated diseases, anti-IL-2 receptor antibodies are the newest class of immunosuppressants to have received regulatory approval. The leading products in this area are the humanized monoclonal antibody (MAb) Zenapax® (daclizumab; Protein Design Labs) and the chimaeric MAb Simulect® (basiliximab; Novartis). These bind tightly to the α-subunit of the receptor, thus blocking its association with the β-subunit and precluding formation of the complete binding site of IL-2. Early murine versions of these antibodies were restricted by several factors, including a short half-life and high immunogenicity. Consequently, daclizumab and basiliximab were constructed with a greater proportion of human genetic regions and fewer murine regions.

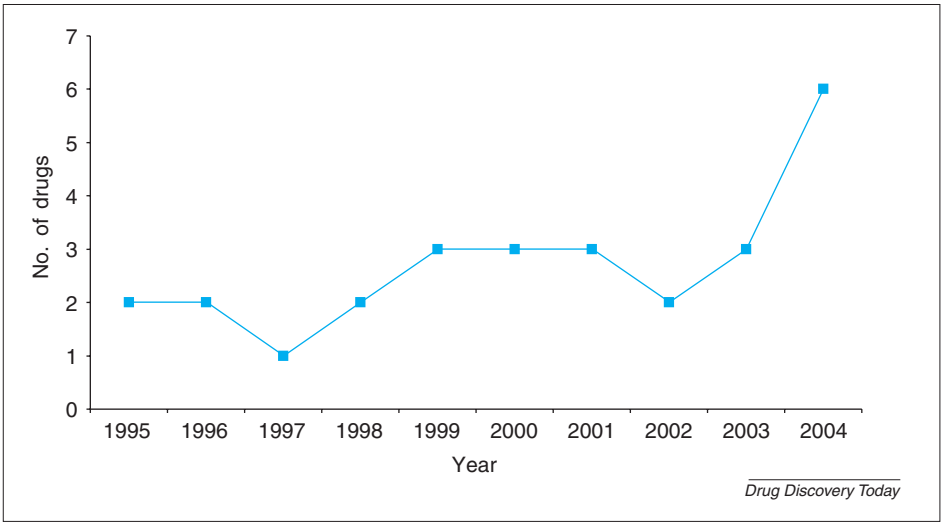

FIGURE 4

mTOR kinase inhibitor immunosuppressants in active development 1995–2004.

The future of transplantation

Pharmaprojects currently details 47 drugs under active development for transplant rejection (Figure 3). Of these, perhaps the greatest hope lies with FTY720, the subject of a collaboration between Mitsubishi Pharma and Novartis, which is currently undergoing Phase III trials. Also isolated from a fungal metabolite, FTY720 has a novel mechanism of action – and thus potential synergy with existing agents. If its elegant approach of directing lymphocytes away from the graft site protects the transplanted organ without any detrimental effect on the lymphocyte response to opportunistic pathogens as intended, FTY720 could replace ciclosporin as the 'gold standard' immunosuppressant.

The best conceivable way of preventing transplant rejection would be to educate the immune system to accept the foreign graft. This scenario would obviate the need for life-long administration of immunosuppressants and the attendant risks of infection and malignancy. Blockade of co-stimulatory molecules for T-cell activation, such as CD28 and CD40 ligands, offers one potential approach, as exemplified by BMS224828 (Bristol-Myers Squibb), which is a fusion protein against CD28. Perhaps this molecule, and others like it, will mitigate earlier failures such as the humanized anti-CD40 ligand MAb ruplizumab (Biogen), which was withdrawn from trials in 1999 after displaying thromboembolic side-effects. Profound T-cell depletion before transplantation also induces a state of tolerance; trials have shown that MabCampath® (alemtuzumab), an anti-CD52 antibody developed by Millennium and ILEX Oncology, can be used effectively in this way. Unfortunately, investigations of an immunotoxin targeting CD3 have yet to yield any promising data.

The most radical tolerizing strategy aims to induce a state whereby donor and host blood cells co-exist: this is referred to as mixed chimerism. The bone marrow of the recipient is depleted with irradiation and immunosuppressant drugs, and is replaced with bone marrow from the donor. As the haematopoietic cells of the donor mature and differentiate into T-cells alongside the native progenitor cells, they are no longer recognized as foreign. Mixed chimerism would therefore eliminate the danger of chronic rejection and enable transplant between human leukocyte antigen-mismatched individuals.

Although the organ transplantation market is too small to merit substantial investment by many drug companies, the potential application of new immunosuppressants or tolerizing therapies in autoimmune disorders such as multiple sclerosis, rheumatoid arthritis, diabetes and psoriasis should ensure the future of research in this field. Nevertheless, tolerizing therapies remain a far-off hope. In the meantime, doctors treating the 91,000 people in the UK and the USA awaiting organ transplantation will live in hope that one compound among the 30 in clinical and 16 in preclinical development (Figure 3) will emerge to supersede a drug developed more than two decades ago.

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