S9-2

Strategy for the Commercialization of Tacrolimus of Macrolide Immunosupressant Using *Streptomyces* sp Mmutant

Chang-Ho Kim

BIOMND Ltd.

Introduction

Immunosupressants are of great use in medicine for organ transplantation. These compounds decrease the immune system's response to new organs, thus improving the chances that the foreign organ will be accepted by the body. When an organ, such as a liver, a heart or a kidney, is transplanted from one person (the donor) into another (the recipient), the immune system of the recipient triggers the same response against the new organ it would have to any foreign material, setting off a chain of events that can damage the transplanted organ. This process is called rejection and it can occur rapidly (acute rejection), or over a long period of time (chronic rejection). Rejection can occur despite close matching of the donated organ and the transplant patient. Immunosuppressant drugs greatly decrease the risks of rejection, protecting the new organ and preserving its function. These drugs act by blocking the immune system so that it is less likely to react against the transplanted organ. A wide variety of drugs are available to achieve this aim but work in different ways to reduce the risk of rejection (Table 1). The market of immunosupressants is getting bigger and bigger according to development of organ transplantation. The size of the world market for immunosuppressants was expected to amount to 3 billion USD per year of 2003 (Fig. 1).

Table 1. Development of Immunosupressants

Year	Immunosupressants	Inventor or Company
1949	Cortisol	Hench, et. al
1959	Cyclophosphamide	Stender
1959	6-mercaptopurine	Schwartz, et. al.
1961	Methotrexate	Friedman, et. al
1975	Mizoribine	Sakaguchi, et. al
1976	Cyclosporine A	**Norvatis;Neoral**
1977	Rapamycin	**Wyeth; Rapamune**
1978	Leflunomide	Schleyerbach
1987	Tacrolimus	**Fusisawa; Prograf**
1991	Mycophenolate mofetil	**Roche; CellCept**

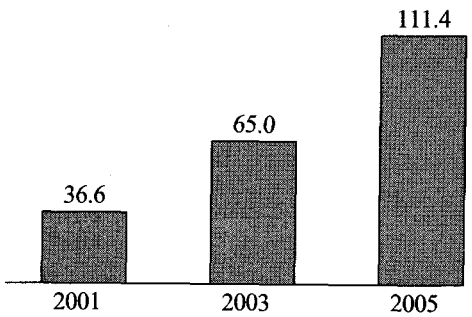

Fig.1 Market of Immunosupressants
(source: Frost & Sulliva; 2000)

The three main immunosuppressant drugs currently are being used in organ transplantations and consist of world market. Fig. 2 shows Market share of main three immunosuprpesants at 2003.

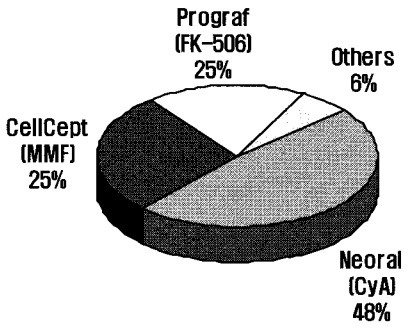

Fig. 2. Market share of main three immunosuprpesants at 2003

In addition to being used to prevent organ rejection, immunosuppressant drugs are also used to treat such severe skin disorders as psoriasis and such other diseases as rheumatoid arthritis, Crohn's disease (chronic inflammation of the digestive tract) and patchy hair loss (alopecia areata). Some of these conditions are termed "autoimmune" diseases, indicating that the immune system is acting against the body itself.

Tacrolimus

Tacrolimus (Fig. 3), also known as FK-506, is an active pharmaceutical ingredient used in formulation of Tacrolimus capsule (PROGRAF Capsule: 0.5 mg; 1 mg; 5 mg), Tacrolimus injection (PROGRAF Injection: 5 mg /mL) and Tacrolimus ointment (PROTOPIC Topical Ointment: 0.03%; 0.1%).

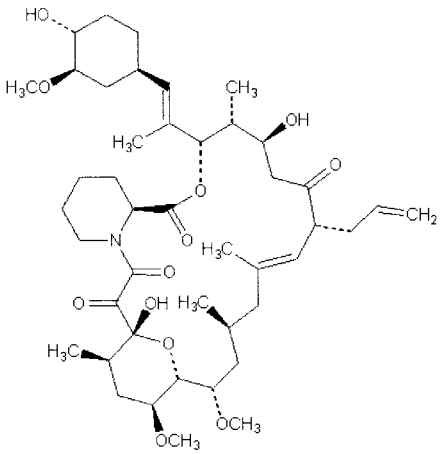

Fig. 3. The structure of Tacrolimus

Tacrolimus was developed and marketed by Fugisawa as a macrolide immunosuppressant at first in the world. Tacrolimus is a white to off-white crystalline powder, soluble in most organic solvents such as methanol, ethanol, acetone, chloroform, dichloromethane, ethyl acetate; insoluble in water; melting point 127 - 129 ℃, optical rotation - 84° (D/23, c = 1 in chloroform). Tacrolimus' mechanisms of action are not unlike those of cyclosporine. Like cyclosporine, tacrolimus inhibits cytokine production, including IL-2, inhibits expression of IL-2 receptors, and blocks cell division.

Commercialization of Tacrolimus

Strain was isolated from a soil sample collected in South Korea. The strain was identified as a new species

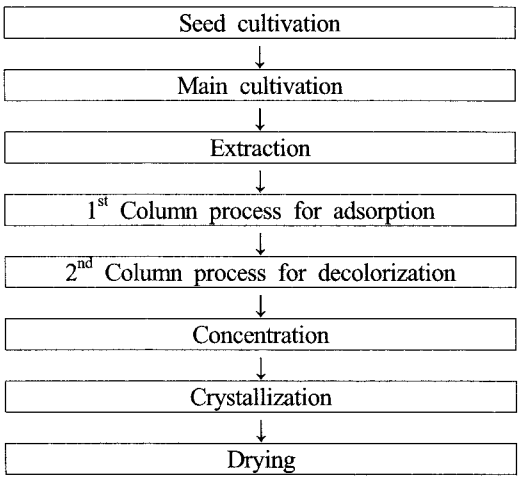

Fig. 4. Process for the production purified Tacrolimus

by comparison with literature. Highly developed strains were obtained through U.V mutation. The concentration of tacrolimus in fermentation broth reached the very high level through optimization of medium and process (Fig. 4.). Purified tacrolimus was made by purification process. The purity of tacrolimus produced is higher than 98.5% based on HPLC analysis.