

EVOLUTION OF LIVER TRANSPLANTATION AND LONG TERM IMMUNOSUPPRESSANT TREATMENTS

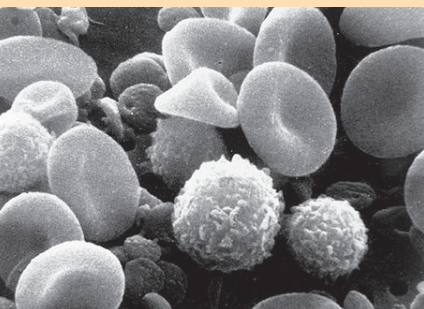
1944

British scientist, **Sir Peter Medawar**, reported that **rejection of a transplant is based on immunologic factors**, a discovery that eventually transforms transplant surgery from a largely unsuccessful experiment to an accepted form of treatment¹



1948

British doctor, Sir James Gowans revealed that **lymphocytes play a major role in transplant rejection**²

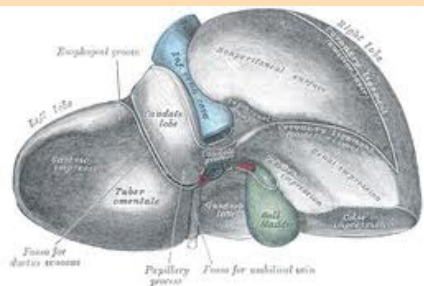


1949

Cortisone is shown to alleviate rheumatoid arthritis³ and has since been used to prevent transplant rejection³

1955

Auxiliary liver transplantation concept originates from experimental work of Professor Stuart Welch⁴



1961

British surgeons, **Joseph Murray and Roy Calne**, showed that **azathioprine therapy suppressed the rejection reaction and prolonged allograft survival**⁵

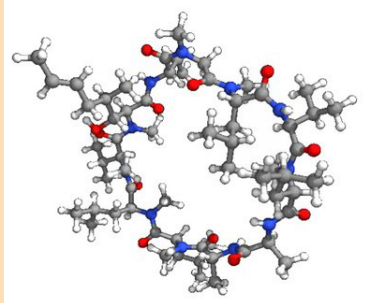
1963

American doctor, **Dr. Thomas E. Starzl** performed the **first human liver transplant** at the University of Colorado Medical School but lack of effective immunosuppressives limited the success⁴



1967

After earlier failures, **Thomas Starzl completes the first successful liver transplant** at the University of Colorado Health Sciences Center, in Denver, U.S.A⁴

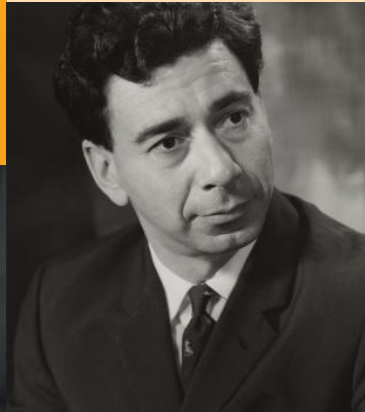


1970

Researchers discover that **cyclosporin**, a compound produced by fungi, **can suppress the human immune system**. Tests demonstrate that cyclosporin can prevent rejection of newly transplanted organs and tissues⁵

1978

The use of **cyclosporin** – an anti-rejection drug – is **approved in Britain** and goes on to play a vital role in all future transplantations. Another 5 years pass before the drug is approved for use in the USA⁶



1983

National Institute of Health Consensus Development Conference concludes that **liver transplantation is not an experimental procedure but an effective therapy deserving broader application**²

1984

The discovery of FK506 set in motion Astellas' commitment to transplant medicine. **FK506**, the immunomacrolide isolated from the organism *Streptomyces tsukubaensis*, was **first discovered in the soil of Japan's Mount Tsukuba in 1984**^{7,8}



1985

At the European Society for Organ Transplantation meeting in Munich, Prof. Henri Bismuth from France, Prof. Rudolf Pichlmayer from Germany and Sir Roy Calne from the UK collaborated to create a **European Liver Transplant Registry (ELTR)**, to register all liver transplantation procedures in Europe⁹



1993-1996

Launch of PROGRAF™ (tacrolimus immediate release) worldwide⁸. PROGRAF™ (formerly known as FK506) inhibits interleukin (IL)-2 production and lymphocyte proliferation,¹¹ and is **shown to significantly reduce acute rejection rates compared with cyclosporin**¹²

1996

Cellcept (mycophenolate mofetil) approved for use in Europe to prevent transplant rejection¹³

2007

Launch of ADVAGRAF™ (tacrolimus prolonged release) in Europe for the **prevention of kidney rejection in adult kidney or liver transplant recipients**¹⁴

Other drugs approved are:

- **Certican® (everolimus)** which was approved for use in **organ rejection after liver transplantation in February 2013**¹⁵

2014

Results from a large, retrospective **European Liver Transplant Registry (ELTR) study** showed that patients who received **early use Advagraf showed improved graft survival** vs those treated with twice daily tacrolimus (tacrolimus BID) by **8%** at 3 years (p=0.01)¹⁶

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 15 Certican. Summary of Product Characteristics
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