Immunobiology of Immunosuppressant Agents
(2003)

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Fig. 1.7 Dr J.E. Murray, Dr J.P. Merrill and Dr J.H. Harkins, who successfully carried out renal transplantation between this set of identical twins on 25 December 1964.
# Renal Transplant in the 20th Century

## A History of Immunosuppressive Drugs

<table>
<thead>
<tr>
<th>Era</th>
<th>Period</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Era 1</td>
<td>1953-63</td>
<td>The Experimental Period</td>
</tr>
<tr>
<td>Era 3</td>
<td>1983-93</td>
<td>The Cyclosporine A Era—Marked Improvement in Early Graft Survival, All Organs Are Not Clinically Transplantable, Chronic Rejection Remains a Problem</td>
</tr>
<tr>
<td>Era 4</td>
<td>1993-?</td>
<td>The Designer Drug Era—Knowledge of Transplant Immunology Allows Grafting of New Agents</td>
</tr>
</tbody>
</table>
Laws of Transplantation

Prehn & Main, 1958

Isograft + Allograft -

A + B A+B

134/137 F₁ F₂
HUMAN MHC COMPLEX

Class II

Class III

Class I
IMMUNOSUPPRESSANTS
Antimetabolites - Azathioprine, Mycophenolate Mofetil, Brequinar
Nonselective Action of Azathioprine

IMP → IMPDH → thio-XMP → thio-GMP
IMP → IMPDH → thio-IMP

Results:
- 5'-phosphoribosylamine ↓
- XMP ↓  PRPP ↑  AMP ↑
- thio-dGTP incorporated into DNA ↑
  - DNA strand breaks
  - delayed cytotoxicity
Selective, Noncompetitive Inhibition of IMPDH by Mycophenolic Acid

MPA inhibition of inosine monophosphate dehydrogenase (IMPDH)

Depletion of dGTP; excess AMP, ADP, dATP

Glycoprotein Synthesis

Inhibition of ribonucleotide reductase
PRPP synthetase

Depletion of deoxyribonucleotide triphosphates

DNA Polymerase

DNA
Mycophenolate Mofetil

A

Lymphocyte

Guanine

HGPRTase

ribose-5P + ATP

PRPP Synthetase

PRPP

IMP

IMPDH

DNA RNA

salvage
de novo

B

Parenchymal Cell

Guanine

HGPRTase

ribose-5P + ATP

PRPP Synthetase

PRPP

IMP

IMPDH

DNA RNA

salvage
de novo

GMP
Immunophyllin Binding Agents

1. Cyclosporines (Sandimmune and Neoral)
2. Tacrolimus (FK506, Prograf)
3. Sirolimus (Rapamycin)
Cyclic undeca-peptide cyclosporin A (CSA)
(a) NF-ATp → NF-Atp-Fos-Jun → NF-Atp-Fos-Jun

Rapid dissociation rate (<2 min)
Slow dissociation rate (>20 min)

(b) Distal murine NF-AT site

GCCCCAAGAGGAAAATTTGTTTCATACAG

Anjana Rao, Immunology Today 1994:15

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Rapamycin

[Chemical structure image]
RAPAMUNE® (sirolimus) inhibits IL-2–mediated cell proliferation without altering IL-2–activated apoptosis.
Mechanism of Action of Rapamycin

Growth factor receptor (e.g. IL2R)

PTK

PL2 kinase

Rapamycin

FKBP

Target

p70 S6 kinase

cdk/cyclin D1 association

cell cycle progression

cyclin A production
p34<sup>cdc2</sup> kinase activity
p33<sup>cdc2</sup> kinase activity

Probable downstream substrates of rapamycin target

nucleus

plasma membrane

Ras, GDP-GTP exchange

Ras, GTP

H<sub>2</sub>O

m-Sos

GTP

Raf-1

MapKK

MapK

S6, Gyr-2

GTP

PI<sub>3</sub> kinase

Growth factor receptor

IL2R
RAPAMUNE® (sirolimus) Has a Distinct Mechanism of Action

<table>
<thead>
<tr>
<th></th>
<th>Cyclosporine</th>
<th>RAPAMUNE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binding protein</td>
<td>Cyclophilin</td>
<td>FKB1P12</td>
</tr>
<tr>
<td>Effector protein</td>
<td>Calcineurin</td>
<td>mTOR</td>
</tr>
<tr>
<td>IL-2 message</td>
<td>Inhibited</td>
<td>–</td>
</tr>
<tr>
<td>IL-2 response</td>
<td>–</td>
<td>Inhibited</td>
</tr>
<tr>
<td>Cell-cycle effect</td>
<td>G₀-G₁</td>
<td>G₁-S</td>
</tr>
</tbody>
</table>

Polyclonal Anti-T-Cell Antibodies

Complement-Dependent Lysis

FC-Receptor-Mediated Cell Lysis
## Specificities in Antibody Preparations

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Antigen Target</th>
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</thead>
<tbody>
<tr>
<td>ATGAM</td>
<td>CD2, CD3, CD4, CD5, CD7</td>
</tr>
<tr>
<td></td>
<td>CD8, CD11α, CD18,</td>
</tr>
<tr>
<td></td>
<td>CD45, TCR</td>
</tr>
<tr>
<td>OKT3</td>
<td>CD3</td>
</tr>
<tr>
<td>OKT4</td>
<td>CD4</td>
</tr>
<tr>
<td>ENLIMOMAB</td>
<td>ICAM-1</td>
</tr>
<tr>
<td>T10 B9</td>
<td>TCR</td>
</tr>
<tr>
<td>ANTI LFA-1</td>
<td>LFA-1</td>
</tr>
<tr>
<td>ANTI-TAC</td>
<td>IL2 Receptor</td>
</tr>
</tbody>
</table>

*Source: Bourdage JS, Hamlin DM. Comparative polyclonal antithymocyte globulin and antilymphocyte/antilymphoblast globulin anti-cd antigen analysis by flow cytometry. Transplantation. April 27, 1995; 59(8).*
Monoclonal Anti-CD3 Antibodies
Opsonization

T Cell

CD3
αCD3
φ

FC

TCR

Mφ

FC Reception

αCD3

TCR

Mφ

Cell
IL-2 RECEPTOR ANTIBODIES

1. TARGET: NONCONSTITUTIVE IL-2R, MOSTLY $\beta$ CHAIN
2. IN ANIMALS HIGHLY CYTOTOXIC AND PROLONGS GRAFTS
3. IN MAN MODULATES RECEPTOR
4. FRENCH STUDY: AS INDUCTION AGENT
   a. FEWER SIDE EFFECTS THAN P ON T CELL AB
   b. GRAFT SURVIVAL THE SAME
   c. TREND FOR MORE REJECTIONS
Murine and Humanized Monoclonal Antibodies

Variable Region

Fc Region

M = Murine

H = Human

Murine Antibody

Chimeric Murine-Human Antibody

Humanized Antibody
RECOMBINANT MONOCLONAL ANTIBODIES

Mouse

Human

Chimeric

Humanized
FTY 720
Potential Advantages

- Unique Action – Alteration of Lymphocyte Traffic
- Synergy With Calcineurin Inhibitors and Sirolimus Permitting Dose Reductions
- Side Effects Are Not Additive to Other I.S. Drugs
- Once Daily Dosing
- Minimal Drug-Drug Interactions
- Low Intra-subject Pharmacologic Variability

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FTY 720

- Immunosuppressive *In Vitro*
- Depletes T and B cells from peripheral blood
- Increases Lymphocyte homing to mesenteric nodes and Peyer’s patches

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POSSIBLE SITES OF ACTION IN T CELLS OF NEW XENOBIOTIC IMMUNOSUPPRESSANTS

Ca²⁺-DEPENDENT
LIGANDS
TCR-CD3 + CD4/CD8
CD2 LFA-1

Ca²⁺-INDEPENDENT
LIGAND + CD28

Cytokines
IL-2

CsA
FK506

RPM
MZR
MPA
BQR

DSG

G₀ → G₁ → LFM → S → G₂ → M

R.Morris '94