Liver Transplantation
Dallas 2013
Early Days

Evolution of Liver Transplantation in Europe
Orthotopic Allografting in Pigs
Garnier et al, 1965
Acad.Sci.Paris
J.Surg.
Soluble HLA Class I

Molecules induce Apoptosis in alloreactive Cytotoxic T Lymphocytes

Zavazava & Kronke
Kiel Institute of Immunology
Nature Medicine 2.9.1996-1005
At the beginning we moved the recipient to the donor hospital
We had to wait for Cardiac Arrest
The logistics were complicated!
Rapamycin or Sirolimus

Inhibits T Cell Proliferation

Not Nephrotoxic Target is TOR
Liver Transplant for Huge Hepatoma In Hep B surface antigen + patient, 1972
Auxillary Liver Transplantation

1988 Trepstra O T, NEJM
1993 Boudjema K, Lancet
Split Liver

1988 Pichlmayr R, Langenbecks Arch.Chir
1989 Bismuth H, Brit J Surg
1990 Otte J B, Surgery
Transplantation of the
Liver, Heart and Lungs

Wallwork J, Williams R and Calne R
Lancet 1987
10 Years post transplant

Gas Gangrene Of Liver Allograft

3rd Liver rejecting
6 years later after 4th liver

Gardener’s Syndrome + Desmoid Tumours

En Block Transplantation of Liver, Kidney, Pancreas, Stomach, Duodenum and Small Bowel
Living Donor

1989 Raia S, Lancet
1990 Strong R, NEJM
1991 Broelsch C, Ann Surg
1944 Tanaka K, Am J Surg
1996 Fan S T, Hepatology
1997 Chen C L, J Gastroenterology
If a wife is willing to donate a kidney to her husband as part of a divorce settlement - in exchange for the house, kids and car.
Would this be acceptable as an emotionally related donor

OR

Unacceptable as a compensated donor?

DAILY NEWS

I gave her my kidney, she broke my heart
(And now I want my kidney back)!

NY Surgeon Divorce

S T Fan’s Patient, Adult to Adult living donor transplant
One Day of Drugs

“WOFIE” Hypothesis

- A window of opportunity for immunologic engagement without destructive HvG or GvH is needed for the induction of
  - Classical tolerance
  - Operational tolerance
  - "Almost or proper" tolerance
- The WOFIE may be an unstable period
**Campath 1H Humanised 1gG1 monoclonal from rat monoclonal Campath 1G**  
*(Waldmann, Winter & Hale)*

- Target CD52 - glycoprotein anchored to cell surface glycolipid of all human lymphocytes, monocytes and macrophages but not stem cells
- Powerful killer of lymphocytes (Complement and Antibody Dependent Cell-mediated lysis)
- Monocytes and β cells regenerate rapidly
- T cells regeneration biased towards CD8+ Cells
- CD4+ Cells may be reduced for months or years
- 1st dose Cytokine Release Syndrome may include bronchospasm and hypotension

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**Campath 1H Pilot Study**  
June 1987 to July 1988

- 31 patients
- Non randomised
- Non blinded
- Single centre

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**Prope Tolerance, Perioperative Campath 1H, and Low-Dose Cyclosporin Monotherapy in Renal Allograft Recipients**

1998 *Lancet*

Caine, R., Friend, P., Moffatt, S., Bradley, A., Hale, G., Firth, J., Stanley, K. and Waldmann, H
Prospective randomised trial of Alemtuzumab vs Basiliximab or ALG (Hanaway et al NEJM 2011)

Less rejection at 6 Months, one and 3 Yrs with Campath, 10% vs 22% at 3 Yrs in low risk patients

Possible Opportunity

Nadir of lymphocyte count optimal moment to induce “Tolerance”

Using methods effective in experimental models

Campath+Belatacept (Fushion Protein 2nd Signal block) + Rapamycin. Living Donors Allan Kirk (Personal Communication 2013)

- 20 Renal allografts
- Campath 30 mg, one dose median follow-up 3 years. No graft loss
- Belatacept monthly dose
- Rapamycin 2mg/kg, attempt to wean, 6 success
- All alive with normal serum creatinine
- One antibody rejection, reversed
Renal Function for Patients Treated with Alemtuzumab Induction and Belatacept/Sirolimus maintenance (n=20)

For poor patients who have to pay for their drugs Campath induction and the reduced maintenance drug dosage can be the critical LIFE SAVING FACTOR as to whether they can receive treatment for their renal failure. They will lose out if the price of Campath is raised.

Treating an illness is profitable, but curing an illness is less so, and preventing an illness perhaps buys more liability than profit.

Allan Kirk editorial American Journal of Transplantation 2013
Prope Tolerance update
2011 More than 2000 Renal Transplants

- Campath induction now used in 13% of renal transplants in the US (Kirk AJT 2013)
- Pittsburgh 200 cases. Living donors At 3 years survival, 93% patients, 86% grafts (Tan et al Am J Trans 2009)
- 1000 cases in Austin Texas over 8 years. Rejection rate <3% at 90 days, survival, patients, 98.8%, grafts 95% (Wright et al Am J Trans 2011)

Finding promising treatments such as alemtuzumab is important. But so is keeping alemtuzumab accessible and affordable if its early success in these trials proves to be of enduring value.

Lancet Nov 2012