



**Oxford University Hospitals**  
NHS Foundation Trust

# **NHSBT Recipient and Live Donor Coordinators Induction workshop**

## **“What’s the blue tablet for?”**

**Andrea Devaney, Consultant Pharmacist-  
Transplantation & Renal Services**

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## Declarations

- Many years experience of medicine use in Tx pts with Tx organs *below* the diaphragm
- Little clinical experience *above* diaphragm
- Work closely with Oxford co-ordinators (MDT)
- Your session – so please ask questions



## Workshop Objective

- Discuss impact of immunosuppression
- Discuss impact of concomitant medications

For all transplant organs  
(above & below diaphragm)

....*Medicine* journey through transplantation....



# Workshop Overview

## DONOR/RECIPIENT medicine related issues

- Donor – LD
  - ☐ co-morbid conditions/preparing for donation
  - ☐ post-op pain & laxative management
- Donor – deceased
  - ☐ micro results affecting recipient/CMV status
- Recipient
  - ☐ Preparation for transplant listing
  - ☐ Transplant immunosuppression & co-medications
    - Induction vs maintenance immunosuppression
    - Transplant co-medications

The image shows a close-up of several clear plastic pill containers arranged on a white surface. Each container holds a different type of tablet, distinguished by color and shape. The colors include red, yellow, green, blue, orange, and white. Some tablets are round, while others are oval or rectangular. The containers are slightly out of focus, creating a sense of depth. The text "What's the blue tablet for?" is overlaid in green on the central part of the image.

What's the blue tablet for?



## **LIVE DONOR – medicine related issues**

- Preparing for donation
  - comprehensive DHx
  - Herbal/OTC medicines (e.g. migraine meds/NSAID)
  - Anti-coagulation bridging therapy or extended VTE prophylaxis post-op
  - Hormonal contraception (POP vs OCP) or HRT
  - Smoking cessation (NRT)
  - Post-op pain & laxative management



## DECEASED DONOR – medicine related issues

- Donor – deceased
  - micro results affecting recipient
    - Anti-HBc positive donor, we request HBV viral load on donor
    - CMV donor status (previous SIRI)
    - HEV RNA positive
    - Hep C positive (still awaited for renal Tx in England)
    - HIV positive



# RECIPIENT – medicine related issues

## Prior to Tx listing – medicine issues (DD & LD)

- Co-morbid states and concomitant medicines
    - HIV, MELAS, RA, epilepsy, chronic HBV
  - Immunosuppression trials
    - tolerability/dose finding/adherence
  - MDT referrals- anticipated medication difficulties post-Tx
    - care homes/learning difficulties/blind/swallowing difficulties/chronic diarrhoea – absorption/drug side effects or intolerances/lactose intolerance
  - Altered body habitus (drug dosing)
- LTBI treatment
    - ideally prior to listing to avoid prophylaxis
  - Vaccination history
    - HBV/HPV
  - Previous Tx history
    - Tailoring immunosuppression to recipient
    - Viral infection BKV/CMV
    - Previous PTLD
    - Immunosuppression s/e
  - On-going clinical trial



## **RECIPIENT – medicine related issues**

**LD recipient meds review prior to Tx (2-3wks pre-Tx)**

- Plan for current medicines after Tx
  - Critical medicines review e.g. diltiazem, gout meds, cinacalcet, alfacalcidol, high dose statin, heart failure meds
  - May need EPO dose adjustment pre-Tx
  - Anti-coagulation bridging therapy or extended VTE prophylaxis post-op
- Smoking cessation (NRT)
- immunosuppression pre-load from day -7/-4





# Why do we need to give immunosuppression?



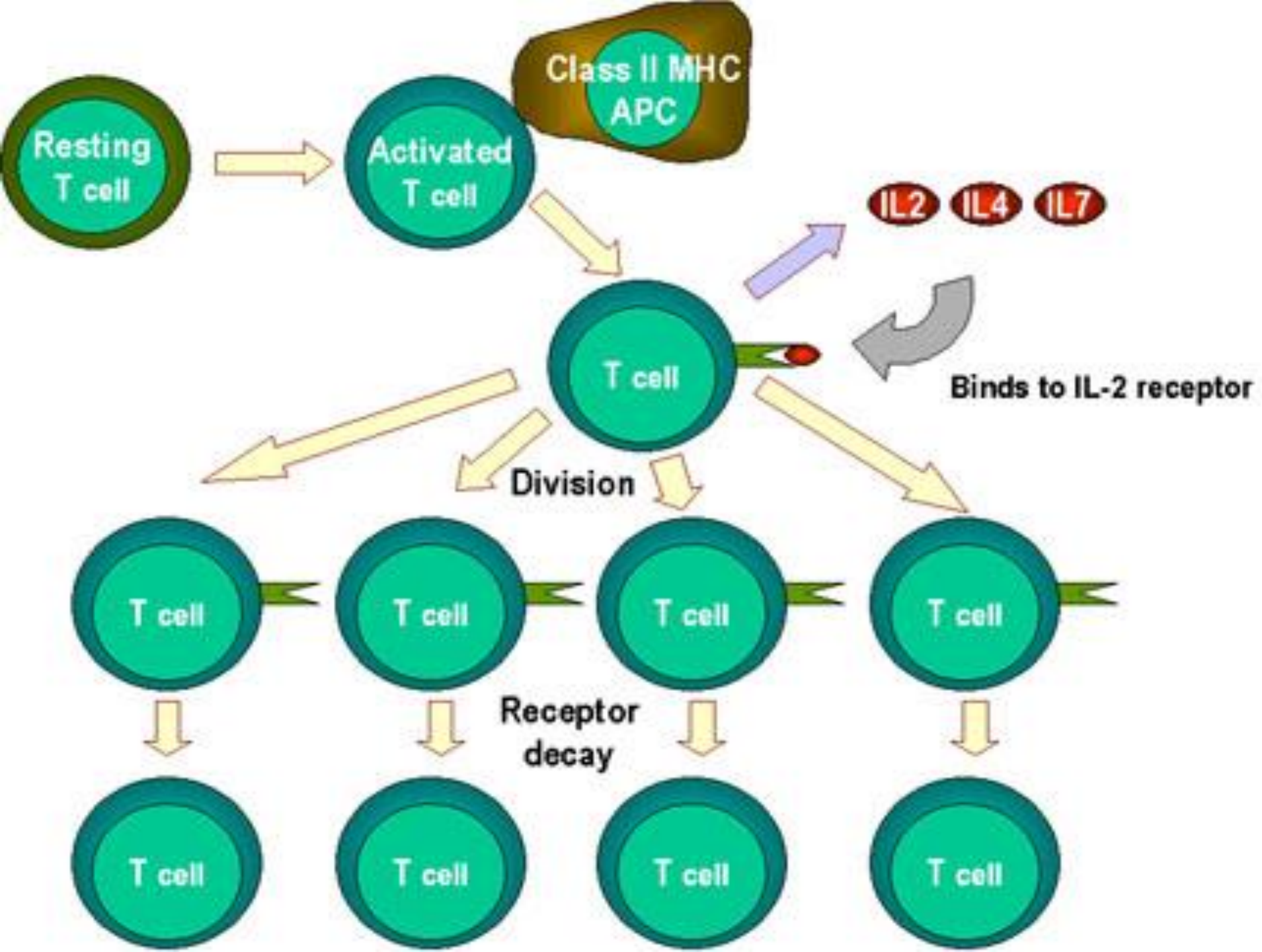
## Transplant Immunology

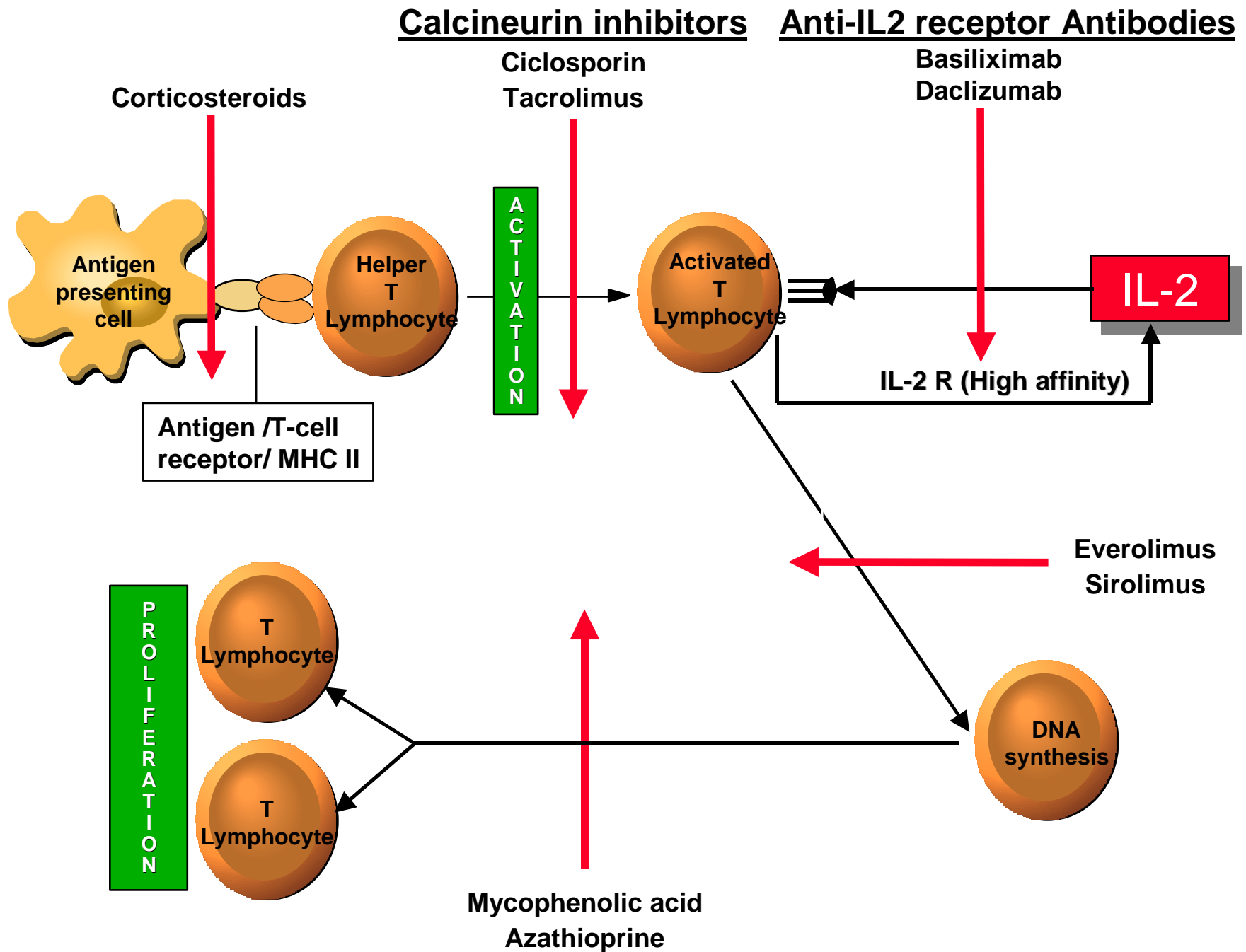
- Only a kidney from an identical twin (monozygotic) will be genetically identical
- In all other cases the organ will be foreign
- An immune response will be invoked to destroy the organ
- So immunosuppression is needed to dampen down the immune system and avoid rejection.



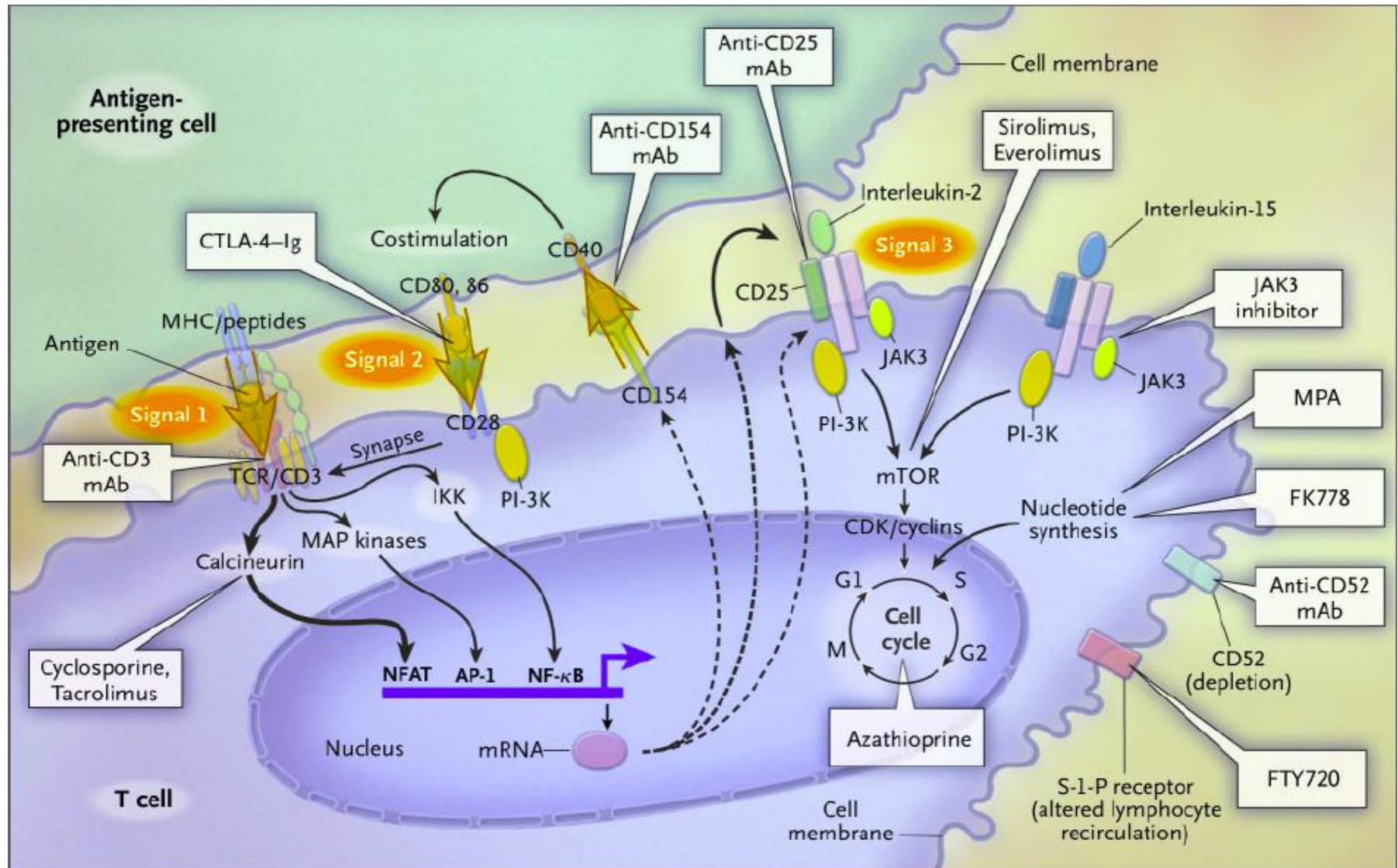
## Immune Response

- Donor HLA molecules are presented via antigen-presenting cells to resting T-cells that have receptors for that specific antigen
- This recognition activates the T-cells which then produce and secrete cytokines (interleukins)





# Targets of immunosuppressive drugs





## Immunosuppression strategies

- Induction (0-6mo) Maintenance (>6mo)

- Induction

bo

or A

+ intra-

- CNI –

- An

azathioprine or MMF

- Steroid

No nationally agreed  
protocols – all centre  
+/- organ specific!

therapy

therapy

rolimus

ng



## Induction antibody

*Caveat: Induction antibody – NOT used routinely in liver Tx*

*Choose from:-*

- IL2 receptor antibody
  - Basiliximab (Simulect®).
- MabCampath® – alemtuzumab – pt access scheme only
- rATG – Thymoglobulin® – UK license March 2008



## Maintenance immunosuppression

### What agents?

- CNI's
- Antimetabolites
- Steroids
- MTOR inhibitors
- Belatacept



# Maintenance immunosuppression

## What combinations?





# Regimens

- Why use a combination?
- Triple therapy still most common *maintenance*
  - Induction antibody (basiliximab, rATG, alemtuzumab)
  - Tac, antimetabolite +/- steroid is standard
  - For renal Tx see NICE guidance 2017 TA481 ([www.nice.org.uk](http://www.nice.org.uk))
- Regimen chosen to fit patient and immunological risk
  - Steroid free
  - Once a day – Young Adults & risk of non-adherence
  - Optimise medicines & prescribe considerately!

# Tacrolimus



- Average dose tacrolimus (Adoport) 2.5mg bd
- Dose adjusted to levels (5-13ng/ml all organs)
- Cost = £500pa Adoport vs £2500pa Prograf
- Food affects amount absorbed – therefore, administration must be consistent in relation to food
- Patients advised to take with food for ease
  - *Not* all centres, some advise 1 hr before or 2 hr after food
- Prescribe by brand – generic preferred

# Tacrolimus drug interactions

- Aminoglycosides, NSAIDs, Amphotericin increase risk of nephrotoxicity
- Metabolised by cytochrome P450 system (cyt 3A4) – Tac levels



Erythromycin, Verapamil, Diltiazem, Ketoconazole, Fluconazole, Voriconazole, Amiodarone, Grapefruit, Omeprazole



Carbamazepine, Phenytoin, Rifampicin, St John's Wort, Caspofungin

# Tacrolimus



- Similar to Ciclosporin
  - Nephrotoxic
  - Neurotoxicity
  - Tremor
- Also diabetogenic
- However, compared to Ciclosporin
  - No gingival hyperplasia
  - Less hirsutism, hypertension, hyperlipidaemia, hyperuricaemia



## New Era - Generic immunosuppression

- CNI's – critical dose drugs.
  - Must be prescribed by brand
  - Different brands are not interchangeable
  - Different brands can not be swapped, unless being monitored by Transplant unit
  - *Tacrolimus* – Prograf, Advagraf, Modigraf, Adoport, Vivadex, Tacni, Envarsus
  - *Ciclosporin* – Neoral, Sandimmun, Deximune, Capimune, Vanquoral
- MMF/MPA – not critical dose drugs



## Tacrolimus M/R

- **Advagraf** capsules 0.5mg/1mg/5mg
  - OD dosing
  - Some units – restricted use
  - Other units – first choice tac product
  - *Liver Tx* routine use – positive longterm outcome data
  - Brand Rxing to avoid errors
  - Increased cost - £3000pa vs £500pa bd Adoport
  - Generic soon?
- **Envarsus** tablets as 4mg/1mg/0.75mg



## Antimetabolites

- Azathioprine & MMF/MPA
- No good evidence to support one over other
- MMF interaction with CyA
  - inhibition MPA enterohepatic recirculation
  - reduced MPA exposure by 30-50% so give increased dose 1g bd with CyA only
- Less MMF with tac/SRL (500-750mg bd)
- ? Role of MPA levels



# Azathioprine

- Daily dosing usually 1.5mg/kg/day, with food
- What drug causes serious drug interaction with azathioprine?
  - ALLOPURINOL
  - Must reduce aza dose to  $\frac{1}{4}$  when starting allopurinol i.e. aza 100mg od  $\downarrow$  to 25mg od
- Side-effects
  - Bone marrow suppression (leucopenia, anaemia, thrombocytopenia, etc)
    - If  $WCC < 3.0 \times 10^9/l$  = review ANC
    - $ANC < 2$ : half aza,  $ANC < 1$ : stop aza
  - Pancreatitis
  - Alopecia
  - Cholestatic hepatotoxicity
- Cytotoxic (avoid halving tablets)

# Mycophenolate mofetil (MMF)

- Dose 500mg-1g bd with food
- Use generic MMF/MPA
- Common side-effects
  - Increased risk of CMV, Herpes simplex, Lymphoma
  - Gastro-intestinal (*most troublesome*)
    - Diarrhoea, Nausea, Vomiting
  - Bone marrow suppression
    - Neutropenia
      - If WCC  $< 3.0 \times 10^9/l$ , review ANC
      - ANC  $< 2 = \downarrow$  MMF 250mg bd
      - ANC  $< 1 =$  stop MMF
    - Anaemia
    - Thrombocytopenia
- Cytotoxic

# Corticosteroids

## Prednisolone

- Ubiquitous action
- Mechanism of action
  - Block the release and inhibit the action of cytokine interleukins
  - Interfere with T-cell activation
  - Inhibit macrophage function
  - Inhibit prostaglandin production
- Anti-inflammatory equivalence vs biological half life
  - Prednisolone 5mg  $\equiv$  hydrocortisone 20mg
  - Prednisolone 5mg  $\equiv$  methylprednisolone 4mg
  - Prednisolone  $t_{1/2}$  12-36hr vs hydrocortisone  $t_{1/2}$  8-12hr
  - Consequently hydrocortisone dose is repeated every 6-8hr





# Corticosteroids

## Adverse Effects

- Increased appetite
- Weight gain
- Indigestion
- Osteoporosis
- Hyperglycaemia
- Moon face
- Thin skin
- Mood changes
- Adrenal suppression
- Impaired wound healing







side effects<sub>x</sub>



## Sirolimus/Everolimus Side Effects

- Hyperlipidaemia
- Gastrointestinal
  - Diarrhoea
- Skin
  - Oedema
  - Rash
  - Ulcers
- Hypertension
- Delayed wound healing
- Bone marrow suppression
  - Anaemia
  - Thrombocytopenia
  - Leucopenia

**NOT NEPHROTOXIC**



# New kid on block ...Belatacept...

- Selective blocker CD28 co-stimulation
- Co-stimulation is nec for full activation of Tcells by Ag on APC.
- Novel – IV infusion over 30 mins every 4 or 8 weeks.
- Phase II trial (Oxford 3 patients), now licensed in renal Tx but using in bowels!
- All pts basiliximab induction, MMF + steroids.  
Control arm on CyA.

# Transplant co-mediations

**NB: Variable practices between centres**

- **Thromboprophylaxis** — Aspirin + standard VTE prophylaxis and if pancreas dalteparin for 6/52
- **Gut protection** — Ranitidine (6/52) 1st choice over PPI
- **CMV prophylaxis**
  - High risk CMV D+/R- (Valganciclovir 6m)
  - All CMV R+ recipients (Valganciclovir 3m)
  - CMV PCR monitoring on stopping prophylaxis/treatment
- **PCP prophylaxis** — co-trimoxazole (6-12m)
- **TB prophylaxis** — Isoniazid/pyridoxine (6-12m)



# Transplant co-mediations

**NB: Variable practices between centres**

- **Statin** — primary CVD prevention, prefer atorvastatin, avoid simvastatin
- **Bone protection**
  - especially if using long term steroids
  - Bisphosphonates contraindicated if  $GFR < 30$
  - Some trial data to support risedronate 5mg daily is safe in  $GFR < 30$
- **Antihypertensives**
- **Diabetes control**

# Multi-compartment compliance aids





## Medication Do's and Don'ts

- **AVOID**

- Live vaccines
- NSAID's
- Macrolides/CBZ/azole antifungals
- ACEI/ARB's (monitor GFR)

- **CAUTION**

- Cyp3A4 inducers/inhibitors
- Herbal meds: St Johns wort/turmeric
- Statins
- Different tacrolimus brands
- Pregnancy

Transplant pharmacist always available for medicine advice



# How do we treat rejection?

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"BOY! TALK ABOUT ORGAN REJECTION!"



Questions  
are  
guaranteed in  
life;  
Answers  
aren't.