# Transplant immunobiology – nature's immigration control

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# Key players in the reject or accept game

- T – Lymphocytes
  - CD4 cells – The cabinet committee on Immigration
  - CD8 cells – The Home office / Customs & Immigration dept
- B – Lymphocytes and the antibodies made by them – the Home office bureaucrats / Police
- DC, macrophages, NK cells, etc

# The players

- Rejection is mainly an acquired/adaptive immune response and T-cell is king in adaptive immune responses

  RAG KO mice *Mason DW, Morris PJ Annual Rev of Immunol 1986 4:119-145*

- CD-4 and CD-8 T-cells probably play equal but different roles in rejection. Tissue and extent of antigenic mismatch dictates relative roles

- Responses are antigen specific

- B-cells are supporting cast. Not essential for rejection but if they get involved, they turbo-charge the rejection response

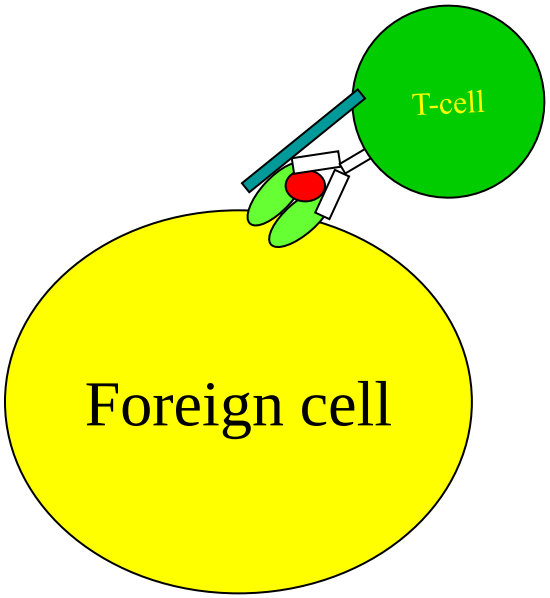
# What happens when a ‘foreigner’ enters the body?

- Recognition of ‘foreign’ [non-self] status
- Once recognition complete decision re evict or keep foreigner
- Mechanisms of eviction

# HLA antigens – nature's ID card

- Major antigens relevant to transplantation have a pre-fix of A, B & DR followed by a number (for example A2, DR7 etc - >200 known)
- Some antigens more common than others – example A2 = 38% of UK population, A30 <2% in UK
- Ethnic variations in HLA incidence – example A30 <2% of caucasians, >20% sub-saharan africans
- In transplants, count the number of antigens not matched in A, B and DR respectively. For example 000 = all matched, 102 = one not matched at A, both matched at B and 2 not matched at DR

# Decision following recognition – shall we let in this asylum seeker?




Accept or ignore foreign cell or
Asylum application successful

Reject or kill foreign cell or
Adopt the Daily Mail approach

# Are we programmed to reject all foreign HLA antigens – how open/closed is the border to asylum seekers

- Default  is to reject everything that is non-self but does not always happen
- Prior knowledge of foreign HLA antigens greatly increases the risk of rejection
- Immune system comes into contact with foreign HLA antigens by blood transfusion, transplantation and in women additionally through pregnancy

# Love or hate at first sight

- Direct (recognition of non-Self HLA on graft cells) and in-direct recognition (recognition of processed non-self HLA on recipient APCs)

- Co-stimulation: the second signal

  KO animal data Dooms H, Abbas AK 2006 Immunol Rev 211;23-38

- The prevailing immune milieu: ischaemia-reperfusion injury

# Chemokines and cytokines – the currency that lubricates all transactions

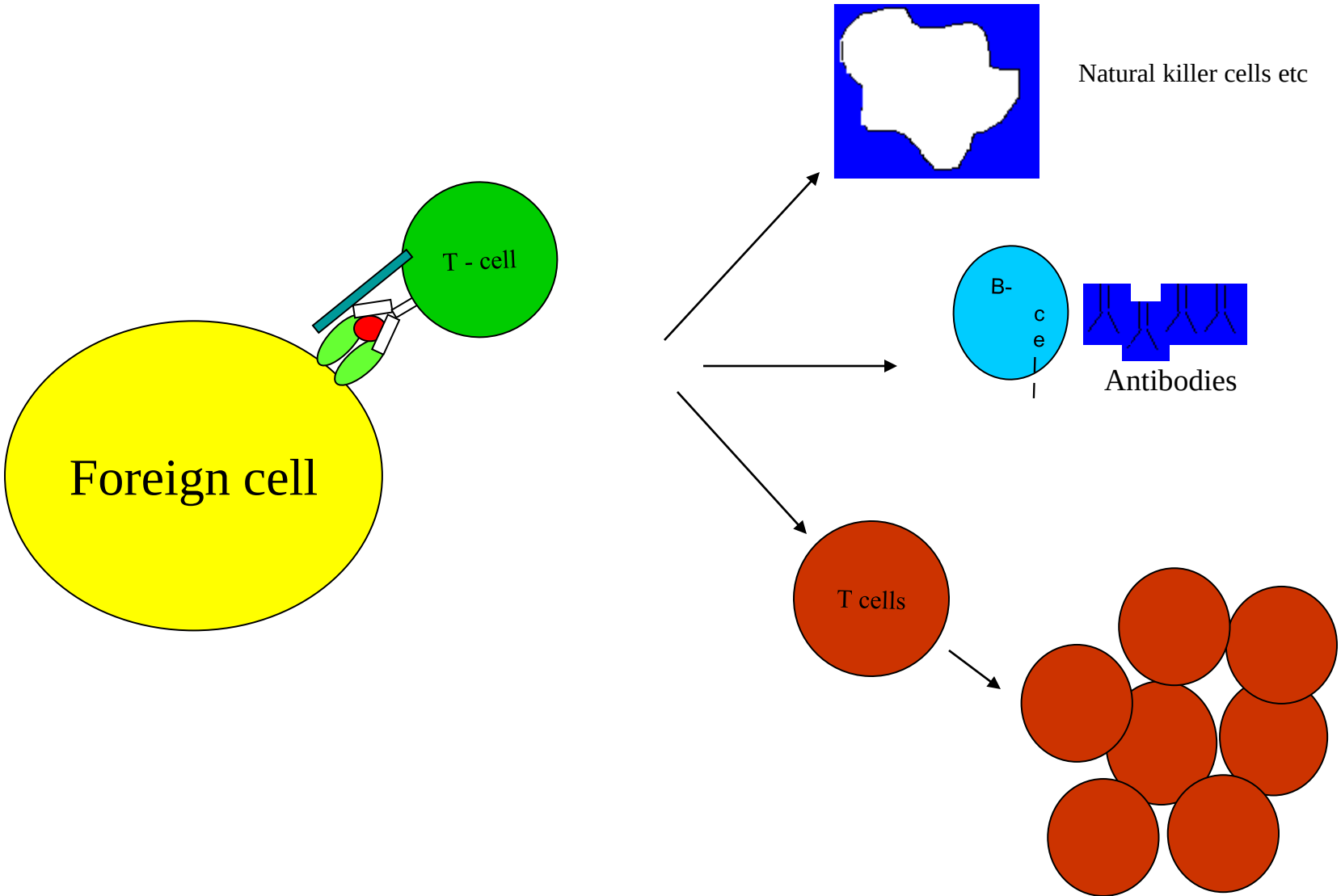
- Chemokines – proteins essential for leucocyte migration

  KO mice data Mechanisms of rejection and acceptance Cornell DL, Smith RN, Colvin RB Annual rev of Pathol 2008; 3: 189-220

- Cytokines – proteins essential for leucocyte function

  KO mice data Mechanisms of rejection and acceptance Cornell DL, Smith RN, Colvin RB Annual rev of Pathol 2008; 3: 189-220

# Rejection mechanisms – evicting the asylum seeker



# Cytolytic pathways – the fire arms

- Monocyte/macrophages (+/- neutrophils): often non-antigen specific cytotoxic mediators (reactive oxygen/nitrogen species)

- T-lymphocytes: antigen specific, localised responses (Fas/FasL, perforin, granzyme)

  Barry M, Bleackley RC Cytotoxic T lymphocytes. All roads lead to death Nat Rev Immunol 2002; 2: 401-409

- B lymphocytes: APC activity + antibody production

# Antibodies in transplant rejection

- Animal models difficult, some lessons from human ABO incompatible transplants
- Newer solid phase HLA antibody detection techniques (Luminex) have resulted in publication ‘trending’
- Consensus on pathology of antibody mediated graft injury
- Complement fixation probably important to effect graft damage

Loupy A et al. Complement binding anti-HLA antibodies and kidney allograft survival N Eng J Med 2013; 92:54-60

# Timing of Rejection

- Hyperacute – “On the table”. Minutes to hours after transplantation
- Accelerated rejection - < 1 week post op
- Acute rejection - > 1 week post op
- Chronic rejection

# Acute rejection

- Very common!
- Most likely after the first week and upto 3 months.
- Can happen any time if immunosuppression actively or passively omitted

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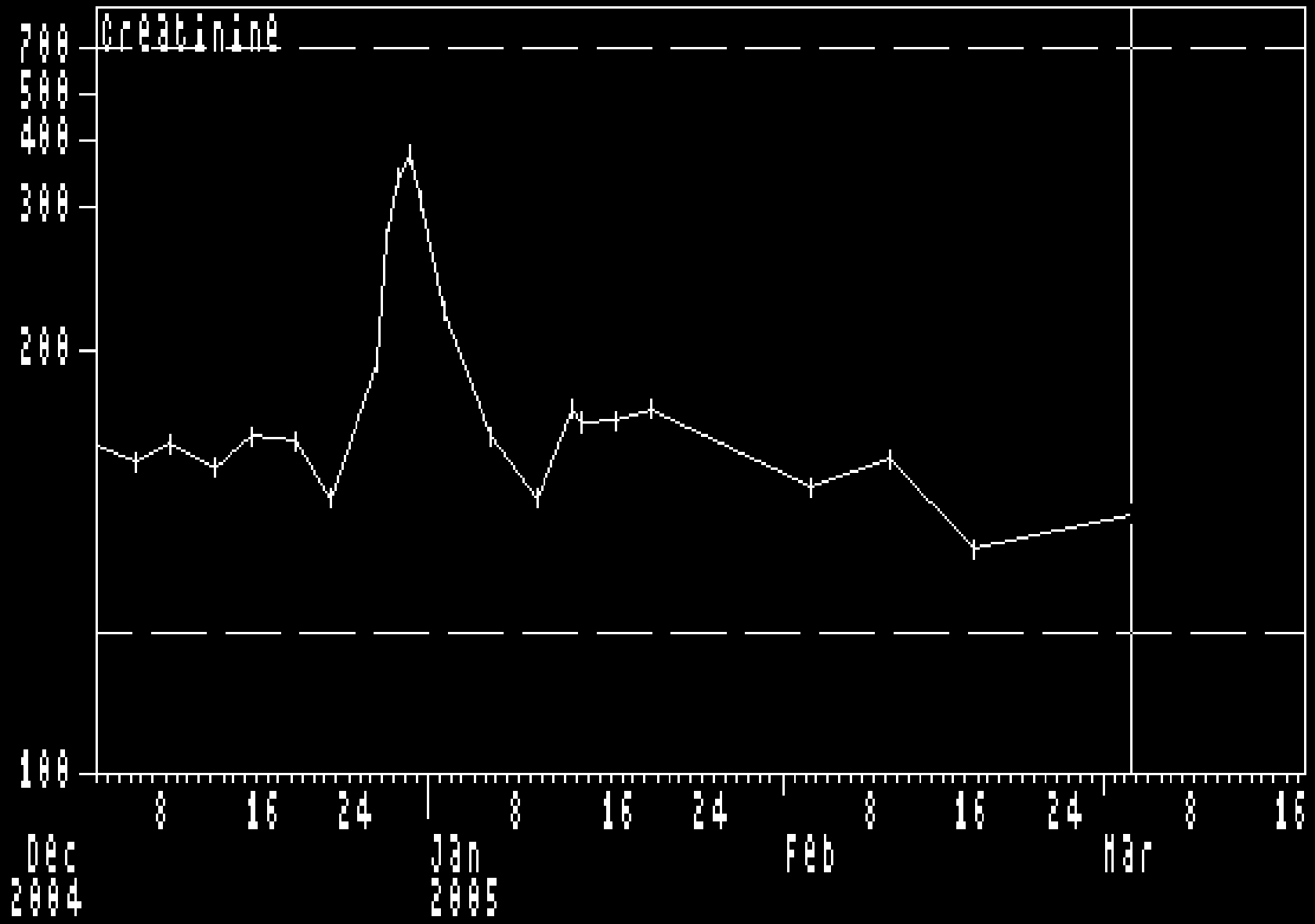

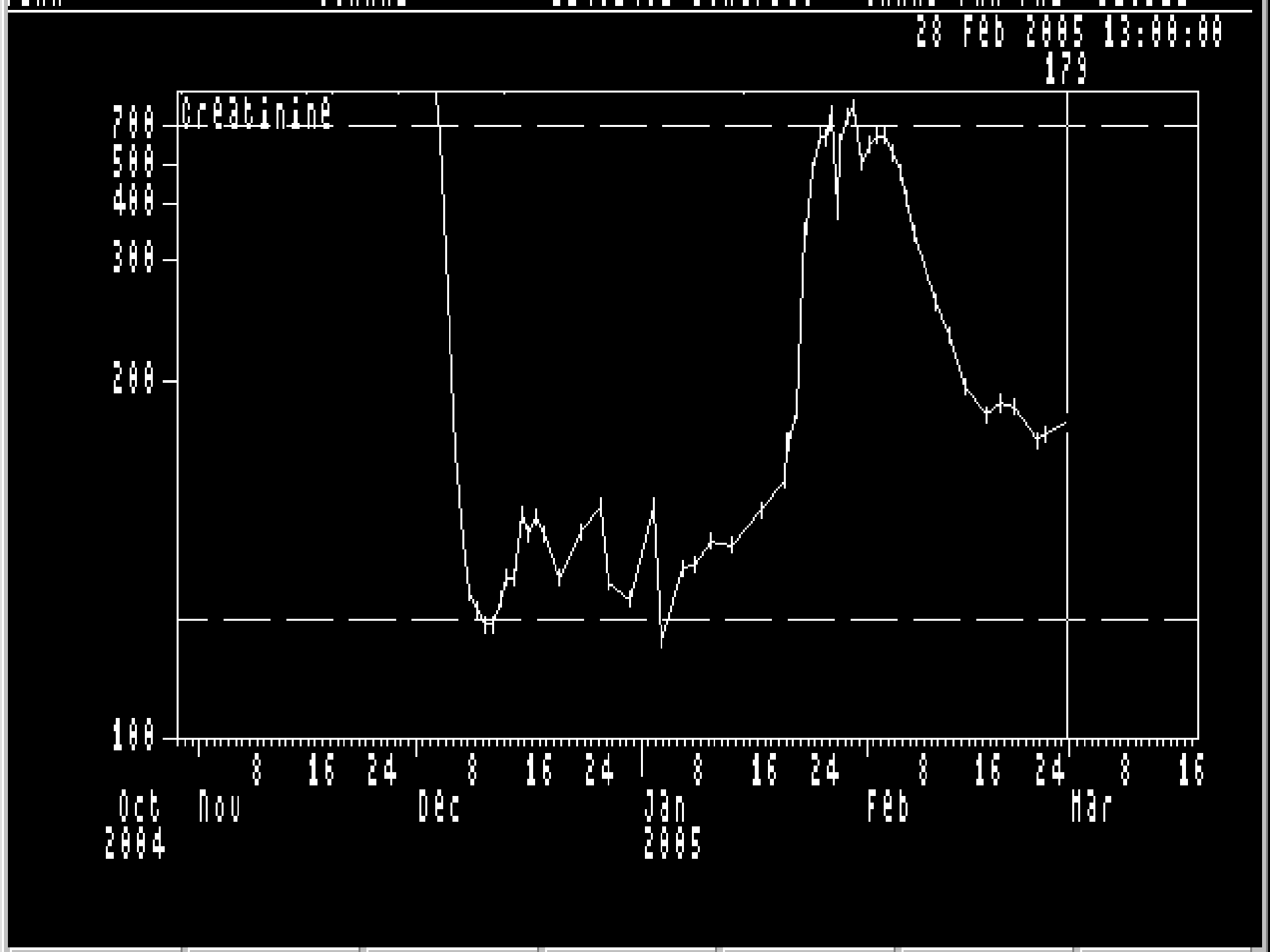
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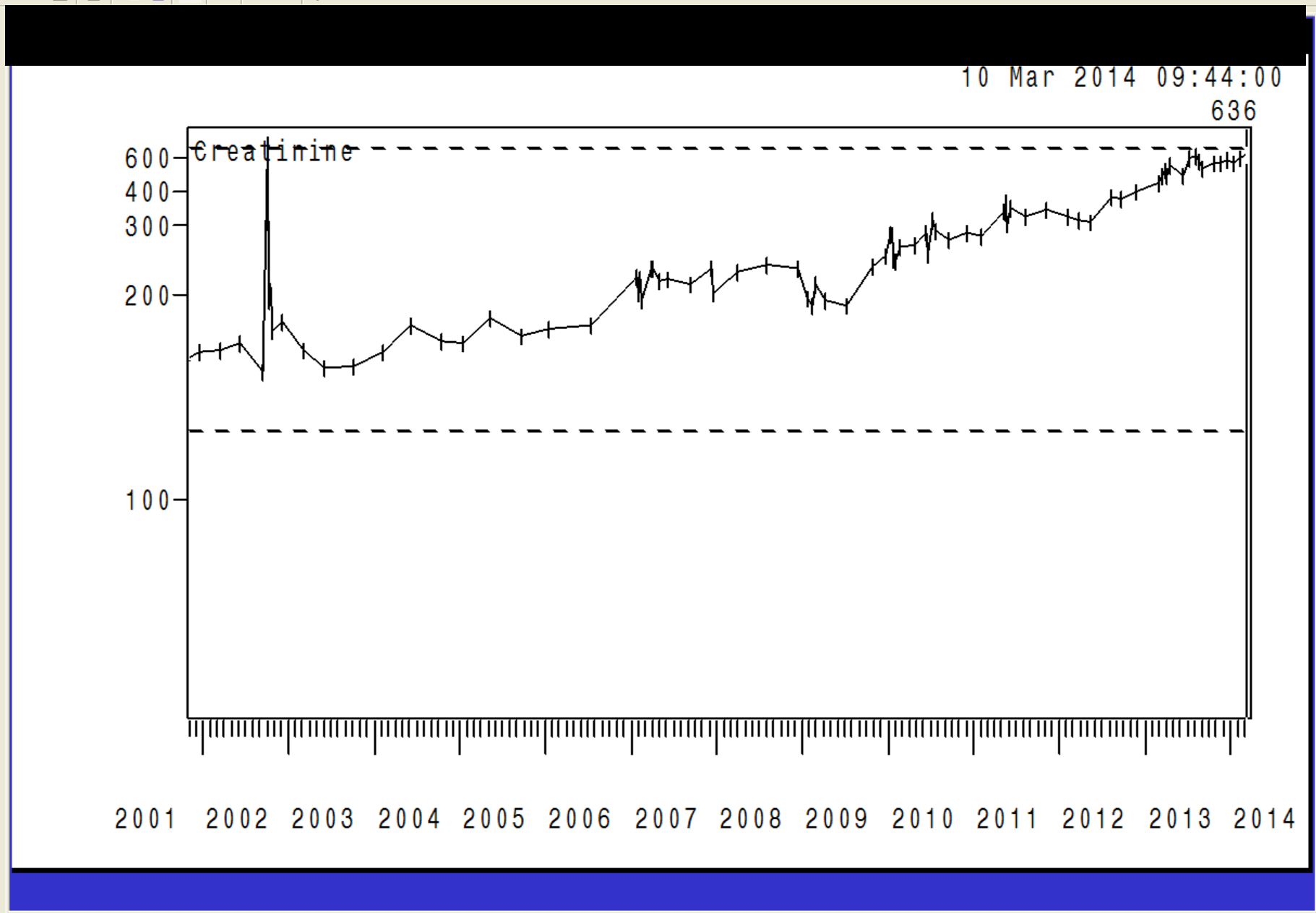
# Chronic rejection

- Good animal model
- Combination of cellular and antibody mediated injury
- Histology characterised by fibrosis of various cell types in the graft
- In clinical practice difficult to distinguish between immunological and non-immunological chronic injury



# Current developments

- Imlifidase

  *IgG Endopeptidase in Highly Sensitized Patients Undergoing Transplantation SC Jordan et al NEJM Aug 2017 377: 442-453*

- 3D bio-printing of stem cell derived ‘kidney cells’

  *3D Bio-printing of tissues and organs. SV Murphy et al. Nature Biotechnology 32(8) 773-85, 2014*

- Xeno-transplantation – CRISPR technology and ‘humanised pigs’