The evolving landscape of combined immunodeficiency

Alison Jones
Great Ormond Street Hospital
London

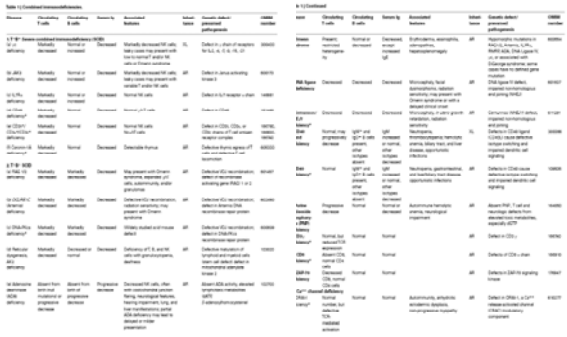
History

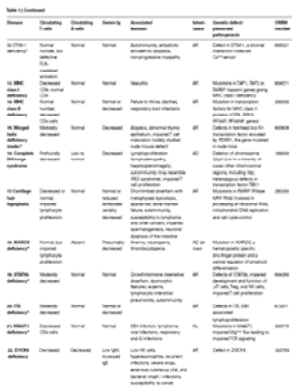
- 1937 Wiskott Aldrich syndrome described
- 1950 'Swiss-type' agammaglobulinemia
  - Candidiasis
  - Lymphopenia
  - Rapidly fatal
- 1963 X-linked form identified
- 1972 ADA deficiency recognised
- 1975 first WHO meeting on primary immunodeficiency
  - renamed Severe Combined Immunodeficiency: 'SCID'

Molecular basis of PID

- Early 1980's ADA gene identified
- Early 1990's genes for defined syndromes identified
  - X-SCID, XLA, XHM, WAS, XLP
- More than 50% SCID cases still genetically undefined
- Increasing recognition of 'undefined combined' immunodeficiencies
- Since then >150 PID genes identified

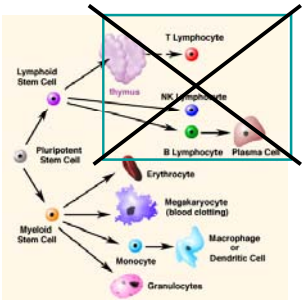
Current known causes of CID (IUIS)





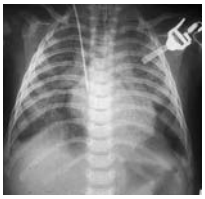
What is Combined immunodeficiency?

- 'Combined'- both T and B cell defects
  - Defective cell-mediated and humoral immunity
  - Susceptible to all types of infection, especially opportunistic & viral infections
  - 'Dyregulatory' complications in patients with residual immune function
  - T/B/NK phenotypes vary



Severe combined immunodeficiency (SCID)

- 'Bubble' babies
- Profound deficiency of cell-mediated and humoral immunity
- Rare – approximately 1:50,000 live births
- Unlikely to survive more than 1-2 years without corrective therapy
- Outlook good with early recognition and treatment



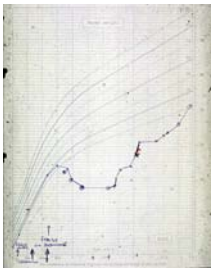
Pneumocystis Jirovecii pneumonia
Absent thymus

SCID

- A clinical syndrome
- Many molecular defects defined
  - Clinical presentations similar
  - Precise genetic diagnosis now possible in most cases
  - Family history NOT always positive
  - Significant numbers remain molecularly undefined
  - Consanguinity increases the likelihood of autosomal recessive disorder
- Immunological phenotype can predict likely molecular defect

SCID – presentation

- Infection
- Failure to thrive
- Skin rashes
- Diarrhoea

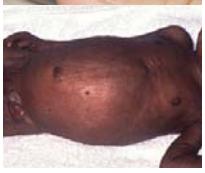


- **Low absolute lymphocyte count** – often goes un-noticed
- Absent thymic shadow
- Family history of early/unexplained infant deaths
- Usually within first six months
  May be later – depends on severity of defect
  - 'Leaky' forms now recognised – may present up to several years of age
  - Immunological phenotype may be incomplete

Infections in SCID

- Common infections cause severe, recurrent or persistent illness
  - Respiratory viruses
    - RSV
    - Parainfluenza
    - Influenza
    - Adenovirus
    - Cytomegalovirus
  - Gastrointestinal – *eg* Rotavirus, Norovirus
  - Skin – Candida
- 'Opportunistic' infections

  - Pneumocystis jirovecii
  - Fungal – esp candida and aspergillus
  - Mycobacterial – BCG



Early diagnosis can be life saving

Severe Combined Immunodeficiency UK 1979-2008

- Index Cases
  - **30%** died before BMT
  - **30%** died during BMT
- **40% Survival**
- Siblings
  - **2%** died before BMT
  - **6%** died during BMT
- **92% Survival**

Brown et al. Blood 2011

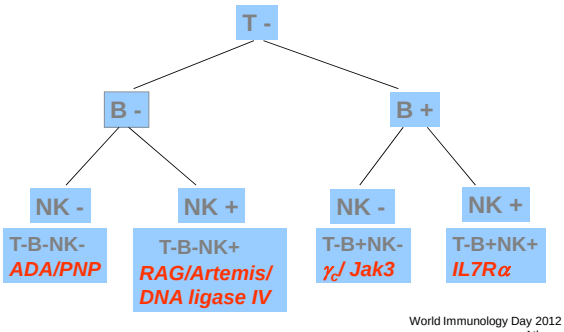
Prenatal/Pre-implantation diagnosis available when molecular diagnosis known

Diagnosis of SCID

• Lymphopenia	almost always
• T cells:	low/absent
• B cells:	low or normal
• Natural killer (NK)cells	low or normal
• T cell proliferation in response to mitogens:	absent/poor
• Immunoglobulin levels:	low (usually)
• Specific antibody production:	absent

Immunological phenotype may predict molecular defect

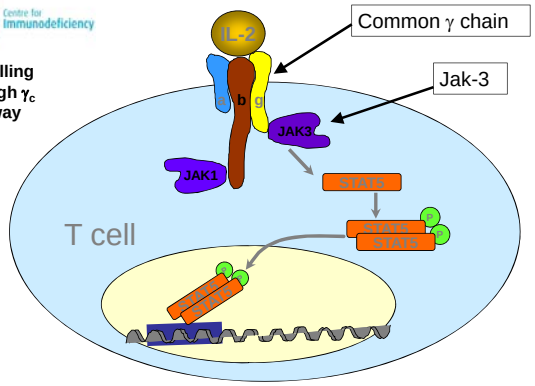
Most frequent molecular defects in SCID



X-linked SCID
'Common γ chain' deficiency

- Most frequent form of SCID: approx 30%
- Positive family history in only 30%
- T-B+NK- (sometimes NK+)
- Defect in 'common γ chain'
  - T cell surface molecule
  - essential component of multiple cytokine receptors (IL-2,4,7,9,15)
  - Absent/defective γ_c affects T and NK cell development

Signalling through γ_c pathway



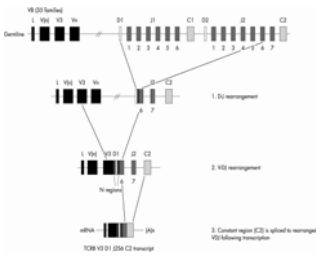
Immunololgical phenotype identical in X-SCID and Jak3 deficiency

ADA deficiency (T- B- NK-)

- Defect in adenosine deaminase
  - Enzyme involved in purine salvage pathway
  - Accumulation of metabolites – toxic to developing lymphocytes
  - 'House-keeping' enzyme - affects many systems
    - Central nervous system
    - Skeletal system
    - Kidneys
- Long term neuro-developmental problems often significant even if immune defect is cured
- Diagnosis:
  - RBC ADA low
  - High urinary/blood deoxyadenosine levels
- Accounts for approximately 30% SCID

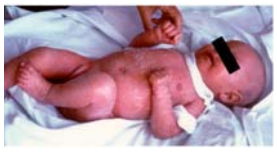
Recombination defects (T- B- NK+)

- Complex mechanism for generating diversity of T and B cell receptors by VDJ recombination
- Enzyme complex includes RAG1&2, Ku 70, Ku80, XXCR4, DNA-PK, Artemis, DNA ligase IV
  - All potential causes of SCID
  - RAG 1 and 2 defects most frequent
- Can cause
  - Complete lack of T and B cell development: T-B-NK+ SCID
  - development of only a few T and B cells – Omenn's syndrome
  - Attenuated variants
  - Phenotype can vary even within a family



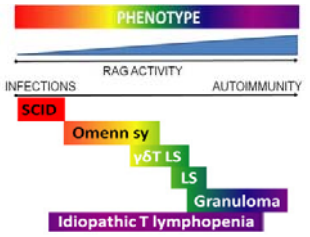
Omenn's syndrome

- Partial defects of RAG1/RAG2/Artemis
- Small numbers of T cells develop or 'escape'
  - Oligoclonal
  - Highly activated and inflammatory
- Clinical syndrome
  - Erythrodermic skin rash
  - Hepatosplenomegaly
  - Lymphadenopathy
- Immunology
  - T cell numbers may be normal – but non- functional
  - B cells usually low
  - Immunoglobulins variable
  - High IgE
  - Eosinophilia
  - Oligoclonal T cells
- Can be clinically and immunologically difficult to distinguish from engraftment of maternal T cells



Attenuated recombination defects – hypomorphic mutations

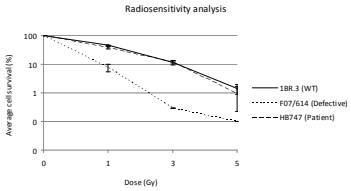
- Later presentation
  - Autoimmunity
    - Haemolysis
    - Neutropenia
    - Thrombocytopenia
  - Enteropathy
  - Granulomas
  - Lymphoma
  - Progressive immune deficiency
- Outlook poor without corrective therapy



Genotype-phenotype correlation in RAG defects

Screening for DNA repair defects

- Abnormal DNA sensitivity to irradiation
- Performed on skin fibroblast cell lines
- Defects in
  - Ku70 and Ku80 (Ku) heterodimer
  - DNA-PKcs (catalytic subunit of the DNA-dependent protein kinase
  - XrCC4
  - DNA ligase IV
  - Artemis

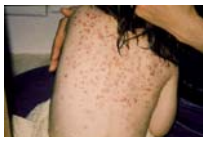


Clinical case
Progressive immune deficiency

Unrelated Caucasian parents

- **Proband** born 1994
- Well first year of life
- Autoimmune haemolytic anaemia, neutropenia, thrombocytopenia
- Progressive fall in Igs, lymphopenia and loss of T cell function
- Massive splenomegaly
- Poor growth and quality of life
- BMT – unsuccessful – died
- Molecular defect unknown

- **Sibling** born Jan 2006
- Cord blood screening
- Low B cells, very low Igs
- Lymphopenia (0.7); normal T %
- Well for 5y on Ig replacement
- Acute severe haemolytic anemia
- MSD BMT Jan 2012 – currently well



Normal DNA irradiation sensitivity
Compound heterozygous mutation in Artemis gene (deletion and point mutation)

Attenuated Artemis defects

- 13 patients (10 kindreds – 4 consanguinous)
- Ages: infancy – 27y
- Commonest manifestation - infection
- Autoimmune cytopenias (5)
- Lymphoma (3) – all EBV associated
- Inflammatory bowel disease (1)
- Outcomes
  - 3 died from disease-related complications
  - 3 died from transplant-related complications
  - 6 successfully transplanted

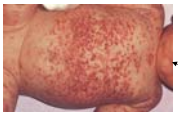
CID in non-paediatric patients?

- Case reports of ADA deficiency diagnosed in adulthood
- Common variable immunodeficiency
  - Subset of patients have severe dysregulatory complications
    - GI disease
    - Granulmoatous disease
    - Lymphoproliferative disease
    - Autoimmunity
  - Some severe enough to consider stem cell transplantation
- Some may have highly attenuated forms of 'SCID' defects

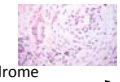
Late onset combined immunodeficiency – 'LOCID'

- France DEFI study
- 28/313 (8.9%) CVID patients
  - Opportunistic infection
  - CD4+ T cells <200 x 10^9/L
- LOCID group
  - 29% consanguinous (vs 8%)
  - Higher incidence of
    - Splenomegaly (64% vs 31%)
    - Granulomatous disease (43% vs 10%)
    - Gastro-intestinal disease (75% vs 42%)
    - Lymphoma (29% vs 4%)
  - More infections
- Molecular defects not yet defined

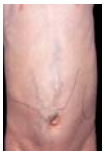
Other well defined CID syndromes



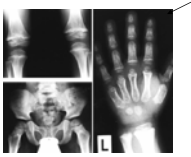
Wiskott Aldrich syndrome



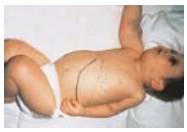
X-linked hyper-IgM syndrome



Cartilage hair hypoplasia



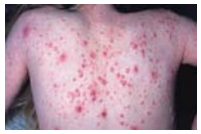
X-linked lymphoproliferative disease

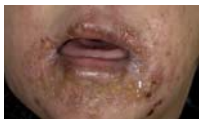


DOCK-8 deficiency

Dedicator of Cytokinesis 8

- Described 2009 (Zhang et al)
- Autosomal recessive hyper-IgE syndrome
- Severe atypical eczema, atopy and allergy
- Staphylococcal skin and lung infections
- Skin viral infections
  - Viral warts
  - Molluscum contagiosum
  - Herpes simplex
- Recurrent pneumonias
- Progressive T and B cell immunodeficiency
- Poor outlook





Undiagnosed CIDs

- Still significant numbers of SCID and CID syndromes without known cause
- Importance of defining defects
  - Genetic counselling, prenatal/preimplantation diagnosis
  - Improve understanding of immune system
  - Possibility for new therapies
  - Gene therapy
- Advances in genetic diagnosis
  - Exome sequencing
  - 'All in one' sequencing
  - Issue of bio-informatics

Management of CID

- Supportive
- Curative

Supportive treatment

SCID

- Protection from infection
  - Protective isolation
  - Anti-PCP/anti-fungal/anti-viral prophylaxis
  - Immunoglobulin replacement
- Aggressive treatment of infection
- Nutrition – frequently parenteral
- Enzyme replacement (in ADA deficiency)

Other CIDs

- Depends on severity of T cell defect
- Immunoglobulin replacement for all patients
- Almost certainly PCP prophylaxis
- Management of complications
  - Inflammatory complications may require immunosuppression
  - Autoimmunity: steroids/Rituximab
  - Other monoclonals

Corrective therapy

- Stem cell transplantation
- Gene therapy

History of BMT

- 1968 First bone marrow transplants - HLA identical sibling transplants
  - SCID
  - Wiskott Aldrich syndrome
  - Successful BMT only using identical sibling donors until 1980's
- 1978 Development of T cell depletion techniques
- 1982 Haplo-identical BMT from parents
- 1980-early 1990's
  - BMT for SCID, Omenn's syndrome, (Wiskott-Aldrich syndrome)
  - Unconditioned matched sibling donor BMT for SCID successful if early diagnosis
  - Conditioned haplo-identical BMT: survival <40%
  - Non-SCID outcomes poor
- 1990's
  - Unrelated donor panels and umbilical cord blood banks
  - Unrelated donor BMT
  - Improvements in tissue-typing techniques
  - Progress in BMT technology and anti-viral drugs
  - Widening range of indications – European and North American collaborations and databases – recognition of poor outlook in many disorders
- Late 1990's- 2000's Gene therapy

Types of transplant

- Matched sibling
- Matched family
- Unrelated
- Haploidentical

Possibility of pre-implantation diagnosis and embryo selection for molecularly defined disorders

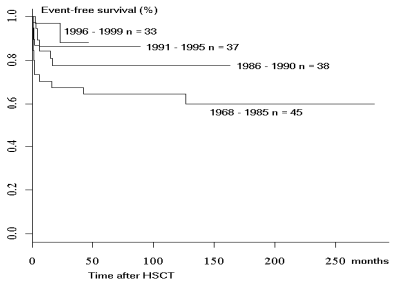
- Bone marrow
- Cord blood
- Peripheral blood stem cells

SCT – what is involved?

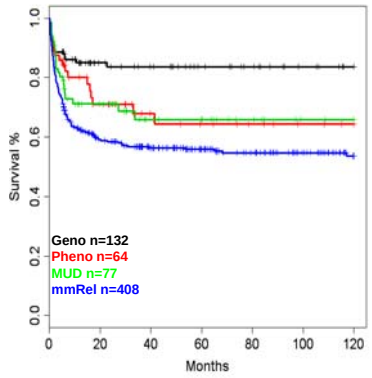
- Immunosuppressive/myeloablative chemotherapy in most
- Prolonged period of pancytopenia – highly susceptible to infection and bleeding
- Infusion of cells
- Prolonged period of isolation in hospital
- Risks
  - Infection
  - Bleeding
  - GvHD
  - Rejection
  - Veno-occlusive disease
- Immune reconstitution can take several years

Cumulative survival after BMT for SCID

(by year of transplant)



Survival in SCID patients after HSCT (by donor-recipient compatibility)



10 year Survival rate

Geno : 84%

MUD : 66%

Pheno : 64%

mmRel : 54%

SCT – possible outcomes

Successful

- Full immune reconstitution
- No GvHD
- Normal growth and development

Partial success

- Partial immune reconstitution – long term Ig in some cases
- Correction of underlying T cell defect
- Prevention of dysregulatory complications

Unsuccessful

- Death
  - Infection
  - Toxicity
  - Veno-occlusive disease
  - GvHD
- Chronic GvHD
- Rejection – may even have worse immune function than pre-BMT

Post-BMT
Undefined CID

- Severe varicella pneumonitis in infancy
  - Abnormal T cell proliferation
  - Immunology otherwise normal
- Maintained on Ig replacement and Cotrimoxazole prophylaxis
- No major problems until teenager
- EBV Lymphoproliferative disease
  - Severe hepatitis
  - Haemophagocytic lymphohistiocytosis
- Unrelated donor BMT
- Defect still unknown

Gene Therapy

- PIDs are ideal candidates for gene therapy
  - Ability to harvest bone marrow
  - Manipulate in laboratory
  - Return to patient
- Clinical trials currently for
  - X-linked SCID
  - ADA deficiency
  - X-linked chronic granulomatous disease
  - Wiskott Aldrich syndrome

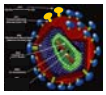
Genes insertion into cells

Disabled viruses

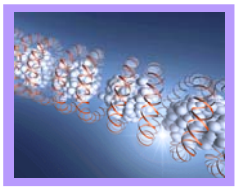
Adenovirus

Adeno-associated virus

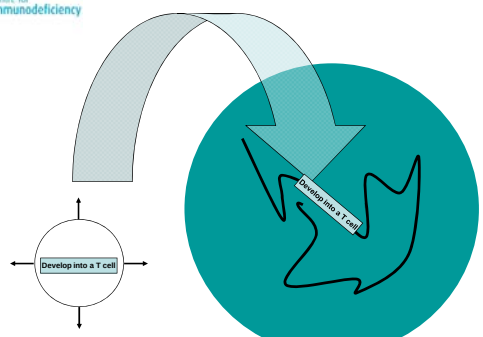
Retrovirus



Non-viral vectors



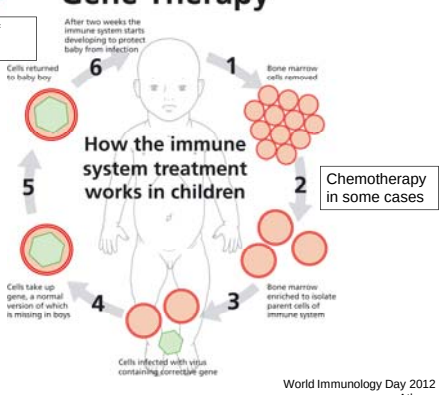
Normal copy of defective gene is integrated into harmless viral or non-viral vector



The harmless virus transports the new gene into the bone marrow cell, where it is integrated into the host genome

Gene Therapy

Minimal risk of GvHD

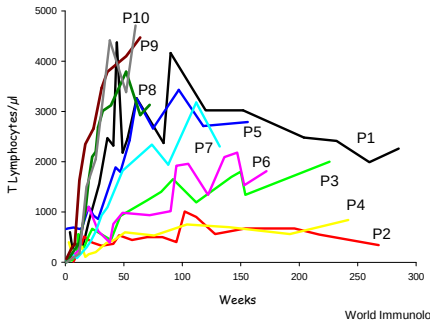


Chemotherapy in some cases

Long term risk of possible oncogenesis

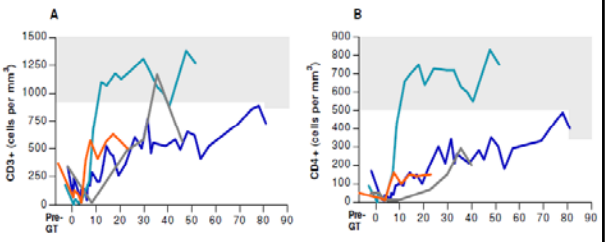
Each case considered individually by Department of Health Advisory Committee

X-SCID: Lymphocyte recovery (CD3) post gene therapy



T cell recovery post ADA gene therapy

(CD3 and CD4)



Summary of gene therapy for ADA-Deficient SCID

Retroviral Vectors, Myeloreductive Conditioning

Milan/London/CHLA-NHGRI, NIH-UCLA

Center	No. Patients	F/U (yrs)[1]	Off Enzyme	Survival	DFS[2]
Milan	17	0.9 – 10.5	14/17	100%	82.4%
London	8	0.5 – 7.5	4/8	100%	50%
CHLA-NHGRI	6	2– 5	3/6	100%	50%
UCLA-NHGRI	5	0.1-2	4/5	100%	80%
TOTAL	**36**	**0.1 – 8.0**	**25/36**	**100%**	**69.4%**

[1] As of April 2011

[2] DFS: Alive without BMT or PEG-ADA re-start

Data: Courtesy HR Gaspar (London) and Alessandro Aiuti (Milan)

Gene therapy

- Promise
  - Allows specific gene correction
  - Host cells used so avoids Graft versus Host Disease
  - In some diseases gene correction in only a percentage of cells may be enough

but

- Problems
  - Regulation of gene expression to physiological levels
  - Random gene insertion sites – may occur in unwanted areas of the genome
  - Possible oncogenesis

Summary

- Huge increase in understanding of combined immunodeficiencies in past 20 years
- Better awareness and recognition
- Progress in transplantation
- Gene therapy
- Prevention by prenatal diagnosis
- Many more disorders will be identified by sophisticated screening techniques

Thank you