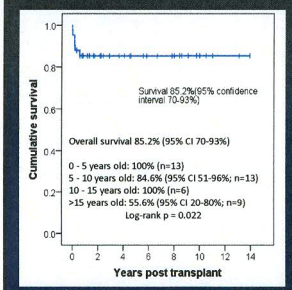
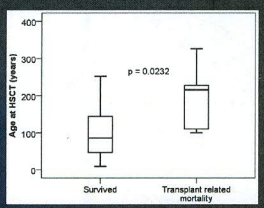
Transplant survival



Overall survival 85.2% (95% CI 70-93%)

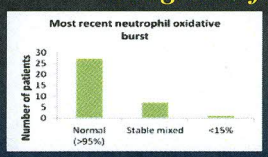
0 - 5 years old: 100% (n=13)
5 - 10 years old: 84.6% (95% CI 51-96%; n=13)
10 - 15 years old: 100% (n=6)
>15 years old: 55.6% (95% CI 20-80%; n=9)
Log-rank p = 0.022

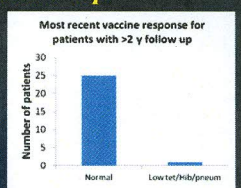


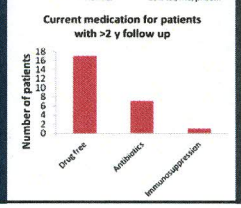
Pre-existing complications and TRM:

- Number of previous fungal infections (p=0.0136)
- Previous brain abscess (p=0.0183)
- Previous bone infection (p=0.0019)

Long term follow-up







- 1 severe chronic gut GvHD unresolved 22 months post HSCT
- 1 severe chronic gut GvHD resolved 5 years post HSCT
- 1 colitis (unknown aetiology) 14 years post HSCT
- 2 chronic lung disease
- 0.017 infections/patient-year beyond 2 years post HSCT (minor skin)
- 1 decreasing neutrophil oxidative burst undergoing further HSCT

Quality of Life Results

	UK norms	No HSCT N=26	Post HSCT N=21	P value: no HSCT vs post HSCT
Parent report	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
Total	84.6 (11.2)	65.31 (20.43)	81.93 (18.74)	0.006
Psychosocial	82.2 (12.7)	66.74 (19.25)	81.17 (16.80)	0.010
Physical	89.1 (12.3)	60.35 (25.74)	85.27 (25.27)	0.002
Emotional	78.3 (15.5)	65.53 (20.08)	78.81 (18.57)	0.024
Social	86.8 (15.4)	71.88 (21.48)	88.33 (17.42)	0.007
School	81.5 (16.1)	55.88 (21.92)	79.13 (22.99)	0.001
Child report		**N=18**	**N=17**	
Total	83.9 (11.8)	75.39 (12.99)	81.79 (20.22)	0.276
Psychosocial	81.8 (13.2)	74.61 (13.27)	80.28 (19.10)	0.318
Physical	88.5 (11.6)	69.68 (17.69)	89.93 (17.20)	0.002
Emotional	78.5 (17.9)	72.64 (14.37)	85.83 (16.20)	0.016
Social	87.7 (16.5)	73.53 (17.12)	89.71 (19.16)	0.014
School	78.9 (15.9)	64.12 (15.64)	79.12 (18.73)	0.016

Features of HIES

Eczema	100%
Characteristic facies (>16y)	100%
Skin boils	87%
Pneumonias	87%
Lung cysts	77%
Mucocutaneous candidiasis	83%
Scoliosis (>16y)	76%
Delayed dental decidiation	72%
Brain T2 hyperintensities	70%
Pathologic fractures	57%
Chiari I malformation	18%

Antibody deficiency & PCP?

- CD40L deficiency
- ICF
- STAT 1
- Hyper IgE
- NEMO

EDA-ID (Anhydrotic ectodermal dysplasia & immunodeficiency)
NEMO – NF-kB essential modulator (XR)

Anhydrotic ectodermal dysplasia with bronchiectasis, but no ID
EDA (XR)

Immunodeficiency in childhood
- bacterial clues

	Antibody deficiency
Haemophilus	Specific antibody failure
Meningococcus	Complement deficiency
Pneumococcus	Asplenia
Staphylococcus	Chronic granulomatous disease
	Hyper IgE

10 warning signs of primary immunodeficiency (I)

1) 8 or more new ear infections within 1 year
2) 2 or more serious sinus infections within 1 year
3) 2 or more months on antibiotics with little effect
4) 2 or more episodes of pneumonia within 1 year
5) Failure of an infant to gain weight or grow normally

(NIAID NIH)

10 warning signs of primary immunodeficiency (II)

6) Recurrent deep skin or organ abscesses
7) Persistent superficial candidiasis after age 1 year
8) Need for intravenous antibiotics to clear infections
9) 2 or more deep seated infections e.g. sepsis, meningitis
10) A family history of primary immune deficiency

NIAID NIH

10 warning signs of PID Which really matter?

- Failure to thrive
- Need for IV antibiotics
- Family history

Subbarayan et al 2011

Have you remembered?

- When to look for PID after Pneumococcal & Meningococcal disease?
- What are underlying causes of PCP?
- Which test to ask for in suspected complement deficiency?

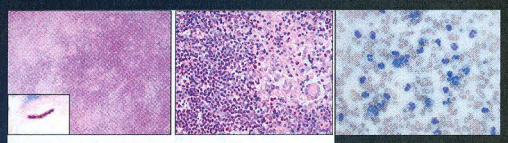
Acknowledgements

- Theresa Cole
- Roy Ward
- Gavin Spickett
- Mario Abinun

Presentation at 3 months of age with disseminated BCG & myeloproliferation

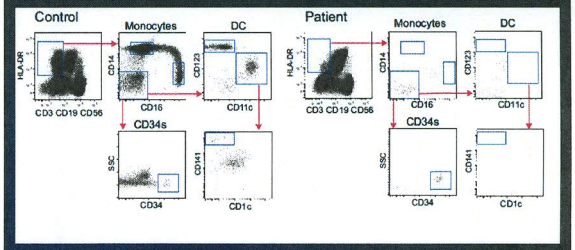
- Cachexia
- Oral candidiasis
- Discharging BCG scar, axillary lymphadenitis
- Hepatosplenomegaly
- Pleural effusions & ascites

Parameter (cells x 10^9/L)	Value	Normal
Haemoglobin (g/dL)	4.6	10.5 - 13.5
Platelets	66	150 - 450
WBC	125.5	6.0 - 17.5
Neutrophils	108	1.0 - 8.5
Lymphocytes	13.8	4.0 - 13.5
Monocytes	0.0	0.7 - 1.5
Eosinophils	3.8	0.3 - 0.8



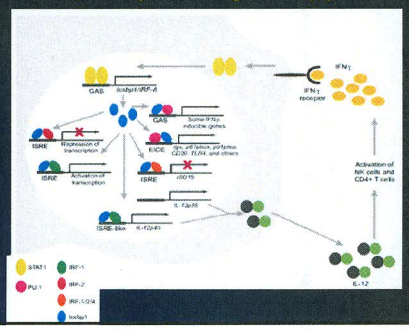
Hambleton et al (2011) New Engl J Med

Profound monocytopenia & lack of blood DC



Hambleton et al (2011) New Engl J Med

ICSBP: Interferon consensus sequence binding protein 1 = IRF8, interferon regulatory factor 8



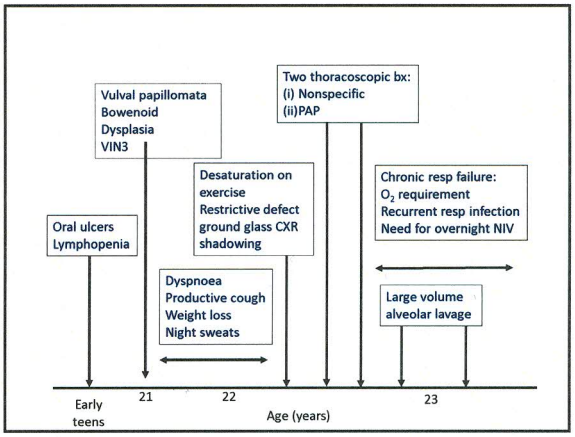
Fortin et al 2007, Annu Rev Genomics Hum Genet

How well did I look at the blood film?

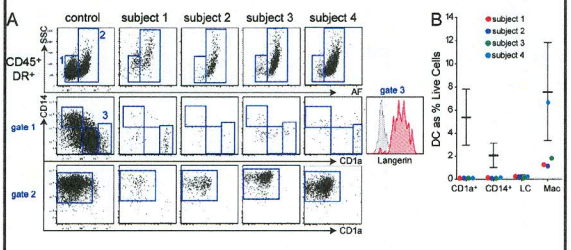
- 13 year old boy
- 3 months fever wt loss night sweats
- BCG 5 months previously
- BCG abscess liver ↑ spleen ↑
- M bovis (BCG) cultured multiple sites

How well did I look at the blood film?

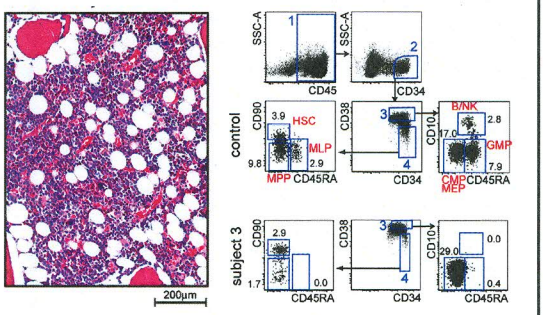
- Better on Anti Mycobacterial Rx
- No monocytes on the blood film
- Leg abscess 3 years earlier
- No monocytes on that blood film either!



Loss of dermal DC but relative preservation of dermal macrophages



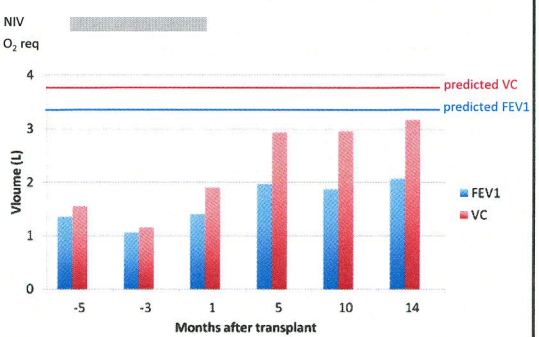
Depletion of MLP, GMP & B/NK precursor compartments in normocellular bone marrow



9/12 matched URD PBSCT

- 2/52 pre-Tx work-up: IV antibiotics, physio, nutrition
- Conditioning:
  - Fludarabine 150 mg/m^2
  - Busulfan 6.4 mg/kg
  - Alemtuzumab 60 mg
- GvHD prophylaxis: cyclosporin, MMF
- Antimicrobial prophylaxis: meropenem, caspofungin
- Engraftment D+12 (neuts), D+16 (plt), D+24 (mono)
- Home D+28 in 2L/min O2
- By D+47, chest noticeably better

Improvement in respiratory function



Outcome of HSCT in this patient

Indication	Outcome
PAP with worsening respiratory failure	Much improved
Recurrent infection	Resolved
Vulval neoplasia	Resolved
Risk of myelodysplasia & strong FH of premature death from malignancy	100% donor myeloid compartment

Complications:

No GVHD or peri-transplant infections

1 episode of autoimmune haemolytic anaemia requiring steroids & Rituximab

blood

2011 118: 2653-2655
Prepublished online June 13, 2011;
doi:10.1182/blood-2011-05-356352

Mutations in *GATA2* are associated with the autosomal dominant and sporadic monocytopenia and mycobacterial infection (MonoMAC) syndrome

Amy P. Hsu, Elizabeth P. Sampaio, Javed Khan, Katherine R. Calvo, Jacob E. Lemieux, Smita Y. Patel, David M. Frucht, Donald C. Vinh, Roger D. Auth, Alexandra F. Freeman, Kenneth N. Olivier, Gulbu Uzel, Christa S. Zerbe, Christine Spalding, Stefania Pittaluga, Mark Raffeld, Douglas B. Kuhns, Li Ding, Michelle L. Paulson, Beatriz E. Marciano, Juan C. Gea-Banacloche, Jordan S. Orange, Jennifer Cuellar-Rodriguez, Dennis D. Hickstein and Steven M. Holland

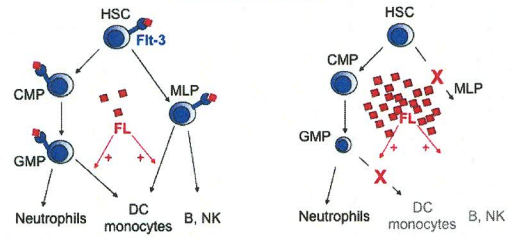
blood

2011 118: 2656-2658
Prepublished online July 15, 2011;
doi:10.1182/blood-2011-06-360313

Exome sequencing identifies GATA-2 mutation as the cause of dendritic cell, monocyte, B and NK lymphoid deficiency

Rachel Emma Dickinson, Helen Griffin, Venetia Bigley, Louise N. Reynard, Rafiqul Hussain, Muzlifah Haniffa, Jeremy H. Lakey, Thahira Rahman, Xiao-Nong Wang, Naomi McGovern, Sarah Pagan, Sharon Cookson, David McDonald, Ignatius Chua, Jonathan Wallis, Andrew Cant, Michael Wright, Bernard Keavney, Patrick F. Chinnery, John Loughlin, Sophie Hambleton, Mauro Santibanez-Koref and Matthew Collin

Pathogenesis – DCML, immunodeficiency & MDS/AML



NORMAL **GATA2 HAPLOINSUFFICIENCY**

Bigley & Collin

3 sisters 7, 6, & 4 years

- Eczema
- Recurrent pneumonia
- Cryptosporidium enteritis
- Severe molluscum contagiosum
- Persistent EBV → lymphoma

Immune studies

CD3+	815/uL	[700 – 4200]
CD8+	512	[300 – 1800]
CD4+	200	[300 – 2000]
NK	192	[92 – 200]

Naïve T cells 0

IgG	18.3	[3.6 – 15.2]
IgA	2.20	[0.40 – 2.18]
IgM	0.60	[0.43 – 1.90]

IgG2 ↓
Pneumococcal response

STK4 deficiency – clinical features

- Bacterial respiratory tract infections
- Pneumonia Bronchiectasis
- Molluscum, HSV, HPV
- Cryptosporidium cholangitis
- EBV lymphoproliferation

Abdollahpour 2012
Nehme 2012

Idiopathic CD4 deficiency

- Not always idiopathic?

Serine threonine Kinase 4 STK 4 – (MST-1)

- Pro-apoptotic & antiapoptotic
- T↓ B↓ as apoptosis↑

Abdollahpour 2012
Nehme 2012

STK4 deficiency – immunophenotype

- Neutrophils ↑ & ↓
- CD4+ ↓↓
- ○ NaiveT
- ○ Class switched memory B
- Igs ↑

Abdollahpour 2012
Nehme 2012

STK4 deficiency treatment

- Septrin
- IVIG
- HSCT

Abdollahpour 2012
Nehme 2012

blood 2012 119: 3450-3457
Prepublished online January 31, 2012;
doi:10.1182/blood-2011-09-378158

The phenotype of human STK4 deficiency

Hengameh Abdollahpour, Giridharan Appaswamy, Daniel Kotlarz, Jana Diestelhorst, Rita Beier, Alejandro A. Schäffer, E. Michael Gertz, Axel Schambach, Hans H. Kreipe, Dietmar Pfeifer, Karin R. Engelhardt, Nima Rezaei, Bodo Grimbacher, Sabine Lohrmann, Roya Sherkat and Christoph Klein

blood 2012 119: 3458-3468
Prepublished online December 14, 2011;
doi:10.1182/blood-2011-09-378364

MST1 mutations in autosomal recessive primary immunodeficiency characterized by defective naive T-cell survival

Nadine T. Nehme, Jana Pachlopnik Schmid, Franck Debeurme, Isabelle André-Schmutz, Annick Lim, Patrick Nitschke, Frédéric Rieux-Laucat, Patrick Lutz, Capucine Picard, Nizar Mahlaoui, Alain Fischer and Geneviève de Saint Basile

EBV & Primary immunodeficiency

- XLP
- XIAP
- HLH
- ITK
- STK4 deficiency
- CD27 deficiency
- ALPS

X linked Lymphoproliferative disease
XLP 1/SAP deficiency

X-linked Lymphoproliferative disease

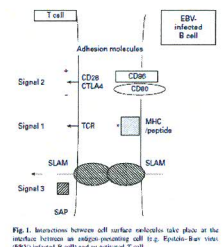
[XLP-1 / SAP deficiency]

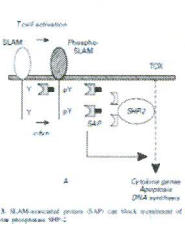
1974 Duncan Kindred – Purtilo

1998 SH2D1A gene

Slam Associated Protein [SAP]

XLP



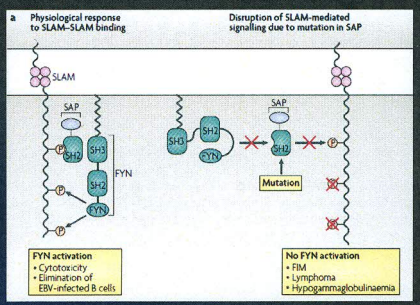


XLP 272 cases 1995

Survival	%	%
Fulminant Infectious Mononucleosis	58	4
Lymphoproliferation	30	35
Dysgammaglobulinaemia	31	55
Marrow aplasia	3	50
Vasculitis	3	29

70% + < 10yrs

Seemayer 1995



Marodi & Notarangelo 2007

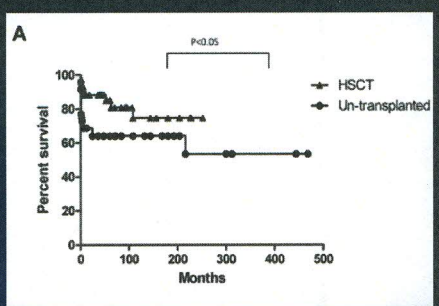
XLP "Catches"

- 10% ill before EBV
- Remember - aplastic anaemia
  - vasculitis
- ALL + Igs ↓
- Colitis & gastritis
- Family history!

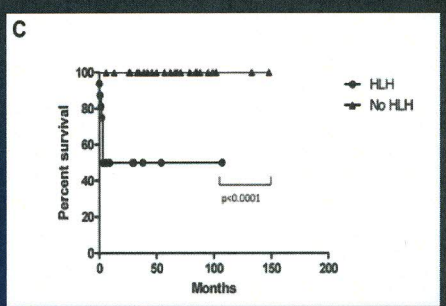
Table 1. Presenting symptoms and features of XLP1 patients with associated mortality

	Incidence	Mortality
Presenting symptom		
HLH	31.9%	65.5%
FIM	7.7%	14.3%
Lymphoma	14.3%	7.7%
Dysgammaglobulinemia	22%	5%
Family history of XLP1 alone	16.5%	20%
Other	7.7%	14.3%
Features occurring at any time		
HLH	35.2%	65.6%
FIM	9.9%	22.2%
Lymphoma	24.2%	9%
Dysgammaglobulinemia	50.5%	13%
Other	15.4%	28.6%

XLP survival HSCT v no HSCT



XLP survival HLH v no HLH



XLP 272 cases 1995

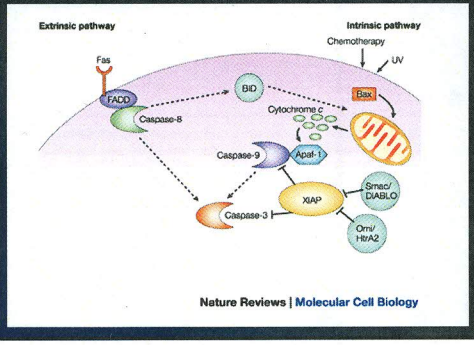
- HSCT 43
- No HSCT 48
- HLH severe risk factor
- 27/27 with HSCT before HLH survived

Booth 2011

X-Linked inhibitor of apoptosis – XIAP/ XLP-2

- Absent XIAP ⇒ abnormal response to EBV
- XIAP-ve lymphocytes vulnerable to cell death
- T B & NK-cell numbers normal
- Almost complete absence of NKT cells
- XIAP critical for NKT survival

Nature Reviews Molecular Cell Biology 2002; IAP proteins: blocking the road to death's door



NKT cells?

- SAP is required for the development of NKT cells
- NKT cells are absent in SAP deficiency

What are NKT cells:

- Sub-population of αβ T cells with restricted repertoire (TCR Vα24-Vβ11)
- Recognises glycosphingolipids presented by CD1b (non-classical MHC molecule)

XIAP clinical features like XLP…. but

- Splenomegaly
- Haemorrhagic colitis
- Lymphoma

Table 3. Comparison of XLP-1 and XLP-2 phenotypes

	SAP-/Y, n (%)	XIAP-/Y, n (%)	P*
HLH	18 of 33 (55)	22 of 29 (76)	NS
HLH relapses (/HLH-survivors)	2 of 7 (29)	11 of 14 (79)	NS
EBV at first HLH	11 of 12 (92)	15 of 18 (83)	NS
Fatal HLH	11 of 33 (33)	5 of 30 (17)	NS
Fatal HLH (/HLH patients)	11 of 18 (61)	5 of 22 (23)	.0230
Hypogammaglobulinemia	14 of 21 (67)	8 of 24 (33)	.0377
Lymphoma	10 of 33 (30)	0 of 30 (0)	.0010
Cytopenias (in the absence of full-blown HLH)	4 of 33 (12)	11 of 21 (52)	.0020
Splenomegaly (in the absence of full-blown HLH)	2 of 29 (7)	20 of 23 (87)	<.0001
Hemorrhagic colitis	0 of 33 (0)	5 of 30 (17)	.0203

*Calculated with Fisher exact tests.