UNIVERSITY OF GOTHENBURG

Region Halland
Hallands sjukhus

10 Important Publications in the field of PID

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Sahlgrenska Akademin vid Göteborgs Universitet

SLIPI´s XI:e
Immunbristmöte

J Clin Immunol (2018) 38:96–128
https://doi.org/10.1007/s10875-017-0464-9

ORIGINAL ARTICLE

International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity

Capucine Picard[1,2] · H. Bobby Gaspar[3] · Waleed Al-Herz[4] · Aziz Bousfiha[5] · Jean-Laurent Casanova[6,7,8,9] · Talal Chatila[10] · Yanick J. Crow[11,12] · Charlotte Cunningham-Rundles[13] · Amos Etzioni[14] · Jose Luis Franco[15] · Steven M. Holland[16] · Christoph Klein[17] · Tomohiro Morio[18] · Hans D. Ochs[19] · Eric Oksenhendler[20] · Jennifer Puck[21] · Mimi L. K. Tang[22,23,24] · Stuart G. Tangye[25,26] · Troy R. Torgerson[19] · Kathleen E. Sullivan[27]

Why is this important?

A critical reference for immunologists and researchers world wide

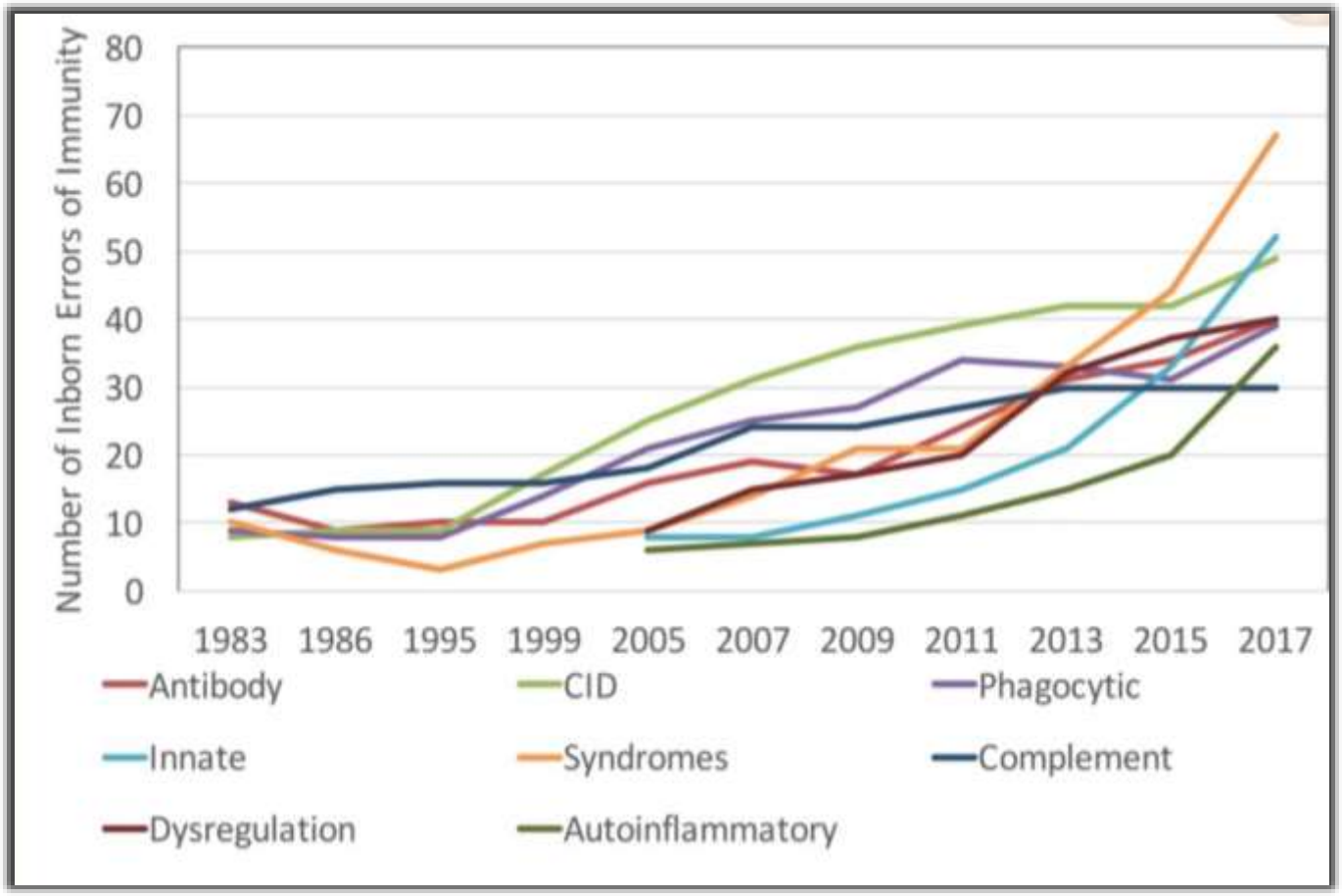
Main purpose *to provide an up to date categorization of immunodeficiency diseases, to increase awareness, facilitate recognition, promote optimal treatment and support research in the field*

Categorization of the inborn errors of immunity

1. Combined immunodeficiencies
2. Combined ID with syndromic features
3. Antibody deficiencies
4. Diseases of immune dysregulation
5. Defects of phagocyte number and function
6. Defects in intrinsic and innate immunity
7. Autoinflammatory diseases
8. Complement deficiencies
9. Phenocopies of inborn errors of immunity

Picard C, et al. J Clin Immunol 2018.

Numbers of inborn errors of immunity



354 total

Picard C, et al. J Clin Immunol 2018.

J Clin Immunol. 2018 Jan;38(1):129-143. doi: 10.1007/s10875-017-0465-8. Epub 2017 Dec 11.

The 2017 IUIS Phenotypic Classification for Primary Immunodeficiencies.

Bousfiha A[1], Jeddane L[2,3], Picard C[4,5], Ailal F[2], Bobby Gaspar H[6], Al-Herz W[7], Chatila T[8], Crow YJ[9,10], Cunningham-Rundles C[11], Etzioni A[12], Franco JL[13], Holland SM[14], Klein C[15], Morio T[16], Ochs HD[17], Oksenhendler E[18], Puck J[19], Tang MLK[20,21,22], Tangye SG[23,24], Torgerson TR[17], Casanova JL[25,26,27,28], Sullivan KE[29].

VI. Defects in Intrinsic and Innate immunity. b : MSMD and Viral infection

Mendelian Susceptibility to mycobacterial disease (MSMD)

Severe phenotypes.

Complete IFNGR1 Def and IFNGR2 Def. *IFNGR1, IFNGR2*. AR.

Serious disseminated BCG and environmental mycobacterial infections (soft tissue, bone marrow, lungs, skin, bones and lymph nodes),

Salmonella spp., *Listeria monocytogenes* and viruses

Moderate phenotypes.

With Susceptibility to *Salmonella*

IL-12 and IL-23 receptor b1 chain deficiency. *IL12RB1* .AR.
IL-12p40 (IL-12 and IL-23) def. *IL12B* .AR.

STAT1 LOF. *STAT1*(AD)

Partial IFNγR1. *IFNGR1*. AR.
Partial IFNγR2. *IFNGR2*.AR.

AD IFNGR1. *IFNGR1*. AD. Mycobacterial osteomyelitis

Tyk2 deficiency. *TYK2*. AR. Susceptibility to viruses, +/- elevated IgE. Multiple cytokine signaling defect.

ISG15 Def. *ISG15*. AR. Brain calcification. IFNg production defect.

Macrophage gp91 phox deficiency. *CYBB*, XL
IRF8 deficiency. *IRF8* AD

IRF8 deficiency. *IRF8* AR Multiple other infectious agents. Myeloproliferation

RORc deficiency. *RORC* AR. Susceptibility to *Candida*. IFNg production defect, complete absence of IL-17A/F-producing Tc

JAK1 (LOF). *JAK1*. AR. Susceptibility to viruses, urothelial carcinoma. IFNg production.

Predominant susceptibility to viral infection

Epidermodysplasia verruciformis (HPV)

EVER1 def. *TMC6*.AR.

EVER2 def. *TMC8*. AR.

WHIM (Warts, Hypogammaglobuline mia, infections, myelo-kathexis) sd. *CXCR4* AD GOF. Warts (HPV) infection, neutropenia, low B cell number, hypogamma-globulinemia.

Predisposition to Severe Viral Infection

STAT1 Def (AR LOF). *STAT1*. *(+ Mycobacteria)*

STAT2 deficiency. *STAT2*. *AR*. Disseminated vaccine-strain measles

IRF7 deficiency. *IRF7*. AR. Severe influenza disease. Defect of IFN-α,β and γ production and IFN-λ production

IFNAR2 deficiency. *IFNAR2* AR. Disseminated vaccine-strain measles, HHV6. No response to IFN-α.

CD16 deficiency. *FCGR3A*. *AR*. Severe herpes viral infections, particularly VZV, Epstein Barr virus (EBV), and HPV.

MDA5 deficiency (LOF). *IFIH1*. *AR*. Rhinovirus and other RNA viruses

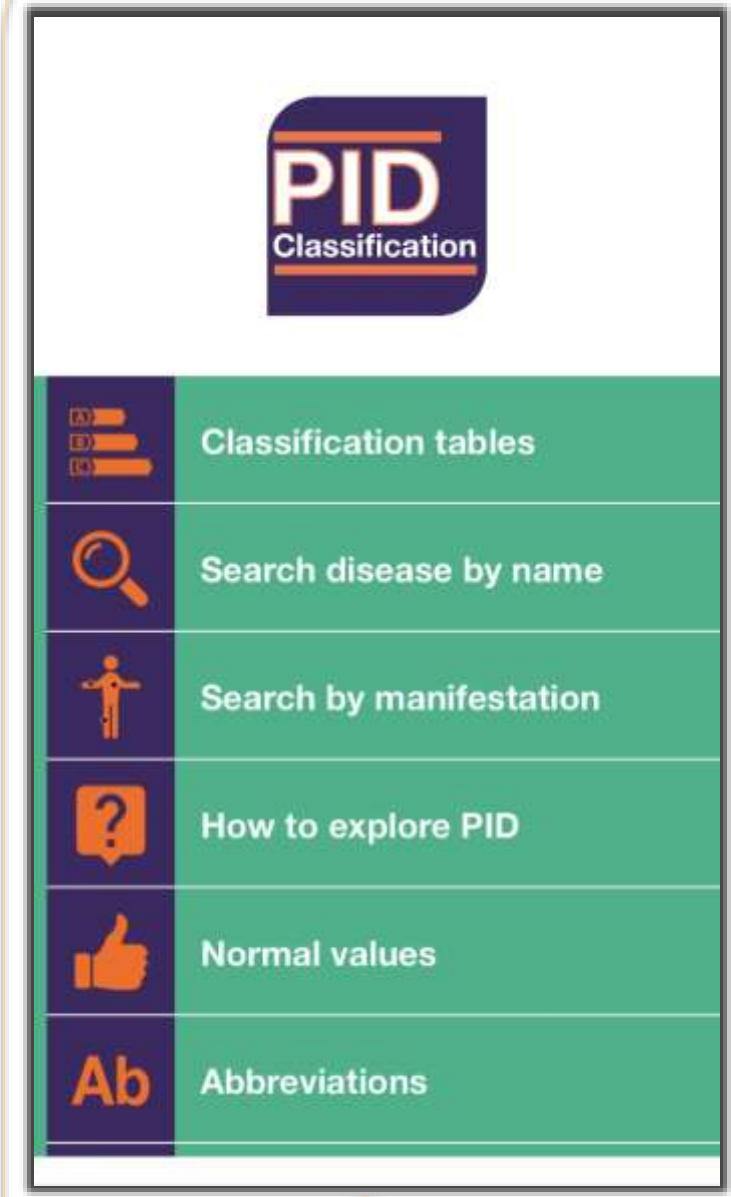
Herpes simplex Encephalitis.

Dominant clinical phenotype is *Herpes simplex* encephalitis (HSE) during primary infection with herpes simplex virus type 1 (HSV1), usually between 3 months and 6 years of age. Incomplete clinical penetrance for all etiologies listed here.

Routine screening tests are normal.

Specific tests examining the TLR3 pathway : marked decrease in the ability of patient's fibroblasts to produce IFN-α and β in response to HSV1 infection.

TLR3 (AD,AR), *UNC93B1* (AR), *TRAF3 (AD)*, *TICAM1 (TRIF) (AR,AD)*, *TBK1 (AD)*, *IRF3 (AD)*.


PID
Classification
Classification tables
Search disease by name
Search by manifestation
How to explore PID
Normal values
Ab
Abbreviations

Pediatrics
February 2019, VOLUME 143 / ISSUE 2
Article

Newborn Screening for Severe Combined Immunodeficiency and T-cell Lymphopenia in California, 2010–2017

George S. Amatuni, Robert J. Currier, Joseph A. Church, Tracey Bishop, Elena Grimbacher, Alan Anh-Chuong Nguyen, Rajni Agarwal-Hashmi, Constantino P. Aznar, Manish J. Butte, Morton J. Cowan, Morna J. Dorsey, Christopher C. Dvorak, Neena Kapoor, Donald B. Kohn, M. Louise Markert, Theodore B. Moore, Stanley J. Naides, Stanley Sciortino, Lisa Feuchtbaum, Rasoul A. Koupaei, Jennifer M. Puck

Why is this important?

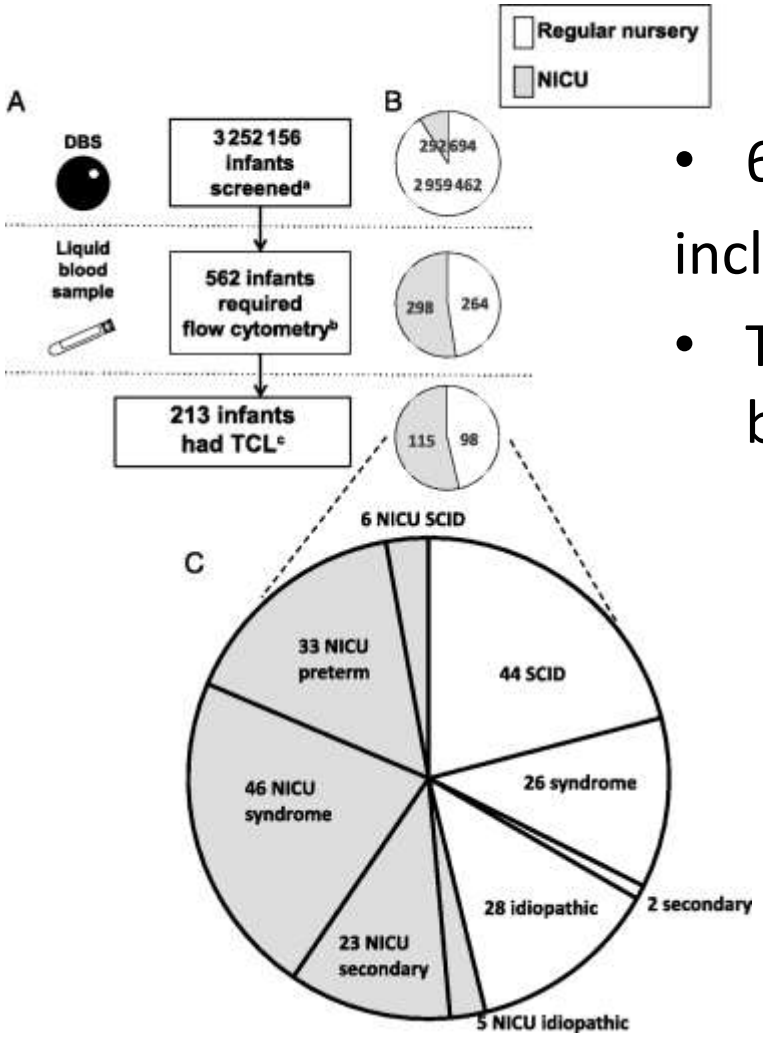
Without early recognition and treatment SCID is a deadly disease

Affected children generally appear healthy at birth

TRECs are found in newly formed, naive T-cells [Douek, Nature 1998]

TREC assay on NBS cards identify babies with SCID regardless of cause [Chan and Puck, JACI 2005]

Summary of Newborn Screening for SCID in California



- 6.5 years of screening,

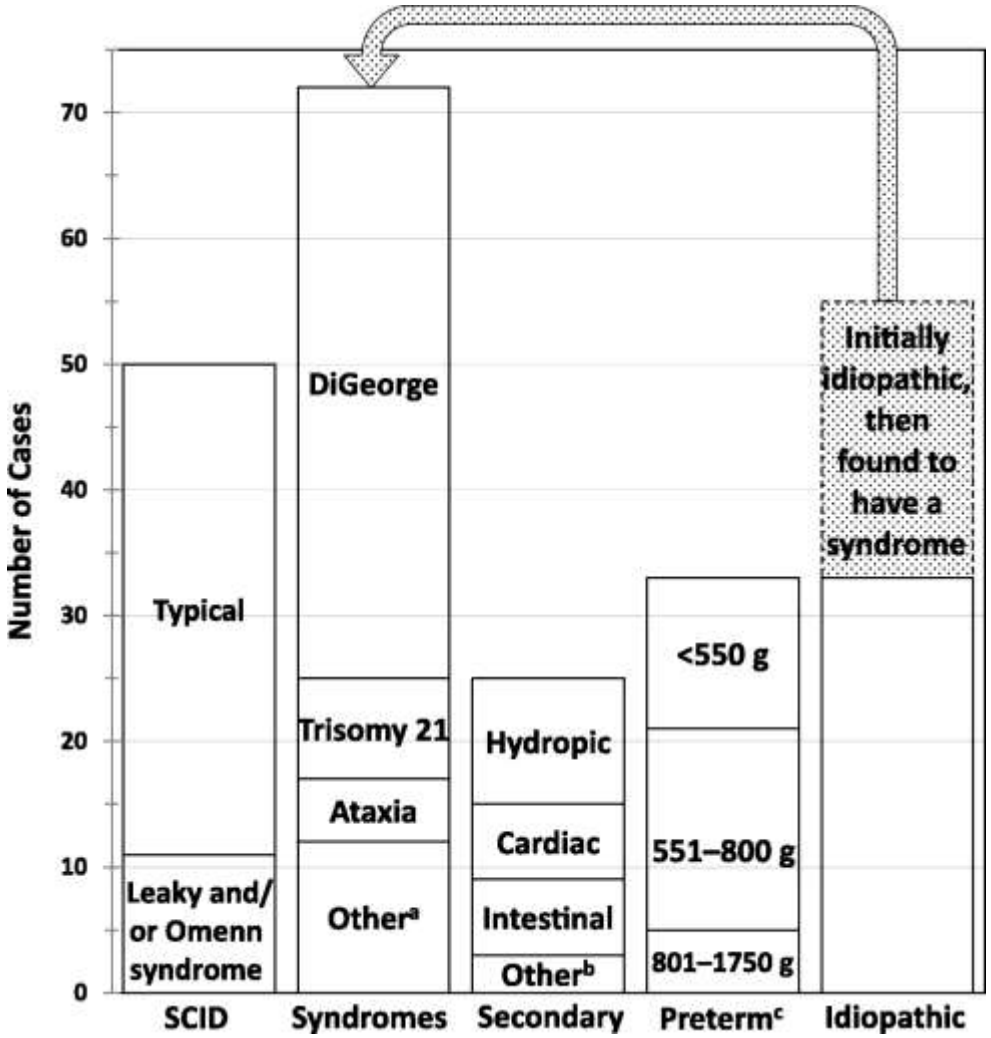
including 3 252 156 infants

- T-cell lymphopenia identified in 1/15300 births

George S. Amatuni et al. Pediatrics 2019;143:e20182300

PEDIATRICS®

Conditions diagnosed in infants with TCL identified by NBS



50 cases of SCID, 1/65 000
No cases missed
94% survival of pts w SCID
Quick turnaround important, as well as individualized conditioning (dosing of busulfan)
Follow up of syndromic/idiopathic pts?

George S. Amatuni et al. Pediatrics 2019;143:e20182300

PEDIATRICS®

Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies

Alain Fischer, MD, PhD,[a,b,c,d,e] Johan Provot, MSc,[a] Jean-Philippe Jais, MD, PhD,[a,c,f] Alexandre Alcais, MD, PhD,[a,c,g] Nizar Mahlaoui, MD, MSc, MPH,[a,b,c,g] and the members of the CEREDIH French PID study group* *Paris, France*

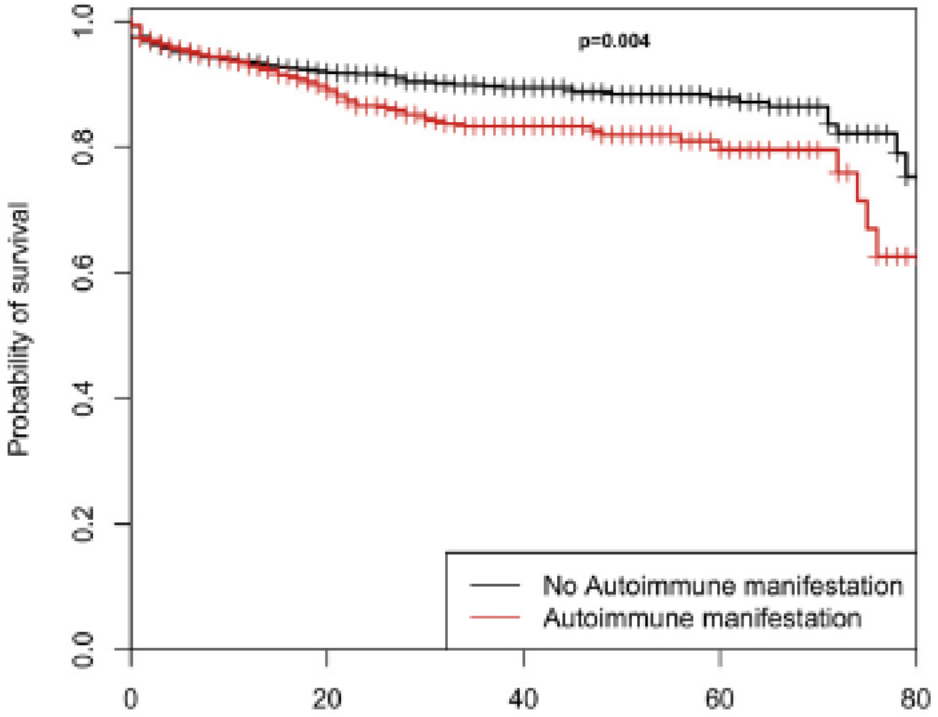
JACI -2017

Why is this important?

Autoimmune diseases occur frequently in patients with PID (26%)

Occurence of autoimmune disease is a negative prognostic factor for survival

Long term survival



Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies

Alain Fischer, MD, PhD,[a,b,c,d,e] Johan Provot, MSc,[a] Jean-Philippe Jais, MD, PhD,[a,c,f] Alexandre Alcais, MD, PhD,[a,c,g] Nizar Mahlaoui, MD, MSc, MPH,[a,b,c,g] and the members of the CEREDIH French PID study group* *Paris, France*

TABLE III. The relative risk of autoimmune disease in patients with PID

	Prevalence per 1 × 10^5 patients with PIDs	Prevalence per 1 × 10^5 of the general population	Relative risk
Cytopenia	12,000	100	120
Autoimmune hemolytic anemia (children, France)†	2,500	3	830
Immune thrombocytopenia (France)‡	6,000	100	60
Rheumatologic disorders*	5,000	860	6
Rheumatoid arthritis (children, France)§	800	20	40
Inflammatory bowel disease (adults, France)‖	7,800	180	43
Inflammatory bowel disease (children, France)‖	5,500	70	80
Skin*	6,000	600	10
Endocrine disorders*	3,000	1,000	3
Eye*	700	100	7
Kidney*	500	63	8
Vasculitis and other systemic disorders*	250	17.5	13
Neurologic disorders*	400	130	3

Greatest risk of autoimmunity in pts with CID

Granulomatous-Lymphocytic Interstitial Lung Disease in CVID

Why is this important?

J Allergy Clin Immunol. 2004 Aug;114(2):415-21.

Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency.

Bates CA[1], Ellison MC, Lynch DA, Cool CD, Brown KK, Routes JM.

J Allergy Clin Immunol Pract. 2017 Jul - Aug;5(4):938-945. doi: 10.1016/j.jaip.2017.01.021. Epub 2017 Mar 25.

British Lung Foundation/United Kingdom Primary Immunodeficiency Network Consensus Statement on the Definition, Diagnosis, and Management of Granulomatous-Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency Disorders.

GLILD

Hurst JR[1], Verma N[2], Lowe D[2], Baxendale HE[3], Jolles S[4], Kelleher P[5], Longhurst HJ[6], Patel SY[7], Renzoni EA[8], Sander CR[9], Avery GR[10], Babar JL[11], Buckland MS[2], Burns S[2], Egner W[12], Gompels MM[13], Gordins P[14], Haddock JA[15], Hart SP[16], Hayman GR[17], Herriot R[18], Hoyles RK[19], Huissoon AP[20], Jacob J[15], Nicholson AG[21], Rassl DM[22], Sargur RB[12], Savic S[23], Seneviratne SL[2], Sheaff M[24], Vaitla PM[25], Walters GI[26], Whitehouse JL[27], Wright PA[28], Condliffe AM[29].

GLILD is a distinct clinico-radio-pathological ILD occuring in patients with CVID, associated with lymphocytic infiltrate, and/or granuloma in the lung and in whom other conditions have been considered and excluded

J Allergy Clin Immunol Pract. 2017 Jul - Aug;5(4):938-945. doi: 10.1016/j.jaip.2017.01.021. Epub 2017 Mar 25.

British Lung Foundation/United Kingdom Primary Immunodeficiency Network Consensus Statement on the Definition, Diagnosis, and Management of Granulomatous-Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency Disorders.

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Diagnostics	Lung function tests
CT	(spirometry, gas transfer)
Bronchoscopy with biopsy	Genetic analysis
	(CID, *LRBA* or *CTLA-4 deficiency*?)
Treatment	2nd line azathioprine, rituximab, mmf
Decisions by multidisciplinary team	Assessment of progression/response by symtoms, CT, lung-function DLCO
Optimized Ig therapy	
Corticosteroids alone	

JCI insight

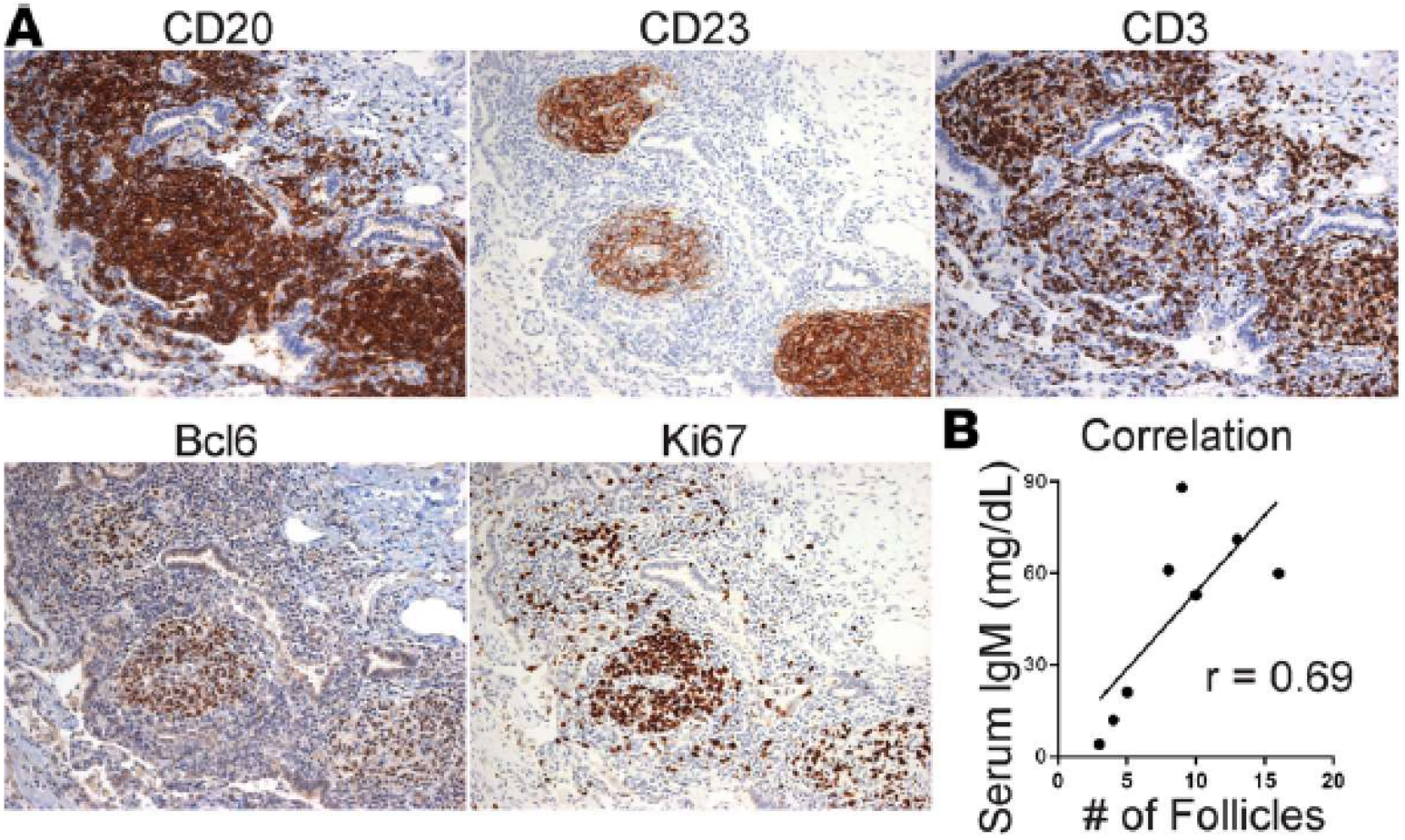
CLINICAL MEDICINE

BAFF-driven B cell hyperplasia underlies lung disease in common variable immunodeficiency

Paul J. Maglione,[1] Gavin Gyimesi,[1] Montserrat Cols,[1] Lin Radigan,[1] Huaibin M. Ko,[2] Tamar Weinberger,[1] Brian H. Lee,[3] Emilie K. Grasset,[1,4] Adeeb H. Rahman,[3] Andrea Cerutti,[1,5,6] and Charlotte Cunningham-Rundles[1]

GLILD is driven by pulmonary B-cell hyperplasia,
reflected by serum IgM elevation (can be used as biomarker)
reinforced by elevated BAFF giving resistance to apoptosis
Efficacy of rituximab monotherapy is shown

Ectopic B-cell follicles in GLILD and correlation to s-IgM



Maglione PJ -2019

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Blood. 2018 Feb 22; 131(8): 917–931.
Prepublished online 2017 Dec 26. doi: 10.1182/blood-2017-09-807487: 10.1182/blood-2017-09-807487
PMCID: PMC6225386
PMID: 29279357

Successful outcome following allogeneic hematopoietic stem cell transplantation in adults with primary immunodeficiency

Thomas A. Fox,[1,2] Ronjon Chakraverty,[2,3,4] Siobhan Burns,[1,2,3] Benjamin Carpenter,[2,5] Kirsty Thomson,[2,4] David Lowe,[1,6] Adele Fielding,[2,3,4] Karl Peggs,[2,4] Panagiotis Kottaridis,[2,3] Benjamin Uttenthal,[7] Venetia Bigley,[8] Matthew Buckland,[1,6] Victoria Grandage,[5] Shari Denovan,[2,3,5] Sarah Grace,[2,3,5] Julia Dahlstrom,[2,5] Sarita Workman,[6] Andrew Symes,[6] Stephen Mackinnon,[2,3,4] Rachael Hough,[5] and Emma Morris[✉1,2,6]

[1]Institute of Immunity and Transplantation, University College London (UCL), London, United Kingdom;
[2]Bone Marrow Transplant (BMT) Programme, UCL Hospital National Health Service Foundation Trust (NHS FT), London, United Kingdom;
[3]Department of Haematology, Royal Free London NHS FT, London, United Kingdom;
[4]Department of Haematology, Cancer Institute, UCL, London, United Kingdom;
[5]Teenage and Young Adult BMT Programme, UCL Hospital NHS FT, London, United Kingdom;
[6]Department of Immunology, Royal Free London NHS FT, London, United Kingdom;
[7]Department of Haematology, Addenbrookes' Hospital, Cambridge, United Kingdom; and
[8]Institute of Cellular Medicine, Newcastle University, Newcastle, United Kingdom
[✉]Corresponding author.

Received 2017 Sep 20; Accepted 2017 Dec 14.

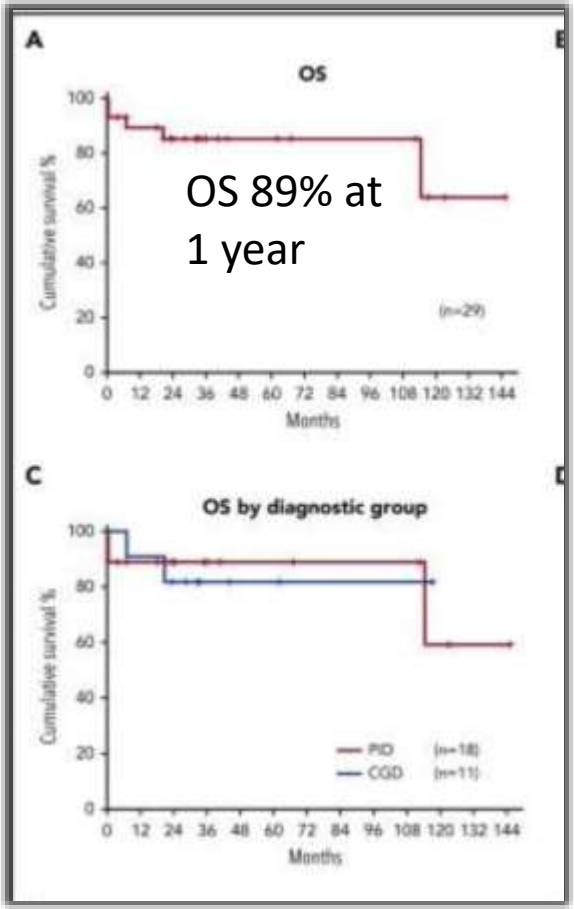
Why is this important?

20 000 published cases of HSCT in PID, but almost exclusively children
Controversy on when to transplant adults with PID, due to lack of experience

Method

29 PID patients (11 CGD)
Mean age 24 yrs (17-50)
18 MUD
11 MSD
RIC

Results



Allo-HSCT with RIC is safe and effective in younger adults with severe PID

Referral triggers should include severe infections, autoimmunity, malignancy and disease progression despite conservative management

Fox TA, et al. *Blood* 2018.

Biol Blood Marrow Transplant 25 (2019) 1363–1373

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Haploidentical Hematopoietic Stem Cell Transplantation with Post-Transplant Cyclophosphamide for Primary Immunodeficiencies and Inherited Disorders in Children

HSCT with PT-CY

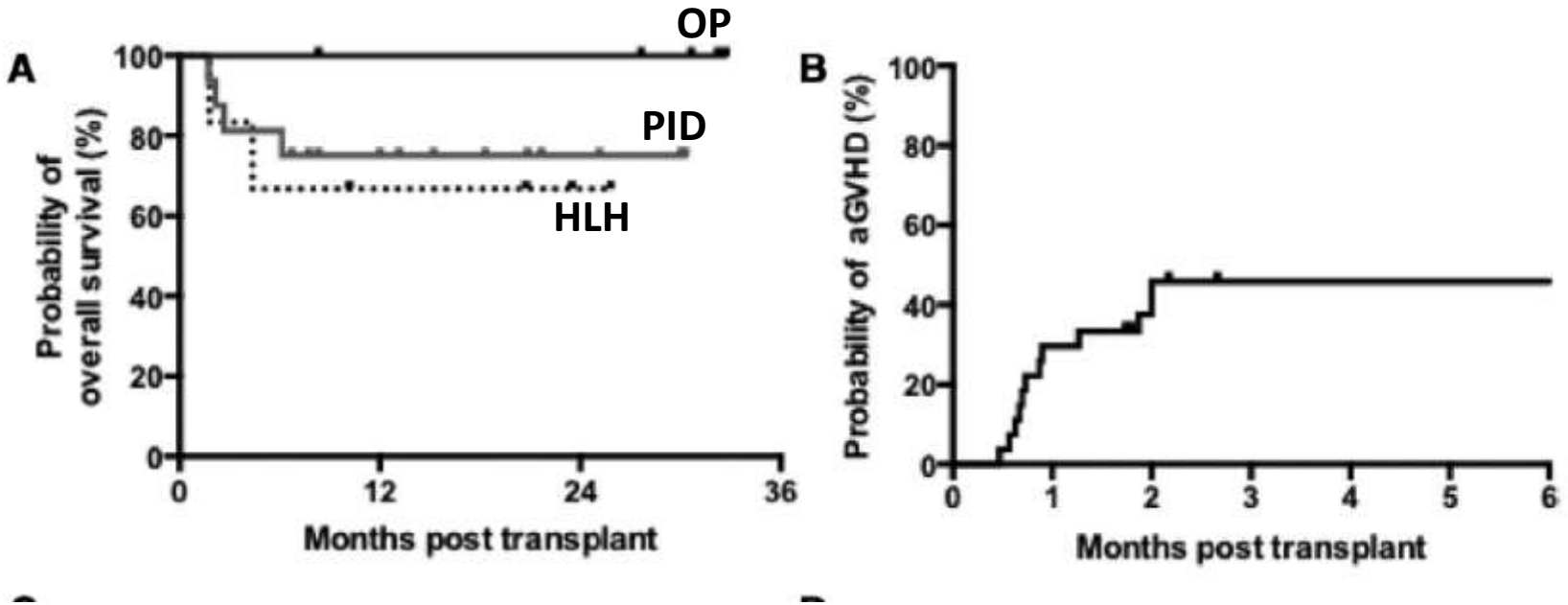
Bénédicte Neven[1,2,3,*], Jean-Sébastien Diana[1,3,4], Martin Castelle[1], Alessandra Magnani[2,3,4], Jérémie Rosain[2,3,5], Fabien Touzot[2,3,4], Baptiste Moreira[6], Marie-Louise Fremond[1,2,3], Coralie Briand[1,3], Matthieu Bendavid[1,3], Romain Levy[1,3], Guillaume Morelle[1,3], Marc Vincent[2,3], Elsa Magrin[2,3,4], Philippe Bourget[7], Lucienne Chatenoud[6], Capucine Picard[1,2,3,5], Alain Fischer[1,2,3,8], Despina Moshous[1,2,3], Stéphane Blanche[1,3]

Why is this important?

Alternative for 40% pts who lack HLA-matched donor

No need for extensive T cell depletion or donor search

Results



"Here, we reported on our experience of haploidentical family donor HSCT with PTCY in 27 consecutive patients suffering from a broad range of PIDs and showed a 2-year OS rate of 77.7%"

Neven B, et al. Biol Blood Marrow Transplant -2019

Indian Pediatr. 2018 Aug 15;55(8):661-664.

Hematopoietic Stem Cell Transplantation for Primary Immunodeficiency Disorders: Experience from a Referral Center in India.

Uppuluri R[1], Jayaraman D[2], Sivasankaran M[2], Patel S[2], Swaminathan VV[2], Vaidhyanathan L[3], Kandath S[4], Raj R[2].

Biol Blood Marrow Transplant. 2017 June ; 23(6): 980–990. doi:10.1016/j.bbmt.2017.03.016.

Haploidentical Related Donor Hematopoietic Stem Cell Transplantation for Dedicator-of-Cytokinesis 8 Deficiency Using Post-Transplantation Cyclophosphamide

Nirali N. Shah[1,*], **Alexandra F. Freeman**[2], **Helen Su**[3], **Kristen Cole**[4], **Mark Parta**[5], **Niki M. Moutsopoulos**[6], **Safa Baris**[7], **Elif Karakoc-Aydiner**[7], **Thomas E. Hughes**[8], **Heidi H. Kong**[9], **Steve M. Holland**[2], and **Dennis D. Hickstein**[4]

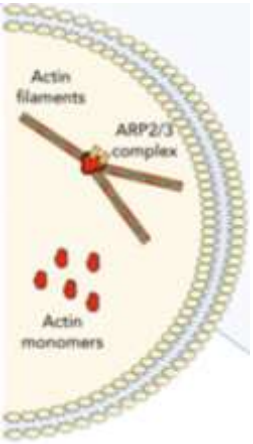
A combined immunodeficiency with severe infections, inflammation, and allergy caused by ARPC1B deficiency.

Volpi S, Cicalese MP, Tuijnenburg P, Tool ATJ, Cuadrado E, Abu-Halaweh M, Ahanchian H, Alzyoud R, Akdemir ZC, Barzaghi F, Blank A, Boisson B, Bottino C, Brigida I, Caorsi R, Casanova JL, Chiesa S, Chinn IK, Dückers G, Enders A, Erichsen HC, Forbes LR, Gambin T, Gattorno M, Karimiani EG, Giliani S, Gold MS, Jacobsen EM, Jansen MH, King JR, Laxer RM, Lupski JR, Mace E, Marcenaro S, Maroofian R, Meijer AB, Niehues T, Notarangelo LD, Orange J, Pannicke U, Pearson C, Picco P, Quinn PJ, Schulz A, Seeborg F, Stray-Pedersen A, Tawamie H, van Leeuwen EMM, Aiuti A, Yeung R, Schwarz K, Kuijpers TW.

J Allergy Clin Immunol. 2019 Jun;143(6):2296-2299. doi: 10.1016/j.jaci.2019.02.003. Epub 2019 Feb 13. No abstract available.

Why is this important?

A recently characterized form of PID



Disease caused by dysfunction of the cytoskeleton

ARPC1B is a component of actin related protein 2/3, an important molecule in cytoskeleton dynamics

ARPC1B deficiency

Similar to WAS!

Volpi S, et al. JACI 2019.

ARPC1 deficiency

Platelets	↓
B-lymphocytes CD19+ (count)	↑
T-helper lymphocytes CD3+4+ (count)	↓
T-cytotoxic lymphocytes CD3+8+ (count)	↓
Naive T-helper lymphocytes CD3+4+ (%)	↓
Naive T-cytotoxic lymphocytes CD3+8+ (%)	↓
IgA	↑↑
IgE	↑↑
T-cell proliferation response	→↓
Response to polysackaride vaccine	→
NK-cells CD3+56++CD16-	↑

Volpi S, et al. JACI 2019.

Nat Commun. 2017 Apr 3;8:14816. doi: 10.1038/ncomms14816.

Loss of the Arp2/3 complex component ARPC1B causes platelet abnormalities and predisposes to inflammatory disease.

Kahr WH[1,2,3], Pluthero FG[1], Elkadri A[1,4,5], Warner N[1,4], Drobac M[1,3], Chen CH[1,3], Lo RW[1,3], Li L[1], Li R[1], Li Q[1,4], Thoeni C[1,4], Pan J[1,4], Leung G[1,4], Lara-Corrales I[6], Murchie R[1,4], Cutz E[6], Laxer RM[7,8], Upton J[9], Roifman CM[9], Yeung RS[1,5,7,10], Brumell JH[1,4,5,11], Muise AM[1,3,4,5].

Combined immunodeficiency with severe inflammation and allergy caused by ARPC1B deficiency.

Kuijpers TW, Tool ATJ, van der Bijl I, de Boer M, van Houdt M, de Cuyper IM, Roos D, van Alphen F, van Leeuwen K, Cambridge EL, Arends MJ, Dougan G, Clare S, Ramirez-Solis R, Pals ST, Adams DJ, Meijer AB, van den Berg TK.

J Allergy Clin Immunol. 2017 Jul;140(1):273-277.e10. doi: 10.1016/j.jaci.2016.09.061. Epub 2016 Dec 10. No abstract

T-cell defects in patients with *ARPC1B* germline mutations account for combined immunodeficiency.

Brigida I, Zoccolillo M, Cicalese MP, Pfajfer L, Barzaghi F, Scala S, Oleaga-Quintas C, Álvarez-Álvarez JA, Sereni L, Giannelli S, Sartirana C, Dionisio F, Pavesi L, Benavides-Nieto M, Basso-Ricci L, Capasso P, Mazzi B, Rosain J, Marcus N, Lee YN, Somech R, Degano M, Raiola G, Caorsi R, Picco P, Moncada Velez M, Khourieh J, Arias AA, Bousfiha A, Issekutz T, Issekutz A, Boisson B, Dobbs K, Villa A, Lombardo A, Neven B, Moshous D, Casanova JL, Franco JL, Notarangelo LD, Scielzo C, Volpi S, Dupré L, Bustamante J, Gattorno M, Aiuti A.

Blood. 2018 Nov 29;132(22):2362-2374. doi: 10.1182/blood-2018-07-863431. Epub 2018 Sep 25.

Science Immunology
AAAS

Tuberculosis and impaired IL-23–dependent IFN-γ immunity in humans homozygous for a common *TYK2* missense variant

by Stéphanie Boisson-Dupuis, Noe Ramirez-Alejo, Zhi Li, Etienne Patin, Geetha Rao, Gaspard Kerner, Che Kang Lim, Dimitry N. Krementsov, Nicholas Hernandez, Cindy S. Ma, Qian Zhang, Janet Markle, Ruben Martinez-Barricarte, Kathryn Payne, Robert Fisch, Caroline Deswarte, Joshua Halpern, Matthieu Bouaziz, Jeanette Mulwa, Durga Sivanesan, Tomi Lazarov, Rodrigo Naves, Patricia Garcia, Yuval Itan, Bertrand Boisson, Alix Checchi, Fabienne Jabot-Hanin, Aurélie Cobat, Andrea Guennoun, Carolyn C. Jackson, Sevgi Pekcan, Zafer Caliskaner, Jaime Inostroza, Beatriz Tavares Costa-Carvalho, Jose Antonio Tavares de Albuquerque, Humberto Garcia-Ortiz, Lorena Orozco, Tayfun Ozcelik, Ahmed Abid, Ismail Abderahmani Rhorfi, Hicham Souhi, Hicham Naji Amrani, Adil Zegmout, Frédéric Geissmann, Stephen W. Michnick, Ingrid Muller-Fleckenstein, Bernhard Fleckenstein, Anne Puel, Michael J. Ciancanelli, Nico Marr, Hassan Abolhassani, María Elvira Balcells, Antonio Condino-Neto, Alexis Strickler, Katia Abarca, Cory Teuscher, Hans D. Ochs, Ismail Reisli, Esra H. Sayar, Jamila El-Baghdadi, Jacinta Bustamante, Lennart Hammarström, Stuart G. Tangye, Sandra Pellegrini, Lluis Quintana-Murci, Laurent Abel, and Jean-Laurent Casanova

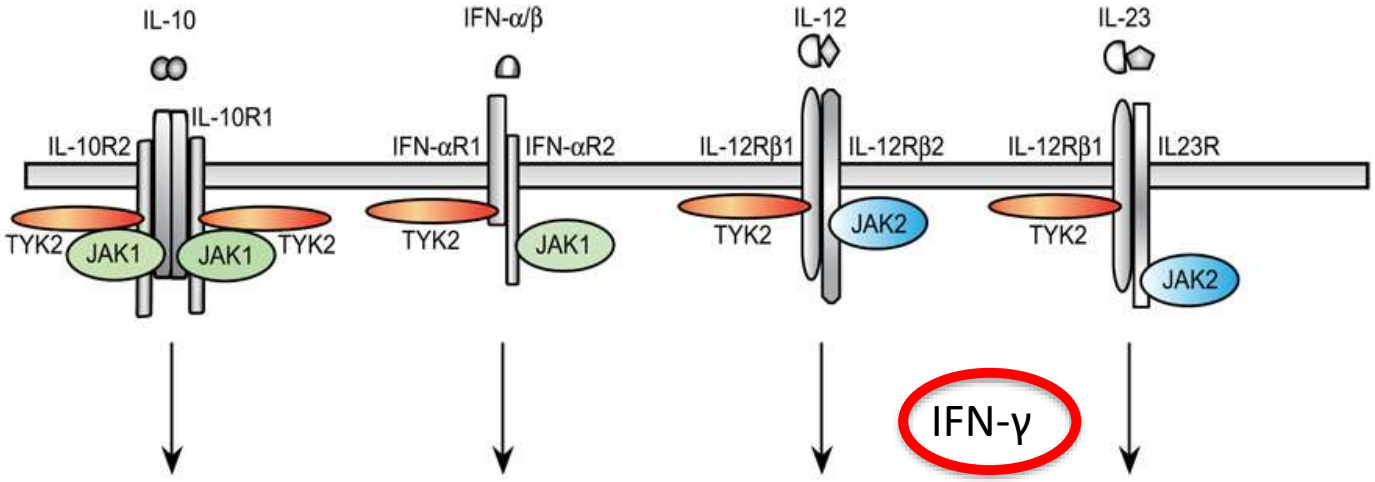
Sci. Immunol.
Volume 3(30):eaau8714
December 21, 2018

Why is this important?

It explains why some otherwise healthy people are susceptible to tuberculosis

- TB is one of the top causes of death worldwide
- 25% of the worlds population are infected, only 10% fall ill
- Clinical and epidemiological studies imply there is a genetic predisposition
- There are a few known PIDs selectively affecting IFN-γ signalling, which is essential in our defence to mycobacteria
- Homozygosity of common *TYK2* variant P1104A increases risk of TB and infections with less virulent mycobacteria
- Frequency of TYK2 variant allele P1104A is 4%
  Homozygosity in Europeans 1/600

Schematic representation of TYK2-dependent signaling pathways



TYK2 genotype	STAT3/STAT3	STAT1/STAT2/p48	STAT4/STAT4	STAT3/STAT3	Clinical phenotype
WT/WT	+++	+++	+++	+++	Healthy individuals
−/−	++	+	+	+	MSMD, TB, viruses
I684S/I684S	+++	+++	+++	+++	Healthy individuals
P1104A/P1104A	+++	+++	+++	+	MSMD, TB

Stéphanie Boisson-Dupuis et al. Sci. Immunol. 2018;3:eaau8714

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Blood. 2017 Nov 23; 130(21): 2307–2316.
Prepublished online 2017 Sep 29.
doi: 10.1182/blood-2017-08-801191: 10.1182/blood-2017-08-801191

PMCID: PMC5701526
PMID: 28972011

Effective "activated PI3Kδ syndrome"–targeted therapy with the PI3Kδ inhibitor leniolisib (APDS, PASLI)

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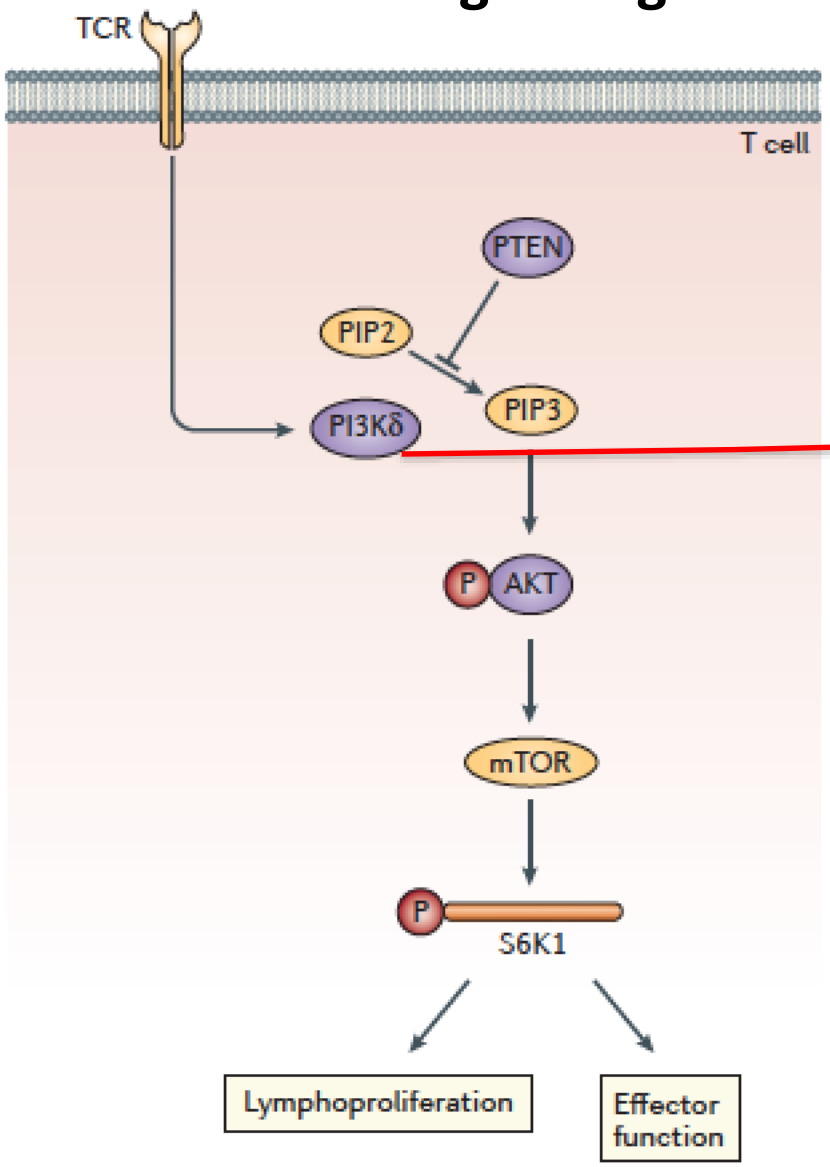
Phenotype

Recurrent ear, lung, sinus infections
Organ damage (bronchiectasis)
Infections with herpes family viruses
Benign lymphoproliferation
Lymphoma
Autoimmunity (immune-cytopenias)
Mild developmental delay
Growth retardation (APDS2)

Immunology

Hypogammaglobulinemia with elevated IgM
B-lymphopenia with elevated transitional B-cells
Reduction in naive CD4/8

T-cell signalling



APDS/PASLI cased by GoF mutations causing hyperactivation of enzyme

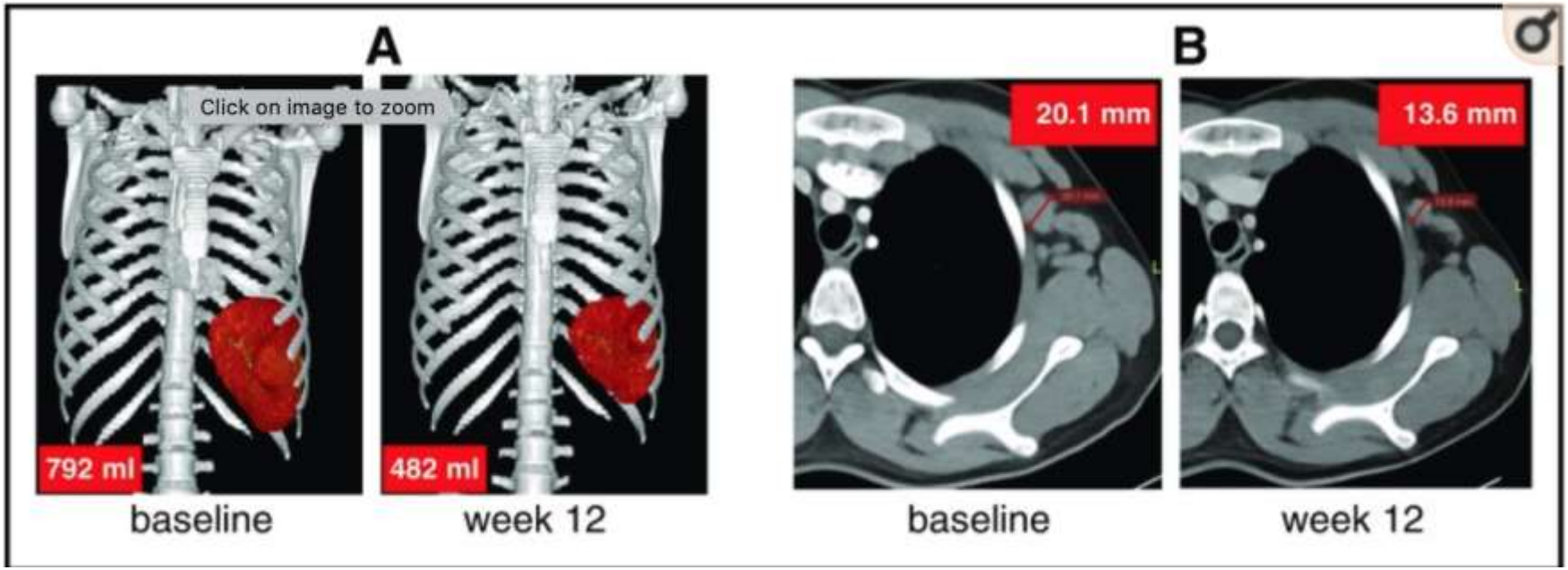
Understanding the genetic etiology led to the hypothesis that treating pts with PI3K pathway inhibitors may provide long term targeted therapy

Leniolisib is a small molecule that inhibits p110d

Koneti et al. -2017

Schmidt RE, et al. Nat Rev -2017

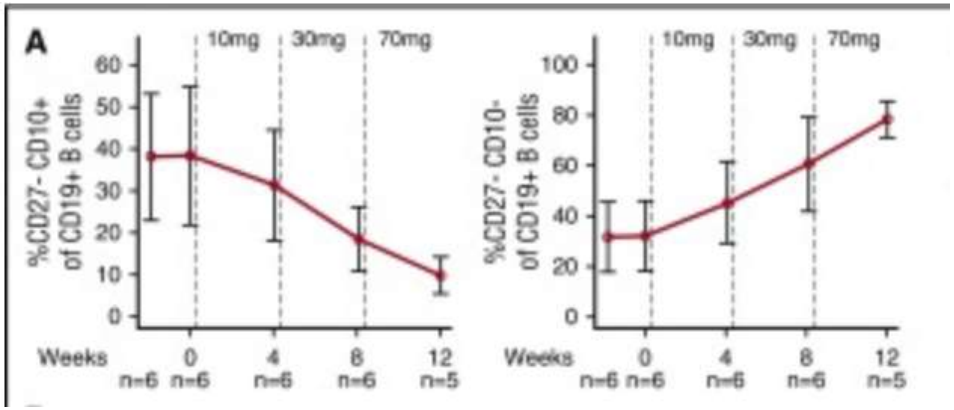
Results



After 12 weeks of oral leniolisib, lymph node and spleen sizes were reduced by 39%

All patients had cytopenias at baseline, and they improved

Immune cell derangements improved



Koneti VR, Blood 2017

frontiers in Immunology

PERSPECTIVE
published: 16 March 2018
doi: 10.3389/fimmu.2018.00543

Disease Evolution and Response to Rapamycin in Activated Phosphoinositide 3-Kinase δ Syndrome: The European Society for Immunodeficiencies-Activated Phosphoinositide 3-Kinase δ Syndrome Registry

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The NEW ENGLAND JOURNAL of MEDICINE

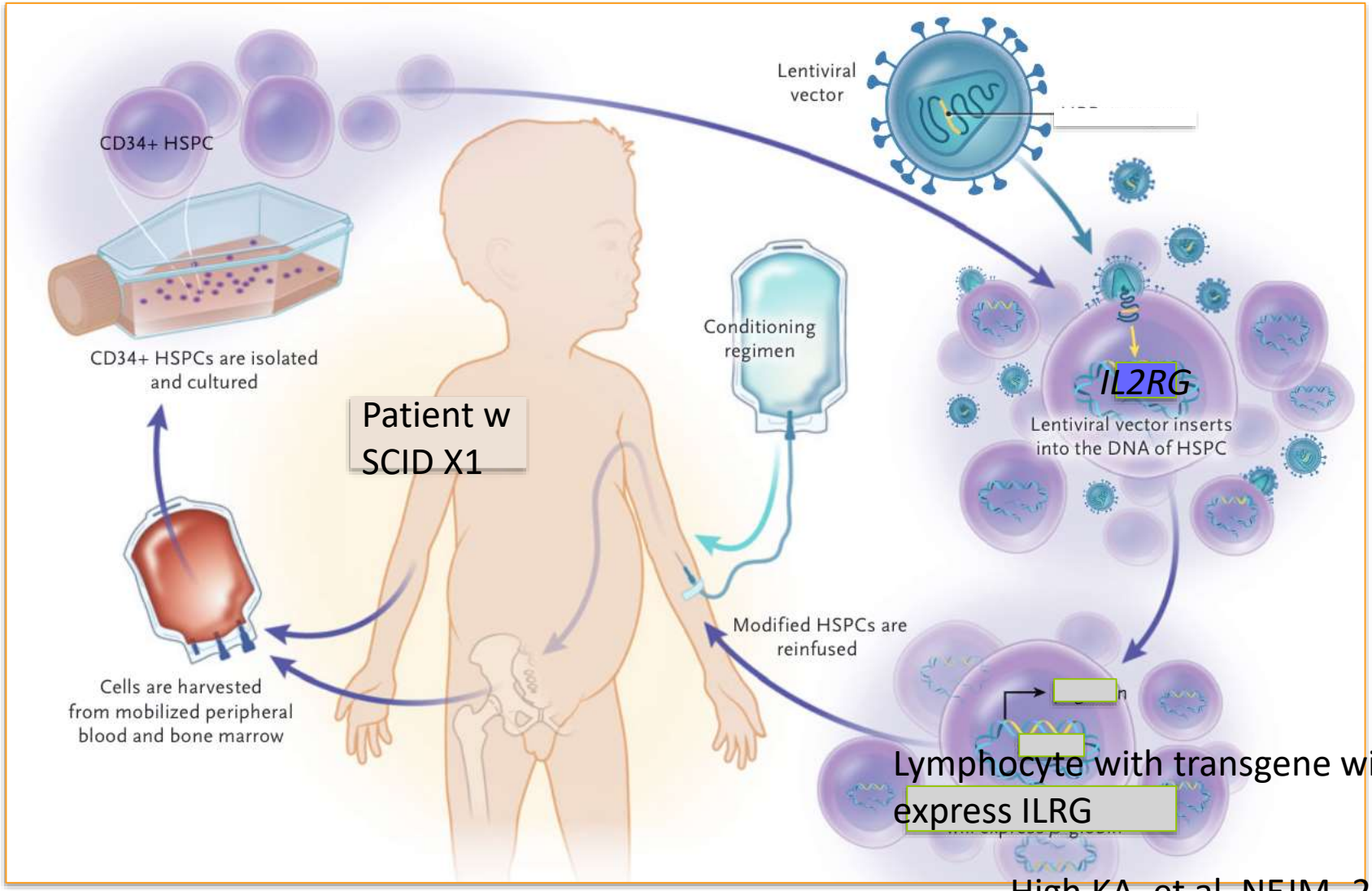
ORIGINAL ARTICLE

Lentiviral Gene Therapy Combined with Low-Dose Busulfan in Infants with SCID-X1

E. Mamcarz, S. Zhou, T. Lockey, H. Abdelsamed, S.J. Cross, G. Kang, Z. Ma, J. Condori, J. Dowdy, B. Triplett, C. Li, G. Maron, J.C. Aldave Becerra, J.A. Church, E. Dokmeci, J.T. Love, A.C. da Matta Ain, H. van der Watt, X. Tang, W. Janssen, B.Y. Ryu, S.S. De Ravin, M.J. Weiss, B. Youngblood, J.R. Long-Boyle, S. Gottschalk, M.M. Meagher, H.L. Malech, J.M. Puck, M.J. Cowan, and B.P. Sorrentino*

SCID-X1 caused by mutations in *IL2RG* gene on X-chromosome
Without treatment affected boys die in first year from infections
HSCT is standard treatment, but in the absence of MSD significant risk of incomplete immun reconstitution, GvHD
Previous trials with gammaretroviral vectors failed to reconstitute B and NK cell immunity and was complicated with vector related leukemia

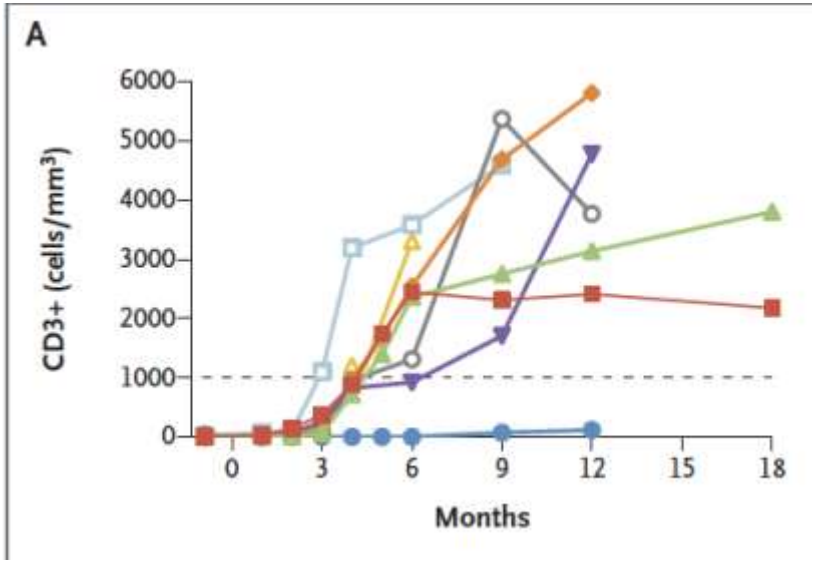
Ex Vivo Delivery of Gene Therapy

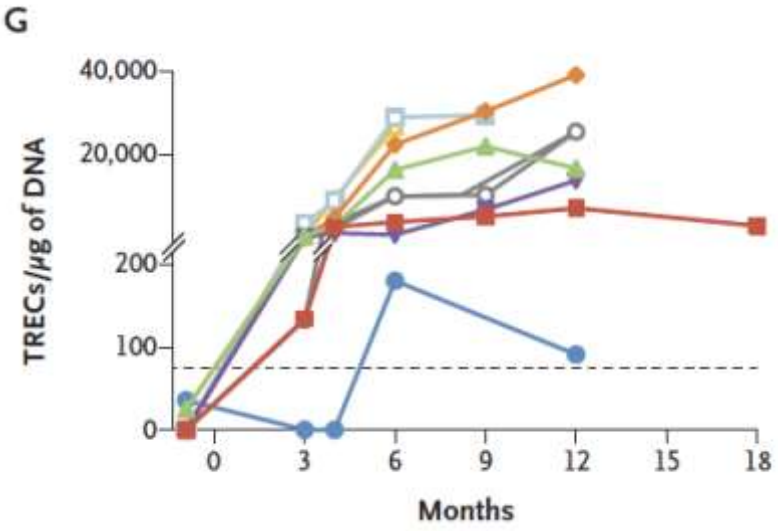


High KA, et al. NEJM -2019.

Results

Absolute numbers in blood of T-cells, over time after infusion





Lentiviral gene therapy combined with low exposure, targeted busulfan conditioning in infants with newly diagnosed SCIDX1 had low grade acute toxic effects and resulted in multilineage engraftment of transduced cells, reconstitution of functional T- and B-cells

Mamcarz E, et al. NEJM 2019.

Update on the safety and efficacy of retroviral gene therapy for immunodeficiency due to adenosine deaminase deficiency

Maria Pia Cicalese,[1,2,*] Francesca Ferrua,[1,2,3,*] Laura Castagnaro,[1] Roberta Pajno,[2,3] Federica Barzaghi,[1,2] Stefania Giannelli,[1] Francesca Dionisio,[1] Immacolata Brigida,[1] Marco Bonopane,[1] Miriam Casiraghi,[1,2] Antonella Tabucchi,[4] Filippo Carlucci,[4] Eyal Grunebaum,[5] Mehdi Adeli,[6] Robbert G. Bredius,[7] Jennifer M. Puck,[8] Polina Stepensky,[9] Ilhan Tezcan,[10] Katie Rolfe,[11] Erika De Boever,[11] Rickey R. Reinhardt,[11] Jonathan Appleby,[11] Fabio Ciceri,[3,12] Maria Grazia Roncarolo,[1,3,13,14] and Alessandro Aiuti[1,2,3]

Lentiviral haemopoietic stem/progenitor cell gene therapy for treatment of Wiskott-Aldrich syndrome: interim results of a non-randomised, open-label, phase 1/2 clinical study

Francesca Ferrua, Maria Pia Cicalese*, Stefania Galimberti, Stefania Giannelli, Francesca Dionisio, Federica Barzaghi, Maddalena Migliavacca, Maria Ester Bernardo, Valeria Calbi, Andrea Angelo Assanelli, Marcella Facchini, Claudia Fossati, Elena Albertazzi, Samantha Scaramuzza, Immacolata Brigida, Serena Scala, Luca Basso-Ricci, Roberta Pajno, Miriam Casiraghi, Daniele Canarutto, Federica Andrea Salerio, Michael H Albert, Antonella Bartoli, Hermann M Wolf, Rossana Fiori, Paolo Silvani, Salvatore Gattillo, Anna Villa, Luca Biasco, Christopher Dott, Emily J Culme-Seymour, Koenraad van Rossem, Gillian Atkinson, Maria Grazia Valsecchi, Maria Grazia Roncarolo, Fabio Ciceri, Luigi Naldini, Alessandro Aiuti*