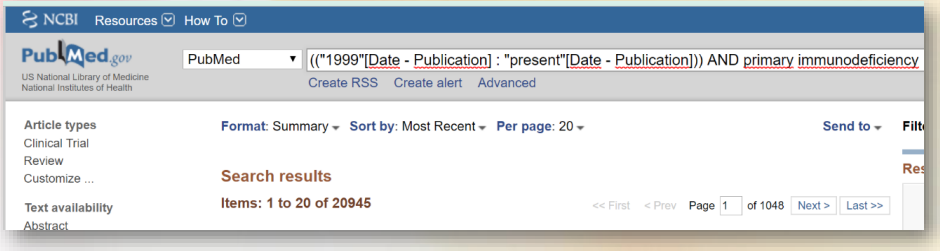
SLIPI

X:e möte

Vetenskapshistoria

Nicholas Brodszki
Barn- och UngdomsSjukhuset, Lund
Nicholas.Brodszki@skane.se

10 artiklar som har publicerats sedan SLIPI bildades 1999 och som har förändrat vår syn på primär immunbrist



SCID

FEBRUARY 2005
Basic and clinical immunology
THE JOURNAL OF Allergy AND Clinical Immunology

Development of population-based newborn screening for severe combined immunodeficiency

Kee Chan, MS,[a,b] and Jennifer M. Puck, MD[a] *Bethesda, Md, and New Haven, Conn*

Newborn screening – VARFÖR ?

SCID meets most of the criteria for disease that should be screened:

1) The patient is symptom-free at birth
2) The condition is lethal if not treated
3) Treatment is available
4) The earlier treatment the better the results

SO, why not been done before?

- SCID is rare
- No available screening method

Development of population-based newborn screening for severe combined immunodeficiency. Chan & Puck, JACI 2005

Method

Measuring TREC (T-cell Receptor Excision Circle) on Guthrie kort

In blood from:

- Healthy newborns
- Children with SCID
- Healthy adults
- As well as T-cell depleted blood from adults

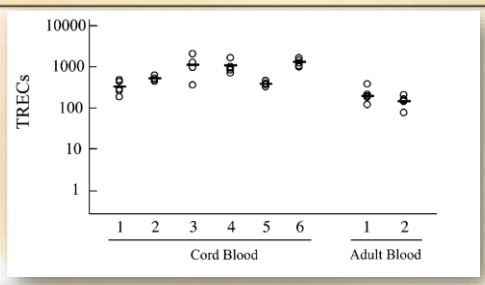
Development of population-based newborn screening for severe combined immunodeficiency. Chan & Puck, JACI 2005

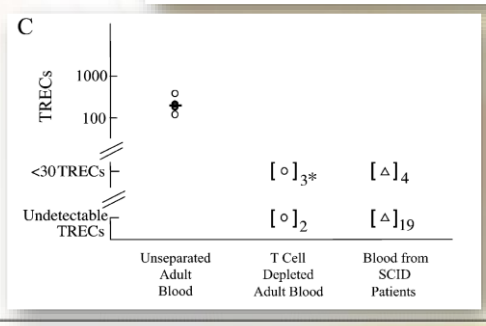
Method

Why TREC and not CD3 / CD4 … etc?

- TREC is formed when naive T cells form their T cell receptor, ie the number of TRECs reflects the production of new T cells
- Children with SCID may have circulating T cells from the mother, => measuring CD3/CD4 etc could give false normal results
- Maternal T cells are of memory type and do not produce TREC
- In healthy newborns, the number of TREC is about 10% of the total number of T cells while healthy adults have about 5 times lower levels

Development of population-based newborn screening for severe combined immunodeficiency. Chan & Puck, JACI 2005





Development of population-based newborn screening for severe combined immunodeficiency.
Chan & Puck, JACI 2005

Analysis of blood spotted onto filters confirmed that at the time of diagnosis SCID patients lack TRECs. Samples from all of 23 patients with various forms of SCID had <30 TRECs in two 3-mm punches (equivalent to <5

Development of population-based newborn screening for severe combined immunodeficiency.
Chan & Puck, JACI 2005

SCID (2)

JAMA, December 9, 2009—Vol 302, No. 22

ORIGINAL CONTRIBUTION

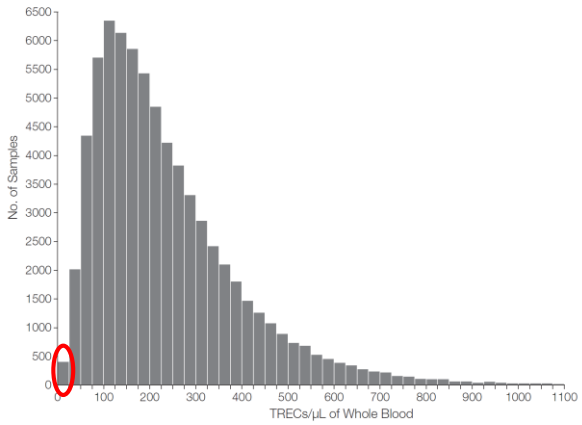
Statewide Newborn Screening for Severe T-Cell Lymphopenia

John M. Routes, MD
James Verbsky, MD, PhD
Gary L. Hoffman, BS
William J. Grossman, MD, PhD
Ronald H. Laessig, PhD†
Charles D. Brokopp, DrPH
Mei W. Baker, MD

LÄKEMEDEL

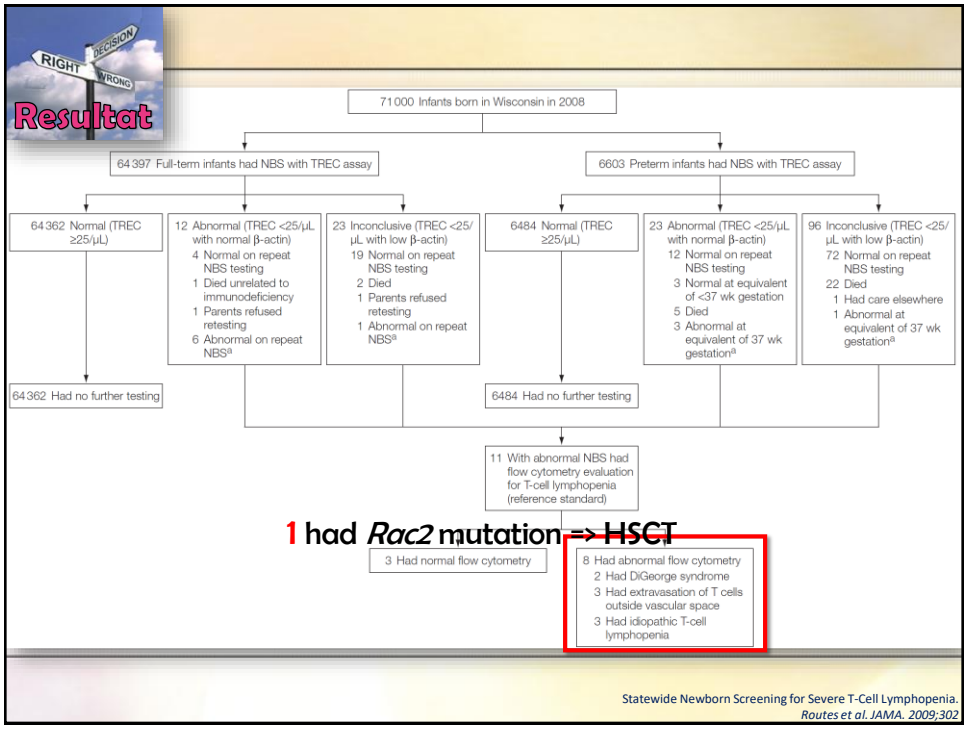
Wisconsin 2008; all newborn (>37 w. gestational age)

Figure 1. Distribution of TRECs in NBS Cards From 71 000 Infants in 2008



TRECs indicate T-cell receptor excision circles; NBS, newborn blood screening. The mean number of TRECs was 225 TRECs/µL of whole blood and the median was 186 TRECs/µL of whole blood.

Statewide Newborn Screening for Severe T-Cell Lymphopenia.
Routes et al. JAMA. 2009;302



Statewide Newborn Screening for Severe T-Cell Lymphopenia.
Routes et al. JAMA. 2009;302

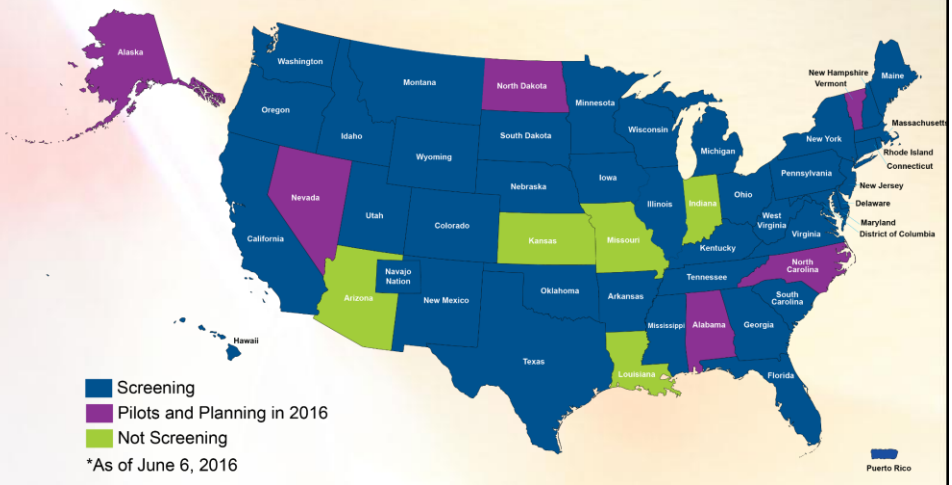
Criteria used for inclusion of specific diseases in state NBS programs

- the incidence of the disease should be at least 1:100 000 live births
- the disease must result in serious morbidity or mortality
- early diagnosis and treatment should significantly improve the prognosis
- the disorder must not be readily detected at birth by a routine physical examination
- a sensitive, specific, and inexpensive test must exist that uses existing NBS cards
- a confirmatory gold standard test for diagnosis must be available

Statewide Newborn Screening for Severe T-Cell Lymphopenia.
Routes et al. JAMA. 2009;302

SCID Newborn Screening: Current Status of Implementation Map*

39 States Currently Screening for SCID - 87% of all newborns in the U.S. are receiving SCID screening



Screening
Pilots and Planning in 2016
Not Screening

*As of June 6, 2016

Immune Deficiency Foundation
www.primaryimmune.org

GENTERAPI

Science 28 APRIL 2000

Gene Therapy of Human Severe Combined Immunodeficiency (SCID)–X1 Disease

Marina Cavazzana-Calvo,*[1,2,3] Salima Hacein-Bey,*[1,2,3] Geneviève de Saint Basile,[1] Fabian Gross,[2] Eric Yvon,[3] Patrick Nusbaum,[2] Françoise Selz,[1] Christophe Hue,[1,2] Stéphanie Certain,[1] Jean-Laurent Casanova,[1,4] Philippe Bousso,[5] Françoise Le Deist,[1] Alain Fischer[1,2,4]†

SCID-X1 = interleukin receptor gamma chain defect
(T-B+NK- SCID)

Why is this paper important?
First report of SCID treatment with gene therapy?

Background:

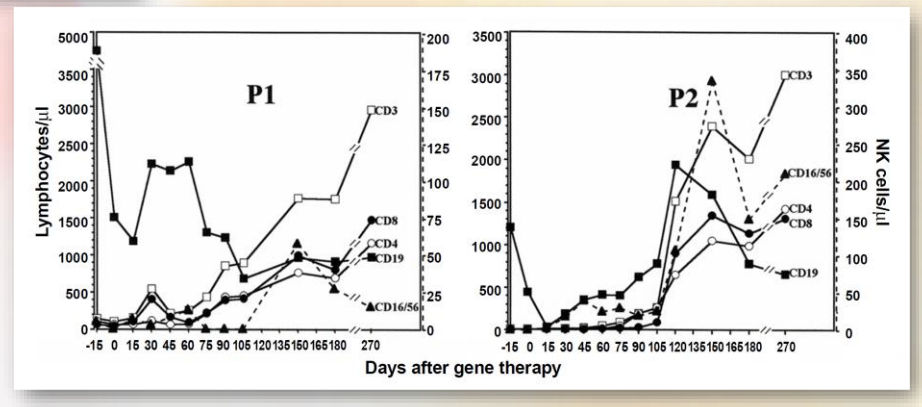
- SCID can be cured by stem cell transplantation
- SCID-X1 = "single gene defect"
- Defect is on the gamma chain (γc) of interleukin receptor
- In mice, the γc-defect has been corrected by gene therapy
- Long-term expression of human γc-gene also been achieved by retroviral infection of canine bone marrow
- γc-gen transfer confer a selective advantage to the transduced T and NK lymphocyte progenitors

Gene Therapy of Human Severe Combined Immunodeficiency (SCID)-X1 Disease
Cavazzana-Calvo,al, Science 2000

Method:

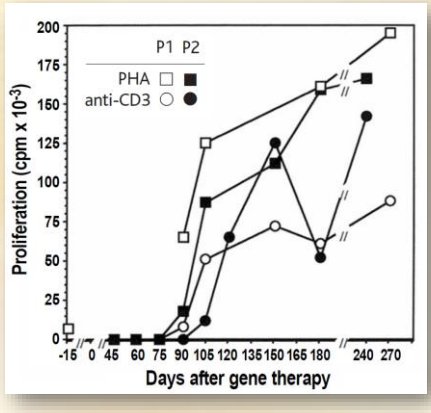
- 2 patients with SCID – 8 and 11 months old
- 4,6 resp 9,8 x 10^6/kg CD34+ cells (marrow harvest)
- The cells were preactivated, then infected daily for 3 days with the γc vector–containing supernatant
- ~20 to 40% of the cells expressed the γc transgene
- Patients were transfused with their own CD34+ (17 resp 19 x 10^6/kg) without prior chemoablation

Gene Therapy of Human Severe Combined Immunodefciency (SCID)-X1 Disease
Cavazzana-Calvo et al, Science 2000



Gene Therapy of Human Severe Combined Immunodefciency (SCID)-X1 Disease
Cavazzana-Calvo et al, Science 2000

		% positive cells	
		P1	P2
CD3	TcR α/β	99	98
	TcR γ/δ	1	2
CD4	CD45R0	19	21
	CD45RA	79	78
CD8	CD45R0	5	25
	CD45RA	94	70



Dag +270 +240
efter re-infusion av CD34+

Gene Therapy of Human Severe Combined Immunodefciency (SCID)-X1 Disease
Cavazzana-Calvo et al, Science 2000

B

	IgG	IgA	IgM	Antibodies to : Tet. tox. (iu/ml)	Dipht. Tox. (iu/ml)	Polio virus I II III Titer x 10^{-1}
		mg/dl				
P1 (d. + 270)	323	41	202	.53	.86	320 160 160
P2 (d. + 240)	309	0	46	.93	.63	640 640 160
Control (age matched)	420-850	16-80	40-90	>.20	>.20	>80

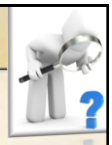
Gene Therapy of Human Severe Combined Immunodefciency (SCID)-X1 Disease
Cavazzana-Calvo et al, Science 2000

Science AAAS

2003

Pyogenic Bacterial Infections in Humans with IRAK-4 Deficiency

Capucine Picard,[1] Anne Puel,[1] Marion Bonnet,[1] Cheng-Lung Ku,[1] Jacinta Bustamante,[1] Kun Yang,[1] Claire Soudais,[1] Stéphanie Dupuis,[1] Jacqueline Feinberg,[1] Claire Fieschi,[1] Carole Elbim,[2] Remi Hitchcock,[3] David Lammas,[4] Graham Davies,[5] Abdulaziz Al-Ghonaium,[6] Hassan Al-Rayes,[6] Sulaiman Al-Jumaah,[6] Sami Al-Hajjar,[6] Ibrahim Zaid Al-Mohsen,[6] Husn H. Frayha,[6] Rajivi Rucker,[3] Thomas R. Hawn,[7] Alan Aderem,[7] Haysam Tufenkeji,[6] Soichi Haraguchi,[3] Noorbibi K. Day,[3] Robert A. Good,[3] Marie-Anne Gougerot-Pocidalo,[2] Adrian Ozinsky,[7] Jean-Laurent Casanova[1,8]*



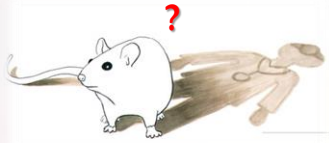
Why is this paper important ?

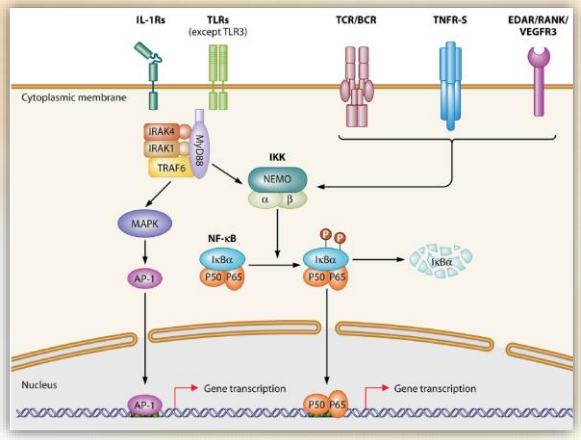
A new form of PID

Background :

TIR-IRAK signal-pathway is important in the immune defence against most pathogens

In mice!



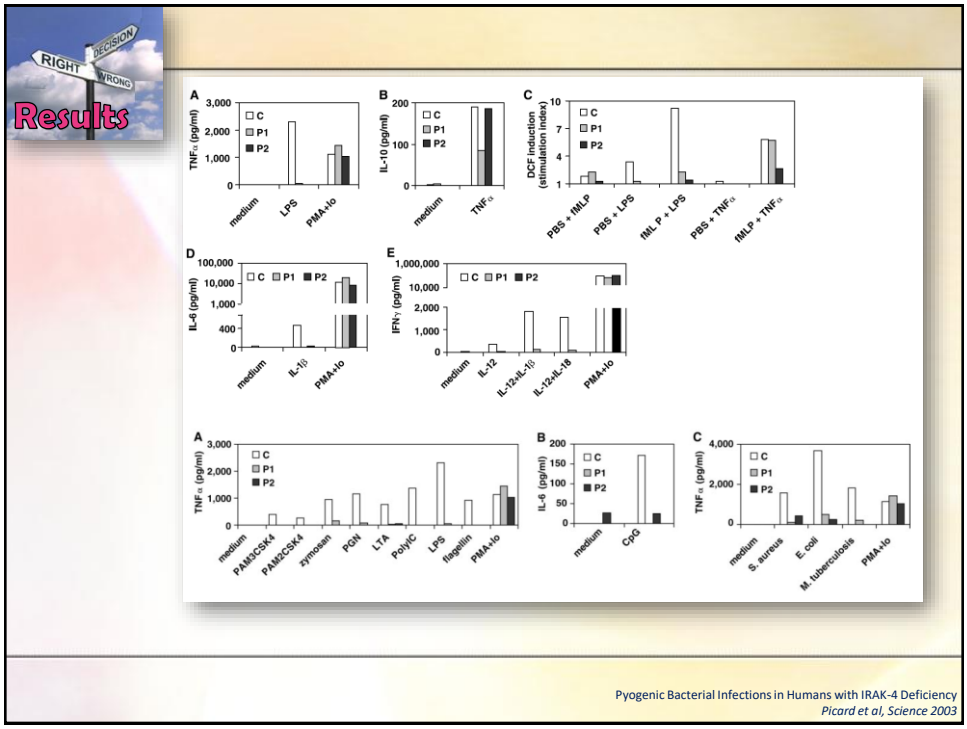


Pyogenic Bacterial Infections in Humans with IRAK-4 Deficiency
Picard et al, Science 2003

Patients :

- **3** children
- Many infections, early in life, with poor inflammatory response
- Almost always *Streptococcus pneumoniae* & *Staphylococcus aureus*
- All known immune deficiencies were excluded
- Normal Ig-levels, incl. specific antibodies against pneumococci (!)
- Conisdered healthy at 6, 7 and 11 years of age

Pyogenic Bacterial Infections in Humans with IRAK-4 Deficiency
Picard et al, Science 2003



Pyogenic Bacterial Infections in Humans with IRAK-4 Deficiency
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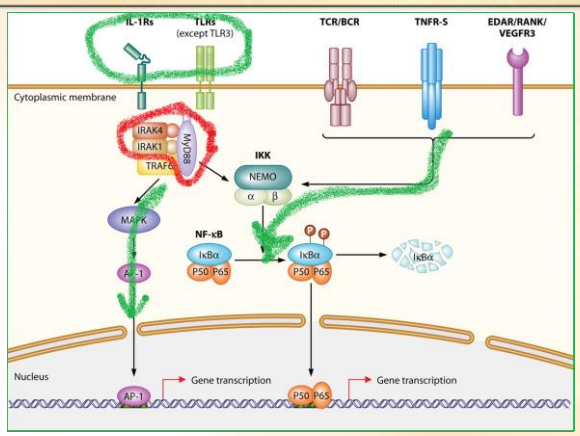


Decreased response on stimulation with LPS (lipopolysaccharide) and IL-1β but not TNFα

=> defect in TIR-IRAK signal pathway

No mutations in *MYD88, TIRAP, IRAK1, IRAK2 & IRAKM* but in ***IRAK4***

Pyogenic Bacterial Infections in Humans with IRAK-4 Deficiency
Picard et al, Science 2003

IRAK4 deficiency

- ✓ Selective immunodeficiency in humans – increased susceptibilty for pnemococci & ***Staph. aureus***
- ✓ Patients otherwise healthy, resistant to most viruses,other bacterias, funghi, parasites
- ✓ Affect patients only early in life

New insight that most infections can be "fought" without TLR, IL-1R och IL-18R inducing the important cytokines: IL-1β, IL-6, IL-12, TNFα, IFN-γ

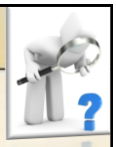
Pyogenic Bacterial Infections in Humans with IRAK-4 Deficiency
Picard et al, Science 2003

nature immunology

march 2003

Homozygous loss of ICOS is associated with adult-onset common variable immunodeficiency

Bodo Grimbacher[1]*, Andreas Hutloff[2]*, Michael Schlesier[1], Erik Glocker[1], Klaus Warnatz[1], Ruth Dräger[1], Hermann Eibel[3], Beate Fischer[3], Alejandro A. Schäffer[4], Hans W. Mages[2], Richard A. Kroczek[2]* and Hans H. Peter[1]*



Why is this paper important?

First gene involved in CVID identified

Background :

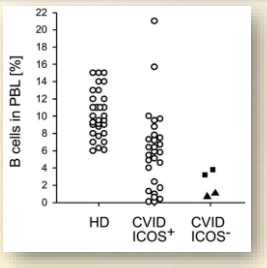
CVID is present in 20-25% of patients in several family members; both autosomal dominant and recessive inhertance

ICOS = "Inducible Costimulator"

- Surface molecules on T cells are expressed only on activated T cells
- Similar to CD28, needed for activation of T cells
- Stimulates all T cell functions (such as proliferation, cytokine production, effective B-cells help for antibody production, etc.)

Homozygous loss of ICOS is associated with adult-onset common variable immunodeficiency
Grimbacher et al, Nature immunology, 2003

Cohort of 32 CVID patients + 20 healthy



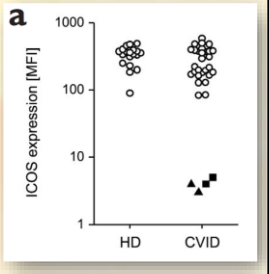
Findings :

- CVID patients have lower numbers of B cells

- Among CVID patients there were 4 patients (in 2 families) who did not have ICOS on activated T cells

- Since one of the pat. is female => autosomal recessive

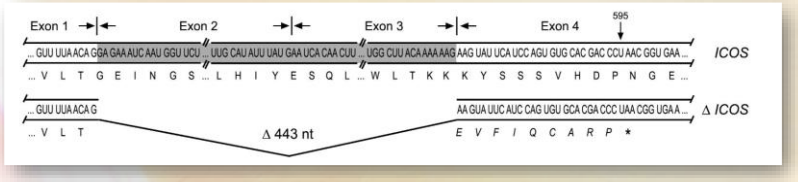
- For ICOS to be expressed, stimulation via TCR and CD28 must work. The signal road worked well; the patients had no other T cell defects
  => ICOS is not expressed due to a genetic defect



Homozygous loss of ICOS is associated with adult-onset common variable immunodeficiency
Grimbacher et al, Nature immunology, 2003

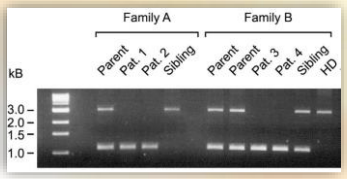
Resultat

443 nucleotide deletion in ICOS mRNA

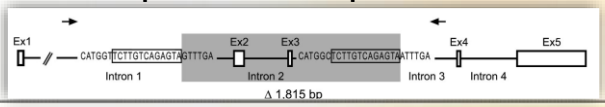


Could be : spilicing defect or a deletion in the *ICOS* gene

DNA amplification:



Found a **1815** base-pair deletion in patients with ICOS-deficiency



Homozygous loss of ICOS is associated with adult-onset common variable immunodeficiency
Grimbacher et al, Nature immunology, 2003

ICOS deficiency :

- ✓ First genetic defect identified in patients with CVID
- ✓ New autosomal recessive immunodeficiency
- ✓ Mechanism: he T cells can not help the B cells in differentiation and isotype switching
- ✓ Patients have very low levels or lack memory B cells
- ✓ IgM and IgG decline gradually - CVID onset usually in childhood

Homozygous loss of ICOS is associated with adult-onset common variable immunodeficiency
Grimbacher et al, Nature immunology, 2003

Science AAAS

13 OCTOBER 2006

Herpes Simplex Virus Encephalitis in Human UNC-93B Deficiency

Armanda Casrouge,[1*] Shen-Ying Zhang,[1,2*] Céline Eidenschenk,[1*] Emmanuelle Jouanguy,[1,2*] Anne Puel,[1] Kun Yang,[1,2] Alexandre Alcais,[1] Capucine Picard,[1,3] Nora Mahfoufi,[1] Nathalie Nicolas,[1] Lazaro Lorenzo,[1] Sabine Plancoulaine,[1] Brigitte Sénéchal,[4] Frédéric Geissmann,[4] Koichi Tabeta,[5]† Kasper Hoebe,[5] Xin Du,[5] Richard L. Miller,[6] Bénédicte Héron,[7] Cyril Mignot,[7] Thierry Billette de Villemeur,[7] Pierre Lebon,[8] Olivier Dulac,[9] Flore Rozenberg,[8] Bruce Beutler,[5] Marc Tardieu,[10] Laurent Abel,[1] Jean-Laurent Casanova[1,2,11]‡

Why is this paper important?

Describes the ethiology of herpes simplex encephalitis (HSE)

Background:

- HSV-1 infection is common
- 80% of young adults have antibodies
- HSE is very unusual - 1: 250,000 person-years
- Before acyclovir mortality was ~ 70%
- Today, most survive, but neurological sequelae are common
- The patients are otherwise completely healthy, without any signs of increased infection susceptibility

Herpes Simplex Virus Encephalitis in Human UNC-93B Deficiency
Casrouge et al, Science 2006

- Observation : Patients with NEMO and STAT1 deficiency develop HSE due to their decreased interferon(IFN) -α/β and -λ-mediated immunity

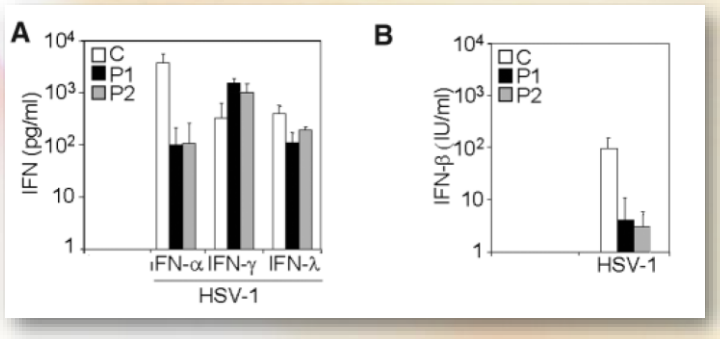
Method :

- Stimulated PBMCs with HSV-1 and other viruses
- Interferon release in otherwise healthy children with sporadic HSE was compared with 50 healthy controls

Herpes Simplex Virus Encephalitis in Human UNC-93B Deficiency
Casrouge et al, Science 2006

1

2 patients with abnormal results



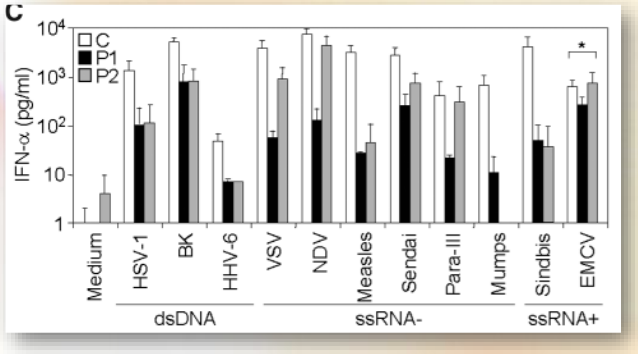
- Decreased Interferon α and β, while λ only slightly decreased
- Normal production of IFN-γ TNFα, IL1 β, and IL-6

Herpes Simplex Virus Encephalitis in Human UNC-93B Deficiency
Casrouge et al, Science 2006

Resultat

2

2 patients with abnormal results



Decreased IFN α production even with 10 other viruses

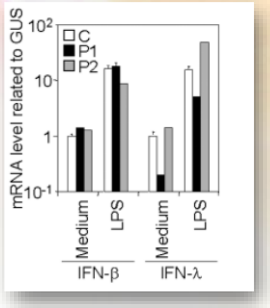
Herpes Simplex Virus Encephalitis in Human UNC-93B Deficiency
Casrouge et al, Science 2006

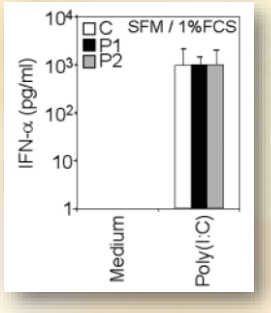
Resultat

3

2 patients with abnormal results

Virus detection and release of IFN α/β happens due to signaling via TLR 3, TLR 7, TLR 8, TLR 9 and partiallys TLR4





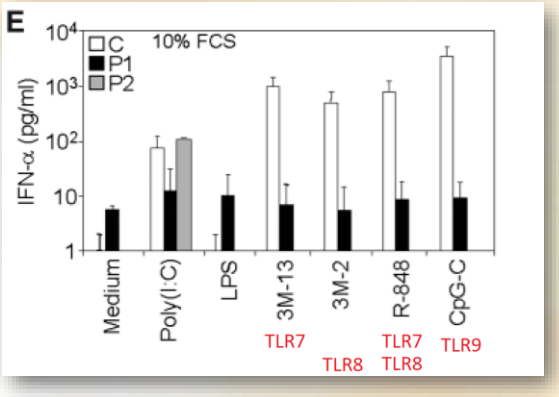
Normal response when stimulated with
- ~~TLR4~~ agonist (LPS)
- ~~TLR3~~ agonist (Poly I:C)

Herpes Simplex Virus Encephalitis in Human UNC-93B Deficiency
Casrouge et al, Science 2006

Resultat

4

2 patients with abnormal results

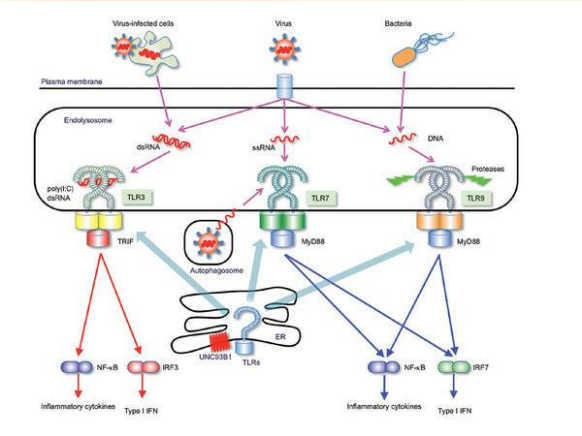


Decreased release of IFN α when stimulated with agonists to TLR 7, TLR 8, TLR 9

Herpes Simplex Virus Encephalitis in Human UNC-93B Deficiency
Casrouge et al, Science 2006

Resultat

5



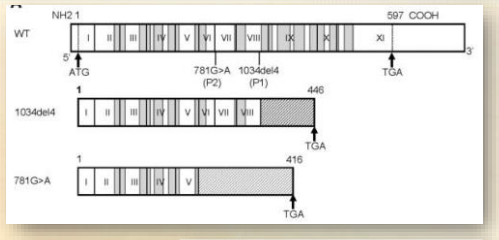
UNC-93B needed for TLR 3, 7, 8, 9 function

Herpes Simplex Virus Encephalitis in Human UNC-93B Deficiency
Casrouge et al, Science 2006

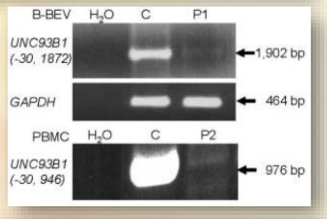
Resultat

6

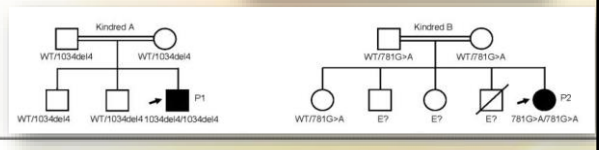
Mutation was found in both patients



UNC-93B was almost non-measurable



Autosomalt recessiv inheritance

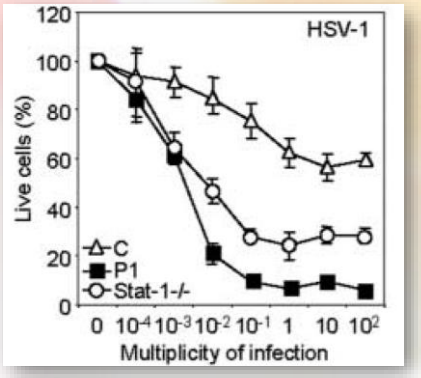


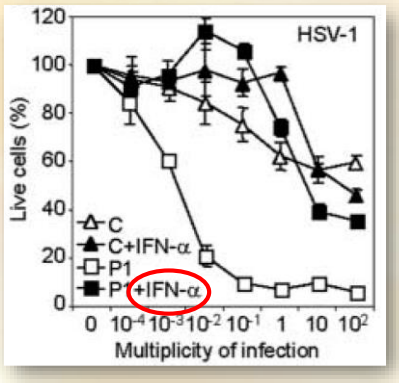
Herpes Simplex Virus Encephalitis in Human UNC-93B Deficiency
Casrouge et al, Science 2006

Resultat

7

Cell-death in HSV-1 infection





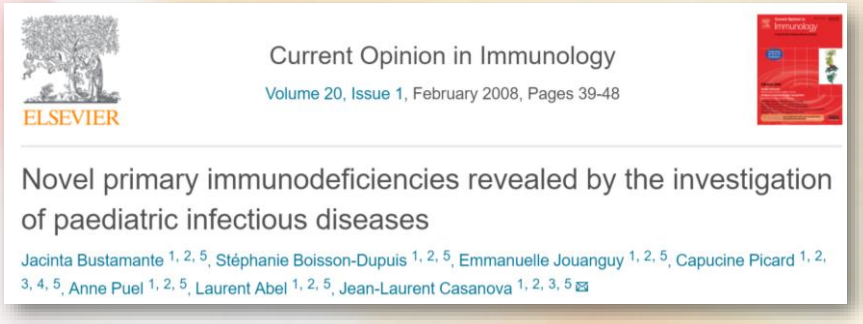
Herpes Simplex Virus Encephalitis in Human UNC-93B Deficiency
Casrouge et al, Science 2006

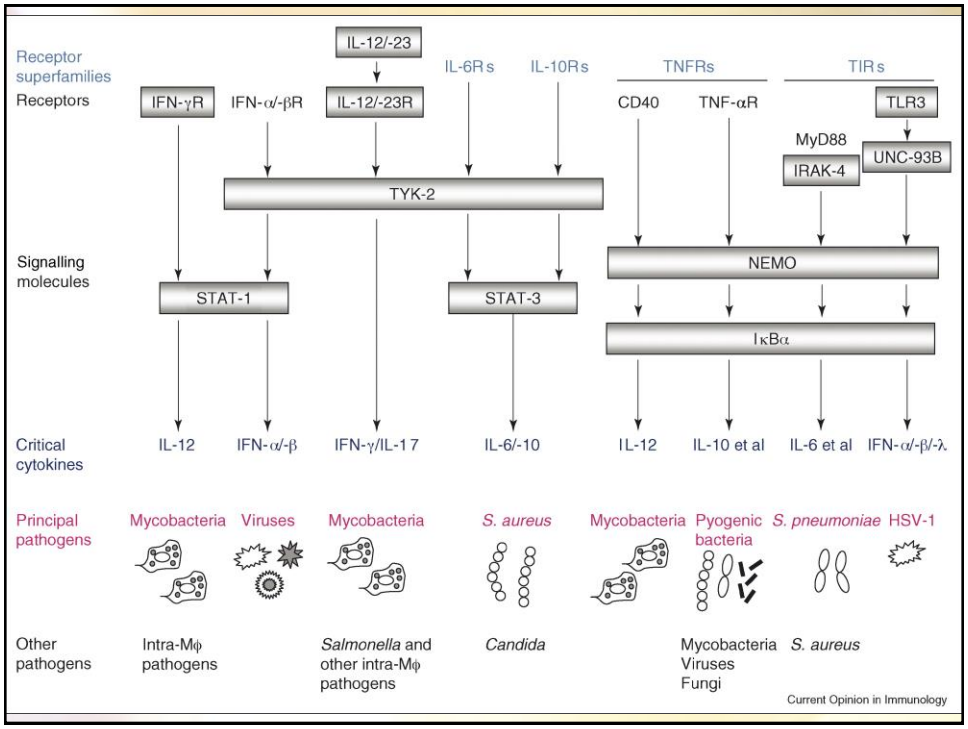
UNC-93B brist:

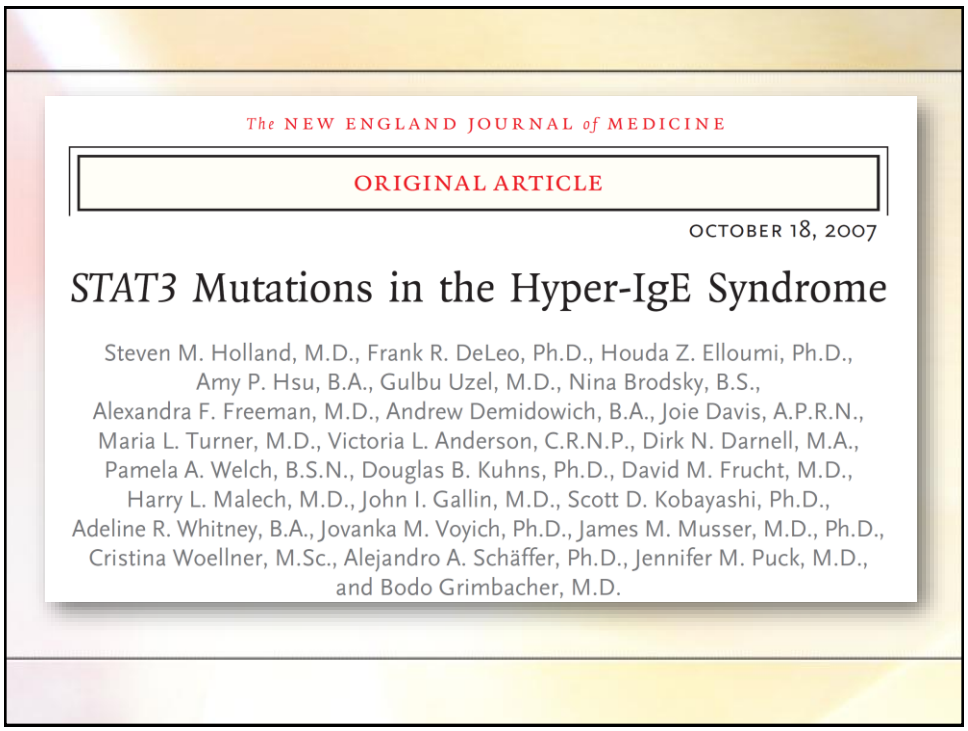
- Caused by autosomal recessive mutation on *UNC-93B1*
- Leads to greatly reduced production of IFN α / β needed to fight HSV-1 infection
- Defense against other viruses or bacteria not affected

ONE gene defect causes defect immunity against **ONE** pathogen

Herpes Simplex Virus Encephalitis in Human UNC-93B Deficiency
Casrouge et al, Science 2006

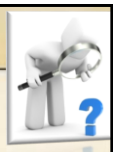



Receptor superfamilies
Receptors
IFN-γR
IFN-α/-βR
IL-12/-23
IL-12/-23R
IL-6Rs
IL-10Rs
TNFRs
CD40
TNF-αR
TIRs
TLR3
MyD88
IRAK-4
UNC-93B
TYK-2
Signalling molecules
STAT-1
STAT-3
NEMO
IκBα
Critical cytokines
IL-12
IFN-α/-β
IFN-γ/IL-17
IL-6/-10
IL-12
IL-10 et al
IL-6 et al
IFN-α/-β/-λ
Principal pathogens
Mycobacteria
Viruses
Mycobacteria
S. aureus
Mycobacteria
Pyogenic bacteria
S. pneumoniae
HSV-1
Other pathogens
Intra-Mφ pathogens
Salmonella and other intra-Mφ pathogens
Candida
Mycobacteria
Viruses
Fungi
S. aureus
Current Opinion in Immunology


The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
OCTOBER 18, 2007
STAT3 Mutations in the Hyper-IgE Syndrome
Steven M. Holland, M.D., Frank R. DeLeo, Ph.D., Houda Z. Elloumi, Ph.D., Amy P. Hsu, B.A., Gulbu Uzel, M.D., Nina Brodsky, B.S., Alexandra F. Freeman, M.D., Andrew Demidowich, B.A., Joie Davis, A.P.R.N., Maria L. Turner, M.D., Victoria L. Anderson, C.R.N.P., Dirk N. Darnell, M.A., Pamela A. Welch, B.S.N., Douglas B. Kuhns, Ph.D., David M. Frucht, M.D., Harry L. Malech, M.D., John I. Gallin, M.D., Scott D. Kobayashi, Ph.D., Adeline R. Whitney, B.A., Jovanka M. Voyich, Ph.D., James M. Musser, M.D., Ph.D., Cristina Woellner, M.Sc., Alejandro A. Schäffer, Ph.D., Jennifer M. Puck, M.D., and Bodo Grimbacher, M.D.

Why is this paper important?

Gene defect in Hyper-IgE syndrome identified



Background:

Hyper-IgE *(Job's yndrome)*

- Recurrent "cold" skin abscesses (usually with staphylococci), other organs can also be affected
- Recurrent pneumonias (can lead to cysts / pneumatocele)
- Eczema
- Skeletal problems - pathologic fractures, scoliosis, hyperextensibility,
- delayed dental deciduation
- Coronary-artery aneurysms
- Eosinophilia
- Very high IgE levels

Can all these be explained by ONE gene defect?

STAT3 Mutations in the Hyper-IgE Syndrome
Holland et al, N Engl J Med 2007

Method:

50 patients, 48 realtives och 158 healthy controlsr

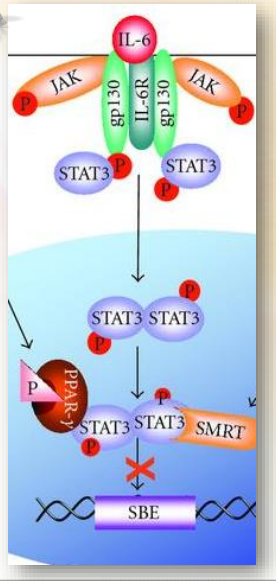
Table 1. Stimulated Cytokine Production in Leukocytes from Patients with the Hyper-IgE Syndrome and in Those from Controls.*

Analyte and Stimulus	Patient	Control	P Value
	pg/ml		
TNF-α			
Unstimulated (LPS)	17.9±6.6 (N=38)	54.3±20.8 (N=32)	0.23
LPS	1368.0±192.3 (N=38)	597.3±86.8 (N=32)	0.003
LPS + interferon-γ	4244.0±382.5 (N=38)	3044.0±311.9 (N=32)	0.02
Unstimulated (SAC)	19.7±8.0 (N=31)	68.1±27.3 (N=24)	0.22
SAC	5651.0±519.9 (N=31)	2404.0±397.3 (N=24)	<0.001
HKLM	2807.0±364.8 (N=30)	862.4±101.7 (N=12)	<0.001
Interleukin-12p70			
Unstimulated	5.8±0.7 (N=31)	10.3±3.4 (N=24)	0.77
LPS	36.5±6.3 (N=30)	12.9±2.7 (N=23)	0.001
LPS + interferon-γ	837.1±132.2 (N=31)	385.3±93.0 (N=24)	0.003
Interferon-γ			
Unstimulated	36.4±4.5 (N=31)	43.7±7.4 (N=25)	0.75
PHA	127,610.0±17,956.0 (N=27)	71,238.0±11,382.0 (N=24)	0.03
PHA + interleukin-12	158,823.0±14,900.0 (N=29)	102,820.0±20,715.0 (N=23)	0.03
MCP-1			
Unstimulated	346.4±263.3 (N=10)	252.5±145.6 (N=6)	0.07
Interleukin-6	1761.0±878.7 (N=10)	4494.0±649.3 (N=6)	0.03

- The defect causes cytokine "storm"
- Defect signaling via IL-6

STAT3 Mutations in the Hyper-IgE Syndrome
Holland et al, N Engl J Med 2007

Resultat



- Signaling through JAK, IL-6R and gp130 were normal
- ⇩
- Defect must be on STAT3

STAT3 Mutations in the Hyper-IgE Syndrome
Holland et al, N Engl J Med 2007

Resultat

ALL 50 patients had defect on STAT3

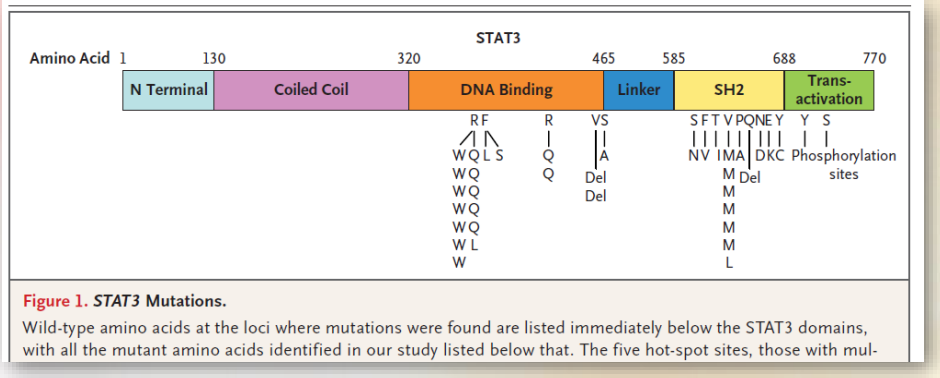


Figure 1. *STAT3* Mutations.
Wild-type amino acids at the loci where mutations were found are listed immediately below the STAT3 domains, with all the mutant amino acids identified in our study listed below that. The five hot-spot sites, those with mul-

STAT3 Mutations in the Hyper-IgE Syndrome
Holland et al, N Engl J Med 2007

STAT3 mutation explains :

- The predilection for skin and lung abscesses due to impaired defensin production and decreased inflammation (mediated via IL6)
- Destructive inflammation in the lung, leading to pneumatoceles
- Eosinophilia
- Skeletal problems (due to osteoclast activation)
- Coronary-artery aneurysms (due to increased production of TNF-α in the cardiac myocytes)

STAT3 Mutations in the Hyper-IgE Syndrome
Holland et al, N Engl J Med 2007

Letter

Nature **448**, 1058-1062 (30 August 2007) | doi:10.1038/nature06096;
Published online 5 August 2007; Corrected 30 August 2007

Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome

Yoshiyuki Minegishi[1], Masako Saito[1], Shigeru Tsuchiya[2], Ikuya Tsuge[3], Hidetoshi Takada[4], Toshiro Hara[4], Nobuaki Kawamura[5], Tadashi Ariga[5], Srdjan Pasic[6], Oliver Stojkovic[7], Ayse Metin[8] & Hajime Karasuyama[1]

ARTICLE LINKS
- Figures and tables
- Supplementary info

ARTICLE TOOLS
- Send to a friend
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- Found that 8 of 15 patients with HIES had *STAT3* mutation

CLINICAL TRIALS AND OBSERVATIONS blood BLOOD, 1 JANUARY 2008 • VOLUME 111, NUMBER 1

The EUROclass trial: defining subgroups in common variable immunodeficiency

Claudia Wehr,[1] Teemu Kivioja,[2] Christian Schmitt,[3] Berne Ferry,[4] Torsten Witte,[5] Efrem Eren,[6] Marcela Vlkova,[7] Manuel Hernandez,[8] Drahomira Detkova,[8] Philip R. Bos,[9] Gonke Poerksen,[10] Horst von Bernuth,[10] Ulrich Baumann,[11] Sigune Goldacker,[1] Sylvia Gutenberger,[1] Michael Schlesier,[1] Florence Bergeron-van der Cruyssen,[3] Magali Le Garff,[3] Patrice Debré,[3] Roland Jacobs,[5] John Jones,[4] Elizabeth Bateman,[4] Jiri Litzman,[7] P. Martin van Hagen,[9] Alessandro Plebani,[12] Reinhold E. Schmidt,[5] Vojtech Thon,[7] Isabella Quinti,[13] Teresa Espanol,[8] A. David Webster,[6] Helen Chapel,[4] Mauno Vihinen,[2,14] Eric Oksenhendler,[3] Hans Hartmut Peter,[1] and Klaus Warnatz[1]

Why is this paper important?

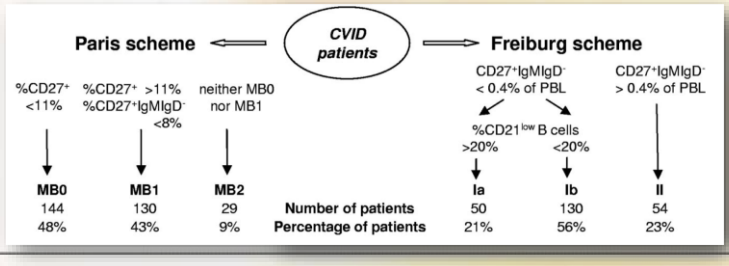
Describes a relation between B-cell populations and CVID phenotypes

Background:

- About 40% of CVID patients have GI problems, autoimmunity, lymphoproliferation, splenomegaly or granulomatous inflammation
- CD19+CD27+ = memory B cells (mB)
- CD19+CD27+IgD– = "switched" memory B cells (smB)
  - express IgG, IgA, eller IgE
  - marker for B-cell activation and development in the germinal centers

Bakgrund:

- CVID classification by B-cell phenotypes:
  - Freiburg "panel" (2002)
    - 3 groups – smB och % CD21^{low}
  - Paris "panel" (2003)
    - 3 groups - mB och smB



The EUROclass trial: defining subgroups in common variable immunodeficiency
Wehr et al, BLOOD 2008

Method:

- 8 immunodeficienty centers in Europe
- **303** patients with CVID (ESID criteria)

Table 1. Epidemiologic data (n = 303)

Characteristics	Clinical data
Sex	169 females, 133 males
Year of birth (± SD)	1957 (± 17)
Age at onset, y (± SD)	27 (± 17)
Age at diagnosis	35 (± 16)
Splenomegaly, %	40.5
Lymphadenopathy, %	26.2
Granulomatous disease, %	11.6
Autoimmune phenomena, %	20.3
Autoimmune cytopenia, %	20.2

The EUROclass trial: defining subgroups in common variable immunodeficiency
Wehr et al, BLOOD 2008

- The symptoms overlap

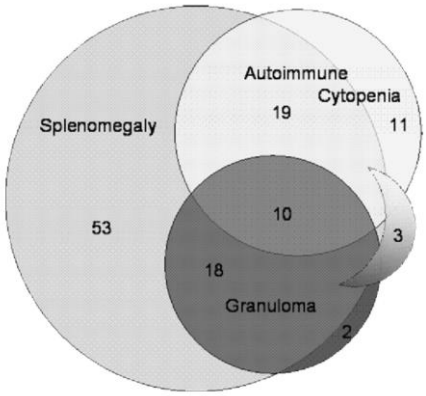
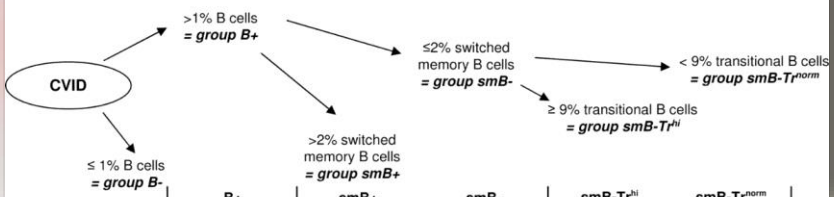


Figure 1. Coincidence of granulomatous disease and autoimmune cytopenia with splenomegaly in patients with CVID.

The EUROclass trial: defining subgroups in common variable immunodeficiency
Wehr et al, BLOOD 2008

smB- is a marker of impaired development in the germinal center

A **European consensus classification for CVID: EUROClass**



	B+	smB+	smB-	smB-Tr^{hi}	smB-Tr^{norm}
Number of patients	303	127 42% of total	176 58% of total	25 19% of smB-	108 81% of smB-
Incidence of (%)					
splenomegaly	115/284 pts./ 41%	28/116 pts./ 24%	**87/168 pts./ 52%***	13/24 pts./ 54%	55/107 pts./ 51%
lymphadenopathy	68/260 pts./26%	23/106 pts./ 22%	45/154 pts./ 24%	**12/21 pts./ 57%‡**	21/95 pts./ 22%
granuloma	35/303 pts./12%	5/127 pts./ 4%	**30/176 pts./ 17%+**	6/25 pts./ 24%	17/108 pts./ 16%
autoimmune cytopenia	43/213 pts./ 20%	22/117 pts./ 19%	36/169 pts./ 21%	4/21 pts./ 19%	24/93 pts./ 26%

?

The EUROclass trial: defining subgroups in common variable immunodeficiency
Wehr et al, BLOOD 2008

B

>1% B cells
= group B+

>2% switched memory B cells
= group smB+

≤2% switched memory B cells
= group smB-

≥ 10% CD21^{low} B cells
= group smB+21^{lo}

< 10% CD21^{low} B cells
= group smB+21^{norm}

≥ 10% CD21^{low} B cells
= group smB-21^{lo}

< 10% CD21^{low} B cells
= group smB-21^{norm}

smB+21^{lo}	smB+21^{norm}		smB-21^{lo}	smB-21^{norm}
29 33% of smB+	60 67% of smB+	Number of patients	69 49% of smB-	71 51% of smB-
		Incidence of (%)		
13/26 pts./ 50%§	8/57 pts./ 14%	splenomegaly	41/68 pts./ 60%¶	30/71 pts./ 42%
4/23 pts./ 17%	10/50 pts./ 20%	lymphadenopathy	24/63 pts./ 38%	15/61 pts./ 25%
4/29 pts./ 14%‖	1/60 pts./ 2%	granuloma	14/69 pts./ 20%#	11/71 pts./ 15%
3/20 pts./ 15%	4/40 pts./ 10%	autoimmune cytopenia	16/60 pts./ 27%	14/59 pts./ 24%

?

The EUROclass trial: defining subgroups in common variable immunodeficiency
Wehr et al, BLOOD 2008

smB-

- Serum IgA and IgG levels were significantly lower in this group
- Patients have a higher incidence of splenomegaly and granulomatous disease
- A subgroup with a strong expansion of transitional B cells could be identified - more than 50% of the patients presented with lymphadenopathy

CD21^{low}

- This grouping demonstrates the best discrimination of patients with splenomegaly and granulomatous disease
- Patients in group smB- 21^{lo} and smB+ 21^{lo} had a significant later onset and diagnosis than other patients

The EUROclass trial: defining subgroups in common variable immunodeficiency
Wehr et al, BLOOD 2008

Clinical Immunology (2010) 137, 21–30

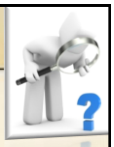
available at www.sciencedirect.com

Clinical Immunology

www.elsevier.com/locate/yclim

Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies

Jordan S. Orange [a,*], William J. Grossman [b], Roberta J. Navickis [c], Mahlon M. Wilkes [c]



Why is this paper important?

IgG trough levels required to minimize infection risk are to be established

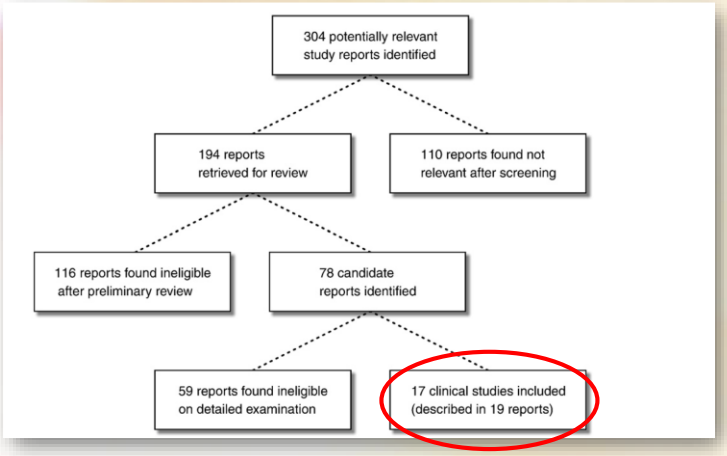
Background:

- IVIG = high doses of IgG can be given
- A study from '82 showed that 93 mg/kg/4w and a trough of 2,93 g/l was enough to avoid penumonias...
- In the 80's - 100-200 mg/kg/month
- 90's- och 00's several publications where IgG through of 5 g/l were considered enough

Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies
Orange et al, Clincal immunology 2010

Method:

Medline + Cochrane 2009

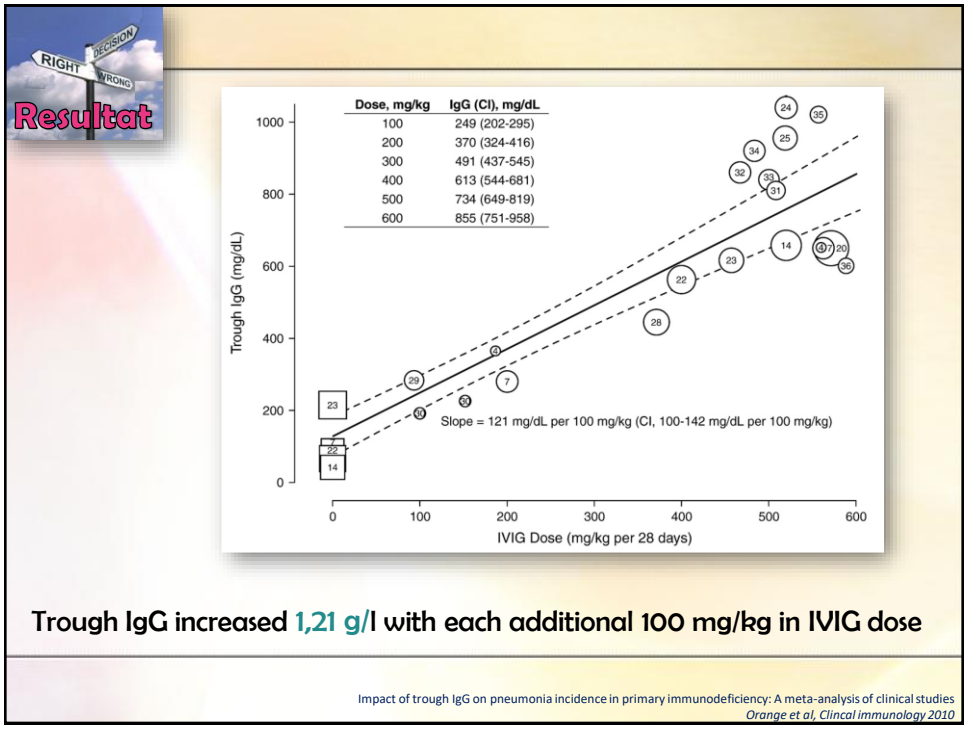


Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies
Orange et al, Clincal immunology 2010

Table 2 Types of PIDD in included clinical studies.

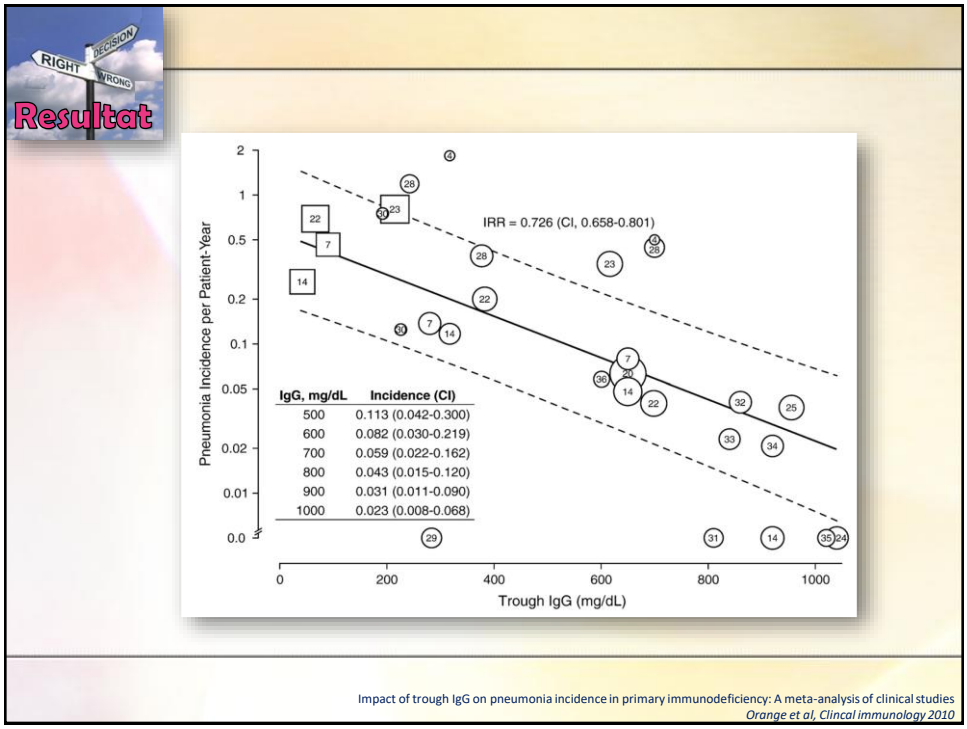
Study	CVID	XLA	AGG	HIM	SD	Other	Total
Ammann et al., 1982 [29]	24	7		3			34
Schiff et al., 1984 [30]	12	2		2			16
Roifman et al., 1987 [4–6]	10	2					12
Liese et al., 1992 [7]		29					29
Quartier et al., 1999 [14]		31					31
Chapel et al., 2000 [31]	18				10	2 [a]	30
Plebani et al., 2002 [20]		73					73
Aghamohammadi et al., 2004 [22]		5	18				23
Berger and Pinciaro, 2004 [32]	37	12	1	1			51
Ochs and Pinciaro, 2004 [33]	28	13		2	1	2 [b]	46
Bayrakci et al., 2005 [28]	20	19		7			46
Church et al., 2006 [24]	22	5		1	1	32 [c]	61
Pourpak et al., 2006 [23]	26						26
Berger, 2007 [34]	35	10				1 [d]	46
Berger et al., 2007 [35]	32	10					42
Krasovec et al., 2007 [36]	10	14	1 [e]			5 [f]	30
Stein et al., 2009 [25]	59	21					80
Total	333	253	20	16	12	42	676

Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies
Orange et al, Clincal immunology 2010



Trough IgG increased 1,21 g/l with each additional 100 mg/kg in IVIG dose

Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies
Orange et al, Clincal immunology 2010



Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies
Orange et al, Clincal immunology 2010

Pneumonia incidence declined by 27% with each 1 g/l increment in trough IgG

Pneumonia incidence with maintenance of 5 g/l IgG trough levels was 5-fold of that with 10 g/l

Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies
Orange et al, Clincal immunology 2010

NATURE REVIEWS | IMMUNOLOGY
VOLUME 12 | MARCH 2012 |

Standardizing immunophenotyping for the Human Immunology Project

Holden T. Maecker[1], J. Philip McCoy[2,3] and Robert Nussenblatt[3,4]

Why is this paper important?

Describes the current state of the flow cytometry standardization process

Summarizes the steps required to enable the Human Immunology Project

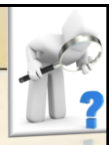
Background :

"... whereas the information content of immunophenotyping assays has grown exponentially in recent years, their level of standardization has not..."

" ... even well-characterized subsets, such as naive and memory T cells, are defined differently in various studies..."

Standardizing immunophenotyping for the Human Immunology Project
Maecker et al. Nat Rev Immunol 2012

The Human Immunology Project

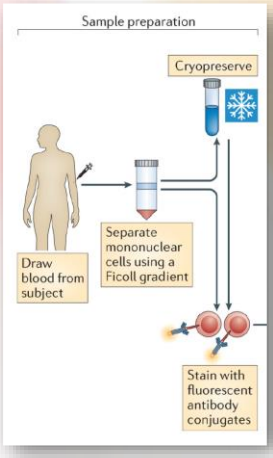


- Consortium program of the NIAID Division of Allergy, Immunology, and Transplantation
- Well-characterized human cohorts are studied using a variety of modern analytic tools

✓ **Consensus regarding markers and definitions, leading to a standardized immunophenotyping panel for human immune monitoring**

✓ **Define profiles/signatures/fingerprints of steady-state and activated human immune system**

Standardizing immunophenotyping for the Human Immunology Project
Maecker et al. Nat Rev Immunol 2012



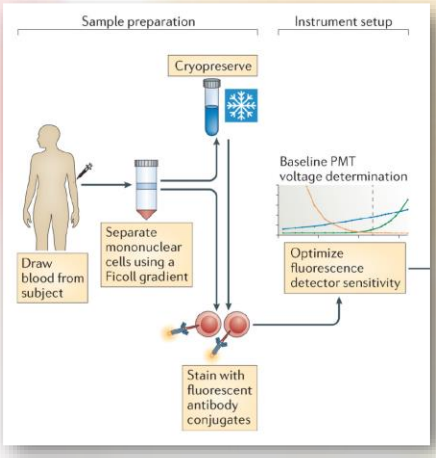
Reagens

- Definition of standard antibody panels for immunophenotyping

Blodprov

- Sample handling
- Training of sites to cryopreserve PBMCs and/or to do staining on-site

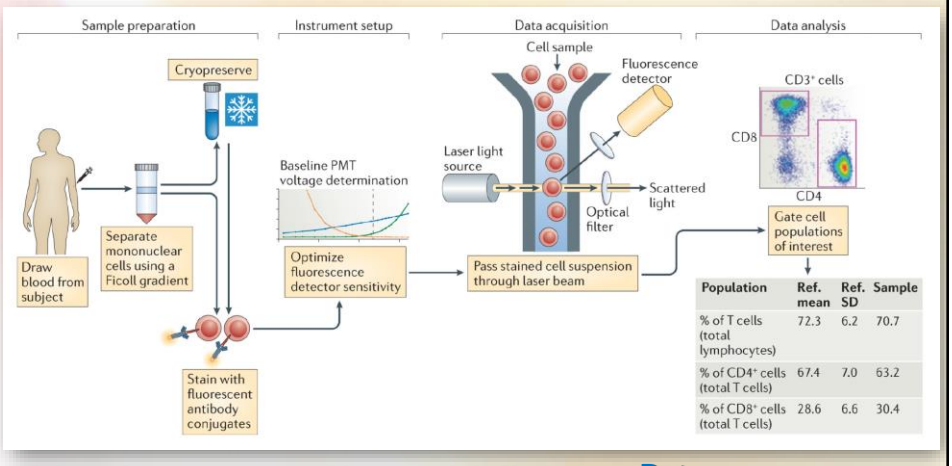
Standardizing immunophenotyping for the Human Immunology Project
Maecker et al. Nat Rev Immunol 2012



Instrument

- Use of software for **automated setting** of voltage gains
- Setting the fluorescence of standard beads to defined target channels, for **reproducible setup** across instruments

Standardizing immunophenotyping for the Human Immunology Project
Maecker et al. Nat Rev Immunol 2012



Data

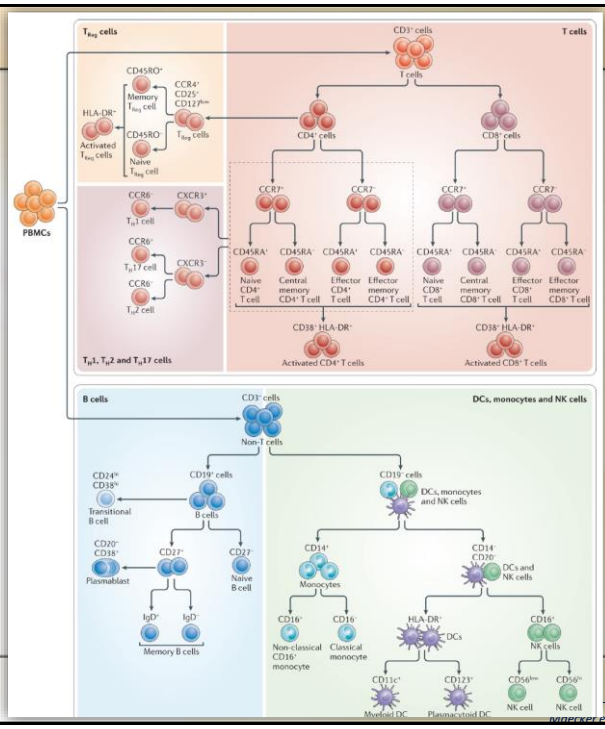
- Central analysis by one or a few coordinated experts
- Use of automated gating algorithms

Standardizing immunophenotyping for the Human Immunology Project
Maecker et al. Nat Rev Immunol 2012

Eight-colour antibody panels proposed by the Human Immunophenotyping Consortium

Fluorochrome	Marker				
	T cells	T_{Reg} cells	T_H1, T_H2 and T_H17 cells	B cells	DCs, monocytes and NK cells
FITC	Live or dead	Live or dead	Live or dead	Live or dead	Live or dead
PE	CCR7	CD25	CXCR3	CD24	CD56
PerCP-Cy5.5	CD4	CD4	CD4	CD19	CD123
PE-Cy7	CD45RA	CCR4	CCR6	CD27	CD11c
APC	CD38	CD127	CD38	CD38	CD16
APC-H7	CD8	CD45RO	CD8	CD20	CD3, CD19 and CD20
V450	CD3	CD3	CD3	CD3	CD14
V500	HLA-DR	HLA-DR	HLA-DR	IgD	HLA-DR

Standardizing immunophenotyping for the Human Immunology Project
Maecker et al. Nat Rev Immunol 2012



Human Immunology Project
Jappenneau et al, Nat Rev Immunol 2012

TRANSPLANTATION — blood — BLOOD, 1 DECEMBER 2001 • VOLUME 98, NUMBER 12

Durable engraftment of major histocompatibility complex–incompatible cells after nonmyeloablative conditioning with fludarabine, low-dose total body irradiation, and posttransplantation cyclophosphamide

Leo Luznik, Sanju Jalla, Laura W. Engstrom, Robert Iannone, and Ephraim J. Fuchs

Bone Marrow Transplantation

2008 October ; 42(8): 523–527. doi:10.1038/bmt.2008.203.

Reduced intensity HLA-haploidentical BMT with post transplantation cyclophosphamide in nonmalignant hematologic diseases

RA Brodsky[1,2], **L Luznik**[2], **J Bolaños-Meade**[2], **MS Leffell**[3], **RJ Jones**[1,2], and **EJ Fuchs**[2]

Why are these papers important?

First publication about haplotransplantation

Bakgrund:

- Transplantationer with HLA-identical donor were ”rutin”
- However ~ 40% of patients lack matching donor…
- Haplotransplantation is associated with many serious risks:

  GVHD, graft-rejection, toxicity of the myeloablative agents etc.

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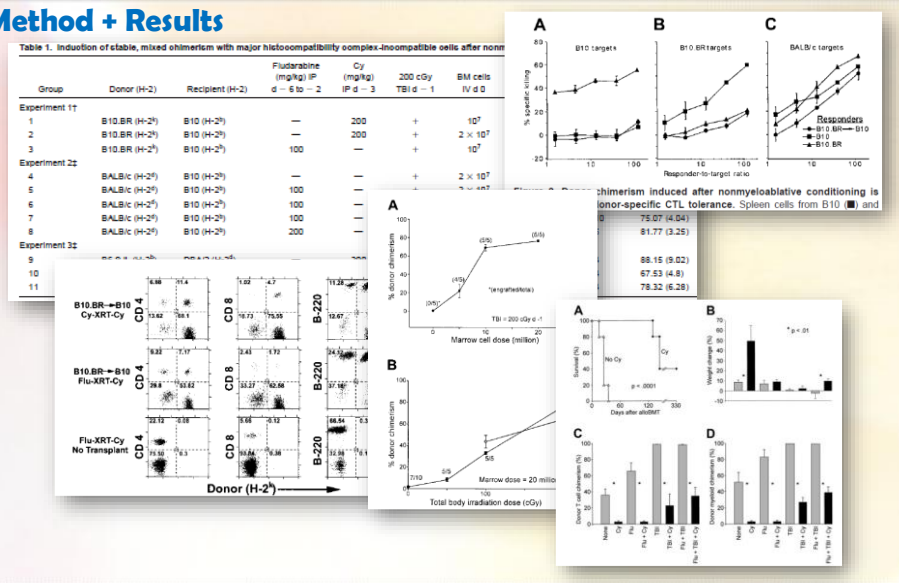
Luznik, *et al*, *Blood 2001*

Method + Results



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"...these results indicate that stable engraftment of MHC-incompatible cells can be induced after fludarabine based, nonmyeloablative conditioning..."

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"...nonmyeloablative, HLA-haploidentical BMT with post-transplant cyclophosphamide is a **promising approach for patients with life-threatening nonmalignant hematologic disease** who lack an HLA-matched sibling donor..."

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Brodsky et al, *Bone Marrow Transplant 2008*