Garvan Institute
of Medical Research

T helper 2 (Th2) and B cells in atopic dermatitis

- learning from inborn errors of immunity

Rajka symposium (ISAD) 2025

Prof Cindy Ma

Experiments of Nature: Inborn errors of Immunity

Garvan Institute of Medical Research

- Are human knock-outs
- Caused by monogenic mutations in key genes
  - result in loss or gain of function
- Compromised immune system
  - severe/recurrent infections
  - allergy/atopic disease
  - autoimmunity
  - Inflammation
  - cancer

Why study Inborn Errors of Immunity?

Garvan Institute of Medical Research

- Often not clear how gene defect results in clinical disease
- Aim: reveal how gene defects result in clinical disease.
  - Provide an explanation for disease pathogenesis
  - Facilitate diagnosis/therapy
  - Determine function of specific genes
  - Lead to development of novel therapies
- Studying rare disorders can provide insights into more common diseases that affect the general population
  - ie allergies, fungal infections (thrush), and viral infections.

Primary Atopic Disorders (PADs)

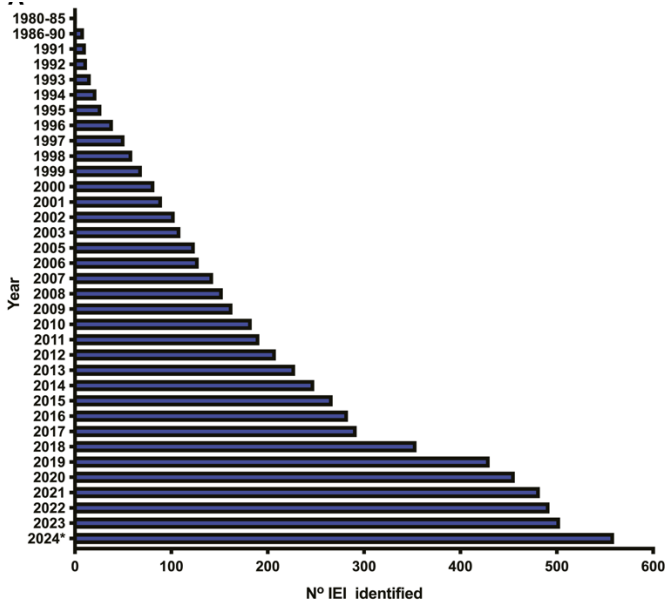
Garvan Institute of Medical Research

JHI Journal of Human Immunity

ARTICLE

Human inborn errors of immunity: 2024 update on the classification from the International Union of Immunological Societies Expert Committee

M. Cecilia Poli[1,2], Ivona Aksentijevich[3], Ahmed Aziz Bousfiha[4,5], Charlotte Cunningham-Rundles[6], Sophie Hambleton[7], Christoph Klein[8], Tomohiro Morio[9], Capucine Picard[10,11], Anne Puel[12,13,14], Nima Rezaei[15], Mikko R.J. Seppänen[16], Raz Somech[17], Helen C. Su[18], Kathleen E. Sullivan[19], Troy R. Torgerson[20], Isabelle Meyts[21]*, and Stuart G. Tangye[22,23]*



- 508 genes causing 559 inborn errors of immunity
- Primary Atopic Disorders refer to ~50 genes associated with atopic manifestations –
  - Early onset, treatment resistant eczema, eosinophilia, food anaphylaxis
- Recent reviews
  - Ma and Hsu *Immunol Rev* 2025
  - Vaseghi-Shanjani et al. *Curr Opin Immunol* 2025
  - James et al. *J Allergy Clin Immunol* 2024

Primary Atopic Disorders

Garvan Institute of Medical Research

- **Skin barrier**
  - **Structural proteins – filaggrin (*FLG*)**
  - **Intracellular adhesion molecules - corneodesmosin (*CDSN*), desmoplakin (*DSP*), desmoglein 1 (*DSG1*)**
  - **Protease inhibitors - *SPINK5***
- **Granulocyte dysregulation (increased mast cell degranulation)**
  - **phospholipase C gamma 2 (*PLCG2*), adhesion G protein-coupled receptor E2 (*ADGRE2*), *TPSAB1***
- **Actinopathies**
  - ***DOCK8*, *WASP*, *WIP*, *ARPC1B*, *NCKAP1L*, *STK4***

Primary Atopic Disorders

Garvan Institute of Medical Research

- **T-cell receptor signaling**
  - ***CARD11* (CARMA1), *BCL10*, *MALT1* – CBM-opathies**
  - **Hypomorphic *ZAP70*, *LAT***
- **Altered T cell receptor development**
  - ***RAG1/2*, *IL7RA*, Artemis, DNA ligase IV, adenosine deaminase**
- **Tregopathies**
  - ***FOXP3*, *CD25* (IL-2RA)/*STAT5B*, *CTLA4*/LRBA, *BACH2***
- **Metabolic defect**
  - ***PGM3***

Primary Atopic Disorders

Garvan Institute of Medical Research

- **Cytokine signaling**
  - ***IL12R*/*IFNGR*/TBX21**
  - ***TGFBR*, *ERBIN***
  - **JAKs/STATs (Gain-of-function *JAK1, STAT6;* Loss-of-function *STAT3*)**

- ***Overlap…***

Hyper IgE syndrome (HIES)

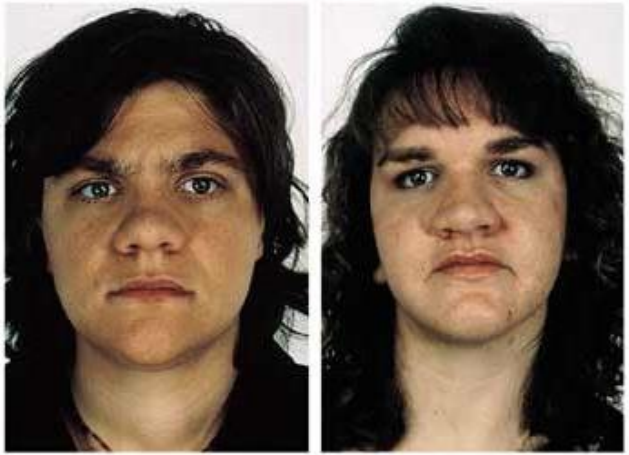
Garvan Institute of Medical Research

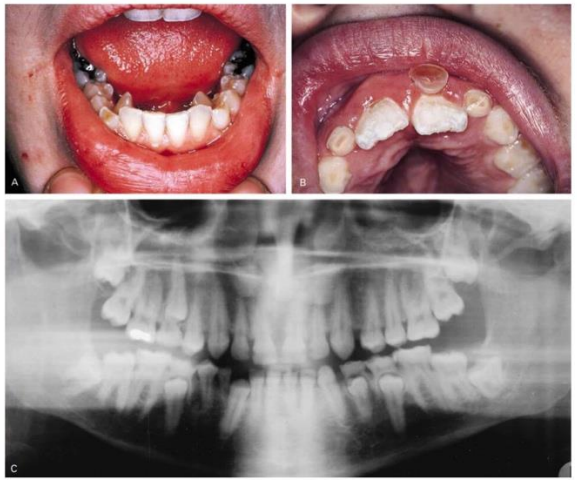
- Rare primary immunodeficiency: ~ 1 in 100,000
- Characterised by clinical triad:
  - Recurrent Staphylococcal and Candida skin abscesses (opportunistic infections)
  - Recurrent cyst-forming pneumonia (*S. aureus, S. pneumoniae, H. influenzae*)
  - Elevated serum IgE (> 10x): other Igs are normal but often lack Ag-specific Abs
  - Atopic disease – eczema and/or food allergies
- Autosomal dominant (AD) and autosomal recessive (AR) forms

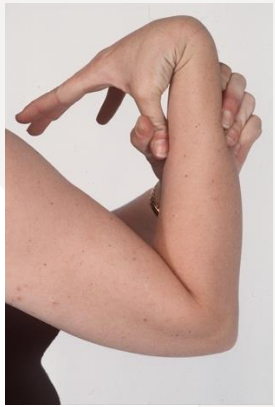
Autosomal dominant hyper IgE syndrome (AD-HIES)

Garvan Institute of Medical Research

- **AD-HIES is associated with skeletal symptoms**
  - typical HIES face, high palate, retained primary teeth, hyperextensibility of joints, scoliosis, osteoporosis, recurrent fractures
  - Defects not restricted to the immune system: connective tissue phenotypes







Grimbacher *et al*. 1999. *NEJM*

2007: AD-HIES is due to mutations in *STAT3*

Garvan Institute of Medical Research

nature Vol 448|30 August 2007|doi:10.1038/nature06096

LETTERS

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

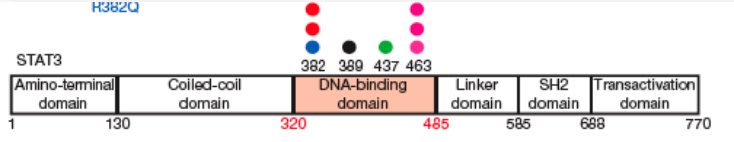
Yoshiyuki Minegishi[1], Masako Saito[1], Shigeru Tsuchiya[2], Ikuya Tsuge[3], Hidetoshi Takada[4], Toshiro Hara[4], Nobuaki Kawamura[5], Tadashi Ariga[5], Srdjan Pasic[6], Oliver Stojkovic[7], Ayse Metin[8] & Hajime Karasuyama[1]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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.



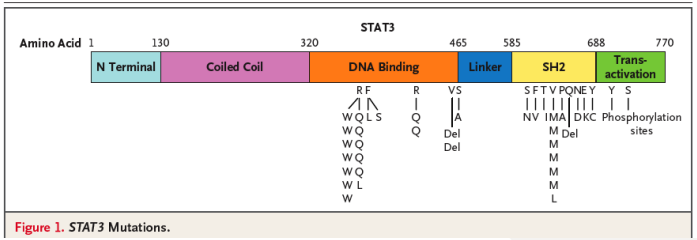
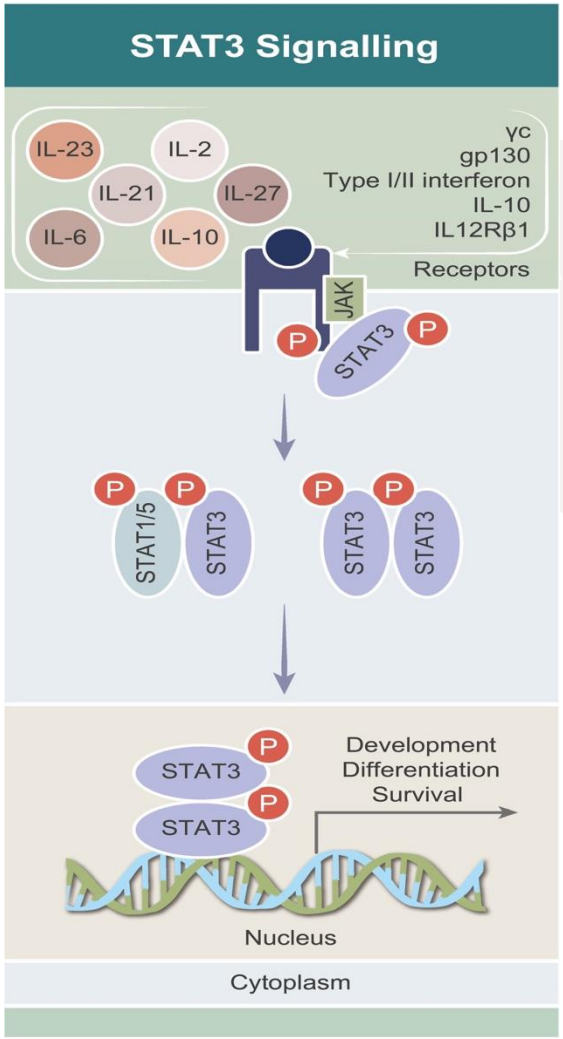


Figure 1. *STAT3* Mutations.



Garvan Institute of Medical Research

Mackie *et al*. 2023. *Clin Exp Immunol*

STAT3 activating cytokines

Garvan Institute of Medical Research

- ***IL-2/γc family of cytokines***
  - IL-2, IL-4, IL-7, IL-9, IL-15, *IL-21*
- ***IL-6/gp130 family***
  - *IL-6*, IL-11, IL-27, IL-31, LIF, oncostatin M, CNTF
- ***IL-10 family***
  - *IL-10*, IL-19, IL-20, IL-22, IL-24, IL-26
- ***IFN family***
  - IFN-γ, IFN-α/β, IL-28, IL-29
- ***CSF's***
  - G-CSF, M-CSF, Flt3L
- ***other***
  - IL-12, *IL-23*, EGF, leptin, growth hormone

STAT3 expression

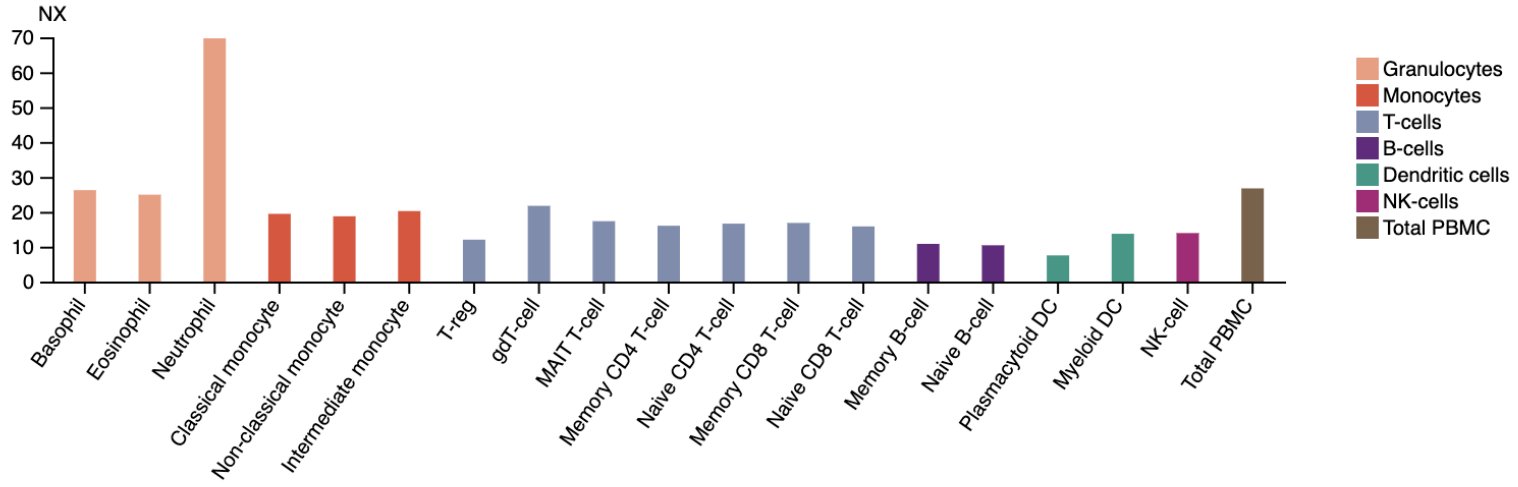
Garvan Institute of Medical Research

BLOOD CELL TYPE EXPRESSION (RNA)[i]

Consensus dataset[i]

RNA cell type specificity: Low cell type specificity

Lineage | Expression | Alphabetical



AD-HIES due to mutations in *STAT3*

Garvan Institute of Medical Research

How do defects in STAT3 explain the phenotype of AD-HIES patients?

1. **Opportunistic infections**
2. **Humoral (antibody) defects**
3. **Atopic disease**

AD-HIES due to mutations in *STAT3*

Garvan Institute of Medical Research

How do defects in STAT3 explain the phenotype of AD-HIES patients?

1. **Opportunistic infections**
2. **Humoral (antibody) defects**
3. **Atopic disease**

AD-HIES due to mutations in *STAT3*

Garvan Institute of Medical Research

How do defects in STAT3 explain the phenotype of AD-HIES patients?

1. **Opportunistic infections**
   - **$CD4^+$ T cell defect in generating Th17 cells (require STAT3-cytokines IL-6, IL-21, IL-23)**

   (Milner et al *Nature* 2008; Ma et al *JEM* 2008; de Beaucoudrey et al *JEM* 2008; Renner et al *JACI* 2008)
2. **Humoral (antibody) defects**
3. **Atopic disease**

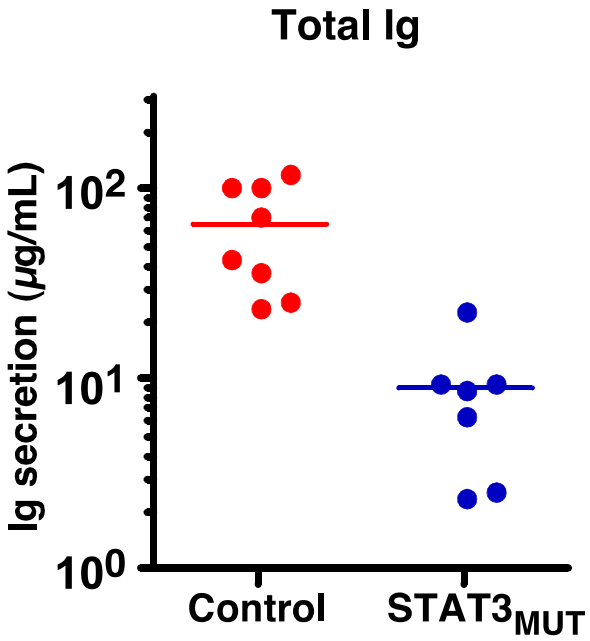
Garvan Institute of Medical Research

1. Opportunistic infections:
2. **Humoral defects:**
   - **STAT3 loss-of-function (LOF) patients have normal Ig levels but often lack Ag-specific Abs**
3. Atopic disease

STAT3 LOF B cells can secrete polyclonal, but not Ag-specific Ig *in vitro*

Garvan Institute of Medical Research

- polyclonally stimulate B cells *in vitro* for 7 days
- determine Ig secretion and Ag (tetanus) specific B cells

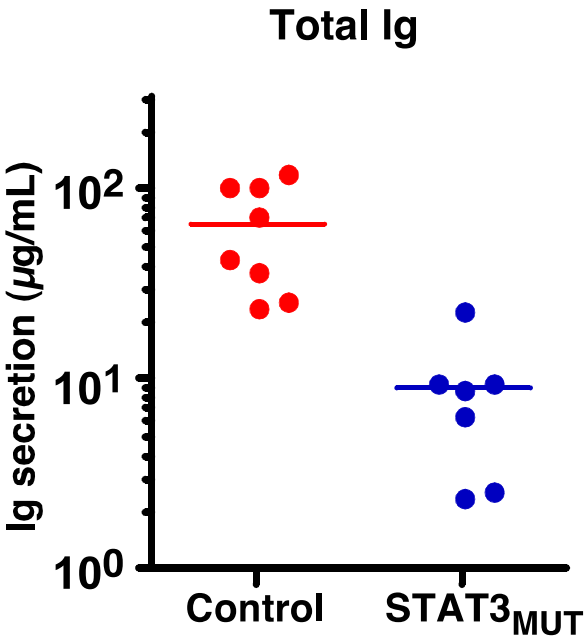


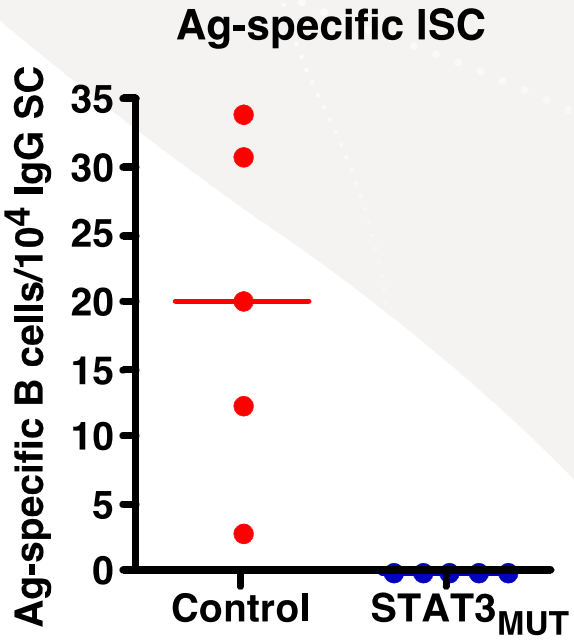
Avery *et al. 2010* JEM

STAT3 LOF B cells can secrete polyclonal, but not Ag-specific Ig *in vitro*

Garvan Institute of Medical Research

- polyclonally stimulate B cells *in vitro* for 7 days
- determine Ig secretion and Ag (tetanus) specific B cells

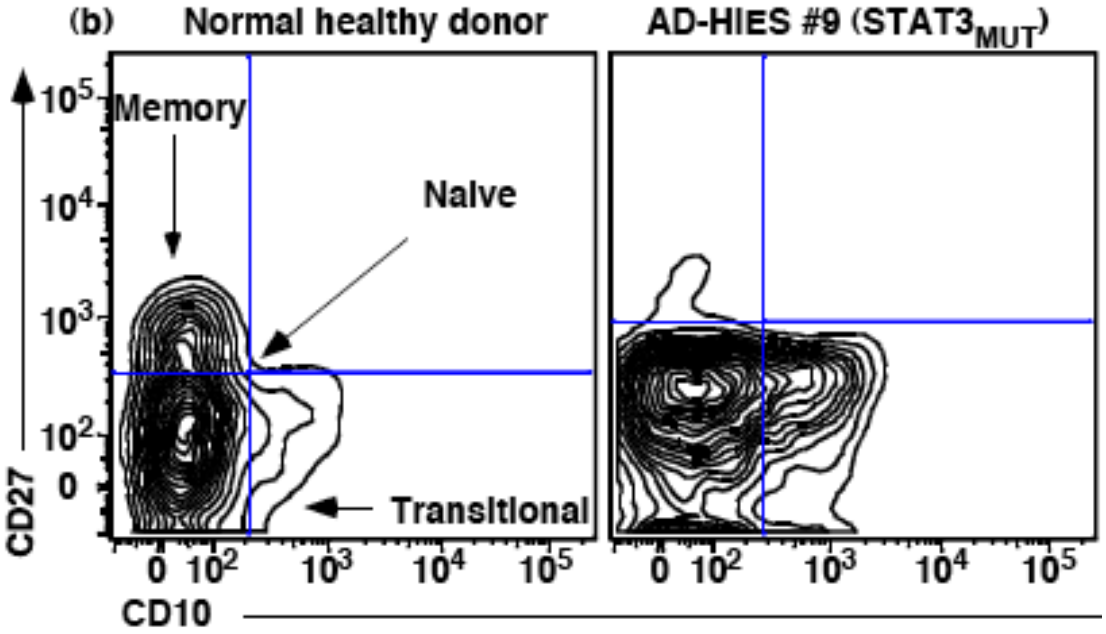


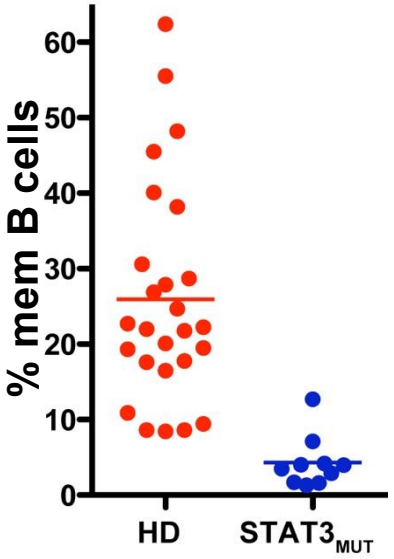


Avery *et al. 2010* JEM

STAT3 mutations impairs the generation of memory B cells

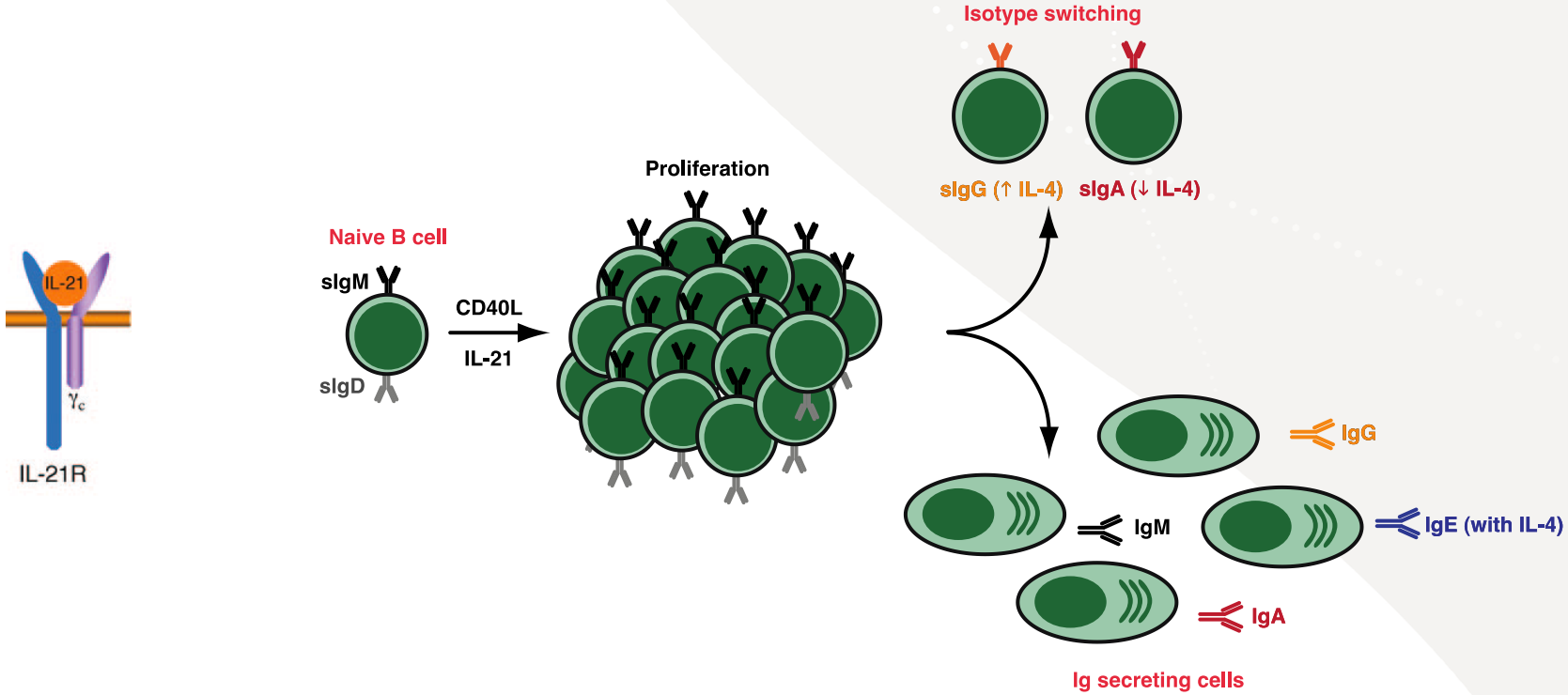
Garvan Institute of Medical Research





IL-21 is a potent inducer of human B cell differentiation

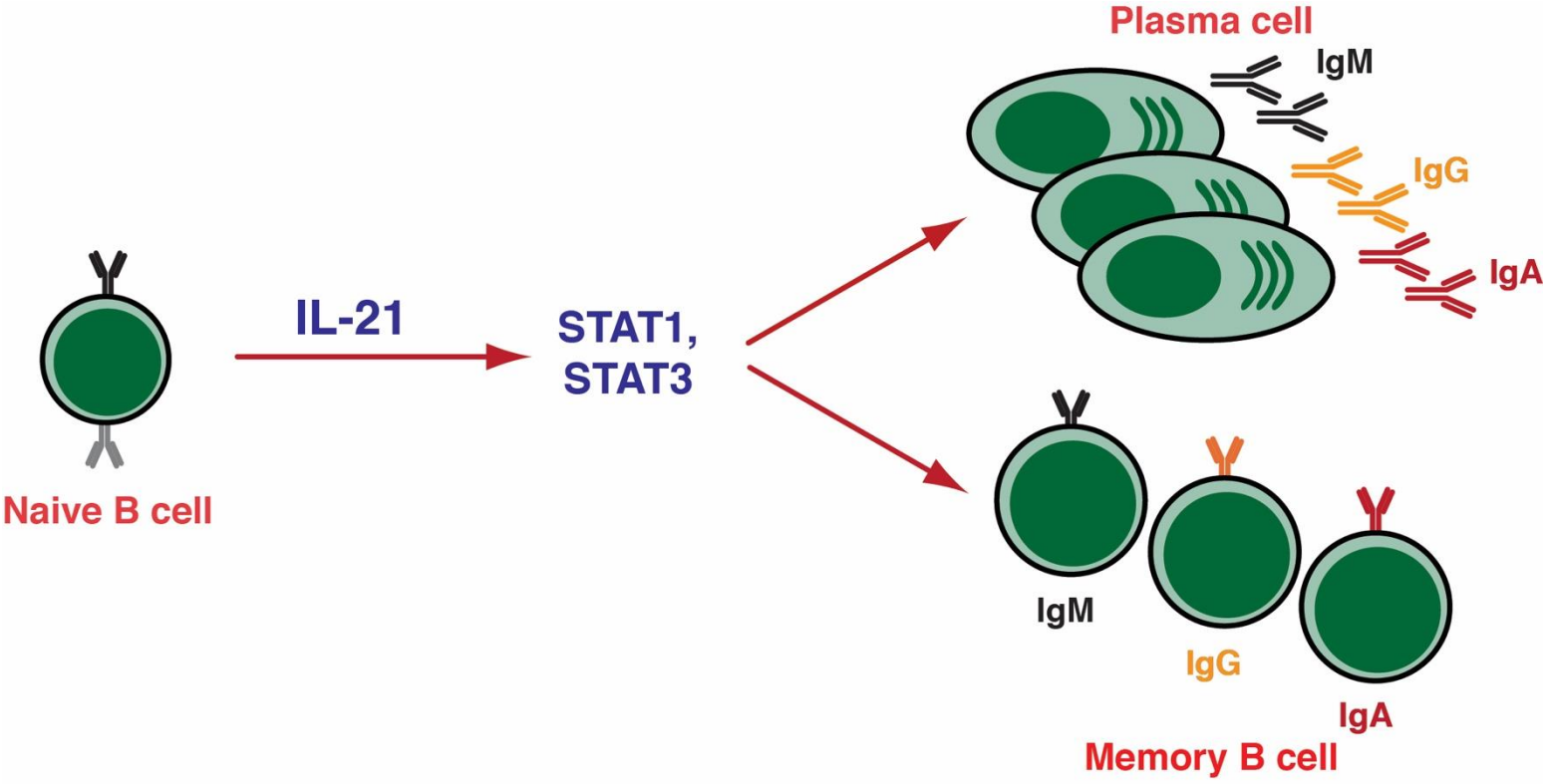
Garvan Institute of Medical Research



- Pene et al., 2004. J Immunol
- Ettinger et al., 2005. J Immunol
- Good et al., 2006. J Immunol
- Bryant et al., 2007. J Immunol
- Kuchen et al., 2007. J Immunol
- Avery et al., 2008. J Immunol
- Diehl et al., J Immunol 2008
- Avery et al., 2008. Blood
- Dullaers et al., 2009. Immunity

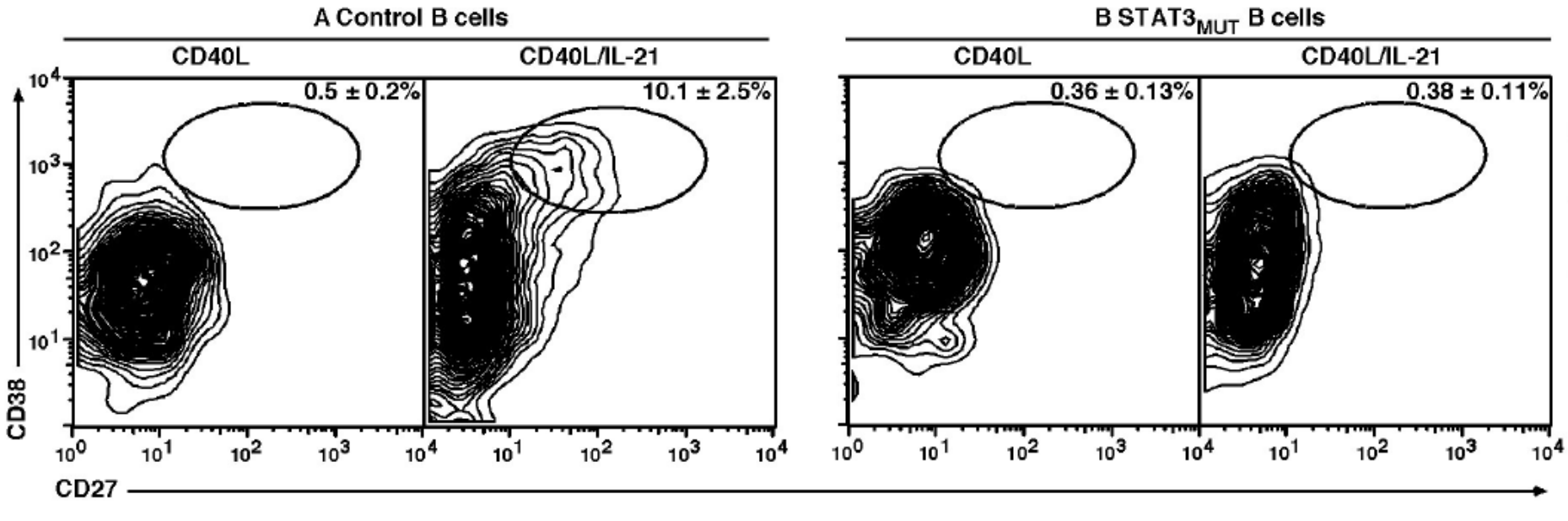
Q: Is IL-21 induced human B cell differentiation dependent on STAT3?

Garvan Institute of Medical Research



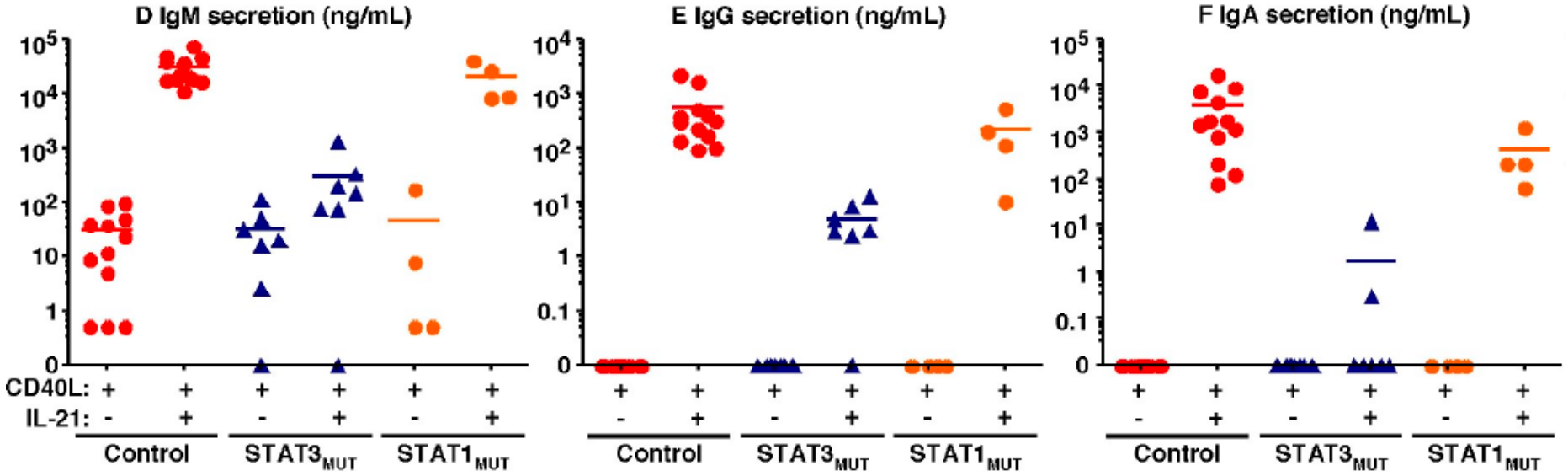
STAT3 is required for IL-21-mediated differentiation of naive B cells into CD38^{+}CD27^{+} plasmablasts

Garvan Institute of Medical Research



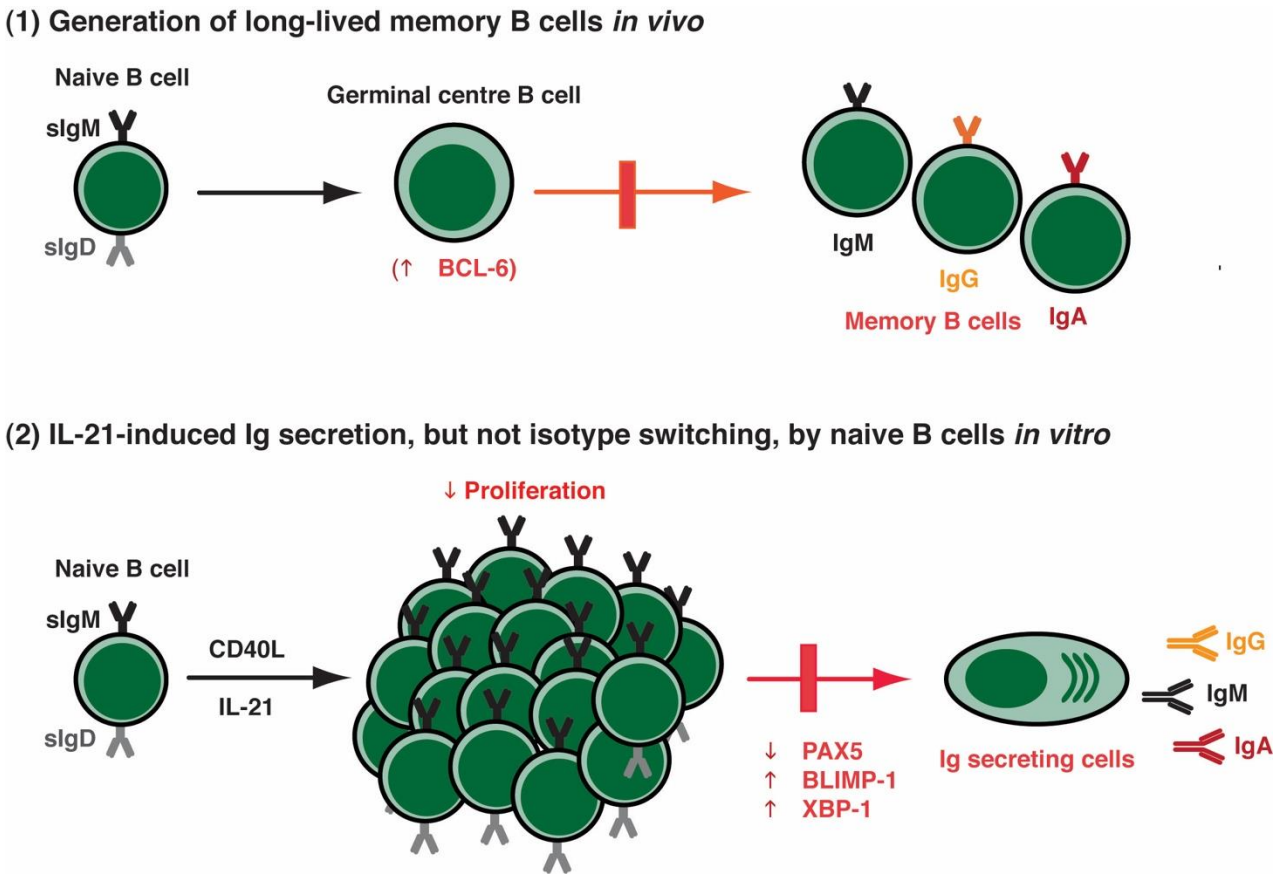
STAT3, but NOT STAT1, is required for IL-21-mediated differentiation of naive B cells into Ig-secreting cells

Garvan Institute of Medical Research



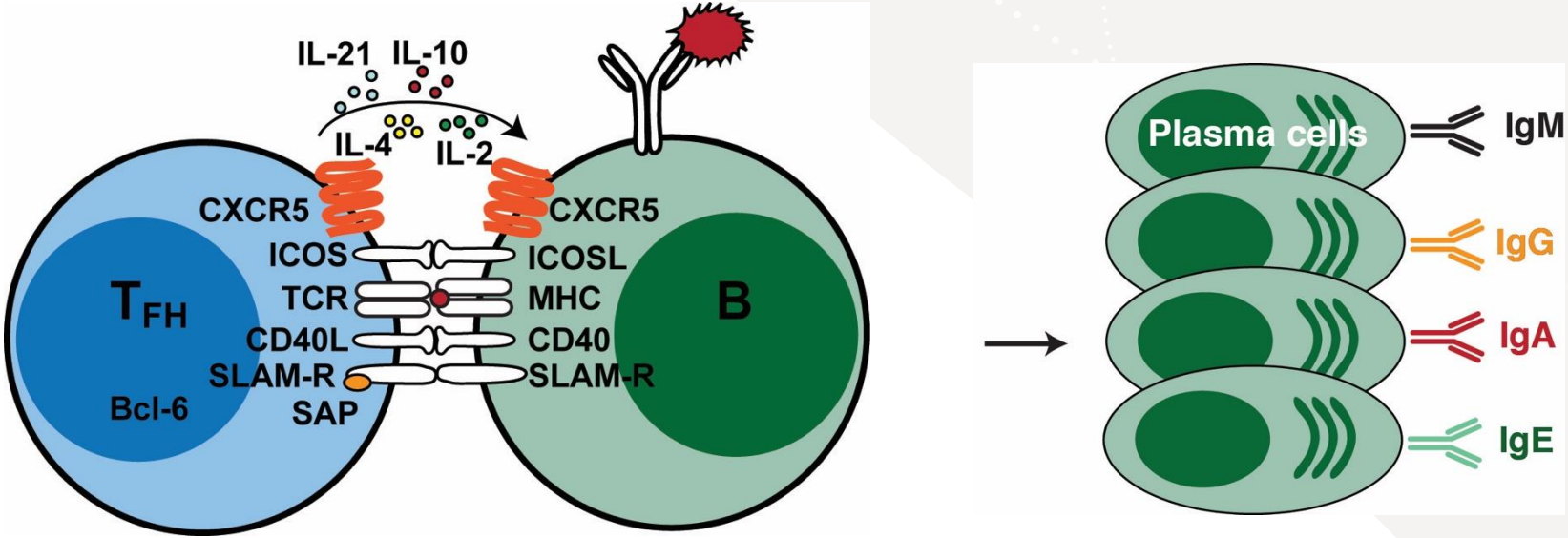
Roles of STAT3 in regulating B-cell responses

Garvan Institute of Medical Research

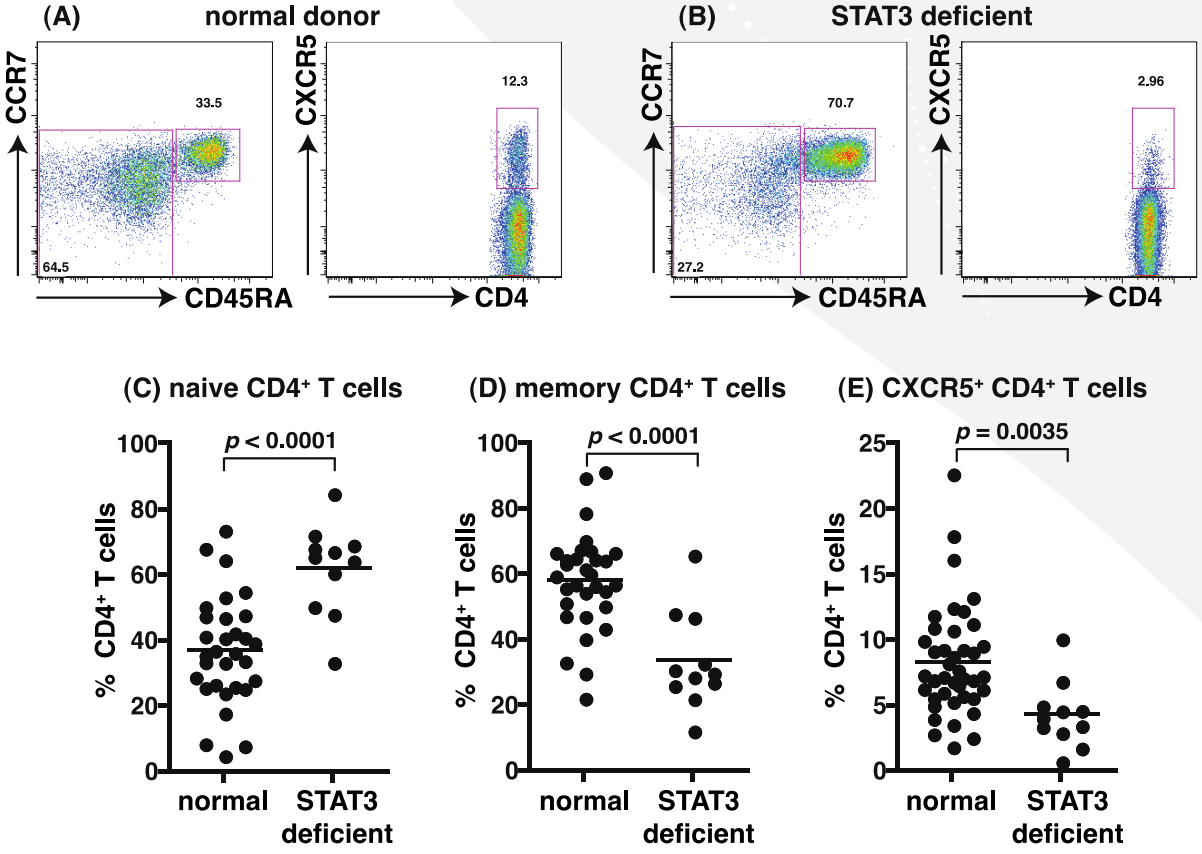


What about T follicular helper (Tfh) cells?

Garvan Institute of Medical Research

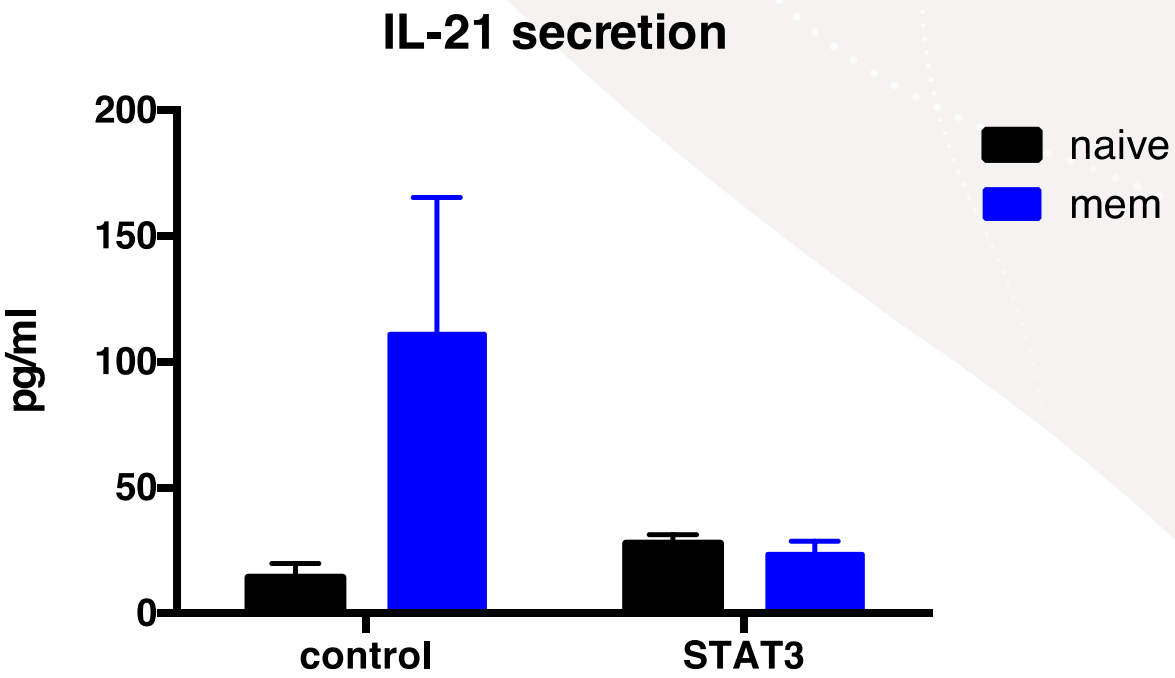


Decrease in CXCR5⁺CD4⁺ Tfh cells in STAT3 LOF patients



Defective secretion of IL-21 by STAT3 LOF memory CD4^{+} T cells *ex vivo*

Garvan Institute of Medical Research



AD-HIES due to mutations in *STAT3*

Garvan Institute of Medical Research

How do defects in STAT3 explain the phenotype of AD-HIES patients?

1. Opportunistic infections
2. Humoral (antibody) defects
   - B cell intrinsic: defect in generating memory/effector B cells
     - Requirement for IL-21 (Avery et al *JExpMed* 2010)
   - B cell extrinsic: defect in generating T follicular helper cells
     - Requirement for IL-6, IL-12, IL-21, IL-23, IL-27 (Ma et al *Blood* 2012; Batten et al *JExpMed* 2010)
3. Atopic disease

AD-HIES due to mutations in *STAT3*

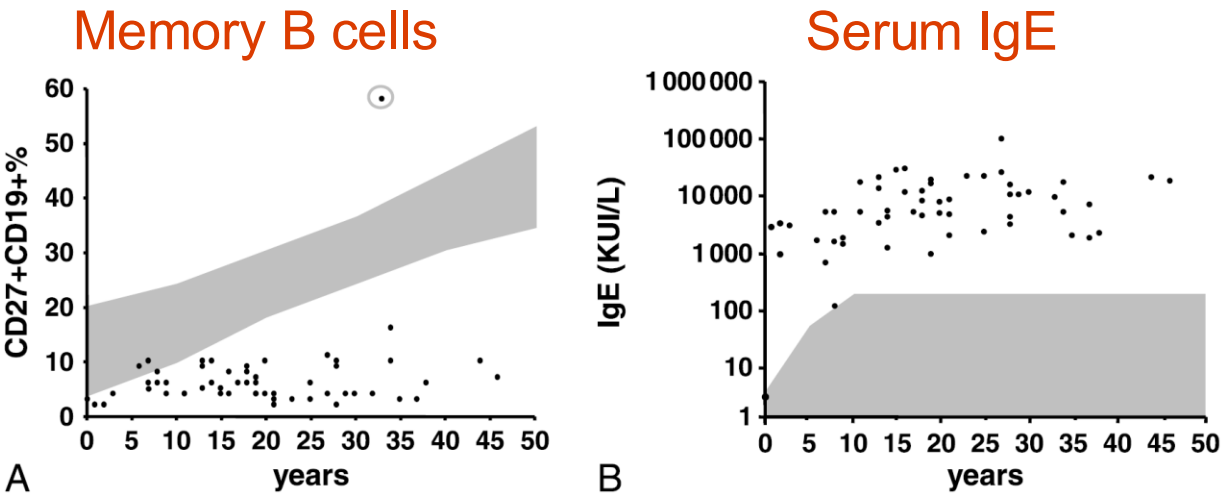
Garvan Institute of Medical Research

How do defects in STAT3 explain the phenotype of AD-HIES patients?

1. Opportunistic infections
2. Humoral (antibody) defects
3. **Atopic disease**

Why do STAT3 LOF patients get Hyper IgE?

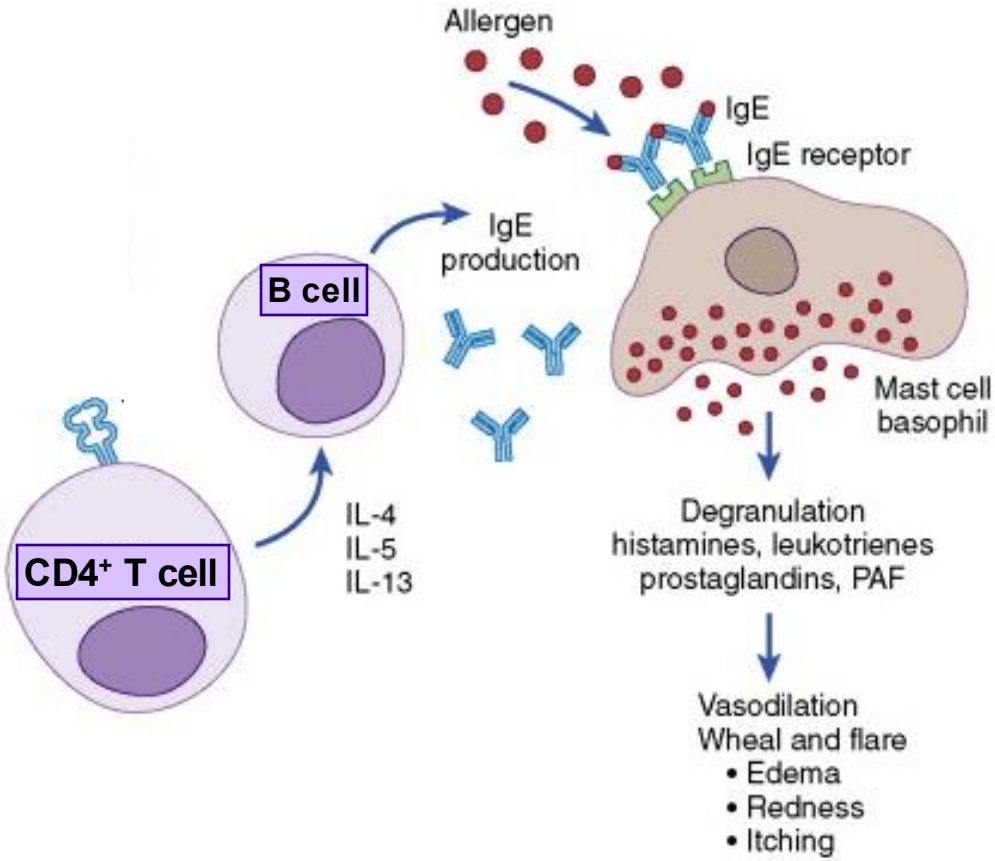
- **STAT3 LOF patients have clear humoral defects**
- **STAT3 LOF patients have increased serum IgE and associated atopic disease**



Chandesris et al. *2012 Medicine*

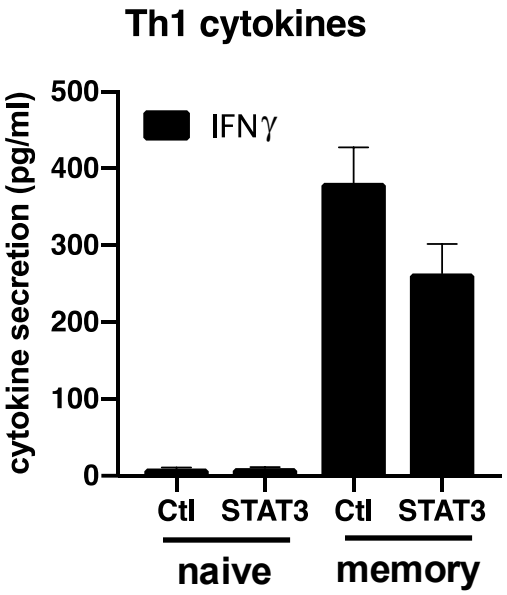
CD4⁺ T cells (IL-4/5/13) cause allergy

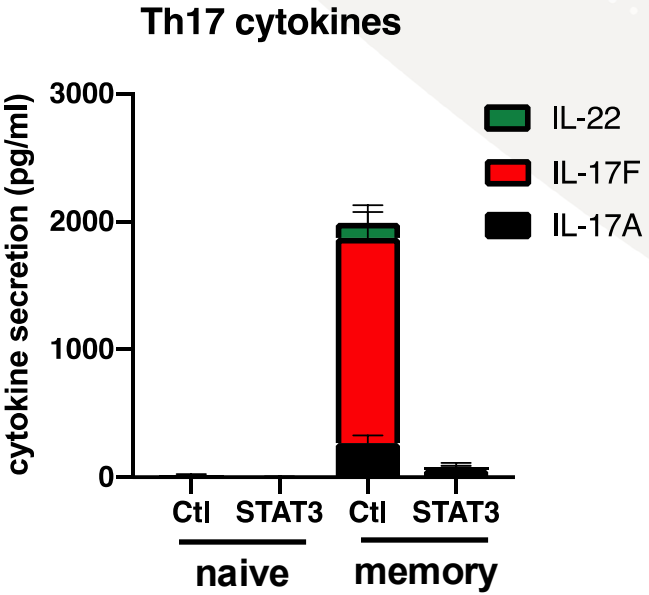
Garvan Institute of Medical Research

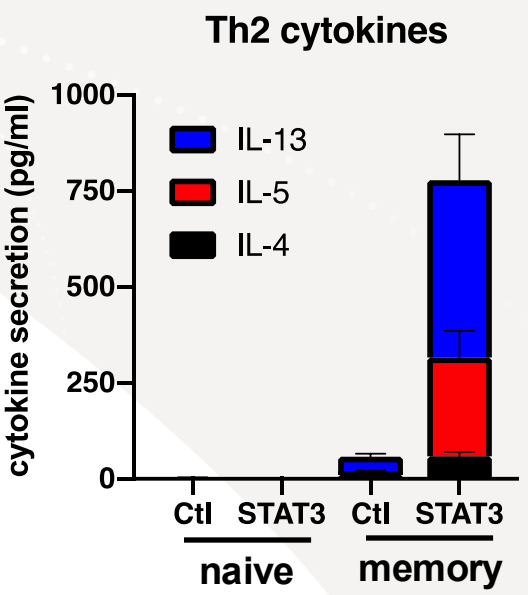


STAT3 LOF CD4+ T cells have increased Th2 cytokine production

Garvan Institute of Medical Research



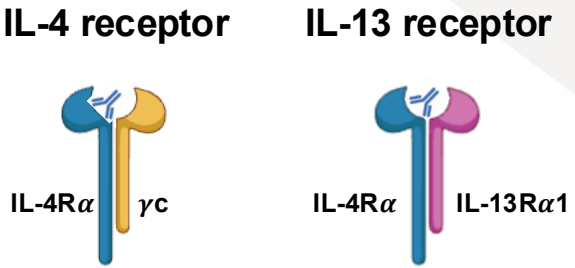




Dupilumab: mAb against IL-4R (IL-4/IL-13)

Garvan Institute of Medical Research

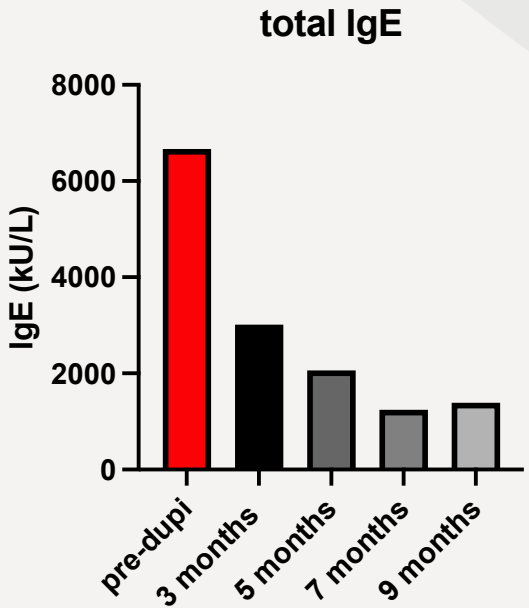
mAb binds to the IL-4Rα subunit of the IL-4 and IL-13 receptors



Dupilumab: STAT3 LOF patient resulted in decrease serum IgE

Garvan Institute of Medical Research

- **STAT3 LOF patient treated with Dupilumab because of increase Th2 cytokines**



Peter McNaughton

Summary 1

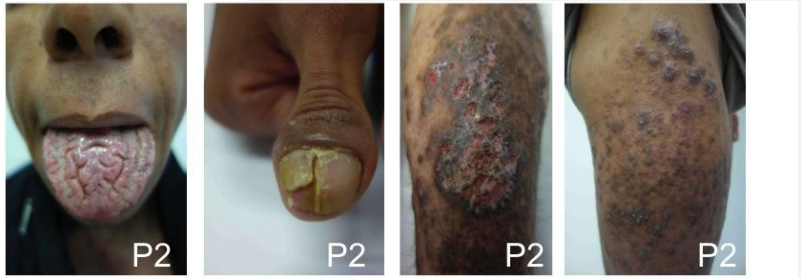
- CD4$^+$ T cells from STAT3 LOF patients are skewed towards IL-4/5/13 producing cells
- Th2 cytokine producing cells likely contribute to allergies in these patients
  - STAT3 restrains Th2 cells

- How does STAT3 restrain Th2 cytokine production?

2018: Unique case of HIES
(Jean-Laurent Casanova, Anne Puel, Vivien Beziat)

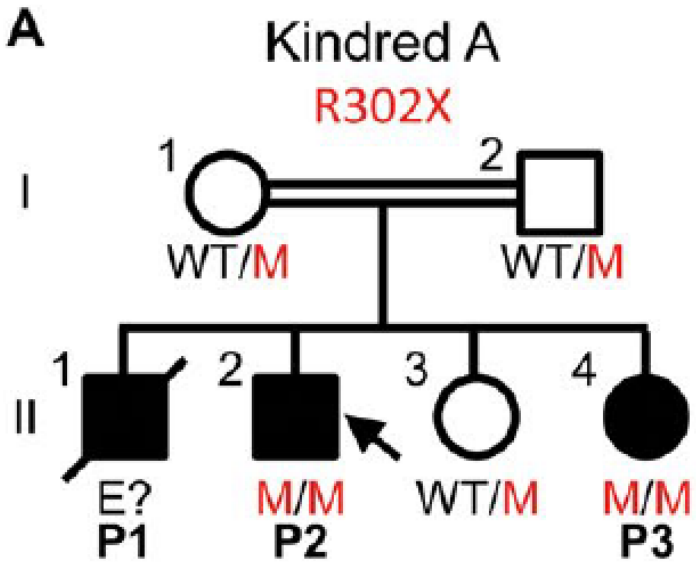
Garvan Institute of Medical Research

- hyper IgE
- atopic dermatitis, eosinophilia, allergy
- recurrent *Staph* infections
- lung disease (bronchiecstasis, pneumatoceles, pneumonia, infections)
- chronic mucocutaneous candidiasis
- connective tissue defects (mild)



Beziat et al. 2018 *Sci Immunol*

NOT STAT3-deficient patient as “autosomal recessive” form of HIES!



- **Performed whole genome sequencing**

Beziat et al. 2018 *Sci Immunol*

Summary 2

- ZNF341 regulates expression of STAT3
- ZNF341 and STAT3-deficient CD4$^+$ T cells are skewed towards Th2 cytokine producing cells.
  - likely to contribute to allergies/atopic disease in these patients

SCIENCE IMMUNOLOGY | RESEARCH ARTICLE

IMMUNODEFICIENCIES

A recessive form of hyper-IgE syndrome by disruption of ZNF341-dependent STAT3 transcription and activity

Vivien Béziat[1,2*], Juan Li[3†], Jian-Xin Lin[4†], Cindy S. Ma[5,6†], Peng Li[4†], Aziz Bousfiha[7‡], Isabelle Pellier[8‡], Samaneh Zoghi[9,10,11‡], Safa Baris[12‡], Sevgi Keles[13‡], Paul Gray[14,15‡], Ning Du[4‡], Yi Wang[1,2‡], Yoann Zerbib[1,2‡], Romain Lévy[1,2‡], Thibaut Leclercq[1,2‡], Frédégonde About[1,2], Ai Ing Lim[16,17], Geetha Rao[5], Kathryn Payne[5], Simon J. Pelham[5,6], Danielle T. Avery[5], Elissa K. Deenick[5,6], Bethany Pillay[5,6], Janet Chou[18,19], Romain Guery[1,2,20], Aziz Belkadi[1,2], Antoine Guérin[1,2], Mélanie Migaud[1,2], Vimel Rattina[1,2], Fatima Ailal[7], Ibtihal Benhsaien[7], Matthieu Bouaziz[1,2], Tanwir Habib[21], Damien Chaussabel[21], Nico Marr[21], Jamel El-Benna[22], Bodo Grimbacher[23], Orli Wargon[24], Jacinta Bustamante[1,2,3,25], Bertrand Boisson[1,2,3], Ingrid Müller-Fleckenstein[26], Bernhard Fleckenstein[26], Marie-Olivia Chandesris[27,28], Matthias Titeux[2,29], Sylvie Fraitag[30], Marie-Alexandra Alyanakian[31], Marianne Leruez-Ville[32,33], Capucine Picard[2,25,33,34], Isabelle Meyts[35], James P. Di Santo[16,17], Alain Hovnanian[2,29,36§], Ayper Somer[37§], Ahmet Ozen[12§], Nima Rezaei[9,10,11§], Talal A. Chatila[18,19¶], Laurent Abel[1,2,3¶], Warren J. Leonard[4‖], Stuart G. Tangye[5,6‖], Anne Puel[1,2,3***], Jean-Laurent Casanova[1,2,3,34,38***]

SCIENCE IMMUNOLOGY | RESEARCH ARTICLE

IMMUNODEFICIENCIES

ZNF341 controls STAT3 expression and thereby immunocompetence

Stefanie Frey-Jakobs[1*], Julia M. Hartberger[1*], Manfred Fliegauf[1*], Claudia Bossen[1*], Magdalena L. Wehmeyer[1], Johanna C. Neubauer[1], Alla Bulashevska[1], Michele Proietti[1], Philipp Fröbel[1], Christina Nöltner[1], Linlin Yang[1], Jessica Rojas-Restrepo[1], Niko Langer[1], Sandra Winzer[1], Karin R. Engelhardt[2], Cristina Glocker[1†], Dietmar Pfeifer[3], Adi Klein[4], Alejandro A. Schäffer[5], Irina Lagovsky[6,7], Idit Lachover-Roth[8], Vivien Béziat[9,10], Anne Puel[9,10,11], Jean-Laurent Casanova[9,10,11,12,13], Bernhard Fleckenstein[14], Stephan Weidinger[15], Sara S. Kilic[16‡], Ben-Zion Garty[6,17‡], Amos Etzioni[18‡], Bodo Grimbacher[1,19,20‡§]

Beziat et al; Frey-Jacobs et al Sci Immunol 2018

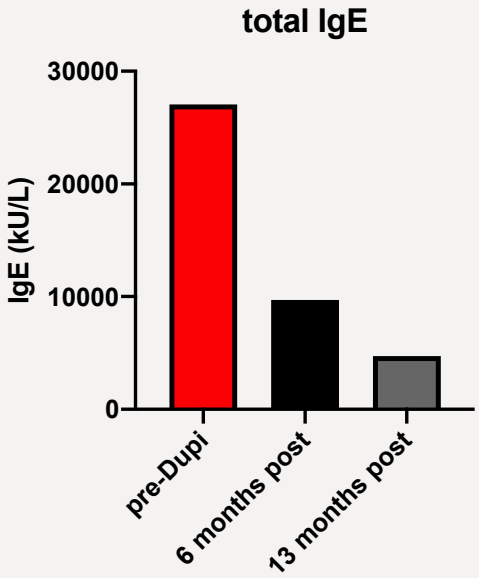
Dupilumab: mAb against IL-4R (IL-4/IL-13)

Garvan Institute of Medical Research

- **ZNF341-deficient patient treated with Dupilumab because of increase Th2 cytokines**

Dupilumab: mAb against IL-4R (IL-4/IL-13)

- **ZNF341-deficient patient treated with Dupilumab because of increase Th2 cytokines**

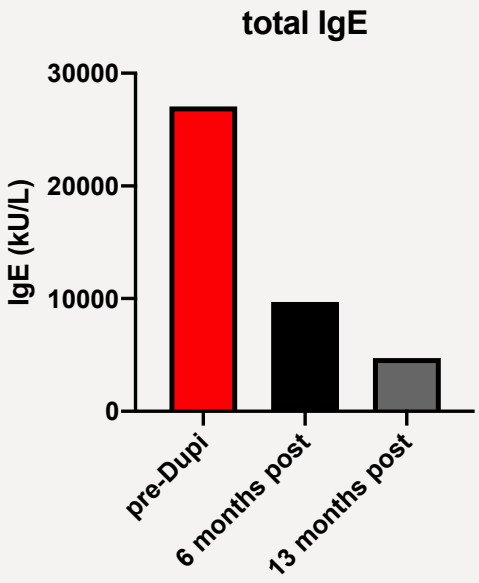


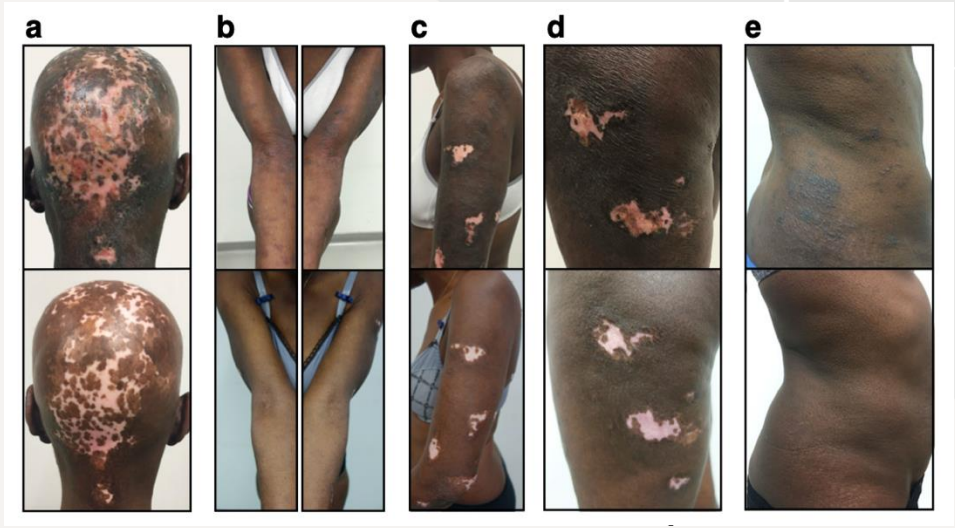
Levy et al. JoCI 2020

Dupilumab: mAb against IL-4R (IL-4/IL-13)

Garvan Institute of Medical Research

- **ZNF341-deficient patient treated with Dupilumab because of increase Th2 cytokines**





Pre-Dupilumab

12-months post-Dupilumab

Levy et al. JoCI 2020

What STAT3 activating cytokine(s) inhibit Th2 cells?

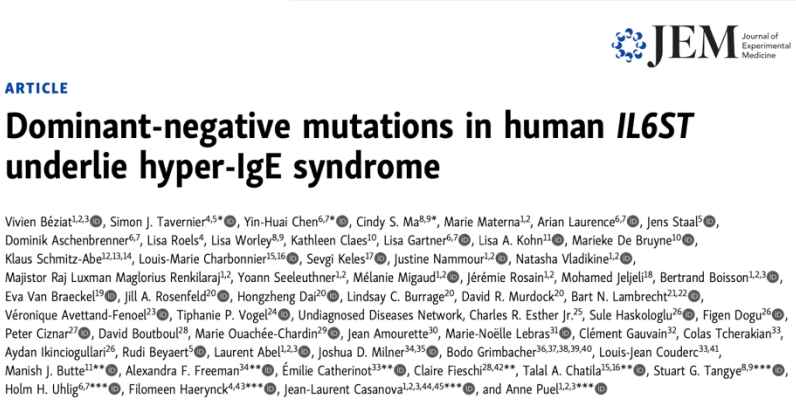
Garvan Institute of Medical Research

- ***IL-21?***
  - **IL-21 or IL-21R deficiency results in combined immunodeficiency (recurrent respiratory infections, impaired humoral immunity, severe cryptosporidiosis)**
  - **50% of IL-21R-deficient patients have mild elevation serum IgE, 20% susceptible to asthma**
- ***IL-10?***
  - **IL-10 or IL-10R deficiency results in inflammatory bowel disease (IBD)**
  - **No reports of atopic disease or increased serum IgE**
- ***IL-23?***
  - **IL-23R deficiency – Mendelian susceptibility to mycobacterial disease**
  - **No reports of atopic disease or increased serum IgE**

WGS hyper IgE syndrome patients

(Vivien Beziat, Anne Puel, Jean-Laurent Casanova)

Garvan Institute of Medical Research



JEM Journal of Experimental Medicine

ARTICLE

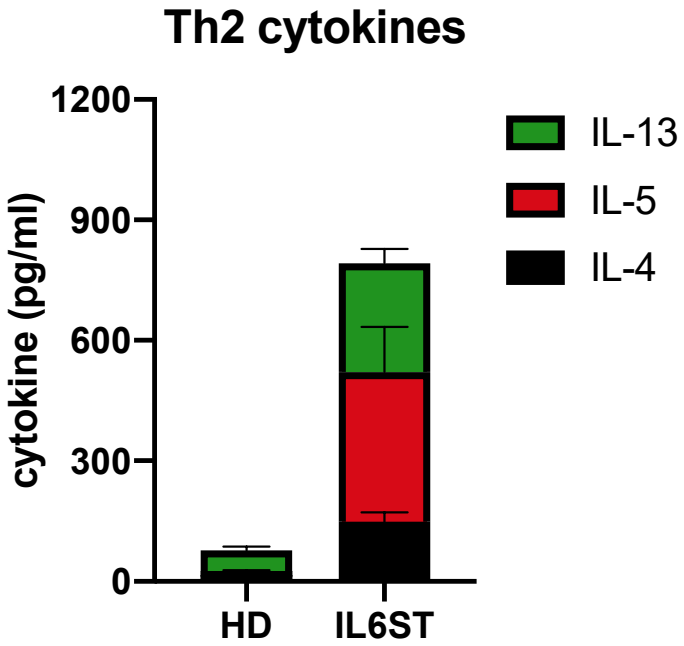
Dominant-negative mutations in human *IL6ST* underlie hyper-IgE syndrome

Vivien Béziat[1,2,3], Simon J. Tavernier[4,5*], Yin-Huai Chen[6,7*], Cindy S. Ma[8,9*], Marie Materna[1,2], Arian Laurence[6,7], Jens Staal[5], Dominik Aschenbrenner[6,7], Lisa Roels[4], Lisa Worley[8,9], Kathleen Claes[10], Lisa Gartner[6,7], Lisa A. Kohn[11], Marieke De Bruyne[10], Klaus Schmitz-Abe[12,13,14], Louis-Marie Charbonnier[15,16], Sevgi Keles[17], Justine Nammour[1,2], Natasha Vladikine[1,2], Majistor Raj Luxman Maglorius Renkilaraj[1,2], Yoann Seeleuthner[1,2], Mélanie Migaud[1,2], Jérémie Rosain[1,2], Mohamed Jeljeli[18], Bertrand Boisson[1,2,3], Eva Van Braeckel[19], Jill A. Rosenfeld[20], Hongzheng Dai[20], Lindsay C. Burrage[20], David R. Murdock[20], Bart N. Lambrecht[21,22], Véronique Avettand-Fenoel[23], Tiphanie P. Vogel[24], Undiagnosed Diseases Network, Charles R. Esther Jr.[25], Sule Haskologlu[26], Figen Dogu[26], Peter Ciznar[27], David Boutboul[28], Marie Ouachée-Chardin[29], Jean Amourette[30], Marie-Noëlle Lebras[31], Clément Gauvain[32], Colas Tcherakian[33], Aydan Ikinciogullari[26], Rudi Beyaert[5], Laurent Abel[1,2,3], Joshua D. Milner[34,35], Bodo Grimbacher[36,37,38,39,40], Louis-Jean Couderc[33,41], Manish J. Butte[11**], Alexandra F. Freeman[34**], Émilie Catherinot[33**], Claire Fieschi[28,42**], Talal A. Chatila[15,16**], Stuart G. Tangye[8,9***], Holm H. Uhlig[6,7***], Filomeen Haerynck[4,43***], Jean-Laurent Casanova[1,2,3,44,45***], and Anne Puel[1,2,3***]

- ***IL-6ST/GP130***
  - ***Receptor for IL-6 family of cytokines (IL-6, IL-11, IL-27, leukemia inhibitory factor, oncostatin M)***
  - ***gp130-deficient mice die in utero of myocardial, haematological and skeletal defects***
  - ***Skeletal symptoms due to defects in IL-11 signalling***
  - ***Atopic disease, hyper IgE due to defects in IL-6***

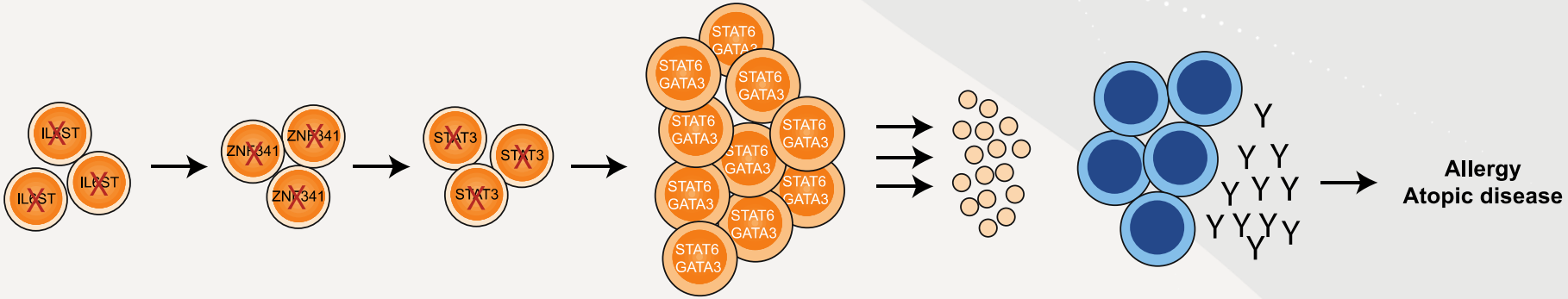
IL-6ST deficiency functionally phenocopies *STAT3* and ZNF341 mutations

Garvan Institute of Medical Research



Summary

- IL-6 working via ZNF341 and STAT3 restrains Th2 cells
  - Absence of IL-6, ZNF341 or STAT3 results in atopic disease



Garvan Institute of Medical Research

1. Opportunistic infections:
2. Humoral defects:
3. **Atopic disease**
   - **B cell extrinsic – increased Th2 cytokine**
   - **B cell intrinsic role?**

Increased IgE in STAT3 LOF: B cell intrinsic role

Garvan Institute of Medical Research

- **Mouse**

LETTER TO THE EDITOR · Volume 138, Issue 5, P1455-1458.E3, November 2016

Download Full Issue

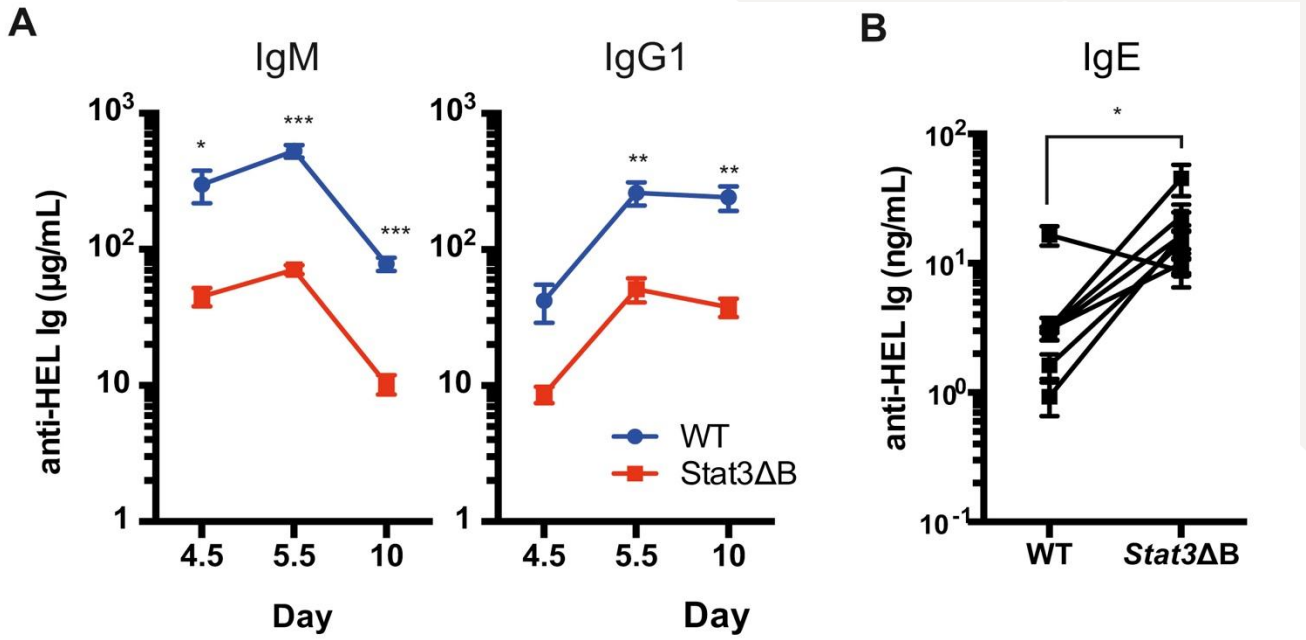
B-cell–specific STAT3 deficiency: Insight into the molecular basis of autosomal-dominant hyper-IgE syndrome

Alisa Kane, MB, BS [a,b] · Anthony Lau [a,c] · Robert Brink, PhD [a,b] · Stuart G. Tangye, PhD [a,b] · Elissa K. Deenick, PhD [a,b] ✉

Increased IgE in STAT3 LOF: B cell intrinsic role

Garvan Institute of Medical Research

- **Mouse**



Increased IgE in STAT3 LOF: B cell intrinsic role

Garvan Institute of Medical Research

- **Human – increased serum IgE**

European Journal of Immunology

Immunodeficiencies and autoimmunity

Short Communication

Somatic mosaicism in B cells of a patient with autosomal dominant hyper IgE syndrome

Julio C. Alcántara-Montiel[1,4], Tamara Staines-Boone[2], Gabriela López-Herrera[3], Laura Berrón-Ruiz[3], Carlos R. Borrego-Montoya[2] and Leopoldo Santos-Argumedo[1]

Apart from that, the HIES mosaic patient showed plaques of erythema with scales and pustules in the nostrils, anterior thorax, gluteal, and inguinal folds. The HIES mosaic patient had cold abscesses in several body parts such as the scalp, frontal region, and limbs. He was treated with antibiotics and antifungals, and on some occasions, surgical drainage was performed. The patient also had high concentrations of IgE range (552–4988 IU/mL), normal eosinophil count range (58–700 cell/μL) see Supporting Information Tables 4 and 5, but low compared to the classical HIES patient; in addition, *Staphylococcus aureus* was isolated several times. Nonimmunological features such as scoliosis, high palate, and hyperextensibility were also present.

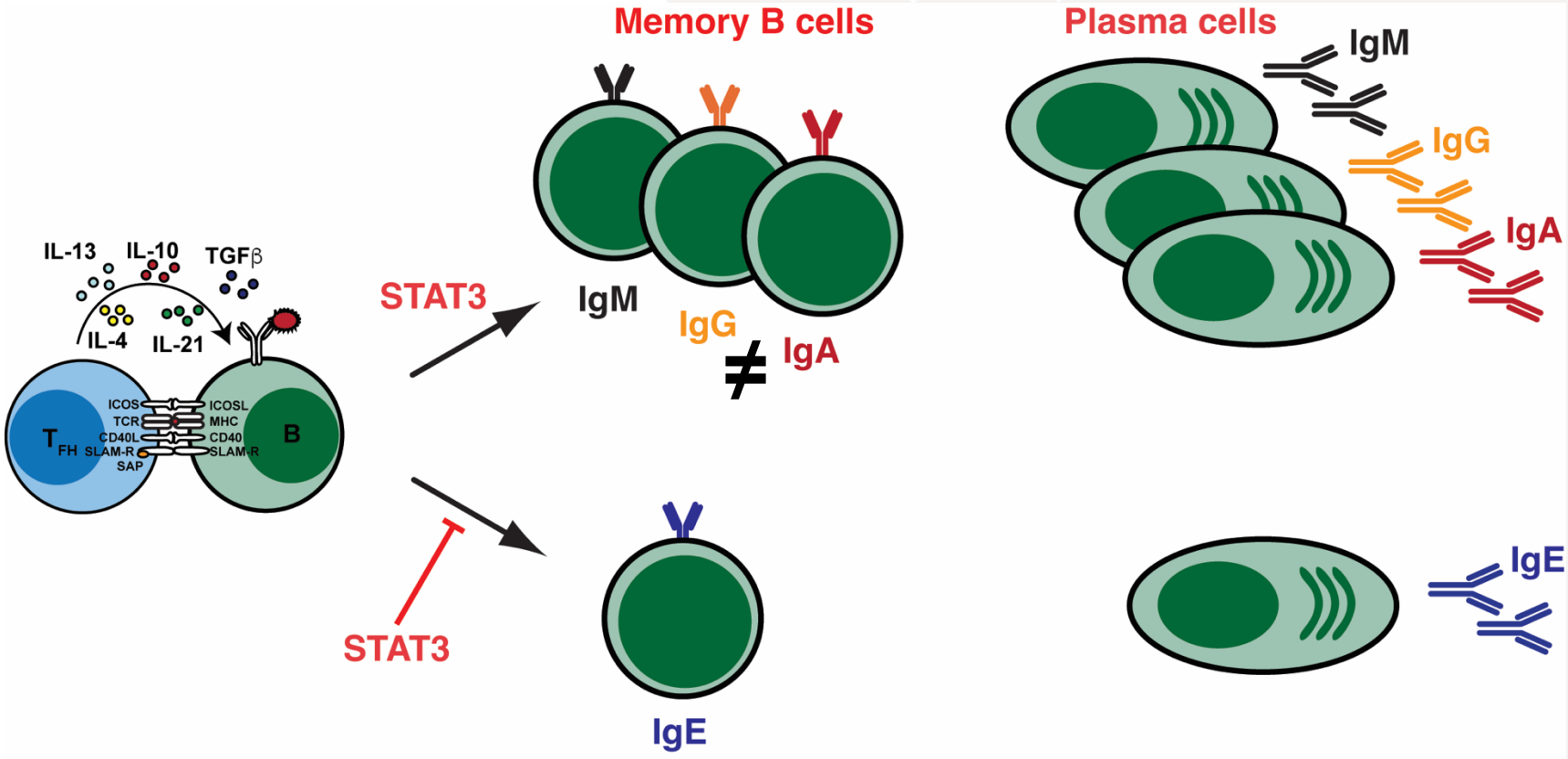
Upon physical examination the HIES mosaic patient did not

Garvan Institute of Medical Research

1. Opportunistic infections:
2. Humoral defects:
3. **Atopic disease**
   - **B cell extrinsic – increased Th2 cytokine**
   - **B cell intrinsic role**

STAT3: an immune dichotomy

Garvan Institute of Medical Research



What is the nature of human IgE?

Garvan Institute of Medical Research

- **Difficult question to answer as:**
  - **IgE is tightly regulated (~0.002% serum Ab)**
  - **circulating IgE cells are hard to detect**

Published in final edited form as:
J Allergy Clin Immunol. 2019 July ; 144(1): 336–339.e6. doi:10.1016/j.jaci.2019.04.001.

Human BCR analysis of single-sorted, putative IgE+ memory B cells in food allergy

Rodrigo Jiménez-Saiz, PhD[1,2,†], Yosef Ellenbogen, BHSc[1,2,†], Kelly Bruton, BSc[1,†], Paul Spill, BHSc[1], Doron D. Sommer, MD[3], Hermenio Lima, MD, PhD[4], Susan Waserman, MD, MSc[4], Sarita U. Patil, MD[2], Wayne G. Shreffler, MD, PhD[2], Manel Jordana, MD, PhD[1,*]

What is the nature of human IgE?

Garvan Institute of Medical Research

- **Difficult question to answer as:**
  - **IgE is tightly regulated (~0.002% serum Ab)**
  - **circulating IgE cells are hard to detect**

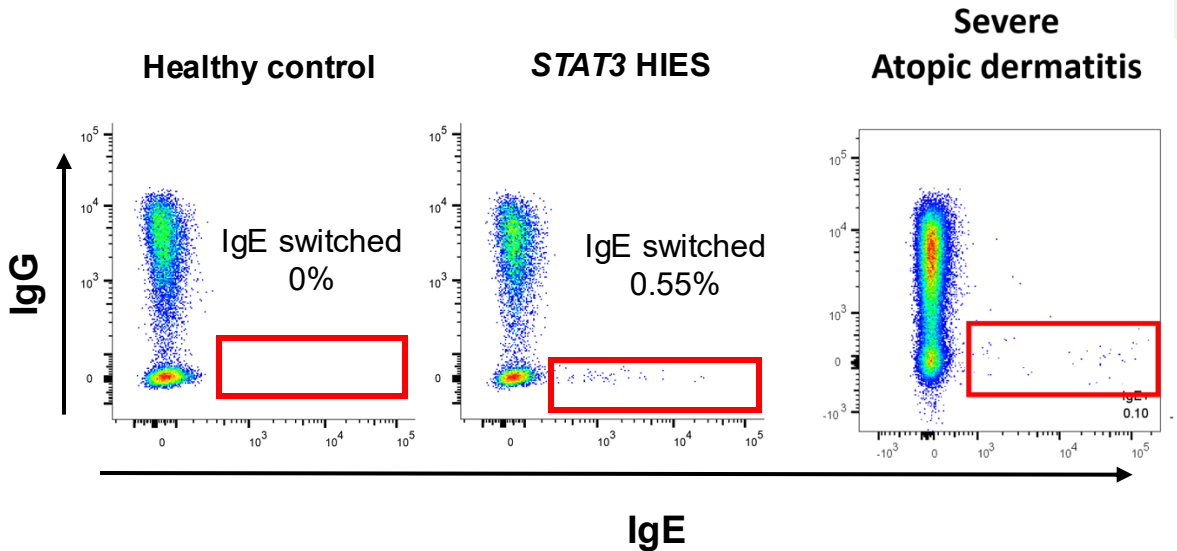
TABLE I. Quantification of IgE$^+$ MBCs in healthy and allergic donors

Tissue	Donor ID	Allergic status	Mononuclear cells	Purified B cells	Events in CD20$^+$ CD38$^{lo\text{-}med}$ gate	Events in IgE gate	Sorted cells	IGHE amplification
Blood	P001	–	250,000,000	9,540,000	600,304	21	6	0
	P003	–	123,000,000	8,640,000	169,267	29	12	0
	P007	–	125,000,000	2,685,000	645,055	5	3	0
	P009	–	98,600,000	4,140,000	325,734	12	12	0
	P014	–	109,000,000	2,820,000	605,535	8	8	0
	P021	–	173,000,000	26,000,000	440,963	2	1	0
	P025	–	86,600,000	1,401,000	246,090	20	20	0
	P026	–	94,200,000	1,494,000	250,018	14	10	0
	P030	–	78,800,000	1,128,000	132,157	4	4	0
	P031	–	85,400,000	945,000	172,260	4	4	0
	P008	Peanut	125,000,000	8,160,000	335,641	20	20	0
	P011	Peanut	250,000,000	7,150,000	520,021	6	3	0
	P013	Peanut	210,000,000	5,450,000	690,015	13	12	0
	P016	Peanut	125,000,000	1,068,000	143,759	5	5	0
	P017	Peanut	125,000,000	1,467,000	213,345	11	10	0
	P020	Peanut	124,000,000	3,900,000	537,856	4	1	0
	P024	Peanut	71,800,000	1,026,000	166,313	3	1	0
	P028	Peanut	94,800,000	1,440,000	157,340	1	1	0
	P029	Peanut	54,000,000	1,467,000	277,359	2	2	0
Tonsils	TP-9	–	10,000,000	–	204,125	10	7	0
	TP-10	–	10,000,000	–	68,461	15	12	0
	TP-11	–	10,000,000	–	56,127	6	6	0

Jimenez-Saiz et al 2019 *JACI*

What is the nature of human IgE?

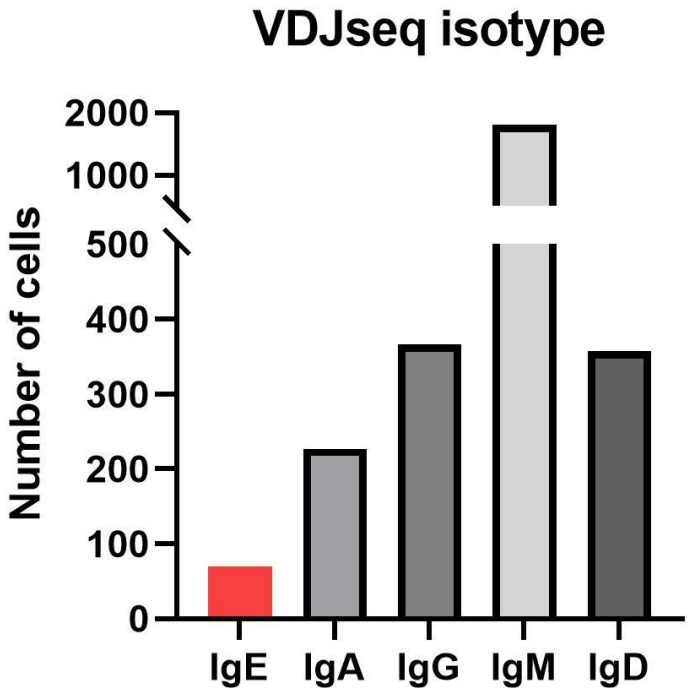
- **Difficult question to answer as:**
  - **IgE is tightly regulated (~0.002% serum Ab)**
  - **circulating IgE cells are hard to detect**



Karrnan Pathmanandavel

sc-RNA-seq: IgE switched B cells are present in STAT3 LOF patients

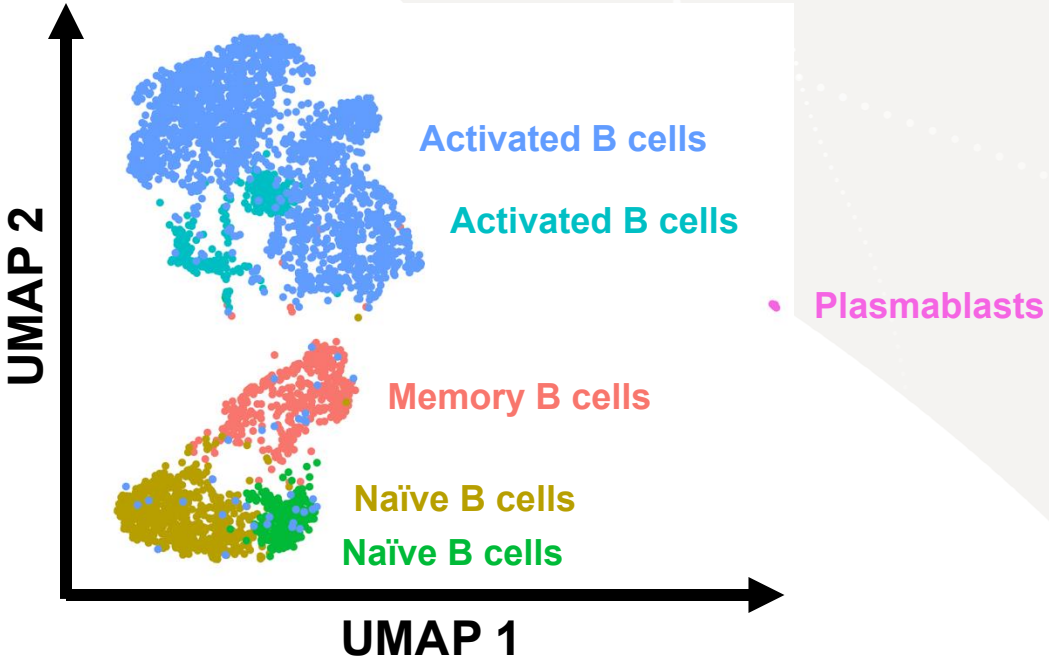
Garvan Institute of Medical Research



Karrnan Pathmanandavel

Single cell RNA/VDJ-seq in STAT3-deficient patient

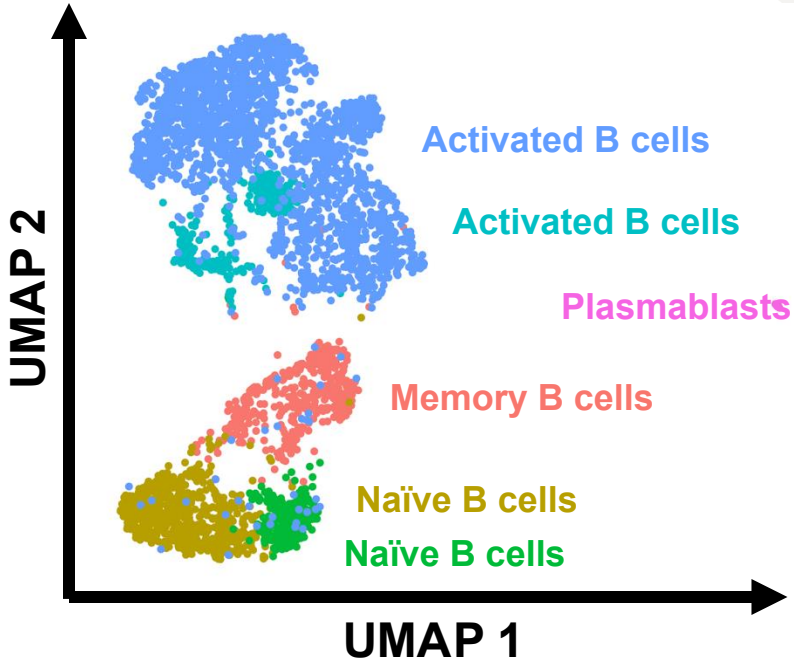
Garvan Institute of Medical Research

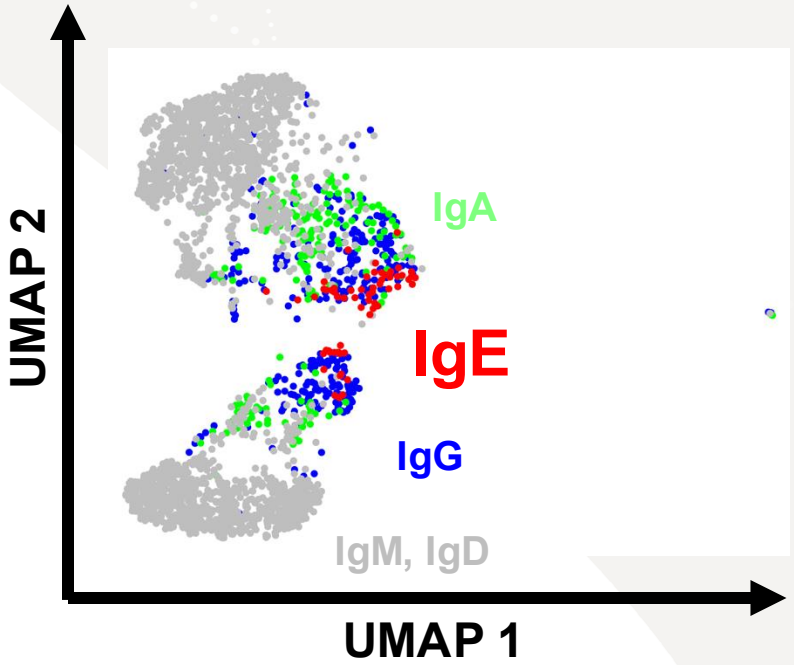


Karrnan Pathmanandavel

IgE switched B cells are present in STAT3-deficient patient

Garvan Institute of Medical Research

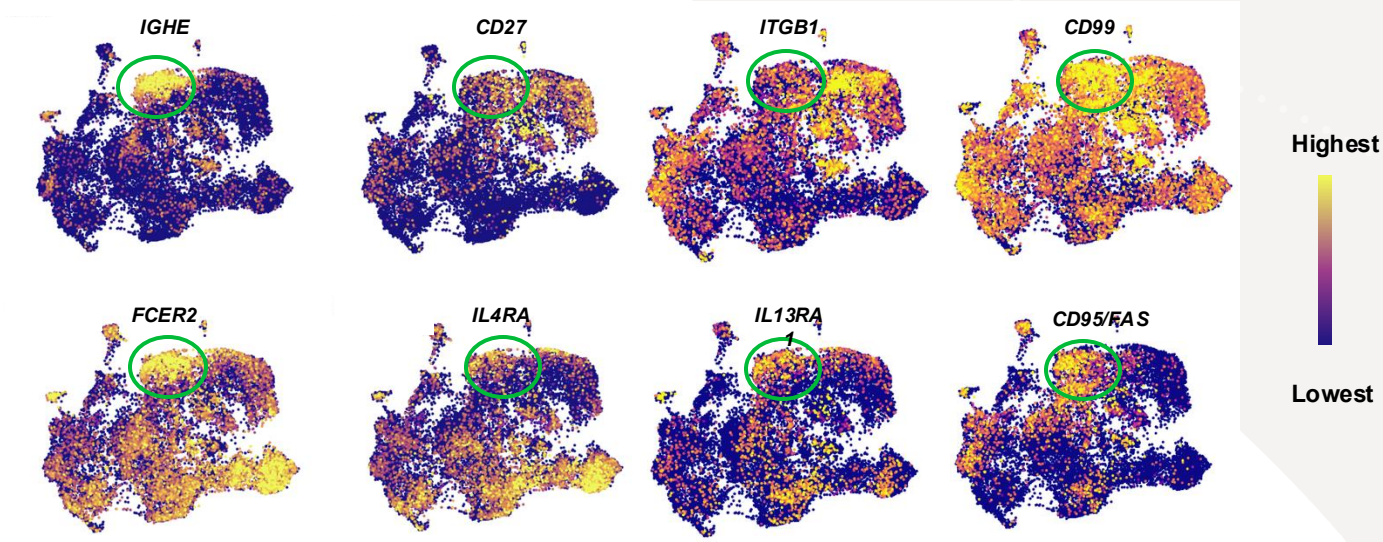




Karrnan Pathmanandavel

scRNA seq: IgE^{+} B cells in STAT3 LOF patients

Garvan Institute of Medical Research



scRNA seq: IgE$^+$ B cells resemble MBC2

Garvan Institute of Medical Research

ORIGINAL ARTICLE
Basic and Translational Allergy Immunology

Allergy WILEY

IgG memory B cells expressing *IL4R* and *FCER2* are associated with atopic diseases

Carlos J. Aranda[1,2] | Edgar Gonzalez-Kozlova[3] | Sean P. Saunders[4] | Weslley Fernandes-Braga[1,2] | Miyo Ota[1,2] | Sriram Narayanan[5] | Jin-Shu He[5] | Ester Del Duca[6] | Bose Swaroop[6] | Sacha Gnjatic[2,7] | Gail Shattner[4] | Joan Reibman[4] Nicholas A. Soter[8] | Emma Guttman-Yassky[6] | Maria A. Curotto de Lafaille[1,2]

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

ALLERGY

CD23$^+$IgG1$^+$ memory B cells are poised to switch to pathogenic IgE production in food allergy

Miyo Ota[1,2]*†‡, Kenneth B. Hoehn[3]†§, Weslley Fernandes-Braga[1,2]†, Takayuki Ota[4], Carlos J. Aranda[1,2]¶, Sara Friedman[1,2], Mariana G. C. Miranda-Waldetario[1,2], Jamie Redes[1,2,5], Maria Suprun[1]#, Galina Grishina[1], Hugh A. Sampson[1], Alefiyah Malbari[6]**, Steven H. Kleinstein[3,7,8], Scott H. Sicherer[1], Maria A. Curotto de Lafaille[1,2]*

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

ALLERGY

Type 2–polarized memory B cells hold allergen-specific IgE memory

Joshua F. E. Koenig[1]*†, Niels Peter H. Knudsen[2]†, Allyssa Phelps[1]†, Kelly Bruton[1]†‡, Ilka Hoof[2]§, Gitte Lund[2], Danielle Della Libera[1], Anders Lund[2], Lars Harder Christensen[2], David R. Glass[3], Tina D. Walker[1], Allison Fang[1], Susan Waserman[1], Manel Jordana[1], Peter S. Andersen[2]*

Garvan Institute of Medical Research

1. Opportunistic infections:
2. Humoral defects:
3. **Atopic disease**
   - **What about food allergies?**

Tfh13 cells drive IgE

Garvan Institute of Medical Research

Science

RESEARCH ARTICLES

Cite as: U. Gowthaman *et al.*, *Science* 10.1126/science.aaw6433 (2019).

Identification of a T follicular helper cell subset that drives anaphylactic IgE

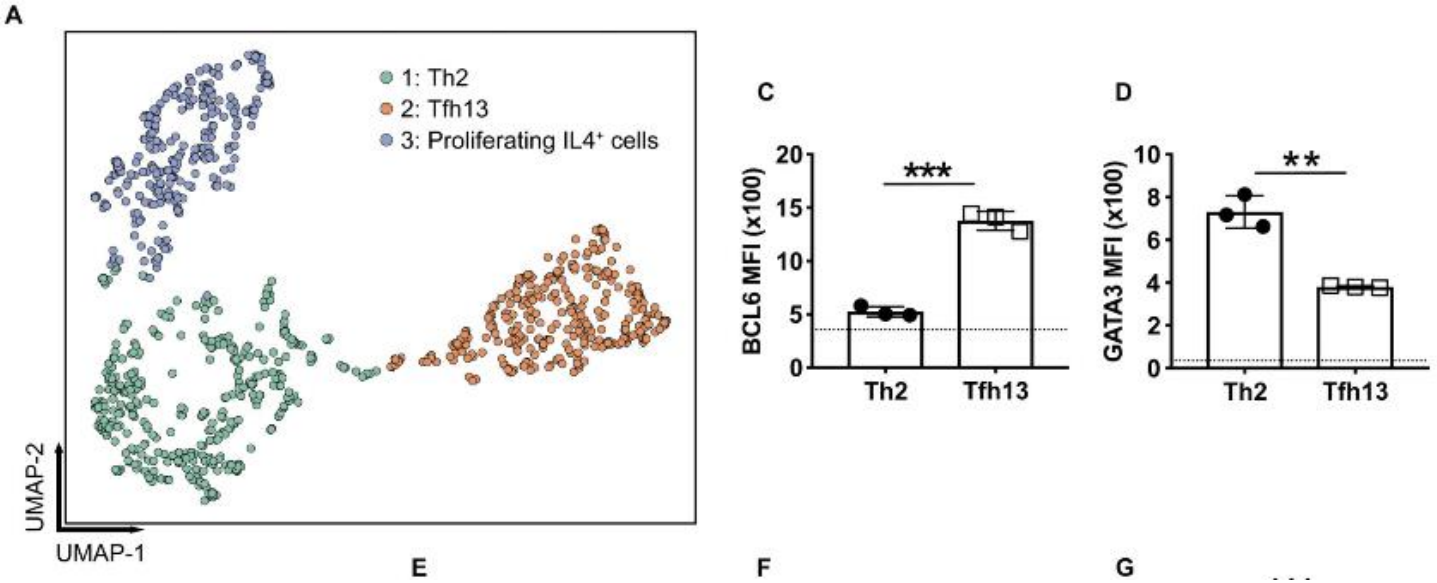
Uthaman Gowthaman[1,2], Jennifer S. Chen[1,2*], Biyan Zhang[1,2*], William F. Flynn[3], Yisi Lu[2], Wenzhi Song[2], Julie Joseph[1], Jake A. Gertie[1,2], Lan Xu[1,2], Magalie A. Collet[3], Jessica D. S. Grassmann[3], Tregony Simoneau[4], David Chiang[5], M. Cecilia Berin[5], Joseph E. Craft[2], Jason S. Weinstein[6], Adam Williams[3,7*†], Stephanie C. Eisenbarth[1,2*†]

- Produce IL-4, IL-5 IL-13, IL-21
- Express GATA3 and BCL6
- Level of IL-21 lower than other Tfh cells

Tfh13 distinct from Th2

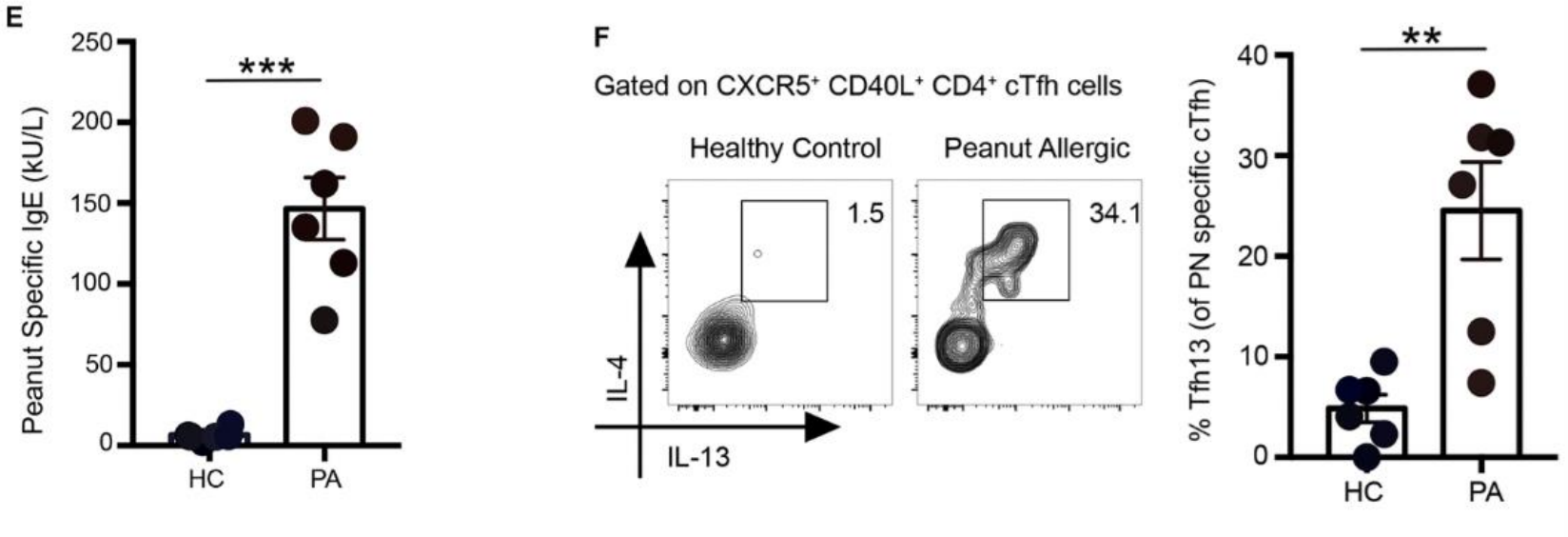
Garvan Institute of Medical Research

Mouse



Gowthaman et al. 2019 *Science*

Human with peanut allergy have Tfh13 cells



Gowthaman et al. 2019 *Science*

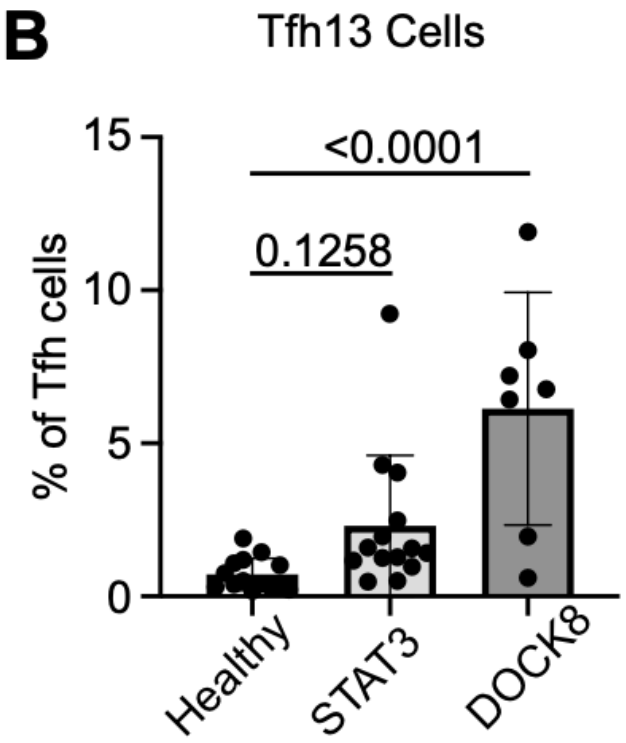
Current projects

Garvan Institute of Medical Research

- Looking in different IEI to see what restraisn and promotes Tfh13 cells
- Compare Tfh13 population between food allergy vs atopic dermatitis vs allergic rhinitis etc
- Assess Tfh13 population after Dupilumab treatment
  - useful in treating food anaphylaxis

Tfh13 cells are elevated in DOCK8 def but not STAT3 LOF

Garvan Institute of Medical Research



Siniscalco et al. 2025 *J Exp Med (accepted)*

Garvan Institute of Medical Research

Ma Lab

- Dr Corinne Mack
- Dr Antoine Guerin
- Geetha Rao
- Francis Gracias Flor
- Dr Shivani Patel
- Dr Alex Crawford
- Mia Gruzin
- Lisa Reed
- Alex Manefield
- Ashley Suh
- Felicity Tu

Tangye Lab

- Prof Stu Tangye
- Danielle Priestley
- Dr Karrnan Pathmanandavel
- Dr Erika Della Mina
- Dr Tina Nguyen
- Dr Joe Mackie
- Dena Al-Rifai
- Pat O'Young
- Monika Vesse
- James Flaherty
- Alexandra Tonkin
- Matali Kodolikar

Australian Government
National Health and Medical Research Council

aifa
allergy and immunology foundation of australasia

jmcn
Jeffrey Modell Centers Network

UNSW SYDNEY

THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS

Acknowledgements

Collaborators - Australia

Paul Gray – SCH, Sydney
Kahn Preece – John Hunter Hospital Newcastle
Dan Suan - Westmead Hospital
Lucinda Berglund - Westmead Hospital
Melanie Wong - Children's Hospital Westmead
Stephen Adelstein – RPAH, Sydney
Nicolas Urriola - RPAH, Sydney
Shruti Swamy - RPAH, Sydney
Andy McLean-Tooke – Sir Gairdner and Perth Children's Hospital
Martyn French - Royal Perth Hospital
Peter McNaughton – QLD Children's Hos
Jane Peake - Children's Hospital Brisbane
Jo Smart – RCH, Melbourne
Winnie Tong – St Vincent's Hospital
Tri Phan - St Vincent's Hospital
Alisa Kane - St Vincent's/Liverpool Hospitals

Collaborators – And Beyond

Isabelle Meyts – Catholic University, Leuven
Peter Arkwright – *Manchester Children's Hospital*
Masao Kobayashi - *Hiroshima University, Japan*
Satashi Okada - *Hiroshima University, Japan*
Capucine Picard – *Hospital Necker*
Kaan Boztug - *CeMM, Vienna*
Bodo Grimbacher - *CCI, Freiburg*
Klaus Warnatz - *CCI, Freiburg*
Jennifer Stoddard - *NIH*
Steve Holland – *NIH*
Yoshiyuki Minegishi – Tokyo Medical Uni, Japan
Vivien Beziat – INSERM
Anne Puel – INSERM
Gulbu Uzel – *NIAID, NIH*
Jean-Laurent Casanova - *Rockefeller University*
Stephanie Eisenbarth – Northwestern Uni
Uthaman Gowthaman – Uni of Massachusetts