IUUIS Expert Committee for Inborn Errors of Immunity: Classification of PIDs

Stuart Tangye

4th International Primary Immunodeficiencies Congress
Madrid, November 2019
Inborn Errors of Immunity Committee

Amos Etzioni   Hans Ochs   Jose Luis Franco
Troy Torgerson  Talal Chatila  Christoph Klein
Aziz Bousfiha  Capucine Picard  Steve Holland  Tomohiro Morio
Jennifer Puck  Kate Sullivan  Waleed Al-Herz  Eric Oksenhendler

Charlotte Cunningham-Rundles  Jean-Laurent Casanova
IUlS-IEI Goals & Objectives

Inborn Errors of Immunity Committee

• provide an up-to-date classification of all “monogenic” immune dysregulatory conditions (inborn errors of immunity)
  • PIDs; autoinflammatory/autoimmunity; allergy; malignancy
• assist with the identification, diagnosis and management of patients with these conditions
• support diagnostic and therapeutic guidelines developed by national societies and others, to assist healthcare providers
• promote awareness, diagnosis and treatment of IEI in all regions of the world
• produce ad hoc reports on any aspect of IEIs and to assist in the welfare of patients with these conditions
Primary Immunodeficiencies

• monogenic mutations causing loss- or gain-of function of a single protein, resulting in human disease

• Immune dysregulation: severe/recurrent infection, autoimmunity/inflammation, allergy, cancer; often fatal

• incidence: “rare”
Primary Immunodeficiencies

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Table 2. Infants Screened and Incidence of SCID (Including Leaky SCID) in 11 Contributing Programs

| Table 2. Infants Screened and Incidence of SCID (Including Leaky SCID) in 11 Contributing Programs |
|---------------------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|                                | California       | Colorado         | Connecticut      | Delaware         | Massachusetts    | Michigan         | Mississippi      | Navajo Nation    | New York         |
| Duration of screening included, mo | 34               | 13               | 19               | 12               | 48               | 18              | 12              | 17               | 24               |
| Infants screened, No.            | 1,384,606        | 70,989           | 57,136           | 11,202           | 293,371          | 162,528         | 37,613          | 3498             | 485,912          |
| Flow cytometry referrals, No. (%) | 206 (14.9)       | 10 (14.1)        | 22 (22.55)       | 9 (80.9)         | 63 (21.5)        | 114 (20.1)      | 5 (13.3)        | 1 (28.6)         | 478 (98.4)       |
| SCID cases                     | 23               | 1                | 3                | 1                | 4                | 2               | 1               | 10               | 2                |
| SCID incidence                 | 1/60,000         | 1/71,000         | 1/119,000        | 1/11,000         | 1/71,000         | 1/81,000        | 1/38,000        | 1/135,000        | 1/49,000         |
| SCID cases per 100,000         | 1.7              | 1.4              | 5.2              | 8.9              | 1.4              | 1.2             | 2.7             | 29               | 2.0              |

~1/58 000
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• incidence: “rare”

Not all PIDs are detected by NBS

Original Investigation

Newborn Screening for Severe Combined Immunodeficiency in 11 Screening Programs in the United States

Antonia Kews, PhD, MCPOA, Roshi S. Abraham, PhD, Robert Currier, PhD, Amy Brower, PhD, Karen Androutsopoulos, BS, Jordan K. Abbott, MD, Mel Bailer, MD, Mari Ballow, MD, Louis E. Bartoldovsky, MD, Vincent R. Bonagura, MD, Francisco A. Bonilla, MD, PhD, Charles Brosco, PhD, DPH; Edward Brooks, MD, Michelle Cagnone, ScD, Jonathan Coleman, MD, Joseph A. Church, MD, Anne Marie Comeau, PhD, James A. Connelly, MD, Morton J. Cowan, MD, Charlotte Cunningham-Rundles, MD, Trivikram Dasa, PhD, Nina Dove, MD, Mario T. De La Morena, MD, Ulrich Duffner, MD, Chi-To Fong, MD, Lisa Forbes, MD, Dilinna Freedenberg, MD, Erwin W. Gelfand, MD, Jaime E. Halle, BS, I. Colene Hanson, MD, Beverly K. Hay, MD, Diana Ho, MD, Anthony Infante, MD, PhD, Daisy Johnson, BSN, Neera Kapooc, MD, Denise M. Kay, PhD, Donna B. Kohl, MD, Rachelle Lazar, PhD, Heather Lehman, MD, Zhi Lin, PhD, Fred Lorey, PhD, Aly Abdel-Mageed, MD, MBA, Adrienne Manning, BS, Sean McNee, MD, Theodore B. Moore, MD, Stanley J. Nadel, MD, Luigi D. Notarangelo, MD, Jordan S. Orange, MD, Sung Hyun Park, MD, Matthew Torrent, MD, PhD, Ray Rodriguez, MD, JD, MPh, MBA, Neil Romberg, MD, John Routes, MD, Mary Rachel, MS, Arne Rubenstein, MD, Carlos A. Sauvedra-Mata, MD, Ginger Scott, RN, Patricia M. Scott, MT, Elizabeth Second, MD, Christine Seragan, MD, William E. Shearer, MD, PhD, Sushiladha Siegel, MD, Stacy K. Silvers, MD, E. Richard Stahkes, MD, Robert W. Sugarman, MD, John L. Sullivan, MD, Susan Tark, PhD, Millard L. Tanen, DO, James Verbisk, MD, PhD, Beth Vogel, MS, Rosaly Walker, MD, Kelly Walkovich, MD, Jolan E. Walter, MD, PhD, Richard L. Wasserman, MD, PhD, Michael S. Watson, MS, PhD, Geoffrey A. Wimborg, MD, Leonard B. Weiner, MD, Heather Wood, MS, Anne B. Yates, MD, Jennifer M. Puck, MD

Borte et al., 2012. Blood. 119: 2552
Primary Immunodeficiencies

- monogenic mutations causing loss- or gain-of function of a single protein, resulting in human disease
- Immune dysregulation: severe/recurrent infection, autoimmunity/inflammation, allergy, cancer; often fatal
- incidence: not so “rare”

Homozygosity for TYK2 P1104A underlies tuberculosis in about 1% of patients in a cohort of European ancestry

Gaspard Kerner\textsuperscript{a,b}, Noe Ramirez-Alejo\textsuperscript{c,1}, Yoann Seeleuthner\textsuperscript{a,b,1}, Rui Yang\textsuperscript{c}, Masato Ogishi\textsuperscript{c}, Aurélie Cobat\textsuperscript{a,b}, Etienne Patin\textsuperscript{d}, Lluis Quintana-Murci\textsuperscript{d}, Stéphanie Boisson-Dupuis\textsuperscript{a,b,c,2}, Jean-Laurent Casanova\textsuperscript{a,b,c,e,f,2,3}, and Laurent Abel\textsuperscript{a,b,c,2}

\textsuperscript{a}Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM UMR 1163, Necker Hospital for Sick Children, 75015 Paris, France; \textsuperscript{b}Imagin Institute, Paris Descartes University, 75015 Paris, France; \textsuperscript{c}St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY 10065; \textsuperscript{d}Human Evolutionary Genetics Unit, Institut Pasteur, CNRS UMR2000, 75015 Paris, France; \textsuperscript{e}Pediatric Hematology-
Primary Immunodeficiencies

• monogenic mutations causing loss- or gain-of function of a single protein, resulting in human disease

• Immune dysregulation: severe/recurrent infection, autoimmunity/inflammation, allergy, cancer; often fatal

• incidence: ~1/5 000 to extremely rare

• discovery of the mutated gene can:
  - Provide an explanation for disease pathogenesis
  - Facilitate diagnosis/therapy
  - Determine function of specific genes
  - Lead to development of novel therapies
    - not just for the affected patients
Clinical Impact due to breakthroughs in PID research

A tale of 2 boys, c.1970
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X-linked severe combined immunodeficiency (SCID)
Interleukin-2 Receptor \( \gamma \) Chain Mutation Results in X-Linked Severe Combined Immunodeficiency in Humans

Masayuki Noguchi,\(^*\) Huafang Yi,\(\dagger\) Howard M. Rosenblatt,\(\ddagger\) Alexandra H. Filipovich,\(\S\) Stephen Adelstein,\(\ast\) William S. Modi,\(\mid\) O. Wesley McBride,\(\dagger\) and Warren J. Leonard\(\ast\)
Genetic Cause of X-SCID, and a treatment

Interleukin-2 Receptor \(\gamma\) Chain Mutation Results in X-Linked Severe Combined Immunodeficiency in Humans

The original PID: Agammaglobulinemia

AGAMMAGLOBULINEMIA

By Col. Ogden C. Bruton, M.C., U.S.A.
Washington, D.C.

Pediatrics. 1952. 6: 722

X-linked agammaglobulinemia

- recurrent infections with extracellular pyogenic pathogens
- chronic fungal infections rarely occur
- viral infections usually cleared
- all serum Ig isotypes very low/absent
- attributed as being the 1st description of a defect in human host defense
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- attributed as being the 1st description of a defect in human host defense
- treated with Ab replacement from donors
XLA and the discovery of B cells

• 1965: lymphocyte subsets had not yet been described
XLA and the discovery of B cells

- 1965: lymphocyte subsets had not yet been described, but XLA provided a clue they did

“a division most clearly seen in the Bruton type of X-linked recessive agammaglobulinemia in which there is virtually complete failure of plasma cell formation and γ-globulin production. Their immunological failure is only partial; they are able to express delayed-type hypersensitivity….and reject grafts”

- circulating B cells usually absent; bone marrow B cells greatly reduced
- T cells present in normal numbers
Identification of the genetic cause of XLA: Mutations in \textit{BTK}

Deficient Expression of a B Cell Cytoplasmic Tyrosine Kinase in Human X-Linked Agammaglobulinemia

Satoshi Tsuchida,\textsuperscript{1,2} Douglas C. Safra,\textsuperscript{2} David J. Rawlings,\textsuperscript{2} Ornella Parolini,\textsuperscript{3} R. Cutler Allen,\textsuperscript{4} Ivana Klisak,\textsuperscript{5} Robert S. Sparkes,\textsuperscript{6} Hiromi Kubagawa,\textsuperscript{7} Thuluvan cheri Mohandas,\textsuperscript{8} Shirley Quan,\textsuperscript{9} John W. Belmont,\textsuperscript{10} Max D. Cooper,\textsuperscript{11} Mary Ellen Conley,\textsuperscript{12} and Owen N. Witte\textsuperscript{13}

The gene involved in X-linked agammaglobulinaemia is a member of the \textit{src} family of protein-tyrosine kinases

David Vetrie\textsuperscript{11}, Igor \textit{Vořechovský}\textsuperscript{11}, Paschalis Sideras\textsuperscript{12}, Jill Holland\textsuperscript{11}, Angela Davies\textsuperscript{11}, Frances Flinter\textsuperscript{11}, Lennart Hammarsström\textsuperscript{11}, Christine Kinnon\textsuperscript{11}, Roland Levinsky\textsuperscript{11}, Martin Bobrow\textsuperscript{11}, C. I. Edvard Smith\textsuperscript{11} & David R. Bentley\textsuperscript{11}

\textsuperscript{1} Division of Medical and Molecular Genetics, UMDN of Guy’s and St. Thomas’s Hospitals, Guy’s Tower, London SE1 9RT, UK
\textsuperscript{2} Center for BioTechnology, Karolinska Institute, NOVUM, S-141 57 Huddinge, Sweden
\textsuperscript{3} Unit for Applied Cell and Molecular Biology, Umeå University, S-901 87 Umeå, Sweden
\textsuperscript{4} Molecular Immunology Unit, Institute of Div Health, 30 Guilford Street, London WC1N 1EH, UK
Ibrutinib in Previously Treated Waldenström’s Macroglobulinemia

Steven P. Treon, M.D., Ph.D., Christina K. Tripsas, M.A., Kirsten Meid, M.P.H., Diane Warren, B.S., Gaurav Varma, M.S.P.H., Rebecca Green, B.S., Kimon V. Argyropoulos, M.D., Guang Yang, Ph.D., Yang Cao, M.D., Lian Xu, M.S., Christopher J. Patterson, M.S., Scott Rodig, M.D., Ph.D., James L. Zehnder, M.D., Jon C. Aster, M.D., Ph.D., Nancy Lee Harris, M.D., Sandra Kanan, M.S., Irene Ghobrial, M.D., Jorge J. Castillo, M.D., Jacob P. Laubach, M.D., Zachary R. Hunter, Ph.D., Zeena Salman, B.A., Jianling Li, M.S., Mei Cheng, Ph.D., Fong Clow, Sc.D., Thorsten Graef, M.D., M. Lia Palomba, M.D., and Ranjana H. Advani, M.D.

Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia

John C. Byrd, M.D., Richard R. Furman, M.D., Steven E. Coutre, M.D., Ian W. Flinn, M.D., Ph.D., Jan A. Burger, M.D., Ph.D., Kristie A. Blum, M.D., Barbara Grant, M.D., Jeff P. Sharman, M.D., Morton Coleman, M.D., William G. Wierda, M.D., Ph.D., Jeffrey A. Jones, M.D., M.P.H., Weiqiang Zhao, M.D., Ph.D., Nyla A. Heerema, Ph.D., Amy J. Johnson, Ph.D., Juthamas Sukburanong, Ph.D., Betty Y. Chang, Ph.D., Fong Clow, Sc.D., Eric Hedrick, M.D., Joseph J. Buggy, Ph.D., Danelle F. James, M.D., and Susan O'Brien, M.D.

Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma

Wyndham H Wilson¹, Ryan M Young¹, Roland Schmitz¹, Yandan Yang¹, Stefania Pittaluga², George Wright³, Chih-Jian Lih⁴, P Mickey Williams⁴, Arthur I. Shaffer¹, John Gerecitano⁵-⁶, Sven de Vis⁶, Andre Goy⁷, Vaishalee P Kenkre⁸, Paul M Barr⁹, Kristie A Blum¹, Andrei Shustov¹⁰, Ranjana Advani¹¹, Nathan H Fowler¹², Julie M Vose¹³, Rebecca L Elstrom¹⁴, Thomas M Habermann¹⁵, Jacqueline C Barrientos¹⁶, Jesse McGreivy¹⁷, Maria Fardis¹⁸, Betty Y Chang¹⁹, Fong Clow²⁰, Brian Munneke²¹, Davina Moussa²², Darrin M Beaupre²² & Louis M Staudt²²

Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma

Michael L. Wang, M.D., Simon Rule, M.D., Peter Martin, M.D., Andre Goy, M.D., Rebecca Auer, M.D., Ph.D., Brad S. Kahl, M.D., Wojciech Jurczak, M.D., Ph.D., Ranjana H. Advani, M.D., Jorge E. Romaguera, M.D., Michael E. Williams, M.D., Jacqueline C. Barrientos, M.D., Ewa Chmielowska, M.D., John Radford, M.D., Stephan Stirkenbauer, M.D., Martin Dreyling, M.D., Wieslaw Wiktor Jedrzejczak, M.D., Peter Johnson, M.D., Stephen E. Spurgeon, M.D., Lei Li, Ph.D., Liang Zhang, M.D., Ph.D., Kate Newbery, Ph.D., Zhishuo Ou, M.D., Nancy Cheng, M.S., Bingfang Fang, Ph.D., Jesse McGreivy, M.D., Fong Clow, Sc.D., Joseph J. Buggy, Ph.D., Betty Y. Chang, Ph.D., Darrin M. Beaupre, M.D., Ph.D., Lori A. Kunkel, M.D., and Kristie A. Blum, M.D.
From a PID to BTK to a pan-therapeutic

“what Dr Bruton could not have known was that his discovery of XLA would open the door to a new target for B-cell malignancy therapy and provide the rationale for the development of the first ever BTK inhibitor to treat B-cell malignancies”

Gayko et al, 2015. Ann NY Acad Sci
Reports by the IUIS PID/IEI Committee

Primary immunodeficiency diseases: An update

Luigi Notarangelo, MD, a Jean-Laurent Casanova, MD, b Alain Fischer, MD, b
Jennifer Puck, MD, c Fred Rosen, MD, d Reinhard Seger, MD, * and
Ralf S. Geha, MD, for the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee.

Brescia, Italy, Paris, France, Bethesda, Md, Boston, Mass, and Zurich, Switzerland

Workshop summary

Primary immunodeficiency diseases: An update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee Meeting in Budapest, 2005

Luigi Notarangelo, MD, a Jean-Laurent Casanova, MD, b Mary Ellen Conley, MD, c Helen Chapel, MD, d Alain Fischer, MD, b Jennifer Puck, MD, c Chaim Roifman, MD, d Reinhard Seger, MD, * and Ralf S. Gehr, MD, b for the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee.

Brescia, Italy, Paris, France, Memphis, Tenn, Oxford, United Kingdom, Bethesda, Md, Toronto, Ontario, Canada, Zurich, Switzerland, and Boston, Mass

Primary immunodeficiencies: 2009 update

Luigi D. Notarangelo, MD, a Alain Fischer, MD, b and Ralf S. Gehr, MD, c (Co-chairs): Jean-Laurent Casanova, MD, c Helen Chapel, MD, d Mary Ellen Conley, MD, c Charlotte Cunningham-Rundles, MD, PhD, d Amos Etzioni, MD, b Lennart Hammarström, MD, f Shigeaki Nonoyama, MD, f Hans D. Ochs, MD, f Jennifer Puck, MD, c Chaim Roifman, MD, d Reinhard Seger, MD, * and Josiah Wedgwood, MD, PhD.

Boston, Mass, Paris, France, New York, NY, Oxford, United Kingdom, Memphis, Tenn, Haifa, Israel, Stockholm, Sweden, Tokorozawa, Japan, Seattle, Wash, San Francisco, Calif, Toronto, Ontario, Canada, Zurich, Switzerland, and Bethesda, Md

International Union of Immunological Societies Expert Committee on Primary Immunodeficiencies: 2011

Primary immunodeficiencies: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency


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

Increasing rate of discovery of Inborn Errors of Immunity
Increasing rate of discovery of Inborn Errors of Immunity
Next-generation sequencing $\rightarrow$ Gene Discovery

Falling fast

In the first few years after the end of the Human Genome Project, the cost of genome sequencing roughly followed Moore’s law, which predicts exponential declines in computing costs. After 2007, sequencing costs dropped precipitously.

![Graph showing falling sequencing costs](image)

- **Whole genome sequencing**
  - Sequencing region: whole genome
  - Sequencing Depth: >30X
  - Covers everything—can identify all kinds of variants including SNPs, INDELS, and SV.

- **Whole exome sequencing**
  - Sequencing region: whole exome
  - Sequencing Depth: >50X ~ 100X
  - Identify all kinds of variants including SNPs, INDELS, and SV in coding region.
  - Cost effective

- **Targeted sequencing**
  - Sequencing region: specific regions (could be customized)
  - Sequencing Depth: >500X
  - Identify all kinds of variants including SNPs, INDELS, and SV in specific regions.
  - Most cost-effective
Criteria for calling a variant “pathogenic”

- 5M variants
- 2.8M good data quality
- 28,000 within genes
- 16,600 nonsilent variants
- 2600 are rare in healthy individuals
- 68 de novo mutations
- 20 predicted pathogenic
- 1 matches phenotype
Criteria that must be met to attribute a clinical phenotype to a candidate genotype in a single patient.

1. Family studies and population studies must indicate that the patient’s candidate genotype is monogenic and does not occur in individuals without the clinical phenotype (complete penetrance).

2. In-depth experimental and mechanistic studies must indicate that the genetic variant destroys or markedly impairs or alters the expression or function of the gene product (or two genetic variants in the case of compound heterozygosity).

3. The causal relationship between the candidate genotype and the clinical phenotype must be established via a relevant cellular or animal phenotype.
Increasing rate of discovery of Inborn Errors of Immunity

Modified from Meyts et al, 2016. J Allergy Clin Immunol
## Classification of Inborn Errors of Immunity

<table>
<thead>
<tr>
<th>Table</th>
<th>Category</th>
<th>Examples</th>
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| 1     | Immunodeficiencies affecting cellular and humoral immunity (3 subtables; 57 genes) | • IL2RG, JAK3, IL7R  
• RAG1/2, ADA, AK2  
• CD40LG, ICOS, DOCK8, TAP1 |
| 2     | Combined immunodeficiencies with associated or syndromic features (9 subtables; 63 genes) | • WAS, ATM, FOXP1  
• STAT3, IL6ST, IKBKG  
• STIM, TTC7A |
| 3     | Predominantly Antibody Deficiencies (4 subtables; 38 genes) | • BTK, TOP2B  
• PIK3CD*, CD19, NFKB1/2, AICDA |
| 4     | Diseases of Immune Dysregulation (7 subtables; 45 genes) | • PRF1, UNC13D  
• FOXP3, IL2RA, CTLA4, AIRE  
• IL10/R, RIPK1; FAS, FADD  
• SH2D1A, CD27/70, TNFRSF9, MAGT1 |
| 5     | Defects of phagocytes (4 subtables; 41 genes) | • ELANE, SRP54, ITGB2, WDR1  
• CYBB, NCF1, GATA2 |
| 6     | Defects in Intrinsic and Innate Immunity (9 subtables; 63 genes) | • IL12RB1/2, CXCR4, IFNAR1, TLR3  
• CARD9, IL17RA, STAT1*, IRAK4 |
| 7     | Autoinflammatory Disorders (3 subtables; 42 genes) | • TREX1, SAMHD1, MEFV, NLRP3, NOD2, TNFAIP3, IL1RN |
| 8     | Complement Deficiencies (35 genes) | • C1QA/B/C, SERPING1, CD46, CD55 |
| 9     | Bone Marrow Failure (46 genes) | • FANCA/B/C, SAMD9/L, TERT, RTE1 |
| 10    | Phenocopies of IEI | • somatic mutations; autoAbs |
Phenotypic Classification of PID/IEIs

The 2017 IUHIS Phenotypic Classification for Primary Immunodeficiencies


I. Immunodeficiencies affecting cellular and humoral immunity
(b) Combined Immunodeficiencies Generally Less Profound than Severe Combined Immunodeficiency

Low CD4: MHCII Expression?
- Absent: MHCII def.
- Present: MAGI1 def.

Low CD8:
- A0, LxI def.:
- ADGC19 def.:

Low Bc:
- DOCK8 def. DOCK2.
- HG16 def. HG17.
- LGD1 def. LGD2.
- LGT1 def. LGT2.

Ig: Often NL
- DOCK1 def. DOCK2.
- HG16 def. HG17.
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Ig Low
- IGE1 def. IGE2.
- IGE3 def. IGE4.
- IGE5 def. IGE6.
- IGE7 def. IGE8.

Normal Ig but Poor Specific Antibody response
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Phenotypic Classification of PID/IEIs

I. Immunodeficiencies affecting cellular and humoral immunity

(b) Combined Immunodeficiencies Generally Less Profound than Severe Combined Immunodeficiency

Low CD4: MHC class II deficiency

Ig DLow: often seen in NL

LGL deficiency: CD4 + T cells low

RHO-K deficiency: Low IgM, IgA, IgG
deficiency

Low CD8: NK cells, natural killer cells

Ig E Low: often seen in NL

MAOI deficiency: Low IgM, IgA, IgG
deficiency

Low Bc: Absent: MHC class II deficiency

Ig F Low: often seen in NL

NKG2A deficiency: Low NK cells, natural killer cells

Ig G Low: often seen in NL

CD8 deficiency: CD8 + T cells low

NOD1 deficiency: Low IgM, IgA, IgG
deficiency

CD4 Low: Low CD4 + T cells

NOD2 deficiency: CD8 + T cells low

CD8 Low: Low CD8 + T cells

NOD2 deficiency: Low CD4 + T cells

The 2017 IUIS Phenotypic Classification for Primary Immunodeficiencies

Azniz Boussifia1, Leila Jedane2, Capucine Picard1,2, Fatima Aïtal1, H. Bobby Garzar1,3, Waleed Al-Herz1, Talal Chatilla1, Yanick J. Crow1,9, Charlotte Cunningham-Rundles2,3, Amos Etzioni2,3, Jose Luis Franco2,3, Steven M. Holland2,3, Christoph Klein4,5, Boshinho Morio2,3, Hans D. Ochs6, Eric Oksenhendler7, Jennifer Puck1,8, HILD, K. Tang1,9,20,31, Stuart G. Tangy1,9,20,31, Troy R. Torgerson1,8, Jean-Laurent Casanova1,8,4,25,26,27, Kathleen E. Sullivan1,8,28

Phenotypical Diagnosis

Amine Ahmouch

PID Classification

App Store Preview

This app is only available on the App Store for iOS devices.

PID Phenotypical Diagnosis

Amine Ahmouch

5.0, 3 rating

Free

iPhone Screenshots

Classification tables:

I. Immunodeficiencies affecting cellular and humoral immunity

II. CD4 with associated or symptomatic features 2015

III. Predominantly antibody deficiencies 2015

IV. Diseases of immune dysregulation 2014

V. Vascular defects of phagocyte number, function, or both 2015

VI. Defects in innate and innate immunity 2015

VII. Auto-inflammatory disorders 2015

Search by manifestation:

- Classification tables
- Search by manifestation
- How to explore PID

Normal values

Ranges for IgG

0 - 2 years

IgG1: 0.32 ± 1.96
IgG2: 0.25 ± 1.03
IgG3: 0.25 ± 1.03
IgG4: 0.25 ± 1.03

Normal values

- IgG1: 0.32 ± 1.96
- IgG2: 0.25 ± 1.03
- IgG3: 0.25 ± 1.03
- IgG4: 0.25 ± 1.03

- IgM: 0.05 ± 0.784
- IgA: 0.42 ± 0.84
- IgE: 0.06 ± 0.78
Allelic variability results in diverse clinical phenotypes: Know your mutation!

<table>
<thead>
<tr>
<th>Gene</th>
<th>AD LOF</th>
<th>AR LOF</th>
<th>AD GOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAT1</td>
<td>MSMD (DN/LOF)</td>
<td>MSMD + viral disease</td>
<td>CMC, autoimmunity</td>
</tr>
<tr>
<td>CARD11</td>
<td>Atopic dermatitis, Allergy + (DN)</td>
<td>CID</td>
<td>Polyclonal B cell expansion</td>
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<tr>
<td>RAC2</td>
<td>Phagocytic defects</td>
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</table>

**STAT1**

- Human STAT1 immunity
- IFN-γ, IFN-α, IFN-λ
- Mycobacteria, Viruses (HSV)
- IL-27
- IL-17A, F. Candida
- IFN-α/β
- Thyroiditis, SLE
- BOISSON-DUPUIS ET AL, 2012. CURR OPIN IMMUNOL

Allelic variability results in diverse clinical phenotypes: Know your mutation!

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</table>

**STAT1**

[Image: Diagram showing the role of STAT1 in human immunity, with different states: normal, LOF, and GOF.]

**CARD11**

[Image: Diagram showing the role of CARD11 in disease progression, with labels for AR and AD pathways.]


HY Lu et al, 2018. Front Immunol
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<tr>
<td>RAC2</td>
<td>Phagocytic defects</td>
<td>CVID</td>
<td>T/B lymphopenia, CID</td>
</tr>
<tr>
<td>STAT5B</td>
<td>GH insensitivity, mild immune dysregulation (DN)</td>
<td>GH insensitivity, severe immune dysregulation, infections</td>
<td>-</td>
</tr>
<tr>
<td>STAT3</td>
<td>AD-HIES (DN)</td>
<td></td>
<td>Autoimmunity, infections, short stature (somatic: LGL)</td>
</tr>
<tr>
<td>PIK3CD</td>
<td>No phenotype</td>
<td>B-cell deficiency, agamma</td>
<td>APDS1</td>
</tr>
<tr>
<td>PIK3R1</td>
<td>APDS2/SHORT syndrome (*no phenotype)</td>
<td>B-cell deficiency, agamma</td>
<td>-</td>
</tr>
<tr>
<td>IKZF1</td>
<td>DN: CID</td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>
Allelic variability results in diverse clinical phenotypes: Know your mutation!

| Gene   | AD LOF                                              | AR LOF                                               | AD GOF                                               |
|--------|-----------------------------------------------------|                                                     |                                                     |
| STAT1  | MSMD (DN/LOF)                                       | MSMD + viral disease                                 | CMC, autoimmunity                                    |
| CARD11 | Atopic dermatitis, Allergy + (DN)                   | CID                                                  | Polyclonal B cell expansion                          |
| RAC2   | Phagocytic defects                                  | CVID                                                 | T/B lymphopenia, CID                                 |
| STAT5B | GH insensitivity, mild immune dysregulation (DN)    | GH insensitivity, severe immune dysregulation, infections | -                                                   |
| STAT3  | AD-HIES (DN)                                        | -                                                    | Autoimmunity, infections, short stature (somatic: LGL) |
| PIK3CD | No phenotype                                        | B-cell deficiency, agamma                            | APDS1                                                |
| PIK3R1 | APDS2/SHORT syndrome (*no phenotype)                | B-cell deficiency, agamma                            | -                                                    |
| IKZF1  | DN: CID                                             | -                                                    | -                                                    |
|        | Haplo: CVID                                         |                                                     |                                                     |

- IFNGR1, WAS, ZAP70, TCF3, IKBKB, JAK1, IFIH1
NGS has enabled gene-targeted therapies for inborn errors of immunity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gene</th>
<th>Targeted therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPEX</td>
<td>FOXP3</td>
<td>Tacrolimus, Cyclosporin, Sirolimus</td>
</tr>
<tr>
<td>STAT1 GOF</td>
<td>STAT1</td>
<td>Ruxolitinib (JAK 1/2 inhibitor), Sirolimus</td>
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<tr>
<td>STAT3 GOF</td>
<td>STAT3</td>
<td>Tocilizumab (IL-6 receptor blocker), Siltuximab (IL-6 blocker), Ruxolitinib (JAK 1/2 inhibitor)</td>
</tr>
<tr>
<td>LRBA deficiency</td>
<td>LRBA</td>
<td>Abatacept, Sirolimus, Hydroxychloroquine</td>
</tr>
<tr>
<td>CTLA4 haploinsufficiency</td>
<td>CTLA4</td>
<td>Sirolimus, Abatacept</td>
</tr>
<tr>
<td>APDS</td>
<td>PIK3CD, PIK3R1</td>
<td>Sirolimus, Leniolisib (PI3K inhibitor)</td>
</tr>
<tr>
<td>XIAP and NLRC4</td>
<td>BIRC4, NLRC4</td>
<td>IL-18 binding protein</td>
</tr>
<tr>
<td>Primary HLH</td>
<td>PRF, UNC13 D, STX11, STXBP2</td>
<td>Emapalumab (IFN-γ blocking antibody), Ruxolitinib (JAK 1/2 inhibitor)</td>
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Leiding & Forbes, 2019. JACI In Pract. 7: 761
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Human DEF6 deficiency underlies an immunodeficiency syndrome with systemic autoimmunity and aberrant CTLA-4 homeostasis

Nina K. Serwas, Birgit Hoeger et al.

Immune responses need to be controlled tightly to prevent autoimmune diseases, yet underlying molecular mechanisms remain partially understood. Here, we identify biallelic mutations in three patients from two unrelated families in differentially expressed in FDCP6 homolog (DEF6) as the molecular cause of an inborn error of immunity with systemic autoimmunity. Patient T cells exhibit impaired regulation of CTLA-4 surface trafficking associated with reduced functional CTLA-4 availability, which is replicated in DEF6-knockout Jurkat cells. Mechanistically, we identify the small GTPase RAB11 as an interactor of the guanine nucleotide exchange factor DEF6, and find disrupted binding of mutant DEF6 to RAB11 as well as reduced RAB11+CTLA-4+ vesicles in DEF6-mutated cells. One of the patients has been treated with CTLA-4-Ig and achieved sustained remission. Collectively, we uncover DEF6 as player in immune homeostasis ensuring availability of the checkpoint protein CTLA-4 at T-cell surface, identifying a potential target for autoimmune and/or cancer therapy.

CIRCA: Clinical Immunogenomics Research Consortium Australasia

Stuart Tangye
Tri Phan
Chris Goodnow
Cindy Ma
Elissa Deenick
Robert Brink
Jin Yap
Owen Siggs
Alisa Kane
Shane Grey
Brian Gloss
Mary Anne Young
Sarah Kummerfeld
Marcel Batten
Leslie Burnett
Aaron Statham
Warren Kaplan
Georgina Hollway
Karen Enthoven

Paul Gray
Rebecca Macintosh
John Ziegler
Katie Frith
Shruti Swamhy
Rohit Saldahna

Stephen Adelstein
Roger Garsia
Ron Fleischer
Amali Mallawaarachchi
Fred Lee

Winnie Tong
Tri Phan
Tony Kelleher
Kathy Wu

Alisa Kane
Louise Evans
Catherine Toong

Kirby Institute
Tony Kelleher
Kate Merlin
Mel Lograsso
Bertha Fsadni

Lucinda Berglund
Ming-Wei Lin

NSW Government
Health Western Sydney Local Health Network

Kahn Preece

Starship
Annaliese Blincoe
Jan Sinclair
Shannon Brothers
Kuang Hsiao

Queensland Government
Children’s Health Queensland Hospital and Health Service

Jane Peake
Luke Droney

IDFA
Christine Jeffery

Sir Charles Gairdner Hospital
Michael O’Sullivan
Andrew McLean-Tooke

Immune Deficiencies Foundation Australia

Jeffrey Modell Centers Network

Jeffrey Modell Centers Network
Genetic variants identified as causes of PID:

- Known mutations/variants in known PID genes
  - *PIK3CD* (x5), *PIK3R1* (3), *STAT3*, *FLG*, *NFkB2* (3 family members)

- Novel mutations in known PID genes
  - *IL7R*, *ATM*, *TMEM173* (*STING*; x3), *TNFAIP3* (~10), *GATA2*, *FAS*, *UNC13D*, *RNASEH2B*, *CECR1* (*ADA2*; 4 pts#), *CTLA4* (>5), *DOCK8* (3 unrelated families), *MAGT1*, *LRBA*#, *STK4*# (2 sibs), *DOCK2*# (3 sibs)

- Novel mutations
  - *ZNF341*
CIRCA Outcomes – Diagnoses/Gene Discovery/Treatments

Genetic variants identified as causes of PIDs

• Known mutations/variants in known PID genes
  • \textit{PIK3CD} (x5), \textit{PIK3R1} (3), \textit{STAT3}, \textit{FLG}, \textit{NFkB2} (3 family members)

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• Novel mutations
  • \textit{ZNF341}

Gene-specific therapies

• Abatacept: \textit{LRBA, CTLA4}
• Sirolimus/Everolimus: \textit{PIK3CD, CTLA4}
• JAK inhibitors: \textit{RNASEH2B, TMEM173 (STING)}
• Mg replacement: \textit{MAGT1}
• Humira: \textit{TNFAIP3}
• HSCT: \textit{MAGT1, DOCK8, STK4} (younger sibling) – excellent outcomes so far
IEIs inform/explain/predict outcomes of treatments for other conditions

CTLA4 deficiency

Immune dysregulation in human subjects with heterozygous germline mutations in CTLA4

Mutations in CTLA4 cause an autosomal-dominant immune dysregulation syndrome in humans
CTLA4 haploinsufficiency phenocopies adverse effects of CTLA4 blockade in cancer immunotherapy

Autoimmunity Correlates With Tumor Regression in Patients With Metastatic Melanoma Treated With Anti-Cytotoxic T-Lymphocyte Antigen-4

Table 1. Patient characteristics, clinical response, and toxicity

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Disease sites</th>
<th>Prior therapy</th>
<th>No. of cycles received*</th>
<th>Response (mos.)</th>
<th>Toxicity (grade III/IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52/M</td>
<td>Lung</td>
<td>I, S</td>
<td>2</td>
<td>PR (15+)</td>
<td>Enterocolitis; dermatitis</td>
</tr>
<tr>
<td>2</td>
<td>40/F</td>
<td>Supraclavicular lymph node</td>
<td>C, I, S</td>
<td>1</td>
<td>NR</td>
<td>Dermatitis; vitiligo†</td>
</tr>
<tr>
<td>3</td>
<td>39/M</td>
<td>Lung, mediastinum, subcutaneous</td>
<td>S</td>
<td>6</td>
<td>NR (mixed)</td>
<td>Pulmonary infiltrates†</td>
</tr>
<tr>
<td>4</td>
<td>55/F</td>
<td>Skin, subcutaneous</td>
<td>I, S</td>
<td>4</td>
<td>NR</td>
<td>ANA+†</td>
</tr>
<tr>
<td>5</td>
<td>67/M</td>
<td>Liver, retroperitoneum, subcutaneous</td>
<td>C, I, R, S</td>
<td>4</td>
<td>NR</td>
<td>Vitiligo†</td>
</tr>
<tr>
<td>6</td>
<td>59/M</td>
<td>Lung, subcutaneous</td>
<td>I, S</td>
<td>2</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>48/M</td>
<td>Lung, brain, adrenal, subcutaneous</td>
<td>I, S</td>
<td>2</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>48/M</td>
<td>Lung, liver, adrenal, mesentry, subcutaneous</td>
<td>C, I, S</td>
<td>2</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>53/M</td>
<td>Mediastinum, mesentry, skin</td>
<td>I, R, S</td>
<td>2</td>
<td>NR</td>
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<tr>
<td>10</td>
<td>62/M</td>
<td>Lung, hilum</td>
<td>C, I, S</td>
<td>2</td>
<td>NR (mixed)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>54/M</td>
<td>Lung, brain, subcutaneous</td>
<td>C, S</td>
<td>5</td>
<td>CR (12+)</td>
<td>Hypophysitis</td>
</tr>
<tr>
<td>12</td>
<td>43/M</td>
<td>Subdiaphragm, muscle, subcutaneous</td>
<td>I, S</td>
<td>3</td>
<td>NR</td>
<td>Hepatitis; ANA+†</td>
</tr>
<tr>
<td>13</td>
<td>49/F</td>
<td>Lung, subcutaneous</td>
<td>C, I, S</td>
<td>4</td>
<td>CR (11+)</td>
<td>Dermatitis</td>
</tr>
<tr>
<td>14</td>
<td>63/M</td>
<td>Lung, pelvic lymph node</td>
<td>S</td>
<td>4</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>
IEIs inform/explain/predict outcomes of treatments for other conditions

### Other targets of immunotherapy
- IL-6R (Tocilizumab) $\rightarrow$ IL6ST, IL6R
- IL-21 $\rightarrow$ IL21R, IL21
- IFN$\gamma$ $\rightarrow$ IFN$\gamma$R1/2
- PD1/VISTA/TIGIT $\rightarrow$ ???

### Table 1: IL-12p40, IL-23p19 and IL-17A and IL-17RA antagonists in clinical development

<table>
<thead>
<tr>
<th>Target</th>
<th>IL-12p40; IL-23p40</th>
<th>IL-123p19</th>
<th>IL-17A; IL-17RA</th>
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<tbody>
<tr>
<td>Psoriasis</td>
<td>Approved</td>
<td>Ph3</td>
<td>Approved</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Approved</td>
<td>Ph2 (terminated)</td>
<td>Ph3</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>Ph3</td>
<td>Ph2</td>
<td>Ph3</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Ph2</td>
<td>Ph2</td>
<td>Ph3 (terminated)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Ph2</td>
<td>Ph2</td>
<td>Ph3</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Ph2</td>
<td>Ph2</td>
<td>Ph3</td>
</tr>
<tr>
<td>Graft-versus-host disease</td>
<td>Ph2</td>
<td>Ph2</td>
<td>Ph3</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>Ph2</td>
<td>Ph2</td>
<td>Ph2</td>
</tr>
<tr>
<td>Hidradenitis suppurativa</td>
<td>Ph2</td>
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</tbody>
</table>

**PID(s)/IEI:** IL12B, IL12RB1, IL23R, IL17RA, IL17F
Acknowledgements

All patients and their families!
Outcomes of Next gen DNA sequencing in PIDs

2. Change in patient management

![Bar chart showing outcomes of Next gen DNA sequencing in PIDs with categories such as Antibody deficiency, Autoimmune disease, Combined (non-SCID) or selective T cell defect, etc., and different colors representing change in diagnosis, change in diagnosis and management, change in management after confirmation of suspected diagnosis, and confirmation of diagnosis, no change in management.](image)
How is genomic testing done?

1. Counselling and consent
2. Blood sample taken
3. Extract DNA
4. Put DNA into sequencer
5. Read entire DNA code (genome)
6. Compare to a reference genome
How is genomic testing done?

1. Counselling and consent
2. Blood sample taken
3. Extract DNA
4. Put DNA into sequencer
5. Read entire DNA code (genome)
6. Compare to a reference genome
7. Analyse the differences
6.4 billion nucleotides
~21,000 protein coding genes

In every individual;
~3.2 million variants
~100 pathogenic variants

Which one caused the patient’s severe disorder?
Which ones predispose to future disease risk?
Which ones could cause adverse drug reactions?
PHASE TWO: INTERPRETATION

I think I found a corner piece.
Outcomes of Next gen DNA sequencing in PIDs

1. Rate of Diagnosis

~30-40% success rate
Table 2. Infants Screened and Incidence of SCID (Including Leaky SCID) in 11 Contributing Programs

<table>
<thead>
<tr>
<th>Duration of screening included, mo</th>
<th>California</th>
<th>Colorado</th>
<th>Connecticut</th>
<th>Delaware</th>
<th>Massachusetts</th>
<th>Michigan</th>
<th>Mississippi</th>
<th>Navajo Nation</th>
<th>New York</th>
<th>Texas</th>
<th>Wisconsin</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants screened, No. (^a)</td>
<td>1384606</td>
<td>70989</td>
<td>57136</td>
<td>11202</td>
<td>293371</td>
<td>162528</td>
<td>37613</td>
<td>3498</td>
<td>485912</td>
<td>183191</td>
<td>340037</td>
<td>3030083</td>
</tr>
<tr>
<td>Flow cytometry referrals, (^b) No. (%) [95% CI] (^c)</td>
<td>206 (14.9) [12-17]</td>
<td>10 (14.1) [5.4-23]</td>
<td>22 (38.5) [22-55]</td>
<td>9 (80.3) [28-133]</td>
<td>63 (21.5) [16-27]</td>
<td>114 (70.1) [57-83]</td>
<td>5 (13.3) [1.6-25]</td>
<td>1 (28.6) [98.4]</td>
<td>478 (135.9) [90-107]</td>
<td>249 (31.8) [26-38]</td>
<td>1265 (41.8) [39-44]</td>
<td></td>
</tr>
<tr>
<td>SCID cases</td>
<td>23</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td>2</td>
<td>4</td>
<td>52</td>
</tr>
<tr>
<td>SCID incidence</td>
<td>1/60000</td>
<td>1/71000</td>
<td>1/19000(^d)</td>
<td>1/11000(^d)</td>
<td>1/73000</td>
<td>1/81000</td>
<td>1/38000</td>
<td>1/3500(^d)</td>
<td>1/49000</td>
<td>1/92000</td>
<td>1/85000</td>
<td>1/58000(^f) [1/46000-1/80000]</td>
</tr>
<tr>
<td>SCID cases per 100000 screened, No. [95% CI] (^c)</td>
<td>1.7 [1.0-2.3]</td>
<td>1.4 [0.3-5.2]</td>
<td>5.2 [1.9-15]</td>
<td>8.9 [2.2-49]</td>
<td>1.4 [0.4-3.5]</td>
<td>1.2 [0.4-4.4]</td>
<td>2.7 [0.6-5]</td>
<td>29 [6.9-159]</td>
<td>2.0 [0.8-3.3]</td>
<td>1.1 [0.3-3.9]</td>
<td>1.2 [0.3-3.0]</td>
<td>1.72 [1.3-2.2]</td>
</tr>
<tr>
<td>SCID infant survival, No./Total No. (%) [95% CI] (^c,e)</td>
<td>21/23 (91) [83-100]</td>
<td>1/1 (100)</td>
<td>3/3 (100)</td>
<td>1/1 (100)</td>
<td>4/4 (100)</td>
<td>1/2 (50)</td>
<td>0/1 (100)</td>
<td>1/1 (100)</td>
<td>9/10 (90) [70-100]</td>
<td>0/2 (100)</td>
<td>4/4 (100)</td>
<td>45/52(^f) [86] [79-98]</td>
</tr>
</tbody>
</table>
Genetic testing

BASIC TYPES OF DATA

PARTICIPANT

SAMPLE

Sequencing

Sequence types shown as examples

→ not constrained by sample type

Gene panel

Whole genome seq

Exome seq

Whole genome sequencing

Whole exome sequencing

Targeted sequencing

- Sequencing region: whole genome
- Sequencing Depth: >30X
- Covers everything – can identify all kinds of variants including SNPs, INDELs and SV.

- Sequencing region: whole exome
- Sequencing Depth: >50X ~ 100X
- Identify all kinds of variants including SNPs, INDELs and SV in coding region.
- Cost effective

- Sequencing region: specific regions
  (could be customized)
- Sequencing Depth: >500X
- Identify all kinds of variants including SNPs, INDELs in specific regions
- Most Cost effective

Garvan Institute of Medical Research
~350 genes
2019 Lasker Prize: JFAP Miller & Max Cooper

B and T cells—the organizing principle of the adaptive immune system

Max D. Cooper  
Emory University School of Medicine

Jacques Miller  
The Walter and Eliza Hall Institute of Medical Research

Two-lymphocyte lineage model of adaptive immunity

BLOOD-FORMING TISSUES

THYMUS

STEM CELL

T cells

Cell-mediated immunity

Activated T cells

Crosstalk

BURSA OF FABRICIUS

B cells

Antibody-based (humoral) immunity

Plasma cells

Antibodies
CIRCA Pipeline: start with patients; take findings back to the patient/clinic, take research possibilities to the lab.

Likely monogenic Extreme phenotype

CIRCA

Biobanking

GENOME.ONE

Research

Publication
Novel disease gene

Animal models

Prioritise variants

MEGA

Phenotyping patient cells

RNA Seq

Check if variants impact protein

Expression/functional analysis of variants in primary cells, cell lines, animal models
CIRCA Outcomes – Research spin offs

Research projects

- patients added to existing cohorts under study (Tangye/Ma/Deenick/Goodnow labs)
  - *STAT3*, *NFKB2*, *DOCK8* LOF; *PIK3CD* GOF
- new collaborative projects; investigating mechanisms of disease pathogenesis, expanding the phenotype/informing the natural history of new PIDs, basic research
  - *TNFAIP3* (A20) (Shane Grey/Goodnow/Siggs/Brink/Gray/Wong)
  - *STK4* (Phan/Wong/Tangye/Ma)
  - *TMEM173* (STING) (Gray/Wong/Seth Masters [WEHI])
  - *ADA2* (Tangye/Kelleher/Kane/Lin/Isabelle Meyts [Luven])
  - *MAGT1* (Gray/Andy McLean-Tooke [WA]/Tangye)
  - *NFKB2* (Gray/Goodnow/Tangye/Vanessa Bryant [WEHI])
  - *FOXP3* (Gray/Ma/John Andersson [Karolinska])
  - *CTLA4* (Phan/Peter Hsu/Gulbu Uzel [NIH])
- generation of CRISPR gene-edited mice bearing pathogenic germline mutations
  - *Lrba*, *Stk4*, *Pik3cd*, *Pik3r1*, *MVK*, *Stat3* GOF ..........(Phan/Deenick/Goodnow/Brink labs)
NGS enabled gene-targeted therapies for inborn errors of immunity

Leiding & Forbes, 2019. JACI In Pract. 7: 761
