Primary Immunodeficiency: Where We Are & Where We Are Going

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Disclosures

- CSL-Behring Publication Research Grants
- Speaker Bureau and Advisory Board Member (Shire and CSL-Behring)
- X4 Pharma – screening for and treatment in WHIM syndrome
- Principal Investigator on Pediatric studies with Hyqvia (Shire)
What will we learn?

1. Basic immunology of T, B cells and neutrophils
2. Basic information about PIDD
3. Genetics of PIDD
4. Current and novel approach to therapy
**WHY** are we committed to advance Immunology research and diagnostics?

We aim to

- **Change lives** of children and adults with PID
- **Advance understanding** of disease mechanisms
- **Precisely treat**
- **Promote prevention** to avoid disease
Immunobiology of T, B cells and neutrophils
Lymphocyte by electron microscopy
Dr. Triche NCI 1976
T cell

- Directly fights viral and yeast infections: Cytotoxic T cell
- Helps B cells to make antibodies to fight bacterial (viral, fungal) infections: Helper T cells
- Regulates inflammation: Regulatory T cell

**SCID**
Severe combined immunodeficiency

**B cell**
Makes antibodies

**XLA**
X-linked agammaglobulinemia

**SAD**
Specific antibody deficiency

**IgA def**
Specific antibody deficiency

**CVID**
Common variable immunodeficiency

**CID**
Combined immunodeficiency
- Hyper IgM syndrome
- DOCK8 (Hyper IgE syndrome)
- Wiskott-Aldrich syndrome

**Hyper IgA def**
Specific antibody deficiency
ADAPTIVE IMMUNE SYSTEM

- Diversifies with age and exposure
- Pathogen specific
- Response to previous exposure

**B cells**

B cells “antibody deficiencies”
50% of all PIDs
recurrent sinopulmonary infections
Chronic and recurrent gastroenteritis
Chronic enteroviral meningitis (XLA)
Arthritis, unexplained bronchiectasis

Laboratory test:
1. **Number:** B cell count and subsets
2. **Function:**
   - Age appropriate immunoglobulin levels
     *Catch them early!*
     - dx can be delayed by 2-5 years in childhood
   - Vaccine-specific titers (tetanus > Hib > pneumococcus)
     (Prevnar13 and Pneumovax23)

**T cells**

T cells “cellular deficiencies”
Viral infections (warts, herpes, EBV)
Fungal infections
Malignancy

Laboratory test:
1. **Number:** T cell count
2. **Function:** T cell proliferation
INNATE IMMUNE SYSTEM

- Inborn and non-specific
- First line defense
- Does not require previous exposure

Complement

A. Early defects (C1q – C3):
- Recurrent pyogenic infections
- Encapsulated organisms
- Glomerulonephritis and SLE (40-90%)

B. Late defects (C5-C9):
- Recurrent Neisseria infections

C. Disrupted Control of complement activation: (Factor I, Factor H, MCP)
- Familial HUS
- Age related macular degeneration

Laboratory test: CH50 test

Phagocytosis (neutrophils)

A. Neutrophil adhesion defects
- Can not adhere and cross vessel wall
- Soft tissue abscesses, lymphadenopathy
- Neutrophils missing in abscess
- Poor wound healing, chronic gingivitis, periodontitis

Laboratory test: Flow cytometry
- β2 integrins: CD11 and CD18 (LAD I)
- CD15 (LAD II), platelet aggregation (LAD III)

B. Chronic granulomatous disease (CGD)
- Can not kill the organisms
- Catalase (+) (Staph, Aspergillus)
- Osteomyelitis, skin and liver abscesses
- Inflammatory bowel disease

Laboratory test: Flow cytometry

Number: CBC with differential

Function: Neutrophil oxidative burst (NBT vs DHR test)
HOW can we change YOUR our YOUR FAMILY’s life?

- Advocacy/awareness
- Screening (prevention)
- Early diagnosis and targeted treatment (intervention)
Diagnosis of PIDD from onset of symptoms may take a decade: we need increased awareness.
Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.

1. Four or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or fungal infection on skin.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections including septicemia.
10. A family history of PI.

1. Too many infections
2. Weird infections
3. Weird autoimmunity
4. Lymphopenia
5. Failure to thrive
Weird infections

**Bacterial infections:**
- Broad spectrum: respiratory tract
- Narrow spectrum: catalase+ (Staph, Pseudo) encapsulated (Neisseria)

**Antibody deficiencies**

**Chronic granulomatous disease**

**Complement deficiency**

**Viral infections:**
- Skin warts: HPV
- Severe lower respiratory
- Persistent GI bugs: norovirus

**T cell deficiencies (SCID, CID), neutrophil (WHIM)**

**Innate defect (MDA5 deficiency)**

**Combined immunodeficiencies**

**Fungal infections:**
- Fungi: candidiasis
- Mold: aspergillus
- Atypical fungi: pneumocystis

**T and innate cell deficiencies (SCID, NEMO, STAT1 LOF)**

**T cell deficiencies, CGD, Hyper IgE sy**

**T cell deficiencies (SCID, Hyper IgM sy)**
Infections
Autoimmunity
Inflammation
Malignancy
Lymphoproliferation
Severe allergies
Rheumatology
Gastroenterology
Hematology/Oncology
Infectious Disease
Neonatology
Cardiology
REFERRALS
Walter JE, unpublished
HOW can we change YOUR our YOUR FAMILY’s life?

- Advocacy/awareness
- Screening (prevention)
- Early diagnosis and targeted treatment (intervention)
Late Diagnosis of severe PIDD may be fatal:
we need screening programs
Why is newborn screening for SCID approved?

- incidence (at least 1:100,000)
- fatal without treatment
- early treatment improves outcome
- robust feasible test
- reasonable “false positive” rate
SCID incidence of 1:60K
4M birth / year in US: we expect 70 SCID patients / year
Changing face of SCID in the era of NBS

- Good news: we find most infants in asymptomatic stage

- Bad news: we find many infants who are not classical SCID
  - SCID variants (where to draw the line for HSCT?)
  - other causes of T cell lymphopenia
Where are we going with screening programs from newborn Guthrie cards (DNA-based assay)?

### Pilot programs for impaired B cell maturation

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCID (TREC/KRECs) - EU</td>
<td>1:60,000</td>
</tr>
<tr>
<td>XLA screening (KRECs) - EU, Brazil</td>
<td>1:250,000</td>
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</table>

### Could we extend NBS to CGD or antibody def?

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<th>Condition</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>CGD</td>
<td>1:200,000</td>
</tr>
<tr>
<td>Antibody deficiency syndromes</td>
<td>1:10,000 - 1:2,000</td>
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DNA-based whole exome sequencing may be a solution in the future.
HOW can we change YOUR our YOUR FAMILY’s life?

- Advocacy/awareness
- Screening (prevention)
- Early diagnosis and targeted treatment (intervention)
## Layers of diagnoses – why does it matter?

<table>
<thead>
<tr>
<th>Diagnosis #1: Infections</th>
<th>Adaptive Antigen deficiency sy</th>
<th>Adaptive SCID</th>
<th>Innate CGD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic recurrent broad spectrum bacterial</td>
<td>Early severe viral, bacterial fungal</td>
<td>Intermittent narrow spectrum bacterial and fungal</td>
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</table>

<table>
<thead>
<tr>
<th>Diagnosis #2: Autoimmunity</th>
<th>Adaptive Autoimmune cytopenia arthritis, vasculitis</th>
<th>Adaptive rare (Omenn sy)</th>
<th>Innate Autoimmune cytopenia arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune cytopenia arthritis, vasculitis</td>
<td>rare (Omenn sy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory bowel granulomatous lung</td>
<td>Abnormal T cell quantity and/or quality with low antibody production</td>
<td>Abnormal neutrophil killing (CGD)</td>
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</tbody>
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<tr>
<th>Diagnosis #3: Inflammation</th>
<th>Adaptive Abnormal quantity or quality of antibodies (CVID, SAD, IgA def)</th>
<th>Adaptive (SCID vs. athymia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza bowel granulomatous lung</td>
<td>Abnormal T cell quantity and/or quality with low antibody production (SCID vs. athymia)</td>
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<th>Diagnosis #4: Immunology</th>
<th>Adaptive Abnormal quantity or quality of antibodies (CVID, SAD, IgA def)</th>
<th>Adaptive Abnormal neutrophil killing (CGD)</th>
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</thead>
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## Genetics – why does it matter?

<table>
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<th>Diagnosis #5: Genetics</th>
<th>Adaptive Antibody deficiency sy</th>
<th>SCID</th>
<th>Innate CGD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very limited</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVID: 20-40%</td>
<td></td>
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<tr>
<td>SAD: &lt;1%</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>IgA def: 0%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Agammaglobulinemia (30%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XLA: 100% (BTK gene)</td>
<td>High success rate (75%)</td>
<td></td>
<td>High success rate (95%?)</td>
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**SCID**

- High success rate (75%)

**CGD**

- High success rate (95%?)
Genetics of CVID

**Several US-based companies offer fast and reliable genetic testing**

**Heterogenous disease:**
Known genes only represent 30-40% of cases

**B cells:**
BTK, IKZF1, CD27, PLCG2, BLK, RAC2, VAV1

**Tregs:**
LRBA/CTLA4, STAT1/STAT3 GOF

**Combined immunodeficiency:**
RAG1/2, POLE

**GC reaction:**
IL-21, IL21R, SAP

**Signaling molecules:**
PIK3CD/PIK3R1
NFkB1/NFkB2/NEMO
CBM complex (CARD11)
IRF2BP2, DNMT3B, ZBTB24

*Bogaert JMG 2015 Genes associated with common variable immunodeficiency: one diagnosis to rule them all*
HOW can we change YOUR our YOUR FAMILY’s life?

- Advocacy/awareness
- Screening (prevention)
- Early diagnosis and targeted treatment (intervention)
## Genetics-driven therapy – why does it matter?

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<th>Therapy</th>
<th>Adaptive</th>
<th>Innate</th>
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<tr>
<td><strong>Bridge therapy</strong></td>
<td>Immunoglobulin, antibiotics, immune modulation</td>
<td>Antimicrobial IFNγ, immune mod.</td>
</tr>
<tr>
<td><strong>Genetics-based therapy</strong></td>
<td>Targeted therapy for AI</td>
<td>Gene therapy vs HSCT</td>
</tr>
<tr>
<td><em><em>HSCT</em> limited</em>*</td>
<td>Gene therapy</td>
<td>Gene therapy vs HSCT</td>
</tr>
<tr>
<td>Family planning</td>
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* Hematopoietic stem cell transplant (bone marrow transplant)
Definitive therapies for PID: from bone marrow transplant (HSCT) to gene therapy (GT)
First HSCT
Outcome of HSCT in SCID

Optimal
• T and B cells normal count and function
• Sustained stem cell presence in bone marrow (engraftment)
• No autoimmune complication after HSCT

Risk factors for increased mortality/morbidity
• Decreased HLA compatibility
• Active infections
• Age (>3 mo) in combination with infections
• Autoimmune complications before transplant

Pai NEJM 2014, Fisher JACI 2017
SCID Transplant Outcomes

- **Mortality** - 20-40%
- Complication with graft-versus-host
- Autoimmunity
- Inadequate antibody production - 30-60%
- Growth and development problems
- Cognitive problems
- **Decline in T cell function?**
Gene Therapy for SCID
Basic process of gene therapy using HSC

**Patient**

**Blood sample**

Bone marrow or GCSF-mobilized peripheral blood

**Gene therapy preparation in test tube:**

Correct gene transfer with viral vector

Hematopoietic stem cells

**Corrected hematopoietic stem cells**

**Infusion** of corrected HSC

one allele is corrected (PID X-linked or AR)

**Patient**

“Transplant”
Gene Therapy for SCID: Rationale

• correct the disease at its roots by inserting one normal copy of the gene into the patient’s hematopoietic stem cells

• no risks of Graft-versus-Host Disease

• selective advantage expected for gene-corrected cells in T cell development

• no or little chemotherapy needed

• an alternative to MMRD-HCT for patients who lack HLA-identical donors

• stem cells readily available (patients own cells!)
Changing approach for CVID/CID

1. Clinical features
   - severe infections while on IgRT (fungal, viral)
   - non-infectious complications (cytopenias, granulomas, lymphomas)

2. Immune phenotyping
   - CD19\textsuperscript{hi}/21\textsuperscript{low} B cells, naïve/memory T and B cells, IgM

3. Genetic evaluation
   - SCID/CID and primary antibody deficiency gene panel
HSCT and Gene Therapy for non-SCID PIDs

**CVID/CID**
- **HSCT:** CTLA4, LRBA, PI3K, STAT1GOF, RAG genetic defects
- **GT on horizon:** for Hyper IgM syndrome, RAG-CID and XLA

**CGD**
- **HSCT/GT**
  
  no selective advantage of stem cell in bone marrow
  
  overall promising
Our mission

In the era of Prevention:
Newborn screening for SCID (and other PIDs)

Diversity:
unprecedented phenotypic and immunological diversity
overlapping disease phenotypes

We need to utilize
Advanced diagnostic studies
Search for genetic cause (targeted, WES, WGS)
Confirmatory functional assays

We can advance
Early recognition of specific PID disease
Promote targeted and definitive treatment strategies
Family planning
Thank you for your attention!

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Children’s Research Institute, University of South Florida

Johns Hopkins All Children’s Hospital
Bogaert JMG 2015 Genes associated with common variable immunodeficiency: one diagnosis to rule them all
How to read a genetic report?

Type of mutations (change in nucleotide code in the gene):
1. Disease-causing (pathogenic) mutation
2. Variant of unknown significance
3. Polymorphism

Heterozygous mutation in a gene only relevant:
- when two alleles are effected (autosomal recessive)
- X-linked disease
- Gain-of-function or dominant negative mutations