# Diagnostic clues to primary immunodeficiencies

Ásgeir Haraldsson Professor in peadiatrics Faculty Chairman and chair Children's Hospital Iceland







# Review of the immune system and diagnostic clues to primary immunodeficiencies

Ásgeir Haraldsson Professor in peadiatrics Faculty Chairman and chair Children's Hospital Iceland











Protein to protein interactions



Airplane traffic over Europe



Internet traffic









# Neutrophils !



### Neutrophils

storage pool marginating pool circulating pool tissue

> Releas: 80 millj. per min !!! Life-span:2-3 days (or less)

### Granulocyte disorders



Neutrophil numbers

Neutrophil function

- Recurrent resp inf
- +/- fever
- Skin infections
- Mucous membranes infections
- GE infections / disorders
- Sepsis
- Granulomas and abscesses
- Unusual pathogens
- Umbilical cord !

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#### Neutropenia and neutrophil dysfunction

- Aplastic anaemia
  Pancytopenia (drugs, toxins, infections, etc.)
- Postinfectious neutropenia
  Autoimmune / benign
- ✓ Iatrogen (drugs, irradiation)



Neutrophil numbers

Neutrophil function

- Recurrent resp inf
- **-** +/- fever
- **V**− Skin infections
- $\mathbf{v}$  Mucous membranes infections
- $\mathbf{v}$  GE infections / disorders
  - Sepsis
  - Granulomas
- V − Unusual pathogens
- $\mathbf{V}$  Umbilical cord !





# Macrophages

## Macrophages / dendritic cells



# From stimulus (infection) to specific antibodies (immunoglobulins)



### The beautiful TLR!



#### Herpes Simplex Virus Encephalitis in Human UNC-93B Deficiency

Jean-Laurent Casanova Science 13 October 2006



# Komplement



- V Recurrent bacterial infections
- V Inf with capsulated bacteria (meningococcus, pneumococcus)
- V Autoimmune disorders
  - SLE
  - Glomerulonephritis
  - HUS
  - Angio-oedema

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IMMUNOLOGY REPORTS

#### OPEN

#### Immunodeficiency Among Children with Recurrent Invasive Pneumococcal Disease

Helene Ingels, PhD,\*† Lone Schejbel, PhD,‡ A.C. Lundstedt, PhD,‡ Lise Jensen, MD,† Inga A. Laursen, PhD,§ Lars P. Ryder, MSc,‡ Niels H.H. Heegaard, DMSc, DNSc,§ Helle Konradsen, DMSc,\* Jens Jørgen Christensen, DMSc\*¶, Carsten Heilmann, DMsc,† and Hanne V. Marquart, PhD‡

Conclusion: Of an unselected cohort of children with rIPD at least 11% were C2 deficient. Data suggest that screening for complement deficiencies and deficient antibody response to pneumococcal vaccines in patients with more than 1 episode of IPD is warranted.

The Pediatric Infectious Disease Journal • Volume 34, Number 6, June 2015

#### Invasive Pneumococcal Disease in Children Can Reveal a Primary Immunodeficiency

Jean Gaschignard,<sup>1,2,3</sup> Corinne Levy,<sup>3,4,5</sup> Maya Chrabieh,<sup>1,2</sup> Bertrand Boisson,<sup>6</sup> Cécile Bost-Bru,<sup>7</sup> Stéphane Dauger,<sup>8</sup> François Dubos,<sup>3,9</sup> Philippe Durand,<sup>10</sup> Joël Gaudelus,<sup>3,11</sup> Dominique Gendrel,<sup>3,12</sup> Christèle Gras Le Guen,<sup>3,13</sup> Emmanuel Grimprel,<sup>3,14</sup> Gaël Guyon,<sup>15</sup> Catherine Jeudy,<sup>16</sup> Eric Jeziorski,<sup>15</sup> Francis Leclerc,<sup>17</sup> Pierre-Louis Léger,<sup>14</sup> Fabrice Lesage,<sup>18</sup> Mathie Lorrot,<sup>19</sup> Isabelle Pellier,<sup>16</sup> Didier Pinquier,<sup>3,20</sup> Loïc de Pontual,<sup>3,11</sup> Philippe Sachs,<sup>8</sup> Caroline Thomas,<sup>21</sup> Pierre Tissières,<sup>10</sup> Frédéric V. Valla,<sup>22</sup> Philippe Desprez,<sup>23</sup> Véronique Frémeaux-Bacchi,<sup>24</sup> Emmanuelle Varon,<sup>3,25</sup> Xavier Bossuyt,<sup>26</sup> Robert Cohen,<sup>3,4,5</sup> Laurent Abel,<sup>1,2,6</sup> Jean-Laurent Casanova,<sup>1,2,6,27,28</sup> Anne Puel,<sup>1,2</sup> and Capucine Picard<sup>1,2,27,29</sup>

*Conclusions.* Children with IPD should undergo immunological investigations, particularly those aged >2 years, as PIDs may be discovered in up to 26% of cases.

Clinical Infectious Diseases 2014;59(2):244–51

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  - SLE
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#### Microbe —— specific antibodies











#### B-cell development





Kristbjörn Orri Guðmundsson

## Immunoglobulins





#### Immunoglobulins Unbelievable diversity



Hypervariable CDRs are located on loops at the end of the Fv regions



Hypervariable regions







#### Base pairs....!!?





#### "Rearrangement"

# Amsterdam-Keflavík-Reykjavík-Paris damaRk Danmark

#### "Rearrangement"



#### "Rearrangement"

# Amsterdam-Keflavík-Reykjavík-Paris Adam eve í Paris Adam and Eve in Paradise

#### Rearrangement – kappa keðjan





#### Serum immunoglobulins



Agammaglobulinaemia Hypogammaglobulinaemia Transient hypogamma of infancy IgA deficiency Subclass deficiency (IgG2 def) Antibody deficiency

HyprerIgE Sx Hyper IgM Sx Hyper IgD

#### CVID



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HyprerIgE Sx Hyper IgM Sx Hyper IgD



#### CVID

B-cell defects (T-cell defects?) Number and function

- ✓ Recurrent infections (RTI)
- $\checkmark \quad \text{Not in first months of life}$
- ✓ Bacterial infections (esp. capsulated)
- ✓ Recurrent inf with same microorganisms

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# T-cells



## From the beginning ..... !











#### Helper (CD4+), several subtypes Control/activering/cytokine production









#### Cytotoxic (CD8+, CTL), several subtypes Destroy abnormal/virus infected/malignant/ cells











#### **T-cells**

Helper (CD4+), several subsets

Cytotoxic (CD8+, CTL), several subsets

Memory (CD4+ eða CD8+)

Regulatory  $(T_{reg})$ 

NK (NKT fr)



## More T-cells

Memory (CD4+ eða CD8+)

Regulatory (T<sub>reg</sub>) (Autoimmunity and immunol tolerance)

NK (NKT fr) Direct killing Cytoken production



Cellular defects

(with B- cell involvement)

- $\checkmark$  Early in life
- $\checkmark \quad \text{Failur to thrive}$
- Recurrent infections,
  viral, fungal and parasitic
- ✓ Autoinflammatory reactions
- ✓ Malignancies
- etc etc

Cellular defects

(with B- cell involvement)

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- Cellular defects
- (with B- cell involvement)
- **V** Early in life
- **V** Failure to thrive
- Recurrent infections, viral, fungal and parasitic Autoinflammatory reactions
- V Malignancies

etc



## Combined immunodeficiencies

## T and B cell interaction


## T and B cell interaction





## APC and T and B cell interaction





# Summary !

## Immunological diseases

#### Neutrophil defects

- Number or function
- Skin infections
- Mucous membranes infections
  - Granulomas
  - Umbilical cord

#### Complement defects

- Recurrent bacterial infections
- Inf with capsulated bacteria (meningococcus, pneumococcus)
  - Autoimmune disorders

#### Humoral defects

- B-cell defects
- Number and function
- ✓ Not in first months of life
- ✓ Recurrent infections (RTI)
- ✓ Bacterial infections (esp. capsulated)

#### Cellular defects

- Early in life
- Recurrent infections,
  - viral, fungal and parasitic
- 🗸 Malignancies





# A practical approach to serious infections in children



An ESPID supported three day training course in Iceland 2-4 February 2017

(Reduced price for ESPID members)

The aim of the course is to train frontline doctors who look after children, using a practical approach to recognise and manage a wide range of serious infections, identifying the seriously unwell child and considering differential diagnoses. The emphasis will be on interactive small-group workshops (max 10 people per workshop). The number of participants is therefore limited.



**Further information:** http://www.cpreykjavik.is/static/files/ESPID/2017/espid\_-2017\_program.pdf

#### A practical approach to serious infections in children 2<sup>nd</sup>-4<sup>th</sup> February 2017, Reykjavík, Iceland



The course is sponsored by ESPID (European Society for Paediatric Infectious Diseases, <u>www.espid.org</u>) and The Children's Hospital Iceland







# **FIN** !!!