Role of Academia in Rare Diseases

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My background

- Pediatrician, with focus on hematology and oncology in children
  - → Public University Hospital (Karolinska University Hospital)

1. I regularly meet and care for patients with rare diseases (RD)

2. In my function as an academic clinical scientist, I also:
   - → Define disease mechanisms for RD
   - → Develop diagnostic tools for RD
   - → Develop monitoring tools for RD
   - → Develop treatments for RD (using previously known drugs)
     - More than 1000 patients treated by these treatment protocols
   - → Support the development of a new Orphan Drug

Structure of the presentation

1. **The Role of Academia in Rare Disease Research**
2. Organize specific research networks
3. Some thoughts on ICORD
   = International Conference for Rare Diseases and Orphan Drugs

Is Academic Research Important for RD?

Can Academic Researchers:

- Identify clinical syndromes
- Develop diagnostic tools (essential for proper therapy)
  → Improve patient monitoring
- Improve therapies with existing drugs
  → Run clinical trials
  → Find new indications for old drugs
- Identify new treatments and new potential drugs

Improved survival in childhood cancer

- **We can now cure around 75% of all children with cancer.**

- This is mainly the result of collaborative studies among academic reseachers.
- We mainly use chemotherapy, surgery and irradiation.
- Note: The drugs we use are old drugs, used in novel combinations.
- Almost all these studies have been academia driven, and usually international efforts (as within SIOP).

One personal example: The Histiocytosis

Two types of histiocytoses

1. Dendritic cell-related disorders
   → Langerhans Cell Histiocytosis (LCH) (Histiocytosis X)

2. Macrophage-related disorders

→ **Hemophagocytic Lymphohistiocytosis (HLH)**

- Familial hemophagocytic lymphohistiocytosis (FHL)
- Secondary hemophagocytic lymphohistiocytosis

Some major steps

1. Develop diagnostic tools
2. Develop international collaborative treatments
3. Register international treatment data centrally
4. Spread information gained

HLH – Diagnostic Guidelines 1991

- Fever
- Splenomegaly (usually with hepatomegaly)

- Cytopenia (≥ 2 lineages) (Hb <90 g/L, ANC <1.0, platelets <100)
- Hypertriglyceridemia or Hypofibrinogenemia

- Hemophagocytosis

Henter et al. Semin Oncol 1991; 18: 29-33

Diagnostic HLH Criteria in 2004

Five of the eight criteria below:

* Fever
* Splenomegaly
* Bi-Cytopenia

  Hb< 90g/L, Platelets <100x10^9/L, ANC<1.0x 10^9/L
* Hypertriglyceridemia and/or hypofibrinogenemia

  (fasting triglycerides ≥3.0 mmol/L, fibrinogen ≤1.5 g/L)
* Hemophagocytosis

* Low NK cell activity
* Hyperferritinemia (>500 microgram/L)
* High sCD25 (sIL-2r) (>2400 U/ml)

Henter et al. Pediatr Blood Cancer 2007; 48: 124-31

Karolinska Institutet

The 1st International HLH Treatment Study

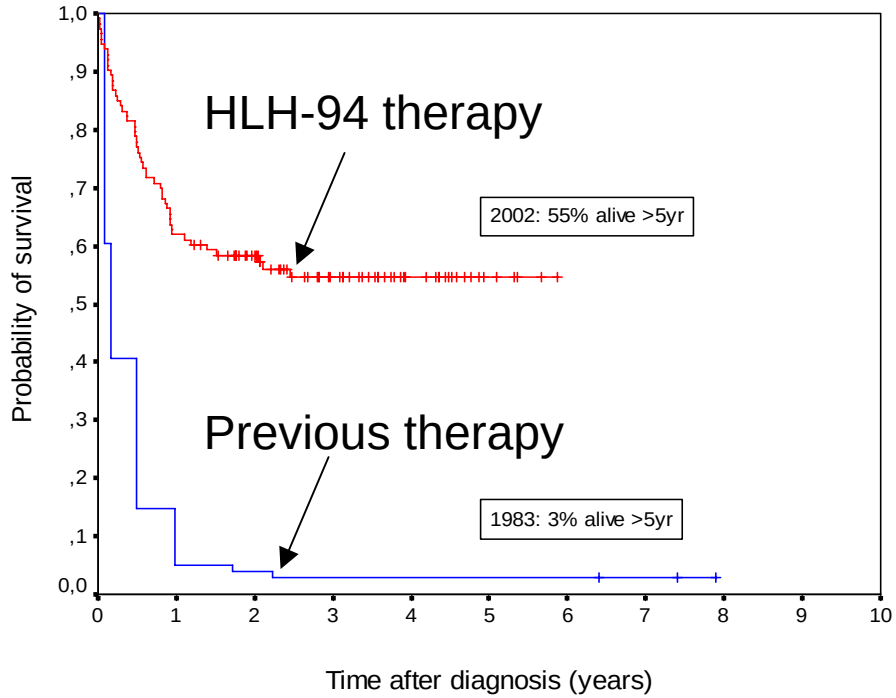
HLH-94

The HLH Study Group of the Histiocyte Society

HISTIOCYTE SOCIETY

Improved survival in HLH (Hemophagocytic Lymphohistiocytosis)

- **Familial hemophagocytic lymphohistiocytosis (familial HLH)**
- Immune defect
  - → Defect immune down-regulation
  - → Typically rapidly fatal
- Markedly improved survival
  - → From 0% to around 50%
- An international collaborative academic study in >25 countries



1983-data: Janka, Eur J Pediatr 1983; 140: 221-230

2002-data: Henter et al. Blood 2002; 100: 2367-2373

Karolinska Institutet

The 2nd International HLH Treatment Study

HLH-2004 is ongoing

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HISTIOCYTE SOCIETY

HLH lessons on immune system regulation

- **Rare Diseases can teach us on human biology!**
- **HLH can teach us on the regulation of the Immune System!**

1) Familial HLH = defect immune regulation (apoptosis deficiency).
   Fadeel et al. Br J Haematol 1999;106:406-15.

2) The perforin system that is deficient in FHL, is central in human immune regulation.
   Stepp et al. Science 1999; 286:1957-59.

3) CENTRAL FUNCTIONS of the PERFORIN SYSTEM:
- Downregulate the immune system
- Eliminate virus infected cells
- Eliminate cancer transformed cells

HLH and how to identify new potential drugs

1. Elevated levels of Interferon (IFN)-gamma in HLH
   → Henter JI, et al, Blood 1991;78:2918-22.

2. CD8+ T cells and Interferon-gamma are essential for HLH
   → Jordan MB, et al. Blood 2004;104:735-43.

3. Neutralization of IFN-gamma defeats hemophagocytosis in mice
   → Pachlopnik Schmid J, et al. EMBO Mol Med 2009;1:112-124.

4. Can anti-Interferon-gamma be used in patients with HLH
   → Collaborative effort with academia + pharma industry

Is Academic Research Important for RD?

YES – Since Academic Researchers can:

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Added Value of Research in Rare Diseases

1. For patients with Rare Diseases (RD) - and their families
2. + For individuals with other, related diseases
3. + For individuals with other, non-related diseases
4. = For the Society as a whole

Structure of the presentation

1. The Role of Academia in Rare Disease Research

2. **Organize specific research networks**

3. Some thoughts on ICORD
   = International Conference for Rare Diseases and Orphan Drugs

How to run clinical studies in many countries?

- Problems (for us):
  → We are non-profit
  → We have very limited money and staff (and nothing when we started)

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- Answer: Organize Specific Research Networks !
  → As the International HLH Study Group

  → Through International Scientific Societies

  → Annual Meetings are valuable!
    - There we meet to discuss and distribute information
    - More than 30 countries participate

How to organize Annual Meetings?

- Problems:
  - → We are non-profit.
  - → We have very limited money and staff

- Answer:
  - → Annual Meetings – can be arranged by the patient organizations!
    - Win-Win – for all - For more than 20 years
    - Allows scientists to meet, despite a rare disease
    - Allows patients' organizations access to recent scientific advances

The Histiocytosis Association of America (Parent/patient organisation)

- Created in 1986 by two parents
  (a partnership of patients, families, physicians, and friends). Aims:
  → To promote research aiming for improving cure
  → To support patients and their families.
  → To promote education related to the histiocytoses

- More than 5,000 registered members

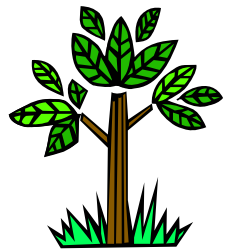
- Over 80 research projects have been substantially funded

- Supports the scientific international Histiocyte Society
- (thereby providing access for patients to recent scientific advances)

Collaboration Academia - Patients on Rare Diseases

- Collaboration Academia – Patients/Parents can be very valuable
  - Supporting clinical studies
  - Supporting research grants
  - Supporting administrative duties
  - = Access to physicians, new treatments and research data

- Academic International Clinical Studies can be very successful in Rare Diseases



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ICORD History

- 2005: 1st ICORD conference (Stockholm)
  → The idea of regular meetings and a society was mentioned
- 2006: 2nd ICORD conference (Madrid)
- 2007: 3rd ICORD conference (Brussels)
- 2008: 4th ICORD conference (Washington DC)
- 2009: 5th ICORD conference (Rome)
- 2010: 6th ICORD conference (Buenos Aires)

- The ICORD Society was constituted in Brussels, Sept 13, 2007.
- The Society was formally approved by tax authorities Feb 22, 2008.

ICORD Mission

- To improve the welfare of patients with rare diseases and their families world-wide

  through better knowledge, research, care, information, education and awareness.

ICORD Aims

1. To organize International Conferences on Rare Diseases and Orphan Drugs (ICORD)
2. To promote research, ethics, policies and actions on rare diseases and orphan products in all regions of the world
3. To facilitate and provide a global forum for all stakeholders for effective communication, formation of opinion and public debate, concerning rare diseases and orphan products
4. To enhance international discussion, cooperation and coordination of research, policies and actions of all bodies active in the field of rare diseases and orphan products
5. To exchange best practices between existing bodies and develop international approaches and tools to address common issues in rare diseases and orphan products

ICORD Opportunities

- Multiply the success we have had in HLH to many other diseases, and provide a forum to facilitate rapid collaborative progress.

- ICORD can develop to a Large Rare Disease Forum
  → Scientific Societies in Rare Diseases can meet at ICORD
  → Bridging Academia, Industry, Authorities and Patients

Make ICORD a Large Rare Disease Forum

- Scientific Society Meetings in conjunction with ICORD!
  → One common day for ICORD and all the Societies
  - Access to excellent statistical experts
  - Support and ideas on clinical trials, ethical applications etc
  - Access to authorities (incl grant issues)
  - Access to and support on regulatory issues (FDA/COMP)

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- Industry get many meetings in one
- Regulators get close to researchers and industry

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- Industry get many meetings in one
- Regulators get close to researchers and industry
- Family Organizations can support by arranging Scientific Meetings
  - → Family organizations can teach each other
  - → Access to physicians, new therapy and research
  - → Support academic clinical trials in ”their disease(s)”

Grand Hôtel, Stockholm

Nobel Prize Laureate Accommodation