



**Karolinska  
Institutet**

# **Added Values of Research on Rare Diseases**

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**ICORD, Buenos Aires, March 18, 2010**

# 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

# 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, non-related diseases
4. For the Society as a whole

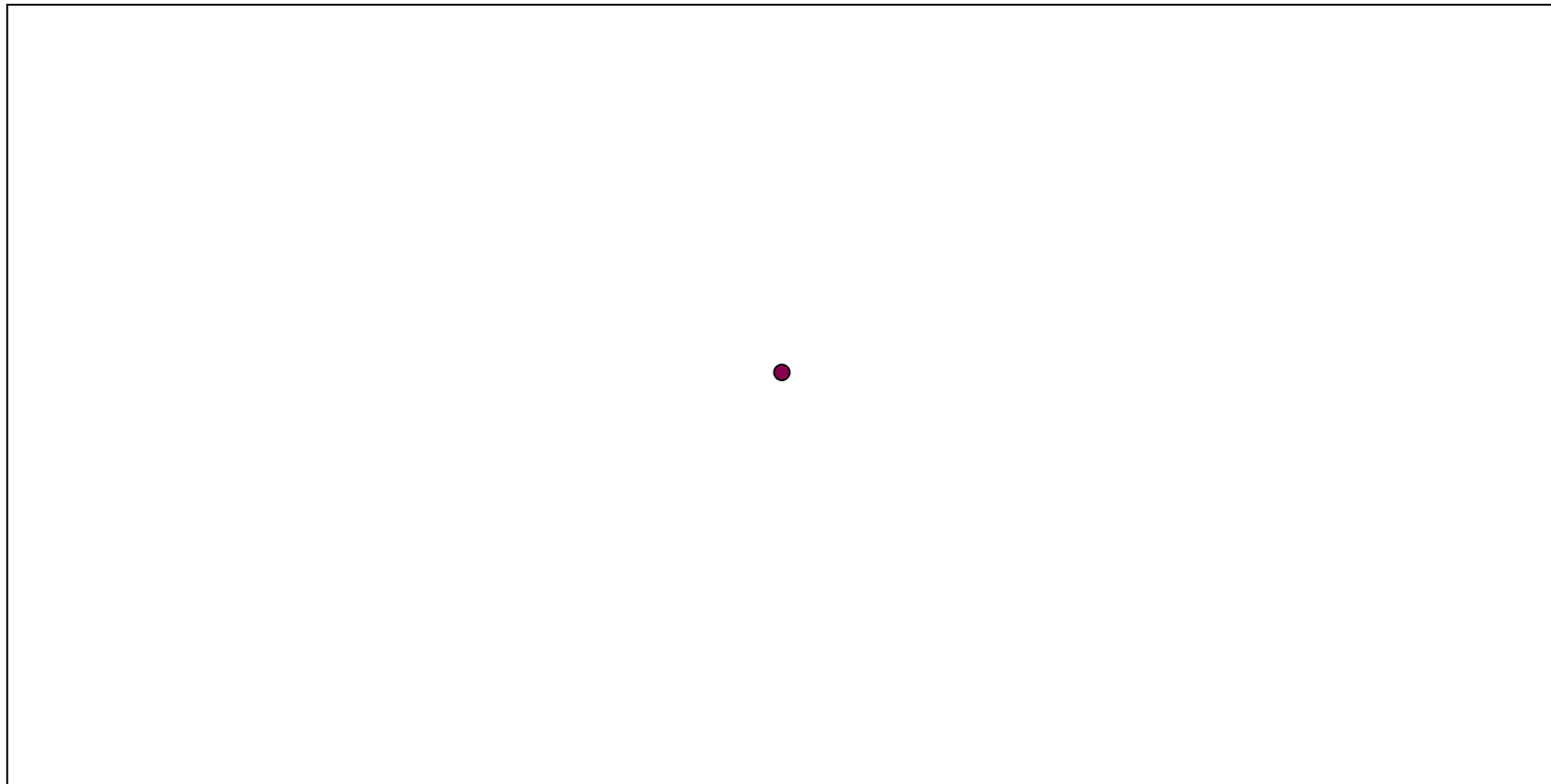
# 1. Value of Research in Rare Diseases

- Rare Diseases are not rare
- Rare Diseases are becoming more frequent
  - >6.000 diseases are "Rare Diseases"
  - About 5 new diseases / week (250/year) in the medical literature
  - **Common diseases are re- and subclassified**
    - **...and will become additional rare diseases**

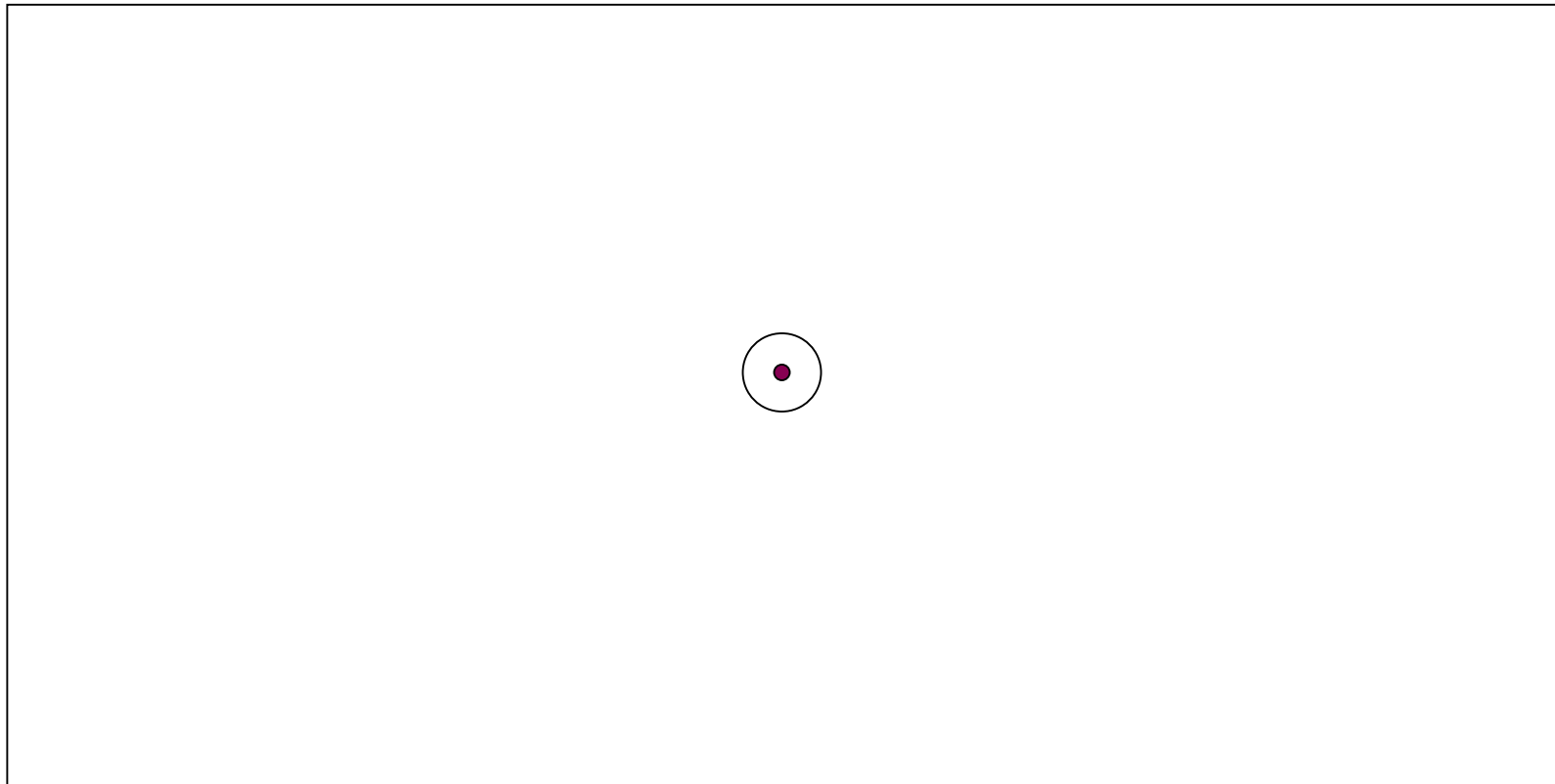
# 1. Value of Research in Rare Diseases

- Rare Diseases are not rare
- EU: Prevalence < 5 per 10.000 (<1/2000) inhabitants
  - Referred to as affecting 6-8% of the population. Then:
  - About **22-30 millions in South America** (pop 371 millions, 2005)
  - About **30-40 millions in the European Union** (pop >500 millions)
    - **With 4 independent relatives each = >200 million individuals + relatives**
  - **Major value in itself** to help all these individuals and families!!

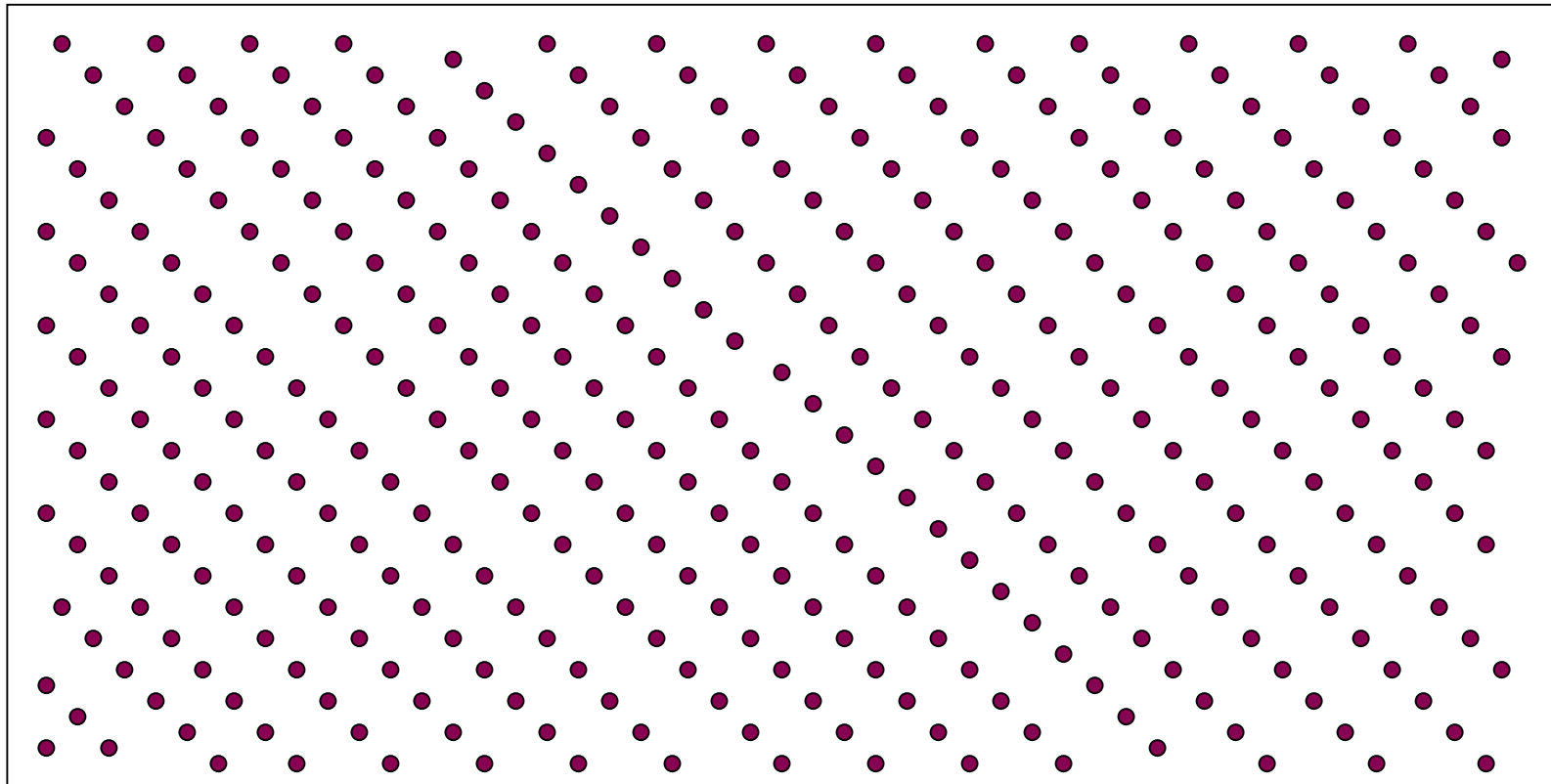
# 1. Value for affected individuals with a RD



# 1. Value for affected families, with one individual affected by a Rare Disease

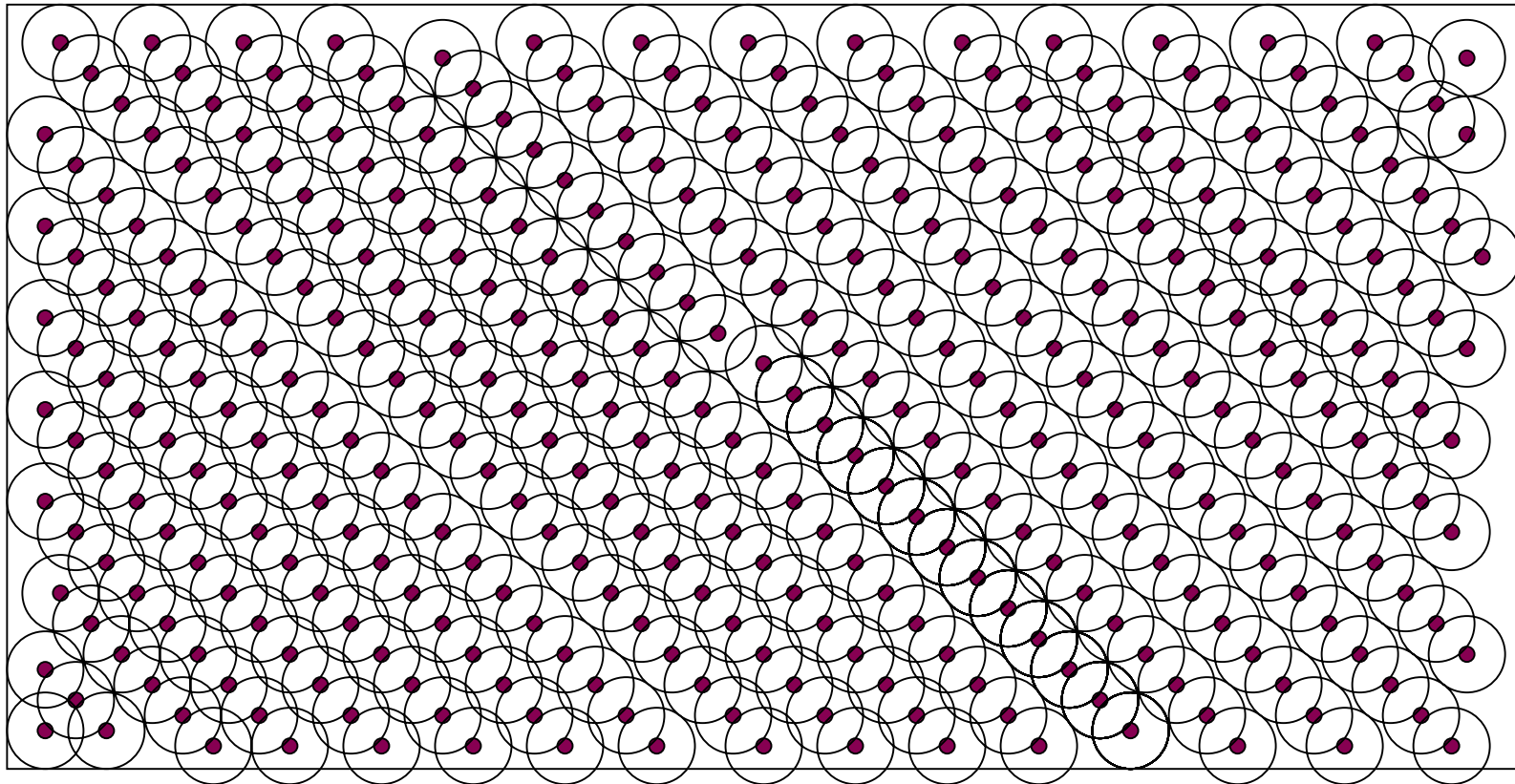


# 1. Value for all affected individuals with RD





# 1. Value for all families affected by a RD



# 1. One personal example: HISTIOCYTOSSES

- Two major types of diseases

→ 1. Dendritic cell-related disorders

- Langerhans Cell Histiocytosis (LCH) (Histiocytosis X)

→ 2. Macrophage-related disorders

- Hemophagocytic Lymphohistiocytosis (HLH)

→ Familial hemophagocytic lymphohistiocytosis (FHL)

**100% fatal** (median survival **1-2 months** after onset, untreated)

**Incidence 1:50.000 live born** (2 in Sweden per year). **Worth studying???**

→ Secondary hemophagocytic lymphohistiocytosis



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**The 1st International HLH Treatment Study**

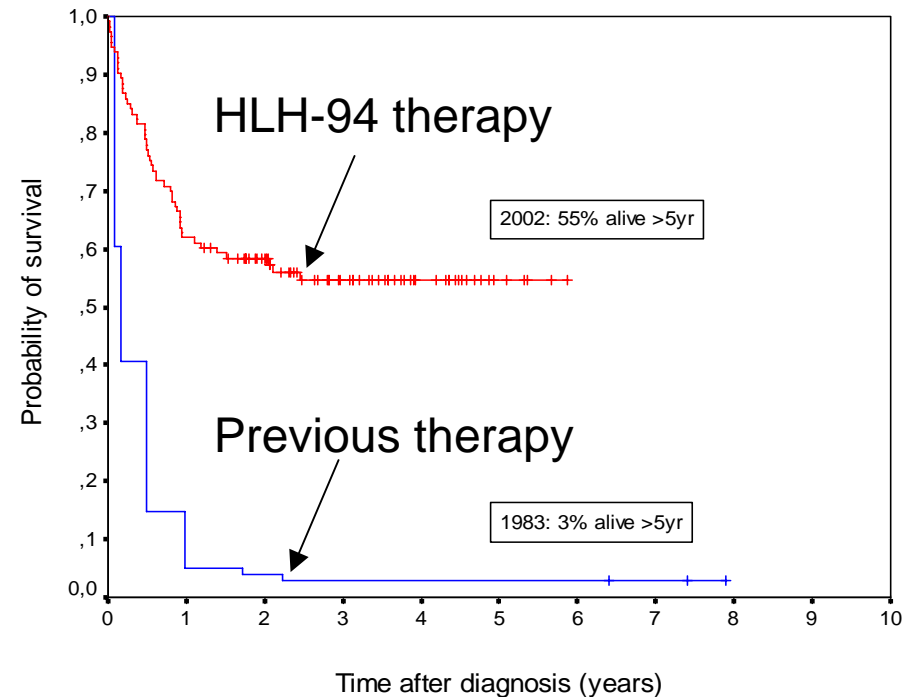
**HLH-94**

**The HLH Study Group  
of the Histiocyte Society**



# Improved survival in HLH by the study HLH-94

- **Familial hemophagocytic lymphohistiocytosis (familial HLH)**
- Immune defect
  - Defect immune down-regulation
  - Twice as common as SCID
- **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



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**The 2nd International HLH Treatment Study  
HLH-2004 is ongoing**

**The HLH Study Group of the  
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# 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

## 2. Value for individuals with related diseases

- Main Message:

A Rare Disease can teach us on other diseases, that may be more common

## 2. Value for individuals with related diseases

- Basic research:

A Rare Disease can be seen as an experimental model

Note: All lessons learned are relevant to human biology

- Clinical research:

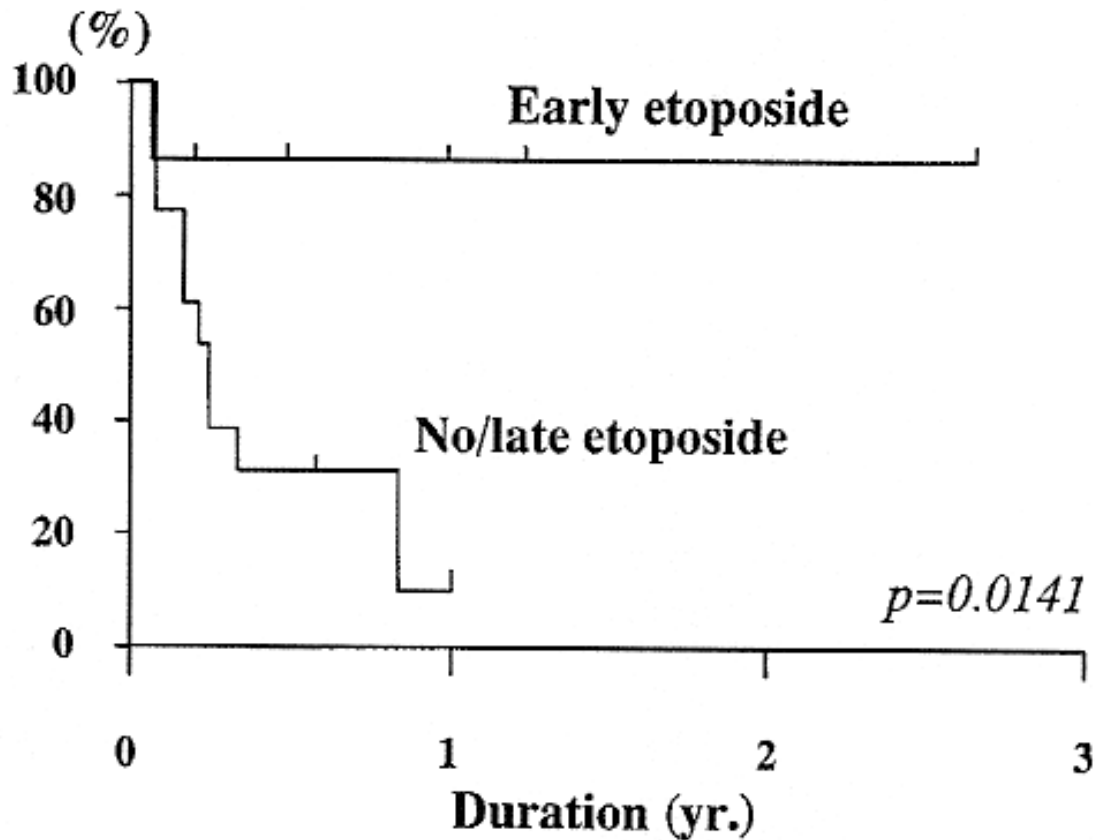
Studies on a RD may improve our knowledge on many related diseases, rare as well as common diseases.

→ On diagnostics, disease monitoring and treatments



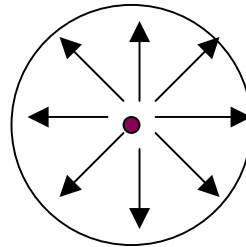
# Virus-associated HLH

Better survival with early VP-16 in Epstein-Barr-Virus-HLH in young adults



Imashuku et al, Med Pediatr Oncol 2003; 41: 103-09

## 2. Value for individuals with related diseases, and their families



### 3. Value for individuals with non-related diseases

- Main Message:  
A Rare Disease can teach us on other diseases, related or non-related, that may be more common
- Studies on human biology are relevant to human biology!
- Some personal experiences

# Familial (primary) HLH – the tip of an ice-berg !!

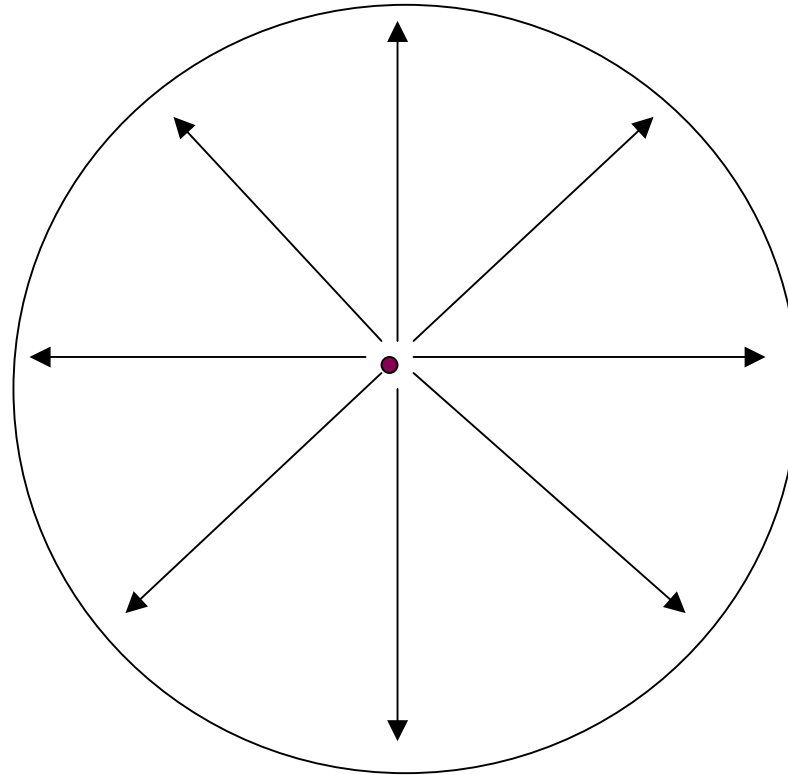
- **SECONDARY HLH:**
  - Virus-associated HLH (as EBV)
  - Bacteria-associated HLH
  - Malignancy-associated HLH
  - Rheuma-associated HLH
    - Macrophage activating syndrome
- **At one Intensive Care Unit, 64 % of the deceased had signs of hemophagocytosis!**
  - Strauss et al, Crit Care Med 2004;32:1316-21



(Ilulissat, Jakobshavn, Greenland)

### 3. Value for individuals with non-related diseases, and their families

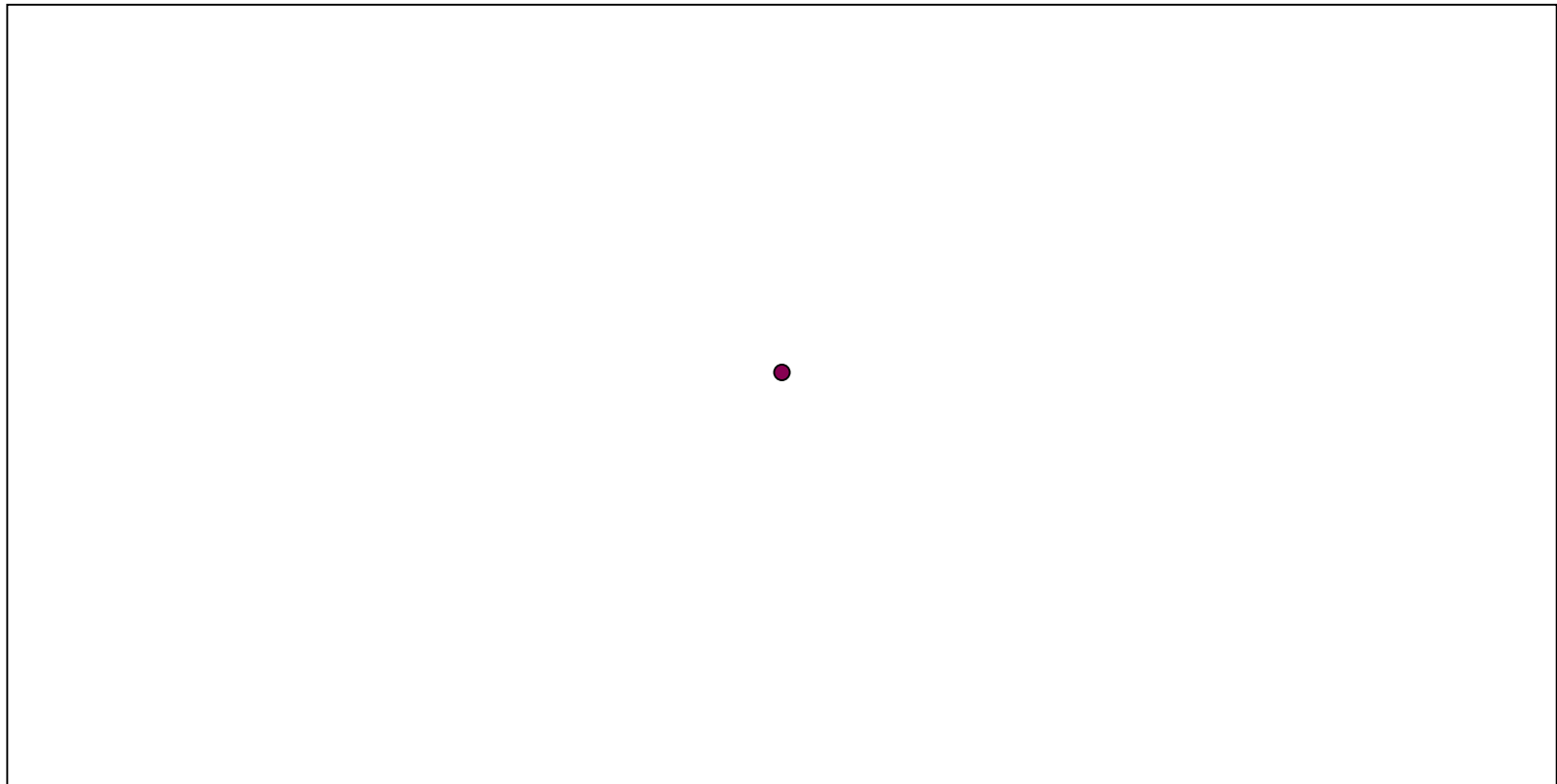
Studies on one single disease may affect a large proportion of the population



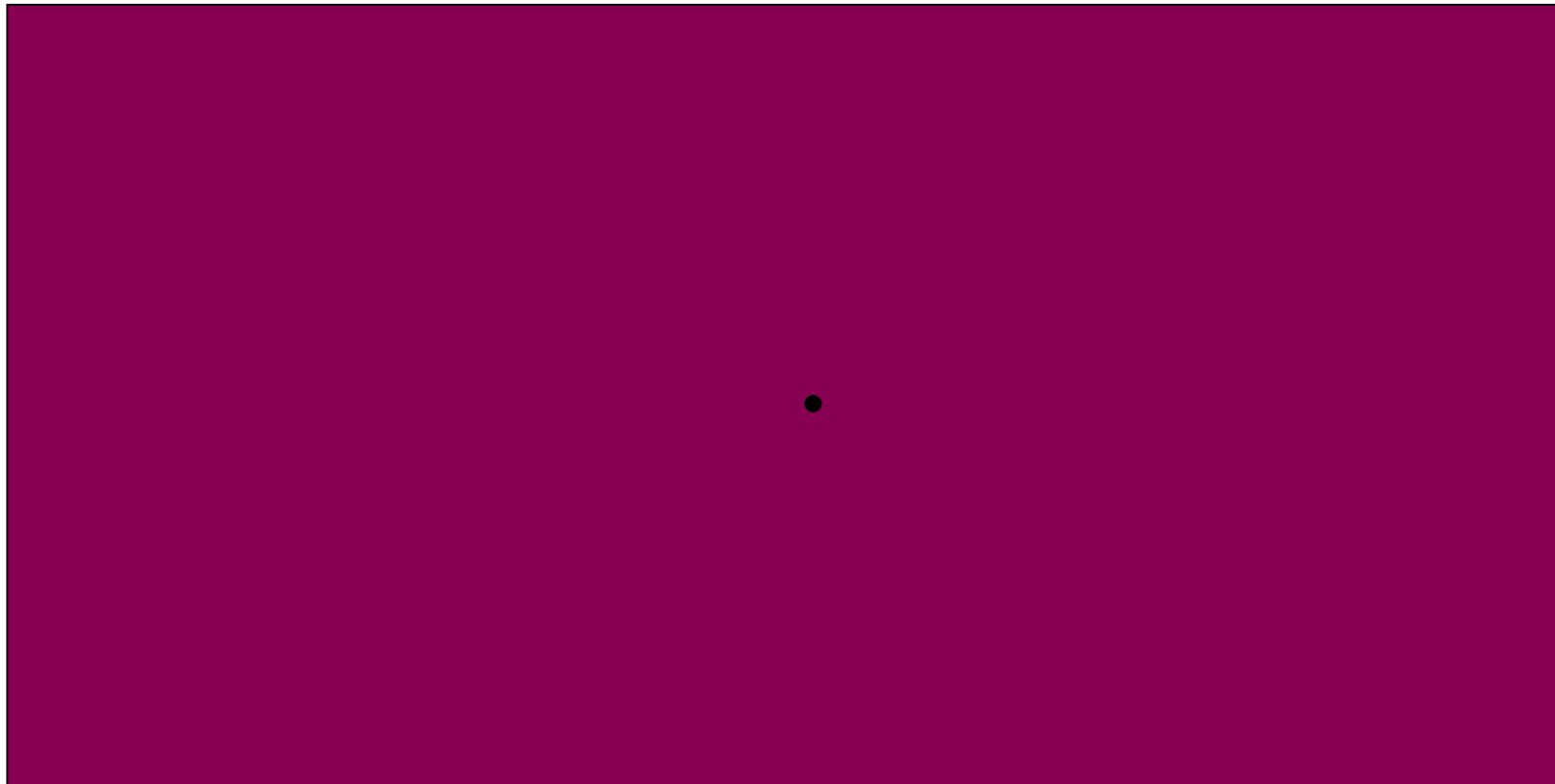
## 4. Research value for the Society as a whole

- Main Message:  
Studies on RD may actually be one of the most fruitful and most economic ways to support medical development, for the Society.
- We can learn about human biology.
- We can improve care on many rare, and common, diseases
  - on diagnostics
  - on disease monitoring
  - on treatment, and
  - can provide new drugs that can be used with novel indications.

## 4. Studies on affected individuals with RD ...



## 4. ... may give value for the Society as a whole





## 4. Added Values of Research on Rare Diseases

- We learn about human biology
- We improve care on many rare, and common, diseases
  - on diagnostics, disease monitoring, and treatment
  - Improved health is economically beneficial for the Society
- Can generate new drugs - that can be used also on novel indications
  - Economically beneficial with pharma-industry
- Investments by the Society in studies on RD may be very productive!
- Studies on RD may actually be one of the most fruitful and most economic ways to support medical development, for the Society.

# Is Academic Research Important for RD?

## YES – Since Academic Researchers can:

- 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

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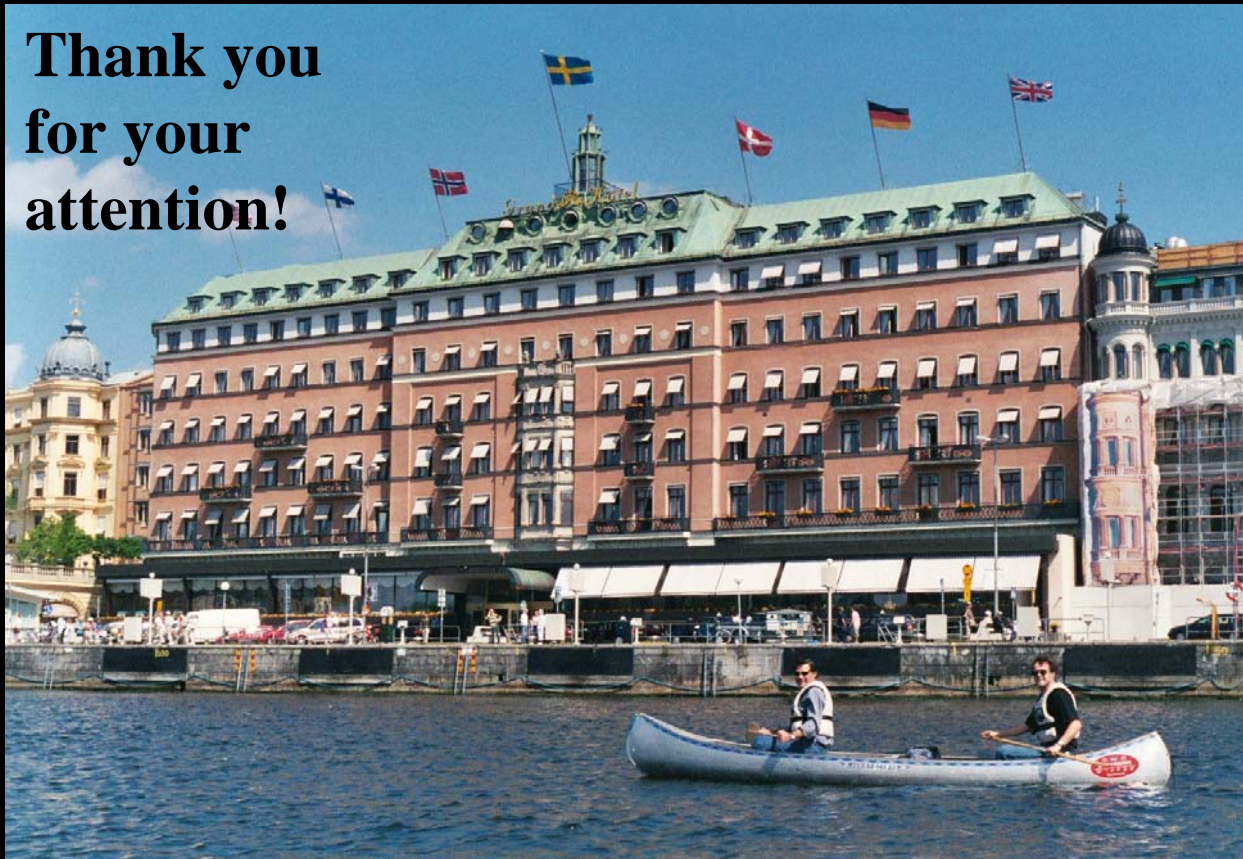
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- Industry get many meetings in one
- Regulators get close to researchers and industry

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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

Thank you  
for your  
attention!



Nobel Prize Laureate Accommodation