# Added Values of Research on 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

# 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 litterature

  → **Common diseases are re- and subclassified**

    - **…and will become additional rare diseases**

# 1. Value of Research in Rare Diseases

- Rare Diseases are not rare

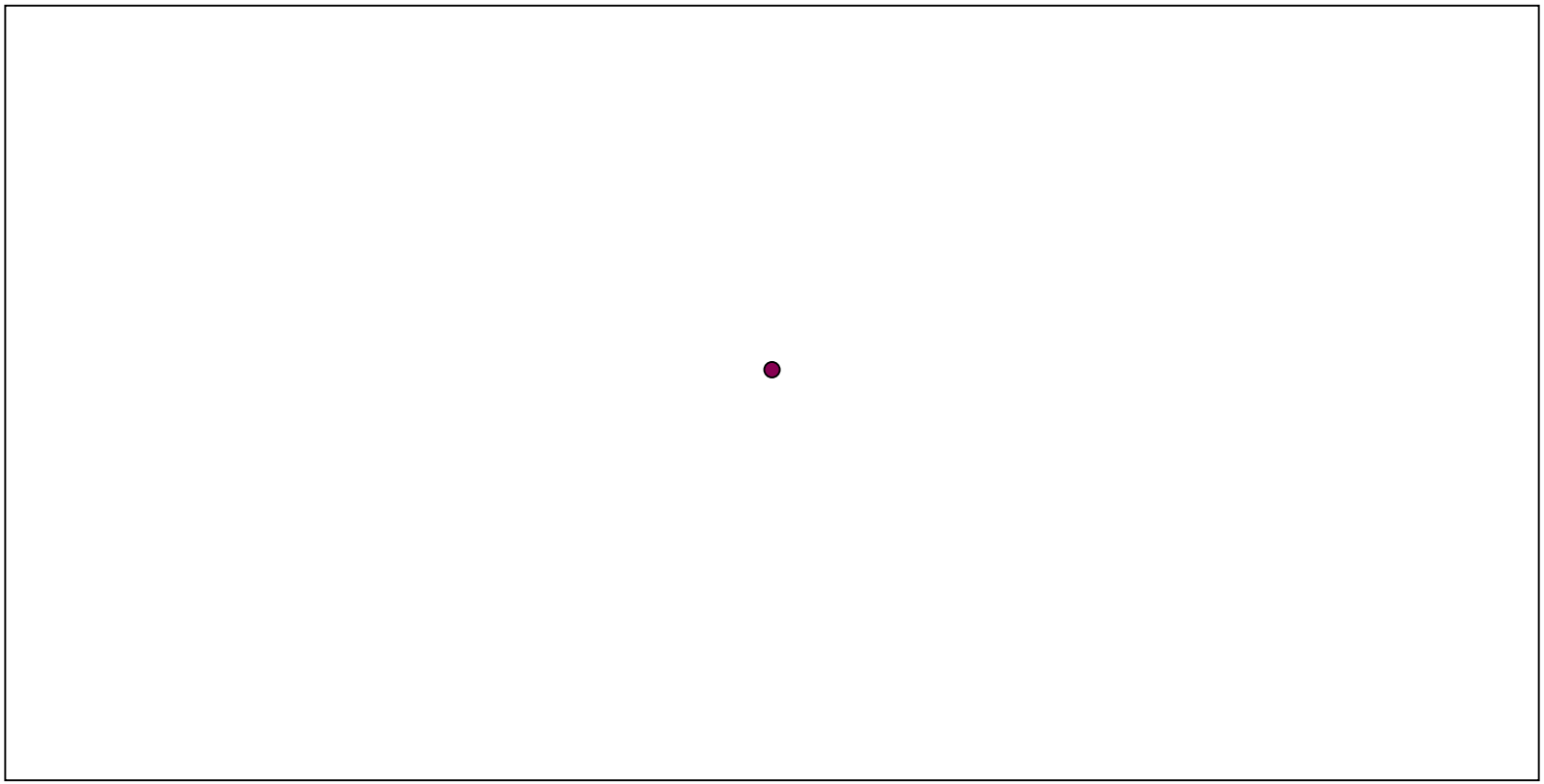
- EU: Prevalence < 5 per 10.000 (<1/2000) inhabitants

  → Referred to as affecting 6-8% of the population. Then:

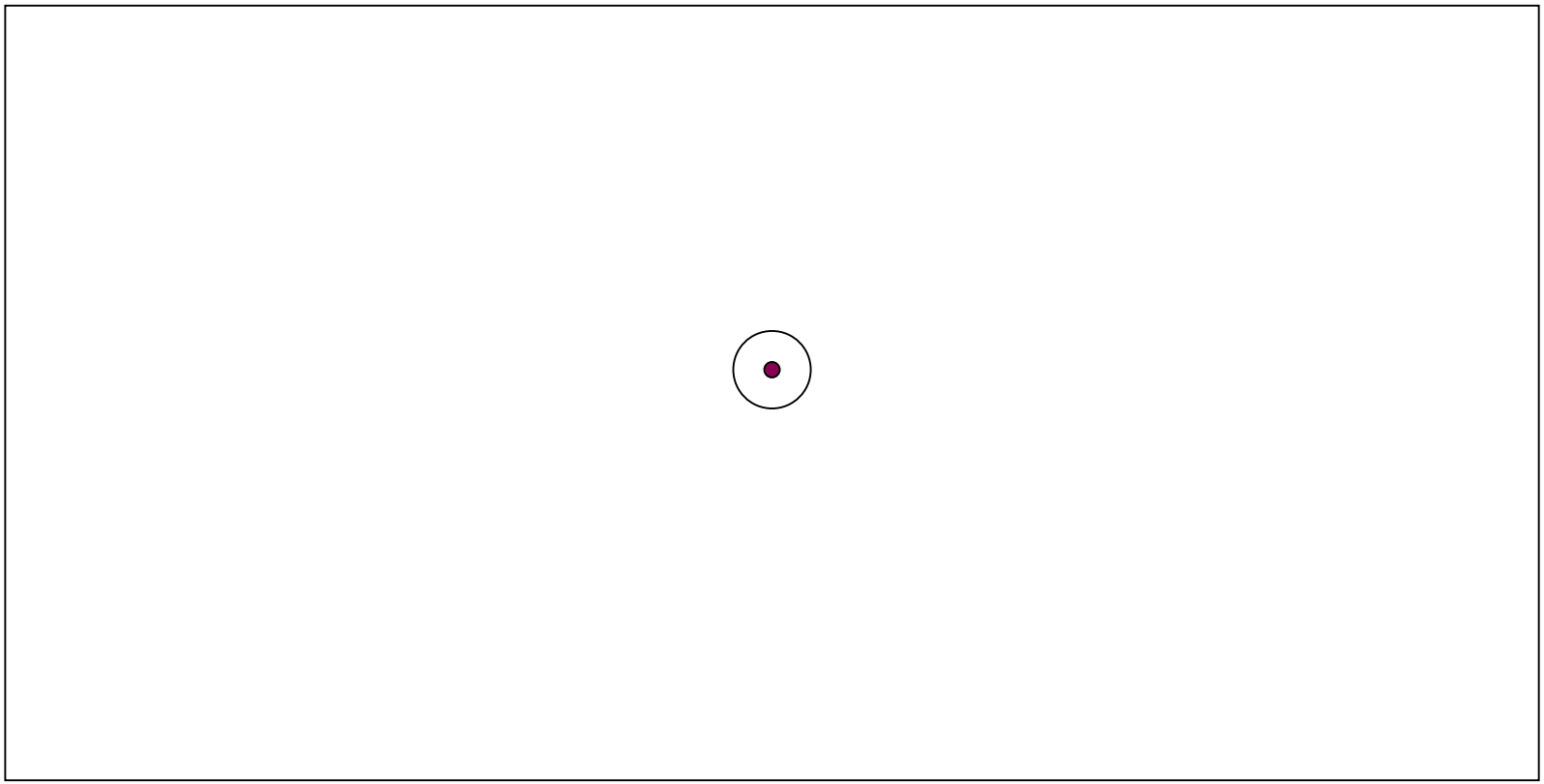
  → About **22-30 millions in South America** (pop 371 millions, 2005)
  → About **30-40 millions in the European Union** (pop >500 millions)
    - **With 4 independent relatives each = >200 million individuals + relatives**

  → **Major value in itself** to help all these individuals and families!!

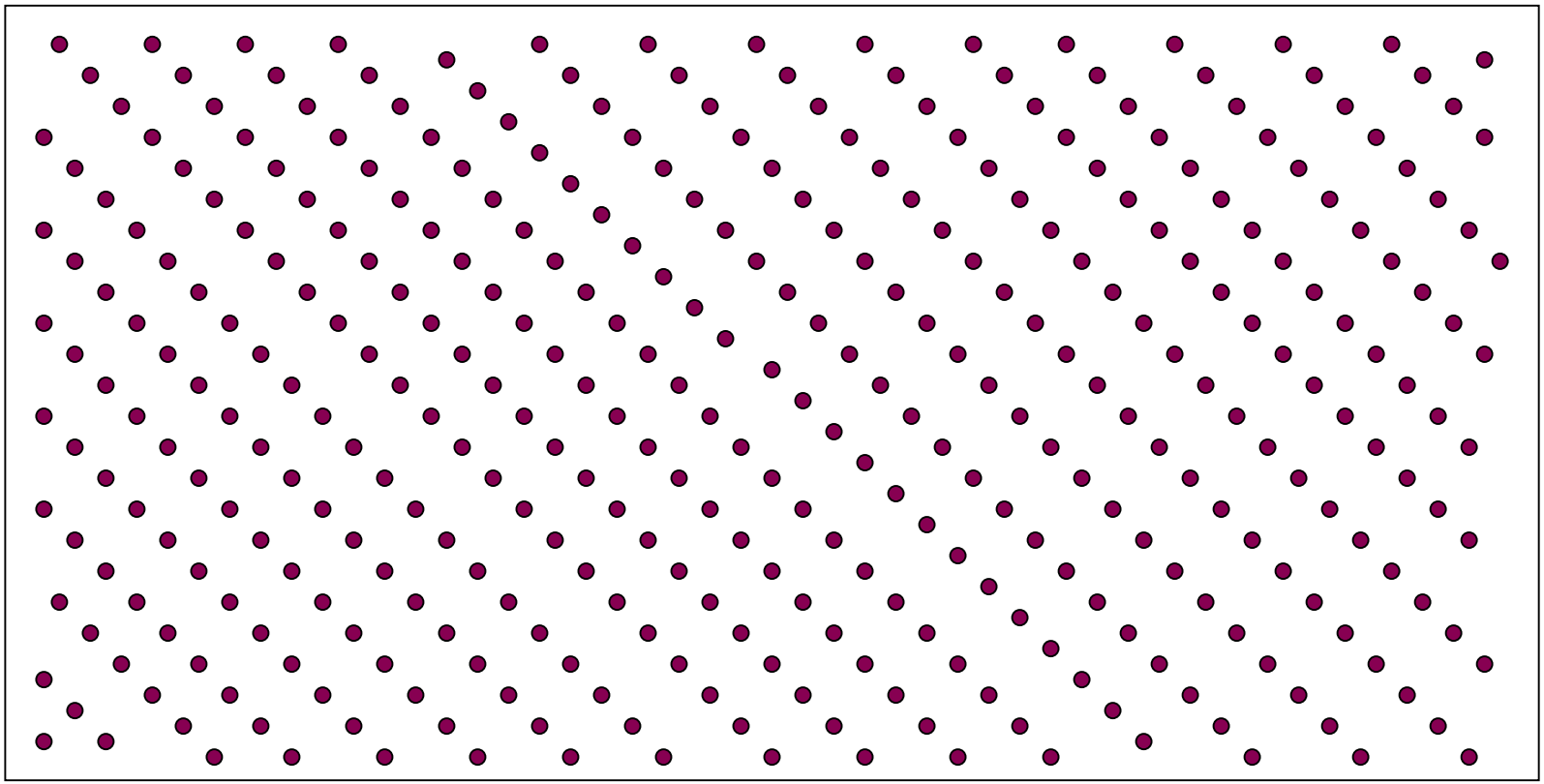
# 1. Value for affected individuals with a RD



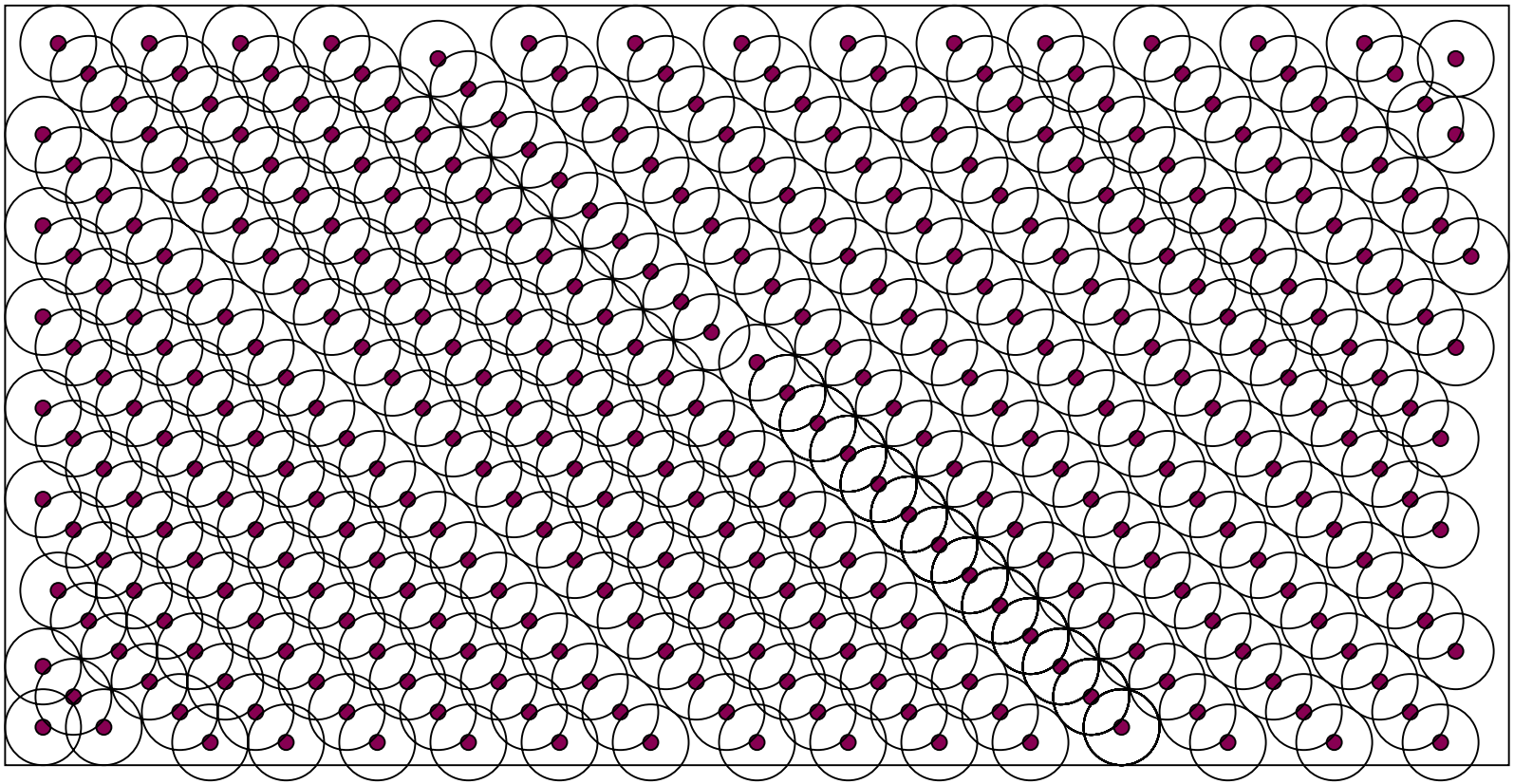
# 1. Value for affected families, with one individual affected by a Rare Disease



# 1. Value for all affected individuals with RD



# 1. Value for all families affected by a RD



# 1. One personal example: HISTIOCYTOSES

- **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

Karolinska Institutet

## The 1st International HLH Treatment Study

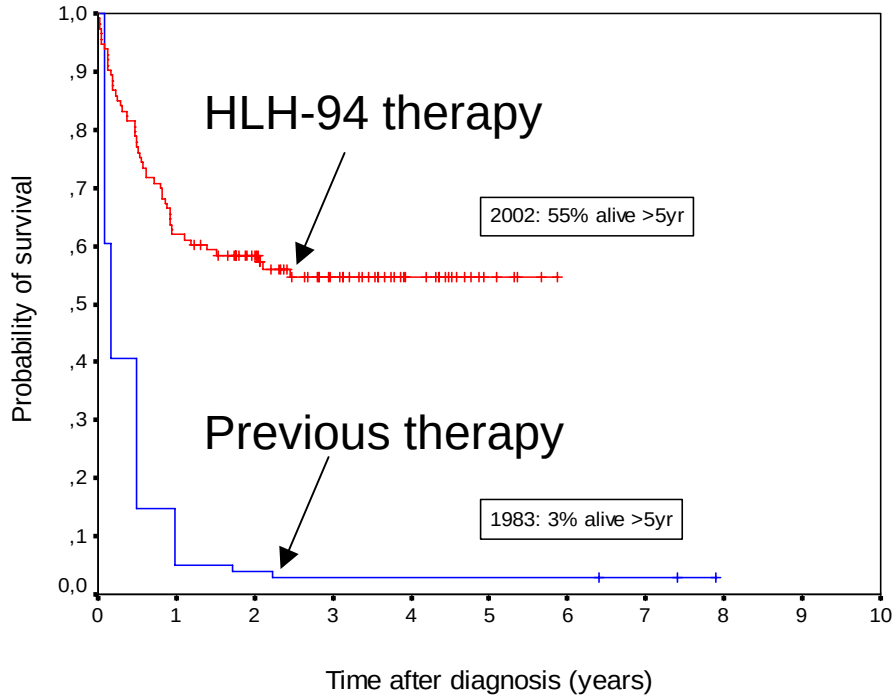
# HLH-94

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

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 Histiocyte Society

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

# 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

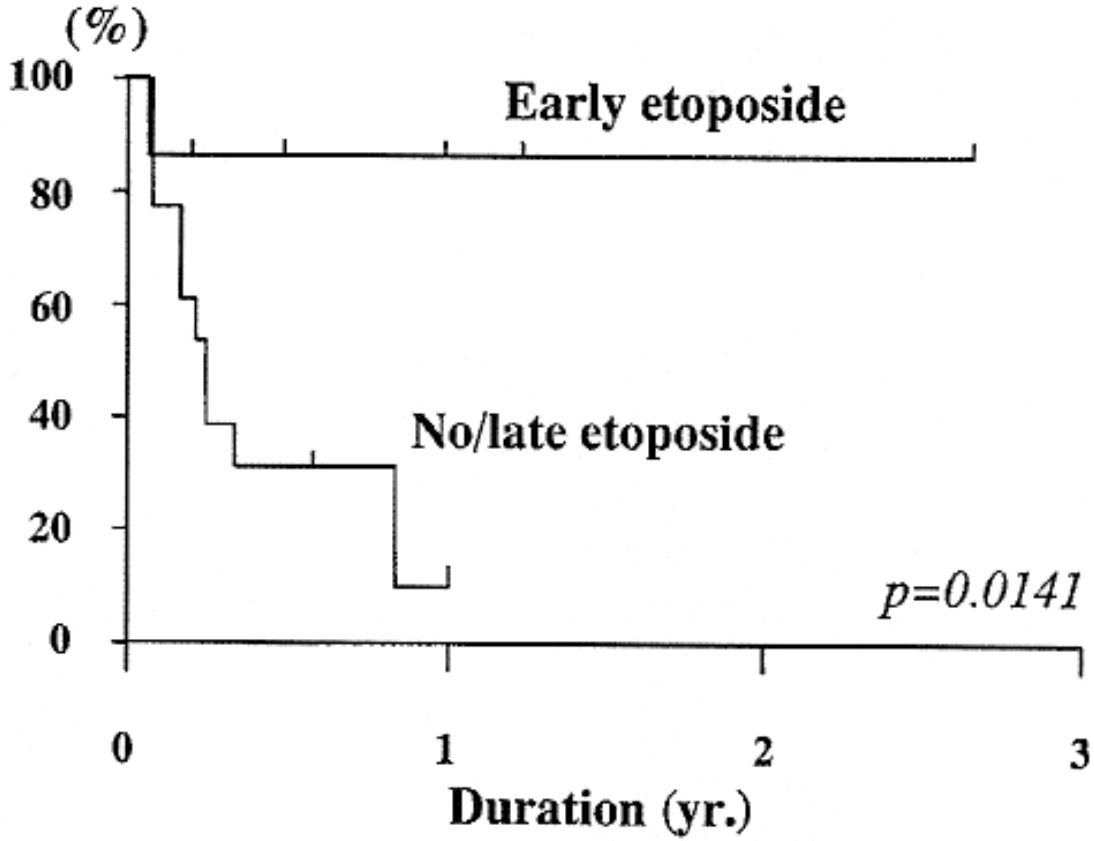
- Clinical research:

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

→ On diagnostics, disease monitoring and treatments

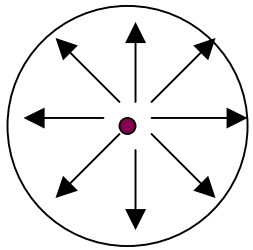
# Virus-associated HLH

**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

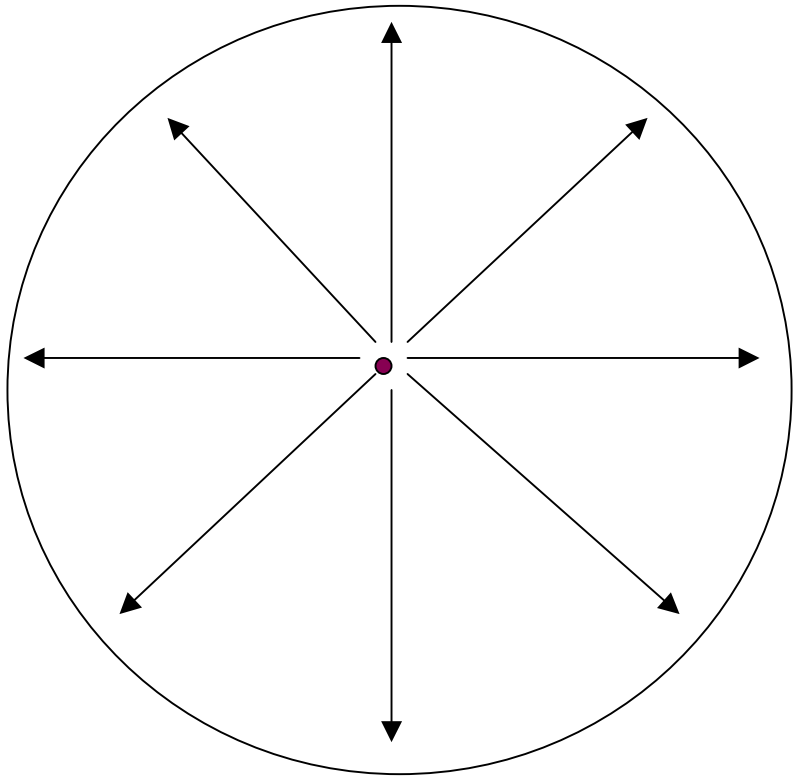
- Malignancy-associated HLH
- Rheuma-associated HLH
  → Macrophage activating syndrome

- **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

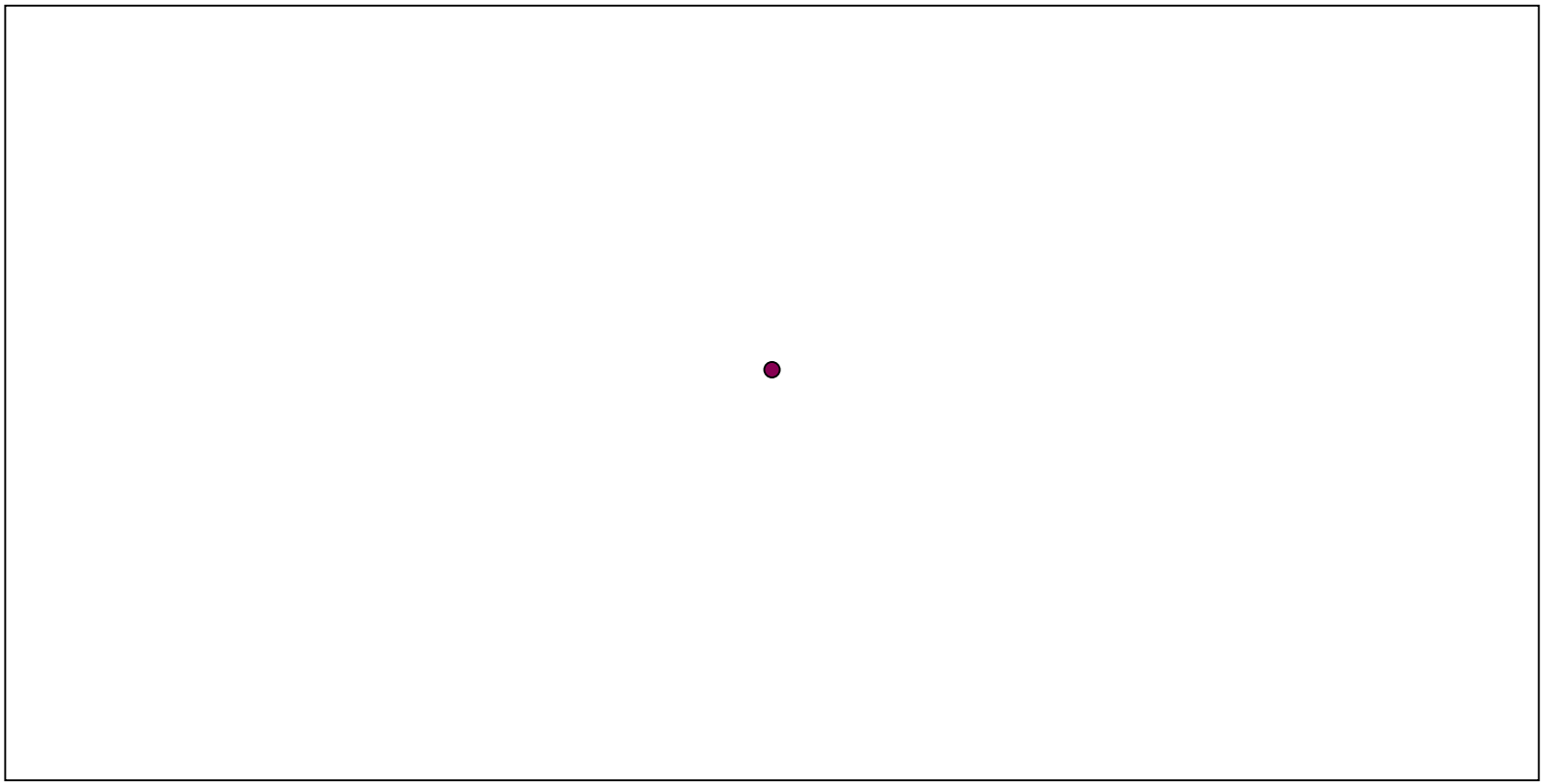
- Main Message:

  Studies on RD may actually be one of the most fruitful and most economic ways to support medical development, for the Society.

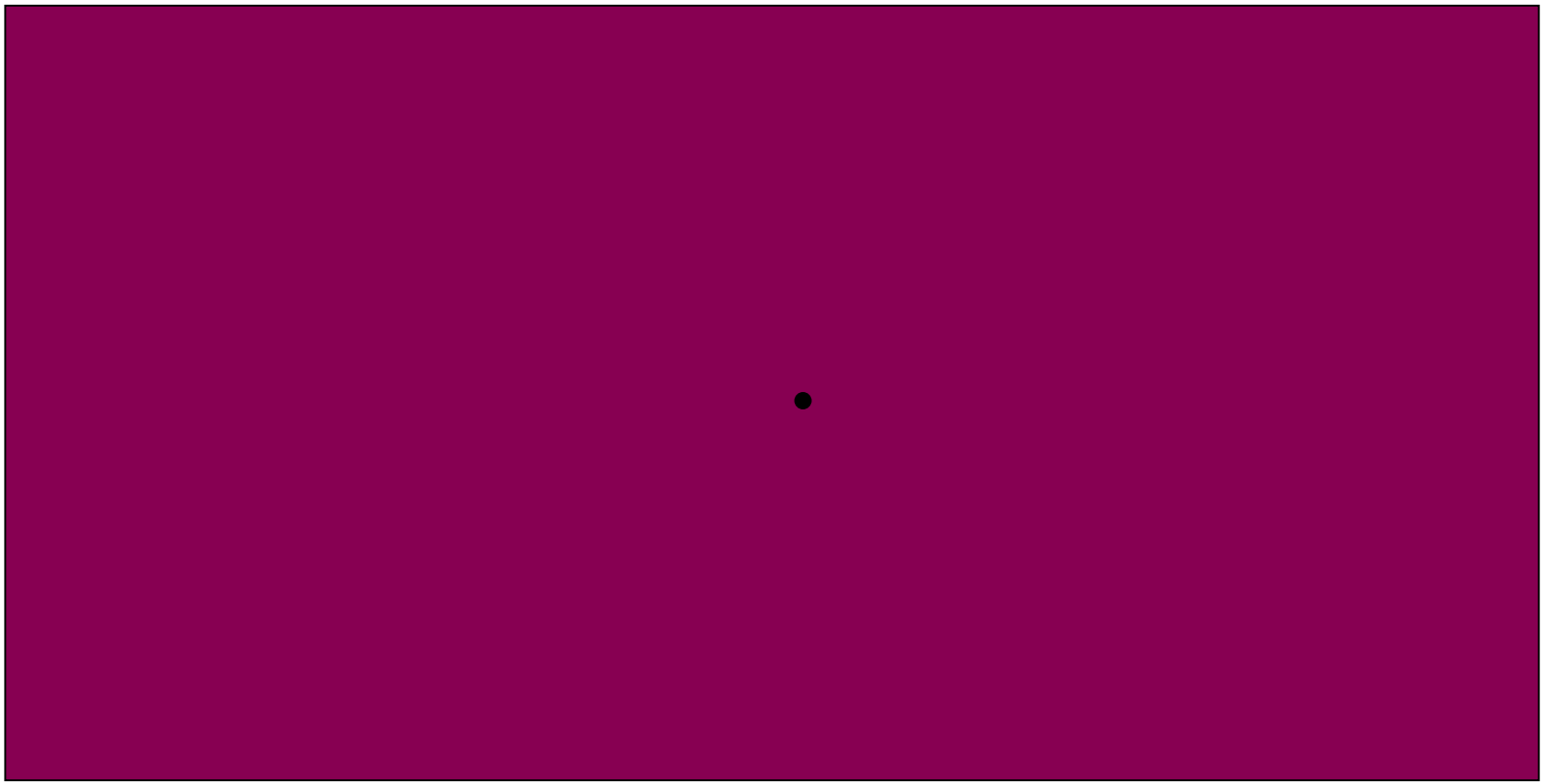
- We can learn about human biology.

- 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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- 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