



German Network on Congenital  
Bone Marrow Failure Syndromes

SEVERE CHRONIC

NEUTROPENIA

International Registry

Severe Chronic Neutropenia  
International Registry-Europe

**Cornelia Zeidler**

**Severe Chronic Neutropenia International Registry - Europe**

**German Network on  
Congenital Bone Marrow Failure Syndromes**

**Paediatric Haematology/Oncology  
Medical School Hannover  
Germany**

## BENEFITS OF A REGISTRY

### Sufficient Patient numbers to identify:

- Epidemiology and demographics
- Natural course of the disease
- Subgroups and new disorders
- Late sequelae and concomittant symptoms
- Treatment response and outcome
- Quality of life

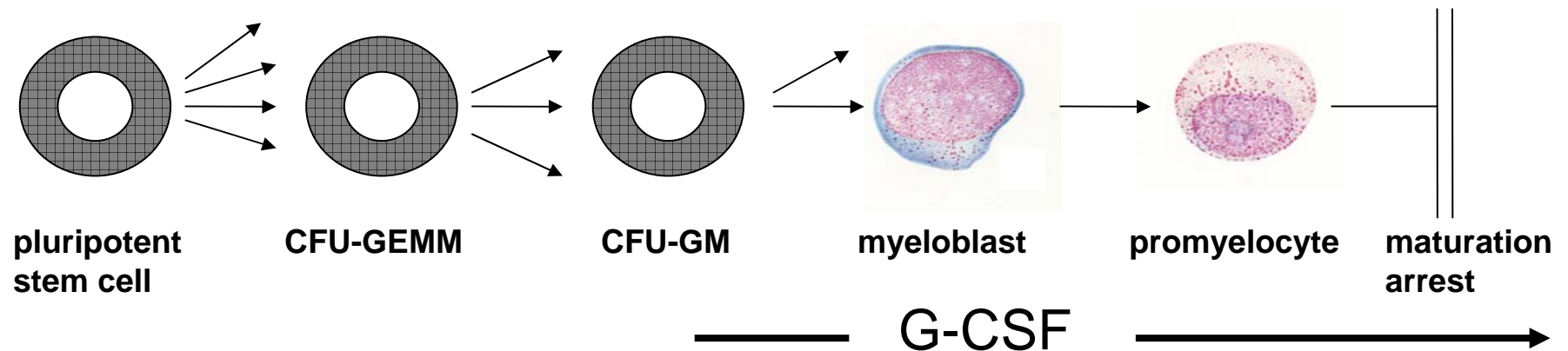


**Improve diagnosis and therapy**

## Knowledge on Severe Congenital Neutropenia in the 1980s

- Rolf Kostmann described an autosomal recessive trait with severe neutropenia in Northern Sweden in 1956 – „Morbus Kostmann“
- Absolute neutrophil counts (ANC) at diagnosis were below 500 per mm<sup>3</sup> or even absent in the peripheral blood
- Severe bacterial infections were frequent and might already occur during the first months of life
- Most patients died from bacterial infections during early childhood inspite antibiotic treatment
- Single cases of malignant transformation into leukemia were reported in the literature
- Stem cell transplantation was the only treatment available

## Severe congenital neutropenia



## Severe Chronic Neutropenia International Registry - SCNIR

- 1987: first clinical trial with the haematopoietic growth factor G-CSF (granulocyte - colony stimulating factor) was initiated
- 1994: SCNIR was established
- 1994 – 2000: SCNIR was funded by Amgen Inc. for the collection of safety data on G-CSF (filgrastim) treatment annually reported to the FDA:
  - Clinical course of SCN during filgrastim long term treatment (response, adverse events)

## Severe Chronic Neutropenia International Registry - SCNIR

- 2000: continuing financial support was stopped after the final FDA safety report → SCNIR became an independent US foundation
- since 2000: data collection was expanded, but financial support of European part was dramatically decreased:
  - new neutropenia subdiagnoses included
  - treatment independent enrollment

## Grants

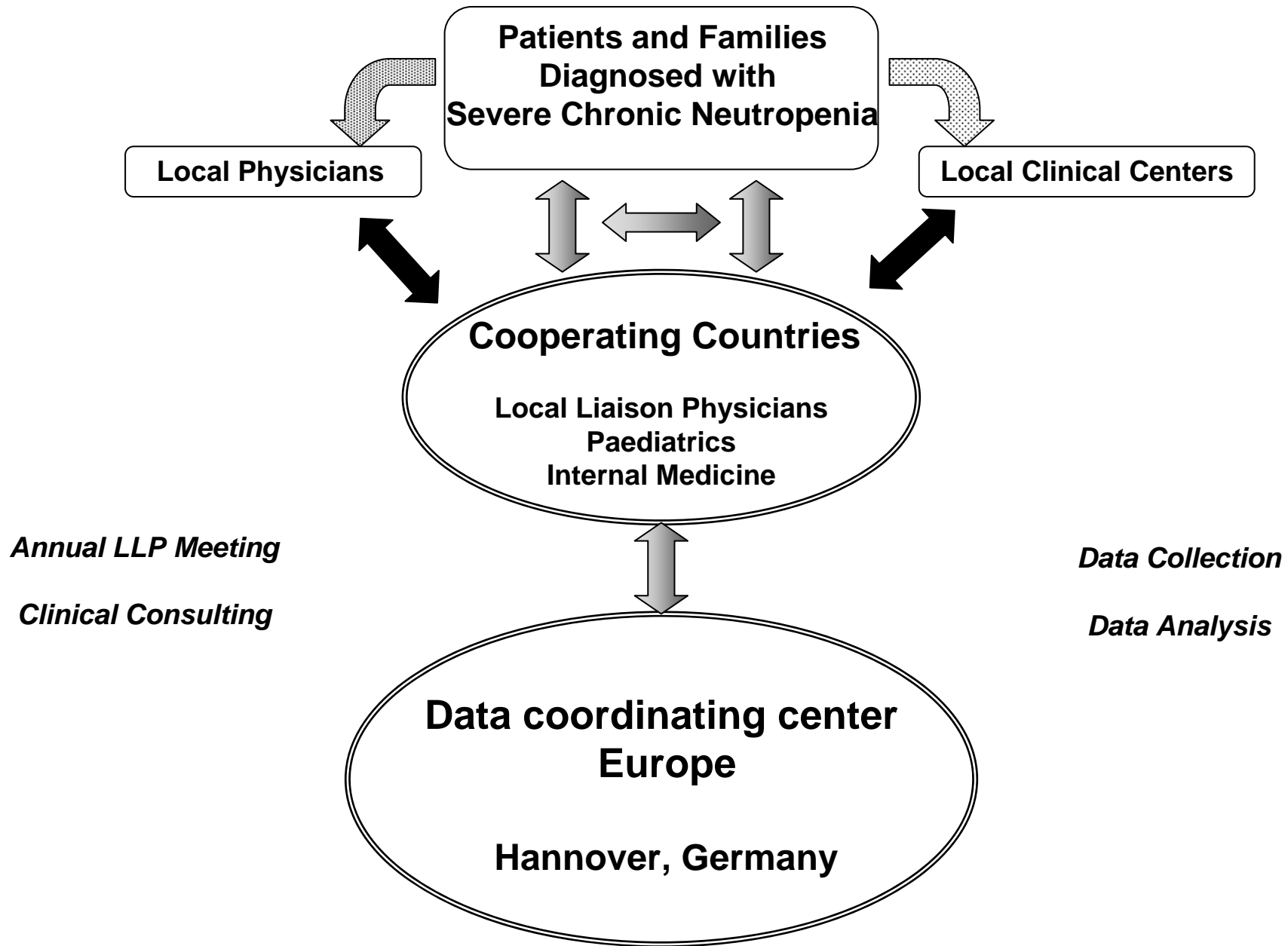
### EU grant

- Grant period 31.December 2001 – 30.December 2004
- Programme on Community action on rare diseases
- Directorate - General Health & Consumer Protection
- European Network on the Epidemiology, Pathophysiology and Treatment of Severe Chronic Neutropenia

### German BMBF grant

- Grant period October 2003 – ongoing
- Programme on Networks for Rare Diseases
- German Network on Congenital Bone Marrow Failure Syndromes

# European SCN network





## European Enrollment of SCN Patients (Total 393 patients)

Country	Pts.	Country	Pts.
Austria	12	Morocco	1
Belgium	25	The Netherlands	11
Czech Republic	3	Norway	13
France	6	Poland	4
Germany	128	Portugal	1
United Kingdom	62	Russia	1
Greece	10	Serbia-Montenegro	2
Ireland	10	Spain	19
Israel	11	Sweden	26
Italy	35	Switzerland	5
Luxembourg	2	Turkey	5

## The Major Known Congenital Neutropenia Subdiagnoses

### 1) Congenital Neutropenia

- Kostmann syndrome
- Shwachman-Diamond syndrome
- Glycogen storage disease type 1b
- Barth's syndrome
- Others

### 2) Cyclic Neutropenia

## Neutropenia Subdiagnoses

Diagnosis	Pts.
<b>Congenital</b>	<b>182</b>
• Severe Congenital Neutropenia	141
• Shwachman-Diamond-Syndrome	16
• Gycogen Storage Disease Type Ib	4
• Others (Autos. dom., Hyper IgM, Barth syndrome)	21
<b>Cyclic Neutropenia</b>	<b>48</b>
<b>Idiopathic Neutropenia</b>	<b>75</b>
<b>Autoimmunneutropenia</b>	<b>33</b>
<b>Other (LGL etc.)</b>	<b>2</b>

## INTERNET - ACCESSIBLE DATABASE (ProMISe)

### Type of the database:

- Remote data entry database in ProMISe, download as Access database or Excel spreadsheet possible
- FileMaker Pro for re-identification of anonymized data

## DATA COLLECTION INTERNET - ACCESSIBLE DATABASE (ProMISe)

- **Data collection on a yearly basis:**
  - infections, non-infectious events, physical assessment, treatment, pregnancy and death
  - examinations (bone marrow, cytogenetics, bone density, CBCs)
- **Specific questionnaires for:**
  - MDS/Leukemia, BMT, Pregnancy, Osteoporosis, Splenectomy, Vasculitis, Glomerulonephritis, Death

## INTERNET - ACCESSIBLE DATABASE (ProMISe)

### Access to the database:

- Restricted access for network partners via individual password
- Data entry at the data coordinating center in Hannover
- Data analysis and descriptive statistical comparison with the total database available for each network partner

## Current Knowledge on Severe Congenital Neutropenia (CN) I

- Congenital neutropenia occurs in the population of all European MS
- Incidence is approximately 2 cases per million people further epidemiologic data is required
- Different genetic disorders are summarized under the term CN:
  - recessive trait from Northern Sweden – M. Kostmann
  - consanguineous families in Southern European countries – recessive gene defect
  - dominant inheritance in families from Northern European countries
  - spontaneous occurrence in the majority of patients
- The genetic defects for some subgroups have been identified, but are still unknown in other subgroups of CN

## Current Knowledge on Severe Congenital Neutropenia (CN) II

- New subgroups can be identified by concomitant symptoms, e. g. growth retardation, organ defects
- In the majority of patients daily G-CSF administration induces sufficient ANCs, which prevent from bacterial infections
- In subgroups of CN the risk for malignant transformation into leukemia is increased to approximately 15%
- Osteopenia/osteoporosis is reported in about 30-50% of CN patients examined for bone mineral content



## PROMOTE EDUCATION OF PATIENTS AND PHYSICIANS

- **Patient Handbook**

- So far available as booklet or online in:  
English, German, Spanish, Greek, Hungarian
- Translations in preparation:  
French, Russian, Swedish
- English Physician Handbook (in preparation)

- **European Web Page**

- German and English Web Page of the SCNIR
- National links

## IMPROVE DIAGNOSIS AND THERAPY

- **Initiation and coordination of international research activities**
  - Pathophysiology
  - Early diagnosis of late sequelae
- **Establishment of international therapy protocols**
  - European BMT protocol for SCN patients

## From Data collection to Database for Rare Diseases

### General considerations:

Is it necessary to document every assessment available?

Adaptation of database in case of new requirements

What to do with missing data?

Type of variables: yes/no, selection of possible answers, free text  
free text- difficult for statistical analysis

Time variant versus time- invariant variables – main form versus follow up  
For follow-up information it is essential to give a date of assessment

## Best Practice Guidelines

### Require:

- Knowledge on the natural course of a disease, late sequelae, treatment response and treatment related adverse events
- Sufficient patient numbers, which often cannot be achieved nationally

### For Severe Congenital Neutropenia Patients:

- Different subtypes by heterogeneous patterns of inheritance and clinical phenotypes → specific treatment recommendations
- Incidence of malignant transformation in congenital neutropenia subtypes  
→ patients at risk are under close observation
- Outcome of treatment for leukemia
  - BMT has become frontline therapy
  - a European BMT protocol was submitted to the EBMT

## LIMITATIONS OF A RARE DISEASE NETWORK

- **Continuous financial support is required to keep up good quality of a registry:**
  - Maintenance of database
  - Regular meetings with partners for exchange of information
  - Organization of educational sessions and workshops
  - Publications and scientific presentations
- **Rare diseases are not eligible for most of the national or international grants**
- **Rare disease foundations lack sufficient funds to support registries or networks continuously**



SEVERE CHRONIC

NEUTROPENIA

International Registry

**German Network on Congenital  
Bone Marrow Failure Syndromes**

**Severe Chronic Neutropenia  
International Registry-Europe**

Tore Abrahamsen (N)

Phil Ancliff (GB)

Yigal Barak (IL)

Marrie Bruin (NL)

Göran Carlsson (S)

Katharina Clodi (A)

Emília Cortesão (P)

Cristina Díaz de Heredia (E)

Jean Donadieu (F)

Jan V. Droogenbroeck (B)

George Eliopoulos (GR)

Piero Farrugia (I)

Evaristo Feliu (E)

Mirjana Gotic (YU)

Aydan Ikinçiogullari (TR)

Krzysztof Kalwak (PL)

Antonis Kattamis (GR)

Sally Kinsey (GB)

Laszlo Marodi (H)

Gundula Notheis (D)

Jan Palmblad (S)

Helen Papadaki (GR)

Theoni Petropoulou (GR)

Sergey A. Rumiantsev (RUS)

A.Y.N. Schouten v. Meeteren (NL)

Owen Smith (IRL)

Asbjørg Stray-Pedersen (N)

Geir E. Tjønnfjord (N)

Fabio Tucci (I)

Christiane Vermylen (B)

Jaroslava Voglova (CZ)

Blanca Xicoy (E)

Sonja Zweegmann (NL)

THE EUROPEAN DATA COORDINATING CENTER IN HANNOVER:  
Gusal Pracht, Beate Schwinzer, Cornelia Zeidler and Karl Welte

•[www.schwere-chronische-neutropenie.de](http://www.schwere-chronische-neutropenie.de)

•[www.severe-chronic-neutropenia.org](http://www.severe-chronic-neutropenia.org)

## ProMISe: data management aspects

- The crucial difference between a clinical trial and an ongoing registration study is:
    - in a clinical trial we have a limited set of questions which will not change over time, neither in their meaning nor in their scope
    - in a registry for rare a disease we have varying definitions (e. g. subdiagnosis), varying goals and varying scopes.
  - The data base needs an infrastructure that can cope
    - with the data already collected
    - with future (and even unforeseen) developments in the field.
  - Problem: how to maintain a perfect and permanent translation between
    - the data structure
    - the data-analytical and statistical analyses to be expected
  - The design of the data base must reflect
    - the clinical viewpoint
    - the analytical requirements imposed by the intended analyses
- This is always a trade-off, which is easy in clinical trials and very difficult in registries

## ProMISe: Projects realized

### **ProMISe is used for more than 3 years in over 500 hospitals in Europe**

- Some of the Current Projects:
  - **Blood and Marrow Transplantation data in Europe**
    - 195 hospitals entered >10.000 transplant over the past 2 years totaling now 150.000 transplants and 300.000 follow-up records
  - **Dutch Knee Society**
    - 11 departments of Orthopedics running a permanent registry on knee-related data
  - **Study registration in chronic leukemia in Europe**
    - All currently going-on analyses in the CLWP available to all member-researchers
  - **Clinical trials in Bone Marrow Transplantation**
    - Several multi-country trials in CLL and CML
  - **European registry on Neutropenia**
  - **Clinical trial in the Netherlands on leukocyte depletion**
  - **Dutch CONCOR registry of cardiovascular events**
  - **Clinical trial on transfusion triggers in orthopedic surgery**