The Severe Chronic Neutropenia International Registry (SCNIR)
An example for a multipurpose disease registry

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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\(^3\) 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
History of the Severe Chronic Neutropenia International Registry

- 1987: first clinical trial with the haematopoietic growth factor G-CSF (granulocyte - colony stimulating factor) was initiated

- 1994: SCNIR was established and funded by Amgen Inc. for the collection of safety data on G-CSF (filgrastim) treatment annually reported to the FDA

- 2000: continuous financial support from Amgen ended after the final FDA safety report:
  - SCNIR became an independent US foundation,
  - European Branch received final payment

since 2000 the European part of the SCNIR received separate funding:

  - Research grants:
    - EU Commission (DG Sanco)
    - German Ministry of Research and Education (BMBF)
    - USA - National Institute of Health (NIH)

  - Pharmaceutical Industries
    - Amgen, Hospira, Sandoz-Hexal, Teva
Research Projects

- **EU (DG Sanco):**
  - European Network on the Epidemiology, Pathophysiology and Treatment of SCN

- **German Ministry of Research and Education (BMBF):**
  - Part of the German Network on Congenital Bone Marrow Failure Syndromes (bmfs network): Natural course of congenital neutropenia, genotype-phentype correlations

- **E-Rare (Germany, Israel, The Netherlands, Turkey):**
  - Leukemogenesis in ELANE – Congenital Neutropenia

- **National Institute of Health in the USA (NIH):**
  - SCNIR International cooperation

- **German Society for Paediatric Haematology and Oncology (GPOH):**
  - Long-term observational study for severe chronic neutropenia
Achievement over the past 15 Years

- Conducting clinical and basic research to improve knowledge on SCN
  - Identifying severe chronic neutropenia subgroups allowing the detection of causative genetic defects
  - Revealing unknown late sequelae, e.g. leukemia
  - Stratification of leukemia risk factors
  - Genotype-Phenotype correlation
  - Collecting patient material for investigating pathomechanisms related to treatment response and leukemogenesis

- International Treatment and Management Recommendations
  - European BMT protocol for SCN patients
  - Safety and outcome of pregnancies in patients on long-term G-CSF

- Networking with families and treating physicians
  - Patient handbooks, web-information, helpline

- Providing Data to Industry for Pharmacovigilence-Reports
  - Long-term post-marketing surveillance of filgrastim biosimilars
**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
Time Course of gene detections

Establishment of the SCNIR


SBDS
Boocock GR, et. al. (2003)

P14*
Bohn G, et. al. (2007)

ELANE*
Horwitz M, et. al. (1999)

CXCR4
Hernandez PA, et. al. (2003)

HAX1*
Klein C, et. al. (2007)

G6PC3*
Boztug K, et. al. (2009)

* In cooperation with SCNIR
<table>
<thead>
<tr>
<th>Gene Mutation</th>
<th>Patients</th>
<th>Gene Mutation</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital neutropenia (CN) total</td>
<td>346</td>
<td>• WHIM Syndrome (CXCR4+)</td>
<td>1</td>
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<tr>
<td>• CN nt</td>
<td>67</td>
<td>• Congenital white Cell Aplasia</td>
<td>1</td>
</tr>
<tr>
<td>• ELANE-/HAX-</td>
<td>35</td>
<td>• Cohen Syndrome</td>
<td>1</td>
</tr>
<tr>
<td>• ELANE +</td>
<td>89</td>
<td>• Pearson Syndrome</td>
<td>1</td>
</tr>
<tr>
<td>• ELANE -</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• HAX1 +</td>
<td>30</td>
<td>Cyclic neutropenia</td>
<td>73</td>
</tr>
<tr>
<td>• G6PC3 +</td>
<td>9</td>
<td>• ELANE +</td>
<td>32</td>
</tr>
<tr>
<td>• Digenic mutations</td>
<td>4</td>
<td>• ELANE -</td>
<td>6</td>
</tr>
<tr>
<td>• ELA&amp;HAX&amp;G6PC3 -</td>
<td>8</td>
<td>• ELANE not tested</td>
<td>35</td>
</tr>
<tr>
<td>• G6PC3 or HAX or SBDS -</td>
<td>4</td>
<td></td>
<td></td>
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<tr>
<td>• Shwachman Diamond Syndrome</td>
<td>52</td>
<td>Idiopathic neutropenia</td>
<td>85</td>
</tr>
<tr>
<td>SBDS not tested</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBDS +</td>
<td>37</td>
<td>Autoimmune neutropenia</td>
<td>56</td>
</tr>
<tr>
<td>SBDS -</td>
<td>1</td>
<td>Others</td>
<td>11</td>
</tr>
<tr>
<td>• Glycogen storage disease Ib</td>
<td>21</td>
<td>• Hyper IGM Syndrome</td>
<td>3</td>
</tr>
<tr>
<td>• Myelokathexis</td>
<td>3</td>
<td>• LGL</td>
<td>5</td>
</tr>
<tr>
<td>• Barth Syndrome (TAZ+)</td>
<td>6</td>
<td>• Granulopenia</td>
<td>1</td>
</tr>
<tr>
<td>• WAS mutation</td>
<td>5</td>
<td>• diagnosis not approved</td>
<td>2</td>
</tr>
<tr>
<td>• P 14 mutation</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>571</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
(8/2012) Congenital neutropenia
Genetic distribution in Europe

- ELANE+: 89 (31%)
- HAX1+: 30 (10%)
- CN nt: 81 (27%)
- G6PC3+: 9 (3%)
- other mutation: 11 (4%)
- DIGENIC: 4 (1%)
- SBDS+: 37 (12%)
- G6PT+: 21 (7%)
- TAZ+: 6 (2%)
- WAS+: 5 (2%)
- P14+: 4 (1%)
Comparison of Clinical Parameters in ELANE versus HAX1 patients

Mutation: ELANE  HAX1

Age: 11 years  12 years

Bone marrow
Morphology at diagnosis:
Maturation arrest at the promyelocyte/myelocyte stage

Dental status at 11 and 12 years:
Gingiva hyperplasia and Gingivitis

X-ray of jawbone with signs of parodontitis

Zeidler et al., BJH 2009
Distribution of *ELANE* Mutations

### Congenital neutropenia

- **Exon 1**
  - c.116C>G; p.39A>G

- **Exon 2**
  - c.165T>C; p.F43L
  - c.175C>T; p.S46F
  - c.201T>A; p.C55S
  - c.207G>A; p.A57T (3 patients, 2 related)
  - c.208C>T, p.A57V (3 patients, 2 related)
  - c.238C>G; p.S67W
  - c.249T>C; p.C71R
  - c.250G>A; p.C71Y

- **Exon 3**
  - c.280G>C; p.R81P
  - c.292G>A; p.G85E
  - c.339G>A; p.V101M (2 Patients)
  - c.346G>T; p.R103L
  - c.347C>T; p.R103P (2 Patients, both related)

- **Exon 4**
  - c.406T>A; p.L123H
  - c.415C>T; p.S126L (5 Patients)
  - c.418G>A; p.A127D
  - c.436A>T; p.I120F (3 Patients, all related)
  - c.493T>C; p.L152P (2 patients)
  - c.495C>G; p.A153P
  - c.580+1 G>A
    - c.580+1 G>T (2 Patients, both related)

- **Exon 5**
  - Q194*
  - c.635C>A; p.C208G
  - c.678G>A; p.G214R
  - c.693G>A; p.V219I
  - c.763T>A; p.L242N
  - c.808C>T; p.P257L
  - W241*
  - c.759T>G; p.W241G
  - c.761C>G; p.W241L
  - Y227*
  - c.697G>A; p.R220Q (4 Patients, 2 related)
  - c.618C>T; p.Q194* (2 Patients, both related)

### Cyclic neutropenia

- **Exon 1**
  - c.182C>T, p.A61V

- **Exon 2**
  - c.339G>A; p.V101M
  - c.328A>T; p.Q97L

- **Exon 3**
  - c.454C>T; p.P139L
  - c.580+1 G>A
    - (8 Patients, 2 related and 3 related)

- **Exon 4**
  - c.618C>T; p.Q194* (2 Patients, both related)
Long Term Course of Median ANC in CN Patients

Absolute Neutrophil Count / µL

Years of G-CSF Treatment
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total patient number (n)</th>
<th>MDS/Leukemia (n/%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Congenital Neutropenia</strong></td>
<td>294 (without SDS)</td>
<td>35 (11,9 %)</td>
</tr>
<tr>
<td>• ELANE-CN pos.</td>
<td>89</td>
<td>12 (13,48 %)</td>
</tr>
<tr>
<td>• HAX1-CN pos.</td>
<td>30</td>
<td>6 (20,0 %)</td>
</tr>
<tr>
<td>• WAS pos.</td>
<td>5</td>
<td>2 (40,0 %)</td>
</tr>
<tr>
<td>• not tested</td>
<td>67</td>
<td>8 (11,94%)</td>
</tr>
<tr>
<td>• ELANE neg.</td>
<td>5</td>
<td>1 (20,0 %)</td>
</tr>
<tr>
<td>• ELANE neg + HAX1 neg</td>
<td>35</td>
<td>6 (17,14 %)</td>
</tr>
<tr>
<td>• Other (G6PC3, GSD1b, TAZ etc.)</td>
<td>63</td>
<td>0</td>
</tr>
<tr>
<td>• SDS</td>
<td>52</td>
<td>4 (7,69%)</td>
</tr>
<tr>
<td>- SBDS not tested</td>
<td>14</td>
<td>1 (7,14%)</td>
</tr>
<tr>
<td>- SBDS positiv</td>
<td>37</td>
<td>3 (8,1 %)</td>
</tr>
<tr>
<td>- SBDS negativ</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Cyclic Neutropenia</strong></td>
<td>73</td>
<td>1 (1,36%)</td>
</tr>
<tr>
<td>ELANE-positiv</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>ELANE neg</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>ELANE not tested</td>
<td>35</td>
<td>1 (2,85%)</td>
</tr>
<tr>
<td><strong>Idiopathic Neutropenia</strong></td>
<td>85</td>
<td>2 (2,35%)</td>
</tr>
</tbody>
</table>
Model of the malignant transformation in Congenital Neutropenia

G-CSF treatment

Severe congenital neutropenia

- ELA2 and HAX-1 mutations
- Genotoxic stress
- ER-stress
- Genetic instability

- G-CSF receptor mutations
- Selective pressure

- Cooperating mutations (e.g. RUNX1)

- Monosomy 7 or
- Trisomy 21

- Sustained STAT5 activation,
- Deacetylation of p53 and FOXO3a

Leukemia
BMT/SCT Protocol:
Comparison of Survival after BMT/SCT

Leukemia and SCT
- yes/BMT>=2001 Events/N=3/21
- no/BMT>=2001 Events/N=7/31
- no/BMT<2001 Events/N=5/11
- yes/BMT<2001 Events/N=8/11

P=0.002 (Log Rank)
Age at Neutropenia Diagnosis 10/2012

- born before 2000
- born in/after 2000

N=174  N=108  N=54  N=11
Summary

The SCNIR is a model for a successful international multi-purpose registry serving patients and advancing understanding of rare diseases.
Acknowledgement

We are grateful to the many physicians worldwide who faithfully and generously submitted data on their patients, our collaborating partners from 22 countries within Europe and the patients for their consent.
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THE EUROPEAN DATA COORDINATING CENTER IN HANNOVER:
Ulrike Grote, Sabine Mellor-Heineke, Sabrina Mende, Anna Nickel,
Cornelia Zeidler and Karl Welte
Current Knowledge on Severe Congenital Neutropenia (CN)

- Congenital neutropenia occurs in the population of all European MS
- Incidence is approximately 4 cases per million people further epidemiologic data is required
- Different genetic disorders are summarized under the term CN
- The majority of patients can be categorized by gene mutations
- In the majority of patients daily G-CSF administration induces sufficient ANC, which prevent from bacterial infections und prolong life expectancy
- In subgroups of CN the risk for malignant transformation into leukemia is greater than 10%
The SCNIR: An example of a multi-purpose registry

Coordinated by International Advisory Board
Run by Academia

SCNIR database and biobank

- research coordination
- data publication and presentation
- annual EU network meetings
- annual EU/US meeting

Patient Support Groups
- regular reports
- meetings

Pharmaceutical Industries
- Clinical trials
- Pharmacovigilance
  - New products
  - Biosimilars

Research
- Conducting basic and clinical research

Patients and Treating Physicians
- Handbook, website
- Helpline