Pre-MDS Conditions: CHIP, ICUS, IDUS
Pathobiology and Diagnosis

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Disclosure of speaker’s interests
(potentially conflicting interests)

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WHY IS THERE A NEED TO DEFINE?

1) Genome Era of Medicine
2) More and More such Referals
3) No generally accepted Criteria
4) Separation from LR MDS
5) Clinical Relevance:

Pre-MDS / Pre-Leukemic Conditions: Proposed Criteria and Categories

BM Neoplasms
Vascular Events
So far, only little is known about LSC-Niche Interactions and related Mechanisms that may contribute to LSC Evolution and Resistance.
How to translate the LSC Concept into Clinical Application?

How to develop LSC-Eradicating (=Curative) Treatment Concepts?

- DEFINITION OF LSC: LONG-TERM \textit{in vivo} L-PROPAGATING CELLS
- IDENTIFICATION AND PURIFICATION OF LSC
- IDENTIFICATION AND VALIDATION OF TARGETS
- EFFECTS OF TARGETED DRUGS
- PROVIDE A SUITABLE BASIS FOR THE DEVELOPMENT OF LSC-ERADICATING APPROACHES
Premalignant Neoplastic Stem Cells

Malignant Neoplastic Stem Cells = Cancer Stem Cells (LSC)

- Long Latency Periods (Decades) in early Phases of LSC Evolution
- Premalignant Neoplastic Stem Cells versus Malignant SC = CSC/LSC
- Extensive Subclone Formation
- Each Subclone contains its own Stem Cell Compartment
- Phenotypic, Biochemical and Functional Heterogeneity
- Different Mechanisms of Drug Resistance in Subclones

*Many Observations were made in the Paradigmatic CML Model, based on Evolution of Subclones carrying BCR/ABL Mutations
The Hydra Model of LSC Evolution: CML

- CML as Paradigmatic Model
- Subclone Formation
- Long Latency Periods
- Separate LSC Populations
- Different Target-Profiles
- Subclone-Specific Profiles
- Plasticity of LSC

LSC-Marker:
BCR-ABL1 mutants

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From Hydra to the “Snakepit Model“ of LSC Evolution

CML as Paradigmatic Model
Subclone Formation
Long Latency Periods
Separate LSC Populations
Different Target-Profiles
Subclone-Specific Profiles
Plasticity of LSC

Marker: BCR-ABL1 mutants

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A Patient with Imatinib-Resistant CML: Subclone Formation

**Mutation-Specific qPCR**
Preuner et al, Leukemia 2008;22:1956
Ligation-Dependent PCR Technique

**Preuner et al, Eur J Cancer, in press, 2011**

**BCR/ABL (%):**

**Mutant clone (% of total BCR/ABL):**

**Dasatinib (100 mg/d)**

**HU**

**SCT**

**post SCT/ no**

**HU**

**HU = Hydroxyurea**

**SCT, Hematopoietic Stem Cell Transplantation**
A Patient with Imatinib-Resistant CML: Subclone Formation

Preuner et al, Eur J Cancer 2012;48:233-236
A Patient with Imatinib-Resistant CML: Subclone Formation

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Valent, Lancet Oncol 2010
Valent, CCDT 2011
Valent et al, Nat Rev Cancer 2012
Valent et al, Cancer Res 2013
Valent et al, Nat Rev Cancer 2012
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Definition of Cure: Basic Considerations

- Cytoreductive therapy sparing cancer stem cells
- Early relapse
- Late relapse
- Specific eradication of CSCs (sparing a few resistant NSCs)
- Resistant subclones
Ph+ ALL after Autologous HSCT: Untreated! 
Stable BCR/ABL\textsubscript{p190}+ MRD over a Decade

Alternative Explanations:
- New Clone / New Disease?  no
- BCR-ABL1 in non-SC fraction?  no
- Clonal Stability?  no
- Immunosurveillance?  no
- Competition in the SC-Niche?  no

most likely Explanation:

NORMAL STABLE BLOOD COUNTS!

Böhm et al, Leuk Lymphoma 2011;52:842-848

Valent, Lancet Oncol 2010;11:1010

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Effects of Treatment with Imatinib

STIM Study MR-free Survival in CML
François-Xavier Mahon et al,
*Lancet Oncology*
2010;11:1029-35

CML AS PARADIGMATIC DISEASE MODEL

Operational Cure with or without a detectable MRD

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Conditions Apparently Caused by Premalignant Neoplastic Stem Cells

- Clonal Hematopoiesis of Indeterminate Potential = CHIP (Pre-MDS)*
- Other Similar Conditions: MGUS, MCAS, ...
- ICUS, IDUS, CCUS, CHEP, ....
- Low Risk MDS
- Indolent Systemic Mastocytosis
- Some Forms of Indolent NHLs
- Early Phase MPN and CML, etc. etc.

* CHIP = Age-Related Clonal Hematopoiesis = ARCH
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Overt Cancer

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Six Phases of Cancer Evolution

0 = Genetic Background
I = Stable Somatic Process without any LSC expansion (usually no Driver)
II = Somatic Process with Driver Lesion without relevant LSC expansion
III = Somatic Process with Driver Lesion replacing and mimicking the normal organ (differentiated tissue cells)
IV = Premalignant Overt Neoplasm
V = Overt Malignancy = Cancer
VI = Resistant Advanced Malignancy

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Six Phases of sAML Evolution

0 = Genetic background
1 = Age-related somatic mutations (ARCH=CHIP) in small-sized clones (e.g. DNMT3A, TET2)
II = Multiple somatic mutations (drivers) with (IDUS) or without (CHIP) dysplasia
III = Mutant clones replaces the normal BM: may cause cytopenia: CCUS or early LR MDS
IV = LR MDS
V = HR MDS
VI = sAML
Clonal expansion of a premalignant progenitor cell population leading to ineffective (impaired) erythropoiesis / hematopoiesis

First hits - mutagenic event/s?

EPO production adequate and sufficient to prevent anemia

Inadequate 'EPO-response' to ineffective erythropoiesis → anemia

no MDS detected as no anemia develops – these patients have dysplasia without cytopenia = IDUS

LOW RISK MDS often responsive to EPO therapy (15-25% of patients)

Disease progression/clonal expansion

HIGH RISK MDS (cytopenia found invariably)

Further oncogenic hits that lead to maturation arrest and proliferation

SECONDARY ACUTE MYELOCYTOID LEUKEMIA

Low EPO in the elderly & ICUS / IDUS

CHIP / IDUS = Phase I-II

EPO-responsive progenitors

EPO as co-factor in MDS

Normal Hematopoiesis in the elderly

Low EPO in elderly → anemia / AOE

ICUS-A

Normal Hematopoietic Stem Cell
Equation: Role of Decrease in EPO Production in the Etiology and Manifestation of MDS

\[ \text{IDUS} + \text{ICUS} = \text{MDS} \]
Six Phases in Ph+ CML

0 = Genetic Background

I = Stable ARCH/CHIP mutations (may rarely lead to a Ph-negative relapse/progress)

II = BCR-ABL1 in healthy individuals (CHEP)

Stable Ph+ MRD during TKI therapy and:

small subclones bearing BCR-ABL1 mutations

III = Very early chronic phase CML

IV = Chronic phase CML

V = Accelerated phase CML

VI = Blast phase / blast crisis
IMPORTANT NOTES:

• When an overt malignancy has developed, all the premalignant stages and ARCH+ subclones are also still around (MRD) and:

1) may produce new malignant sub-clones over time
2) may also increase the risk for other diseases
3) may create the disease-related microenvironment (niche)
4) may be highly resistant (MRD after “successful“ therapy)
IMPORTANT NOTES:

• When an overt malignancy has developed, all the premalignant stages and ARCH+ subclones are also still around (MRD) and:

1) may produce new malignant sub-clones over time
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3) may create the disease-related microenvironment (niche)
4) may be highly resistant (MRD after “successful“ therapy)
The two Clinically Important Endpoints of CHIP/ARCH

1. Hematopoietic/Myeloid Neoplasm (e.g. MDS or CML)
2. Severe Cardiovascular Disease (e.g. AOD)

Age-related clonal hematopoiesis associated with adverse outcomes

CONCLUSIONS
Age-related clonal hematopoiesis is a common condition that is associated with increases in the risk of hematologic cancer and in all-cause mortality, with the latter possibly due to an increased risk of cardiovascular disease
The two Clinically Important Endpoints of CHIP/ARCH

1. Hematopoietic/Myeloid Neoplasm (e.g. MDS)
2. Severe Cardiovascular Disease (e.g. AOD)

What is the clinical implication:
We need to think in a more multi-disciplinary way
Associations between Cardiovascular Problems and Myeloid / Myeloproliferative Disorders

1) Increased incidence of Thromboembolic Events in *JAK V617F*-mutated MPN (often long before an overt MPN is detected = clonal prephase?)

2) Increased risk of Occurrence of Thromboembolic Events in Patients with F/P+ MPN-eo/CEL

3) Occurrence of Vascular Occlusive Diseases in CML Patients receiving Ponatinib or Nilotinib

4) Another Example may be: PNH
   Many more relationships may be deciphered in the near future!

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FIRST ATTEMPT TO ESTABLISH CRITERIA, A NOMENCLATURE AND A CLASSIFICATION

EU-US multicenter cooperative initiative to standardize parameters of disease and diagnostics for practice and clinical trials in patients with MDS

10 YEAR ANNIVERSARY AND UPDATE 2016

- Morphology
- Histopathology
- Flow Cytometry
- Cytogenetics and Molecular Markers
- Prognostic Factors and Scoring System
- Therapy and Clinical Outcome

Topics addressed in 2006 and 2016

Aims of the MDS WC in 2006:
- Minimal Diagnostic Criteria
- Pre-MDS Conditions
- New Diagnostic Approaches
- Diagnostic Standards
- Diagnostic Algorithms
- Prognostication Standards
- Position Paper
- EU-US Collaborations
- Topic-related Groups
- Consecutive Meetings

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MDS: Minimal Diagnostic Criteria 2007

A. Prerequisite Criteria (BOTH MUST be fulfilled)
   - Constant Cytopenia* (one or more lines, 6 mo unless abnormal karyotype present)
   - Exclusion of all other hematopoietic and non-hematopoietic diseases as primary reason for cytopenia/dysplasia. *Hb <11; ANC <1,500; PLT <100,000.

B. MDS-related (decisive) Criteria (at least ONE)
   - Dysplasia in at least 10% of: erythrocytes or/and megakaryocyte or/and neutrophils or/and >15% ring sideroblasts (iron stain)
   - 5-19% blast cells in bm smears
   - Typical karyotype abnormality (conventional cytogenetics or FISH)

C. Co-Criteria* (pts fulfilling A but not B & typical clinical features)
   - Abnormal phenotype of bm cells by flow cytometry (or IHC)
   - Molecular features indicative of a monoclonal disease process
   - Constantly reduced bm function (e.g. low CFU levels)

*In the absence of B, Co-Criteria may lead to the prefinal diagnosis: highly suspective of MDS

Valent et al., Leuk Res 2007;31:727
FIRST ATTEMPTS TO ESTABLISH CRITERIA, A NOMENCLATURE AND A CLASSIFICATION

MDS vs Pre-MDS Conditions

Meetings after 2006 in Vienna:

Position Papers:

- Definitions and standards in the diagnosis and treatment of the myelodysplastic syndromes: consensus statements and report from a working conference

- Standards and impact of hematopathology in myelodysplastic syndromes (MDS)

**Major EU-US / Global Collaborations**
- Flow Group Advances
- Cytogenetic and Molecular Studies
- MDS Foundation Efforts
- WHO Assists
- IPSS-R Assists

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Pre-MDS Conditions

2007: **ICUS**: - Unexplained Cytopenia over at least 6 mo
  - Insufficient Criteria to diagnose MDS
  - Special Variant: Anemia of the Elderly

2008: **IDUS**: - Unexplained Dysplasia over at least 6 mo
  - Insufficient Criteria to diagnose MDS

2012: **CHIP**: - Somatic Mutations in Myeloid Cells
  - No Cytopenia

2012: **CCUS**: - Somatic Mutations in Myeloid Cells
  - Cytopenia also present (often Anemia)
  - Insufficient Criteria to diagnose MDS

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FIRST ATTEMPTS TO ESTABLISH CRITERIA, A NOMENCLATURE AND A CLASSIFICATION

Pre-MDS Conditions

2007: ICUS:
- Unexplained Cytopenia over at least 6 mo
- Insufficient Criteria to diagnose MDS
- Special Variant: Anemia of the Elderly

2012: ICUS
ICUS Variants = Classification of ICUS:

ICUS-A  Anemia
ICUS-N  Neutropenia
ICUS-T  Thrombocytopenia (ITP must be excluded)
ICUS-BI/PAN  Bi- or Pancytopenia

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Comparison between ICUS, IDUS, CHIP, CCUS, and MDS - and Proposed Criteria and Terminology*

<table>
<thead>
<tr>
<th></th>
<th>ICUS</th>
<th>IDUS</th>
<th>CHIP</th>
<th>CHEP**</th>
<th>CCUS (vs CCEP?)</th>
<th>Low risk MDS</th>
<th>High risk MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonality</td>
<td>-</td>
<td>-/+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>% bm blasts</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>Estimated Risk</td>
<td>Low</td>
<td>Low (?)</td>
<td>Low</td>
<td>Low/Int</td>
<td>Low (?)</td>
<td>Low/Int</td>
<td>High</td>
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<tr>
<td>Management Options and Therapy</td>
<td>Obs/BSC/GF</td>
<td>Obs</td>
<td>Obs</td>
<td>Obs</td>
<td>Obs/BSC/GF</td>
<td>Obs/BSC/GF/Imid/HMA</td>
<td>BSC/GF/HMA/CT/SCT</td>
</tr>
</tbody>
</table>

*adapted from Steensma et al, Blood 2015

**CHEP: clonal hematopoiesis with evident potential

Clonal Cytopenias

eg P53 or RAS, SF3B1 or combis ??
Mutations detected in cases with CCUS & MDS

<table>
<thead>
<tr>
<th>Mutated Gene</th>
<th>All pts (%)</th>
<th>MDS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNMT3A</td>
<td>1.89</td>
<td>11.4</td>
</tr>
<tr>
<td>TET2</td>
<td>0.35</td>
<td>26.6</td>
</tr>
<tr>
<td>ASXL1</td>
<td>0.32</td>
<td>17.6</td>
</tr>
<tr>
<td>JAK2</td>
<td>0.20</td>
<td>3.6</td>
</tr>
<tr>
<td>GNB1</td>
<td>0.13</td>
<td>-</td>
</tr>
<tr>
<td>TP53</td>
<td>0.13</td>
<td>6.0</td>
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<tr>
<td>PPM1D</td>
<td>0.11</td>
<td>-</td>
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<tr>
<td>SF3B1</td>
<td>0.10</td>
<td>29.0</td>
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<tr>
<td>BCROR1</td>
<td>0.07</td>
<td>-</td>
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<tr>
<td>SRSF2</td>
<td>0.06</td>
<td>15.9</td>
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<tr>
<td>GNAS</td>
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<tr>
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<tr>
<td>MYD88</td>
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<td>-</td>
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<tr>
<td>U2AF1</td>
<td>0.01</td>
<td>7.0</td>
</tr>
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<td>IDH2</td>
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<td>2.2</td>
</tr>
<tr>
<td>ATM</td>
<td>0.01</td>
<td>-</td>
</tr>
</tbody>
</table>

Kwok et al, Blood 2015

Sperr, MDS 2016
The real Question

Can we diagnose MDS in the absence of cytopenia?

Can we diagnose MDS in individuals who have completely normal blood counts?
Definition of Diagnostic Cytopenia* regarding MDS and ICUS: proposal:

1) Simple Solution: WHO Cytopenia Definition

2) IWG-MDS (as WHO and: PLT = 100,000)

3) EU-US (2007) (Hb 11, ANC 1,500, PLT 100,000)

4) Other proposal?

*Must be persistent over at least 4 months
MDS: Minimal Diagnostic Criteria

A. Prerequisite Criteria (BOTH MUST be fulfilled)
   - Constant Cytopenia (one or more lines, 4 mo unless abnormal karyotype present)
   - Exclusion of all other hematopoietic and non-hematopoietic diseases as primary reason for cytopenia/dysplasia

B. MDS-related (decisive) Criteria (at least ONE)
   - Dysplasia in at least 10% of: erythrocytes or/and megakaryocyte or/and neutrophils or/and >15% ring sideroblasts (>5% when an SF3B1 mutation is present)
   - 5-19% blast cells in bone marrow (BM) smears
   - Typical karyotype abnormality (conventional cytogenetics or FISH)

C. Co-Criteria* (patients fulfilling A but not B & typical clinical features)
   - Abnormal phenotype of BM cells by flow cytometry (or IHC) suggesting MDS
   - Molecular aberration profile indicative of a myeoid neoplasm (MDS)**
   - Hematopathology report suggests the presence of MDS

*In the absence of B, multiple Co-Criteria may lead to the diagnosis: MDS or highly suspective of MDS

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MDS: Minimal Diagnostic Criteria

C. Co-Criteria* (patients fulfilling A but not B & typical clinical features)
- Abnormal phenotype of BM cells by flow cytometry (or IHC) suggesting MDS
- Molecular aberration profile indicative of a myeoid neoplasm (MDS)
- Hematopathology report suggests the presence of MDS

*In the absence of B, multiple Co-Criteria may lead to the diagnosis: MDS or highly suspective of MDS

OPEN QUESTIONS:
- What combinations of co-criteria are most indicative of MDS?
- What flow abnormalities qualify as MDS-related/specific?
- What molecular markers (e.g. somatic mutations) qualify?
- What allele burden is sufficient to count as a Co-Criterion of MDS?
- What allele burden counts as Criterion of CHIP and CCUS (2%)?
- What assays (flow and molecular Seq) can be regarded standard?
- Is there a standard algorithm for applying ´C´ co-criteria
ICUS: Minimal Diagnostic Criteria

A. Prerequisite Criteria (BOTH MUST be fulfilled)
   - Constant Cytopenia (one or more lines, persisting for ≥ 4 mo)
   - Exclusion of hematopoietic and non-hematopoietic diseases including MDS

B. No MDS-related Criteria
   - No dysplasia in ≥10% of: erythrocytes or/and megakaryocyte or/and neutrophils
     and <5% (<15%) ring sideroblasts (iron stain) and:
   - <5% blast cells in bone marrow (BM) smears and:
   - No karyotype abnormality by conventional cytogenetics and FISH

C. No Co-Criteria*
   - No abnormal (MDS-related) phenotype of BM cells by flow cytometry and IHC
   - No molecular features indicative of a myeloid neoplasm (MDS)
     [- No constantly reduced bm function (e.g. low CFU levels)]
   - Hematopathology report also excludes MDS

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**IDUS**: Minimal Diagnostic Criteria

**A. No Cytopenia (of any degree) and:**
- Exclusion of all other hematopoietic and non-hematopoietic diseases as primary reason for dysplasia

**B. MDS-related (decisive) Criteria (at least ONE) for 4 mo !**
- Dysplasia in at least 10% of: erythrocytes or/and megakaryocyte or/and neutrophils
- >15% ring sideroblasts (iron stain)
- Typical karyotype abnormality (conventional cytogenetics or FISH)?

**C. ± Co-Criteria*:**
- Abnormal phenotype of bone marrow (BM) cells by flow cytometry (or IHC)
- Molecular features indicative of a monoclonal disease process? (DD CHIP)
- Constantly reduced BM function (e.g. low CFU levels)
- Hematopathology report suggests MDS

*Multiple B- and C-Criteria may lead to the prefinal diagnosis: MDS or imminent MDS
Thank You for Your Attention

Peter Valent and the M-Team in Vienna

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