



From Detection of G-CSF and bcr-abl to Application in Clinical Practice

G - CSF in Clinical Practice

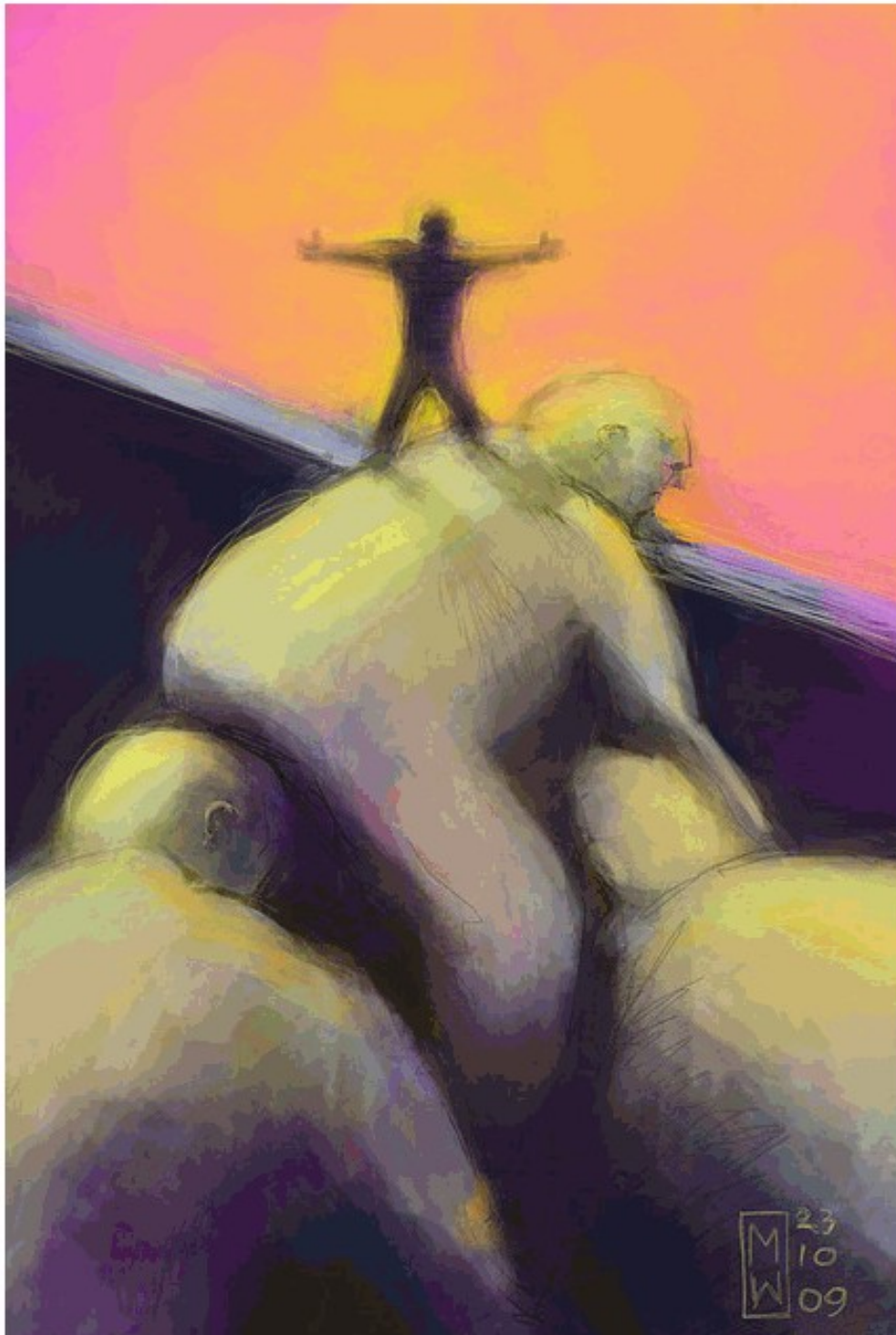
20th International Leukemia-Workshop

July 2, 2011

Mannheim, Germany

Professor Dr. Roland Mertelsmann

Medical Director and Chairman
Department of Hematology, Oncology and Stem Cell Transplantation
Freiburg University Medical Center



"If I have seen further, it is by standing on the shoulders of giants."

-- Sir Isaac Newton

Mathew Watkins, "This is an iphone fingerpainting for my friends at RAI educational. You can see me painting it on RAI Art News here: [07/11/2009 Puntata VIII.](#) "



- 1. The Past: The Basis of G-CSF Development**
- 2. The Present**
- 3. The Future**

Hämatopoiesis



Neuman 1868

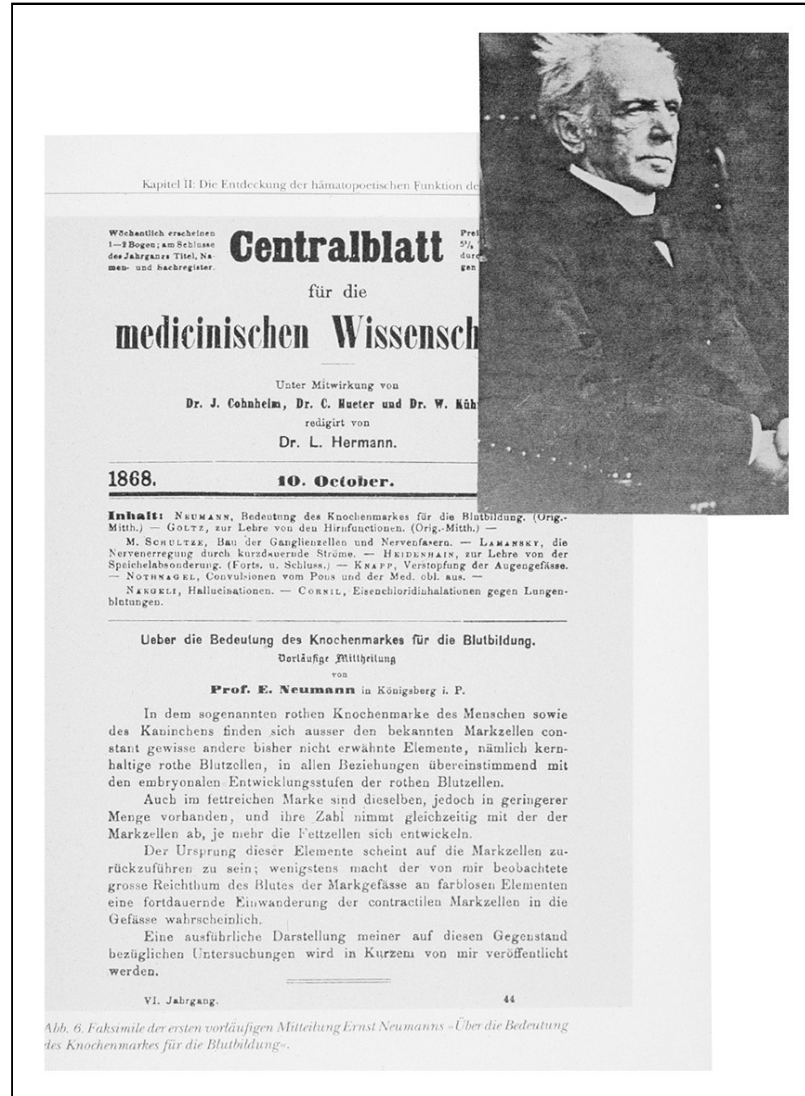


Abb. 6. Faksimile der ersten vorläufigen Mittheilung Ernst Neumanns: „Ueber die Bedeutung des Knochenmarkes für die Blutbildung.“

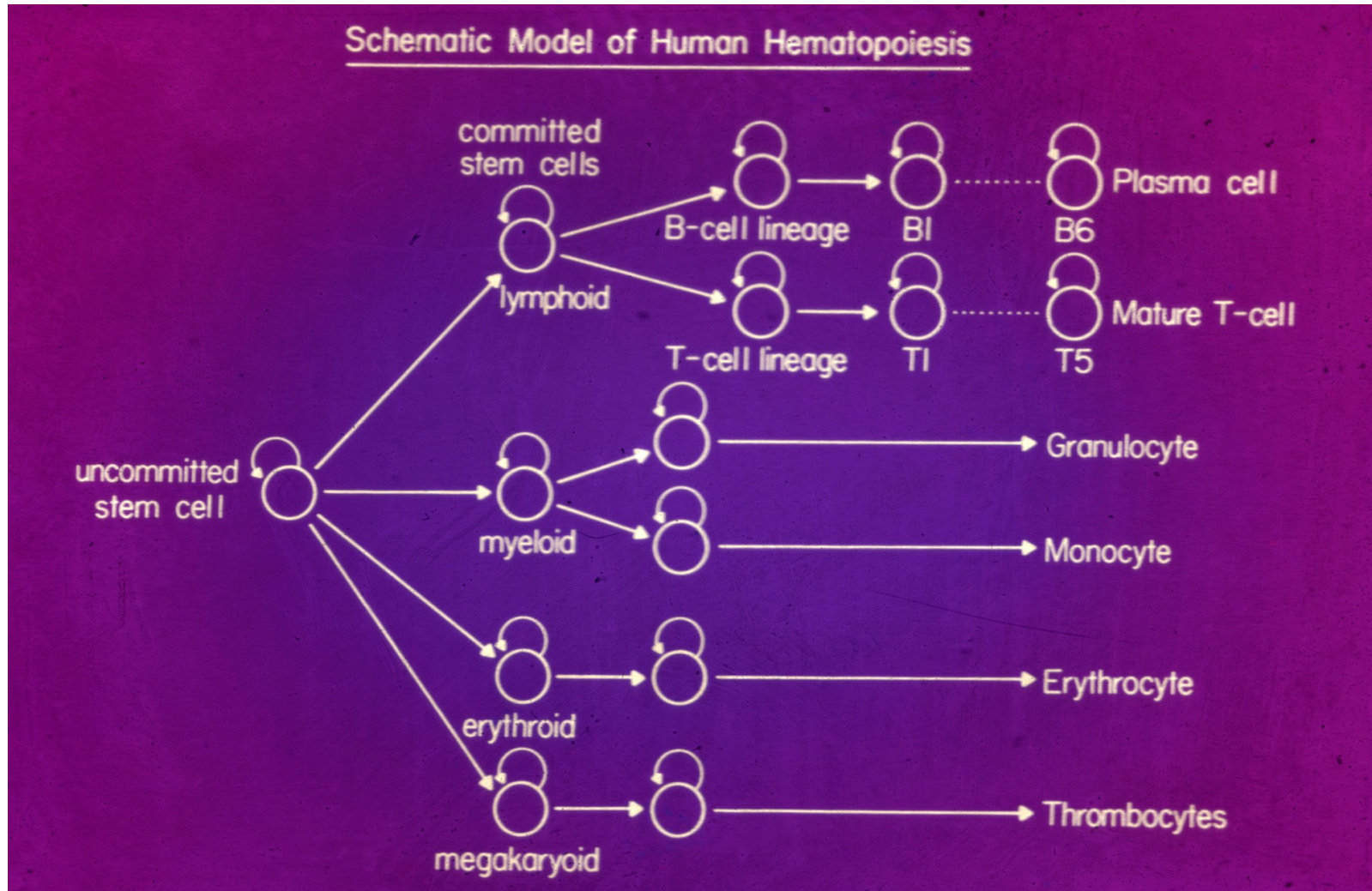
Bone marrow is the
location of hematopoiesis

Maximov 1909

The "lymphocyte" is
the stem cell of the
different blood cells



- 1961 Discovery of the Genetic Code, Matthaei and Nirenberg
- 1961 CFU-s, Till & McCulloch
- 1965-66 CFU-c, Pluznik & Saks, Bradley & Metcalf, Moore
- 1970s Colony Stimulating Factors, Metcalf, Moore, Saks et al.
- 1971 First Wilsede Conference "Modern Trends in Human Leukemia"
Rolf Neth, Bob Gallo et al.





- 1985 Identification and Biochemical Characterization of "huG-CSF"
Welte, Platzer, Gahrville, Mertelsmann, Moore (Science 1985)
- 1987 + Clinical Studies with recombinant G-CSF
- 1991 G-CSF (Filgrastim) approved for clinical use



1. The Past
2. The Present: G-CSF in Chemotherapy and Transplantation
3. The Future



G-CSF



Suche

Ungefähr 4.830.000 Ergebnisse (0,14 Sekunden)

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Seiten auf Deutsch

Seiten aus Deutschland
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Zeitleiste

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► **G-CSF – Wikipedia**

Der Granulozyten-Kolonie stimulierender Faktor (engl. Granulocyte-Colony Stimulating Factor, **G-CSF**) ist ein Peptidhormon, das als Cytokin unter anderem bei ...

Struktur - Biologische Funktion - Arzneistoffe - Einzelnachweise
de.wikipedia.org/wiki/G-CSF - Im Cache - Ähnliche Seiten

Granulocyte colony-stimulating factor - Wikipedia, the free ... - [Diese Seite übersetzen]

Granulocyte colony-stimulating factor (**G-CSF** or **GCSF**) is a colony ...
en.wikipedia.org/.../Granulocyte_colony-stimulating_factor - Im Cache - Ähnliche Seiten

Weitere Ergebnisse von wikipedia.org

Leukämie Kompetenznetz: G-CSF (Neupogen®, Granocyte®), GM-CSF ...

von G Maschmeyer - Ähnliche Artikel

16. Mai 2007 ... Der klinische Einsatz von **G-CSF** (Neupogen®, Granocyte®) und GM-CSF (Leucomax®) bedarf hinsichtlich seines objektiven Nutzens einer ...

www.kompetenznetz-leukaemie.de/.../g_csf__gm_csf/ - Im Cache - Ähnliche Seiten

Chugai Pharma - G-CSF

G-CSF ist ein körpereigenes glykosyliertes Protein, das seit einigen Jahren auch als Medikament hergestellt werden kann. Eingesetzt wird der **G-CSF** entweder ...

www.chugaipharma.de/html/index.php?... - Im Cache - Ähnliche Seiten

PDF] O4 Stimulation der Granulopoese mit G-CSF

Dateiformat: PDF/Adobe Acrobat - Schnellansicht

Leitlinien empfehlen, **G-CSF** bereits bei einem Risiko der febrilen Neutropenie ...

Empfehlungen für **G-CSF** bei definierten Patientengruppen mit Neutropenie ...

www.krebsgesellschaft.de/download/ll_o_04.pdf - Ähnliche Seiten

G-CSF - Cancer information - Mamillan Cancer Support - [Diese Seite übersetzen]

Information about **G-CSF** (granulocyte-colony stimulating factor) a growth factor that stimulates the bone marrow to make more white blood cells.

www.macmillan.org.uk/.../HaematopoieticGrowthFactors.aspx - Im Cache - Ähnliche Seiten

6.1 Hämatopoetische Wachstumsfaktoren - Stimulation der ...

25. Jan. 2006 ... 6.1 Hämatopoetische Wachstumsfaktoren - Stimulation der Granulopoese mit Granulozytenkolonie-stimulierendem-Faktor (**G-CSF**): Rationale ...

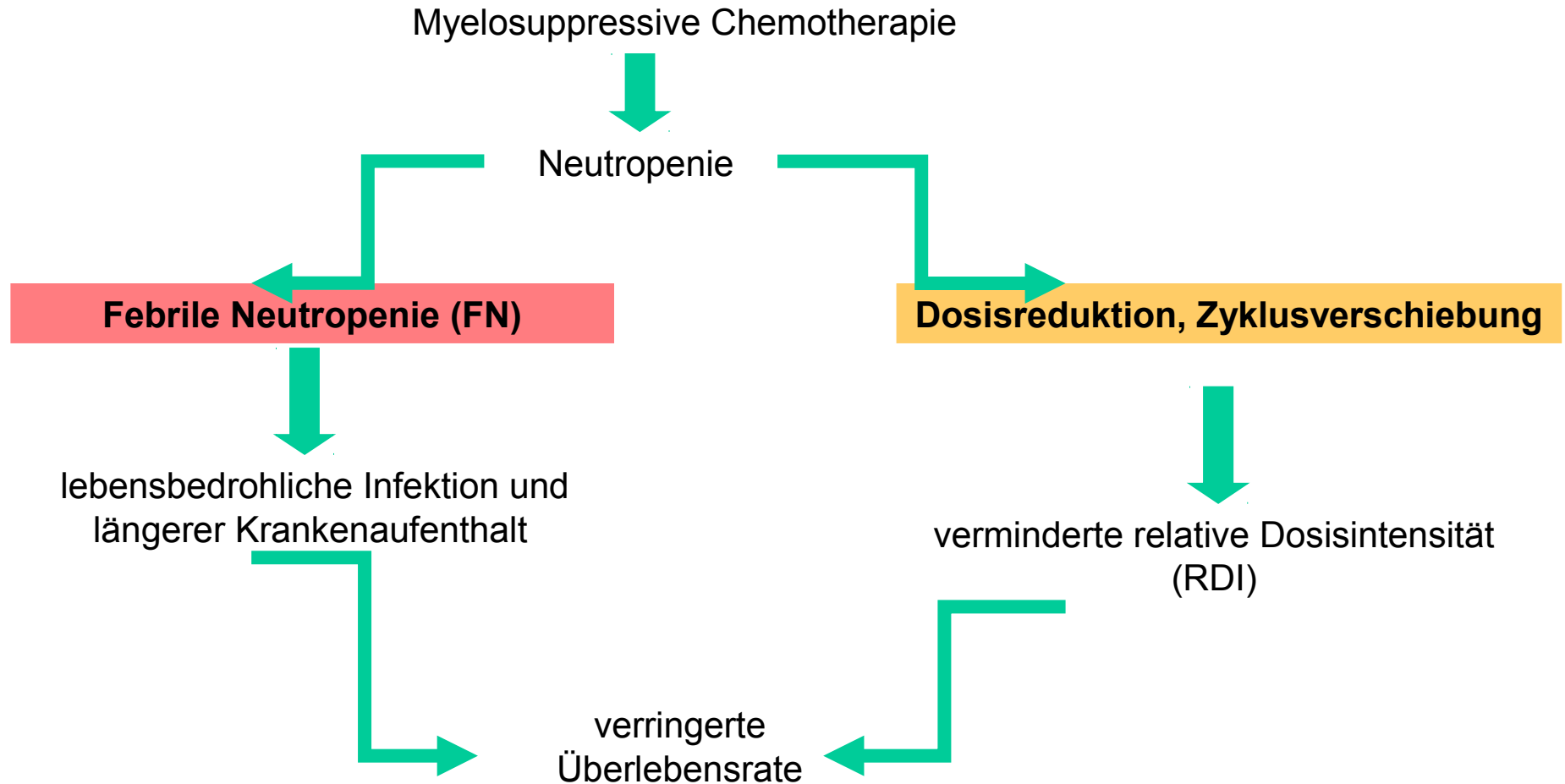
www.onkodin.de/e6/e38842/e42879/.../index_ger.html - Im Cache

- Hematologic manifestations of HIV infection: Neutropenia



1. Neutropenien, neutropenischen Fiebers ...zytotoxischer Chemotherapie
2. myeloablative Behandlung ... Knochenmarktransplantation
3. Mobilisierung peripherer Blutstammzellen.
4. kongenitaler, zyklischer oder idiopathischer ...Neutropenie.
5. Neutropenie ... HIV-Infektion

Impact of Chemotherapy-induced Neutropenia



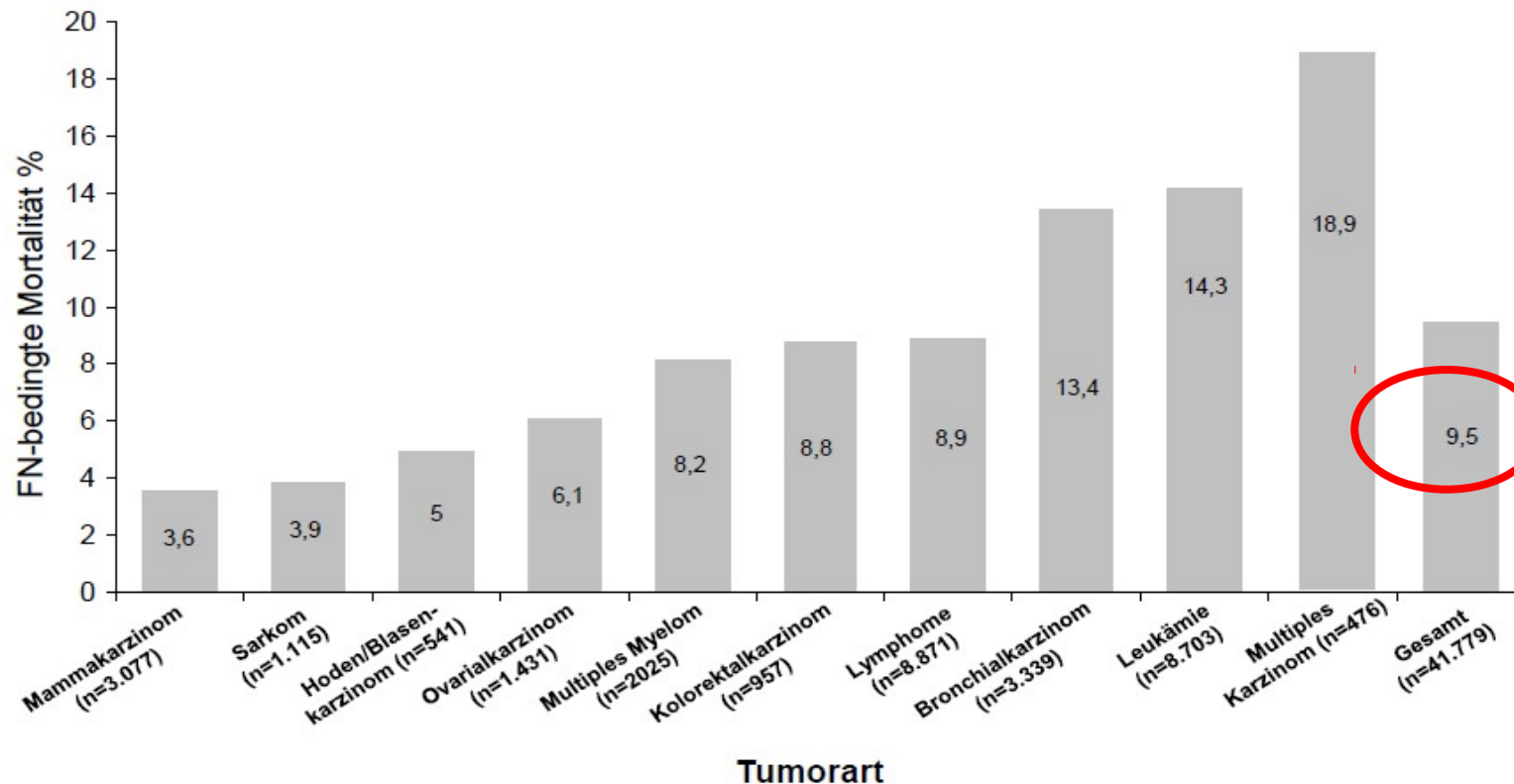
Kuderer NM et al. *Cancer* 2006;106:2258–2266.

Chirivella I et al. *Breast Cancer Res Treat* 2009;114:479–484.

Bosly A et al. *Ann Hematol* 2008;87:277–283.

FN-associated Mortality after Chemotherapy

Mortalitätsrate bei Patienten*, die wegen febriler Neutropenie hospitalisiert wurden



Studiendesign

Retrospektive Analyse von 115 US Einrichtungen.

Patienten

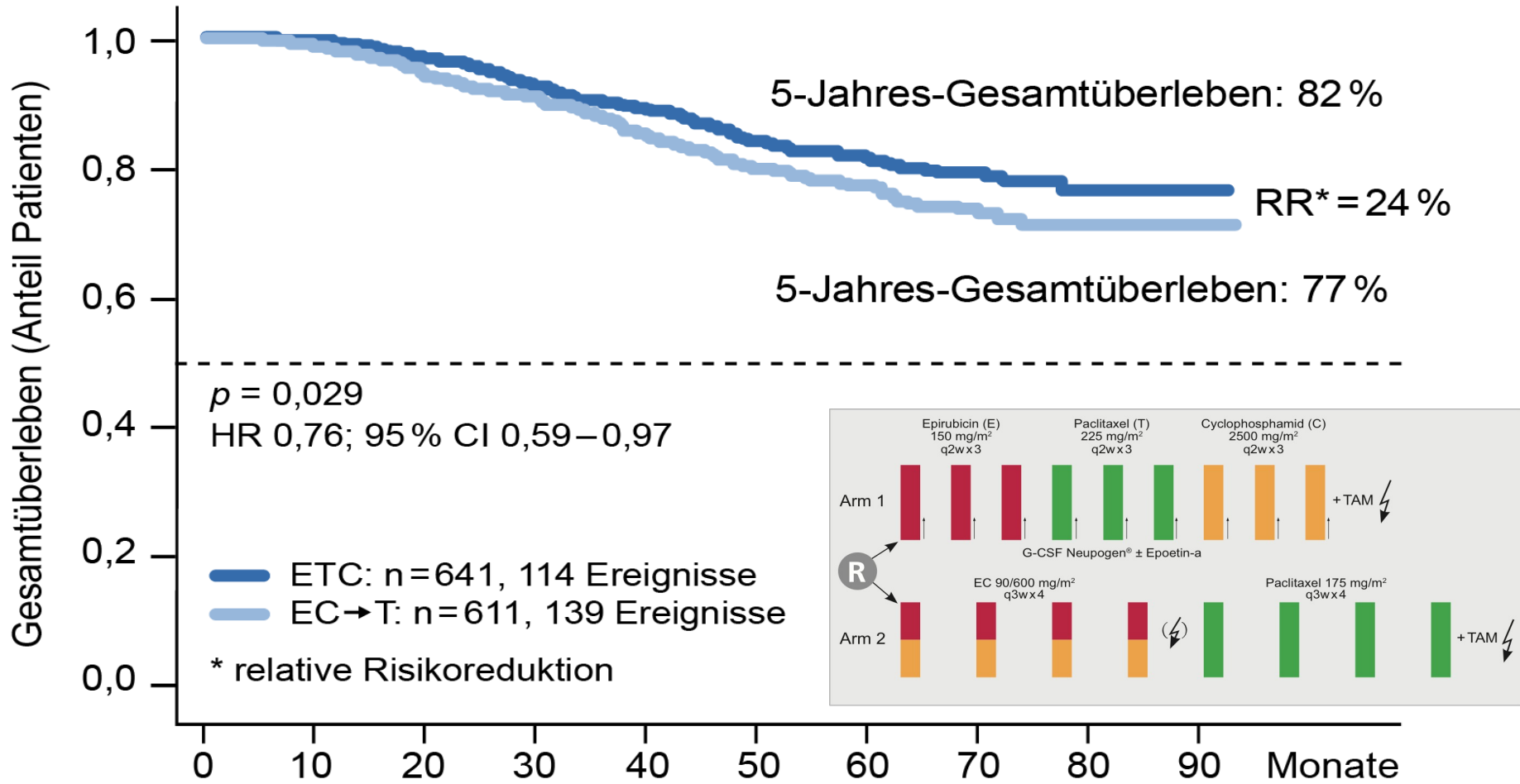
41.779 Krebspatienten, die zwischen 1995 und 2000 wegen febriler Neutropenie stationär aufgenommen wurden.

Chemotherapie

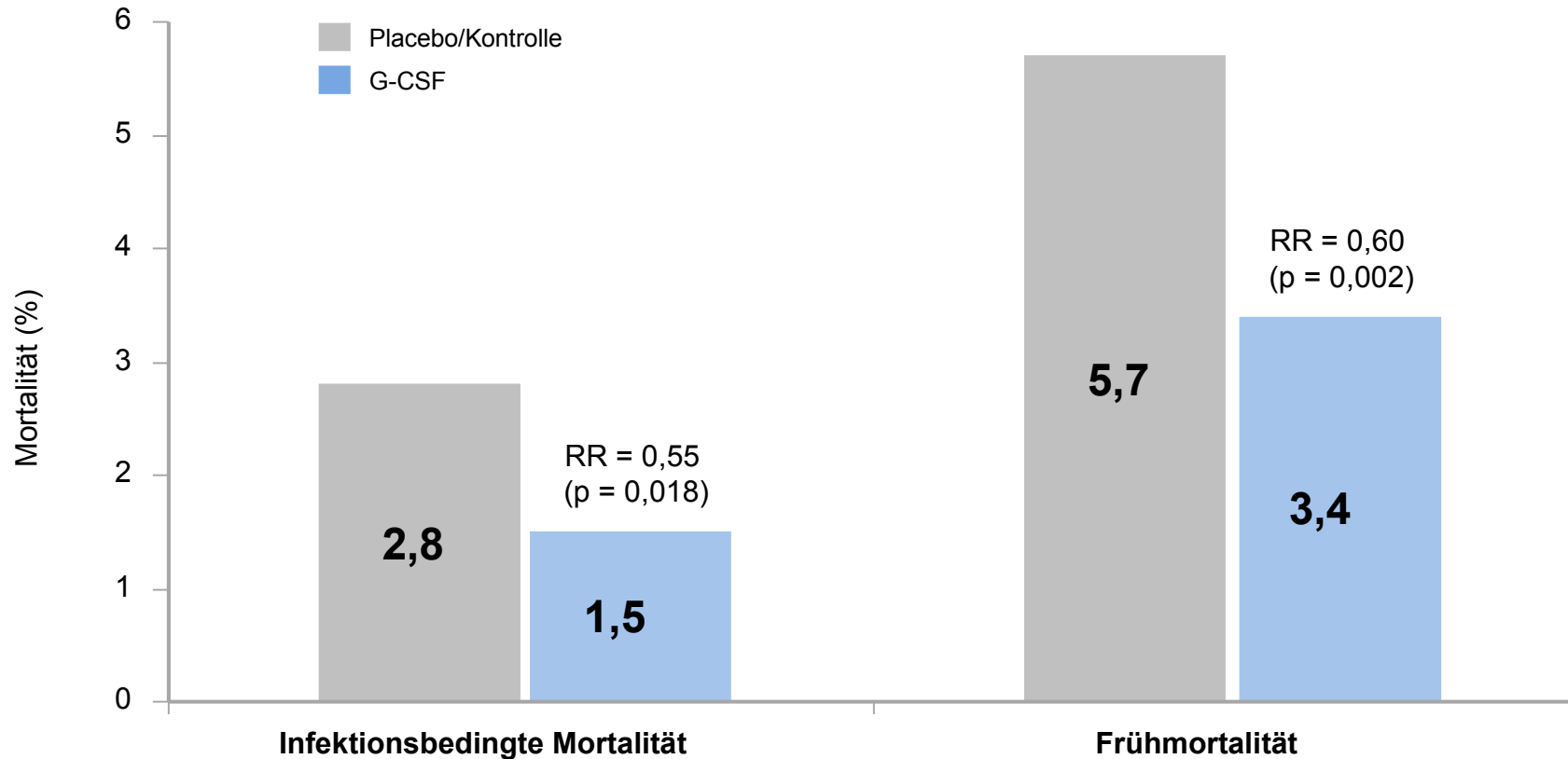
Keine Angaben

*Alle übrigen malignen Tumore Diagnosen (n =11.244) wurden als „Andere“ klassifiziert (nicht angezeigt).

Overall Survival

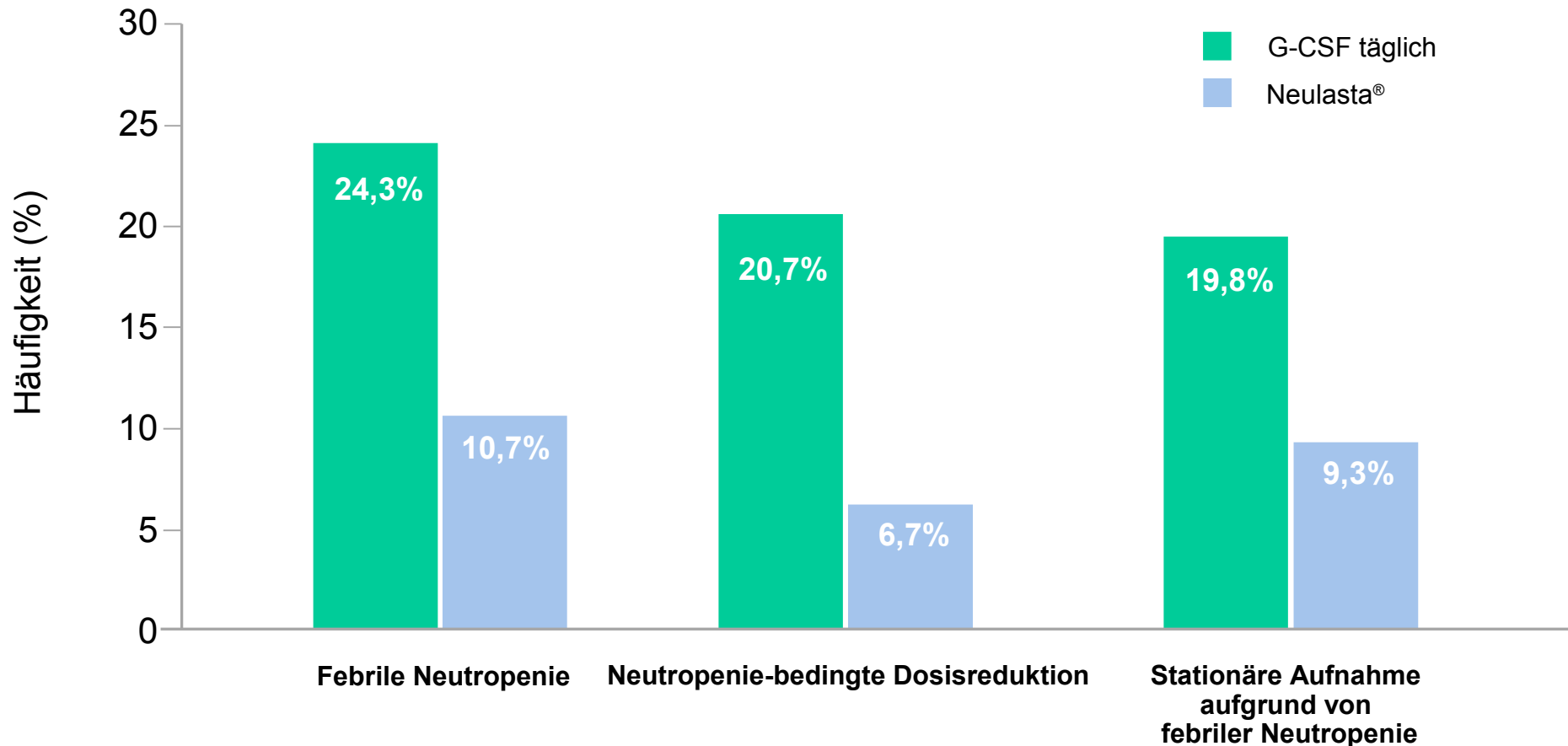


Primary Prophylaxis with G-CSF vs. Placebo: Mortality



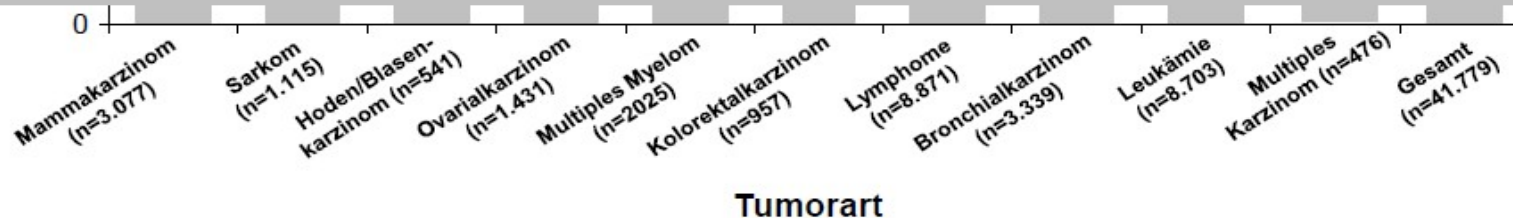
Clinical Benefit of Pegfilgrastim vs. G-CSF

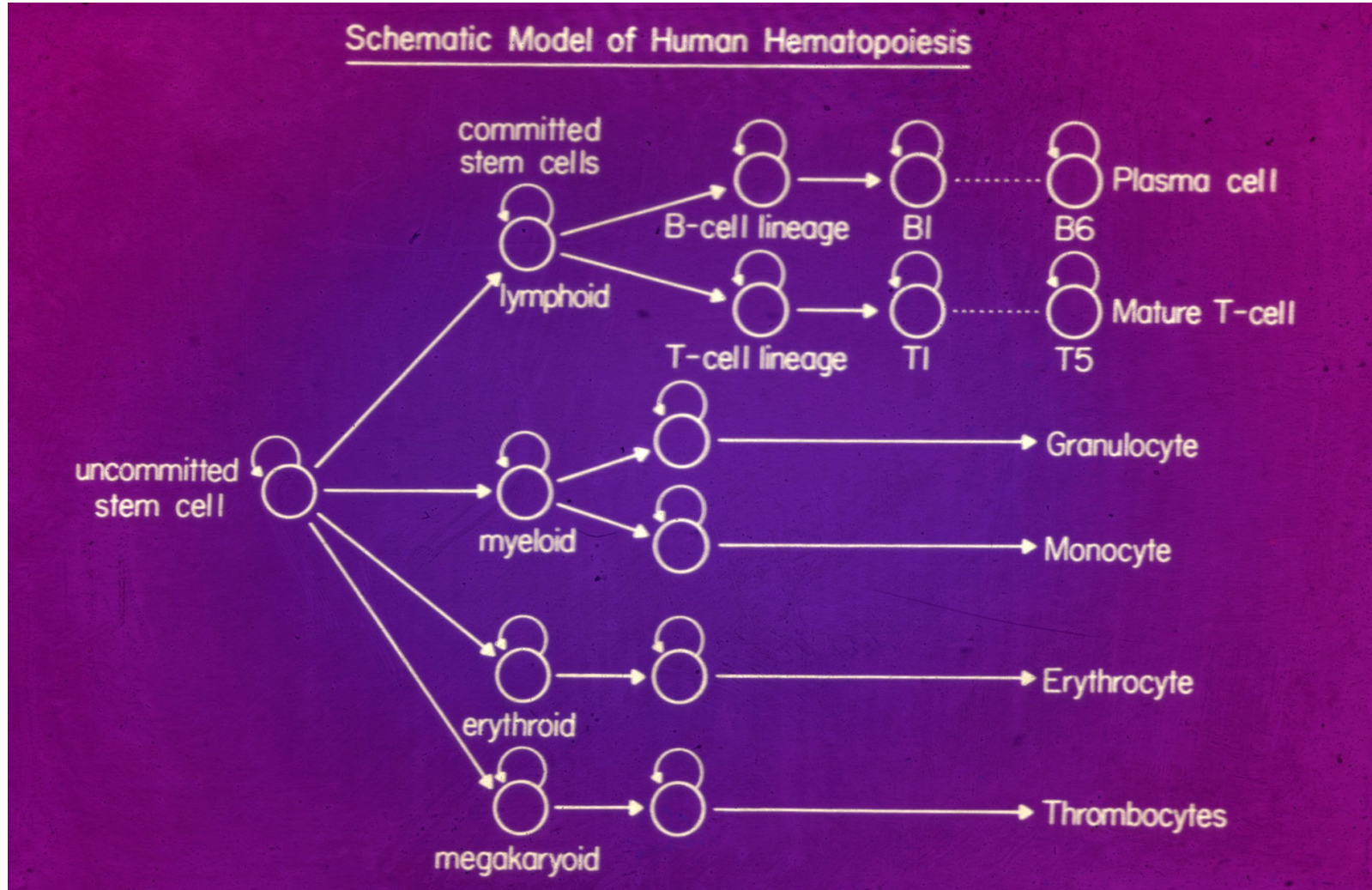
Häufigkeit Neutropenie-bedingter Komplikationen



Reduction of FN-associated Mortality after Chemotherapy by G-CSF

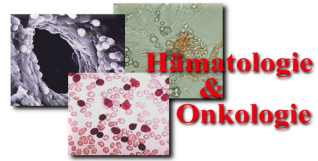
- 9.5 % correspond to 3969 of 41779 Patients in these FN studies
- ca. 50% reduction of mortality from 9.5% to 4.75 %, i.e. 2000 fewer deaths
- reduction of mortality from 5.7% to 3.4% in other studies
- ca. 2 - 5 % better OS with G-CSF in various studies
- *highly significant reduction in morbidity and mortality in cancer patients by G-CSF*
- *60 000 cancer patients treated annually with G-CSF in Germany*







G-CSF and Hematopoietic Stem Cell Therapy



- 1967** **Thomas**, 1st successful human bone marrow transplantation, in vivo demonstration of human HSC

- 1980** **Körbling**. transplantation of HSC from peripheral blood (Scand. J. Hemat., 1980)

- 1985** Identification and Biochemical Characterization of "huG-CSF" by **Welte, Platzer, Gabilove, Mertelsmann, Moore** (Science 1985)

- 1988** **Gluckman**, HSC transplantation from cord blood (Gluckman et al, NEJM, 1989)

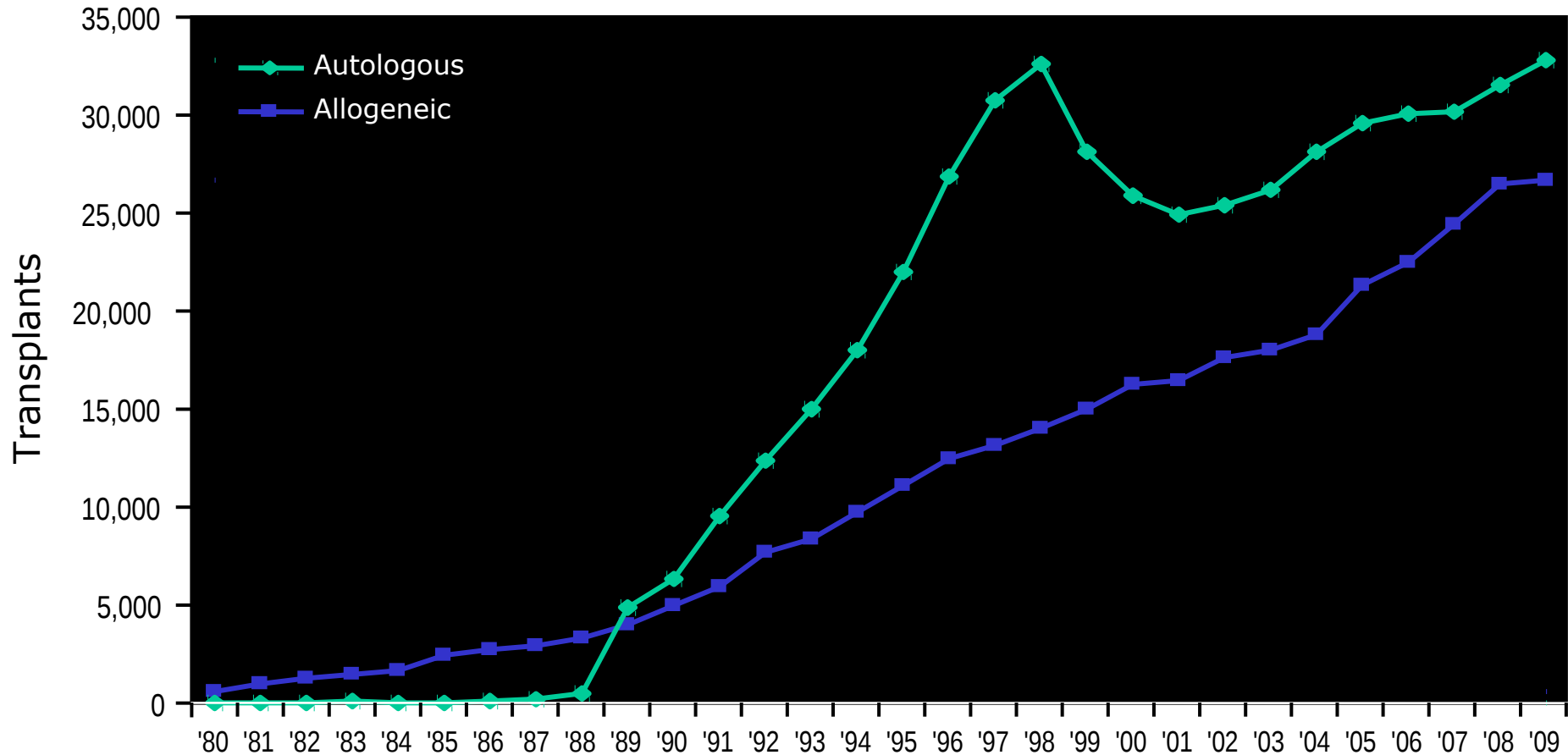
- 1990+** Transplantation of CD34-selected HSC

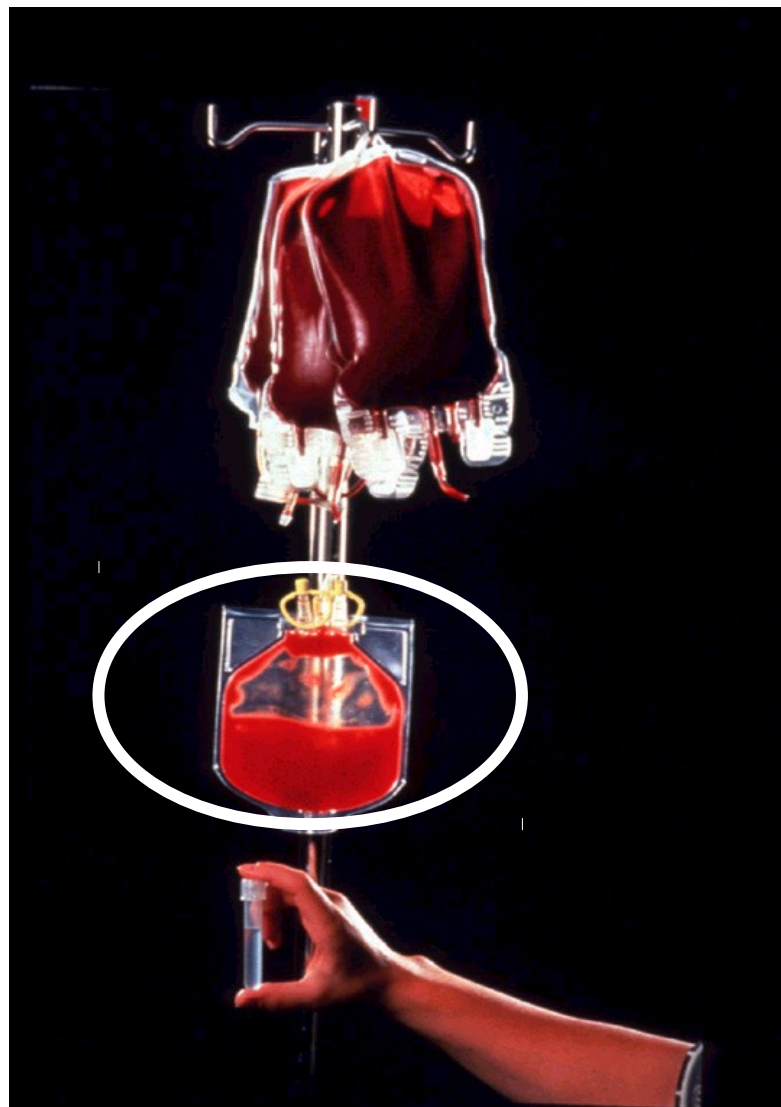
- 1991** **G-CSF** (Filgrastim approved) for clinical use

- 1995 + Henschler, Brugger** Transplantation of ex vivo cultured HSC (Blood 1994)

- 2000+** **v. Kalle**, various groups, Transplantation of gene transduced HSC

Transplant activity worldwide 1980-2009





Total HSCT/year
auto 33 000
allo 27 000

Bone marrow

PBSC auto/allo 99%/ 80%

Cord Blood

CD34 HSC



1. **The Past**
2. **The Present**
3. **The Future:
Stem Cell Reprogramming**

1874 Haeckel "Stammzelle", application to ontogeny, fertilized egg a stem cell

1867, 92 Boveri, stem cell of the nematode *Ascaris*

1908 Maximov, Pappenheim: Hematopoietic Stem Cell (HSC)

1981+ ES Cells, Capecchi et al.

1997+ Dolly: in vivo induction of totipotence in somatic cells

2006 Yamanaka et al. Induction of Pluripotent Stem Cells (**IPS Cells**) with ES-Properties from differentiated Cells by gene transfer of 4 genes: **Oct4, Sox2, Klf-4, c-Myc**

2007 Cells selected for NANOG are **germ line competent**

Takahashi and Yamanaka, Cell 126, 663-76 2006, K. Okita et al., Nature 448:313, 2007

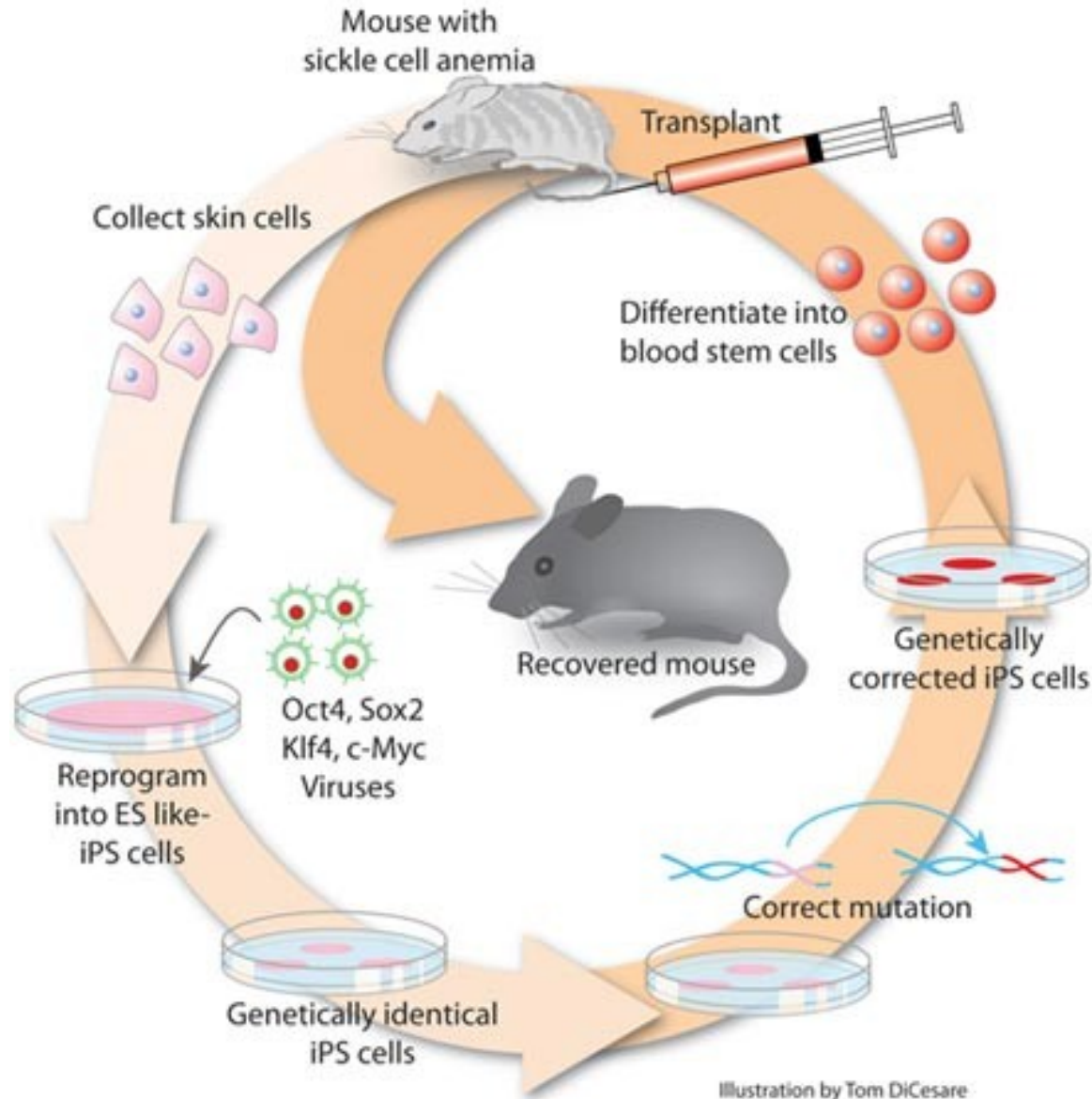
2010 Dailey et al. Generation of induced pluripotent stem cells from **human blood**



**Epigenetic Regulation
of Gene Expression**



Transplantation of HSC generated from skin-derived and genetically corrected iPS Cells

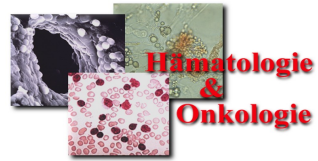


Higgs NEJM 2008

Jaenisch et al.



Stem Cells From Bench to Bedside



The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL IMPLICATIONS OF BASIC RESEARCH

A New Dawn for Stem-Cell Therapy

Douglas R. Higgs, M.D., D.Sc.

N ENGL J MED 358;9 WWW.NEJM.ORG FEBRUARY 28, 2008

HSC or Skin → iPS Cell

iPS Cell → any therapeutic cell type +/- correction of defective genes



1. The Past

2. The Present

G-CSF has not cured cancer

G-CSF has significantly reduced morbidity and mortality in cancer patients

3. The Future

G-CSF has opened up stimulating und promising new areas of research



1964 MPI Exp. Med., Göttingen
Matthaei, Neth et al.

1968 I. Med. Klinik, Hamburg
Neth, Bartelheimer, Sill, Greul, Garbrecht

1976-86 MSKCC, NY
Moore, Clarkson, Koziner, Welte et al.

1986 -89 U. Mainz Medical Center, 3. Med. Klinik
Meyer zum Büschenfelde et al.

1989- present U. Freiburg Medical Center, Dept. Med. I
Löhr, Gerok, Freiburg Medical Faculty,

1974 - present colleagues, patients and students, family and friends

Reduction of FN-associated Mortality after Chemotherapy by G-CSF

- 9.5 % correspond to 3969 of 41779 Patients in these FN studies
- ca. 50% reduction of mortality from 9.5% to 4.75 %, i.e. 2000 fewer deaths
- reduction of mortality from 5.7% to 3.4% in other studies
- ca. 2 - 5 % better OS with G-CSF in various studies
- *highly significant reduction in morbidity and mortality in cancer patients by G-CSF*
- *60 000 cancer patients treated annually with G-CSF in Germany*
- *2% estimated reduction of cancer deaths by G-CSF*
 - in Germany: 1 200/year*
 - in EU + USA: 12 000/year*