

# DES d'hématologie : Journée syndromes

**myélodysplasiques (SMD)** *20 octobre 2011, Amphithéâtre du Centre Hayem, Hôpital St Louis, Paris*

**10 h** Introduction et Epidémiologie des SMD (primitifs et secondaires) **P Fenaux 10 mn**

**10h 15** Cytogénétique des SMD **V Eclache 15 mn**

**10h30** Mécanismes physiopathologiques dans les SMD (*incluant les anomalies génétiques dont le 5q-, le rôle des troubles de l'immunité, de l'hyperméthylation*) **M Fontenay 35mn**

**11h05** Diagnostic morphologique et classification OMS **J Goasguen 25 mn**

**11h30** Scores pronostiques et autres tests à visée pronostique dans les SMD (y compris les facteurs de comorbidité, y compris en fonction des traitements) **travail présenté par un interne en DES 20 mn (R Itzykson)**

**11 h50 Discussion (tous les intervenants et la salle) : quels examens diagnostiques et pronostiques demander dans les SMD ? 15 mn**

**12h05** Perspectives thérapeutiques dans les SMD (nouveaux agents, associations, immunothérapie...) **N Vey 20 mn**

**12h25-13h30** REPAS SUR PLACE

**13h30** Traitement des SMD de faible risque (à l'exception des formes avec del 5q) **F Dreyfus**  
**30 mn**

**14h** Traitement des SMD haut risque (à l'exception de l'allogreffe) **P Fenaux** 30 mn

**14h30** Prise en charge transfusionnelle et de la surcharge en fer dans les SMD **C Rose** 20 mn

**15h** Biologie de la leucémie myélomonocytaire chronique de l'adulte et du jeune enfant **E Solary** 20 mn

**15h20** Traitement des formes particulières

-SMD avec del 5q **L Adès** 15 mn

-LMMC de l'adulte **T Braun** 15 mn

**15h50** Place de l'allogreffe dans les SMD (y compris la LMMC) **N Dhédin** 25 mn

**16h15** Prise en charge des SMD de l'enfant 20 mn

**16h35** Le rôle des patients et de leurs associations : **P Festy** 10 mn

**16h45** *Discussion autour du traitement des SMD (tous les intervenants et la salle) : 15 mn*

**fin 17h00**

# Syndromes myélodysplasiques (SMD) introduction

Pierre FENAUX (Hopital Avicenne  
Paris 13, university)

GFM



# SMD

Hémopathies clonales des cellules souches hématopoïétiques caractérisées par:

- une hématopoïèse inefficace aboutissant à des cytopénies sanguines
- Une évolution en LAM dans 30-40% des cas
- Une prédominance chez les sujets âgés

# SMD

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- Une prédominance chez les sujets âgés
- **Récemment:**
  - Très gros progrès dans la biologie des SMD
  - Progrès thérapeutiques

# Incidence and prevalence of myelodysplastic syndromes: Data from the Düsseldorf MDS-registry.

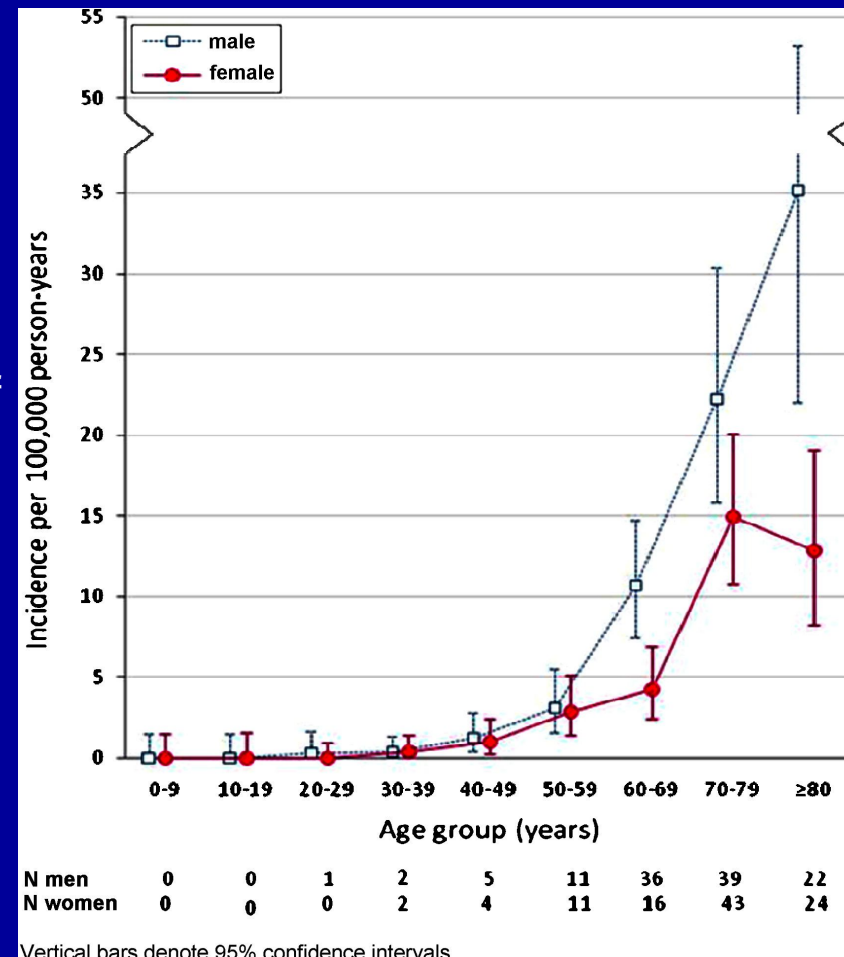
## Neukirchen J, 2011

crude incidence rate 4.15/100,000/year

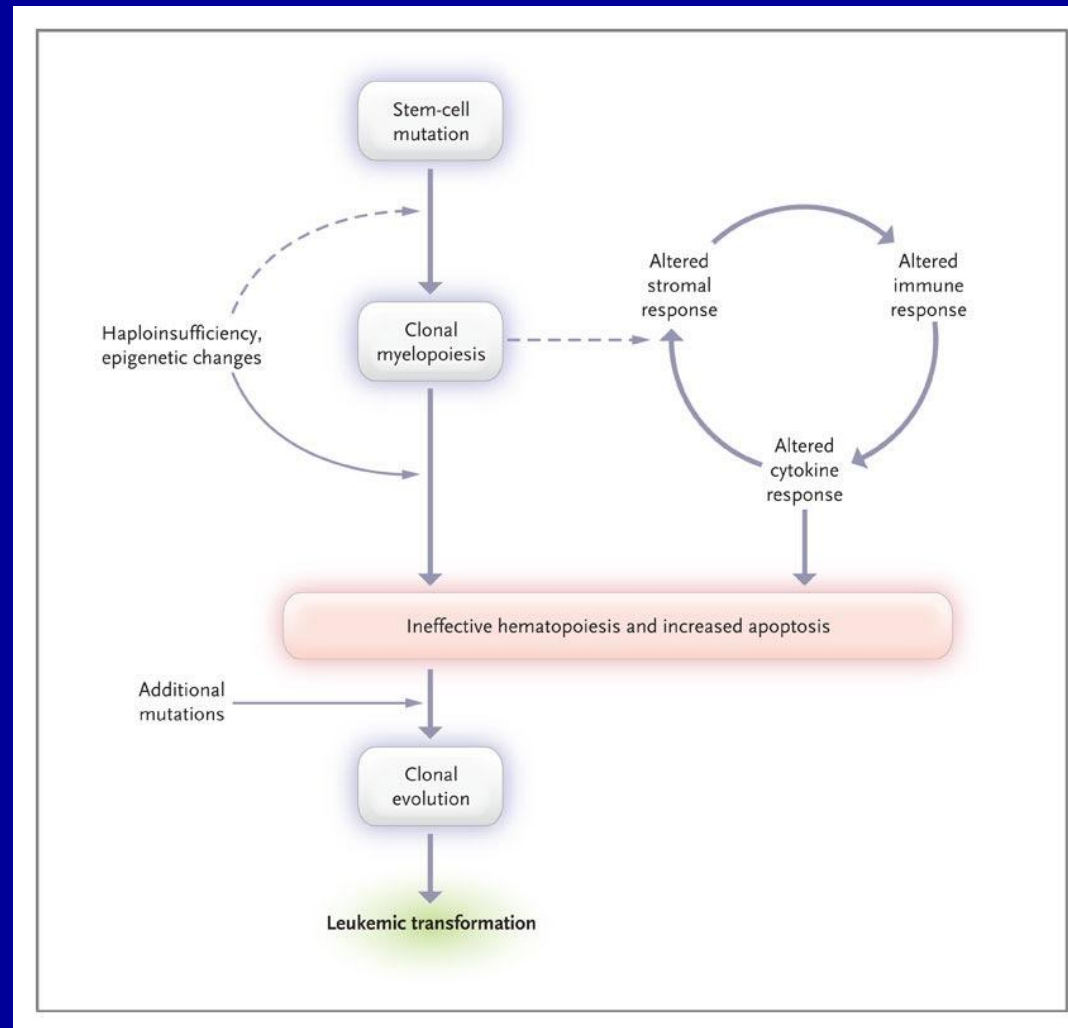
point prevalence 7 per 100,000 persons of 7.

incidence and prevalence of MDS higher in men than women

increased sharply with increasing age.



# Putative Pathogenetic Mechanisms and Their Interaction in the Myelodysplastic Syndromes



Tefferi A, Vardiman J. N Engl J Med 2009;361:1872-1885



The NEW ENGLAND  
JOURNAL of MEDICINE

# Bone progenitor dysfunction induces myelodysplasia and secondary leukaemia.

Raaijmakers MH Nature 2010

*Primary stromal dysfunction can result in secondary neoplastic disease, supporting the concept of niche-induced oncogenesis.*

- deletion of Dicer 1 in mouse osteoprogenitors results in MDS having intact Dicer1.
- reduced expression of Sbds ( Schwachman-Bodian-Diamond syndrome) protein in osteoprogenitors

# Etiology of MDS

- Inherited factors
- Exogenous factors
- Immunological disorders

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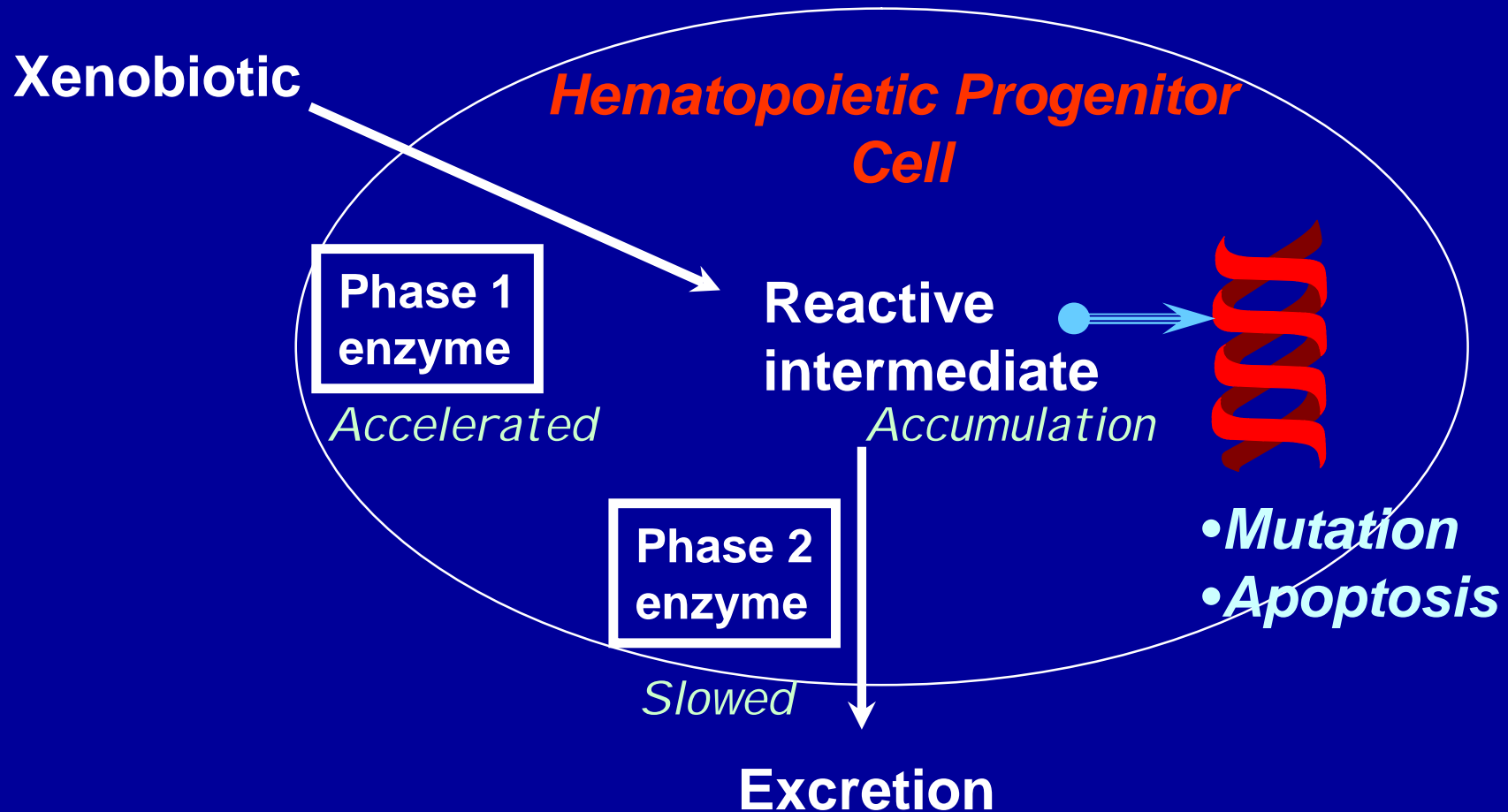
# Inherited factors

- Chromosomal defects (Down's syndrome)
- Gene mutations
- Allelic variants in xenobiotic-metabolising genes

# Inherited Gene mutations in MDS

- Fanconi anemia (FAN...)
- Bloom's syndrome (BLM)
- Telomerase complex genes (TERT, TERC,DKC1)
- Schwachman –Diamond syndrome (SBDS)
- AML 1 gene (FPD)\*
- TP 53 gene (Li Fraumeni)\*
- CEBPa gene\*
- GATA 2 gene
- G-CSF Receptor Glu785Lys mutation
- Juvenile myelomonocytic leukemia
  - NF1\*
  - PTPN11(N Noonan's syndrome)\*
  - Cbl\*

# Allelic variants in xenobiotic-metabolising genes risk factors of tMDS ?



NADP(H) quinone  
oxidoreductase  
(NQO1)  
Pro187Ser

+ increased CYP2E1  
activity

Benzene  
haematotoxicity

Therapy  
related  
MDS/AML

- NQO1 functions to detoxify benzene metabolites and products of oxidative stress

## **NQO1 deficiency conjoint with marginal vitamin C deficiency causes cigarette smoke induced myelodysplastic syndromes.**

**Das A, PLOs 1,2011**

Exposure to cigarette smoke (CS) is reported to be associated with MDS risk. There is inconsistent evidence that deficiency of NAD(P)H-quinone: oxidoreductase 1 (NQO1) increases the risk of MDS. Earlier we had shown that CS induces toxicity only in marginal vitamin C-deficient guinea pigs but not in vitamin C-sufficient ones. We therefore considered that NQO1 deficiency along with marginal vitamin C deficiency might produce MDS in CS-exposed guinea pigs.

### **METHODOLOGY AND PRINCIPAL FINDINGS:**

Here we show that CS exposure for 21 days produces MDS in guinea pigs having deficiency of NQO1 (fed 3 mg dicoumarol/day) conjoint with marginal vitamin C deficiency (fed 0.5 mg vitamin C/day). As evidenced by morphology, histology and cytogenetics, MDS produced in the guinea pigs falls in the category of refractory cytopenia with unilineage dysplasia (RCUD): refractory anemia; refractory thrombocytopenia that is associated with ring sideroblasts, micromegakaryocytes, myeloid hyperplasia and aneuploidy. MDS is accompanied by increased CD34(+) cells and oxidative stress as shown by the formation of protein carbonyls and 8-oxodeoxyguanosine. Apoptosis precedes MDS but disappears later with marked decrease in the p53 protein. MDS produced in the guinea pigs are irreversible. MDS and all the aforesaid pathophysiological events do not occur in vitamin C-sufficient guinea pigs. However, after the onset of MDS vitamin C becomes ineffective.

### **CONCLUSIONS AND SIGNIFICANCE:**

CS exposure causes MDS in guinea pigs having deficiency of NQO1 conjoint with marginal vitamin C deficiency. The syndromes are not produced in singular deficiency of NQO1 or marginal vitamin C deficiency. Our results suggest that human smokers having NQO1 deficiency combined with marginal vitamin C deficiency are likely to be at high risk for developing MDS and that intake of a moderately large dose of vitamin C would prevent MDS

## Enzyme variants and predisposition to MDS/AML

	Phase 1 enzyme		Phase 2 enzyme	DNA repair enzyme
Therapy-related AML	increased CYP1A1*2A, CYP2E1	-	<ul style="list-style-type: none"> <li>•<b>GSTP1</b> Ile105Val [OR, 4.34; 95% CI, 1.43-13.20]</li> <li>•<b>NQO1</b> Pro187Ser [OR 2.6; 95% CI, 2.16-3.28]</li> </ul>	<b>XRCC1</b> Arg399Gly [OR 0.44; 95% CI, 0.20-0.93] NB Protective in AML controls

# Etiology of MDS

- Inherited factors
- Exogenous factors

# MDS: occupational or environmental factors

- Benzene and derivatives
- Tobacco smoke
- Solvents
- Ionizing radiations
- Pesticides, weed killers, fertilizers
- Heavy metals

# Occupational exposures

Crane	West	Nisse	Rigolin	Ido	Goldberg	
<b>Chemical exposure</b>	+	+	+		+	
Inorganic gases/fumes	+/-					
Halogenated organics	+					
Hydrogen peroxide	+					
Exhaust gases	+					
Metals	+					
<b>Pesticides</b>	-	+	+	+	+	
<b>Organic solvents</b>		+/-		+	+	+
Electro-magnetic fields	+/-			+		

# Environmental factors

	West 400	Nisse 204	Rigolin 178	Ido 111	Goldberg 52	Crane 46
<b>Smoking</b>	+	+		+		
Alcohol drinking					+	
Diagnostic X ray	+					
close to power plant	+					
Living in a farm		+				
Hairdyes gardening					+	
Childless		+				

**Effect of smoking confirmed in 2 further case control studies : Pasqualetti (1997) : 85 cases ; Bjork (2001) : 330 cases**

# Therapy related MDS and AML (Pedersen Bjergaard et al)

## 1) “classical” tMDS and AML

- after **alkylating agents**
- relatively long interval from chemotherapy
- usual **preleukemic phase**
- rearrangements of **chromosome 7 and 5**, often complex

## 2) “recently described” tAML

- after epipodophyllotoxins (**VP 16**) or other agents targeted at topo II (**anthracyclines**)
- **short interval** from chemotherapy
- **no preleukemic phase**
- **t(11q23),t(15;17)** (or less often t(8;21), inv(16)) rearrangements :

# t AML/MDS after autologous stem cell transplantation

- 1.5 to 14%
- Generally MDS, and abnormal chrom 5 and/or 7, already present in stem cells
- Risk factors:
  - previous treatment (alkylators, fludarabine) +++
  - age
  - TBI as conditioning regimen
  - Stem cell mobilization by VP 16

# Other Drugs associated with t MDS and AML

- **Drugs used in MPD:** Hydroxyurea and Pipobroman (Bjorkholm, Blood, 2011)
- **Drugs used in autoimmune disorders and organ transplantation** (Cyclophosphamide, azathioprine)
- **« Newer drugs »:**
  - taxanes,
  - fludarabine,
  - platinum,
  - G-CSF
  - Radioimmunoconjugates
  - dexrazoxane

# Leukemogenic role of ionizing radiations

## **Demonstrated for:**

- Nuclear explosions of 1945 :increased risk persisting after > 50 years Iwanaga,JCO, 2011)
- breast cancer(RR = 2)
- carcinoma of the cervix (Broice, 1987)
- prostate cancer(0,1% AML in some series)

## **Now anecdotal**

- Spine irradiation for ankylosing spondylarthritis

## Mouse models of MDS

- Xeno transplantation in immunodeficient mice
- Genetically engineered models (transgenic mice)

# Modèles murins de MDS

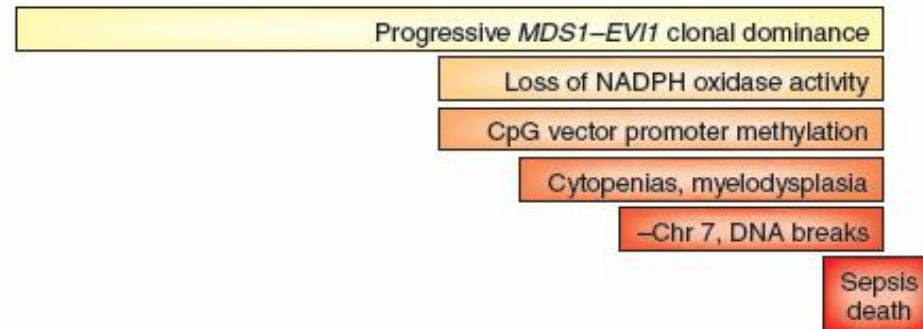
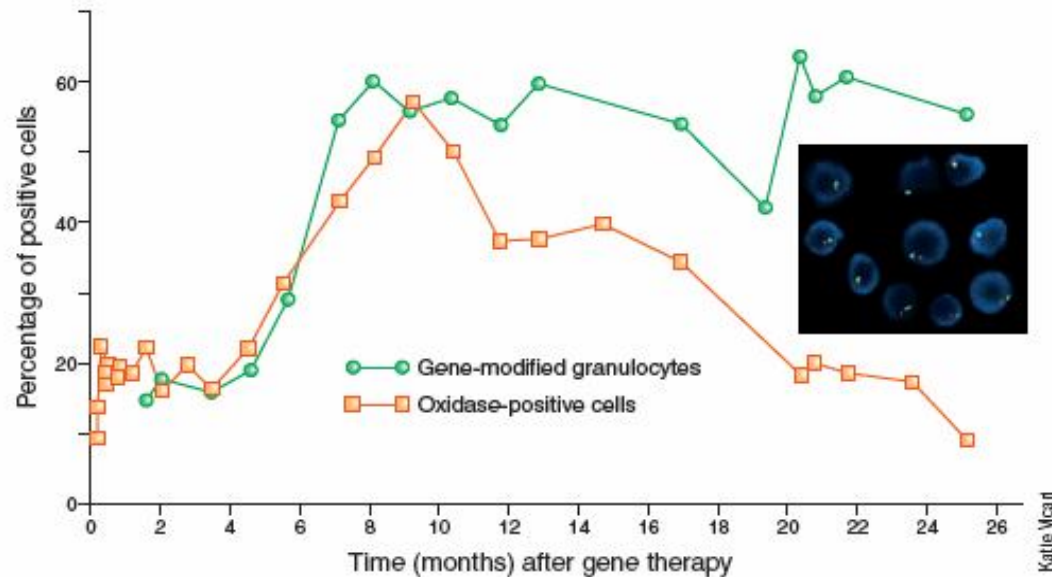
## EVI1 induces myelodysplastic syndrome in mice

Silvia Buonamici, Donglan Li, Yiqing Chi, Rui Zhao, Xuerong Wang, Larry Brace, Hongyu Ni,  
Yogen Sauntharajah, and Giuseppina Nucifora

Department of Pathology and Cancer Center, University of Illinois at Chicago, Chicago, Illinois, USA.

# Genomic instability and myelodysplasia with monosomy 7 consequent to *EV11* activation after gene therapy for chronic granulomatous disease

Stefan Stein<sup>1,15</sup>, Marion G Ott<sup>2,15</sup>, Stephan Schultze-Strasser<sup>1</sup>, Anna Jauch<sup>3</sup>, Barbara Burwinkel<sup>4,5</sup>, Andrea Kinner<sup>1</sup>, Manfred Schmidt<sup>6</sup>, Alwin Krämer<sup>7</sup>, Joachim Schwäble<sup>2</sup>, Hanno Glimm<sup>6</sup>, Ulrike Koehl<sup>8</sup>, Carolin Preiss<sup>1</sup>, Claudia Ball<sup>6</sup>, Hans Martin<sup>2</sup>, Gudrun Göhring<sup>9</sup>, Kerstin Schwarzwaelder<sup>6</sup>, Wolf-Karsten Hofmann<sup>10</sup>, Kadin Karakaya<sup>7</sup>, Sandrine Tchatchou<sup>4,5</sup>, Rongxi Yang<sup>4,5</sup>, Petra Reinecke<sup>11</sup>, Klaus Köhlcke<sup>12</sup>, Brigitte Schlegelberger<sup>9</sup>, Adrian J Thrasher<sup>13</sup>, Dieter Hoelzer<sup>2,15</sup>, Reinhard Seger<sup>14,15</sup>, Christof von Kalle<sup>6,15</sup> & Manuel Grez<sup>1,15</sup>



# Groupe Francophone des Myélodysplasies

- Activates clinical trials in MDS (> 40 centers in France , Belgium , Switzerland, Tunisia))
- Website: [www.gfmgroup.org](http://www.gfmgroup.org)
- Online registry of French MDS cases
- Cooperation for translational research projects ( M Fontenay)
- Close cooperation with a patient support group: CONNAÎTRE ET COMBATTRE LES MYÉLODYSPLASIES (CCM)

