# Implication de la mutation *V617F* de la protéine Jak2 dans la physiopathologie des Syndromes Myéloprolifératifs

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Juin 2006

# Syndromes myéloprolifératifs

- 1950s Dameshek:

1. Dameshek W. Some speculations on the myeloproliferative syndromes. *Blood*. 1951;6:372-375.

Maladie de Vaquez, thrombocytémie essentielle, myélofibrose avec métaplasie myéloïde, érythroleucémie et LMC

- Caractéristiques phénotypiques communes:
  - Maladie HSC multipotente,
  - Hyperproduction cell. myéloïdes matures,
  - Splénomégalie, érythropoïèse extra médullaire
  - ↑ risque thrombo-hémorragique, fibrose médullaire

# Classification OMS des SMPs

- Chronic myelogenous leukemia [Ph chromosome, t(9;22)(q34;q11), *BCR/ABL* positive]
- Polycythemia vera
- Chronic idiopathic myelofibrosis (with extramedullary hematopoiesis)
- Essential thrombocythemia
- Chronic neutrophilic leukemia
- Chronic eosinophilic leukemia (and the hypereosinophilic syndrome)
- Chronic myeloproliferative disease, unclassifiable

James W. Vardiman, Nancy Lee Harris, and Richard D. Brunning
BLOOD, 2002, VOLUME 100, NUMBER 7

# Syndromes myéloprolifératifs

- Maladies hématopoïétiques CLONALES
- Mutations acquises
- Transformation de cellules souches progénitrices PLURIPOTENTES

# Tests de clonalité

- Profil d'inactivation gènes liés à l'X (XCIPDS G6PD–HUMARA assays)
  - Hématopoïèse clonale / certains patients
  - → seules XX analysables

- Étude translocations chromosomiques balancées acquises entreprenant des gènes encodants des Tk (BCR-ABL; c-KIT, FIP1L1-PDGFRA)
  - → démonstration présence aN clonale ds HSC

# *Anomalies cytogénétiques conduisant à une activation constitutive de tyrosines kinases*

Table 1. Partial list of constitutively active tyrosine kinases in *bcr/abl*-negative chronic myeloid disorders that are predicted or documented to be imatinib sensitive

| Fusion | Translocation | Deletion | Mutation | Disease association | Imatinib response* | Study |
|---|---|---|---|---|---|---|
| *PDGFRB* | | | | | | |
| ETV6/PDGFRB | t(5;12)(q33;p13) | — | — | CMML | Yes | Golub et al[10] |
| CEV14/PDGFRB | t(5;14)(q33;q32) | — | — | AML | — | Abe et al[36] |
| HIP1/PDGFRB | t(5;7)(q33;q11) | — | — | CMML | — | Ross et al[23] |
| H4 (D10S170)/PDGFRB | t(5;10)(q33;q21) | — | — | uCMPD | Yes | Kulkarni et al[34], Schwaller et al[35] |
| RAB5/PDGFRB | t(5;17)(q33;p13) | — | — | CMML | — | Magnusson et al[33] |
| PDE4DIP/PDGFRB | t(1;5)(q23;q33) | — | — | uCMPD | Yes | Wilkinson et al[18] |
| *PDGFRA* | | | | | | |
| BCR/PDGFRA | t(4;22)(q12;q11) | — | — | uCMPD | Yes | Trempat et al [37], Baxter et al[38] |
| F1P1L1/PDGFRA | — | 4q12‡ | — | SM-eos/CEL | Yes | Cools et al[11], Pardanani et al[14] |
| c-*kit* | | | | | | |
| — | — | — | D816V/F/Y§ | MCD | No | Ma et al[87] |
| — | — | — | V560G | — | — | Furitsu et al[51] |
| — | — | — | E839K | — | — | Longley et al[28] |
| — | — | — | D820G | — | — | Pignon et al[29] |
| *Abl* | | | | | | |
| ETV6/ABL | Complex† | — | — | uCMPD | Yes | Van Limbergen et al[30], Andreasson et al[31] |
| ET6/ARG | t(1;12)(q25;p13) | — | — | AML | Yes | Nishimura et al[32] |

aCML indicates atypical chronic myeloid leukemia; uCMPD, unclassified chronic myeloproliferative disorder (some of these patients are described as having atypical CML); SM-eos, eosinophilia-associated systemic mastocytosis; MCD, mast cell disease; ETV6, ets variant gene 6 (TEL oncogene); CEV14, clonal evolution-related gene on chromosome 14; HIP1, Huntington interacting protein 1; RAB5, rabaptin 5; BCR, breakpoint cluster region; D10S170, DNA segment on chromosome 10 (unique) 170; PDE4DIP, phosphodiesterase 4D interacting protein (myomegalin); FIP1L1, FIP1-like 1; and —, not applicable.

*Clinical response to imatinib therapy documented (where tested).

†All patients have complex chromosomal rearrangements that require at least 3 chromosomal breaks.

‡Deletion is submicroscopic.

§Imatinib resistant.

# De nouvelles cibles thérapeutiques

→ SMP « classiques » ?

# Polycytémie vraie (maladie de Vaquez)

- Seuls 13 à 29% des PV anomalies caryotypiques
- 8 à 15% des cas: délétion du bras long du chr 20 (del 20q).
- Délétion non spécifique et observée classiquement pendant le décours de la maladie → probablement événement secondaire.
- Rarement des trisomies 1, 8 et 9 et des del 13q et 5q (0,5 à 3% des cas)

# Hétérogénéités des SMPs

- Tests de clonalité → hétérogénéïté SMPs !

  cell. progénitrices hématopoiétiques circulantes démontrées polyclonales pour certains patients avec PV et TE

- ⇨ limitations tests préalablement disponibles

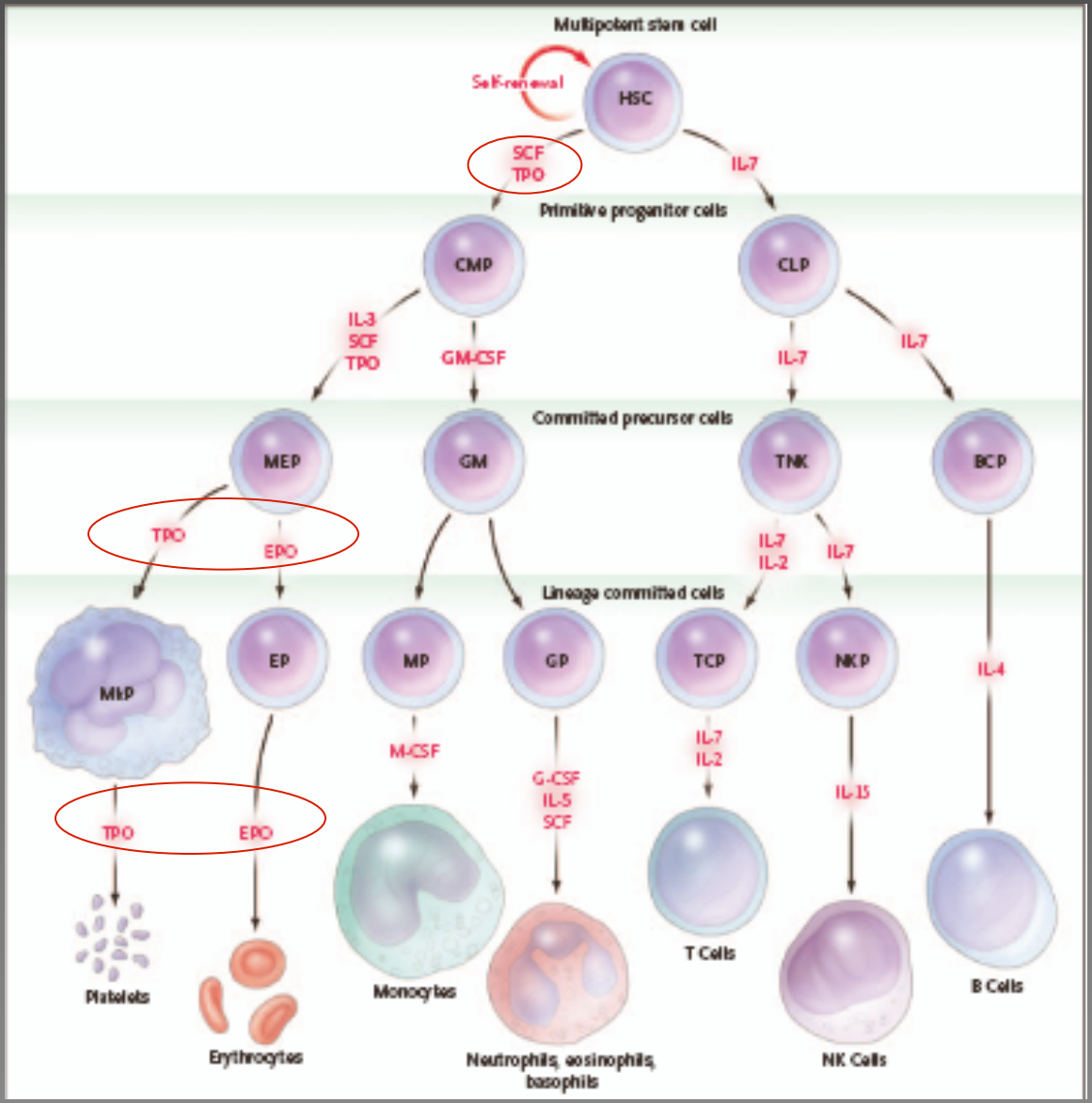
# Mécanismes moléculaires responsables PV – TE – MMM ?

- PV: fraction des progéniteurs EPO indépendant ou hypersensibles IL-3, IGF-1, GM-CSF et EPO

- ET et IMF, progéniteurs mégacaryocytic hypersensibles thrombopoïetine.

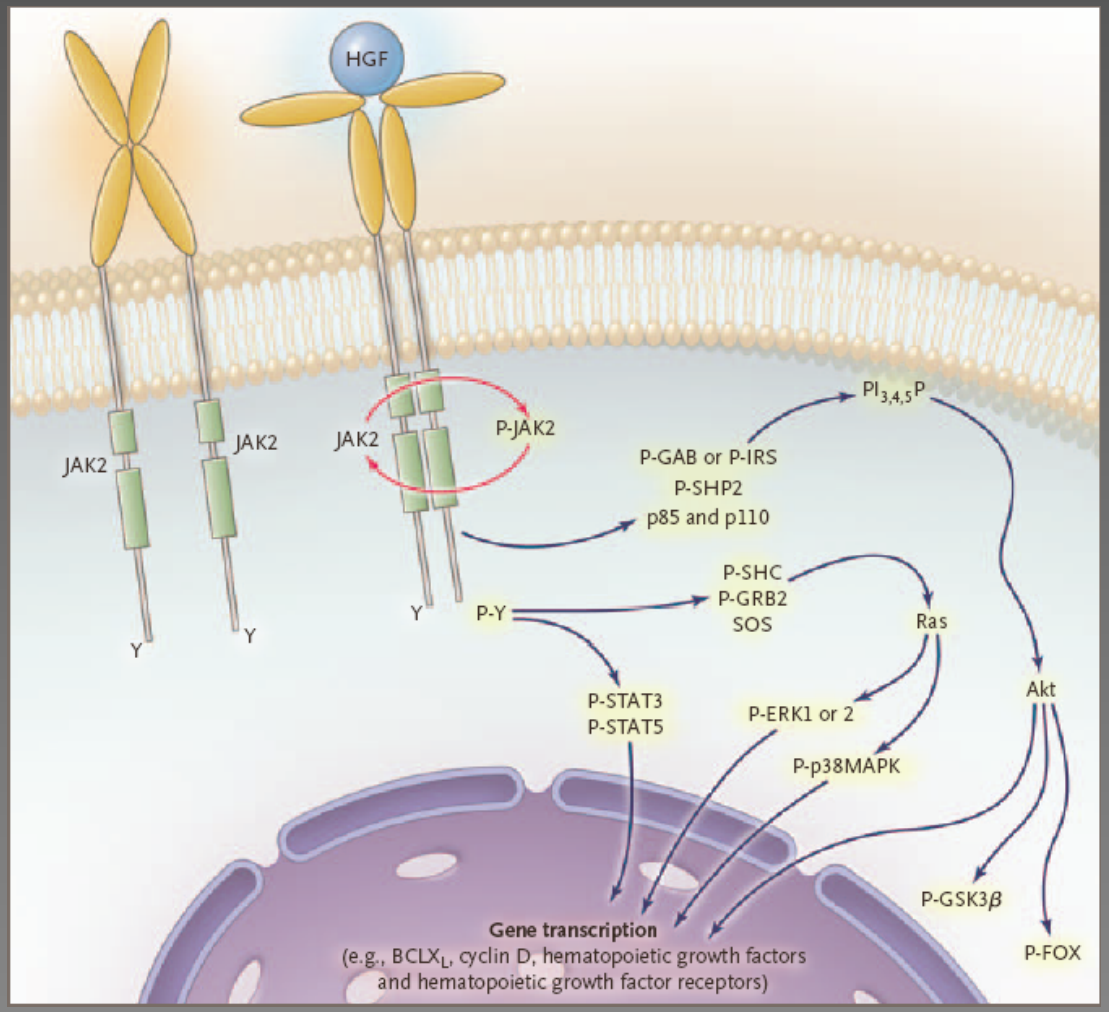
HYPOTHESES

# Sécrétion paracrine ou autocrine ?




Kaushansky, N engl j med 354;19 may 11, 2006

# Mutation(s) Epo/Epo-R/Tpo/TpoR ?




Kaushansky, N engl j med 354;19 may 11, 2006

Formes acquises polycythémies et thrombocytoses

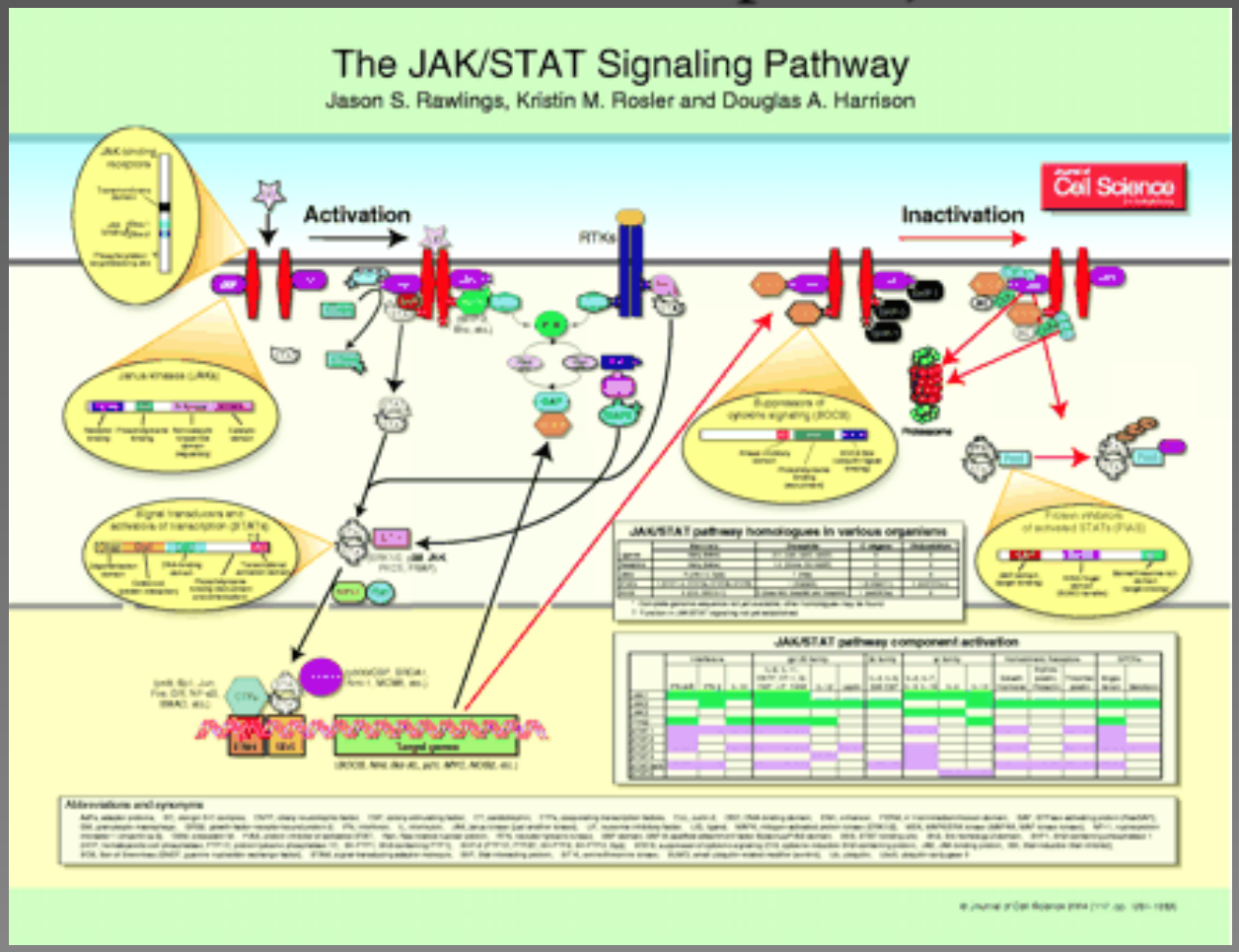
Pas de mutations Epo-R, TPO-R, ou cytokines

↓

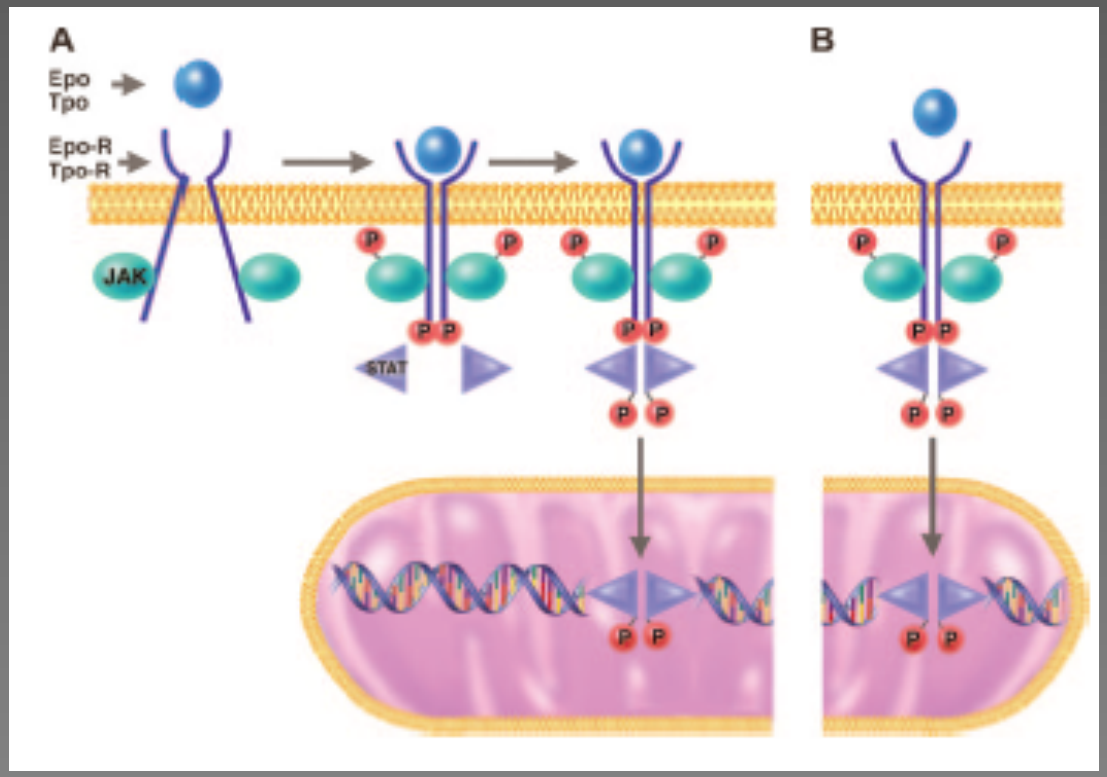
Hypothèse

aN moléculaire(s) «en aval du récepteur» dans voies de transmission du signal ?

# Signalisation en aval des récepteurs: voie JAK/STAT(Signal Transducers and Activator of Transcription)



# Voies de signalisation des facteurs de croissance hématopoïétiques : JAK/STAT(Signal Transducers and Activator of Transcription)




Schafer, BLOOD, 1 JUNE 2006, 107, 11

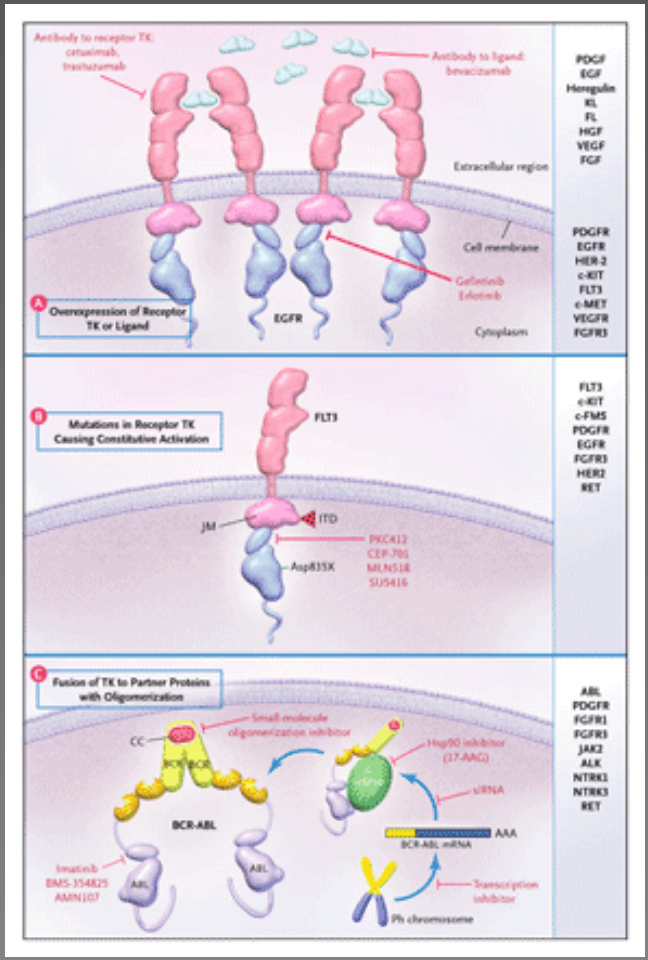
# Nouvelles hypothèses

- Gain de fonction d'une kinase ?
- Perte de fonction d'un régulateur négatif (PPtase) ?

→ Enzyme commune à toutes ces voies de transduction ?

Arguments en faveur d'une kinase:

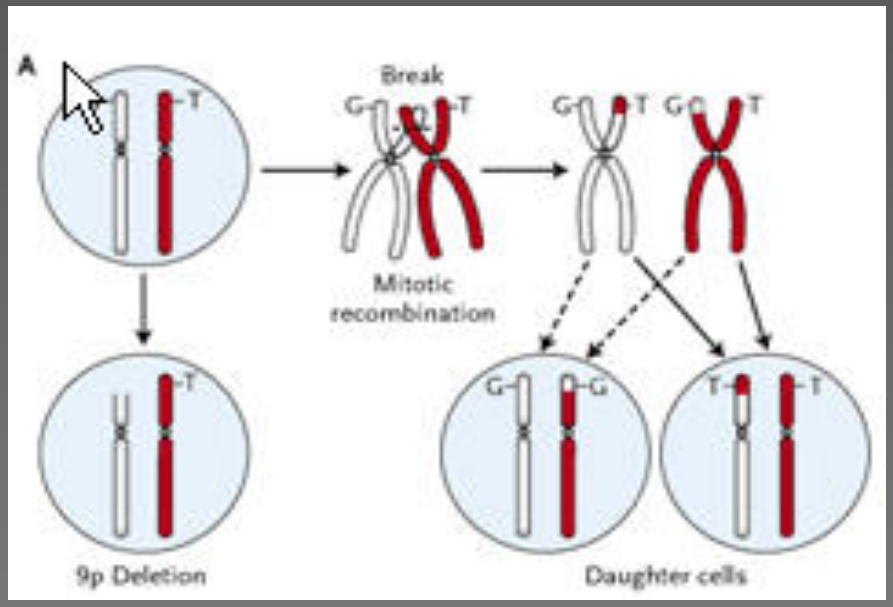
- Bcr-**abl** /LMC
- FIP1L1-**PDGRFα** /HES/CEL.
- c-Kit Asp816Val/SMCDs…

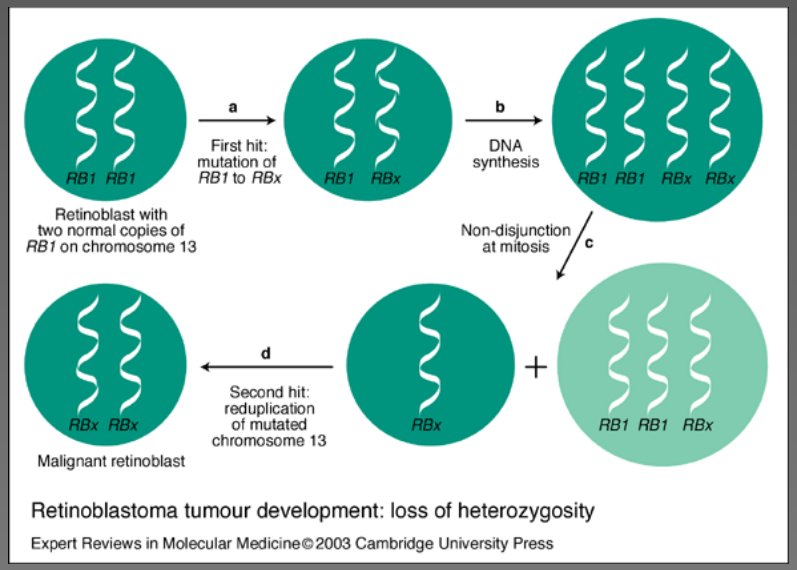


# Apports des études familiales

- 1999 Etude génétique Kralovics *et al* : possibilité de LOH.
- 20 patients (non familiaux): 30% des cas, LOH au niveau du chromosome 9p
- Une autre équipe montre alors par FISH l'existence de 21% de cas supplémentaires de 9p cryptiques

# La perte d'hétérozygosité (LOH)

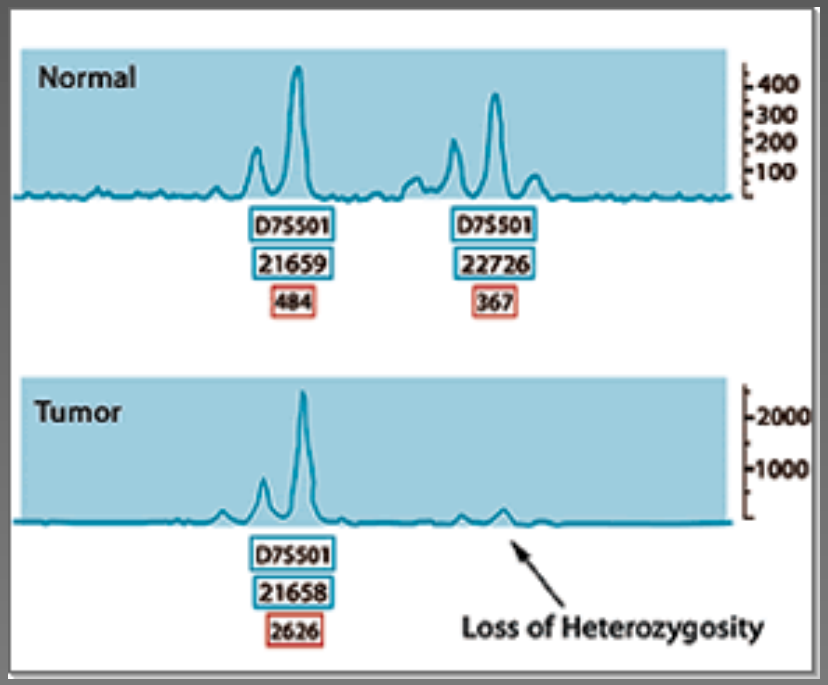


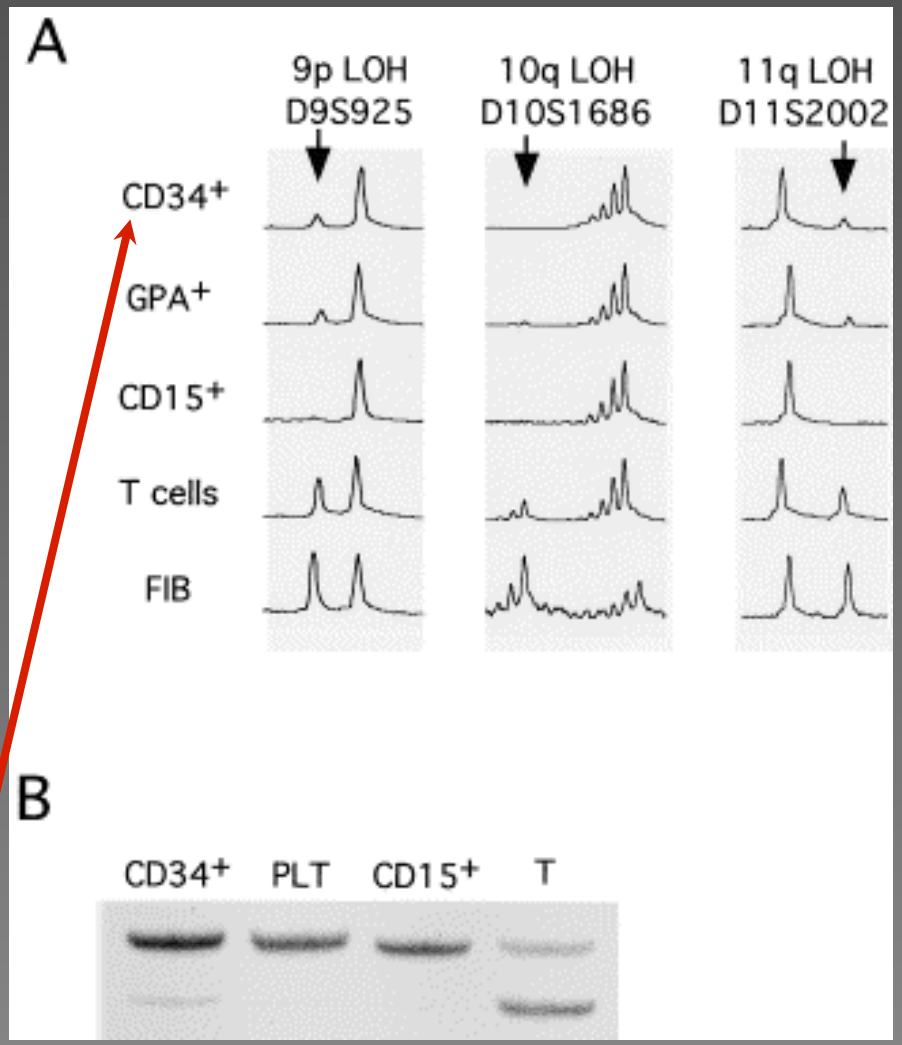




Perte d' hétérozygotie ⇨ disomie uniparentale

Kralovics et al NEJM 2005

# La perte d'hétérozygosité (LOH)




**Démontre l'origine de l'anomalie dans les cellules-souches**

Kralovics et al. Exp. Hematology 1999

# Hypothèses concernant le LOH

- Inactivation d'un suppresseur de tumeur par perte physique d'un allèle (délétion) ⇨ événement supplémentaire (mutation inactivatrice) sur la copie restante ⇨ inactivation d'un suppresseur de tumeur

- Inactivation d'un suppresseur de tumeur / mutation inactivatrice suivie d'une recombinaison mitotique.

# 2005

**A Unifying Mutation in Chronic Myeloproliferative Disorders**

John M. Goldman, D.M.

Kralovivs et al, NEJM
James et al, Nature
Levine et Al, Cancer Cell
Baxter et al, The Lancet
Zhao et al, JBC

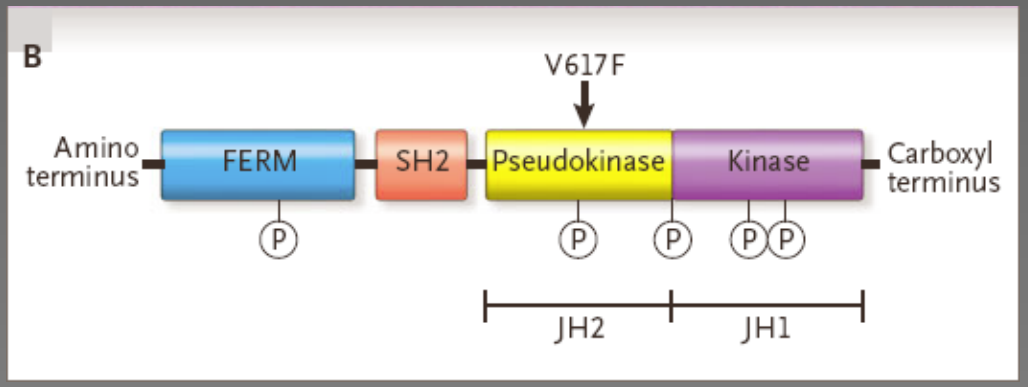
Mutation acquise exon 12 gène JAK2

5 équipes avec approches méthodologiques différentes

# JAK2 (« Janus kinase » ou « Just another kinase » !)

- Famille des protéines « Janus Kinase »
- JAK1, 2, 3 et tyrosine kinase 2 « TYK2 »

- Un domaine kinase, JAK homology 1 « **JH1** »
- Un domaine « pseudokinase », JAK homology 2 « **JH2** »

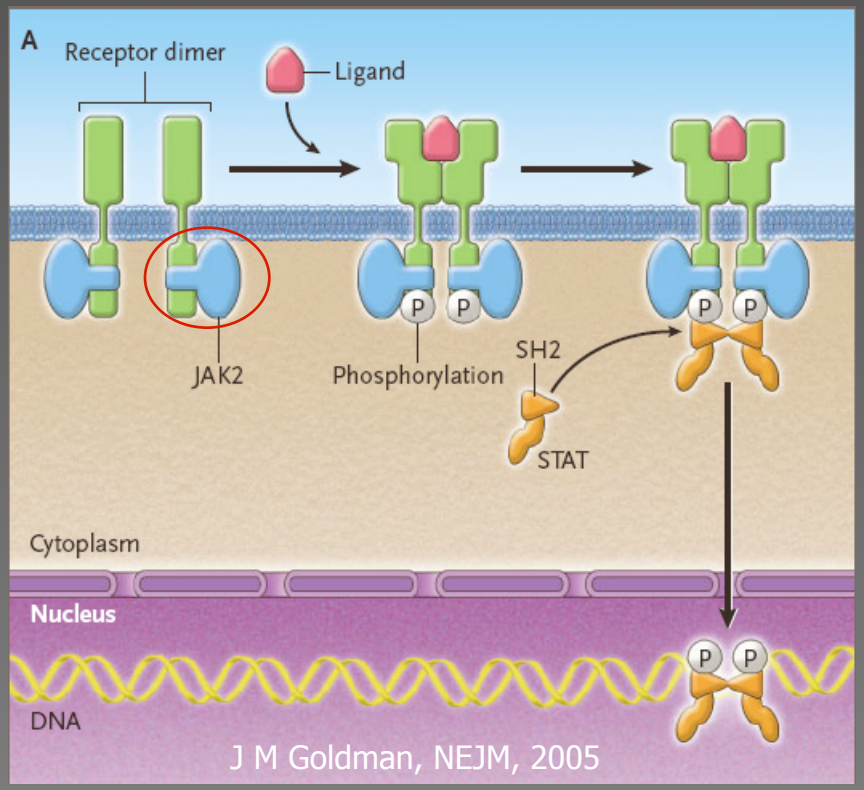


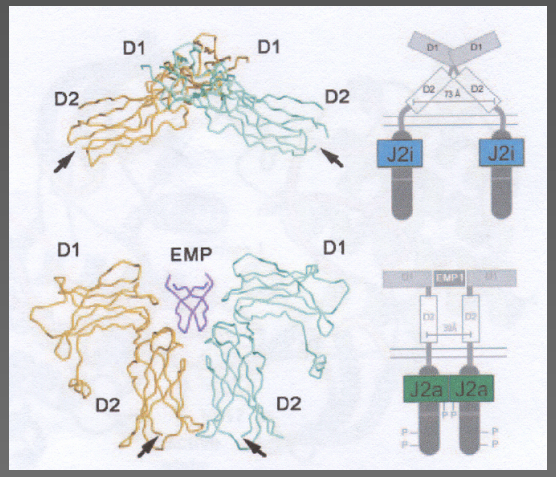

JH2 : similaire à JH1,mais domaine kinase non actif: fonction autorégulatrice de JH1

J M Goldman, NEJM, 2005

# JAK2 : Tyrosine Kinase JANUS KINASE 2
## JAK/STAT (Signal Transducers and Activator of Transcription)

- transduction des signaux médiés par les récepteurs de facteurs de croissance hématopoïétiques (Epo, Tpo).




## Mécanisme :

a. Etat sans ligand : Dimère, domaines transmembranaires éloignés (73Å)

b. Avec ligand : Dimère, domaines transmembranaires rapprochés (39Å), Cross phosphorylation.

# Approches méthodologiques (I)

- *Approche de type « carpet bombing »!*

  - Gilliland (Cancer Cell 2005): 345 patients – séquençage boucle d'activation et domaines autoinhibiteurs de 85 kinases connues !

  - Zhao (JBC 2005): 8 PPtases et 4 kinases testées (connues pour jouer un rôle dans l'erythropoïèse)

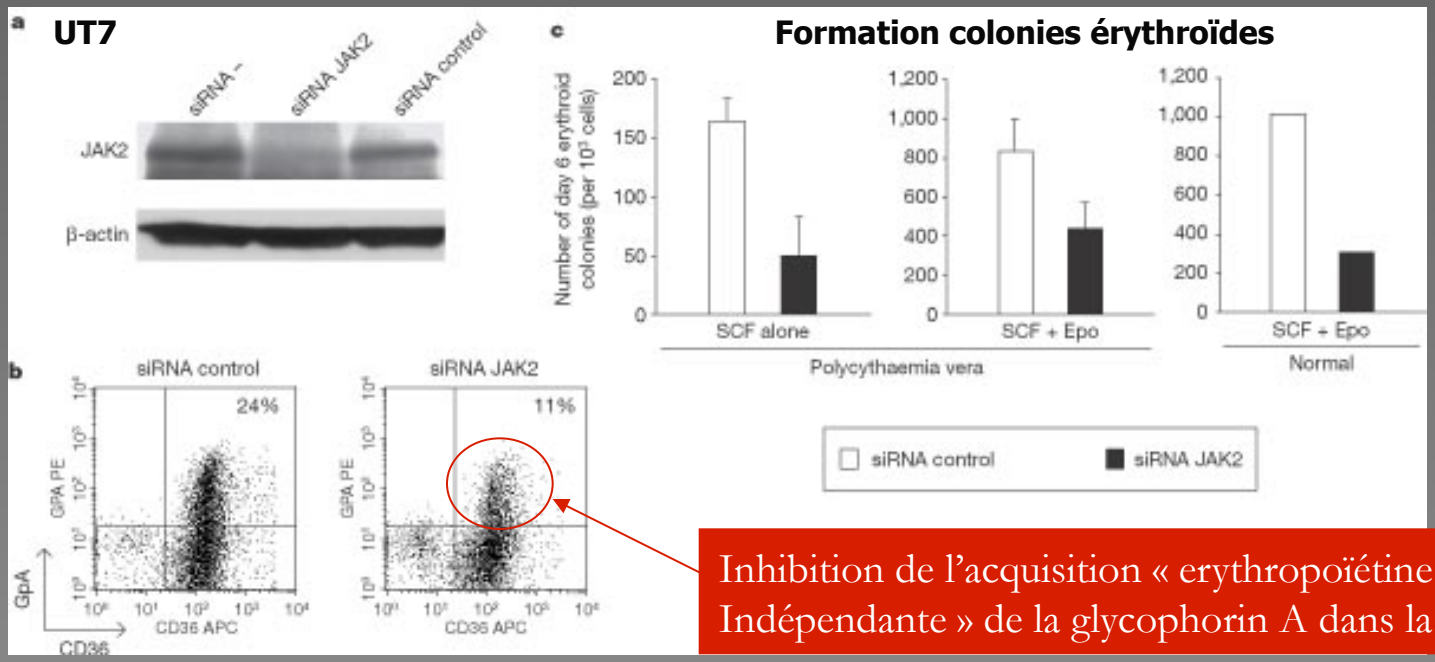
  - Equipe de Green (The Lancet 2005)

# Approches méthodologiques (II)

- *Approche française (James et al Nature 2005)*

Rôle clé de la protéine JAK2 dans la transformation EPO indépendante des progéniteurs érythroïdes dans la PV

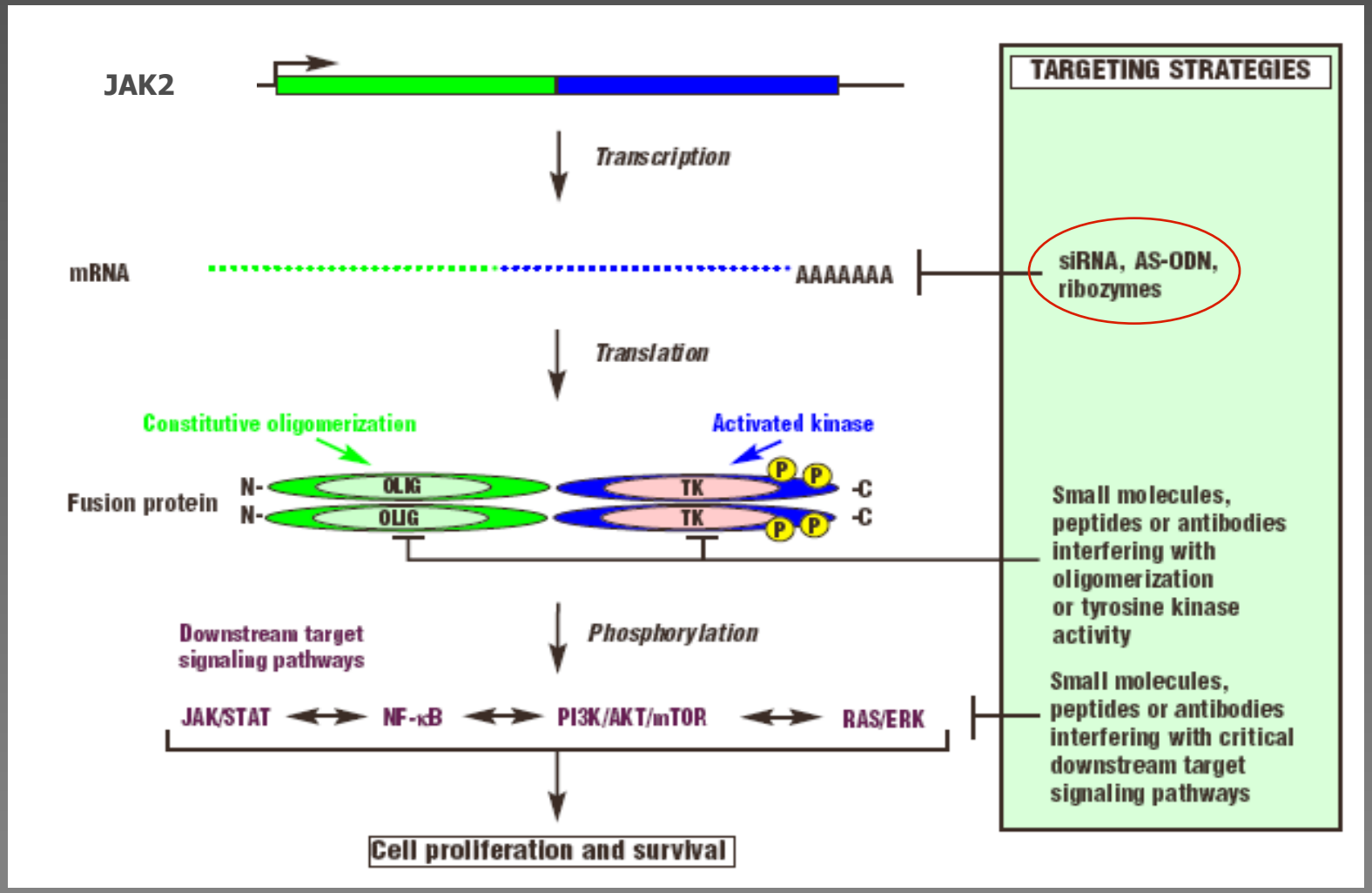
→ un inhibiteur de Jak2 (AG490), PI3K et SRC et un siRNA
→ empêche la différenciation terminale érythroïde dans la PV
→ confirmation spécificité JAK2 par approche siRNA
→ séquençage le gène JAK2 patients PV




Inhibition de l'acquisition « erythropoïétine Indépendante » de la glycophorin A dans la PV

James et al Nature 2005

# RNA interférants, siRNA JAK2

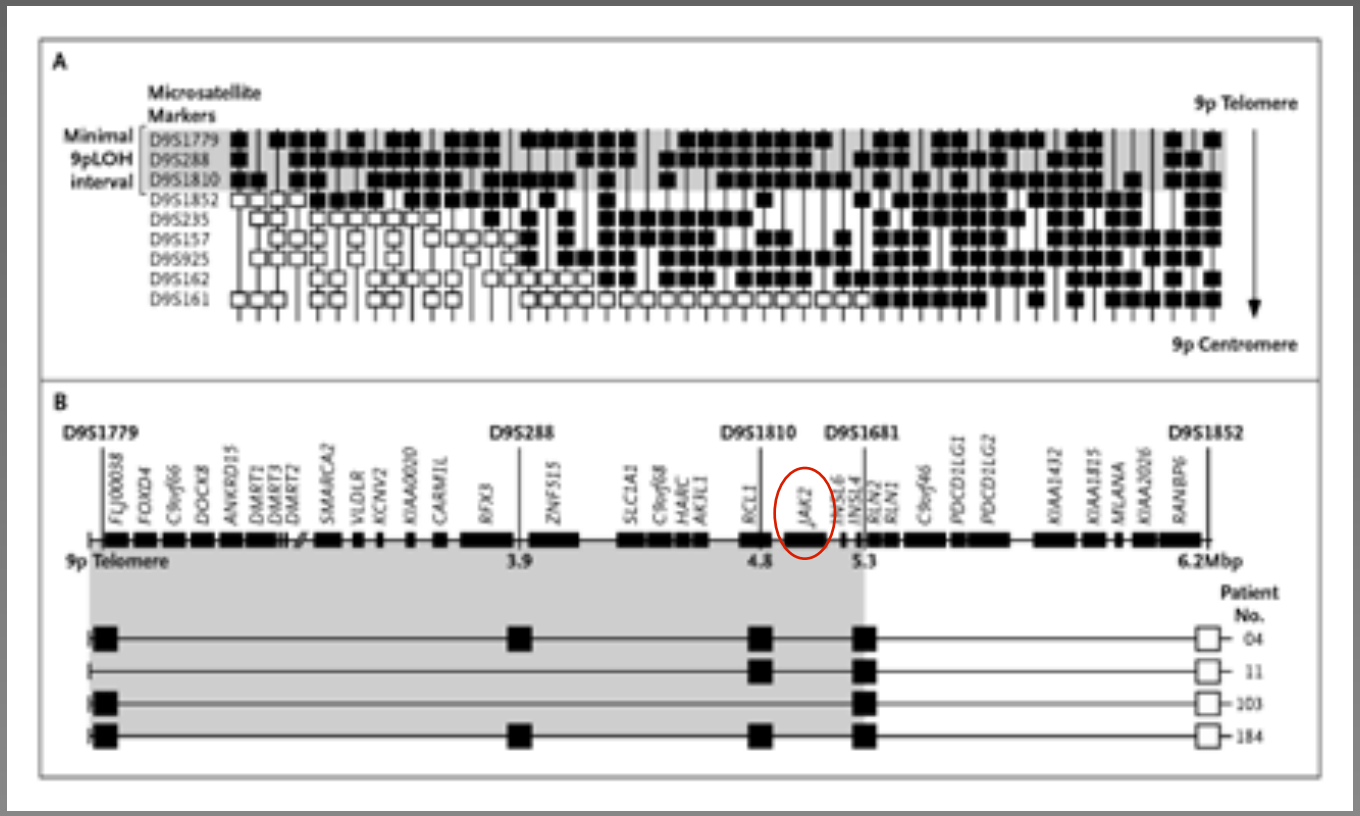



Y. Chalandon *et al*, Haematologica, 2005

# Approches méthodologiques(III)

Les mutations dans le domaine pseudo-kinase sont associées avec la transformation maligne des cellules hématopoïétiques dans la thrombocythémie

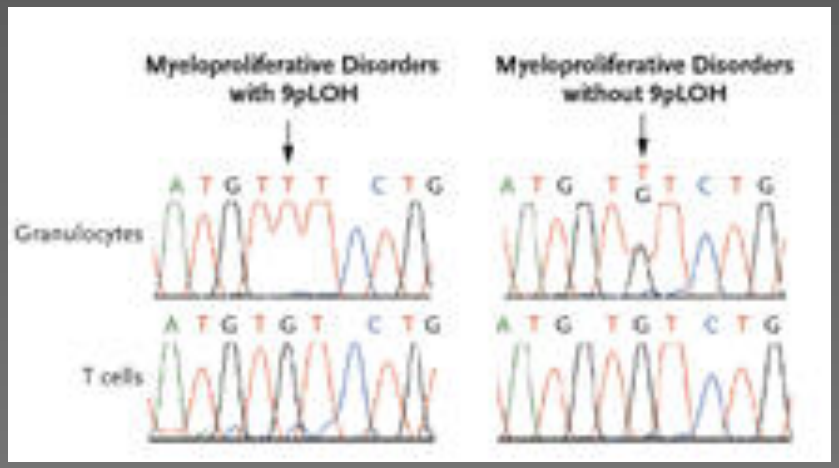
- *Approche Italo-Suisse (Kralovics et al NEJM 2005)*
  - Recherche de gène candidat dans la région minimale entreprise dans la 9p LOH.

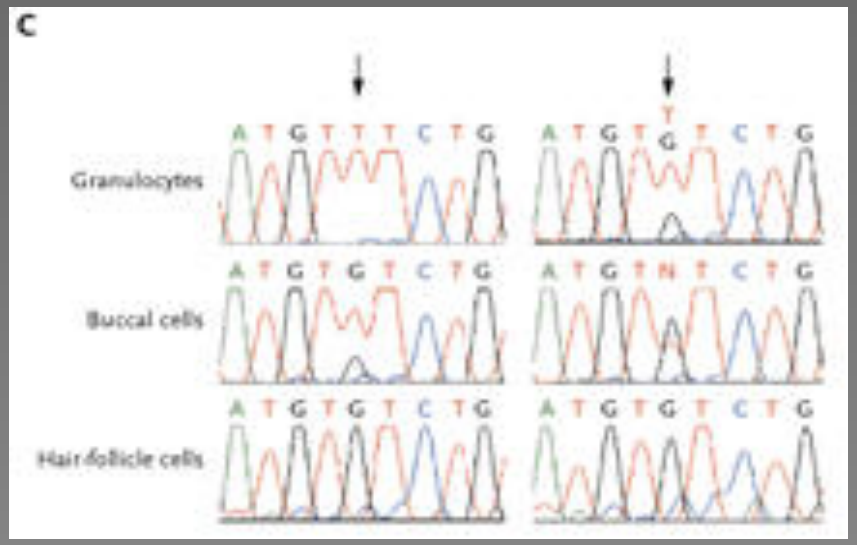



Kralovics et al NEJM 2005

# Mutation somatique

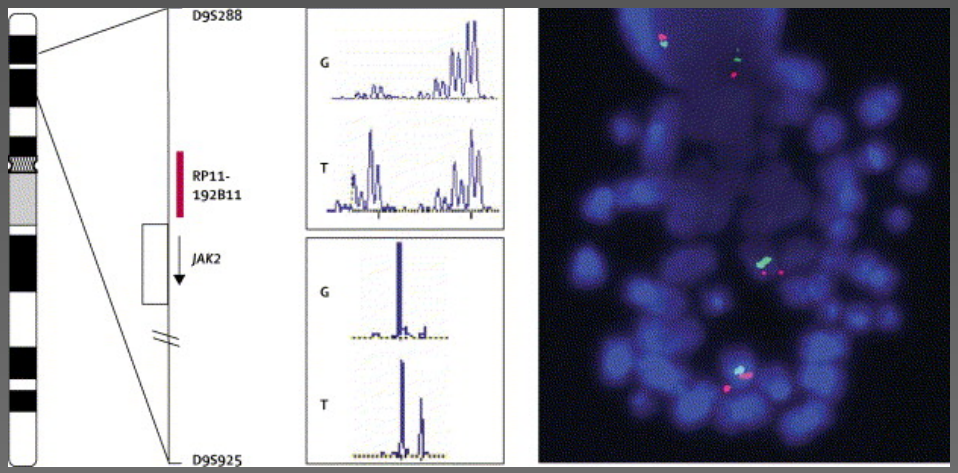
Mutations domaine pseudo-kinase « JH2 » associées transformation maligne des cellules hématopoïétiques dans la drosophile



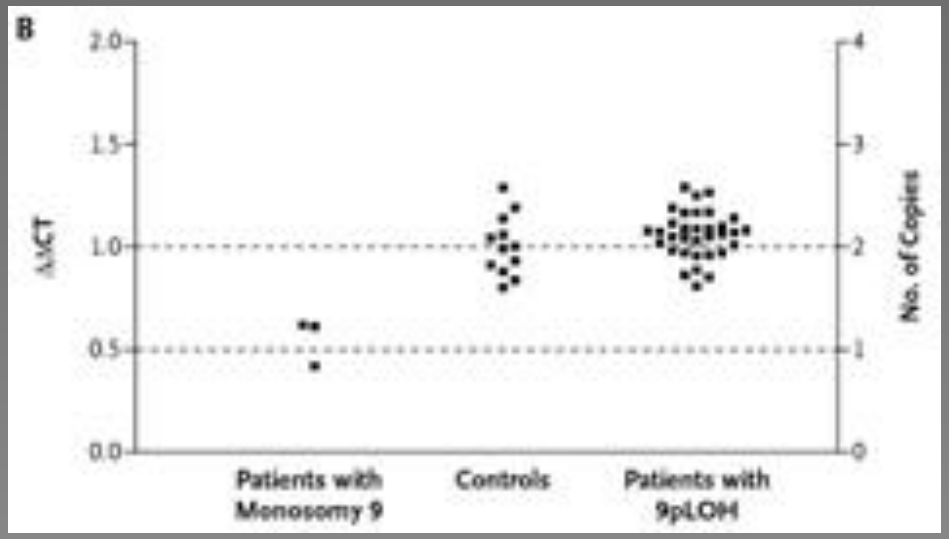




Kralovics et al NEJM 2005

# LOH par recombinaison mitotique!



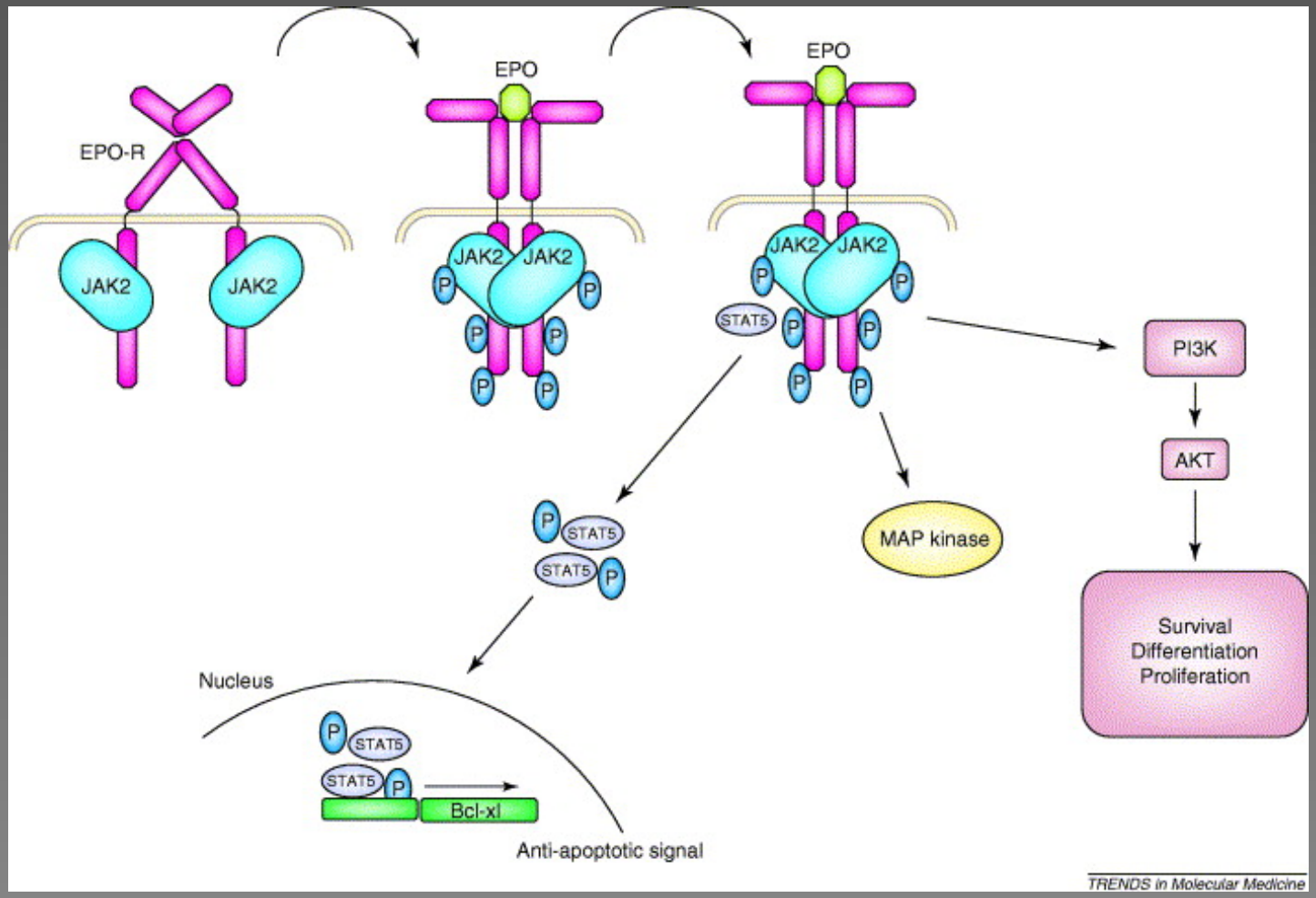

Baxter et al The Lancet 2005




Kralovics et al NEJM 2005

Environ ¼ des PV sont homozygote V617F
Durée de la maladie augmentée chez ces patients

# Voies de transduction du signal



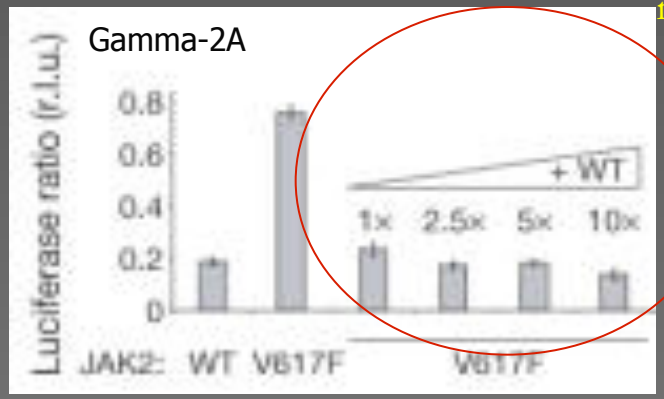

Jak2 et EPOR interagissent déjà au niveau du Golgi.
Jak2 joue rôle dans le « trafficking » de EPOR

James et al TIMM 2005

# Physiopathologie moléculaire de la mutation

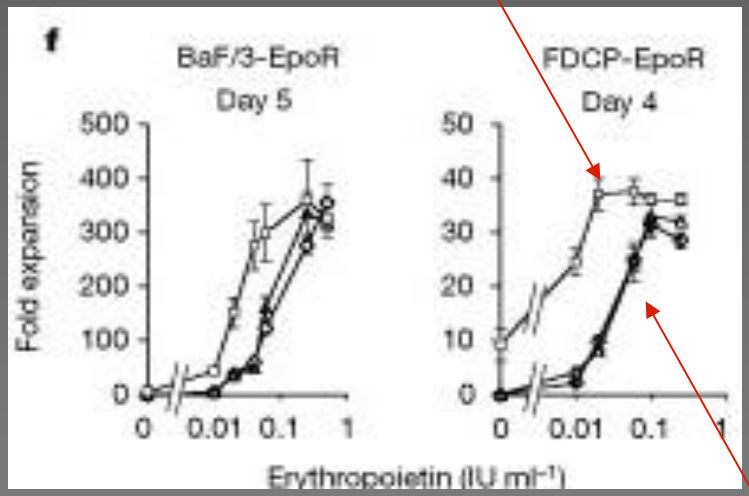
Activité transcriptionnelle de STAT-5

Effet dominant négatif du WT

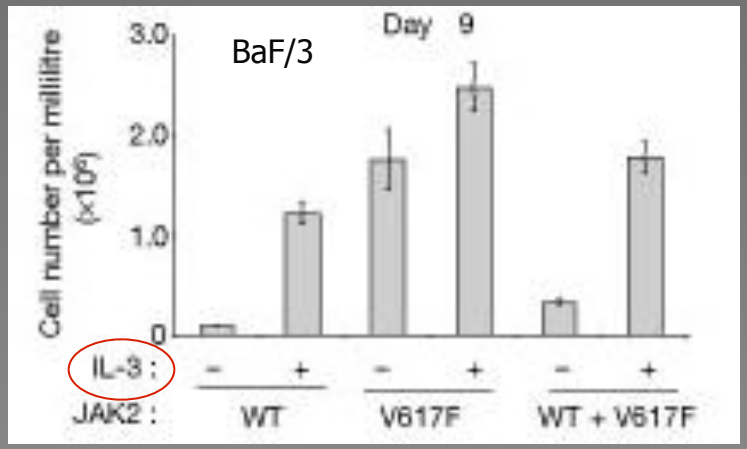



V617F

Hypersensibilité à l'érythropoïétine



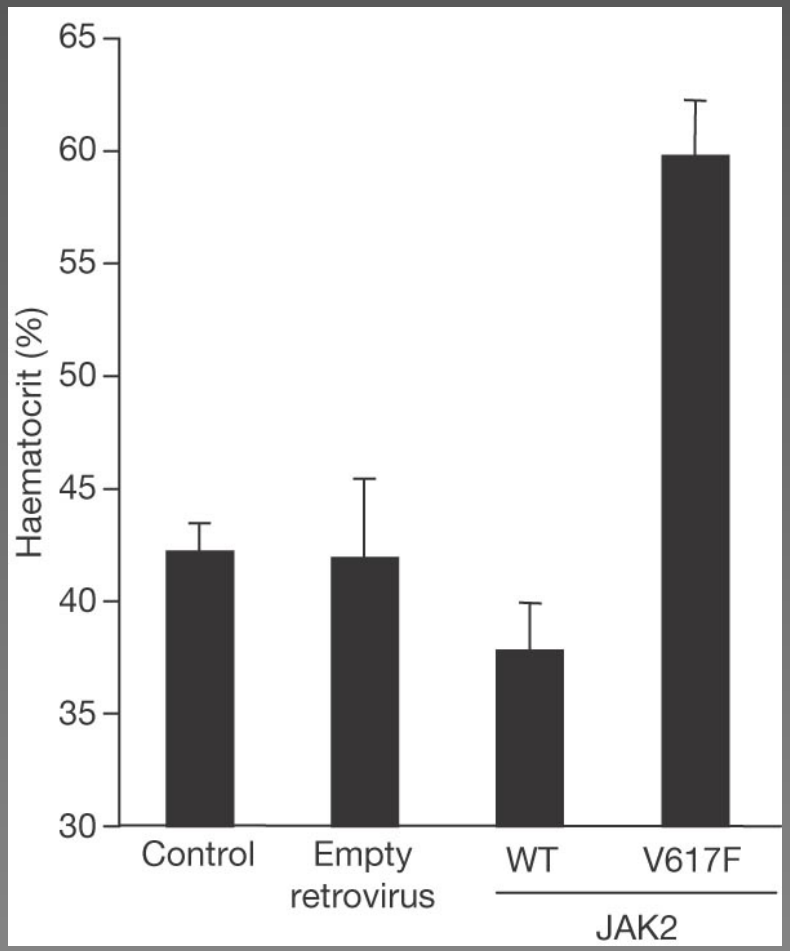

WT et Vecteur vide




Hypersensibilité à certaines cytokines et effet dominant négatif du WT

James et al. Nature 2005

# Physiopathologie moléculaire de la mutation




Modèle murin: souris
greffés avec cellules de moelle osseuse
transfectées par Jak2 V617F

Détermination de l'hématocrite après
4 semaines

James et al. Nature 2005

# Modèle murin

Blood, 1 June 2006, Vol. 107, No. 11, pp. 4274-4281.
Prepublished online as a Blood First Edition Paper on February 14, 2006; DOI 10.1182/blood-2005-12-4824.

HEMATOPOIESIS

**Expression of Jak2V617F causes a polycythemia vera–like disease with associated myelofibrosis in a murine bone marrow transplant model**

**Gerlinde Wernig, Thomas Mercher, Rachel Okabe, Ross L. Levine, Benjamin H. Lee, and D. Gary Gilliland**

From the Division of Hematology, Department of Medicine, the Howard Hughes Medical Institute, and the Department of Pathology, Brigham and Women's Hospital, Boston; and the Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA.

Différences observées entre différentes lignées de souris

Pourrait expliquer chez l'humain la diversité des phénotypes associés à la mutation V617F

Mutation acquise exon 12 gène JAK2

Transversion Guanine → Thymine

Substitution Valine → Phénylalanine en position 617 protéine JAK2

Domaine auto-régulateur JH2

Activation constitutive de la protéine

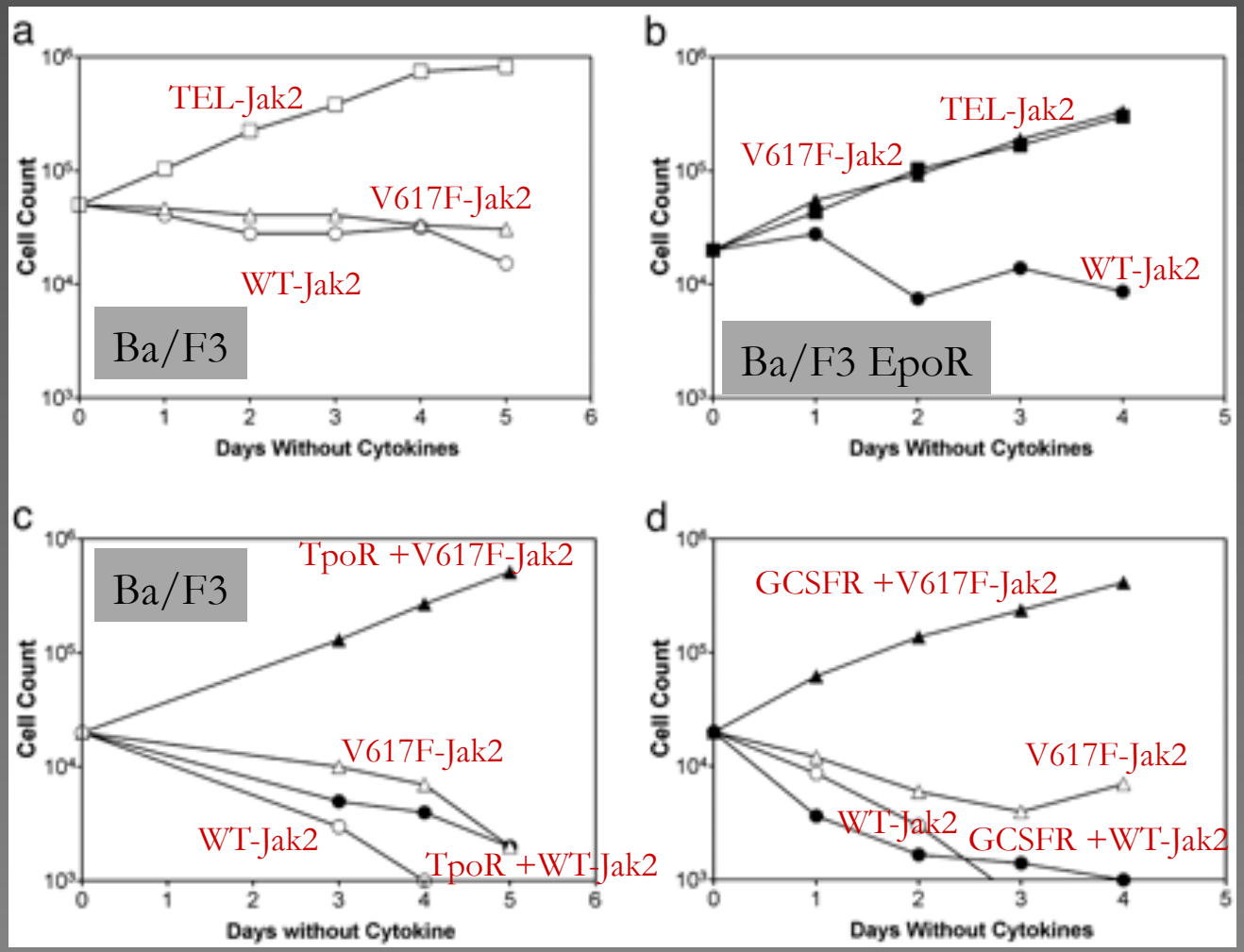
Croissance autonome des progéniteurs hématopoïétiques

# Questions

# Pourquoi la lignée myéloïde ?

Rôle joué par l'interaction entre les récepteurs cytokine type I homodimérique et Jak2 (Liu et al. PNAS 2005)

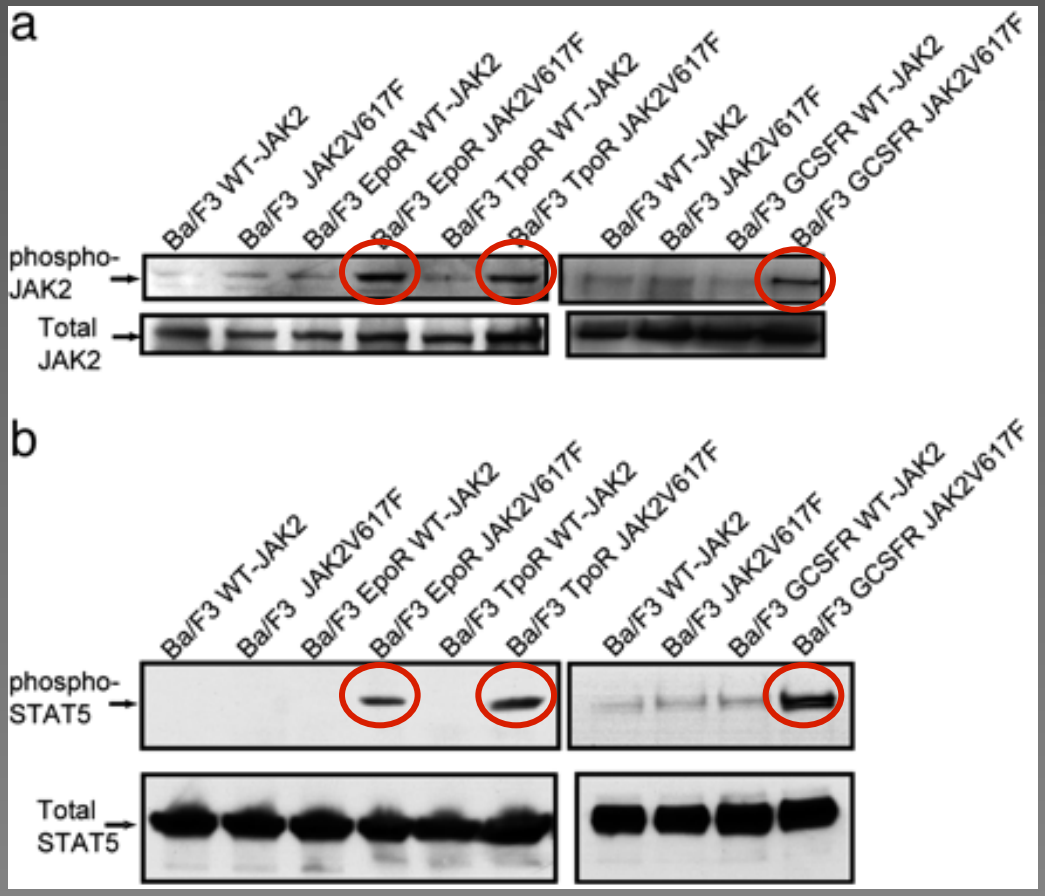
# Transformation nécessite interaction (I)




Cellules Ba/F3 cultivées en l'**ABSENCE** d'IL-3

Liu et al PNAS 2005

# Transformation nécessite interaction (II)




Liu et al PNAS 2005

# Fréquences rapportées de la mutation V617F SMPs

**Table 1.** Frequency of the *JAK2* V617F mutation in patients with chronic myeloproliferative disorders.

| *Authors* | *Polycythemia vera* | *Essential thrombocythemia* | *Idiopathic myelofibrosis* |
|---|---|---|---|
| **DNA sequencing** | | | |
| James *et al.*[4] | 40/45 (89%) | 9/21 (43%) | 3/7 (43%) |
| Levine *et al.*[6] | 121/164 (74%) | 37/115 (32%) | 16/46 (35%) |
| Kralovics *et al.*[7] | 83/128 (65%) | 21/93 (23%) | 13/23 (57%) |
| Baxter *et al.*[5] | *53/73 (73%) | 6/51 (12%) | 7/16 (44%) |
| Zhao *et al.*[9] | 20/24 (83%) | n.d. | n.d. |
| Jones *et al.*[10] | 58/81 (81%) | 24/59 (41%) | 15/35 (43%) |
| Total | 375/506 (74%) | 97/339 (29%) | 55/127 (43%) |
| **Allele-specific PCR** | | | |
| Baxter *et al.*[5] | 71/73 (97%) | 29/51 (57%) | 8/16 (50%) |

Cozzala M, Haematologica 2006

# Fréquences rapportées de la mutation V617F SMPs

TABLE 1. **Summary of Published Literature on JAK2$^{V617F}$ Mutational Frequencies in Myeloproliferative Disorders***

| Reference | Overall (homozygous) JAK2$^{V617F}$ mutational frequencies in myeloproliferative disorders | | | |
|---|---|---|---|---|
| | Polycythemia vera | Essential thrombocythemia | Myelofibrosis with myeloid metaplasia | Other myeloid disorders |
| Baxter et al[72] | 97% (26%)<br>N=73 | 57% (0%)<br>N=51 | 50% (19%)<br>N=16 | NA |
| James et al[73] | 89% (30%)<br>N=45 | 43% (NA)<br>N=21 | 43% (NA)<br>N=7 | NA |
| Kralovics et al[74] | 65% (27%)<br>N=128 | 23% (3%)<br>N= 93 | 57% (22%)<br>N=23 | CML 0% (n=9) |
| Levine et al[75] | 74% (25%)<br>N=164 | 32% (3%)<br>N=115 | 35% (9%)<br>N=46 | NA |
| Zhao et al[76] | 83% (NA)<br>N=24 | NA<br>NA | NA<br>NA | NA |
| Steensma et al[77] | NA | NA | NA | MDS 5% (n=101)<br>CMML 3% (n=119)<br>HES 0% (n=11)<br>SM 25% (n=8)<br>CNL 17% (n=6) |
| Jones et al[78] | 81% (33%)<br>N=72 | 41% (7%)<br>N=59 | 43% (29%)<br>N=35 | CML 0% (n=18)<br>CMML/UMPD 20% (n=152)<br>HES/CEL 2% (n=134)<br>SM 0% (n=28)<br>CNL 33% (n=6)<br>AML 0% (n=17) |

*Mutational frequencies in different studies are not comparable because of the use of assays with variable sensitivity. AML = acute myeloid leukemia; CEL = chronic eosinophilic leukemia; CML = chronic myeloid leukemia; CMML = chronic myelomonocytic leukemia; CNL = chronic neutrophilic leukemia; HES = hypereosinophilic syndrome; MDS = myelodysplastic syndrome; NA = not applicable; SM = systemic mastocytosis; UMPD = unclassified MPD.

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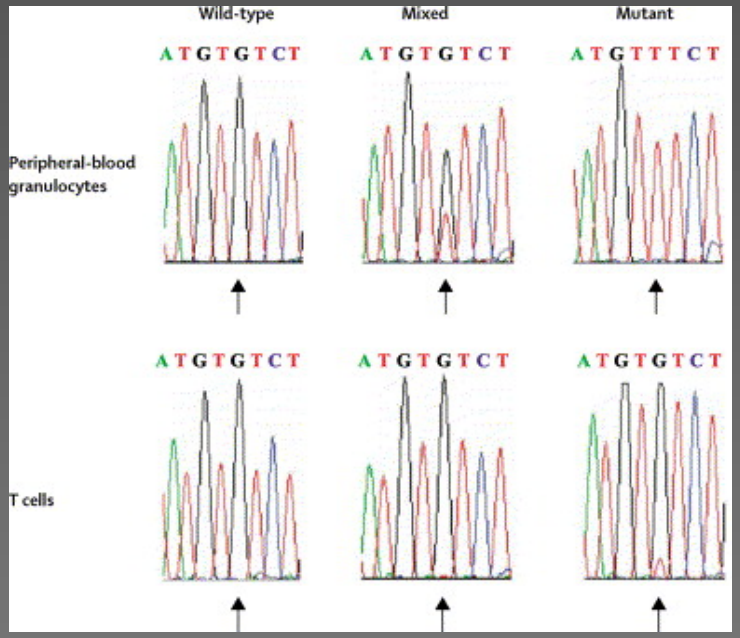
Tefferi, Mayo Clin Proc, July 2006

Pourquoi une telle disparité dans les fréquences rapportées ?

# Comment expliquer les différences dans les fréquences rapportées?

- Classification des patients (WHO vs PVSG)
- Sensibilité des techniques utilisées:
  - Séquençage: nécessite >10% allèles mutés
  - Diverses techniques PCR plus sensibles: 0,01% à 1%

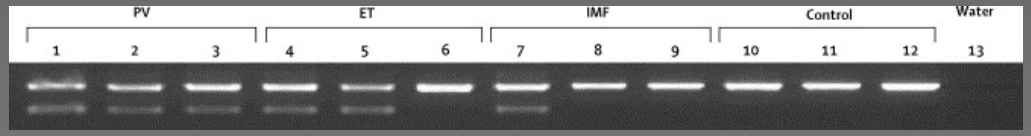
# Approches methodologiques (I): Séquençage et ASO PCR




Sensitivity: ~ 20%

Somatic mutation

Sensitivity: 3%



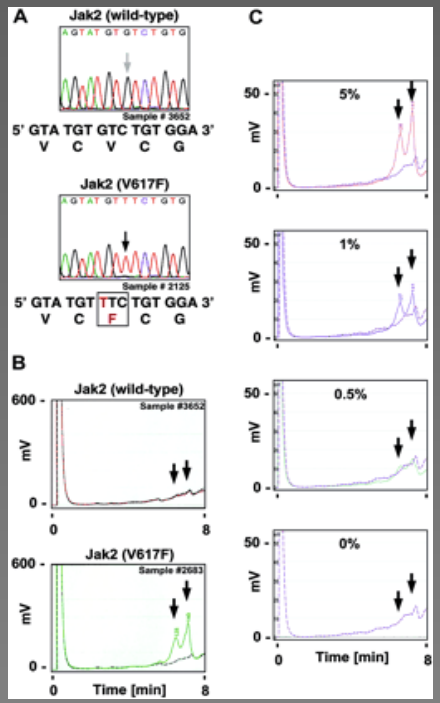

| | Sequencing | | | | Allele-specific PCR | | | Overall | |
|---|---|---|---|---|---|---|---|---|---|
| | Number tested | Mutant* | Mixed | Wild-type | Number tested | Mutant | Wild-type | Number | Proportion (95% CI) |
| Polycythaemia vera | 73 | 19 | 34 | 20 | 20 | 18 | 2 | 71/73 | 97% (93–100) |
| Essential thrombocythaemia | 51 | 0 | 6 | 45 | 45 | 23 | 22 | 29/51 | 57% (43–70) |
| Idiopathic myelofibrosis | 16 | 3 | 4 | 9 | 9 | 1 | 8 | 8/16 | 50% (26–74) |
| Controls | 90 | 0 | 0 | 90 | 90 | 0 | 90 | 0/90 | 0% |

Baxter et al Lancet 2005

# Approches methodologiques (II):

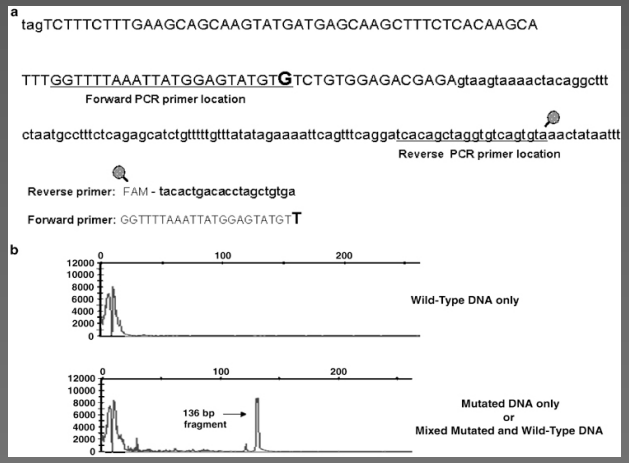
## Multistep process

DHPLC



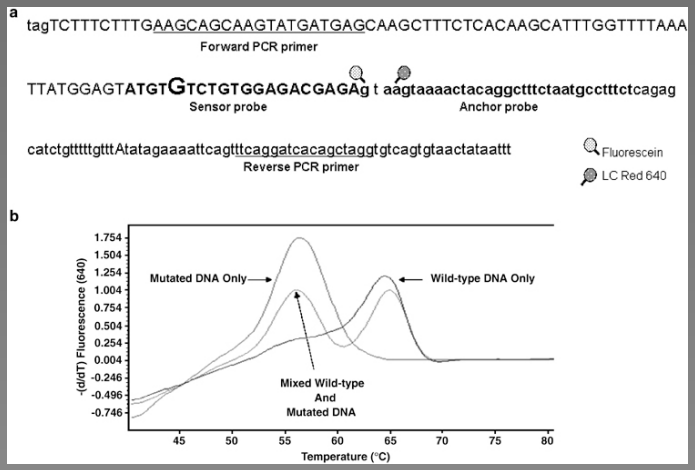

**Sensitivity: ~ 1%**

Sattler et al Blood 2006




**Sensitivity: 0.1 to 0.01%**

Fluorescent ASO PCR
(no internal control!)

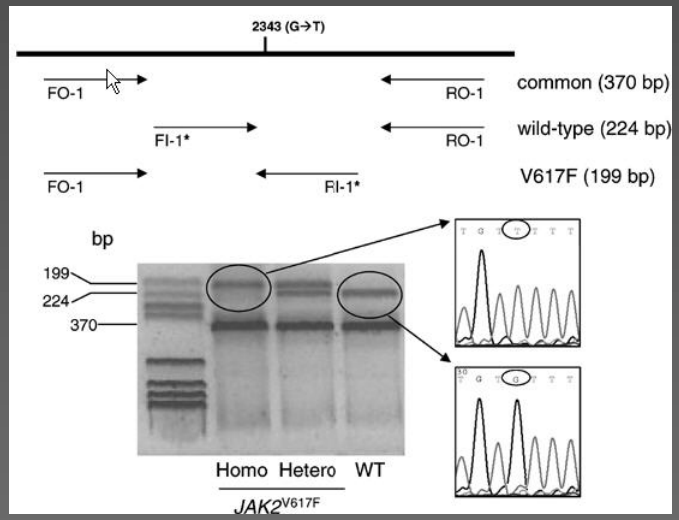



**Sensitivity: 1-10 %**

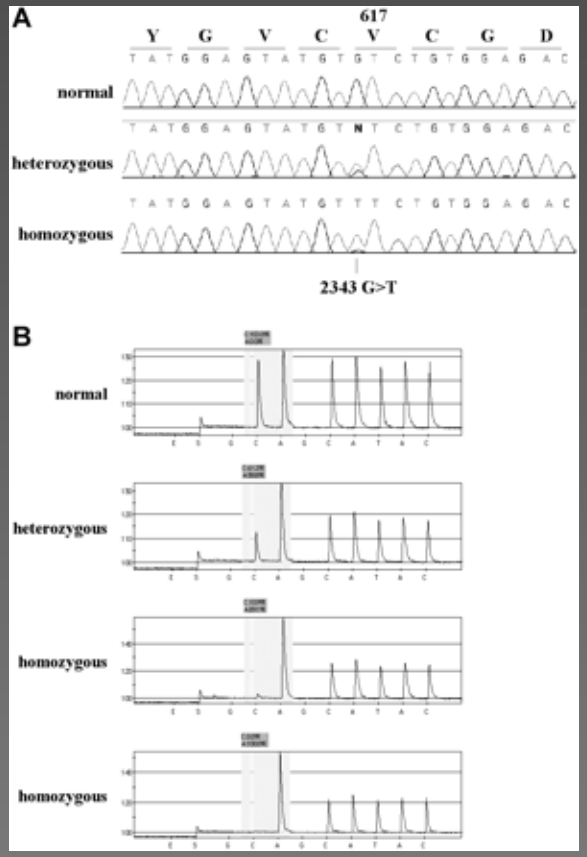
Melting curve

**McClure et al ; Leukemia 2006**

# Approches methodologiques (III):

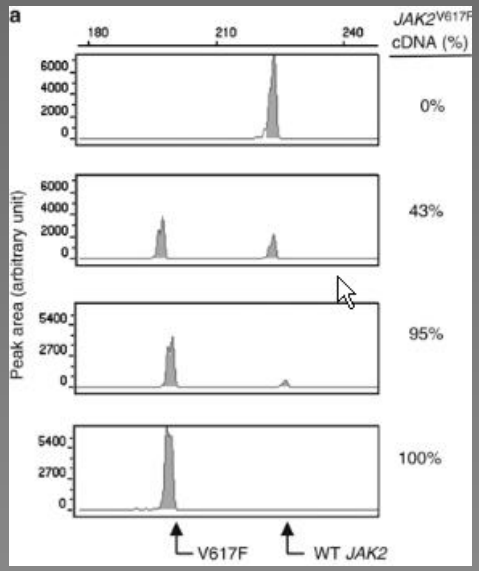



ARMS-PCR




**Sensitivity: ~ 5%**

Jones A et al Blood 2005




Quantitative ARMS-PCR

**Sensitivity: ~1%**

Vannucchi et al Leukemia 2006

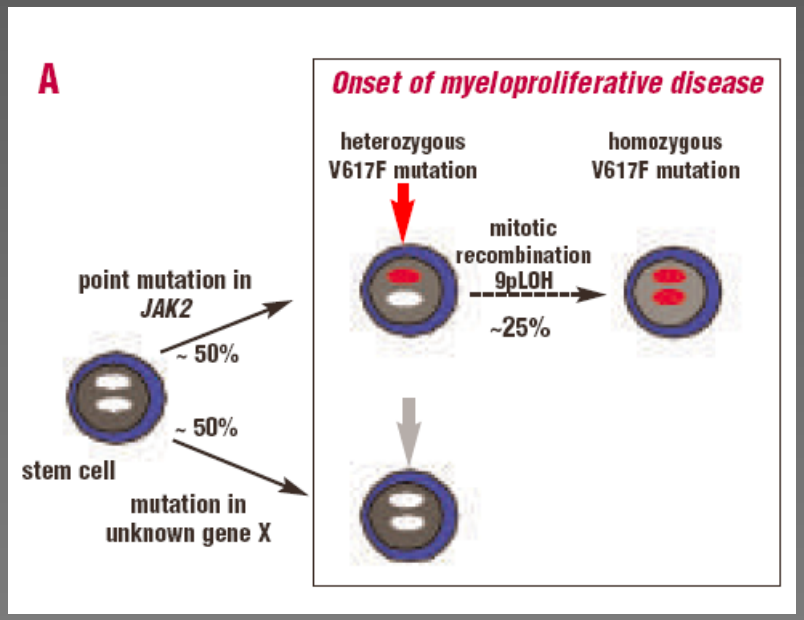
# JAK2 V617F
# phénomène primaire ou secondaire ?

# Controverses

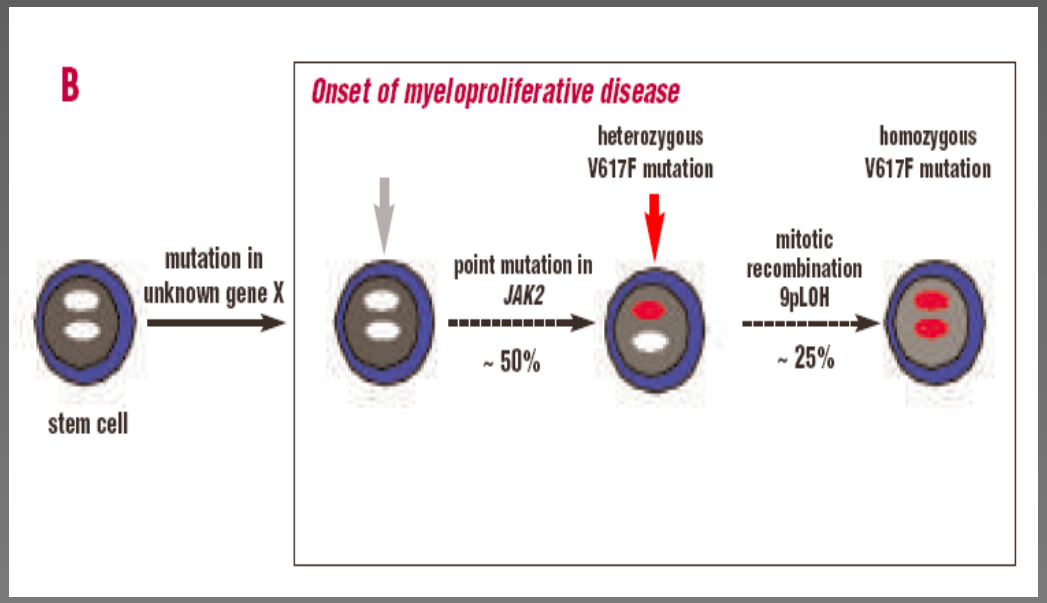
- « Acquisition of the V617F mutation of Jak2 is a late genetic event in a subset of patients with myeloproliferative disorders » Kralovics *et al.* 2006
- « The Jak2 V617F mutation occurs in hematopoietic stem cells in PV and predisposes toward erythroid differentiation » Jamieson *et al* 2006

# Modèles de transformations

Phénomène primaire ?




Phénomène secondaire ?



# Modèle de dominance clonale

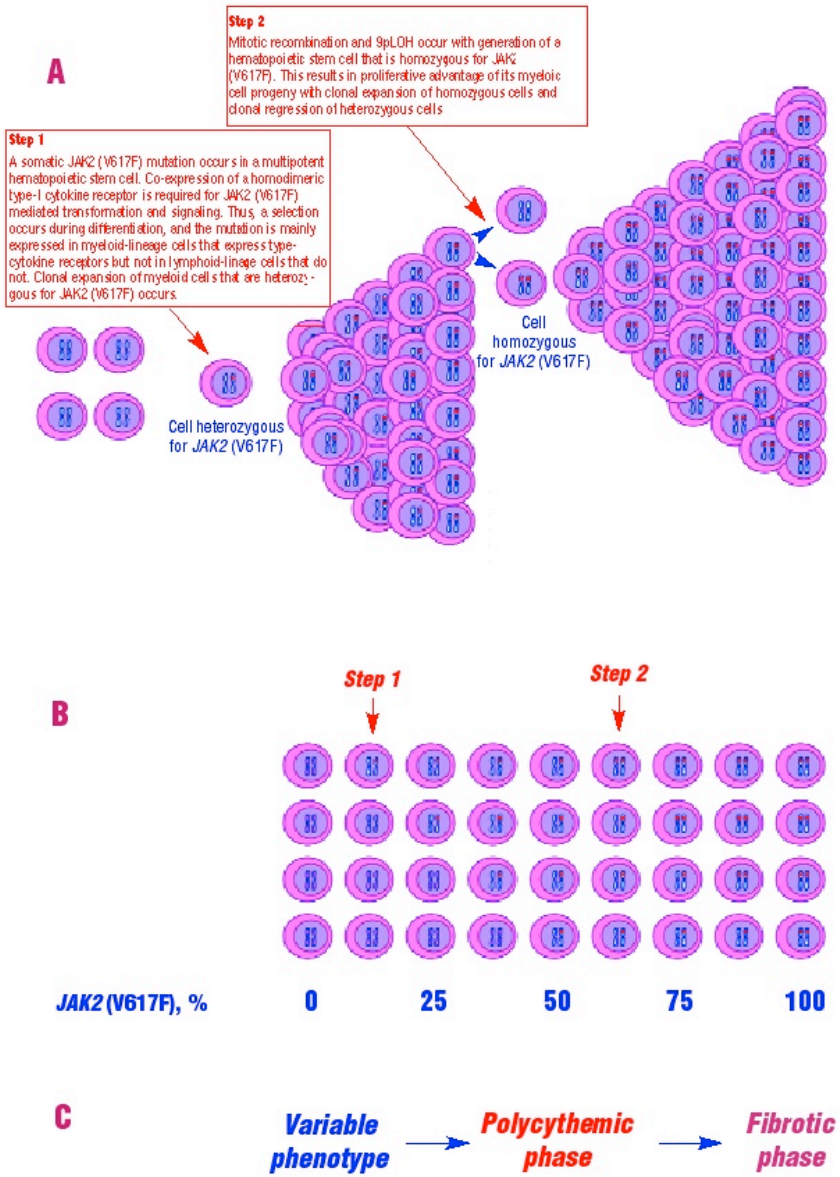



Figure 1. Two-step model for the role of *JAK2* (V617F) in the clonal evolution of myeloproliferative disorders. A. The first step consists of a G-to-T transversion (red dot) that changes a valine to a phenylalanine at position 617 in one *JAK2* allele on chromosome 9p: this gives rise to a clone that is heterozygous for *JAK2* (V617F) which expands to replace hematopoietic cells without the *JAK2* mutation. The second step consists of a mitotic recombination in a hematopoietic cell that is heterozygous for *JAK2* (V617F): this generates uniparental disomy and loss of heterozygosity of 9p (9pLOH) in one of the two daughter cells. The daughter cell that is homozygous for *JAK2* (V617F) gives rise to a new clone that expands and replaces the previous heterozygous clone (clonal dominance). Both the transition from normal hematopoiesis to a clonal population of heterozygous cells, and that from heterozygous to homozygous clonal dominance are continuous processes characterized by mixed populations of cells. B. Expected percentages of *JAK2* (V617F) mutant alleles in the mixed cell populations generated by the above described clonal evolutions. These calculations are based on the assumption that the mitotic recombination (step 2) occurs once clonal dominance of cells that are heterozygous for *JAK2* (V617F) is fully established. Should step 2 occur earlier, the result would be a mixed population of normal, heterozygous and homozygous cell, and proportions of these cell types might vary considerable. For instance, 50% of mutant alleles might also reflect the following cell population: 25% normal cells, 50% heterozygous cells and 25% homozygous cells. C. Relation between different stages of polycythemia vera and granulocyte *JAK2* (V617F) mutation status. A small proportion of mutant alleles may be associated with variable phenotype. On the other hand, transition from heterozygosity to homozygosity for *JAK2* (V617F) appears to be associated with evolution from the polycythemic to the fibrotic phase of the disease, which is characterized by constitutive mobilization of $CD34^+$ cells into peripheral blood.

# JAK2 V617F et SMPs : Implications cliniques

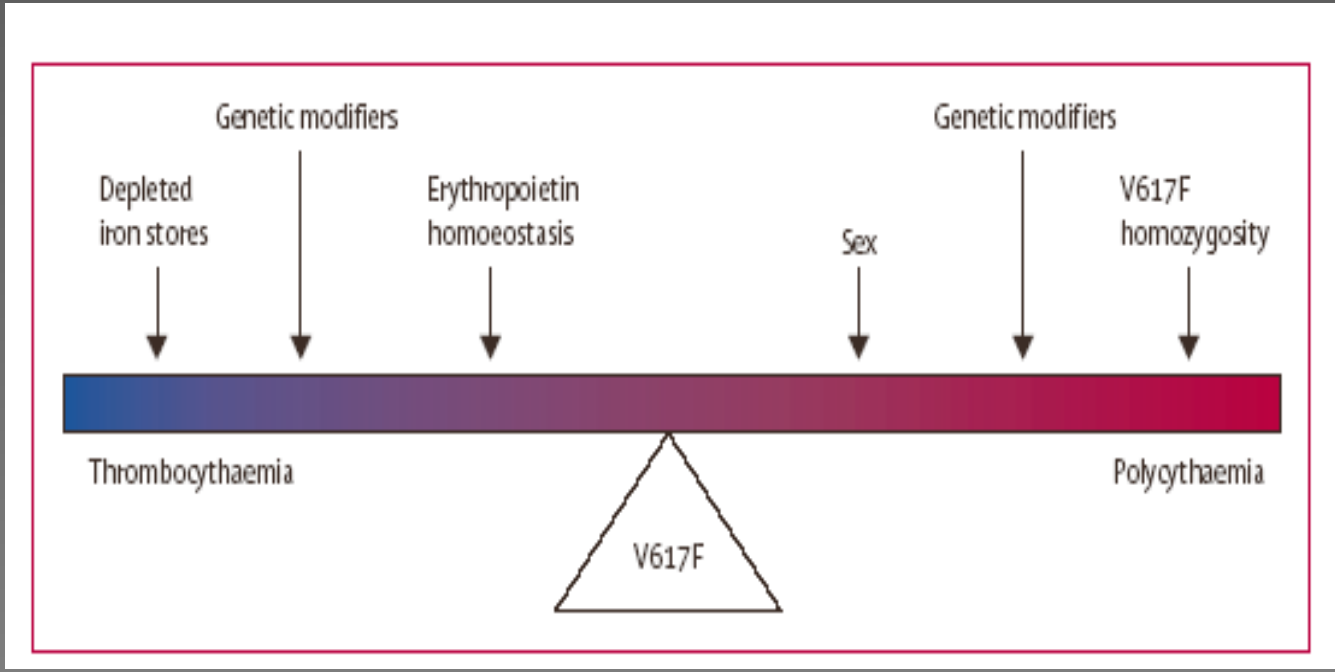
# Thrombocytémie Essentielle

- **Antonioli et al** (Leukemia 2005):
  - 130 TE testées
  - environ 50% V617F
  - pas de corrélation particulière avec des caractéristiques clinico-biologiques.

# Thrombocytémie Essentielle

- **Campbell et al** (The Lancet 2005):
  - 806 patients testés:
  - Les patients porteurs de la mutation sont plus sensibles à l'hydroxyurée (mais pas l'anagrélide) que les patients non-mutés
  - Suggèrent également que la TE et la PV forment un continuum biologique avec un degré d'érythrocytose déterminé par des modificateurs physiologiques ou génétiques.

# PV – TE, un continuum ?




Campbell, The Lancet, 2005

# Thrombocytémie Essentielle

- **Cheung et al** (BJH 2006):
  - mutation serait associée avec un taux d' hémoglobine plus élevée et un risque augmenté de thrombose.

# Myélofibrose idiopathique et V617F

- **Campbell et al** (Blood 2006):
  - Mutation → survie globale plus faible.

# Perspectives

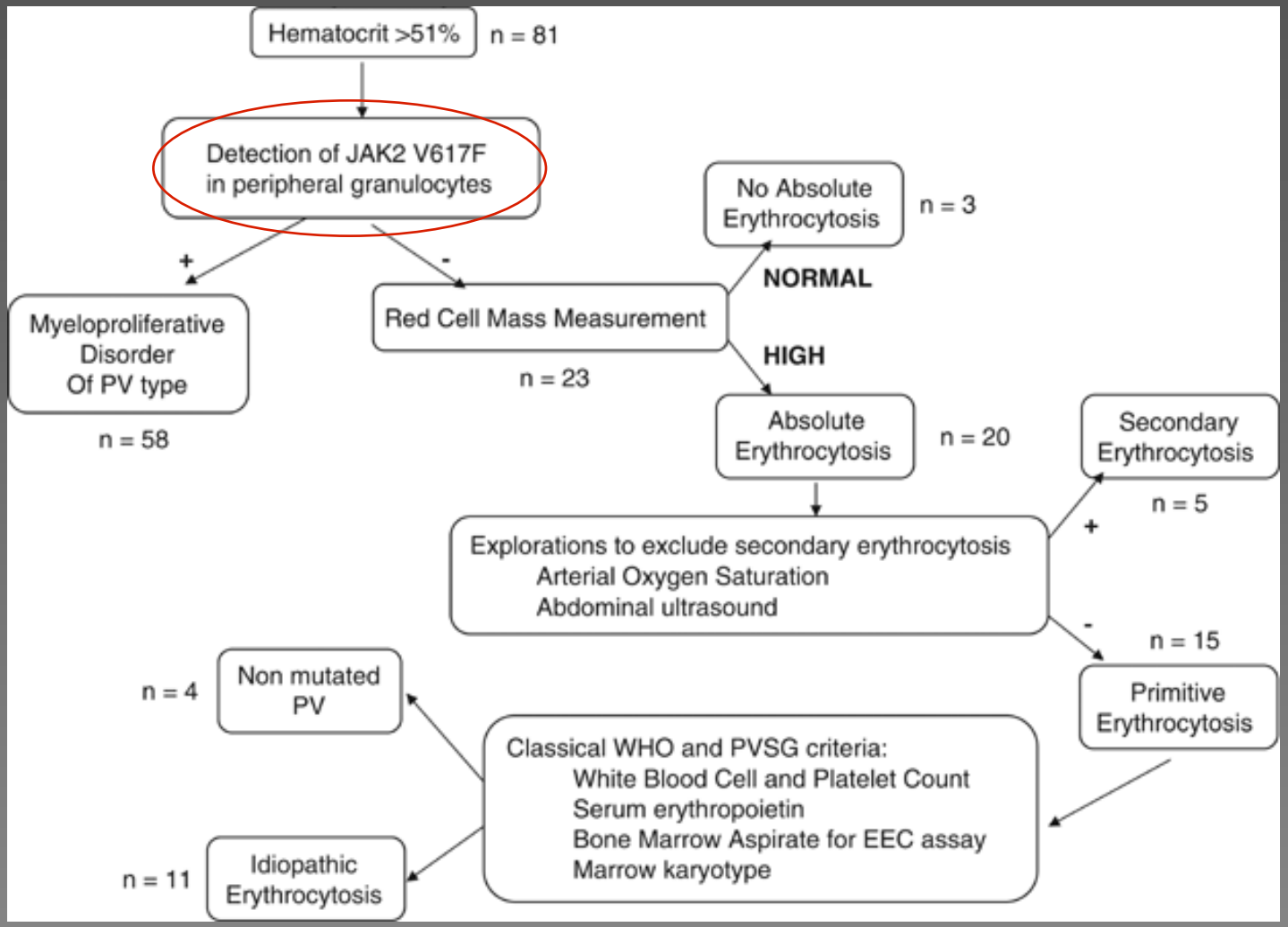
# 1. Classification « Semi-moléculaire » des SMPs

- Chronic myelogenous leukemia — *BCR/ABL*
- Polycythemia vera
- Chronic idiopathic myelofibrosis (with extramedullary hematopoiesis)
- Essential thrombocythemia — JAK2 V617F
- Chronic neutrophilic leukemia
- Chronic eosinophilic leukemia / HES — FIP1L1-PDGFRA
- Chronic myeloproliferative disease, unclassifiable — X-PDGFRX

James W. Vardiman, Nancy Lee Harris, and Richard D. Brunning
BLOOD, 2002, VOLUME 100, NUMBER 7

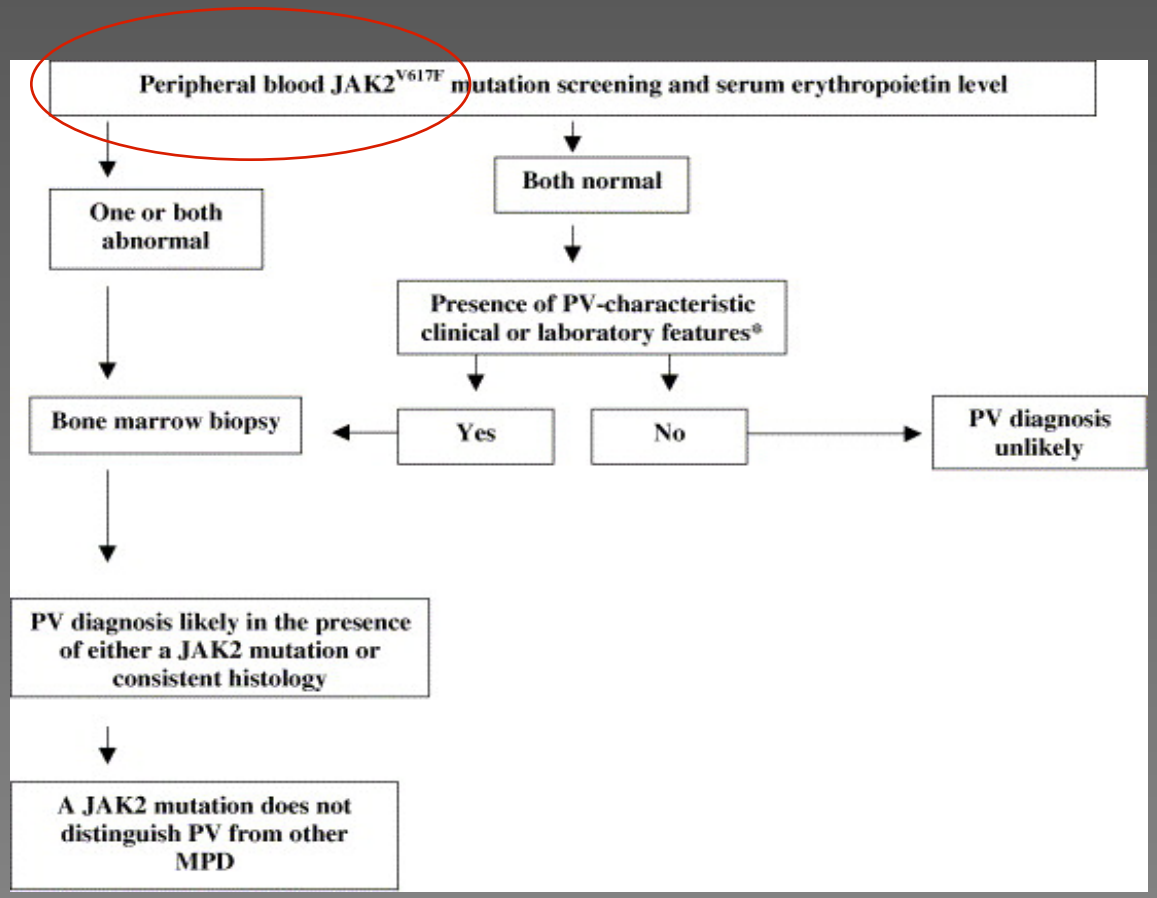
# 2. Nouveaux algorithmes diagnostics

# Organigramme décisionnel (I)
# PV



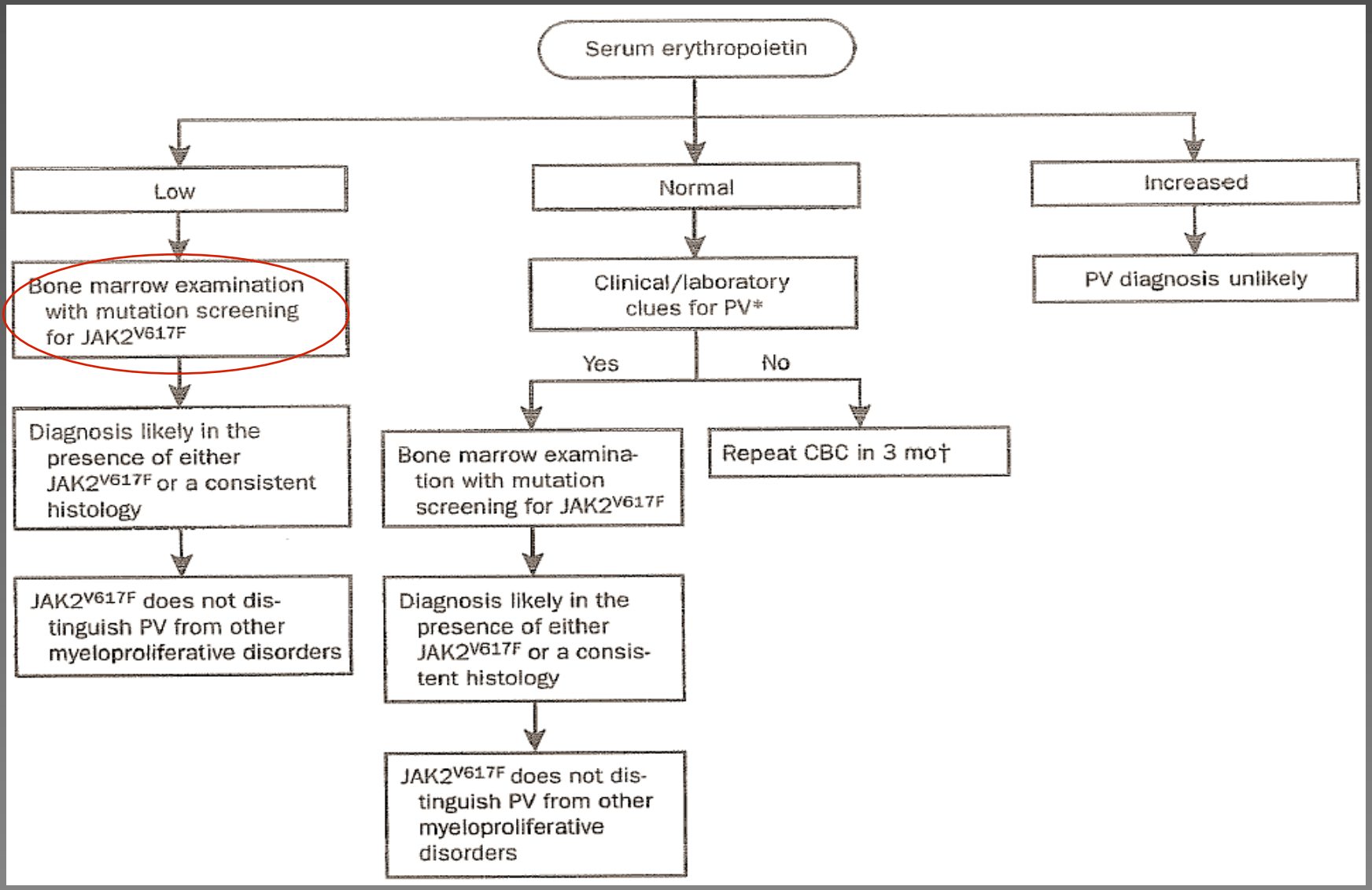

James et al Leukemia 2006 2006

# Organigramme décisionnel (II)
# PV



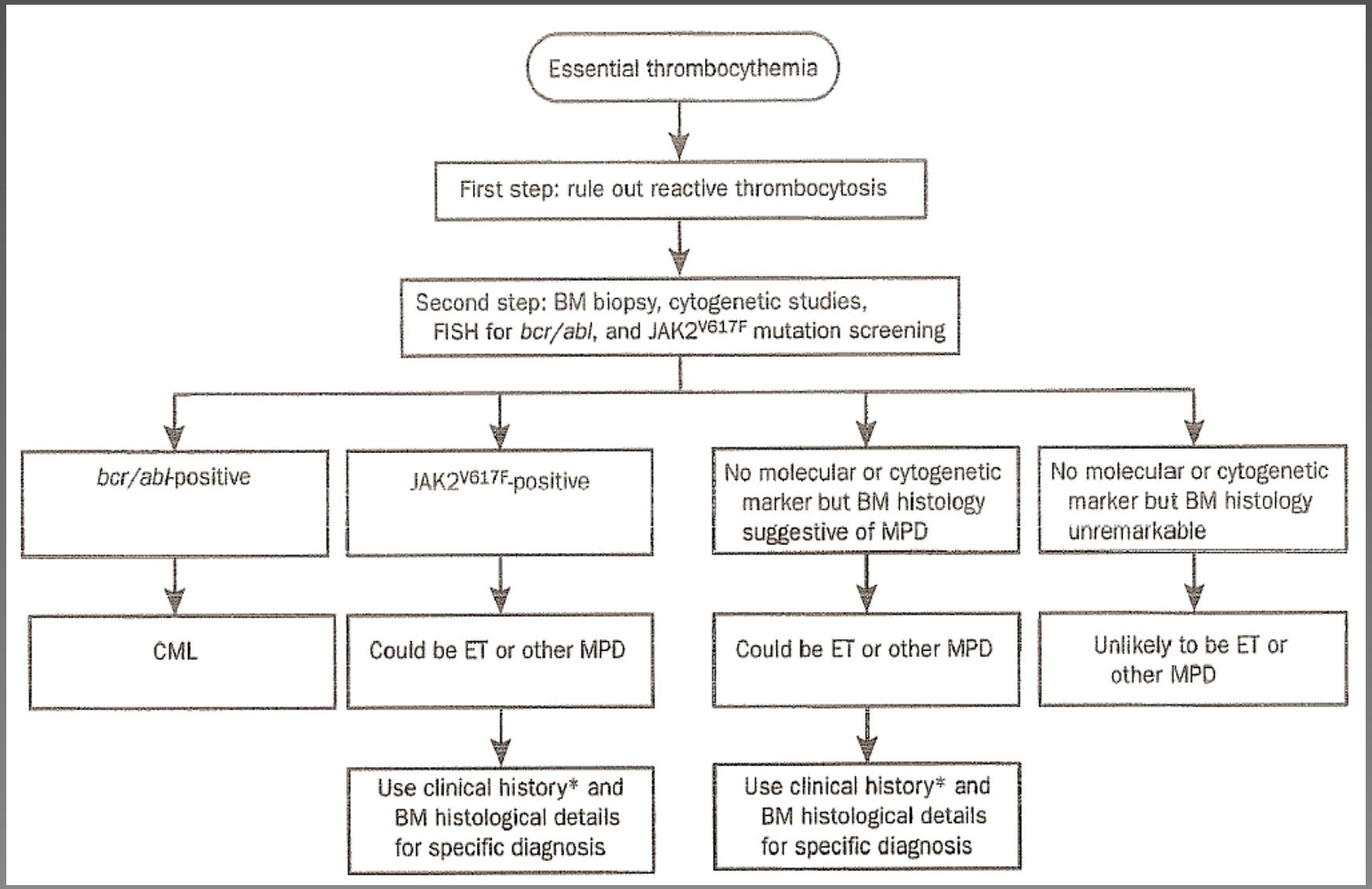

Tefferi et al Leukemia Res 2006

# Algorithme de DD des PV




Tefferi et al, Mayo Clin Proc, 2005

# Organigramme décisionnel (III)
# TE

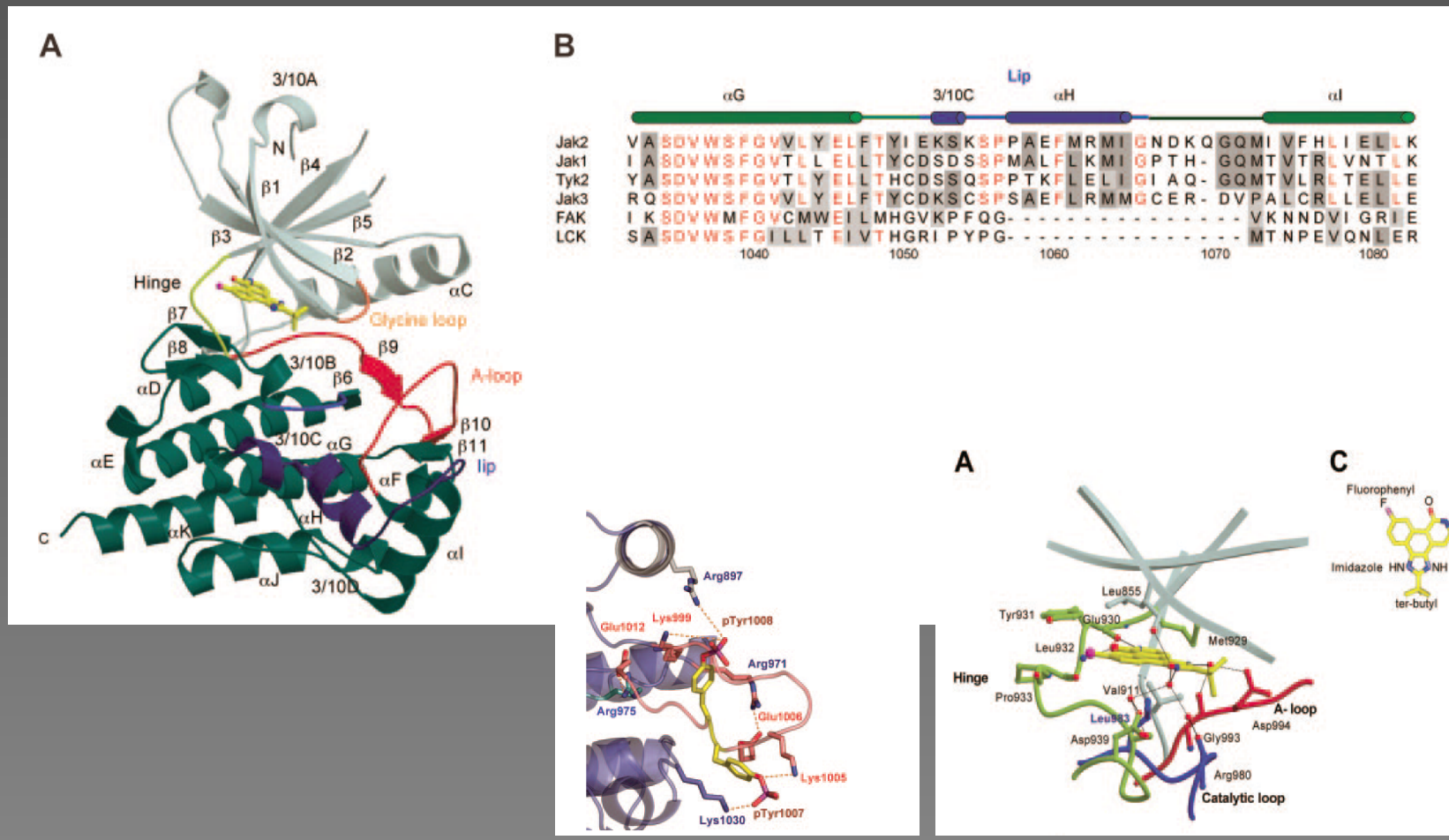



Tefferi et al, Mayo Clin Proc, 2005

# 3. Des inhibiteurs spécifiques de JAK2 V617F à usage clinique ?

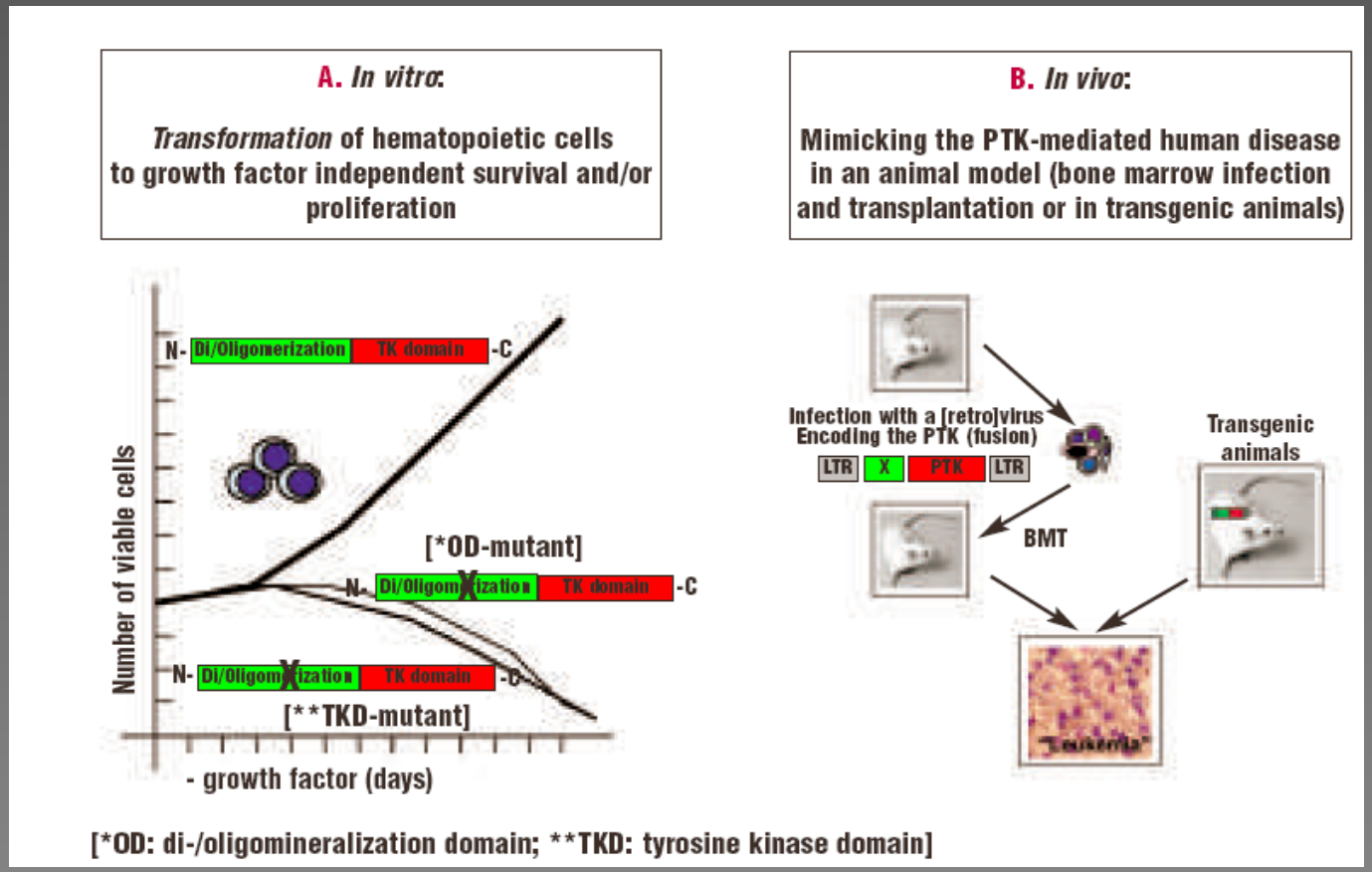
# The structural basis of Janus kinase 2 inhibition by a potent and specific pan–Janus kinase inhibitor

Isabelle S. Lucet, Emmanuelle Fantino, Michelle Styles, Rebecca Bamert, Onisha Patel, Sophie E. Broughton, Mark Walter, Christopher J. Burns, Herbert Treutlein, Andrew F. Wilks, and Jamie Rossjohn



Fin

# Modèles d' étude du pouvoir transformant d' un oncogène




Y. Chalandon *et al*, Haematologica, 2005

# Fréquences rapportées de la mutation V617F SMPs et autres pathologies

| Disease | Frequency | % | Refs |
|---|---|---|---|
| Polycythemia vera | 71/73 | 97 | [11] |
| | 40/45 | 89 | [8] |
| | 25/29 | 86 | [60] |
| | 58/72 | 81 | [59] |
| | 83/128 | 65 | [9] |
| | 121/164 | 74 | [10] |
| | 20/24 | 83 | [12] |
| Essential thrombocythemia | 29/51 | 23 | [11] |
| | 9/21 | 43 | [8] |
| | 3/10 | 30 | [60] |
| | 24/59 | 41 | [59] |
| | 21/93 | 23 | [9] |
| | 37/115 | 32 | [10] |
| Idiopathic myelofibrosis | 8/16 | 50 | [11] |
| | 3/7 | 50 | [8] |
| | 18/19 | 95 | [60] |
| | 15/35 | 43 | [59] |
| | 13/23 | 57 | [9] |
| | 16/46 | 35 | [10] |
| Unclassified chronic myeloproliferative disorders | 3/16 | 19 | [60] |
| | 30/152 | 20 | [59] |
| Chronic myelomonocytic leukemia | 7/52 | 13 | [60] |
| | 3/119 | 2 | [58] |
| Myelodysplastic syndromes | 1/68 | 1 | [60] |
| | 2/48 | 4 | [56] |
| | 5/101 | 5 | [58] |
| Systemic mastocytosis | 0/28 | 0 | [59] |
| | 2/8 | 20 | [58] |
| Chronic neutrophilic leukemia | 1/6 | 17 | [58] |
| Hypereosinophilic syndromes | 2/134 | 1 | [59] |
| Chronic myeloid leukemia | 0/99 | 0 | [60] |
| | 0/18 | 0 | [59] |
| Acute myeloid leukemia (except megakaryocytic leukemia) | 0/28 | 0 | [60] |
| | 0/17 | 0 | [59] |
| Megakaryocytic leukemia (acute myeloid leukemia M7) | 2/11 | 18 | [60] |
| Acute myeloid leukemia and a history of chronic myeloproliferative disorders | 12/22 | 55 | [60] |
| B-lineage acute lymphoblastic leukemia | 0/83 | 0 | [56] |
| T-cell acute lymphoblastic leukemia | 0/93 | 0 | [56] |
| Chronic lymphocytic leukemia | 0/45 | 0 | [56] |

LMA II

Brief report

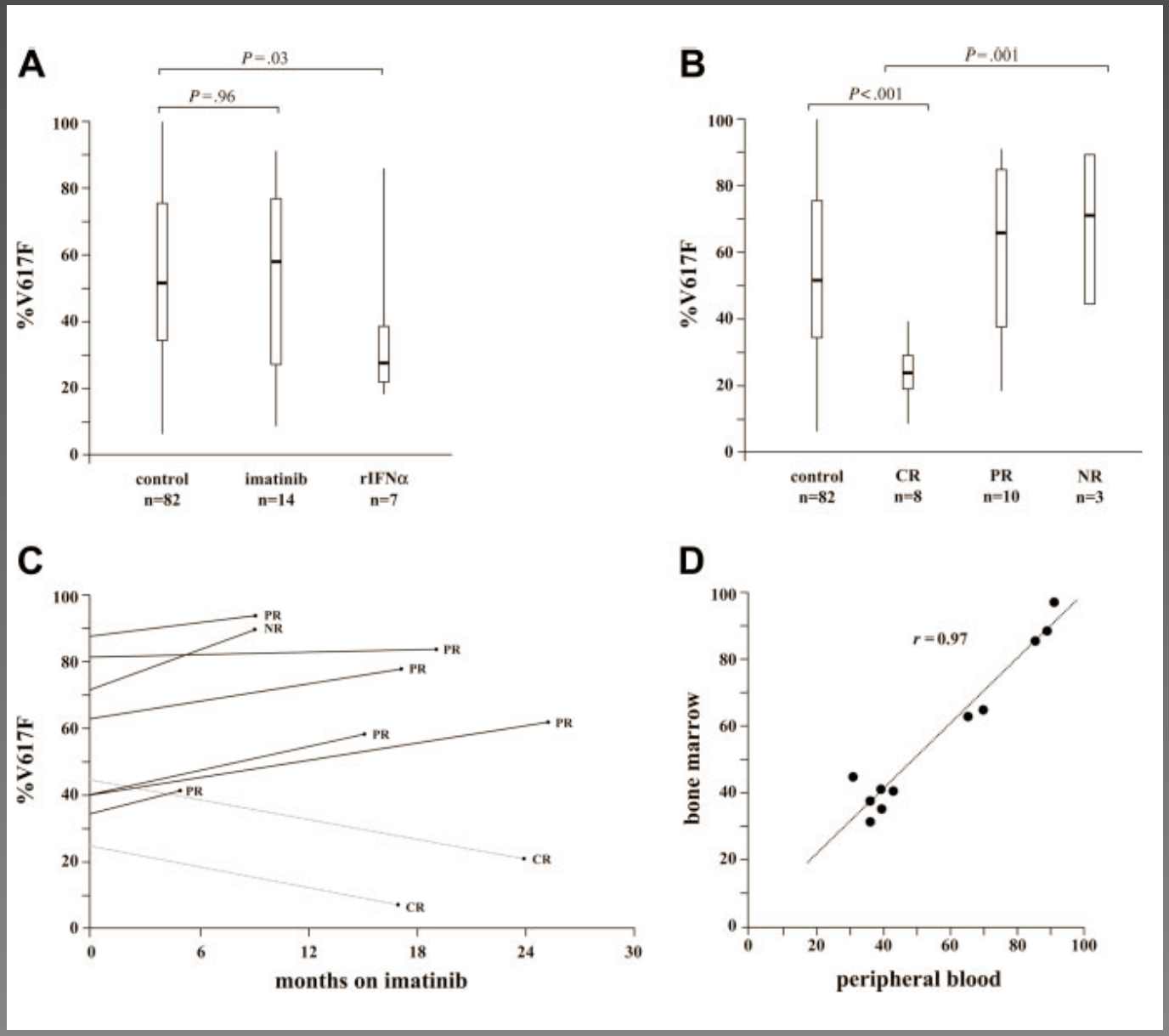
# Minimal molecular response in polycythemia vera patients treated with imatinib or interferon alpha

Amy V. Jones, Richard T. Silver, Katherine Waghorn, Claire Curtis, Sebastian Kreil, Katerina Zoi, Andreas Hochhaus, David Oscier, Georgia Metzgeroth, Eva Lengfelder, Andreas Reiter, Andrew J. Chase, and Nicholas C. P. Cross

**Table 1. Summary of patient characteristics and results for cases undergoing therapy with imatinib or rIFNα**

| Patient no. | Sex | Age at diagnosis, y | Rx | Dose | F/U, mo | Response | % V617F on treatment | % V617F before treatment |
|---|---|---|---|---|---|---|---|---|
| 1 | M | 26 | Imatinib | 800 mg/d | 5 | NR | 44 | ND |
| 2 | F | 60 | Imatinib | 700 mg/d | 5 | PR | 41 | 34 |
| 3 | M | 49 | Imatinib | 800 mg/d | 9 | NR | 89 | 71 |
| 4 | F | 67 | Imatinib | 500 mg/d | 9 | PR | 91 | 88 |
| 5 | M | 58 | Imatinib | 400 mg/d | 10 | PR | 72 | ND |
| 6 | M | 48 | Imatinib | 800 mg/d | 15 | PR | 57 | 40 |
| 7 | M | 31 | Imatinib | 800 mg/d | 17 | PR | 76 | 63 |
| 8 | F | 48 | Imatinib | 500 mg/d | 17 | CR | 8 | 25 |
| 9 | F | 28 | Imatinib | 800 mg/d | 19 | PR | 83 | 82 |
| 10 | M | 72 | Imatinib | 400 mg/d | 21 | NR | 72 | ND |
| 11 | M | 54 | Imatinib | 300 mg/d | 24 | CR | 21 | 44 |
| 12 | M | 43 | Imatinib | 400 mg/d | 25 | PR | 60 | 40 |
| 13 | M | 30 | Imatinib | 600 mg/d | 25 | PR | 19 | ND |
| 14 | M | 53 | Imatinib | 700 mg/d | 31 | PR | 30 | ND |
| 15 | F | 32 | rIFNα | 3 MU 3 times/wk | 13 | CR | 19 | ND |
| 16 | F | 39 | rIFNα | 3 MU 5 days/wk | 45 | CR | 39 | ND |
| 17 | M | 53 | rIFNα | 3 MU/day | 50 | CR | 29 | ND |
| 18 | F | 48 | rIFNα | 4 MU, alternate d | 60 | PR | 87 | ND |
| 19 | M | 42 | rIFNα | 2 MU 3 times/wk | 60 | CR | 27 | ND |
| 20 | M | 52 | rIFNα | 4.25 MU 3 times/wk | 108 | CR | 22 | ND |
| 21 | M | 39 | rIFNα | 3.5 MU/d | 132 | CR | 25 | ND |

Rx indicates treatment; F/U, follow-up (= time of sampling) after starting rIFNα or imatinib; NR, no response; ND, not determined; PR, partial response; CR, complete response; and MU, million units.


A
P=.03
P=.96
%V617F
control n=82
imatinib n=14
rIFNα n=7
B
P=.001
P<.001
%V617F
control n=82
CR n=8
PR n=10
NR n=3
C
%V617F
PR
NR
CR
months on imatinib
D
r=0.97
bone marrow
peripheral blood