Roma, 3 dicembre 2012

RICERCA, INNOVAZIONE E COMPETITIVITÀ:

QUALI VANTAGGI PER IL PAESE E PER I PAZIENTI?

RICERCA TRASNAZIONALE e TRASLAZIONALE

Gianluca Gaidano, M.D., Ph.D

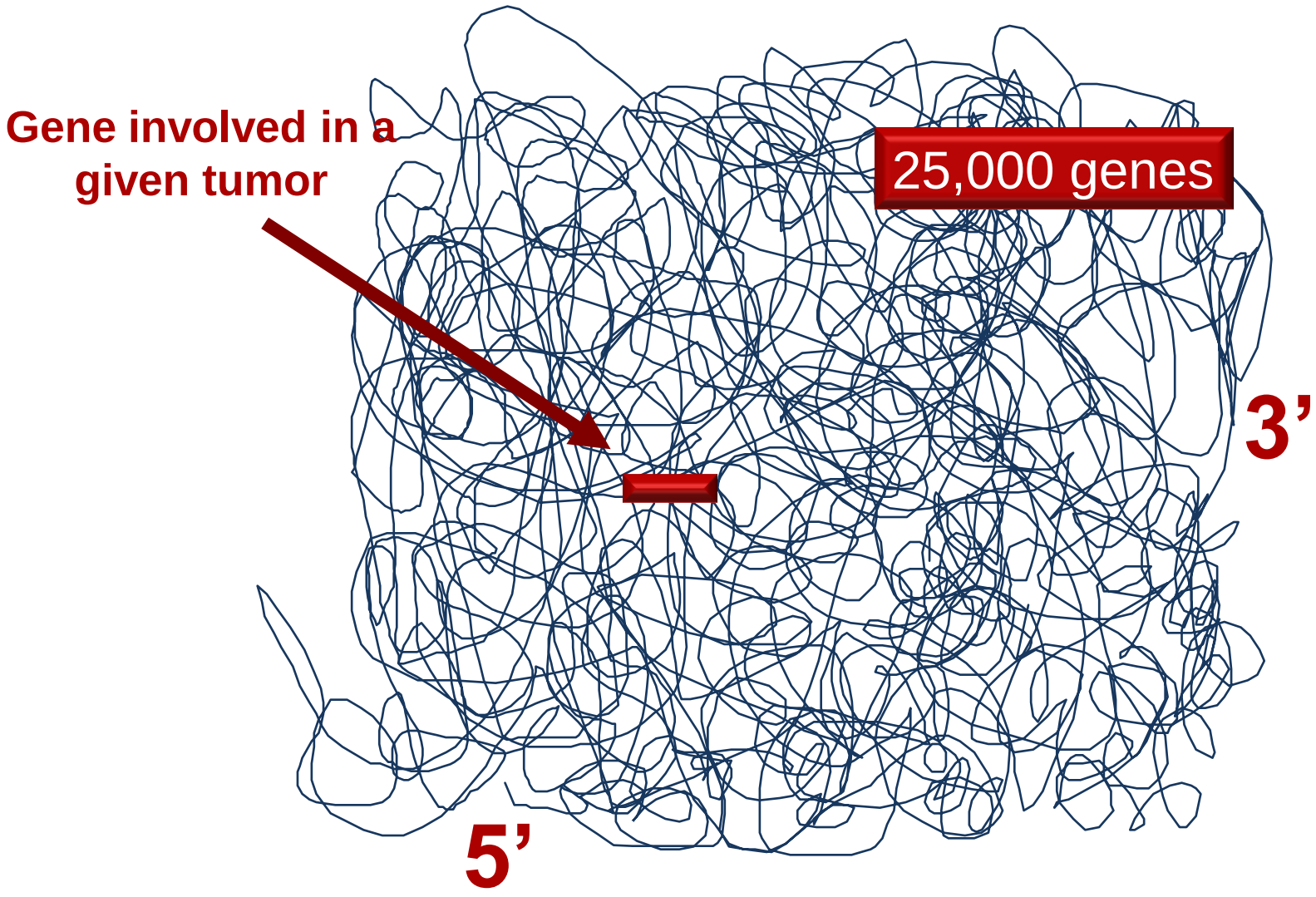
Division of Hematology
Department of Translational Medicine
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Novara-Italy

Obiettivi della ricerca traslazionale in Ematologia

Identificazione ed applicazione di marcatori biologici utili a:

- Raffinare la diagnosi
- Stratificare la prognosi
- Rendere possibile una terapia “personalizzata” (e.g. “target therapy”)

Identification of molecular markers in hematologic neoplasia



Two conceptually different approaches

Candidate gene approach



How ***our*** neurons ***think*** that leukemia cells ***would*** “reason”

Whole exome sequencing approach



How **leukemia** cells ***actually*** “reason”

Obiettivi della ricerca traslazionale in Ematologia

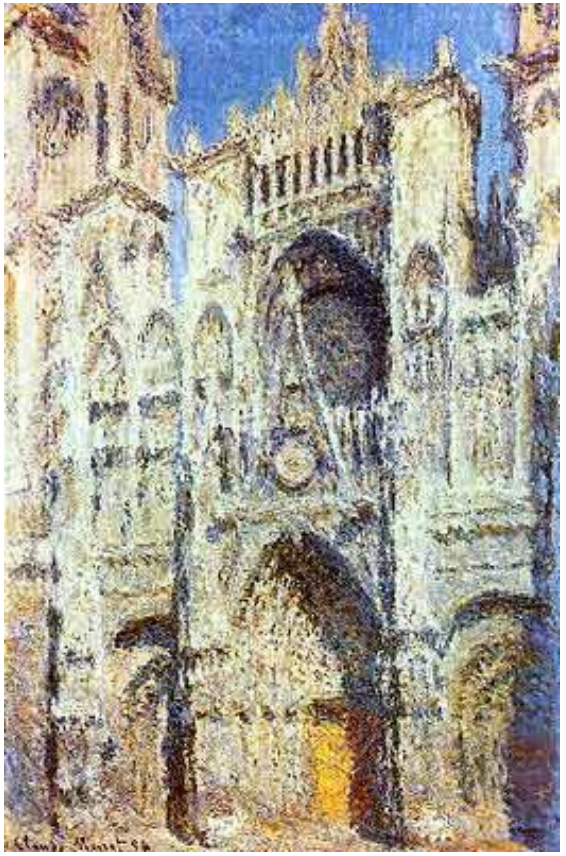
Identificazione ed applicazione di marcatori biologici utili a:

- **Raffinare la diagnosi**
- Stratificare la prognosi
- Rendere possibile una terapia “personalizzata” (e.g. “target therapy”

Neoplasie linfoidi: diagnostica differenziale
L'esempio della cattedrale di Rouen



(A)



(B)

Neoplasie linfoidi: diagnostica differenziale
L'esempio della cattedrale di Rouen



(A)



(D)

Neoplasie linfoidi: diagnostica differenziale
L'esempio della cattedrale di Rouen

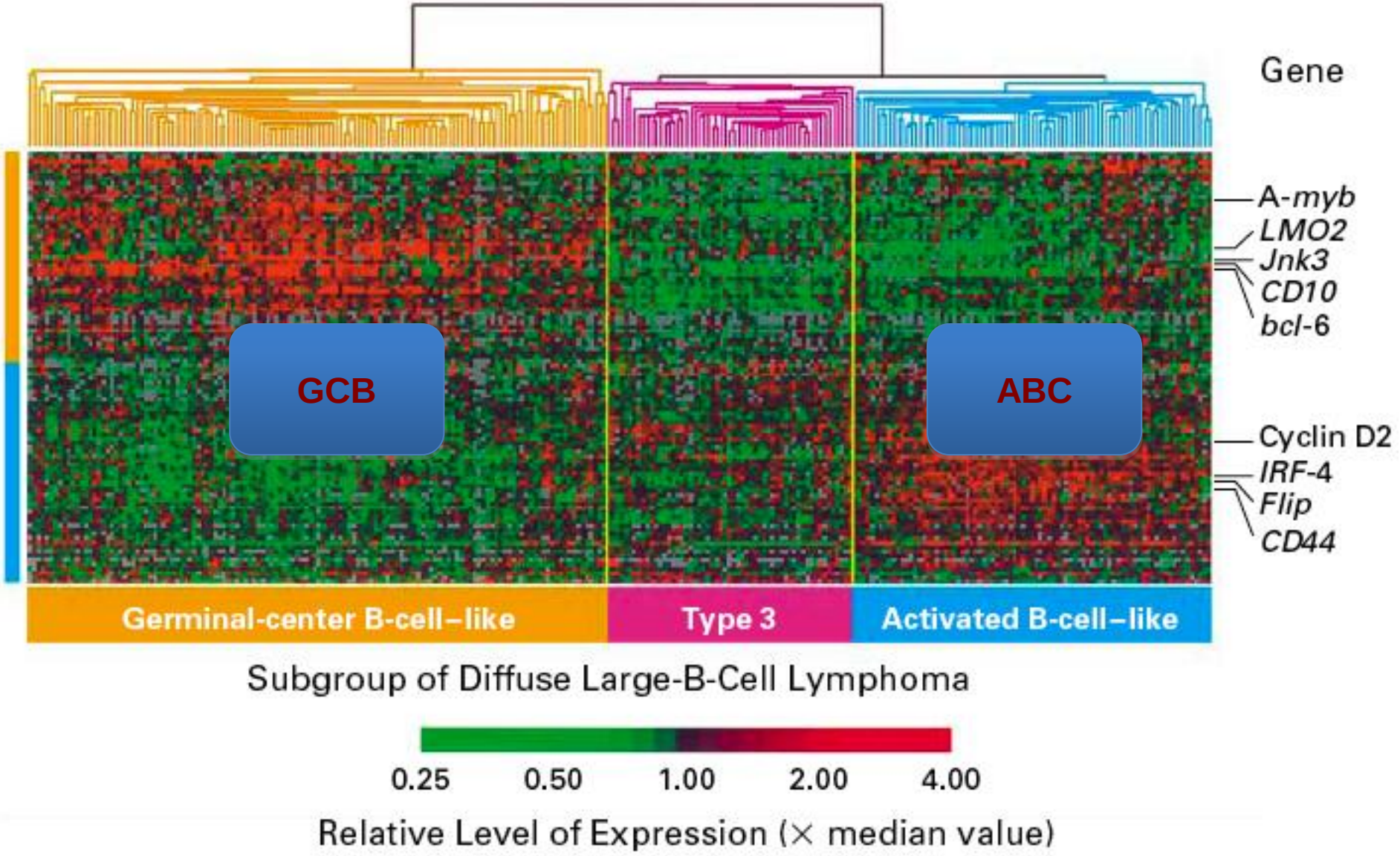


(A): Claude Monet, 1894

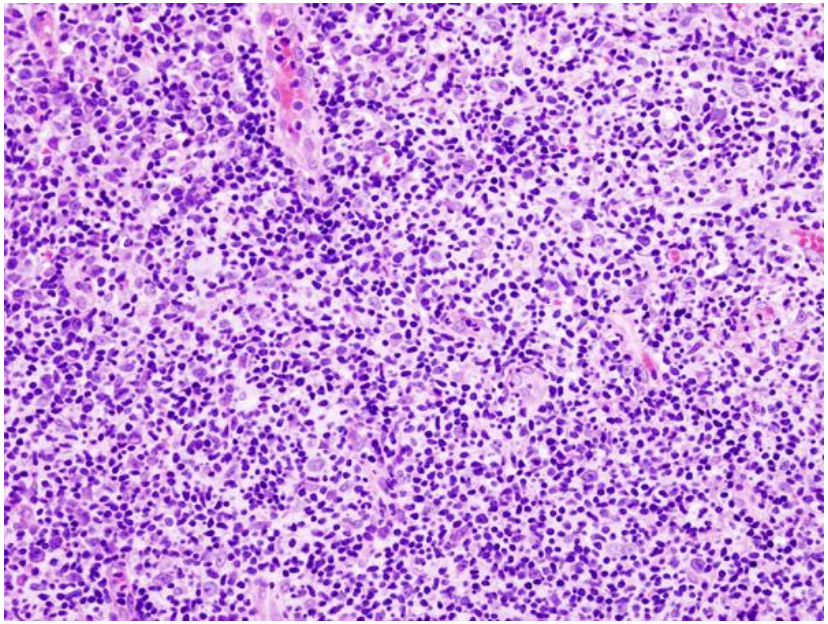


(D): Falso, 1997

Linfoma diffuso a grandi cellule B: GCB vs ABC in base a Gene Expression Profiling

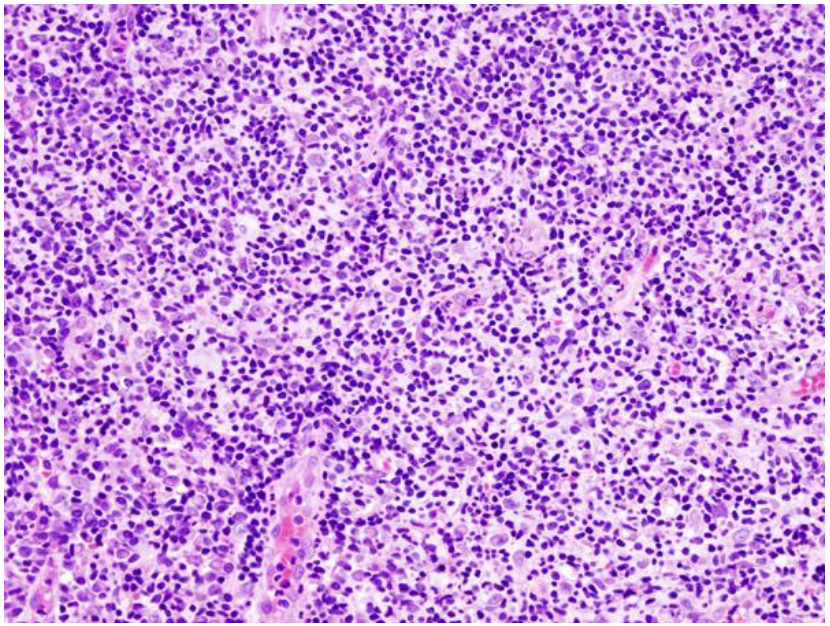


Eterogeneità clinico-molecolare del linfoma diffuso a grandi cellule B



Caso A

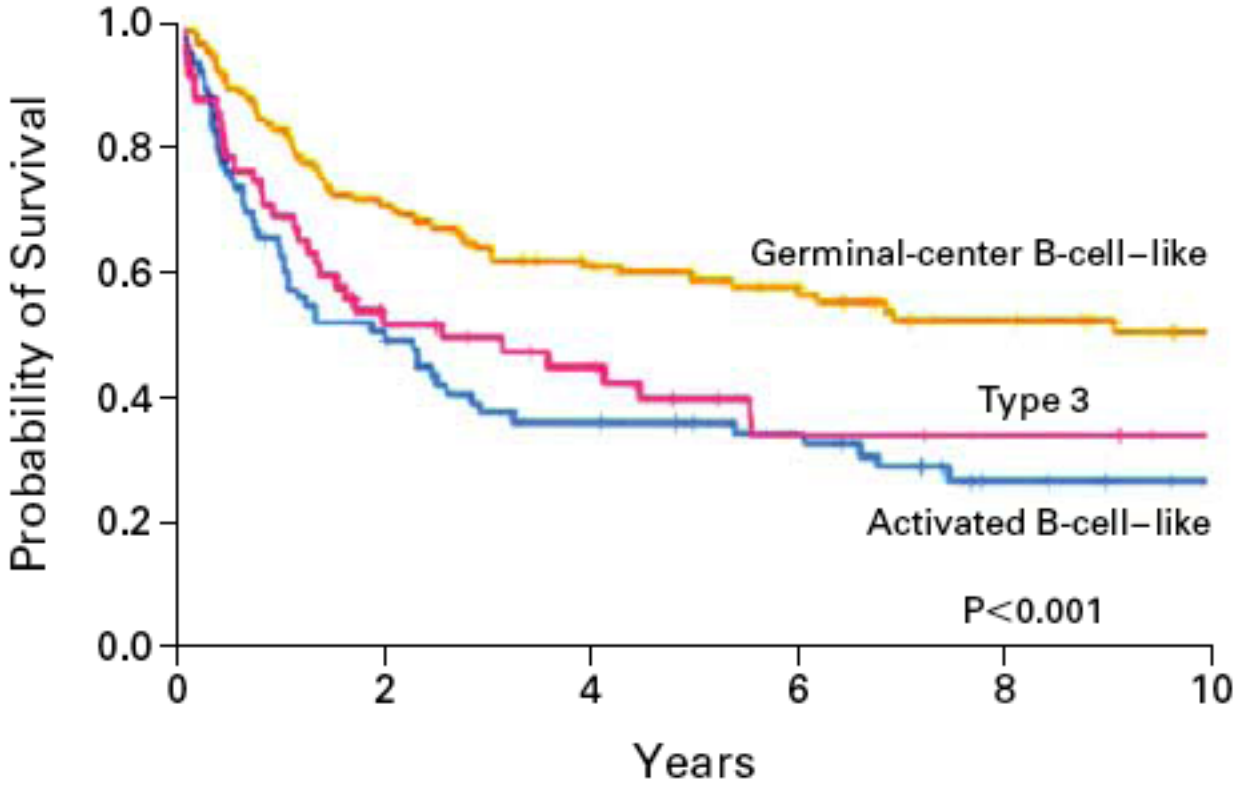
GCB



Caso B

ABC

Linfoma diffuso a grandi cellule B: Stratificazione prognostica in base a GEP



No. at Risk						
Germinal-center B-cell–like	115	81	60	46	32	19
Type 3	52	24	18	10	8	5
Activated B-cell–like	73	35	23	19	8	5

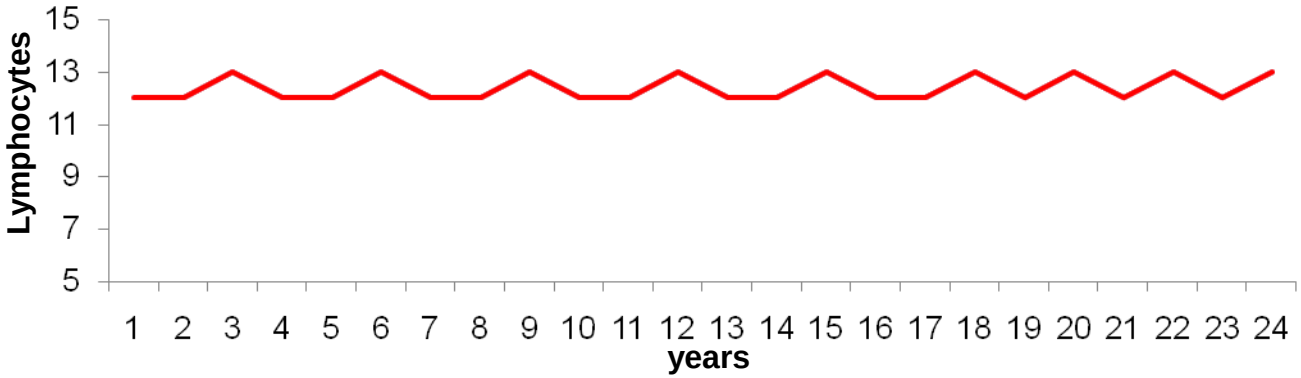
Obiettivi della ricerca traslazionale in Ematologia

Identificazione ed applicazione di marcatori biologici utili a:

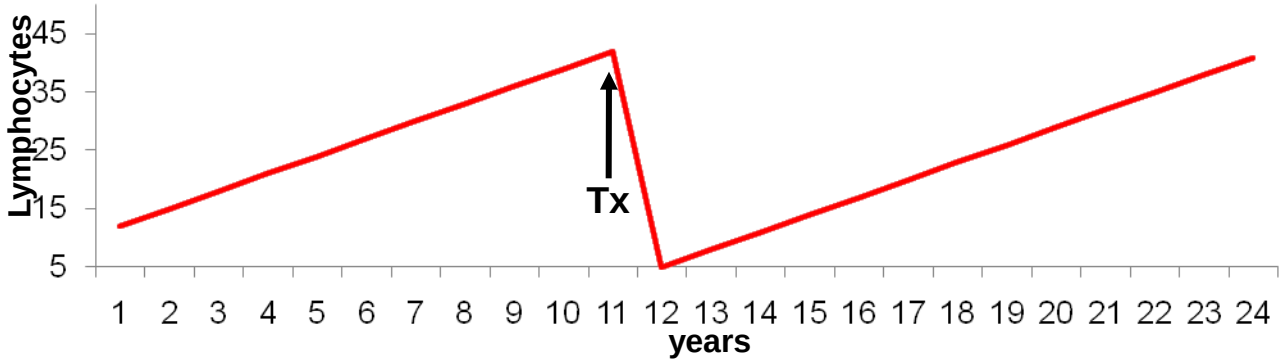
- Raffinare la diagnosi
- **Stratificare la prognosi**
- Rendere possibile una terapia “personalizzata” (e.g. “target therapy”

CLL: Homogeneous phenotype but heterogeneous clinical course

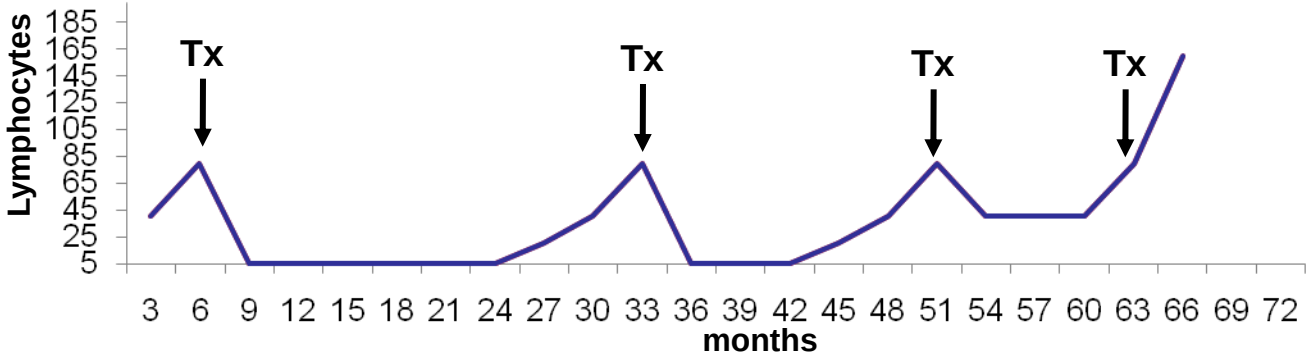
Highly stable



Slowly progressive



Rapidly progressive



Whole exome capture and sequencing approach

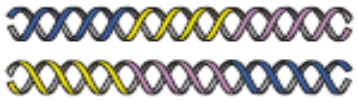
Exon capture
SureSelect
Human All Exon
Agilent

NimbleGen
Array

Sequencing
454 GS FLX
Roche

SOliD 3 Plus
Applied
biosystems

HiSeq2000
Illumina



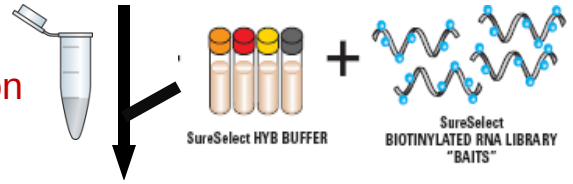
3µg of human genomic DNA
(N=10 paired N/F-ref CLL)
(N=9 paired CLL/RS)

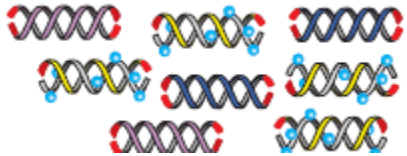
DNA shearing

linker ligation-PCR

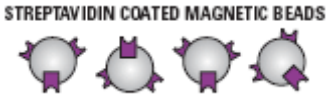


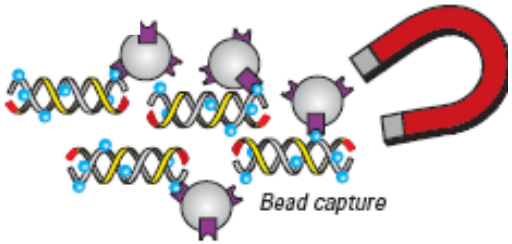
Hybridization





Magnetic beads selection

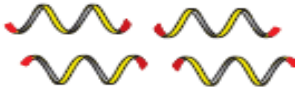




Wash beads

Digest RNA

Enriched target DNA



LM-PCR

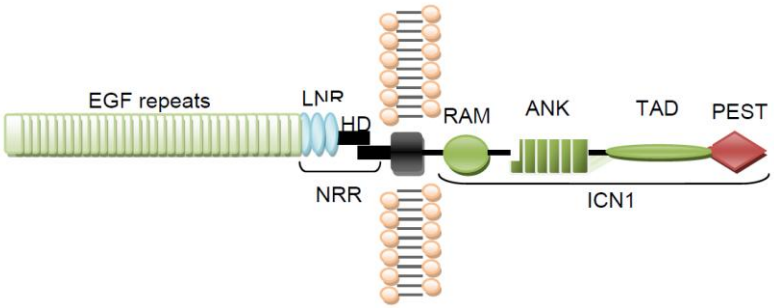
amplification

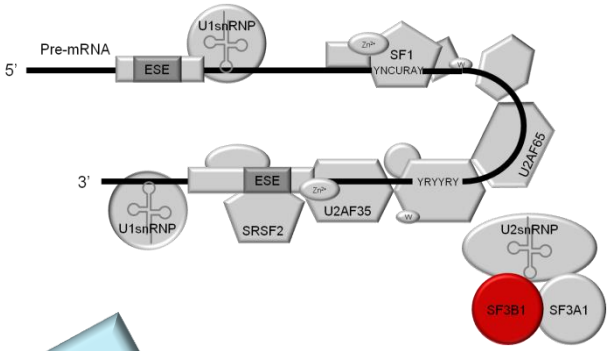
Amplified
target
pool



High Throughput
Sequencing

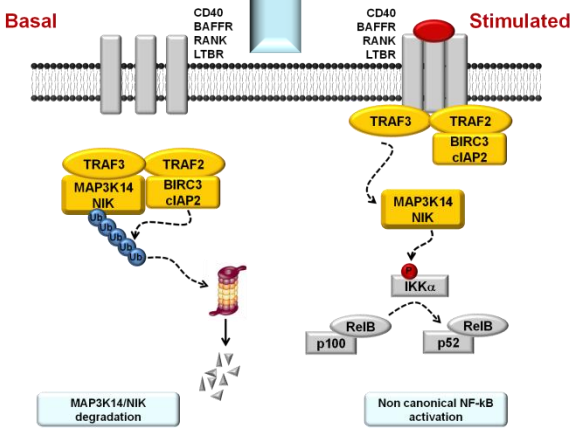
3 novel pathways in CLL





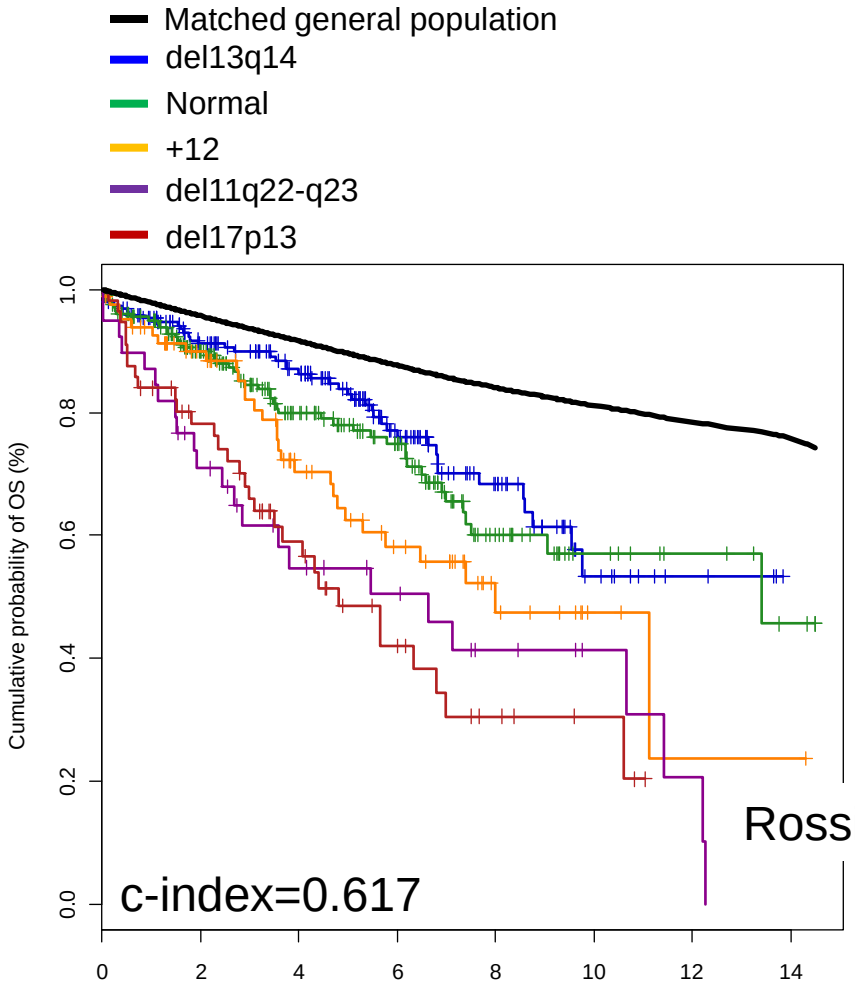
NOTCH

Splicing



NF-κB

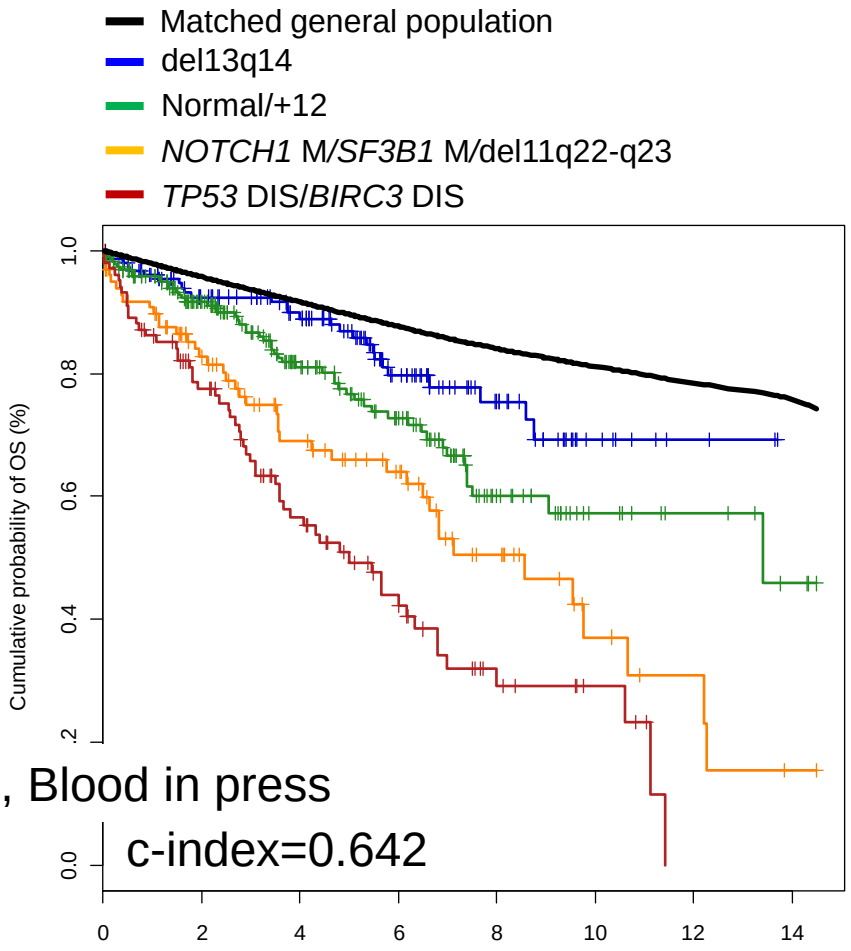
Inclusion of mutations in addition to FISH abnormalities significantly improves the accuracy of CLL prognostication



Years from diagnosis

N	Observed events	Expected events*	5-year OS (%)	10-year OS (%)	10-year relative OS*	p*
194	44	24.9	83.9	53.3	68.1%	<0.0001
212	50	24.7	78.0	57.1	72.8%	<0.0001
82	30	12.4	62.5	47.5	62.4%	<0.0001
39	23	6.1	54.7	41.3	54.4%	<0.0001
56	31	6.1	48.5	30.6	38.1%	<0.0001

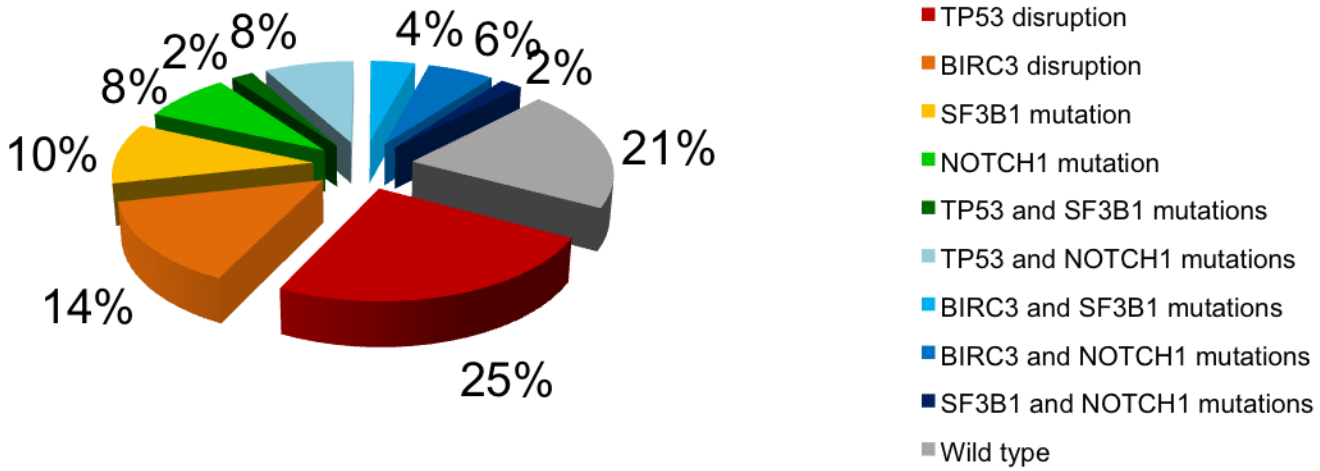
Rossi et al, Blood in press

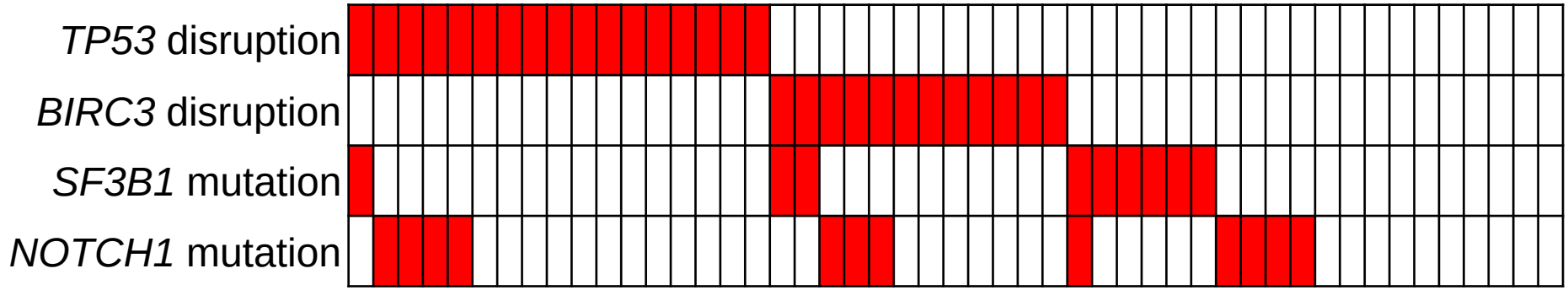


Years from diagnosis

N	Observed events	Expected events*	5-year OS (%)	10-year OS (%)	10-year relative OS*	p*
155	27	20.4	86.9	69.3	84.2%	0.1455
228	53	30.9	77.6	57.3	70.7%	<0.0001
99	41	10.4	65.9	37.1	48.5%	<0.0001
101	57	12.6	50.9	29.1	37.7%	<0.0001

A model for understanding the molecular basis of fludarabine-refractory CLL





Fludarabine-refractory CLL (n=49)

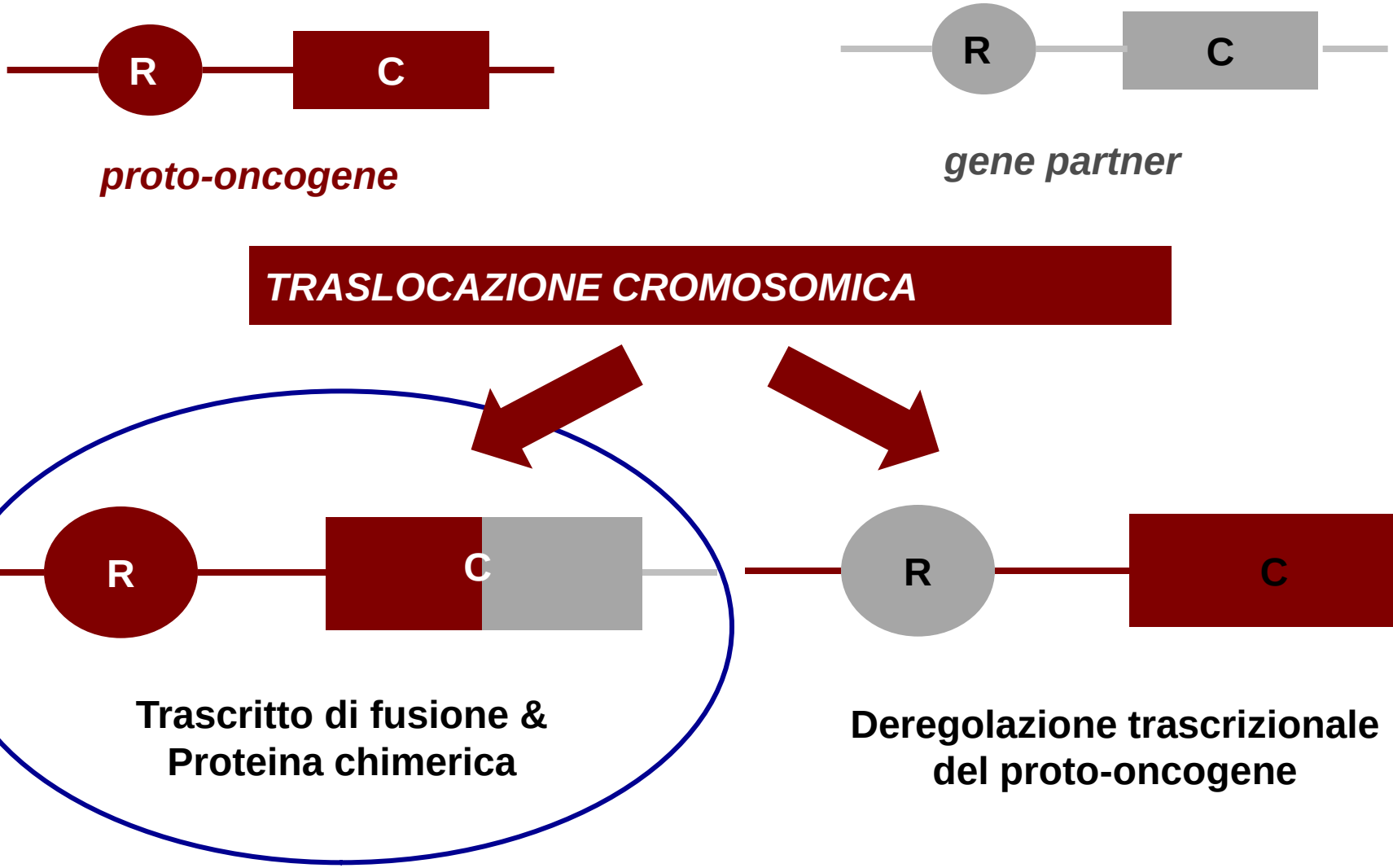
Rossi et al, Blood 2011
Rossi et al, Blood 2012a
Rossi et al, Blood 2012b
Rossi et al, Blood in press
Rossi et al, J Exp Med 2012

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Leucemia mieloide cronica:
Una malattia dovuta a un gene di fusione



Trascritti di fusione

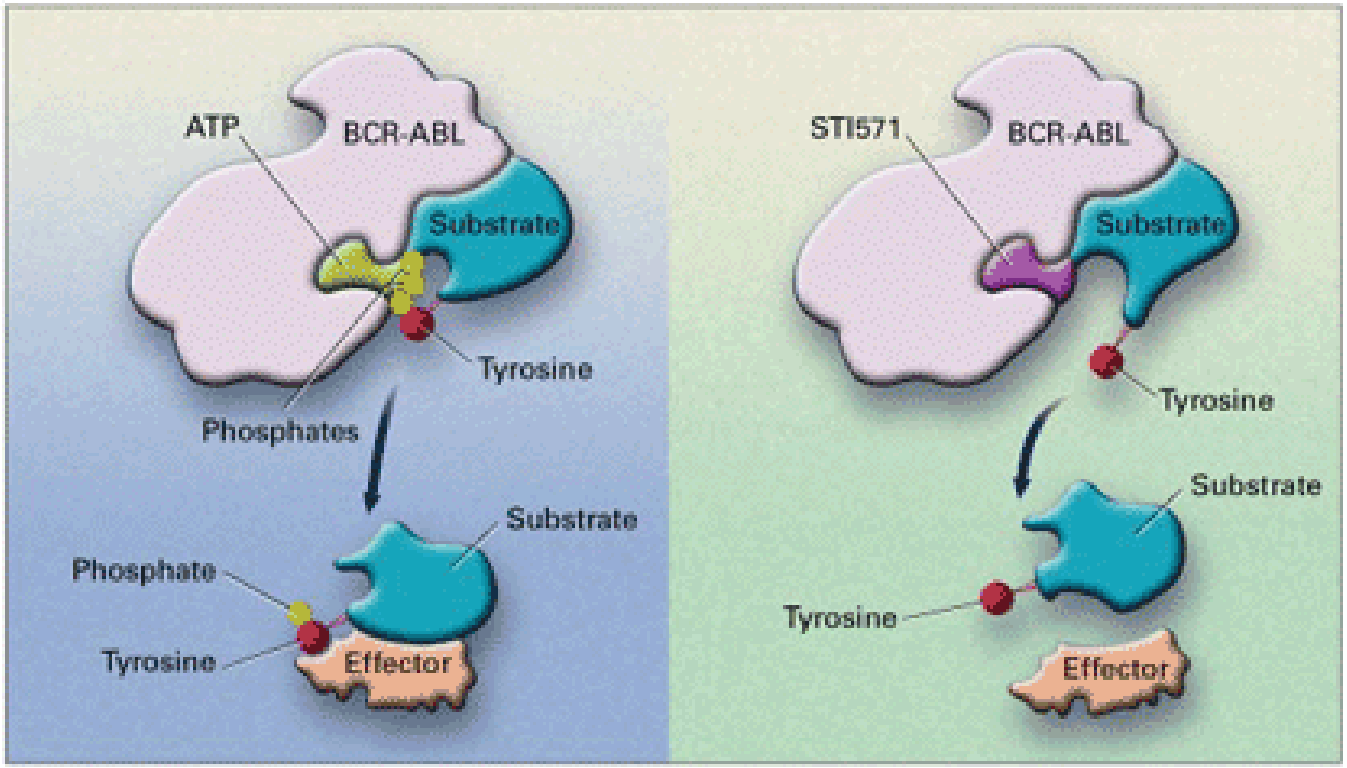


Leucemia mieloide cronica
1st generation tyrosine kinase inhibitors (TKI)

IMATINIB (Gleevec™)

Derivato della 2-fenildiaminopirimidina

Attivo su BCR-ABL, ABL, c-KIT, PDGRF



Leucemia mieloide cronica
Imatinib "*makes the cover*" di Time Magazine

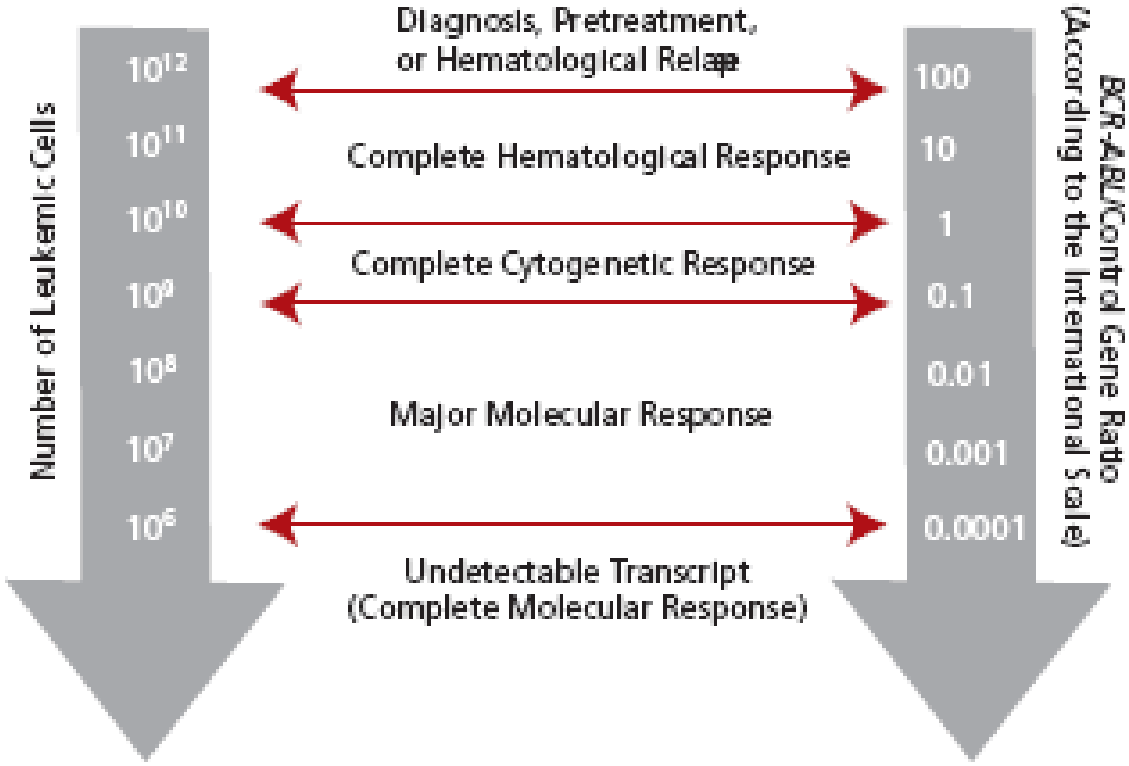


Leucemia mieloide cronica
Impatto di Imatinib sulla storia naturale della malattia

95%

80%

50%



Adapted with permission from Baccarani M et al. Blood. 2006;108:1809-1820.[10]

Quesiti sulla applicazione delle conoscenze generate dalla ricerca traslazionale in Ematologia

Garantire:

- **Sostenibilità** economica nel tempo dell'utilizzo delle conoscenze generate dalla ricerca traslazionale

- **Accessibilità** a tutti dei benefici per la salute dell'uomo indotti dalle conoscenze della ricerca traslazionale

Quesiti sulla applicazione delle conoscenze generate dalla ricerca traslazionale in Ematologia

Garantire **sostenibilità economica nel tempo**:

- Selezione dei marcatori che veramente impattino significativamente sulla salute dell'uomo
- Necessità di linee guida codificate ed EBM sulla applicazione dei nuovi biomarcatori nella pratica clinica
- Centralizzazione dell'esecuzione di tali test in centri di riferimento (modello "hub & spoke")
- Ottimizzazione dell'uso delle risorse condiviso fra politici della salute e medici

Quesiti sulla applicazione delle conoscenze generate dalla ricerca traslazionale in Ematologia

Garantire:

- **Sostenibilità** economica nel tempo dell'utilizzo delle conoscenze generate dalla ricerca traslazionale

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Ricerca trasnazionale in Ematologia



Obiettivi della ricerca traslazionale in Ematologia
Interrogativi

E' giusto che molti degli investimenti economici che vengono fatti a scopo scientifico vadano alla fine a vantaggio di pochi? Oppure non sarebbe piu' etico finalizzare i fondi della medicina di base da distribuire in maniera piu' omogenea a livello mondiale?

Card. Carlo Maria Martini
in CM Martini, I. Marino - "Credere e conoscere" – Einaudi 2012

Strategie di accessibilità delle conoscenze generate dalla ricerca traslazionale in Ematologia

INCTR

International Network for
Cancer Treatment and Research

INCTR is an NGO in official relations with WHO

