INTRODUZIONE ALL'EMATOLOGIA

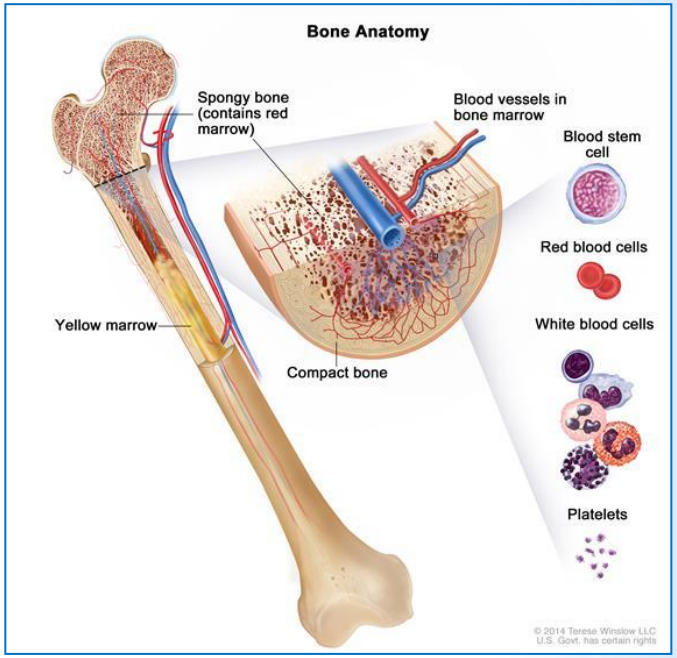
LEUCEMIA MIELOIDE CRONICA

R. Piazza

EMOPOIESI NORMALE

CON IL TERMINE EMOPOIESI SI IDENTIFICA IL PROCESSO DI PRODUZIONE DI TUTTE LE COMPONENTI CORPUSCOLATE DEL SANGUE, IN PARTICOLARE:

- ***ERITROCITI***
- ***LEUCOCITI***
- ***PIASTRINE***

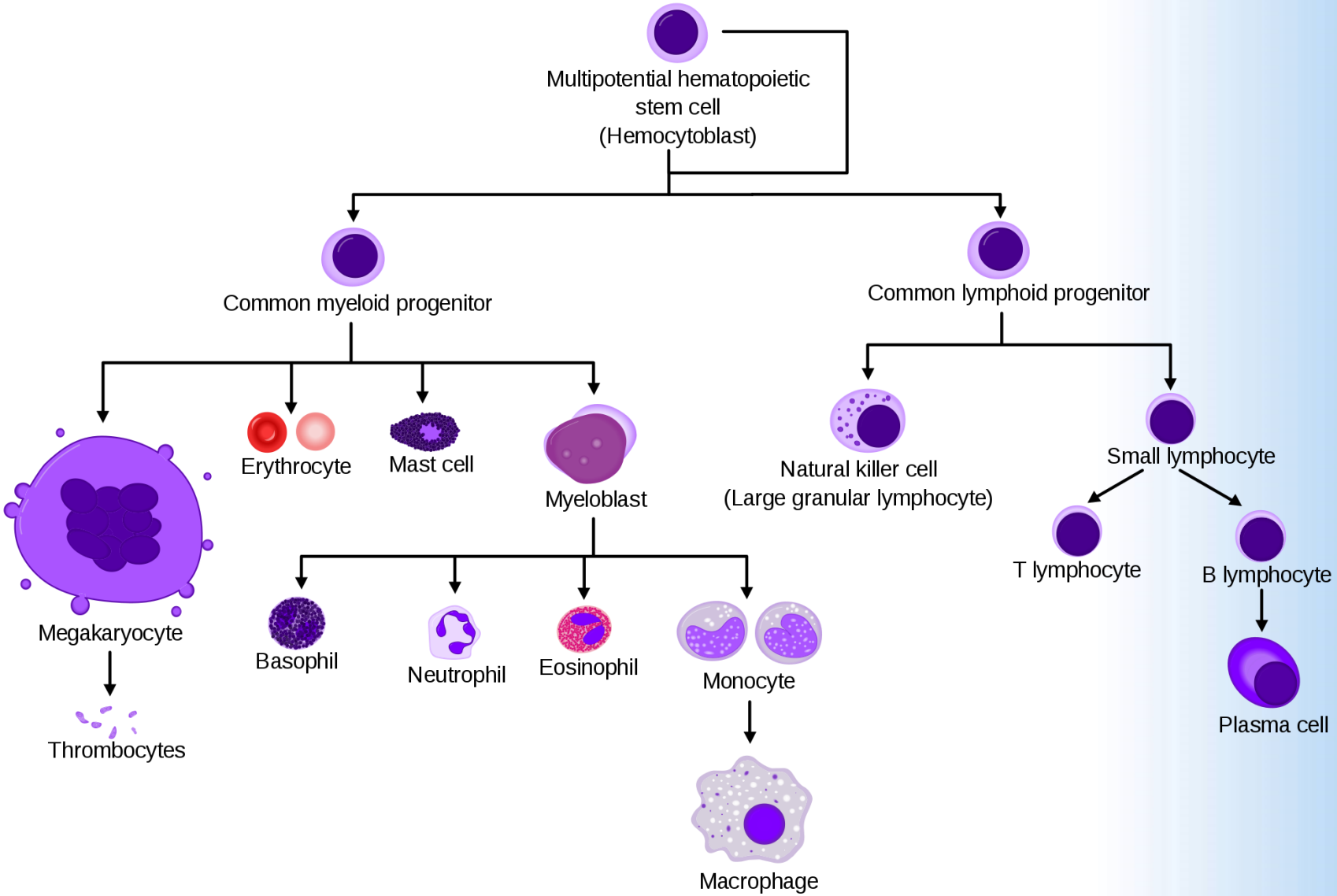


https://www.cancer.gov/publications/dictionaries/cancer-terms/def/bone-marrow

EMOPOIESI NORMALE

IL NOSTRO ORGANISMO SI TROVA IN UNA CONDIZIONE DI EQUILIBRIO DINAMICO IN CUI IL TURNOVER CELLULARE ESTREMAMENTE RAPIDO A CUI E' SOTTOPOSTO E' ESSENZIALE PER LA SOPRAVVIVENZA

CARDINE DI QUESTO SISTEMA DI CONTINUO RINNOVO CELLULARE E' RAPPRESENTATO DALLA CELLULA STAMINALE



By Mikael Häggström and A. Rad - Image:Hematopoiesis

POTENZA CELLULARE

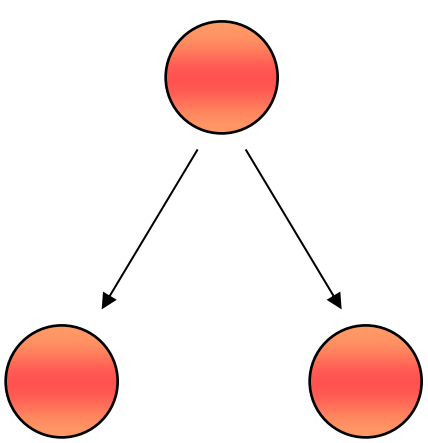
TOTIPOTENZA: *CAPACITA' DI GENERARE TUTTI I TESSUTI EMBRIONALI ED EXTRAEMBRIONALI, TIPICA DELLA MORULA*

PLURIPOTENZA: *CAPACITA' DI GENERARE TUTTI I TESSUTI EMBRIONALI, TIPICA DELLE EMBRYONIC STEM CELLS*

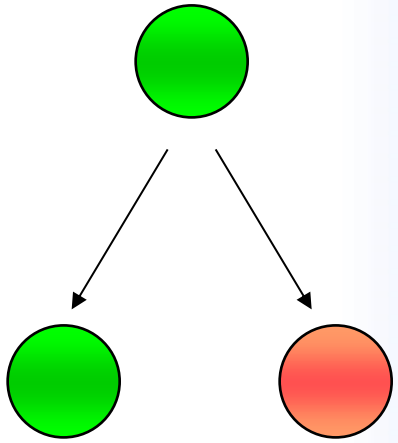
MULTIPOTENZA: *CAPACITA' DI GENERARE MOLTEPLICI TIPI CELLULARI PROVENIENTI DA UN SINGOLO FOGLIETTO, TIPICA DELLE CELLULE STAMINALI TISSUTALI*

UNIPOTENZA: *CAPACITA' DI GENERARE UN UNICO TIPO CELLULARE, TIPICO DEI PROGENITORI*

CELLULE STAMINALI – PROPRIETA’



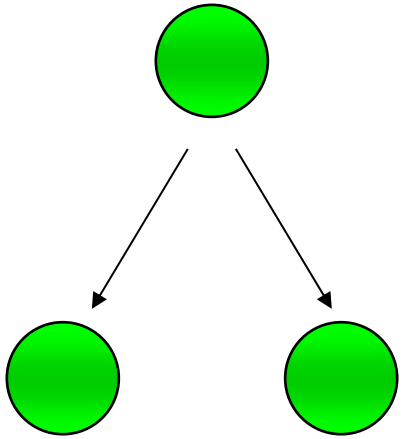
DIVISIONE SIMMETRICA



DIVISIONE ASIMMETRICA

LE CELLULE NON STAMINALI POSSONO DIVIDERSI SIA IN MODO SIMMETRICO CHE ASIMMETRICO

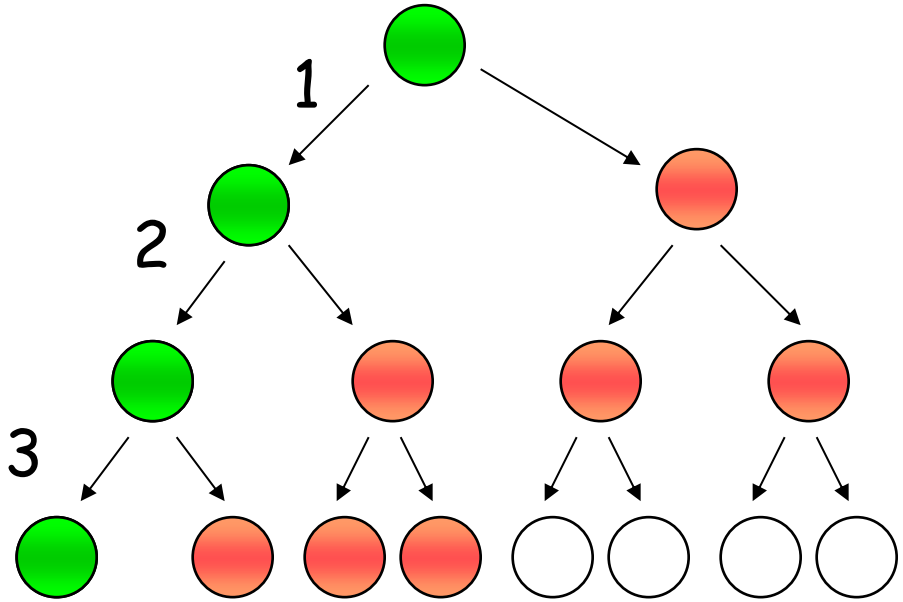
CELLULE STAMINALI – PROPRIETA’



DIVISIONE CELLULARE SIMMETRICA

DIVISIONE SIMMETRICA: E’ ATTIVA QUANDO E’ NECESSARIO RICOSTITUIRE IL POOL DI CELLULE STAMINALI

CELLULE STAMINALI – PROPRIETA’



LE CELLULE NON STAMINALI HANNO UN CICLO VITALE LIMITATO

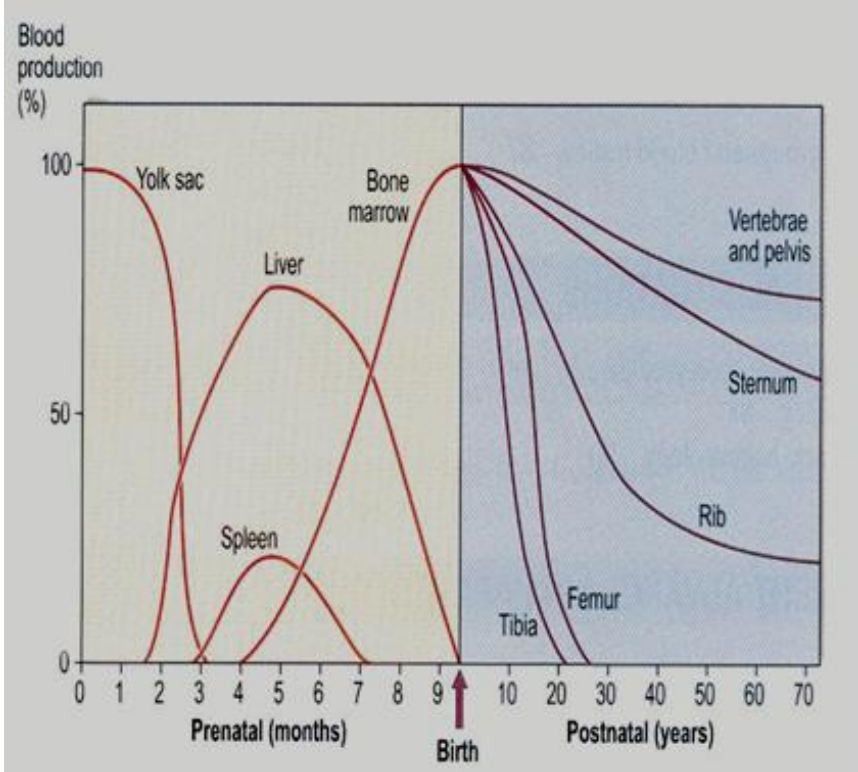
LE CELLULE STAMINALI SONO AL CONTRARIO ‘IMMORTALI’

SISTEMA EMATOPOIETICO

SACCO VITELLINO

FEGATO E MILZA

MIDOLLO OSSEO

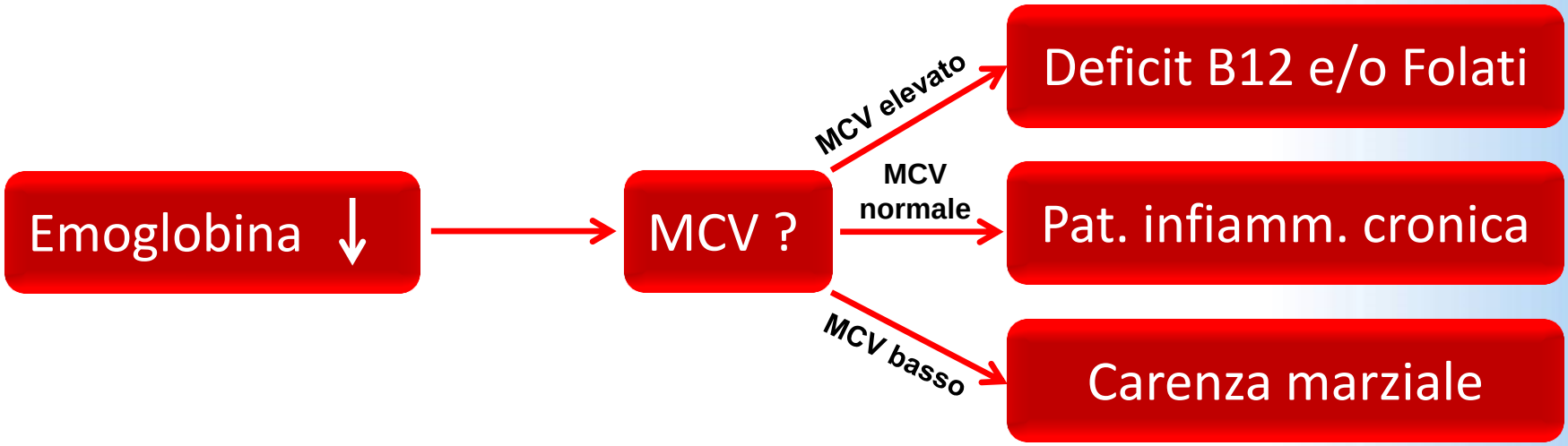


PRINCIPALI PARAMETRI EMATOLOGICI

	Valori convenzionali	Valori SI
Ematocrito: uomo	45-52%	0.45-0.52
donna	37-48%	0.37-0.48
Emoglobina: uomo	13-18 g/100 ml	8.1-11.2 mmol/l
donna	12-16 g/100 ml	7.4-9.9 mmol/l
Leucociti	4300-10800/mm^3	4.3-10.8 x 10^9/l
Eritrociti	4.2-5.9 milioni/mm^3	4.2-5.9 x 10^{12}/l
Volume corpuscolare medio (MCV)	86-98 μm^3	86-98 fl
Emoglobina corpuscolare media (MCH)	27-32 pg/mm^3 eritrocitario	1.7-2.0 pg/cellula
Concentrazione emoglobinica corpuscolare media (MCHC)	32-36%	0.32-0.36
Piastrine	150.000-350.000/mm^3	150-350 x 10^9/l
Reticolociti	0.5-2.5% eritrociti	0.005-0.025
Sideremia	50-150 µg/100 ml	9.0-26.9 µmol/l
Aptoglobina	40-336 mg/100 ml	0.4-3.36 g/l
Vitamina B_{12}	205-876 pg/ml	150-647 pmol/l
Acido folico	> 3.3 ng/ml	> 7.3 nmol/l
Elettroforesi per: emoglobina A_2	> 3.0%	0.015-0.035
emoglobina F	< 2%	< 0.02
Enzimi eritrocitari:		
G6PD	5-15 U./g Hb	5-15 U./g
PK	13-17 U./g Hb	13-17 U./g
Ferritina	13-20 ng/ml	5.2-8 nmol/l

ANEMIA

La parola ‘anemia’ deriva da un termine greco che significa ‘assenza di sangue’. Si tratta di una condizione clinica caratterizzata dalla diminuzione della quantità totale di emoglobina trasportata dai globuli rossi al di sotto dei valori di riferimento



ESAME EMOCROMOCITOMETRICO

Emocromo: valori normali

Fornisce informazioni circa le tre filiere circolanti: Quantitative (numeriche)

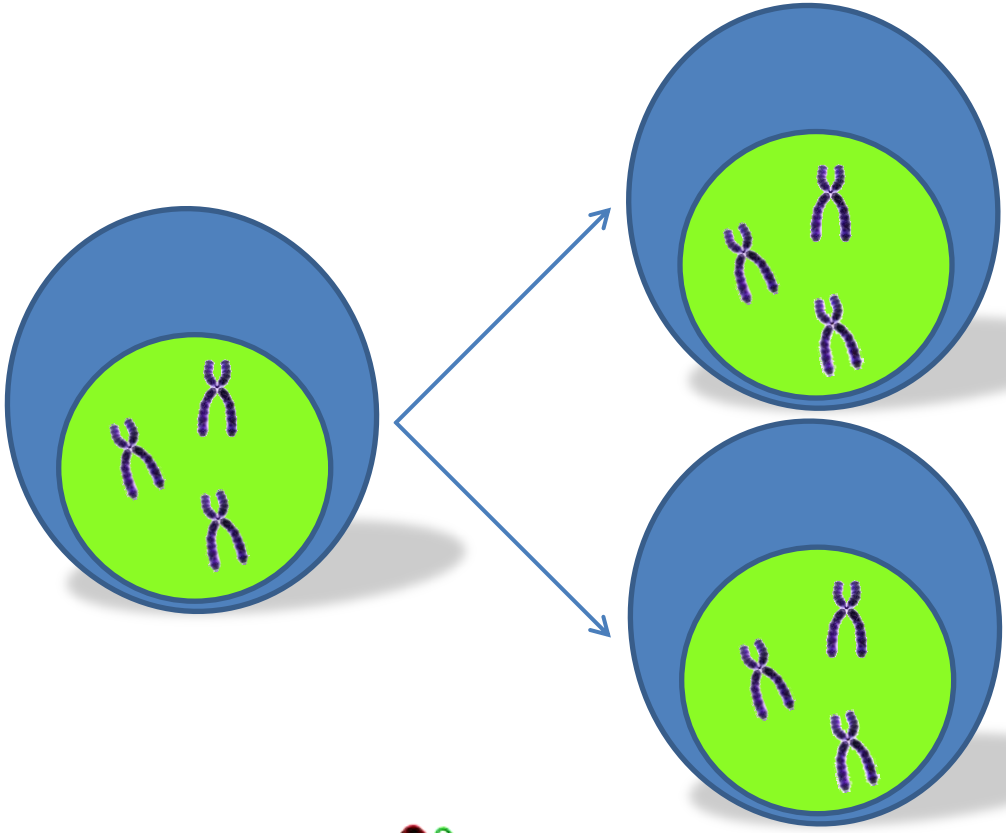
Morfologiche

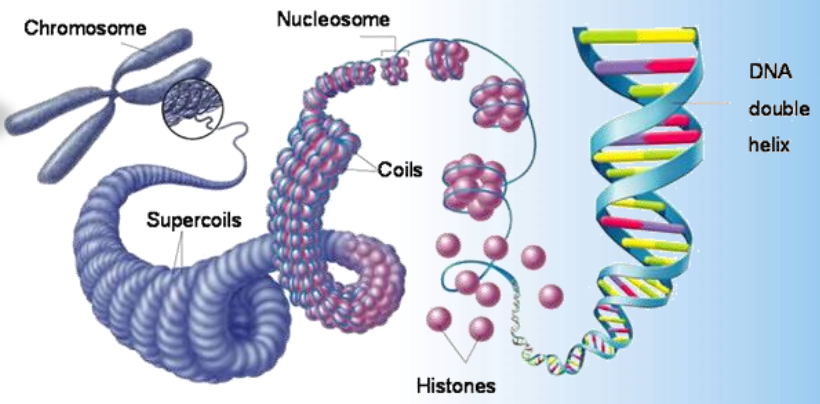
Formula leucocitaria

CELLULE	DIMENSIONI	VALORE ASSOLUTO	FORMULA %
Eritrociti	**7 – 8 µ**	**4.200.000-5.400.000/mm³**	
Leucociti		**4500 – 8500/mm3**	
PMN neutrofili	**10-15 µ**	**2700-6000/mm3**	**60-70%**
eosinofili	**10-15 µ**	**45-260/mm3**	**1-3%**
basofili	**10-15 µ**	**20-85/mm3**	**0.5-1%**
Monociti	**10-15 µ**	**135-510/mm3**	**3-6%**
Linfociti	**10-15 µ**	**900-3000/mm3**	**20-35%**
Piastrine	**2-3 µ**	**200.000 – 400.000/mm3**	

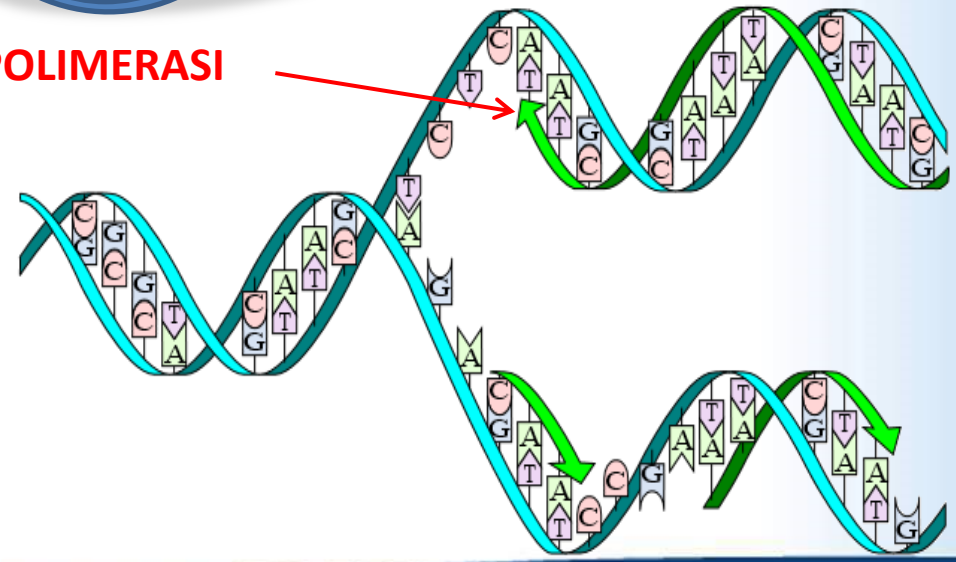
PRODUZIONE DELLE CELLULE DEL SANGUE – QUALCHE NUMERO

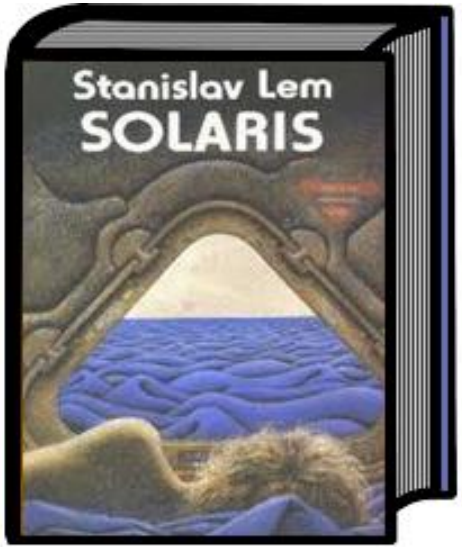
Tipo Cellulare	Vita media	Produzione (cellule/die)	Produzione (cellule/sec)	Produzione (Kg/anno)
Globuli rossi	**100 giorni**	**2×10^{11}**	**2.3 milioni**	**7.3**
Neutrofili	**6 ore**	**3×10^{10}**	**350000**	**10.9**
Piastrine	**7 giorni**	**1×10^{11}**	**1.2 milioni**	**4.6**
Linfociti	**10 giorni**	**1×10^{10}**	**116000**	**3.7**
			Totale Annuo	26.5 Kg





DNA POLIMERASI



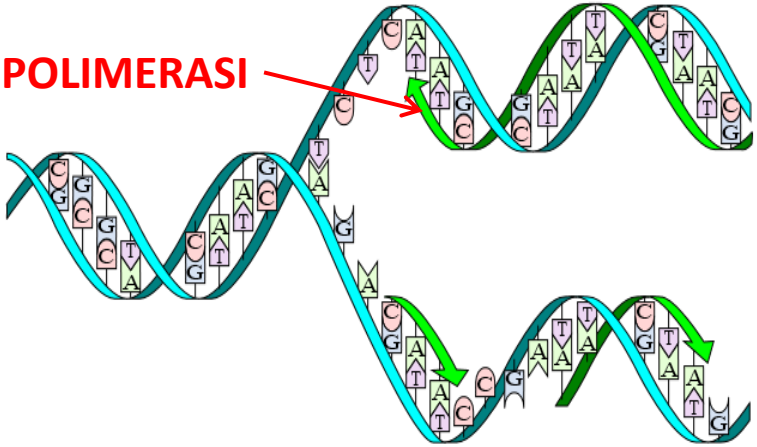


LIBRO: 300 PAGINE

1500 CARATTERI PER PAGINA

450000 CARATTERI

DNA POLIMERASI

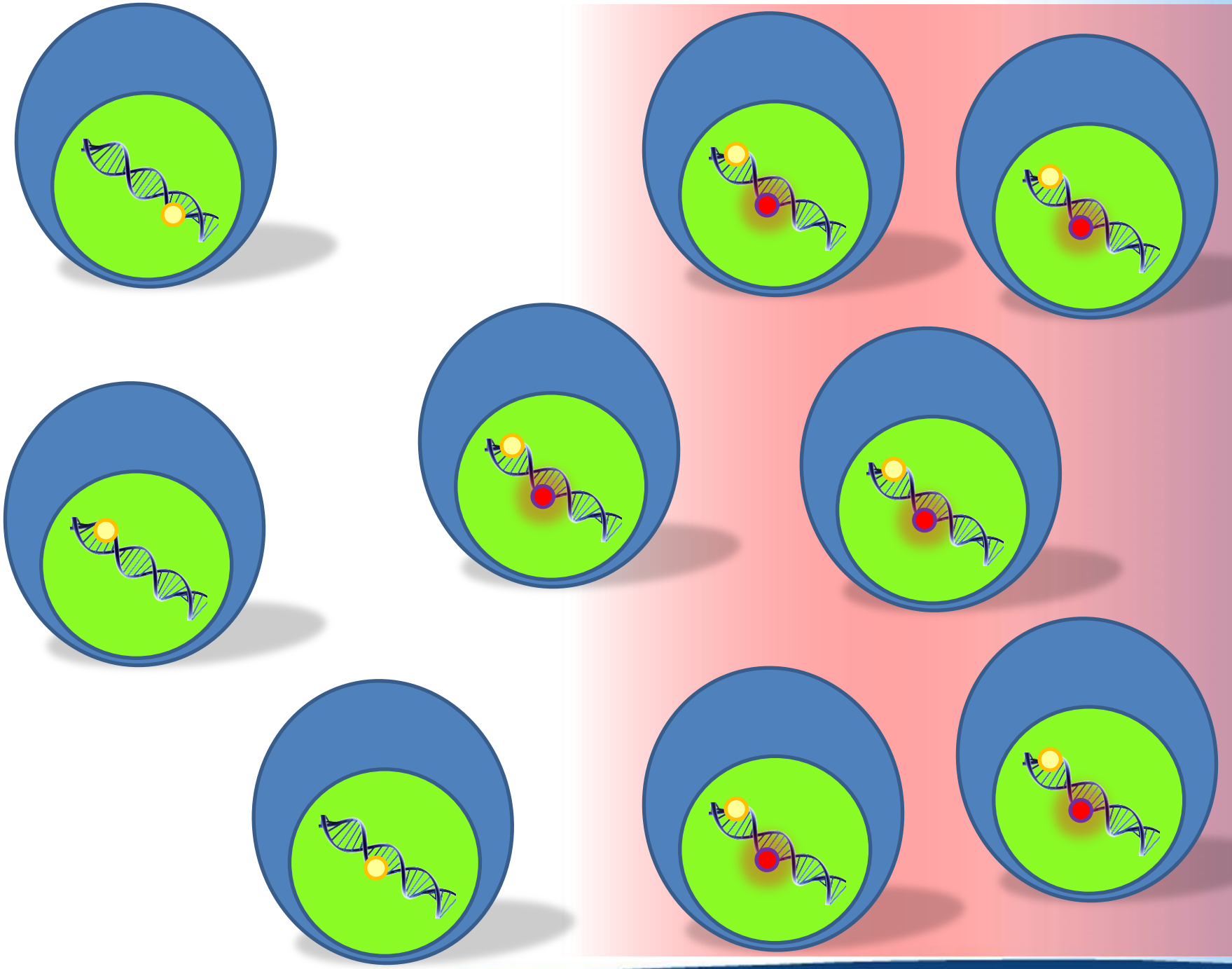


DNA GENOMICO UMANO:

6000000000 DI 'CARATTERI' (BASI)

L'EQUIVALENTE DI 13000 LIBRI!!

TURN-OVER CELLULARE: OLTRE 100 MILIARDI DI CELLULE AL GIORNO.
LE DNA POLIMERASI DEVONO LEGGERE E 'COPIARE' IN MEDIA 600 MILIARDI DI MILIARDI DI BASI AL GIORNO: OLTRE UN MILIONE DI MILIARDI DI LIBRI !!



LEUCEMIE

INSIEME DI PATOLOGIE CLONALI CARATTERIZZATE DALLA PROLIFERAZIONE NEOPLASTICA DI UNA CELLULA STAMINALE EMATOPOIETICA CHE SI TRADUCE IN UNA PRODUZIONE INCONTROLLATA DI GLOBULI BIANCHI O DI LORO PRECURSORI

- ***LEUCEMIA MIELOIDE CRONICA***
- ***LEUCEMIA LINFATICA CRONICA***
- ***LEUCEMIA MIELOIDE ACUTA***
- ***LEUCEMIA LINFOBLASTICA ACUTA***

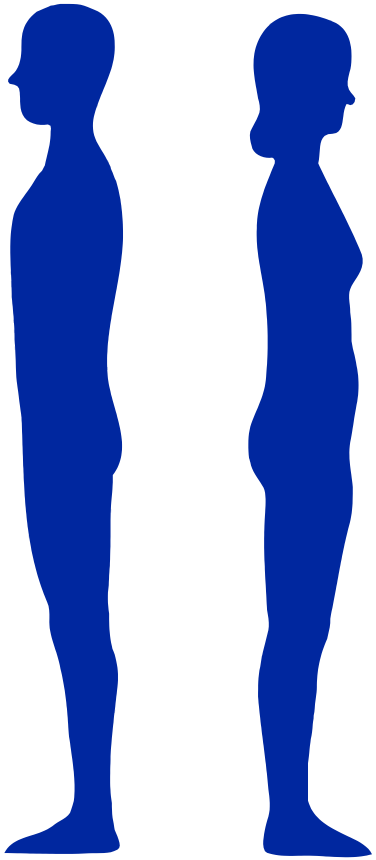
LEUCEMIE – INCIDENZA

INCIDENZA PER TIPO DI LEUCEMIA SU 100000 ABITANTI

GLOBALE	*10–14*
CML	*2–3*
CLL	*4–5*
AML	*3–4*
ALL	*1–2*

LEUCEMIE – MORTALITA’

Lung and bronchus	33%
Prostate	10%
Colon and rectum	10%
Pancreas	5%
Leukemia	4%
Non-Hodgkin’s lymphoma	4%
Esophagus	4%
Bile duct	3%
Urinary bladder	3%
Kidney	3%
All other sites	21%



26%	Lung and bronchus
15%	Breast
10%	Colon and rectum
6%	Pancreas
6%	Ovary
4%	Leukemia
3%	Non-Hodgkin’s lymphoma
3%	Uterine corpus
2%	Brain/nervous system
2%	Multiple myeloma
22%	All other sites

LEUCEMIA MIELOIDE CRONICA

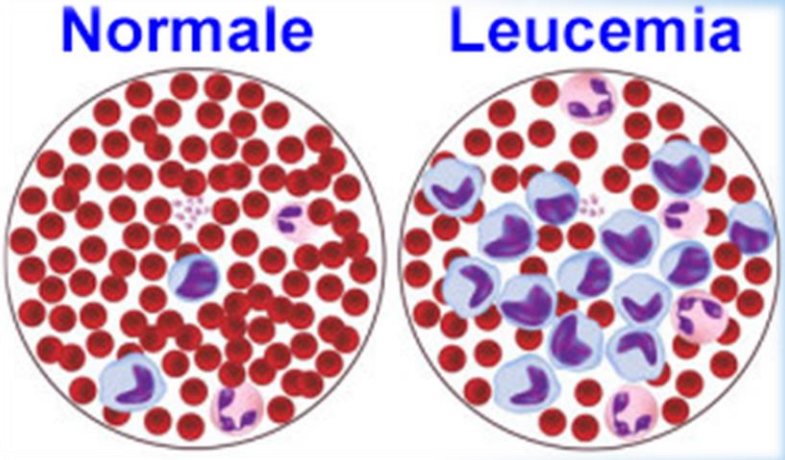
LEUCEMIA MIELOIDE CRONICA

Rudolf Virchow ‘Il padre della patologia’

Siamo nani sulle spalle di giganti

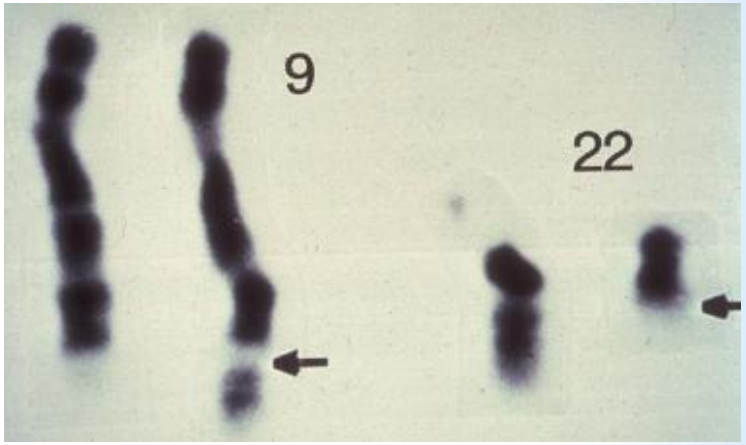
Bernardo di Chartres

- **1847: VIRCHOW NOTA COME IN PAZIENTI AFFETTI DA UNA PATOLOGIA SCONOSCIUTA E INVARIABILMENTE MORTALE IL SANGUE AVESSE PERSO IL SUO NORMALE COLORE ROSSO, PER ACQUISIRE UN COLORE BIANCASTRO**
- **VIRCHOW CONIA IL TERMINE: ‘LEUCEMIA’**



LEUCEMIA MIELOIDE CRONICA

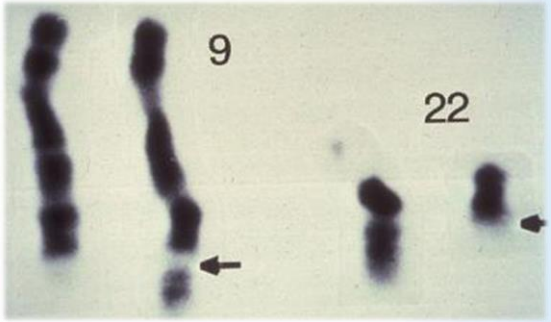
Peter Nowell e David Hungerford
Philadelphia, 1959

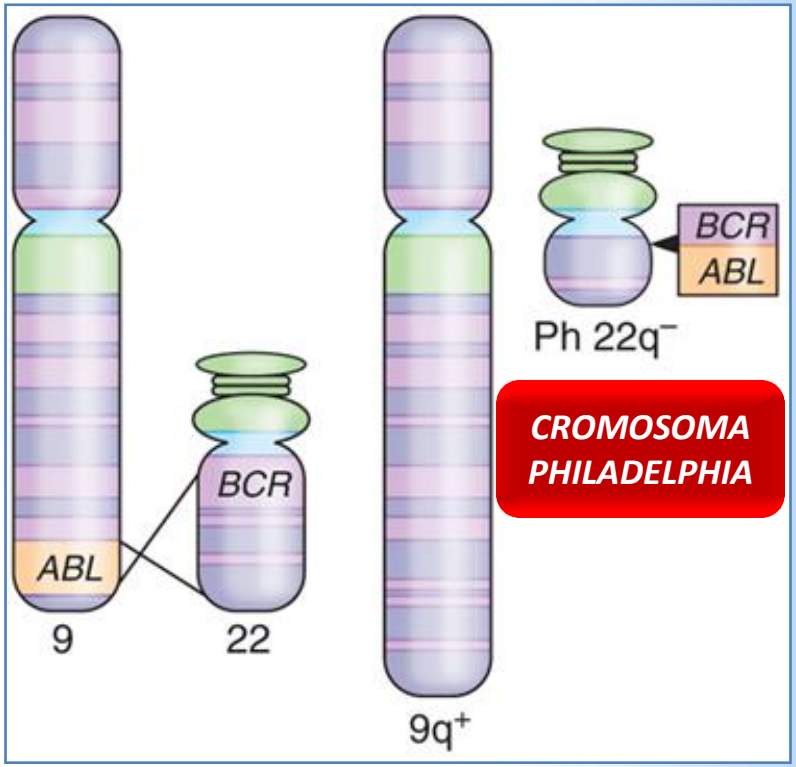


LEUCEMIA MIELOIDE CRONICA

Janet Rowley, 1973

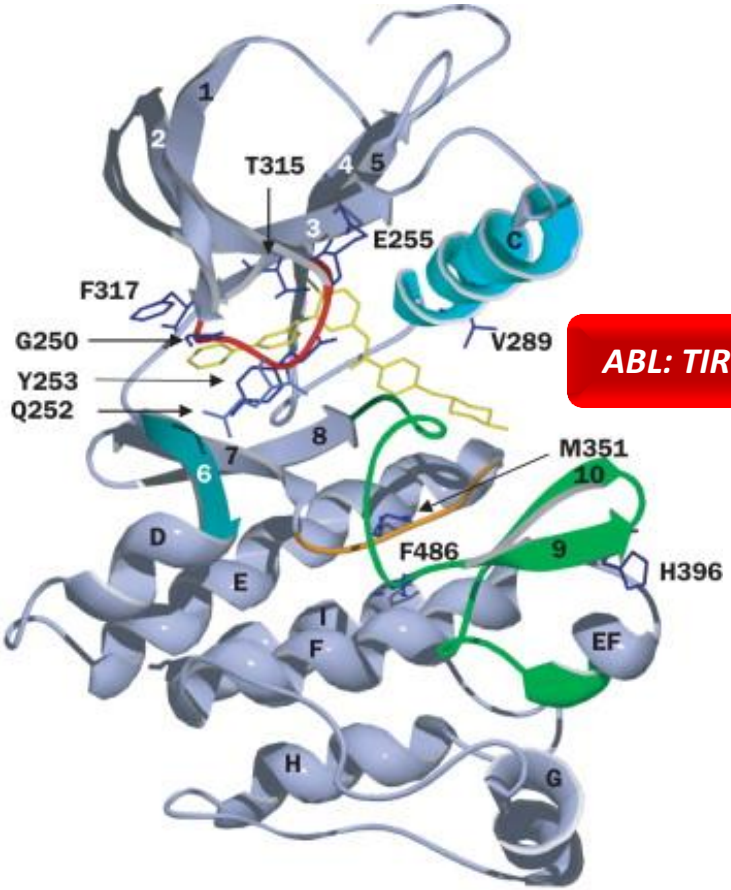
Rowley JD (1973). "Letter: A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining". Nature. ***243*** *(5405): 290–3.*



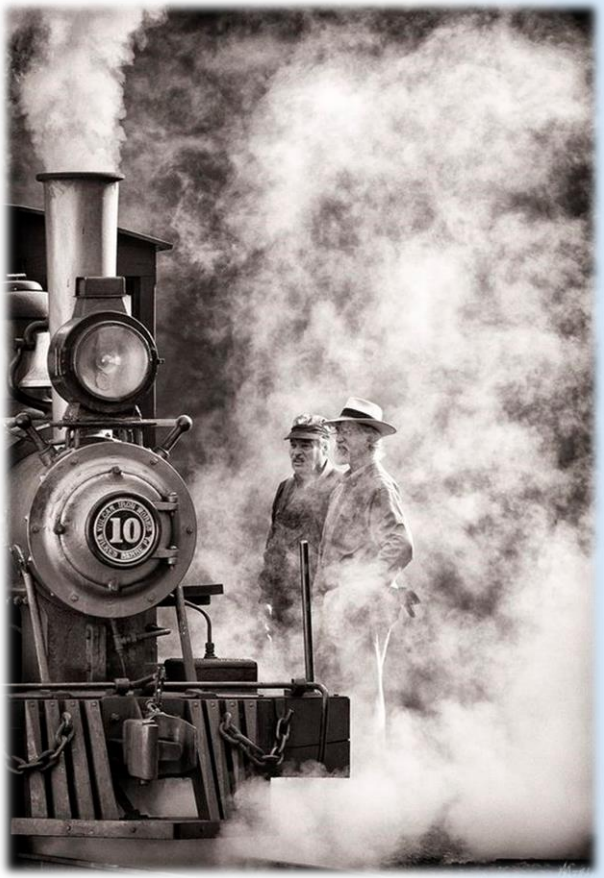


LEUCEMIA MIELOIDE CRONICA: FUSIONE BCR-ABL

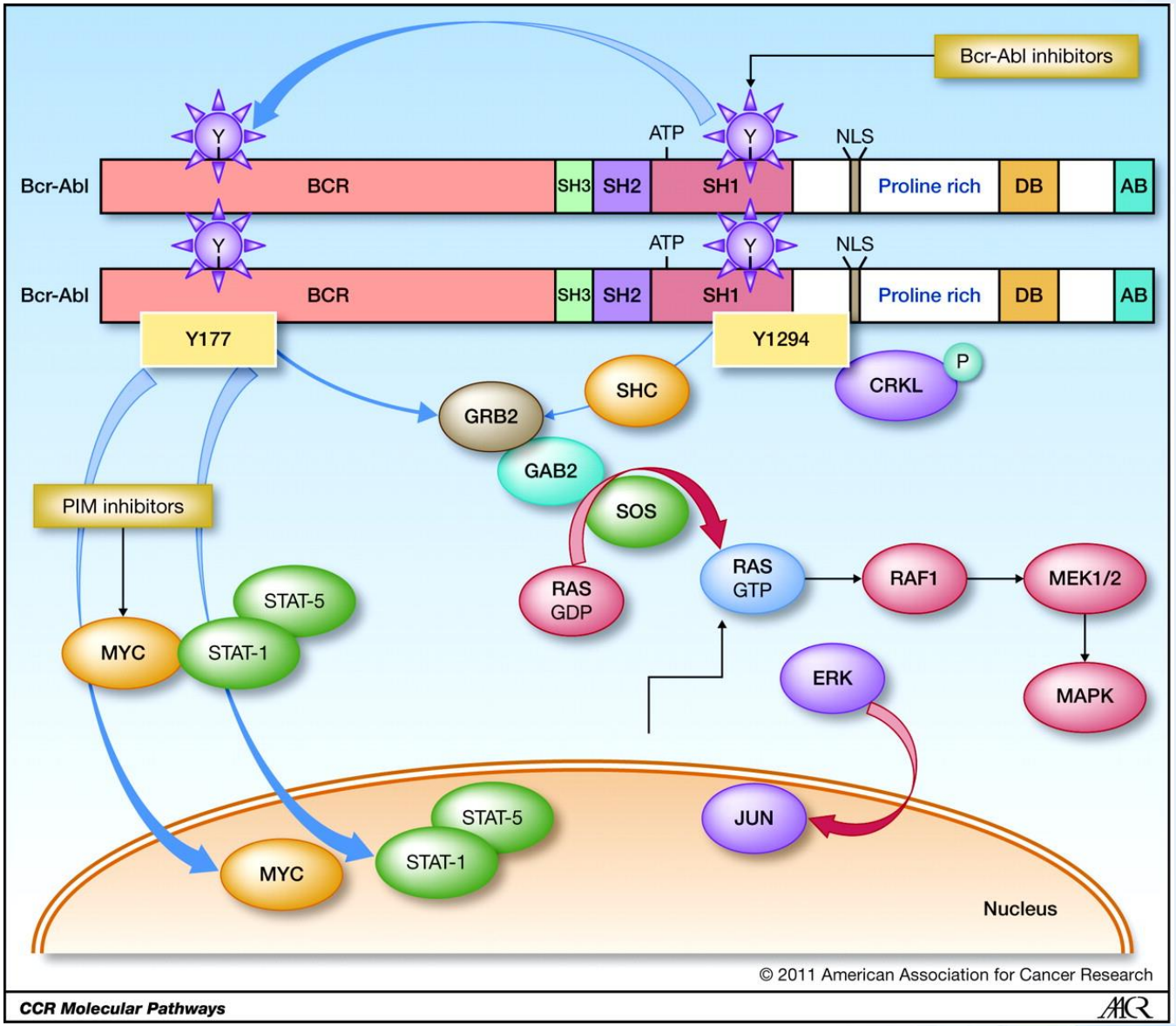
Chr.22 | Chr. 9 | Gene di Fusione



ABL: TIROSIN-CHINASI



LEUCEMIA MIELOIDE CRONICA: FUSIONE BCR-ABL



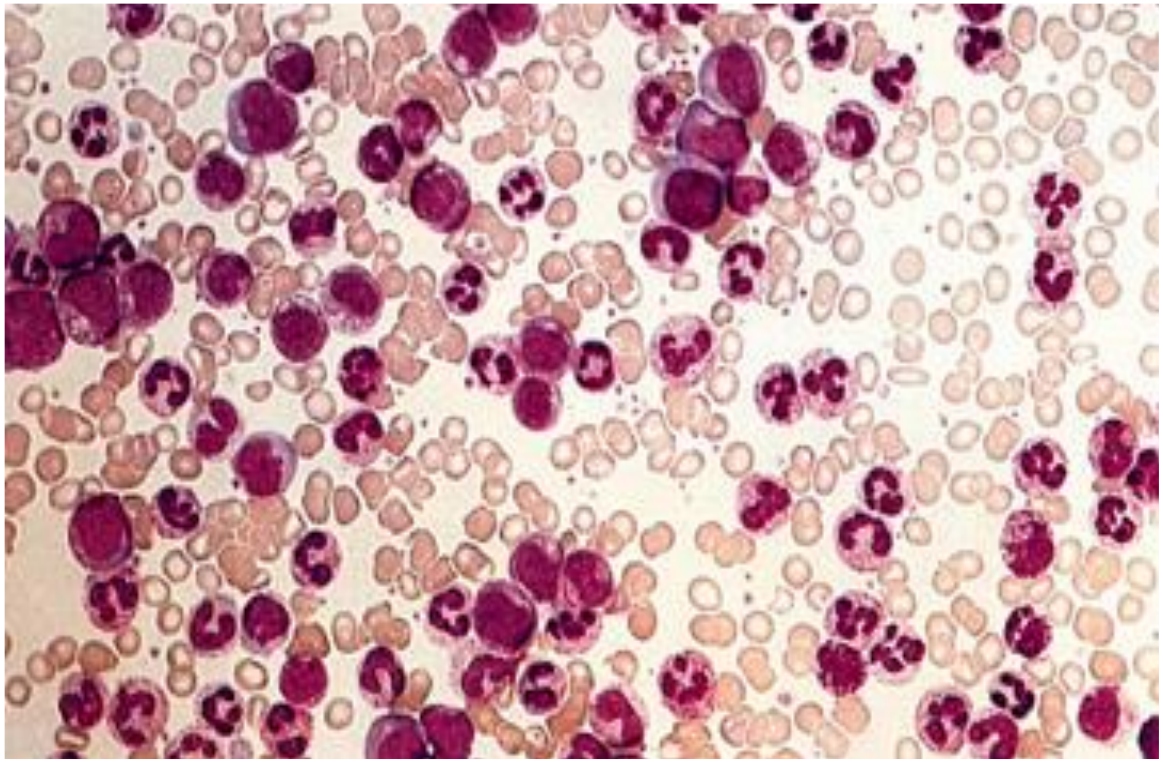
IL CROMOSOMA PHILADELPHIA NELLE LEUCEMIE

Leucemia	% di pazienti Ph+
CML	95
ALL (Adult)	15–30
ALL (Pediatric)	5
AML	2

Faderl S et al. *Oncology (Huntingt)*. 1999;13:169-184

DIAGNOSI

CML – STRISCIO DA SANGUE PERIFERICO



CML

Hoffbrand AV, Pettit JE, eds. In: *Color Atlas of Clinical Hematology*. 2nd ed. Mosby-Wolfe; 1994:198

CML – EPIDEMIOLOGIA

Età mediana all'esordio: 45 - 55 anni

L'incidenza aumenta con l'età: 12% - 30% dei pazienti ha un'età superiore ai 60 anni

Il rapporto maschi / femmine è pari a: 1.3:1

CML – PRESENTAZIONE CLINICA

Nel 50% dei pazienti la diagnosi avviene a causa di esami del sangue di routine

L’85% dei pazienti è diagnosticato in fase iniziale, anche nota come ‘fase cronica’

CML – PRESENTAZIONE CLINICA

SINTOMI COMUNI

ASTENIA

ANORESSIA

PERDITA DI PESO

DISPEPSIA

SEGNI COMUNI

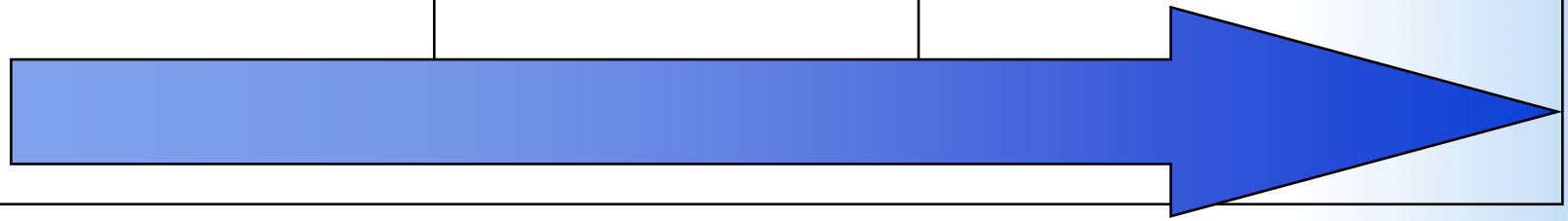
SPLENOMEGALIA

LABORATORIO

LEUCOCITOSI PREVALENTEMENTE NEUTROFILA, TROMBOCITOSI, BASOFILIA, ANEMIA

CML – DECORSO CLINICO – FASI DELLA MALATTIA

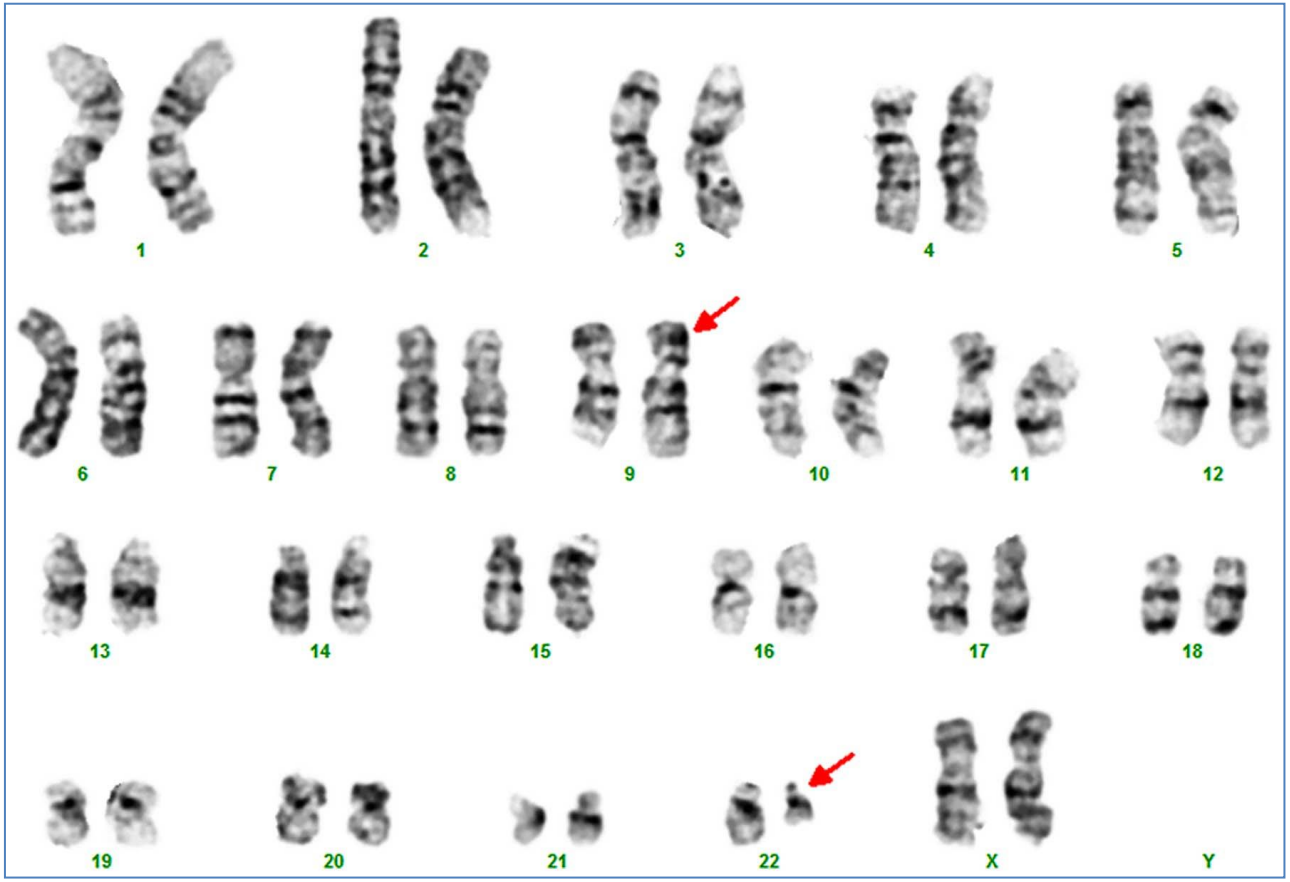
Fase cronica	Fasi avanzate	
	Fase accelerata	Fase blastica (crisi blastica)
Durata mediana in assenza di terapia: 4-6 anni	Durata mediana: fino ad un anno	Fase terminale: sopravvivenza 3-8 mesi

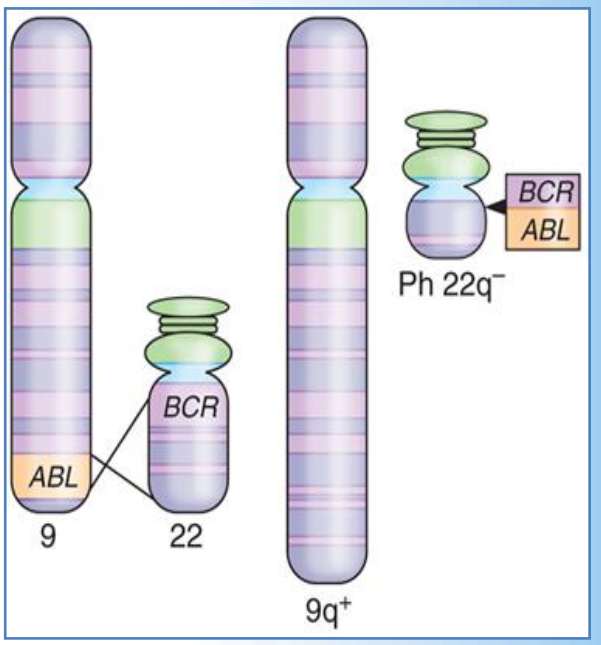


CML – PARAMETRI DI LABORATORIO PER FASE DI MALATTIA

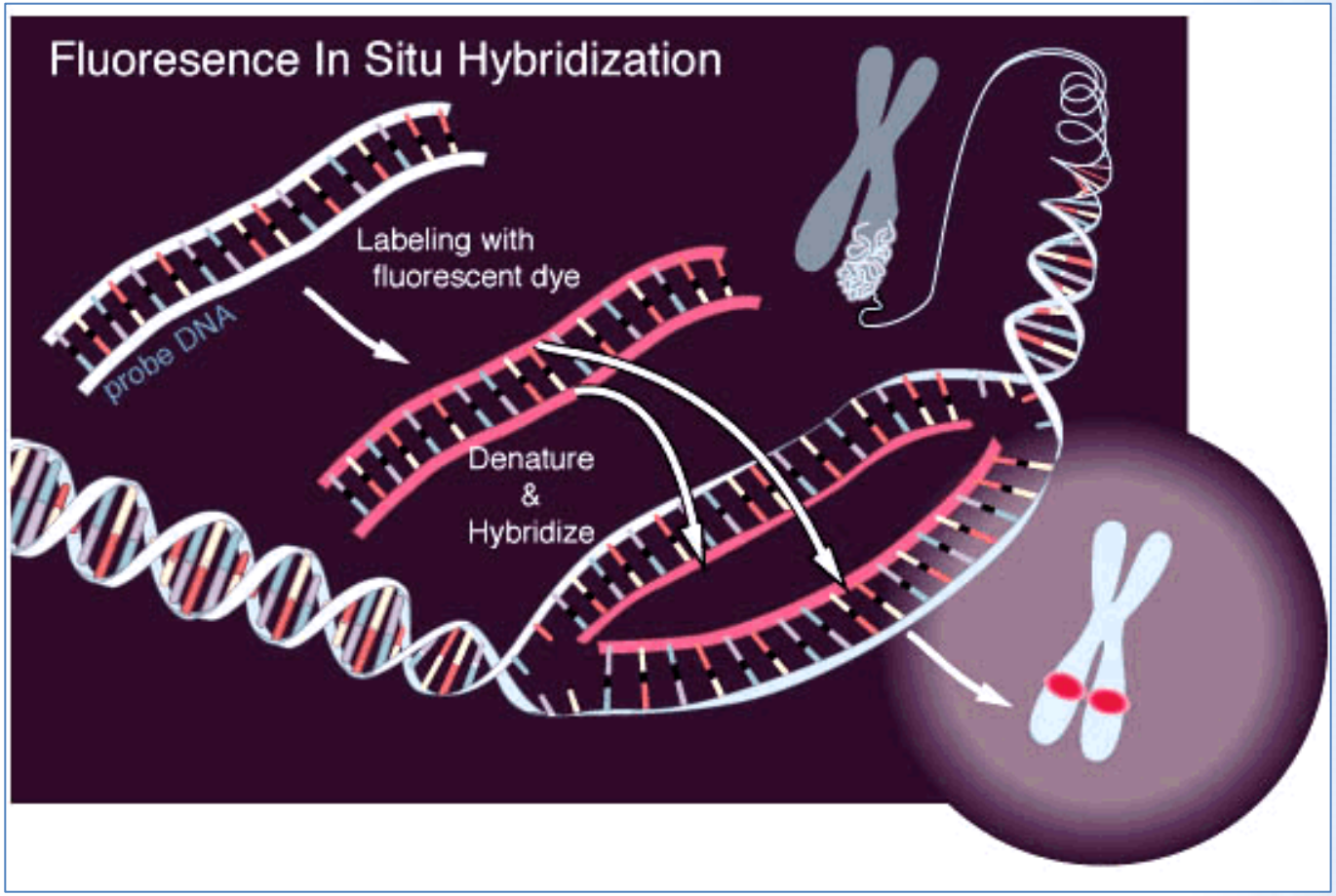
Parametro	Fase cronica	Fase accelerata	Crisi Blastica
Bianchi	≥20 x 10^9/L	—	—
Blasti	3%–10%	≥15%	≥30%
Basofili		≥20%	—
Piastrine	Elevate o normali	o -	—
Midollo	Iperplasia mieloide		
Citogenetica	Ph+	Ph+	Ph+
BCR-ABL	+	+	+

CML – CITOGENETICA

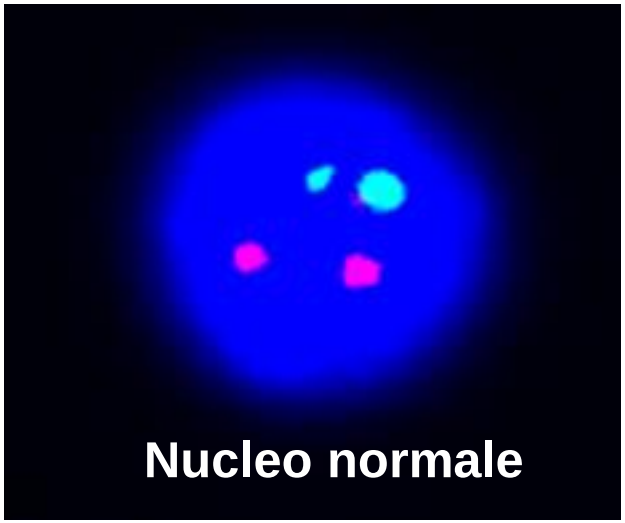


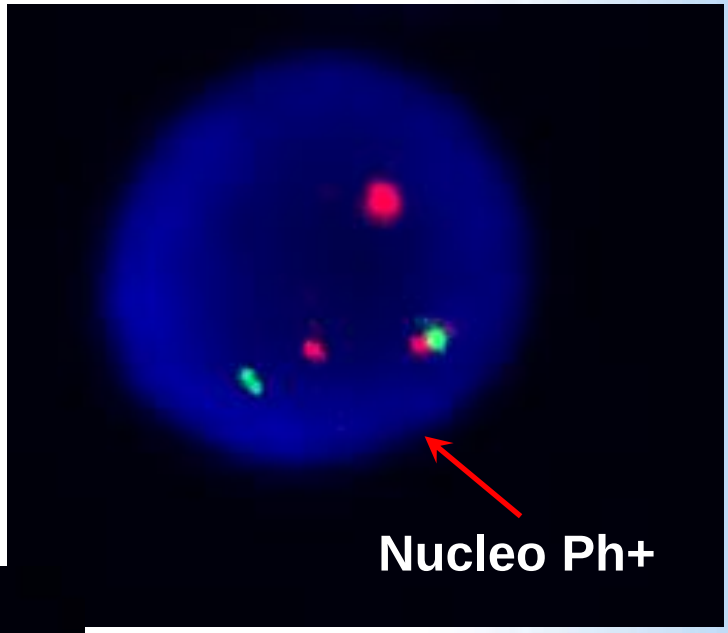


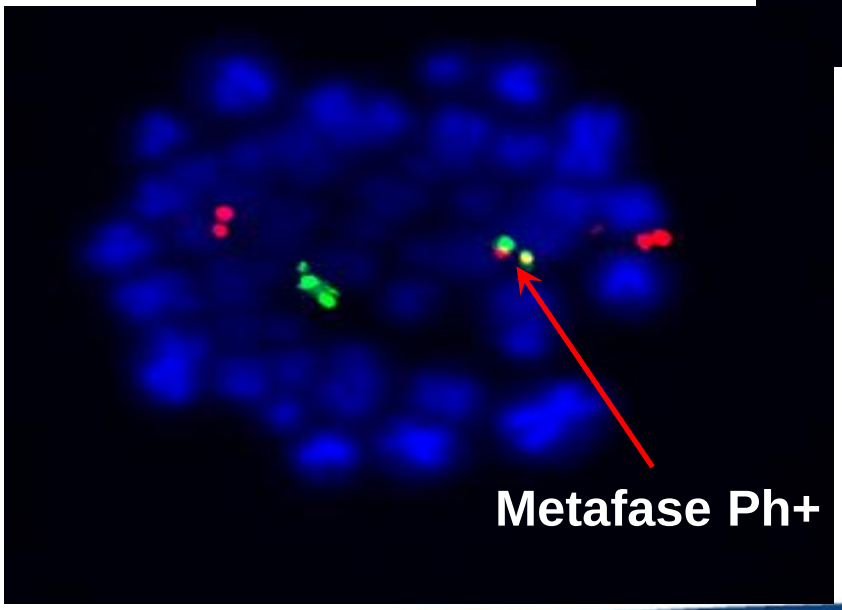
CML – FISH


Fluoresence In Situ Hybridization
Labeling with
fluorescent dye
probe DNA
Denature
&
Hybridize

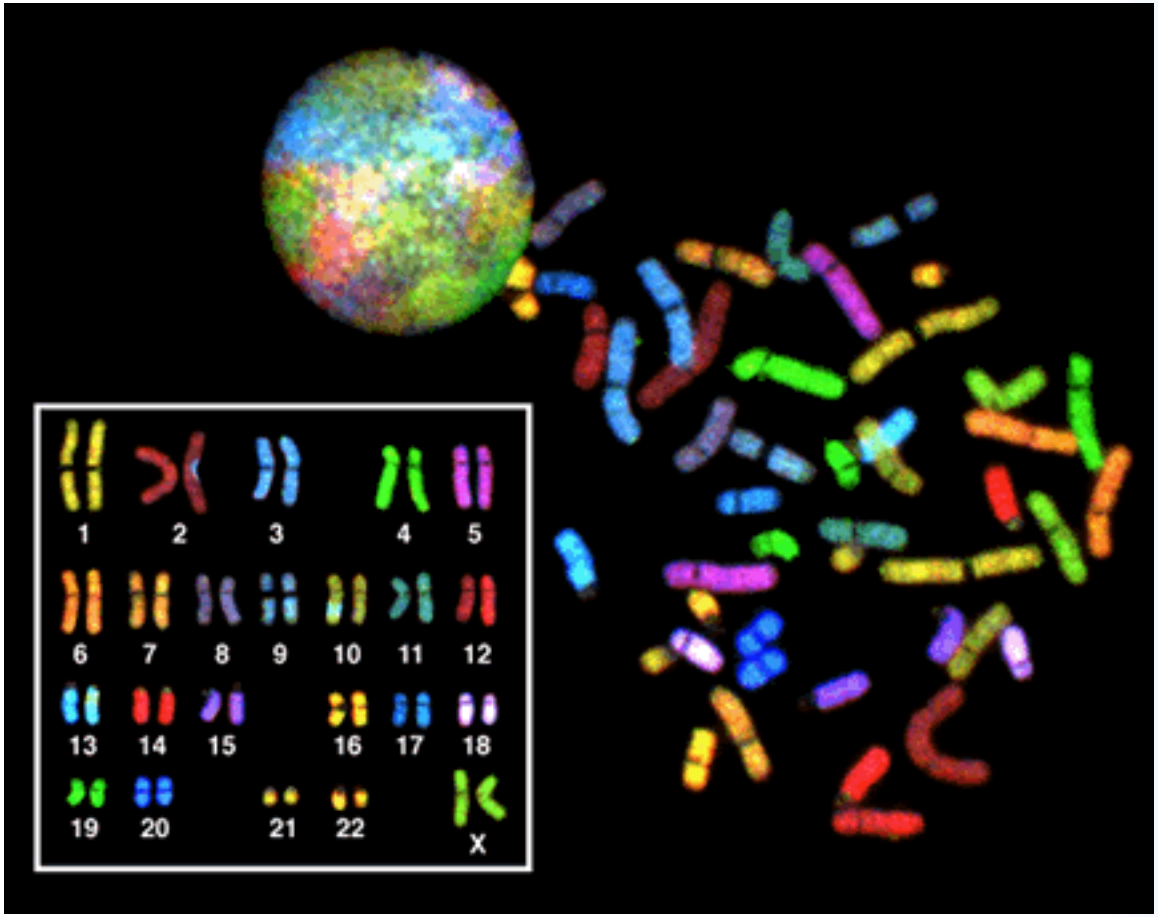
CML – FISH



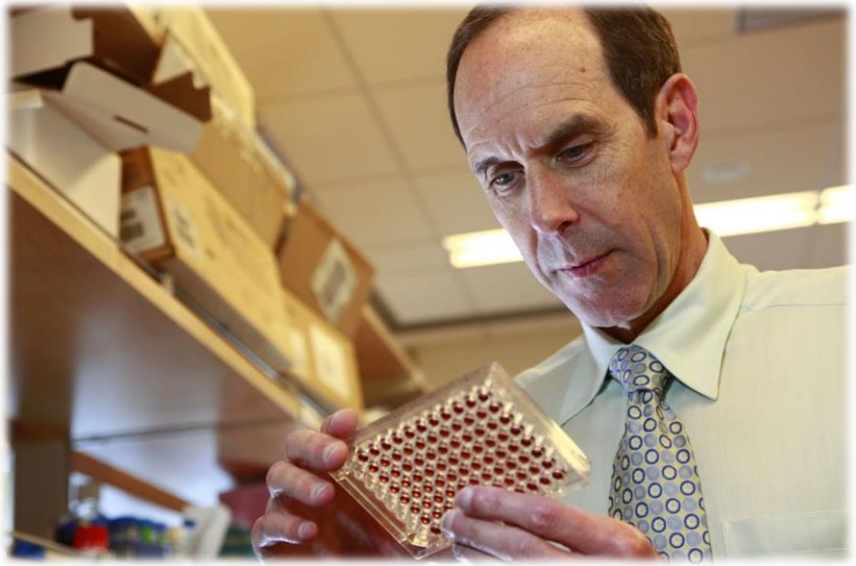




CML – FISH

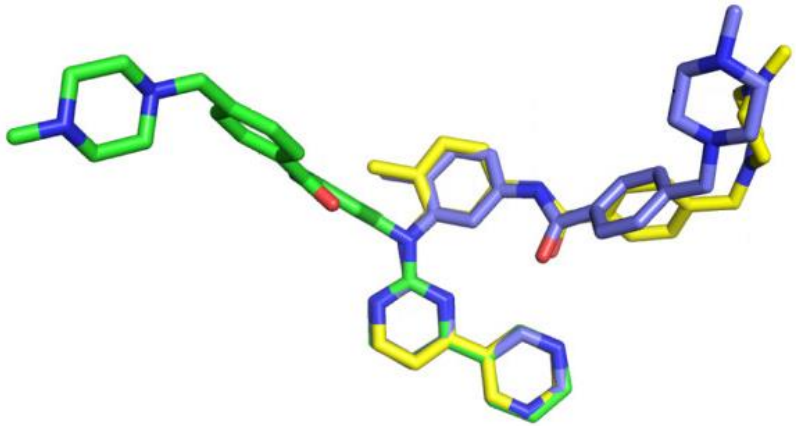


LEUCEMIA MIELOIDE CRONICA: TERAPIA



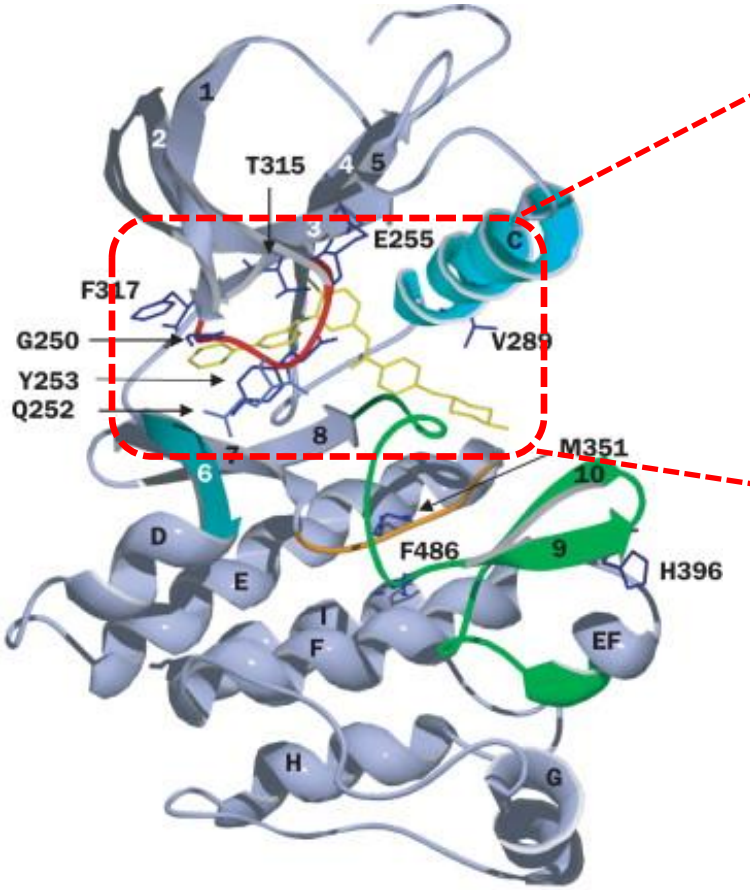
Brian Druker

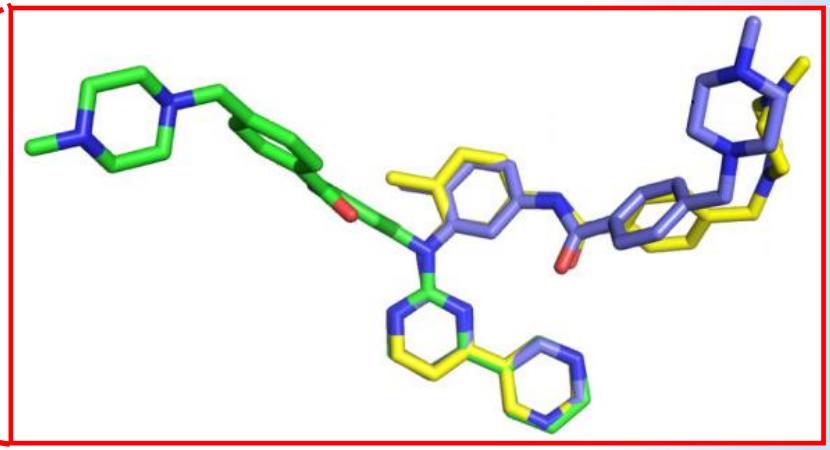
Nicholas Lydon

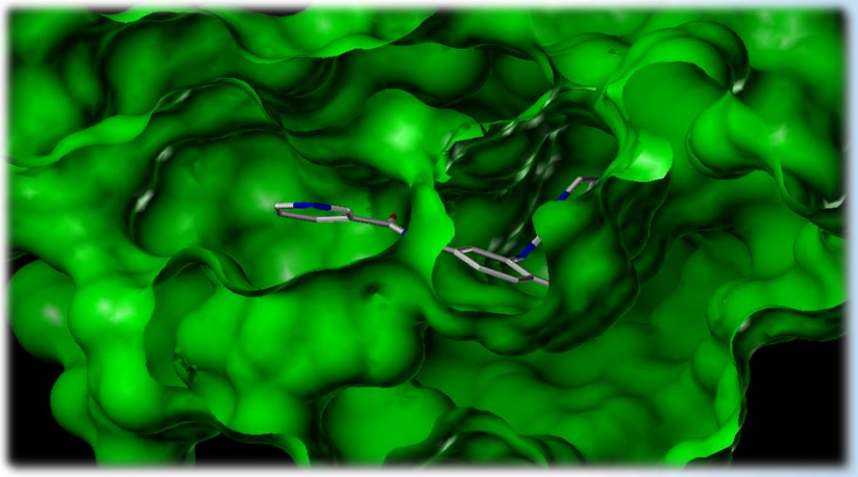


IMATINIB

LEUCEMIA MIELOIDE CRONICA: TERAPIA

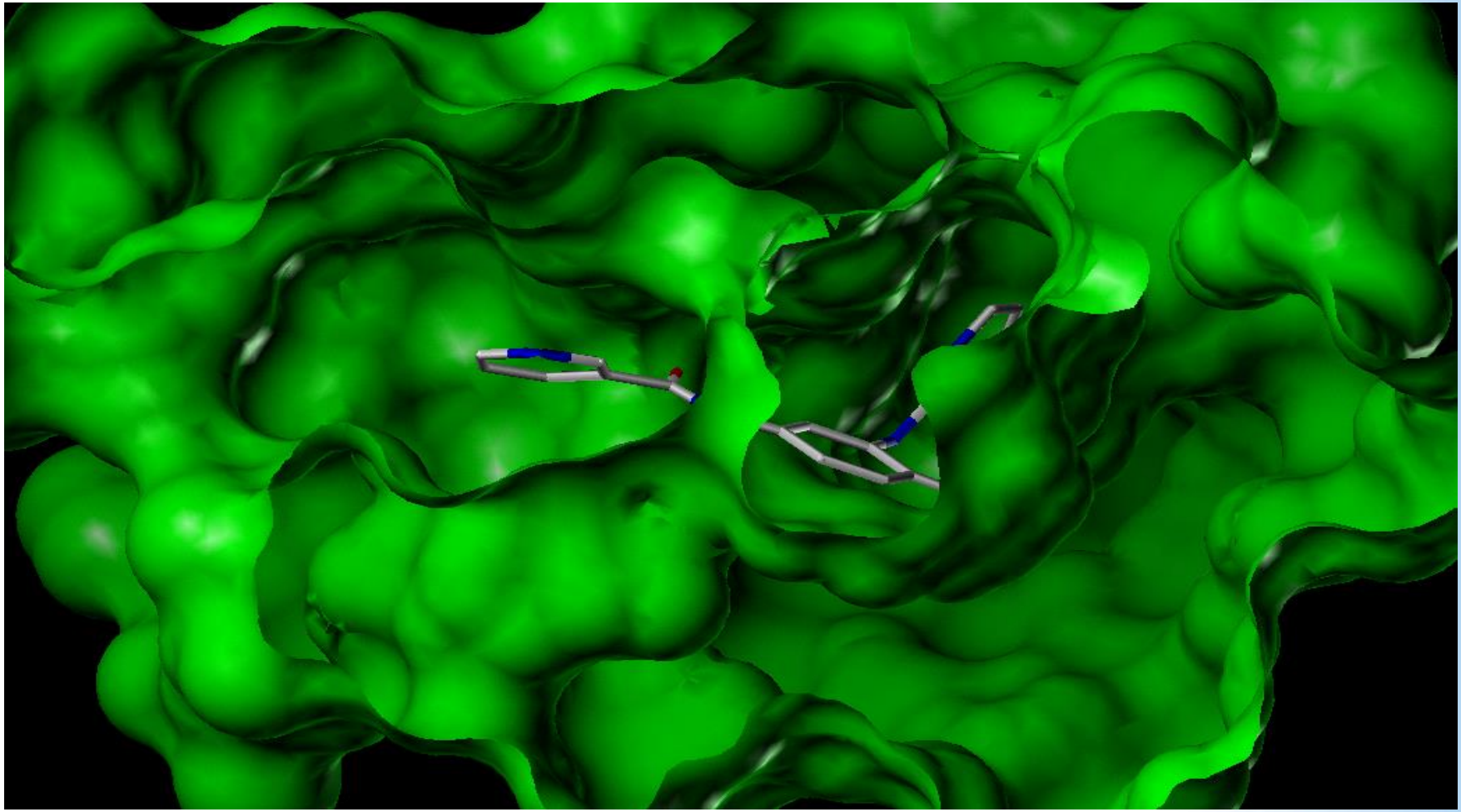






Gene di Fusione

ABL ED IMATINIB



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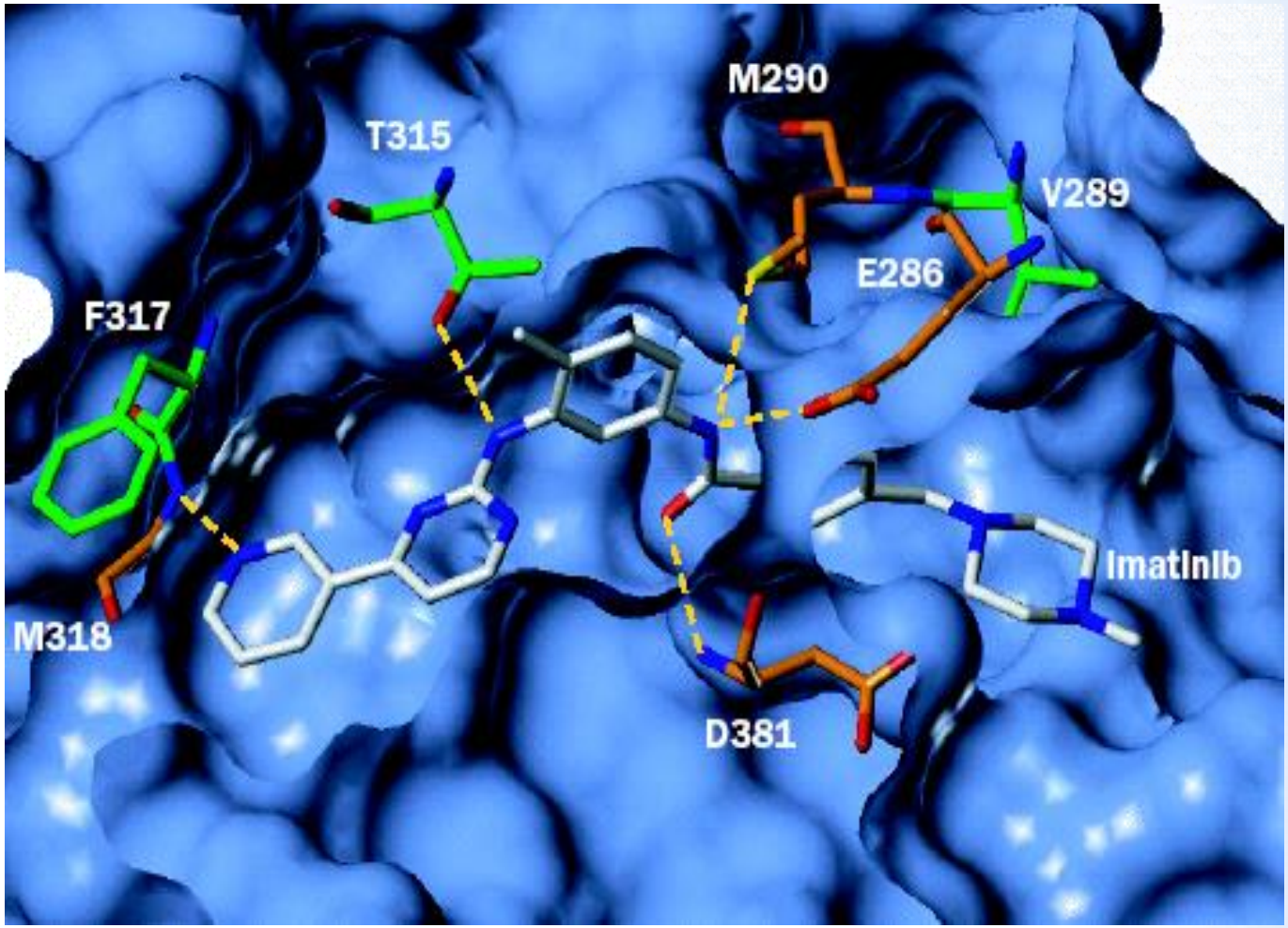
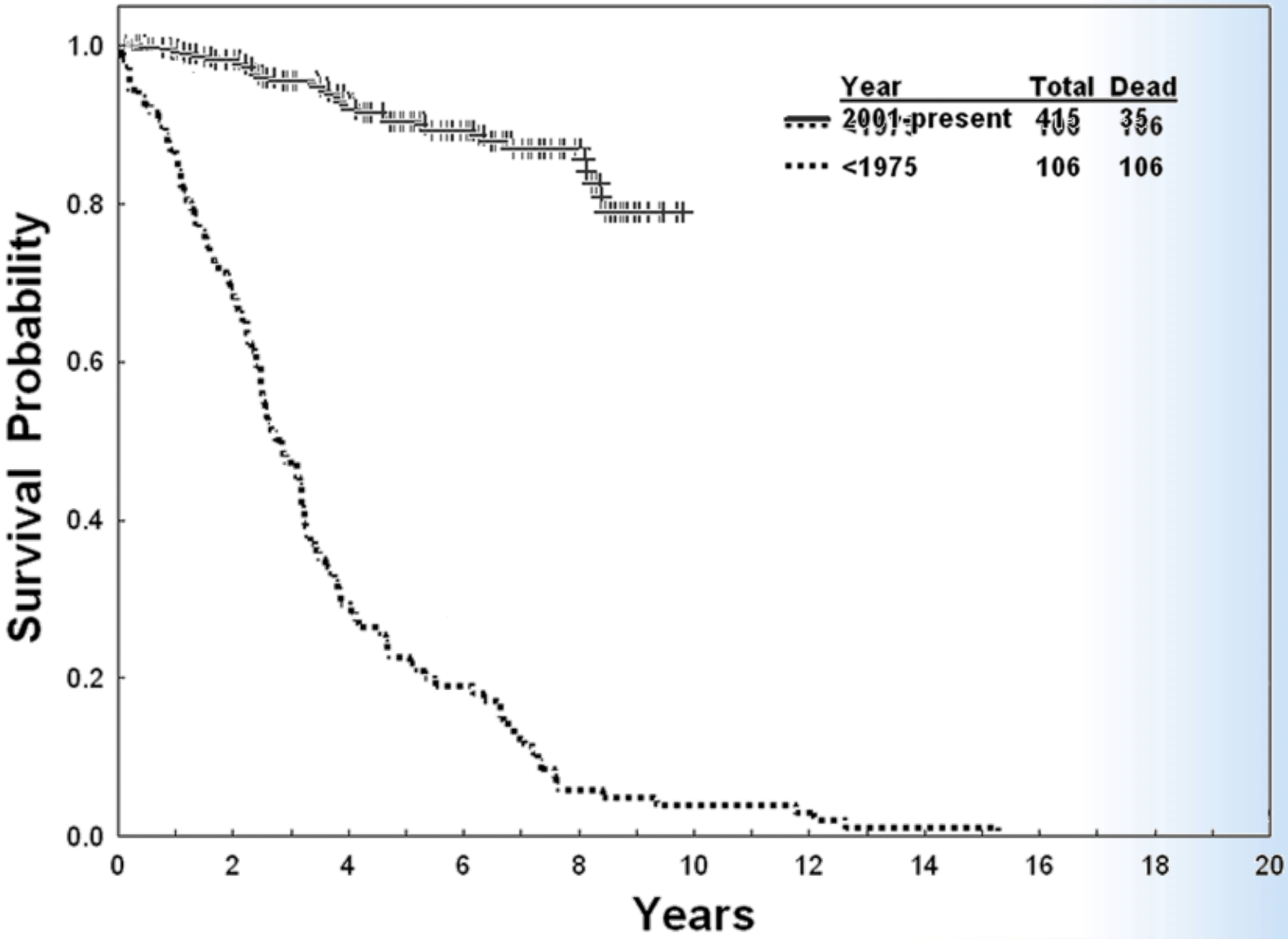


IMATINIB – EFFETTI COLLATERALI

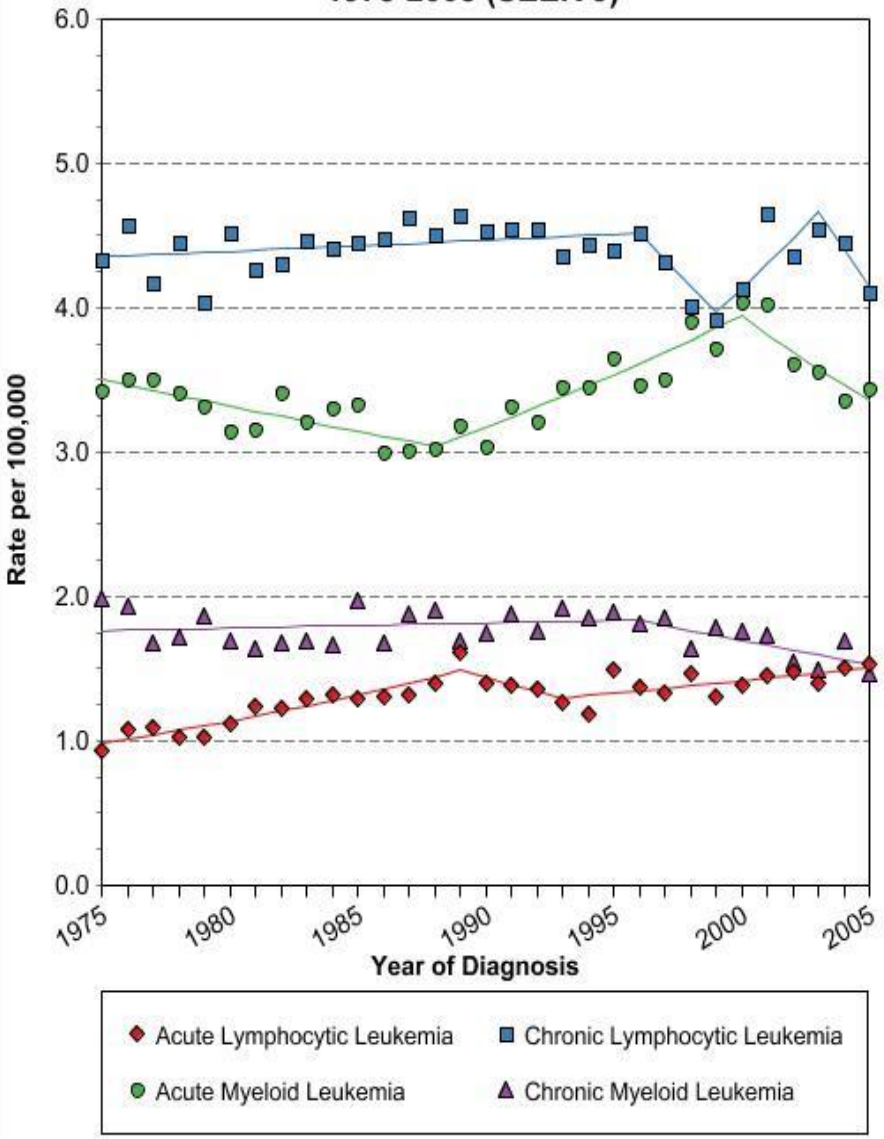
TABLE 4. ADVERSE EVENTS RELATED TO TREATMENT WITH IMATINIB MESYLATE.*

EVENT	NO. OF PATIENTS WITH EVENT (%)	
	ANY GRADE	GRADE 3 OR 4
Nonhematologic		
Superficial edema	318 (60)	6 (1.1)
Nausea	293 (55)	8 (1.5)
Muscle cramps	261 (49)	5 (0.9)
Rash and related events	171 (32)	16 (3.0)
Diarrhea	152 (29)	5 (0.9)
Weight gain	137 (26)	23 (4.3)
Vomiting	125 (23)	3 (0.6)
Myalgia	108 (20)	1 (0.2)
Arthralgia	100 (19)	4 (0.8)
Abdominal pain	99 (19)	0
Fatigue	95 (18)	2 (0.4)
Dyspepsia	93 (17)	0
Musculoskeletal pain	71 (13)	3 (0.6)
Headache	69 (13)	0
Pruritus	46 (9)	2 (0.4)
	GRADE 3	GRADE 4
Hematologic		
Anemia	30 (6)	6 (1.1)
Thrombocytopenia	101 (19)	5 (0.9)
Leukopenia	115 (22)	9 (1.7)
Neutropenia	143 (27)	43 (8.1)

LEUCEMIA MIELOIDE CRONICA: TERAPIA

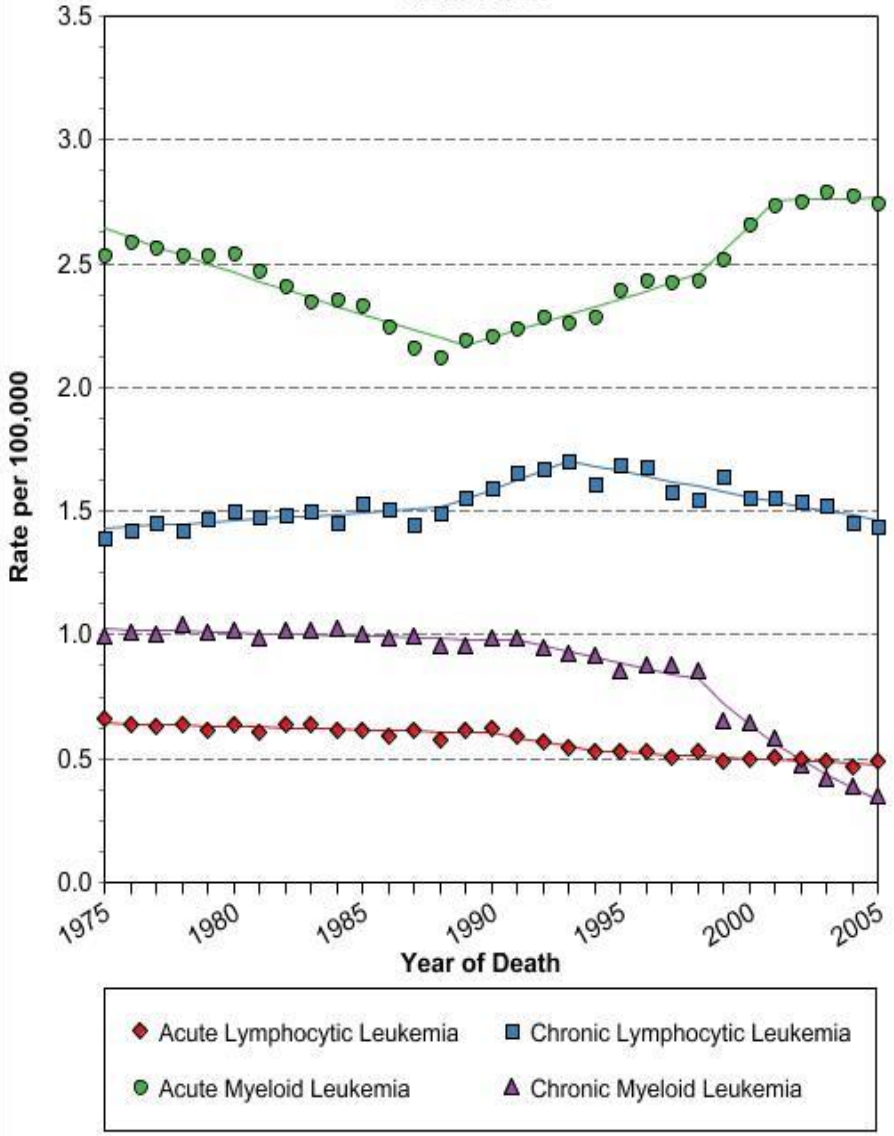


Age-Adjusted SEER Incidence Rates By Cancer Site For All Ages, All Races, Both Sexes 1975-2005 (SEER 9)



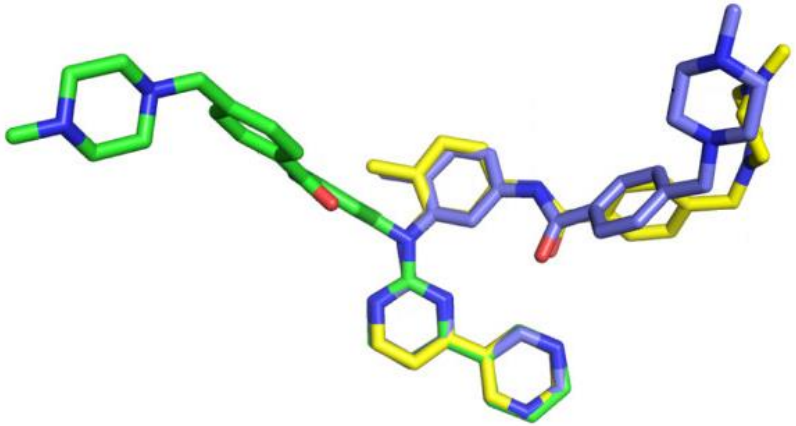
Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.3, April 2008, National Cancer Institute.

Age-Adjusted U.S. Mortality Rates By Cancer Site For All Ages, All Races, Both Sexes 1975-2005



Mortality source: US Mortality Files, National Center for Health Statistics, CDC.
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.3, April 2008, National Cancer Institute.

LEUCEMIA MIELOIDE CRONICA: TERAPIA



IMATINIB (GLEEVEC)

GRAZIE PER L'ATTENZIONE