Mecanismos Genéticos e Epigenéticos do Câncer

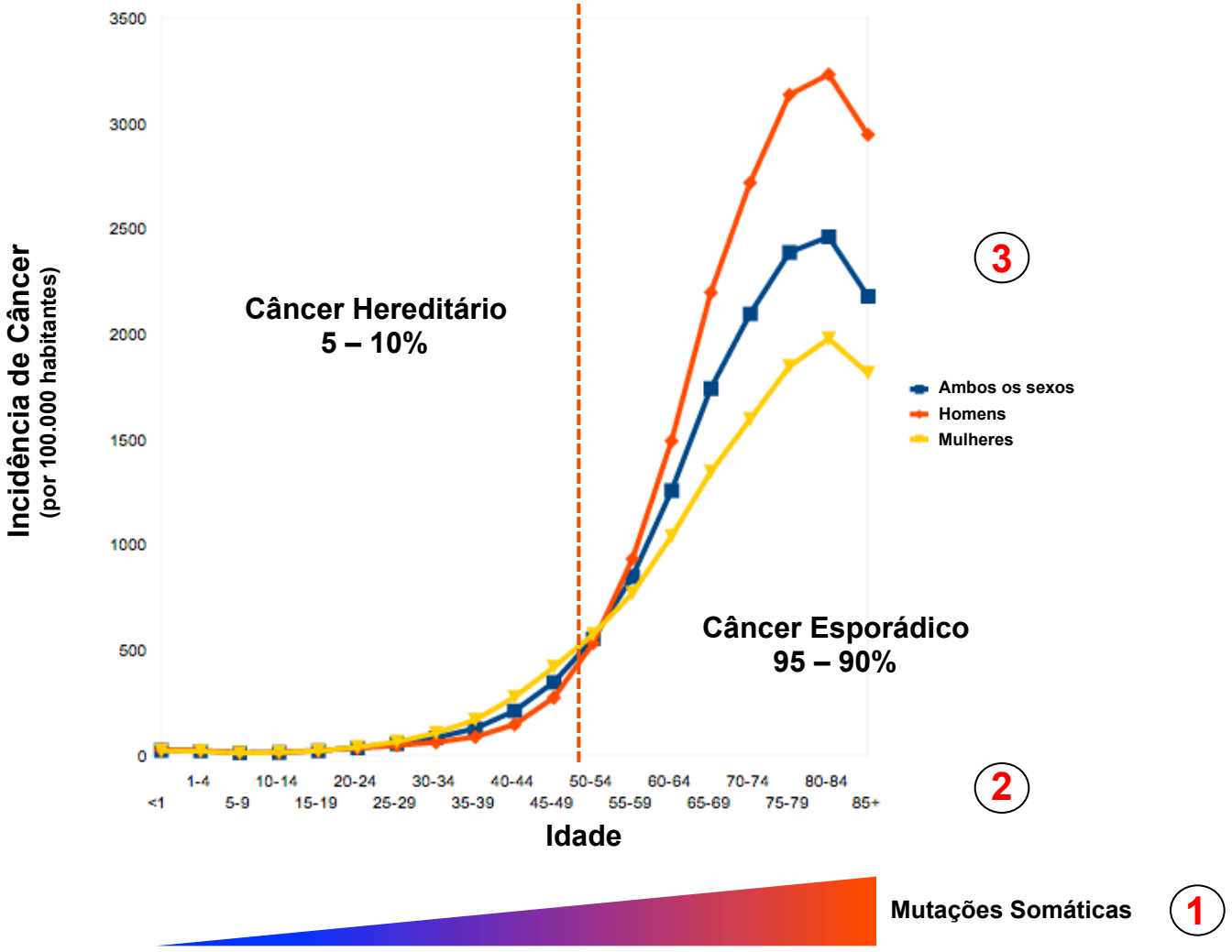
IBM1027 – Genética Molecular

Wilson Araújo Silva Jr

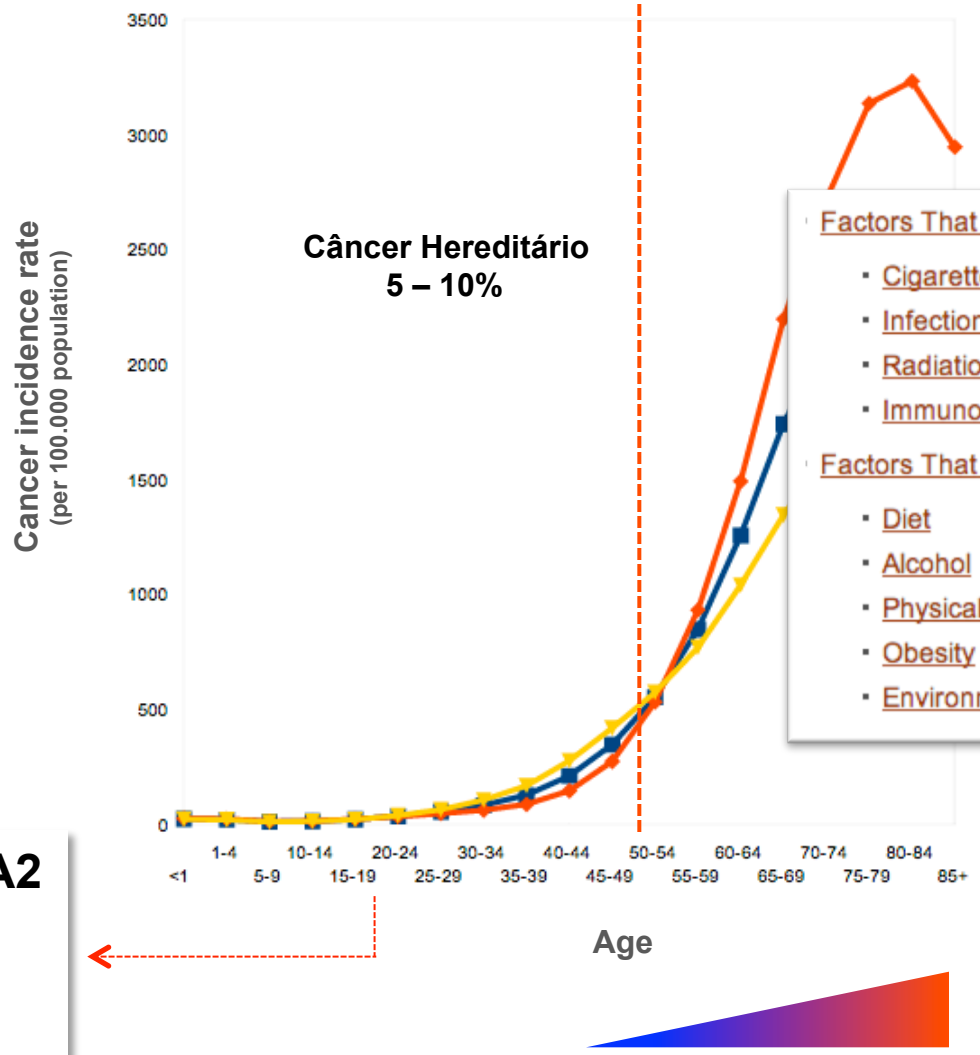
O câncer é uma doença genética?

Hereditário
Esporádico

Eventos genéticos	→	genômicos
Eventos epigenético	→	epigenômicos


Incidência de Câncer
(por 100.000 habitantes)
3500
3000
2500
2000
1500
1000
500
0
Câncer Hereditário
5 – 10%
Câncer Esporádico
95 – 90%
Ambos os sexos
Homens
Mulheres
<1
1-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85+
Idade
3
2
Mutações Somáticas
1

O câncer é um processo natural do envelhecimento



Factors That are Known to Increase the Risk of Cancer

- Cigarette Smoking and Tobacco Use
- Infections
- Radiation
- Immunosuppressive Medicines

Factors That May Affect the Risk of Cancer

- Diet
- Alcohol
- Physical Activity
- Obesity
- Environmental Risk Factors

BRCA1/BRCA2
APC
VHL
TP53

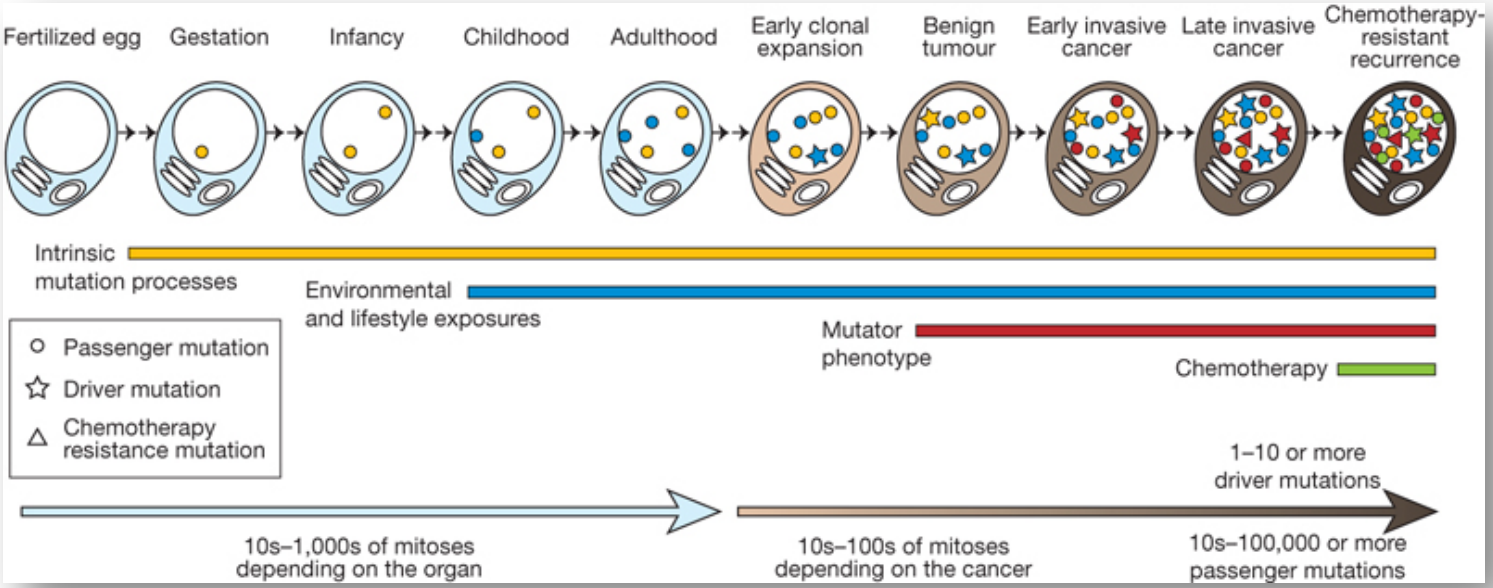
SEER Cancer Statistics 2010, 'Age-Specific SEER Incidence Rates

Driver mutation (mutações condutoras)

Mutações envolvidas com a oncogênese. Conferem vantagem no crescimento clonal das células tumorais.

Passenger mutation (mutações passageiras)

Mutações que não estão envolvidas com a oncogênese. Não conferem vantagem no crescimento clonal das células tumorais.



Quantas mutações condutoras em quantos genes são necessárias para iniciar o processo tumoral?

MR Stratton *et al. Nature* 458, 719-724 (2009) doi:10.1038/nature07943

GATEKEEPERS (GENES PROTETORES)

São genes de suscetibilidade para câncer que regulam diretamente o ciclo celular. Exp. *P53, RB1, APC*, etc.

CARETAKERS (GENES DE MANUTENÇÃO)

Genes que atuam reparando danos no DNA, mantendo a integridade genômica e evitando a instabilidade genética.

Sozinhos não induzem a formação de neoplasia, pois alterações nesses genes não conferem vantagens proliferativas à célula, mas facilitam a ocorrência de mutações nos genes gatekeepers, as quais darão *início à carcinogênese. Exp.* BRCA1 e BRCA2, MLH1, MSH2, PMSL1, etc.

COSMIC
Catalogue of somatic mutations in cancer

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Search | Analysis | Resources

The cancer Gene Census is an ongoing effort to catalogue those genes for which mutations have been causally implicated in cancer. The original census and analysis was published in Nature Reviews Cancer and supplemental analysis information related to the paper is also available.

The census is not static but rather is updated regularly/as needed. In particular we are grateful to Felix Mitelman and his colleagues in providing information on more genes involved in uncommon translocations in leukaemias and lymphomas. Currently, more than 1% of all human genes are implicated via mutation in cancer. Of these, approximately 90% have somatic mutations in cancer, 20% bear germline mutations that predispose to cancer and 10% show both somatic and germline mutations.

Statistics

Show All entries Search:

Sorted By	Number
Amplifications	16
Chromosome	522
Frameshift Mutations	114
Gene Symbol	522
Germline Mutations	82
Large Deletions	39
Missense Mutations	172
Nonsense Mutations	104
Other Mutations	28
Somatic Mutations	483
Splicing Mutations	69
Translocations	327

Showing 1 to 12 of 12 entries

Complete Census

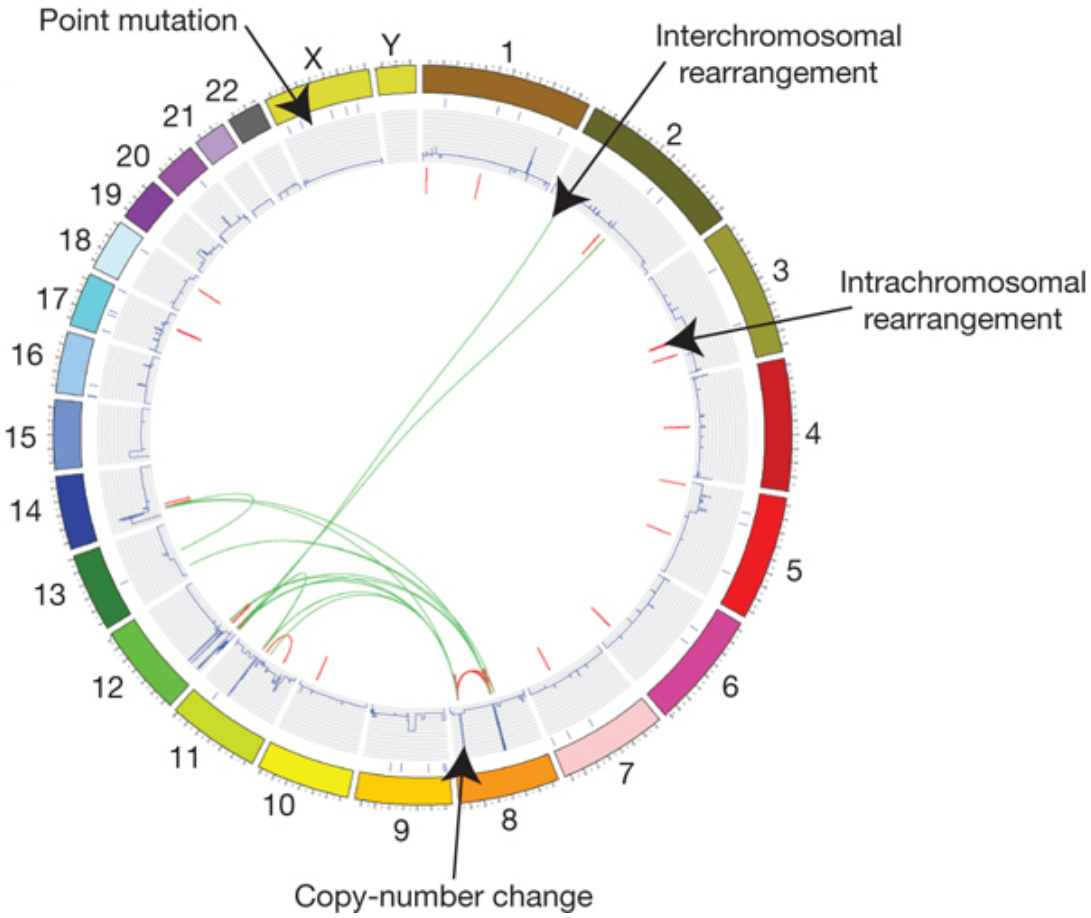
Excel Sheet

Tab Delimited text file

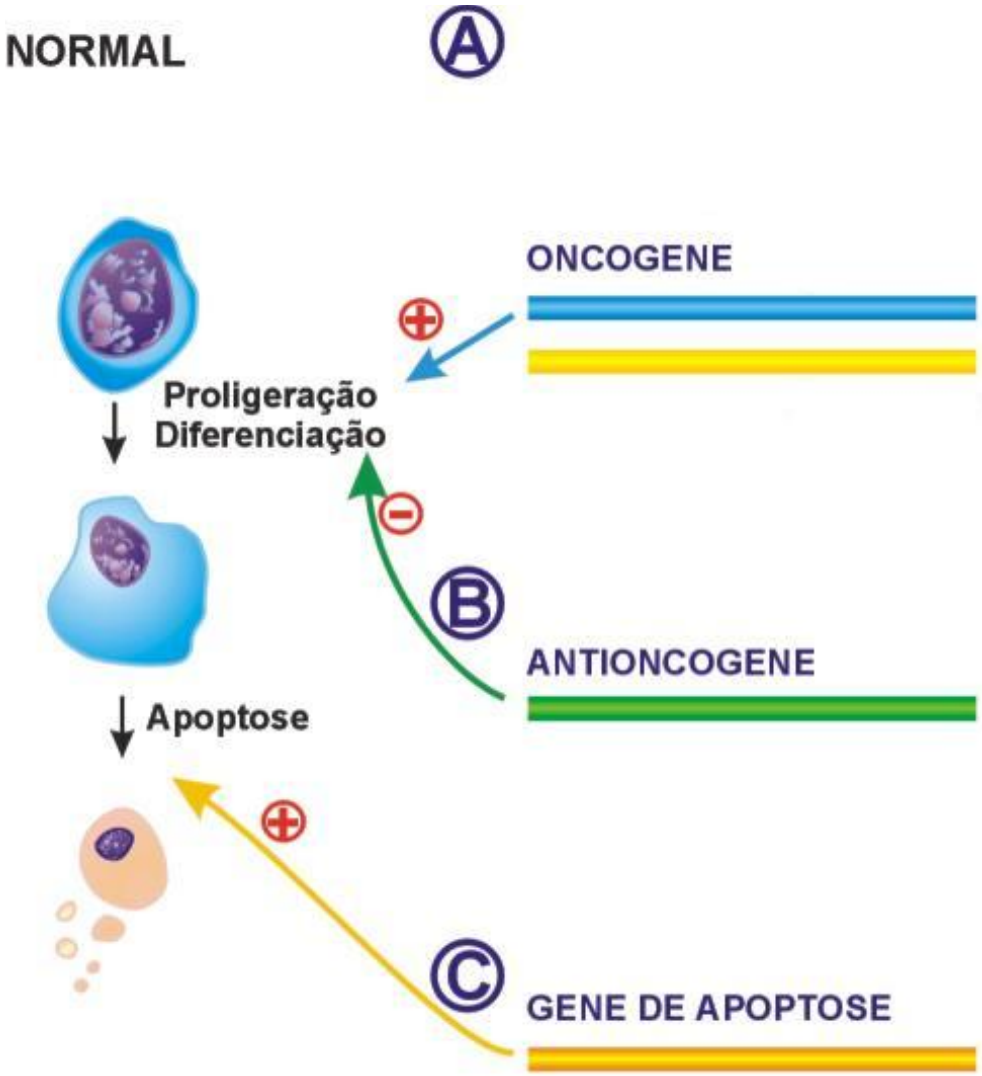
Wellcome Trust Sanger Institute, Genome Research Limited (reg no. 2742969) is a charity registered in England with number 1021457

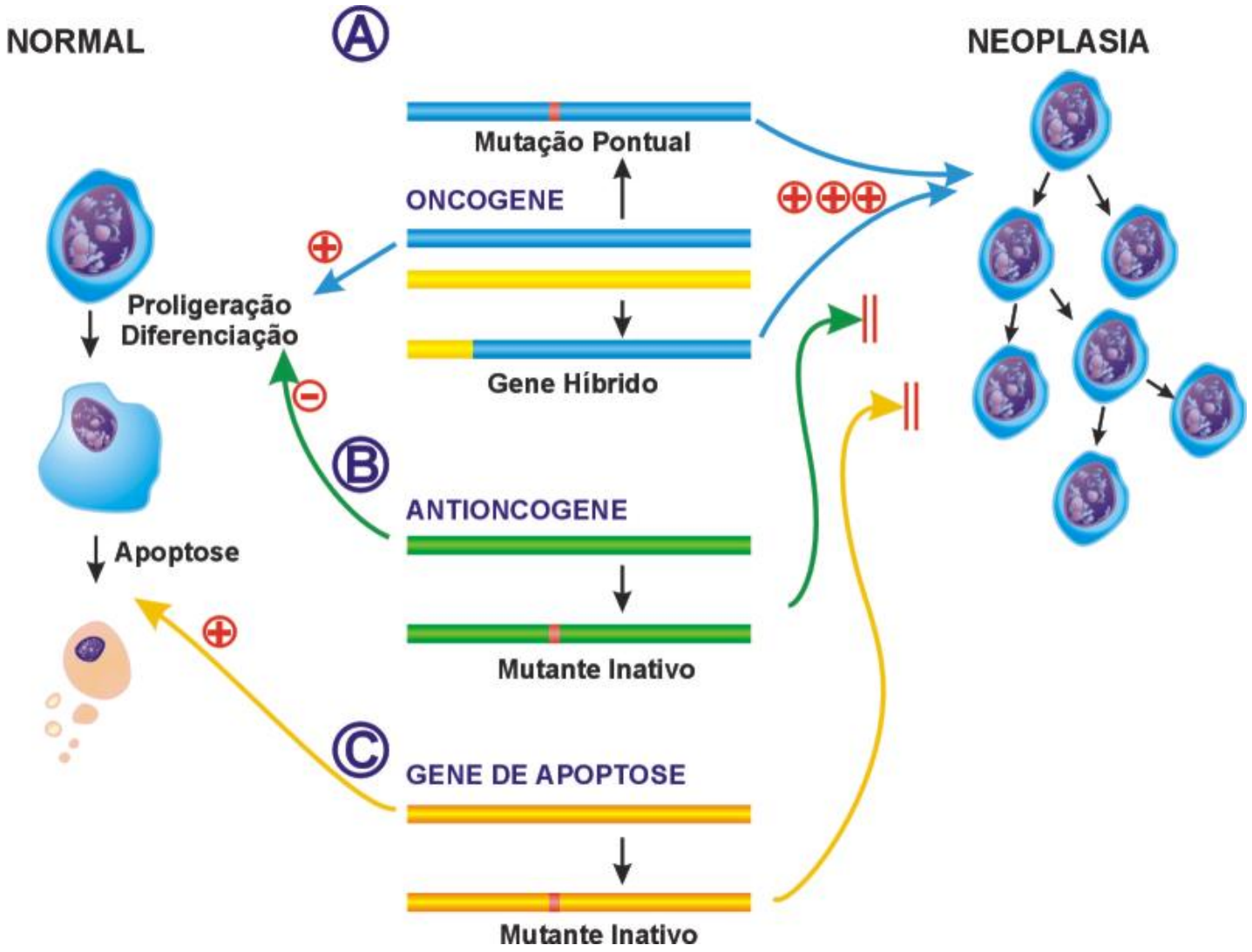
http://cancer.sanger.ac.uk/cancergenome/projects/census/

Representação esquemática dos tipos de mutações somáticas em escala genômica em um tumor



MR Stratton *et al. Nature* 458, 719-724 (2009) doi:10.1038/nature07943


NORMAL
A
ONCOGENE
Proligeração
Diferenciação
B
ANTIONCOGENE
Apoptose
C
GENE DE APOPTOSE


NORMAL
A
NEOPLASIA
Mutação Pontual
ONCOGENE
Proligeração
Diferenciação
Gene Híbrido
B
ANTIONCOGENE
Apoptose
Mutante Inativo
C
GENE DE APOPTOSE
Mutante Inativo

Genes e herança do câncer

Oncogenes
ganho de função

Herança dominante

- *v-sis* → *glioma e fibrosarcoma*
- *v-erbB* → *sarcoma*
- *v-abl* → *leucemia*
- *neu* → *neuroblastoma*

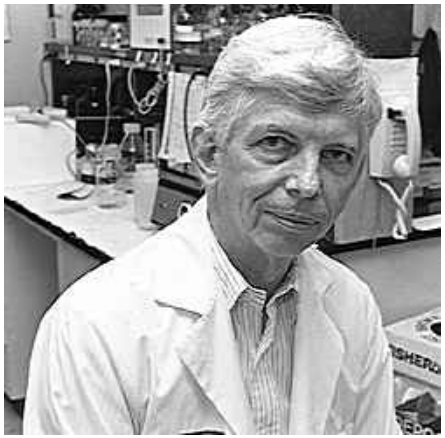
Supressores de tumor
perda de função

Herança recessiva

- *Rb1* → *retinoblastoma hereditário*
- *p53* → *síndrome de Li-Fraumeni*
- *BRCA1* → *câncer mamário e ovariano*
- *VHL* → *von Hippel-Lindau*

Predisposição ao câncer

Hipótese de Knudson

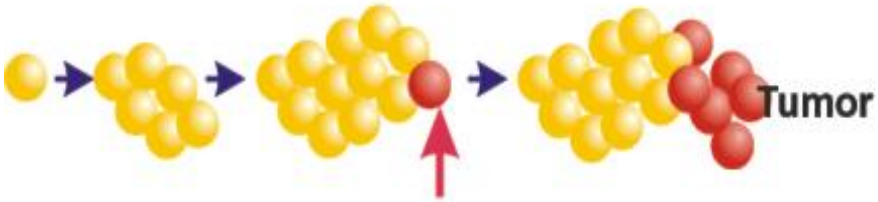


Alfred George Knudson, Jr. M.D., Ph.D.

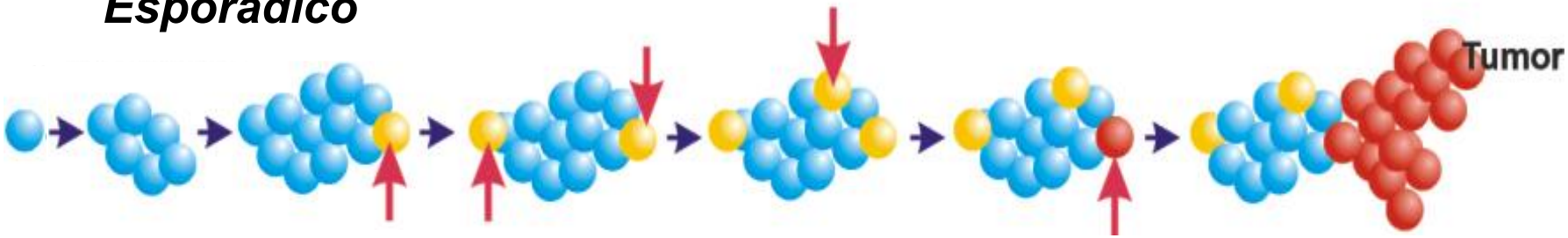
Em 1971, o Dr. Alfred Knudson propôs a hipótese de dois *hit*s para explicar a forma hereditária do retinoblastoma.

Nordling C (1953). "A new theory on cancer-inducing mechanism".
Br J Cancer 7 (1): 68–72.
Knudson A (1971). "Mutation and cancer: statistical study of retinoblastoma" Proc Natl Acad Sci U S A 68 (4): 820–823.

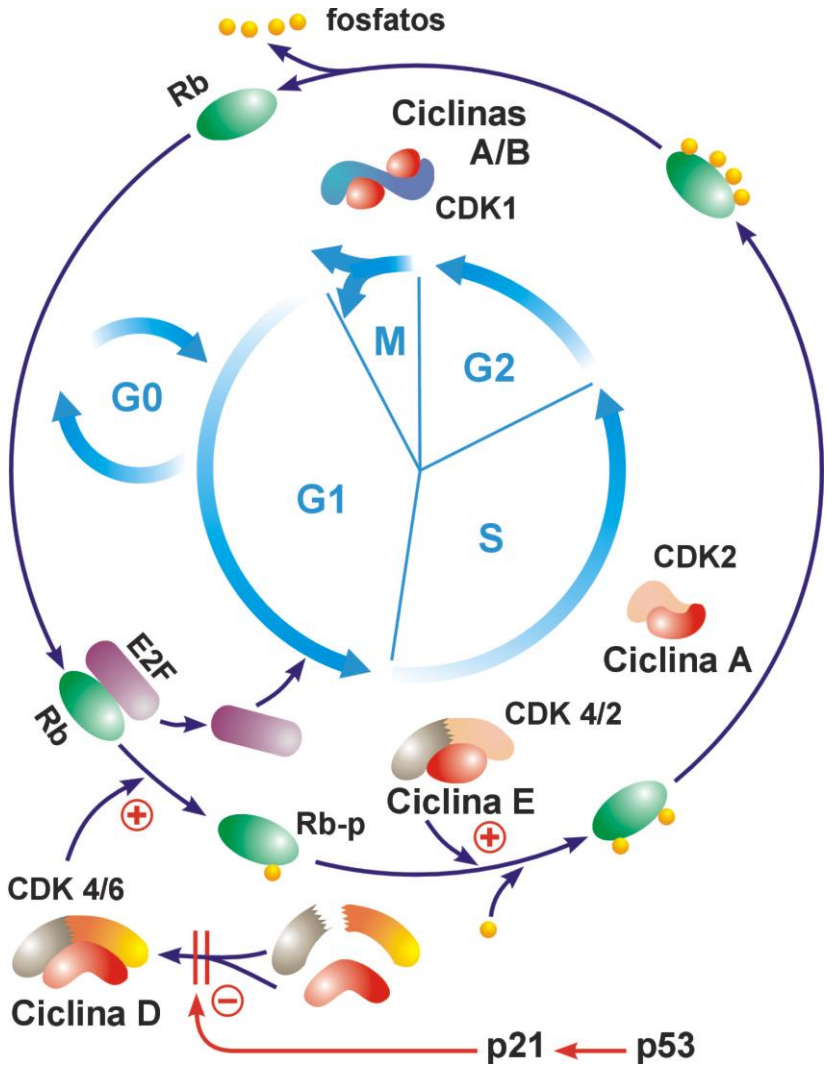
Familial



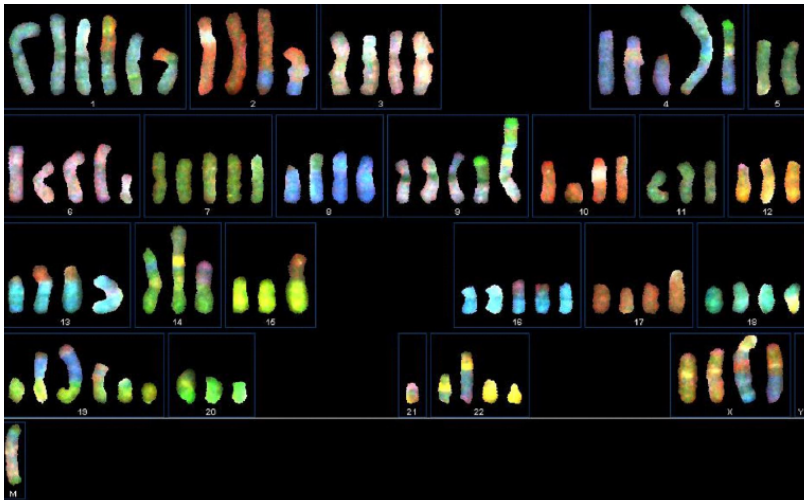
Esporádico



Base genética do Retinoblastoma

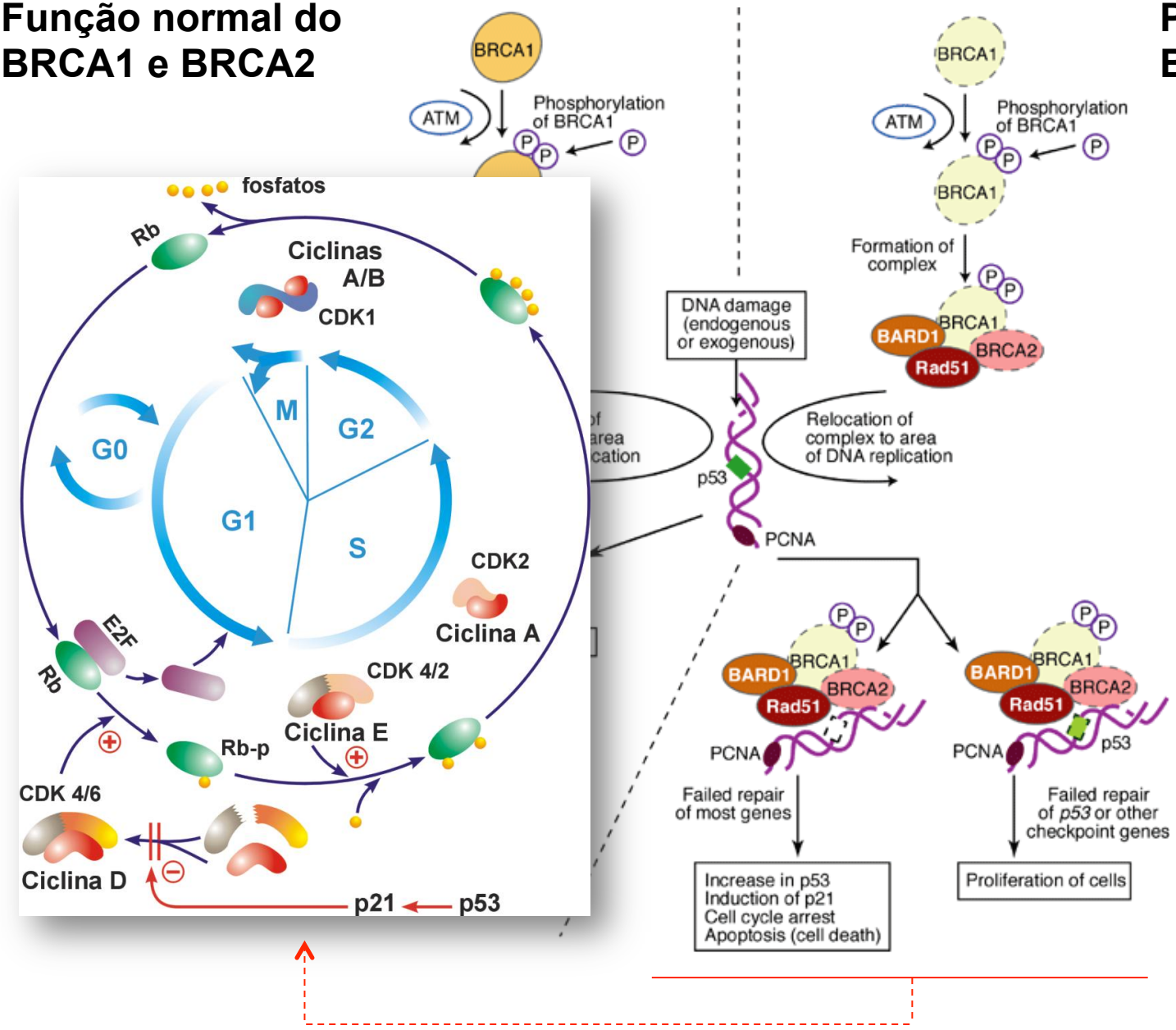


Algumas mutações afetam a estabilidade do genoma inteiro, ao nível do DNA e dos cromossomos, aumentando a taxa geral de mutações.



hMSH6	**Câncer uterino**
hPMS2	**Ca cólon hereditário não-polipose**
ATM	**Ataxia telangiectasia**
XPA,C,D,F	**Xeroderma pigmentosum**
FAC,A,D	**Anemia de Fanconi**
SMAD4	**Polipose juvenil**

Função normal do BRCA1 e BRCA2



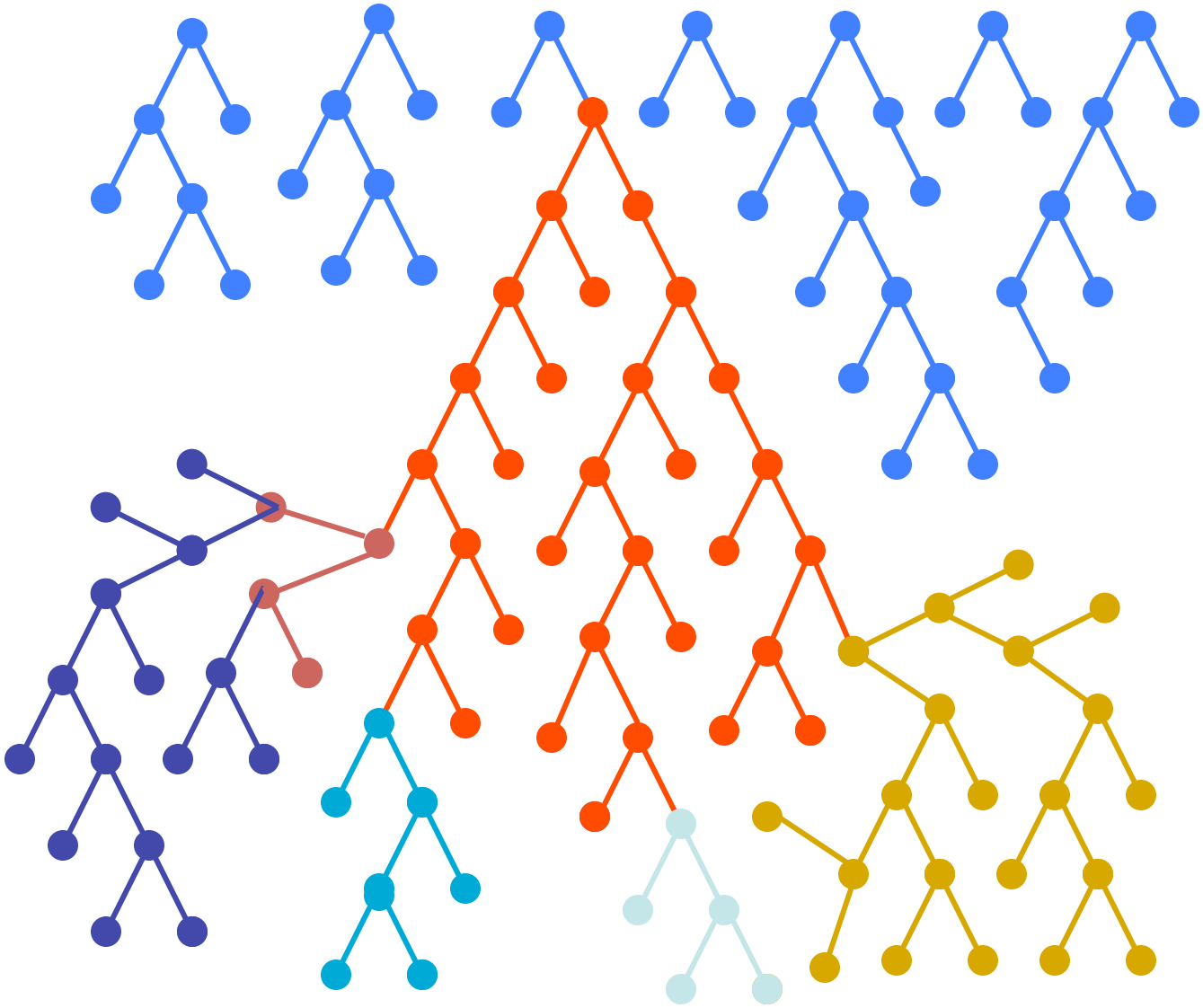
Perda da função do BRCA1 e BRCA2

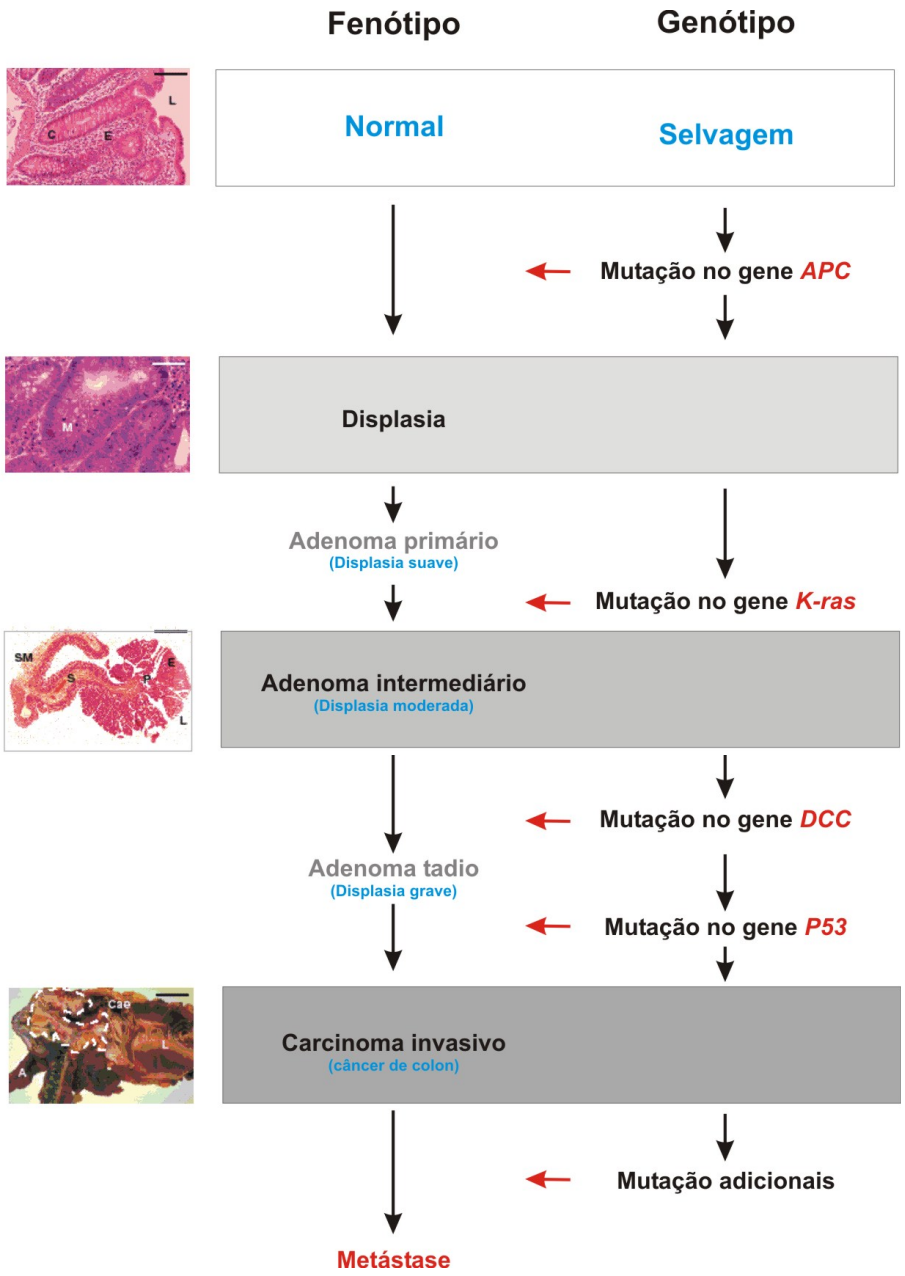
A chance de uma mulher ter câncer de mama aumenta com a idade	
Com 30 anos	1 em 2.212
Com 40 anos	1 em 235
Com 50 anos	1 em 54
Com 60 anos	1 em 23
Com 70 anos	1 em 14
Com 80 anos	1 em 10

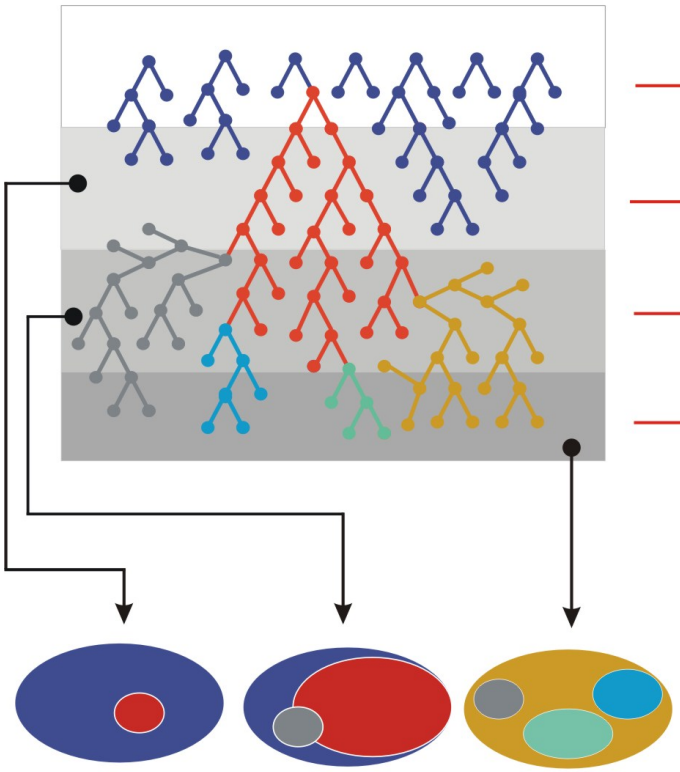
Risco de Ocorrência de Câncer de Mama

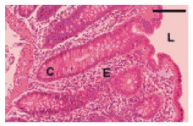
	Até 50 anos	Até 70 anos
BRCA1	**51%**	
BRCA2	**28%**	
BRCA1 e BRCA2		**83 - 88%**
Câncer esporádico	**2%**	**11%**

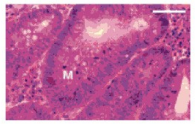
Algumas mutações aumentam a proliferação celular, criando uma população-alvo maior para a mutação seguinte.

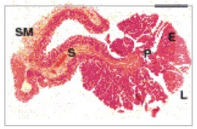


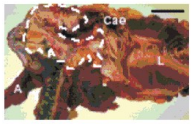

Fenótipo
Genótipo
Normal
Selvagem
Mutação no gene APC
Displasia
Adenoma primário
(Displasia suave)
Mutação no gene K-ras
Adenoma intermediário
(Displasia moderada)
Mutação no gene DCC
Adenoma tadio
(Displasia grave)
Mutação no gene P53
Carcinoma invasivo
(câncer de colon)
Mutação adicionais
Metástase



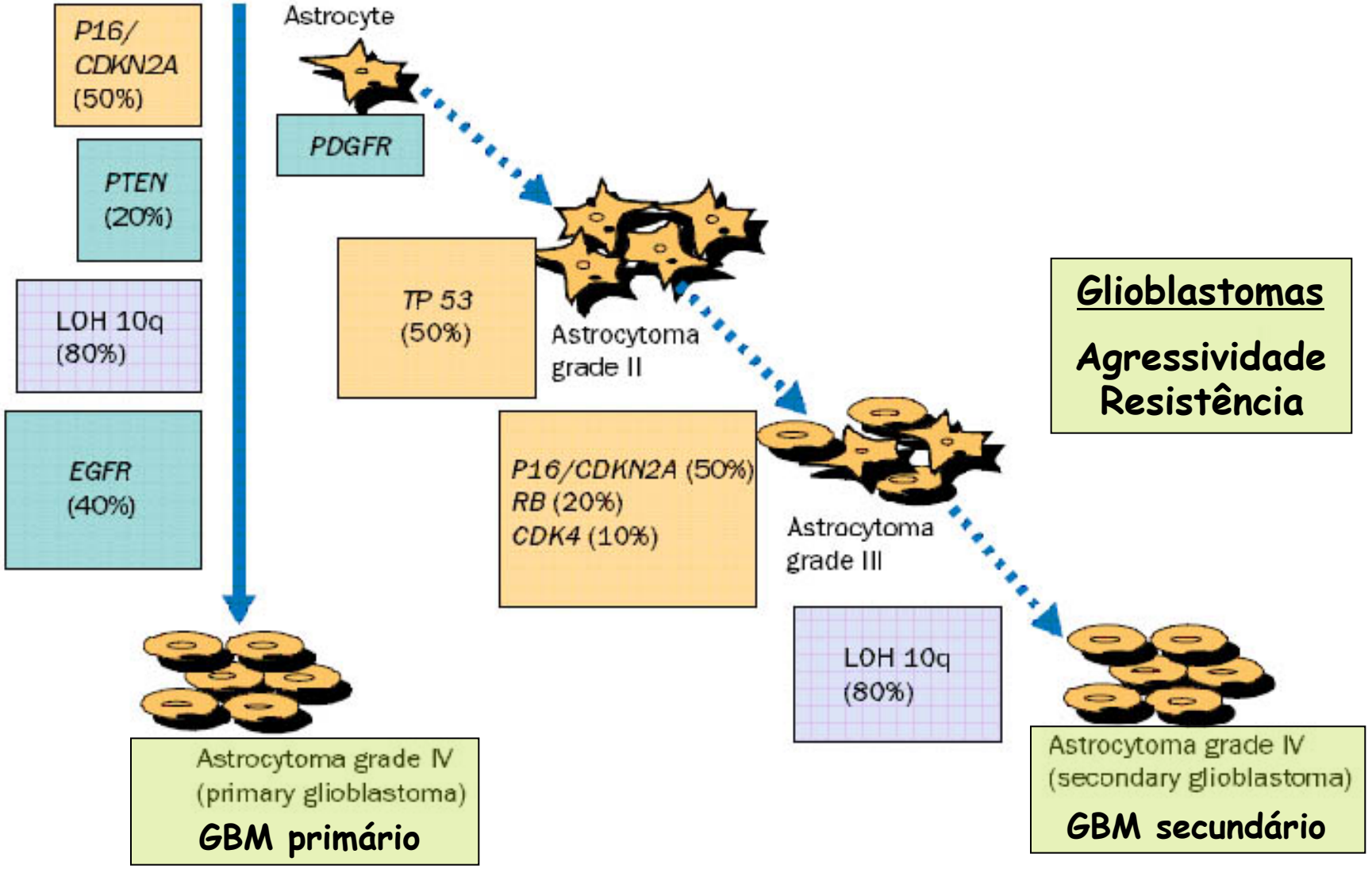




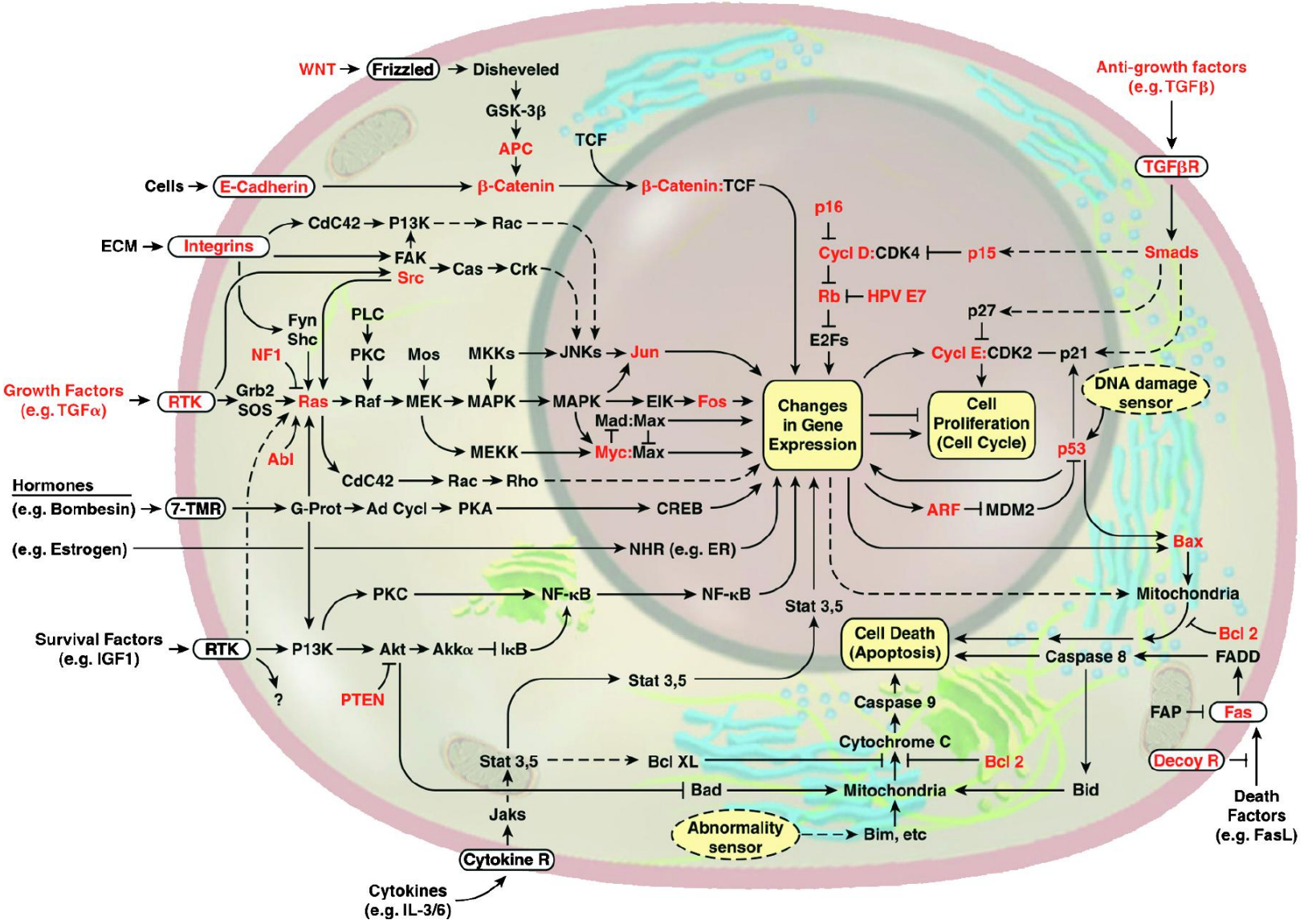




Fenótipo	Genótipo
Normal	Selvagem
	← Mutação no gene *APC*
Displasia	
Adenoma primário (Displasia suave)	
	← Mutação no gene *K-ras*
Adenoma intermediário (Displasia moderada)	
	← Mutação no gene *DCC*
Adenoma tadio (Displasia grave)	
	← Mutação no gene *P53*
Carcinoma invasivo (câncer de colon)	
	← Mutação adicionais
Metástase	

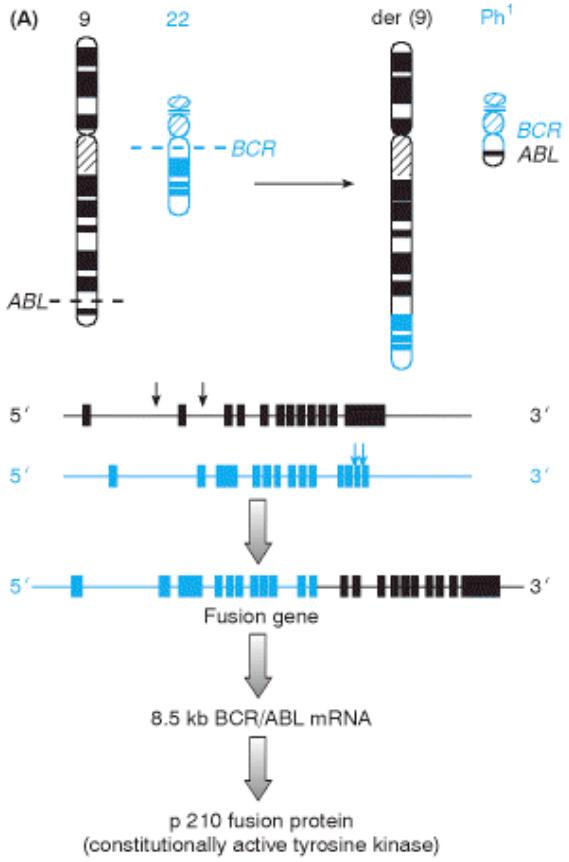


Behin A et al, 2003 Lancet 361(9354): 323-31.

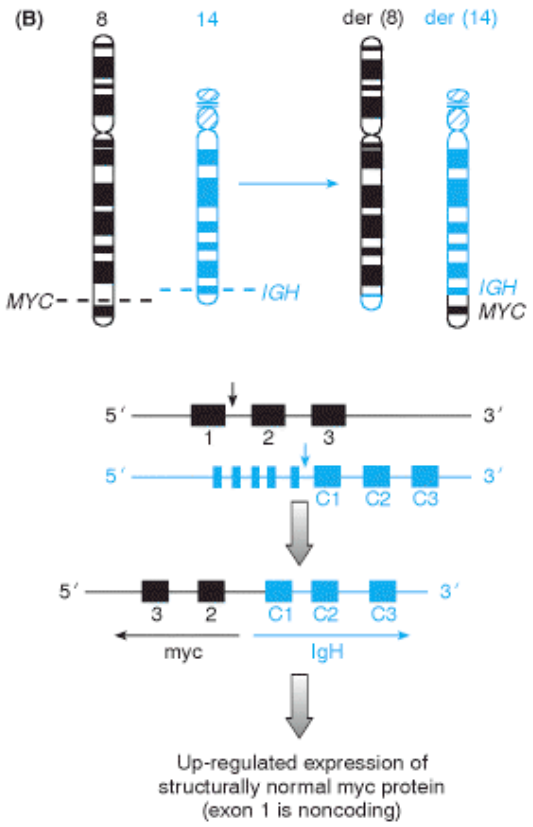

WNT
Frizzled
Disheveled
GSK-3β
APC
TCF
Cells
E-Cadherin
β-Catenin
β-Catenin:TCF
Anti-growth factors
(e.g. TGFβ)
TGFβR
p16
Cycl D:CDK4
p15
Smads
ECM
Integrins
CdC42
P13K
Rac
FAK
Src
Cas
Crk
Rb
HPV E7
p27
E2Fs
Cycl E:CDK2
p21
Fyn
Shc
PLC
NF1
PKC
Mos
MKKs
JNKs
Jun
Growth Factors
(e.g. TGFα)
RTK
Grb2
SOS
Ras
Raf
MEK
MAPK
MAPK
Elk
Fos
Mad:Max
Changes
in Gene
Expression
Cell
Proliferation
(Cell Cycle)
DNA damage
sensor
Abl
MEKK
Myc:Max
p53
CdC42
Rac
Rho
Hormones
(e.g. Bombesin)
7-TMR
G-Prot
Ad Cycl
PKA
CREB
ARF
MDM2
(e.g. Estrogen)
NHR (e.g. ER)
Bax
PKC
NF-κB
NF-κB
Stat 3,5
Mitochondria
Survival Factors
(e.g. IGF1)
RTK
P13K
Akt
Akkα
IκB
Cell Death
(Apoptosis)
Bcl 2
Caspase 8
FADD
?
PTEN
Stat 3,5
Caspase 9
FAP
Fas
Cytochrome C
Stat 3,5
Bcl XL
Bcl 2
Decoy R
Bad
Mitochondria
Bid
Jaks
Abnormality
sensor
Bim, etc
Death
Factors
(e.g. FasL)
Cytokine R
Cytokines
(e.g. IL-3/6)

Ativação de proto-oncogenes

Ativados pela transposição para um domínio de cromatina ativa:



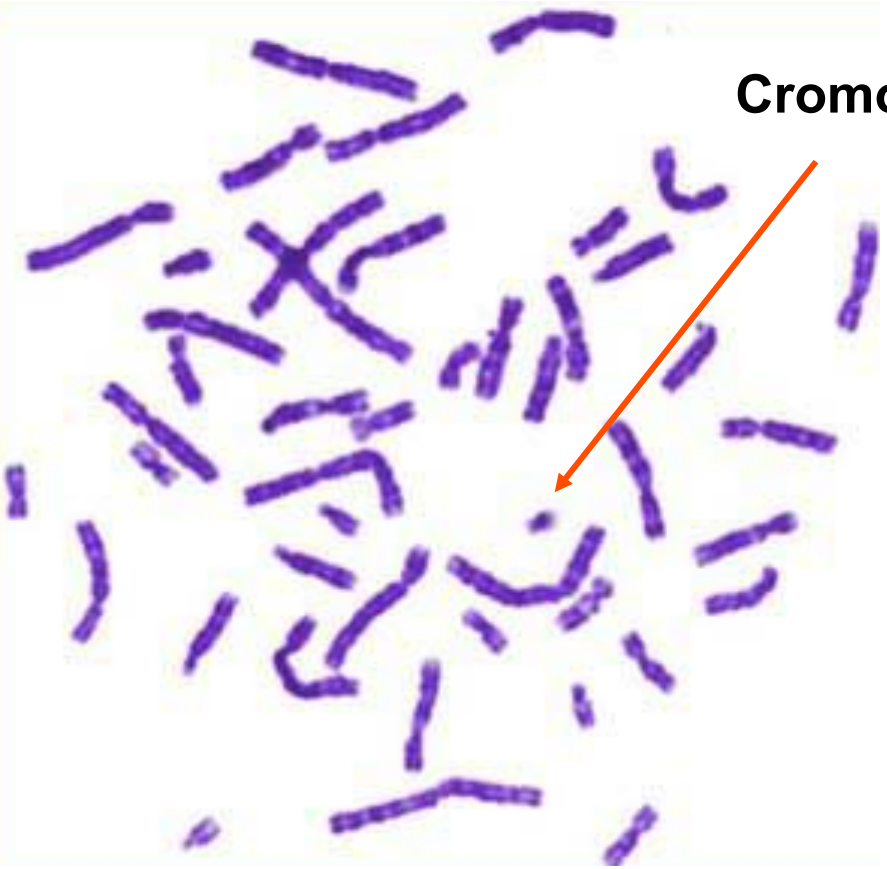
LMC



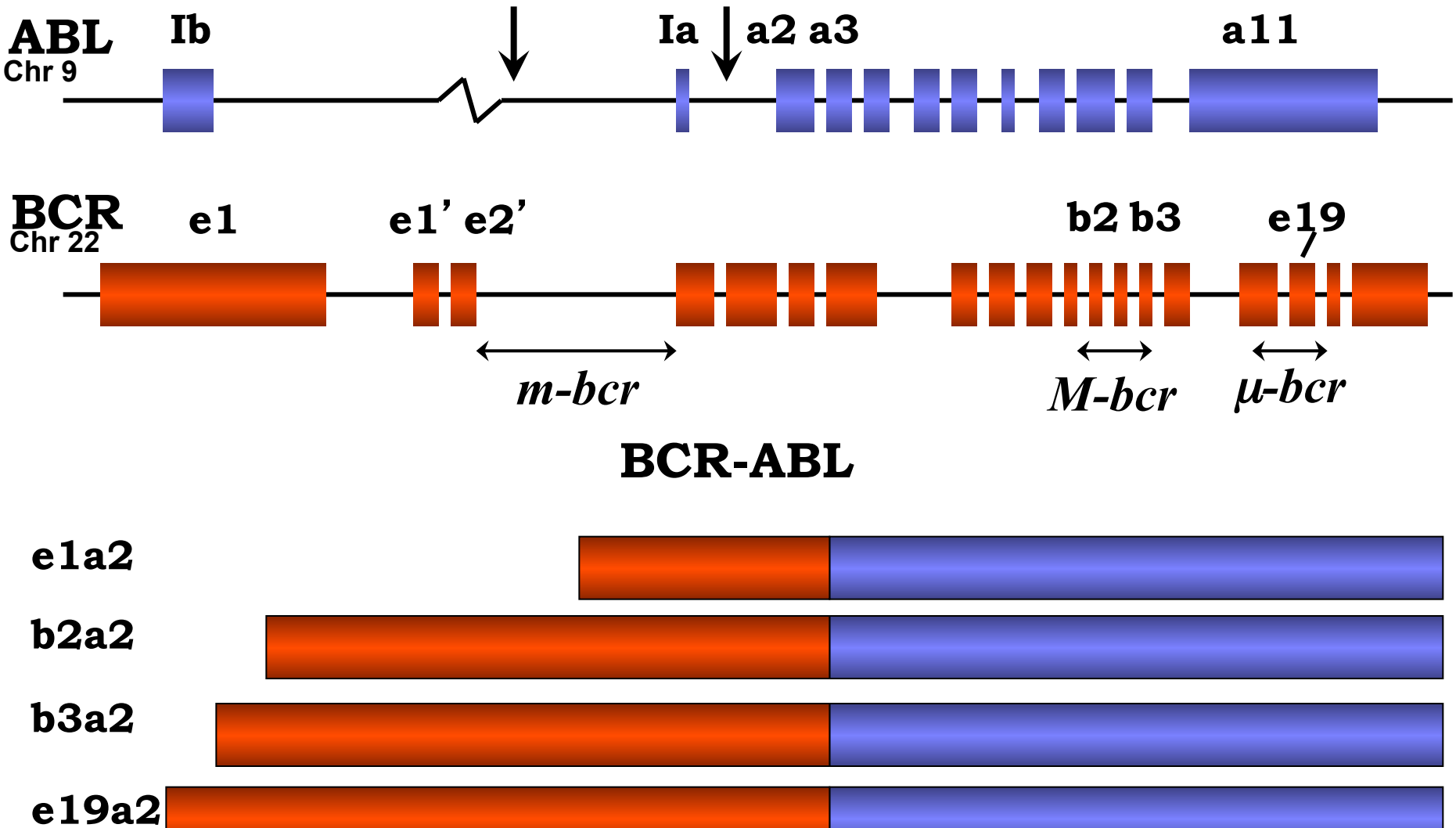
Linfoma de Burkitt

LEUCEMIA MIELÓIDE CRÔNICA

Cromossomo Filadélfia – t(9;22)(q34;q11)

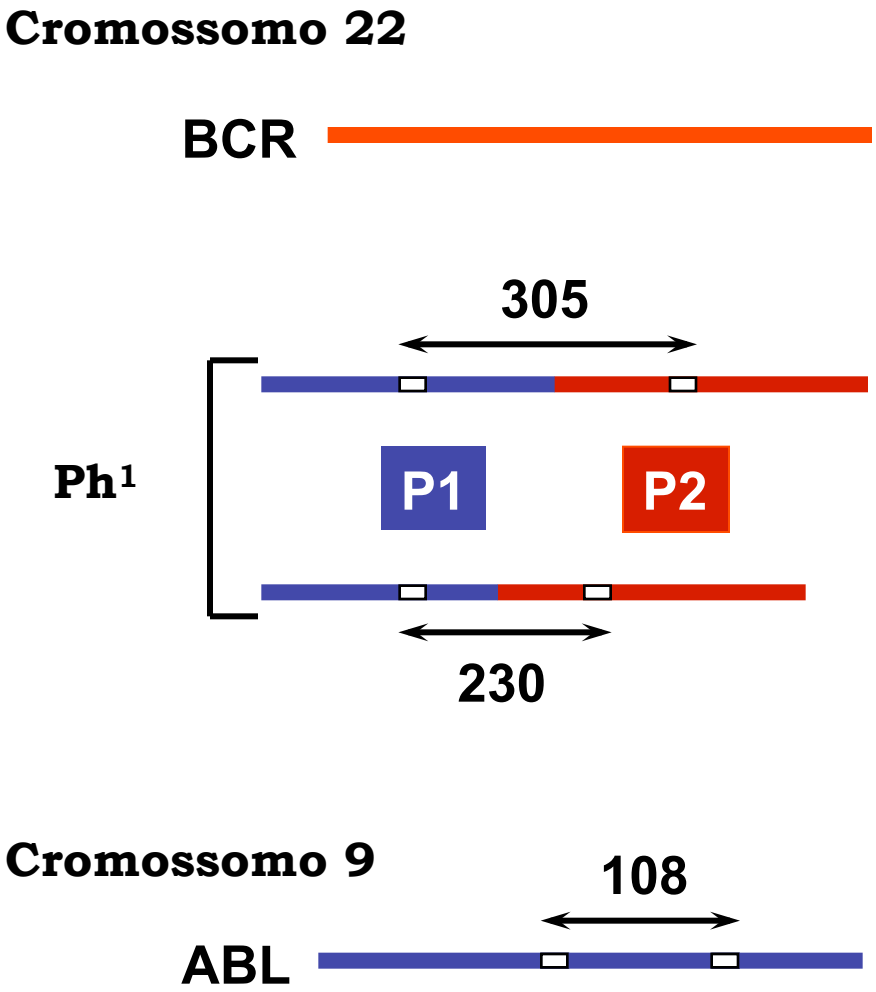


Genes e herança do câncer

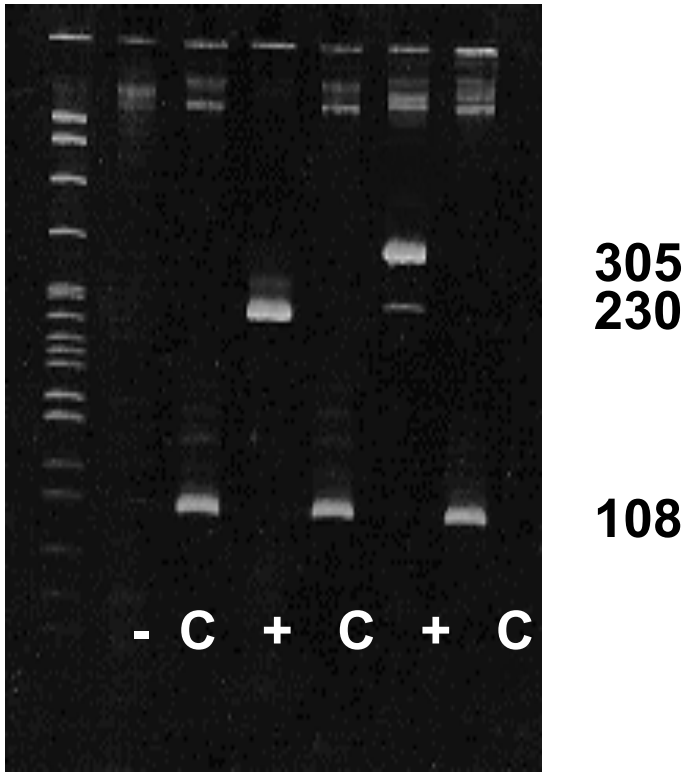


LEUCEMIA MIELÓIDE CRÔNICA

Diagnóstico molecular – t(9;22)(q34;q11)



PCR para bcr/abl

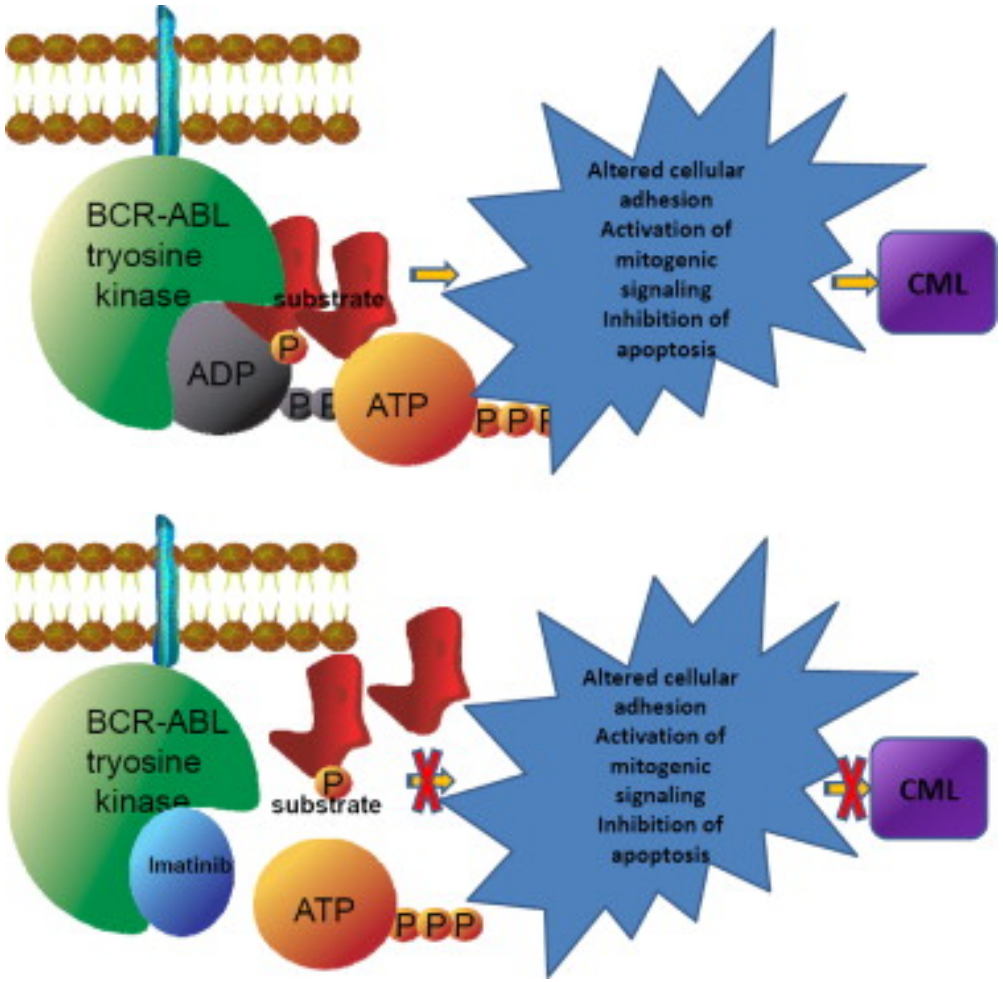


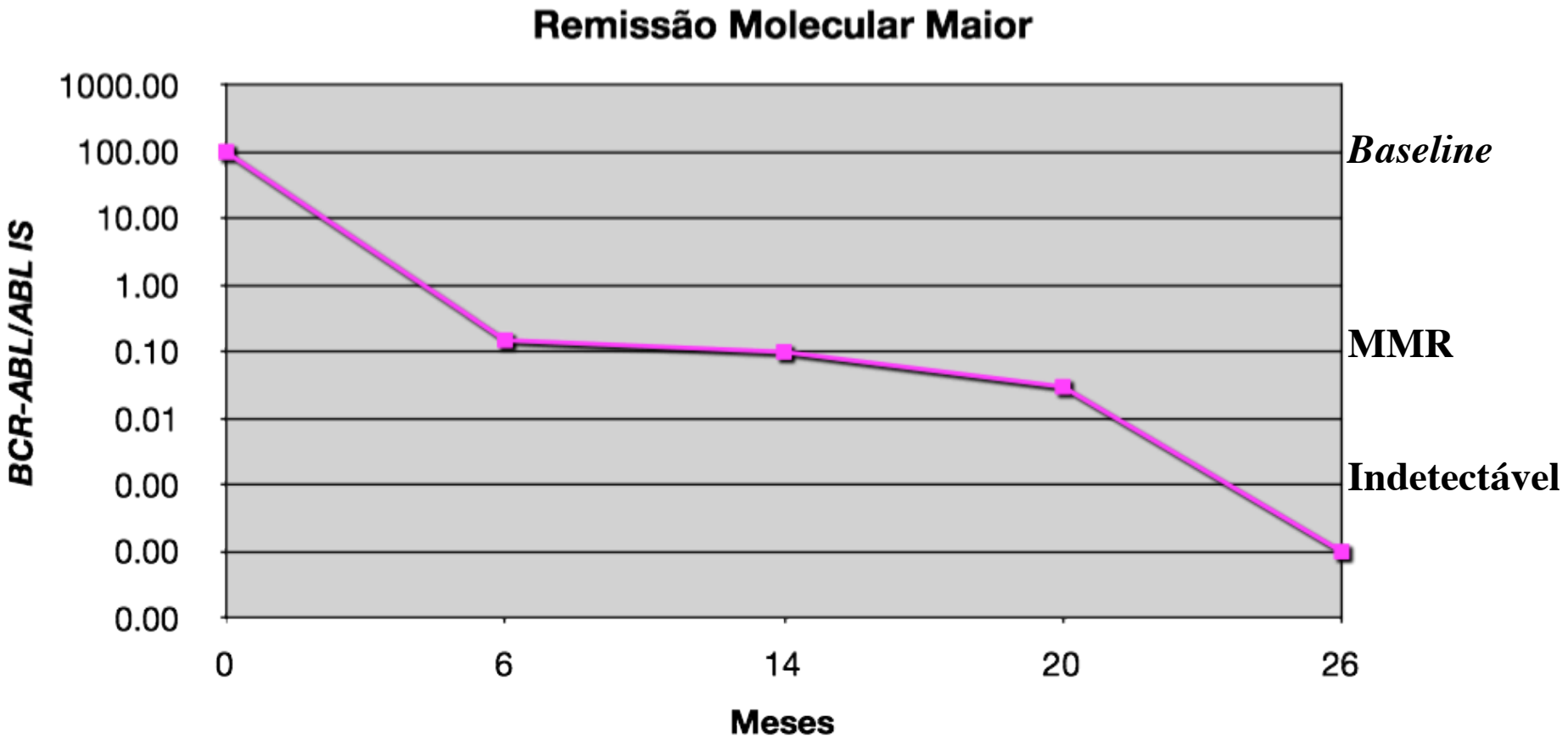
Invited review

BCR-ABL tyrosine kinase inhibitors in the treatment of Philadelphia chromosome positive chronic myeloid leukemia: A review

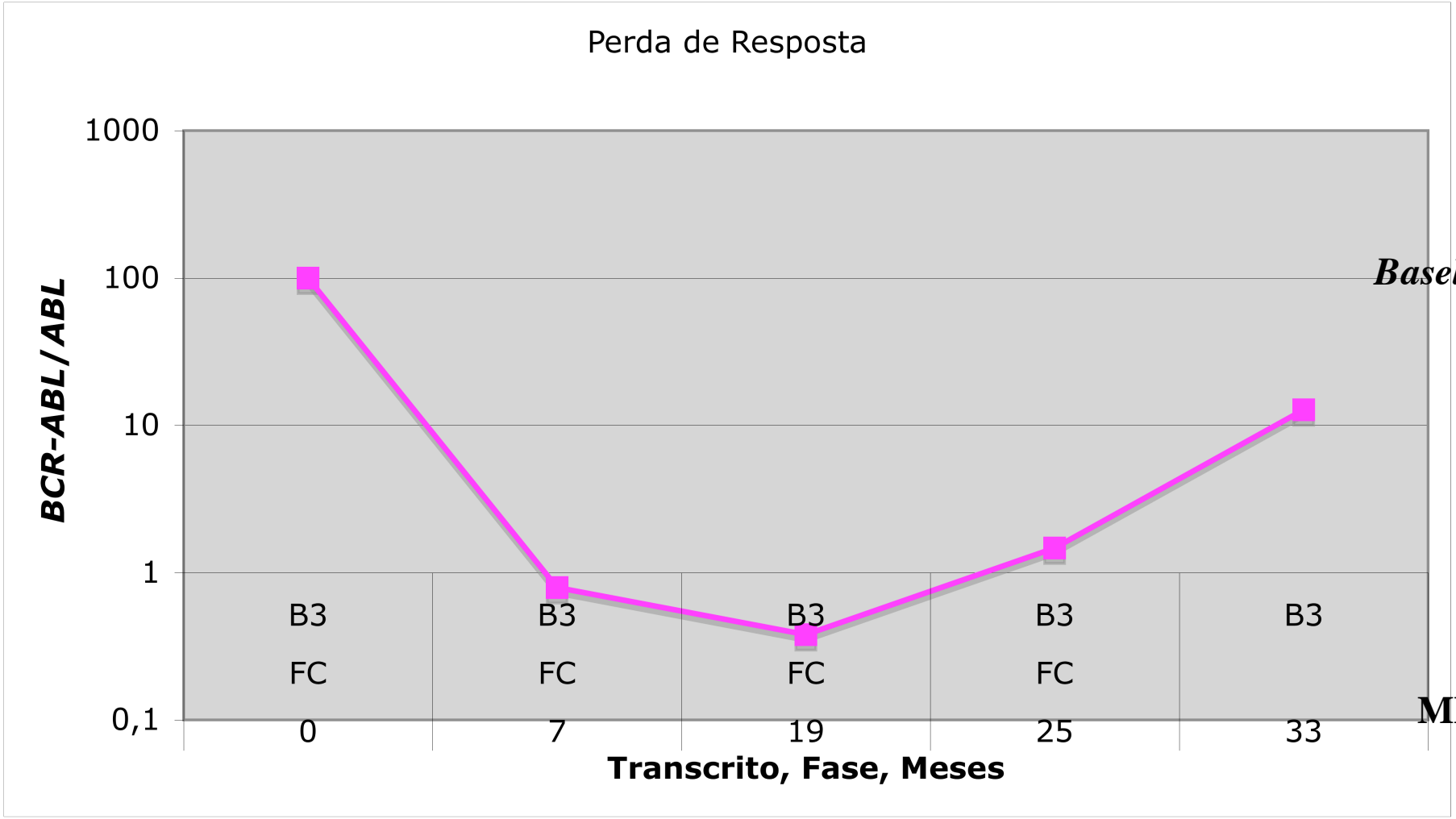
Xin An[a,b,c,1], Amit K. Tiwari[a,1], Yibo Sun[a,1], Pei-Rong Ding[a,b,c,1], Charles R. Ashby Jr.[a], Zhe-Sheng Chen[a,*]

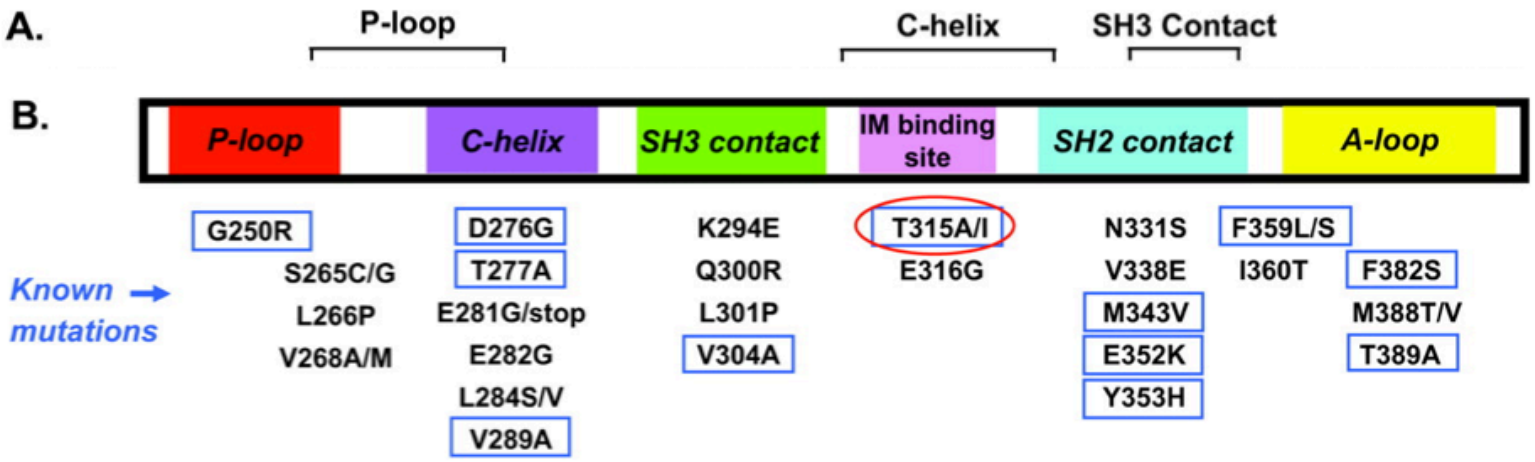
[a] Department of Pharmaceutical Sciences, College of Pharmacy and Allied Health Professions, St. John's University, 8000 Utopia Parkway, Jamaica, NY 11439, USA
[b] Department of Medical Oncology, Cancer Center, Sun Yat-Sen University, Guangzhou, China
[c] State Key Laboratory of Oncology in South China, Sun Yat-Sen University, Guangzhou, China



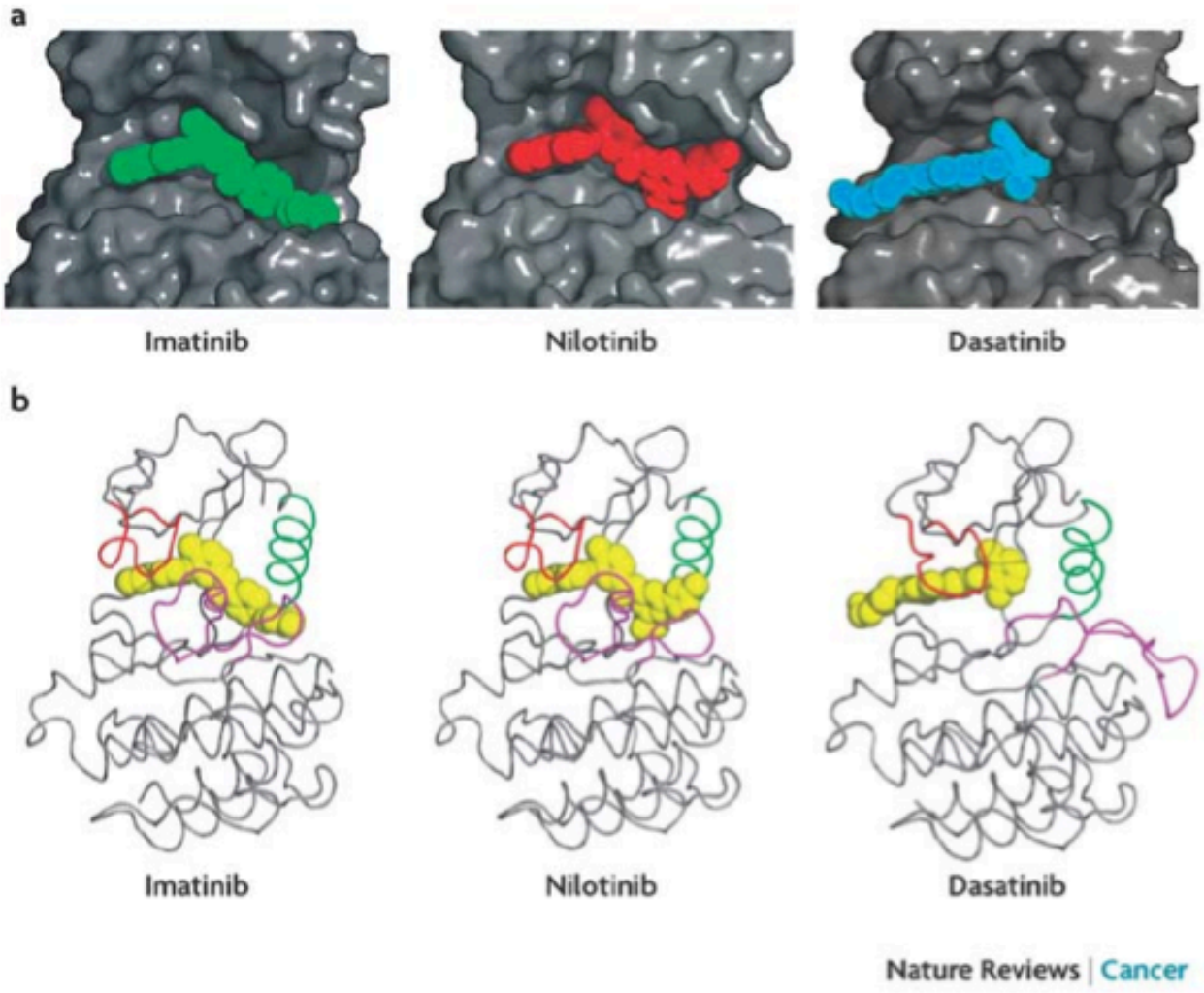

Remissão Molecular Maior
BCR-ABL/ABL IS
1000.00
100.00
10.00
1.00
0.10
0.01
0.00
0.00
0.00
0
6
14
20
26
Meses
Baseline
MMR
Indetectável

70 a 80% dos casos com perda de resposta ao Imatinibe





JNCI
Jiang X et al. JNCI J Natl Cancer Inst 2007;99:680-693 © 2007 The Author(s).


a
Imatinib
Nilotinib
Dasatinib
b
Imatinib
Nilotinib
Dasatinib
Nature Reviews | Cancer

Dasatinibe tem uma Atividade Ampla contra mutações BCR-ABL

MOST COMMON

LESS COMMON

Mutation	Patients (%)	Mutation class for therapeutic decision: Nilotinib	Mutation class for therapeutic decision: Dasatinib
T315I	14	D	D
M351T	12	A	A
G250E	12	A	A
F359V	9	C	A
M224V	9	A	A
Y253H	8	C	A
E255K	7	C	B
H396R	7	A	A
F317L	6	A	C
E355G	4	A	A
Q252H	4	B	B
E255V	4	C	B
E459K	4	A	A
F486S	3	A	A
L248V	3	A	A
D276G	3	A	A
E279K	3	A	A
Y253F	2	B	A
F359C	2	C	A
F359I	2	B	A

A	Sensitive to inhibitor
B	Clinical evidence suggestive of reduced sensitivity, but presence of mutation should have no impact on clinical decisions
C	Compelling clinical evidence to recommend an alternative inhibitor
D	No role for second-generation TKI therapy

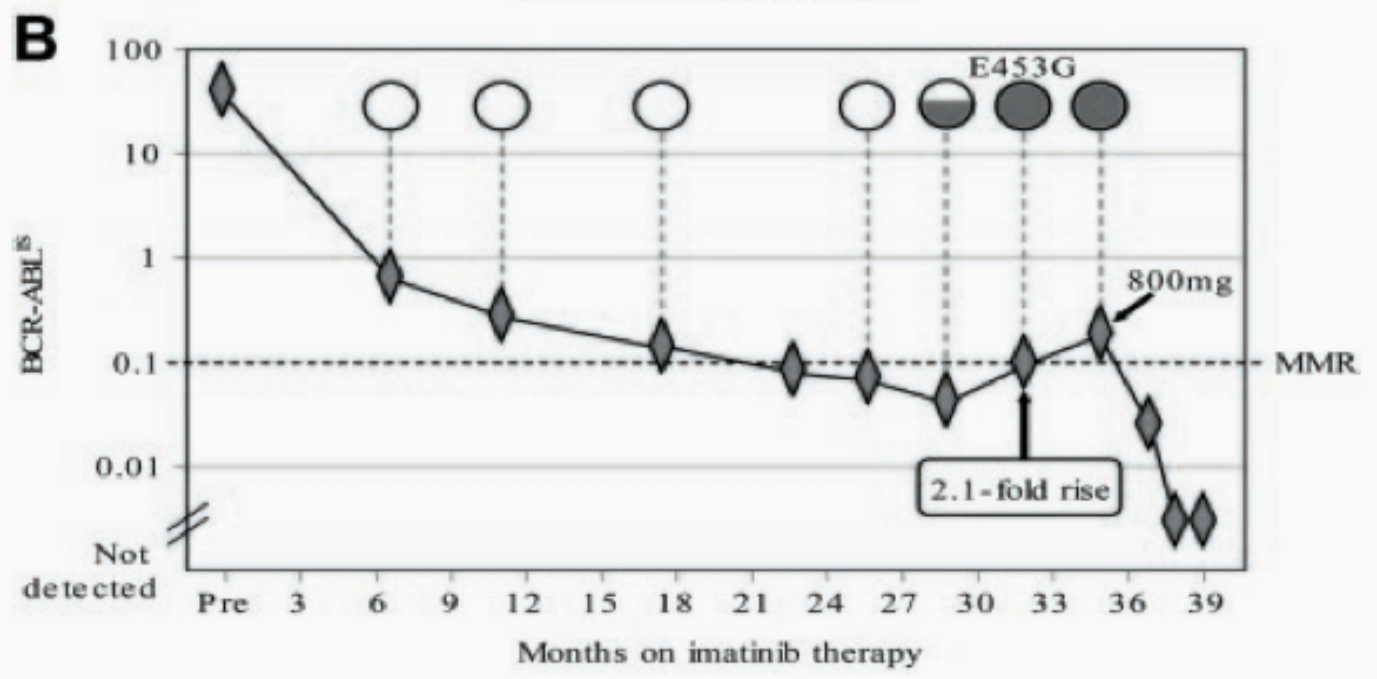
Mutations detected across all phases of CML or Ph+ ALL after imatinib therapy (n=386)

Branford S, et al. Blood 2009;114:5426–35

Material destinado a profissionais de saúde

Mutação e resistência ao imatinibe - Branford *et al*. (2005)

70 a 80% dos casos de perda de resposta ao Imatinibe



Branford S, Hughes TP. Diagnosis and monitoring of chronic myeloid leukemia by qualitative and quantitative RT-PCR. In: Iland HJ, Hertzberg M, Marlton P, eds. Myeloid Leukemia: Methods and Protocols, Methods in Molecular Medicine, Vol. 125. Totawa, NJ: Humana Press; 2006: 69-92.

Mecanismos epigenéticos do câncer

É um mecanismo herdável, modificações na estrutura da cromatina sem mudanças na sequência do DNA

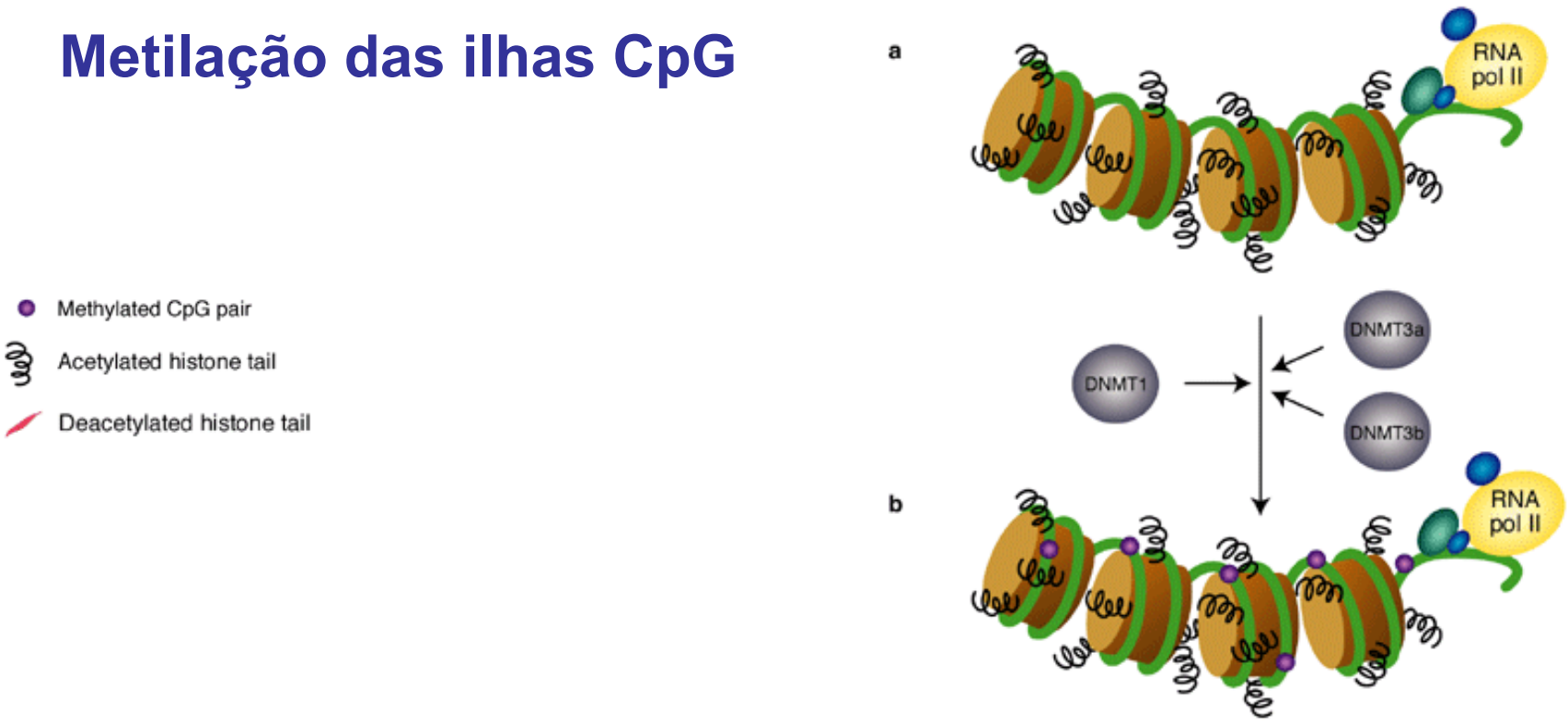
Metilação do DNA e das Histonas

Desacetilação das histonas

Mecanismos epigenéticos do câncer

É um mecanismo herdável, modificações na estrutura da cromatina sem mudanças na sequência do DNA

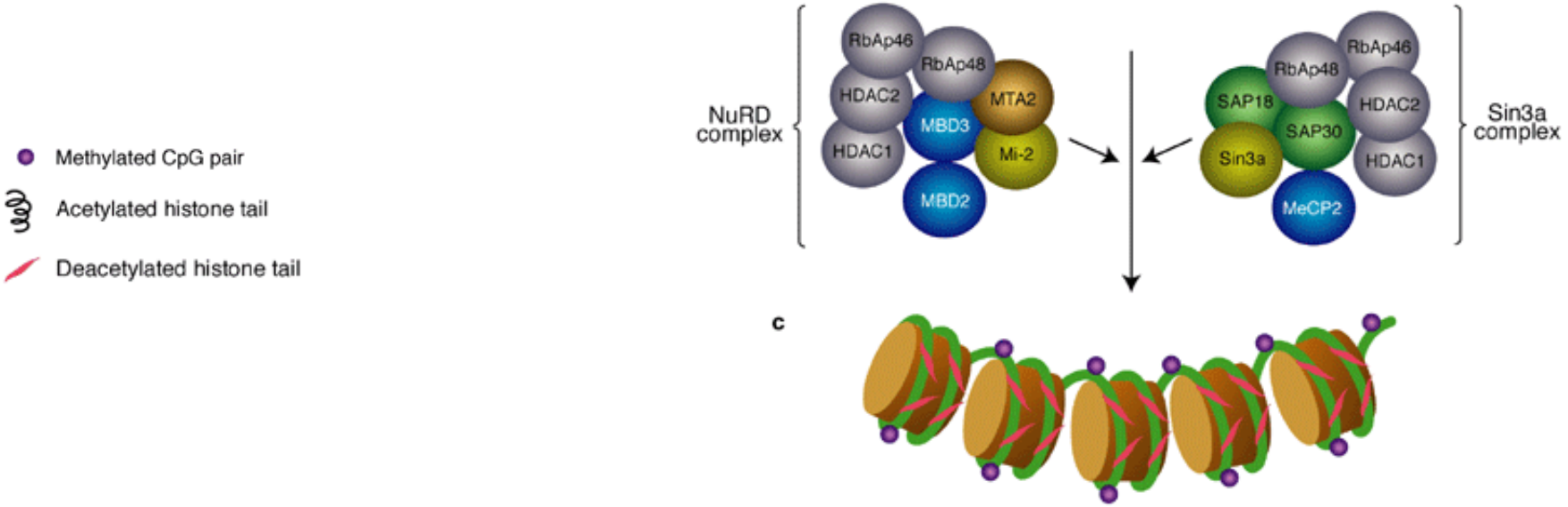
Metilação das ilhas CpG



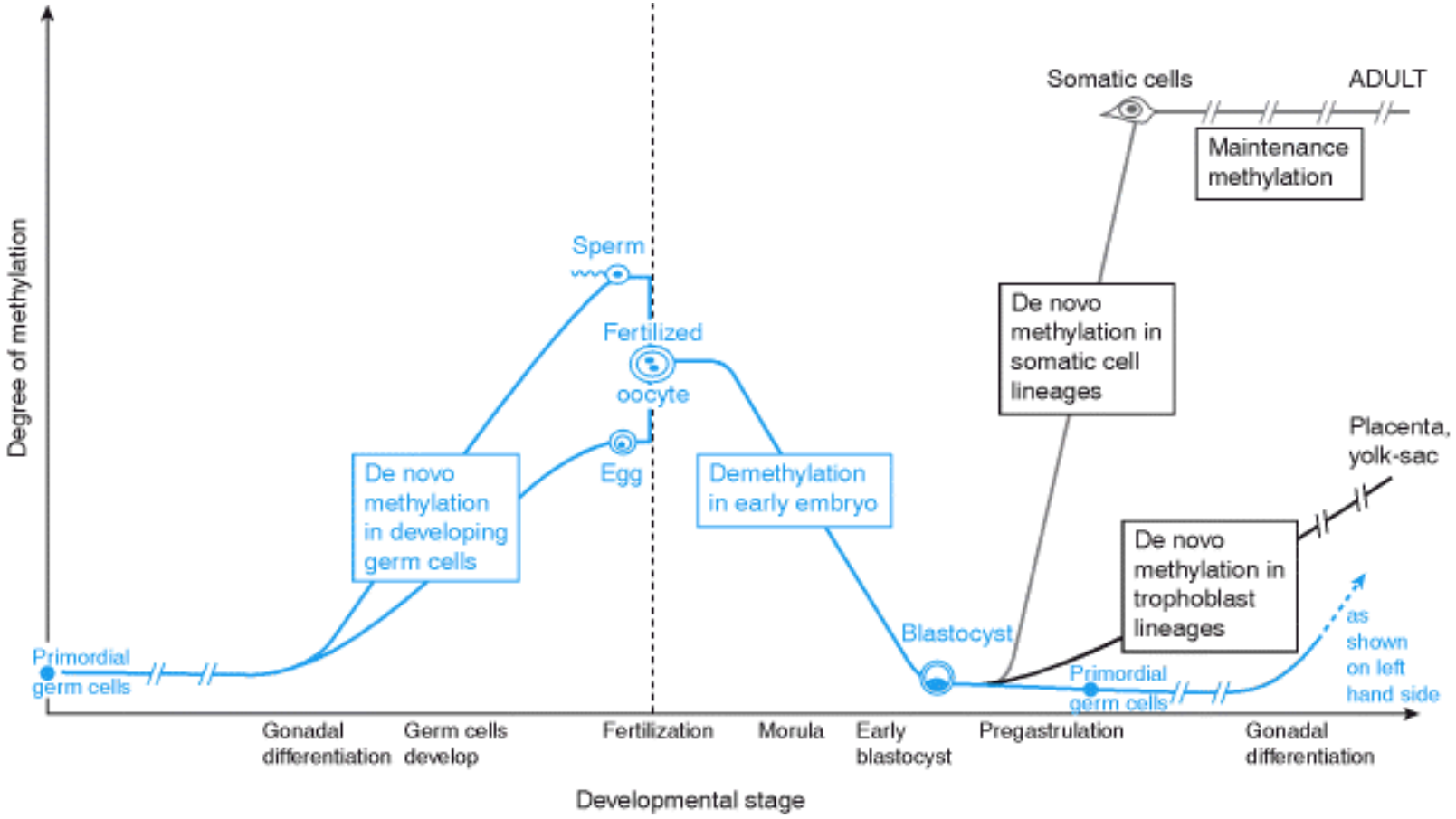
Mecanismos epigenéticos do câncer

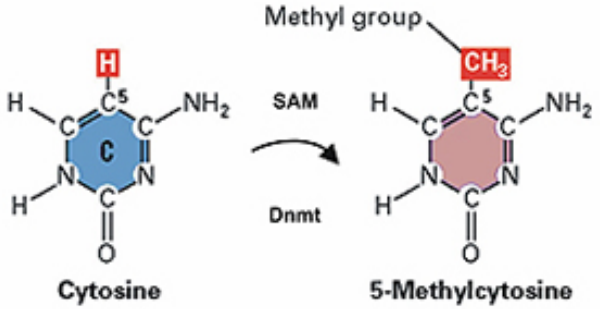
É um mecanismo herdável, mas não produzido por mudanças na sequência do DNA

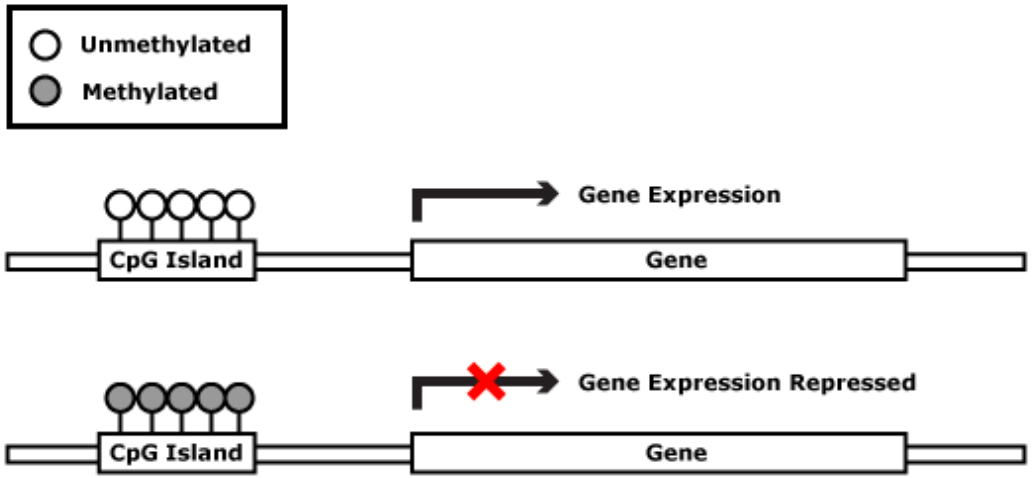
Desacetilação das histonas

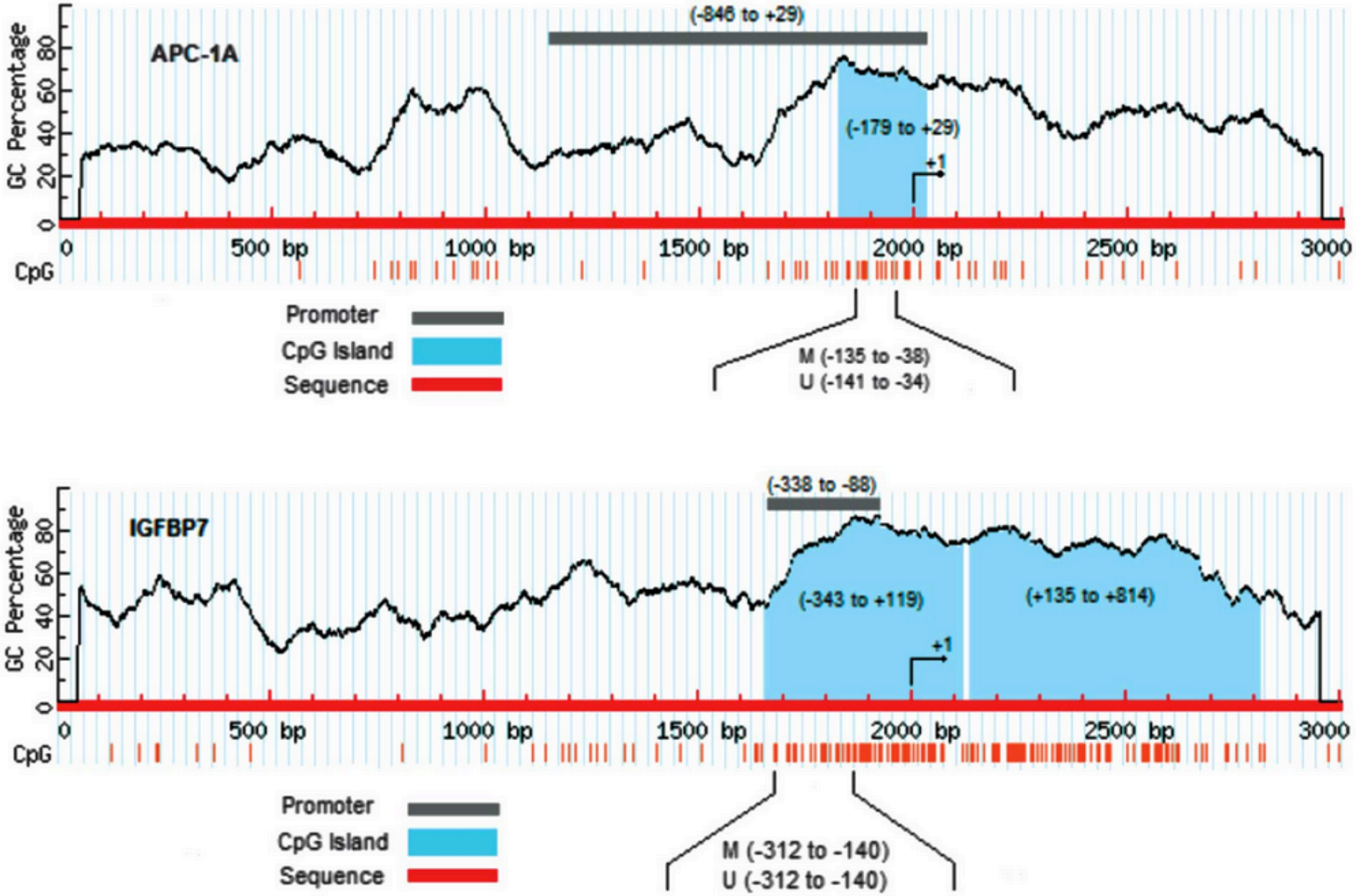


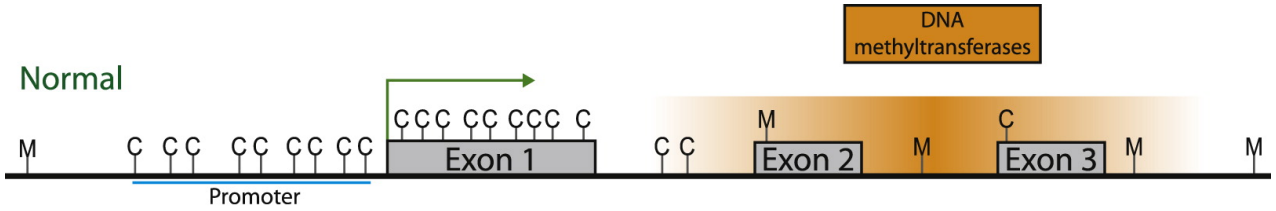
Mecanismos epigenéticos do câncer

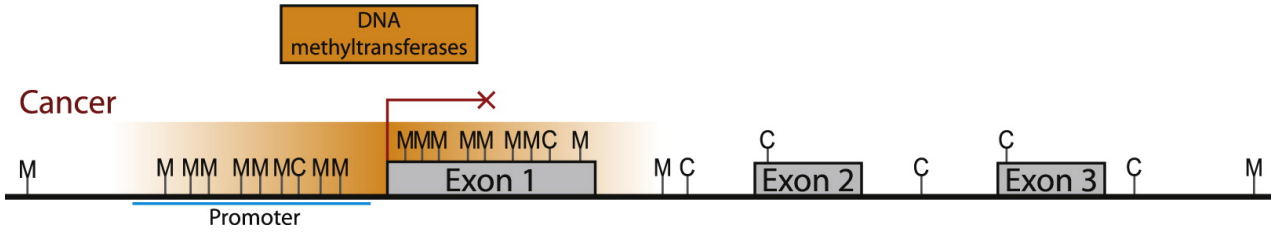


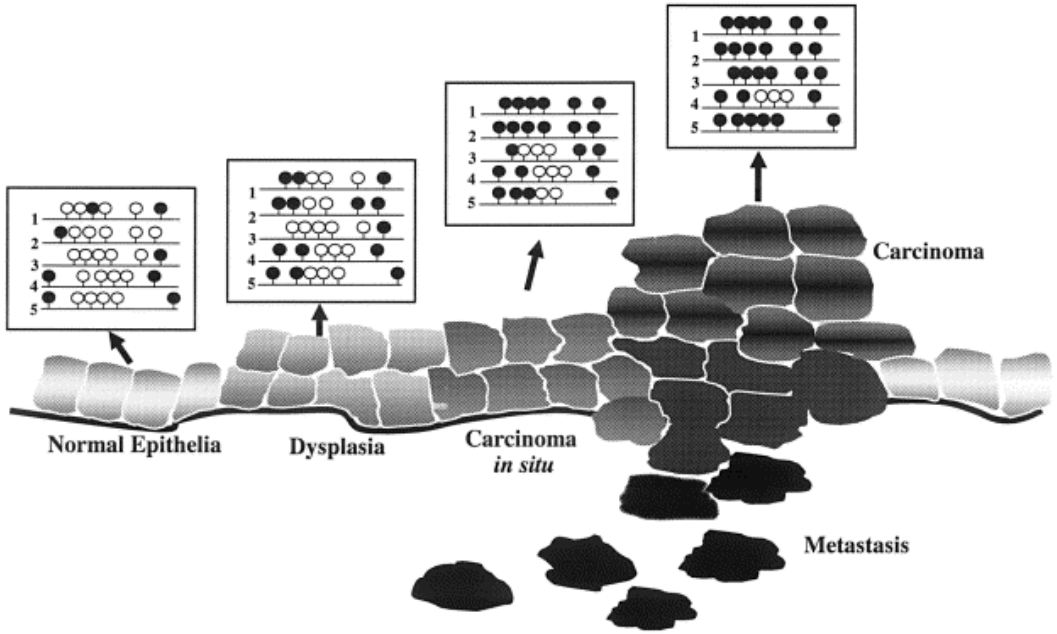

Methyl group
H
CH3
SAM
Dnmt
NH2
Cytosine
5-Methylcytosine


Unmethylated
Methylated
Gene Expression
CpG Island
Gene
Gene Expression Repressed
CpG Island
Gene

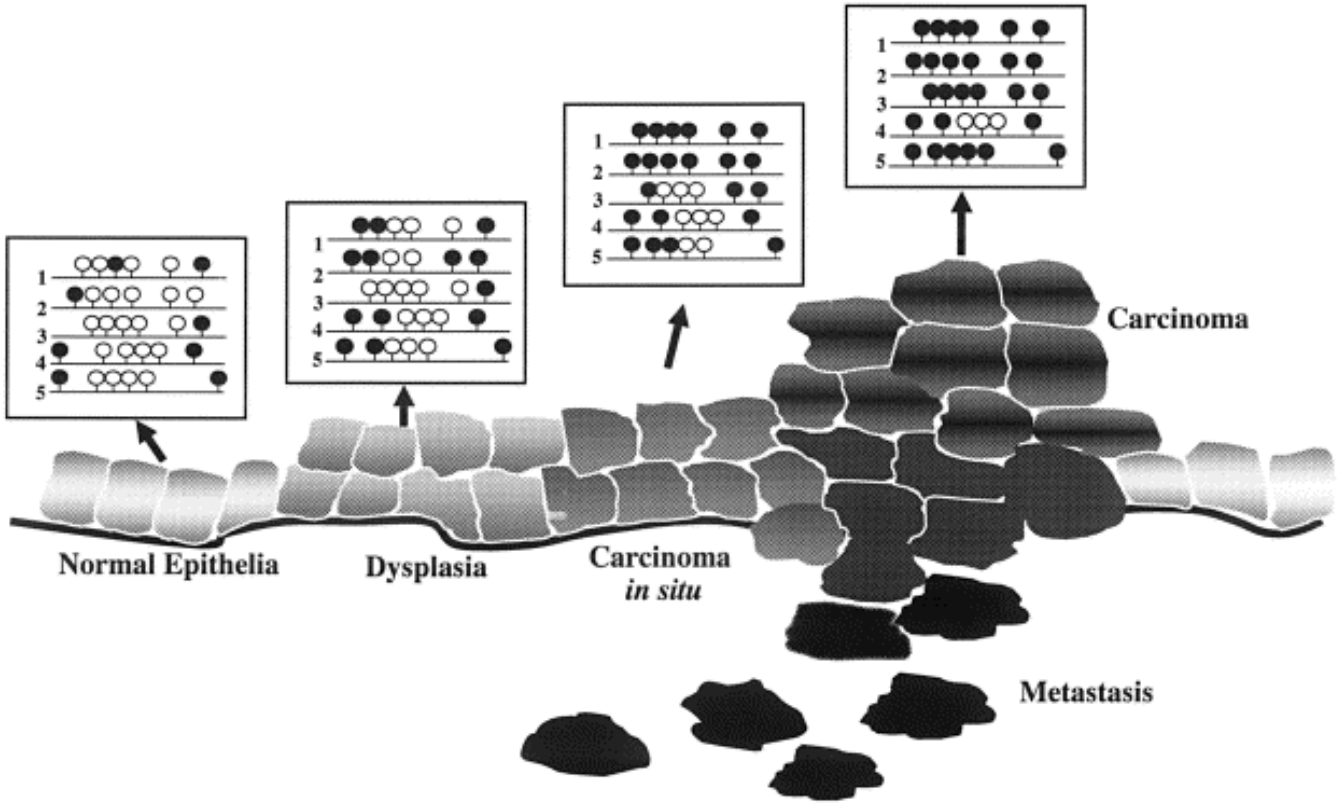

APC-1A
(-846 to +29)
(-179 to +29)
+1
GC Percentage
0
20
40
60
80
0
500 bp
1000 bp
1500 bp
2000 bp
2500 bp
3000
CpG
Promoter
CpG Island
Sequence
M (-135 to -38)
U (-141 to -34)
IGFBP7
(-338 to -88)
(-343 to +119)
(+135 to +814)
+1
GC Percentage
0
20
40
60
80
0
500 bp
1000 bp
1500 bp
2000 bp
2500 bp
3000
CpG
Promoter
CpG Island
Sequence
M (-312 to -140)
U (-312 to -140)

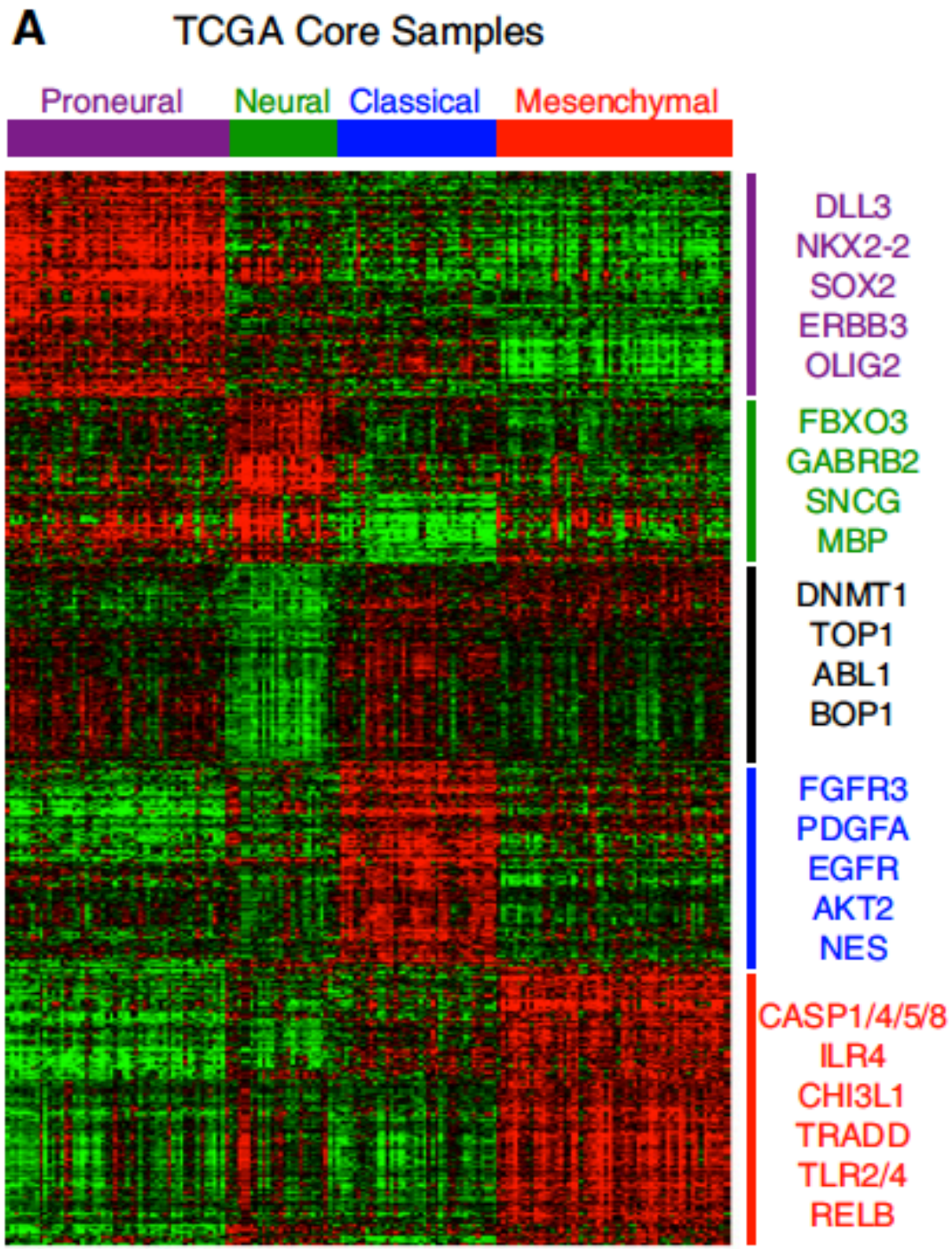

Normal
DNA
methyltransferases
M
C C C
C C C C C C C
Exon 1
C C
M
Exon 2
M
C
Exon 3
M
M
Promoter


DNA
methyltransferases
Cancer
M
M MM MM MC MM
MMM MM MMC M
Exon 1
M C
C
Exon 2
C
C
Exon 3
C
M
Promoter


1
2
3
4
5
Carcinoma
Normal Epithelia
Dysplasia
Carcinoma
in situ
Metastasis

Mecanismos epigenéticos do câncer



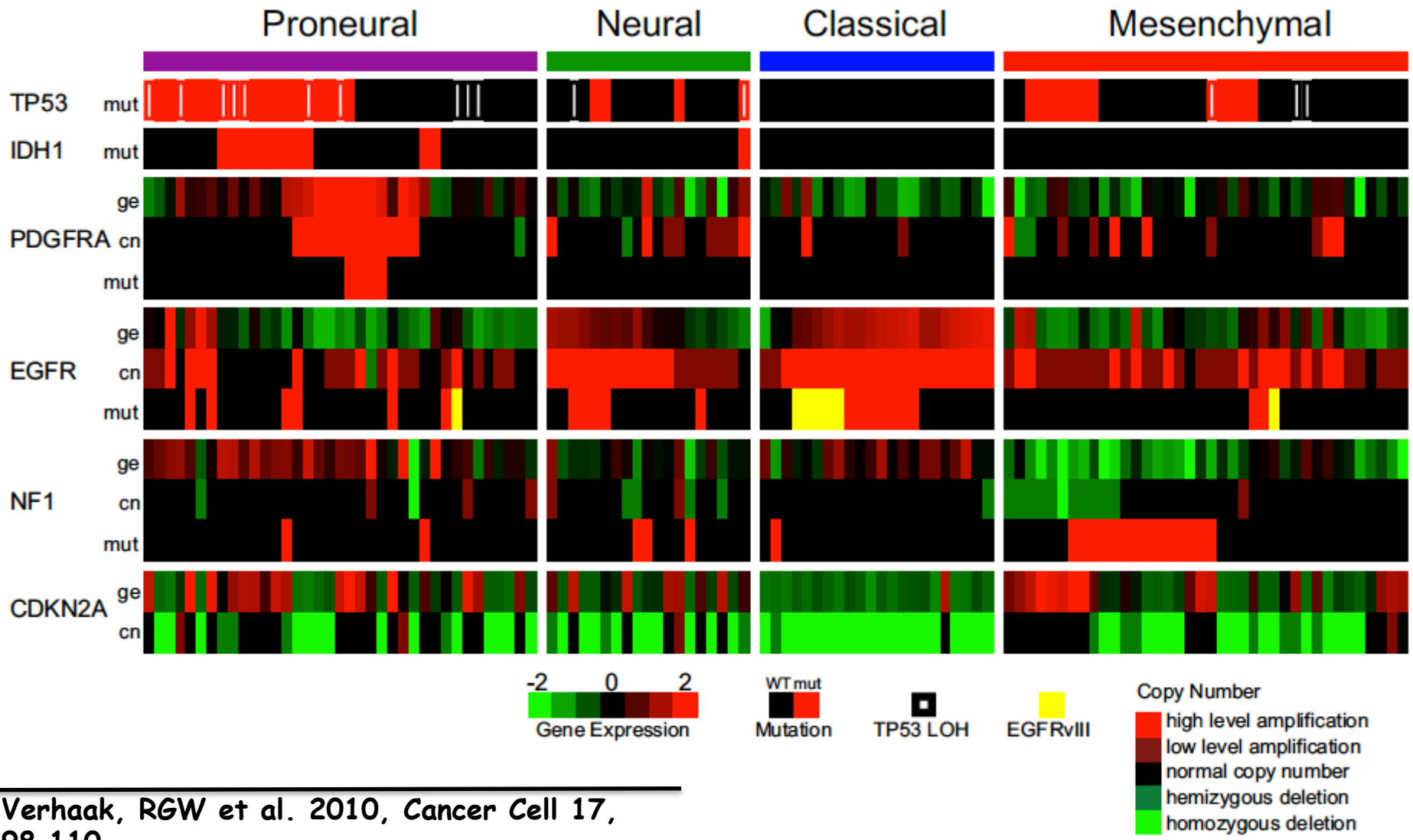


Padrão Global de Expressão Gênica:

4 subtipos de GBM distintos

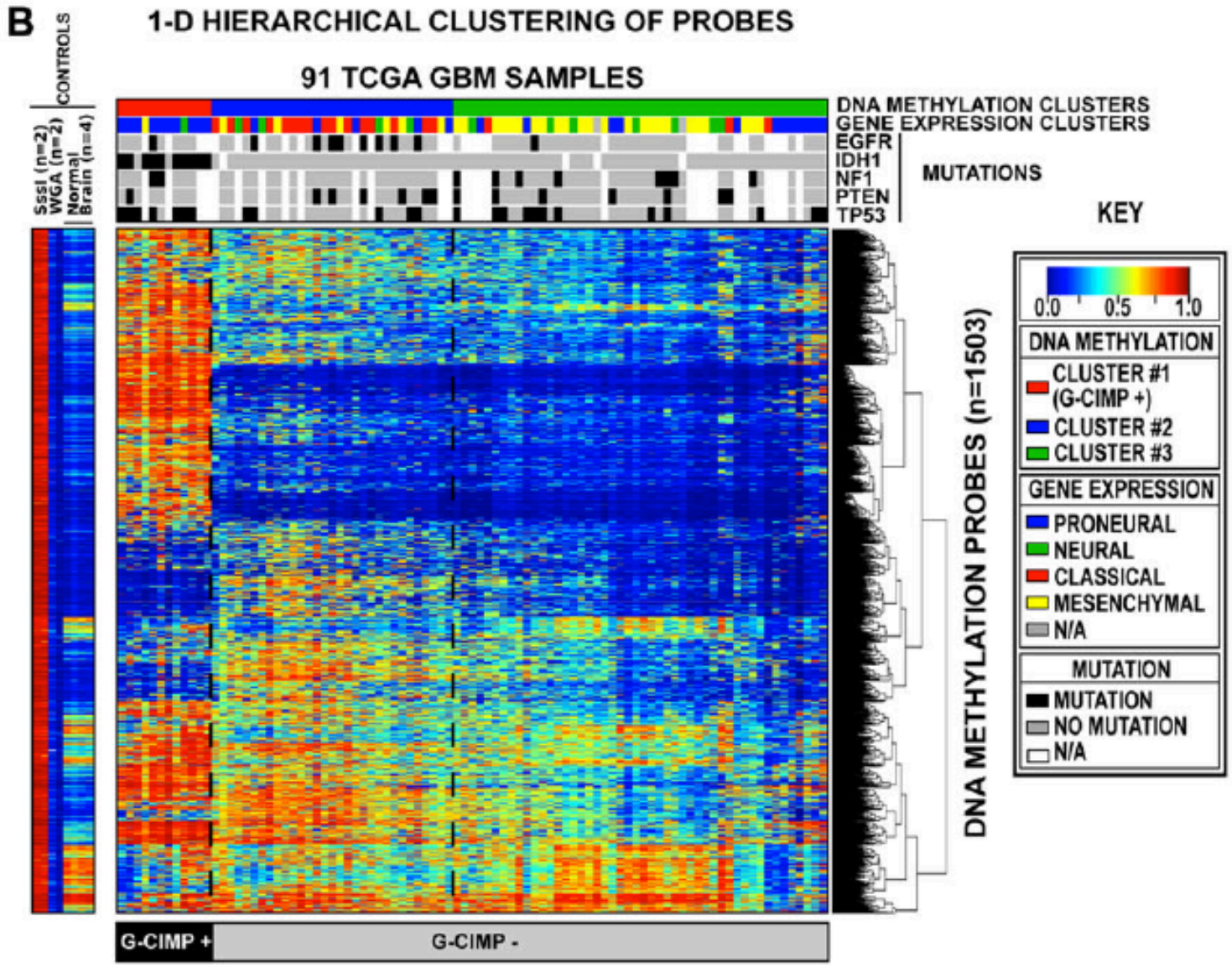
Verhaak, RGW et al. 2010, Cancer Cell 17, 98–110.

Visão integrada das alterações de expressão e estruturais nos diferentes subtipos



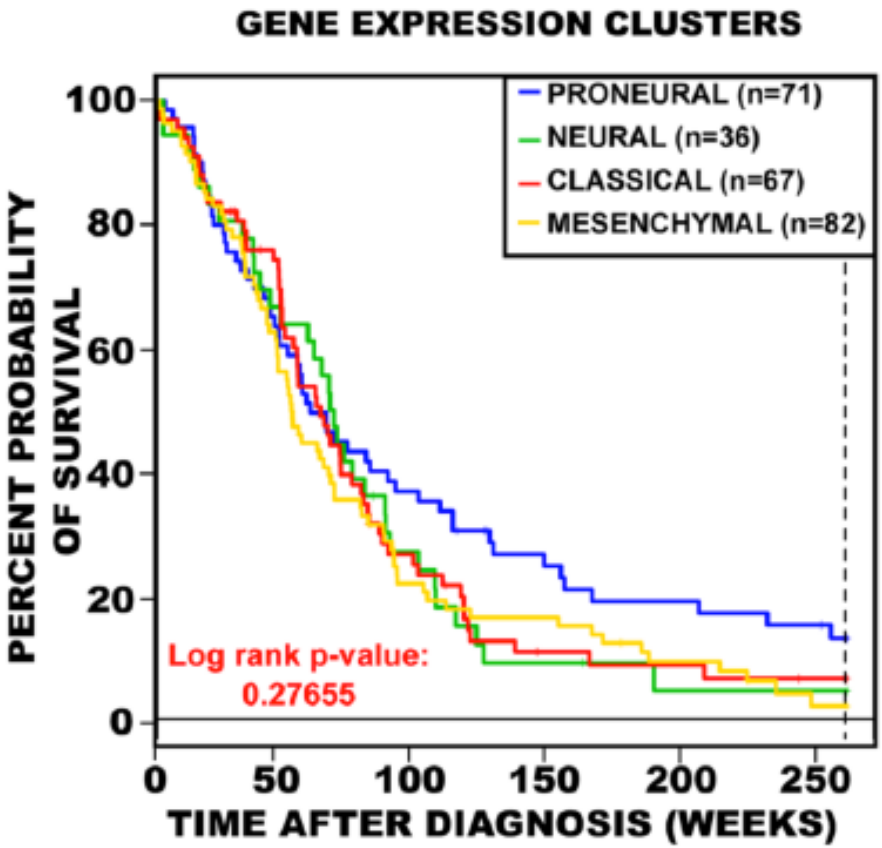
Verhaak, RGW et al. 2010, Cancer Cell 17, 98–110.

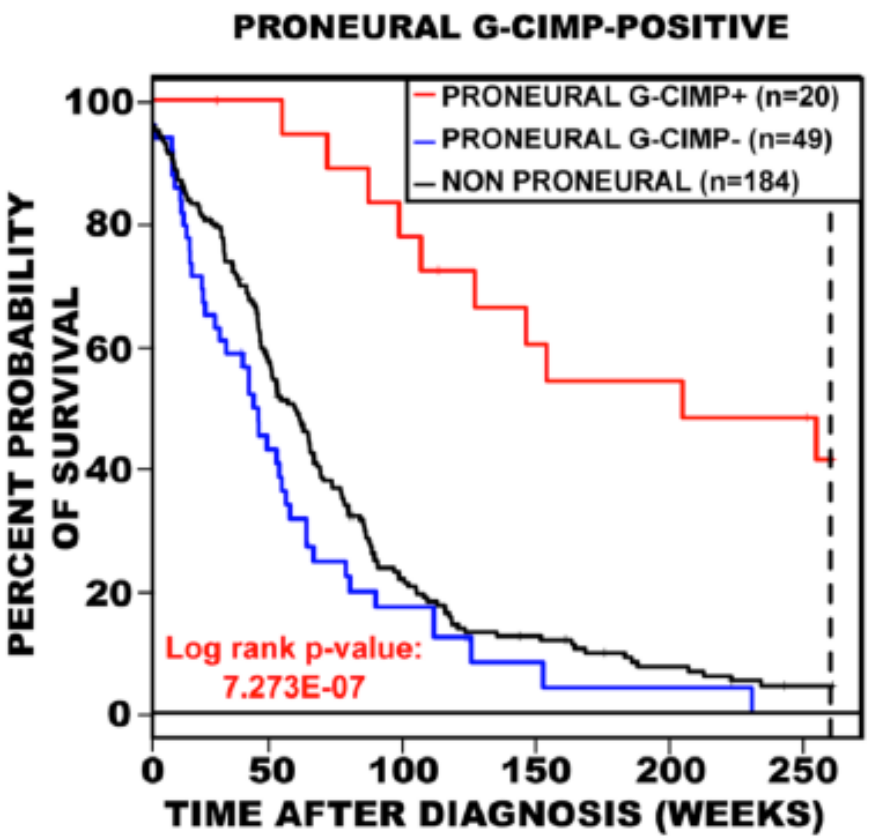
Identificação do fenótipo de ilhas CpG hipermetiladas - gCIMP



Noushmehr, H et al. 2010, Cancer Cell. 18; 17(5): 510–522.

Impacto do fenótipo *gCIMP* no prognóstico dos pacientes





Noushmehr, H et al. 2010, Cancer Cell. 18; 17(5): 510-