SOMATIC MUTATIONS AND CANCER

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Florence, ITALY

Doctorate in Genetics Seminar Series,
University of Siena
October 12, 2012

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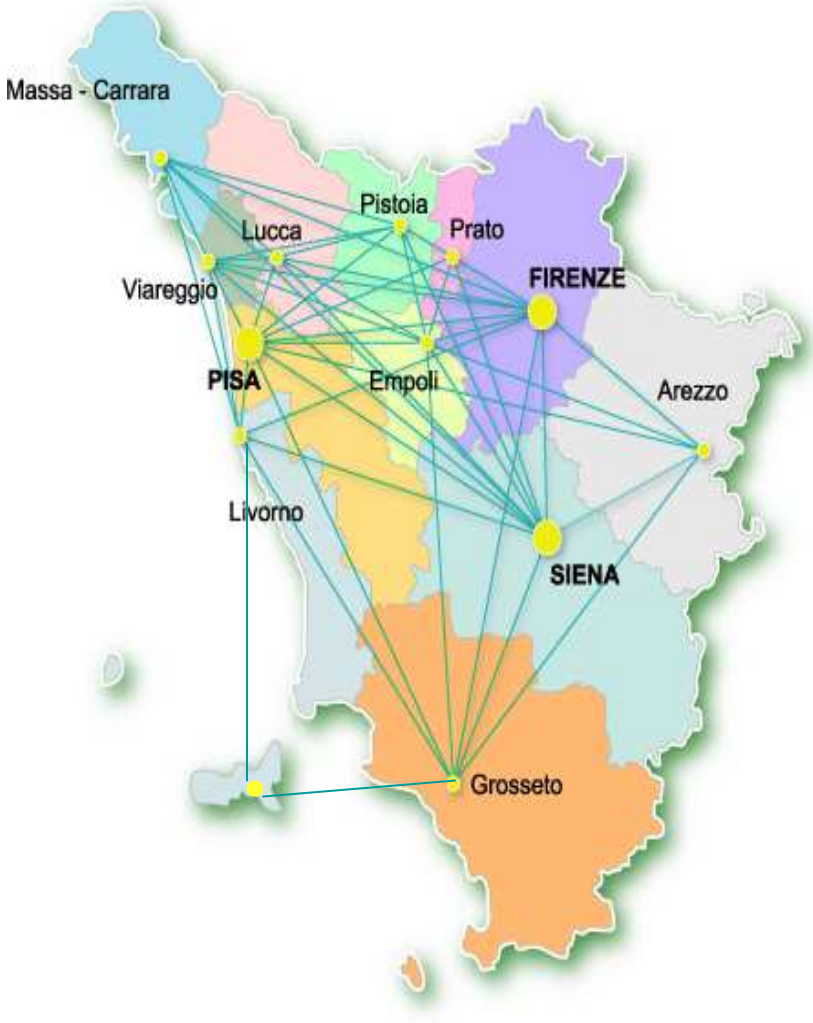
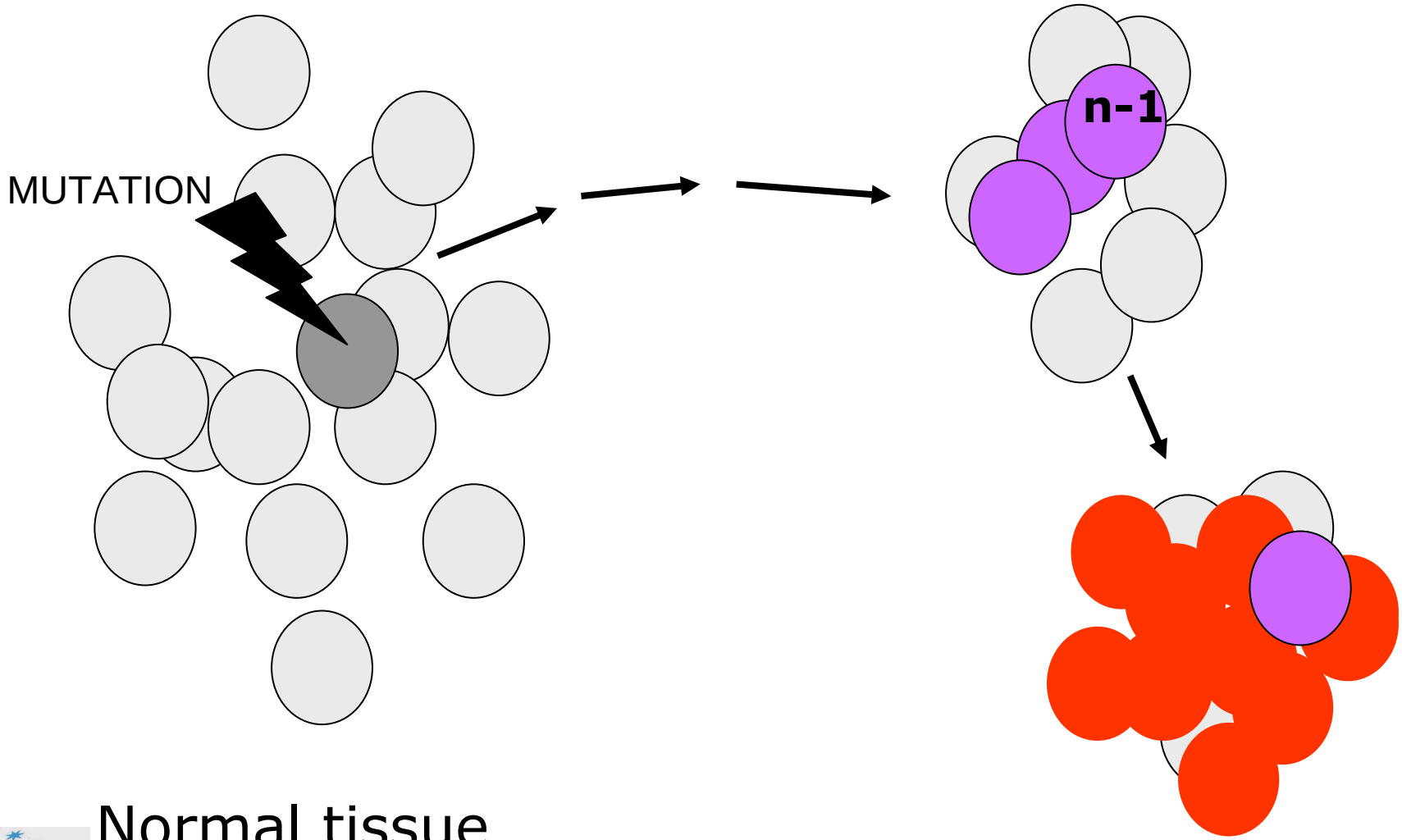
TO UNDERSTAND,
TO TREAT
TO PREVENT CANCER
AT BEST FOR ALL



ISTITUTO PER LO STUDIO
E LA PREVENZIONE ONCOLOGICA

FORMATION OF A TUMOR RESULTS FROM SOMATIC MUTATIONS AND DARWINIAN SELECTION



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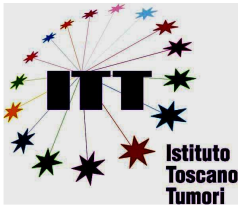
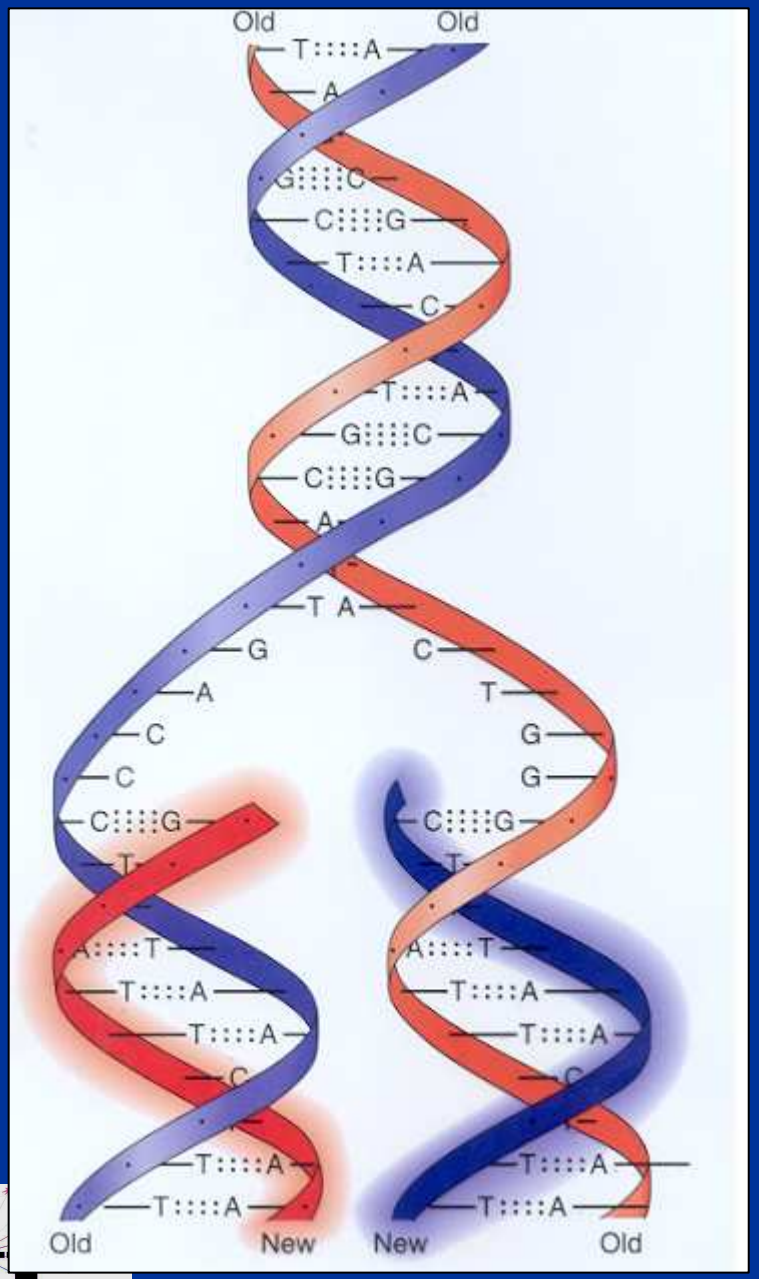
SOMATIC MUTATIONS IN CANCER: SYNOPSIS

1. No cancer without somatic mutations
2. The rate of mutation is important
3. Mutations are stochastic events





Rarely,
errors can take place
in the course
of DNA replication

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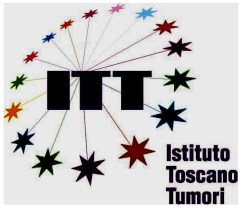
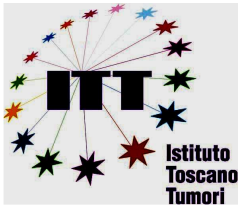
NUMEROLOGY OF SOMATIC MUTATIONS

- Estimated rate of somatic mutation in an individual gene: 2×10^{-7}/cell division
- Approximate number of cells in human body: 10^{14} (about 10^{9} per G)
- Approximate number of 'deep' cell divisions to make an adult: 10^{15}
- Approximate number of genes in human genome: 24,000.
- Approximate number of expected somatic mutations accumulated in an adult: **5×10^{12}**

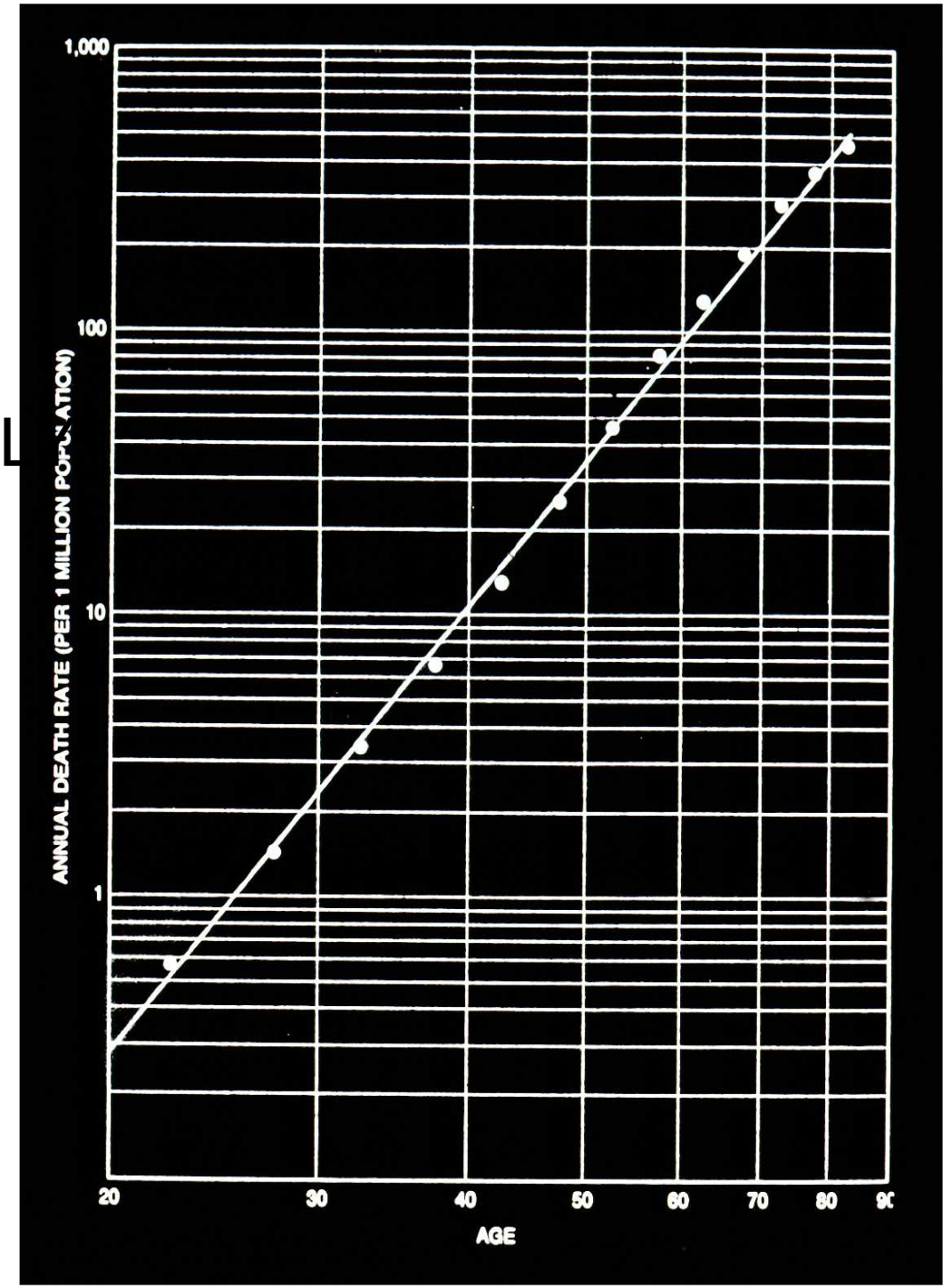


SOMATIC MUTATIONS IN CANCER

- How many mutations
- Which cells are mutated
- What causes mutations
- What kind of mutations
- What genes are mutated



THE INCIDENCE OF CANCER DEPENDS STRONGL ON AGE



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SOMATIC MUTATIONS IN CANCER

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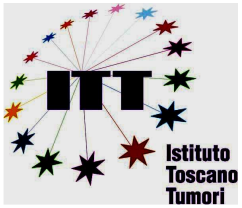
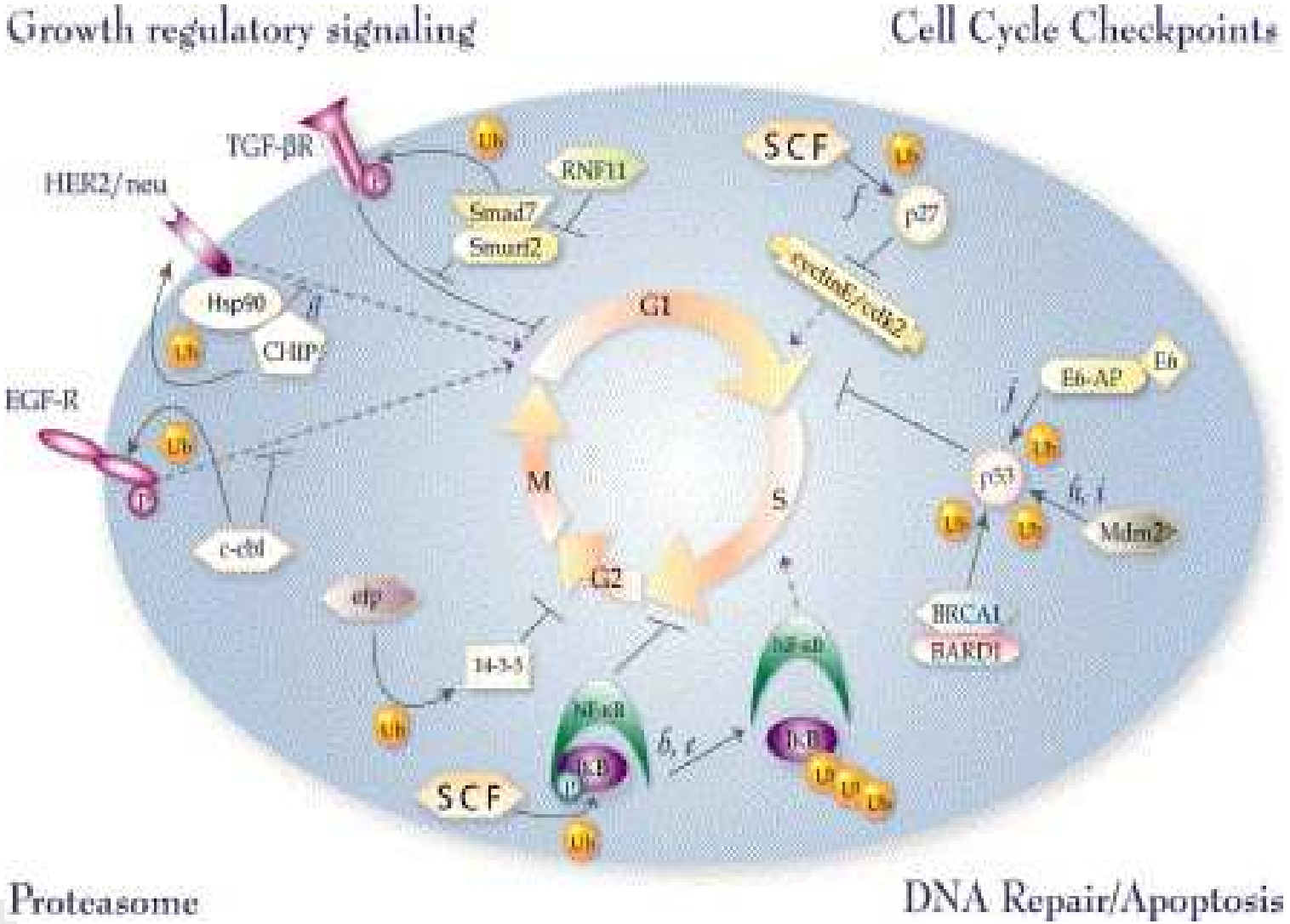
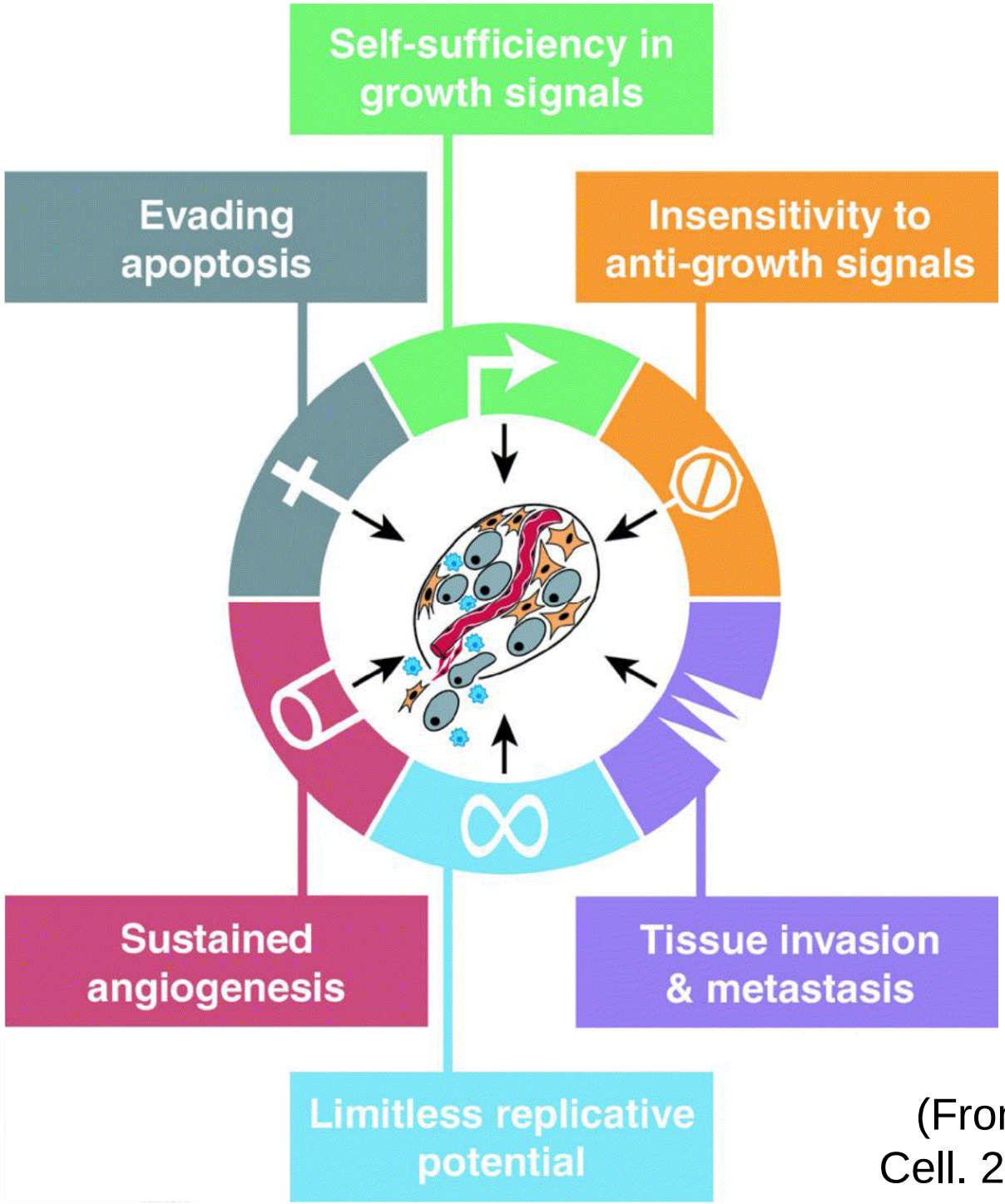



Growth regulatory signaling
Cell Cycle Checkpoints
TGF-βR
HER2/neu
EGF-R
Hsp90
CHIP
Ub
RNF11
Smad7
Smurf2
SCF
p27
cyclinE/cdk2
G1
S
G2
M
E6-AP
E6
p53
Mdm2
BRCA1
BARD1
c-cbl
elp
14-3-3
NF-κB
IκB
SCF
Proteasome
DNA Repair/Apoptosis



(From Hanahan D, Weinberg RA Cell. 2000 Jan 7;100(1):57-70.

ONCOGENE ADDICTION

…The apparent dependency of some cancers on one or a few genes for the maintenance of the malignant phenotype

Bernard Weinstein

Clin Cancer Res **3**:2696,1997
Science **297**:63,2002
Cancer Res **68**:3077,2008

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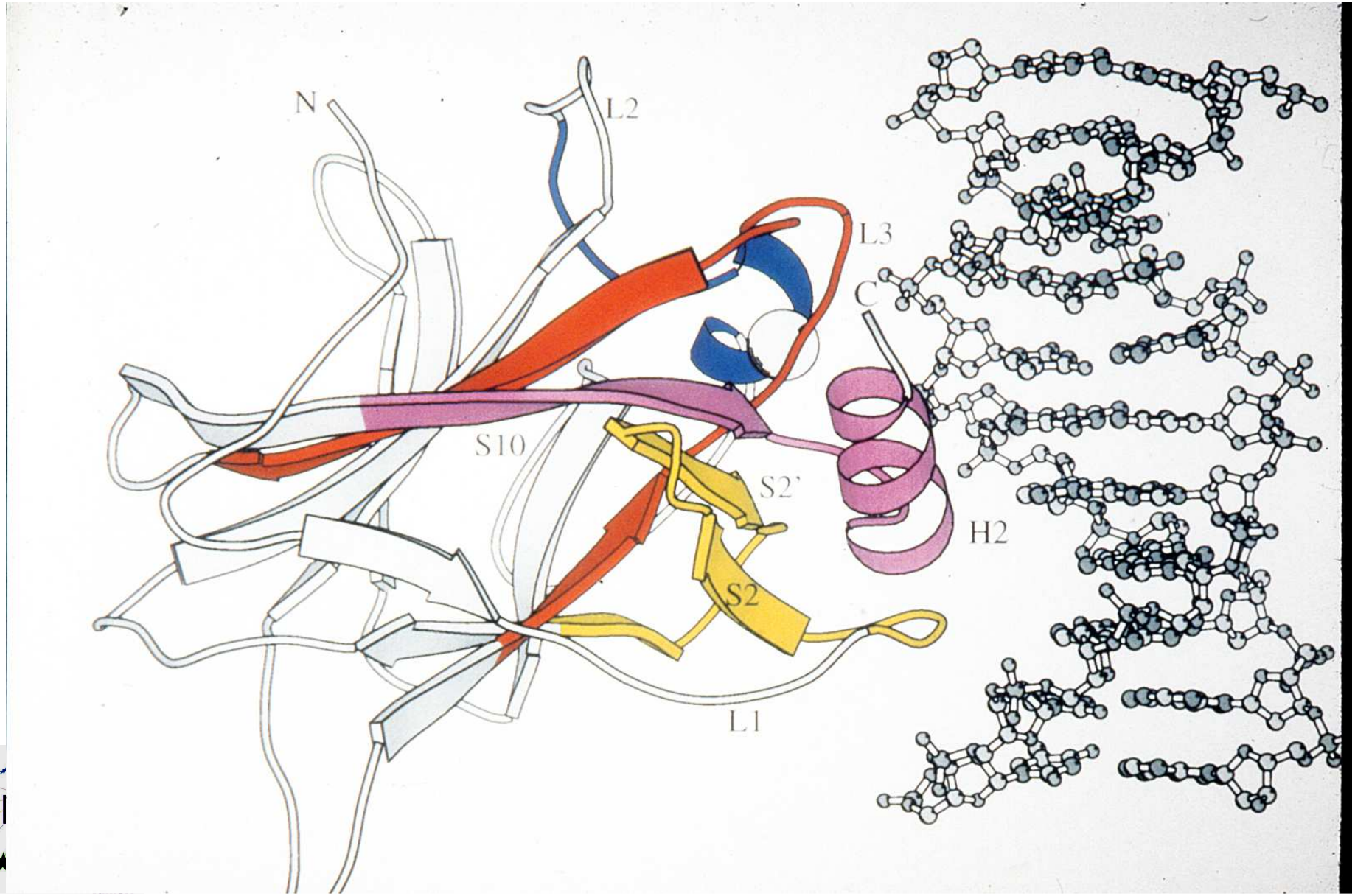
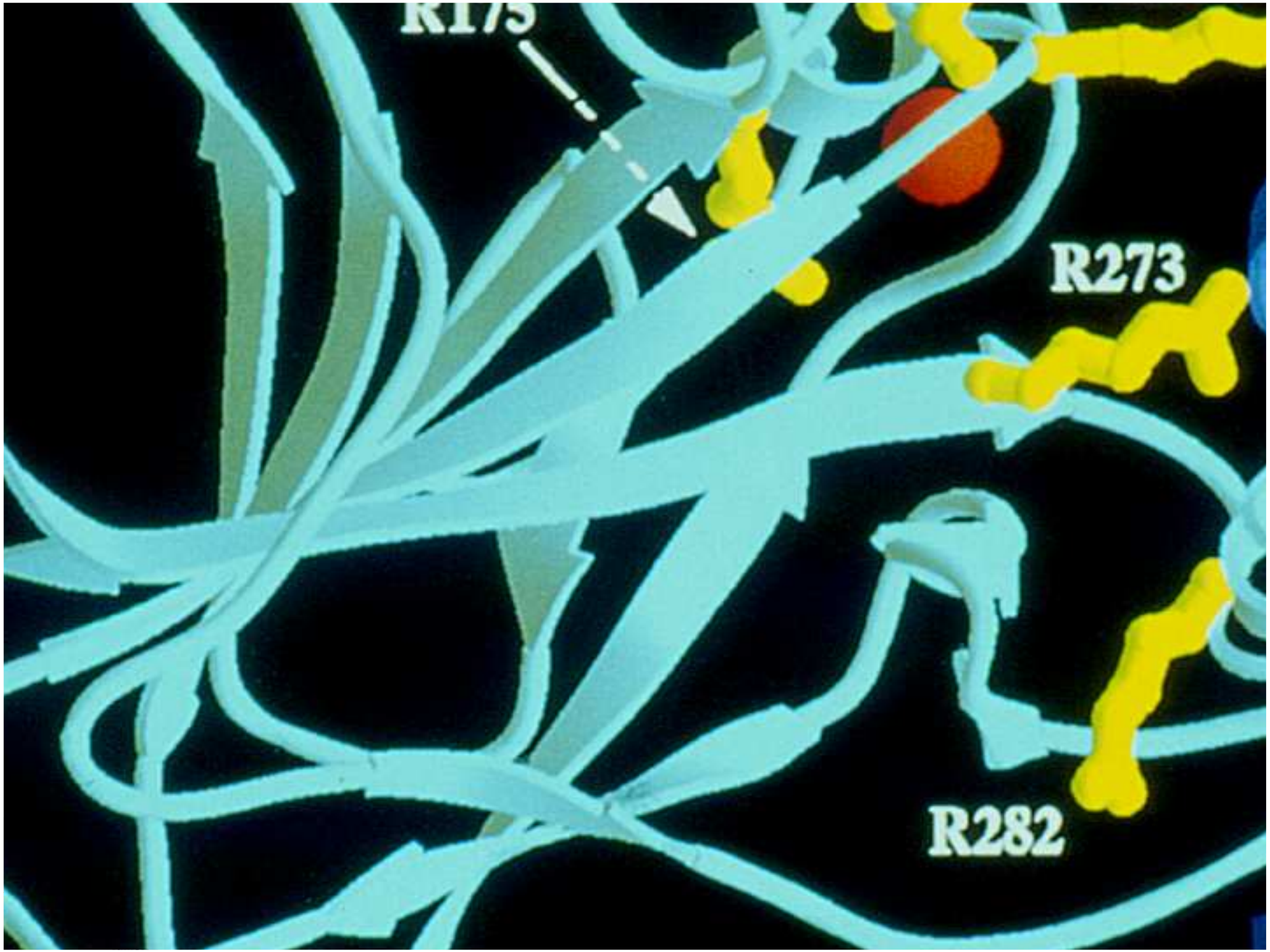
MODELS OF ONCOGENE ADDICTION

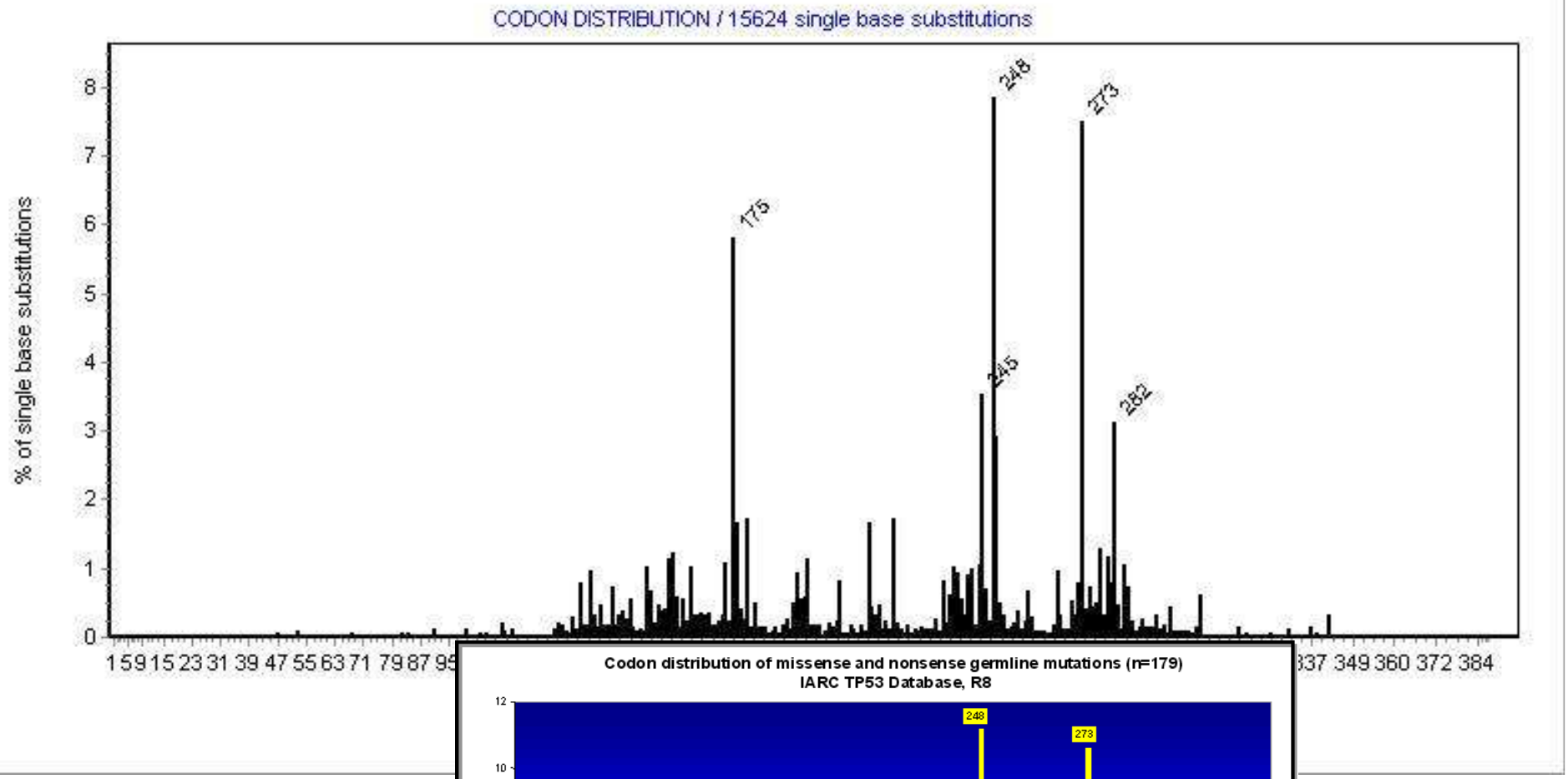
QuickTime™ and a
decompressor
are needed to see this picture.

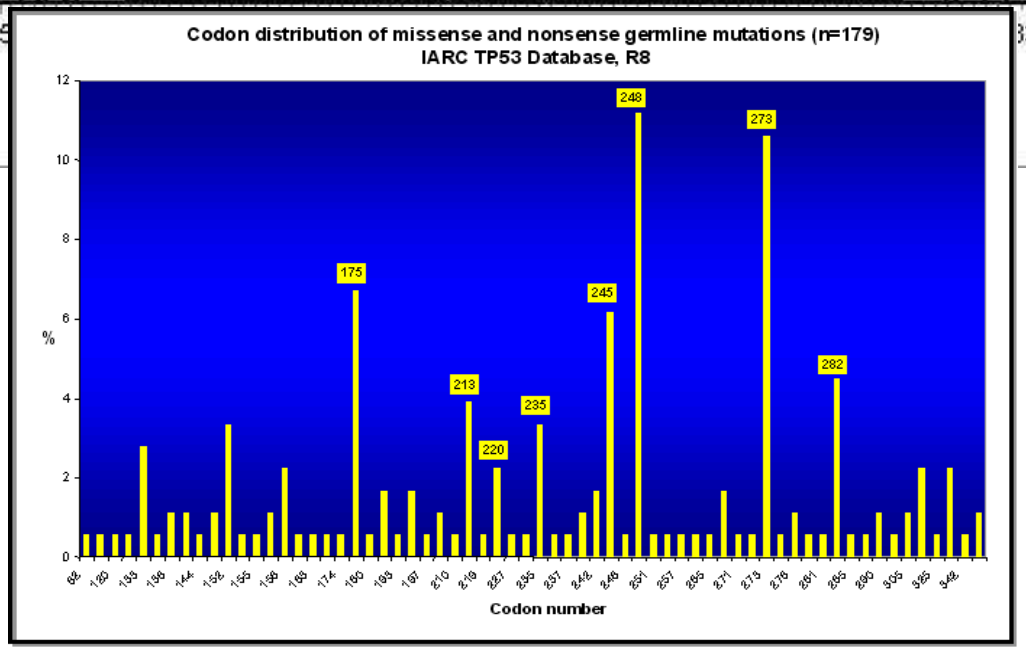
(From Torti & Trusolino *EMBO Mol Med* **3**:623,2011)

BINDING TO CERTAIN SPECIFIC DNA ELEMENTS IS CRUCIAL TO THE FUNCTIONS OF p53




R175
R273
R282





p53:
SOMATIC
MUTATIONS
versus
GERM-LINE
MUTATIONS

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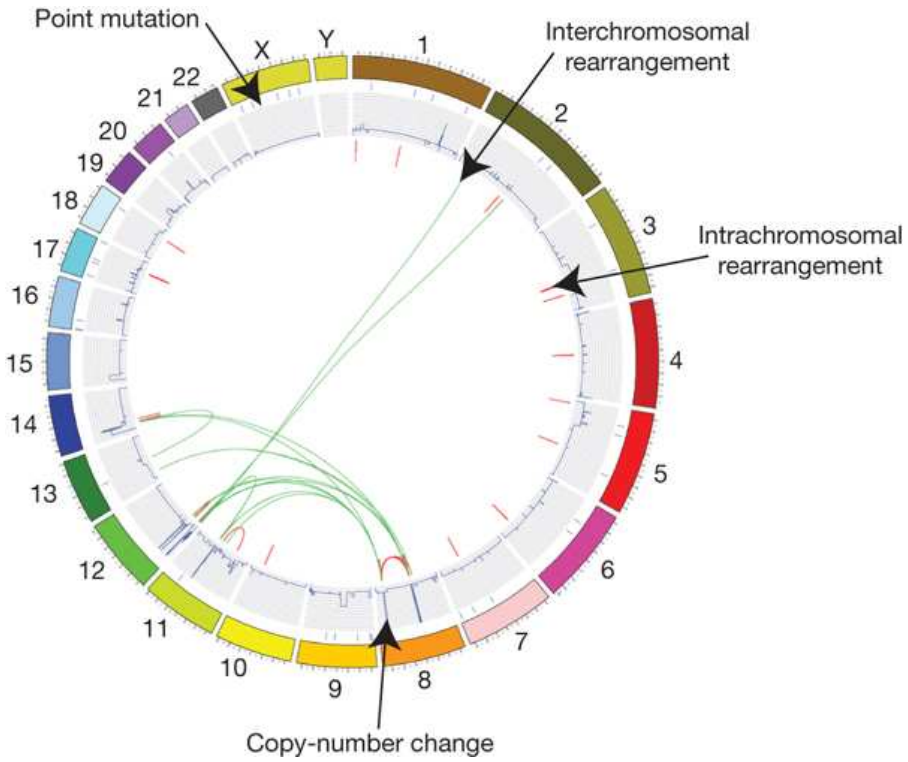
Figurative depiction of the landscape of
somatic mutations present in a single cancer genome.



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

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nature

FEATURES OF HUMAN RETINOBLASTOMA ARE RERMARKABLY CONSERVED

Original tumor

QuickTime™ and a
decompressor
are needed to see this picture.

Xenograft from above

(From Zhang *et al.*, *Nature*, 2012)

GENOMIC PROFILE OF RETINOBLASTOMA IN TWO INDIVIDUAL PATIENTS

QuickTime™ and a
decompressor
are needed to see this picture.

From Zhang *et al.*, *Nature*, 2012

RETINOBLASTOMA HAS FEW MUTATIONS WHEN COMPARED TO OVARIAN CANCER

QuickTime™ and a
decompressor
are needed to see this picture.

From Zhang *et al.*, *Nature*, 2012

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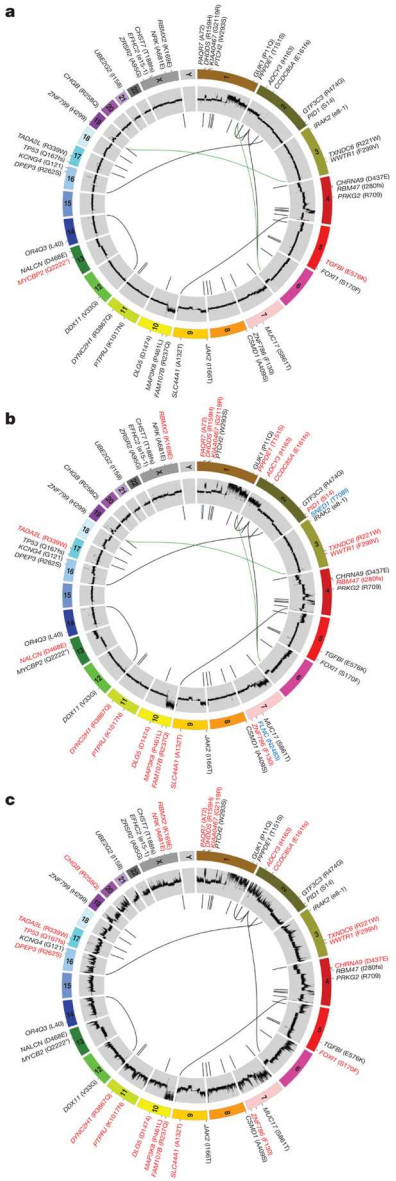
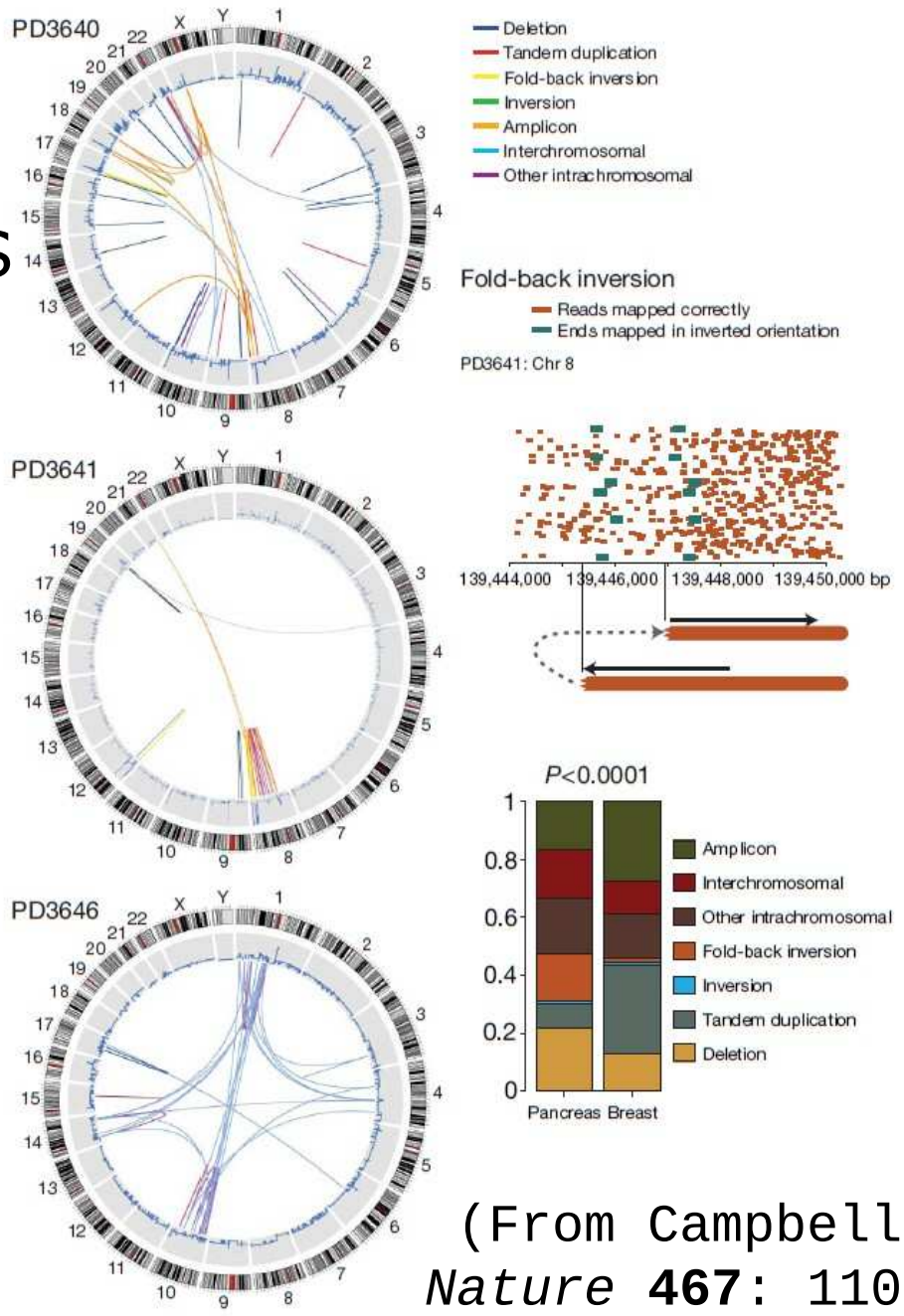
Circos plots
for the primary tumor,
metastasis,
and xenograft genomes
of a basal breast tumor



(From Ding et al.,
Nature **464**:999, 2010)

PATTERNS OF SOMATIC GENOMIC REARRANGEMENTS IN PANCREATIC CANCER



(From Campbell et al., *Nature* **467**: 1109, 2010)

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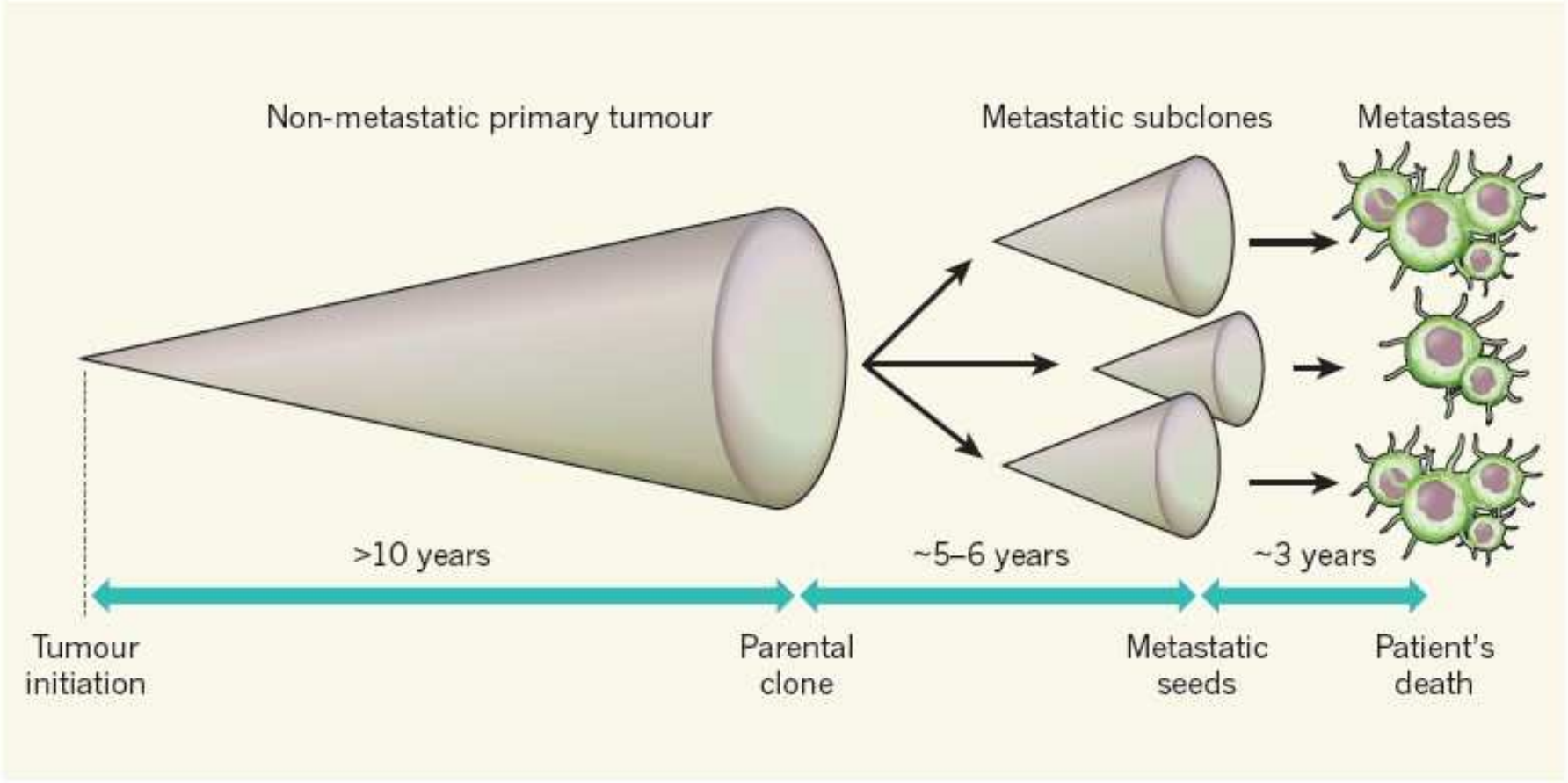
TENTATIVE TIMELINE OF PANCREATIC CANCER



(From E G Luebeck *Nature* **467**: 1055, 2010)

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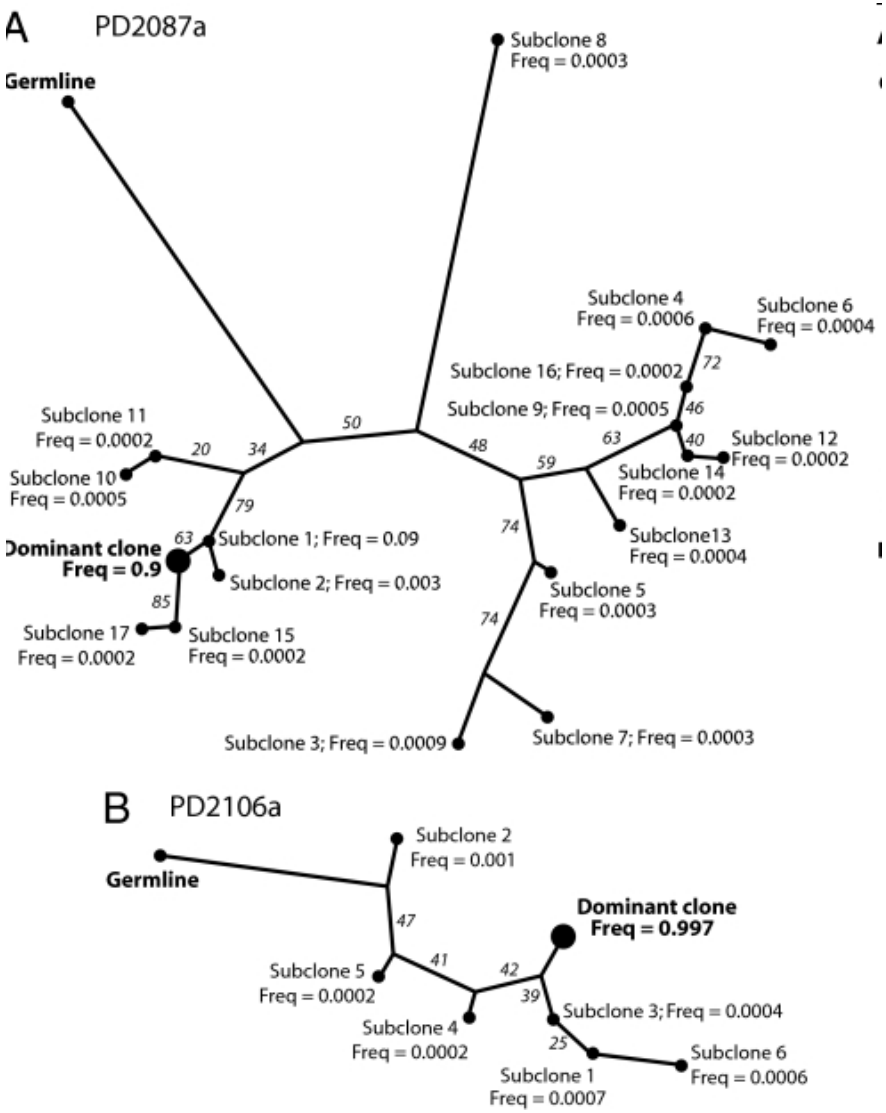
CLONAL EVOLUTION IN TWO PATIENTS WITH CLL DEMONSTRATED BY 'ULTRA-DEEP' SEQUENCING



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Campbell et al., *Proc Natl Acad Sci U S A.* **105**:: 13081–13086, 2008

QuickTime™ and a
decompressor
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(From Patel et al., NEJM 366:1079,2012)

COMPLEXITY OF SOMATIC MUTATIONS IN ACUTE MYELOID LEUKAEMIA

QuickTime™ and a
decompressor
are needed to see this picture.

(From Patel et al.,
NEJM 366:1079,2012)

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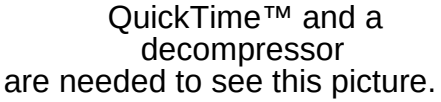
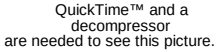
CLONAL EVOLUTION FROM MDS TO AML

QuickTime™ and a
decompressor
are needed to see this picture.

(From Walter et al., NEJM 366:1090,2012)

WNT AND *SHH* SUB-TYPES OF MEDULLOBLASTOMA ARE ANATOMICALLY DISTINCT





(From Gibson et al., *Nature* **468**:1095, 2010)

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QuickTime™ and a
decompressor
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Other major initiatives accessible on line:

WELLCOME TRUST SANGER INSTITUTE CANCER GENOME PROJECT
http://www.sanger.ac.uk/research/projects/cancergenome/

NIH-NCI CANCER GENOME ANATOMY PROJECT
http://cgap.nci.nih.gov/

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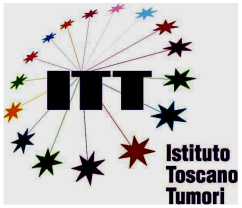
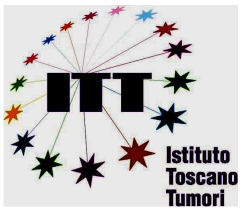


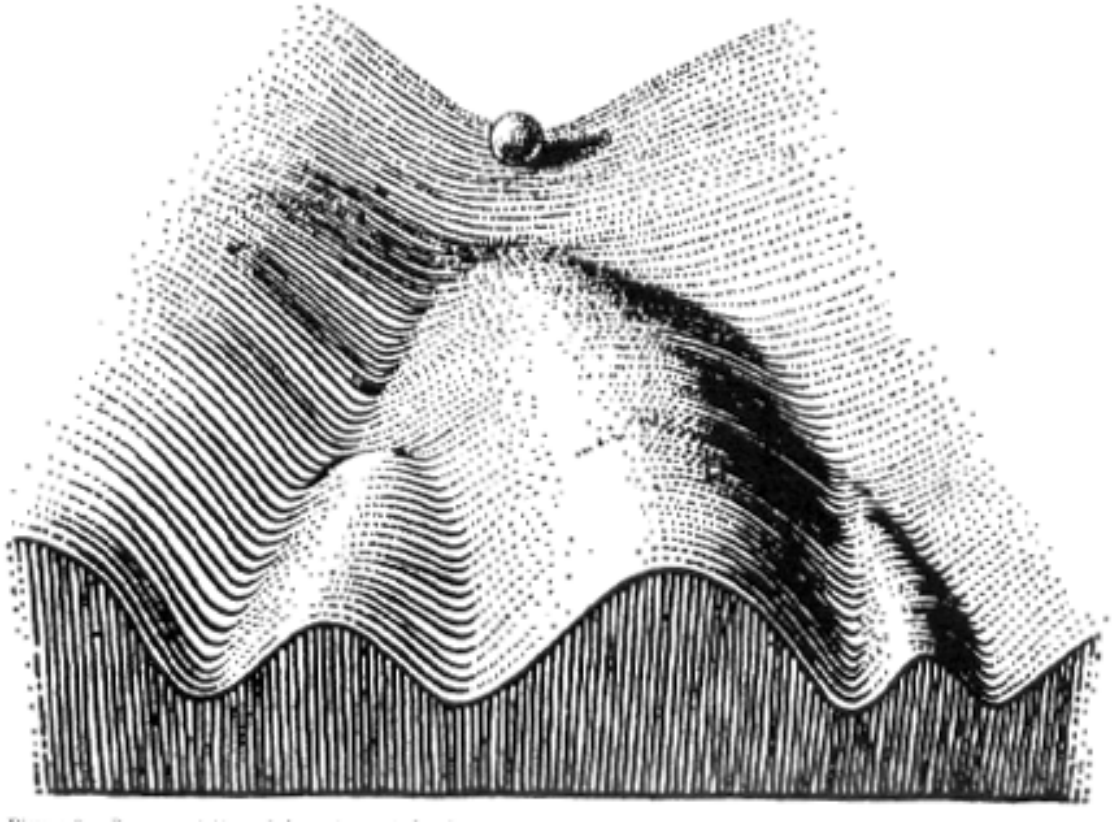
EPIGENETICS

…. The switching on and off of genes during development, the segregation of gene activities following somatic cell division, and **the stable (somatic) inheritance of a given spectrum of gene activities in specific cells'**…..
…..possibly explained by 'changes in the pattern of DNA methylation".

Robin Holliday 1989

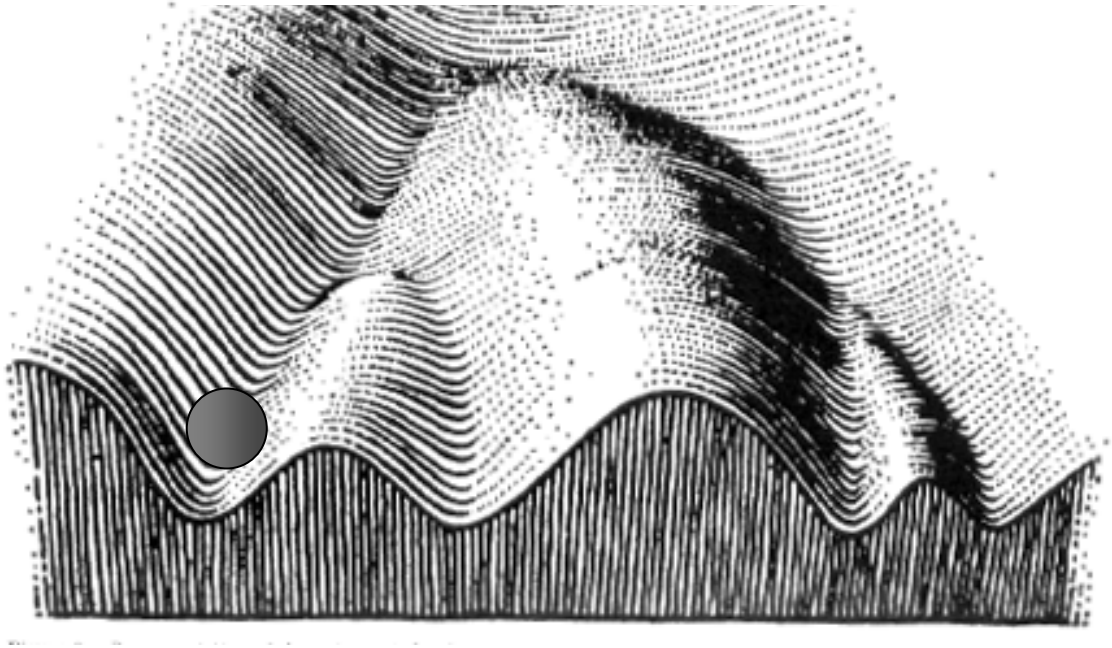


DEVELOPMENT and DIFFERENTIATION:
GOING DOWN DIFFERENT PATHWAYS



C D Waddington 1957

DEVELOPMENT and DIFFERENTIATION:
GOING DOWN DIFFERENT PATHWAYS



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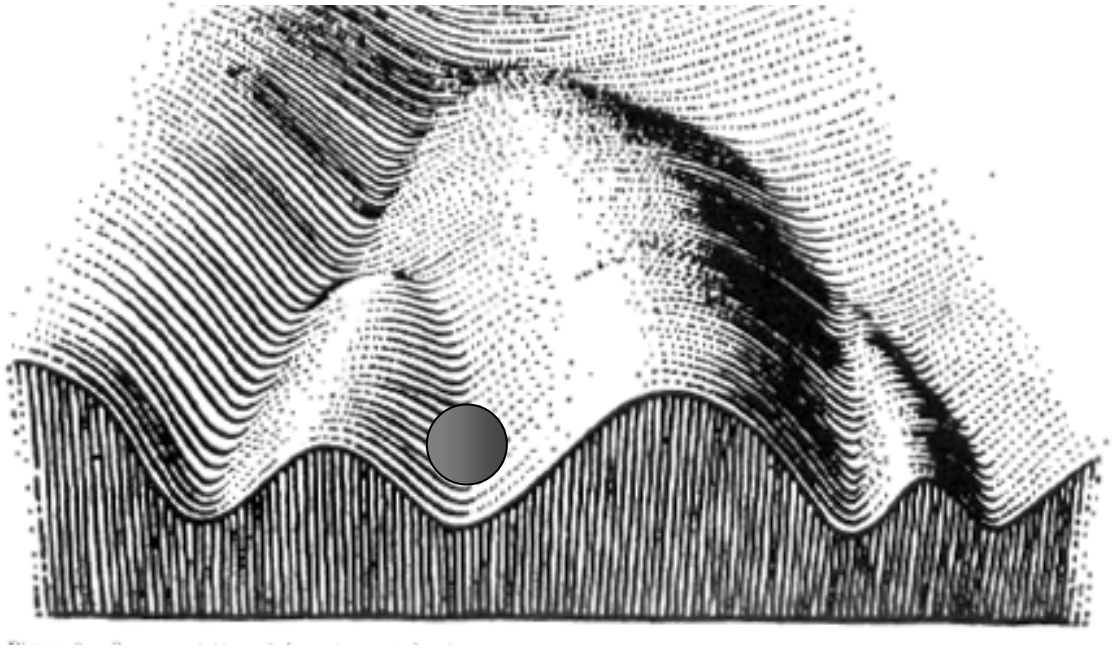
DEVELOPMENT and DIFFERENTIATION:
GOING DOWN DIFFERENT PATHWAYS



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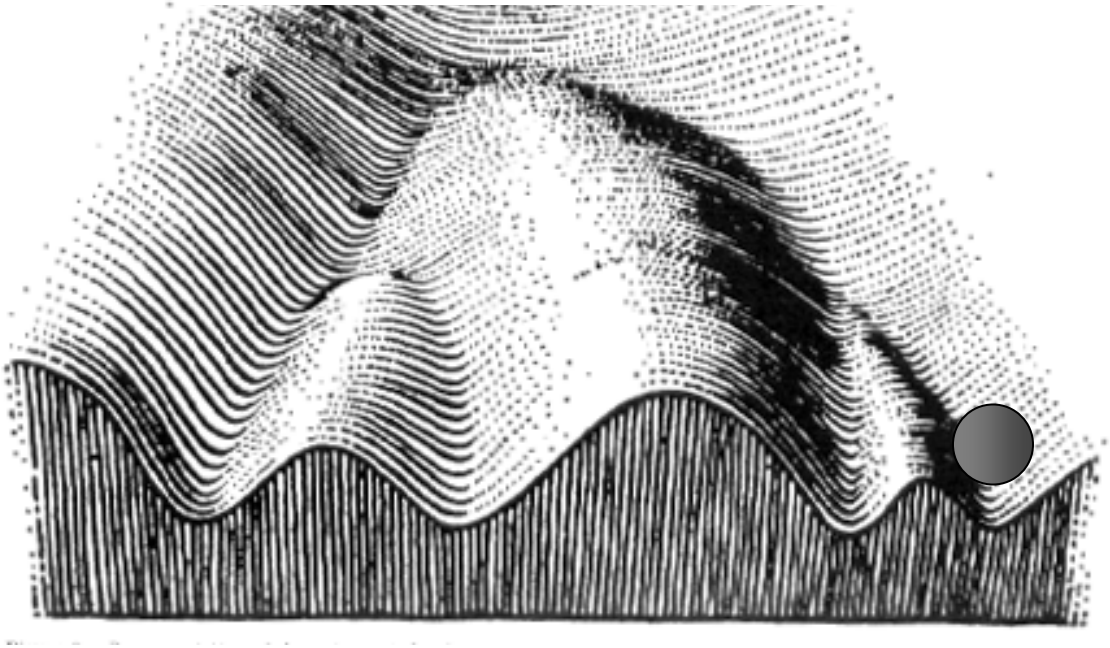
DEVELOPMENT and DIFFERENTIATION:
GOING DOWN DIFFERENT PATHWAYS



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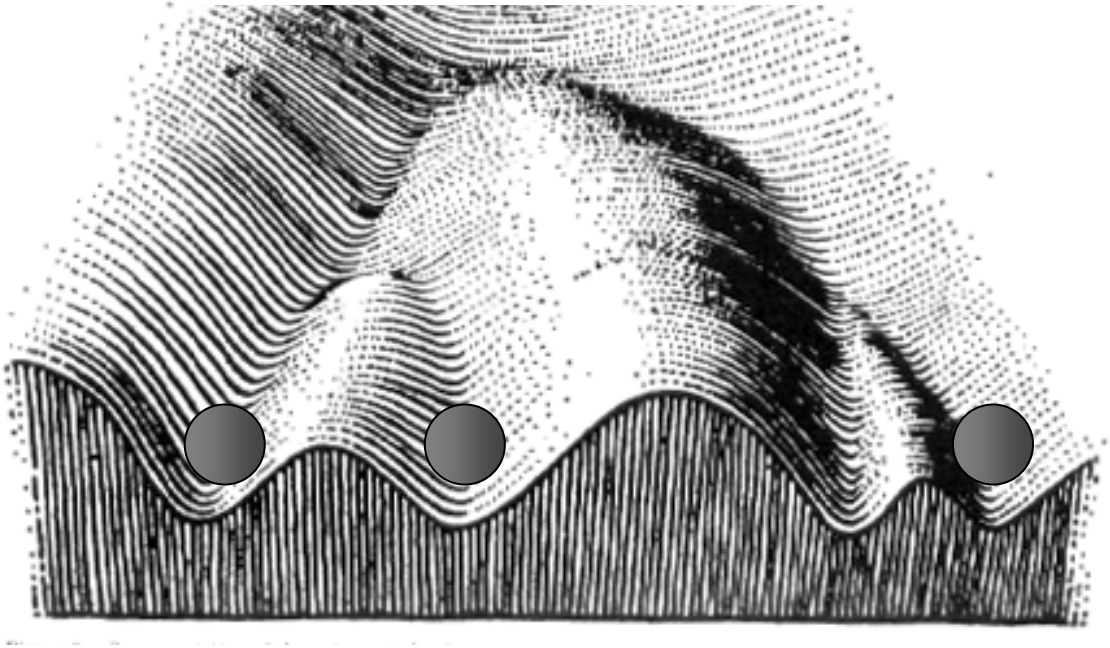
DEVELOPMENT and DIFFERENTIATION:
IS THE PROCESS REVERSIBLE?



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A MODEL OF HOW CHROMATIN CAN REGULATE GENE EXPRESSION

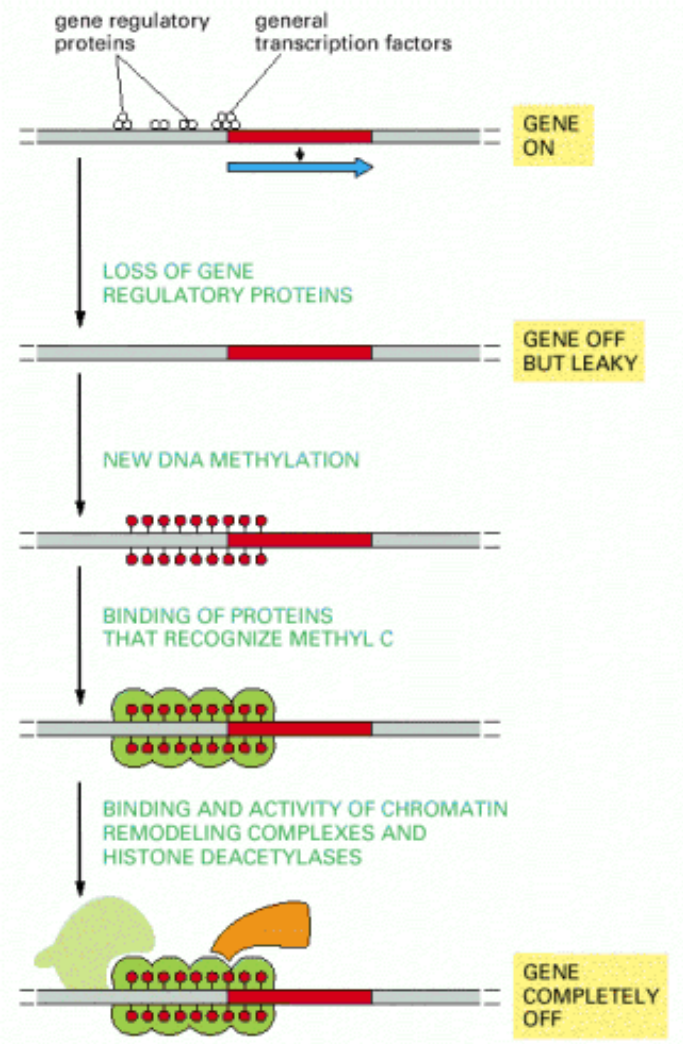

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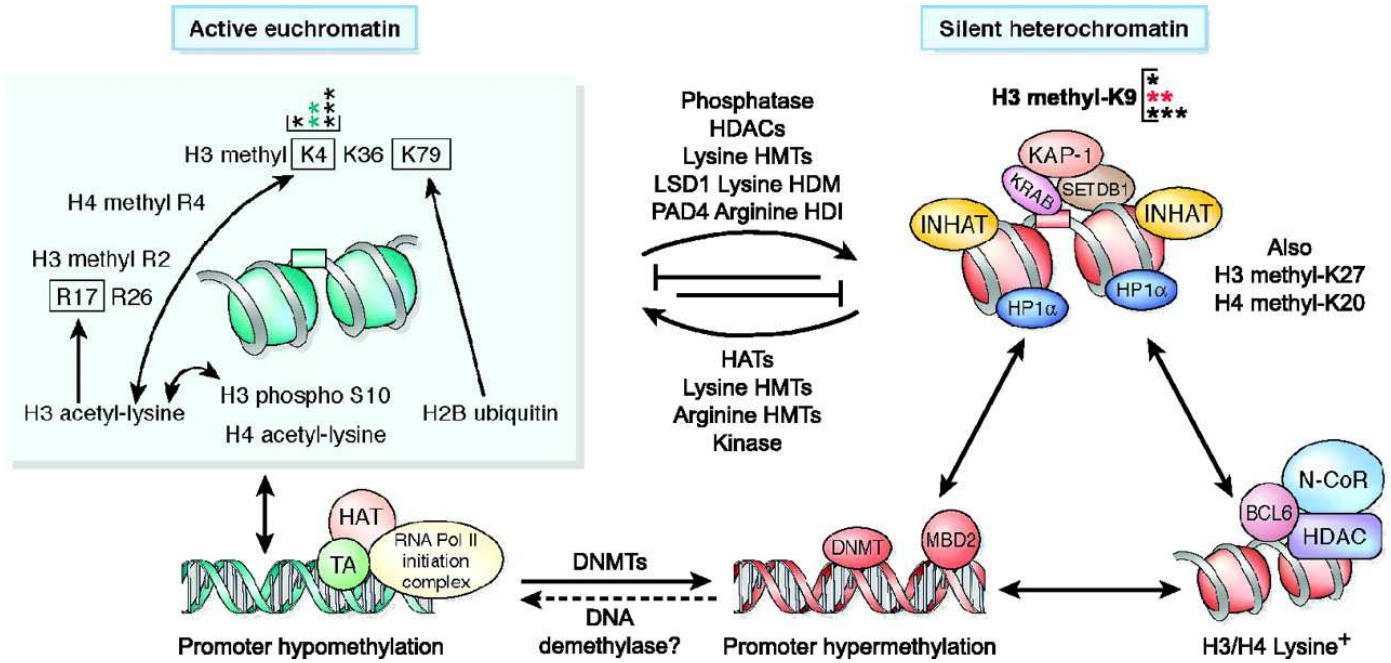
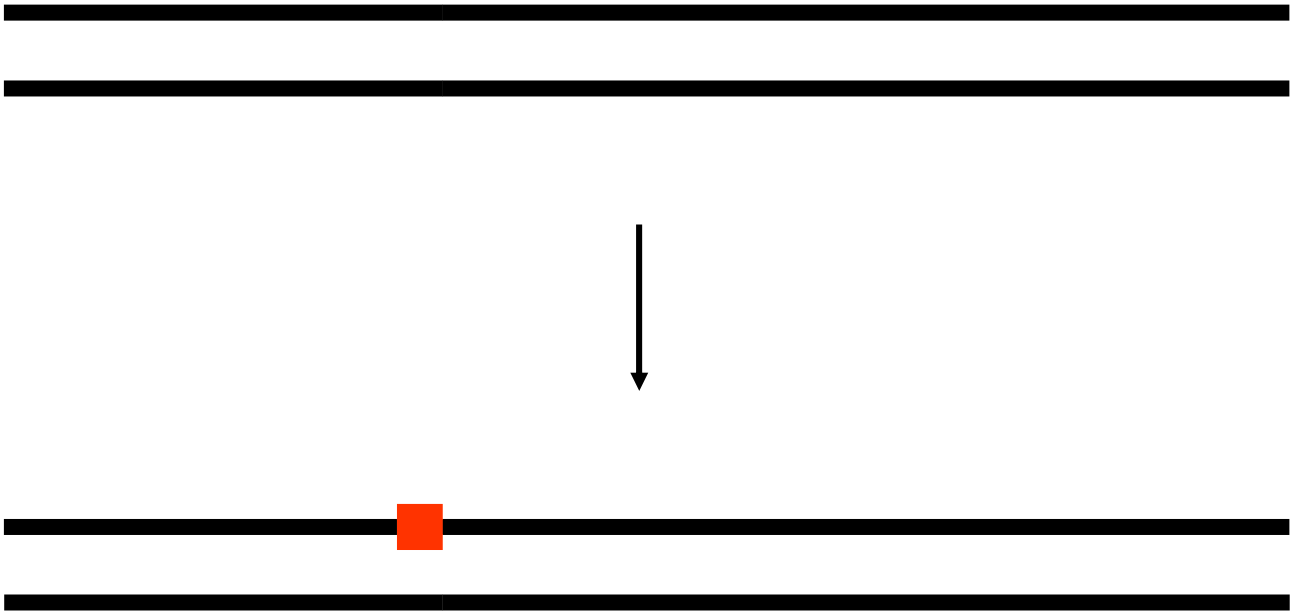
Figure 2. Schematic representation of epigenetics associated with active and silenced loci



Zelent, A. et al. Mol Cancer Ther 2005;4:1810-1819

POINT MUTATION



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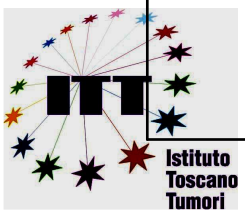
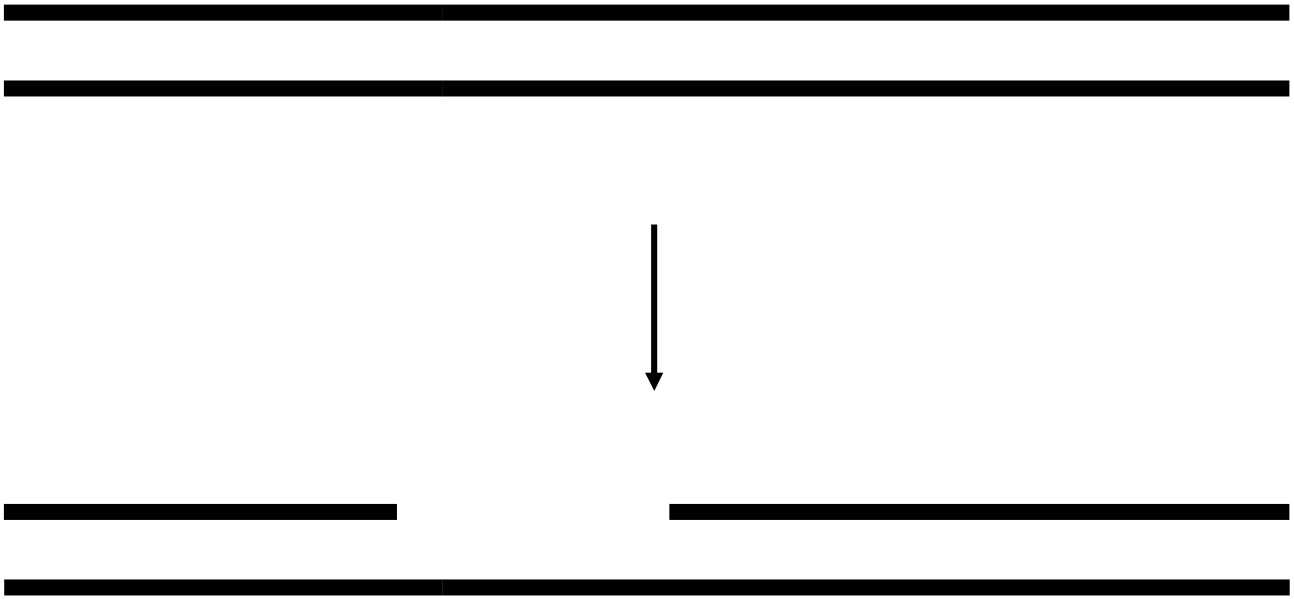
SOME SPECIFIC TYPES OF SOMATIC MUTATIONS FOUND IN TUMORS

		COLON	BREAST	TOTAL
Substitutions at CG base pairs	CG to TA	413 (**59.3**)	289 (34.5)	702 (45.8)
	CG to GC	48 (6.9)	239 (**28.5**)	287 (18.7)
	CG to AT	93 (13.4)	148 (17.7)	241 (15.7)
Substitutions at TA base pairs	TA to CG	56 (8.0)	72 (8.6)	128 (8.3)
	TA to GC	51 (7.3)	35 (4.2)	86 (5.6)
	TA to AT	35 (5.0)	55 (6.6)	90 (5.9)
Substitutions at specific dinucleotides	5'-CpG-3'	309 (**44.4**)	139 (**16.6**)	448 (29.2)
	5'-TpC-3'	79 (11.4)	257 (30.7)	336 (21.9)
TOTAL		696	838	1534



COPY LOSS



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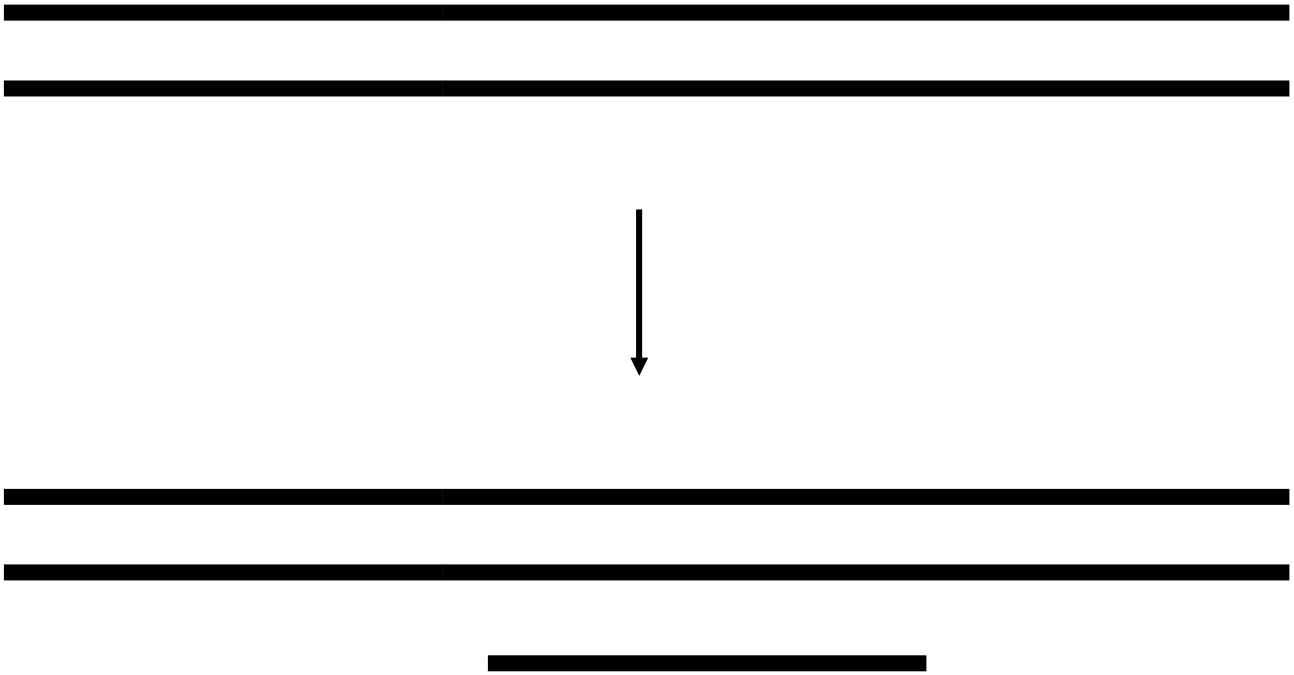
COPY GAIN



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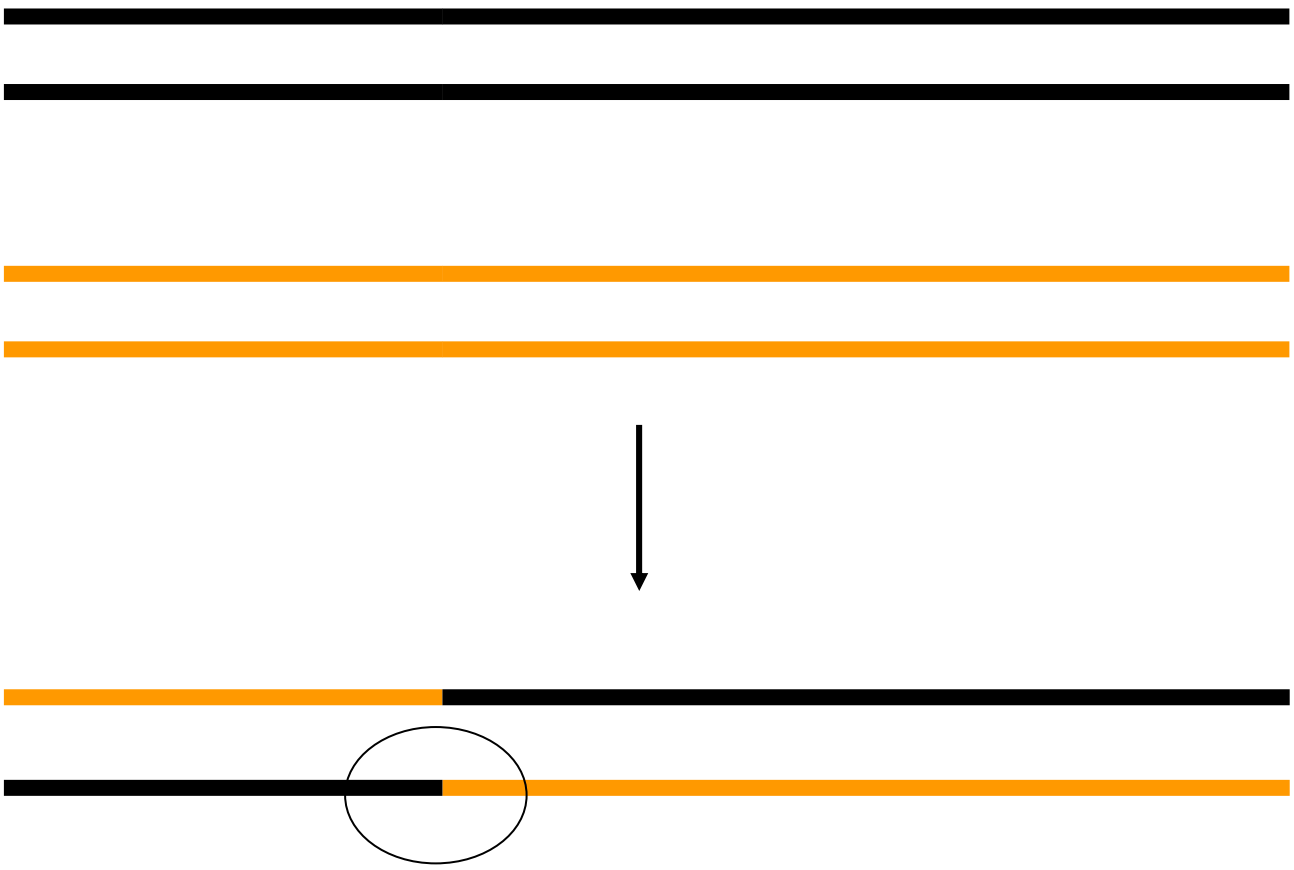
REECIPROCAL TRANSLOCATION



GENE FUSION

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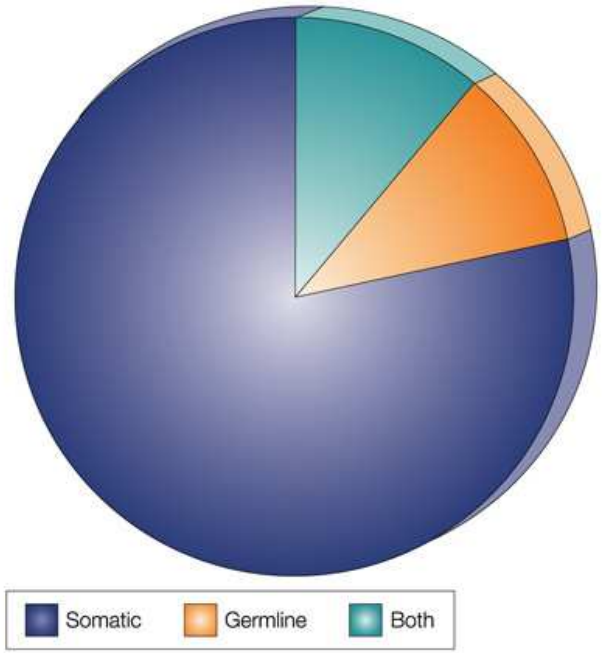
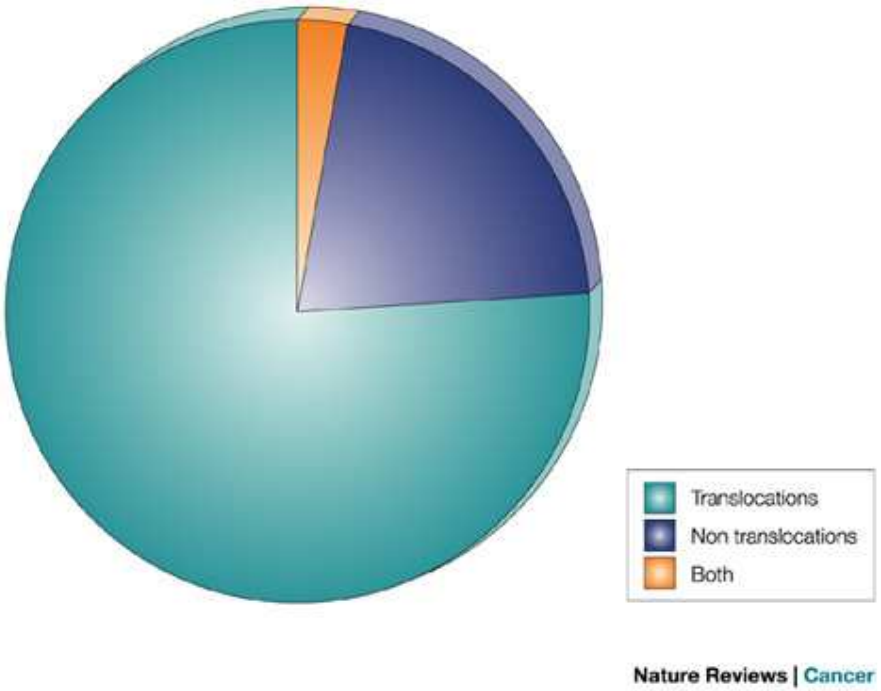
TYPES OF MUTATIONS IN HUMAN CANCER

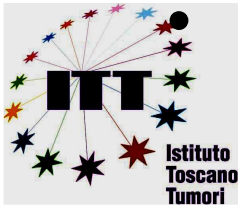




(From Futreal et al., 2004)

FUSION GENES
IN EPITHELIAL (and other) CANCERS

• RET-PTC1	*Papillary thyroid cancer*
• TMPRSS2-ERG	*Prostate cancer*
• ETV6-NTRK3	*Breast cancer*
• ARID1A-MAST2	*Breast cancer*
• EML4-ALK	*Adenocarcinoma of the lung*
• MYB-NFIB	*Adenoid cystic carcinoma of salivary gland*
• KIAA1549-BRAF	*Glioma*
• EWS-FLI1	*Ewing sarcoma*
• SYT-SSX2	*Synovial sarcoma*



QuickTime™ and a
decompressor
are needed to see this picture.

144:9,2011

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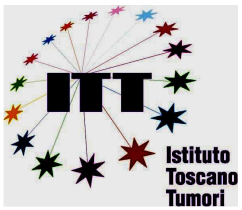

CHROMOTHRYPSIS IN MEDULLOBLASTOMA IN LI-FRAUMENI PATIENTS

QuickTime™ and a
decompressor
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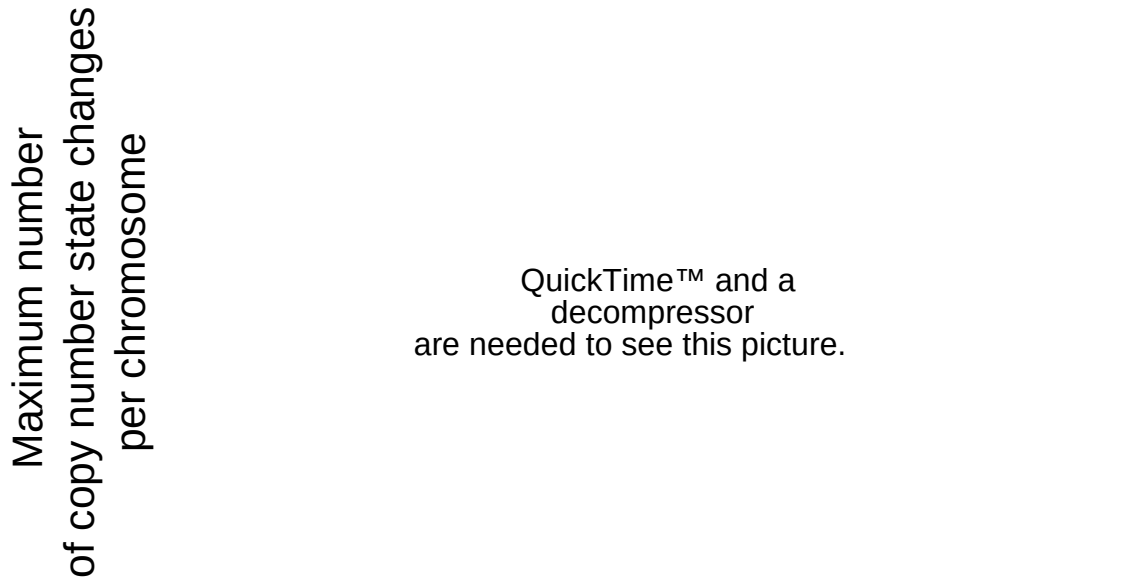
(From Rausch et al., *Cell* **148**:59, 2012)

CORRELATION BETWEEN p53 STATUS AND CHROMOTRYPSIS IN MEDULLOBLASTOMA

Maximum number of copy number state changes per chromosome



Maximum amplicon count per chromosome

(From Rausch et al., *Cell* **148**:59,2012)

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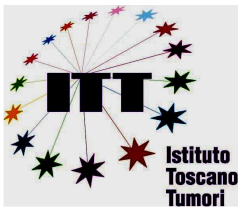
CHROMOTHRIPSIS 2011-2012

Seminal paper by P J Stephens et al.,
Cell **144**: 27–40 (January 7), 2011.
Coined term and reported occurrence in several types of tumors, including:

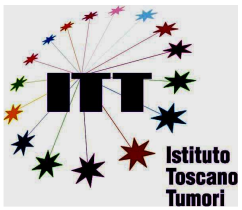
- Osteosarcoma (~25%)

Then, confirmatory papers:

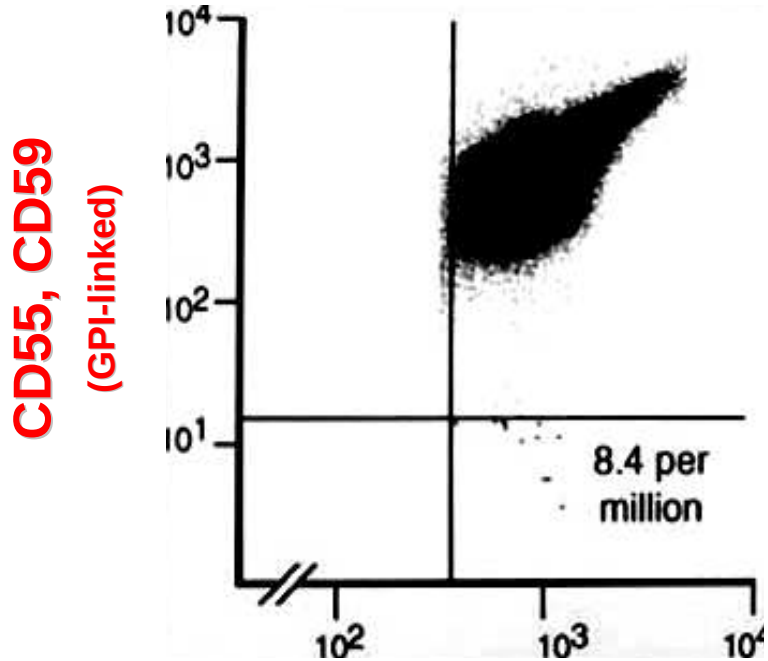
- Neuroblastoma 10
- Medulloblastoma 4
- Prostate 1
- Multiple myeloma (~1.3%)
- Colon common



The intrinsic
rate of somatic mutation
of an individual may be a determinant of the risk of cancer



Rare GPI(–) granulocytes can be found in a normal person



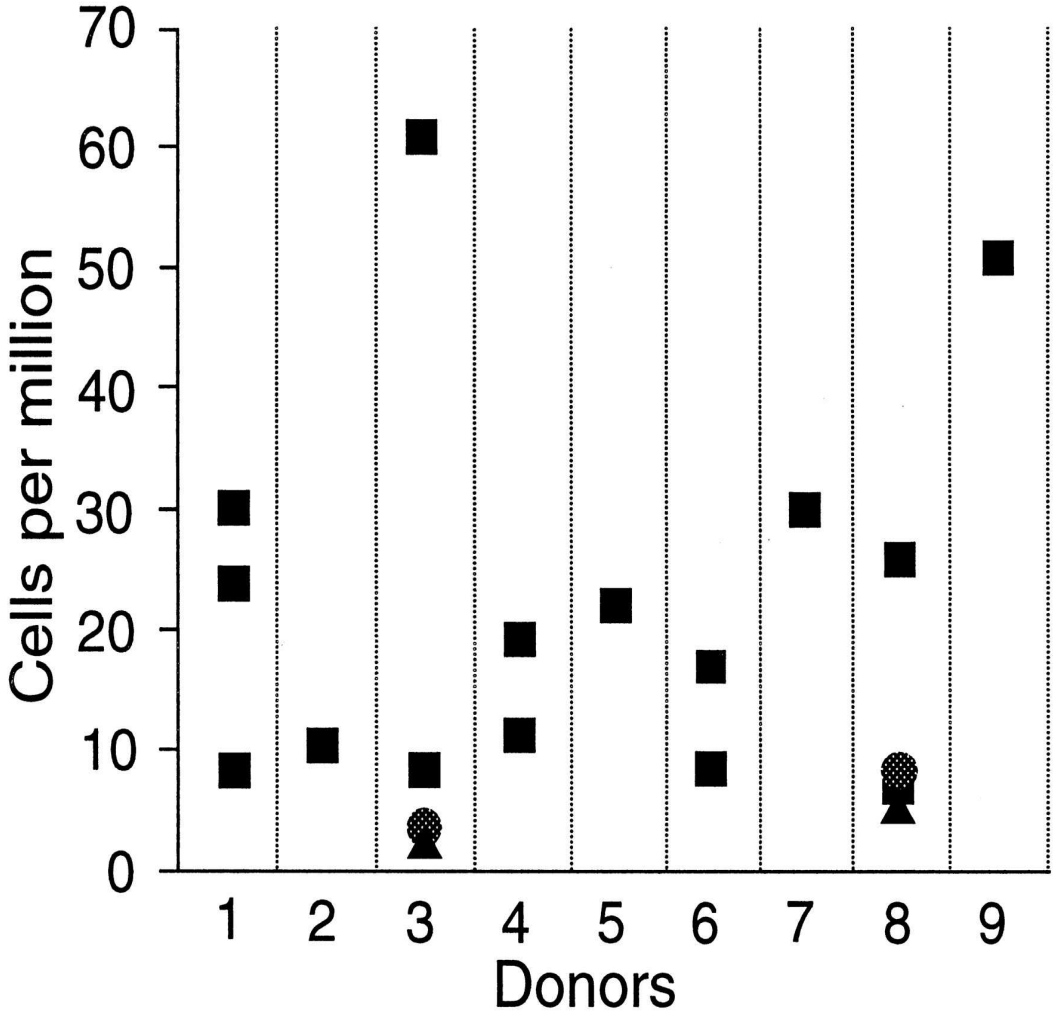
(**Araten** et al..*Proc Natl Acad Sci U S A*. **96**:5209,1999)

Rare GPI(−) red cells are found in a normal person and are susceptible to complement lysis

QuickTime™ and a
decompressor
are needed to see this picture.

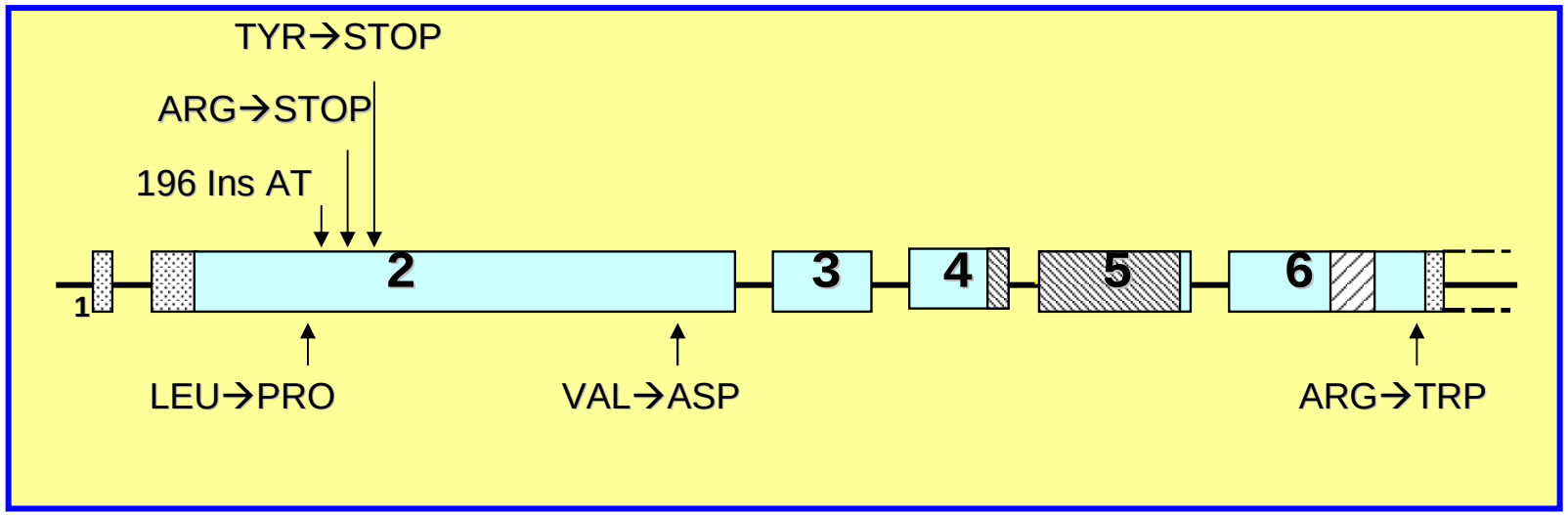
(Araten et al..*Proc Natl Acad Sci U S A*. **96**:5209,1999)

Rare GPI(–) granulocytes are present in most normal persons



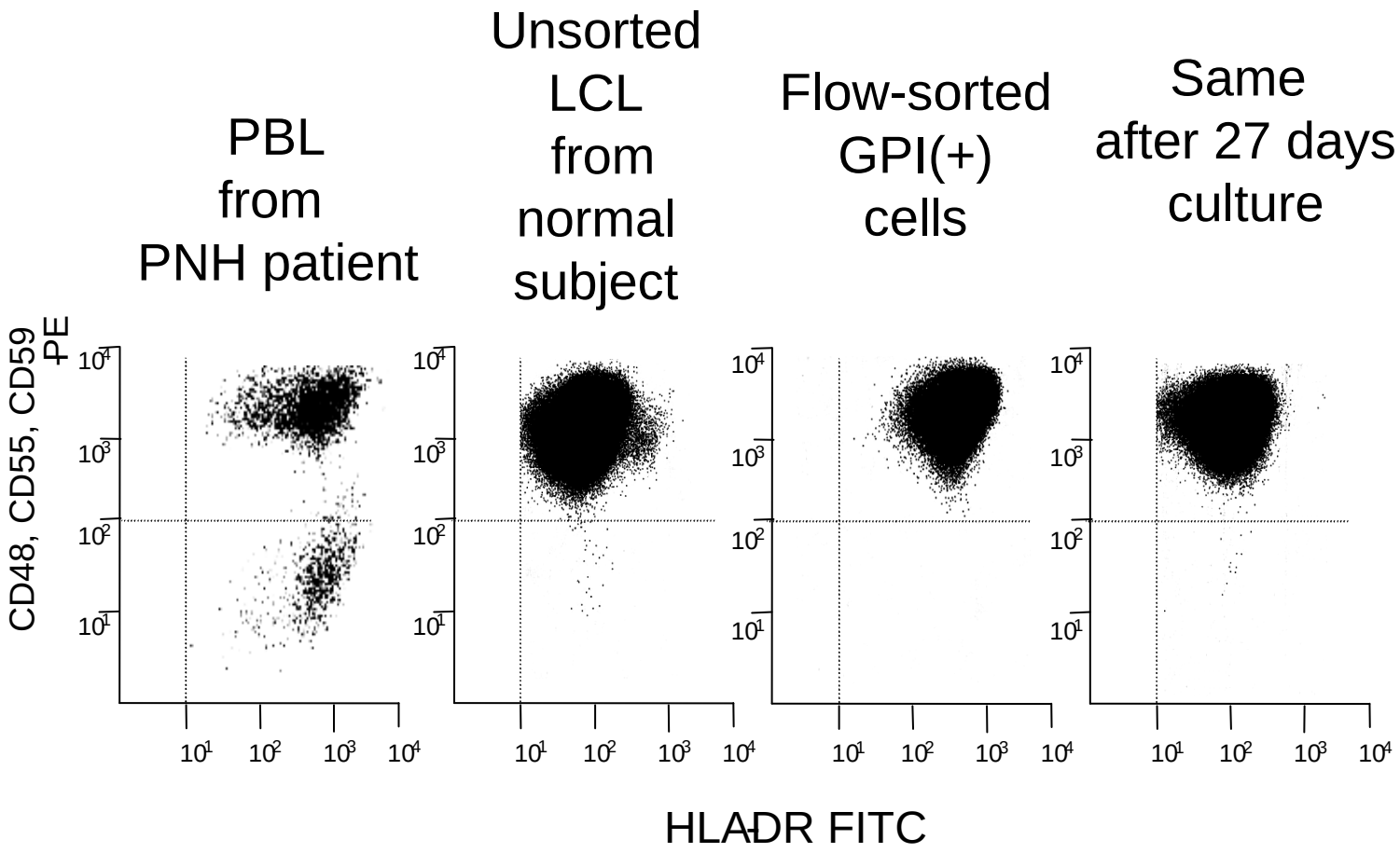
(**Araten** et al..*Proc Natl Acad Sci U S A*. **96**:5209,1999)

GPI(–) granulocytes from normal persons have PIG-A *mutations*



(Araten et al..*Proc Natl Acad Sci U S A*. **96**:5209,1999)

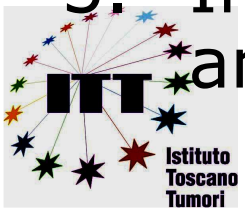
The Rate of Somatic Mutation Can Be Measured in Humans



(Araten et al..*Cancer Res*. 2005)

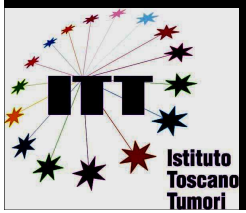
ADVANTAGES OF *PIG-A* AS A SENTINEL GENE

1. X-linked gene: therefore mutations are phenotypically expressed.
2. The *PIG-A* product is a subunit of an enzyme required for GPI synthesis: therefore mutations can be detected by testing for GPI-linked proteins.
3. GPI-linked proteins are ubiquitously expressed on the cell surface: therefore a variety of cells can be studied individually by flow cytometry.
4. In view of (2), amplification provides high sensitivity.
5. In view of (3), multiple proteins can be analyzed, thus avoiding artefacts



Biological correlates of μ

- Normal range
- Genetic deteminants
- Environmental factors that affect μ
- Acquired changes in μ
- Risk of cancer
- Changes of μ in cancer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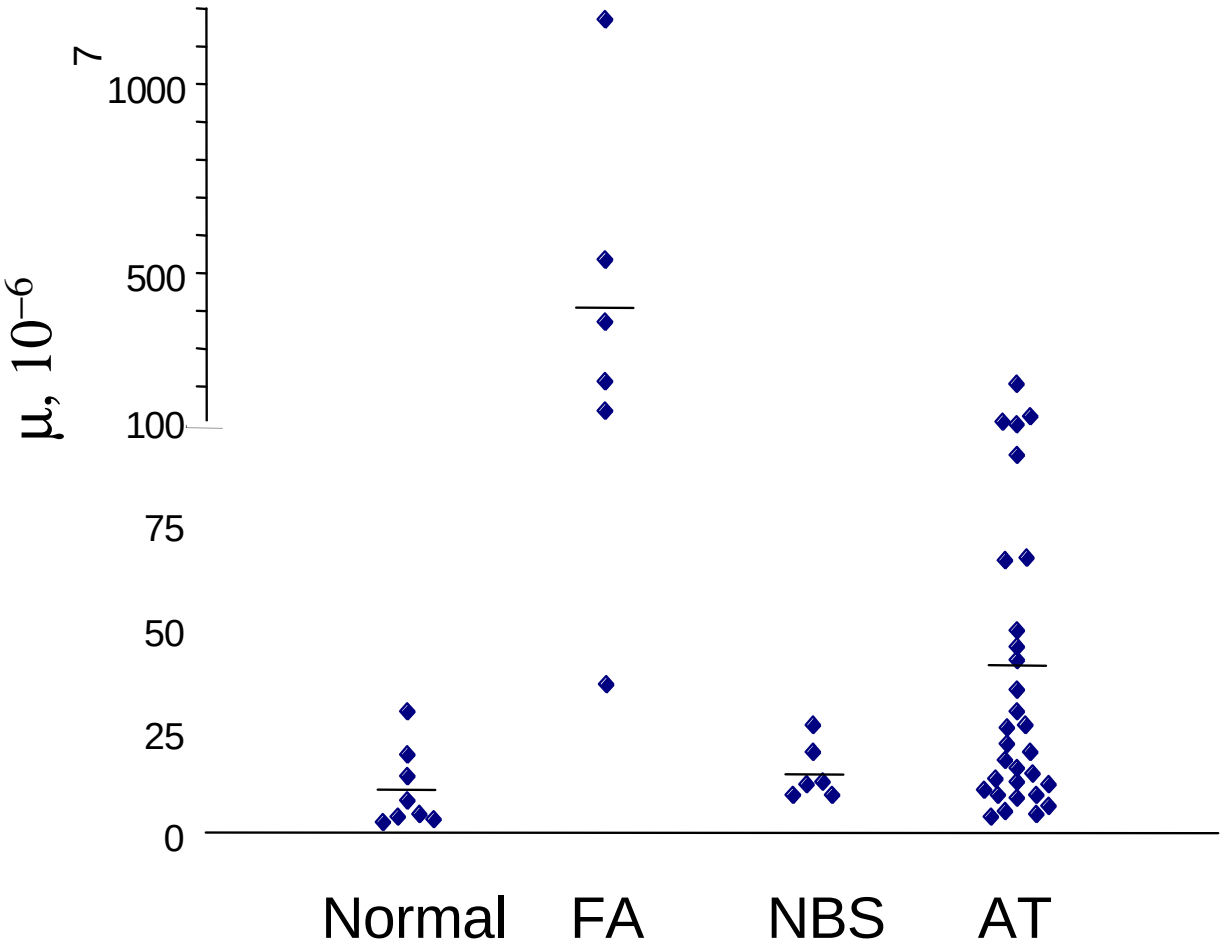
THE MUTATION RATE IS INCREASED IN CONDITIONS ASSOCIATED WITH INCREASED SUSCEPTIBILITY TO CANCER



(**Araten** et al..*Cancer Res*. 2005)

Personalized
Cancer
Medicine

What is it?

Optimizing the care

of each individual patient with cancer in terms of the tumor

and in terms of the host

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PCM - II

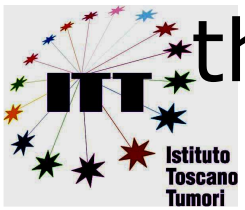
Optimizing the care of each individual patient with cancer

in terms of the tumor:

it means to make a full diagnosis at the molecular level

in terms of the host:

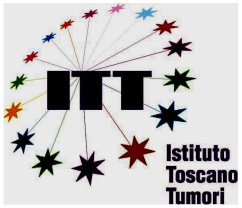
it means to identify factors that may affect the course of the tumor and/or the response to therapy



PCM - III

Personalized medicine is very important:

It means to treat the patient as a whole person



Anti-angiogenici
Anti-infiammatori
Immunomodulatori

Farmaci che agiscono sul DNA e sulla mitosi
(chemioterapici classici)

Inibitori di un *signal transduction pathway* importante in un certo tumore
(p.es. *sunitinib*)

Interferenza con molecole mutate oncogeniche
(p.es. *imatinib, gefitinib*)

Interferenza con molecola iper-espressa in un tumore
(p.es. *trastuzumab*)

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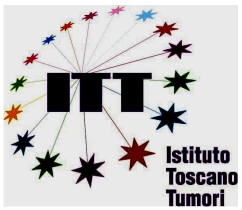
ABOUT THE CAUSES OF DISEASES

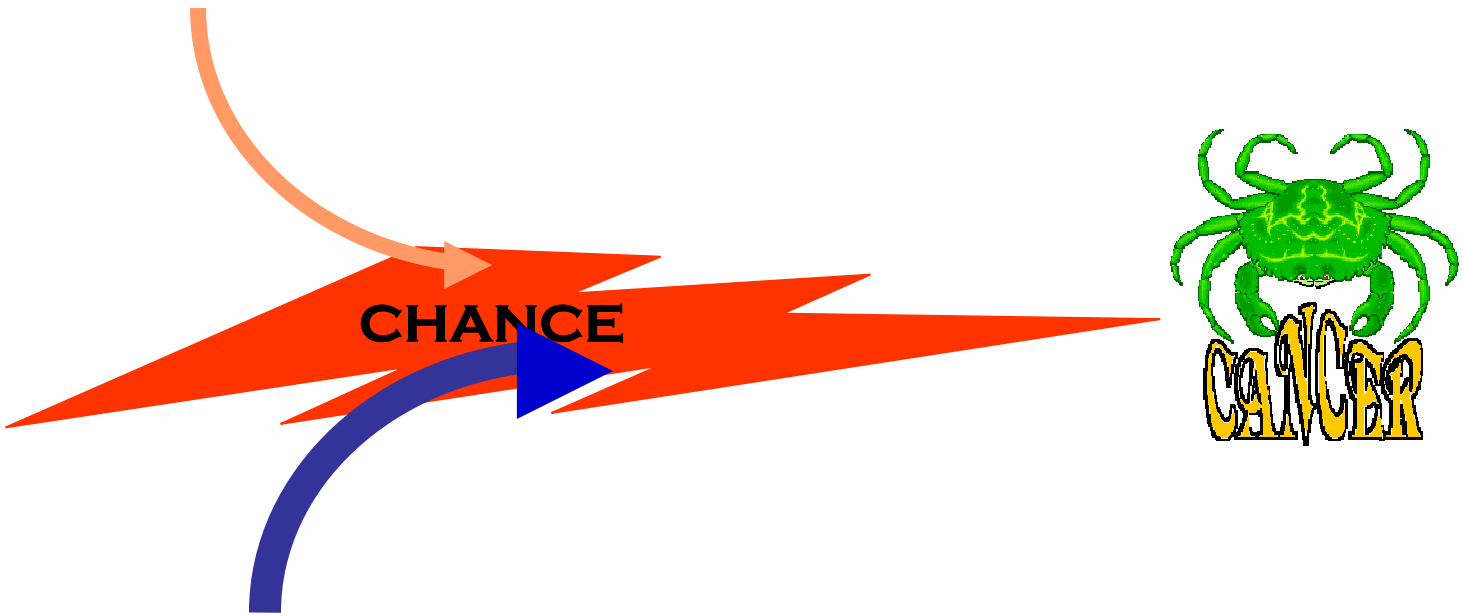
People prefer to be satisfied with a single causative factor….

[In fact], accidental factors and constitutional factors both play a role….We refuse to posit any contrast in principle between the two sets of aetiological factors…. [that] regularly act jointly….

Sigmund Freud, 1912



INHERITANCE



ENVIRONMENT

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