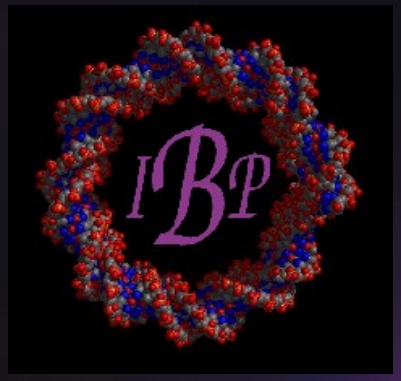
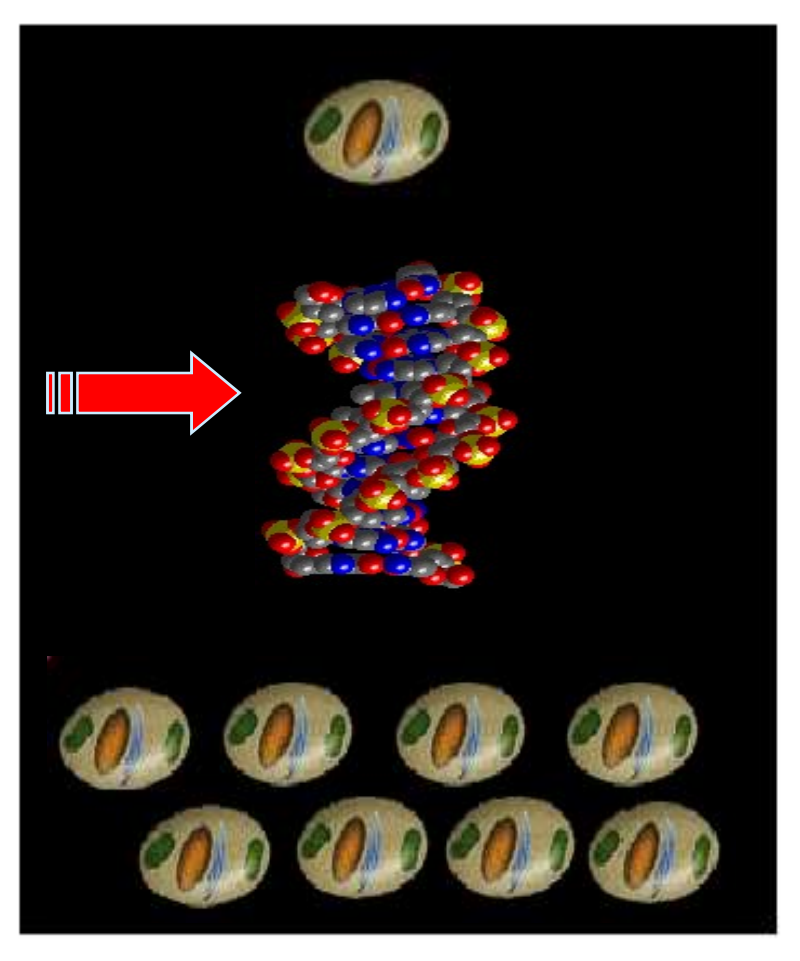


Cytogenetika nádorových buněk

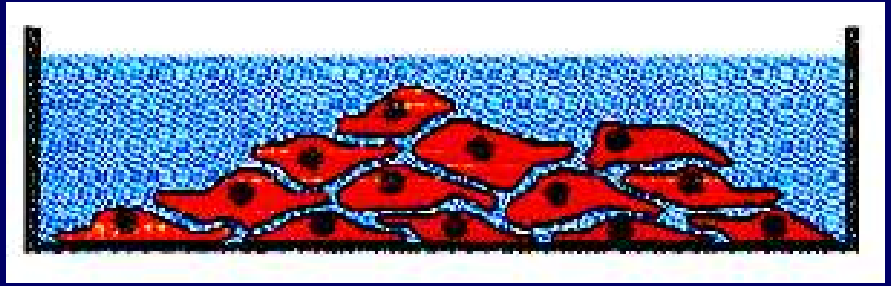
E. Bártová, Harničarová A., Kroupová J.

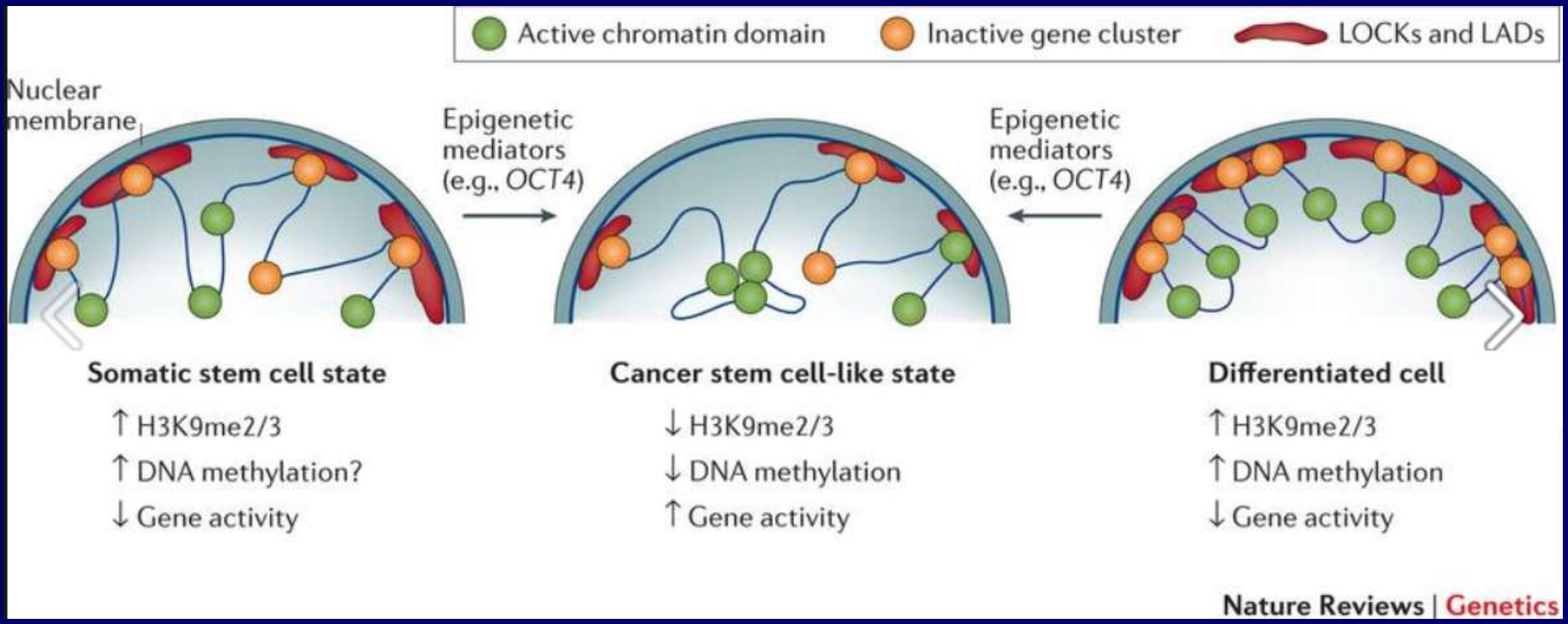
Biofyzikální ústav AV ČR BRNO

Cancer cells



1. Most cancers are derived from a single abnormal cell.
2. Cancers are initiated by changes in a cell's DNA sequences.
3. A single mutation is not enough to cause cancer.
4. Tumour progression involves successive rounds of mutation and natural selection.
5. Uncontrolled proliferation.
6. Loss of contact inhibition.
7. Cancerogenous growth often depends on degraded control of differentiation and apoptosis.




Active chromatin domain
Inactive gene cluster
LOCKs and LADs
Nuclear membrane
Epigenetic mediators (e.g., OCT4)
Epigenetic mediators (e.g., OCT4)
Somatic stem cell state
↑ H3K9me2/3
↑ DNA methylation?
↓ Gene activity
Cancer stem cell-like state
↓ H3K9me2/3
↓ DNA methylation
↑ Gene activity
Differentiated cell
↑ H3K9me2/3
↑ DNA methylation
↓ Gene activity
Nature Reviews | Genetics

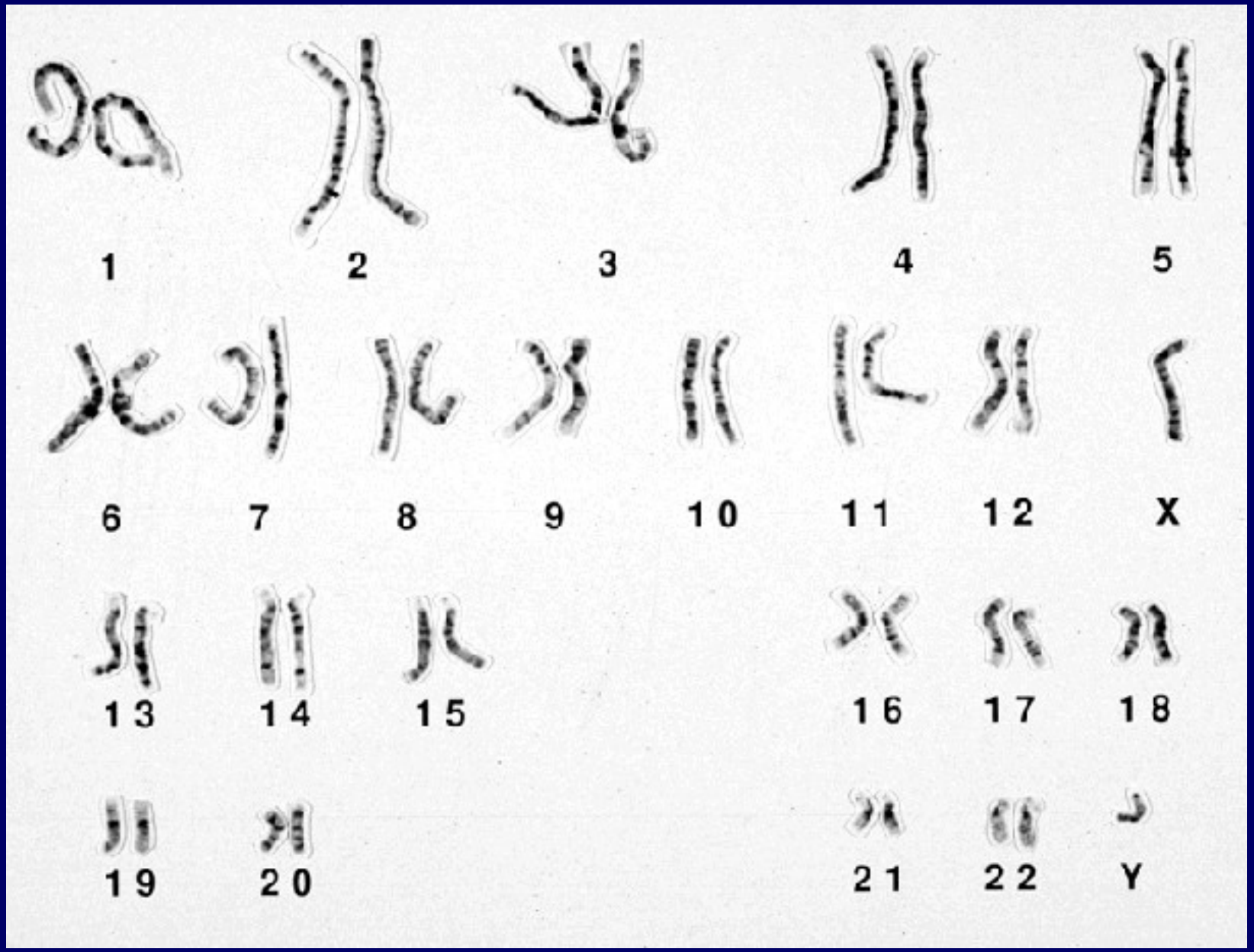
CYTOGENETIKA

Cytogenetika se zabývá studiem chromosomů a jejich abnormalit.
Chromosomy se skládají z DNA, histonů a proteinů nehistonové povahy.
Každý chromosom nese několik tisíc genu, které mají svou specifickou funkci v mnoha biologických procesech.
Počet lidských chromosomů je 46, z toho 22 typů autozomů a dva typy pohlavních chromosomů.
Standardní karyotypování chromosomů pomocí vizualizace G a R pruhů bylo objeveno již v 60. létech.

G-pruhování

Definition: Technique for producing banding patterns in eukaryotic chromosomes. Bands are produced by staining with Giemsa stain after pretreating chromosomes with trypsin. Each homologous chromosome pair has a unique pattern of g-bands, enabling recognition of particular chromosomes.

- G-bands: light, tend to be heterochromatic, late replicating , AT rich
- R-bands: reverse to G-bands, dark regions, are euchromatic, GC-rich


1
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X
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21
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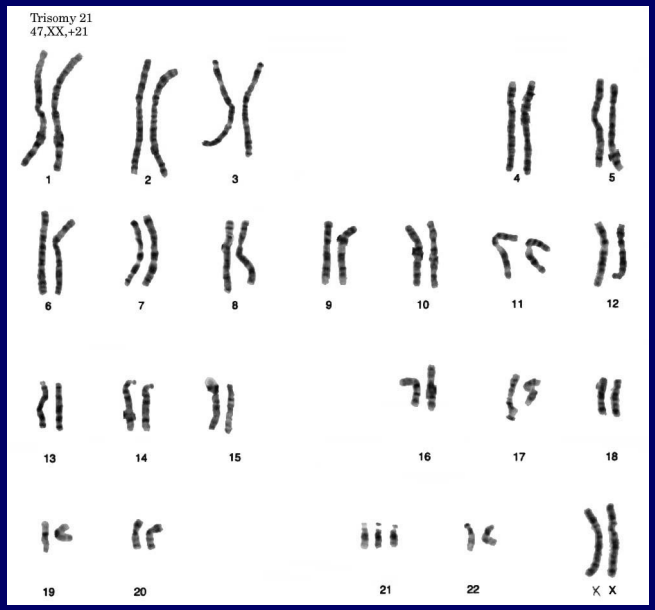
Y

Cytogenetické abnormality:

Konstitucionární (vrozené):

Robertsonian translocation: t(13;14)

- **Trizomie 21:**

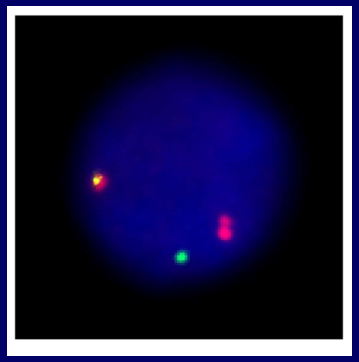


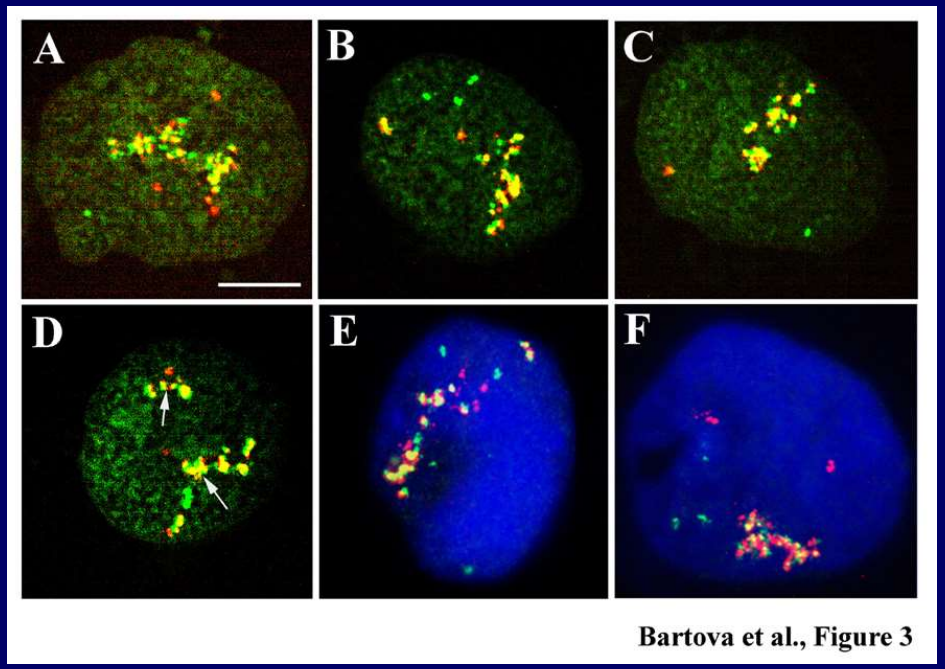
- **Klinefelterův syndrom 49, XXXXY (muži, Xi turn off, ginecomastia, hypogonadismus**
- **DiGeorge syndrom (delece na dlouhém ramínku HSA 22, kardiatic deffects)**

Cytogenetické abnormality:

Získané:

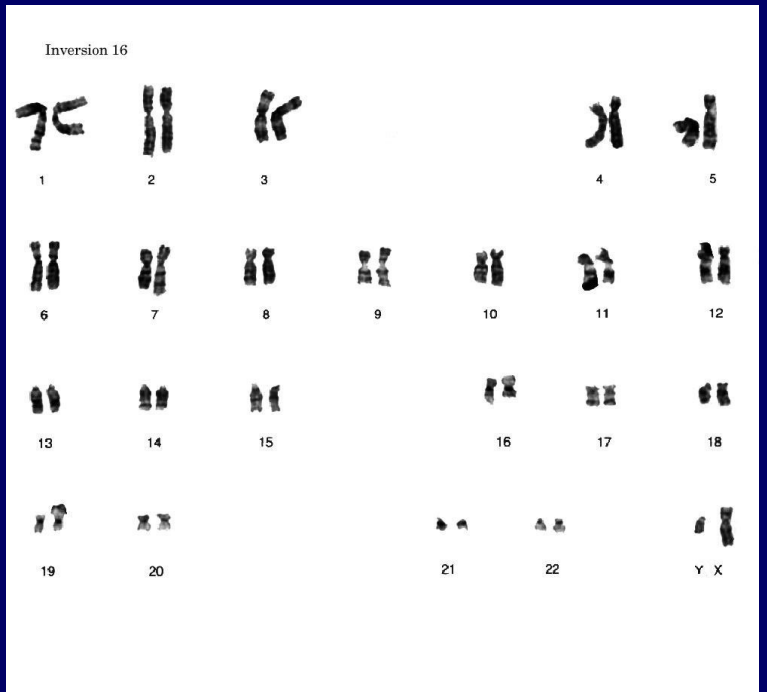
- **Ph chromosom**

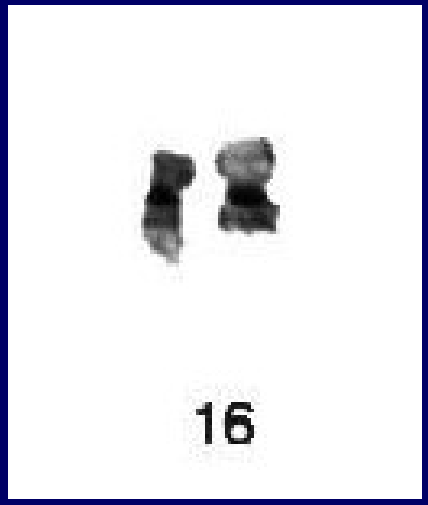




Bartova et al., Figure 3

- **Inverze**

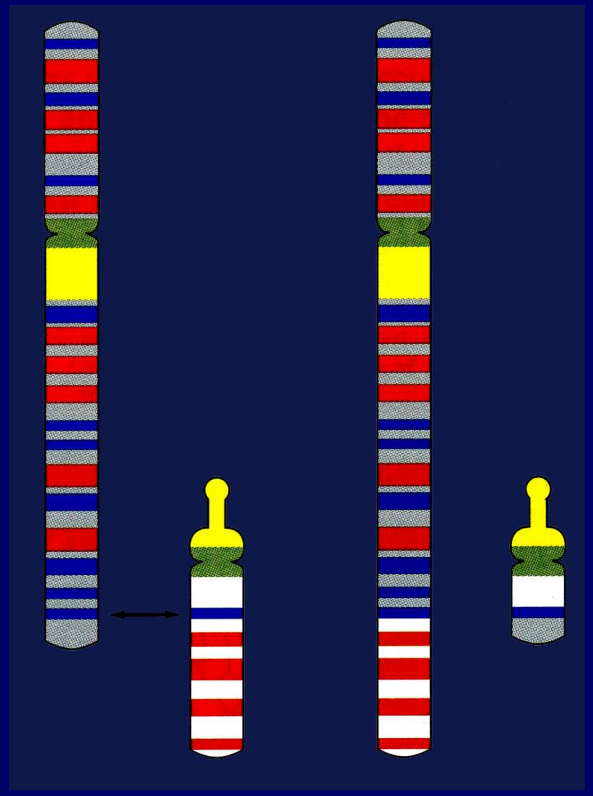




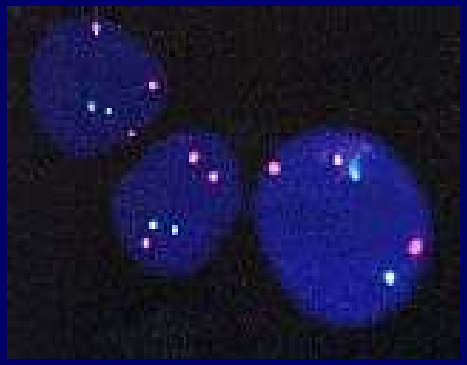
Inverze HSA 16

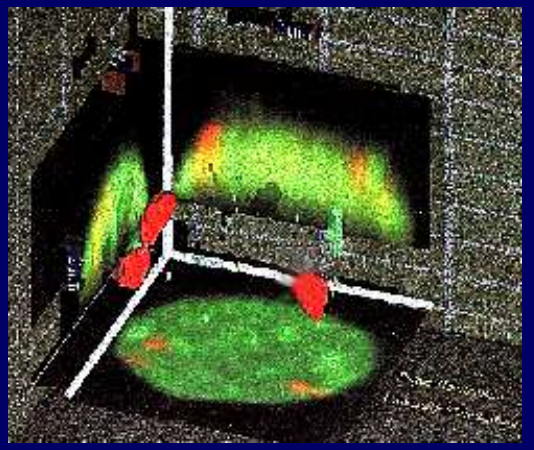
Chromosome abnormalities in cancer cells

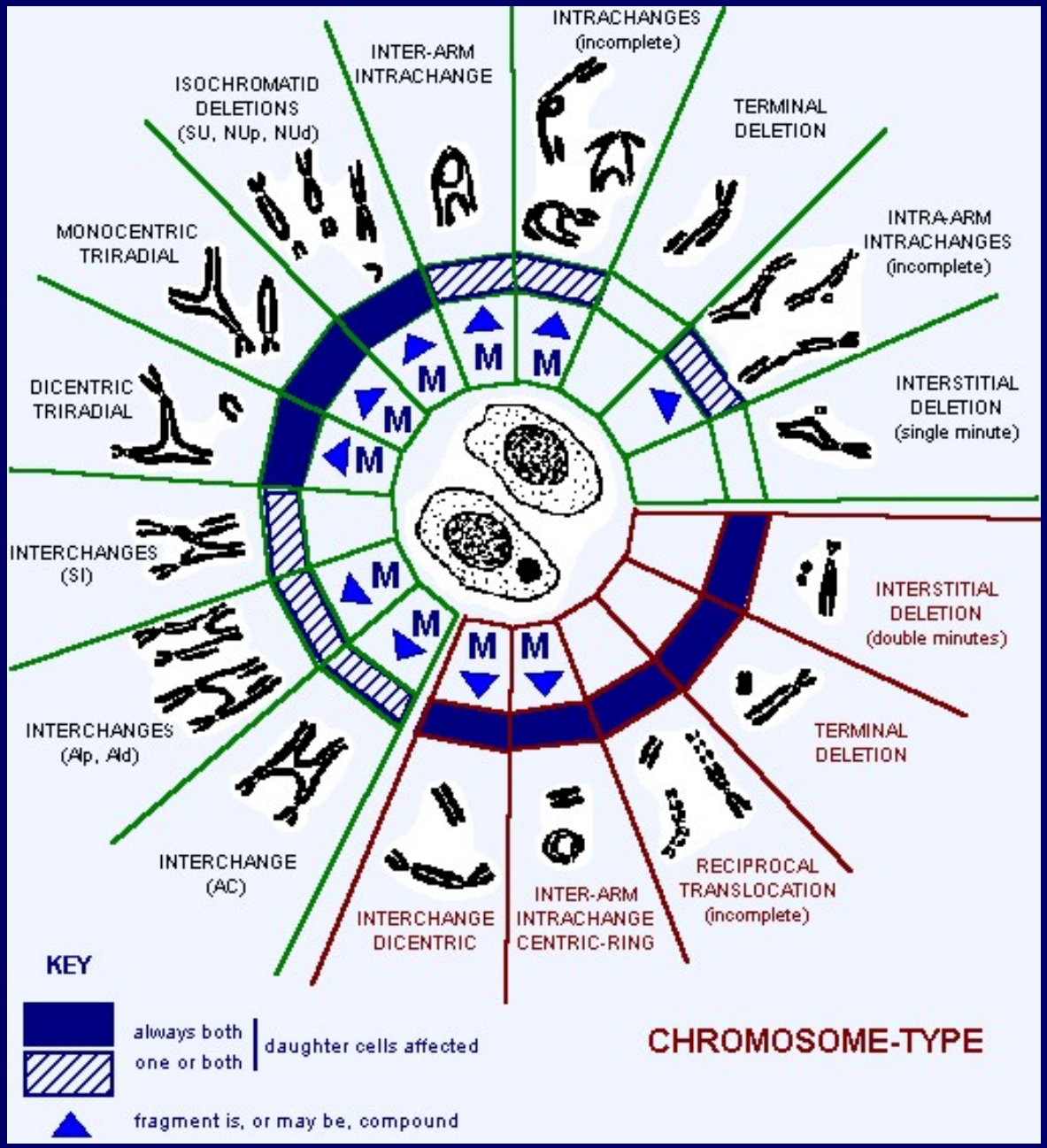
Structural aberrations



Numerical aberrations

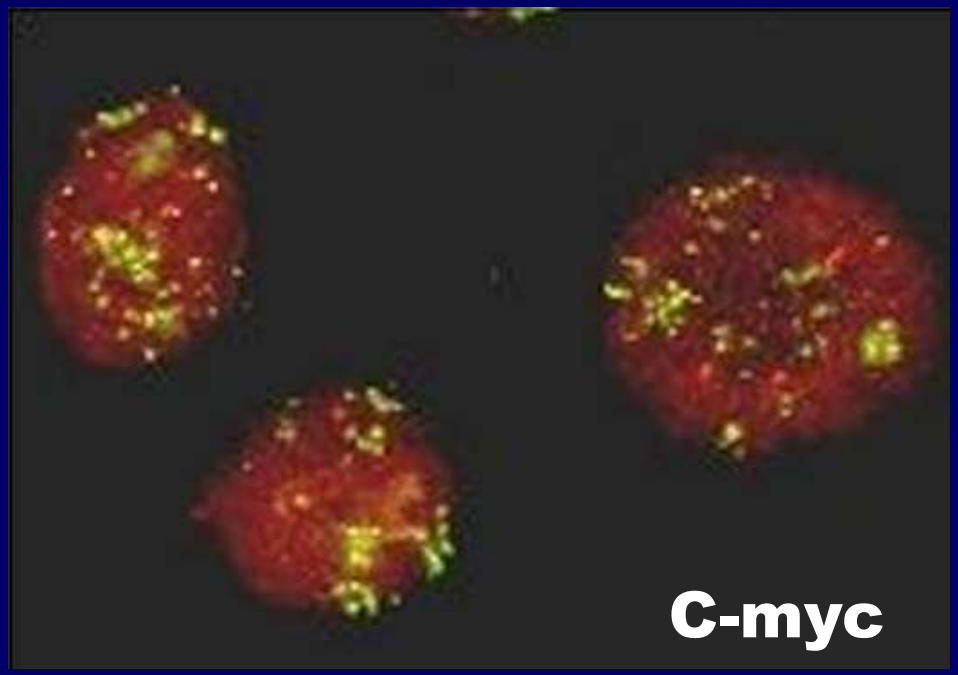


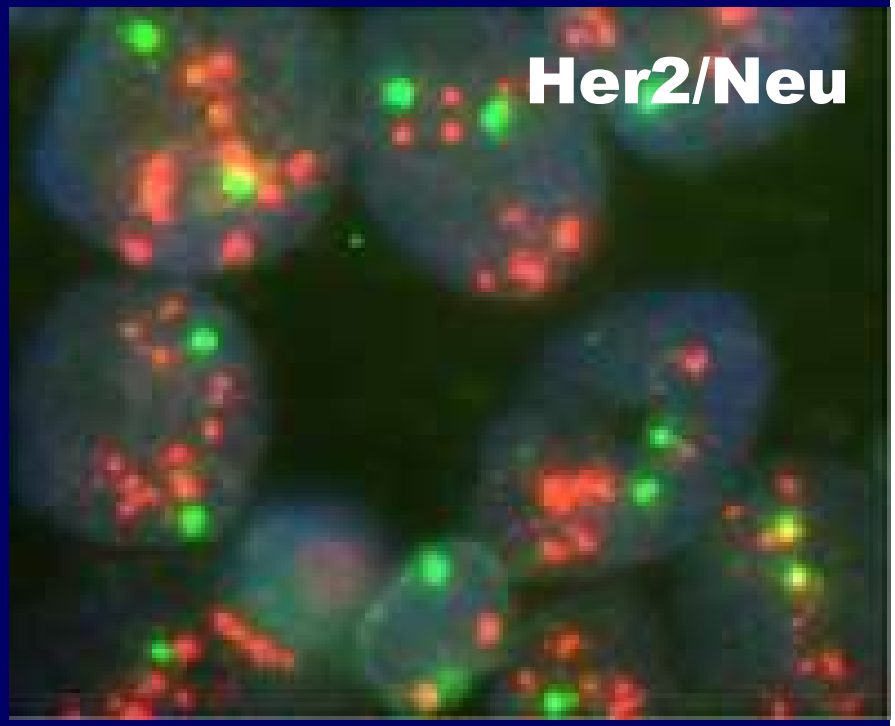


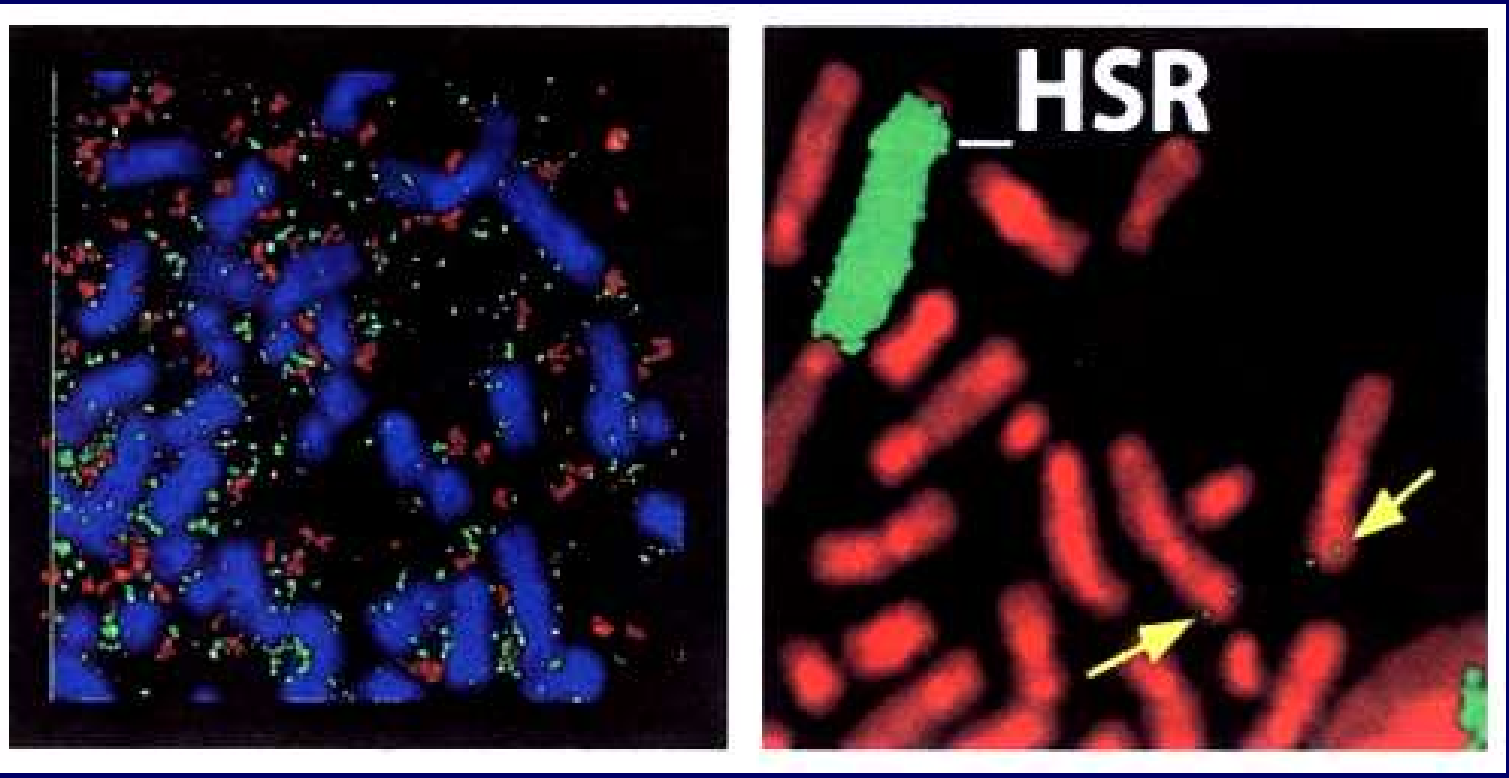


U nádorových buněk je možné pozorovat řadu genetických abnormalit

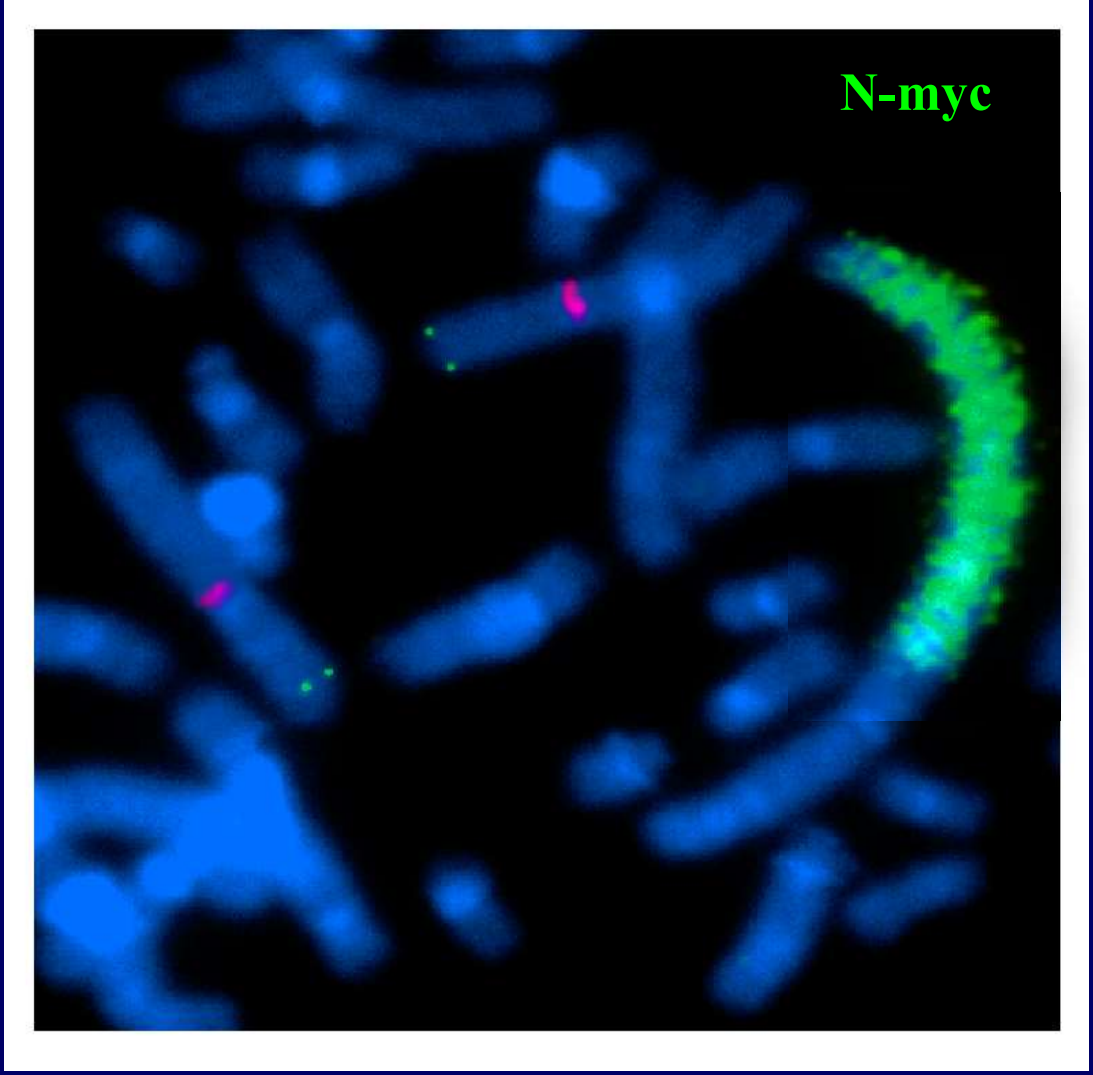
Gene amplification: DMs and HSRs



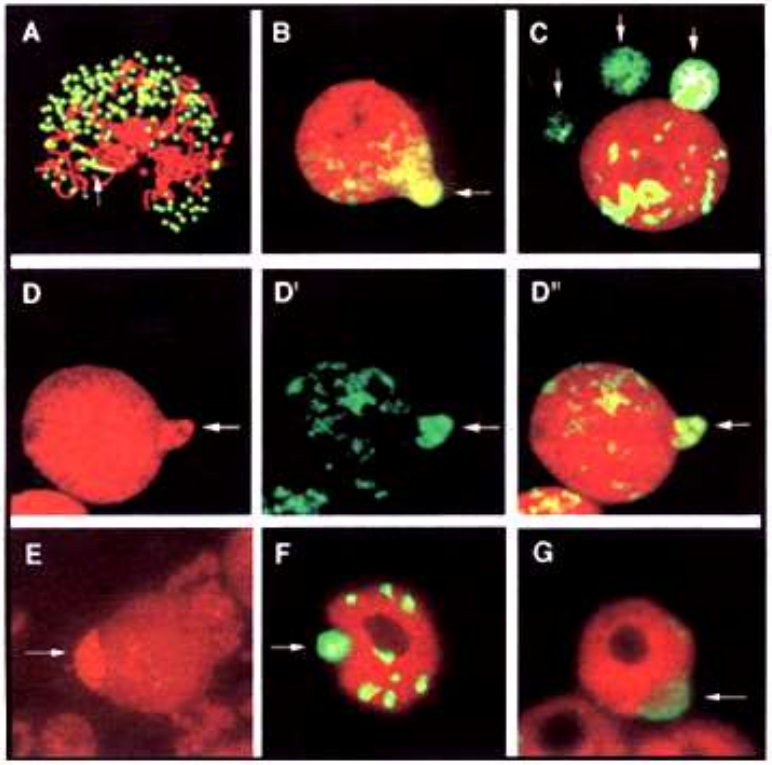



_HSR

Gene amplification in tumour cells



Schwab M., 1998


A
B
C
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D'
D''
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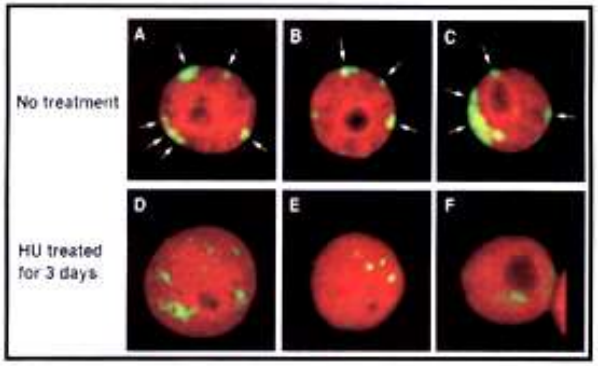
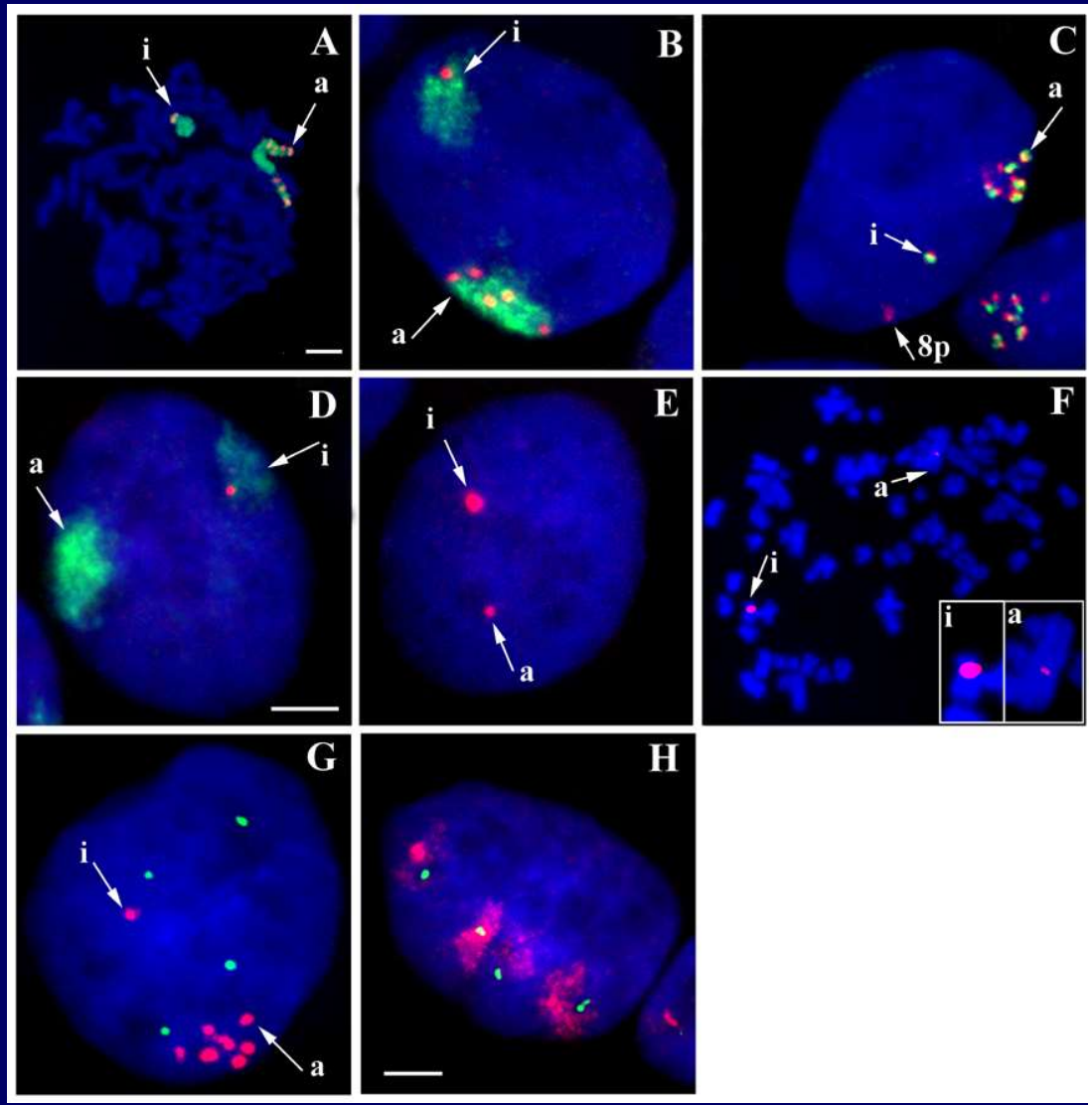
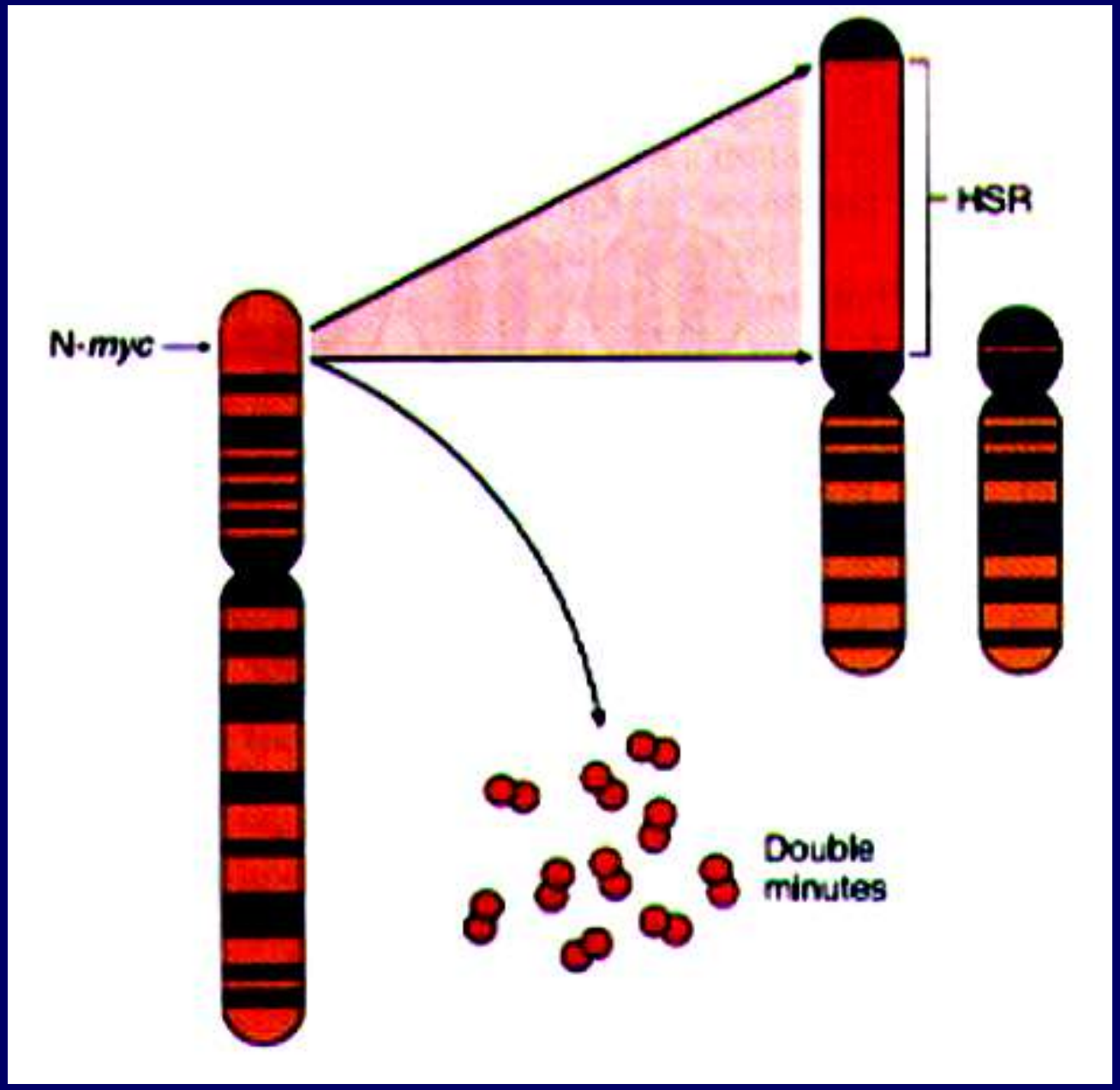
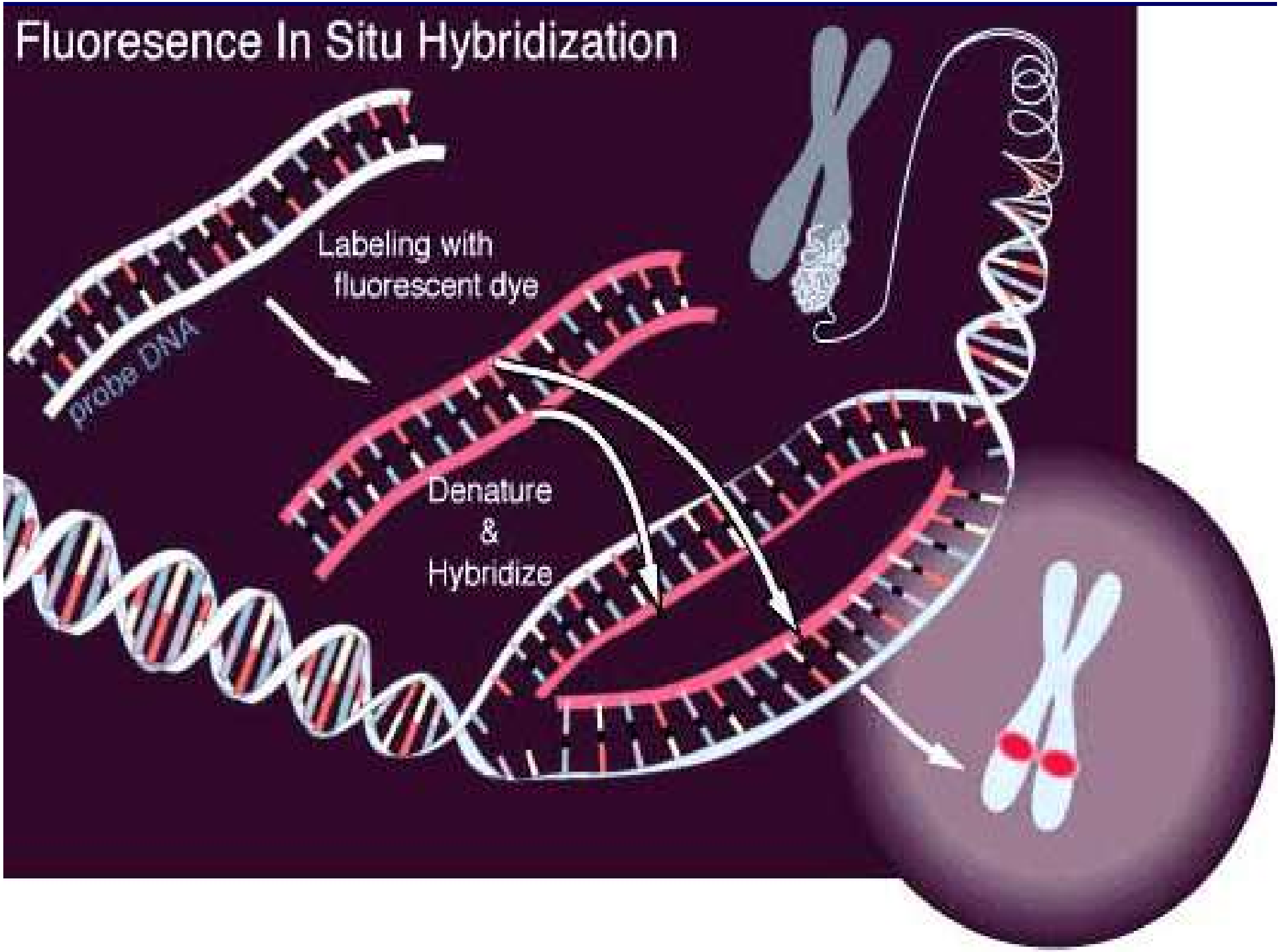
G


No treatment
HU treated
for 3 days
A
B
C
D
E
F

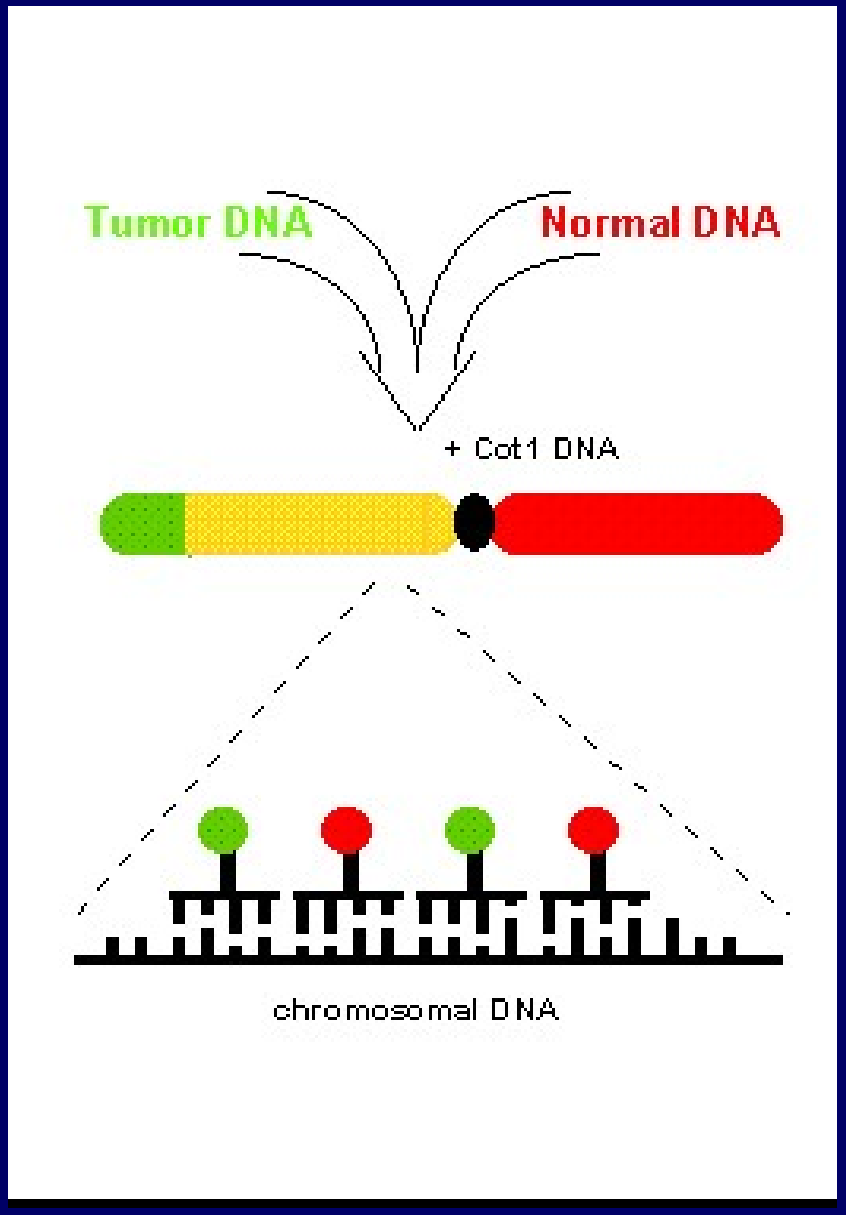
HSR of the c-myc gene

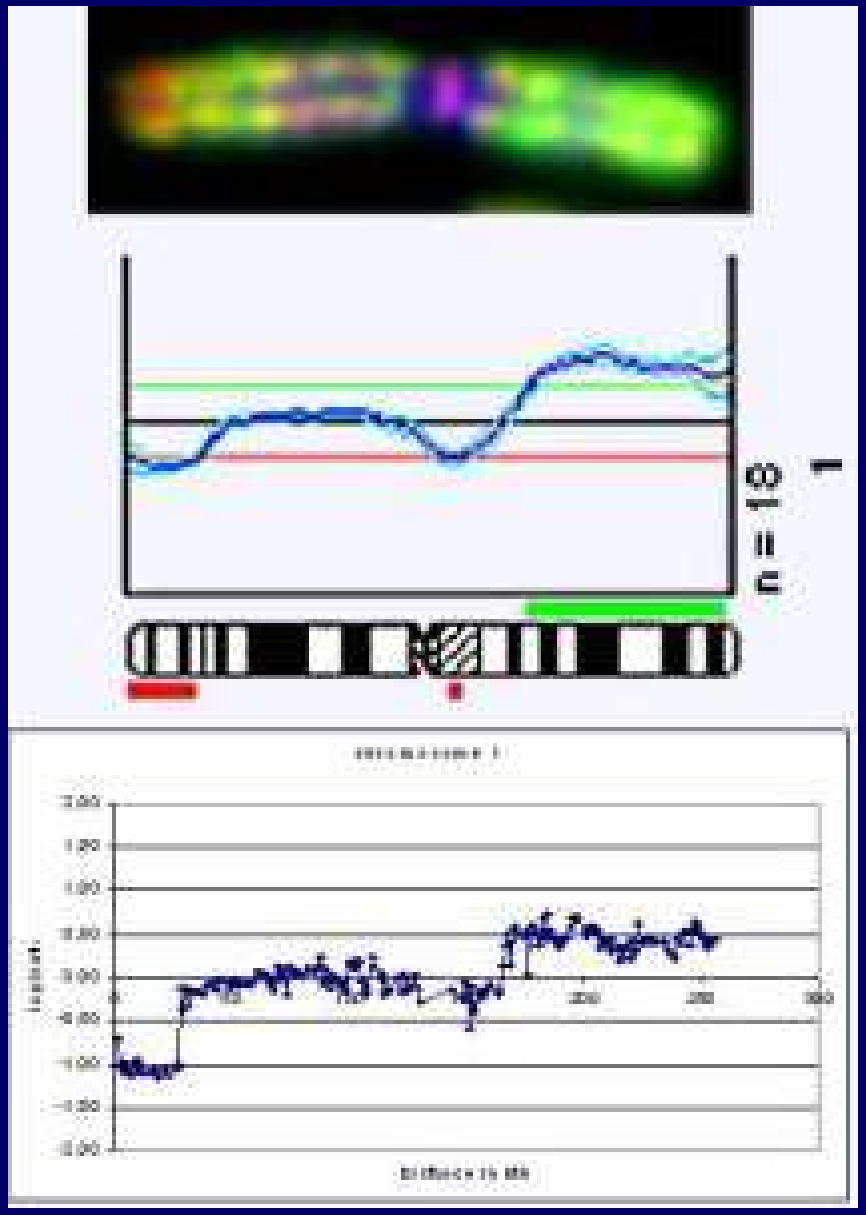


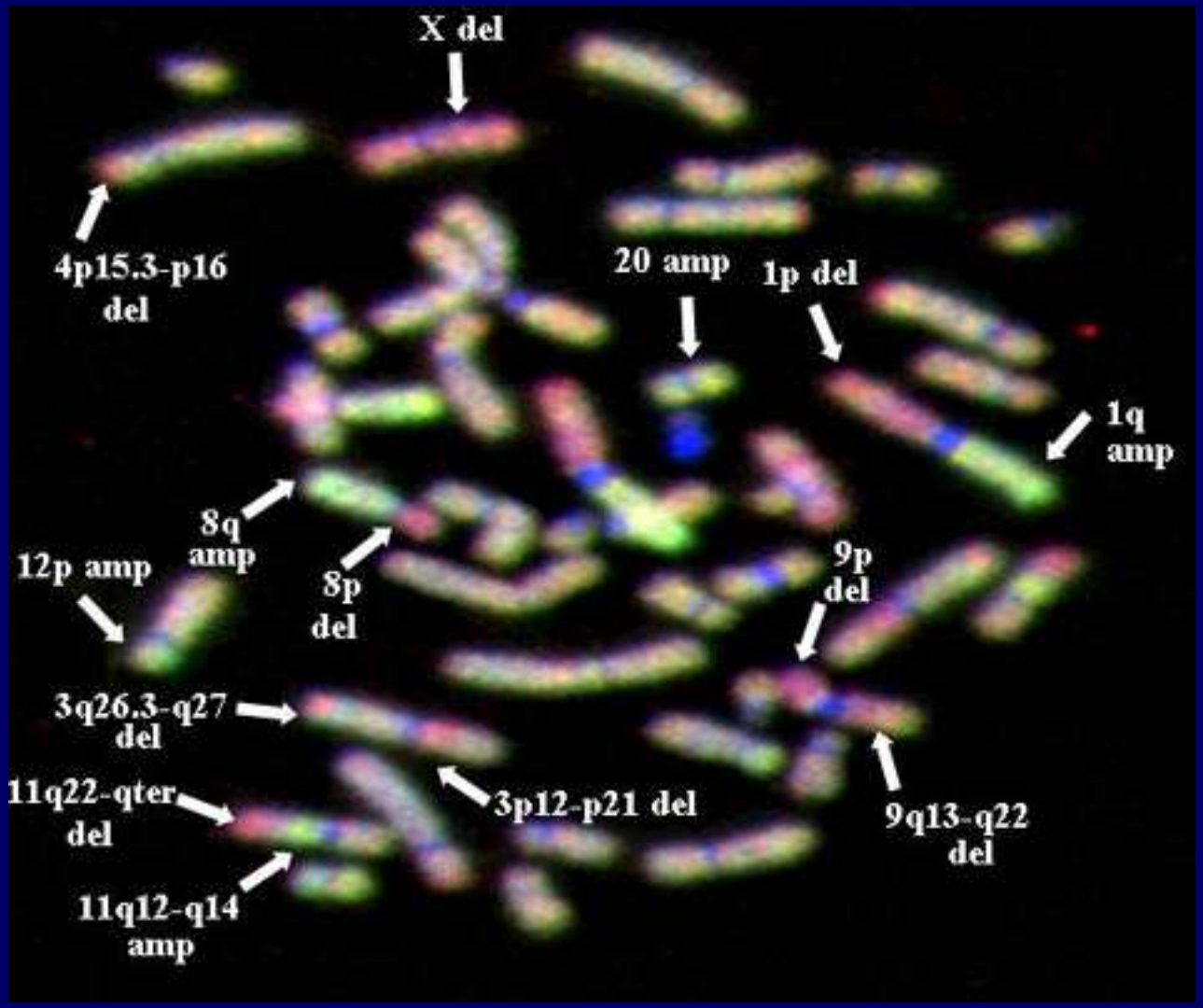

N-myc
HSR
Double
minutes

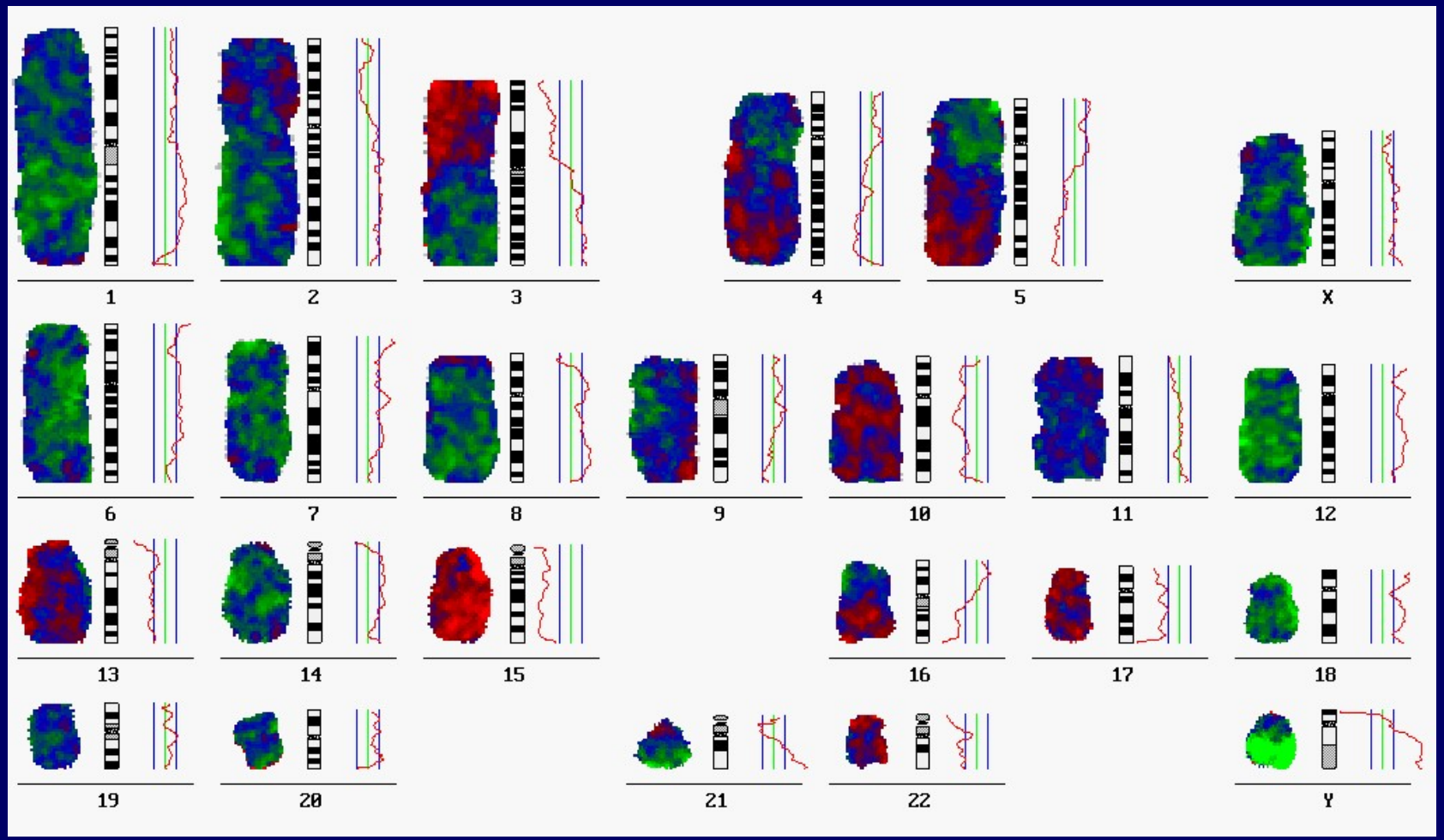

Fluoresence In Situ Hybridization
Labeling with
fluorescent dye
probe DNA
Denature
&
Hybridize

CGH on metaphase spreads






X del
4p15.3-p16 del
20 amp
1p del
1q amp
8q amp
12p amp
8p del
9p del
3q26.3-q27 del
11q22-qter del
3p12-p21 del
9q13-q22 del
11q12-q14 amp


1
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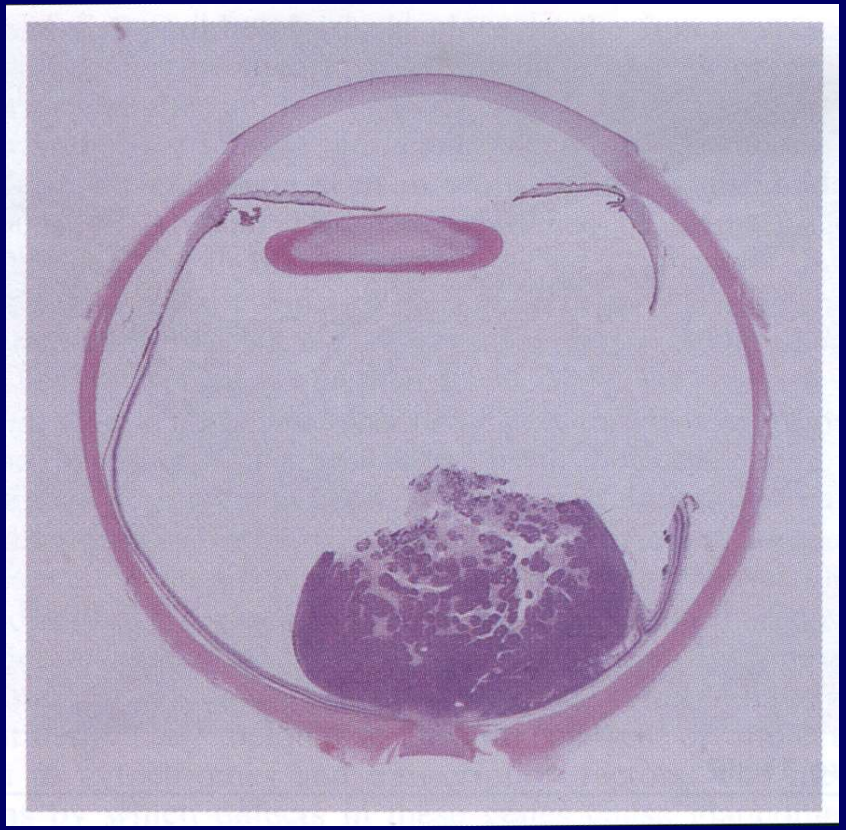
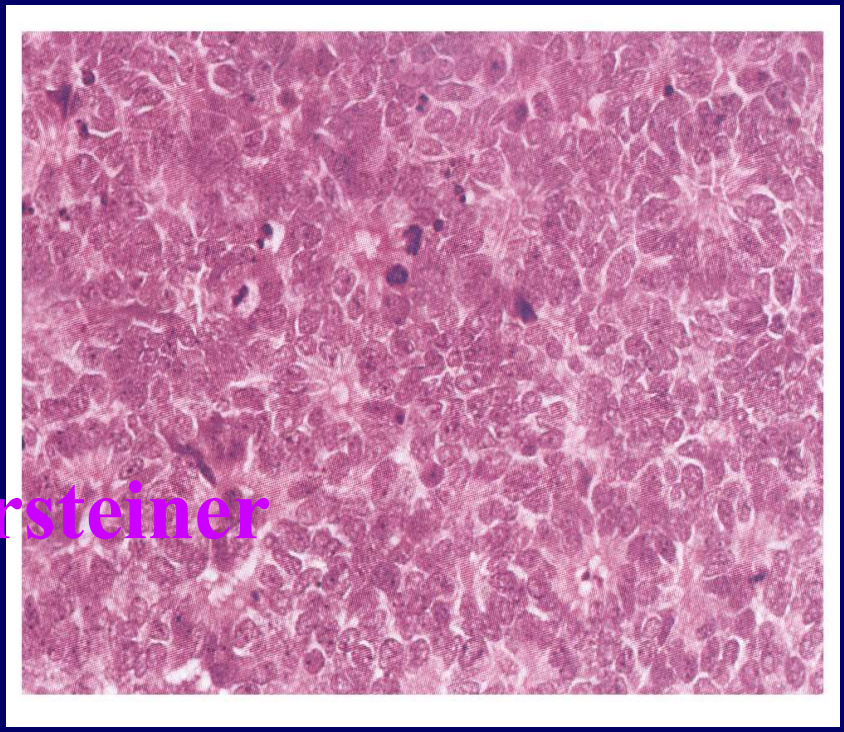
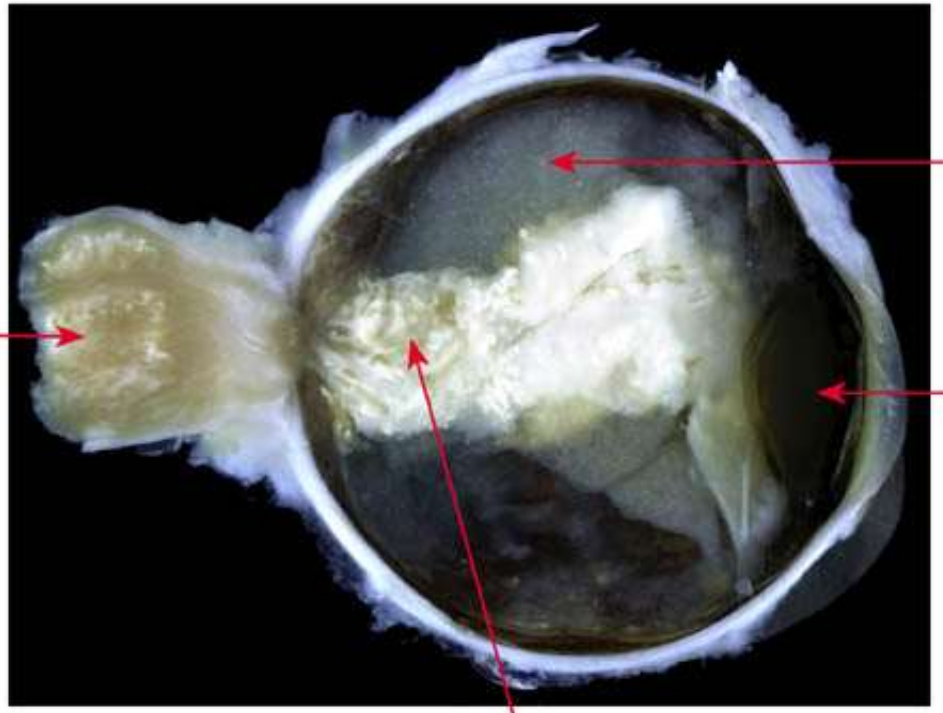


Retinoblastoma tumour



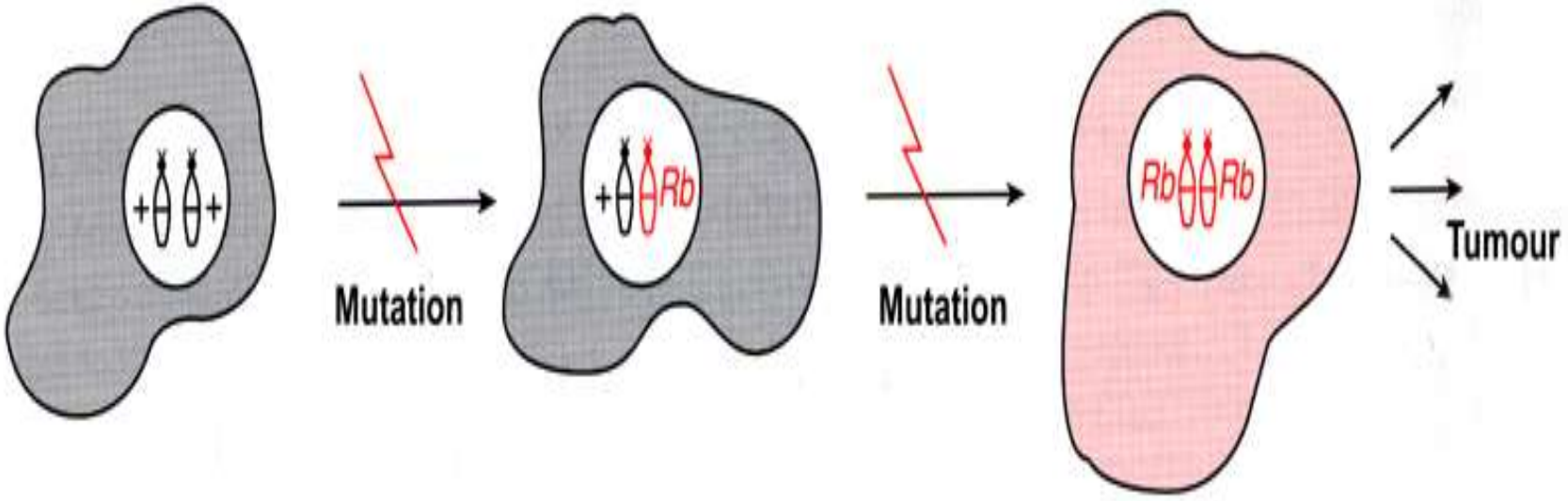
Flexner – Wintersteiner rosettes

A cross section of the eyeball-retinoblastoma



V.121

Knudson's hypothesis

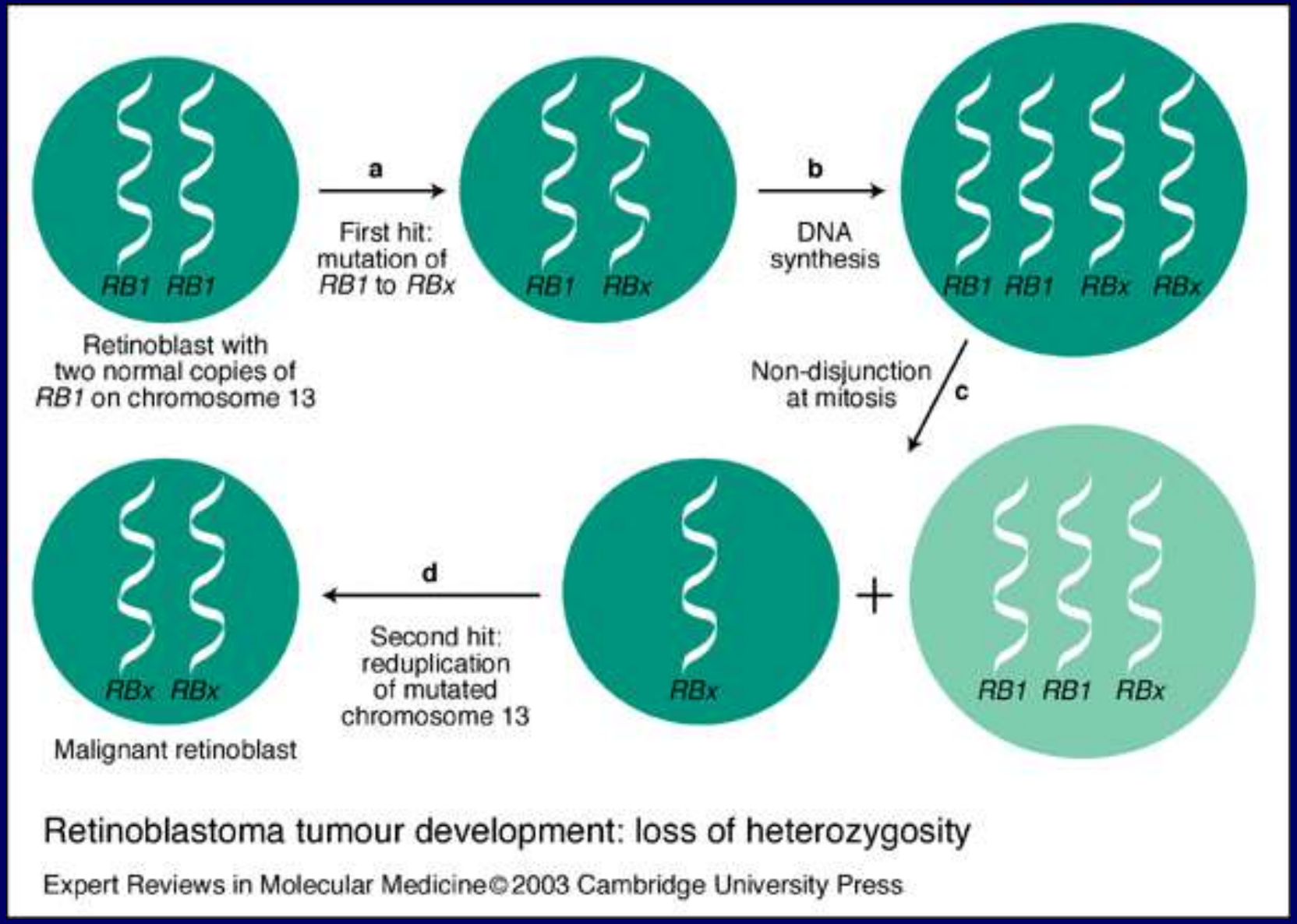


Somatic cell in normal person

Rare somatic cells in normal person; *all* somatic cells in person with familial retinoblastoma

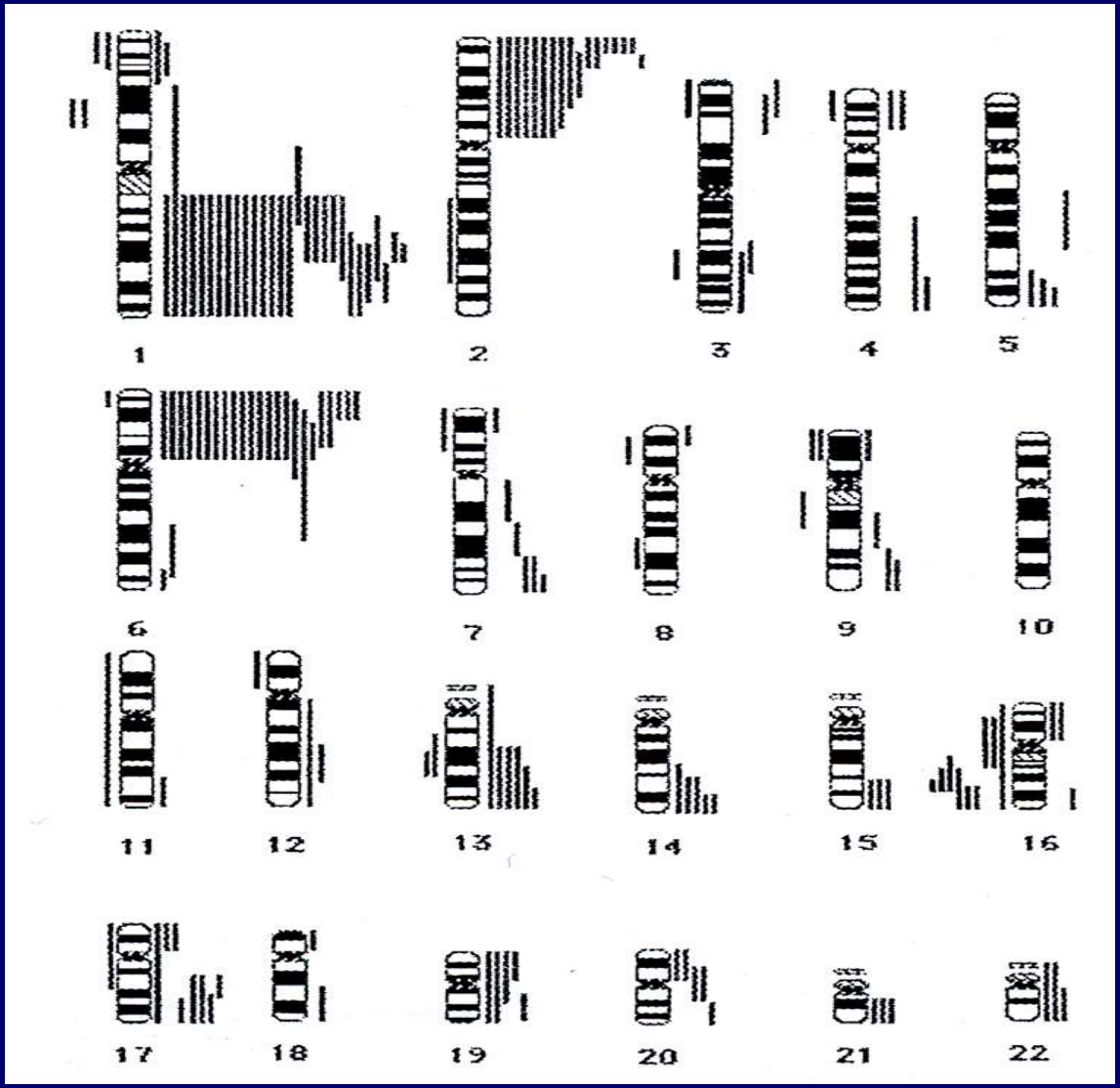
Founder cell of tumor

Knudson's two-hit hypothesis.

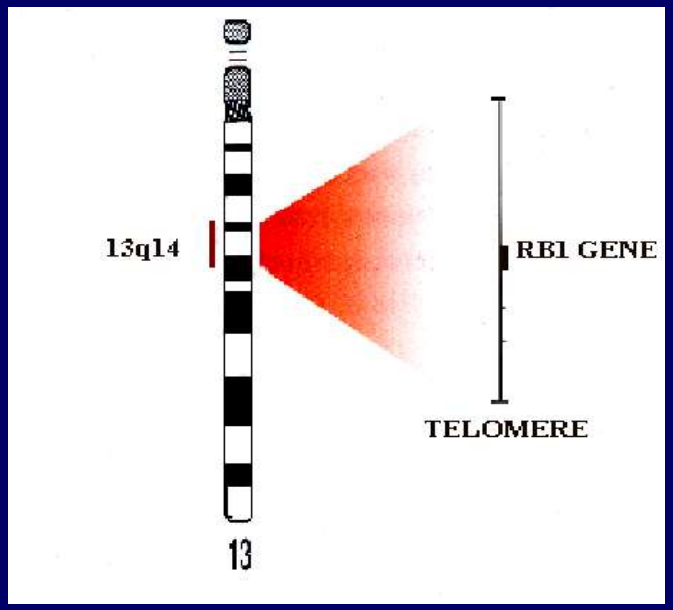


Retinoblastoma tumour development: loss of heterozygosity

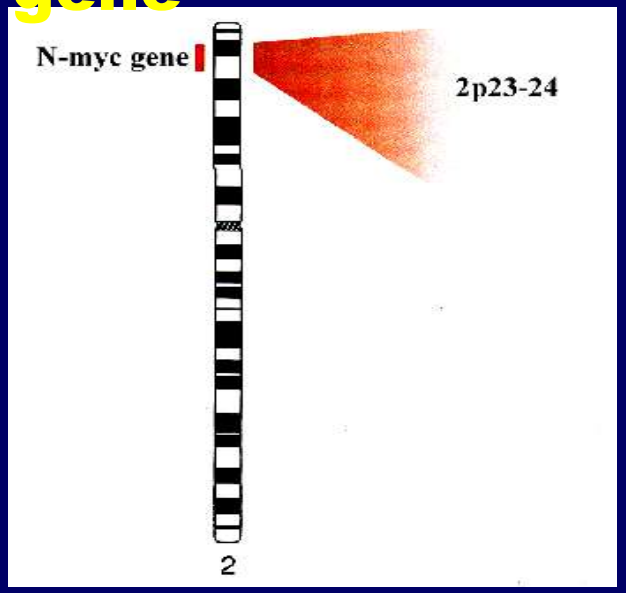
Chen D. et al., 2001 : Chromosomal imbalance in retinoblastoma detected by CGH

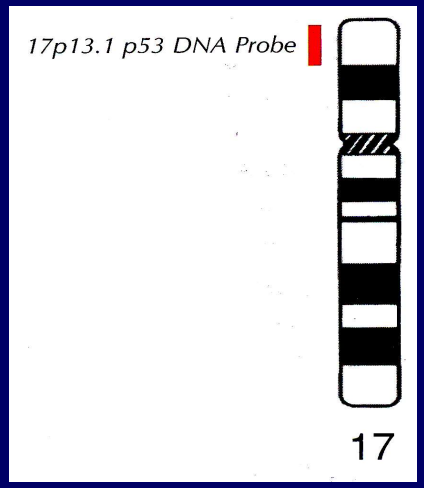


The Rb1 gene



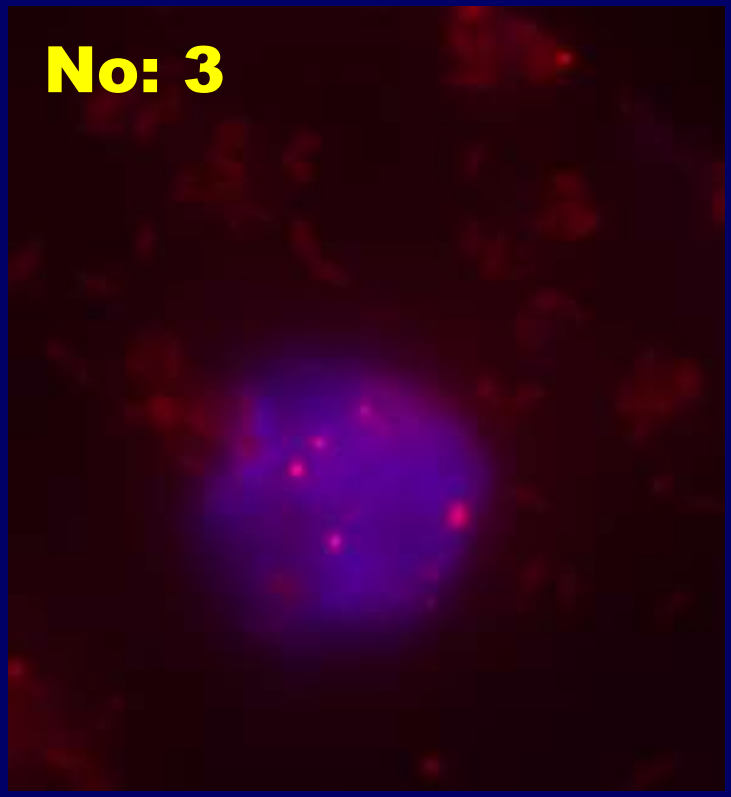
The N-myc gene

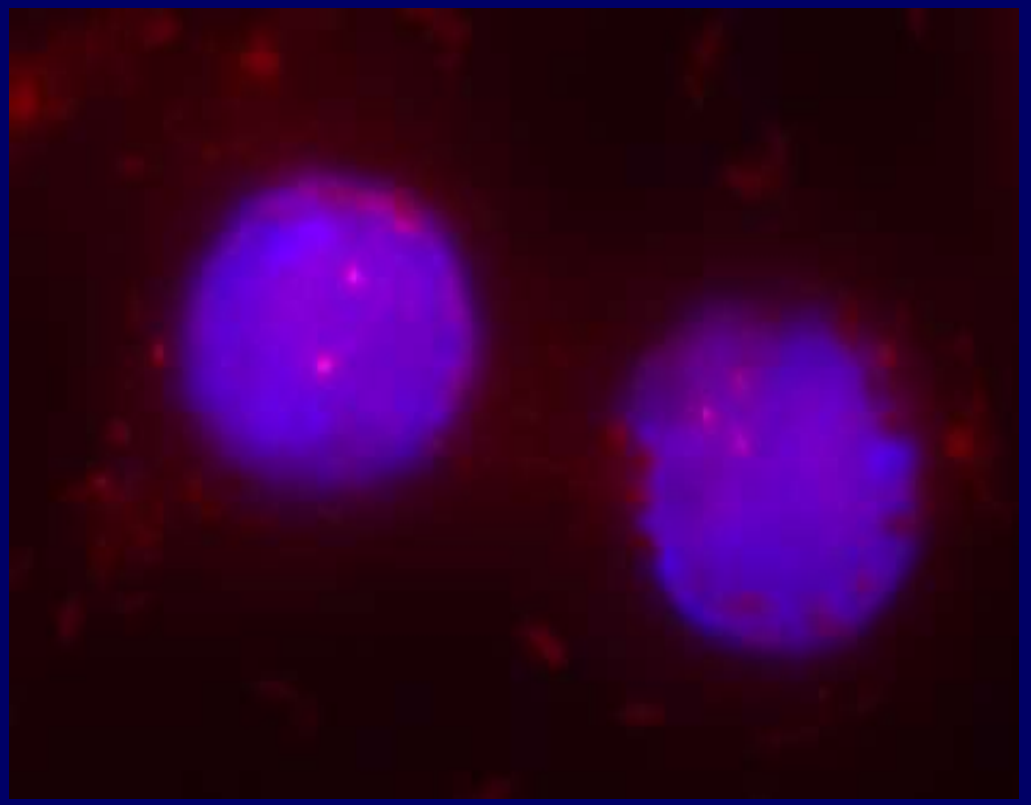




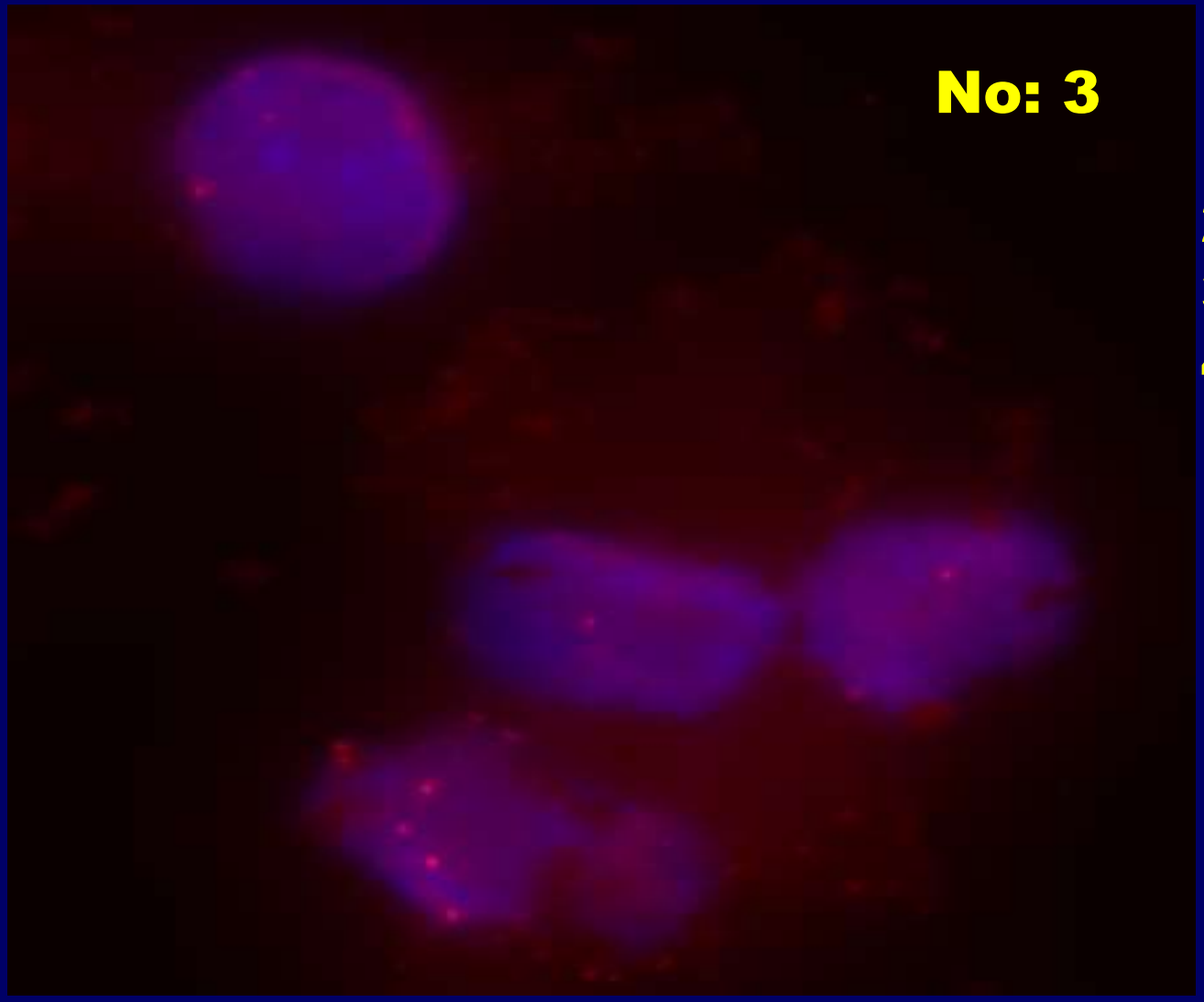
The TP53 gene

The N-myc gene in male retinoblastoma patient





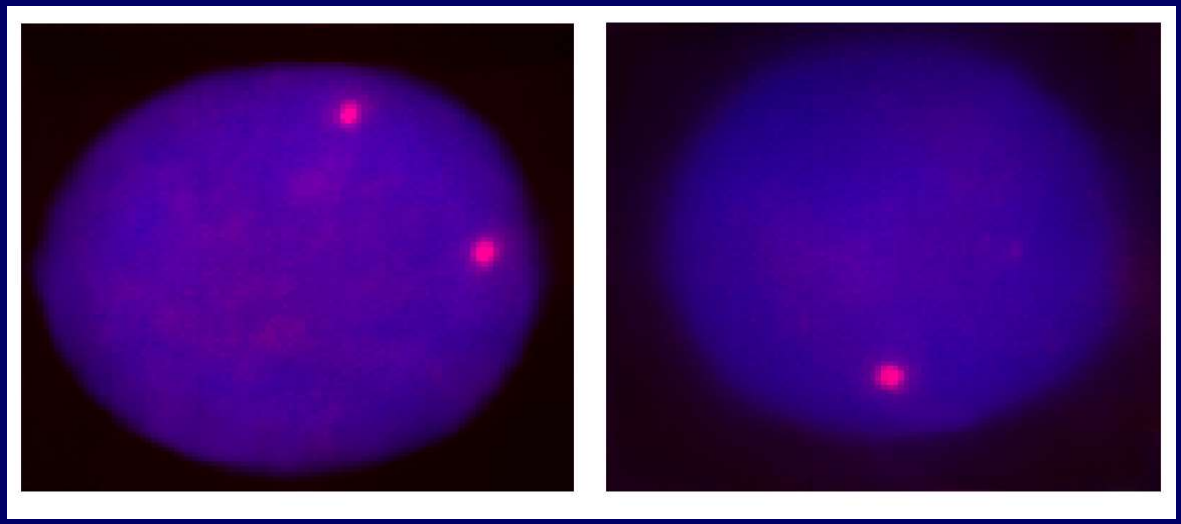
The N-myc gene in male retinoblastoma patient



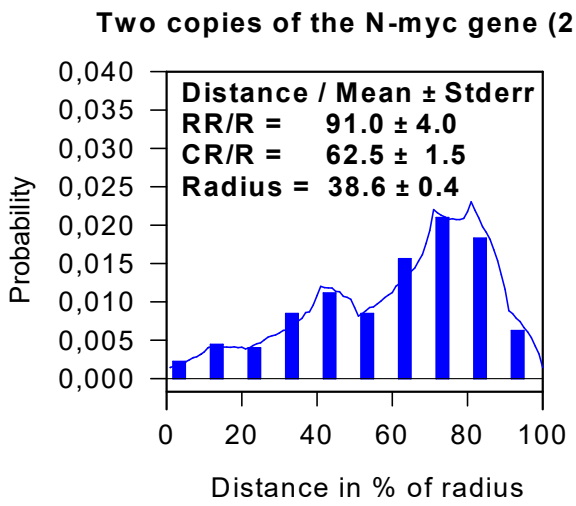
1 copy: 9.8%
2 copies: 55.3%
3 copies: 28.8%
4 copies: 6.1%

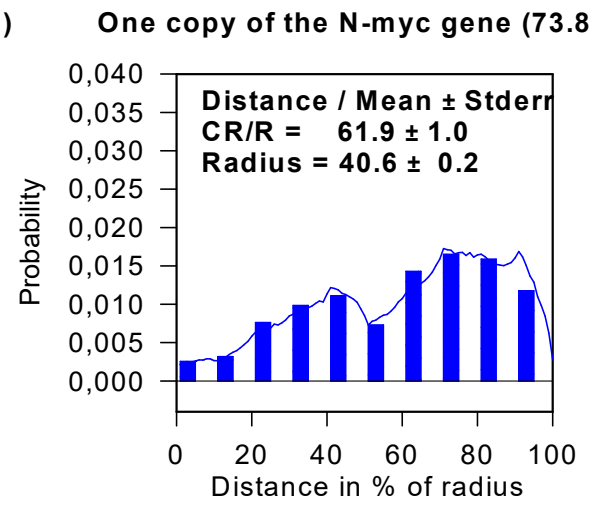
Loss of one copy of the N-myc gene

Chen et al., 2001

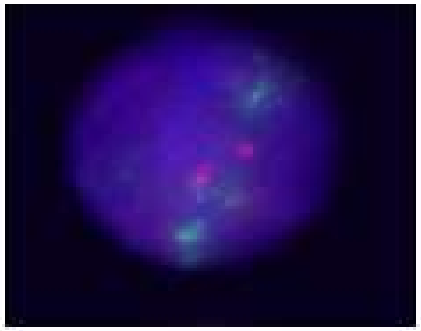


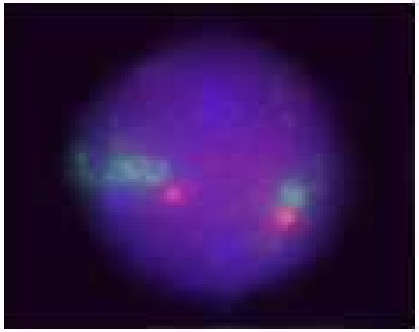
No: 8

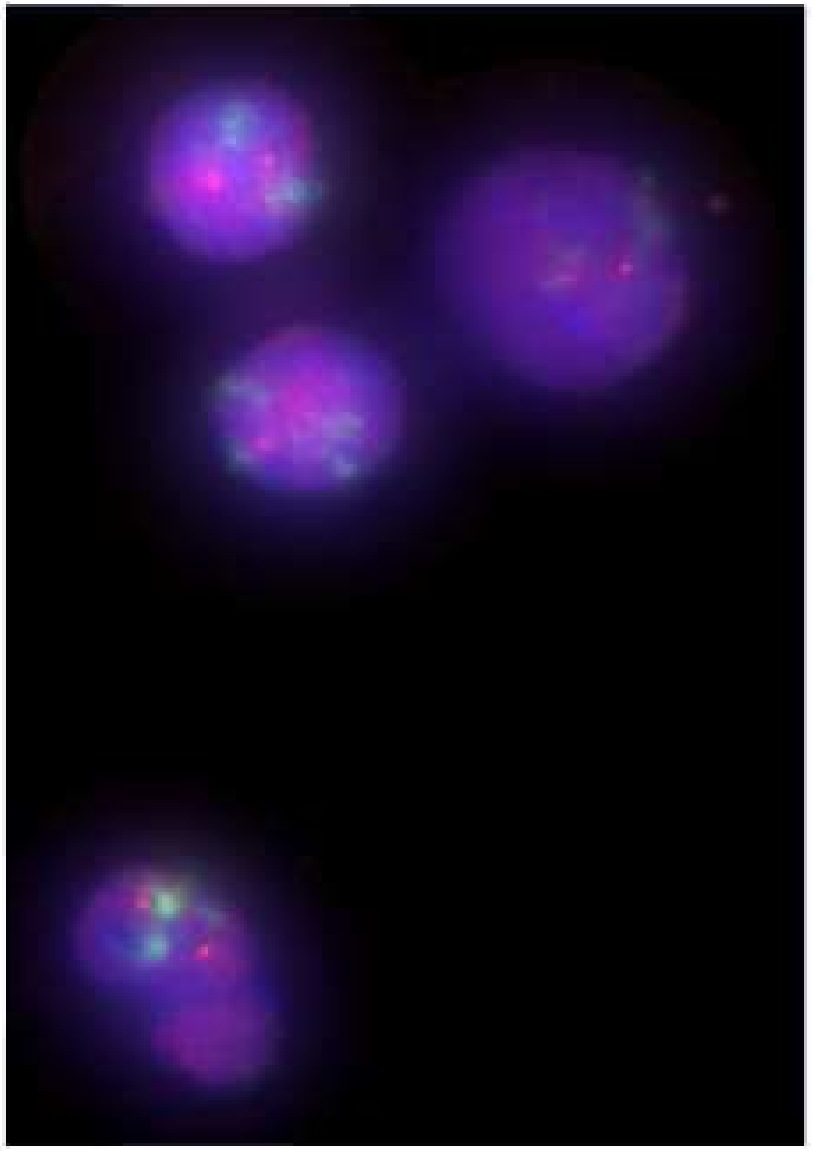




TP53 gene and HSA 17 in lymphocytes of patient No 3

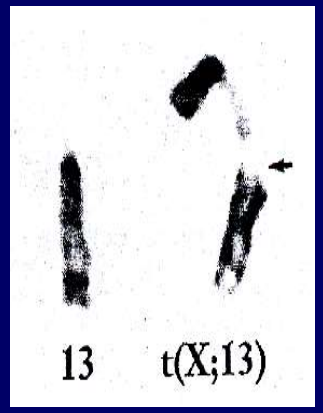




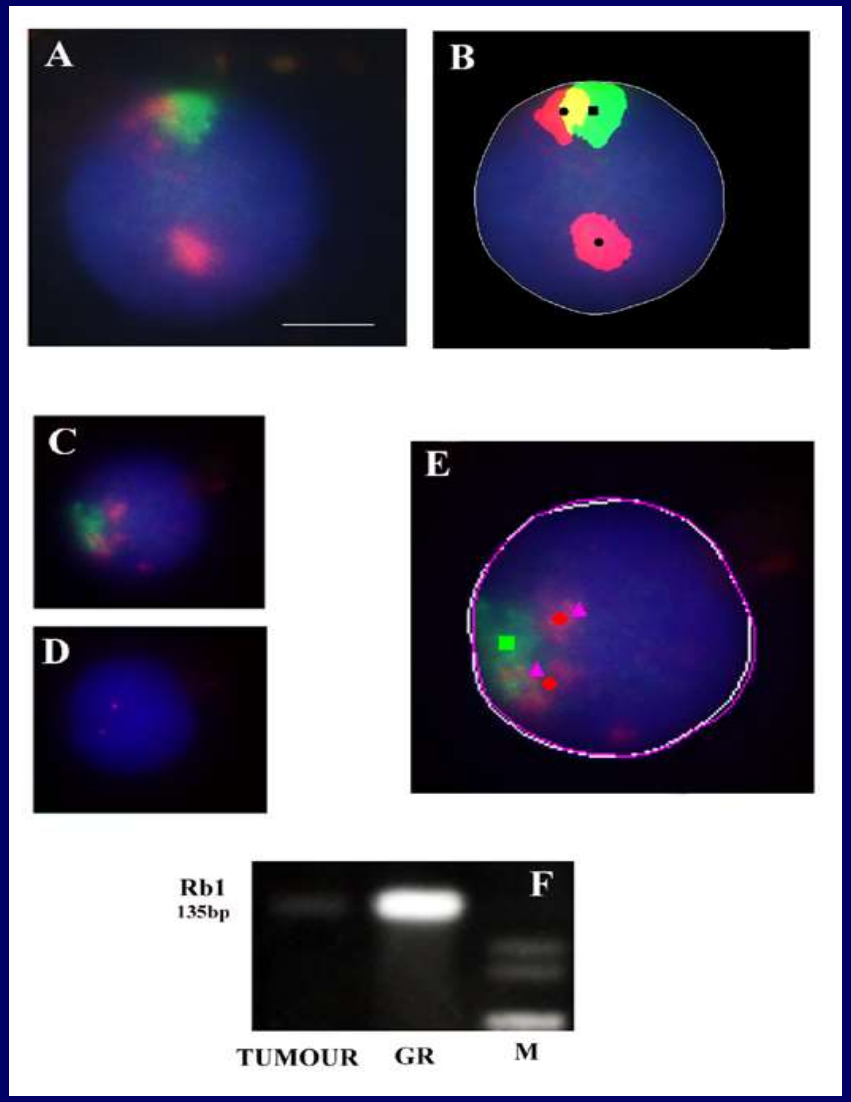


Chromosome 13 , X and Rb1 gene in human retinoblastoma tumour

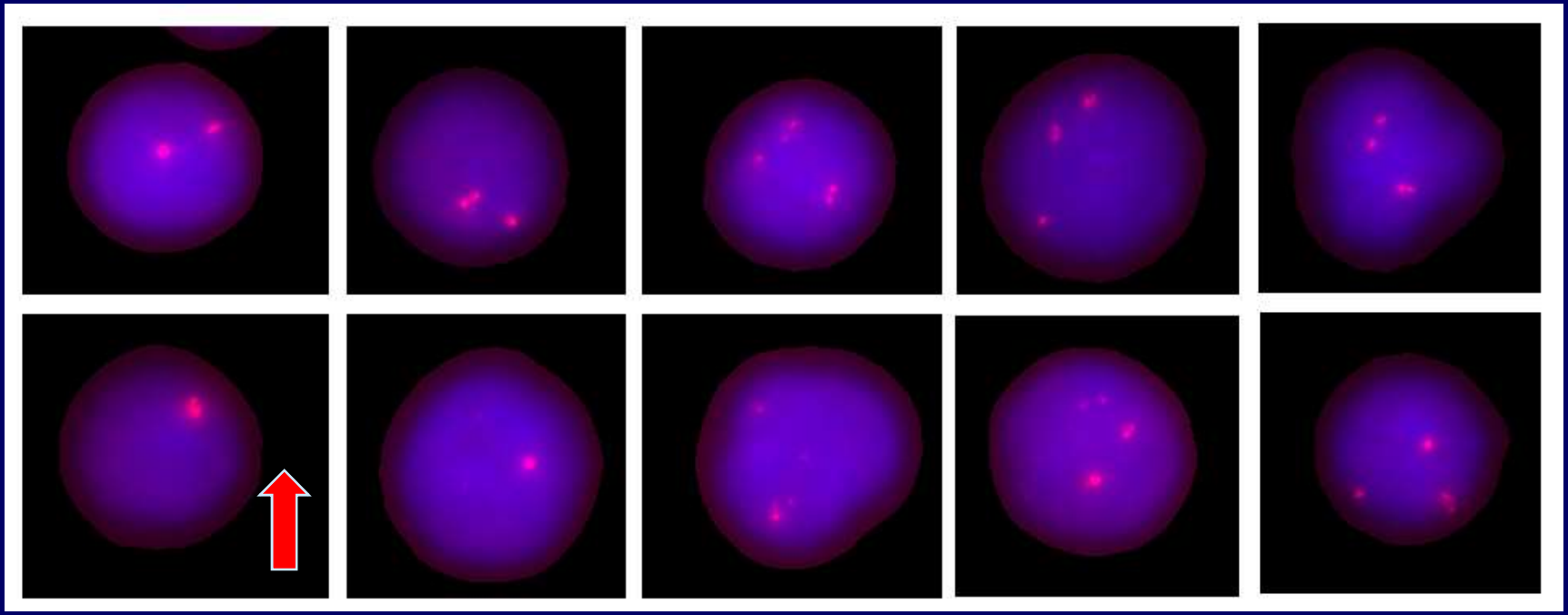
No: 3



Jones et al., 1997

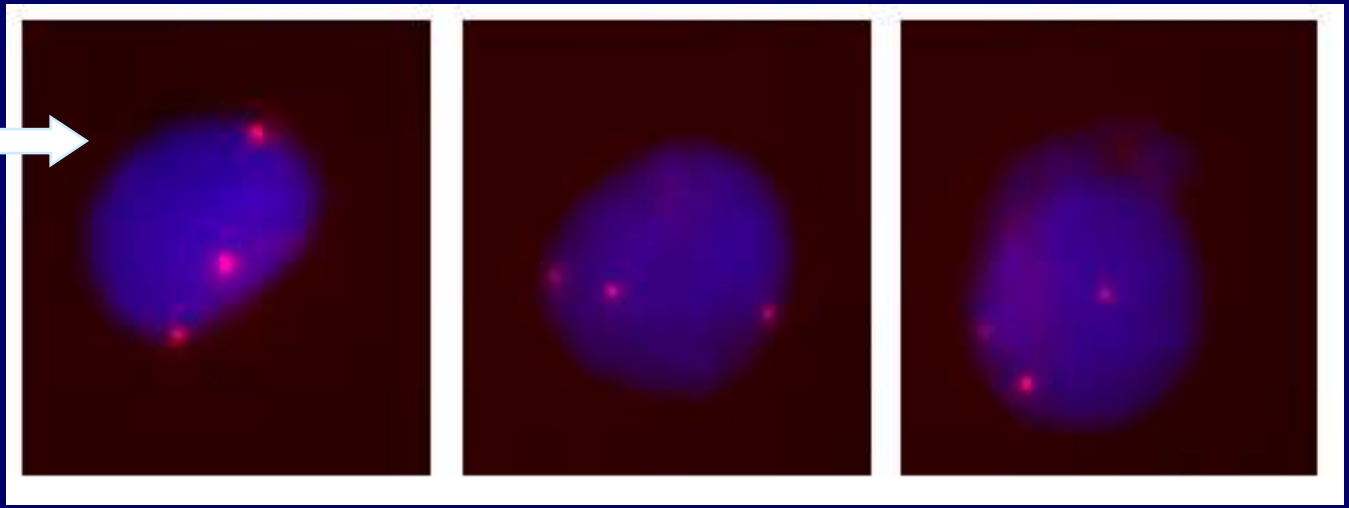


Copy number changes of Rb1 locus

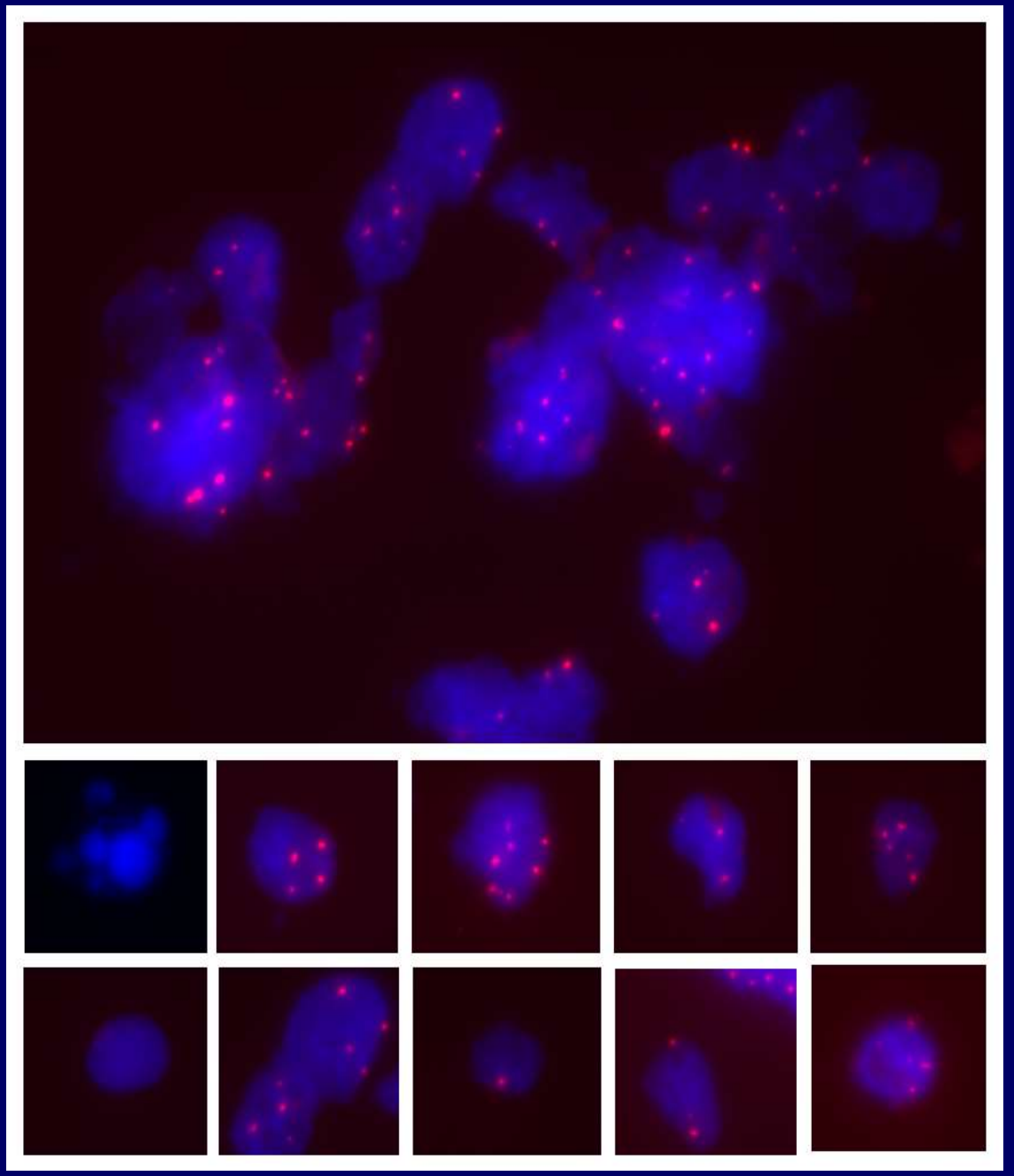


MONOSOMI

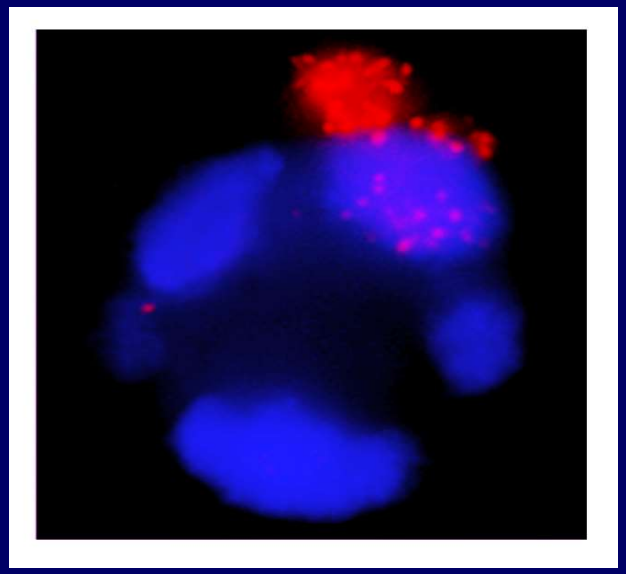
TRISOMI OF HSA 6 in RTB

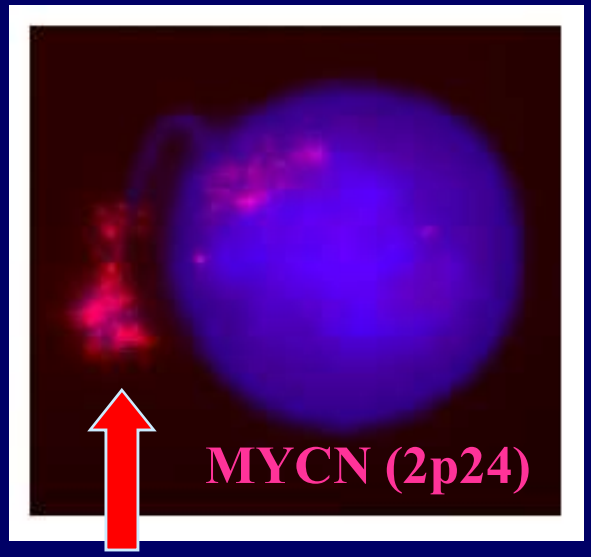


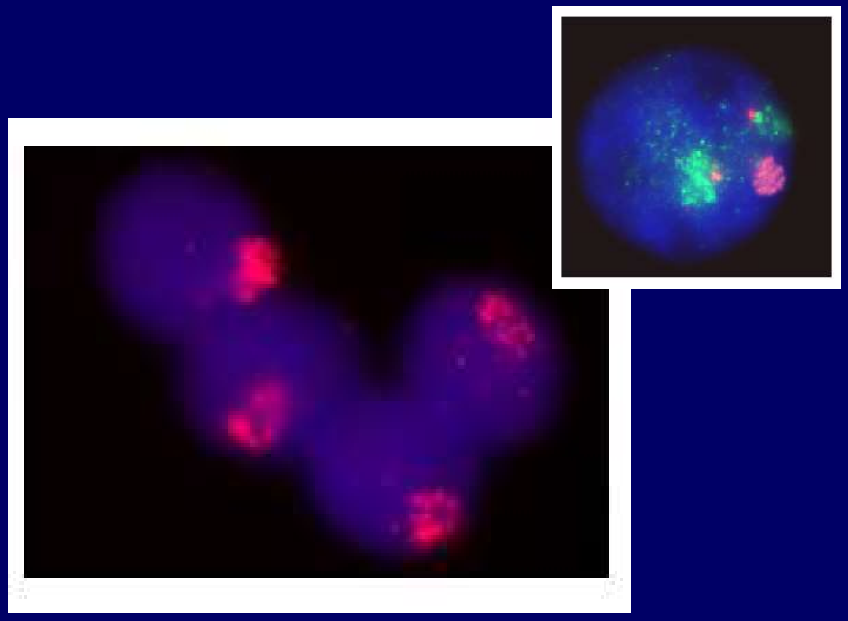
Centromeric region of chromosome 6 detected on paraffin embedded sections

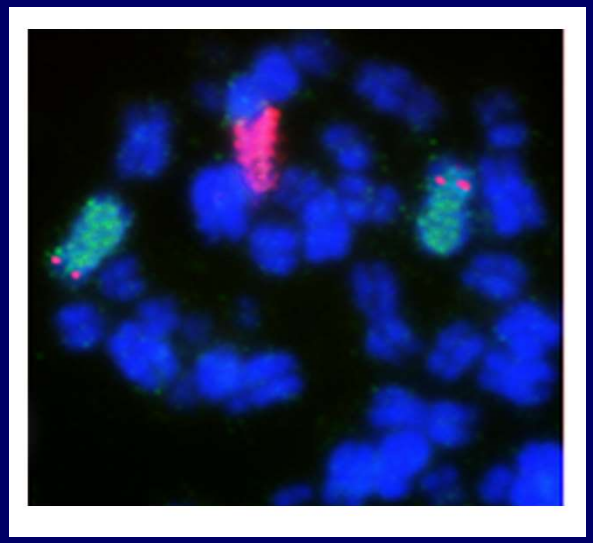


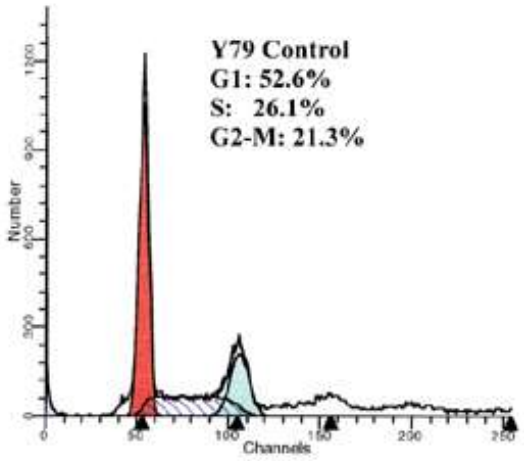
Retinoblastoma Y79 cells and HSR

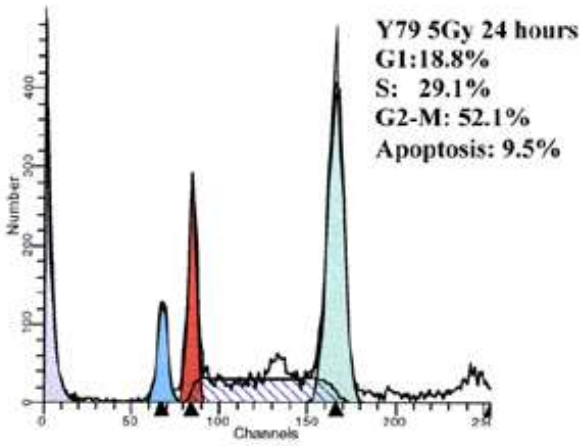


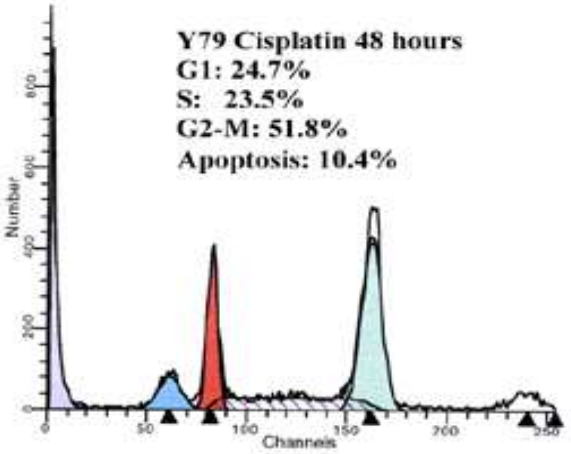




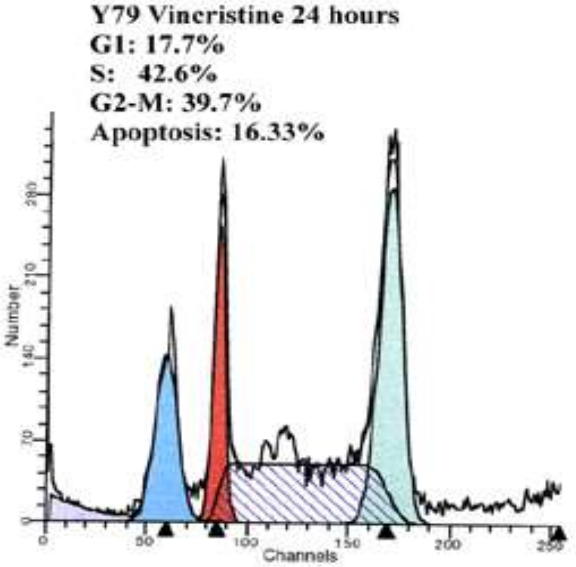








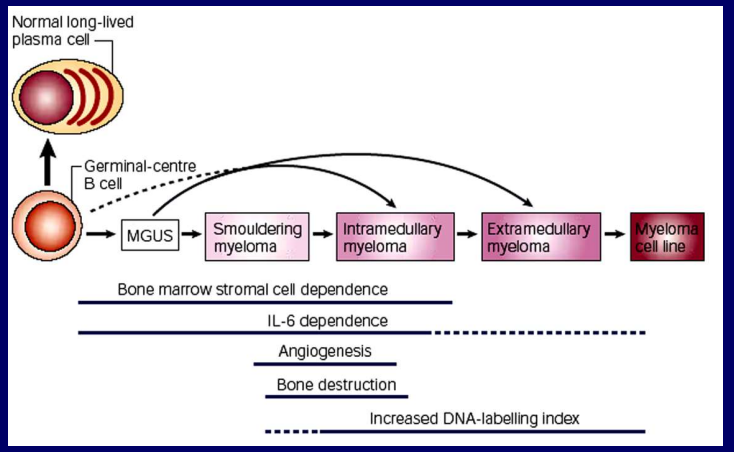
Ovlivnění RTB linie Y79 Cytostatiky a gama zářením



SHRNUTÍ

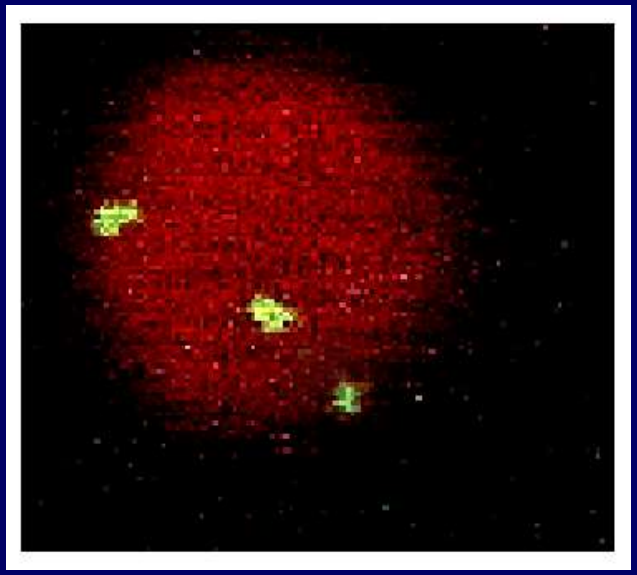
Nádorové buňky jsou charakteristické mnoha aberacemi. Bylo vyvinuto mnoho technik pro detekci cytogenetických změn. Metody mají rozsáhlé klinické využití

Multiple myeloma (MM)



Colorectal carcinoma

U937 leukemic cells



APC, p53, c-myc