Personalized medicine: hype or hope

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CSIC

RTICC

Disclosure slide

No Conflicts of Interest to declare

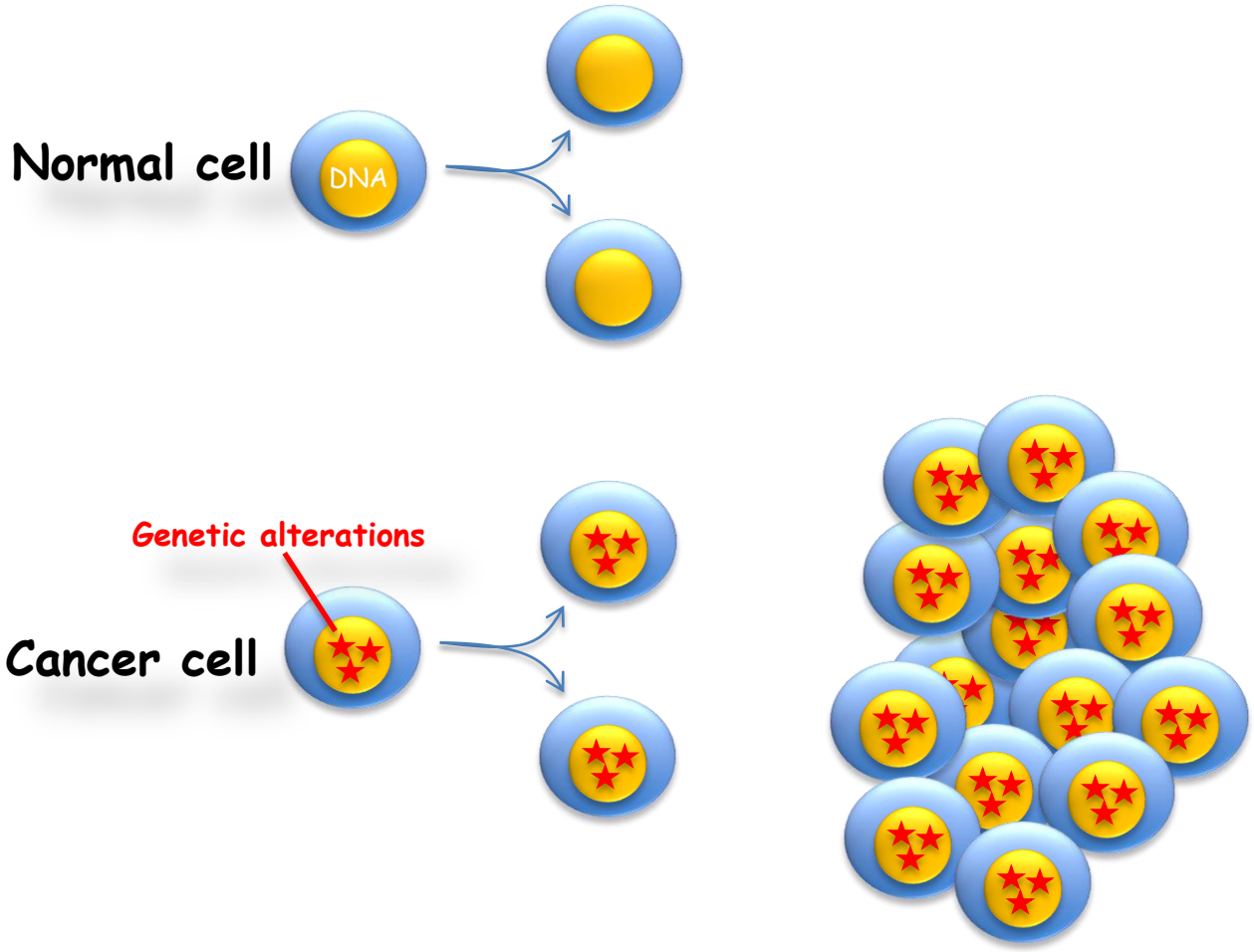
Personalised therapies in cancer

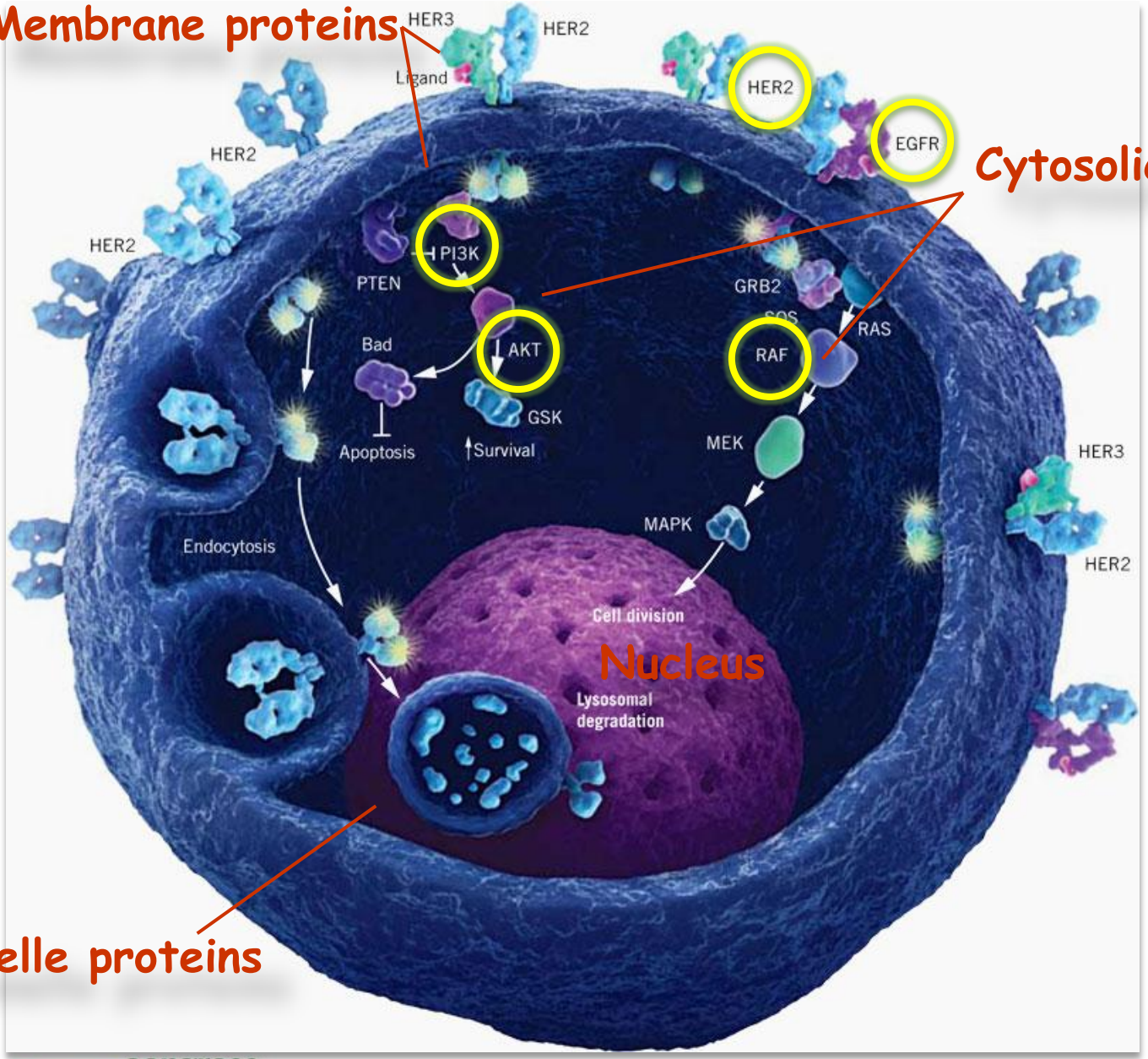
To find out the correct therapy for each patient…

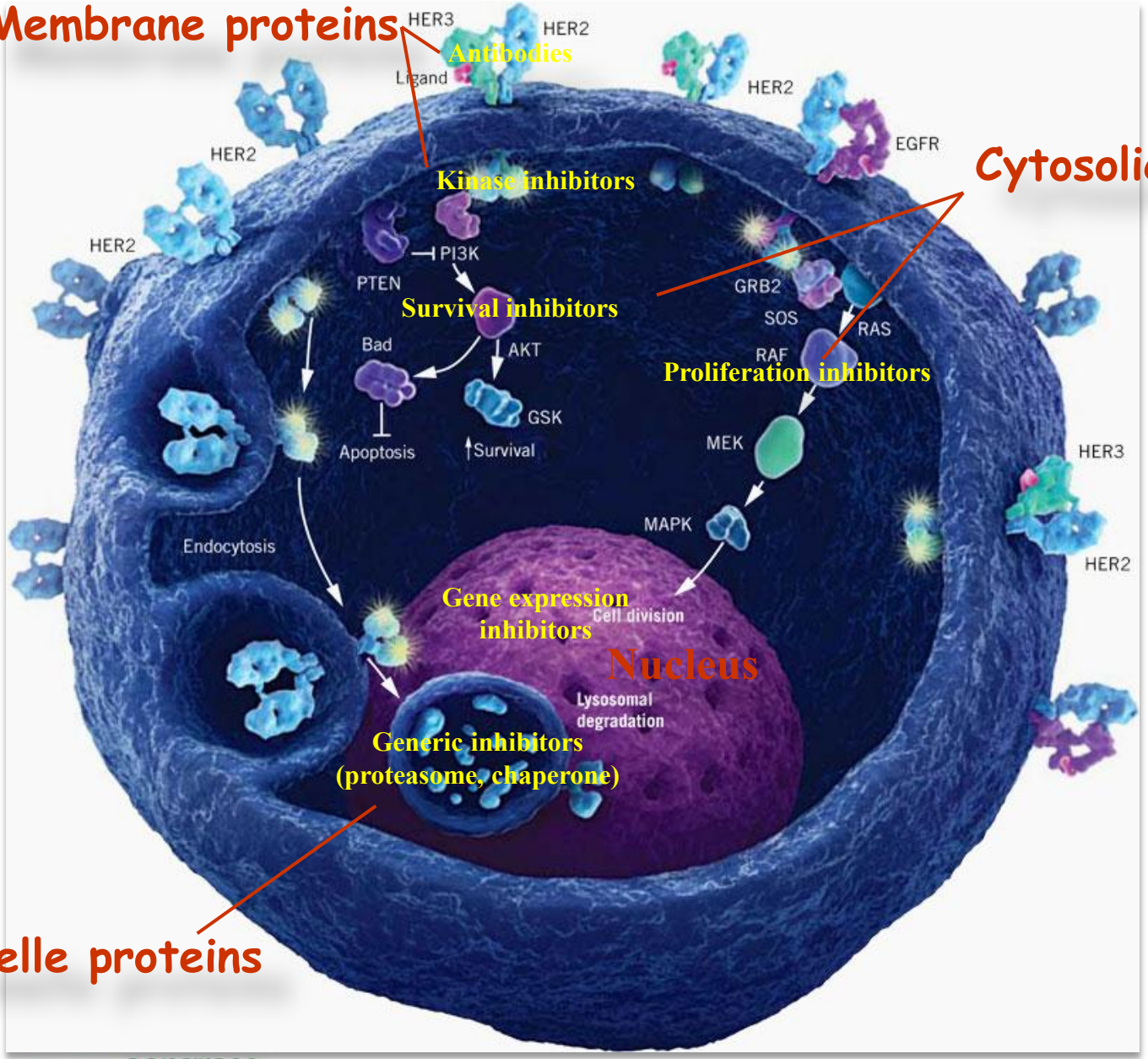
(More efficacy, Less toxicity, minimize relapses)

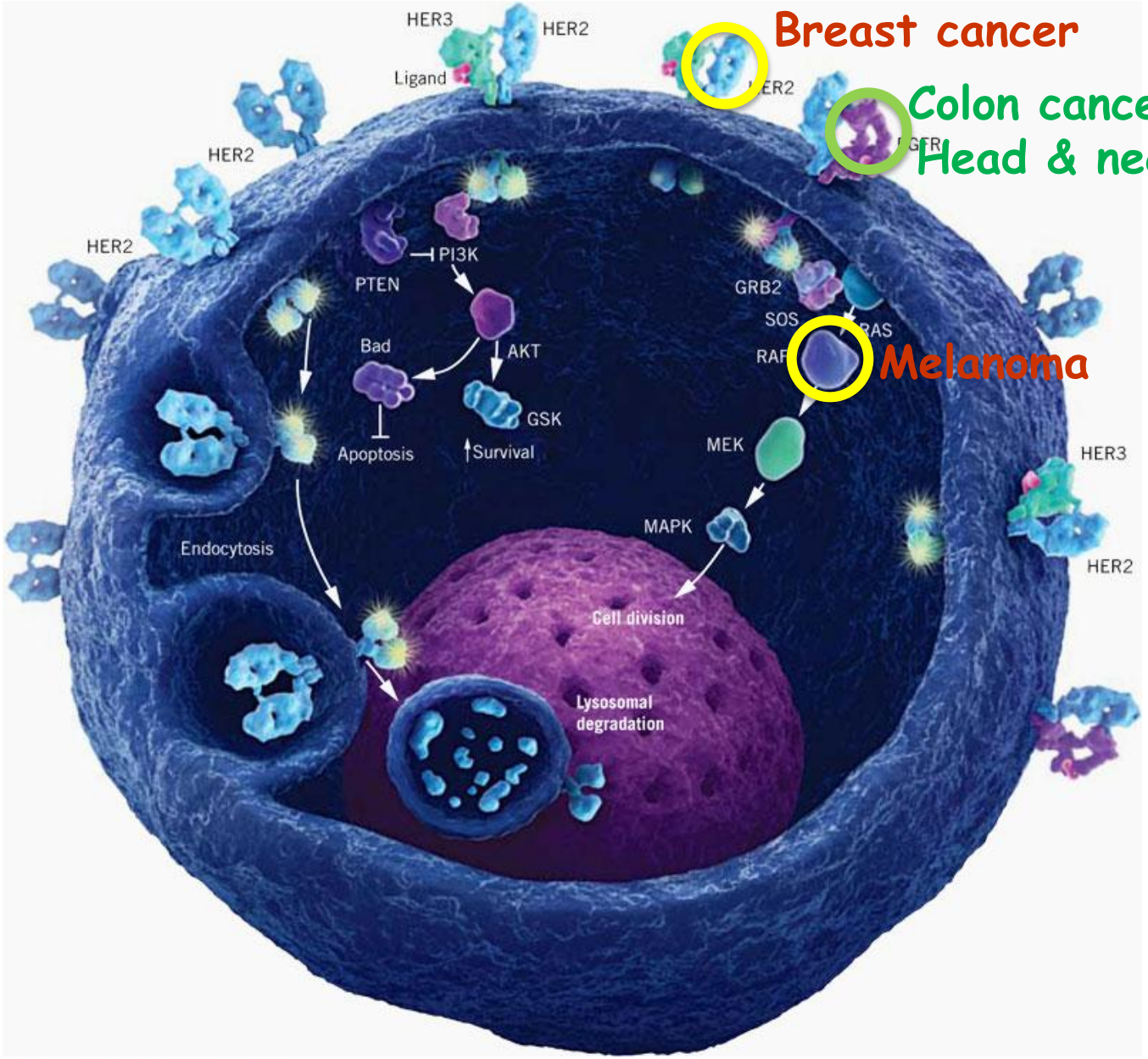
…which requires knowing better the tumors to design effective treatments

Cancer is caused by uncontrolled accumulation of cells, provoked by genetic alterations




Membrane proteins
HER3
HER2
Ligand
HER2
EGFR
HER2
HER2
Cytosolic proteins
PI3K
PTEN
GRB2
SOS
RAS
Bad
AKT
RAF
GSK
Apoptosis
Survival
MEK
HER3
MAPK
Endocytosis
HER2
Cell division
Nucleus
Lysosomal degradation
Organelle proteins


Membrane proteins
HER3
HER2
Antibodies
Ligand
HER2
HER2
EGFR
Cytosolic proteins
Kinase inhibitors
HER2
PI3K
PTEN
Survival inhibitors
GRB2
SOS
RAS
RAF
Bad
AKT
Proliferation inhibitors
GSK
Apoptosis
Survival
MEK
HER3
MAPK
Endocytosis
HER2
Gene expression
inhibitors
Cell division
Nucleus
Lysosomal
degradation
Generic inhibitors
(proteasome, chaperone)
Organelle proteins


HER3
HER2
Ligand
HER2
HER2
HER2
PI3K
PTEN
Bad
AKT
GSK
Apoptosis
Survival
GRB2
SOS
RAS
RAF
MEK
MAPK
HER3
HER2
Endocytosis
Cell division
Lysosomal degradation
Breast cancer
Colon cancer,
Head & neck
Melanoma

Personalised therapies in cancer

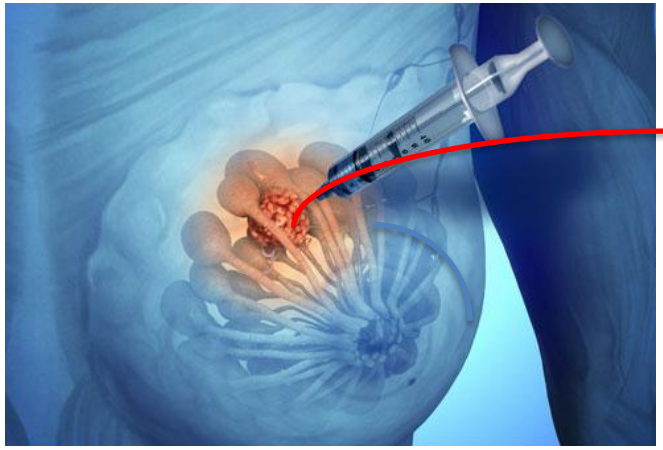
To find out the correct therapy for each patient…

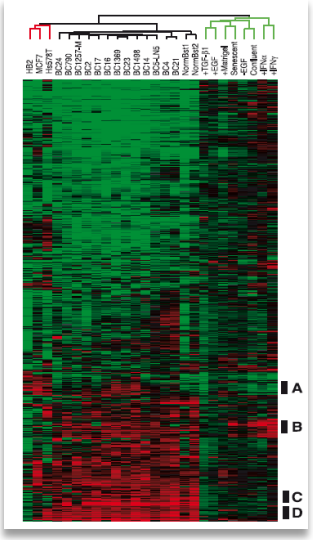
(More efficacy, Less toxicity, minimize relapses)

…which requires knowing better the tumors to design effective treatments

To know better the genetic and proteic characteristics of cancer cells…

…to act on them more efficiently





Genomic and proteomic analyses

How many genetic alterations exist?

Are all important?

How can we desing effective treatments on the bases of these alterations?

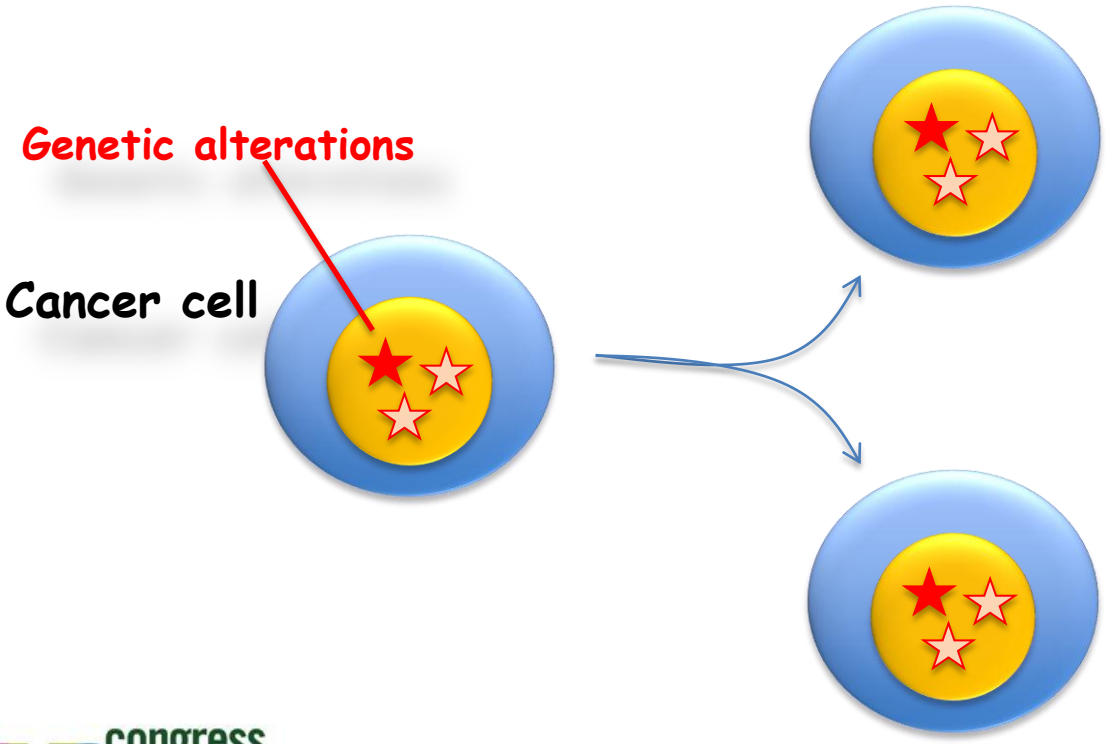
Etiopathogenic alterations:

1.- A single alteration

2.- Multiple alterations

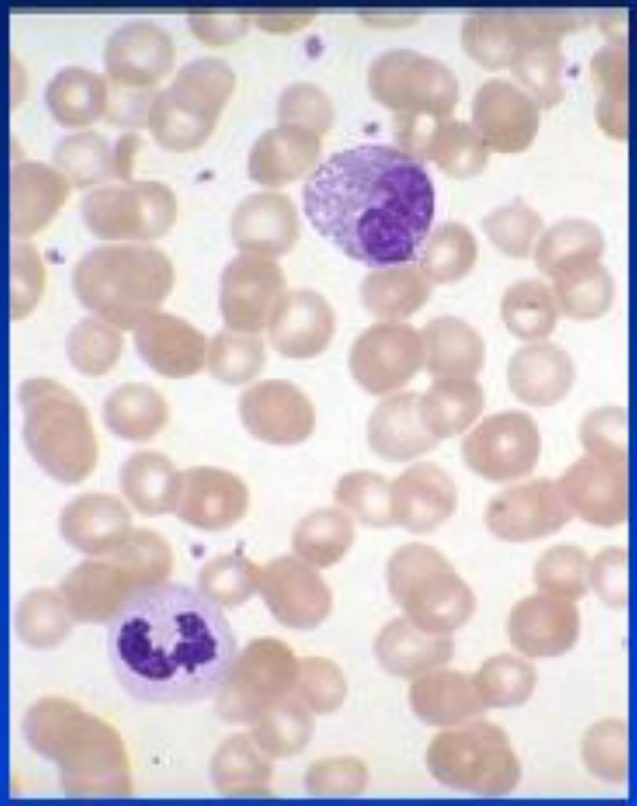
Etiopathogenic alterations:

1.- A single alteration

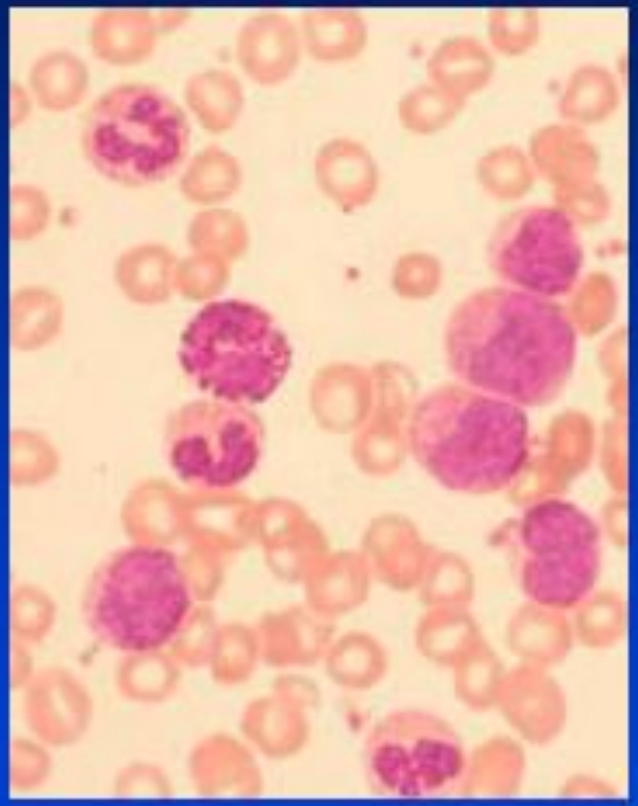


CML: Peripheral Blood Smear

Normal

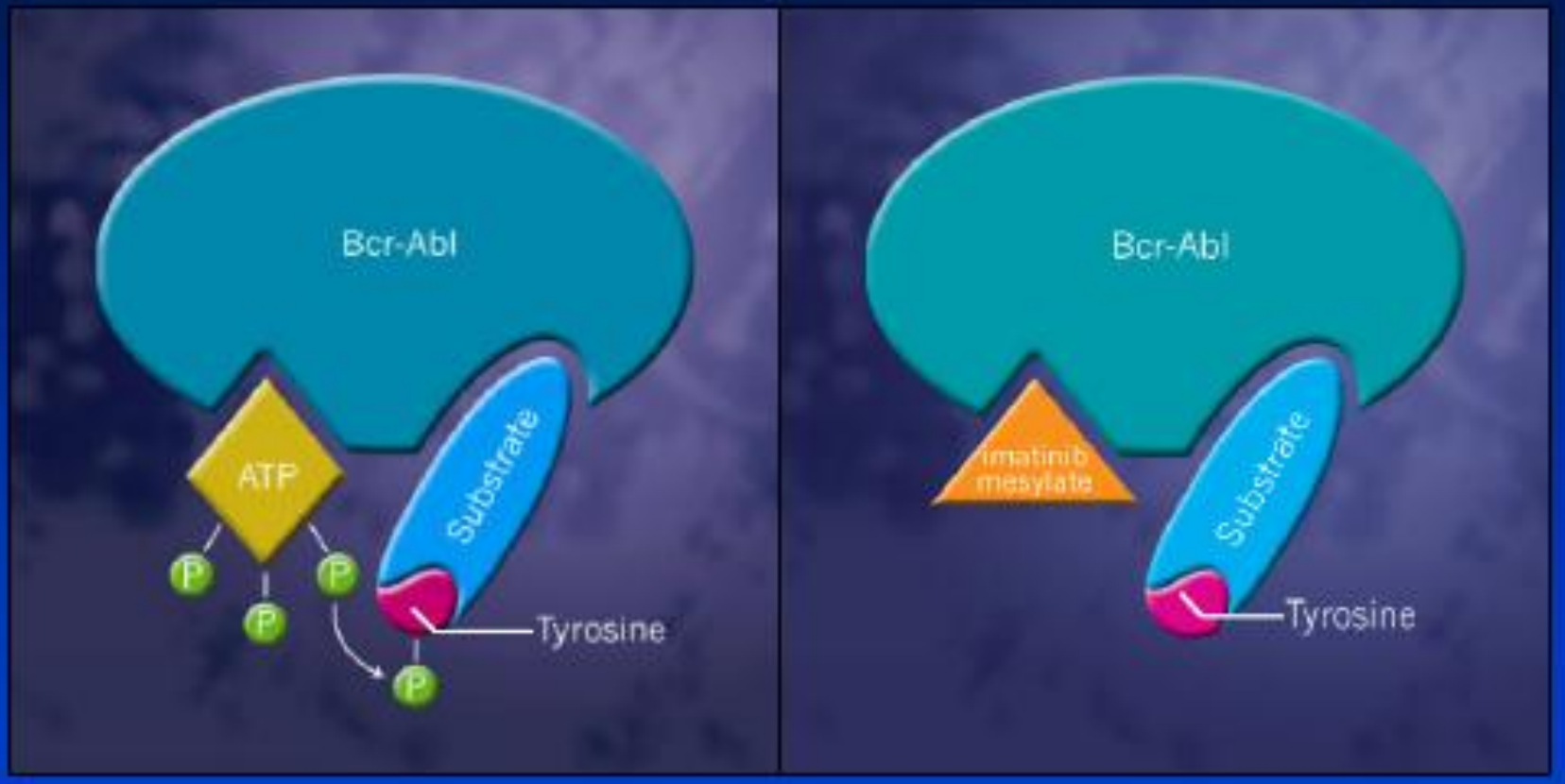


Chronic phase CML



Courtesy of John K. Choi, MD, PhD, University of Pennsylvania.

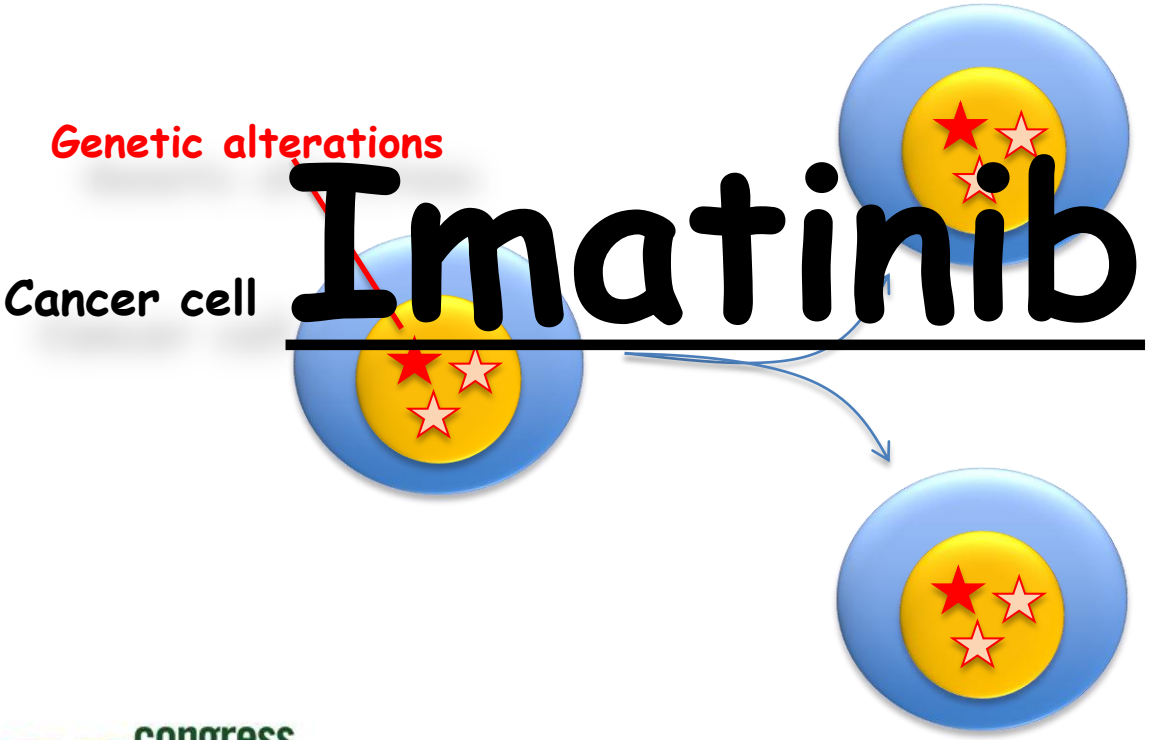
Imatinib Targets the Cause of CML



- Imatinib—a specific inhibitor of a small family of tyrosine kinases, including Bcr-Abl

Etiopathogenic alterations:

1.- A single alteration



Science 16 November 2007:

The Genomic Landscapes of Human Breast and Colorectal Cancers

Laura D. Wood,1 D. Williams Parsons,1 Siân Jones,1 Jimmy Lin,1 Tobias Sjöblom,1 Rebecca J. Leary,1 Dong Shen,1 Simina M. Boca,1,2 Thomas Barber,1 Janine Ptak,1 Natalie Silliman,1 Steve Szabo,1 Zoltan Dezso,3 Vadim Ustyanksky,3 Tatiana Nikolskaya,3,4 Yuri Nikolsky,3 Rachel Karchin,5 Paul A. Wilson,5 Joshua S. Kaminker,6 Zemin Zhang,6 Randal Croshaw,7 Joseph Willis,8 Dawn Dawson,8 Michail Shipitsin,9 James K. V. Willson,10 Saraswati Sukumar,11 Kornelia Polyak,9 Ben Ho Park,11 Charit L. Pethiyagoda,12 P. V. Krishna Pant,12 Dennis G. Ballinger,12 Andrew B. Sparks,12 James Hartigan,13 Douglas R. Smith,13 Erick Suh,13 Nickolas Papadopoulos,1 Phillip Buckhaults,7 Sanford D. Markowitz,14 Giovanni Parmigiani,1 Kenneth W. Kinzler,1 Victor E. Velculescu,1 Bert Vogelstein1

Massive sequencing of:

- 11 colon cancer tumors
- 11 breast cancer tumors

- *2 cDNAs from normal tissues*

Colorectal Cancers

Co74	123
Co92	90
Co108	82
Mx22	69
Mx27	86
Mx30	57
Mx32	76
Mx38	77
Mx41	99
Mx42	81
Mx43	102

Breast Cancers

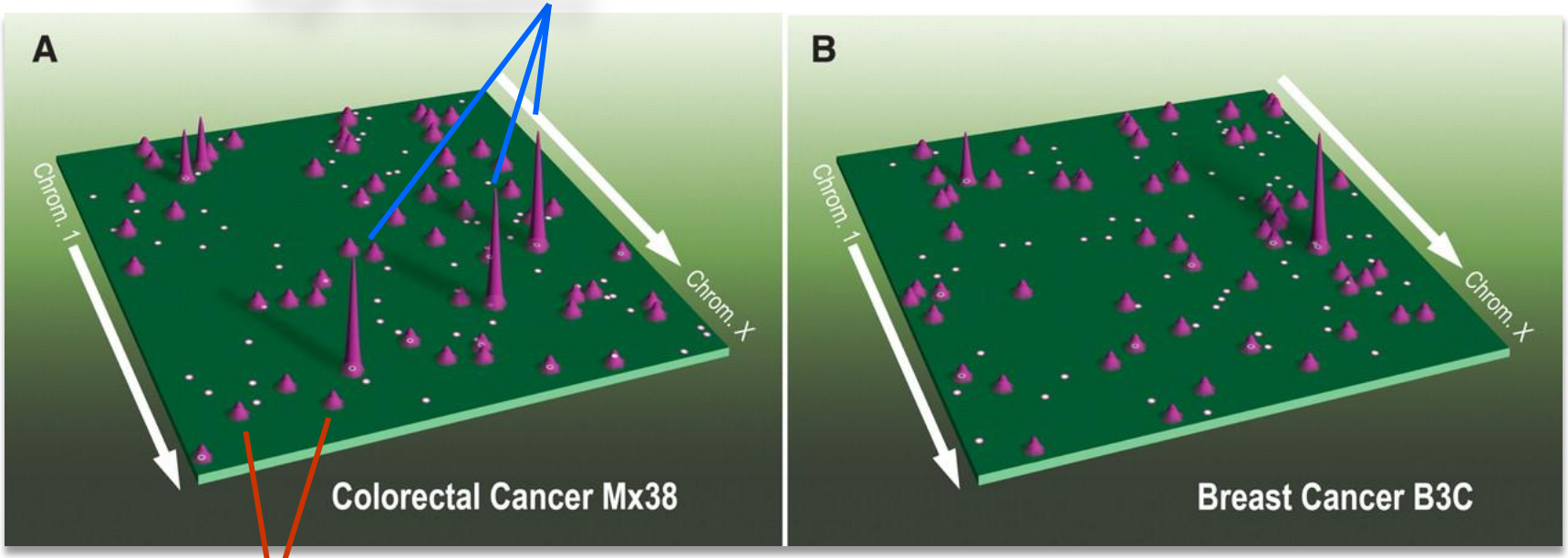
B1C	41
B2C	176
B3C	83
B4C	76
B5C	95
B6C	79
B7C	221
B8C	95
B9C	85
B10C	130
B11C	162

Massive sequencing of:

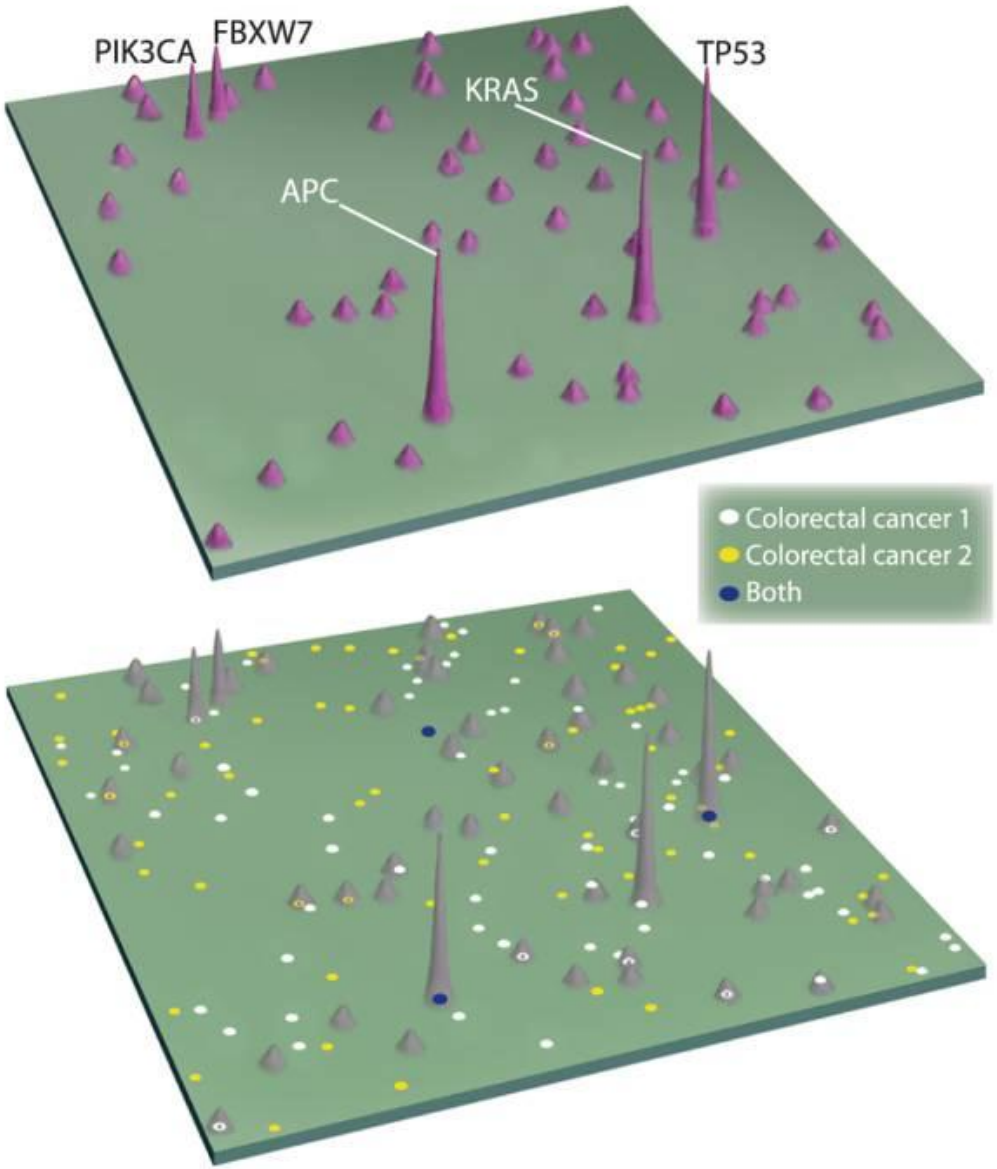
- 11 colon cancer tumors: 76 mutations/tumor
- 11 breast cancer tumors: 84 mutations/tumor

…..but only some (15?) of these genes appear to drive cancer (CAN/driver genes).

CAN genes mutated at high frequency



CAN genes mutated at low frequency


PIK3CA
FBXW7
KRAS
TP53
APC
Colorectal cancer 1
Colorectal cancer 2
Both

Multiple genetic alterations

How many genetic alterations exist?

≈80 mutations/tumor

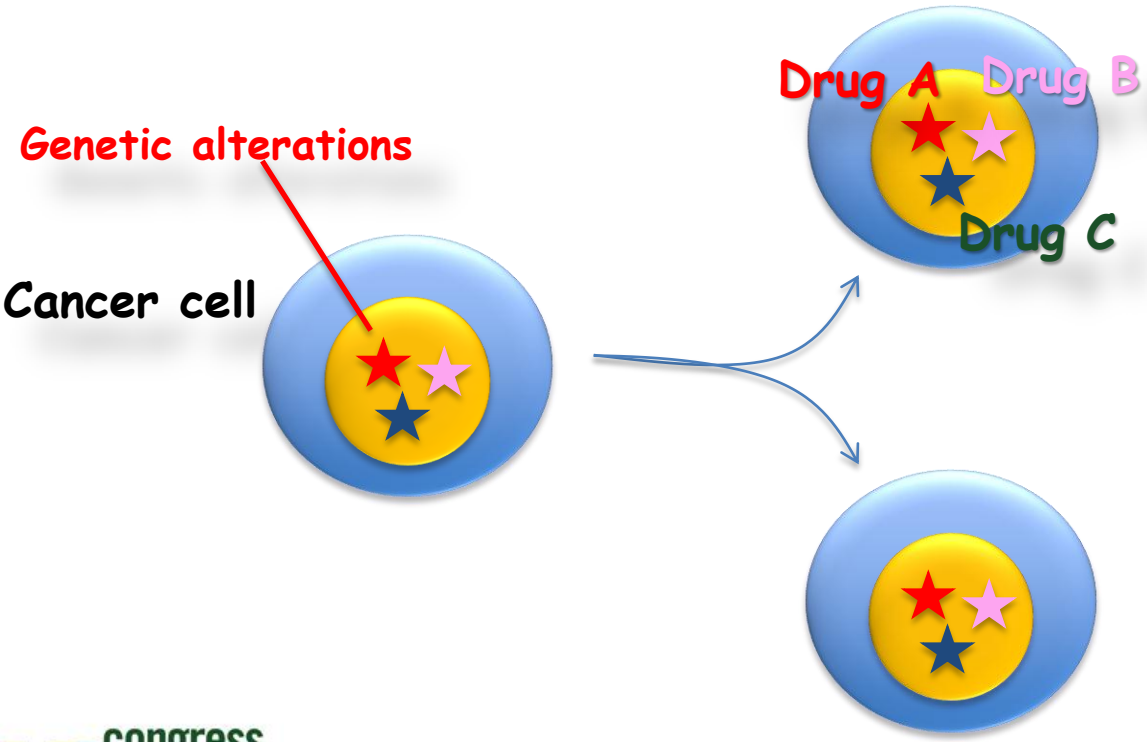
Are all important?

≈ 15 "driver" tumor mutations

How can we desing effective treatments on the bases of these alterations?

Etiopathogenic alterations:

2.- Multiple alterations



Etiopathogenic alterations:

1.- A single alteration

2.- Multiple alterations

Drug combinations against different targets are efficient!!!

Cancer Research Center, *Salamanca (Spain)*

A comprehensive cancer center