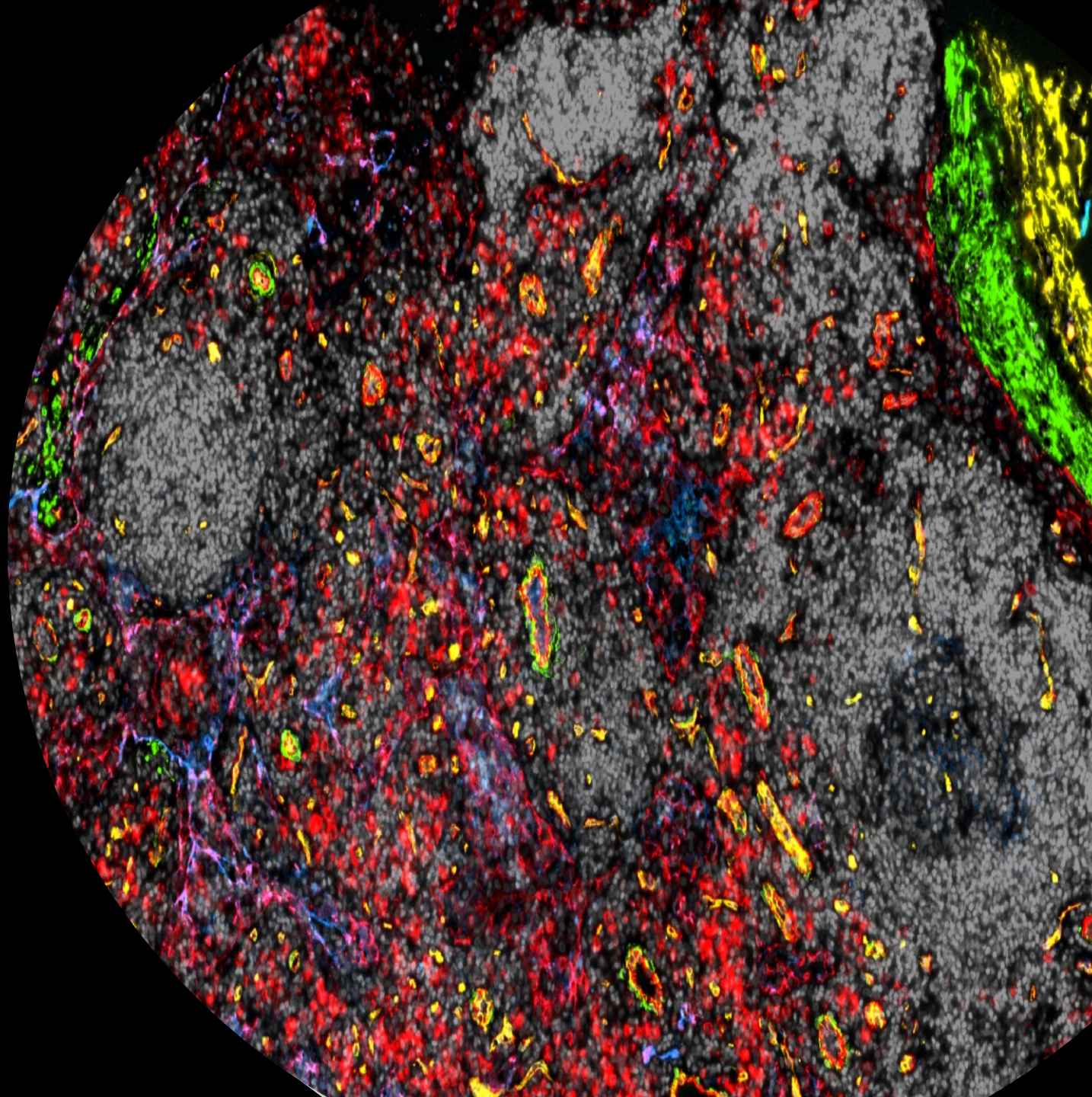
Cancer Biology I

Part-II

Week 12



AGENDA

Nov 5th: Cancer genomics- mutations

Nov 11th: Cancer genomics-copy number alteration, heterogeneity, evolution *(recording)*

Nov 18th: Cancer Epigenetics- chromatin 3D structure, cell plasticity

Nov 25th: – Major signaling pathways leading to cancer

Dec 2th: Cancer Therapies – chemo and targeted therapies

Dec 9th: Introduction to immunotherapies –

Dec 16th: questions for the exam

Dec 18th: Exam 1.30 PM-3.30 PM

Did we improve cancer treatment in the past 20-30 years?

HOW DO WE TREAT CANCER?

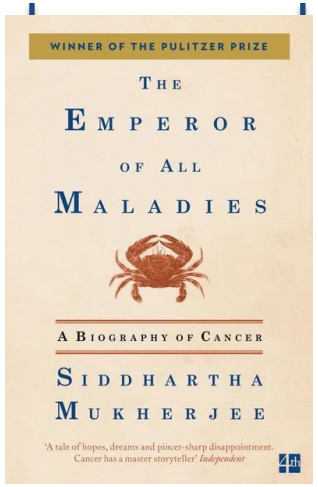
<1900 | 1950 | 1980 | 2010 | 2016

SURGERY

Physical Removal of the tumor

RADIOTHERAPIE

High-energy particles or waves, such as x-rays, gamma rays, electron beams, or protons, to destroy or damage cancer cells.
Developed at the beginning 1900s for the treatment of different diseases



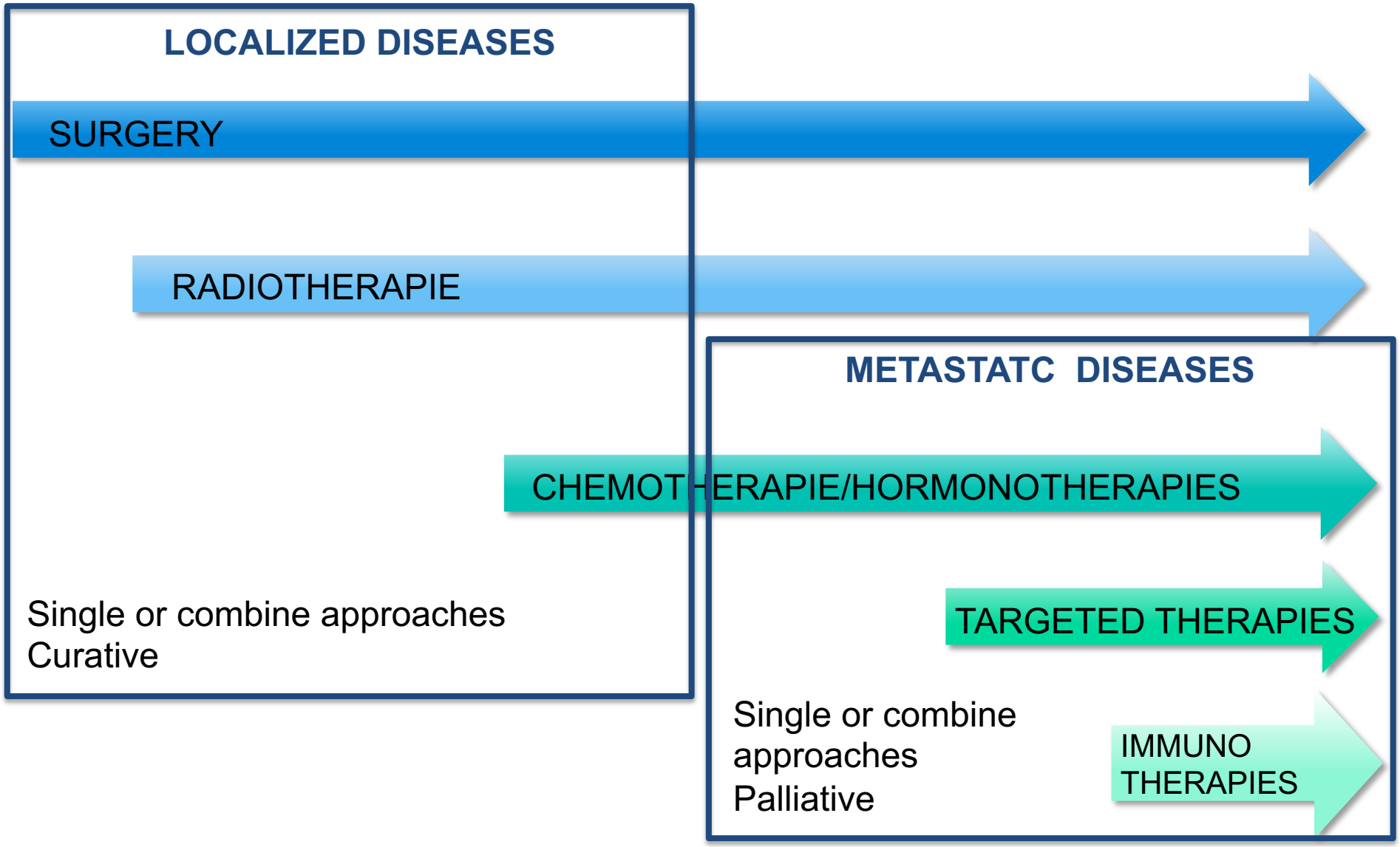
CHEMOTHERAPIE/HORMONOTHERAPIES

Use chemical substances to treat cancer
Developed in the 1970s

TARGETED THERAPIES

IMMUNO THERAPIES

HOW DO WE TREAT CANCER?



TUMOR GROWTH

1 clone → 10^9 cells → 10^{12} cells

Regulated by the length of the cellular cycle, which controls the number of cells and the size of the tumor

Compare to normal cells:

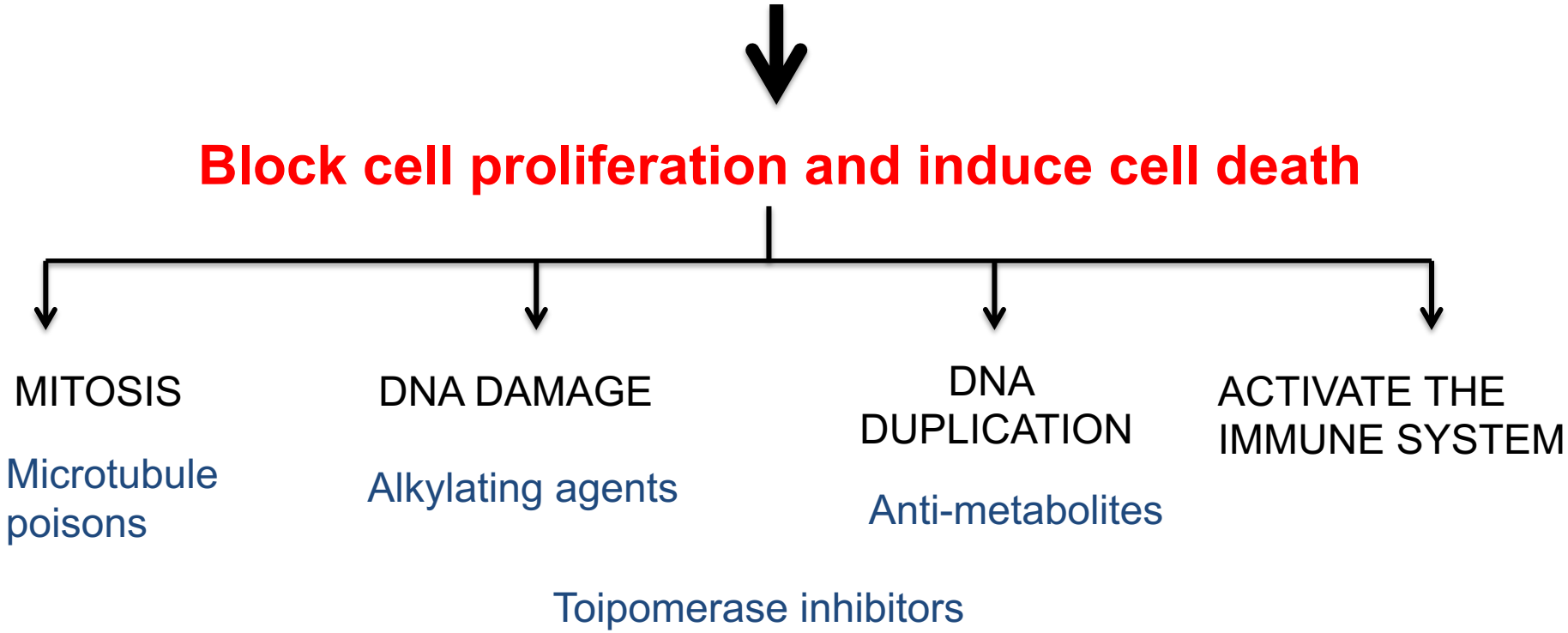
- Duration is similar
- The growth fraction (proportion of cells in the cycle) is larger
  - Very variable in different tumors
  - Dictate the doubling time of the tumor which influences the type and timing of treatment

SENSITIVITY OF VARIOUS TISSUE TO CHEMO

High	Intermediate	Low
Lymphoma	Breast	Head and neck
Leukemia	Colon	Prostate
Small Cell Lung cancer	Non-small cell lung cancer	Gastric
Testicular cancer		Pancreatic

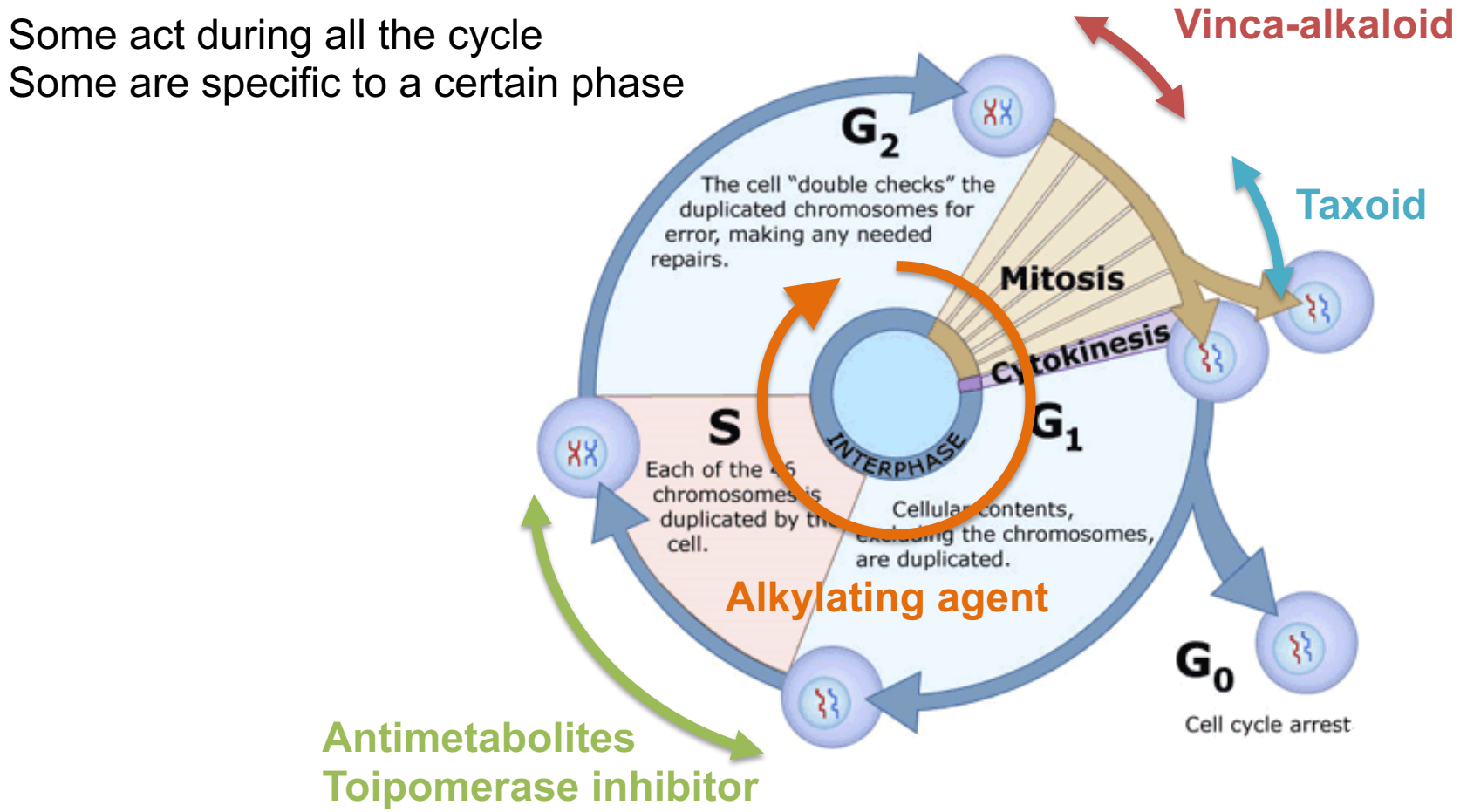
CHEMOTHERAPIES

Cytotoxic agents



TUMOR GROWTH

Some act during all the cycle
Some are specific to a certain phase



CHEMOTHERAPIES

About 20 molecules classified in 5 mechanisms of actions
Represent 95% of anti-cancer prescription

Alkylating Agents	Anti-Metabolites	Mitotic Inhibitors	Antibiotics	Others UFOs
Busulfan	Cytarabine	Etoposide*	Bleomycin	L-asparaginase
Carmustine	Fluorouracil	Teniposide*	Dactinomycin	Hydroxyurea
Chlorambucil	Methotrexate	Vinblastine	Daunorubicin	Procarbazine
Cisplatin	Pemetrexed	Vincristine	Doxorubicin	
Cyclophosphamide	Fludarabine	Mitomycin-c	Mitoxantrone	
Mercaptopurine		Taxanes	Plicamycin	
Ifosfamide				
Melphalan				

For info only

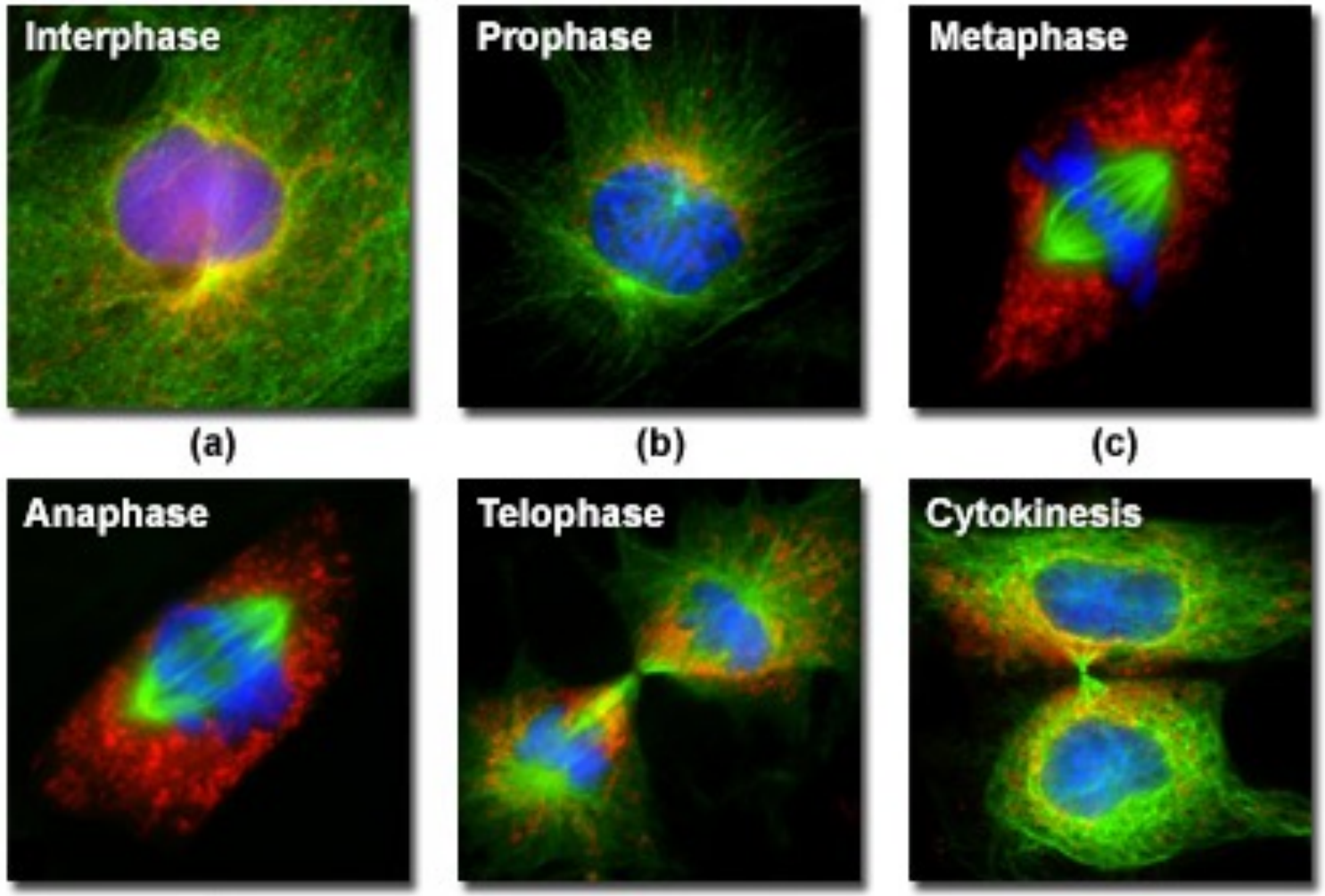
BLOCK CELL DIVISION:MITOSIS

MICROTUBULES POISONS:

VINCRISTINE/VINBLASTINE

PACLITAXEL/TAXOLO

MICROTUBULES



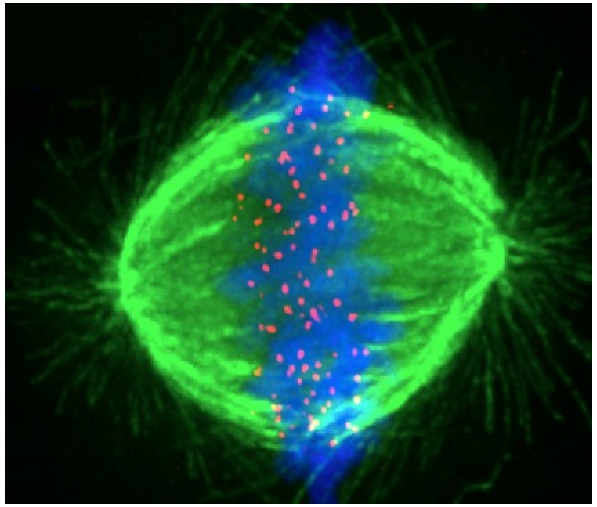
VINCRISTINE/VINBLASTIN

VINCA ALKALOIDS:

Inhibit the microtubules assembly/polymerization

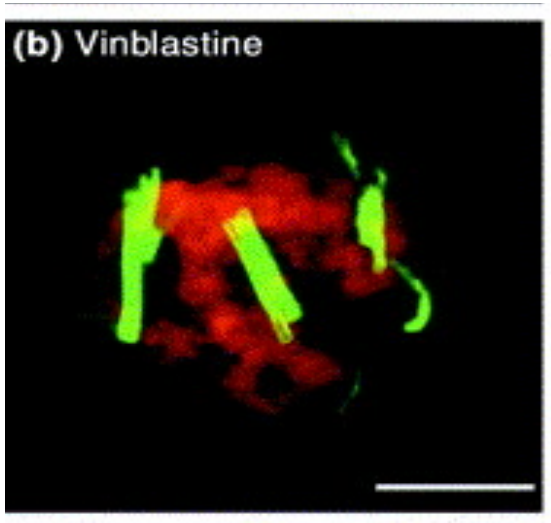
Arrest mitosis in metaphase

NORMAL MITOSIS



DNA blue/Centromeres red
Microtubules green

CELLS TREATED WITH VINBLASTINE



DNA Red
Microtubules Green

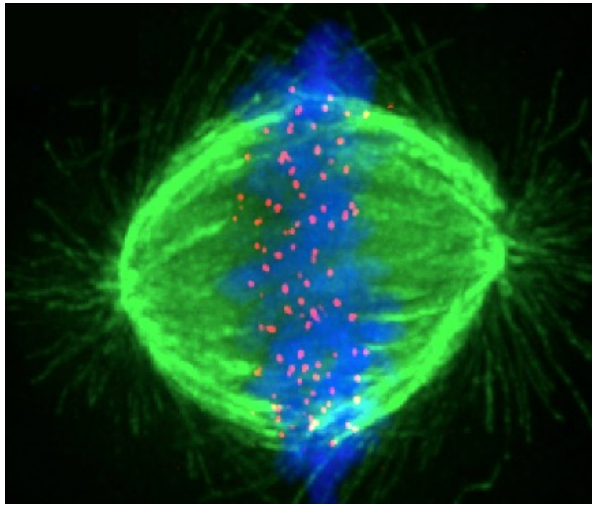
PACLITAXEL or TAXOLO

TAXANE:

Stabilize microtubules and protect from disassembling

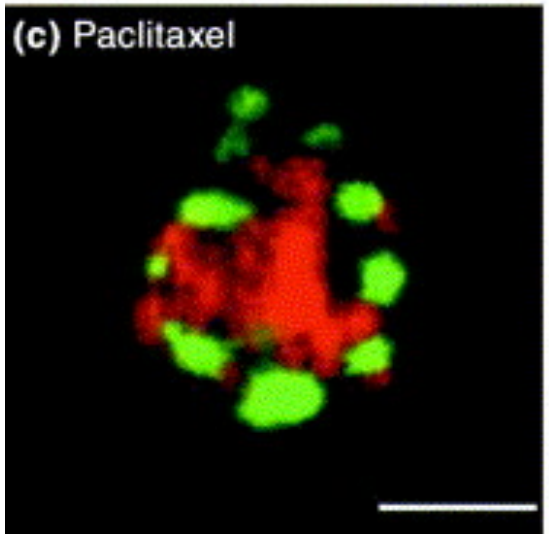
Block mitosis progression and trigger apoptosis

NORMAL MITOSIS

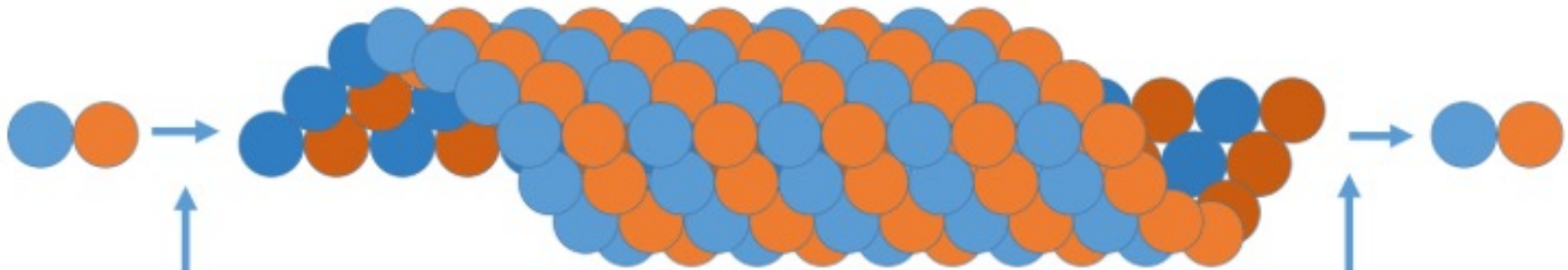


DNA blue/Centromeres red
Microtubules green

CELLS TREATED WITH TAXOLO



DNA Red
Microtubules Green



Alpha tubulin

Beta tubulin

Vinca alkaloids prevent microtubule assembly.

Taxanes prevent microtubule disassembly.

INDUCING DNA DAMAGE

TOPOISOMERASE

REGULATE DNA SUPERCOIL / UNWINDING DNA

TOPOISOMERASE 1: Single strand breaks and repair

TOPOISOMERASE 2: Double strand breaks and repair

https://www.youtube.com/watch?v=EYGrElVyHnU#

INDUCING DNA DAMAGE

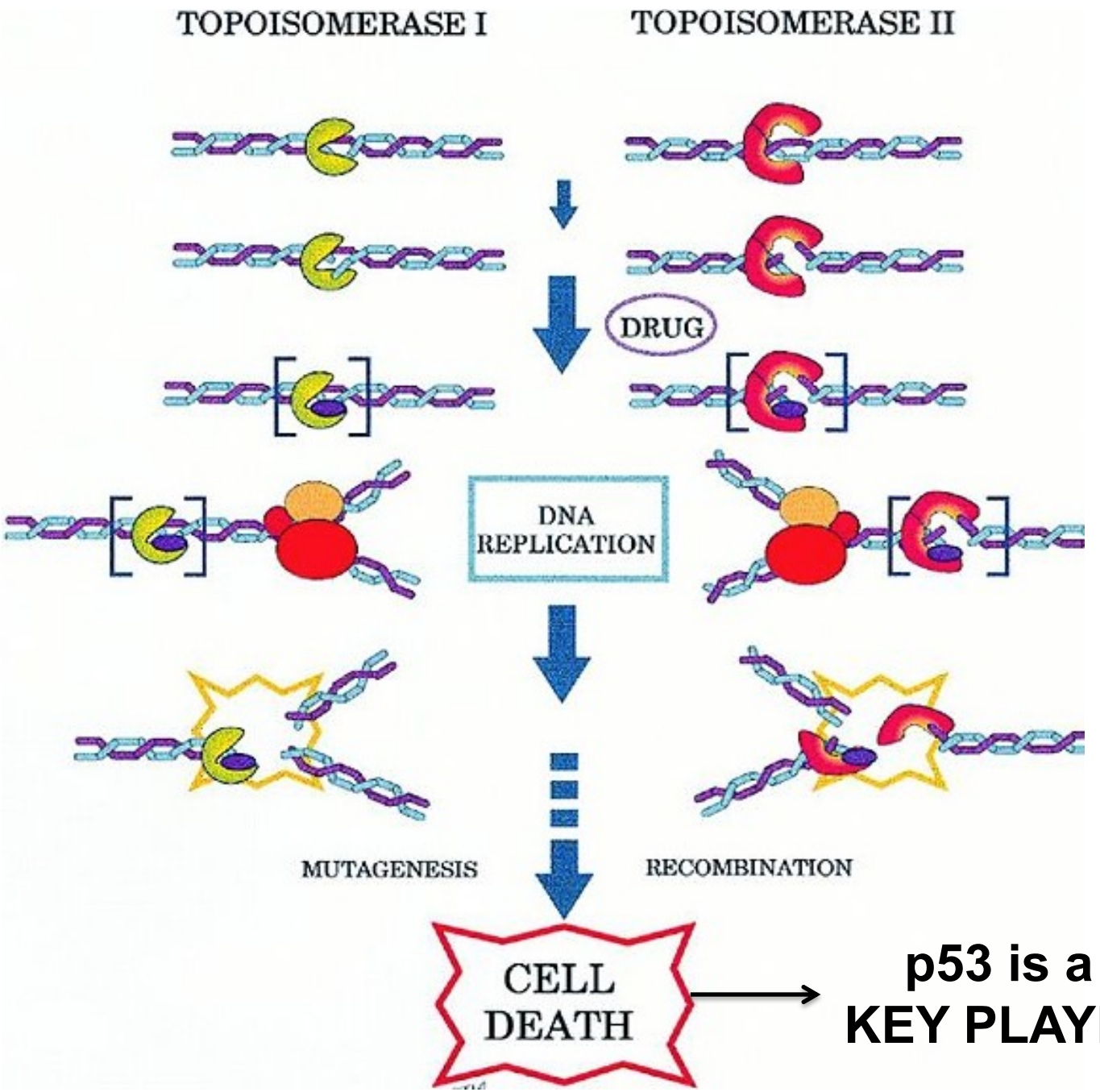
TOPOISOMERASE INHIBITORS

Topoisomerase I: e.g. Camptothecin

Topoisomerase II: e.g. Etoposide
Doxorubicin

How they work:

Intercalating DNA agents that prevent DNA re-ligation and therefore cause DNA damage and activation of apoptotic program



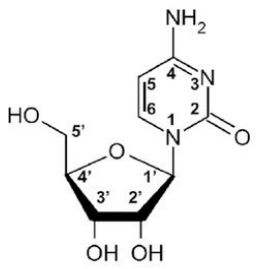
p53 is a KEY PLAYER

INHIBITION OF DNA SYNTHESIS

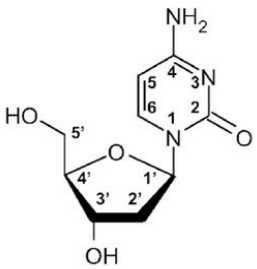
***ANTI-METABOLITES*: similar structure of purine and pyrimidine**

2 categories: Purine analogs (adenine and guanine analogs)
Pyrimidine analogs (cytosine and thymine and uracil analogs)

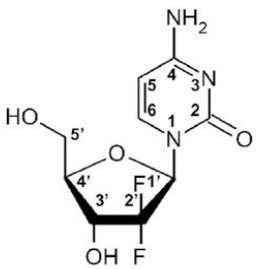
Activation by cellular enzymes
Block Synthesis
Incorporation in DNA, creating stereo-hindrance and inhibition of DNA synthesis



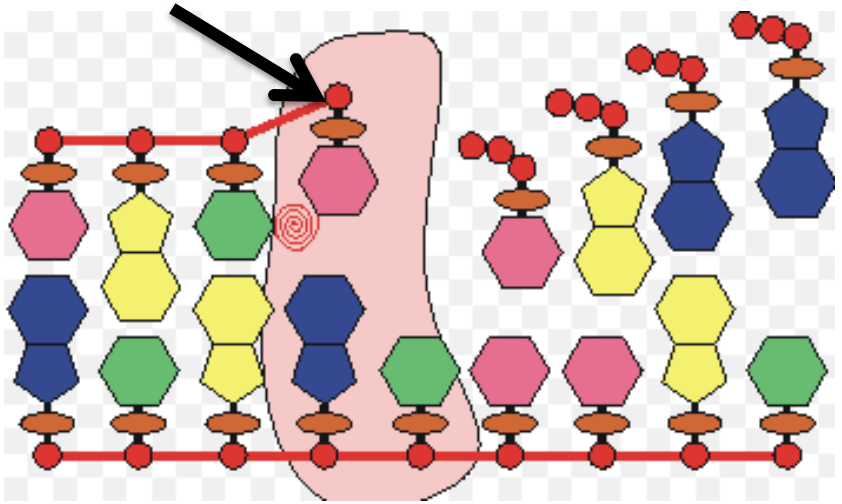
Cytidine



Deoxycytidine



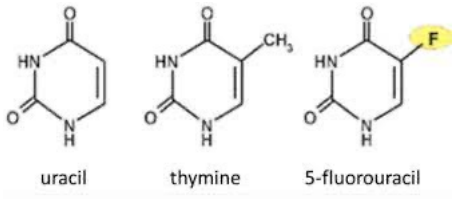
Gemcitabine



INHIBITION OF DNA SYNTHESIS

***ANTIMETABOLITES*: Inhibits production of Thymidine.**

5' FLUOROURACIL: *inhibits the enzymes (*thymidylate synthase (TYMS)) *required to generate thymidine for DNA synthesis*



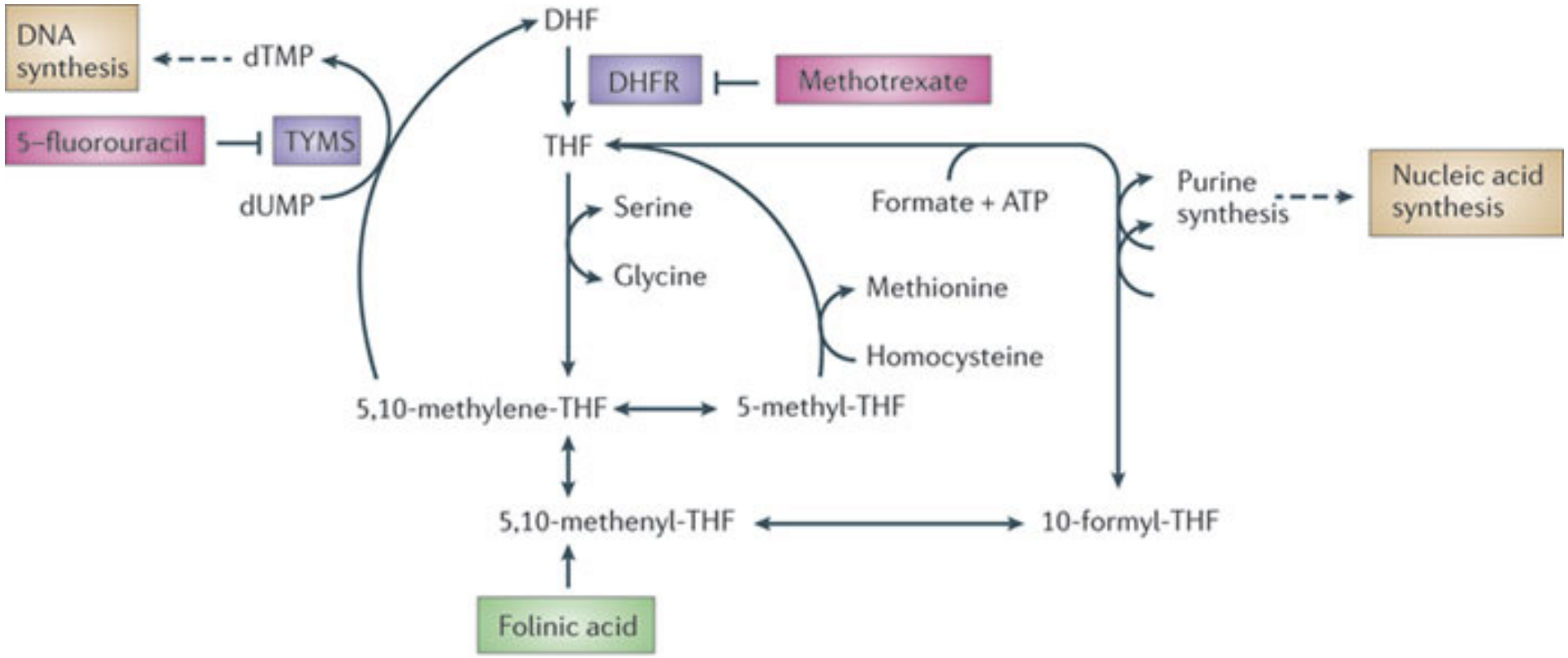
***ANTIMETABOLITES* : Anti-Folate (METHOTREXATE)**

Folic Acid is the B-vitamin is essential for several body function

Human body needs Folate to DNA synthesis and DNA repair.

Methotrexate inhibits dihydrofolate reductase (DHFR) interrupting folate metabolism. This compromises thymidine synthesis, but also interferes with purine synthesis

INHIBITION OF DNA SYNTHESIS



Nature Reviews | Drug Discovery

CHEMOTHERAPIES IN COMBINATION

Common combination chemotherapy regimens[1]

Cancer type	Drugs	Acronym
Breast cancer	Cyclophosphamide, methotrexate, 5-fluorouracil	CMF
	Doxorubicin, cyclophosphamide	AC
Hodgkin's disease	Mustine, vincristine, procarbazine, prednisolone	MOPP
	Doxorubicin, bleomycin, vinblastine, dacarbazine	ABVD
Non-Hodgkin's lymphoma	Cyclophosphamide, doxorubicin, vincristine, prednisolone	CHOP
Germ cell tumor	Bleomycin, etoposide, cisplatin	BEP
Stomach cancer	Epirubicin, cisplatin, 5-fluorouracil	ECF
	Epirubicin, cisplatin, capecitabine	ECX
Bladder cancer	Methotrexate, vincristine, doxorubicin, cisplatin	MVAC
Lung cancer	Cyclophosphamide, doxorubicin, vincristine,	CAV
Colorectal cancer	5-fluorouracil, folinic acid, oxaliplatin	FOLFOX

LIMITATIONS

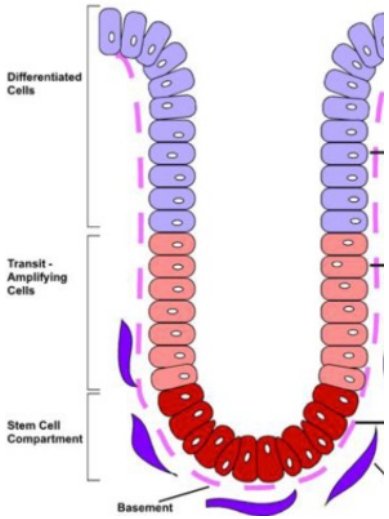
- ***Side Effects***
  Chemotherapies kill other proliferating cells in the body
  High and Effective doses are toxic

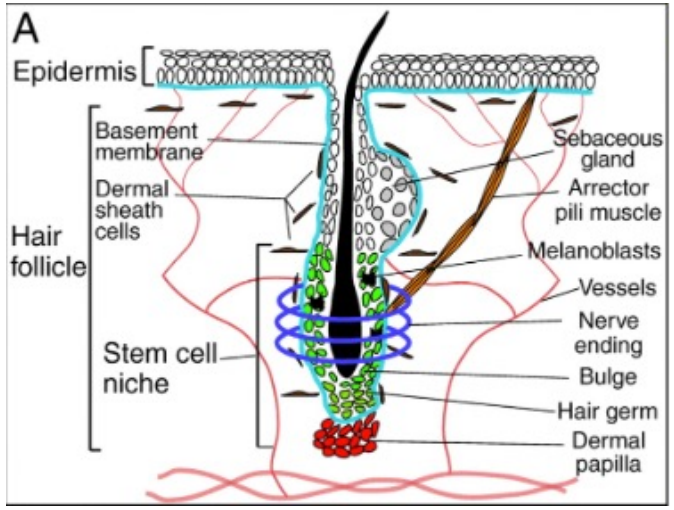
- ***RESPONSE AND RELAPSE***

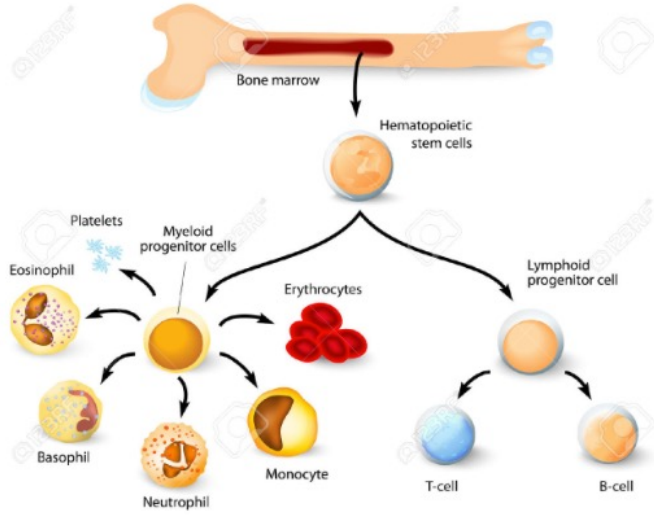
- ***RESISTANCE***

PROLIFERATING CELLS IN OUR BODY

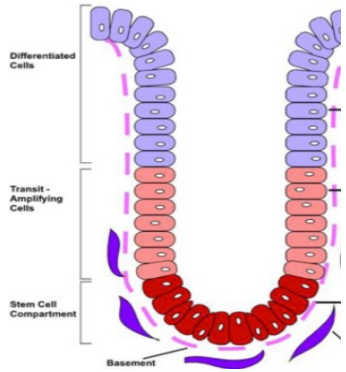
Chemotherapies are not cancer specific but they affect other proliferating cells



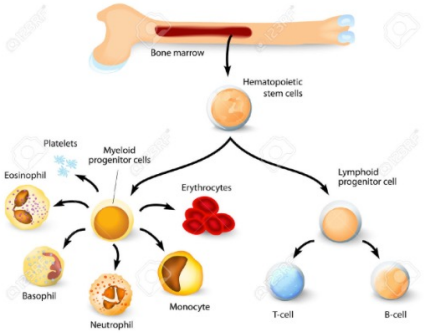




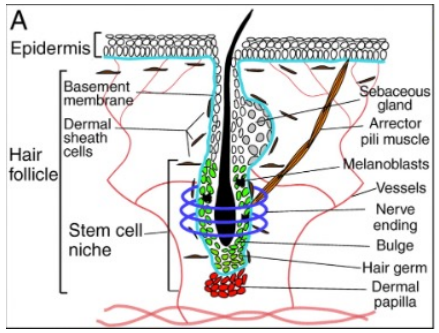
PROLIFERATING CELLS IN OUR BODY: SIDE EFFECT



TOXICITY/INTESTINAL PROBLEM



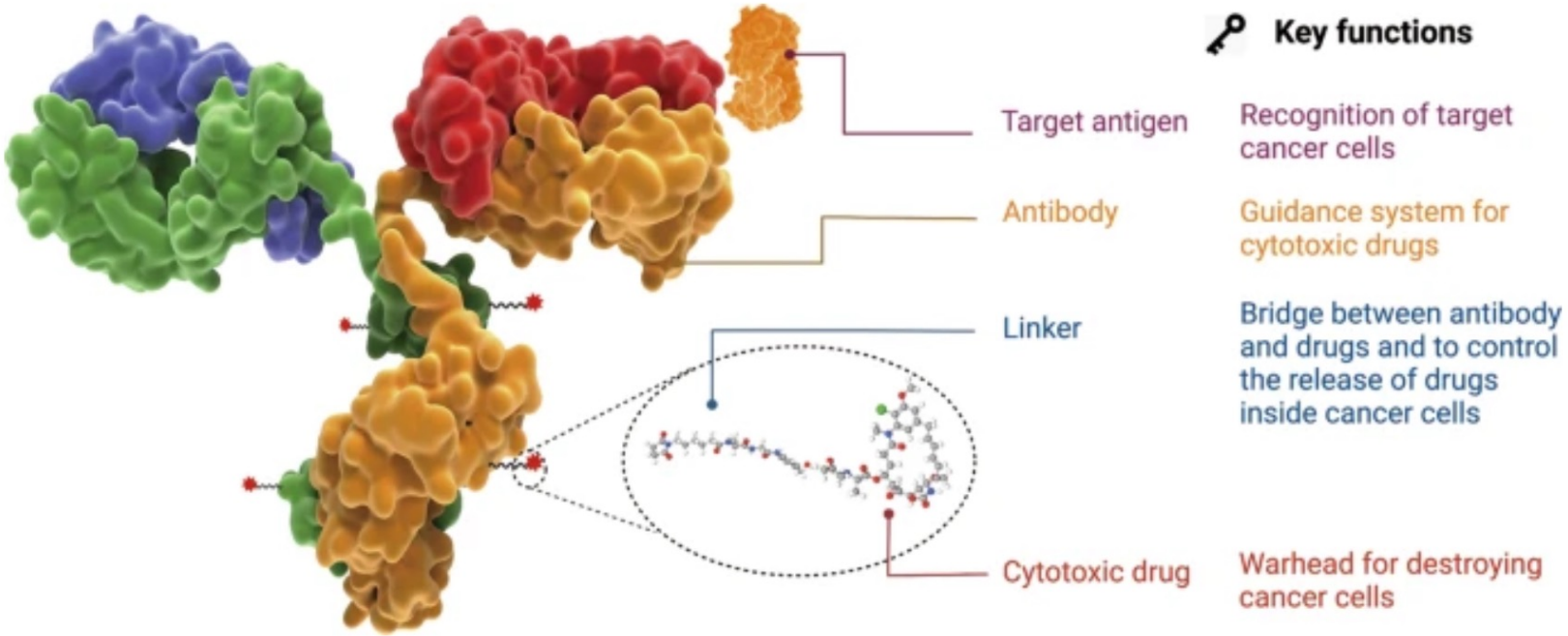
ANEMIA/RISK OF INFECTIONS



LOSS OF HAIR

NEW PROMISING THERAPIES: ANTIBODIES DRUG CONJUGATES (ADCs)

Fig. 2: The structure and characteristic of an ADC drug.



The core components including target antigen, antibody, linker, cytotoxic drug along with their key functions are demonstrated.

NEW PROMISING THERAPIES: ANTIBODIES DRUG CONJUGATES (ADCs) Mechanism of action

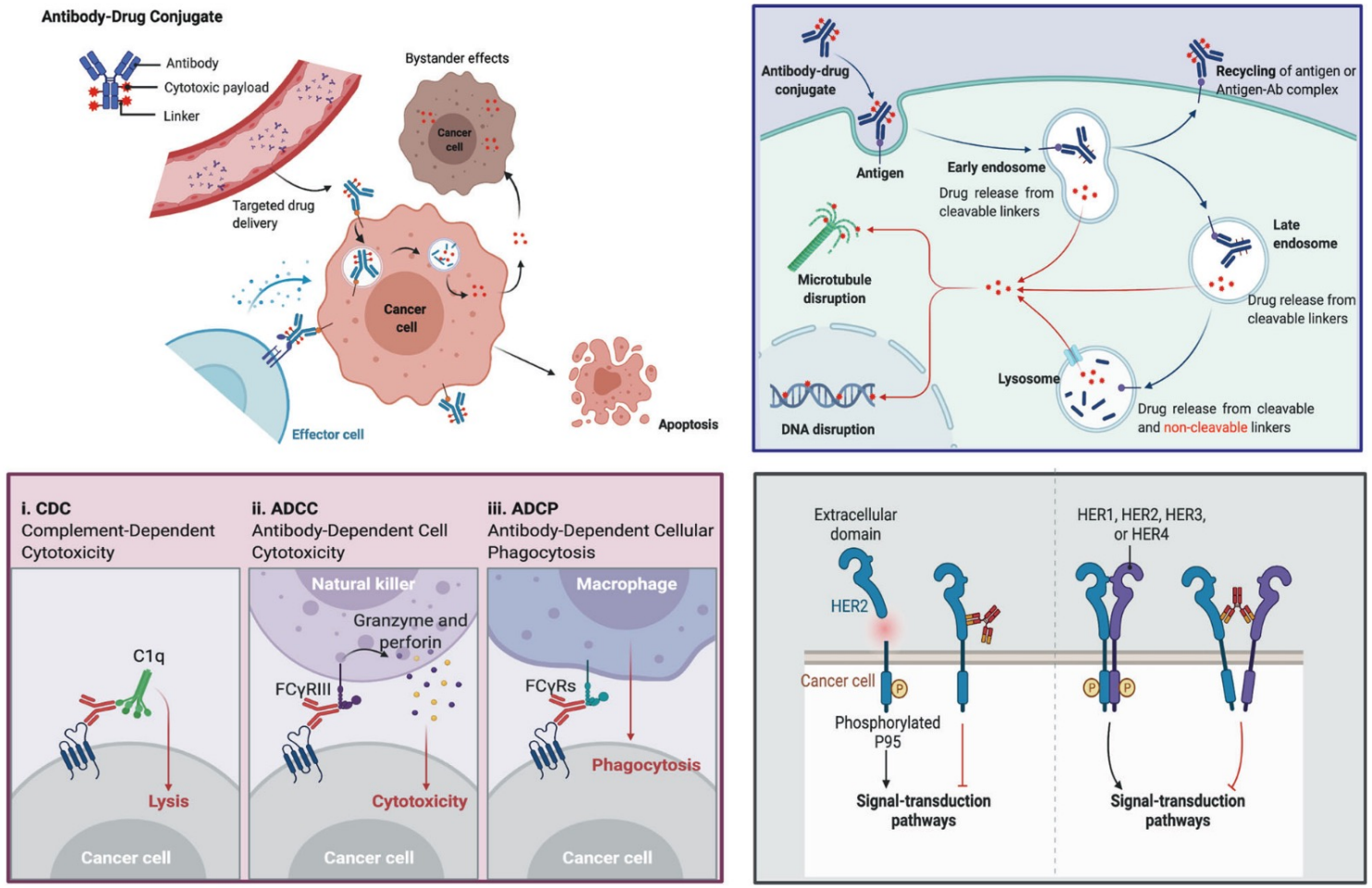


Fig. 4 **The overview of the mechanisms of ADC for killing cancer cells via different approaches. Upper-Right:** The main core mechanism of action of ADCs; **Lower-Left:** The antibody component of ADCs engages with immune effector cells to elicit antitumor immunity including CDC, ADCC, and ADCP effects; **Lower-Right:** The antibody component of ADCs retains its activity profile and can therefore interfere with target function, dampen downstream signaling to inhibit tumor growth. Created with BioRender.com

New promising therapies that will be developed over the next years

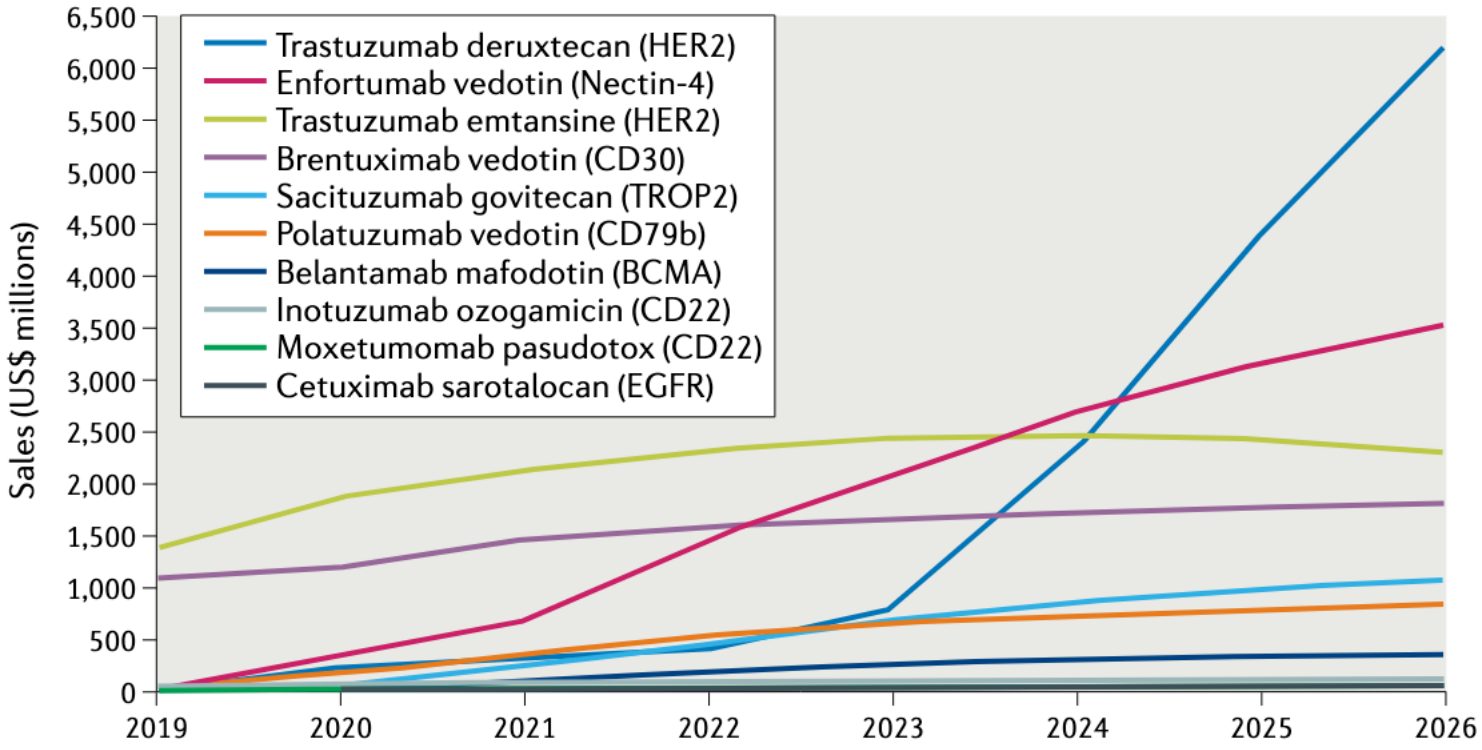
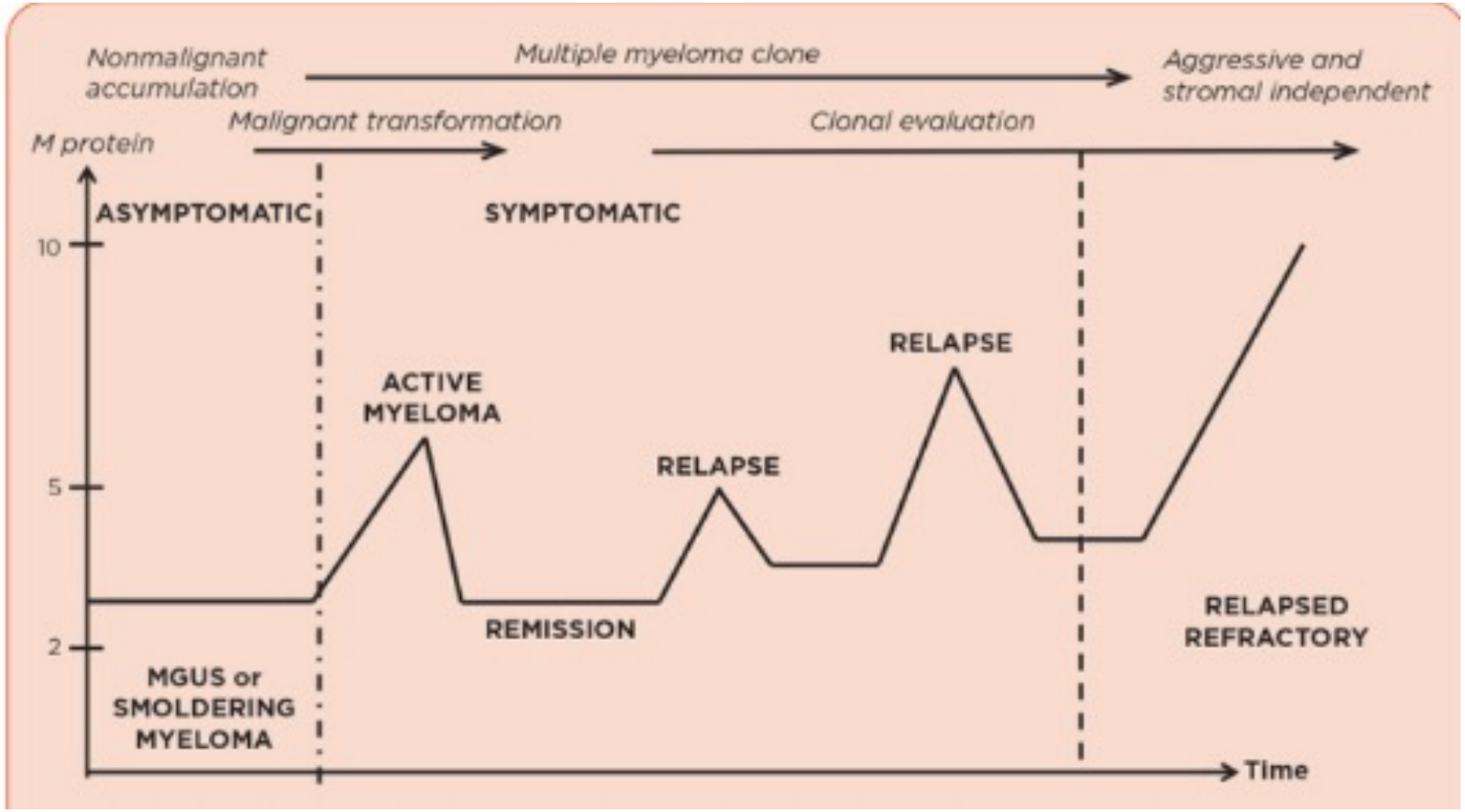


Fig. 1 | **Forecast global sales of select approved antibody–drug conjugates.** Sales from 2020 to 2026 are forecast as of 1 December 2020. Sales of cetuximab sarotalocan reflect the following markets only: USA, France, Germany, Italy, Spain, United Kingdom, Japan. EGFR, epidermal growth factor receptor.

RESPONSE AND RELAPSE

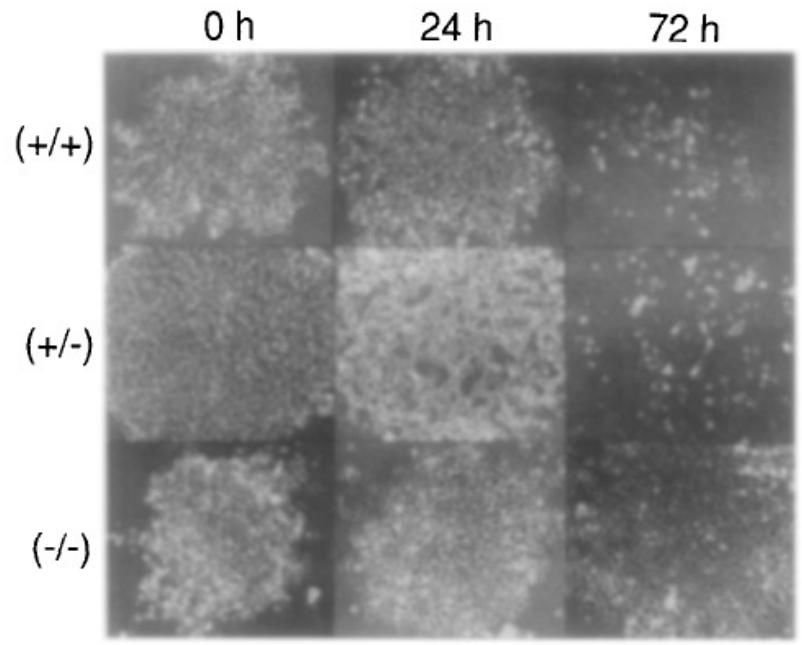


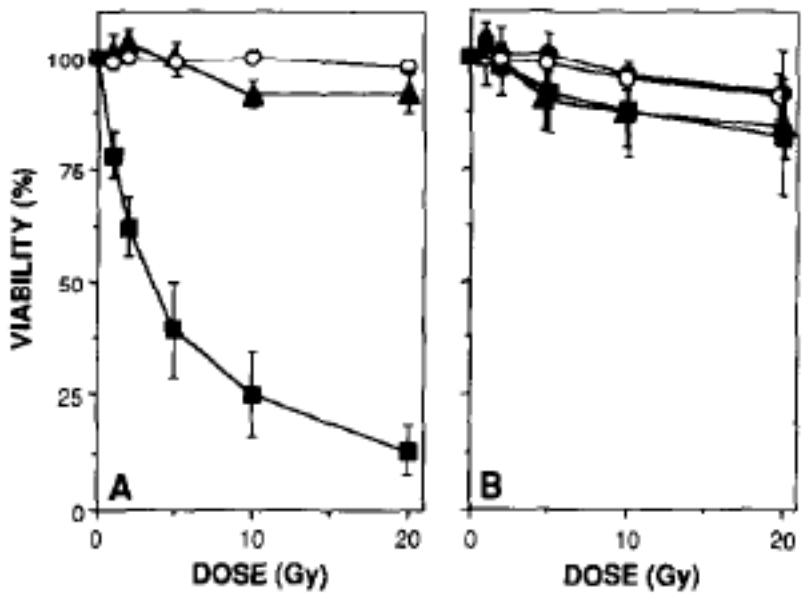
RESISTANCE

How does the tumor become resistant to therapies?

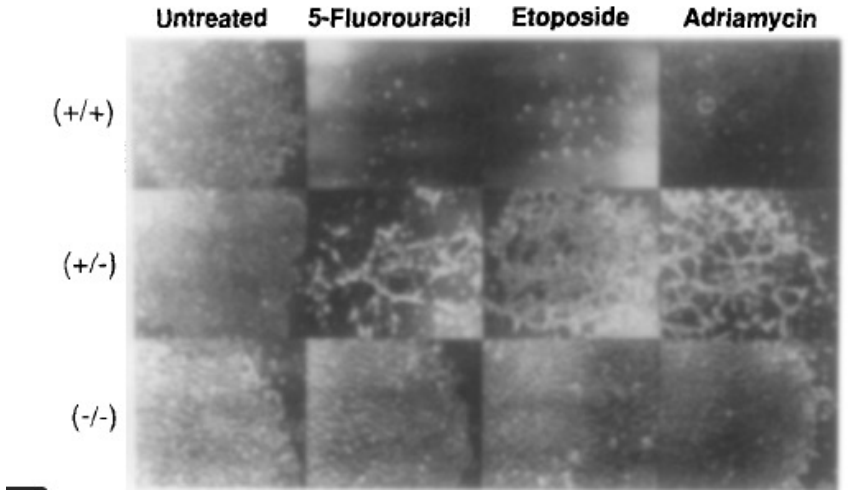
Lowe et al. 1993: p53 modulates apoptosis and cytotoxicity of Anticancer Agents *in vitro*

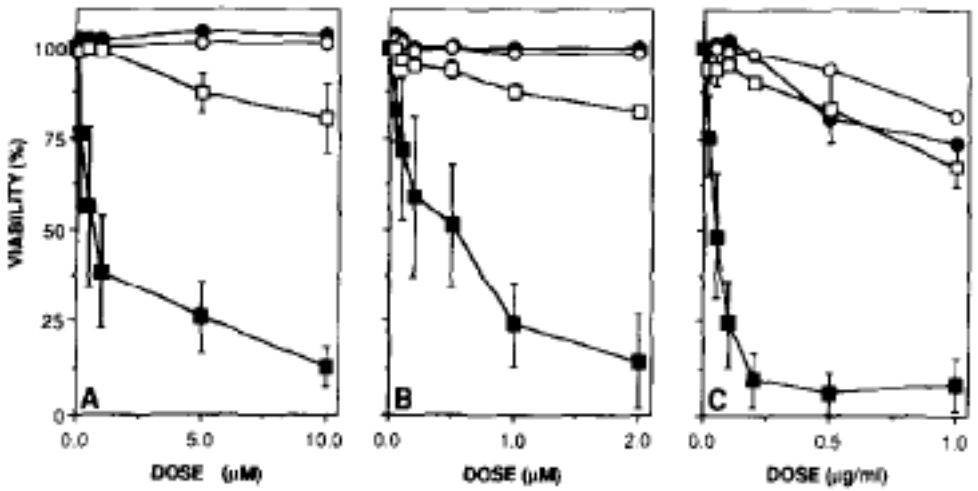
Irradiated cells Irradiated cells



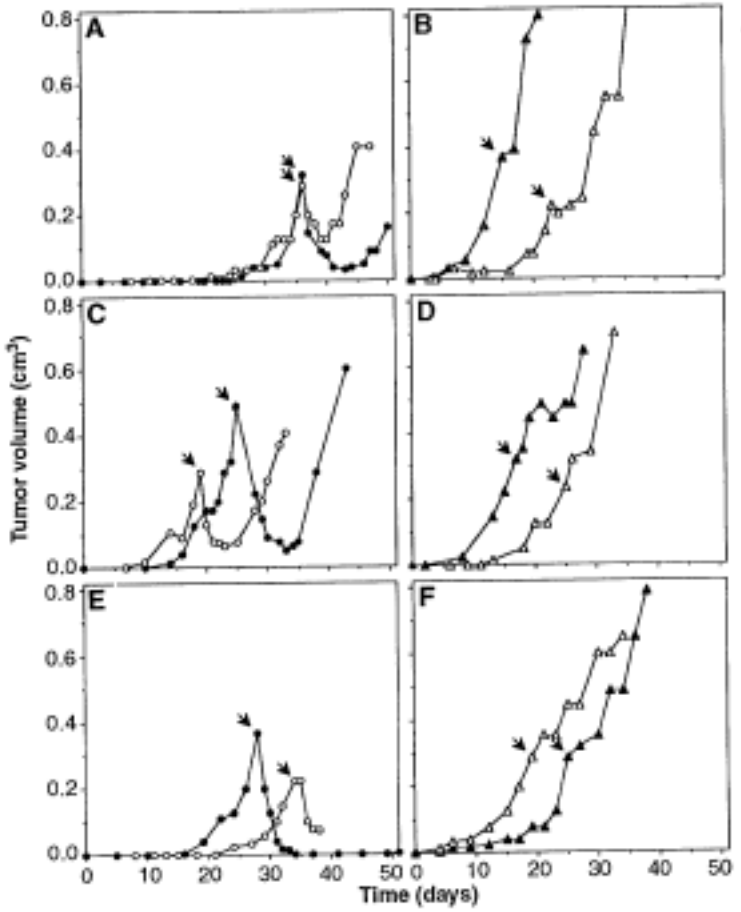


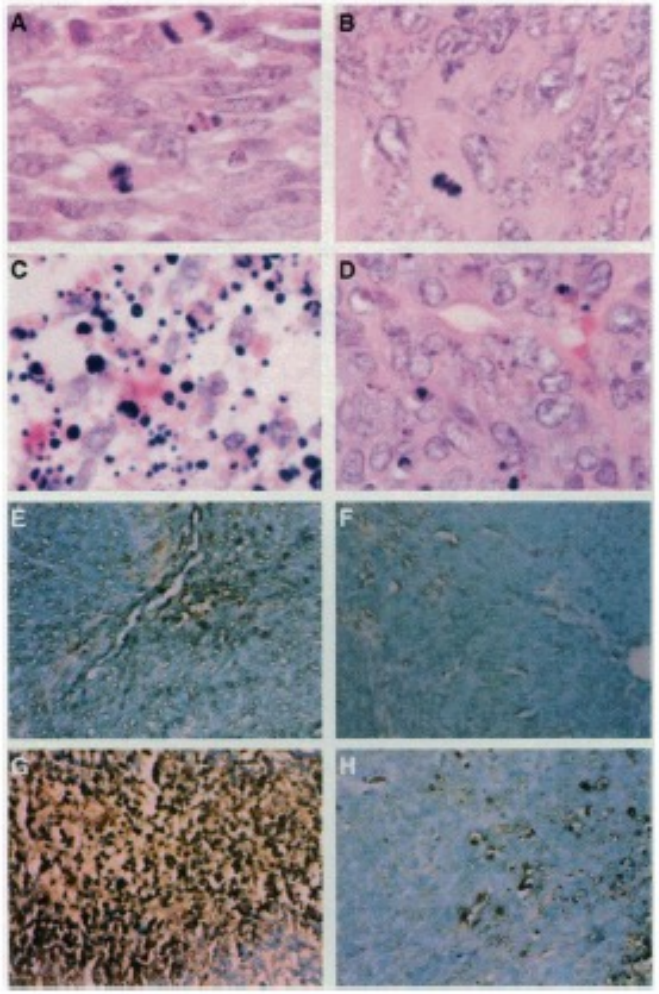
Lowe et al. 1993: p53 modulates apoptosis and cytotoxicity of Anticancer Agents *in vitro*





Lowe et al. 1994: p53 status and the efficacy of Cancer therapy *in vivo*

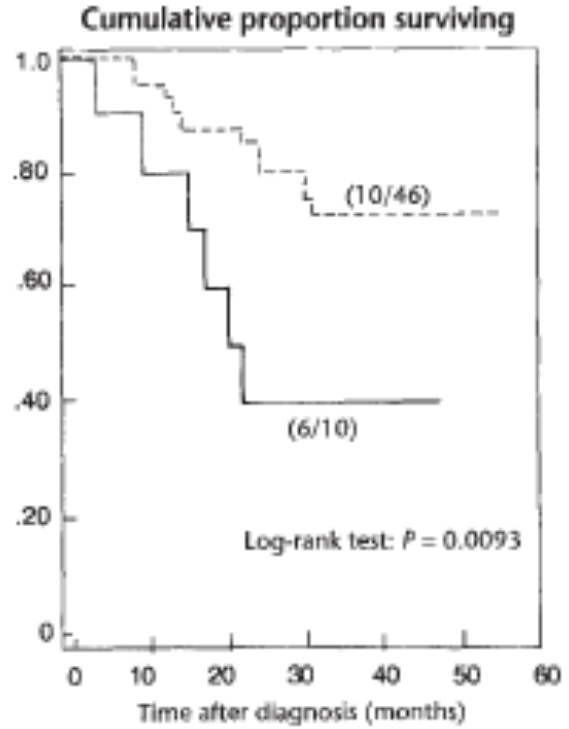




Aas et al. 1996: p53 mutations associated with resistance to doxorubicin in ***breast cancer patients***

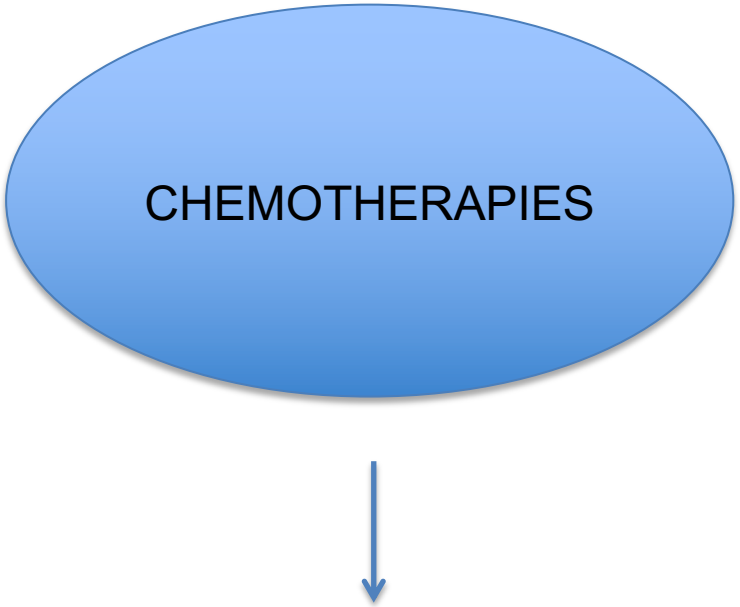
Table 3 p53 mutations

Patient no.	Mutations	Affecting L2/L3	Staining index[a]	Response[b]	Time to R or BCD[c] (months)			
	Nonsense/splice							
5	G→A 1 bp upstream exon 5	L2/L3	9	SD	R	5	BCD	12
11	Glu→stop codon 204	L3	1	PD	R–		BCD	11
20[d]	G→A 1 bp upstream exon 5	L2/L3	0	PR	R–		BCD	12
	Missense/deletions							
1	Pro→Ser codon 151	–	6	PR	R	11	BCD	21
7	Arg→His codon 273	–	6	PR	R	36	alive	48
15	Tyr→Cys codon 163	L2	9	PR	RF	43		
19	Arg→Gly codon 249	L3	1	PD	R–		BCD	16
22	Gly→Arg codon 266	–	9	MC	R	7	BCD	21
26	del. 14 bp codon 217–221	L3	0	PD	R–		alive	35
37	Cys→Phe codon 176	L2	9	MC	R	7	BCD	17
39	Met→Ile codon 237	L3	6	PR	RF	25		
51	del. 6 bp codon 232–234	–	6	MC	RF	17		
53	del. 11 bp codon 239–242	L3	1	PR	R	16	alive	17
55	Pro→Leu codon 190	L2	0	SD	R	5	BCD	12
57	Arg→Gln codon 248	L3	9	PD	R–		BCD	5
63	Glu→Lys codon 286	–	6	MC	RF	13		
64	Arg→His codon 273	–	4	SD	RF	12		
41[d]	Arg→His codon 273	–	9	PR	R–		BCD	4

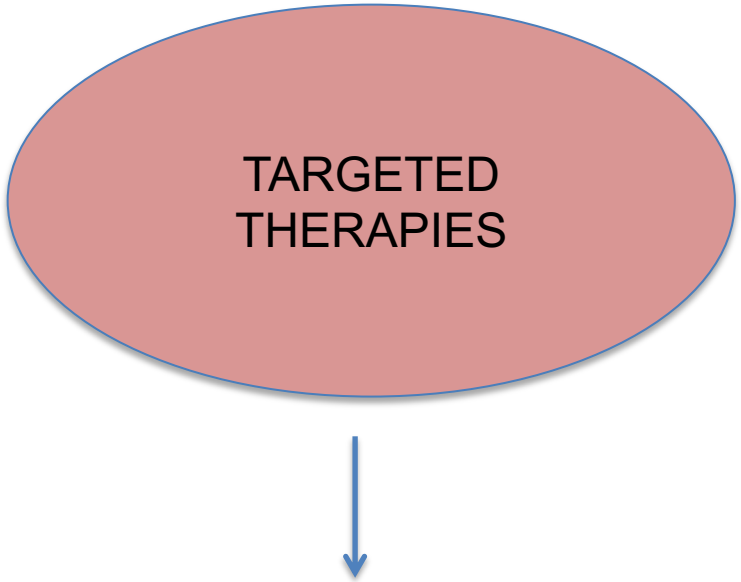


TARGETED THERAPIES

GENOMIC ANALYSIS TO DESIGN NOVEL THERAPIES



INDUCE DNA DAMAGE AND
ACTIVATE THE APOPTOTIC PROGRAM



BLOCK THE ACTIVITY OF AN
ONCOGENIC PROTEIN ALTERED
IN CANCER

THE DESIGN OF ANTI-CANCER DRUGS

Disease specific:

- **Leukemia**
- **Lymphoma**
- **Melanoma**

Pathway specific:

- **APOPTOSIS**
- **CELL CYCLE**
- **PI3K/mTOR**

SYNTHETIC LETHAL INTERACTION

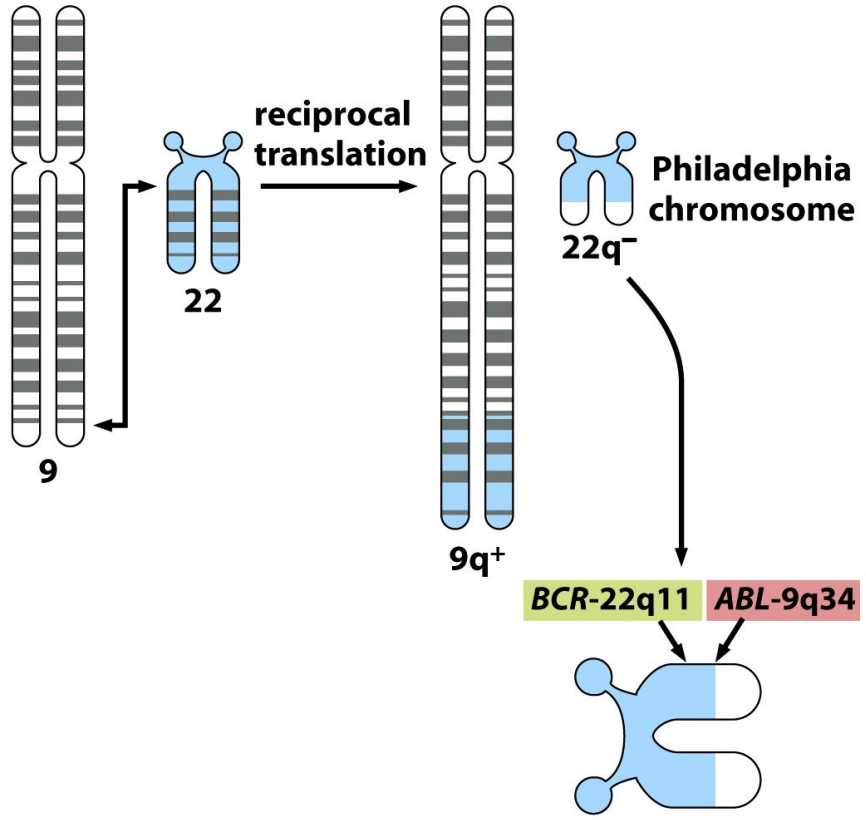
- **BRCA1/2 and PARP inhibitor (Breast and Ovarian cancer)**

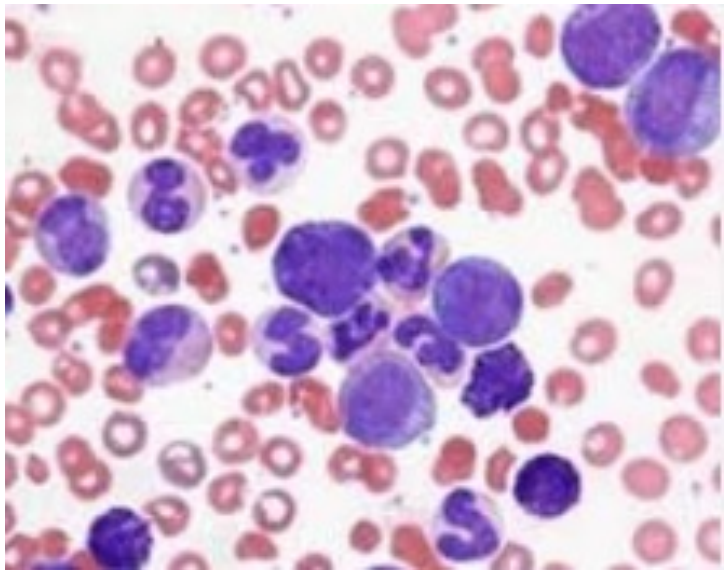
FIRST TARGETED THERAPY

BLOCK BCR-ABL in CML

Chromic Myeloid Leukemia (CML)

Genomic: 95% of the cases have t(9;22)(q34;q11)





BCR-ABL

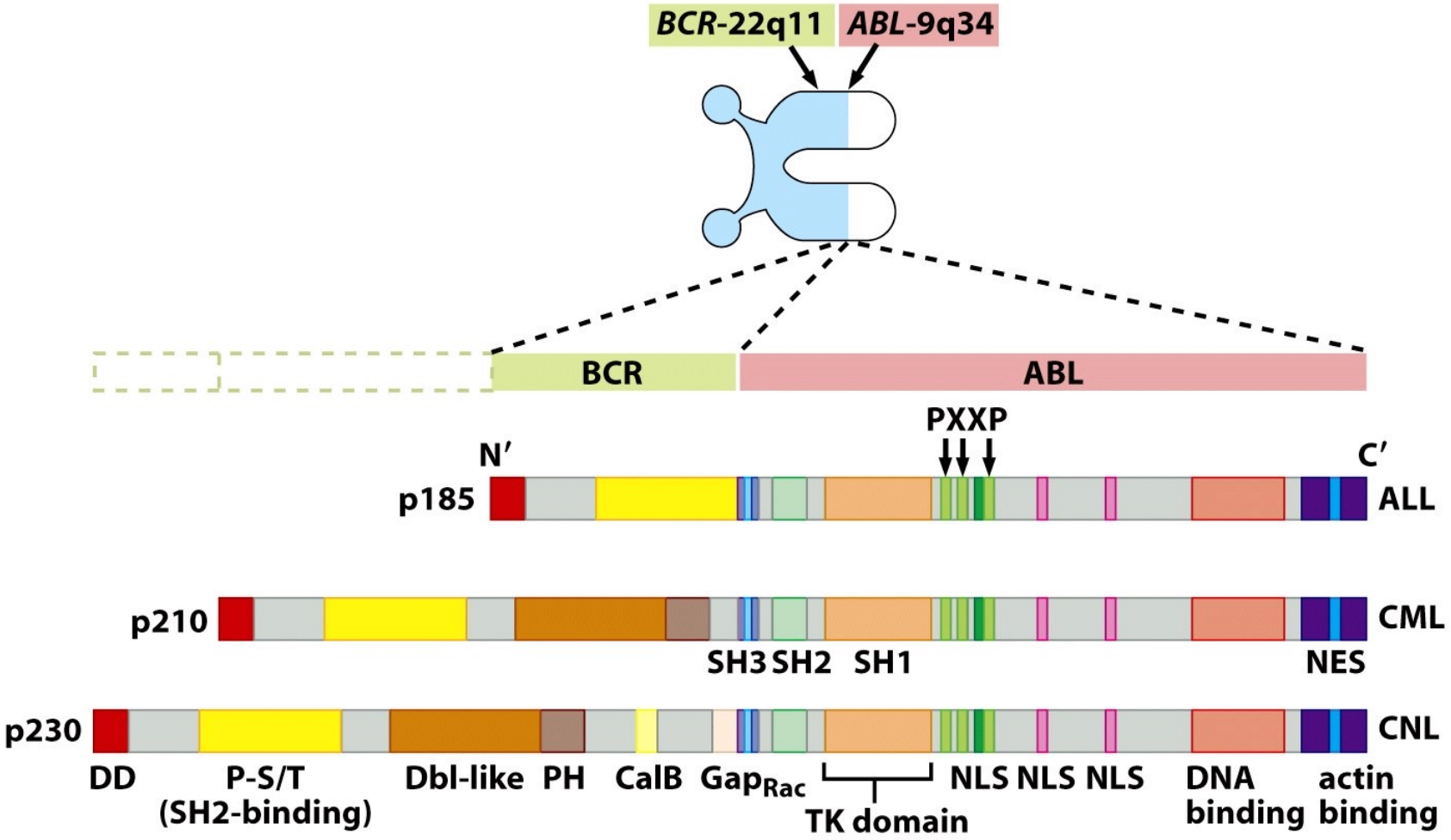
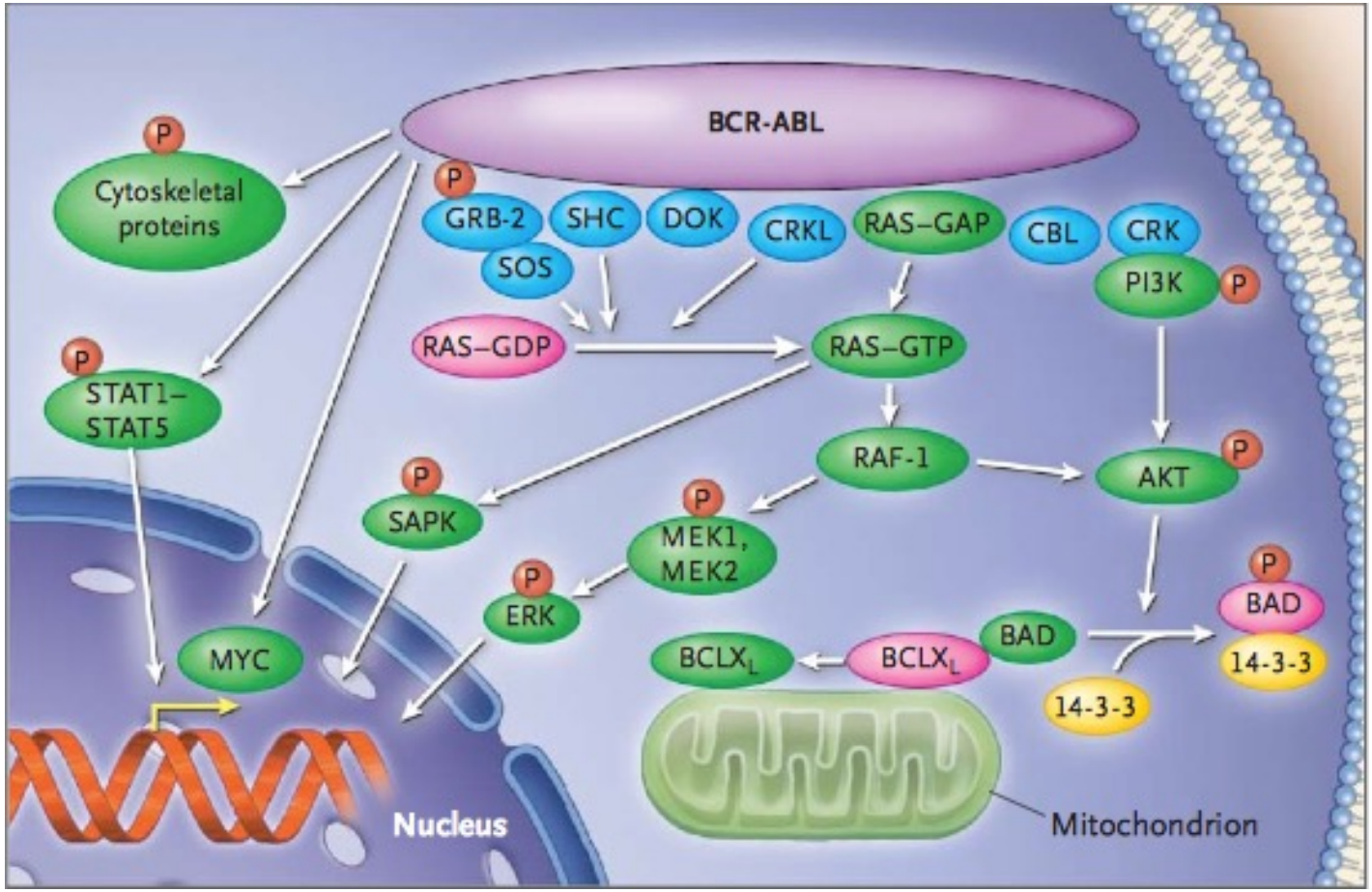


Figure 16.24b *The Biology of Cancer* (© Garland Science 2007)

BCR-ABL

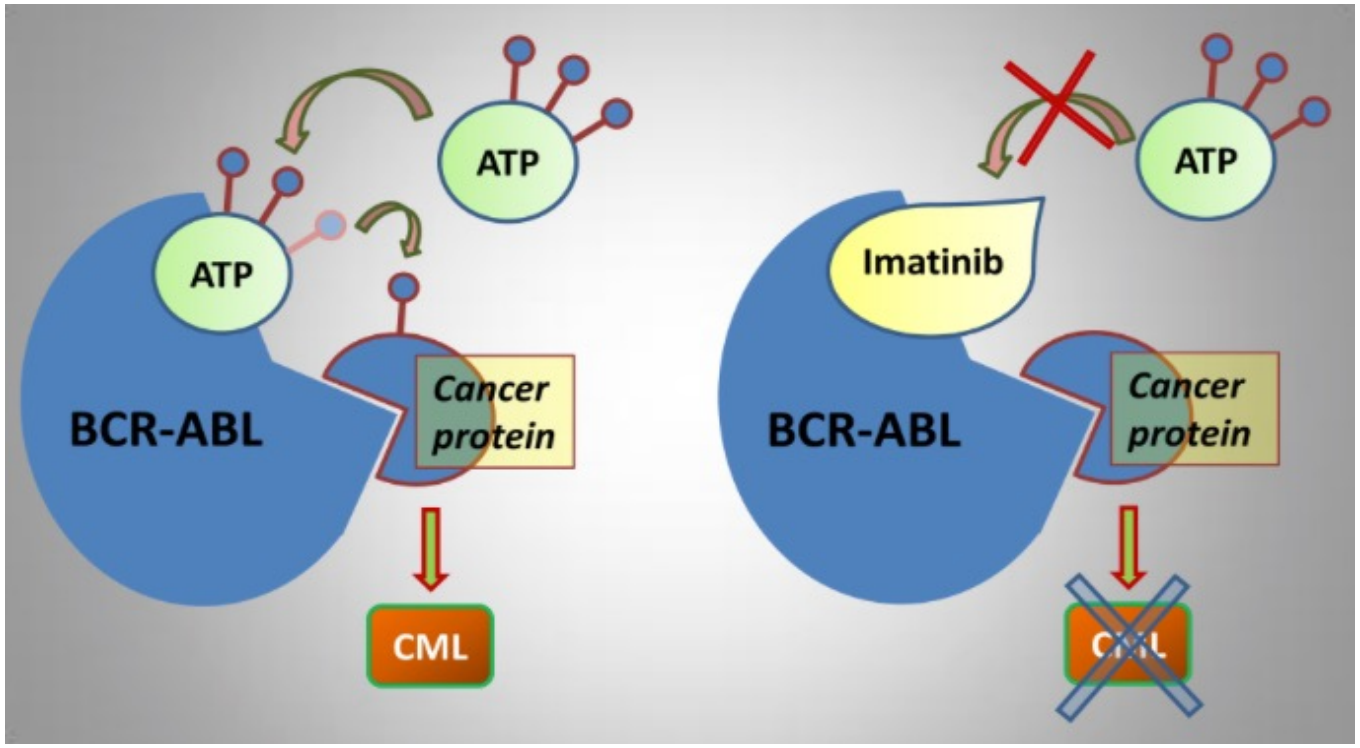


NEJM, 2003

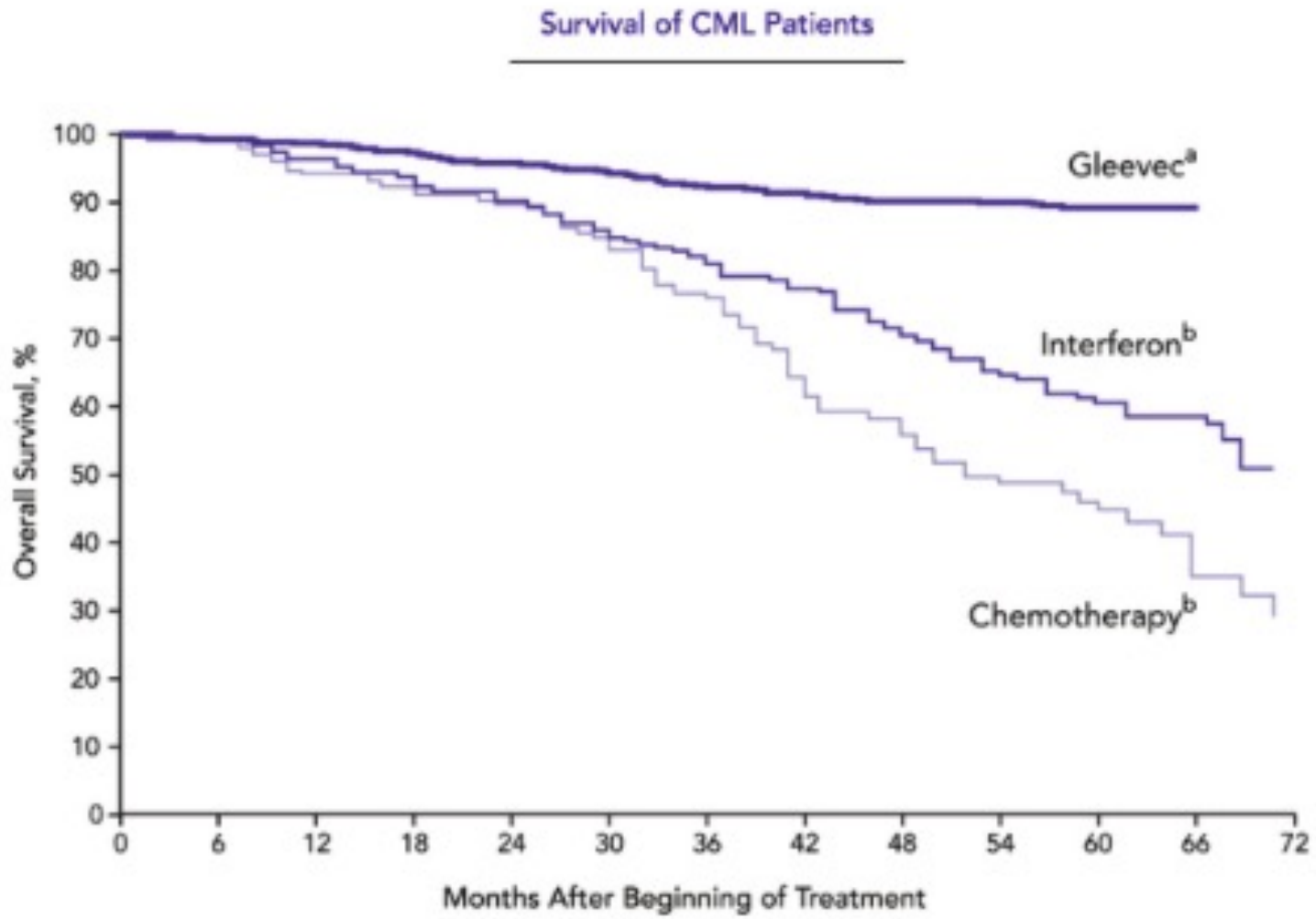
IMATINIB/GLEVEC: First successful example of target therapy

Charles Sawyers

Gleevec has been approved in the clinic in 2001

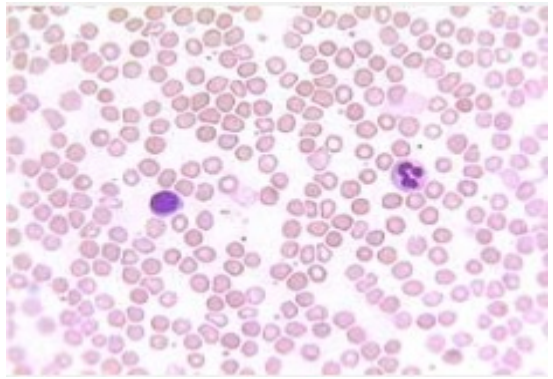


IMATINIB/GLEEVEC

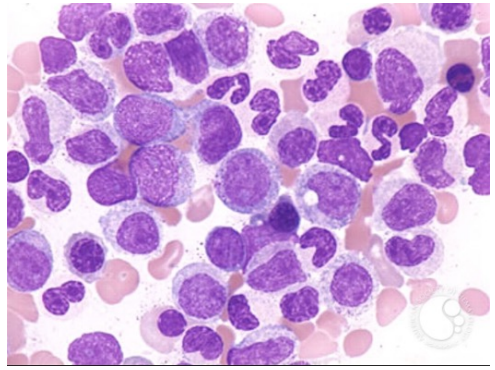


Initial response to therapy but then tumor relapse

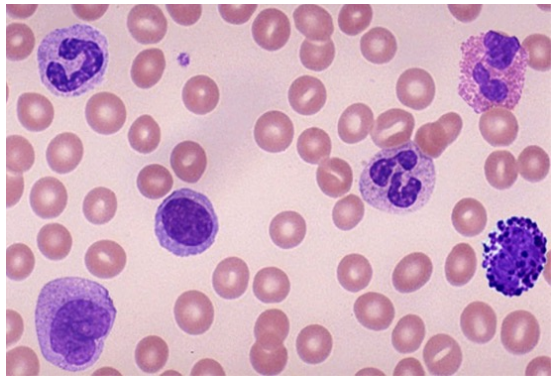
Normal blood



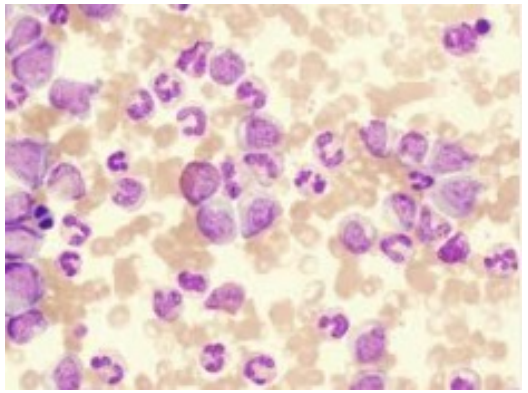
Tumor CML



Initial response to gleevec

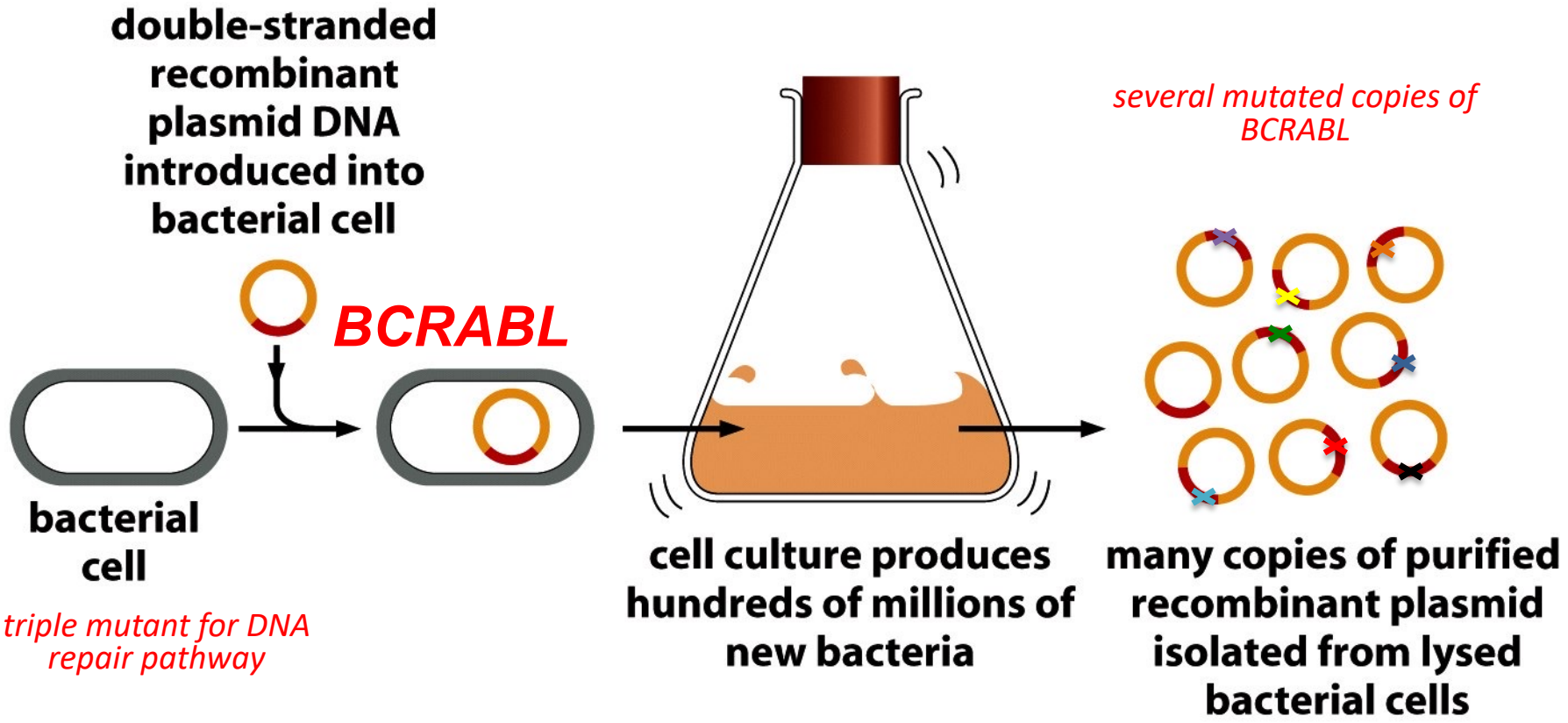


Tumor relapse



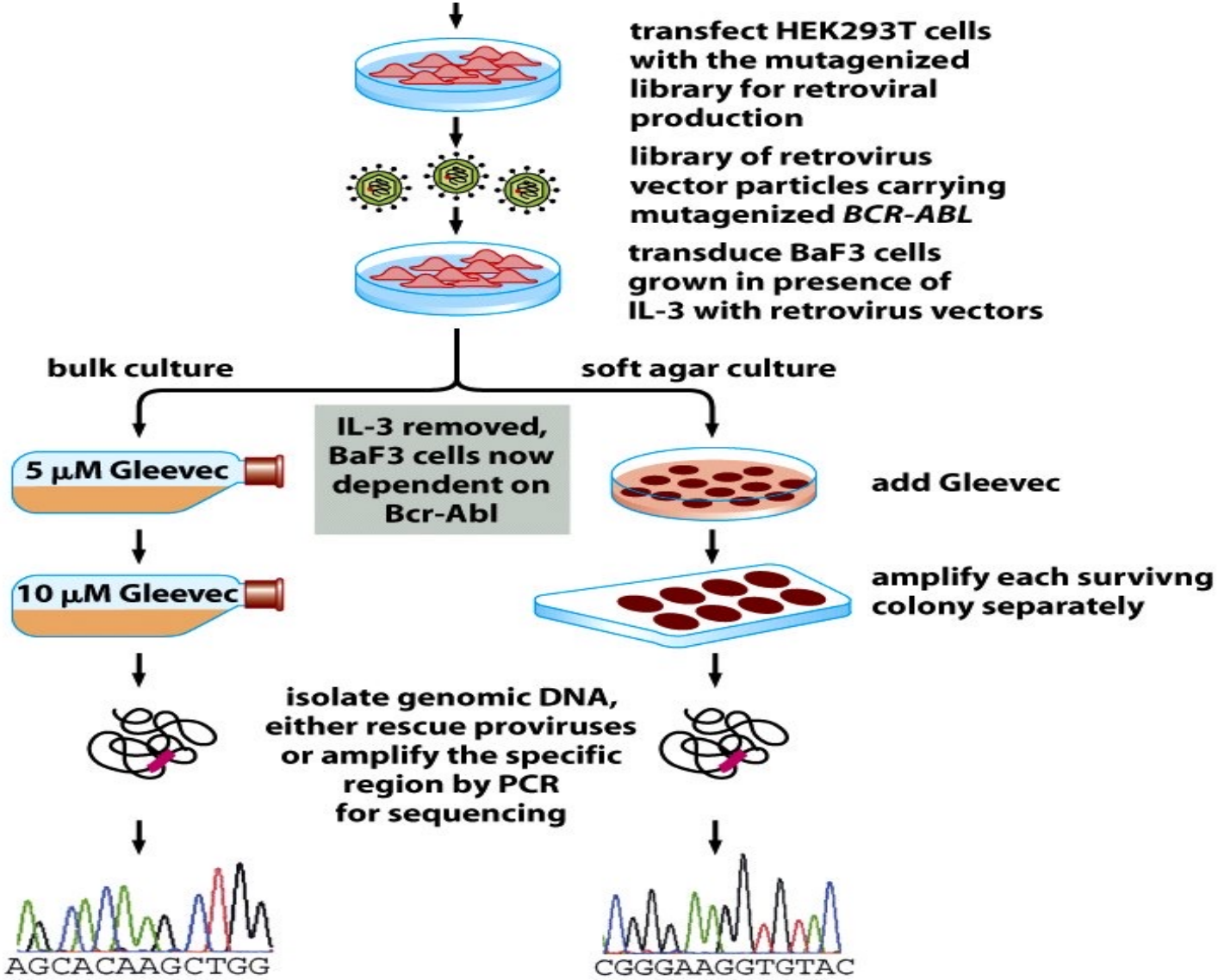
RANDOM MUTAGENESIS SCREEN

Introduce random mutations in the gene sequence using a strain of bacteria deficient in three of the primary DNA repair pathways

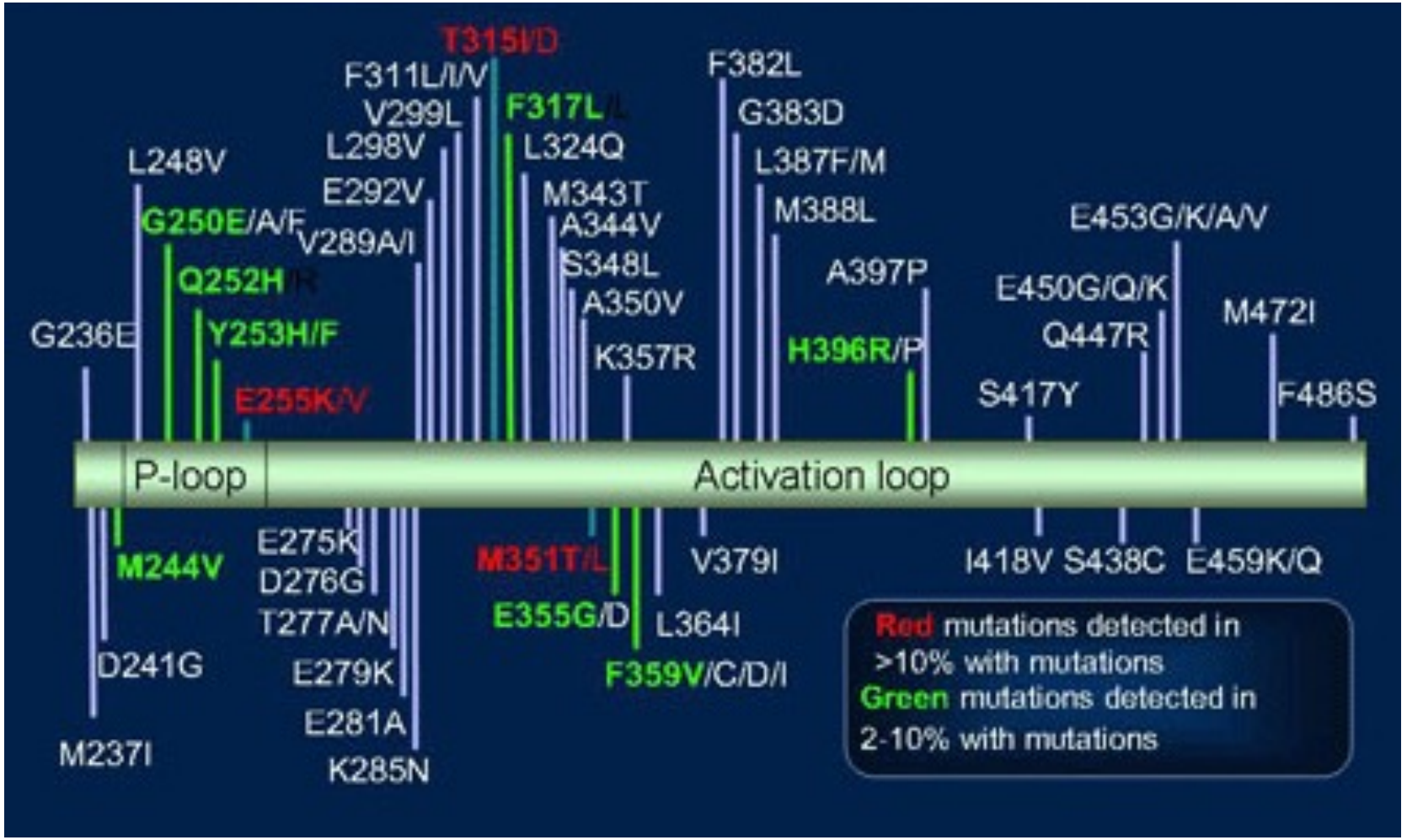


DISCOVER MECHANISM OF DRUG RESISTANCE IN THE LAB

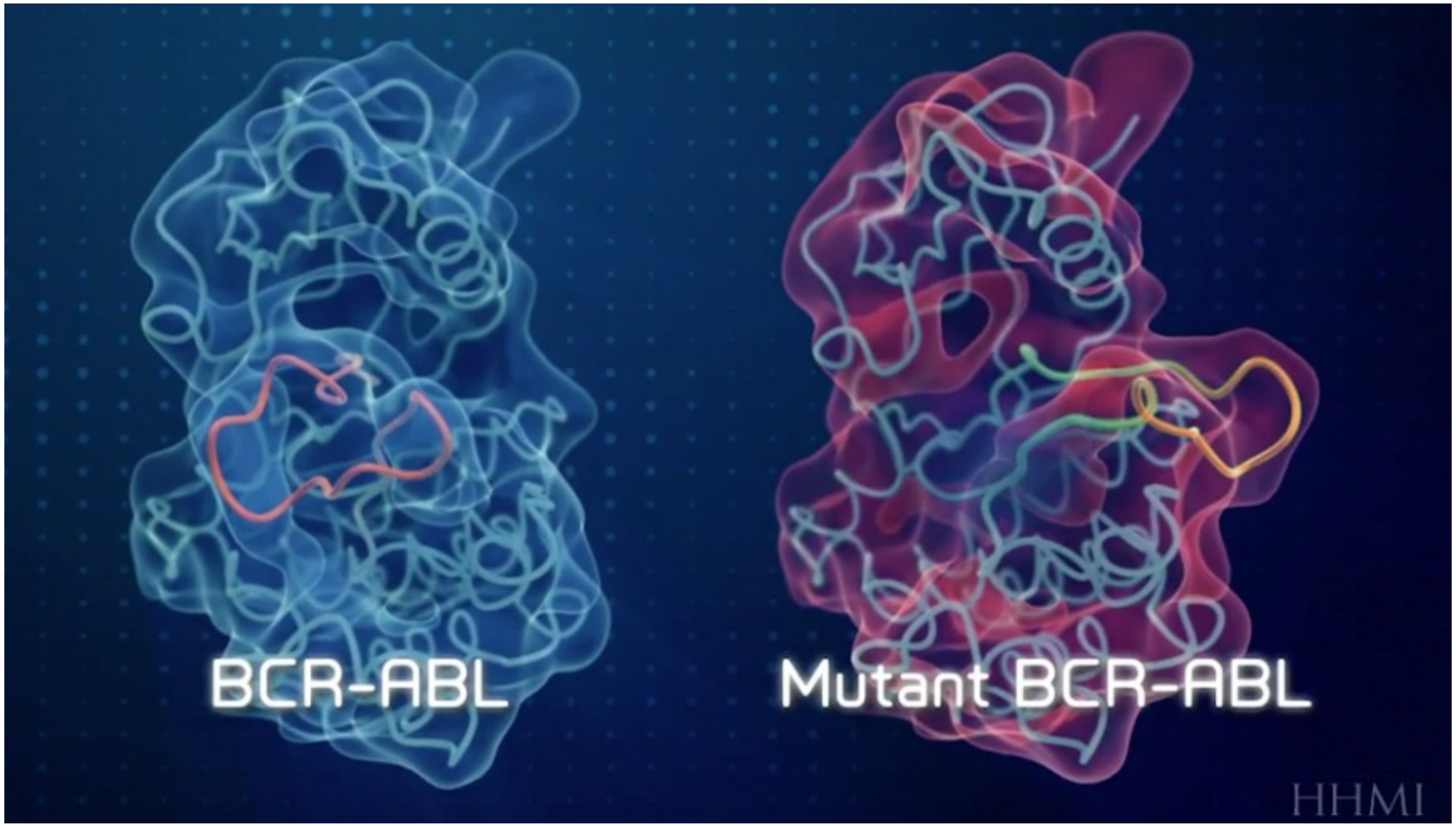
BCR-ABL mutagenize library



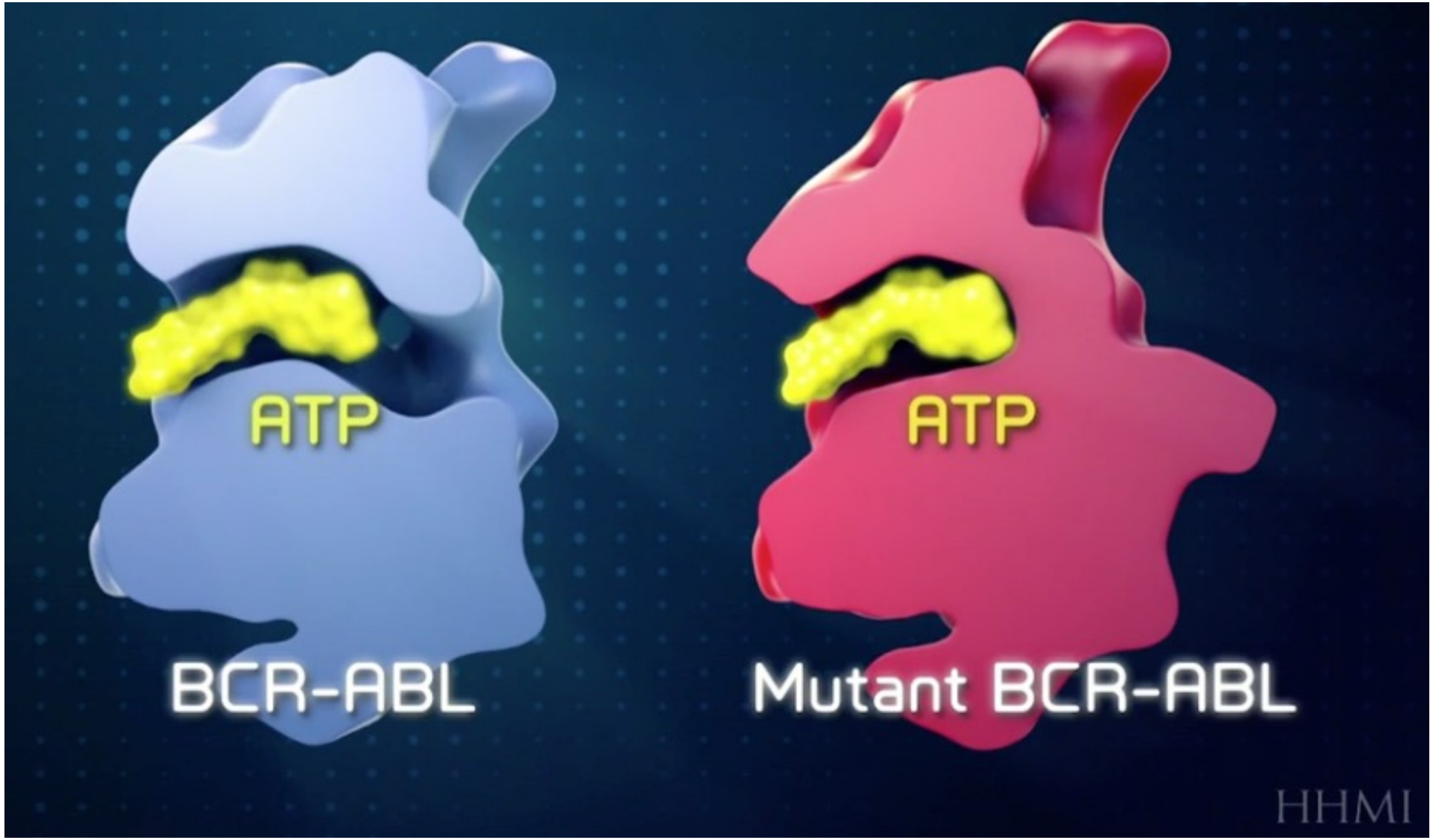
Several mutations are associated to Imatinib resistance

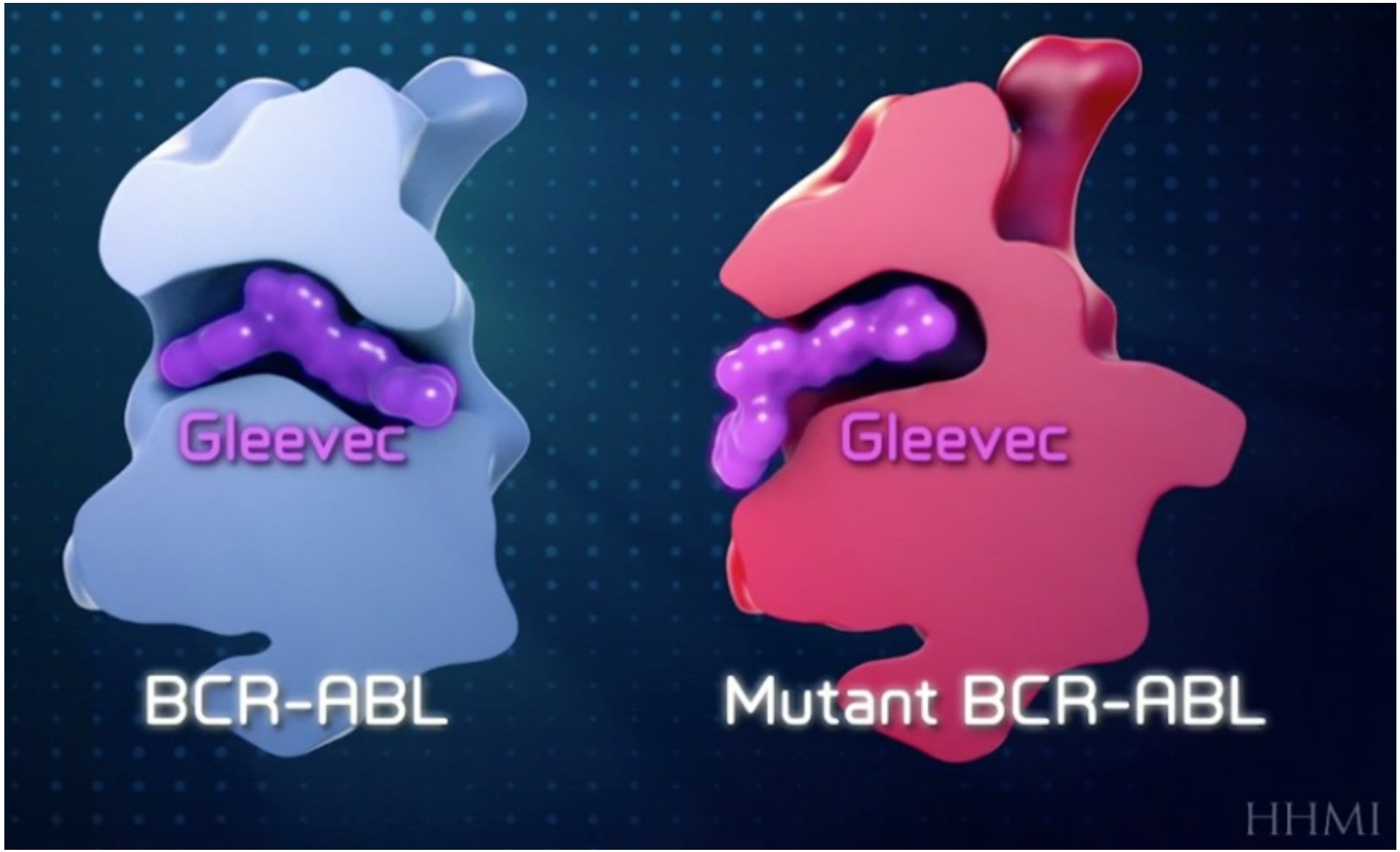


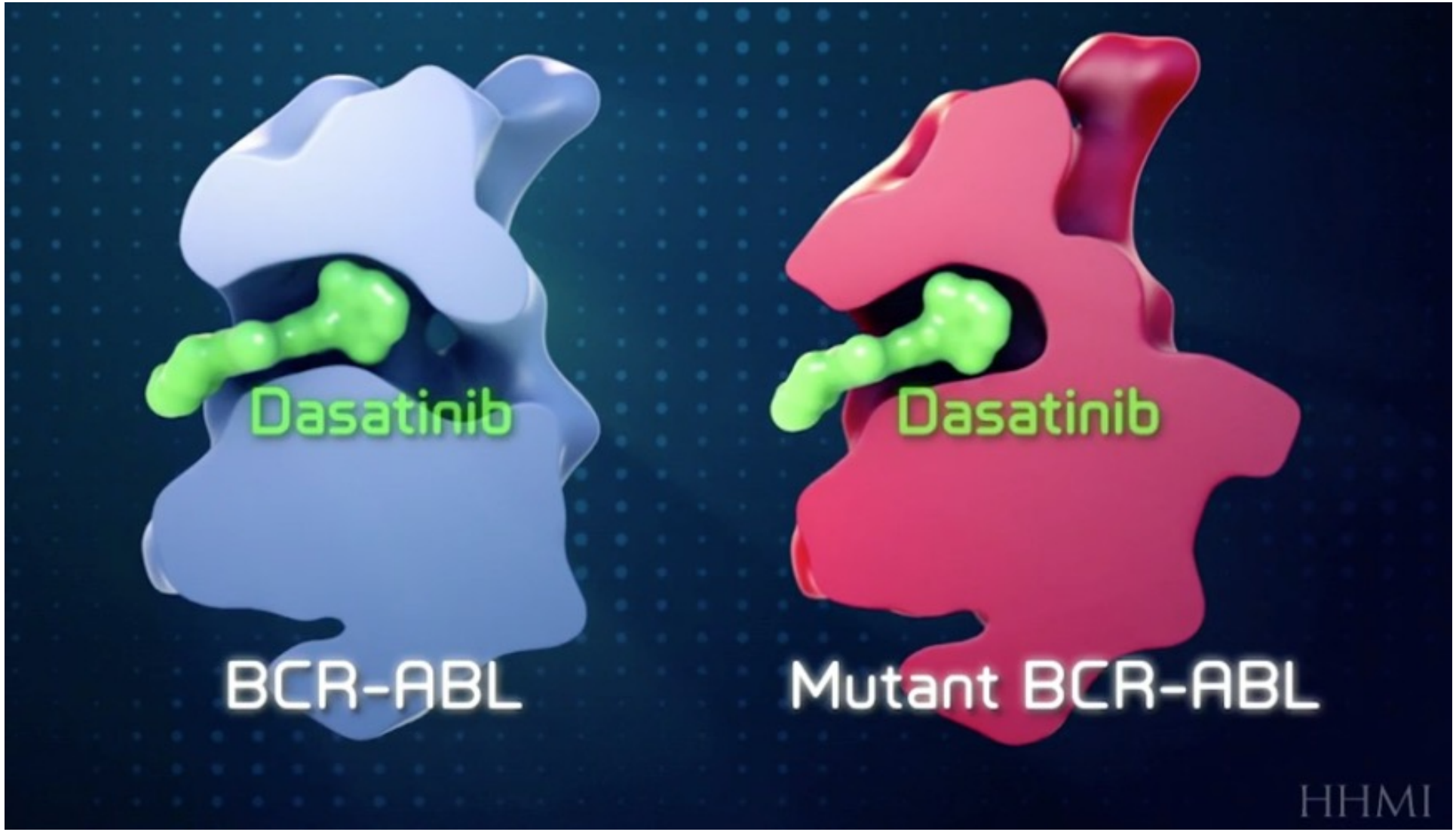
Several mutations are associated to Imatinib resistance cause protein conformation change



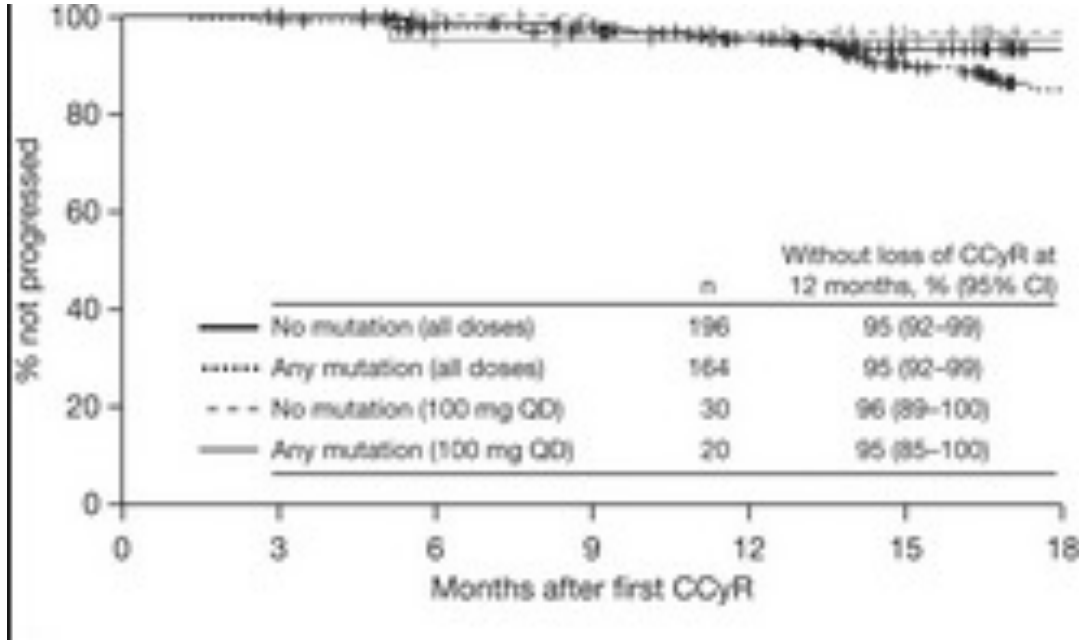
http://www.hhmi.org/biointeractive/gleevec-resistant-form-kinase-bcr-abl


ATP
ATP
BCR-ABL
Mutant BCR-ABL
HHMI


Gleevec
Gleevec
BCR-ABL
Mutant BCR-ABL
HHMI

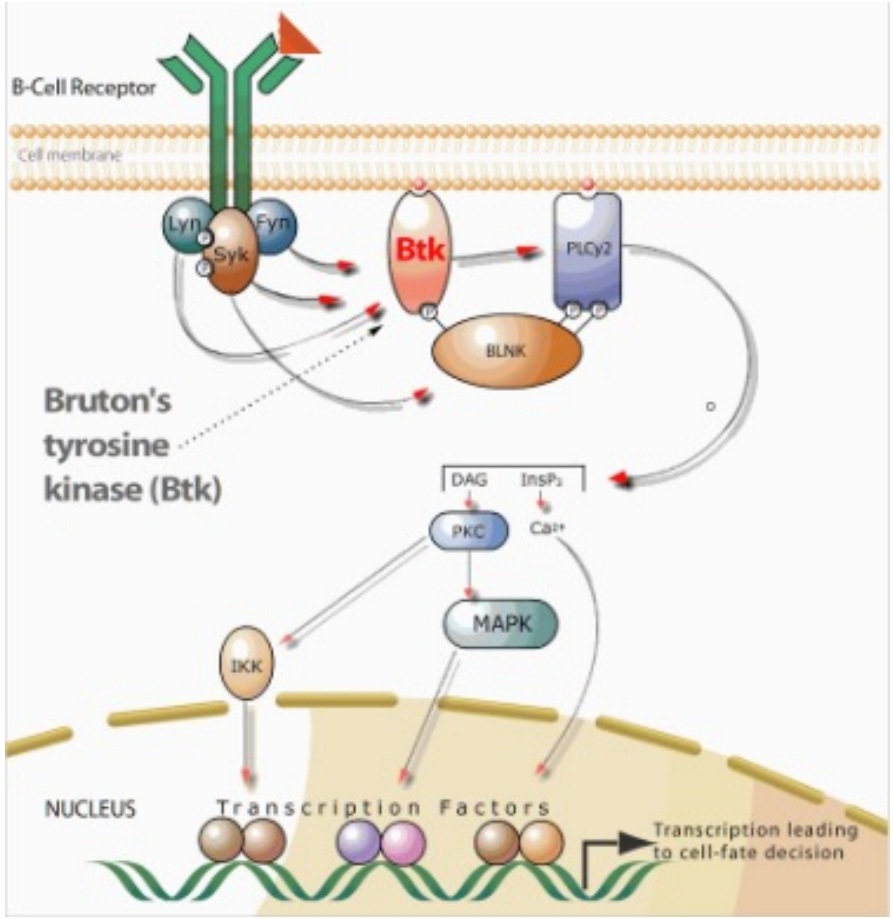

Dasatinib
Dasatinib
BCR-ABL
Mutant BCR-ABL
HHMI

Multiple inhibitors to prevent resistance to therapy



Generation	TKI	Approbation		
		1st line	2nd line	3rd line
1st	Imatinib	2003	2001	
2nd	Nilotinib	2011	2008	
	Dasatinib	2011	2007	
3rd	Bosutinib	Clinical trial	Clinical trial	2014
	Ponatinib	Clinical trial		

LYMPHOMA AND LEUKEMIA
B-CELL RECEPTOR SIGNALING DEPENDENCIES



B-Cell Lymphomas

Occur in the lymphonodes
Several subtypes

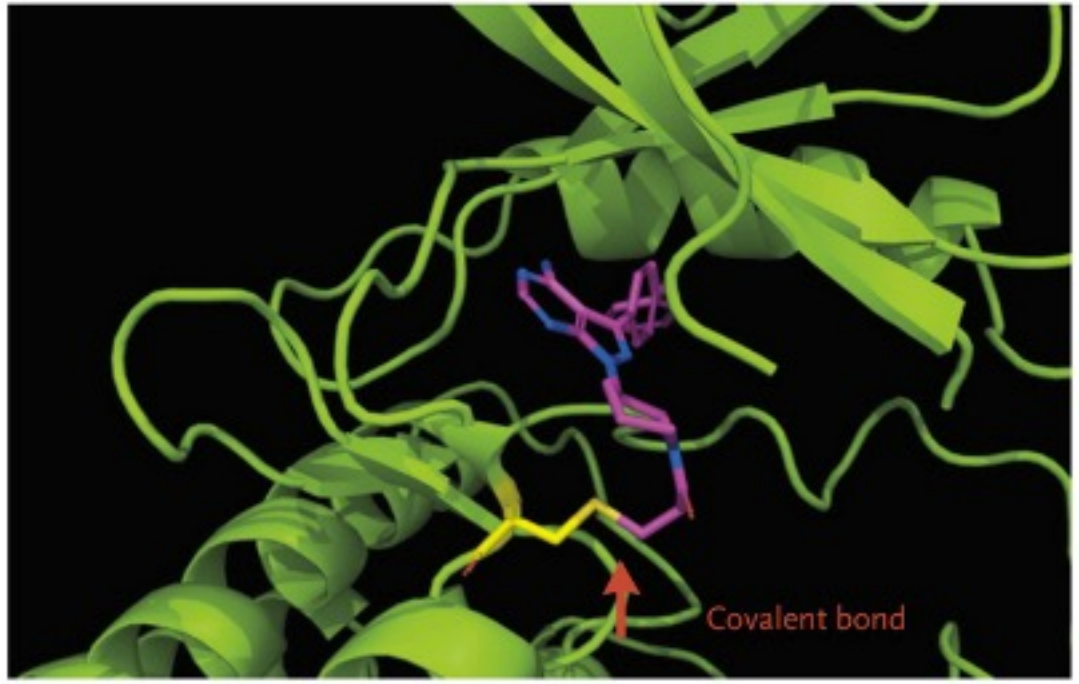
Chronic Lymphocytic Leukemia (CLL)

The most common type of Leukemia
Increase the number of B-cells

Transform in aggressive lymphoma

IBRUTINIB: BTK INHIBITION

IBRUTINIB: IRREVERSIBLE KINASE INHIBITOR



Approve for the treatment of B-cell malignancies in 2013-2014

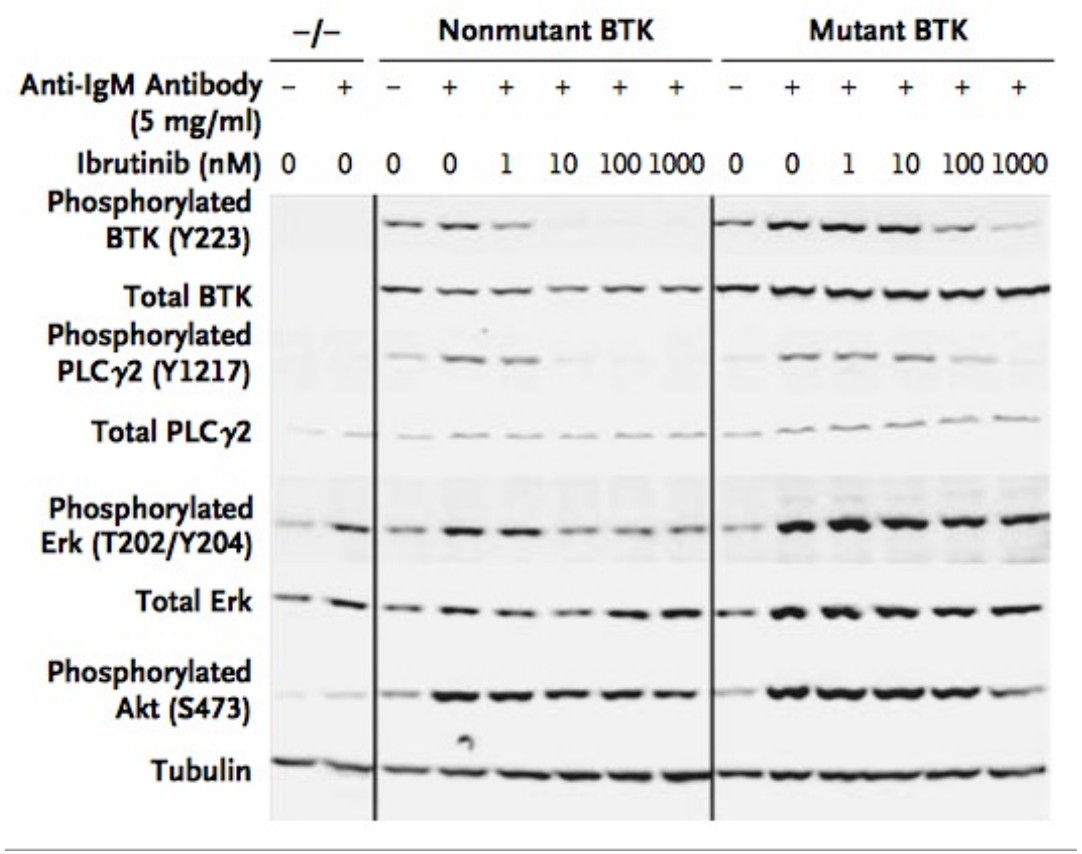
ORIGINAL ARTICLE

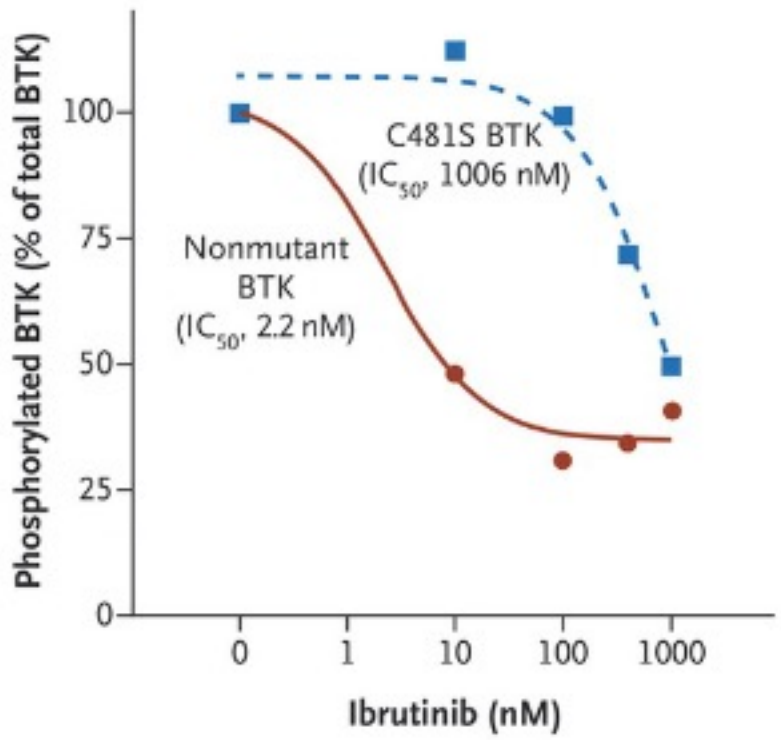
Resistance Mechanisms for the Bruton's Tyrosine Kinase Inhibitor Ibrutinib

Table 1. Characteristics of Six Patients with Resistance to Ibrutinib.

Patient No.	Age	Prior Therapies	Baseline Cytogenetic Features*	Study Treatment and Daily Dose†	Duration of Ibrutinib Treatment	Best Response	Time to First Response	Identified Mutations of Interest‡
	yr	*no.*			*days*		*days*	
1	59	5	del(17p13.1), trisomy 12	Ibrutinib, 560 mg	621	Partial	70	C481S mutation in BTK
2	59	3	del(11q22.3)	Bendamustine–rituximab for 6 cycles; ibrutinib, 420 mg	388	Complete	70	C481S mutation in BTK
3	51	2	complex karyotype	Ofatumumab for 24 wk; ibrutinib, 420 mg	674	Complete	85	C481S mutation in BTK
4	69	9	del(17p13.1), complex karyotype	Ibrutinib, 840 mg	868	Partial	133	C481S mutation in BTK
5	61	4	del(17p13.1), complex karyotype	Ofatumumab for 24 wk; ibrutinib, 420 mg	505	Partial	85	L845F, R665W, and S707Y mutations in PLCγ2 and C481S mutation in BTK
6	75	2	del(17p13.1), complex karyotype	Ibrutinib, 420 mg	673	Partial	159	R665W mutation in PLCγ2

DISCOVER DRUG RESISTANCE IN THE LAB-2



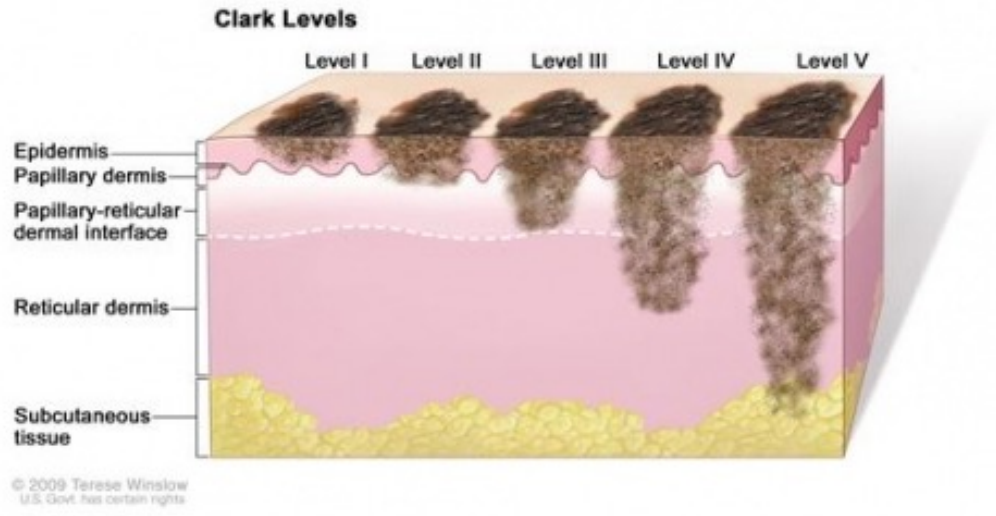


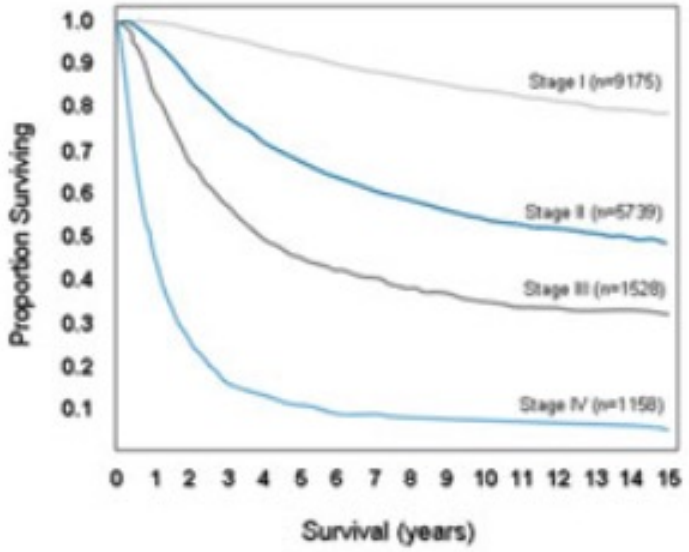
MELANOMA: EXAMPLE 3

SKIN TUMOR

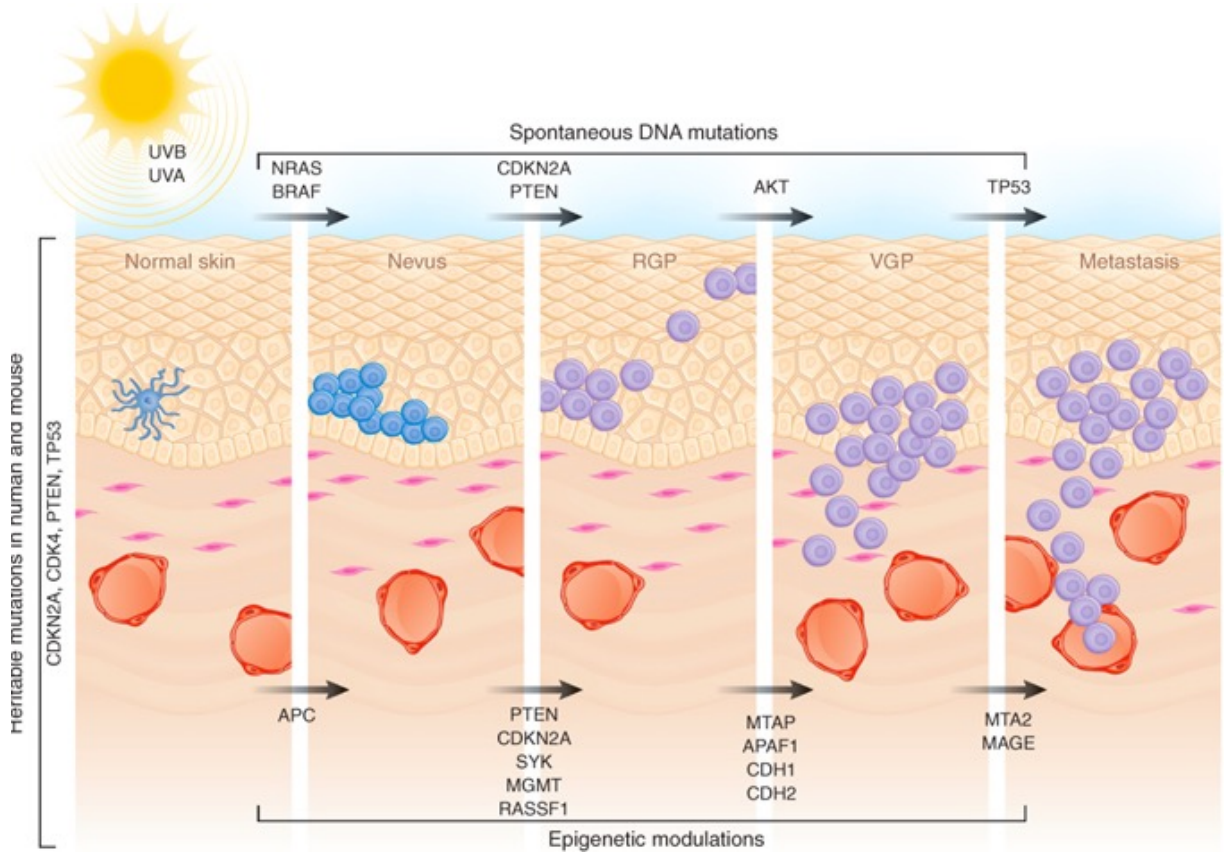
~70000 new cases every year

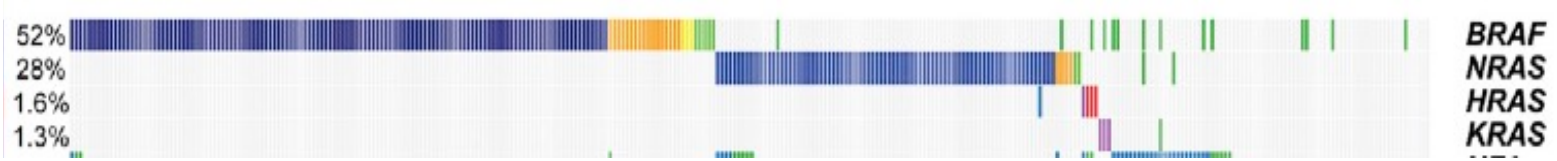
Resistant to chemotherapies





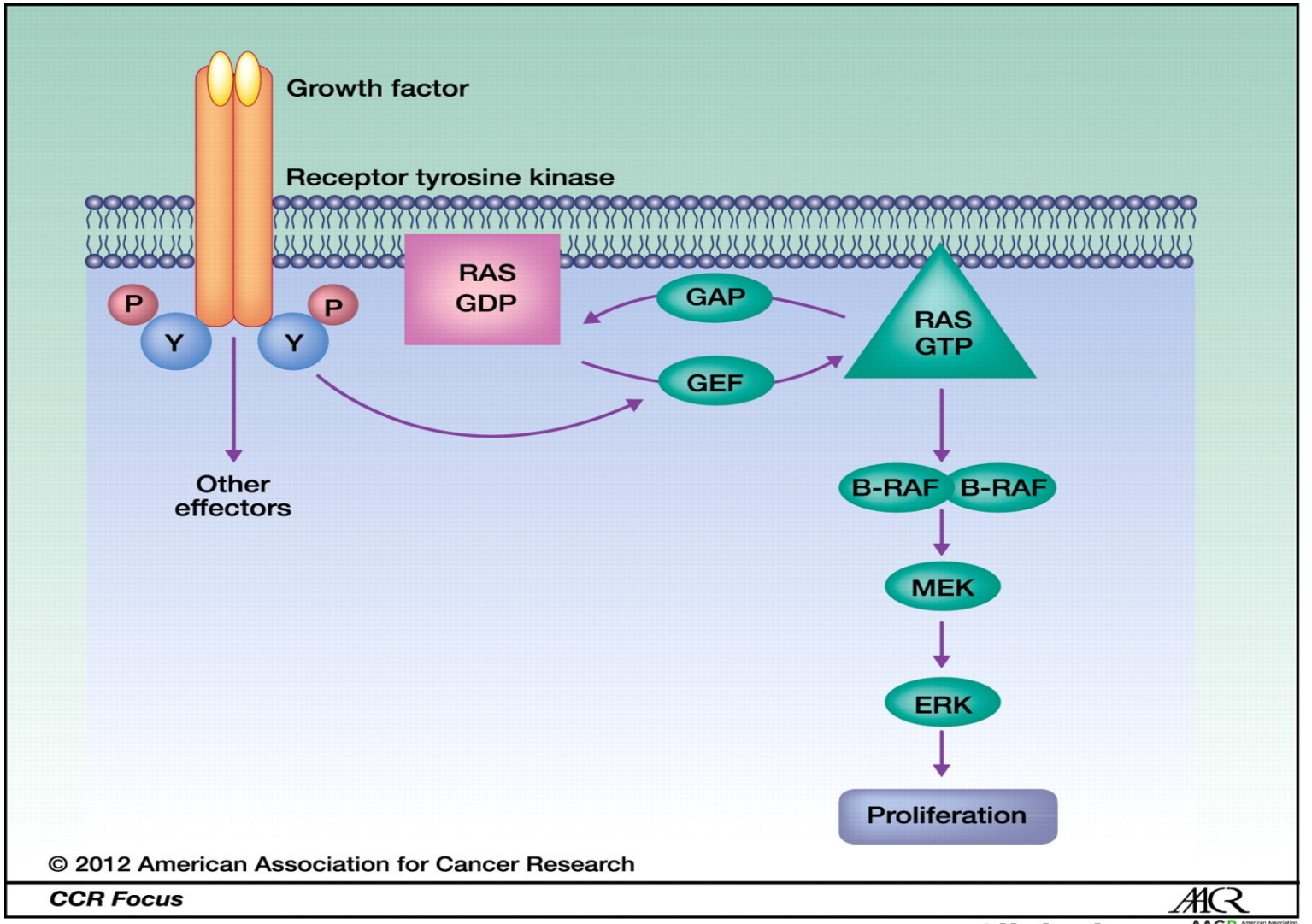
COMMON GENOMIC LESIONS



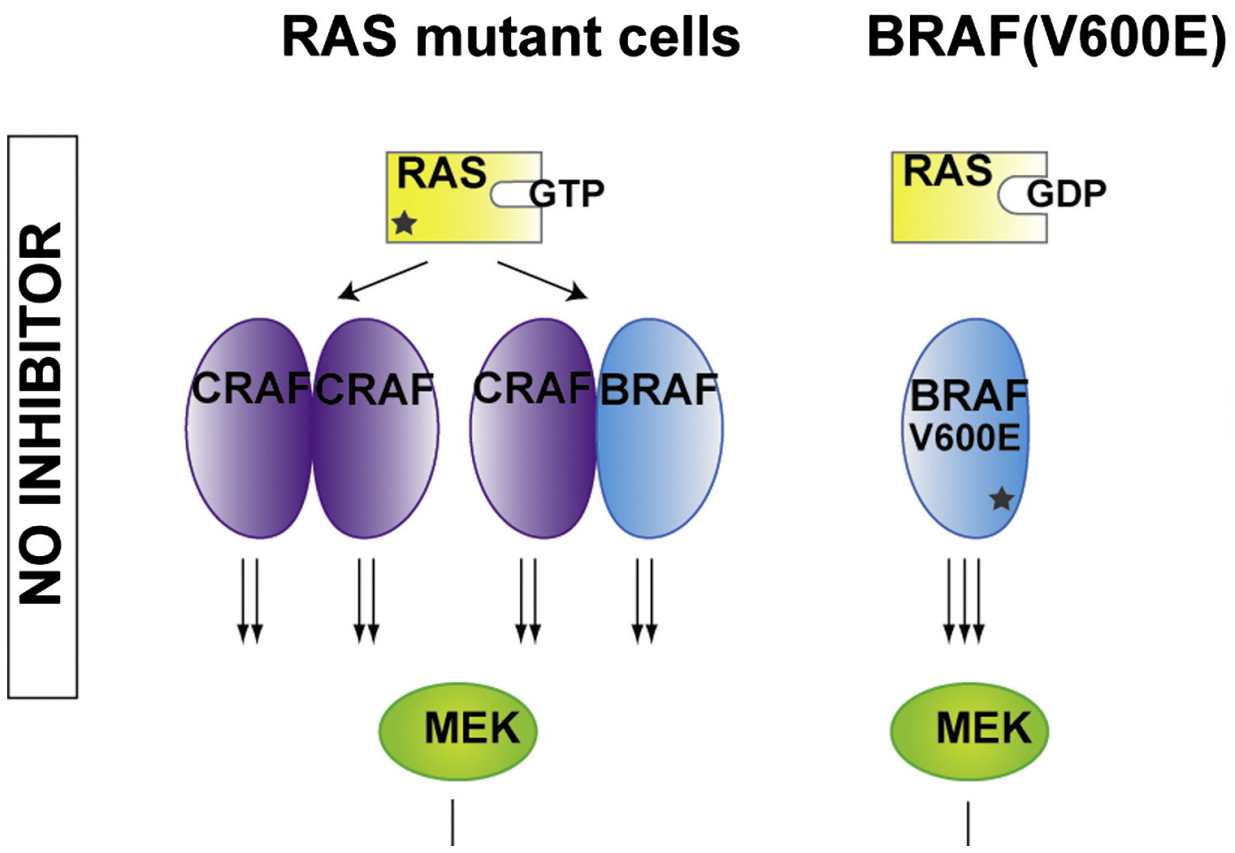


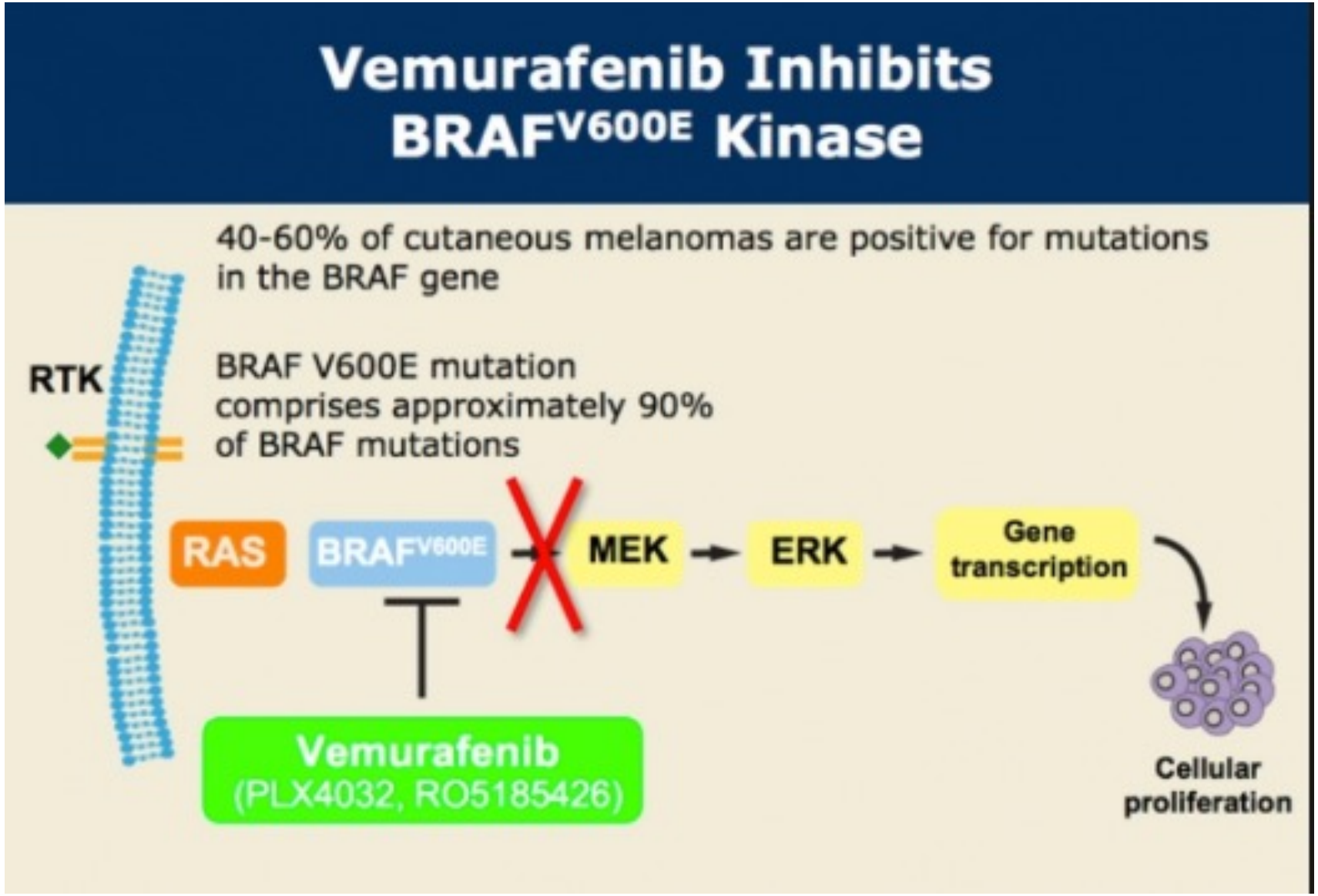
V600E

RAS/RAF and MAPK



RAS AND BRAF V600E MUTATIONS IN METASTATIC MELANOMA





Approve for the treatment of melanoma in 2011

PLX4032

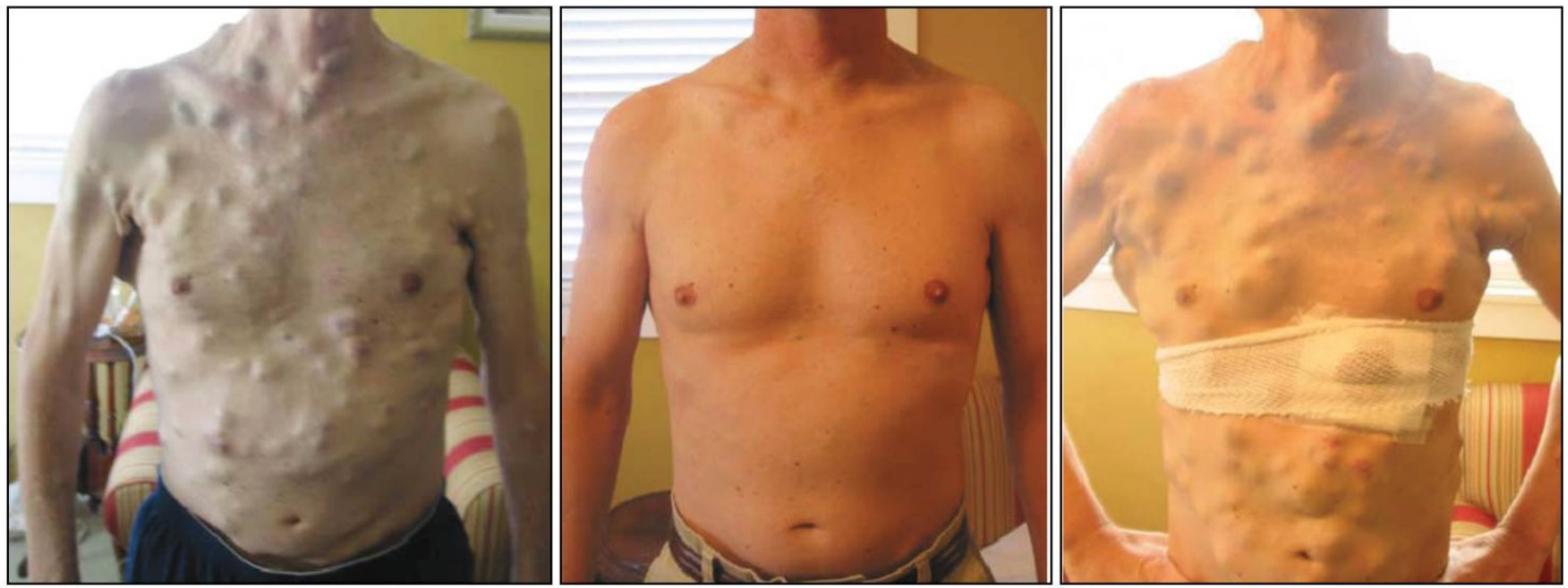
Vemurafenib

Zelboraf

Dissecting Therapeutic Resistance to RAF Inhibition in Melanoma by Tumor Genomic Profiling

Nikhil Wagle, Caroline Emery, Michael F. Berger, Matthew J. Davis, Allison Sawyer, Panisa Pochanard, Sarah M. Kehoe, Cory M. Johannessen, Laura E. MacConaill, William C. Hahn, Matthew Meyerson, and Levi A. Garraway

JOURNAL OF CLINICAL ONCOLOGY BIOLOGY OF NEOPLASIA



Before

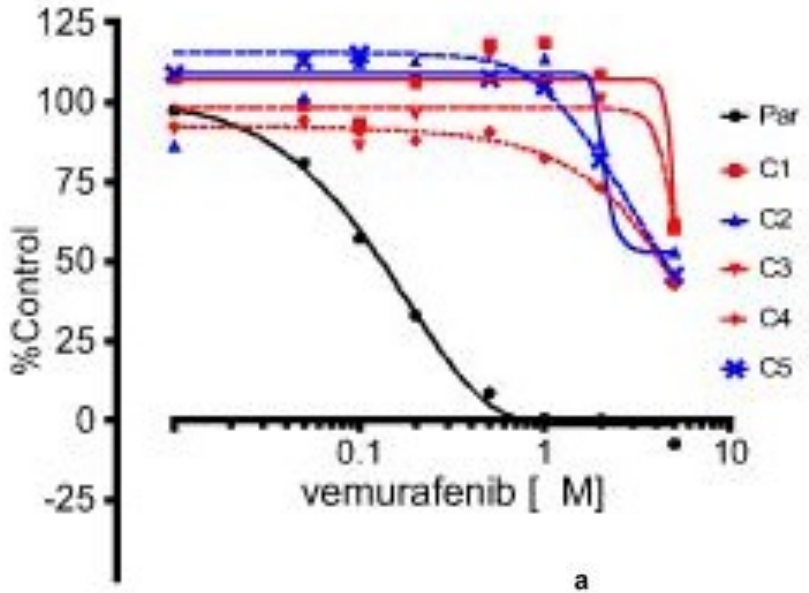
15 weeks

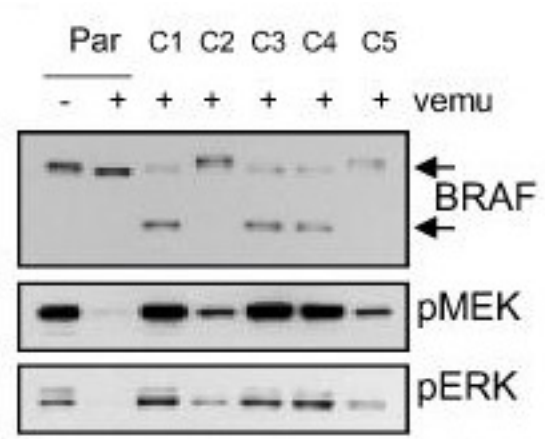
Post treatment

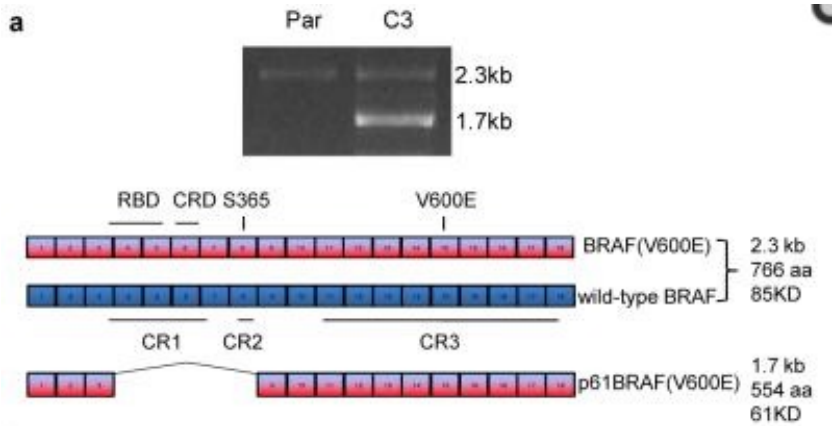
23 weeks

Post treatment

DISCOVER DRUG RESISTANCE IN THE LAB-3

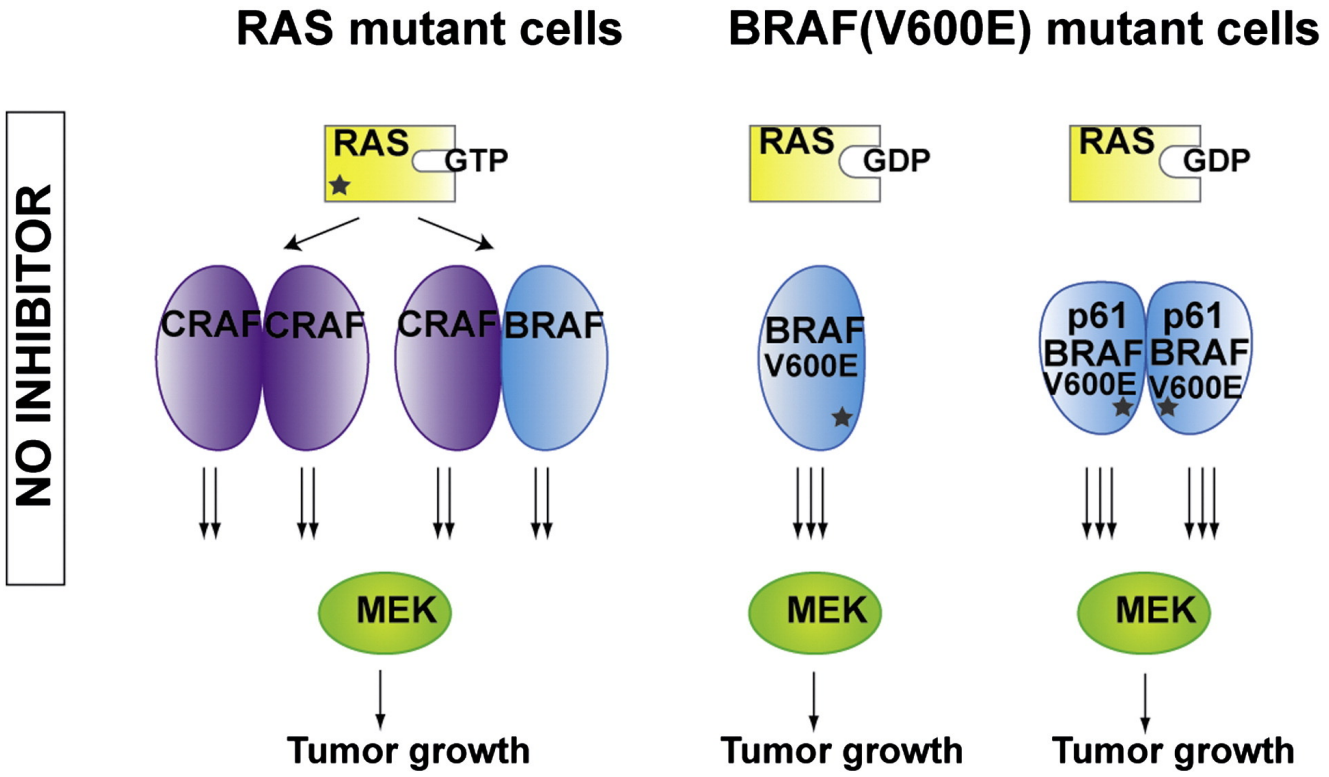






Poulikakous et al. Nature, 2011

MECHANISM OF RESISTANCE



SUMMARY of MECHANISMs OF RESISTANCE

ACQUIRED NOVEL MUTATIONS (BCR-ABL and BTK)

EXPRESS DIFFERENT SPLICING VARIANT OF THE PROTEIN (BRAF)

HOW TO IDENTIFY MECHANISM OF RESISTANCE?

Library screening of mutated protein
Sequencing resistant patients
Generating resistant cell, using high doses of the drug.

Genetic screen to predict resistance to therapy

GENETIC SCREEN

SIMULTANEOUSLY GENETICALLY MODIFY MULTIPLE GENES

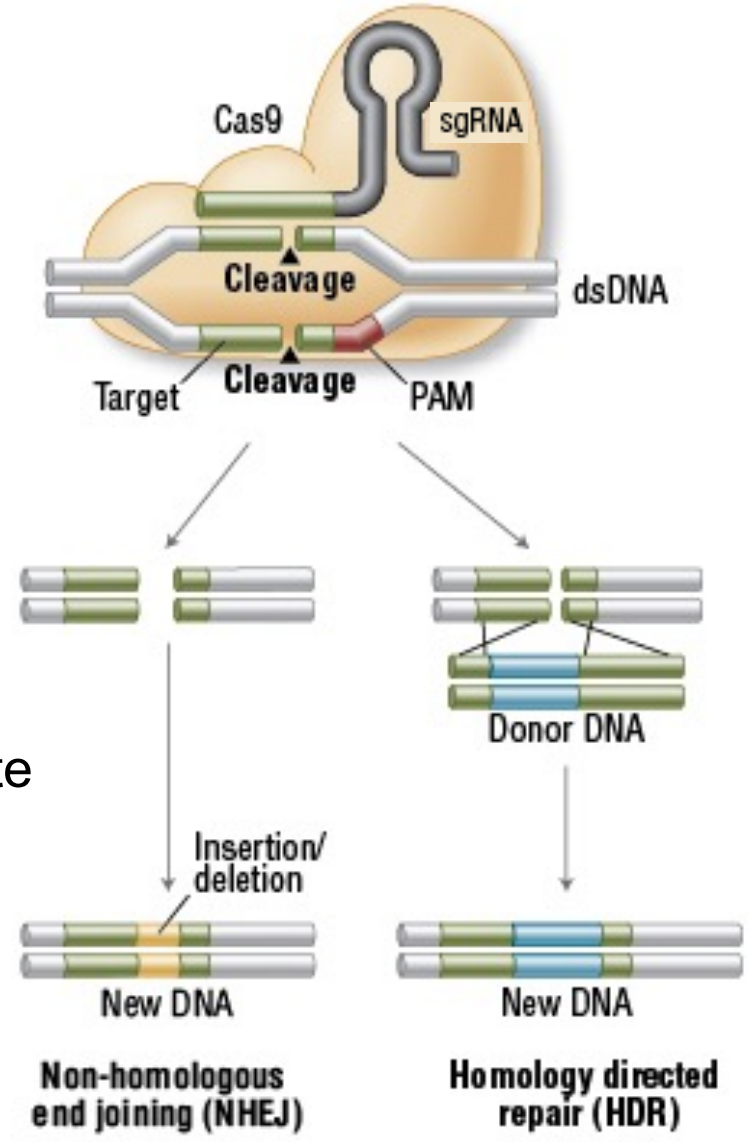
Crispr Screen (introduce mutations in the gene sequence)
siRNA or shRNA screen (block gene expression, act on the mRNA)

Gene editing by engineered CRISPR/Cas9

=> Cas9 induce **DNA double-strand breaks**

=> Cas9 can ***induce DNA repair by NHEJ or HDR*** in all species examined:

=> repair enzymes of the host either generate small insertion/deletion mutations (*'indels'*) or integrate homologous 'donor DNA' *at specific loci that match the design of the guide RNA*



https://www.neb.com/tools-and-resources/feature-articles/crispr-cas9-and-targeted-genome-editing-a-new-era-in-molecular-biology

CRISPRs SCREEN

STEP 1

GENERATE A LIBRARY OF sgRNA targeting the genes of interest

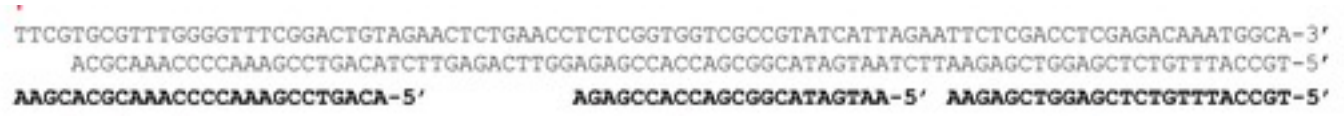
Each gene is targeted by multiple sgRNA to increase reproducibility

Library can be designed to target few genes or the whole genome

It is possible to study the function of non coding region

CRISPRs SCREEN
generate a sgRNA library

Gene-1



sgRNA-1 sgRNA-2 sgRNA-3

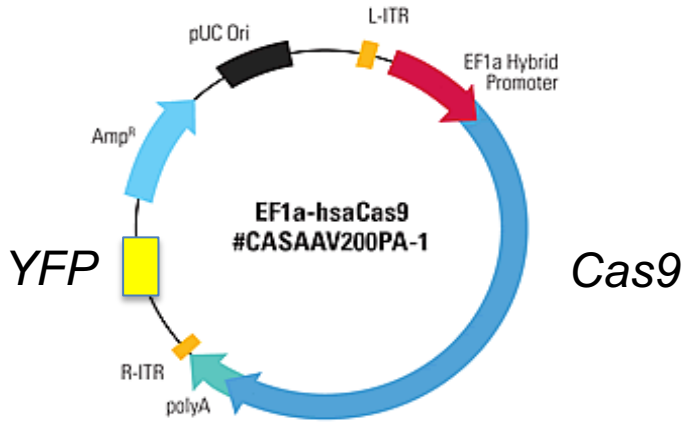
Genes in human are ~ 20000 = library has at least 60000 sgRNA

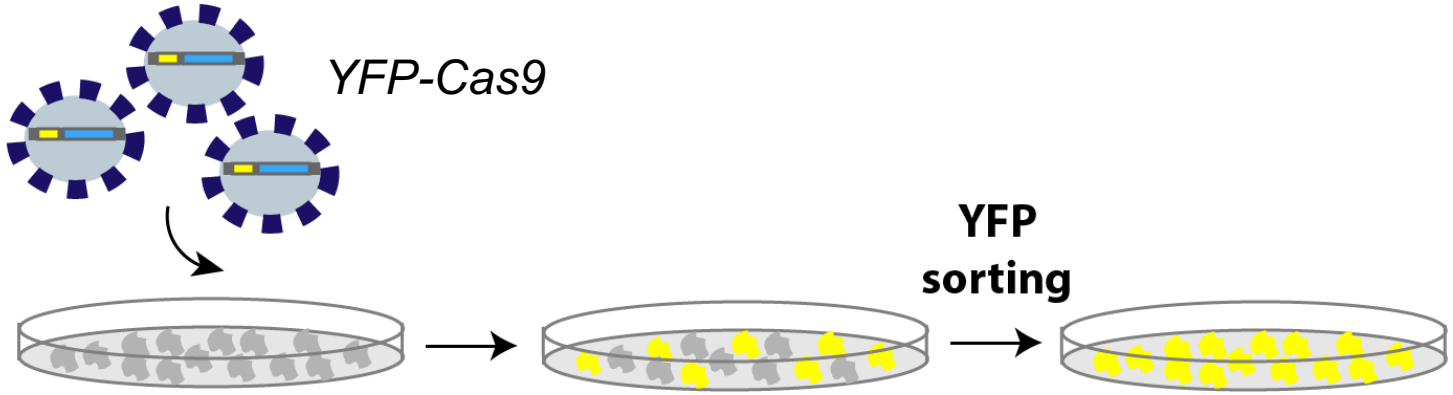
Target only gene with specific function (e.g. kinases)
500 genes = library with at least 1500 shRNA

STEP 2

CRISPRs SCREEN

GENETICALLY MODIFY THE CELLS TO EXPRESS THE Cas9



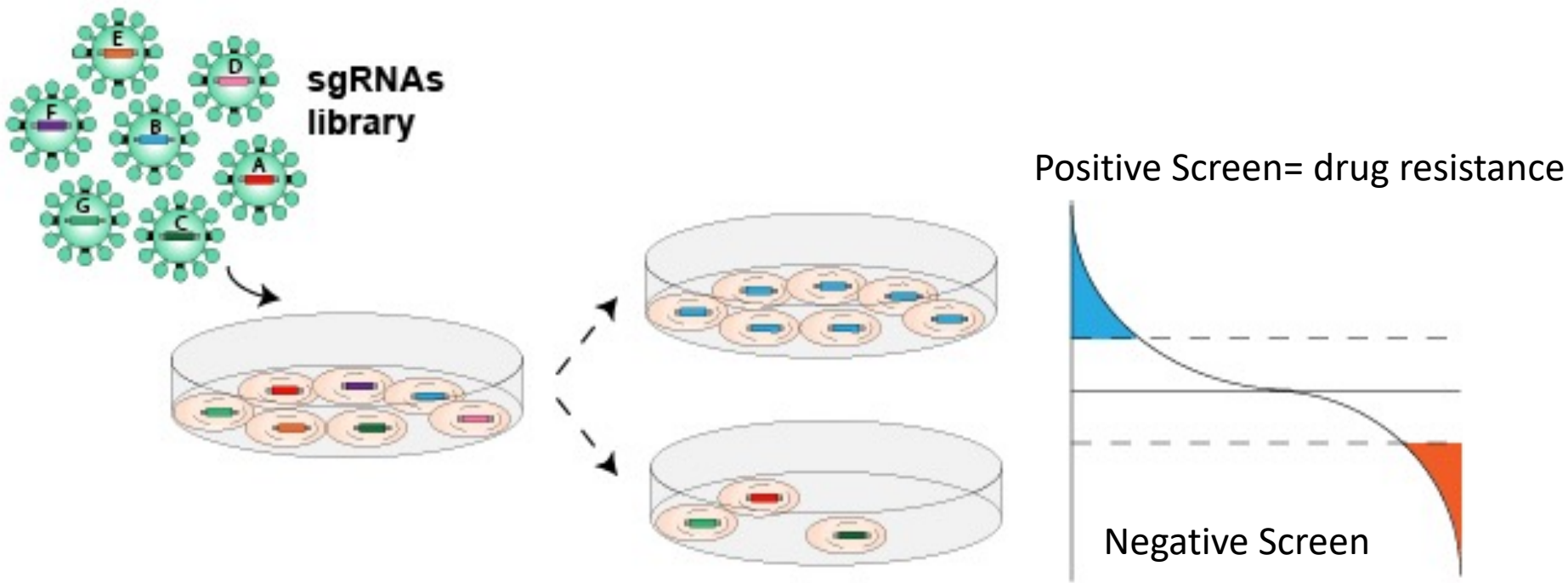


Use a lentiviral vector to transduce the cell and express Cas9

Select YFP positive cells

CRISPRs SCREEN

STEP 3: Transduce the cells with sgRNA library and check for the phenotype



CRISPRs SCREEN

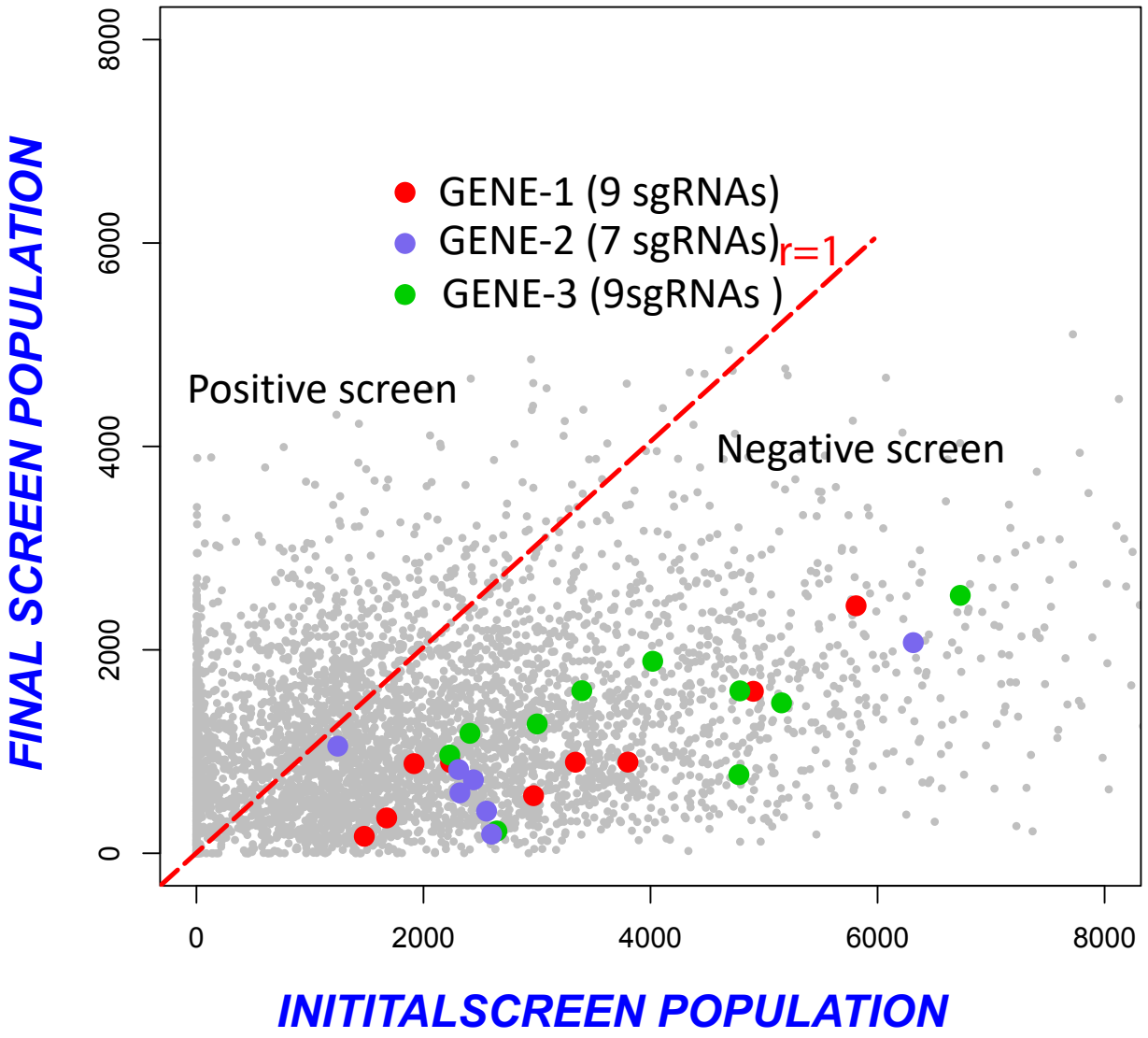
STEP 4: Extract the DNA for the cells and sequence (e.g Illumina platform)

Use high throughput sequencing to know how many sgRNA proportionally were present in initial and final population

Initial population	*Final population*
100 cells expressing sgRNA-1	40 cells expressing sgRNA-1
50 cells expressing sgRNA-2	55 cells expressing sgRNA-2
5 cells expressing sgRNA-3	1001 cells expressing sgRNA-3
etc….	etc….

CRISPRs SCREEN

STEP 4: Extract the DNA for the cells and sequence (e.g Illumina platform)



THE DESIGN OF ANTI-CANCER DRUGS

Disease specific:

- Leukemia
- Lymphoma
- Melanoma

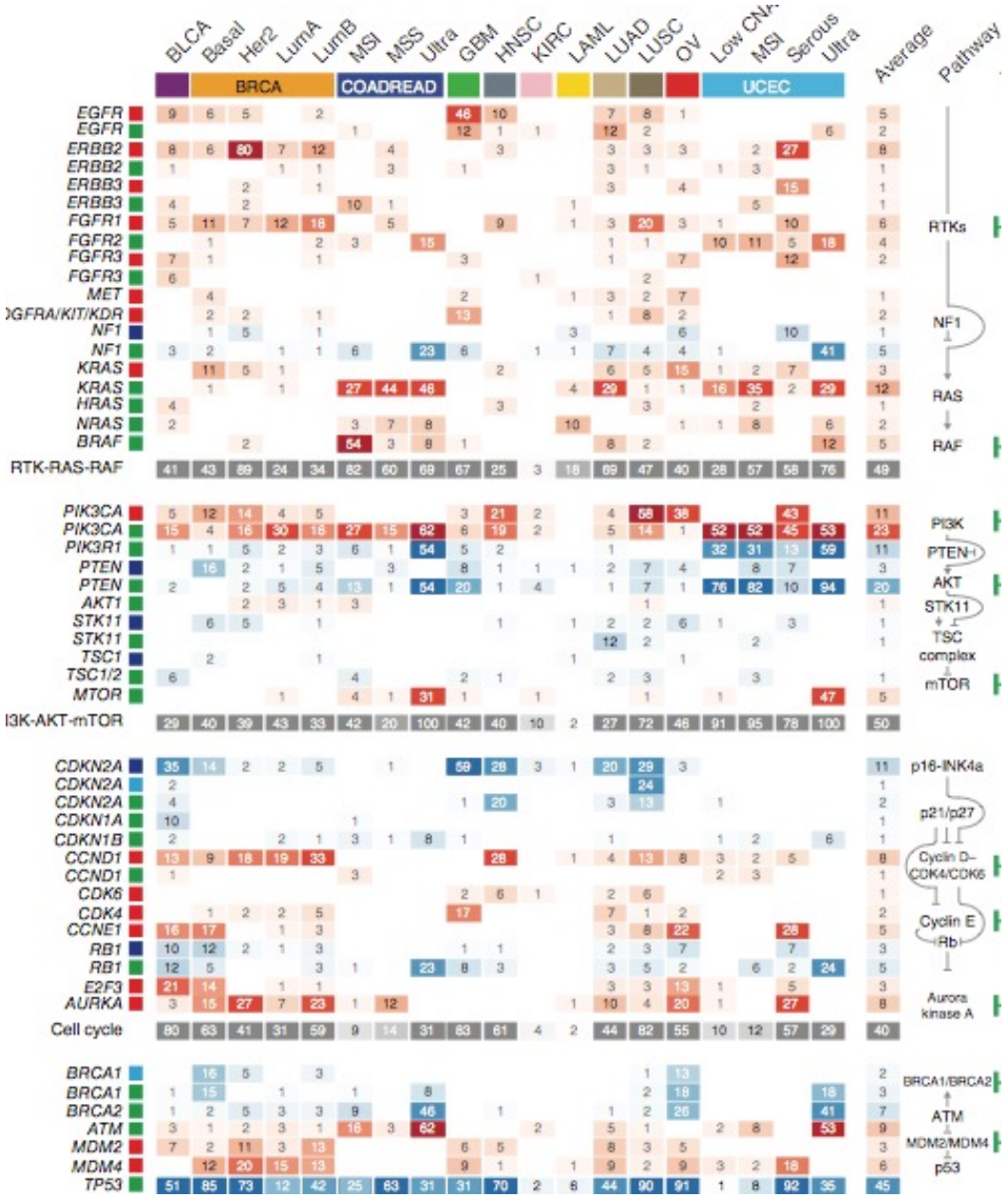
Pathway specific:

- **APOPTOSIS**
- **CELL CYCLE**
- **PI3K/mTOR**

SYNTHETIC LETHAL INTERACTION

- BRCA1/2 and PARP inhibitor (Breast and Ovarian cancer)

COMMONLY ALTERED PATHWAYS



Receptor Tyrosine Kinases

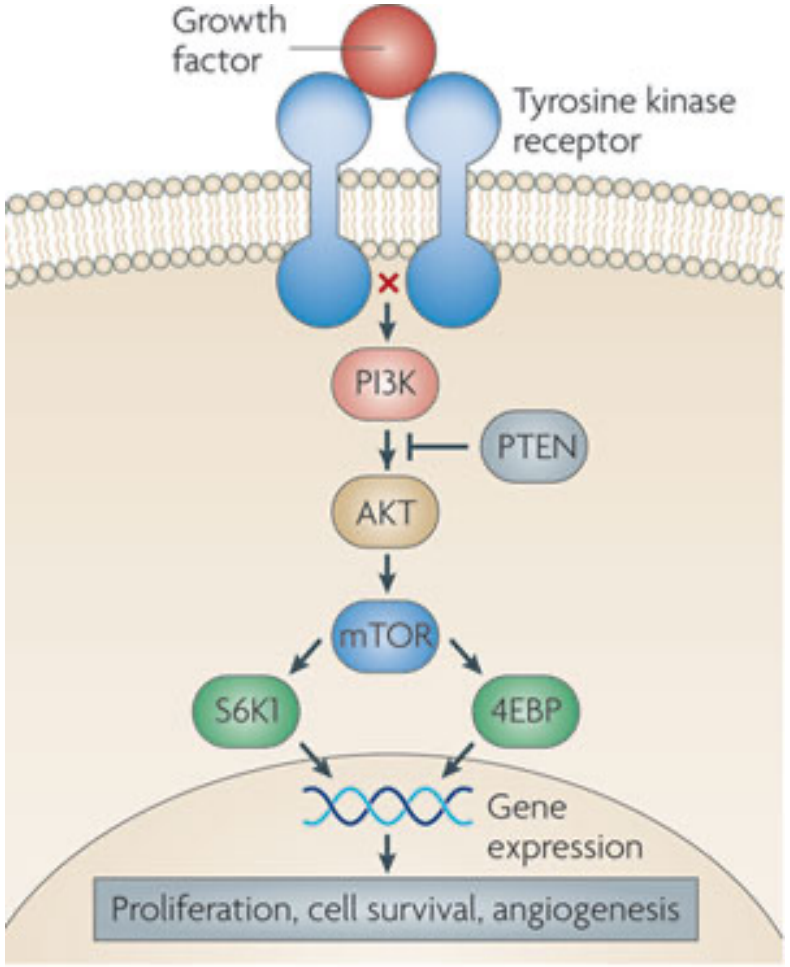
PI3K/mTOR

Cell Cycle

DNA Damage/p53

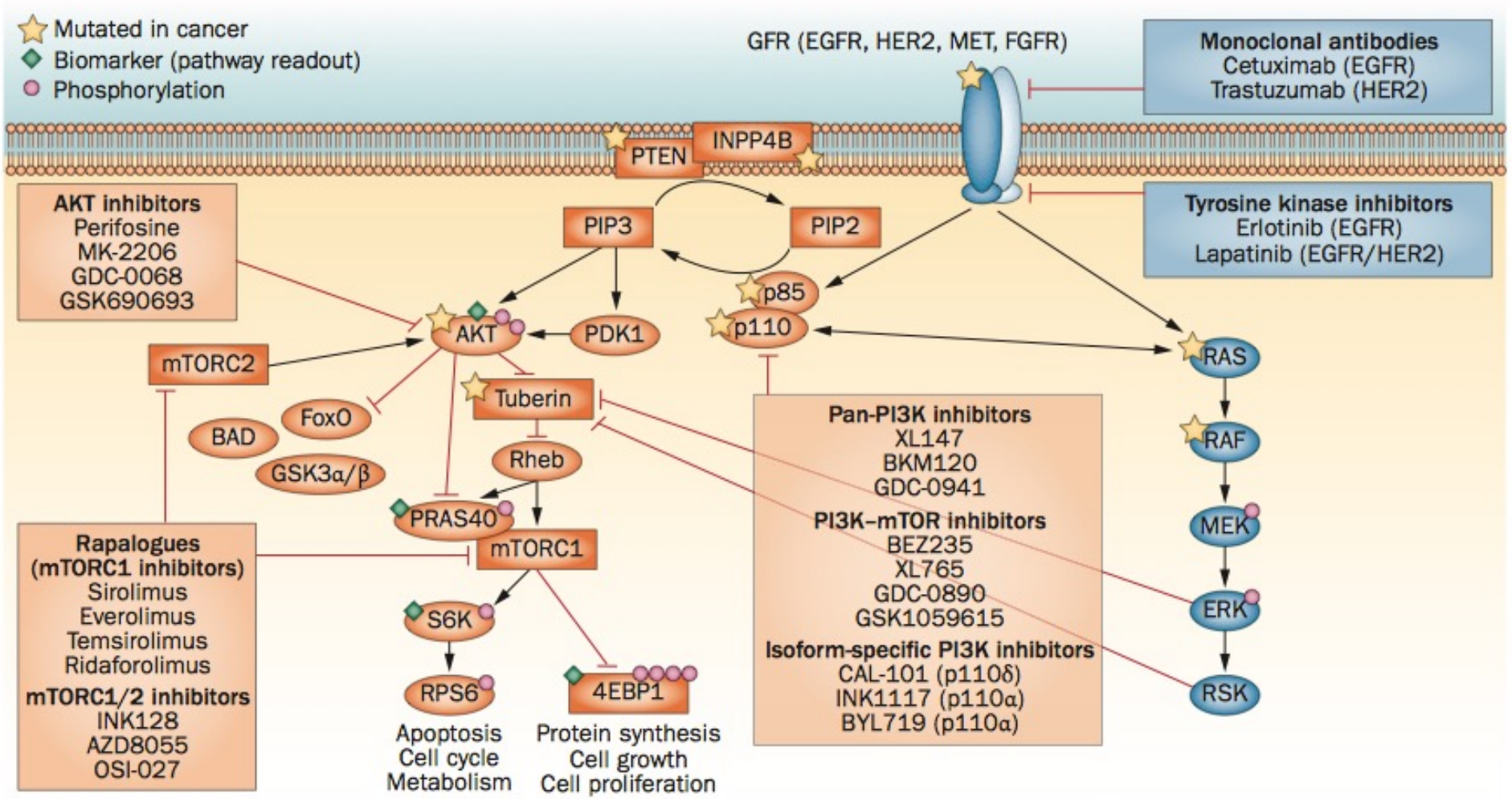
Ciriello et al. Nature Gen, 2013

PI3K-AKT-mTOR



Nature Reviews | Drug Discovery

PI3K inhibitors/mTOR

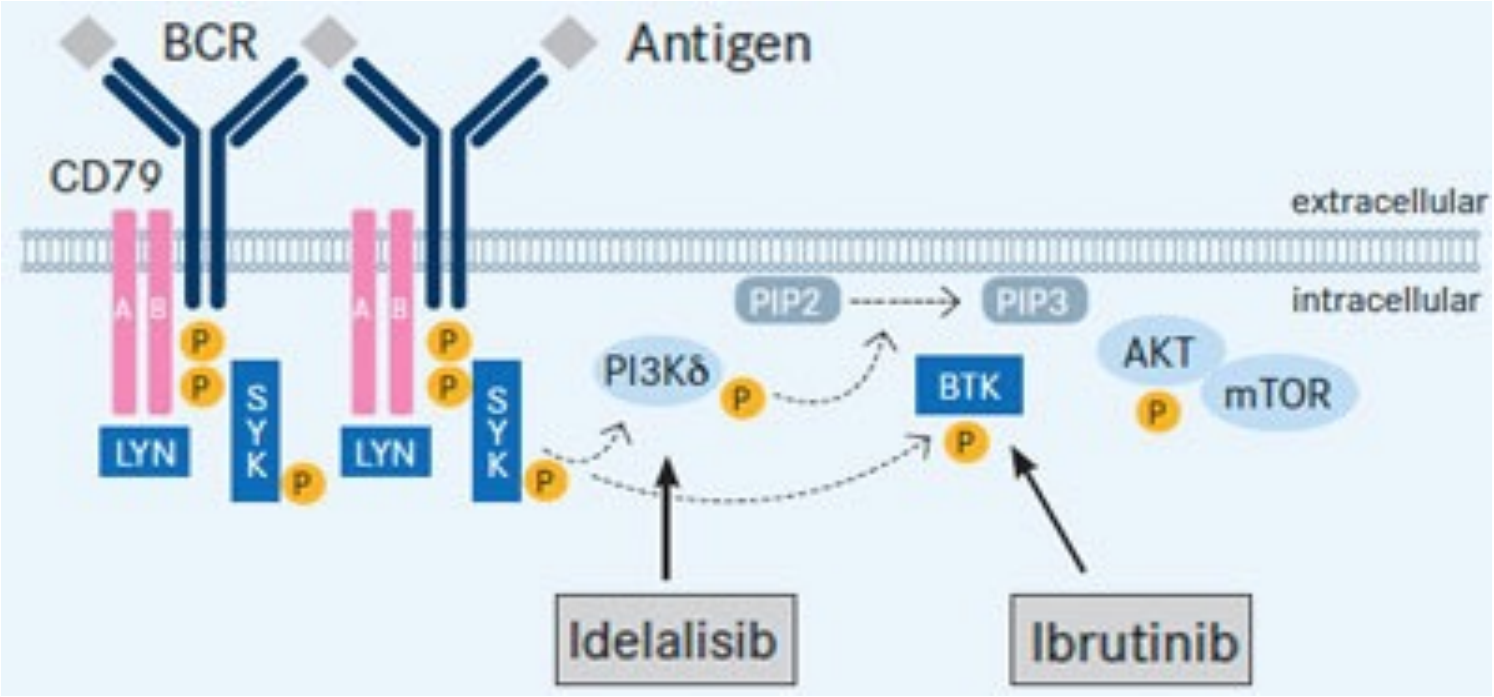


http://www.nature.com/nrclinonc/journal/v10/n3/pdf/nrclinonc.2013.10.pdf

PI3K inhibitors

IDELASILIB or CAL101: Approve for the treatment of Leukemia and Lymphoma 2014

Inhibit specific isoform PI3Kδ



mTOR inhibitor

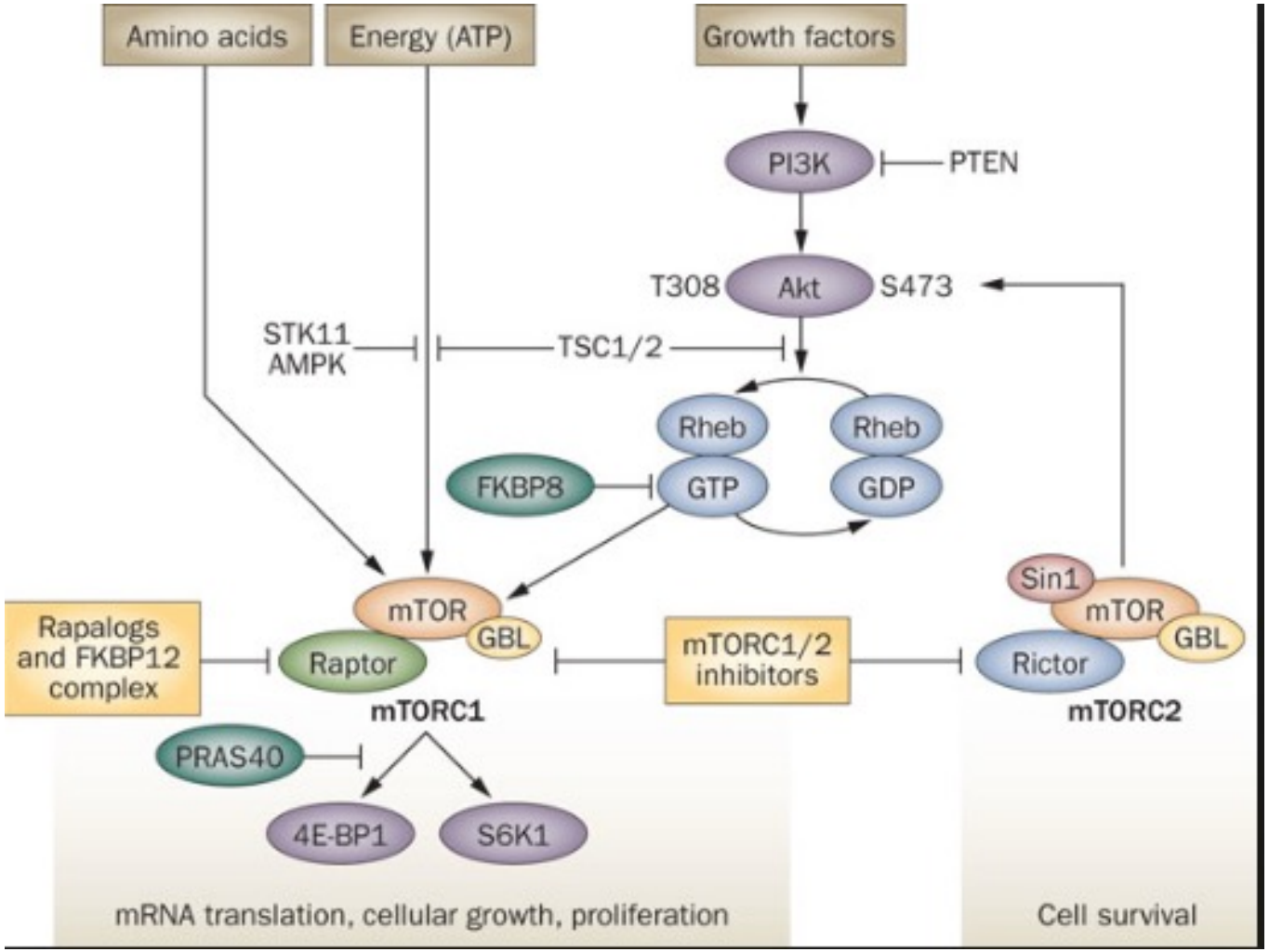
mTOR= Mammalian Target Of Rapamycin

DRUG= RAPAMYCIN/Sirolimus

Isolated in 1960 from a Bacteria growing RAPA NUI (Easter Island)

mTOR inhibitor

mTOR= Mammalian Target Of Rapamycin



mTOR inhibitor

mTOR= Mammalian Target Of Rapamycin

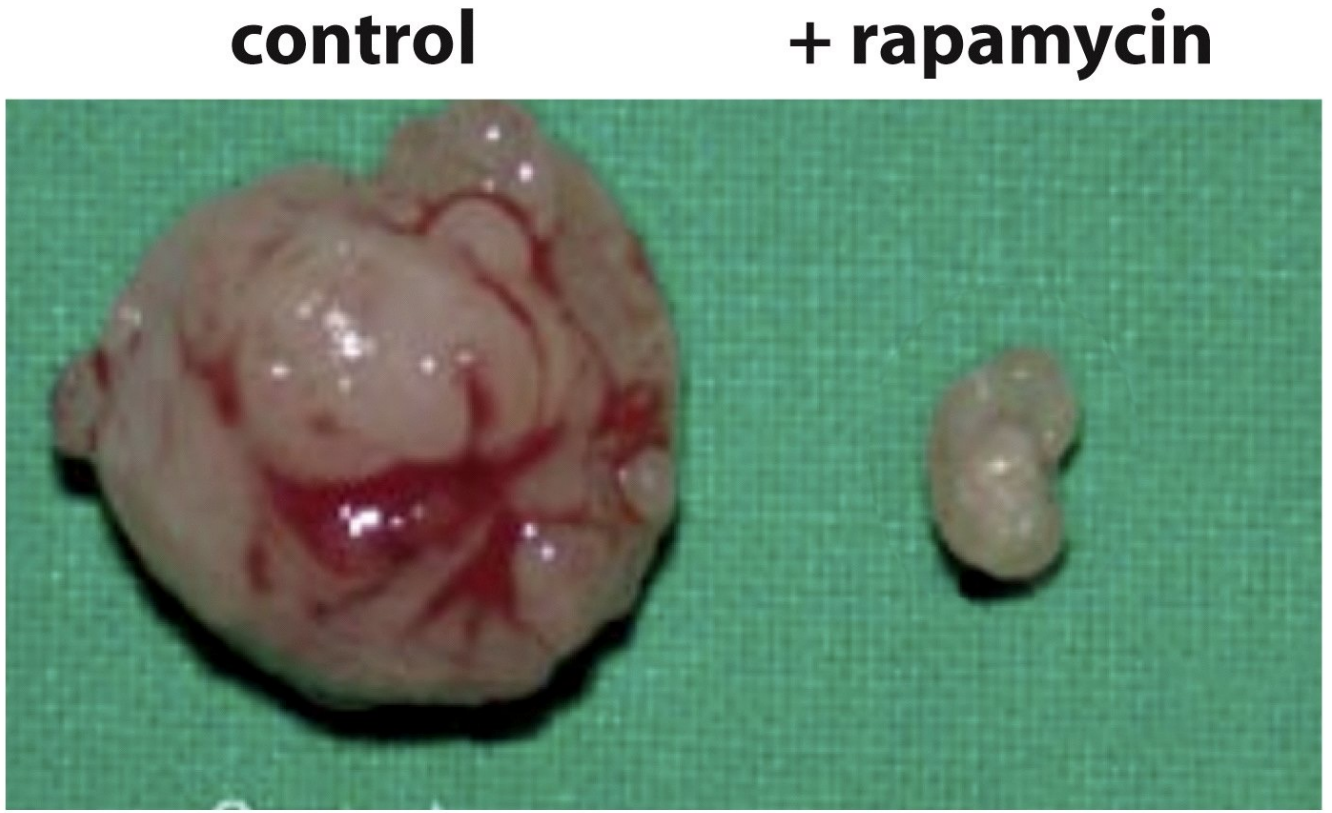
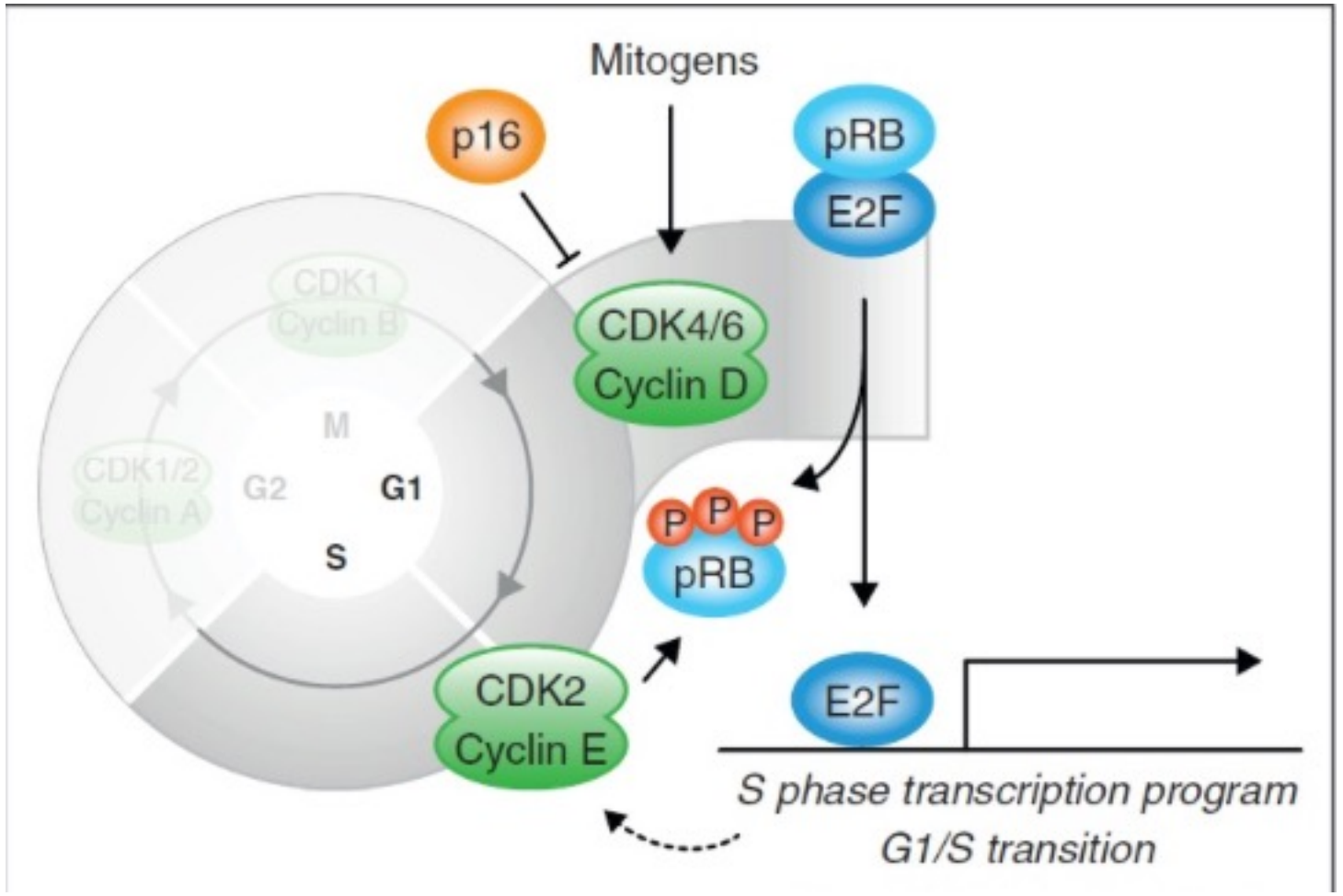


Figure 16.44b *The Biology of Cancer* (© Garland Science 2007)

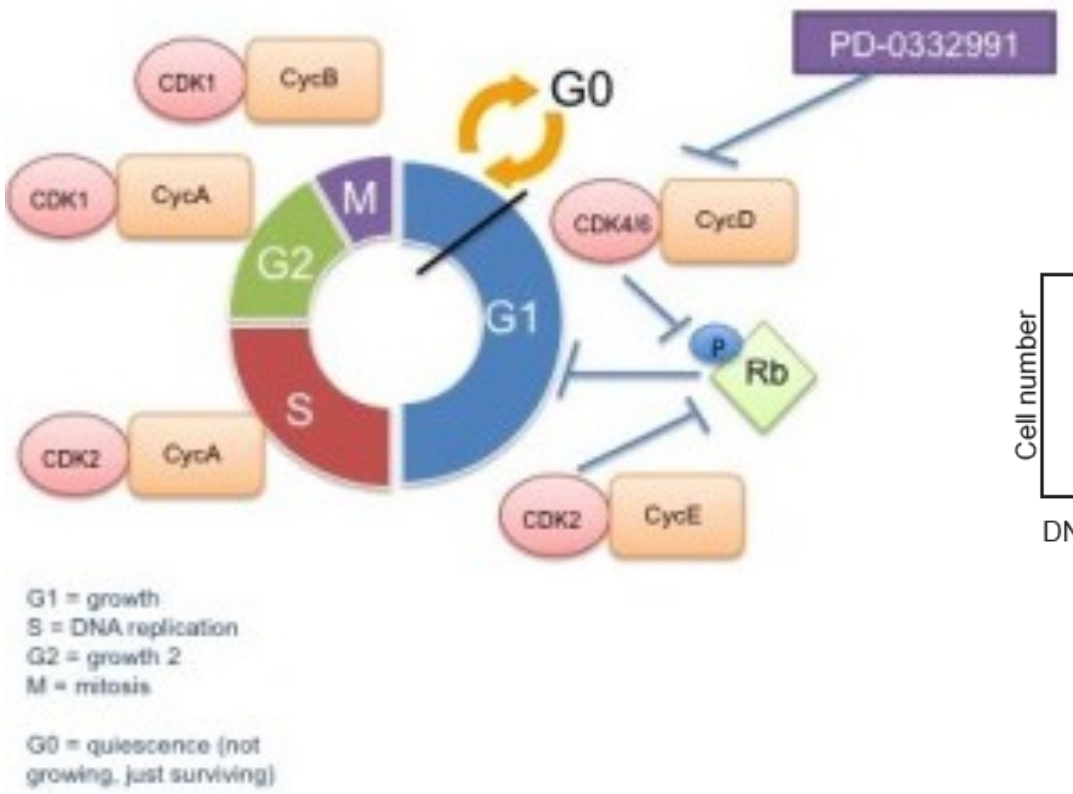
SIDE EFFECT: Immunosuppressant/ cardiac problem

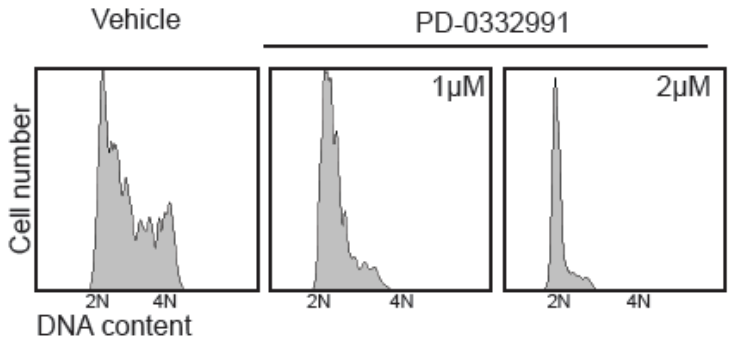
Cell Cycle


Mitogens
p16
pRB
E2F
CDK1
Cyclin B
CDK4/6
Cyclin D
M
CDK1/2
Cyclin A
G2
G1
S
P P P
pRB
CDK2
Cyclin E
E2F
S phase transcription program
G1/S transition

Cell Cycle Inhibition

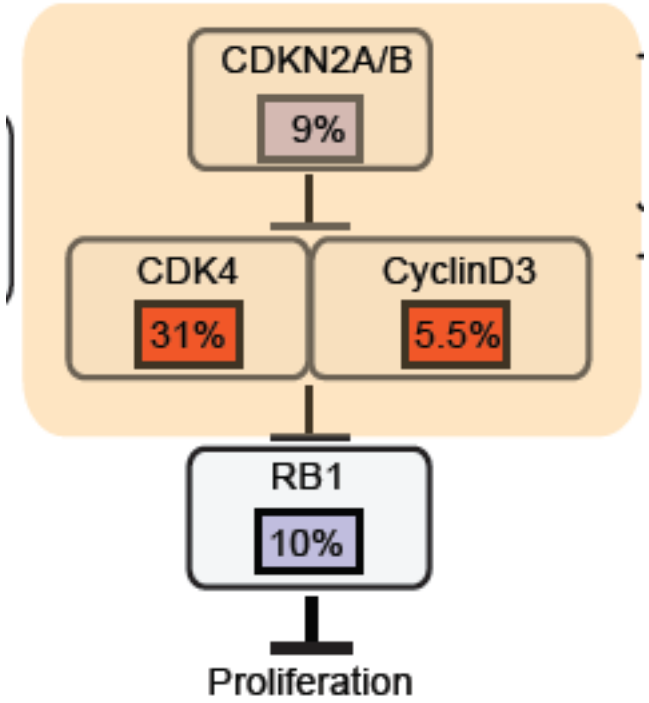
CDK4/6 Inhbitor : Palbociclib (PD0332991) approved for breast cancer 2015

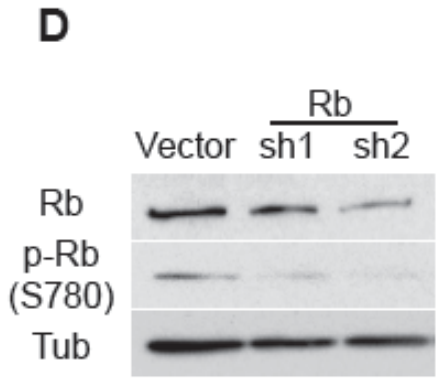


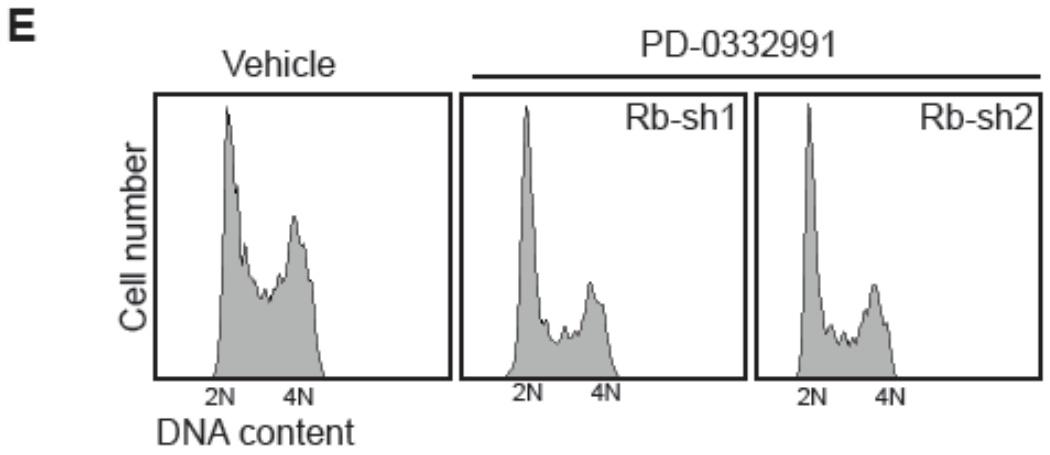


http://www.nature.com/nrd/journal/v14/n2/full/nrd4504.html

Cell Cycle Inhibition/Resistant Patients





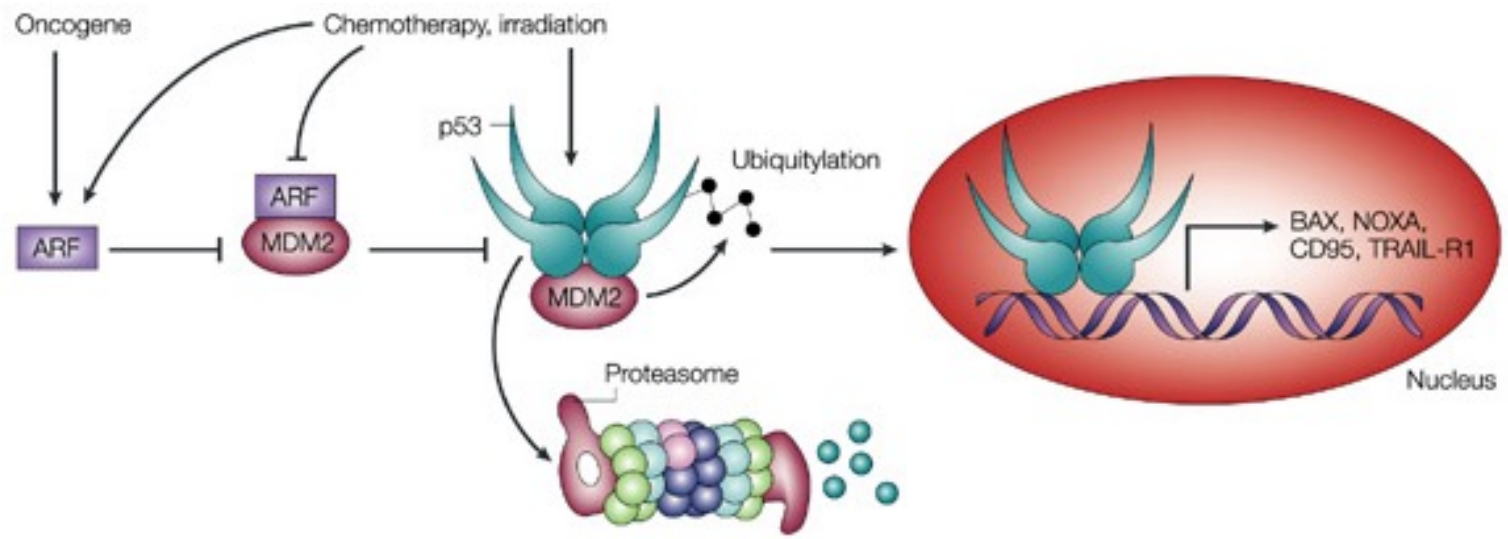


CAN WE TARGET p53?

Can we target tumor suppressor gene?

p53 is one of the most frequently mutated gene in cancer

Proteasome or MDM2 Inhibitors

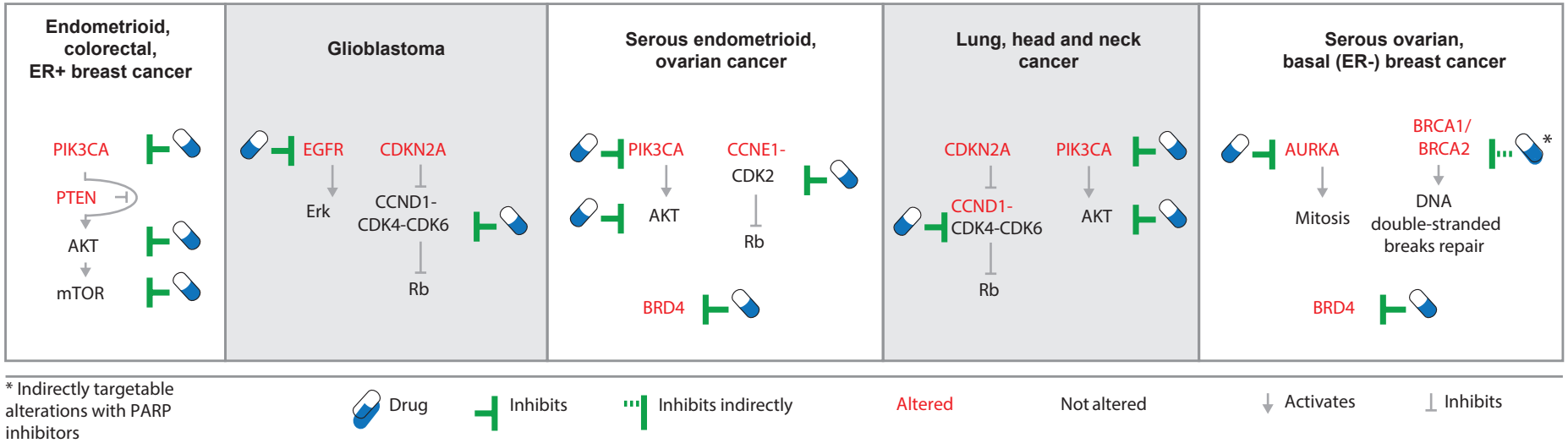


Nature Reviews | Cancer

Proteasome Inhibitor: BORTEZOMIB
Approve in 2003 for the treatment of Multiple Myeloma

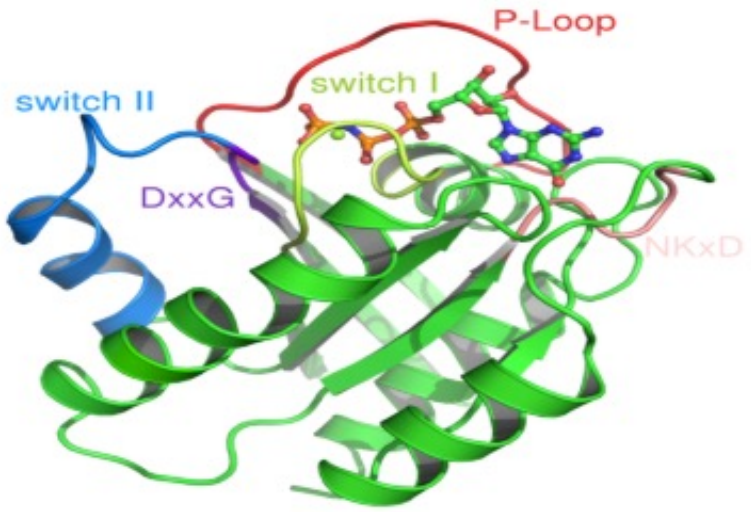
MDM2 inhibitor: Nutlins
Block the interaction between MDM2 and p53
Not approve for clinical use

RATIONAL COMBINATION THERAPIES

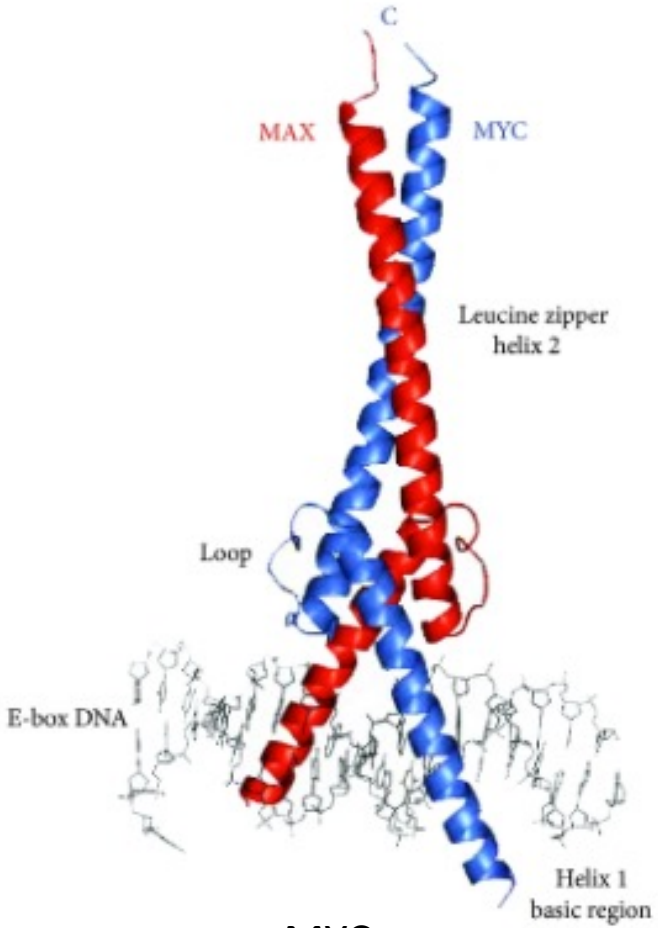


Ciriello et al. Nature Gen, 2013

UNDRUGGABLE ONCOGENES



RAS



MYC

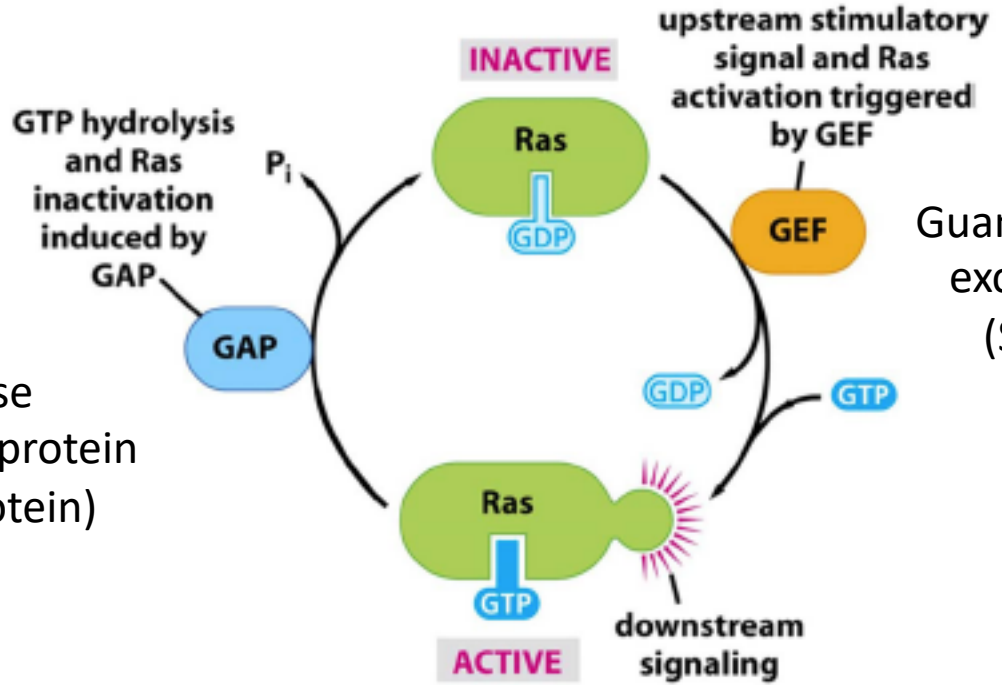
RAS: Oncogene

Ras is a family of proteins including K-RAS, H-RAS, N-RAS

GTPase protein: use GTP to transmit the signal

H-RAS: Harvey sarcoma virus
K-RAS: Kirsten sarcoma virus

*The C-terminal of the protein is **lipid-modified***



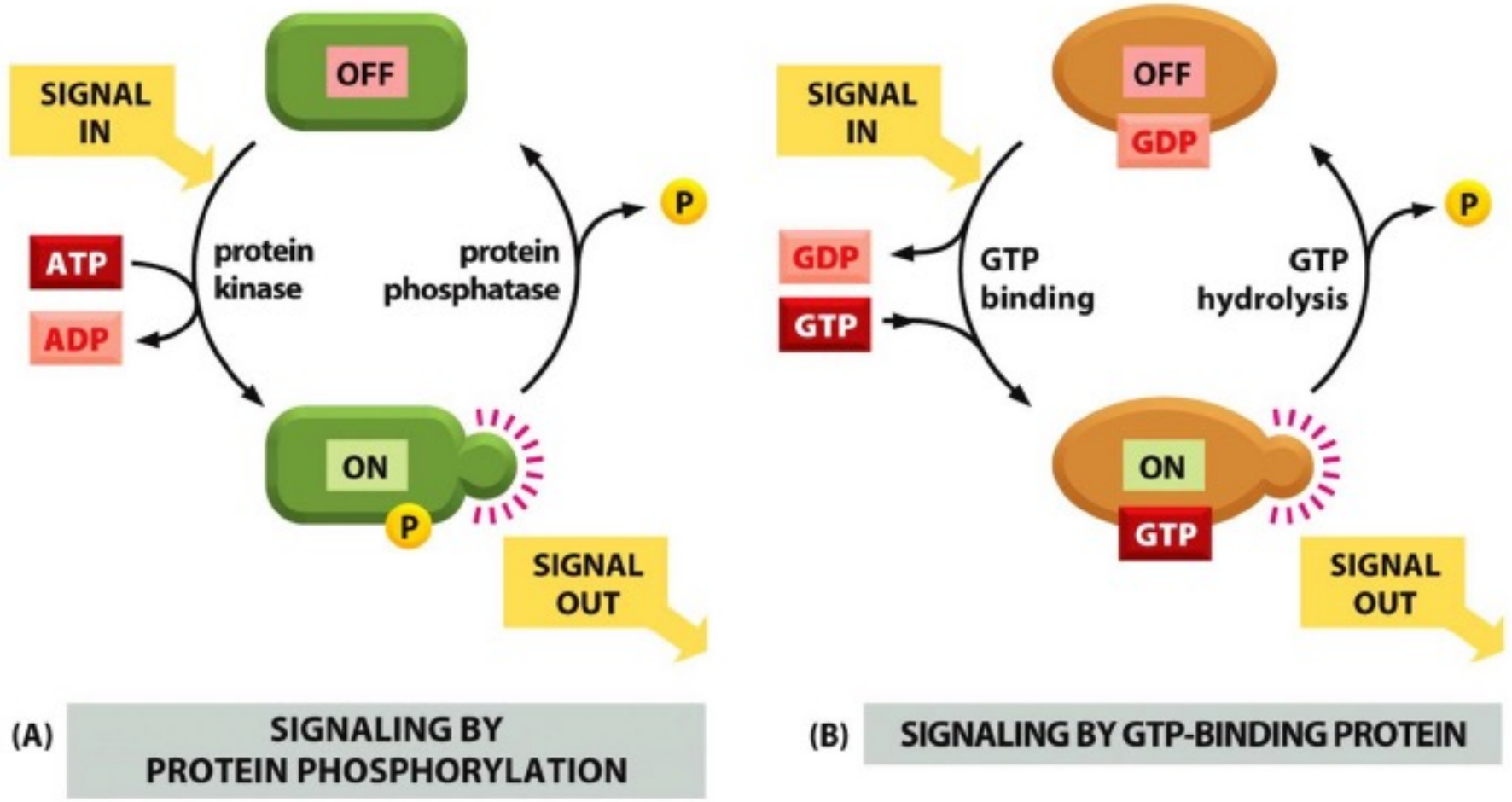
Guanine nucleotide exchange factors (SOS protein)

GTPase activating protein (NF1 protein)

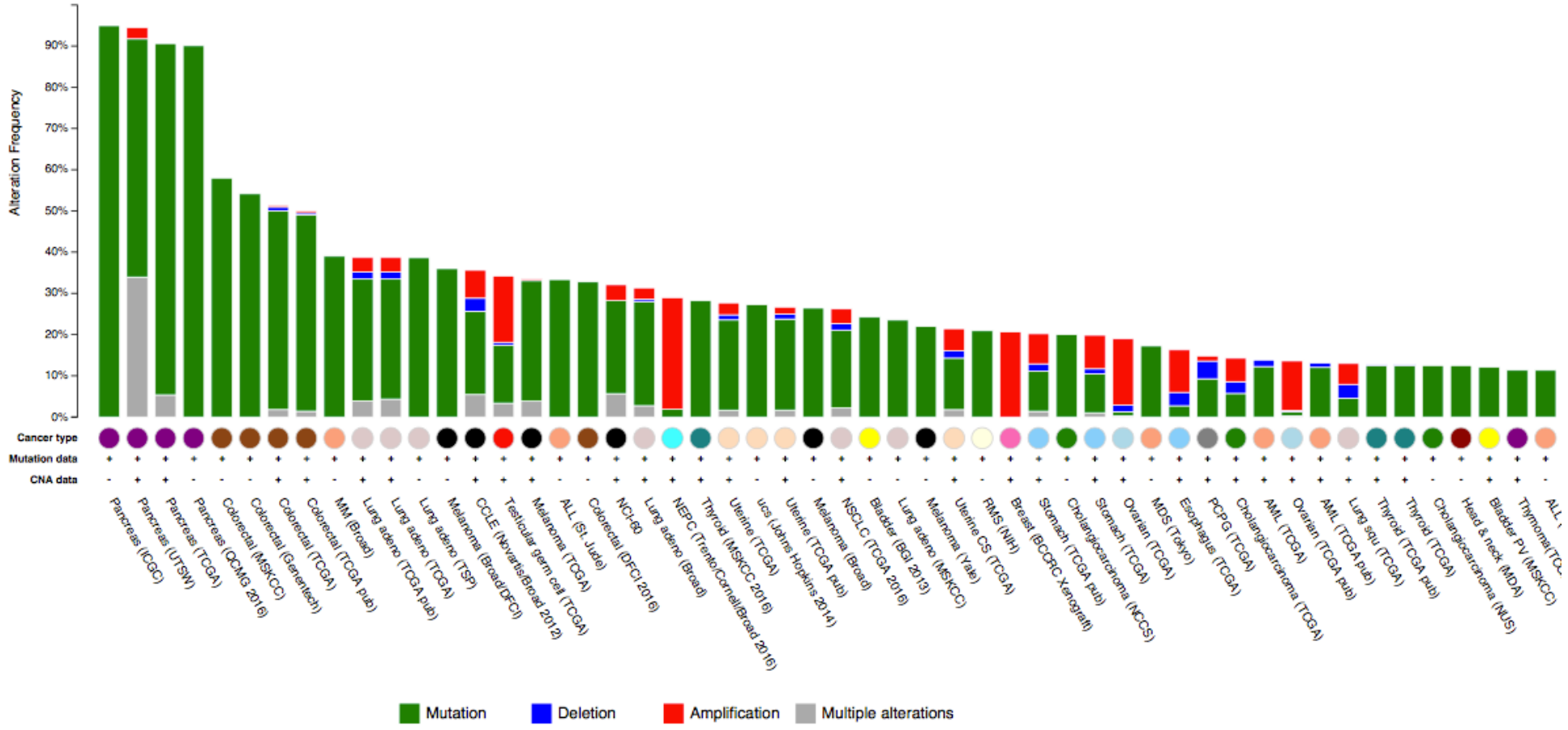
ATP or GTP

Kinase transmission signal

RAS-GTPase signal

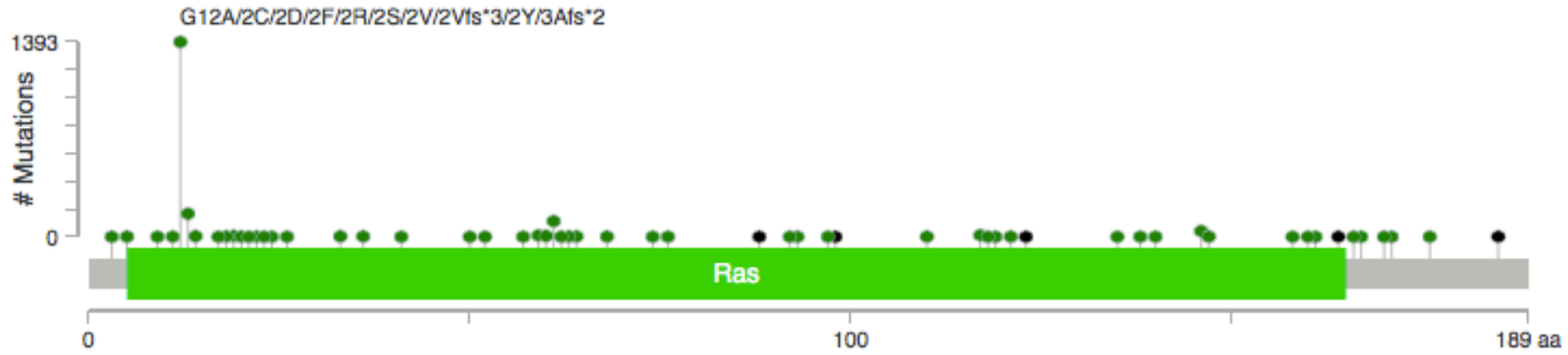


RAS alterations in tumors

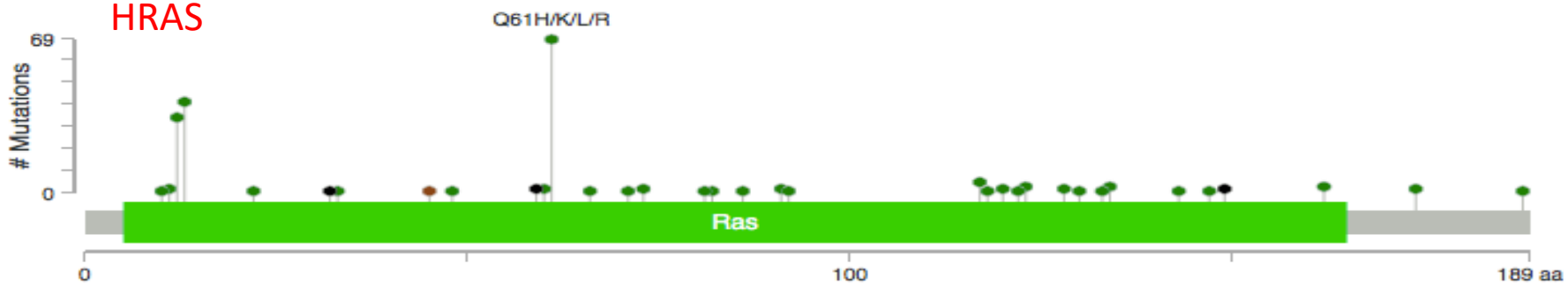


RAS hotspot mutations

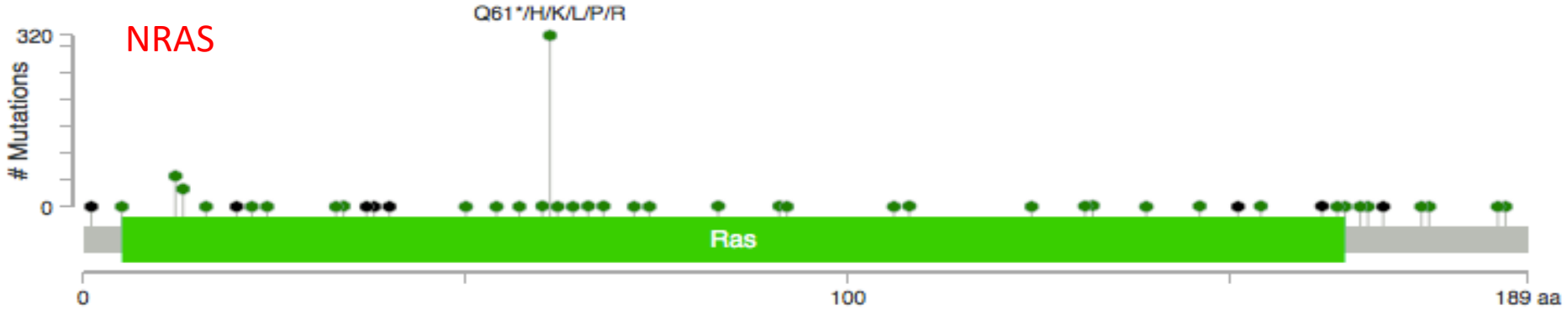
K-RAS mutation G12V



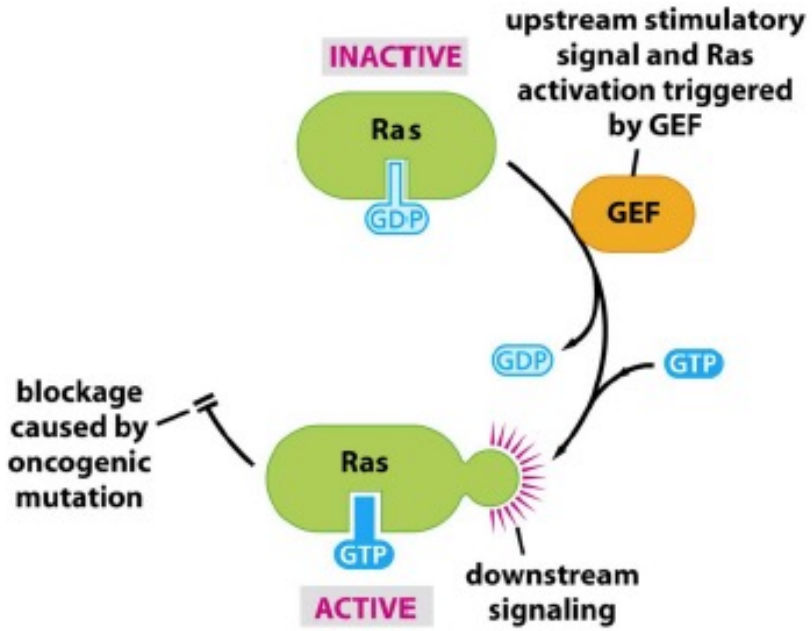
HRAS

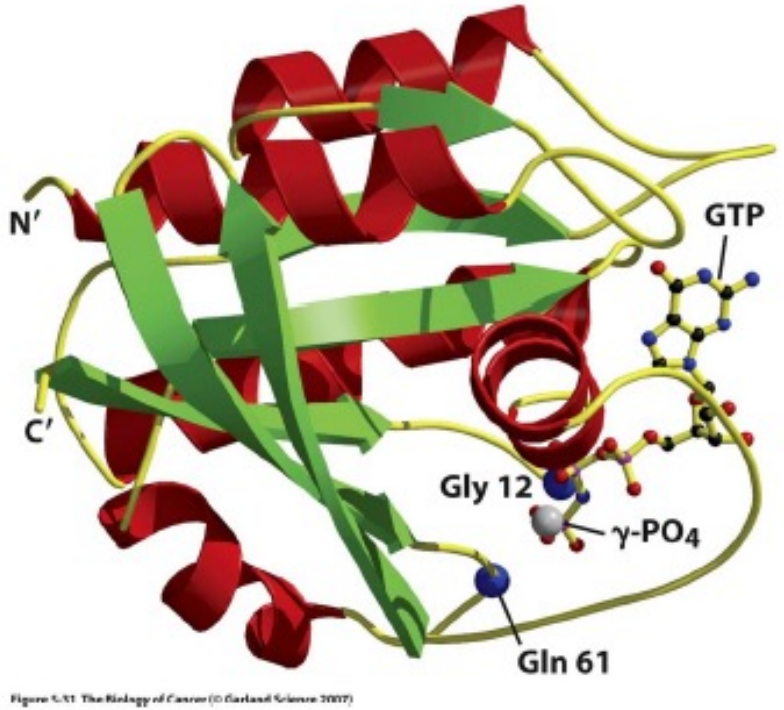


NRAS



RAS hotspot mutations maintains the protein in a constitutive active form





- Gly12 and Gln61 interact with GTP
- mutations in either of these residues block GTP hydrolysis

RAS downstream signals

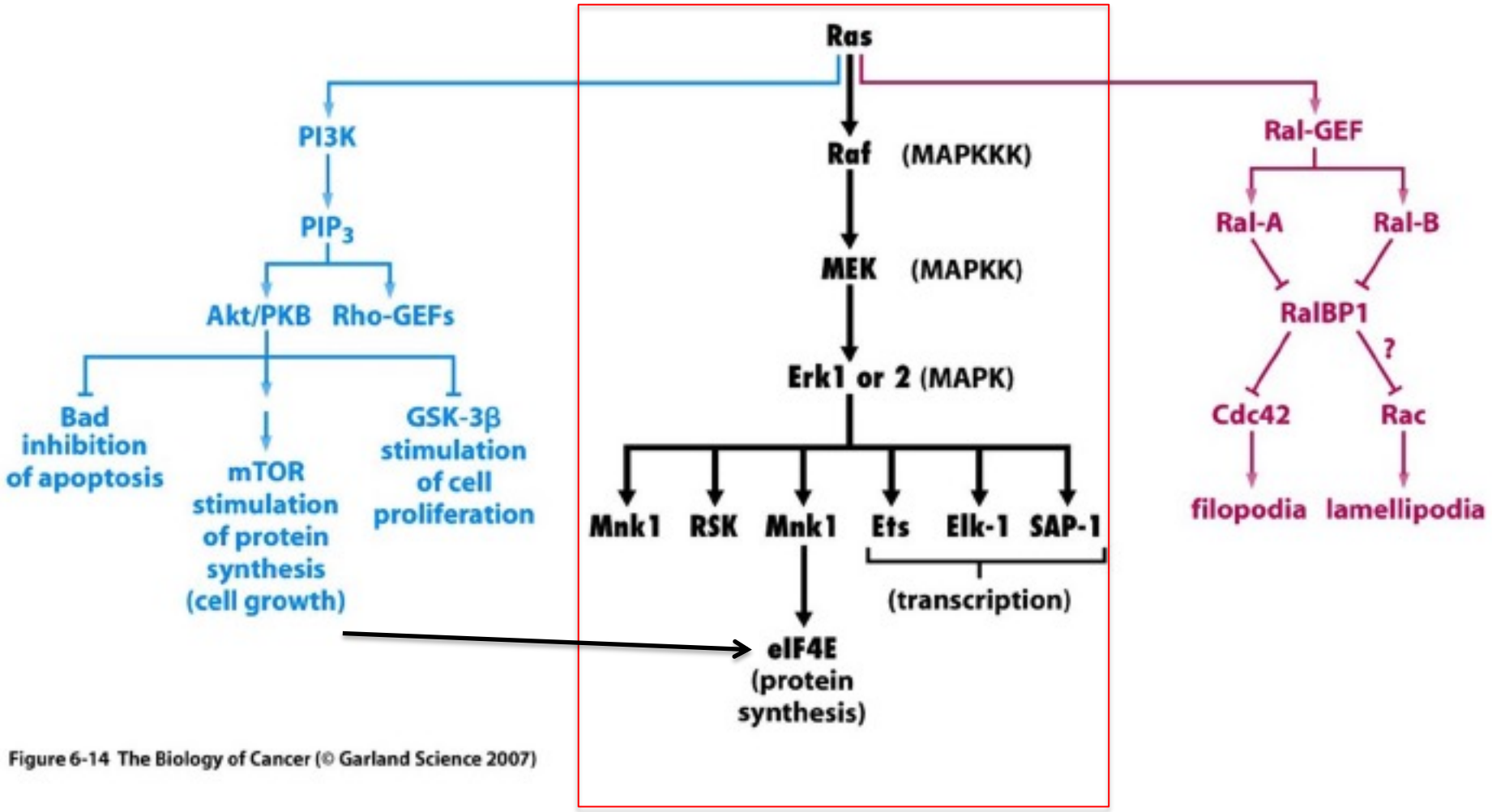
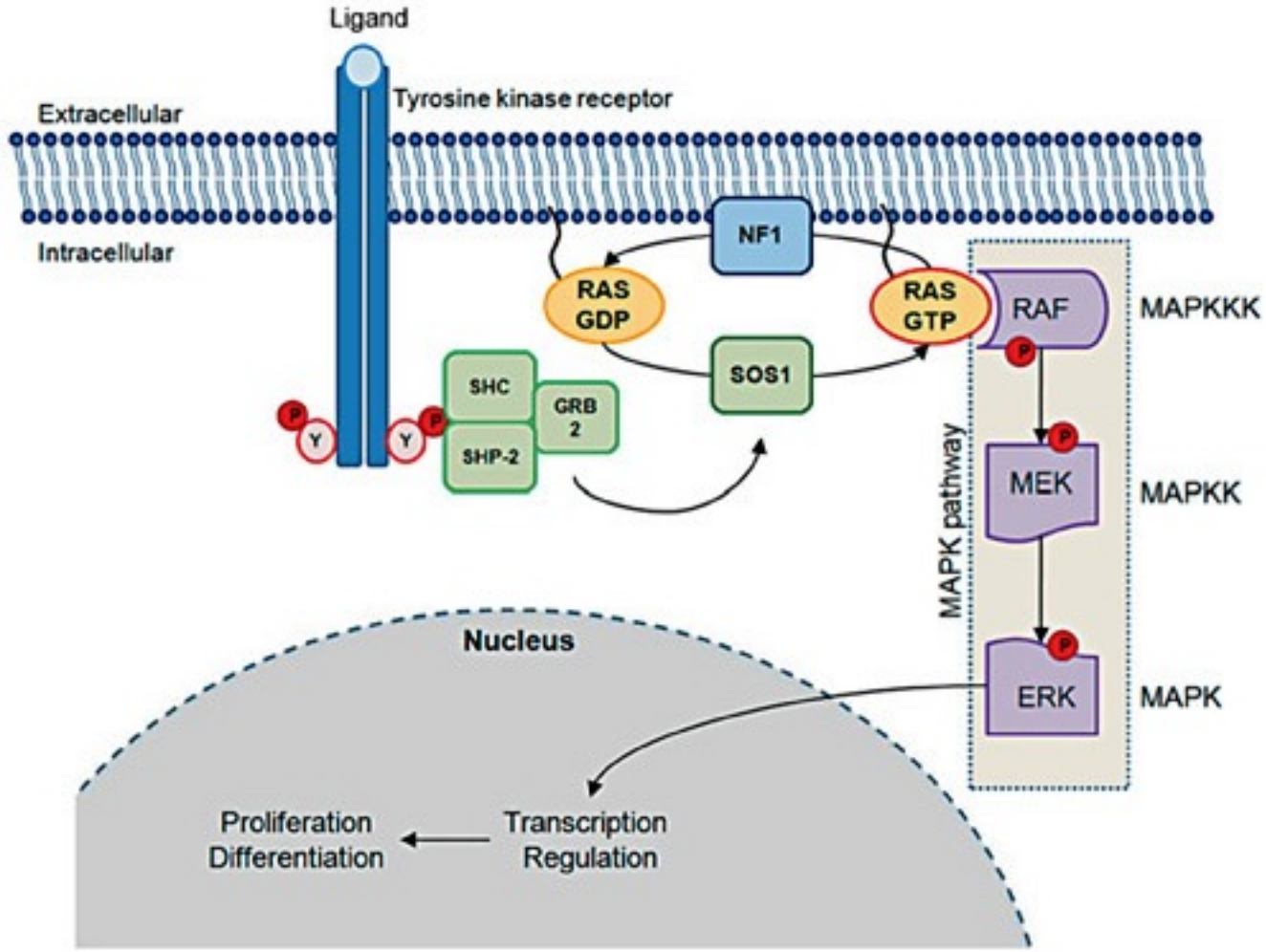
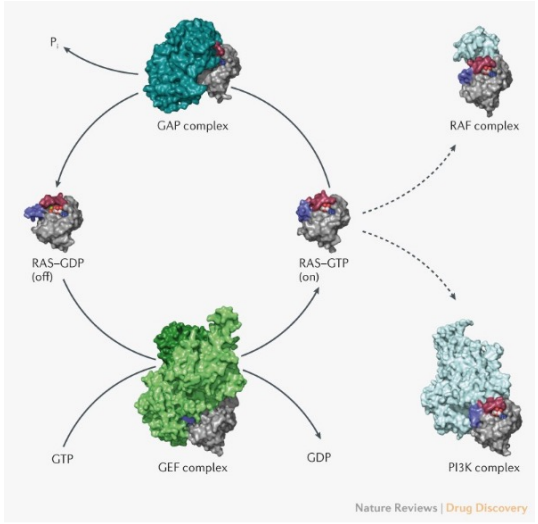


Figure 6-14 The Biology of Cancer (© Garland Science 2007)

RAS and MAPK signaling



UNDRUGGABLE ONCOGENES : RAS



The RAS Initiative

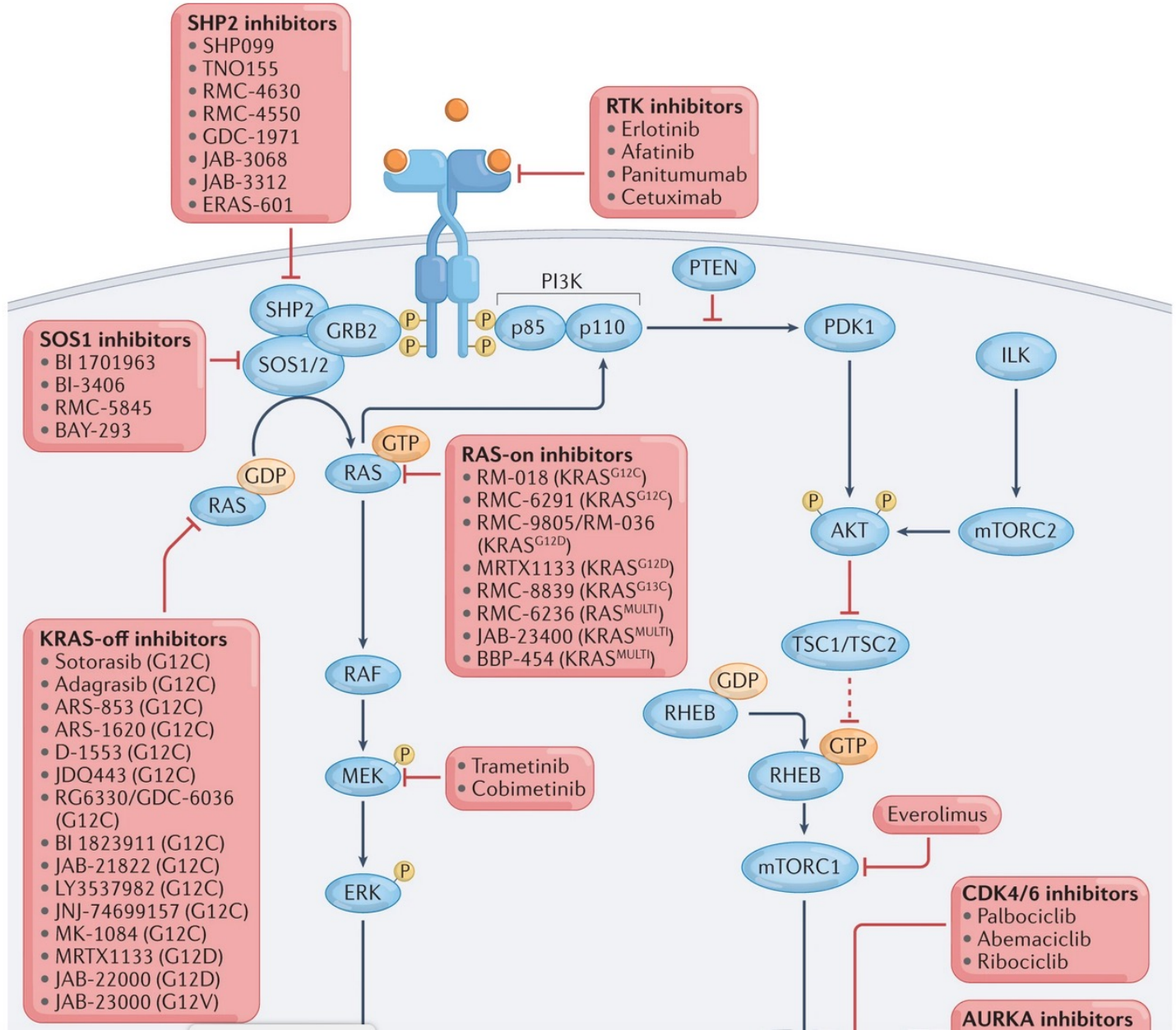
More than 30 percent of all human cancers – including 95 percent of pancreatic cancers and 45 percent of colorectal cancers — are driven by mutations of the *RAS* family of genes. NCI established the RAS initiative in 2013 to explore innovative approaches for attacking the proteins encoded by mutant forms of *RAS* genes and to ultimately create effective, new therapies for *RAS*-related cancers.

TABLE 1 | SELECT KRAS PROGRAMMES

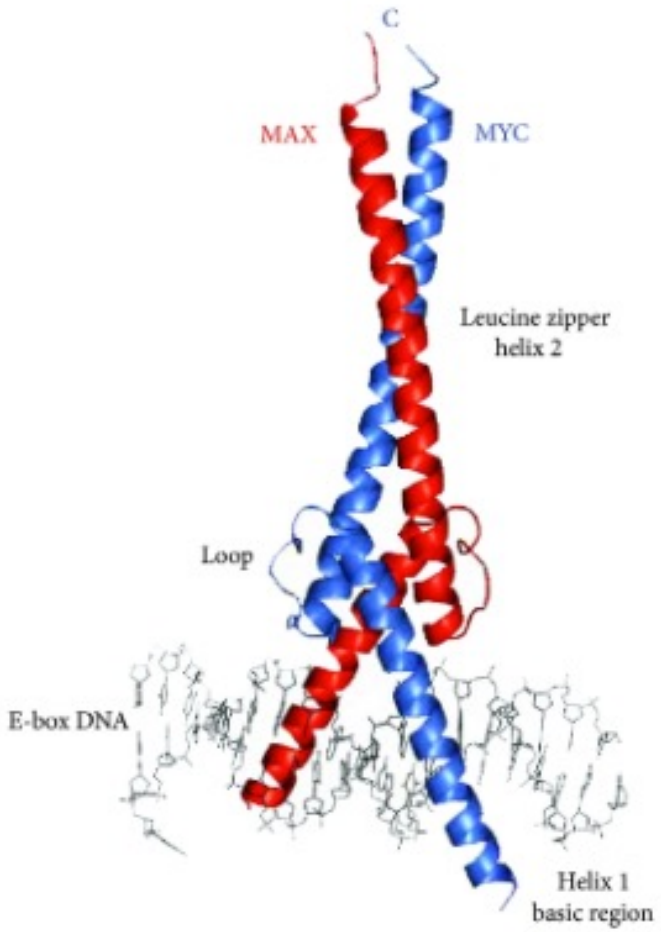
Drug	Company	Properties	Status
AMG 510	Amgen	G12C inhibitor[a]	Phase I/II, monotherapy and with PD1 blocker
MRTX849	Mirati Therapeutics	G12C inhibitor[a]	Phase I/II
JNJ-74699157/ ARS-3248	J&J and Wellspring Biosciences	G12C inhibitor[a]	Phase I
BI 1701963	Boehringer Ingelheim	KRAS–SOS1 inhibitor	Phase I, monotherapy and with MEK inhibitor trametinib
mRNA-5671	Moderna Therapeutics	Cancer vaccine for G12C, G12D, G13D, G12V	Phase I, monotherapy and with PD1-blocker pembrolizumab
G12D inhibitor	Mirati Therapeutics	G12D inhibitor	IND-enabling studies in 2020
RAS(ON) inhibitors	Revolution Medicines	Tri-complex inhibitors of mutated GTP-bound KRAS	Preclinical
NA	Bayer	KRAS–SOS1 inhibitor	Preclinical
NA	Sanofi/X-Chem	G12C inhibitor	Preclinical
NA	X-Chem	G12C inhibitor, for active and inactive KRAS	Preclinical
BBP-454	BridgeBio Pharma	Pan-KRAS inhibitors	Preclinical

Fig. 1: The RAS signalling pathway and therapeutic approaches to target this pathway in cancer.

From: The current state of the art and future trends in RAS-targeted cancer therapies



UNDRUGGABLE ONCOGENES

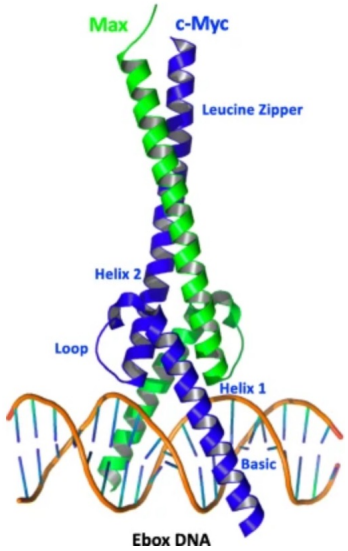


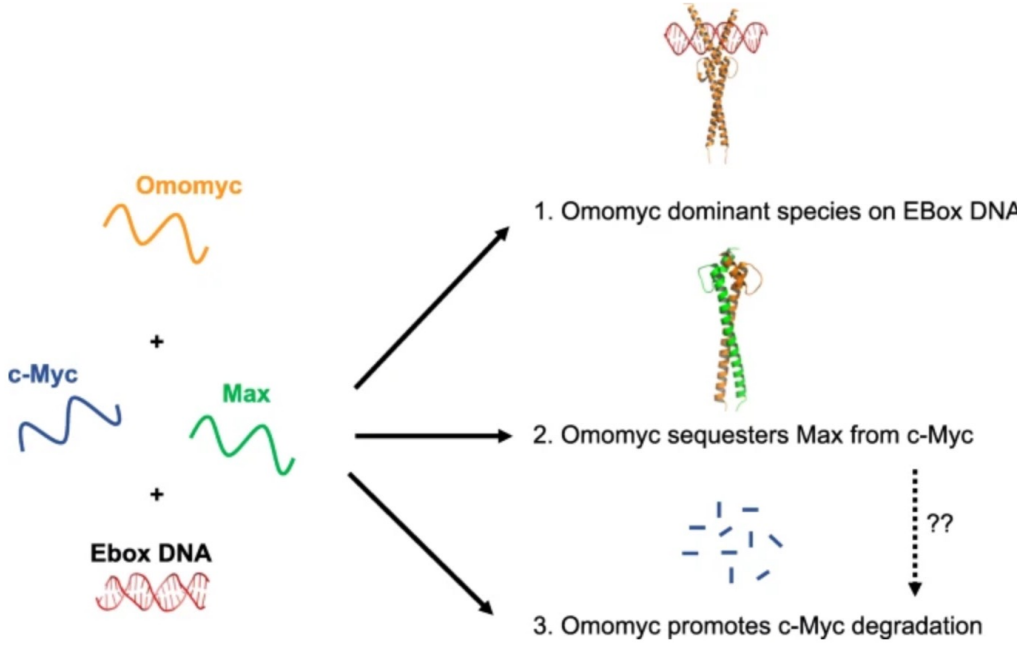
MYC

Targeting MYC

Currently, no drugs are available

A genetic construct called OMOMYC was developed as a peptide inhibitor

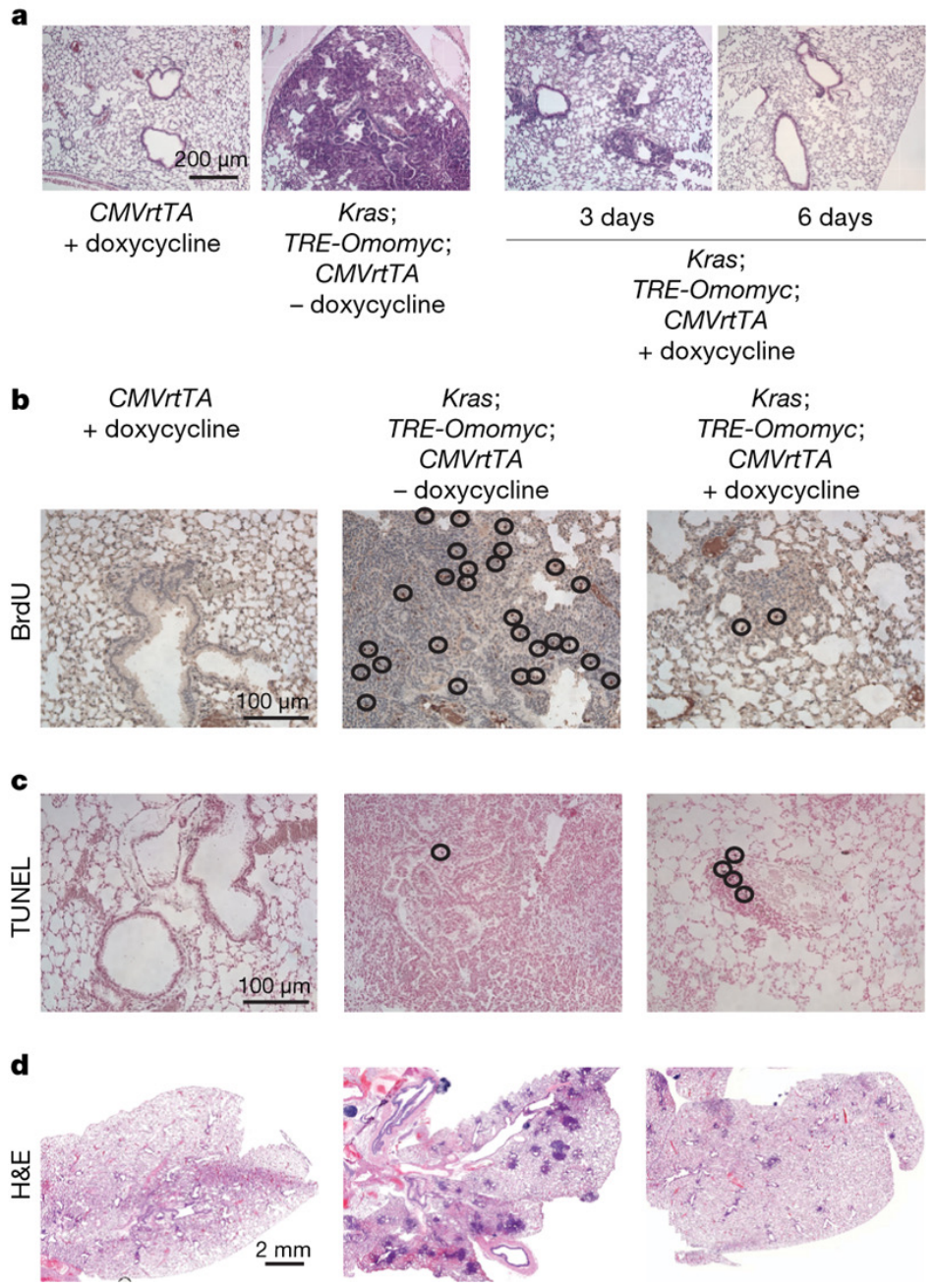




› Cancer Res. 2002 Jun 15;62(12):3507-10.

Omomyc, a potential Myc dominant negative, enhances Myc-induced apoptosis

Laura Soucek [1], Richard Jucker, Laura Panacchia, Ruggero Ricordy, Franco Tatò, Sergio Nasi



L Soucek *et al. Nature* **000**, 1-5 (2008) doi:10.1038/nature07260

OMOMYC clinical trail

Phase 1/2 Study to Evaluate Safety, PK and Efficacy of the MYC-Inhibitor OMO-103 in Solid Tumours (MYCure)

ClinicalTrials.gov Identifier: NCT04808362

Recruitment Status : Active, not recruiting
First Posted : March 22, 2021
Last Update Posted : September 28, 2022

View this study on Beta.ClinicalTrials.gov

Sponsor:
Peptomyc S.L.

Information provided by (Responsible Party):
Peptomyc S.L.

Study Description

Go to

Brief Summary:
This study is an open label, two-part, First in Human (FIH) Phase 1/2 dose-finding study designed to determine the safety, tolerability, Pharmacokinetics (PK), Pharmacodynamics (PD) and proof-of-concept (POC) of OMO-103 in patients with advanced solid tumours.

Condition or disease	Intervention/treatment	Phase
Advanced Solid Tumors	Biological: OMO-103	Phase 1
NSCLC		Phase 2
Triple-negative Breast Cancer		
CRC		

Exercises

https://www.nature.com/articles/s41586-019-1694-1