

Cancer Bio Course

Session 1: Introduction to course and basic techniques applied in basic cancer research

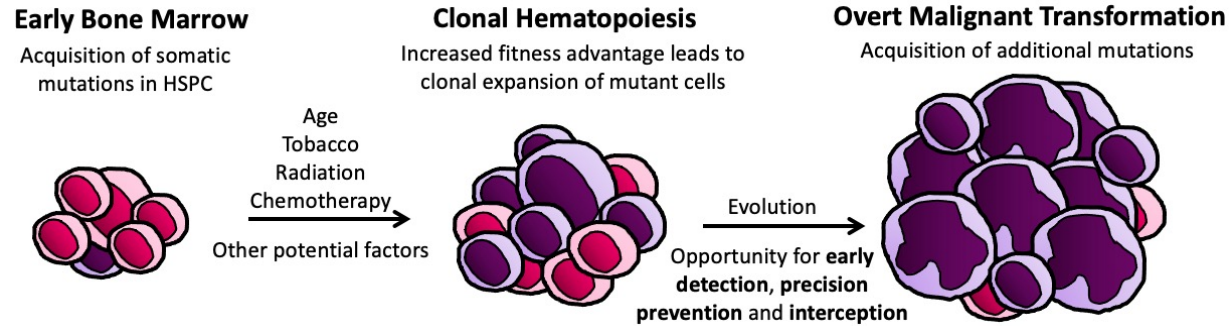
August 7th, 2024



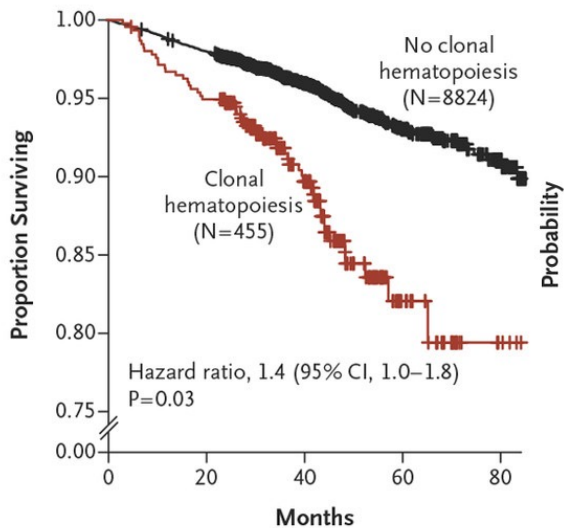
Memorial Sloan Kettering
Cancer Center

Pablo Sánchez Vela, MD
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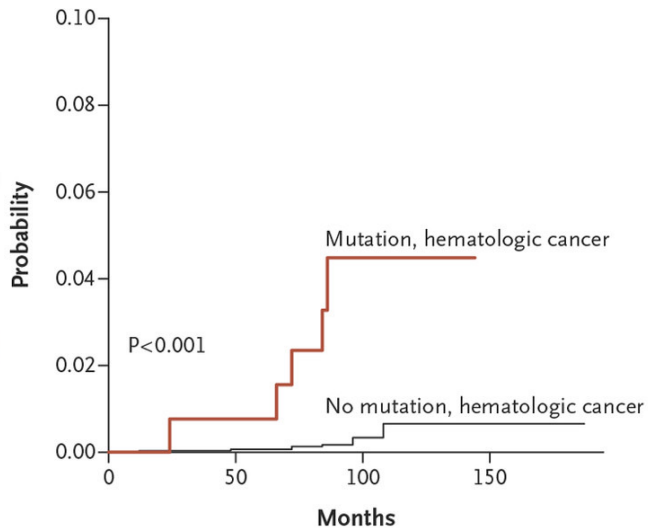
Questions I decided to tackle during my time at MSK



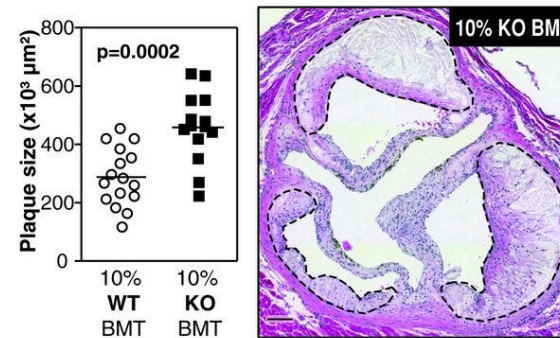
Genovese et al. NEJM 2014
Overall Mortality



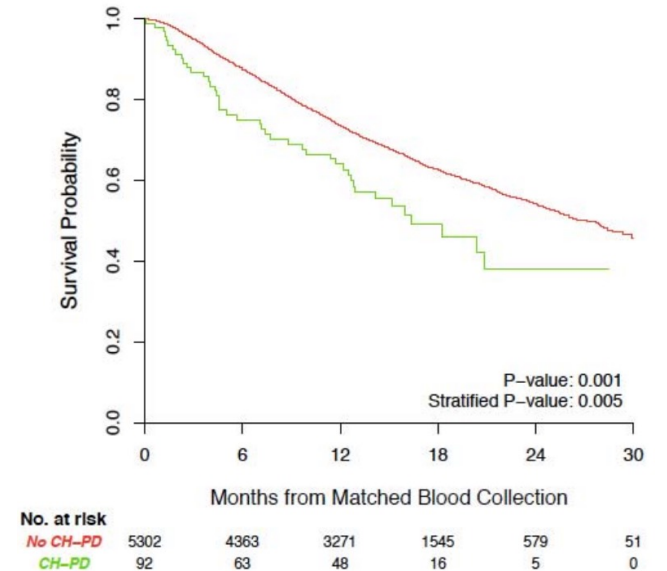
Jaiswal et al. NEJM 2014
Hematologic Malignancies



Fuster et al. Science 2017
Cardiovascular Disease



Coombs et al. CellStemCell 2017
Solid Tumors



Course structure

Scientific topics covered will include:

- Cancer as a disease
- Genetic and epigenetic mechanisms
- Computational biology and oncology
- Cancer signaling
- Cancer metabolism
- Metastasis
- Tumor modeling and heterogeneity
- Cancer types and microenvironments

This course will:

- Provide a review of advanced concepts in cancer biology
- Expose students to techniques and experimental design applied to basic-translational cancer research
- Potentiate the ability to perform critical analysis of basic-translational research
- Strengthen capacities to develop a research project

**RECORDED
LECTURES**

**IN-PERSON
ACTIVITIES**

Course structure

In-person activities:

- Session 1 – Introduction to course and basic techniques applied in basic cancer research

- Session 2 – Paper discussion
- Session 3 – Paper discussion
- Session 4 – Paper discussion

- Session 5 – Guided live research activity

- **Explanation of the question under research - why on earth did they decide to do this?**
- **Discussion figure by figure – is this paper not as good as authors think?:**
 - What is the point of each figure/panel?
 - Are there any missing experimental conditions?
 - Are results interpretable?
 - Do the results support the conclusions by the authors?
 - Would you have done anything differently?
 - Are there any missing experiments?
 - What are the limitations of the work?
 - What experiments could be done as a follow-up to the paper?

Cancer Cell
Article

The Genomic Landscape of Endocrine-Resistant Advanced Breast Cancers

Pedram Razavi,^{1,2} Matthew T. Chang,^{1,2,3} Guotai Xu,^{1,2} Chaitanya Bandlamudi,¹ Dara S. Ross,⁴ Neil Vasani,^{1,2} Yaryan Cai,⁵ Craig M. Beisak,^{1,2} Mark T.A. Donoghue,¹ Philip Jonsson,^{1,2} Alexander Persson,^{1,2} Hengsha Shen,^{1,2} Frestia Parajuli, Biksha Kundra,¹ Samit Mishra,¹ Michael L. Cheng,¹ Ahmet Zehir,¹ Carlos Kandoth,¹ Huzha Patel,¹ Kelly Huberman,⁴ Lillian M. Smyth,¹ Komal Jhaveri,¹ Sharu Modi,¹ Tiffany A. Traina,¹ Chau Dang,¹ Wen Zhang,¹ Britta Weigelt,^{1,2} Bob T. Li,² Marc Ladanyi,^{1,2} David M. Hyman,¹ Nicholas Schmitt,^{1,2} Mark E. Robinson,¹ Clifford Hudis,^{1,2} Ed Brogi,¹ Agnes Viale,^{1,2} Larry Norton,¹ Maura N. Dickler,¹ Michael F. Berger,^{1,2} Christine A. Iacobuzio-Donahue,^{1,2} Sarat Chandrasekhar,^{1,2} Maurizio Scarlatti,^{1,2} Jorge S. Reis-Filho,^{1,2} David B. Sella,^{1,2,3} Barry S. Taylor,^{1,2,3} and Joshi Basalgia^{1,2,3}

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https://doi.org/10.1016/j.ccr.2018.08.008

CellPress
Article

Lung adenocarcinoma promotion by air pollutants

https://doi.org/10.1016/j.ccr.2018.08.008
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Published online 5 April 2023
Check for updates

William Hill^{1,2}, Emilia L. Liu^{1,2,3,4}, Clare E. Weeden^{1,2}, Claudia Lee^{1,2}, Marcellina Augustina^{1,2}, Kaizhong Chen¹, Feng-Chen Kuan², Fabio Marongiu², Edward J. Evans Jr.², David A. Moore^{1,2}, Felipe S. Rodrigues¹, Onof Pichl¹, Bjorn Bakker¹, Hongqi Cha^{1,2}, Renelle Myers^{1,2}, Febe van Malsbergen^{1,2}, Jesse Boumetta¹, Selvaraju Venkai¹, Andrew Rowan¹, Cristina Naeve Lombardelli¹, Takahiro Karasaka^{1,2}, Monica Sivakumar¹, Sureshmani De¹, Debobish R. Chatterjee¹, Arunagiri¹, James R. M. Blaud^{1,2}, Carlos Martinez-Ruiz^{1,2}, Min Hyung Ryu^{1,2}, Ryan D. Huff^{1,2}, Shijia Liu^{1,2}, Mario-Julia Fava¹, Alastair Magnusson¹, Alejandro Salazar-Bonilla^{1,2}, Shiron L. Pridemore^{1,2}, Margaret Lightenberg^{1,2}, Katrina Lovell¹, Frances Petrick¹, Steven Hardy¹, Fiona E. McRonald¹, Meng-Hung Lin¹, Clara I. Troccoli¹, Mounira Ghosh¹, York E. Miller¹, Daniel T. Merritt¹, Robert L. Keith^{1,2}, Mouna Al-Bakri¹, Chris Bailey¹, Mark S. Hill¹, Leo H. Saal^{1,2}, Yilin Chen^{1,2}, Anthony M. George^{1,2}, Christopher Abbosh¹, Nirmalya Karu¹, Se-Hoon Lee¹, Nicholas McCranahan¹, Christine D. Berg¹, Peter Rasmussen¹, Richard Houston¹, Claire Turnbull¹, Stephen Lam¹, Philip Bendall¹, Eva Orntoft¹, Julian Downward¹, Tyler Jacka^{1,2}, Christopher Carlsson¹, Maria Malanchi¹, Allan Hackshaw¹, Kevin Litchfield¹, TRACE2 Consortium¹, James DeGroot^{1,2}, Marian Jamal-Hanjani^{1,2,3,4} & Charles Swanton^{1,2,3,4}

RESEARCH BRIEF

Jak2^{V617F} Reversible Activation Shows Its Essential Requirement in Myeloproliferative Neoplasms

Andrew J. Dunbar^{1,2,3}, Robert L. Bowman¹, Young C. Park¹, Kavi O'Connor¹, Franco Izzo^{4,5}, Robert M. Myers^{4,5}, Abdul Karim¹, Zachary Zarogian¹, Won Jun Kim¹, Inés Fernández-Maestre^{1,2}, Michael R. Waarts^{1,2}, Abbas Nazir¹, Wenbin Xiao¹, Tamara Coddipati¹, Max Brodsky^{1,2}, Mirko Farina^{1,2}, Louise Gaji¹, Shang F. Cao^{1,2}, Benjamin Wang¹, Wenbin Ansh¹, Julie L. Yang^{1,2}, Sitron Mowla¹, Shira E. Elman¹, Amritha Varshini Hanasoge Somasundara¹, Jacob L. Glass^{1,2,3}, Tanmay Mishra¹, Remis Houston¹, Emily Guzzardi¹, Anthony R. Martinez Benitez¹, Aaron D. Viny^{1,3}, Richard P. Koche^{1,2}, Sara C. Meyer^{1,4}, Dan A. Landau^{4,5}, and Ross L. Levine^{1,2,3,12}

Course evaluation

Class participation and attendance (33%)

- All scholars are expected **to attend all sessions**. A scholar must notify the Bridge team and instructor prior to class if they will absent. This notice should be sent by email.

Take Home (67%)

- A research question (project) will be assigned to you, in groups of 2-3 people.
- You will have to propose a series of experiments to address that research question (i.e. a light version of the Research Strategy section of a grant) – **Max. 2 pages**
- **Due date is September 18th, 2024**
- Your work will be reviewed and feedback will be provided **by October 2nd, 2024**. You will have the chance to made modifications according to the comments provided (**due October 15th, 2024**).
- Your revised work will be graded.

Course evaluation

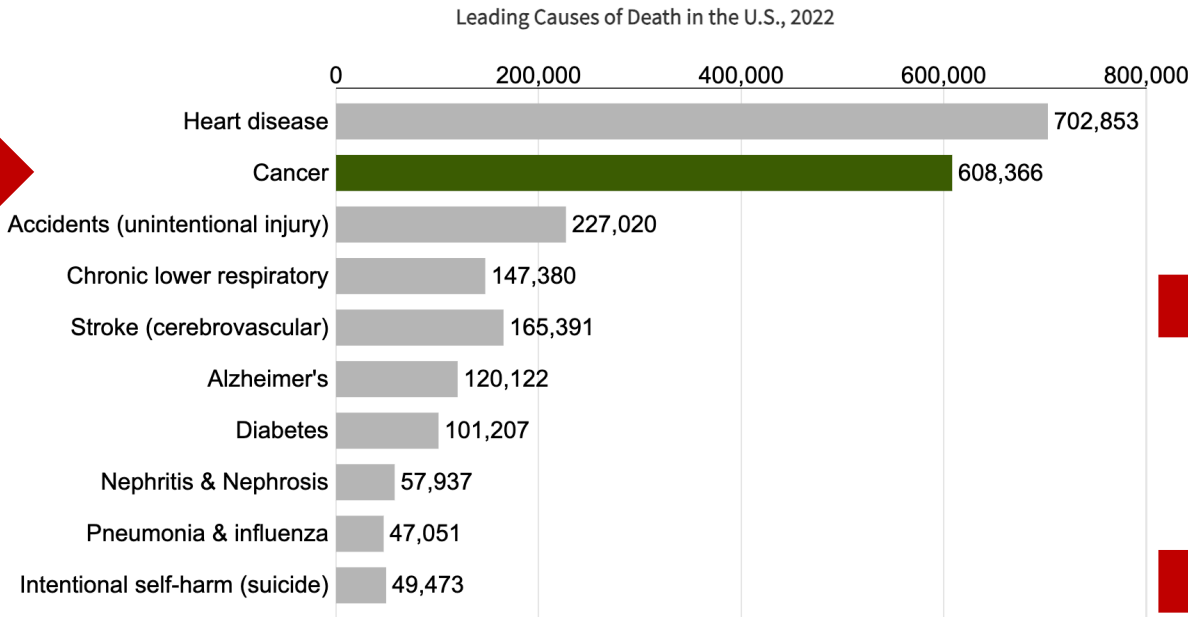
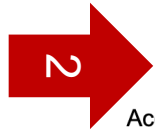
Letter Grade	Range
A	85-100
A-	82-85
B+	78-82
B	75-78
B-	72-75
C+	68-72
C	65-68
C-	62-65
F	<62



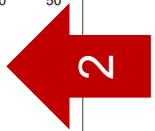
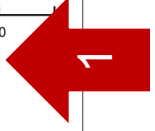
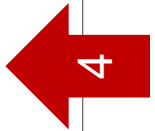
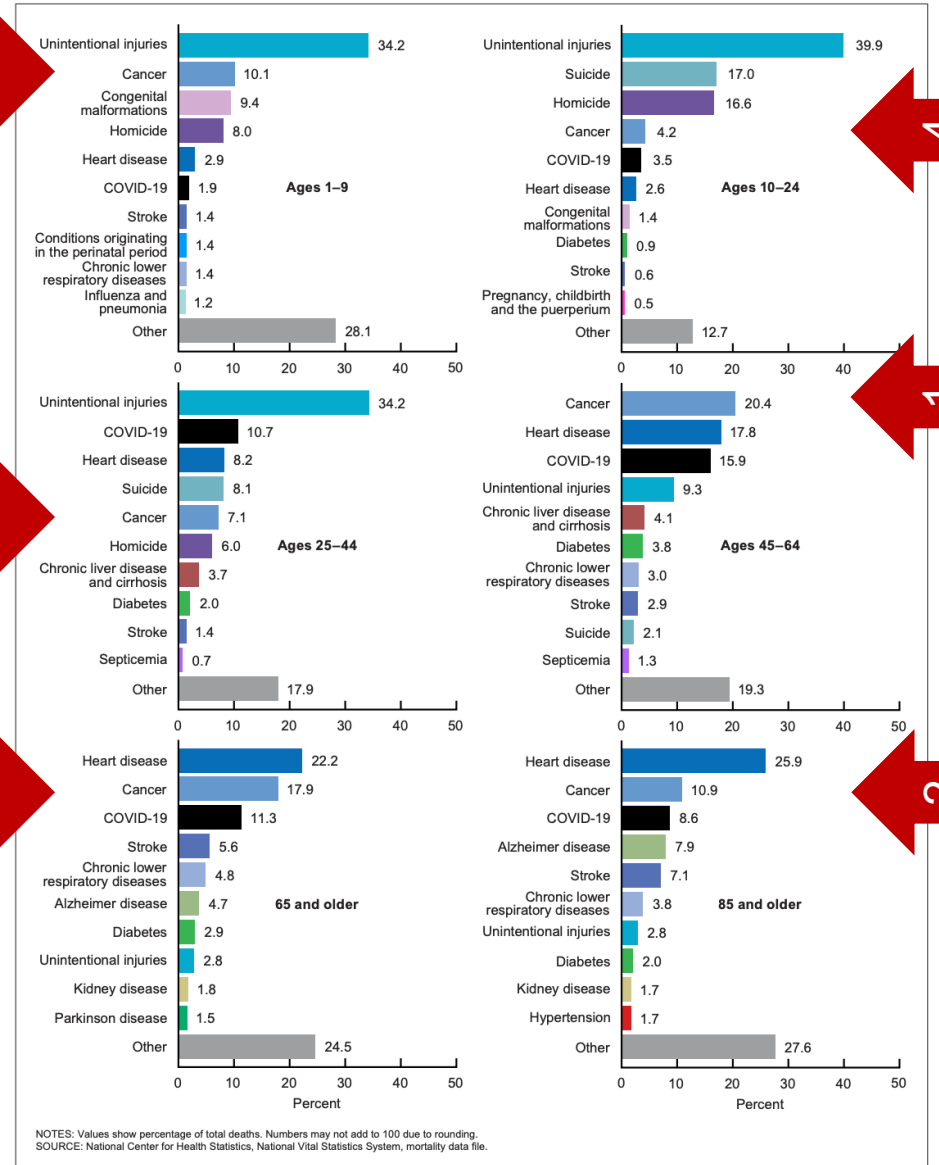
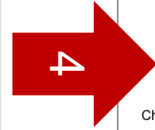
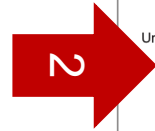
Cancer 101



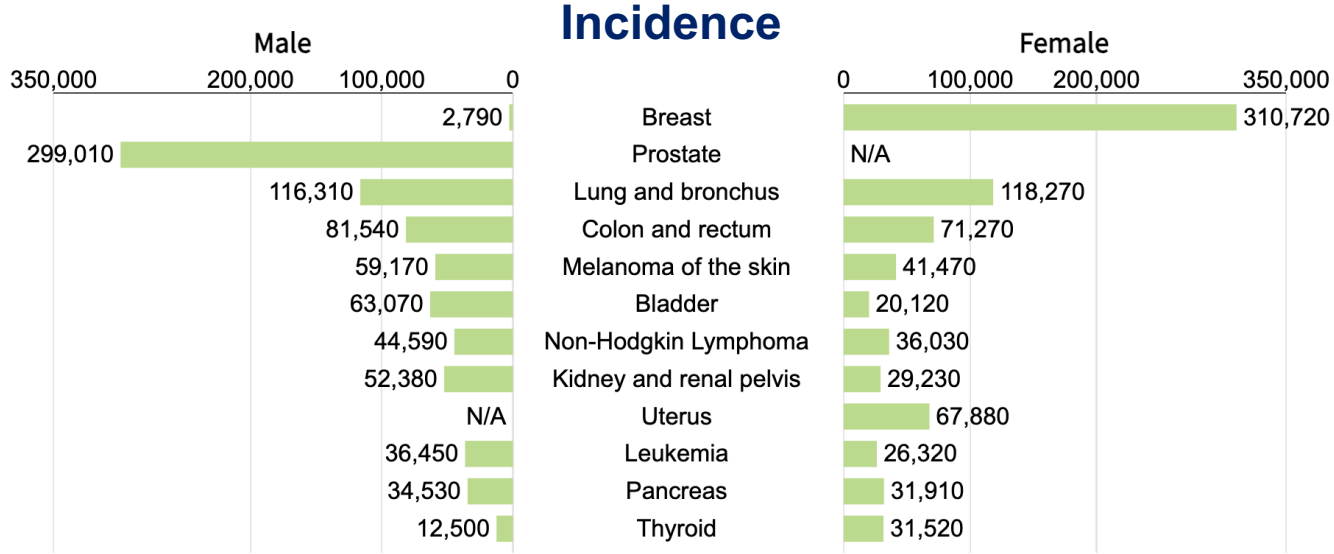
Cancer 101: Why do we study cancer?



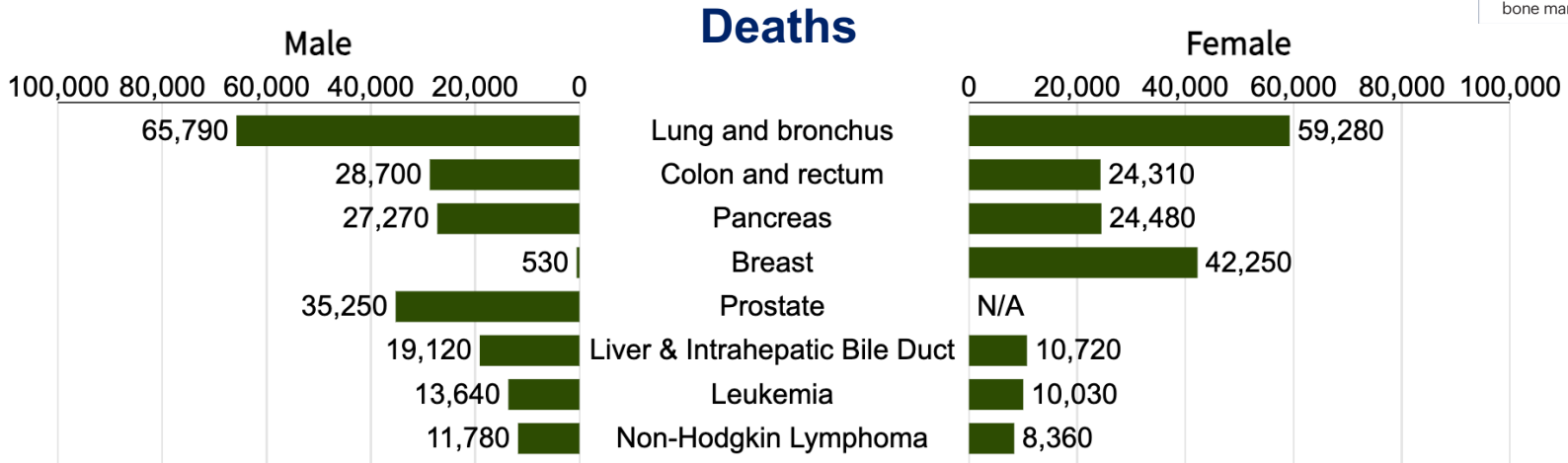
NCHS Data Brief, Number 492, December 2023



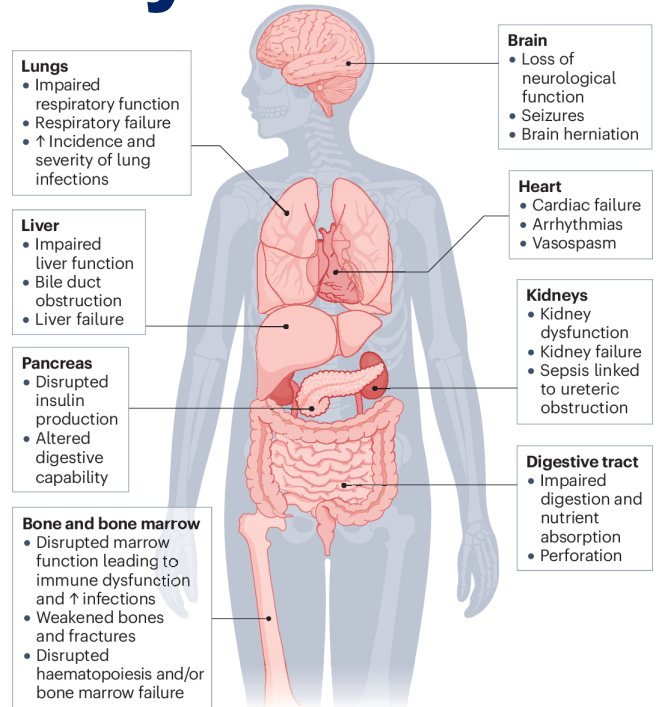
Cancer 101: Cancer diagnosis and mortality



Source: Cancer Facts & Figures 2024, American Cancer Society (ACS), Atlanta, Georgia, 2024.



Source: Cancer Facts & Figures 2024, American Cancer Society (ACS), Atlanta, Georgia, 2024.



Boire, A., Burke, K., Cox, T.R. *et al.* Why do patients with cancer die?. *Nat Rev Cancer* 24, 578–589 (2024).

2 types of treatment:
 - Local
 - Systemic

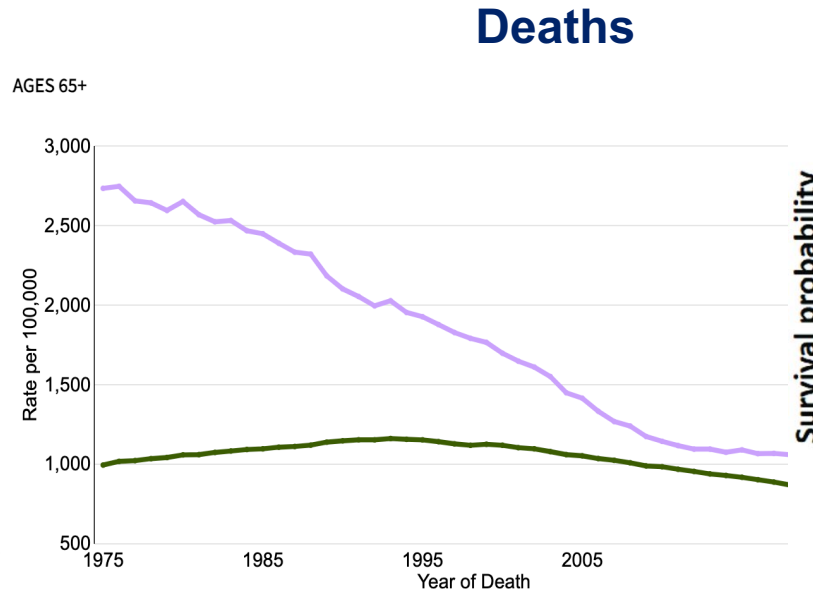
Cancer 101: How are we doing so far?



**Mr. Nixon:
You can
cure
cancer**

It proves we need to harness the power of the human genome. As we do this, there is not a doubt in the mind of the most sophisticated scientists that the cure for cancer will be found. Already, a great deal of research is being done to identify the genes that are involved in cancer. It is only a matter of time before we will have the tools to identify the genes that are involved in cancer. It is only a matter of time before we will have the tools to identify the genes that are involved in cancer. It is only a matter of time before we will have the tools to identify the genes that are involved in cancer.

Mary Lasker. Washington Post 1969

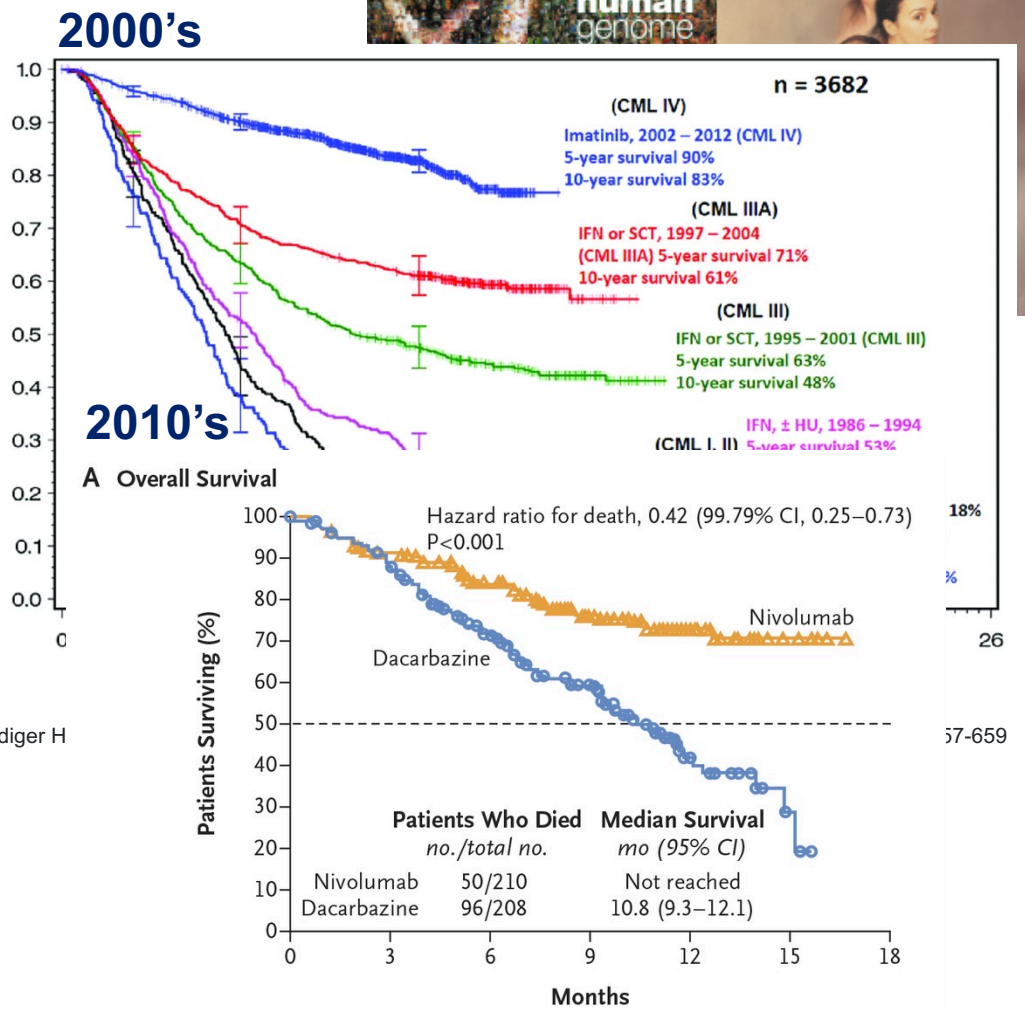


Source: U.S. Mortality Files, National Center for Health Statistics, Centers for Disease Control Rates are age-adjusted.



Richard Nixon. Rockefeller Research Laboratories, 1971

“Whether it was Cancer or Alzheimer’s or another condition [...] We clearly needed fundamental basic research to understand those diseases before we could hope to cure them.” — Benno Schmidt 1995



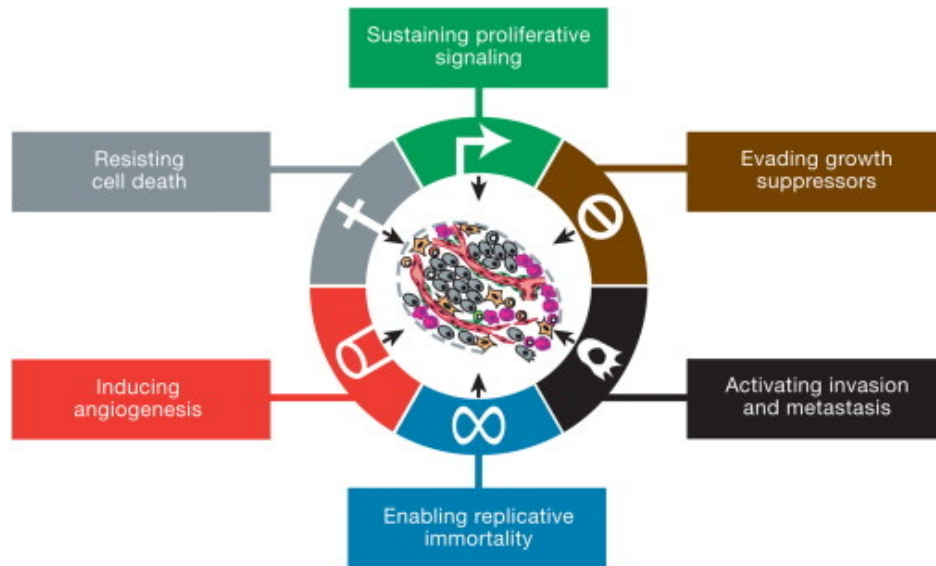
Rüdiger H

No. at Risk	210	185	150	105	45	8	0
Nivolumab	210	185	150	105	45	8	0
Dacarbazine	208	177	123	82	22	3	0

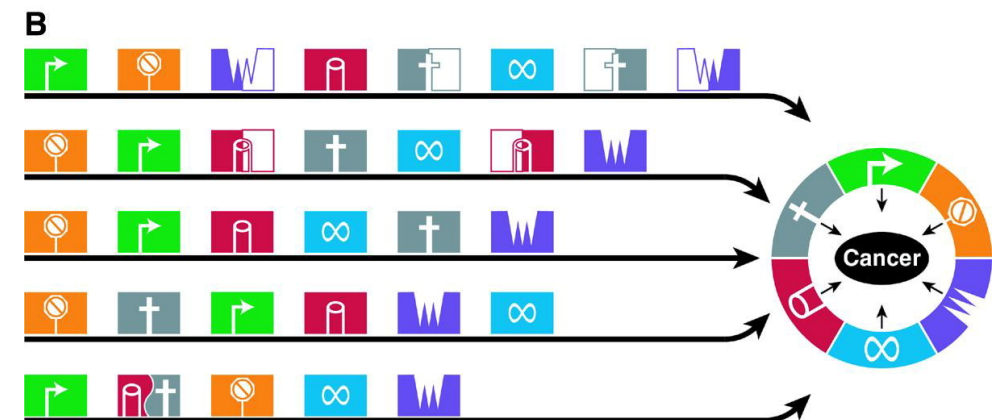
Robert C et al. N Engl J Med 2015;372:320-330

Cancer 101: What is a cancer cell?

“Cells”: Basic unit of life

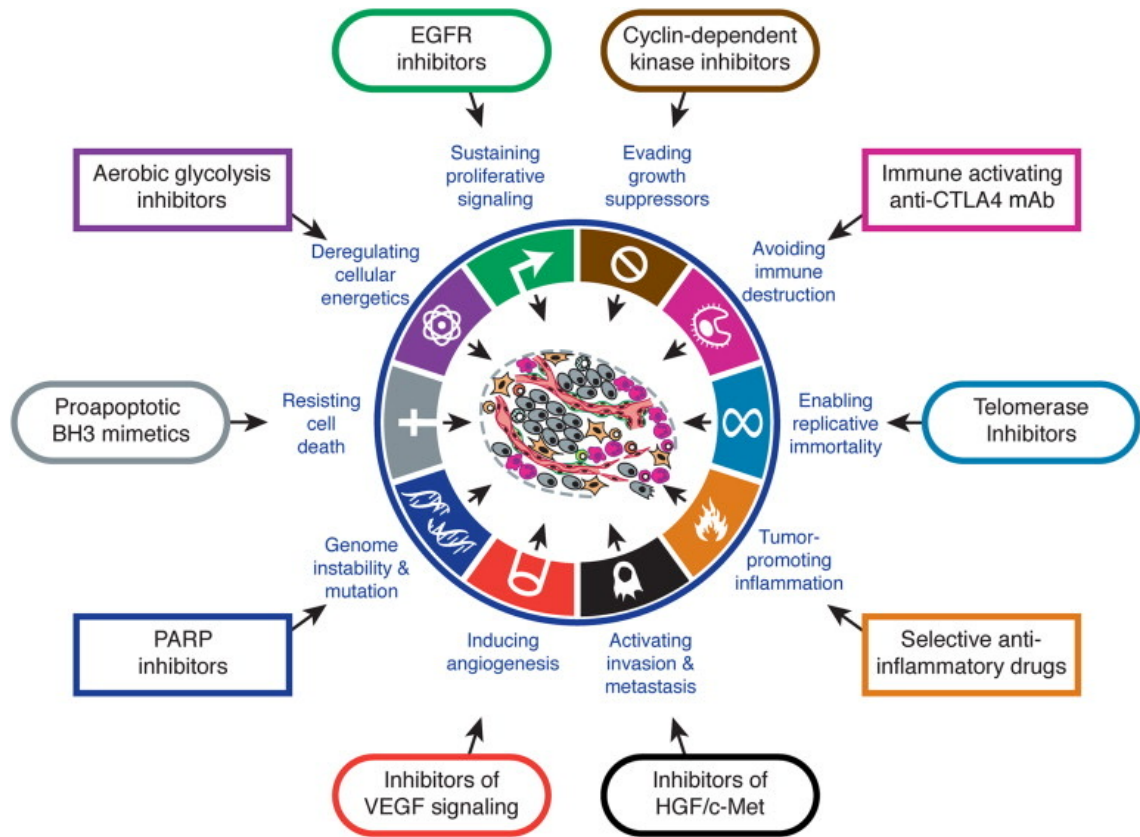


A	Component	Acquired Capability	Example of Mechanism
		Self-sufficiency in growth signals	Activate H-Ras oncogene
		Insensitivity to anti-growth signals	Lose retinoblastoma suppressor
		Evading apoptosis	Produce IGF survival factors
		Limitless replicative potential	Turn on telomerase
		Sustained angiogenesis	Produce VEGF inducer
		Tissue invasion & metastasis	Inactivate E-cadherin

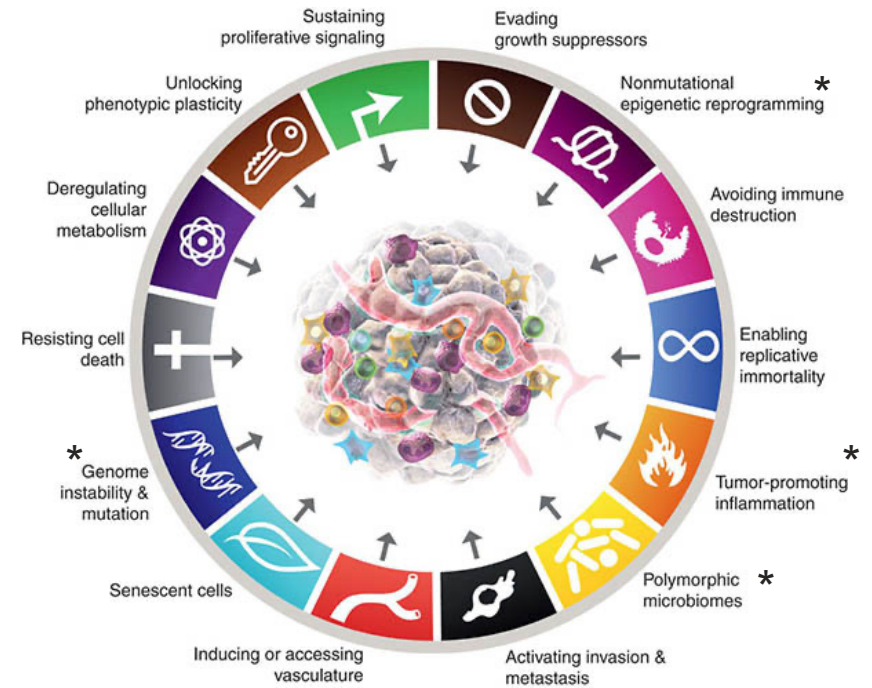


Cancer 101: What is a cancer cell?

“Cells”: Basic unit of life

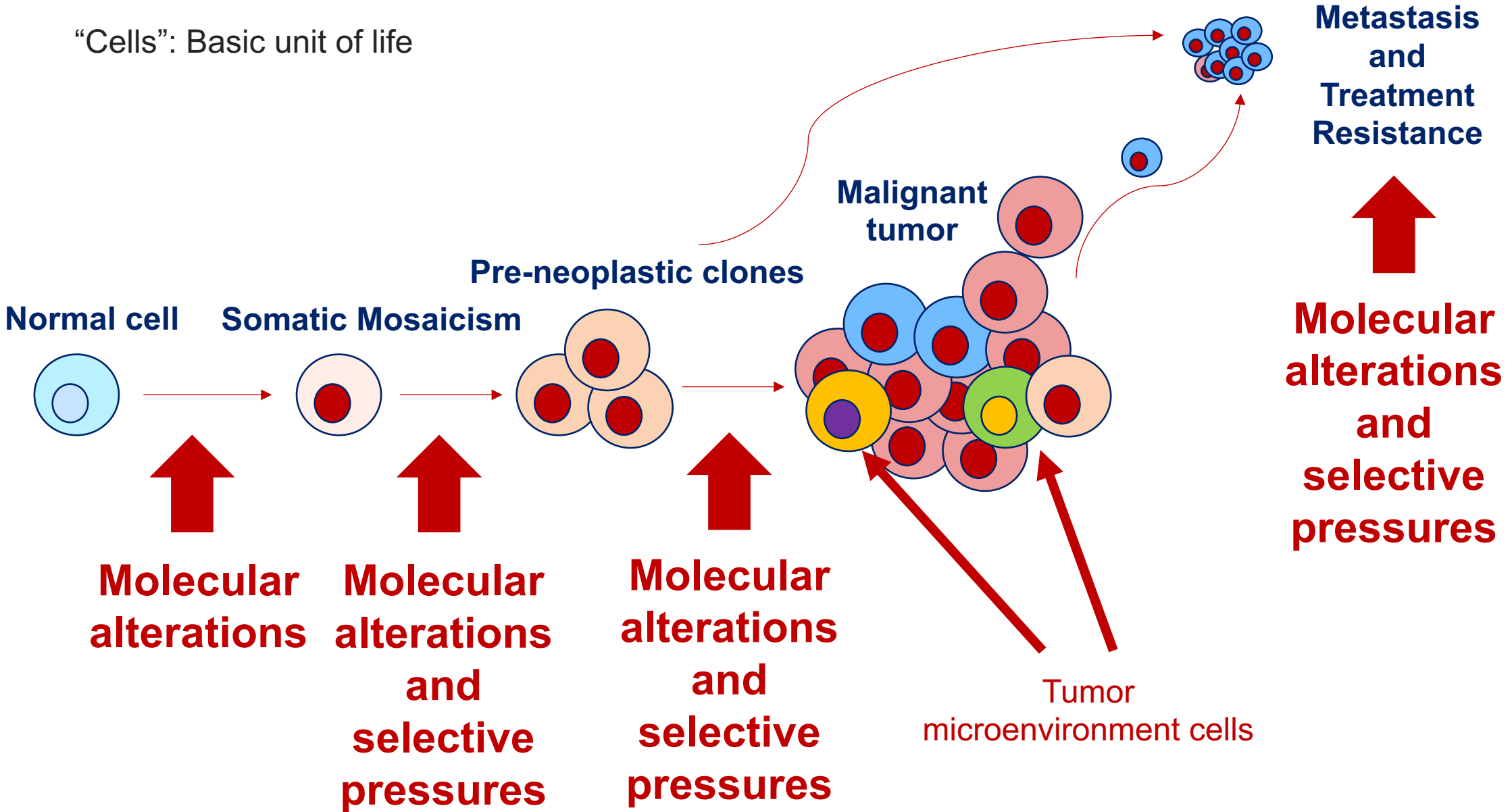


Cancer Hallmarks and Enabling Characteristics*



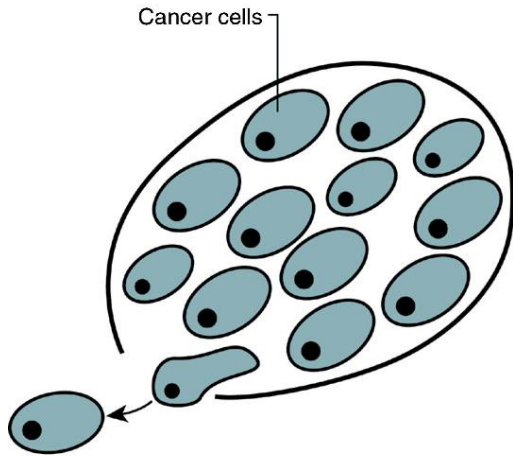
Cancer 101: Tumor evolution

“Cells”: Basic unit of life

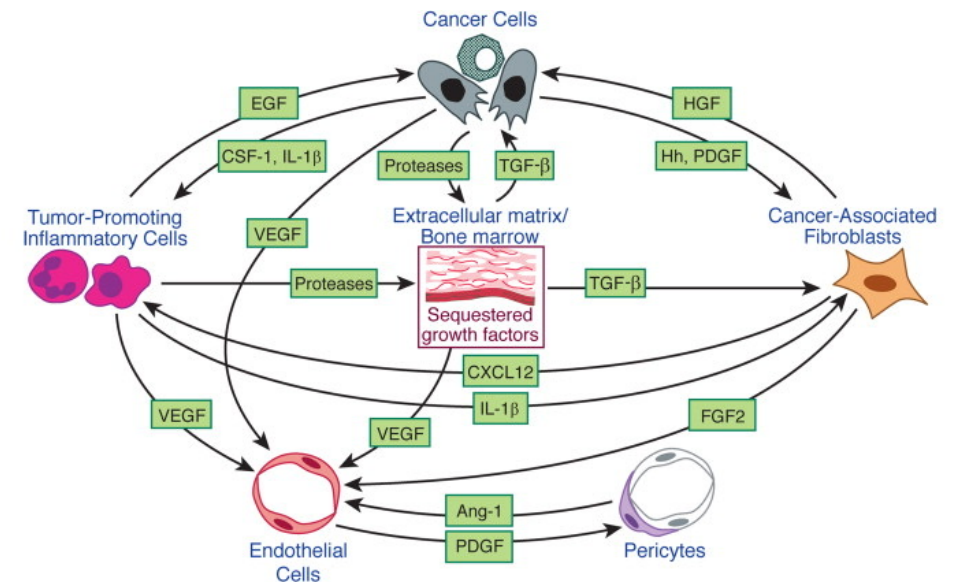
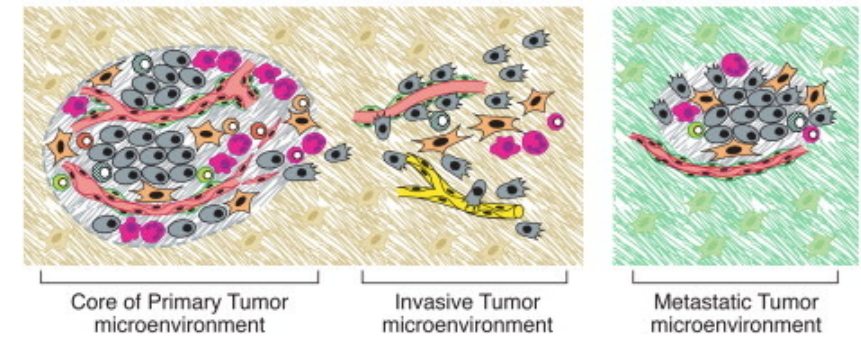
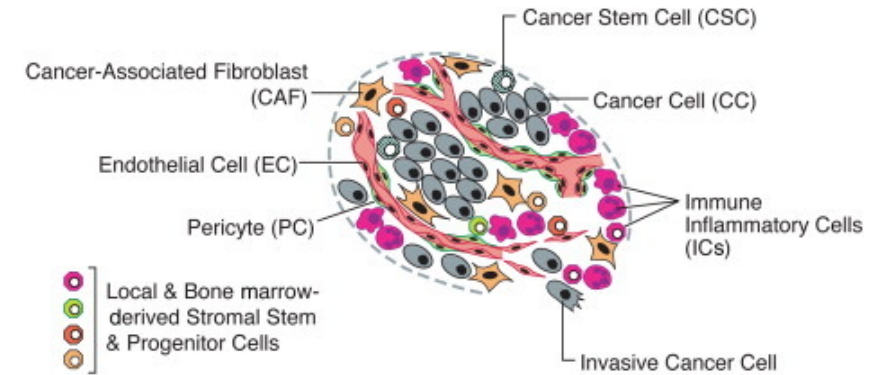
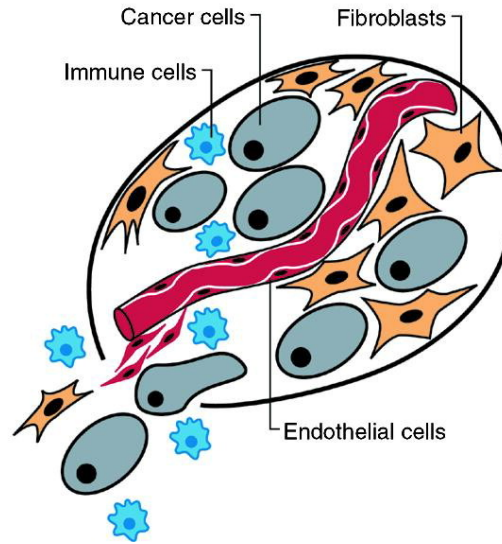


The importance of context

The Reductionist View

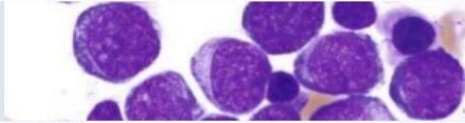
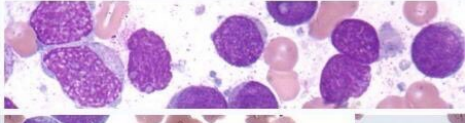

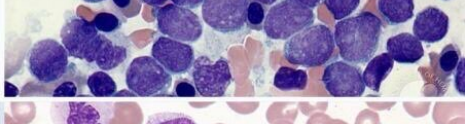
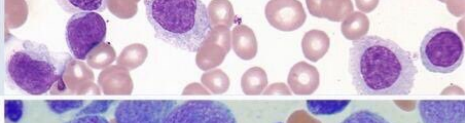
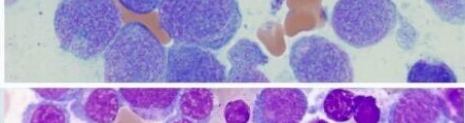
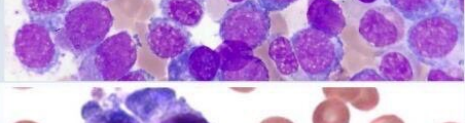



A Heterotypic Cell Biology



Historical classification of blood cancer

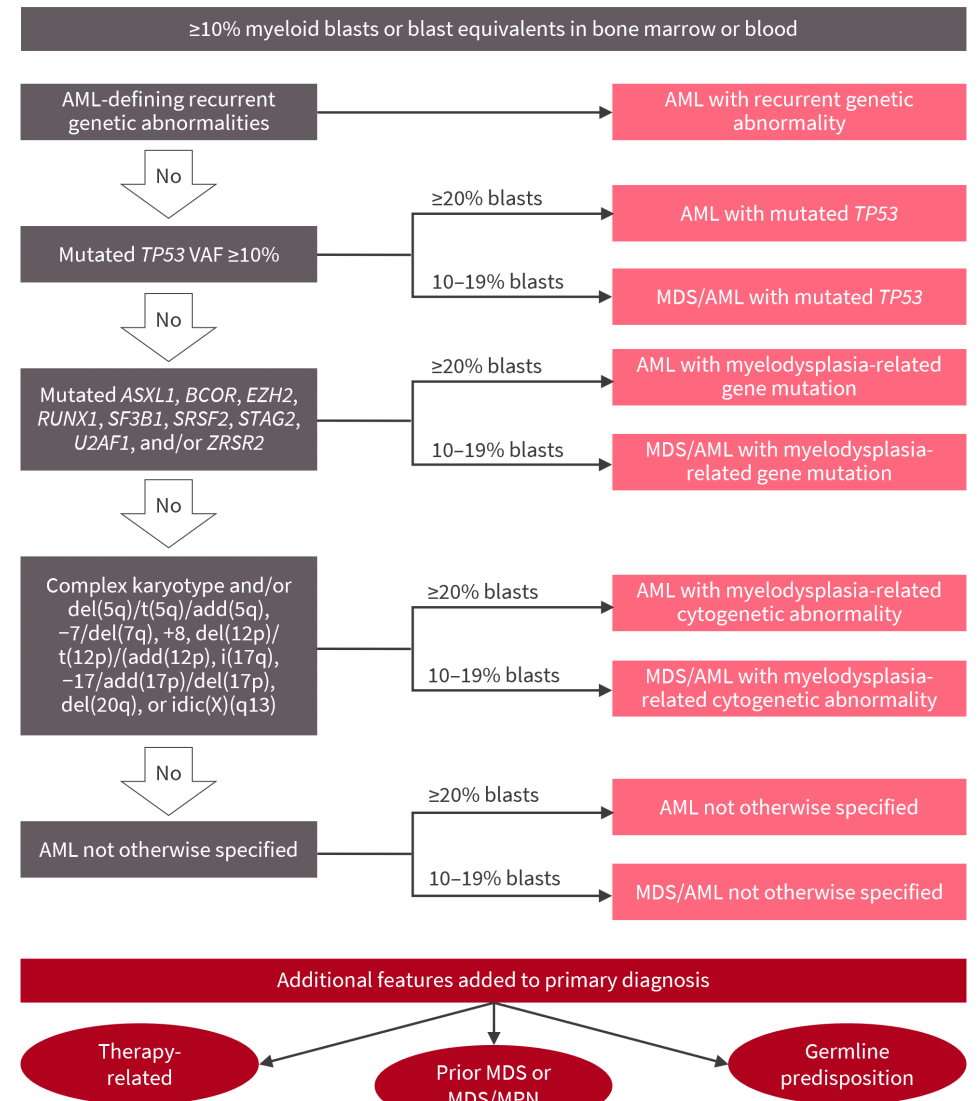
MORPHOLOGY-based: How things look?

FAB CLASSIFICATION SYSTEM OF ACUTE MYELOID LEUKAEMIA		
M0	AML with minimal differentiation	
M1	AML without maturation	
M2	AML with maturation	
M3	Acute promyelocytic leukaemia	
M4	Acute myelomonocytic leukaemia	
M5	Acute monoblastic and monocytic leukaemia	
M6	Pure erythroid leukaemia	
M7	Acute megakaryoblastic leukemia	

WWW.BLOOD-ACADEMY.COM

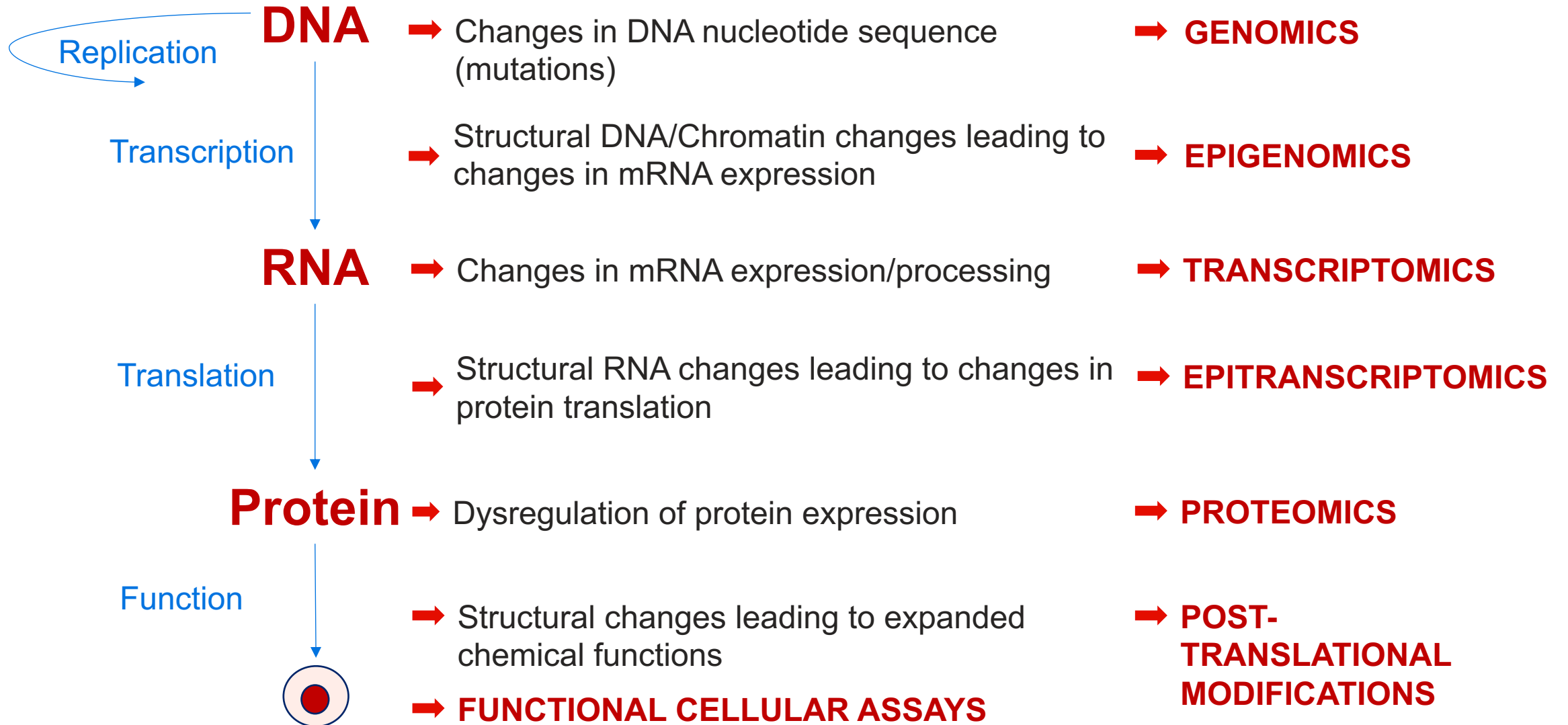
Current classification of blood cancer

MOLECULAR-based: What genetic abnormalities do you carry?

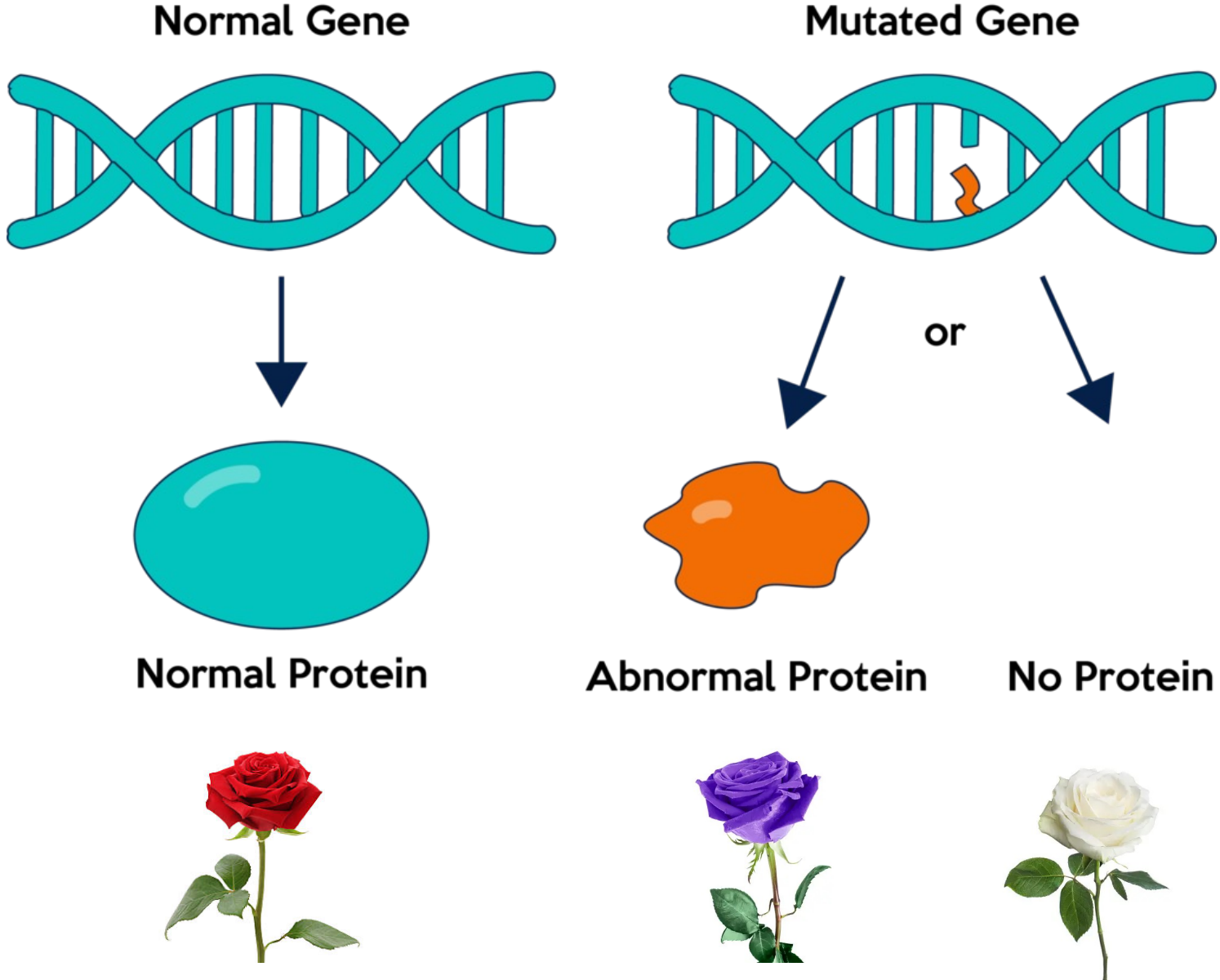


Cancer 101: Main Molecular alterations

“Genes”: Basic units of heredity

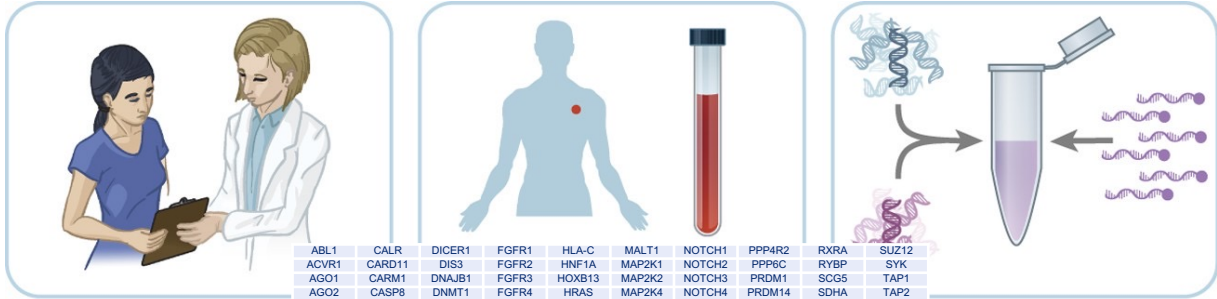


Mutations in the DNA have functional consequences



MSK-IMPACT

(Integrated Mutation Profiling of Actionable Cancer Targets)



1. Patient consent

Sample preparation



4. Sequencing



Case review and sign out

ABL1	CALR	DICER1	FGFR1	HLA-C	MALT1	NOTCH1	PPP4R2	RYR2	SUZ12
ACVR1	CARD11	DIS3	FGFR2	HNF1A	MAP2K1	NOTCH2	PPP6C	RYPB	SYK
AGO1	CARM1	DNAJB1	FGFR3	HOXB13	MAP2K2	NOTCH3	PRDM1	SCG5	TAP1
AGO2	CASP8	DNMT1	FGFR4	HIF1A	MAP2K4	NOTCH4	PRDM14	SDHA	TAP2
AKT1	CBFB	DNMT3A	FGFR3	ICOL5L	MAP3K1	NPM1	PREK2	SDHAF2	TBK3
AKT2	CBL	DNMT3B	FLCN	ID3	MAP3K13	NRAS	PRKAR1A	SDHB	TCEB1
AKT3	CCND1	DOT1L	FLT1	IDH1	MAP3K14	NSD1	PRKCI	SDHC	TCF3
ALB	CCND2	DROSHA	FLT3	IDH2	MAPK1	NTHL1	PRKD1	SDHD	TCF7L2
ALK	CCND3	DUSP4	FLT4	IFNGR1	MAPK3	NTRK1	PTCH1	SERPINE3	TEK
ALOX12B	CCNE1	E2F3	FOXA1	IGF1	MAPKAP1	NTRK2	PTEN	SERPINE4	TERT
ANKRD11	CD274	EED	FOXF1	IGF1R	MAX	NTRK3	PTP4A1	SESN1	TE11
APC	CD276	EGFL7	FOXO2	IGF2	MCL1	NUP2	PTPN11	SESN2	TE22
APLN	CD79B	EGFR	FOXO1	IKZF1	MDC1	NUP3	PTPRD	SESN3	TGFBRI1
AR	CD79B	EIF1AX	FOXO1	IKZF1	MDM2	PAK1	PTPRS	SETD2	TGFBRI2
ARAF	CDCC42	EJF4A2	FUBP1	IL10	MDM4	PAK7	PTPRT	SETDB1	TMEM127
ARHGAP35	CD273	EJF4E	FYN	IL7R	MED12	PALB2	RAB35	SF3B1	TMPPRSS2
ARID1A	CDH1	ELF3	GAB1	INHA	MEF2B	PARK2	RAC1	SH2B3	TNFAIP3
ARID1B	CDK12	EP300	GAB2	INHBA	MEN1	PARP1	RAC2	SH2D1A	TNFRSF14
ARID2	CDK4	EPAS1	GATA1	INPP4A	MET	PAX5	RAD21	SHOC2	TOP1
ARID5B	CDK6	EPCAM	GATA2	INPP4B	MGA	PBRM1	RAD50	SHQ1	TP53
ASXL1	CDK8	EPHA3	GATA3	INFP1	MITF	PDCD1	RAD51	SLFN11	TP53BP1
ASXL2	CDKN1A	EPHA5	GLI1	INSR	MLL1	PDCD1LG2	RAD51C	SLX4	TP63
ATM	CDKN1B	EPHA7	GNA11	IRF4	MLL2	PDGFRA	RADS1L1	SMAD2	TRAF2
ATR	CDKN2A	EPHB1	GNAQ	IRS1	MPL	PDGFRB	RADS1L3	SMAD3	TRAF7
ATRX	CDKN2B	ERBB2	GNAS	IRS2	MRE11A	PDPK1	RAD52	SMAD4	TRIP13
ATXN7	CDKN2C	ERBB3	GNB1	JAK1	MSH2	PGBD5	RAD54L	SMARCA2	TSC1
AURKA	CEPNA	ERCC2	GRIN2A	JUN	MSH1	PHOX2B	RASA1	SMARCB1	U2AF1
AURKB	CEPNA	ERCC3	GRIN2A	JUN	MSH1	PHOX2B	RASA1	SMARCB1	U2AF1
AXIN1	CHEK1	ERCC3	GRIN2A	JUN	MSH1	PHOX2B	RASA1	SMARCB1	U2AF1
AXIN2	CHEK2	ERCC4	GSK3B	KBTBD4	MSI2	PIK3C2G	RB1	SMARCE1	UFP1
AXL	CIC	ERCC5	H3F3A	KDM5A	MSI1	PIK3C3	RBM10	SMO	USP8
B2M	CMTR2	ERF	H3F3B	KDM5C	MSI1R	PIK3CA	RECQL4	SOS1	VHL
BABAM1	CREBBP	ERG	H3F3C	KDM6A	MTAP	PIK3CB	RECQL4	SOS1	VHL
BAP1	KRLL2	ESR1	HIST1H1C	KEAP1	MUTYH	PIK3CG	REST	SOX17	WHSC1
BARD1	CSF1R	ETV1	HIST1H3A	KLF4	MYCL1	PIK3R2	RFWD2	SOX9	WT1
BBC3	CD274	EED	FOXF1	IGF1R	MAX	NTRK3	PTP4A1	SESN1	TE11
BCL1	CD276	EGFL7	FOXO2	IGF2	MCL1	NUP2	PTPN11	SESN2	TE22
BCL2	CSF3R	ETV6	HIST1H3B	KLF5	MYCN	PIK3R3	RHEB	SPEN	WWTR1
BCL2L1	CTCF	EZH1	HIST1H3C	KMT2A	MYO9B	PHF1	RHOA	SPPO	XAP1
BCL2L11	CTLA4	EZH2	HIST1H3D	KMT2B	MYO10	PLCG2	RICTOR	SPRED1	XPC1
BCL6	CXCR4	FAM123B	HIST1H3E	KMT2C	NADK	PLK2	RIT1	SPRNT	XRC2
BCOR	CTSL	FAM123B	HIST1H3E	KMT2C	NADK	PLK2	RIT1	SPRNT	XRC2
BCOR	CTSL	FAM123B	HIST1H3E	KMT2C	NADK	PLK2	RIT1	SPRNT	XRC2
BIRC3	CUL3	FAM46C	HIST1H3G	KMT5A	NCOA3	PMS1	ROSI	SRSF2	YES1
BLM	CXCR4	FAM58A	HIST1H3H	KNSTRN	NCOR1	PMS2	RPS6KA4	STAG2	ZFH3
BMPR1A	CXORF67	FANCA	HIST1H3I	KRAS	NEGR1	PNRC1	RPS6KB2	STAG3	ZNF3
BRAF	CYLD	FANCC	HIST1H3J	LATS1	NF1	POLD1	RPTOR	STAT5A	ZRSR2
BRCA1	CYP19A1	FAT1	HIST2H3C	LATS2	NF2	POLE	RRAGC	STAT5B	ZRSR2
BRCA2	CYSLTR2	FBXW7	HIST2H3D	LMO1	NFE2L2	POT1	RASGEF1B	STK11	ZRSR2
BRD4	DAXX	FGF19	HIST3H3	LYN	NFKBIA	PPARG	RRAS2	STK19	ZRSR2
BRIAP1	DCUN1D1	FGF3	HLA-A	LZTR1	NKX2-1	PPM1D	RTEL1	STK40	ZRSR2
BTK	DDR2	FGF4	HLA-B	MAD2L2	NKX3-1	PPP2R1A	RUNX1	SUFU	ZRSR2

cBioPortal for Cancer Genomics -->

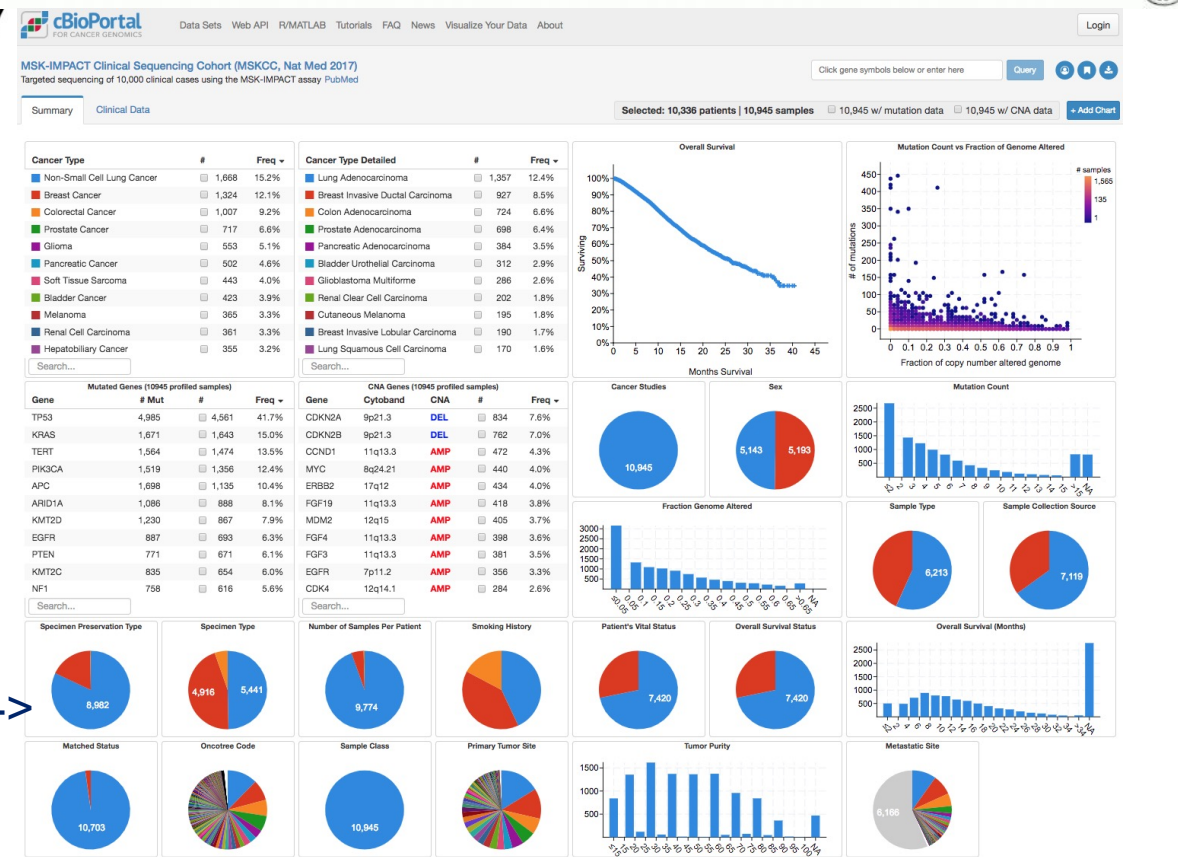
<https://www.cbioportal.org>

Patient Name	Redacted	Medical Record #	Redacted
Date of Birth	Redacted	Accession #	Redacted
Gender	Redacted	Specimen Submitted	LYMPH NODE
Tumor Type	Redacted	Surgical Path. #	Redacted
Ref. Physician	Redacted	Account #	Redacted
Date of Receipt	Redacted	Date of Report	Redacted

Summary: 2 mutations, 10 copy number alterations, no structural variants detected. 2 alterations have ClinVar interpretations.
 MSI Status: MICROSATELLITE STABLE (MSI). See MSI notes below.
 Tumor Mutation Burden: The estimated tumor mutation burden (TMB) for this sample is 1.8 mutations per megabase (per 100 Mb) as assessed by MSK-IMPACT for all patients or 3.9 mutations per megabase (per 100 Mb) for patients with Non-Small Cell Lung Cancer. See all of the data in this report was issued.
 Comments: Note: The number and pattern of mutations is consistent with a hypermutator phenotype arising from a mechanism such as telomerase or similar agents.

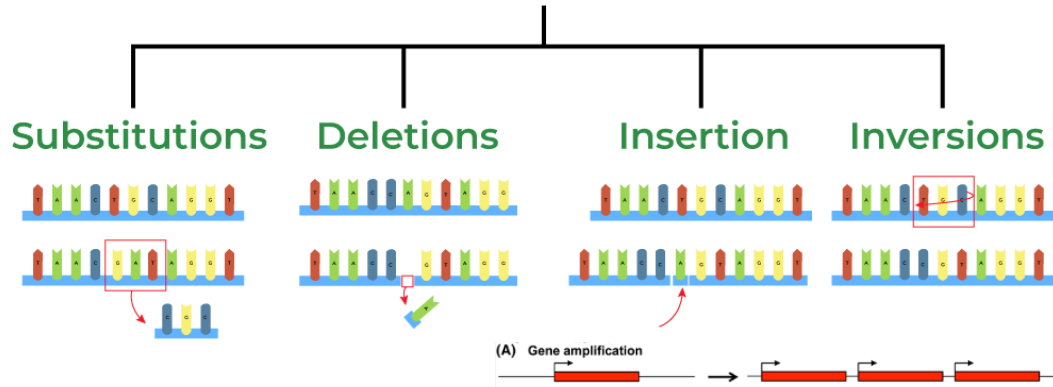
Gene	Type	Alteration	Location	Additional Info
EGFR	In-frame Deletion	L747_P753delinsS	exon 19	MAF: 42.3%
CTNNA1	Misense Mutation	S49P (p.131T>C)	exon 3	MAF: 29.5%

Alteration(s)	Drugs(s)	Annotation
Level 1 EGFR L747_P753delinsS MAF: 42.3%	Erlotinib, Afatinib, Gefitinib	EGFR, a receptor tyrosine kinase, is altered by amplification, mutation and/or overexpression in various cancers, most frequently in lung and brain cancers. The EGFR L747_P753delinsS alteration is known to be oncogenic. The EGFR tyrosine kinase inhibitors erlotinib, afatinib and gefitinib are FDA-approved for the treatment of patients with non-small cell lung cancer harboring an EGFR exon 19 deletion such as L747_P753delinsS. OncoKB version: v1.12.
Level 2B EML4-ALK Fusion	Crizotinib, Ceritinib, Alectinib, Brigatinib	ALK, a receptor tyrosine kinase, is recurrently altered by chromosomal rearrangements in various cancers including anaplastic large cell lymphoma, non-small cell lung cancer and inflammatory myofibroblastic tumor. The EML4-ALK fusion is known to be oncogenic. While crizotinib, ceritinib, alectinib and brigatinib are FDA-approved for the treatment of patients with ALK-fusion positive lung cancer, their clinical utility in patients with ALK-fusion positive adenocarcinoma, NOS is unknown. OncoKB version: v1.12.
Level 3B MDM2 Amplification FC: 13.5	RG7112, DS-3032b	MDM2, a ubiquitin ligase and p53 inhibitor, is amplified in a diverse range of cancers including well-differentiated liposarcomas. MDM2 amplification is known to be oncogenic. While there is promising clinical data supporting the use of MDM2-inhibitors such as RG7112 and DS-3032b in patients with MDM2-amplified liposarcomas, their clinical utility in patients with MDM2-amplified lung adenocarcinoma is unknown. OncoKB version: v1.12.

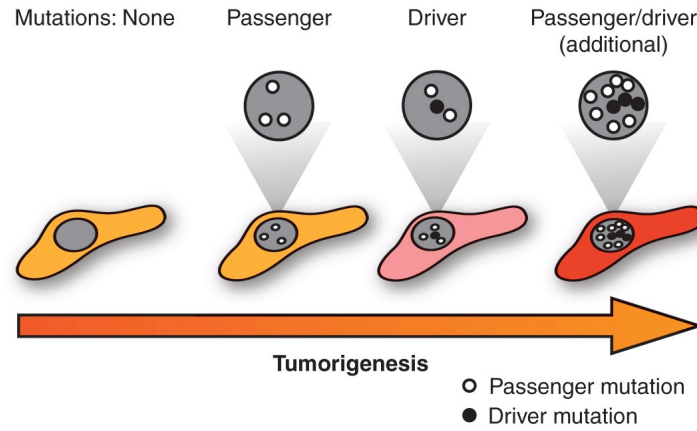
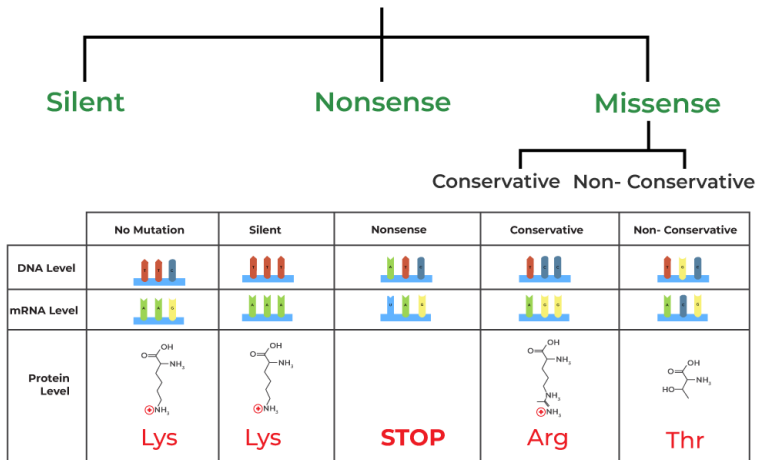


Cancer 101: Mutations glossary

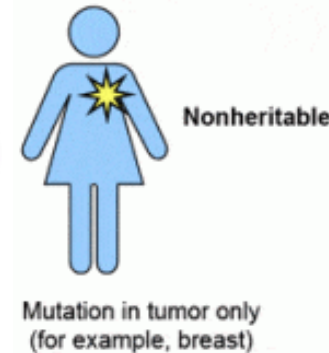
Types of Mutations (At the DNA level)



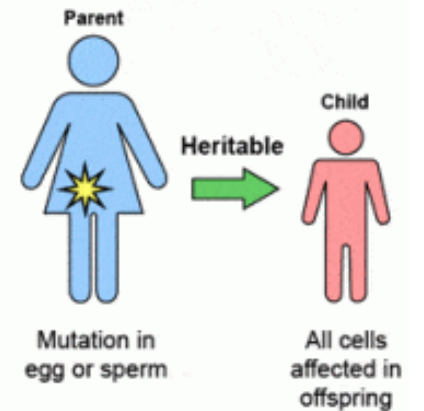
Types of Mutations (At the Protein level)



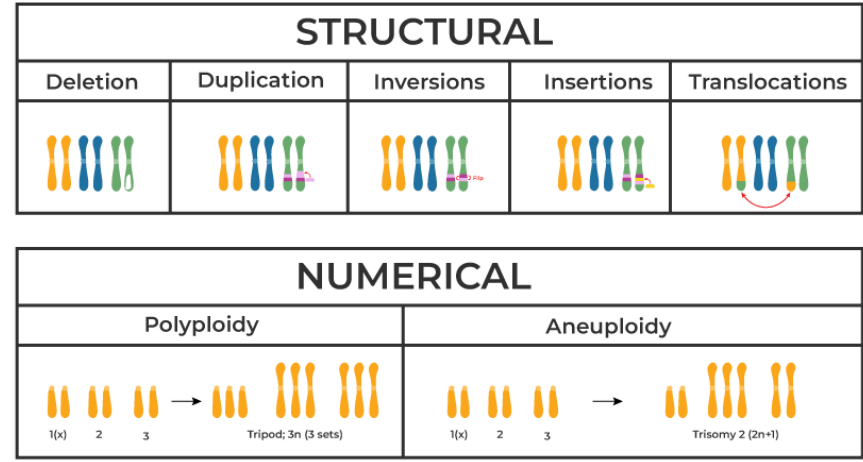
Somatic mutations
 • Occur in *nongermline* tissues
 • Cannot be inherited



Germline mutations
 • Present in egg or sperm
 • Can be inherited
 • Cause cancer family syndrome



Types of Mutations (At the Chromosomal level)



Adapted from the National Cancer Institute and the American Society of Clinical Oncology

Cancer 101: Cancer is a genetic disease

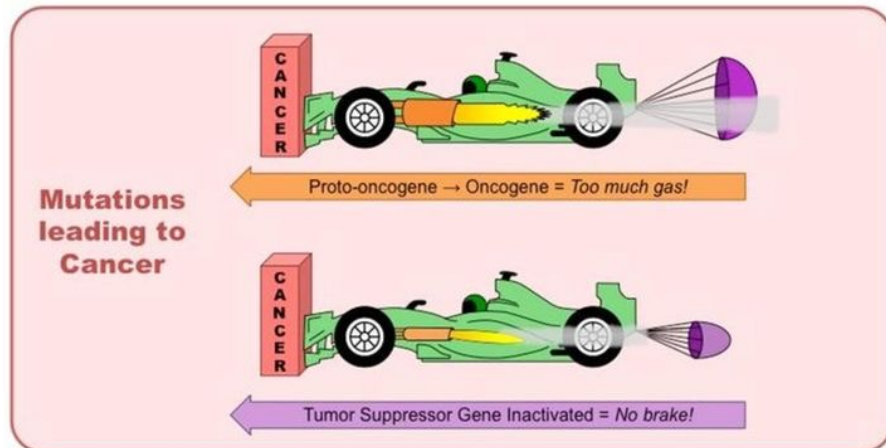
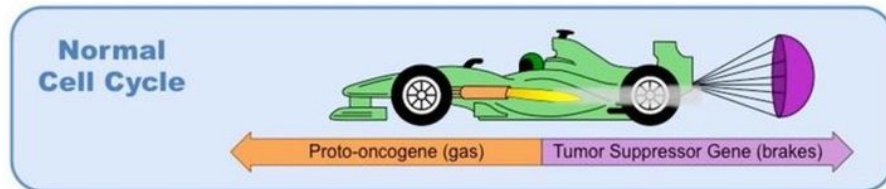
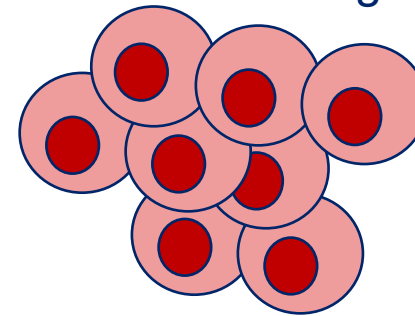
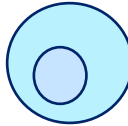
(Proto-)Oncogene

Gene with the potential to promote cancer

Overactivation of proto-oncogenes

Malignant cells

“Normal” cell

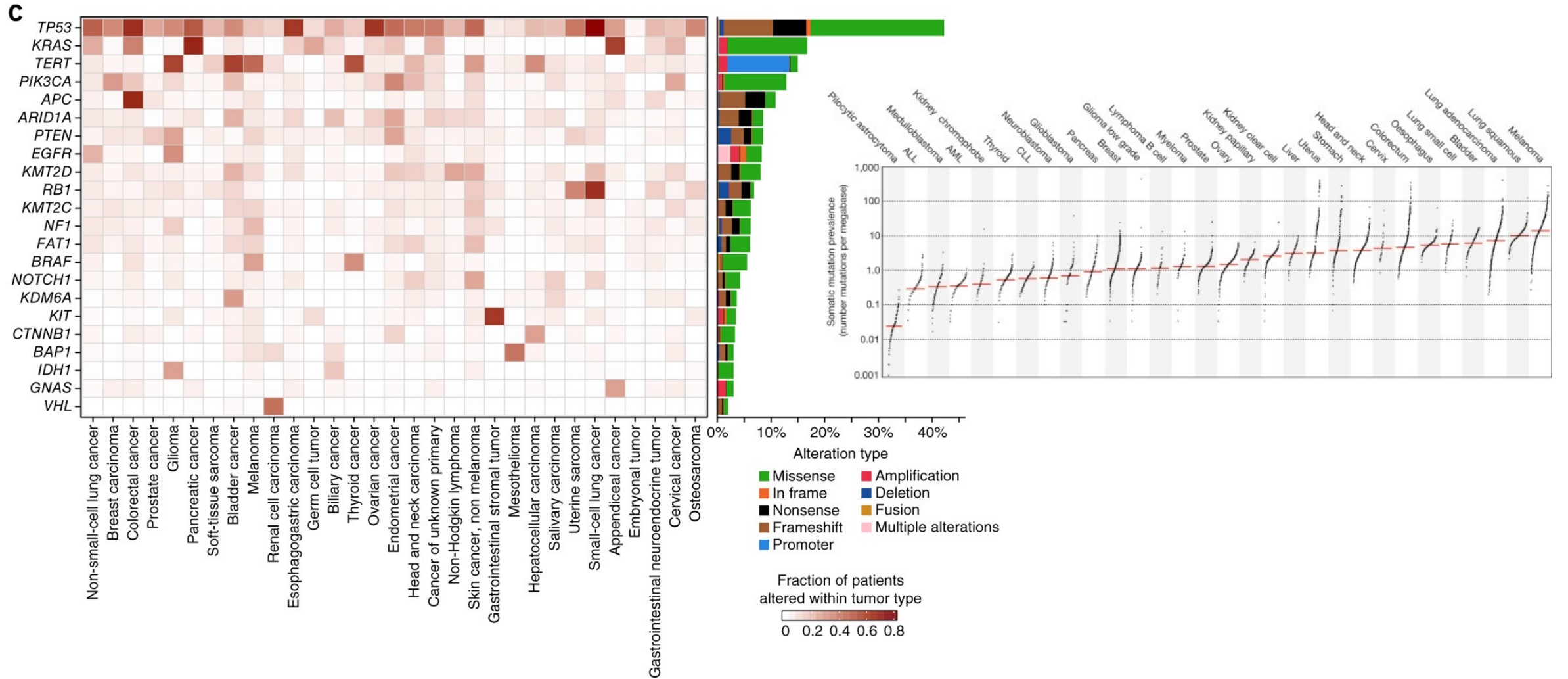


Tumor suppressor gene

Gene whose loss/dysfunction contributes to cancer

Inactivation of tumor suppressor genes

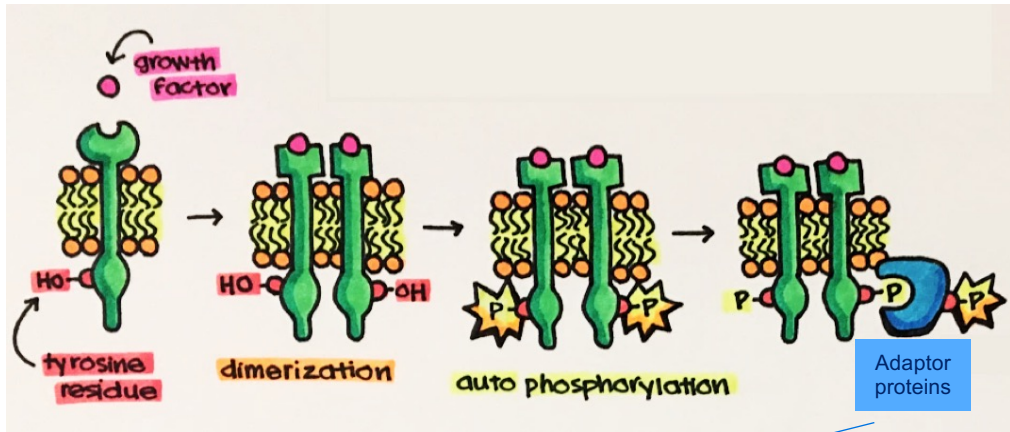
Commonly mutated cancer genes



Cancer Genes

Receptor tyrosine kinases (RTKs)

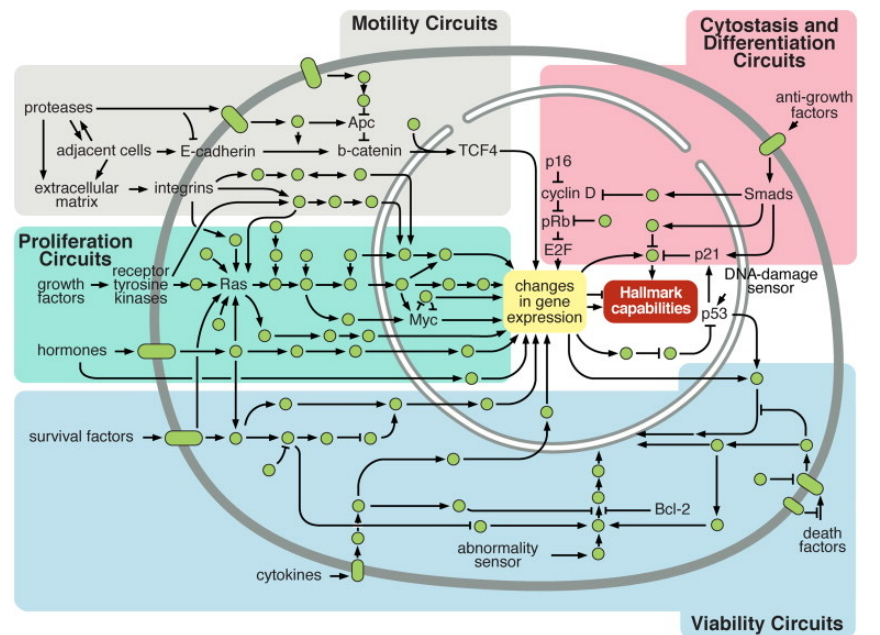
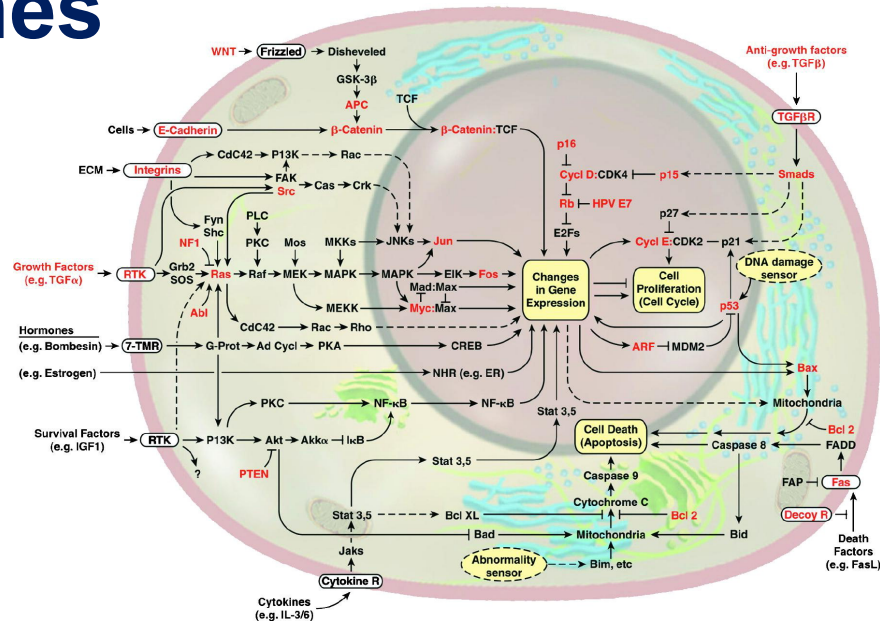
RTK activation



Signaling cascade

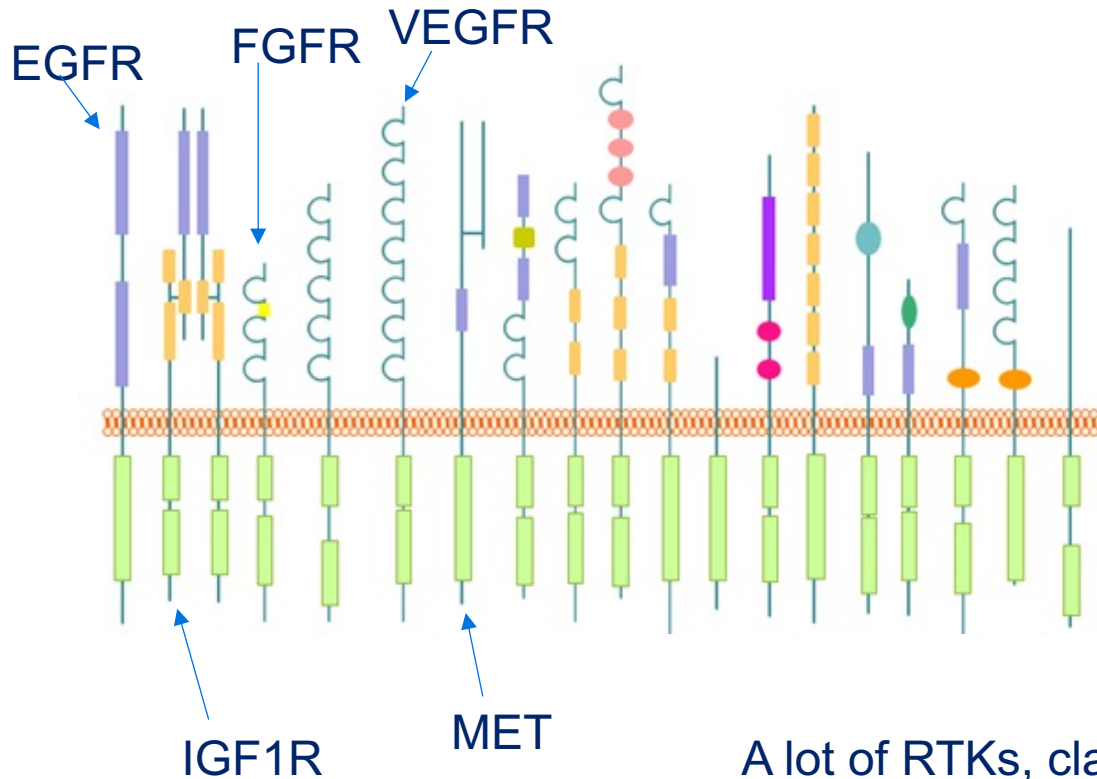
Activation/deactivation of TFs

Transcriptomic changes

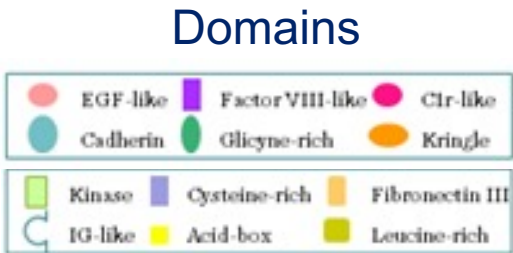


Cancer genes

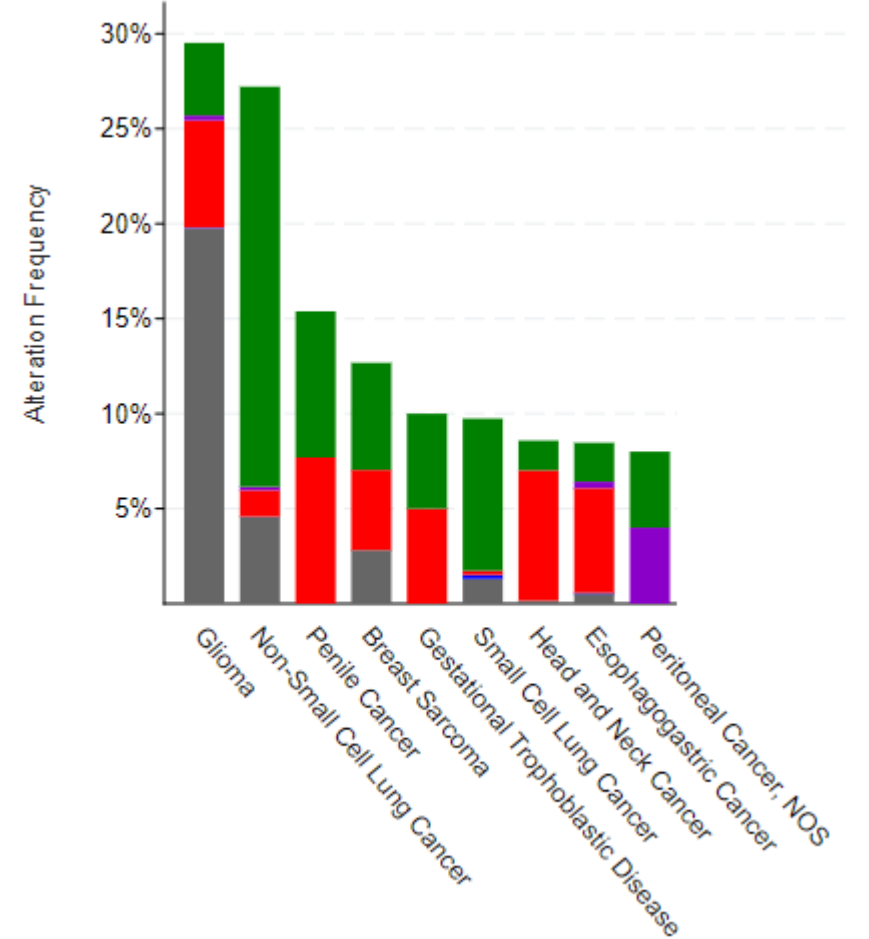
Receptor tyrosine kinases (RTKs): RTK families



A lot of RTKs, classified in families, with different functions and involvement in cancer



EGFR genomic alterations



● Mutation ● Fusion ● Amplification ● Deep Deletion ● Multiple Alterations

(Adapted from Critchley et al., Cells 2018)

Cancer genes

Receptor tyrosine kinases (RTKs): Pathways activated by RTKs

RAS/MAPK pathway

- Cell growth, cell cycle regulation
- Cell migration
- Angiogenesis

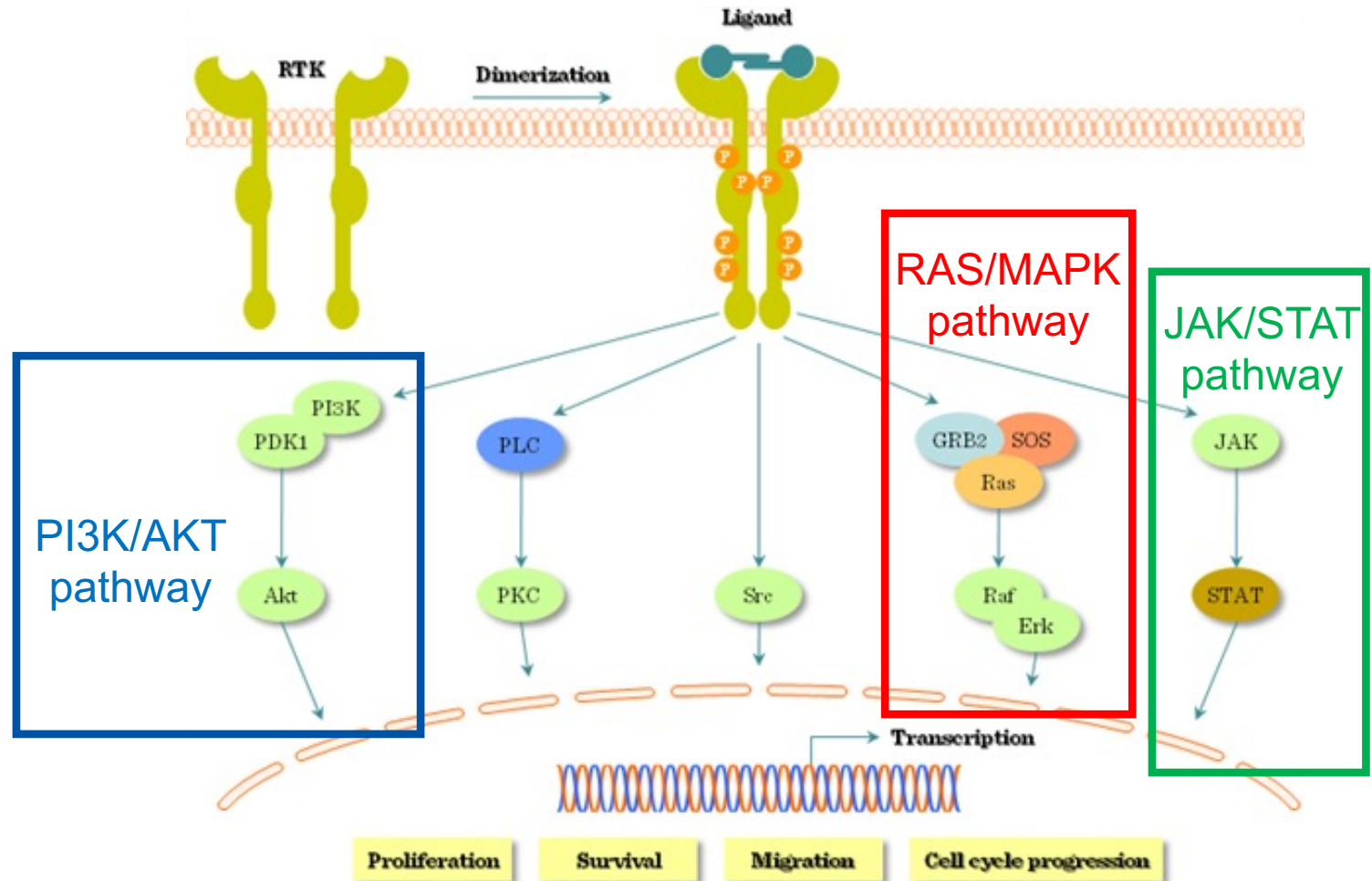
PI3K/AKT pathway

- Cell proliferation
- Apoptosis
- Metabolism
- Angiogenesis

JAK/STAT pathway

- Cell proliferation
- Apoptosis
- Immune response / inflammation
- Angiogenesis
- Metastasis

Some signaling pathways activated by

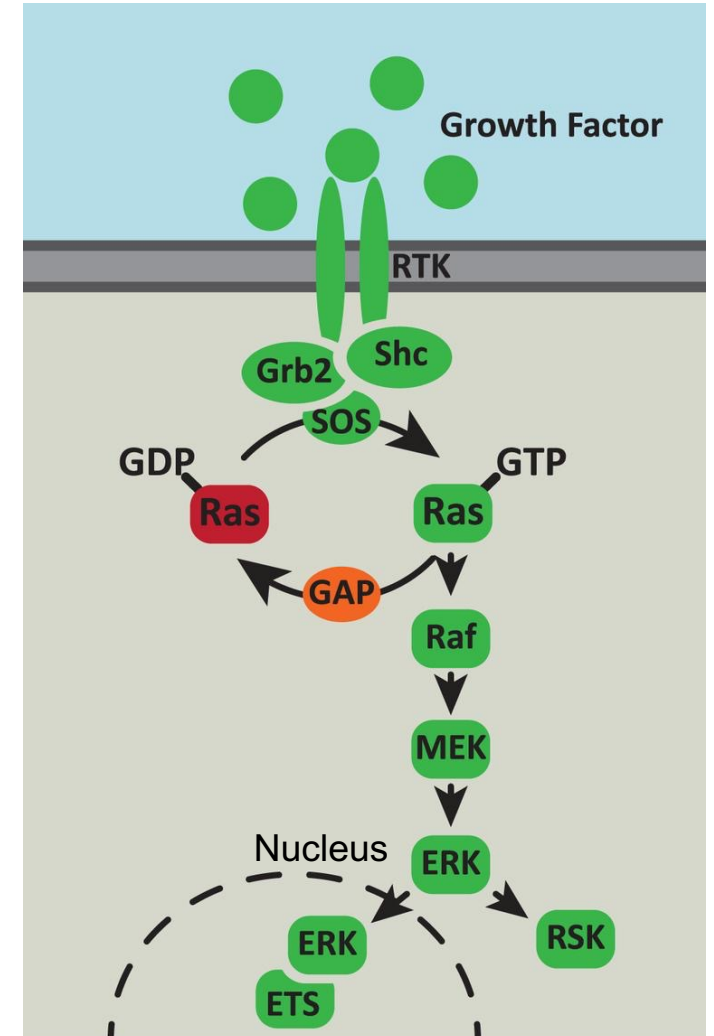


Cancer genes

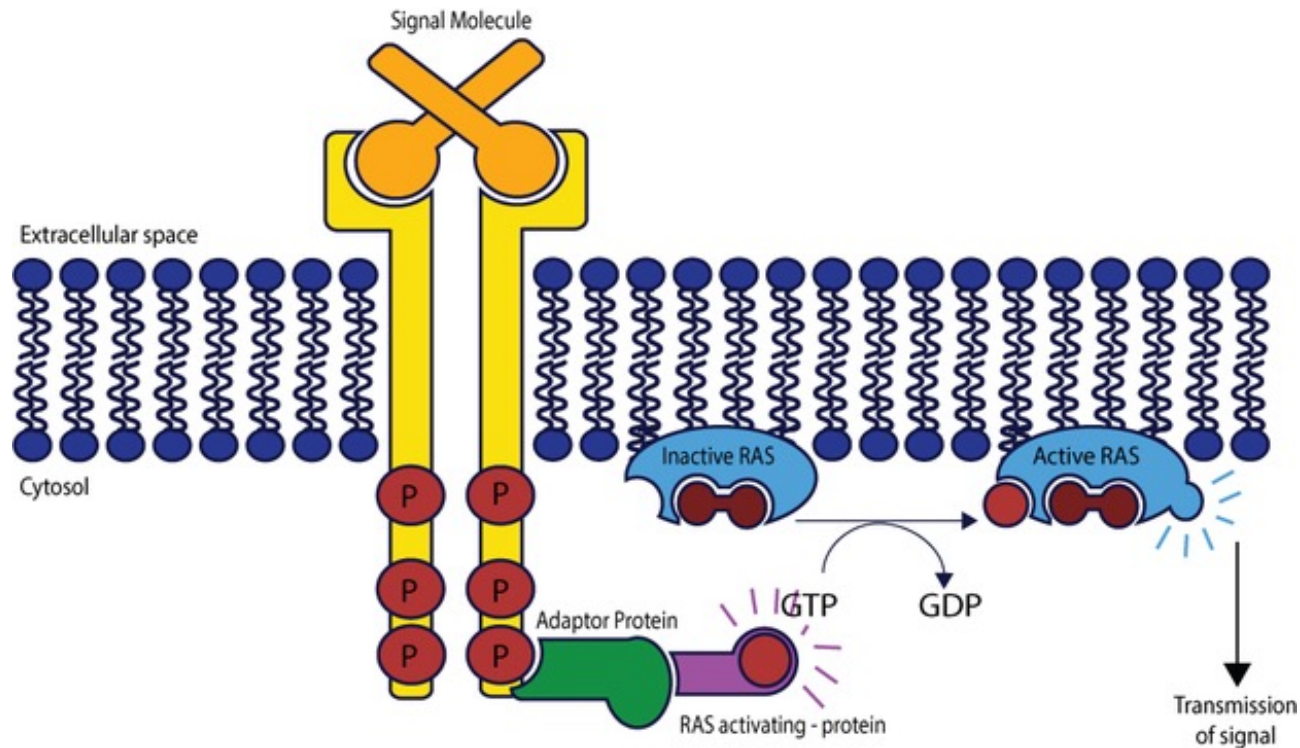
RAS (KRAS, NRAS, HRAS...)

Involved in...cellular proliferation, differentiation, and survival

MAPK pathway



RAS activation

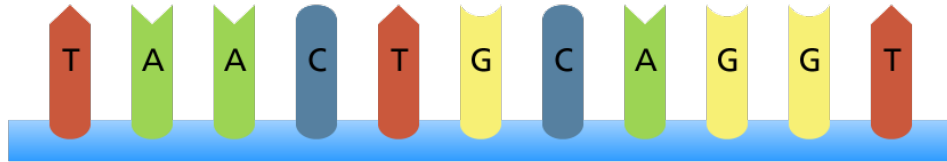


Take home messages

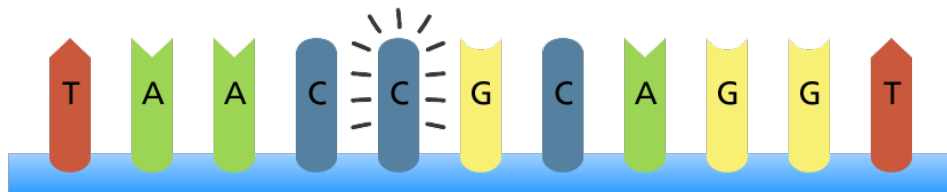
1. Cancer is a disease with a strong genetic component. Molecular alterations leading to loss of function of tumor suppressors (e.g. *TP53*, *RB1*) or to overactivation of proto-oncogenes (e.g. *RAS*, RTKs) may facilitate the occurrence of cancer or induce it.

DNA mutation vs DNA methylation:

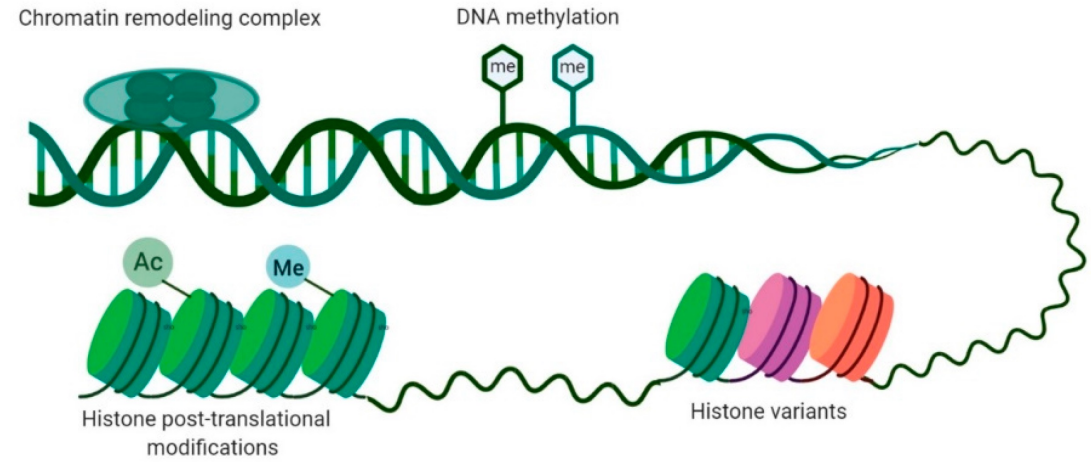
Original sequence



Point mutation

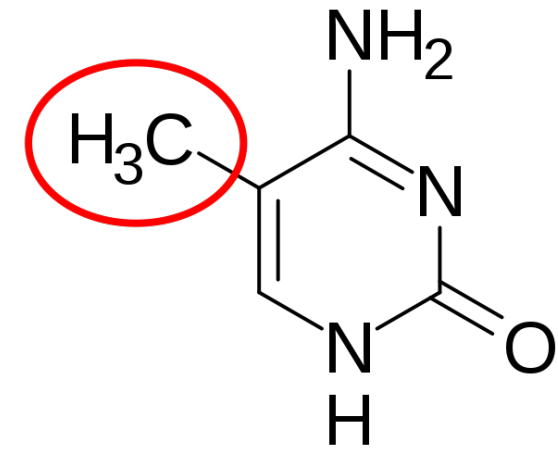
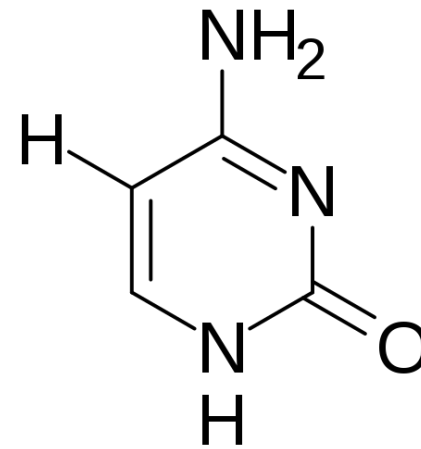


a vs á



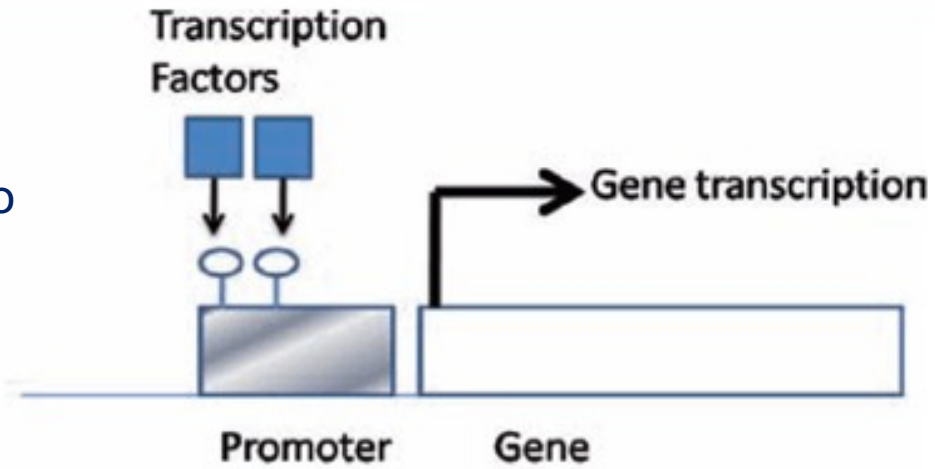
Epigenetics:

Methylation as an example of an epigenetic modification

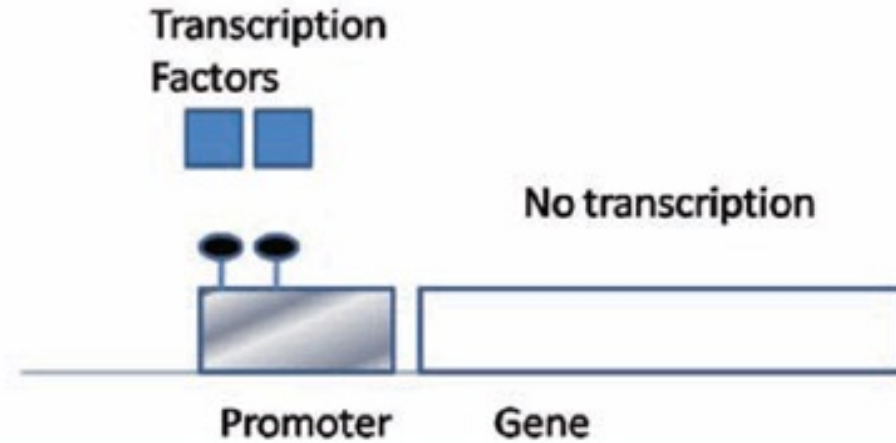
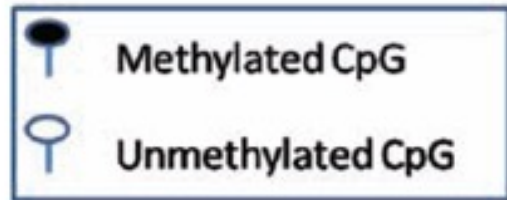


Effects of Promoter Methylation

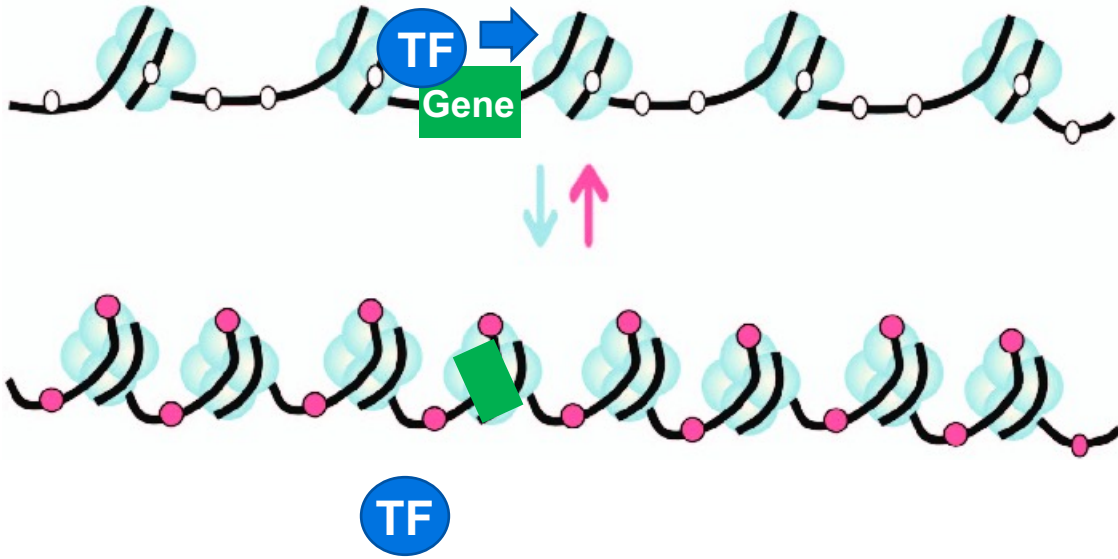
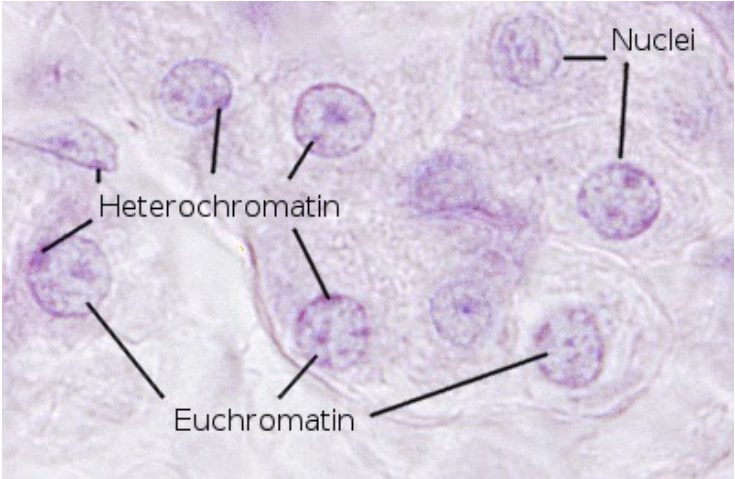
UNMETHYLATED PROMOTER:
Transcription Factors CAN bind to initiate transcription



METHYLATED PROMOTER:
Transcription Factors CAN NOT bind to initiate transcription



Alterations at the epigenetic/transcriptomic level



Open chromatin
(Transcription factor can access DNA and induce gene expression)

Condensed chromatin
(Transcription factor cannot access DNA)

Interaction among different molecular alterations

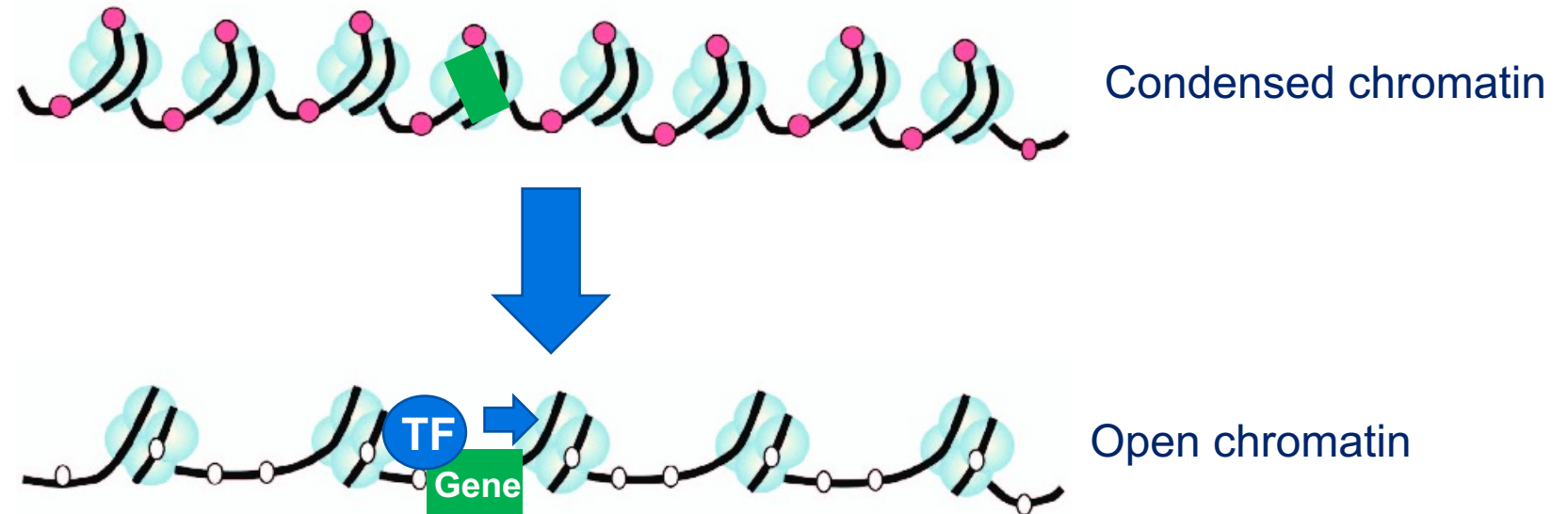
Example 1:

mutation on a transcription factor (TF) leading to inefficient DNA binding capacity (and then gene expression induction)

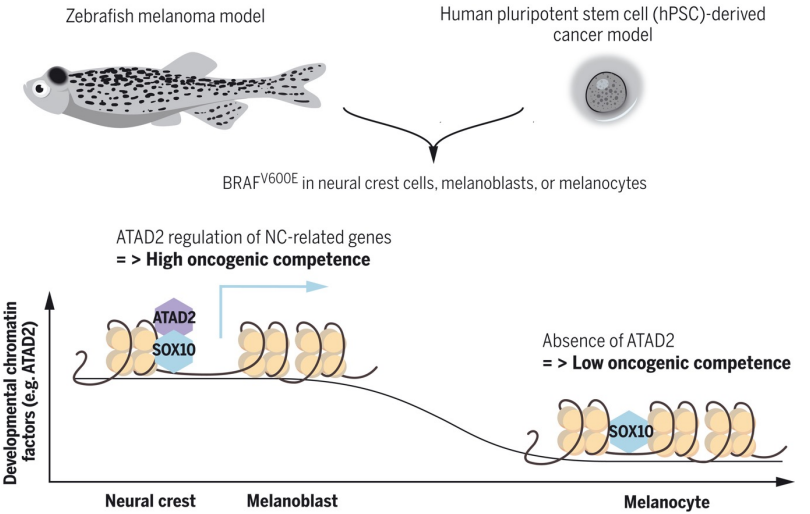
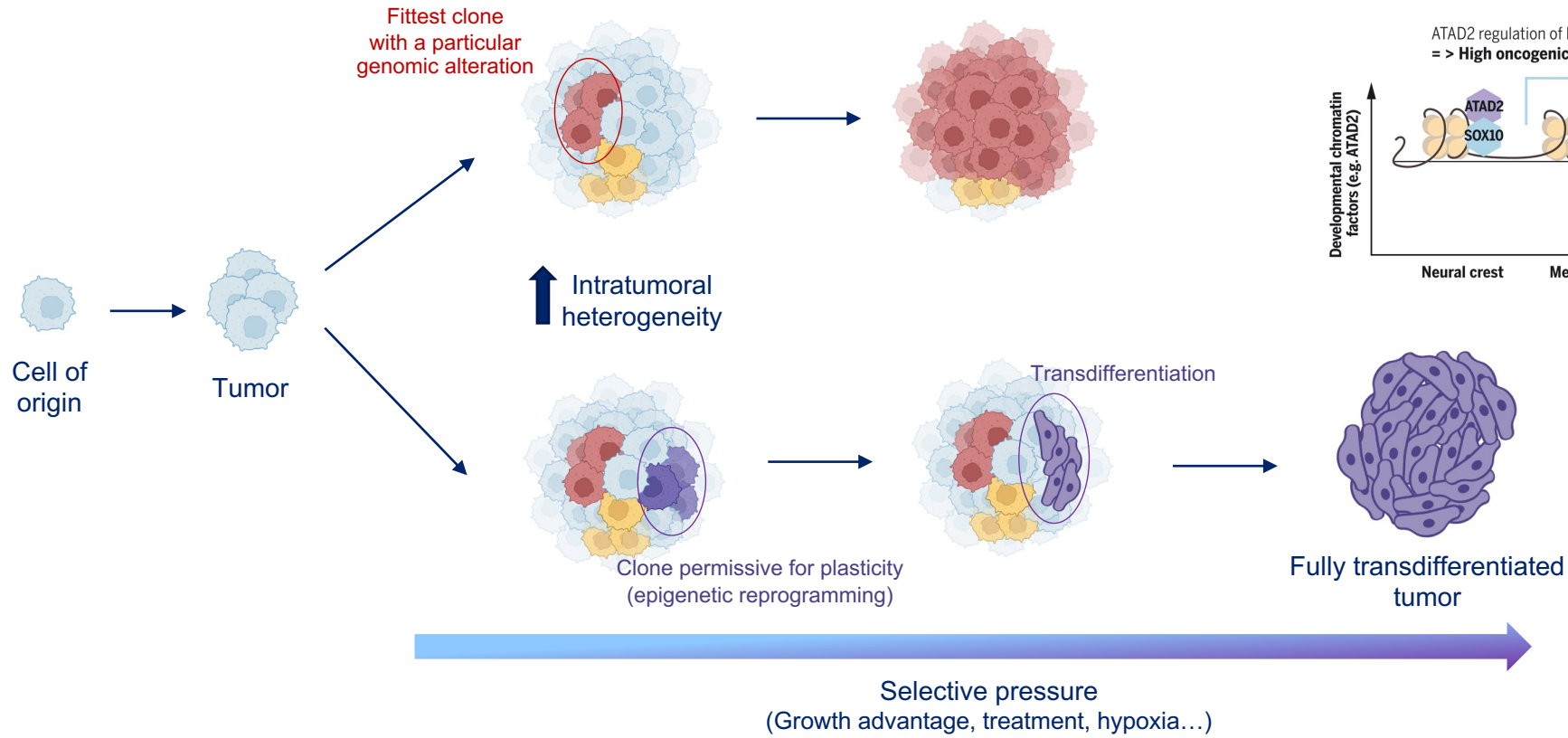


Example 2:

mutation on enzymes responsible to make the chromatin compact leading to open chromatin and increased expression of genes in those genomic loci



Tumor heterogeneity, plasticity, competence and evolution



Take home messages

1. Cancer is a disease with a strong genetic component. Molecular alterations leading to loss of function of tumor suppressors (e.g. *TP53*, *RB1*) or to overactivation of proto-oncogenes (e.g. *RAS*, RTKs) may facilitate the occurrence of cancer or induce it.
2. Tumors usually exhibit a number of different molecular alterations (genomic, epigenomic, transcriptomic,...) in a variety of genes, but not all of them contribute significantly to the oncogenic phenotype. It is important to identify which are driving the oncogenic phenotype (*drivers*) and study the molecular biology behind it (*mechanism*).

As part of your project, you are interested in modelling mutations that frequently occur in cancer patients. For this purpose, you are reviewing MSK-IMPACT clinical sequencing results using the cBioPortal platform. One of the genes that most commonly is found to be mutated in this dataset is TP53, a known tumor suppressor gene. What are the characteristics of these types of genes?

- A) In cancer patients, inactivating mutations are the most frequent type of mutations occurring in tumor suppressors genes.
- B) Loss of function in tumor suppressors genes cannot occur due to non-mutational processes like promoter methylation.
- C) Loss of tumor suppressors decreases the likelihood of malignant transformation.
- D) Mutation in tumor suppressors genes can only be somatic, and they don't occur in the germline.

As part of your project, you are interested in **modelling** mutations that frequently occur in **cancer patients**. For this purpose, you are reviewing **MSK-IMPACT** clinical sequencing results using the **cBioPortal** platform. One of the genes that most commonly is found to be mutated in this dataset is **TP53**, a known **tumor suppressor** gene. What are the characteristics of these types of genes?

- A) In cancer patients, **inactivating mutations** are the most frequent type of mutations occurring in tumor suppressors genes.
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- C) Loss of tumor suppressors decreases the likelihood of **malignant transformation**.
- D) Mutation in tumor suppressors genes can only be **somatic**, and they don't occur in the **germline**.

After acknowledging the importance of TP53 as a tumor suppressor, you are interested in understanding the effect of other tumor suppressors. Which of the following genes is not a tumor suppressor?

- a) RB, a gene involved in controlling the pass through a cell cycle checkpoint.
- b) APC, a gene involved in downregulating the expression of beta-catenin, a known proto-oncogene.
- c) BRCA, a gene responsible for the reparation of DNA.
- d) KRAS, a gene involved in promoting cell growth.

Thanks for your attention!

Any questions?



Memorial Sloan Kettering
Cancer Center