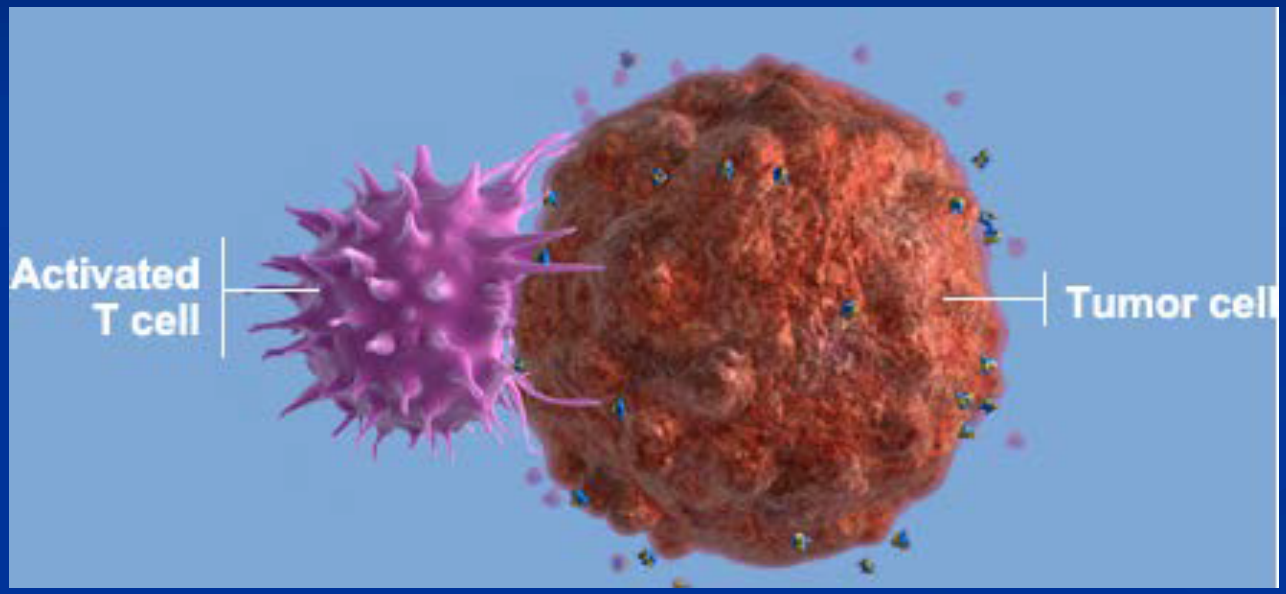
Cancer Therapies

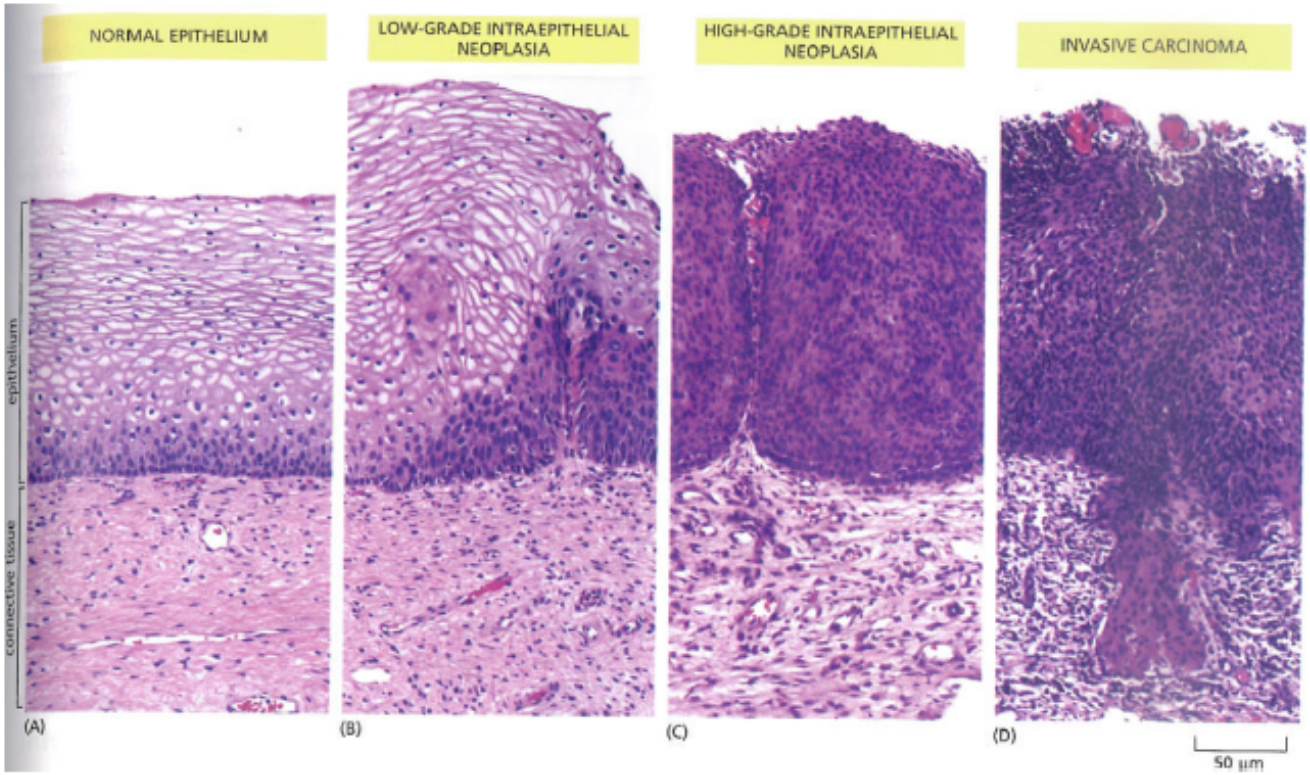


January 28, 2020

Prof. Hans Bluyssen
Department of Human Molecular Genetics
Rm. J1-116

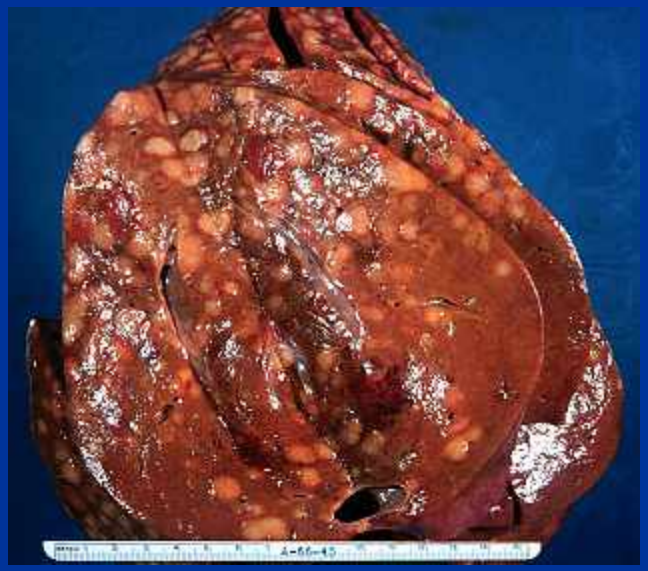
Carcinogenesis

- Stages of progression in the development of cancer of the epithelium of the uterine cervix.

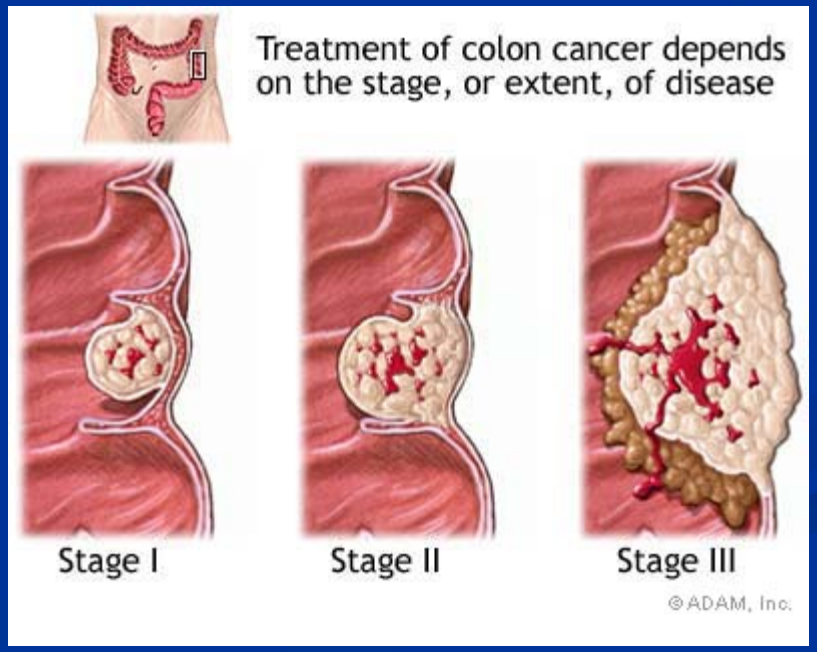


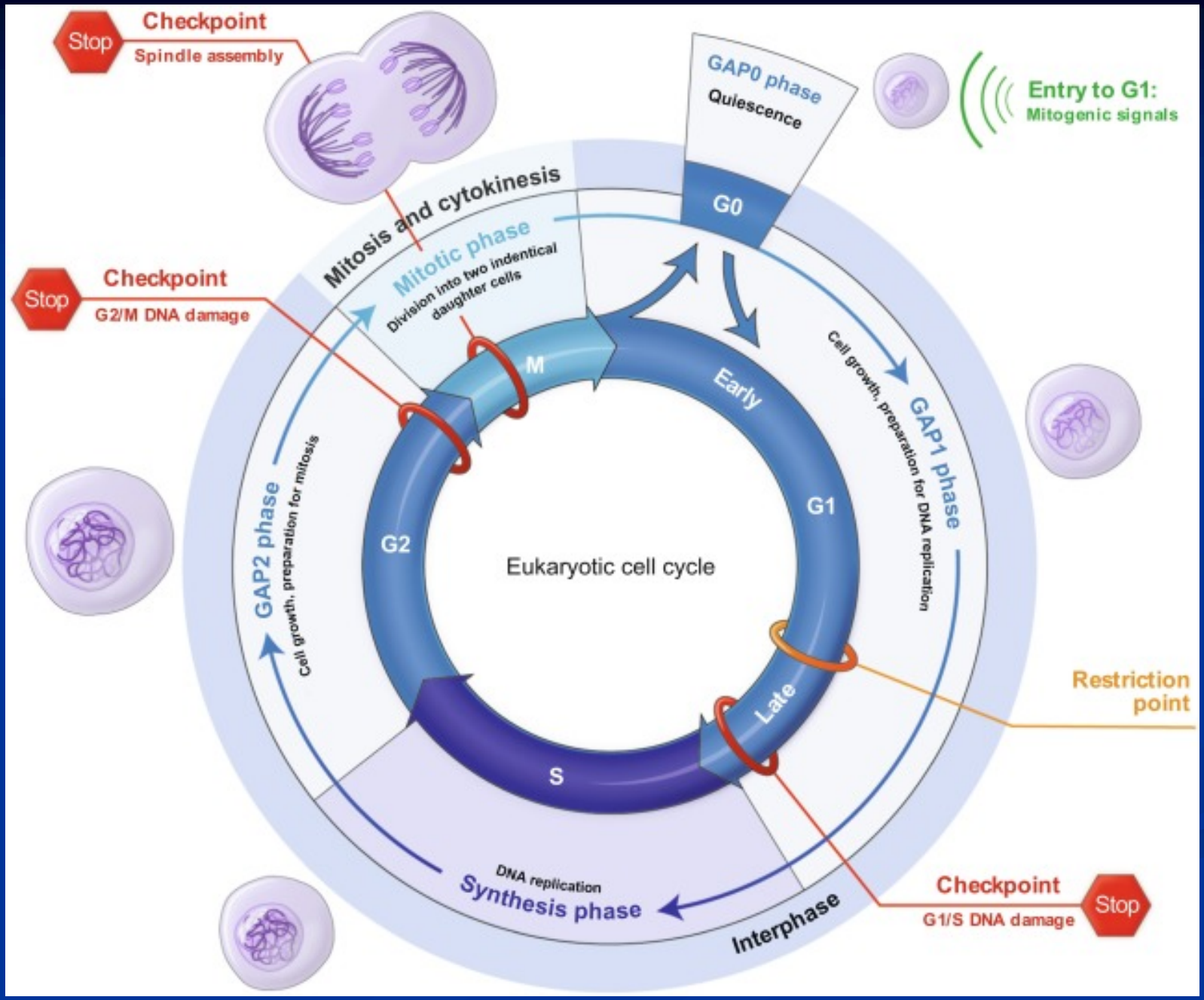
Cancer is a disease of the cell cycle. Some of the body's cells divide uncontrollably and tumors form.

Tumors in Liver

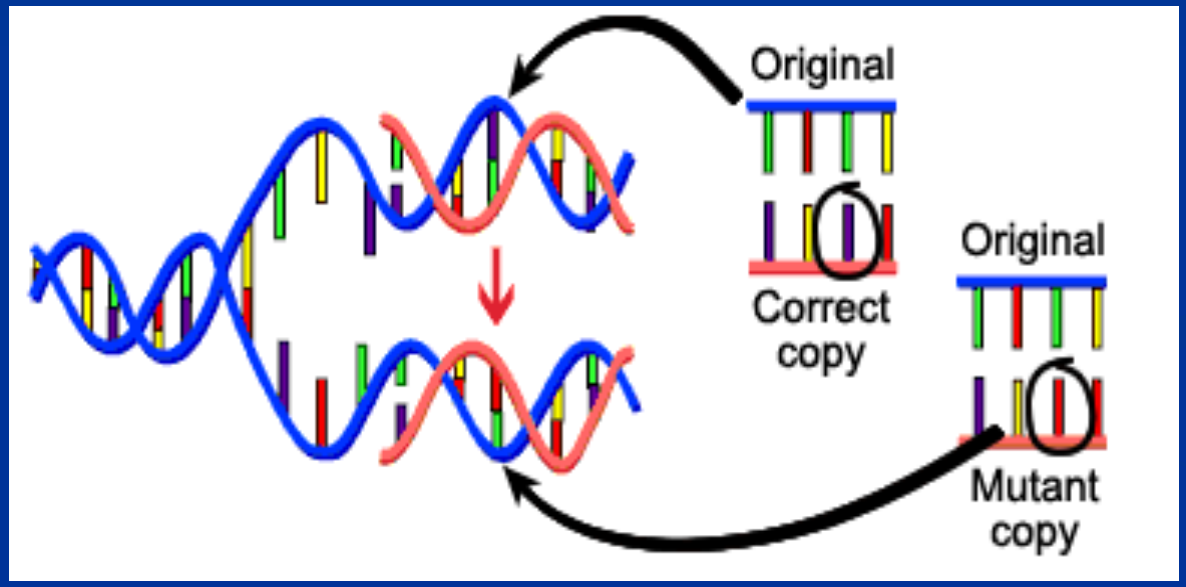


Tumor in Colon




Stop
Checkpoint
Spindle assembly
GAP0 phase
Quiescence
Entry to G1:
Mitogenic signals
Mitosis and cytokinesis
Mitotic phase
Division into two indentical daughter cells
G0
Stop
Checkpoint
G2/M DNA damage
M
Early
G1
Cell growth, preparation for DNA replication
GAP1 phase
GAP2 phase
Cell growth, preparation for mitosis
G2
Eukaryotic cell cycle
Late
Restriction point
S
DNA replication
Synthesis phase
Interphase
Checkpoint
G1/S DNA damage
Stop

DNA mutations disrupt the cell cycle.

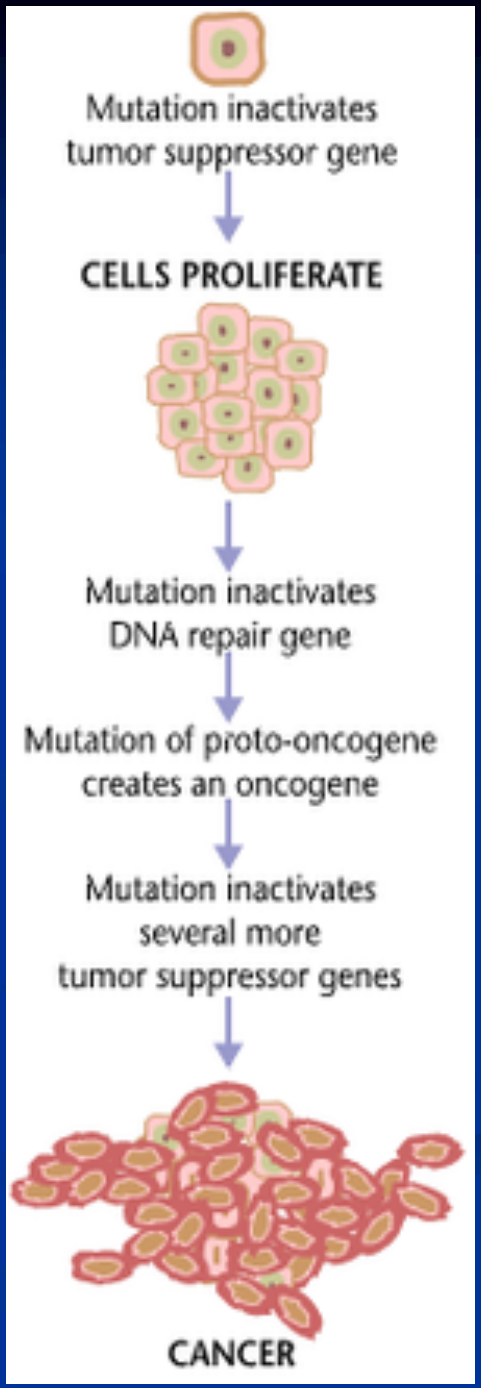


Mutations may be caused by:

1. radiation
2. smoking
3. Pollutants
4. chemicals
5. viruses

Cancer Begins with a Single Cell

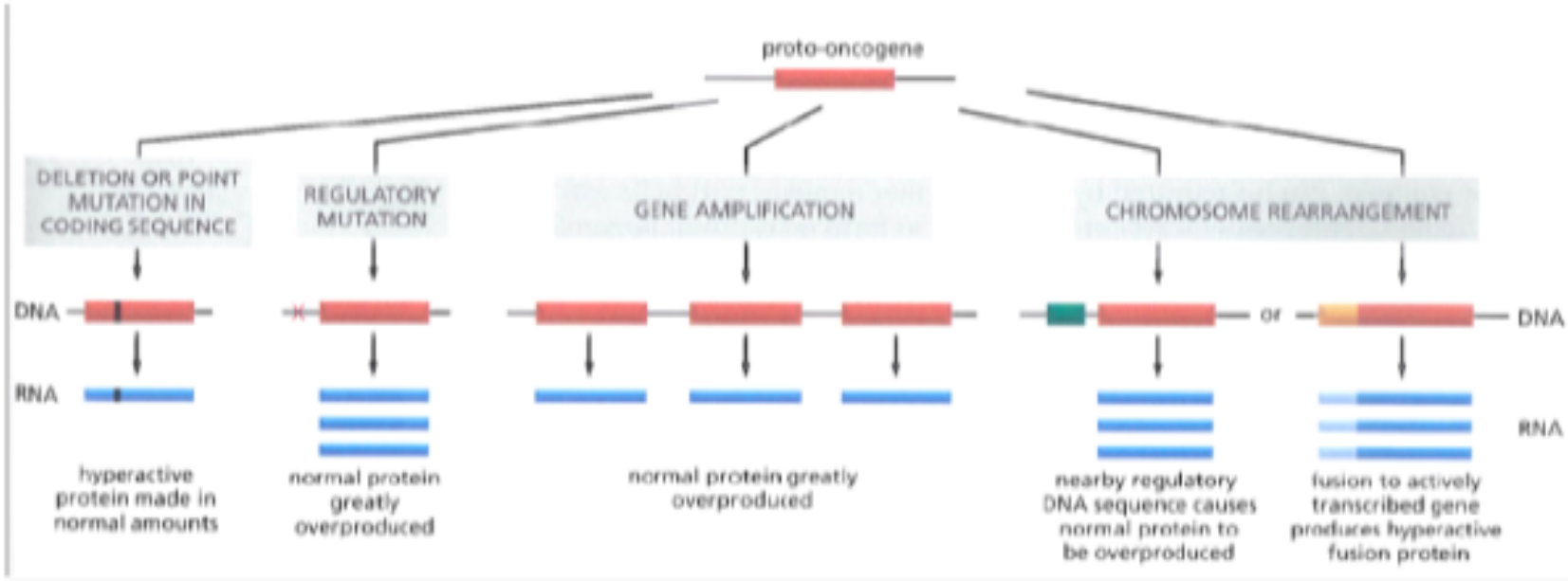
- All cells in the tumor are derived from a single cell that has gained the ability to undergo repeated mitotic divisions
- Most cancers develop after a cell accumulates a number of mutations over a long period of time
- These mutations/chromosome rearrangements vary from one type of cancer to another
- Once formed cancer cells can divide continuously
- Mutations continue to accumulate in the dividing cells and the cancer may become more aggressive and be able to grow faster, metastasize, and/or become resistant to chemotherapy agents



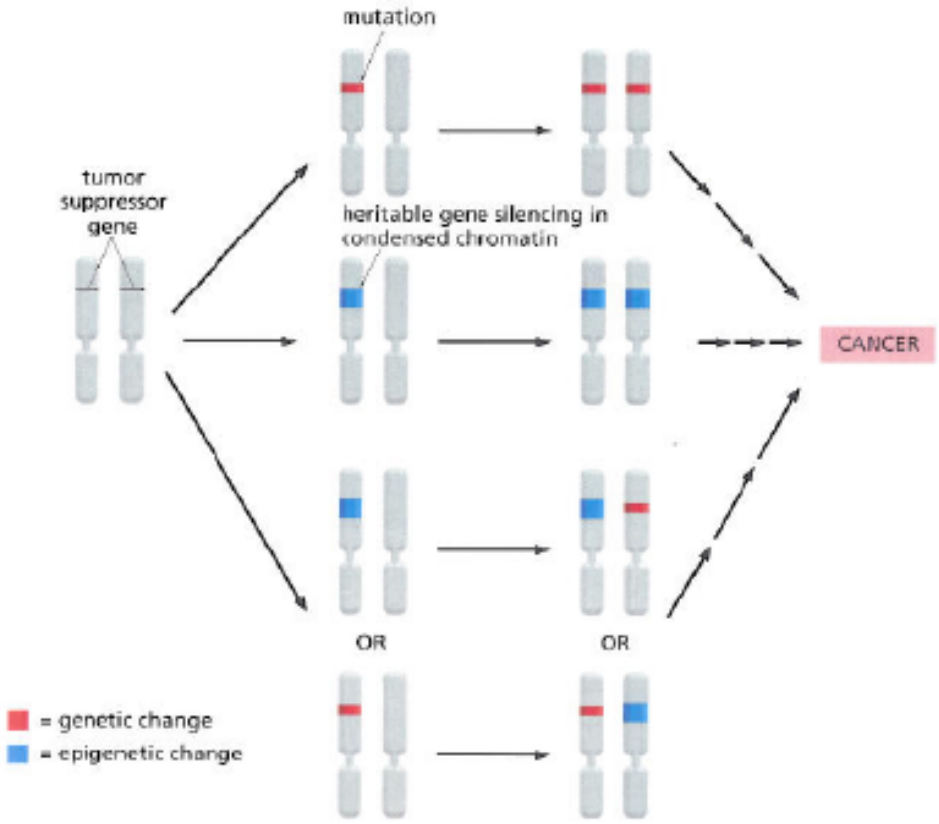
Cancer-Causing Genes

- Oncogenes
  - Mutations that confer gain of functions to oncogenes can promote cancer
  - Mutations with growth-promoting effects on the cell
  - Often heterozygous
- Tumor suppressor genes
  - Mutations that confer loss of function can contribute to cancer
  - Typically homozygous
- DNA maintenance genes
  - Indirect effects on cancer development by not repairing DNA or correcting mutations

Mutations in Oncogenes



Mutations in Tumor Suppressor Genes



Driver and Passenger Mutations

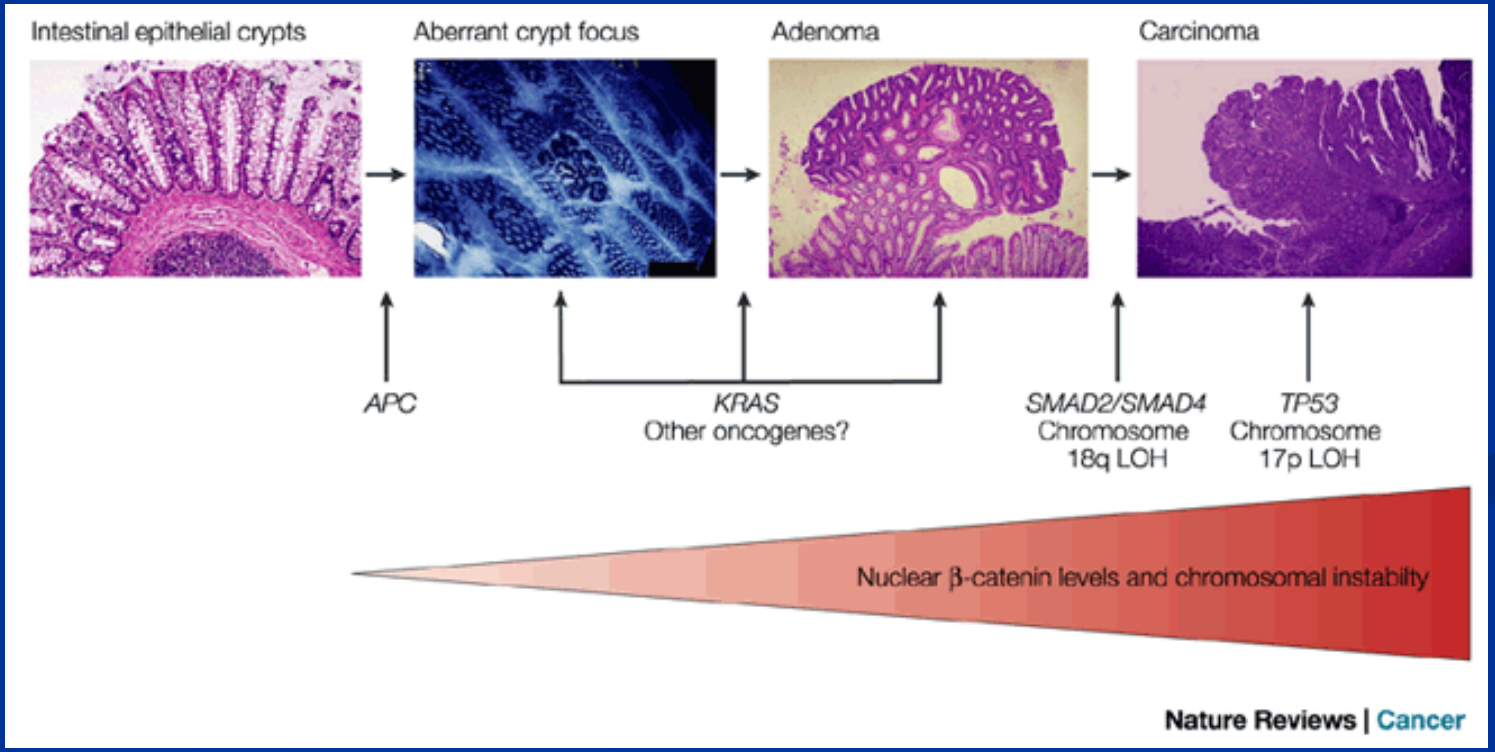
- Driver mutations
  - Causally implicated in oncogenesis
  - Gives growth advantage to cancer cells
  - positively selected in the microenvironment of the tissue
  - E.g., mutations that de-activate tumor suppressor genes
- Passenger mutations
  - Somatic mutations with no functional consequences
  - Does not give growth advantage to cancer cells

Familial Adenomatous Polyposis

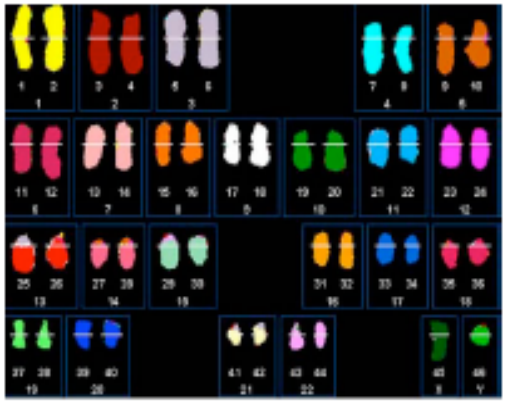
*is an autosomal dominant trait involving mutation of the APC (adenomatous polyposis cancer) gene

*Results in development of polyps and benign growths in the colon.

*These polyps often become malignant



Chromosomal Abnormalities are Common in Cancer Cells



chromosomes of a normal cell

chromosomes of a cancer cell

In many cancers, aneuploidy, or chromosome loss is observed, with 25-30% of alleles present in normal cells, lost in the cancer cell.

This is called loss of heterozygosity

Mutation Details

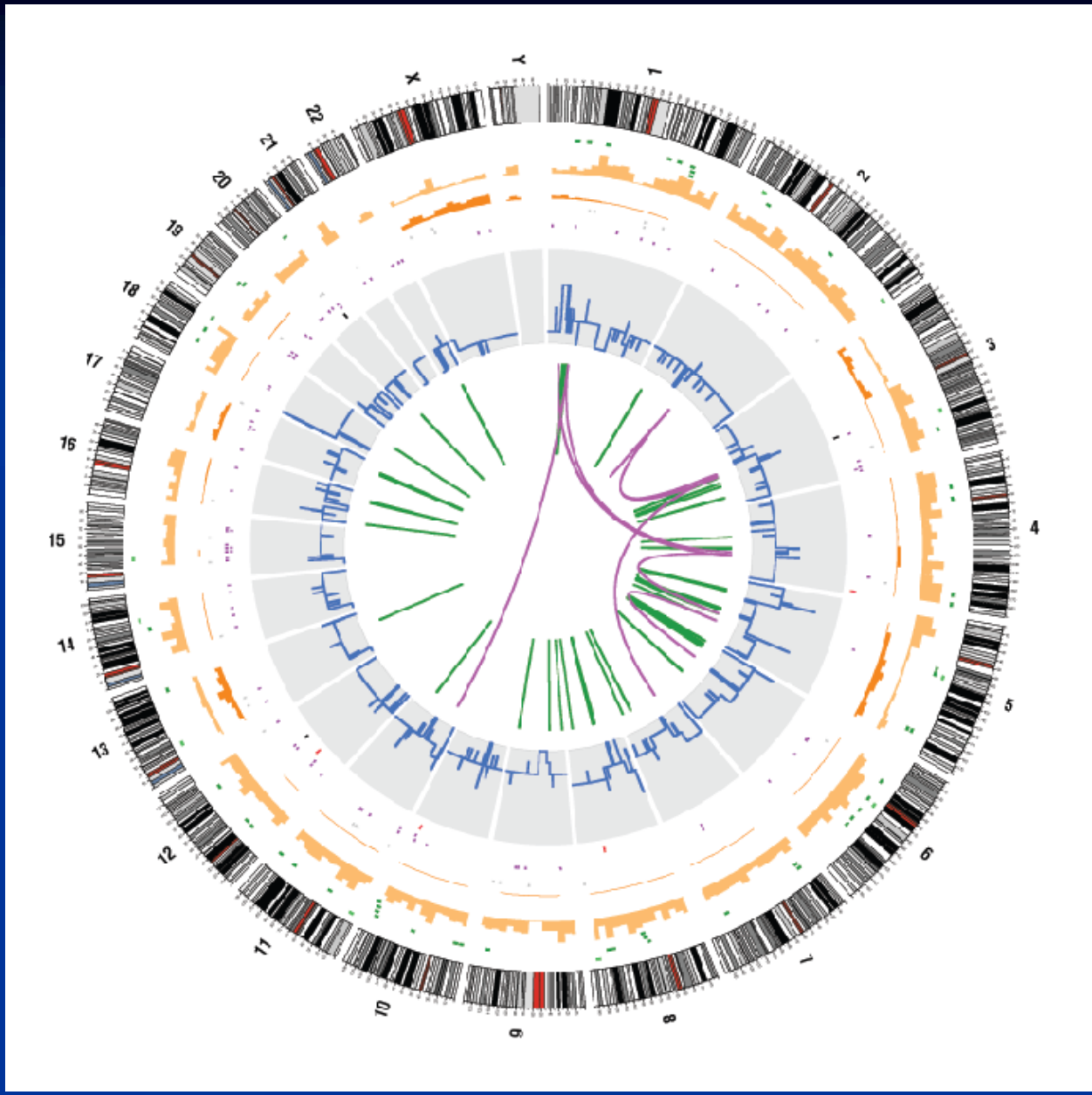
Lung Carcinoma genome

- Nature 2010 463; 184-90.

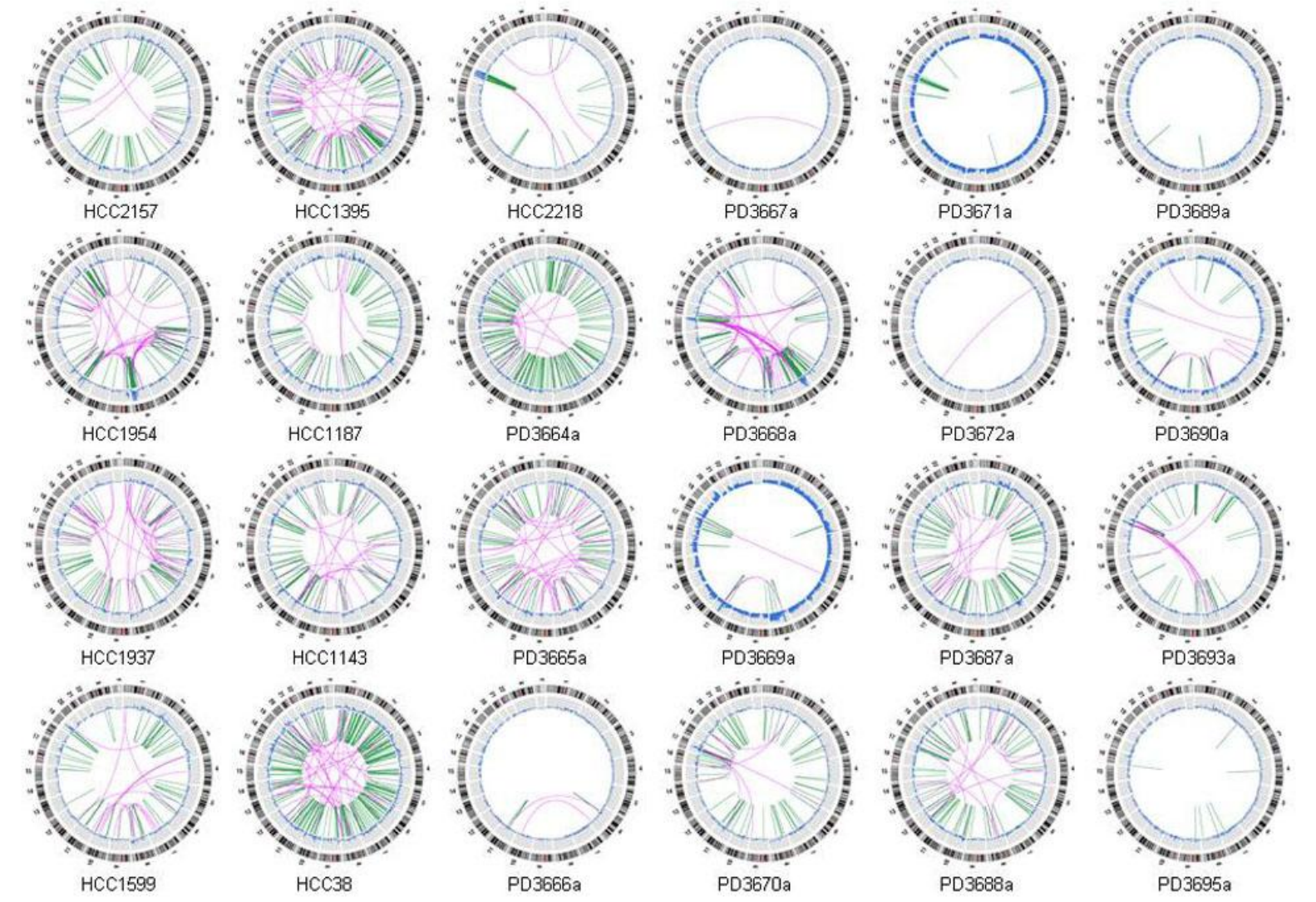
22,910 mutations

58 rearrangements

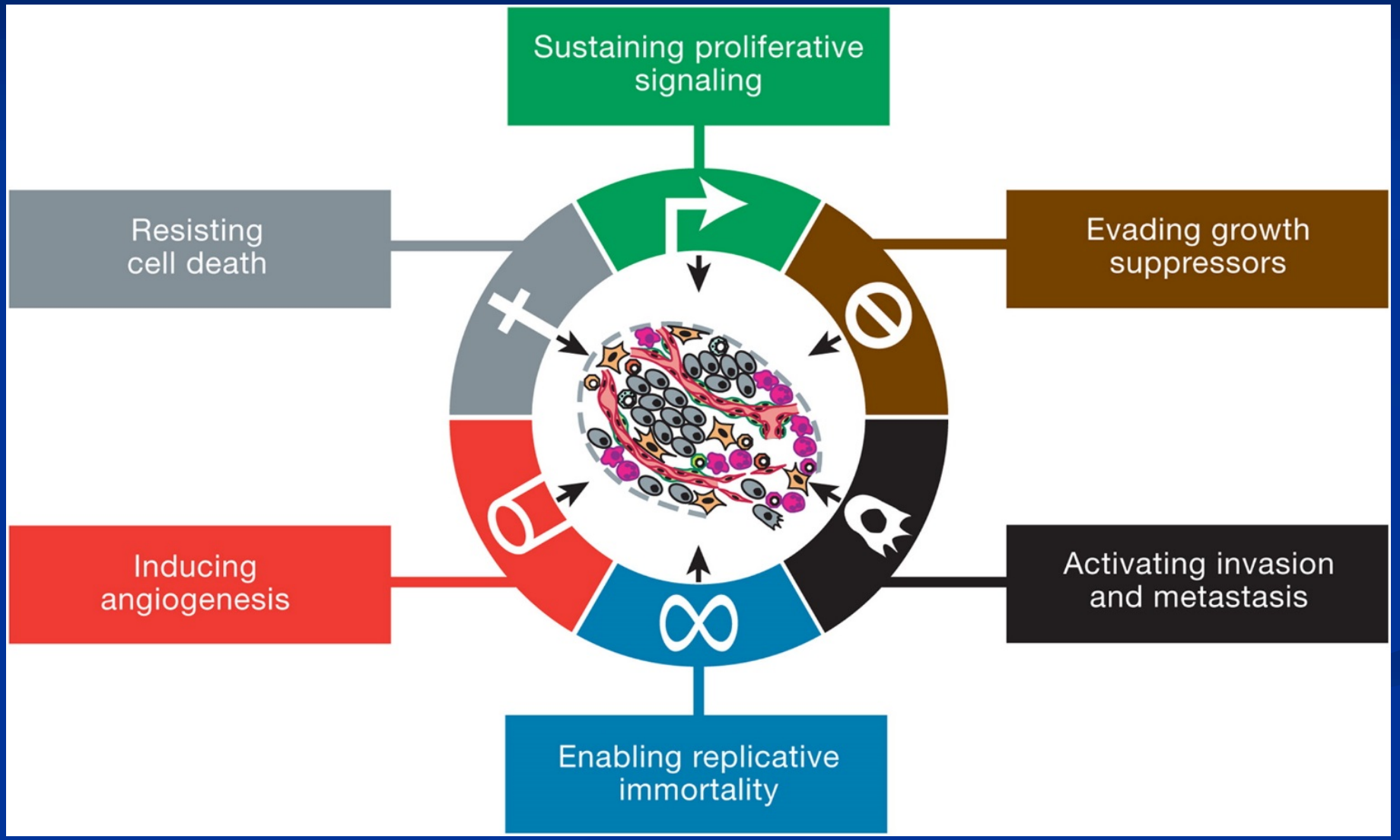
334 copy number segments



Genome wide circus plots of somatic rearrangements in 24 breast cancers



What qualifications do you need to be a cancer cell?



Sustaining proliferative signaling:

- Normal cells need external signals from growth factors to divide

- Cancer cells are not dependent on normal growth factor signaling

- Acquired mutations short-circuit growth factor pathways leading to unregulated growth

- Disruptions of Negative-Feedback Mechanisms that Attenuate Proliferative Signaling

B-RAF,
catalytic subunit of PI3-kinase

RAS / Ras GTPase activity
PI3-kinase / PTEN, mTOR

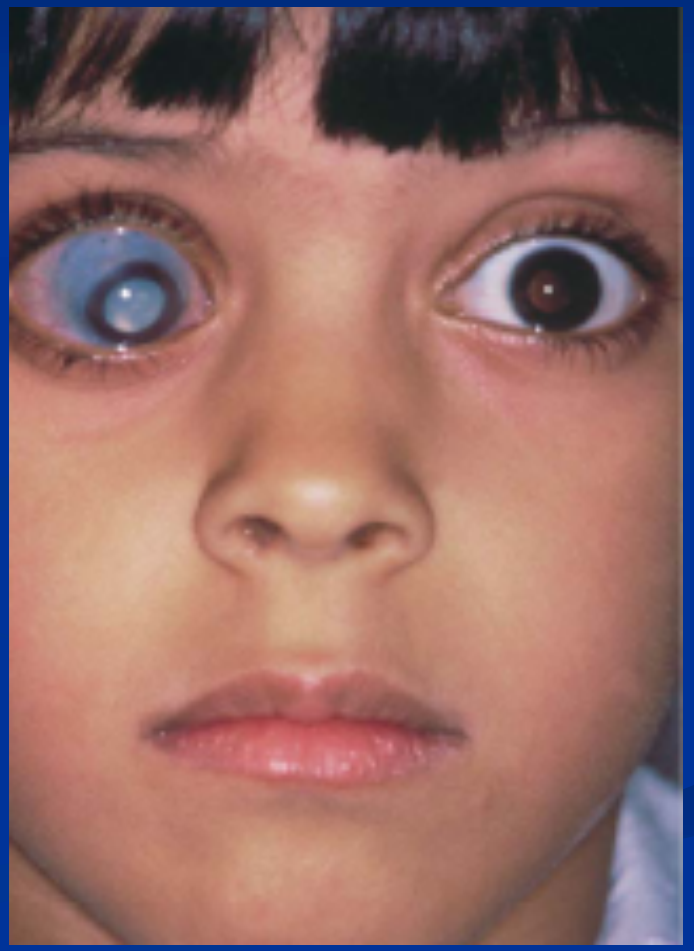
Evasion of growth inhibitory signals:

- Normal cells respond to inhibitory signals to maintain homeostasis (most cells of the body are not actively dividing)

- Cancer cells do not respond to growth inhibitory signals

- Acquired mutations or gene silencing interfere with the inhibitory pathways.

Tumor Suppressors:
RB (retinoblastoma)
TP53
APC (adenomatous polyposis cancer)



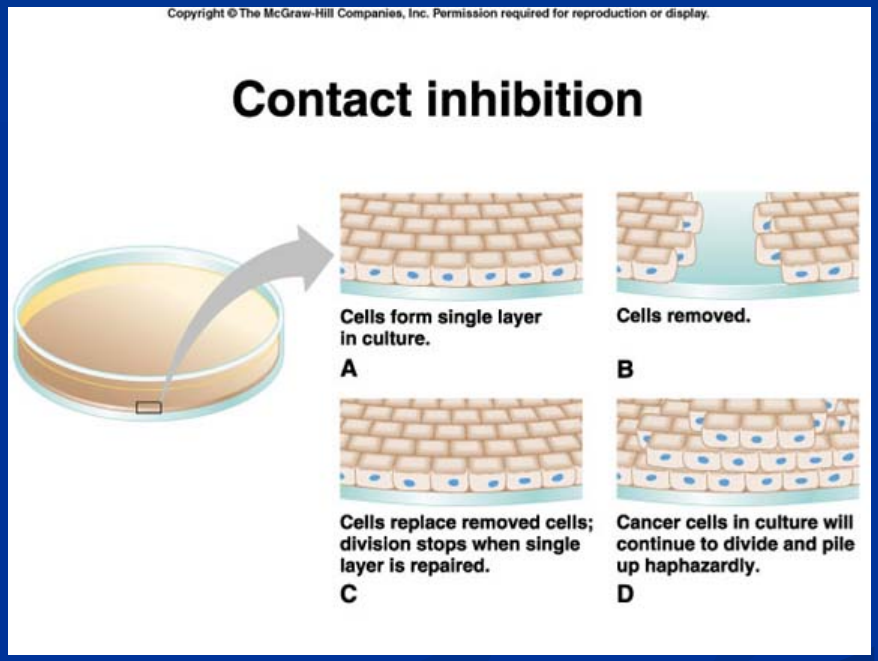
Evasion of growth inhibitory signals:

- Mechanisms of Contact Inhibition and Its Evasion

Tumor Suppressor NF2 (Merlin)
LKB1 epithelial polarity protein / MYC

- Corruption of the TGF-b Pathway Promotes Malignancy

TGF-b = antiproliferative



Resisting cell death

- Normal cells are removed by apoptosis, often in response to DNA damage

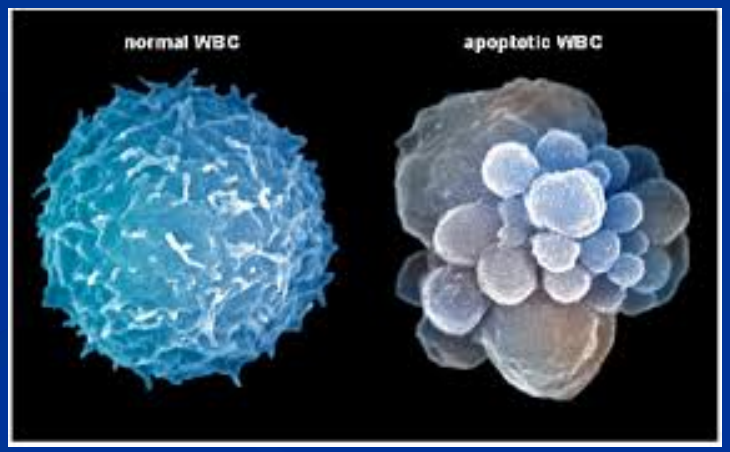
- Cancer cells evade apoptotic signals.

  Bcl-2 family of regulatory proteins

  Anti: Bcl-xL, Bcl-w, Mcl-1, A1

  Pro: Bax and Bak

  TP53



Enabling replicative immortality

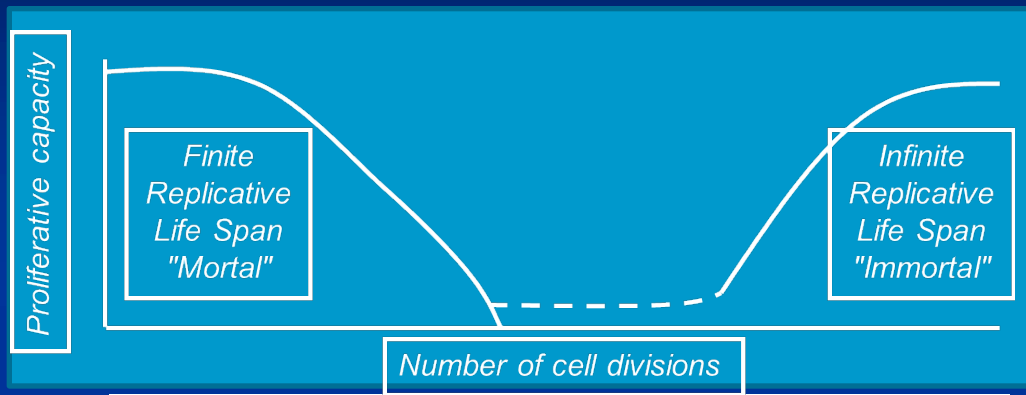
- Normal cells: a finite number of cell doublings after which they become senescent.

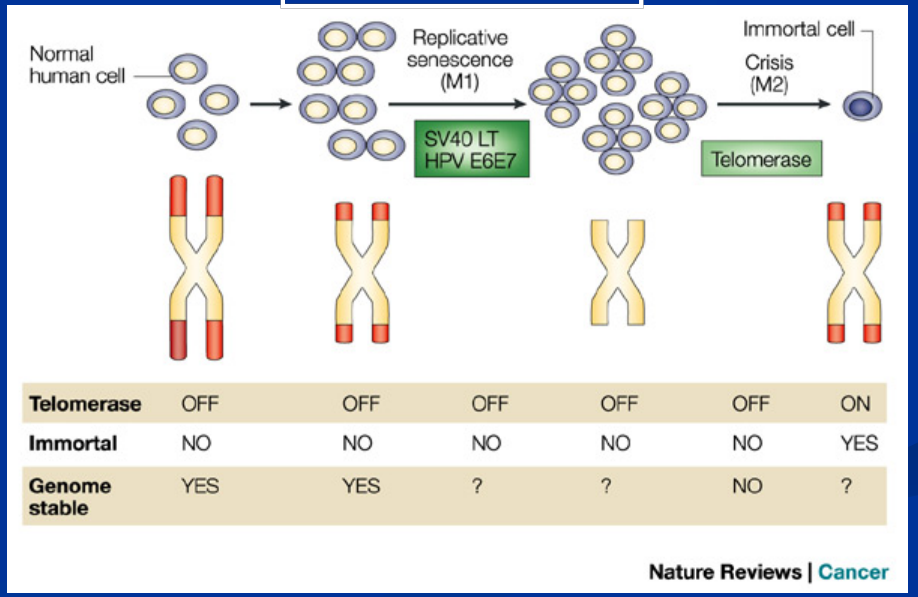
This cellular counting device is the shortening of chromosomal ends, telomeres: occurs during every round of DNA replication

- Cancer cells maintain the length of their telomeres

- Altered regulation of telomere maintenance results in unlimited replicative potential

Telomerase



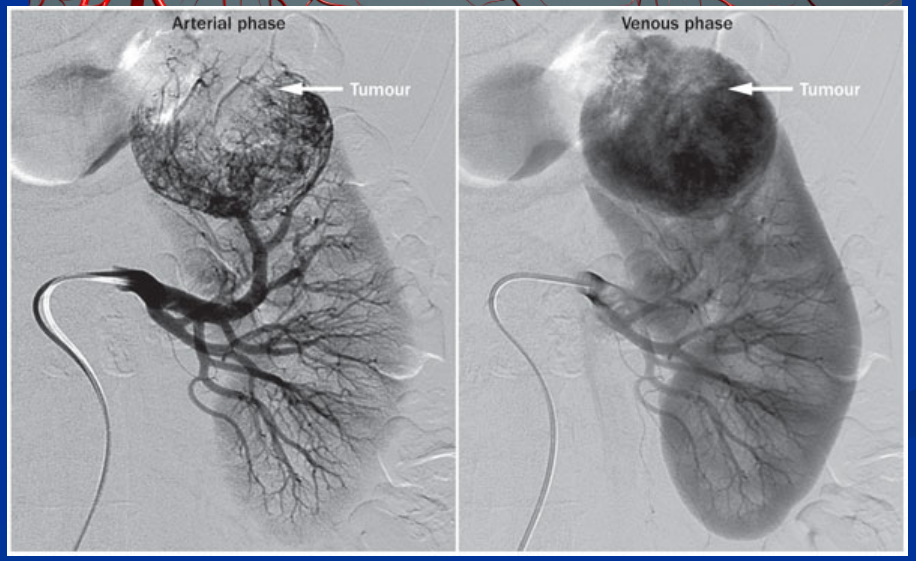


Telomerase	OFF	OFF	OFF	OFF	OFF	ON
Immortal	NO	NO	NO	NO	NO	YES
Genome stable	YES	YES	?	?	NO	?

Inducing Angiogenesis

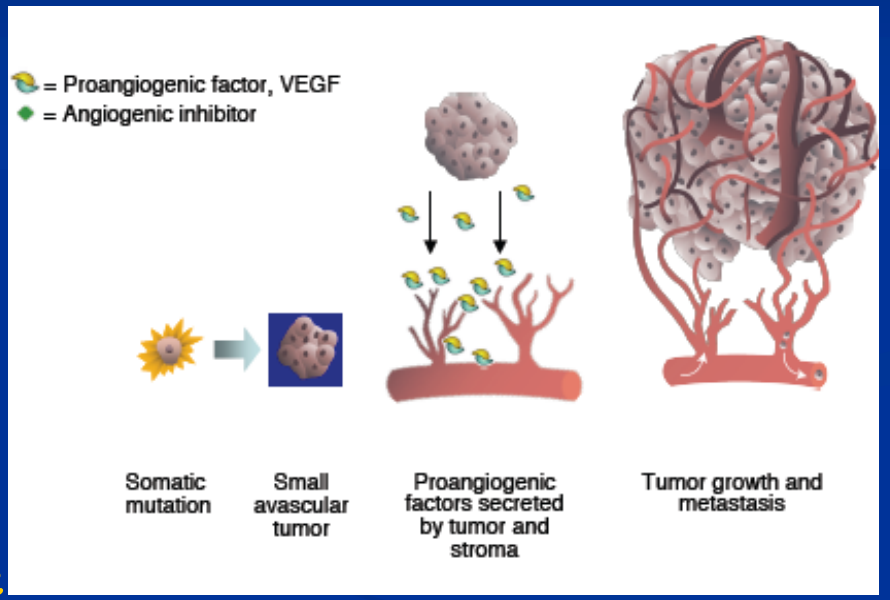
- Normal cells:
(1) blood vessels supply oxygen and nutrients
(2) the vascular architecture is more or less constant in the adult

- Cancer cells:
(1) induce angiogenesis, required for tumor survival and expansion
(2) Altered balance between angiogenic inducers and inhibitors can activate the "angiogenic switch"



Inducing Angiogenesis

- Angiogenesis inducers and inhibitors:
  VEGF-A, Angiopoietin, FGF
  TSP-1, Angiostatin, Endostatin



- Pericytes Are Important components of the Tumor Neovasculature

- Bone Marrow-Derived Cells Contribute to Tumor Angiogenesis:
  macrophages, neutrophils, mast cells, and myeloid progenitors
  vascular progenitor cells

Activating Invasion and metastasis (complex!)

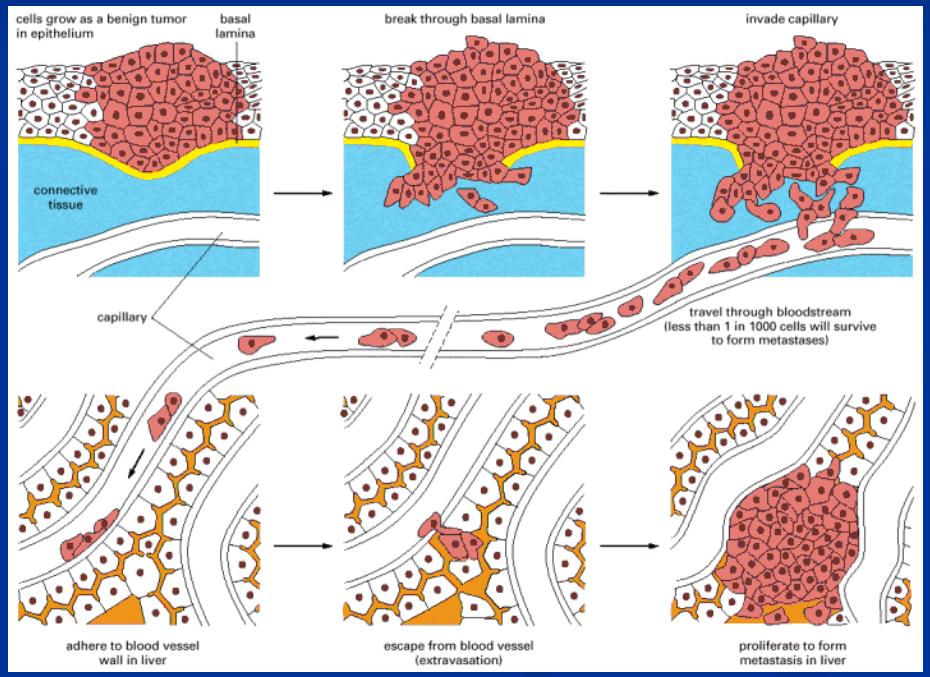
- Normal cells: generally do not migrate

- The movement of cancer cells to other parts of the body- metastasis - is a major cause of cancer Deaths

- mutations may affect the activity and/or levels of enzymes involved in invasion or molecules involved in cell-cell or cellular-extracellular adhesion

E-cadherin (down)

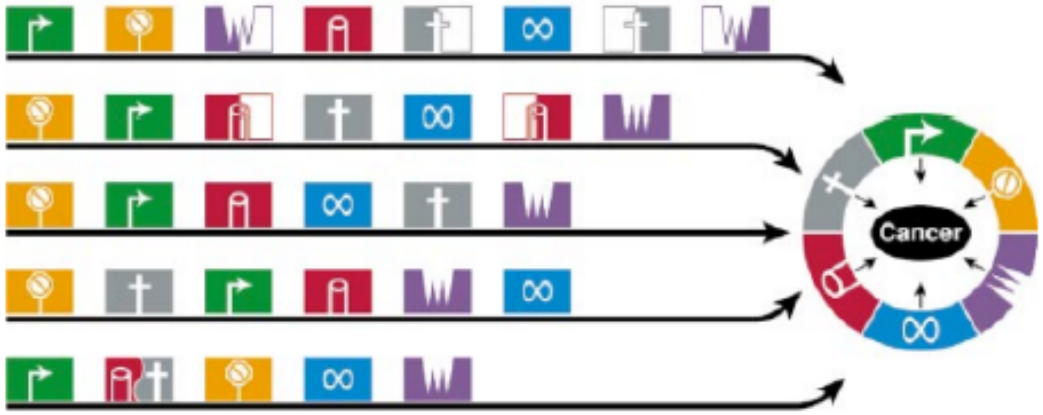
N-cadherin (up)



- The EMT Program Broadly Regulates Invasion and Metastasis

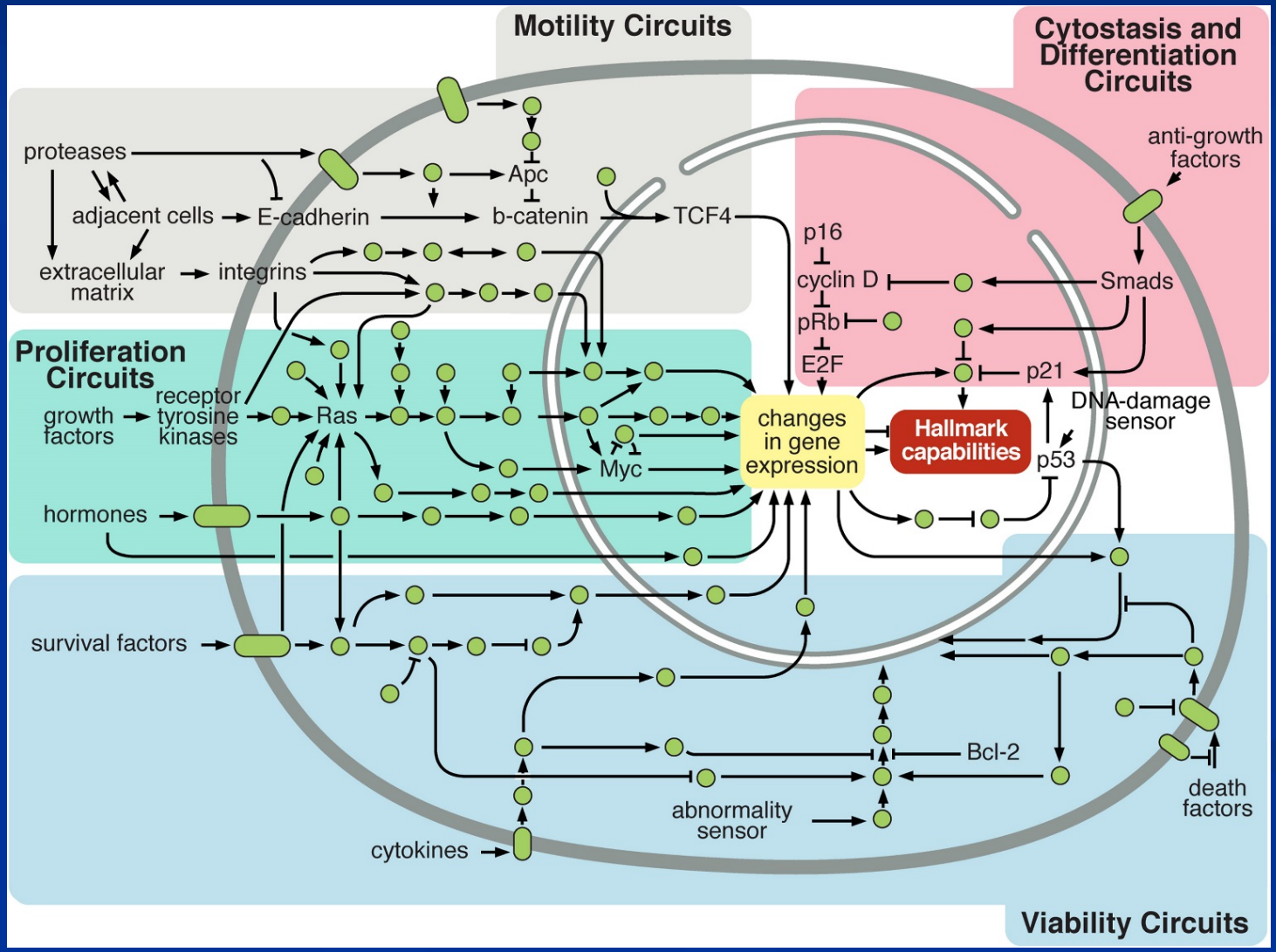
"epithelial-mesenchymal transition"

Pathways of Tumorigenesis



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

Programming of Hallmark Capabilities by Intracellular Circuitry



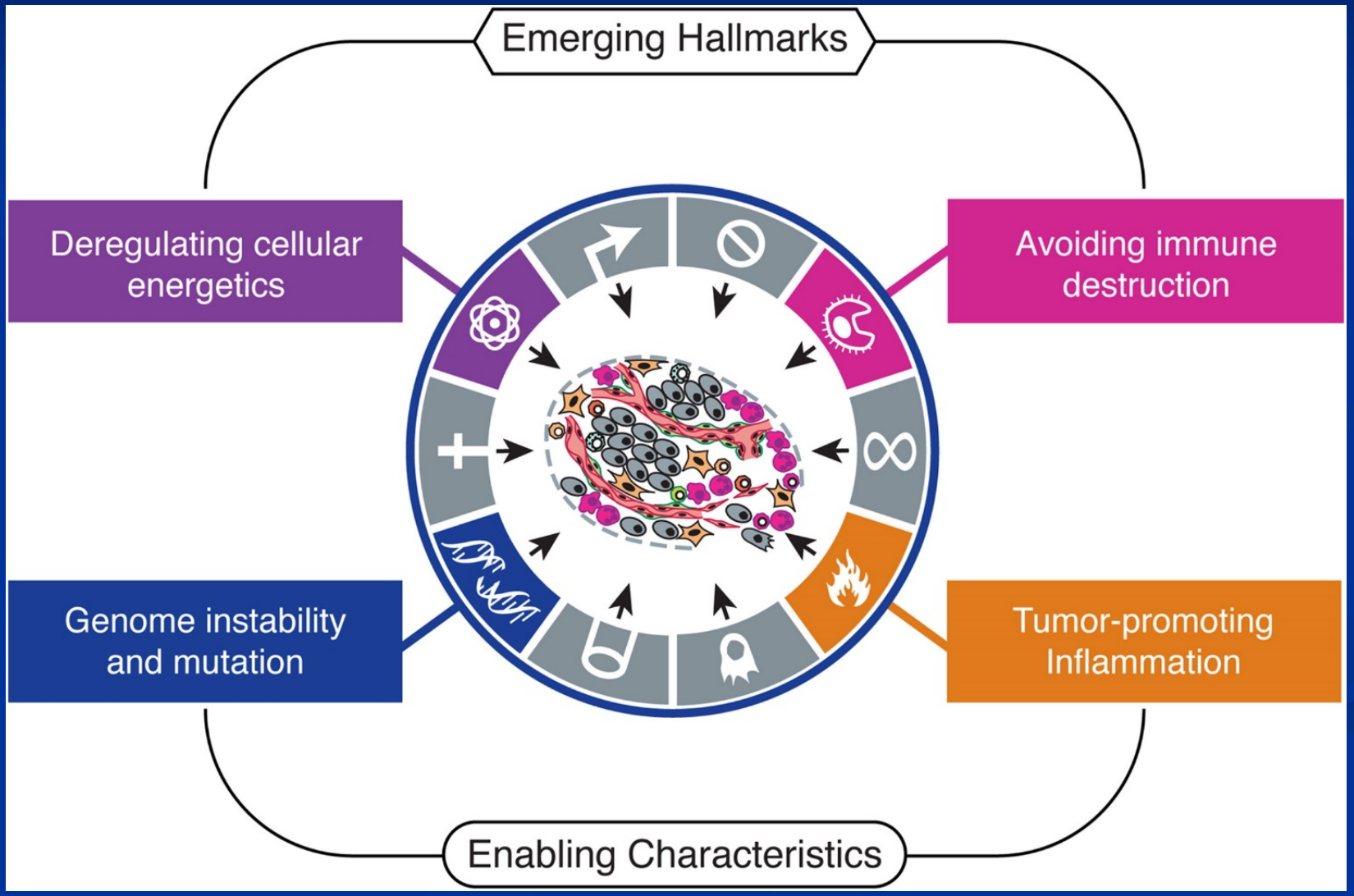
Programming of Hallmark Capabilities by Intracellular Circuitry

Each circuit can be segmented into distinct subcircuits, each of which is specialized to support a discrete cell-biological property in normal cells and is reprogrammed in order to implement a hallmark capability in cancer cells

Crosstalk between the individual subcircuits:

For example, certain oncogenic events can affect multiple capabilities, as illustrated by the diverse effects that prominent oncogenes, such as mutant RAS and upregulated MYC, have on multiple hallmark capabilities (e.g., proliferative signaling, energy metabolism, angiogenesis, invasion, and survival).

Emerging Hallmarks & Enabling Characteristics

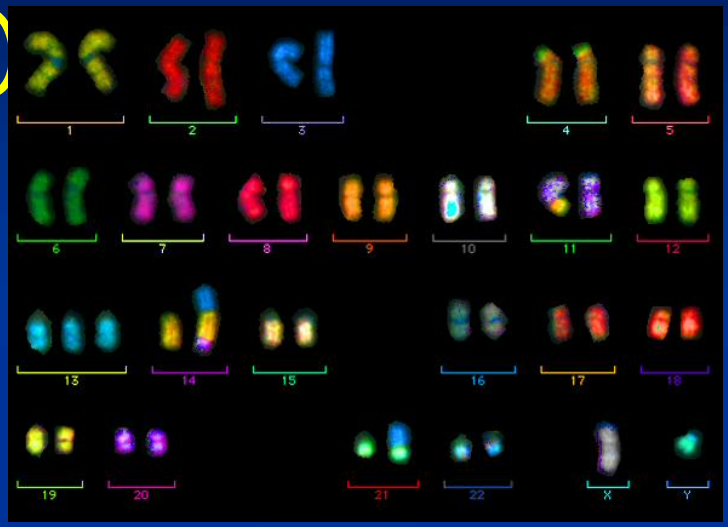


Enabling Characteristics

1) Genome instability and mutation:
Most prominent is the development of genomic instability in cancer cells, which generates random mutations including chromosomal rearrangements; among these are the rare genetic changes that can orchestrate hallmark capabilities.

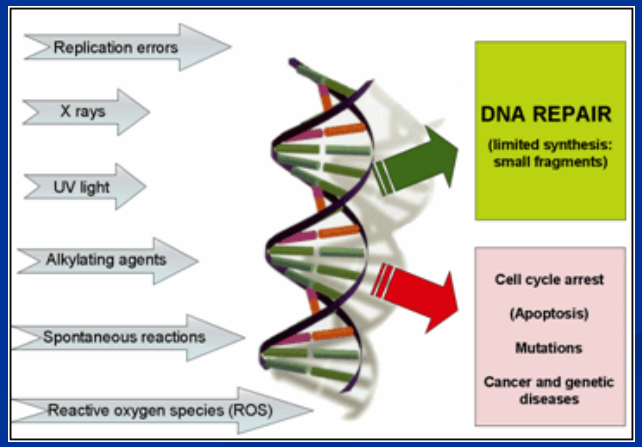
2) Tumor-promoting inflammation:
A second enabling characteristic involves the inflammatory state of premalignant and frankly malignant lesions that is driven by cells of the immune system, some of which serve to promote tumor progression through various means.

Genome instability and mutation (an enabling characteristic)



- Acquiring the core hallmarks of cancer usually depends on genomic alterations

- Faulty DNA repair pathways can contribute to genomic instability.



Tumor-promoting inflammation (an enabling characteristic)

– all tumors contain inflammatory immune cells

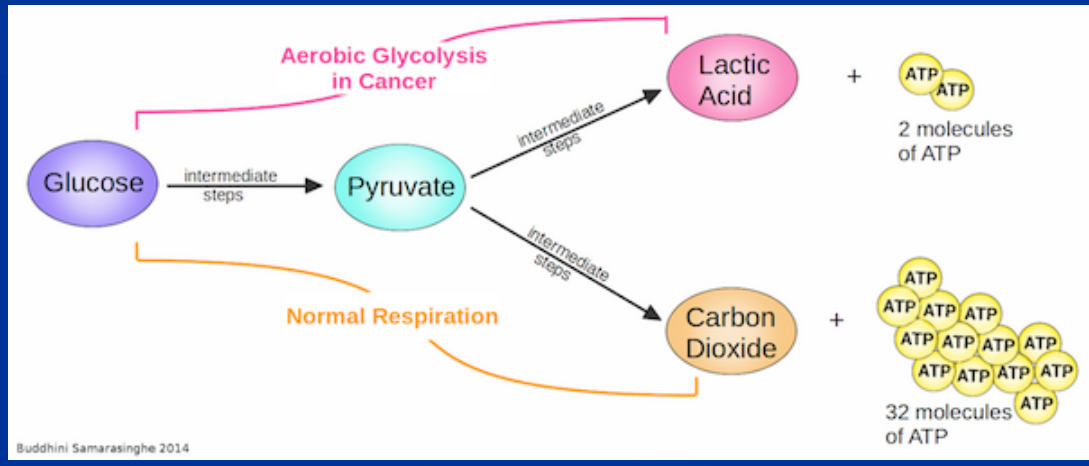
(1) inflammatory cells can provide growth factors and enzymes that promote angiogenesis and invasion

(2) inflammatory cells can release oxygen species that are mutagenic

Reprogramming energy metabolism (emerging hallmark)

- Uncontrolled cell division demands increases in fuel and biosynthetic precursors that is obtained by adjusting energy metabolism

- Cancer cells modify, or reprogram, cellular metabolism in order to most effectively fuel cell growth and division



"aerobic glycolysis": metabolic switch

Reprogramming energy metabolism (emerging hallmark)

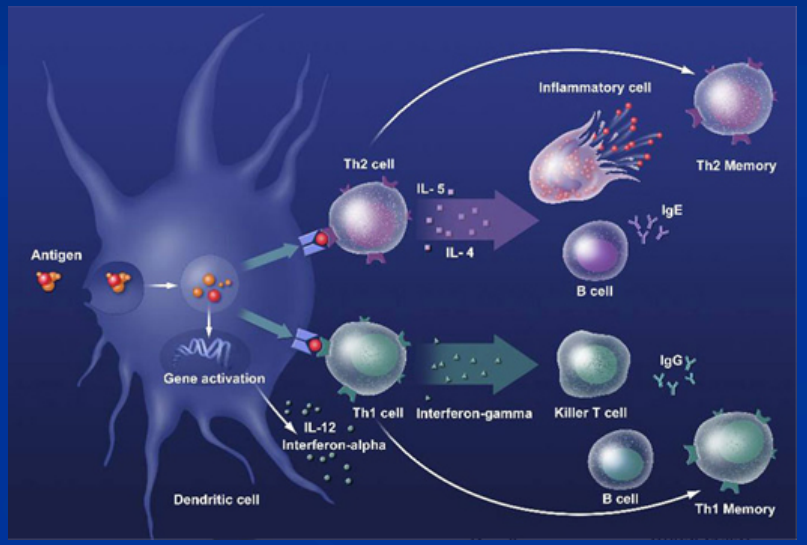
Glucose transporters:
GLUT1 (up)

hypoxia response system acts pleiotropically to upregulate glucose transporters and multiple enzymes of the glycolytic pathway

Glycolytic fueling has been shown to be associated with activated oncogenes (e.g., RAS, MYC) and mutant tumor suppressors (e.g., TP53)

HIF1a and HIF2a transcription factors, which in turn upregulate glycolysis

Avoiding immune destruction (emerging hallmark)



-the theory of immune surveillance: the immune system can recognize and eliminate cancer cells: Immunoediting

by T and B lymphocytes, macrophages, and natural killer cells

- successful cancer cells :
(1) no stimulation of the immune response

(2) interference with the immune response to avoid immune destruction

Avoiding immune destruction (emerging hallmark)

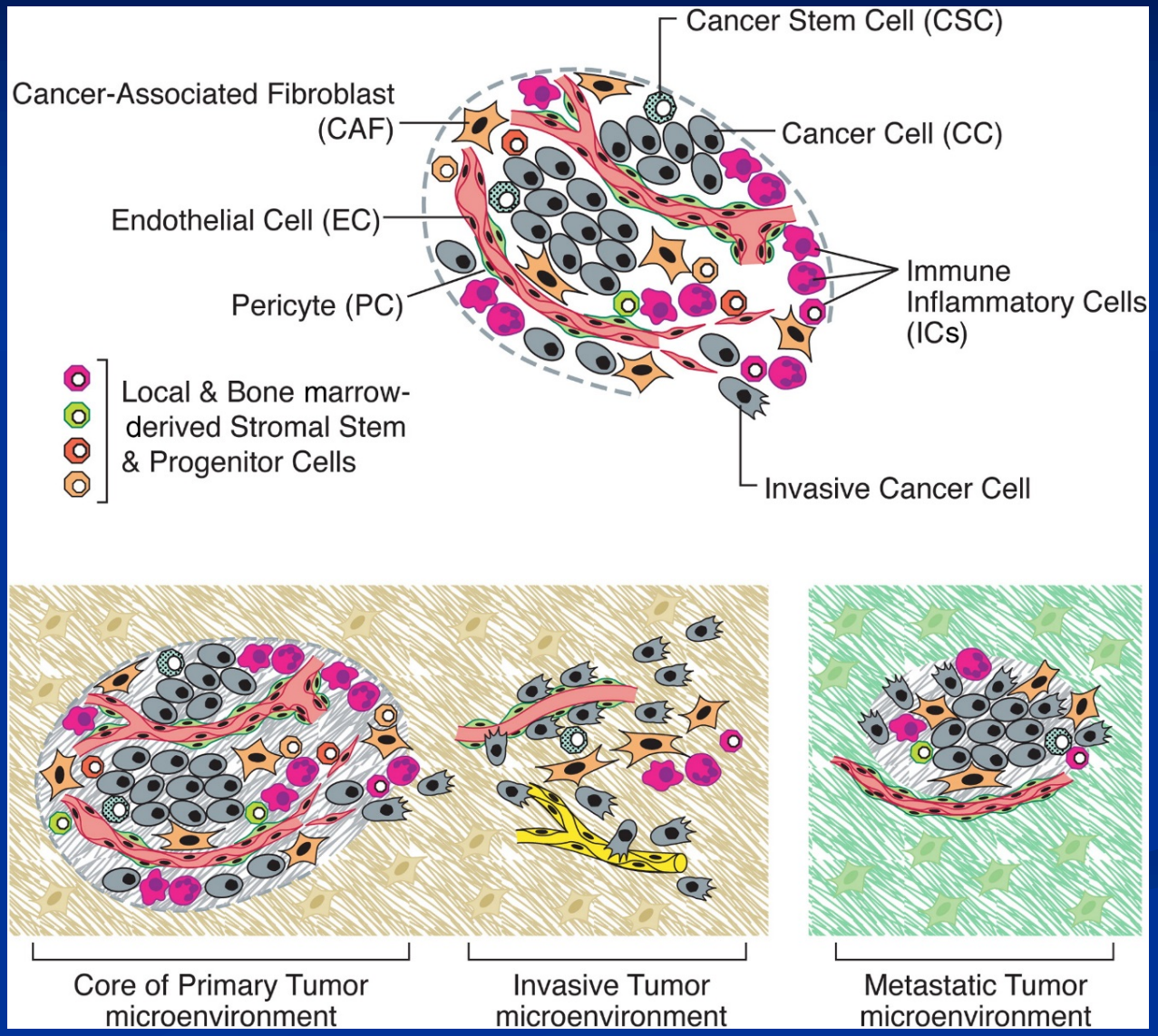
CD8+ cytotoxic T lymphocytes (CTLs), CD4+ Th1 helper T cells

cancer cells may paralyze infiltrating CTLs and NK cells, by secreting TGF-b or other immunosuppressive factors

recruitment of inflammatory cells that are actively immunosuppressive, including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs)

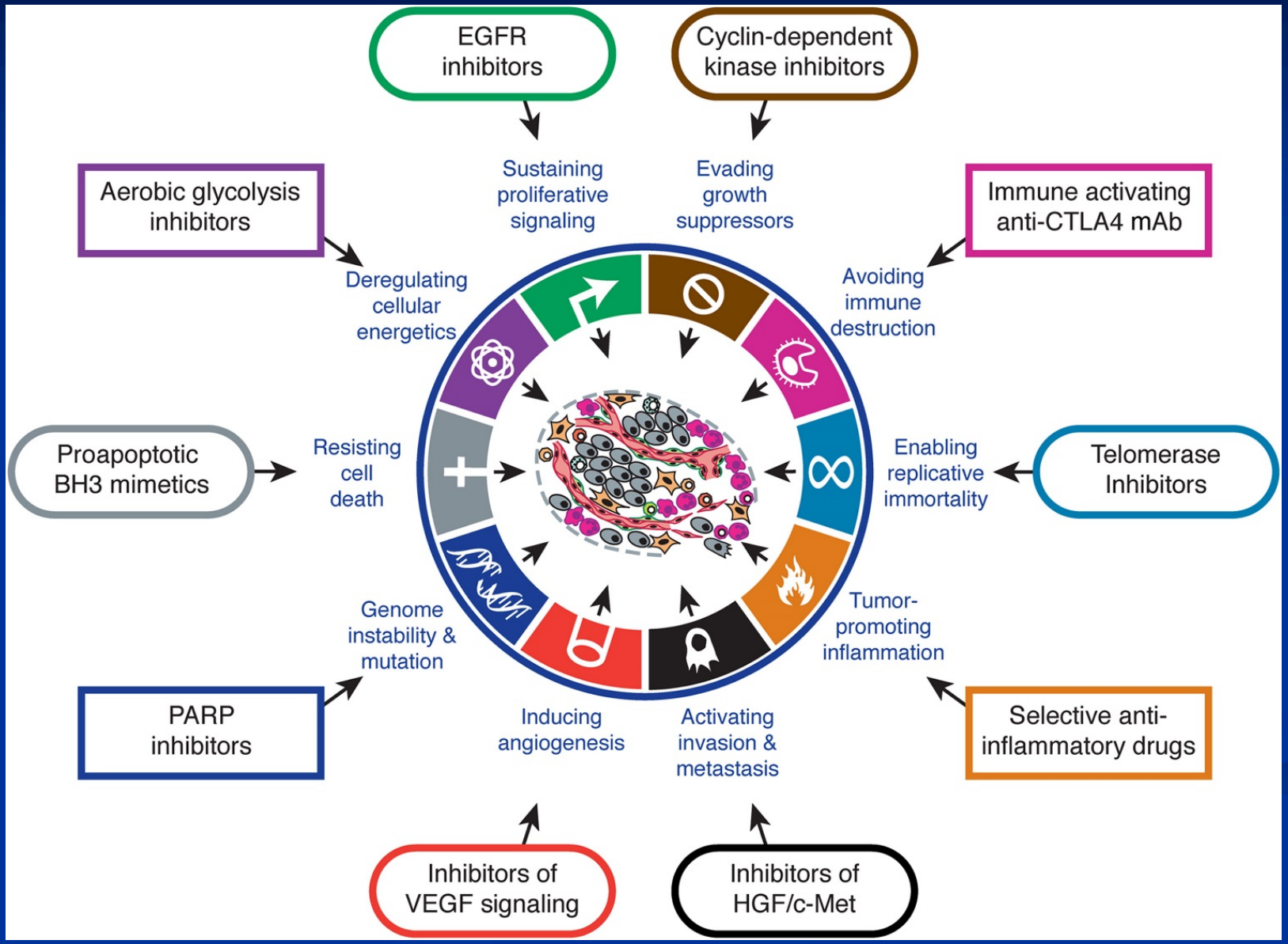
The Tumor microenvironment

Tumor growth & progression



Cell 2011 144, 646-674DOI: (10.1016/j.cell.2011.02.013)

Tumor Targeted Therapy



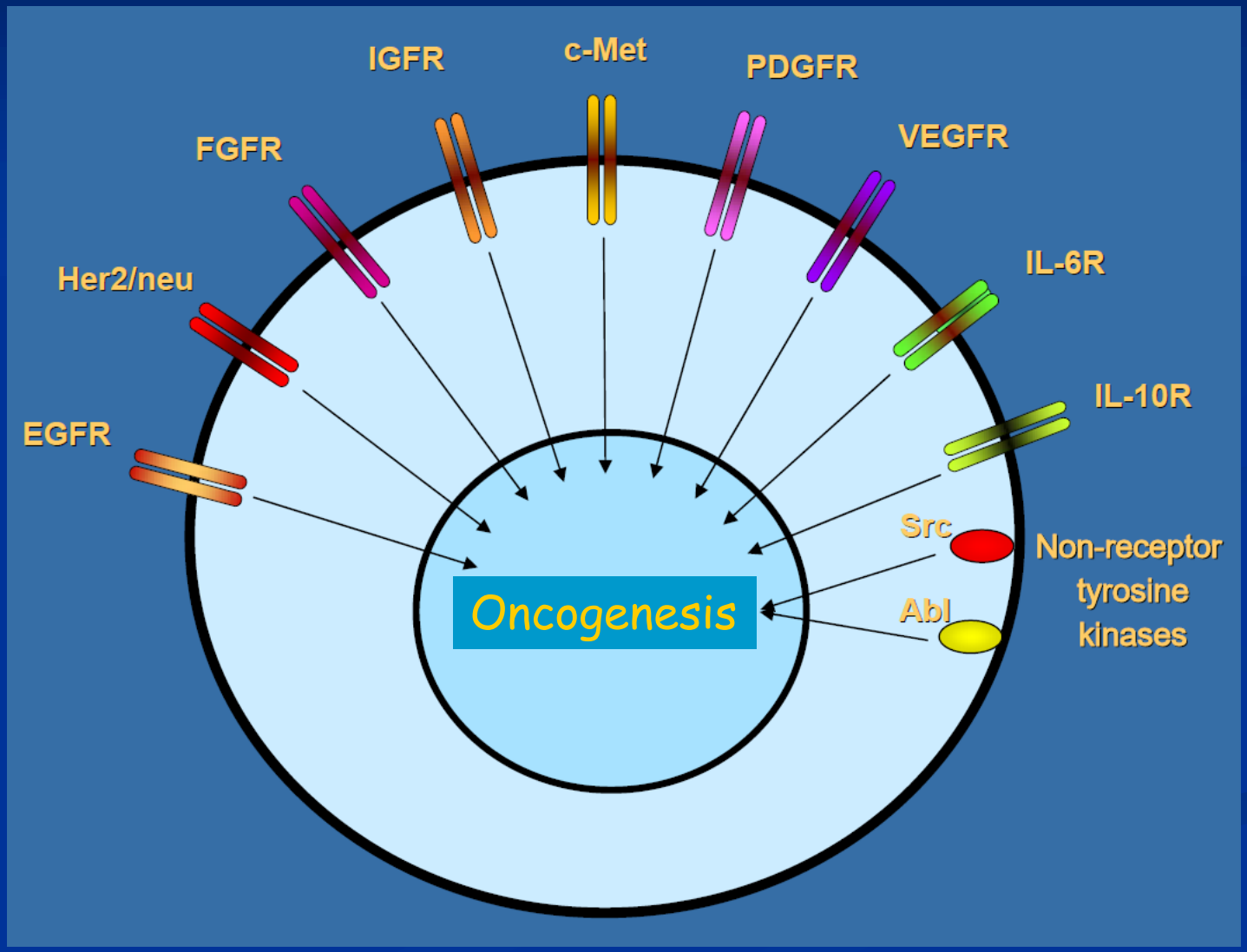
Tumor Targeted Therapy: Challenge

Core hallmark capabilities is regulated by partially redundant signaling pathways

Consequently, a targeted therapeutic agent inhibiting one key pathway in a tumor may not completely shut off a hallmark capability, allowing some cancer cells to survive and adapt to the selective pressure imposed by the therapy being applied. Such adaptation can reestablish the functional capability, permitting renewed tumor growth and clinical relapse.

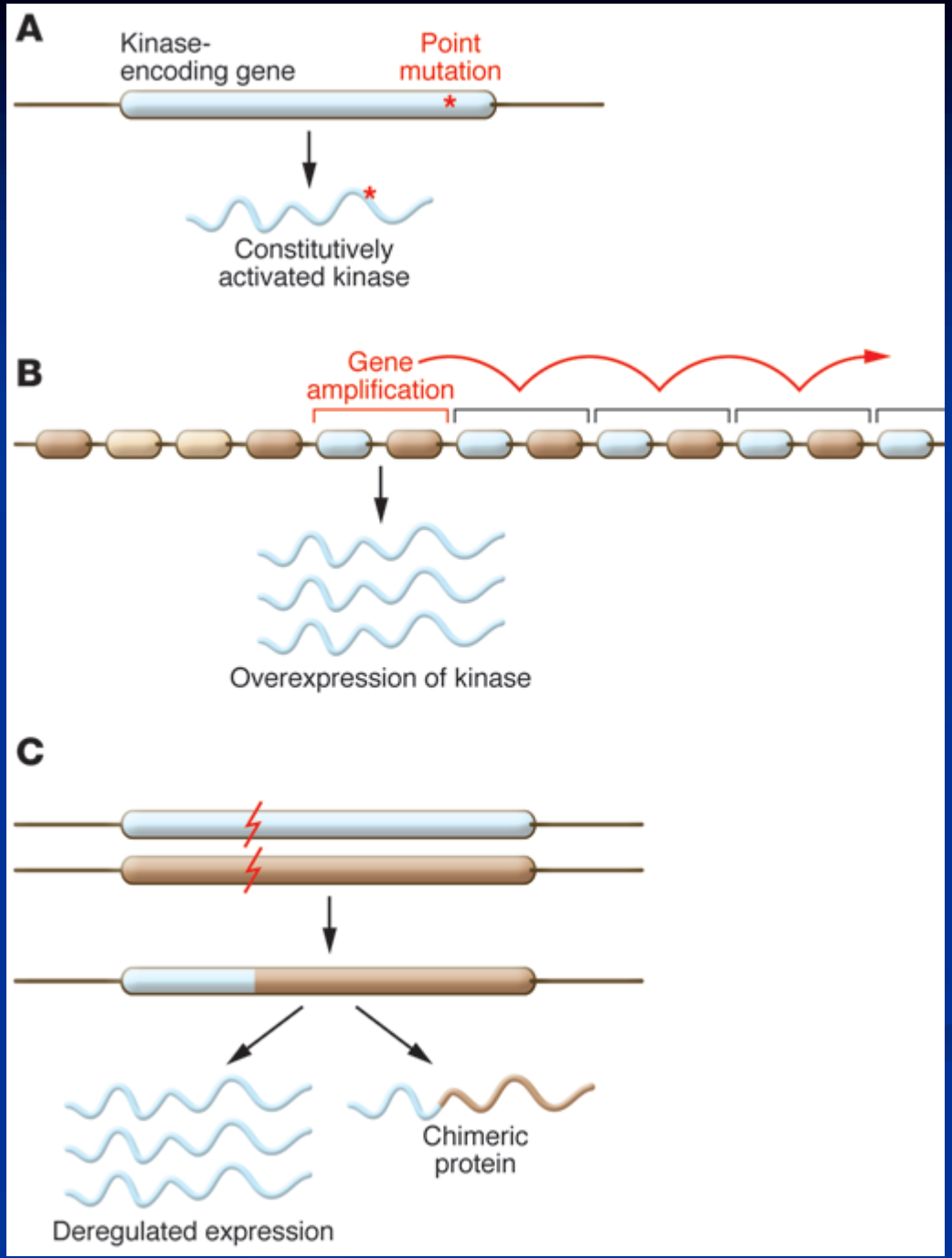
Given that the number of parallel signaling pathways supporting a given hallmark must be limited, it may become possible to target all of these supporting pathways therapeutically, thereby preventing the development of adaptive resistance.

Kinases in Cancer



Kinases in Cancer

Activation



Kinases in Cancer: Activation

Table 1. Examples of known mechanisms of kinase activation in cancer

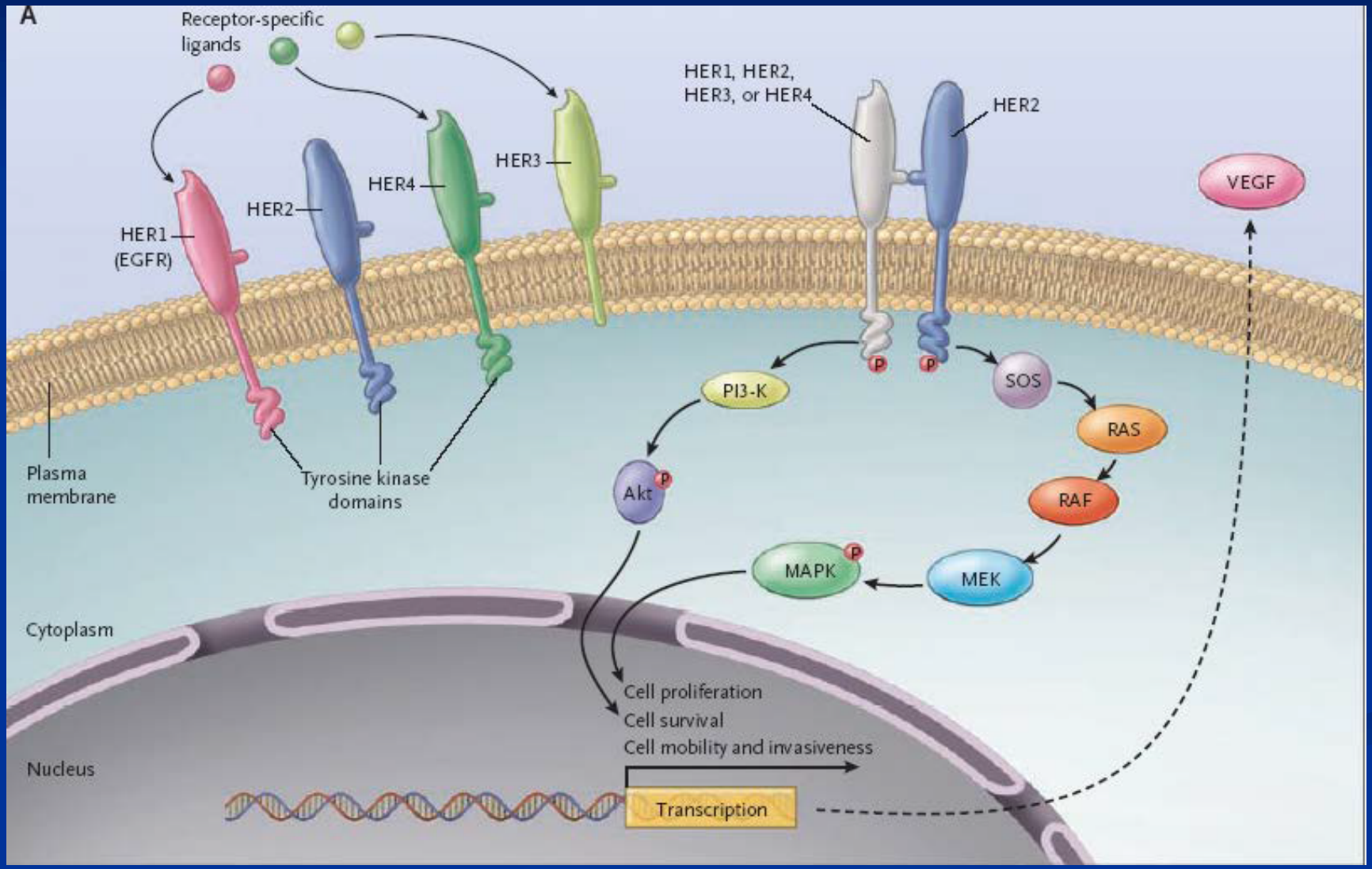
Activation mechanism	Kinases
Point mutations	*ACVR1B, ACVR2B, AKT1, ALK, ALPK2, ATM, BRAF, CDK12, CDK4, EGFR, EPHA2, ERBB2, ERBB3, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, JAK2, KIT, MAP2K1, MAP3K1, MAP4K3, MET, MTOR, PIK3CA, SGK1, STK19, TGFBR2*
Gene amplification	*CDK4, CDK6, CRKL, EGFR, ERBB2, FGFR1, FGFR2, FGFR3, FLT3, IGF1R, KIT, MET, PAK1, PDGFRA, PIK3CA, PRKCI*
Gene amplification or fusion of a kinase ligand	*FGF19 (FGFR4), HGF (MET), NRG1 (ERBB3), VEGFA (VEGFR)*
Gene fusions	*ALK, ABL1, BRAF, EGFR, FGFR1, FGFR2, FGFR3, FGR, JAK2, MET, NTRK1, NTRK2, NTRK3, PDGFRA, PDGFRB, PIK3CA, PRKACA, PRKCA, PRKCB, RAF1, RET, ROS1, SYK*

Point mutations in kinases are derived from the list of significantly mutated cancer genes found by analysis with the MutSig (http://www.broadinstitute.org/cancer/cga/mutsig) suite across 4,742 human cancers and their matched normal-tissue samples in 21 cancer types in TCGA (21). Kinases activated by gene amplifications in cancer were obtained from the list of significantly amplified regions in a set of 10,570 cancer samples across 31 cancer types in TCGA, analyzed with GISTIC (http://www.broadinstitute.org/tcga) (23). Finally, kinases activated by gene fusions were compiled from the list of recurrent fusions discovered in solid tumors (26), complemented with hematopoietic tumors (Catalogue of Somatic Mutations in Cancer [COSMIC], http://cancer.sanger.ac.uk/cosmic).

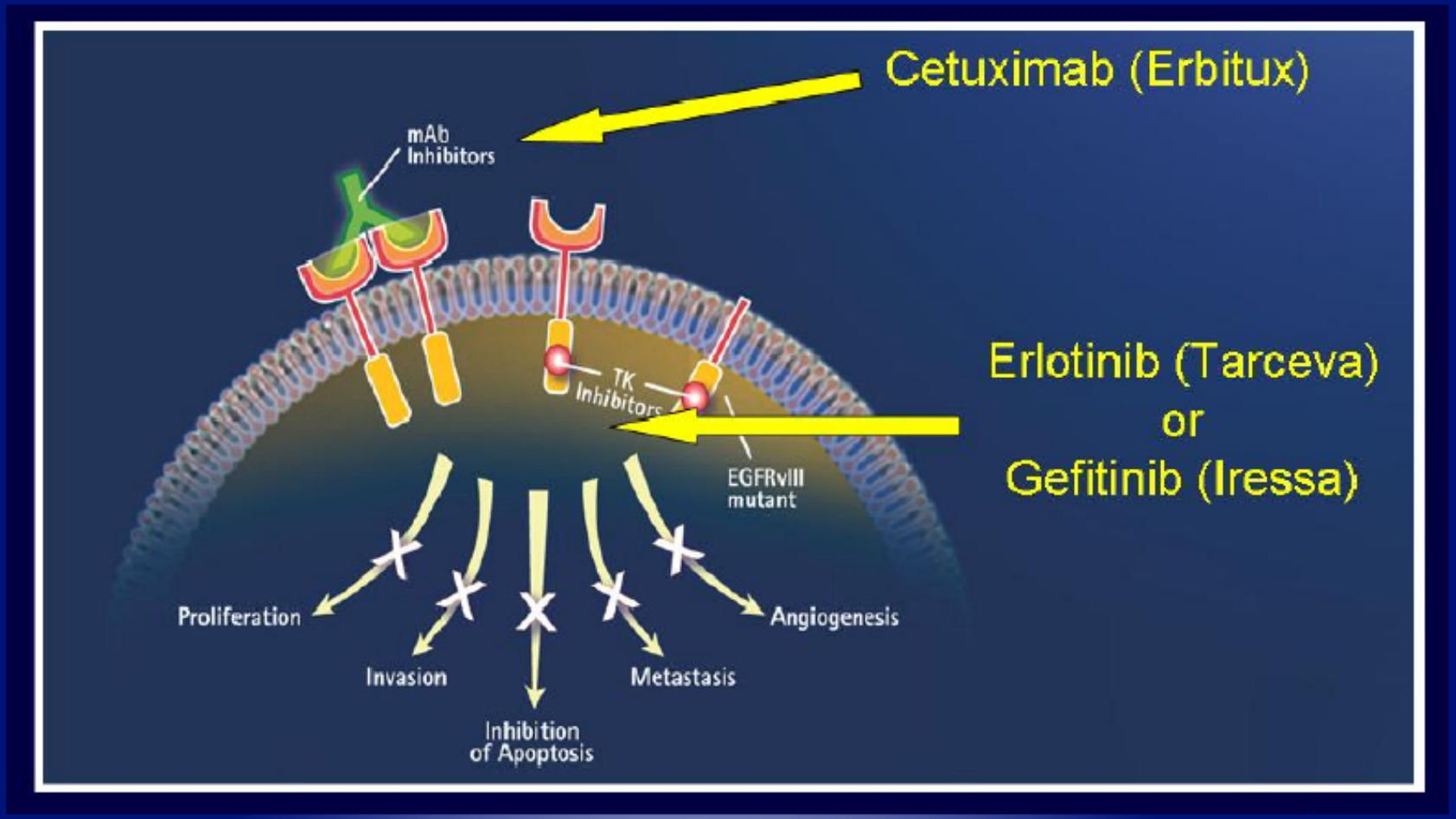
CURRENT DEVELOPMENT OF TARGETED THERAPY IN ONCOLOGY

- The development is particularly active and concerns principally in two types of agents which are monoclonal antibodies (MABs) and tyrosine kinase inhibitors (TKIs).
- Epidermal growth factor receptor (EGFR) signaling pathways play a key role in the regulation of cell proliferation, survival and differentiation.
- Consequently, EGFR is one of the most-studied ligand–receptor systems and specific EGFR inhibition approaches are currently among the most promising and the most advanced in the clinical setting.

The EGFR axis

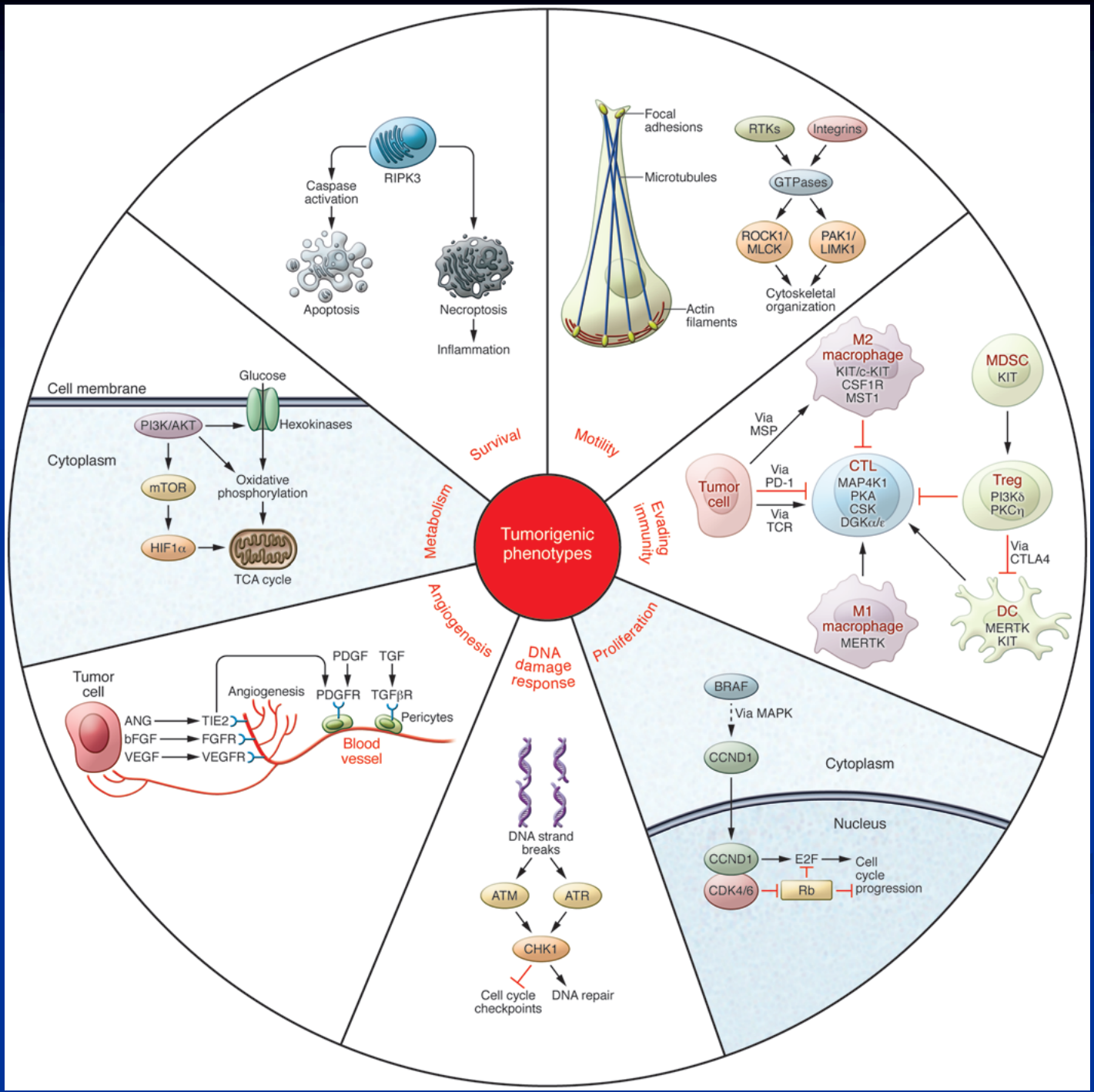


Common Approaches for inhibiting the Epidermal Growth Factor (EGFR) Axis

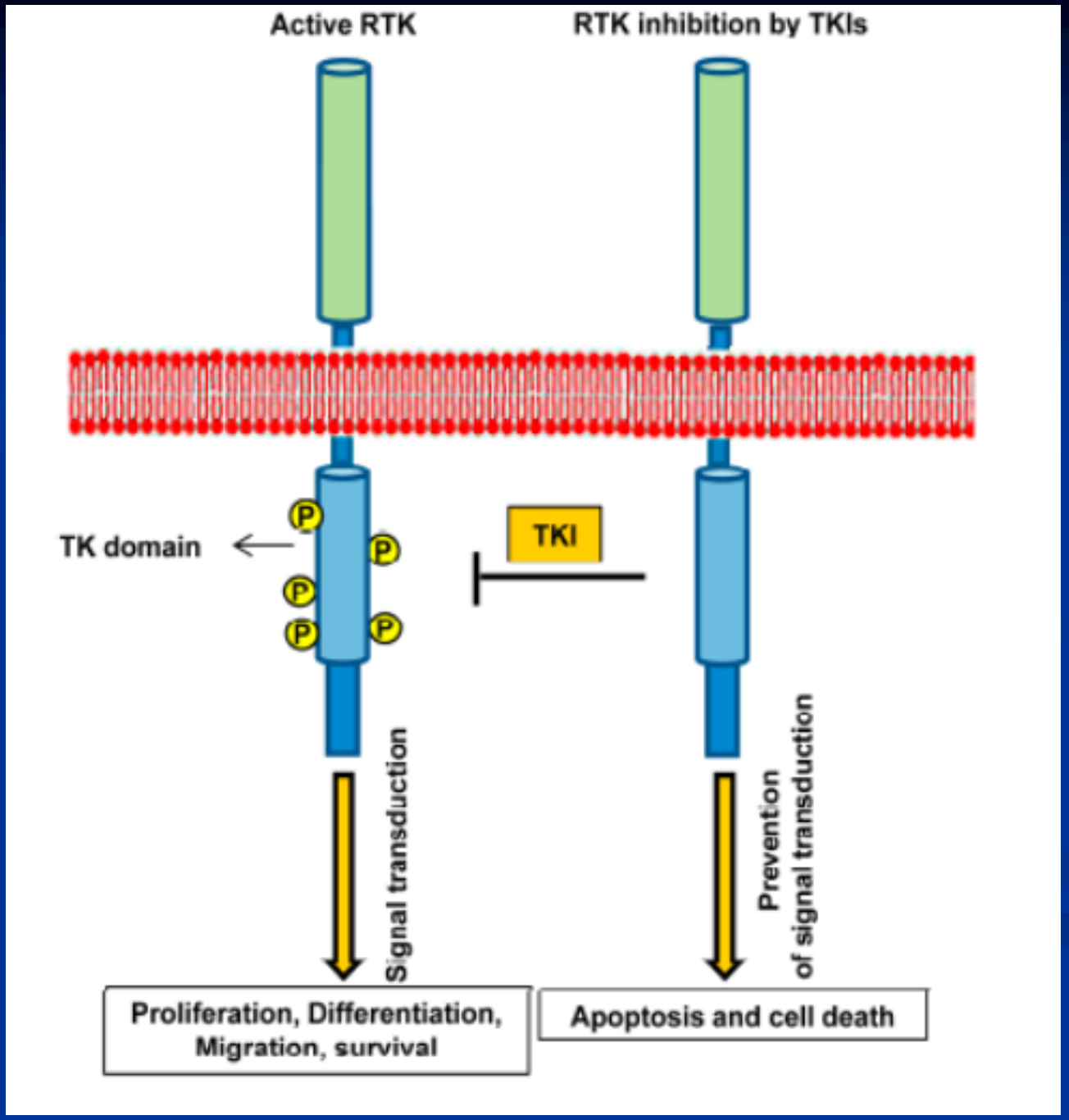


Cetuximab, belonging to the MABs family, gefitinib and erlotinib, and other inhibitors belonging to the TKIs family, are among the most advanced anti-EGFR drugs at the clinical level.

Targeting Cancer with Kinase Inhibitors



Targeting Cancer with Kinase Inhibitors

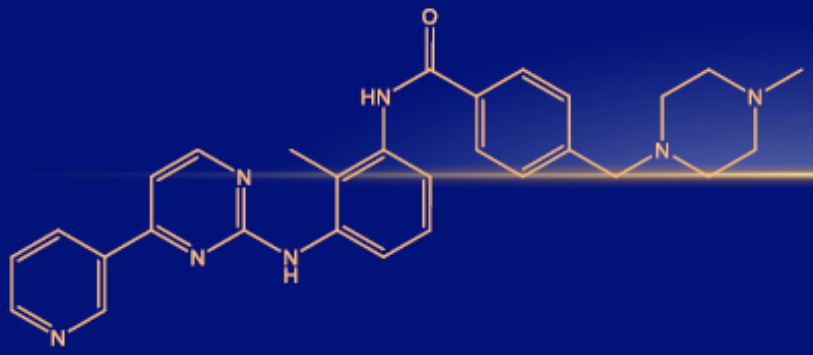


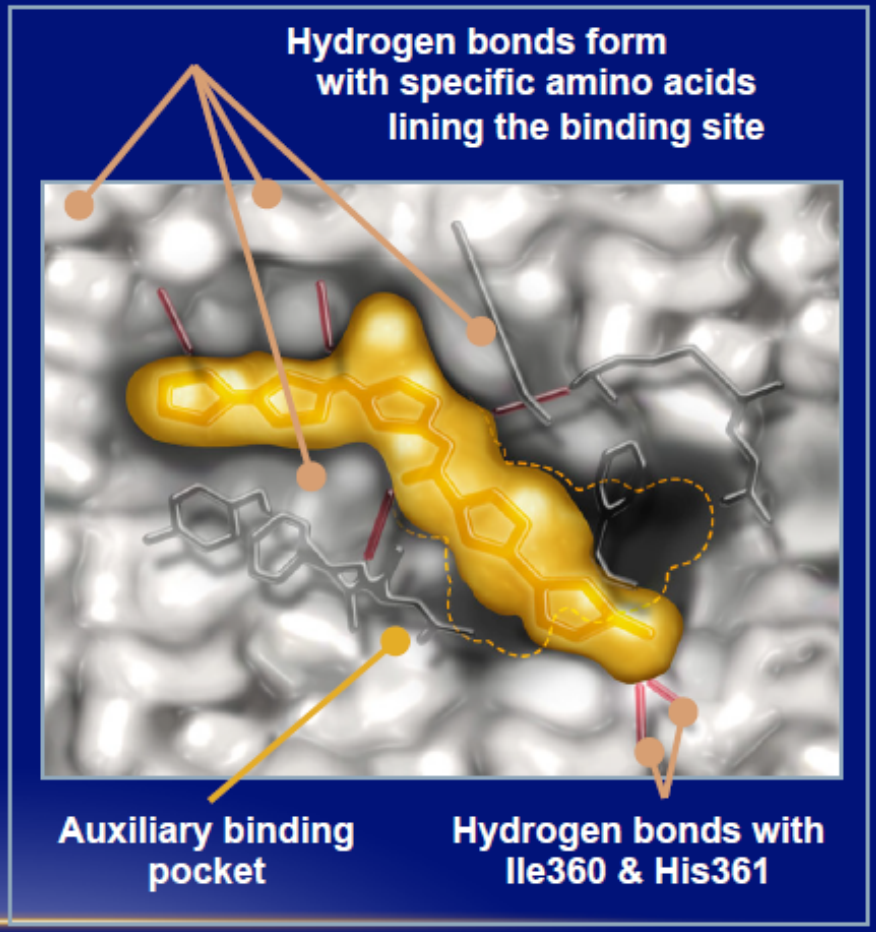
TYROSINE KINASE INHIBITORS' (TKIs) CLASSIFICATION

- **BCR-ABL TKIs, eg. imatinib mesylate, dasatinib and nilotinib**
  - They bind to a segment of the kinase domain that fixes the enzyme in a closed or nonfunctional site in which the protein is unable to bind its supstrate/ phosphate donor, ATP.
- **Epidermal Growth Factor Receptor TKIs, e.g. gefitinob, lapatinib**
  - They inhibit the EGFR tyrosine kinase by virtue of competitive blockade of ATP binding (By blokade of downstream EGFR signal transduction pathways, cell cycle arest and inhibition of angiogenesis)
- **Vascualar Endothelial Growth Factor TKIs, eg. vatalanib, sunitinib, sorafenib**
  - Inhibition of multiple receptor tyrosine kinases, some of which are implicated in tumor growth, pathological angiogenesis and methasthatic progression of cancer
  - Competitive inhibit the binding of ATP to tyrosine kinase domain on the VEGF receptors.

Imatinib: First targeted therapy for cancer

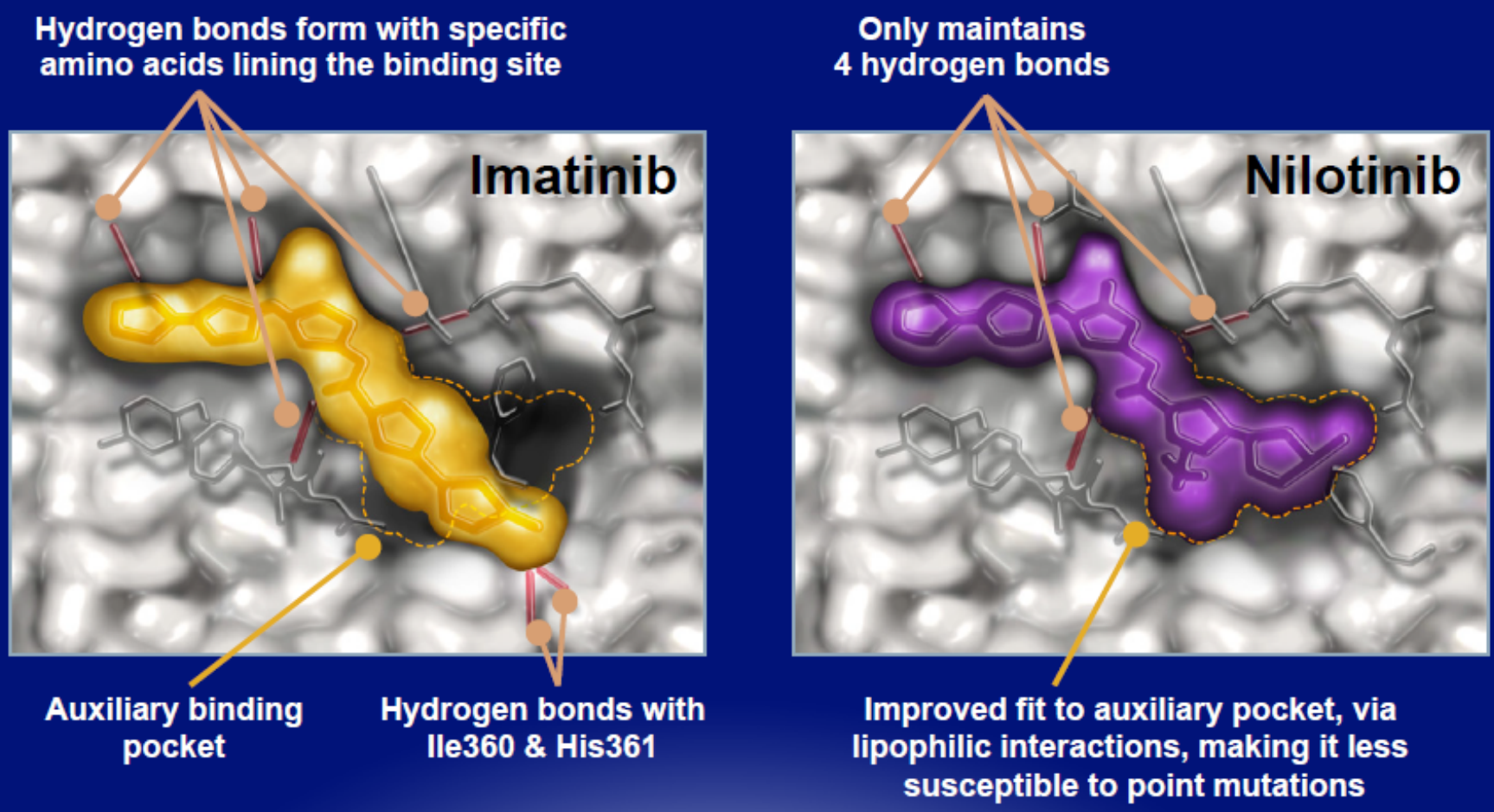
- Imatinib mesylate is a first molecular targeted PTKI received the FDA approval (May 2001).
- It targets the BCR-ABL tyrosine kinase which underlines chronic myelogenous leukemia (CLM) and present in virtually all patients with CLM.
- It inhibits the binding of adenosine triphosphate (ATP) and thus blocks the downstream BCR-ABL signaling pathway.



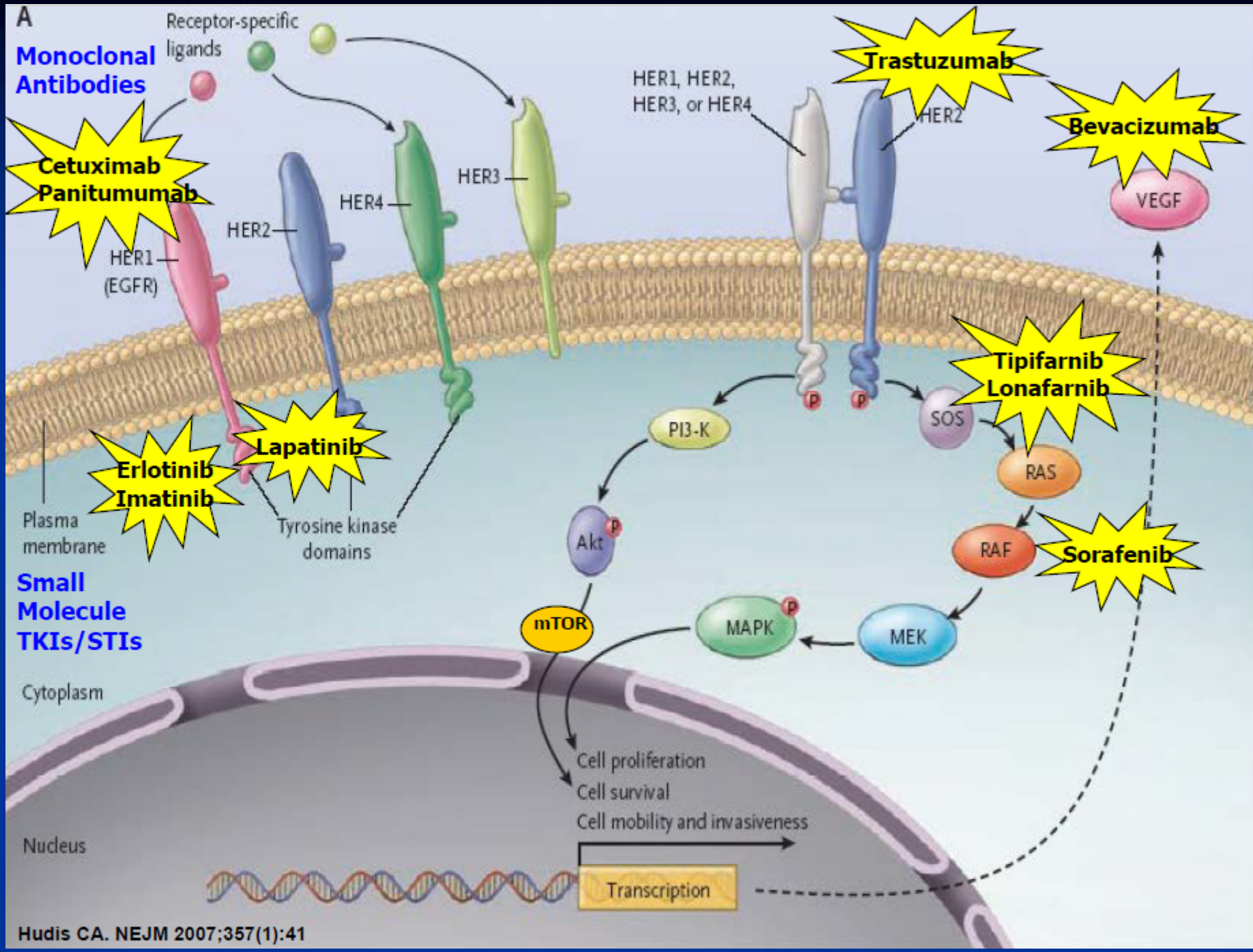


Weisberg E, et al. *Cancer Cell*. 2005;7:129-14

Nilotinib: Improved Imatinib

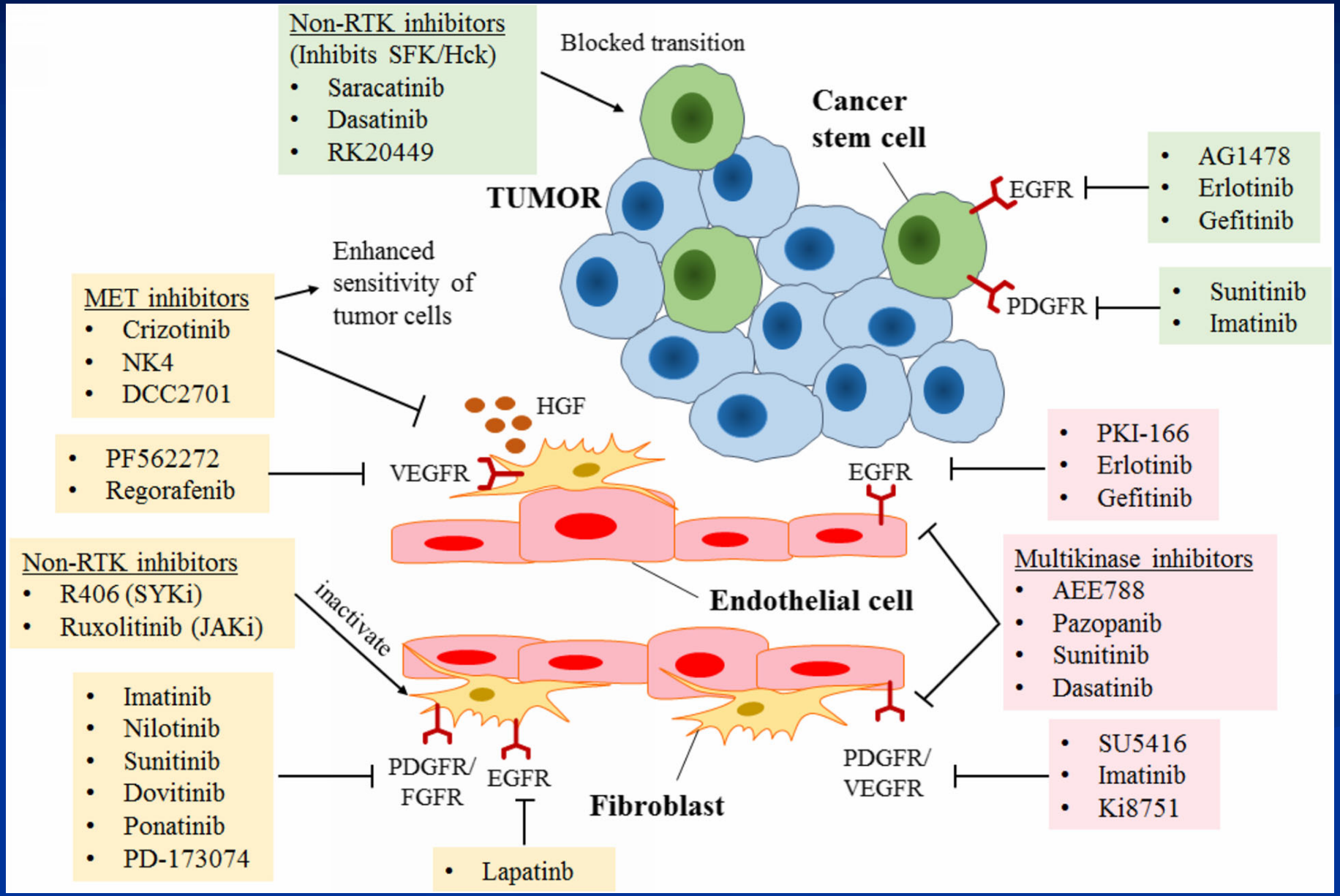


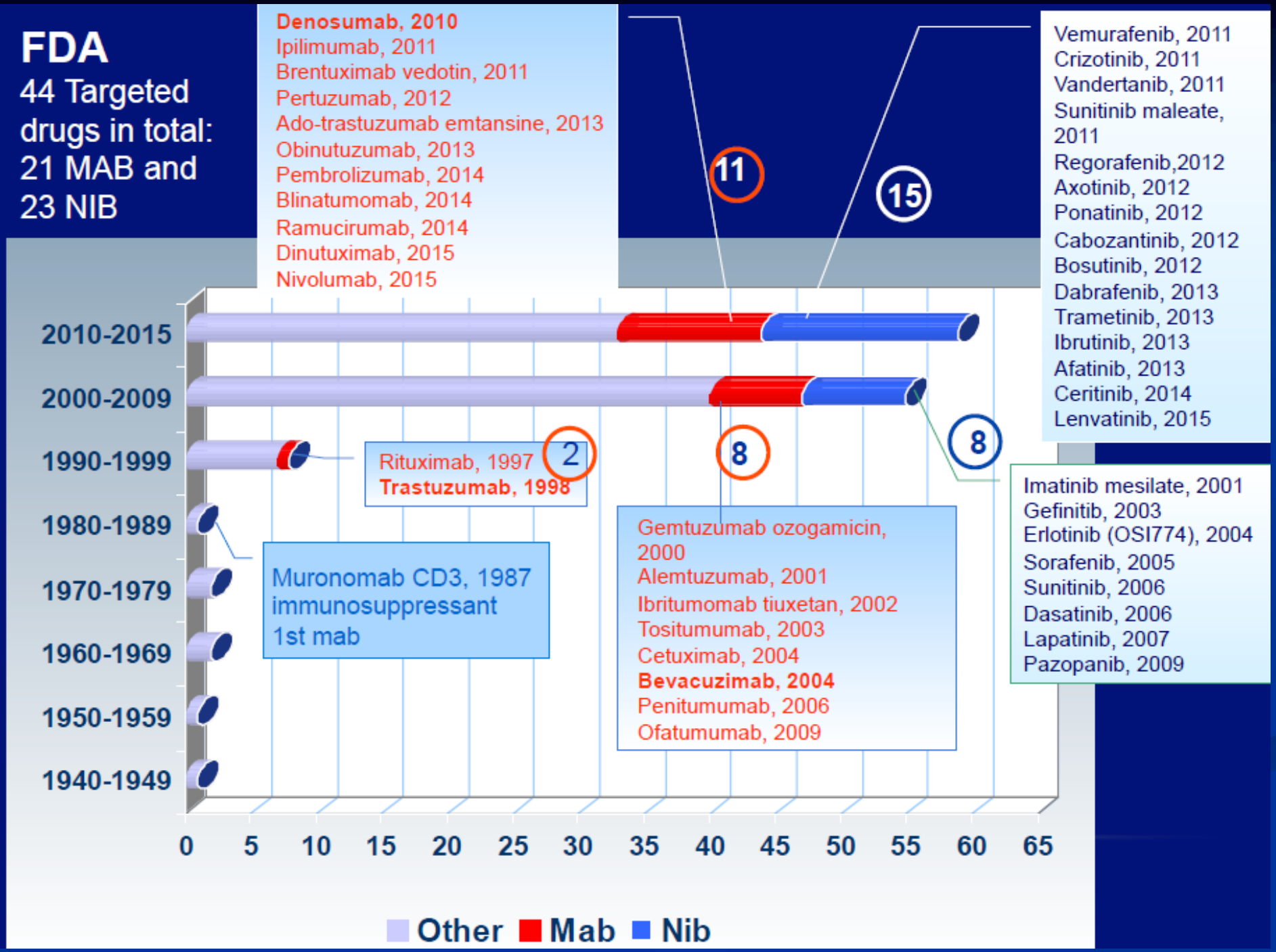
Weisberg E, et al. *Cancer Cell*. 2005;7:129-141



Hudis CA. NEJM 2007;357(1):41

Targeting the Tumor Microenvironment




FDA
44 Targeted drugs in total: 21 MAB and 23 NIB
Denosumab, 2010
Ipilimumab, 2011
Brentuximab vedotin, 2011
Pertuzumab, 2012
Ado-trastuzumab emtansine, 2013
Obinutuzumab, 2013
Pembrolizumab, 2014
Blinatumomab, 2014
Ramucirumab, 2014
Dinutuximab, 2015
Nivolumab, 2015
11
15
Vemurafenib, 2011
Crizotinib, 2011
Vandertanib, 2011
Sunitinib maleate, 2011
Regorafenib,2012
Axotinib, 2012
Ponatinib, 2012
Cabozantinib, 2012
Bosutinib, 2012
Dabrafenib, 2013
Trametinib, 2013
Ibrutinib, 2013
Afatinib, 2013
Ceritinib, 2014
Lenvatinib, 2015
2010-2015
2000-2009
1990-1999
1980-1989
1970-1979
1960-1969
1950-1959
1940-1949
Rituximab, 1997
Trastuzumab, 1998
2
8
8
Muronomab CD3, 1987
immunosuppressant
1st mab
Gemtuzumab ozogamicin, 2000
Alemtuzumab, 2001
Ibritumomab tiuxetan, 2002
Tositumumab, 2003
Cetuximab, 2004
Bevacuzimab, 2004
Penitumumab, 2006
Ofatumumab, 2009
Imatinib mesilate, 2001
Gefinitib, 2003
Erlotinib (OSI774), 2004
Sorafenib, 2005
Sunitinib, 2006
Dasatinib, 2006
Lapatinib, 2007
Pazopanib, 2009
0 5 10 15 20 25 30 35 40 45 50 55 60 65
Other
Mab
Nib

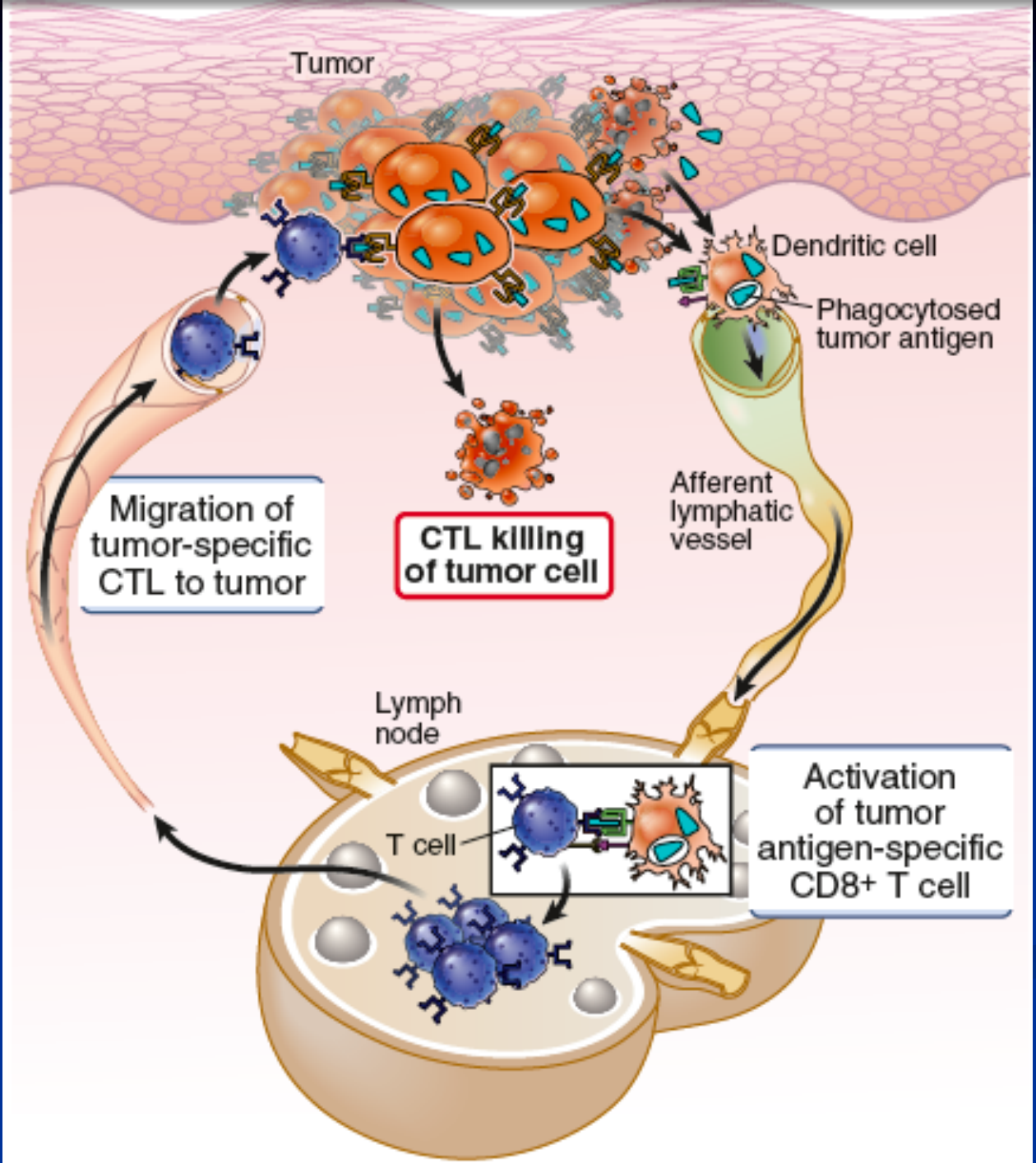
2015: more than 25 TKIs have been approved, and numerous additional therapeutics are in various stages of clinical evaluation.

Table 1 General information on anti-cancer TKI

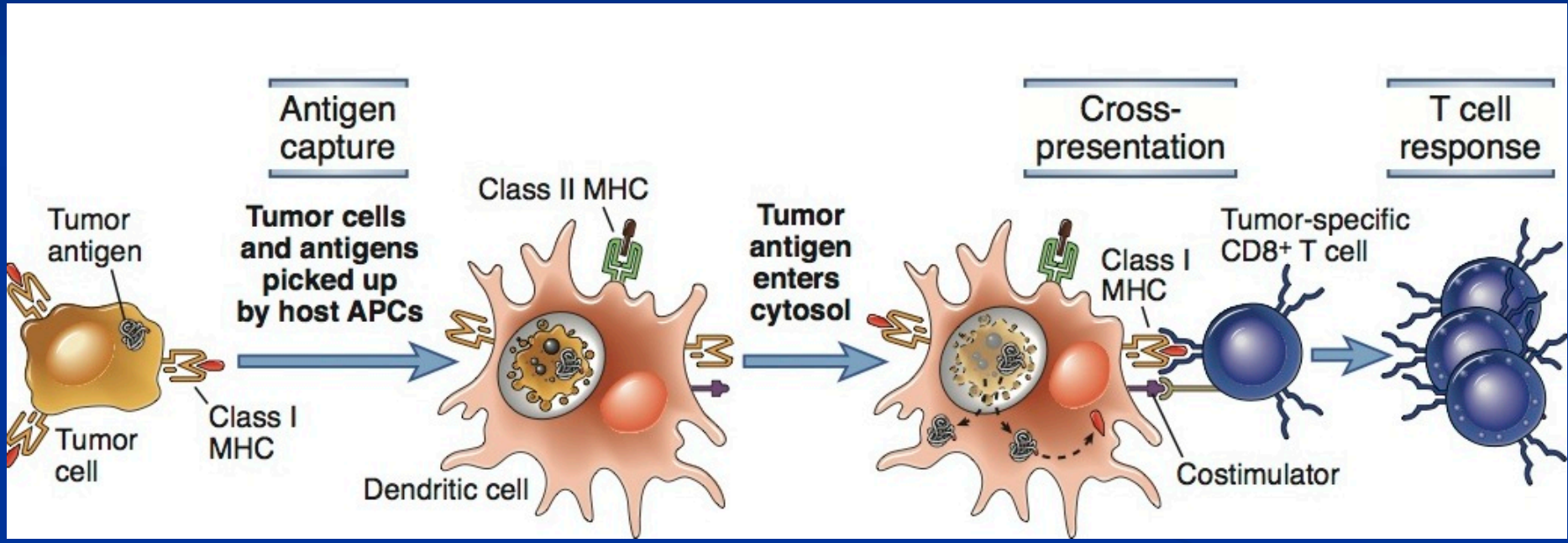
Tyrosine kinase inhibitor (INN)	Branded name	Market Authorization Holder (MAH)	Target tyrosine kinases	Indication(s)	European birth date	CMA	Orphan designation
Bosutinib	Bosulif®	Pfizer	BCR-ABL,SRC	Patients with CML for which Imatinib, Nilotinib, and Dasatinib are not appropriate	27th March 2013	Yes	CML
Dasatinib	Sprycel®	Bristol-Myers Squibb	BCR-ABL	CML	23th December 2005	No	CML, ALL
Erlotinib	Tarceva®	Hoffman-La Roche	EGFR	NSCLC, pancreatic cancer	19th September 2005	No	No
Gefitinib	Iressa®	Astra Zeneca	EGFR	NSCLC in carriers of activating EGFR-mutations	24th June 2010	No	No
Imatinib	Glivec®	Novartis	BCR-ABL, KIT, PDGFR-A, PDGFR-B	CML, GIST, BCR-ABL- positive ALL, dermatofibrosarcoma protuberans, myeloproliferative neoplasms, hypereosinophilic syndromes	7th of November 2001	No	Expired and withdrawn
Lapatinib	Tyverb®	Glaxo Smith Kline	ERBB2 (HER-2)	HER-2 positive breast cancer	10th June 2008	Yes	No
Nilotinib[1]	Tasigna®	Novartis	BCR-ABL, KIT,PDGFR-A, PDGFR-B	CML	19th November 2007	No	CML
Pazopanib	Votrient®	Glaxo Smith Kline	VEGFR, PDGFR, KIT	Renal cell carcinoma, STS	14th June 2010	No	Withdrawn
Ponatinib[2]	Iclusig®	Ariad	BCR-ABL	Patients with CML for which Imatinib, Nilotinib, and Dasatinib are not appropriate (or patients carrying a T315I single-point-mutation)	1st July 2013		CML, ALL
Sorafenib	Nexavar®	Bayer	VEGFR-2,VEGFR-3	Renal cell carcinoma, hepatocellular carcinoma	19th July 2006	No	Renal cell carcinoma, Hepatocellular carcinoma
Sunitinib	Sutent®	Pfizer	VEGFR 1-3, PDGFR-A, PDGFR-B; KIT, FLT3	Renal cell carcinoma, GIST, pNET	19th July 2006	Initially, then full approval	Withdrawn

2014 Eckstein et al.

T cell responses to tumors



Cross-presentation of tumor antigens



Chimeric Antigen Receptor (CAR) T-cells In Cancer Therapy

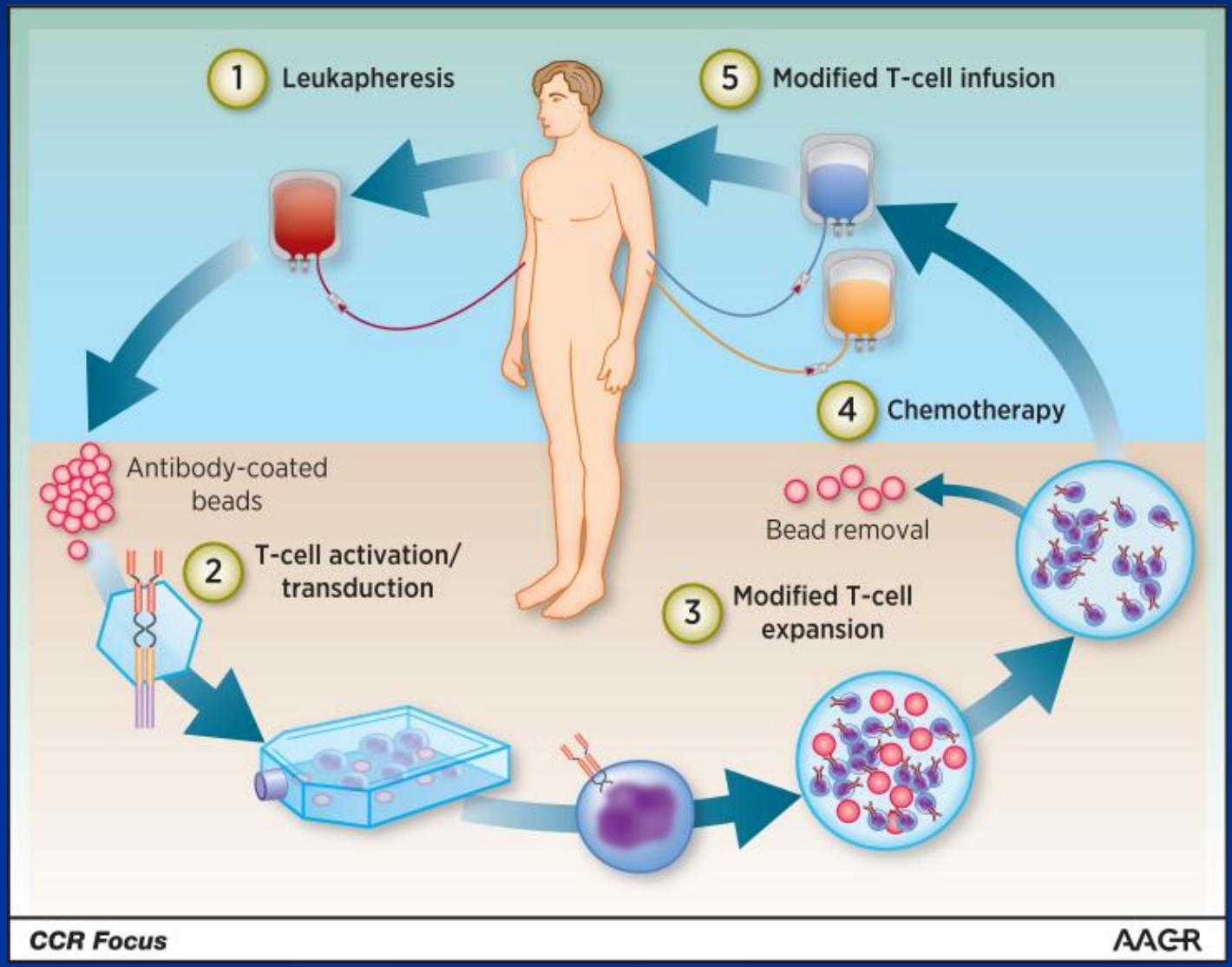
Chimeric antigen receptors (CARs) consist of an extracellular antigen-recognition domain, which is usually an antibody single-chain variable fragment (scFv), but can also be a peptide or another protein, linked to an intracellular signalling domain — usually the CD3ζ (CD3 zeta) chain of the T-cell receptor.

The extracellular portion of the CAR permits the recognition of a specific antigen by a T cell and, subsequently, the signalling domains stimulate T-cell proliferation, cytolysis and cytokine secretion to eliminate the target cell.

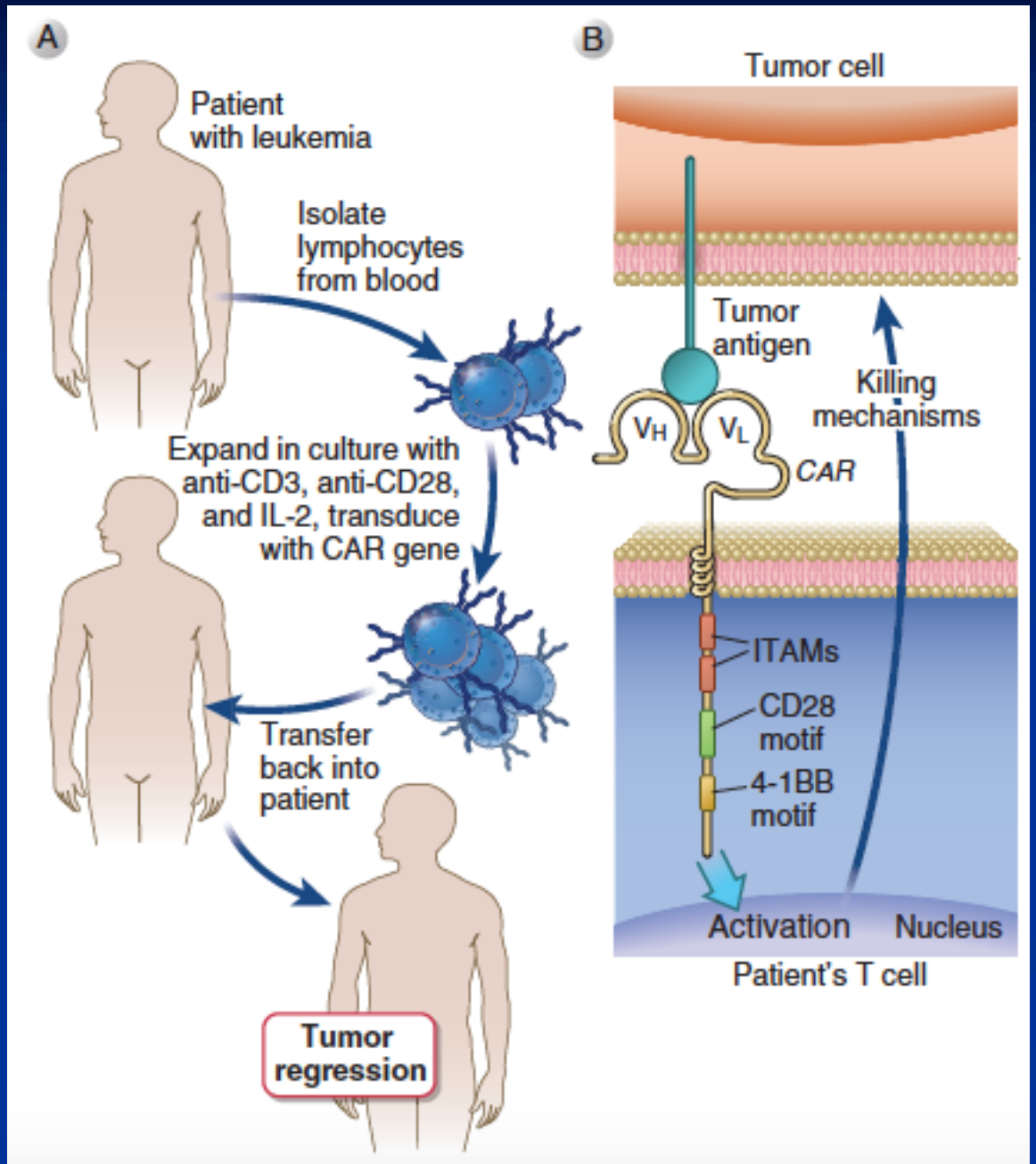
The patients' own T cells (or those from an allogeneic donor) are isolated, activated and genetically modified to generate CAR T cells, which are then infused into the same patient.

Adoptive Cell Therapy – CAR-T

Engineered cancer-killing immune cells



Chimeric antigen receptors



- *Remarkable success in B cell acute leukemia (targeting CD19);*
- *up to 90% complete remission*

Development of chimeric antigen receptors

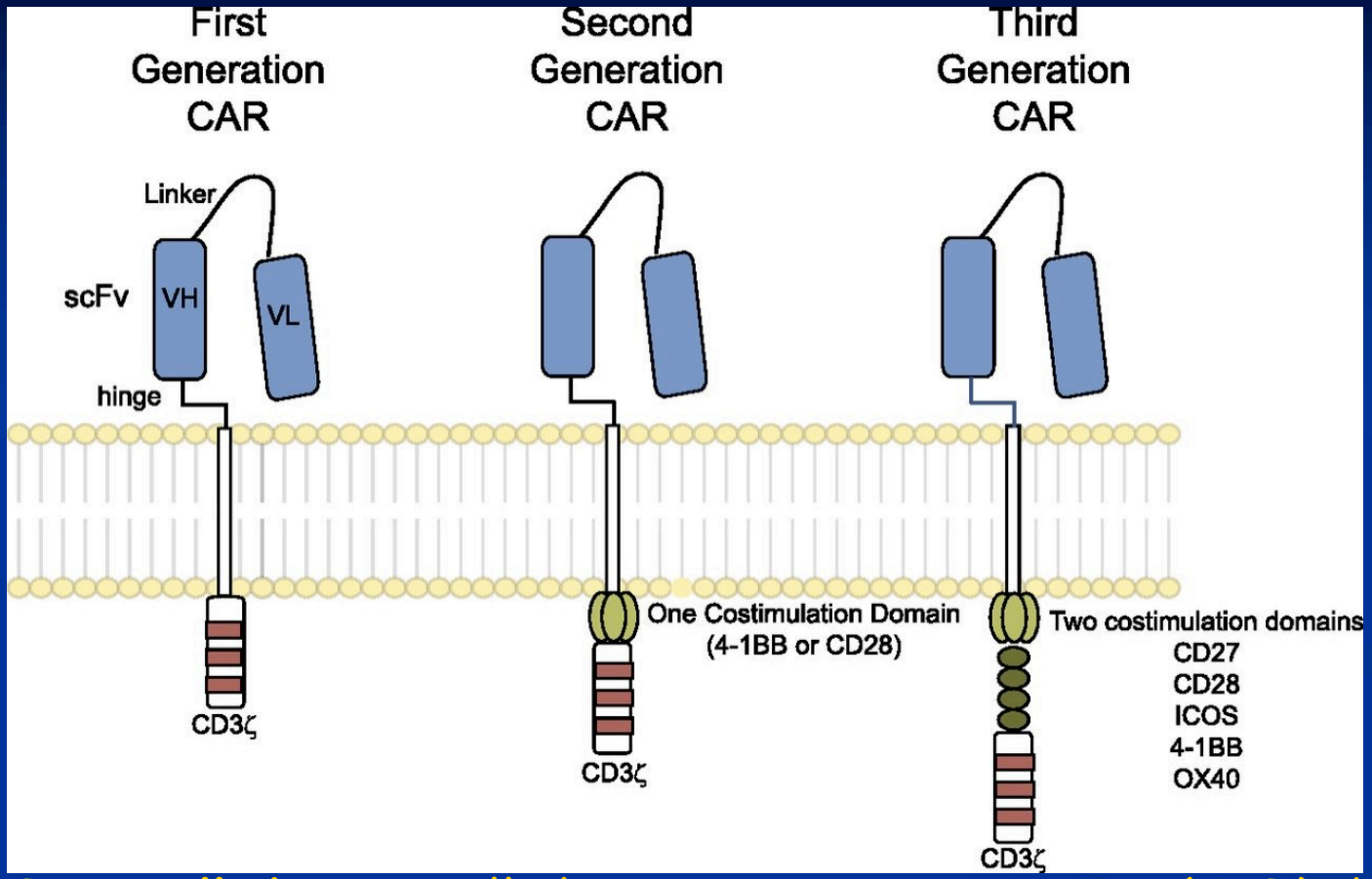


Figure 1 | **CAR-T-cell design.** All chimeric antigen receptor (CAR) designs contain an antigen-recognition domain and a signalling domain that provides 'signal 1' to activate T cells. Only this signalling domain is present in first-generation CARs. By contrast, a co-stimulatory signalling domain that provides 'signal 2' is added in second-generation CARs, and in third-generation CARs two co-stimulatory signalling domains are added.

CAR T-cell Therapy in Cancer

Table 1 | **CD19-specific-CAR T-cell therapy outcomes in patients with B-ALL**

Institution	CAR design	Patient population	Outcome	Toxicities	Reference
MSKCC	CD28, CD3ζ	• *n* = 32 adults • R/R B-ALL	91% CR	• B-cell aplasia • CRS	NCT01044069 (REF. 13)
UPenn/ CHOP	4-1BB, CD3ζ	• *n* = 30 children and young adults • B-ALL	90% CR	• B-cell aplasia • CRS	NCT01626495 (REF. 15)
NCI	CD28, CD3ζ	• *n* = 20 children and young adults • B-ALL	70% CR	• B-cell aplasia • CRS	NCT01593696 (REF. 17)
Fred Hutchinson	4-1BB, CD3ζ	• *n* = 20 adults • B-ALL	83% CR	CRS	NCT01865617 (REF. 18)

Preconditioning chemotherapy was used in all the trials shown in this table. B-ALL, B-cell acute lymphoblastic leukaemia; chemo, chemotherapy; CHOP, Children's Hospital of Philadelphia; CR, complete response; CRS, cytokine-release syndrome; Fred Hutchinson, Fred Hutchinson Cancer Research Center; MSKCC, Memorial Sloan Kettering Cancer Center; NCI, National Cancer Institute; R/R, relapsed and/or refractory; UPenn, The University of Pennsylvania.

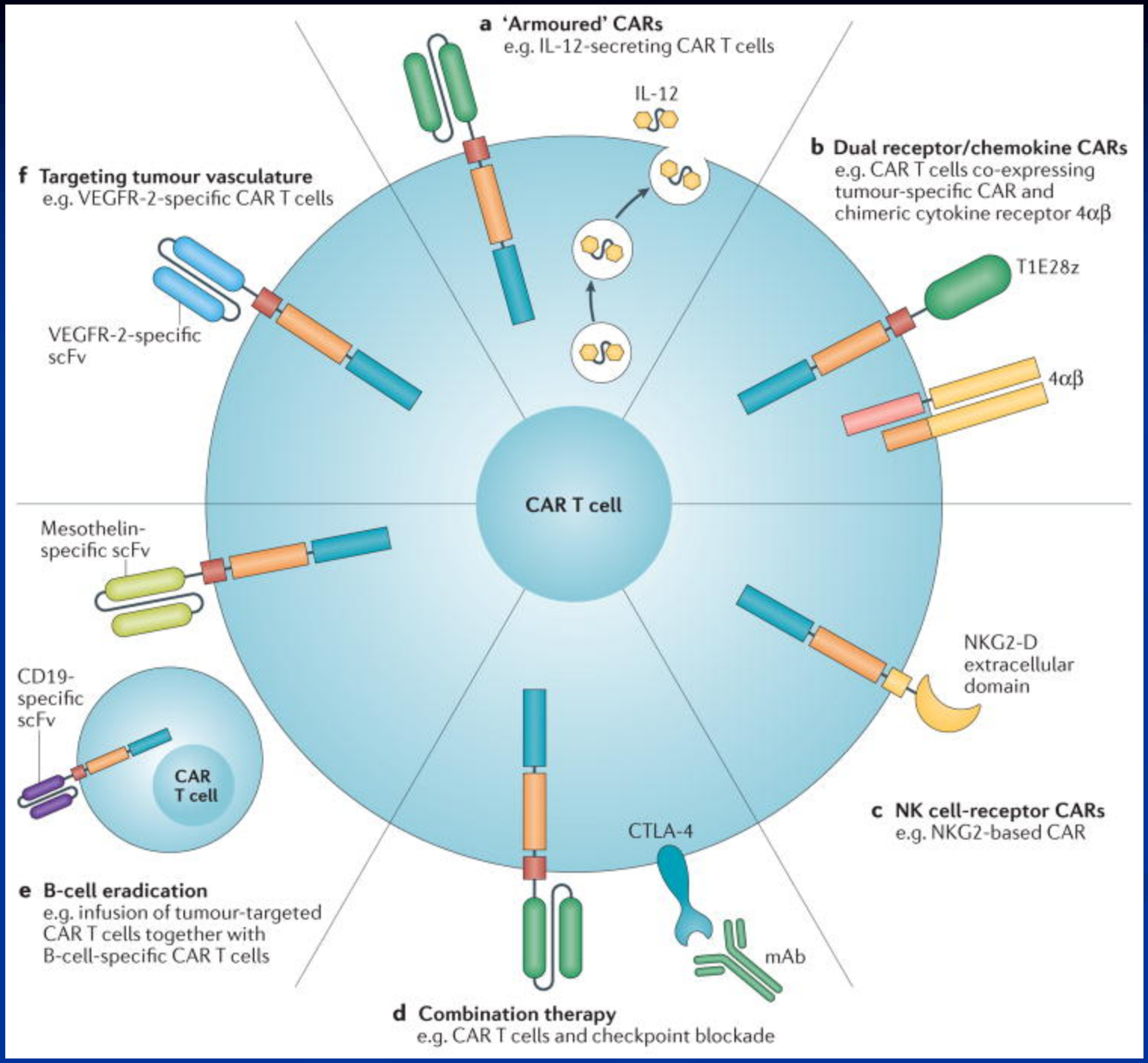
CAR-T cell therapy

Engineered cancer-killing immune cells

CAR T-cell Therapy in Cancer

Key points

- Chimeric antigen receptor (CAR)-T-cell therapy has shown enormous promise in the treatment of B-cell acute lymphoblastic leukaemia; at present, CD19-targeted CAR-T-cell-based treatment of other B-cell malignancies is less effective
- Other targets for CAR-T-cell therapy of haematological malignancies that are undergoing clinical testing include CD20, CD22, ROR1, IgK, BCMA, CD138, CD33, CD123 and LewisY antigen
- Targets for CAR-T-cell therapy of solid malignancies currently being tested in the clinic include PSMA, FAP, CEA, CD171, GD2, glypican-3, HER2 and IL-13Rα
- Several strategies are under development to improve CAR-T-cell-mediated antitumour responses; these include, among others, 'armoured' CAR T cells, dual receptor/cytokine-based CARs, CARs based on natural-killer-cell receptors and other cell receptors
- Strategies to improve the safety of CAR-T-cell therapy involve improved management of cytokine-release syndrome, as well as engineered CAR T cells that are easier to eradicate in case of adverse events


a 'Armoured' CARs
e.g. IL-12-secreting CAR T cells
IL-12
b Dual receptor/chemokine CARs
e.g. CAR T cells co-expressing tumour-specific CAR and chimeric cytokine receptor 4αβ
T1E28z
4αβ
f Targeting tumour vasculature
e.g. VEGFR-2-specific CAR T cells
VEGFR-2-specific scFv
CAR T cell
Mesothelin-specific scFv
CD19-specific scFv
CAR T cell
NKG2-D extracellular domain
c NK cell-receptor CARs
e.g. NKG2-based CAR
CTLA-4
mAb
e B-cell eradication
e.g. infusion of tumour-targeted CAR T cells together with B-cell-specific CAR T cells
d Combination therapy
e.g. CAR T cells and checkpoint blockade

Limitations and challenges of CAR-T cell therapy

- Cytokine storm – many T cells respond to target antigen
  - Requires anti-inflammatory therapy (anti-IL-6R)
  - Risk of long-term damage (especially brain)
- Unclear how well it will work against solid tumors
  - Problem of T cells entering tumor site
- Will tumors lose target antigen and develop resistance?
- Technical and regulatory challenges of producing genetically modified CAR-T cells for each patient

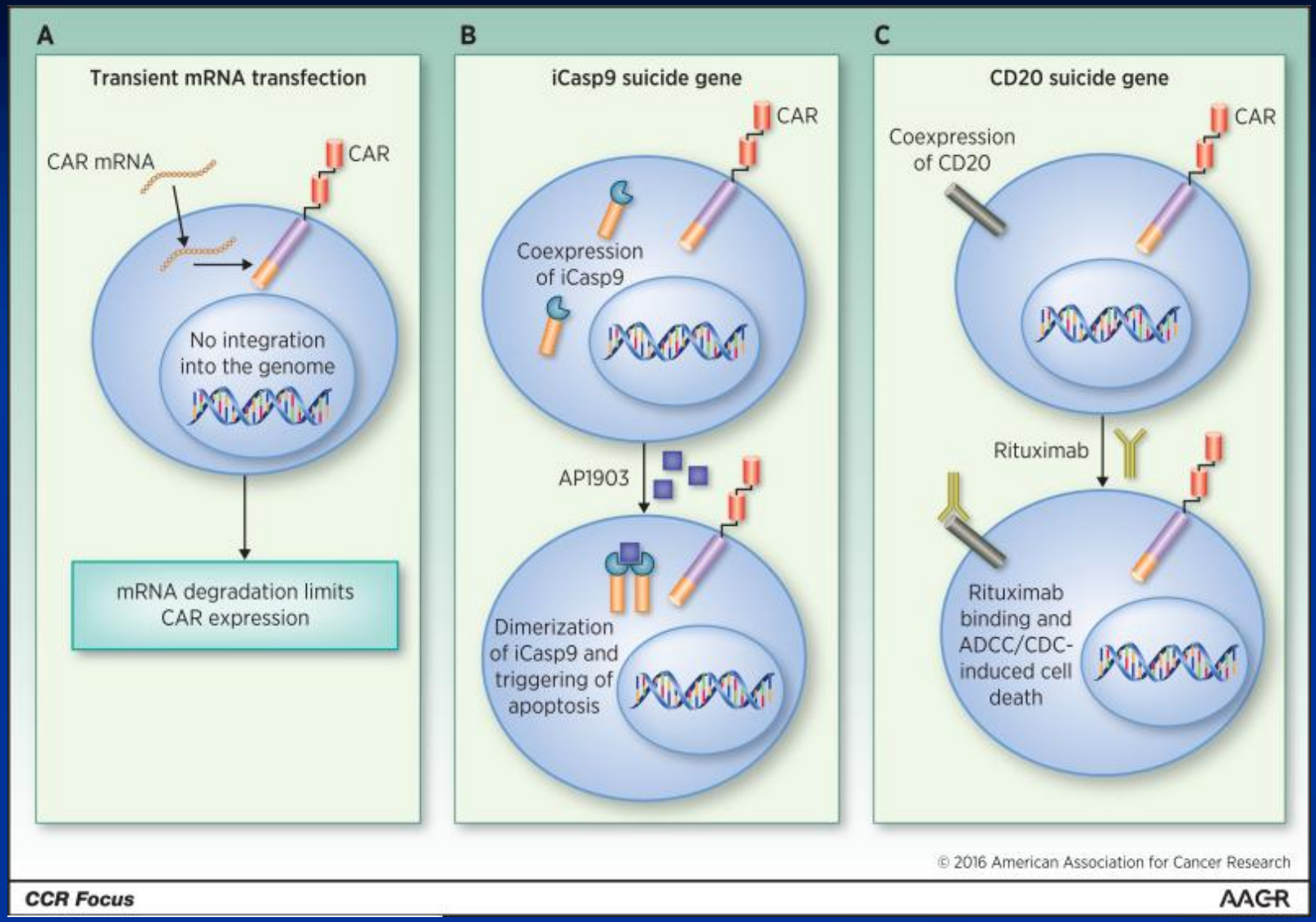
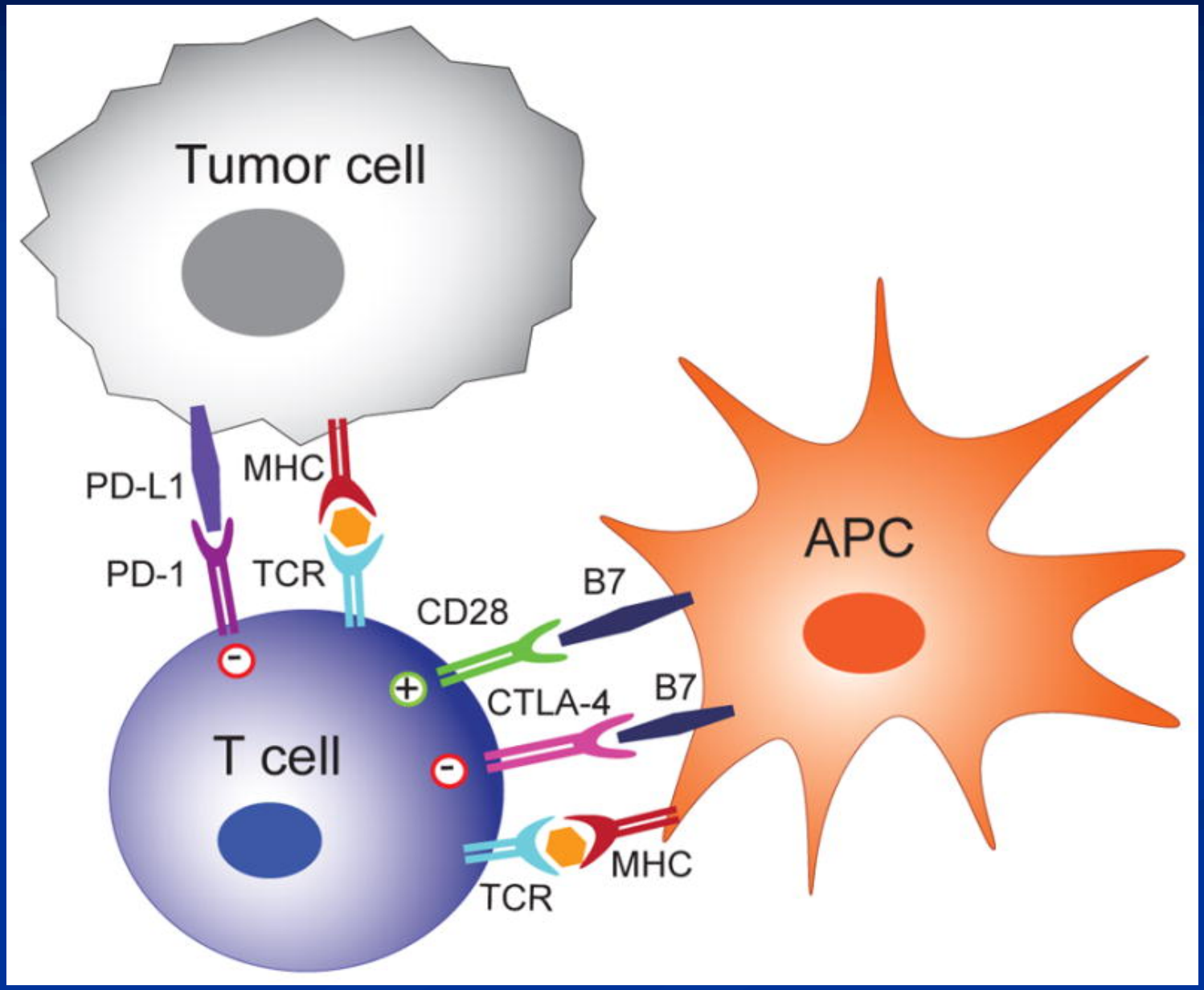
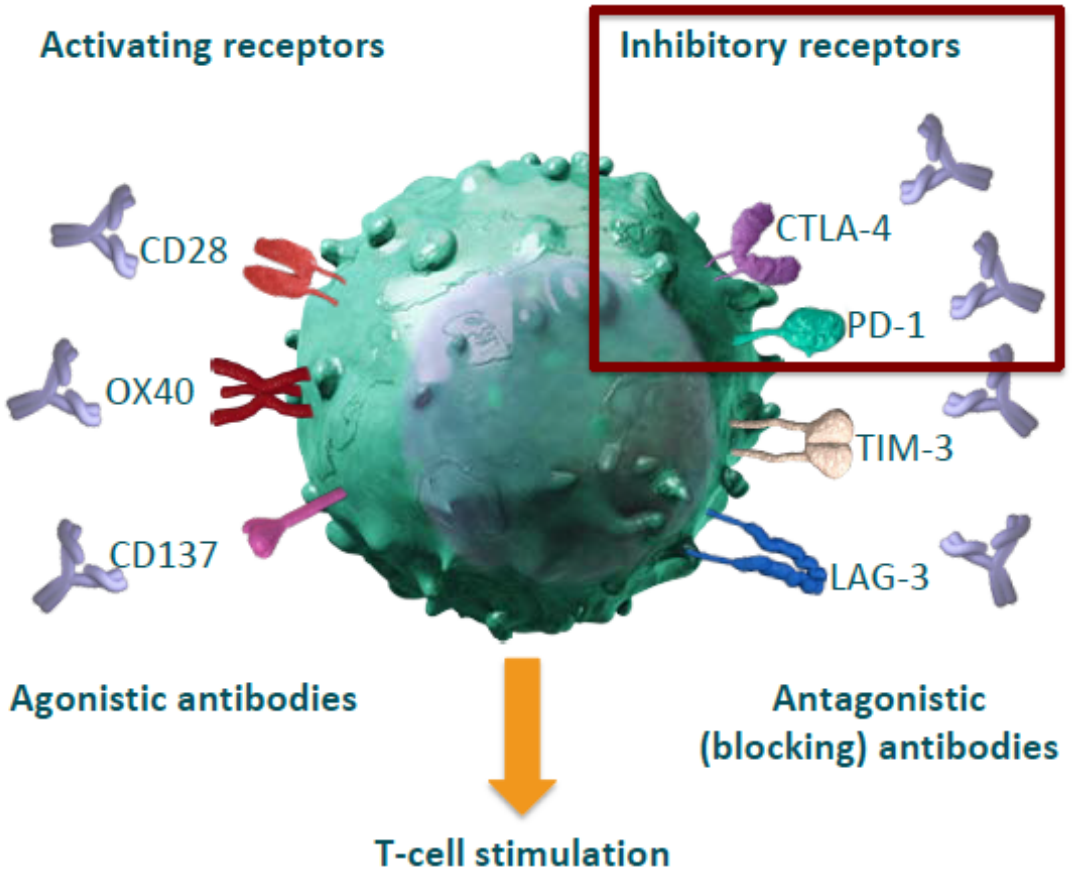


Figure 2. Strategies to regulate CAR T-cell persistence.

T-cell Activation Checkpoints



T-Cell Checkpoint Regulation is an Evolving Approach to Cancer Therapy

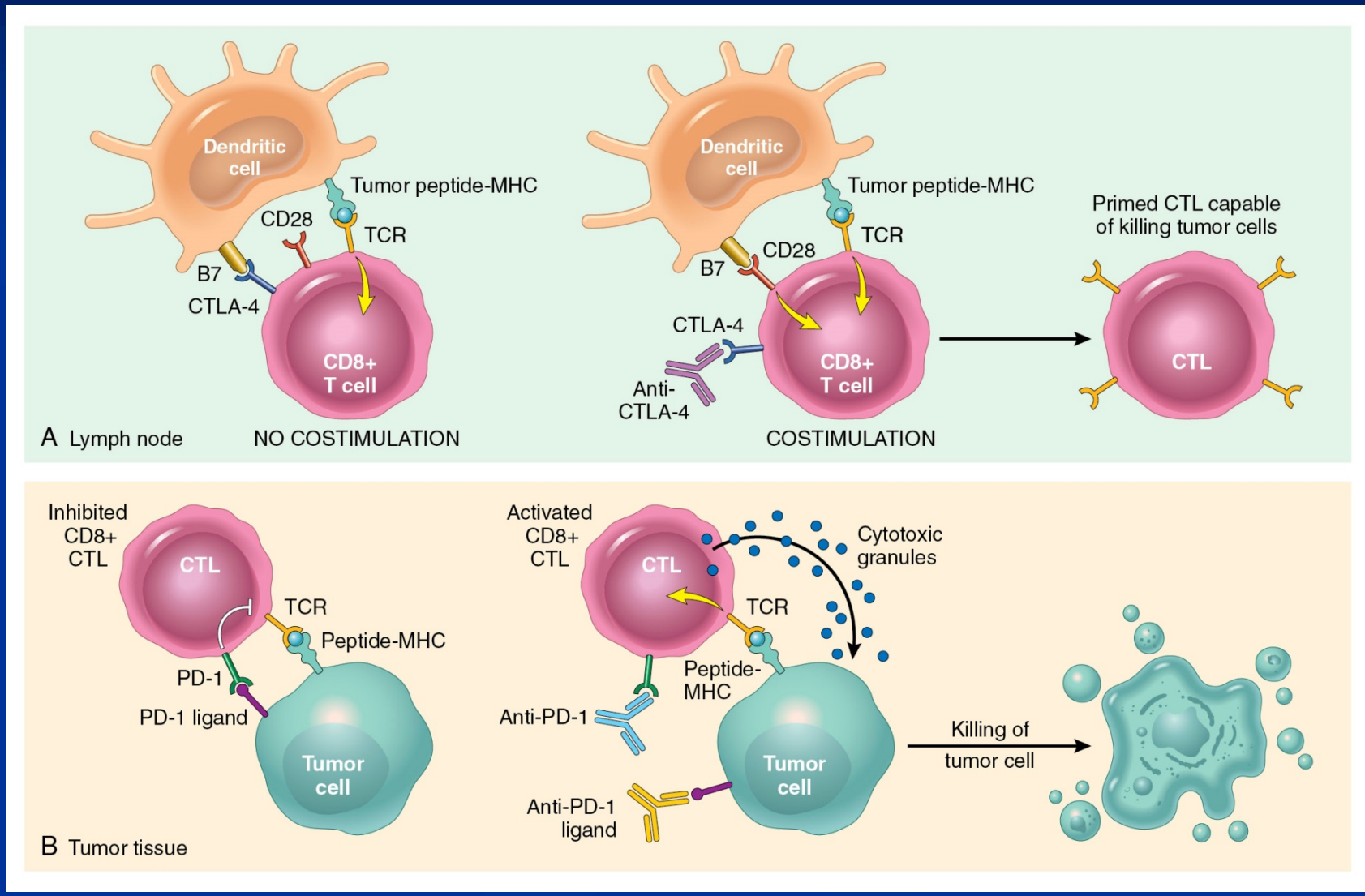


- T-cell responses are regulated though a complex balance of inhibitory ("checkpoint") and activating signals
- Tumours can dysregulate these pathways, and consequently the immune response
- Targeting these pathways is an evolving approach to cancer therapy

Adapted from Mellman I, *et al. Nature* 2011; 480(7378):480-9; Pardoll DM. *Nat Rev Cancer* 2012; 12(4):252-64.

Checkpoint Blockade in Cancer Immunotherapy

Checkpoint blockade



Immune Checkpoint Antibodies

Anti-CTLA-4

Tremelimumab (AZ)

Ipilimumab (BMS)

Approved

YERVOY™

Anti-PD-1

Nivolumab (BMS) & Pembrolizumab (MSD)

Approved

OPDIVO™

KEYTRUDA®

Anti-PD-L1

Durvalumab (AZ/Medimmune)

Avelumab (Pfizer)

Atezolizumab (Roche/Genentech)

Approved

TECENTRIQ™

BAVENCIO®

IMFINZI™

Checkpoint Blockade in Cancer Immunotherapy

Table 1
Approved cancer therapies targeting negative immune regulation.

Target	Drug	Approval year	Indication	Dose/schedule
CTLA-4	Ipilimumab	2011	Melanoma (metastatic/unresectable)	3 mg/kg IV every 3 weeks for a maximum of 4 doses
		2015	Melanoma (adjuvant)	10 mg/kg IV every 3 weeks for 4 doses, then every 12 weeks up to 3 years
PD-1	Pembrolizumab	2014	Melanoma (metastatic/unresectable)	2 mg/kg IV every 3 weeks
		2015	Non-small cell lung cancer (first-line if PD-L1 > 50%)	200 mg IV every 3 weeks
		2015	Non-small cell lung cancer (post-platinum chemotherapy if PD-L1 > 1%)	
		2016	Head and neck cancer	
	Nivolumab	2014	Melanoma (metastatic/unresectable)	240 mg IV every 2 weeks
		2015	Non-small cell lung cancer (post-platinum chemotherapy)	
		2015	Renal cell carcinoma	
		2016	Hodgkin Lymphoma	3 mg/kg IV every 2 weeks
		2016	Head and neck cancer	
		2017	Urothelial cancer	240 mg IV every 2 weeks
PD-L1	Atezolizumab	2016	Urothelial cancer, lung cancer	1200 mg IV every 3 weeks
		2016	Non-small cell lung cancer (post-platinum chemotherapy)	
CTLA-4 + PD-1	Ipilimumab + Nivolumab	2015	Melanoma (metastatic/unresectable)	Nivolumab 1 mg/kg IV with ipilimumab 3 mg/kg IV every 3 weeks for 4 doses, then nivolumab 240 mg IV every 2 weeks

Checkpoint Blockade in Cancer Immunotherapy

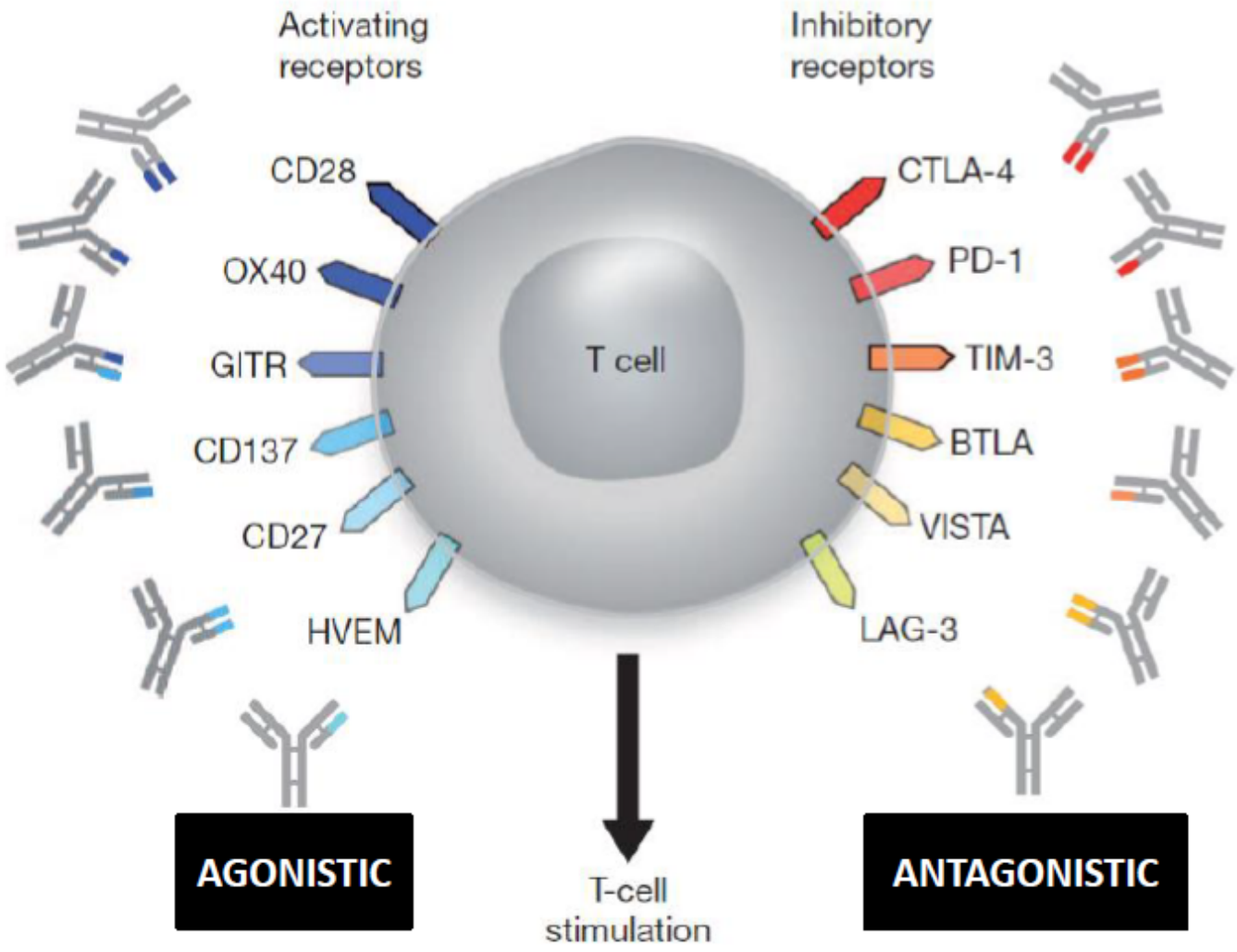
Table 1. FDA-approved immune checkpoint blocking antibodies.

Target	Antibody Drug	Trade Name	Tumor Type (FDA Approval Year)
PD-1	Nivolumab (IgG4)	Opdivo	Melanoma (2014) Non-small-cell lung cancer (2015) Hodgkin lymphoma (2016) Head and neck squamous cell carcinoma (2016) Urothelial carcinoma (2017) Hepatocellular carcinoma (2017)
	Pembrolizumab (IgG4)	Keytruda	Melanoma (2014) Non-small-cell lung cancer (2015) Head and neck squamous cell carcinoma (2016) Hodgkin lymphoma (2017) Urothelial carcinoma (2017) Gastic and gastroesophageal carcinoma (2017)
	Cemiplimab (IgG4)	Libtayo	Cutaneous squamous cell carcinoma (2018)
PD-L1	Atezolizumab (IgG1)	Tecentriq	Urothelial carcinoma (2016) Non-small-cell lung cancer (2016)
	Durvalumab (IgG1)	Imfinzi	Urothelial carcinoma (2017) Non-small-cell lung cancer (2018)
	Avelumab (IgG1)	Bavencio	Merkel cell carcinoma (2017) Urothelial carcinoma (2017)
CTLA-4	Ipilimumab (IgG1)	Yervoy	Melanoma (2011)

Targeting Inhibitory Receptors in Cancer Immunotherapy

- Blocking inhibitory receptors induces tumor regression
  - Partial or complete responses in up to 40%
  - Biomarkers for therapeutic responses?
- May be more effective than vaccination (DCs presenting tumor antigen)
  - Vaccines have to overcome tumor-induced regulation/tolerance
- Adverse effects (inflammatory autoimmune reactions)
  - Typically manageable (risk-benefit analysis)

This is just the beginning



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Combination Strategies for Cancer Immunotherapy

- Combinations of checkpoint blockers, or bispecific antibodies targeting two checkpoints
  - Already done with CTLA-4 and PD-1
- Checkpoint blockade (anti-PD1 or -CTLA-4) + vaccination (DCs presenting tumor antigen)
- Checkpoint blockade + agonist antibody specific for activating receptor
- Checkpoint blockade + kinase inhibitor to target oncogene

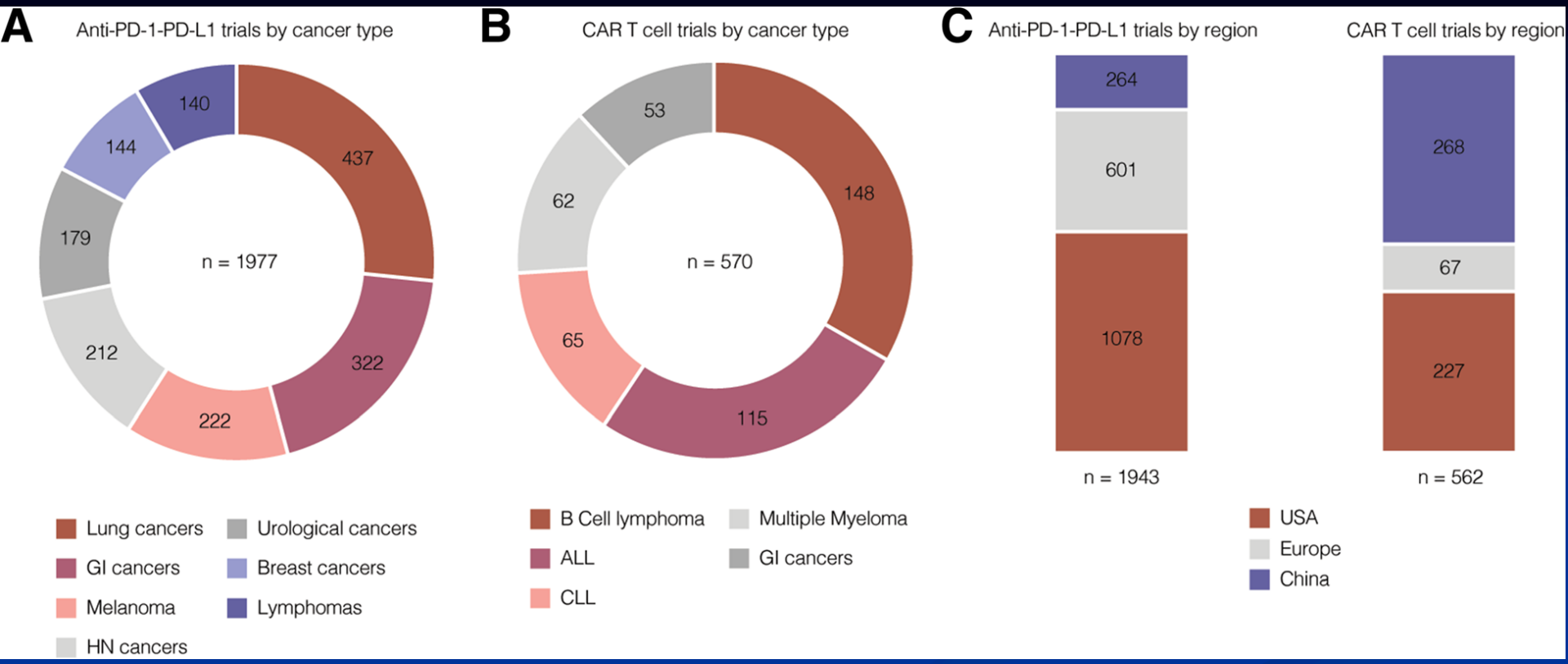

Fig. 1 Included tumor types (a, b) and regional distribution (c) of clinical PD-1 / PD-L1 and CAR T cell trials in 2019. ClinicalTrials.gov was searched for "pd-l1" OR "pd-1" OR "programmed death ligand" OR "car t cell" OR "chimeric antigen receptor". All registered trials were sorted for tumor type and country/region. Search was performed on 2019-05-06. Most frequent tumor types (a, b) and regions (c) are shown as indicated. Several clinical trials included multiple tumor types or were performed in more than one country/region. Abbreviations: GI: gastrointestinal, HN: head and neck