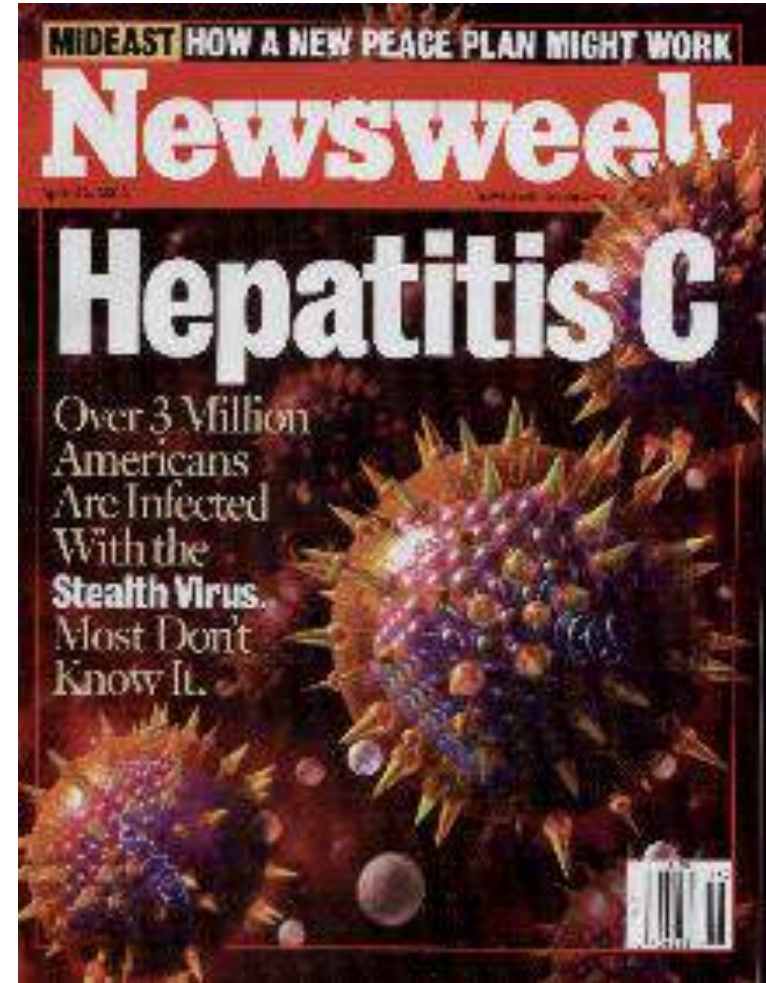




Enkele nieuwe geneesmiddelen 2017

Prof. Koen Augustyns

Farmant, Antwerpen, 19/12/2017





Part 1

CANCER THERAPY WITH A FOCUS ON IMMUNOTHERAPY



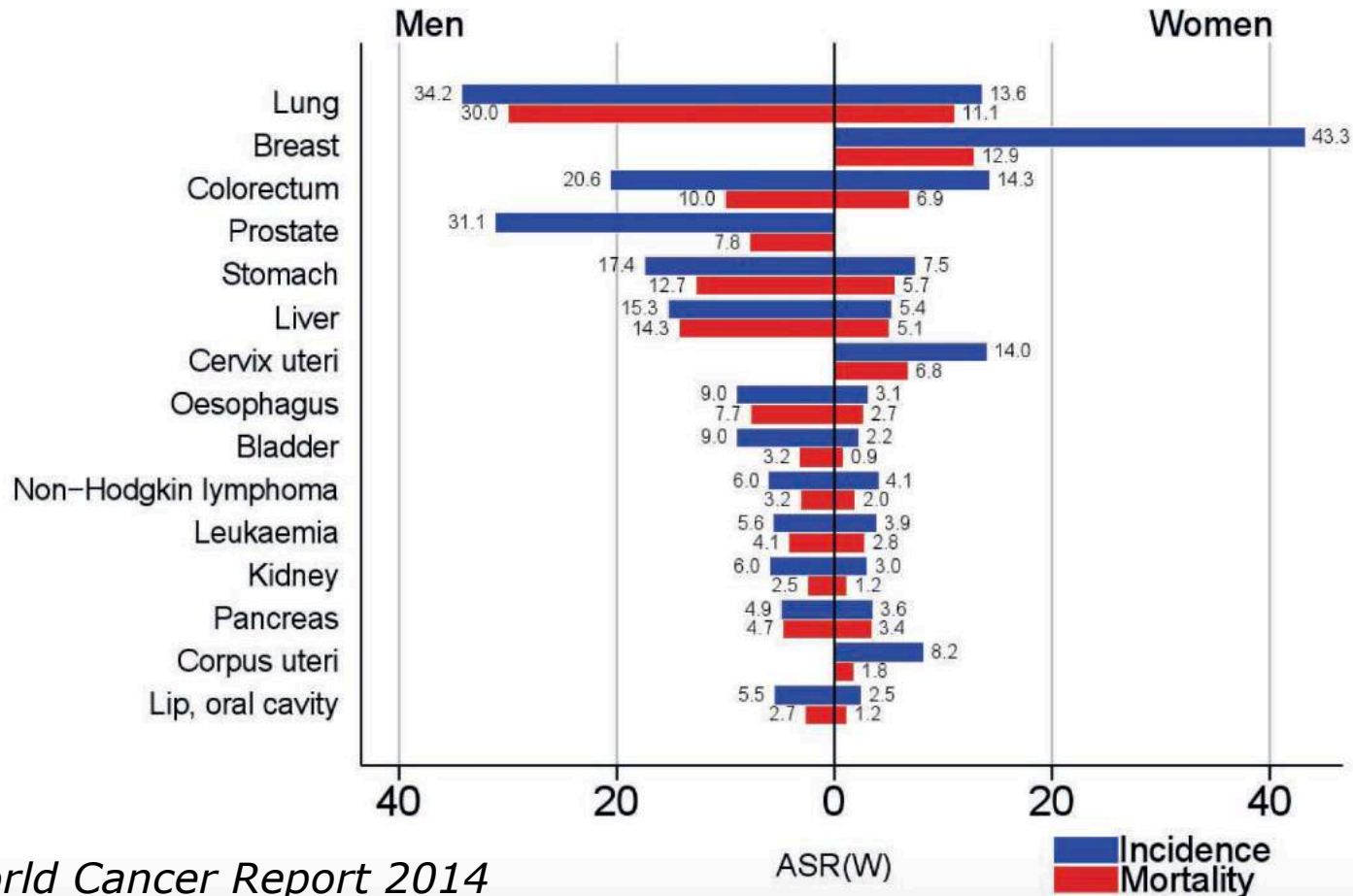
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- Cancer Immunotherapy
- Future



Cancer is not one disease: Different organs

Estimated age-standardized (World) cancer incidence and mortality rates (ASR) per 100 000, by major sites, in men and women, 2012



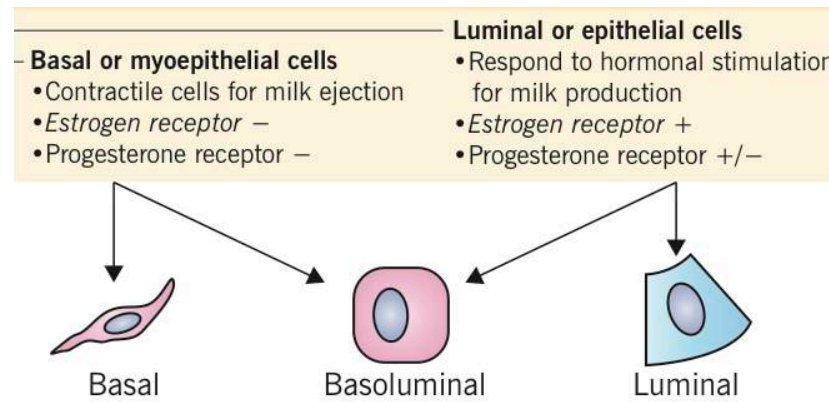
WHO – World Cancer Report 2014

Universiteit Antwerpen

Cancer is not one disease: Different cells and molecular subtypes

Breast Cancer

Cancer cell phenotype



Molecular subtypes

Triple negative HER2+ Luminal B Luminal A
ER-, PR-, HER2-

% of breast cancers

15-20% 10-15% 20% 40%

Receptor expression

HER2 ER+/PR+

Histologic grade

Level of cell differentiation

High (grade III) Low (grade I)

Prognosis

Correlates to histologic grade

Poor Good

Response to medical therapy

Chemotherapy Trastuzumab Endocrine

Triple negative tumours respond best to chemotherapy, similar to other aggressive cancers.

Luminal A tumours respond best to endocrine therapy, e.g. antiestrogen or aromatase inhibitor.

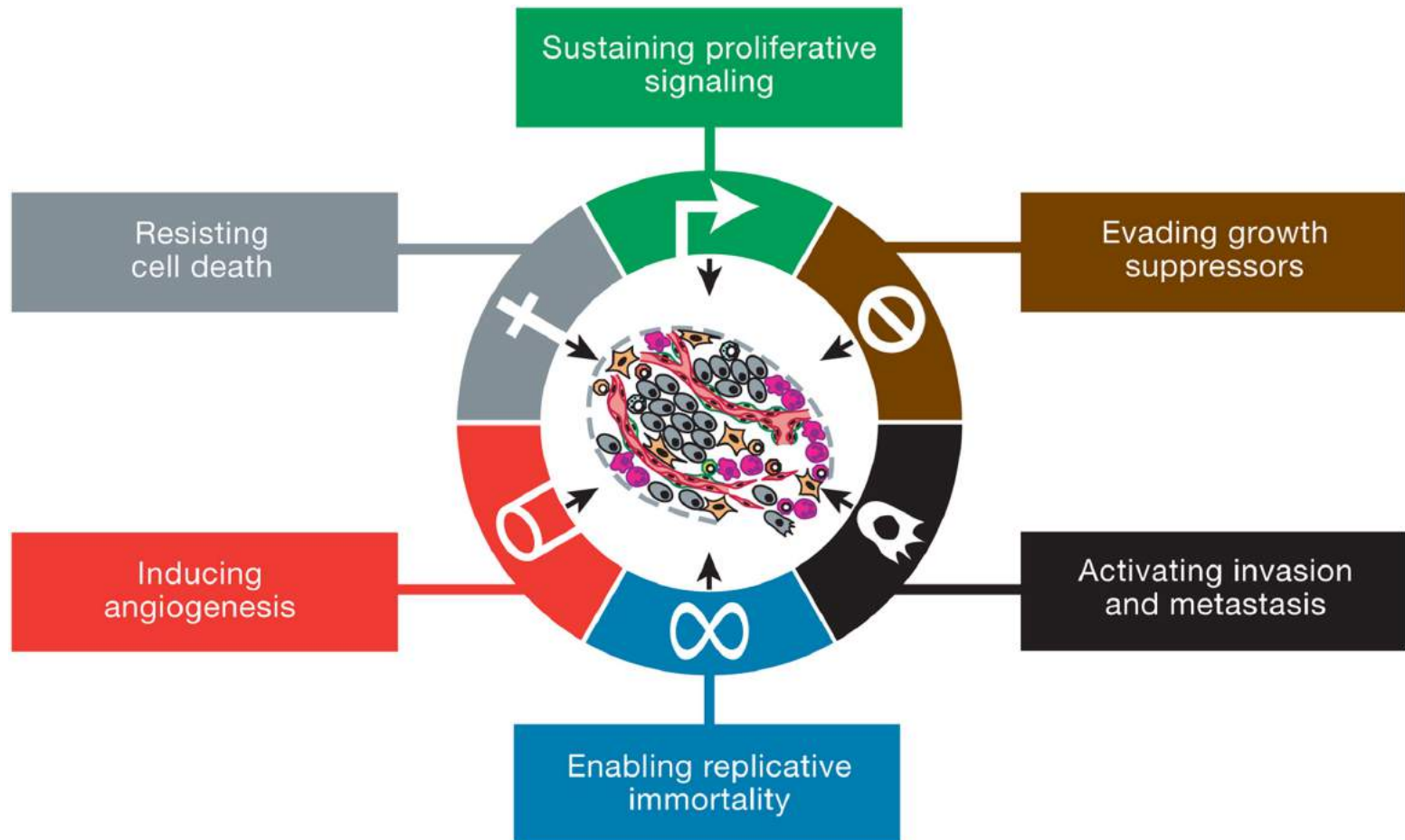


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What are the hallmarks of cancer?

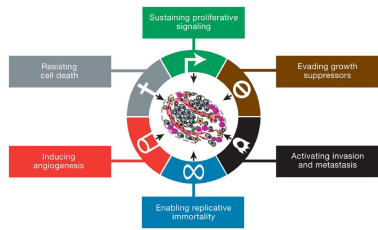


Hanahan, D. et al. Cell, 2011, 144, 646



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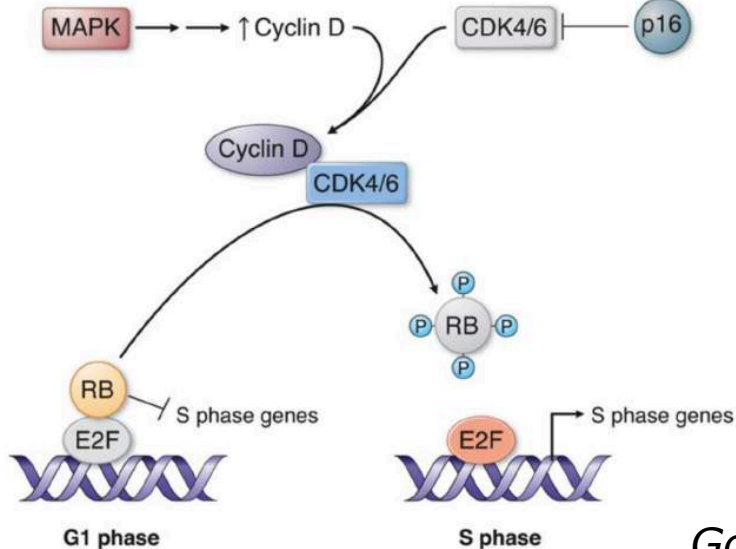


1. Sustaining proliferative signaling

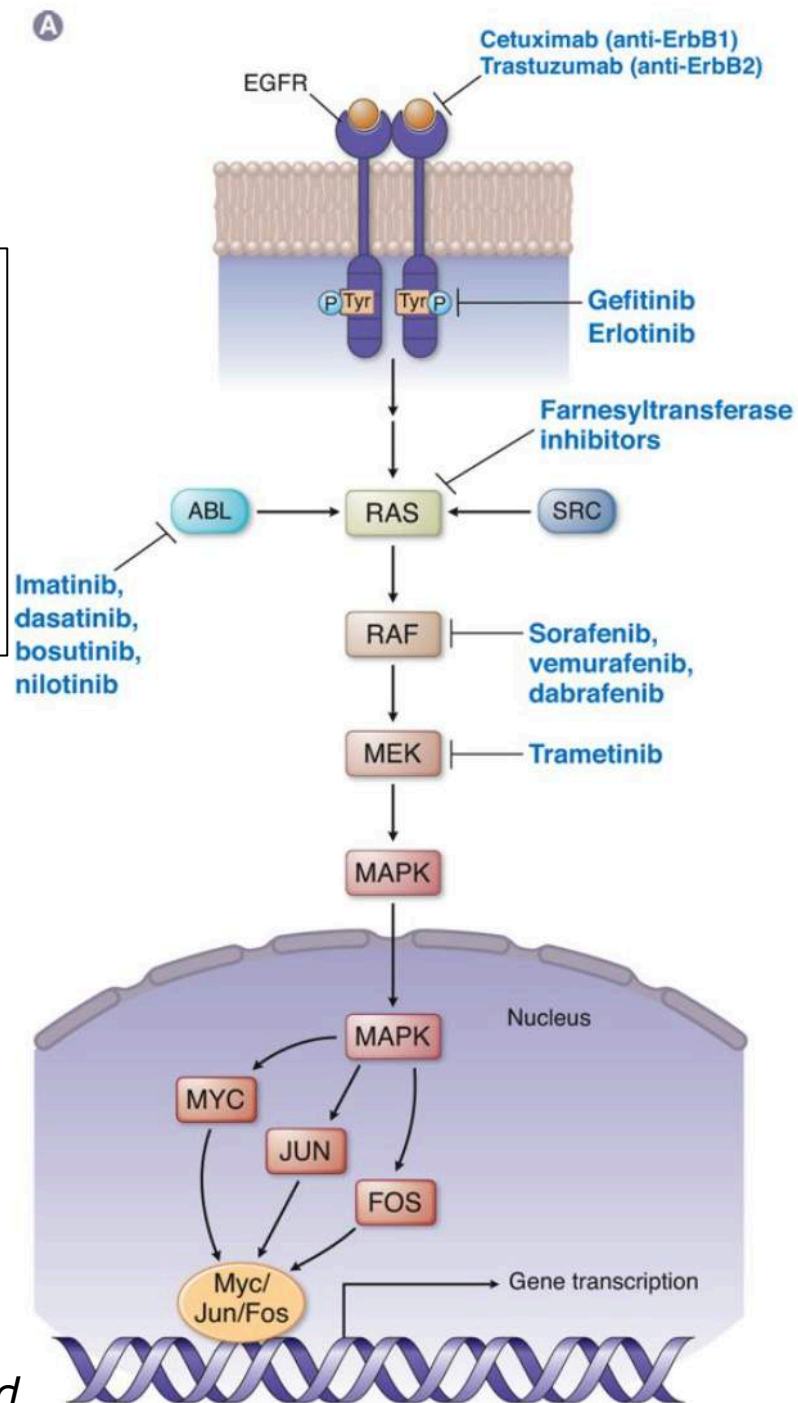
Cancer Mechanisms

- More growth factor
- More tyrosine-kinase linked receptor
- Constitutively active receptors
- Activating mutations in kinases of signalling pathway

Cell proliferation G1-S cell cycle transition



Golan, 4th ed.





Stop proliferation: traditional chemotherapy

- Inhibitors of nucleotide biosynthesis
 - Methotrexate, 5-fluorouracil, thiopurines, ...
- Inhibitors of DNA biosynthesis
 - Gemcitabine, DNA intercalators, topoisomerase inhibitors, ...
- Direct DNA binding and modification
 - Cyclophosphamide, cisplatin, bleomycin, ...
- Inhibition of microtubule polymerization or depolymerization
 - Vinblastine
 - Paclitaxel



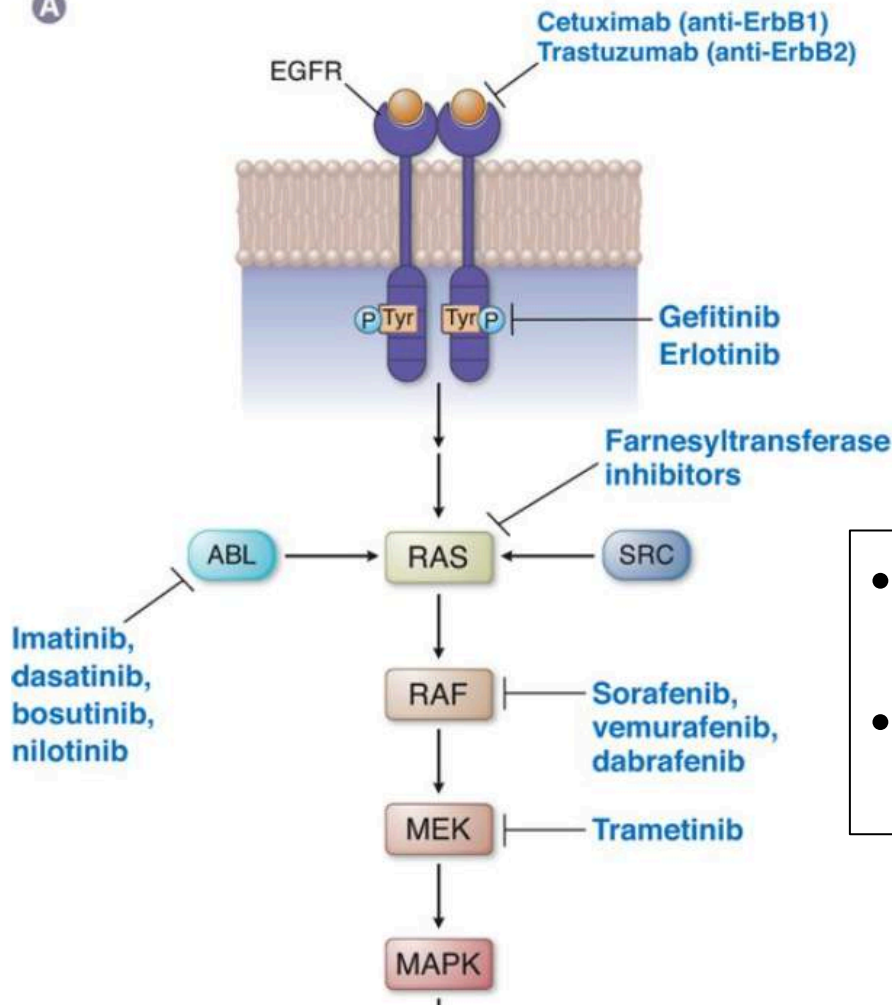
Stop proliferation: Hormones in oncology

- Estrogen receptor
 - Selective estrogen receptor modulator (SERM)
 - Tamoxifen
 - Estrogen receptor antagonist
 - Fulvestrant (Faslodex®)
- Estrogen biosynthesis (aromatase inhibitors)
 - Anastrozol, Letrozol, Exemestan
- Androgen receptor (prostate carcinoma)
 - Androgen receptor antagonist
 - Bicalutamide, Enzalutamide, Flutamide
 - Total antiandrogen
 - Cyproteron (Androcur®)
- Androgen biosynthesis (CYP17A1 inhibitor)
 - Abirateron (Zytiga®, prostate carcinoma)



Stop proliferation: Targeted drugs

A

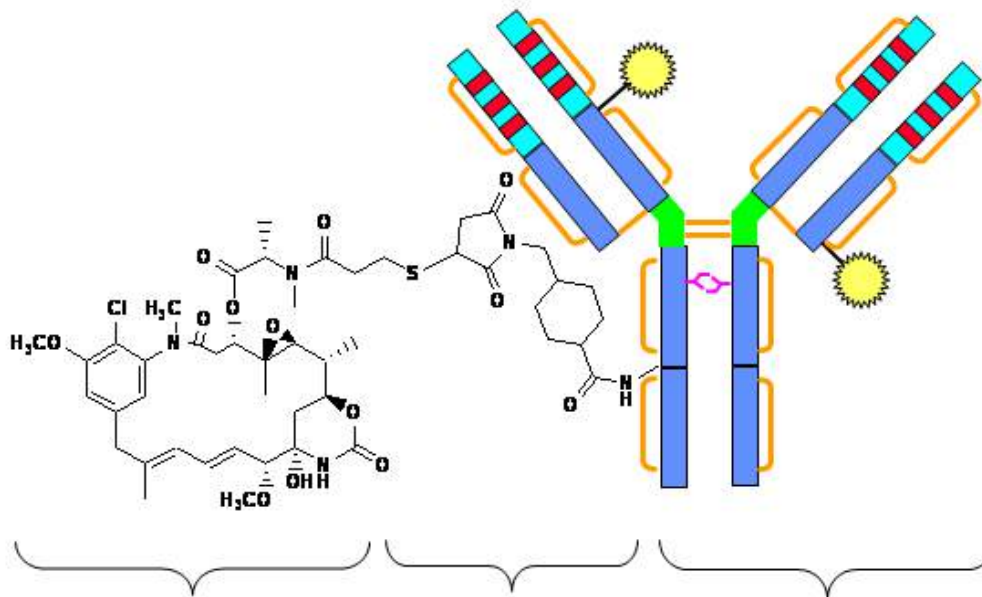


- Monoclonal antibodies
 - Trastuzumab (Herceptin®)
- Tyrosine kinase inhibitors
 - Lapatinib (Tyverb®)



Stop proliferation: antibody-drug conjugates

Trastuzumab emtansine (Kadcyla®, Roche, EMA 2013)



For HER-2 overexpressing
advanced or metastatic
breast cancer

Emtansine is a tubulin
binder that blocks mitosis
once in the cell

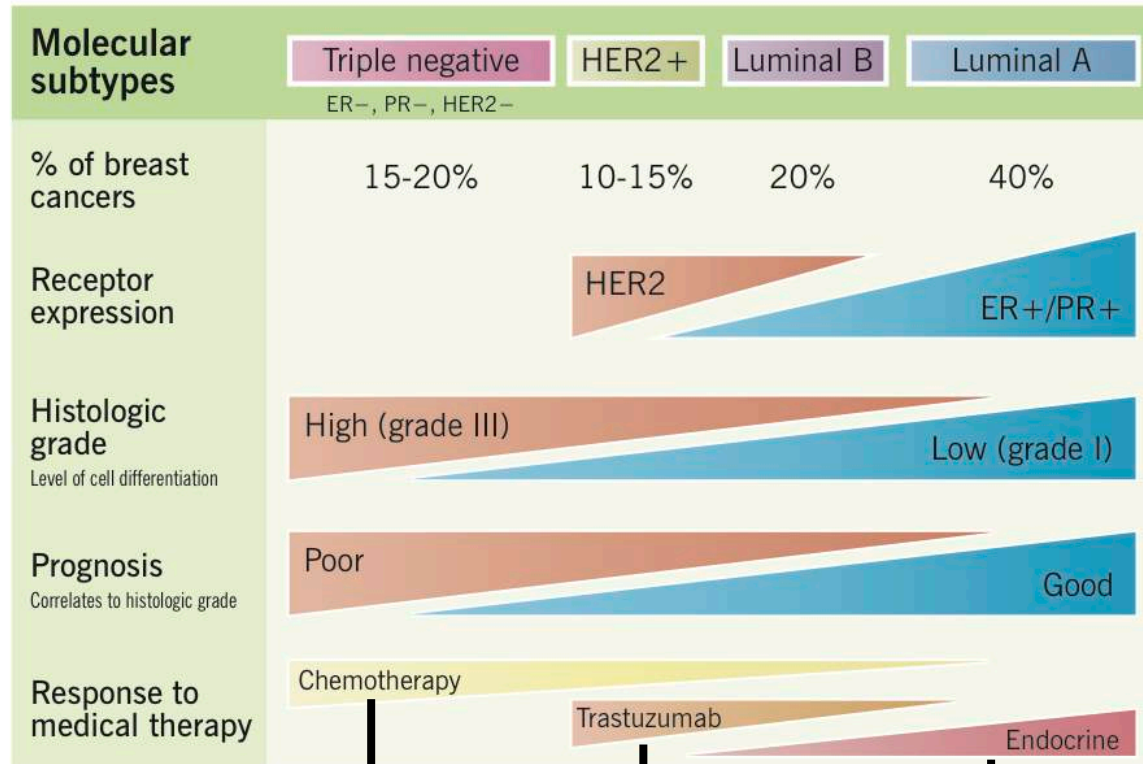
DM1 = 
(3 to 4 per IgG)

Linker
-thioether-

Trastuzumab
(H2IgG1)
-LysNH₂ (random)



Options for breast cancer depending on the phenotype



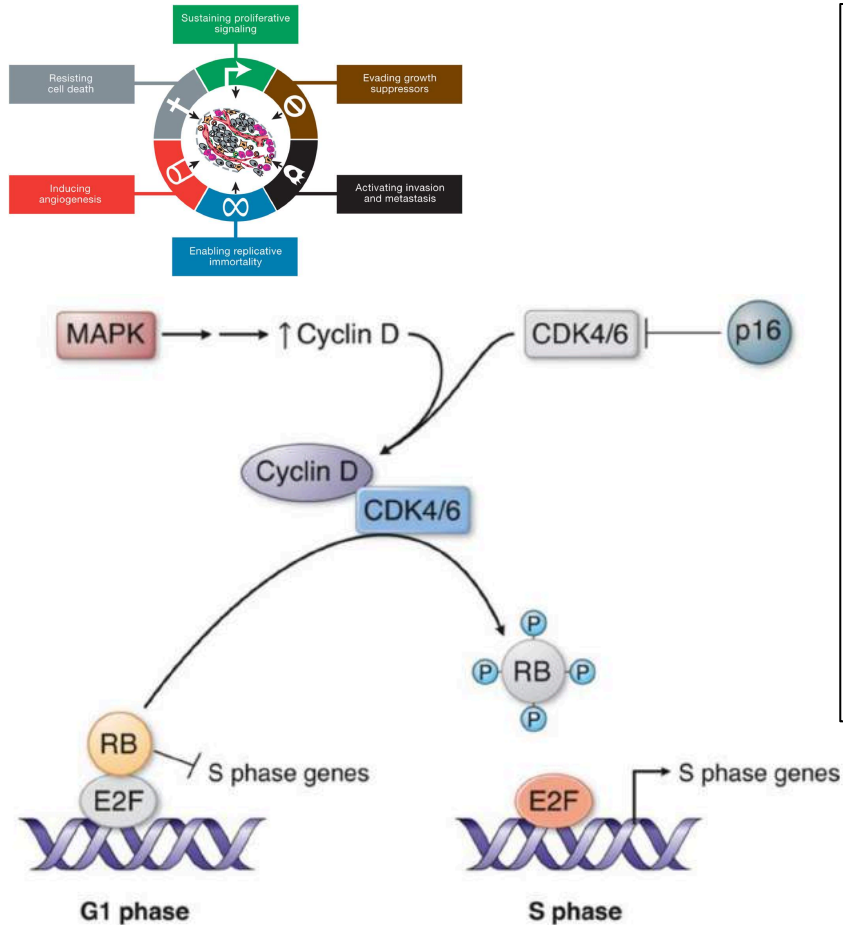
Doxorubicin, Paclitaxel, 5-FU, cyclophosphamide, paclitaxel, ...

Herceptin®
Kadcyla®

Tamoxifen
Fulvestrant
Anastrozol



2. Evading growth suppressors



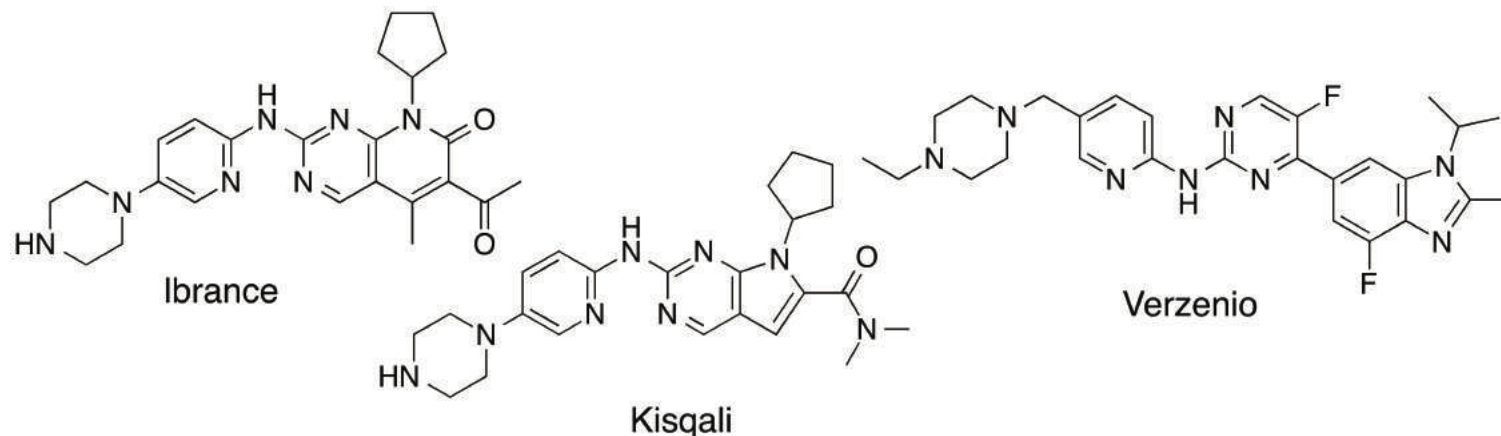
- Retinoblastoma (RB) protein is a tumour suppressor
- Phosphorylated RB is inactive and allows cell cycle progression
- Inhibition of CDK4/6 will stop phosphorylation of RB and stops cell cycle progression



The first CDK4/6 inhibitors recently entered the market

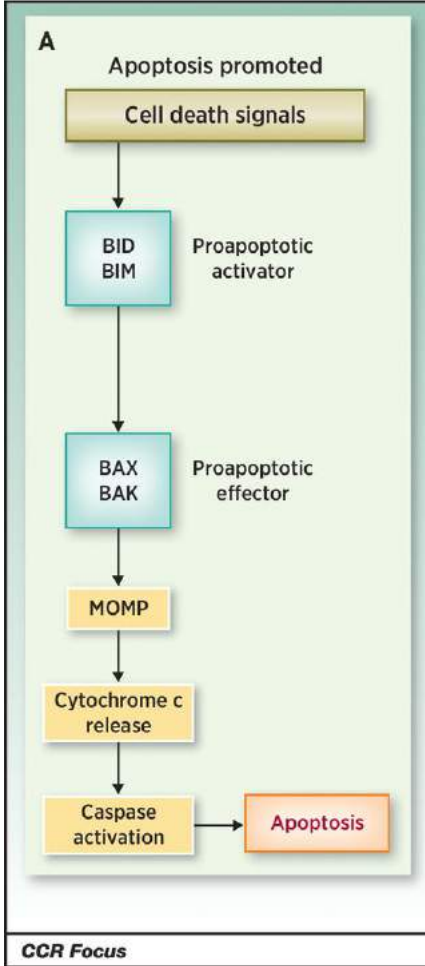
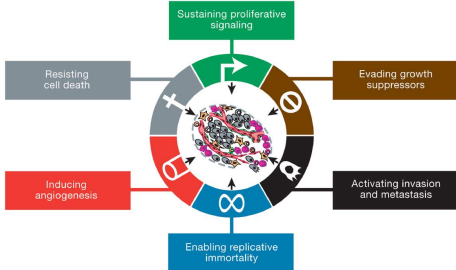
MOA	Name	Active substance	Company	EMA	FDA
CDK4/6	Ibrance	Palbociclib	Pfizer	2016	2015
CDK4/6	Kisqali	Ribociclib	Novartis	2017	2017
CDK4/6	Verzenio	Abemaciclib	Eli Lilly	-	2017

To treat hormone-receptor positive, HER2 negative advanced metastatic breast cancer in combination with an aromatase inhibitor



3. Resisting Cell Death

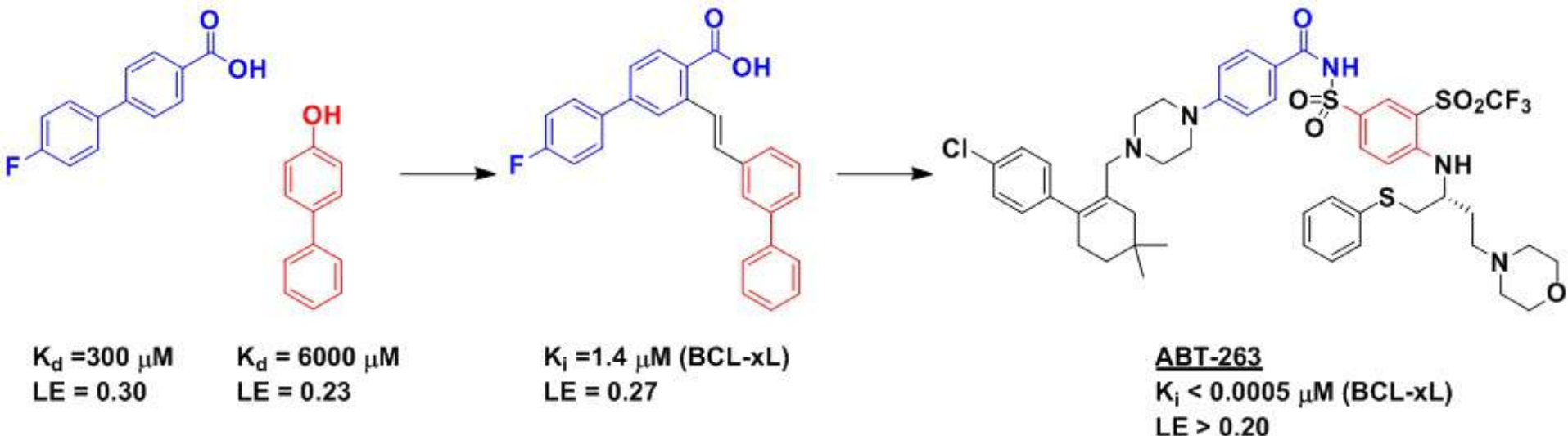
Programmed cell death, apoptosis, is a natural barrier to cancer
Apoptosis is reduced in malignant tumours and tumours resistant to therapy



BH3-only proteins

Mitochondrial outer membrane permeabilisation

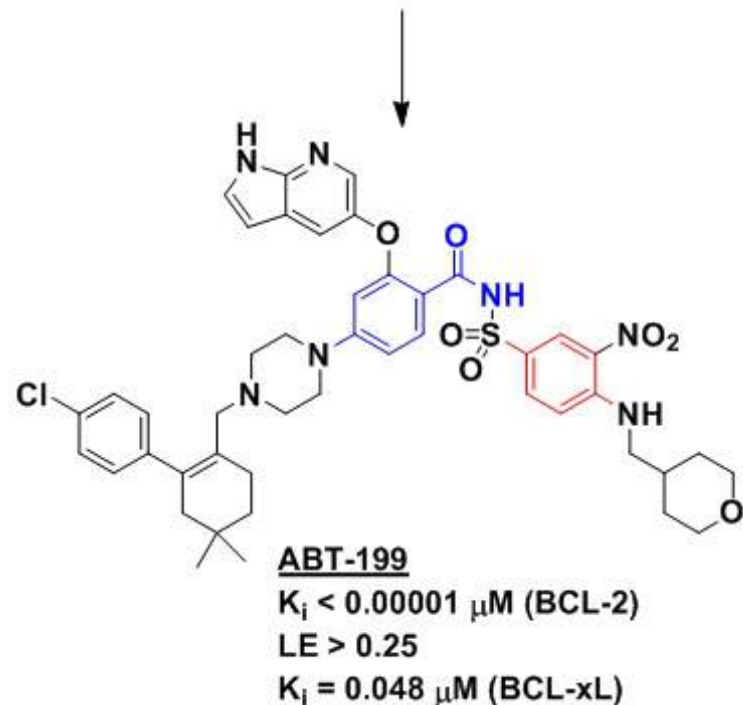
BH3 mimetic to inhibit BCL-2



Difficult target:
protein-protein interaction
Fragment-based drug discovery

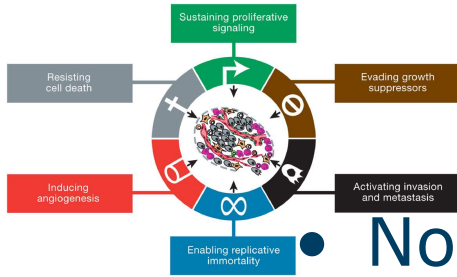
Venetoclax (Venclyxto®)
AbbVie, EMA 2016, FDA 2016

chronic lymphocytic leukaemia (CLL)
when other treatments have failed





4. Replicative immortality



- Normal cells

- Limited number of cell growth-and-division cycles
- Then enter into
 - Senescence = a non-proliferative but viable state
 - Or cell death

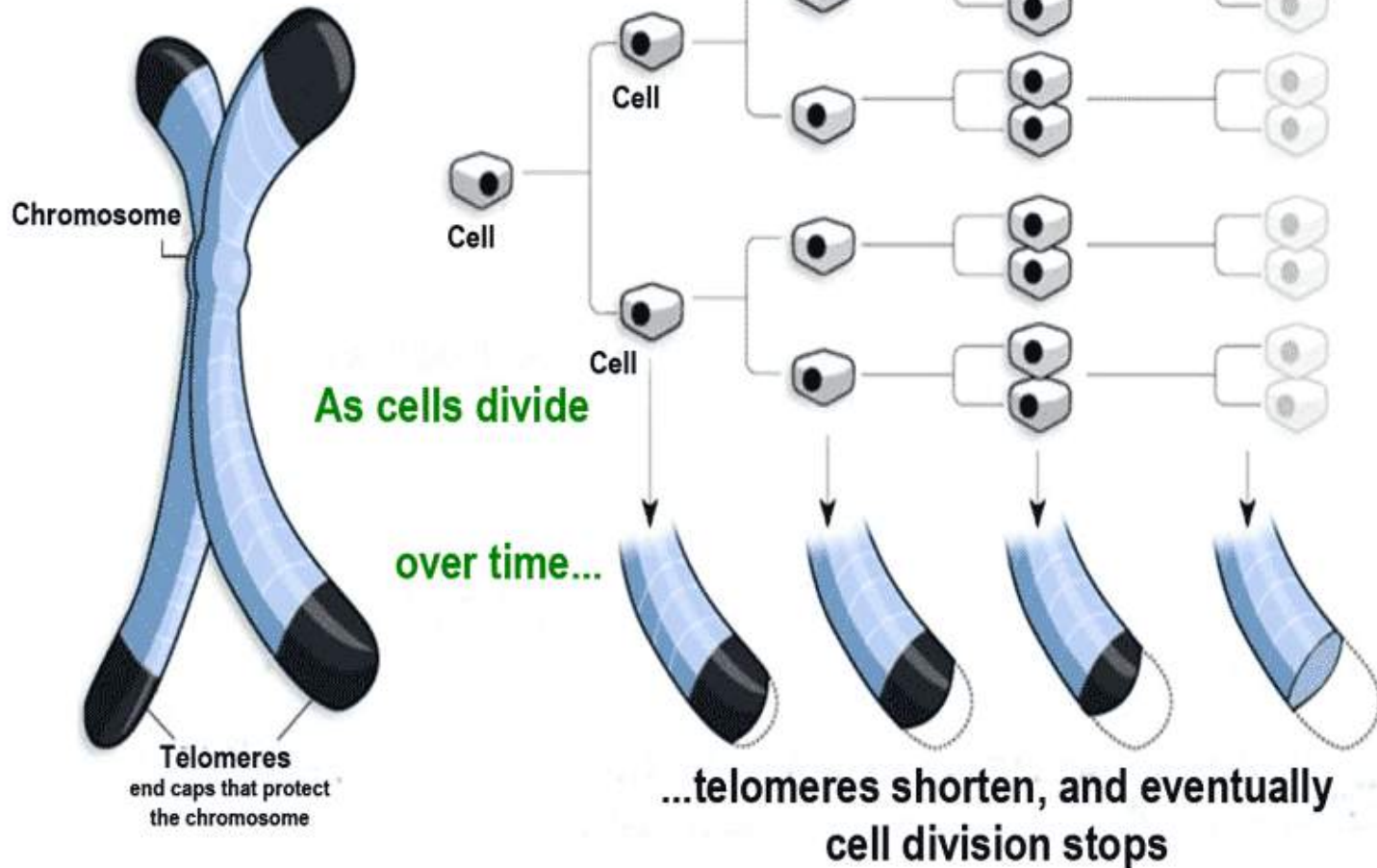
- Cancer cells

- Unlimited replicative potential = immortalization

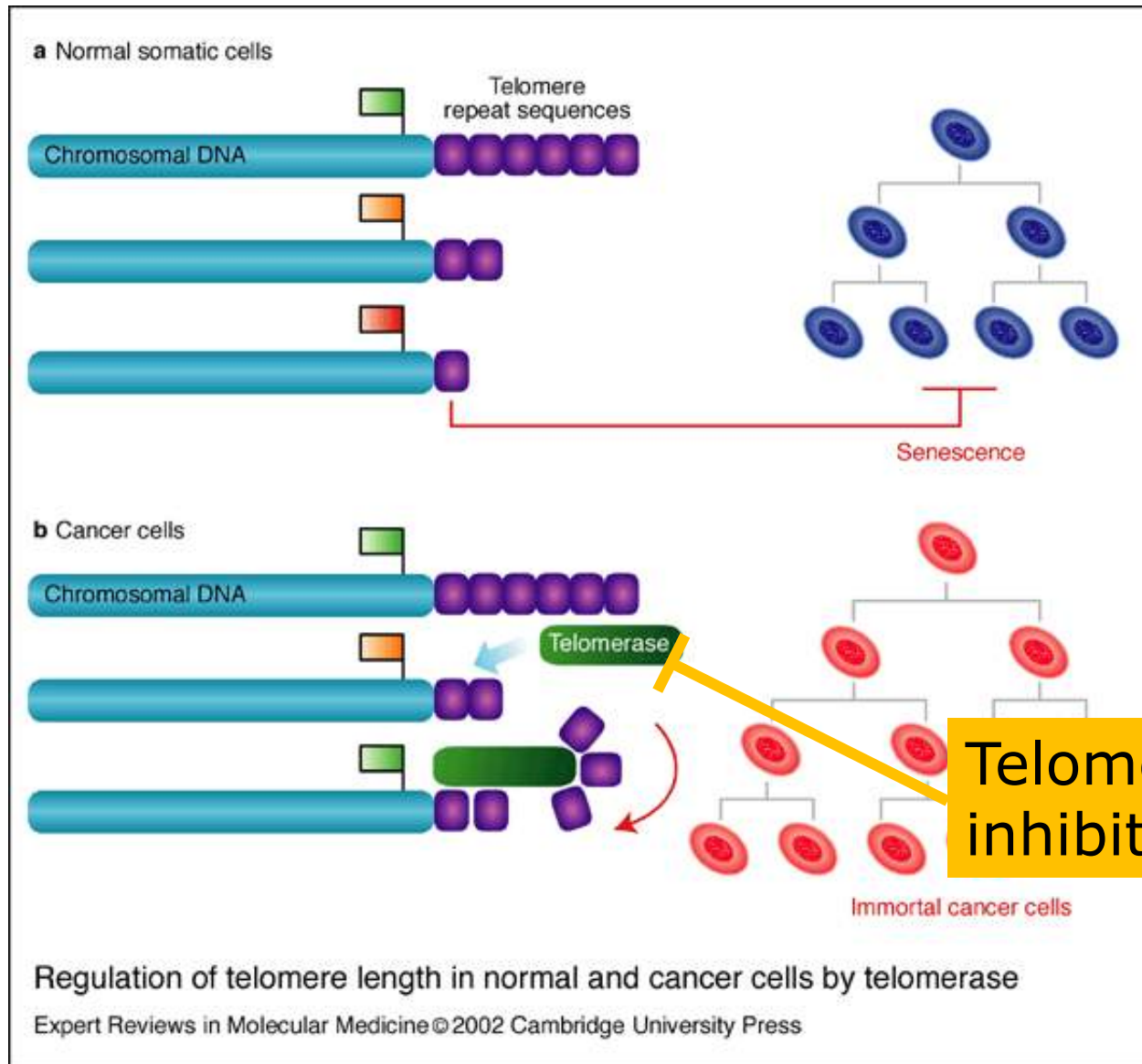


Stop replicative immortality

What We Lose With Age

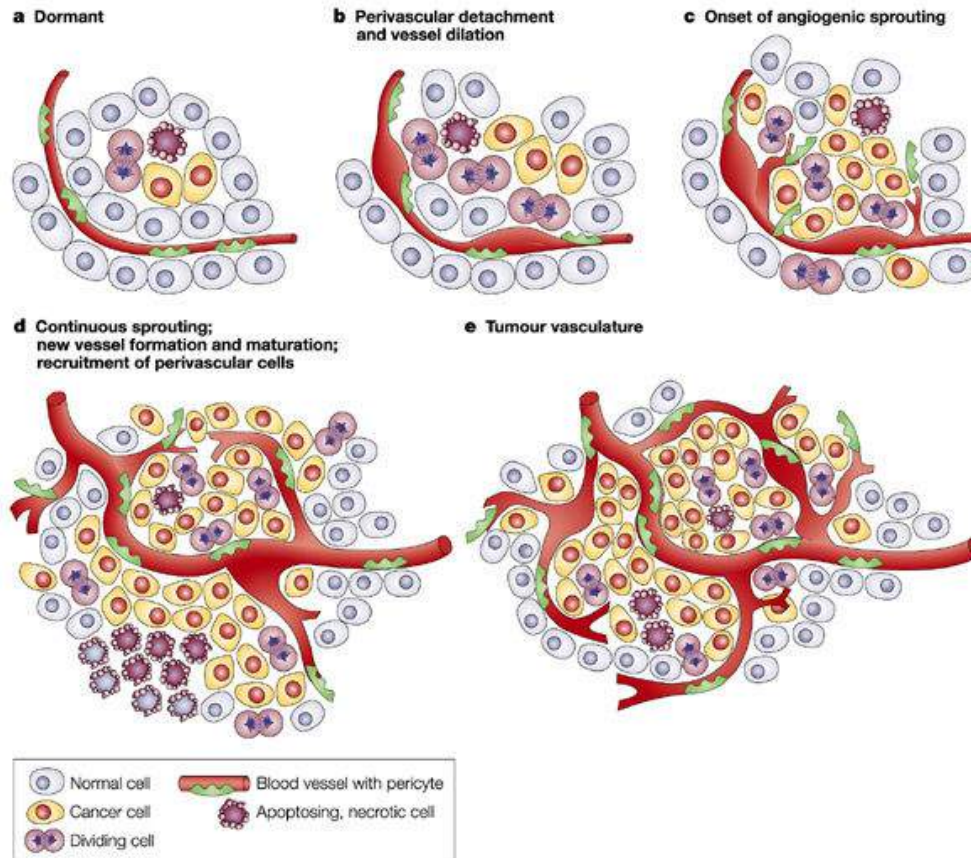
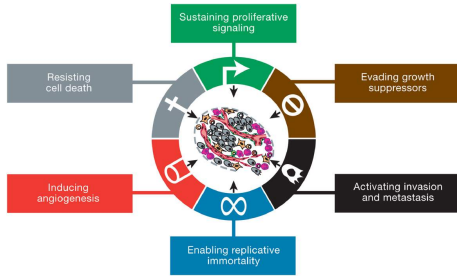


Stop replicative immortality



5. Inducing angiogenesis

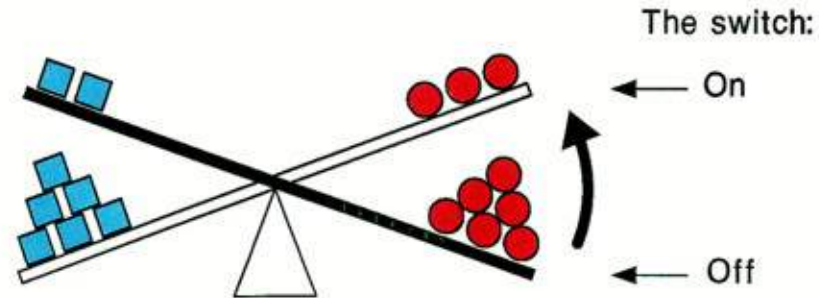
Tumours continuously need new vessel formation for the delivery of nutrients and oxygen and for the evacuation of metabolic waste and CO₂





The angiogenic switch

THE BALANCE HYPOTHESIS FOR THE ANGIOGENIC SWITCH



■ Activators

aFGF
bFGF
VEGF
⋮
⋮

● Inhibitors

Thrombospondin-1
16 kD Prolactin
Interferon α/β
Platelet factor-4

VEGF and VEGFR
neutralizing Abs

VEGFR tyrosine
kinase inhibitors



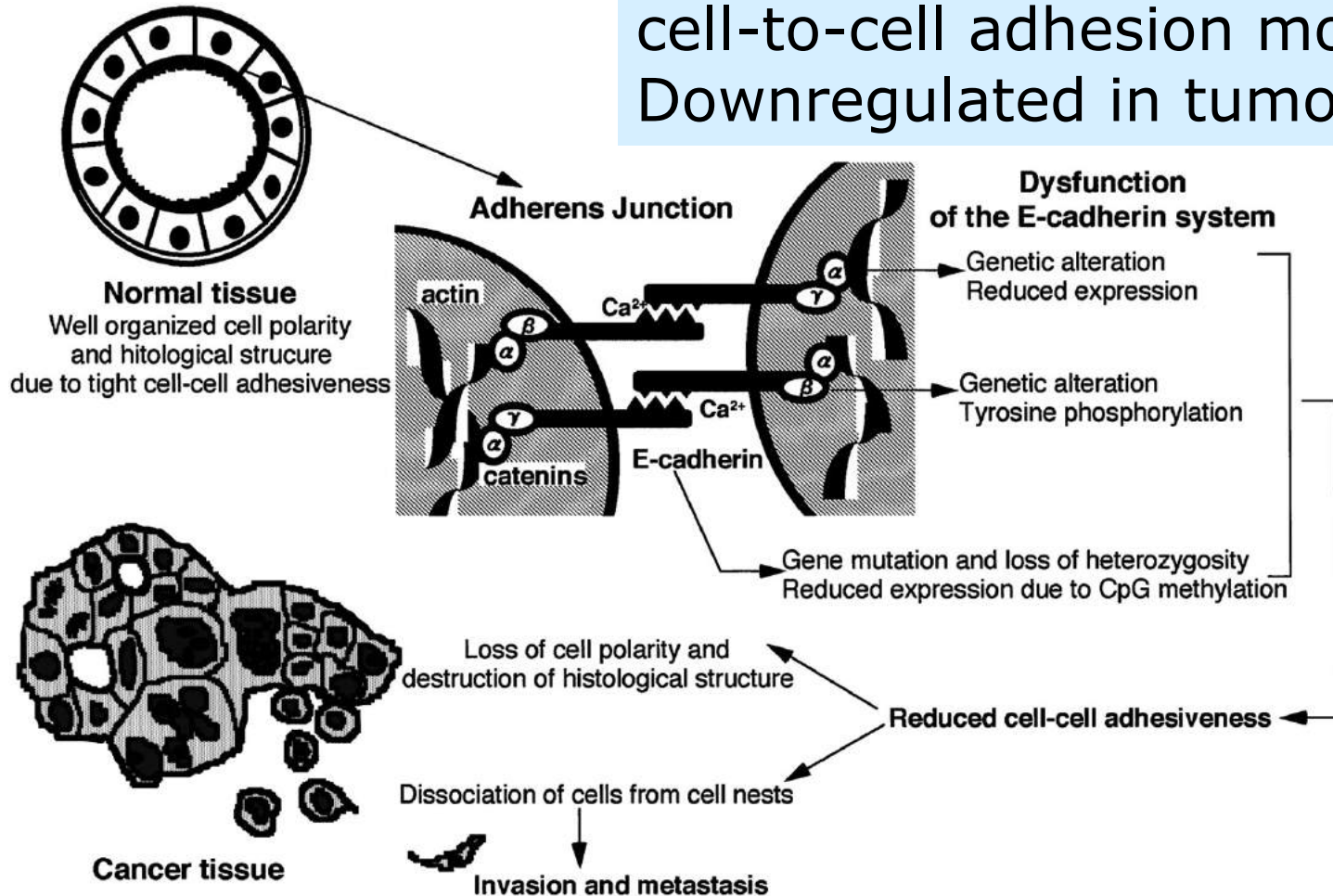
Angiogenesis inhibitors

MOA	Name	Active substance	Company	EMA	FDA
VEGF-A	Avastin	Bevacizumab	Roche	2005	2004
VEGF, PIGF	Zaltrap Eylea	Aflibercept (macular degen.)	Sanofi- Aventis	2013	2012
VEGFR-2	Cyramza	Ramucirumab	Eli Lilly	2014	2014
TKI	Nexavar	Sorafenib	Bayer	2006	2005
TKI	Sutent	Sunitinib	Pfizer	2006	2006
TKI	Votrient	Pazopanib	Novartis	2010	2009
TKI	Caprelsa	Vandetanib	Sanofi	2012	2011
TKI	Inlyta	Axitinib	Pfizer	2012	2012
TKI	Stivarga	Regorafenib	Bayer	2013	2012
TKI	Cometriq	Cabozantinib	Ipsen	2014	2012
TKI	Lenvima	Lenvatinib	Eisai	2015	2015



6. Invasion and metastasis

E-cadherin =
cell-to-cell adhesion molecule
Downregulated in tumours



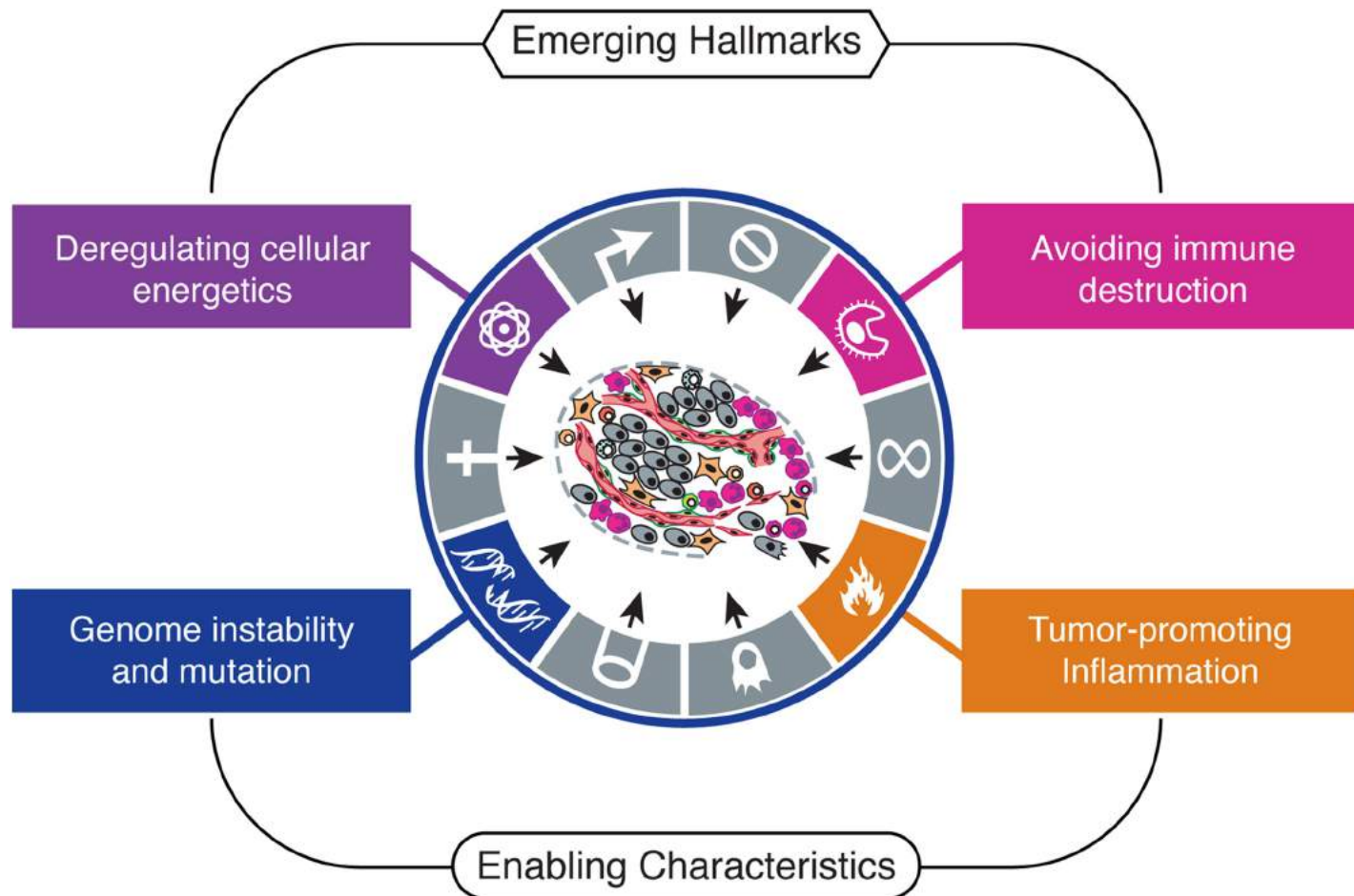


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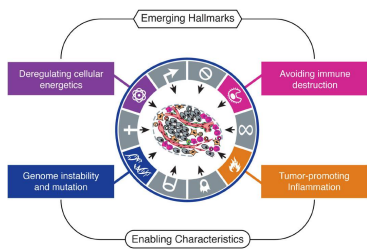
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Emerging Hallmarks and new enabling characteristics

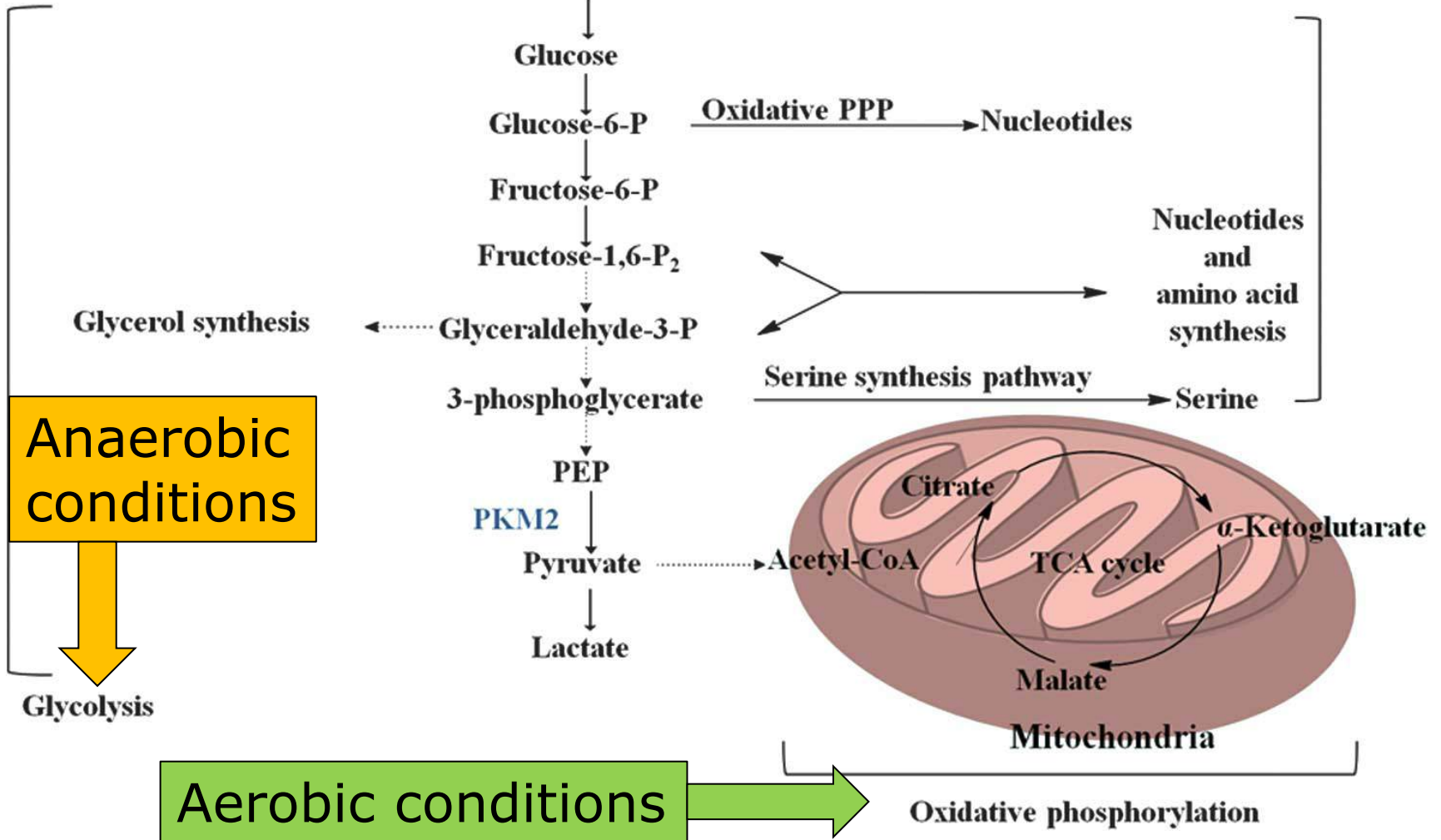


7. Reprogrammed energy metabolism



Normal Cells

Glucose transporter 1



18-FDG
PET scans

7. Reprogrammed energy metabolism

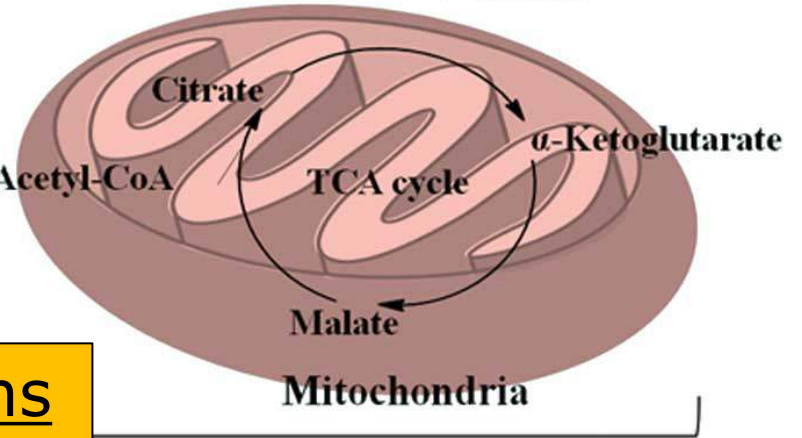
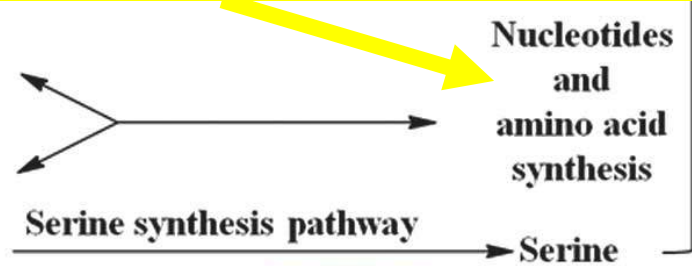
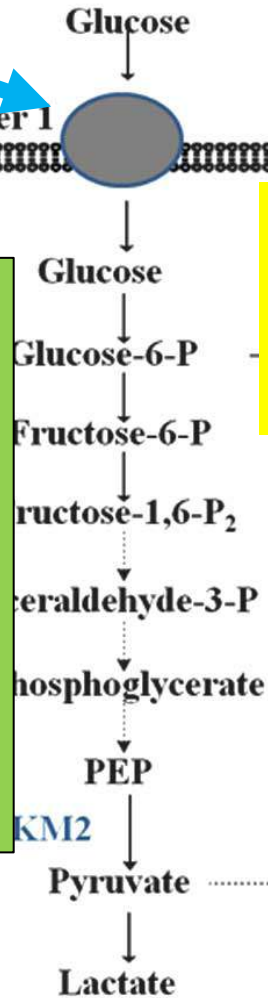
Cancer Cells

Why? Hypothesis:
more building blocks
from glycolytic intermediates

Aerobic conditions
Warburg effect:
glycolysis is favoured

18x less efficient
ATP production

GLUT-1 upregulated



Glycolysis

Anaerobic conditions
even more pronounced

Oxidative phosphorylation



8. Evading immune destruction

- Both the innate and adaptive immune system operate as a significant barrier to tumour formation and progression
- Tumours have found ways to avoid this immune barrier

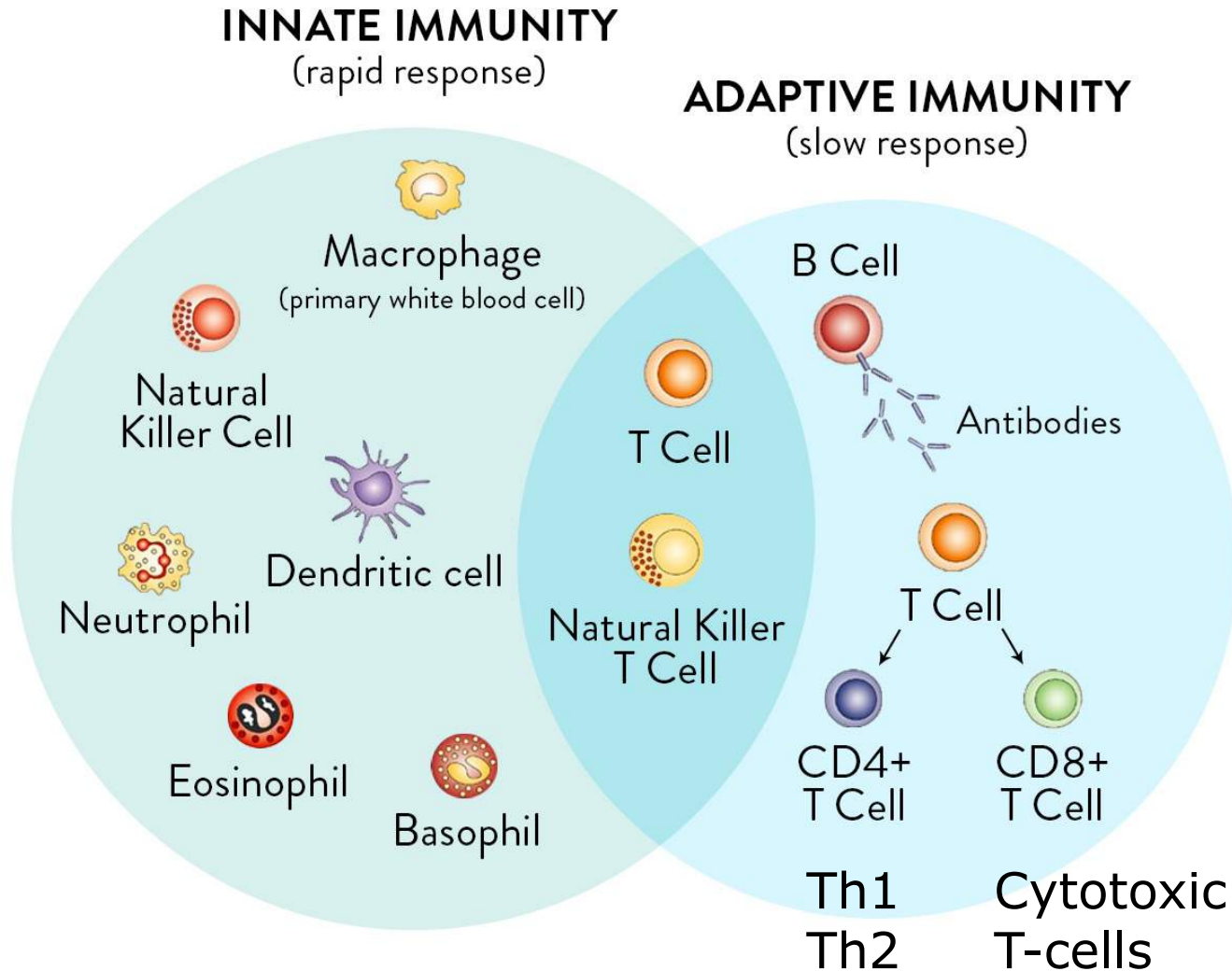


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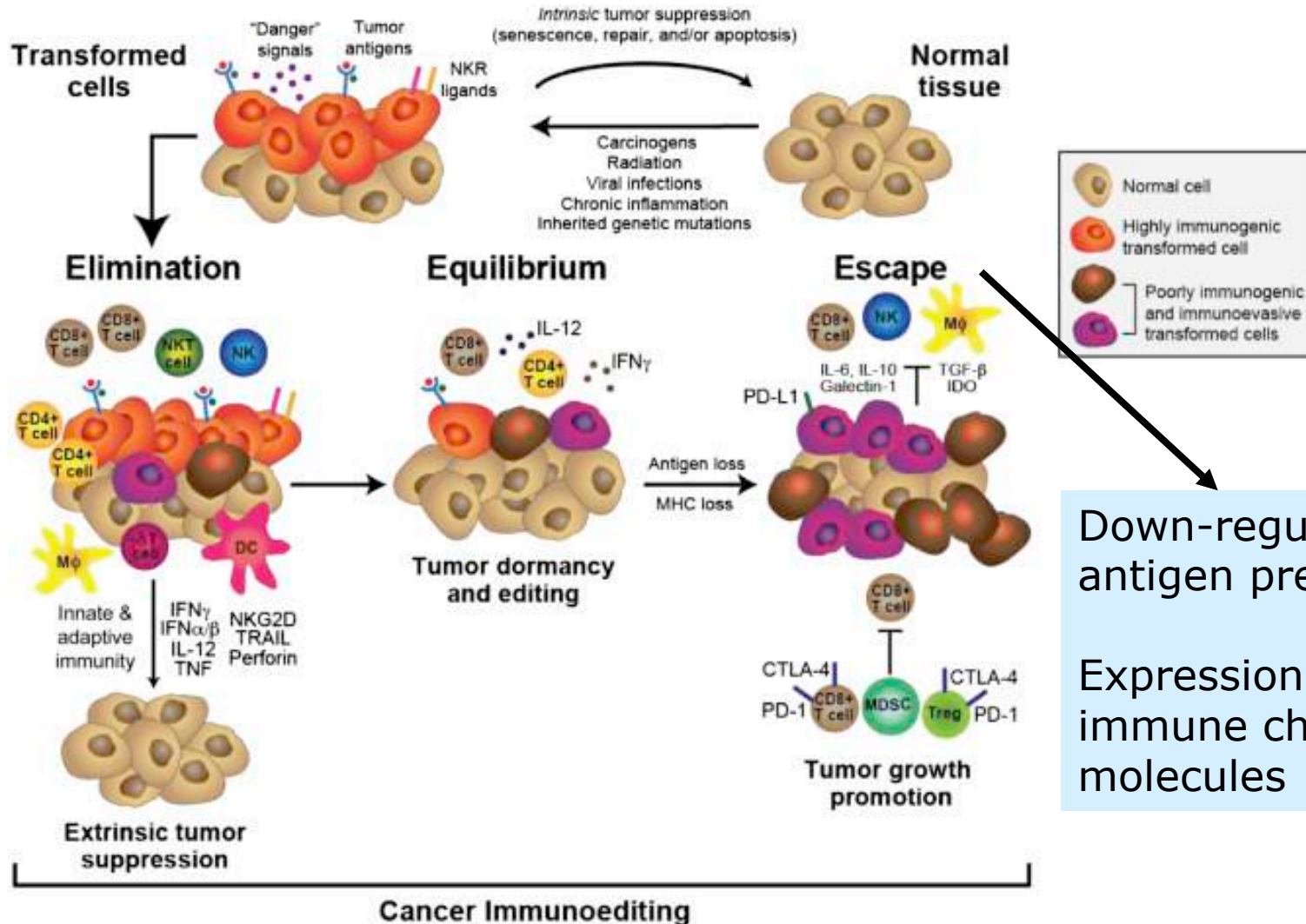


The immune system and cancer





Cancer immunoediting



Down-regulation of antigen presentation

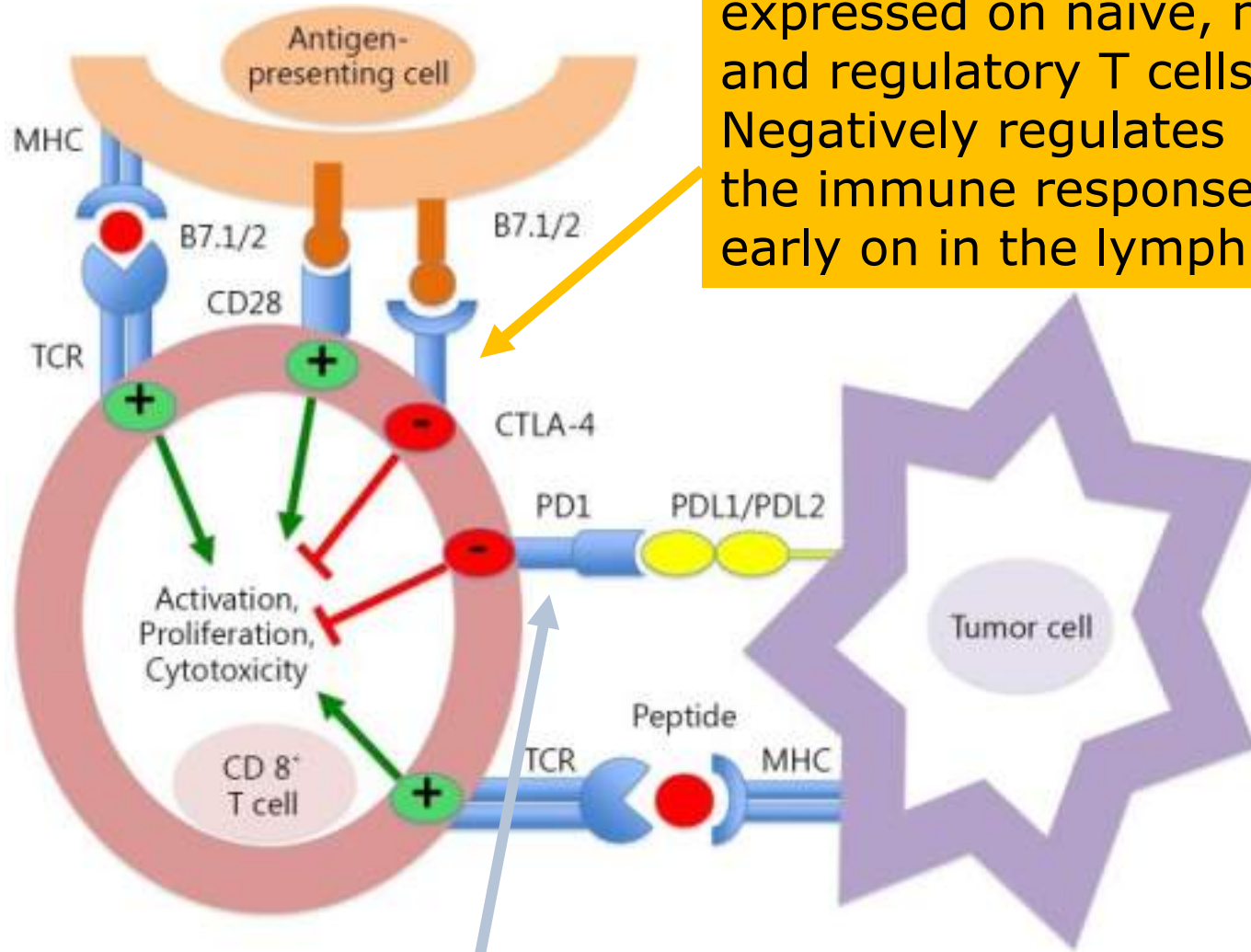
Expression of immune checkpoint molecules



Immune checkpoint molecules

- Are important gatekeepers of T-cell function
 - Prevent self-destruction
 - Counteract excessive immune reaction
- Examples of inhibitory checkpoint molecules are
 - CTLA-4: cytotoxic T-lymphocyte-associated protein 4
 - PD-1: programmed death 1 receptor
 - PD-L1 and PD-L2: ligands for the PD-1 receptor
- Tumours have co-opted these gatekeeping mechanisms to allow immune escape

Immune escape

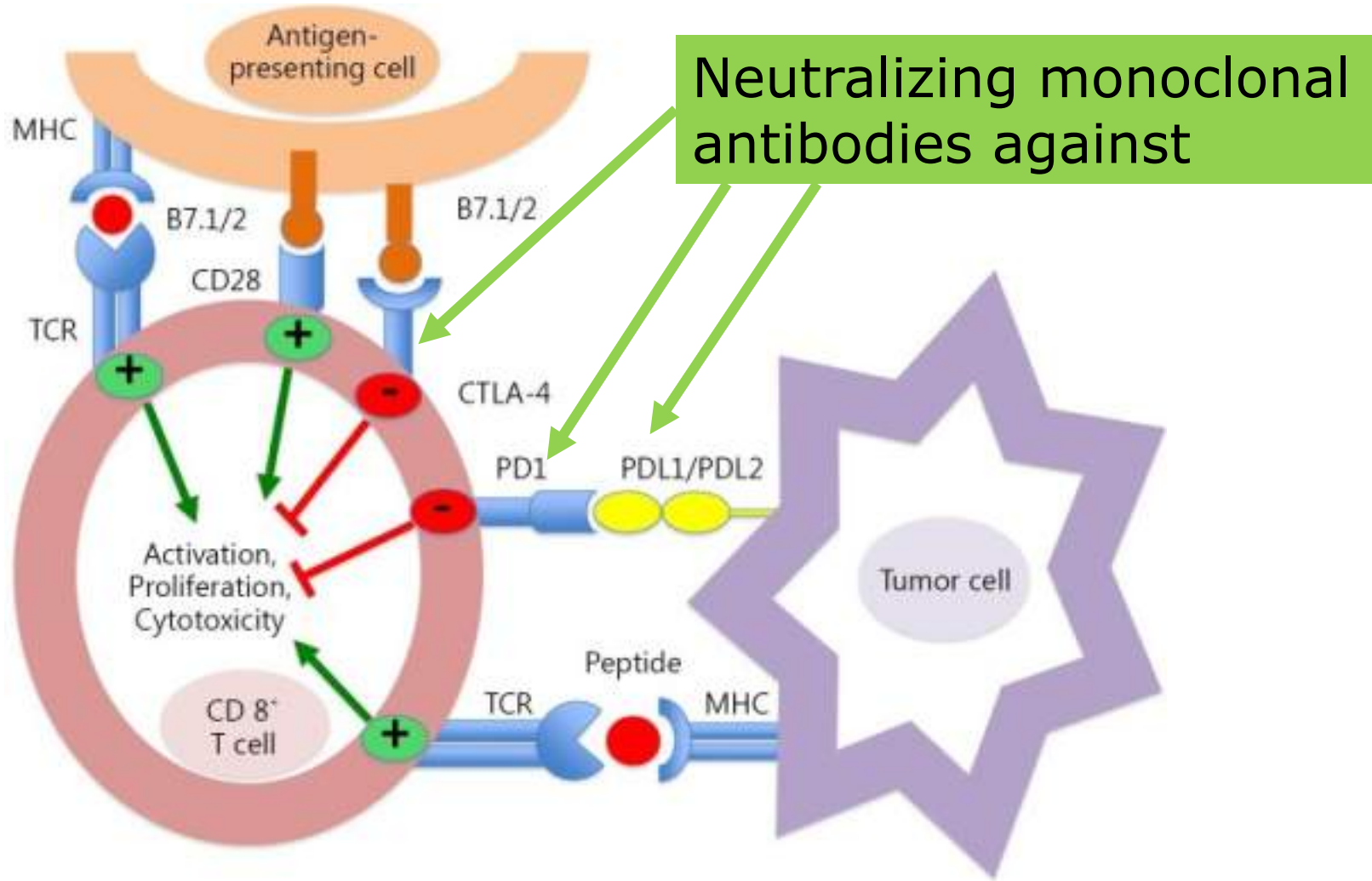


CTLA-4

expressed on naïve, memory and regulatory T cells
Negatively regulates the immune response early on in the lymph nodes

PD1 negative regulator of previously activated T cells in the periphery

Immune checkpoint blockade





Monoclonal antibodies on the market

MOA	Name	Active substance	Company	EMA	FDA
CTLA-4	Yervoy	Ipilimumab	BMS	2011	2011
PD-1	Keytruda	Pembrolizumab	MSD	2015	2014
PD-1	Opdivo	Nivolumab	BMS	2015	2015
PD-L1	Tecentriq	Atezolizumab	Roche	2017	2016
PD-L1	Bavencio	Avelumab	Merck Serono	2017	2017
PD-L1	Imfinzi	Durvalumab	Astra Zeneca	-	2017



Therapeutic use

- Yervoy® (CTLA-4)
 - **Melanoma**: unresectable stage III and stage IV in patients who have received prior therapy
- Keytruda® (PD-1)
 - Advanced **melanoma**
 - Advanced or metastatic **NSCLC**, expressing PD-L1
 - **Hodgkin lymphoma** after failure of brentuximab vedotin and autologous stem cell transplant
 - Advanced or metastatic **urothelial cancer** after treatment with platinum chemotherapeutics



Therapeutic use

- Opdivo® (PD-1)
 - Advanced **melanoma**, alone or in combination with Yervoy®
 - Advanced or metastatic **NSCLC** that has previously been treated with chemotherapy
 - **Hodgkin lymphoma** after failure of brentuximab vedotin and autologous stem cell transplant
 - Advanced or metastatic **urothelial cancer** after treatment with platinum chemotherapeutics
 - Advanced **renal cell carcinoma** in patients who have been treated before
 - **squamous cell cancer of the head and neck** (SCCHN) where platinum chemotherapy has not worked



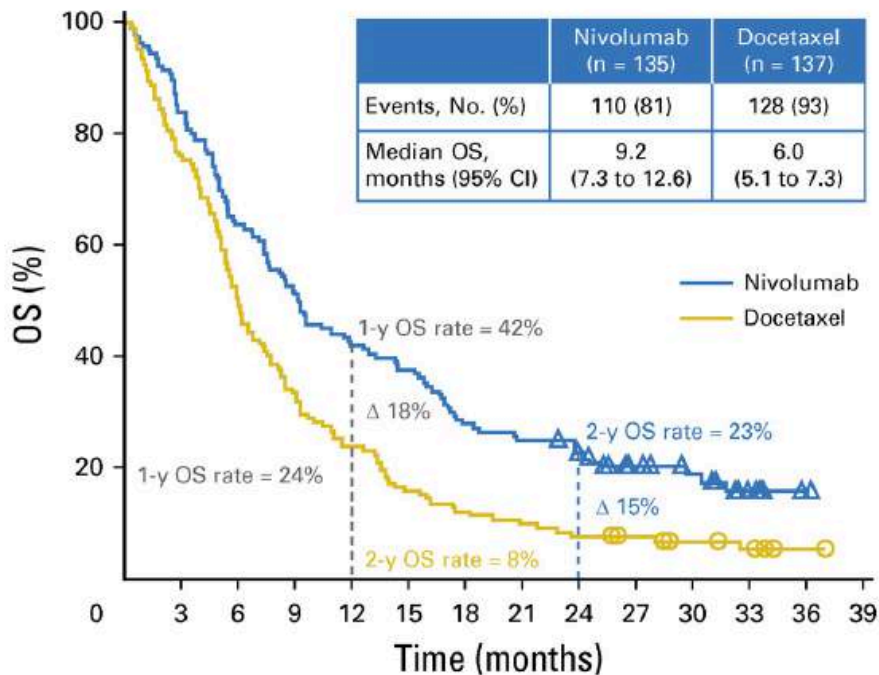
Therapeutic use

- Tecentriq® (PD-L1)
 - Advanced or metastatic **NSCLC** that has previously been treated with chemotherapy
 - Advanced or metastatic **urothelial cancer** after treatment with platinum chemotherapeutics
- Bavencio® (PD-L1)
 - Advanced **Merkel cell carcinoma** (MCC), a type of skin cancer (rare disease)
- Imfinzi® (PD-L1)
 - Advanced or metastatic **urothelial cancer** after treatment with platinum chemotherapeutics

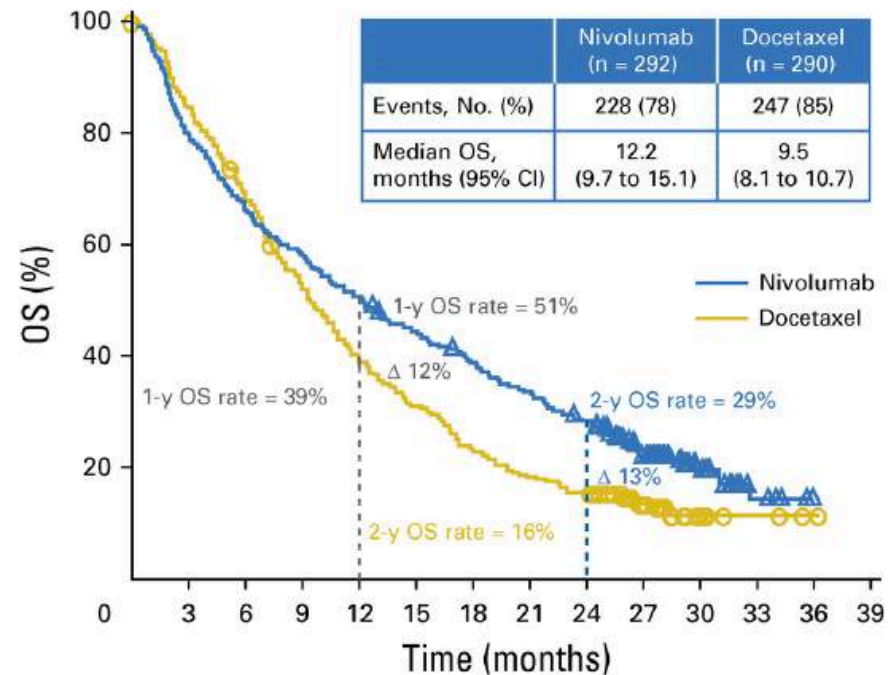


Opdivo® vs docetaxel in NSCLC

Squamous



Nonsquamous

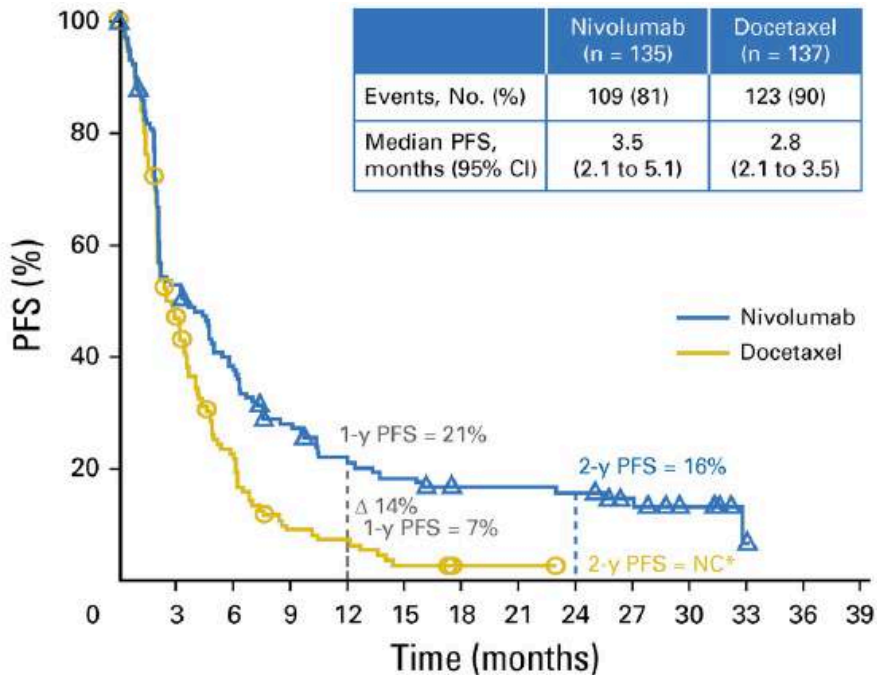


Horn, L. et al. CheckMate 017 and CheckMate 057, *J. Clin. Oncol.* 2017, 35, 3924

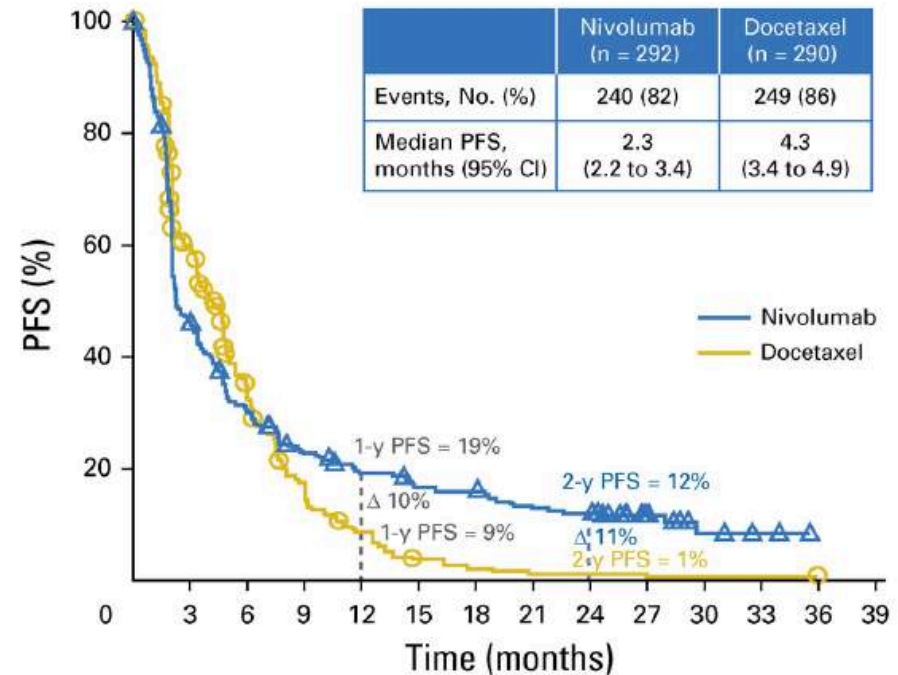


Opdivo® vs docetaxel in NSCLC

Squamous



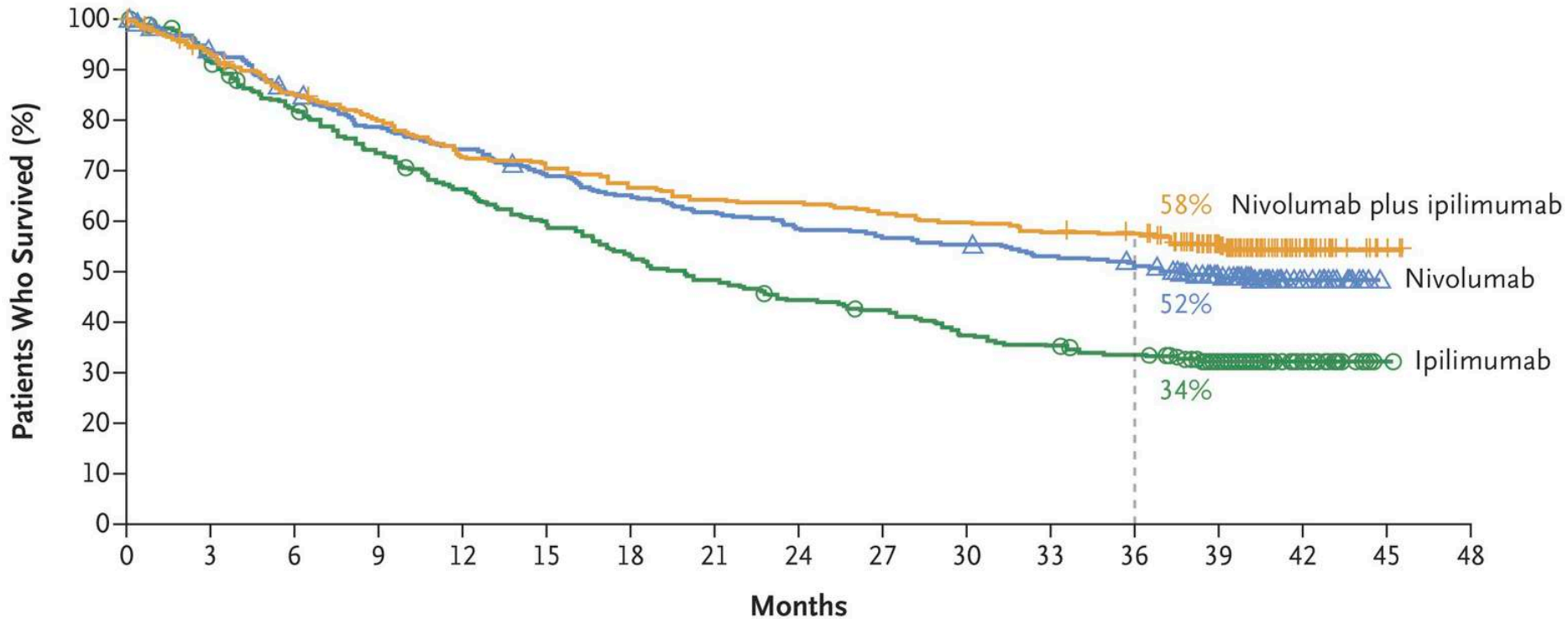
Nonsquamous



Horn, L. et al. CheckMate 017 and CheckMate 057, *J. Clin. Oncol.* 2017, 35, 3924



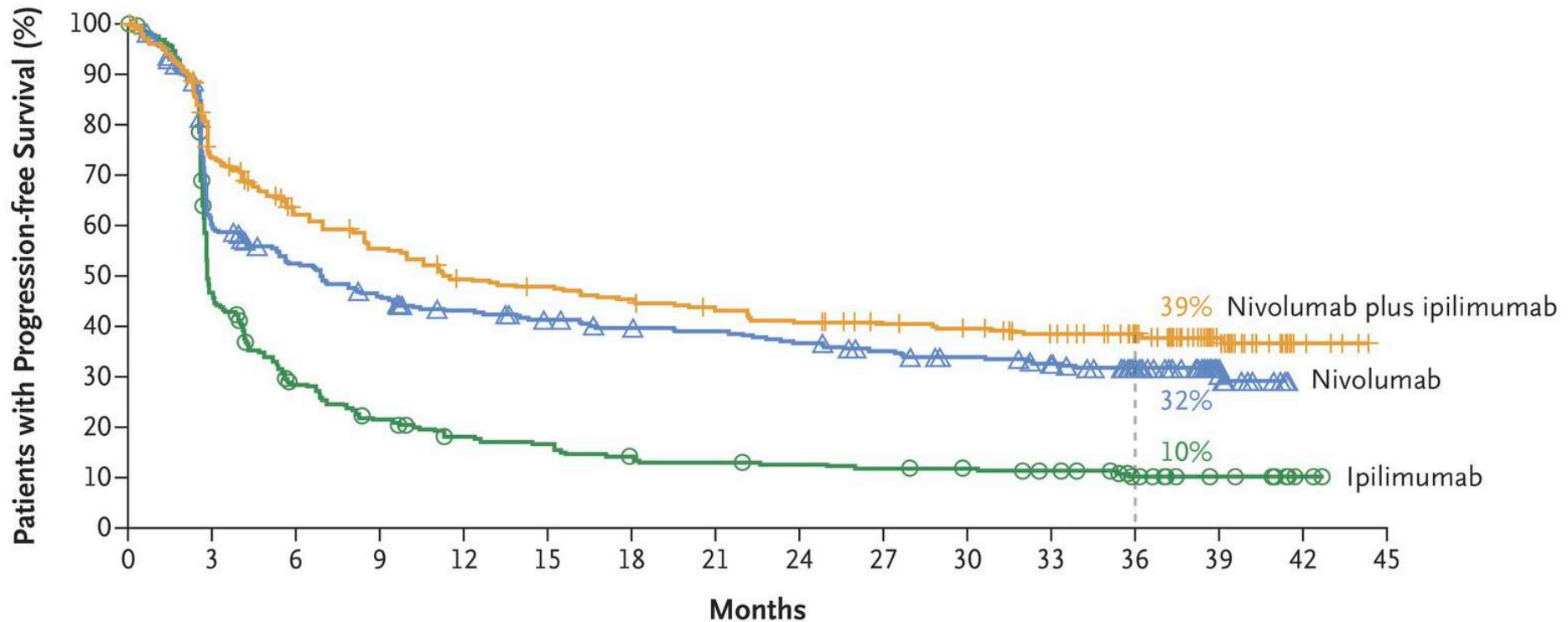
Combination of Opdivo® and Yervoy® in advanced melanoma



Wolchok, J.D. et al. CheckMate 067, New Eng. J. Med. 2017, 377, 1345



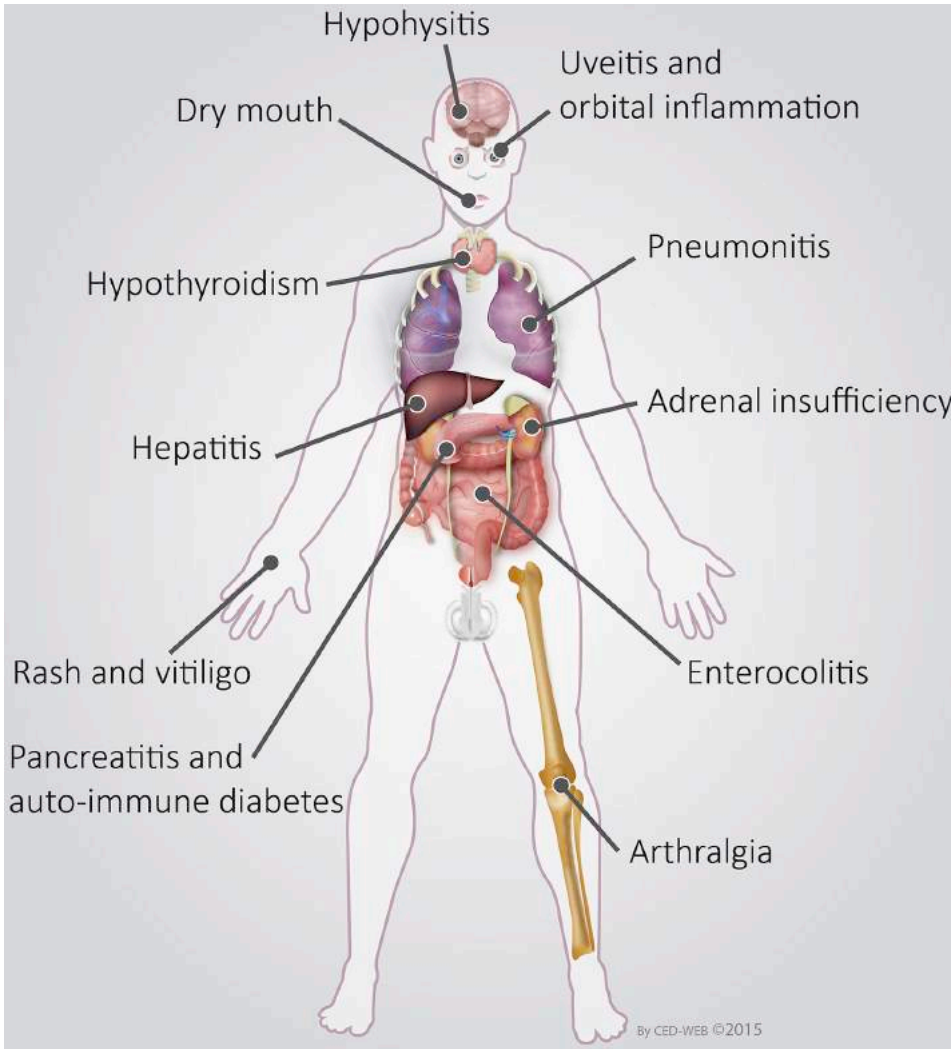
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Wolchok, J.D. et al. CheckMate 067, *New Eng. J. Med.* 2017, 377, 1345



Immune-related adverse events



- Pneumonitis, colitis, hepatitis, nephritis, hypophysitis, rash
- Up to several months after the last administration
- Requires close follow-up by organ specialists
- Can be treated with glucocorticoids, but this can diminish the antitumour response



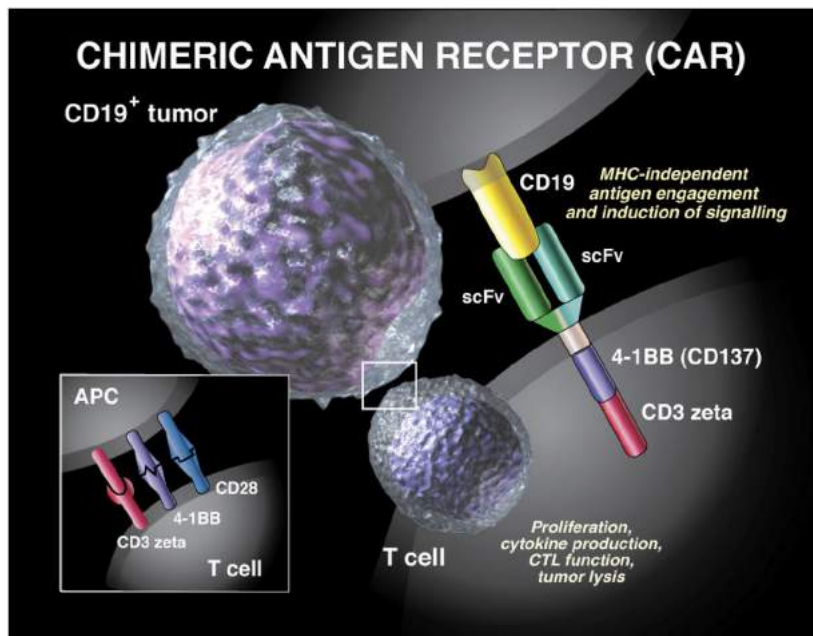
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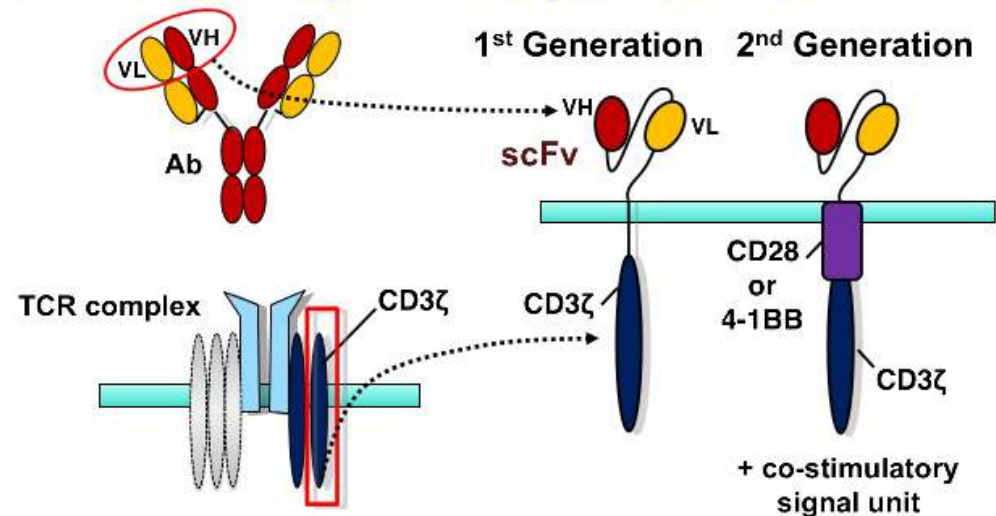


Future: first CAR-T cell immunotherapy approved, August 30, 2017

A chimeric antigen receptor (CAR) expressed on T cells recognizes CD-19 on B-cells (MHC-independent), which leads to T cell proliferation cytokine production, CTL function and tumour lysis



Chimeric Antigen Receptor (CAR)



CARs are hybrid proteins consisting of an extracellular single chain fragment of variable region (scFv) fused to co-stimulatory signaling domains CD28 or 4-1BB (CD137), coupled with CD3ζ to mediate T-cell activation.

4. Preparing the patient. The patient gets chemotherapy to kill some white blood cells and help the body accept the modified T cells.

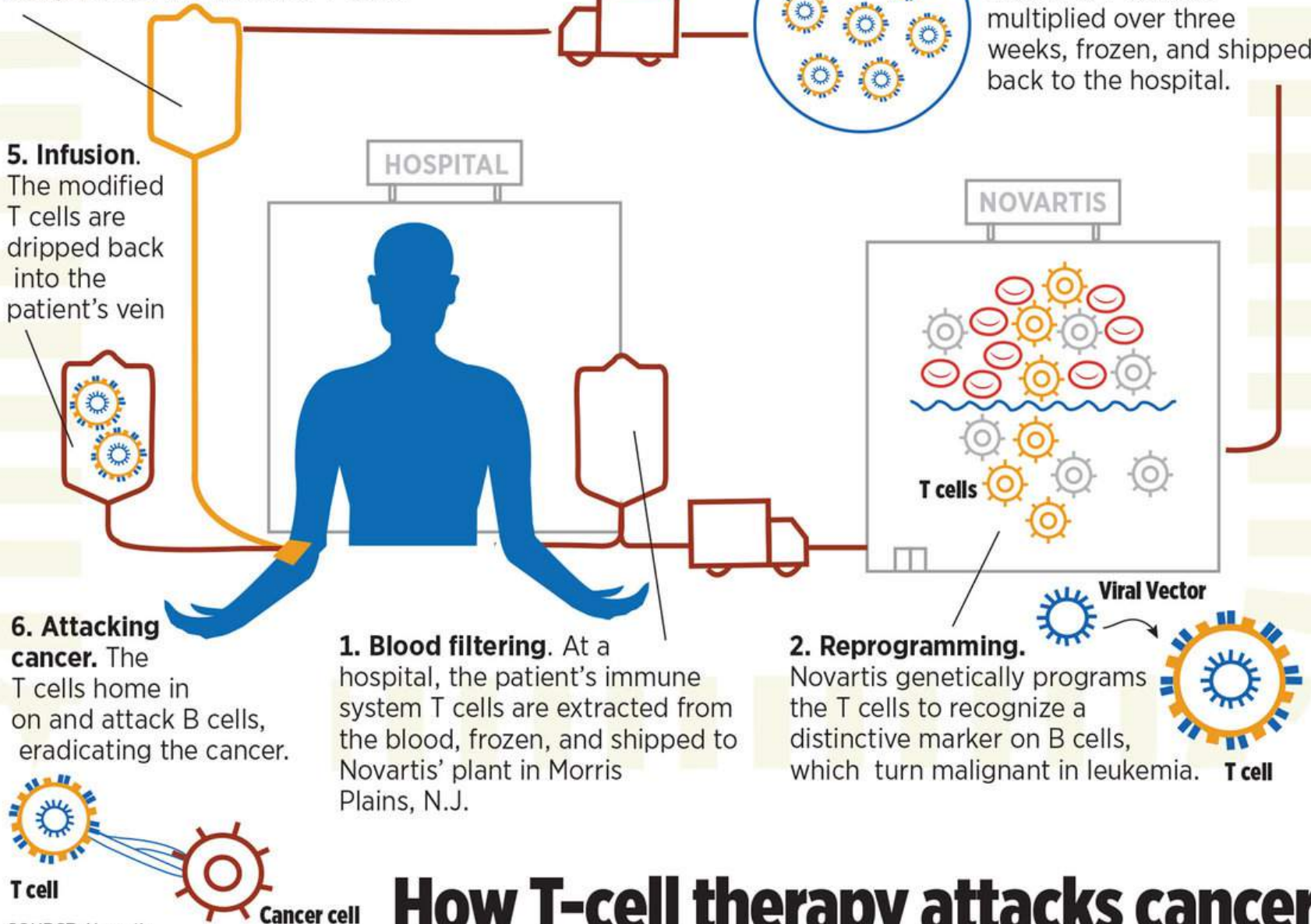
5. Infusion. The modified T cells are dripped back into the patient's vein

6. Attacking cancer. The T cells home in on and attack B cells, eradicating the cancer.

1. Blood filtering. At a hospital, the patient's immune system T cells are extracted from the blood, frozen, and shipped to Novartis' plant in Morris Plains, N.J.

2. Reprogramming. Novartis genetically programs the T cells to recognize a distinctive marker on B cells, which turn malignant in leukemia.

3. Expansion. The modified T cells are multiplied over three weeks, frozen, and shipped back to the hospital.



T cell

Cancer cell

SOURCE: Novartis

How T-cell therapy attacks cancer

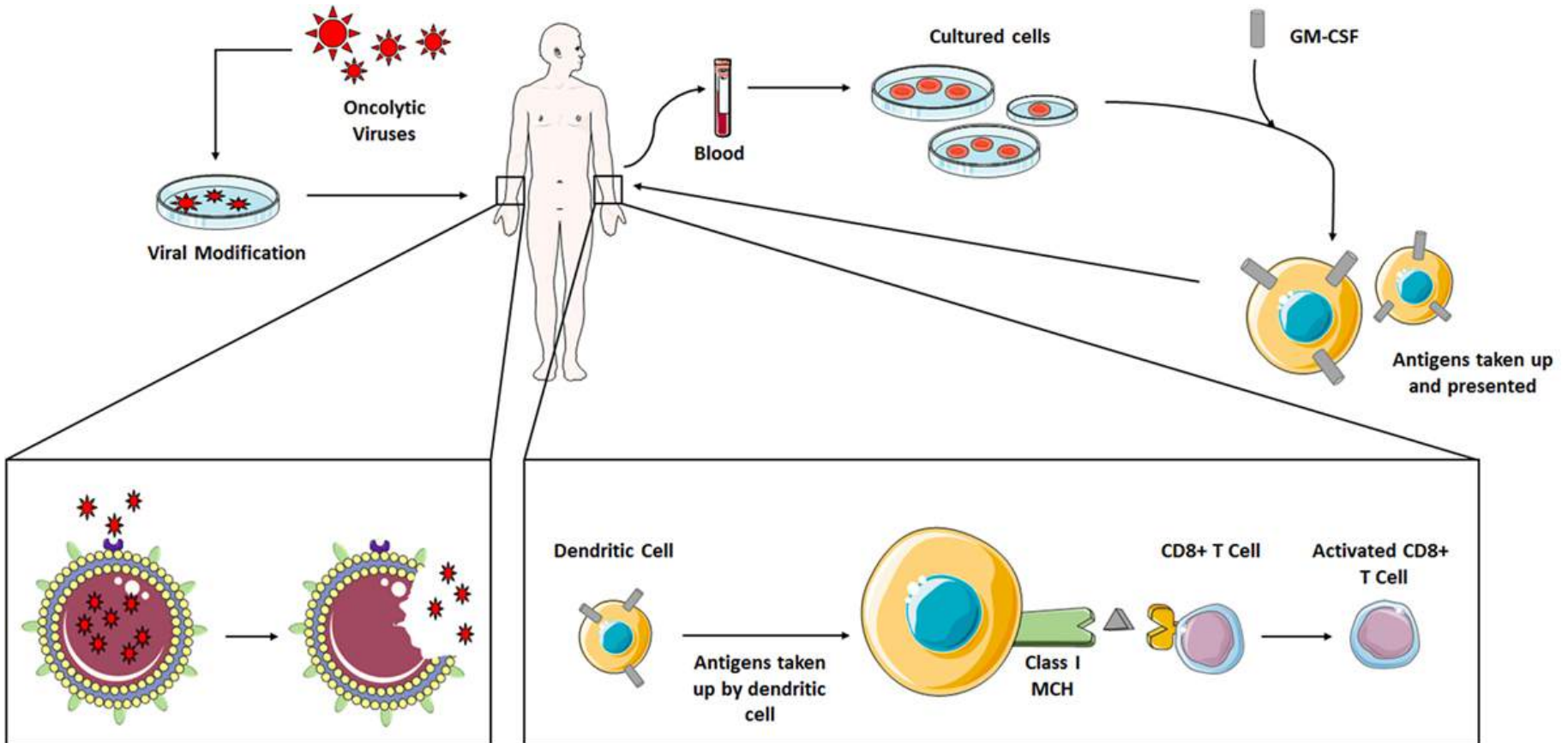


Kymriah® (Tisagenlecleucel) Novartis

- Approved for patients up to 25 years of age with **B-cell precursor acute lymphoblastic leukemia** (ALL) that is refractory or in second or later relapse
- Relapsed patients have a poor prognosis
- 63 patients: overall remission rate at 3 months = 83%
- Adverse events
 - Cytokine release syndrome 79%
 - Transient neurological events 65%
 - Infections 59%



Future: oncolytic viruses, dendritic cell vaccines



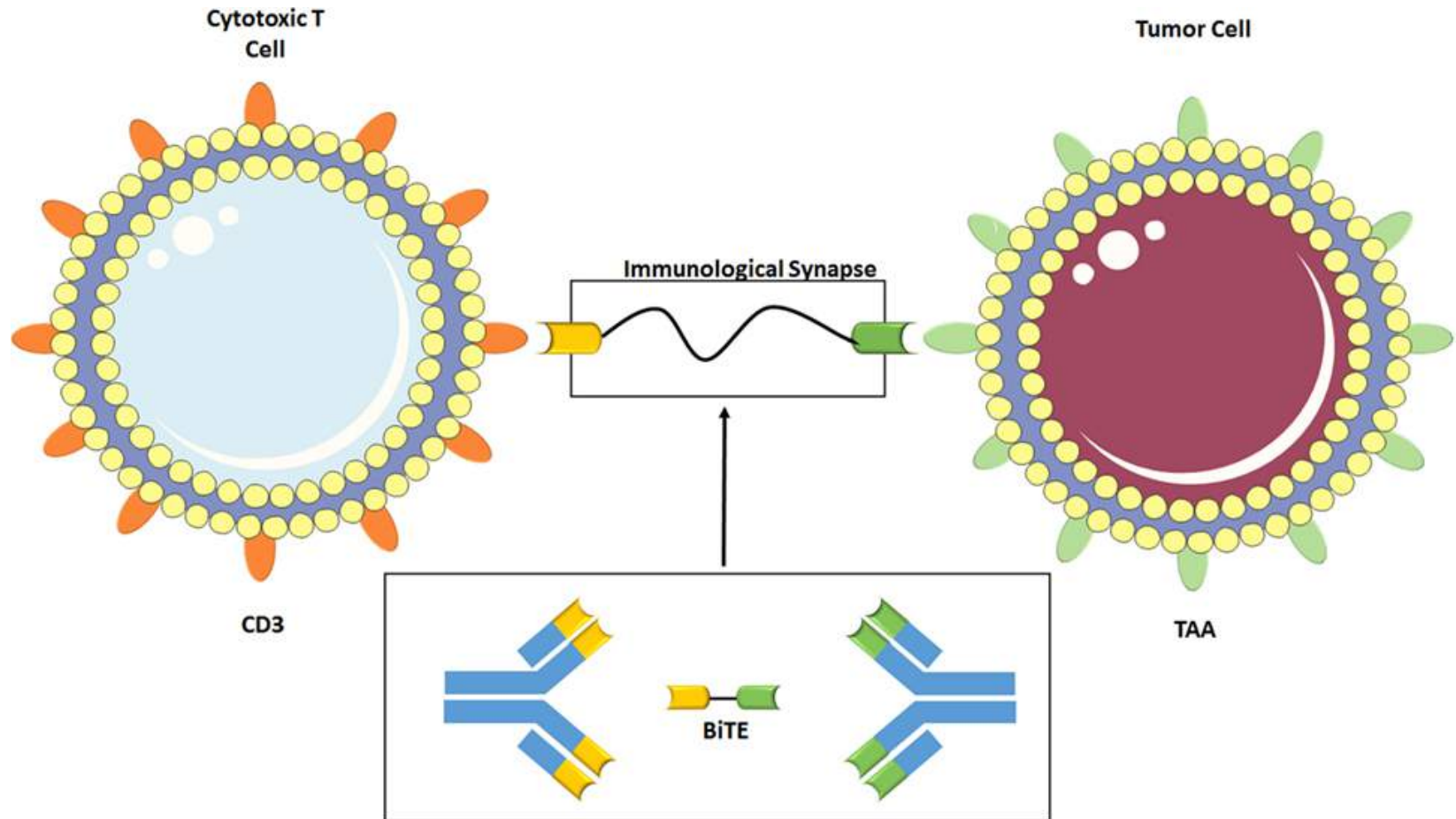
A. Oncolytic Viruses

B. Dendritic Cell Vaccines

Kamta, J. et al. Frontiers in Oncology, 2017, 7, 64



Future: Bispecific T cell Engagers (BiTE)





Part 2



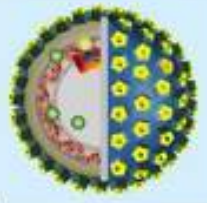

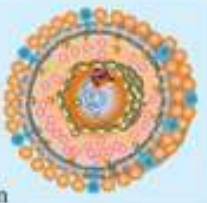

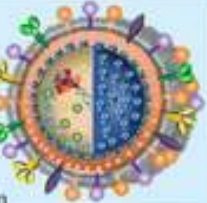



DRUGS TO TREAT **HEPATITIS C** INFECTIONS



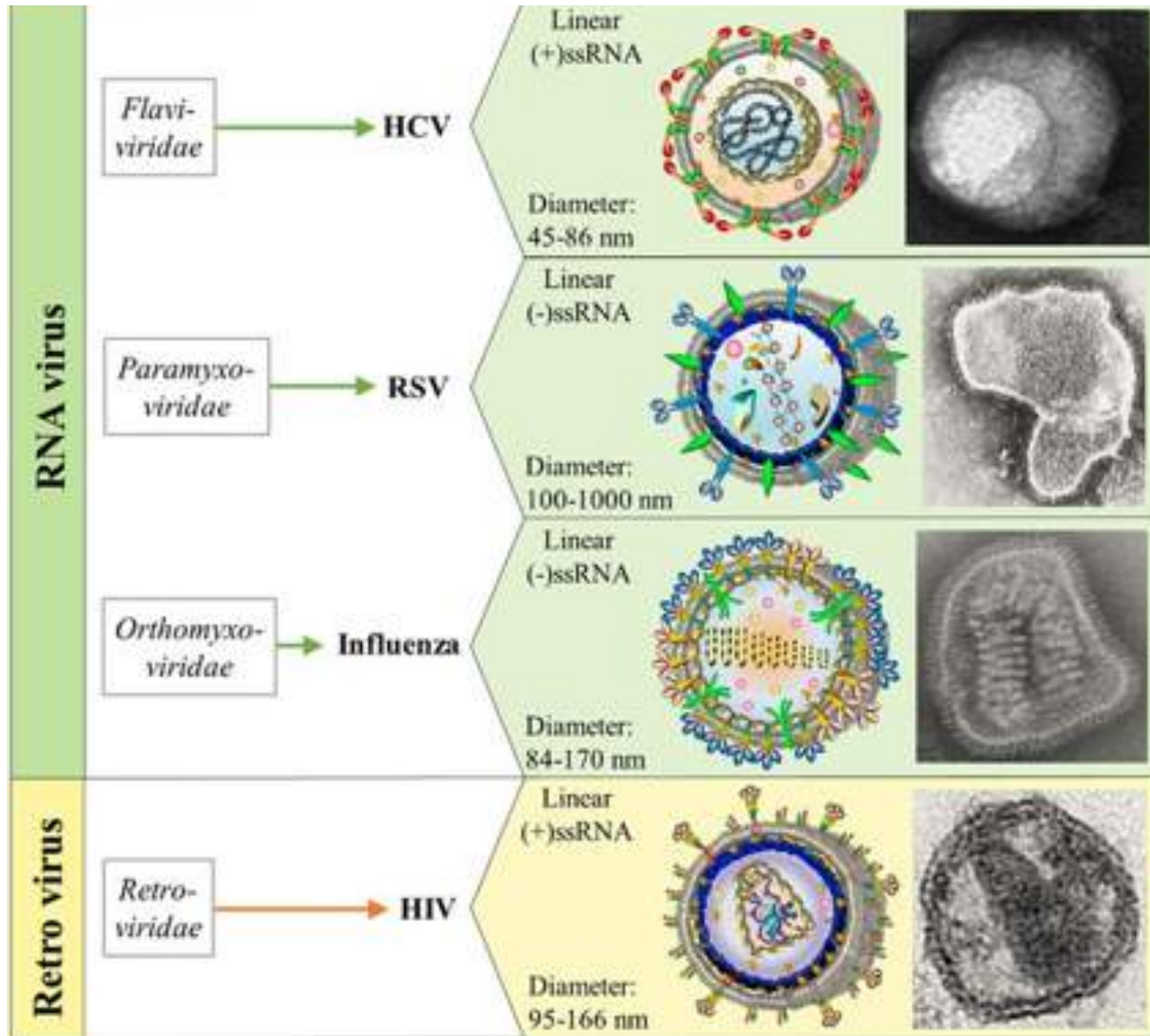
Content

- Hepatitis C introduction
- HCV: viral cycle and targets
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 - NS5A
 - NS5B
- HCV direct-acting antivirals
- Sofosbuvir

Different human pathogenic viruses

		Virus family	Virus	Viral particle		
DNA virus	Hepadna- viridae	→	HBV	Circular dsDNA		
				Diameter: 42-46 nm		
	Papilloma- viridae	→	HPV	Circular dsDNA		
				Diameter: 65-120 nm		
	Herpes- viridae	→	HCMV	Linear dsDNA		
Diameter: 150-200 nm						
HSV				Linear dsDNA		
	Diameter: 209-239 nm					
			VZV	Linear dsDNA		
				Diameter: 150-200 nm		

Different human pathogenic viruses





Flaviviridae

Virus Family	Genus	Species
Flaviviridae	Flaviviruses	West Nile
		Yellow fever
		Dengue
		Japanese encephalitis disease
		Tick-borne encephalitis
		St. Louis encephalitis
		Zika
	Hepaciviruses	Hepatitis C
	Pestiviruses	Bovine viral diarrhea

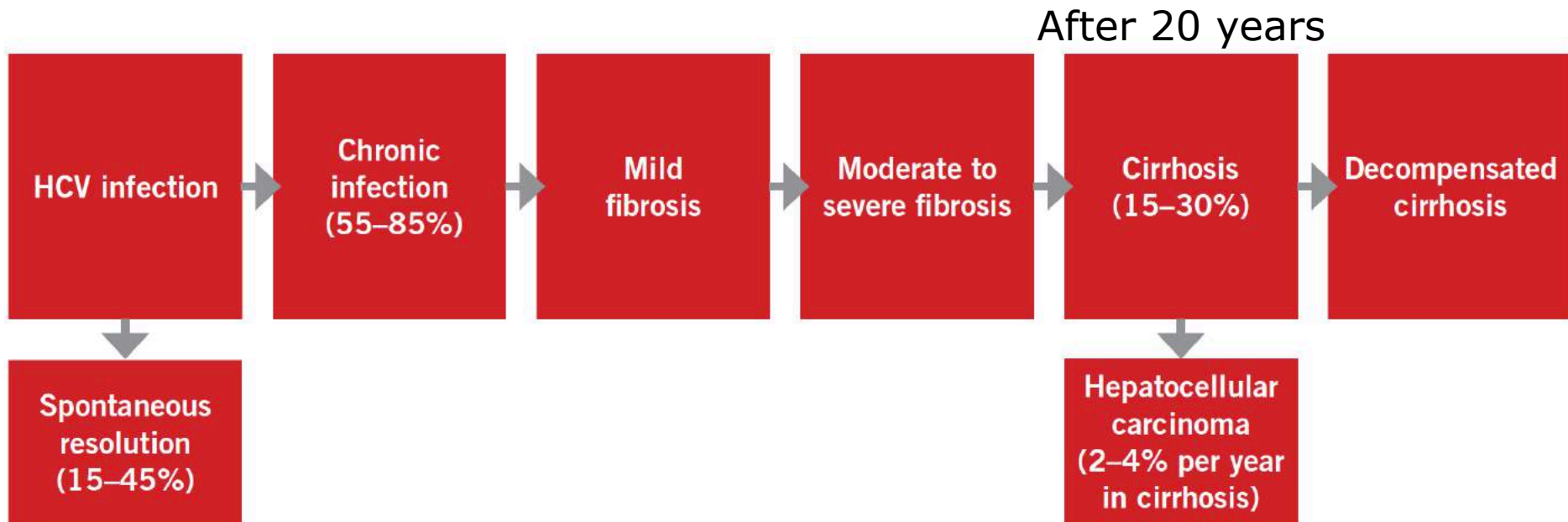


Hepatitis C

- A liver disease caused by the Hepatitis C virus (HCV)
- A bloodborne virus
- Most common mode of infections through exposure to small quantities of infected blood
 - injection drug use
 - unsafe injection practices
 - unsafe health care
 - transfusion of unscreened blood and blood products
 - Mother-to-child: 4-8% of births
 - Sexual transmission: infrequent
- Acute or chronic hepatitis
 - mild illness lasting a few weeks
 - serious, lifelong illness



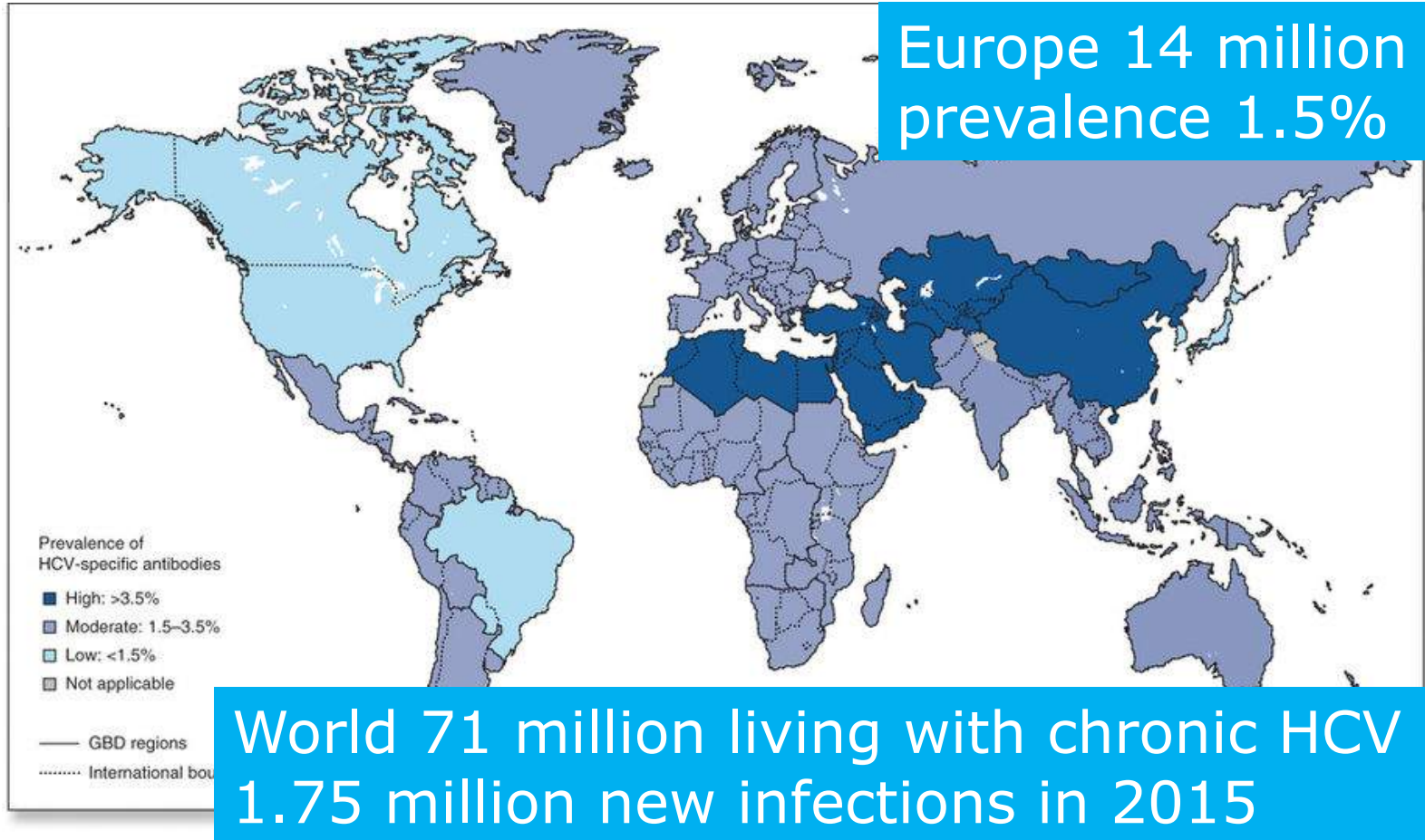
Natural history of an untreated HCV infection



WHO, Guidelines HCV, April 2016



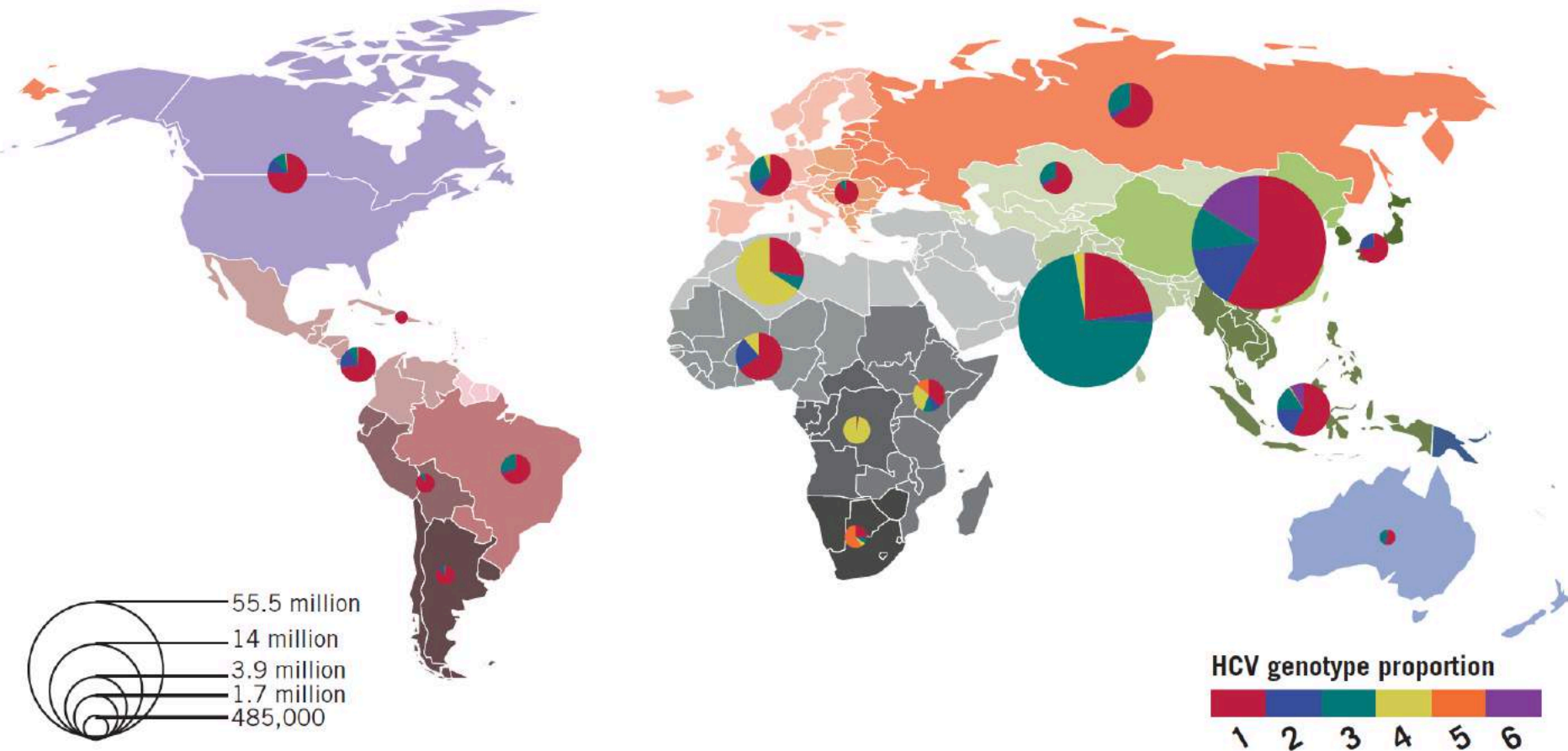
Global incidence of HCV



WHO, *Global Hepatitis Report, 2017*
Thomas, D.L. et al. *Nature Medicine*, 2013, 19, 850



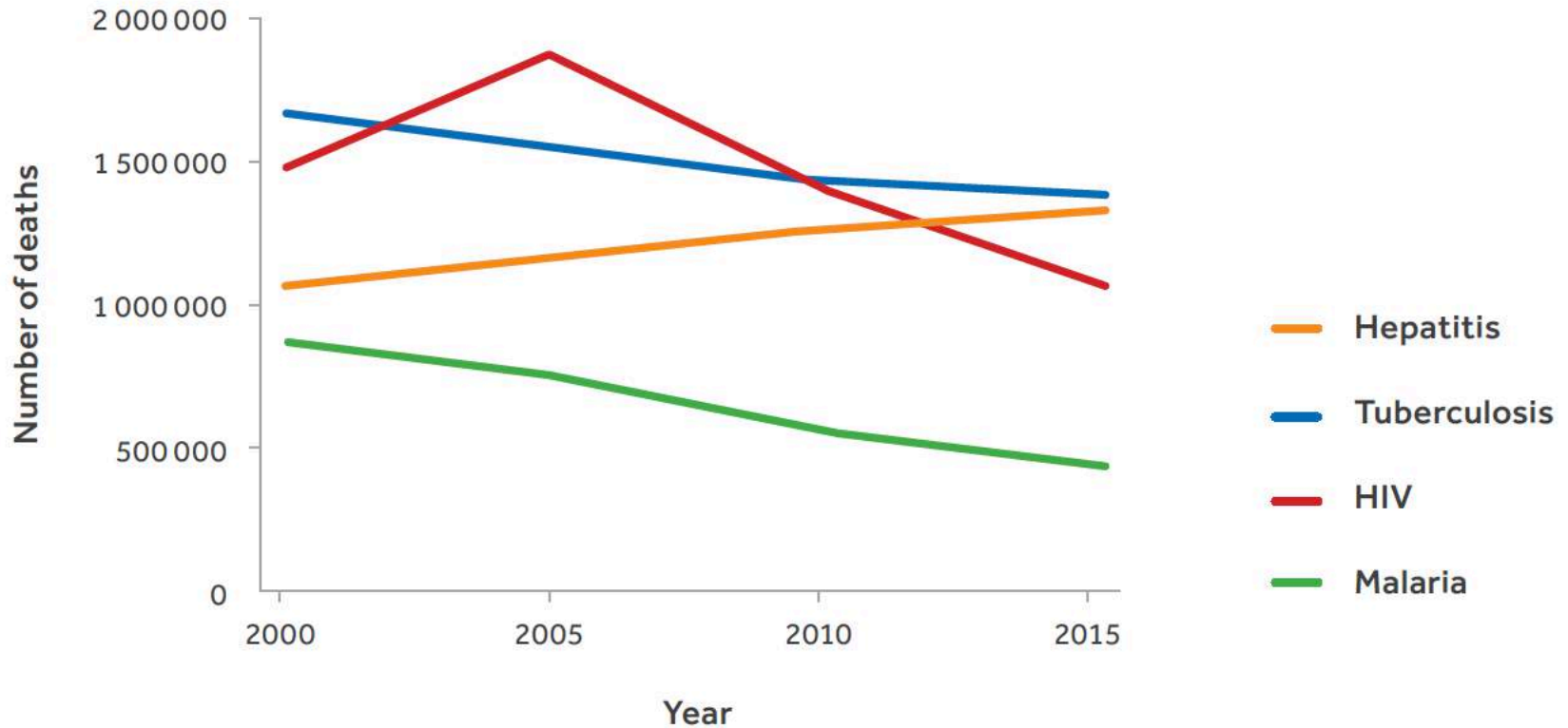
Global distribution of HCV genotypes



WHO, Guidelines HCV, April 2016



Global annual mortality



WHO, Global Hepatitis Report, 2017

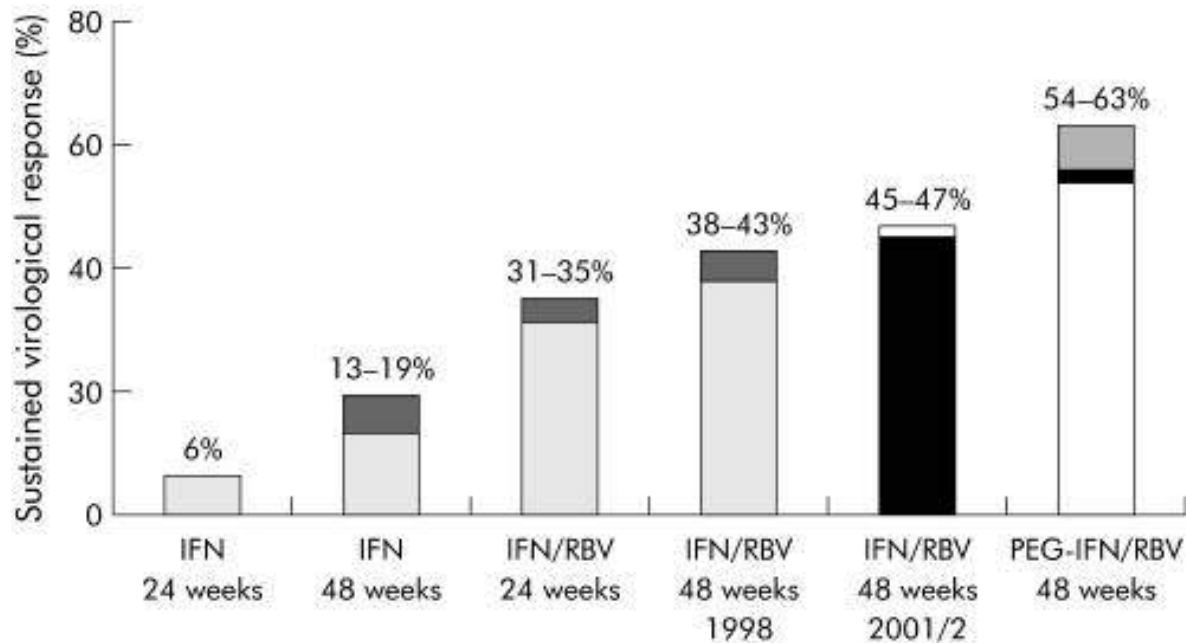


Screening, diagnosis, prevention

- Acute infections is usually asymptomatic
- Undiagnosed for decades until symptoms due to serious liver damage develop
- Prevention
 - No vaccine for HCV
 - Hand hygiene
 - Safe and appropriate handling of needles and injections
 - Testing of donated blood
 - Use of condoms
 - Training of health care personnel



HCV treatment before 2010



Interferon or
PEG-interferon

And

Ribavirin

Development of therapy for chronic hepatitis C is a story of success. Sustained virological response rates have been improved from approximately 5% with interferon (IFN) monotherapy in the early 1990s to >60% with the optimised standard therapy of pegylated IFN (PEG-IFN) and ribavirin in **2006**.

Manns, M.P. et al. Gut, 2006, 55, 1350



Treatment recommendations for patients with chronic HCV (2006)

HCV genotype	Duration (weeks)	PEG-IFN dose (1×/week sc)	Ribavirin dose (daily orally)
Genotype 1	48	180 µg PEG-IFN alpha-2a	1000 mg (<75 kg)
Genotypes 4–6*			1200 mg (≥75 kg)
		1.5 µg/kg PEG-IFN alpha-2b	800 mg (<65 kg)
			1000 mg (65–85 kg)
			1200 mg (>85 kg)
Genotypes 2/3	24	180 µg PEG-IFN alpha-2a	800 mg (all)
		1.5 µg/kg PEG-IFN alpha-2b	800 mg (<65 kg)
			1000 mg (65–85 kg)
			1200 mg (>85 kg)

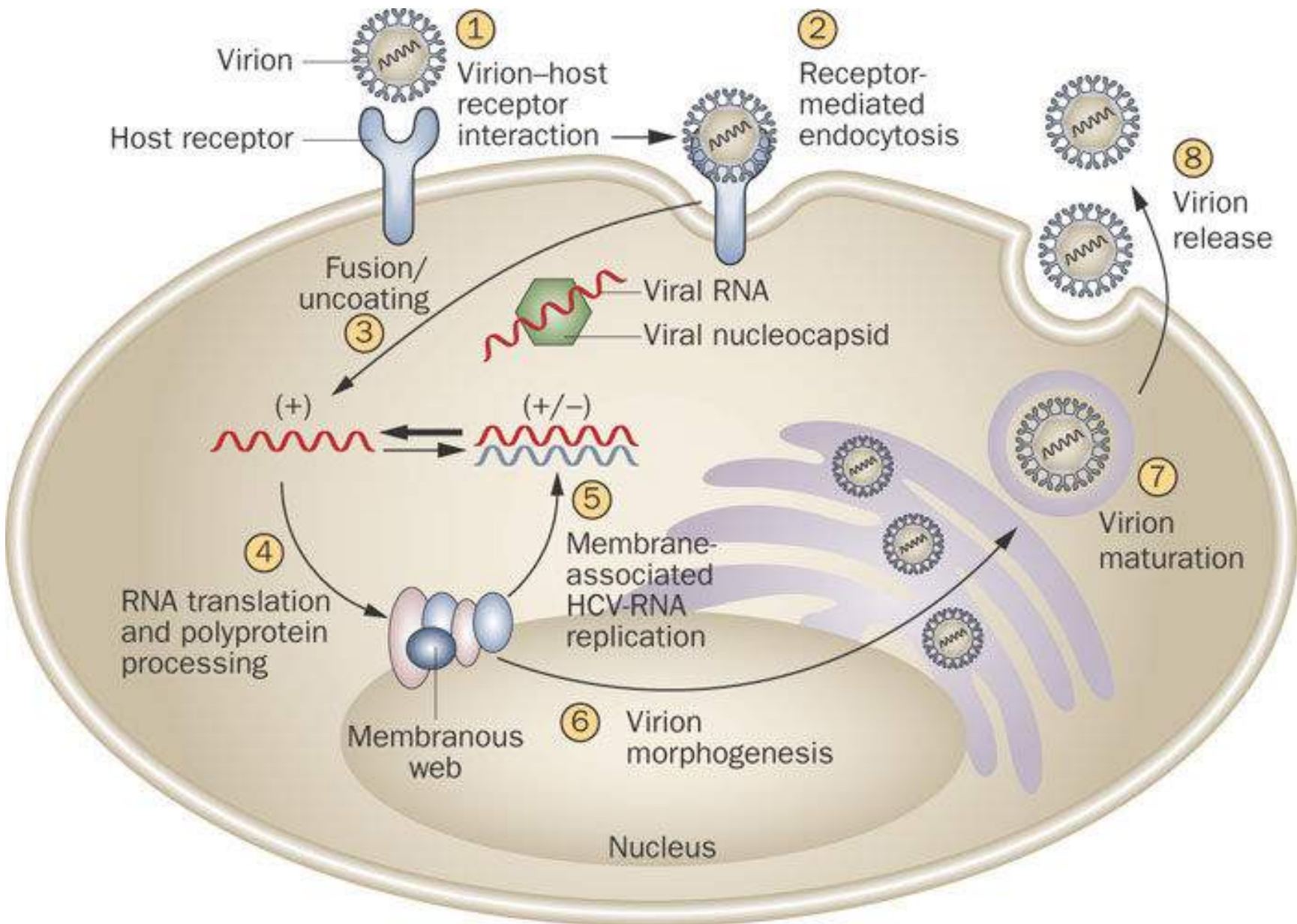
Manns, M.P. et al. Gut, 2006, 55, 1350



Content

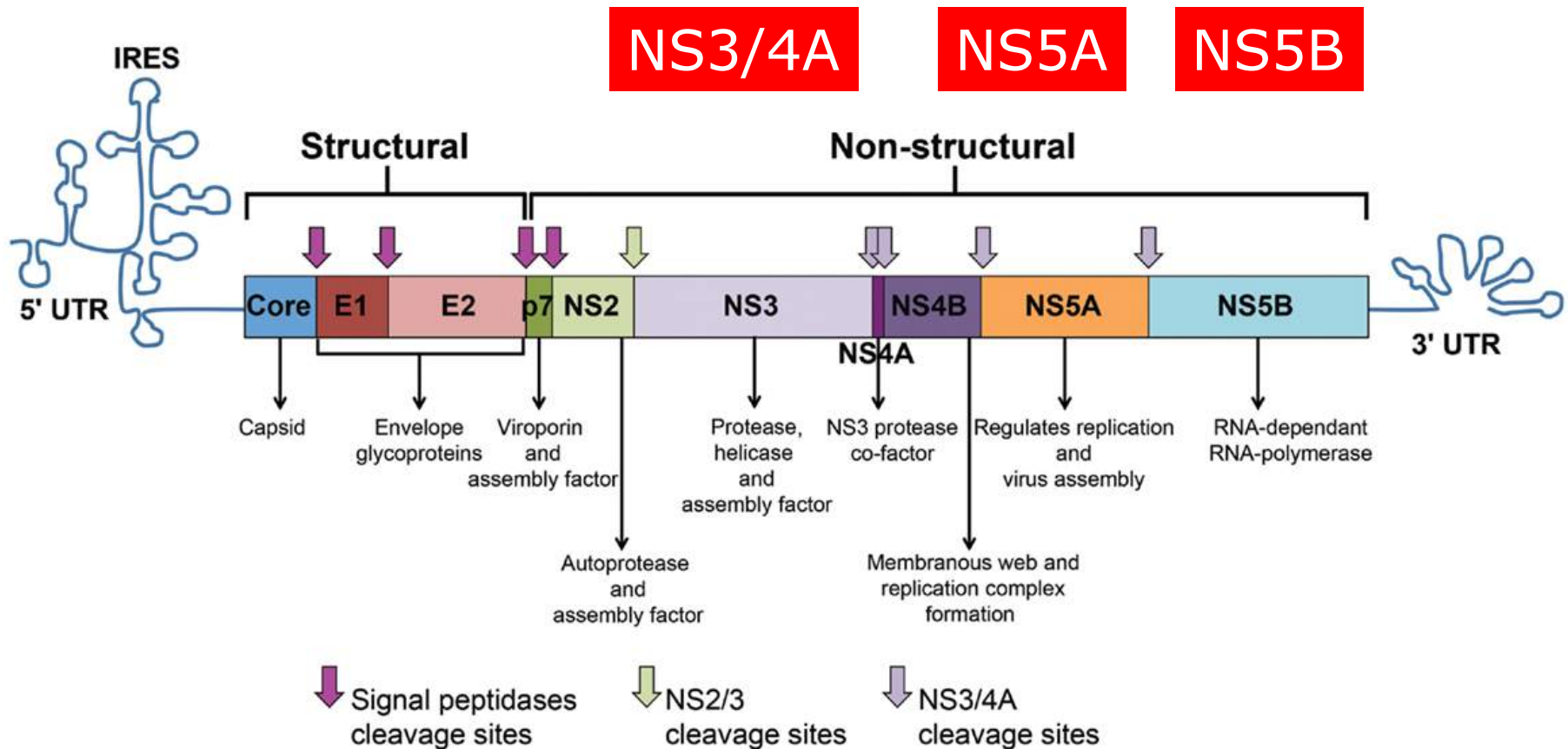
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HCV viral cycle





HCV targets





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Direct-acting antivirals

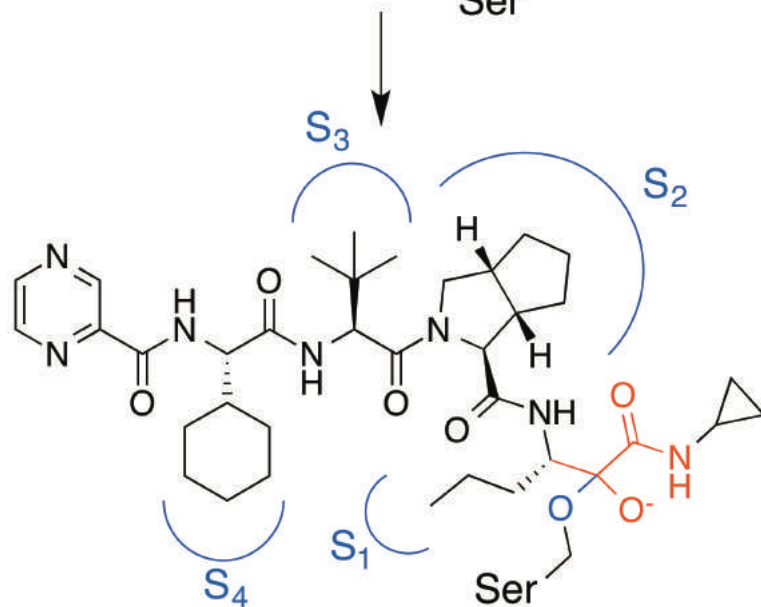
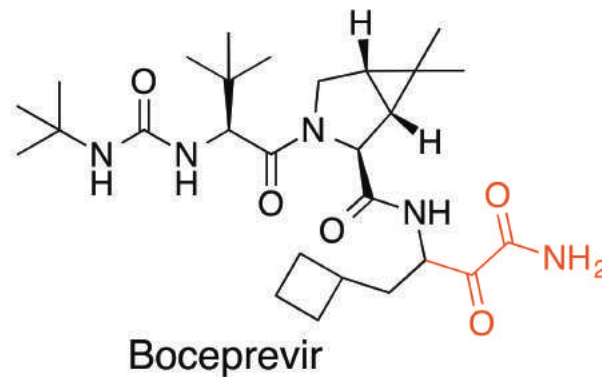
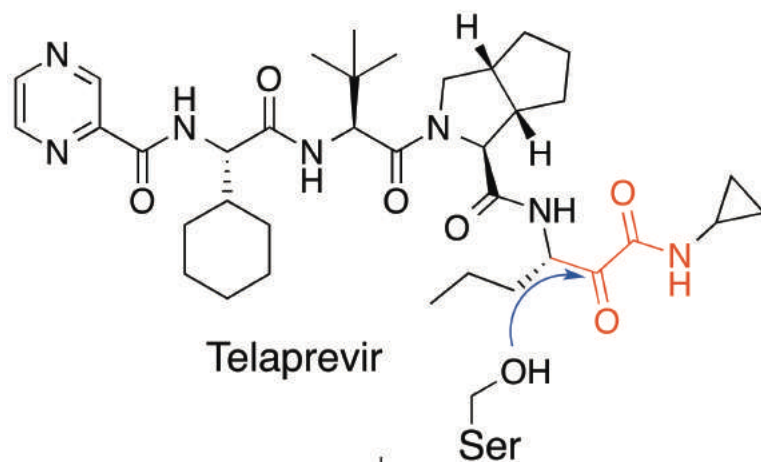
- May 2011
- First direct-acting antivirals were approved
- Incivo® (telaprevir), Janssen
 - Withdrawn in 2016
- Victrelis® (boceprevir), MSD

HCV direct-acting antivirals

MOA	Name	Active substance	Company	EMA	FDA
NS5B	Sovaldi	Sofosbuvir	Gilead	2014	2013
NS5B	Exviera	Dasabuvir	AbbVie	2015	-
NS5A	Daklinza	Daclatasvir	BMS	2014	2015
NS5A	Harvoni (+sofosbuvir)	Ledipasvir	Gilead	2014	2014
NS5A	Epclusa (+sofosbuvir)	Velpatasvir	Gilead	2016	2016
NS3/4A	Olysio	Simeprevir	Janssen	2014	2013
NS5A	Viekirax	Ombitasvir	AbbVie	2015	2015
NS3/4A		Paritaprevir			
NS5A	Zepatier	Elbasvir	MSD	2016	2016
NS3/4A		Grazoprevir			
NS3/4A	Vosevi (+sofosbuvir, +velpatasvir)	Voxilaprevir	Gilead	2017	2017
NS5A	Maviret	Pibrentasvir	AbbVie	2017	2017
NS3/4A		Glecaprevir			



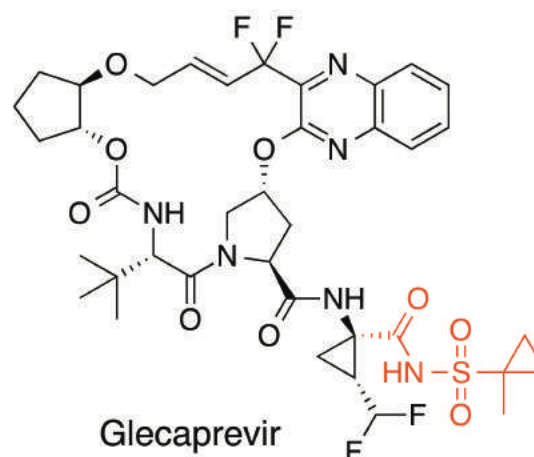
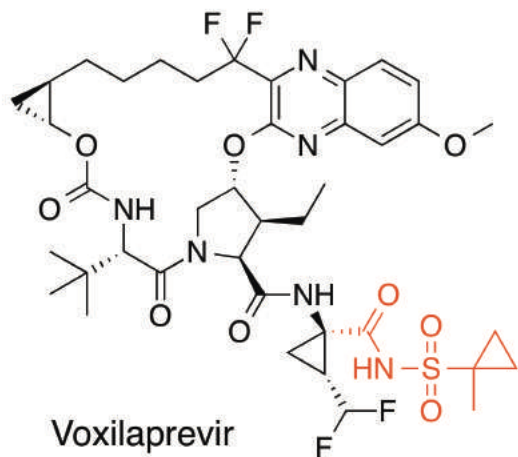
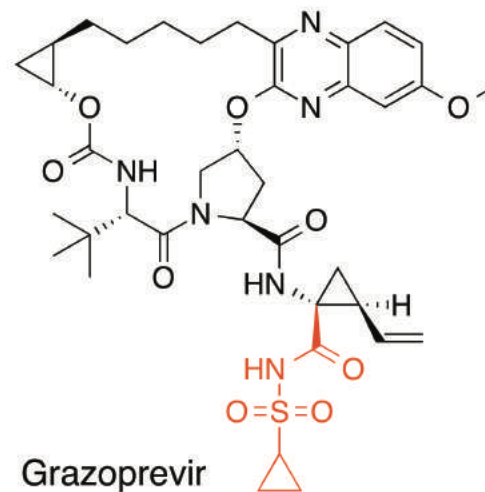
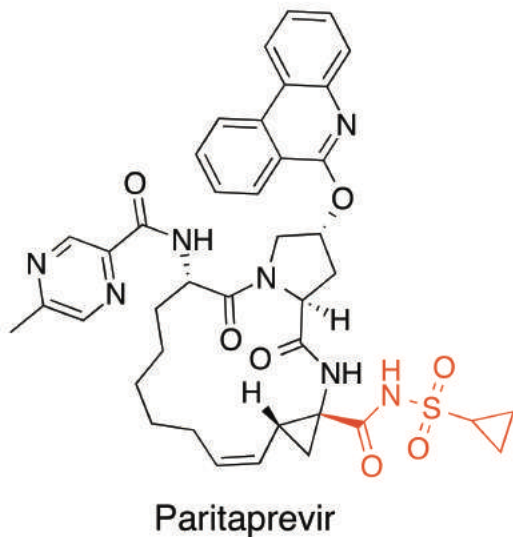
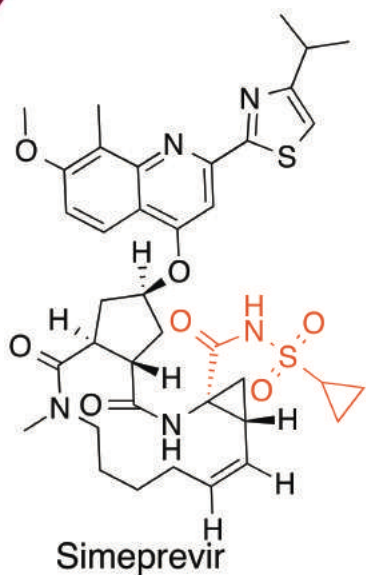
NS3/4A inhibitors

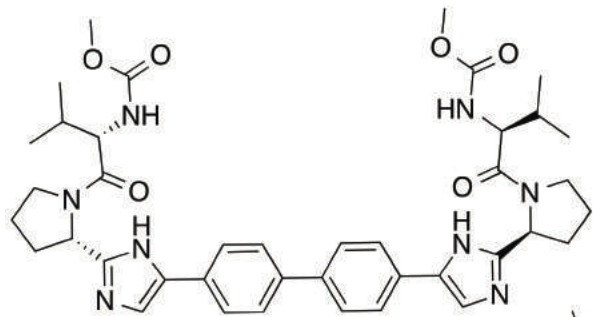


Serine protease
***α*-ketoamide** inhibitors
Covalent binders

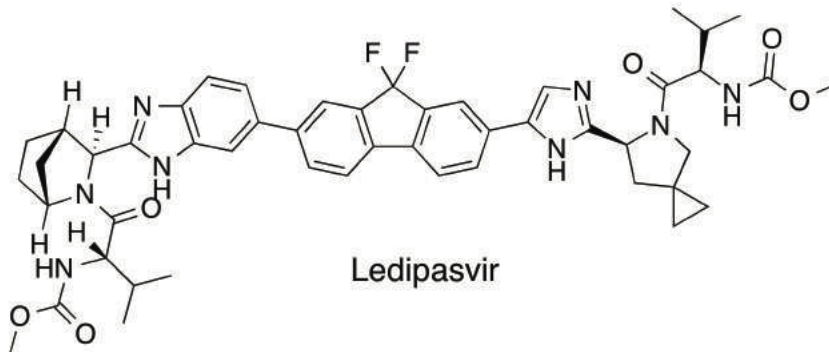


NS3/4A inhibitors

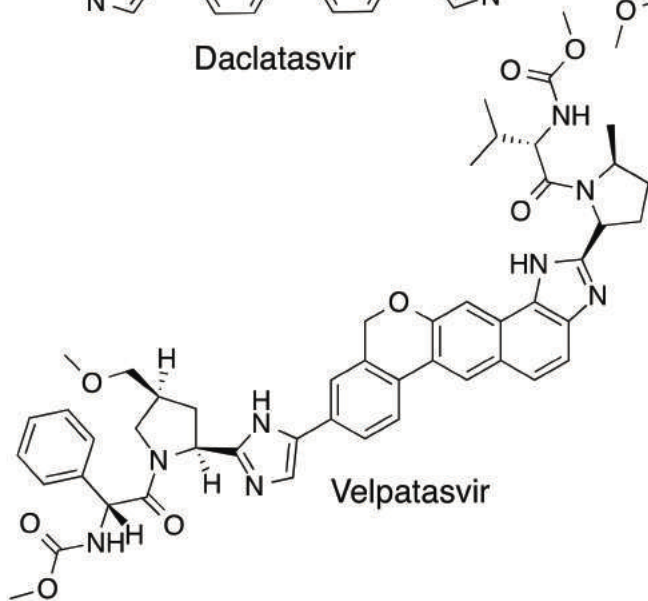




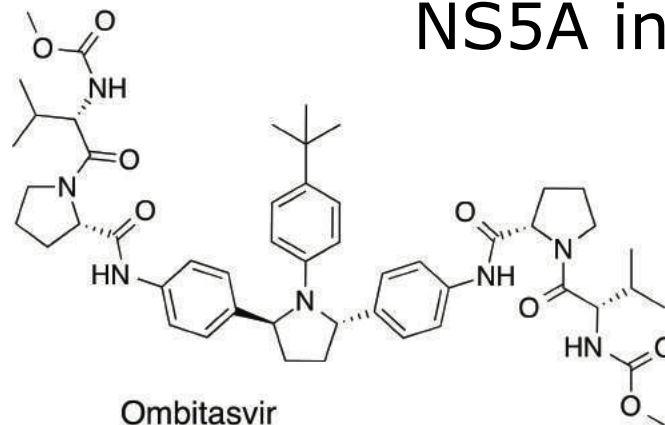
Daclatasvir



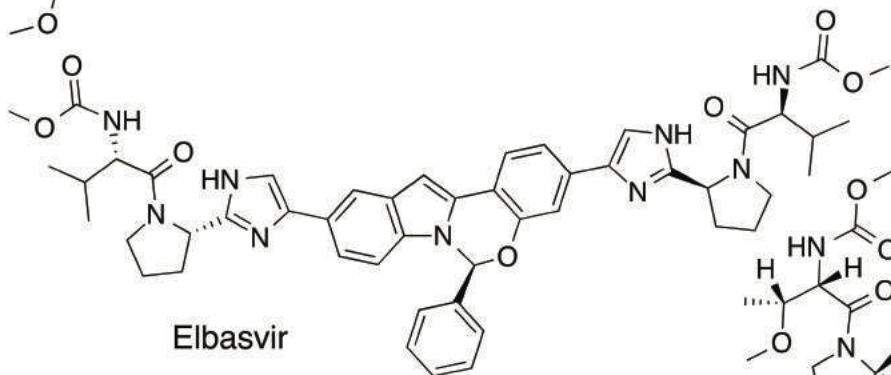
Ledipasvir



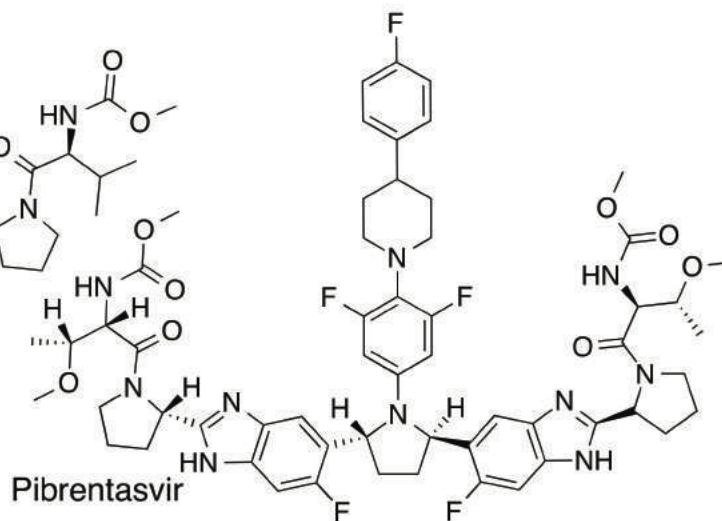
Velpatasvir



Ombitasvir



Elbasvir



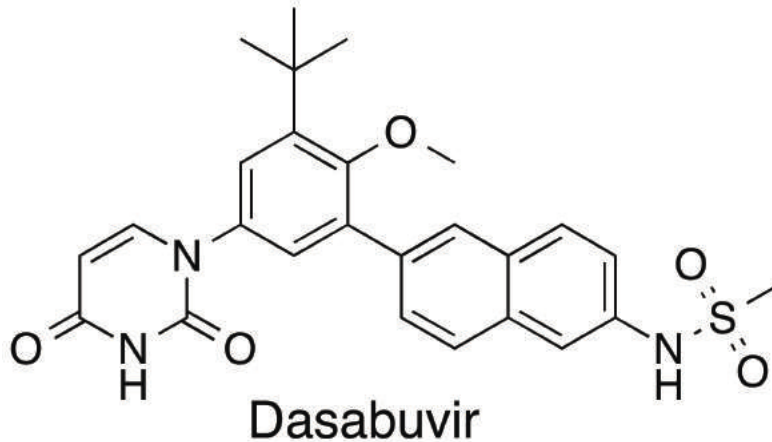
Pibrentasvir

NS5A inhibitors

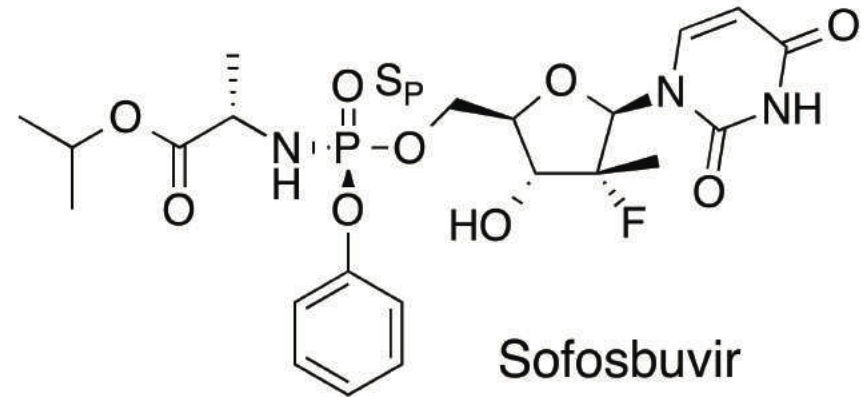


NS5B inhibitors

A RNA-dependent RNA polymerase (RdRp)



Non-nucleoside inhibitor



Nucleotide inhibitor of NS5B RdRp

Targets the active site, which is highly conserved

- Effective against all genotypes
- Less development of resistance
- Triphosphate is the active form



Content

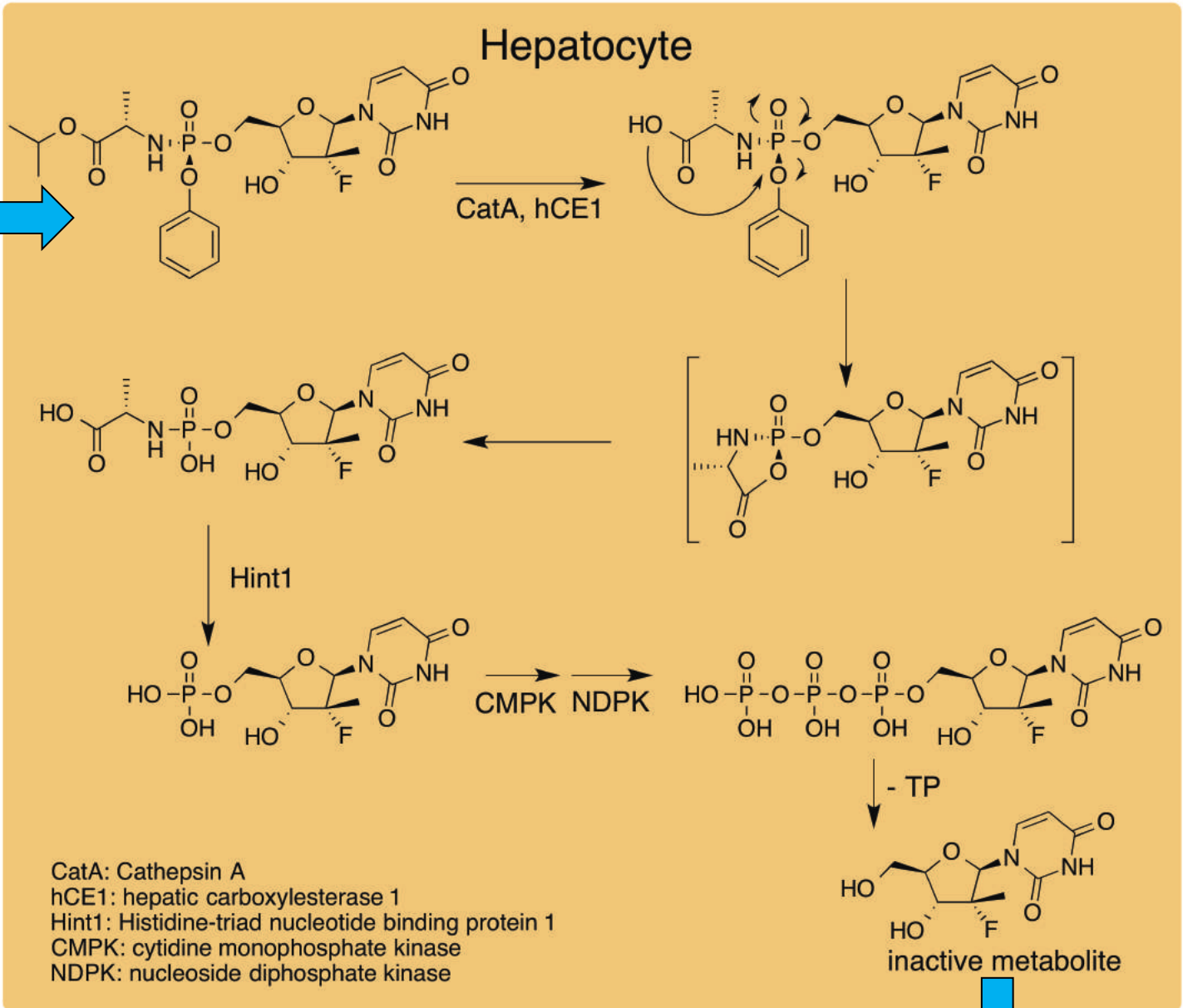
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Sofosbuvir is a prodrug targeting the liver

SOF



Enters the liver
with first-pass
metabolism

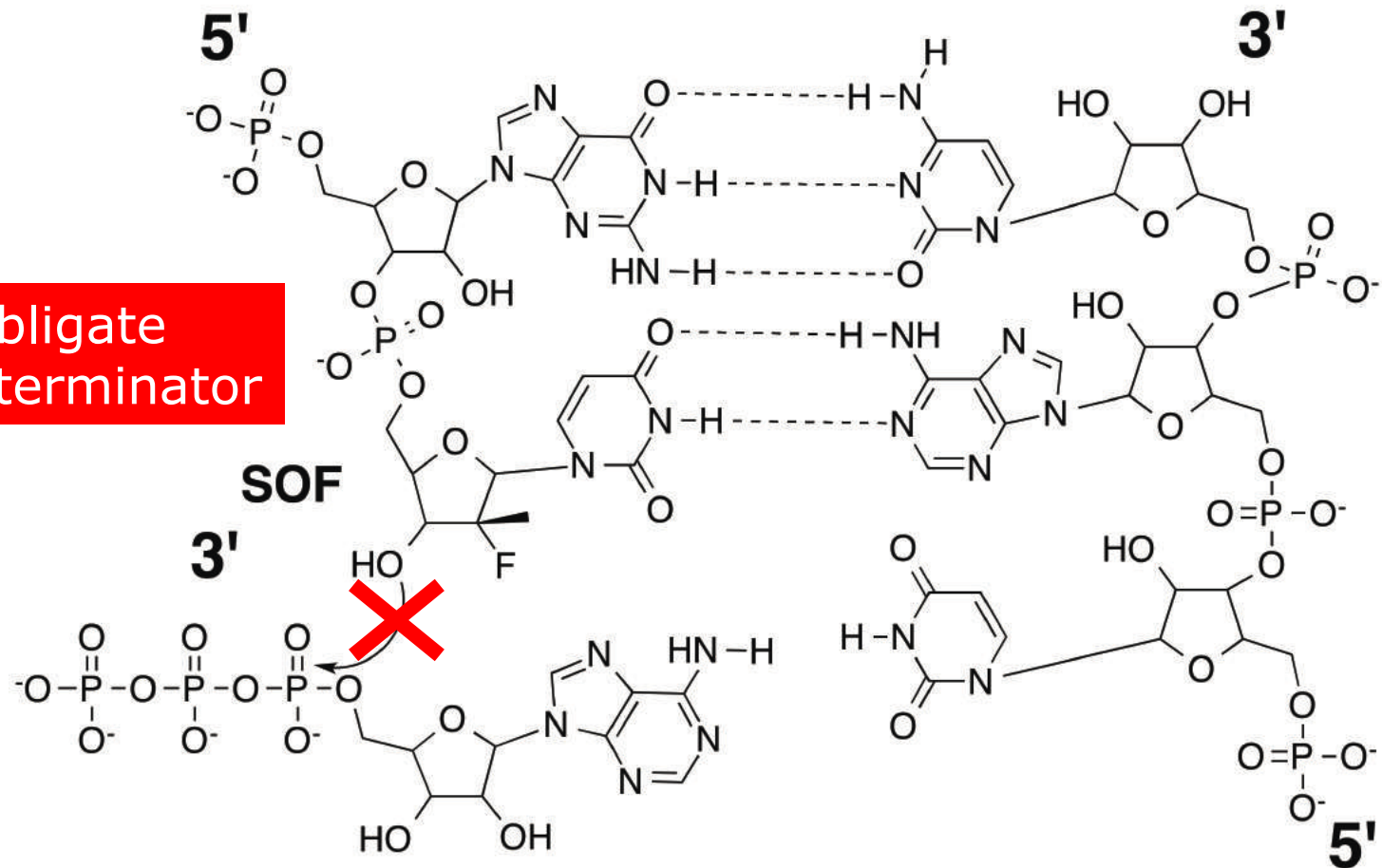




The triphosphate inhibits HCV NS5B RdRp

Primer strand


Template strand





Treatment results with Vosevi®

Sofosbuvir 400 mg, Velpatasvir 100 mg, Voxilaprevir 100 mg

Genotype 1, 2, 3, 4, 5, or 6 Patients 12 Weeks of Treatment		
Genotype	Dosing	Cure Rates [‡]
1	 One Pill per Day With Food	97%
2		100%
3		95%
4		91%
5		100%
6		100%



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