Dúvidas

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Arquivo

Medicamentos Utilizados no Tratamento do de Câncer I

Site:

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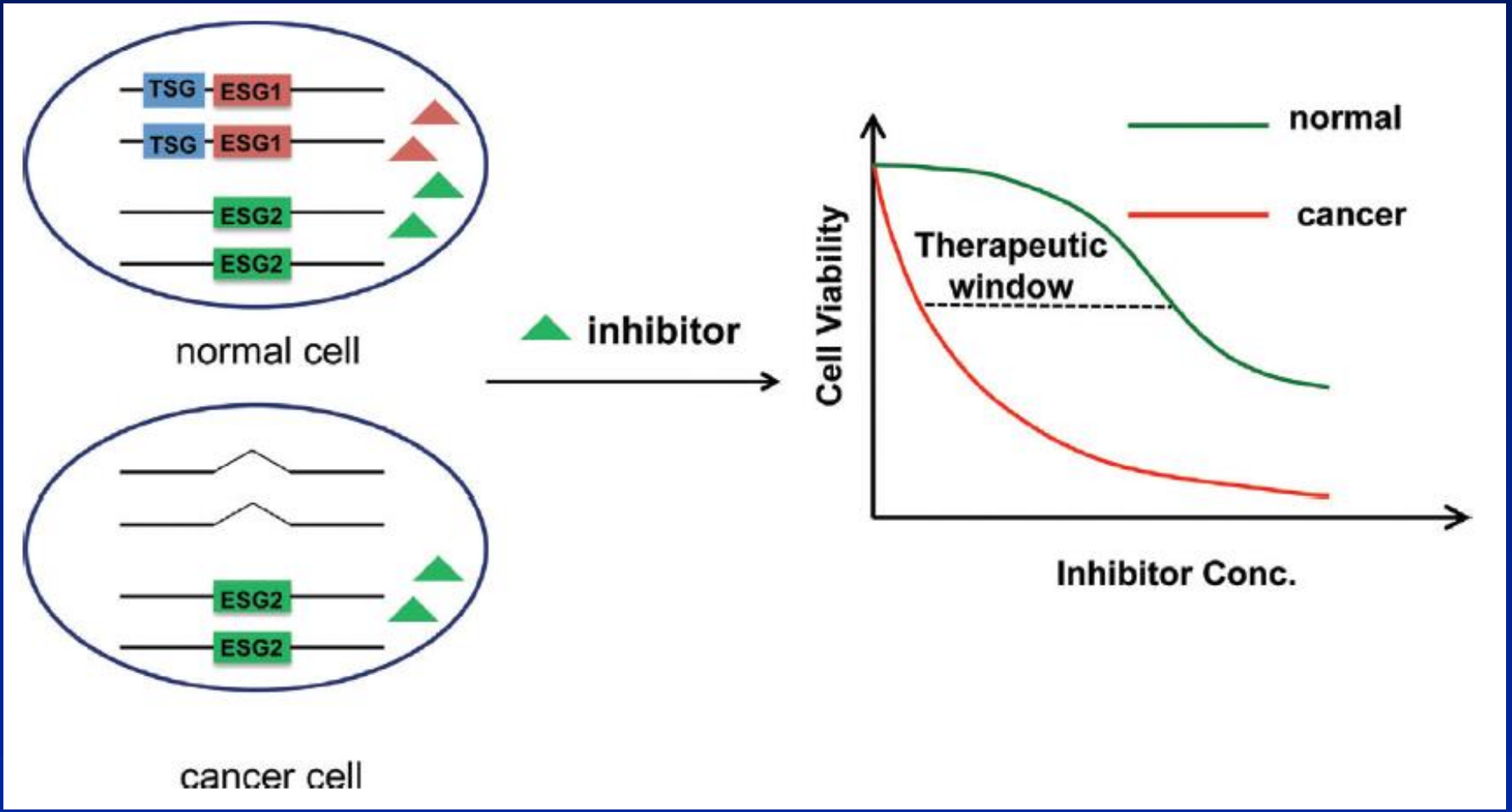
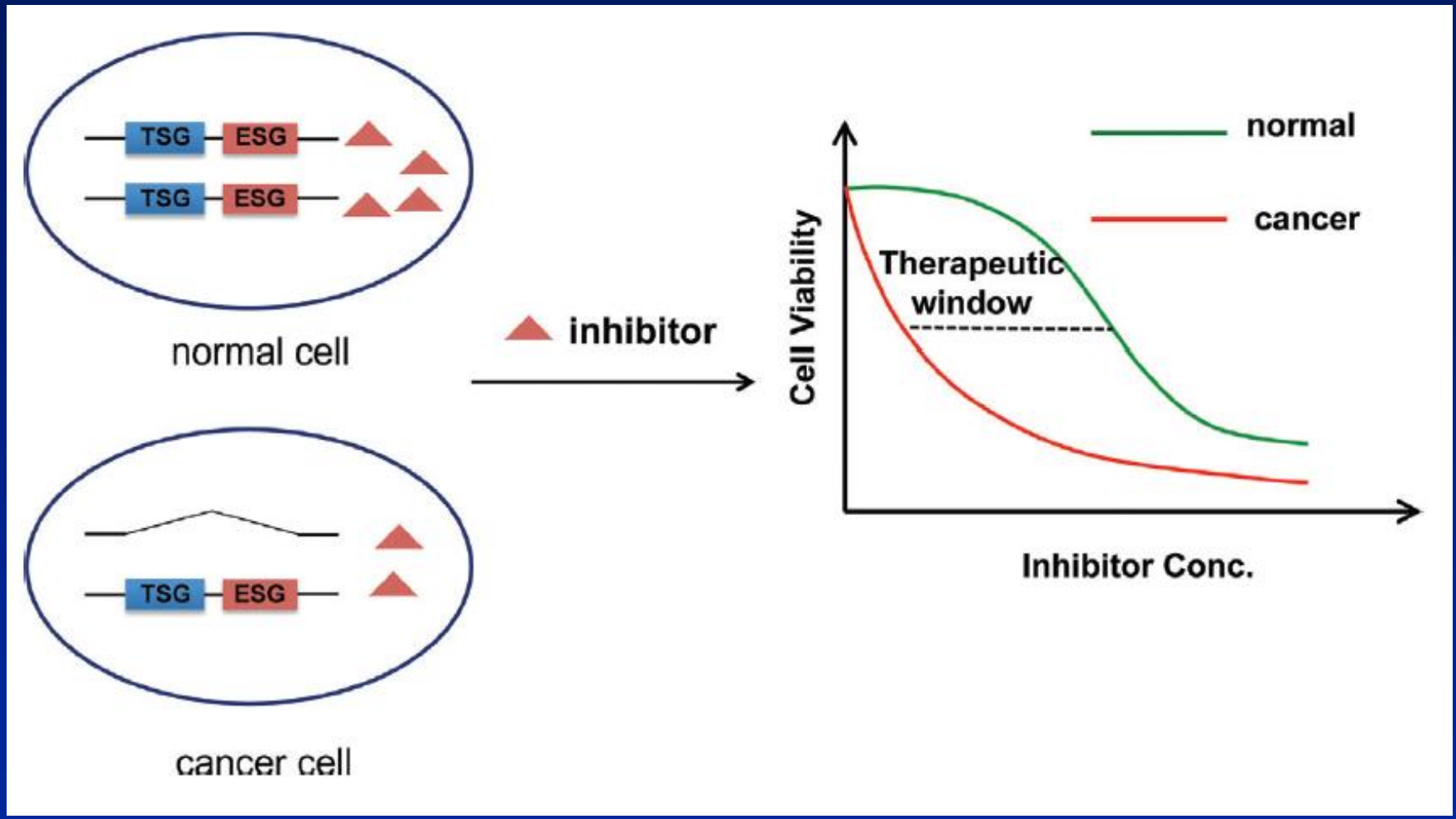
Homozygous co-deletion of passenger genes with a tumor suppressor gene generates therapeutic vulnerabilities in cancer

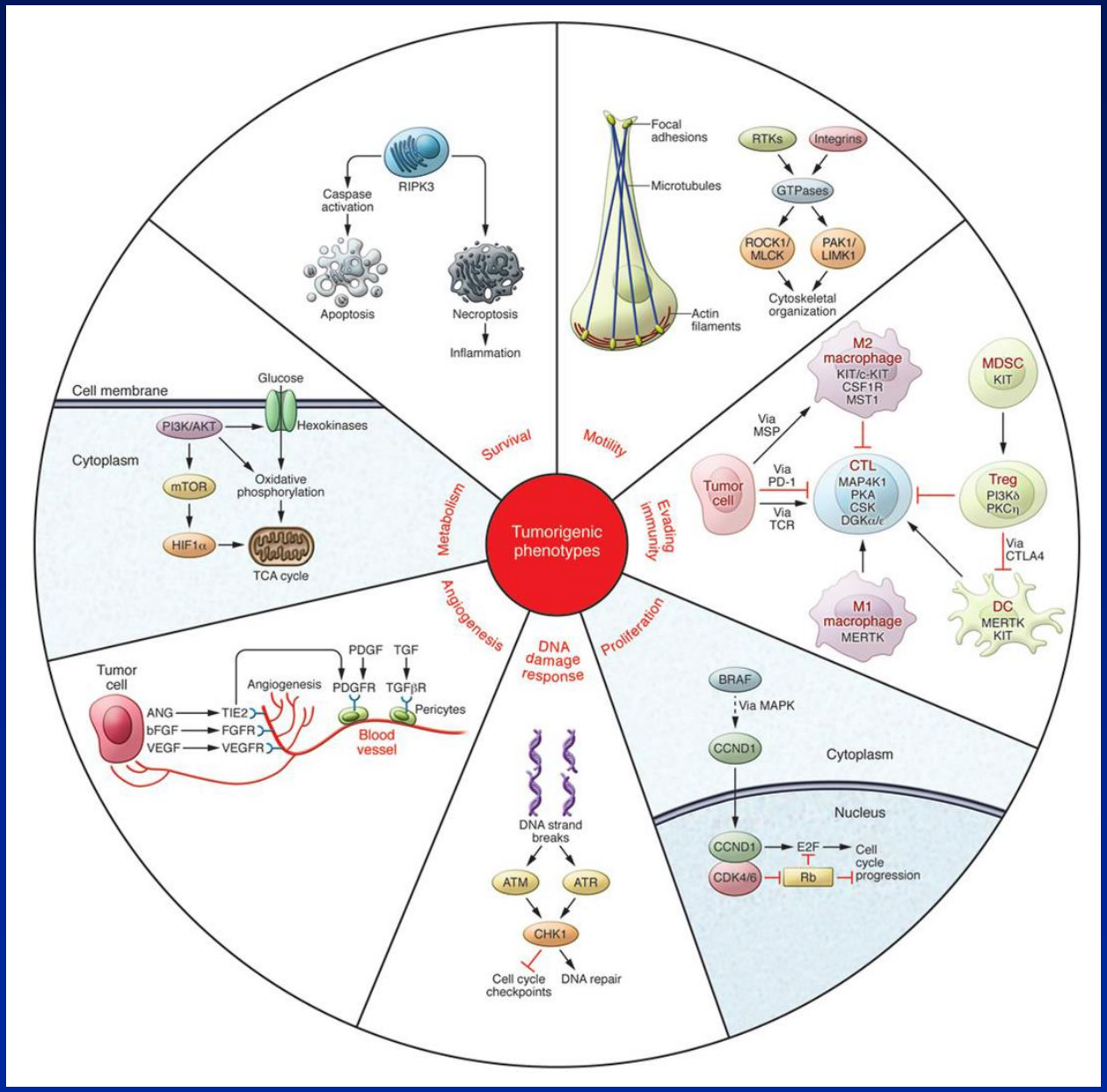


Targeting tumor suppressor genes for cancer therapy - Bioessays 37: 0000–0000, 2015 WILEY Periodicals, Inc. – Fig 02

Hemizygous co-deletion of essential genes with a tumor suppressor gene generates therapeutic vulnerabilities in cancer



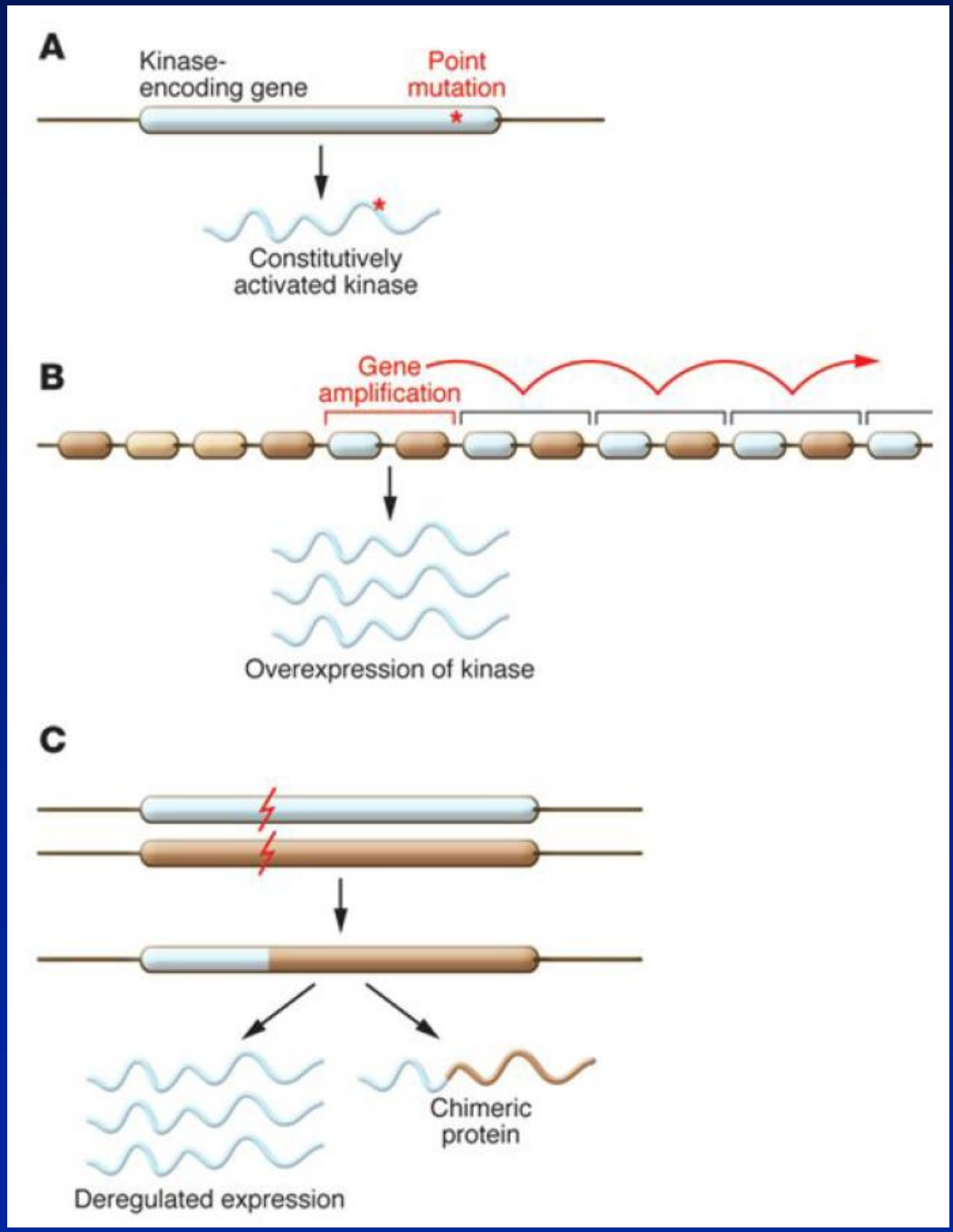
Regulation of tumorigenic programming by activation of kinases



Targeting Cancer With Kinase Inhibitors – The Journal of Clinical Investigation – 2015;125(5):1780-1789 – Fig 01

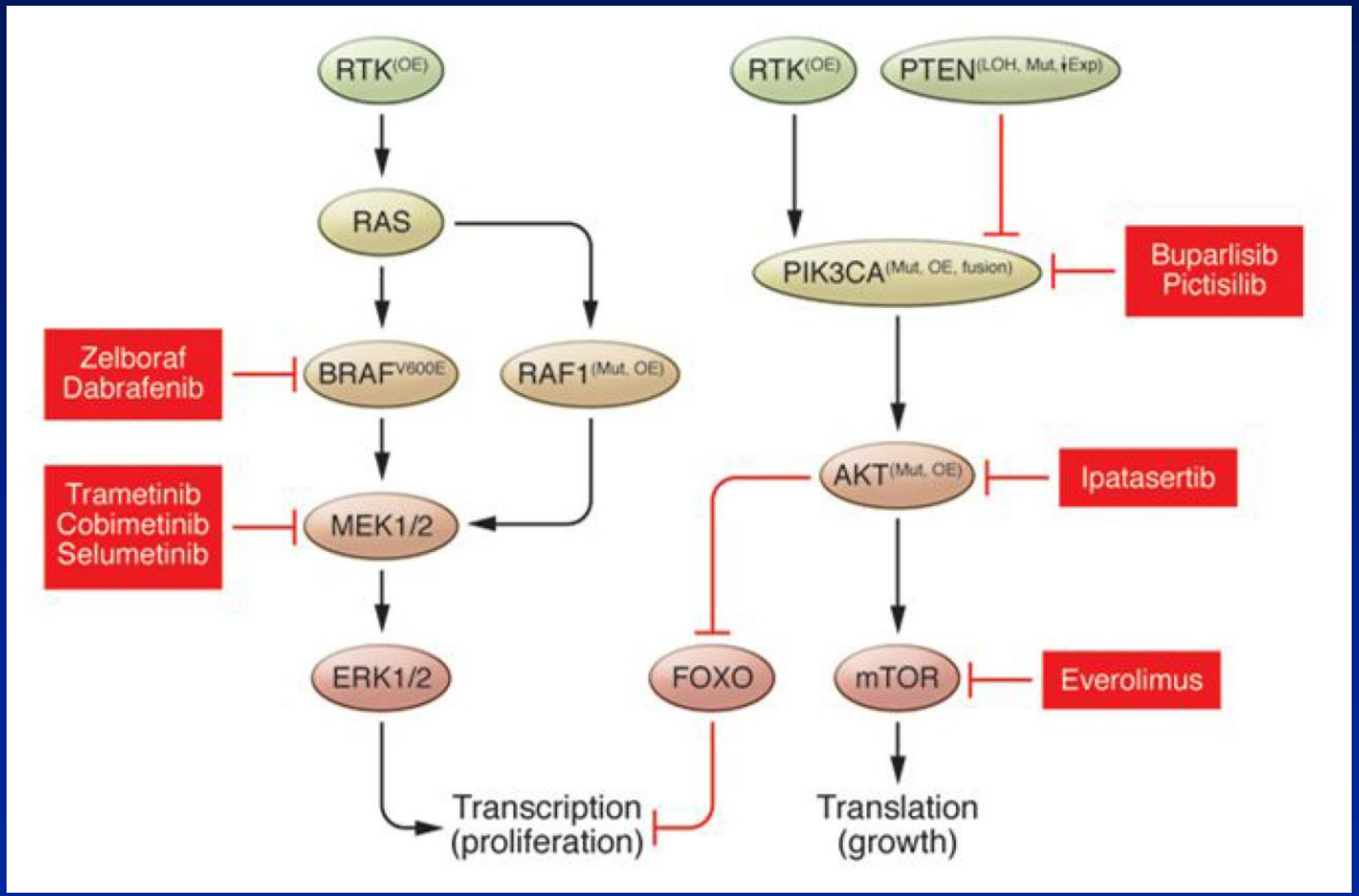
Activating genomic alterations of protein and lipid kinases

(**A**) Activating point mutations in genes coding for kinases lead to the expression of a constitutively activated kinase. Such mutations either lead to an amino acid substitution in the catalytic site, rendering it active; or change the general properties of the protein, for instance by disrupting the interaction with negative regulators, by releasing a mechanism of autoinhibition within the kinase itself, or by inducing constitutive dimerization. Last, they can cause changes in the splicing of the mRNA. Point mutations are the most common mechanism of kinase activation. (**B**) Chromosomal amplification of a region containing a kinase leads to its increased transcription and the production of an increased amount of protein in the cell. Consequently, the downstream pathway becomes overactivated. (**C**) Chromosomal alterations such as translocations or deletions can localize a kinase gene in proximity to another gene and lead to the expression of a constitutively activated chimeric or truncated kinase, or deregulate the expression of the kinase by putting it under the control of another promoter.



Targeting Cancer With Kinase Inhibitors – The Journal of Clinical Investigation – 2015;125(5):1780-1789 – Fig 02

Potential therapeutic combinations to overcome resistance to BRAF inhibitors

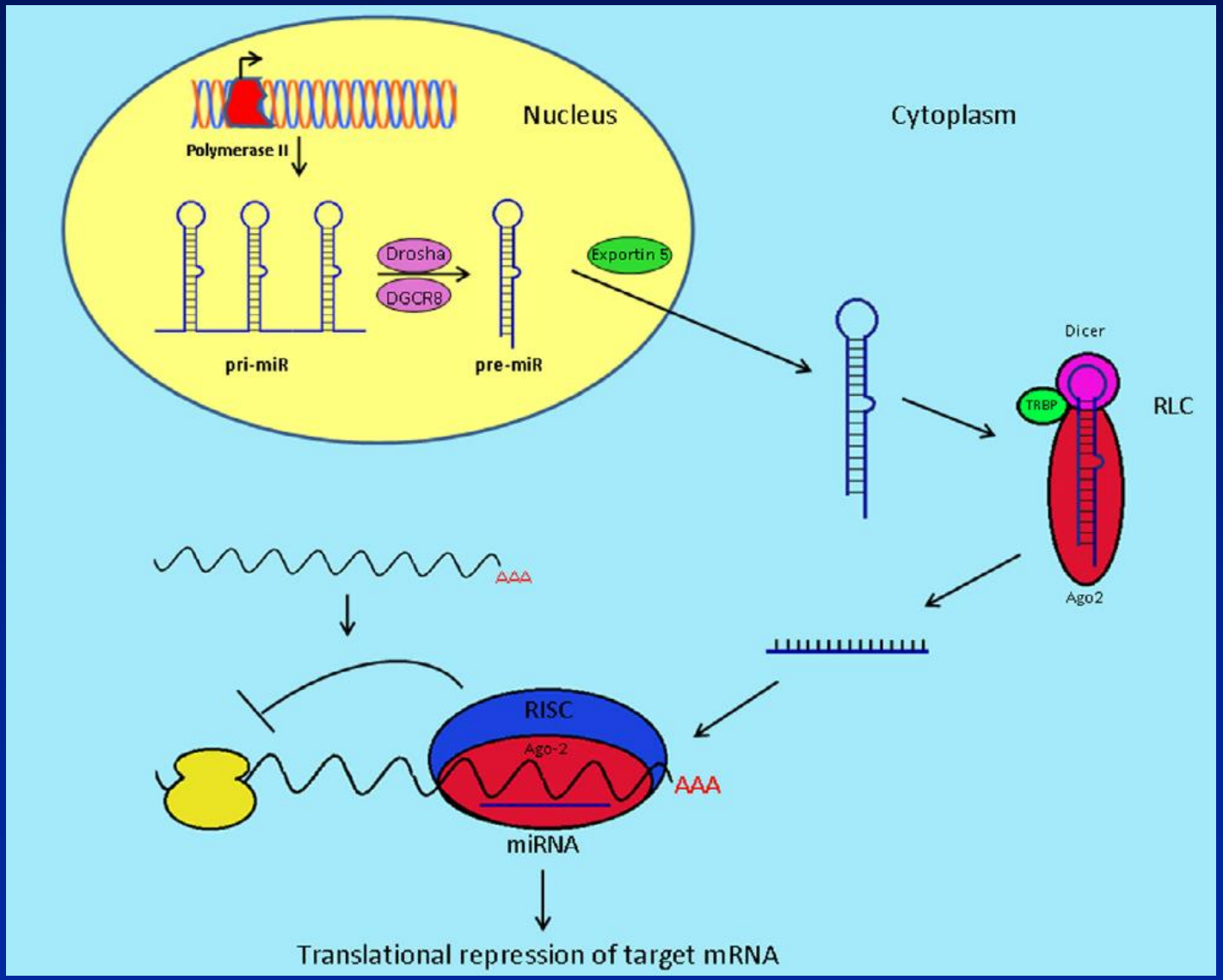


Example of known mechanisms of kinase activation in cancer

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*

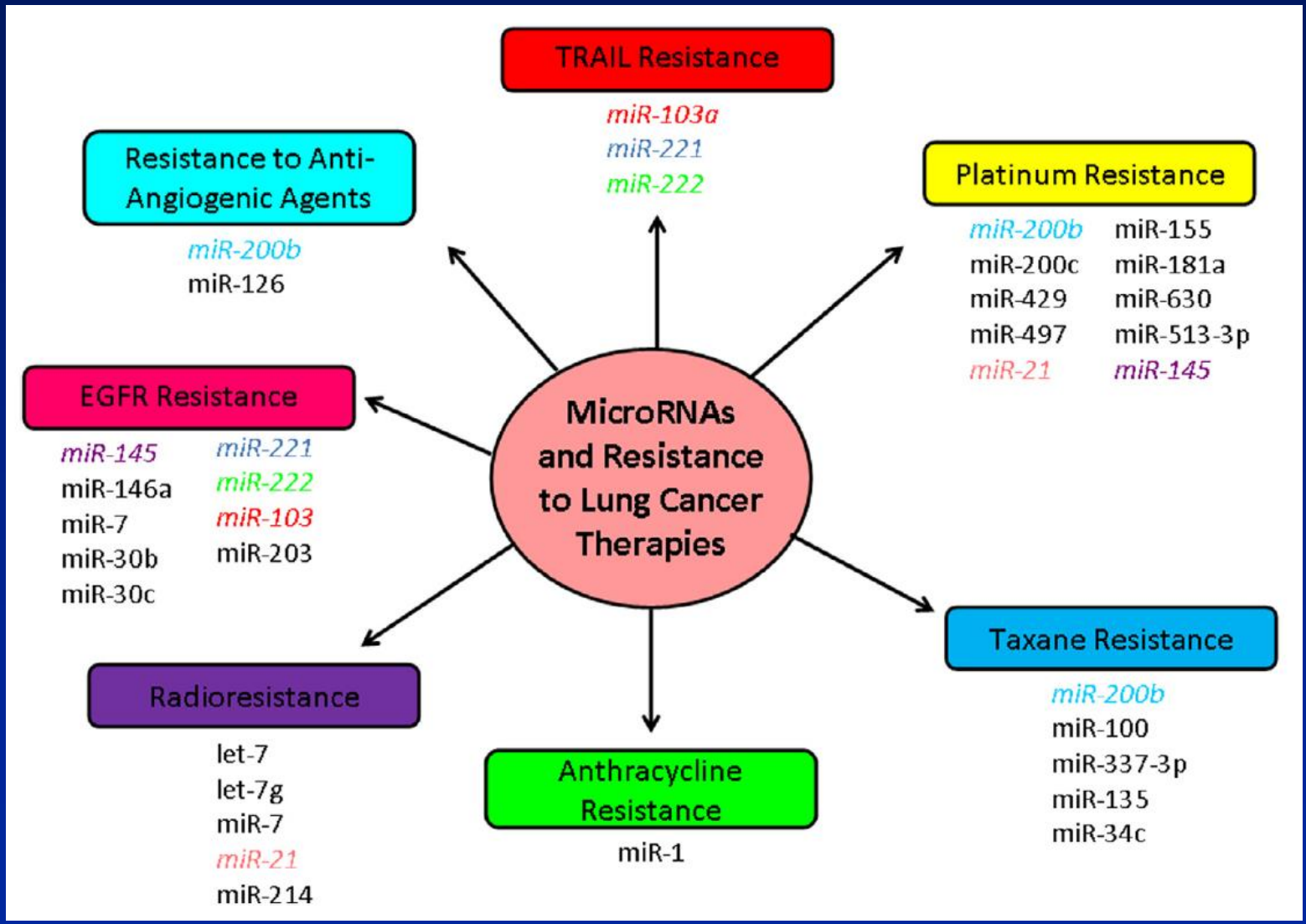
Targeting Cancer With Kinase Inhibitors – The Journal of Clinical Investigation – 2015;125(5):1780-1789 – Table 01

MicroRNA biosynthesis. Biosynthesis of miRNAs begins with transcription of the encoded genes by RNA polymerase II



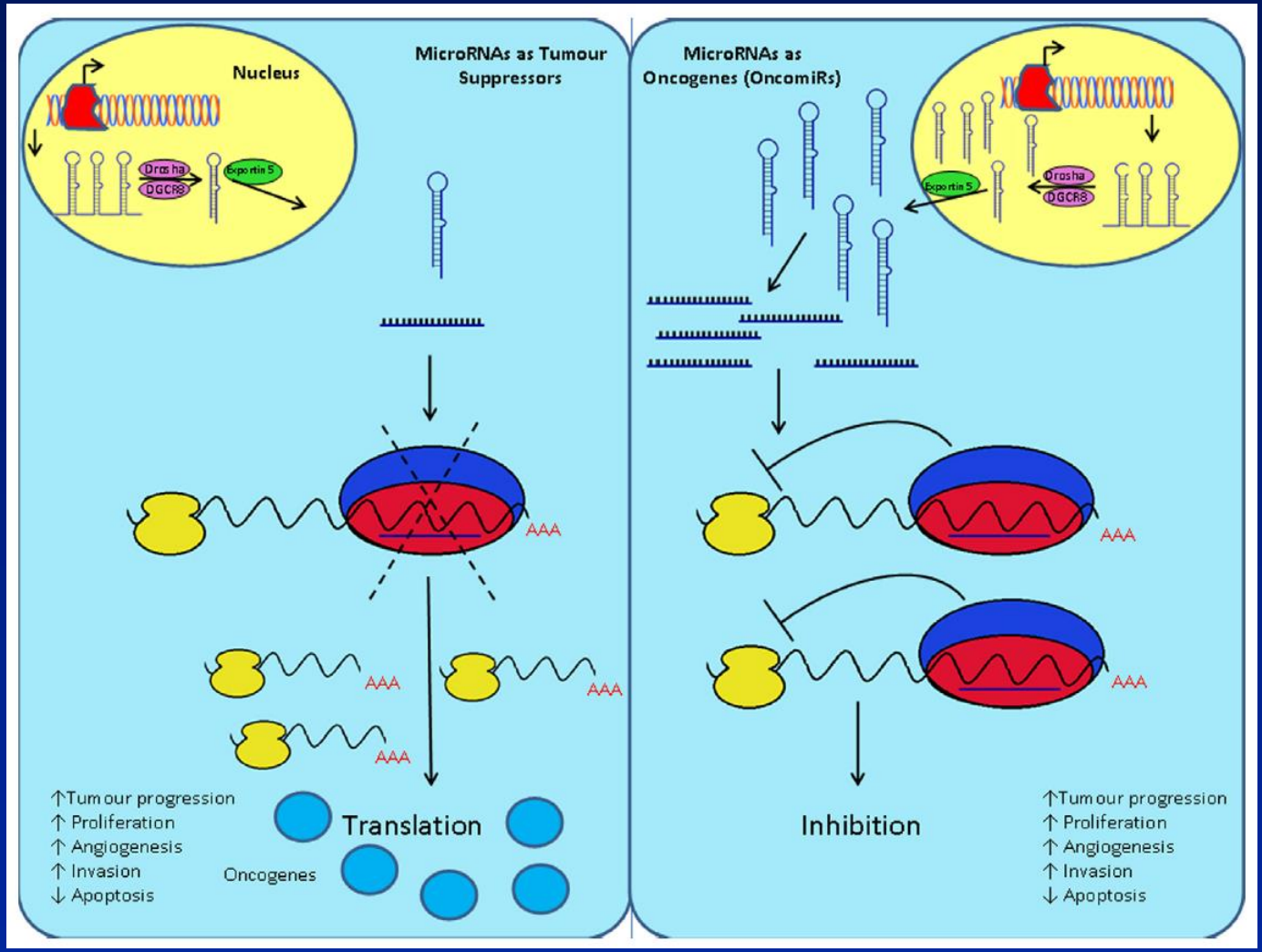
The emerging role of microRNAs in resistance to lung cancer treatments - Cancer Treatment Reviews 41 (2015) 160–169 – Fig 01

Aberrant expression of miRNAs plays a critical role in anti-cancer drug resistance in lung cancer.



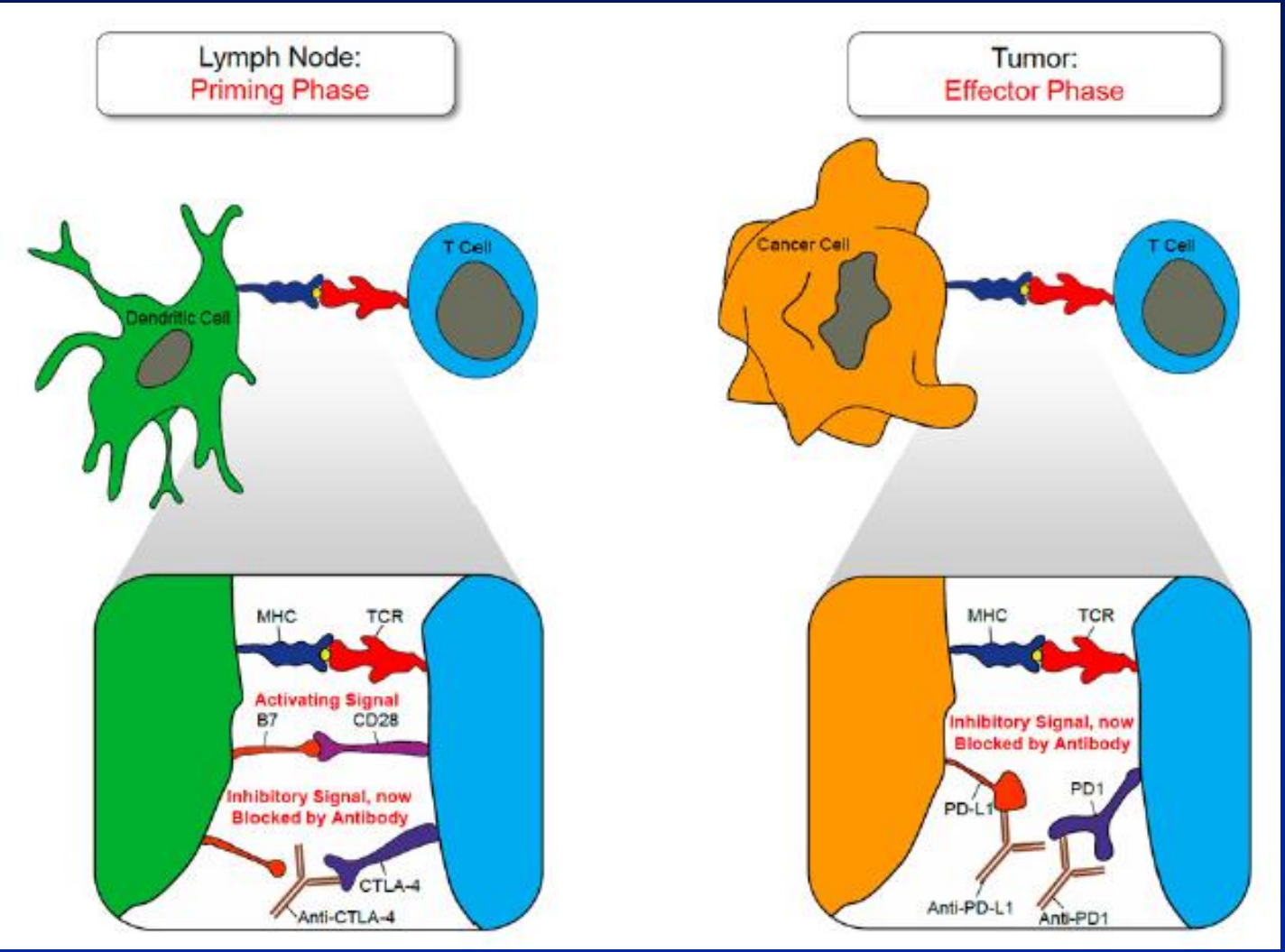
The emerging role of microRNAs in resistance to lung cancer treatments - Cancer Treatment Reviews 41 (2015) 160–169 – Fig 03

The role of miRNAs as tumour suppressor genes and oncogenes. While regulatory RNAs have not been considered an important class of tumour suppressor genes or oncogenes, the ability of miRNAs to act in either capacity is strengthened by evidence, demonstrating that miRNAs are dysregulated in diverse tumour types, gain or loss of miRNA function as a result of deletions, amplifications or mutations, in addition to the tumour-suppressing and tumour-promoting activities of miRNAs in vivo. In cancer, loss of the tumour-suppressive function of miRNAs leads to expression of target oncogenes, while increased expression of oncogenic miRNAs (oncomirs) can repress tumour suppressor genes.



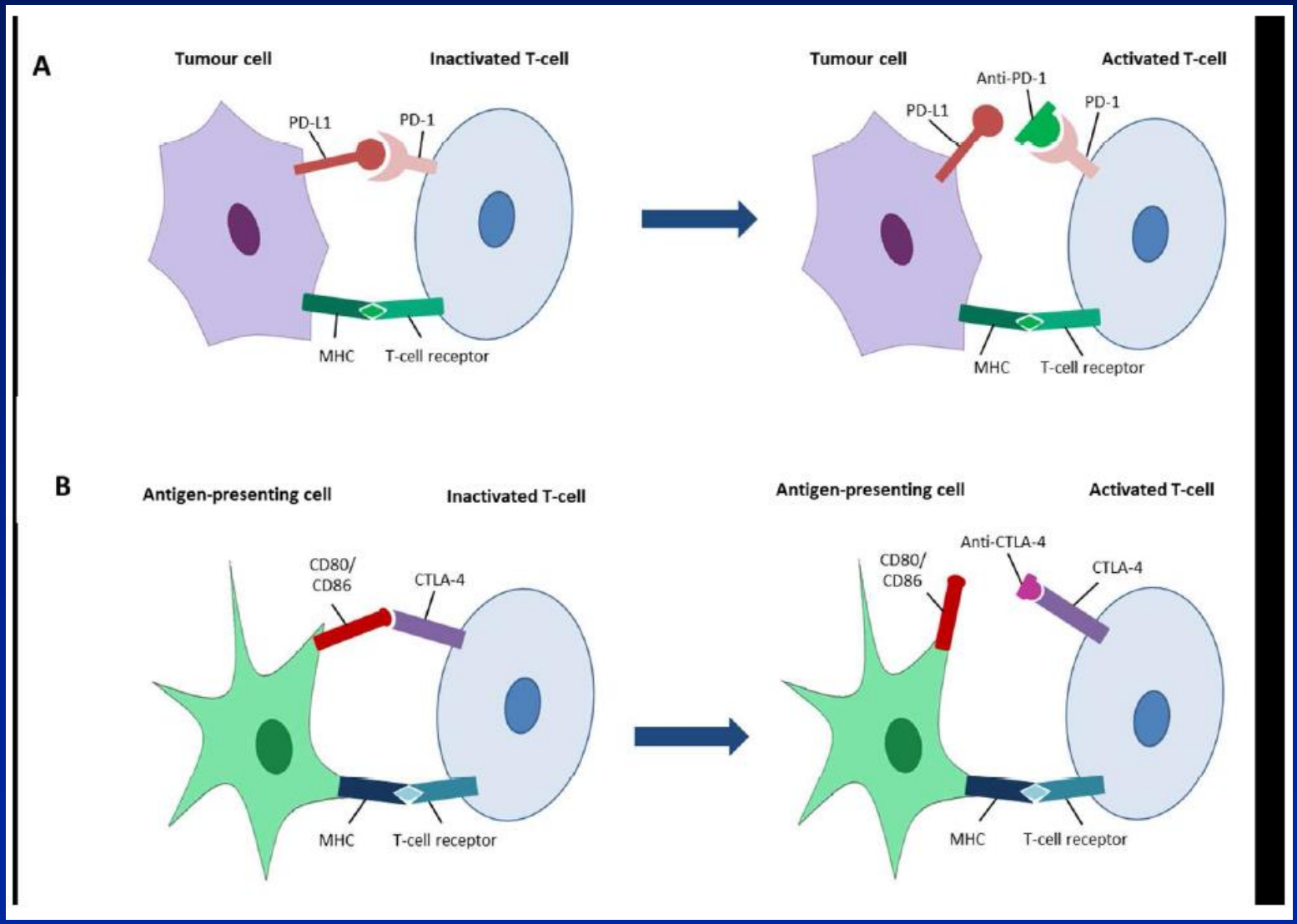
The emerging role of microRNAs in resistance to lung cancer treatments - Cancer Treatment Reviews 41 (2015) 160–169 – Fig 02

Blockade of CTLA-4 or PD-1 signalling in anti-cancer immunotherapy:

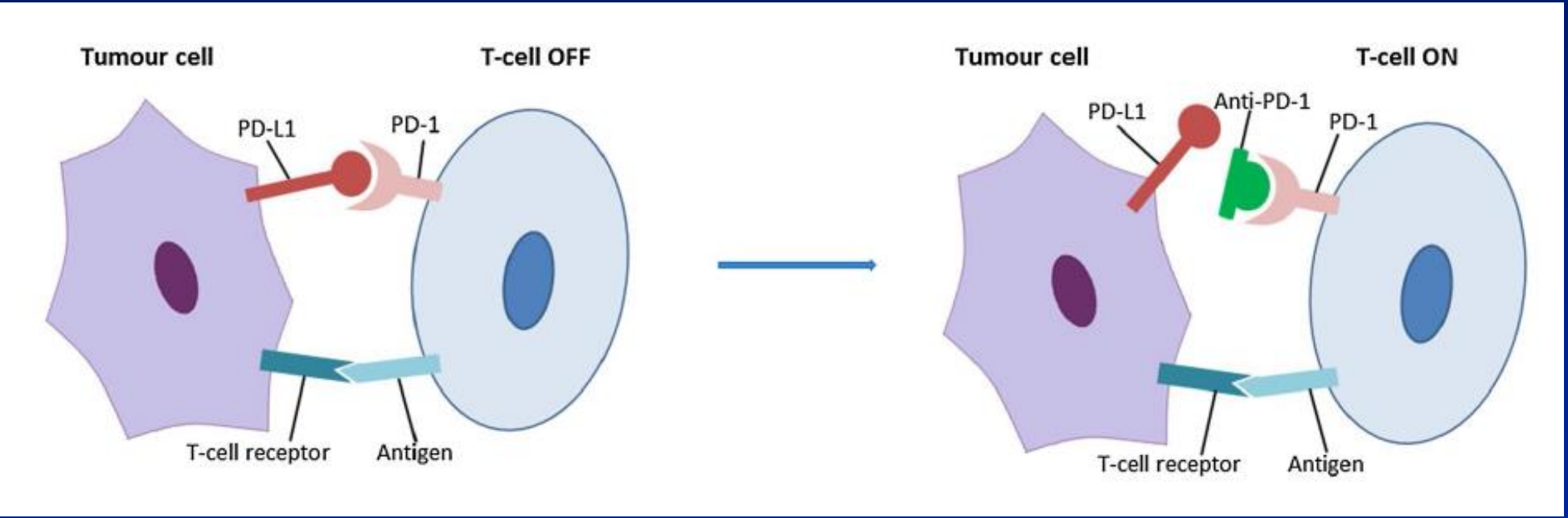


The T cell priming phase is schematically depicted on the left site. T cells engage APCs, such as dendritic cells (DCs) via their t-cell receptor (TCR). Recognition of the cognate MHC/peptide complex by the TCR results in the intracellular transmission of an activating signal in the T cell, which is complemented by a co-activating signal provided by the CD28/B7 interaction. In order to down-modulate T cell priming and expansion CTLA-4 is up regulated on activated T cells after 2–3 days and competes with CD28 for B7. CTLA-4 blocking antibodies can therapeutically inhibit the co-inhibitory signal provided by CTLA-4. On the right site the effector phase is outlined. During this phase immune effector function can be dampened by PD-1/PD-L1 interaction. PD-1 or PD-L1 blocking antibodies can therapeutically inhibit the co-inhibitory signal provided by the PD-1/PD-L1 interaction and restore effector function in tumour resident effector T cells.

Schematic depiction of the mechanisms of action of PD-1 and CTLA-4 checkpoint inhibitors



Schematic depiction of PD-1 induced immunosuppression

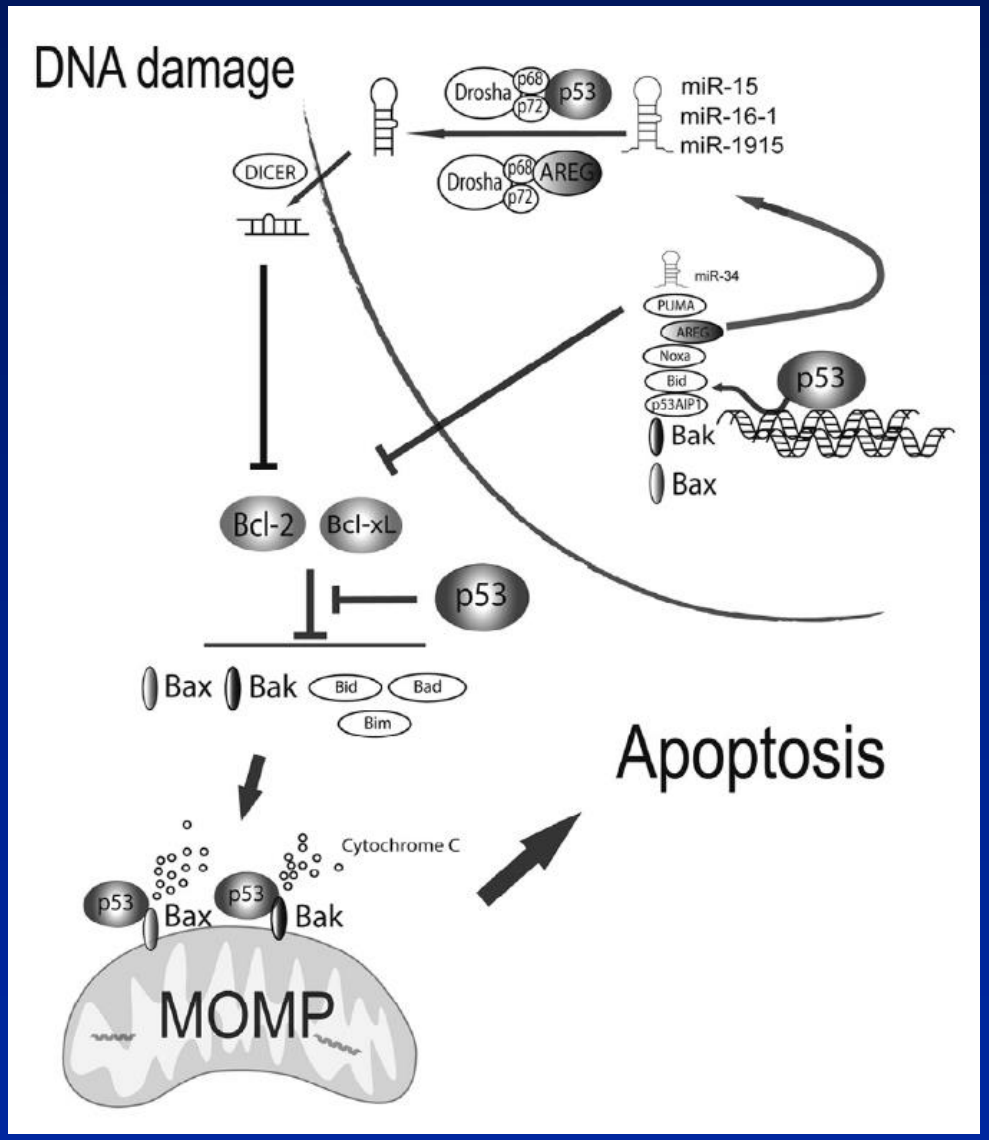


Targeted therapies for treatment of renal cell carcinoma: recent advances and future perspectives - Cancer Chemother Pharmacol (2015) 76:219–233 – Fig 02

Overview of phase I trials including anti-PD-1 or -PD-L1 monoclonal antibodies in metastatic melanoma.

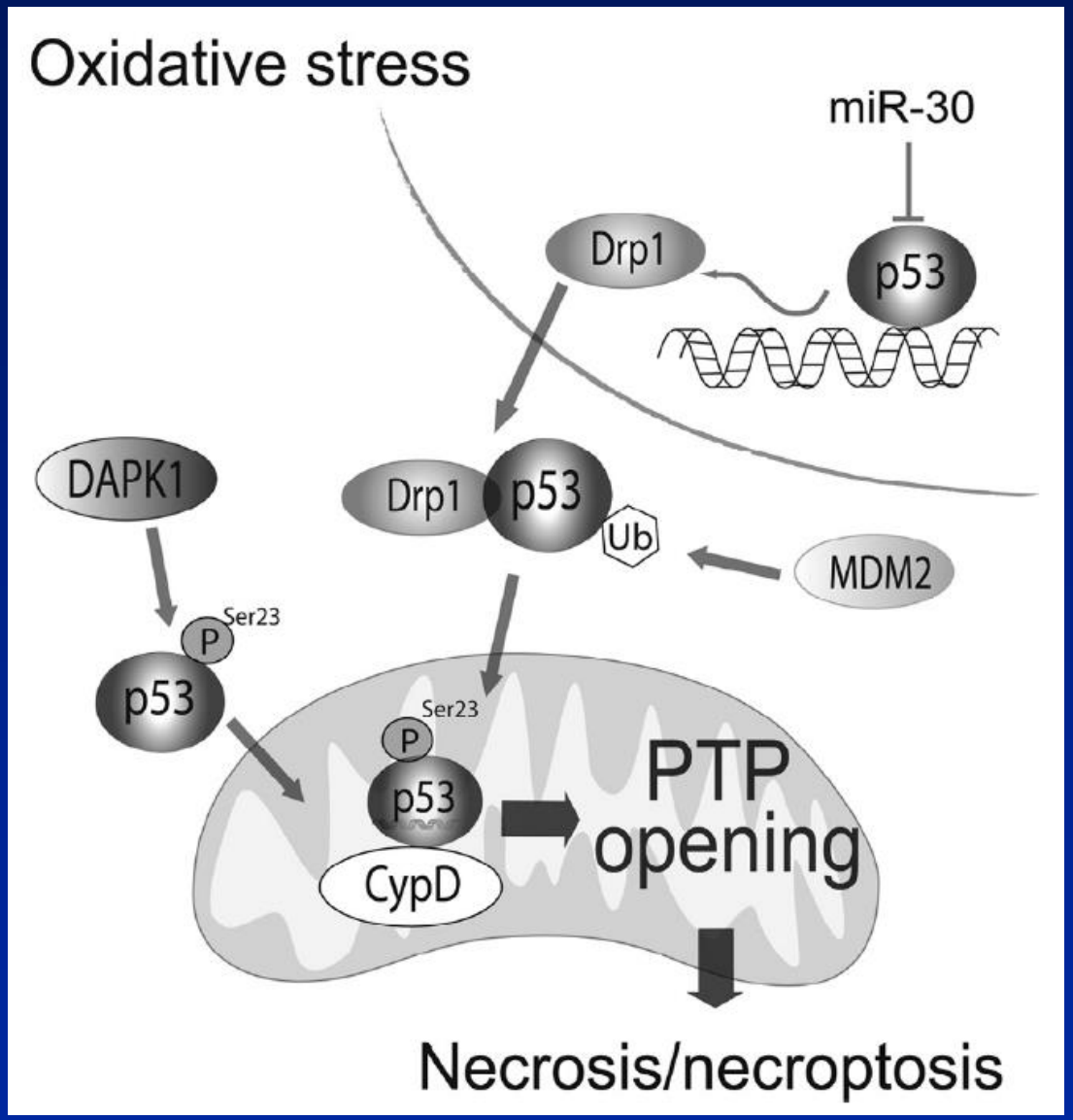
Target	Agent	n	ORR%	CR	OS	
					1 yr	2 yr
PD-1	Pembrolizumab (10 mg/kg q2, 10 mg/kg q3, 2 mg/kg q3)	135	32%	9%	81%	n.a.
	Nivolumab + peptide vaccine (1, 3, 10 mg/kg q2)	87	25%	2%	n.a.	n.a.
	Nivolumab (0.1, 1, 3, 10 mg/kg q2)	107	31%	?	62%	43%
					PFS 24 weeks	
PD-L1	MPDL3280A (0.3, 1, 3, 10, 20 mg/kg q2)	45	28%	?	41%	
	BMS-936559 (0.3, 1, 3, 10 mg/kg q2)	52	17%	6%	42%	

Illustration of the regulation of apoptosis by p53 via MOMP



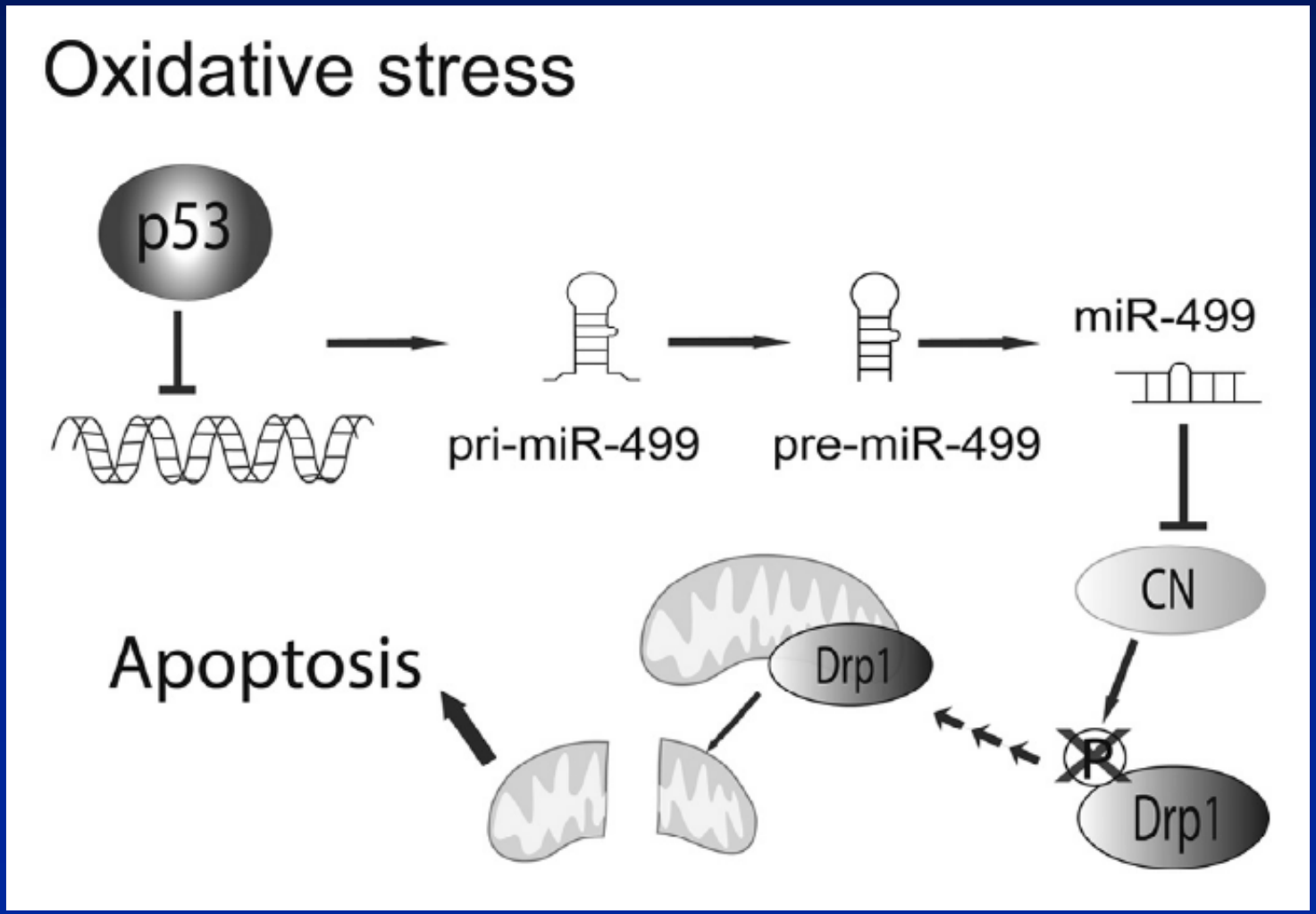
Cell death decision by p53 via control of the mitochondrial membrane - Cancer Letters 367 (2015) 108–112 – Fig 01

Illustration of the regulation of necroptosis by p53 via mitochondrial PTP opening



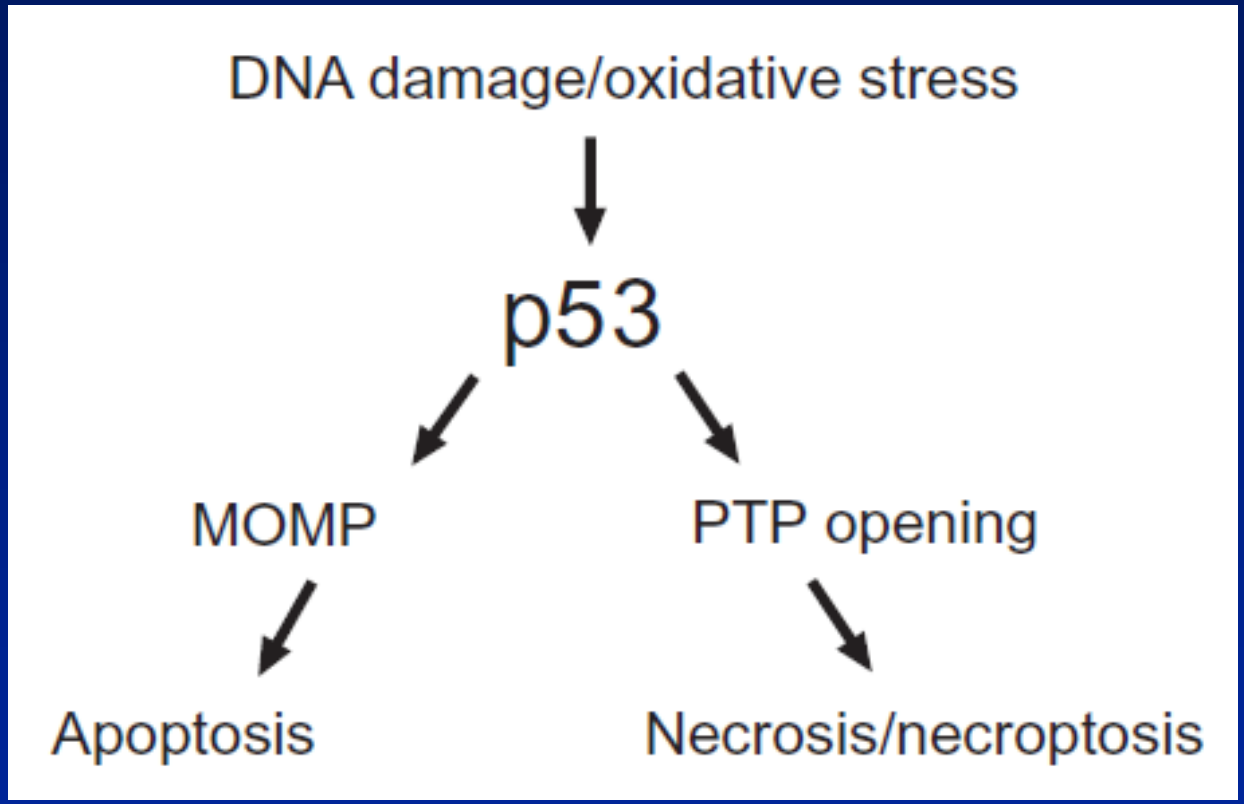
Cell death decision by p53 via control of the mitochondrial membrane - Cancer Letters 367 (2015) 108–112 – Fig. 02

Illustration of the regulation of Drp1 by p53



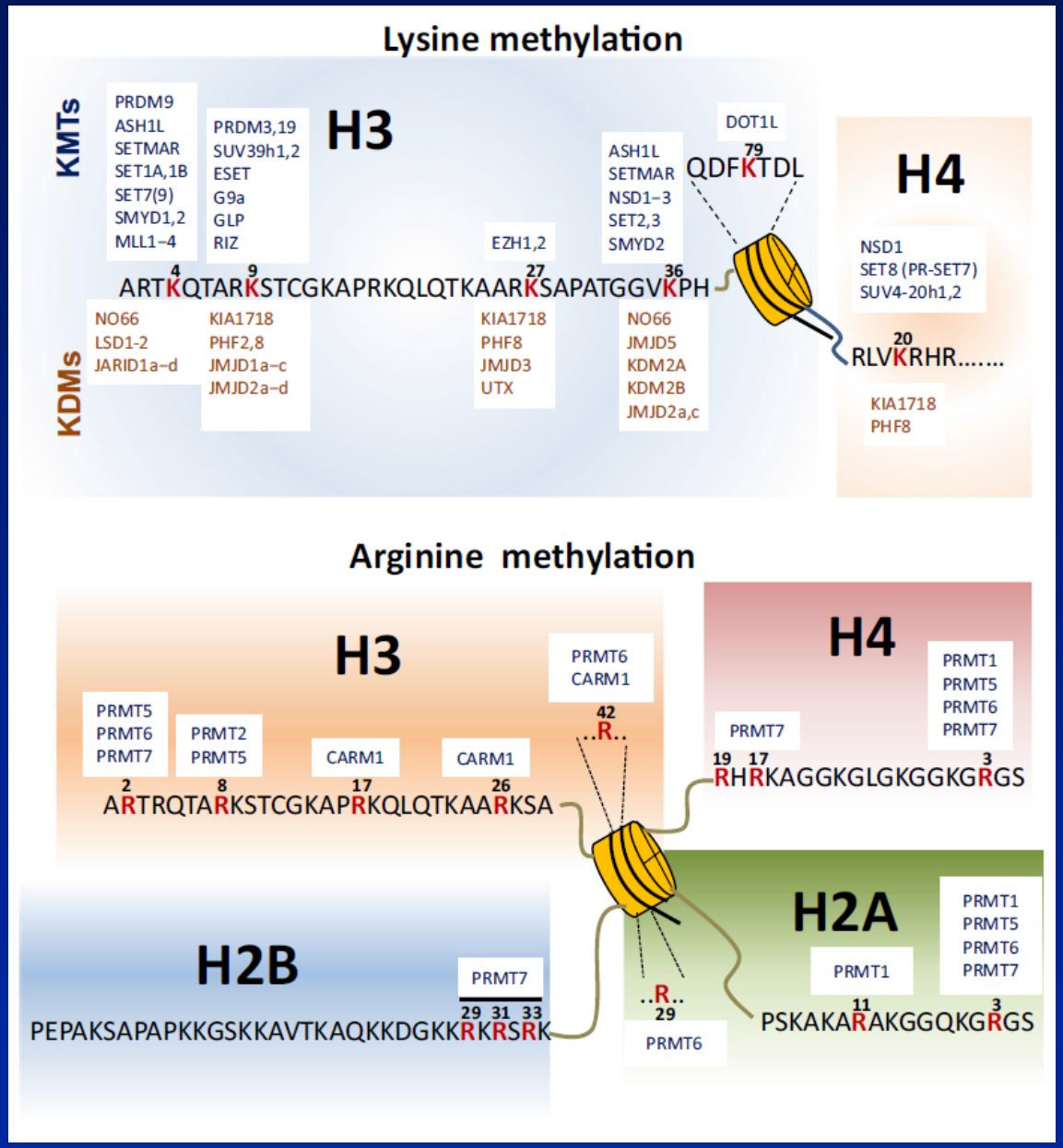
Cell death decision by p53 via control of the mitochondrial membrane - Cancer Letters 367 (2015) 108–112 – Fig. 03

Illustration of the regulation of the cell death decision by p53 via MOMP and PTP opening. In response to DNA damage, p53 mediates apoptosis through MOMP



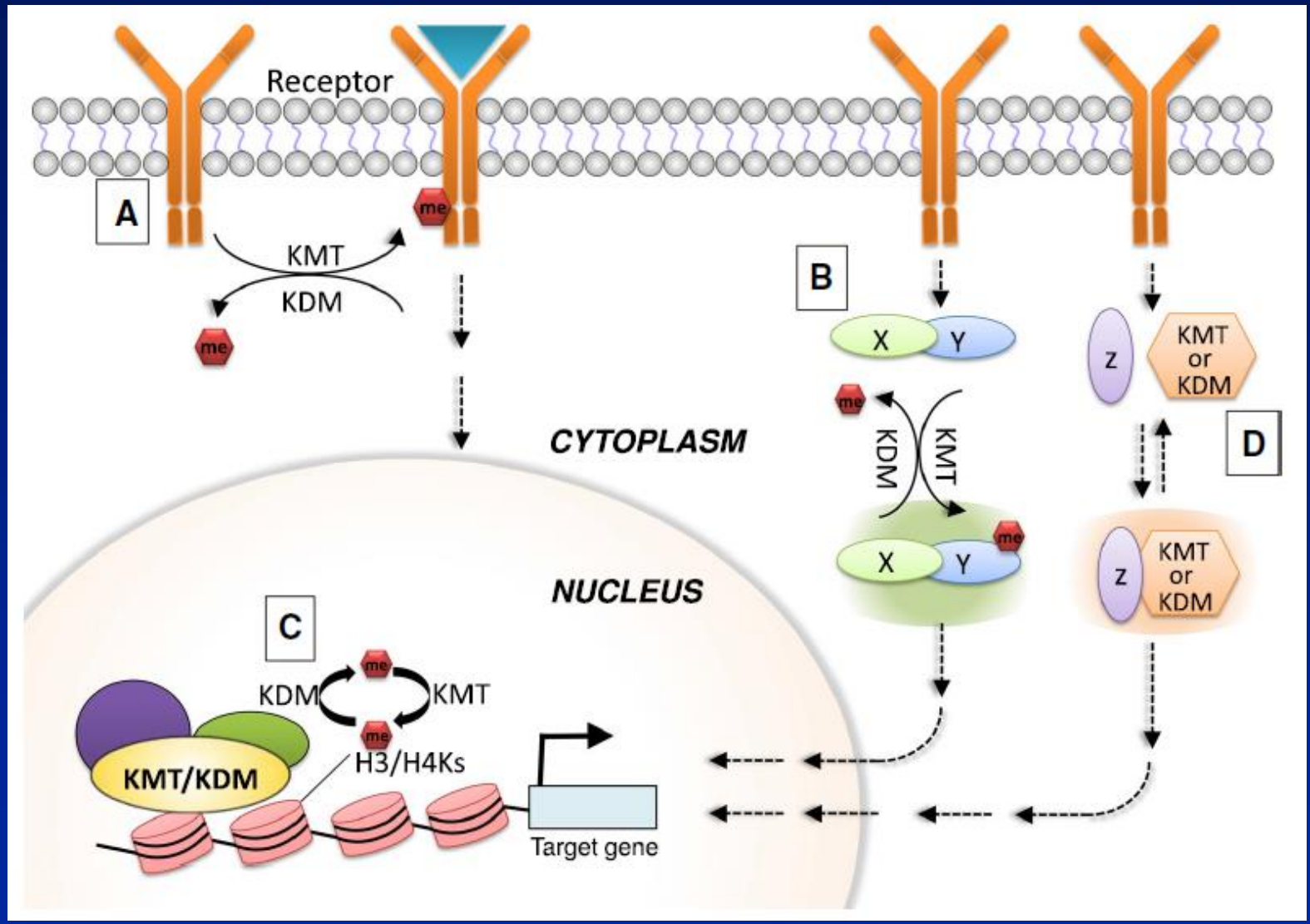
Cell death decision by p53 via control of the mitochondrial membrane - Cancer Letters 367 (2015) 108–112 – Fig. 04

Histone methylation and its modifiers



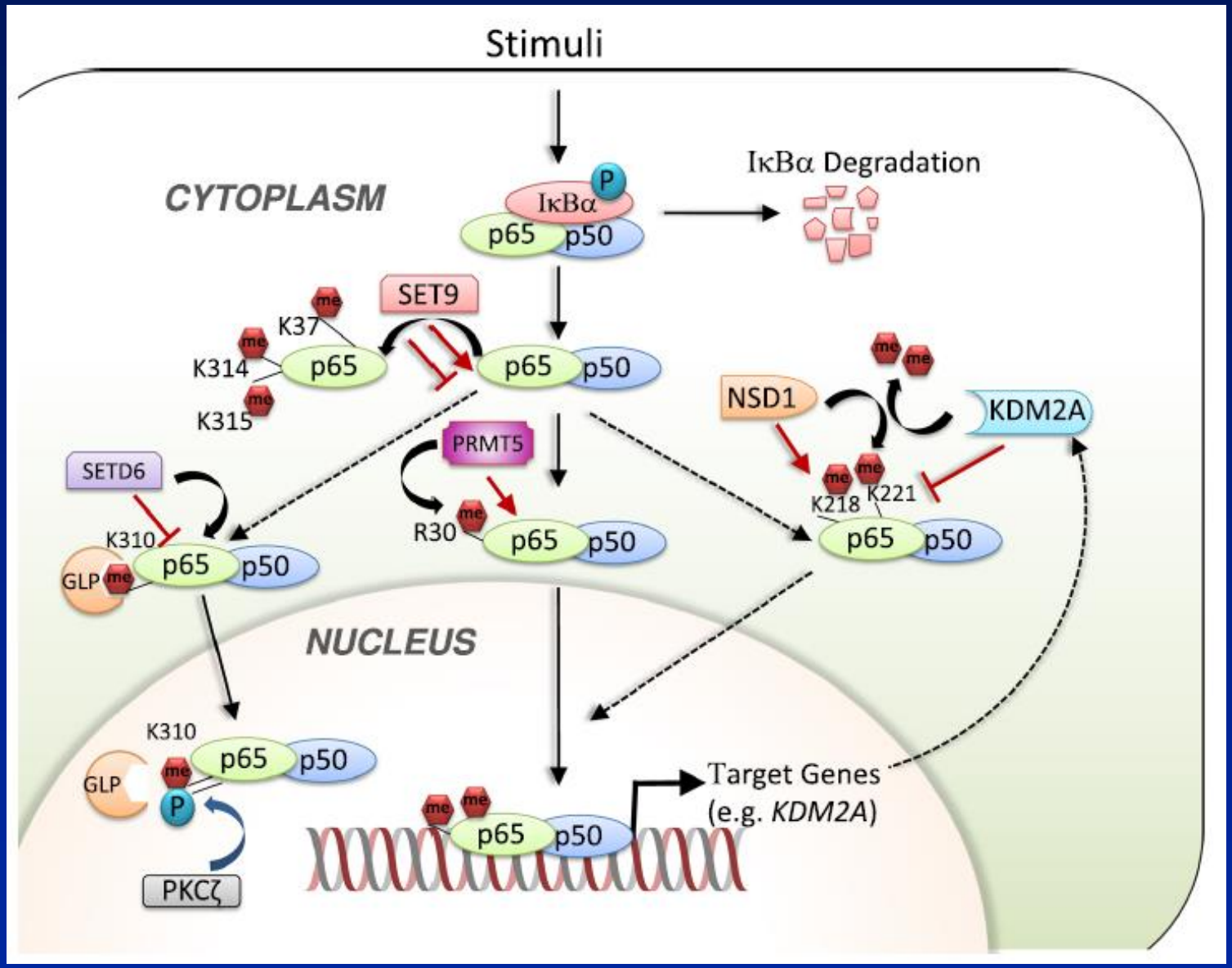
Histone methylation modifiers in cellular signaling pathways - Cell. Mol. Life Sci. (2015) 72:4577–4592 – Fig. 01

Overview of the molecular mechanisms underlying regulation of signaling pathways by methylation modifiers



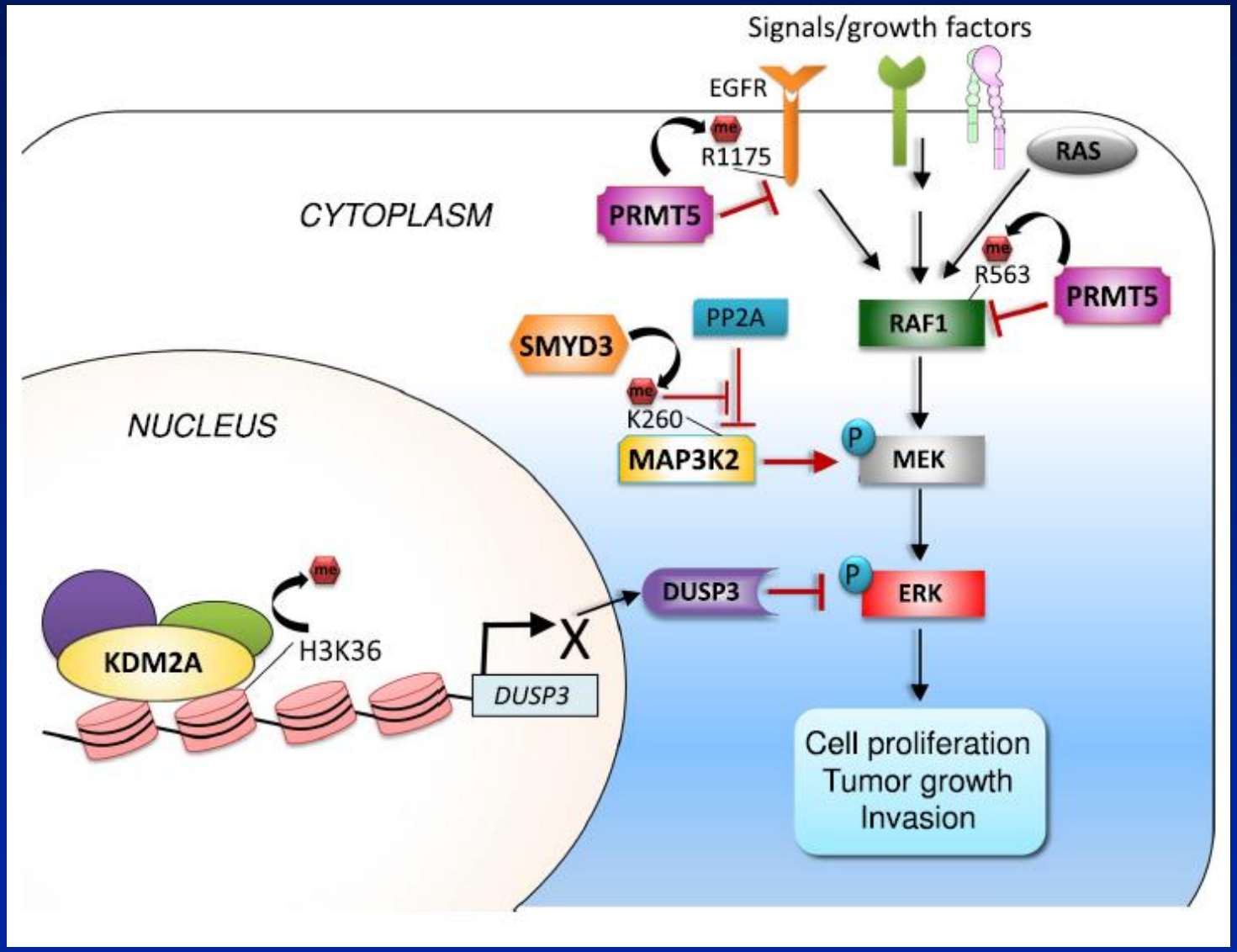
Histone methylation modifiers in cellular signaling pathways - Cell. Mol. Life Sci. (2015) 72:4577–4592 – Fig. 02

Regulation of NF-kB signaling pathways by methylation modifiers



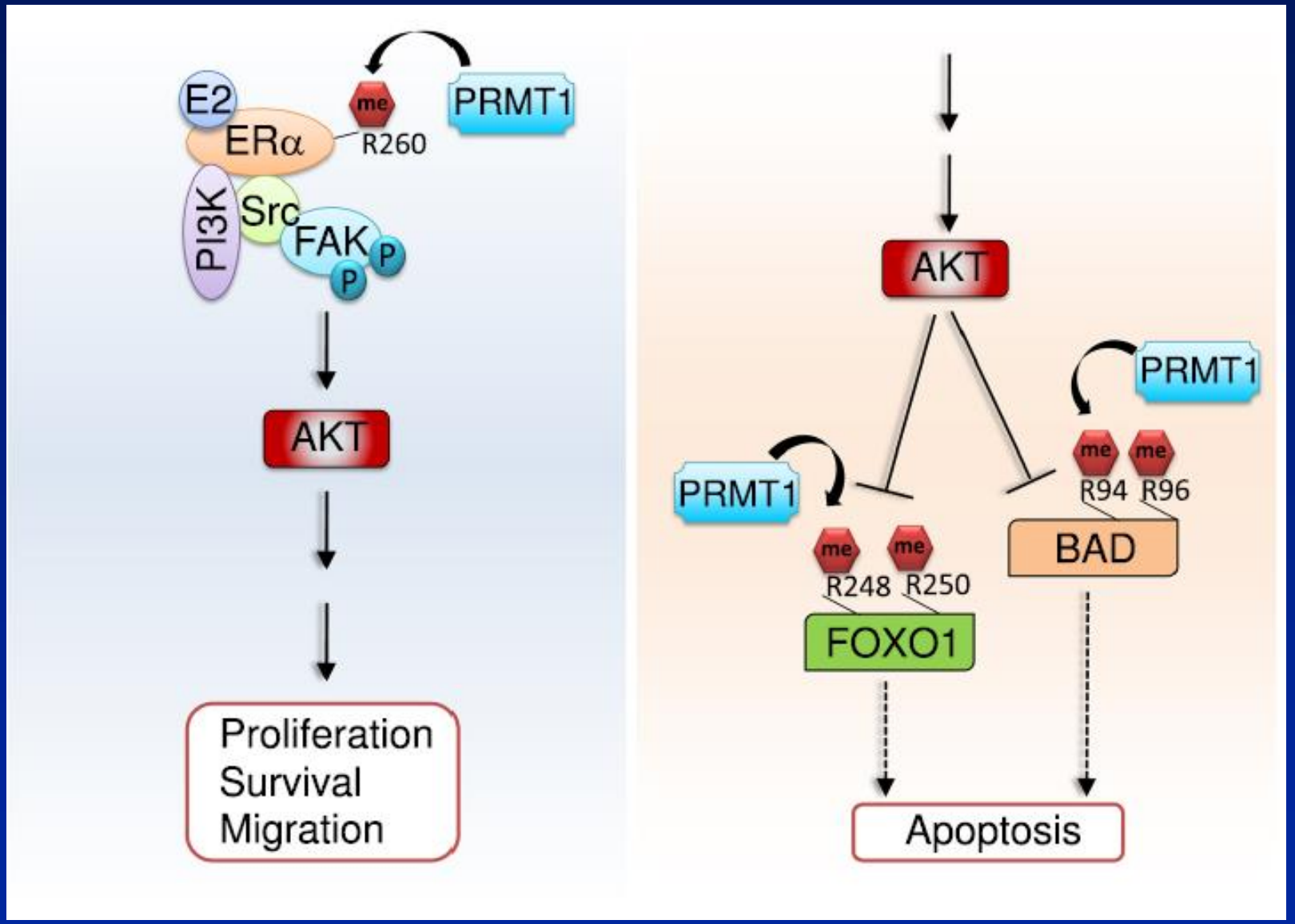
Histone methylation modifiers in cellular signaling pathways - Cell. Mol. Life Sci. (2015) 72:4577–4592 – Fig. 03

Methylation modifiers and MAPK signaling pathways



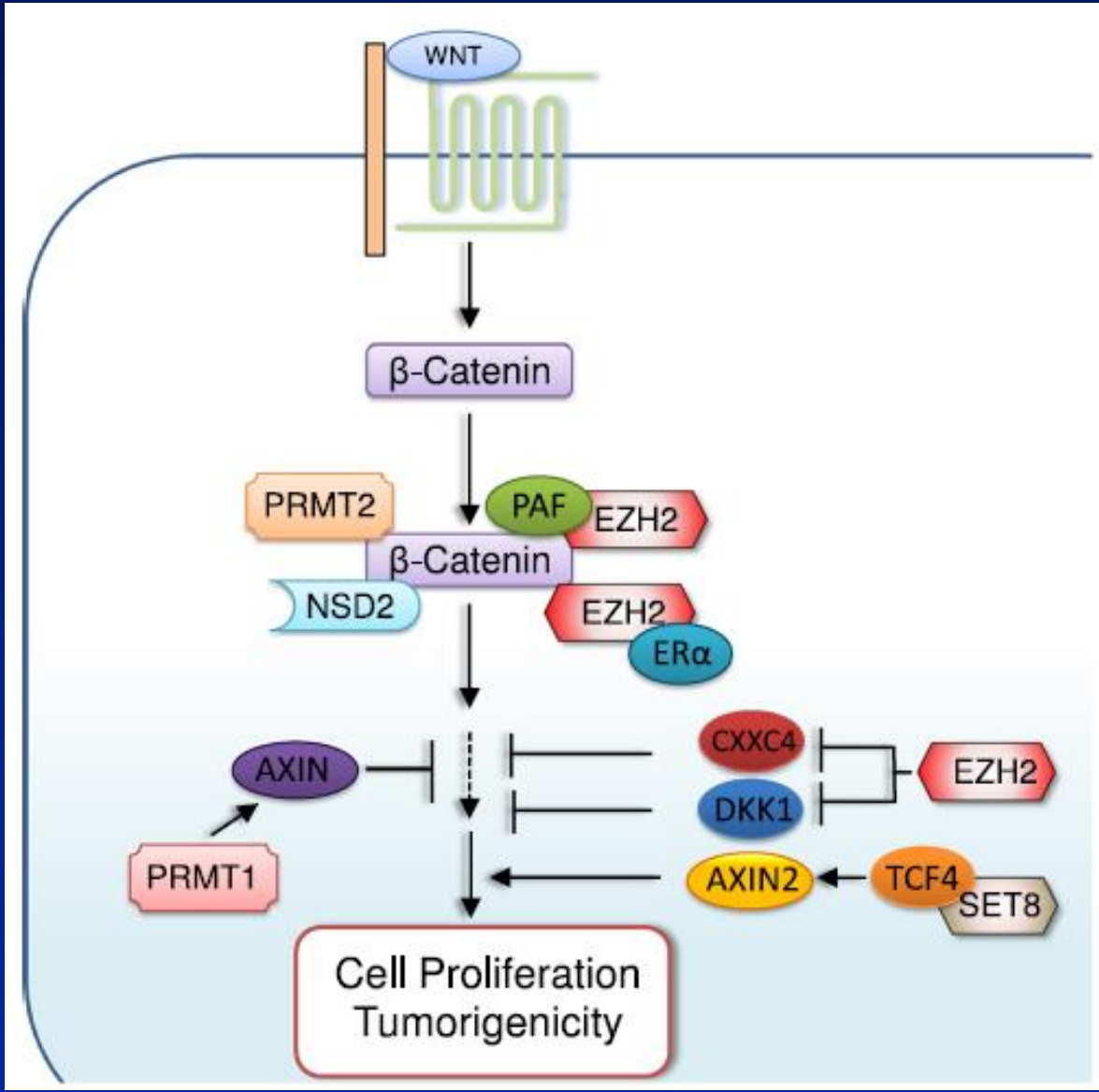
Histone methylation modifiers in cellular signaling pathways - Cell. Mol. Life Sci. (2015) 72:4577–4592 – Fig. 04

Regulation of AKT signaling pathways by PRMT1



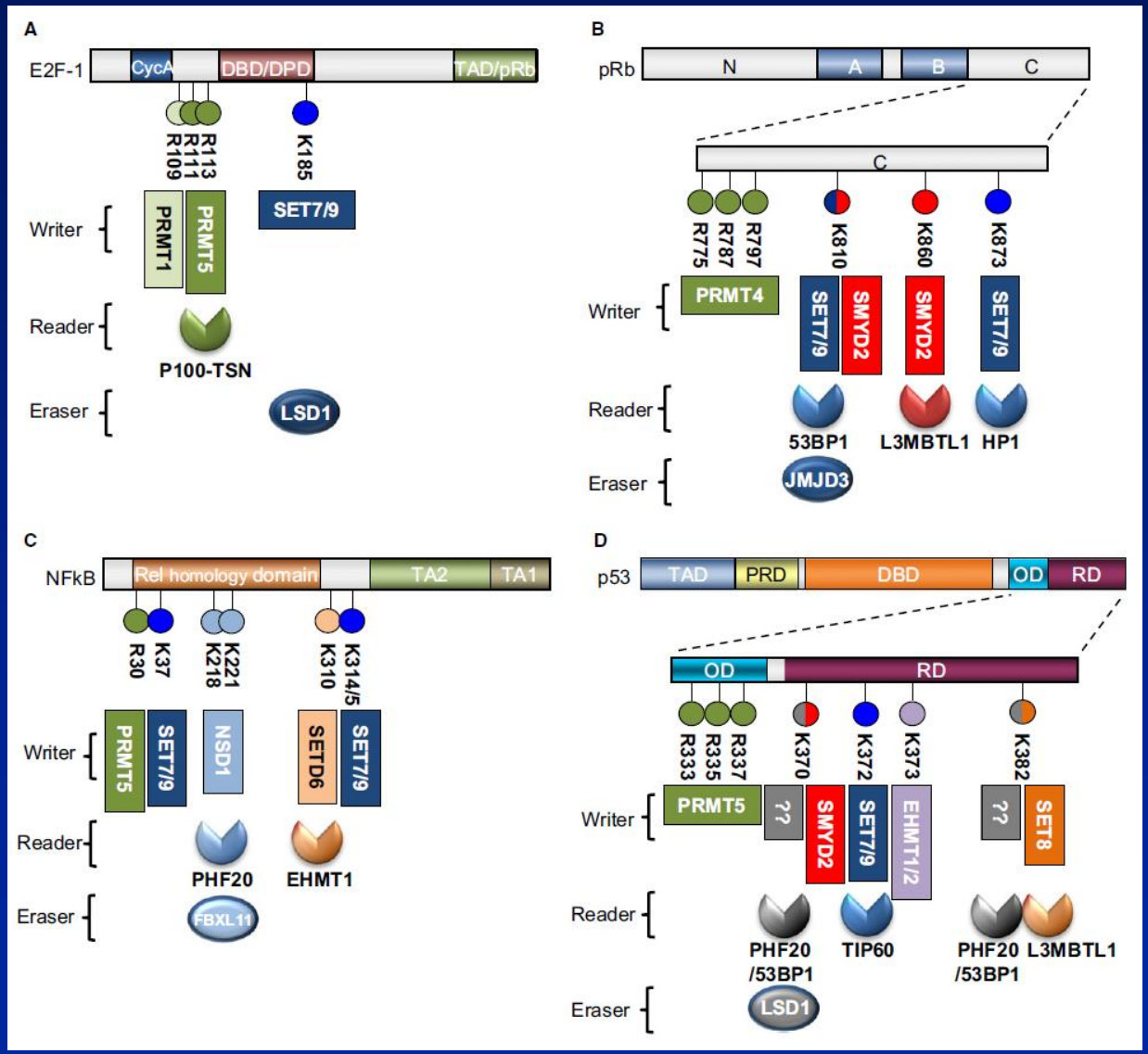
Histone methylation modifiers in cellular signaling pathways - Cell. Mol. Life Sci. (2015) 72:4577–4592 – Fig. 05

Regulation of Wnt/b-catenin signaling pathways by methylation modifiers.

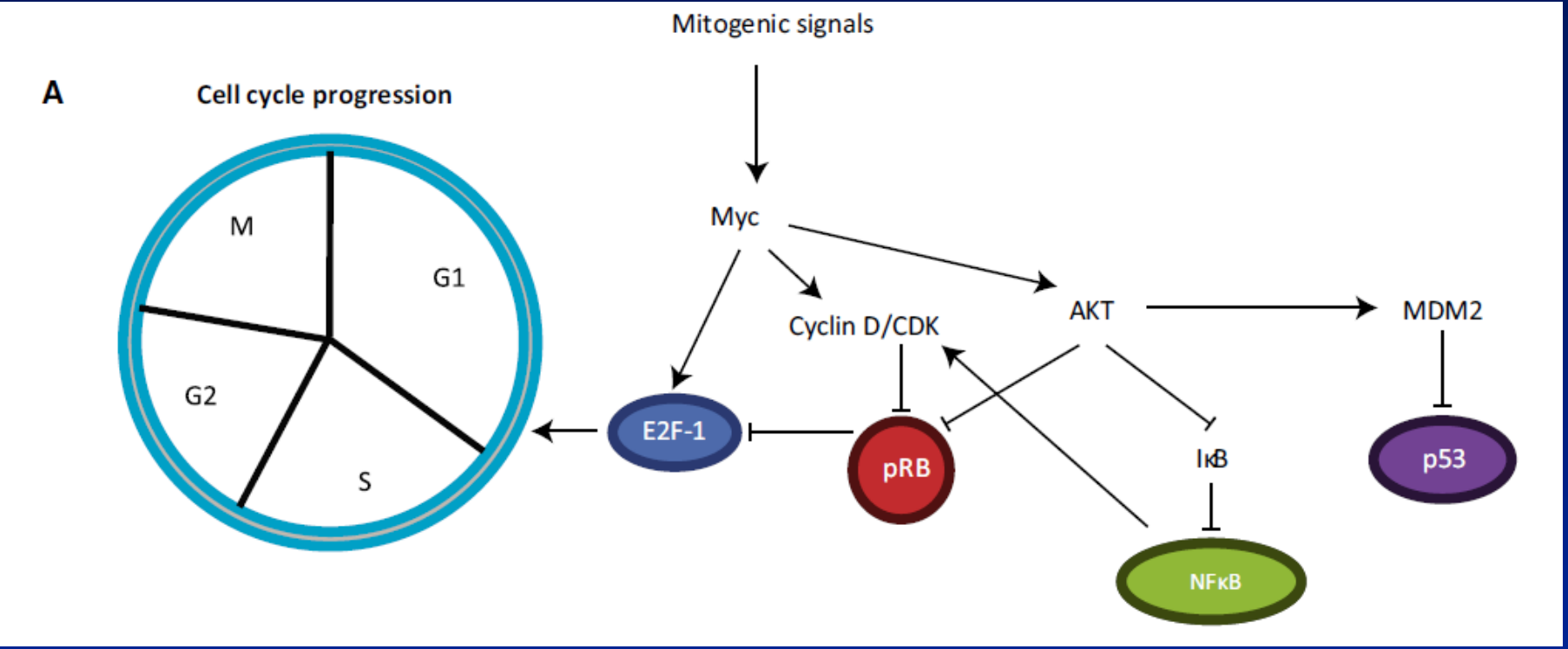


Histone methylation modifiers in cellular signaling pathways - Cell. Mol. Life Sci. (2015) 72:4577–4592 – Fig. 06

Representation of E2F-1 (A), pRB (B), NFjB (C) and p53 (D) highlighting their various protein domains and sites of arginine and lysine methylation. The ‘writers’, ‘readers’ and ‘erasers’ of these methyl marks are also indicated beneath each diagram, and are colour coded for clarity.

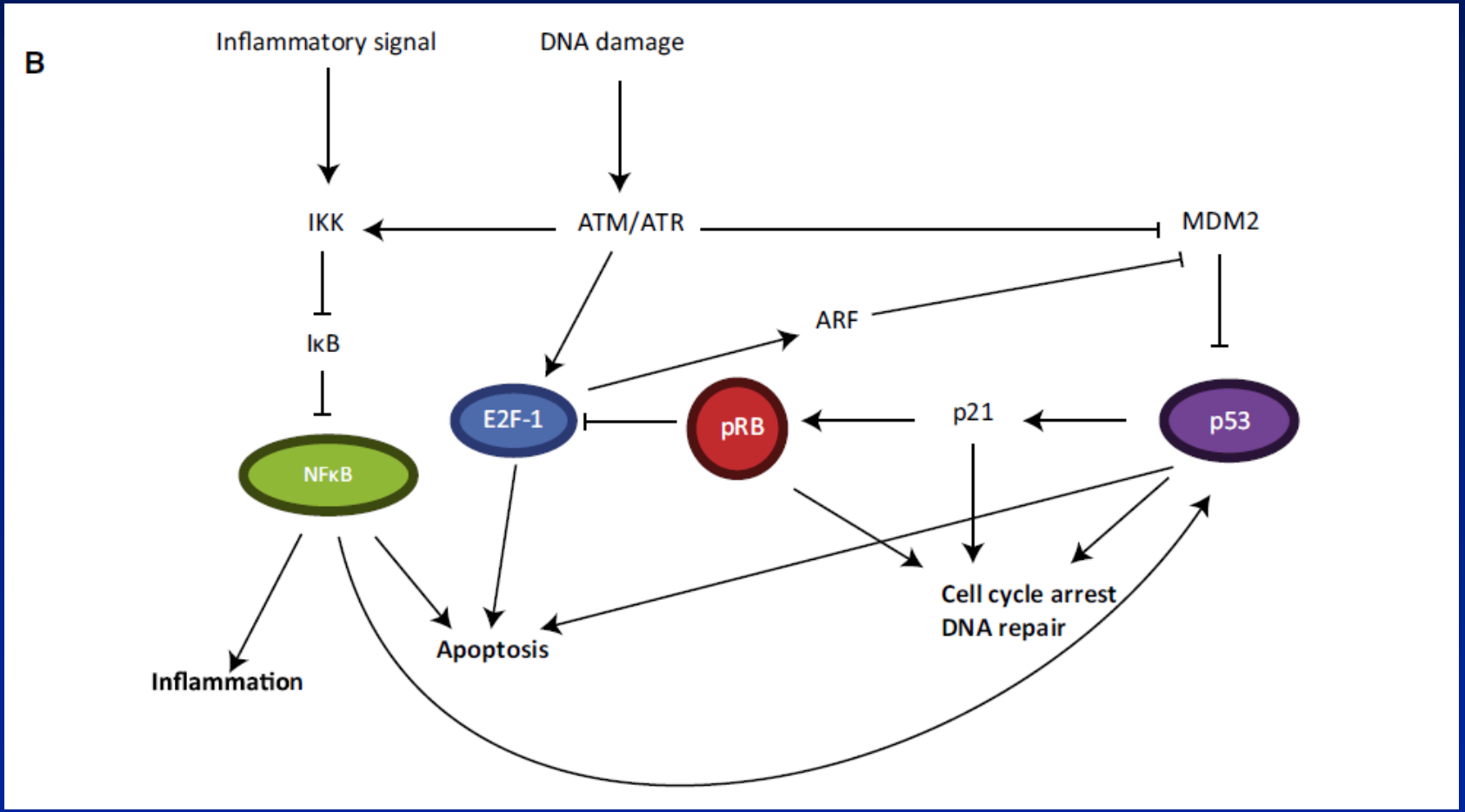


Cell signalling pathways influenced by E2F-1, pRB, NFjB and p53



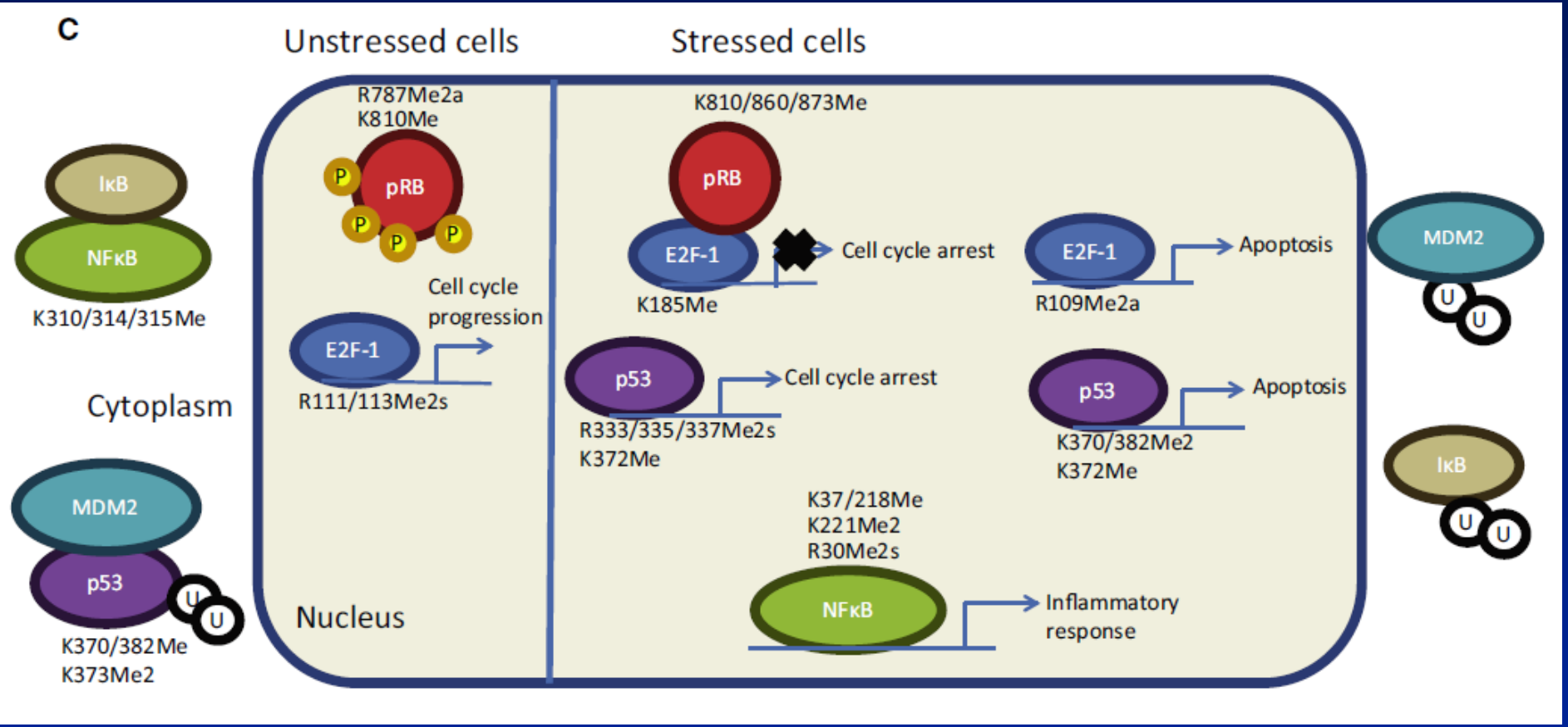
(A) Under conditions of mitogenic signalling pRB is inactivated by CDK-mediated phosphorylation events, resulting in the release of E2F-1 and the transcription of target genes associated with cell cycle progression. Under these conditions p53 is sequestered and poly-ubiquitinated by MDM2, resulting in its degradation. NFjB can also stimulate cell cycle progression via inhibition of pRB, although this is usually driven by inflammation

Cell signalling pathways influenced by E2F-1, pRB, NFjB and p53



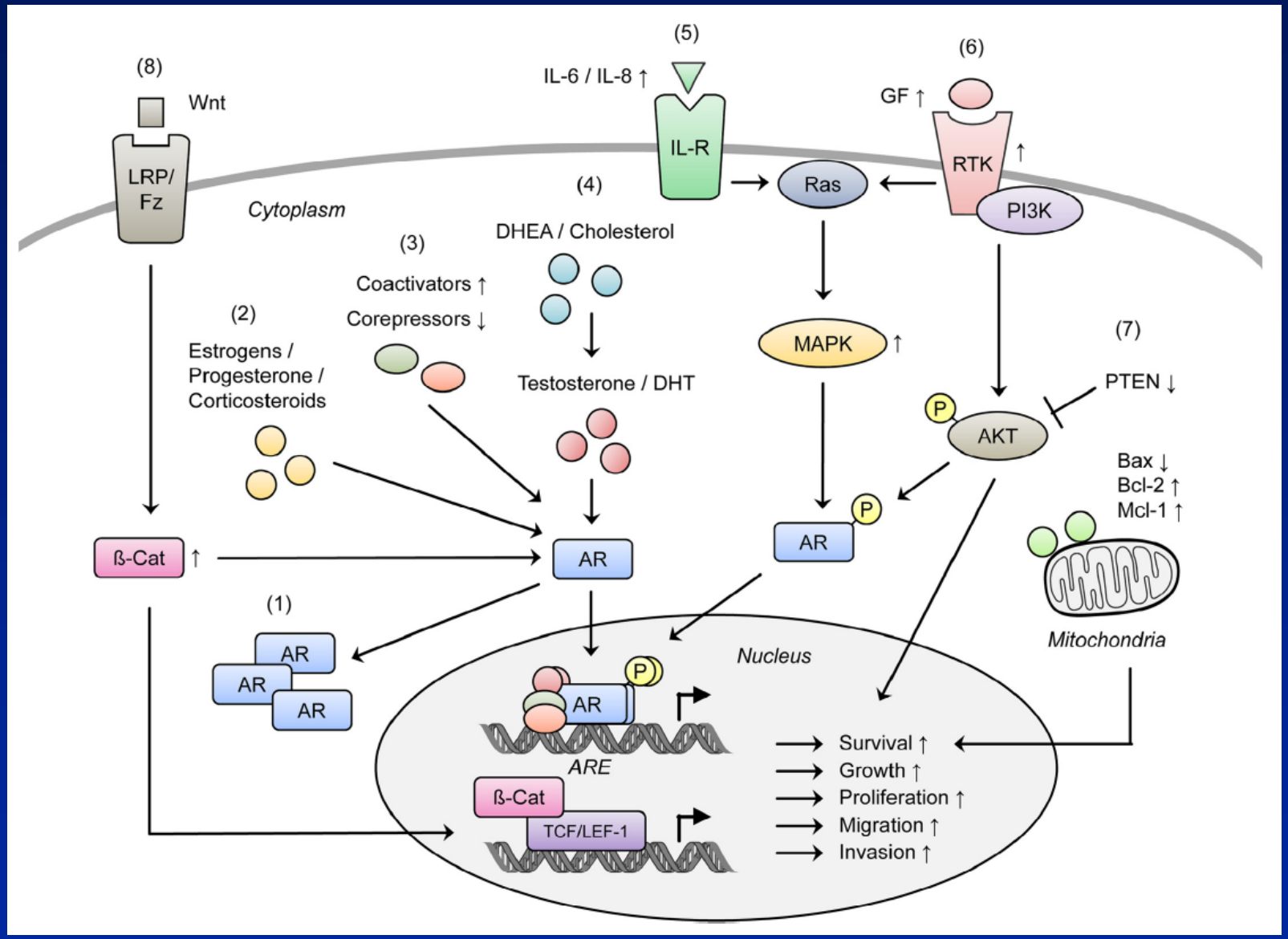
(B) DNA damage stimulates the activity of the sensor kinases ATM and ATR, resulting in the phosphorylation of downstream targets. This leads to the activation and stabilization of p53 and E2F-1, which can drive cell cycle arrest or apoptosis depending on the nature and severity of the damage sustained. For example, p53 can drive expression of the CDK inhibitor p21, which will cause pRB activation and cell cycle arrest. Alternatively, p53 and E2F-1 can both upregulate the expression of pro-apoptotic target genes or genes involved in DNA repair. During inflammation, NFjB translocates to the nucleus and can upregulate target genes involved in the inflammatory response, as well as inducing p53-dependent apoptosis under some circumstances.

Cell signalling pathways influenced by E2F-1, pRB, NFjB and p53



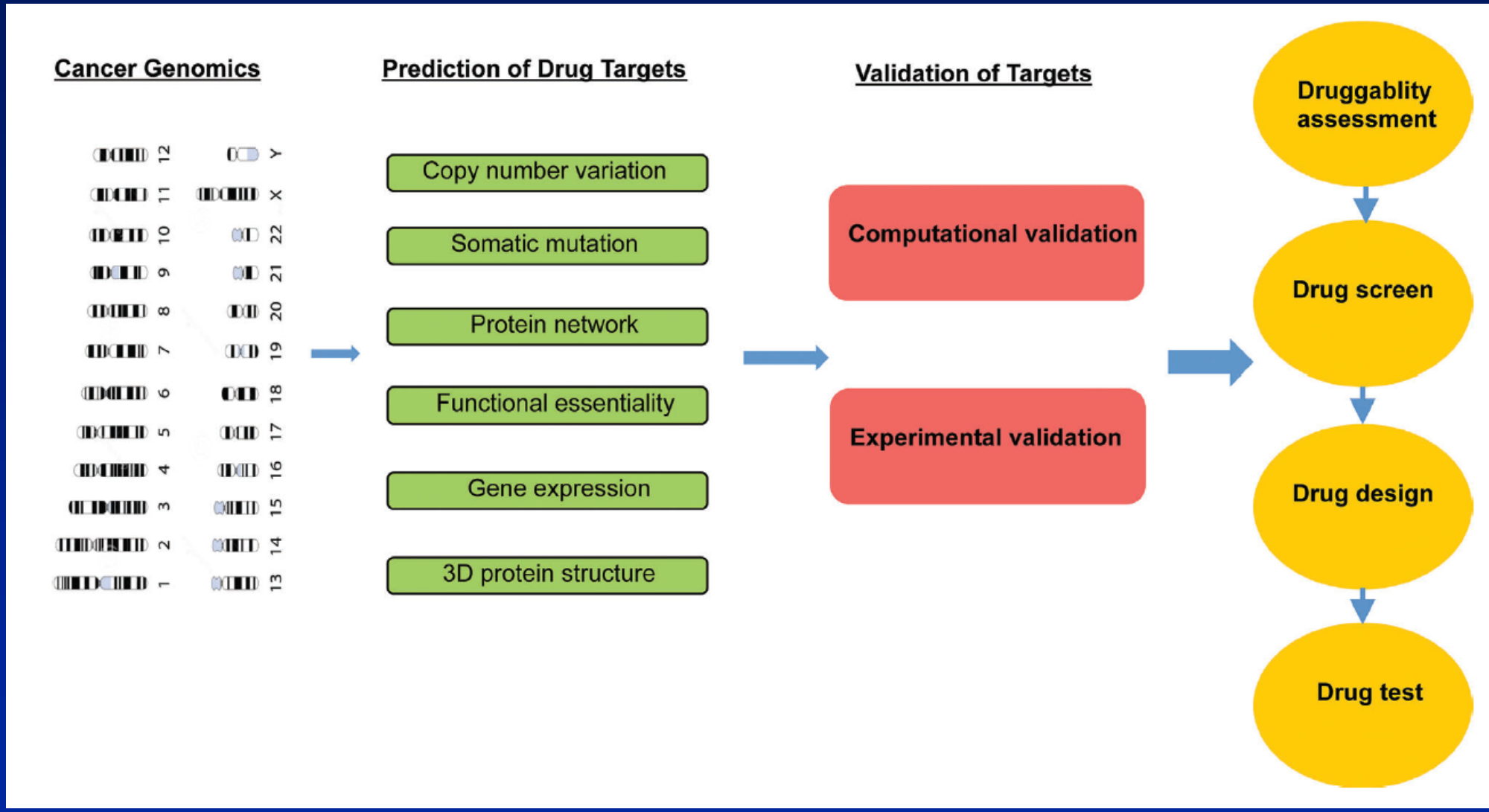
(C) Overview of methylation marks seen on E2F-1, pRB, NFjB and p53 in stressed and unstressed cells, and the outcome these modifications have on transcription.

Schematic representation of molecular alterations in castration resistant prostate cancer

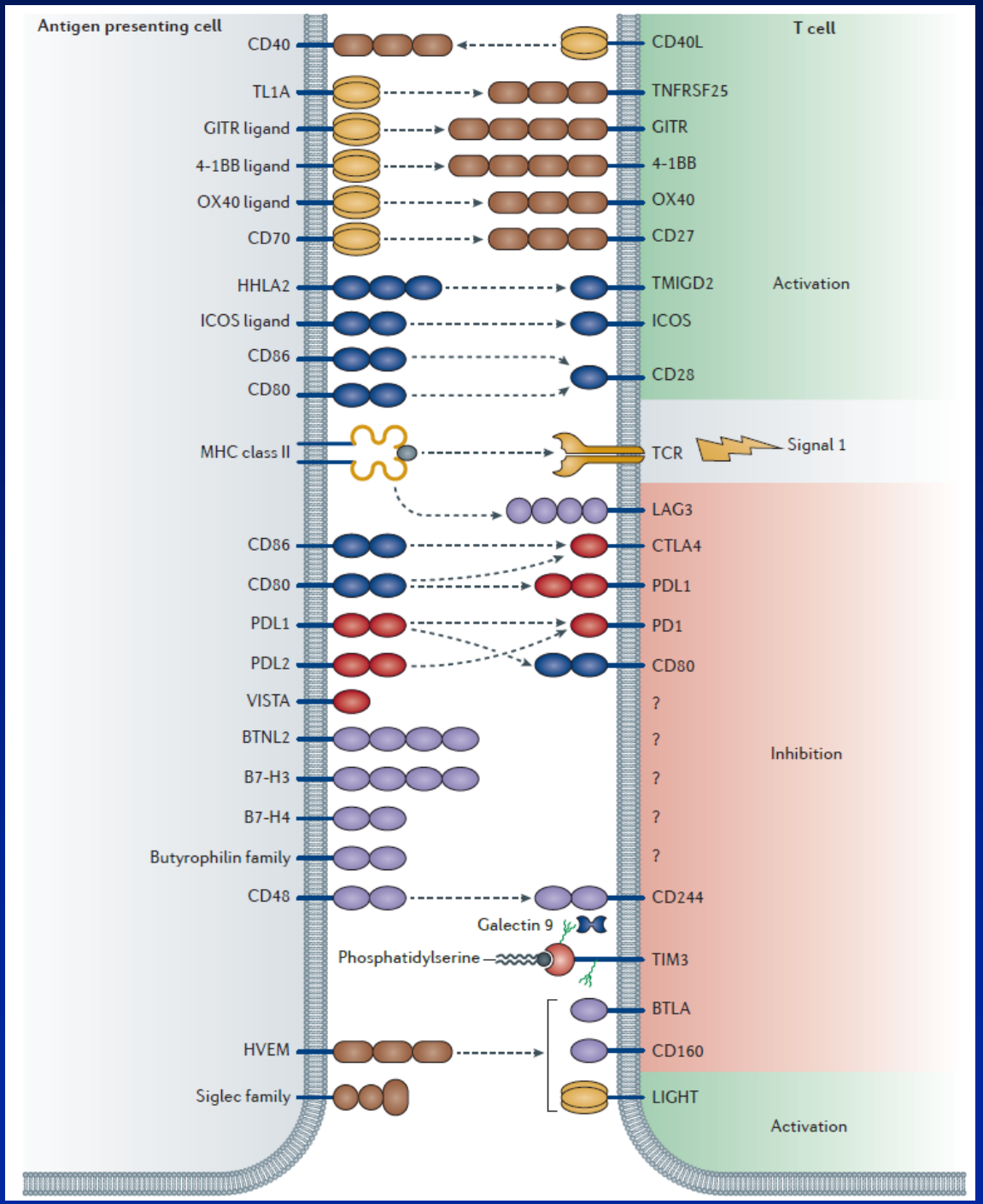


Androgen deprivation of prostate cancer: Leading to a therapeutic dead end - Cancer Letters 367 (2015) 12–17 – Fig 01

Overview of the systematic approach to identify and validate new cancer drug targets.

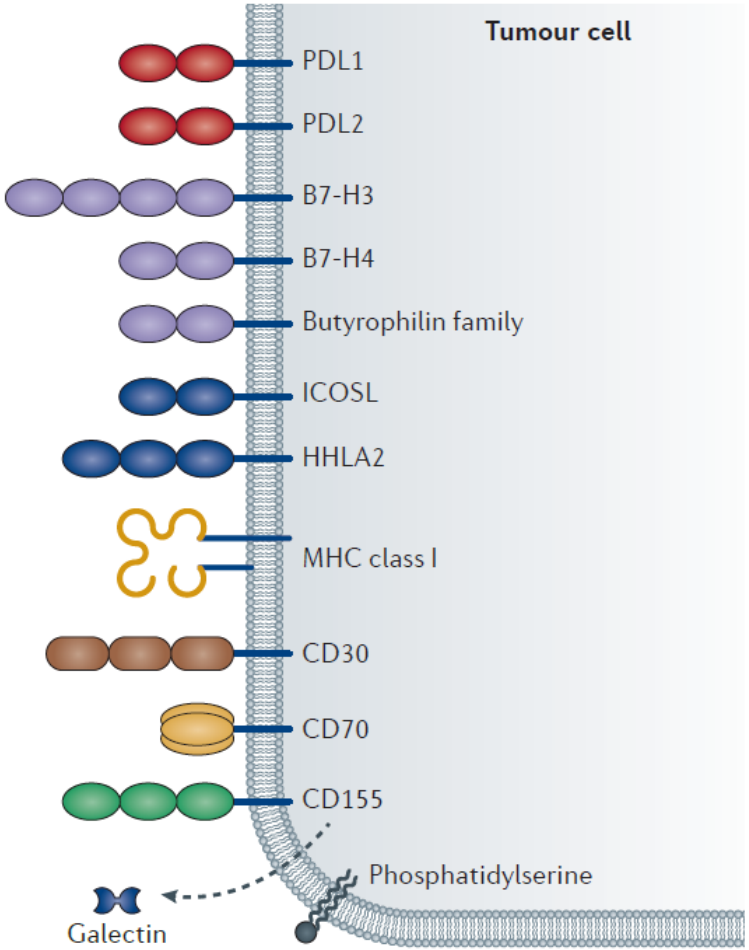


T cell activation is a multiple-signal process



Combination cancer immunotherapy and new immunomodulatory targets - NATURE REVIEWS | DRUG DISCOVERY – VOLUME 14 | AUGUST 2015 - Fig 01

Tumours can express co-inhibitory and co-stimulatory ligands



Ligands	Tumor Expression	Refs
PDL1	Melanoma, renal cell, head and neck, cervical, glioblastoma, bladder, oesophageal, breast, hepatocellular, Hodgkin lymphoma, mediastinal large B-cell lymphoma, among others	189, 196, 223, 230-232
PDL2	Oesophageal, ovarian, pancreatic, hepatocellular, breast, Hodgkin, mediastinal large B-cell lymphoma, among others	233–238
B7-H3	Prostate, renal cell, non-small cell lung, pancreatic, gastric, ovarian, colorectal, urothelial cell, among others	239–246
B7-H4	Breast, renal cell, ovarian, oesophageal, gastric, pancreatic, melanoma, among others	247–257
HHLA2	Breast, lung, thyroid, melanoma, pancreas, ovary, liver, bladder, colon, prostate, kidney, oesophagus	129
Galectins	Non-small cell lung, colorectal, gastric, among others	258–261
CD30	Hodgkin lymphoma, embryonal, anaplastic large cell lymphoma	262
CD70	Non-Hodgkin lymphoma, renal cell	263, 264
ICOSL	Glioblastoma, melanoma	265, 266
CD155	Kidney, prostate, pancreatic, glioblastoma	267

Immunological targets currently in clinical or preclinical development

Immunological pathway	Examples in clinical trials	Most advanced stage of clinical development
CTLA4	Ipilimumab	FDA approved
	Tremelimumab	Phase III
PD1–PDL1	Pembrolizumab (PD1)	FDA approved
	Nivolumab (PD1)	FDA approved
	Atezolizumab (formerly MPDL3280A) (PDL1)	Phase III
	MEDI4736 (PDL1)	Phase III
	Avelumab (PDL1)	Phase I
	PDR001 (PD1)	Phase I
TNF and TNFR superfamilies		
4-1BB–4-1BB ligand	Urelumab, PF-05082566	Phase II
OX40–OX40 ligand	MEDI6469	Phase II
GITR	TRX518	Phase I
CD27	Varlilumab	Phase II
TNFRSF25–TL1A		Preclinical
CD40–CD40 ligand	CP-870893	Phase I
HVEM–LIGHT–LTA		Preclinical
HVEM–BTLA–CD160		Preclinical
IgSF		
LAG3	BMS-986016	Phase I
TIM3		Preclinical
Siglecs		Preclinical
B7 and CD28-related proteins		
ICOS–ICOS ligand		Preclinical
B7-H3	MGA271	Phase I
B7-H4		Preclinical
VISTA		Preclinical
HHLA2–TMIGD2		Preclinical

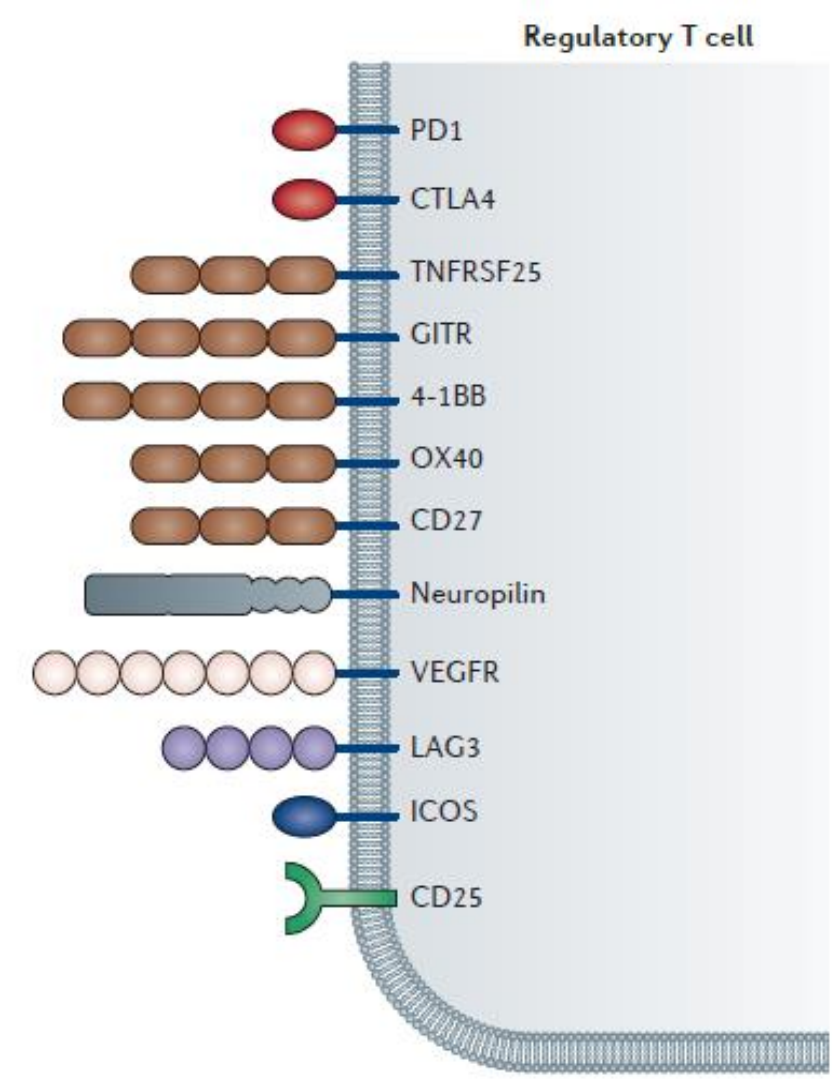
Combination cancer immunotherapy and new immunomodulatory targets - NATURE REVIEWS | DRUG DISCOVERY –VOLUME 14 | AUGUST 2015 - Table 01

Immunological targets currently in clinical or preclinical development

Immunological pathway	Examples in clinical trials	Most advanced stage of clinical development
Butyrophilins, including BTNL2		Preclinical
CD244–CD48		Preclinical
TIGIT and PVR family members		Preclinical
Natural killer cell targets		
KIRs	Lirilumab	Phase II
ILTs and LIRs		Preclinical
NKG2D and NKG2A	IPH2201	Phase I
MICA and MICB		Preclinical
CD244		Preclinical
Suppressive myeloid cells		
CSF1R	Emactuzumab	Phase I
Soluble mediators		
IDO	INCB024360	Phase II
TGFβ	Galunisertib	Phase I
Adenosine–CD39–CD73		Preclinical
CXCR4–CXCL12	Ulocuplumab, BKT140	Phase I/II*
Other		
Phosphatidylserine	Bavituximab	Phase II/III
SIRPA–CD47	CC-90002	Phase I
VEGF	Bevacizumab	FDA approved
Neuropilin	MNRP1685A	Phase I

Combination cancer immunotherapy and new immunomodulatory targets - NATURE REVIEWS | DRUG DISCOVERY –VOLUME 14 | AUGUST 2015 - Table 01 Cont.

Immunoregulatory receptors expressed on the cell surface of regulatory T cells



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PDL2	Oesophageal, ovarian, pancreatic, hepatocellular, breast, Hodgkin, mediastinal large B-cell lymphoma, among others	233–238
B7-H3	Prostate, renal cell, non-small cell lung, pancreatic, gastric, ovarian, colorectal, urothelial cell, among others	239–246
B7-H4	Breast, renal cell, ovarian, oesophageal, gastric, pancreatic, melanoma, among others	247–257
HHLA2	Breast, lung, thyroid, melanoma, pancreas, ovary, liver, bladder, colon, prostate, kidney, oesophagus	129
Galectins	Non-small cell lung, colorectal, gastric, among others	258–261
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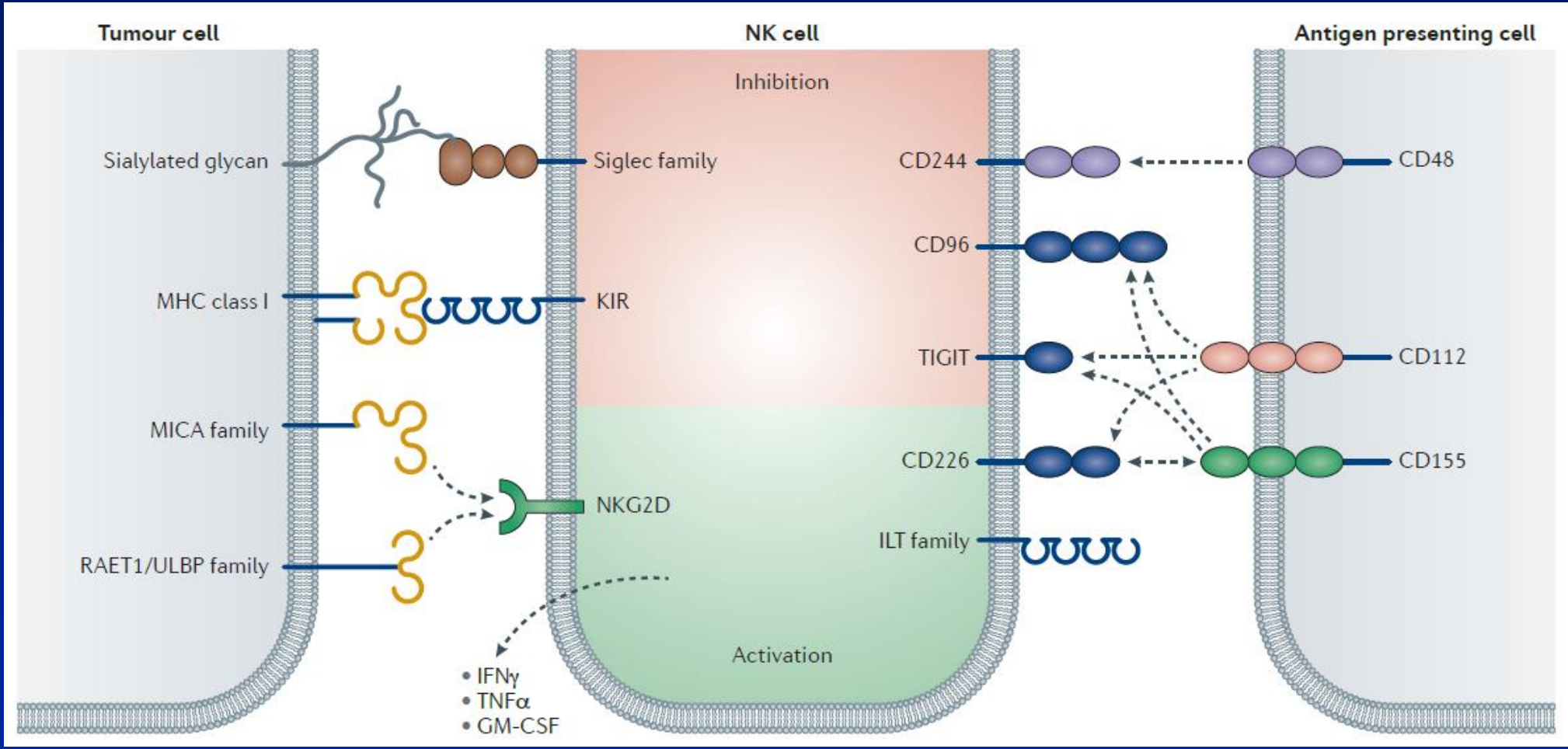
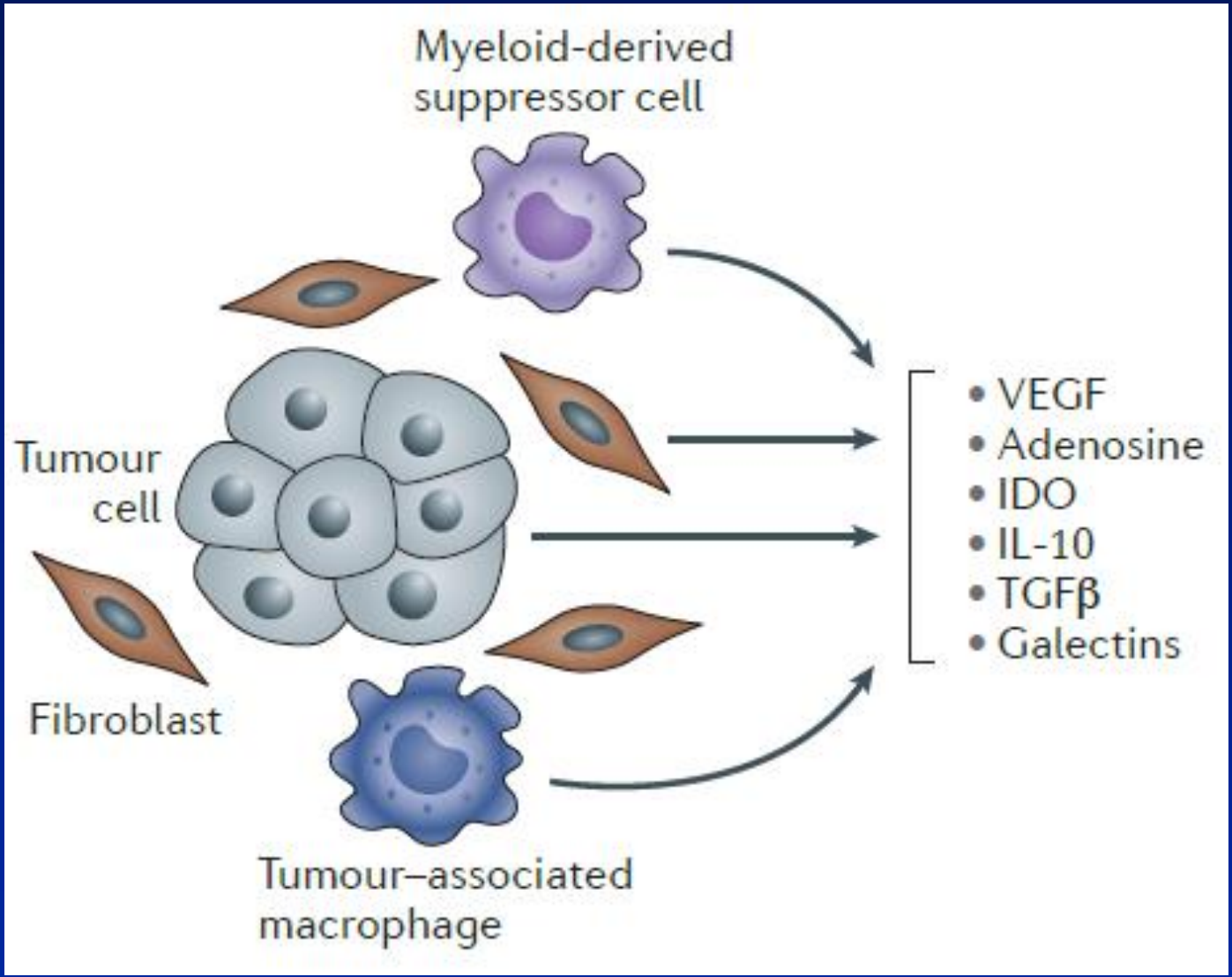
CD70	Non-Hodgkin lymphoma, renal cell	263, 264
ICOSL	Glioblastoma, melanoma	265, 266
CD155	Kidney, prostate, pancreatic, glioblastoma	267

Activating and inhibitory receptors on natural killer cells.



Immunosuppressive factors in the tumour microenvironment



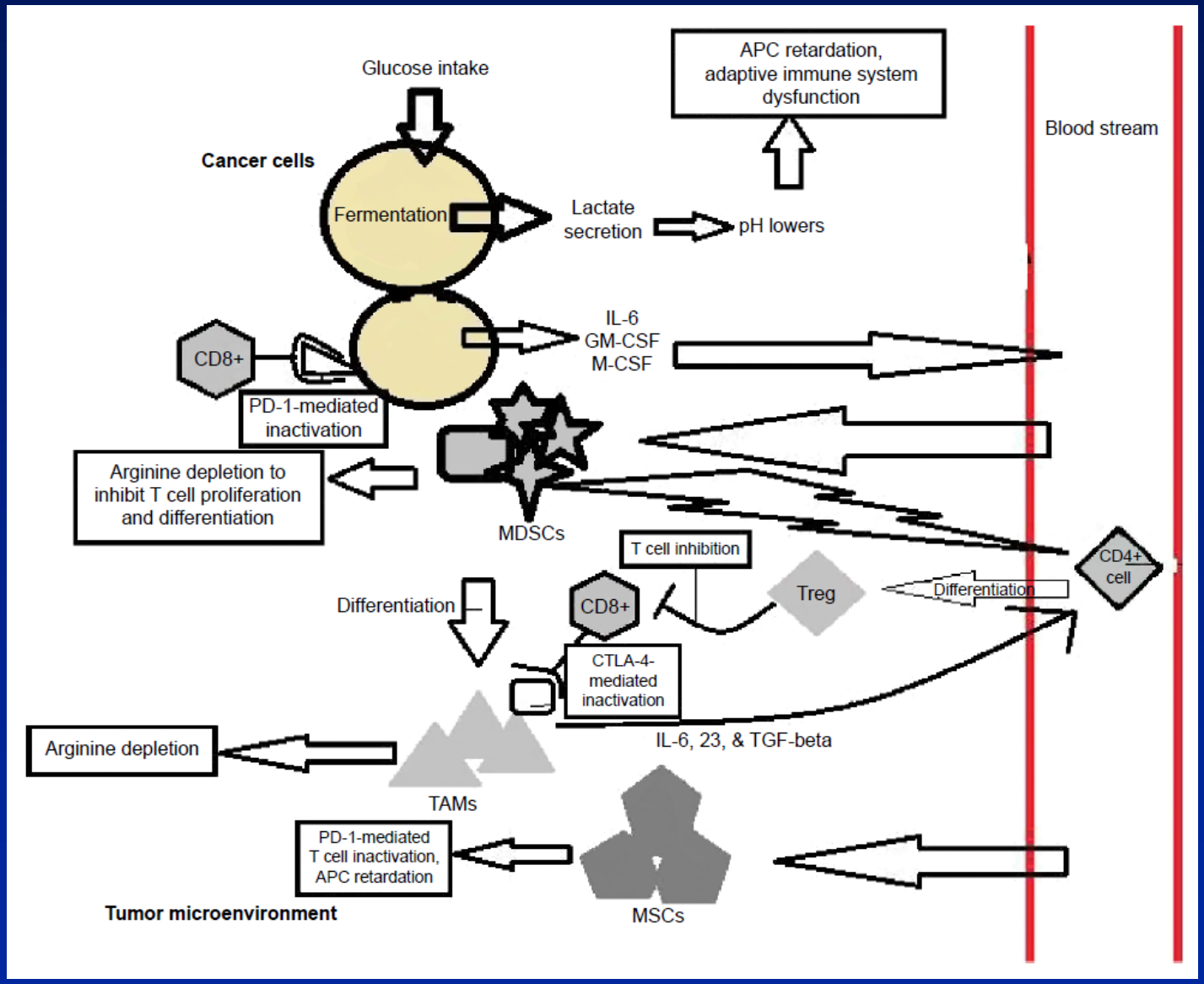
Combination cancer immunotherapy and new immunomodulatory targets - NATURE REVIEWS | DRUG DISCOVERY –VOLUME 14 | AUGUST 2015 - Fig. 05

Anticancer Medications and their Targets

Drugs	*Targets*
VEGF Inhibitors	
Axitinib	VEGF
Bevacizumab	VEGF
Cabozantinib	VEGF, c-KIT, FLT-3, RET, MET, TRKB, AXL, TIE-2
Pazopanib	c-KIT, PDGF, VEGF, c-Fms, FGFR, Itk, Lck
Ramucirumab	VEGF
Regorafenib	c-KIT, ABL, PDGF, VEGF, FGFR, RAF, BRAF, EPHR, RET, TIE-2, DDR2, Trk2A, SAPK2, PTK5
Sorafenib	c-KIT, VEGF, PDGF, FLT-3, RAF, BRAF, p38-alpha
Sunitinib	c-KIT, VEGF, PDGF, FLT-3, CSF-1R, RET
Vandetanib	EGFR, VEGF, BRK, SRC-kinases, EPH-Kinases, RET, TIE-2
Ziv-aflibercept	VEGF
EGFR Inhibitors	
Afatinib	EGFR (Erb1), HER2 (Erb2), HER4 (Erb4)
Erlotinib	EGFR (Erb1)
Gefitinib	EGFR (Erb1)
Lapatinib	EGFR (Erb1), HER2 (Erb2)
Vandetanib	EGFR, VEGF, BRK, SRC-kinases, EPH-Kinases, RET, TIE-2
mTOR Inhibitors	
Sirolimus	mTOR
Everolimus	mTOR
Temsirolimus	mTOR
BCR-ABL Tyrosine Kinase Inhibitors	
Bosutinib	BCR-ABL, SCR (SRC, LYN, HCK), c-KIT, PDGF
Dasatinib	PDGF, c-KIT, BCR-ABL, SRC kinases
Imatinib	PDGF, c-KIT, BCR-ABL
Nilotinib	PDGF, c-KIT, BCR-ABL
Ponatinib	PDGF, c-KIT, FLT-3, BCR-ABL, FGFR, EPHR, SRC kinases, RET, TIE-2

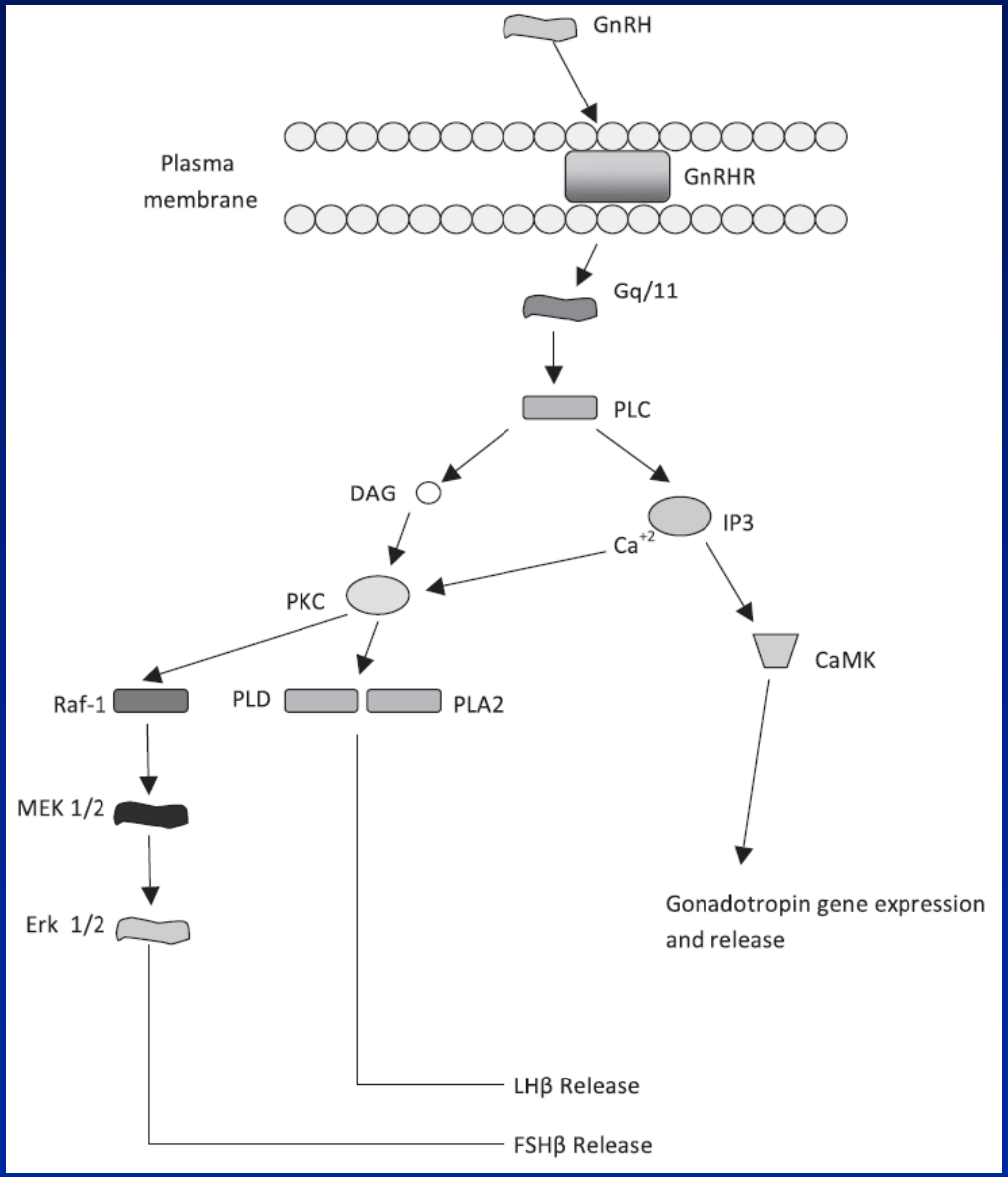
Targeted Cancer Therapy: Class Related Toxicities - DRUG INFORMATION UPDATE: HARTFORD HOSPITAL - VOLUME 79, NO. 2 – Table 01

Summary of the various immune suppression activities by cancer cells and the cancer microenvironment. Actions that directly trigger immune suppression are boxed



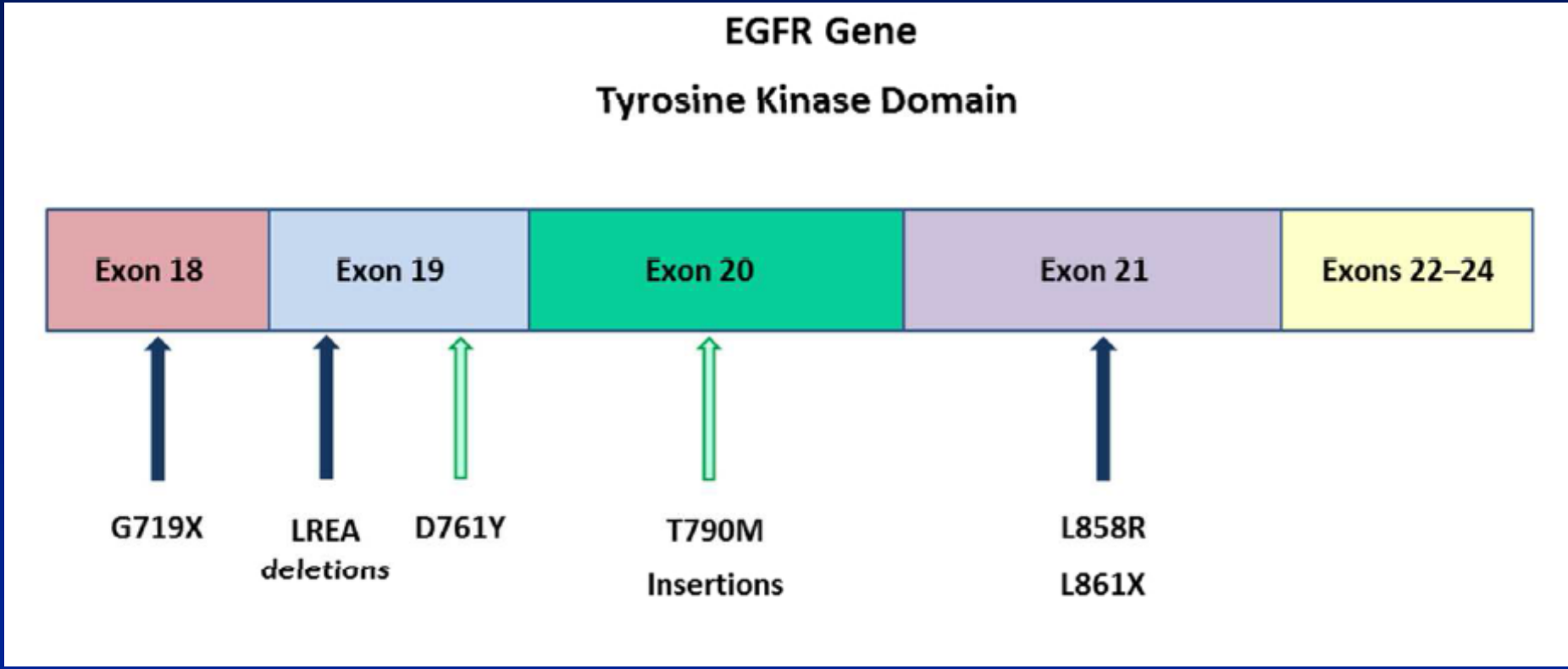
Subverting Subversion: A Review on the Breast Cancer Microenvironment and Therapeutic Opportunities - Clinical Research 2015:9(S2) 7–15 – Fig. 01

The GnRH activating pathways



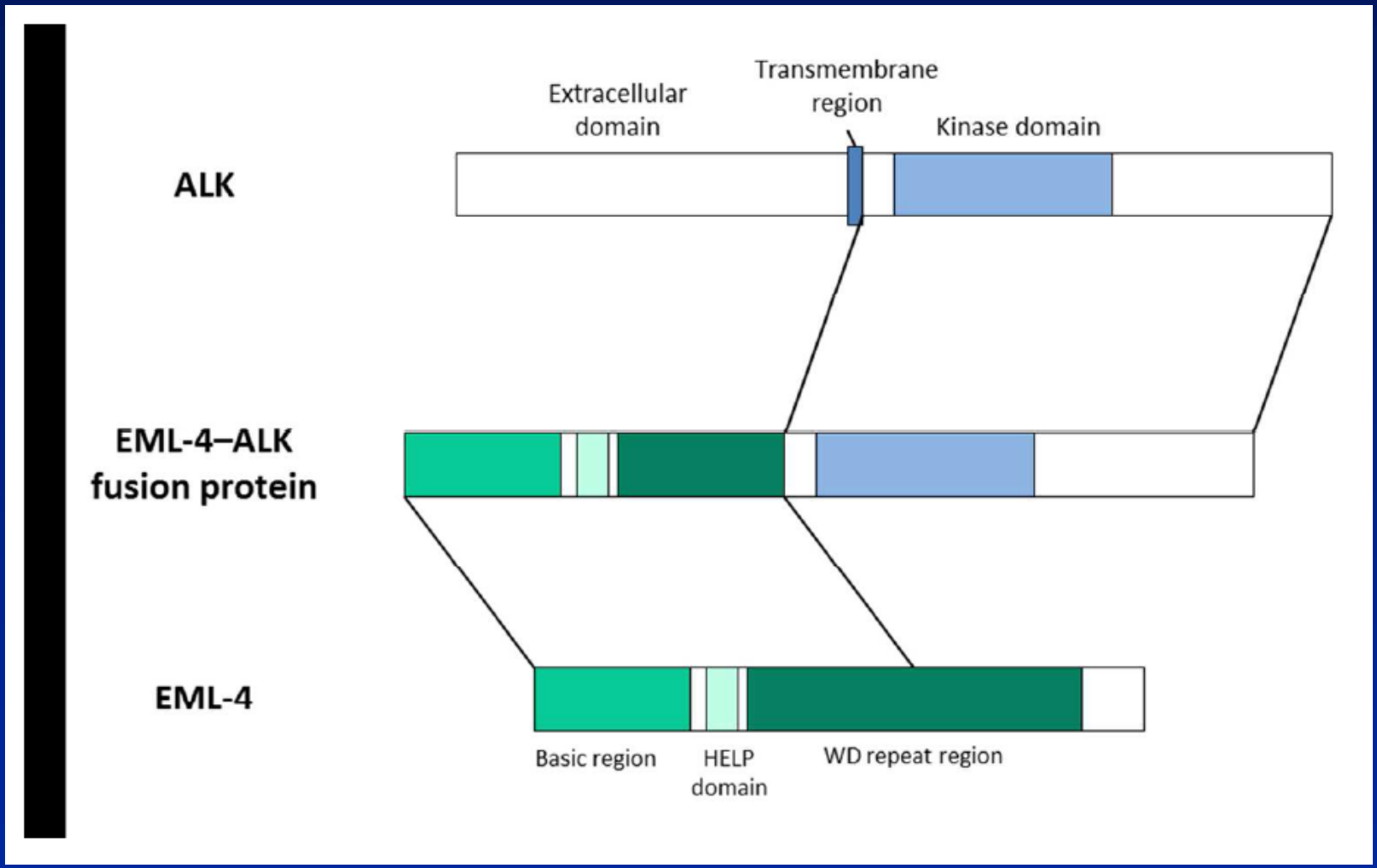
Molecular aspects and clinical methods for preserving ovarian reserves in women receiving cancer treatment - Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663 – Fig 01

Schematic depiction of the EGFR gene and the mutations associated with sensitivity and resistance to drugs

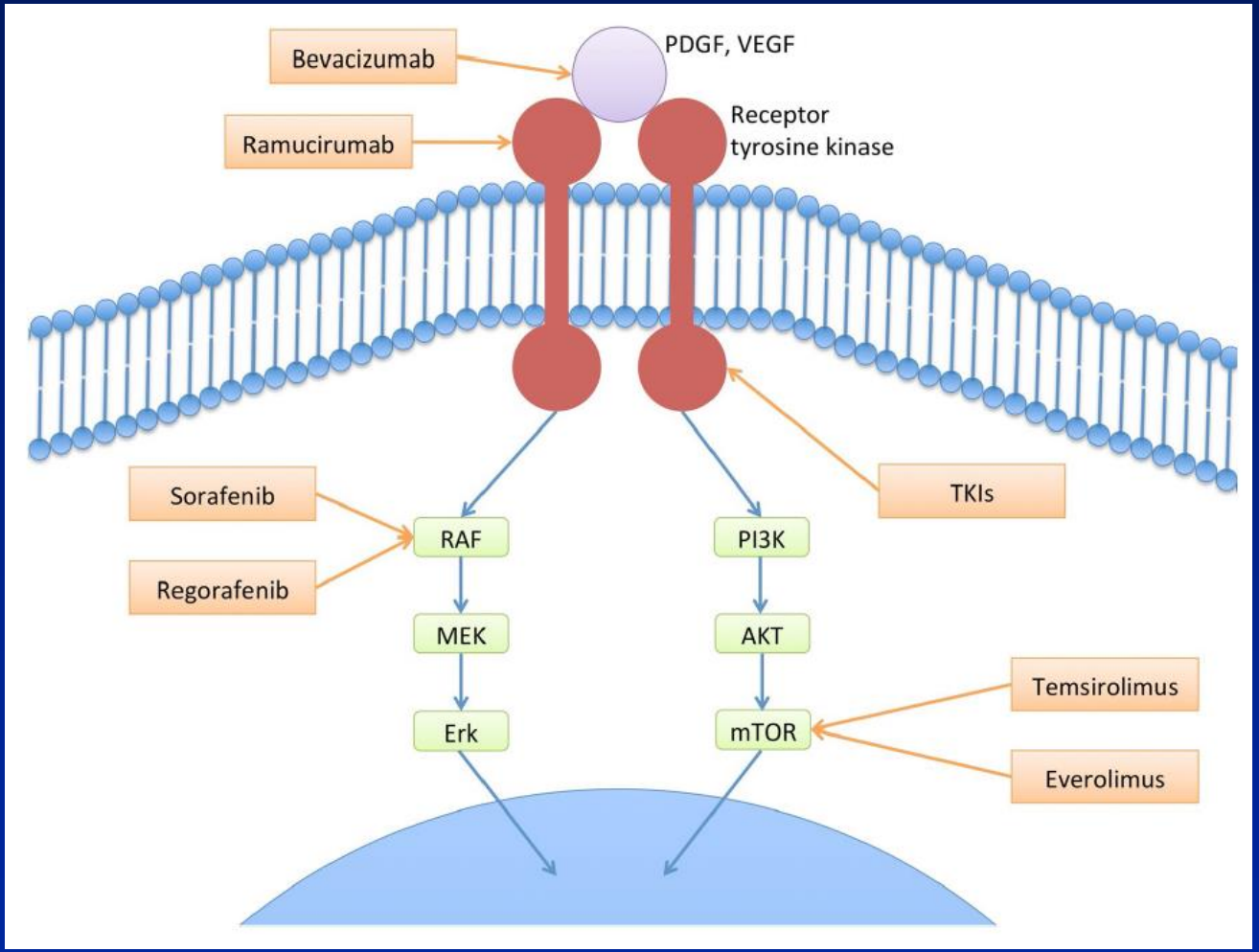


Targeted therapies for treatment of non-small cell lung cancer – recent advances and future perspectives - Int J Cancer - Article version: 30.10.2015 – Fig 01

Schematic depiction of the EML-4–ALK fusion protein



Schematic depiction of tumour angiogenesis signalling pathways



Targeted therapies for treatment of renal cell carcinoma: recent advances and future perspectives - Cancer Chemother Pharmacol (2015) 76:219–233 – Fig 01

Frequent immune-related adverse events reported with immune checkpoint inhibitors.

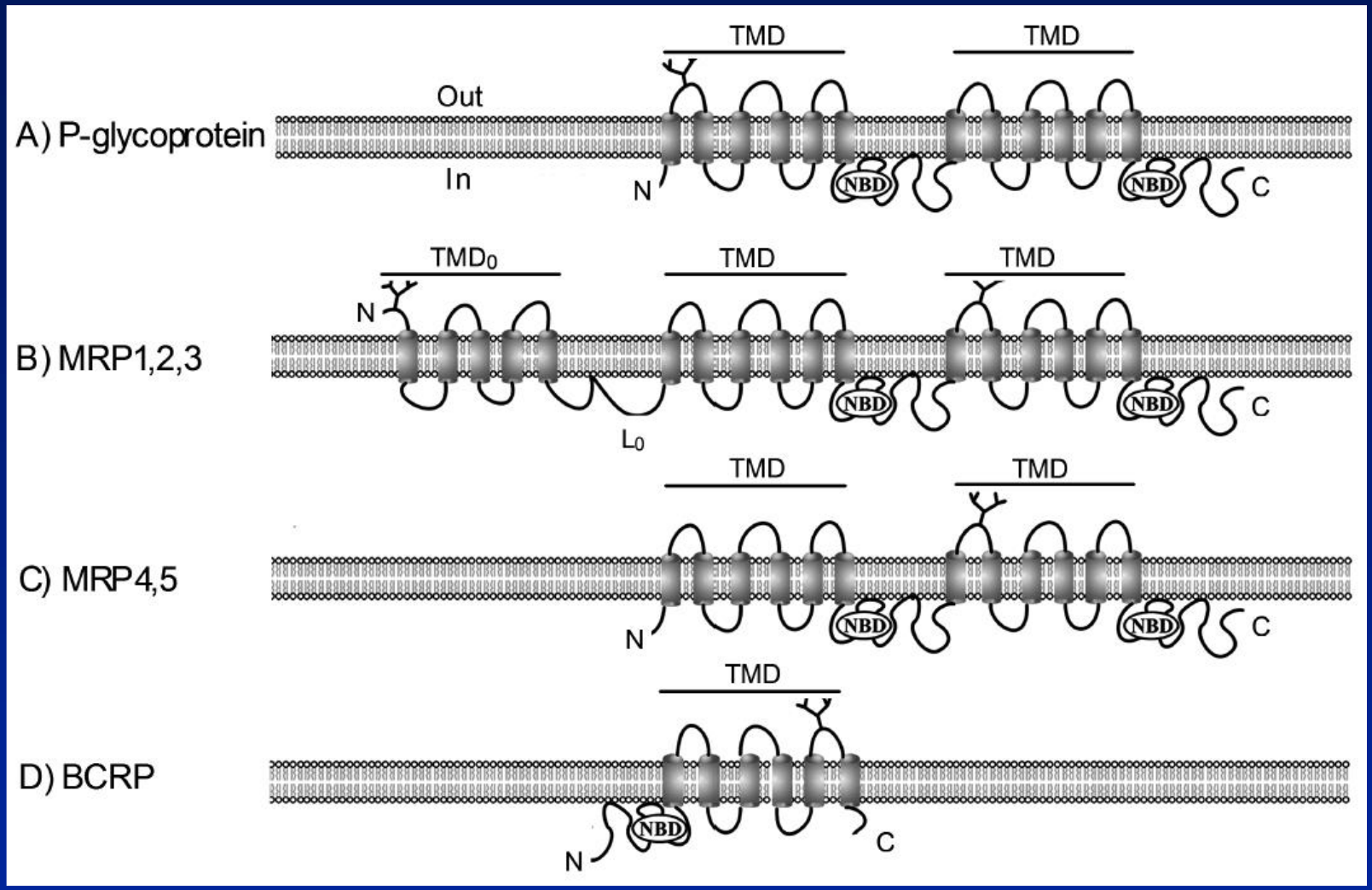
Organ	Adverse events
Dermatological	Pruritus, rash, vitiligo, urticaria, alopecia, pruritic rash, macular rash, hypopigmentation, erythema, erythematous rash
Endocrine	Hypothyroidism, hyperthyroidism, hypopituitarism, hypophysitis, adrenal insufficiency
Gastrointestinal	Diarrhoea, colitis, hepatitis, pancreatitis
Pulmonary	Pneumonitis, pulmonary oedema
Ocular	Uveitis, episcleritis

Some clinically relevant drug efflux transporters of the ATP binding cassette (ABC) family

Protein	Gene name	Polarized localization (in MDCK or kidney cells)	Typical substrates	Inhibitors
MDR1(P-gp)	ABCB	Apical	Vinca alkaloids, Taxanes, Doxorubicin, Mitoxantrone, Etoposide	Verapamil, Cyclosporine, GF120918, Amiodarone
MRP1, MRP2	ABCC	Basolateral, Apical	Etoposide, Vincristine, Doxorubicin, Methotrexate	Cyclosporine, Indomethacin, Probenecid
MRP3	ABCC	Basolateral	Etoposide, Teniposide, Methotrexate, Vincristine	Benzbromarone, Indomethacin, Probenecid
BCRP	ABCG	Apical	Mitoxantrone, Doxorubicin, Daunorubicin, Camptothecin, Etoposide	GF120918, Pantoprazole, Fumitremorgin

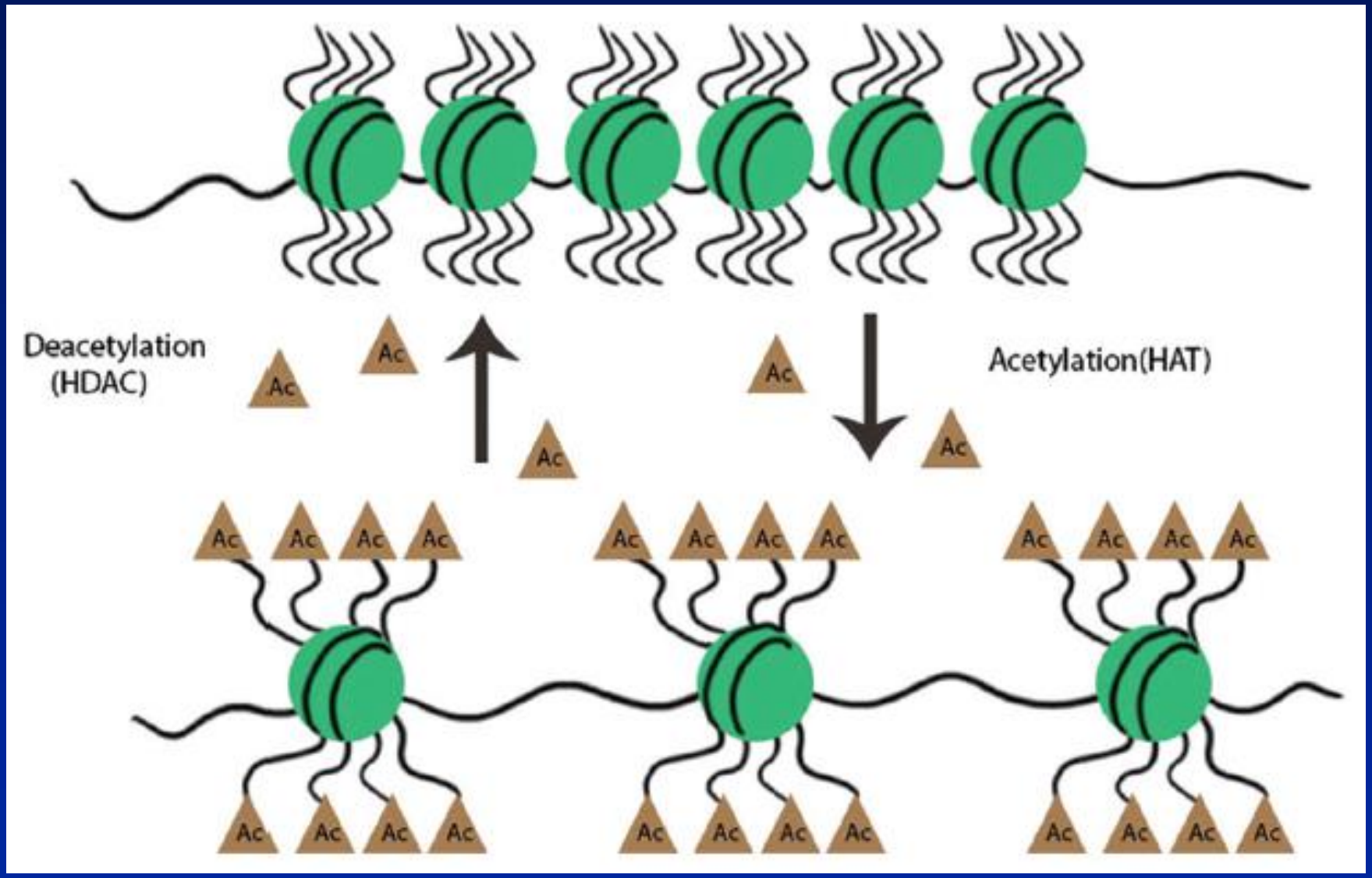
Resveratrol-Mediated Reversal of Tumor Multi-Drug Resistance - Current Drug Metabolism, 2014, 15, 703-710 – Table 01

Structures of ABC transporter family.



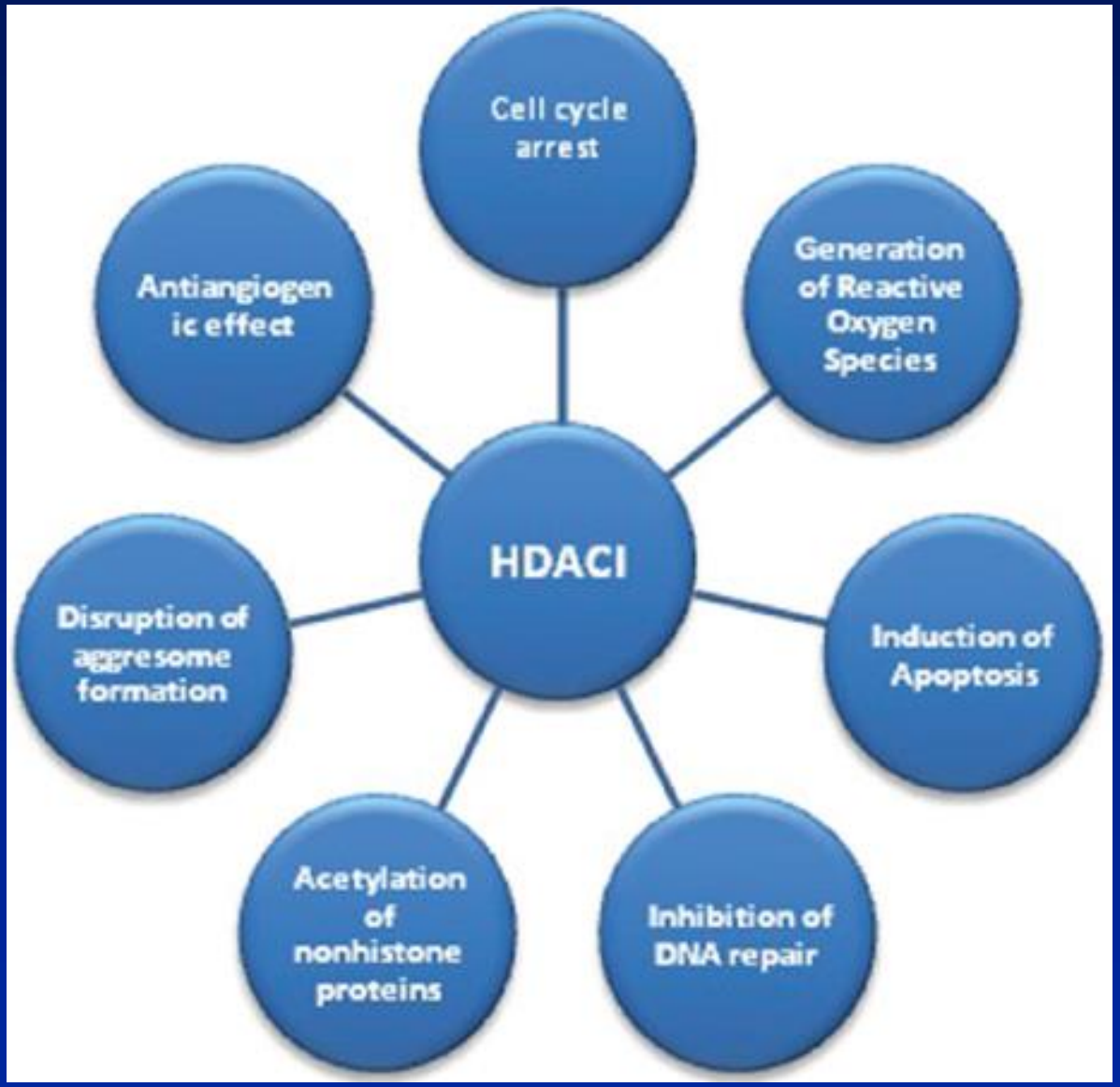
A) P-gp, with 1280 amino acids, is consisting of two transmembrane domains (TMDs) and two nucleotidebinding domains (NBDs); B) MRP1 (1531 amino acids), MRP2 (1545 amino acids) and MRP3 (1527 amino acids) have two TMDs, two NBDs and an extra Nterminal extension (TMD0) with five transmembrane segments connected with a cytoplasmic linker (L0); C) MRP4 (1325 amino acids) and MRP5 (1436 amino acids) both consist of two TMDs and two NBDs; D) BCRP, with 655 amino acids, contains only one TMD and one NBD. Out and In represent extracellular and cytoplasmic, respectively

Regulation of gene expression by histone acetylation



Epigenetic therapy of cancer with histone deacetylase inhibitors - Journal of Cancer Research and Therapeutics - July-September 2014 - Volume 10 - Issue 3 – Fig 01

Mechanisms of action of histone deacetylase inhibitors



Epigenetic therapy of cancer with histone deacetylase inhibitors - Journal of Cancer Research and Therapeutics - July-September 2014 - Volume 10 - Issue 3 – Fig 02

Classification of HDAC

Group	Class	Name	Location in cell	Location in body
Classical (Zn dependent)	Class I (Rpd3)	HDAC1	Nucleus	Ubiquitous
		HDAC2		
		HDAC3		
		HDAC8		
	Class IIa (Hda1)	HDAC4	Nucleus/ cytoplasm	Tissue specific
		HDAC5		
		HDAC7		
		HDAC9		
	Class IIb (Hda1)	HDAC6	Cytoplasm	Tissue specific
		HDAC10		
	Class IV (Rpd3/Hda1)	HDAC11	Nucleus/ cytoplasm	Tissue specific
NAD dependent	Class III	SIRT (1-7)	Nucleus/ cytoplasm	

HDAC=Histone deacetylase, NAD=Nicotinamide adenine dinucleotide, SIRT=Sirtuin

Summary of HDACI

Classification	Drug	HDAC class specificity	Route of administration	Plasma half-life	Dosage
Short chain fatty acids	Sodium butyrate	I, II	IV	9-18 h	
	Phenylbutyrate	I, II	IV		
	Valproic acid	I, II	Oral, IV		50-60 mg/kg/day
Second generation					
Hydroxamic acids	Vorinostat (SAHA)	I, II, IV	Oral	91-127 min	200 mg twice a day
	Belinostat (PXD101)	I, II, IV	Oral, IV	0.3-1.3 h	1 g/m^2 IV D1-D5
	Panabinostat (LBH-589)	I, II	Oral	16 h	20 mg thrice a week
Cyclic peptides	Depsipeptide	I, II	IV, oral	3 h	14 mg/m^2 IV
Synthetic benzamides	Entinostat (MS-275)	I	Oral	60-150 h	5 mg once a week
	Mocetinostat (MGCD0103)	HDAC1	Oral	6-13 h	85 mg thrice a week

HDAC=Histone deacetylase, SAHA=Suberoylanilide hydroxamic acid, HDACI=Histone deacetylase inhibitors, IV=Intravenous

Clinical trials of vorinostat in combination therapy in patients with hematologic malignancies

Disease/phase	Regimen	Number of patients	PFS	Efficacy
Relapsed or refractory multiple myeloma (VANTAGE 088)[53]/(Phase III)	Bortezomib with oral vorinostat (400 mg) or placebo once-daily on days 1-14	317 vorinostat group, 320 placebo group	7.63 months 6.83 months	HR: 0·77 95% CI, 0·64-0·94; (*P*=0·0100)
Relapsed lymphoma[54]/(Phase I)	Vorinostat (escalating doses 400-700 mg BD for 5 days with RICE D3-D5	29	Responses observed in 19 of 27 evaluable patients (70%) including 8 Cru	
AML/MDS[55]/(Phase II)	Vorinostat 500 mg TDS D1-D3 with idarubicin 12 mg/m^2 D4-D6 and cytarabine 1.5 g/m^2 D4-D7	75	Induction mortality 4% ORR 85% (including CR 76%, CR with incomplete platelet recovery 9%: EFS 47 weeks, OS 82 weeks	
Elderly AML[57]/(Phase II)	Vorinostat 400 mg OD D1-D9; gemtuzumab 3 mg/m^2 on D8	31	CR 6 out of 31 (19.4%) CRp 1 out of 31 (3.2%) Median OS in responders 553 days versus 131 days in nonresponders (*P*=0.0026)	
Prevention of GVHD after allogenic HSCT[58]/(Phase I/II)	Mycophenolate mofetil 1 g TDS D0-D28; tacrolimus 0.03 mg/kg/day D3-D100; vorinostat 100/200 mg BD 10 days before HSCT until D100	50	The cumulative incidence of grade 2-4 acute GVHD by day 100 was 22% (95% CI, 13-36)	

AML=Acute myeloid leukemia, MDS=Myelodysplastic syndrome, GVHD=Graft versus host disease, RICE=Rituximab to the ifosfamide-carboplatin-etoposide, TDS=Thrice a day, HSCT=Hematopoietic stem cell transplant, ORR=Overall response rate, Cru=Complete response/unconfirmed, CR=Complete remission, CRp=Complete remission with incomplete platelet recovery, EFS=Event free survival, OS=Overall survival

Trials of vorinostat in combination therapy in patients with solid tumors

Disease	Phase	Regimen	Number of patient	Efficacy
Metastatic breast cancer[61]	I/II	Vorinostat 200/300 mg BD (D1-D3, D8-D10, D15-D17) with paclitaxel 90 mg/m^2 on D2, D9, D16 and bevacizumab 10 mg/kg D2 and D16 q 28 days	54	ORR: 24/54 (55%)
Hormone therapy resistant breast cancer[62]	II	Vorinostat 400 mg/day for 3 weeks in 28 day cycle and tamoxifen 20 mg/day	43	ORR: 19% Clinical benefit rate 40%
Refractory colorectal cancer[63]	II	Vorinostat 800 or 1400 mg/day for 3 days and 5 FU and LV on D2 and D3 q 2 weeks	Low dose: 15 High dose: 43	2 month PFS rate Low dose: 8/15 (53%) High dose: 23/43 (53%)
Gastrointestinal carcinoma. PRAVO[64]	I	Pelvic radiation 30 Gy in 3 Gy/day fractions over 2 weeks, and escalating dose of vorinostat 100-400 mg/day	16	Well tolerated, MTD of vorinostat with radiation 300 mg OD

PRAVO=Pelvic Radiation and Vorinostat, FU=Fluorouracil, LV=Leucovorin, ORR=Overall response rate, PFS=Progression-free survival, MTD=Maximum tolerated dose

Trials of panabinostat and belinostat

Disease	Phase	Regimen	Number of patients	Efficacy
Medullary thyroid cancer and differentiated thyroid cancer[65]	II	Panabinostat 20 mg oral three times a week	13	SD: 7 Median PFS: 3.6 months (95% CI, 1.8-5.8)
Relapsed and bortezoib refractory multiple myeloma (PANORAMA 2)[66]	II	Panabinostat Dexamethasone Bortezomib	55	ORR: 34.5% (1 near CR, 18 PR) clinical benefit rate 52.7%
Platinum resistant EOC and LMP ovarian tumors[67]	II	Belinostat: 1 g/m^2 IV on days 1-5 of a 21-day cycle	32	EOC: SD 9/15 patients LMP: PR 2/12 patients
Advanced solid tumors (the Phase I part of the study) and soft tissue sarcoma (the Phase II part of the study) (CLN14)[68]	I/II	Belinostat 1000 mg/m^2 days 1-5 with 75 mg/m^2 doxorubicin on day 5 in a three-week schedule	25 (Phase I) 20 (Phase II)	72% disease control. Four objective responses one CR, and 25 patients had SD)

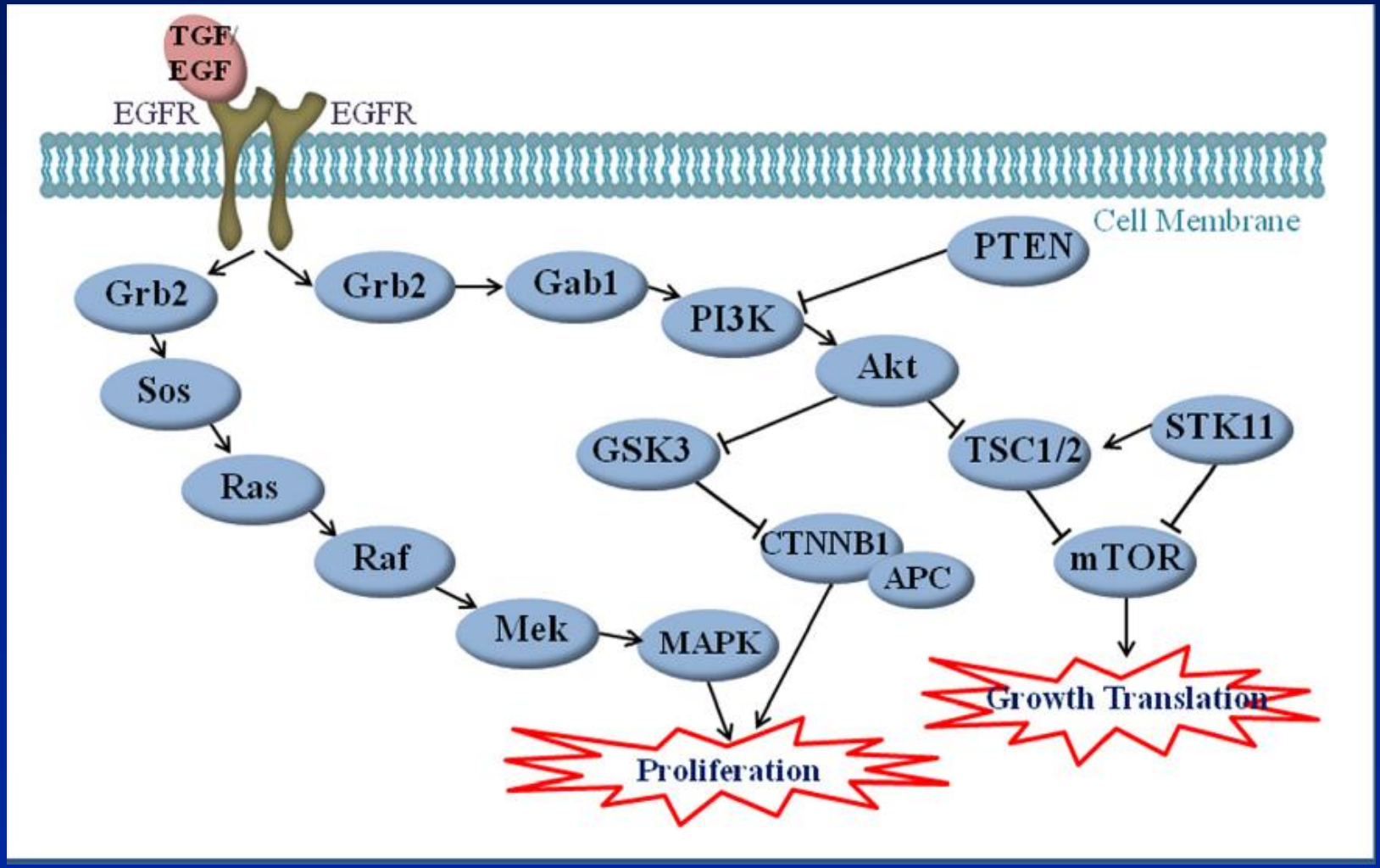
EOC=Epithelial ovarian cancer, LMP=Low malignant potential, IV=Intravenous, PFS=progression-free survival, CI=Confidence interval, ORR=Overall response rate, CR=Complete response, PR=Partial response, SD=Stable disease, PANORAMA=PANabinostat ORAl in Multiple myelomA

Trials of mocetinostat and entinostat

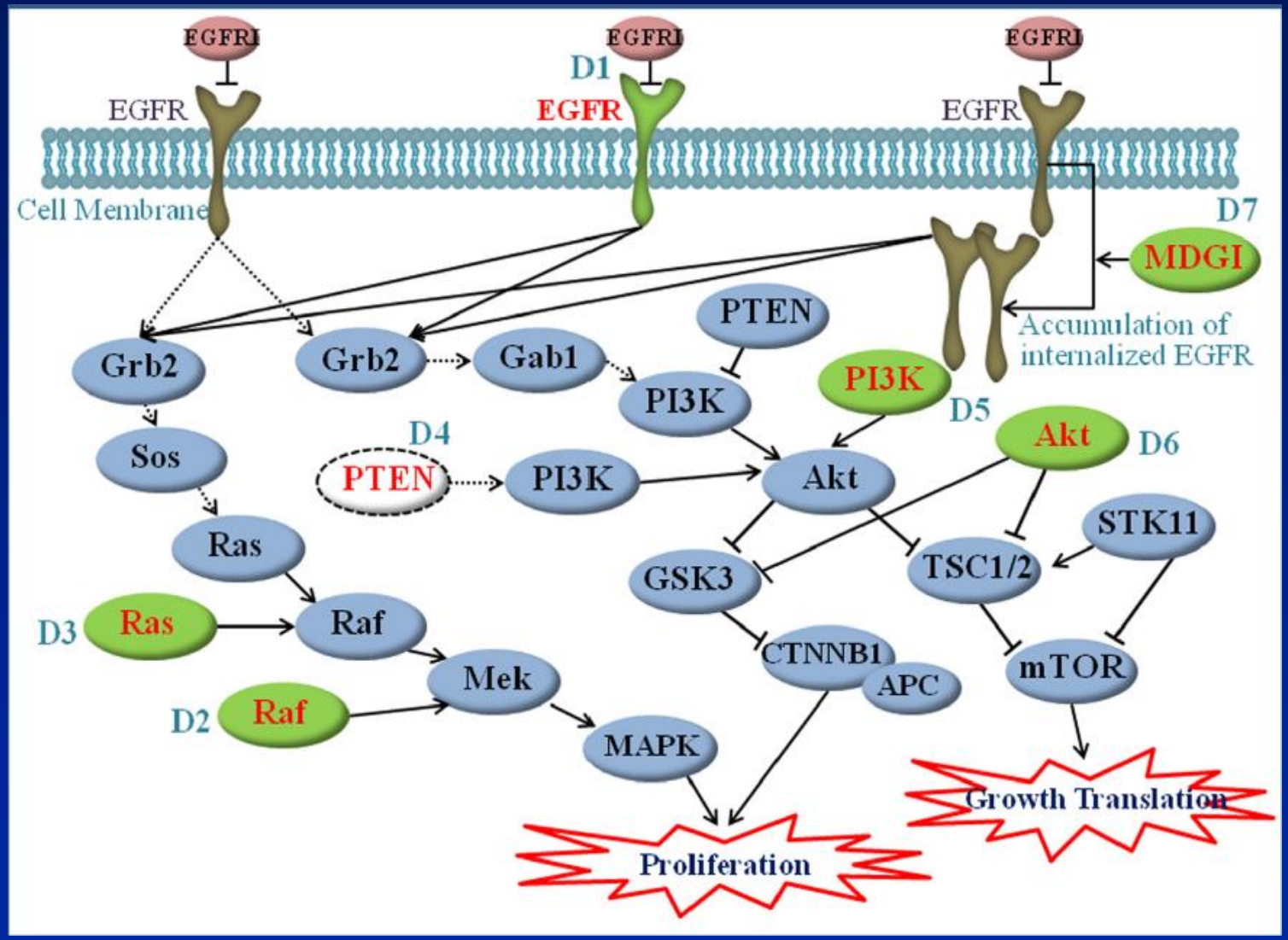
Disease	Phase	Regimen	Number of patient	Efficacy
Relapsed classical Hodgkin lymphoma[74]	II	Mocetinostat 85 mg/110 mg thrice a week in 28 day cycle	51	Disease control rate 7/28 (25%) in 85 mg group 8/23 (35%) in 110 mg group
Relapsed/ refractory MDS/AML[75]	II	5 AZA 75 mg/m^2 s/c for 7 days; mocetinostat 35 mg 3 times a week beginning on D5	MDS 28 AML 38	ORR MDS 61%, AML 32% Median OS MDS 12.9 months, AML 5.1 months
Recurrent/ metastatic breast cancer (ER positive)[77]	II	Entinostat 5 mg once a week with exemestane 25 mg/day (EE) or Exemestane and placebo (EP)	130	Median PFS EE: 4.3 months EP: 2.3 months HR: 0.73 *P*=0.055

ER=Estrogen receptor, MDS=Myelodysplastic syndrome, AML=Acute myeloid leukemia, ORR=Overall response rate, OS=Overall survival, PFS=Progression-free survival, EE=Entinostat and exemestane, EP=Exemestane and placebo, HR=Hazard ratio

Map of the major signaling pathways of the EGFR and downstream effectors relevant to cancers. Binding of specific ligands (e.g., EGF, heparin-binding EGF, TGF-a)may generate homodimeric complexes resulting in conformational changes in the intracellular EGFR kinase domain, which lead to autophosphorylation and activation

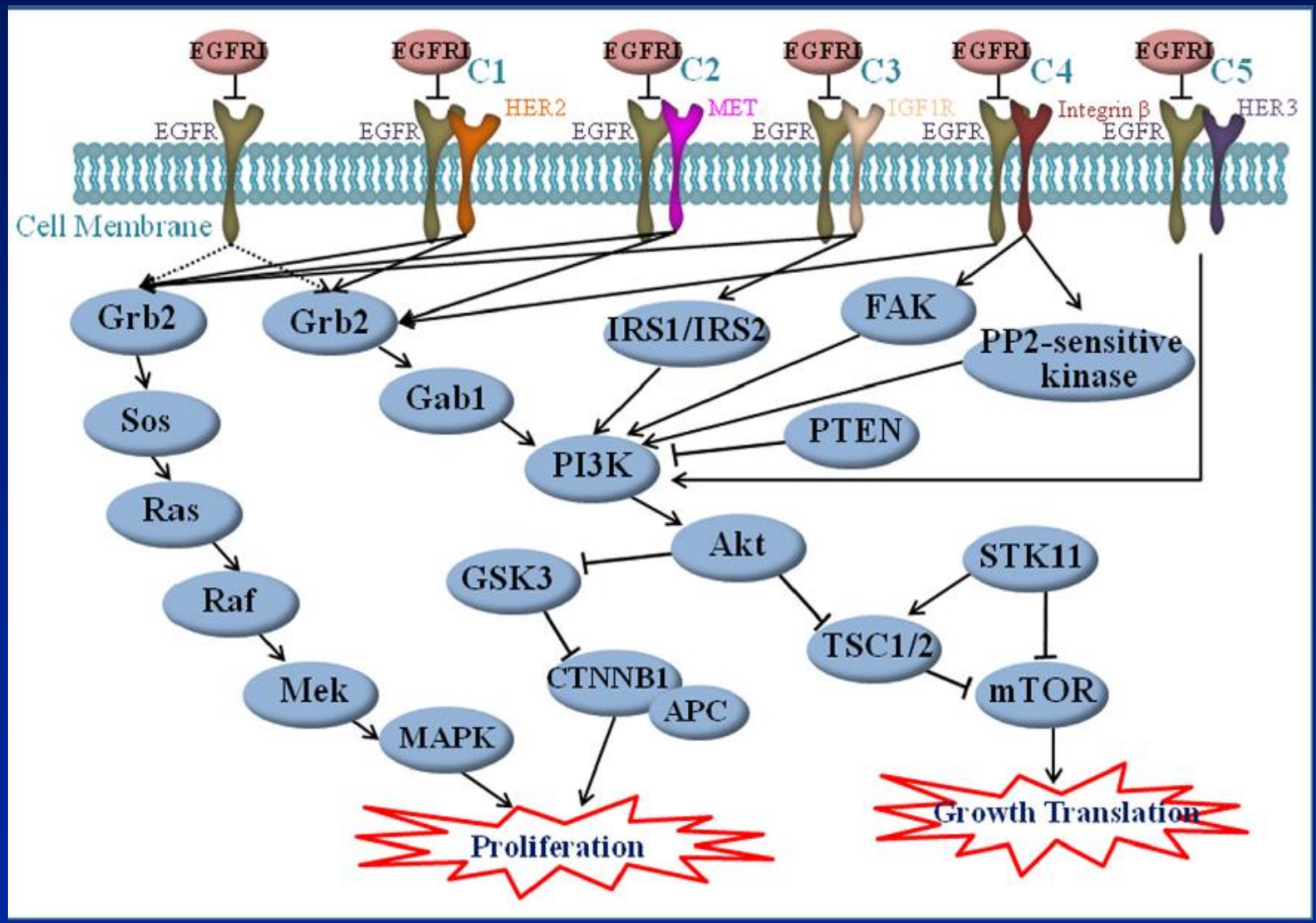


Map of EGFR pathway showing EGFR tyrosine kinase inhibitor (EGFRI) bypass mechanisms due to downstream EGFR-independent signaling involving mutationsresistant to EGFRI (D1), activating mutations in Raf (D2), Ras (D3), PI3K (D5), and AkT (D6), PTEN loss of function (D4), and enhanced accumulation of internalized EGFR byMDGI (D7)

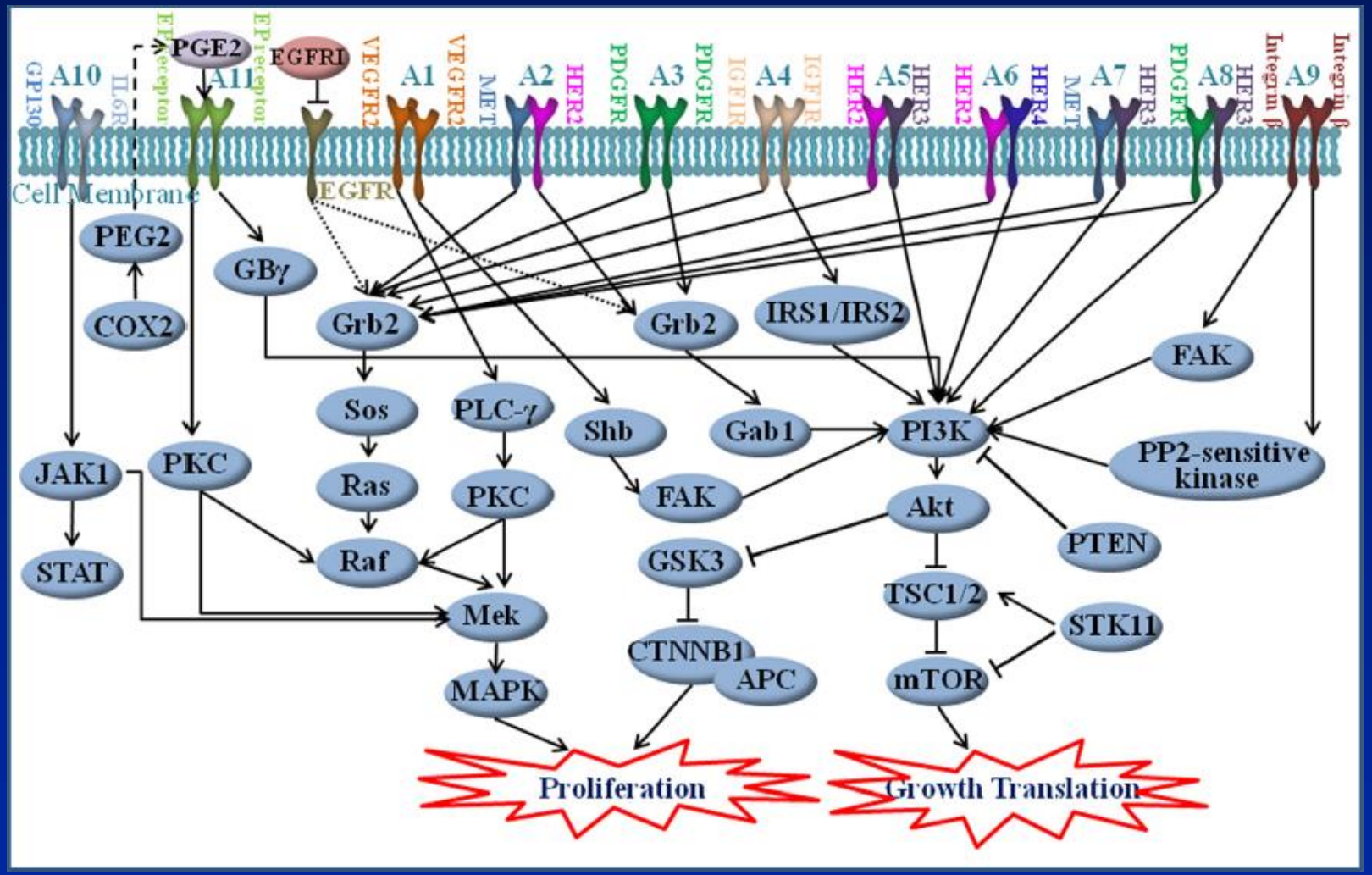


Co-targeting cancer drug escape pathways confers clinical advantage for multi-target anticancer drugs - Pharmacological Research 102 (2015) 123–131 - Fig 02

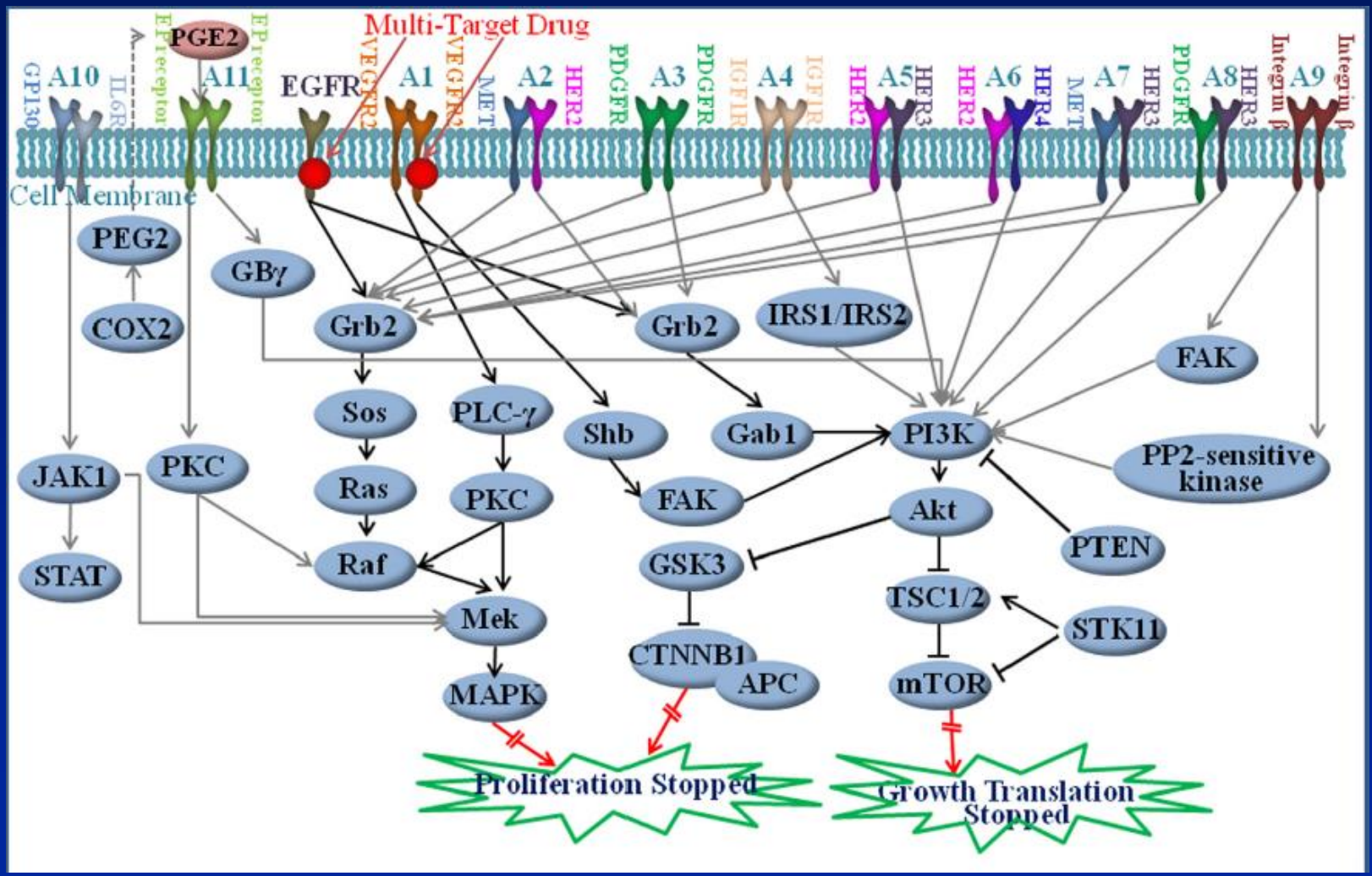
Map of EGFR pathway showing EGFR tyrosine kinase inhibitor (EGFRI) bypass mechanisms due to compensatory signaling of EGFR transactivation with HER2 (C1), MET(C2), IGF1R (C3), Integrin β1 (C4), and HER3 (C5). In particular, C3, C4 and C5 activates PI3K via IRS1/IRS2, FAK or a PP2-sensitive kinase, and direct interaction respectively



Map of EGFR pathway showing EGFR tyrosine kinase inhibitor (EGFR-I) bypass mechanisms due to alternative signaling of VEGFR2 activation (A1), HER2–METtransactivation (A2), PDGFR activation (A3), IGF1R activation (A4), HER2–HER3 transactivation (A5), HER2–HER4 transactivation (A6), MET–HER3 transactivation (A7),PDGFR–HER3 transactivation (A8), Integrin β1 activation (A9), IL6 activation of IL6R–GP130 complex (A10), and Cox2 mediated activation of EP receptors (A11)



Map of EGFR pathway showing EGFR tyrosine kinase inhibitor bypass mechanisms due to alternative signaling of VEGFR2 activation (A1), HER2–MET transactivation(A2), PDGFR activation (A3), IGF1R activation (A4), HER2–HER3 transactivation (A5), HER2–HER4 transactivation (A6), MET–HER3 transactivation (A7), PDGFR–HER3 trans-activation (A8), Integrin a/ß activation (A9), IL6 activation of IL6R–GP130 complex (A10), and Cox2 mediated activation of EP receptors (A11).



Co-targeting cancer drug escape pathways confers clinical advantage for multi-target anticancer drugs - Pharmacological Research 102 (2015) 123–131 - Fig 06

Statistics of the approved, clinical trials, and discontinued multi-target anticancer drugs targeting and not targeting a known cancer drug escape pathway

Drug category	Total no. of multi-target drugs	No. (%) of multi-target drugs targeting a known cancer drug escape pathway	No. (%) of multi-target drugs not targeting any known cancer drug escape pathway
Approved	23	17 (73.9%)	6 (26.1%)
Phase III	20	15 (75.0%)	5 (25.0%)
Phase II	43	27 (62.8%)	16 (37.2%)
Phase I	56	30 (53.6%)	26 (46.4%)
Discontinued	17	6 (35.3%)	11 (64.7%)
Total	159	94 (59.1%)	65 (40.9%)

Co-targeting cancer drug escape pathways confers clinical advantage for multi-target anticancer drugs - Pharmacological Research 102 (2015) 123–131 - Table 01

Cancer escape pathways targeted by the approved, clinical trial, and discontinued multi-target anticancer drugs

Drug class	Targeted cancers	No. of known cancer drug-escape pathways	No. of drug escape regulatory proteins	Drug escape regulatory protein (escape pathway) targeted by multi-target anticancer drugs	No. of multi-target anticancer drugs targeting the bypass protein					Total no. of multi-target drugs targeting/not targeting a known drug escape pathway
					Approved	Phase III	Phase II	Phase I	Discontinued	
EGFR inhibitor	Lung, pancreatic, colon, head and neck, liver, brain	14	18	HER2 (ErbB)	2	3	3	5	0	19/0
				HER3 (ErbB)	0	0	5	0	0	
				VEGFR2 (VEGF)	1	0	0	0	0	
				IGF1R (IGFR)	0	0	1	0	0	
				ALK (ALK)	0	0	1	0	0	
HER2 inhibitor	Breast	7	11	EGFR (ErbB)	2	3	3	5	0	14/1
				HER3 (ErbB)	0	0	3	0	0	
BCR-Abl inhibitor	Leukemia	13	20	Src (SFK-dependent)	2	0	1	0	2	11/2
				Aurora (Aurora)	0	0	2	0	1	
				PDGFR(PDGFR & SFK-dependent)	2	0	0	0	0	
				Kit (Kit)	2	0	0	0	0	
				Fyn (SFK-dependent)	1	0	1	0	0	
				Lyn (SFK-dependent)	0	0	1	0	0	
				JAK2 (Jak2/Stat5, apoptosis)	0	0	1	0	0	
				Flt3 (Flt3)	0	0	0	0	1	
VEGFR2 inhibitor	GIST, kidney, liver, renal, lung, colon, breast, AML leukemia, solid tumor	20	28	PDGFR (PDGFR)	6	4	3	2	1	37/6
				VEGFR3 (VEGF)	3	4	2	5	0	
				c-Met (HGFR)	1	0	3	1	0	
				FGFR (FGFR)	2	4	3	2	0	
				Kit (Kit)	3	2	2	2	1	
				EGFR (ErbB)	1	1	0	0	0	
				CSF-1R (CSF1R mediated pathways)	1	1	0	0	0	
				Heparanase (SFK-RTK)	0	0	1	0	0	
				Raf (MAPK)	1	0	0	1	0	

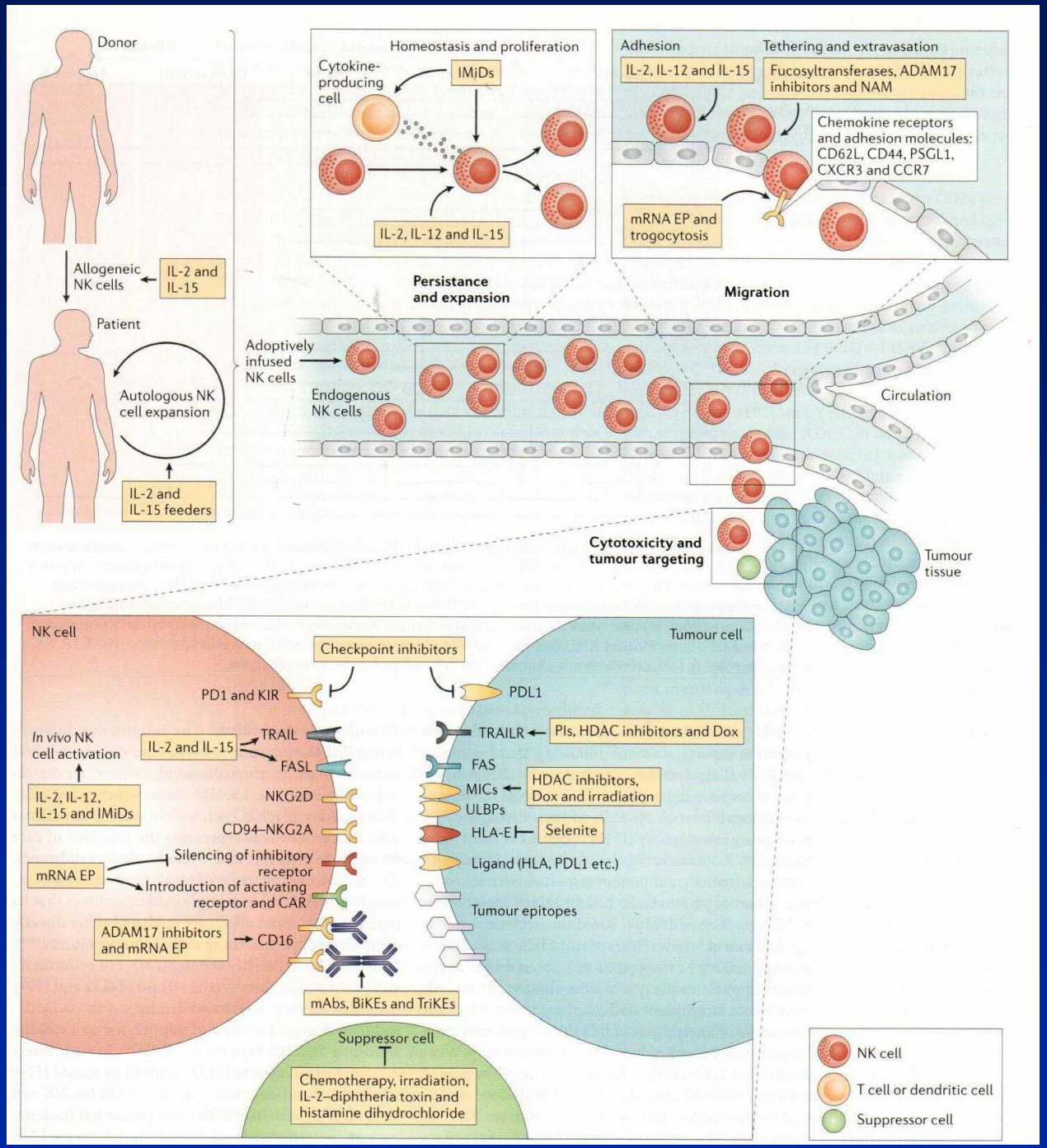
Co-targeting cancer drug escape pathways confers clinical advantage for multi-target anticancer drugs - Pharmacological Research 102 (2015) 123–131 - Table 02

Cancer escape pathways targeted by the approved, clinical trial, and discontinued multi-target anticancer drugs (Cont.)

Drug class	Targeted cancers	No. of known cancer drug-escape pathways	No. of drug escape regulatory proteins	Drug escape regulatory protein (escape pathway) targeted by multi-target anticancer drugs	No. of multi-target anticancer drugs targeting the bypass protein					Total no. of multi-target drugs targeting/not targeting a known drug escape pathway
					Approved	Phase III	Phase II	Phase I	Discontinued	
mTOR inhibitor	Breast, brain, lung, renal, solid tumor	6	7	PI3K (Akt-mTOR)	0	0	4	5	0	9/1
PI3K inhibitor	Breast, brain, NSCLC, solid tumor	5	5	mTOR (Akt-mTOR)	0	0	4	5	0	12/0
				Akt (Akt-mTOR)	0	0	0	1	0	
				Plk1 (Plk-PTEN-Akt)	0	1	0	0	0	
				HDAC (HDAC-histone H3 acetylation –Akt)	0	0	0	1	0	
Alk inhibitor	Non-small cell lung cancer	7	6	ROS1 (FIG-ROS1)	2	0	0	1	0	6/1
				c-MET (HGFR)	1	0	0	0	0	
				IGF1R (IGFR)	1	0	0	0	0	
				EGFR (ErbB)	0	0	1	0	0	
				TRK (TRK)	0	0	0	2	0	
				RET (RET)	1	0	0	0	0	
Mek inhibitor	Solid tumor	2	3	Raf (MAPK)	0	0	0	4	0	5/0
				MEKK (MAPK)	0	0	0	1	0	
Kit inhibitor	Solid tumor, melanoma, pancreas	4	5	PDGFR (PDGFR)	4	5	2	1	1	13/1
DNA Topoiso-merase inhibitor	Breast, head and neck, leukemia, ovary, prostate	10	20	XIAP (Apoptosis)	0	1	0	0	0	1/11

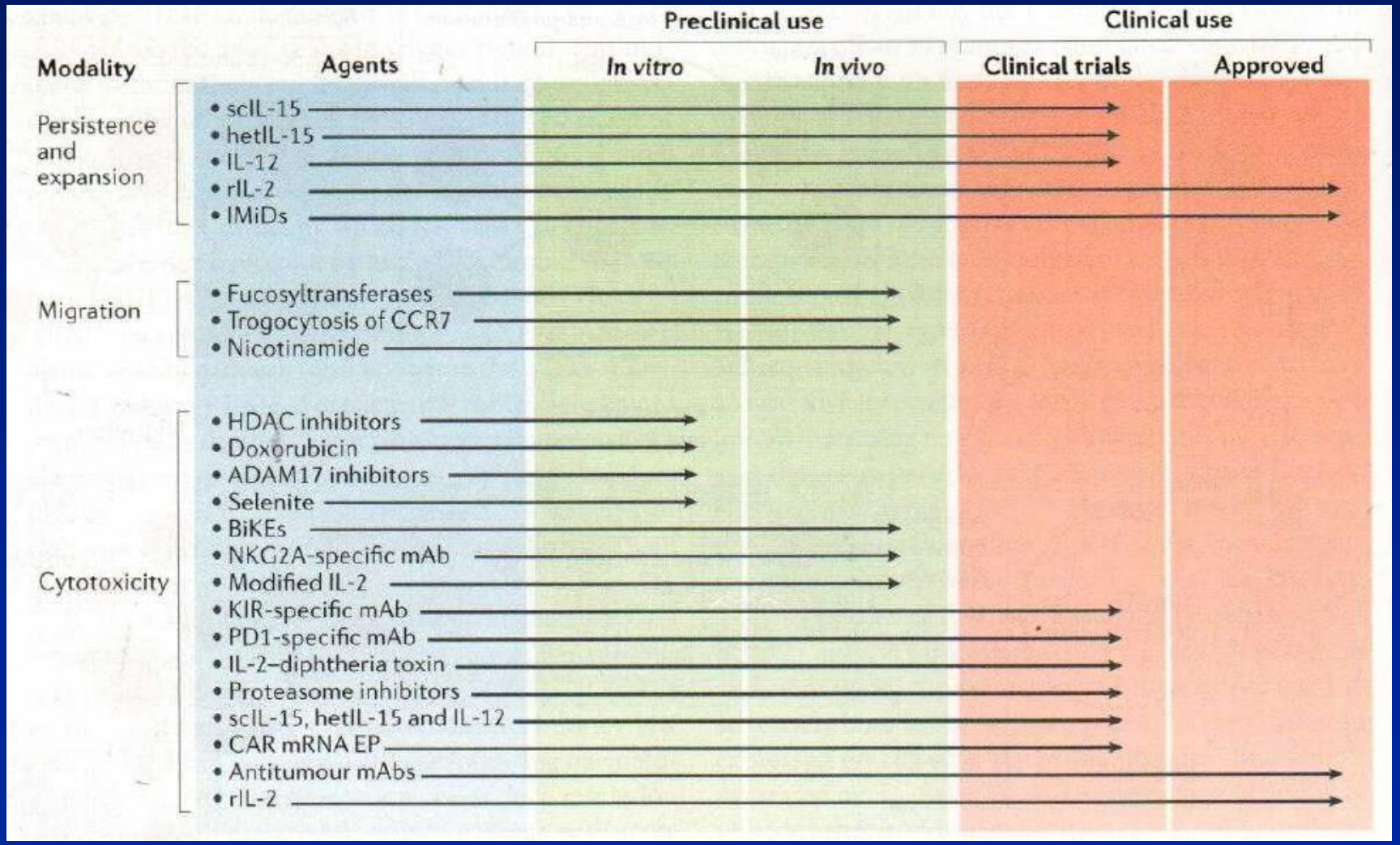
Co-targeting cancer drug escape pathways confers clinical advantage for multi-target anticancer drugs - Pharmacological Research 102 (2015) 123–131 - Table 02 – Cont.

Schematic overview of drugs that bolster NK cell antitumour immunity and their interaction points



Therapeutic approaches to enhance natural killer cell cytotoxicity against cancer: The force awakens
Nature Reviews Drug Discovery 14, 487-498 (2015) – Fig 01

Development status of drugs designed to augment NK cell antitumour immunity



Therapeutic approaches to enhance natural killer cell cytotoxicity against cancer: The force awakens
Nature Reviews Drug Discovery 14, 487-498 (2015) – Fig 02

Clinical studies evaluating the ability of drugs to bolster NK cell antitumour immunity

Drug	Effect on NK cells	Patient population	Clinical trials (number of active trials)	Comments
Cytokines				
IL-2	↑Persistence and expansion; ↑cytotoxicity	Melanoma, RCC, AML, neuroblastoma, breast cancer, ovarian carcinoma, Fallopian tube cancer and peritoneal cancer	6 (2)	Some studies combined IL-2 with antitumour mAbs
IL-15	↑Persistence and expansion; ↑cytotoxicity	Melanoma, RCC, lung cancer, SCC and multiple myeloma	4 (3)	Single-chain recombinant IL-15 and heterodimeric IL-15 used
IL-12	↑Migration; ↑cytotoxicity	Healthy volunteers	1 (1)	Lower doses used than initial studies
Cytokines after NK cell infusion				
IL-2	↑Persistence and expansion; ↑cytotoxicity	AML and myelodysplastic syndromes	58 (30)	Lower doses used than initial studies
IL-15	↑Persistence and expansion; ↑cytotoxicity	AML	3 (2)	Intended to more specifically bolster NK cell antitumour activity compared to IL-2
Checkpoint inhibitors				
PD1-specific mAbs	↑Cytotoxicity	Solid tumours and multiple myeloma	2 (2)	Used in combination with IPH2102 (lirilumab)
KIR-specific mAbs	↑Cytotoxicity	Multiple myeloma, AML, melanoma, lung cancer and peritoneal cancer	9 (4)	IPH2101 and IPH2102 (lirilumab) used
Other immunomodulatory drugs				
Lenalidomide	↑Persistence and expansion; ↑cytotoxicity	Multiple myeloma, BCL and neuroblastoma	15 (10)	–
Tumour-targeting mAbs				
CD20-specific mAbs	↑Cytotoxicity	BCL and multiple myeloma	10 (4)	Mostly rituximab but veltuzumab also used
GD2-specific mAbs	↑Cytotoxicity	Neuroblastoma	6 (5)	Several different GD2-specific mAbs are being evaluated
EGFR-specific mAbs	↑Cytotoxicity	SCC	4 (3)	Cetuximab used in all studies
ERBB2-specific mAbs	↑Cytotoxicity	Breast cancer	2 (1)	Trastuzumab used in all studies
Tumour-sensitizing agents prior to NK cell infusion				
Bortezomib	↑Cytotoxicity	CLL, RCC, lung cancer, multiple myeloma and sarcoma	1 (1)	Bortezomib administered to sensitize tumours to NK cell TRAIL
Regulatory T cell eradication prior to NK cell infusion				
IL-2–diphtheria toxin fusion protein	↑Persistence and expansion; ↑cytotoxicity	AML, non-Hodgkin lymphoma and CLL	2 (1)	In one study, IL-2-diphteria toxin fusion protein was combined with pentostatin and rituximab

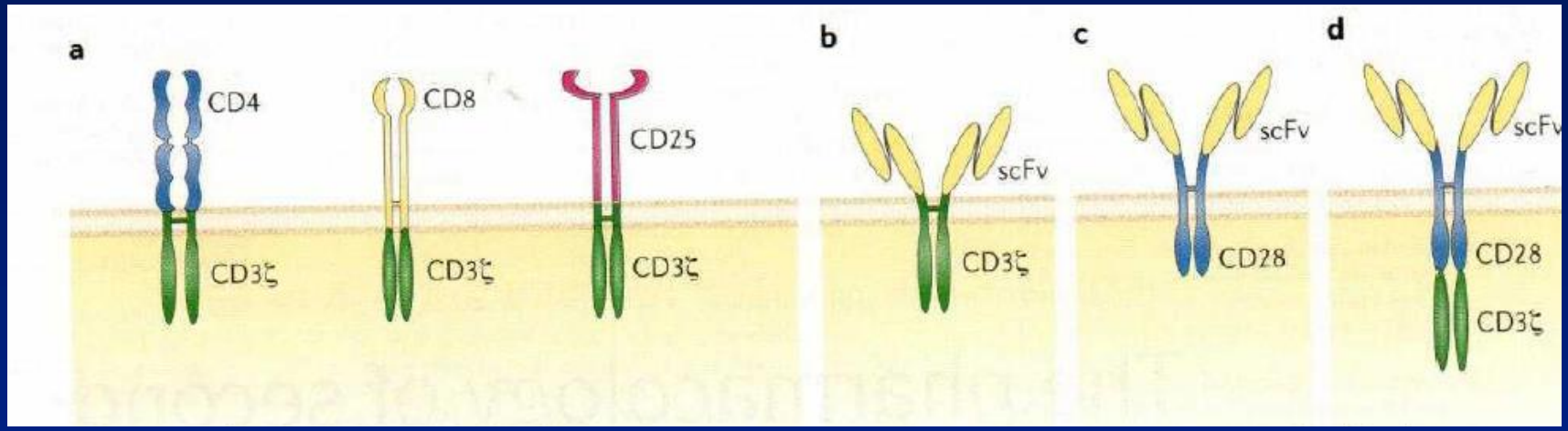
Therapeutic approaches to enhance natural killer cell cytotoxicity against cancer: The force awakens
Nature Reviews Drug Discovery 14, 487-498 (2015) – Table 01

Clinical studies evaluating the efficacy of adoptively infused NK cells

Method	Patient population	Total number of clinical trials (number of active trials)	Comments
Non-expanded NK cells			
Autologous NK cells + IL-2	Melanoma, RCC, lung cancer and nasopharyngeal cancer	3 (1)	–
Autologous NK cells + IL-15	Neuroblastoma, sarcoma, Wilms tumour and rhabdomyosarcoma	1 (1)	Intended to more specifically bolster NK cell antitumour activity than IL-2
Allogeneic NK cells + IL-2	AML, multiple myeloma, myelodysplastic syndromes, lymphoma, ovarian carcinoma, melanoma, neuroblastoma, Ewing sarcoma, breast cancer and Fallopian tube cancer	55 (29)	Most data published on adoptive NK cell therapy are from these studies
Allogeneic NK cells + IL-15	AML and myelodysplastic syndromes	2 (1)	Intended to more specifically bolster NK cell antitumour activity than IL-2
Expanded NK cells			
Autologous NK cells	CLL, RCC, lung cancer, multiple myeloma, sarcoma, colon cancer, melanoma, neuroblastoma, prostate cancer, ALL and pancreatic cancer	7 (6)	Various expansion methods used, including EBV-LCL and membrane-bound cytokine or 4-1BBL feeder cells; some studies use IL-2 post NK cell infusion
Allogeneic NK cells	AML, myelodysplastic syndromes, T cell lymphoma and multiple myeloma	11 (8)	Various expansion methods used, including EBV-LCL and membrane-bound cytokine or 4-1BBL feeder cells; some studies use IL-2 post NK cell infusion
Genetically manipulated NK cells			
CD19 CAR mRNA (expanded NK cells)	BCL	2 (2)	Designed to redirect tumour targeting. Haploidentical NK cells expanded with K562 membrane-bound IL-15 or 4-1BBL feeder cells; in Phase II clinical trials
NK cell lines			
NK-92	AML, multiple myeloma and lymphoma	2 (2)	Off-the-shelf NK cells; in dose-escalating Phase I clinical trials

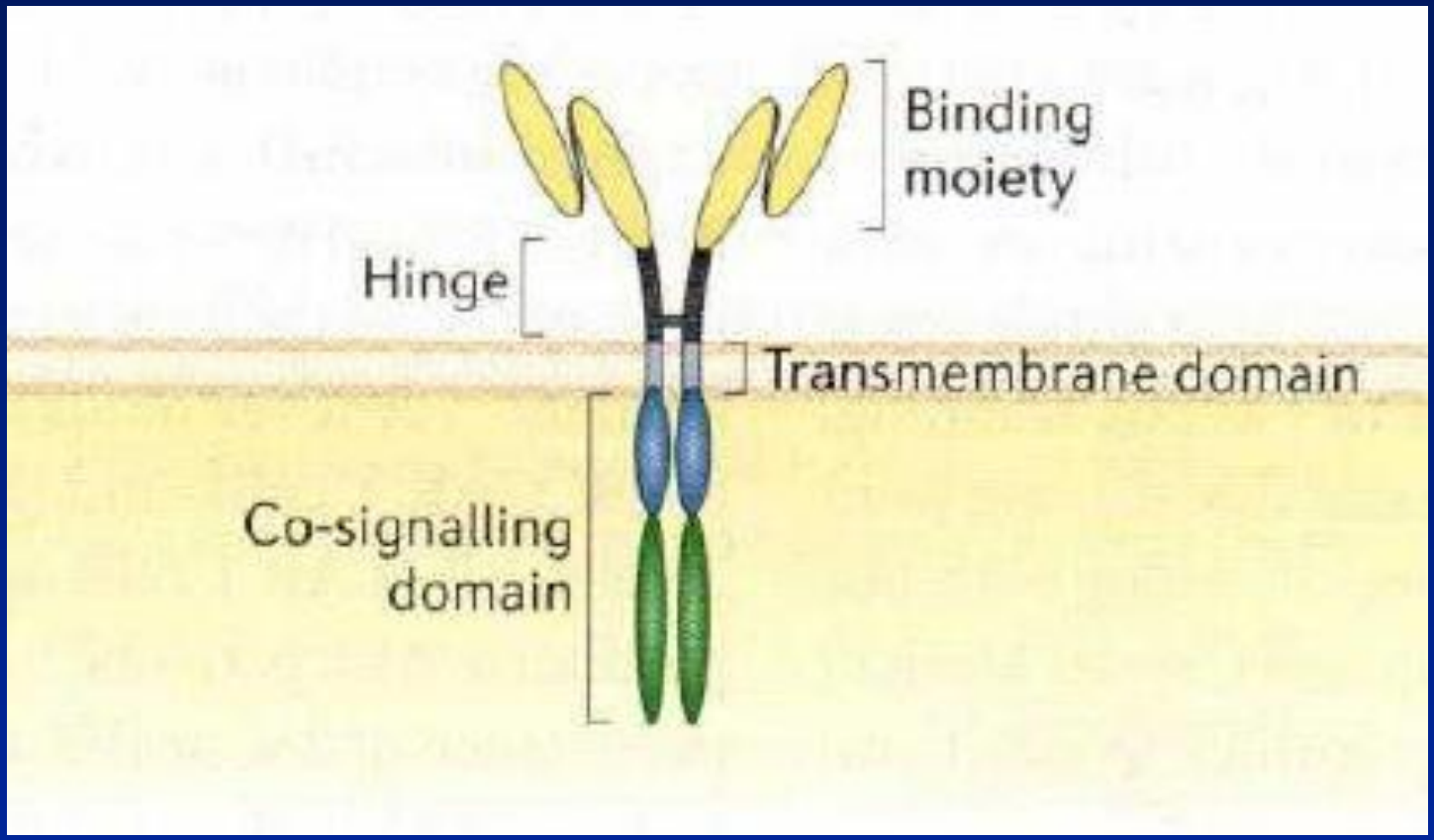
Therapeutic approaches to enhance natural killer cell cytotoxicity against cancer: The force awakens
Nature Reviews Drug Discovery 14, 487-498 (2015) – Table 02

Evolution of chimeric antigen receptors



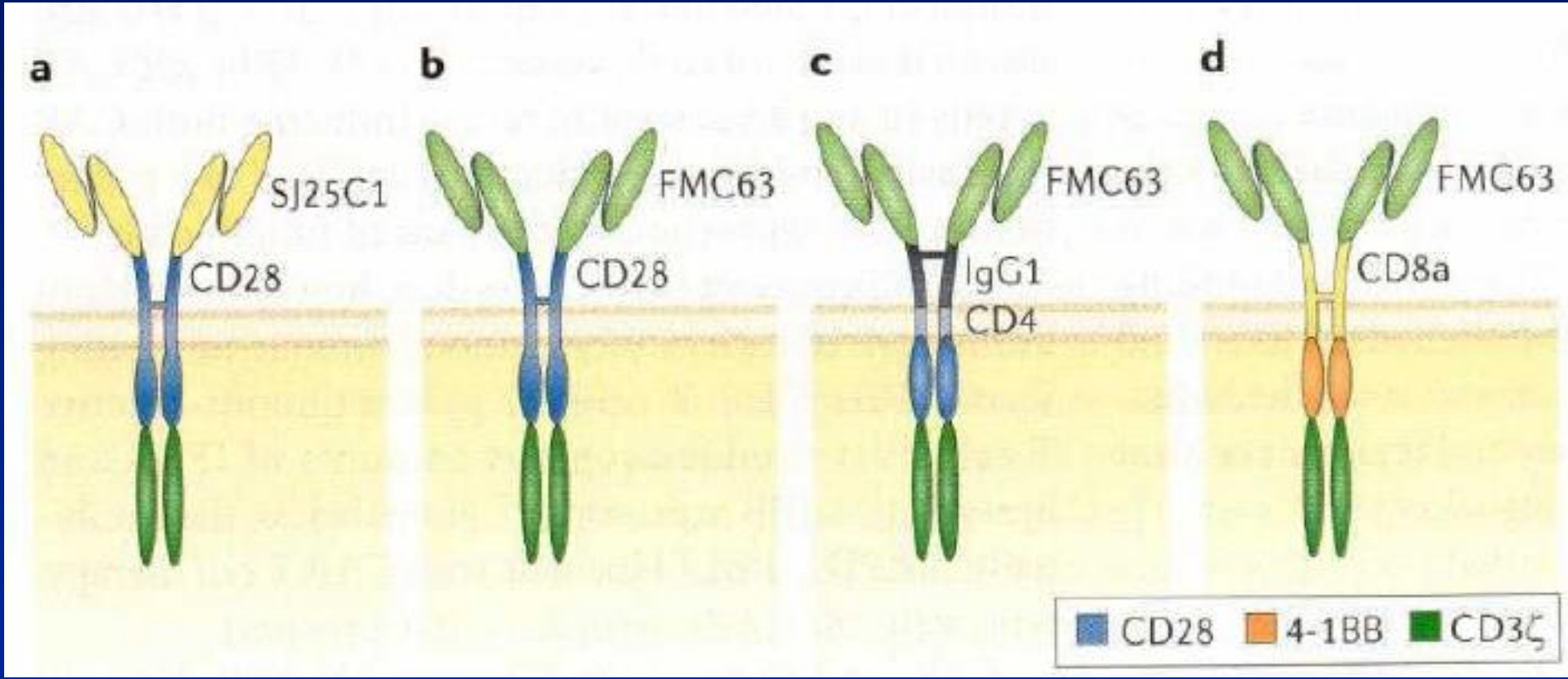
The pharmacology of second-generation chimeric antigen receptors - Nature Reviews Drug Discovery 14, 499-509 (2015) – Fig 01

Structural features of chimeric antigen receptors



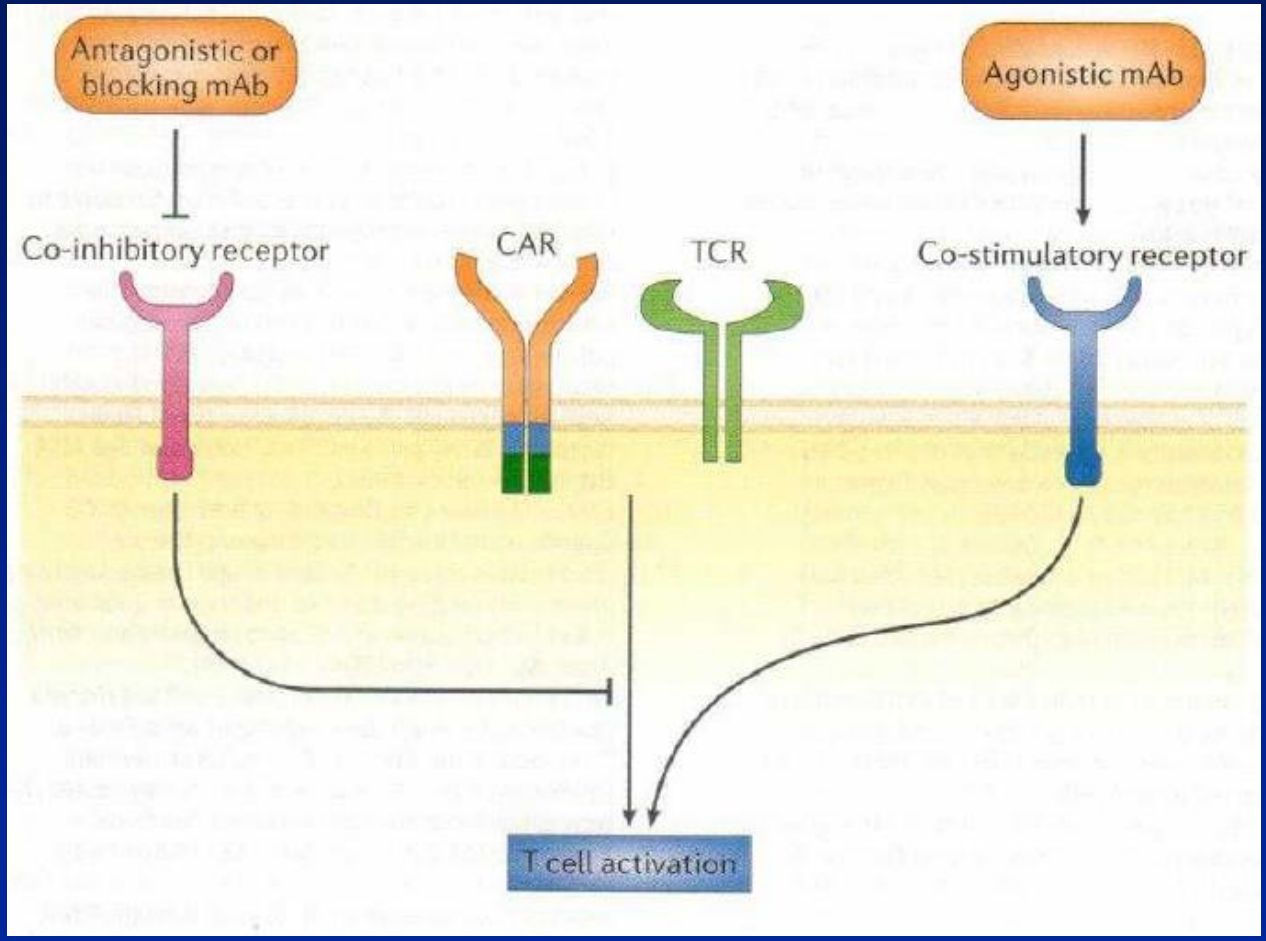
The pharmacology of second-generation chimeric antigen receptors - Nature Reviews Drug Discovery 14, 499-509 (2015) – Box 01

Second-generation anti-CD19 chimeric antigen receptors used in clinical trials to treat acute lymphoblastic leukaemia



The pharmacology of second-generation chimeric antigen receptors - Nature Reviews Drug Discovery 14, 499-509 (2015) – Fig 02

Co-stimulation targeted by monoclonal antibodies



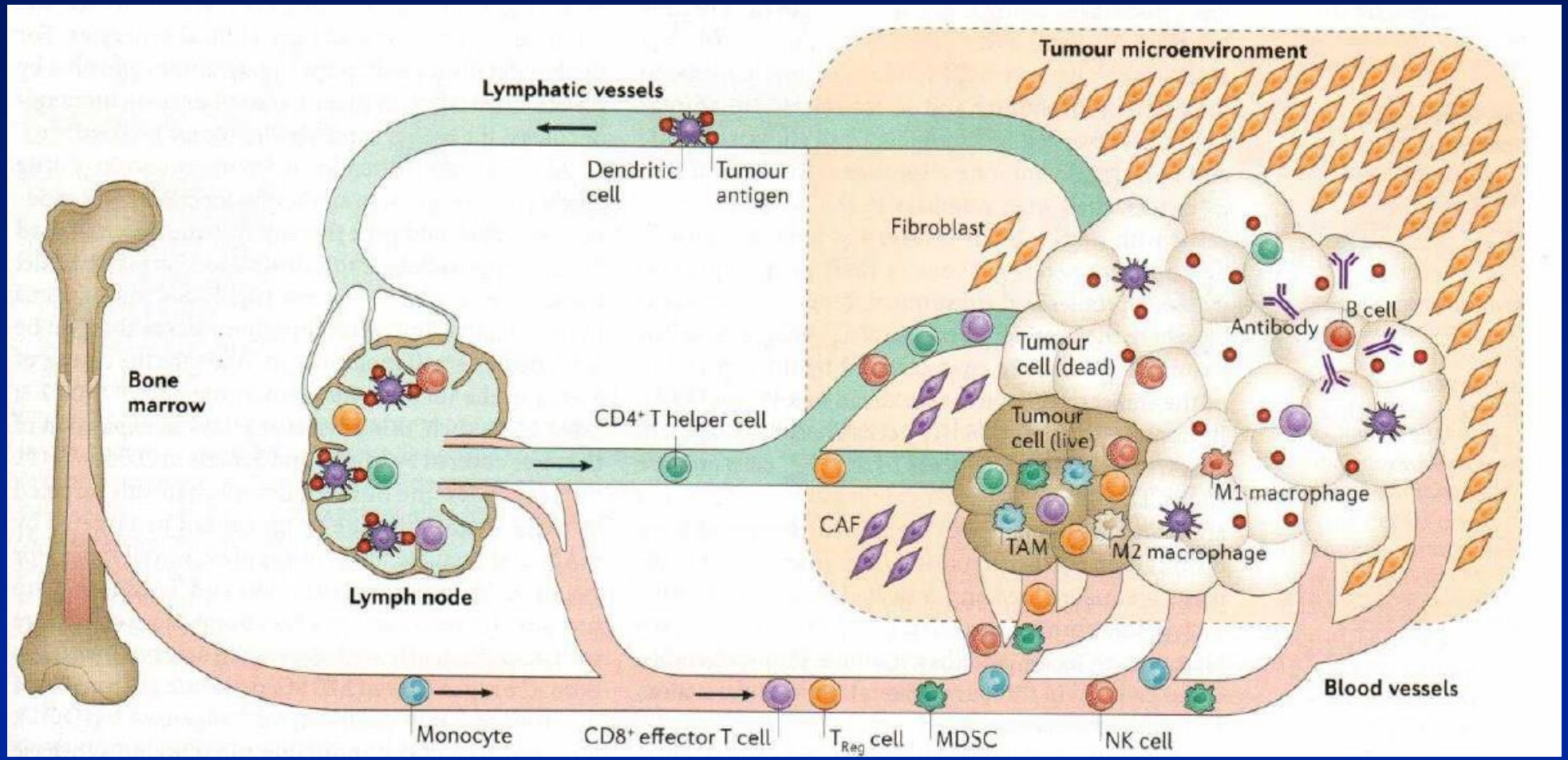
The pharmacology of second-generation chimeric antigen receptors - Nature Reviews Drug Discovery 14, 499-509 (2015) – Box 02

Therapeutic modalities targeting immune regulation of cancer

Modality	General use or utility	Limitations	Examples	Status	Refs
Vaccines	Prime patient immune response to tumour-specific antigens	Heterogeneous tumour antigen composition and expression; prone to be hampered by mechanisms of immune suppression	Vaccines against targets such as gp100, MUC1, MAGEA3	Various approaches in clinical trials	9
Recombinant cytokines	Agonism or blockade of protein–protein immune pathways	Antigenicity; poor pharmacokinetics; high toxicity	GM-CSF, IL-7, IL-12, IL-15, IL-18, IL-21	IL-2 for metastatic melanoma and renal cell carcinoma, and IFNα for the adjuvant therapy of stage III melanoma are approved	8
mAbs	Highly selective agonism or blockade of extracellular protein–protein immune pathways; long half-life; non-immunogenic (human or humanized)	Expensive and time-consuming manufacturing and development costs; challenges in achieving high tumour exposures	mAbs targeted against CTLA4, PD1, PDL1 (T cell checkpoint blockers)	Ipilimumab (CTLA4-specific), nivolumab and pembrolizumab (both PD1-specific) are approved for melanoma; others in clinical development for melanoma, lung cancer, kidney cancer and other diseases	11
Autologous T cells	Tumour-targeted cytotoxicity of extracellular and intracellular tumour-specific antigens	Heterogeneous tumour antigen composition and expression; on-target, off-tumour toxicity	CAR T cells, TCR T cells	None approved, but several in clinical development	10
Small molecules	Uniquely suited for intracellular targets, but also equally applicable to cell surface or extracellular targets	Off-target activities; dose-limiting toxicities; ineffective at blocking protein–protein interactions; require daily dosing	IDO1 and COX2 inhibitors, TLR agonist and chemokine antagonist	Topical imiquimod (a TLR7 and TLR8 agonist) approved for the treatment of basal cell carcinoma; IDO inhibitors in clinical trials	12

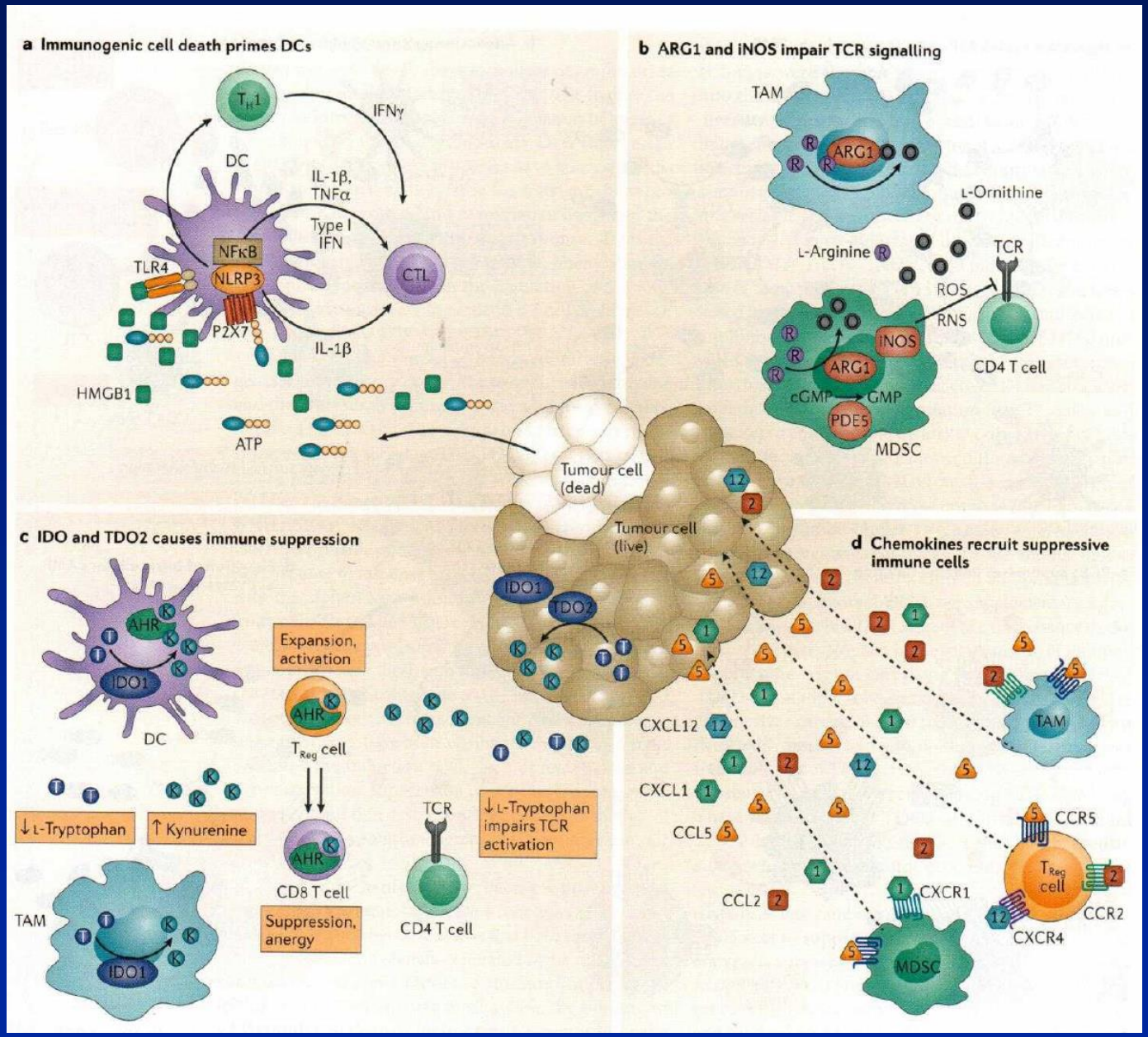
Big opportunities for small molecules in immuno-oncology - Nature Reviews Drug Discovery 14, 603-622(2015) – Table 01

Immune function and the immune response to cancer

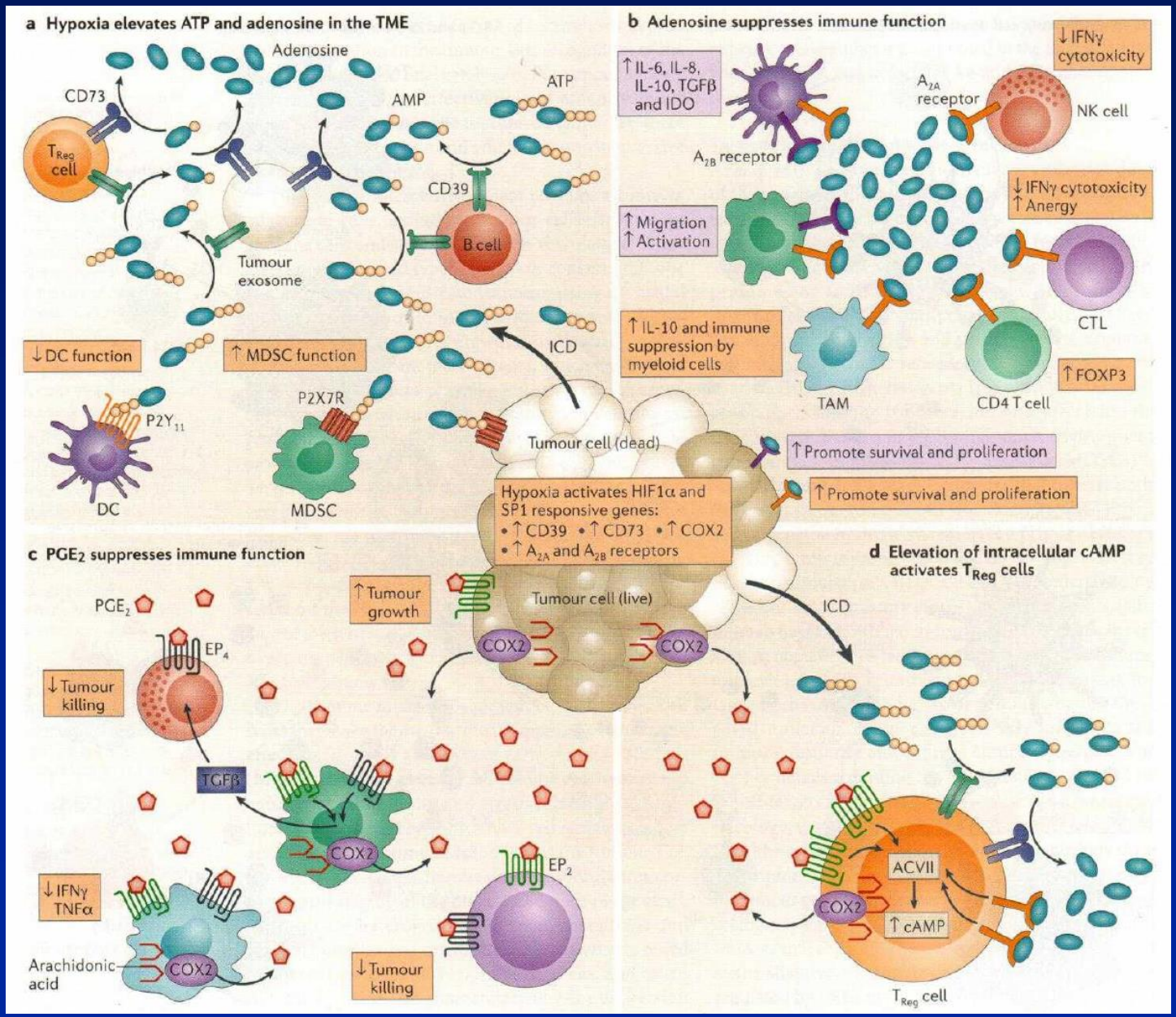


Big opportunities for small molecules in immuno-oncology - Nature Reviews Drug Discovery 14, 603-622(2015) – Fig 01

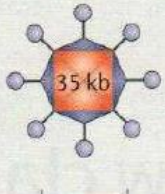
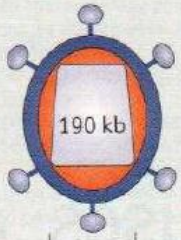
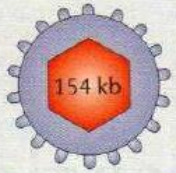
Small-molecule drug targets to restore cancer immunity in the tumour



Purinergic and PGE_2 signaling in immune cells

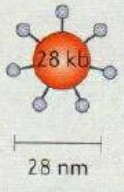
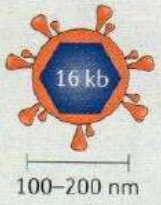
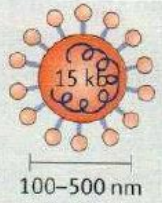
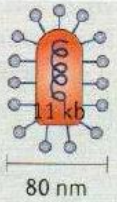


Properties of select DNA viruses

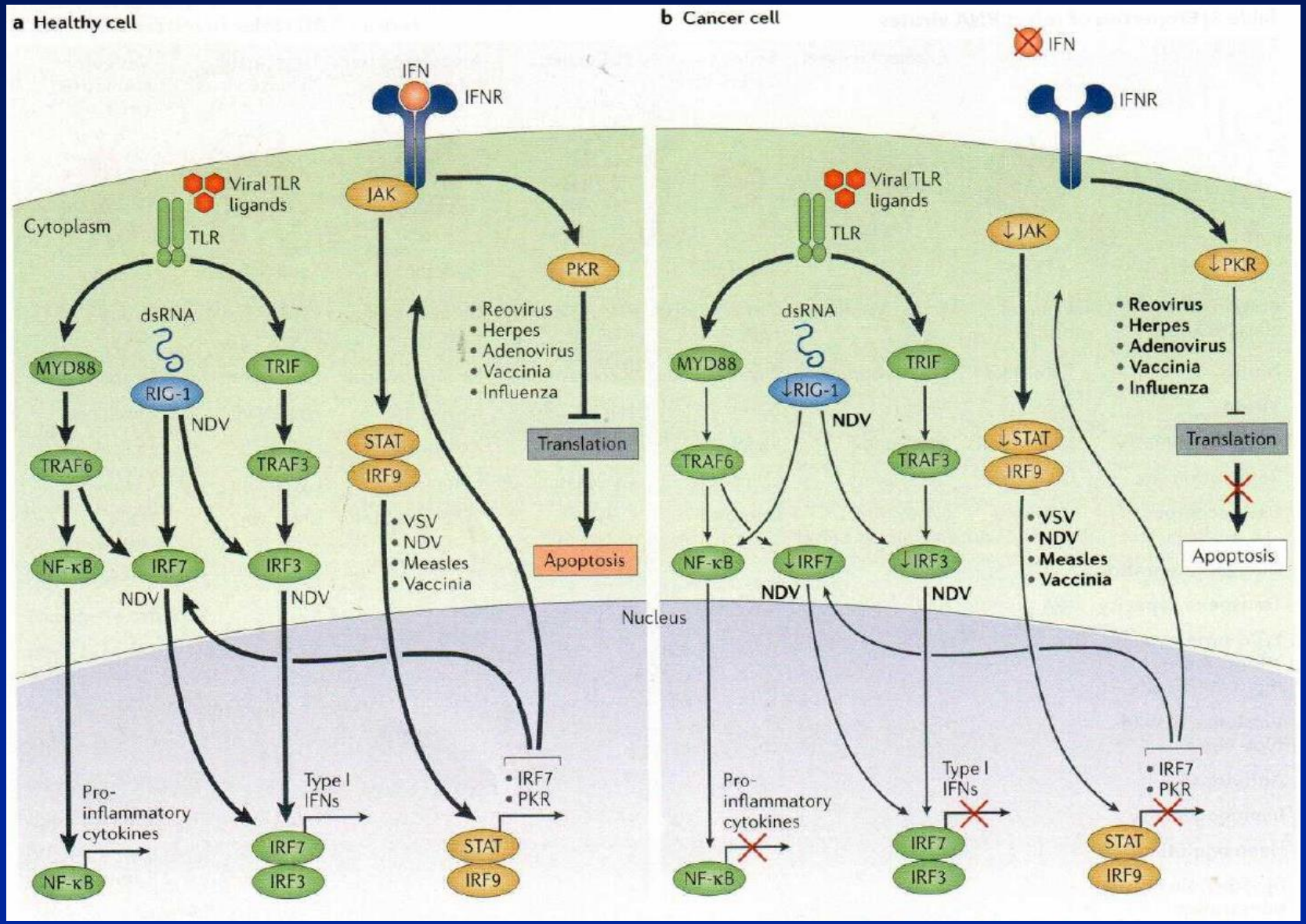
	Adenovirus	Vaccinia virus	Herpesvirus	Parvovirus H1
	 70–90 nm	 70–100 nm	 200 nm	 18–28 nm
Baltimore classification	Group I: dsDNA	Group I: dsDNA	Group I: dsDNA	Group II: ssDNA
Family	Adenoviridae	Poxviridae	Herpesviridae	Parvoviridae
Virion	Naked	Complex coats	Enveloped	Naked
Capsid symmetry	Icosahedral	Complex	Icosahedral	Icosahedral
Replication site	Nucleus and cytoplasm	Cytoplasm	Nucleus and cytoplasm	Nucleus and cytoplasm
Cell receptor	CAR	Unknown	HVEM, nectin 1, nectin 2	Sialic acid residues
Nuclear integration	+	+	+	+
Transgene capacity	++	+++	+++	N/A
Wild-type virus infects non-replicating cells	–	–	–	+
Virulence of wild-type virus	+/–	+/–	–	+
Antivirals	+	+	+	–
Immunogenicity	–	–	–	+
Haemagglutination	–	–	–	+
Blood–brain barrier penetration	–	–	–	+
Achievable titre (PFU per ml)	10^{12}	10^{9}	10^{10}	5×10^{8}
MTD	3×10^{12}	3×10^{9}	10^{9}	N/A

Oncolytic viruses: a new class of immunotherapy drugs - Nature Reviews Drug Discovery 14, 642-662 (2015) – Table 01

Properties of select DNA viruses

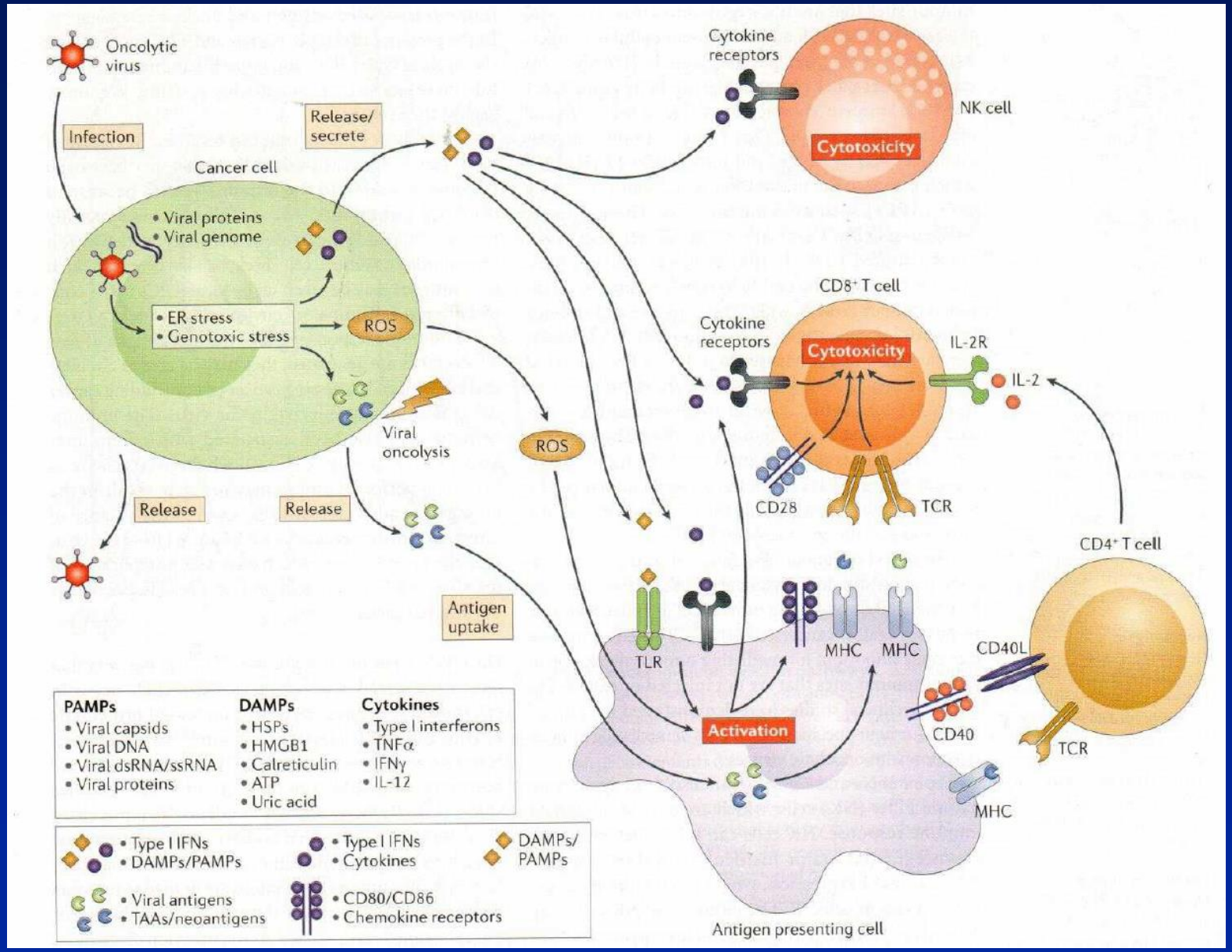
	Reovirus	Coxsackievirus	Seneca Valley Virus	Poliovirus	Measles virus	Newcastle disease virus	Vesicular stomatitis virus
							
Baltimore classification	Group III: dsRNA	Group IV: ssRNA	Group IV: ss(+) RNA	Group IV: ss(+) RNA	Group V: ss(–) RNA	Group V: ss(–) RNA	Group V ss(–) RNA
Family	Reoviridae	Picornaviridae	Picornaviridae	Picornaviridae	Paramyxoviridae	Paramyxoviridae	Rhabdoviridae
Virion	Naked	Naked	Naked	Naked	Enveloped	Enveloped	Enveloped
Capsid symmetry	Icosahedral	Icosahedral	Icosahedral	Icosahedral	Icosahedral	Helical	Helical
Replication site	Cytoplasm	Cytoplasm	Cytoplasm	Cytoplasm	Cytoplasm	Cytoplasm	Cytoplasm
Cell receptor	Unknown	CAR/ICAM-1/ DAF	Unknown	CD155	SLAM and CD46	Unknown	LDLR
Nuclear integration	+	+	+	+	+	+	+
Transgene capacity	N/A	N/A	N/A	N/A	+	+	+
Wild-type virus infects non-replicating cells	+	–	+	–	–	–	+
Virulence of wild-type virus	+	+/–	+	–	–	+	+
Antivirals	–	–	–	–	–	–	–
Immunogenicity	–	–	+	+/–	–	–	–
Haemagglutination	–	+	+	+	–	–	–
Blood–brain barrier penetration	+	–	+	+	–	+	–
Achievable titre (PFU per ml)	10^9	10^9	N/A	10^8	10^{11}	10^8	2×10^{10}
MTD	3×10^{10}	10^9	10^{11} VP per kg	NA	10^9	Initial 10^9; subsequent 10^{10}	N/A

Oncolytic viruses can exploit cancer immune evasion pathways

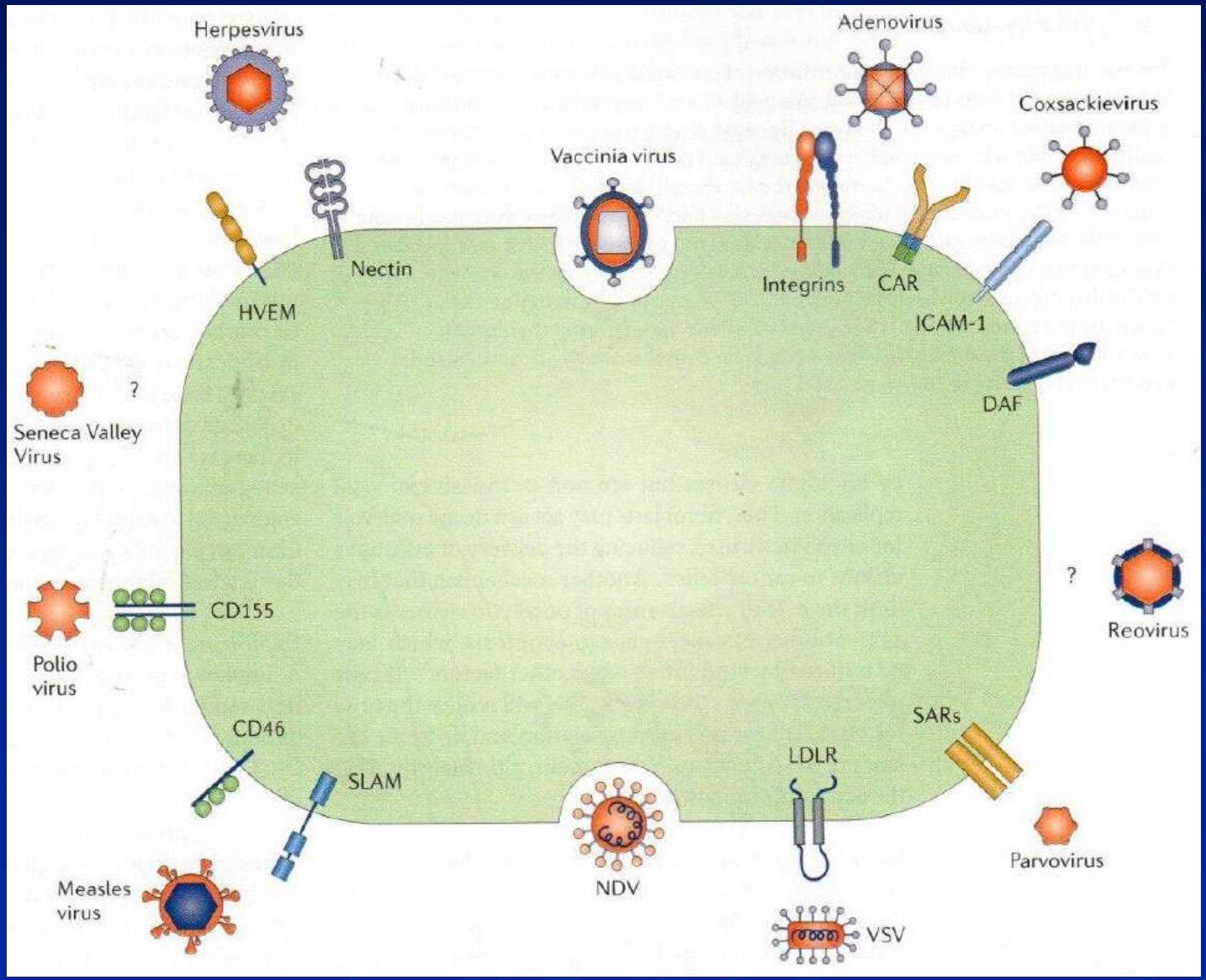


Oncolytic viruses: a new class of immunotherapy drugs - Nature Reviews Drug Discovery 14, 642-662 (2015) – Fig 01

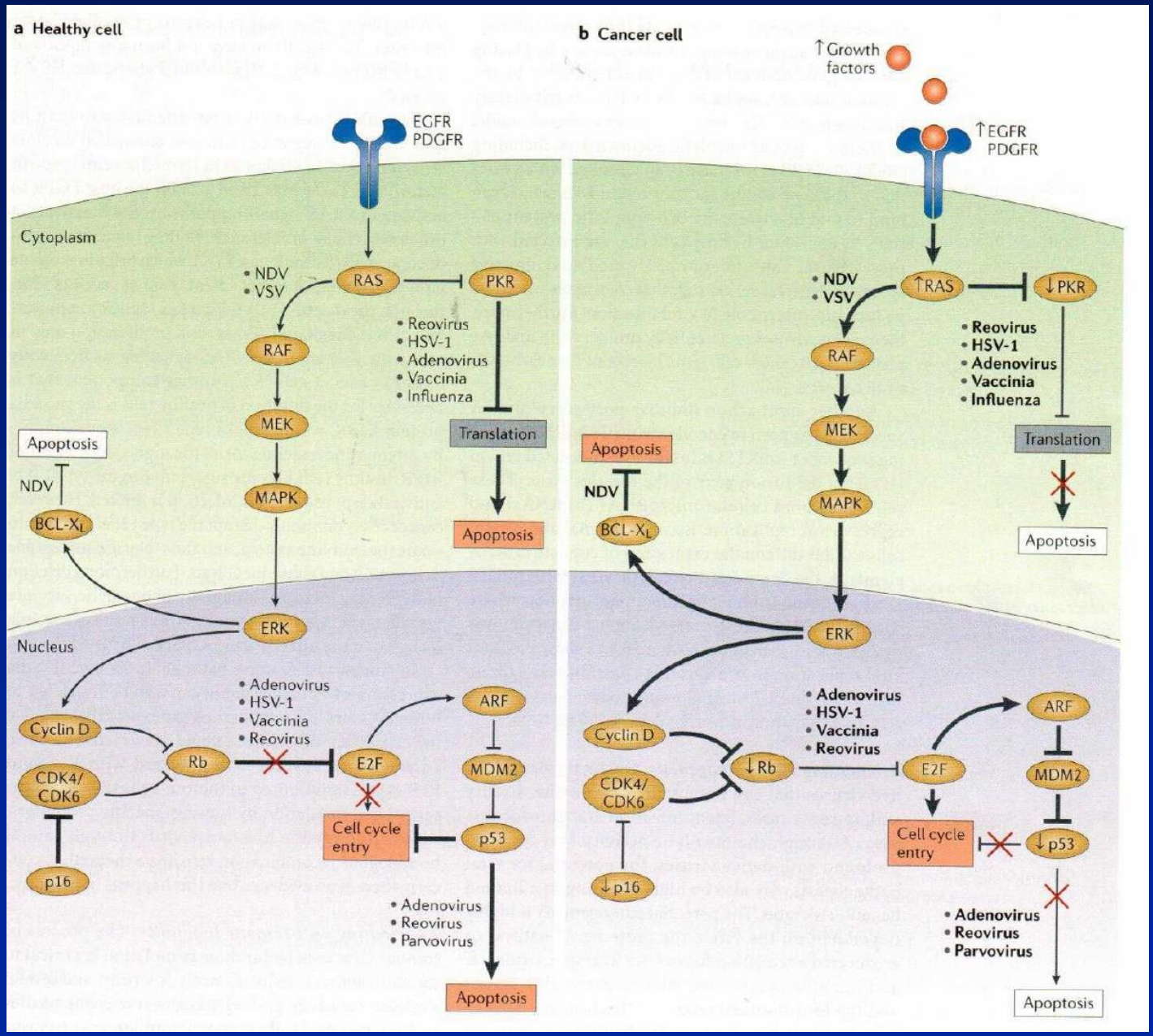
The induction of local and systemic anti-tumour immunity by oncolytic viruses



Mechanisms of viral entry into cancer cells

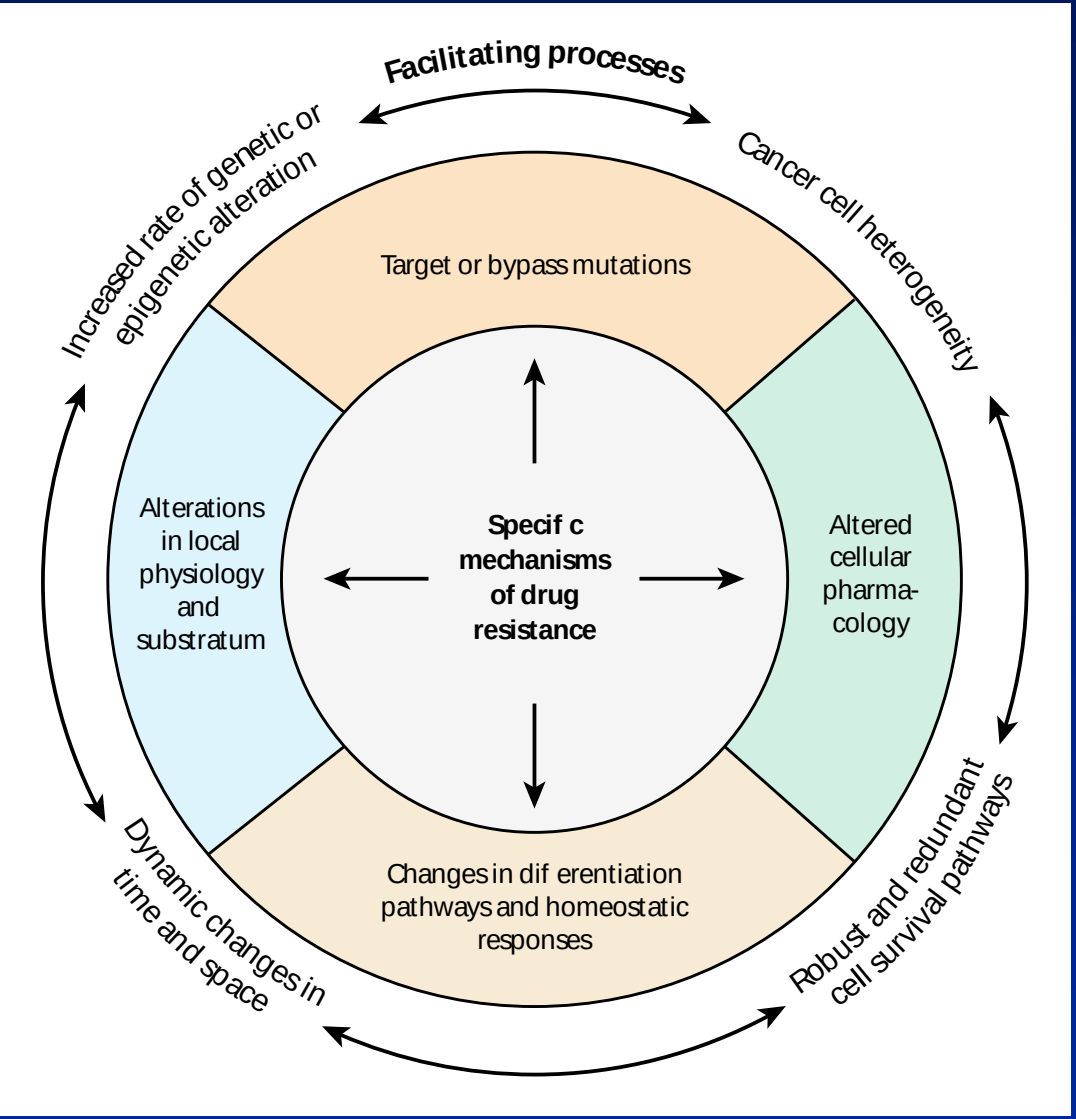


Oncolytic viruses can target oncogenic pathways



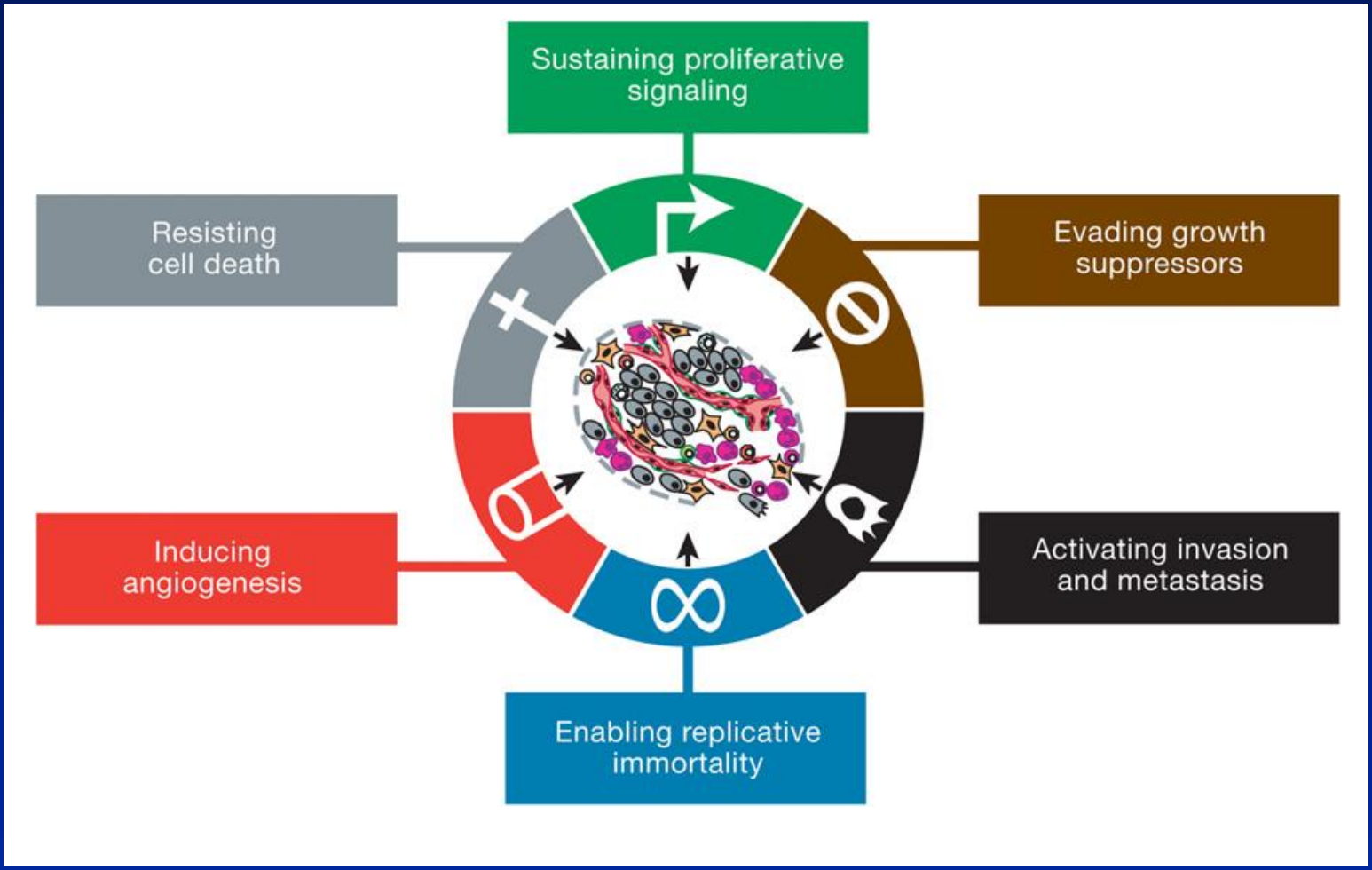
Oncolytic viruses: a new class of immunotherapy drugs - Nature Reviews Drug Discovery 14, 642-662 (2015) – Fig 04

Drug resistance is a complex process that results from one or more specific mechanisms that render cells resistant to anticancer drugs.

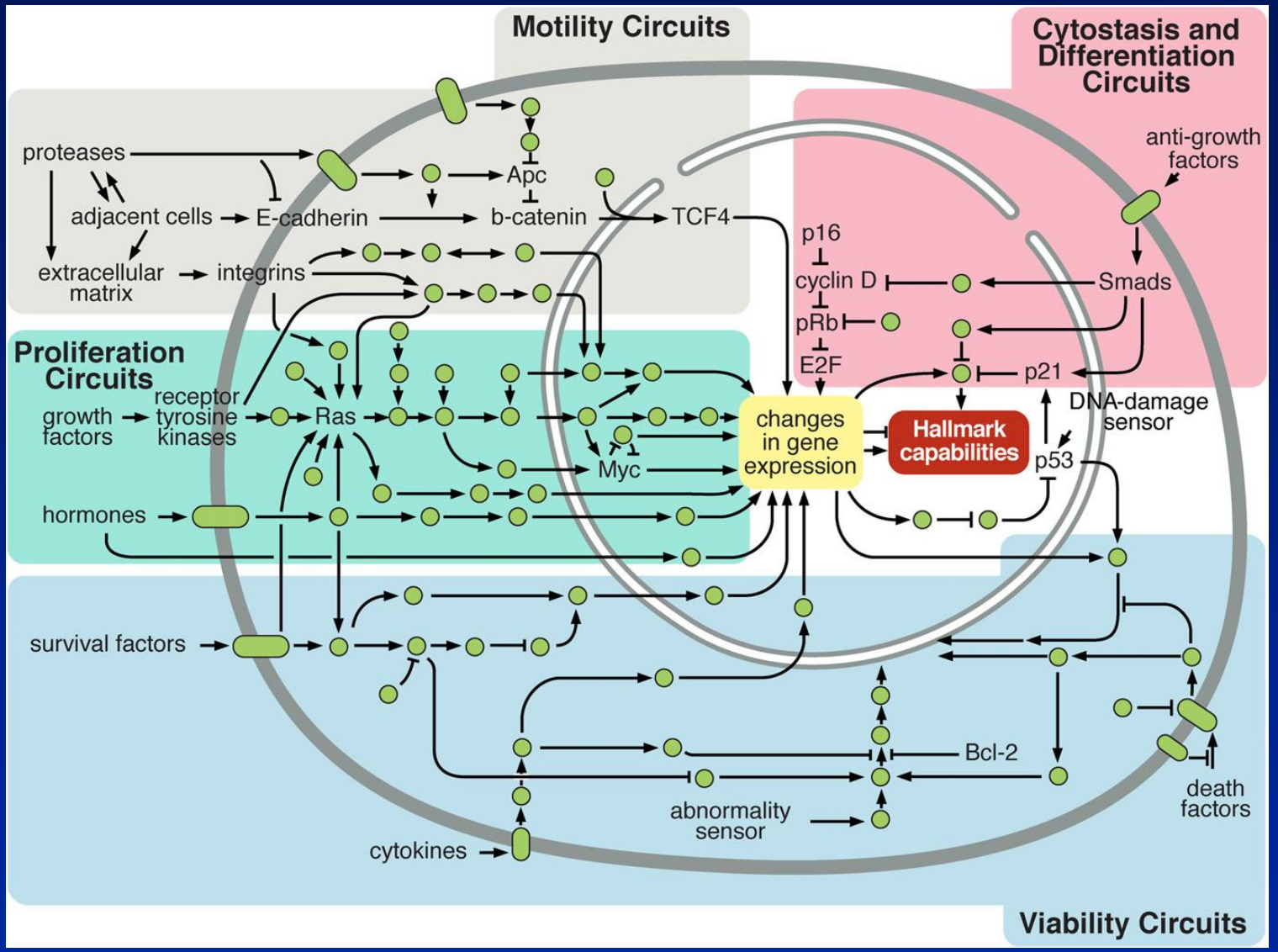


Toward a Better Understanding of the Complexity of Cancer Drug Resistance - Review in Advance first posted online on October 28, 2015. – Fig 01

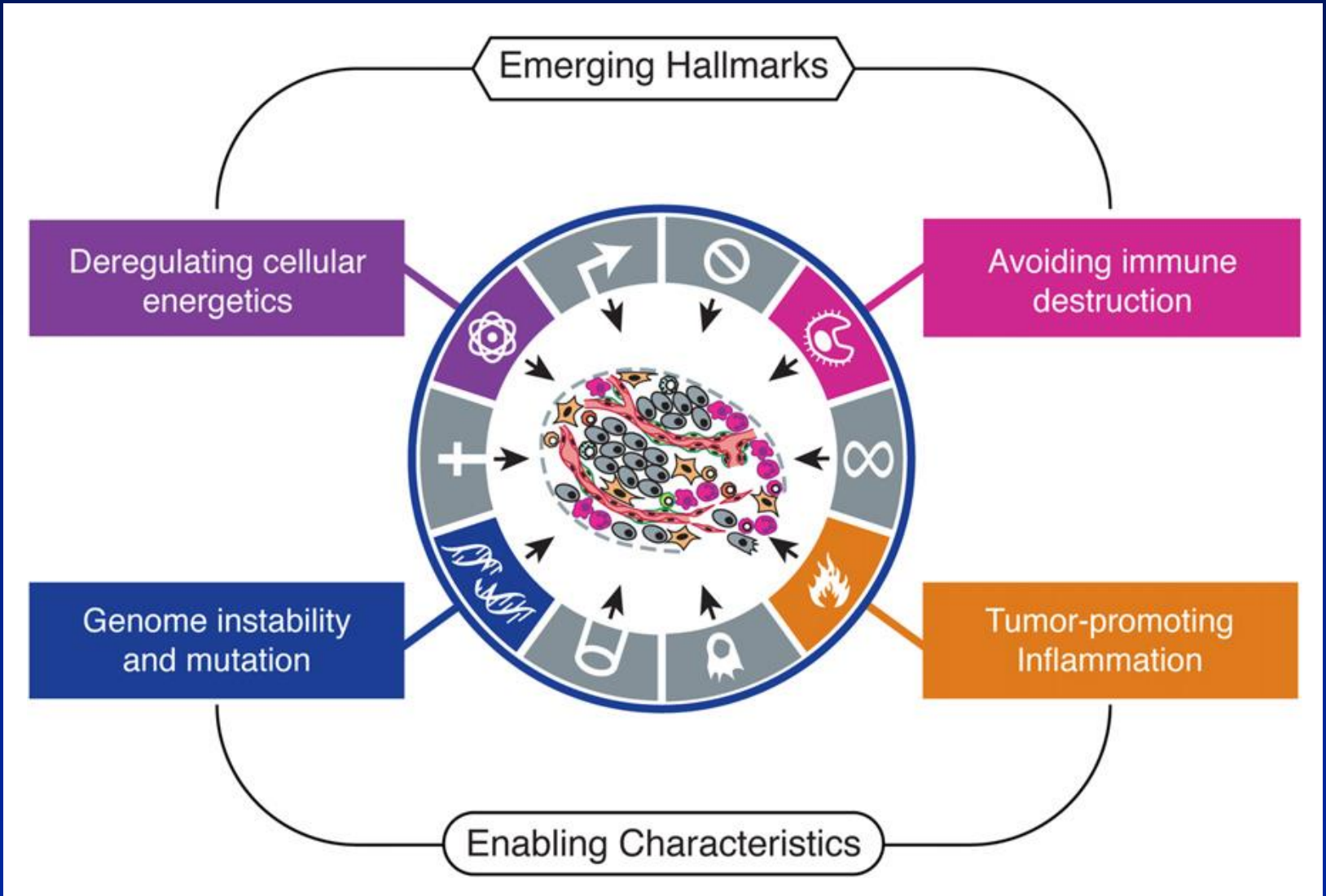
The Hallmarks of Cancer



Intracellular Signaling Networks Regulate the Operations of the Cancer Cell

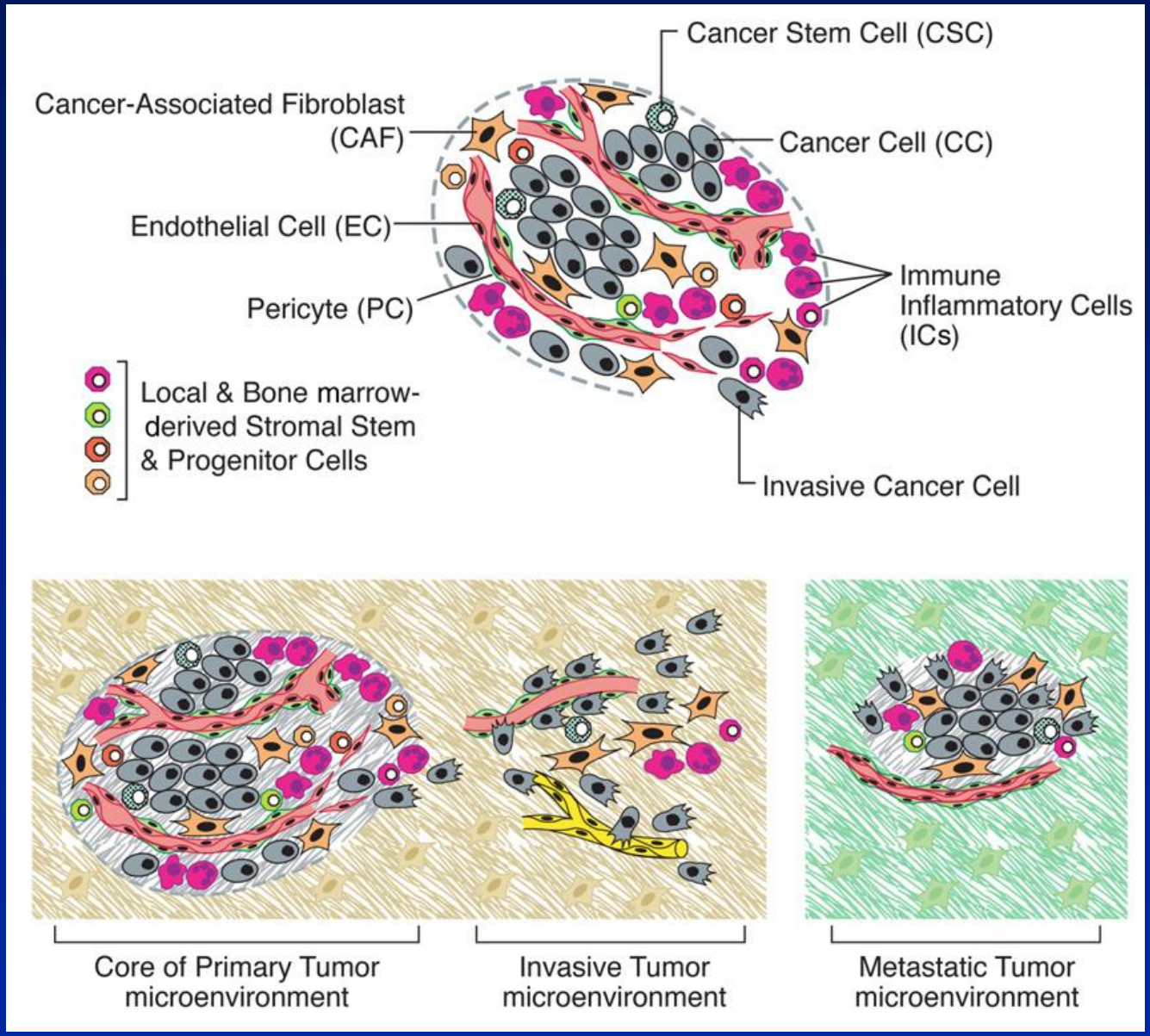


Emerging Hallmarks and Enabling Characteristics

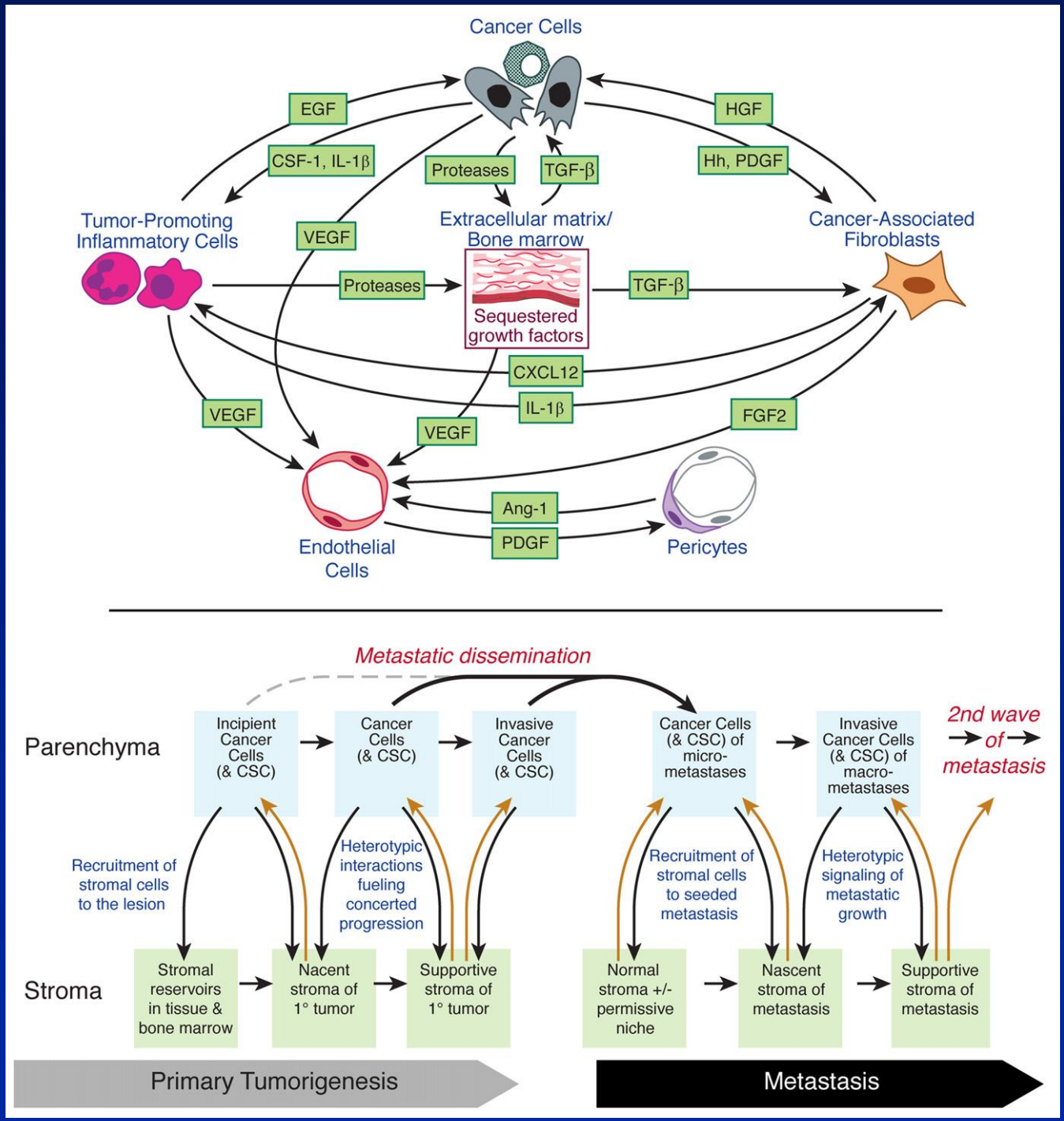


Hallmarks of Cancer: The Next Generation - Cell 144, March 4, 2011 a2011 Elsevier Inc. - Fig 03

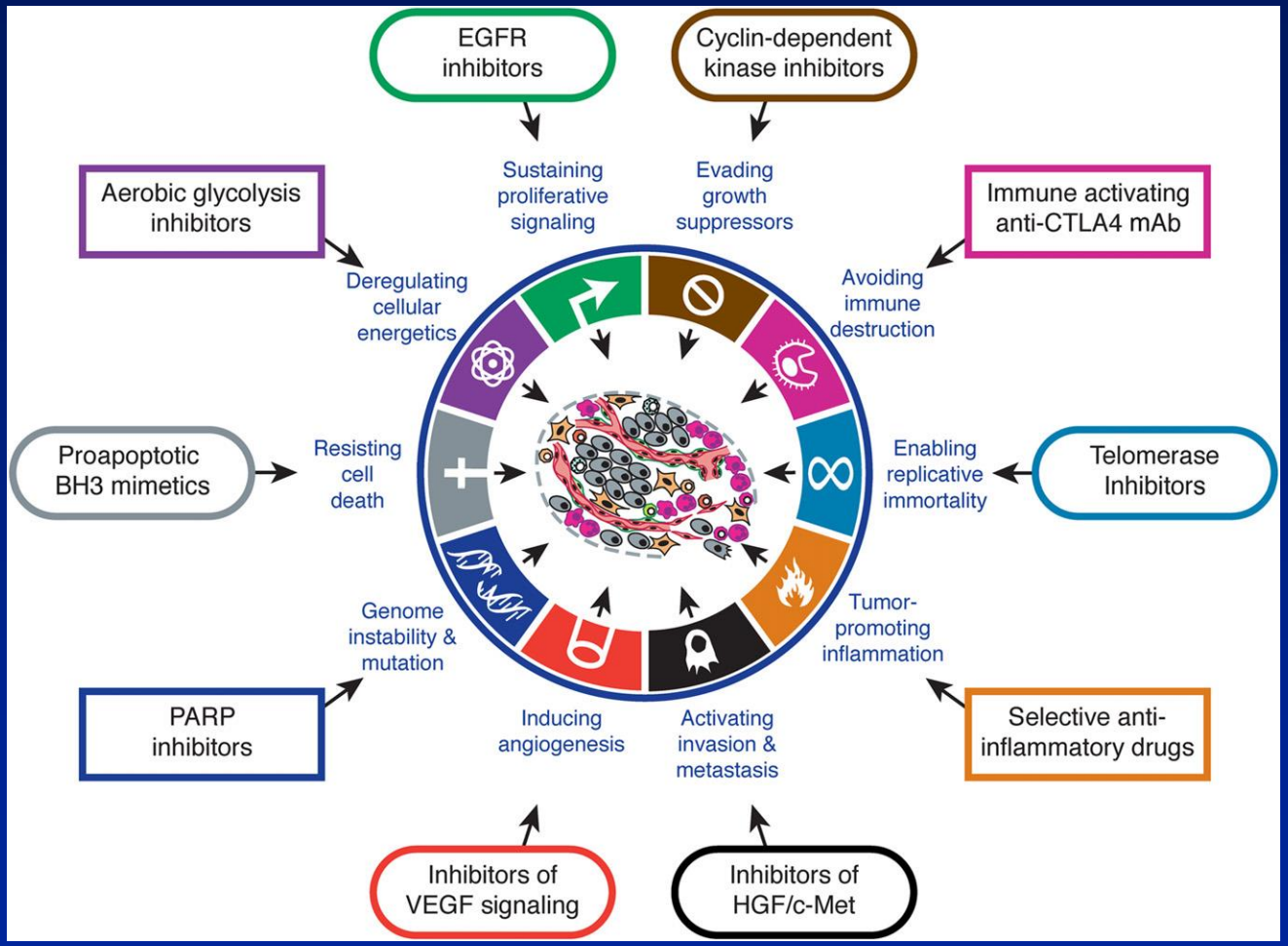
The Cells of the Tumor Microenviroment



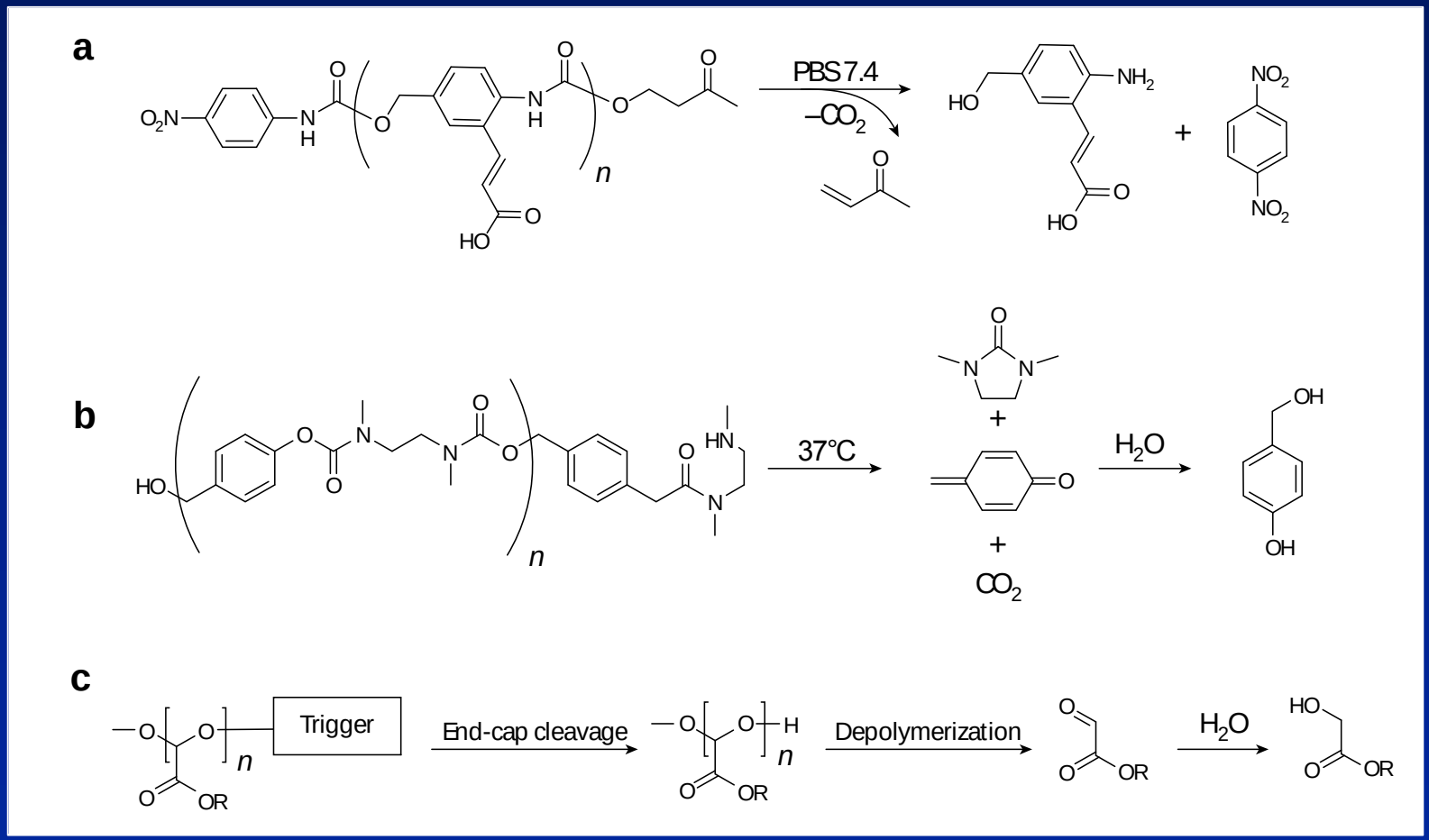
Signaling Interactions in the Tumor Microenvironment during Malignant Progression



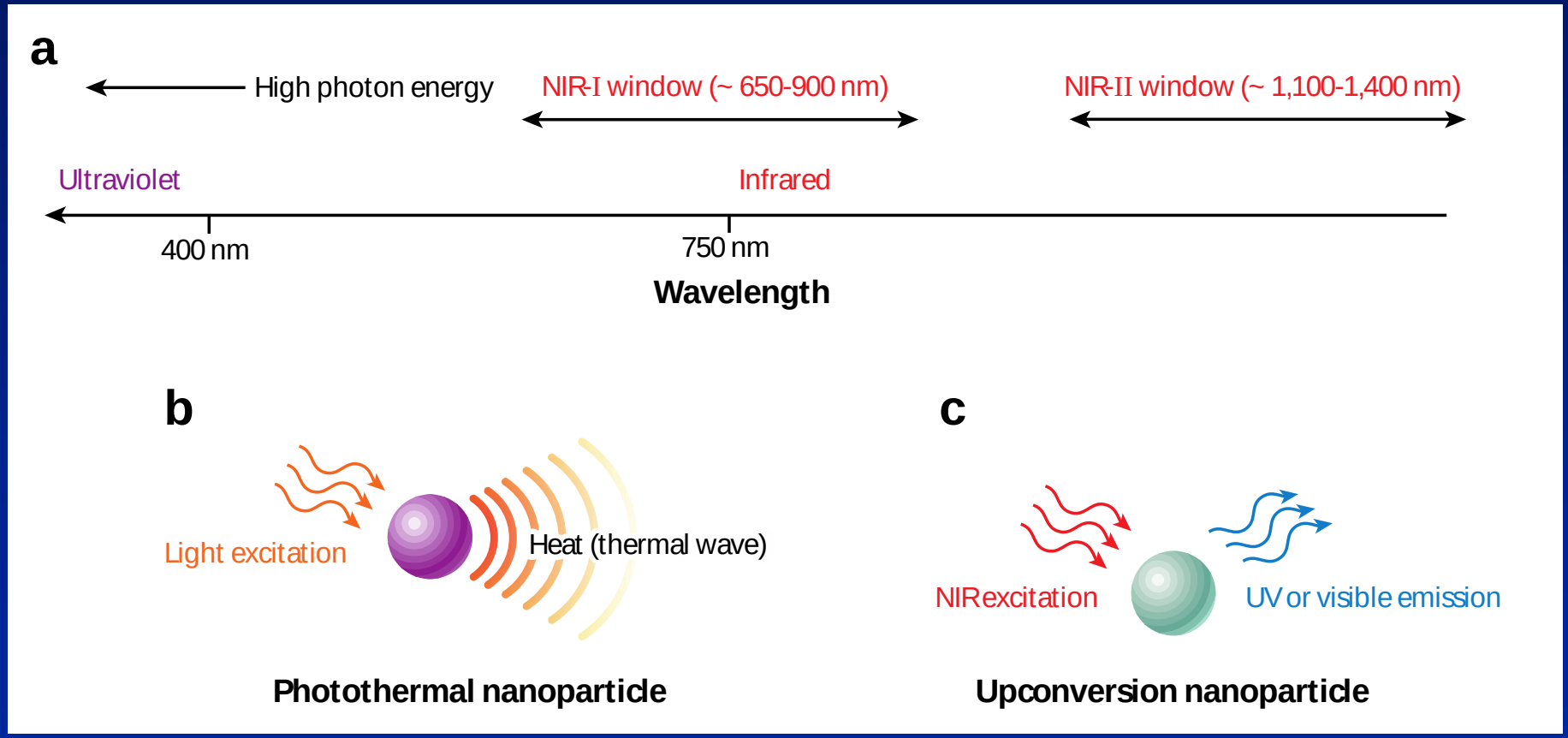
Therapeutic Targeting of the Hallmarks of Cancer



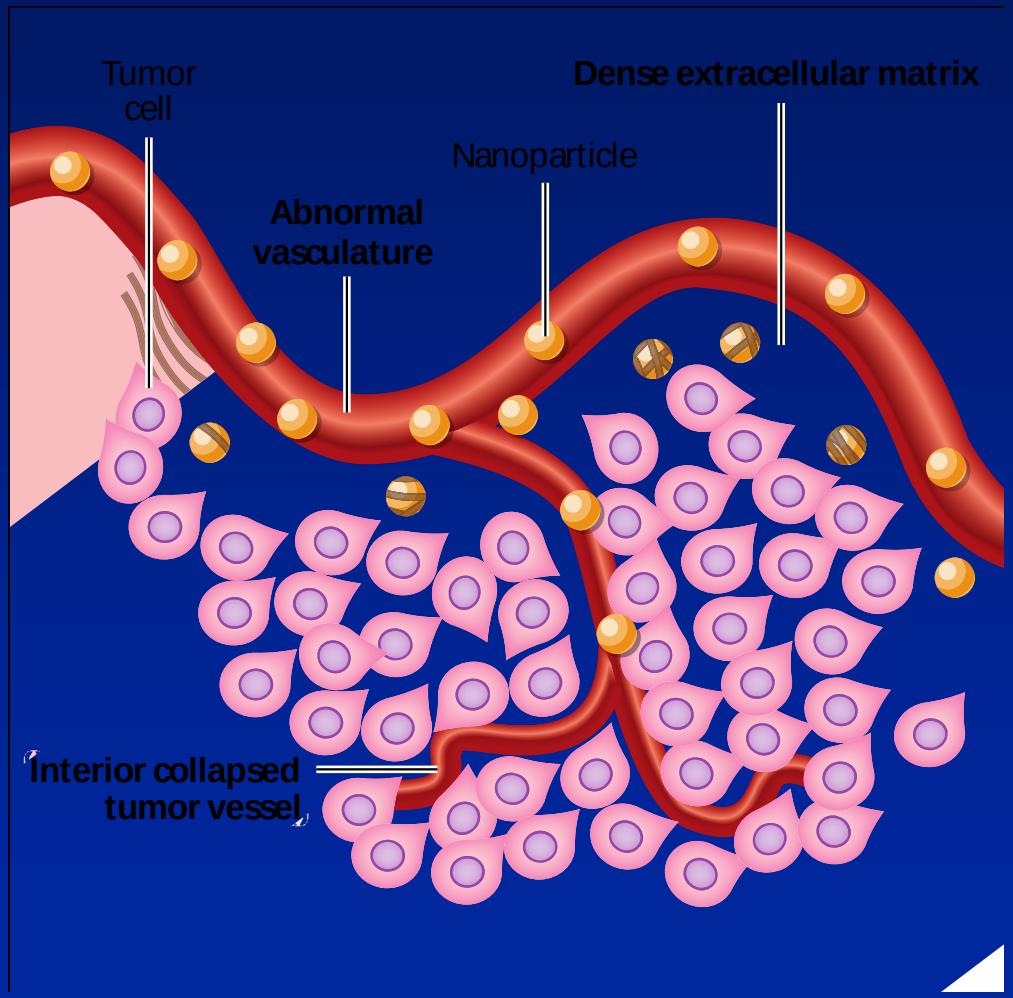
Self-immolative polymers degrade upon triggering. (a) A polycarbamate depolymerizes via a quinone-methide intermediate. (b) A different polycarbamate depolymerizes via alternating cyclization and elimination. (c) Polyglyoxylate self-depolymerizes to glyoxylic acid.



Light for in vivo imaging and therapy, and light-triggered nanoparticles (NPs). (a) The electromagnetic spectrum of ultraviolet (UV), visible, and infrared (IR) light and of the near-infrared (NIR)-I and NIR-II window for in vivo imaging and phototherapy. (b) Schematic illustration of a metallic NP that can absorb visible or NIR light and dissipate such absorbed light energy as heat (photothermal effect). (c) Schematic illustration of upconversion NPs that can be excited by NIR light to emit UV or visible light.

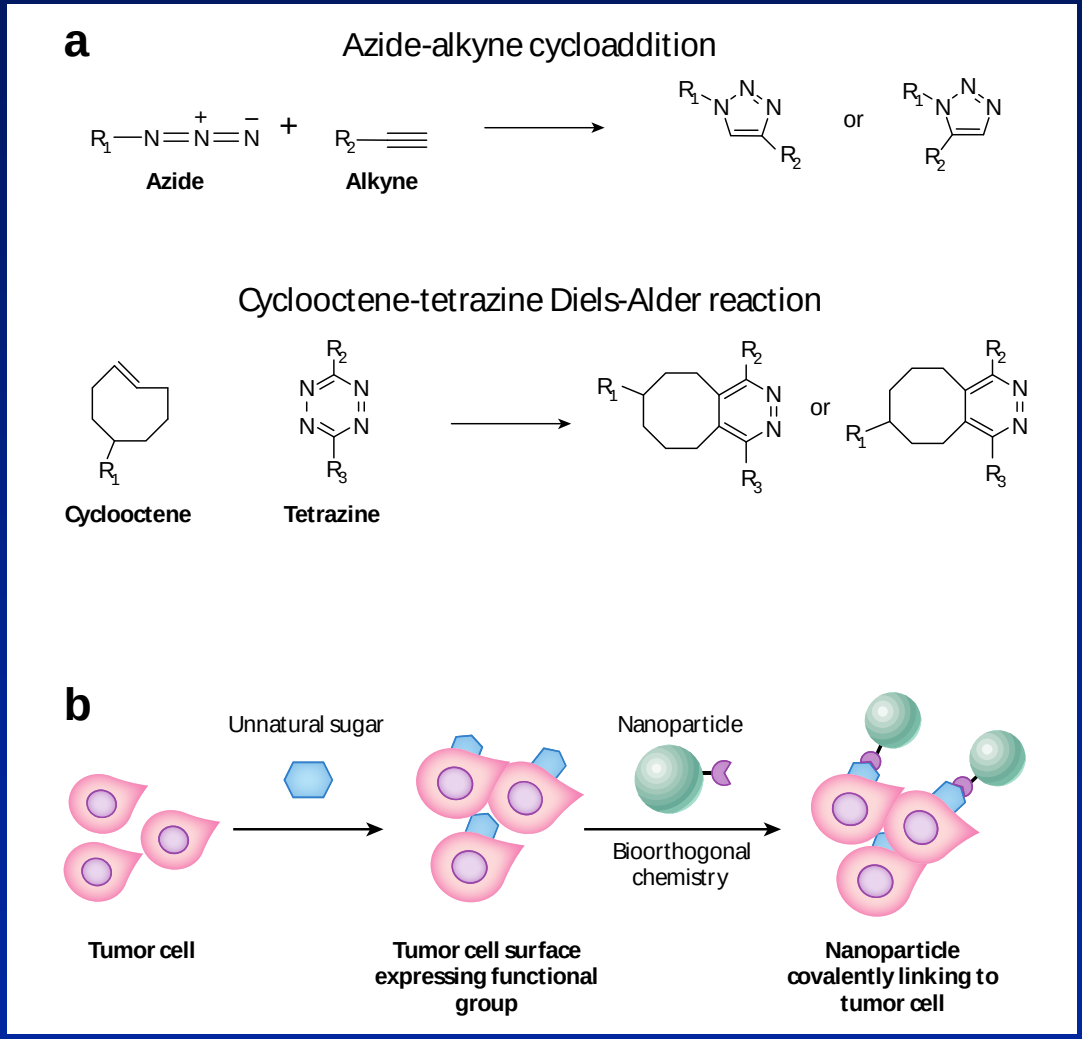


Barriers to deep tumor penetration. Scheme of the delivery barriers that prevent deep penetration of nanoparticles (NPs) in tumors. The abnormal tumor vasculature, dense collagen matrix, and collapsed vessels in the tumor interior present barriers to NP penetration deep into tumors.

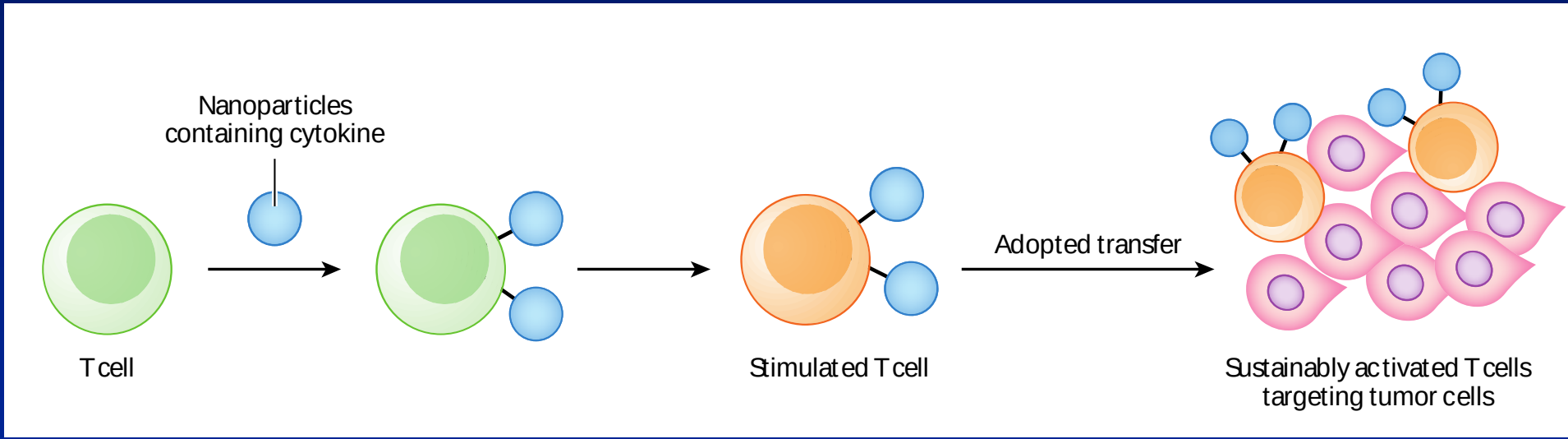


New Strategies in Cancer Nanomedicine - Review in Advance first posted online on October 28, 2015. Fig 03

Bioorthogonal reactions for tumor targeting. (a) Examples of bioorthogonal reactions: azide-alkyne cycloaddition and cyclooctene-tetrazine Diels-Alder reaction. (b) Schematic illustration of tumor targeting using bioorthogonal reactions.

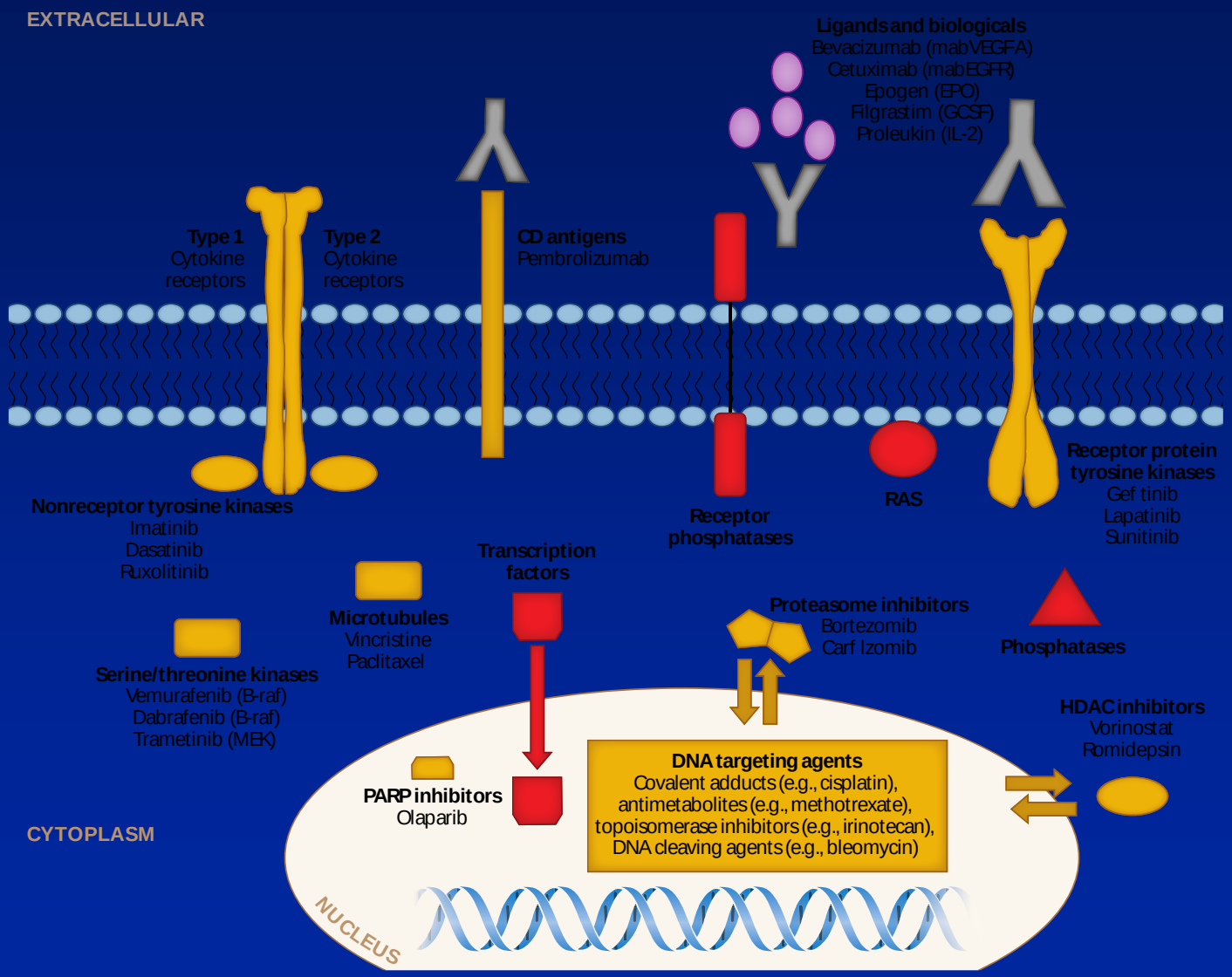


Scheme of nanoparticle (NP)-tethering T cells for adoptive cancer immunotherapy.



New Strategies in Cancer Nanomedicine - Review in Advance first posted online on October 28, 2015. Fig 05

A schematic representation of contemporary molecular cancer drug target classes.



Drugging Undruggable Molecular Cancer Targets - Review in Advance first posted online on November 2, 2015. Fig 01

Small molecules in clinical trials for traditionally undruggable targets

Experimental therapeutic	Molecular target class	Cancer indication	Development phase
Phosphatases			
LB100	Protein phosphatase 2A inhibitor	Solid tumors	Phase I
RAS superfamily			
KD032 (Salirasib)	RAS antagonist; inhibits RAS methylation	Colorectal cancer	Phase I
GI-4000	Mutated RAS cancer vaccine	Resected pancreatic cancer, lung	Phase II
Transcription factors			
CPI-0610	BET inhibition	Myelodysplastic syndromes	Phase I
TEN-010	BET inhibitor	Advanced solid tumors	Phase I
GSK525762	Bromodomain inhibitor	NUT gene midline carcinoma	Phase I
PRI-724	CBP/β-catenin	Acute myeloid leukemia, chronic myelogenous leukemia	Phase I/II
ARQ-761	E2F1 transcription factor stimulant	Solid tumors	Phase I
SAR405838	HDM2/p53 antagonist	Solid tumors	Phase I
APTO-253	KLA4 activator	Late-stage tumors	Phase I
DS-3032	MDM2	Lymphoma, Solid tumors	Phase I
AMG232	MDM2-p53	Acute myeloid leukemia, chronic, solid tumors	Phase I
MK-8242	MDM-2	Solid tumors	Phase I
CGM097	p53/MDM2-interaction inhibitor	Late-stage tumors	Phase I
RG7112[b]	MDM2-p53	Leukemia, sarcoma	Phase I
HDM201	p53	Hematological malignancies	Phase I
ABT-RTA-408	Nrf2	Metastatic non-small-cell lung cancer, skin	Phase I

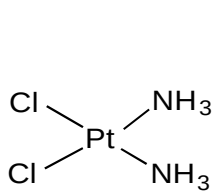
Biological agents in clinical trials for traditionally undruggable cancer targets

Experimental therapeutic	Targeted mechanism of action	Cancer indication	Development phase
AZD9150	STAT3	Hematological malignancies	Phase I
Custirsen (OGX-111)	Antisense oligonucleotide (TRPM-2)	Non-small-cell lung cancer, prostate	Phase III
DCR-MYC	c-MYC	Hepatocellular carcinoma	Phase I
Imetelstat	Telomerase—oligonucleotide	Hematological malignancies	Phase I
ISIS-EIF4ERX	Antisense oligonucleotide [eukaryotic translation initiation factor 4E (eIF4E)]	Non-small-cell lung cancer, prostate	Phase II
MRX34	miR-34 mimic	Hematological malignancies	Phase I
NTO-1151	Ribonuclease inhibitor	Cervical cancer, vaginal cancer	Phase II
QBI-139	Variant of the human pancreatic ribonuclease 1	Solid tumor	Phase I
TKM-PLK1	RNA Polo-like kinase 1	Hepatocellular carcinoma	Phase II

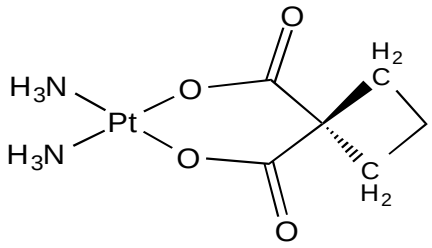
Examples of preclinical inhibitors and activators of cancer-associated phosphatases

Phosphatase	Compound	Action	Reference(s)
PPM			
PP2Cδ (PPM1D or WIP1)	Peptide	Catalytic site inhibitor	27, 92
PP2Cδ (PPM1D or WIP1)	CCT007093	Catalytic site inhibitor	30
PP2Cδ (PPM1D or WIP1)	SPI-001	Catalytic site inhibitor	29
PP2Cδ (PPM1D or WIP1)	GSK2830371	Allosteric inhibitor	28
PPP			
PP2A/CIP2A	Rabdocoetsin B	Transcription inhibitor	93
PP2A/SET	FTY720	Activator by disruption of protein-protein interaction	94
PP2A/SET	OP449	Activator by disruption of protein-protein interaction	36
PP4	Fostriecin	Catalytic site inhibitor	95
PTP			
PTPN1 (PTP1B)	MSI-1436	Allosteric inhibitor	44
PTP-1D (SHP2)	Hydroxyindole carboxylic acid	Catalytic site inhibitor	96, 97
TC-PTP	Mitoxantrone	Allosteric activator	98
CDC25A	Quinones	Catalytic site inhibitor	25, 45
CDC25B	Aminoisoquinolinones	Catalytic site inhibitor	46
PTP4A3 (PRL)	Thienopyridone	Catalytic site inhibitor	99
PTP4A (PRL)	BR-1 and CG-707	Catalytic site inhibitor	100
PTP4A (PRL)	Antibody	Antibody	49, 50
R-PTPη	Peptide	Activator by disruption of protein-protein interaction	101
Eya2	MSL000544460	Allosteric inhibitor	80, 81

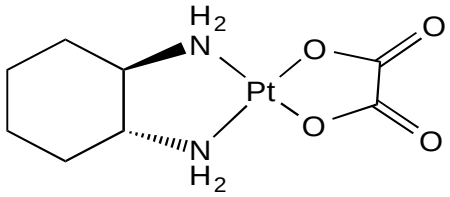
Chemical structures of clinical and experimental metal-based anticancer agents



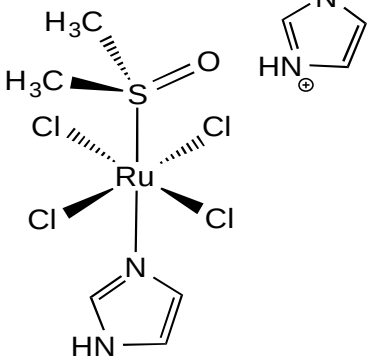
Cisplatin



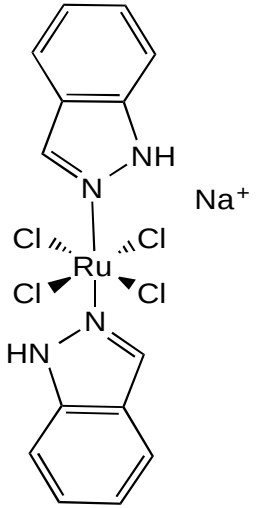
Carboplatin



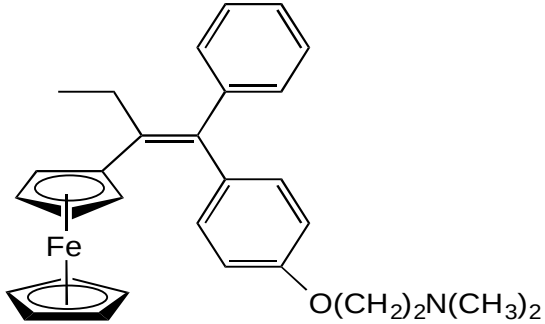
Oxaliplatin



NAMI-A

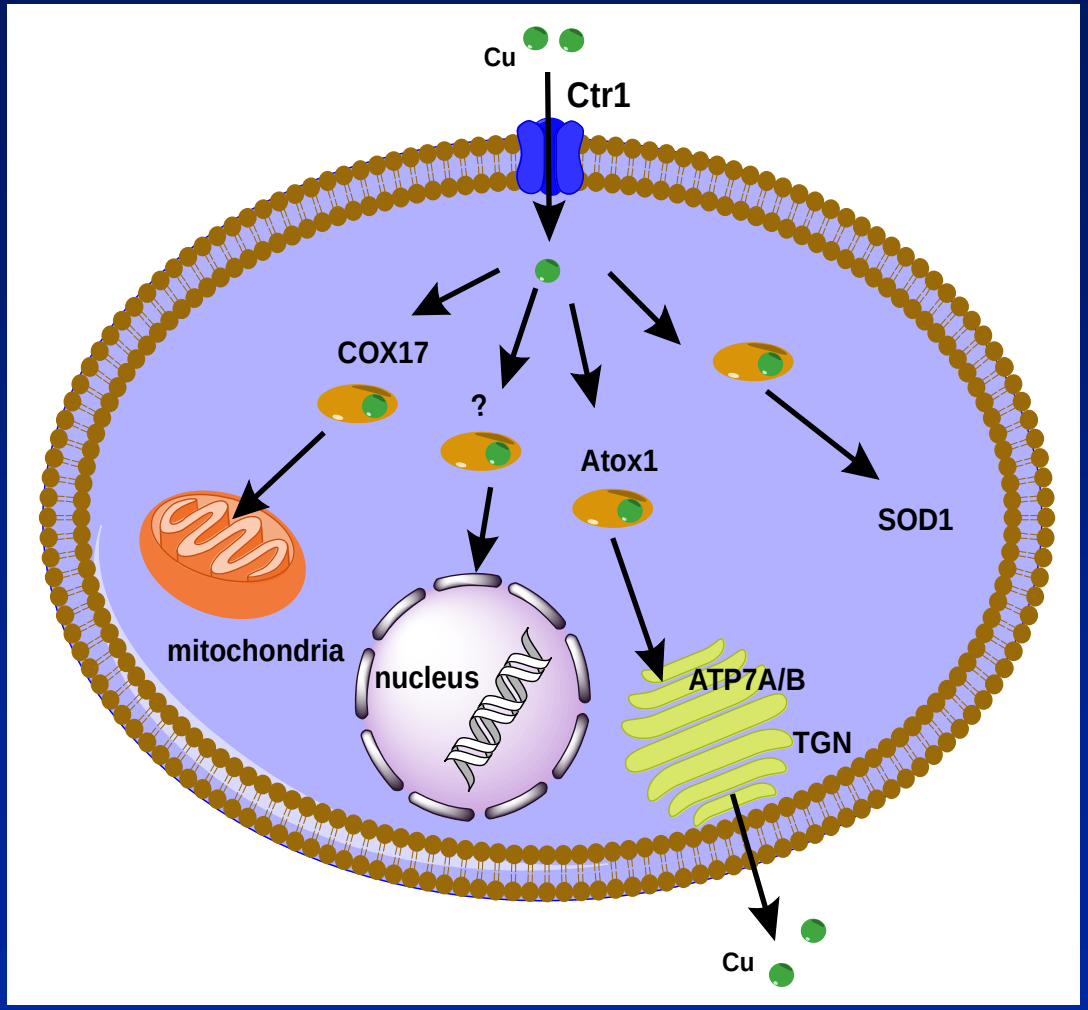


NKP-1339

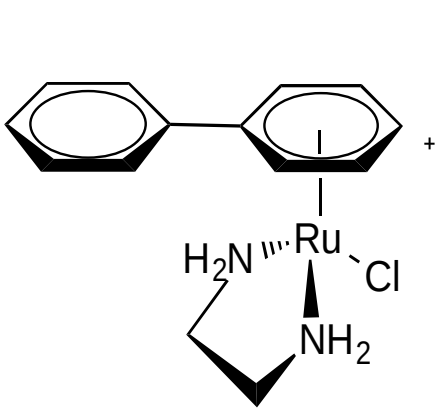


Ferrocifen

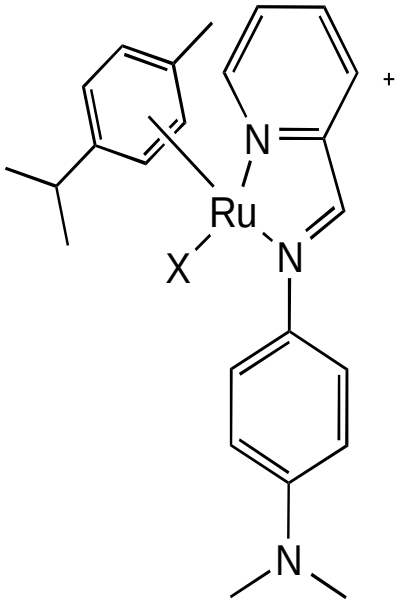
Schematic drawing of the major intracellular human Cu trafficking pathways.



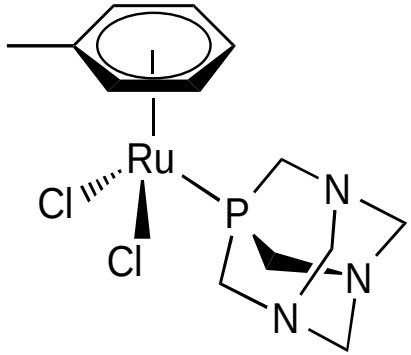
Organometallic Ru(II) arene complexes.



[(*h*^{6}-biphenyl)Ru(en)Cl]$^+$

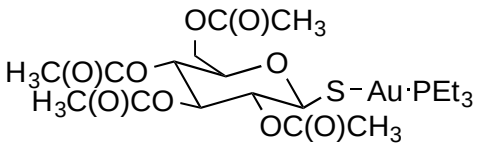


X = Cl, I

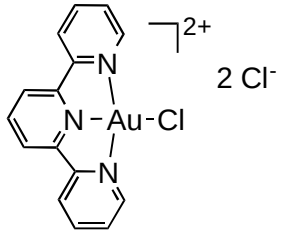


RAPTA-T

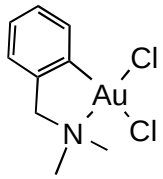
Examples of cytotoxic coordination and organometallic gold(I) and gold(III) compounds.

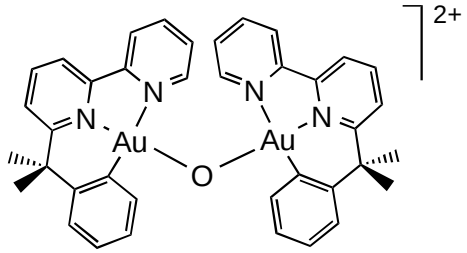


phosphanes
(auranofin**)**

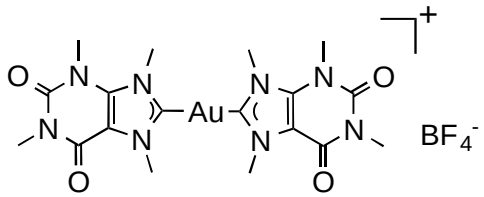


N-donor ligands

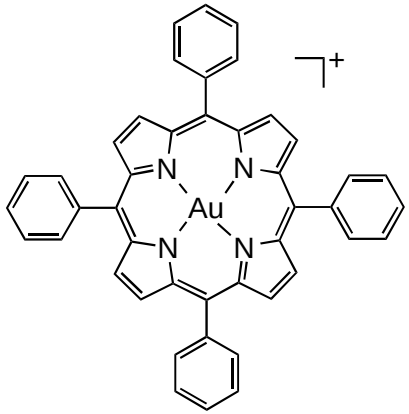




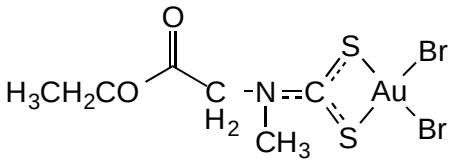
cyclometallated



N-heterocyclic carbenes

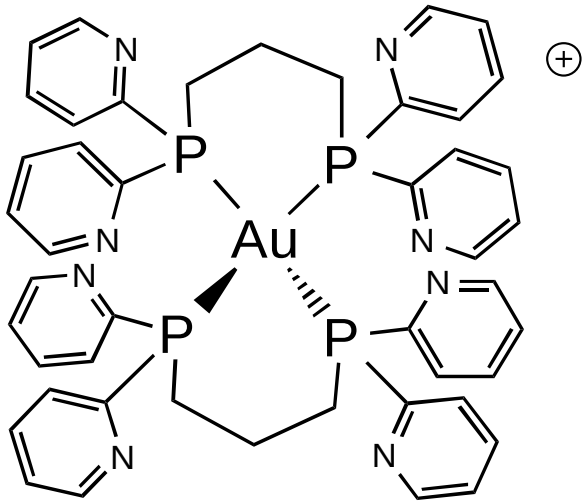


porphyrins

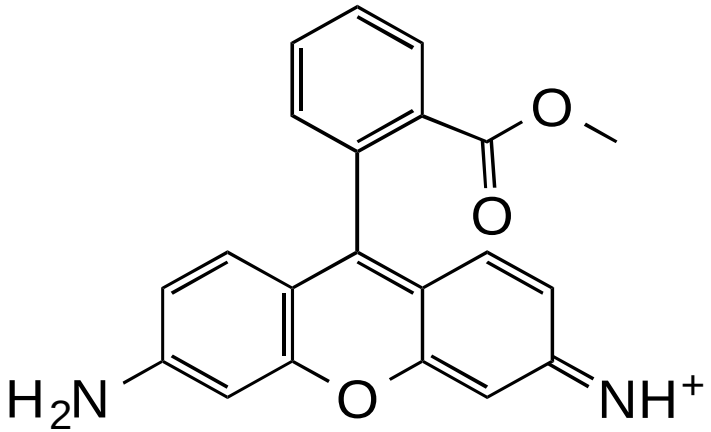


dithiocarbammates

Examples of delocalized lipophilic cations (DLCs) including a Au(I) complex.

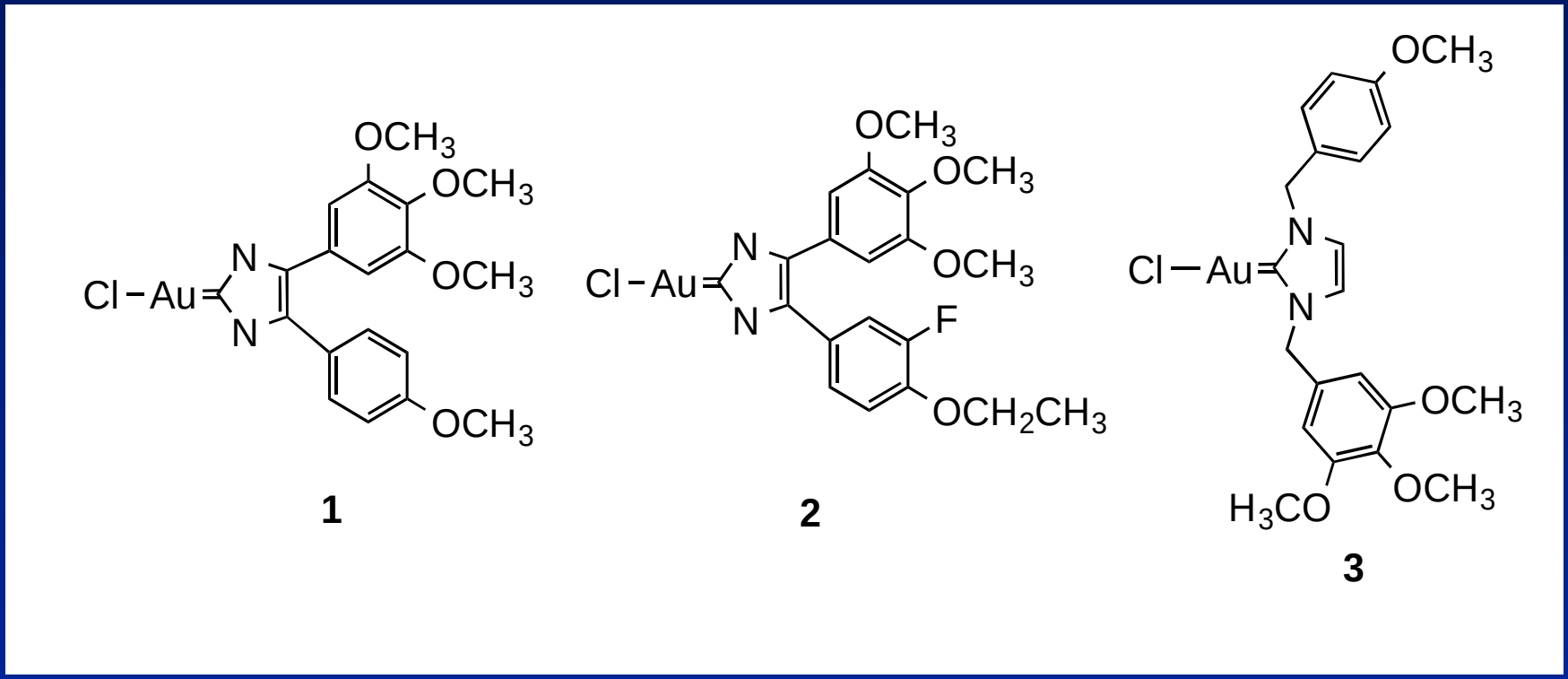


[Au(d2pypp)$_2$]Cl

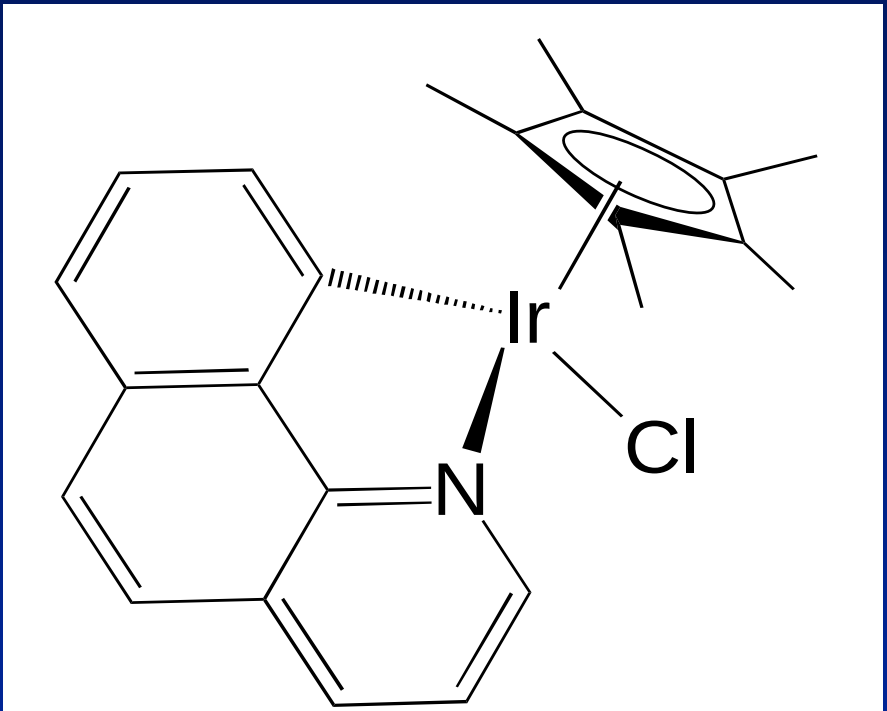


Rhodamine 123

Au(I) NHC complexes chloride-[1,3-dimethyl-4,5-diarylimidazol-2-ylidene]gold(I) 1–2 and chloride-[1,3-dibenzylimidazol-2-ylidene]gold(I) 3.

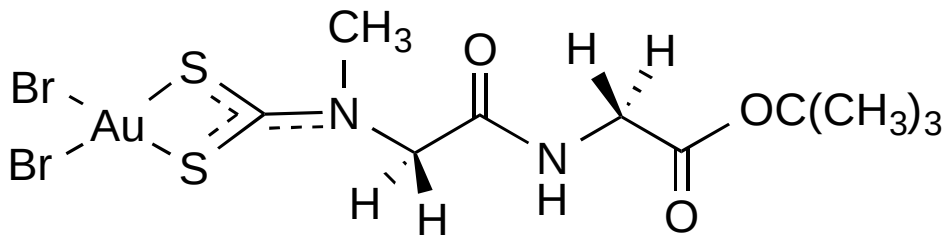


Schematic drawing of the organometallic compound [(η5-Cp*)(Ir)(7,8-benzoquinoline)Cl].



4

Au(III) dipeptidedithiocarbamato and Au(I)-thiosugar complexes.



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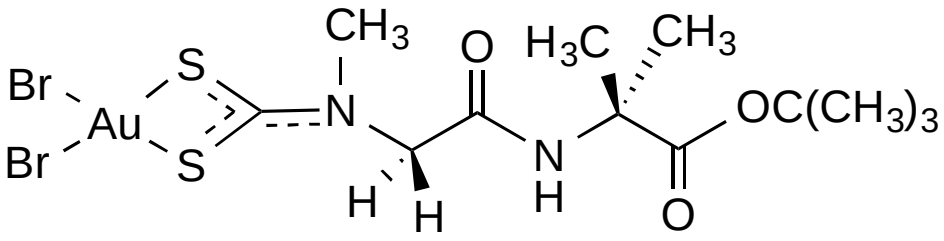

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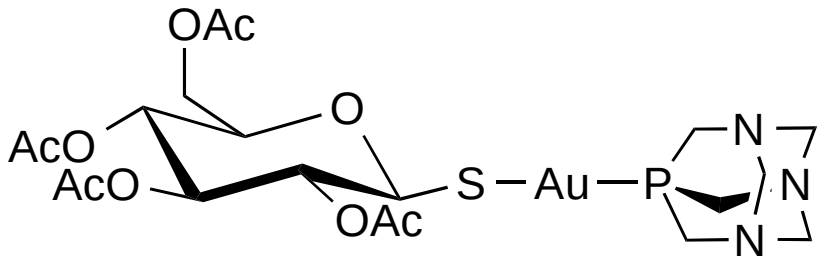
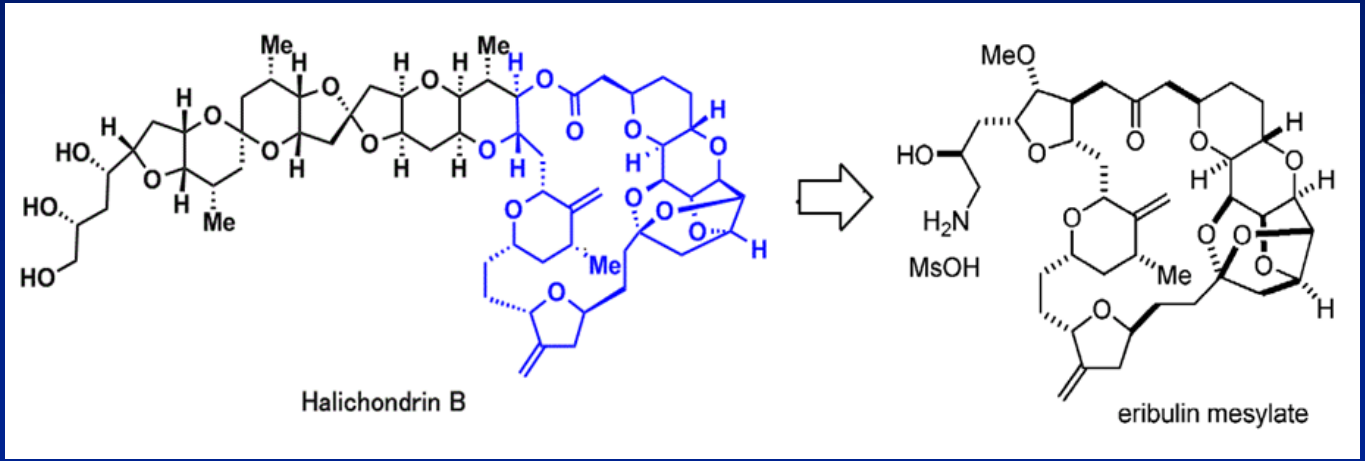
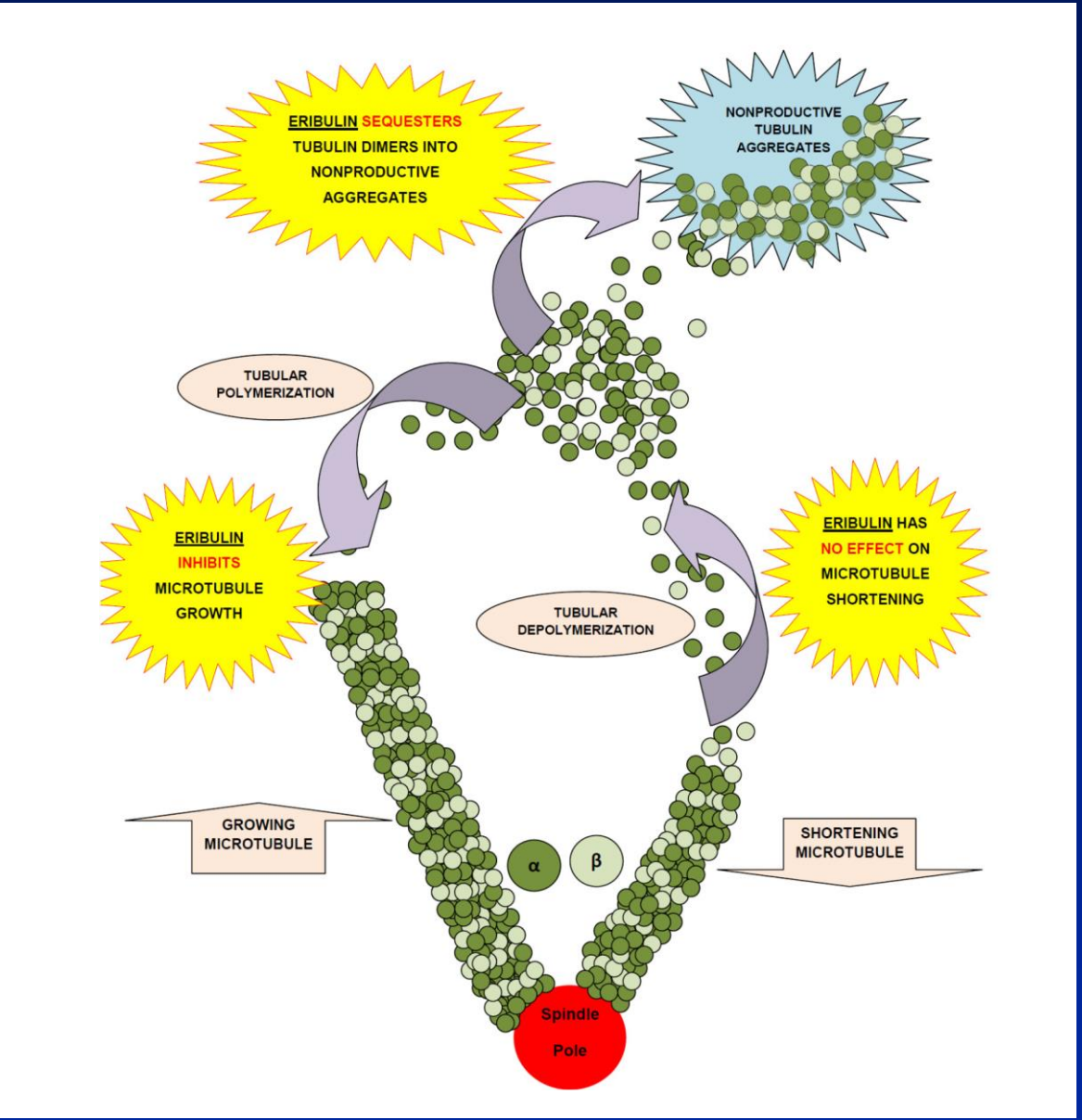


7

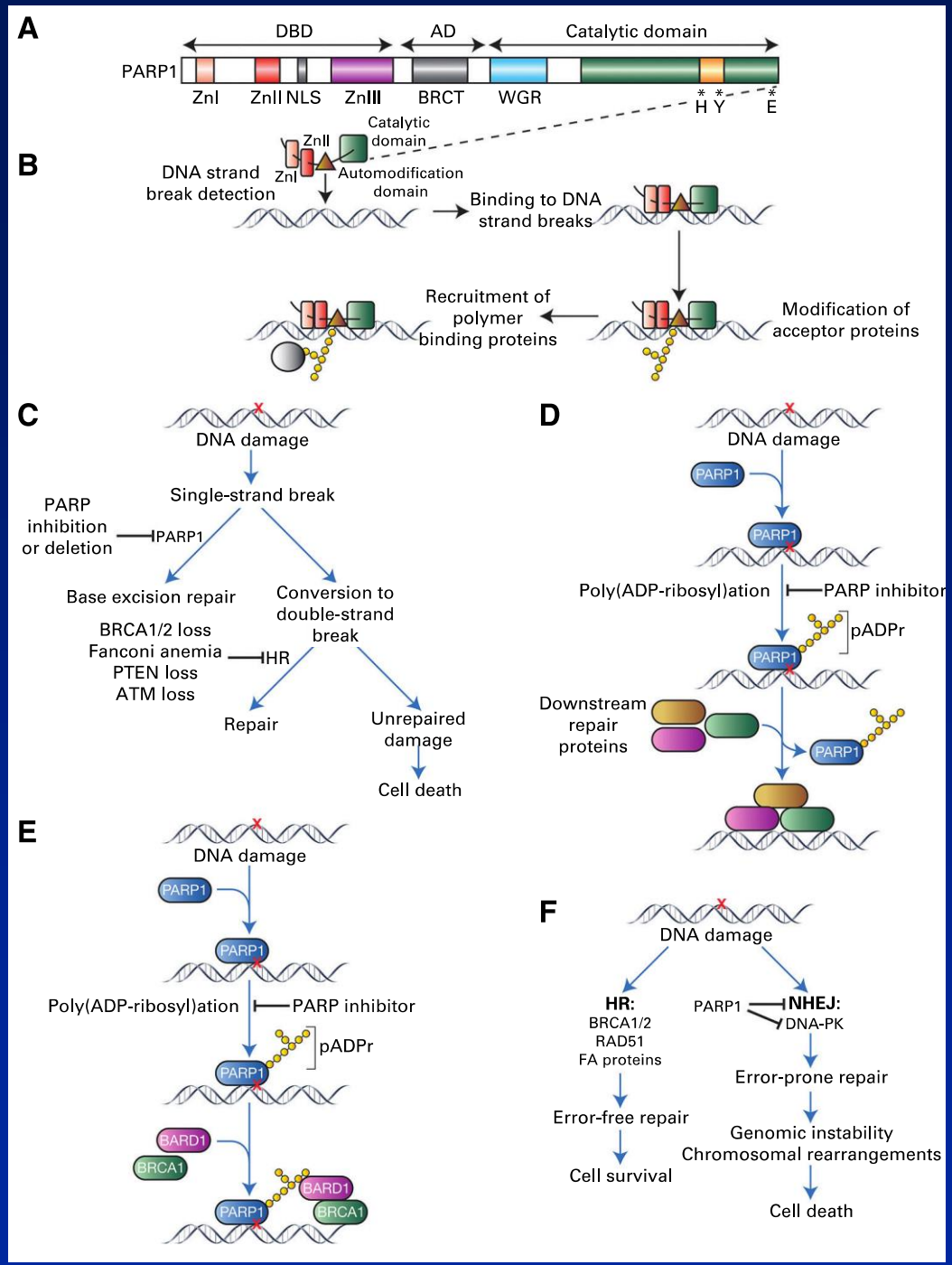
Chemical structures of Halichondrin B and eribulin mesylate.



Mechanism of action of eribulin mesylate.

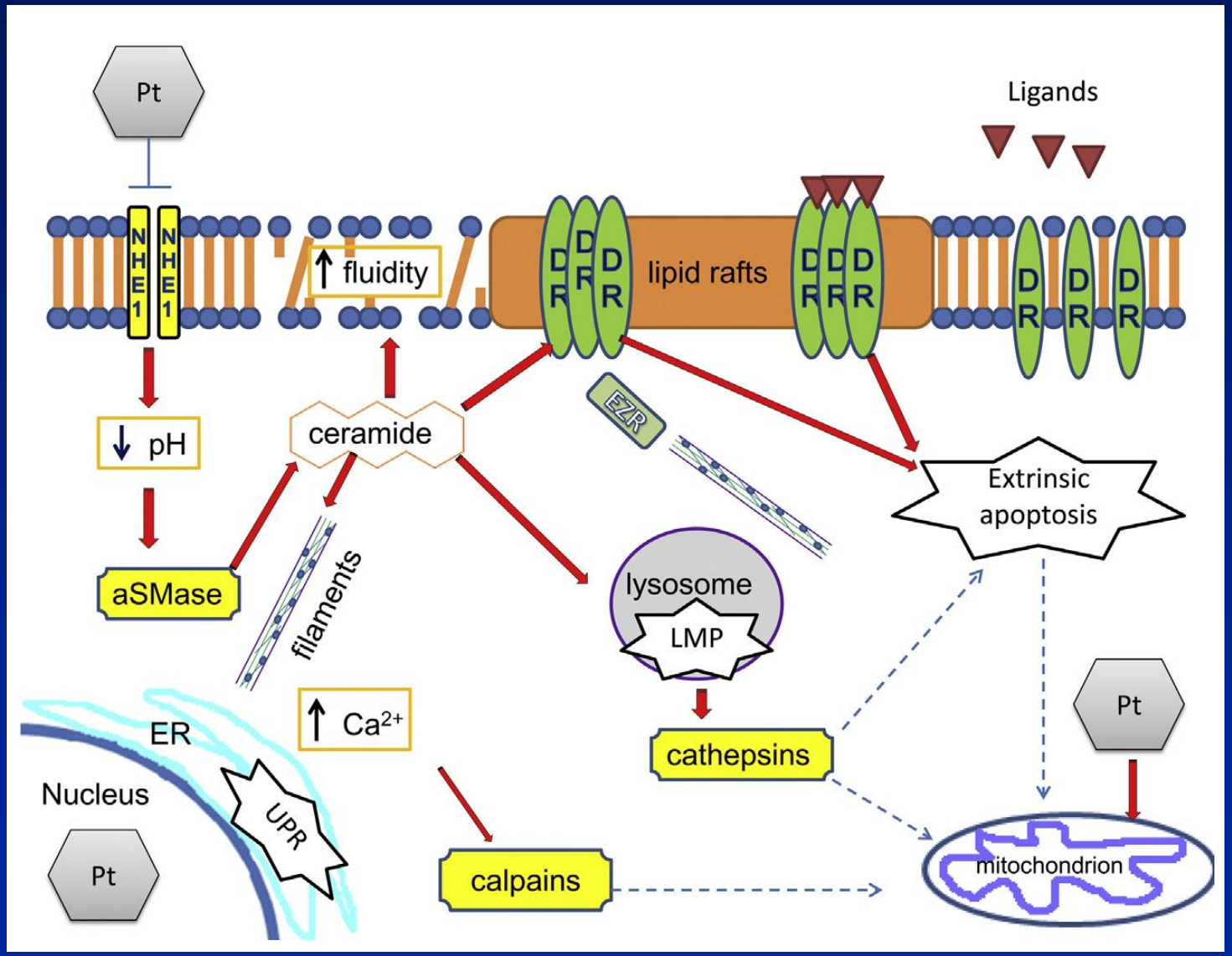


Summary of poly (ADP-ribose) [pADPr] polymerase 1 (PARP1) structure, function, and proposed contribution to synthetic lethality.



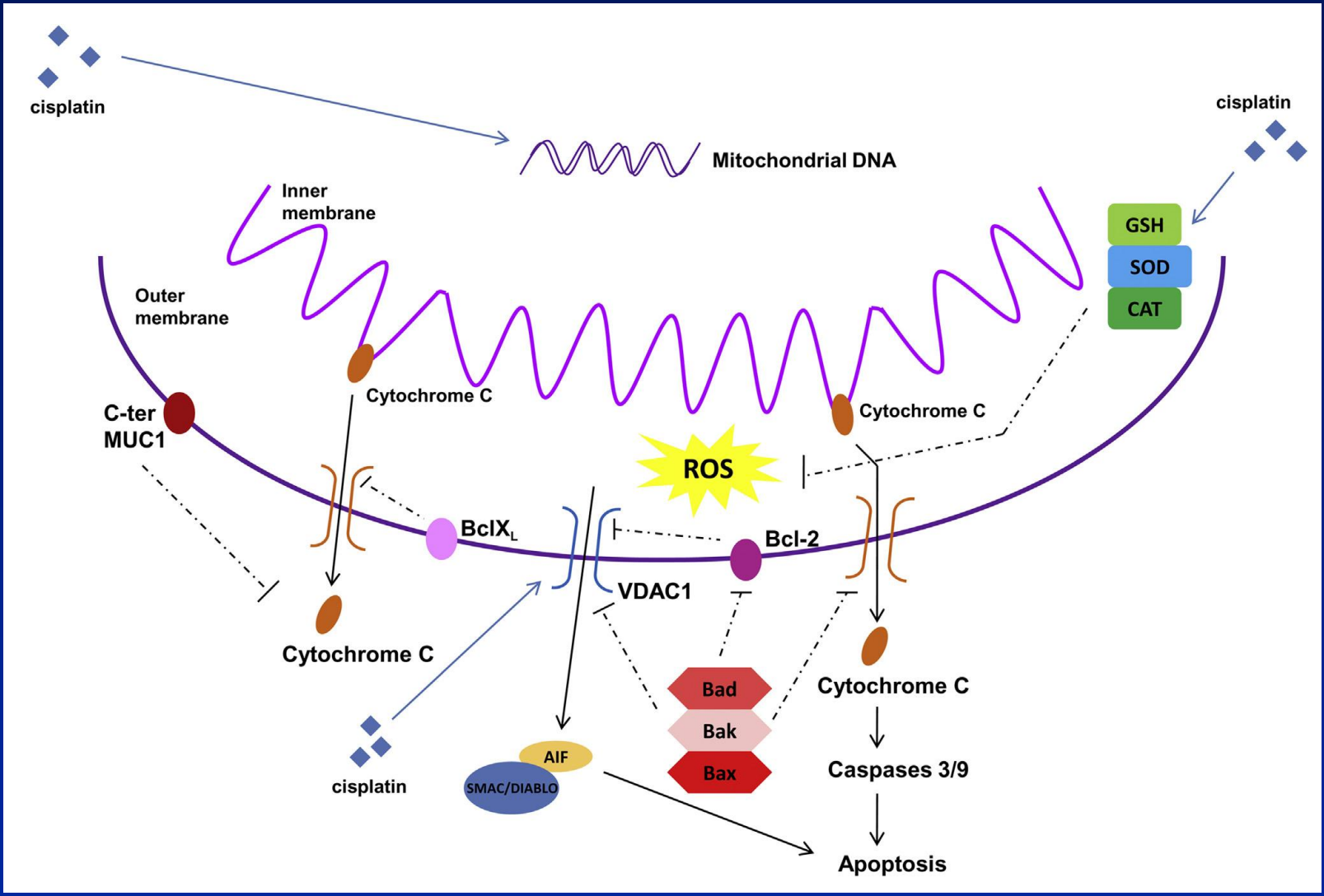
(A) Schematic of PARP1 structure. (B) On binding to damaged DNA, PARP1 undergoes conformation change that increases its catalytic activity, leading to cleavage of NAD□ and addition of ADP- ribose units to various proteins, including its own automodification domain. Result- ing pADPr polymers (depicted as chains of yellow circles) alter function of proteins that are modified (eg, by decreasing affin- ity of PARP1 for damaged DNA)29 and also recruit additional proteins that bind to polymer noncovalently.30,31 (C-F) Mod- els proposed to explain observed syn- thetic lethality between homologous recombination (HR) deficiency and PARP inhibition. These models emphasize (C) role of PARP1 in base excision repair, (D) recruitment of DNA repair proteins, (E) recruitment of BARD1-BRCA1 complex, and (F) suppression of nonhomologous end joining (NHEJ). AD, automodification domain; BRCT, BRCA1 C-terminal do- main; DBD, DNA binding domain; FA, Fan- coni anemia; NLS, nuclear localization signal; PK, protein kinase; WGR, tyrptophan-glycine-arginine-rich domain; Zn, zinc finger.

Schematic representation of the effects of platinum compounds on subcellular compartments.



New mechanisms for old drugs: Insights into DNA-unrelated effects of platinum compounds and drug resistance determinants - Drug Resistance Updates 20 (2015) 1–11 - Fig 01

Mitochondria as subcellular targets of platinum complexes.



Agentes Citotóxicos

Agentes Alquilantes
Antimetabólitos
Produtos Naturais

Agentes Alquilantes

Mostardas nitrogenadas
Derivado da metilhidrazina
Alquil sulfonado
Nitrosuréias
Triazenos
Complexos de Platina

Mostardas Nitrogenadas

Mecloroetamina
Ciclofosfamida
Ifosfamida
Melfalan
Clorambucil

Devidado da metilhidrazina

Procarbazina

Alquil Sulfonado

Busulfan

Nitrosuréias

Carmustina
Estreptozotocina
Bendamustina

Triazenos

Dacarbazina
Temozolomida

Complexos de Platina

Cisplatina
Carboplatina
Oxaliplatina

Antimetabólitos

Análogos do ácido fólico
Análogos de pirimidina
Análogos de purina

Análogos do Ácido Fólico

Metotrexato
Pemetrexed

Análogos de Pirimidina

Fluouracil
Capecitabina
Citarabina
Gemcitabina
5-aza-citidina
Deoxi-5-aza-citidina

Análogos de Purina

Mercaptopurina
Pentostatina
Fludarabina
Clofarabina
Nelarabina

Produtos Naturais

Alcalóides da Vinca
Taxanos
Epipodofilotoxina
Camptotecinas
Antibióticos
Equinocandinas
Antracenos
Enzimas

Alcalóides da Vinca

Vinblastina
Vincristina
Vinorelbina

Taxanos

Paclitaxel
Docetaxel

Epipodofilotoxina

Etoposídeo

Camptotecinas

Topotecan
Irinotecan

Antibióticos

Actnomicina D
Daunorubicina
Doxorubicina

Equinocandinas

Yondelis

Antracenos

Mitoxantrona
Bleomicina

Enzimas

L-asparaginase