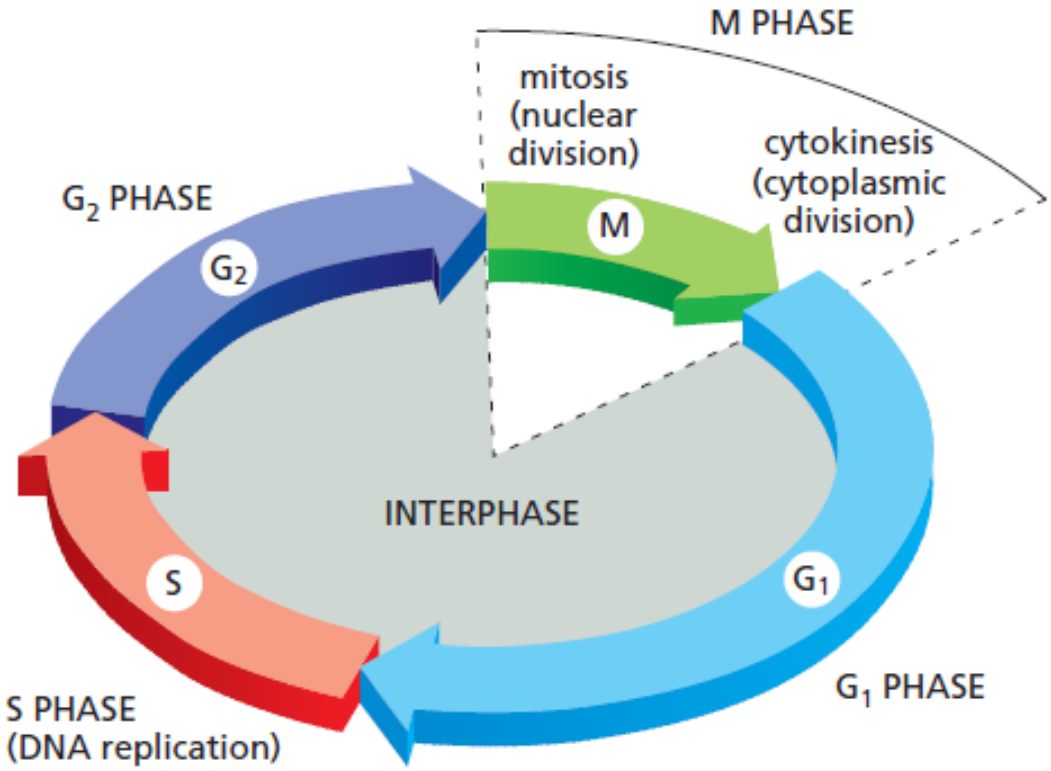
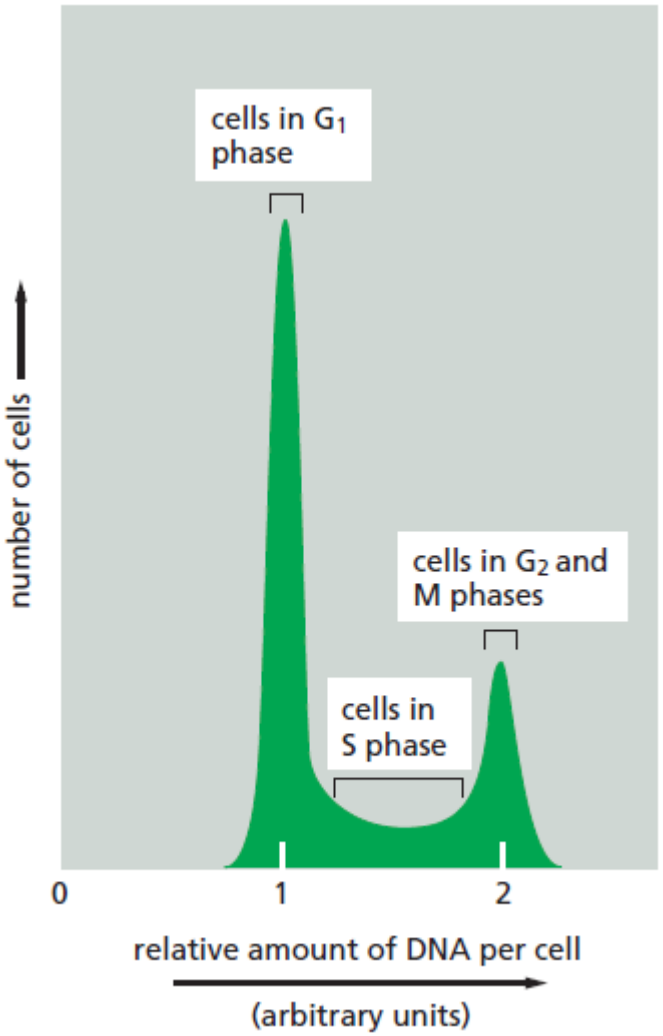
Chemical aspects of the cell

Compounds that induce cell proliferation, differentiation and death

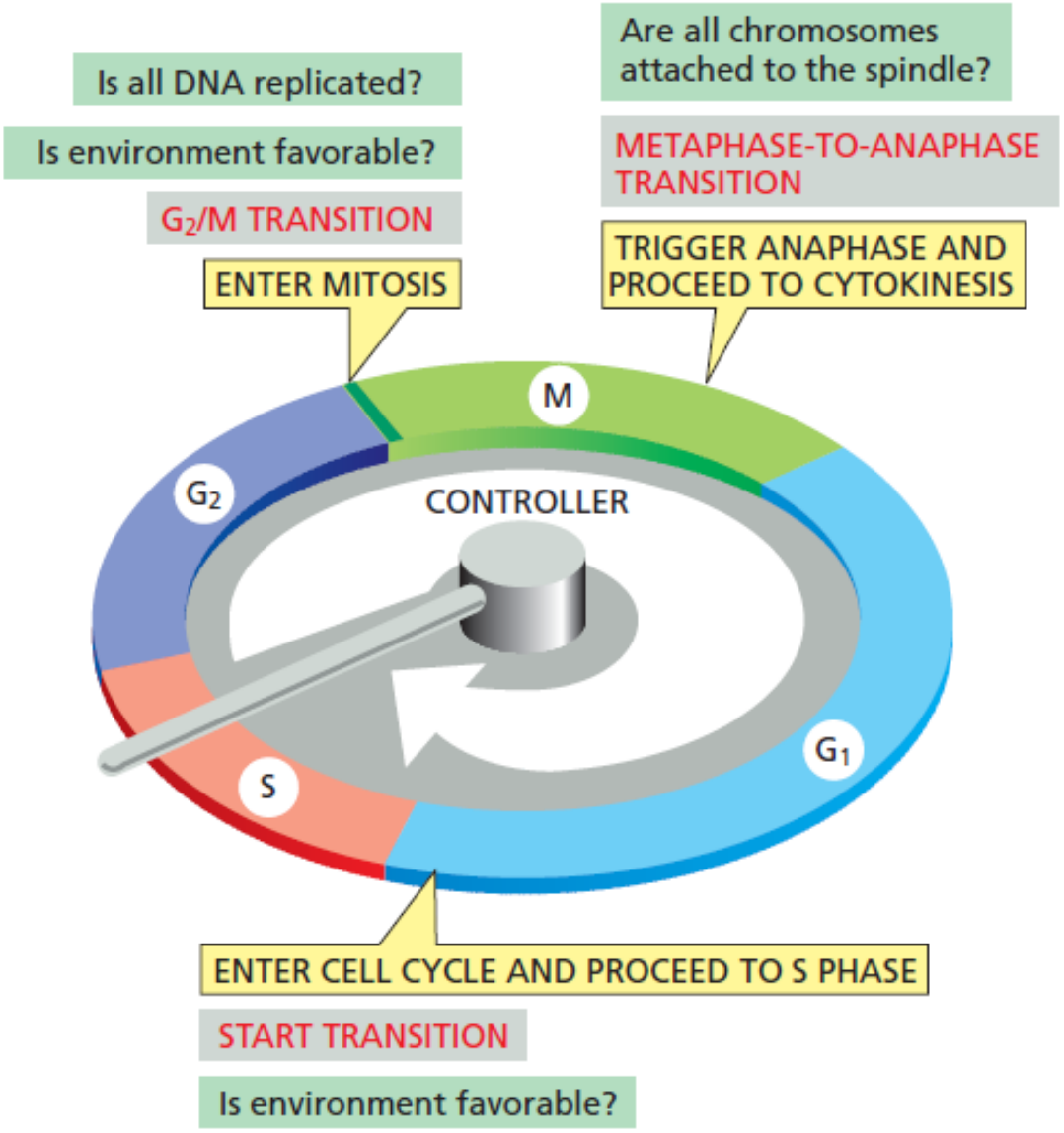
Cell proliferation

The cell cycle

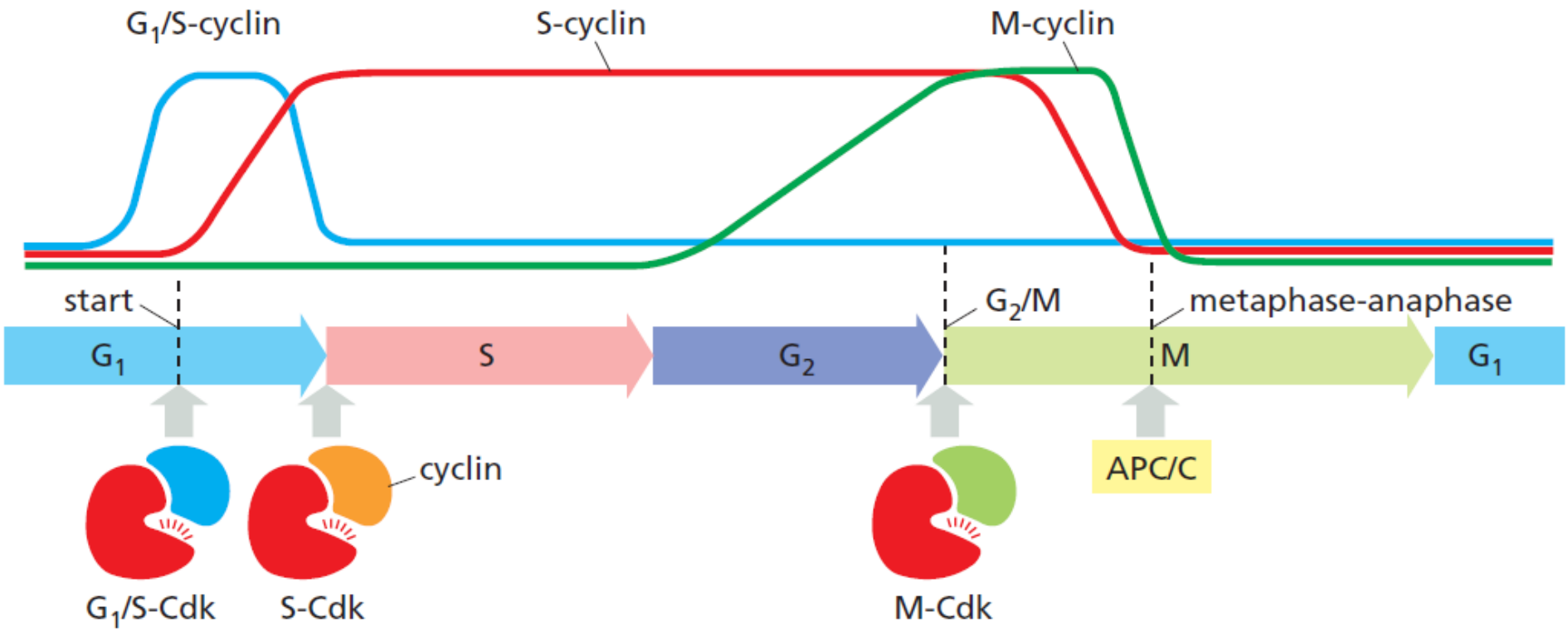




Cell cycle


Are all chromosomes attached to the spindle?
Is all DNA replicated?
METAPHASE-TO-ANAPHASE TRANSITION
Is environment favorable?
G_2/M TRANSITION
TRIGGER ANAPHASE AND PROCEED TO CYTOKINESIS
ENTER MITOSIS
M
G_2
CONTROLLER
G_1
S
ENTER CELL CYCLE AND PROCEED TO S PHASE
START TRANSITION
Is environment favorable?

Cell cycle control



G1/S-cyclins activate Cdks in late G1 and thereby help trigger progression through Start, resulting in a commitment to cell-cycle entry. Their levels fall in S phase.

S-cyclins bind Cdks soon after progression through Start and help stimulate chromosome duplication. S-cyclin levels remain elevated until mitosis, and these cyclins also contribute to the control of some early mitotic events.

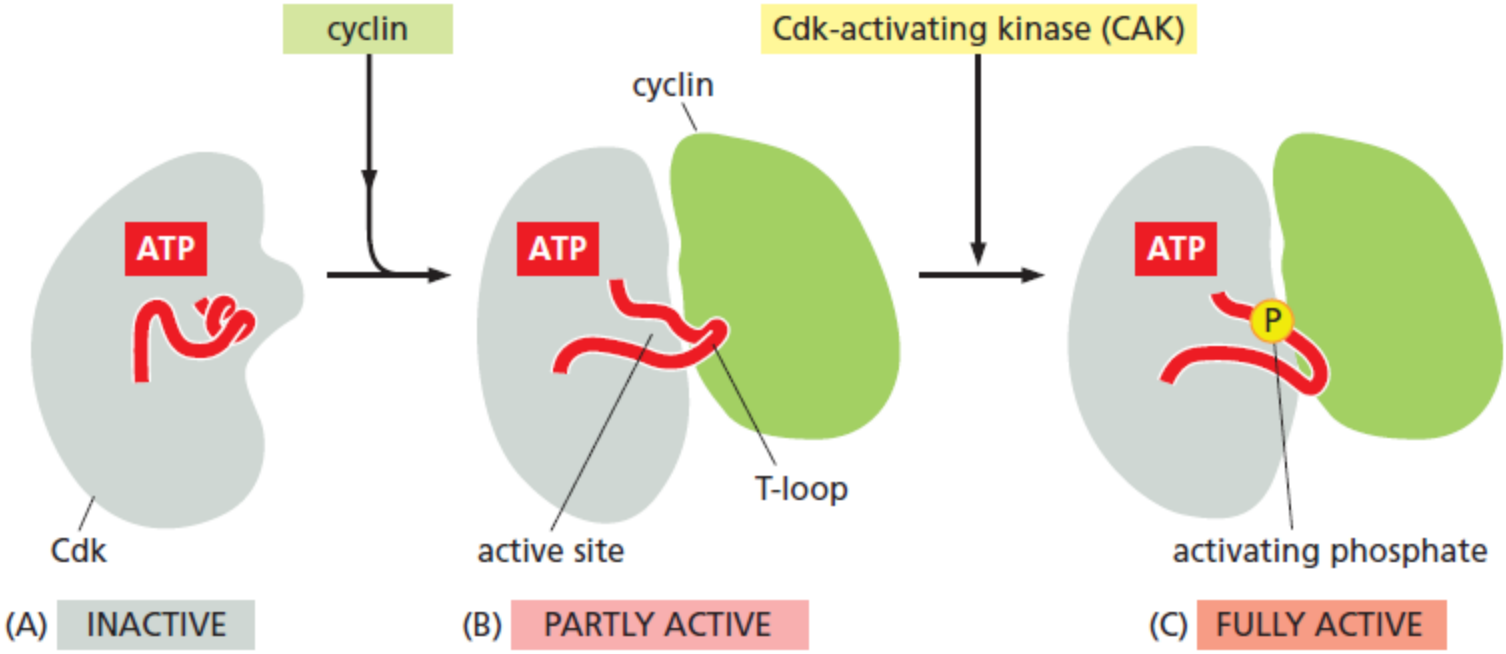
M-cyclins activate Cdks that stimulate entry into mitosis at the G2/M transition. M-cyclin levels fall in mid-mitosis.

Cell cycle control

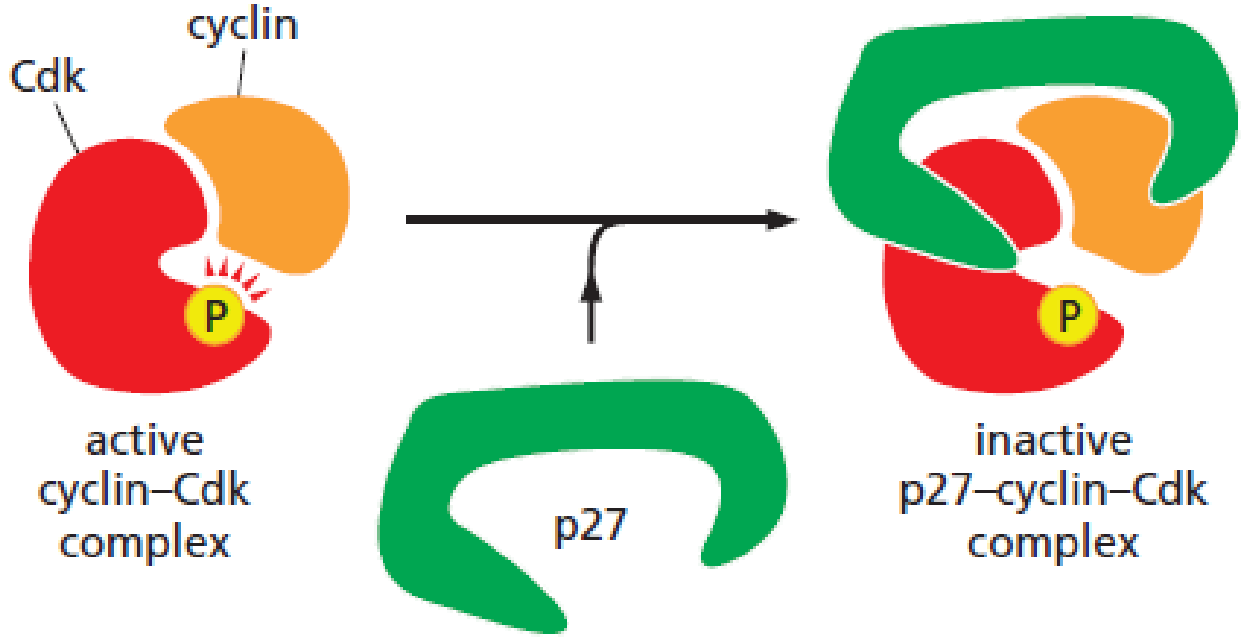
TABLE 17–1 The Major Cyclins and Cdks of Vertebrates and Budding Yeast				
	Vertebrates		Budding yeast	
Cyclin–Cdk complex	Cyclin	Cdk partner	Cyclin	Cdk partner
G_1-Cdk	Cyclin D*	Cdk4, Cdk6	Cln3	Cdk1**
G_1/S-Cdk	Cyclin E	Cdk2	Cln1, 2	Cdk1
S-Cdk	Cyclin A	Cdk2, Cdk1**	Clb5, 6	Cdk1
M-Cdk	Cyclin B	Cdk1	Clb1, 2, 3, 4	Cdk1

* There are three D cyclins in mammals (cyclins D1, D2, and D3).
** The original name of Cdk1 was Cdc2 in both vertebrates and fission yeast, and Cdc28 in budding yeast.

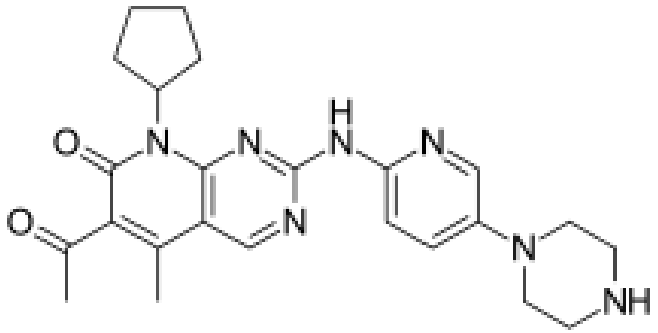
Cell cycle control – CDK activation



Cell cycle control – CDK regulation

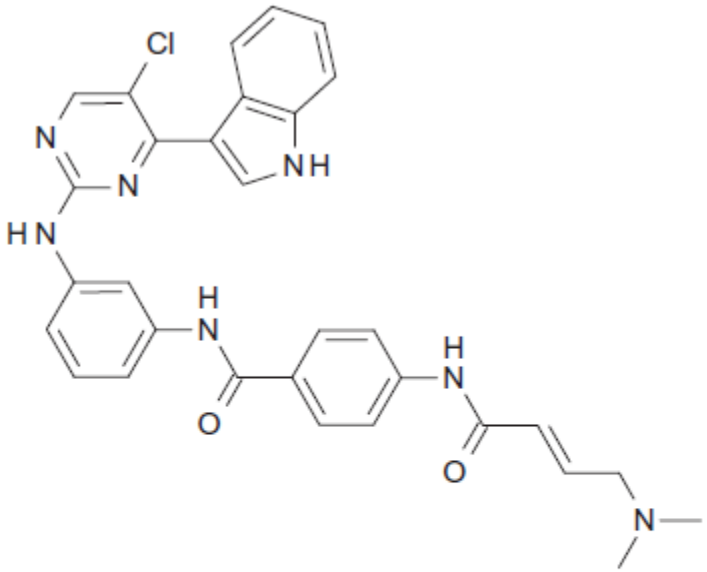


Cell cycle control – CDK inhibitors



Palbociclib: inhibitor of CDK4 and 6
Drug in use for a type of breast cancer

Rocca A, Farolfi A, Bravaccini S, Schirone A, Amadori D. *Expert Opin. Pharmacother.* **2014**, *15*, 407-420.



THZ1
First covalent, irreversible and selective CDK7 inhibitor
Type II inhibitor (ATP competitive)
CDK7 IC_{50}= 3.2nM
Jurkat IC_{50} = 50nM

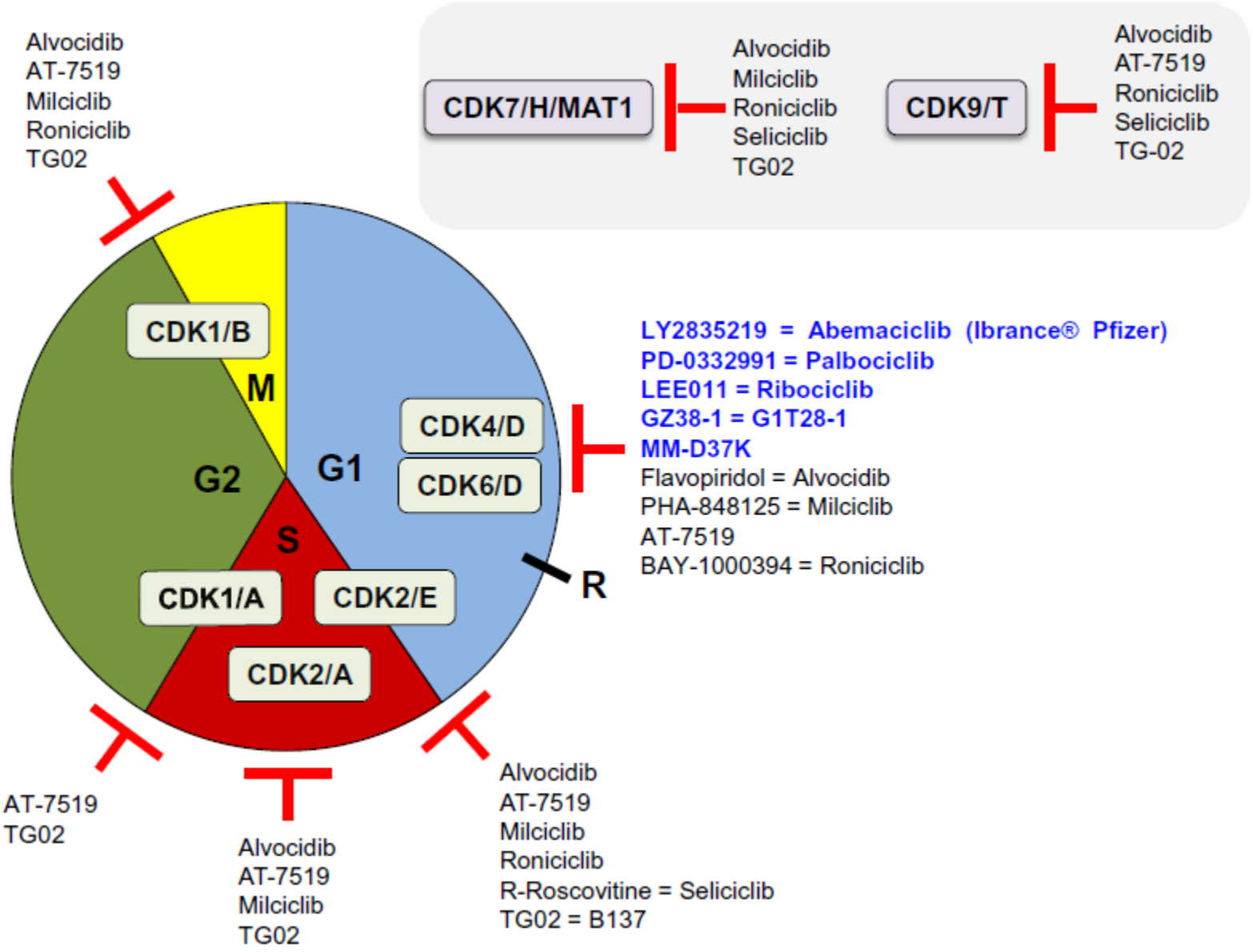
Sánchez-Martínez, C.; Gelbert L.M.; Lallena, M.J.; de Dios, A. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3420-3435.

Cell cycle control – CDK inhibitors

Drug	Company (Sponsor)	Primary Target	Other targets	Stage of development	Delivery	References
Palbociclib = PD-0332991	Pfizer (Onyx Pharmaceuticals)	CDK4/6		FDA approved	PO	64
Abemaciclib = LY2835219	Eli Lilly	CDK4/6		Phase III	PO	65
Ribociclib = LEE-011	Novartis/Astex	CDK4/6		Phase III	PO	66
Alvocidib = Flavopiridol	Sanofi (Tolero)	CDK1/4/9	CDK5/6/7	Phase II	IV	44
Milciclib = PHA-848125	Nerviano	CDK2, TrKA	CDK1/4/5/7	Phase II	PO	59
MM-D37K	MetaMax	CDK4		Phase I/II	IV	34
G1T28-1 = GZ38-1	G-1 Therapeutics	CDK4/6		Phase I	IV	71
TG-02 = SB-1317 = EX45	Tragara Pharmaceuticals	CDK1/2/3/5/7/9	FLT3, JAK2, MAPK7	Phase I	PO	62
Seliciclib = R-Roscovitine = CY-202	Cyclacel	CDK1/2/5/7/9		Phase II	PO	45
AT-7519	Astex (NCIC)	CDK2/5/9	CDK1/3/4/6, GSK3β	Phase II	IV	61
Roniciclib = BAY-1000394	Bayer	CDK1/2/4/7/9	VEGFR	Phase II	PO	60
Dinaciclib = SCH-727965 = MK-7965	Merck (NCI)	CDK1/2/5/9		No devlopment reported	IV	56
RGB-286638	Agennix	CDK1/2/3/4/5/6/7/9	GSK3β, JAK2, MEK1, TAK1, C-src, AMPK	Discontinued	IV	48
AZD5438	AstraZeneca	CDK1/2/5/9	CDK4/7	Discontinued	PO	50
ZK-304709	Bayer/Schering	CDK1/2/9	CDK4/7, VEGFR1-3, PDGFRβ	Discontinued	PO	51
R547 = RO-4584820	Hoffmann-La Roche Inc	CDK1/2/4		Discontinued	IV	49
PHA-793887	Nerviano	CDK2/5/7	CDK1/4/9, GSK3b	Discontinued	IV	47
AG-024322	Pfizer	CDK1/2/4		Discontinued	IV	52
P1446A-05	Piramal	CDK4		Discontinued	PO	54
Riviciclib = P276-00	Piramal	CDK1/4/9	CDK2/6/7, PKC, PKA, MAPK1	Discontinued	IV	55
BMS-387032 = SNS-032	Sunesis/BMS	CDK2/7/9	CDK1/4/5, GSK3αβ	Discontinued	IV	46

Sánchez-Martínez, C.; Gelbert L.M.; Lallena, M.J.; de Dios, A. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3420-3435.

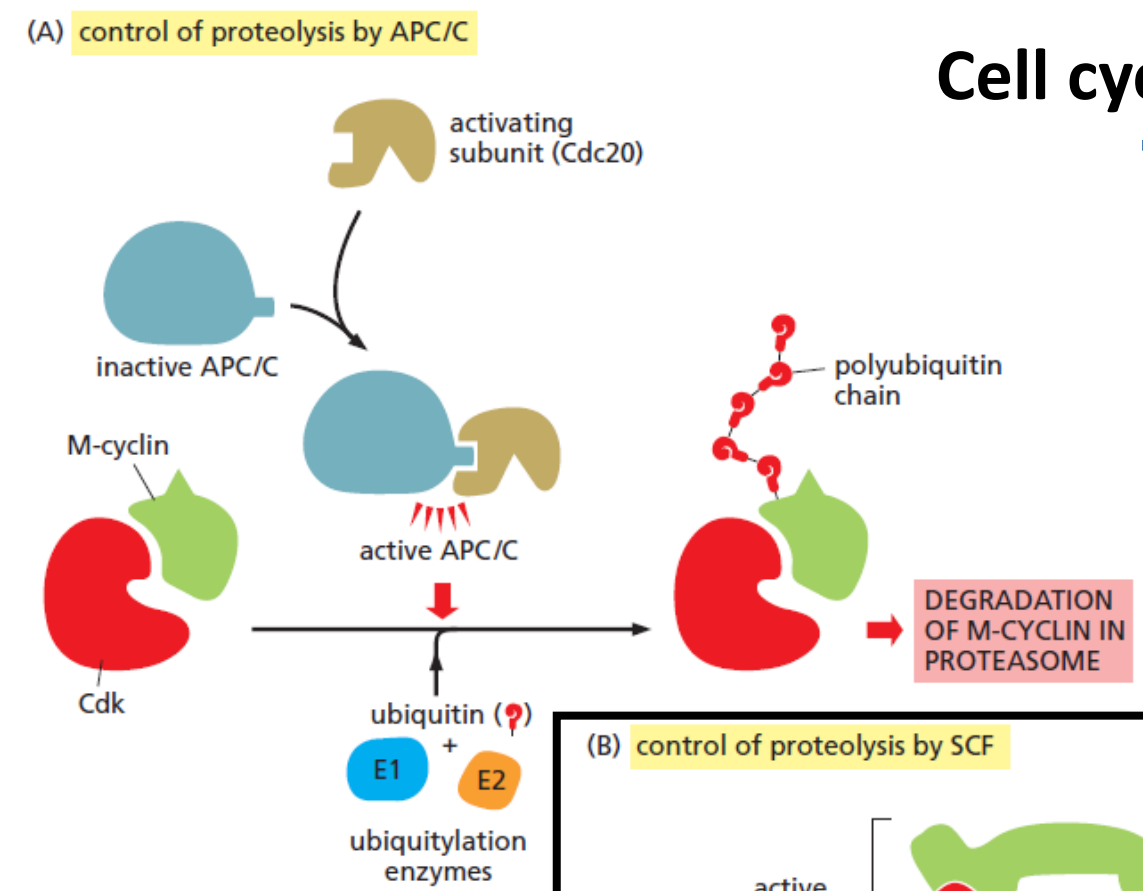
Cell cycle control – CDK inhibitors

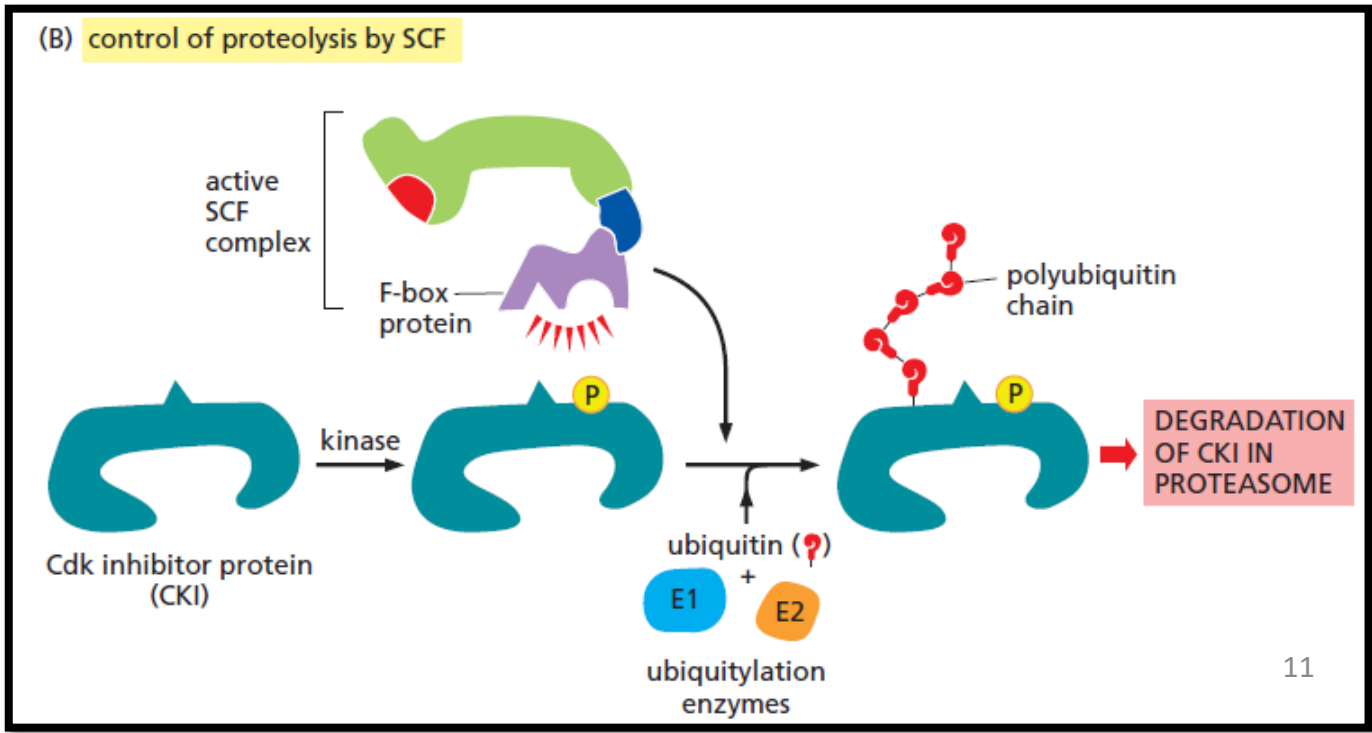


Sánchez-Martínez, C.; Gelbert L.M.; Lallena, M.J.; de Dios, A. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3420-3435.

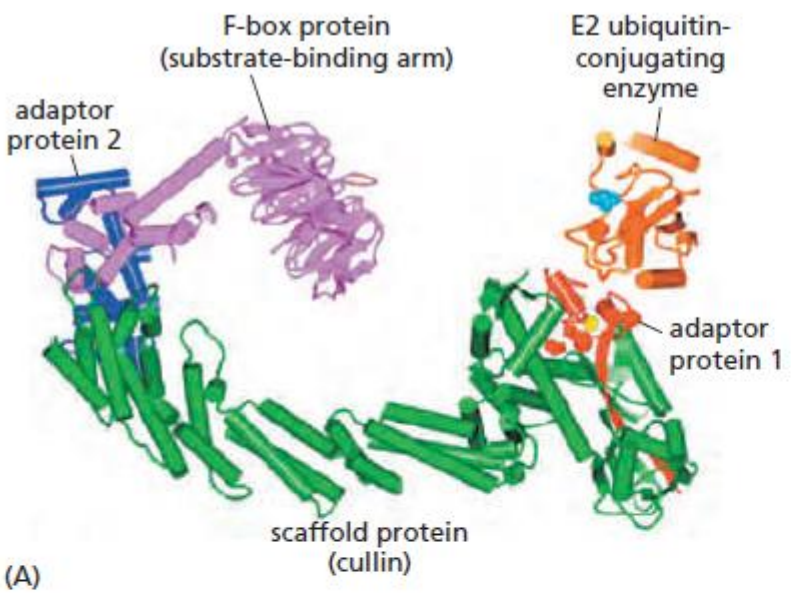
Cell cycle control – proteolysis

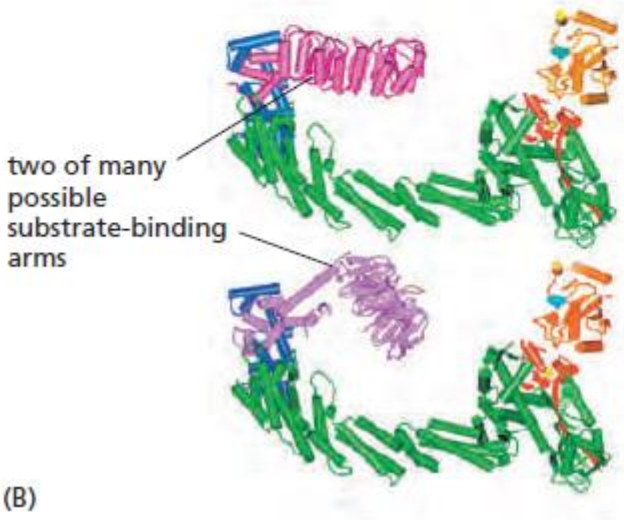
The key regulator is the anaphase-promoting complex, or cyclosome (APC/C) for proteolysis. SCF is also important.

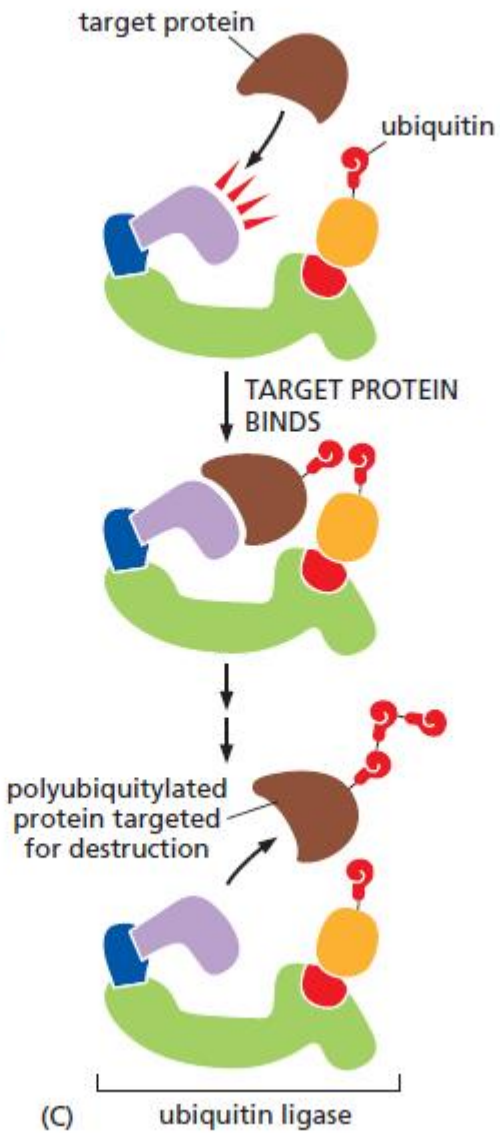




Structure of Skp, Cullin, F-box (SCF) complex







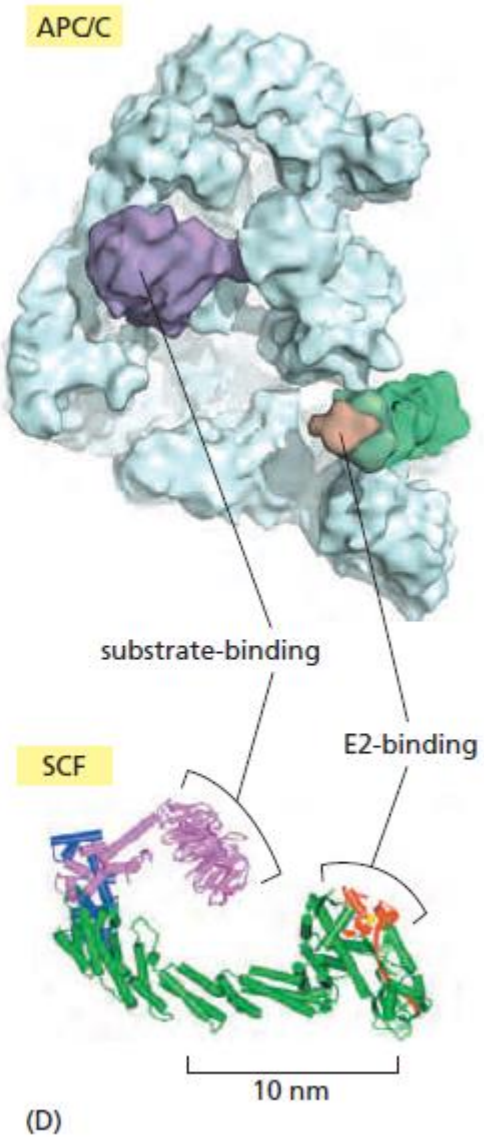
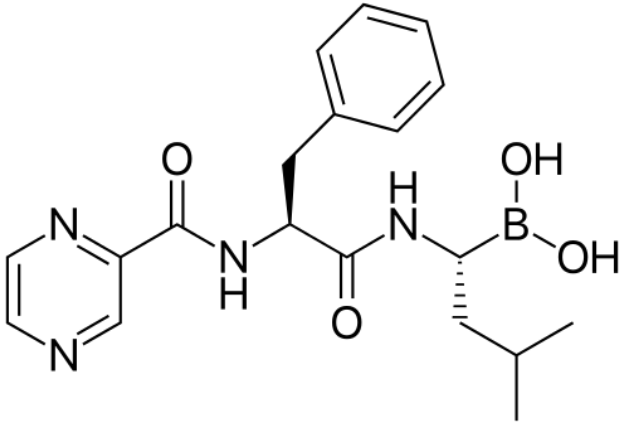
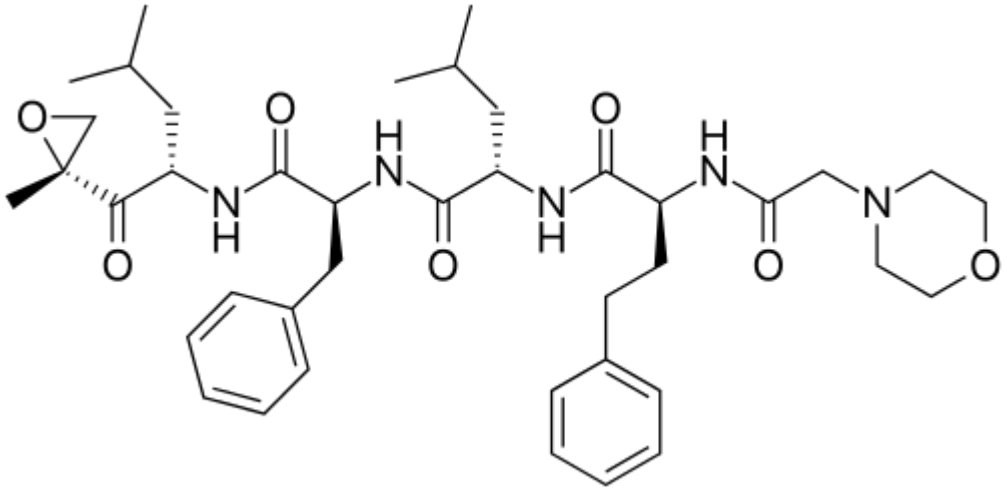


Fig. 3.71 -Molecular Biology of the Cell

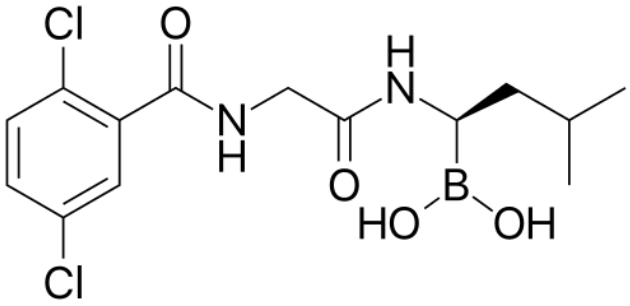
Proteasome inhibitors



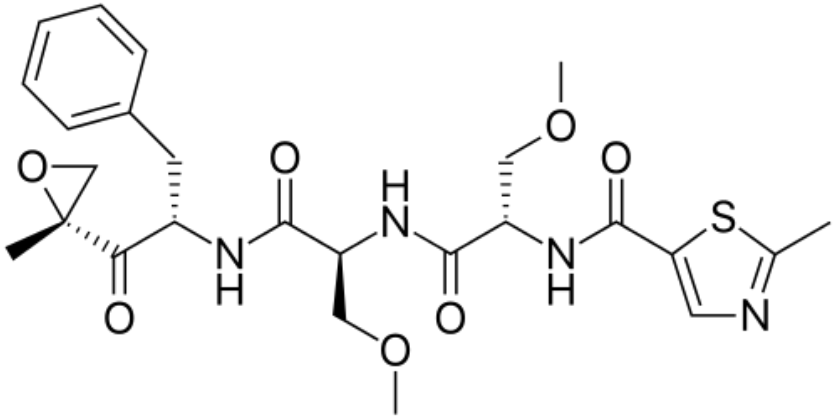
Bortezomib (drug)



Carfilzomib (drug)



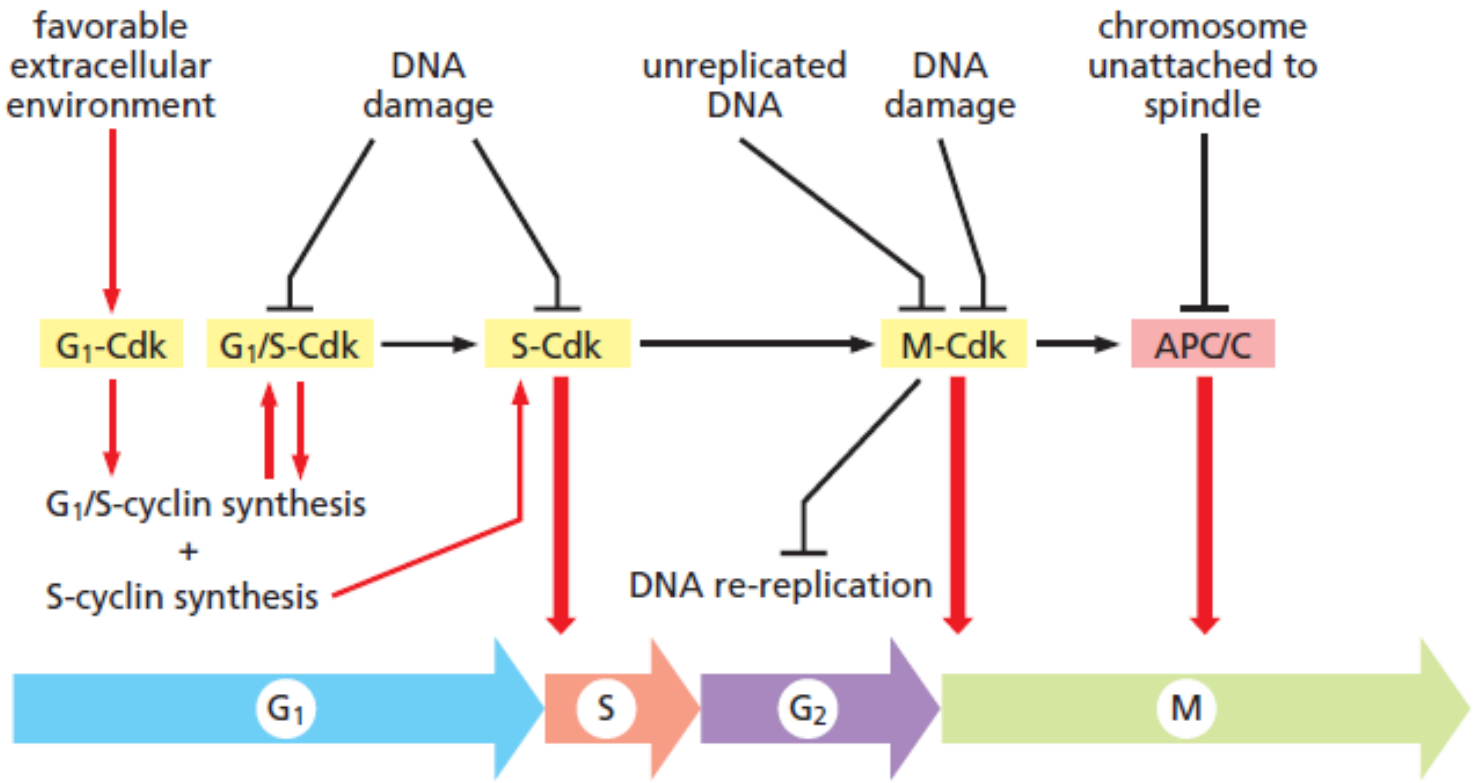
Ixazomib (drug)



Oprozomib (investigational)

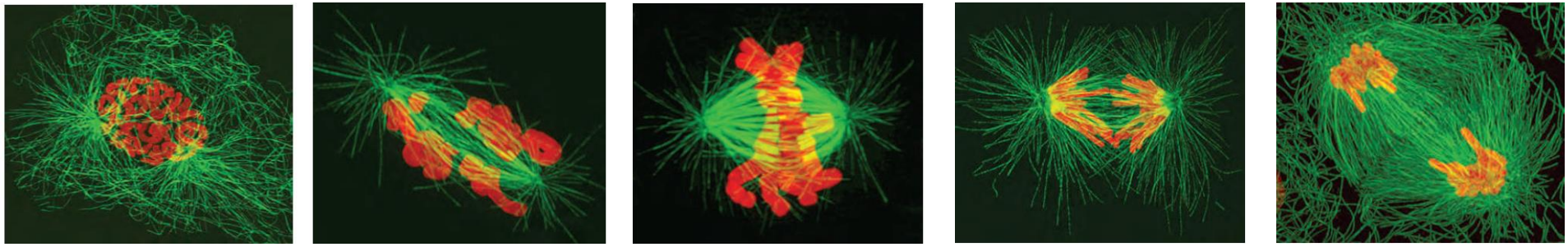
Manasanch, E.E.; Orlowski, R.Z. *Nat. Rev. Clin. Oncol.* **2017**, in press, doi:10.1038/nrclinonc.2016.206

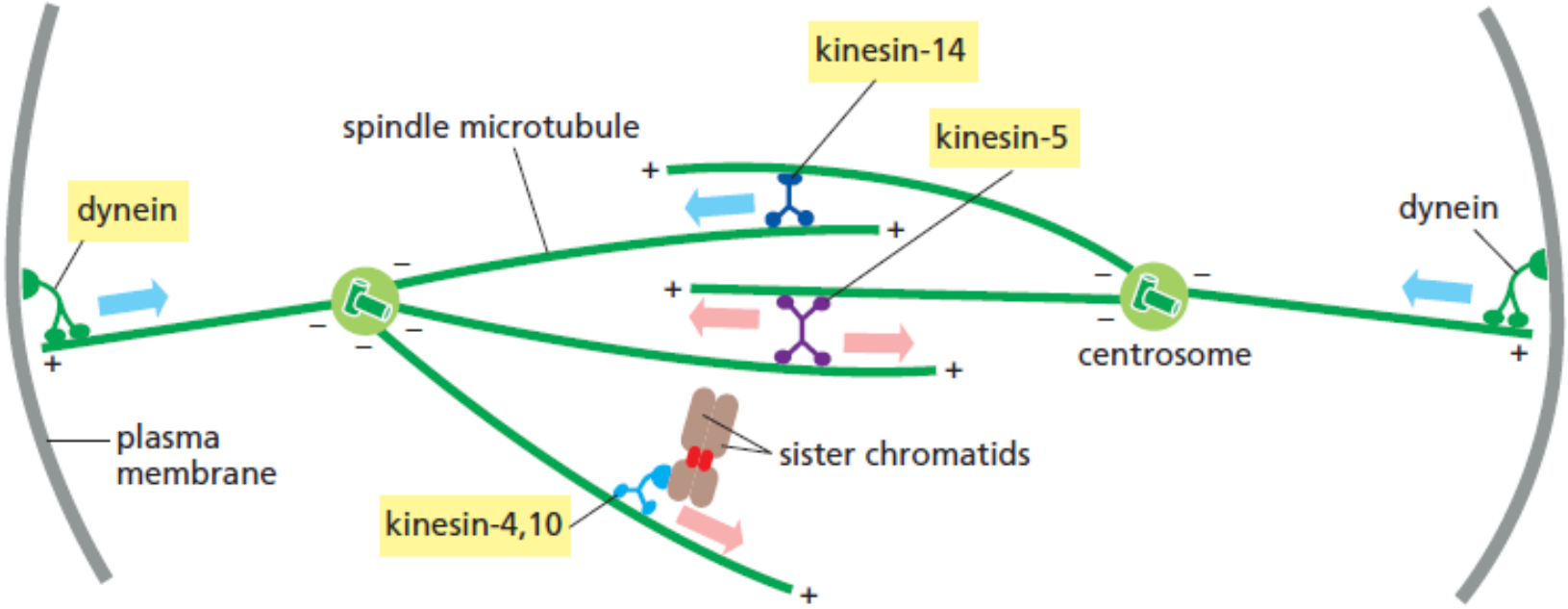
Cell cycle control



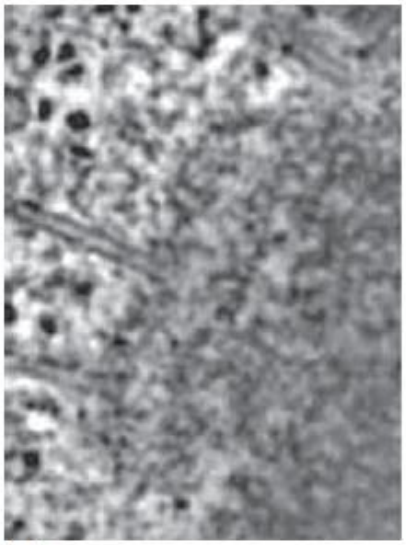
Cell cycle – mitosis

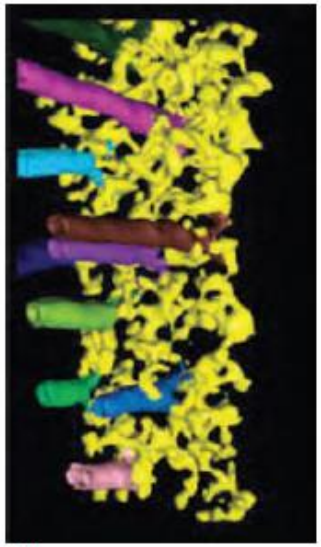
Prophase | Prometaphase | Metaphase | Anaphase | Telophase



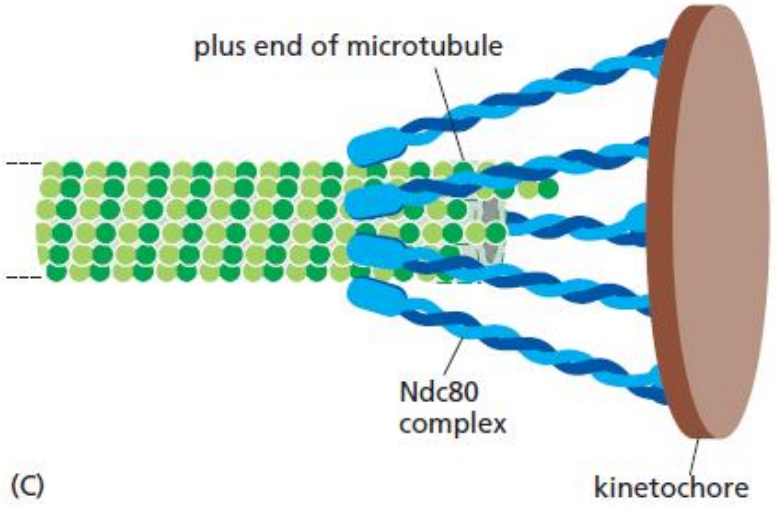


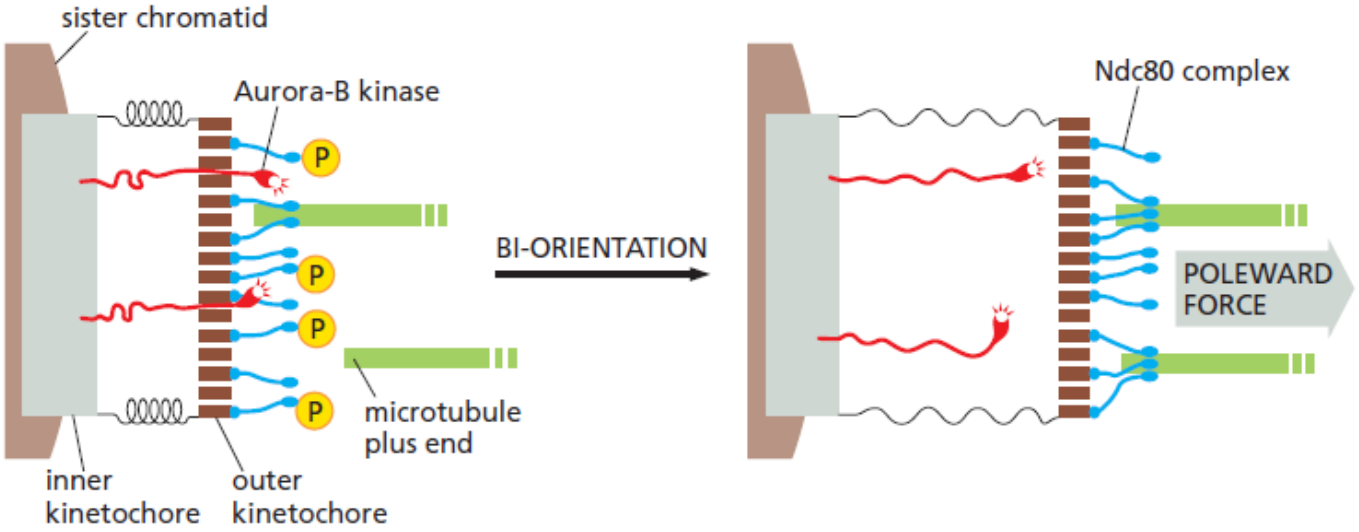
Cell cycle – traction force





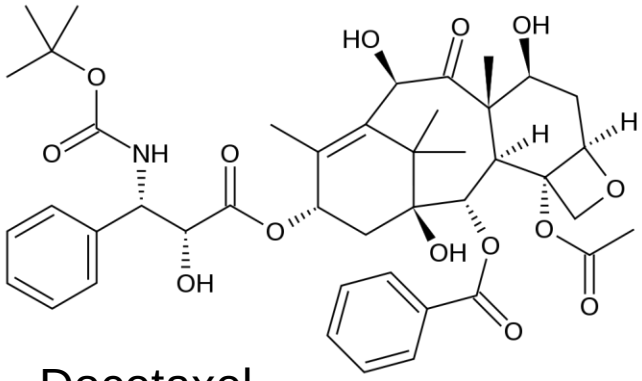
Microtubule attachment sites in the kinetochore



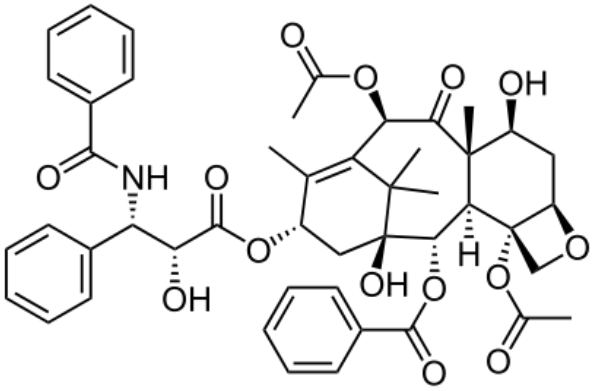


Inhibition of the mitotic spindle

Taxanes



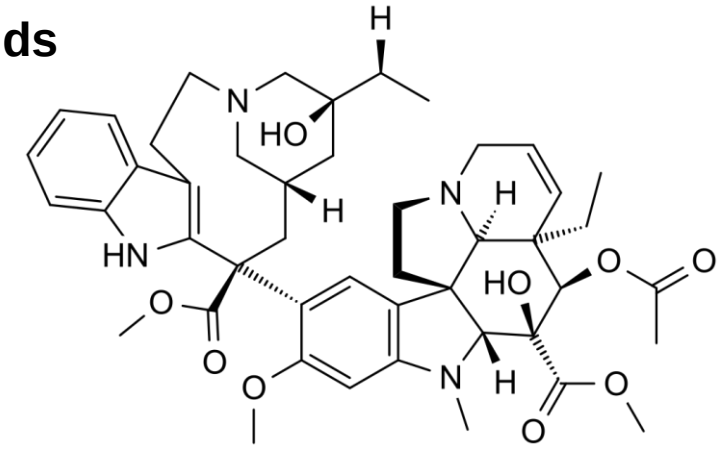
Docetaxel



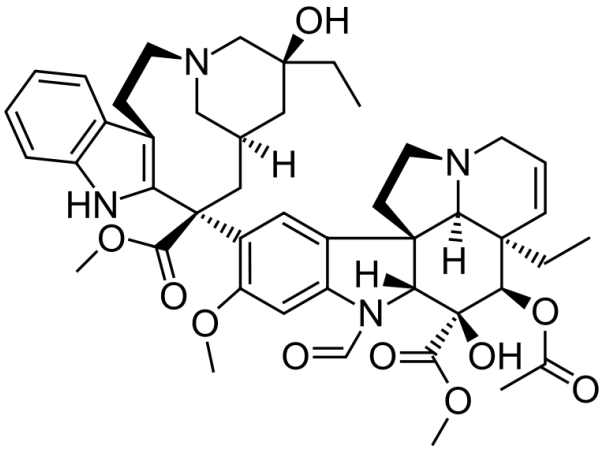
Placlitaxel

Vinca alkaloids

Vinblastine



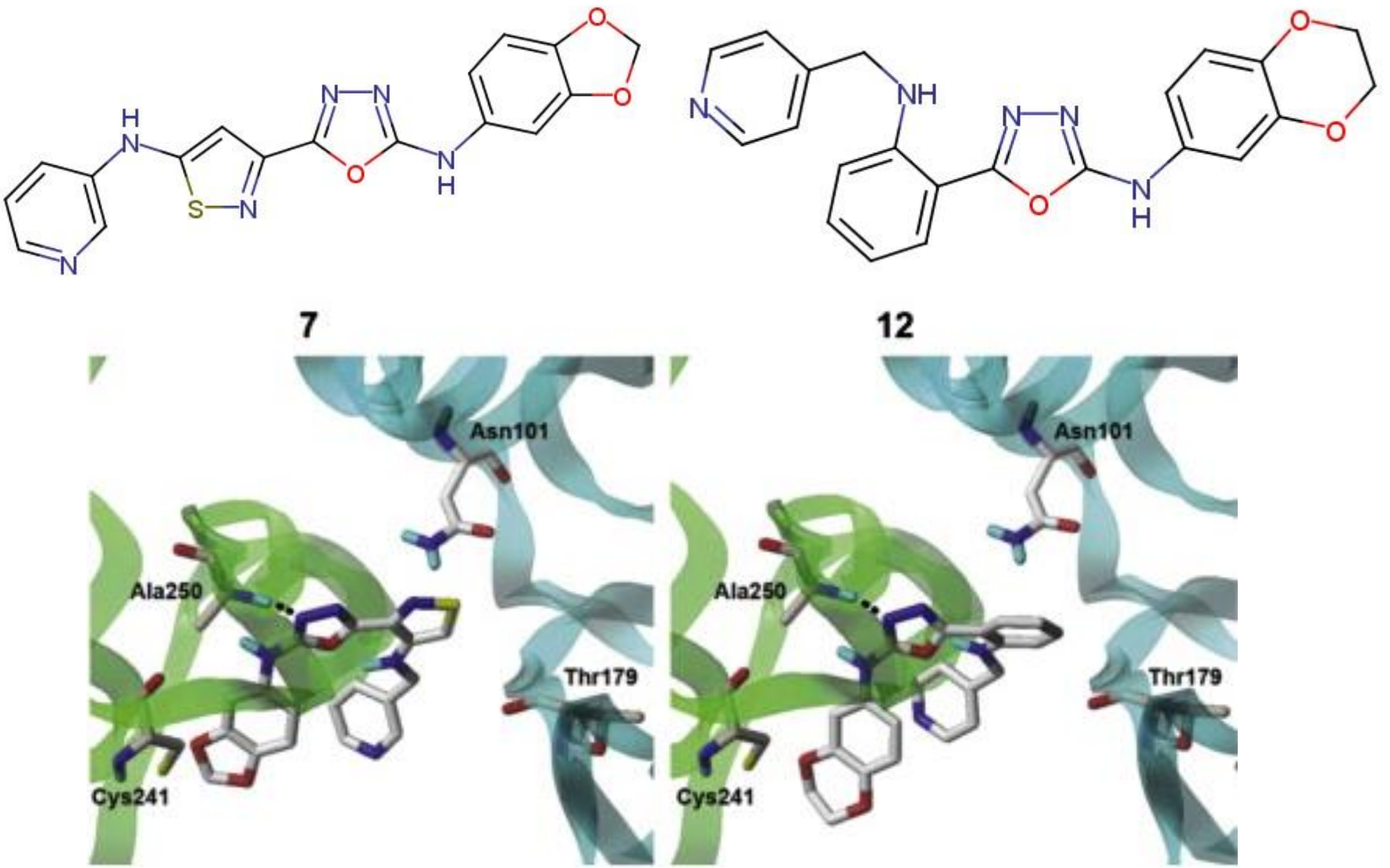
Vincristine



Colchicine and podophylotoxin are some other drugs.

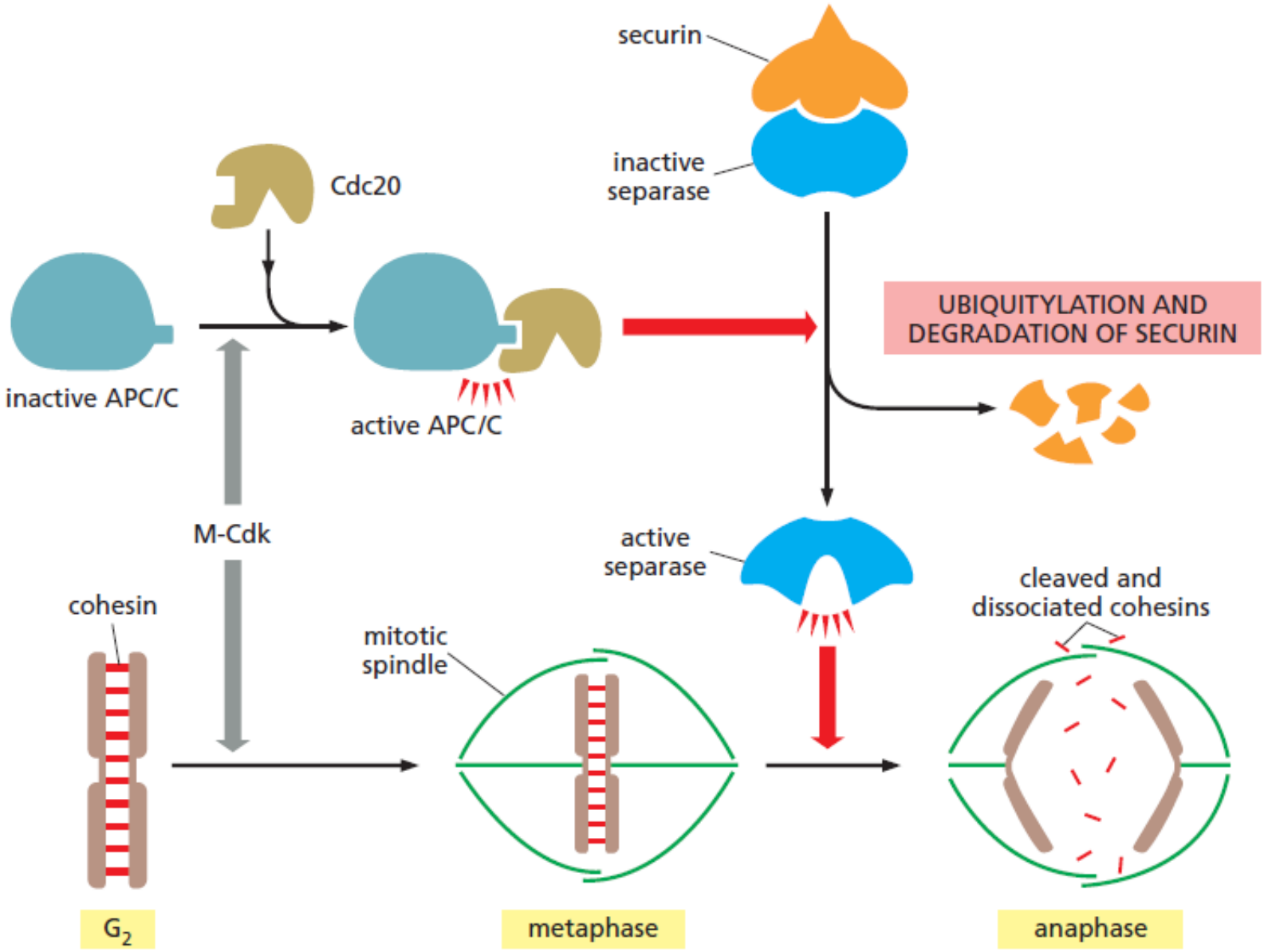
https://www.drugs.com/drug-class/mitotic-inhibitors.html

Inhibition of the mitotic spindle

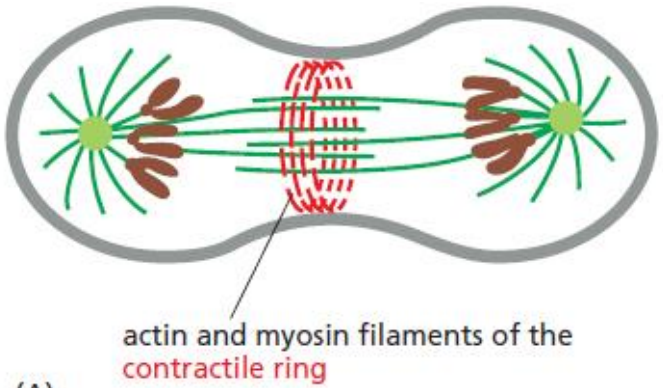


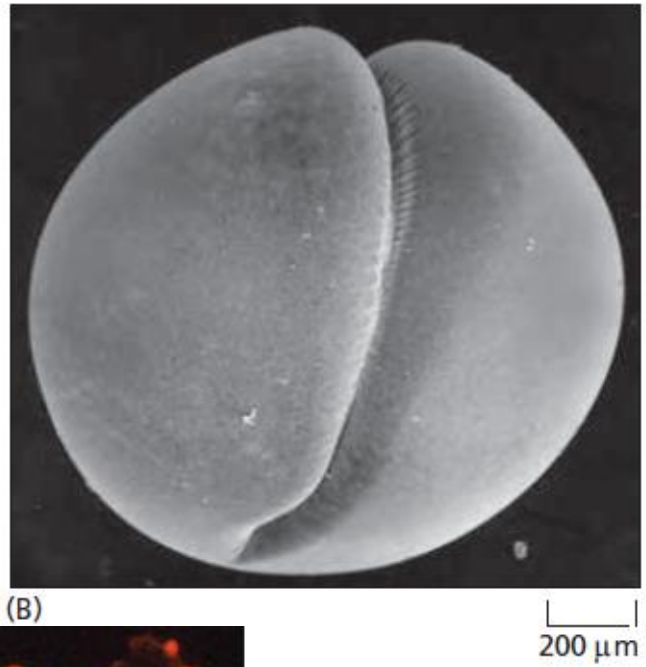
Kiselyov, A.S. *et al*. *Eur. J. Med. Chem.* **2010**, *45*, 1683-1697

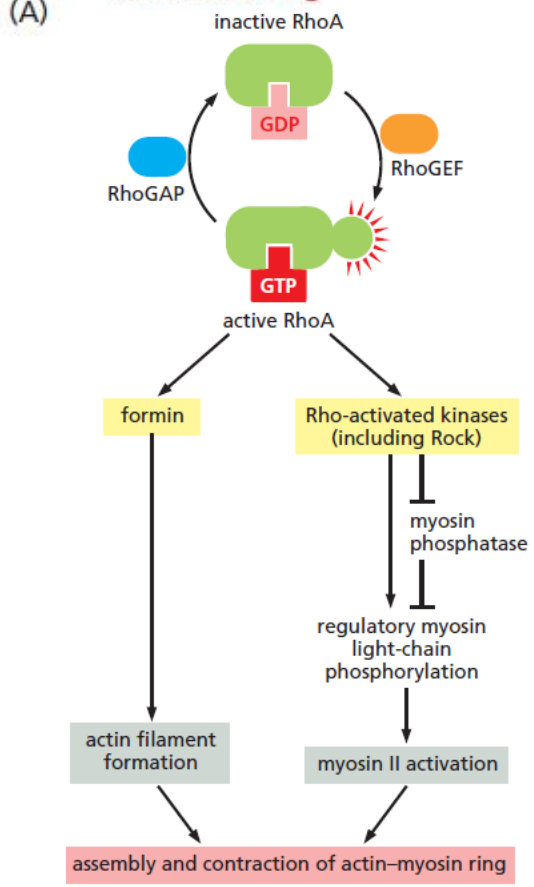
Cell cycle – chromatin separation

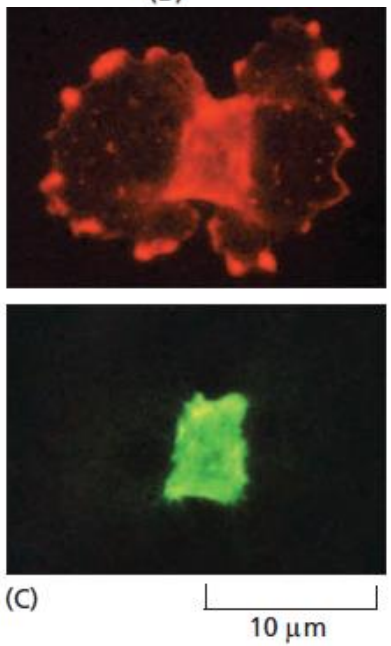


Cell cycle – cytokineses



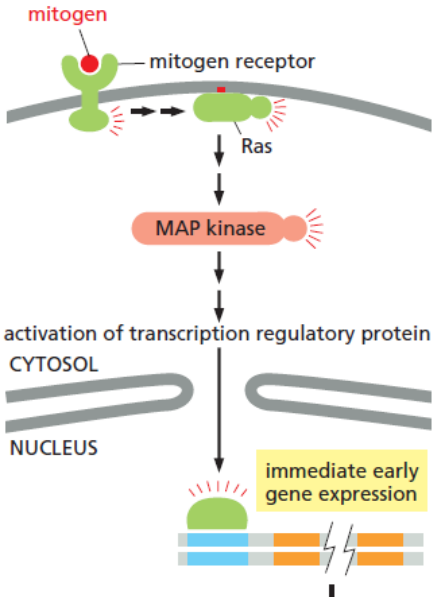


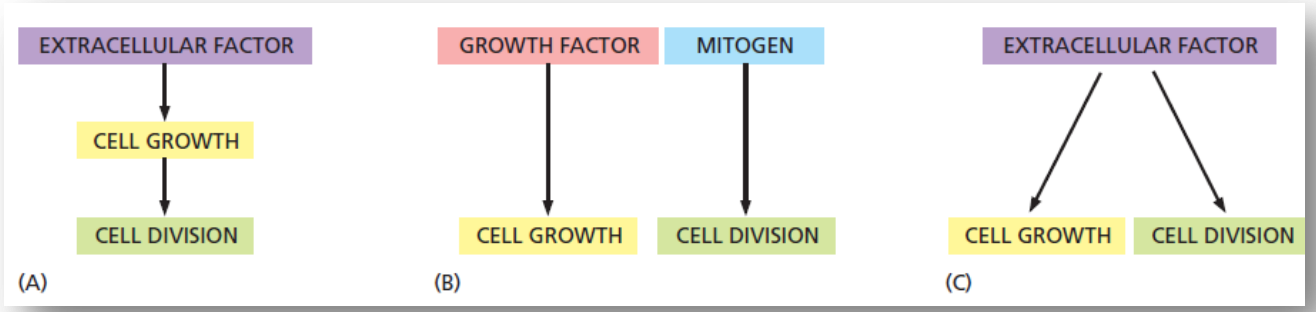




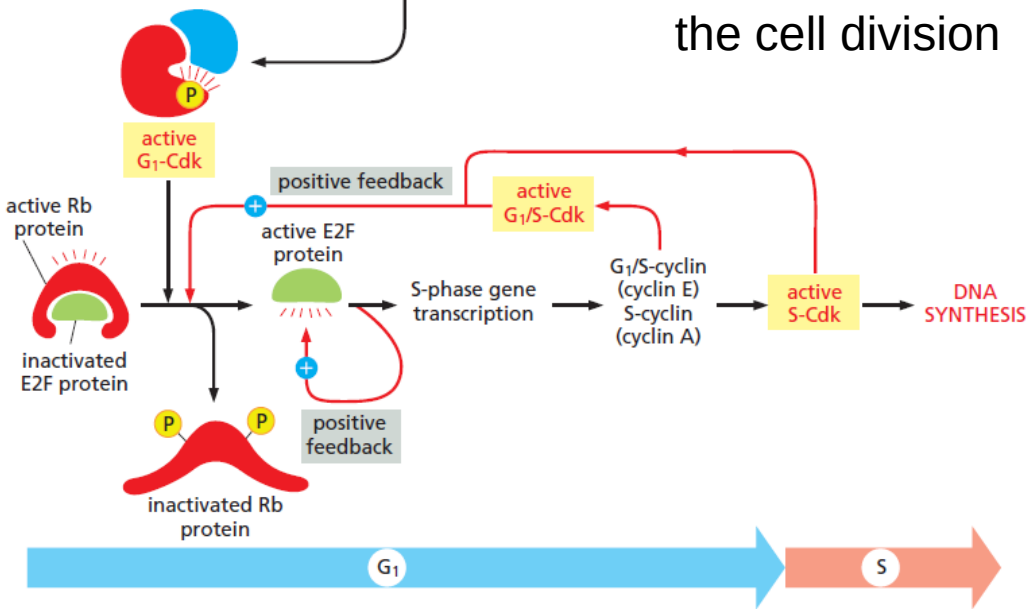
RhoA: Ras homolog gene family, member A
RhoGAP domain: evolutionary conserved protein domain of GTPase activating proteins
RhoGEF domain: structural domain of guanine nucleotide exchange factors

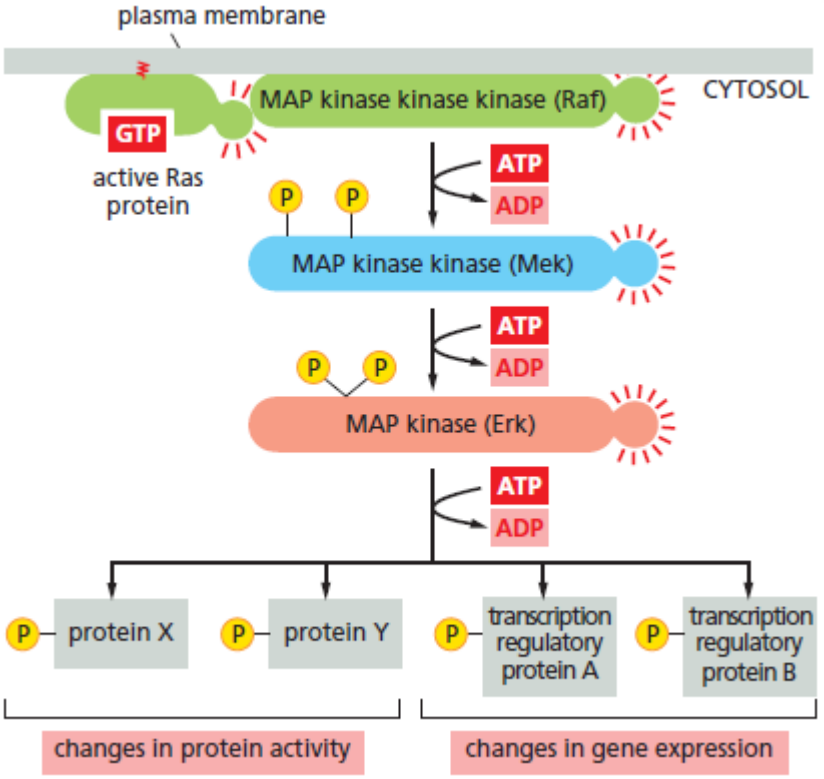
Cell stimulation



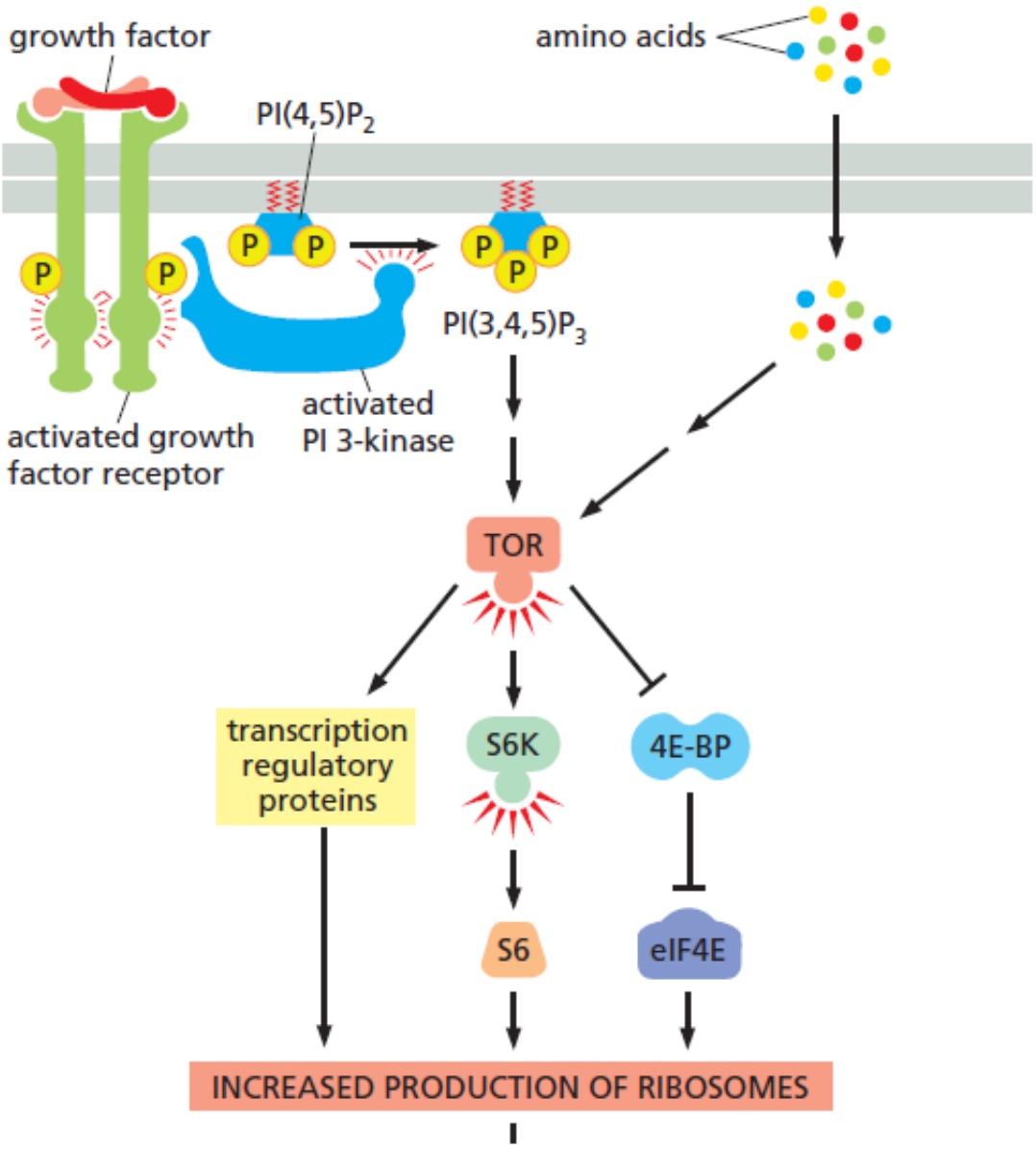


Stimulation of the cell division

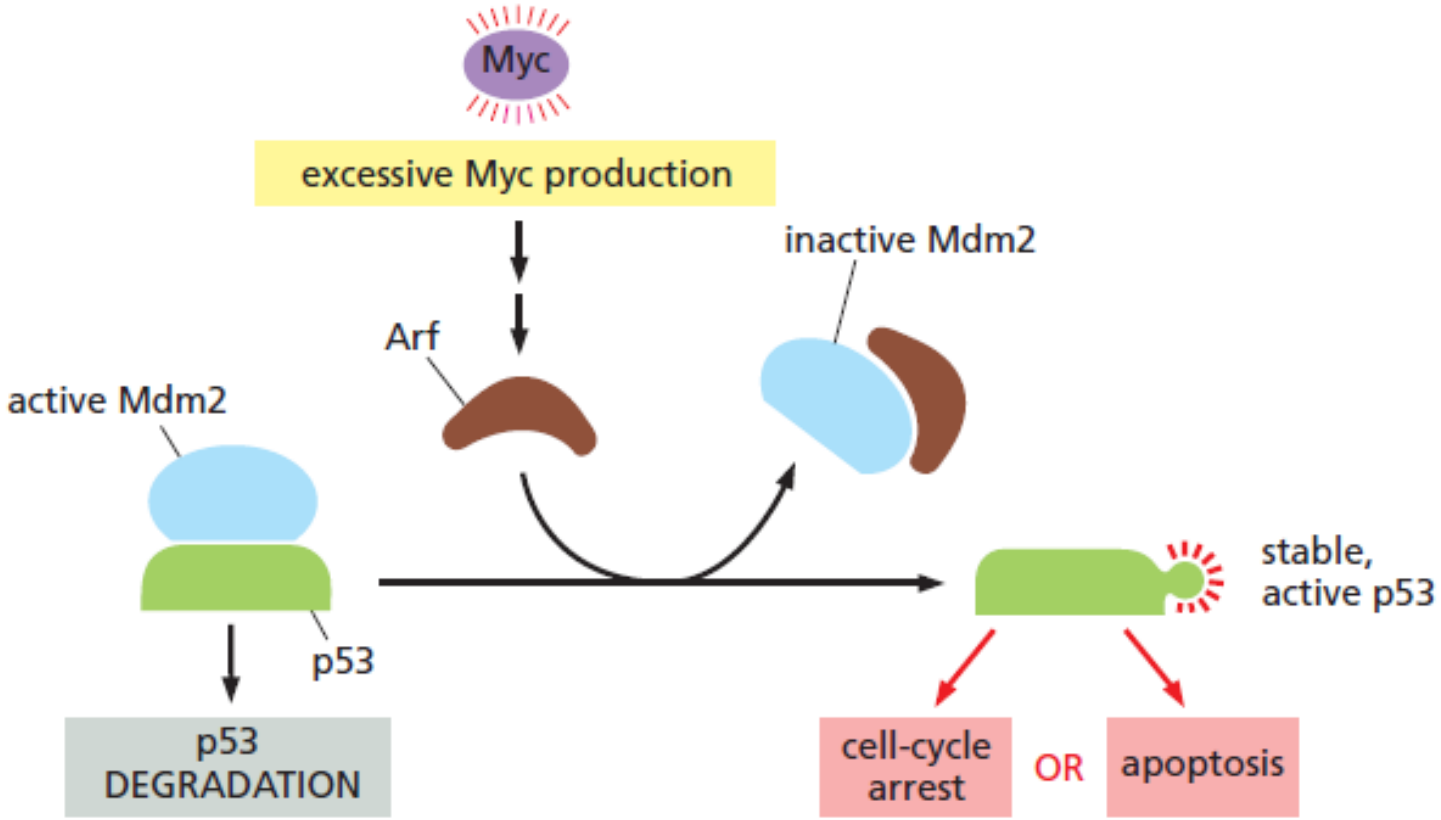




Cell growth


growth factor
amino acids
PI(4,5)P2
P
P
P
P
P
P
PI(3,4,5)P3
activated growth factor receptor
activated PI 3-kinase
TOR
transcription regulatory proteins
S6K
4E-BP
S6
eIF4E
INCREASED PRODUCTION OF RIBOSOMES

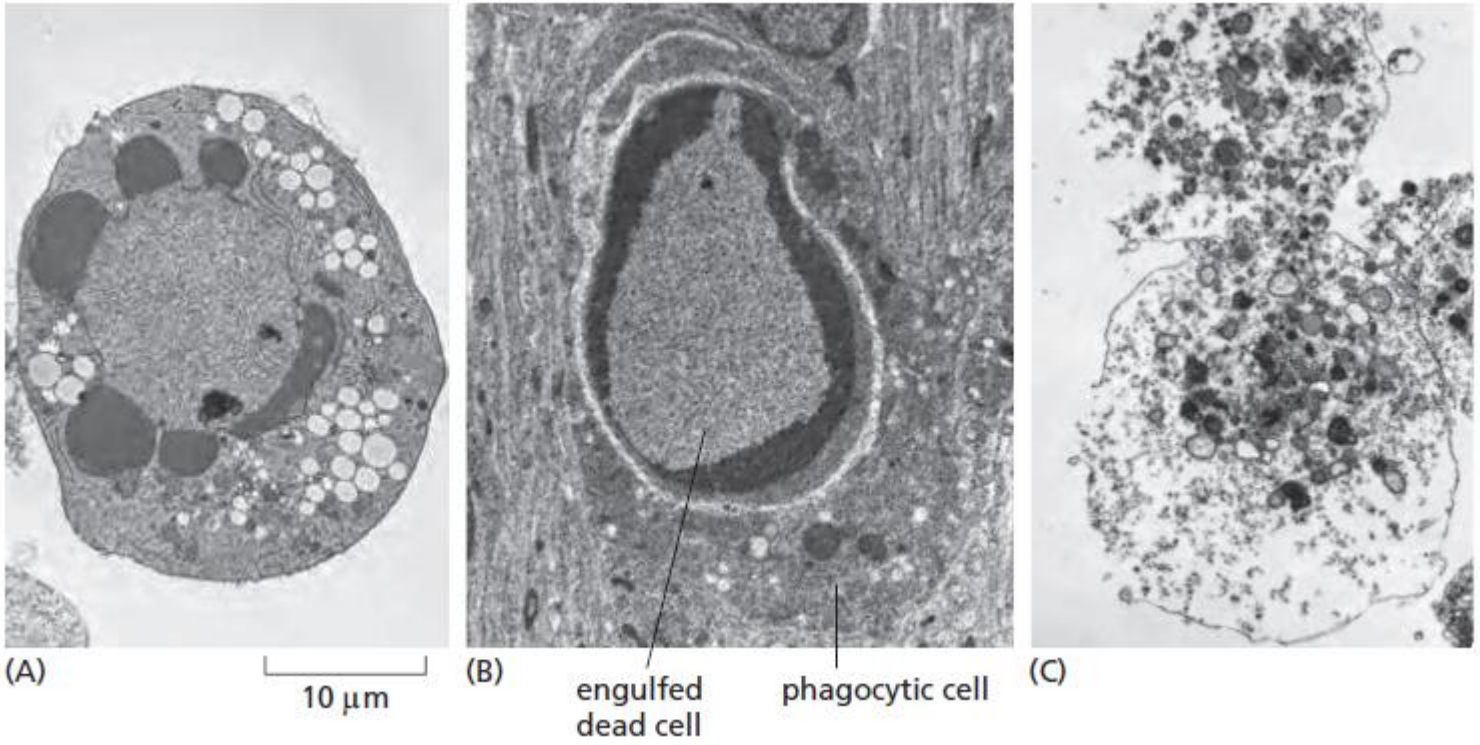
Cell arrest and death



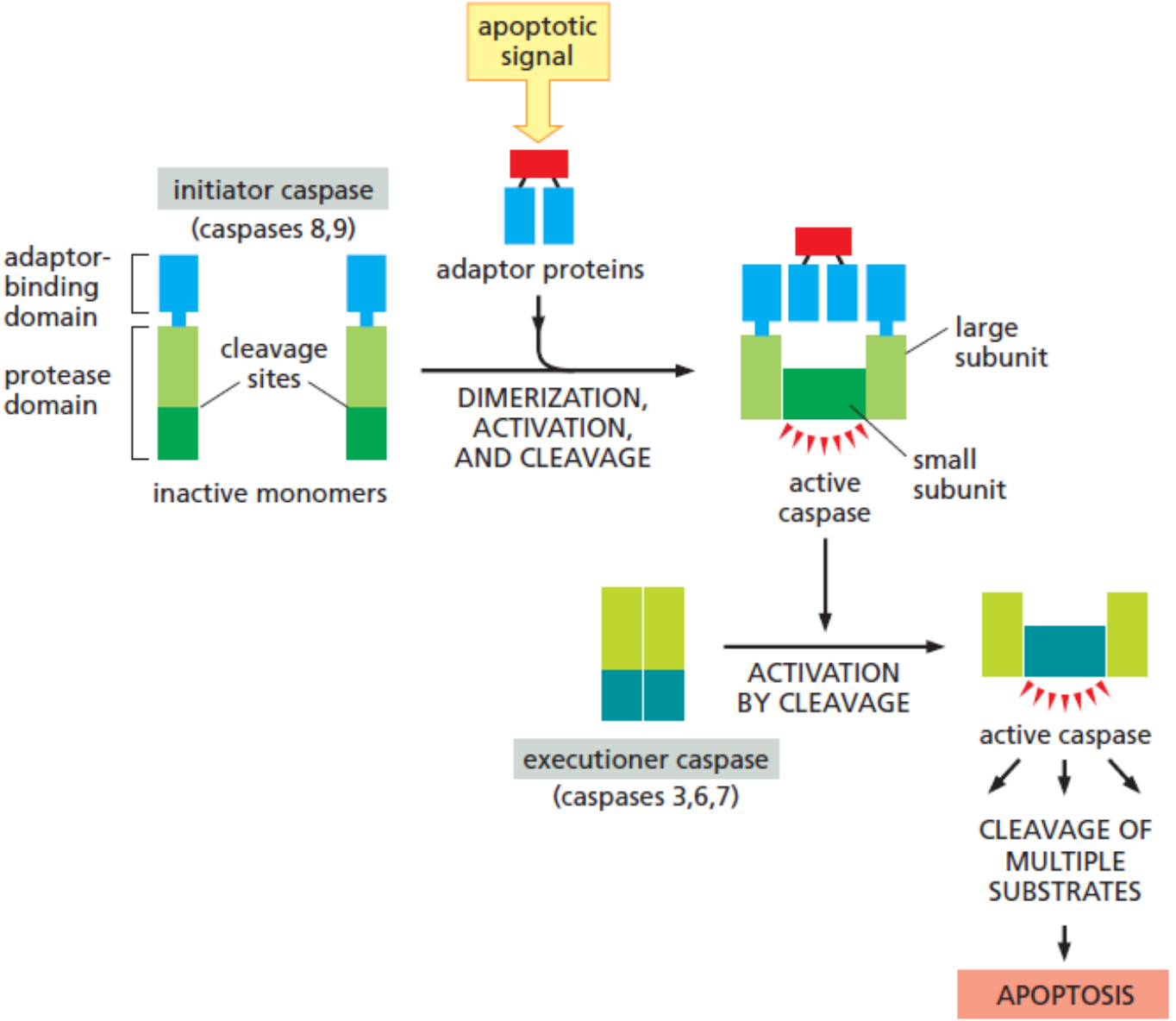
Cell-cycle arrest or apoptosis induced by excessive stimulation of mitogenic pathways. Abnormally high levels of Myc cause the activation of Arf, which binds and inhibits Mdm2 and thereby increases p53 levels.

Cell death

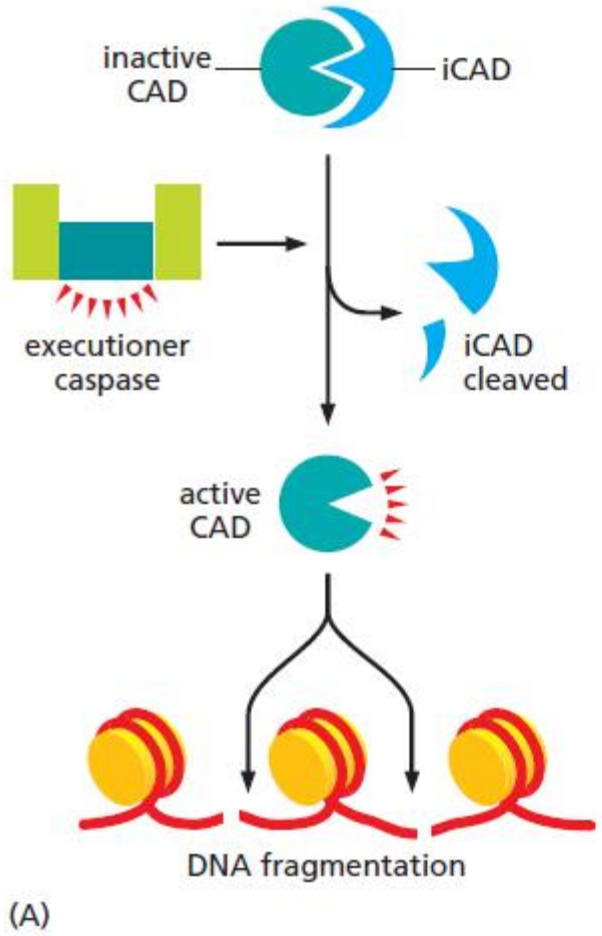
Apoptosis (A and B) and Necrosis (C)



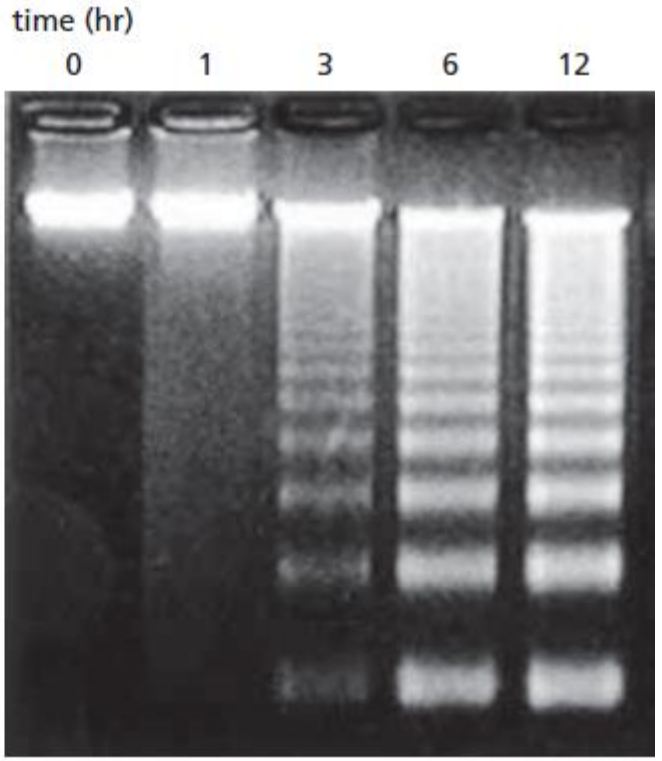
Cell death - apoptosis



Apoptosis – DNA fragmentation



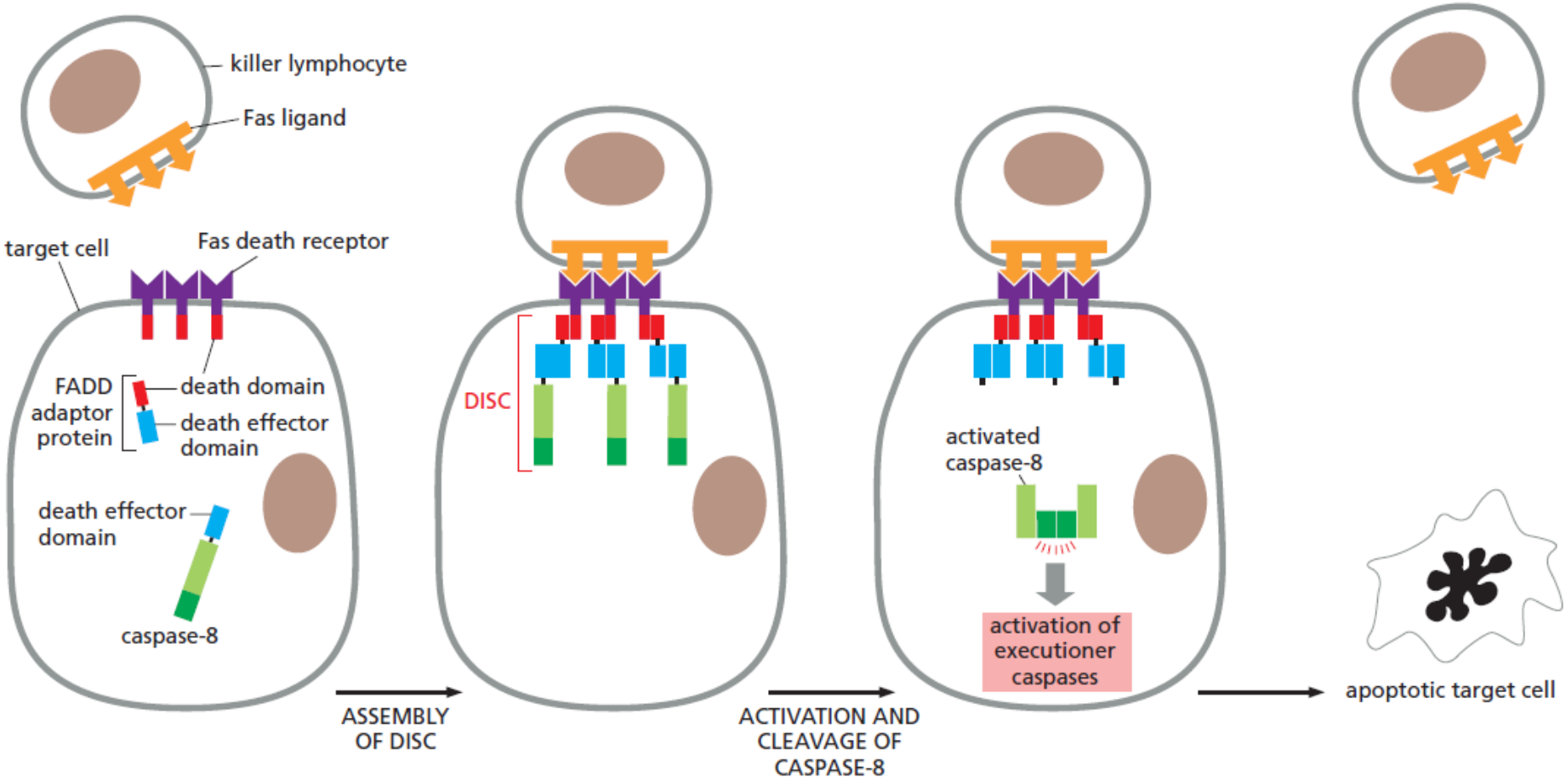
(A)



(B)

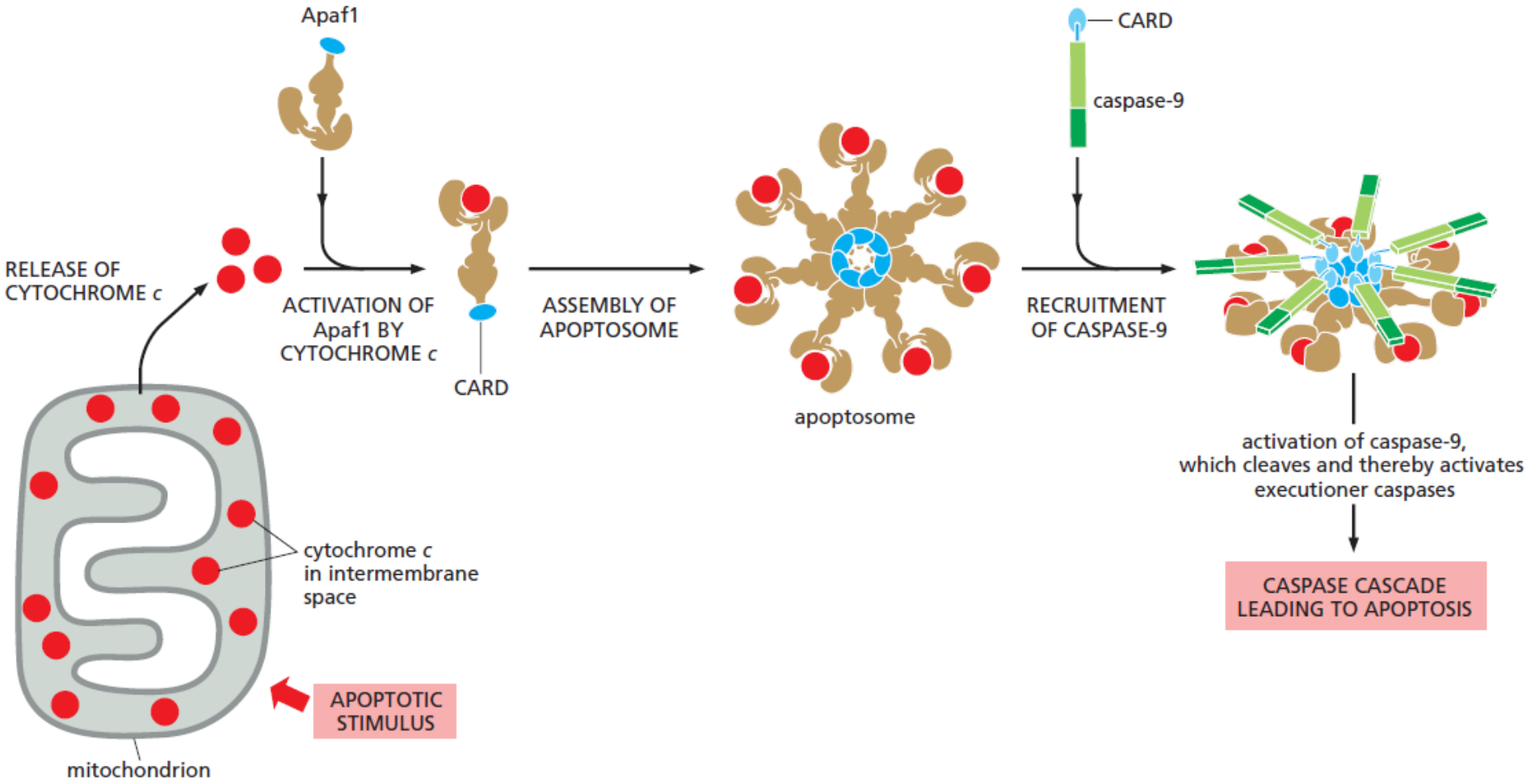
Apoptosis – extrinsic pathway

DISC: Death-inducing signaling complex
FADD: Fas-associated protein with death domain



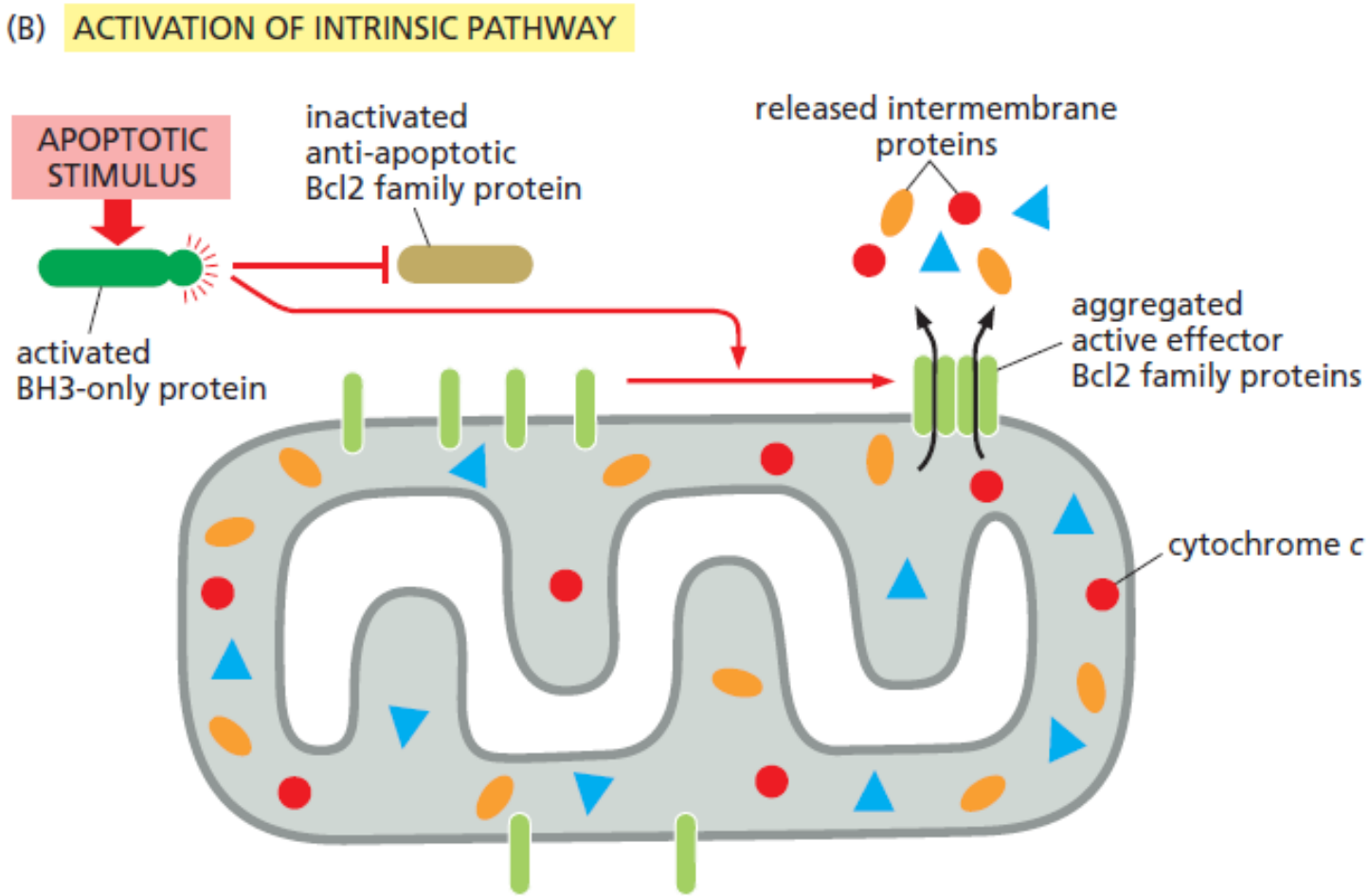
Apoptosis – intrinsic pathway

Apaf1: apoptotic protease activating factor-1
CARD: Caspase recruitment domain from Apaf1

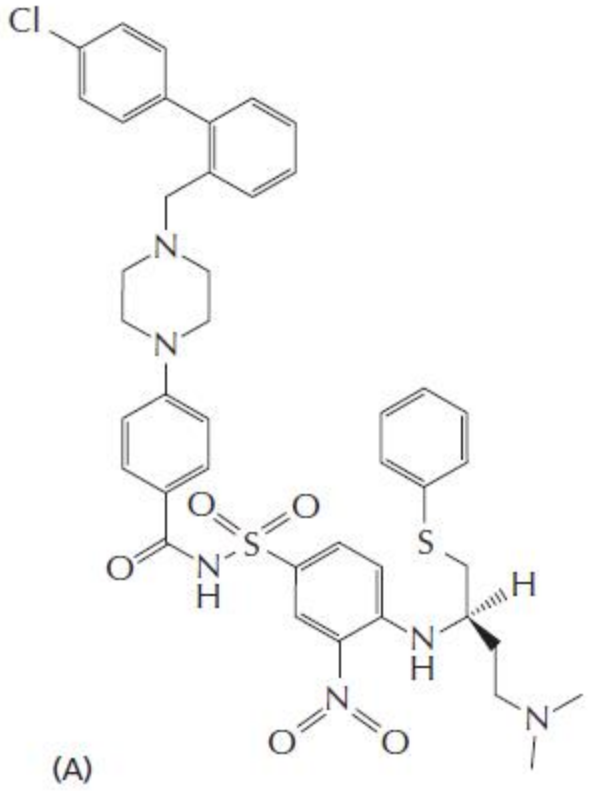


Apoptosis – intrinsic pathway

Pro-apoptotic effector Bcl2 family proteins (mainly Bax and Bak) lead to the release of mitochondrial intermembrane proteins in the intrinsic pathway of apoptosis.
BID: BH3 interacting-domain death agonist

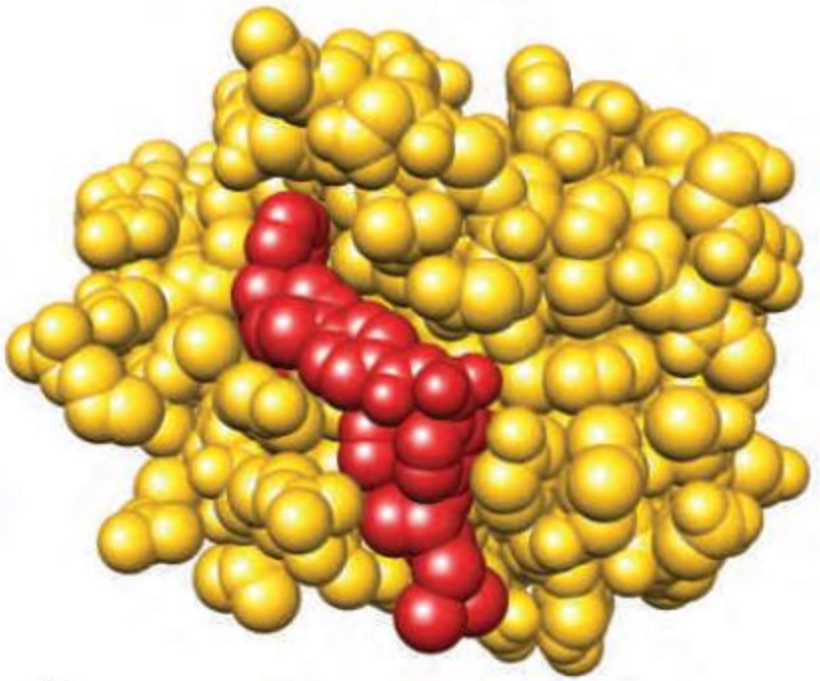


Apoptosis – inhibition of $BclX_L$



(A)

2YXJ



(B)

Apoptosis – role of IAP