Identifying new targets for cancer treatment

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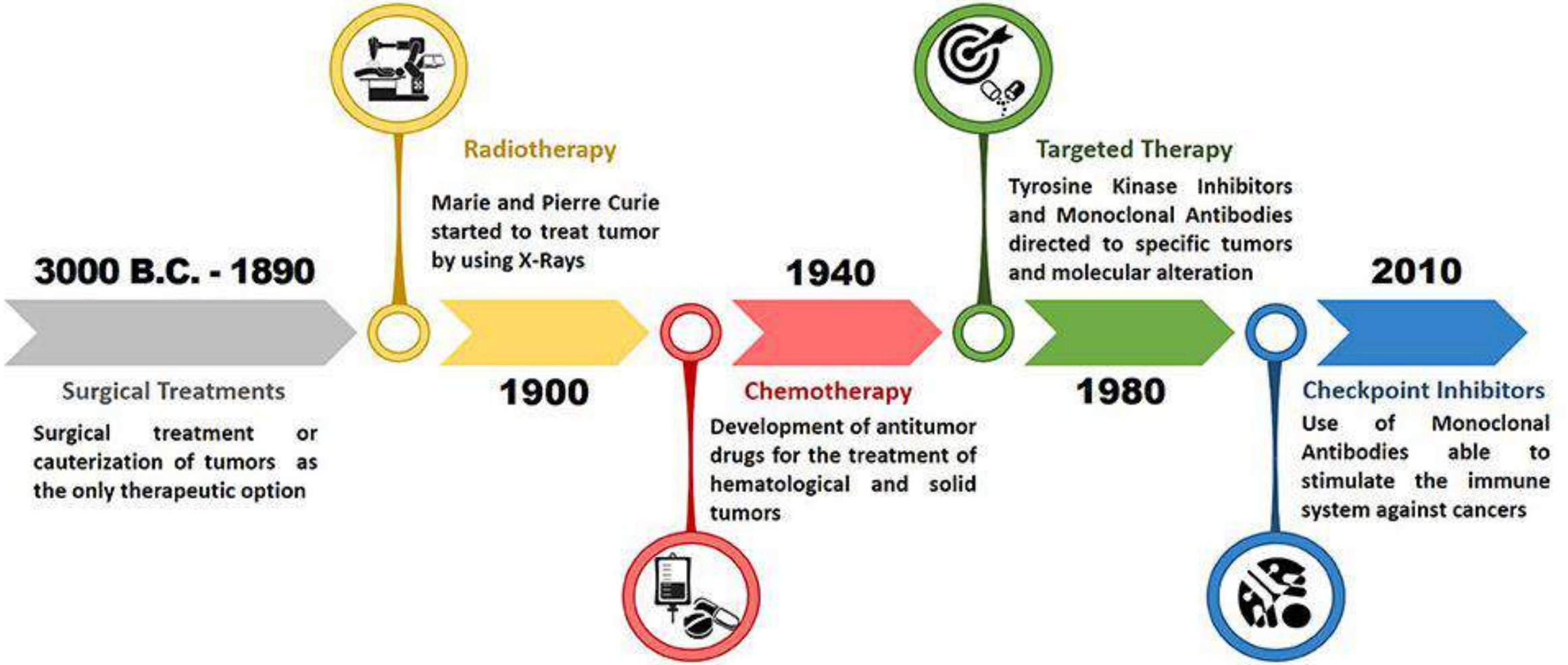
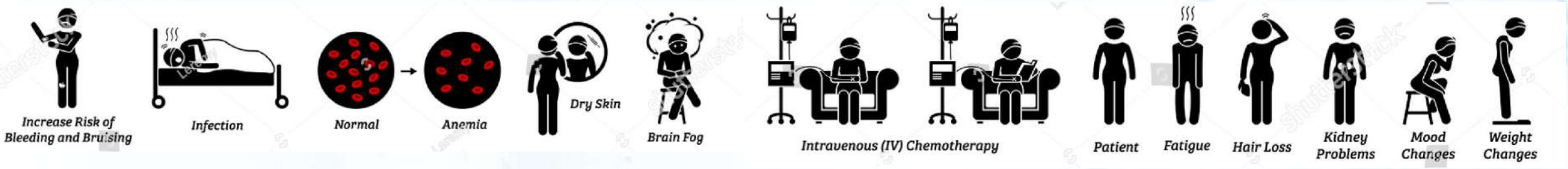
Timeline of cancer treatments

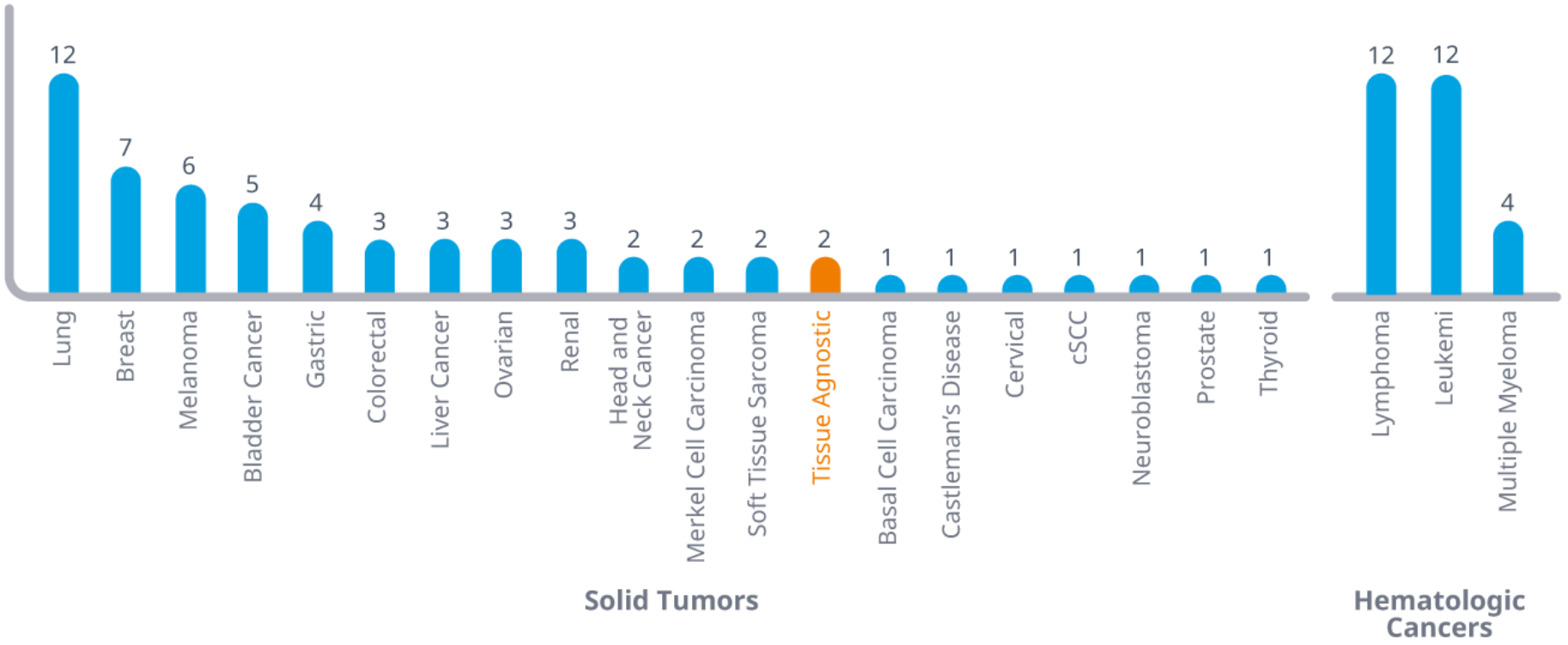


(Falzone *et al.*, 2018)

Cancer treatment	Side effects
• Surgery	• Bleeding, blood clots, damage to nearby tissuse, pain, and infection
• Radiation therapy	• Fatigue, skin irritation, fever/chills, and mild-faint
• Chemotherapy	• Damage in many organ cells like the bladder, heart, kidneys, lungs, and nervous system, as well as hair follicles
• Targeted cancer therapy	• Skin problems, intense itching, allergies in the skin, trouble breathing, and dizziness.



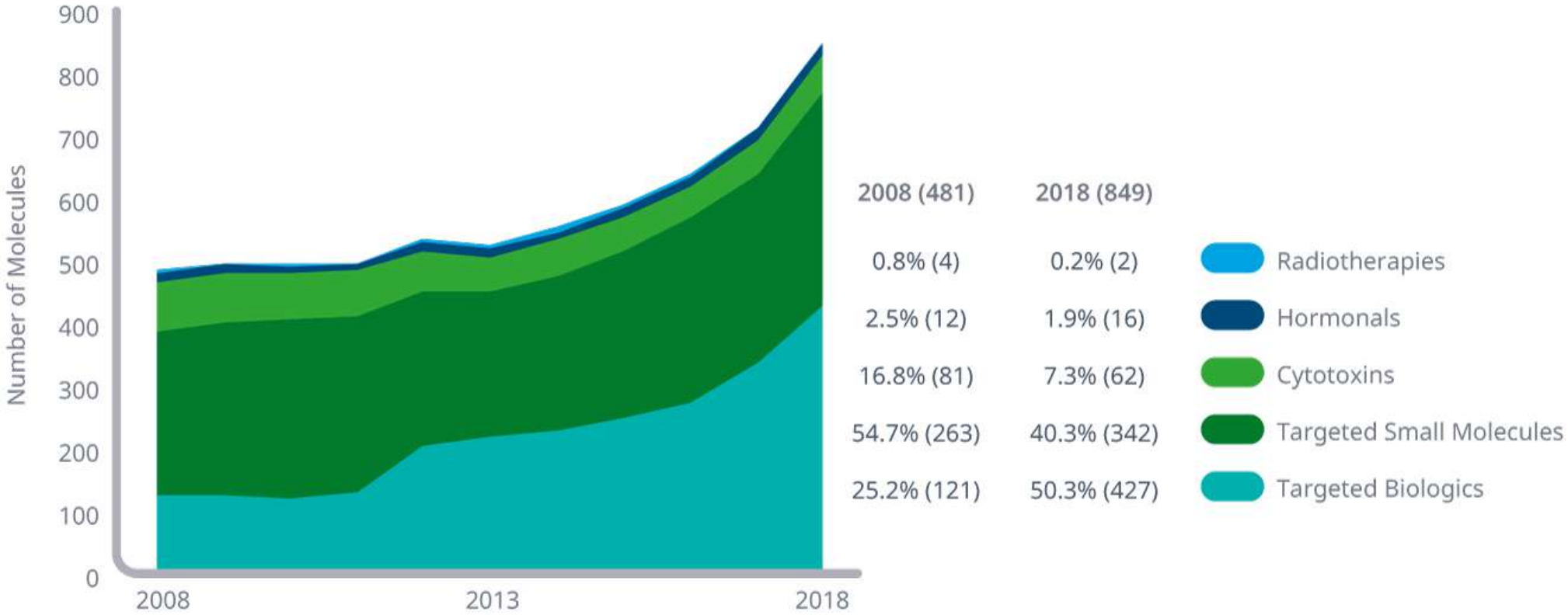
Past 5 years, 57 newly launched oncology therapeutics received approval, with some drugs treating multiple tumor types



Source: IQVIA Institute, Apr 2019

Chart notes: Excludes supportive care. cSCC = Cutaneous squamous cell carcinoma; mogamulizumab is approved for multiple lymphoma indications: Mycosis fungoides and Sézary syndrome. Pembrolizumab is approved for multiple lymphoma indications: classical Hodgkin lymphoma (cHL) and primary mediastinal large b-cell lymphoma (PMBCL). Chart includes three indication approvals that occurred for NAS candidates within the time frame of launch within 2014 to 2018 that had subsequent indication approvals as of May 2019: pembrolizumab, trifluridine/tipiracil and atezolizumab for renal, gastric and breast, respectively.

Report: Global Oncology Trends 2019 – Therapeutics, Clinical Development and Health System Implications. IQVIA Institute for Human Data Science, May 2019



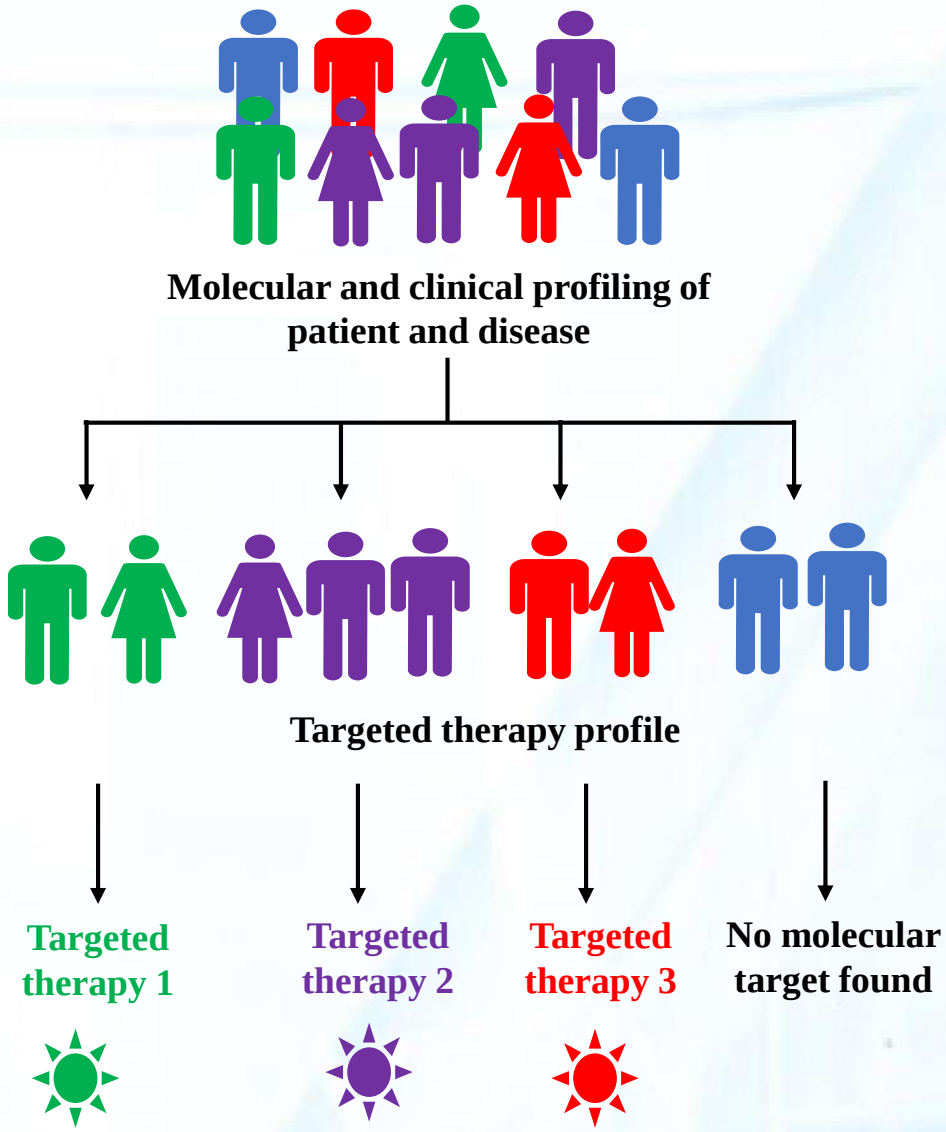
Source: IQVIA Pipeline Intelligence, Dec 2018; IQVIA Institute, May 2019
Chart notes: Late phase pipeline includes trials in Phase II or higher for the most advanced indication. Phase I/II trials are included as Phase II.
Report: Global Oncology Trends 2019 – Therapeutics, Clinical Development and Health System Implications. IQVIA Institute for Human Data Science, May 2019

The late-stage oncology pipeline included 849 molecules in 2018, up 77% since 2008, due to the increasing number of targeted therapies

What is targeted therapy?

- ✓ Targeted therapy is a cancer treatment that uses drugs to target specific proteins that control how cancer cells grow, divide, and spread.
- ✓ According to the National Cancer Institute :
  - ➢ Targeted therapy is "a type of treatment that use drugs or other substances, such as monoclonal antibodies, to identify and attack specific cancer cells without harming normal cells".

Most targeted therapies are either small-molecule drugs or monoclonal antibodies.

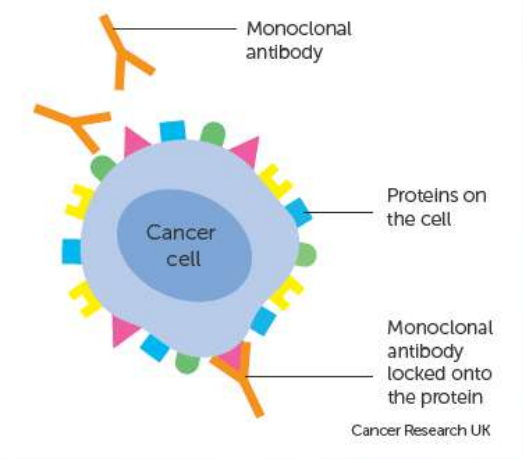


Are there different types of targeted therapy?

There are two main types of targeted therapy:

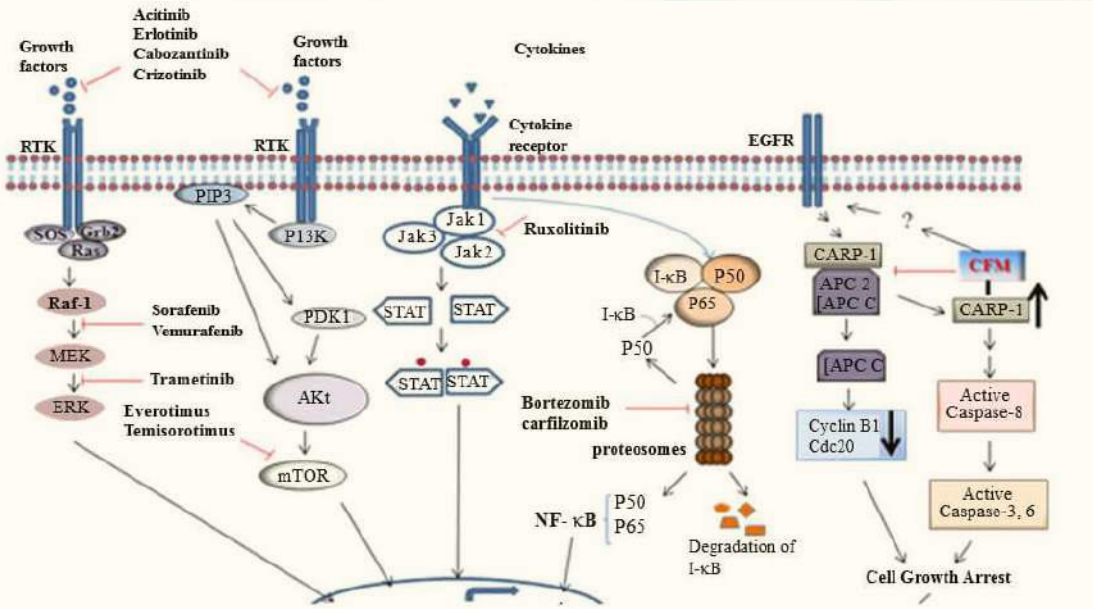
1) **Monoclonal antibodies**:

- Target specific antigens outside a cell such as receptors or extracellular growth factors
- These drugs block a specific target on the outside of cancer cells.
- They can also send toxic substances directly to cancer cells.
- Some are conjugated to radio-isotopes or toxins



2) **Small-molecule drugs:**

- Interact with targets inside a cell
- These drugs aim to block the process that helps cancer cells multiply and spread.
- They are usually designed to interfere with enzymatic activity of the target protein



Major differences between monoclonal antibodies and small molecules

	Monoclonal antibodies	Small molecules
• Size	• ~150,000 daltons	• ~400 daltons
• Administration	• Intravenous	• Oral or parenteral
• Target availability	• Extracellular	• Intracellular
• Cost	• $4,200/month (trastuzumab)	• $1,800/month (gefitinib)
• Toxicity	• Low toxicity	• Mid-high toxicity
• Half-life	• Days-weeks	• <72 h
• Mechanisms of action	• Disrupt ligand-receptor or receptor-receptor interactions • Receptor downregulation • Induction of apoptosis	• Bind to target kinase(s) • Inhibit phosphorylation and downstream signaling pathways • Induce apoptosis

Generic naming formula

Name = prefix + substem (s) + stem

-mab	monoclonal antibody
-ib	small molecule with inhibitory properties

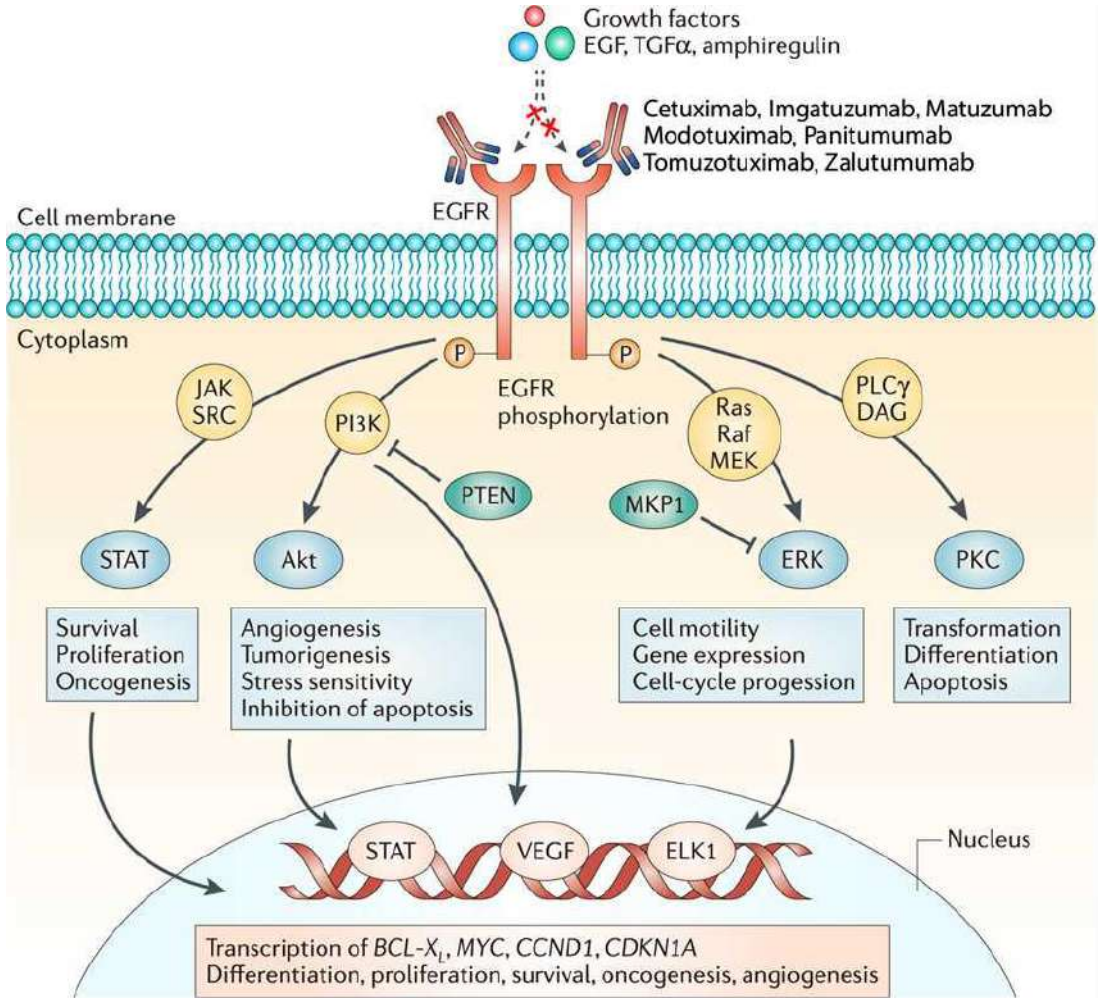
variable

Monoclonal antibodies

Target		*Source*	
-ci(r)-	circulatory system	-ximab	chimeric human-mouse
-li(m)-	immune system	-zumab	humanized mouse
-t(u)-	tumor	-mumab	fully human

Small molecules

-tinib	tyrosine kinase inhibitor
-zomib	proteasome inhibitor
-ciclib	cyclin-dependent kinase inhibitor
-parib	poly ADP-ribose polymerase inhibitor

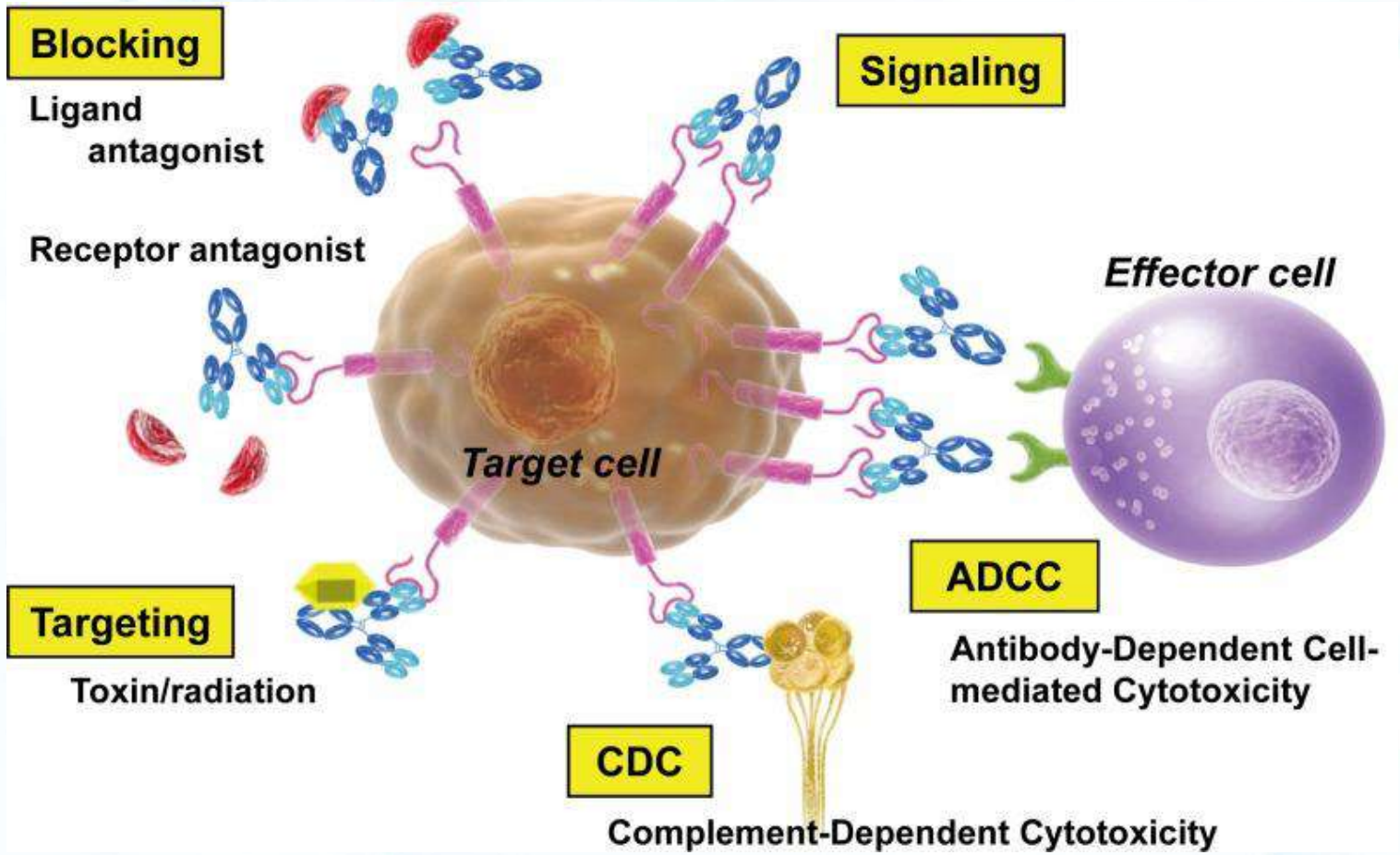


- ✓ Some targeted therapy used in squamous cell cancers include cetuximab, imgatuzumab, matuzumab, erlotinib, modotuximab, and bevacizumab.
- ✓ Drugs that block the action of enzymes, proteins or other molecules that cause disease
  - ➢ Interfere with specific molecules involved in tumor growth and progression
  - ➢ Target key cells and mediators that drive inflammatory responses

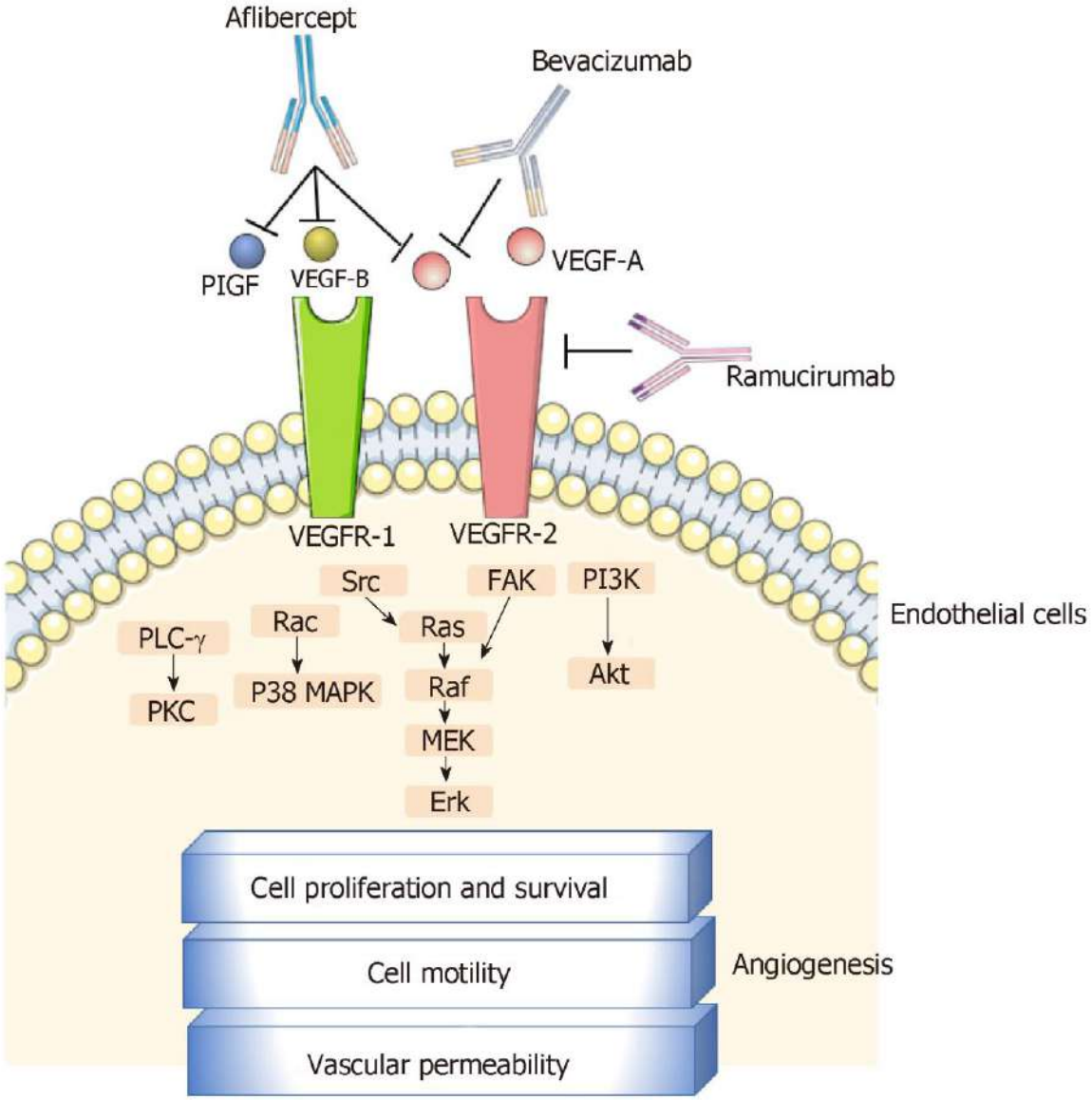
Monoclonal antibodies can be classified as either a targeted therapy or immunotherapy, depending on the type of monoclonal antibody. Examples of targeted therapy monoclonal antibodies include:

Angiogenesis inhibitors	• These drugs are designed to reduce the blood supply to a tumour to slow or stop it growing. • They target various receptors or proteins linked with the growth of cancer cells and stop them from working. • For example, **bevacizumab** targets **vascular endothelial growth factor (VEGF),** a protein that helps new blood vessels form.
HER2-targeted agents	• HER2 is a protein that causes cancer cells to grow uncontrollably. • Some targeted therapy drugs destroy the HER2 positive cancer cells, or reduce their ability to divide and grow. • Examples include **trastuzumab** and **pertuzumab**, which are used to treat HER2 positive breast cancer.
Anti-CD20 monoclonal antibodies	• These drugs target a protein called CD20 found on some B-cell leukaemias and non-Hodgkin lymphomas. • Examples include **rituximab** and **obinutuzumab**.

Mechanism of action of monoclonal antibody



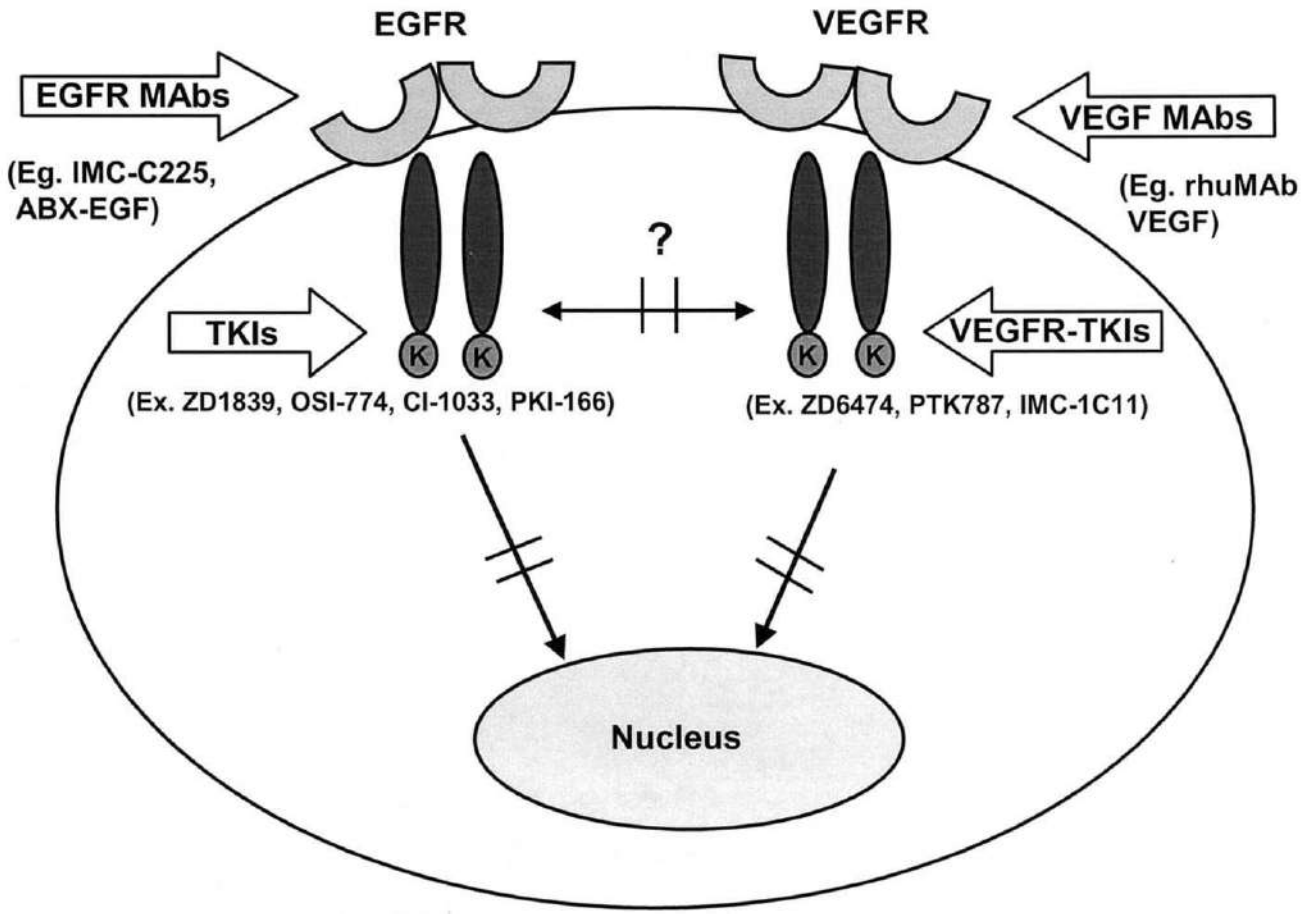
(Suzuki et al., 2015)



(Kanat and Ertas, 2019)

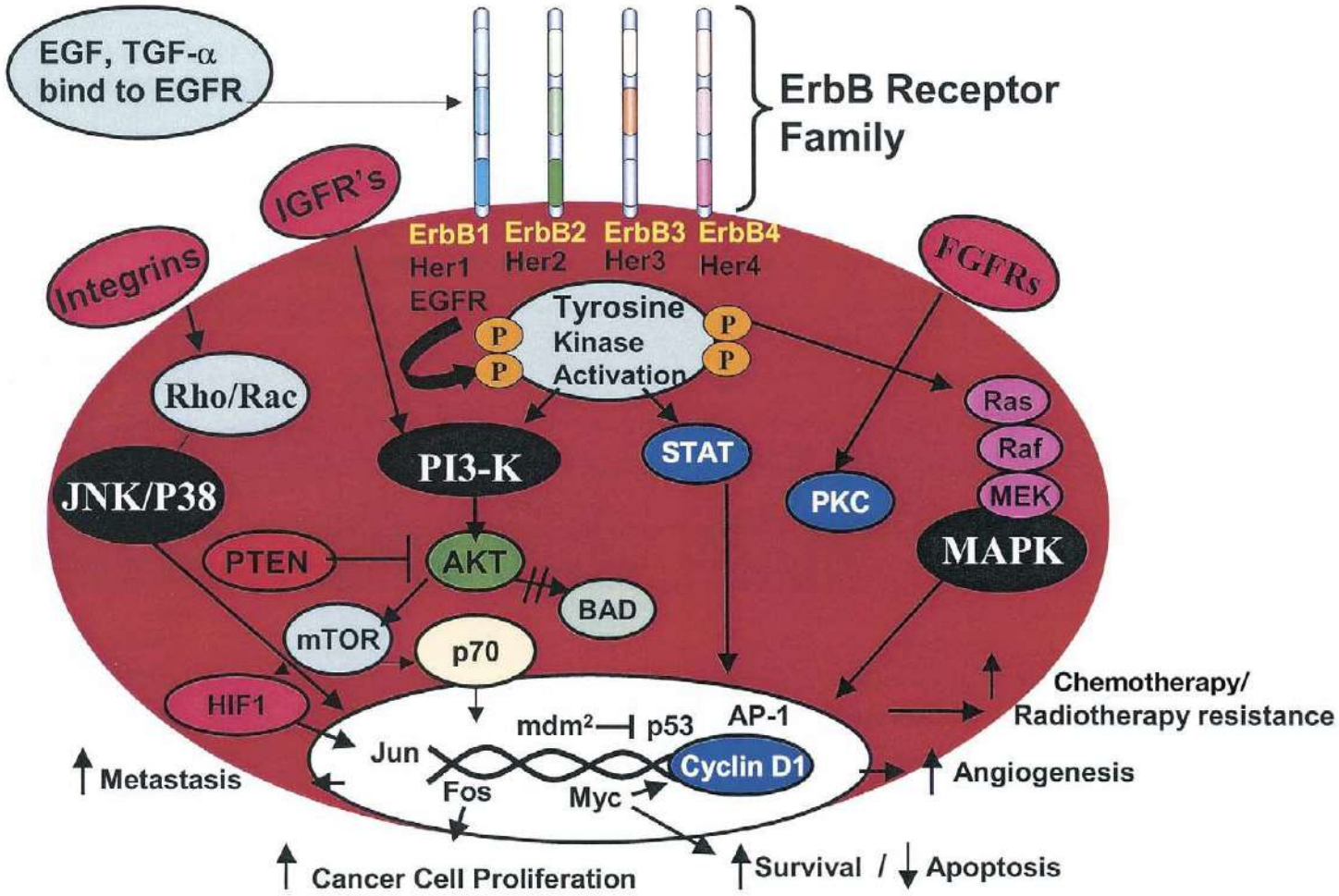
Angiogenesis inhibitors

- ✓ Anti-angiogenic treatment is an essential part of the current armamentarium against metastatic colorectal cancer (mCRC).
- ✓ **Bevacizumab** is a murine-derived monoclonal antibody (muMAb A4.6.1) that inhibits angiogenesis by targeting the vascular endothelial growth factor (VEGF)-A.



A simplifed version of possible effects on tumor cells and surrounding endothelial cells when **both EGFR and VEGF/VEGFR inhibitors** are combined to interfere with the cross-communication occurring between the tumor and expanding tumor endothelium. Extracellular biological response modifiers (monoclonal antibodies) targeted to the EGFR and the VEGF/VEGFR and intracellular biological response modifiers (tyrosine kinase inhibitors) targeted to the EGFR and/or the VEGFR on surrounding endothelium. Combinations of EGFR and VEGF/VEGFR inhibitors may optimize interference with cancer cell growth over either agent alone.

(Raben et al., 2004)

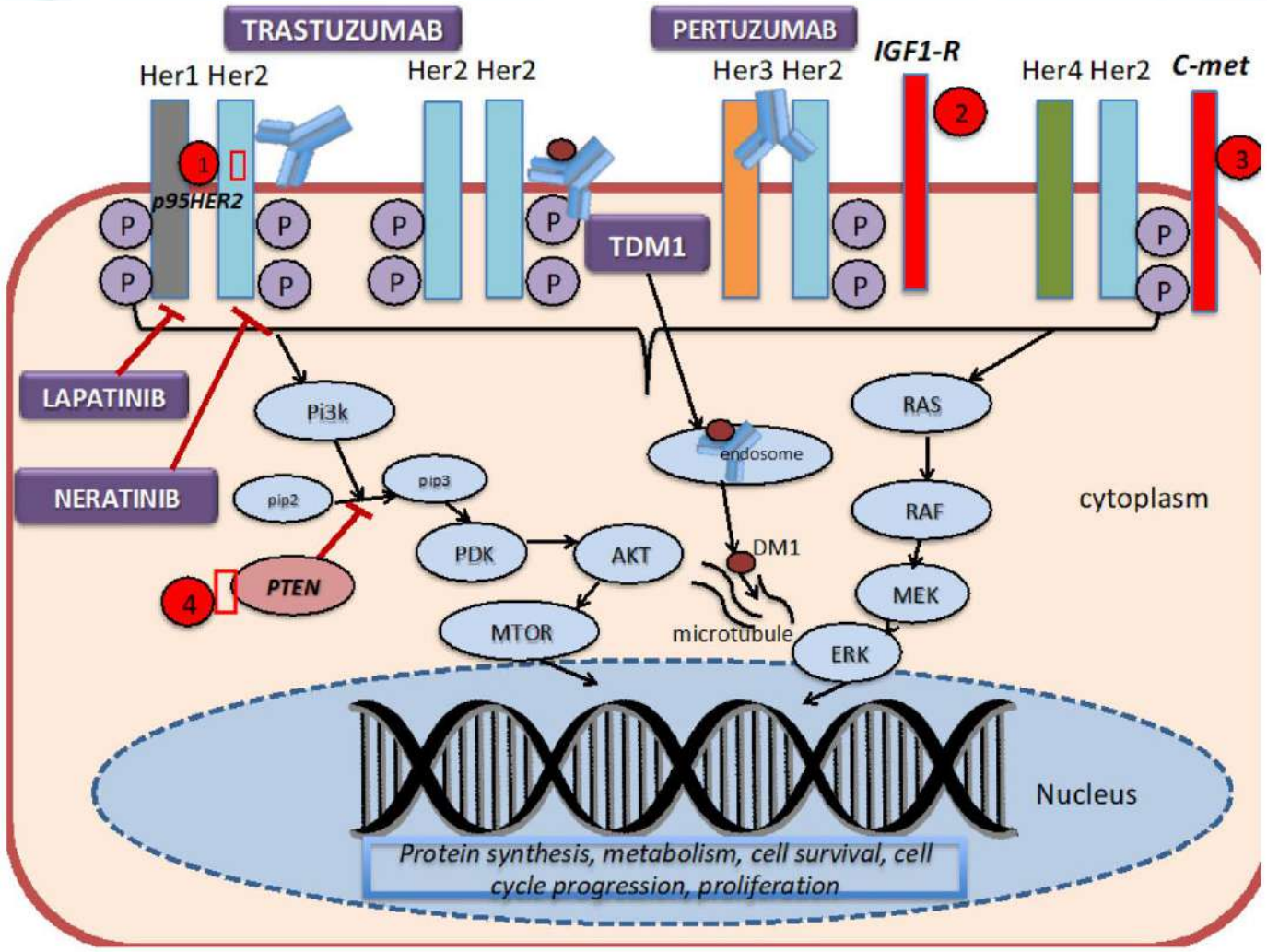


The EGFR family of receptors consists of four family members. The major ligands binding to this family of receptors are EGF and tumor growth factor– (TGF-). Ligand binding activates multiple signaling pathways, resulting in increased cancer cell survival.

(Raben et al., 2004)

HER2-targeted agents

- The HER superfamily consists of four tyrosine kinase receptors: HER1 (epidermal growth factor receptor), HER2 (neu, c-erbB2), HER3 and HER4.
- **The HER2**, or epidermal growth factor receptor 2, is the target for many HER2-directed therapies.
- **Trastuzumab (Herceptin)** was first approved in 1998 as the first anti-HER2 directed therapy in <u>metastatic HER2+ invasive breast cancer</u>.

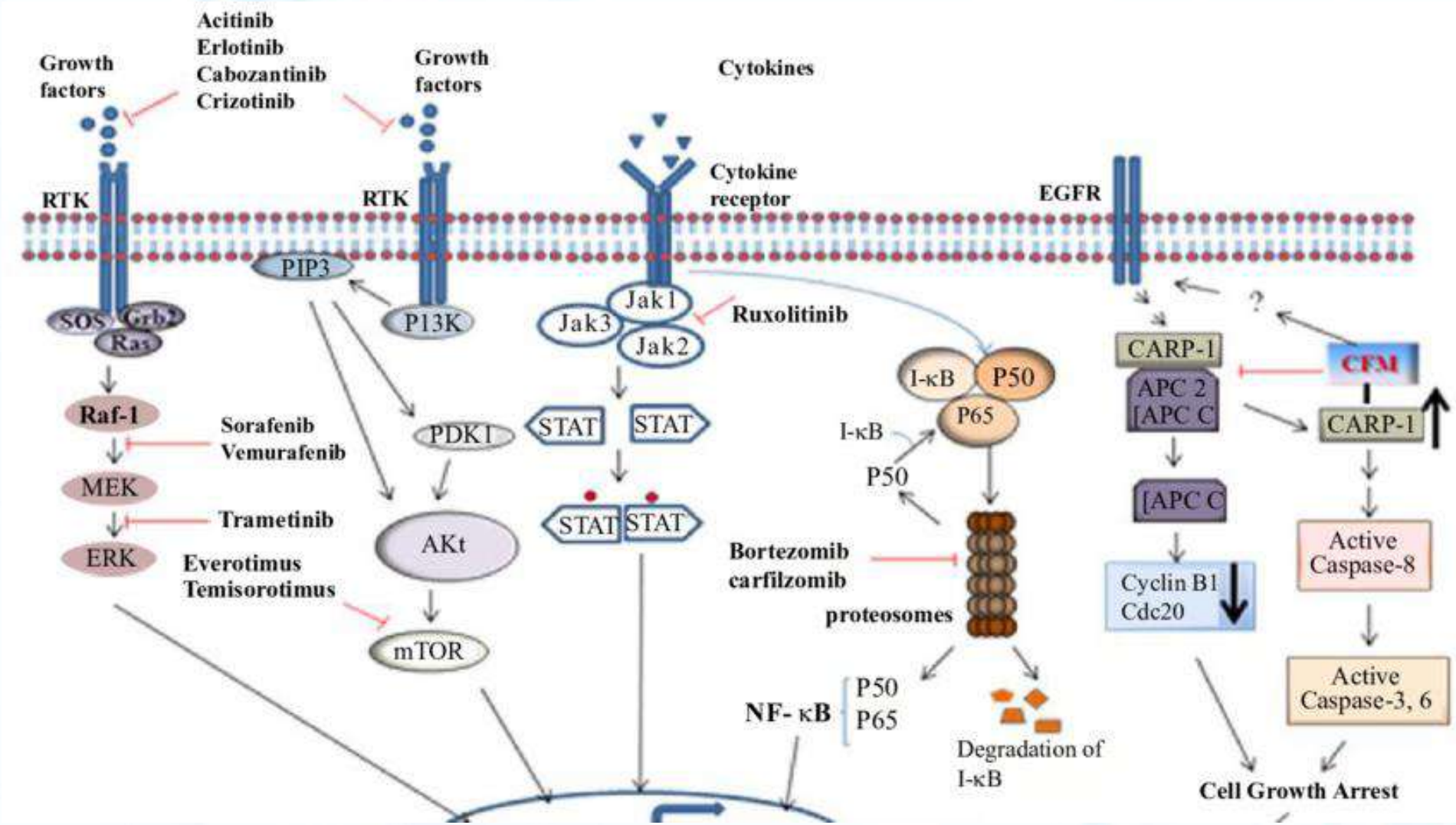


(Patel *et al*., 2020)

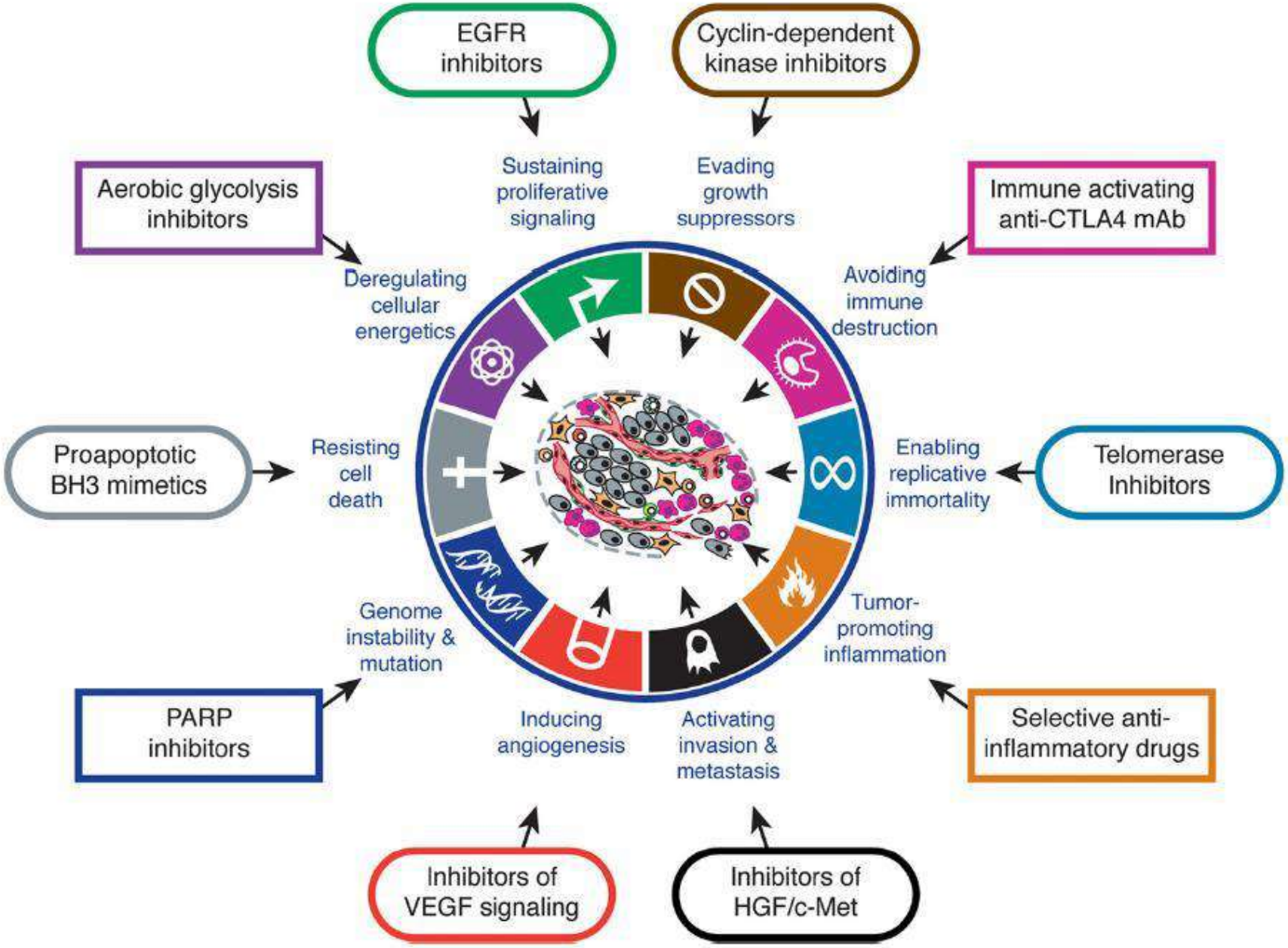
Small molecule inhibitors can get inside cancer cells and block certain enzymes and proteins that tell cancer cells to grow. Examples of small molecule inhibitors include:

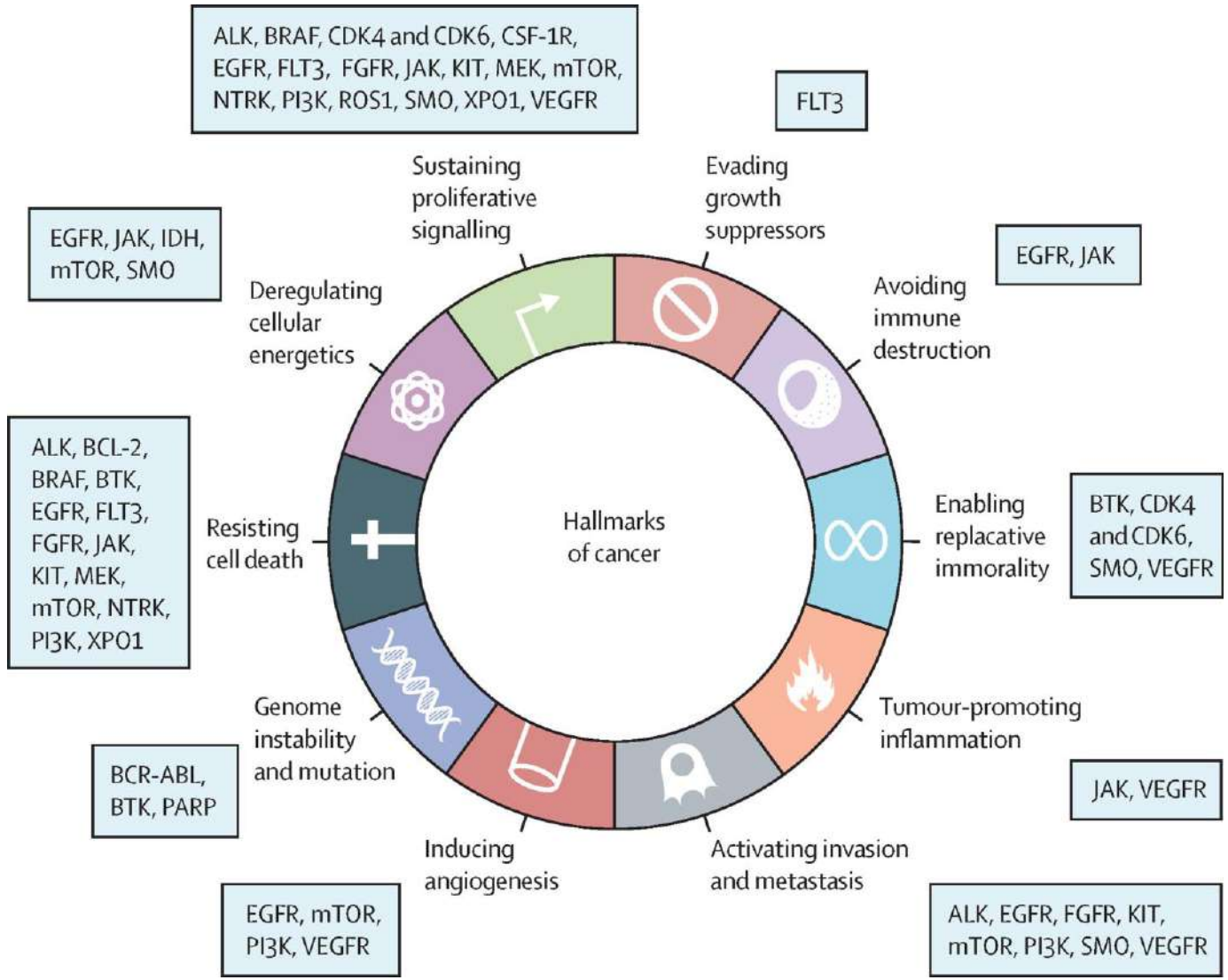
Tyrosine kinase inhibitors (TKIs)	• These drugs block a group of enzymes called tyrosine kinases from sending signals that tell cancer cells to grow, multiply and spread. • Without this signal, the cancer cells die. • Examples of TKIs include **erlotinib, sunitinib, lapatinib** and **ibrutinib**.
Mammalian target of rapamycin (mTOR) inhibitors	• These drugs block mTOR, an enzyme that tells cancer cells to grow and spread. • Everolimus is an mTOR inhibitor approved for use for some types of kidney cancer.
PARP inhibitors	• These drugs stop the protein known as PARP from repairing damaged DNA in cancer cells. • **Olaparib** is a PARP inhibitor approved for use in some ovarian, fallopian tube and peritoneal cancers.

Summarized known small molecule inhibitors as targeted therapy



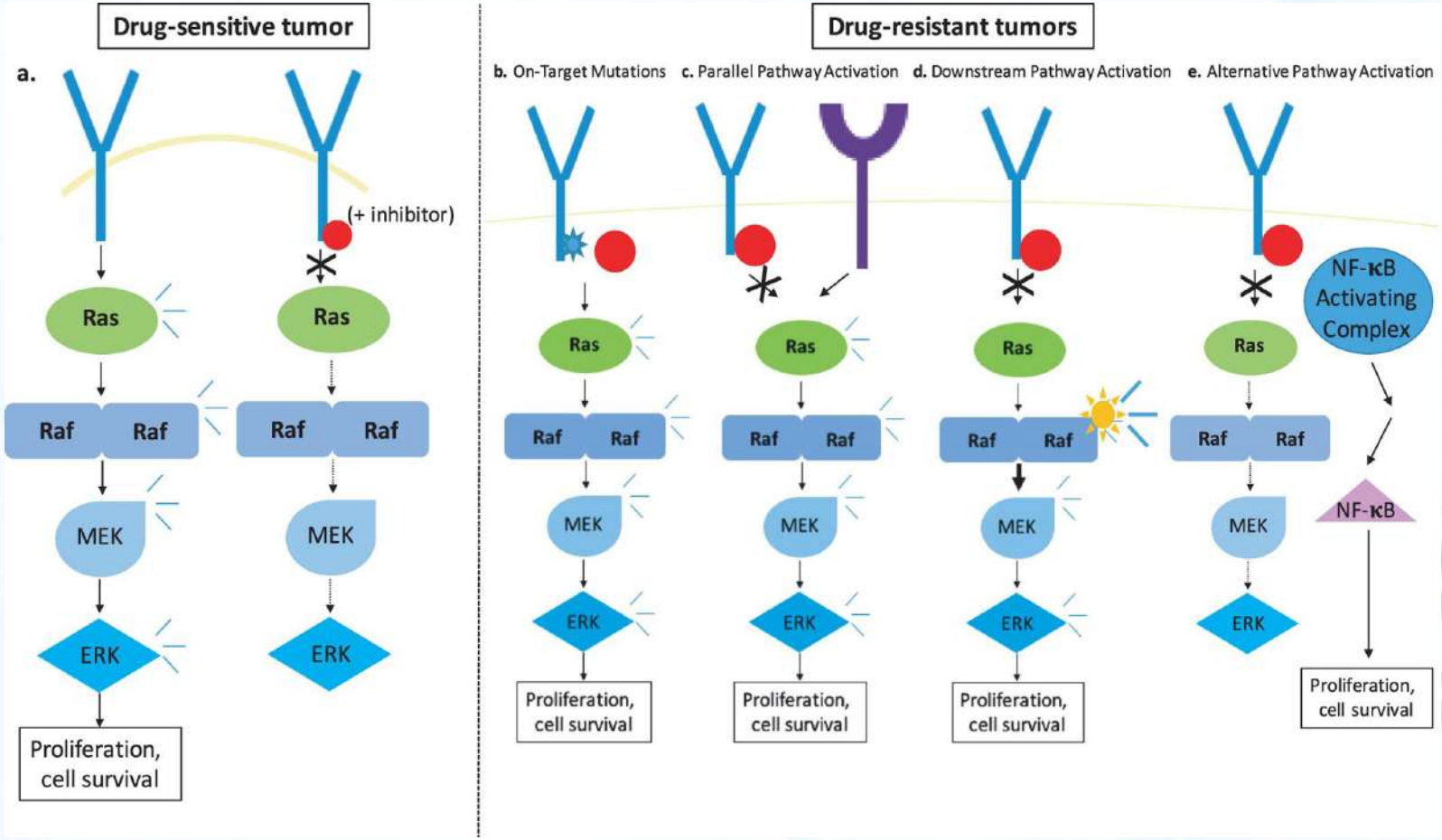
(Lavanya *et al*., 2014)


EGFR inhibitors
Cyclin-dependent kinase inhibitors
Sustaining proliferative signaling
Evading growth suppressors
Aerobic glycolysis inhibitors
Immune activating anti-CTLA4 mAb
Deregulating cellular energetics
Avoiding immune destruction
Proapoptotic BH3 mimetics
Resisting cell death
Enabling replicative immortality
Telomerase Inhibitors
Genome instability & mutation
Tumor-promoting inflammation
PARP inhibitors
Inducing angiogenesis
Activating invasion & metastasis
Selective anti-inflammatory drugs
Inhibitors of VEGF signaling
Inhibitors of HGF/c-Met


ALK, BRAF, CDK4 and CDK6, CSF-1R, EGFR, FLT3, FGFR, JAK, KIT, MEK, mTOR, NTRK, PI3K, ROS1, SMO, XPO1, VEGFR
FLT3
Sustaining proliferative signalling
Evading growth suppressors
EGFR, JAK, IDH, mTOR, SMO
EGFR, JAK
Deregulating cellular energetics
Avoiding immune destruction
ALK, BCL-2, BRAF, BTK, EGFR, FLT3, FGFR, JAK, KIT, MEK, mTOR, NTRK, PI3K, XPO1
Hallmarks of cancer
Resisting cell death
Enabling replacative immorality
BTK, CDK4 and CDK6, SMO, VEGFR
Genome instability and mutation
Tumour-promoting inflammation
BCR-ABL, BTK, PARP
JAK, VEGFR
Inducing angiogenesis
Activating invasion and metastasis
EGFR, mTOR, PI3K, VEGFR
ALK, EGFR, FGFR, KIT, mTOR, PI3K, SMO, VEGFR

Limitations of targeted cancer therapy

- Cancer cells can develop resistance to the action of the therapy.
- Drugs are difficult to develop because of the target's structure and/or the way its function is regulated in the cell.



Mechanisms of resistance to targeted therapies

Signal Transduction and Targeted Therapy

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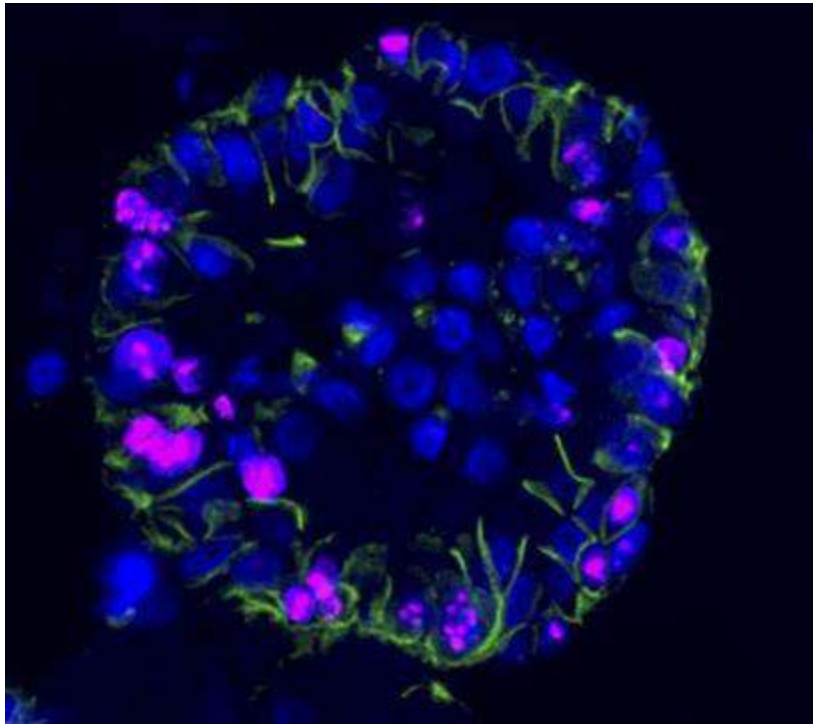
Review Article | Open Access | Published: 07 February 2020

Targeting cancer stem cell pathways for cancer therapy

Liqun Yang, Pengfei Shi, Gaichao Zhao, Jie Xu, Wen Peng, Jiayi Zhang, Guanghui Zhang, Xiaowen Wang, Zhen Dong, Fei Chen & Hongjuan Cui ✉

Signal Transduction and Targeted Therapy **5**, Article number: 8 (2020) | Cite this article



ELSEVIER

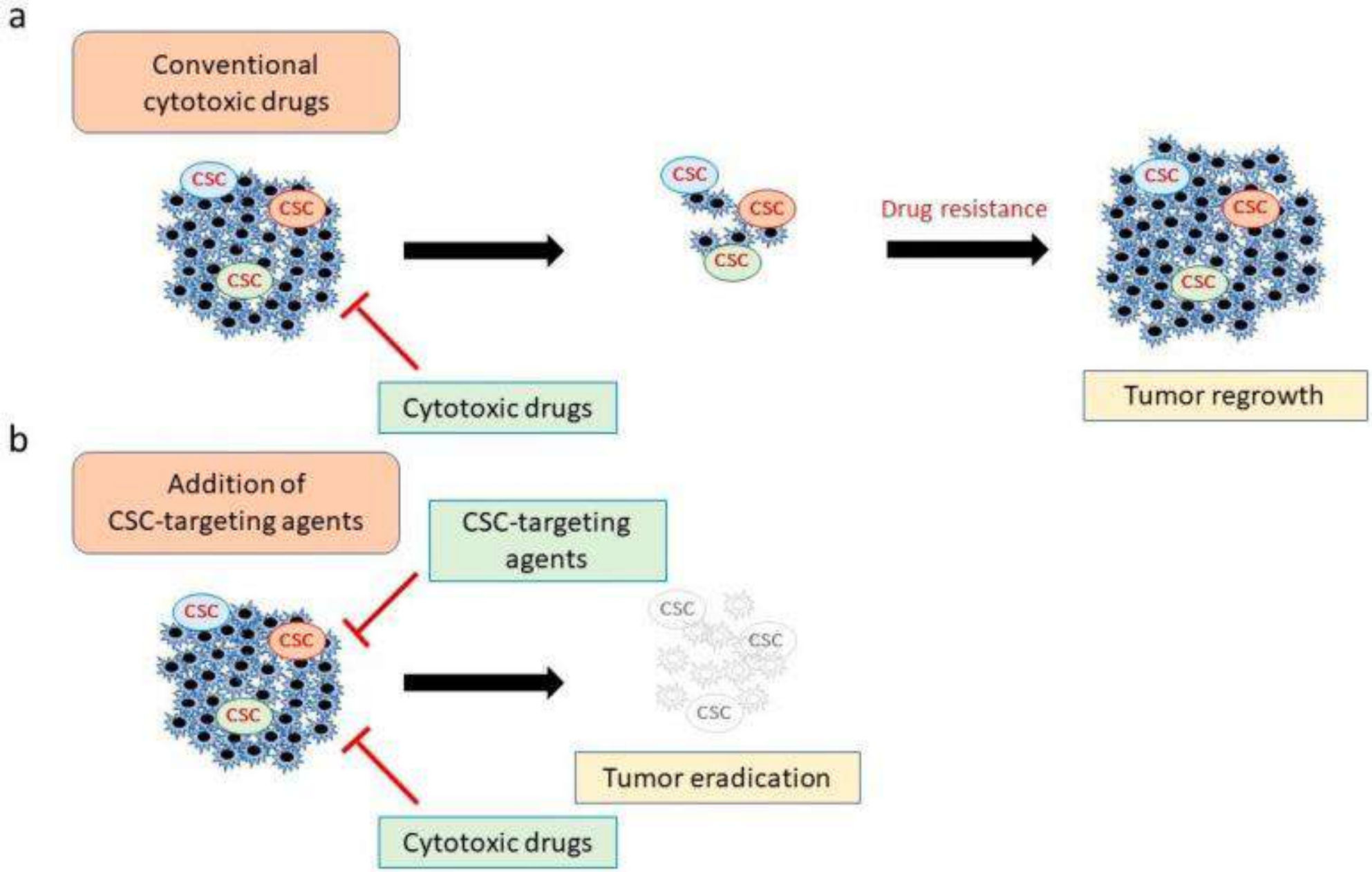
Cancer Letters

Volume 385, 28 January 2017, Pages 87-96

Mini-review

At the crossroads of cancer stem cells and targeted therapy resistance

Anbang Wang [a], Le Qu [b] ✉, Linhui Wang [a] ✉


a
Conventional cytotoxic drugs
CSC
CSC
CSC
CSC
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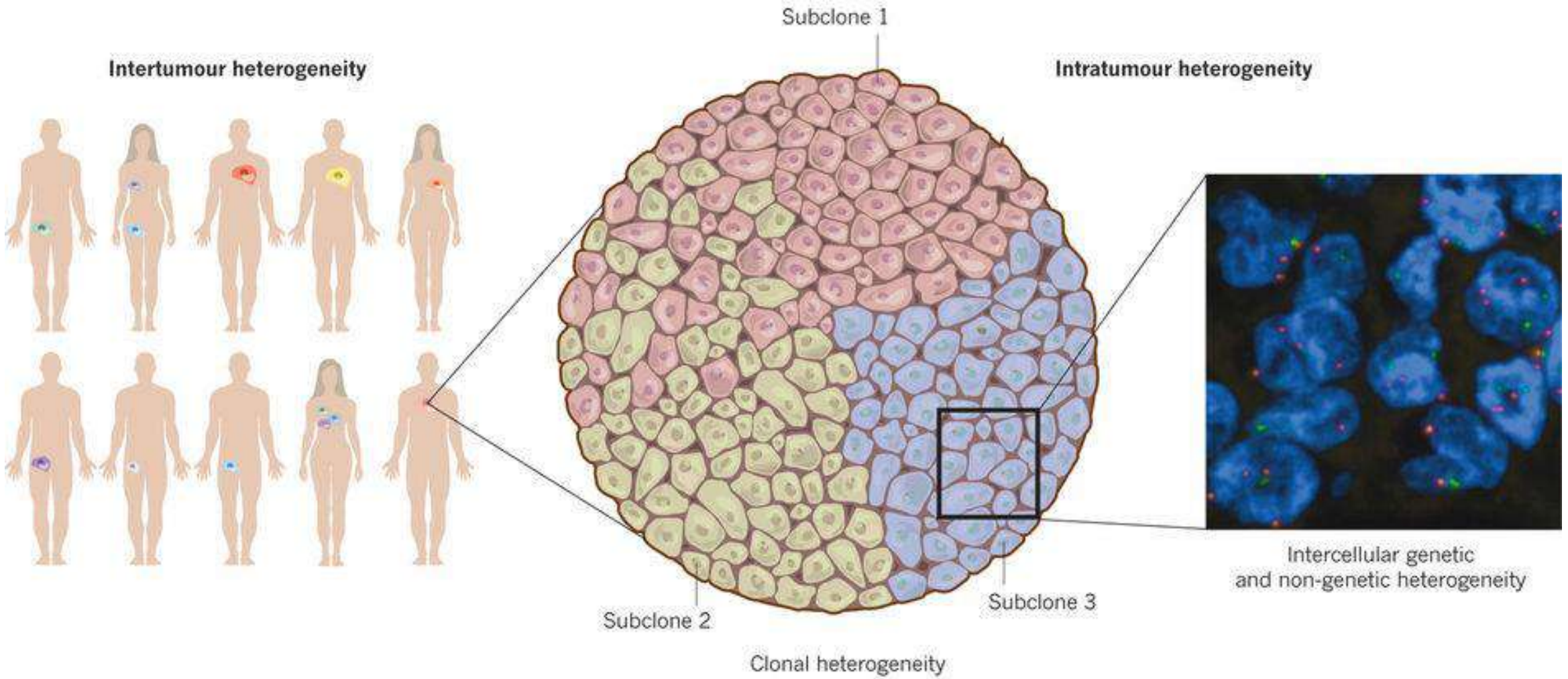
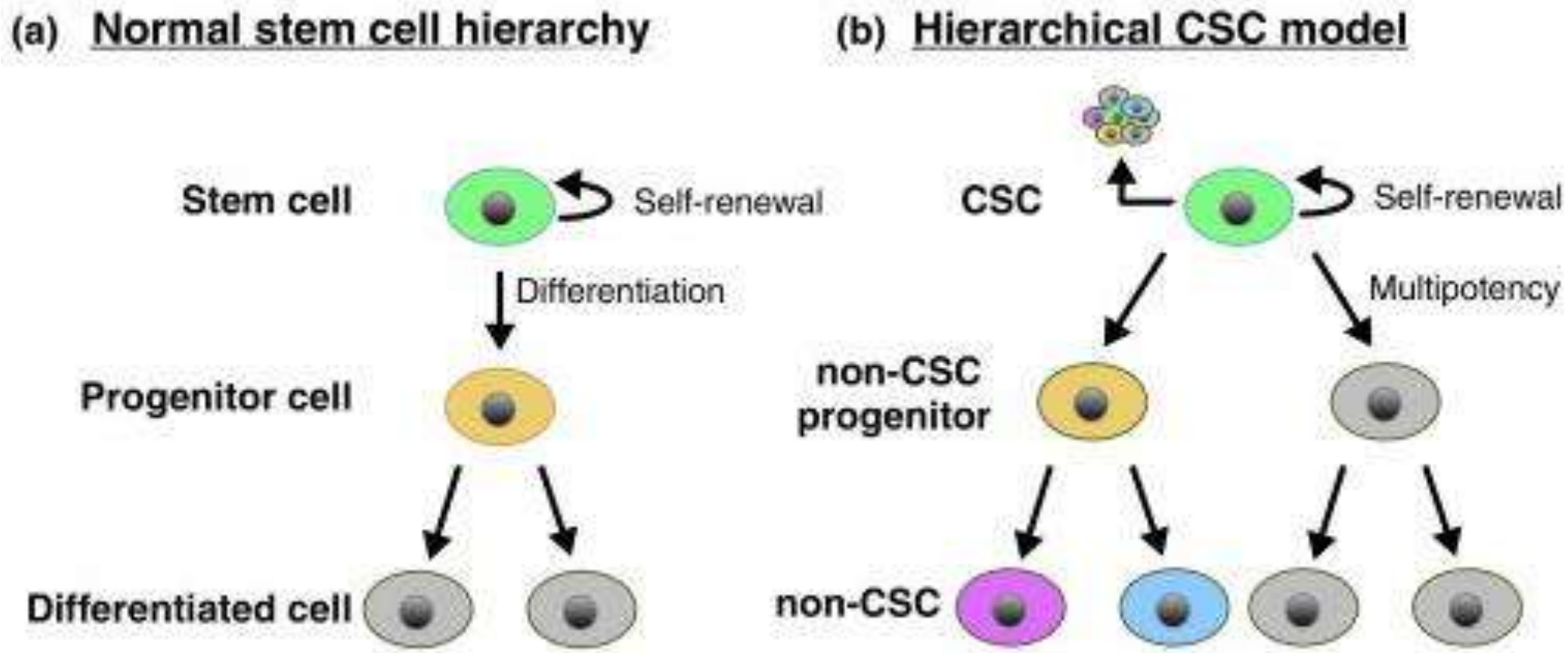
CSC
Drug resistance
CSC
CSC
CSC
Tumor regrowth
Cytotoxic drugs
b
Addition of CSC-targeting agents
CSC-targeting agents
CSC
CSC
CSC
CSC
CSC
CSC
Tumor eradication
Cytotoxic drugs

Cancer is a heterogeneous disease

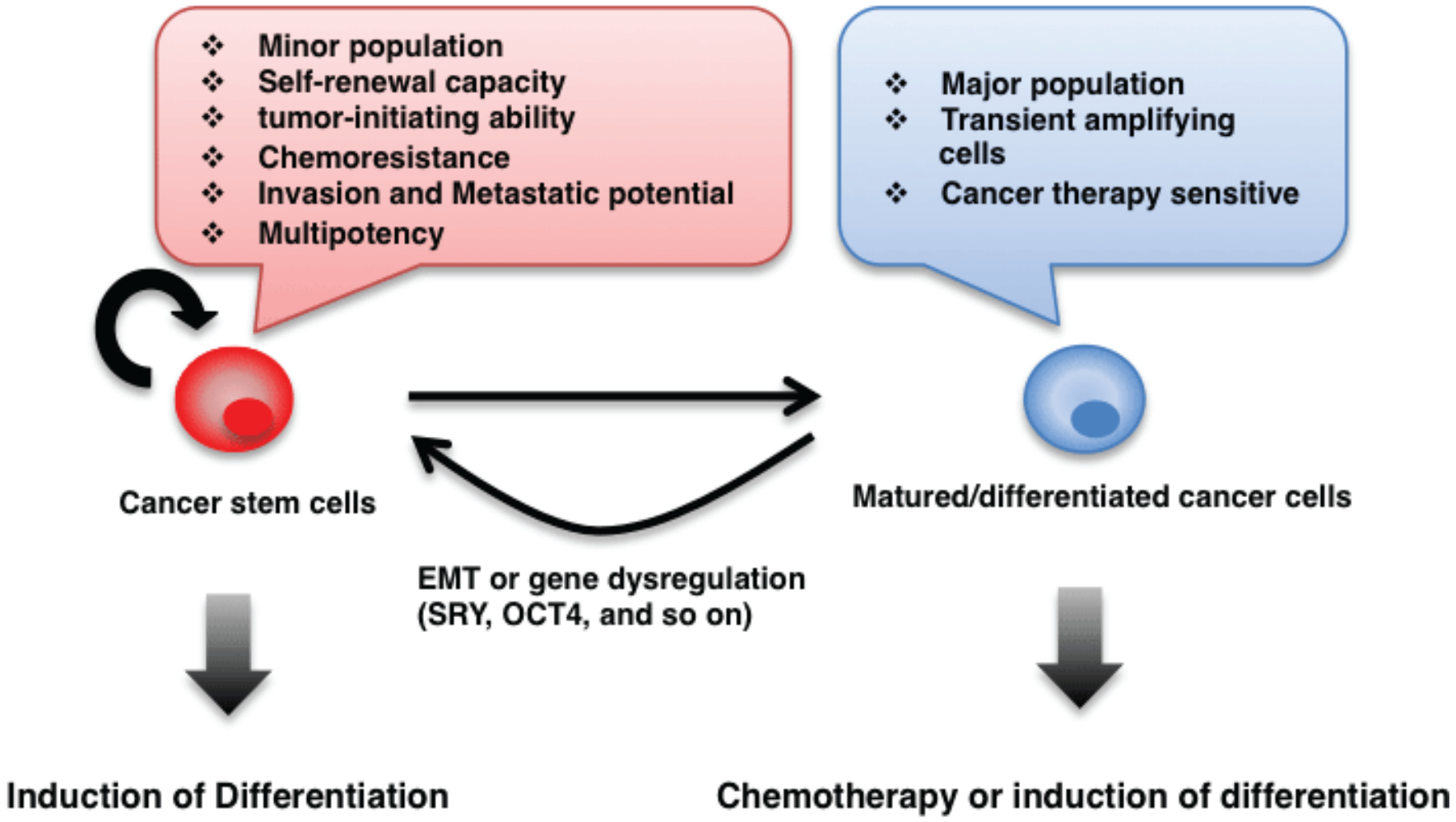


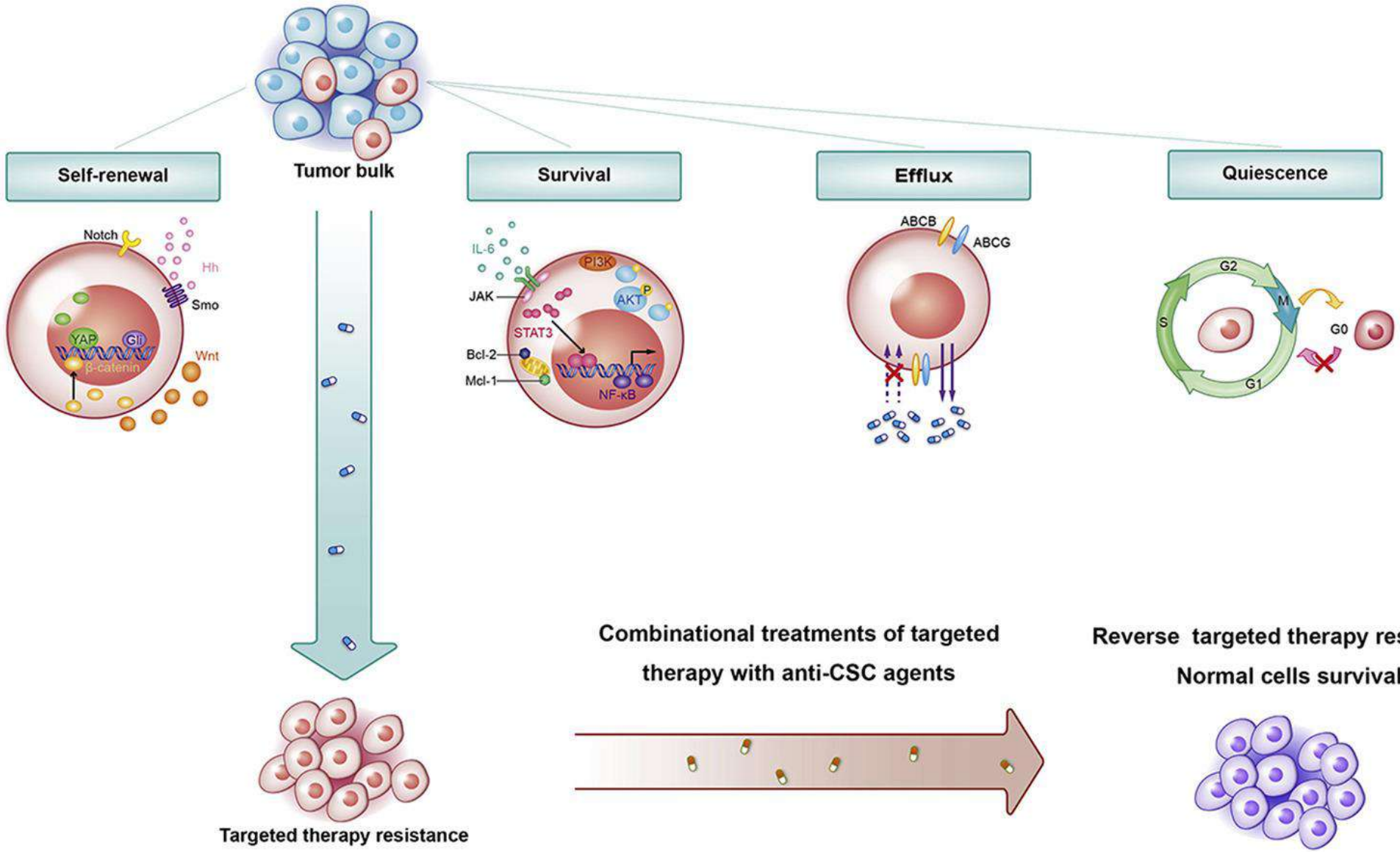
Model of cancer stem cell (CSC)

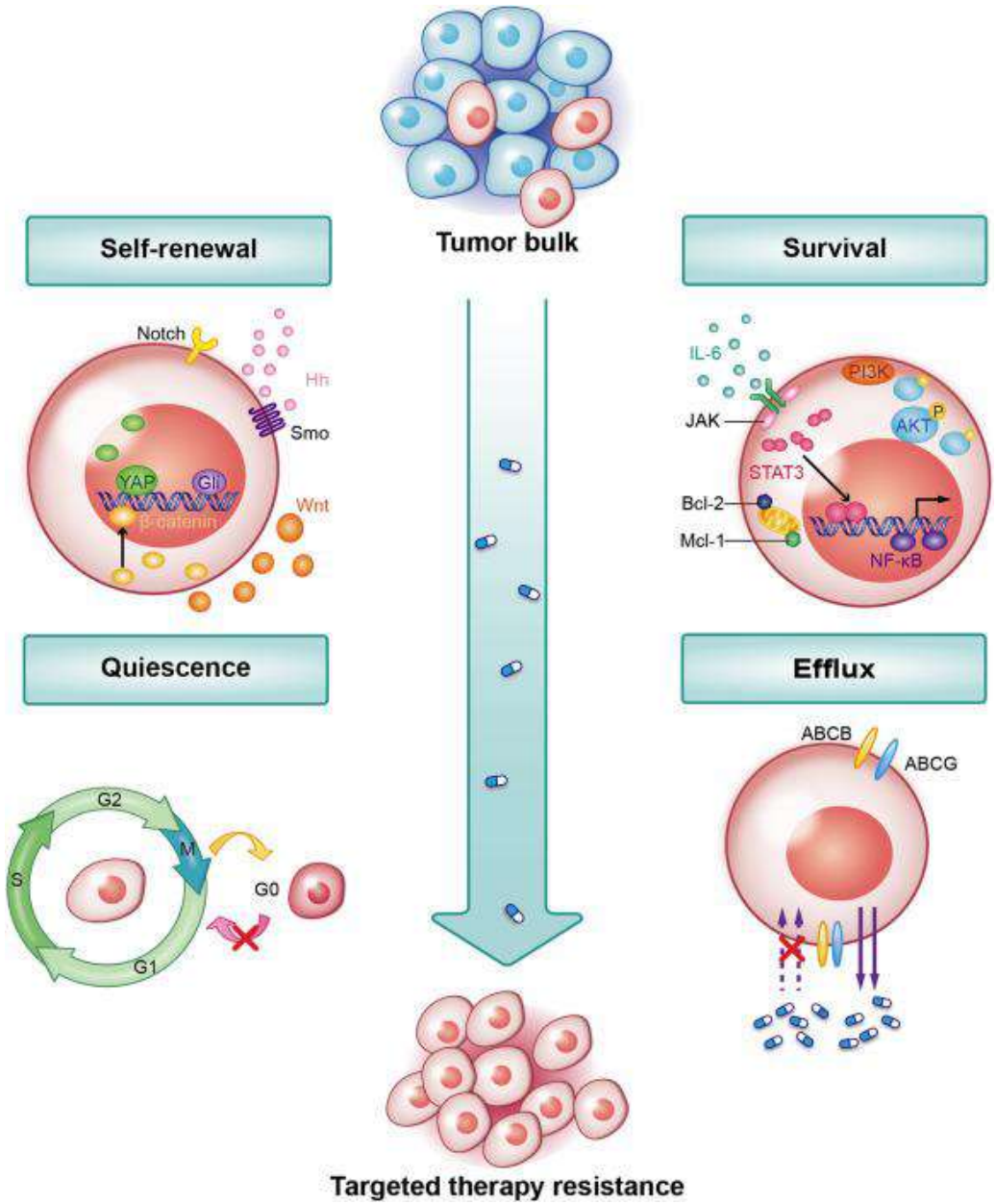


Current Opinion in Genetics & Development
Volume 36, February 2016, Pages 8-15

Characteristics of cancer stem cell (CSC)




Tumor bulk
Self-renewal
Notch
Hh
Smo
YAP
Gli
β-catenin
Wnt
Survival
IL-6
JAK
PI3K
AKT
P
STAT3
Bcl-2
Mcl-1
NF-κB
Efflux
ABCB
ABCG
Quiescence
G2
M
S
G0
G1
Targeted therapy resistance
Combinational treatments of targeted therapy with anti-CSC agents
Reverse targeted therapy resistance
Normal cells survival


Tumor bulk
Self-renewal
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β-catenin
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AKT
P
STAT3
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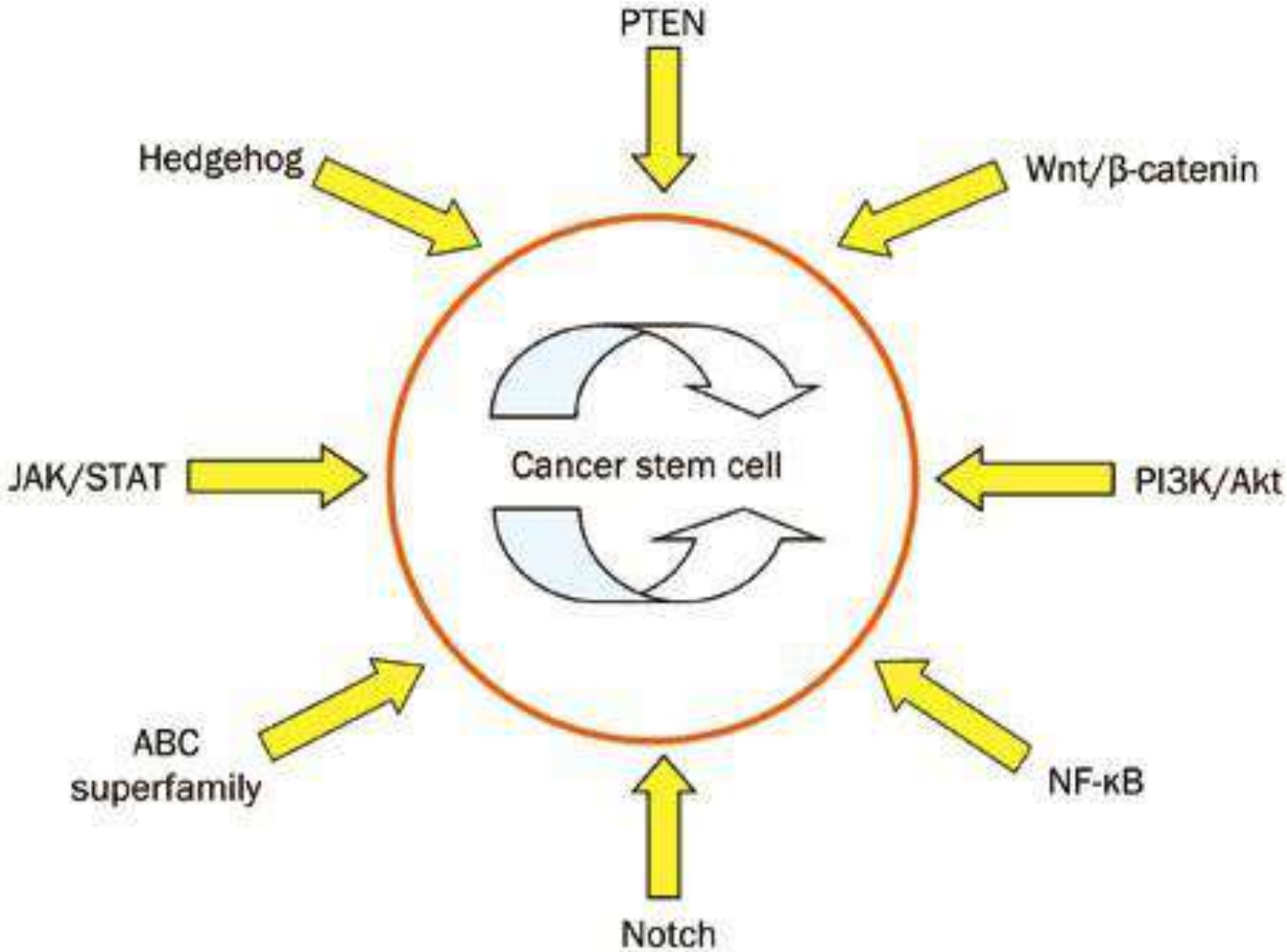
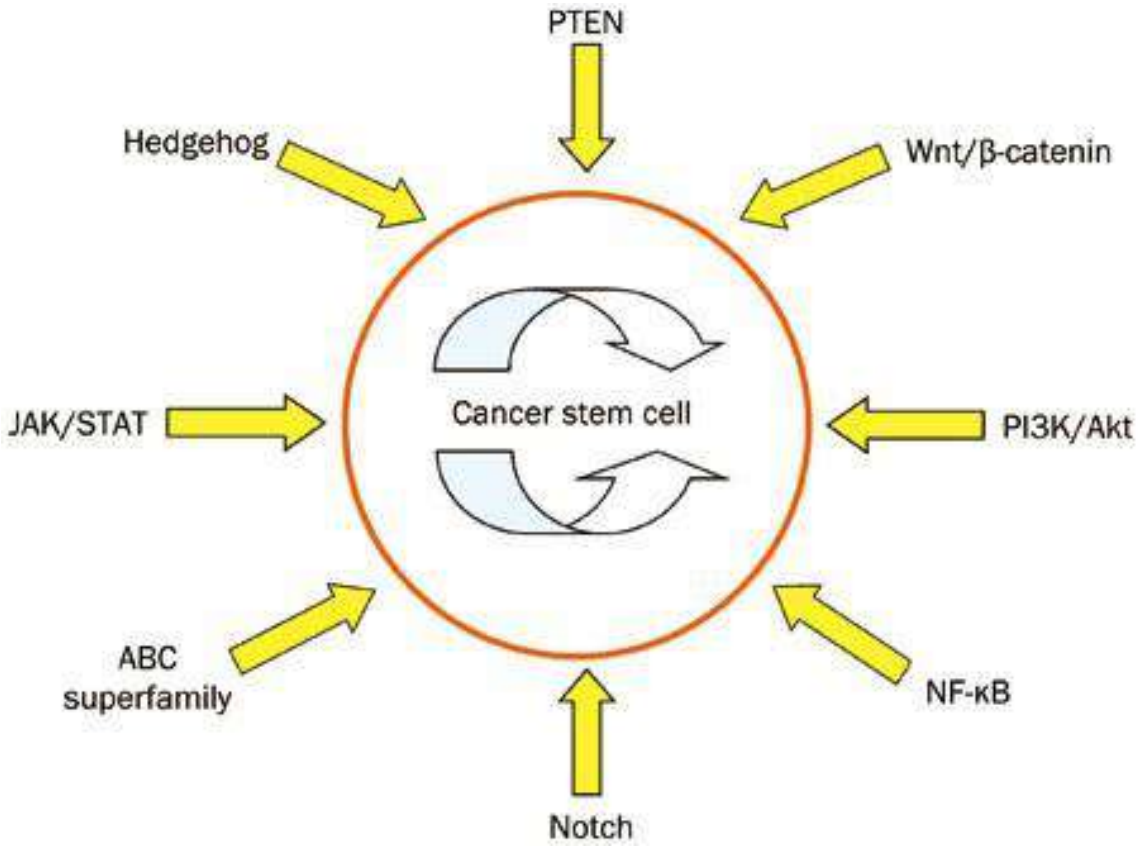
NF-κB
Quiescence
G2
M
S
G0
G1
Efflux
ABCB
ABCG
Targeted therapy resistance


PTEN
Hedgehog
Wnt/β-catenin
Cancer stem cell
JAK/STAT
PI3K/Akt
ABC
superfamily
NF-κB
Notch

Therapeutic opportunities of combining targeted therapy and anti-CSC therapy

Table 1
Combinational treatments of TT with anti-CSC agents in diverse cancer types.

Mechanism	Therapeutic target	Inhibitory agent	Tumor type
Self-renewal	Hedgehog	GLI inhibitor GANT61/rapamycin	Pancreatic cancer
		Cyclopamine/imatinib	Myeloid leukemia
		Cyclopamine/erlotinib	Glioma
		Cyclopamine/gefitinib	Non-Small-Cell Lung Cancer/prostate cancer
		Hh inhibitor IPI-926/Cetuximab	Head and Neck Cancer
	Notch	γ-secretase inhibitor/erlotinib	Lung cancer
		γ-secretase inhibitor/cediranib	Solid tumors
		Notch1 blockade/mTOR inhibition	Triple-negative breast cancer
		Notch-1 siRNA/gefitinib	Lung cancer
	Wnt/β-catenin	β-catenin inhibition/imatinib	Chronic myeloid leukemia
		Trifluoperazine/gefitinib	Lung cancer
		ICG-001 or shRNA/sorafenib	Hepatocellular Carcinoma
	YAP	YAP/RAF or MEK inhibition	BRAF/BRAF-mutant tumors
Survival	TGFβ	TGFβ inhibitor Ly364947/imatinib	Chronic myeloid leukemia
	PI3K/AKT	Anti-ErbB-3 antibody/vemurafenib	Colon cancer
		PI3K inhibitor XL147/trastuzumab	Breast cancer
		MiR-205/gefitinib or lapatinib	Breast cancer
	JAK/STAT3	BMS-911543/imatinib	Chronic myeloid leukemia
		Upstream IL-6 receptor antibody/trastuzumab	Breast cancer
		STAT3 inhibitor niclosamide/erlotinib	Non-Small-Cell Lung Cancer/prostate cancer
		STAT3 inhibitor Stattic/trastuzumab	Breast cancer
	STAT5	STAT5A siRNA/imatinib	Chronic myeloid leukemia
		STAT5 inhibitor pimozide/imatinib or nilotinib	Chronic myeloid leukemia
	NK-κB	Bortezomib/erlotinib	Lung cancer
	PAK1/NF-κB/IL-6	PAK1/NF-κB/IL-6 inhibition and sunitinib	Renal cell carcinoma
	Anti-apoptotic protein	Bcl inhibitor/dasatinib	Leukemia
		Mcl inhibitor obatoclax/erlotinib	Lung cancer
		Active mutant of BIK/lapatinib	Breast cancer
	IL-8	IL-8 neutralizing antibody/sunitinib	Renal cell carcinoma
CSC markers	ALDH	Silibinin/erlotinib	Non-small cell lung cancer
		ALDH inhibitor DEAB or CD44 siRNA/gefitinib	Lung cancer
		Disulfiram/erlotinib	Lung adenocarcinoma
	HDAC	Vorinostat/erlotinib	Non-small cell lung cancer
		SIRT1 inhibitor Tenovin-6/imatinib	Chronic myeloid leukemia
		HDAC inhibition/imatinib	Chronic myeloid leukemia
Microenvironment	CXCR4	Plerixafor/imatinib	Chronic myeloid leukemia
	HGF	Anti-HGF antibody or HGF antagonist NK4/gefitinib	Lung cancer
Others	CD70	CD70 blockade/imatinib	Leukemia
	AXL	AXL inhibitor/erlotinib	Lung cancer
	HIF	HIF1α inhibitor YC-1/gefitinib	Lung cancer
		Oxythiamine/imatinib	Chronic myeloid leukemia


PTEN
Hedgehog
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JAK/STAT
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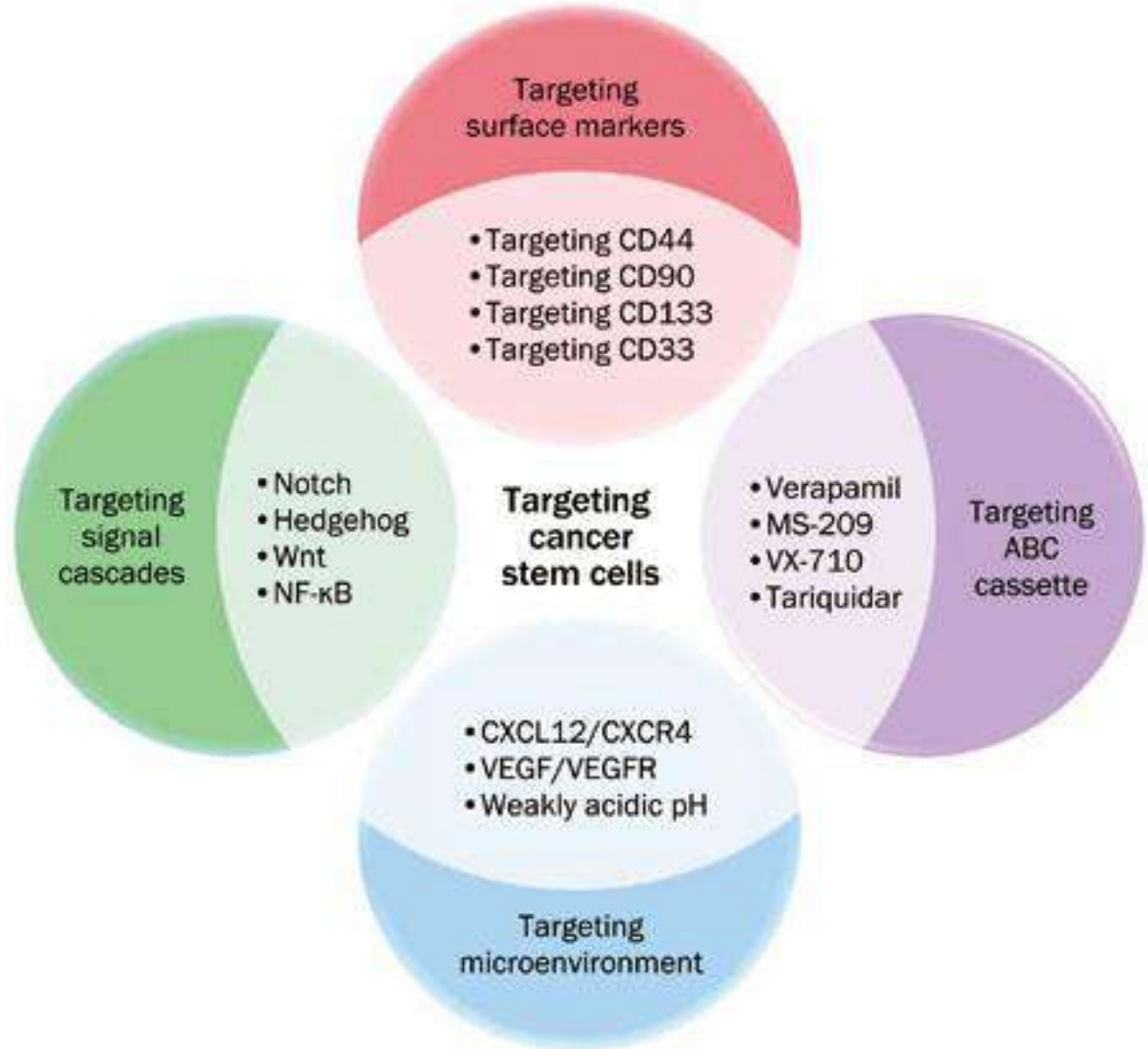
NF-κB
Notch

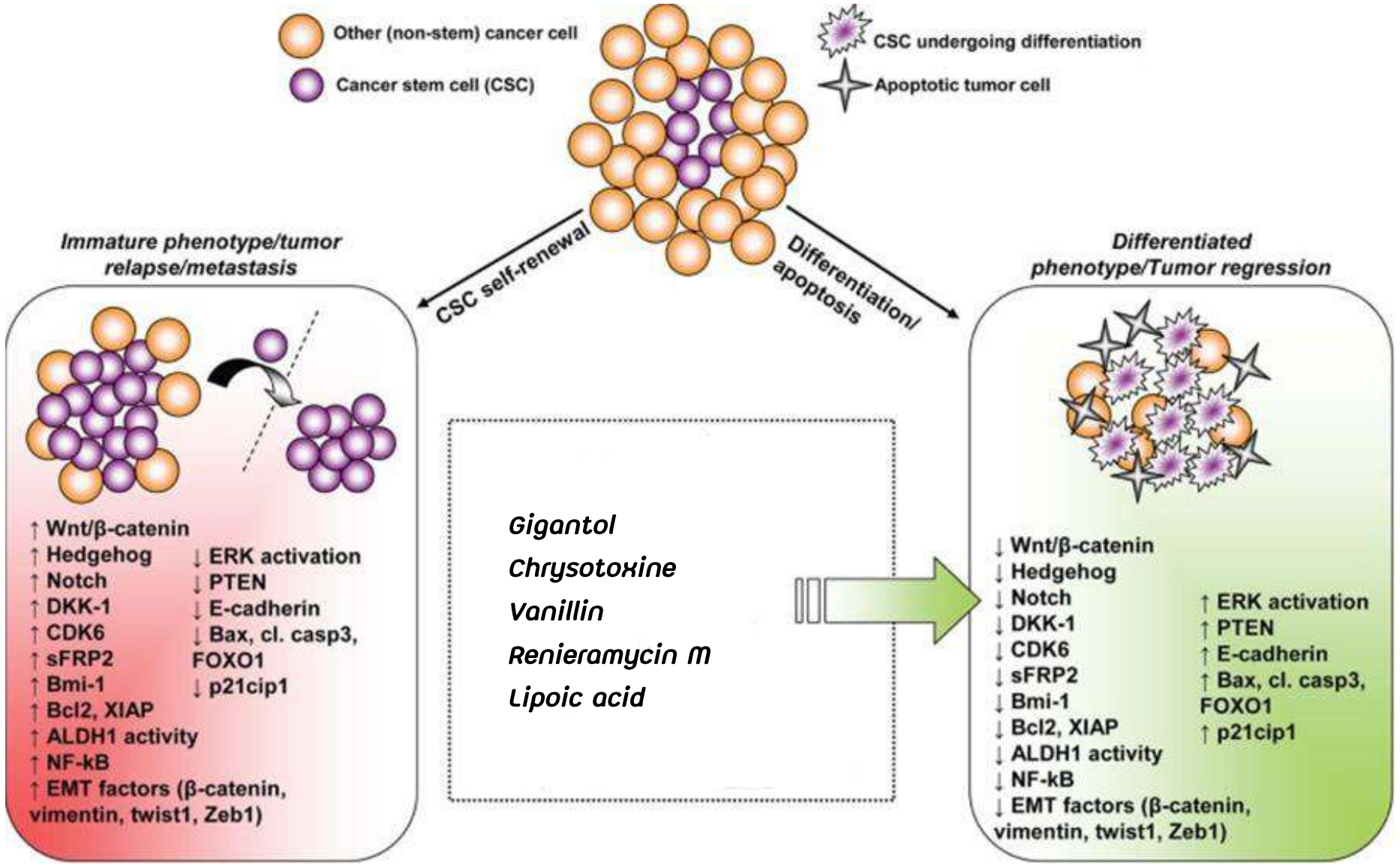

Targeting surface markers
• Targeting CD44
• Targeting CD90
• Targeting CD133
• Targeting CD33
Targeting signal cascades
• Notch
• Hedgehog
• Wnt
• NF-κB
Targeting cancer stem cells
• Verapamil
• MS-209
• VX-710
• Tariquidar
Targeting ABC cassette
• CXCL12/CXCR4
• VEGF/VEGFR
• Weakly acidic pH
Targeting microenvironment

Therapeutic attempts to target cancer stem cell (CSC).

Target	Cancer Type	Inhibitor	Result
ALDH1	Breast	Histone deacetylase inhibitor	$CD44^{+}CD24^{-/low}$ cell population was decreased and stemness markers were downregulated.
	NSCLC	Disulfiram	Combination of disulfiram and copper downregulated stemness-related genes.
			When combined with diethylamino-benzaldehyde resensitized resistant cells to cisplatin.
			A phase II trial showed prolonged survival when disulfiram was combined with cisplatin and vinorelbine.
	Ovary	Solanum incanum extract	Notch1 and FoxM1 were downregulated, which resulted in increased chemotherapeutic sensitivities.
CD44	Breast	Anti CD44 antibody	Nanoparticles with CD44 antibody and gemcitabine specifically targeted $CD44^{+}$ cells.
CD133	Ovary	Anti CD133 antibody-toxin conjugate	Cellular growth was inhibited and tumor progression was suppressed in a mouse model.
Hedgehog	Bladder	Cyclopamine	Tumor formation was suppressed via inhibition of GALNT1 that mediates SHH signaling.
	Lung	GDC-0449	Stemness-related features were suppressed in both NSCLC and small-cell lung cancer cells.
KLF5	Breast	Metformin	CSC growth was inhibited through suppression of *NANOG* and *FGF-BP1* (downstream targets of KLF5).
Notch2 and Notch3	Various cancers	Tarextumab	Tumorigenesis and cellular growth were suppressed and chemotherapeutic efficacy was increased.
	Small-cell lung		A phase Ib trial showed good tolerability and anti-tumor effect.
PI3K/AKT	Bladder	Myrtucommulone-A	Several stem cell markers were downregulated and stemness-related features were attenuated.
	Bladder	Motesanib	Survival-related genes in the PI3K/AKT pathway were decreased and cisplatin sensitivity was enhanced.
STAT3	Breast	STAT3 inhibitor VII	Combination of STAT3 inhibitor and carboplatin abrogated carboplatin-induced $ALDH^{+}$ cell enrichment.
	Colon	Napabucasin	*c-Myc*, *Nanog* and *Sox2*, were downregulated, which attenuated metastasis in a mouse model.
			Napabucasin showed prolonged survival in phosphorylated STAT3 positive patients.
	Pancreas	Napabucasin	Cancer relapse and metastasis were blocked in mice.
	NSCLC	OPB-51602	A phase I trial suggested that NSCLC patients were likely to obtain better response.
Wnt/β-catenin	Breast	Pyrvinium pamoate	$CD44^{+}CD24^{-/low}$ and $ALDH^{+}$ cells were suppressed by downregulating *NANOG*, *OCT4*, and *SOX2*.
	Breast	Resveratol	Resveratol, which suppressed Wnt/β-catenin pathway, inhibited CSCs and induced autophagy.
	Ovary	Imatinib	CSC activity was suppressed when combined with platinum chemotherapy.
			Phase II clinical trials had only a modest impact on the prognosis of ovarian cancer patients.

Cancers (Basel). 2019 May; 11(5): 732.
Published online 2019 May 27. doi: 10.3390/cancers11050732

Targeting CSCs with Natural Product-derived Compounds

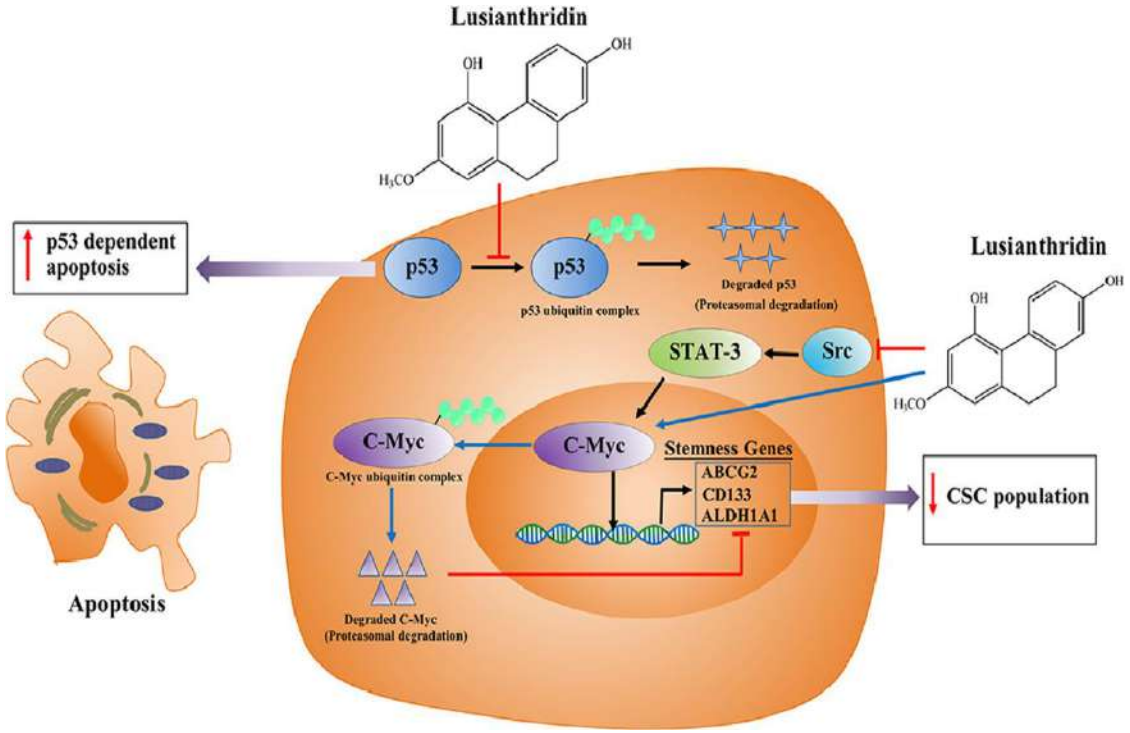


ELSEVIER

Phytomedicine
Volume 62, September 2019, 152932

Lusianthridin targeting of lung cancer stem cells via Src-STAT3 suppression

Narumol Bhummaphan [a, b], Nalinrat Petpiroon [b, c], Ornjira Prakhongcheep [b, c], Boonchoo Sritularak [d], Pithi Chanvorachote [b, c]



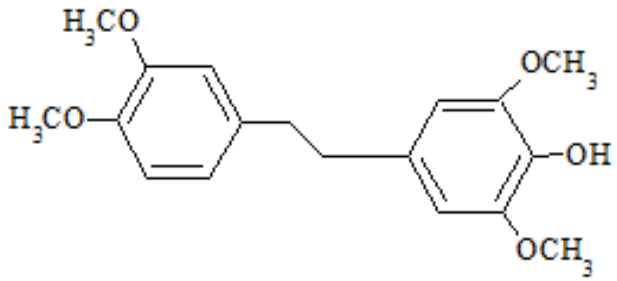
ASPET | THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

1521-0103/364/2/332–346$25.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

https://doi.org/10.1124/jpet.117.244467
J Pharmacol Exp Ther 364:332–346, February 2018

Cancer Stem Cell–Suppressing Activity of Chrysotoxine, a Bibenzyl from *Dendrobium pulchellum*

Narumol Bhummaphan, Varisa Pongrakhananon, Boonchoo Sritularak, and Pithi Chanvorachote



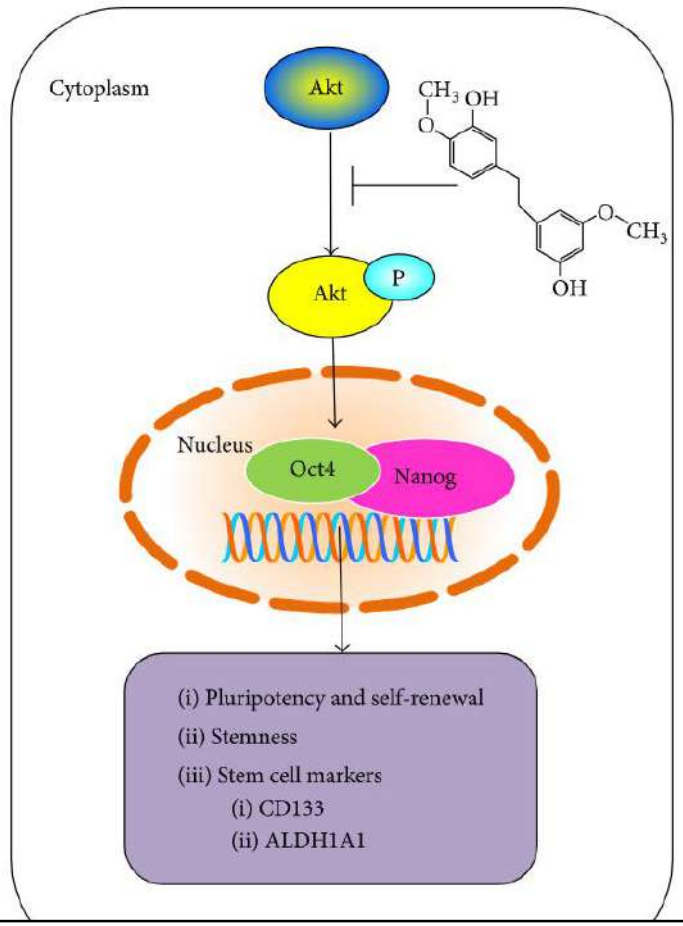
Chrysotoxine

Evidence-Based Complementary and Alternative Medicine
Volume 2015, Article ID 836564, 10 pages
http://dx.doi.org/10.1155/2015/836564

Research Article

Gigantol Suppresses Cancer Stem Cell-Like Phenotypes in Lung Cancer Cells

Narumol Bhummaphan[1] and Pithi Chanvorachote[1,2]



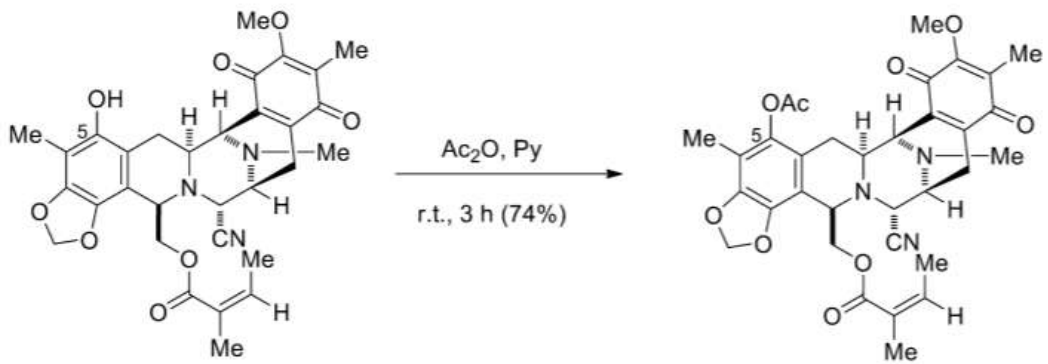
marine drugs

MDPI

Article

5-*O*-Acetyl-Renieramycin T from Blue Sponge *Xestospongia* sp. Induces Lung Cancer Stem Cell Apoptosis

Wipa Chantarawong [1,2], Supakarn Chamni [3], Khanit Suwanborirux [3], Naoki Saito [4] and Pithi Chanvorachote [1,2,*]



renieramycin T

5-*O*-acetyl-renieramycin T

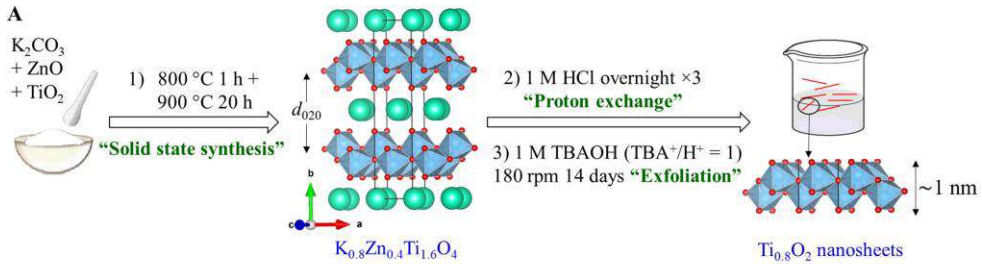
ASPET | MOLECULAR PHARMACOLOGY

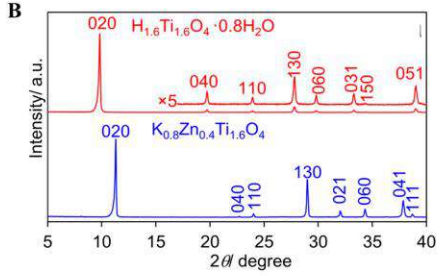
Research Article | Article

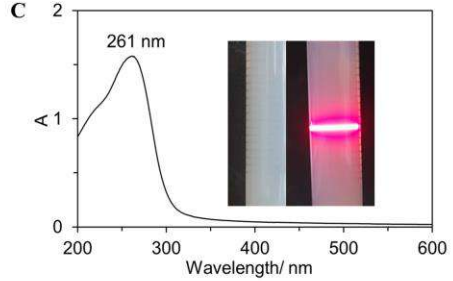
Tio.8O2 Nanosheets Inhibit Lung Cancer Stem Cells by Inducing Production of Superoxide Anion

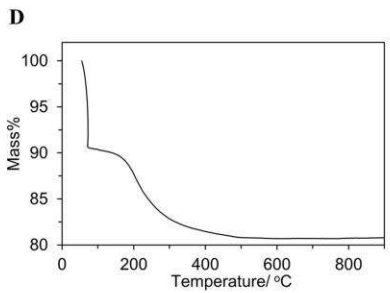
Nalinrat Petpiroon, Narumol Bhummaphan, Rapeepun Soonnarong, Wipa Chantarawong, Tosapol Maluangnont, Varisa Pongrakhananon, and Pithi Chanvorachote

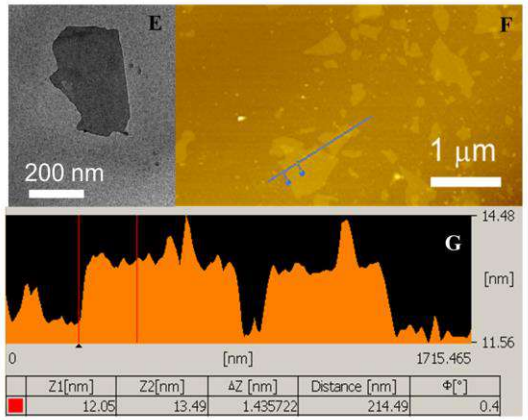
Molecular Pharmacology February 8, 2019, mol.118.114447; DOI: https://doi.org/10.1124/mol.118.114447

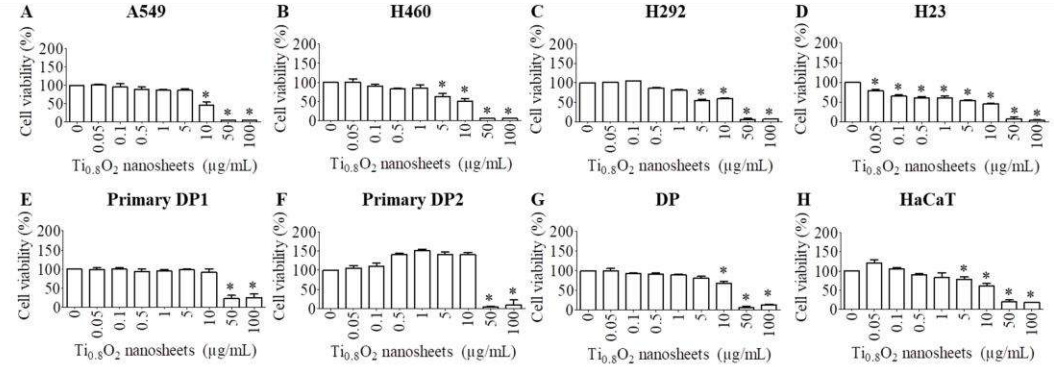

A
K_2CO_3
+ ZnO
+ TiO_2
"Solid state synthesis"
1) 800 °C 1 h +
900 °C 20 h
d_{020}
$K_{0.8}Zn_{0.4}Ti_{1.6}O_4$
2) 1 M HCl overnight ×3
"Proton exchange"
3) 1 M TBAOH (TBA^+/H^+ = 1)
180 rpm 14 days "Exfoliation"
~1 nm
$Ti_{0.8}O_2$ nanosheets

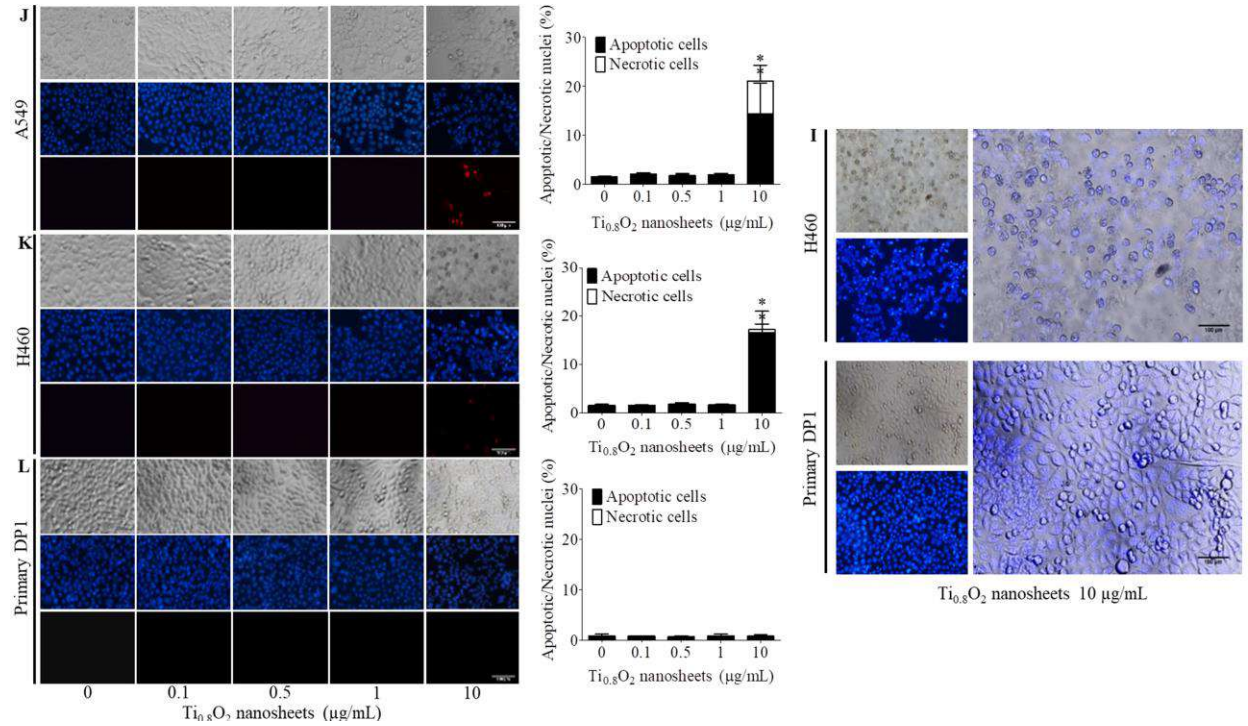

B
020
$H_{1.6}Ti_{1.6}O_4 \cdot 0.8H_2O$
040
110
130
060
031
150
051
×5
020
$K_{0.8}Zn_{0.4}Ti_{1.6}O_4$
130
040
110
021
060
041
111
Intensity/ a.u.
2θ/ degree


C
261 nm
A
Wavelength/ nm


D
Mass%
Temperature/ °C

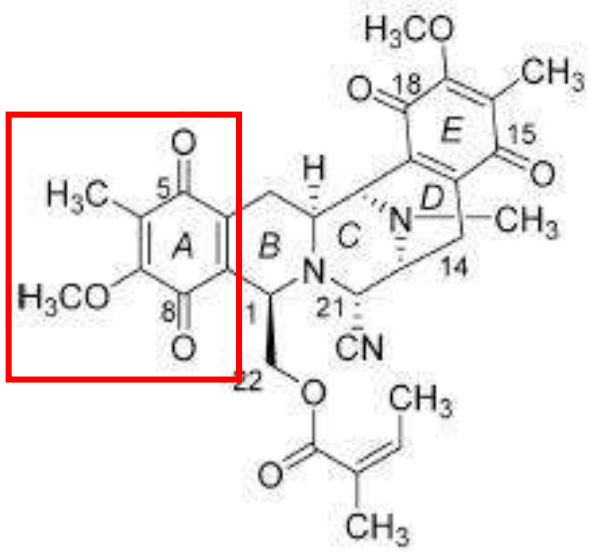

E
200 nm
F
1 μm
G
14.48
[nm]
11.56
0
[nm]
1715.465
Z1[nm]
Z2[nm]
ΔZ [nm]
Distance [nm]
Φ[°]
12.05
13.49
1.435722
214.49
0.4


A
A549
B
H460
C
H292
D
H23
E
Primary DP1
F
Primary DP2
G
DP
H
HaCaT
Cell viability (%)
$Ti_{0.8}O_2$ nanosheets (μg/mL)

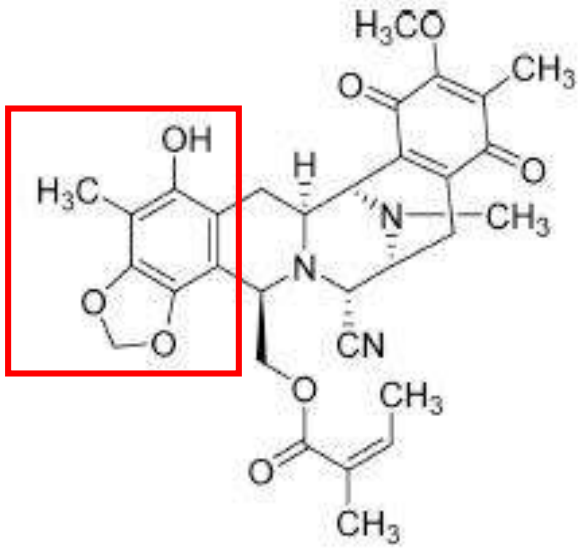

J
A549
K
H460
L
Primary DP1
Apoptotic cells
Necrotic cells
Apoptotic/Necrotic nuclei (%)
$Ti_{0.8}O_2$ nanosheets (μg/mL)
I
H460
Primary DP1
$Ti_{0.8}O_2$ nanosheets 10 μg/mL

Renieramycin T (RT)

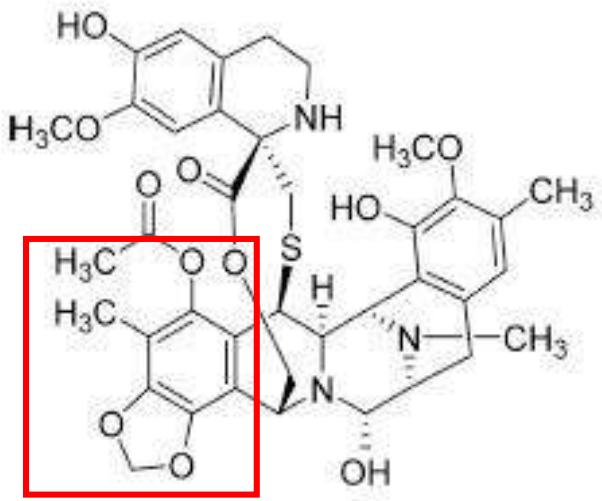
- **Renieramycin T is the renieramycin–ecteinascidin hybrids in the tetrahydroisoquinoline alkaloid family.**



renieramycin M

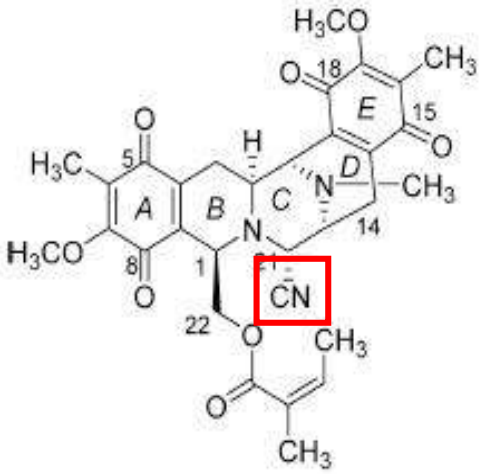


renieramycin T

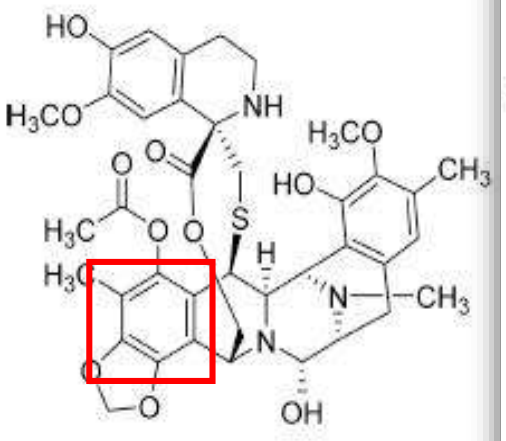


ecteinascidin 743

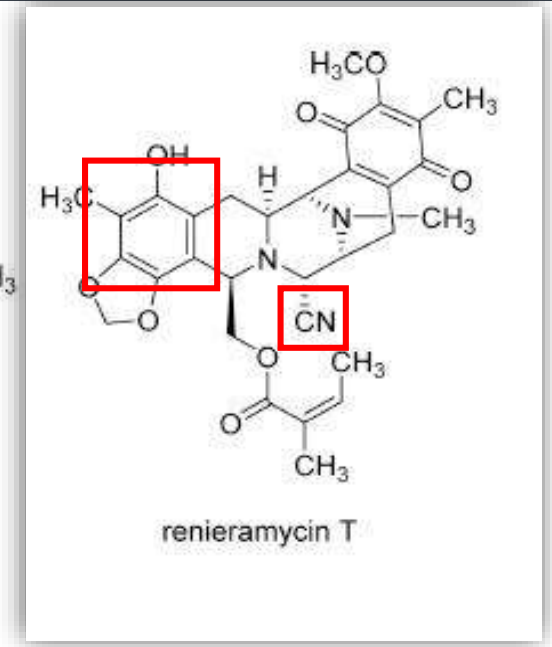
Renieramycin T (RT)



renieramycin M



ecteinascidin 743



renieramycin T

- **Aromatic ring and cyanide have an ability to bind with positive charge amino acids that are component of MAPK docking motif in Mcl-1 sequence.**

bind

PEPLGKRPAVLPLLELVGES

MAPK docking site

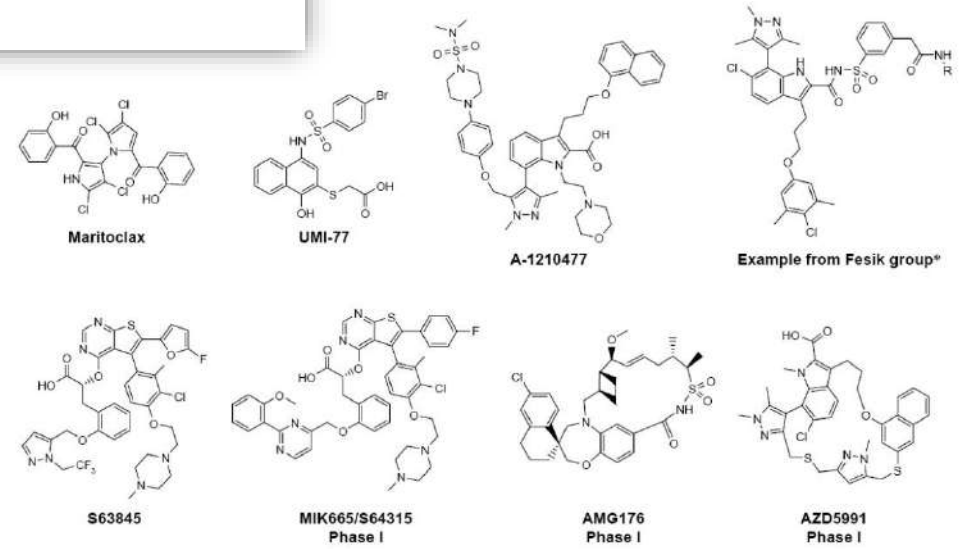
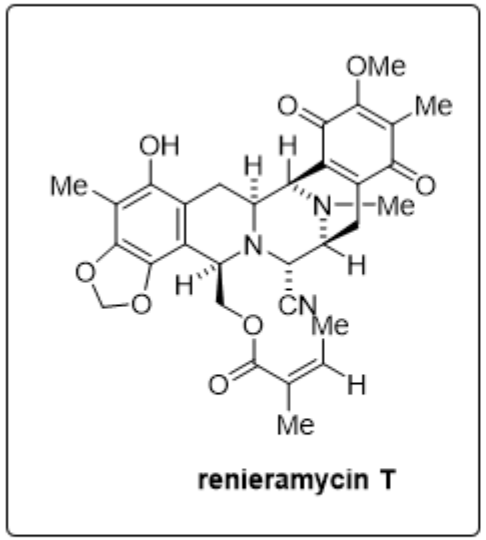


Figure 4 Selective MCL-1 inhibitors.
Note: *R stands for different substitutions based on Fesik's papers.

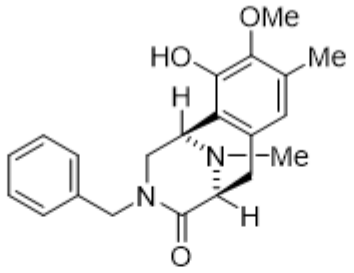
Mcl-1 inhibitors

Structure-activity relationship

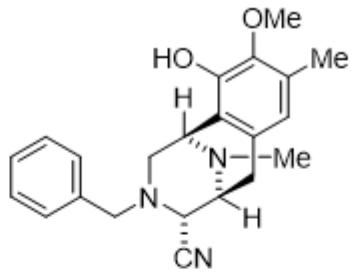
- RT was used as a lead compound to synthesize some of RT analogs or simplified right-half model compounds for SAR study.



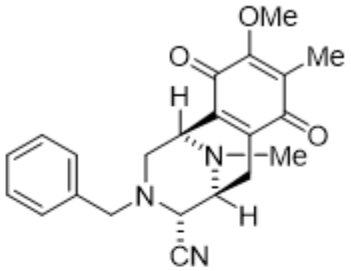
renieramycin T



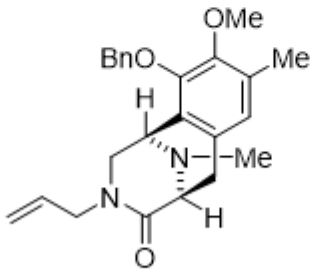
TM-(–)-45



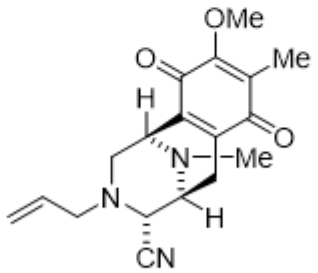
TM-(–)-18



TM-(–)-4a



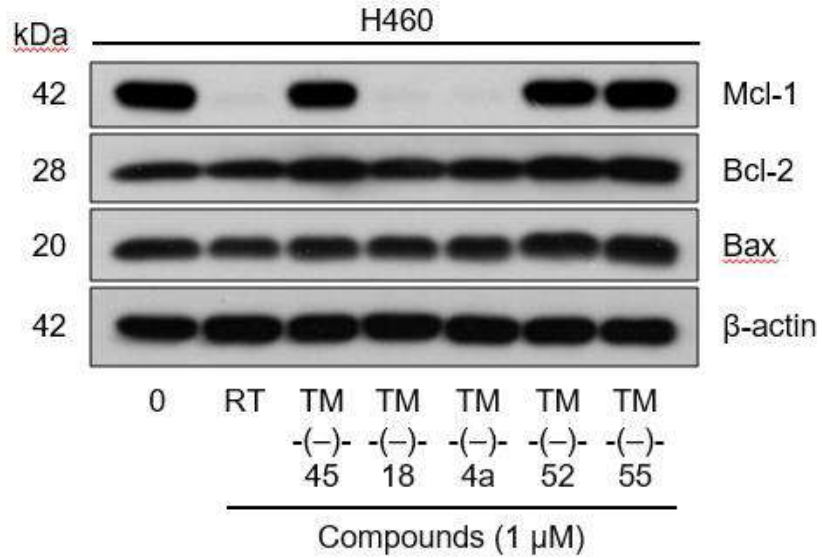
TM-(–)-52



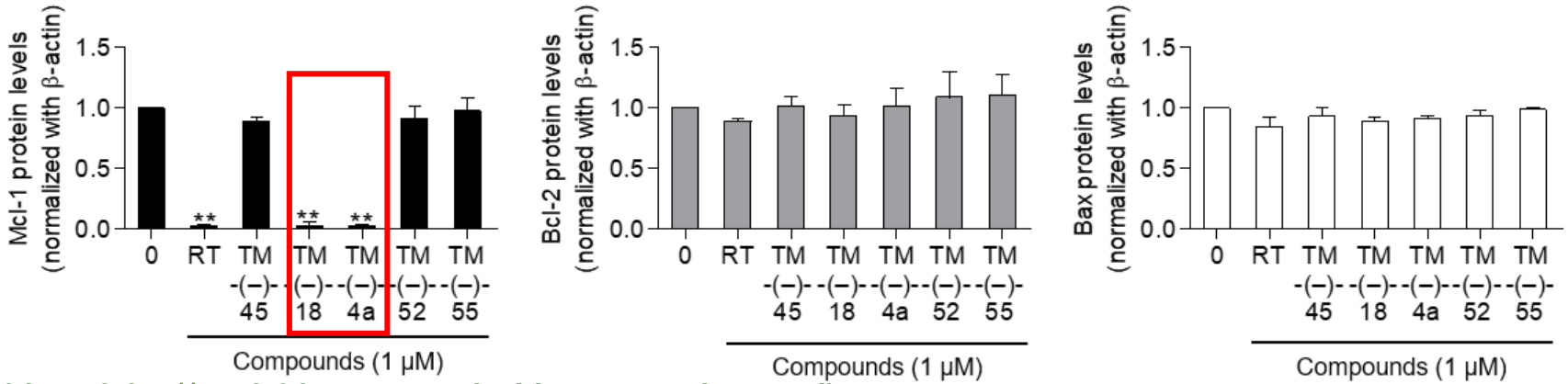
TM-(–)-55

Investigation of right-half model compounds effects on Mcl-1 and other apoptotic proteins in NSCLC cells

Western blot analysis



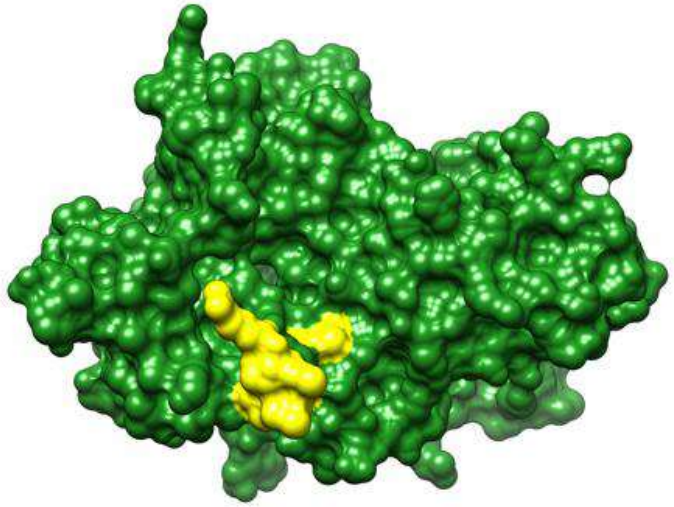
- Only TM-(–)-18 and TM-(–)-4a →↓Mcl-1 in NSCLC (H460) cells
- The cytotoxic action of TM-(–)-18 and TM-(–)-4a depended on their Mcl-1-targeting activity.

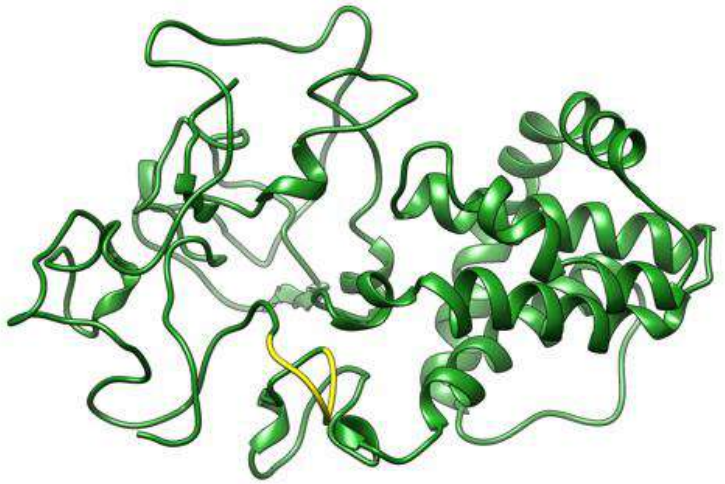


(* 0.01≤p<0.05, ** p<0.01, compared with untreated control)

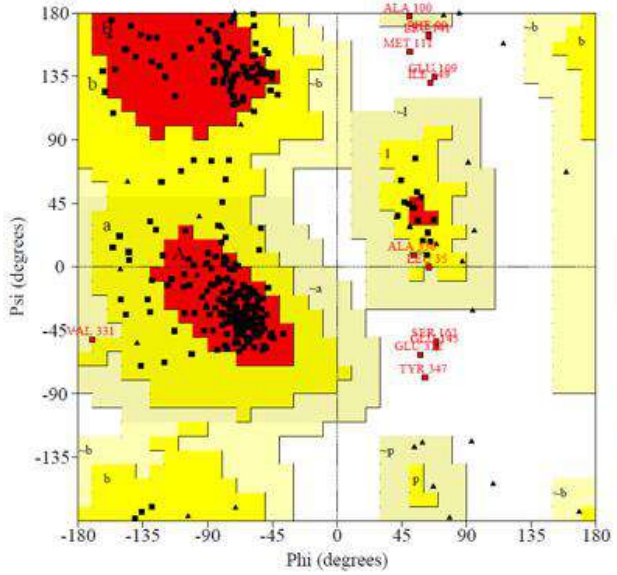
Investigation of structure-activity relationship (SAR) among test compounds

Molecular docking





Mcl-1 structure from homology modelling



Plot statistics

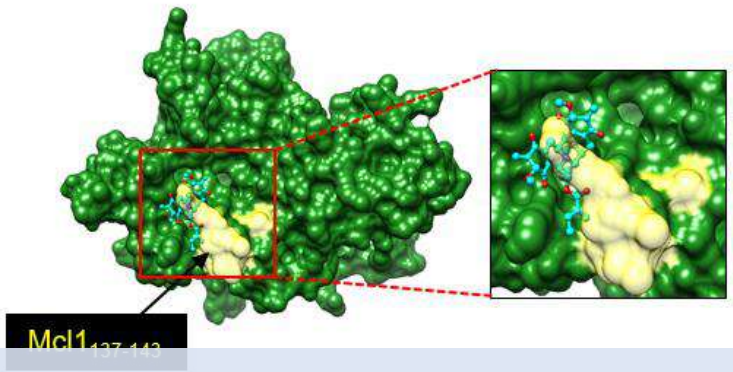
Residues in most favoured regions [A,B,L]	221	77.8%
Residues in additional allowed regions [a,b,l,p]	50	17.6%
Residues in generously allowed regions [~a,~b,~l,~p]	4	1.4%
Residues in disallowed regions	9	3.2%
Number of non-glycine and non-proline residues	284	100.0%
Number of end-residues (excl. Gly and Pro)	2	
Number of glycine residues (shown as triangles)	41	
Number of proline residues	23	
Total number of residues	350	

Investigation of structure-activity relationship (SAR) among test compounds

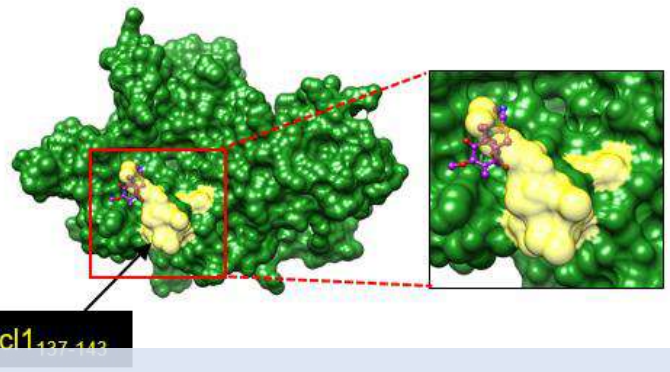
Molecular docking

↑Binding affinity of the compound →↓Docking energy

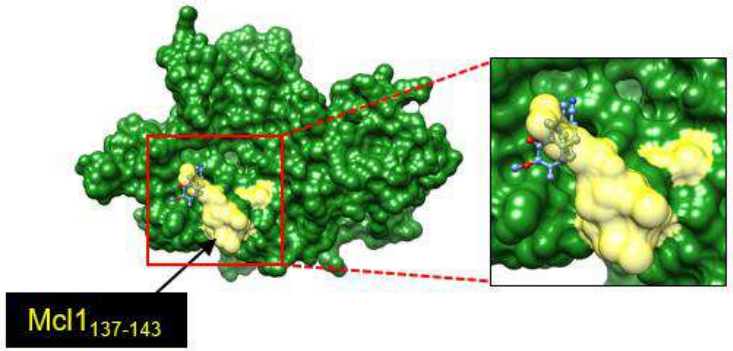
Mcl-1- renieramycin T (RT) complex



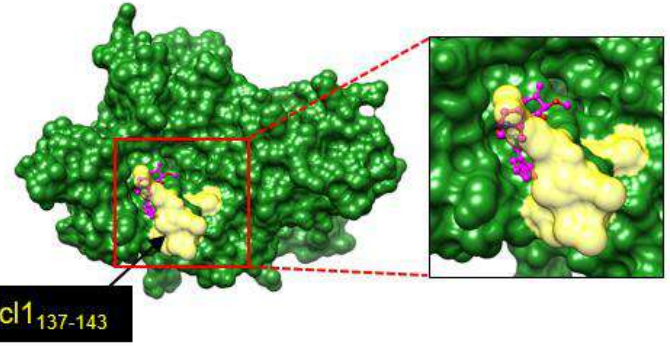
Mcl-1-TM-(–)-4a complex



Both cyanide and benzene ring were found to be a necessary for the induction of Mcl-1 destabilization

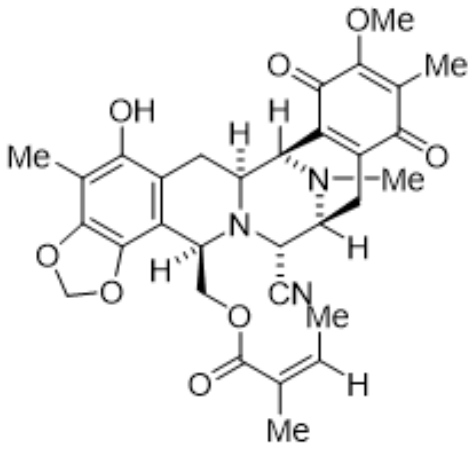


Autodock vina docking score = -6.9 kcal/mol

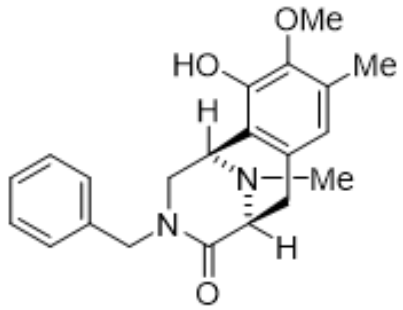


Autodock vina docking score = -6.0 kcal/mol

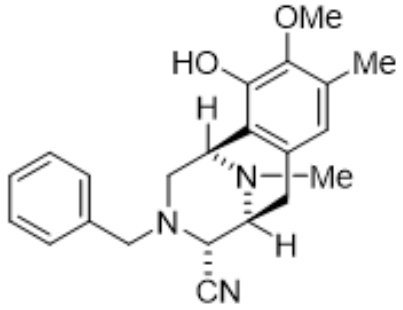
Investigation of structure-activity relationship (SAR) among test compounds



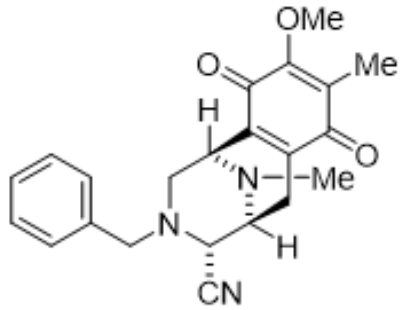
renieramycin T



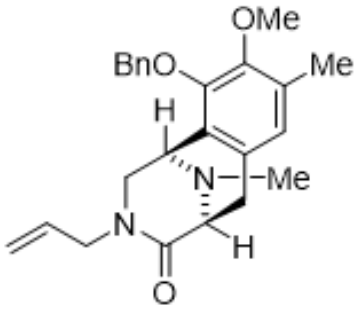
TM-(−)-45



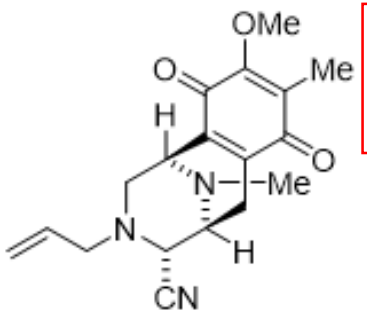
TM-(−)-18



TM-(−)-4a



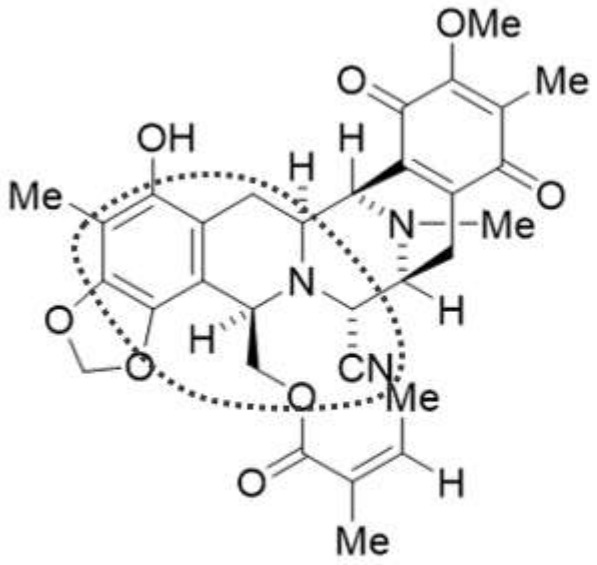
TM-(−)-52



TM-(−)-55

Mcl-1 targeting activity

Investigation of structure-activity relationship (SAR) among test compounds



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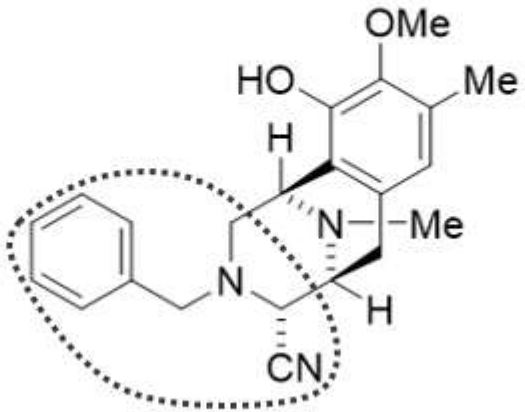
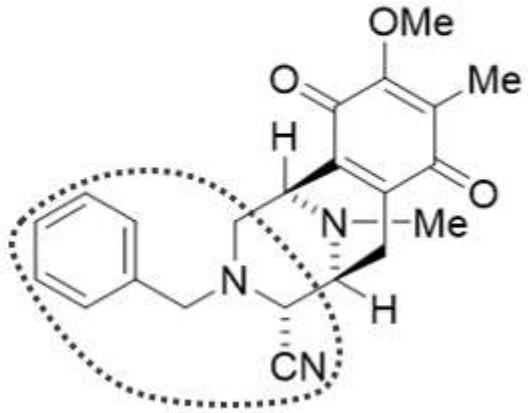


TM-(–)-18



TM-(–)-4a

Cyanide and benzene ring could be important for Mcl-1 suppression

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Thank you