Institut für Experimentelle Innere Medizin
Medizinische Fakultät
Otto-von-Guericke-Universität Magdeburg

VL 5 (Dr. Dawadschargal Dubiel)

The Ubiquitin Proteasome System (UPS) and Autophagy, as new drug targets

Outlines:

-Definition: Drug target
-Types of drug targets, examples
-Functions of targets and drugs: Treatment
-Drug approval process
-Drugs: Classifications, natural & chemical drugs
-Drug side effects
-Target-Drug-action
-Therapeutic drugs: diversity
-Distribution of targets in therapeutic areas
-Development of drugs: Identification of drug targets
-Properties of an ideal drug target:
-UPS and autophagy as a drug target?
-Why?
-Drug targets of UPS and Autophagy
-Drug targets, Diagnostic tools
-Questions

What is a drug-target and what is drug?

we consider a **target** to be a molecular structure which must be chemically definable by at least a molecular mass

that will undergo a specific interaction with chemicals that we call **drugs**

Because they are administered to treat or diagnose a disease, the interaction has a connection with the clinical effect(s).

Nature Reviews Drug Discovery 5, 821-834 (October 2006)

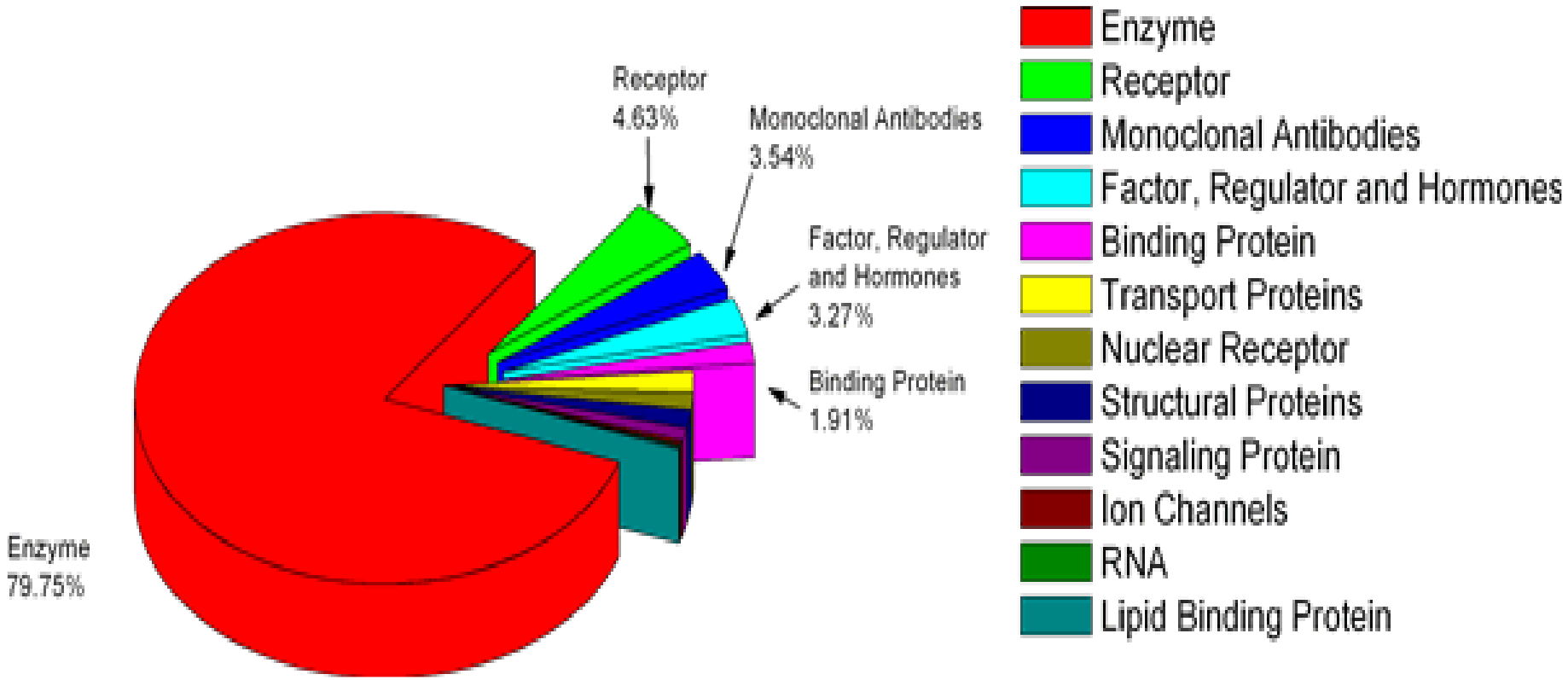
Wikipedia:

A **biological target** is anything within a living organism to which some other entity (like an endogenous ligand or a drug) is directed and/or binds, resulting in a change in its behavior or function. Examples of common classes of biological targets are proteins and nucleic acids

What are drug targets?

- Enzymes
- Substrates, metabolites and proteins
- Receptors
- Ion channels
- Transport proteins
- DNA/RNA and the ribosome
- Targets of monoclonal antibodies
- Various physicochemical mechanisms
- Unknown mechanism of action

Statistics: Distribution of targets by biochemical criteria



Examples of targets and their drugs (oldest? most studied, most used)

Table 1a | **Enzymes**

Type	Activity of drug	Drug examples
Oxidoreductases		
Aldehyde dehydrogenase	Inhibitor	Disulfiram[39]
Monoamine oxidases (MAOs)	MAO-A inhibitor	Tranylcypromine[40], moclobemide[41]
	MAO-B inhibitor	Tranylcypromine[40]
Cyclooxygenases (COXs)	COX1 inhibitor	Acetylsalicylic acid, profens, acetaminophen and dipyrone (as arachidonylamides)[42,43]
	COX2 inhibitor	Acetylsalicylic acid, profens, acetaminophen and dipyrone (as arachidonylamides)[44]
Vitamin K epoxide reductase	Inhibitor	Warfarin, phenprocoumon[45]
Aromatase	Inhibitor	Exemestane[46]
Lanosterol demethylase (fungal)	Inhibitor	Azole antifungals[47]
Lipoxygenases	Inhibitor	Mesalazine[48]
	5-lipoxygenase inhibitor	Zileuton[49]

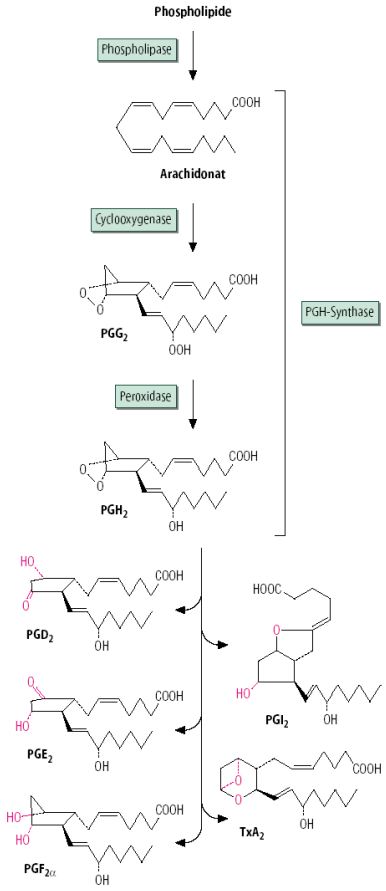
Table 2 | **Substrates, metabolites and proteins**

Substrate	Drug substance
Asparagine	Asparaginase[137]
Urate	Rasburicase (a urate oxidase)[138]
VAMP–synaptobrevin, SNAP25, Syntaxin	Light chain of the botulinum neurotoxin (Zn-endopeptidase)[139]

SNAP, synaptosomal-associated protein; VAMP, vesicle-associated membrane protein.

Gout

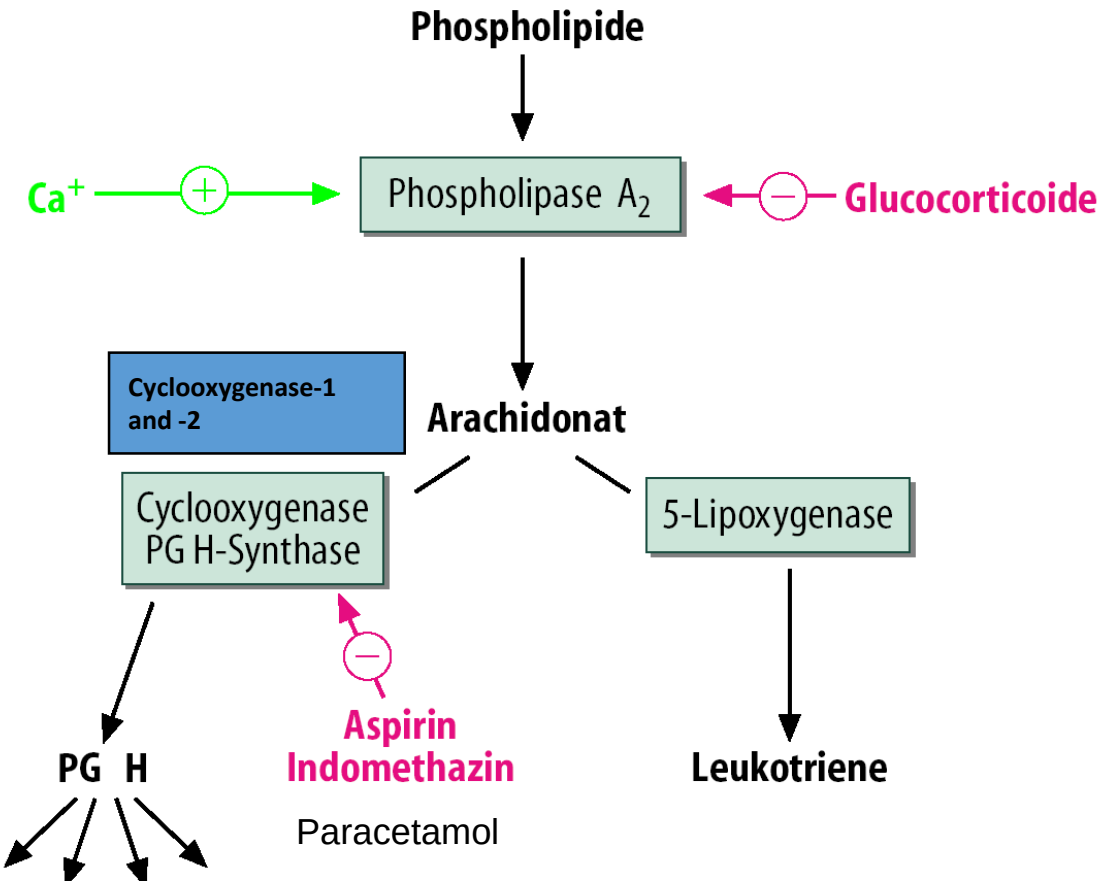
Cyclooxygenase-2 (COX-2) action



Transformation of arachidonic acid into
Prostaglandines:
- Important for blood clotting
- involved in inflammation and in immun-response
- **involved in generation of pain**
-**fever**
-pro-angiogenic factors responsible for
tumor growth

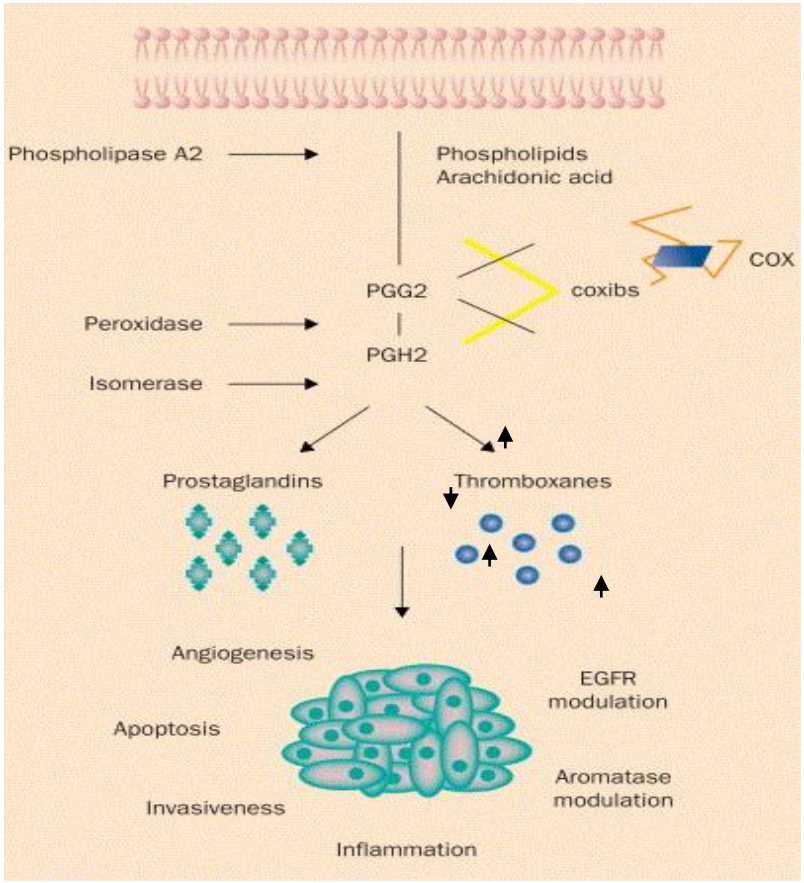
→ **VEGF**

Aspirin is an inhibitor of COX enzymes



COX-2 is induced under conditions of inflamation and tumor growth

Gasparini et al. 2003 The Lancet Oncology 4, 605-615

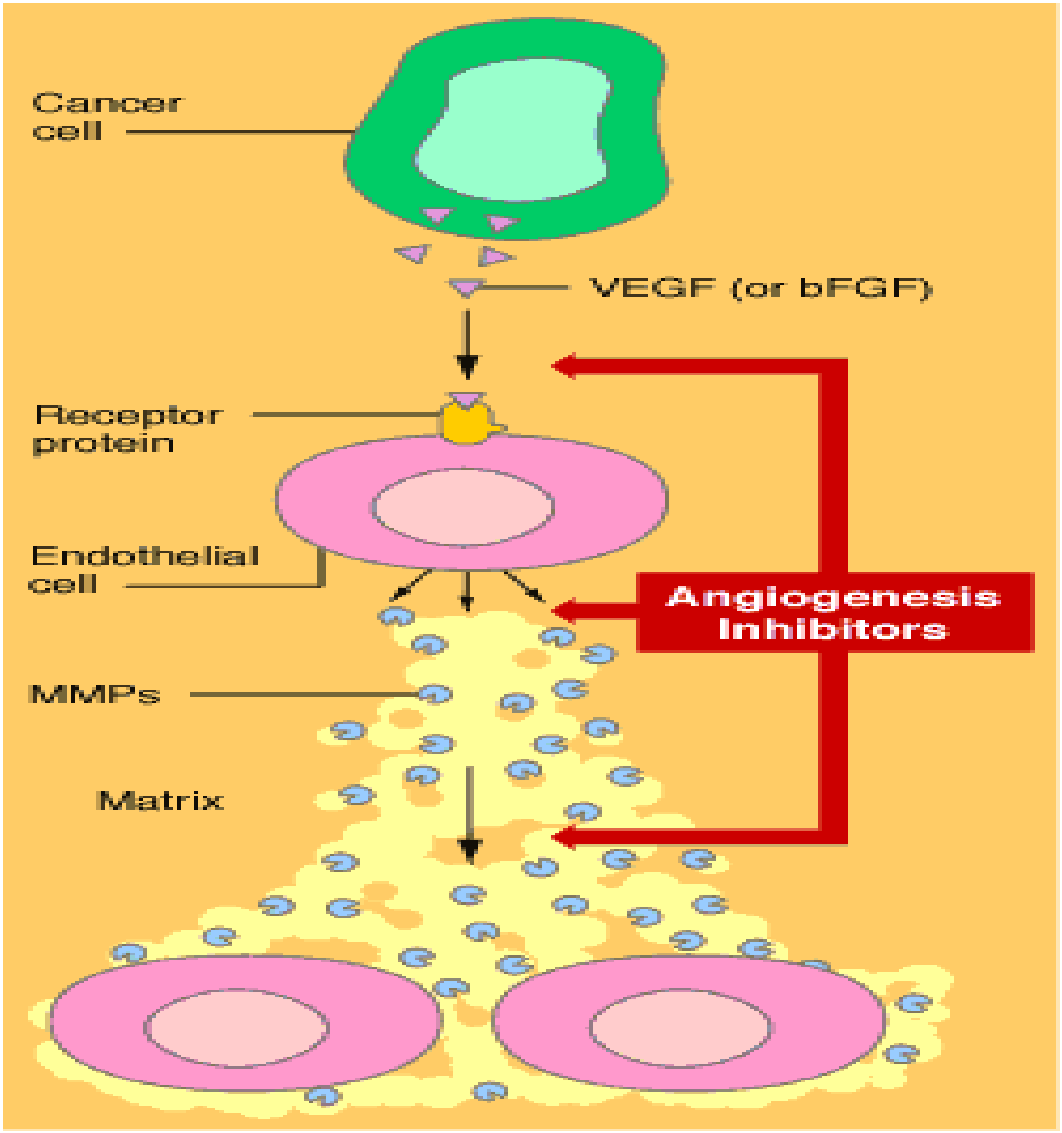


Premalignant or malignant lesion	COX2 expression (%)
Colorectal	80–90
Gastric	80
Oesophageal	70
Hepatocellular (liver cirrhosis)	54 (81)
Pancreatic	67
Head and neck	80
Non-small-cell lung cancer	70
Breast (ductal carcinoma-in-situ)	40 (60)
Prostatic	83–93
Bladder	86
Cervix	43
Endometrial	37
Cutaneous basal cell	25
Cutaneous squamous cell	80
pPNET	100
Glioblastoma multiforme	71–74
Anaplastic astrocytoma (low grade)	44 (30)

References available at http://image.thelancet.com/extras/03oncl205webfr.pdf

Specific inhibition or degradation of COX-2 has high anti-tumor therapeutic significance?

At which points tumor angiogenesis can be blocked?



Receptors as targets in tumor therapy

Clinical trials of anti-angiogenic agents in malignant gliomas (March 2009)

Mechanism of action	Drug	Trials[ref]
Monoclonal antibodies		
Anti-VEGF	Bevacizumab	Phase II[230–232]
RTK inhibitors		
VEGFR, PDGFR, Raf, c-Kit	Sorafenib	Phase I/II[235]
VEGFR	AZD2171	Phase II[236]
VEGFR, PDGFR, c-Kit, c-Fms	Vatalanib	Phase I[240]
VEGFR2, EGFR, HER2	AEE788	Phase I[242]
Other inhibitors		
mTOR inhibitor	Temsirolimus	Phase II[244,245]
mTOR inhibitor	Everolimus	Phase I/II[246]
mTOR inhibitor	AP23573	Phase I (no published data)
Proteosome inhibitor	Bortezomib	Phase I[247,248]
PKC inhibitor	Enzastaurin	Phase I/II[251,252]
Inhibits VEGF, IL-6 expression	Thalidomide	Phase II[255–257]
Inhibits VEGF, IL-6 expression	Lenalidomide	Phase I[259]
Endostatin enhancer	Celecoxib	Phase I/II[261]
Inhibits MMP-9, IL-8, bFGF	IFN-α	Phase I/II[266,267]
Integrin $\alpha_v\beta_3$ and $\alpha_v\beta_5$ antagonist	Cilengitide	Phase I/II[270,271]
Integrin $\alpha_v\beta_3$ and $\alpha_5\beta_1$ antagonist	ATN-161	Phase I/II (no published data)
MMP inhibitor	Prinomastat	Phase II[274]
Inhibits HIF-1α and tubulin polymerisation	2-methoxyestradiol	Phase II[276]

Functions of drugs and targets:

-Treatment

-Diagnostics

Drugs and their function:

we consider a **target** to be a molecular structure which must be chemically definable by at least a molecular mass

that will undergo a specific interaction with chemicals that we call **drugs**

Because they are administered to treat or diagnose a disease, the interaction has a connection with the clinical effect(s).

Drug approval process in USA

USA: The Food and Drug Administration (FDA) is responsible for protecting and promoting public health. Like general drug approval process, FDA's new drug approval process is also accomplished in two phases: **clinical trials (CT) and new drug application (NDA) approval**[7]. FDA approval process begins only after submission of **investigational new drug (IND) application**. The IND application should provide high quality preclinical data to justify the testing of the drug in humans. Almost 85% of drugs are subjected to clinical trials, for which IND applications are filed. The next step is **phase I clinical trials (1-3 years) on human subjects (~100).** The drug's **safety profile and pharmacokinetics of drug are focused in this phase. Phase II trials (2 years) are performed if the drug successfully passes phase I. To evaluate dosage, broad efficacy and additional safety in people (~300) are the main objective of the phase II.** If evidence of effectiveness is shown in phase II, **phase III studies (3-4 years) begins. These phase III concerns more about safety and effectiveness of drug from data of different populations, dosages and its combination with other drugs in several hundred to about 3,000 peoples**[8, 9, 10]. A new drug application (NDA) can be filed only when the drug successfully passes all three phases of clinical trials and includes all animal and human data, data analyses, pharmacokinetics of drug and its manufacturing and proposed labelling.

EU: EMA

(European Medicines Agency)

Europa: Similarly, the drug approval process in European countries is also accomplished in two phases: **clinical trial and marketing authorization.** A clinical trial application (CTA) is filed to the competent authority of the state to conduct the clinical trial within EU. The competent authority of that member state evaluates the application. The clinical trials are conducted only after the approval. **The purpose and phases of clinical trials are similar as specified in FDA drug approval process**[13].

Drug approval process in China

China: The approval process of **New Drug Applications (NDA) includes sufficient preclinical data** for verification of drug's safety and **justification of the commencement of clinical trials**. The Drug Administrative Law was further revised in 2001 requiring premarket testing, approval for new drug products, and prohibits drug adulteration[22].

The Drug Administrative Law authorizes **the State Food and Drug Administration (SFDA) to approve new drugs for marketing**. The new drug registration process also consists of the clinical study application and the new drug application. The Provincial Drug Administration Authorities (PDAAs) should organize the works of the formal review of submitted materials i.e. on-site examination and sampling just after receiving the drug registration application.

9-12 years

Drug approval process

- **High quality preclinical data to justify the testing of the drug in humans (investigational new drug (IND) application)**
- **Phase I clinical trials (1-3 years) on human subjects (~100) to test safety profile and pharmacokinetics of drug**
- **Phase II trials (2 years) are performed to evaluate dosage, broad efficacy and additional safety in people (~300)**
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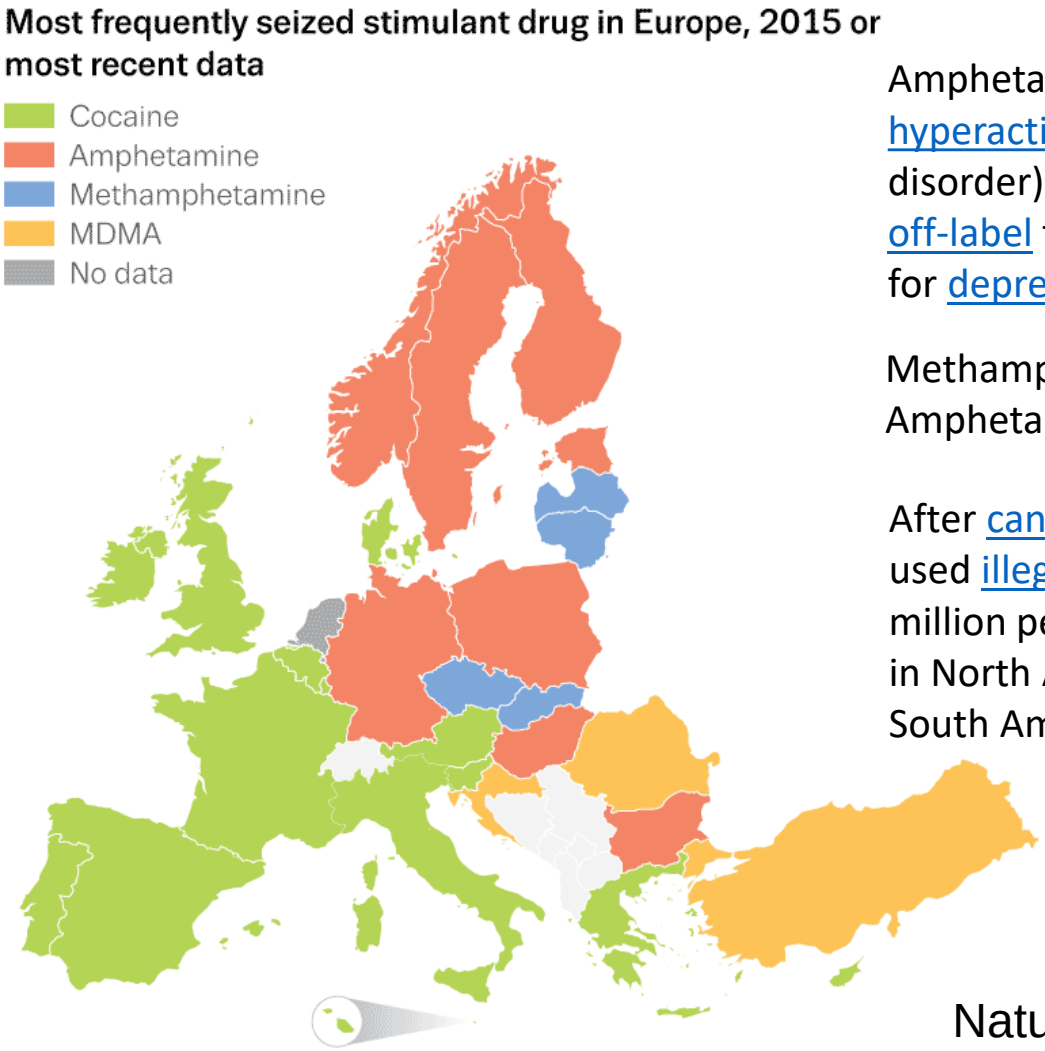
- **A new drug application approval (NDA) can be filed only when the drug successfully passes all three phases of clinical trials and includes all animal and human data, data analyses, pharmacokinetics of drug and its manufacturing and proposed labelling.**

Legal and illegal drugs:



Amphetamine is used to treat attention deficit hyperactivity disorder (ADHD), narcolepsy (a sleep disorder), and obesity, and is sometimes prescribed off-label for its past medical indications, particularly for depression and chronic pain.

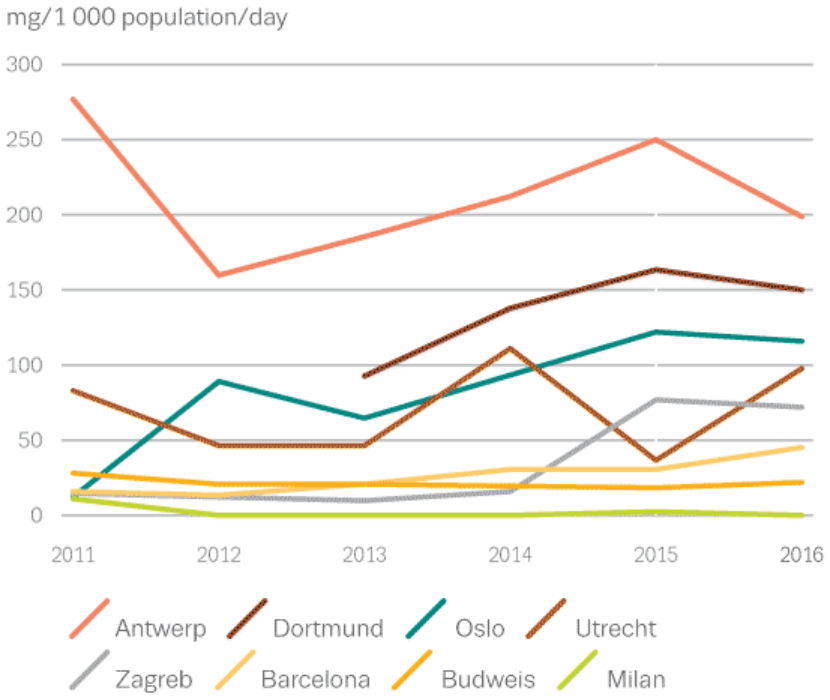
Methamphetamine and MDMA are derivatives of Amphetamine.

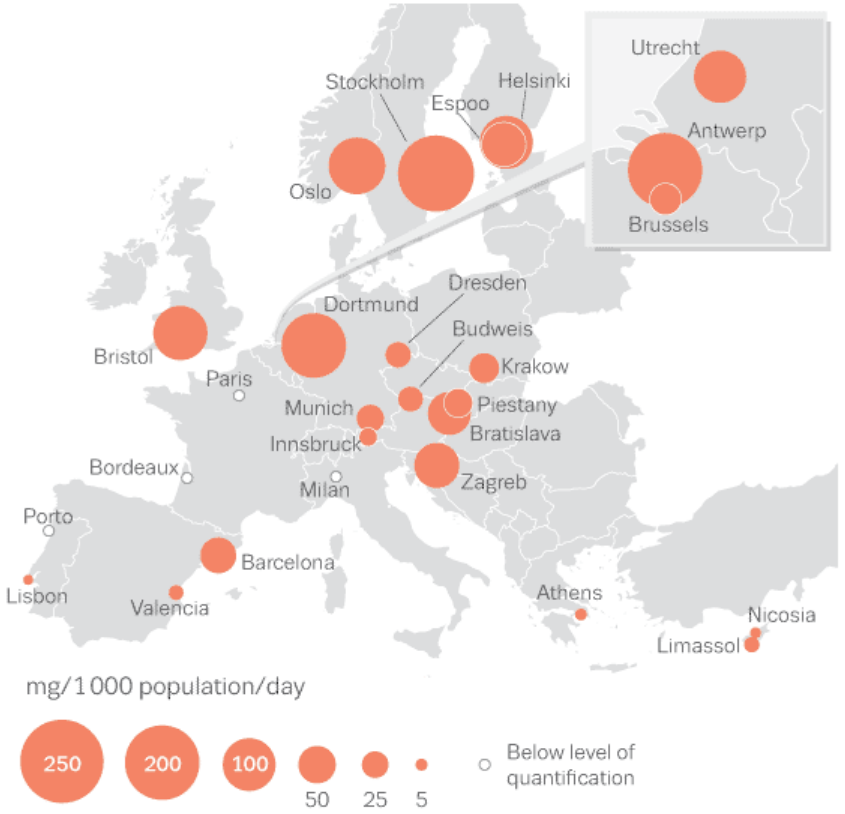
After cannabis, cocaine is the most frequently used illegal drug globally. Between 14 and 21 million people use the drug each year mostly in North America followed by Europe and South America.

Natural drugs, chemical drugs

Distribution of iilegal drugs:

Amphetamine residues in wastewater in selected European cities: trends and most recent data

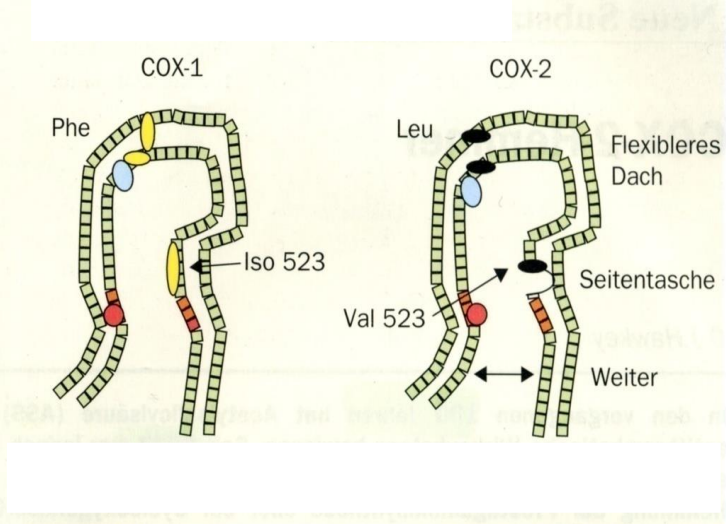




NB: Mean daily amounts of amphetamine in milligrams per 1 000 population. Sampling was carried out in selected European cities over a week in 2016.
Source: Sewage Analysis Core Group Europe (SCORE).

Drug side effects

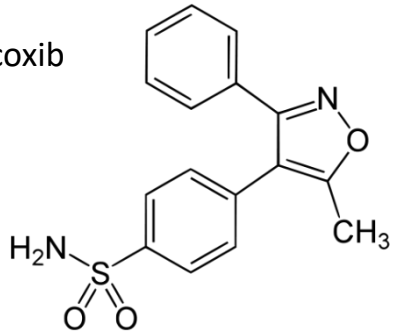
Isoforms of Cyclooxygenase



Hawkey, The Lancet 1999.

- There is a single amino acid exchange in the active site between the isoforms
- This is the binding site of coxibs, specific inhibitors of COX-2:
  - Viox
  - Valdecoxib
  - Celecoxib etc.
- **Unfortunately coxibs possess side effects: increase of heart attacks, stroke and kidney diseases**
- Anti-tumor effects

Valdecoxib



Therefore, withdraw from the market.

Drug side effects

- Contergan-Skandal (1950-1960)

Wirkstoff: Thalidomide

Targets of Thalidomide:

1. E3 Ligase: Cereblon as a receptor protein in Cul4 E3 Ub Ligase

(in Nature, 2021)

2. Angiogenesis

How many targets do we have?

30000 Krankheiten,
davon 8000 seltene Krankheiten

Number of molecular targets and approved drugs. We curate a total of **893 human and pathogen-derived biomolecules (targets)** through which **1,578 US FDA-approved drugs act**. These biomolecules include 667 human-genome-derived proteins targeted by drugs for human disease.

The Food and Drug Administration (FDA)-USA

Rita Santos et al NATURE REVIEWS | **DRUG DISCOVERY** VOLUME 16 | JANUARY 2017. 19-34

Targets and their classes:

-targets in human bodies: body‘s own targets

-targets in human bodies: foreign, alien
e.g. pathogen-derived drugs

How many targets do we have?

Table 1 | **Molecular targets of FDA-approved drugs**

Drug target class	Targets			Drugs		
	Total targets	Small-molecule drug targets	Biologic drug targets	Total drugs	Small molecules	Biologics
Human protein	667	549	146	1,194	999	195
Pathogen protein	189	184	7	220	215	5
Other human biomolecules	28	9	22	98	63	35
Other pathogen biomolecules	9	7	4	79	71	8

The list also includes antimalarial drugs approved elsewhere in the world.

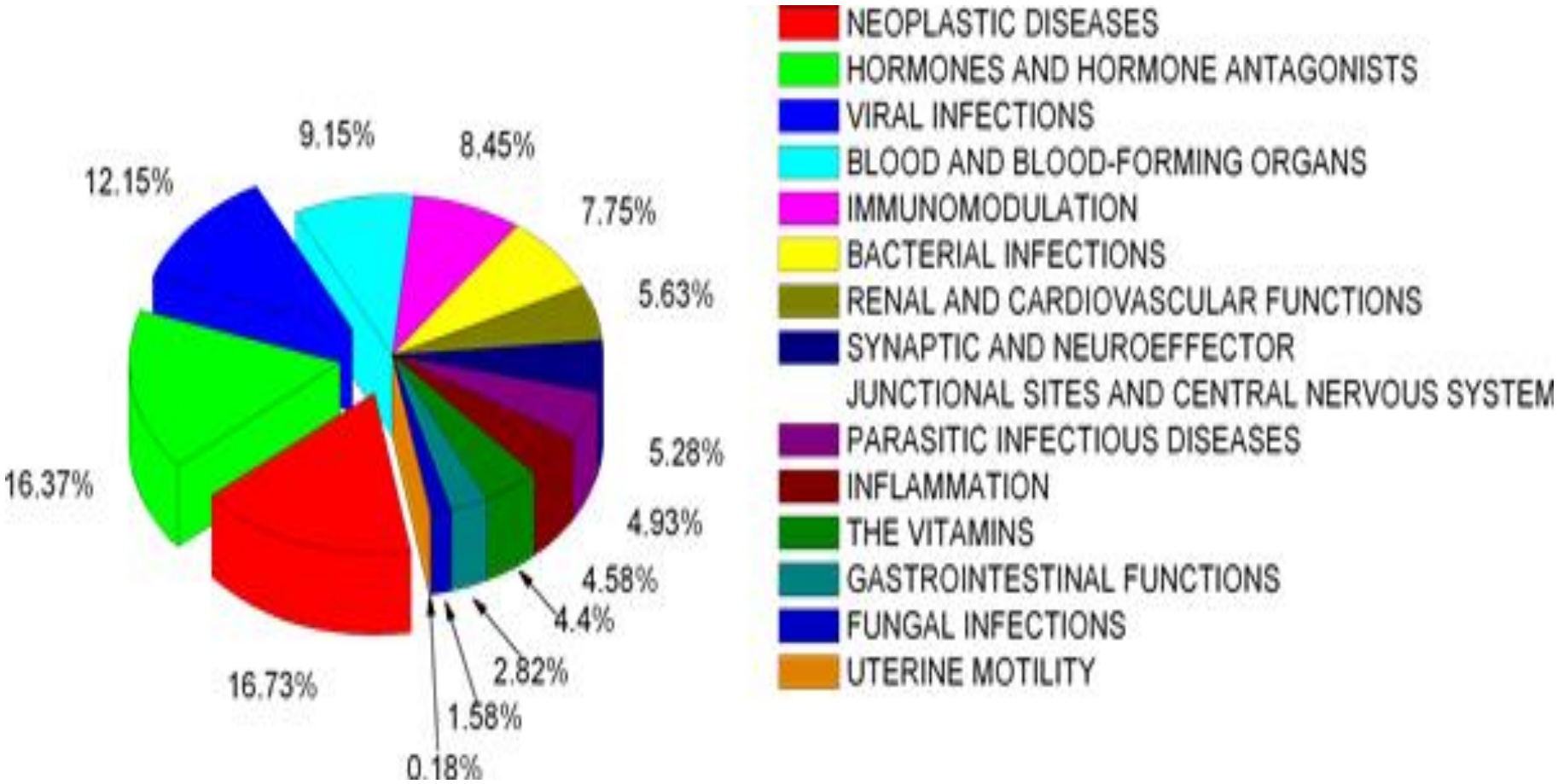
The Food and Drug Administration (FDA)-USA

Table 2 | **Therapeutic areas of FDA-approved drugs**

ATC category	Therapeutic area	Number of small molecules	Number of biologics
A	Alimentary tract and metabolism system	158	32
B	Blood and blood-forming organs	33	28
C	Cardiovascular system	200	5
D	Dermatologicals	141	5
G	Genito urinary system	94	5
H	Hormonal system	44	31
J	Anti-infectives for systemic use	194	10
L	Antineoplastic and immunomodulating agents	142	67
M	Musculoskeletal system	62	6
N	Nervous system	239	1
P	Antiparasitic products, insecticides and repellents	38	1
R	Respiratory system	118	4
S	Sensory organs	143	11
V	Various	30	12
U	Unclassified	156	51

The list also includes antimalarial drugs approved elsewhere in the world. ATC, WHO Anatomical Therapeutic Chemical Classification System.

Statistics: Distribution of targets in therapeutic areas



Target-Drug-Action

1. Drugs directly bind their targets and inhibit/modulate

2. Drugs have no direct physical interactions with their targets but influence the behavoir their targets

3. Vaccination strategy: exogenous target, drugs are produced in the host

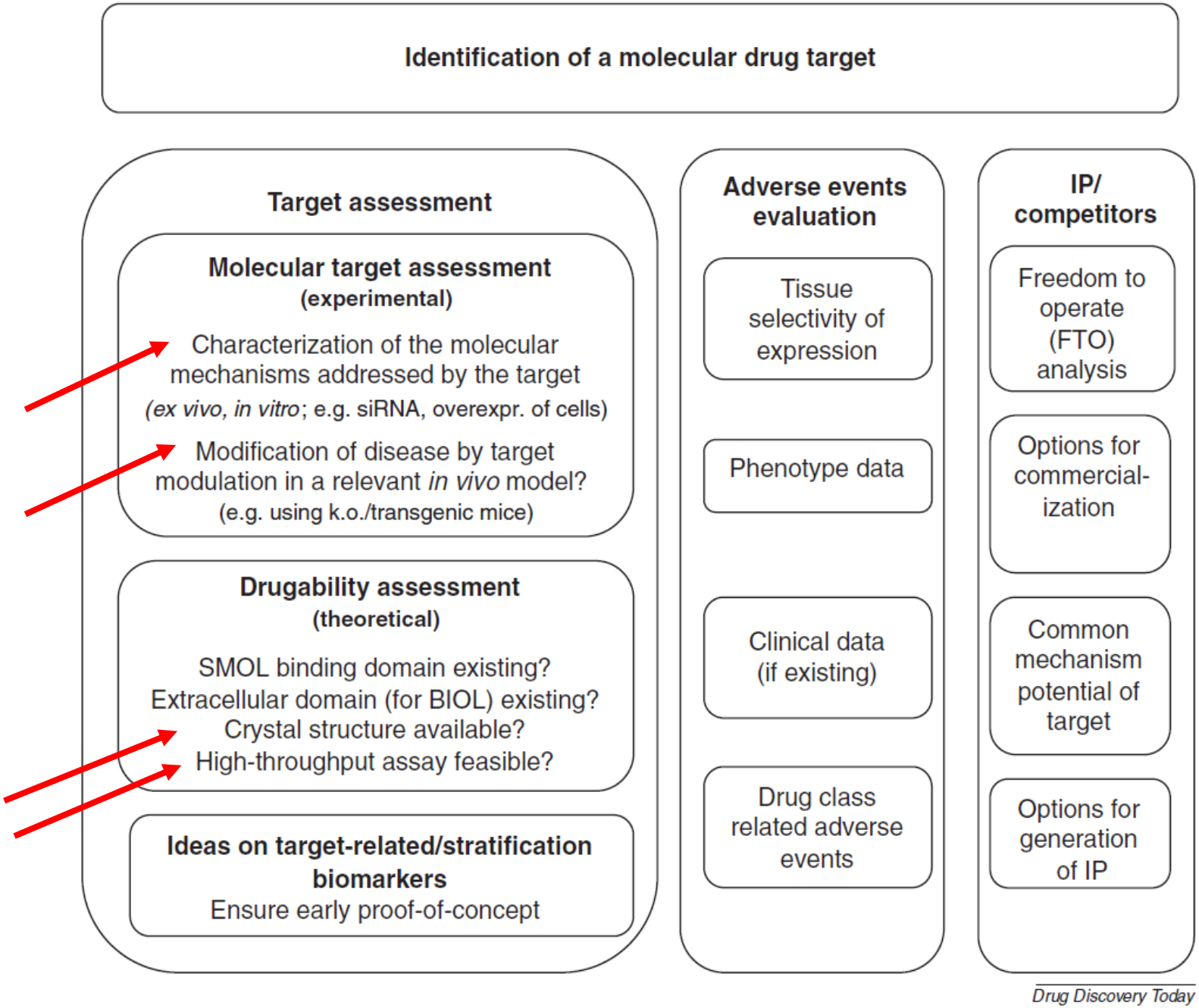
Target classes: proteins, lipids, nucleic acids

TABLE 1

Target classes addressed by SMOLs, BIOLs and nucleic acids and their modes of action

Drug	Covered target classes	Mode of action
Small molecular weight chemical compound (SMOL)	Enzymes	Inhibitors, activators[a]
	Receptors	Agonists, antagonists, modulators, allosteric activators, sensitizers
	Transcription factors	Inhibitors, activators
	Ion channels	Inhibitors, openers
	Transport proteins	Inhibitors
	Protein–protein interface	Inhibitors of protein–protein interaction[a]
	Nucleic acids	Alkylation, complexation, intercalation
Biologics (BIOL)	(Extracellular) proteins	Antibodies
	Transmembrane receptors, extracellular proteins	Recombinant proteins
	Cell surface receptors	Antibody–drug conjugates (ADCs)
	Substrates and metabolites	Enzymatic cleavage
Nucleic acids	RNA	RNA interference

Development of drugs



Properties of an ideal drug target:

1. **Target is disease-modifying and/or has a proven function in the pathophysiology of a disease.**
2. **Modulation of the target is less important under physiological conditions or in other diseases.**
3. **If the druggability is not obvious (e.g. as for kinases) a 3D-structure for the target protein or a close homolog should be available for a druggability assessment.**
4. **Target has a favorable 'assayability' enabling high throughput screening.**
5. **Target expression is not uniformly distributed throughout the body.**
6. **A target/disease-specific biomarker exists to monitor therapeutic efficacy.**
7. **Favorable prediction of potential side effects according to phenotype data (e.g. in k.o. mice or genetic mutation databases).**
8. **Target has a favorable IP situation (no competitors on target freedom to operate).**

IP: intellectual property

Eigenschaften eines idealen Wirkstofftargets

1. Das Target/Ziel ist krankheitsmodifizierend und/oder hat eine nachgewiesene Funktion bei der Pathophysiologie einer Krankheit.

2. Die Modulation des Targets ist unter normalen physiologischen Bedingungen weniger wichtig oder bei anderen Krankheiten.

3. Wenn der Wirkungsmechanismus eines Arzneimittels nicht offensichtlich ist (z.B. wie bei Kinasen), sollte eine 3D-Struktur für das Zielprotein oder ein enges Homolog für eine Beurteilung des Wirkungsmechanismus eines Arzneimittels zur Verfügung stehen.

4. Das Target hat eine günstige "Testbarkeit", die eine high-throughput screening ermöglicht.

5. Die Target-Expression ist nicht gleichmäßig über den Körper verteilt.

6. Es existiert ein target-/krankheitsspezifischer Biomarker, um die therapeutische Wirksamkeit zu überwachen.

7. Günstige Vorhersage möglicher Nebenwirkungen anhand von Phänotyp-Daten (z.B. bei k.o. Mäusen oder genetischen Mutationsdatenbanken).

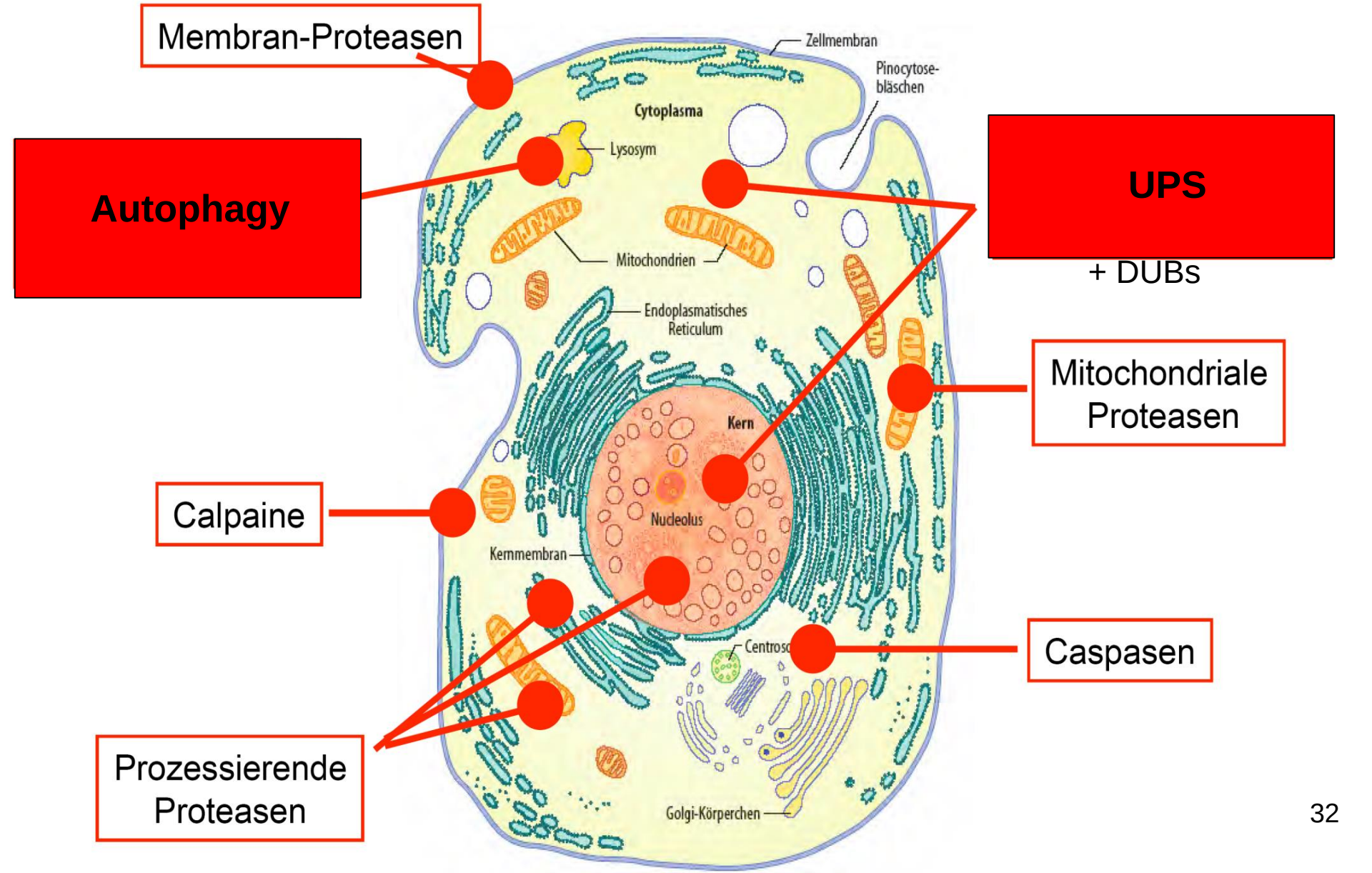
8. Target hat eine günstige IP-Situation (keine Wettbewerber auf Target Freedom to Operate).

IP: intellectual property

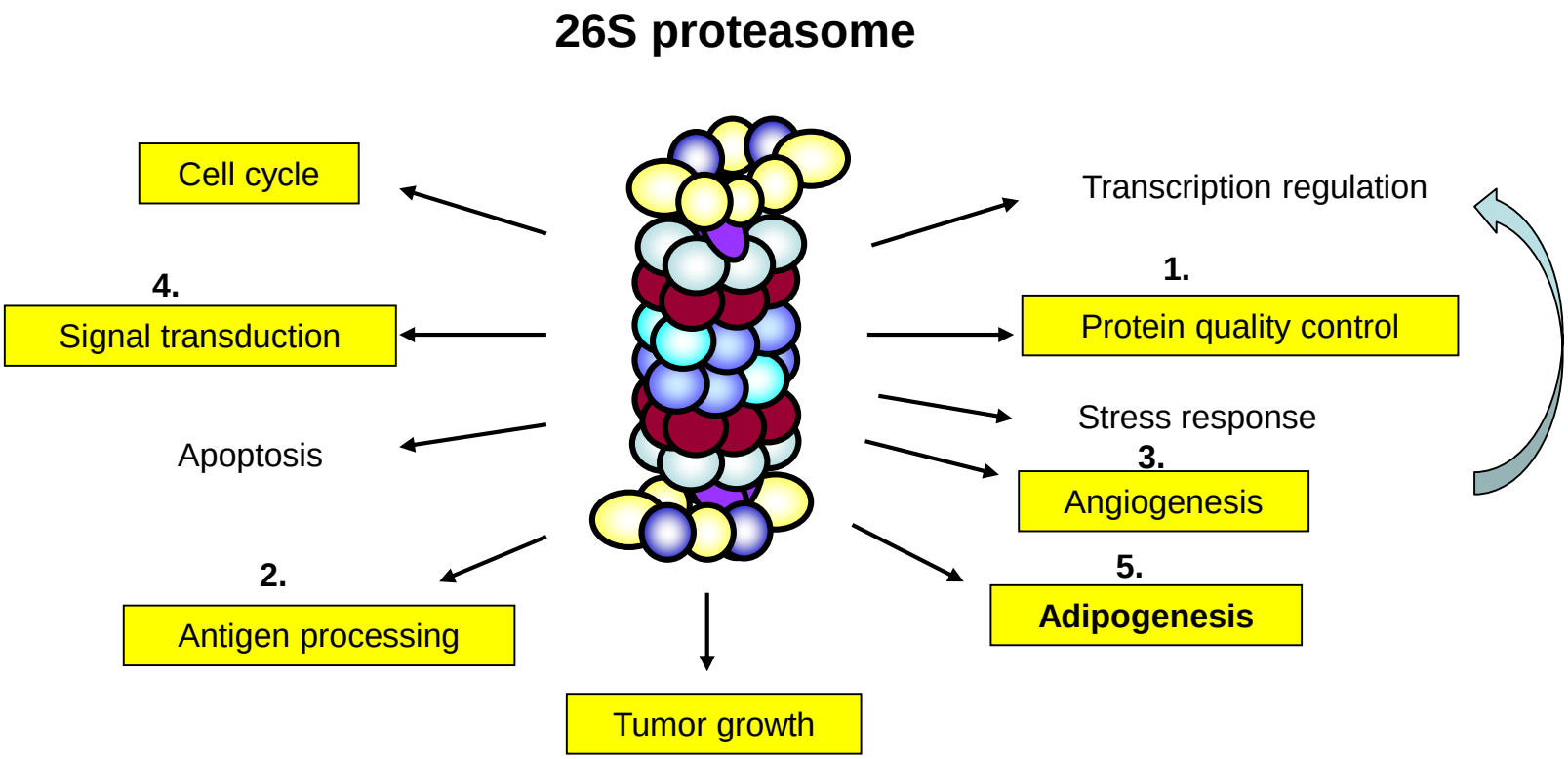
Why are the Ubiquitin Proteasome System (UPS) and Autophagy important new drug targets?

- They are the most important proteolytic systems in eukaryotic cells.
- It is involved in all essential cell functions.
- It degrades tumor suppressor proteins such as p27 and p53.
- UPS degrades oncogenes.
- They both degrade mutated, unsoluble protein aggregates and misfolded proteins.
- It degrades mailfunctioning and mutant organelles.

Localization of cellular proteases

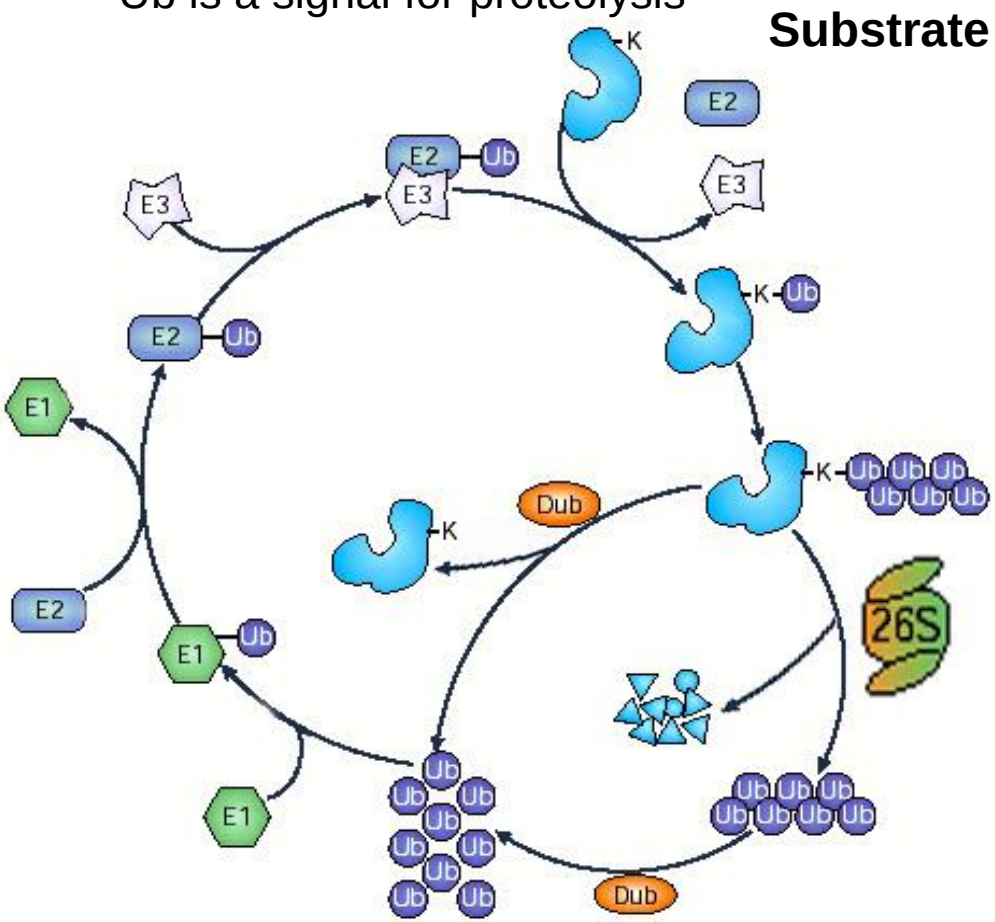


Functions of the ubiquitin proteasome system (UPS) in cells



The Ubiquitin (Ub) Proteasome System (UPS)

-Major proteolytic system in eukaryotic cells
-Ub is a signal for proteolysis

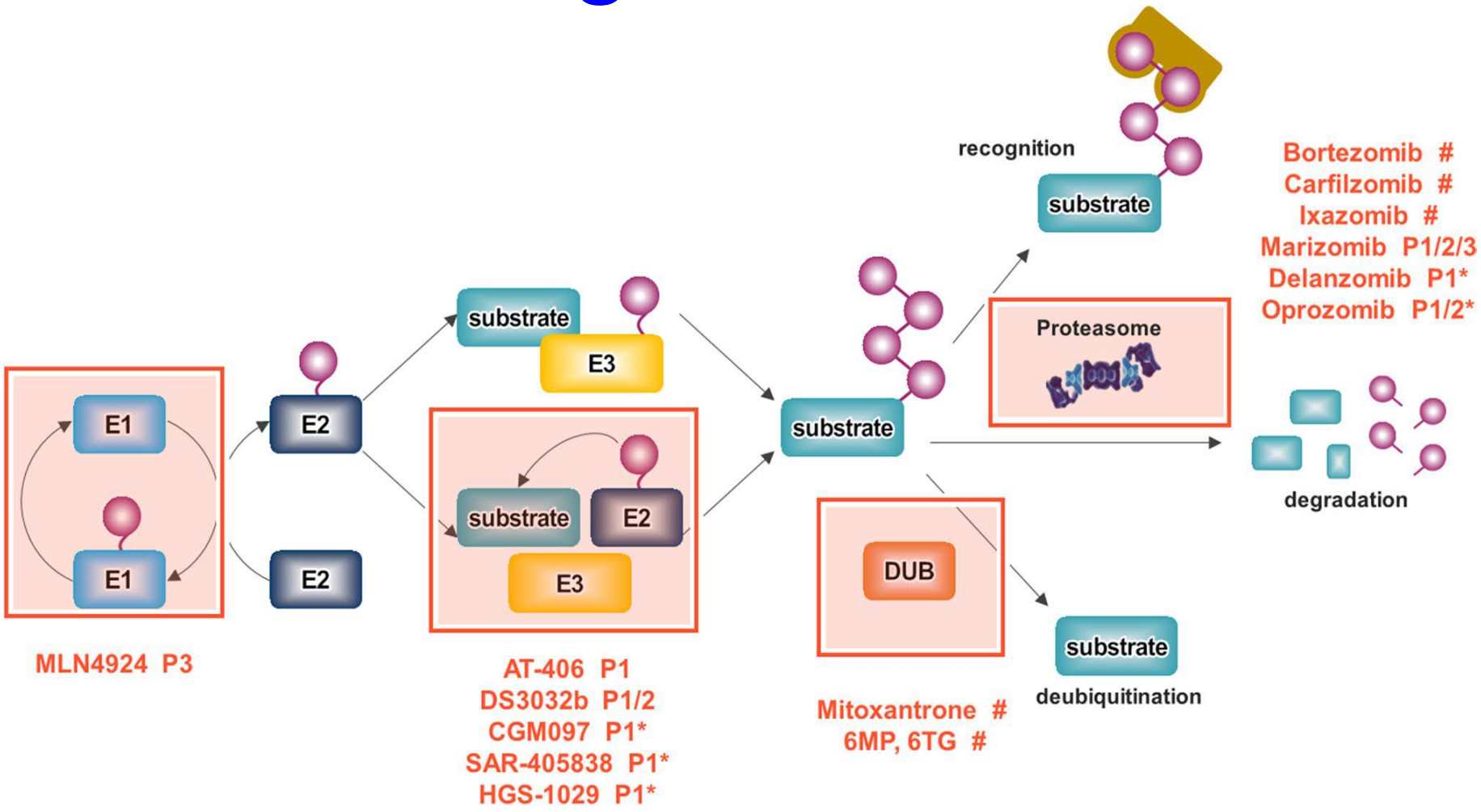


Components of the UPS

- E1 – Ub activating enzymes
- E2 – family of Ub conjugating enzymes
- E3 – families of Ub ligating enzymes
- The 26S proteasome
- Family of deubiquitinating enzymes (DUBs)

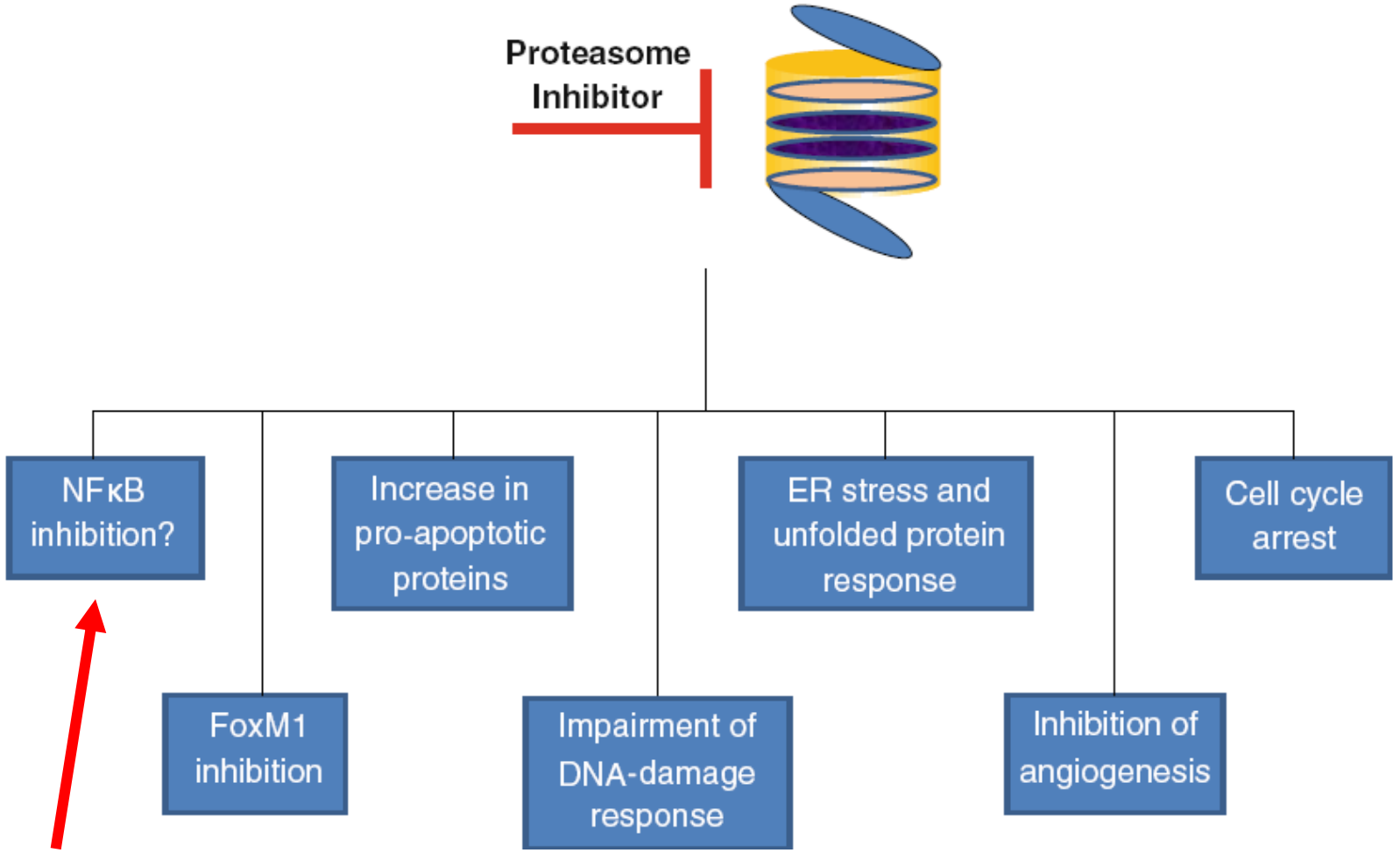
Modified from Sullivan et al., 2003

Different target sites in the UPS



Why is the UPS a target for tumor therapy?

1. It is involved in all essential cell functions.



Proteasome inhibitors in the tumor therapy

Deregulation of protein homeostasis in cancer

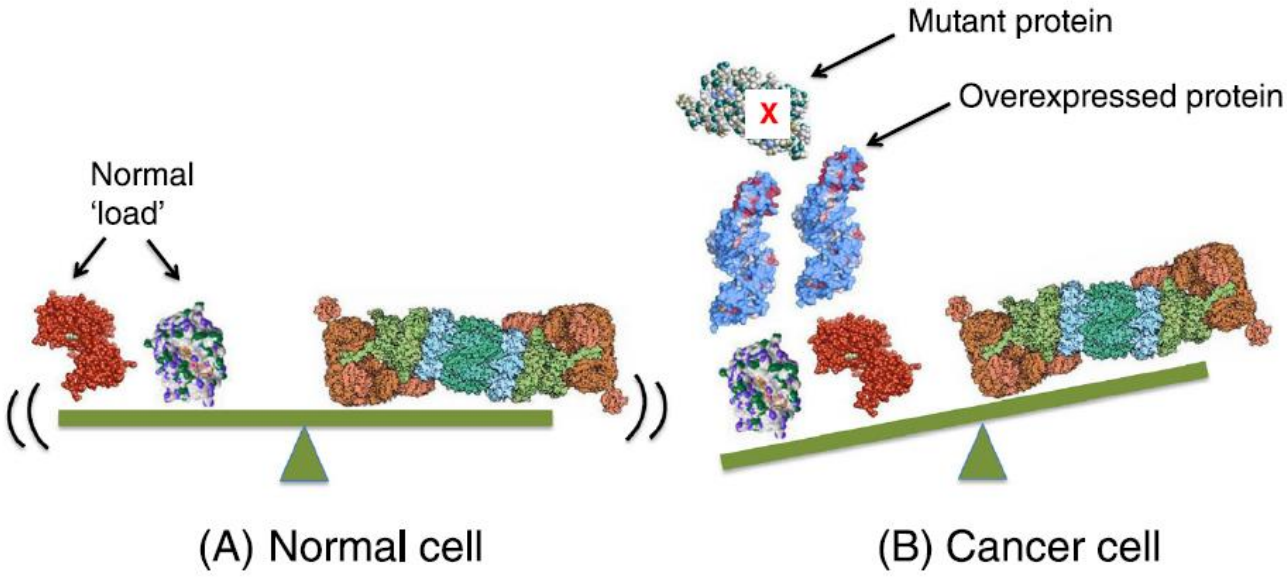


Figure 1. Proteotoxic crisis in cancer cells. (A) In normal cells, the natural load of degradation substrates on the left is in balance with the capacity of the cellular ubiquitin-proteasome system (UPS), signified by the proteasome on the right. **(B)** In cancer cells, the load is increased due to expression of mutant proteins and/or expression of excess proteins due to aneuploidy. This results in an imbalance where the degradation load exceeds the capacity of the UPS.

Deshaies BMC Biology 2014, 12:94
http://www.biomedcentral.com/1741-7007/12/94

2. Small dosis?

Poly-ubiquitinated proteins are recognized and degraded by the 26S proteasome (proteolytic machinery)

Composition of the 26S proteasome

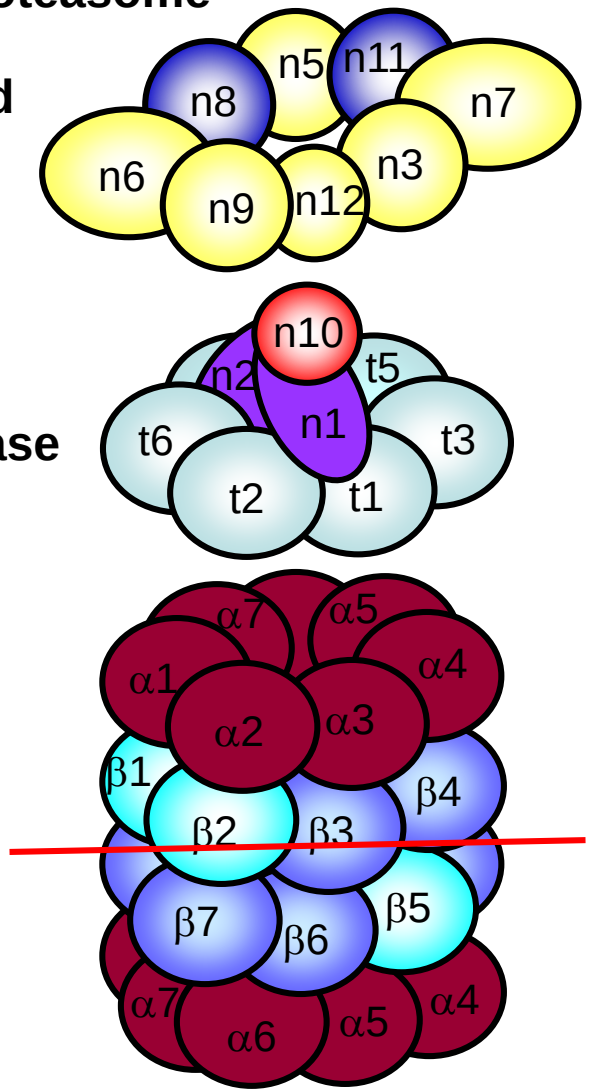
19S regulatory complex

Lid

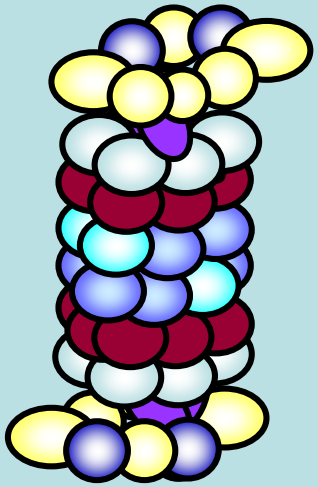
Base

n = Rpn
t = Rpt

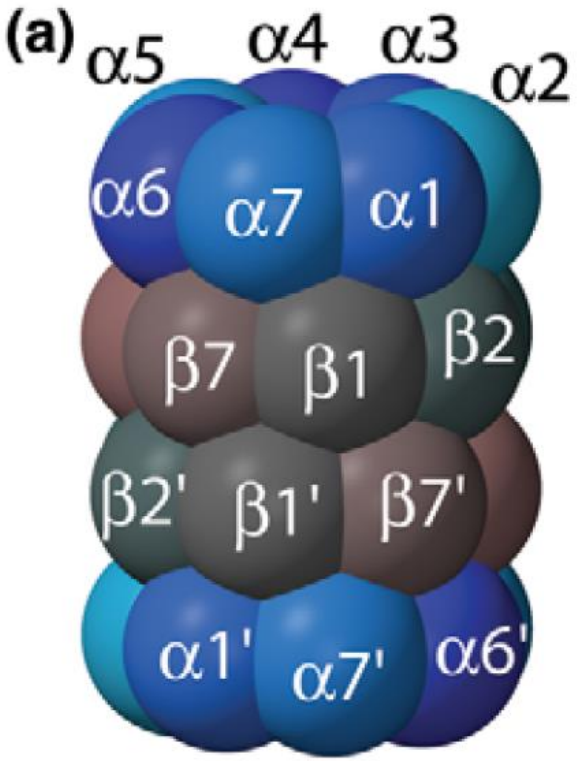
20S proteasome



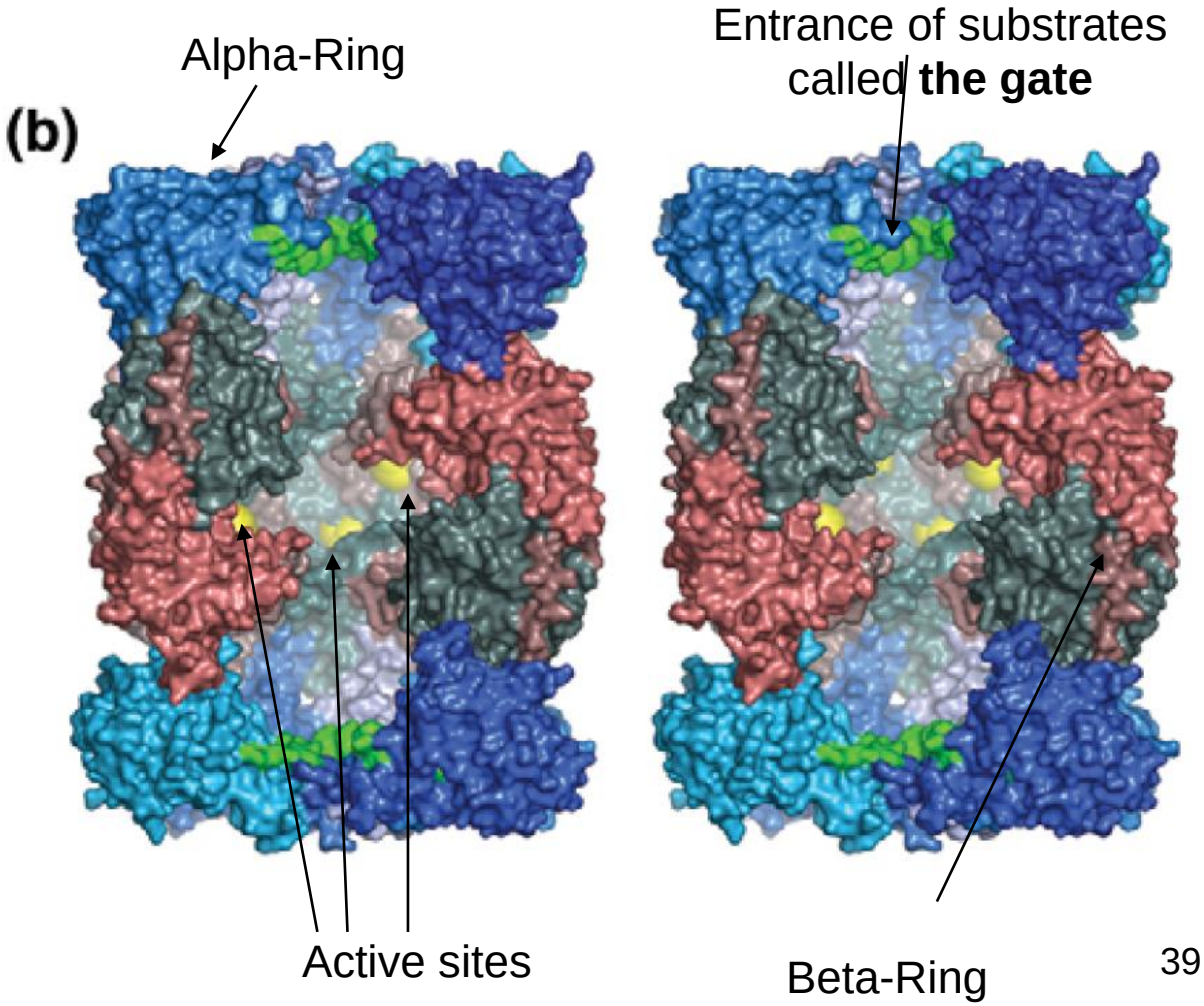
26S proteasome



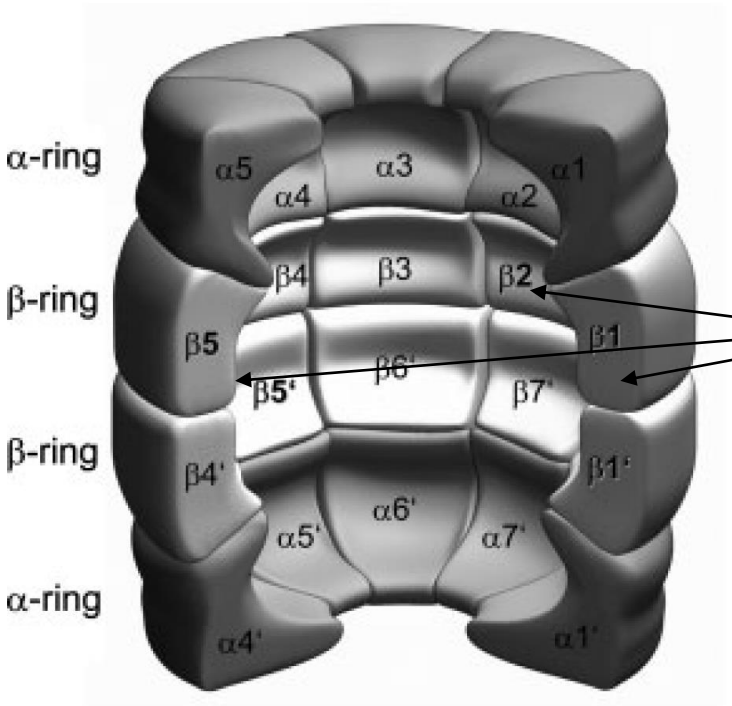
Structure of the 20S core proteasome



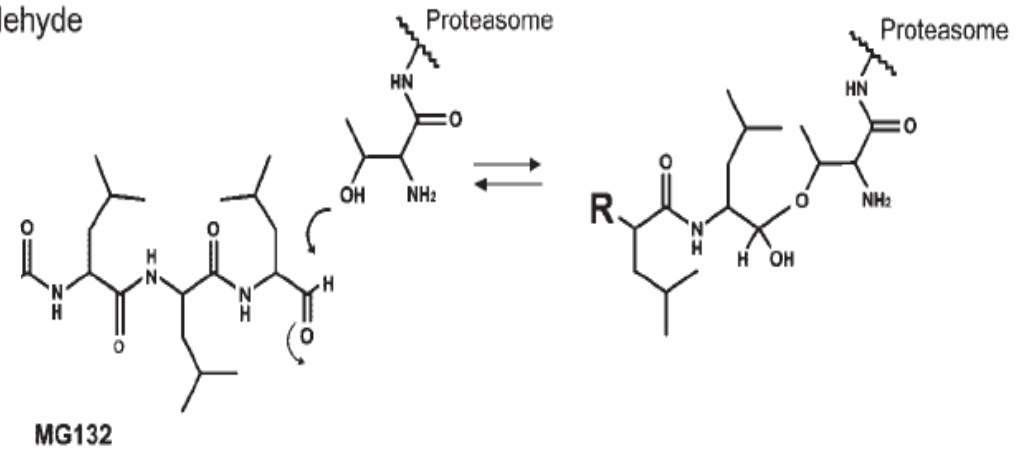
Threonine: Thr



Complete inhibition of the proteasome is lethal



Active sites

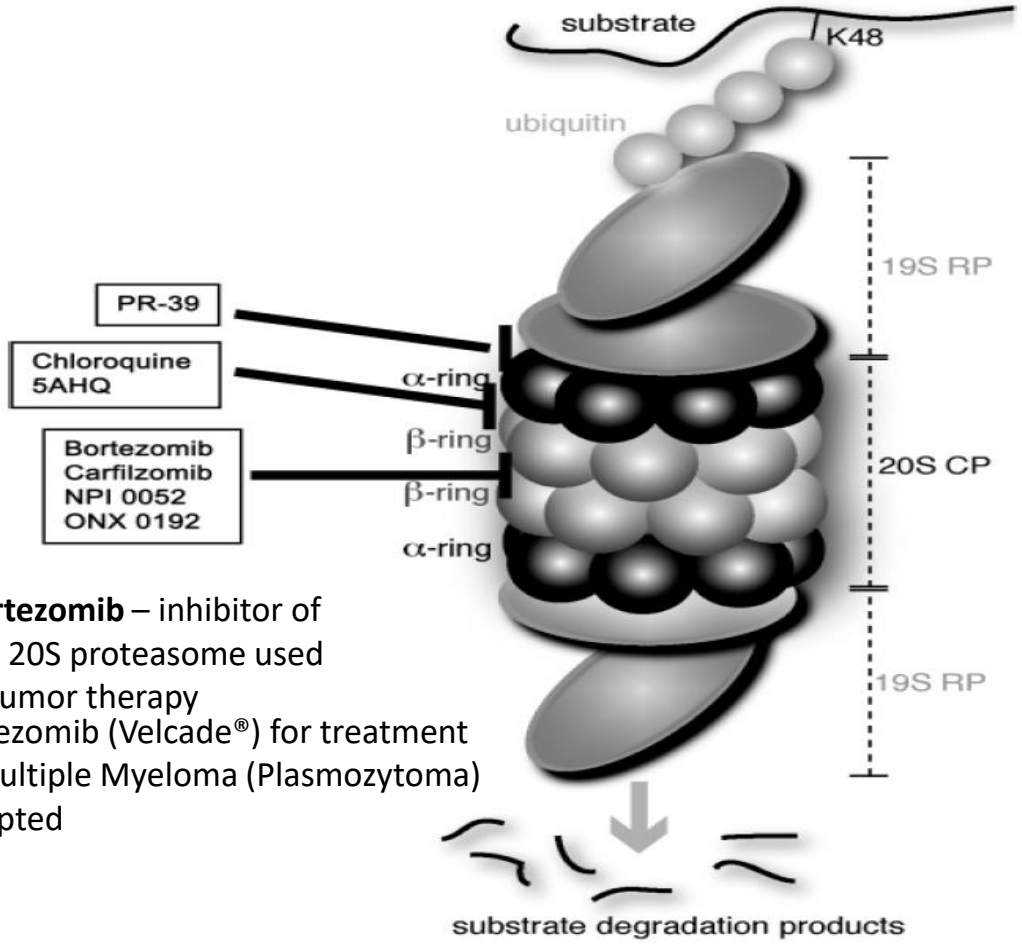


Inhibition of the proteasome blocks tumor growth

Table I. Proteasome Inhibitors According to the Mode of Inhibition

Mode of inhibition	Proteasome inhibitor
Non active-site inhibition	
Gating α-subunits	PR-39, PI31, viral proteins such as HIV-1 tat, HbX
Active-site inhibition	
Reversible covalent bond with active site Thr	Synthetic peptide boronates: e.g., bortezomib, MLN273, MG262
	Synthetic peptide aldehydes: e.g., MG132, PSI, ALLN, Tripeptides
Irreversible covalent bond with Thr	Synthetic peptide vinyl sulfones: e.g., NLVS, YLVS
Irreversible ester bond with Thr of β5	Lactacystin (β-lactone, β-clasto-lactone), MLN519, salinosporamide A (NPI-0052) and B
Irreversible morpholino formation with Thr	Peptide epoxyketones: epoxomicin, eponemicin
Non-covalent binding to active sites	TMC-95s from Apiospora montagnei

Proteasome inhibitors relevant for tumor therapy



Bortezomib – inhibitor of the 20S proteasome used in tumor therapy

Bortezomib (Velcade®) for treatment of Multiple Myeloma (Plasmozytoma) accepted

Proteasome inhibitors in clinical trials or in use

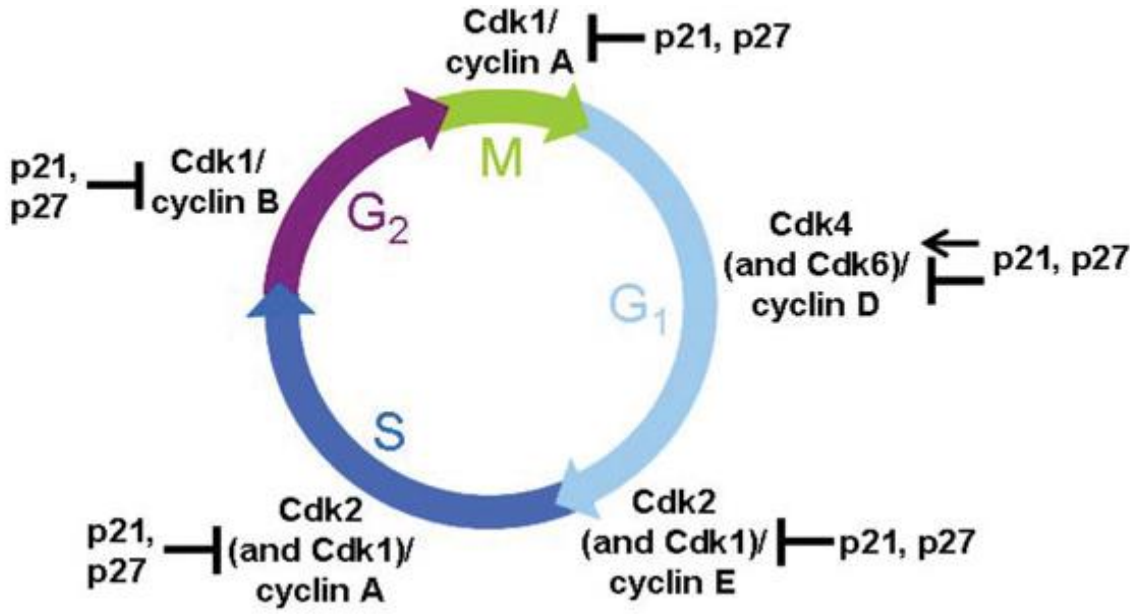
Compound	Type	Mode of binding	Route of administration	Dose	Common grade 3/4 toxicities	Clinical stage	Comment
Bortezomib	Boronate	Reversible	IV/SC	0.7–1.3 mg/m^2 [30]	Peripheral neuropathy, thrombocytopenia, neutropenia	Approved	Used in combination with conventional chemotherapy and novel agents in induction, maintenance and salva therapy for PCM. Licenced as a single agent for relapsed MCL. Potential use in acute leukaemias.
Carfilzomib	Epoxyketone	Irreversible	IV	20–27 mg/m^2 [126]	Lymphopenia, neutropenia, anaemia, thrombocytopenia	Approved	Approved for PCM with disease progression after 2 prior therapies. Likely to be approved for additional treatment protocols for PCM.
Ixazomib	Boronate	Reversible	Oral	4 mg [127]	Rash, neutropenia	Phase 1/2	Under evaluation for the treatment of PCM and lymphoma.
Marizomib	β-lactone	Irreversible	IV/Oral	0.5 mg/m^2 [128]	Lymphopenia	Phase 1/2	Under evaluation for the treatment of PCM and lymphoma.
Delanzomib	Boronate	Reversible	Or Plasma Cell Myeloma	n^2 [62]	Skin rash	Phase 1	Under evaluation for the treatment of PCM.
Oprozomib	Epoxyketone	Irreversible	Oral	120–180 mg [129]	Thrombocytopenia	Phase 1	Under evaluation for the treatment of PCM.

IV – intravenous; SC – subcutaneous; PCM – plasma cell lymphoma; MCL – mantle cell lymphoma.

Site effects of bortezomib: emesis, stomach pain, fever etc.

2. The UPS degrades regulatory proteins in all phases of cell cycle

<u>The UPS degrades:</u>
- cyclins
- p21
- p27
- Securin, anaphase promoting complex (APC)



In most cancer cells: tumor suppressors p53, p27 and p21 are down-regulated or mutated

2. The UPS is a target in tumor therapy, because it degrades tumor suppressors

1. Proteasome inhibitors are already used in tumor therapy

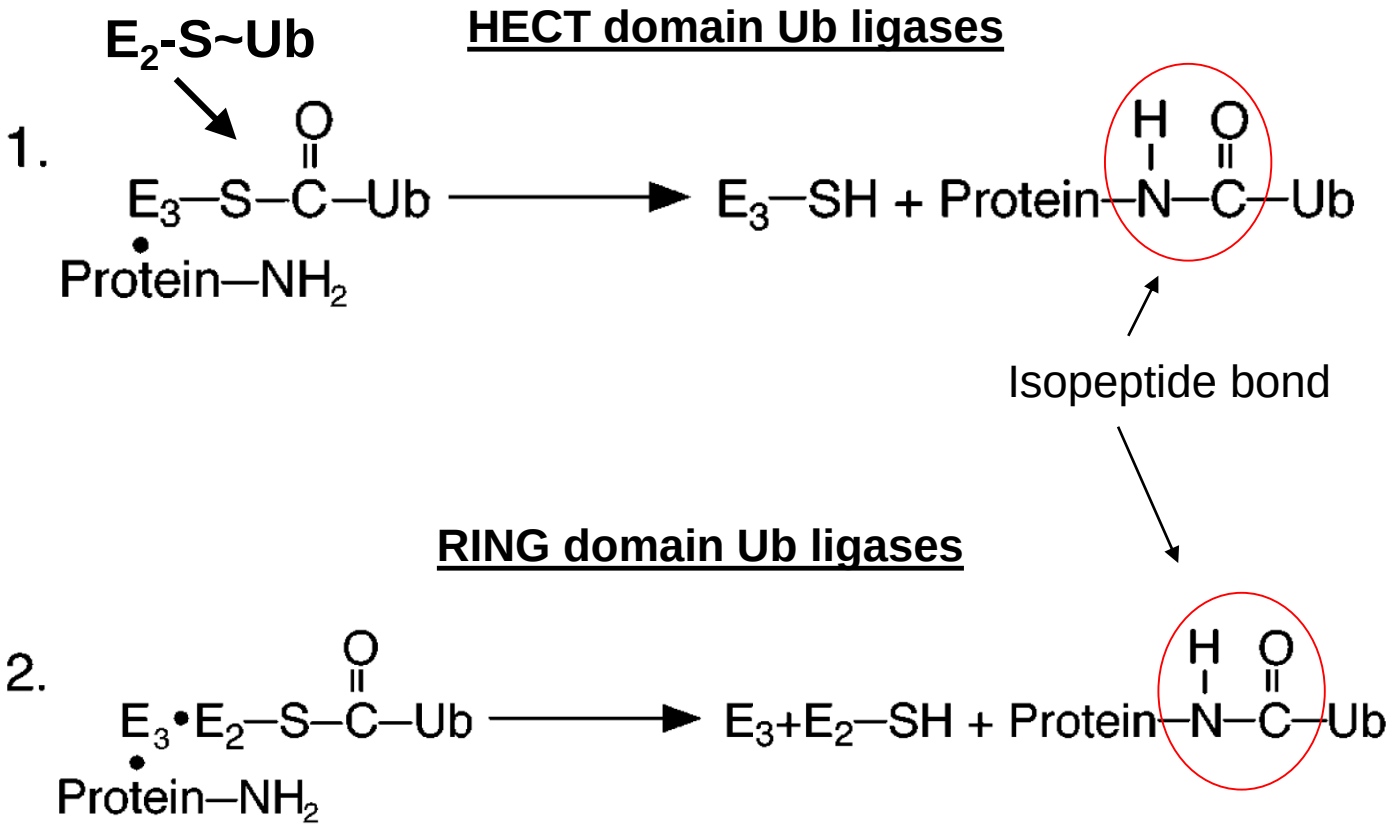
2. Inhibitors of Ub ligases E3s might be more specific as compared to inhibitors of the proteasome

- A major problem of proteosome inhibition are site effects and resistance by proteasome synthesis

- Targeting steps upstream of the proteasome such as Ub ligases E3s e.g. cullin-RING Ub ligases (CRLs) could be more specific
and efficient than inhibition of the proteasome

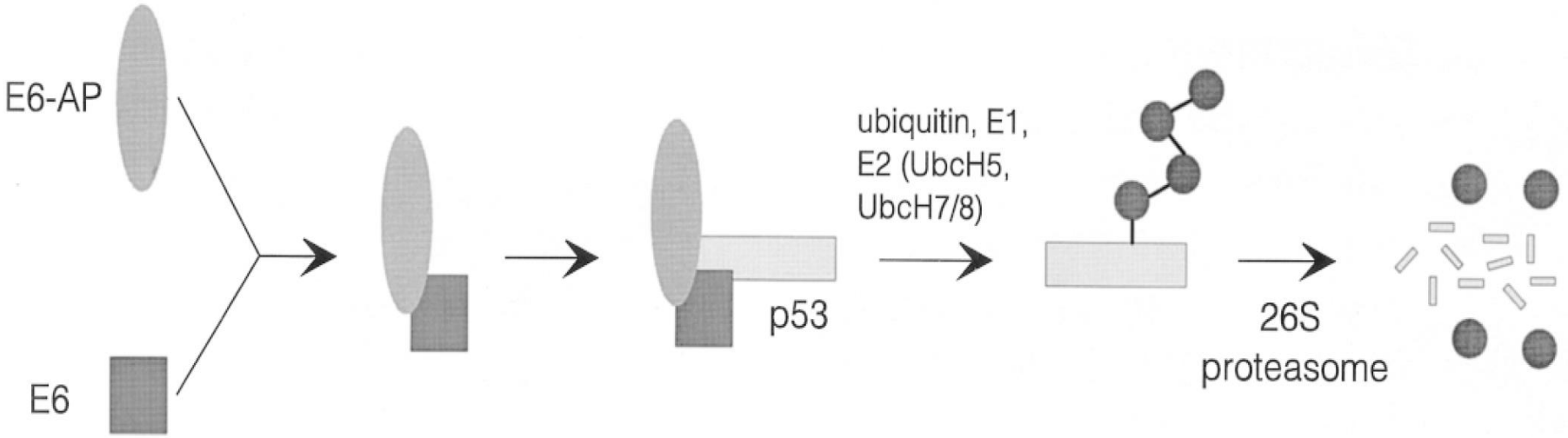
Ub ligases (E3s)

The Ub ligases (E3s) ligate specifically Ub to protein substrates. They determine the specificity of the UPS.



In cervical tumor cells p53 is degraded by the E6-AP Ub ligase

The human papillomavirus (HPV) protein E6 is produced in the host cells. This protein interacts with the host E6-AP protein and forms an active E3.



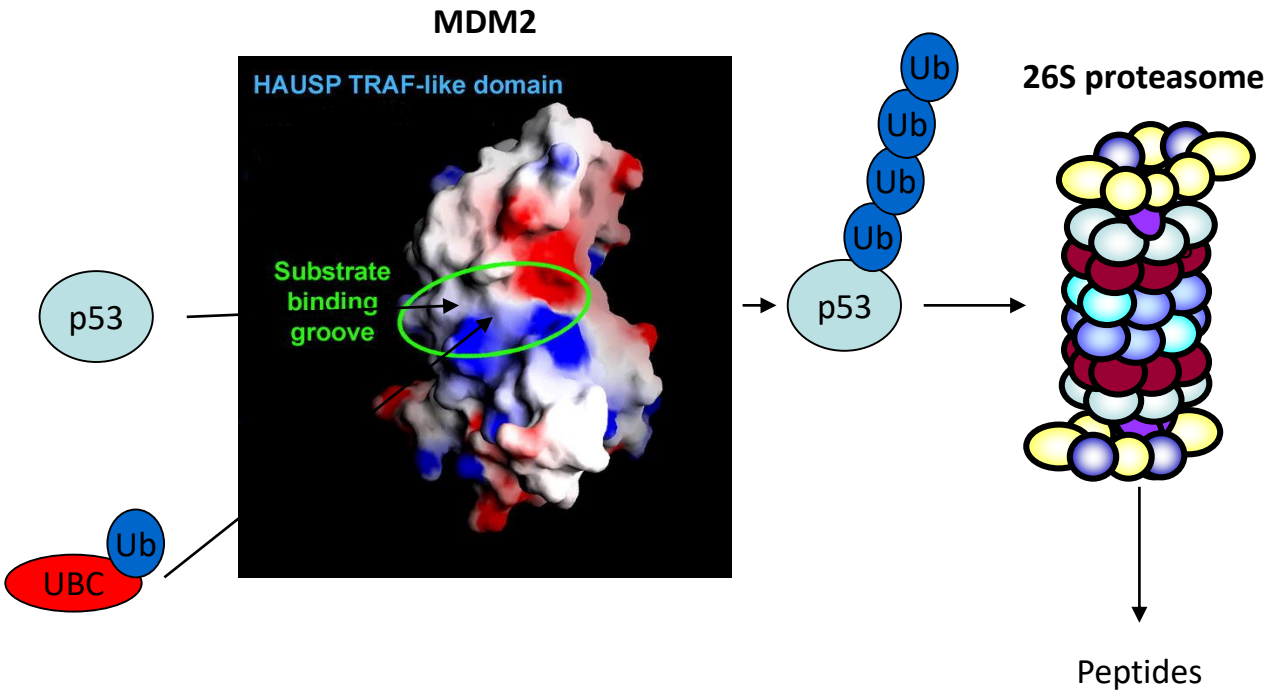
Treatment of HPV-induced cervical tumor by immunization/vaccination!

Nobel price for physiology or medicine 2008

Harald zur Hausen

for his discovery of human papilloma viruses causing cervical cancer

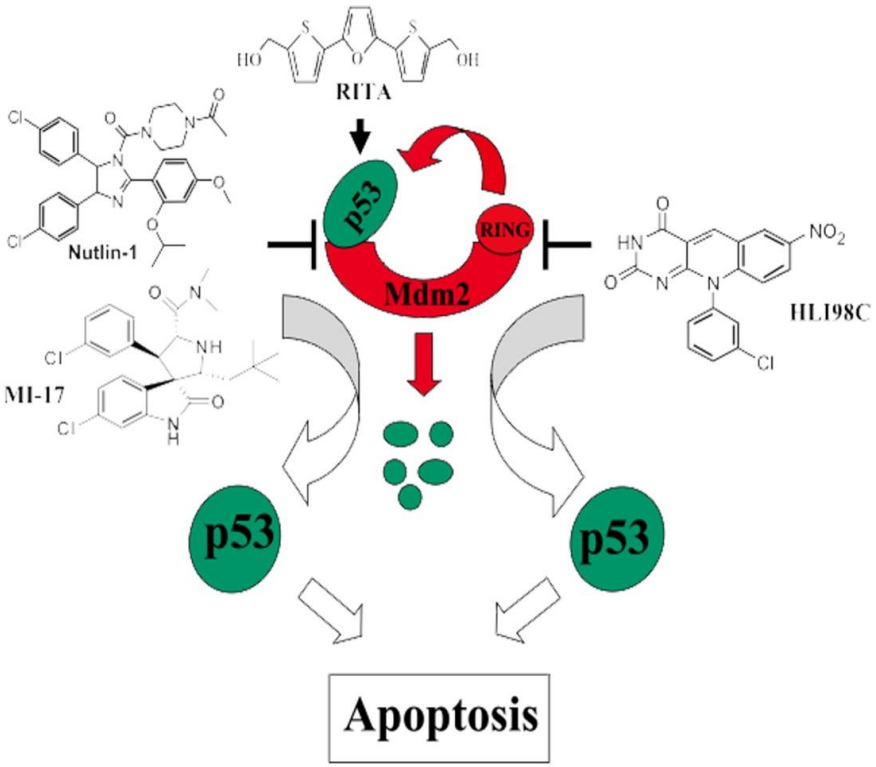
MDM2 ubiquitinates p53



MDM2 E3 ligase inhibitors and compounds disrupting MDM2-p53 binding

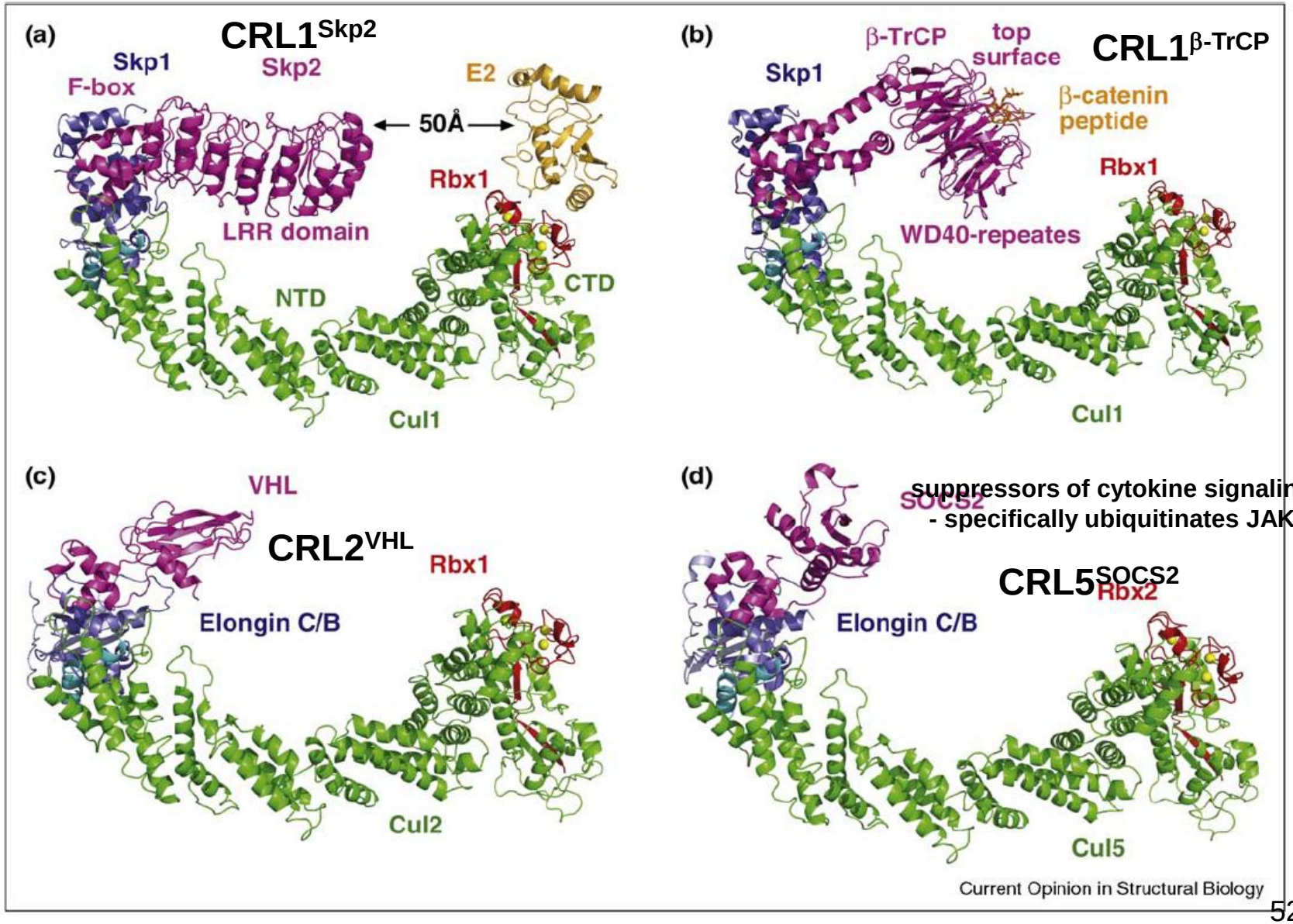
- Nutlin, a compound disrupting MDM2-p53 binding
- RITA (Reactivation of p53 and Induction of Tumor cell Apoptosis)
- MI-17 (a nonpeptide MDM2 inhibitor)
- HL198C inhibits MDM2

Lead to growth arrest, apoptosis and *in vivo* tumor growth inhibition



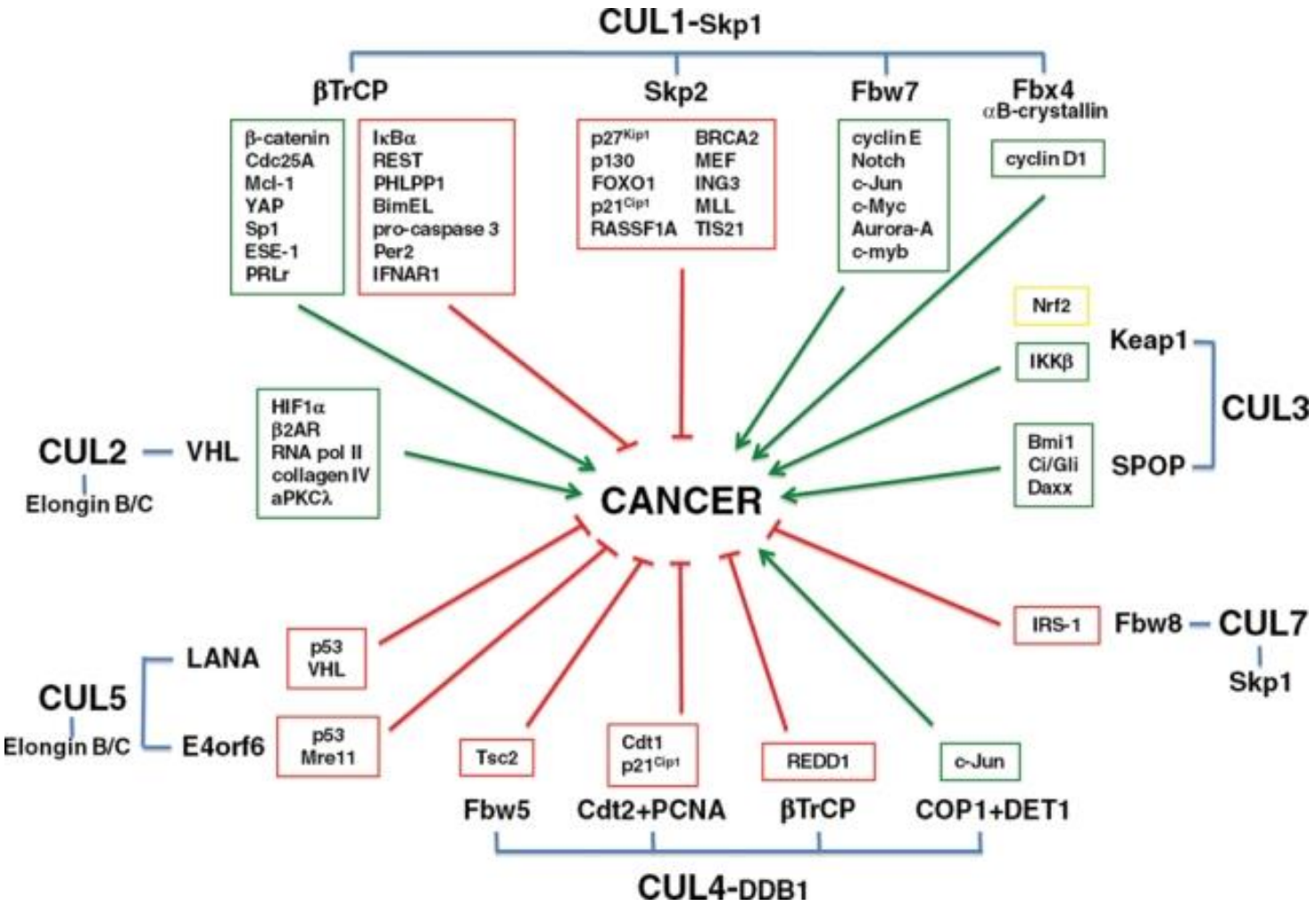
In most cancer cells p53 is promoted degraded

Structure of CRLs

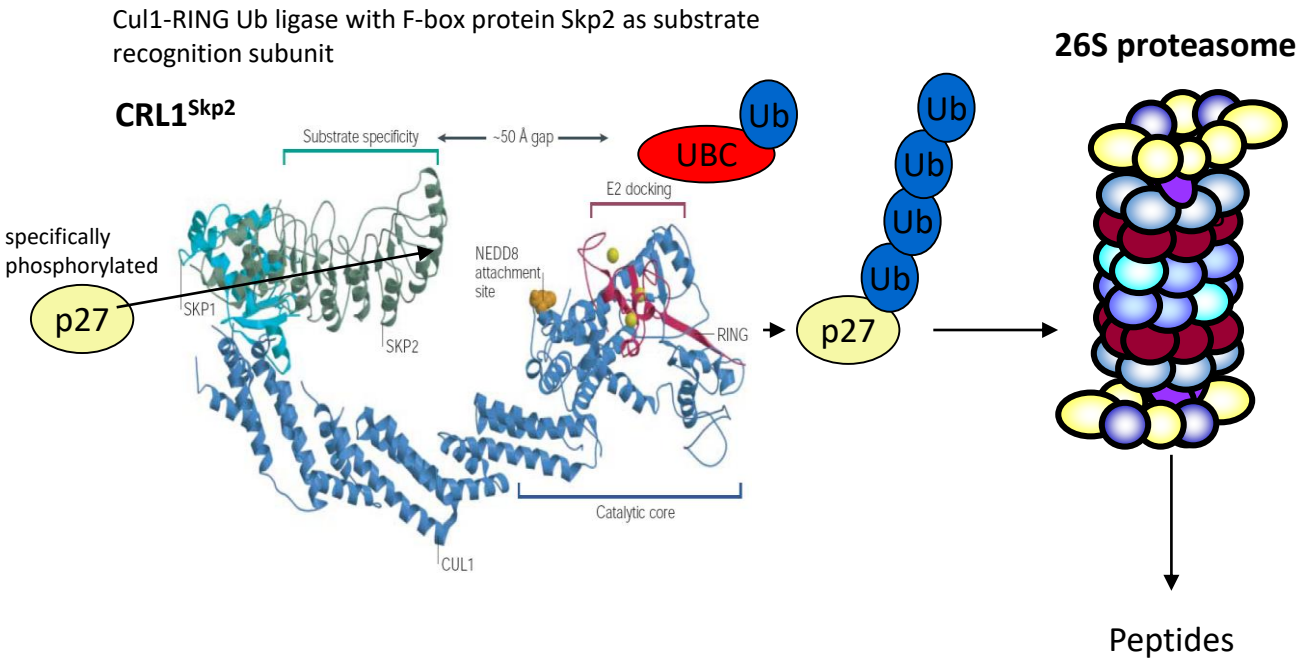


VHL (von Hippel Lindau protein) is the Ub E3 Ligas for HIF1 alpha

Cullin-RING Ubiquitin Ligases (CRLs). Schematic diagram of cullin/adaptor complexes, substrate receptors, and substrates. The roles of cullin substrates in promoting (green boxes/arrows) or inhibiting (red boxes/arrows) growth or survival, thus impacting oncogenesis, are indicated.

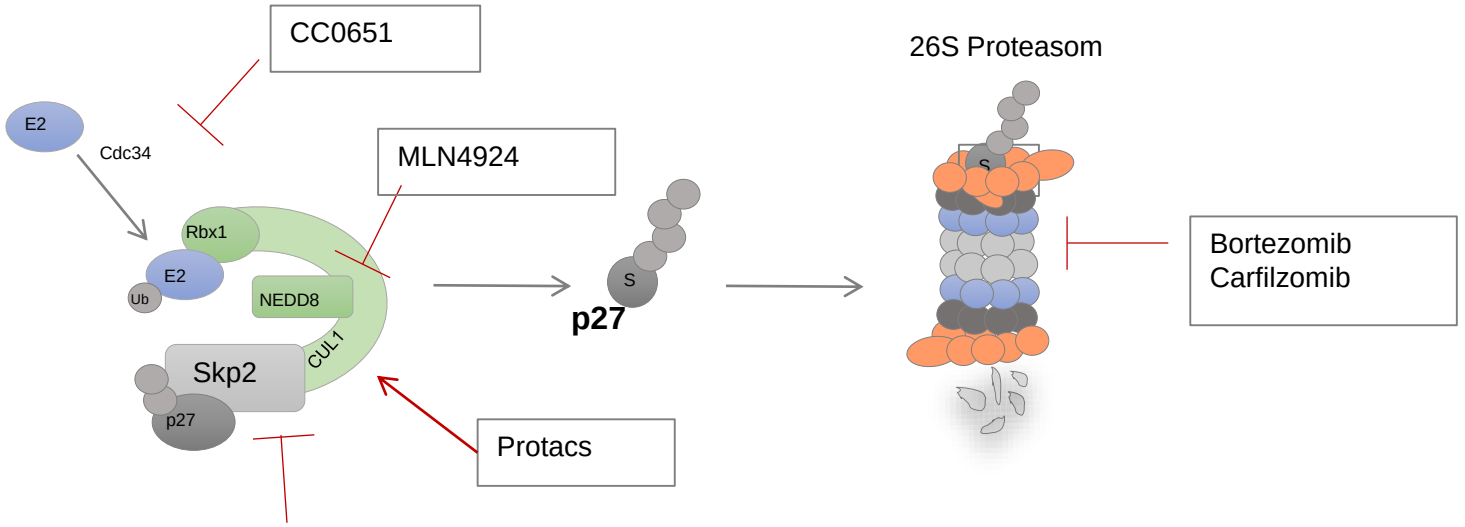


The cell cycle regulator and tumor suppressor p27 is ubiquitinated by CRL1



p27 is reduced in colon cancer cells

The Cul1-based CRL that ubiquitylates p27 is an important target

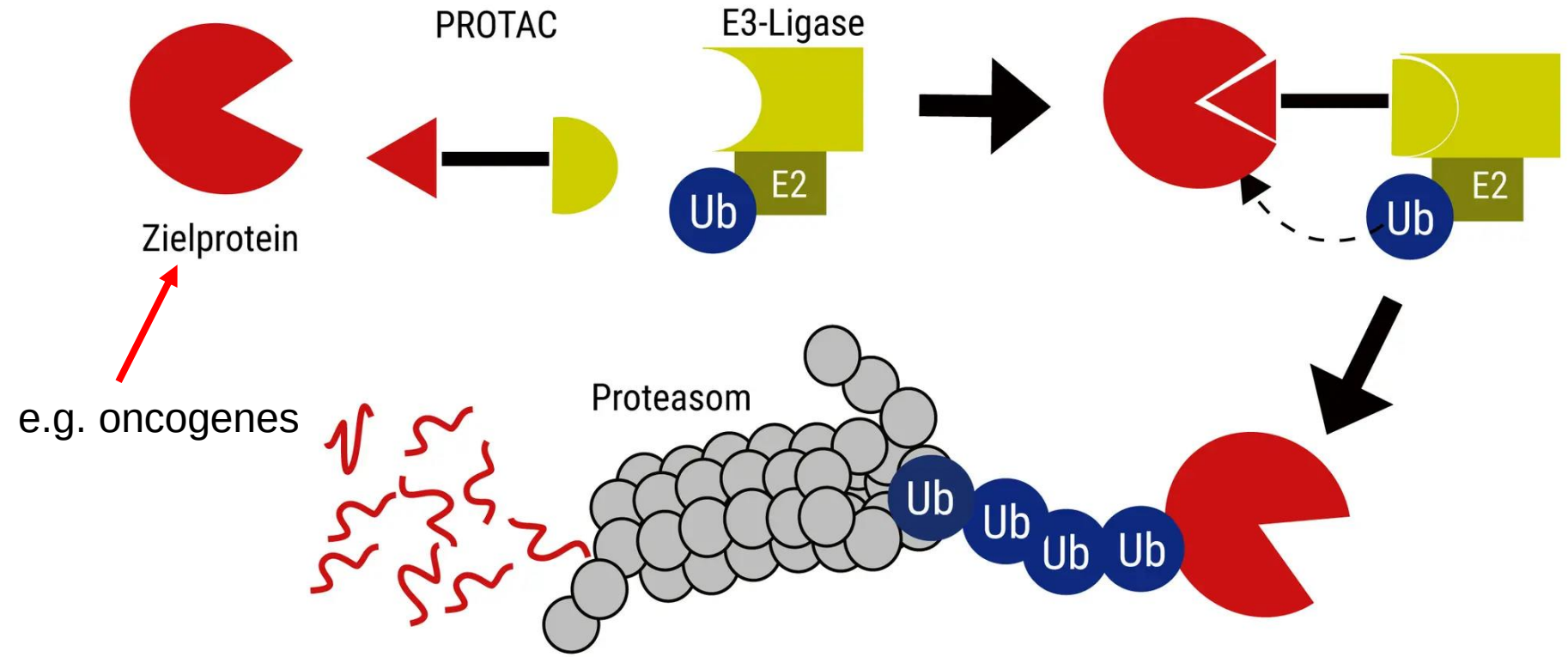


Skp2

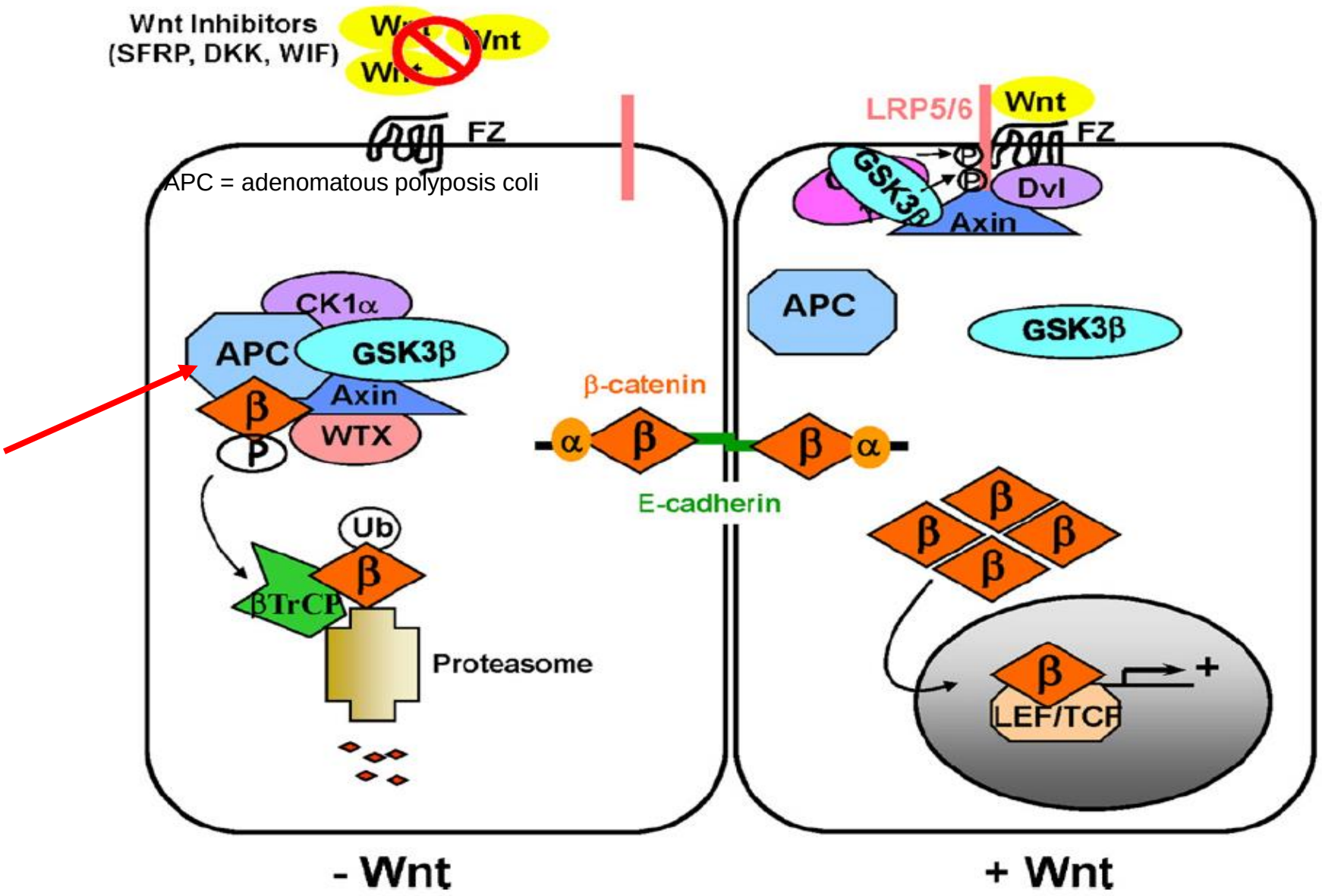
Compound CpdA
Arsenic trooxide (ATO)
Wogonin
Tubacapsanolide
Flavonoid, Ampelospin (AMP)
Natural agents

3. The UPS is a target in tumor therapy, because it degrades oncogenes PROTACs (proteolysis targeting chimeras)

-oncogenes in cancer cells more expressed

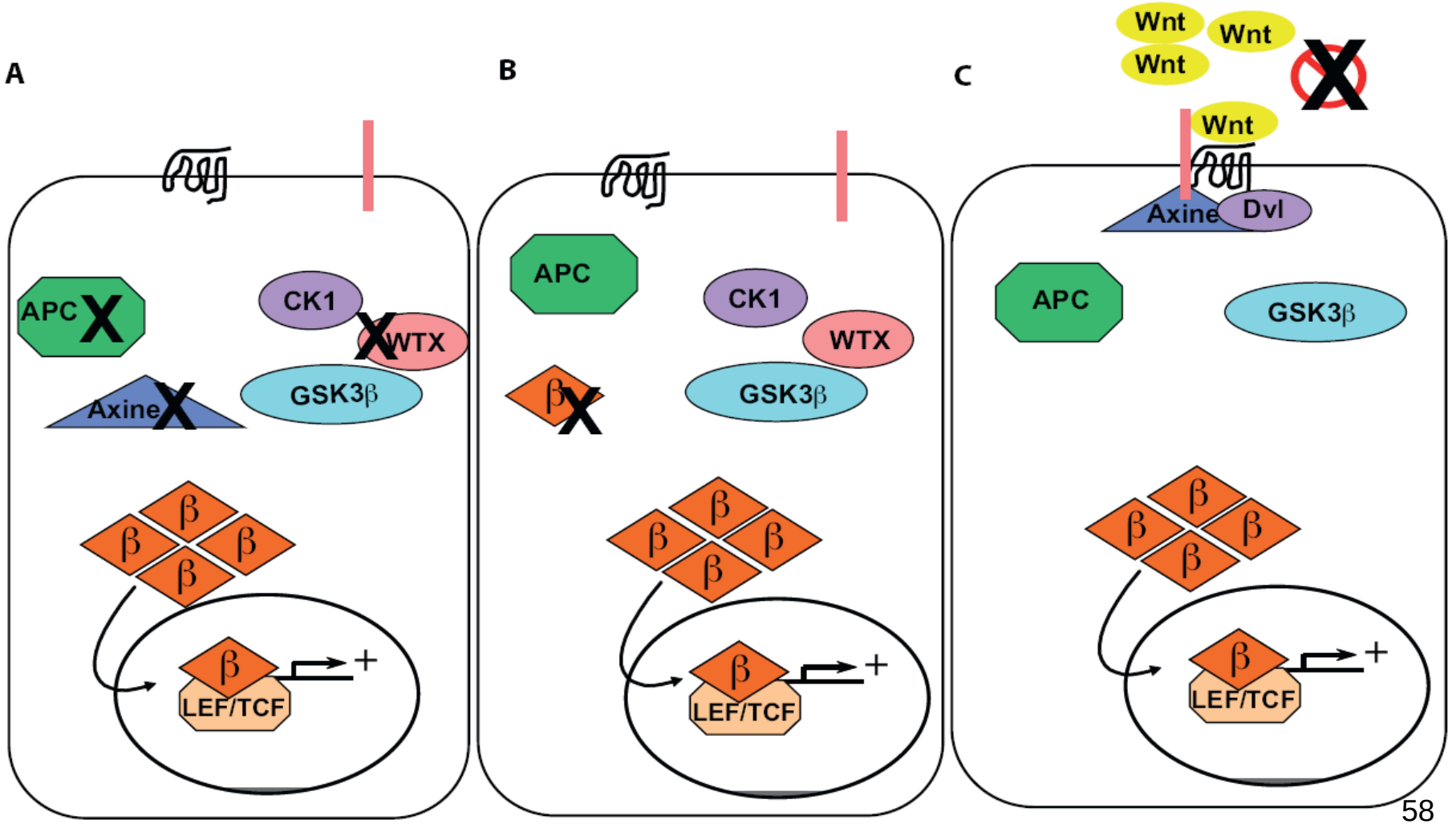


The Wnt/β-catenin signaling pathway



VEGF
c-Jun
c-Myc
cyclin D

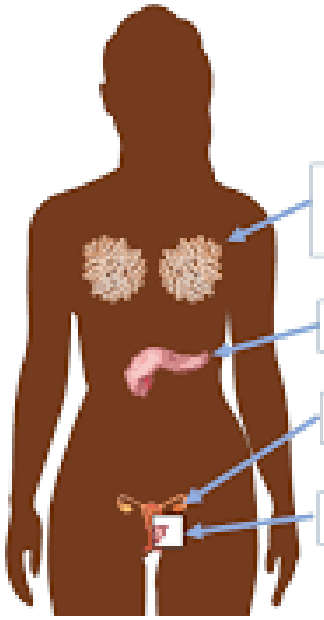
Mutations in components of the Wnt/β-catenin pathway result in cancer



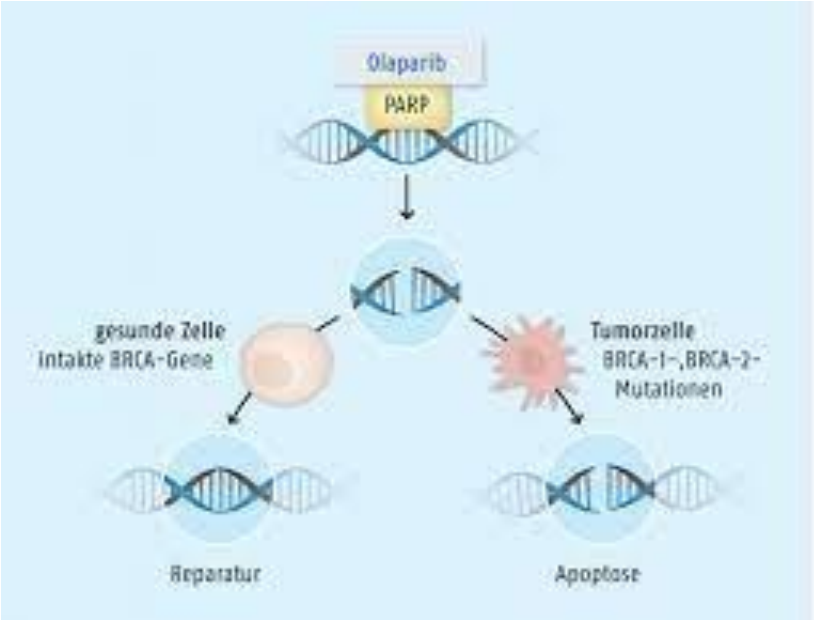
(WTX=Wilms tumor suppressor)

Ring domain E3 Ligases as a diagnostic tool:

BRCA1 and BRCA2 Ub ligases

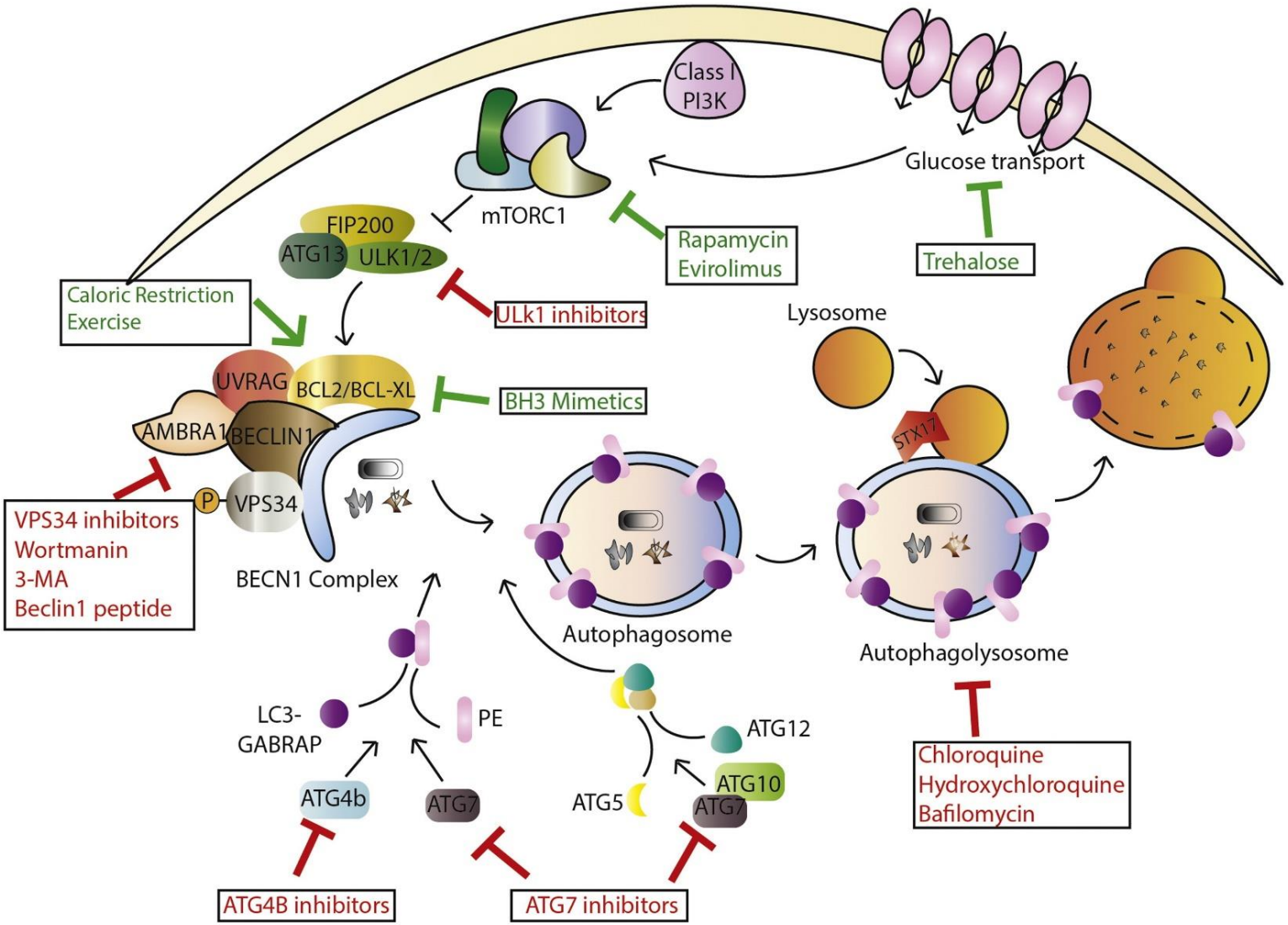


	BRCA1	BRCA2
Breast cancer:	**50% to 65%** Males: 1.2%	**40% to 55%** Males: Up to 9%
Pancreas cancer:	1-3%	2-7%
Ovarian cancer:	**40% to 65%**	**15% to 25%**
Prostate cancer:	9%	15%



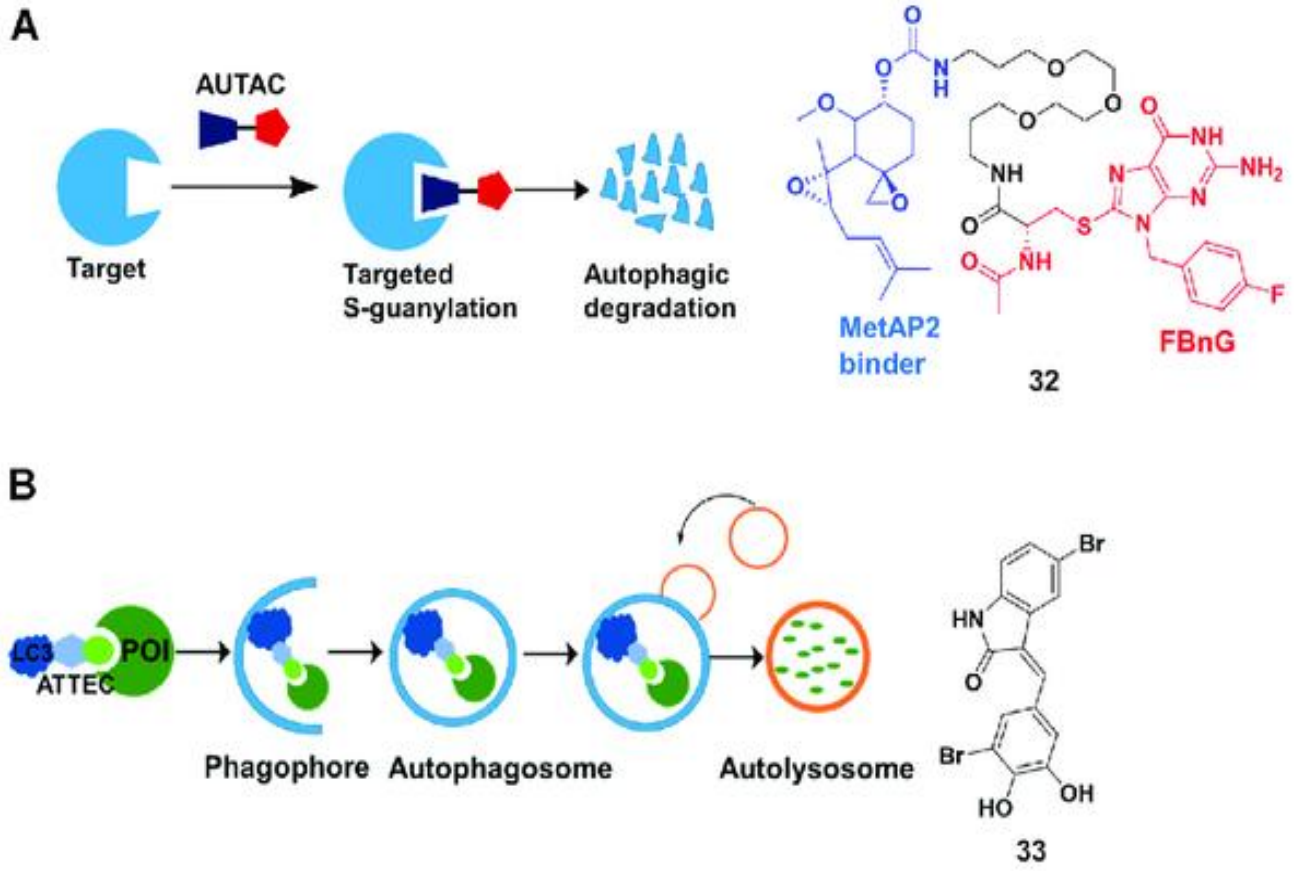
Different target sites in the Autophagy

1. Autophagy is modulated in some cancer cells



AUTACs
(Autophagy targeting chimercs)

2. Autophagy degrades mutated, unsoluble protein aggregates and misfolded proteins.



Eigenschaften eines idealen Wirkstofftargets

1. Das Target/Ziel ist krankheitsmodifizierend und/oder hat eine nachgewiesene Funktion bei der Pathophysiologie einer Krankheit.

2. Die Modulation des Targets ist unter normalen physiologischen Bedingungen weniger wichtig oder bei anderen Krankheiten.

3. Wenn der Wirkungsmechanismus eines Arzneimittels nicht offensichtlich ist (z.B. wie bei Kinasen), sollte eine 3D-Struktur für das Zielprotein oder ein enges Homolog für eine Beurteilung des Wirkungsmechanismus eines Arzneimittels zur Verfügung stehen.

4. Das Target hat eine günstige "Testbarkeit", die eine high-throughput screening ermöglicht.

5. Die Target-Expression ist nicht gleichmäßig über den Körper verteilt.

6. Es existiert ein target-/krankheitsspezifischer Biomarker, um die therapeutische Wirksamkeit zu überwachen.

7. Günstige Vorhersage möglicher Nebenwirkungen anhand von Phänotyp-Daten (z.B. bei k.o. Mäusen oder genetischen Mutationsdatenbanken).

8. Target hat eine günstige IP-Situation (keine Wettbewerber auf Target Freedom to Operate).

IP: intellectual property