Qu'en est-il de nos médicaments dans la nature, et au-delà ?

Marc LE BORGNE

PU Chimie Thérapeutique - ISPB

Faculté de Pharmacie de Lyon – ISPB, 19 janvier 2023

Articulation de la Conférence

- **Partie 1** : Les médicaments du « quotidien » issus de nos ressources naturelles (*échelle macroscopique*)

- **Partie 2** : Exploration et investigation autour des cellules humaines (*échelle microscopique*)

- **Partie 3** : Les médicaments qui impactent notre environnement… (*échelle planétaire*)

Partie 1 : Les médicaments du « quotidien » issus de nos ressources naturelles

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LA NATURE FOURNIE UN GRAND NOMBRE D'IPAS

- *Salix alba* (saule blanc) et *Filipendula ulmaria* (spirée, reine-des-prés) : Acide salicylique, Aspirine

- *Papaver somniferum* var. *album* (pavot blanc, pavot à opium) : Morphine, Codéine et Désomorphine

- *Nauclea latifolia* (pêcher africain) : Tramadol (IXPRIM®, TOPALGIC®)

- *Erythroxylon coca* (Coca) : Cocaïne

- *Helix pomatia* (escargot de Bourgogne, gros blanc, ou escargot de Champagne) : HELICIDINE®

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LA NATURE FOURNIE UN GRAND NOMBRE D'IPAS

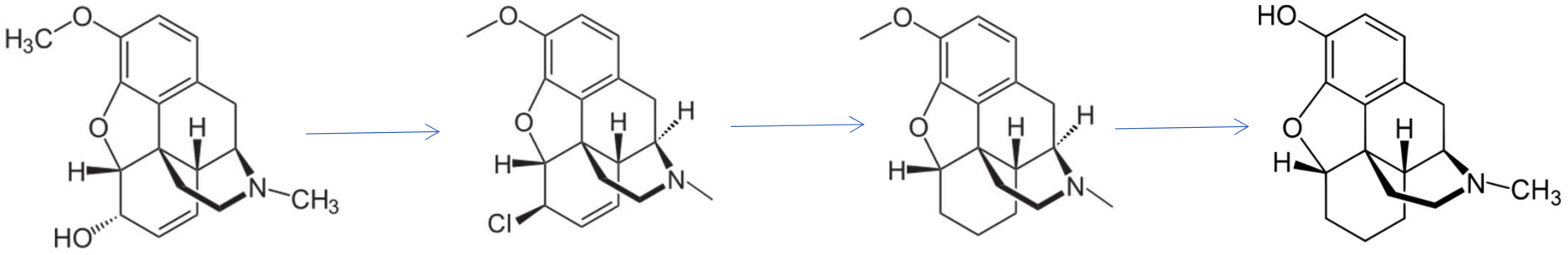
- Riz fermenté avec *Monascus purpureus* (levure de riz rouge) : Lovastatine (monacoline K)
- *Cinchona officinalis* (quinquina gris) : Quinine
- *Artemisia annua* (armoise annuelle) : Artémisinine et ACT
- *Taxus brevifolia* (If du pacifique) : Paclitaxel (TAXOL®)
- *Taxus baccata* (If commun, if à baies) : 10-Désacétylbaccatine III (10-DAB)
- *Amanita phalloides* : Amanitines
- *Conus magus* (escargot marin) : Ziconotide (PRIALT®)
- *Actinomadura* sp., *Streptosporangium* sp. (bact. marines): Iodinine

CODÉINE, DÉSOMORPHINE (KROKODIL)

Usage détournée de la codéine

Sizzurp : sirop à la codéine associé à un anti-histaminique et du soda (légère euphorie et bien être)

Krokodil : désomorphine



codéine — α-**c**hlo**rocodi**de — dihydrodesoxycodeine — désomorphine

CODÉINE, DÉSOMORPHINE (KROKODIL)

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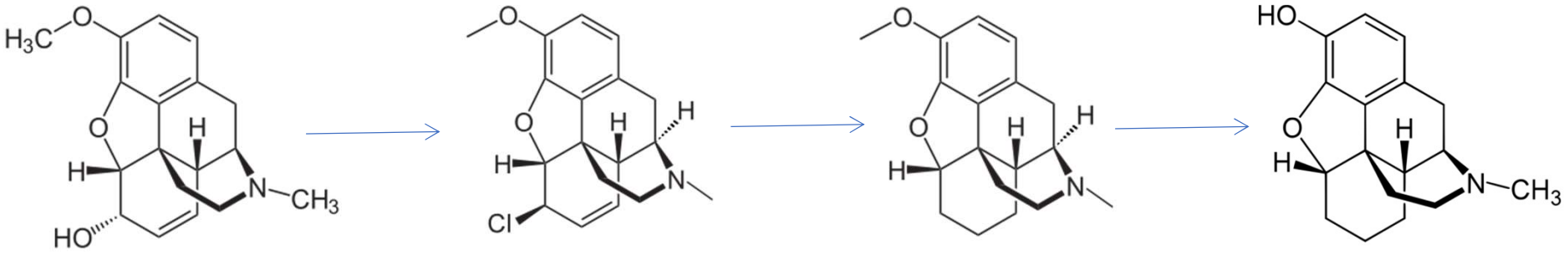
krokodil qui permet de contourner les ruptures d'héroïne à cause de la guerre en Afghanistan…



codéine — α-**c**hlo**rocodi**de — dihydrodesoxycodeine — désomorphine

CODÉINE, DÉSOMORPHINE (KROKODIL)

Attention ! Cette drogue peut tuer dès la première injection

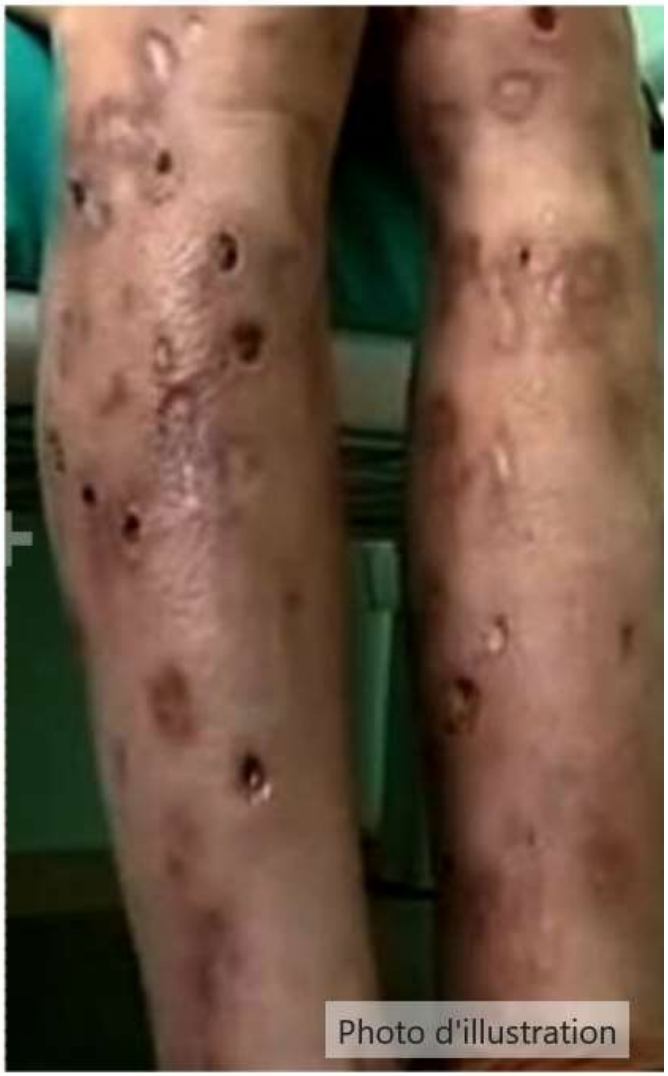
La Krokodil a un aspect pâteux, obtenu après combustion, et provoque des dégâts incurables. Le membre où est administrée la drogue se gangrène et doit souvent être amputé.

Espérance de vie : un à trois ans pour tous les consommateurs, qui meurent soit d'un empoisonnement du sang, d'une méningite, d'une pneumonie ou de pourrissement.

La désomorphine ou drogue "crocodile" : ce produit de synthèse qui abîme la peau
Jeanne Le Borgne, 27/01/2022, Doctissimo

La drogue "crocodile" (ou "krokodil") est considérée comme "la drogue la plus dangereuse au monde" : elle réduit l'espérance de vie de ses consommateurs à trois ans. Mais si elle est répandue en Russie où elle fait des ravages, cette "héroïne du pauvre" ne serait pas consommée en France.

CODÉINE, DÉSOMORPHINE (KROKODIL)

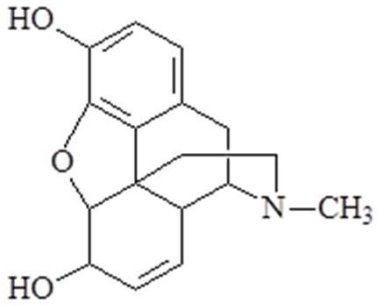


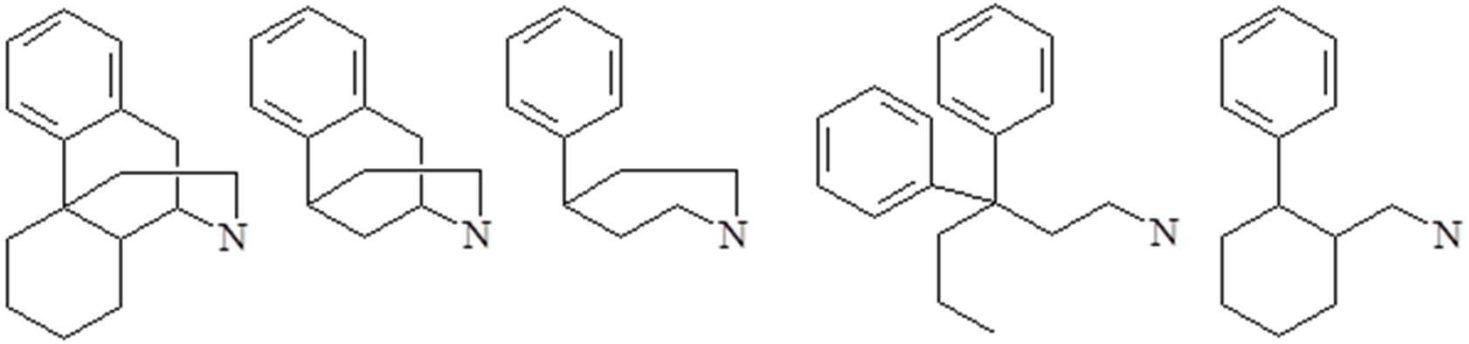
Alice Lafontaine, 18 janvier 2017. Russie: Voici la drogue la plus dangereuse et mortelle au monde ! Regardez les effets destructeurs sur le corps !

ANALOGUES SIMPLIFIÉS DE LA MORPHINE

Dérivés **synthétiques**

Simplification de la morphine :





(1) (2) (3) (4) (5)

Morphinane

Benzomorphane

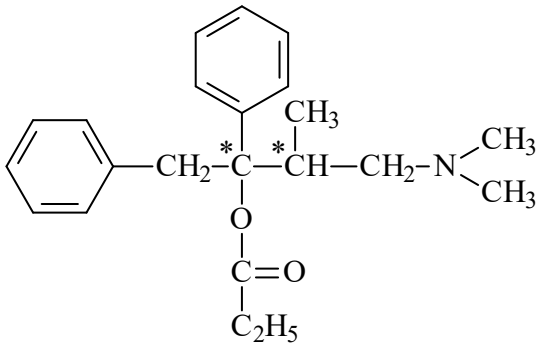
Phénylpipéridine

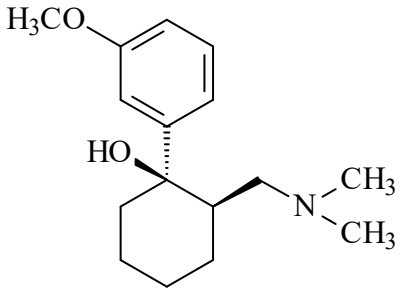
Diphénylpropylamine

Phénylaminométhylcyclohexane

ANALOGUES SIMPLIFIÉS DE LA MORPHINE

Dextropropoxyphène et **Tramadol**





Dérivés de la diphénylpropylamine

DI-ANTALVIC®

Retrait du marché le 1er mars 2011

Cardiotoxicité

Dérivés du phénylaminométhylcyclohexane

TOPALGIC®

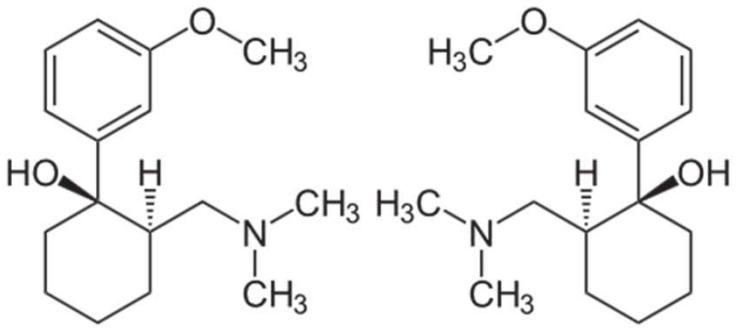
Firme allemande Grünenthal GmbH

ANALOGUES SIMPLIFIÉS DE LA MORPHINE

Tramadol[G] (seul ou en association avec paracétamol)

Seul (Contramal® gél, Monoalgic® LP cpr…)

+ Paracétamol IXPRIM® ZALDIAR®

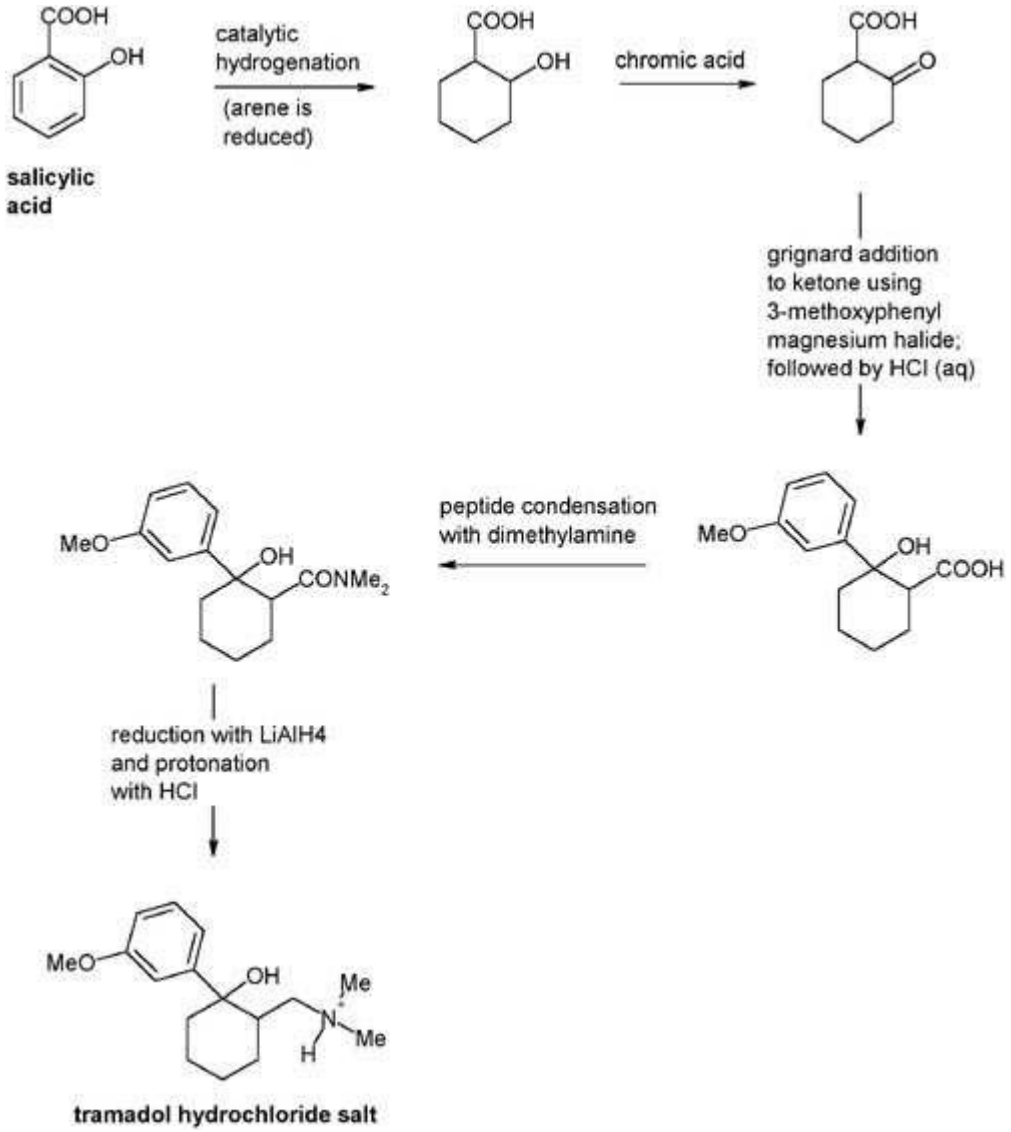


Phénylaminométhylcyclohexane (1*R*,2*R*)-TMD (1*S*,2*S*)-TMD

Il est commercialisé sous forme d'un mélange racémique de deux énantiomères : (±)-cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol

Depuis le 15 avril 2020, la prescription de tramadol par voie orale est limitée à 12 semaines. Si le traitement doit être poursuivi au-delà de 3 mois, une nouvelle ordonnance est nécessaire.

TRAMADOL SYNTHÉTIQUE

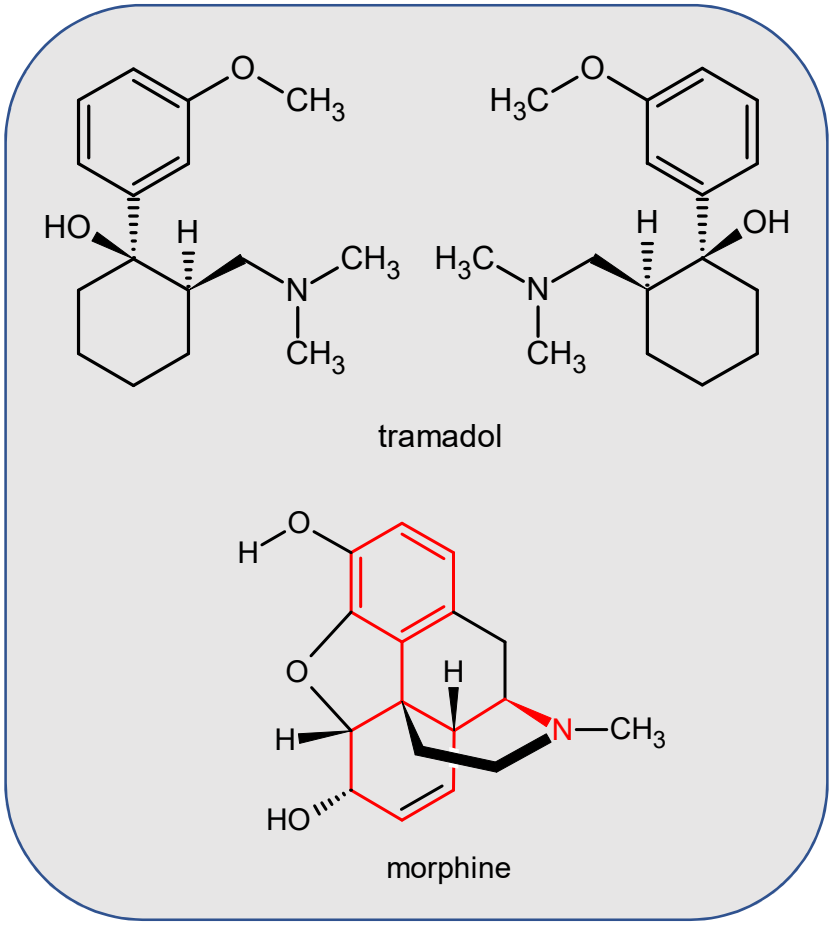


TRAMADOL NATUREL

Nauclea latifolia
« pêcher africain »

DÉCOUVERTE – Une équipe de scientifiques multi-sites a récemment découvert une molécule synthétique, le tramadol, à l'état naturel et en grandes quantités dans les racines d'un arbre africain. Une première mondiale aux retombées prometteuses.

C'est en effet la première fois que des scientifiques retrouvent une molécule de synthèse présente à l'état naturel à de telles concentrations. « Avec 20 grammes de cette plante, on obtient une pilule de tramadol », précise le directeur de recherche à l'Inserm. M. De Waard



Biomimetic synthesis of tramadol. Lecerf-Schmidt F, et al. Chem Commun (Camb). 2015;51(77):14451-3.
Occurrence of the synthetic analgesic tramadol in an African medicinal plant. Boumendjel A, et al. Angew Chem Int Ed Engl. 2013;52(45):11780-4.

TRAMADOL NATUREL

better anti-HIV drugs.

The protein CCR5 resides on the surface of certain immune cells. A team led by Beili Wu at the Chinese Academy of Sciences' Shanghai Institute of Materia Medica successfully crystallized CCR5 bound to the anti-HIV drug maraviroc. The structure suggests that the drug works by making CCR5 more rigid, and so prevents movements that allow HIV to enter cells. It also reveals why such HIV drugs fail to work with certain CCR5 mutants.

Differences between CCR5 and CXCR4, another protein used by HIV to enter cells, may explain why some HIV strains favour one protein gateway over the other.

Science **http://doi.org/ntj (2013)**

ZOOLOGY

Fertility smells like preen spirit

A bird's scent may indicate how many offspring it will produce.

Danielle Whittaker of Michigan State University in East Lansing and her colleagues analysed compounds that evaporate from the oily secretions that birds spread over their feathers when preening. The team collected oil from 12 female and 22 male dark-eyed juncos (*Junco hyemalis*; **pictured**) and found that the oil's chemical profile differed between the sexes.

Birds that released more chemicals characteristic of their sex produced more offspring. And males with more 'female' odours fledged more hatchlings fathered by other birds from their nests. Overall, the smell of a bird was a better predictor of reproductive success than either size or plumage.

Anim. Behav. **http://doi.org/nr3 (2013)**

DONALD M. JONES/MINDEN PICTURES/FLPA

NATURAL PRODUCTS

African tree gets to the root of pain

An African plant used in traditional medicine for pain relief contains the same active ingredient as an artificial pain killer.

Together with scientists in Cameroon, France and Switzerland, Michel De Waard at Joseph Fourier University in Grenoble, France, collected extracts from the pincushion tree (*Nauclea latifolia*), separated compounds into groups on the basis of their mass and chemical properties, then tested each group in mice for its ability to relieve pain.

The team found an oily yellow compound in the most potent group and determined its chemical structure to be that of tramadol, which has been sold as a synthetic analgesic since the 1970s. The compound was detected only in the plant's roots — the same parts used in traditional remedies to treat pain. The researchers believe that this is the first time a widely prescribed synthetic drug has been found in a plant at clinically relevant concentrations.

Angew. Chem. **http://doi.org/f2dv27 (2013)**

GENETICS

Ancient bear bone yields a sequence

The mitochondrial genome of a Pleistocene cave bear (*Ursus deningeri*) has been reconstructed using extremely short DNA molecules from a bone that is more than 300,000 years old. Apart from rare specimens preserved in permafrost, the fossil is some 200,000 years older than any other material used to generate a complete DNA sequence.

By reworking methods to purify the tiny amounts of damaged DNA that are typical of old samples, Jesse Dabney at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, and his colleagues collected and sequenced DNA strands as short as 30 basepairs. More than 90% of the sequences used to produce the genome were less than 50 basepairs long — too short to be used efficiently with conventional methods.

The technique could allow researchers to recover DNA from ancient humans and other specimens that are currently considered too degraded for most analyses.

Proc. Natl Acad. Sci. USA **http://doi.org/nr4 (2013)**

COMMUNITY CHOICE

The most viewed papers in science

NUTRITION

Fruits shrink diabetes risk

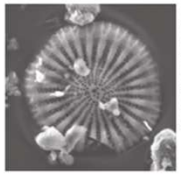
HIGHLY READ on www.bmj.com in August

Three large, long-running health surveys suggest that some fruits — but not fruit juice — reduce the risk of diabetes.

Researchers led by Qi Sun at the Harvard School of Public Health in Boston, Massachusetts, looked at people's reports of how often they ate certain fruits and whether they developed diabetes. Results came from a total of 187,382 US health professionals whose health and habits have been tracked for more than two decades, during which time more than 12,000 of the study participants developed diabetes.

Eating whole fruits such as apples, pears, grapes, raisins and particularly blueberries was associated with a lower risk of diabetes. By contrast, drinking fruit juice was associated with a slight increase in risk, perhaps because juices contain fewer fruit-specific chemicals and introduce more sugar into the bloodstream more quickly.

Br. Med. J. 347, **f5001 (2013)**



ALEXA R. VAN EATON/ DAVID FLYNN

VOLCANOLOGY

Eruption sent microbes flying

Fragments of once-living creatures inside volcanic rocks can help to trace an eruption to its source.

New Zealand's North Island is blanketed in debris from a super-eruption of the Taupo volcano at the island's centre, which happened some 25,000 years ago. A team led by Alexa Van Eaton at the Victoria University of Wellington searched for microfossils in rocks as far as 850 kilometres from the volcano. They found abundant skeletons of algae known as diatoms (**pictured**), including a type that lives only in lakes on the North Island. This confirms the findings of earlier work that the eruption blasted through a lake on that island.

Such fossils could help volcanologists to work out the locations and environmental settings of past eruptions, the authors say. They speculate that volcanoes might even disperse living cells across long distances.

Geology **http://doi.org/nr8 (2013)**

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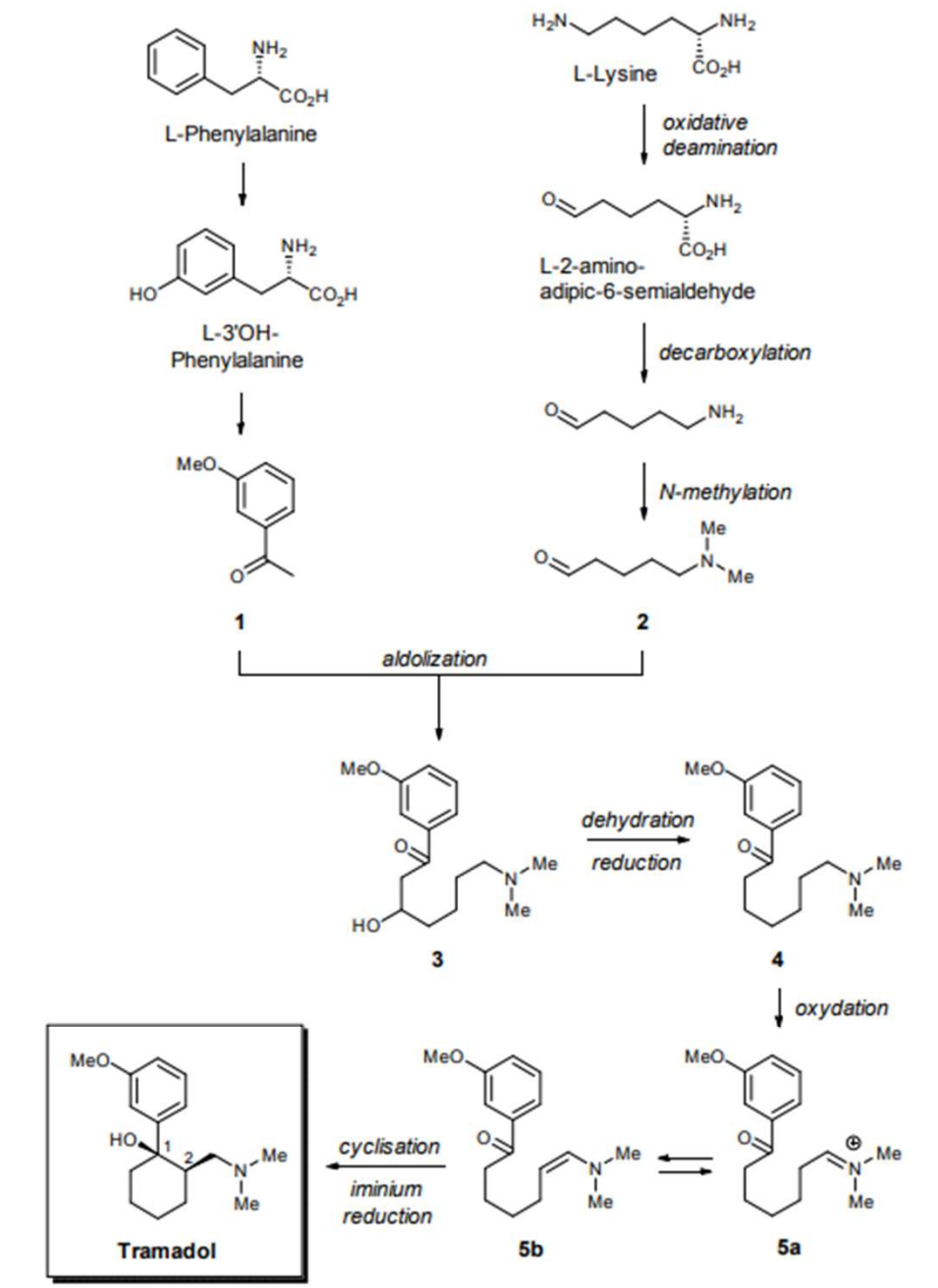


Scheme 1 Key intermediates and steps in the proposed biosynthesis of Tramadol, partially corroborated by a recent position-specific isotope analysis.[8]

TRAMADOL

Le Tramadol, la nouvelle drogue de Gaza

« Depuis la fin de l'intervention militaire israélienne à Gaza en janvier, le tramadol, un anti-douleur très puissant, est devenu la drogue la plus répandue sur ce territoire. Rencontre avec des trafiquants, des consommateurs et des médecins » 27 juillet 2009

https://www.youtube.com/watch?v=0sW4aVjuvlM, consulté le 19 janv 2023

PACLITAXEL

IPAs facilement synthétisables au niveau industriel

Paclitaxel (TAXOL®) – anti-cancer drug

Biological target: tubulin (inhibitor of the tubulin depolymerization)

First discovered in the bark of *Taxus brevifolia* (If du Pacifique)

Côtes du NO de l'Amérique du Nord,

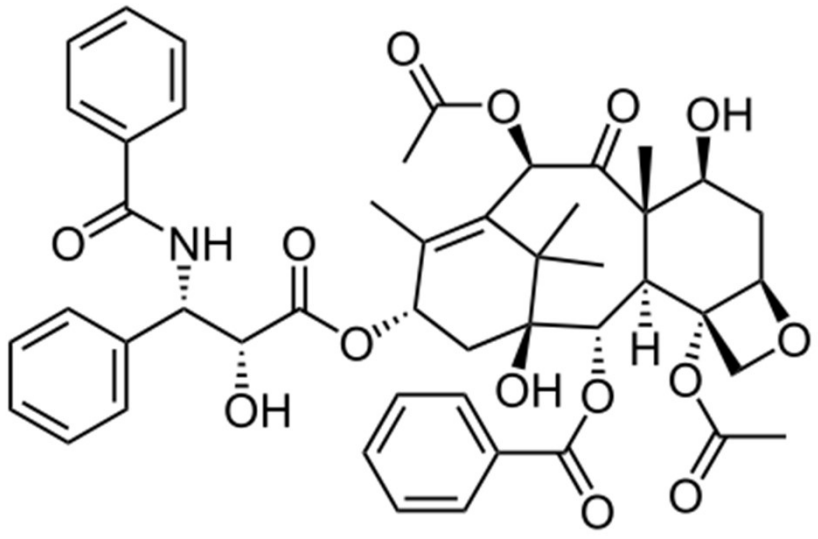
de l'Alaska à la Californie,

Etat de Washington et dans l'Orégon)

To get enough drug to treat one patient:

You need to destroy 8-10 trees

(century old trees)



Diterpènes des feuilles et tiges de divers ifs

PACLITAXEL

Un arbre centenaire produit 3 kg d'écorces, soit au maximum 300 mg de taxol. 7 arbres centenaires (20 kg d'écorces) étaient nécessaires pour traiter 1 malade !!!

Diterpènes des feuilles et tiges de divers ifs présents aussi chez :

- une bactérie, *Erwinia* sp., isolée de *Taxus canadensis,*

- des micromycètes, dont *Taxomyces andreanae,* isolé de l'écorce de l'If du Pacifique, *Taxus brevifolia...*

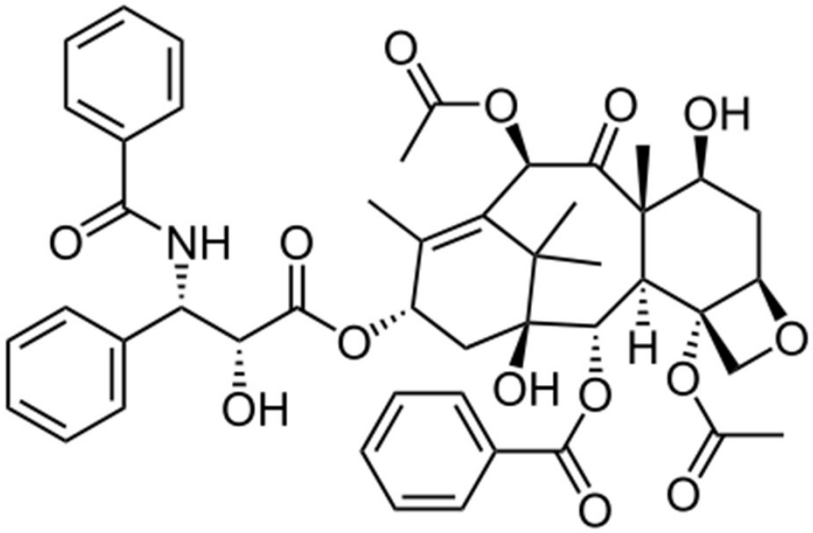
PACLITAXEL

Facilement synthétisable au niveau industriel : **NON**

A success but more than 70 chemical steps…

K. C. Nicolaou et al. Total synthesis of taxol.
Nature **1994**, 367, 630 – 634

Taxol, a substance originally isolated from the Pacific yew tree (Taxus brevifolia) more than two decades ago, has recently been approved for the clinical treatment of cancer patients… The scarcity of taxol and the ecological impact of harvesting it have prompted extension searches for alternative sources including semisynthesis, cellular culture production and chemical synthesis. The latter has been attempted for almost two decades, … Here we report the total synthesis of taxol by a **convergent strategy**, which opens a chemical pathway for the production of both the natural product itself and a variety of designed taxoids.



Synthèse totale : Rdt ≤ 0,06%

Essais de (bio)productions alternatives : Procaryotes / cellules végétales en culture (cellules d'Ifs divers et micro-organismes)

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PACLITAXEL

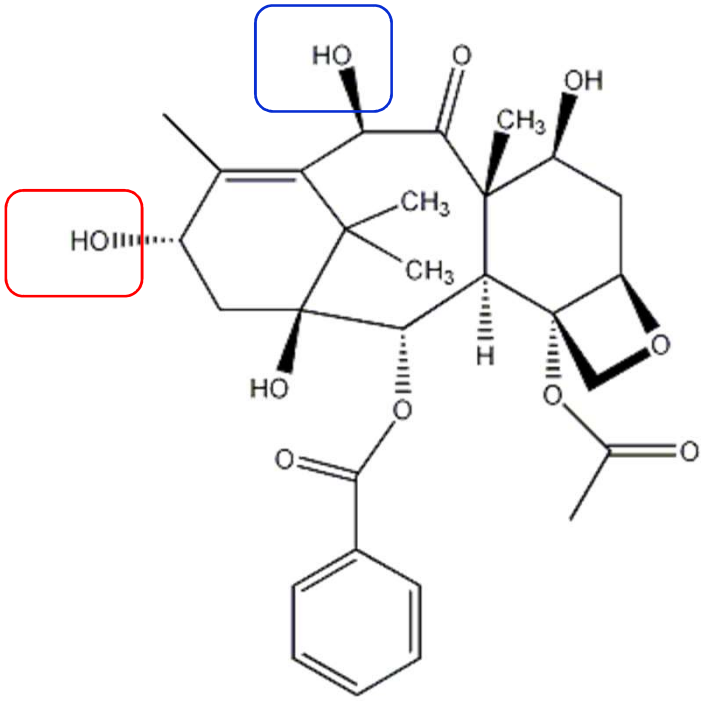
Facilement synthétisable au niveau industriel : **OUI**

The solution: **Hémisynthèse**

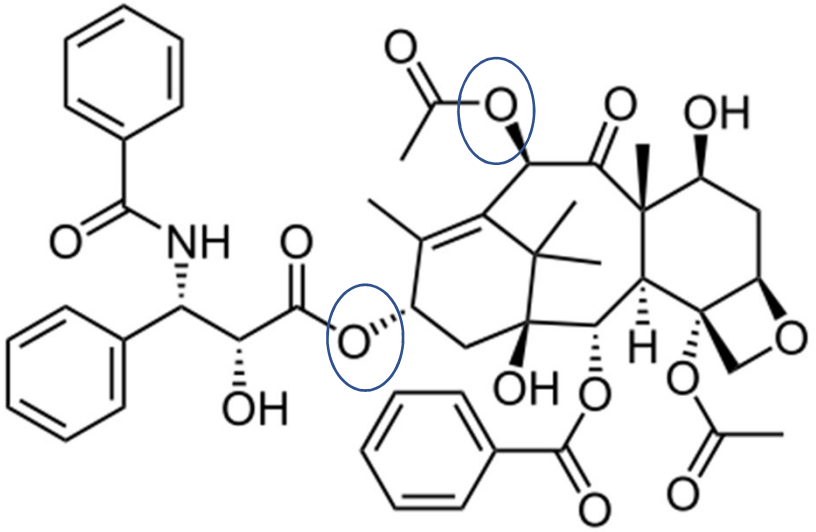
A french researcher (**Pierre Potier**) discovered
a key intermediate (10-deacetyl baccatin III) in *Taxus baccata (needles)* to synthesis paclitaxel via two esterification reactions

PACLITAXEL

10-Désacétylbaccatine III (10-DAB III)

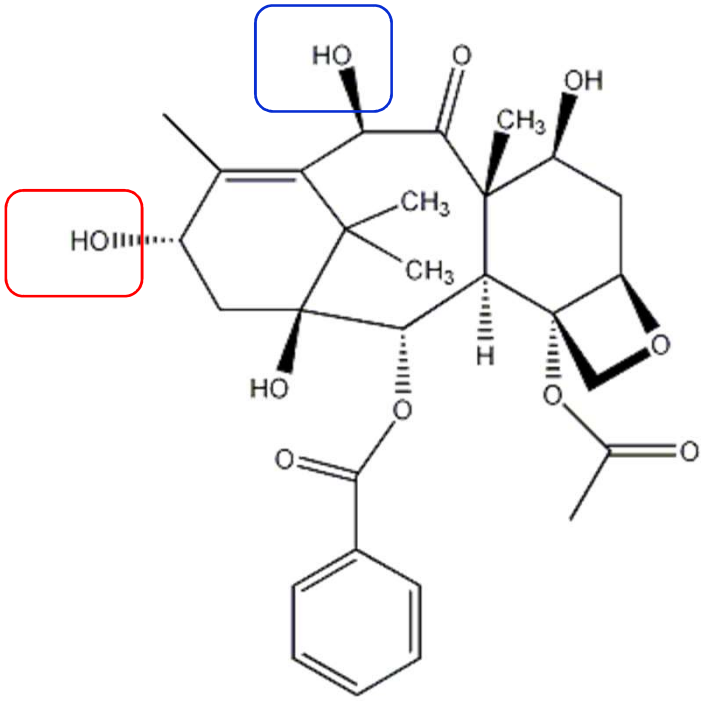


Paclitaxel

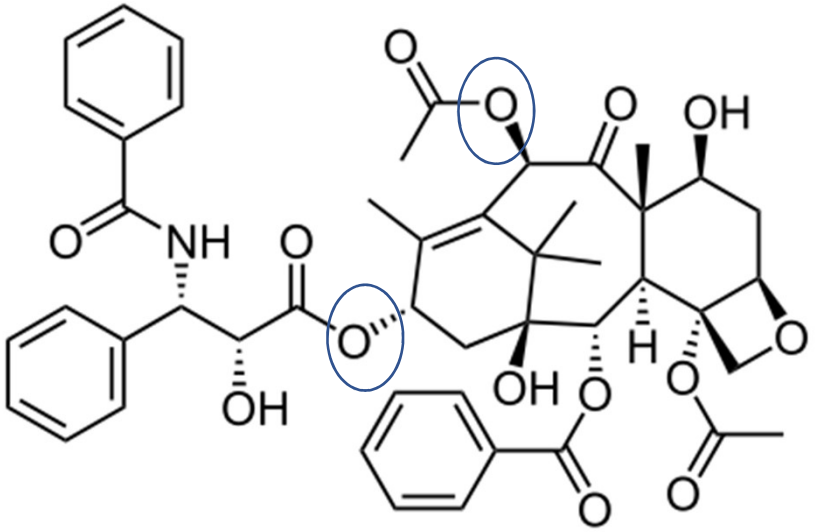


PACLITAXEL

10-Désacétylbaccatine III (10-DAB III)



Paclitaxel



(*2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS*)- 12b-(Acetyloxy)-12-(benzoyloxy)- 1,2a,3,4,4a,6,9,10,11,12,12a,12b-dodecahydro-4,6,9,11-tetrahydroxy- 4a,8,13,13-tetramethyl-7,11-methano- *5H*-cyclodeca(3,4)benz(1,2-b) oxet-5-one

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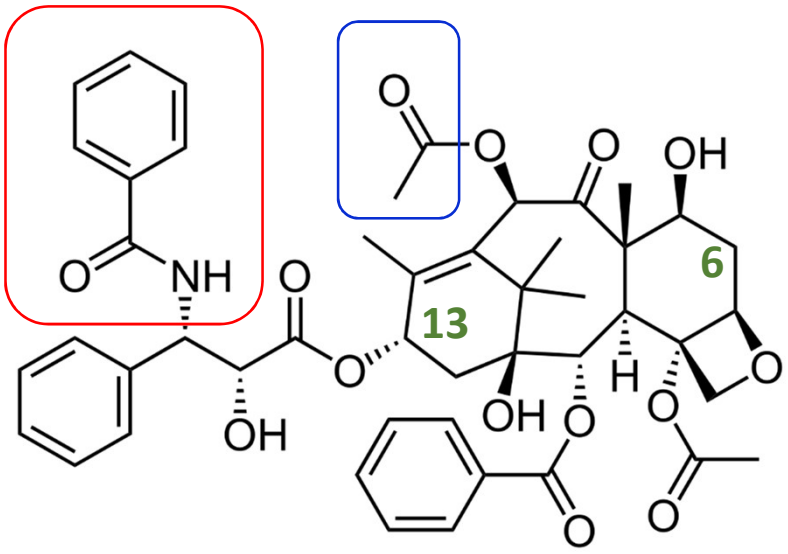
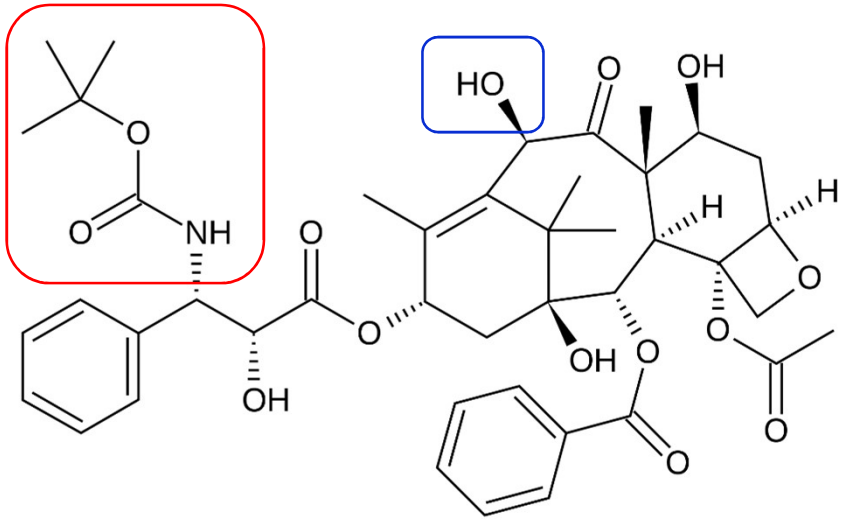
PACLITAXEL

TAXANES
Stabilisants du fuseau

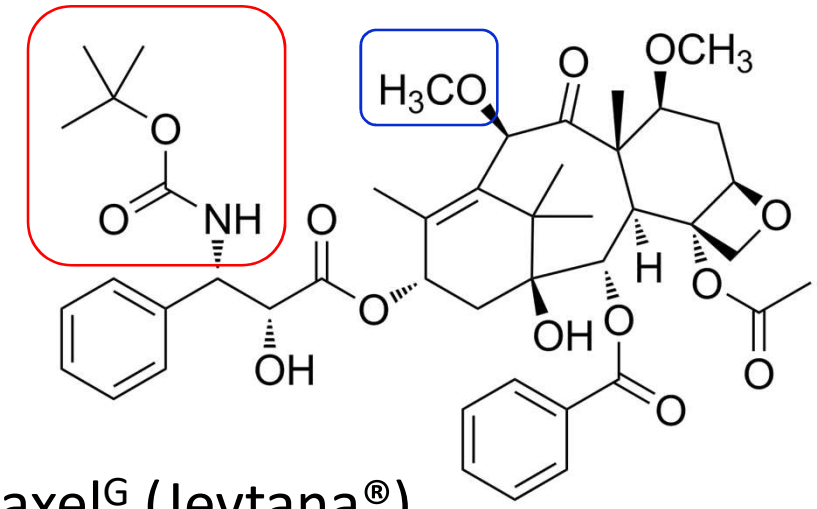


paclitaxel[G]



docétaxel[G]

Il existe également une forme Paclitaxel albumine[G] (Nab-paclitaxel)



cabazitaxel[G] (Jevtana®)

PHARMASEA: ZICONOTIDE

CATEGORIES MEDIAS PLUS PARTENAIRES

DAILY SCIENCE

DÉCOUVREZ LA SCIENCE, LA RECHERCHE ET L'INNOVATION "MADE IN BELGIUM"

CONUS, LE MOLLUSQUE DONT LE VENIN PEUT APAISER LA DOULEUR

Publié le 10 avril 2017

PHARMASEA: ZICONOTIDE

- Oméga conotoxine utilisée pour atténuer les douleurs neuropathiques

- Oméga conotoxine qui se retrouve dans le venin du *Conus magus*, le cône magicien

- Toxines de type oméga sont des peptides d'environ 30 acides aminés qui empêchent la pénétration de calcium dans les terminaisons nerveuses.

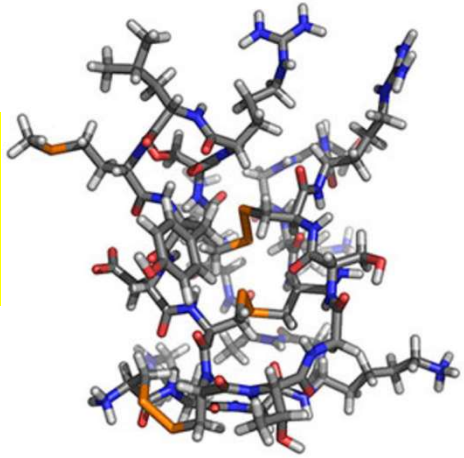
- Antalgique non opioïde

PHARMASEA: ZICONOTIDE

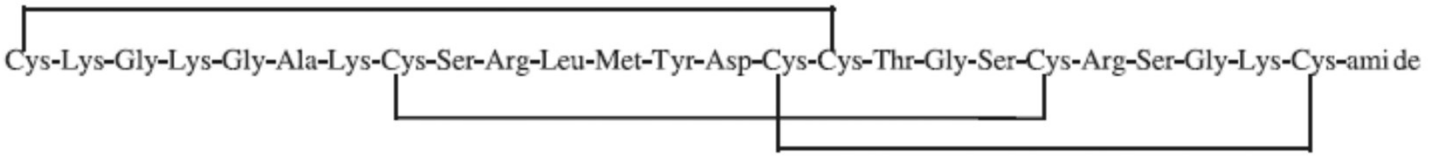
Ziconotide

Prialt® sol p perf

Classé dans les **thérapies intrathécales** (comme morphine, baclofène, certains anesthésiques)



« A synthetic equivalent of a naturally occurring conopeptide found in the piscivorous marine snail, *Conus magus.*
Ziconotide is a 25 amino acid, poly-basic peptide containing three disulfide bridges : $C_{102}H_{172}N_{36}O_{32}S_7$.

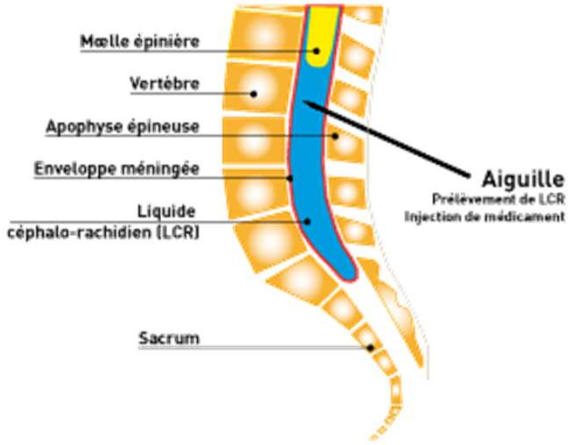


Conotoxine découverte et étudiée dans les années 1980 dans le laboratoire de Baldomero Olivera (Univ. Utah). Vingt-cinq ans plus tard, elle est enfin commercialisée sous sa forme synthétique. Ses atouts ? Elle est dix fois plus efficace que la morphine.

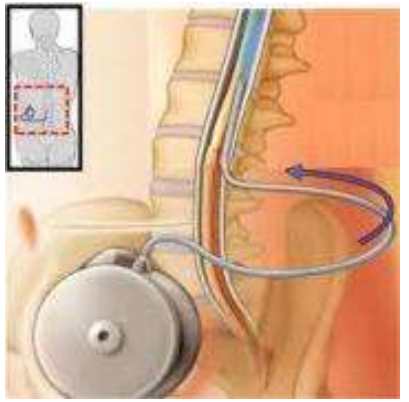
PHARMASEA: ZICONOTIDE

- Franchissement mécanique

injection intrathécale



Etudes menées :
Association ziconotide et baclofène,
Association ziconotide et morphine
→ Douleurs chroniques réfractaires

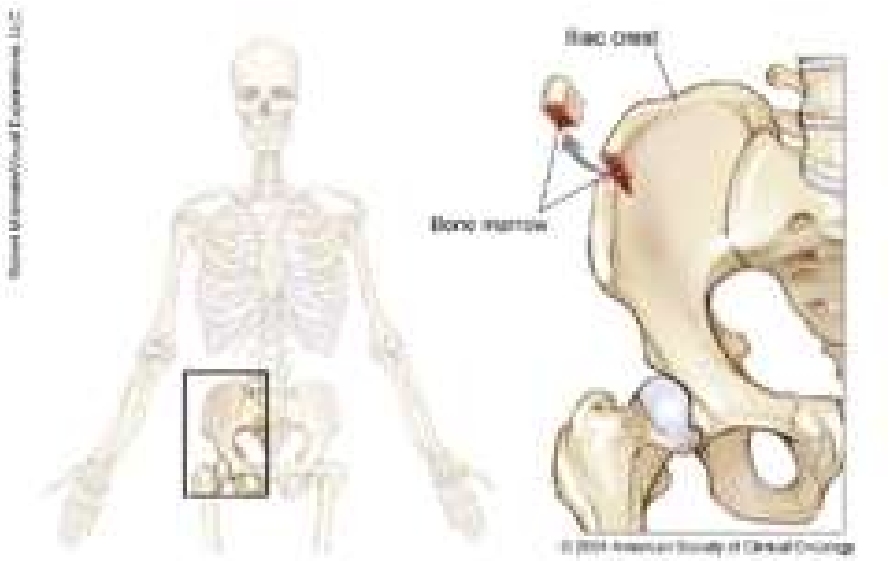


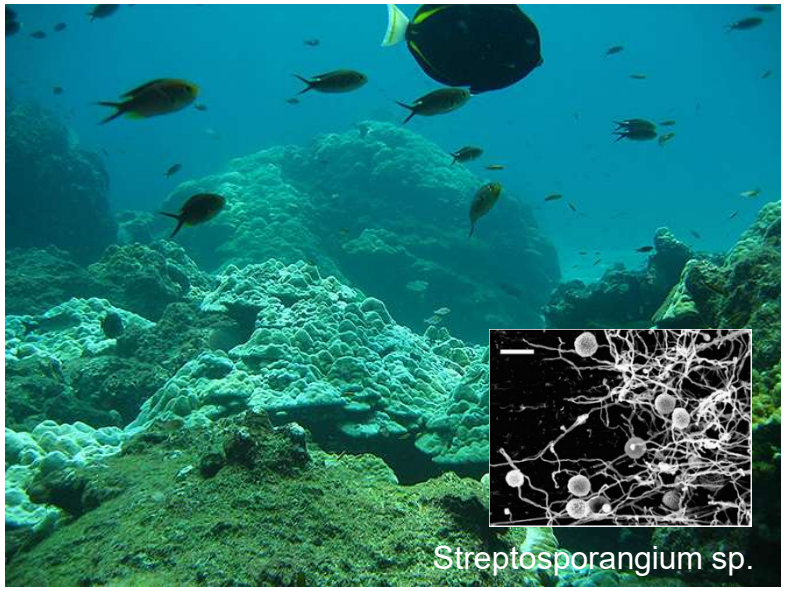
Administration du baclofène (réduire la spasticité) avant mise en place d'une pompe

Spasticité = étirement rapide d'un muscle qui entraîne trop facilement sa contraction réflexe

PHARMASEA: IODININE

Iodinin, a marine compound: New potential selective drugs against leukemia (AML)



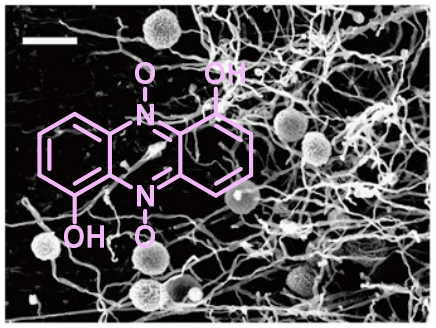


Bio prospecting – treasures from the sea?

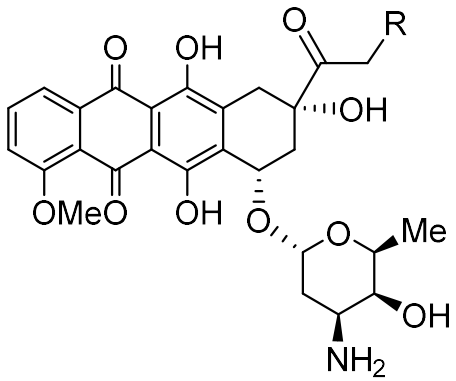
- AML (***A***cute ***M***yeloid ***L***eukemia) – one of the most aggressive cancer forms today!
- The drugs in use (cytarabin, anthracyclines..) – low selectivity – side effects
- Strong medical need for new, more selective drugs in AML therapy

PHARMASEA: IODININE

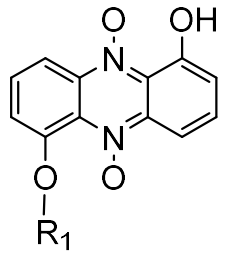
Iodinin, a marine compound: New potential selective drugs against leukemia (AML)

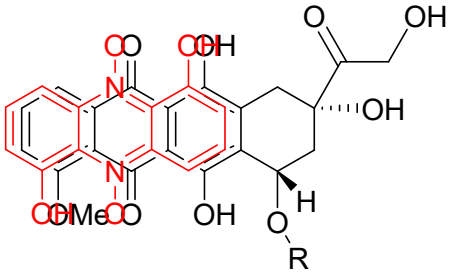


A



B

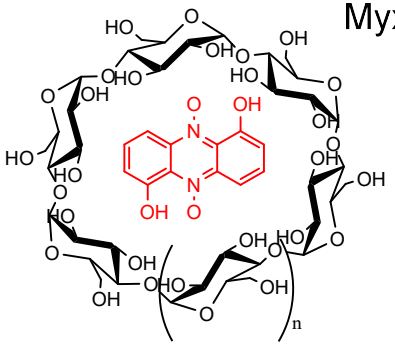




Doxorubicin/Iodinine superimposed

Doxorubicin: R = OH
Daunorubicin: R = H

Iodinin: R1 = H
Myxin: R1 = Me



Iodinine cyclodextrin (UCB Lyon)

Døskeland, SO, L. Herfindal *et al,* Mar. Drugs **2013**, *11*, 332-349;

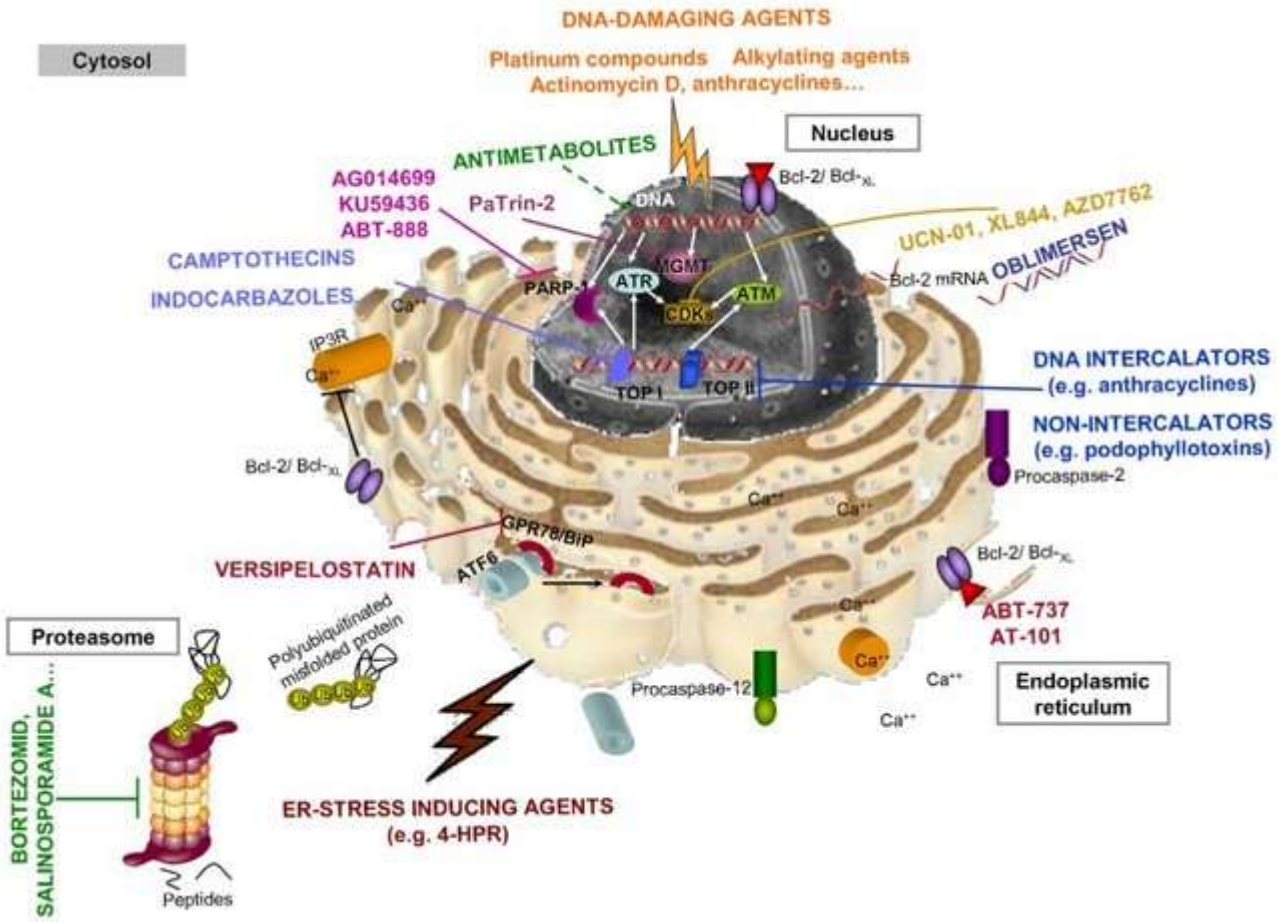
Partie 2 : Exploration et investigation autour des cellules humaines

- Découvrir comment nos cellules fonctionnent et ainsi de nouvelles aventures démarrent…

Cancers (Basel). 2011 Mar 3;3(1):1042-80. doi: 10.3390/cancers3011042.

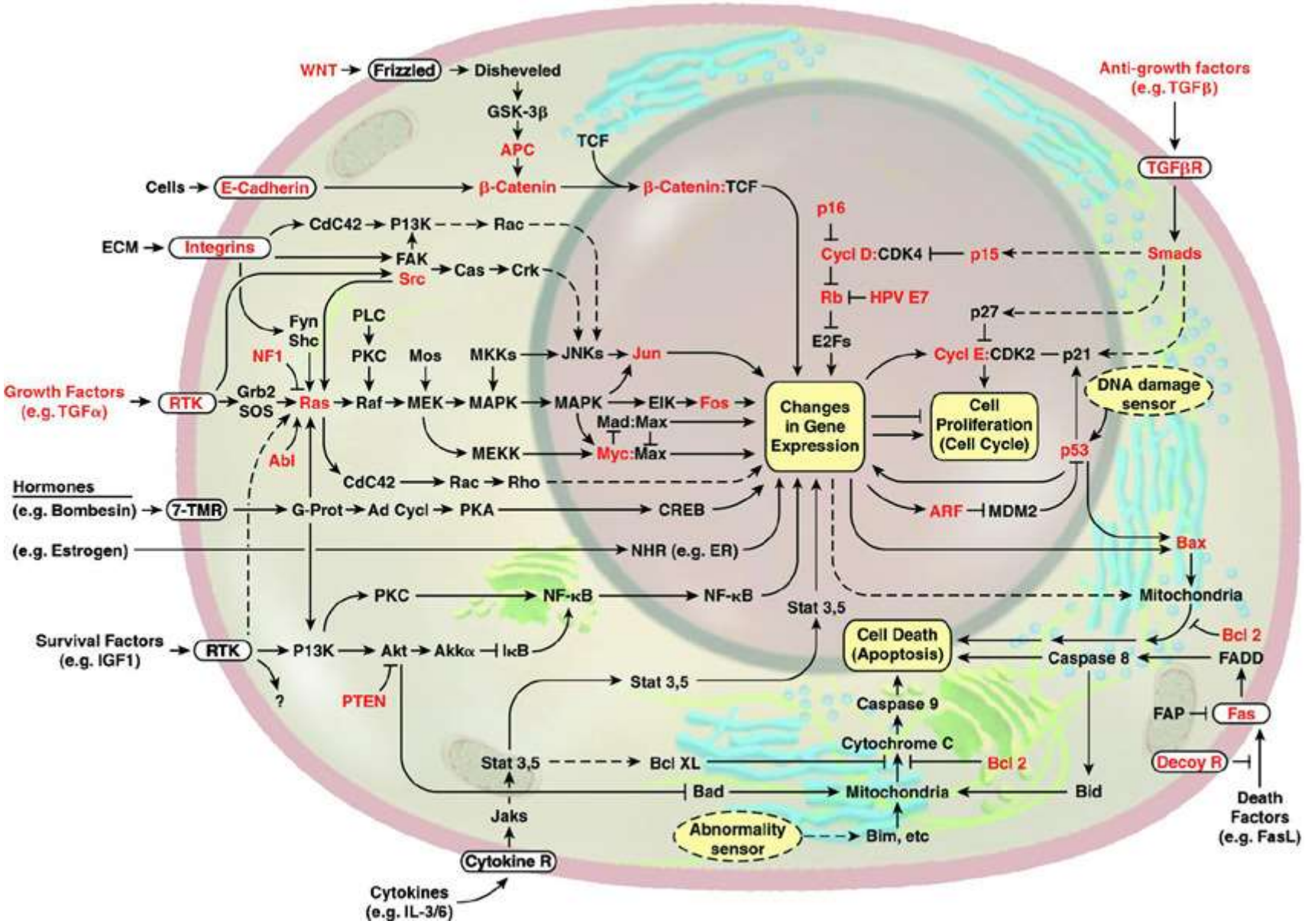
Cell-centric view of apoptosis and apoptotic cell death-inducing antitumoral strategies.

Apraiz A[1], Boyano MD, Asumendi A.



Classical Chemotherapy (without precise or known molecular target)	Specific Molecule-Targeted Agents
1. DNA damaging agents 1.1. Platinum compounds (e.g., cisplatin, carboplatin, oxaliplatin) 1.2. Alkylating agents (nitrogen mustards) 1.3. Cytotoxic antibiotics (e.g., actinomycin D, anthracyclines, mitomycins, bleomycins)	**1. Bcl-2 (and related molecule) targeted compounds** (e.g., AT-101, ABT-737, oblimersen sodium)
2. Oxidative stress-mediated cell death inducers (e.g., 4-HPR, PEITC)	**2. DNA damaging agents** 2.1. Antimetabolites (e.g., methotrexate) 2.2. DNA topoisomerase (I and II) inhibitors (e.g., camtothecins, podophyllotoxins)
	3. Drugs to target DNA-damage repairing systems 3.1. CDK inhibitors (e.g., UCN-01, XL844) 3.2. PARP-1 inhibitors (e.g., AG014699) 3.3. MGMT inhibitors (e.g., PaTrin-2)
	4. Telomere/Telomerase-targeted anticancer drugs (BIBR1532, telomestatin, BRACO19)
	5. Compounds to disrupt cytoskeleton dynamisn (Vinca alkaloids, taxanes, epothilones)
	6. ER-stress response altering agents **Proteasome inhibitors** 6.1. Proteasome inhibitors (e.g., bortezomib, salinosporamide A) 6.2. Inhibitors of unfolded protein response (UPR) molecules (e.g., versipelostatin)
	7. Kinases inhibiting agents 7.1. Antibody-based therapies (e.g., beracizumab, trastuzumab) 7.2. Small molecule-based therapies (e.g., imatinib, erlotinib, AZD1152, temsirolimus)
	8. Others 8.1. IAP inhibitors 8.2. Lysosome permeabilization inducing agents 8.3. Mitochondria-targeted compounds

Le Boom de la Thérapie ciblée



Douglas Hanahan and Robert A. Weinberg, The Hallmarks of Cancer, Cell, Vol. 100, 57–70, January 7, 2000

Partie 2 : Exploration et investigation autour des cellules humaines

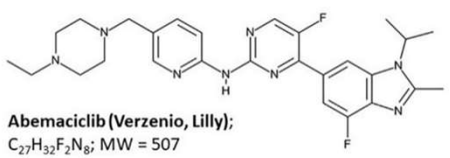
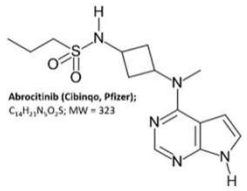
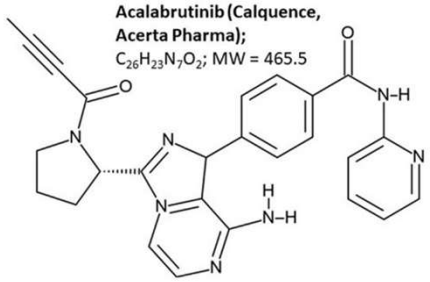
- Découvrir comment nos cellules fonctionnent et ainsi de nouvelles aventures démarrent

- Le boom des thérapies ciblées
    - [Inhibiteurs de kinases (IKs)]
    - Anticorps conjugués (ADCs)
    - Dégradeurs de protéines ciblés (PTD)
        - PROTACs
        - Incroyable retour « en grâce » du thalidomide
        - Colles moléculaires (molecular glues)

Inhibiteurs de kinases (IKs)

From the Blue Ridge Institute for Medical Research curated by R Roskoski Jr — BRIMR. — 29-mai-21

US Food and Drug Administration approved small molecule protein kinase inhibitors[a,b]

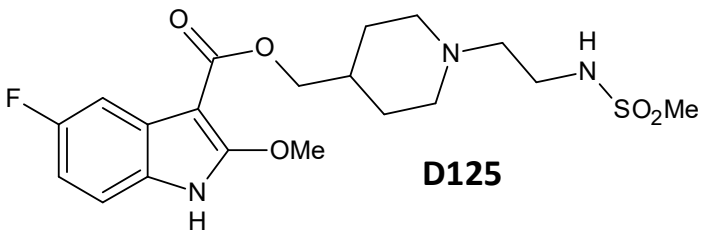
Drug[c]	Structure	Company	MW	D[d]	A[d]	Total rings	Aromatic rings	ALogP	cLogD[e]	Rotatable bonds	Inhibtor type[f]	Year approved	Known targets	Class of kinase[g]	Disease	Monthly cost in USA (2018) JAMA 321 2025 2019	FDA label
Abemaciclib, LY2835219, Verzenio, 6ZV, PDB ID: 5L2S with CDK6	 Abemaciclib (Verzenio, Lilly); $C_{27}H_{32}F_2N_8$; MW = 507	Lilly	507	1	9	5	4	4,9	3,8	7	I1/2B	2017	CDK4/6	S/T	Breast Ca		For the label click here
Abrocitinib, PF-04965842, Cibinqo, PDB ID: 6BBU, with JAK1, 6BBV, with JAK2	 Abrocitinib (Cibinqo, Pfizer); $C_{12}H_{17}N_5O_2S$; MW = 323	Pfizer	323	2	6	3	2	1,3	0,8	6	I	2022	JAK1	NRY	Atopic dermatitis		For the label click here
Acalabrutinib, ACP-196, Calquence	 Acalabrutinib (Calquence, Acerta Pharma); $C_{26}H_{23}N_7O_2$; MW = 465.5	Acerta Pharma	466	2	6	5	4	3,3	2,6	4	VI	2017	Bruton tyrosine kinase	NRY	Mantle cell lymphoma, CLL, small cell lymphoma	$14 065	For the label click here

http://www.brimr.org/PKI/PKIs.htm, accessed Jan 19, 2023 – **73 FDA-approved KIs**

ISPB Lyon 1

XPLOR_CK2

INHIBITORS OF THE INTERFACE CK2α-CK2β



D125

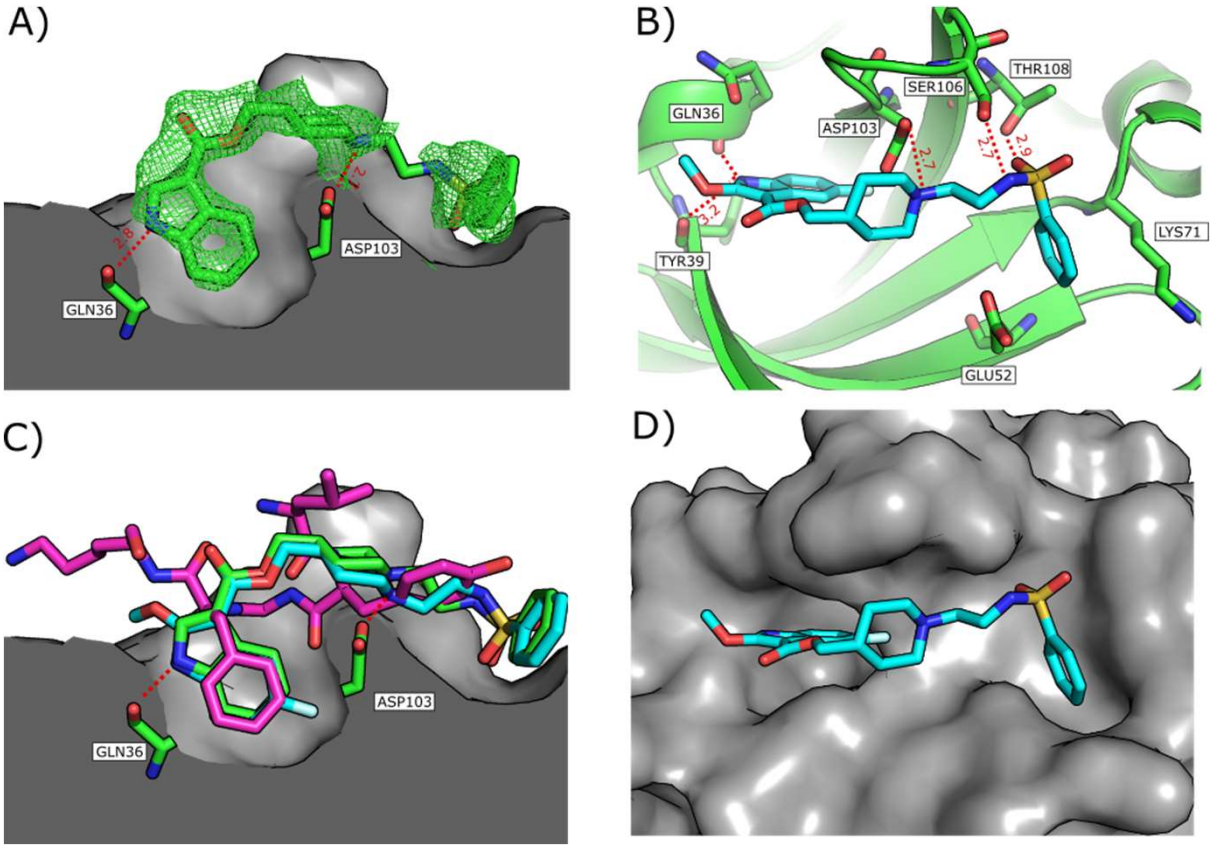
The Crystal structures of 4 and 6 bound to CK2α.

A) The structure of **4** (green, pdb:6FVF) bound to the interface site of CK2α.

B) The Interactions of **6** (blue, pdb:6FVG) with the interface site of CK2α (green).

C) The superimposed structures of **4** (green), **6** (blue) and CK2β (purple) binding in the interface site of CK2α.

D) The structure of **6** binding to the interface site of CK2α shown as the surface representation.

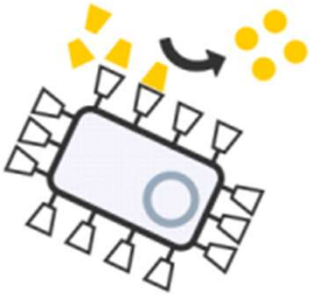


Kufareva I. et al. Discovery of holoenzyme-disrupting chemicals as substrate-selective CK2 inhibitors. Sci Rep. 2019;9:15893

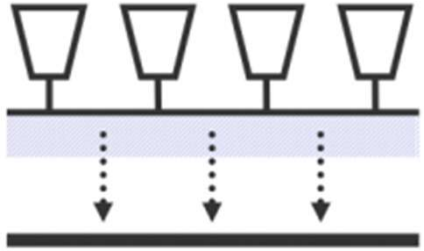
XPLOR_CK2: AUTODISPLAY BIOTECHNOLOGY

STARTING POINT: BIOPRODUCTION OF PROTEIN KINASE CK2

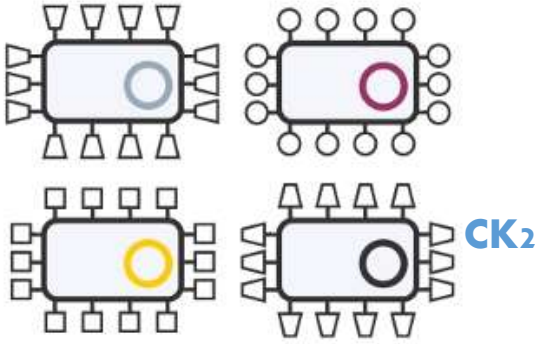
Whole Cell Biocatalysts



Functionalizing Solid Surfaces

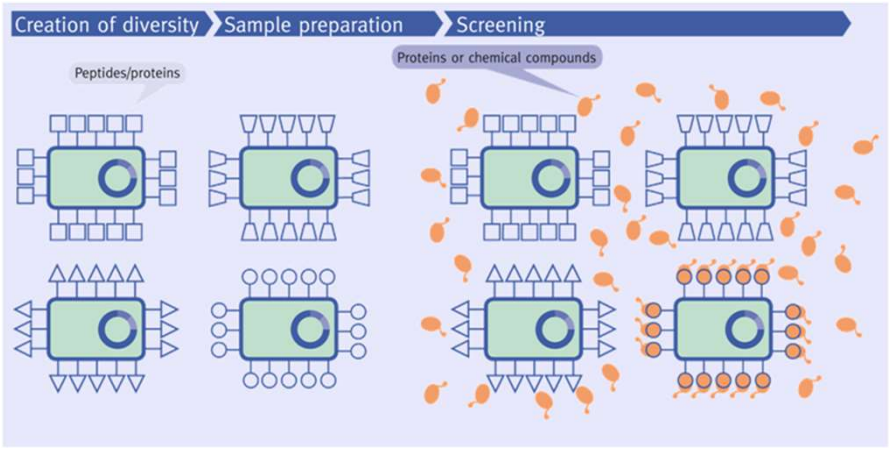


Faster Screening



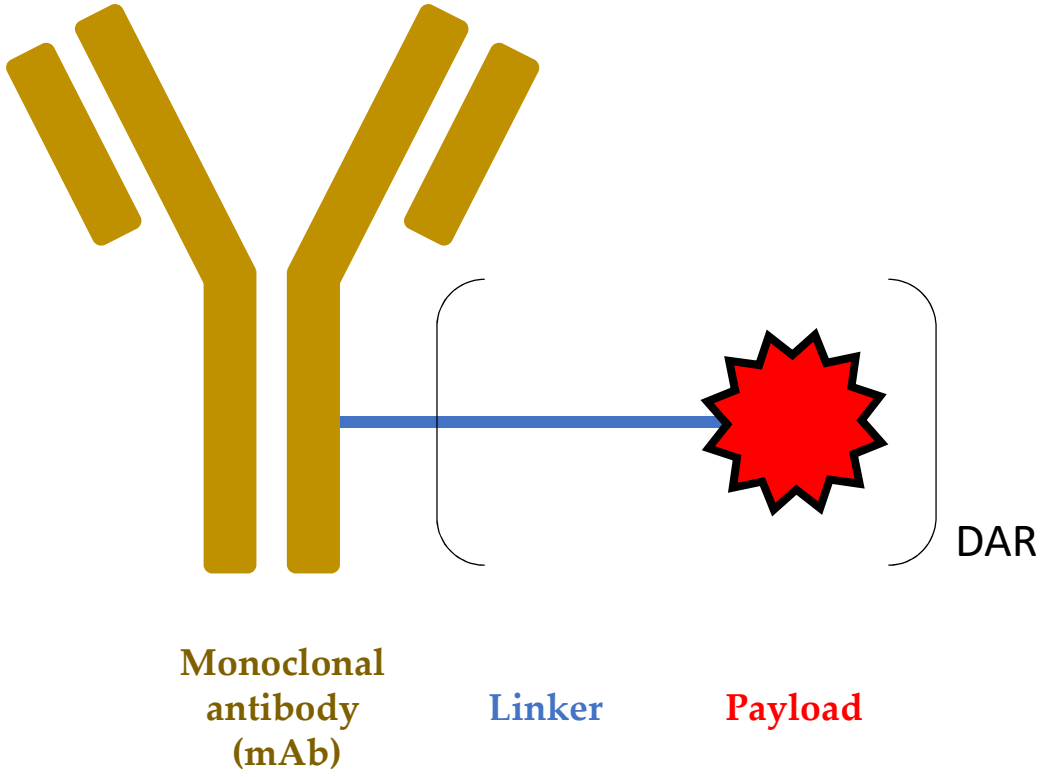
Gratz A. *et al.* Functional display of heterotetrameric human protein kinase CK2 on *Escherichia coli*: a novel tool for drug discovery. **Microb Cell Fact 2015**

Bollacke A. *et al.* Toward selective CK2alpha and CK2alpha' inhibitors: Development of a novel whole-cell kinase assay by Autodisplay of catalytic CK2alpha'. **J Pharm Biomed Anal. 2016**



Anticorps conjugués (ADCs)

TRIPARTITE MOLECULE



mAb

Payload

Drug

- **DAR**

Linker

- **Cleavable**
- **Non-cleavable**

Therapeutic window

Pharmacokinetics

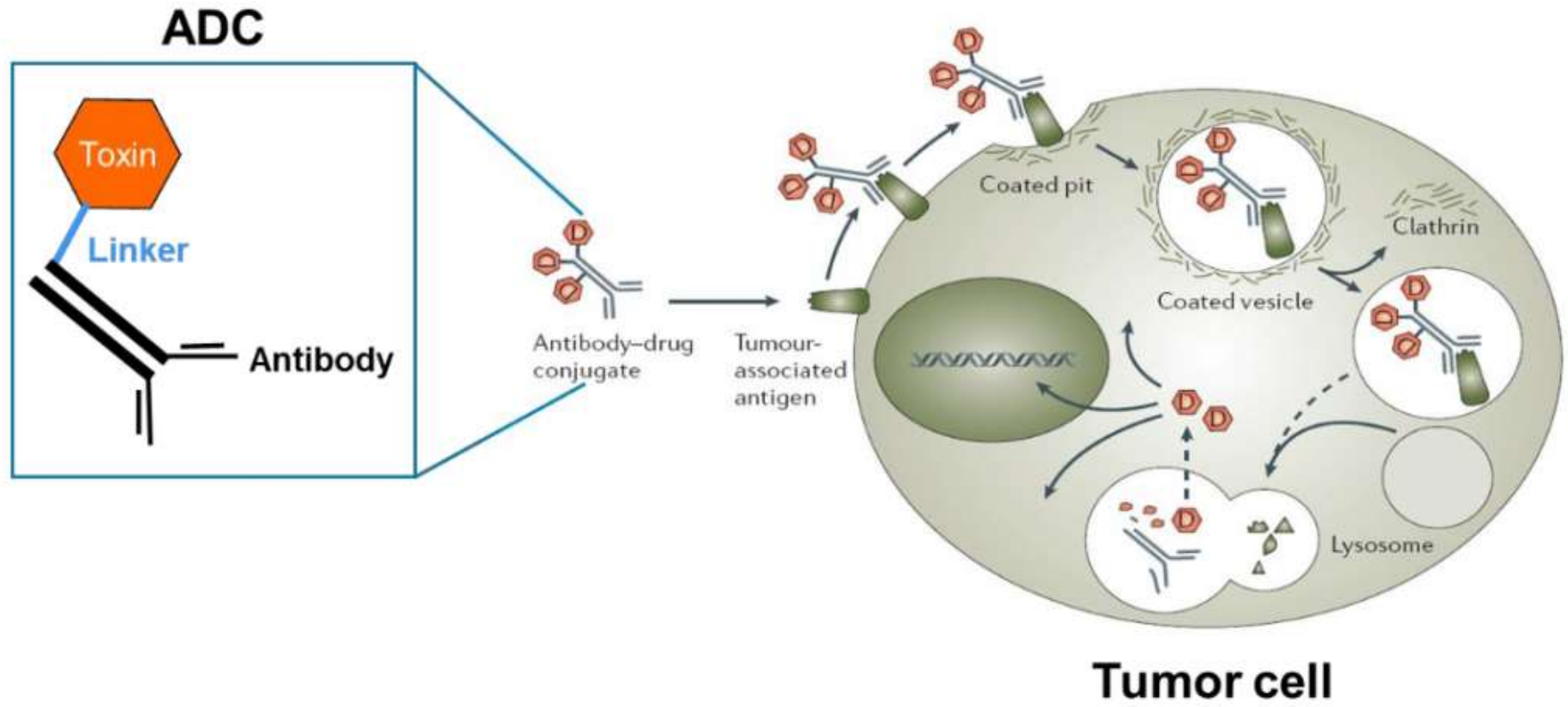
Toolbox

- **Quality control**

Conjugation methods (Chemical, Enymatic)

ANTIBODY DRUG CONJUGATES: HISTORY

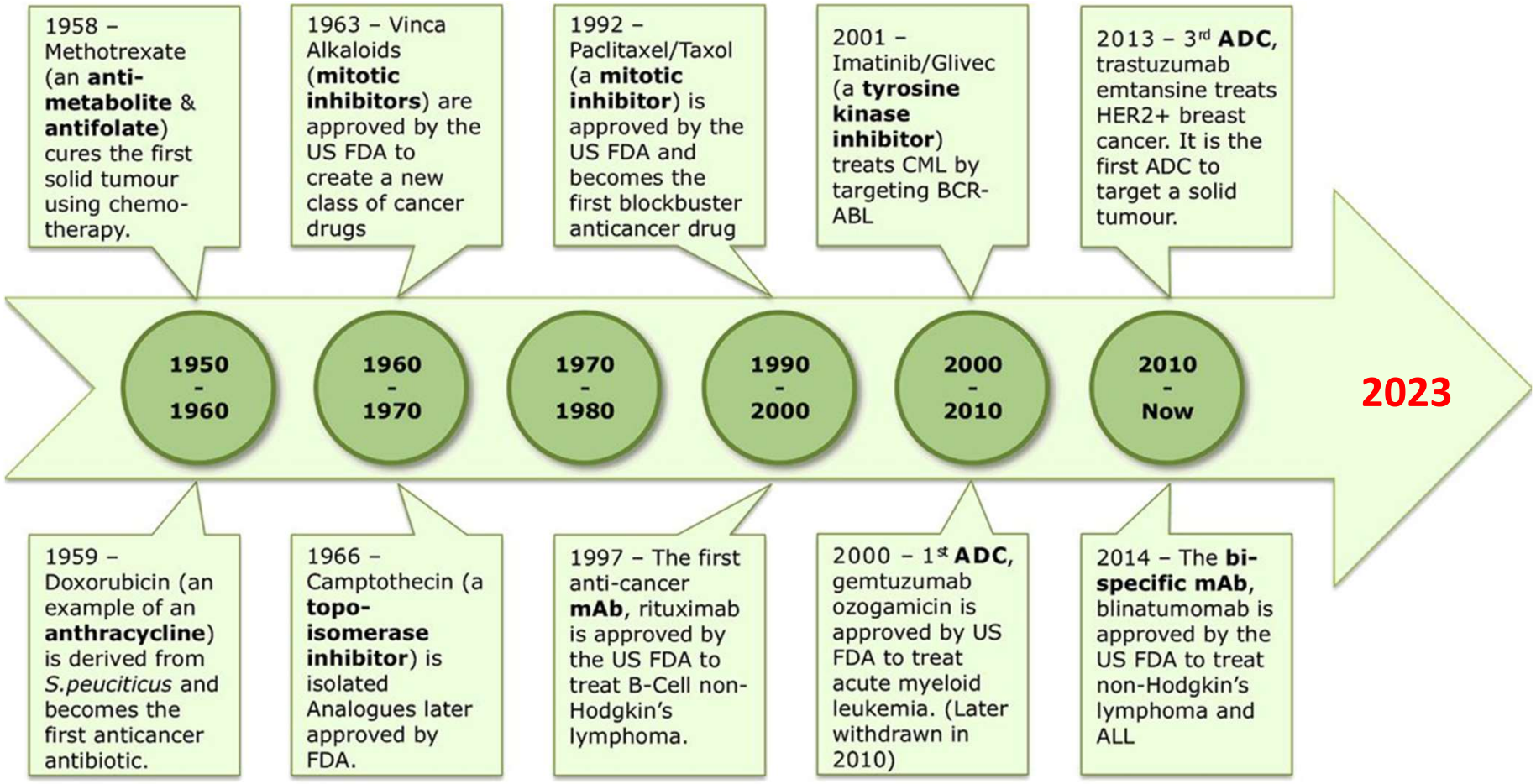
Reconnaissance Anticorps-Antigène



https://labiotech.eu/features/antibody-drug-conjugates-adc-review/, accessed Nov 08, 2022

ANTIBODY DRUG CONJUGATES: HISTORY

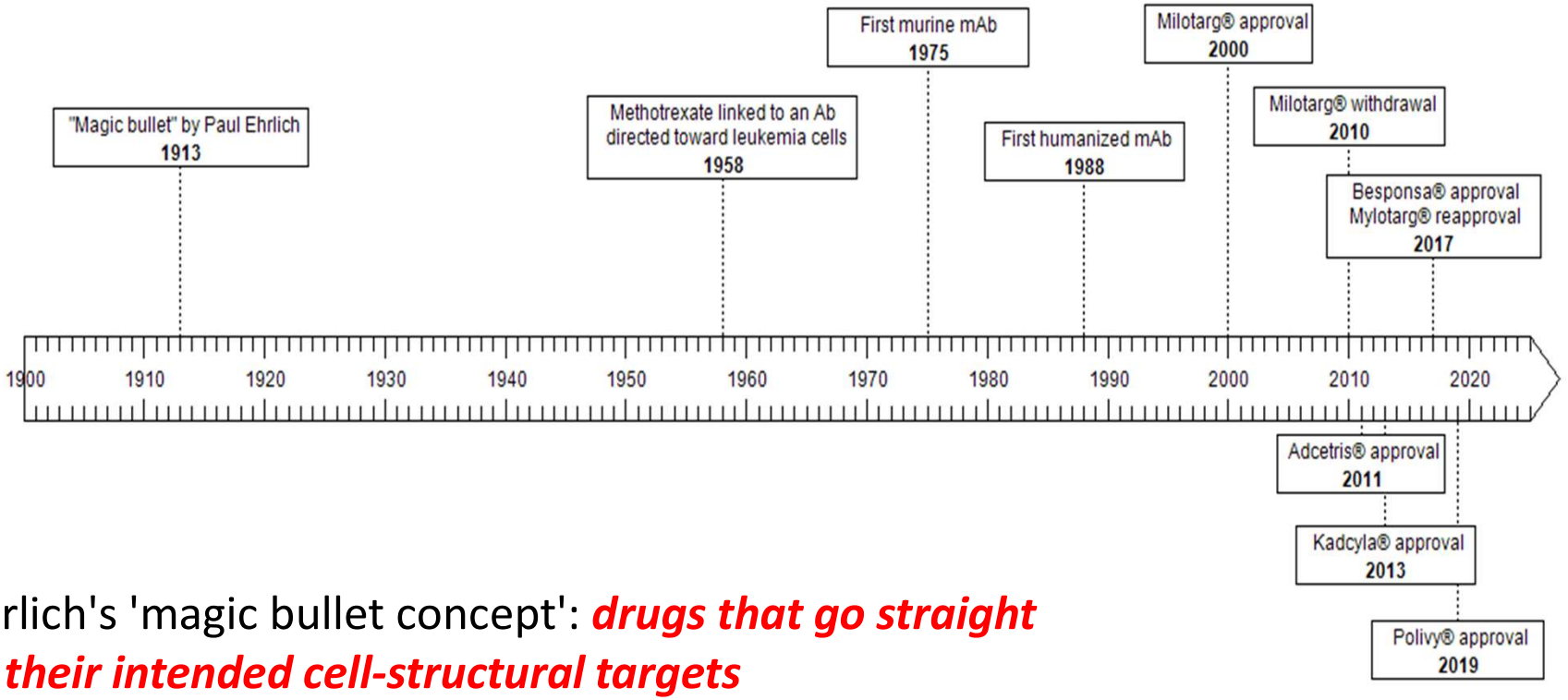
Nature : point de départ de la saga…



Peters C et al. Antibody–drug conjugates as novel anti-cancer chemotherapeutics**.** Bioscience Reports Jul 14, 2015, 35 (4) e00225; DOI: 10.1042/BSR20150089

ANTIBODY DRUG CONJUGATES: HISTORY

Simplified timeline



Ehrlich's 'magic bullet concept': ***drugs that go straight to their intended cell-structural targets***

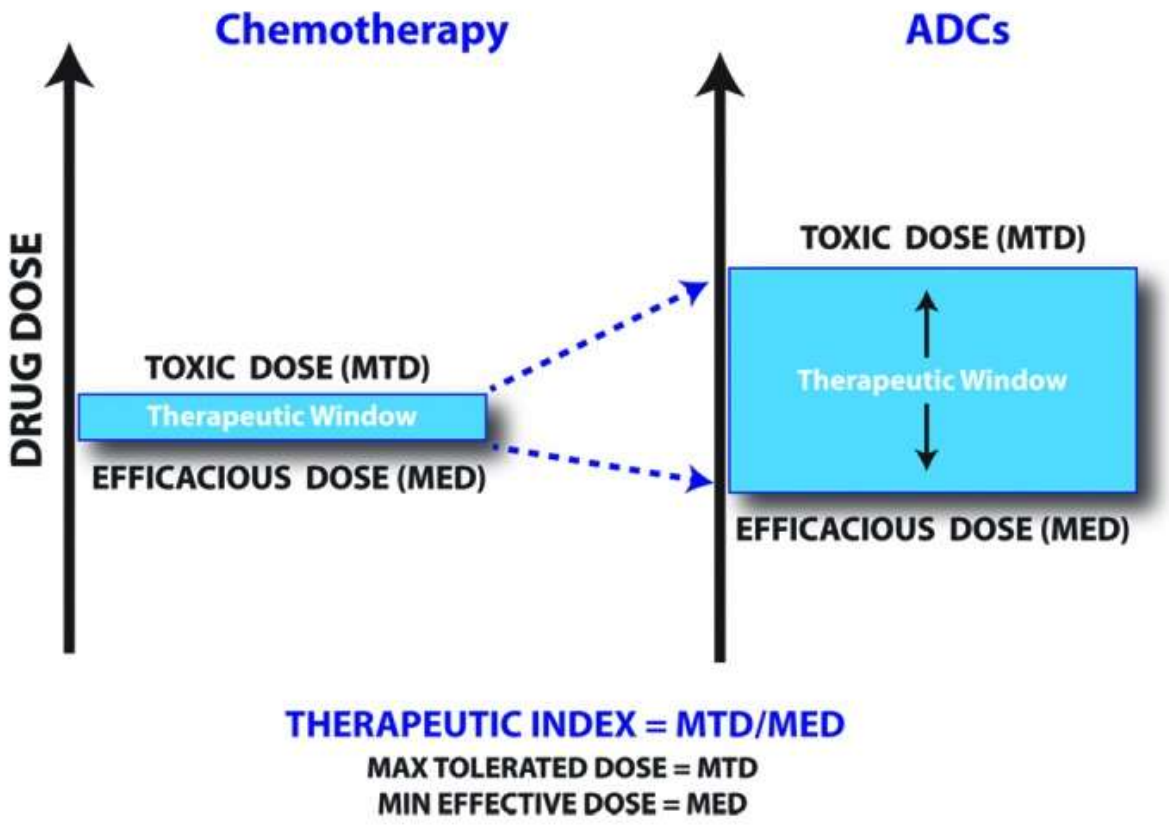
“wir müssen chemisch zielen lernen”
(“we have to learn how to aim chemically”)

→ **ADCs conform to this concept**

ANTIBODY DRUG CONJUGATES: KEY POINTS

THERAPEUTIC WINDOW

Figure 1. ADCs expand the therapeutic window. ADC therapeutics can increase efficacy and decrease toxicity in comparison to traditional chemotherapeutic cancer treatments. Select delivery of drugs to cancer cells increases the percent of dosed drug reaching the tumor, thus lowering the minimum effective dose (MED). The maximum tolerated dose (MTD) is increased, as less drug reaches normal, non-target tissue due to targeted delivery by the antibody. Taken together, the therapeutic window is improved by the use of ADCs

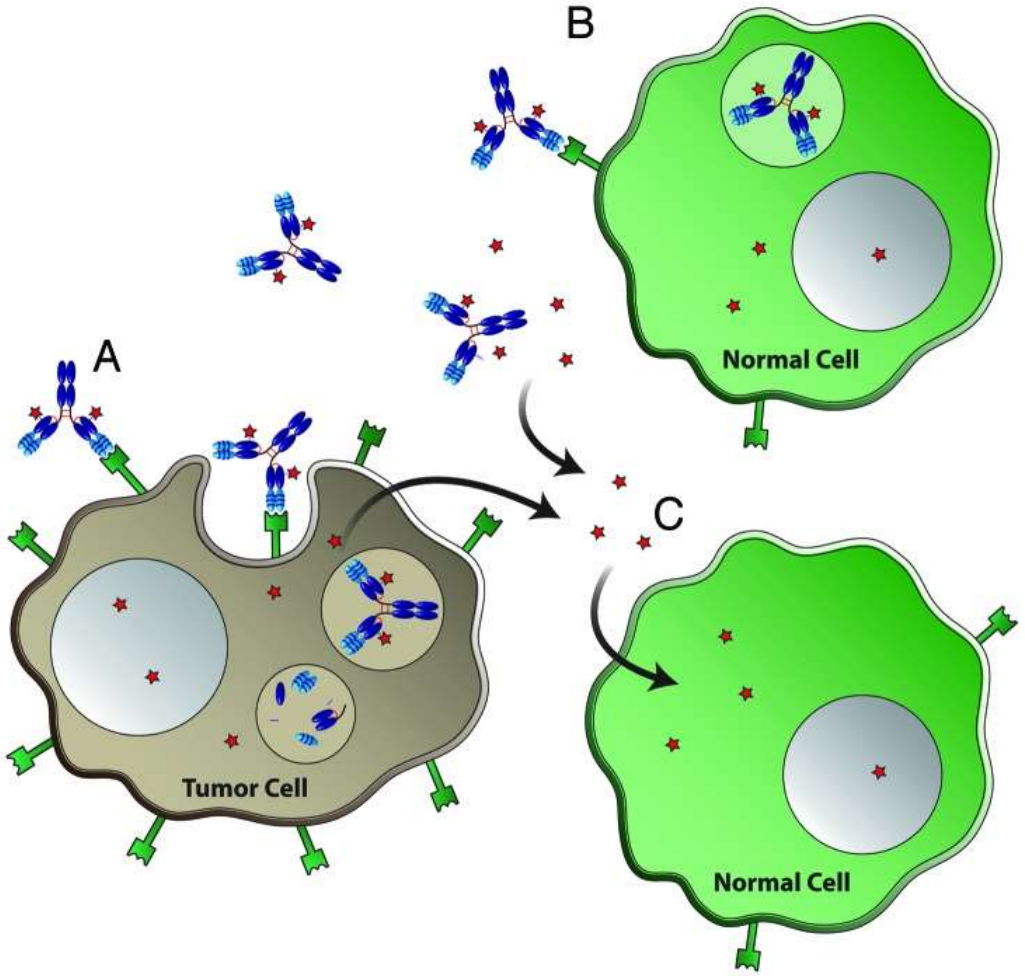


S. Panowski *et al*. Site-specific antibody drug conjugates for cancer therapy. mAbs 2014;6(1):34–45

ANTIBODY DRUG CONJUGATES: KEY POINTS

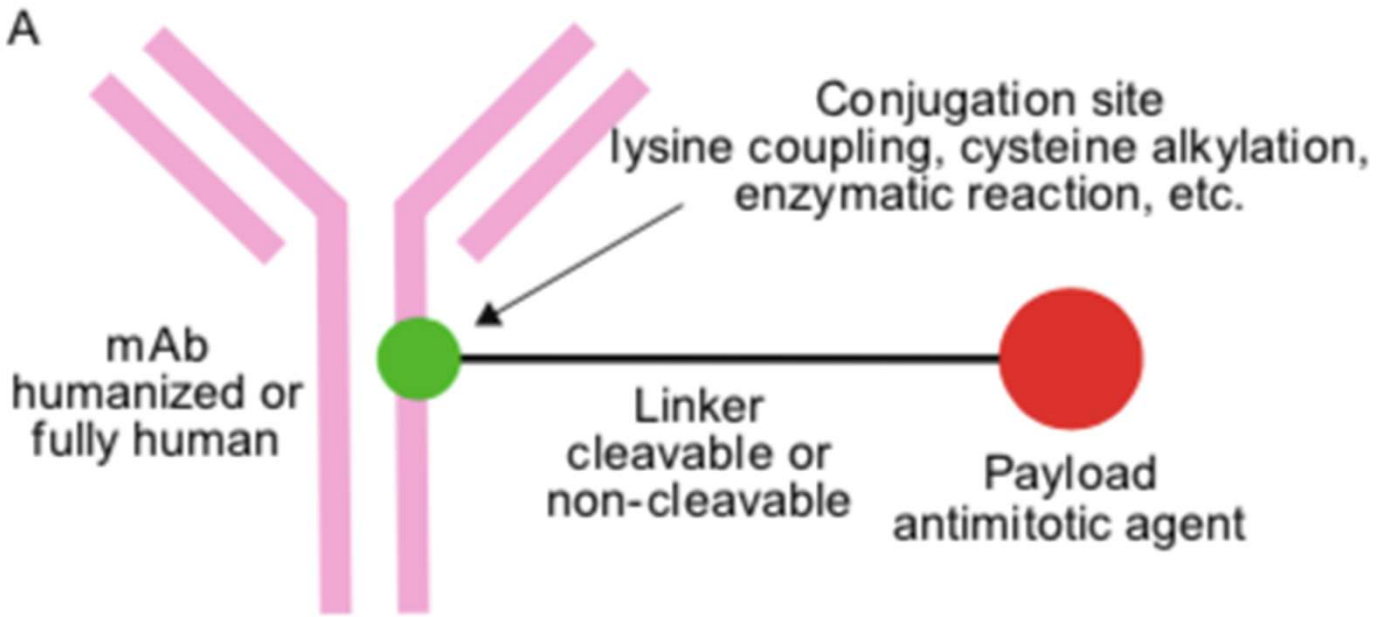
PHARMACOKINETICS

Figure 4. ADC metabolism in vivo. The therapeutic window of an ADC depends on the optimization of the delicate balance between efficacy and toxicity.
(**A**) The desired effect of ADCs is the target-dependent killing of tumor cells expressing high levels of target antigen. Side effects can be caused by (**B**) target-dependent toxicity and killing of normal cells expressing low levels of target antigen, or (**C**) by target-independent toxicity caused by entry of free drug into normal cells. Free drug can be released by ADC catabolism or **by unstable labile linkers in the plasma**



S. Panowski *et al*. Site-specific antibody drug conjugates for cancer therapy. mAbs 2014;6(1):34–45

ANTIBODY DRUG CONJUGATES: A tripartite drug

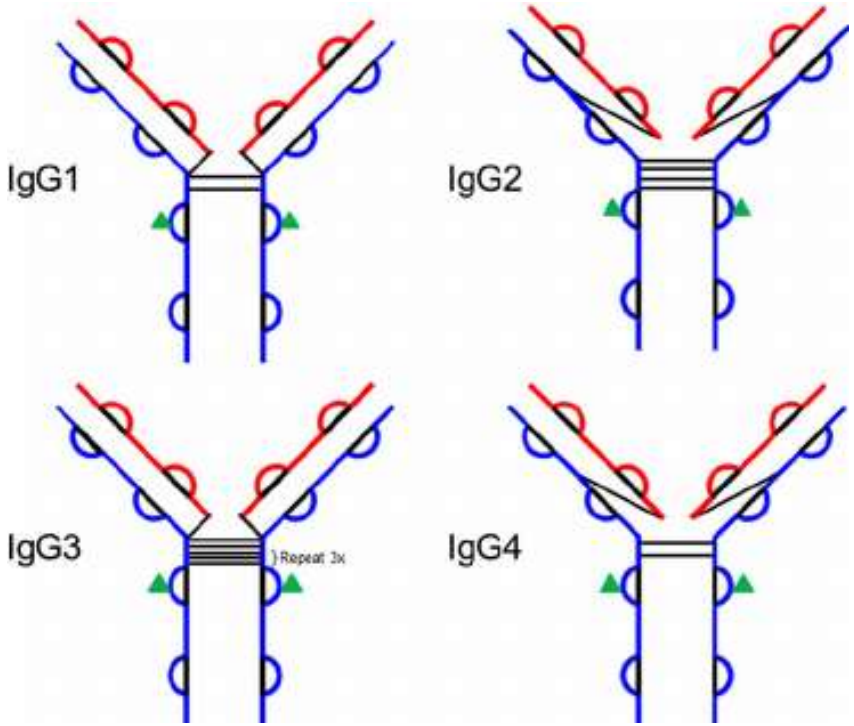


Tsuchikama K, An Z. Antibody-drug conjugates: recent advances in conjugation and linker chemistries. Protein Cell. 2018;9(1):33-46

ANTIBODY DRUG CONJUGATES: mAb

IgG1 are the most abundant in the blood (66%). Next come IgG2 (23%), IgG3 (7%) and finally IgG4, the least abundant (4%).

The IgG subclasses are differentiated by the number of S-S bridges between the heavy chains with 2 for IgG1 and IgG4, 4 for IgG2 or 15 for IgG3

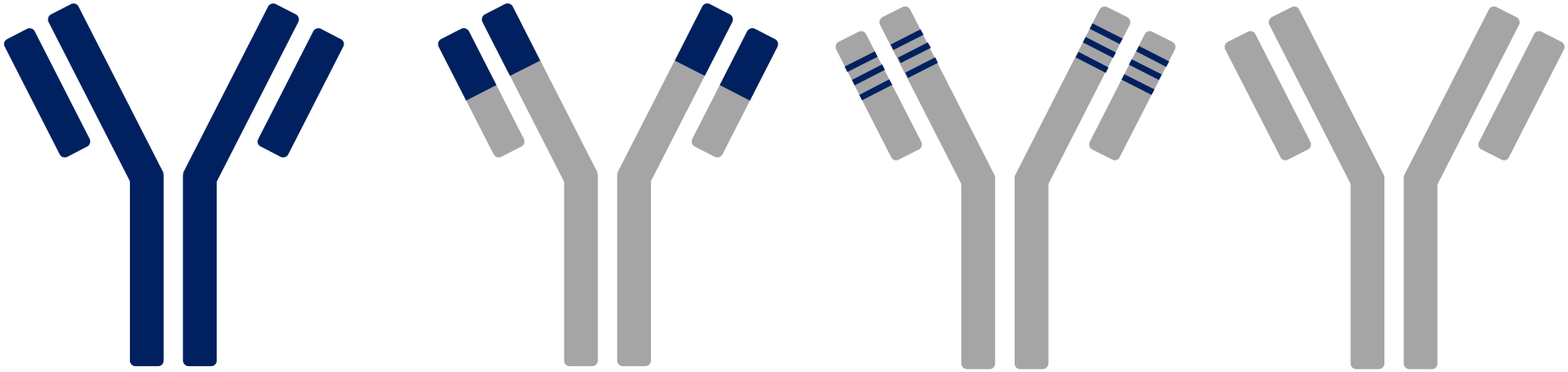


Schematic representations
of IgG subclasses.
Adapted from Correia IR (2010)
Stability of IgG isotypes in serum.
MAbs 2:221-232

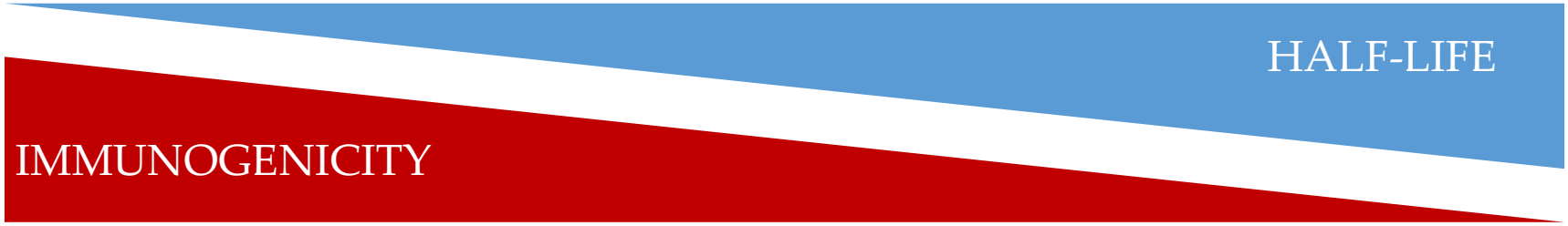
Molecules. 2021 May 15;26(10):2943. doi: 10.3390/molecules26102943.

ANTIBODY DRUG CONJUGATES: mAb

Mouse sequence
Human sequence



Murine	Chimeric	Humanised	Human
-momab	-ximab	-zumab	-mumab



ISPB Lyon 1

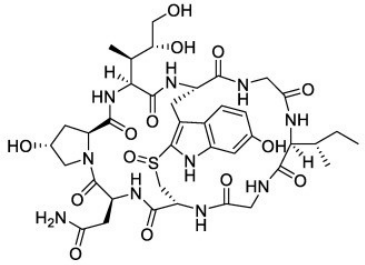
ANTIBODY DRUG CONJUGATES: PAYLOADS

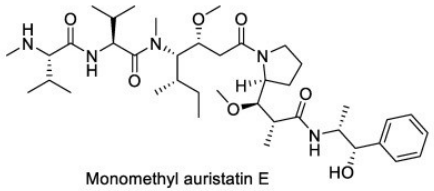
- Drug/payload/cytotoxic agent/cytotoxic warhead
- A large structural diversity of payloads is used to design ADCs
- Several main groups of payloads are actually studied for designing ADCs
- INN of payloads are usually the combination of drug + linker:

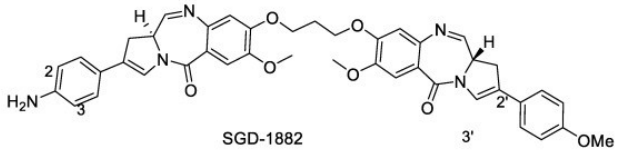
  Linker + INN = ozogamicin, vedotin, emtansine

ANTIBODY DRUG CONJUGATES: PAYLOADS

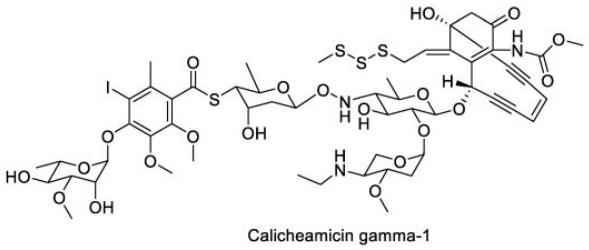
Structures of representative members of the various payload classes used in ADCs

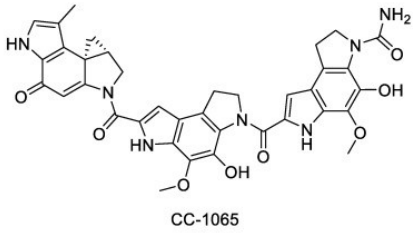


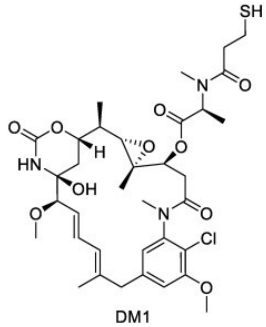




Maitansines (DM1)
Pyrrolobenzodiazépine (SGD-1882)
Monomethylauristatins (MMAE)
Duocarmycins (CC-1065)
Amanitins (α-amanitin)
Calicheamicins (calicheamicin γ1)







Molecules. 2021 May 15;26(10):2943. doi: 10.3390/molecules26102943.

ANTIBODY DRUG CONJUGATES: PAYLOADS

Famous mushrooms

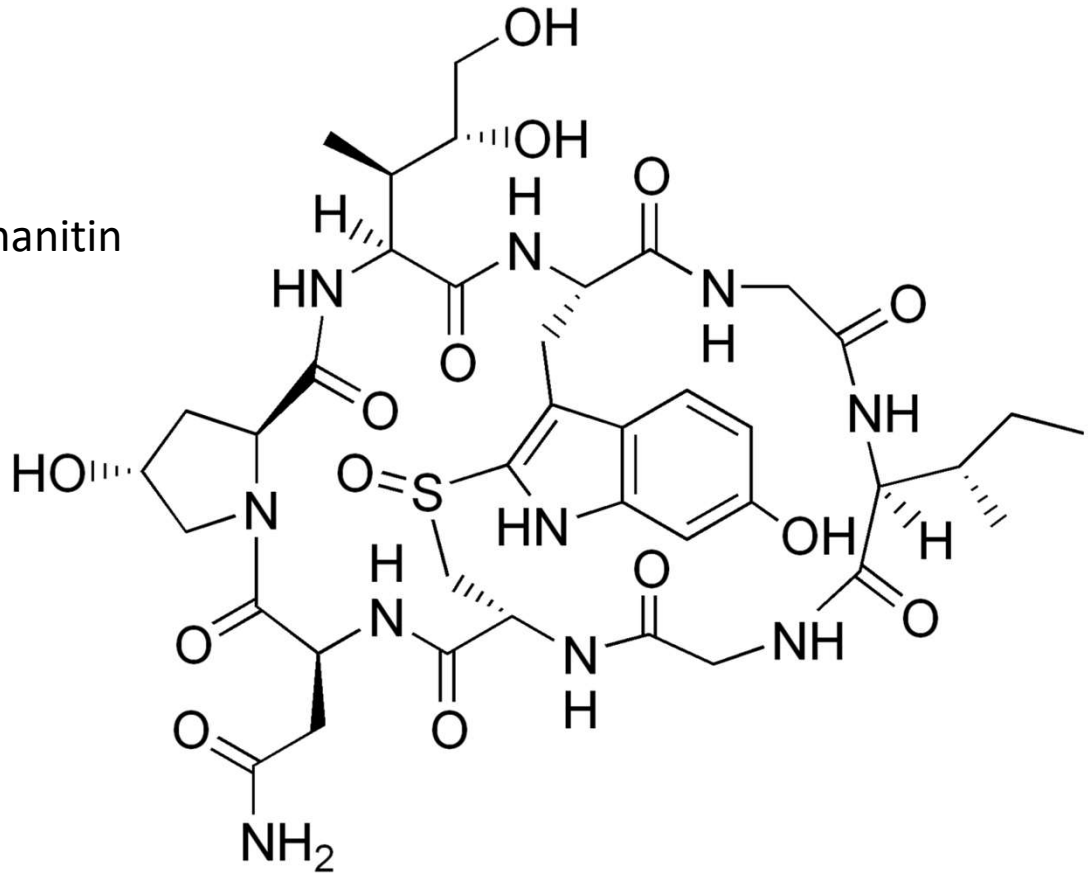
ANTIBODY DRUG CONJUGATES: PAYLOADS

Amanita phalloides

ANTIBODY DRUG CONJUGATES: PAYLOADS

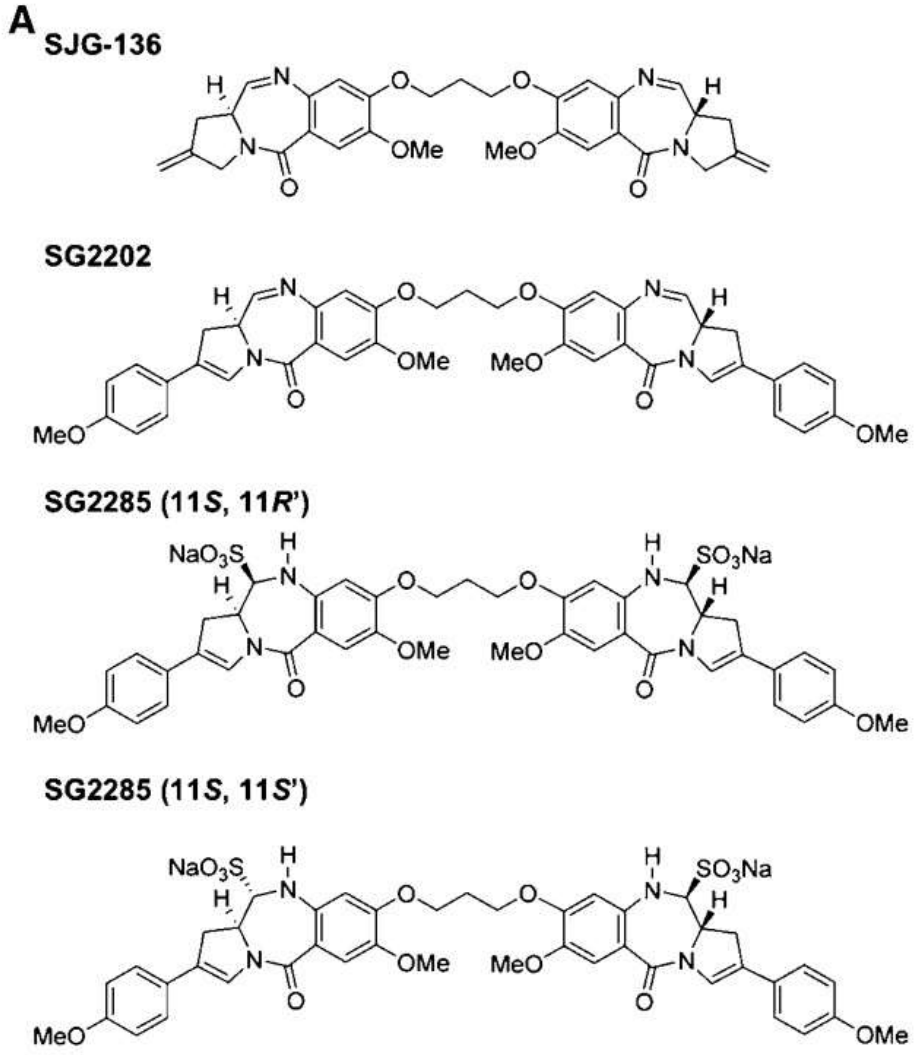
Amanitins

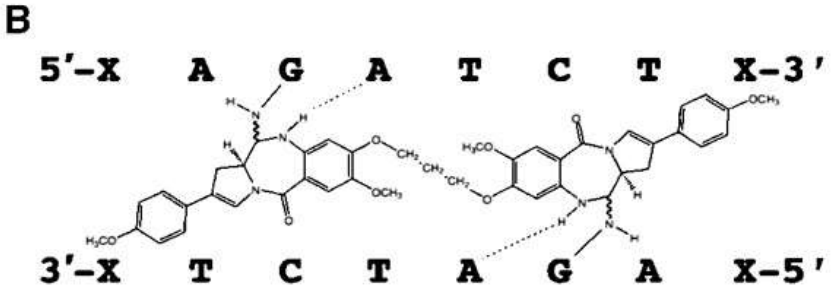
α-Amanitin

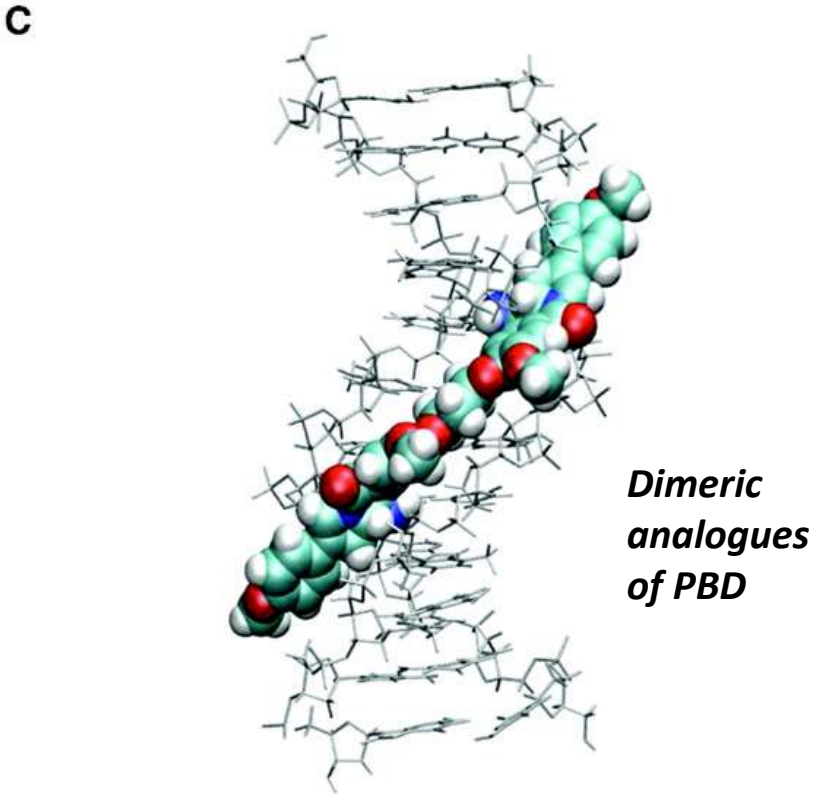


→ Selective inhibitor of RNA polymerases II and III

ANTIBODY DRUG CONJUGATES: PAYLOADS





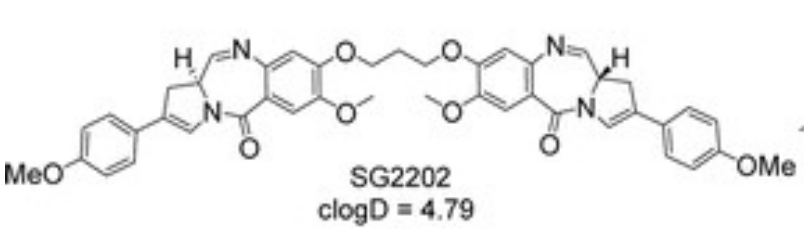


Hartley JA et al. SG2285, a Novel C2-Aryl-Substituted Pyrrolobenzodiazepine Dimer Prodrug That Cross-links DNA and Exerts Highly Potent Antitumor Activity. Cancer Res. 2010;70(17):6849-6858

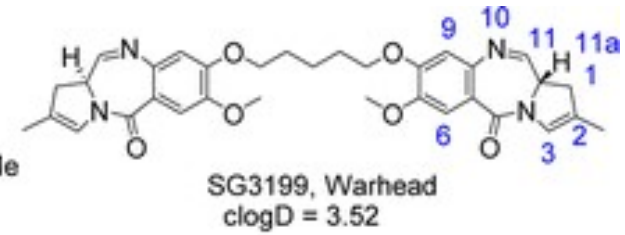
ANTIBODY DRUG CONJUGATES: PHYSICOCHEMISTRY

Physicochemistry of linkers (clogD)

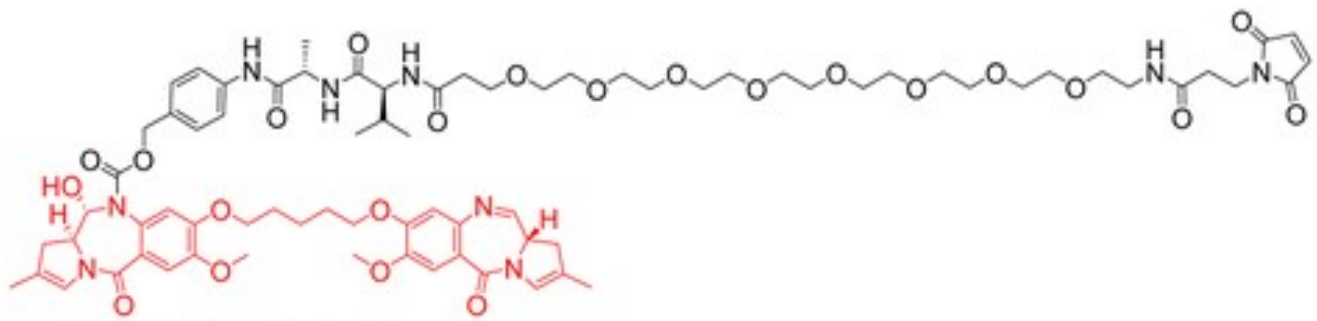
Tiberghien et al.
Design and Synthesis of Tesirine, a Clinical Antibody–Drug Conjugate Pyrrolobenzodiazepine Dimer Payload.
ACS Med. Chem. Lett. 2016, 7, 983–987



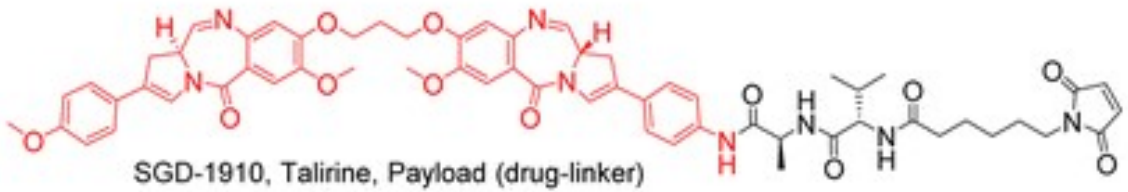
SG2202
clogD = 4.79



SG3199, Warhead
clogD = 3.52



SG3249, Tesirine, Payload (drug-linker)
clogD = 2.11



SGD-1910, Talirine, Payload (drug-linker)
clogD = 4.71

ANTIBODY DRUG CONJUGATES: PHYSICOCHEMISTRY

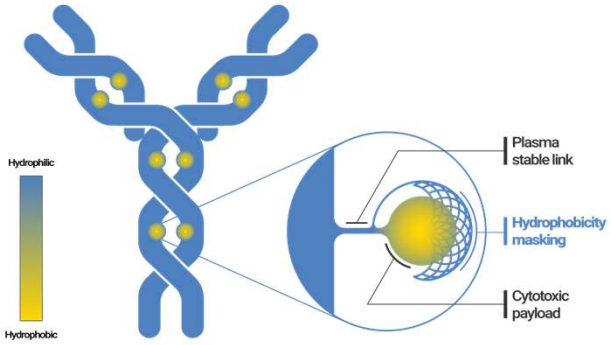
Physicochemistry of linkers

mablink

Transforming cancer immunotherapy with next generation ADCs

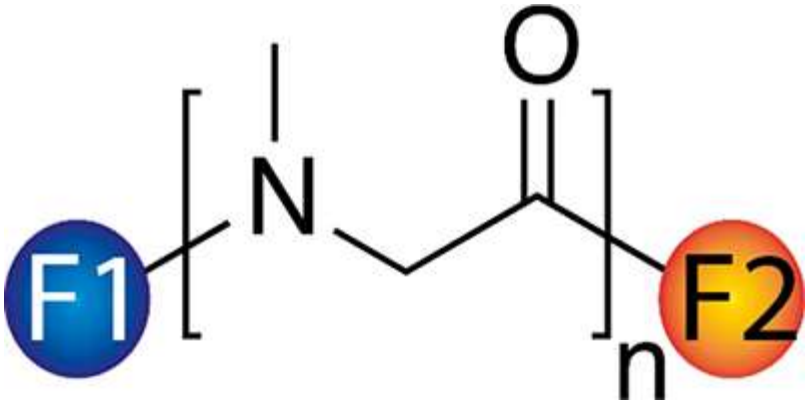
Mablink Bioscience is a French-based biotechnology company specialized in the development of an emerging class of cancer drugs, called antibody-drug conjugates (ADCs). Mablink leverages its patented hydrophilic technology PSARlink™ that enables the design of homogenous, plasma-stable next generation ADCs with a high DAR, whilst retaining excellent pharmacological properties, in order to quickly bring new and better treatment options to cancer patients.

Our PSARlink™ platform “masks” the hydrophobicity of the cytotoxic drugs by adding a chain of polysarcosine on the linker, which dramatically improves the pharmacological properties of ADCs, restoring the pharmacokinetics (PK) profile of the native antibody, even with DAR8 (8 cytotoxic drugs per antibody) ADCs.



https://www.mablink.com/psarlink/

Polysarcosine – a True Alternative to PEG



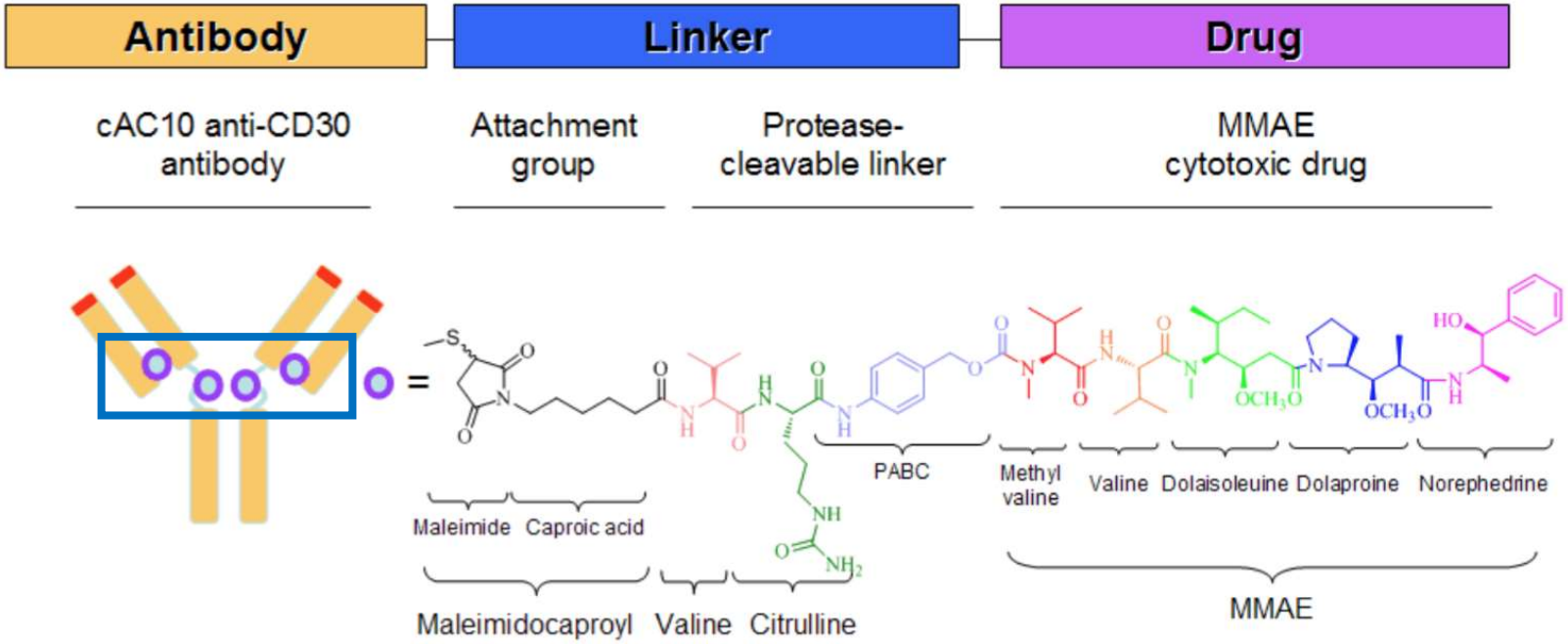
Monofunctional, homo- and heterobifunctional polysarcosine (PSR) with a wide variety of functional groups F1 and F2 are offered.

Degrees of polymerization n may range from below 10 to above 1.000

https://www.iris-biotech.de/en/kbase/article/view/id/31/, accessed Nov 9, 2022

ANTIBODY DRUG CONJUGATES: BRENTUXIMAB VEDOTIN

Brentuximab vedotin (ADCETRIS®) is an ADC directed to CD30, which is expressed in classical *hodgkin lymphoma* (HL) and *systemic anaplastic large cell lymphoma* (sALCL)

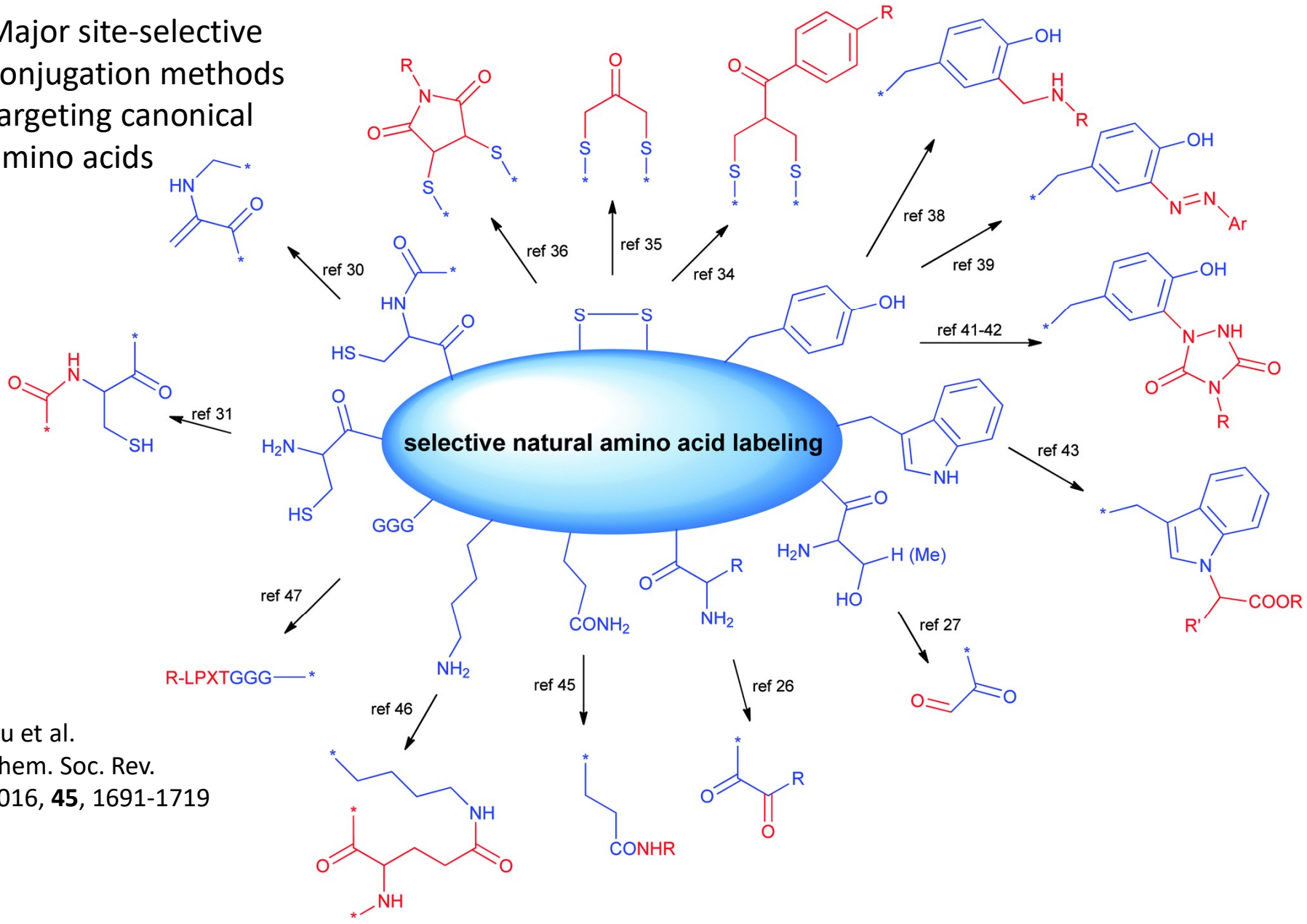


Brentu(ximab) = chimeric mAb

https://www.adcreview.com/brentuximab-vedotin-sgn35/
https://go.drugbank.com/drugs/DB08870

ANTIBODY DRUG CONJUGATES: SITE-SELECTIVE CONJUGATION

Major site-selective conjugation methods targeting canonical amino acids



Hu et al.
Chem. Soc. Rev.
2016, **45**, 1691-1719

BRENTUXIMAB VEDOTIN: CLEAVABLE LINKER

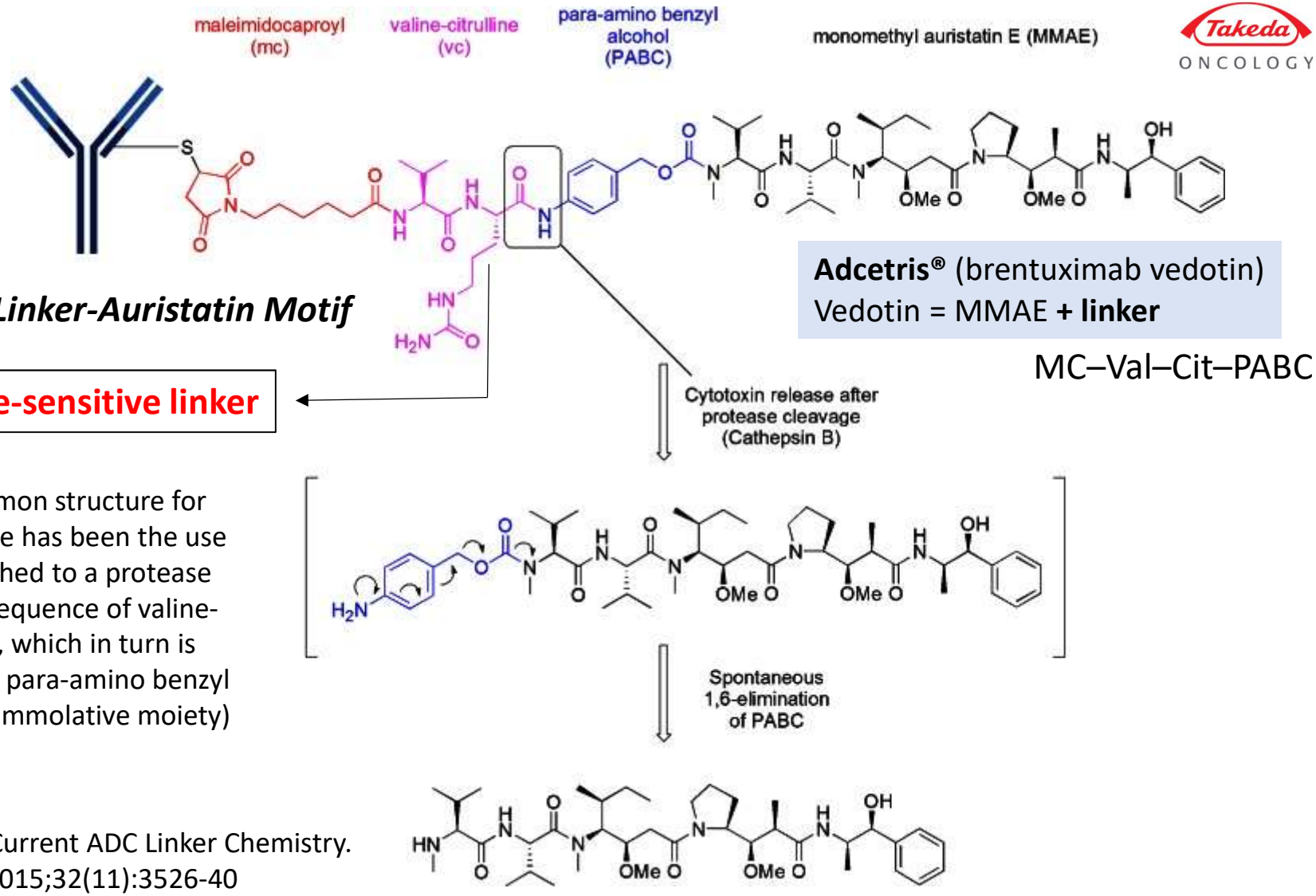


Fig. 5. A common structure for MMAE linkage has been the use of “mc” attached to a protease recognition sequence of valine-citrulline (vc), which in turn is attached to a para-amino benzyl alcohol (self-immolative moiety)

Jain N et al. Current ADC Linker Chemistry. Pharm Res. 2015;32(11):3526-40

ANTIBODY DRUG CONJUGATES: NON-CLEAVABLE LINKER

Cysteine-Linker-Auristatin Motif

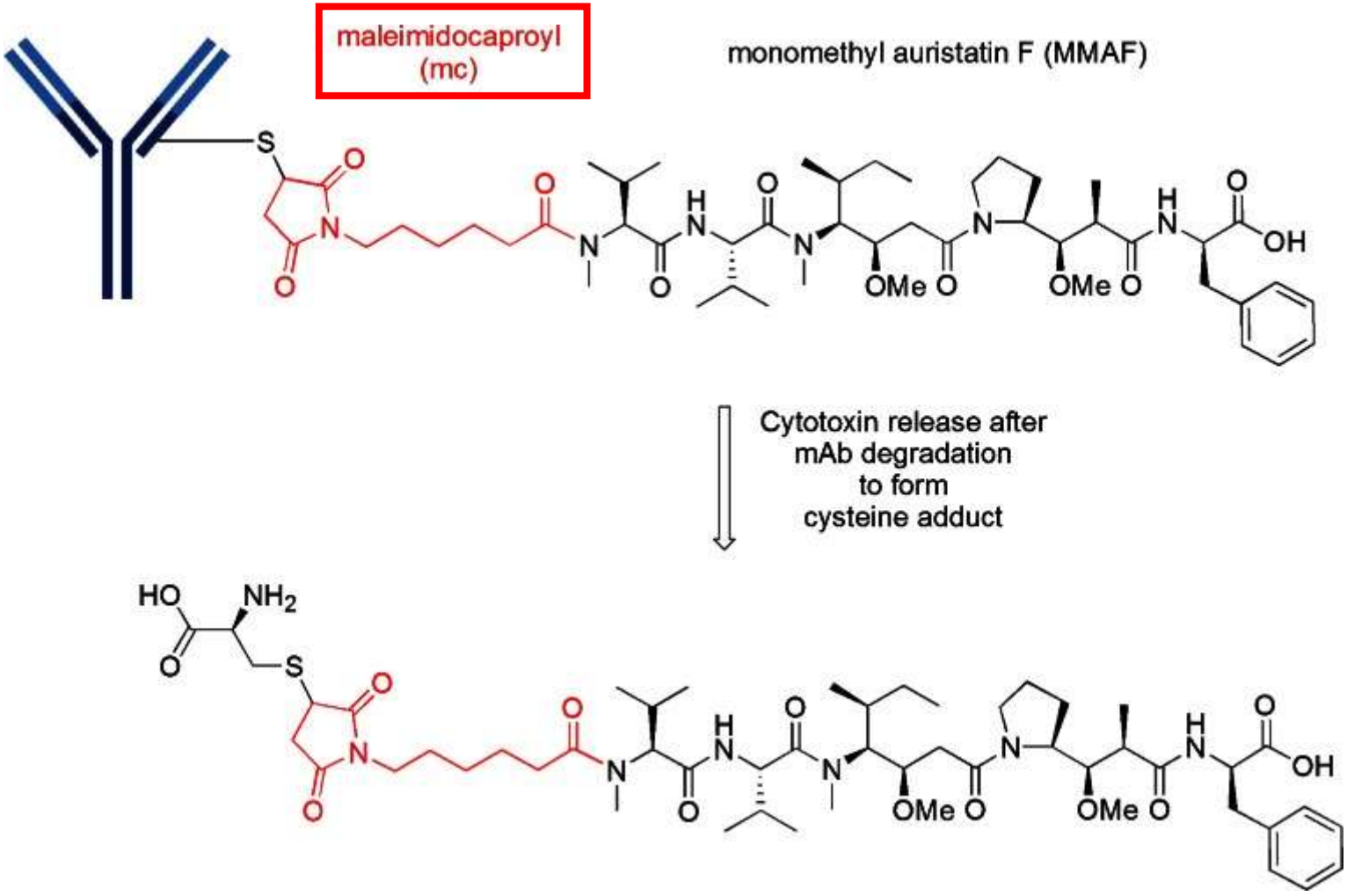
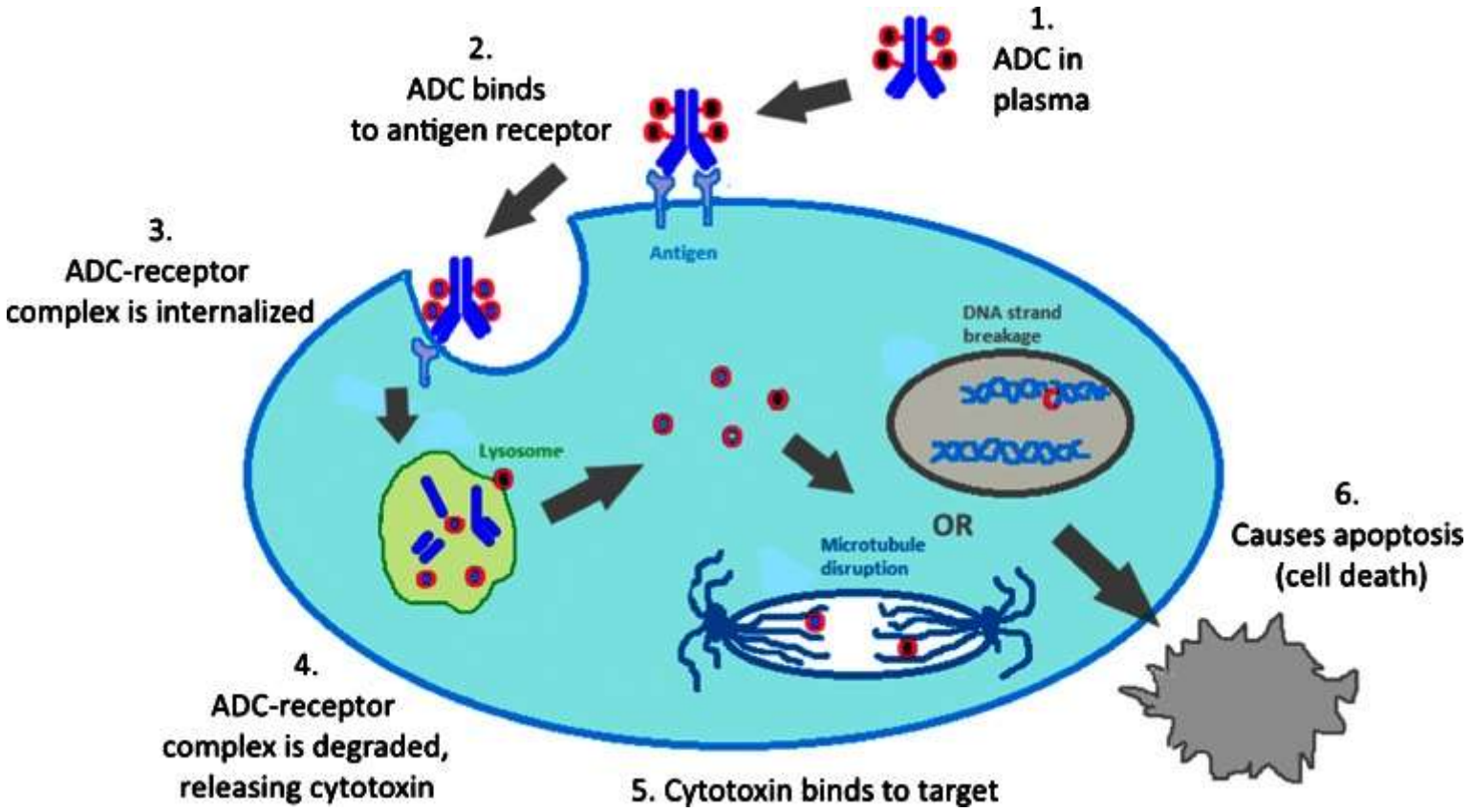


Fig. 6. Construct of a mc-MMAF ADC

Pharm Res. 2015;32(11):3526-40

ANTIBODY DRUG CONJUGATES: IN VIVO

Six main steps



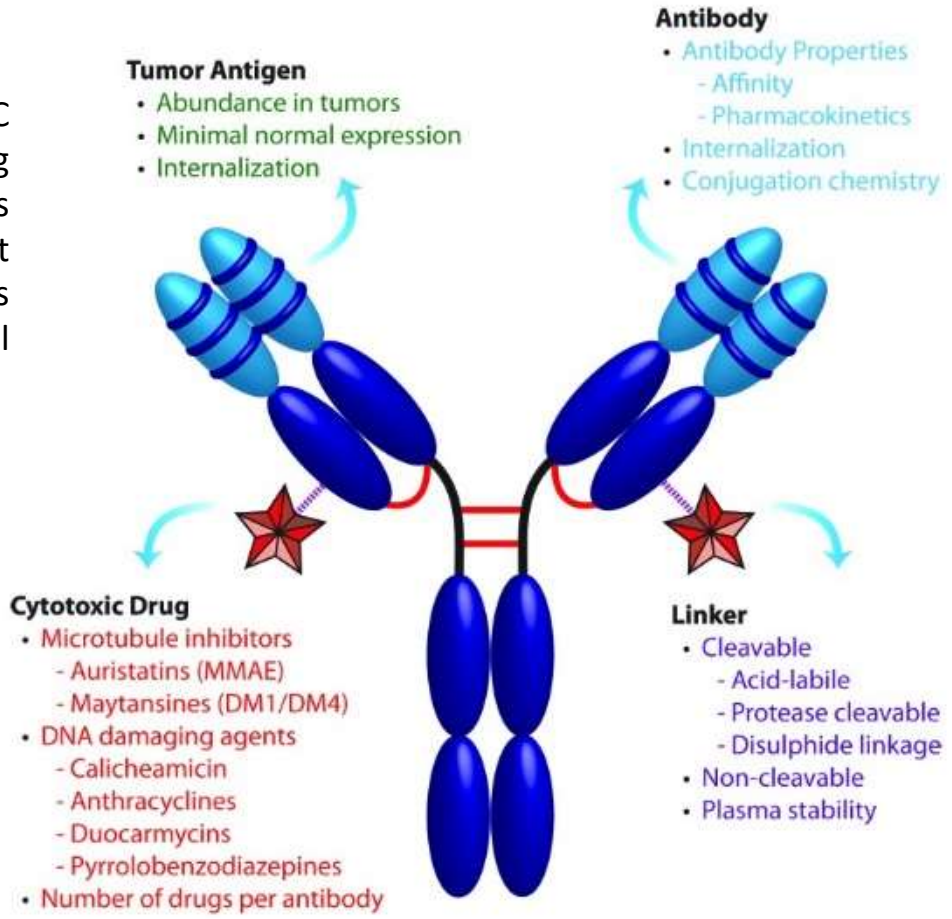
Mechanism of action of ADCs: The antibody portion of an ADC hones onto a cell-surface antigen that is ideally specific to a cancer cell. Upon binding, the ADC-antigen protein complex becomes internalized into the cancer cell. When the complex is degraded, it releases the cytotoxin which then binds to its target to cause cancer cell apoptosis. Jain N et al. Current ADC Linker Chemistry. Pharm Res. 2015;32(11):3526-40

ANTIBODY DRUG CONJUGATES: KEY POINTS

MOLECULAR DIVERSITY

Figure 3. Critical factors that influence ADC therapeutics. ADCs consist of a cytotoxic drug conjugated to a monoclonal antibody by means of a **select linker**. These components all affect ADC performance and their optimization is essential for development of successful conjugates

S. Panowski *et al*. Site-specific antibody drug conjugates for cancer therapy. mAbs 2014;6(1):34–45



ANTIBODY DRUG CONJUGATES

APPLICATIONS +++

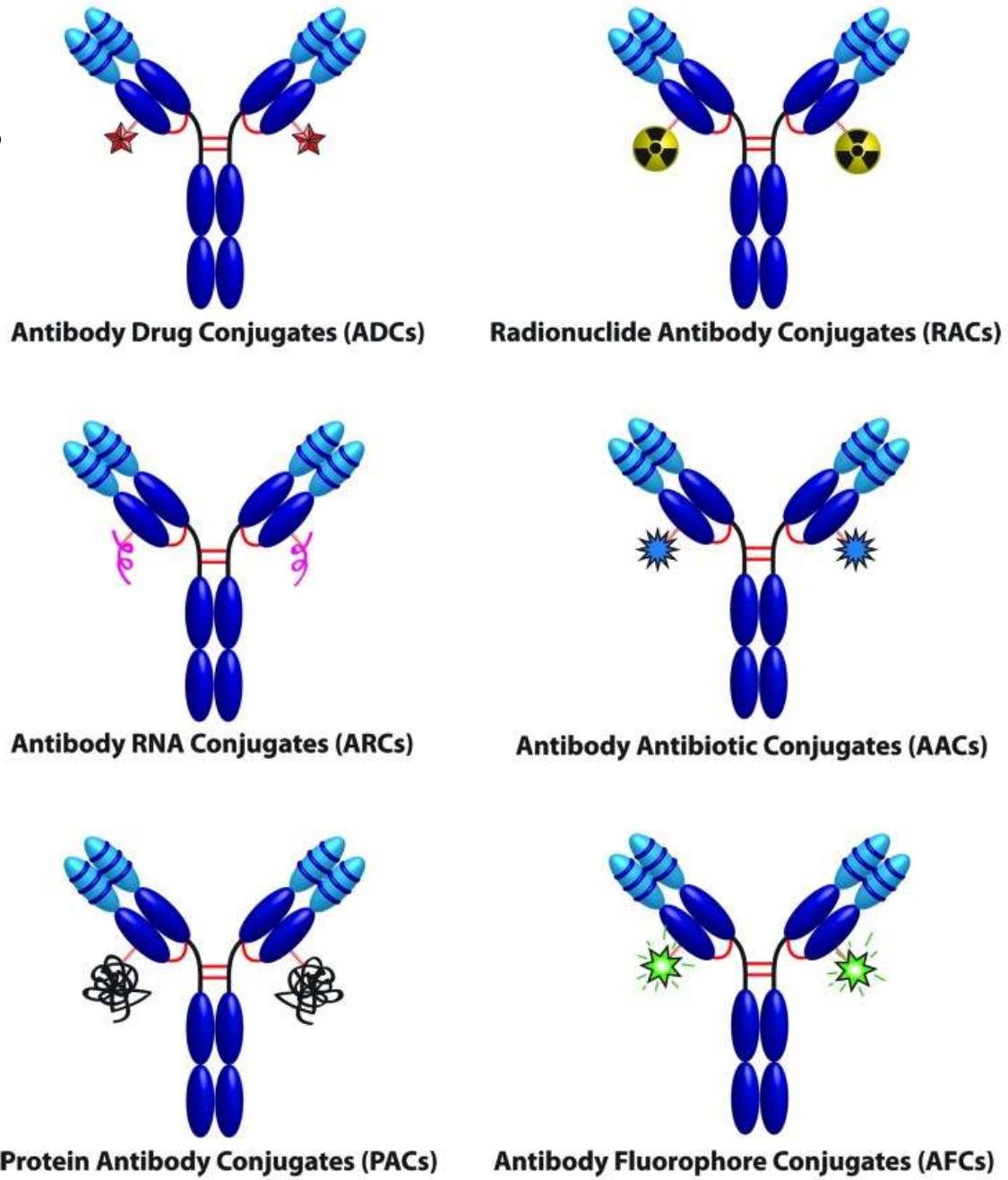


Figure 6. Applications of site-specific antibody conjugates. The site-specific conjugation of molecules to monoclonal antibodies has a wide range of applications. Site-specific conjugation decreases conjugate heterogeneity and improves stability and function. A number of possible antibody conjugates are represented here and include antibody-drug conjugates (ADCs) for cancer treatment, radionuclide-antibody conjugates (RACs) for imaging, antibody-antibiotic conjugates (AACs) to fight infectious disease, and antibody fluorophore conjugates (AFCs) for imaging and detection

ANTIBODY DRUG CONJUGATES: TWO PAYLOADS

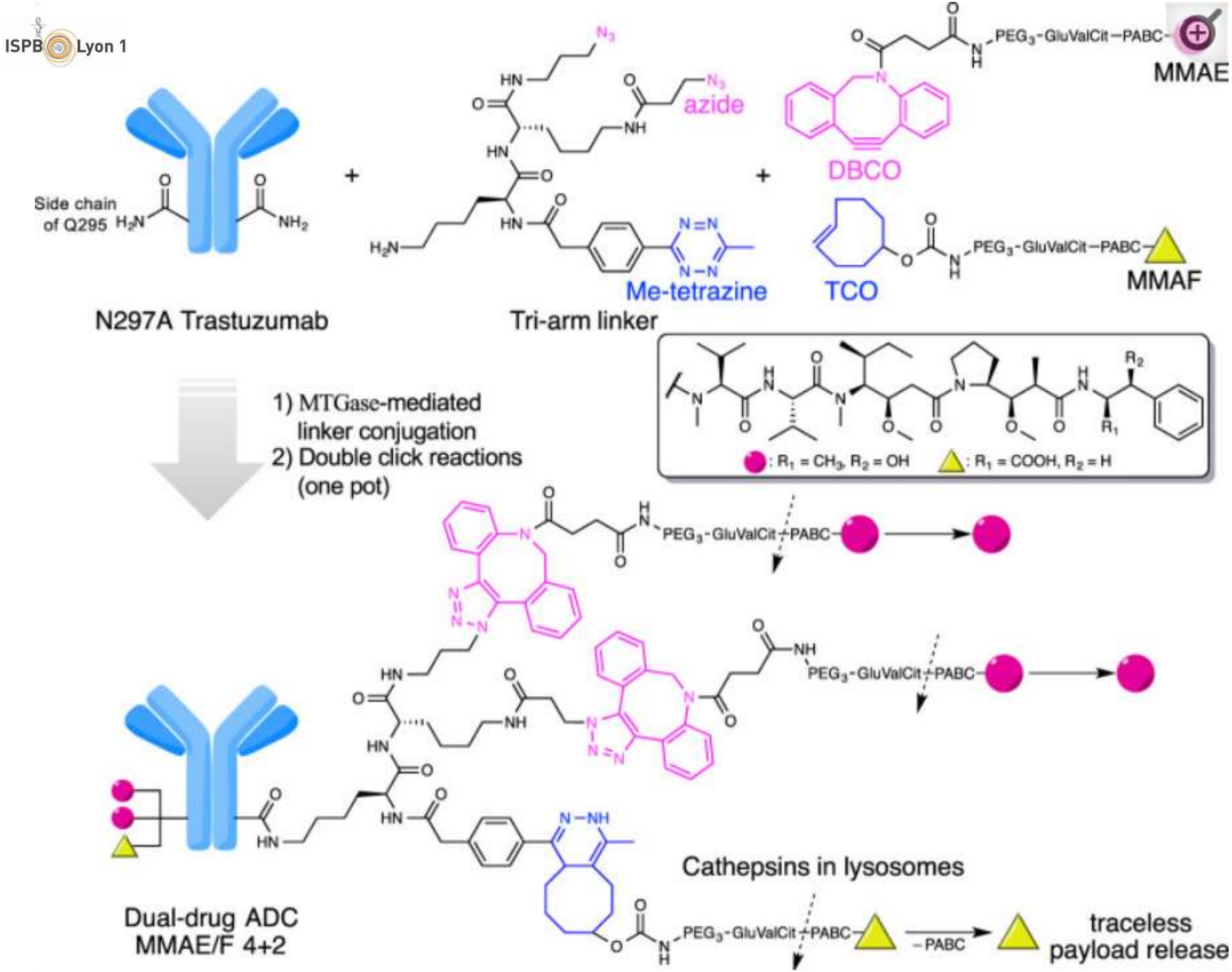
Antibody-drug conjugates with dual **payloads** for combating breast tumor heterogeneity and drug resistance.

Yamazaki CM, Yamaguchi A, Anami Y, Xiong W, Otani Y, Lee J, Ueno NT, Zhang N, An Z, Tsuchikama K.

Nat Commun. 2021 Jun 10;12(1):3528. doi: 10.1038/s41467-021-23793-7.

PMID: 34112795 **Free PMC article.**

However, these ADCs often suffer from issues associated with intratumor heterogeneity. Here, we show that homogeneous ADCs containing **two** distinct **payloads** are a promising drug class for addressing this clinical challenge. Our conjugates show HER2-specific cell kill ...


ISPB Lyon 1
Side chain of Q295
azide
DBCO
MMAE
MMAF
Me-tetrazine
TCO
N297A Trastuzumab
Tri-arm linker
1) MTGase-mediated linker conjugation
2) Double click reactions (one pot)
: R1 = CH3, R2 = OH
: R1 = COOH, R2 = H
Cathepsins in lysosomes
Dual-drug ADC MMAE/F 4+2
traceless payload release
– PABC

ANTIBODY DRUG CONJUGATES: RESISTANCES

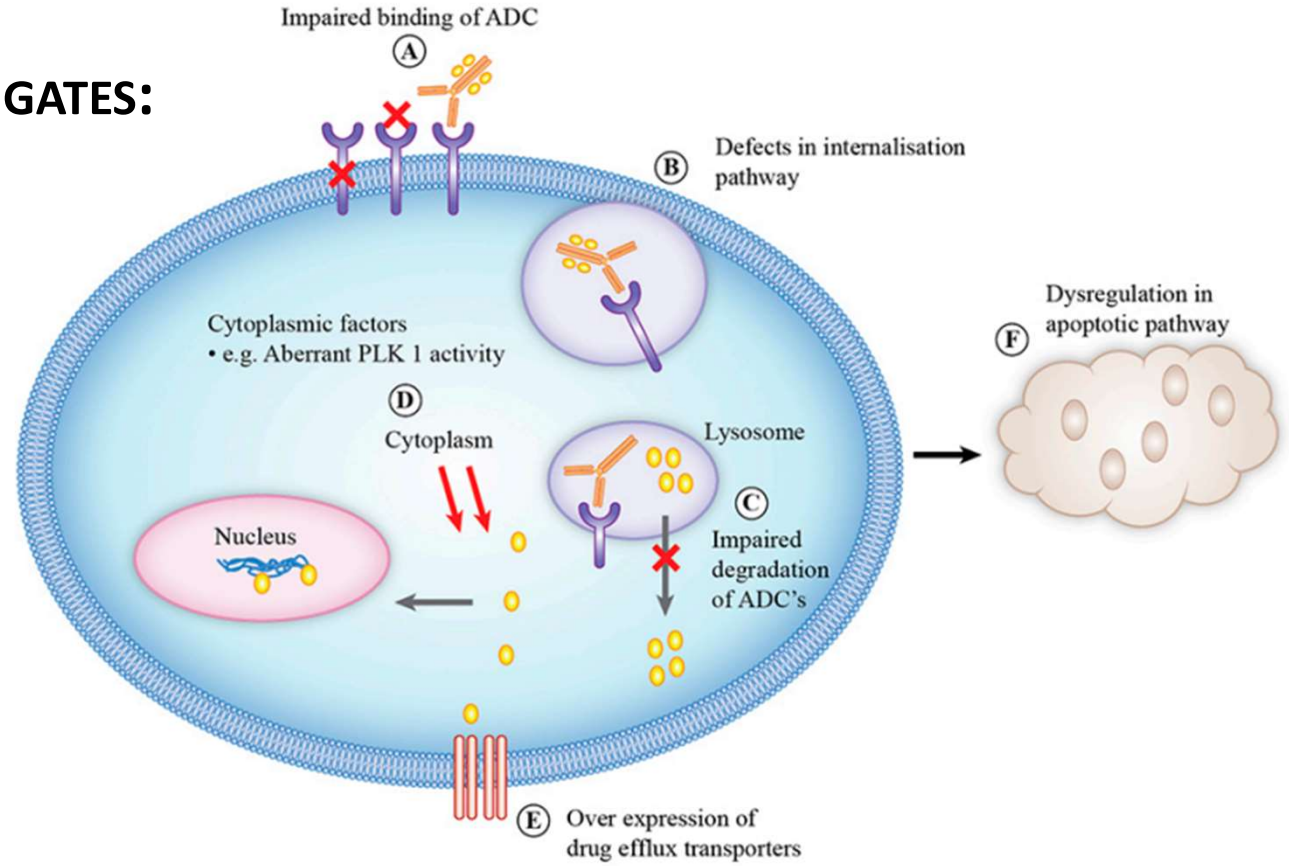


Figure 3. Mechanism of resistance: (**A**) impaired binding of the ADC to the target antigen by antigen downregulation, loss of antigen expression or mutations in the antigen; (**B**) defects in the internalization pathway and reduced cell surface trafficking; (**C**) impaired degradation of ADCs in lysosomes due to reduced lysosomal proteolytic or acidification function or loss of lysosomal transporter expression inhibiting the release of cytotoxic payload lysosomes to the cytoplasm; (**D**) cytoplasmic factors, e.g., aberrant polo-like kinase 1 activity preventing mitotic arrest or due to defective cyclin B1 induction; (**E**) the overexpression of drug efflux transporters; (**F**) dysregulation in the apoptotic pathway through the deficient activity of proapoptotic proteins Bak and Bax or the overexpression of antiapoptotic proteins BCl-2 and Bcl-x.

Hafeez et al. Molecules 2020

ISPB Lyon 1

Dégradeurs de protéines ciblés

An **emerging strategy** in drug discovery to access difficult-to-treat diseases is targeted protein degradation.

While traditional small-molecule or antibody drugs may only allow access to ~20% of the proteome, **degradation techniques may open the door to the other 80%**.

The molecules used in these approaches are often called PROTACs (**PRO**teolysis **T**Argeting **C**himera**s**), bifunctional molecules that eliminate target proteins from cells

PROTEASOME

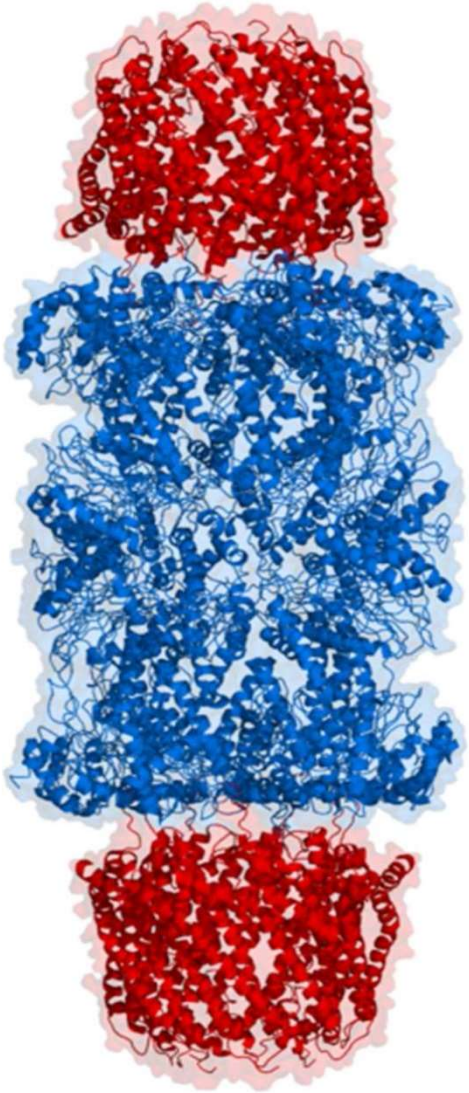
Les **protéasomes** sont des complexes enzymatiques multiprotéiques que l'on retrouve chez les ***eucaryotes***

Dégrader les protéines mal repliées, dénaturées

Dégradation par protéolyse (***activité chymotrypsine-like***…)

Au préalable : marquage de la protéine à dégrader (par 4 ubiquitines*)

Prix Nobel **2004** de chimie (A. Ciechanover, A. Hershko, I. Rose)



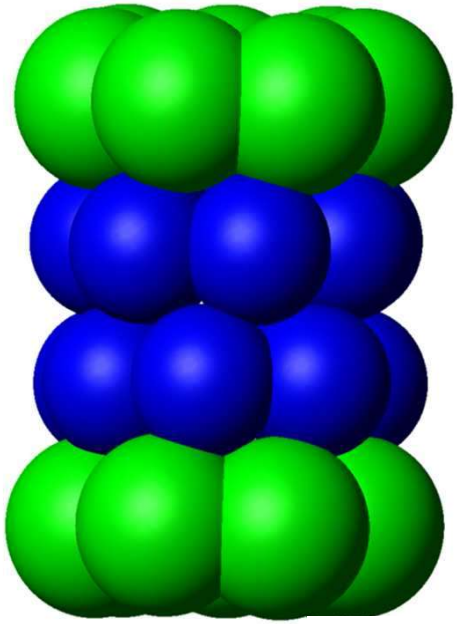
Représentation du protéasome obtenue par diffractométrie de rayons X après cristallisation (coeur catalytique 20S et 2 complexes régulateurs 11S)

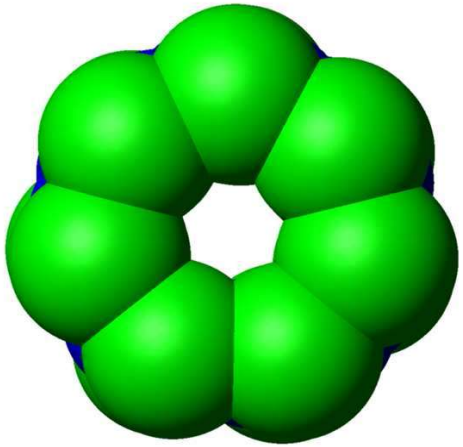
* Protéine de 76 acides aminés (8500 Da) : système de marquage hautement spécifique

PROTEASOME

Schéma du coeur catalytique :
7 sous-unités α formant les deux anneaux externes (***reconnaissance des protéines à dégrader***),

7 sous-unités β constituant les anneaux internes en bleu (***site actif de l'activité enzymatique***).

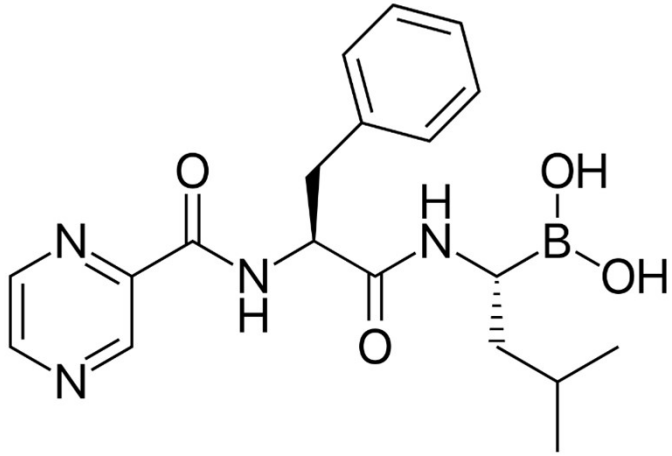




Vue du dessus du complexe 20S illustrant la septuple symétrie des anneaux

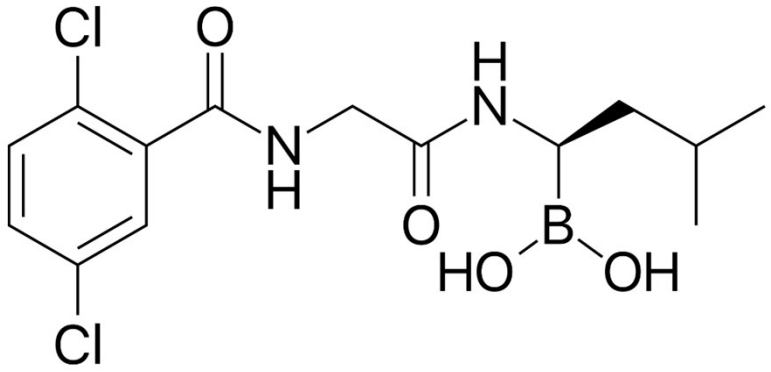
PROTEASOME INHIBITORS

Treatment of multiple myelome – Adults: Inhibition of chymotrypsin-like activity of the 26S proteasome of mammal cells



Bortezomib VELCADE®

In patients who received at least one previous treatment and who are ineligible for a bone marrow transplant



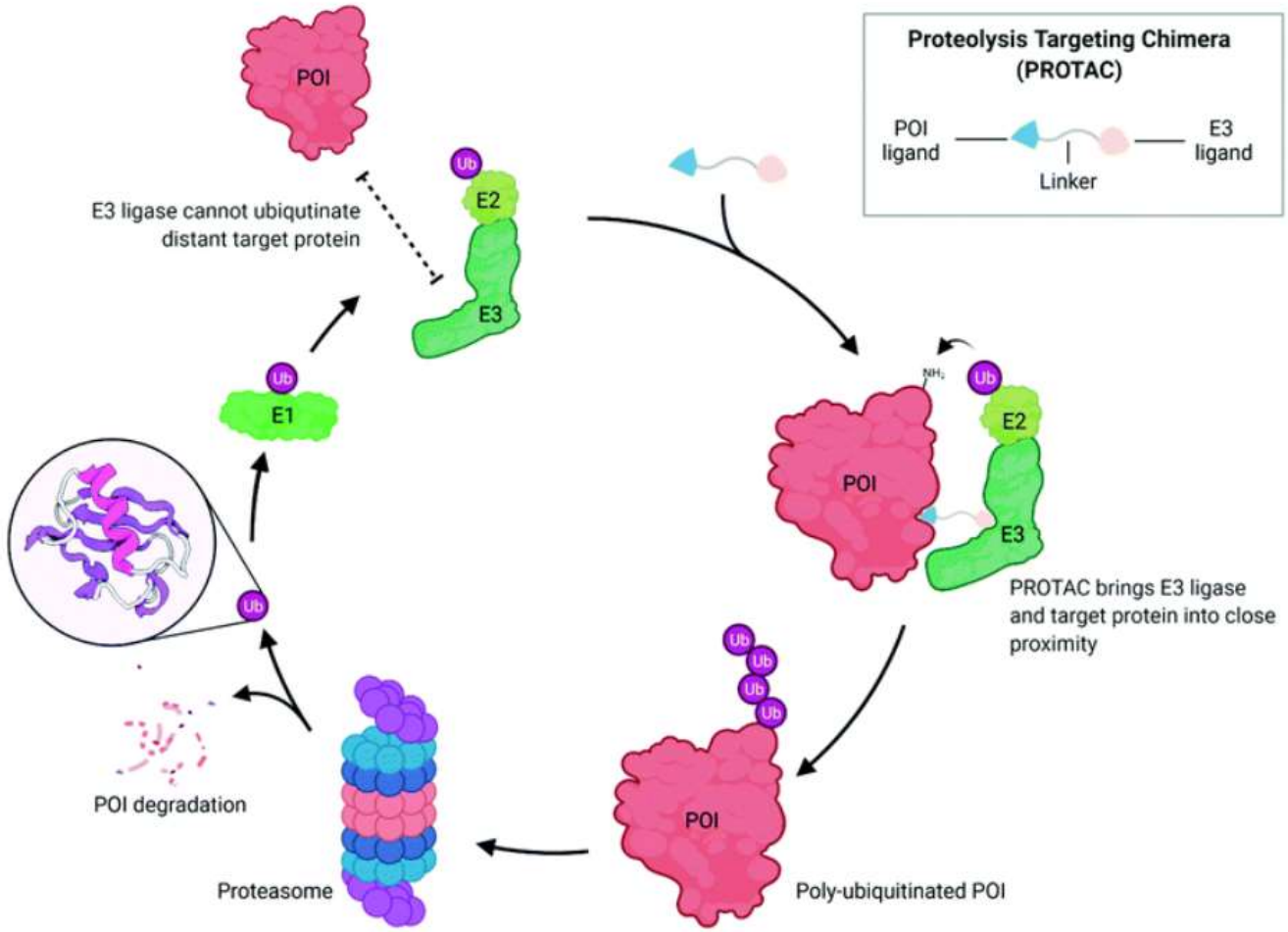
Ixazomib citrate NINLARO®

Used in combination with lenalidomide and dexamethasone

Carfilzomib (KYPROLIS®)

Tétrapeptide époxycétone

PRINCIPLE OF THE PROTAC STRATEGY



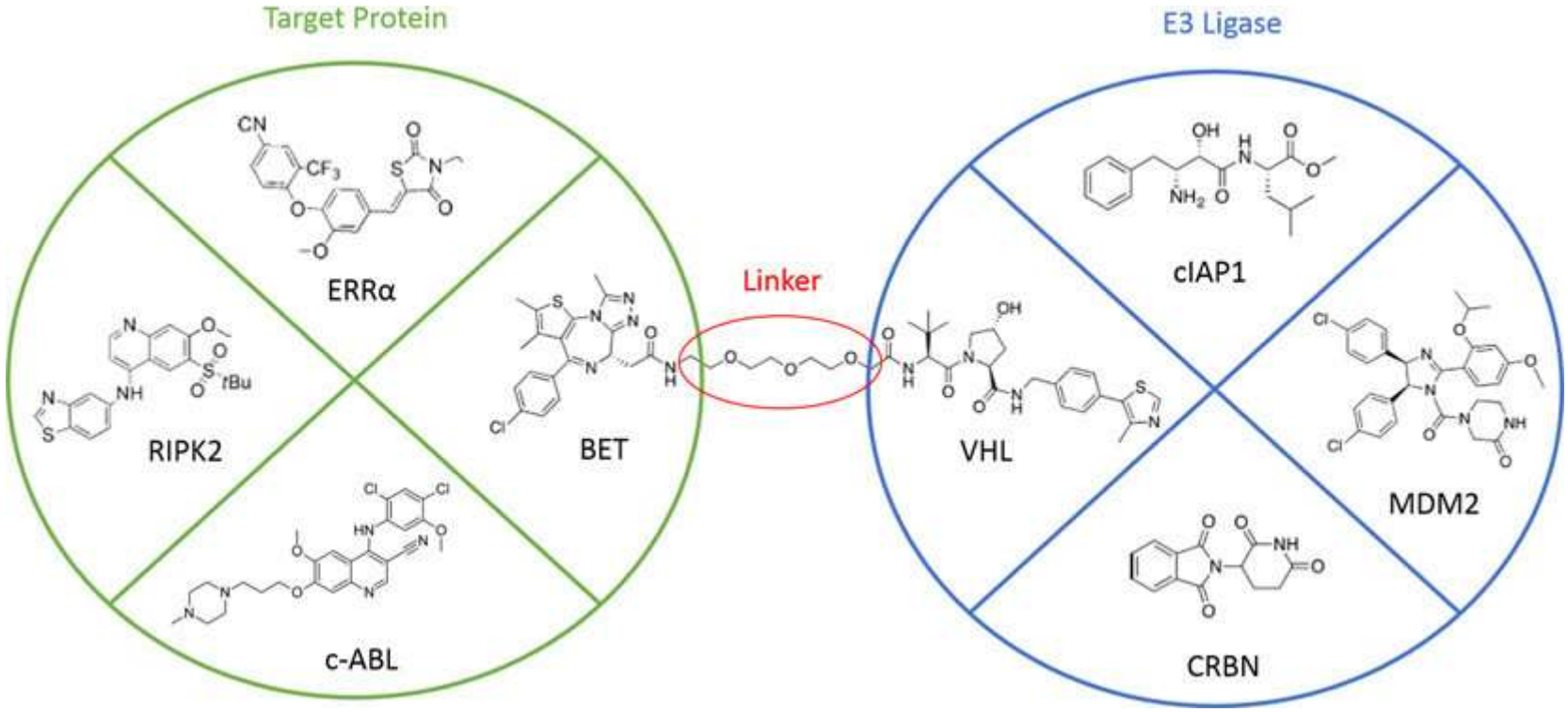
Li et al.
Chem. Soc. Rev.
2022

Fig. 1 PROTACs hijack the UPS to induce targeted protein degradation. The figure was created with BioRender.com.

PRINCIPLE OF THE PROTAC STRATEGY

Are there any limits to PROTACs? and the future will tell us the real potential of this new approach…

The human genome encodes more than 600 E3 ligases



Hughes S.J. *et al.* Molecular recognition of ternary complexes: A new dimension in the structure-guided design of chemical degraders. Assays in Biochemistry 2017;61(5):505-516

Cereblon (CRBN)
Von Hippel Lindau (VHL)

RETOUR EN GRÂCE DU THALIDOMIDE ET ANALOGUES

Scheepstra M et al. Bivalent Ligands for Protein Degradation in Drug Discovery. Comput Struct Biotechnol J. 2019 Jan 25;17:160-176

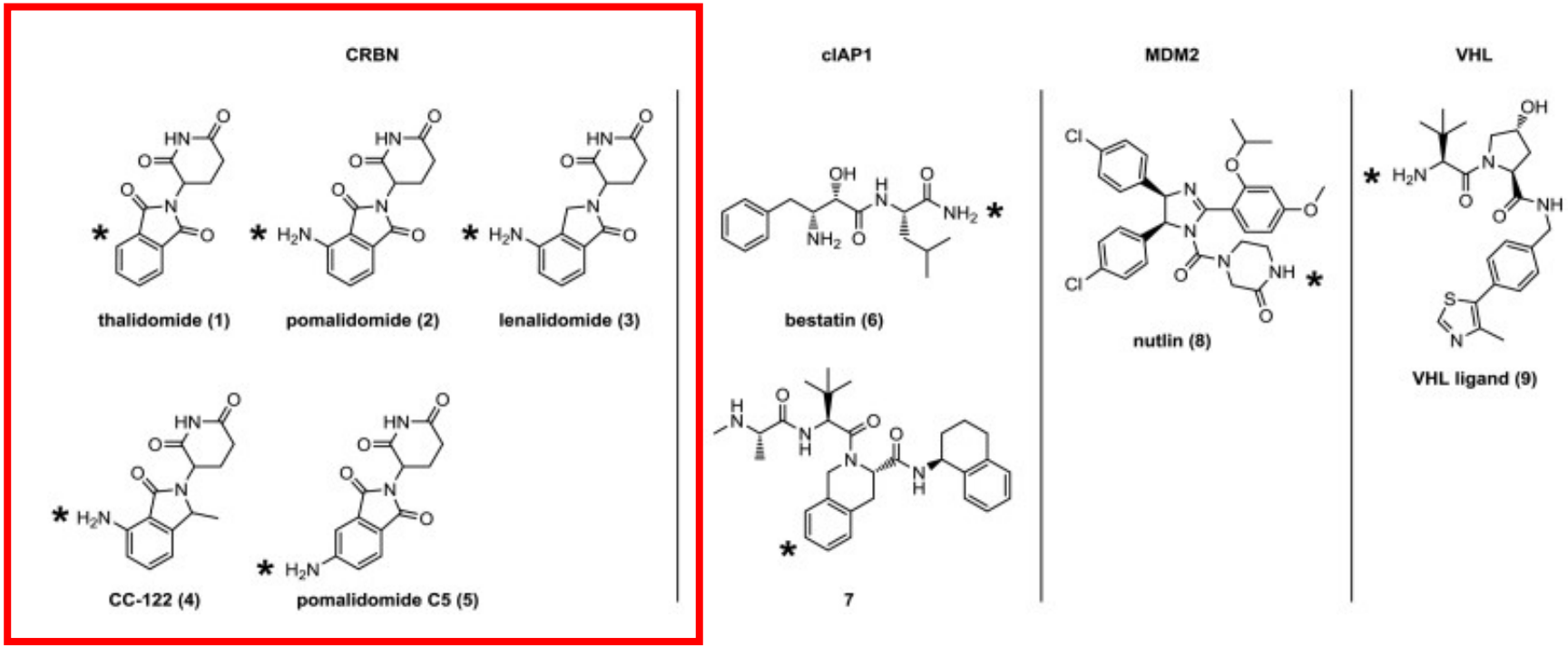


Fig. 1 E3 ligase ligands used for PROTACs: **thalidomide derivatives** targeting Cereblon.

The asterisk shows the attachment point for the linker.

https://igeahub.com/2017/09/23/top-30-oncology-drugs-2017/

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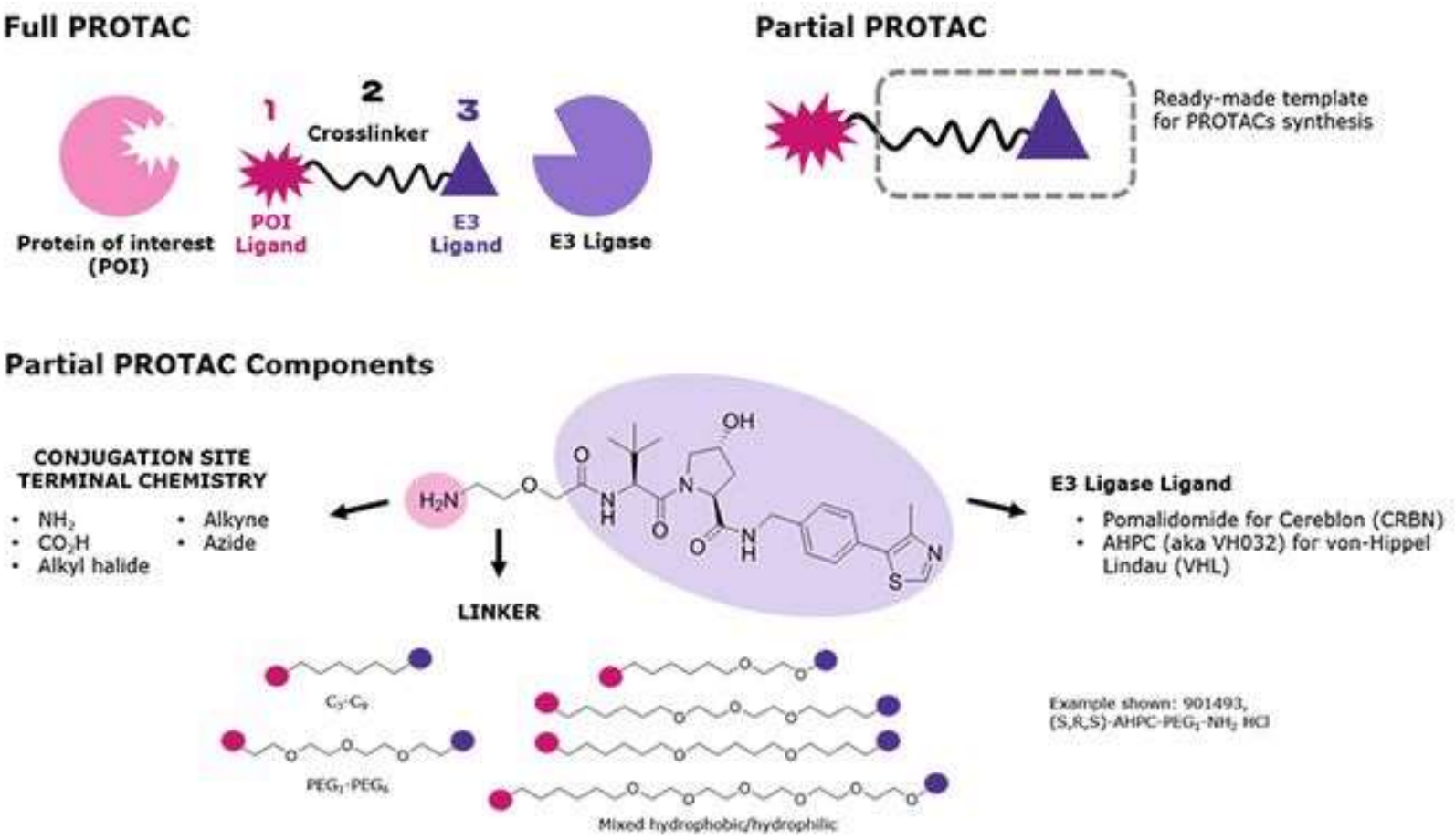
LINKEROLOGY

- ✓ **MODIFICATION OF LINKER LENGTH, COMPOSITION AND RIGIDITY**

plays a critical role in adjusting both the biological and physicochemical properties of PROTACs, such as target selectivity, cooperativity, biodistribution, metabolic stability, membrane permeability, aqueous solubility

LINKEROLOGY



Ligands targeting the E3 ligase Cereblon (CRBN) or von Hippel–Lindau (VHL)
Crosslinkers with varied lengths and compositions

https://www.sigmaaldrich.com/technical-documents/articles/technology-spotlights/partial-protacs.html

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WHICH PROTEINS ARE TARGETED BY PROTACS?

✓ **Proteins targeted by PROTACs include:**

protein kinases, nuclear receptors,
epigenetic readers,
neurodegenerative disease-related proteins,
regulatory proteins, enzymes,
anti-apoptotic proteins, transcription factors,
scaffolding proteins, cytokines, virus-related proteins

Arvinas: first small molecule targeted protein degraders began clinic trials in 2019

15 PROTAC degraders have entered or are approaching clinical studies

Cancer, except two compounds for ***autoimmune diseases***

PROTACs and Kinases

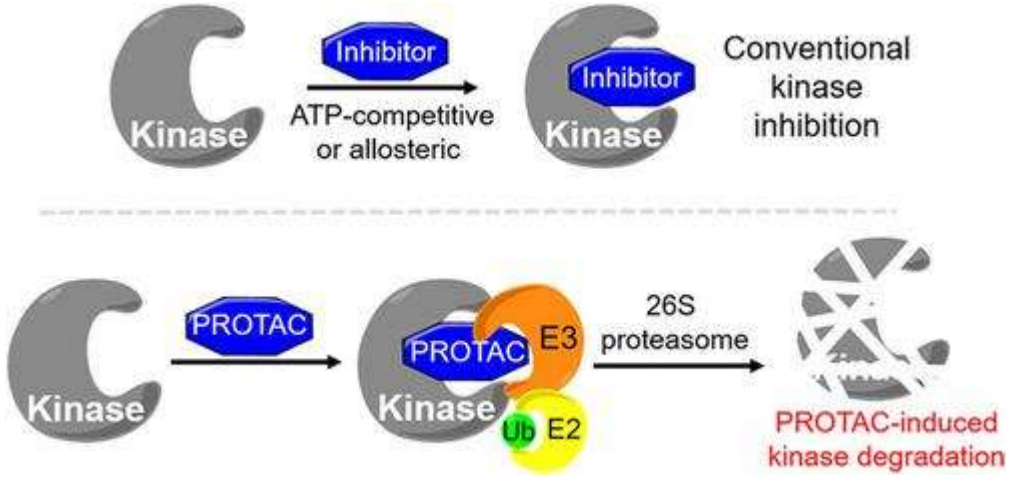
When Kinases Meet PROTACs†

Li Tan, Nathanael S. Gray

First published: 15 July 2018 | https://doi.org/10.1002/cjoc.201800293 | Citations: 15

† Dedicated to Professor Xiyan Lu on the occasion of his 90th birthday.

The majority of small molecule degraders are bispecific molecules called proteolysis targeting chimeras (PROTACs), and their mechanism of action is based on simultaneous recruitment of the target of interest and an E3 ligase, resulting in target polyubiquitination and eventual destruction by the proteasome. Over the last couple of years, PROTAC strategy has been developed and validated for a range of targets, including kinases (ERK1/2…)

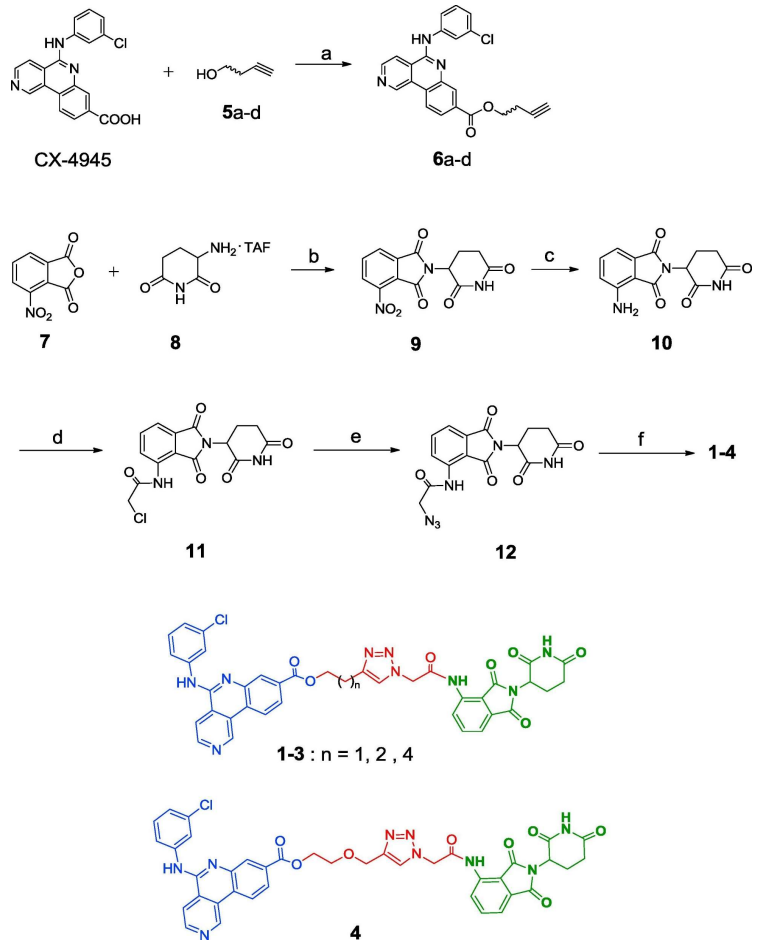


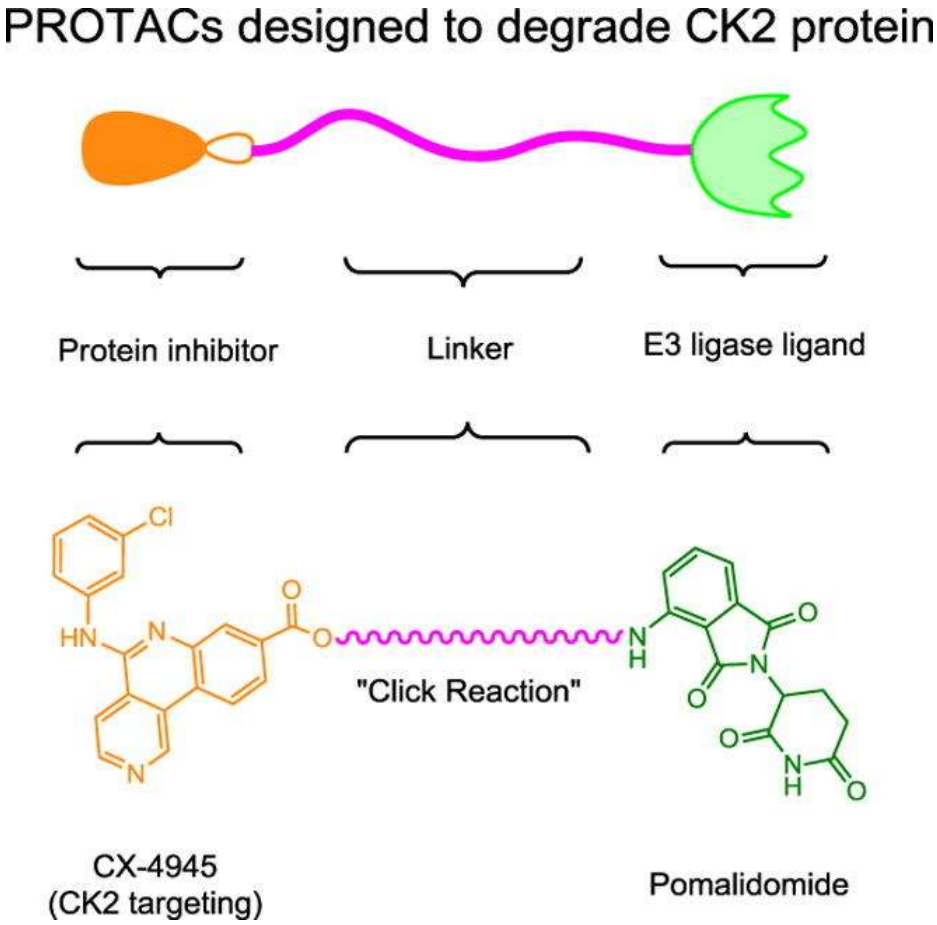
LITERATURE REVIEW

Bioorg Chem. 2018 Dec;81:536-544. doi: 10.1016/j.bioorg.2018.09.005. Epub 2018 Sep 12.

Chemically induced degradation of CK2 by proteolysis targeting chimeras based on a ubiquitin-proteasome pathway

Hong Chen [1], Feihong Chen [1], Nannan Liu [1], Xinyi Wang [1], Shaohua Gou [2]





CONDITIONAL ACTIVATION OF PROTACS

Folate-caged PROTACs

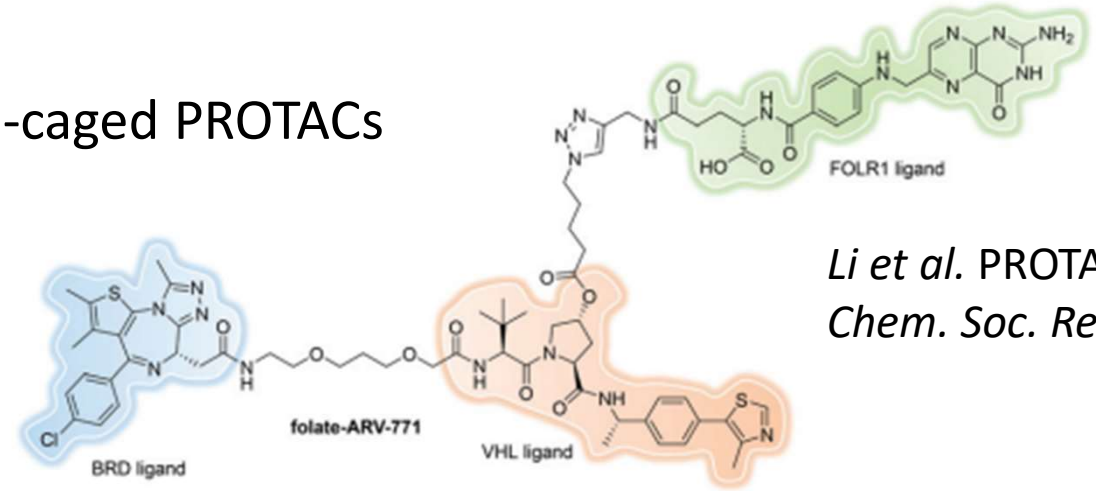


Fig. 16 Folate-Caged PROTAC.

Li et al. PROTACs: past, present and future. *Chem. Soc. Rev.* 2022, 51, 5214-5236

To control the on-target degradation activity of a PROTAC in a tissue-selective manner, Liu and Chen et al. developed a strategy for PROTACs by conjugating a folate group to the degraders (e.g. folate-ARV-771, a BRD-PROTAC). Because folate receptor α (FOLR1) is highly expressed in many cancer types compared to normal tissues, the folate-caged PROTAC allows the specific delivery of PROTACs into cancer cells to reduce the off-tissue, on-target toxicity.

Folate-ARV-771 was generated and demonstrated effective degradation of BRDs, in a FOLR1-dependent manner in cancer cells.

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DEGRADERS IN CLINIC TRIALS

Table 1 | **Selected degraders in and approaching the clinic**

Drug	Sponsor	Properties	Lead indication	Status
Heterobifunctional degraders (PROTACs, BiDACs, etc.)				
ARV-110	Arvinas	Androgen receptor degrader	Prostate cancer	Phase II
ARV-471	Arvinas	Oestrogen receptor degrader	Breast cancer	Phase II
ARV-766	Arvinas	Androgen receptor degrader	Prostate cancer	Phase I in 2021
AR-LDD	Bristol Myers Squibb	Androgen receptor degrader	Prostate cancer	Phase I
DT2216	Dialectic	BCL-XL degrader	Liquid and solid cancers	Phase I
KT-474	Kymera/Sanofi	IRAK4 degrader	Autoimmune including AD, HS and RA	Phase I
KT-413	Kymera	IRAK4 degrader with IMiD activity	MYD88-mutant DLBCL	Phase I in 2H2021
KT-333	Kymera	STAT3 degrader	Liquid and solid tumours	Phase I in 2H2021
NX-2127	Nurix	BTK degrader with IMiD activity	B cell malignancies	Phase I
NX-5948	Nurix	BTK degrader	B cell malignancies and autoimmune	Phase I in 2H2021
CG001419	Cullgen	TRK degrader	Cancer and other diseases	IND in 2021
CFT8634	C4 Therapeutics	BRD9 degrader	Synovial sarcoma	IND in 2H2021
FHD-609	Foghorn	BRD9 degrader	Synovial sarcoma	IND in 1H2021
Molecular glue degrader (CELMoDs, MonoDACs, etc.)				
DKY709	Novartis	Helios (IKZF2) degrader	Solid cancers	Phase I
CC-90009	Bristol Myers Squibb	GSPT1 degrader	Acute myeloid leukaemia	Phase I
CC-92480	Bristol Myers Squibb	Ikaros/Aiolos (IKZF1/3) degrader	Multiple myeloma	Phase I
CC-99282	Bristol Myers Squibb	Ikaros/Aiolos (IKZF1/3) degrader	Lymphoma	Phase I
CFT7455	C4 Therapeutics	Ikaros/Aiolos (IKZF1/3) degrader	Multiple myeloma and lymphoma	Phase I in 1H2021

AD, atopic dermatitis; DLBCL, diffuse large B cell lymphoma; HS, hidradenitis suppurativa; IMiD, immunomodulatory drug; RA, rheumatoid arthritis.

Nature Reviews Drug Discovery **20**, 247-250 (2021)

Colles moléculaires

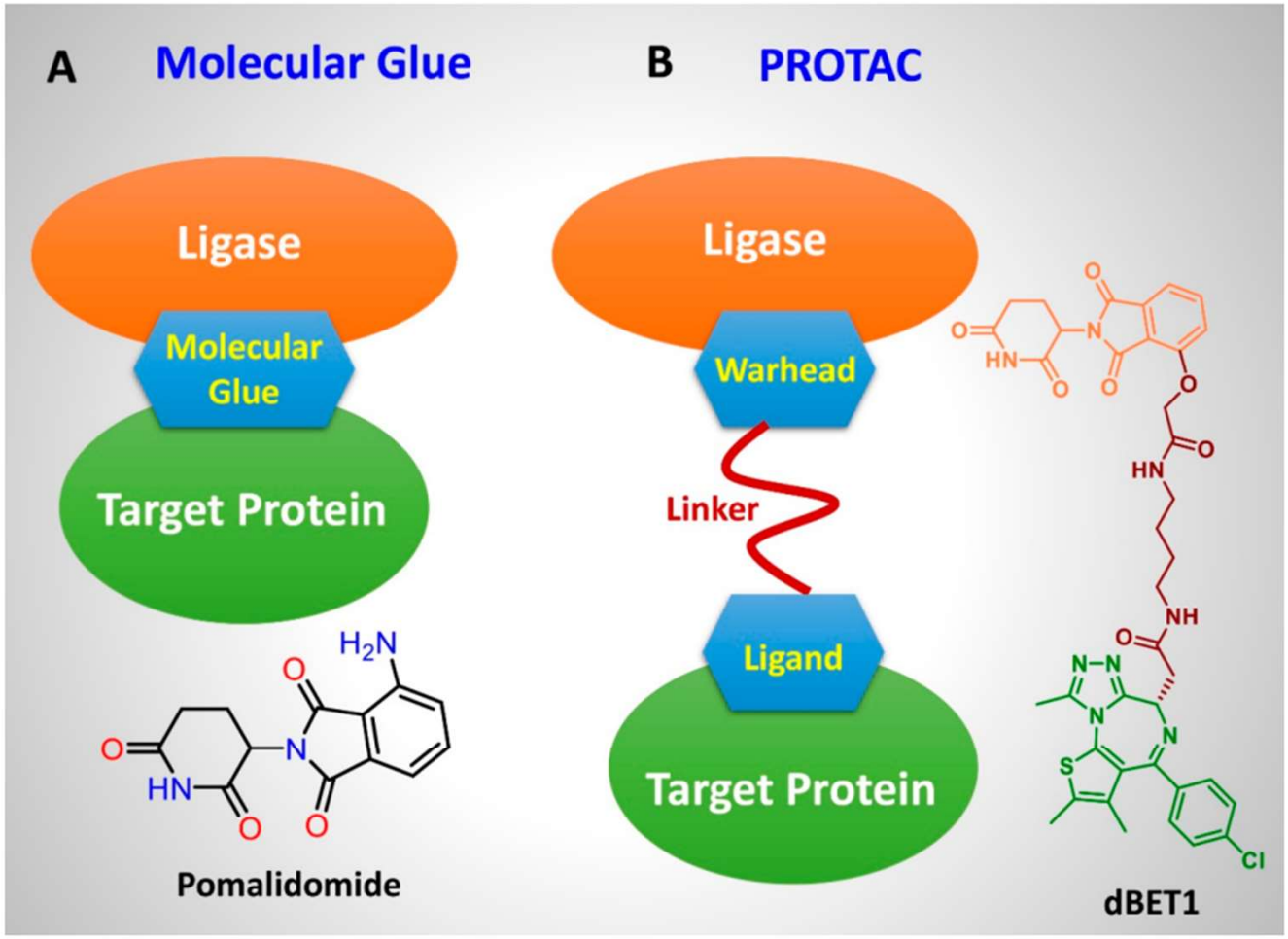

Figure 2. Mode of action and structural features of molecular glue and PROTAC. (a) Molecular glue acts as a PPI inducer to enhance or induce interactions between E3 ligase and the target protein and thereby trigger ubiquitination and degradation. The structural characteristics of molecular glue are exemplified by pomalidomide. (b) PROTAC is a heterobifunctional compound containing an E3 ligase-binding warhead, a linker, and a ligand of a target protein. The structural characteristics of PROTAC are exemplified by BET degrader dBET1 with an CRBN E3 ligase binder (pomalidomide derivative, colored orange), an amide linker (colored purple) and a BET ligand (colored green).

J. Med. Chem. 2021, 64, 15, 10606–10620

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MOLECULAR GLUES

Molecular Glues for Targeted Protein Degradation: From Serendipity to Rational Discovery

Guoqiang Dong, Yu Ding, Shipeng He, and Chunquan Sheng*

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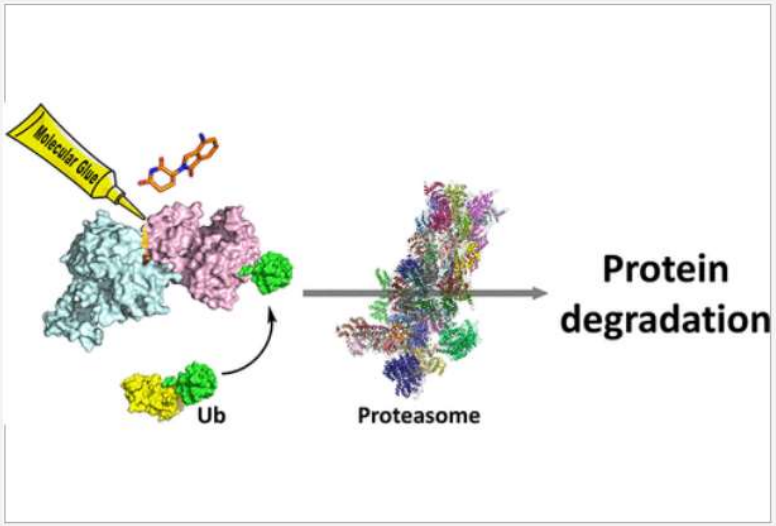
Abstract

Targeted protein degradation is a promising area in the discovery and development of innovative therapeutics. Molecular glues mediate proximity-induced protein degradation and have intrinsic advantages over heterobifunctional proteolysis-targeting chimeras, including unprecedented mechanisms, distinct biological activities, and favorable physicochemical properties. Classical molecular glue degraders have been identified serendipitously, but rational discovery and design strategies are emerging rapidly. In this review, we aim to highlight the recent advances in molecular glues for targeted protein degradation and discuss the challenges in developing molecular glues into therapeutic agents. In particular, discovery strategies, action mechanisms, and representative case studies will be addressed.



MOLECULAR GLUES

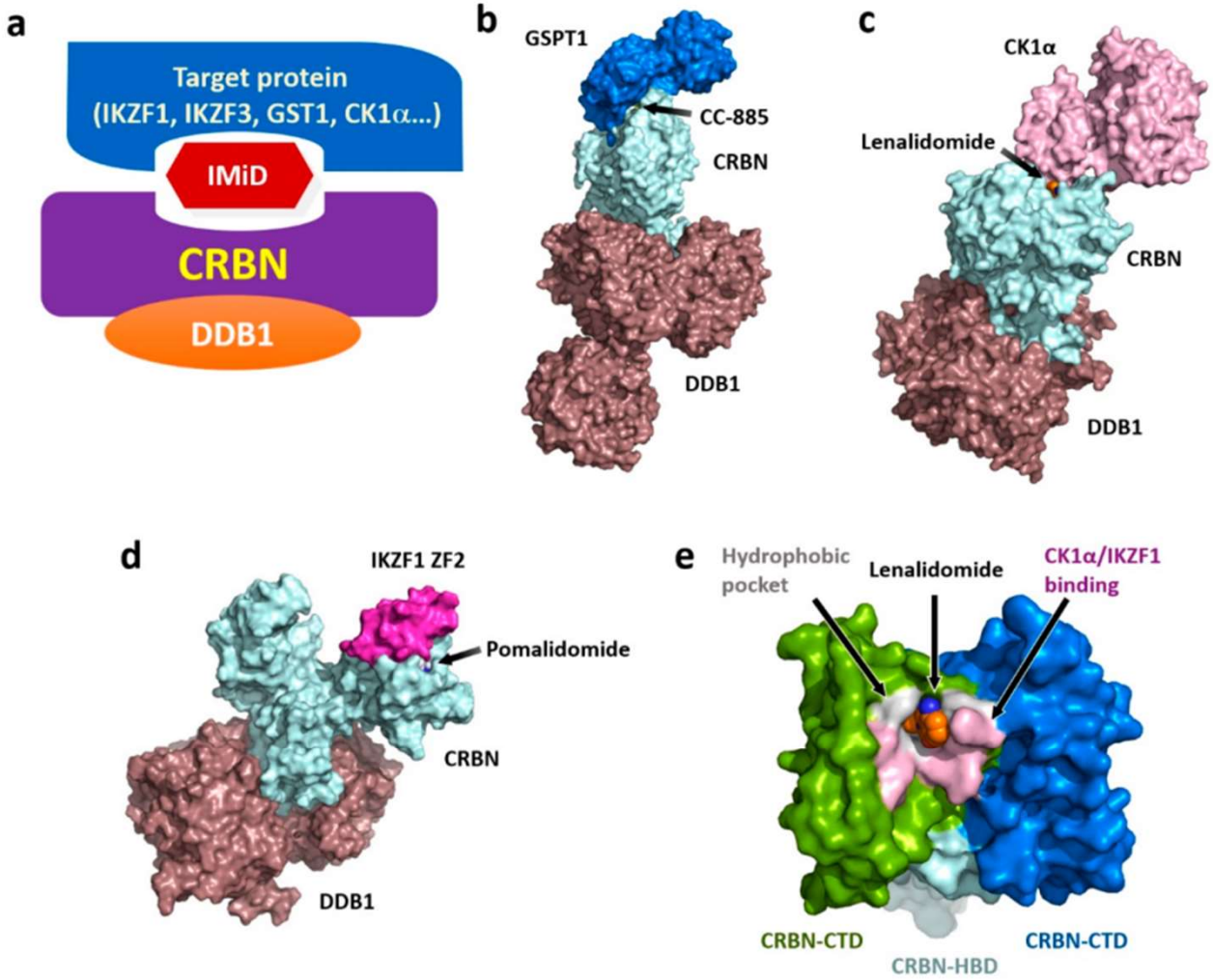


Figure 3. Thalidomide analogs as molecular glue degraders. (a) Schematic representations of neosubstrate recruitment to CRBN by IMiD. (b) Crystal structure of the CRBN-DDB1-GSPT1-CC-885 complex (PDB code: 5HXB). (c) Crystal structure of the CRBN-DDB1-CK1α-lenalidomide complex (PDB code: 5FQD). (d) Crystal structure of the CRBN-DDB1-IKZF1-pomalidomide complex (PDB code: 6H0F). (e) The CRBN surface interacted with CK1α and IKZF1 (PDB code: 4TZ4). The figures were generated in PyMOL 1.7.

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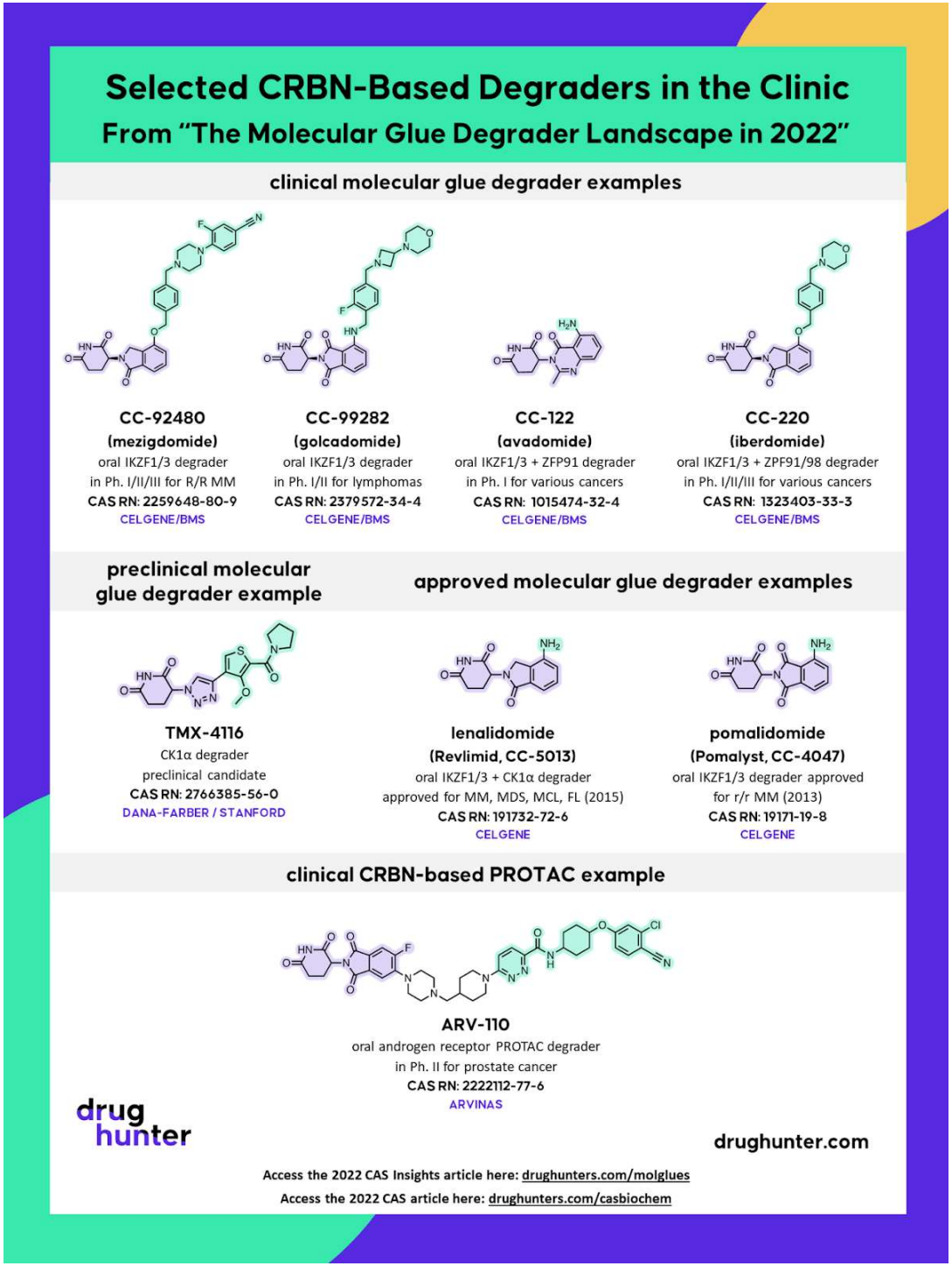
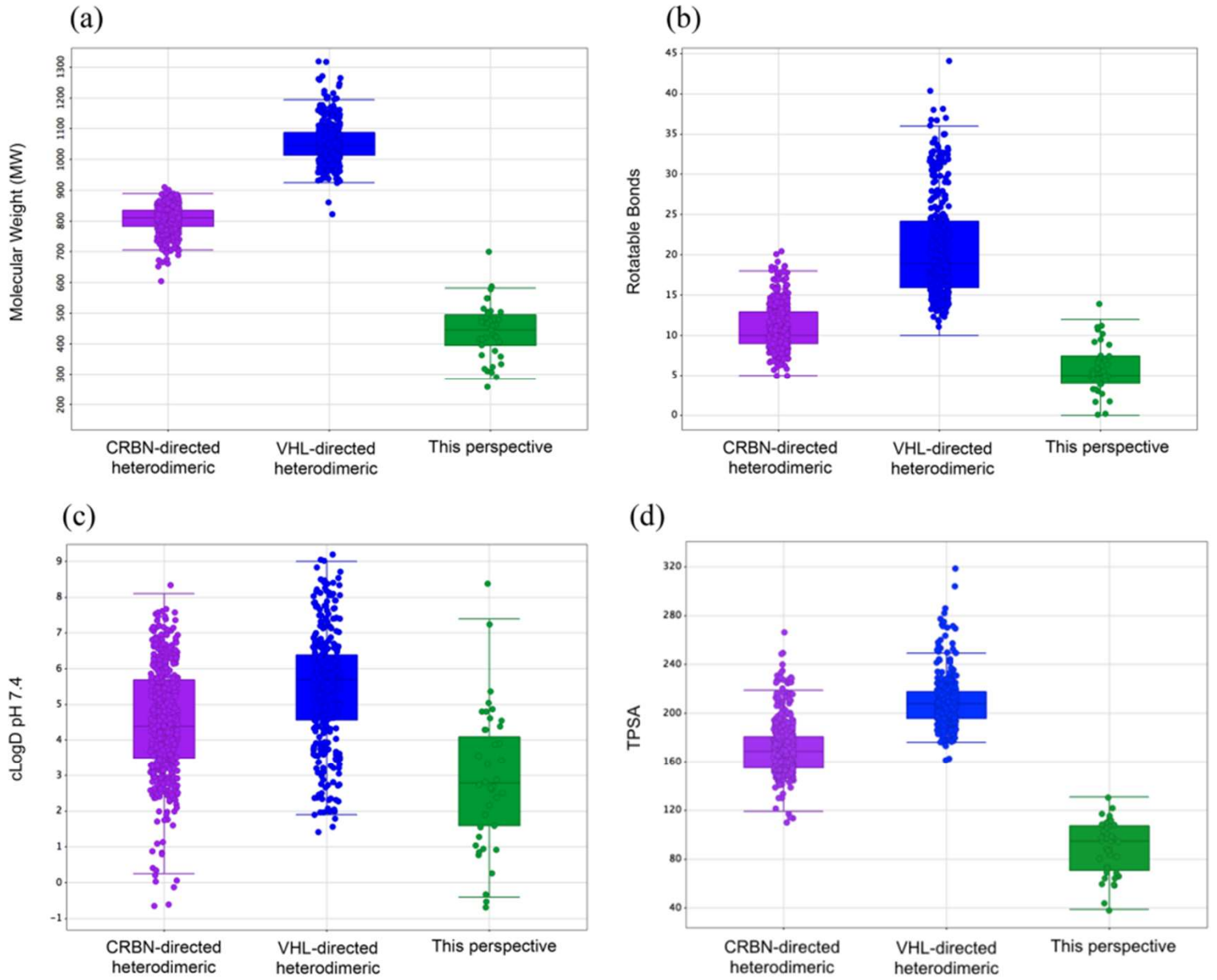
MOLECULAR GLUES

Figure 2. Selected examples of disclosed CRBN-based molecular glue degrader drugs, clinical candidates, and preclinical candidates from the 2022 CAS Insights article and the 2022 *Biochemistry* article. The E3 ligase modulator (CRBN) is highlighted in purple and the protein targeting moiety is highlighted in green.

Compared to PROTACs, molecular glue degraders tend to have chemical properties that are more favorable for oral drug development.



MOLECULAR GLUES



Hanan EJ, et al.
J Med Chem.
2020;63(20):11330-11361

Figure 27. Calculated properties of CRBN-directed heterodimeric compounds (n = 488), VHL-directed heterodimeric compounds (n = 344), and representative monomeric compounds from this Perspective (n = 39, 1−3 per target protein discussed): (a) molecular weight comparison; (b) number of rotatable bonds comparison, prediction of rotatable bonds using the standard methods implemented in the Open Eye software package; (c) TPSA comparison, showing calculated topological polar surface area estimated using the standard methods implemented in the Open Eye software package;[224] (d) calculated log D at pH = 7.4, showing the logarithm of the distribution coefficient calculated using MoKa (Molecular Discovery, version 2.6.4).

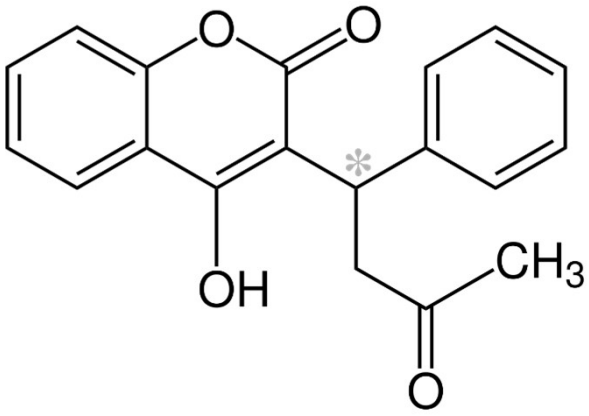
Partie 3 : Les médicaments qui impactent notre environnement…

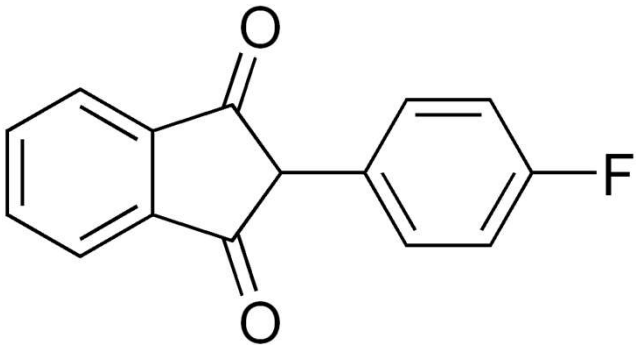
WARFARINE ET AVK

- Chez l'homme

→ AVK

→ 2 groupes chimiques : coumarines et indanediones





WARFARINE ET AVK

- Comme produit phytosanitaire (rodenticide)

→ Conteneurs spéciaux

→ Problème de rémanence

→ Empoisonnement secondaire

BIOCIDES

- Les biocides sont des **substances ou des préparations destinées à détruire, repousser ou rendre inoffensifs les organismes nuisibles**, à en prévenir l'action ou à les combattre de toute autre manière, par une action chimique ou biologique. Dans le cadre des demandes d'autorisation de mise sur le marché de ces produits, l'Anses a pour mission d'évaluer les substances actives biocides et les produits les contenant. Cette évaluation se fait dans un cadre réglementaire européen.

- Les substances actives et les produits biocides font l'objet d'un **règlement européen** (règlement UE N°528/2012) visant à harmoniser la mise sur le marché et l'utilisation de ces produits en Europe. L'objectif principal de cette réglementation est d'assurer un **niveau de protection élevé de l'homme, des animaux et de l'environnement** en limitant la mise sur le marché aux seuls produits biocides efficaces et ne présentant pas de risques inacceptables.

http://echa.europa.eu/fr/regulations/biocidal-products-regulation

BIOCIDES

- Organismes nuisibles ?

Champignons

Bactéries

Virus

Rongeurs

Insectes

…

http://echa.europa.eu/fr/regulations/biocidal-products-regulation

BIOCIDES

- Types et usages

Il existe actuellement **22 types de produits biocides répartis en 4 groupes** :

- les **désinfectants**, types de produits 1 à 5 (ex : désinfectants pour les mains, désinfectants pour l'eau) ;

- les **produits de protection**, types de produits 6 à 13 (ex : produits de protection du bois contre les insectes ou les champignons, produits de protection du cuir, produits de protection des fluides utilisés dans la transformation des métaux) ;

- les **produits de lutte contre les nuisibles**, types de produits 14 à 20 (ex : **rodenticides**, insecticides) ;

- les **autres produits**, types de produits 21 et 22 (ex : peintures antisalissures appliquées sur les bateaux, fluides utilisés dans la taxidermie et la thanatopraxie).

https://www.anses.fr/fr/content/les-produits-biocides

BIOCIDES

- Types et usages

Il existe actuellement **22 types de produits biocides répartis en 4 groupes** :

- les **produits de lutte contre les nuisibles**, types de produits 14 à 20 (ex : **rodenticides**, insecticides)

Permanent baiting (ou *appâtage permanent*) est le fait de maintenir en place de façon illimitée des appâts rodonticides à base d'anticoagulants :

- traitements préventifs ont été limités au niveau européen dès 2017 (règlements d'exécution 2017/1376 à 2017/1383 de la Commission du 25 juillet 2017) – 2 AVK possibles (Difénacoum et Bromadiolone)
- **Interdit en France**

WARFARINE ET AVK

- Cas des AVK : bovins argentins et chauve-souris

Desmodus rotundus (vampire commun, 9 cm de long, envergure ailes déployées de 35 cm et poids de 40 gr), s'attaque aux grands mammifères (chevaux, bœufs, porcs, cervidés, singes..) et à l'homme.

Modèle avancé de chauve-souris = un habile voilier ; elle peut aussi courir, se catapulter dans les airs au moyen de bonds extraordinaires, de ramper à travers d'étroites crevasses et si besoin de sauter.

Principale source de nourriture : bétail et découpe de peau

Le vampire peut transmettre la rage :
Traitement préventif du bétail

DICLOFENAC

« Le diclofénac, mauvais karma pour les vautours »

C'est probablement l'hécatombe animale la plus importante et la plus rapide jamais survenue : dans les années 1990 et 2000, 80 à 90 millions de vautours indiens (*Gyps bengalensis*) sont morts, soit 99% de la population que comptait le pays (Inde). En cause, le diclofénac, anti-inflammatoire pour l'homme et les animaux d'élevage, mais véritable poison pour les vautours : ceux-ci décèdent quelques jours après s'être repus d'une carcasse contaminée, d'une insuffisance rénale foudroyante.

→ De nouveau autorisé en Italie (2006), Espagne (2013)…

http://www.journaldelenvironnement.net/article/le-diclofenac-mauvais-karma-pour-les-vautours,44234

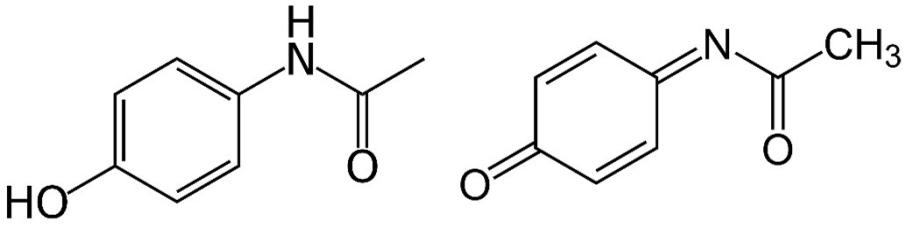
AUTOMÉDICATION PAR LE PARACÉTAMOL POUR LES FÉLINS

Il ne faut pas en donner à votre chat car il s'agit d'un médicament très toxique pour eux !

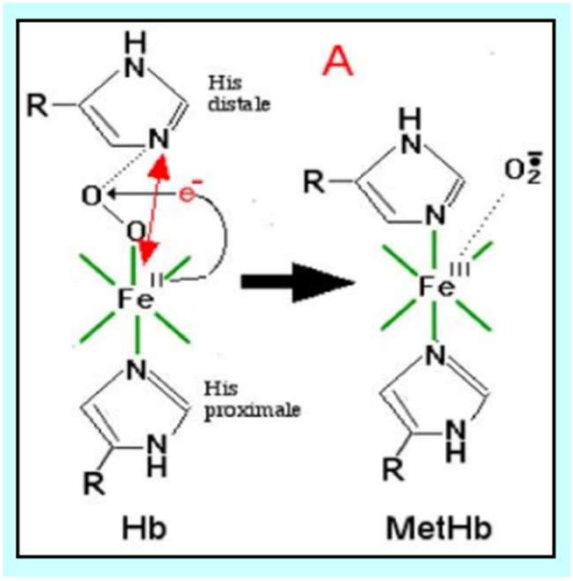
Cas d'intoxication : **Automédication** par les propriétaires.

Chat particulièrement **sensible au paracétamol** car il présente une hémoglobine qui est plus sensible aux attaques oxydatives : METHEMOGLOBINE (ne transporte plus l'O_2).

Faible capacité de glucuronoconjugaison sur les phénols
→ Métabolisme plus lent, NAPQI



dose toxique du paracétamol par voie orale chez le chat est de **50 à 100 mg/kg**



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Conclusion

- Les médicaments du « quotidien » issus de nos ressources naturelles : Bioprospection et **PROTOCOLE DE NAGOYA (2010, 2014)**

- Les médicaments qui impactent notre environnement : **Stations d'épuration** et recherche systématisée ? (ATB, stéroïdes, rodenticides…)

- **Développement durable** et production des médicaments…

DEVELOPPEMENT DURABLE: SYNTHÈSE EN FLUX CONTINU

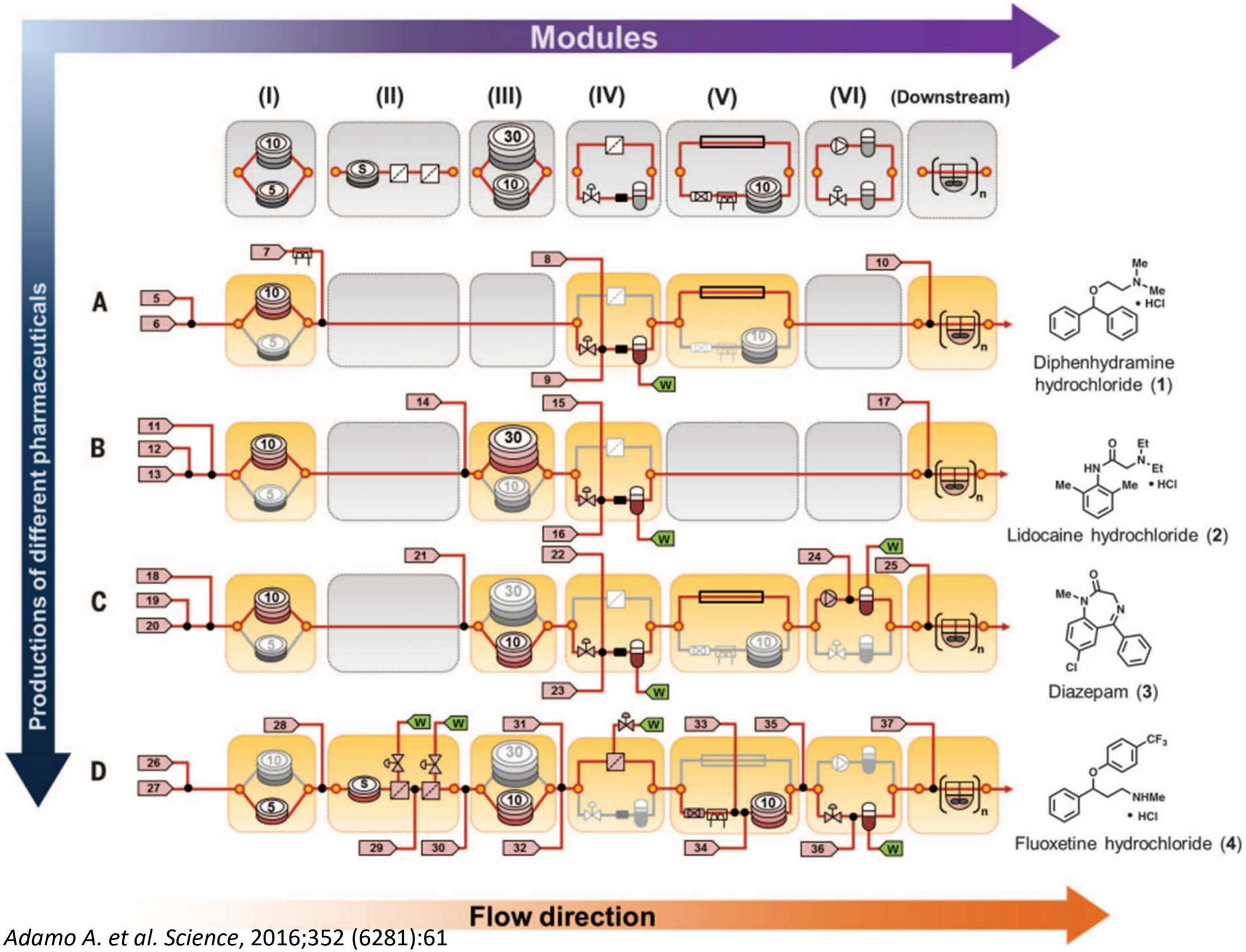
Une usine portable de fabrication de médicaments

Massachussetts **I**nstitute of **T**echnology à Cambridge aux USA
Projet « Pharmacy on Demand » financé par la Defense Advanced Research Projects Agency (DARPA) - Département de la défense US

Synthèse de quatre médicaments très différents.
Cette unité permet aussi la purification et la formulation

Ce dispositif mis en place par des chercheurs du MIT peut être reconfiguré afin de fabriquer différents types de médicaments.

https://www.reflexions.uliege.be/cms/c_426090/fr/une-usine-portable-de-fabrication-de-medicaments?part=2, consulté le 20 mars 2022



Adamo A. et al. Science, 2016;352 (6281):61

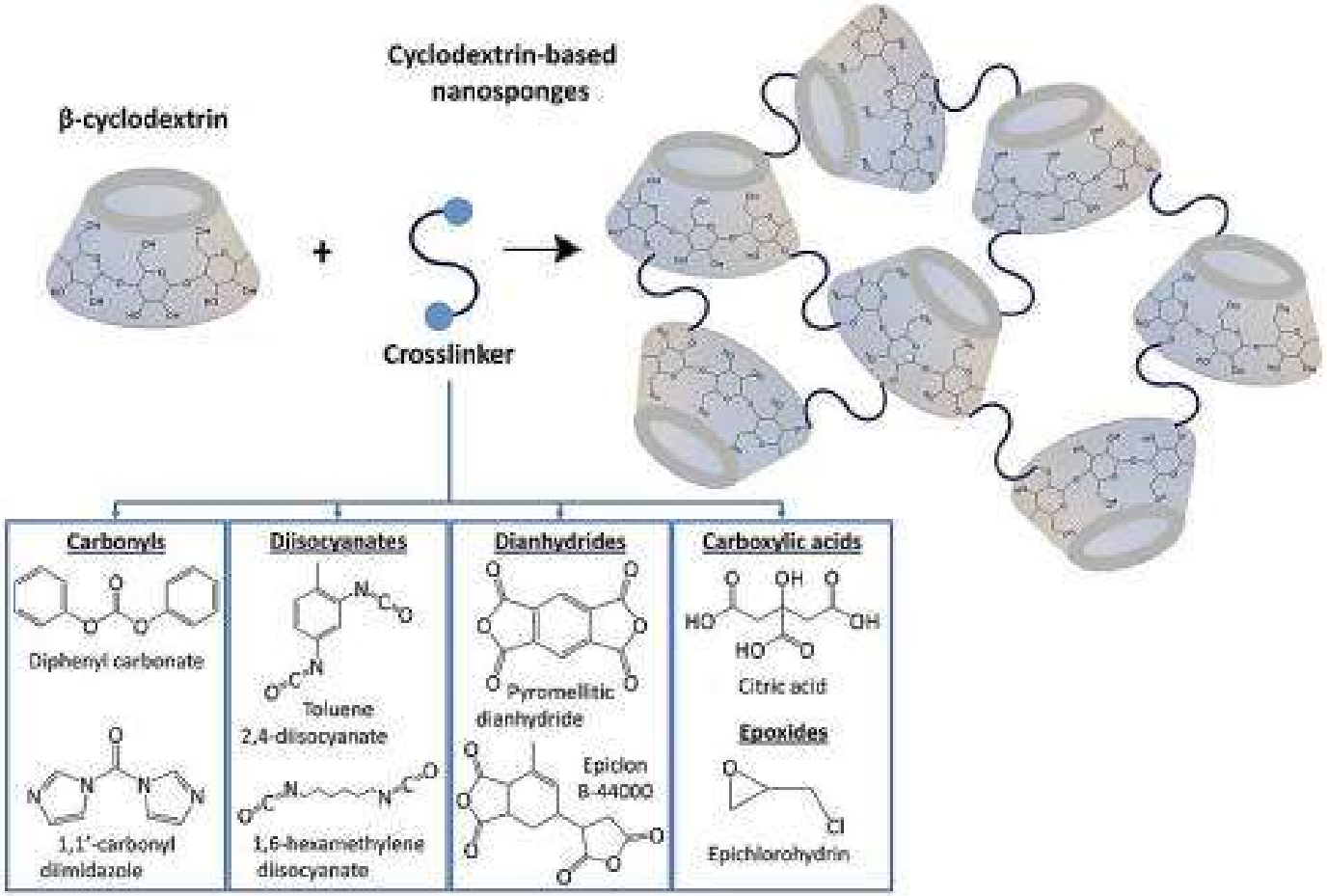
Nanosponges for Drug Delivery and Cancer Therapy: Recent Advances.

Iravani S, Varma RS.

Nanomaterials (Basel). 2022 Jul 16;12(14):2440. doi: 10.3390/nano12142440.

PMID: 35889665 **Free PMC article.** Review.

In this context, the drug loading within **nanosponges** is influenced by the crystallization degree. Notably, 3D printing technologies can be applied for the development of novel **nanosponge**-based systems for biomedical applications. ...Herein, the recent advancements a ...



Merci de votre attention