Il concetto del “drug conjugate” nel CD19 come target terapeutico nel DLBCL

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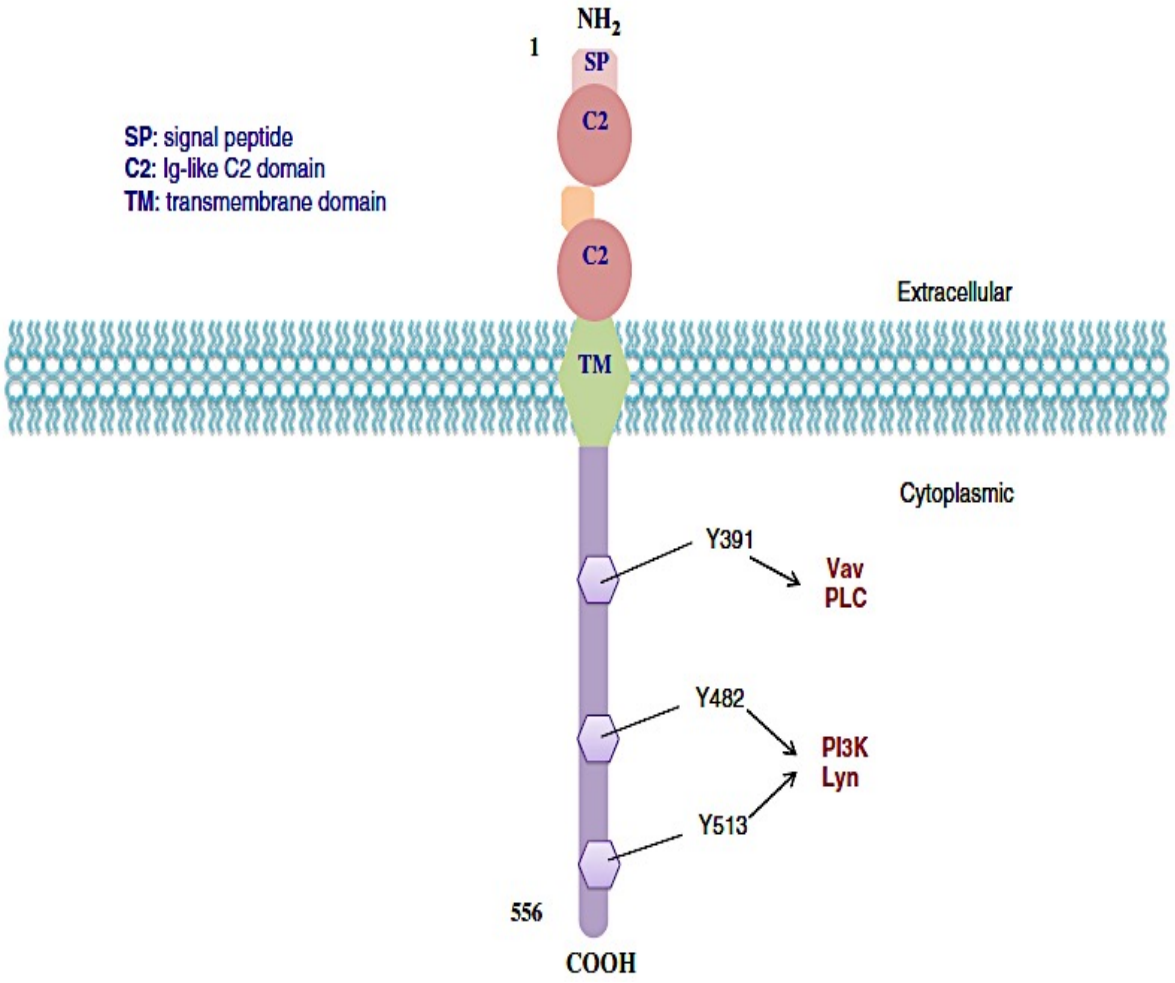
Disclosures

Consultant:

- *MSD*
- *Lilly*
- *AstraZeneca*
- *GSK*
- *Gilead*
- *BeiGene*
- *Seagen*
- *InCyte*
- *Pfizer*
- *Novartis*
- *Roche*

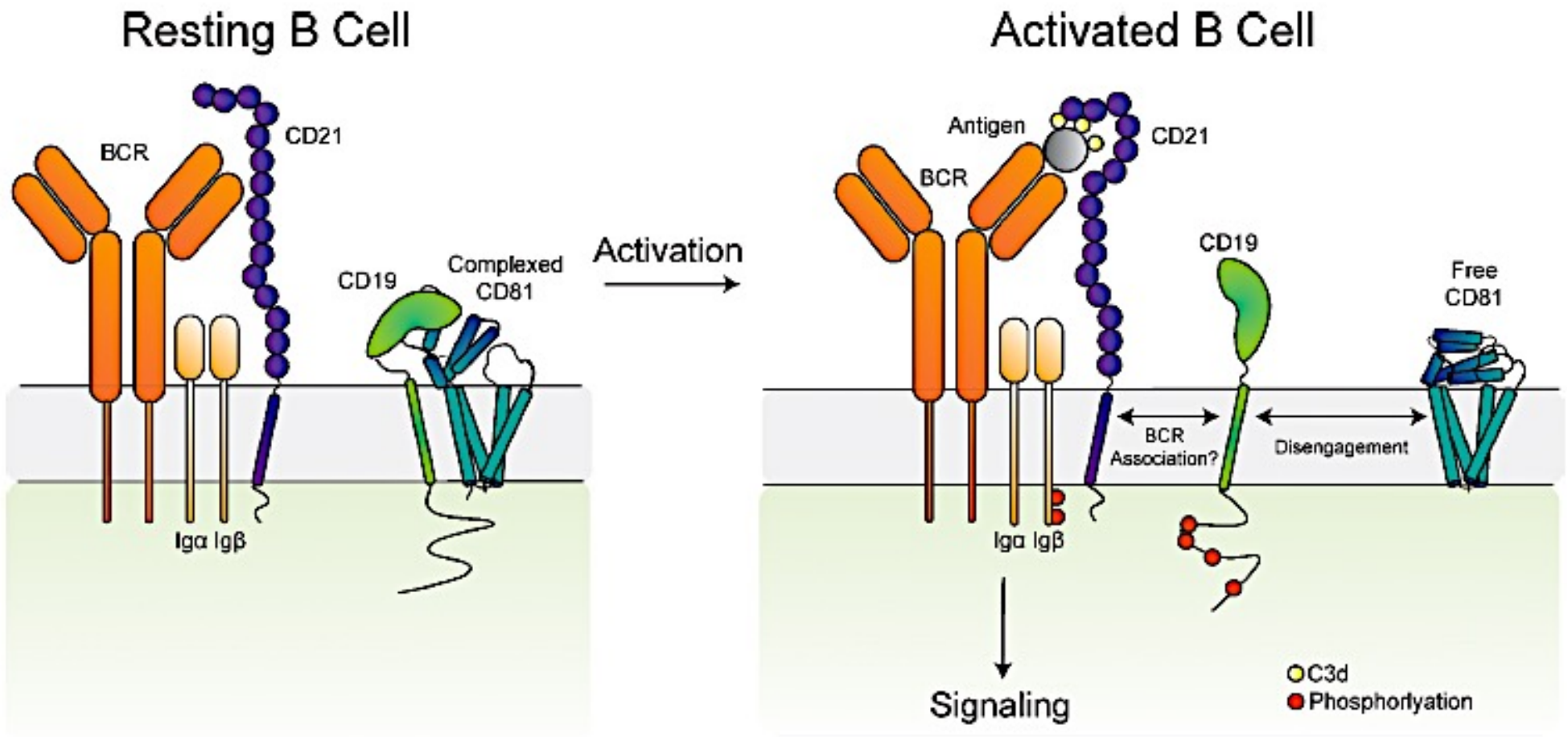
CD19 molecular structure



- The human CD19 antigen is a 95 kd transmembrane glycoprotein belonging to the Ig superfamily
- CD19 has a single transmembrane domain, a cytoplasmic C-terminus, and extracellular N-terminus.
- The extracellular domain contains two C2-type Ig-like domains.
- The biologic functions of CD19 are dependent on cytoplasmic tyrosine residues – Y391, Y482 and Y513.

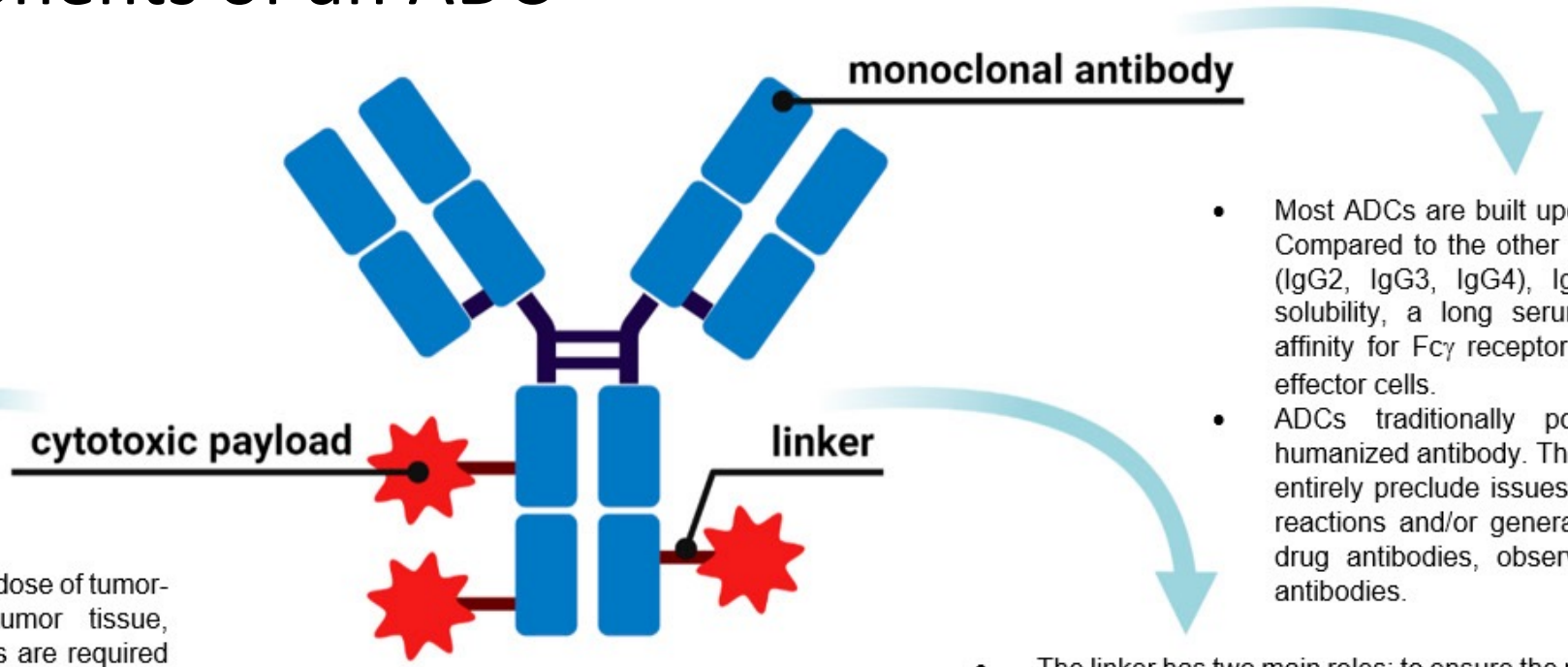
Wang et al. Experimental Hematology & Oncology 2012, 1:36

CD19 is involved in BCR signal transduction and part of a multimeric complex



Susa et al. eLife 2020;9:e52337

Key components of an ADC



- Most ADCs are built upon the IgG1 architecture. Compared to the other IgG antibody subclasses (IgG2, IgG3, IgG4), IgG1 optimally combines solubility, a long serum half-life, and binding affinity for Fcγ receptors expressed on immune effector cells.
- ADCs traditionally possess a chimeric or humanized antibody. This minimizes but does not entirely preclude issues such as hypersensitivity reactions and/or generation of neutralizing anti-drug antibodies, observed when using murine antibodies.

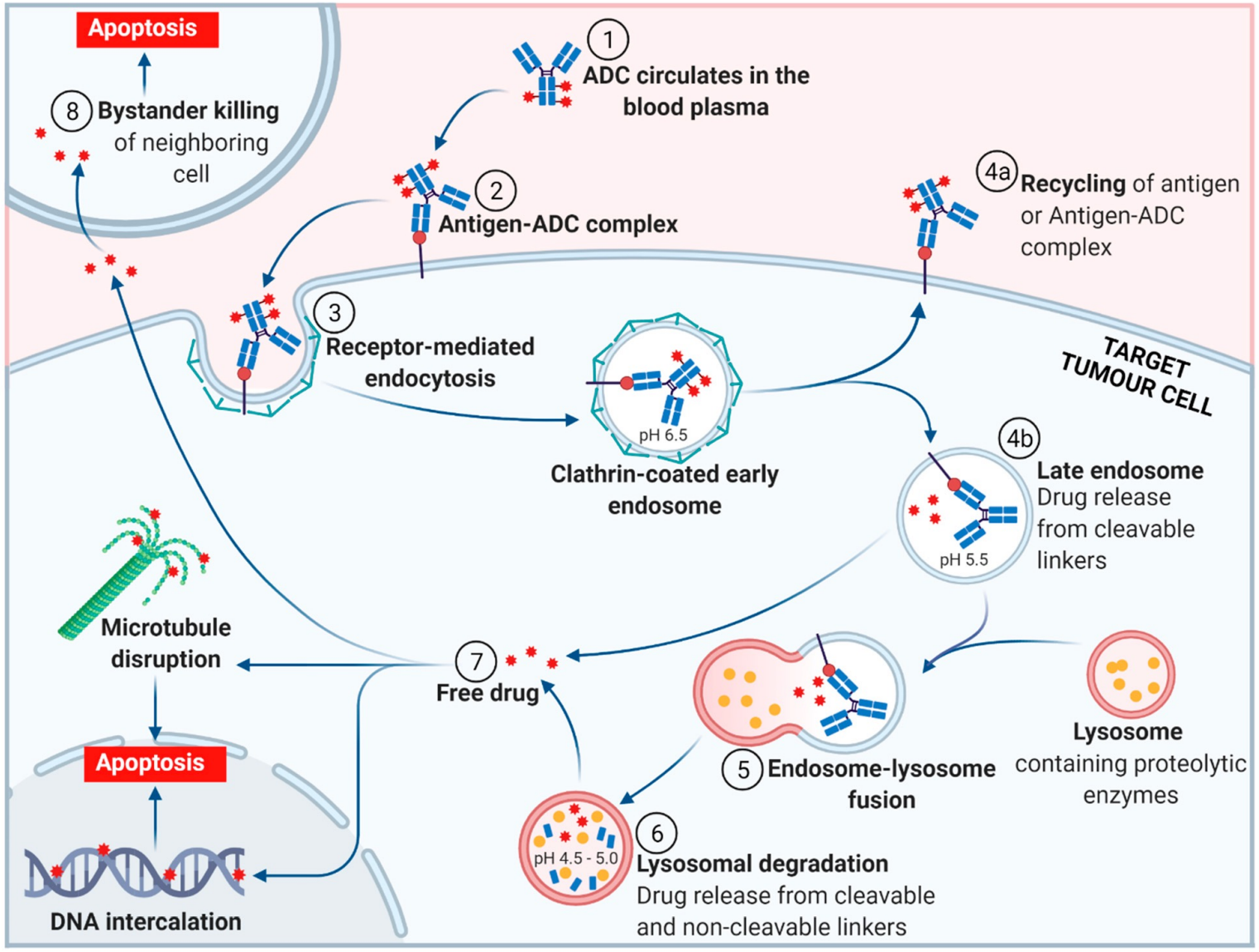
- Only ~0.1% of the administered dose of tumor-targeted mAbs reach the tumor tissue, therefore highly potent payloads are required to achieve therapeutic efficacy.
- ADCs exhibit both on-target and off-target toxicities. While most toxicities are related to the payload being released off-target, notable examples of target-dependent toxicities exist.

- The drug-to-antibody ratio (DAR) is the average number of payload moieties attached to each mAb. The synthetic techniques used to prepare certain ADCs enable tight control over this parameter, but those currently on the market rely on conjugating payloads to native cysteine or lysine residues of the mAb, resulting in products with substantial heterogeneity and DAR variation (DAR ranging from 2 to 8).

- The linker has two main roles: to ensure the payload remains attached to the mAb while the drug circulates in plasma, and to enable efficient release of the payload inside the target tumor cell. Conjugates that do not properly deliver their payload forego the unique advantage of ADC therapy – selective delivery with minimal off-target toxicity.
- Linkers are classified as cleavable or non-cleavable. Cleavable linkers release the payload in response to tumor-associated factors (e.g. acidic or reducing conditions, or an abundance of proteolytic enzymes) whereas non-cleavable linkers rely on lysosomal degradation of the entire antibody-linker construct, often resulting in retention of charged amino acids on the payload, which may affect its action or cell permeability.

Tong JTW et al. Molecules 2021, 26, 5847

Intracellular metabolism of an ADC



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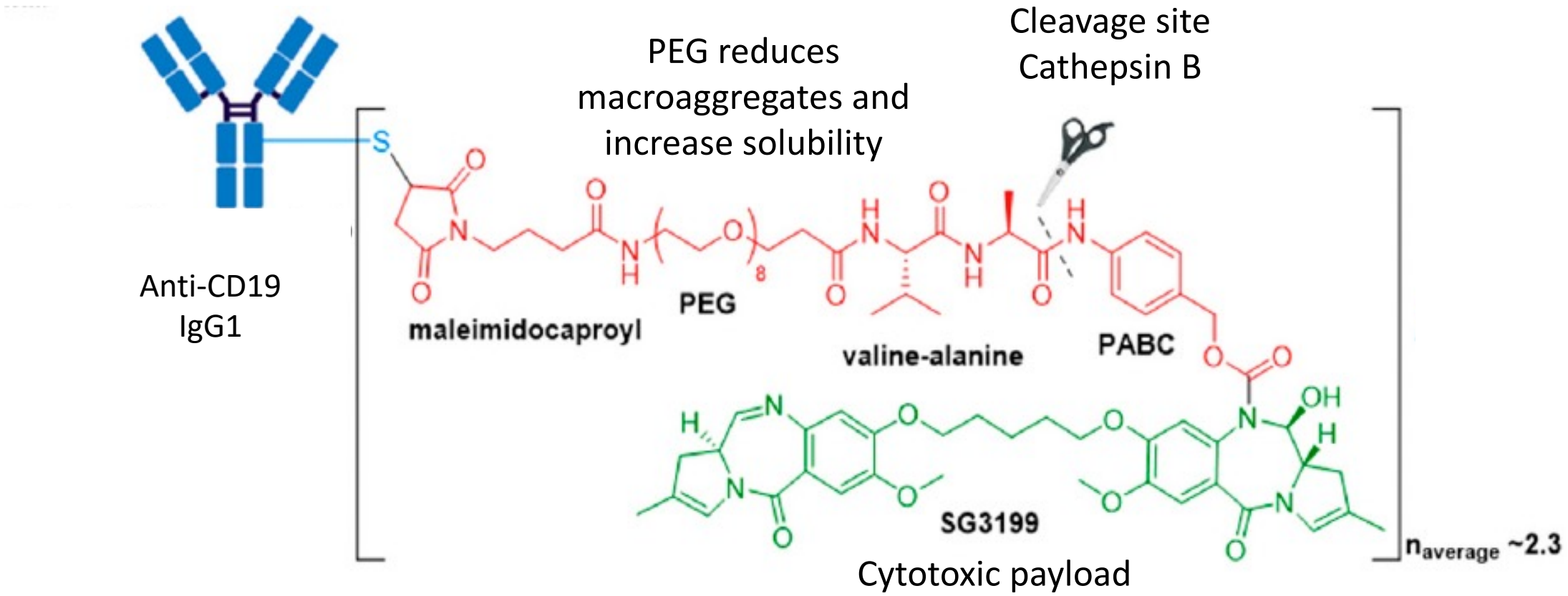
Molecular structure of loncastuximab tesirine



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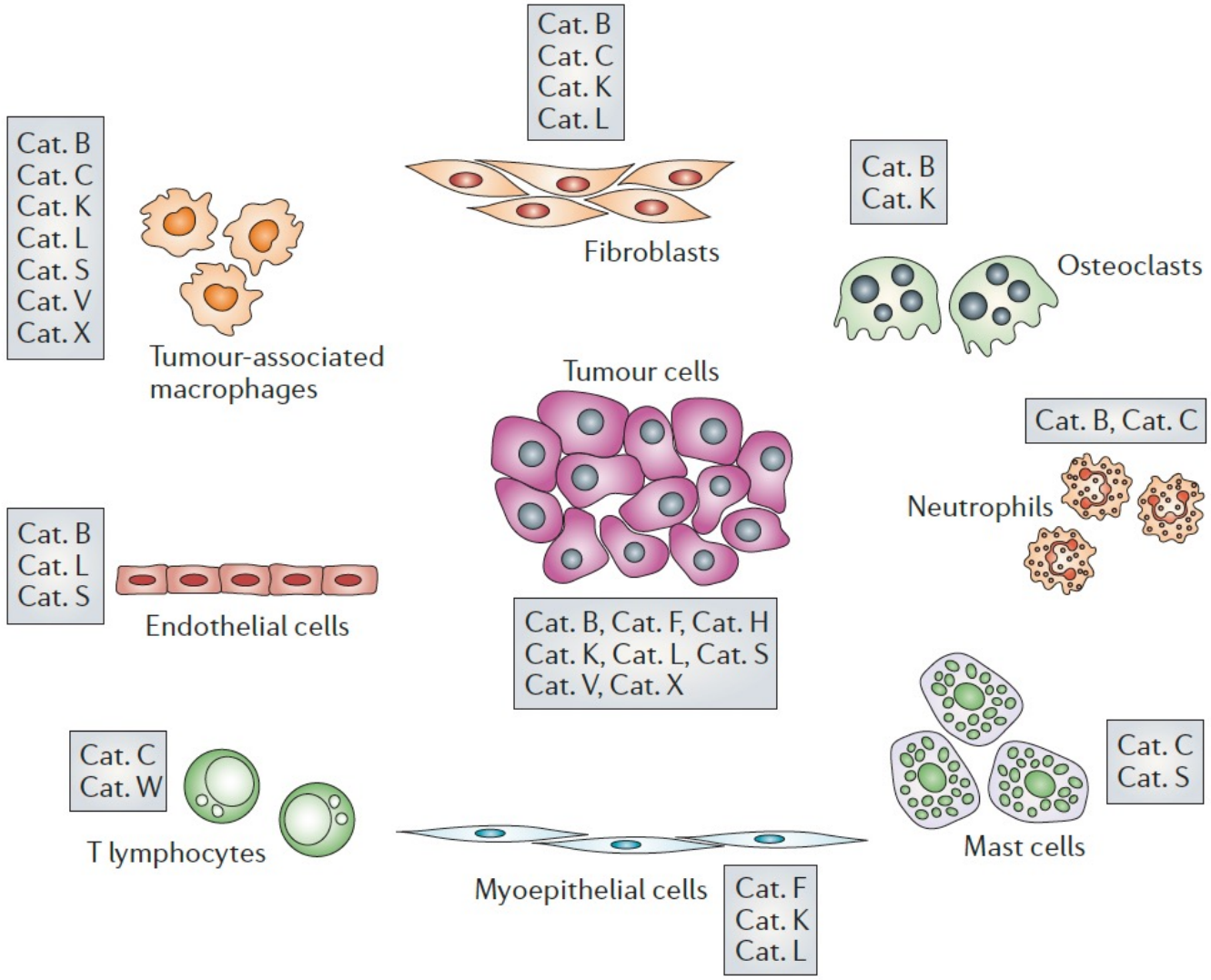
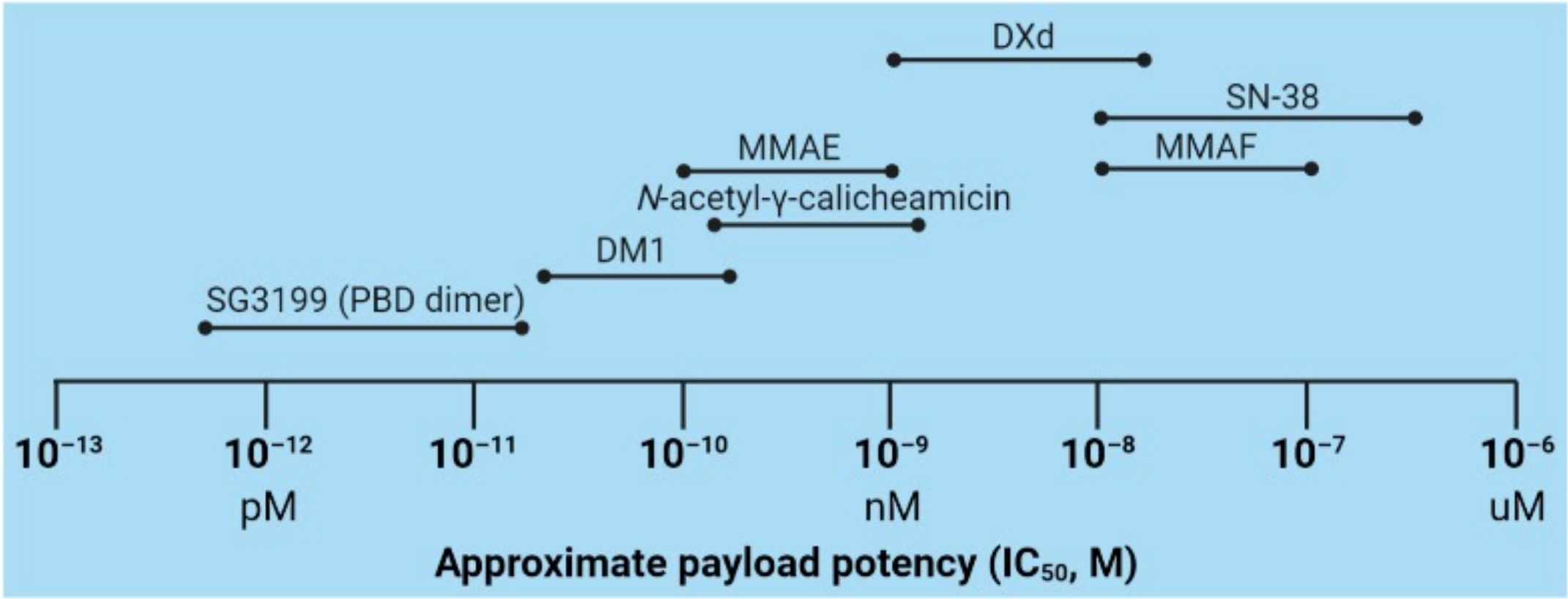
The cysteine cathepsins that are known to be expressed in tumour cells and tumour-associated cells, and have been identified as contributing to neoplastic progression



Mona Mostafa Mohamed and Bonnie F. Sloane. NATURE REVIEWS CANCER 6 (2006) 765

Comparison of approximate payload potency ranges



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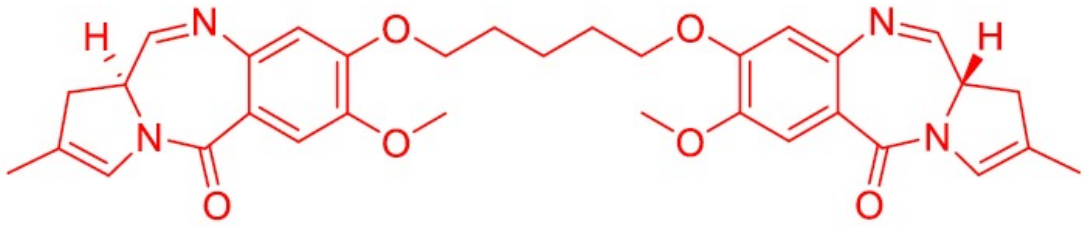
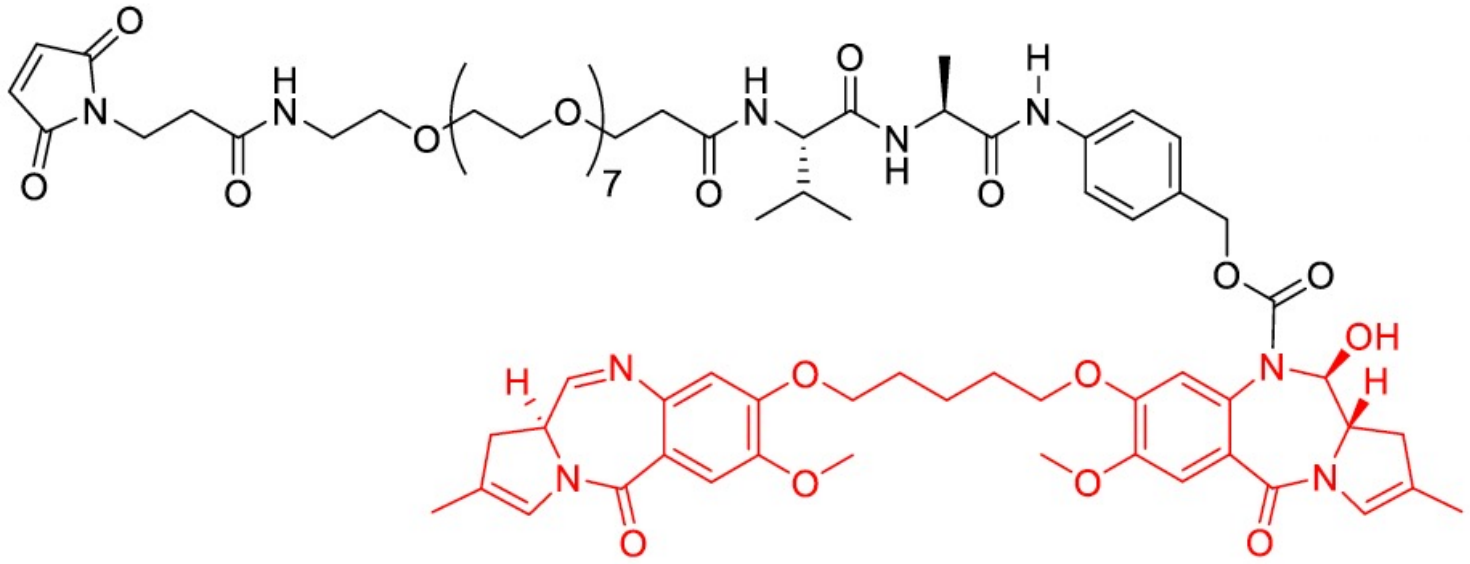
Molecular structure of SG3199 and tesirine



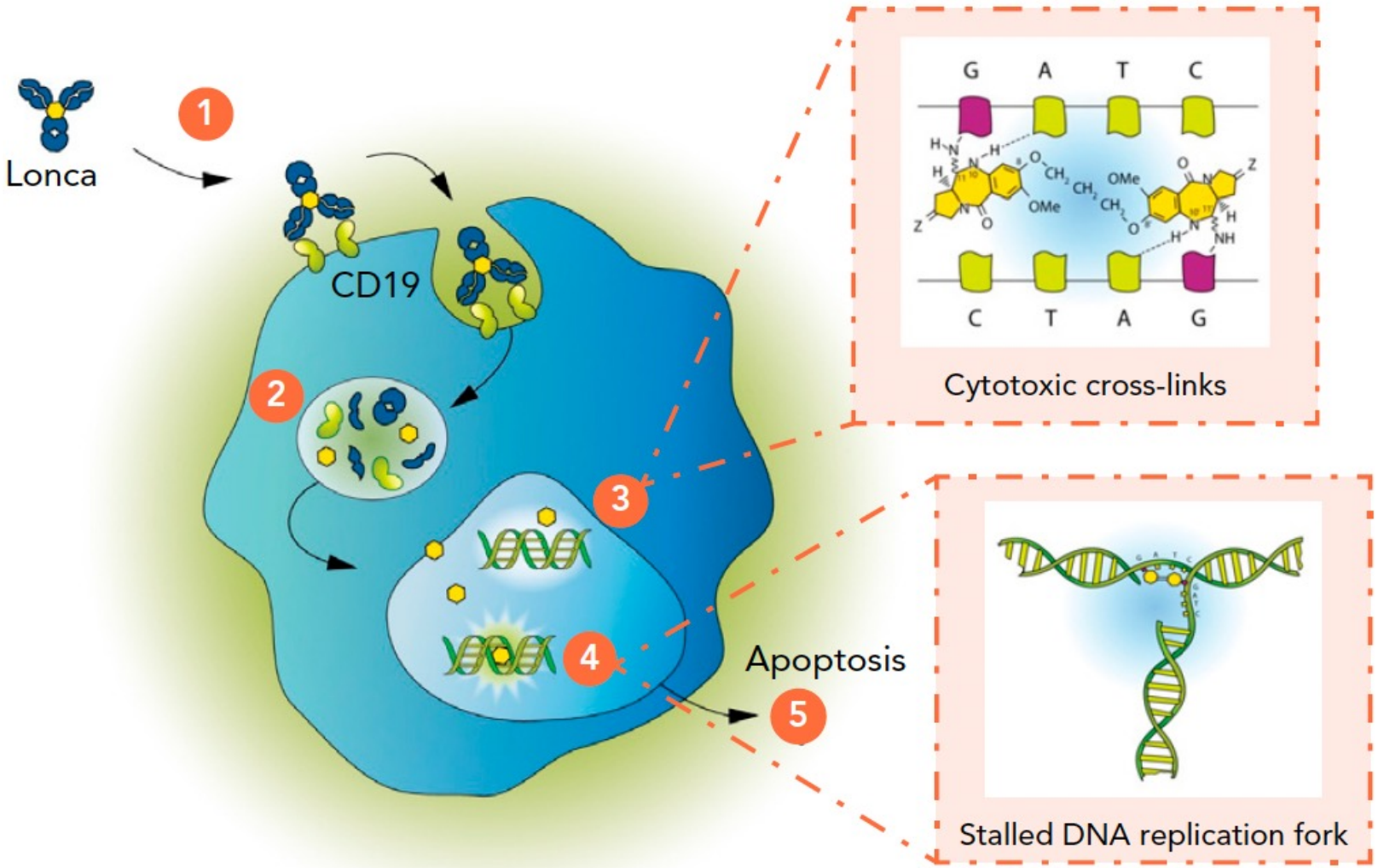
SG3199



Tesirine (SG3249)

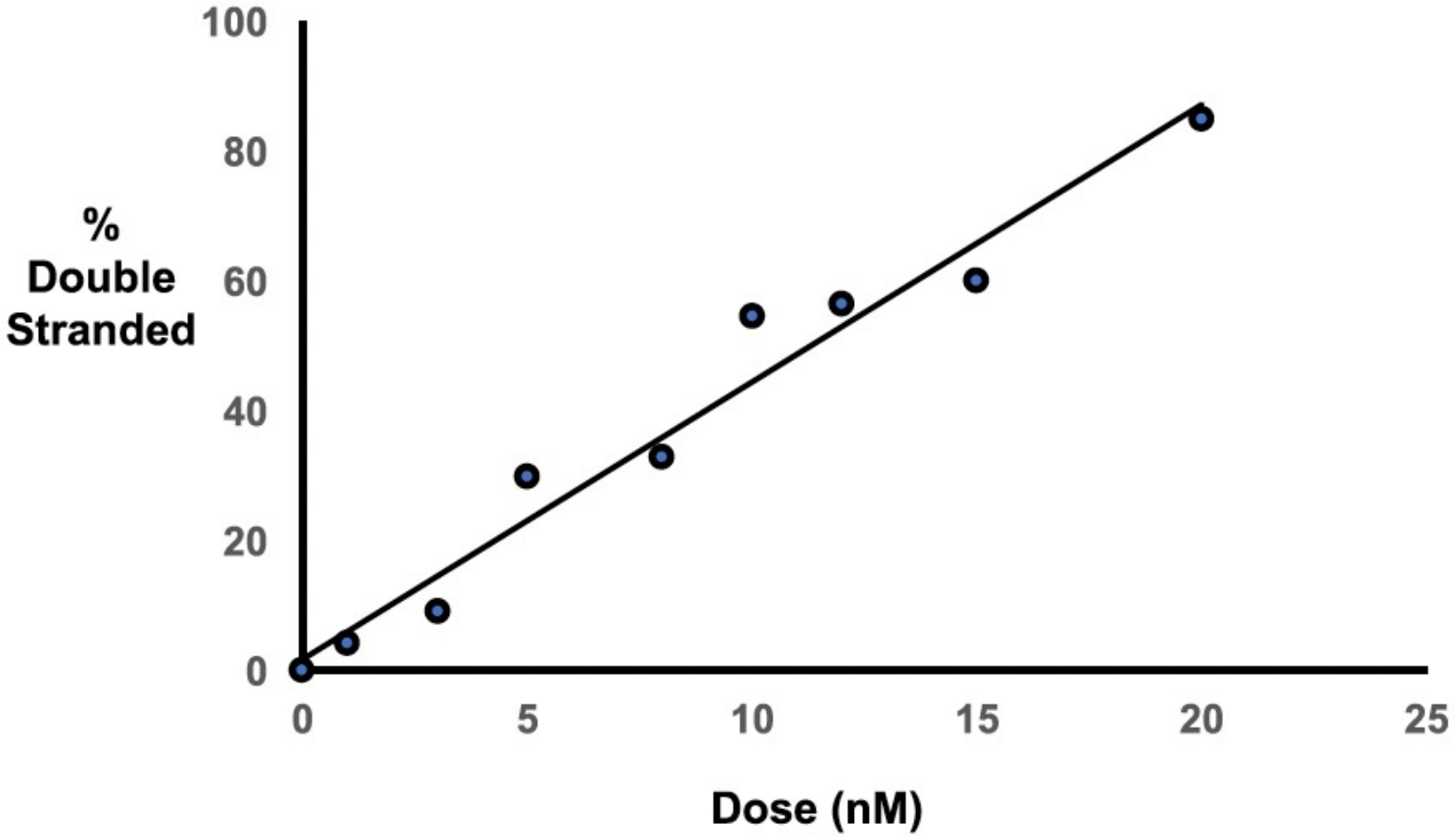
John A. Hartley et al. Sci Rep (2018) 8:10479

Mechanism of action of PBD-ADCs (loncastuximab tesirine)



Calabretta E, Zinzani P L, Carlo Stella C et al. Blood 2022;140:303

Quantitation of the % double stranded (cross-linked) DNA following SG3199 treatment



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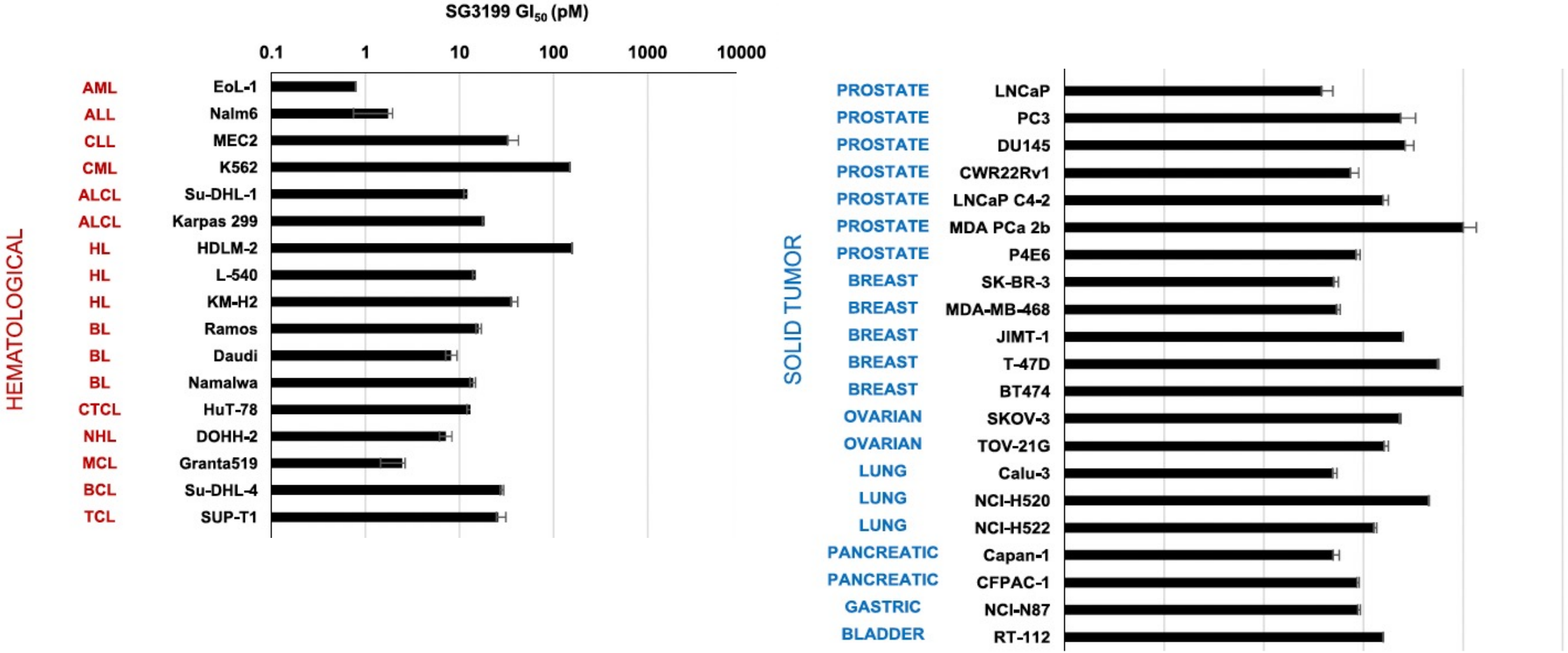
Sensitivity of a panel of human tumour haematological and solid tumour cell lines to SG3199



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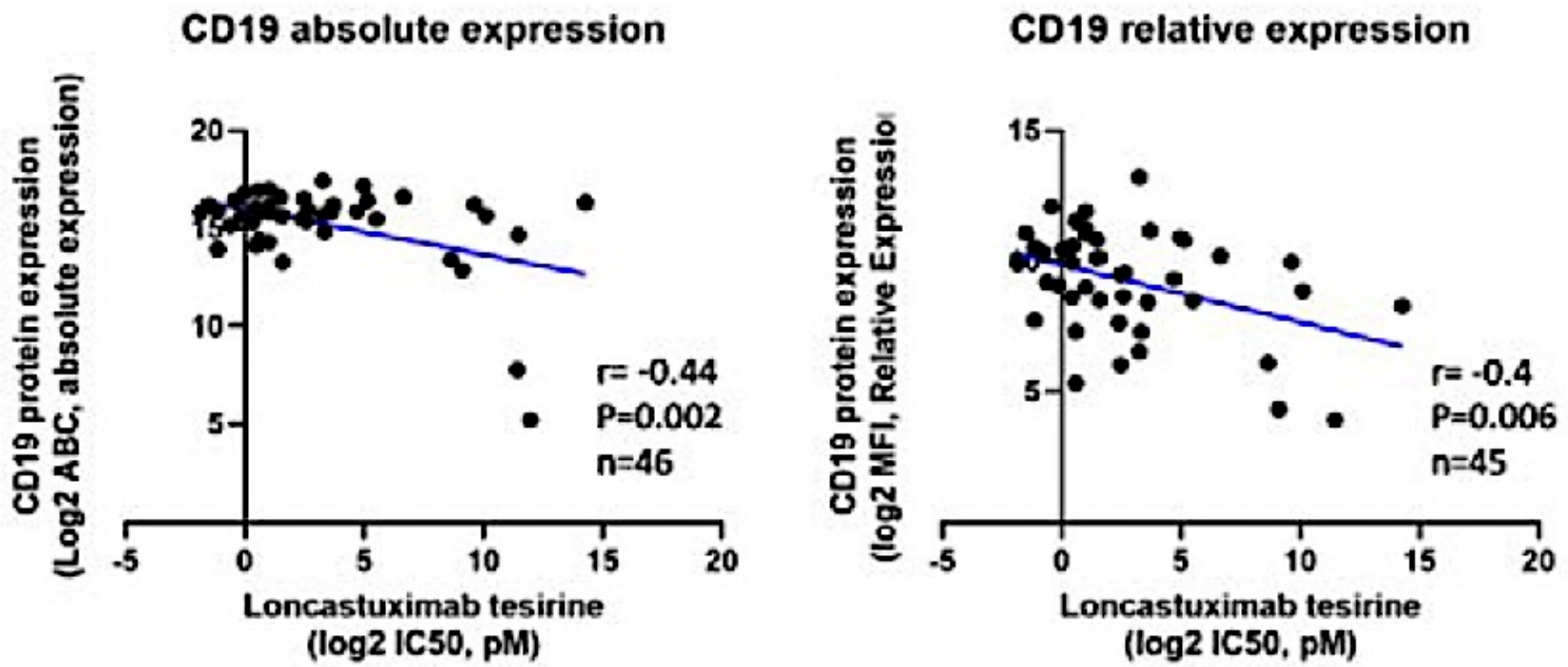
The in vitro anti-proliferative activities of loncastuximab tesirine correlates with CD19 expression



Tarantelli C et al. doi: https://doi.org/10.1101/2023.08.17.553668

Anti-tumor activity of loncastuximab tesirine in lymphoma cell lines

	No.	Median IC_{50} (pM)	95% confidence interval (pM)
ABC DLBCL	7	35	7.3-880
GCB DLBCL	19	2	1.17-10.6
MCL	10	1.75	1.1-5.4
MZL	6	2.5	0.47-496
CLL	2	15.75	5.5-26 *
HL	3	2750	600-14000 *
PMBCL	1	1.5	n.d.
ALCL	4	4875	700-11500 *
CTCL	4	2500	900-35000 *
PTCL-NOS	1	850	n.d.

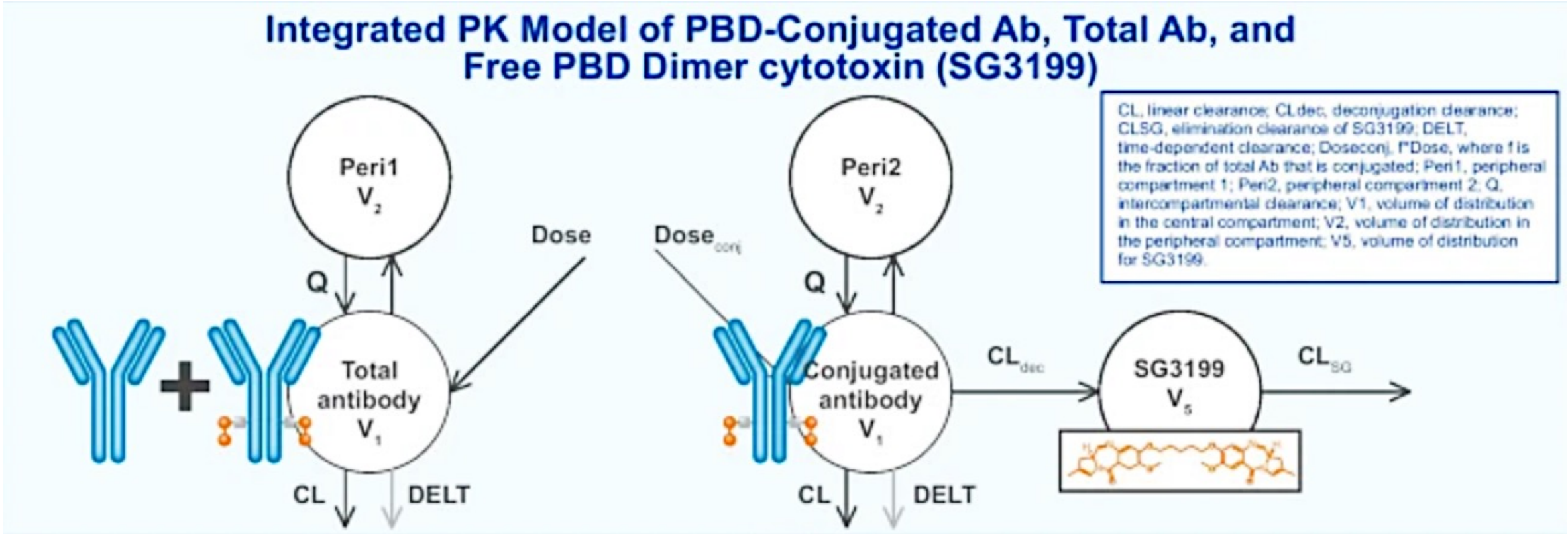
Tarantelli C et al. doi: https://doi.org/10.1101/2023.08.17.553668

Anti-tumor activity of the SG3199 in lymphoma cell lines

	No.	Median IC_{50} (pM)	95% confidence interval (pM)
ABC DLBCL	7	1.17	0.63-7.85
GCB DLBCL	19	1.14	0.75-1.53
MCL	10	0.53	0.53-1.66
MZL	6	0.53	0.53-0.85
CLL	2	0.83	0.53-1.14*
HL	3	4.97	0.85-29.24*
PMBCL	1	0.56	n.d.
ALCL	4	2.34	0.85-17.54*
CTCL	4	1.59	0.53-23.39*
PTCL-NOS	1	0.53	n.d.

Tarantelli C et al. doi: https://doi.org/10.1101/2023.08.17.553668

PK model of loncastuximab tesirine



Hess H et al. The AAPS Journal (2022) 24: 11

PK/PD model of loncastuximab tesirine

Pharmacometric modeling demonstrated significant exposure-response relationships between cAb exposure and efficacy/safety outcomes

- The estimated half-life of cAb at steady state was 20.6 days by ~15 weeks.

Higher cAb exposure was significantly associated with		Lower cAb exposure was associated with			
Improved ORR, PFS, and OS	Increased specific Grade ≥2 TEAEs	ECOG Status >1	Non-DLBCL subtype	Low albumin	Mild/moderate hepatic impairment

Identified as covariates that also significantly impact survival in patients with DLBCL

Hess H et al. The AAPS Journal (2022) 24: 11

Conclusions

- CD19 is an important target of therapeutic intervention
- Its involvement in signal transduction pathways of pathologic B-cells is well documented.
- CD19 is highly expressed on cell membrane
- The CD19 targeting ADC loncastuximab tesirine has a strong cytotoxic activity in a large panel of cell lines derived from B cell lymphomas
- Its in vitro activity correlated with CD19 expression level