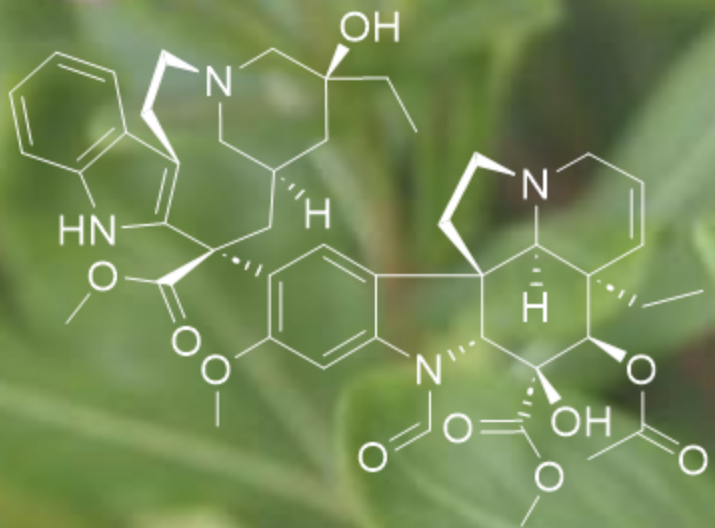




Antibody-Vincristine Conjugates as Potent Anticancer Therapeutic Agents

Dr. Héloïse Cahuzac

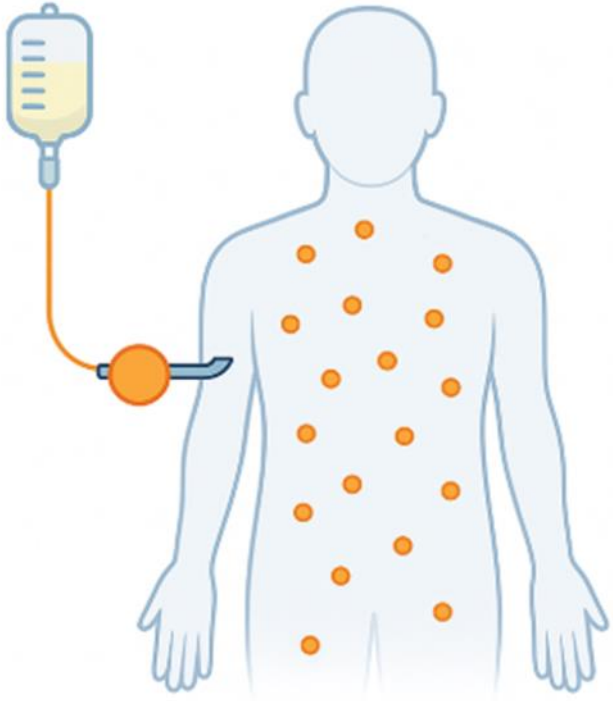
BioFunctional Chemistry laboratory
University of Strasbourg
hcahuzac@unistra.fr

28 November 2025 • 14^e Forum du Cancéropôle Est • Besançon, France



What targeted therapies aim to achieve

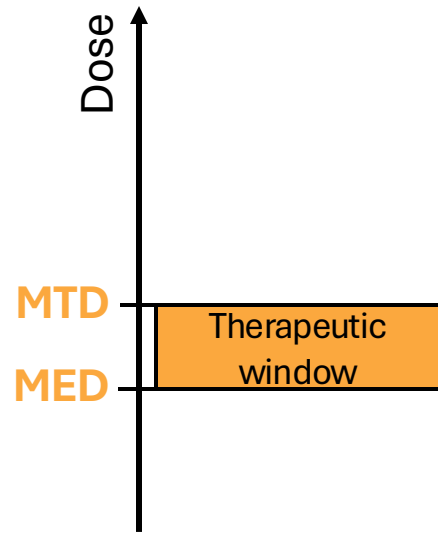
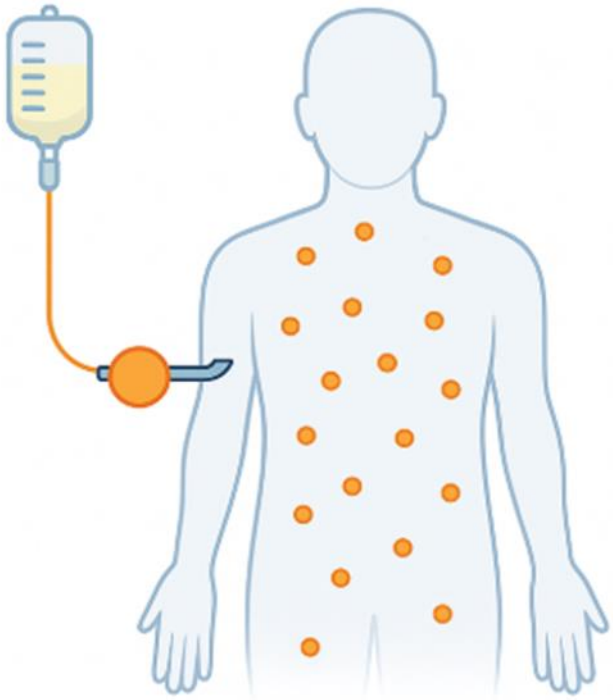
- **Chemotherapy**



- Systemic cytotoxic treatment
- Severe side effects

What targeted therapies aim to achieve

- **Chemotherapy**

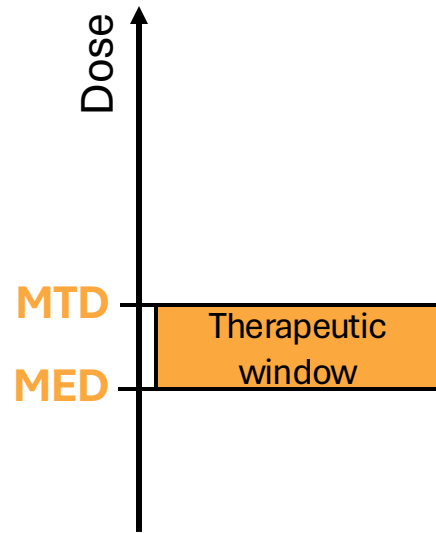
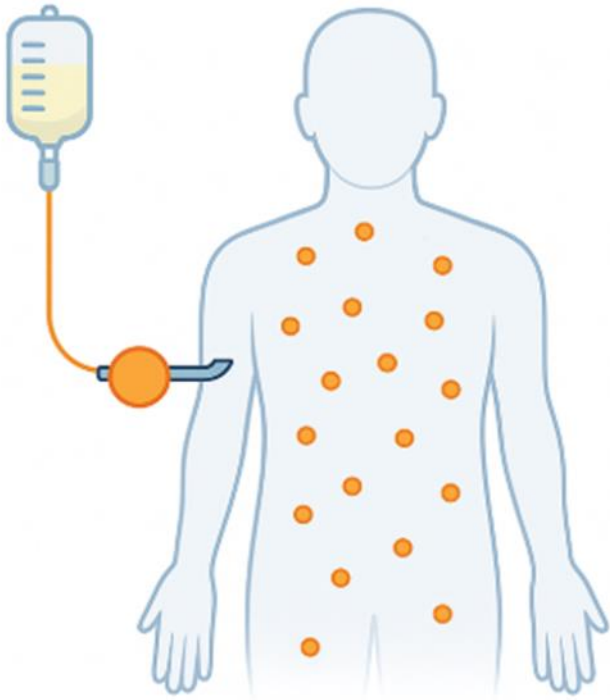


- Systemic cytotoxic treatment
- Severe side effects

Min effective dose = MED
Max tolerated dose = MTD

What targeted therapies aim to achieve

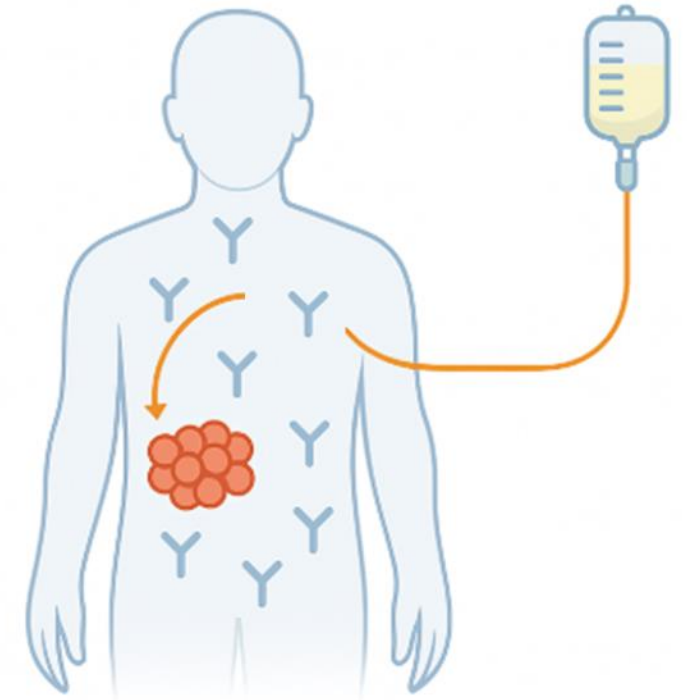
• Chemotherapy



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Max tolerated dose = MTD

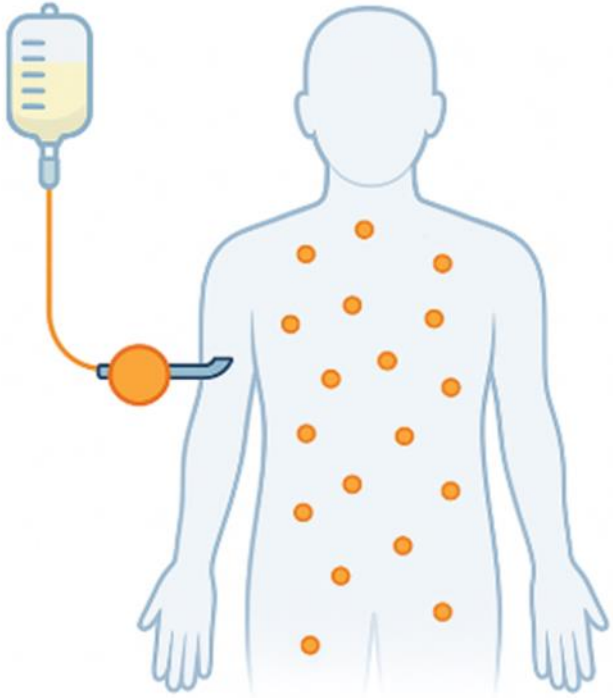
Y Targeted therapies



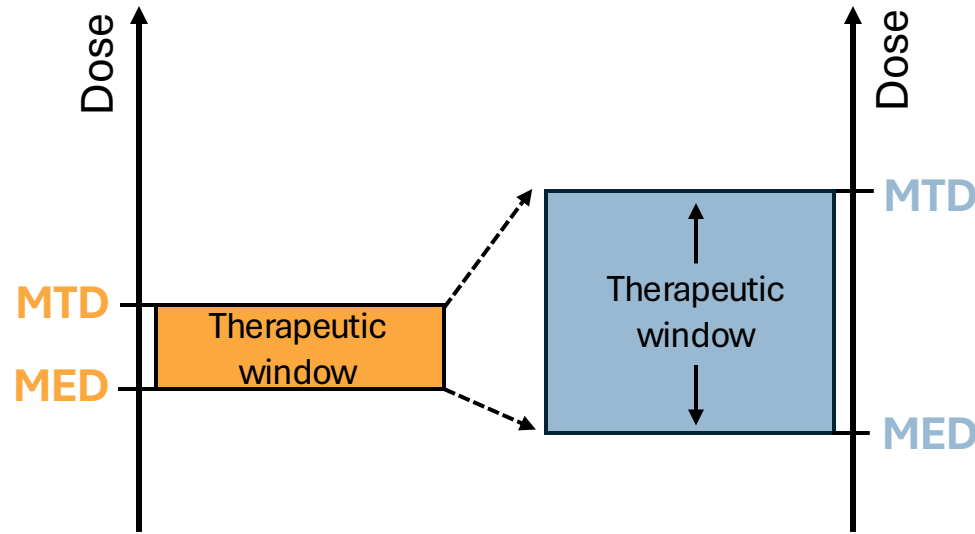
- Delivery system targeted to the tumor
- Increased efficacy
- Reduced side effects

What targeted therapies aim to achieve

• Chemotherapy

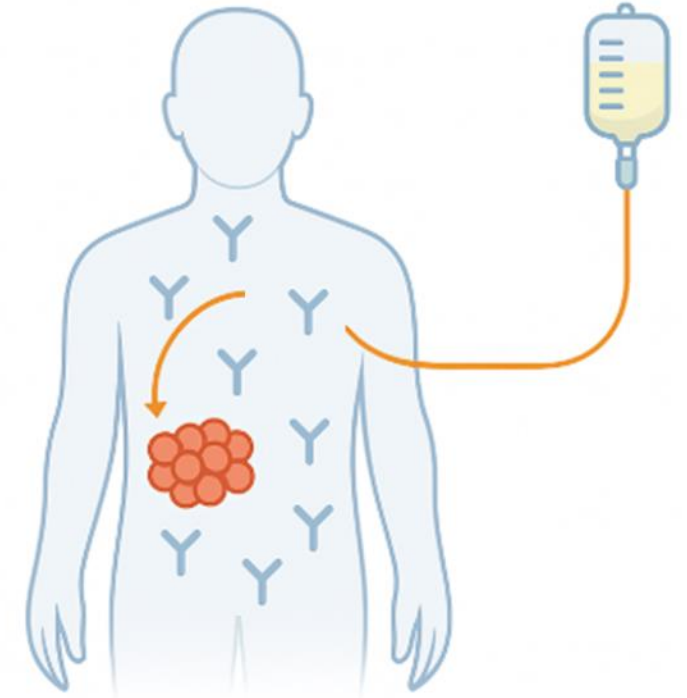


- Systemic cytotoxic treatment
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Min effective dose = MED
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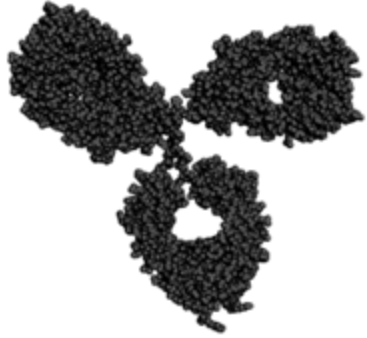
Y Targeted therapies



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Structure of anticancer bioconjugates

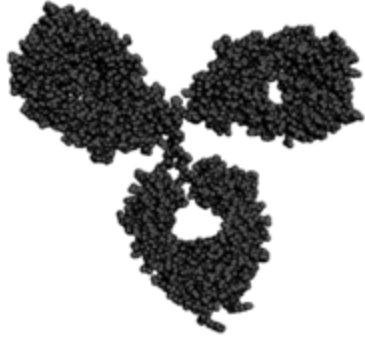
A VECTOR



Provides tumor targeting
(*antibody, fragments,*
peptides...)

Structure of anticancer bioconjugates

A VECTOR



Provides tumor targeting
*(antibody, fragments,
peptides...)*

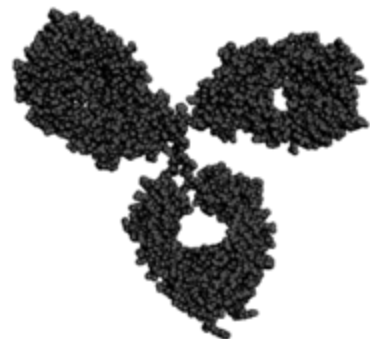
A PAYLOAD



Executes tumor cell killing
*(cytotoxic drug, radioisotope,
oligonucleotide)*

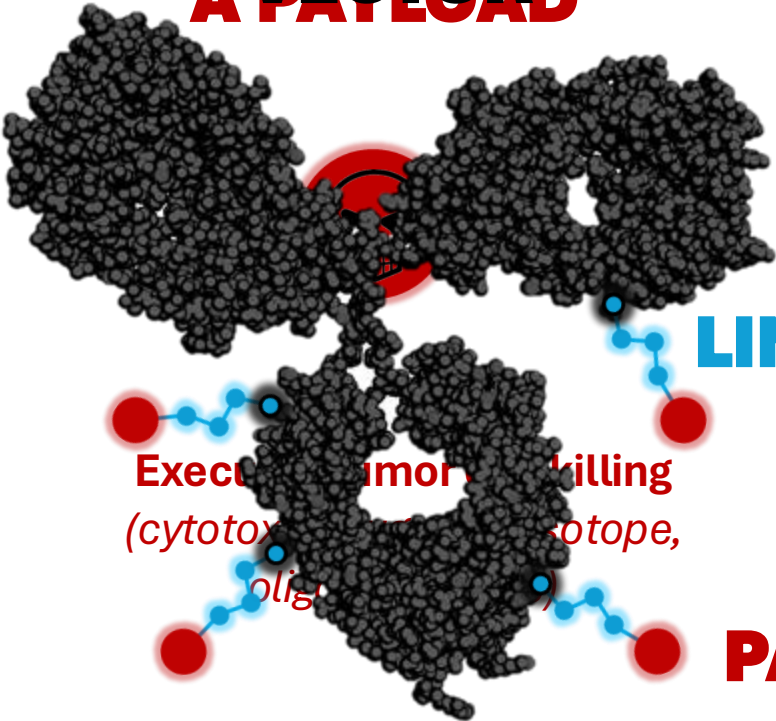
Structure of anticancer bioconjugates

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VECTOR A PAYLOAD



Execution of tumor killing
(cytotoxic drug, radioisotope,
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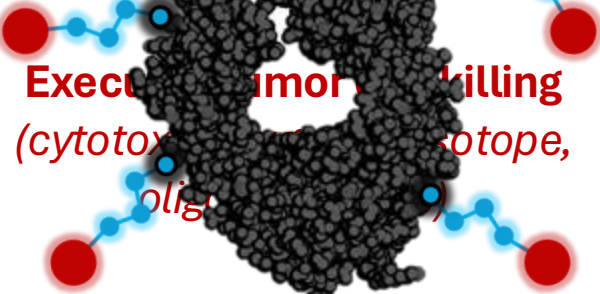
A LINKER



LINKER

Controls stability and release
(cleavable or non-cleavable)

PAYLOAD

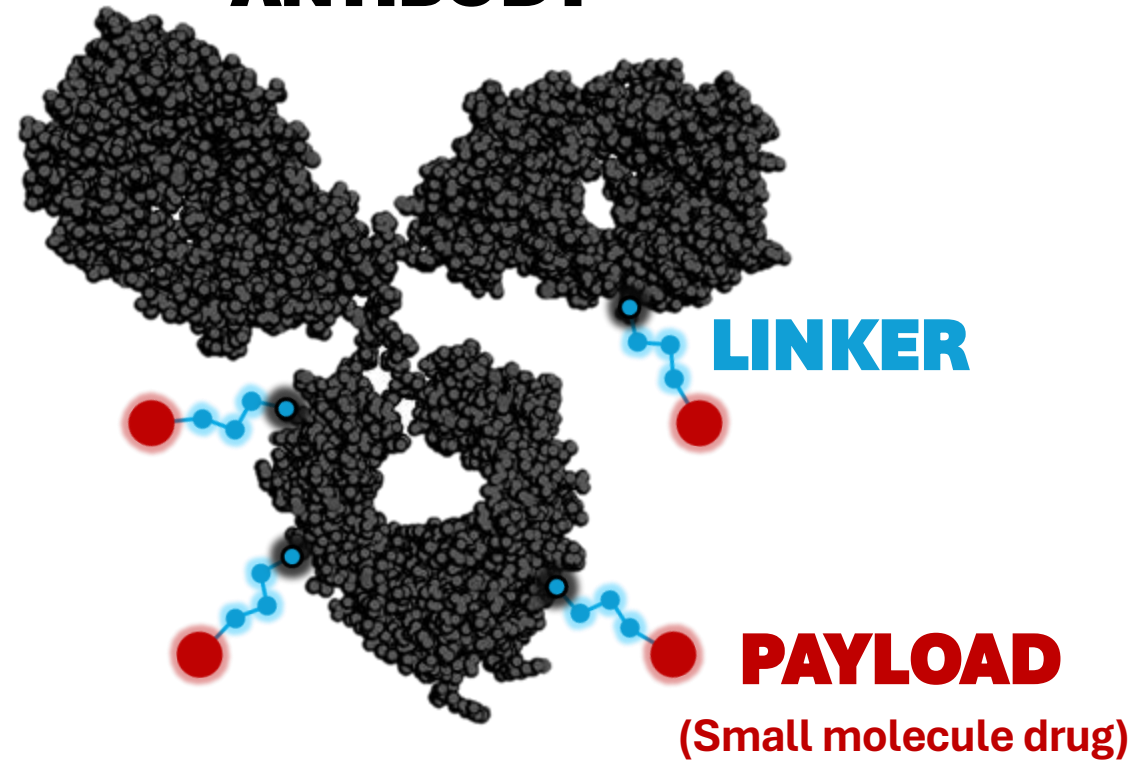


ADCs as the most advanced bioconjugates

ANTIBODY

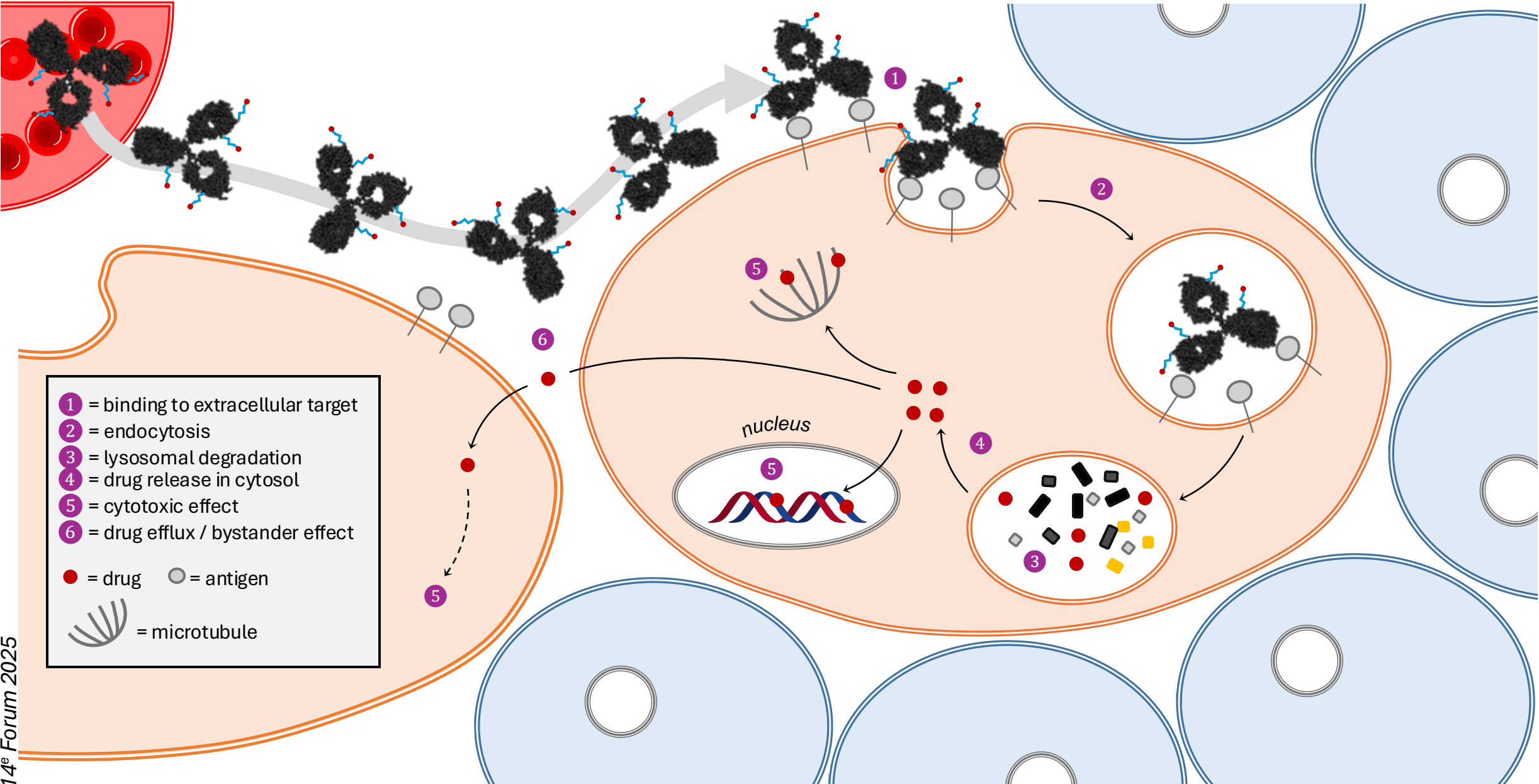
Drug-to-Antibody Ratio (DAR)

Number of drugs
per antibody
(DAR 4)



Antibody-Drug Conjugates (ADCs),
the most clinically advanced bioconjugates in oncology

Mechanism of action of ADCs



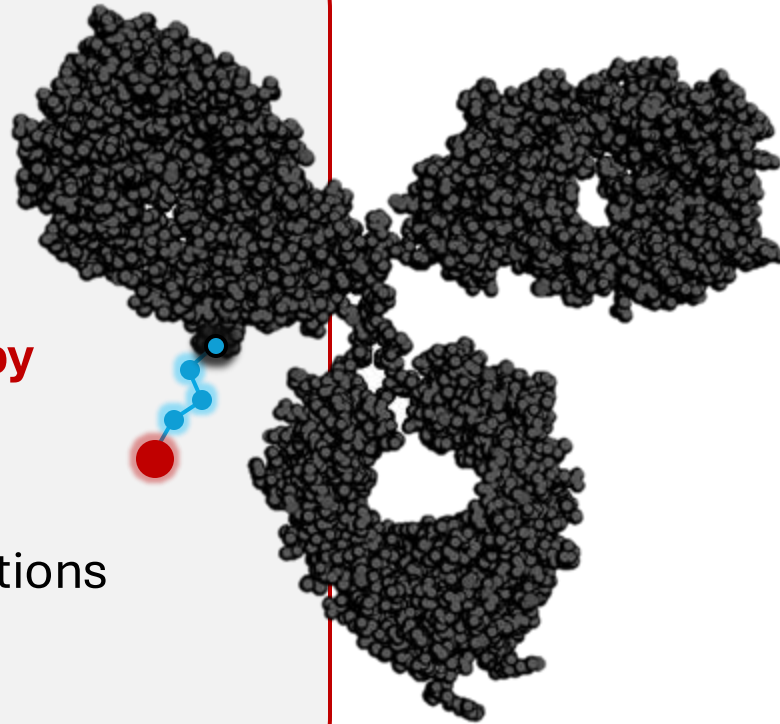
Toward safer ADCs

Conventional ADCs

- Ultra-potent cytotoxic payloads ($IC_{50} < 1$ nM)

Severe side effects comparable to chemotherapy

- 30% dose reductions
- 13% treatment discontinuations



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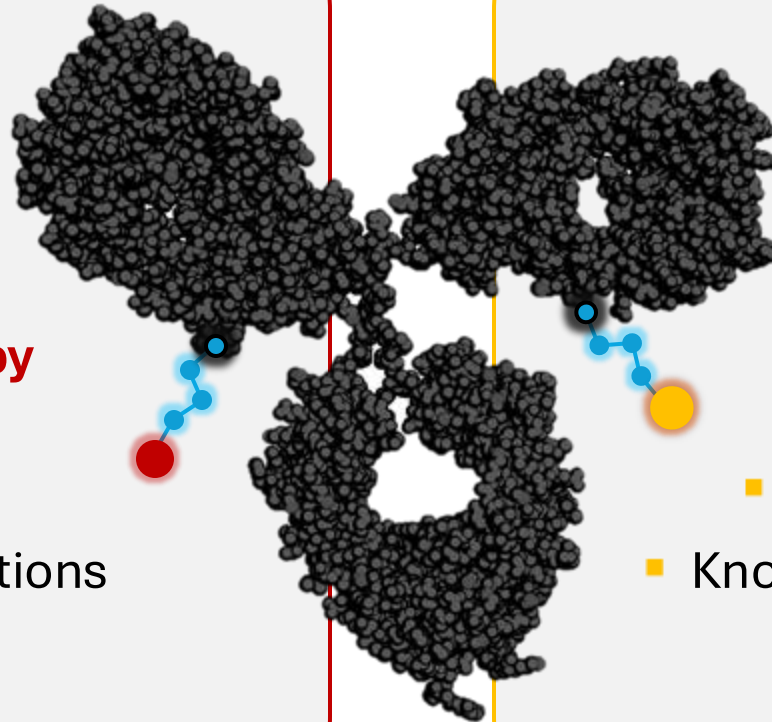


Our approach

- Repositioned chemotherapy payloads ($IC_{50} > 1$ nM)

Reconsidering potency in favor of tolerability

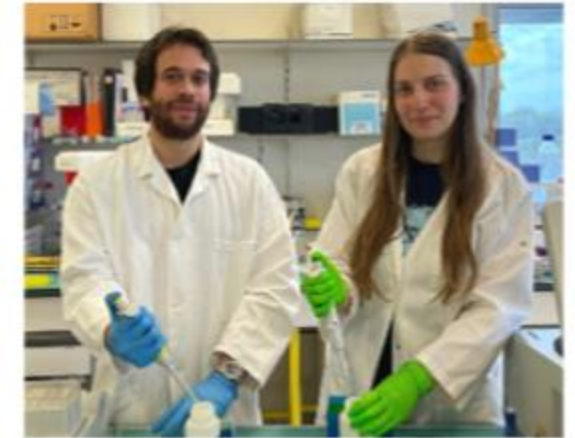
- Improved therapeutic window
- Known and manageable toxicity profiles



Toward safer ADCs • ADC-Vincristine

Collaborative project between:

- Biofunctional Chemistry laboratory, Wagner/Chaubet group
- Poly-ADP ribosylation and genome integrity laboratory, Dantzer group

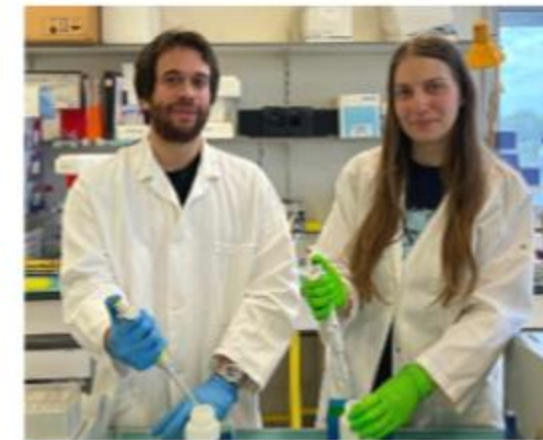


Julien MOST & Agathe BOOS

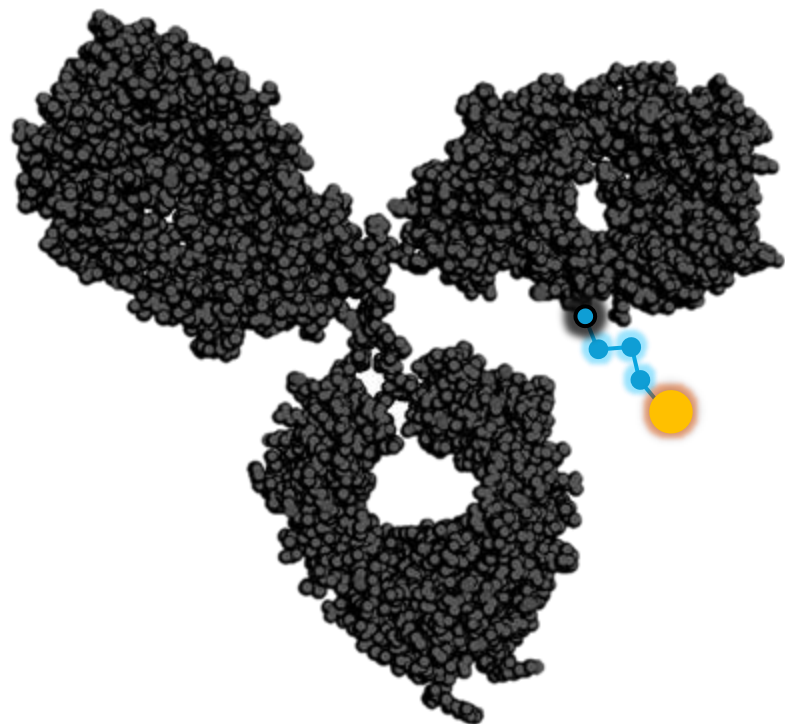
Toward safer ADCs • ADC-Vincristine

Collaborative project between:

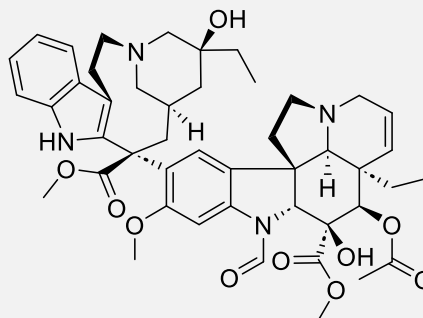
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Julien MOST & Agathe BOOS

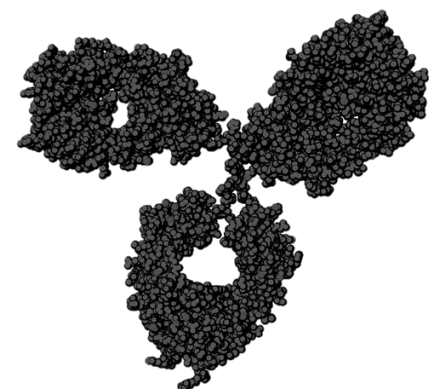


Vincristine ($IC_{50} \sim 10^{-7}$ - 10^{-8} M)



- Inhibitor of microtubule polymerization
- Widely used in the treatment of hematological malignancies

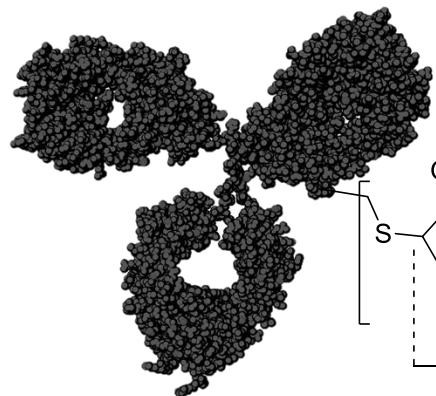
ADC-Vincristine • Analytical characterization



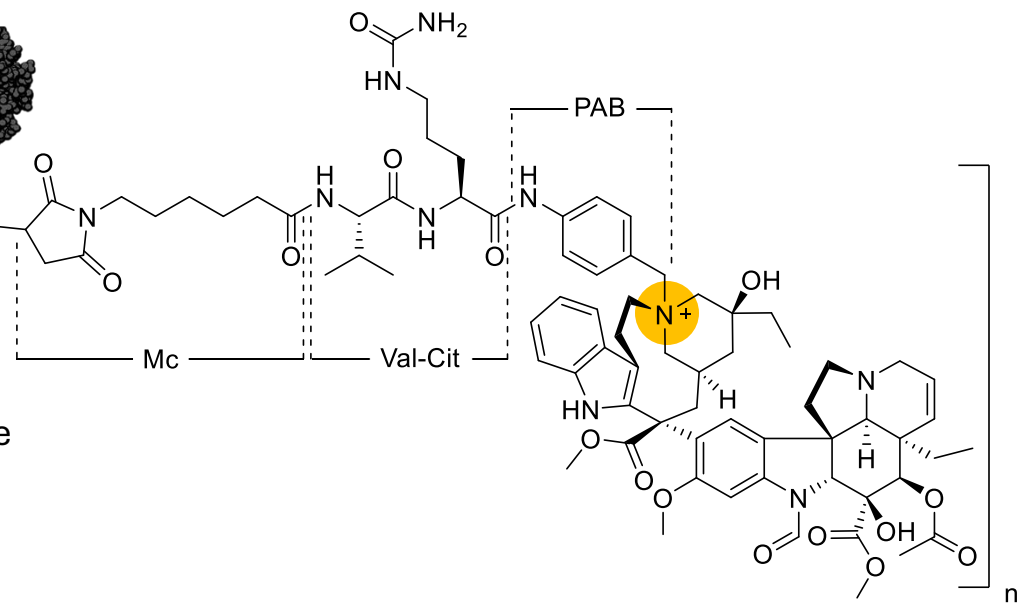
Trastuzumab

1/ TCEP, EDTA (1%)
DPBS 1X, pH 6.5,
37 °C, 1 h

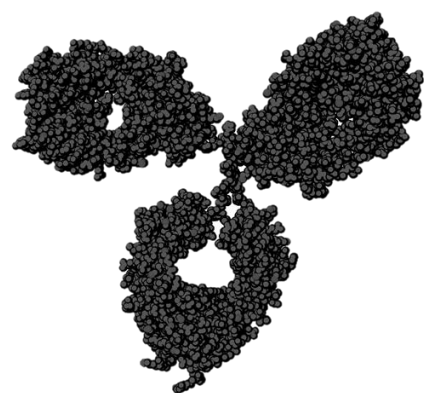
2/ Linker-payload (20 equiv.)
25 °C, 2.5 h
85-90%



Trastuzumab-Vincristine
T-VCR



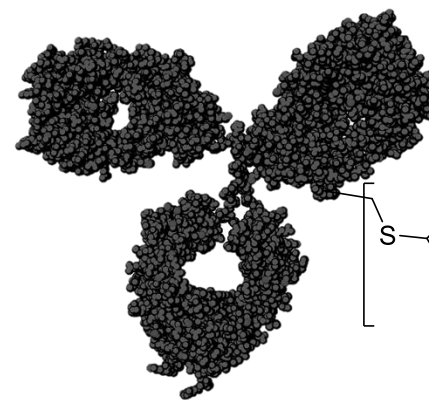
ADC-Vincristine • Analytical characterization



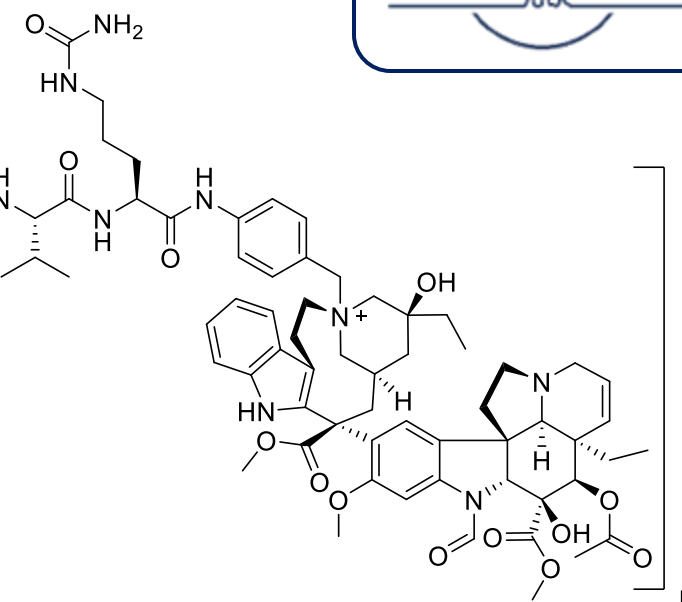
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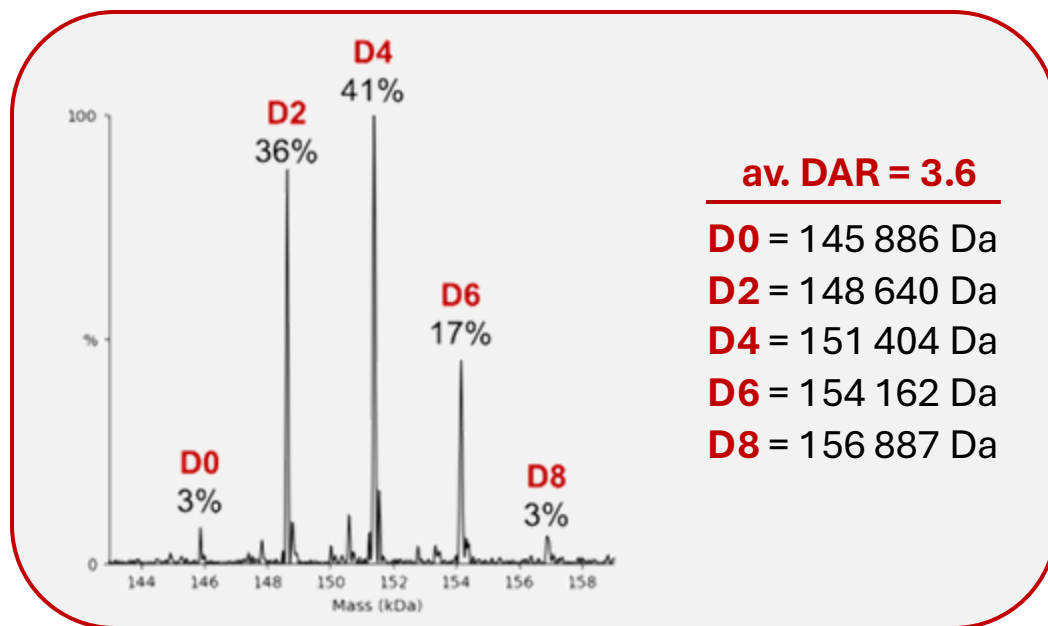
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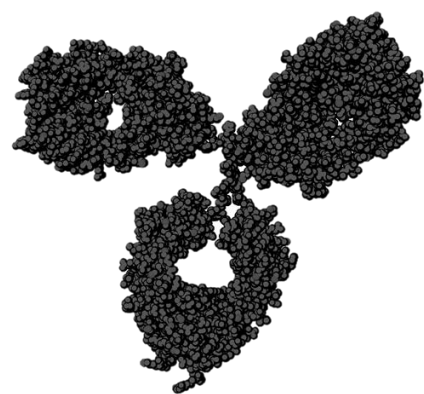
Trastuzumab-Vincristine
T-VCR



■ Native MS analysis (LSMBO, University of Strasbourg)



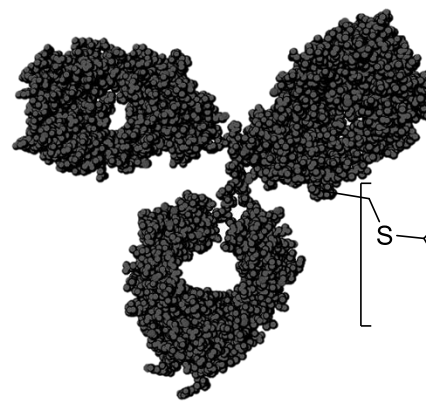
ADC-Vincristine • Analytical characterization



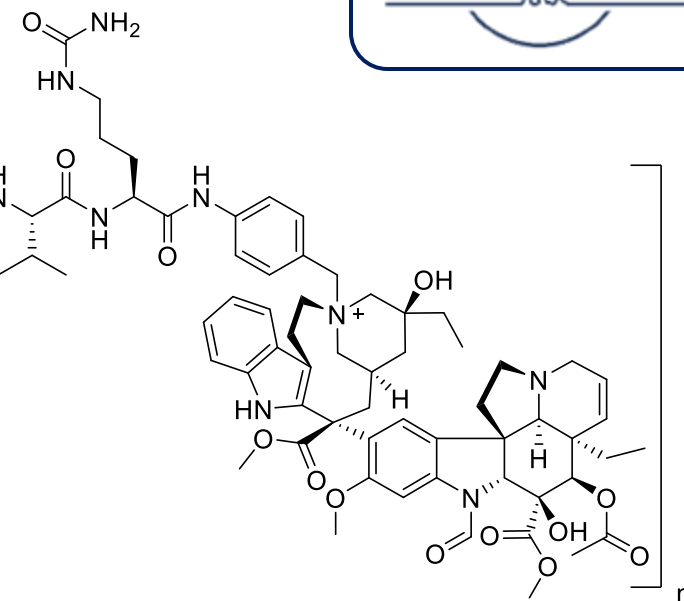
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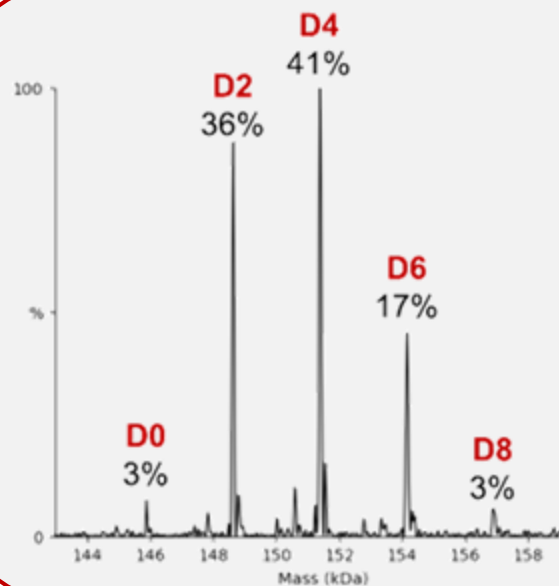
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Trastuzumab-Vincristine
T-VCR

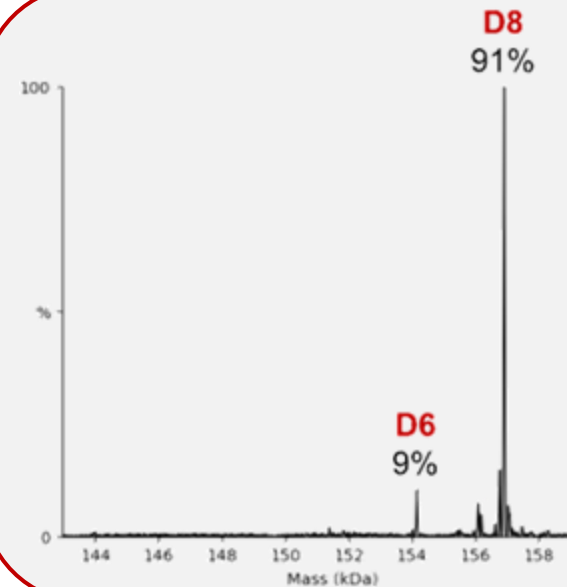


■ Native MS analysis (LSMBO, University of Strasbourg)



av. DAR = 3.6

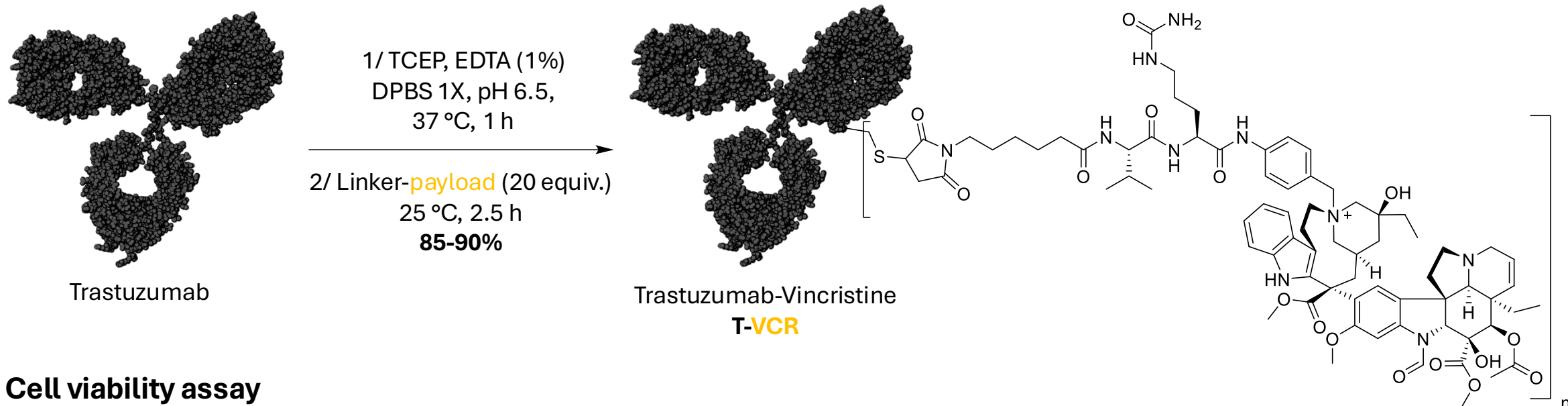
D0 = 145 886 Da
D2 = 148 640 Da
D4 = 151 404 Da
D6 = 154 162 Da
D8 = 156 887 Da



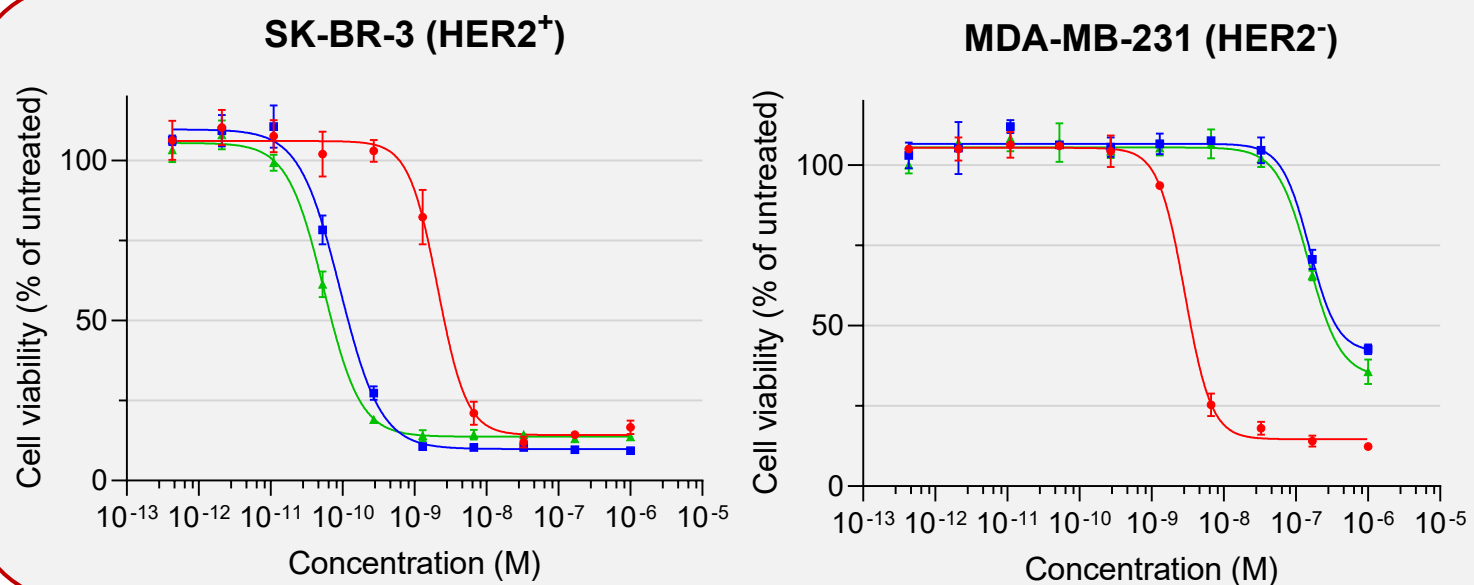
av. DAR = 7.8

D6 = 154 161 Da
D8 = 156 887 Da

ADC-Vincristine • *In vitro* evaluation



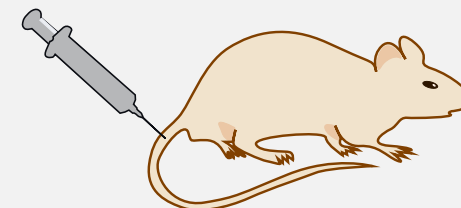
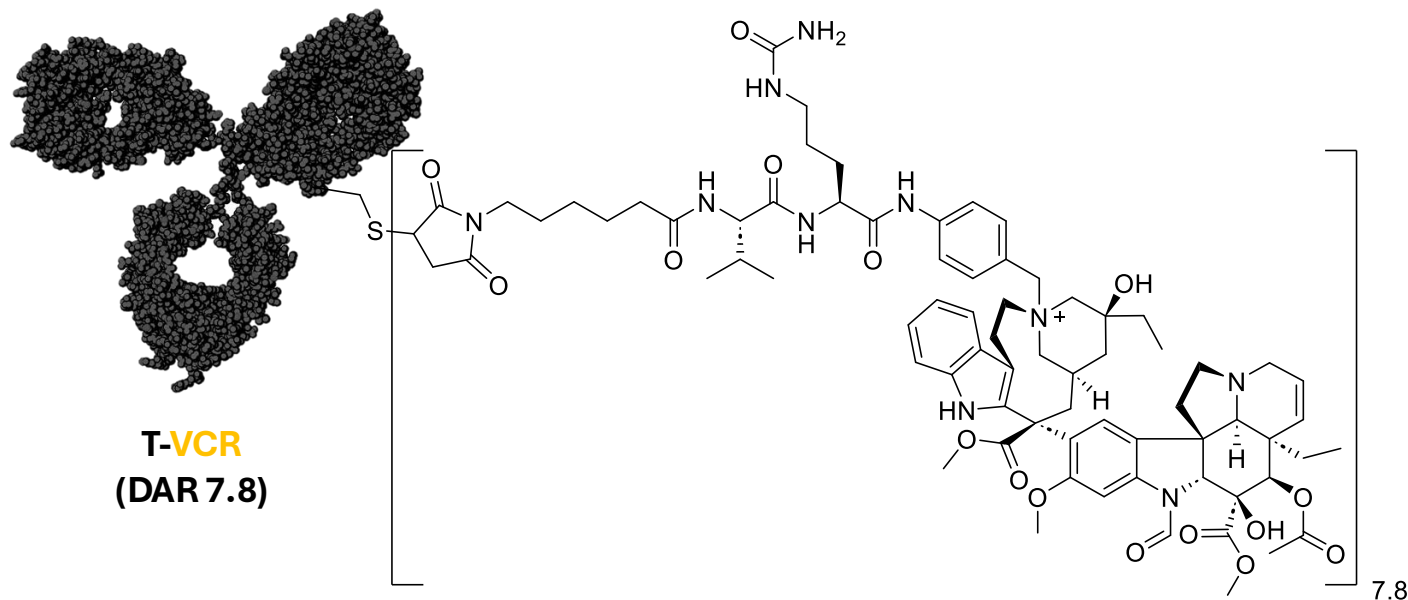
■ Cell viability assay



- VCR
- T-VCR (DAR = 3.6)
- ▲ T-VCR (DAR = 7.8)

		IC ₅₀ (nM)		
		VCR	T-VCR (3.6)	T-VCR (7.8)
cells	SK-BR-3	2.1 ± 0.3	0.092 ± 0.008	0.055 ± 0.006
	MDA-MB-231	2.3 ± 0.5	NA	NA

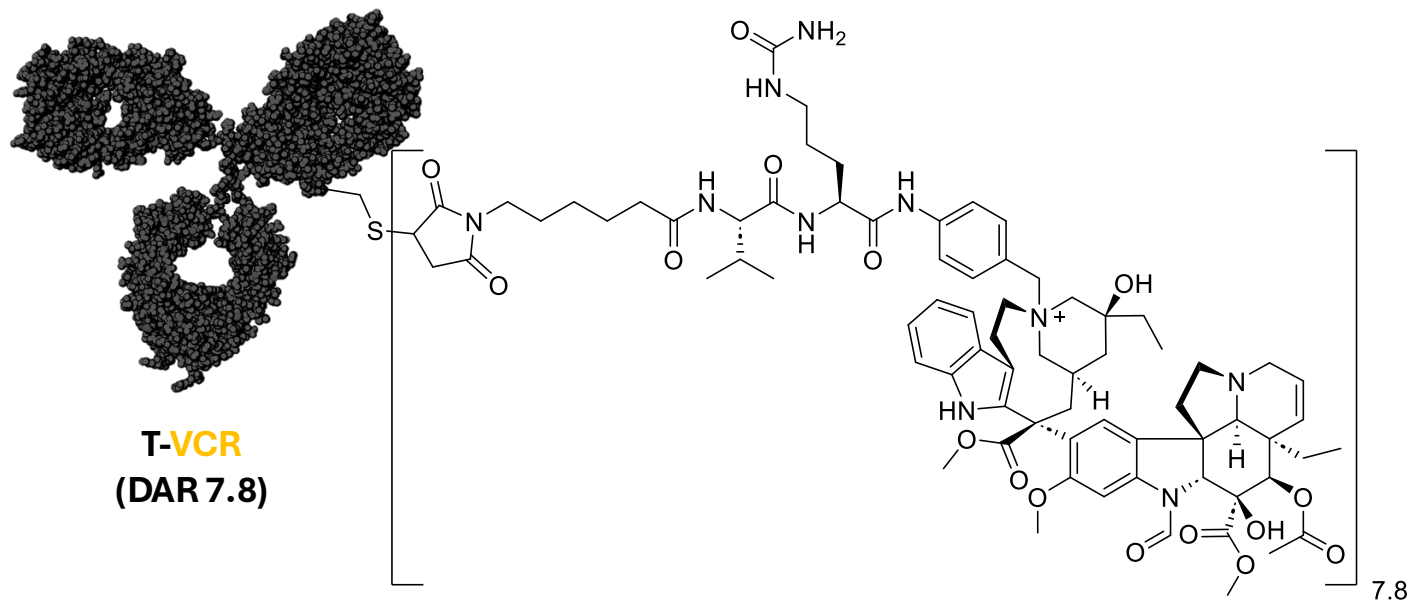
ADC-Vincristine • *In vivo* study



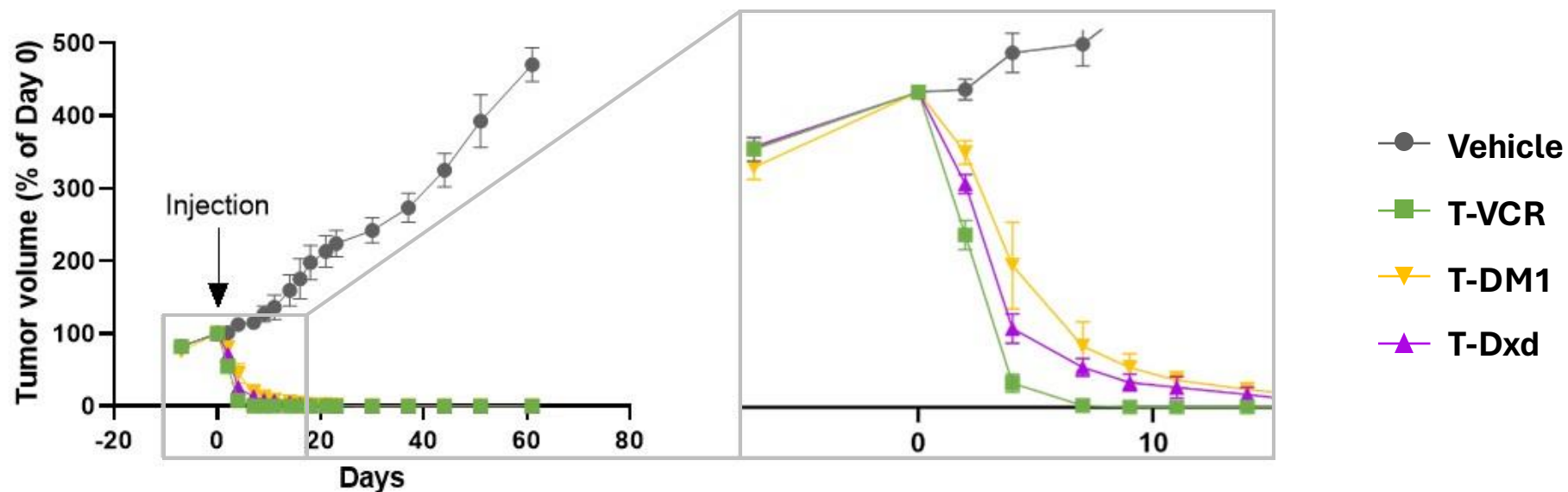
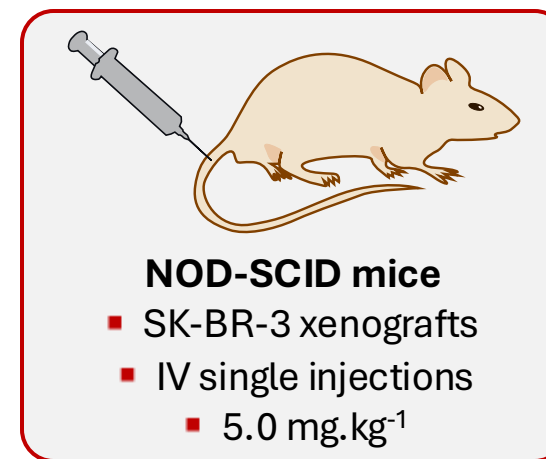
NOD-SCID mice

- SK-BR-3 xenografts
- IV single injections
 - 5.0 mg.kg⁻¹

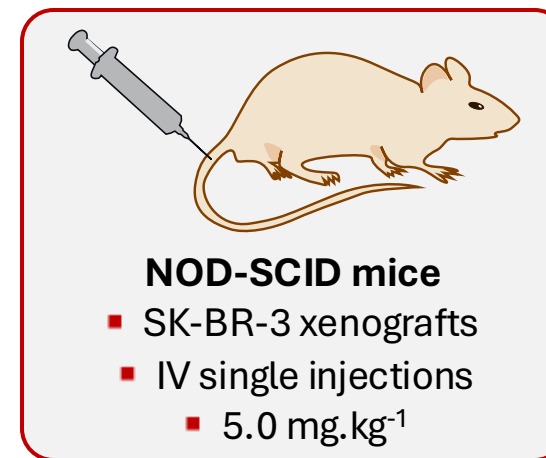
ADC-Vincristine • *In vivo* study



T-VCR
(DAR 7.8)



- 14^e Forum 2025



Key achievements



Robust chemistry



Improved activity vs free drug
Confirmed bystander effect



Complete tumor regression in 9
days after a single injection



Excellent tolerability

ADC-Vincristine • Achievements and perspectives

Key achievements



Robust chemistry



Improved activity vs free drug
Confirmed bystander effect



Complete tumor regression in 9
days after a single injection



Excellent tolerability

What's next?

**Toward a clinically relevant, safer
ADC based on a well-known payload**



Expand *in vitro* evaluation

Confirm efficacy across multiple
tumor models



Define tolerability limits

MTD determination, early toxicity
markers

Acknowledgements



■ BFC group

- Julien Most
- Louis Moreira da Silva
- Caroline Mursch
- Dr Alain Wagner
- Dr Guilhem Chaubet

■ Dantzer group

- Agathe Boos
- Dr Maria Zeniou
- Dr Françoise Dantzer

■ PCBIS

- François Daubeuf
- Pascal Villa

■ LSMBO

- Stéphane Erb
- Dr Sarah Cianferani
- Dr Oscar Hernandez-Alba

■ Syndivia

- Dr Sasha Koniev
- Dr Sergii Kolodych
- Dr Igor Dovgan
- Dr Constantin Semenchenko



A close-up photograph of several bright pink flowers with five petals each, set against a background of lush green leaves. The flowers are in sharp focus, while the leaves are slightly blurred.

THANK YOU FOR YOUR ATTENTION