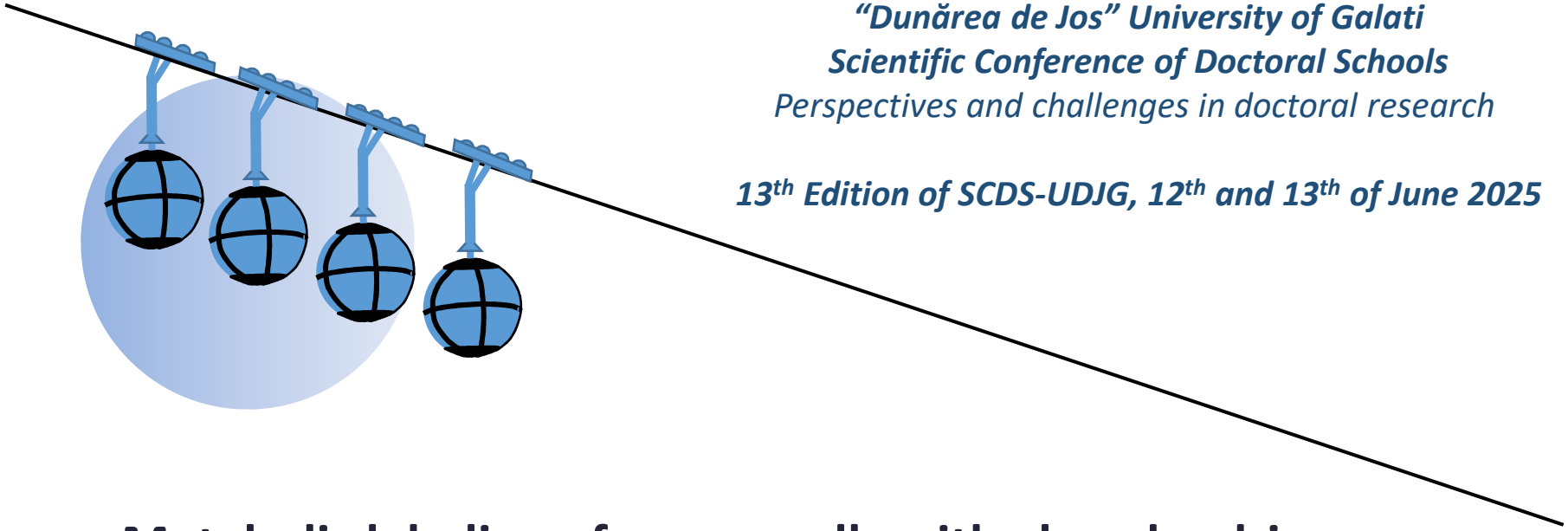
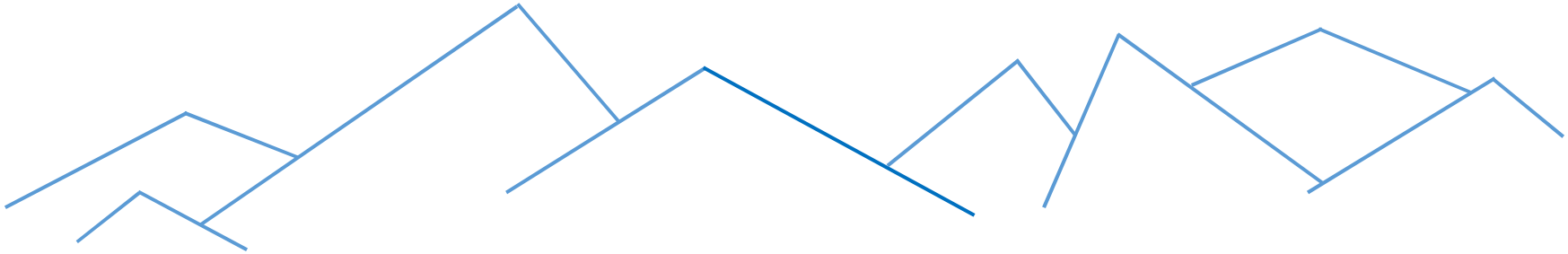


"Dunărea de Jos" University of Galati
Scientific Conference of Doctoral Schools
Perspectives and challenges in doctoral research

13th Edition of SCDS-UDJG, 12th and 13th of June 2025

Metabolic labeling of cancer cells with glycodendrimers stimulate immune-mediated cytotoxicity

Nathalie Berthet



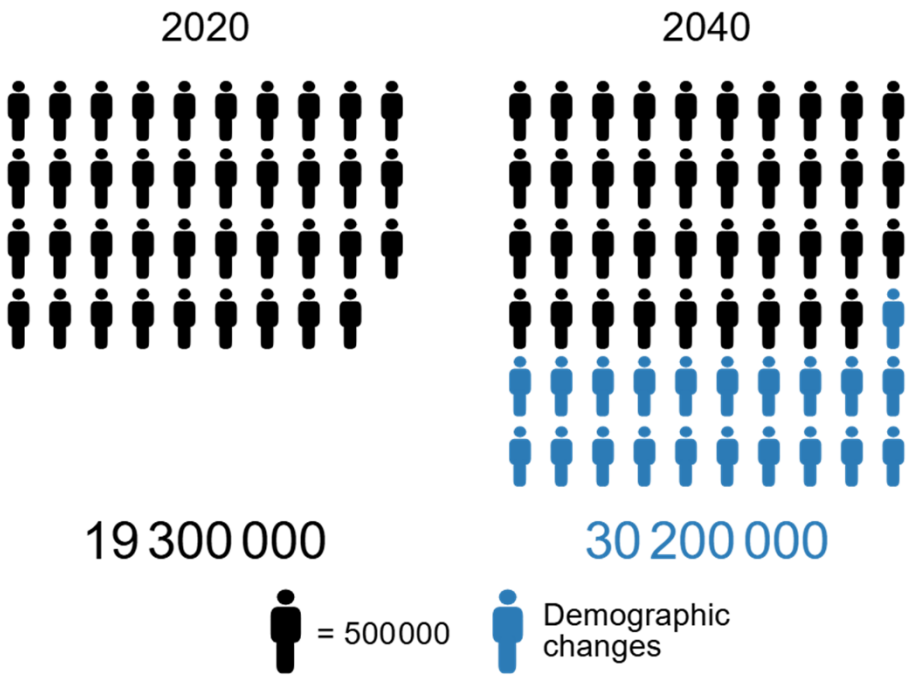
UNIVERSITÉ Grenoble Alpes

dcm département de chimie moléculaire

Ingénierie et Interactions i2bm BioMoléculaires

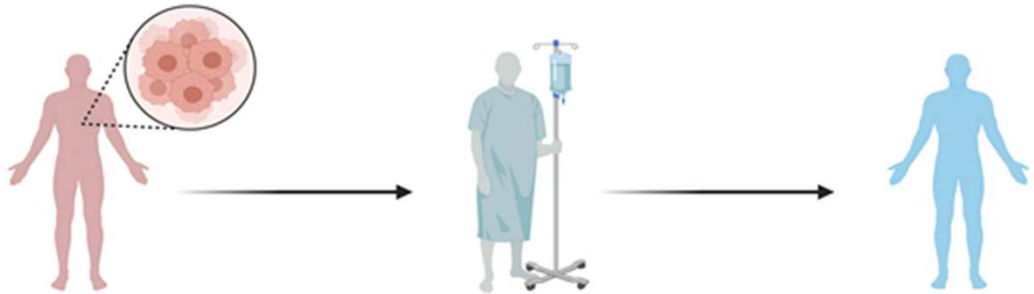
The Global Cancer Burden Keeps Growing

Estimated number of new cancer cases and deaths worldwide in 2040



International Agency for Research on Cancer

cancer therapies

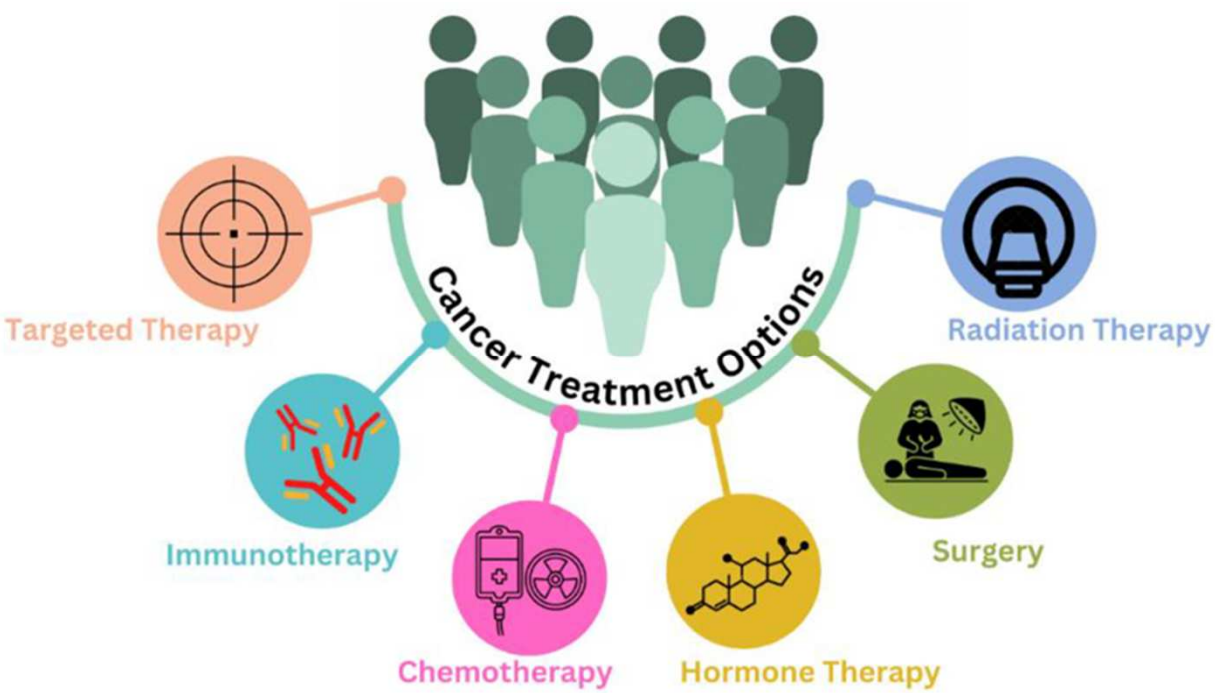


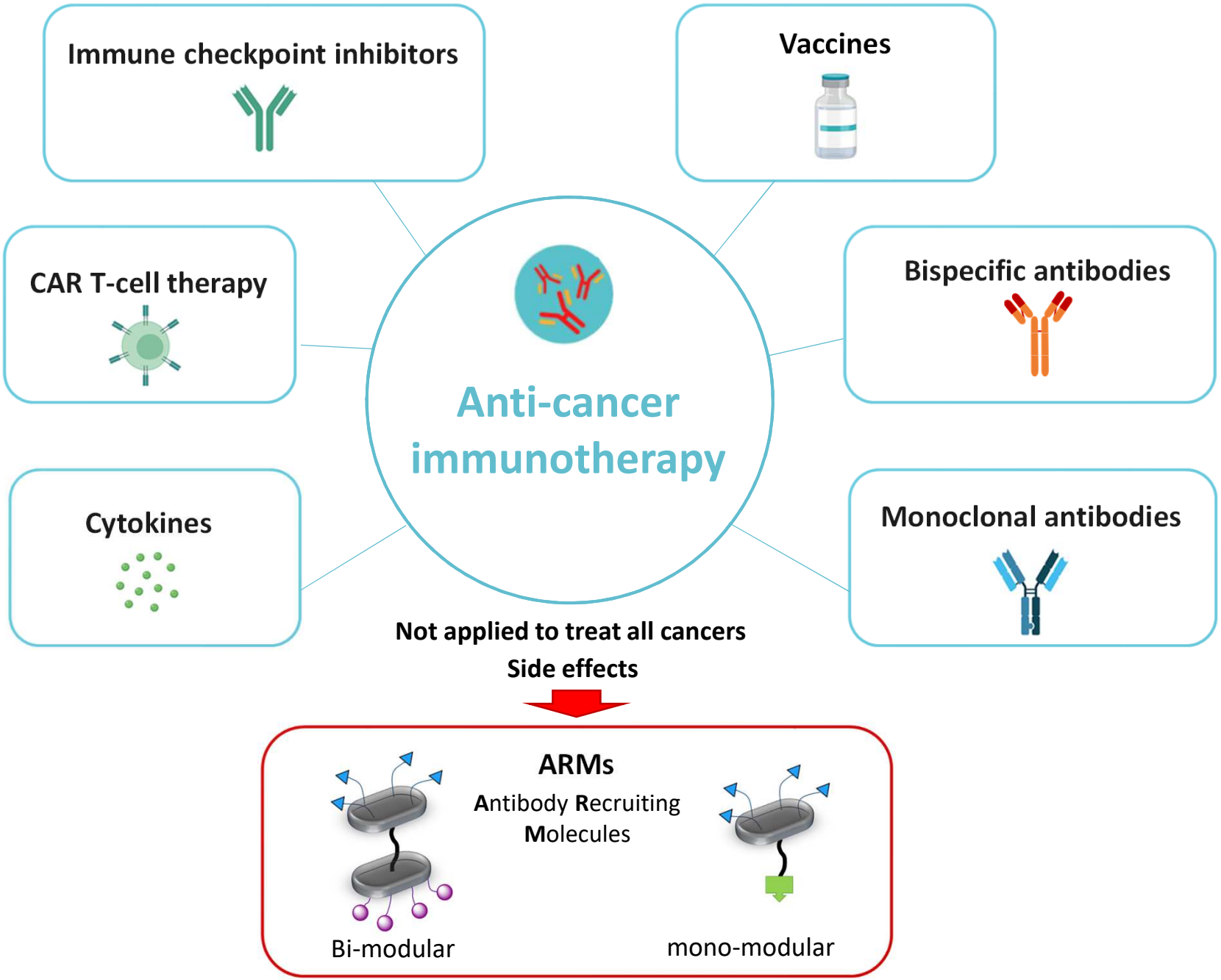
Patient with cancer

Treatment

Recovery

?




Immune checkpoint inhibitors
Vaccines
CAR T-cell therapy
Bispecific antibodies
Anti-cancer immunotherapy
Cytokines
Monoclonal antibodies
Not applied to treat all cancers
Side effects
ARMs
Antibody Recruiting Molecules
Bi-modular
mono-modular

ANTI-TUMORAL IMMUNOTHERAPY

ARM Strategy « Antibody Recruiting Molecule »

McEnaney, P. J.; Parker, C. G.; Zhang, A. X., *Annual Reports in Medicinal Chemistry*, **2017**, *50*, 481-518.
Uvyn, A.; De Geest, B. *ChemBioChem.*, **2020**, *21*, 3036-3043.
Achilli, S.; Berthet, N.; Renaudet, ORSC Chem. Biol., **2021**, *2*, 713-724.

Harnessing naturally occuring antibodies present in the bloodstream

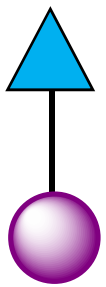
↓

Redirection towards cancer cells

Bimodular ARMs molecules :

Antibody-Binding Module (ABM)

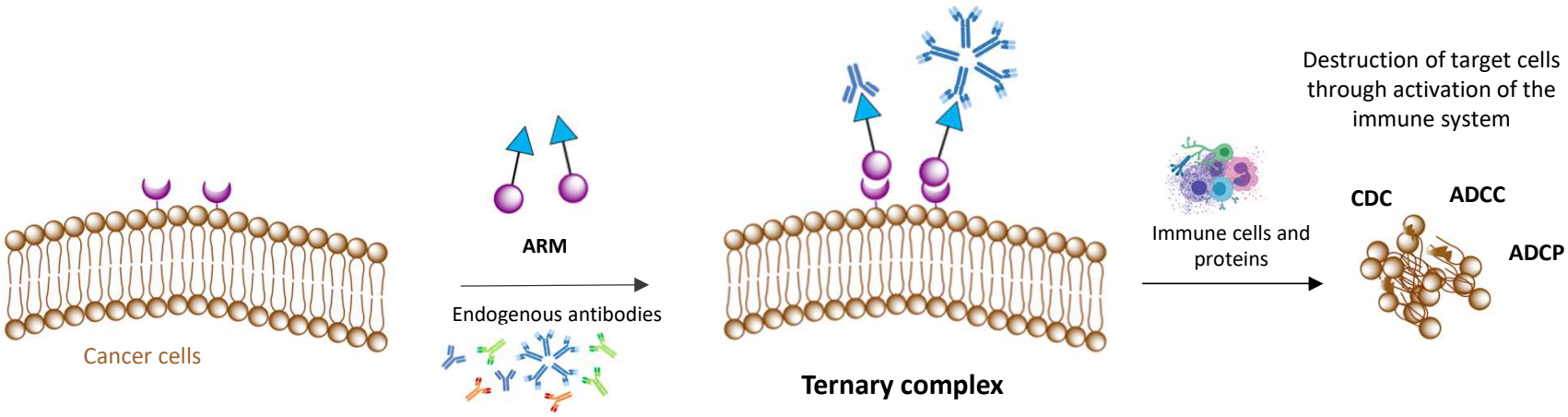
Tumoral-Binding Module (TBM)



α-L-Rhamnose (α-L-Rha), galactose-α-1,3-galactose (α–Gal), 2,4-dinitrophényl (DNP) → Recruitment of endogenous antibodies naturally present in human serum

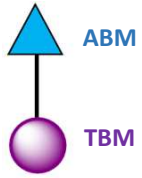
Specific ligands for :
- $\alpha_v\beta_3$ integrines
- EGF growth factor receptors, Folic acid receptor
- PSMA protein markers

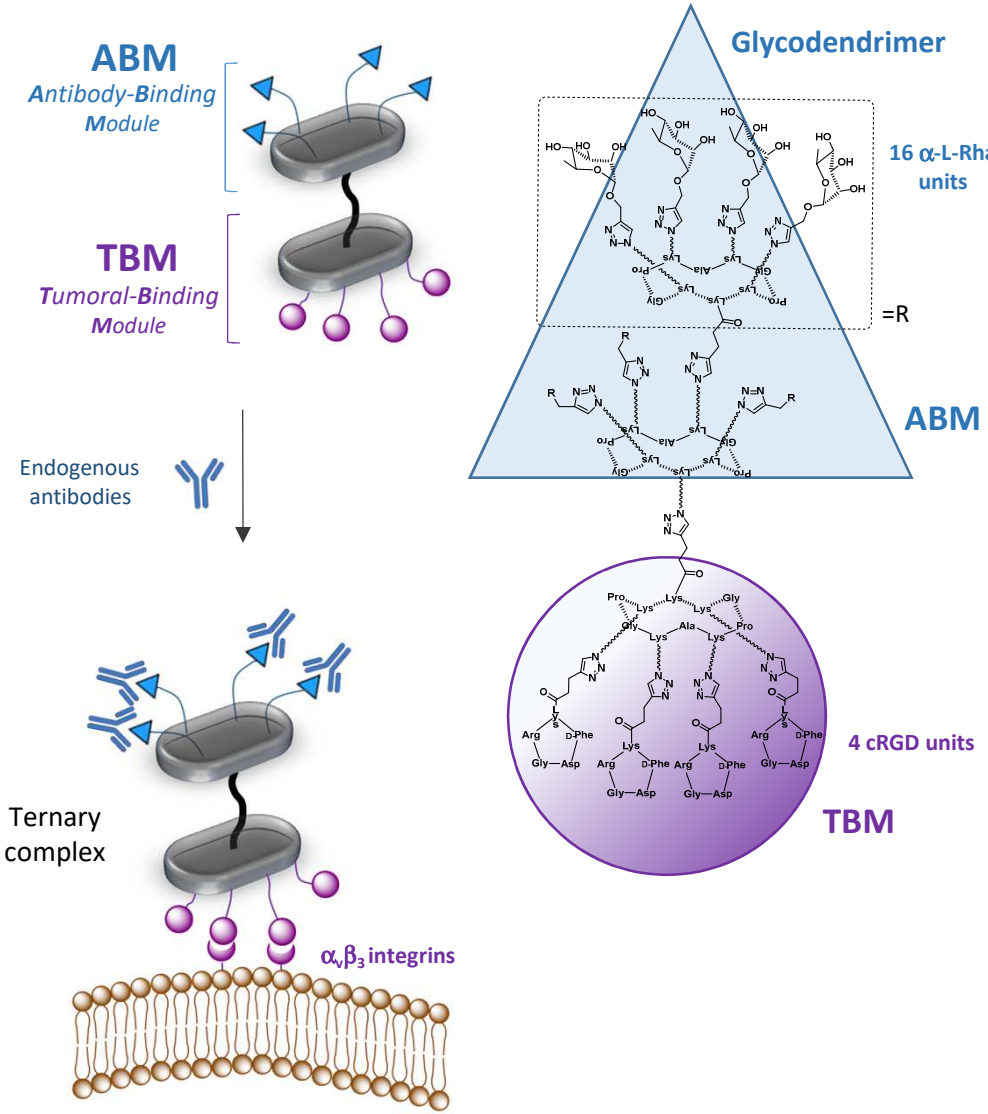
→ Interaction with cancer cell surface and proteins



Bimodular ARM synthesized in the Grenoble laboratory

Molecular Chemistry Department, I2BM team





Weaknesses…

- Ternary complex formation

  Non covalent interactions:
  - TBM / cellular receptors
  - ABM / antibodies

- ARM internalisation

Todaro, B.; Achilli, S.; Liet, B.; Laigre, E.; Tiertant, C.; Goyard, D.; Berthet, N. and Renaudet, O., *Biomater Sci.*, **2021**, *9*, 4076-4085.

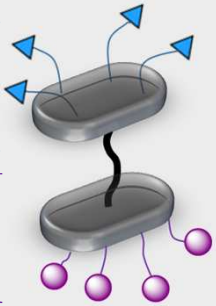
Liet, B.; Laigre, E.; Goyard, D.; Todaro, B; Tiertant, C.; Boturyn, D.; Berthet, N. and Renaudet, O., *Chem. – Eur. J.*, **2019**, *25*, 15508-15515.

Bimodular ARM Strategy

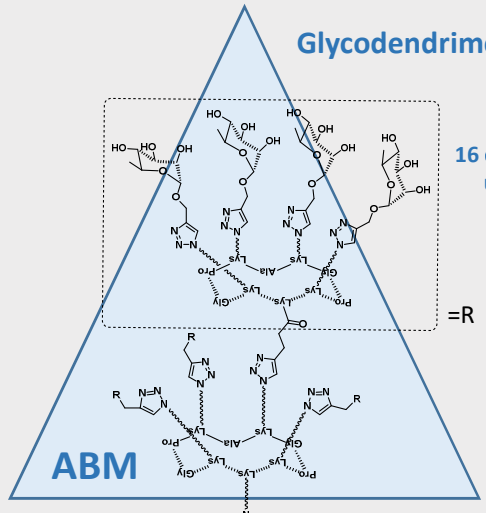
« **A**ntibody **R**ecruiting **M**olecules »

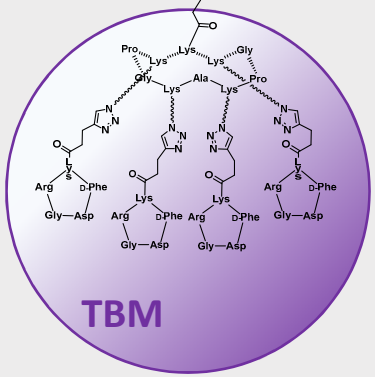
ABM
Antibody-Binding Module

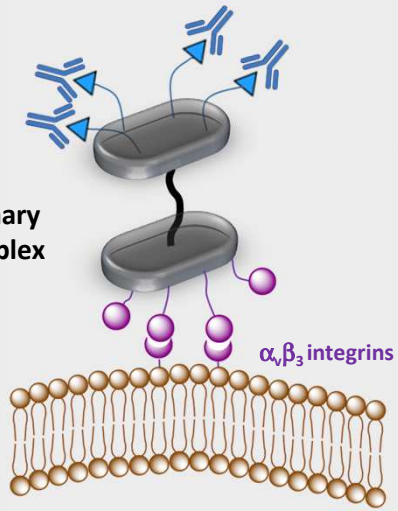
TBM
Tumoral-Binding Module



Endogenous antibodies



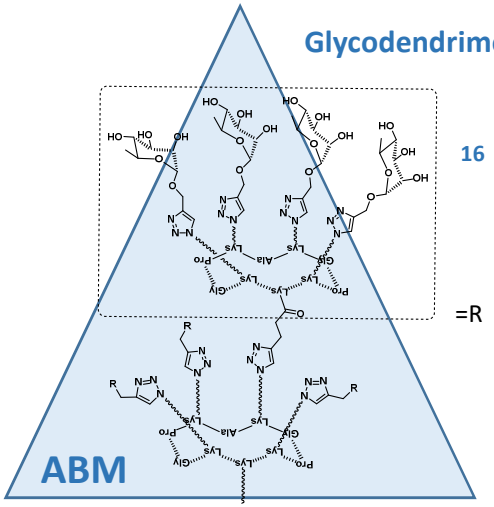




Weaknesses…

Monomodular ARM Strategy :

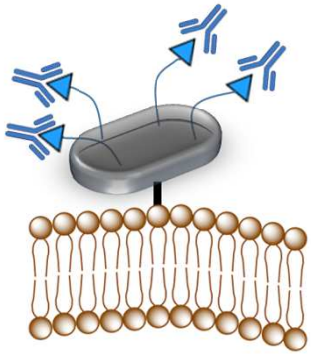
Covalent binding of ABM at the cell surface



Cellular glycometabolism (MCR)

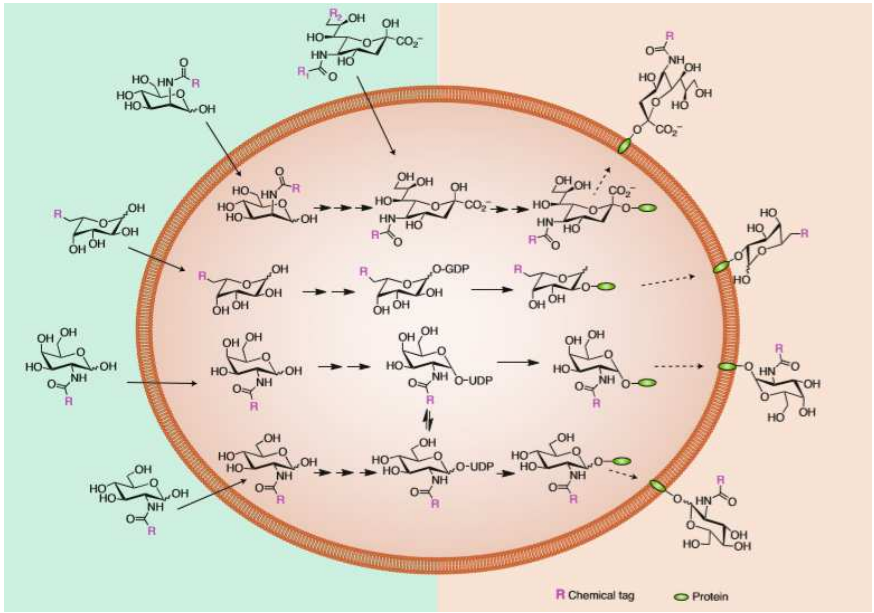
+

Bioorthogonal chemistry

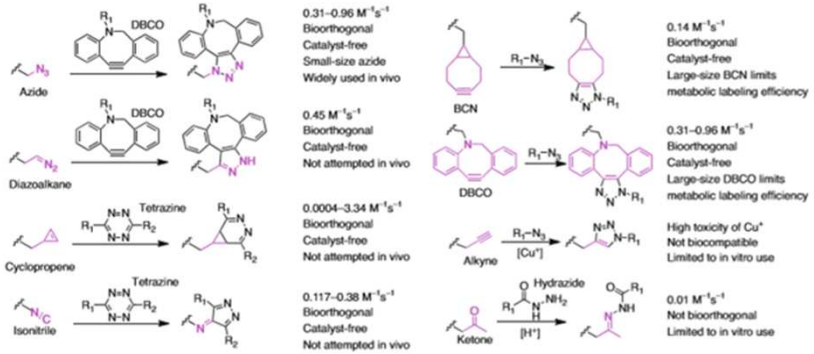


Metabolic labeling of cancer cells with reactive chemical tags via unnatural monosaccharides

Unnatural sugars

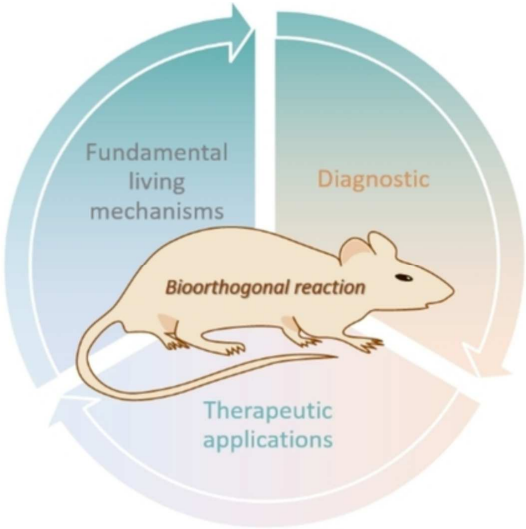


Bioorthogonal reactions



H. Wang and D. J. Mooney. Metabolic glycan labelling for cancer-targeted therapy. *Nature Chemistry* **2020**, *12*, 110-1114.

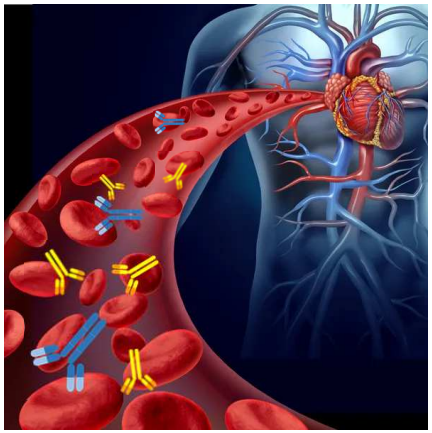
Bioorthogonal Reactions in animals



K. Porte, M. Riberaud, R. Châtre, D. Audisio, S. Papot, F. Taran. Bioorthogonal reactions in animals. *Chembiochem.* **2021**, *22*, 100-113.

Cell labelling with antigenic glycodendrimers : ABMs *(**A**ntibody-**B**inding **M**odule)*

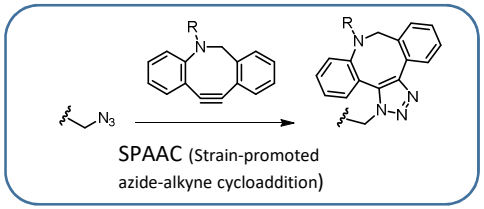
Alternative strategy in immunotherapy



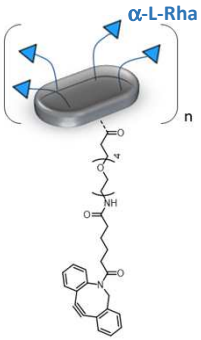
3 **Stimulation of immune-mediated cytotoxicity**

Endogenous anti-Rha antibodies recruitment

2 **Bioorthogonal reaction**

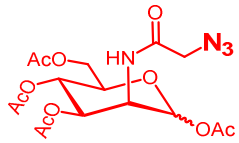


DBCO-ABMs



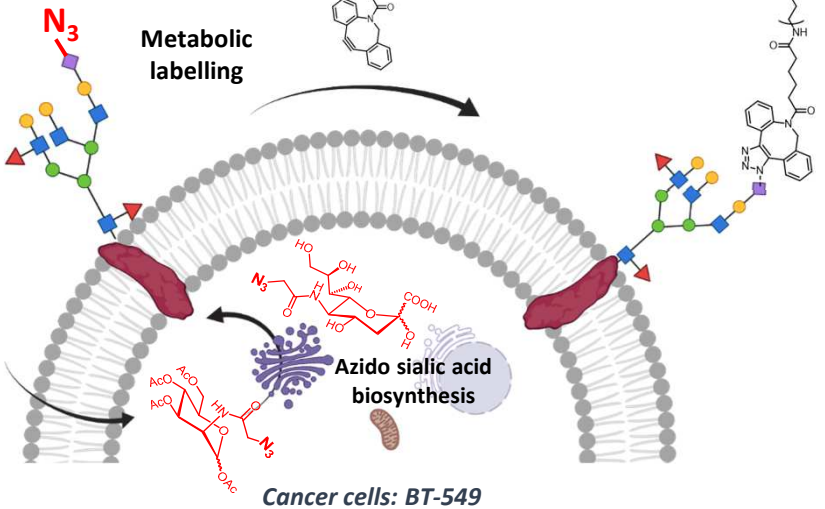
1 **Metabolic Chemical Reporters**

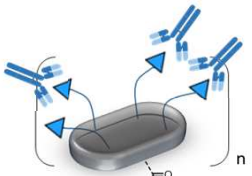
MCR :



Tetraacetyl-N-azidoacetylmannosamine

Ac_4ManNAz

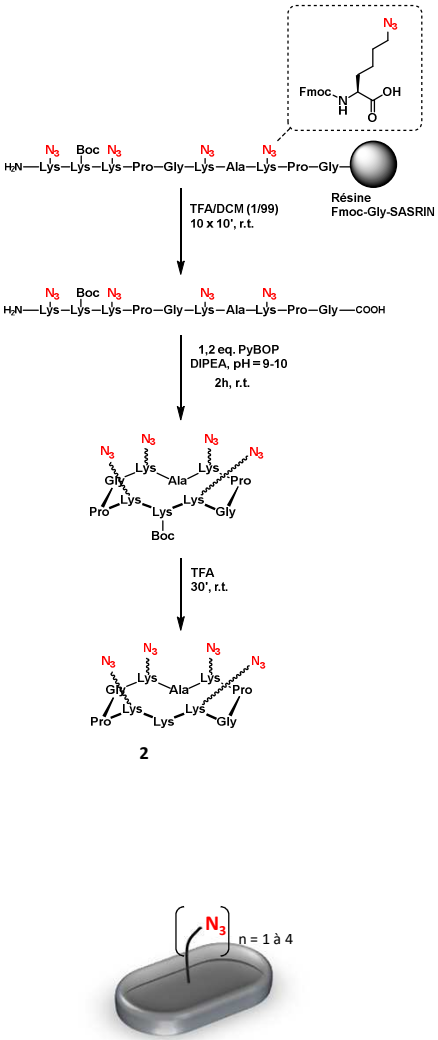




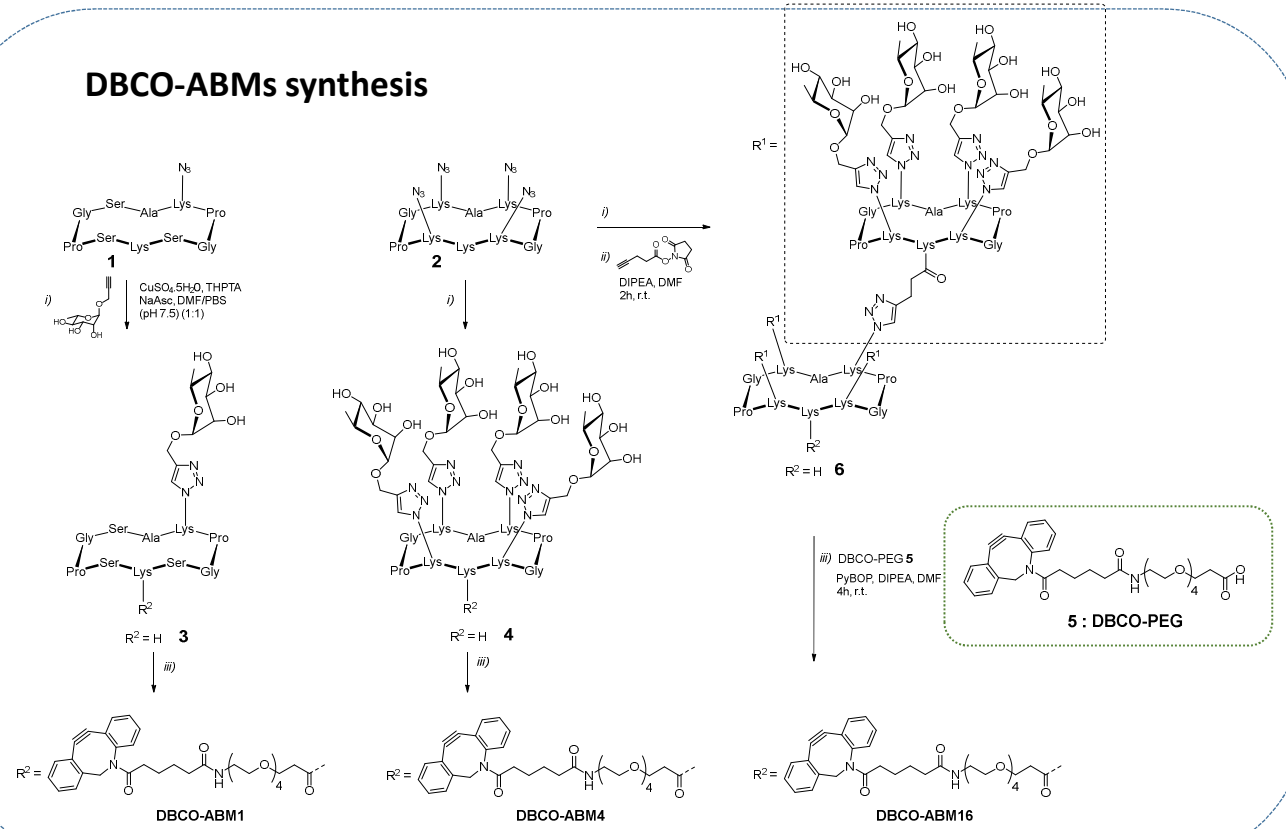
4 **Cell Killing**

Goyard, D.; Iyanu Diriwari, P. and Berthet, N., *RSC Med. Chem.*, **2022**, *13*, 72-78.

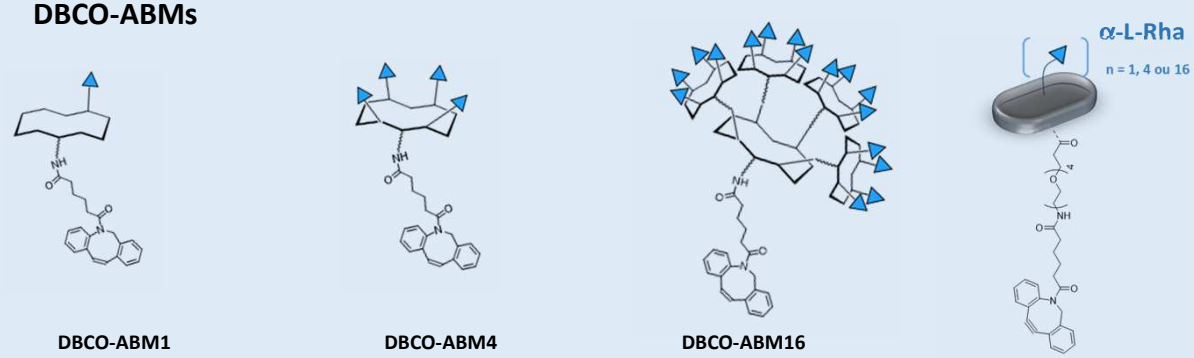
Peptitic scaffold synthesis



DBCO-ABMs synthesis

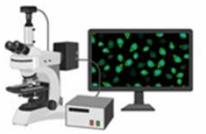


DBCO-ABMs



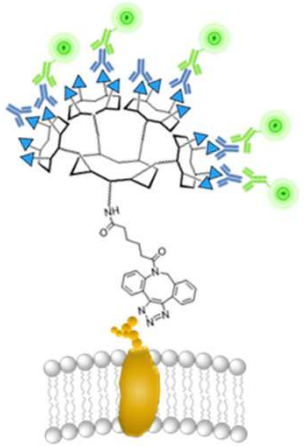
Biological evaluations

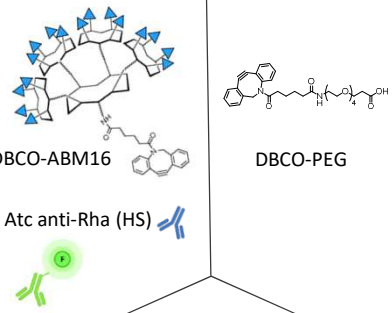
DBCO-ABM16 coupling to N_3 groups exposed at the cells surface and anti-Rha recruitment

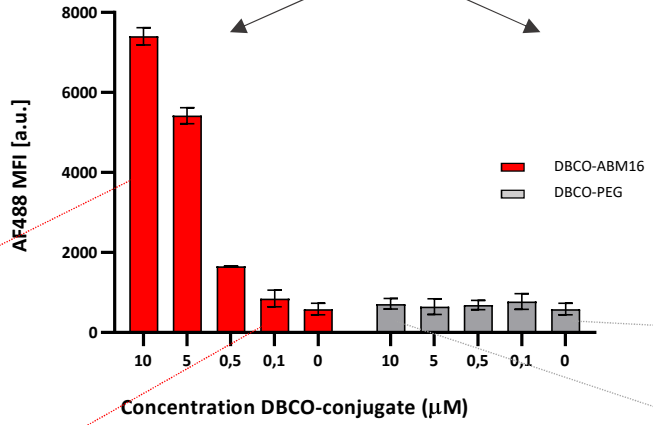


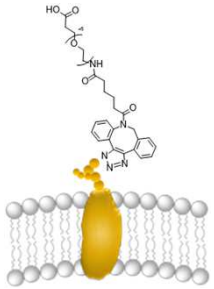
BT-549 cells

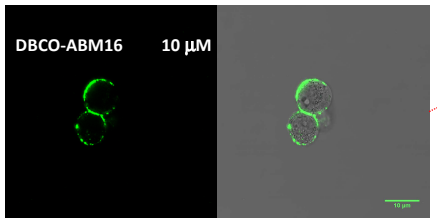
Cancer cells : BT-549
(mammary gland breast carcinoma)

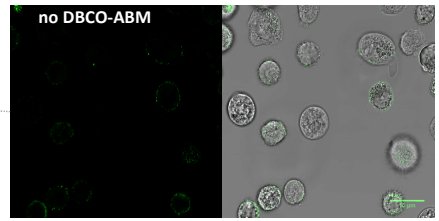


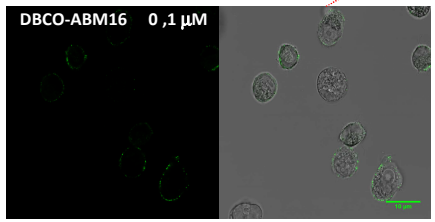


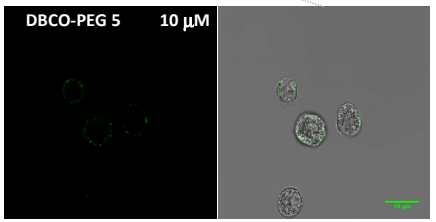




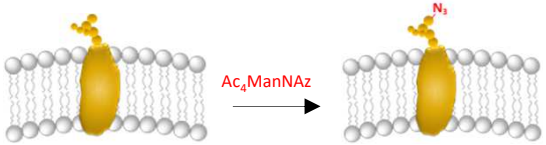


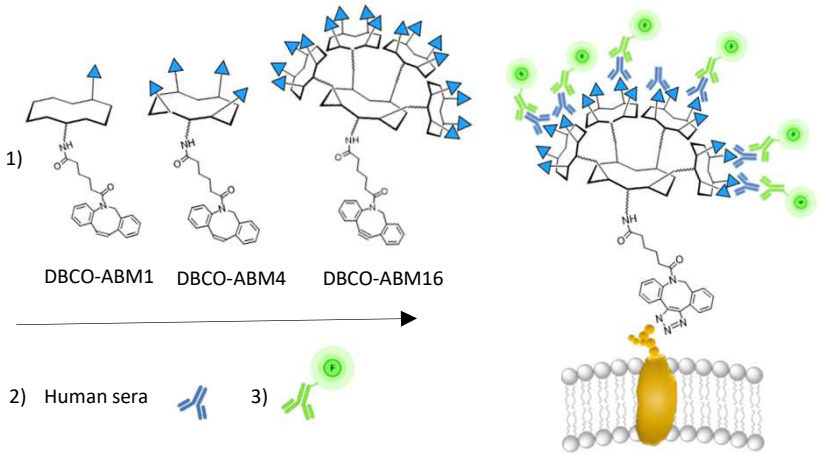


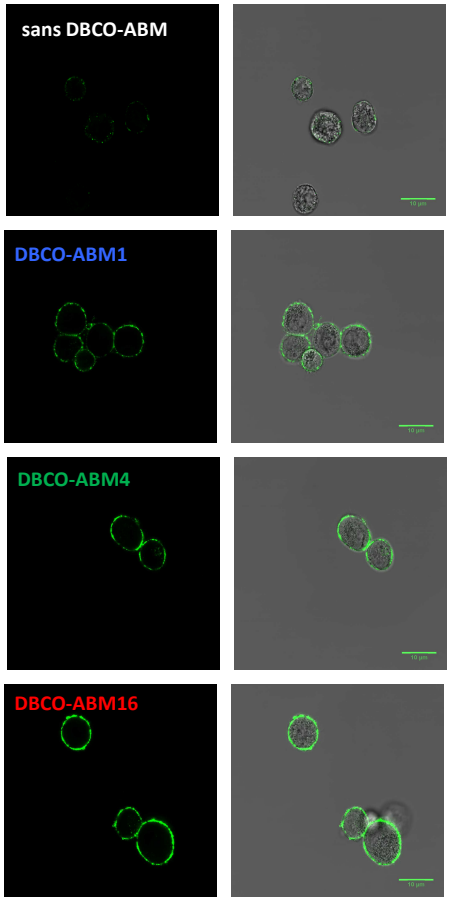


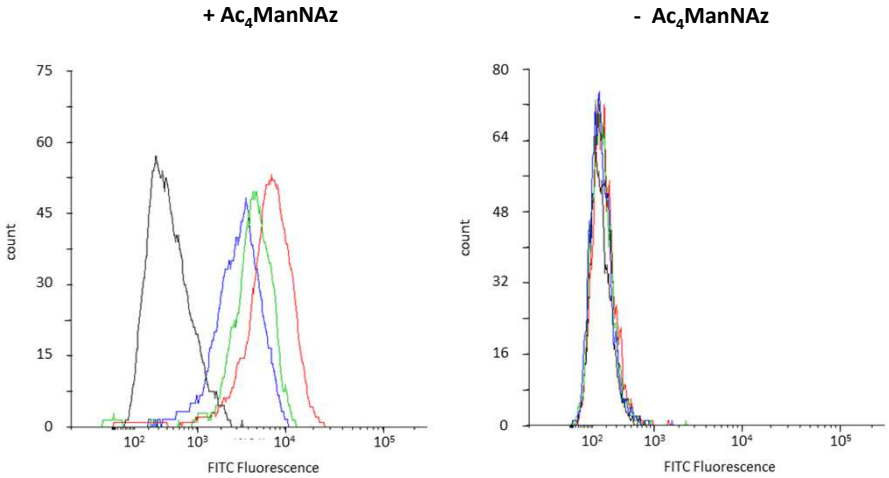


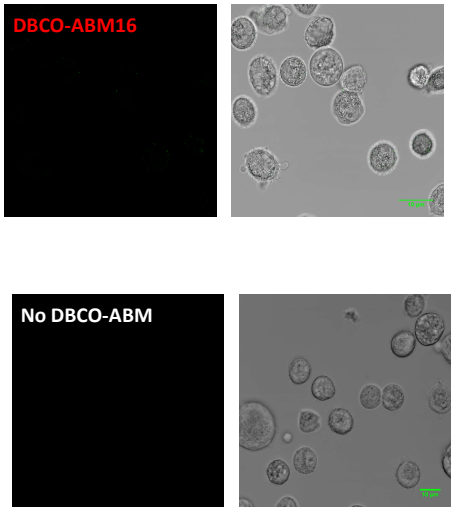
Influence of the Rha density on the recruitment of serum antibodies

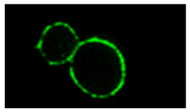




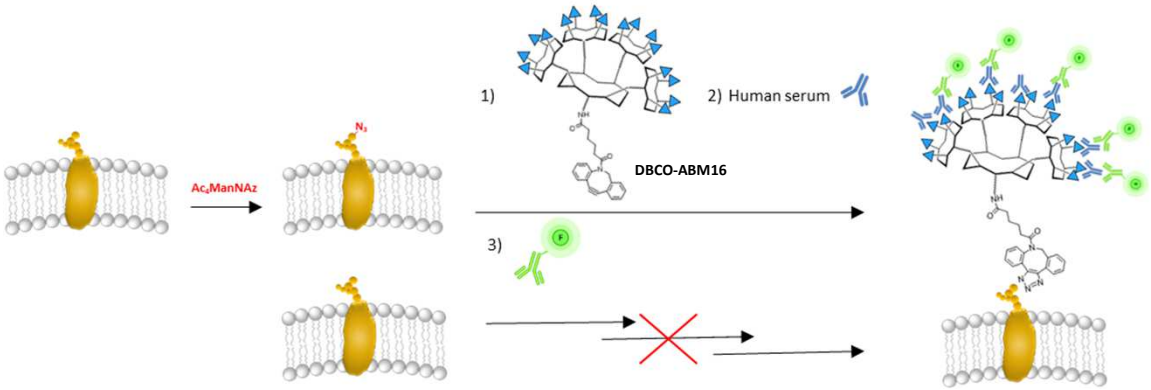


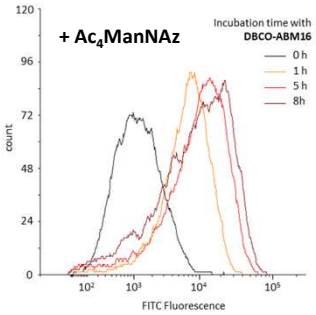


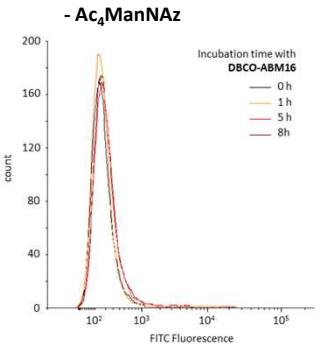


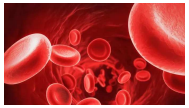


Stability of the cell labelling with ABM

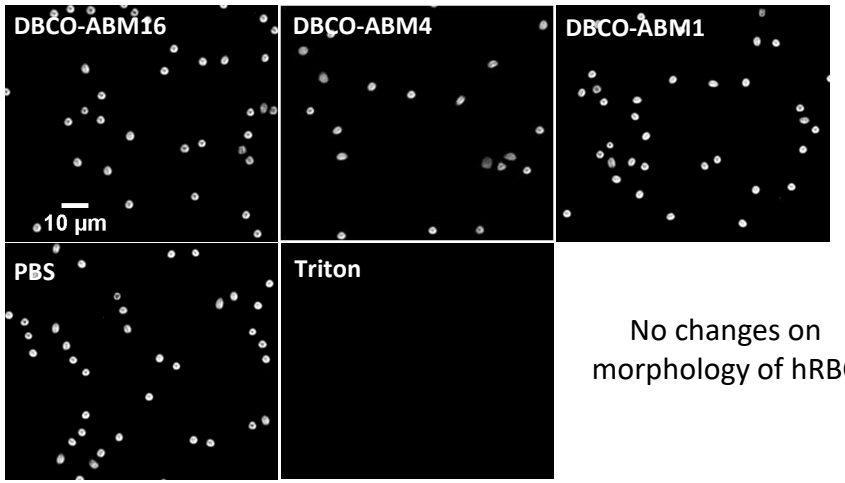






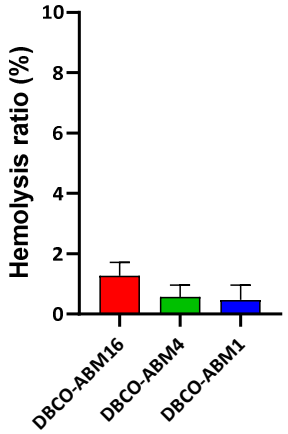


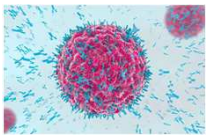
In vitro human blood compatibility of DBCO-ABMs



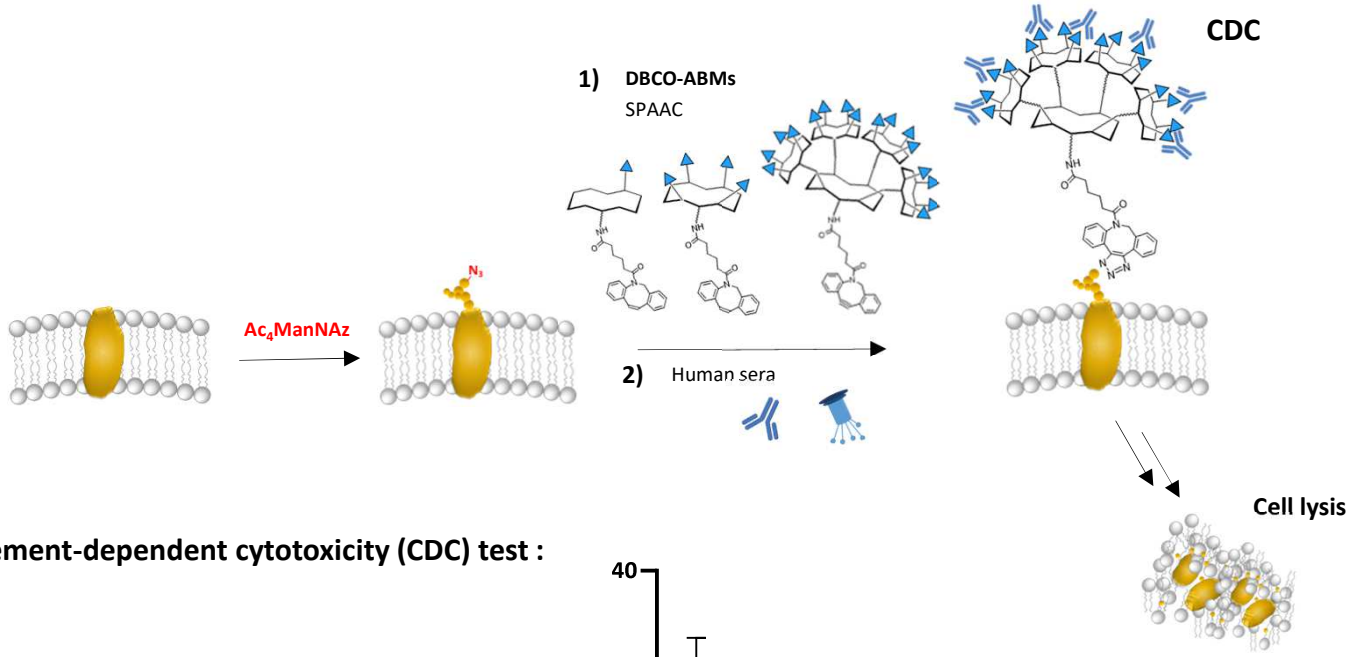
No changes on morphology of hRBC

Hemolysis test

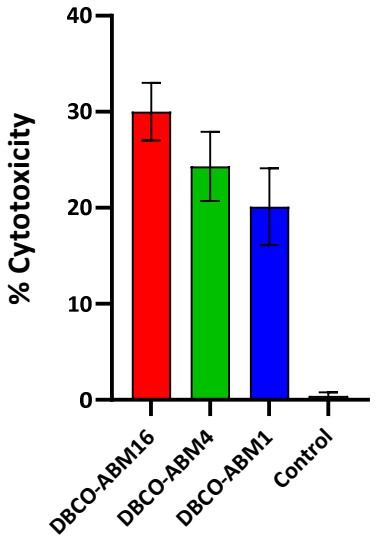




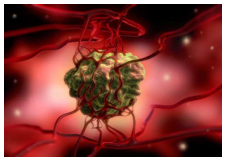
Ability of the recruited antibodies to promote immunes response leading to cancer cell destruction.



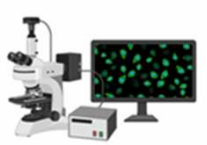
Complement-dependent cytotoxicity (CDC) test :

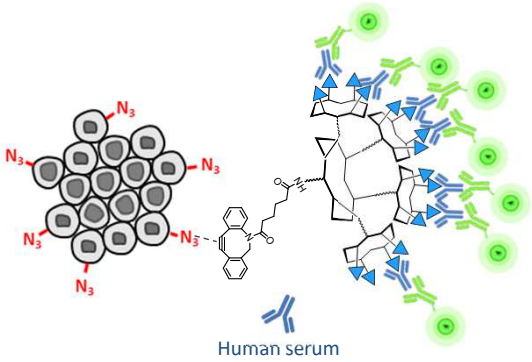


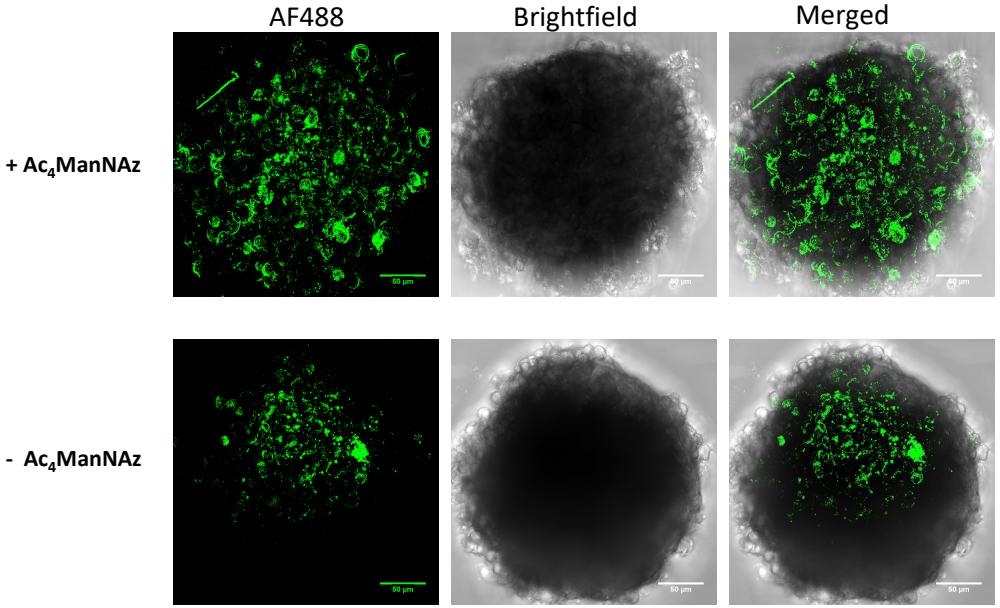
Cytotoxicity effect increase with ABM valency

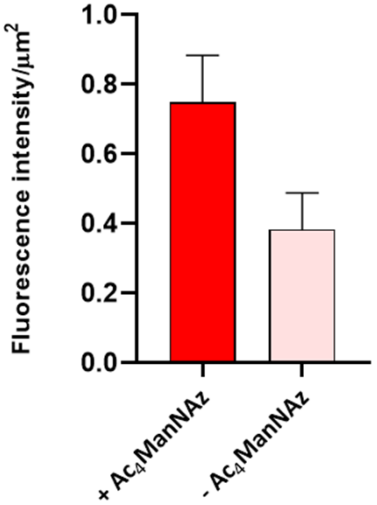


Ability of ABMs to recruit antibody on cancer cell spheroids (solid tumor model)





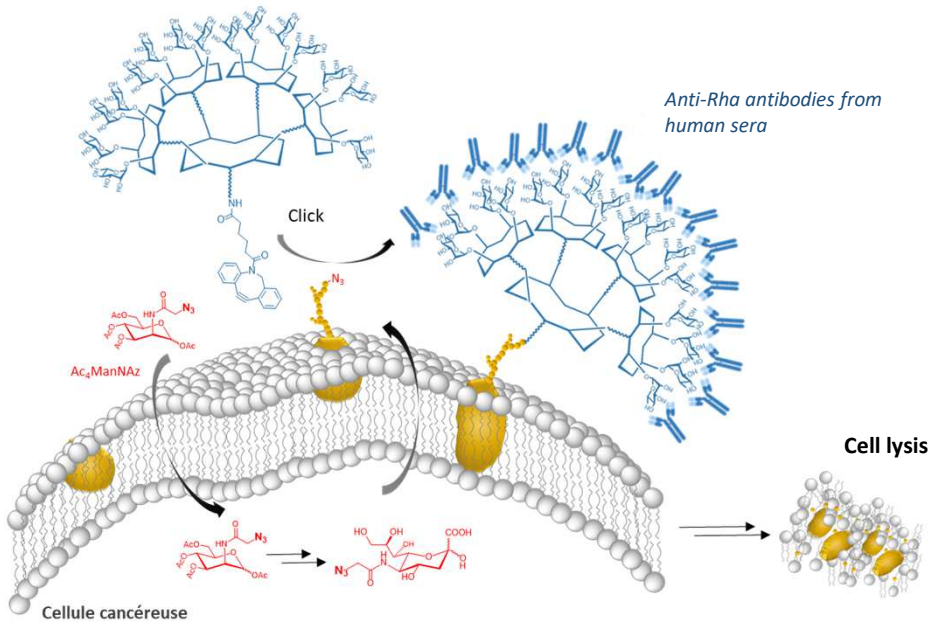




- Robustnesss of cell glycometabolism and bioorthogonal click to decorate the cell glycocalyx with ABMs

- Redirection of natural antibodies (HS) against cancer cells / solid tumor model

- ABM with high Rha density grafted at the cell suface stimule immune-mediated cytotoxicity of cancer cells



Perspectives :

- Cancer cell targeting
  (targeting released of $Ac_4ManNAz$)

- New ABMs to improve antibody recruitment

→ Promizing strategy in immunotherapy

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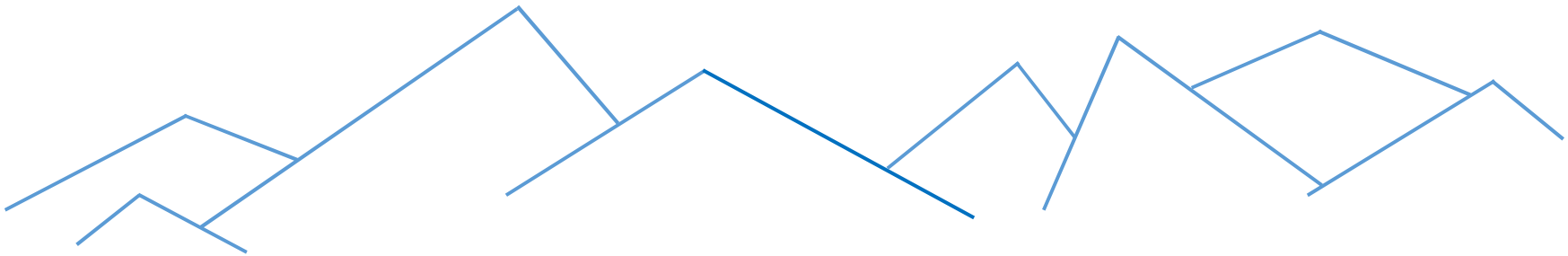

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