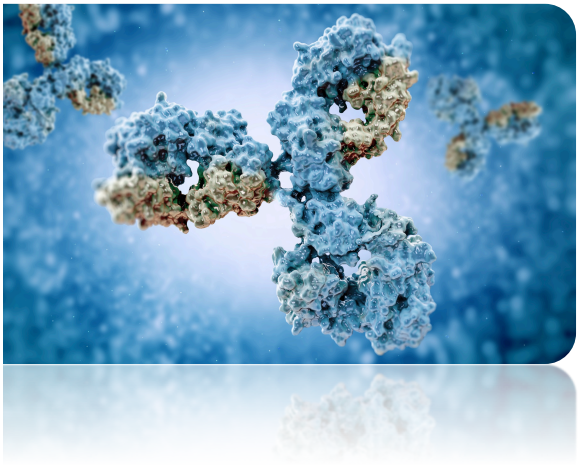

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ANTIBODY DRUG CONJUGATES
PROPRIETARY TECHNOLOGY
SITE SPECIFIC / DAR CONTROL

Increasing demand for targeted therapies, and more specifically for antibody drug conjugates in oncology, finds its scientific rationale and answers a high medical need : being able to deliver in a selective manner a cytotoxic drug into tumoral cells, with the promise to avoid healthy ones, by using specific targeting scheme of antibodies, let us imagine a more efficient and less devastating strategy than chemotherapies.

Since Adcetris® (bretuximab vedotin) & Kadcyla® (trastuzumab emtansine, T-DM1) approvals in 2011 & 2013, not less than 95 ADCs are currently ongoing clinical trials.

In spite of their incredible growing success, each ADC presents main drawbacks inherent to its structure, more complex and heterogeneous than the native antibody.

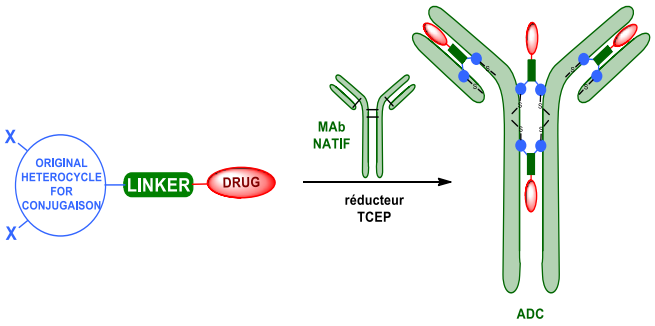
Beside possible decline of selectivity once the coupling site is not controlled – and could interfere with specific recognition scheme of the native antibody – it is also important to control the Drug to Antibody Ratio (DAR).
If not, the resulting entities in a complex mix of structures, would lead to a possible lower therapeutic index, and a complex PK/PD profile, difficult to reproduce.

In the specific case of Adcetris® & Kadcyla®, the DAR is not controlled, and competing technologies leading to both site specific and DAR control of resulting ADCs are rare.

In this context, our team has set-up a new process to generate homogenous ADCs, by selective synthesis, which allows to control both the coupling site in a specific manner, but also the DAR, without modifying the antibody's native structure.

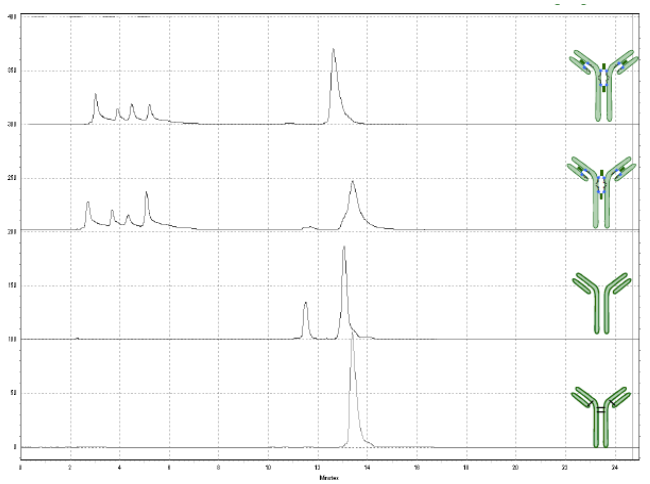
This process, which has been patented, is quite simple to set-up and robust in terms of reproducibility.

It allows the production of homogenous ADCs with a DAR control of 2:1 or 4:1 antibody/toxin ratios, in minimum synthesis steps.



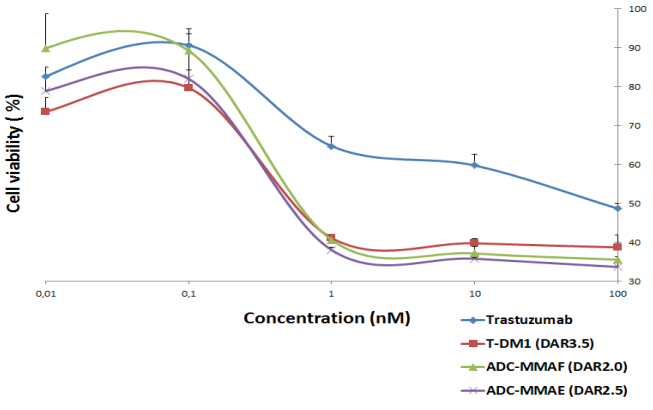
Several advantages:

- ✧ Lead to unique and homogenous ADC of defined DAR
- ✧ Maintain the antibody native structure
- ✧ Avoid amino-acid introduction in the process
- ✧ Minimize the toxin release into the plasma and the off-target toxicity by a great coupling stability



Conjugation kinetics on DAR 4.
RP HPLC follow-up. @McSAF

Furthermore, in vitro studies aiming to compare ADCs activities from either commercial ADC models (Ex T-DM1, anti-HER-2) and the corresponding ones synthetized by our own process, revealed that our technology is up to guarantee an increased cytotoxic activity, on a more specific/targeted manner.
Internalization studies by ICMS & Flux imaging confirmed those points. Animal studies are on-going.



Compared cytotoxic activities on SK-BR3 (HER2++).
Even with DAR 2.0 & 2.5, results revealed similar activities on cell viability that the commercial ADC model T-DM1 (DAR 3.5 heterogeneous).

The technology is available for licence or other forms of collaborations to anyone interested to develop their own ADC(s).

REFERENCES

- ✧ New antibody-drug conjugates and their use in therapy. Joubert, N; Viaud-Massuard, MC; Respaud, R. Patent. **WO2015004400A1.**
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