GlycoConnect® ADC Toolbox Expansion with Dual-Payload ADC (dpADC) Technology

Remon van Geel, Lieke Kraaijvanger, Mick Verhagen, Marie Nassiet, Nick Burgers, Elias Post, Marcel Scheepstra, Sander van Berkel, Floris van Delft, Anette Sommer

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Synaffix BV, Kloosterstraat 9, 5349 AC, Oss, the Netherlands. E-mail: anette.sommer@lonza.com

Introduction to dpADCs

- Drug-induced resistance is frequently observed in cancer therapy, and has now also been observed for ADCs
- Intra-tumoral heterogeneity (genetic alterations, payload sensitivity, low antigen density) and high tumor cell proliferation rates have been shown to result in tumor evolution and therapy resistance that limits efficacy of therapy and decreases duration of response (DoR).
- Combining 2 payloads with distinct modes-of-action (MoAs) may allow to limit occurrence of resistance, provide deeper and longer DoR.

- Dual-payload ADCs (dpADCs), i.e. ADCs consisting of two payloads with a different mode-of action (MoA) conjugated to the same antibody, are an attractive route for developing ADCs that may address tumor heterogeneity, enhance antitumor efficacy, extend duration of response and overcome treatment resistance.

GlycoConnect® and HydraSpace® Technologies

We have shown[1] that chemoenzymatic attachment of payloads to the antibody glycan (GlycoConnect® technology) results in stable, homogeneous ADCs with tailored drug-to-antibody ratio (DAR) and excellent therapeutic index (TI). Incorporation of a short and polar spacer moiety (HydraSpace®) enables ADCs with further enhanced TI.[2]

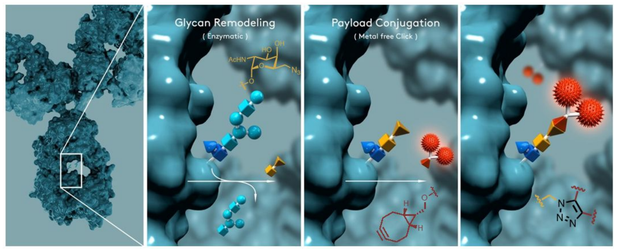


Fig. 1. GlycoConnect® technology: Two-stage approach to ADCs by (a) enzymatic glycan remodling and transfer of azidosugar, and (b) metal-free click attachment of a BCN-modified linker-payload.

[1] (a) van Geel *et al. Bioconj. Chem.* 2015, 26, 2233–2242. (b) Wijdeven *et al. Mabs* 2022,14:1,doi:10.1080/19420862.2022.2078466.
[2] Verkade *et al. Antibodies* 2018, 7, 12, doi:10.3390/antib7010012.

toxSYN® Platform – Expansion to dpADCs

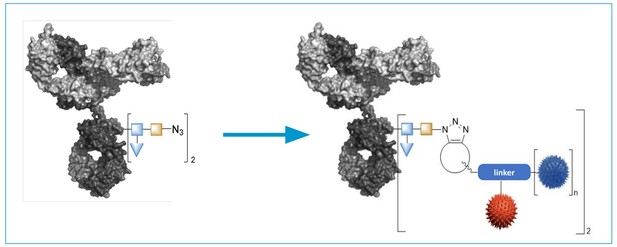
The toxSYN® platform provides proprietary linker-payloads with different MoAs.

Linker-Payload	Mode-of-Action	Chemical Structure Derivative
SYNtecan E™	TOP1 Inhibitor	Camptothecin
SYNeamicin D™ SYNeamicin G™	DNA Damaging Agent	Calicheamicin
SYN-PNU™		Nemorubicin
SYN-PBD™		Pyrrolobenzodiazepine
SYNstatin E™	Microtubule Inh. (MTi)	Auristatin
SYN-duo™ CA	Dual-payload TOP1i + MTi	Camptothecin + Auristatin

Expansion of the toxSYN® platform with dpADCs with proprietary linker-payloads and combination of MT inhibitor and TOP1 inhibitor (SYN-duo™ CA).

GlycoConnect® Dual Payload ADCs (dpADCs)

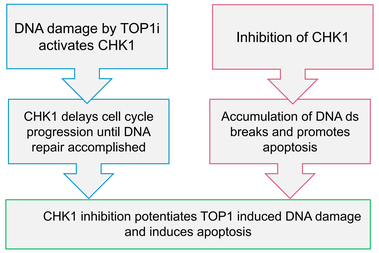
After glycan remodeling, two different payloads are introduced allowing combination of desired payload ratios.
Our dual-payload ADC technology can be applied to combine different payloads from our toxSYN® platform and to combine payloads from our toxSYN® platform with novel payloads.



Tailored ratios: Payload A with DAR2 + Payload B with DAR 2, 4, 6

Fig. 2. After antibody remodeling, payload A and payload B are introduced.

Combination of TOP1 inhibition with a DDR Inhibitor

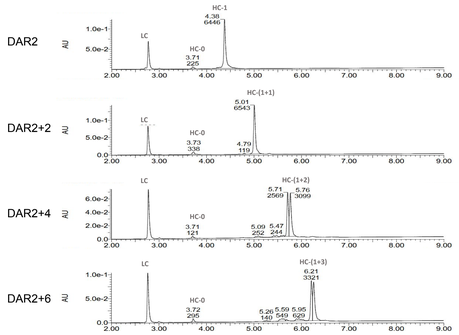


- CHK1, checkpoint kinase 1 is a Ser/Thr kinase
- Several CHK1 small molecule inhibitors in clinical trials

DAR Format and Stability

SYN-duo™ CA dpADCs were generated based on trastuzumab.
DAR ratios ranging from DAR2+2 to DAR2+6. SYN-duo™ CA dpADCs were obtained with >90% conversion (Fig. 3A, 3B) and good stability (Fig. 3C).

A



B

DAR	MTi	TOP1i
2	1.93	—
2+2	1.90	1.90
2+4	1.96	3.85
2+6	1.94	5.60

C

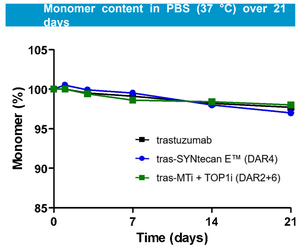


Fig. 3. RP-UPLC traces of SYN-duo™ CA dpADCs with different DAR ratios (A) and DAR values based on RP-UPLC traces (B). Stability in PBS was evaluated for DAR2+6 (C).

Antitumor activity of dpADCs with TOP1i + CHK1i

Anti-tumor efficacy of a HER2-targeting GlycoConnect® TOP1i+CHK1i dpADC (Fig. 4) was compared to single payload ADCs. The dpADC showed enhanced anti-tumor activity compared to both single payload ADCs, indicating that tumor cells can be further sensitized to TOP1i-ADCs by simultaneous inhibition of the DDR by a CHK1 inhibitor payload.

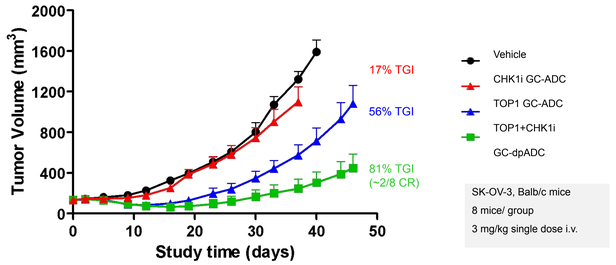


Fig. 4. *In vivo* efficacy of dpADCs with TOP1i/CHK1i compared to single payload ADCs. ADCs are evaluated in SK-OV-3 CDX model. Tumor growth inhibition (TGI) was calculated on day 37.
CR: complete response – tumor no longer palpable

Conclusions

- GlycoConnect® technology extended to generate dpADCs with different payload combinations, and defined stoichiometry of the two payloads
- GlycoConnect® dpADCs show high purity and stability
- Combining a TOP1i with a CHK1 inhibitor enhanced antitumor activity in a xenograft mouse model

About Synaffix

- Synaffix B.V. holds granted patents to its technology. The business model of Synaffix is target-specific technology out-licensing, as exemplified through its partnered pipeline.
- Synaffix has entered into target-specific license agreements with numerous companies. Up to date, eight GlycoConnect® ADCs have entered the clinic, with up to 30 ADCs rapidly advancing through preclinical development. The most advanced partnered asset is in Phase 3 clinical trials.
- For more information, contact bd.synaffix@lonza.com

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