

VERAXA's tumor-specific, dual-targeting BiTAC-ADC technology abolishes off-tumor toxicity of ADCs

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Abstract

The primary limitation of ADCs is their systemic toxicity. This is caused by the fact, that only 1% of the injected dose actually reaches the tumor site, whereas 99% of the cytotoxic payload is catabolized off-tumor, causing toxicity in healthy tissues.

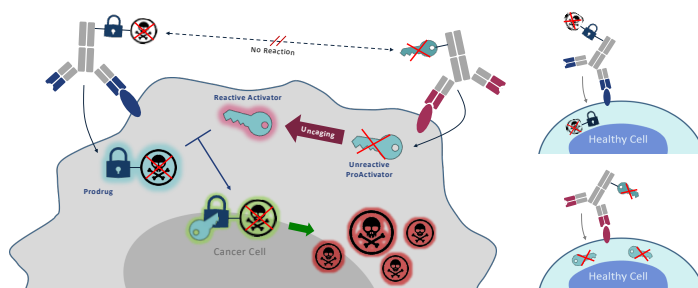
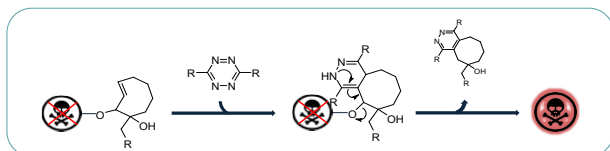
VERAXA is applying dual-targeting ADC concepts to broaden the therapeutic window of targeted chemotherapies. Here, we highlight the next generation in tumor-selective dual-targeting concepts for ADCs: VERAXA's BiTAC-ADC platform, which enables selective killing of tumor cells while sparing healthy tissue.

Here we showcase *in vitro* and *in vivo* proof-of-concept data for selected antigen pairs to underline feasibility and to shed light on the underlying concept and mechanism of prodrug activation.

1

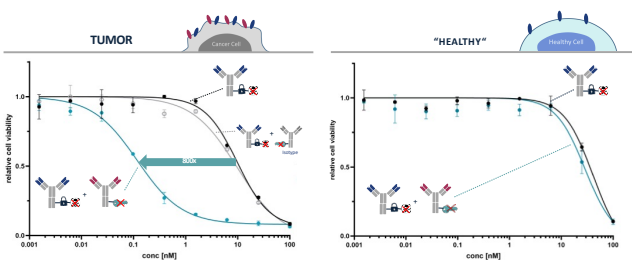
The BiTAC-ADC technology - AND-gate specific, selective payload release in cancer cells

The BiTAC-ADC platform comprises two distinct chemical components, that are being delivered to tumor cells individually, by separate antibodies, targeting different antigens. One component is a Prodrug, while the other is a chemical ProActivator able to uncage the toxicity of the Prodrug. During circulation those cannot react with each other. Only if both components are internalized into the same cell, the ProActivator is converted into the reactive Activator and a chemical reaction releases the free drug, leading to efficient cell killing. Hereby, the prodrug can only be chemically activated by the activator and not via metabolic processes. If only one of the components is delivered into a cell there is no toxicity induced.



2

In vitro Proof-of-Concept demonstrates selective killing of double-positive cancer cells, opposed to single-positive surrogate healthy cells

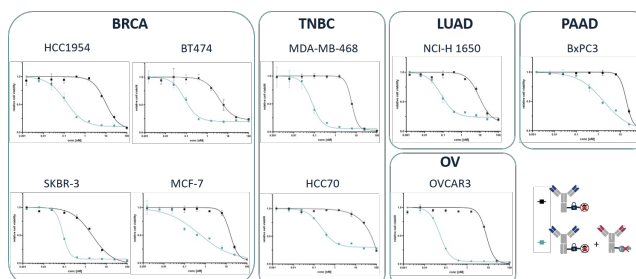


- Target-specific uptake of ProActivator AND Prodrug leads to cell killing
- Uptake of Prodrug without ProActivator on single-positive cells is non-toxic

3

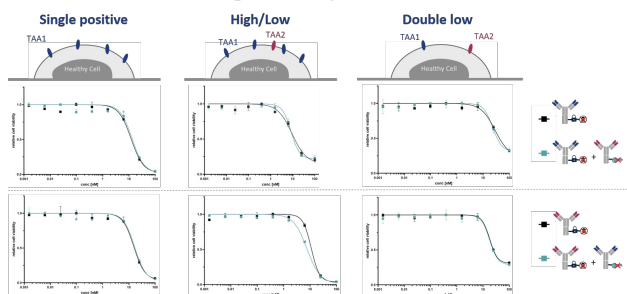
BiTAC-ADC is effective on various cell lines from different indications

The concept has been shown to be feasible on a multitude of cell lines from various indications. Additionally, combinations of several clinically validated ADC targets could be validated.



4

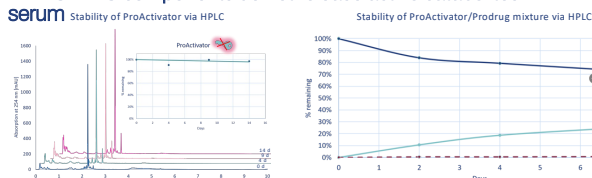
BiTAC-ADC spares surrogate healthy cells



BiTAC-ADCs do not show activation on surrogate healthy cell lines. Additional to single positive cell lines, low expression of one or both targets – in healthy tissue – leads to no observable activation.

5

BiTAC-ADC components do not release active catabolites in serum

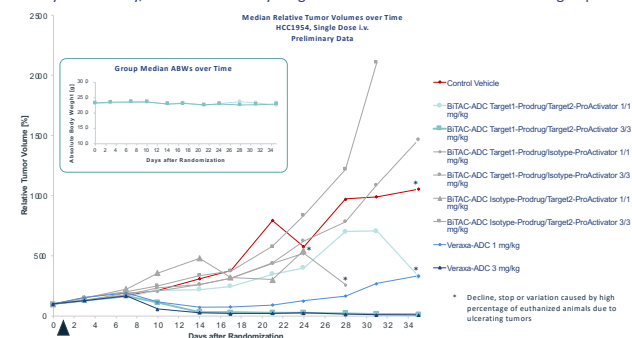


Coincubation of Prodrug and ProActivator in mouse serum does not lead to release of significant amounts of active catabolite, neither by hydrolysis nor unprecedented side reactions.

6

In vivo validation in CDX mouse model

Translation of our BiTAC-ADC technology in an *in vivo* CDX mouse model demonstrated high single dose efficacy comparable to control ADC, which leveraged the same conjugation and linker-payload at the same DAR. Combinations using either Isotype-Prodrug or Isotype-ProActivator did not show efficacy. Additionally, no decrease in body weight could be observed for the BiTAC-ADC groups.



Conclusion

- BiTAC-ADC represents a highly promising approach to
 - minimize on-target off-tumor toxicities – by selectively killing double-positive tumor cells while sparing single-positive surrogate healthy cells
 - abolish off-target toxicities – by design, the prodrug/ProActivator concept will not lead to systemic activation and toxic levels of active catabolite
- In vitro* and *in vivo* proof-of-concept highlight the potential for further platform development towards therapeutic BiTAC-ADC candidates for treatment of various solid tumors