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New frontiers in ADCs and SMDCs

Using a suite of proprietary components, Vincerx Pharma has created a tuneable, modular platform to develop a new generation of novel conjugated cancer therapies with improved safety and efficacy.

Vincerx Pharma, a clinical-stage biotechnology company, has developed a proprietary toolbox of interchangeable components to generate bespoke drug conjugates, including antibody–drug conjugates (ADCs) and small molecule–drug conjugates (SMDCs), each tailored to address the specific biology of the cancer (Fig. 1). The company is seeking partnerships to advance a new generation of modular bioconjugates intended to vastly improve the treatment of aggressive cancers.

The frontrunner of Vincerx's bioconjugate programs, VIP236, is an SMDC engineered to bind an $\alpha_v\beta_3$ integrin adhesion molecule that is abundantly expressed on cancer cells and activated tumor stroma and is a hallmark of aggressive cancers and poor prognosis. To unleash its cytotoxic potency, the SMDC is selectively cleaved by neutrophil elastase, a highly specific protease overexpressed in the tumor microenvironment of many malignant tumors. Cleavage of the linker releases and activates the drug payload, an optimized camptothecin with a clinically validated mode of action. Animal studies show that this two-step targeting to-, and activation in-, the tumor microenvironment increases the tumor-to-plasma concentration ratio of the released camptothecin ten-fold.

To reduce side effects and overcome known drug resistance mechanisms, the optimized camptothecin is designed to have high permeability and a low efflux ratio[1]. VIP236 shows elastase-dependent cytotoxicity, even in cancer cells that overexpress drug transporters, which cause resistance to standard camptothecins. Consequently, VIP236 demonstrates high efficacy and tolerability across multiple patient-derived in vivo cancer models, leading to long-term regression and superior activity.

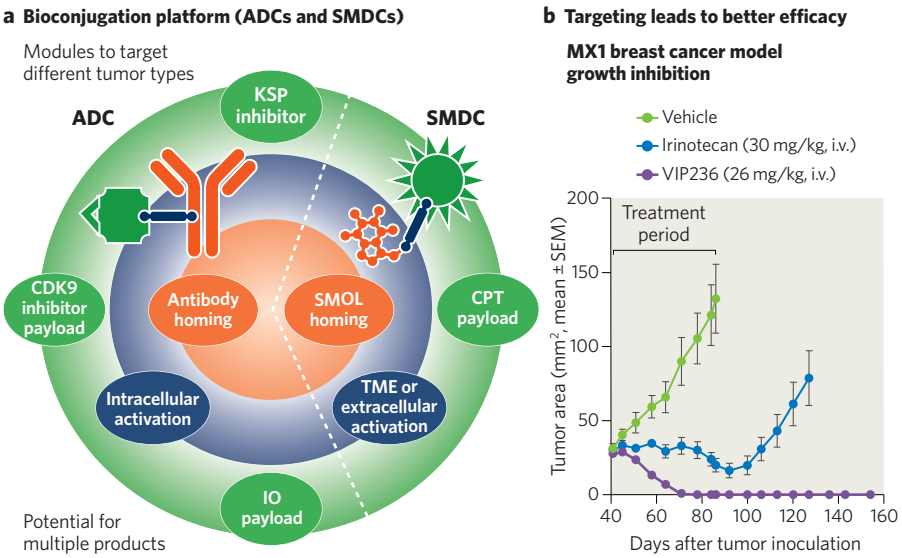

Fig. 1 | Advancing a new generation of modular bioconjugates. (a) The bioconjugation platform. **(b)** VIP236, a SMDC-targeted CPT, is much more efficacious than the clinically used CPT, irinotecan. In the MX1 breast cancer xenograft model, VIP236 induces complete and long-term tumor regression that lasts beyond the treatment period. ADC, antibody–drug conjugate; CPT, camptothecin; IO, immuno-oncology; KSP, kinesin spindle protein inhibitor; SMDC; small molecule–drug conjugate; SMOL, small molecule; TME, tumor microenvironment.

Library of tunable components

The cutting-edge technologies used to create VIP236 are just a few examples of the range of Vincerx's proprietary components, which are able to create unique targeted therapeutics for a broad range of solid and liquid tumors. "We have a diverse, modular platform of linkers and payloads that can be conjugated with typical antibodies, bispecifics and small molecules, creating the potential for novel drugs with greater efficacy and better tolerability than current antibody–drug conjugates," said Hans-Georg Lerchen, CSO at Vincerx. "We have linkers that are designed to be cleaved extracellularly in the tumor microenvironment or only inside the target cells. Our system is flexible and tuneable to exquisitely hone targeting based on the biology of specific cancer types."

In addition to VIP236, Vincerx's pipeline has a clinical-stage cyclin-dependent kinase-9 (CDK9) inhibitor program, VIP152[2], and two preclinical ADC candidates that exemplify the differentiated and novel features of the company's bioconjugation platform. VIP943 (anti-CD123) and VIP924 (anti-CXCR5) are ADCs with best-in-class and first-in-class potential, respectively. Both ADCs contain a state-of-the art linker that is selectively cleaved by legumain, a lysosomal protease overexpressed in cancer cells.

These ADCs also use a proprietary payload system, based on a kinesin spindle protein inhibitor (KSPi). KSP is essential for mitosis, so when administered systemically, small-molecule KSPis are extremely toxic to rapidly dividing cancer and normal cells. "We have harnessed the potency of KSPis through conjugation to tumor-specific antibodies. To further augment the safety and efficacy of the KSPi payload released from the antibody, we've modified it with a polar CellTrapper moiety. This traps the payload in the target cancer cells and prevents efflux or reuptake by neighbouring normal cells," explained Lerchen. Even after multiple exposures to high doses of these ADCs, non-human primates have shown no liver toxicity, neutropenia or thrombocytopenia, toxicities typically seen with the current generation of ADCs.

Vincerx is led by a management team of biopharmaceutical experts including Ahmed Hamdy, the CEO, and Raquel Izumi, the COO, pioneers of the Bruton's tyrosine kinase (BTK) inhibitor field and co-founders of Acerta Pharma, which was acquired by AstraZeneca. The team has a track record of identifying and rapidly developing paradigm-shifting therapeutics. Vincerx is interested in working with partners who want to advance targeted therapies to the next level, to improve the safety and efficacy of treatments for aggressive cancers. As Hamdy said: "With our next-generation bioconjugation platform, we feel we are poised to deliver on the promise of a Zauberkugel (magic bullet) compound that selectively targets disease-causing cells without affecting healthy cells."

1. Lerchen, H. G. et al. *Cancers* **14**, 391 (2022). https://doi.org/10.3390/cancers14020391
2. Diamond, J. R. et al. *Clin. Cancer Res.* (2022) online; https://doi.org/10.1158/1078-0432.CCR-21-3617

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