

Vincerx Pharma, Inc.

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Vincerx—next-generation antibody-drug conjugates with enhanced therapeutic windows

Vincerx applies a modular approach in the development of antibody-drug conjugates by incorporating novel targeting and safety features. The company's lead compounds exhibit high efficacies with minimal toxicities that are expected to improve therapeutic windows. Vincerx believes that partners with first-in-class antibodies, clinical stage antibodies or ADCs against promising targets will benefit from Vincerx's next-generation payload-linker technologies.

Vincerx Pharma is a clinical-stage biotechnology company, with aspirations to address the unmet medical needs of cancer patients with paradigm-shifting therapies. The company's antibody-drug conjugate (ADC) platform combines cutting edge effector chemistries, payloads, and linkers to enhance the efficacy and safety of ADCs. The key features of the Vincerx platform are:

- a large toolbox of effector chemistries and potent payload classes, including kinesin spindle protein (KSP) inhibitors, with a novel mode of action, to address a broad range of cancer targets,
- tunable features that allow optimization of a payload's physicochemical profile, e.g., intracellular trapping or bystander killing, to match target tumor biology,
- novel linker chemistries for tumor specific payload release by legumain, a protease with a unique cleavage sequence overexpressed in cancers.

Vincerx's pipeline includes a clinical-stage small molecule drug program in diffuse large B cell lymphoma and other select cancers and a pre-clinical stage bioconjugation platform and next-generation antibody-drug conjugates to tackle solid and liquid tumors.

"Vincerx is a young company poised to deliver paradigm-shifting therapeutics to address the unmet medical needs of cancer patients worldwide," said Ahmed Hamdy, CEO and cofounder of Vincerx. "We are particularly focused on harnessing our versatile toolbox of innovative linkers, payloads and bioconjugation chemistries to advance the next generation of small molecule and antibody-drug conjugates with potential for making significant inroads into the fight against some of the more intractable forms of cancer."

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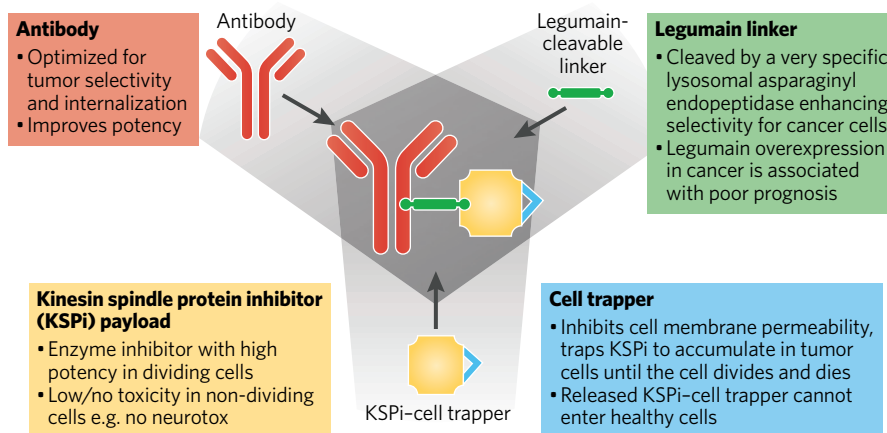


Fig. 1 | Vincerx's next-generation, modular antibody-drug conjugates for cancer. Vincerx has developed a customizable antibody-drug conjugate platform that allows for the modular combination of antibodies optimized for tumor selectivity and internalization, with (1) a legumain linker for improved cancer cell-specific cargo release, (2) a novel kinesin spindle protein inhibitor (KSPi) payload of high potency in dividing cells, and (3) a cell trapper moiety that reduces KSPi's cell membrane permeability, 'trapping' it inside the target cancer cells. Target-specific combination of these individually optimized building blocks allows the precise tuning of therapeutic windows.

Vincerx has an experienced management team to advance the company's therapeutic platform of next generation ADC technologies from discovery to approval, including leveraging the synergies of licensing or strategic partnerships. The company's goal is to rapidly identify candidate ADCs against promising targets or address challenges of clinical-stage antibodies whose development into ADCs has been limited by current payload-linker chemistries.

Rekindling the magic bullet

More than a century ago, the German physician-scientist Paul Ehrlich introduced the concept of a *Zauberkegel* (*magic bullet*) compound that selectively targets a disease-causing microorganism or cell without affecting other beneficial microorganisms or healthy cells. Initially, the *Zauberkegel* concept drove the design of chemical compounds exhibiting improved differential affinities for particular pathogens or target cells. Eventually, the daunting challenge of trying to improve target specificity and toxicity of a single molecule using medicinal chemistry led to the idea of deconstructing the *Zauberkegel* concept and developing each of its parts separately to then combine them into a new and improved hybrid *Zauberkegel*.

This is how ADCs were born, therapeutic agents combining a targeting moiety, the antibody, with a cytotoxic moiety, the drug payload.

In the second half of the 20th century, ADCs rapidly progressed from rudimentary constructs of polyclonal antibodies noncovalently linked to a cytotoxin, to mouse monoclonal antibodies (mAbs), and eventually humanized mAbs, covalently linked to a drug payload. Along the way, many lessons were learned regarding drug potency, antibody specificity, and stability of the linker binding the drug to the mAb. All those efforts led to the US Food and Drug Administration approving the first ADC, Mylotarg, for the treatment of acute myeloid leukemia in 2000 and to a surge of ADCs in the pharma pipeline—a total of nine have been approved, five of them in the last two years.

"While the pharma pipeline of ADCs for oncological applications remains vibrant, the ADCs in the clinic have revealed a number of safety and efficacy challenges," said Hamdy. "At Vincerx we have taken a modular engineering approach to improve the performance of key ADC components, such as conjugation chemistry, linker stability and functionality, and drug payload design. This allows us to customize ADC development using individually optimized

components and layering them in ways that maximize on-target effects and minimize off-target toxicities.”

Vincerx’s two lead ADCs in preclinical development for hematologic malignancies are VIP943 and VIP924, targeting IL3RA and CXCR5, respectively. They both incorporate the company’s novel legumain linker and KSPi payload.

Vital links

Functionally, the antibody component of an ADC, its targeting moiety, and the drug payload of an ADC, its pharmacologically active moiety—are the main building blocks of ADCs. Operationally, though, the linker binding the two functional moieties is arguably another critical component of an ADC because it provides not only a physical backbone to the ADC but also plays a central role in determining its therapeutic window. Ideally, an effective linker is designed (1) to stably attach to the antibody to preempt premature release of the drug payload in systemic circulation, and (2) to provide a target-specific trigger to efficiently release the drug payload at its intended destination.

Vincerx’s proprietary linker technology takes advantage of a lysosomal protease called legumain that is overexpressed in cancer cells and associated with poor prognosis. Legumain has exquisite sequence specificity and cleaves at a positionally constrained asparagine sequence. The antibody with the legumain linker enhances the tumor specificity of Vincerx’s ADC. As a result, the accidental release of the drug payload into systemic circulation and a non-tumor target is minimized by focusing the payload targeting and release in a highly specific manner (Fig. 1).

Our unique combination of cell trapper and legumain linker chemistries are a first in the industry, and we are very excited about its potential to significantly improve the therapeutic window of ADCs

Hans-Georg Lerchen,
CSO, Vincerx

Safely capping it off

For most ADCs, the cytotoxic effect of the drug payload is activated upon cleavage of the drug payload from the antibody-linker portion of the ADC. While the release of the drug payload has been engineered to be target cell-specific in most ADCs, a certain proportion of non-specific cleavage remains a safety liability for many ADCs. One way to circumvent this problem is by engineering a prodrug principle into the payload (Fig. 2).

A prodrug technology is another differentiation in Vincerx’s bioconjugation toolbox to increase the therapeutic window of ADCs. The prodrug principle is implemented with a legumain-cleavable peptide cap on the KSP inhibitor payload. Activation of the prodrug occurs upon internalization and cleavage of the peptide cap by the legumain present in tumor cell lysosomes.

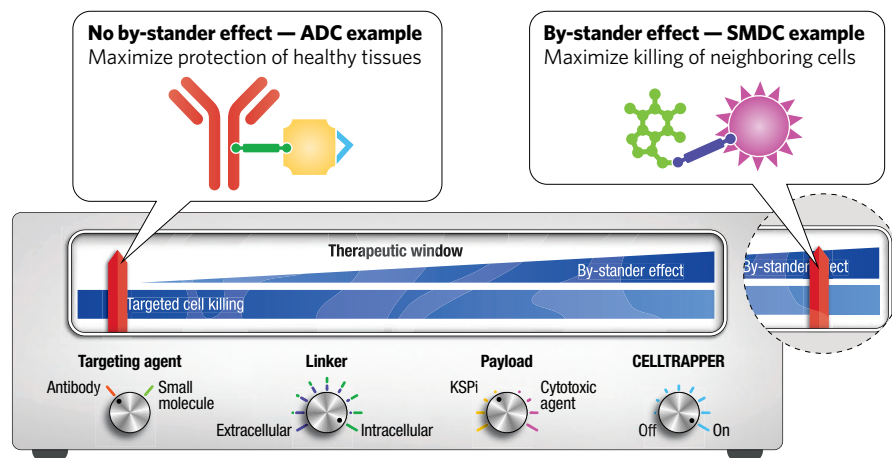


Fig. 2 | Vincerx’s modular bioconjugation platform provides flexibility in targeting. Vincerx’s versatile bioconjugation platform allows for the precise tuning of the desired bystander effect of a therapeutic agent. The range of possibilities is illustrated by the design of highly tumor cell-specific antibody–drug conjugates (ADCs) with minimal bystander effect to small molecule–drug conjugates (SMDCs) that maximize killing of surrounding cells. KSPi, kinesin spindle protein inhibitor.

Novel anti-mitotic bullets

The efficacy of an ADC is highly dependent on the potency of its drug payload. Most ADCs in development and on the market use one of two classes of very potent ADC drug payloads that bind and disrupt microtubules or DNA. These cytotoxic payloads have been selected for their high potency in the picomolar range to maximize cell killing but they are also toxic to non-dividing or non-cancer cells.

The discovery of novel cytotoxic payloads is complex due to the need to minimize their hydrophobicity to preempt ADC aggregation and the need to generate chemistries amenable to stable linker conjugation. Ultimately, the goal is to discover novel payload classes based on alternative mechanisms of action that will result in ADCs with expanded therapeutic windows.

Vincerx’s KSP inhibitor represents a new class of ADC payload with multiple technology enhancements. KSP is involved in the separation of centrosomes in the G2/M phase of the cell cycle. Inhibiting this critical step in the cell cycle has a marked antitumor effect, but healthy, non-dividing cells are not affected by it. The KSP inhibitor exhibits sub-nanomolar cytotoxic potency and is compatible with a variety of linker chemistries at different attachment sites allowing for stable conjugation to antibodies. In hematologic malignancies, cancer cells are juxtaposed against normal cells. In this context, bystander activities associated with typical ADCs are undesirable and may contribute to dose-limiting toxicities. This issue is addressed by modifying the payload with a hydrophilic moiety called ‘cell trapper’. This modification enables intratumoral accumulation of the active payload and further blocks uptake into healthy cells once it is released into circulation, thus having a beneficial impact on efficacy and safety. Finally, due to the hydrophilicity of the KSP inhibitor payload, high drug to antibody ratios (DARs) can be achieved without any risks for aggregation, or associated side effects. By contrast, the hydrophobicity of many existing drug payloads allows passive diffusion through the cell membranes. The company’s two lead ADC programs use this novel KSP inhibitor as their drug payloads.

“ADC engineering has come a long way over the past few decades, but at Vincerx we feel that the development of next-generation ADCs that incorporate extra safety features in a modular way and optimized for specific applications is going to be the deciding factor in propelling the promise of ADCs to the next level,” said Hans-Georg Lerchen, CSO of Vincerx. “Our unique combination of cell trapper and legumain linker chemistries are a first in the industry, and we are very excited about its potential to significantly improve the therapeutic window of ADCs.”

Partnerships in ADC innovation

Backed by a strong IP portfolio and an excellent R&D team, Vincerx is poised to deliver the next generation of ADCs in short order over the next two to three years. The company’s modular platform offers many partnership possibilities to develop innovative next-generation ADCs.

Vincerx’s pipeline of ADCs in preclinical development for a range of intractable forms of cancer exemplifies opportunities for discovery and development partnerships. The flexibility of the platform could also help accelerate partner’s ADC development programs by incorporating select Vincerx innovations into their ADC designs. As a result, Vincerx believes its platform will be attractive to partners with antibody technologies to address promising targets or clinically validated antibodies, which ran into limitations with conventional payload linker chemistries.

According to Hamdy, “the full promise of Ehrlich’s *Zauberkegel* concept has long eluded us, but we feel that the innovation platform we have developed at Vincerx will allow us, in collaboration with our partners, to bring better and safer cures for cancer patients around the world.”

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