Synaffix
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Hitting the antibody–drug conjugate sweet spot

Synaffix's glycan-based antibody–drug conjugate technology is experiencing strong demand, based on its potential to improve safety and efficacy of cancer therapies without genetic engineering.

Synaffix, a rapidly growing Dutch biotechnology company, offers a clinical-stage antibody–drug conjugate (ADC) and targeted delivery platform with broad relevance across the therapeutic spectrum. By consolidating essential proprietary ADC technologies, Synaffix enables any company with an antibody to develop its own differentiated ADC under a single technology license. The company's approach has been recognized by the scientific community and was peer-voted 'Best ADC Platform Technology' at the 2020 World ADC Awards, as well as through commercial success, with more than $3 billion in ADC technology out-licensing deals secured to date. Collectively, Synaffix's nine biotech and pharma partners (including Genmab, Innovent Biologics, and Kyowa Kirin) have approximately 20 Synaffix technology-based ADCs in their pipelines, including three in clinical development. Additionally, Synaffix is expanding its clinical-stage antibody conjugation technology to targeted gene therapy and immunostimulatory antibody conjugates.

A new generation of ADC technology

ADCs have proved to be a powerful tool in fighting cancer, with 11 US Food and Drug Administration (FDA)-approved cancer therapies on the market currently. These are produced (without exception) based on first-generation ADC technology that randomly attaches the cytotoxic payload to the antibody, typically resulting in a heterogeneous mixture with variable amounts of drug associated with each antibody. This leads to the conjugates being relatively unstable, dissociating into potentially harmful free drug and disarmed antibody. These factors complicate pharmacokinetics and limit the efficacy and tolerability profiles, resulting in a narrower therapeutic window.

Second-generation ADC technology addressed the problems of random attachment and varied drug-to-antibody ratios through antibody sequence engineering to create a specific site for drug conjugation. However, these approaches typically require long lead times, and remain inherently unstable and/or show significantly lower production titers.

Synaffix's clinical-stage ADC technology platform represents a third generation of ADC technology that offers the benefits of a site-specific approach and a stable product without requiring any genetic engineering of the antibody.

Synaffix offers a consolidated and easy-to-use ADC technology platform

Synaffix has pioneered three core ADC innovations (GlycoConnect, HydraSpace, and toxSYN linker-payloads), which culminate in a consolidated technology platform available to ADC developers. This enables any company with an antibody to develop its own proprietary ADC. The platform is protected by more than 30 patent families, decades of chemistry and biochemistry know-how, and rich experience gained through the clinical pipeline of ADCs that are based on these technologies.

GlycoConnect, the foundation of the Synaffix platform, is an antibody conjugation technology that replaces the native antibody glycan with a therapeutic payload, using enzymes and metal-free 'click' chemistry. Starting from any off-the-shelf antibody, GlycoConnect can attach a therapeutic payload to the antibody glycan, which is located within the same three-dimensional 'pocket' found in all immunoglobulin (Ig) constant regions (Fig. 1a). The process involves two steps.

In the first step, 'glycan remodeling' is achieved by enzymatically trimming the original heterogenous glycans back to a homogenous intermediate (the

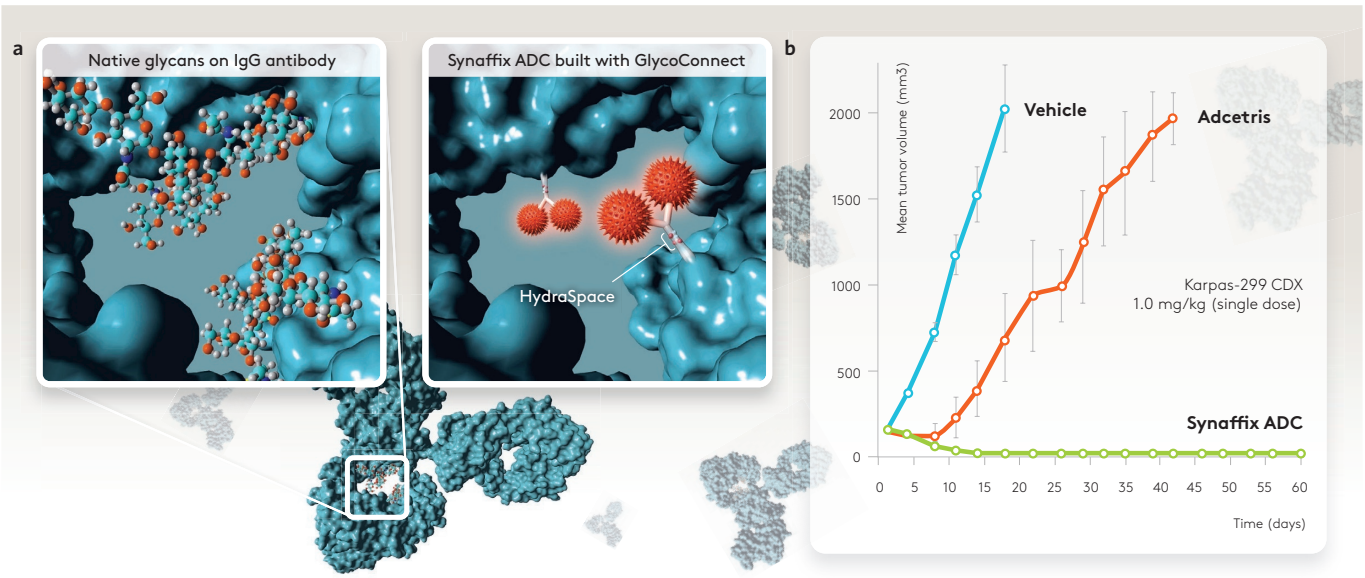

Fig. 1 | (a) GlycoConnect chemoenzymatic attachment of therapeutic payloads to the antibody glycan. The left panel depicts the two glycans that sit within the three-dimensional pocket of the constant domain of IgG antibodies. GlycoConnect uses a combination of enzymes and metal-free click chemistry (a 'chemoenzymatic' process) to generate the ADC shown in the right panel, here depicted with two payloads attached to each glycan and with a drug-to-antibody ratio (DAR) of 4.0. Ig, immunoglobulin. **(b) The therapeutic performance of Synaffix technology.** The graph shows a head-to-head study in a mouse xenograft model, comparing an FDA-approved ADC benchmark (Adcetris) to an ADC built using Synaffix technology (Synaffix ADC), prepared from the identical antibody and payload as compared to the negative control (Vehicle). Adcetris was sourced from the pharmacy with an average DAR of 4.0 (with a range from zero to eight drugs attached per antibody) while the Synaffix ADC was prepared using the site-specific GlycoConnect technology, resulting in an DAR of 3.8. ADC, antibody–drug conjugate.

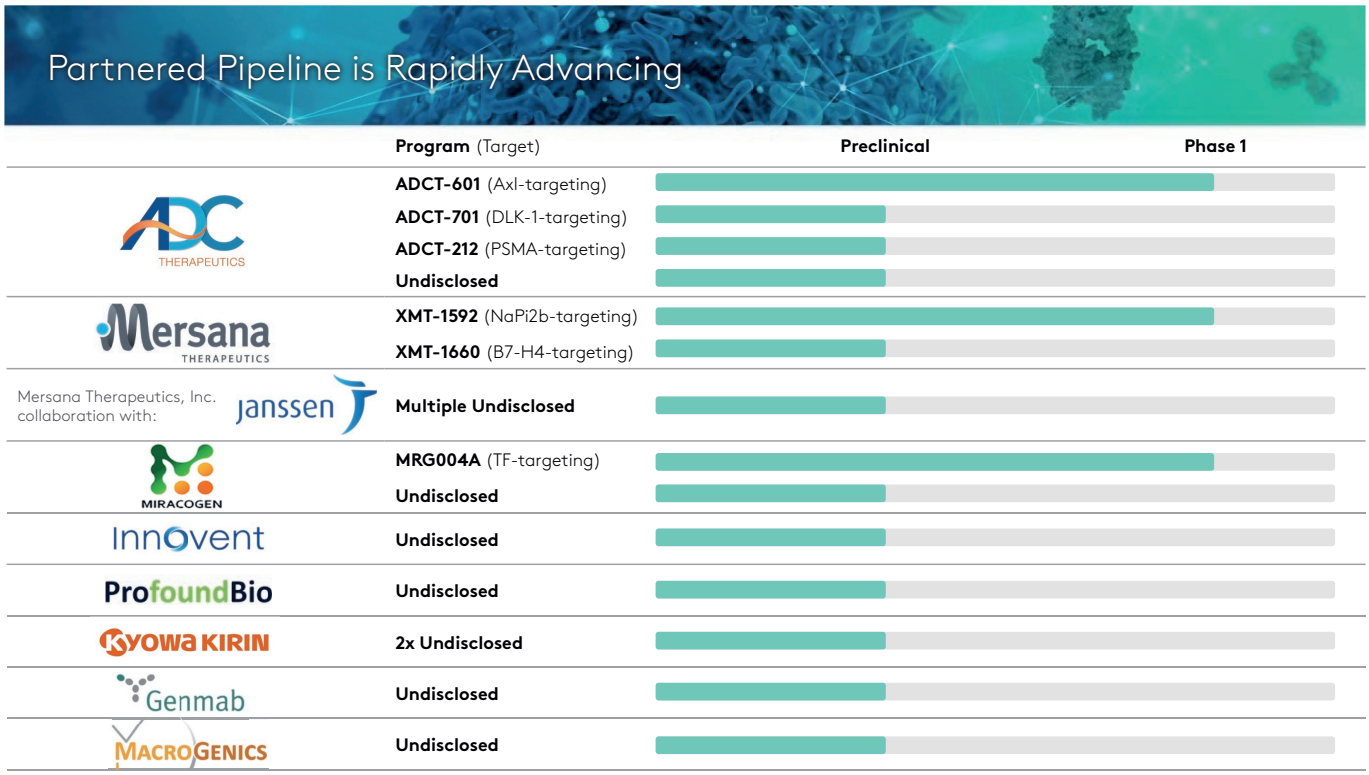

Fig. 2 | The pipeline of antibody–drug conjugate programs being developed under license agreements by partners of Synaffix.

'core' GlcNAc) and directly tagging these trimmed glycans with an azido-sugar, producing the azido-antibody. In the second step, the therapeutic payload is stably attached using metal-free click chemistry, which allows precisely tunable drug loading of exactly 1, 2 or 4 payloads per antibody.

The second ADC innovation, HydraSpace, is a highly polar (negatively charged), compact spacer technology, that further improves the drug properties of GlycoConnect ADCs, particularly in the case of poorly soluble, hydrophobic drugs, resulting in further enhancement of efficacy, safety, and pharmacokinetic profile.

The third pillar of the Synaffix ADC technology portfolio is the toxSYN linker-payload platform, which is represented by a set of six unique linker-payloads, with well understood mechanisms of action—for example, topoisomerase 1 inhibition, DNA damaging, and microtubule inhibition. Each of these contain HydraSpace and are attached to the antibody using GlycoConnect. With the option to choose from a variety of payload mechanisms of action, the toxSYN linker-payloads further maximizes the efficacy profile of ADCs produced using Synaffix technology by best matching the payload mechanism of action with the tumor biology.

Key data and differentiation

Synaffix ADC technology not only hits the 'sweet spot' literally, by modifying the glycan (an oligosaccharide) and stably attaching therapeutic payloads in the three-dimensional glycan pocket, but also because this approach typically leads to significant increases in therapeutic index versus attachment to other locations on the antibody. It is well established that the specific location of payload attachment is critical to favorable therapeutic properties. Synaffix has demonstrated from its own site-scanning experiments that the native glycan is a privileged site on the antibody in terms of ADC efficacy. As further evidence, ADCs built using Synaffix technology have repeatedly demonstrated superior efficacy and tolerability to other clinical-stage and marketed ADC technologies in head-to-head laboratory studies.

Experimental in vivo testing in-house and by its existing licensees has shown that ADCs built using Synaffix technology offer an improved therapeutic index over ADCs prepared from antibody–drug combinations created with earlier generations of ADC technologies. Sample results in rodents of the efficacy data are shown in Figure 1b. Here, using the same antibody and payload as a starting point, the ADC built using Synaffix technology, delivered at the same dose and schedule, showed significantly superior impact on tumor volume regression, demonstrating a curative outcome, when compared to the approved ADC, Adcetris. Furthermore, when the same ADCs were compared in a rat tolerability study, the ADC built using Synaffix technology demonstrated a four-fold higher maximum tolerated dose compared to Adcetris, resulting in a significantly increased therapeutic index. Similar tolerability improvements were observed across multiple primate safety studies.

Further validation of the promise of improved efficacy and tolerability with Synaffix ADCs has emerged from work with Synaffix partners (Fig. 2), many of whom selected the platform after conducting their own comparisons against alternative ADC technologies and, based on the resulting data, are now rapidly advancing a growing number of clinical programs based on the Synaffix platform.

Business model and commercial traction

The business model of Synaffix is based on technology out-licensing, which is structured around the partner's antibody target and specific therapeutic payload(s). While some deals are non-exclusive, others confer exclusive rights to the specific target-and-payload combination(s). Under the license and following the initial preclinical research period, partners can rapidly scale up current good manufacturing practice production of the ADC and file an investigational new drug application within nine months, provided a stable antibody-producing cell line is already available.

Synaffix has generated significant commercial traction in the past year, attracting six additional partners through new licensing deals. This has more than doubled the number of ADCs being developed under license agreements to approximately twenty across its nine current partners (Fig. 2), with total potential value of secured deals exceeding $3 billion. Its partnerships include top-tier biotech and pharma companies such as Genmab, Innovent Biologics, Kyowa Kirin and Macrogenics as well as leading ADC developers such as ADC Therapeutics, Mersana Therapeutics and Shanghai Miracogen (fully owned by Lepu Biopharma). With clear and growing momentum, Synaffix seems well on track for delivering on its vision of becoming the most prevalent ADC technology across new clinical-stage ADCs and growing the therapeutic utility of its platform further into targeted gene therapy and immunostimulatory antibody conjugate fields.

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