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Lonza Biologics

White Paper

From Discovery to Patients: an Integrated Service for ADC Development by Lonza and Synaffix

How Synaffix technology combined with Lonza's end-to-end capabilities help tackle challenges with designing and developing best-in-class antibody-drug conjugates

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Antibody-drug conjugate (ADC) therapies combine the specificity of monoclonal antibodies with potent small molecules to selectively target and destroy diseased cells. However, ADC design and development poses significant challenges due to their complex structure and cytotoxicity. This can make developing safe, effective ADCs time-consuming and costly.

The emergence of technologies such as the Synaffix GlycoConnect™ platform has improved the design and manufacturability of ADCs by offering more stable, site-specific conjugation methods. This addresses issues such as premature payload release, which can cause off-target toxicities. The integration of these technologies into development pipelines, via Lonza's Ibex® Design ADC program, provides a streamlined, end-to-end solution from discovery stages through to clinical production. By enabling drug developers to optimize ADC lead candidates more efficiently while mitigating risks associated with supply chain disruptions and process transfers, Lonza supports the rapid delivery of these innovative therapeutics.

Introduction

Antibody-drug conjugates (ADCs) are therapies that leverage the specificity of monoclonal antibodies (mAbs) to deliver a specific payload to a target area in the body. The payload can for example be a cytotoxic small molecule drug, while the antibody specifically targets diseased cells in a tumor. As well as cancer treatments, ADCs could also be used to treat conditions such atherosclerosis, bacteremia, and inflammatory diseases, more recently application in targeted delivery of

oligonucleotides, small proteins, anti-inflammatory, immune cell engagers, PROTACs and other small and large molecules is being investigated.[1]

However, ADCs can be demanding to develop as they consist of three components, a mAb, a payload (often cytotoxic) and a chemical linker, and each of these elements affect the final drug. Moreover, ensuring the quality and efficacy, as well as the supply of all three components on their own and in combination can be difficult and expensive. This makes rapidly developing clinically effective ADCs and then affordably manufacturing them a major challenge as it requires a multidisciplinary approach involving expertise in antibody engineering, medicinal chemistry, pharmacology, toxicology, process engineering, program planning and logistics. Today, an estimated 70–80% of ADC projects are outsourced to contract development and manufacturing organizations (CDMOs).[2]

ADCs that are currently approved for therapeutic use also have some disadvantages. One major challenge is toxic side effects, resulting in "off-target, off-tumor"-related adverse events.[3] These include systemic toxicities such as neutropenia, thrombocytopenia, leukopenia, and anemia caused by the premature release of the cytotoxic payload into the blood circulation.[4] This is often due to linker instability, and in many older ADCs with first generation linkers, the indiscriminate release of payload and off-target toxicities has been problematic.[5]

In the past five years, various technological advances have improved ADC efficacy and safety, and one important trend is being able to generate stable, site-specific ADCs using novel linker technology.[6] These upgrades in molecule design have triggered renewed interest in developing ADCs. By combining established molecules (such as chemotherapy) with new mAbs, or marketed mAbs with new payload molecules has the potential to enhance both safety and efficacy for patients. This approach also revitalizes de-risked existing assets, explaining why many pharmaceutical companies are investing in acquisitions of site-specific ADCs to strengthen their drug pipelines.[7] Recently, notable deals include Pfizer's $43 billion acquisition of Seagen [8], Johnson & Johnson's $2 billion investment in Ambrx Biopharma[9], and Merck's collaboration with Daiichi Sankyo to develop multiple next generation ADCs, potentially worth up to $22 billion.[10]

The award-winning Synaffix ADC technology platform comprises the proprietary GlycoConnect™, HydraSpace® and toxSYN® technologies (Figure 1) that can considerably enhance the efficacy and tolerability of ADCs. GlycoConnect™ is a conjugation approach that involves enzymatic remodeling of the existing antibody glycan to introduce an activated sugar molecule. This allows fully stable, site-specific conjugation with a therapeutic payload, via metal-free click chemistry without the need for antibody engineering. HydraSpace® is a polar spacer which forms an integral part of every toxSYN® linker-payload. HydraSpace® has a negative charge at physiological pH which can help improve efficacy and manufacturability. Finally, toxSYN® linker-payloads are a set of different standardized linker payloads based on well-established modes of action (see Figure 2, next page) which can be attached to mAb candidates for a technology evaluation of the optimum linker for an ADC.

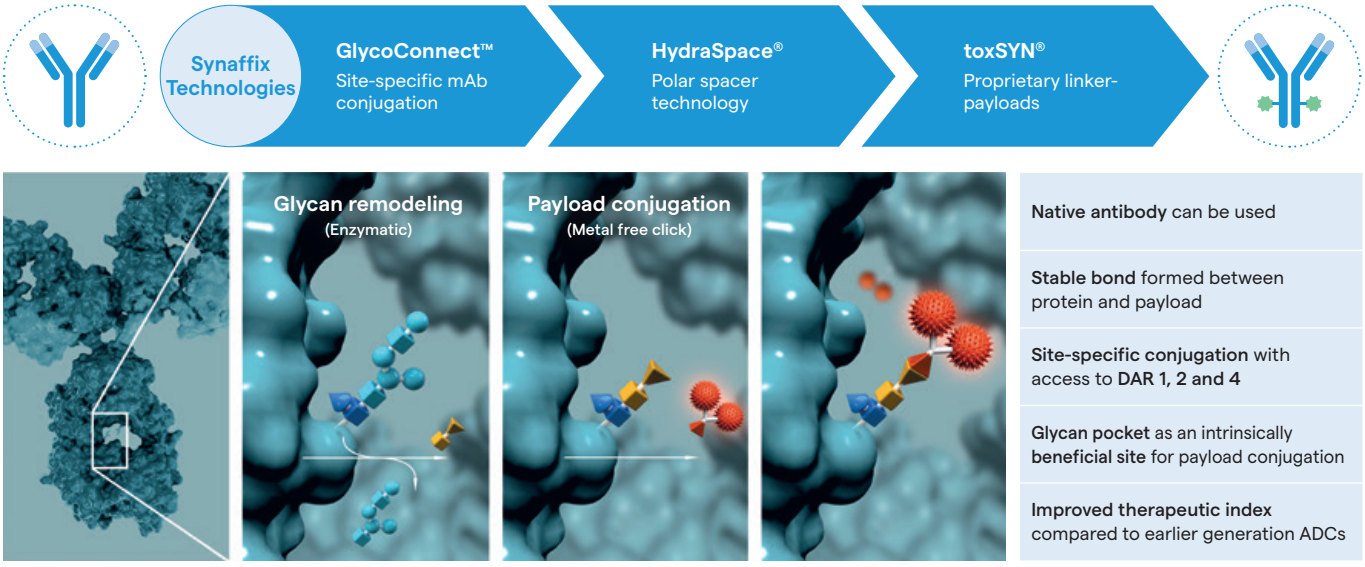

Figure 1
Synaffix Platform for ADC discovery and development. Using GlycoConnect™ technology, antibodies can be site-specifically conjugated without the need for protein engineering.

Multiple linker-payloads available to address any target biology		
1 **SYNtecan E™***	Topoisomerase 1 inhibitor	Camptothecin-based
2 **SYNeamicin D™***	DNA damaging agent	Calicheamicin-based
3 **SYNeamicin G™***		
4 **SYN-PNU™***		Nemorubicin-based
5 **SYNstatin E™**	Microtubule inhibitors	Auristatin-based
6 **SYNstatin F™**		
7 **SYNtansine™**		Maytansine-based

Figure 2
Synaffix' toxSYN® Linker-payloads for ADC discovery and development. The panel includes well-established, clinically validated cytotoxic payloads for the generation of different ADC leads.

The potential of the Synaffix platform to build more advanced ADCs is evidenced by the fact that increasing numbers of ADCs are being built using this technology. Additionally, this platform is under clinical evaluation by a range of license holders including both smaller biotechs and large pharma companies. A recent report has detailed that the Synaffix ADC platform is among the top three site-specific conjugation technologies and to date has the most active clinical assets[11].

Through the acquisition of Synaffix by Lonza[12], ADC drug developers can now access an integrated one-stop service covering the whole lifecycle, from the generation of ADC leads and technology licensing to clinical development and finally commercial manufacture of the product.

In this white paper, we discuss the challenges that ADC developers face and why the innovative Synaffix technology platform in combination with Lonza's Ibex® Design ADC program can help overcome them and accelerate the path to clinic.

Generating de-risked ADC lead candidates with Synaffix GlycoConnect™ technology

Designing robust, optimal ADC molecules is not an easy task due to their complex nature. Once a promising target has been selected, the corresponding antibody needs to be matched with the right payload and linker in the right drug-to-antibody ratio (DAR) to maximize therapeutic efficacy while minimizing toxicity. This is why at Lonza we offer drug developers a suite of early development services (EDS) to support drug development from the start with best-in-class technology, while always keeping later scale-up and GMP manufacturability in mind.

Depending on customer needs, this service starts with optimization and de-risking of the antibody component in terms of developability, followed by rapid generation of sufficient amounts of pre-clinical antibody. Using this material, the Synaffix team generates a panel of ADC variants, for example using different mAb variants and/or different toxSYN® payloads. Typically, up to g-amounts of early-stage material can be provided to provide sufficient material for various pre-clinical evaluation. Lead ADCs and mAbs are sent back to drug developers for comparability or proof-of-concept studies. Through this service, drug developers can utilize the Synaffix platform on a low-risk basis to obtain material for comprehensive lead candidate evaluation *in-vivo* or *in-vitro* before committing to licensing any technology.

Bringing Synaffix ADC leads to IND with Lonza's Ibex® Design ADC Program

After the initial discovery and pre-clinical evaluation stage, full development can be initiated. There are several hurdles when advancing an ADC lead that has shown promise in pre-clinical evaluation through Chemistry, Manufacturing, and Controls (CMC) towards an investigational new drug (IND) application. One of the greatest of these is a lack of integrated drug substance (DS)/drug product (DP) fill/finish services. At Lonza, we are among a handful of strategic development partners that have the capabilities to take ADC lead candidates into the clinic and beyond, by covering all the processes to scale mAb, payload-linker, conjugation (DS) and fill/finish (DP) activities with cytotoxic molecules.

A major advantage of planning an ADC program with a CDMO that can offer full end-to-end services both with early development and large-scale manufacturing capabilities in-house is that it ensures smooth transfer of the lead candidates through the various CMC stages, avoiding unnecessary technology transfer steps. The knowledge generated during the early development work and during lead generation can be directly leveraged for later process development, overall de-risking and accelerating the IND program.

To minimize timelines and simplify the path to IND through a high level of integration, we recently launched Ibex® Design ADC, which leverages our development and manufacturing capabilities for mammalian expression, bioconjugation and DP fill/finish.[13] This program has the potential to accelerate the time from DNA to IND to just 15 months by using a combination of our fast-track mAb development program for typical IgG molecules (Ibex® Design 2.0), sophisticated analytical platform methods and a platform-driven approach for formulation development (see Figure 3).

Due to the highly specific, enzymatic conjugation approach that underpins the GlycoConnect™ process, a high degree of standardization is possible. Additionally, a platform process can be defined which is readily applicable to different products without requiring lengthy product specific development. Through the integration of this platform process into our manufacturing assets we are now able to include GlycoConnect™ based ADCs in our molecule portfolio for the Ibex® Design ADC program and enable a DP delivery in the same 15-month timeline as ADCs built with generic technology. This timeline includes delivery of submission-ready CMC data for IND filing.

Key to achieve the 15-month timeline for the development of an ADC from DNA to IND is the parallelization of several development activities (see Figure 4, next page). For example, material from early mAb supply runs is used to kick-start tech transfer and development activities for the conjugation part while mAb development and expression work is progressing towards pilot and eventually GMP batch. As soon as first conjugated material is available, we begin early formulation development so that initial formulation data is available within six months. This allows us to deliver a toxicology batch for the conjugated drug substance in just eight months, and a current Good Manufacturing Practices (cGMP) DS batch in 12 months. DP manufacturing is completed within three months during which time the regulatory documentation is prepared to be ready for IND submission after a total of 15 months from start of transfection.

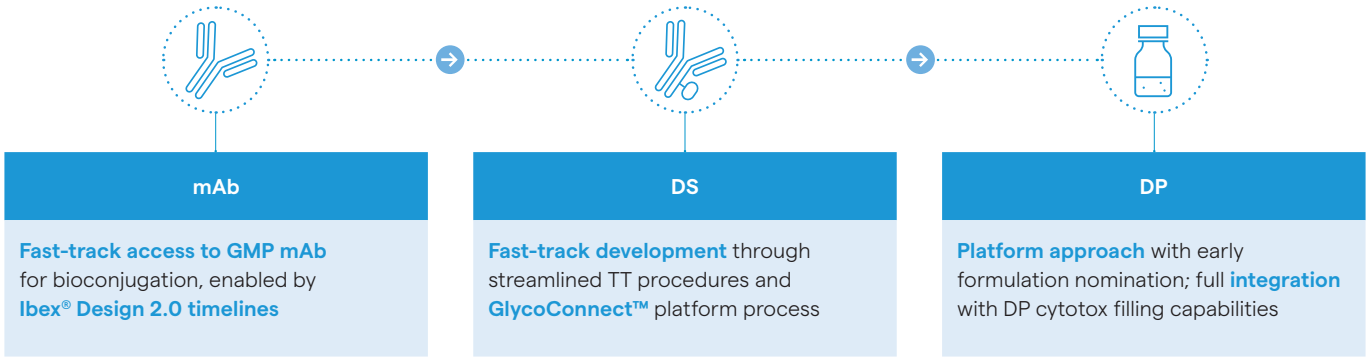

Figure 3
Enabling factors for Lonza's Ibex® Design ADC Program. Standardization and platform approaches for fast-tracking development of mAb, drug substance and formulation.

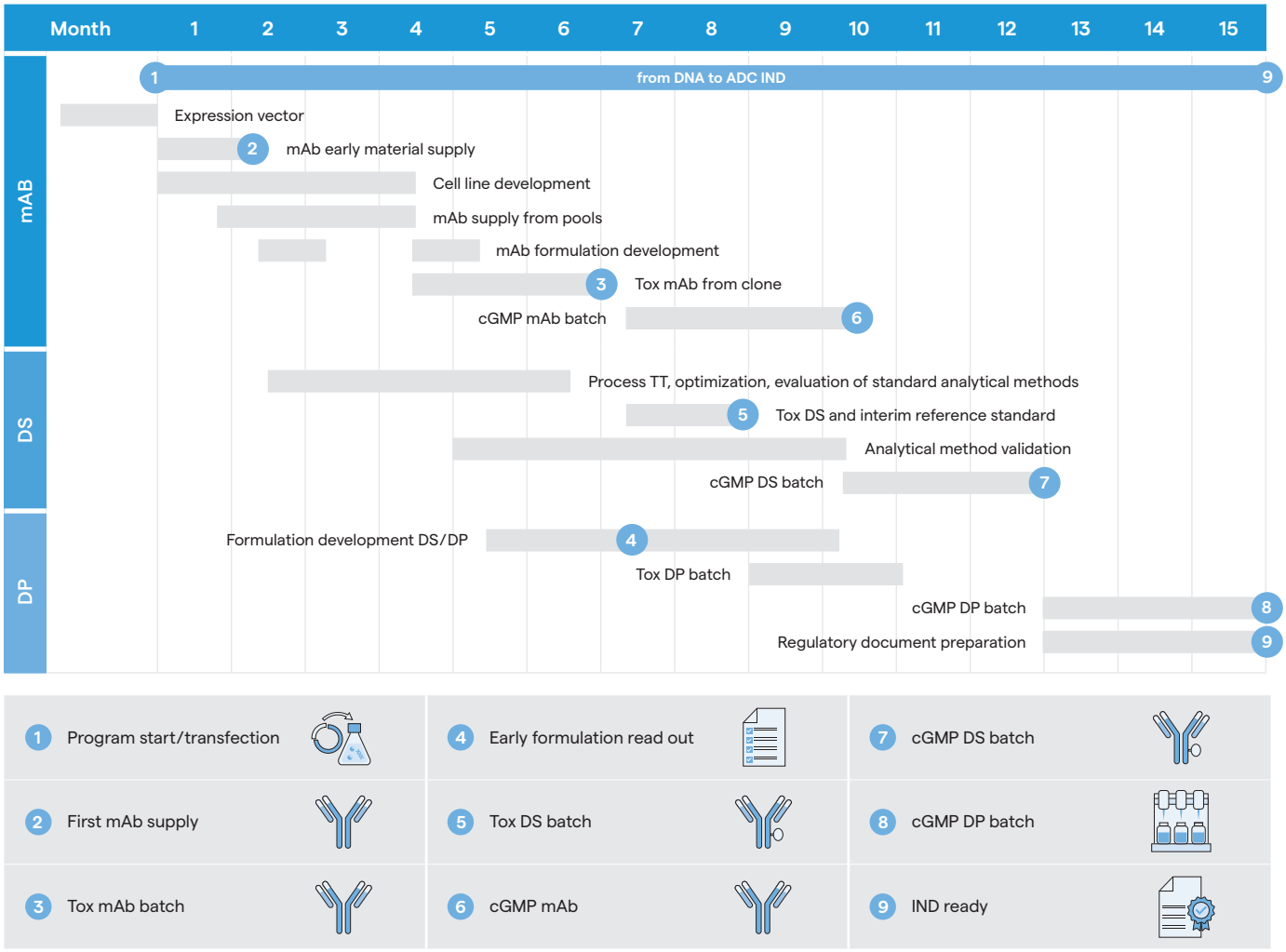

Figure 4
Overview of activities for mAb, conjugation (DS) and drug product (DP) in the Ibex® Design ADC program.[13]
The streamlined development and manufacturing program can be applied to ADCs built with Synaffix technology to bring a lead candidate from DNA to IND in 15 months.*

*The mAb must be a typical IgG in terms of molecular weight and chain number and it must have a glycosylation site at position 297 and must be stable at low pH (3.5). Currently offered for SYNtecan and SYNstatin E payloads with ADCs in DAR2 or DAR4 format. The DS and the DP concentrations should be in the range 5–50 mg/mL. mAbs and ADCs outside these criteria may still be eligible for the program, but will require a more detailed evaluation to assess impact on development work and ADC delivery timelines.

Integration of the supply chain for Synaffix-specific raw materials

Coordinating the supply of ADC and process components that come from different companies and countries, as well as having different production timelines is a major task for many biotechs and CDMOs developing ADCs.

In ADC programs where separate CDMOs are being contracted for mAb manufacturing, payload production, ADC construction and fill/finish, coordinating all these activities is the responsibility of the original drug developer. Due to issues such as cross-border shipments, incoming quality control testing, and other logistical constraints, significant time can be lost when transferring products from one manufacturing site to another. Additionally, each CDMO or supplier must be individually contracted and qualified, adding to the legal, quality management and time burden. These combined technical, supply chain and administrative hurdles can result in longer development timelines, resulting in delays getting an ADC to clinic and/or market.

Alongside the increasing use and clinical promise of the Synaffix platform, the Synaffix team has established a phase-appropriate, robust cGMP supply chain (see Figure 5, next page) for all the necessary proprietary components (enzymes for glycan remodeling, azido sugar and toxSYN® payload). A sophisticated forecast system ensures sufficient stock to enable delivery of raw materials within two months

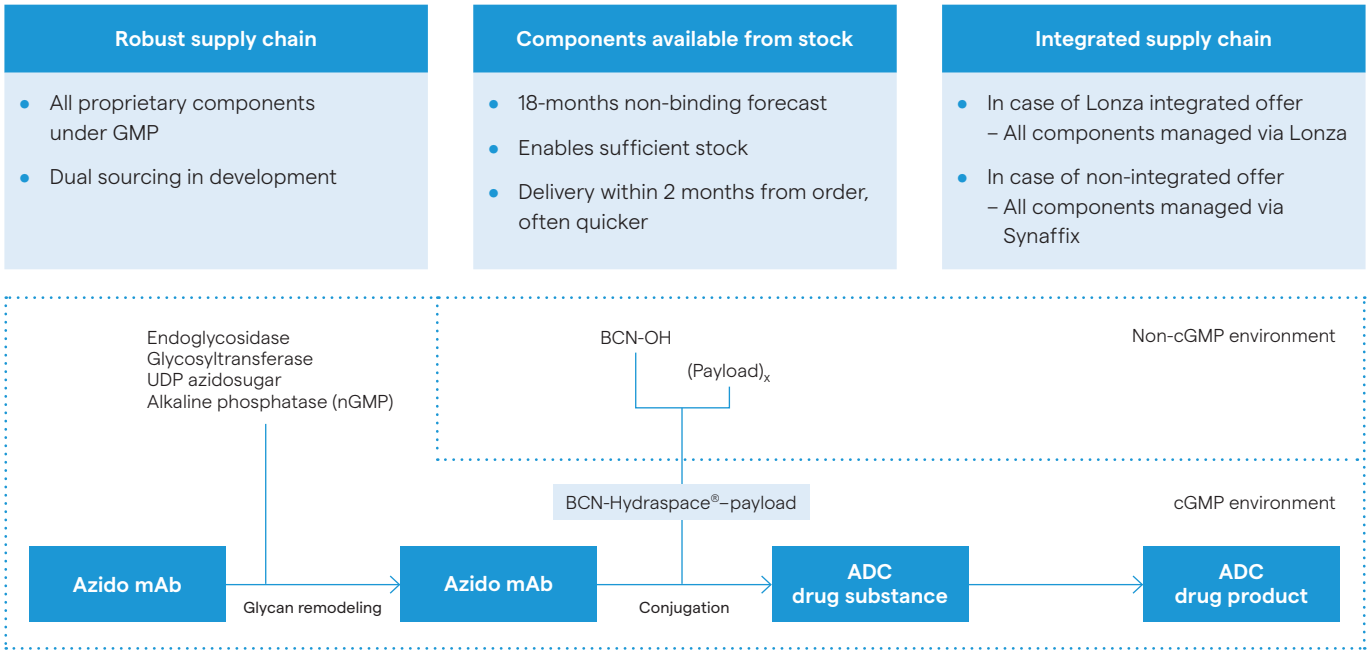

Figure 5
Flexible supply chain for GlycoConnect™ materials. As part of the integrated offer with Synaffix, Lonza fully manages sourcing and supply of the components for the GlycoConnect™ process.

at the latest from order. This allows for flexibility when planning an ADC program, for example if there are changes in demand or timelines.

By accessing Lonza's integrated offering with Synaffix, management and coordination of this supply chain and network of qualified cGMP vendors for the toxSYN® payloads and GlycoConnect™ platform components, is now greatly simplified for the customer as all these aspects are handled by one company.

Lonza has supported the development and manufacturing of a diverse portfolio of ADC payload-linkers over the last 15 years. Manufacturing capacity ranges from grams to tens of kilo batches across multiple GMP assets. This strong in-house small molecule capabilities for highly potent payloads at Lonza allow further integration and simplification for the customer, including GMP supply of customer-specific payload/HydraSpace™ combinations, which can be offered in tandem with the 15-months DNA to IND timeline of an Ibex® Design ADC program.

Flexible solutions shaped around different needs

While fully integrated DNA-to-IND solutions may be the preferred option for many drug developers, others may have different requirements. Therefore, our offerings are shaped such that complete flexibility remains possible with molecule design and program planning through to commercialization. For example, drug developers can join us at any point in their ADC program; using a train analogy (see Figure 6, next page), they can hop on and off at different stations with their molecules, partnering with us for development, manufacturing or just for the fill/finish part of their ADC journey. Moreover, it is possible to utilize toxSYN® payloads, or to bring in a custom payload that can be equipped with the HydraSpace® linker.

If ADCs developed by our Ibex® Design ADC program are successful during first in human (FIH) trials, customers can continue their development journey with Lonza through late phase and to commercialization, benefiting from our decades long experience in conjugation process qualification, scale-up activities and process validation as well as regulatory support for a Biologics License Application (BLA) filing.

Fast-tracking Your Drug Development Success

Shaping our offerings around your needs: molecule, program and supply-chain

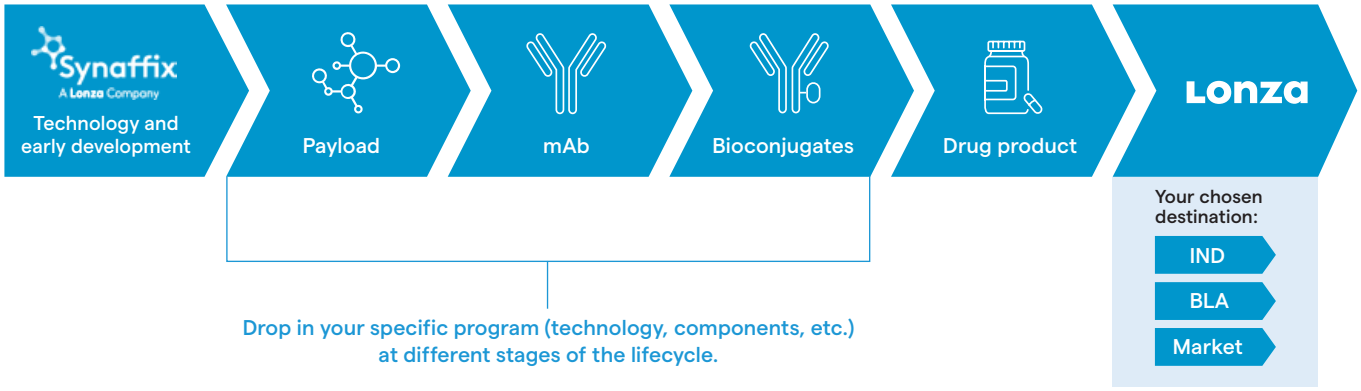

Figure 6

Lonza's flexible solutions for ADC design, development and manufacturing.

Conclusion

ADCs offer a promising therapeutic avenue with their high specificity and targeted therapeutic effect, such as cytotoxicity, but their complexity demands advanced technologies and meticulous coordination.

The combination of Lonza's integrated development and manufacturing offering with Synaffix technology, provides customers with a clear development path with access to Synaffix standardized ADC technology as part of the early development services and a streamlined IND program for the selected ADCs. The Ibex® Design ADC program facilitates seamless transition from discovery to clinical stages, while minimizing the risks associated with poor molecule design, technology transfer and supply chain disruptions. As a one-stop ADC shop, Lonza will manage all the GlycoConnect™ component supply, and interim services as one integrated offering, making managing timelines and costs more convenient for drug developers.

Ultimately, overcoming the inherent challenges in ADC development accelerates the path to IND/IMPD filing and commercialization. Our commitment to innovation and end-to-end integrated services ensures that as a strategic development partner, we provide drug developers with the right solutions to build a successful ADC pipeline.

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