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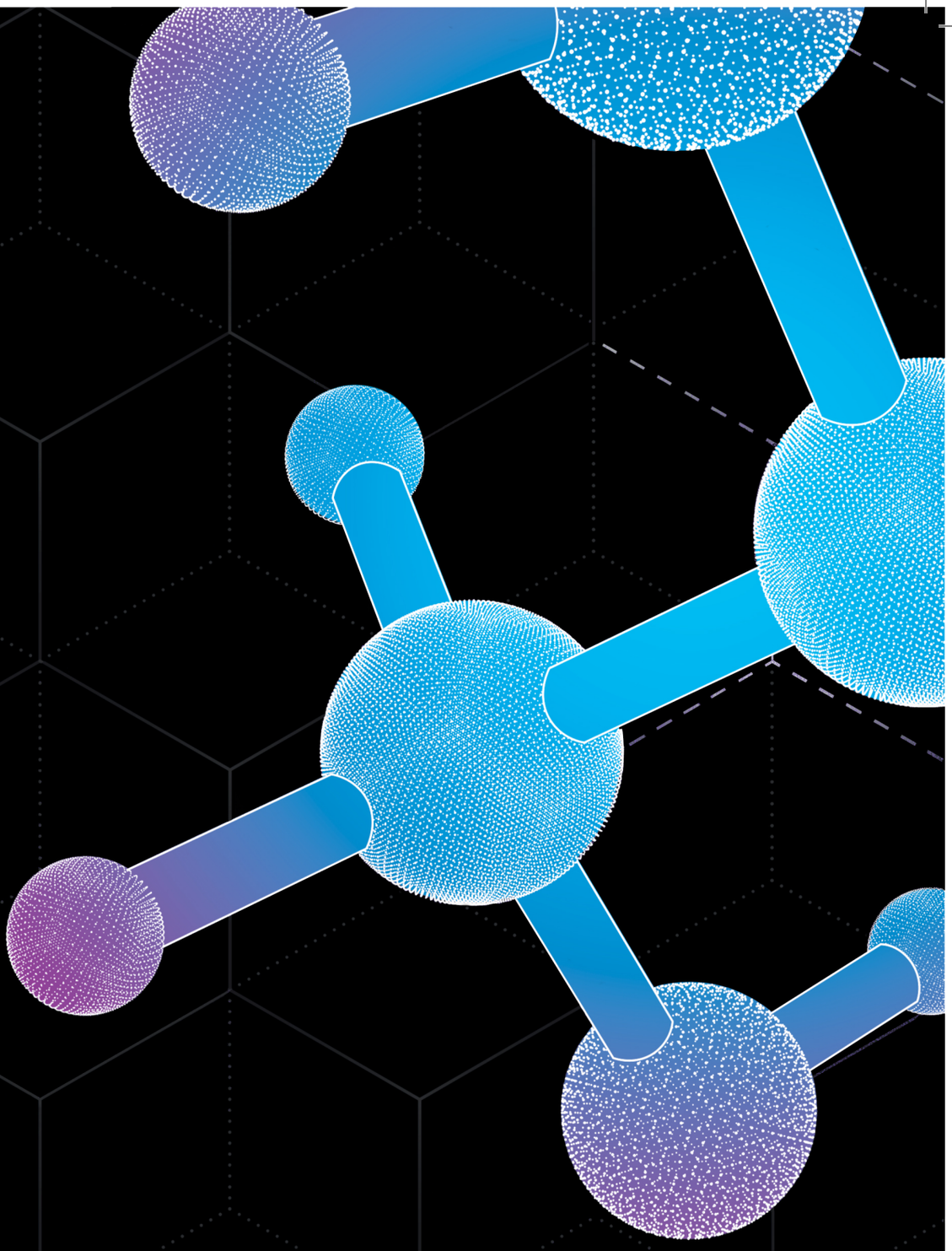

BioDesign™

Building and Delivering Bioconjugate Linkers.

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1

The Rise of Bioconjugate Therapeutics

Bioconjugate therapeutics are among the most promising new biopharmaceutical modalities, receiving interest from biopharmaceutical companies, researchers, investors, and contract organizations. The rise of bioconjugates, which combine synthetic chemistry and biological principles for their activity, can be largely attributed to the advancement of chemical biology and click chemistry in the preceding decades.

Antibody Drug Conjugates Leading the Way for Bioconjugate Therapeutics

Though the bioconjugate class includes several different modalities, antibody-drug conjugates (ADCs) are undoubtedly leading the way in terms of active development and progress to the clinic. A 30% increase in the number of ADC-associated publications has been reported in the last three years.[1] Investments for ADCs skyrocketed in 2018 and has continued since, with an estimated global market of **$8.6 billion in 2022** and **forecast to reach $23.9 billion by 2032**.[2] Even with a struggling biotech investment environment, ADCs saw significant commercial activity, with 76 ADC deals made during 2023 (licensing agreements, collaborations, and acquisitions) and $760 million in venture capital investment into ADC start-ups.[3] ADC progress has also manifested in 15 approved drugs and over 150 active clinical trials, including ~12% in late-phase trials.[1] Existing ADC drugs and current clinical trials are largely focused on oncology, though companies are also exploring additional therapeutic areas, like infectious diseases and immunomodulation.

The Significance of Linkerand Bioconjugation Chemistry

Despite the immense potential of ADCs, the off-target toxicity associated with early ADCs delayed the class's expansion. There was a decade between the first ADC FDA approval (Mylotarg® in 2000) and the next two: Adcetris® in 2011 and Kadcycla® in 2013. It wasn't until 2017 that FDA approved a new one.[4]

Over time, researchers continued to explore how ADC design affects efficacy and off-target toxicity.[5] In the first-generation ADCs, researchers had yet to explore how linker chemistry and bioconjugation strategy impact the controlled delivery of drug payloads. These early linkers were simple alkyl or short linear polyethylene glycol (PEG) chains intended simply to tie an antibody and drug together. Now, it is well understood that careful linker design, including architecture, hydrophilicity, and charge considerations, is essential to impart effective tumor targeting properties without affecting the non-tumorous entity.[6]

Recent advancements and innovations in linker technologies and conjugation approaches reignited interest in ADC biopharmaceuticals and have been driving development and investment ever since. In fact, the majority of 2023's ADC deals focused on technology platforms, such as linker and conjugation technologies. More specifically, ~28% of deals with named targets and technologies focused specifically on linkers, including Eli Lilly's acquisition of Mablink Biosciences, an early-stage company with no active clinical programs but a proprietary linker/conjugation platform.[3] It is clear that linker design technologies and expertise are in high demand in the biopharma sector, as they strongly influence ADC performance.

Parameters for ADC Linker Design and Development

The core challenge of ADC linker design and development relates to understanding the tunable parameters such as the ones listed below to achieve efficacy, while reducing premature payload release and off-target ADC accumulation.

1. The drug-to-antibody ratio (DAR) directly impacts ADC potency and therapeutic index.[7] Though a higher DAR improves *in vitro* potency, it can have potential consequences *in vivo* due to unfavorable effects on pharmacokinetics (PK)/ biodistribution (BD) and differences in tumor biology. Therefore, ADC linkers must provide the optimal DAR for best functionality.

2. Aggregation of ADCs can lead to increased blood clearance,[8] which is problematic, given the hydrophobic nature of many drug payloads. Thus, linkers must modulate ADC's hydrophilicity to improve solubility and minimize aggregation.[4]

3. A linker needs to provide ADC stability in blood plasma to protect from premature drug release and still remain labile at the target.

4. Ideally, ADC linkers must minimize heterogeneity, given that ADCs with mixed structure populations can include fractions with undesirable pharmacological properties that negatively impact efficacy and the therapeutic index.[9, 10, 11]

2

BioDesign: Expert Guided Linker Design with Vector Laboratories

Vector Laboratories can work with biopharmaceutical companies to employ BioDesign™ for their ADC candidates, consolidating chemical synthesis mastery, bioconjugation expertise, and linker know-how for the benefit of bioconjugate drug developers. Combining the long-established credibility of Vector Laboratories in life science reagents with new proprietary capabilities and technologies, the BioDesign process provides expert-guided support for linker selection strategy while supplying both off-the-shelf and custom linker development options, depending on client needs.

What is BioDesign?

BioDesign is an expert-guided, collaborative linker development process with Vector Laboratories, assembled to support your bioconjugate therapeutic development.

Selecting and optimizing the right linker for your bioconjugate drug candidate is easy in theory but hard to do alone. With BioDesign from Vector Laboratories, you can deliver your therapeutic's potential, harnessing proprietary architectures, chemical biology expertise, and over 20 years of linker chemistry experience.

With BioDesign, you can actualize an application-specific, guided selection of linker technologies from a portfolio of versatile architectures. With our specialized chemical biology skillset we can also modify and manipulate linkers to further optimize the performance of your candidate. Through this consultative and collaborative BioDesign approach, you have an expert partner to support the implementation of the right linker to unlock the potential of your bioconjugate, thereby advancing candidates and increasing the likelihood and pace of success. Your drug development team can also access critical bioconjugation support and a unique linker IP portfolio to maximize development versatility, decrease time-to-market, and increase confidence. The BioDesign team can also act as an integrated third party with your company and any external partnerships, such as contract organizations. You can then license novel linker technologies with relative ease and transparency regarding IP boundaries as clinical trials proceed.

With it's 45-year history and nimbleness of a small company, Vector Laboratories can offer significant flexibility and an adaptable development path, alongside the ability to manufacture and supply high-purity linkers at scale. Our biopharma customers also enjoy seamless communication and easier audit processes associated with U.S. domestic supply.

To get started on your BioDesign journey, let's talk about the technology at its heart: Discrete Polyethylene Glycol (dPEG®) linker scaffold.

The dPEG® Linker Scaffold

PEG materials are popular as bioconjugate linkers due to their solubility and biocompatibility **(Figure 1)**.[12] A variety of manufacturers can produce short monodisperse linear PEGs (<12 ethylene-oxide, EO, units), including those used in approved ADC drugs like Zynlonta® and Trodelvy®. However, synthesizing longer and more elaborate architectures and linkers remains a persistent challenge for most manufacturers. Our proprietary dPEG® scaffold and its patented synthetic manufacturing processes enables us to synthesize monodisperse linkers with much longer lengths (>12 EO), orthogonal branching, greater functional group customization, and superior purity.

High Purity Linker Manufacturing for Drug Homogeneity

Heterogenous linker products can result in ADCs with mixed structure populations, adversely affecting its pharmacological properties, efficacy, and therapeutic index.[9,10,11] High linker purity is essential for assembling a homogenous ADC product. Vector Laboratories offers a menu of analytical methods to ensure you are confident in the linkers you use. Paired with the technical expertise to identify, characterize, and remove impurities, you have options to customize linker purity to fit your stage of ADC development. This helps ensure accurate structure-function analysis to design conjugates with optimal efficacy and consistency.[12]

With our Laboratories' BioDesign service and dPEG linkers, drug developers can access a wider range of linker functionalities and features without sacrificing homogeneity and purity.

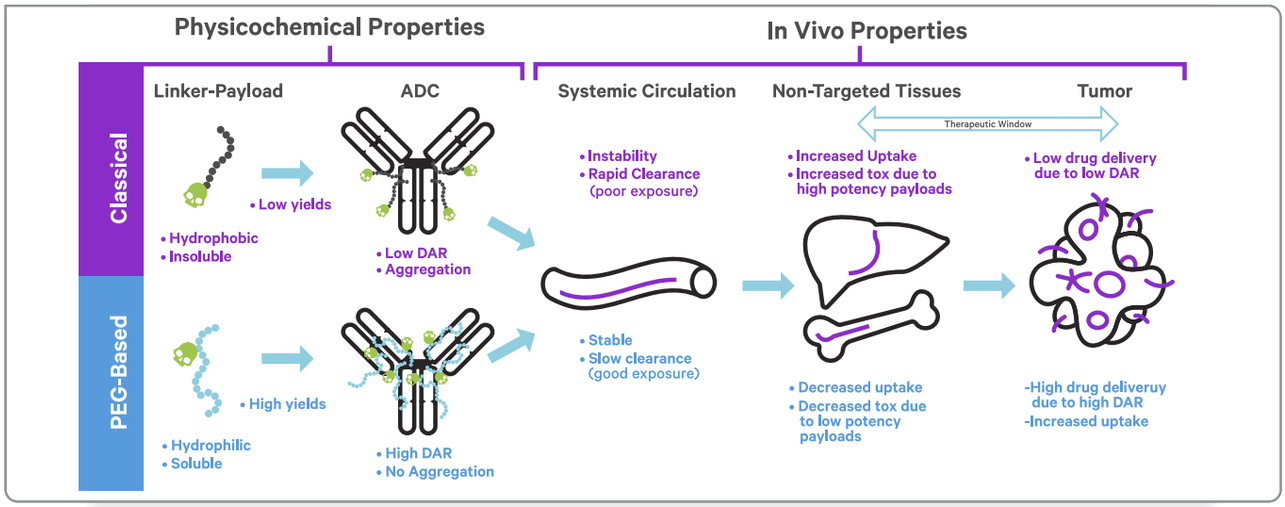


***Figure 1**: Improving Linker-Payload and ADC Properties With dPEGs*

3

Developing Linkers with BioDesign: A Menu of Linker Levers

Linker structures influence ADC efficacy, toxicity, and pharmacology. With BioDesign, there are various structural variables at your disposal during linker selection. These mainly include:

- Reactive groups (position and efficacy)
- Linker architecture (DAR, shielding, and stability)
- Number of EO units (hydrophilicity and shielding)
- Cleavable triggers or non-cleavable linkers (efficacy and stability)
- End-capping (charge compensation)

Reactive Groups and Conjugation Strategy

With the antibody candidate(s) and payload in hand, the first step toward building a complete bioconjugate depends on determining "where" (the placement and amino acid position(s) on the biomolecule) and "how" (the choice of conjugation chemistries) the linker will be added to the biologic. The screening and selection of antibody functional groups and the complementary linker reactive groups impact the maximum possible drug load, the consistency of DAR during assembly, and the difficulty of manufacturing.[1, 13, 14] In addition, the placement of the linker and cargo can impact the ability of the antibody to bind to its target.[15]

ADC bioconjugation strategies can use either native or engineered antibodies **(Figure 2)**. Currently, clinically approved ADCs make use of native antibodies and their naturally occurring functional groups (predominantly amines or thiols). Site-specific reactions are possible in native antibodies, including N-/C-terminal modifications, thiol groups in the hinge region, conjugation through modified glycans,[16] or glutamate (Q295) via microbial transglutaminase (mTG) enzymatic ligation.[17]

Instead of leveraging native amino acids and functional groups, engineered antibody approaches use antibodies that have been manipulated to incorporate either unnatural amino acids bearing unique click chemistry functional groups (like azides or tetrazines) or tags for enzymatic ligations **(Figure 2)**.

To accommodate either native or engineered strategies, Vector Laboratories offers a wide selection of reactive groups for bioconjugation on our linker architectures **(Figure 2)**. Through BioDesign, we can make recommendations

based on your strategy and supply linkers from our off-the-shelf portfolio or synthesize custom ones. In addition, our bioconjugation experts can also support ADC process development by performing antibody/linker conjugations to help arrive at preferred reaction conditions.

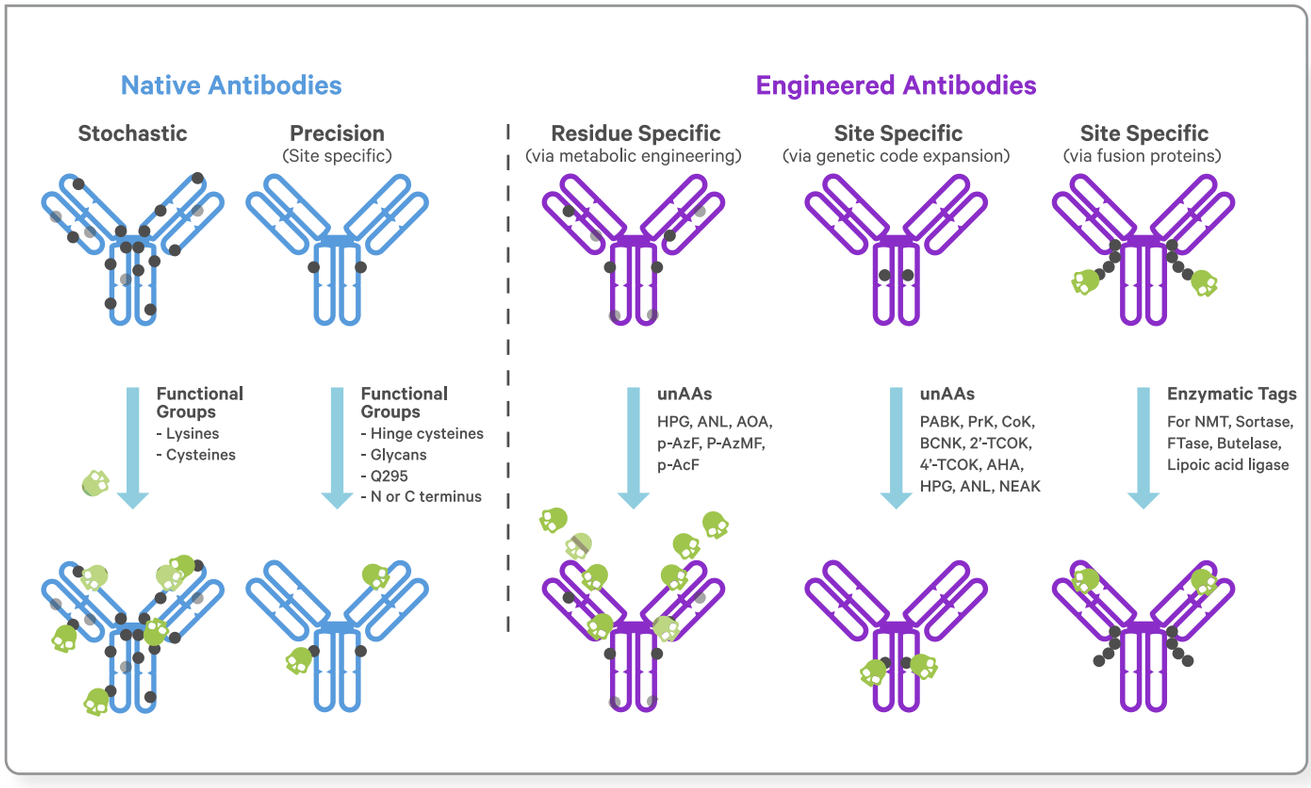


***Figure 2**: Conjugation Sites on Native and Engineering Antibodies*

DAR and Linker Architecture

Determining the most effective DAR ratio for an ADC candidate requires detailed consideration of the interplay between antibody, selected payload, linker design, and tumor biology.[18] In some cases, a higher DAR provides greater ADC efficacy and may be necessary if the drug payload is not potent enough at a lower DAR to reach the therapeutic window. A lower DAR might be preferable if the payload is particularly potent or if its physical properties lead to higher clearance. The relationship between the linker's structure and its drug payload can alter efficacy, stability, hydrophilicity, physicochemical properties, and off-target toxicity. ADC performance also depends on the specific physiology of the target tissue or tumor, requiring further manipulation of the linker and payload.[14,19]

Different biotherapeutic researchers have different aims when looking to construct their linker. To expand the slate of usable payloads, they may need to create ADCs with a higher DAR than those found in currentlyapproved bioconjugates (DAR >8).[1] Or, they might need to develop ADCs with "problematic" payloads **(Figure 3)** by exploring the potential of different DARs or linkers to mitigate off-target toxicity from premature payload release or off-target accumulation.

Antibody Type	Antibody Target Site	Site Specific	Reactive Group (Anchor)	Technology
Native	Amine	X - No	NHS Ester	Acylation
			TFP Ester	Acylation
	Thiol	X - No	Maleimide	Michael
			Halo acetamide	Alkylation
	Disulfide	✓- Yes	Bis-Sulfone	Re-bridging
			Dibromomaleimide	Re-bridging
	Glycan*	✓- Yes	DBCO	Click (SPAAC)
			BCN	Click (SPAAC)
	Glycan**	✓- Yes	Amiooxy	Oxime Ligation
	Q295	✓- Yes	Amine	mTG-Meidated
Engineered	THIOMAB	✓- Yes	Maleimide	Michael
	Carbonyl	✓- Yes	Aminooxy	Oxime Ligation
	Azide	✓- Yes	BCN / DBCO	Click (SPAAC)
	Alkyne	✓- Yes	Azide	Click (CuAAC)
	TCO	✓- Yes	Tetrazine	Click (IEDDA)
	Tetrazine	✓- Yes	TCO	Click (IEDDA)
	LPXTGXXX Motif	✓- Yes	GGG	Sortase-Mediated
	GFEIDKVWYDLDA Motif	✓- Yes	Aliphatic Carboxylic Acid	Lipoic Acid Ligase-Mediated
	CAAX	✓- Yes	Isoprenoid Pyrophosphate	Farnesyl Transferase-Mediated

*after remodeling and functionalization
**after oxidation

Figure 3: *Bioconjugation Approaches Available through BioDesign*

What Makes a Payload "Problematic"?

What makes a payload "problematic" during ADC development is more a matter of application than specific rules. Nevertheless, it is used here generally to describe payloads with some challenging medicinal chemistry and pharmacological limitations. Chiefly, this means particularly hydrophobic payloads that cannot be made adequately hydrophilic through functional group manipulation without compromising activity. In addition, a problematic payload may be one that has metabolic liabilities or can result in severe off-target toxicity if released prematurely.

The highly specific nature of ADC components and their drug target make predicting the behavior of specific candidates extremely difficult until tested *in vivo*. As a result, there is significant value in using a single, yet highly tunable linker scaffold to create and test a medley of different linkers, spanning a range of DARs and physicochemical properties. In doing so, researchers can avoid pharmacokinetic and biodistribution liabilities associated with a single simple linker. Selecting the wrong linkers can significantly delay or disrupt development timelines and budgets.

With BioDesign, you can intelligently and confidently explore linker options, playing around with proprietary "building blocks" to get it right. The variable nature of the dPEG® scaffold is a core benefit of BioDesign. Under the dPEG scaffold umbrella, we offer distinct linker architectures with varied DAR possibilities and pharmacological characteristics **(Figure 4)**. Using the dPEG® linkers, researchers can collaborate with experts to build a multitude of linker options and find the right fit.

Linear

Most similar to traditional ADC designs, the linear architecture dPEG® linkers are ideal for loading a single drug onto a single site. With minimal bulk, these linkers are not sterically hindered and can be conjugated to any position on an antibody.

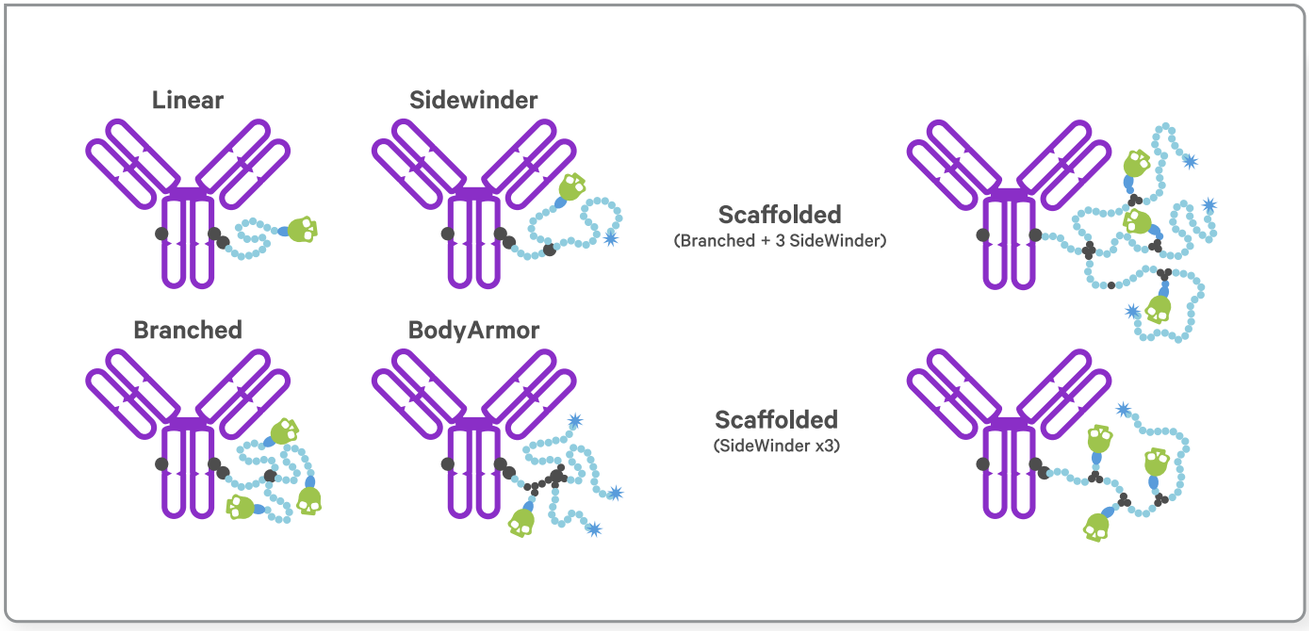


***Figure 4**: BioDesign Linker Architectures*

Three proprietary architectures are also available as BioDesign tools, which offer additional sophistication to linker exploration.

Branched

With the branched architecture **(Figure 4)**, researchers can include additional drug payloads per linker. This architecture can increase DAR without increasing the number of conjugation sites, making them particularly useful for site-specific or site-limited attachments. However, increasing DAR without significantly increasing linker hydrophilicity can make the attachment of highly hydrophobic payloads challenging. Thus, this architecture is particularly useful for less problematic payloads.

SideWinder®

The SideWinder® architecture displays a singular drug and an orthogonal PEG strand **(Figure 4)**. SideWinder is particularly useful for loading highly hydrophobic payloads without increasing the distance between payload and antibody, which is the primary disadvantage of traditional linear linkers. SideWinder allows ADC developers to increase the hydrophilicity of a linker without negatively impacting structure-activity relationships (SAR) and minimizing payload exposure to hydrophobic interactions and metabolic liabilities.

The use of orthogonal linker architectures, such as the SideWinder in antibody conjugates has been shown to positively impact PK and BD. For example, SideWinder antibody conjugates in mouse xenograft models showed slower clearance and >4-fold increase in tumor accumulation compared to antibody alone. The SideWinder conjugate also showed a 47% greater tumor accumulation during a 96-hour time course compared with the same conjugate without SideWinder.[20] These PK results agree with reports from Seagen using a similar orthogonal PEG strand. The clearance of DAR 8 ADCs with orthogonal PEG strands of at least 8 EO units compared to antibody alone in rat xenograft models, resulting in improved efficacy and tolerability.[21] The same set of linker-payloads with orthogonal PEG strands conjugated to non-targeting antibodies was also shown to have less off-target cell and tissue uptake and clinical pathology markers.[22]

The single orthogonal strand found in SideWinder also provides some level of steric protection that modulates esterase and exopeptidase mediated payload release,[23] providing opportunities for less off-target systemic payload release.

BodyArmor™

The BodyArmor™ **(Figure 4)** architecture is similar to SideWinder, but includes additional orthogonal dPEG® strands. These strands can provide further hydrophilicity, charge compensation, and payload protection, slowing the clearance and release rates for tuning controlled delivery. For example a BodyArmor linker with three-fold 8 EO unit strands, showed greater attenuation of payload release in proteolytic conditions when compared to a SideWinder linker with 1 x 24 EO unit strand, demonstrating that BodyArmor provides users with another means to modify release timing.[23]

Scaffolded

Scaffolded linkers mix and match the architectures discussed above to accommodate multiple payloads, hydrophilic spacers, and charged moieties for the ultimate in linker-payload optimization. These linkers are considered an up-and-coming generation of ADC linkers, with similar constructs beginning to show up in pre-clinical and clinical testing.[24, 25, 26, 27]

Linker Length & Ethylene-Oxide Unit Variation

With BioDesign, researchers can partner with us to explore the right linker lengths for their ADCs. Linker length affects ADC efficacy. The use of longer PEG linkers (either in drug-bearing or orthogonal strands) can increase hydrophilicity, thereby reducing aggregation, solubility-related dosing limitations and hepatic clearance.[6] Exploring different linker architectures also provide additional levers for tuning PK and BD. For instance, orthogonal linker architectures have been shown to reduce clearance and off-target tissue uptake of ADCs in a manner that is correlated with the number of EO units in the orthogonal PEG strand,[21,22] while scaffolded linker formats have been shown to improve clearance and efficacy of ADCs in a manner that is inversely correlated with the number of EO units in the hydrophilic component.[28] Furthermore, the number of EO units and linker architecture can be manipulated to affect shielding and timing of cargo release, since both the biologic and linker structure can apply steric limitations.

By manipulating linker structural variables, users can also control rates of payload release in an enzyme-specific manner, dependent on target tissue expression.[26] Researchers explored enzyme-mediated payload release fromantibody conjugates with linear, SideWinder, and BodyArmor linkers while varying distances between the biologic and the payload, the payload and the

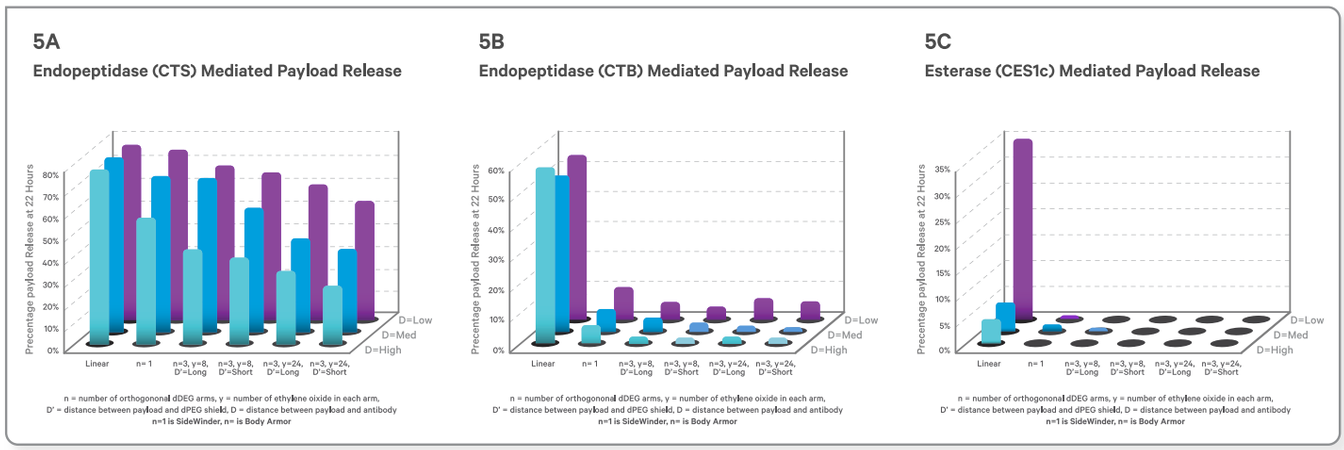
hydrophilic shield, and the number of EO units in the hydrophilic shield **(Figure 5)**.[23] Payload release by enzymes with deeper active sites (like esterases, CES1c) was influenced by only steric shielding from the biologic. Payload release by enzymes with more accessible active sites (like exopeptidases, CTB) required the addition of a single orthogonal PEG strand to influence the release rate. Finally, payload release by promiscuous enzymes with little substrate selectivity (like endopeptidases, CTS) required multiple orthogonal arms for modifiable release rates **(Figure 5)**. Furthermore, the rate of release from endopeptidases could be controlled by the structural variables of the linker-payload.

With BioDesign, researchers can directly explore how changing the antibody-payload distance, the payload-shield distance, and the size of the hydrophilic shield, alters enzyme-mediated payload release and cytotoxin metabolism, ultimately affecting efficacy.

Cleavable Triggers and Non-Cleavable Linkers

The decision to use or not use a cleavable trigger is one of the most common calculations during linker design. This choice is a complex optimization point, that is deeply connected to payload, target, and the features of the target's microenvironment.[6]

Cleavable linkers tend to respond to tumor-associated factors like acidic, reducing conditions, or abundance of proteolytic enzymes (like cathepsins). Cleavable linkers can benefit from the "bystander effect," which describes how payloads internalized and released in target cells can diffuse through the cell membrane and kill neighboring tumor cells to amplify impact.[29] Conversely, non-cleavable linkers rely on lysosomal degradation, which creates charged amino acids that cannot diffuse through the membrane. Non-cleavable linkers tend to benefit from reduced off-target toxicity, but they can also be less potent. While cleavable linkers are currently more common, this may also relate to the higher use of cytotoxic drug payload. ADCs with immunomodulating payloads mostly use non-cleavable linkers because they better localize the immune response to minimize off-target inflammation or immune suppression.[30]



Legend

Linker-payloads with only linear spacers, a linear spacer and a single orthogonal dPEG arm (SideWinder), a linear spacer and three orthogonal dPEG8 arms (BodyArmor), and a linear spacer and three orthogonal dPEG24 arms (BodyArmor) were conjugated to an antibody and evaluated for payload release by enzymes with different active site accessibilities. Endopeptidase is a loosely defined easily accessible binding surface, exopeptidases have an occluding loop that restricts access to the binding site and esterases have a binding site that is very deep in the active site, therefore they have the highest steric hindrance.

Figure 5A: Linear and SideWinder linkers have insignificant effect on payload release, whereas modulation of BodyArmor linker lengths and distances can be used to regulate payload release with endopeptidase.
Figure 5B: Linear linkers have no effect on payload release, whereas SideWinder and BodyArmor inhibit the release independent of their lengths and distances, with exopeptidase.
Figure 5C: With an inaccessible enzyme like esterase, the length of the linear linker effects the payload release as seen with the long linear crosslinker, any additional steric hindrance prohibits payload release completely. Therefore no payload release is seen with SideWinder and BodyArmor linkers.

***Figure 5**: Effect of Steric Shielding on Enzyme-Mediated Payload Release*

During the BioDesign process, researchers can talk with experts about this crucial (i.e., cleavable vs. non-cleavable linker) decision. Vector Laboratories offers some off-the-shelf linkers with cleavable triggers, as well as custom synthesis for BioDesign of new cleavable linkers. Researchers can opt to include triggers like Val-Cit and Val-Ala, which are among the most common triggers because they are cleaved by cathepsin B found over-expressed in tumor cells.[4]

Charge Compensation and End Group Labeling

Researchers can add end-group labels and charge compensating groups to the orthogonal PEG strands. Modifying charge and hydrophilic compensation has been shown to modulate payload exposure and increase efficacy and clearance.[28] SideWinder and BodyArmor linkers are conducive to these manipulations and can be explored during BioDesign. Linkers with various end capping options are available through Vector Laboratories **(Figure 6)**.

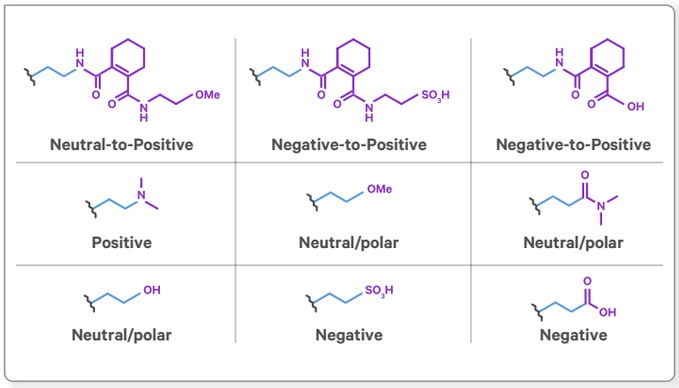


***Figure 6**: End-Capping Options for Charge and Hydrophilic Compensation*

4

Designing Bioconjugates of the Future

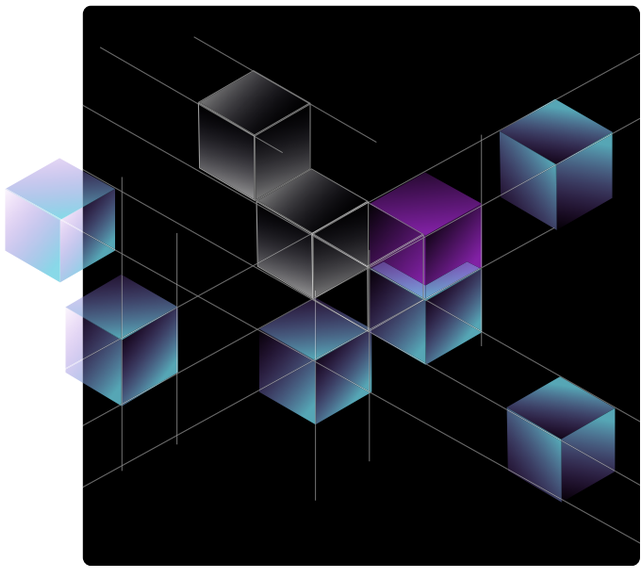
Your goal is clear, but your path to get there might not be. With BioDesign, you have an expert team to help you navigate and succeed.

Start Building to Deliver

Progressing a bioconjugate along the complex journey to the clinic is a daunting yet exceedingly worthwhile challenge. As you delve into the intricate world of linker design, know that you do not need to go at it alone. With BioDesign, you can collaborate with linker design experts and harness a multitude of experimental levers to confidently tune bioconjugate performance.

Though this piece primarily focused on ADCs, the capabilities of Vector Laboratories extend to other bioconjugate modalities as well. Whether you are working on antibody fragments, peptide drug conjugates, vaccines, nanoparticles, colloids, or other bioconjugate therapeutics, you can leverage BioDesign to enhance your candidate's efficacy, pharmacokinetics, and biodistribution.

If you are ready to design the next big bioconjugate with a team of expert chemical biologists, reach out to Vector Laboratories and get building.



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