



CURAPATH

Cristal
Therapeutics

Application Note

Solutions for Active Targeting



REACH OUT



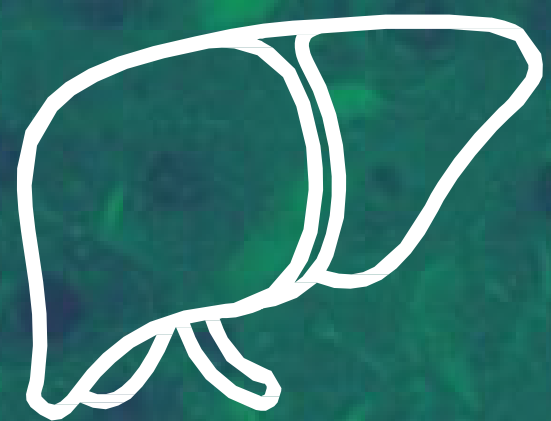
RESOURCES



The Challenge

Extrahepatic Delivery of LNPs

Achieving efficient delivery of lipid nanoparticles (LNPs) beyond the liver remains one of the most critical challenges in the field of nucleic acid therapeutics. While hepatic targeting is relatively well-established, directing LNPs to extrahepatic tissues requires overcoming multiple challenges:



Natural liver tropism

LNPs are preferentially taken up by hepatocytes due to apolipoprotein-mediated recognition, limiting distribution to other tissues.



Biological barriers

Endothelial tight junctions, tissue-specific vasculature, and cellular membranes restrict access to target cells such as T cells, lung, or CNS.



Off-target accumulation & toxicity

Non-specific biodistribution can lead to reduced efficacy and increased safety concerns.

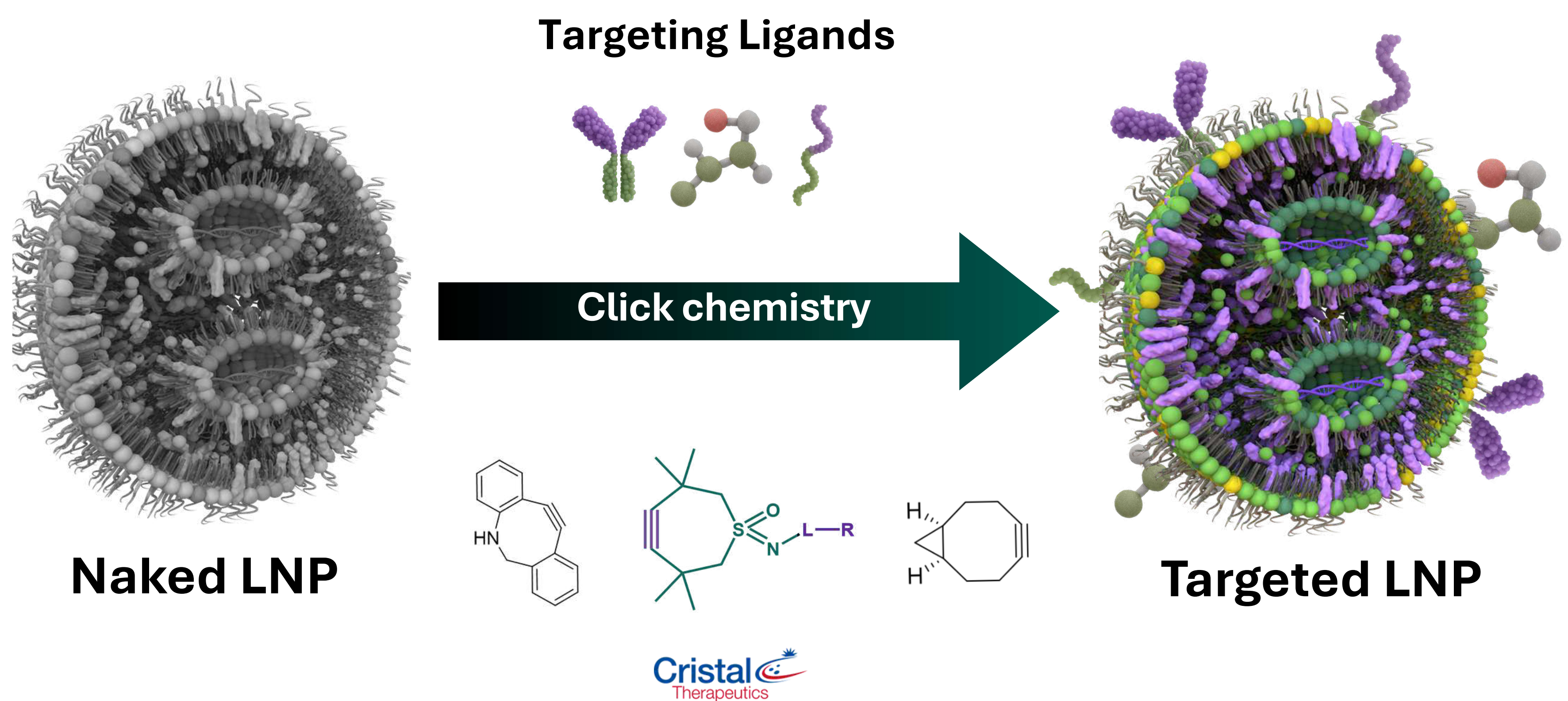
Limited cellular uptake & endosomal escape

Even when reaching target tissues, efficient internalization and cytosolic delivery remain bottlenecks.

Active Targeting

Active targeting refers to the strategy of functionalizing nanoparticles with specific ligands **that enable selective interaction** with target cells through receptor-mediated mechanisms. These ligands can be **antibodies, peptides or small molecules** and are designed to recognize and bind to surface markers expressed on specific cell types. This allows nanoparticles to reach therapeutic concentrations in targets like **T-cells, lungs, bone marrow** or **CNS**

The process



Benefits of this approach



Improved
delivery
specificity



Enhanced
cellular
uptake

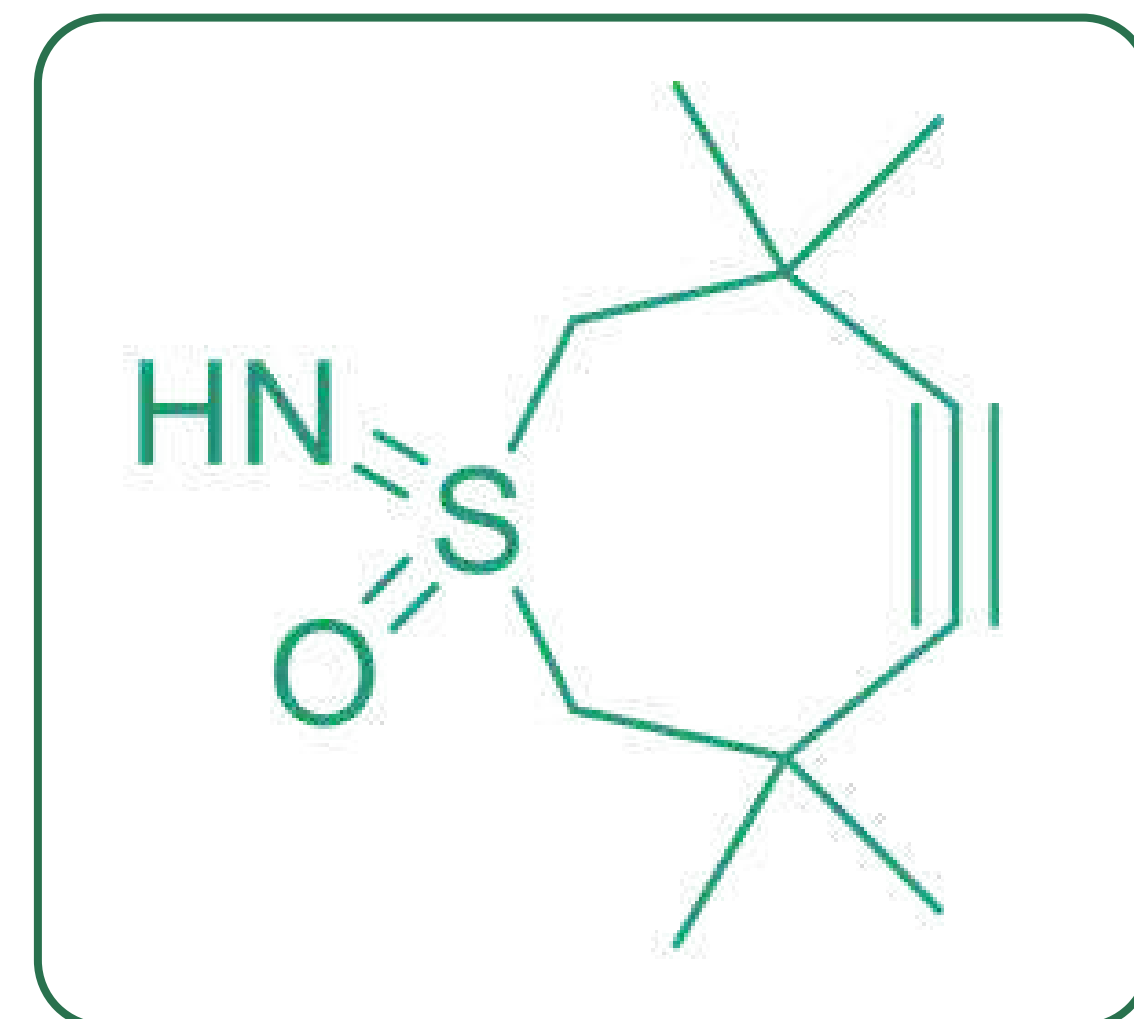


Reduced
systemic
toxicity

Our approach CliCr® based conjugation

CliCr®

CliCr is based on TMTHSI, a proprietary strained alkyne engineered for copper-free click chemistry. Unlike conventional click reagents that are typically hydrophobic and slow-reacting, TMTHSI combines **high reactivity** with **strong water compatibility**, making it particularly suited to nanoparticle functionalization.



Conjugation Performance vs Gold standards (DBCO and BCN)

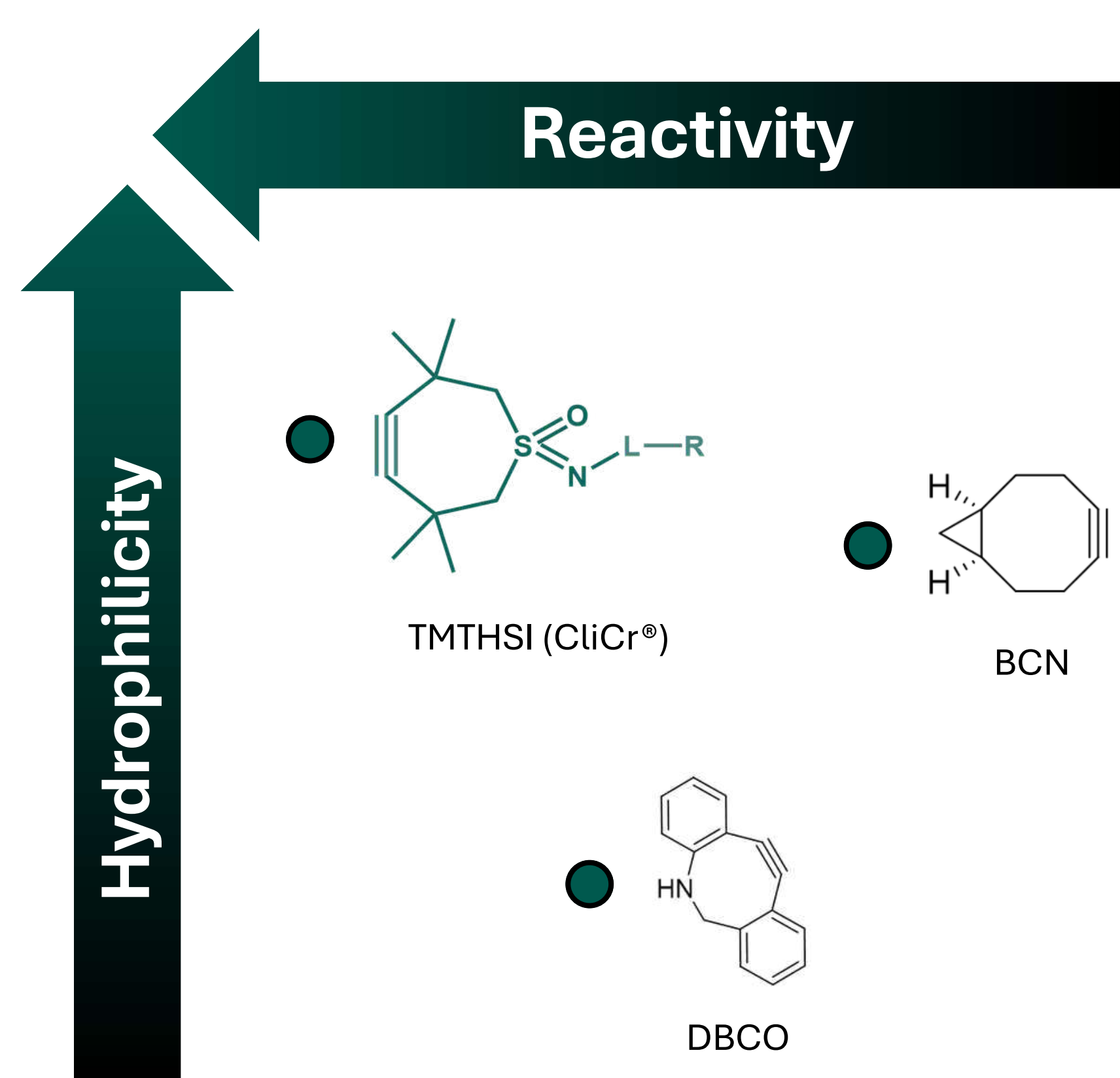


Figure 1: Head to head comparison between CliCr®, DBCO and BCN in terms of hydrophilicity and Reactivity

Higher hydrophilicity

Ensures optimal compatibility with aqueous LNP systems while preserving nanoparticle stability and surface integrity.

Higher reactivity

Enables efficient and selective ligand conjugation with precise control over surface functionalization.

Faster kinetics

Minimizes processing time and exposure to stress conditions, preserving LNP and ligand functionality

➤ CliCr® functionalized LNPs preserve key physicochemical properties such as **size, PDI, and encapsulation efficiency**

➤ CliCr® enables 2x **higher functional lipid loading** without aggregation

Shield. Lipid. Func.	%Shield. Lipid.	Naked LNP			Functionalized tLNP		
		Size (nm)	PdI	E.E. (%)	Size (nm)	PdI	E.E. (%)
TMTHSI (CliCr®)	0,5	76	0,16	>90	77	0,13	>90
	1	82	0	>90	81	0,13	>90
DBCO	0,5	76	0,16	>90	73	0,13	>90
	1	Unstability			Unstability		
BCN	0,5	72	0,17	>90	76	0,13	>90
	1	Unstability			Unstability		

Figure 2: Physicochemical characterization of naked and CliCr®-functionalized LNPs incorporating TMTHSI, DBCO, or BCN functional lipids at different molar percentages.

Using CliCr® for LNP Functionalization

% LNP functionalization with Cy5

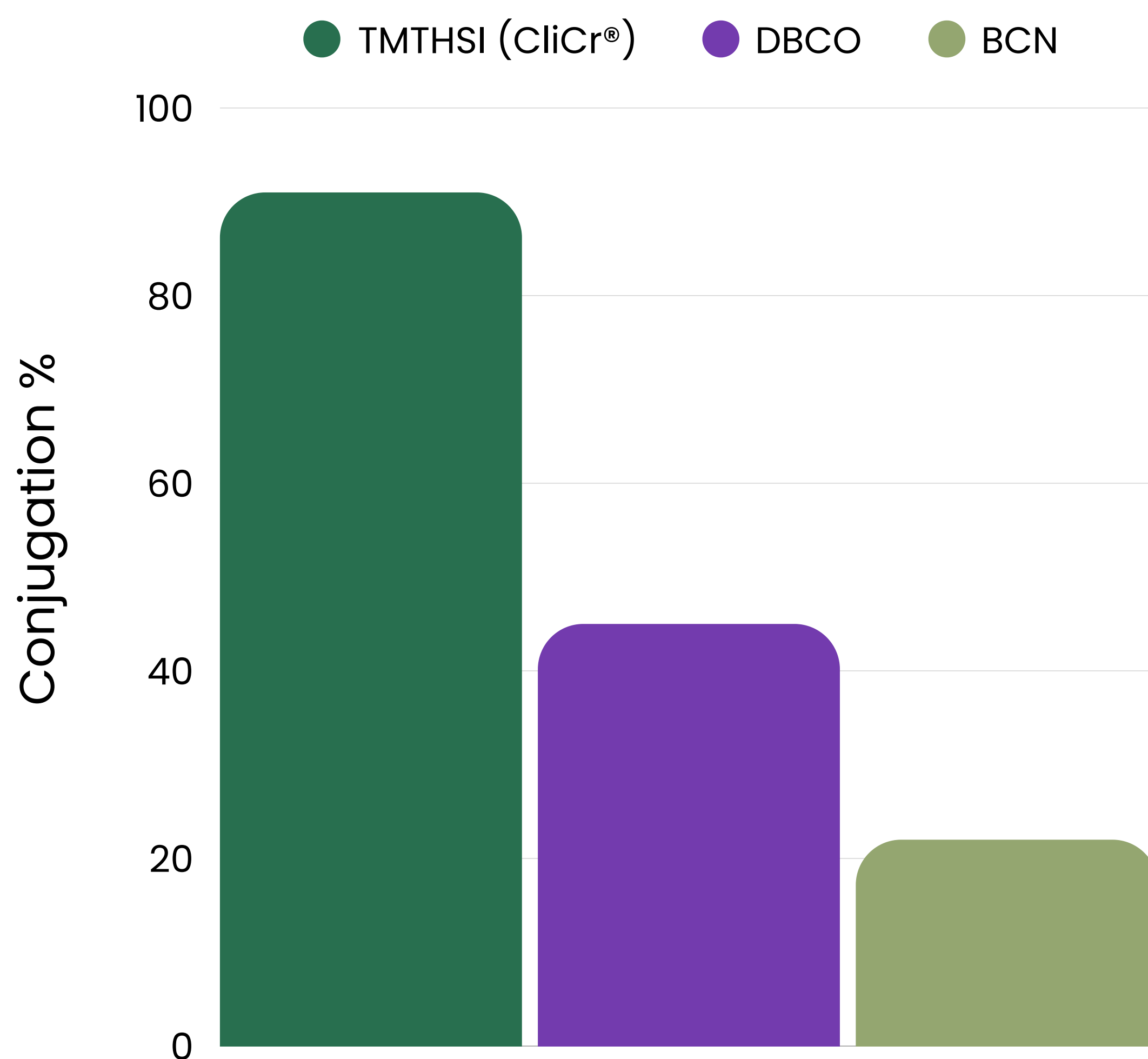


Figure 3: Percentage of Cy5 conjugation achieved for TMTHSI-, DBCO-, and BCN-functionalized LNPs, measured 8 hours after LNP conjugation.

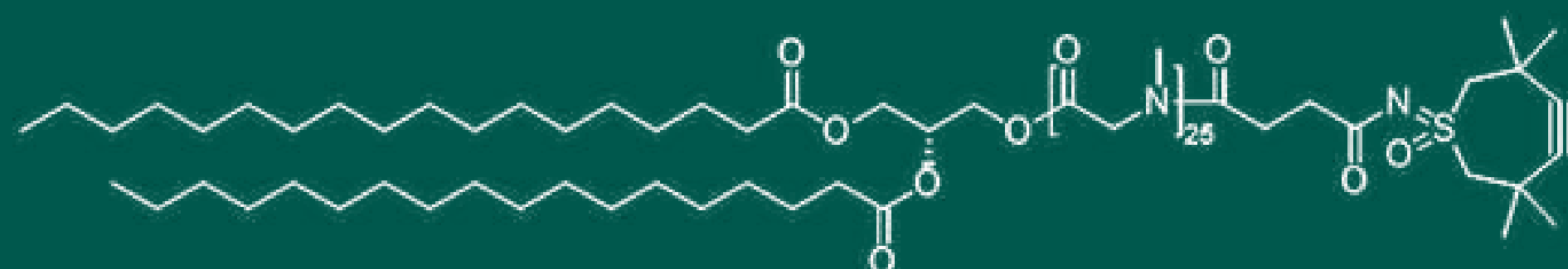


CliCr® conjugation achieves **higher functionalization efficiency**, enabling **increased ligand density** on the LNP surface

Ready-to-use tLNP platform

By combining our **PEG-free shielding lipids with CliCr®** conjugation technology, **we enable the attachment of your targeting ligand of choice directly onto formulated LNPs.**

Targeting PEG-free shielding lipid



DSG-PSar25-succ-CliCr® (CUR-L1533-25)

Targeting Ligand



Peptides or antibodies



Discover all of Curapath Active targeting shielding lipids, powered by CliCr®



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SOCIAL MEDIA

