



Revolutionary Co-Transcriptional Capping Technology



Leading the Way in mRNA™

TriLink BioTechnologies is a CDMO and pioneering manufacturer of custom messenger RNA (mRNA) for research and clinical applications. With a robust portfolio of RNA and associated small molecules, including non-coding RNAs and CleanCap capping solutions, TriLink provides tailored synthesis at milligram to multigram scales, with lengths ranging from a few hundred nucleotides to greater than 10 kilobases. Additionally, TriLink offers custom modified nucleotides that can modulate innate immune recognition to maximize activity for your specific application.





CleanCap technology is a proprietary, co-transcriptional 5' capping solution that generates a natural Cap 1 structure. Compared to traditional methods, CleanCap greatly improves efficiency and quality, while decreasing the cost associated with employing cap analogs and providing the highest quality mRNA 5' cap structure. The unparalleled value of CleanCap mRNA partnered with TriLink scientific expertise and technical support will drive your mRNA project to success.

CleanCap is available in a variety of analogs to support various application needs and criteria with initiation sequencing resulting in high capping efficiency.

CleanCap AG

Over 95% capping efficiency and highly scalable

CleanCap AU

Designed specifically for self-amplifying RNA

CleanCap GG

Performs well with existing 5' GG initiation sequence

Superior Achievement with CleanCap®

Use CleanCap as the optimized co-transcriptional capping choice for all your *in vivo* mRNA-based applications for reduced toxicity and robust expression. CleanCap is available in several versions with specific initiation sequences and structures.

Current applications of CleanCap with mRNA products include:

- *In vivo* and *ex vivo* mRNA expression
- Personalized cancer vaccine development
- Gene editing/CRISPR
- Cell therapy
- Vaccine development
- Reporter gene expression



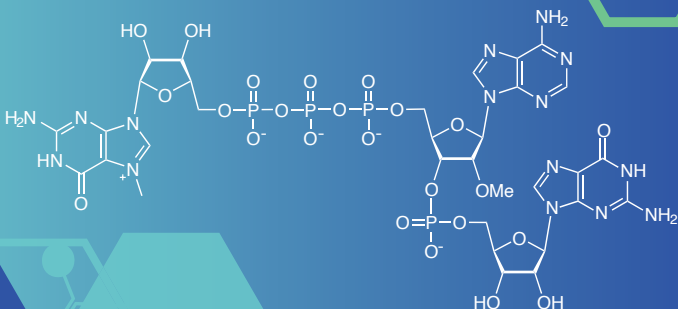
CleanCap Capping Solutions

CleanCap technology is available in several product and service solution formats. CleanCap reagent can be added directly into your transcription reaction for convenient co-transcriptional capping. You can choose from a catalog of off-the-shelf CleanCap mRNAs including a set of commonly used reporter and gene editing mRNAs and dye labeled options. Additionally, custom manufacturing solutions are optimized to the needs of your program, and can include CleanCap as a standalone reagent, or TriLink mRNA capped with CleanCap. CleanCap is available in custom pack sizes and comes with expert guidance from ConsultLink™, the TriLink signature customer solution and support team. Our team has the experience and technical knowledge to advise you on your capping strategy and mRNA production for a clear path to the clinic.

CleanCap is available as:

- GMP mRNA Service
- GMP Capping Reagent
- Research Grade mRNA Service
- GMPLink™ Capping Reagent
- Catalog mRNA
- Capping Reagent

CleanCap AG structure



Outstanding Efficiency and Yields

Synthesized mRNAs do not possess a 5' cap structure without the addition of specialized capping reagents, either co- or post-transcriptionally. Compared to traditional approaches, CleanCap offers the powerful convenience of a scalable, highly efficient (>95%)*, one-pot reaction that produces robust yields (4mg/ml).

	Legacy Cap Analogs		CleanCap®	
Natural Cap	No	-	Yes	+
Immunogenic	Yes	-	Reduced Immunogenicity	+
Capping Efficiency	~70%	-	~95%	+
Yield/mL Transcription	1.5 mg/mL	-	4-6 mg/mL	+
Cost	3 X	-	1 X	+
Available Therapeutic Licenses	No	-	Yes	+

* Final capping is dependent upon the CleanCap Reagent, DNA template and final mRNA sequence. Secondary structure due to RNA length and base composition can affect final capping efficiency.



CleanCap Delivers Multiple *In Vivo* Advantages

A natural cap structure

The 5' cap found on all endogenous eukaryotic mRNAs is crucial for mRNA processing, stability, translation and immunogenicity. Structurally, the 5' cap consists of a 7-methylguanosine linked 5' to 5' by three phosphates to the first nucleotide of the 5' UTR. The methylation status at the 2' position in each of the first two mRNA nucleotides determines whether the cap type is a Cap 0 (no methyl groups), Cap 1 (one methyl group), or Cap 2 (two methyl groups). CleanCap is available in several combinations of initiating trinucleotides with a Cap 1 structure for various applications, including self-amplifying RNAs.

Reduced immunogenicity

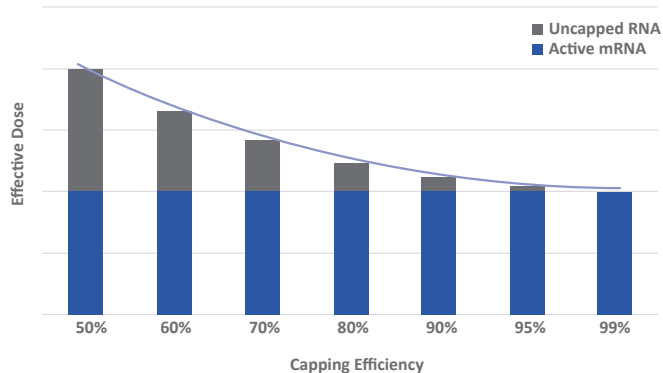
Seemingly minor differences in the chemical structure of the 5' cap can critically influence the expression of an mRNA and whether it is recognized as "self" or "foreign". Importantly, in order to reduce immunogenicity, a mRNA must have a Cap 1 structure. Cap 0 structures are only intermediate structures in cells and are recognized as non-self or viral RNA. The methyl groups present in Cap 1 reduce binding to and activation of pattern recognition receptors. CleanCap mRNAs are proven to most accurately mimic natural mRNAs.

Wide flexibility with T7 promoter design

T7 RNA polymerase strongly prefers a guanosine as the first nucleotide to initiate transcription. This significantly limits the efficiency of transcription with different starting sequences for *in vitro* transcription. CleanCap analogs circumvent this issue by expanding the range of 5' nucleotides compatible with T7 polymerase. CleanCap offers exclusive flexibility to choose your initiating sequence.

Incorporating CleanCap into your mRNA application greatly improves your activity and yield. The superior level of capped mRNA product achieved with CleanCap allows you to maximize translational efficiency and minimize your effective therapeutic dose as compared to mRNA capped using traditional co-transcriptional methods.

Minimize Effective Dose with Highly Capped mRNA
Active mRNA vs. Uncapped RNA





Use CleanCap Early and Often

Integrate CleanCap mRNA early on in your project in order to achieve the optimal path to clinical success. We supply an array of purification options for research to GMP-grade projects. Our new bioreactor platforms enable seamless scale-up and transition to GMP quality. Additionally, our trusted OEM manufacturing has the capabilities to synthesize CleanCap mRNAs in the range of milligrams to multigrams. Contact our ConsultLink team for information on how to best include CleanCap in your project development.

CleanCap Supports Success from Research to the Clinic

Scalability is essential when preparing for clinical applications. When scalable technologies are incorporated during the research phase, they allow a program to continually progress at a rapid pace, without the delays that can be encountered when validating new manufacturing processes. Research evolves with data and must advance despite previously unanticipated demands. Maintaining scalability allows your project to maintain timelines, absorb unexpected surges for product, and remain aligned with your final goals. Our manufacturing facility has over 105,000 square ft of manufacturing space with nine dedicated manufacturing suites and two support labs, ensuring we can support your success across a wide variety of synthesis scales. Additionally, batch records are provided to streamline the IND submission process and carry you through to clinical trials.

Our controlled labs feature:



Compliance

ISO 9001:2015 Certification
ICH Q7, Section 19 GMPs



Batch Record

Batch Record Transfer to Client



Environment

ISO Class 7 or 8 Clean Rooms
Single Pass, HEPA Filtered Air System
Routine Monitoring for Temperature and Humidity Control
Routine Monitoring for Pressure and Particle Counts
Fully Gowned Staff

	Research	GMPLink™	GMP
Compliance	✓	✓	✓
Batch Record	✓	✓	✓
Environment	✓	**	✓
		**	✓
	✓	✓	✓
		**	✓
		**	✓

** Available upon request.

Products are to be used in accordance with all labeling provided by TriLink, included but not limited to: **Research:** For internal research only, not intended for use in diagnostic or therapeutic procedures. Not for use in humans. **GMPLink:** Not intended for use in diagnostic or therapeutic procedures. Not for use in humans. **GMP:** Investigational Use Only.

Our team of experts is available to guide you through the optimal manufacturing process for your therapeutic application. With over five years of experience taking mRNA products to GMP and beyond, we take great pride in our ability to share our knowledge with you and your team. TriLink can be your trusted vendor for superior capping reagents or mRNAs throughout the lifecycle of your project. Our exclusive technical and service support — ConsultLink, is available to offer guidance and technical expertise. We are confident in our ability to drive your CleanCap product from research to the clinic.

