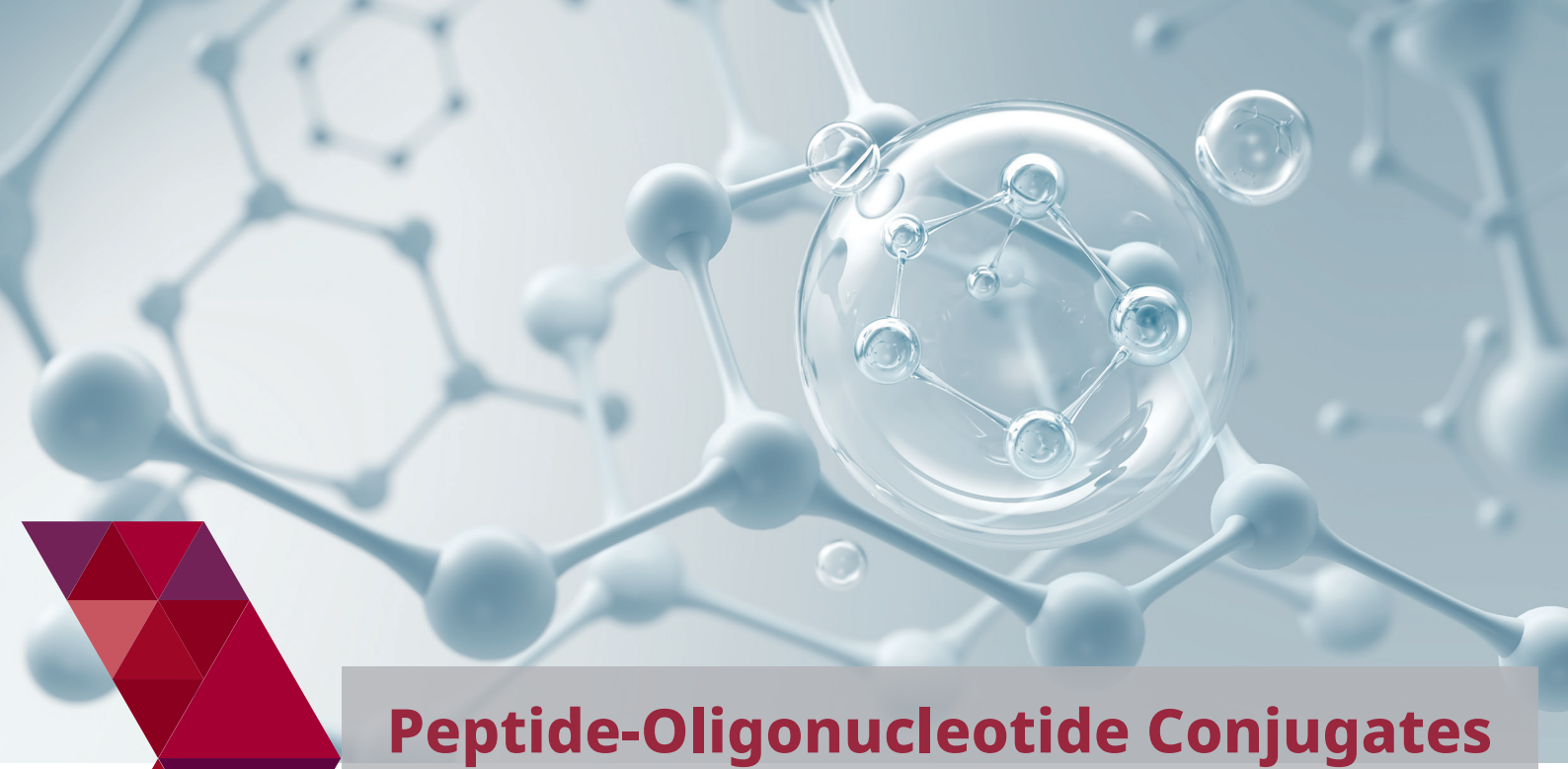


Peptide-Oligonucleotide Conjugates

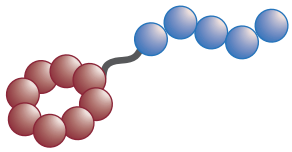
Innovative Approaches with Continuous Purification

Technical Optimization **Low Purification Loss** **Shorten Development Cycle**

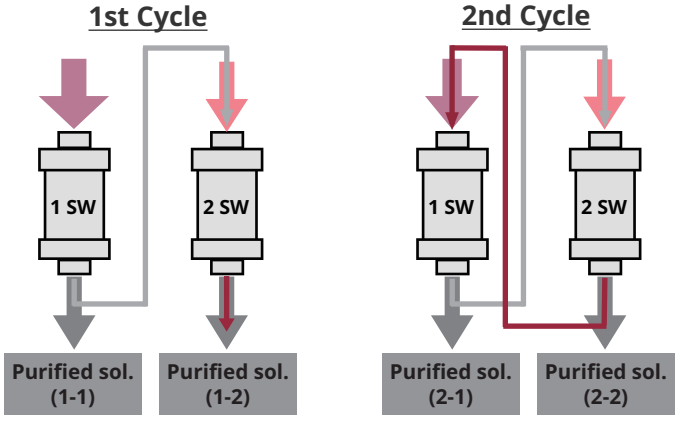
Manufacturing Challenges for Peptide Drug Conjugates (PDCs)

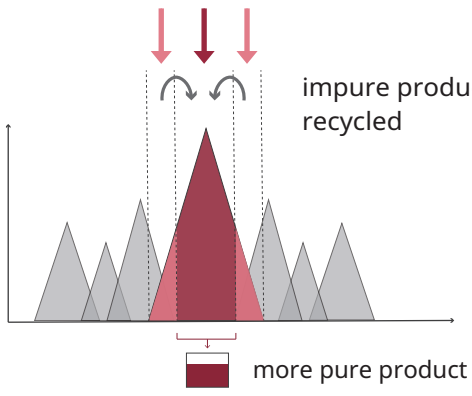
PDCs have demonstrated significant advancements in target-specific delivery, enhancing therapeutic efficacy and reducing toxicity. However, manufacturing challenges persist, including scale-up processes, yield optimization, cost-efficiency balance, and quality assurance through rigorous analytical methods. PeptiStar's expertise in manufacturing and purifying peptides, nucleic acids, and PDCs drives your success, aligning with recent advancements in PDC technology.

Our Solutions



- We can reduce in-process tests to just one, ensuring both efficiency and reliability.
- Continuous chromatography allows you to maximize both purity and yield effectively.
- Peptistar's expertise in manufacturing and purifying peptides, nucleic acids, and PDCs ensures superior quality. We also propose strategies to reduce costs and shorten lead times.





Referenced from YMC HP

Twin Column Continuous Chromatography

Produces high-quality APIs with high yield, we can reduce overall purification costs by 30-50%, including raw material cost.

PeptiStar's continuous chromatography process begins with the development of single-column purification conditions, followed by the development and optimization of continuous chromatography conditions. This method seamlessly scales up, resulting in improved recovery yield while maintaining high purity, without the need for additional development. It also reduces the amount of crude required, thus minimizing the manufacturing scale. This process is beneficial for quality design strategies that require quality improvements according to different development phases. By using a recycle purification process, high purity and high yield are achieved by combining fresh samples with low purity fractions that are not discarded.

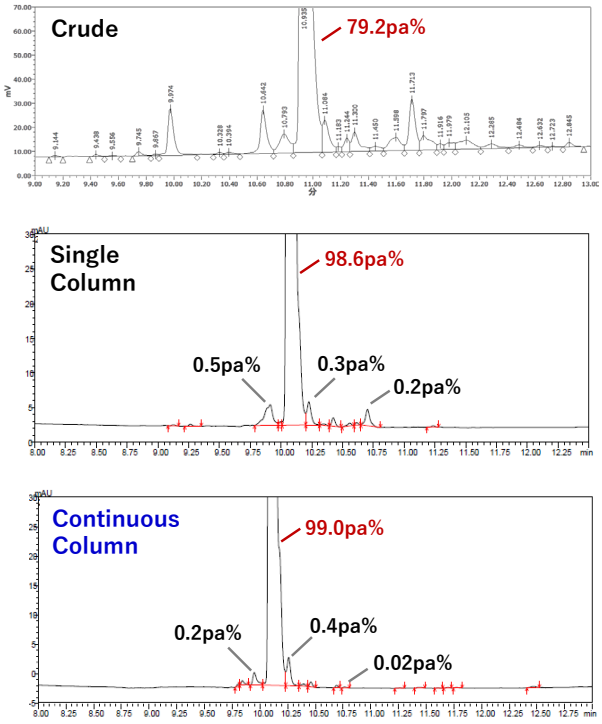
PeptiStar's joint development partner: YMC CO., LTD.

Example for continuous column record （Peptide）

Cyclic[Ac-Phe[1]-Ahp[2]-Lys[3]-Thr[4]-
MePhe[5]-His[6]-MeGly[7]-Bph[8]-Cys[9]]-NH_2

Feasibility study of API 100g

Evaluation	Single-column	Continuous chromatography
Target purity	≥98.5 p.a%	
Recovery rate	34%	83%
Crude amount	355 g	145 g
In-process tests	8 Times	1 Time
Operation	Manual	Automatic
Amount of solvent	Same	
Development period	Single Column: 7 days	Single Column: 7 days Continuous: 7 days
Cost of purification	1	0.2~0.4



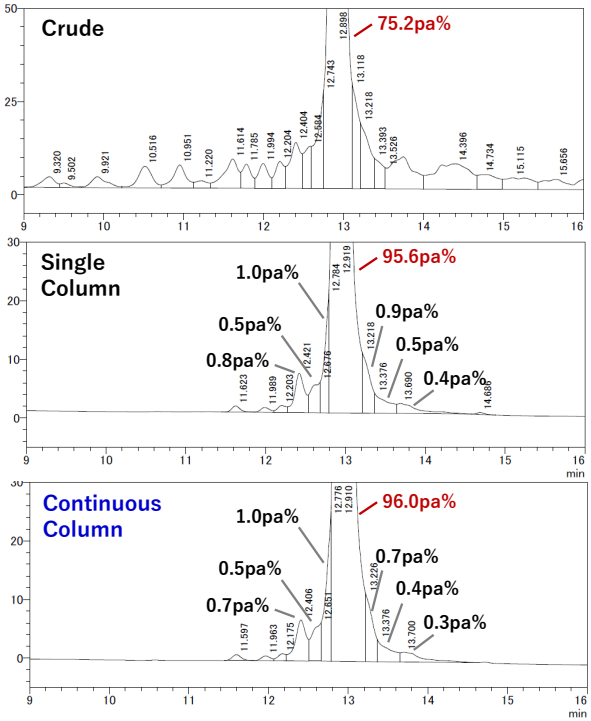
Example for continuous column record （Oligonucleotide）

5’ -CTGCTAGCCTCTGGATTTGA-3’

(DNA 20mer, All PS form)

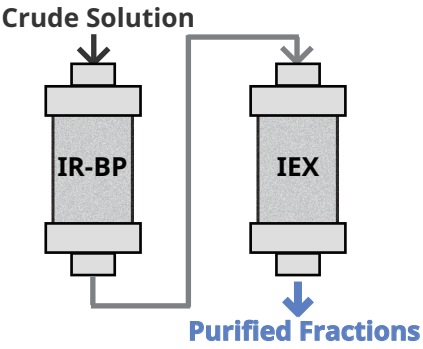
Feasibility study of API 100g

Evaluation	Single-column	Continuous chromatography
Target purity	≥95.0 p.a%	
Recovery rate	49%	78%
Crude amount	269 g	169 g
In-process tests	12 Times	1 Time
Operation	Manual	Automatic
Amount of solvent	Same	
Development period	Single Column: 7 days	Single Column: 7 days Continuous: 7 days
Cost of purification	1	0.3~0.5



Advanced Purification Solutions with Integrated Column

Our Integrated Column technology utilizes two distinct types of columns to achieve remarkable purification results. By integrating the IPRP and IEX purification processes, we can significantly shorten the process duration due to reduced IPT and the ability to perform the two steps continuously without interruption. This technology also boasts a smaller footprint as it eliminates the need for a vessel between the two purification steps. Additionally, the Integrated Column is applicable to PDC, allowing for similar efficiencies in purification and salt exchange processes.



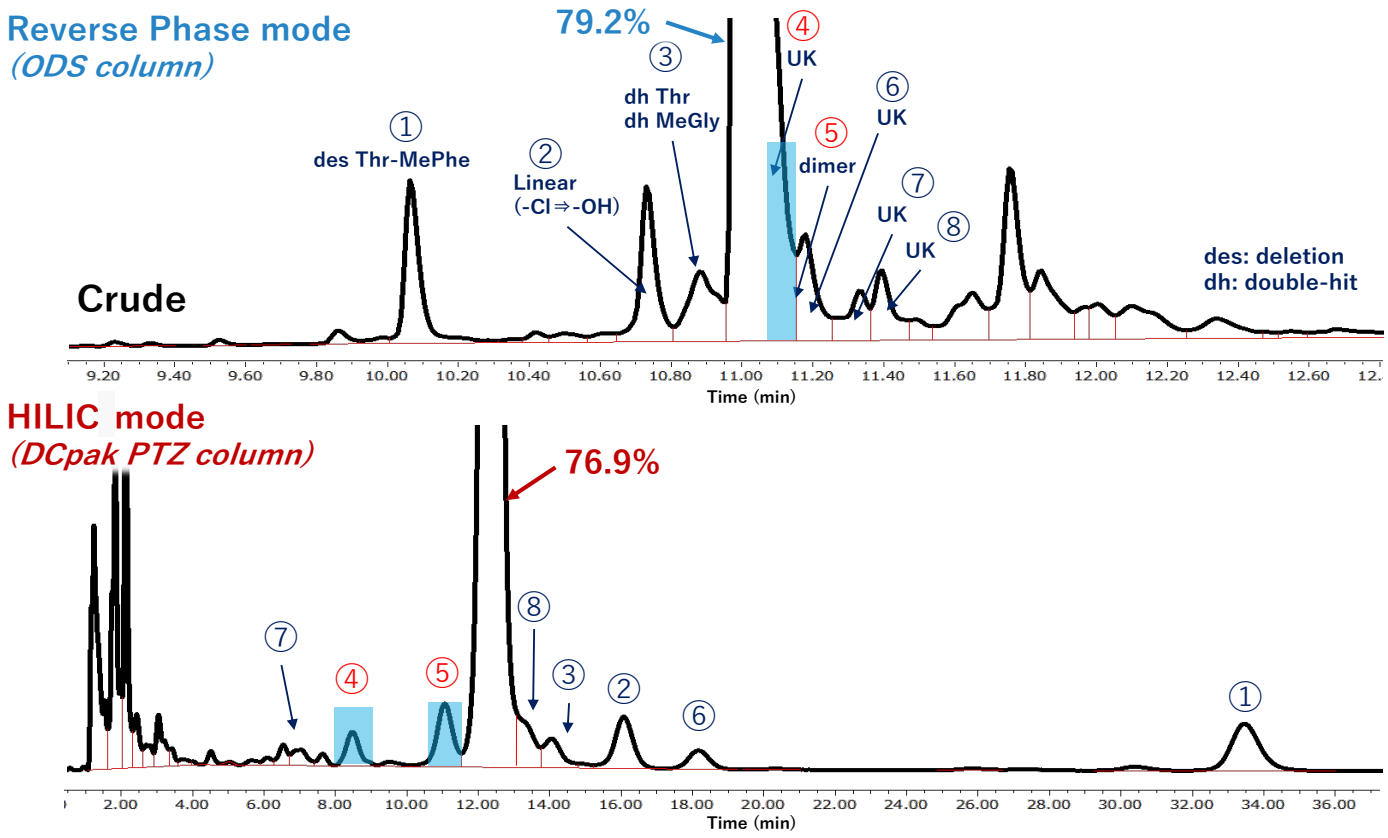
Comprehensive Analytical Capabilities

PeptiStar is equipped with facilities that enable the establishment of standards and test methods, analytical method validation, and stability testing according to the development stage, from early development to the approval application stage. We conduct essential physicochemical tests for peptide drug development in-house using comprehensive equipment, particularly high-resolution LC-MS (Waters Xevo G2-XS, BioAccord) for impurity management.

Using the collaboratively developed Hydrophilic Interaction Liquid Chromatography (HILIC) mode with Daicel Corporation, DCpak P series, we can separate previously undetectable impurities. Designed with a unique and special structure, the stationary phase allows for distinct selectivity, particularly in the analysis of peptides. By targeting the overlapping impurity peaks around the main peaks, that allows for more accurate purity measurements than using reversed-phase conditions alone.

Additionally, impurity management of oligonucleotides is equally important when considering peptide-oligonucleotide conjugates. When measuring both with the same equipment, meticulous attention is needed to prevent contamination. PeptiStar maintains a separate LC-MS for nucleic acids (Orbitrap Exploris 240, Q-TOF), ensuring minimal contamination and reliable results.

Advanced purification using HILIC mode

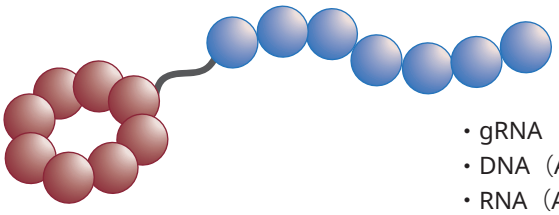


- Purification is possible in HILIC mode for compounds that are difficult to purify in a reverse-phase system
- Detailed analysis is possible when used in conjunction with reverse-phase system
- High purity purification is achievable by using fractioning purification technology that uses a combination of reverse-phase system and HILIC mode

Experiences for Unique Peptides and Oligos Synthesis

PeptiStar produces long-chain peptides (over 100 residues), cyclic peptides, branched peptides, dimeric peptides, and other modified peptides. Additionally, we manufacture oligonucleotides in-house and have a proven track record of creating peptide-oligonucleotide conjugates with various binding patterns.

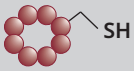
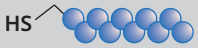
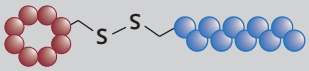
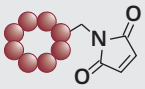
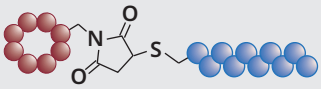
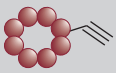
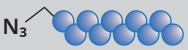
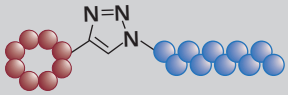
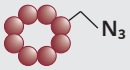
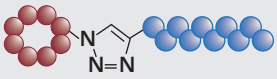
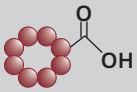
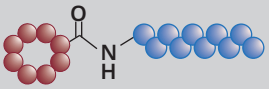
- Cyclic Peptide
  Disulfide Bond, Thioether Bond, Amide Bond, Bicyclic
- Linear Peptide
- Cyclic Homo-dimer Peptide, Cyclic Hetero-dimer
- Peptide, Cyclic Tetramer Peptide



- Peptide/Oligonucleotide Conjugation
- Pegylated
  PEG, Fatty acid, NH_2, SH

- gRNA
- DNA（ASO, Aptamer, CpG Oligo）
- RNA（ASO, Aptamer）
- siRNA
- PMO
- All PS form

Conjugation experiences

Type	Peptide	Oligonucleotide	Conjugate
Disulfide			
Maleimide			
Click			
Click			
Amide			

	Sample (~10 g) Lead time: 3 weeks ~ 2 months	Non-GMP (~1,000 g) Lead time: 1~3 months	GMP Lead time: 3~4 months (Peptide) Lead time: 4~6 months (Oligo)
Peptide	10 mg~1 g: Over 150 products	10 g~100 g: Over 50 products	10 g~300 g: 13 batches
	1 g~10 g: Over 80 products	~1,000 g: Several batches	
Oligo	10 mg~200 g: Over 50 products	Over 100 g: 1 product	Ologonucleotide: 1 batch
	Peptide conjugated: Around 20 products		
Service			
	Small-lot multiproduction	Process development for scale up	Establishing specification for API
	Process development for sample preparation	Process development from SPPS to LPPS	Development of analytical method for API/UNAA and its validation
			Stability test and other required test

PeptiStar

- Specialized in both peptide and oligonucleotide production
- Seamless transition from R&D to commercial manufacturing
- Japanese precision meets flexible solution under GMP compliance

PeptiStar excels in peptide, oligonucleotide, and PDC synthesis, overcoming manufacturing challenges with analytical excellence and continuous feedback.

As your trusted partner, we can propose solutions tailored to your challenges!

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Web for Peptide

Web for Oligonucleotide