药明康德 WuXi AppTec

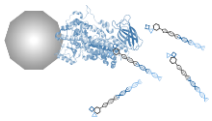
WuXi Biology

Peptide Early Discovery Service

Peptide Hit Discovery

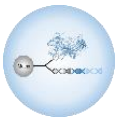
WuXi AppTec provides multiple approaches to discover peptide hits, including DNA-Encoded Library (DEL) and display technologies. Peptide DELs are synthesized through chemical reactions, while display technologies utilize biological synthesis. The combination of DEL and display technologies allows clients to explore vast chemical space.

Peptide DNA-Encoded library (DEL)



Solution DEL

10^11



On-bead DEL

10^6

- High **backbone and side chain diversity**
- Incorporation of **abundant unnatural AAs** and **cyclization reactions**
- '**Permeable** peptide' properties
- Highly **customizable**

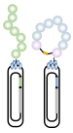
- **Affinity-based** screening
- **Large** diversity

- **Functional-based** & **phenotypic cellular** screening

Oral Peptide & Delivery

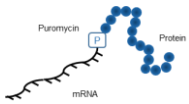
Initial Hit Finding & **Hit-to-Lead Optimization**

Display Technologies



Phage Display

10^9



mRNA Display

> 10^12

- **High throughput decoding and *in silico*** techniques enhanced

- **Natural amino acids** dominate
- Compatible with **cellular selection** and ***in vivo* selection**
- **Larger, polar peptides**
- **Flexible** choice in peptide length

- Incorporation of **limited unnatural AAs**, more **cyclization reactions** than phage
- Compatible with **cellular selection**

Delivery

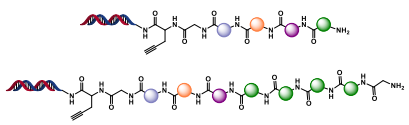
Initial Hit Finding

Bicyclic peptides constrained on a molecular scaffold not provided

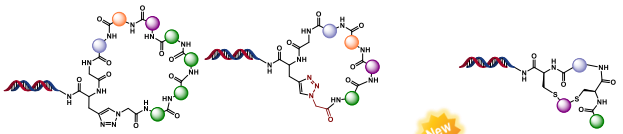
Off-the-shelf & Highly Customizable Peptide Libraries

Peptide DEL

Off-the-Shelf Collection (300+ Billion):



Linear libraries



Cyclic libraries

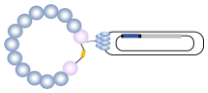
New

Small cyclic libraries

Well-validated Tools for Peptide DEL Customization:

- **1,400+** validated natural and unnatural AAs
- **1000+** α-AAs with diverse side chains (D/L ratio **3:4**)
- **300+** non-alpha AAs with diverse backbones
- **10%** AAs with α*N*-alkylation
- **9 types** of cyclization strategies established
- Peptide fragment **(3~5 AAs)** condensation

Peptide Phage Display



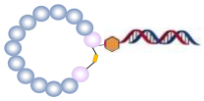
Linear Peptide:

- X7, X12 (commercial)
- X9, X30 (customized)

Cyclic Peptide:

- CX7C, CX13C (customized)
- CX4CX9 (customized)

mRNA Display



Cyclic Library Design

AUG UGC (NNK)$_n$ UGC (GGC AGC)$_3$
Met Cys (NNK)$_n$ Cys (Gly Ser)$_3$

CXnC, n=6-15

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Peptide Hit-to-Lead Optimization

Bioassay Platform for Peptide Profiling

	Binding/PPI	Permeability*	Stability*	Functionality	Specificity/Toxicity
Biophysics	☑				
Biochemistry	☑	☑	☑	☑	☑
Structural Biology	☑				
Cell Biology		☑	☑	☑	☑
ADME		☑	☑		☑
DMPK		☑	☑	☑	☑

*Specific assessments required for peptides in the early stage, e.g.: Aggregation, GI digestion, Circulating stability, Formulation stability

Peptide Modeling:

- Virtual screening
- Virtual residue / alanine scan
- Binding mode and hotspot prediction
- Machine learning
- Molecular dynamics

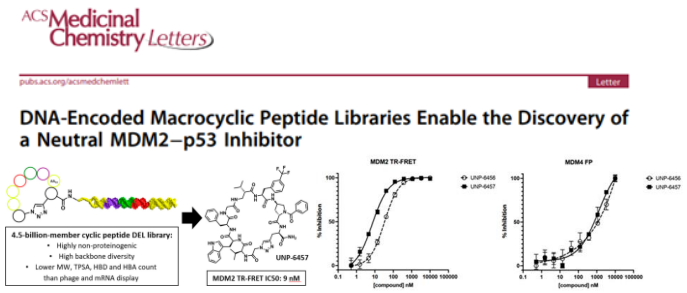
Peptide Conjugation: Linker synthesis & payload modification

Unnatural AA Availability: 3000+ Fmoc-AAs catalog products & customized synthesis

Peptide Synthesis: Linear, cyclic peptides and peptidomimetics

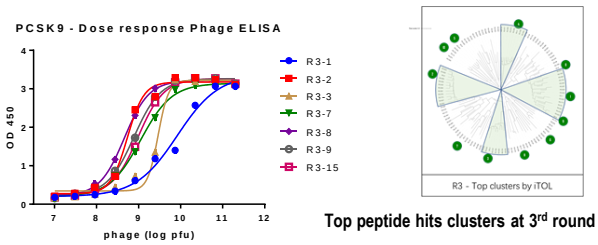
Showcase of Integrated Peptide Discovery

Cyclic Peptide for Protein-Protein Interaction Disruption



- UNP-6457, a neutral nonapeptide discovered in **cyclic peptide DEL**, inhibits MDM2−p53 interaction with an IC_{50} of **8.9 nM**

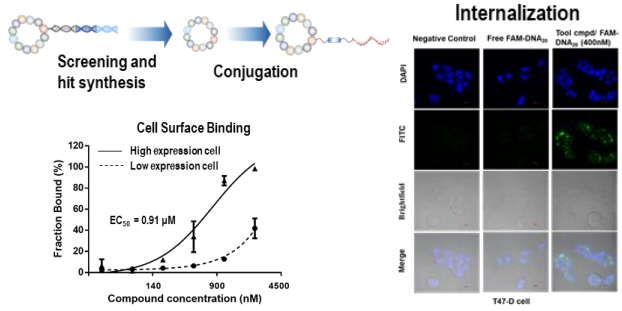
Peptide Discovery Using Phage Display with Decoding



Top peptide hits clusters at 3rd round panning

- 3 rounds panning with 3 NEB linear and cyclic peptide libraries (10^9 each) completed within **5 weeks**
- **High throughput decoding** improves screening efficiency and provides abundant data which is compatible with ***in silico*** **clustering**

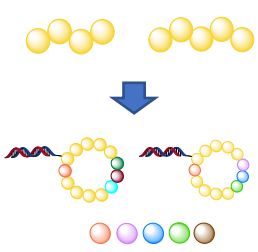
Novel Peptide for Endocytosis Receptor-based Delivery



- **4 weeks** DEL screening identified a novel peptide (EC_{50}=**0.91 μM**) binding to specific tumor-cell for endocytosis
- DEL hits contain **pre-optimized** site for conjugation

Customized DEL for Peptide Optimization

2 Conserved motifs identified from mRNA display



Variable unnatural amino acid

4 Weeks Library Design & Route Development

Tandem macrocyclization strategy

2 Weeks Amino Acid Selection & Validation

800+ compatible amino acids

4 Weeks Library Production

600+ million cyclic peptides

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