# *Peptides & Peptide Mimetics Technology*

# *Peptide Mimetics Technology*

| **Peptide** | **Mimetic** |
| --- | --- |
| + Easy lead for biology | + Takes advantage of peptide data |
| - Poor drug properties | + Drug-like properties |
| - Not stable | + Stable |
| -Low bioavailability | + Bioavailable |
| => Needs optimization for 1st generation drug candidate? | = Drug Candidate |

# *Peptide Optimization for 1st Generation*

*Proof-of-concept or defined clinical target*

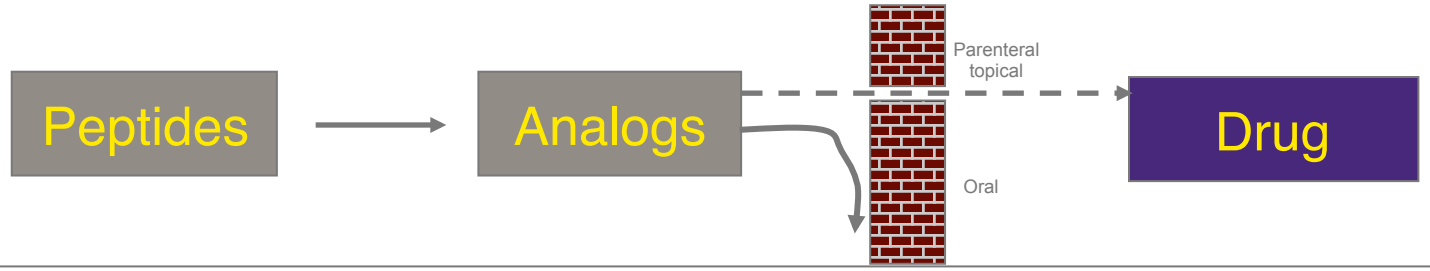
- Define minimally active sequence
- Develop peptide SAR and pharmacophore
  - Side chain variants (natural, unnatural)
  - Backbone recognition (N-Me, cyclic, and amide variants)
  - Use available biostructural data (pharmacophore)
  - Add conformational constraints
  - N- and C-caps
- Stabilize, enhance transport, optimize PK/ADME

==> Peptide analog as drug for some indications

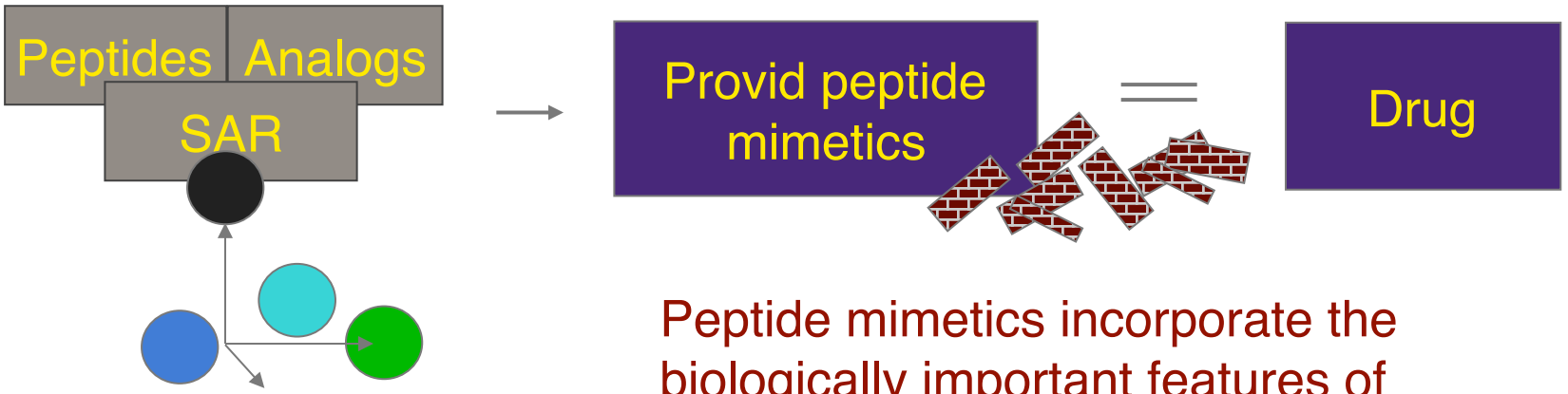
==> Lead for mimetics

# *Provid Peptide Mimetics Approach*

*Traditional approach*



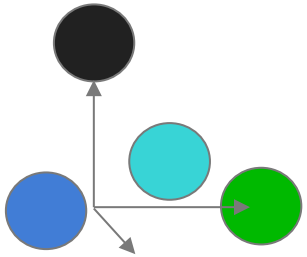

*Provid approach*

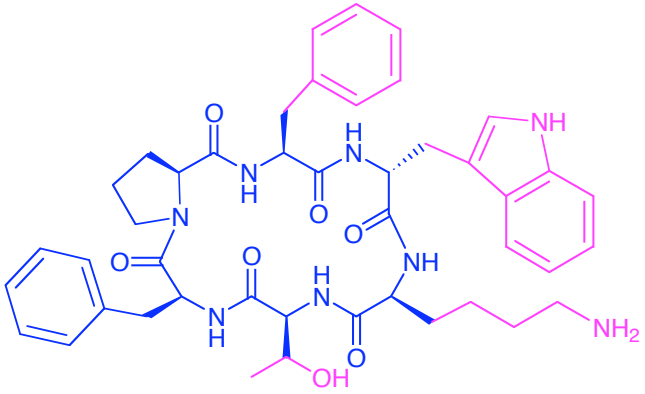


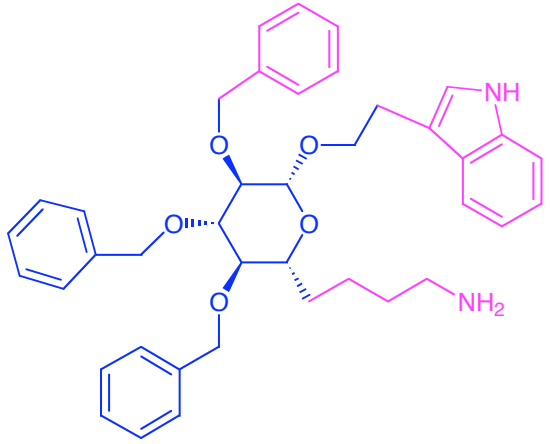

Peptide mimetics incorporate the biologically important features of a peptide on a small molecule, drug-like scaffold.

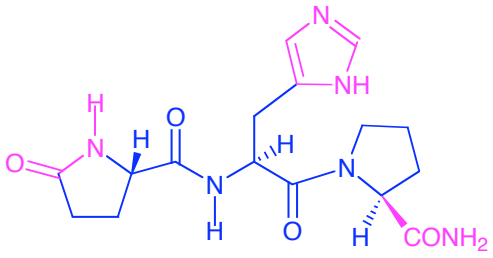
# *Peptide Mimetics–Backbone Replacement*

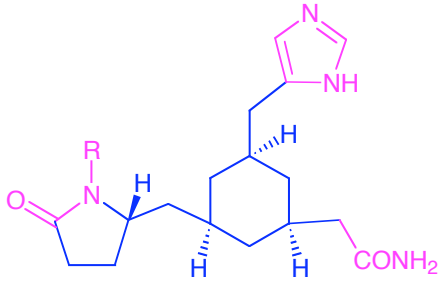
3-Dimensional presentation





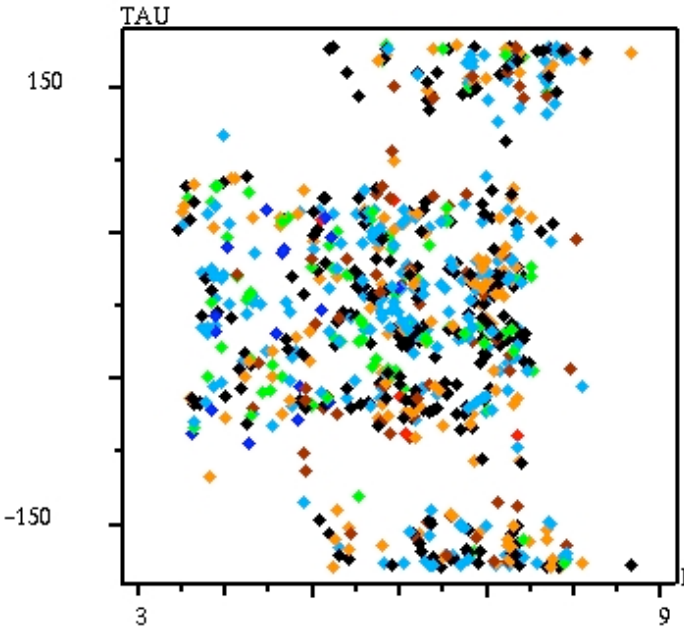



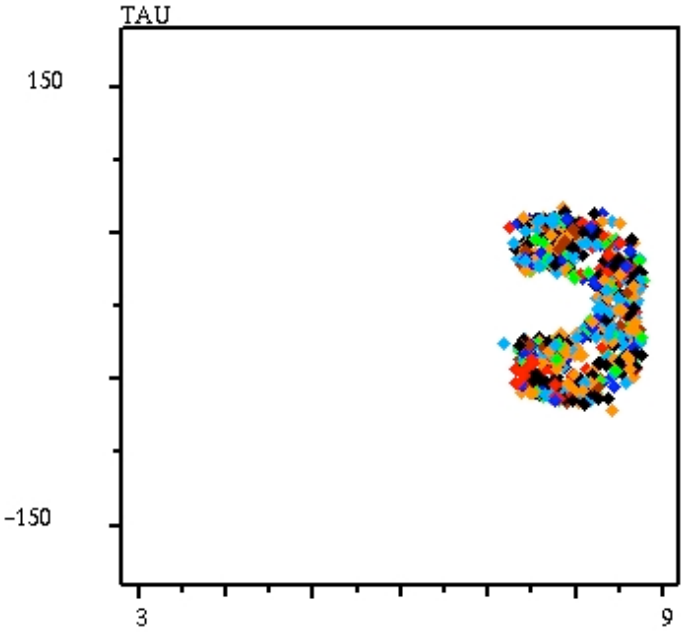



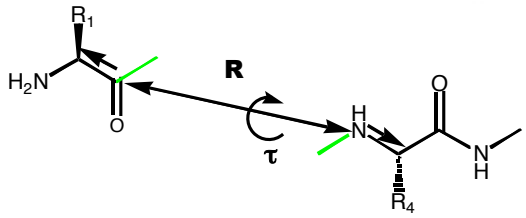



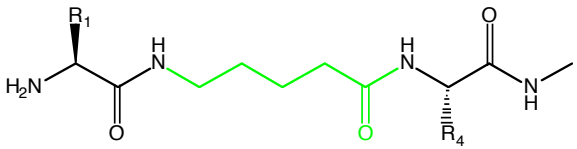

Hirschmann, Smith (U. Penn)
Olson (Roche)

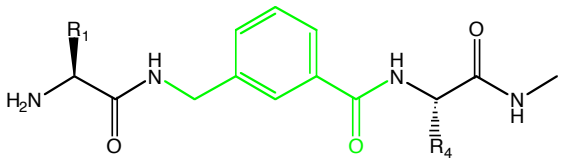
# *Constraints in Peptide Mimetics*





## *Strategy: Peptide Mimetics*

- Develop non-peptide structures that present the binding epitope in the context of a small molecule
  - Design multiple scaffolds and chemotypes to explore "presentation" of pharmacophore in 3D space
  - Use peptide SAR (side chains and backbone)
  - Concurrent with peptide lead SAR and optimization
- *Goal: Identify active mimetic series suitable for optimization as a small molecule peptide mimetic.*

## *Mimetics Optimization*

- Optimization through cycles of pharmacophoric group manipulation on best scaffolds
  - Optimization based on in vivo efficacy, transport/bioavailability, and PK, ADMET characteristics.
  - Assessment of and chemical modifications to achieve high target specificity and to avoid off target side effects
- Selection of development candidate and backup/2nd generation compounds
- Support exemplification for patents.
- Develop prototype process suitable for IND candidate
- *Goal: Small molecule drug candidate suitable for IND*

# *Provid Client Peptide Mimetic Projects*

- Sequenom:  Isoform-specific disruptors of PKA localization (PKA-AKAP interaction)
- Duke:  Inhibitors of polyglutamine aggregation for Huntington's disease
- Pohan U:  Inhibitors of APP cleavage by BACE-1 for Alzheimer's disease
- Cognosci: APO-E mimetics
- Palatin:  Peptide mimetics for MCR
- BTG:  CD23 ligands
- Rutgers:  RNA polymerase inhibitors
- Provid: HLA-DQ2 inhibitors for celiac disease