

Exploration of the peptide drug space

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INTRODUCTION

The chemical properties of peptide drugs, known as the 'peptide-drug space', is considered to be a multi-dimensional subset of the global peptide space.

⇒ Is it possible to predict drug properties of peptides based on their chemical structure?

⇒ Are there over/under crowded subspaces?

METHODS

- 1. Compilation of a representative data set** : peptide drugs + peptides without reported medicinal properties + random created peptides (expected to have no medicinal properties)
- 2. Calculation of the chemical descriptors** which numerically express the peptide structure
- Data-reduction by **Principal Component Analysis (PCA)**
- 4. Localization of the peptide drugs** in the global peptide space: analysis of dense and empty regions

RESULTS and DISCUSSION

1. COMPILING A REPRESENTATIVE DATA SET

Literature + clinical databases (FDA, EMA): **254** peptide therapeutics (clinical development stage 1-4)

⇒ compared with **626** peptides without reported therapeutic properties + **68** random sequences

2. DESCRIPTOR CALCULATION

- > 3000 structural-chemical descriptors } creation PCA model
- mode of action
- development stage
- clinical field

3. DATA REDUCTION BY PCA

A PCA model was created: $R^2: 0.63$ & $Q^2: 0.60$ (PC 1-5)

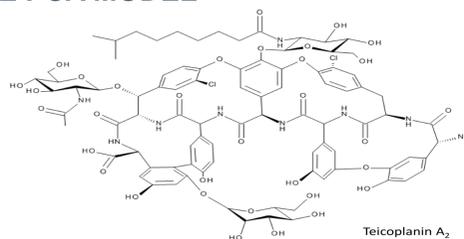
4. ANALYSIS OF THE PCA MODEL

Global peptide space: therapeutic + non-therapeutic peptides mixed => no peptide therapeutic specific areas

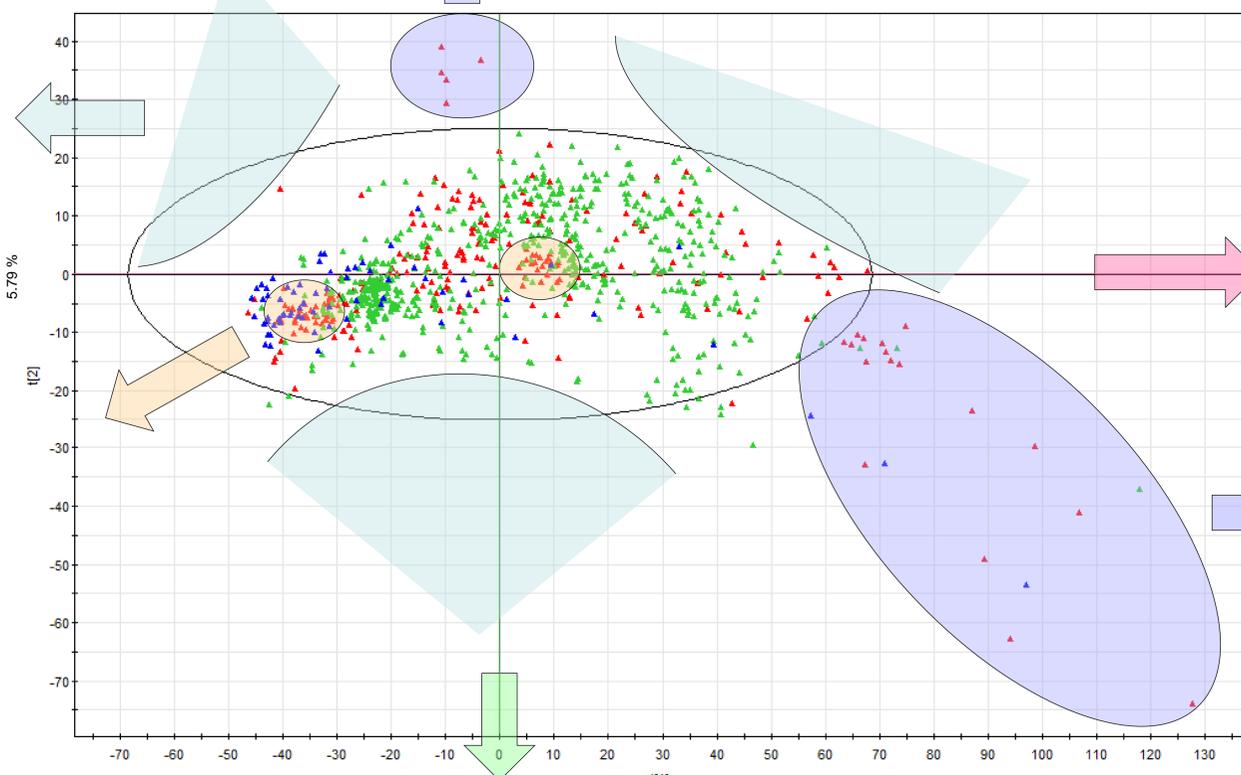
3 empty zones: physical boundaries rather than limitations in structural diversity

Crowded peptide drug zone: peptides active for metabolic diseases ⇒ receptor promiscuity?

Glyco-lipo peptides

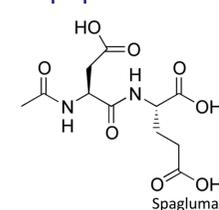


- ▲ Peptide drugs (n = 254)
- ▲ Non-medicinal peptides (n = 626)
- ▲ Random sequenced peptides (n = 68)



PC1: Structural properties (branching, size, compactness, folding symmetry)

Di/tri-peptides



PC2: Chemical properties (presence of heteroatoms, polarity)

CONCLUSION

The peptide-drug space was created and fits in the global peptide space. With the current set of descriptors, no delineated regions of peptide therapeutics can be designated, but peptides with the same mode of action are generally located near each other. The need of peptide-specific descriptors is high.

REFERENCES