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Exploring the chemical-functional space of cell-penetrating peptides

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1. INTRODUCTION

Cell-penetrating peptides (CPPs) are an increasingly growing part of fundamental and applied peptide research. Using their capacity to cross cell barriers, they have already been successfully applied as carriers for problematic cargos like DNA, (si)RNA, proteins and other peptides, (poly/oligo) saccharides and small molecules.[1]

Several hundreds of CPPs, showing different properties and activities, are already reported in the literature. Seen the wide range of techniques, cell lines, peptide concentrations and other operational parameters used to quantify the cellular uptake of CPPs, it is difficult to compare the different types of CPPs at a glance.

2. OBJECTIVE

To determine the chemical-functional characteristics of current CPPs:

- Different chemical clusters → model compounds?
- Relation of structure with cell-penetrating activity?

3. EXPERIMENTAL

DATABASE

- Structure of CPPs:
  - n > 200
  - Literature 2007-2012
  - Quantitative data available
- Unified response: $\frac{\text{Conc. corrected response CPP}}{\text{Conc. corrected response Penetratin}}$

↳ Penetratin = well known and characterised CPP

CLUSTERING

- Three-dimensional optimisation of structures
- Calculation of 3243 chemo-informatic molecular descriptors
  → Correction for constants: 1451 descriptors
- Pre-Processing: autoscaling using Z-score
- Multivariate analysis:
  - Principal Component Analysis (PCA)
  - Hiërarchical Cluster Analysis (HCA)

EVALUATION

- Selection of model CPPs for blood-brain barrier experiments
- QSPR
- Establishing mechanisms of action

4. RESULTS

Clustering of cell-penetrating peptides:

Both PCA and HCA classified the CPPs in several groups (Figure 1 and 2):

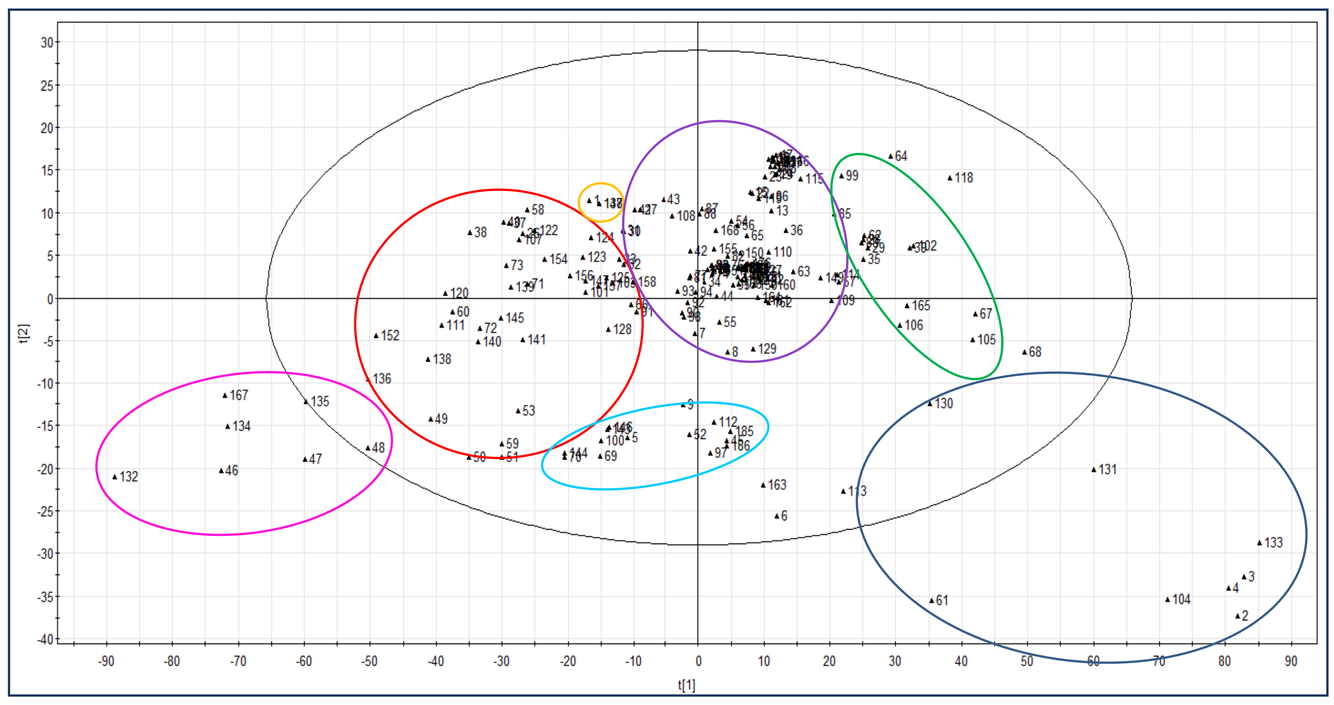

Figure 1: Classification of CPPs using PCA

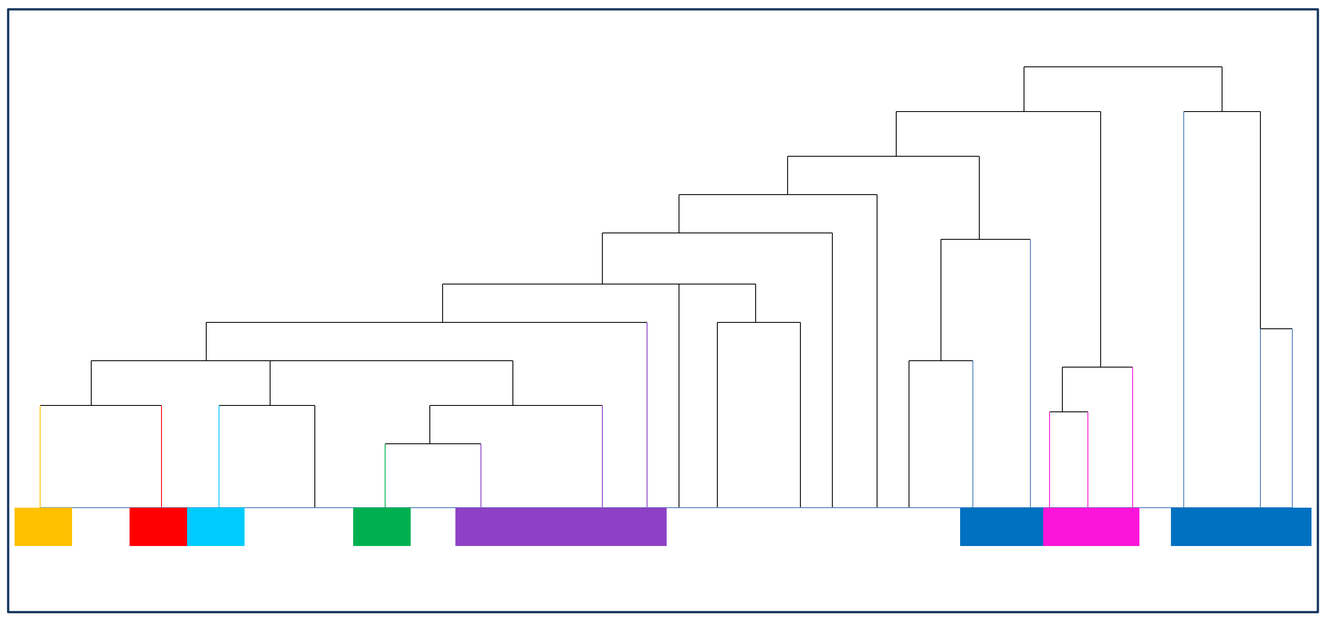

Figure 2: Classification of CPPs using HCA

Different clusters can be explained by different chemo-informatic descriptors, *e.g.*:

- Log P: -3.9 > -5.7 > -6.7 > -6.9 > -9.3 > -13.6 > -18.7
- MW: 730 < 1380 < 1480 < 1826 < 2106 <2821 < 4005
- Distribution of loadings (charge – pH function)

5. CONCLUSIONS

Multivariate analysis of chemo-informatic molecular descriptors of CPPs resulted in several major clusters, which can be used for selecting model compounds for further investigation and studying quantitative structure-property relationships (QSPRs) of cell-penetrating peptides.

6. REFERENCES

[1]Ülo Langel (2011). Cell – Penetrating Peptides – Methods and Protocols. London, Humana Press.