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Peptide-based probes for protein N-Methyltransferases

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Stellingen behorende bij het proefschrift

Propositions accompanying the thesis

Peptide-Based Probes for Protein N-Methyltransferases

1. The transition state analogue methodology based on bi-substrate mimetics can be applied to probe any of the nine known members of the PRMT family.

This thesis: Chapter 2

2. The CARM1 structural studies point to the intriguing possibility that crosstalk between lysine acetylation and arginine methylation may also serve to reinforce PRMT specificity beyond the primary sequence of the peptide substrate.

This thesis: Chapter 3

3. Multiple reaction monitoring (MRM) is a highly selective, sensitive, and robust methodology that can be used to quantify the methylation of peptidic substrates.

This thesis: Chapter 4

4. The macrocyclic peptides identified as NNMT inhibitors via the RaPID selection technology, exhibit no significant competition with the SAM or nicotinamide substrates of NNMT, indicating that they may instead bind at an allosteric site.

This thesis: Chapter 5

5. Transition state analogues ideally mimic key features of short-lived reaction intermediates including bond lengths and angles.

Inspired by Vern L. Schramm. *ACS Chemical Biology* (2013).

6. Histone modifications are numerous and as they are written, read, and erased in a dynamic fashion, their interplay can be seen as a language.

Inspired by J. Lee *et al. Cell.* (2013)

7. Macrocyclic peptides can mimic protein-protein interactions and can interact with larger protein surfaces thereby preventing these interactions.

Inspired by L. K. Buckton *et al. Chemistry A European Journal.* (2020)

8. Truncated peptides are less likely to induce an immune response and can also extend drug half-lives, compared to original natural peptides.

Inspired by C. K. Wang *et al. Journal of biological chemistry* (2020)

9. The important role peptides play as chemical probes for therapeutic targets will facilitate small-molecule drug development.

10. Chemistry is fundamental to explain and understand biology, while biology is Nature's application of chemistry.
11. Scientific research starts from a sparkling thought, often requires multiple rounds of testing and retesting by the curious mind.

Yurui Zhang

Leiden, 06 May 2022