The design of transcription factor-based inhibitors to target Myc: drop the Myc!

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Stellingen

Behorende bij het proefschrift

The Design of Transcription Factor-Based Inhibitors to Target Myc

- Drop the Myc -

1. Protein therapeutics have transformed drug discovery by enabling modulation of challenging targets inaccessible to small molecules (This thesis).
2. Protein based modalities generally hold immense potential in targeting 'undruggable' interactions (This thesis).
3. Intrinsically disordered proteins (IDPs) remain one of the most elusive classes of drug targets, yet their disorder often conceals well-defined structures that emerge upon binding in protein-protein complexes. (This thesis).
4. With continuous developments in the field of peptide engineering and improved understanding on how to improve their pharmacokinetic properties, peptide-based modalities can play an important role in identifying nucleic acid targeted therapies. (This thesis).
5. The central dogma of molecular biology generally states that it goes in only one direction, from DNA to protein. However, transcription factors challenge this dogma. (based on F. Crick *Nature* **1970**, *227,* 561- 563).
6. With our current chemical and AI toolbox we can now design artificial transcription factors that have improved traits to endure problems faced by their endogenous counterpart. (based on E. A. Heiderscheit, et al., *FEBS Lett* **2018**, *592*, 888–900).
7. Artificial intelligence models, such as AlphaFold2, that can predict protein structures and interactions based only on sequence composition will have a significant impact on our understanding of protein-protein and protein-nucleic acid interactions. (based on H. Bret et al. *Nat Commun* **2024**, *15*, 597).
8. Although Transcription factors are partially disordered, they recognize DNA using a well-organized structural fold that differs between family classes, which can be exploited to design high-affinity DNA binding peptides that can target specific DNA sequences. (based on M. E. Vázquez, A. M. Caamaño, J. L. Mascareñas, *Chem Soc Rev* **2003**, *32*, 338–349).
9. Designing or repurposing proteins is like designing a house. You can change the floorplan but you should not remove the support beams otherwise the whole structure will collapse.
10. Taking a step back is only a step back if you don't want to go in that direction.
11. Funding education will have a beneficial impact on our society.

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