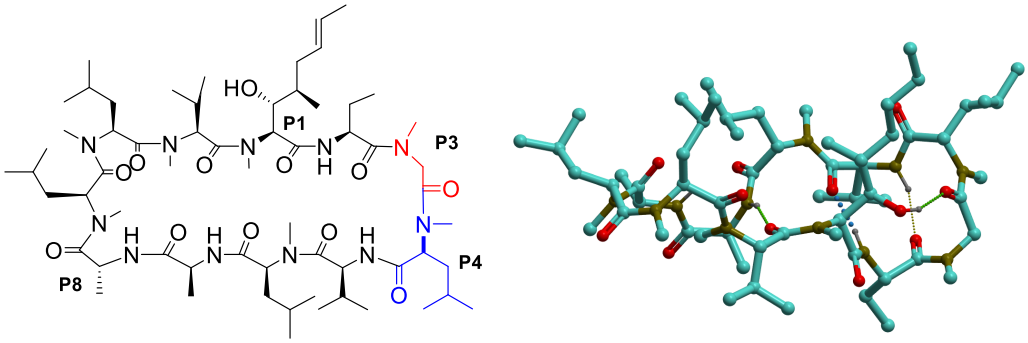
Reengineering and Repurposing of Cyclosporins

Silvio Roggo

Novartis Institutes for BioMedical Research, Novartis Campus, CH- 4056 Basel, Switzerland
silvio.roggo@novartis.com

Cyclosporin A was initially discovered as a moderately active antifungal agent. Its immunosuppressive activity was identified shortly afterwards and opened the door to a new era in organ transplantation. The medical use of this drug substance could be extended to other indications such as psoriasis, rheumatoid arthritis, and uveitis. The immunosuppressive effects have been attributed to the formation of a ternary complex between cyclosporin A, cyclophilin A, and the phosphatase calcineurin.



Certain structural modifications of cyclosporin A prevent binding of calcineurin and reveal non-immunosuppressive activity while retaining cyclophilin A binding. The selective inhibition of cyclophilin A provides an alternative mode of action for the treatment of hepatitis C and other diseases[1].

The search for new drug-like cyclosporin analogs by partial synthesis has been challenging. The modification of cyclosporin A at positions P3-P4 provided a path to the discovery of new cyclophilin inhibitors with potent anti-hepatitis C virus activity and improved pharmacokinetic properties[2,3,4].

The chemistry strategy will be described starting from the medicinal chemistry approach to the identification of a robust and convergent synthesis for a development candidate.

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[2] J. Fu et. al., *J. Med. Chem.*, **2014**, *57*, 8503-8516.
[3] J. Fu et. al., *Bioorg. Med. Chem.*, **2018**, *26*, 957-969.
[4] B. Riss et. al., *Org. Process Res. Dev.,* **2014**, *18*, 1763-1770.