Covalent Inhibitors for the Proteome-wide Identification of New Druggable Targets for Antibiotics

The potency and selectivity offered by covalent inhibitors have led to a resurgence of their application in drug discovery.[1] In this context, modern residue-specific chemoproteomic approaches allow the highly parallel profiling of the ligandability of whole proteomes with resolution of the targeted amino acid.[2,3,4] This enables the simultaneous identification of many new ligandable binding sites in potential target proteins for therapeutic intervention alongside first ligands to interrogate their function.

Our group is developing covalent inhibitors in the context of antibiotics, because new druggable antibacterial targets are urgently needed to overcome bacterial resistance.[5] We have developed a tailored method for residue-specific chemoproteomics in bacteria that we term isoDTB-ABPP.[2] We have applied this technology for the screening of cysteine-directed ligands in *S. aureus* and identified >250 binding sites that can be addressed with covalent ligands and that are starting points for the development of novel antibiotics.

Furthermore, we are developing new chemotypes to globally investigate a variety of other amino acids. Here, we have recently profiled more than 50 electrophilic alkyne probes for their proteome-wide reactivity and selectivity[6] and identified first-in-class probes to globally study aspartates and glutamates[7] as well as arginines, histidines and tryptophans in the proteome.[6] These studies will help us to identify a plethora of new druggable bacterial targets that can be addressed with novel antibiotics.

References:

1. J. Singh *et al.* (**2011**) *Nat. Rev. Drug. Discov. 10*, 307-317.
2. P. R. A. Zanon *et al.* (**2020**) *Angew. Chem. Int. Ed. 59*, 2829-2836.
3. K. M. Backus *et al.* (**2016**) *Nature 534*, 570-574
4. S. M. Hacker *et al.* (**2017**) *Nature Chem. 9*, 1181-1190.
5. M. Lakemeyer *et al.* (**2018**) *Angew. Chem. Int. Ed. 57*, 14440-14475.
6. P. R. A. Zanon *et al.* (**2021**) *ChemRxiv*, doi: 10.33774/chemrxiv-2021-w7rss-v2
7. K. Bach *et al.* (**2020**) *ACS Cent. Sci. 6*, 546-554.