Poster

Fragment-based inhibitor development to fight Shigellosis

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Shigella are highly infectious bacteria and cause the severe disease bacillary dysentery. It occurs predominantly in developing countries, affecting mainly small children, and causes several 100,000 lives per year. The bacteria are able to penetrate into the epithelial cells of the colon and thus develop their pathogenicity. The *Shigella*- specific chaperone IpgC plays an essential role in the active infestation of endothelial cells due to various interactions with invasion proteins. By inhibiting IpgC, the formation of these virulence-specific invasion proteins and translocators is suppressed and, therefore, IpgC is a target for drug development.

Initially, we determined the X-ray structure of IpgC at 1.58 Å resolution [1]. This structure served as the foundation for a crystallographic fragment screening, where we obtained 10 structures in complex with small molecule ligands. Of those, three fragments were selected for further development into larger, more potent binders. By applying the Frag4Lead workflow [2] we finally selected 17 compounds for purchase, of which 3 could be validated as binders by crystallography. Interestingly, one of these molecules binds to a site otherwise required for the binding of the translocator IpaB.

Here, we will present the crystal structures of the IpgC dimer in its apo form and in complex with fragment molecules and enlarged ligands. New developments in IpgC binding to its interaction partners will be included.

[1] Gárdonyi, M., Hasewinkel, C., Wallbaum, J., Wollenhaupt, J., Weiss, M.S., Klebe, G., Reuter, K., Heine, A. (2023). *ACS Omega* **8**, 46051−46065.

[2] Metz, A., Wollenhaupt, J., Glöckner, S., Messini, N., Huber, S., Barthel, T., Merabet, A., Gerber, H. D., Heine, A., Klebe, G., Weiss, M. S. (2021). *Acta Crystallogr., Sect. D: Biol. Crystallogr.* **77**, 1168−1182.

We acknowledge BioSolveIT for providing the SeeSAR licence.