

## Targeting the Shigella-specific chaperone IpgC in drug development

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Shigellosis or bacillary dysentery is a highly infectious disease, affecting approximately 80 million people each year with 700.000 fatalities. The disease emerges predominantly in low- and middle- income countries, but infections in industrial countries are rising. *Shigella* bacteria are able to invade the epithelial cells of the colon and thus develop their pathogenicity. The class-II chaperone IpgC is a key constituent of the *Shigella* type-III secretion system, and therefore, is essential in pathogenicity. IpgC interacts with various virulence-specific invasion proteins and translocators and thus promotes cell infestation. These interactions will be suppressed when IpgC is inhibited by newly developed drugs.

The crystallization of IpgC was optimized to obtain an X-ray structure at 1.58 Å resolution that was the basis for a crystallographic fragment screening. Using a validated fragment library consisting of 96 compounds [1], we obtained ten complex structures [2]. Out of these, three fragment hits were selected for further development using the Frag4Lead workflow [3] that led to 17 enlarged compounds.

Here, we will present the obtained crystal structures in complex with fragment molecules and enlarged compounds in addition to new developments of IpgC binding to its interaction partners.

[1] Hassaan, E., Eriksson, P.O., Geschwindner, S., Heine, A., Klebe, G. (2020). *ChemMedChem* **15**, 324-337.

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[3] 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.

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