

MS02-05 | STRUCTURE-BASED FRAGMENT SCREENING ON DYNAMIN GTPASE DOMAIN

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Structure-based fragment screening concerns finding small organic molecules to occupy the active site or allosteric binding sites of a target protein. Fragments are low molecular weight compounds increasing the probability of finding hits, which can be optimised to higher affinity compounds to probe the biology of the target and to find drug candidates [1]. X-ray crystallography has been shown to be the most reliable and sensitive tool for detecting binders even with very low affinity [2].

The HZB fragment screening workflow provides libraries, for example, a novel 96 fragment F2X Entry Screen based on maximum structural and chemical diversity, tools for sample handling, as well as fully automated data processing and refinement for efficient evaluation of results. Furthermore, downstream optimization of hits with a web-server is used to identify purchasable, versatile follow-up compounds. Here, this workflow is used for finding fragments occupying the GTP binding site or allosteric sites of dynamin.

Dynamin is a multi-domain GTPase, which has a critical role in membrane fission in the endocytic pathway, for example, in cell signalling and nutrient intake [3]. Dynamin forms a helical oligomer around the neck of the invaginating clathrin-coated vesicle, and GTP hydrolysis introduces conformational changes inducing the fission of the tubular membrane. The fission-activity is entirely dependent on the nucleotide binding and hydrolysis, making the GTPase domain potential target for drug development studies.

[1] Murray, C.W. *et al.* (2012) *Trends Pharmacol. Sci.* 33, 224.

[2] Schiebel, J. *et al.* (2016) *Structure* 24, 1398.

[3] Faelber, K. *et al.* (2012) *Structure* 20, 1621.