Characterization of protein family wide chemical probe and chemogenomics sets by structure based hit finding and development

Stefan Knapp[1]

[1]Institute of Pharmaceutical Chemistry and Structural Genomics Consortium (SGC), Goethe-University Frankfurt, Max von Lauestrasse 9, Frankfurt am Main, Germany

e-mail: knapp@pharmchem.uni-frankfurt.de

During this decade, protein crystallography has immensely increased the speed of structure determination, allowing now using this high resolution technology for experimental fragment screening and hit optimization. At the same time, family wide structural genomics efforts elucidated molecular details of entire protein families including the main drug target families such as protein kinases, phosphatases, proteases and others. Our laboratory is interested in contributing and using this wealth of structural information by

a) developing chemical probe sets covering entire protein families of established drug targets. Sharing these well validated compound sets with the community has established new treatment strategies for diseases and it has uncovered now role of the targeted proteins in normal physiology [2–6].

b) Establishing new druggable protein families by high throughput crystallographic fragment screening and biophysical evaluation of the obtained hits.

The main focus of our group is currently on developing highly selective inhibitors for protein kinases, epigenetic modulators as well as finding new chemical starting points for the development of E3 ubiquiting ligases for the development of selective protein degraders [1].

References

(1) Adhikari, B., Bozilovic, J., Diebold, M., Schwarz, J.D., Hofstetter, J., Schroder, M., Wanior, M., Narain, A., Vogt, M., Dudvarski Stankovic, N., Baluapuri, A., Schonemann, L., Eing, L., Bhandare, P., Kuster, B., Schlosser, A., Heinzlmeir, S., Sotriffer, C., Knapp, S., and Wolf, E. (2020). PROTAC-mediated degradation reveals a non-catalytic function of AURORA-A kinase. Nat Chem Biol *16*, 1179-1188.

(2) Arrowsmith, C.H ….. Knapp, S., et al. (2015). The promise and peril of chemical probes. Nat Chem Biol *11*, 536-541.

(3) Barr, A.J., Ugochukwu, E., Lee, W.H., King, O.N., Filippakopoulos, P., Alfano, I., Savitsky, P., Burgess-Brown, N.A., Muller, S., and Knapp, S. (2009). Large-scale structural analysis of the classical human protein tyrosine phosphatome. Cell *136*, 352-363.

(4) Filippakopoulos, P., and Knapp, S. (2020). Next-generation epigenetic inhibitors. Science *368*, 367-368.

(5) Filippakopoulos, P., Picaud, S., Mangos, M., Keates, T., Lambert, J.P., Barsyte-Lovejoy, D., Felletar, I., Volkmer, R., Muller, S., Pawson, T., Gingras, A.C., Arrowsmith, C.H., and Knapp, S. (2012). Histone recognition and large-scale structural analysis of the human bromodomain family. Cell *149*, 214-231.

(6) Schroder, M., Bullock, A.N., Fedorov, O., Bracher, F., Chaikuad, A., and Knapp, S. (2020). DFG-1 Residue Controls Inhibitor Binding Mode and Affinity, Providing a Basis for Rational Design of Kinase Inhibitor Selectivity. J Med Chem *63*, 10224-10234.