MS07-P02 | ONCOGENIC KRAS G12C MUTATION DERIVED INHIBITOR DEVELOPMENT

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KRAS (Kirsten Rat Sarcoma Viral Proto-Oncogene) is a guanine binding signalling protein, which works as a molecular switch in controlling cell growth, differentiation and proliferation. GTP-bound KRAS is in active conformation that can interact with the downstream effectors, like SOS protein, while in the GDP-bound state the signalling decays. It has a high rate of mutagenesis, the most frequent G12C mutation is proven to play a significant role in almost 25 percent of all human cancers. Tumorous malignancies caused by KRAS mutations, such as pancreatic and lung cancer are generally difficult to treat, therefore in the recent years, there was a successful attempt to create promising KRAS inhibitors, that bind covalently to the cysteine of the G12C mutant protein.

In the present work we aim to develop new effective covalent inhibitors to KRAS G12C mutants, since at the time being there is no clinically suitable drugs for cancer therapy.

As a strategy, we applied the fragment-based drug development approach in the research of covalent KRAS inhibitors. Based on this approach we first tested small molecules (fragments) containing the reactive group which is responsible for forming the covalent bond. After validating the most efficient fragment hits, we develop an inhibitor that fits to the binding pocket of KRAS by gradually increasing the size of the fragment.

After successful protein cloning and purification, we managed to crystallize the apo- and inhibited KRAS G12C proteins, collecting X-ray data at BESSY Berlin synchroton, data processing being in progress.