Structure-guided design of histone demethylase inhibitors for cancer therapy.

In the European Union (EU), cancer causes 25% of all deaths. Nowadays the most popular treatment for cancer is chemotherapy but it affects gravely healthy tissues alongside the tumor because it is mostly carried out with unselective compounds. This shows the dire need for development of more targeted therapies.

Recent discoveries in epigenetics, regulation of gene expression, revealed that the enzymes that read, write and erase modifications of histone (DNA organizing proteins) are potential targets for focused cancer therapies. Among those, histone demethylases from KDM4 sub-family were selected as their dysregulation was linked with multiple cancer types such as: prostate, breast, colon or ovarian.

Therefore there is a cry for highly selective, potent inhibitors of KDM4 enzymes, which would be able to cross both the cell membrane and the nuclear membrane.

Their selectivity is a special challenge as they belong to group of enzymes that use the same 2-OG molecule as a co-factor in catalysis. More than 80 of those enzymes are found in almost all of the human cells, while about 30 are involved in histone demethylation. This may explain why the search for specific and potent inhibitors is a challenging journey and no selective compound have become a drug so far.

In the presented project I plan to overcome this barrier for KDM4 inhibitors by reaching away from known and underperforming co-factor binding site towards distal histone binding site.

The structural biology methods will come in help as it can give the most direct information about the binding mode of compounds to target protein. Crystallographic Fragment Screening will be used to probe the protein surface together with its cavities to show us what types of chemical group binds exactly in which places. Most desirable areas to identify bound ligands are those where the catalytic reaction take place and its vicinity. We will treat those bound fragments as puzzles that can be put together by means of combinatorial chemistry to produce a molecule we call LEAD – a potent binder with selectivity within KDM4 subfamily and could lead to potent drug. Those LEAD compound will be checked if they bind according to expectations and for the strength of their binding. We will perform a several rounds of LEAD design, using the information gained to perfect our LEAD. The best LEAD compounds will be additionally assessed for their effect on cancer cells.

This study will result in a solid foundation for further drug development for oncotherapy providing a compounds suitable for subsequent development. Furthermore, LEAD compounds can be used for another basic research aiming at characterization of oncogenesis.