The scientific goal of the project is the synthesis of various types of organometallic conjugates and analogues of selected low-molecular-mass kinesin-5 inhibitors and an investigation of the structure-anticancer activity relationship of the synthesized compounds.

Kinesin Eg5 plays an essential role in mitosis by establishing the bipolar spindle. Inhibition of Eg5 prevents centrosomal separation and mitotic spindle assembly, thus leading to the formation of monopolar spindles. Inhibitors of Eg5 arrest only mitotic cells (cancer cells) and are not expected to affect non-proliferating cells (normal cells). Because of this, inhibitors of Eg5 may not have the severe side effects associated with traditional antimitotic agents. Human kinesin, HsEg5, a member of the kinesin-5 family, is currently under investigation as a prospective cancer drug target. It is worth noticing that Eg5 is overexpressed in many neoplastic tissues (cancer cells), including leukemia, breast, lung, ovarian, bladder and pancreatic cancers, while in non-proliferative tissues Eg5 is almost undetectable.

In this project we will synthesize organometallic low-molecular-mass human kinesin-5 inhibitors and the study of their anticancer activity bearing two fragments: cytotoxic organometallic moieties and the organic vector responsible for binding the molecule to the kinesin-5 protein. The presence of cytotoxic organometallic moieties should increase cytotoxicity of the molecules, and in some cases such compounds should be able to overcome multidrug resistance of cells. Moreover, the presence of the kinesin-5 binding moiety allows to design organometallic compounds which will be able to selectively induce cancer cell death14 by blocking the activity of HsEg5, which plays an essential role in mitosis. We expect that the presence of the organometallic fragment in kinesin-5 inhibitors increases their anticancer activities and, in some cases, provides to overcome the multidrug-resistant barrier toward traditional antimitotic agents