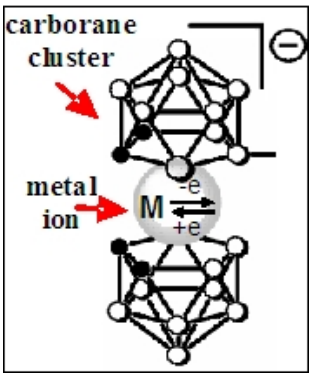
Unique metallacarborane cages, attached to the adenine nucleoside, as a molecular weapon against cancer cells of the ovary

Ovarian cancer is the leading cause of death from gynaecological cancer. Early symptoms may be subtle and presentation is often too late, at an advanced stage of the disease. Moreover, patients with ovarian cancer may have recurrent cancer, resistant to treatment. Therefore, researchers are still looking for drugs that increase the chances in this unequal struggle.

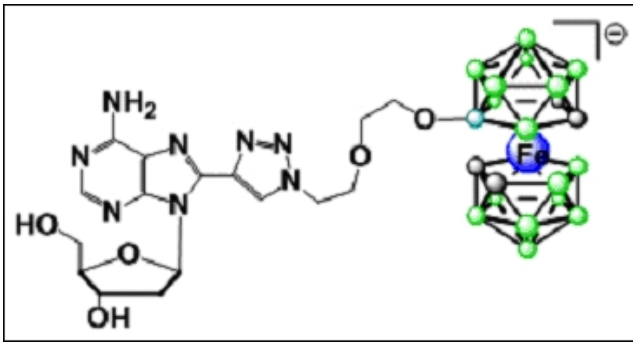
Adenine nucleoside (adenosine) is metabolically friendly endogenous compound, beneficial for cells. However, adenosine chemically modified in the particular way, become killer molecules (called "antimetabolite"), danger for pathologic, tumour cells. Several anticancer analogues of adenine nucleoside were synthesized and tested in the last decades. Some of them become clinically used drugs. For example cladribine is one of the most potent chemotherapeutic used for treatment of leukaemia. Unfortunately, adenosine analogues are not effective against solid tumours, including ovarian cancer, mainly due to a drug resistance.

In this project we would like to take an advantage of new generation of metallacarborane derivatives of adenosine and aim them at ovary cancer cells. We plan to use "friendly" adenosine, as an agent, introducing the metallacarborane into the cancer cell, like a Trojan horse into the city.



How the metallacarborane looks like? Metallacarboranes are "sandwiches", where carborane cages composed of carbon and boron atoms, are paired through a metal ion. In other words, the metal ion (iron, cobalt, chromium) acts as a clasp connecting the two boron clusters resembling spherical cages (an example metallacarborane structure is shown in the figure to the left side).Till recently, bioorganic chemistry has been focused on the construction of high boron-content boron carriers for Boron Neutron Capture Therapy of cancer (BNCT). However, these unique compounds are now attracting more attention as "anchors" (pharmacophores), used in design of novel compounds for treatment of cancer and infectious diseases, in hope to overcome, at least some, limitations of current drugs.

The first experiments carried out in our laboratories indicated, that the selected adenosine and metallacarborane conjugates were toxic to malignant cells of ovarian cancer. Most interesting derivative was compound containing iron ion, which was over twofold more effective in inhibition of cancer cells divisions (proliferation) than cisplatin routinely used in ovarian cancer therapy. Moreover, this molecule does not damage the blood cells. The structure of the molecule containing iron ion is shown in the figure below.



Encouraged by the successful preliminary works, in the current project we will synthesize metallacarborane conjugates containing different metal ions (i.e. iron, cobalt and chromium) and locate them at different positions within adenosine molecule. Next, in the laboratory conditions (in vitro), we will check toxicity of the compounds against the ovarian cancer cells, and their ability to inhibit cancer cell proliferation. On the base of these experiments, compounds that are most efficient cancer cells killers, but safe to the healthy ovarian cells, will be selected.

Next we will look at the mechanisms of these compounds' action: what kinds of the receptors are affected, what genes of the oxidative stress-sensitive enzymes are activated/inhibited and how the compounds enter the cells? We will study the efficiency of the compounds in programming "death signals" in cancer cells. Knowing the molecular "behaviour" of derivatives, we will perform additional modifications of the leading compounds to make them even more effective and selective against cancer cells.

We suppose that the successful switching-on of death signaling in cancer cells by metallacarborane derivatives will be useful in improvement of the treatment of ovarian cancer in the future.