Dual ionophores as multitarget agents against pancreatic cancer

Iron metabolism is one of those processes that are heavily changed during cancerogenesis. In Cancer cells due to their higher rate of multiplication and demand for energy tends to gather more iron than any adjacent tissue. This is maintained by several specific proteins that actively influx and store this element or utilize it in synthesis new enzymes or other proteins. In medicinal chemistry such difference is desirable target for design new more specific drugs. The same can be observed in this field where iron chelators – compounds that are able to catch and complex iron are recently investigated as anticancer agents. First drug of this class triapine has recently entered third phase of clinical trials in several cancer types. Its success become a trigger for further, more detailed research, which help to discover another drug candidates of this type. On the other hand this also revealed gaps in our knowledge in that field. Nowadays the exact mechanism of iron chelators is largely unknown which significantly decrease further development of these experimental drugs. Currently deep knowledge on molecular aspects of such mechanism and all possible side effects that arise from that is a must have before any drug can be accepted for clinical use. In our team, research on iron chelators that belongs to chemical class of thiosemicarbazone derivatives allow us to describe several compounds of exceptionally high activity but also to reveal new mechanism of action. Namely some specific compounds may tends to act as metal ionophores rather than pure chelators. That means mobilizing iron between cellular compartments. This apparently small difference may greatly change effectivity of the anticancer drugs. As mentioned cancer cell under high metabolic stress and higher level of iron have their antioxidative potential shifted to the limits when compared to normal, healthy cells. With this in mind further disruption in iron homeostasis results in collapse of the res-ox balance and cell death with relatively low toxicity to normal ones. What is even more appealing there are some cancer types that seems to be more sensitive to such therapy than the others. Among them pancreatic adenocarcinoma is a primer example. This cancer remains extremely dangerous and difficult to treatment, resulting in very low expected survival rate that do not exceed 5%. In our preliminary results pancreatic cancer seems to be more vulnerable to typical ionophoric compounds as chloroquine.

In current project we plan to exploit this very promising area by design ionophoric compounds with multitargeted mechanism of action. Our approach combine interdisciplinary research on design, synthesis and biological activity evaluation of novel thiosemicarbazones with desired activity profile. Among other we plan to undertake rather abandoned aspect of iron influence on growth of the tumor, hypoxia and subsequent angiogenesis and metastatic activity. Particularly in pancreatic cancer strong dependence on glucose uptake and iron level generate more hypoxic condition than many other cancers. With this in mind targeting iron should be effective strategy to overcome the typical resistance of this cancer. We plan to investigate this in special experimental condition with spheroids 3dimentional cell aggregates that can be respected as model for growing tumor. After that few compounds with best properties will be selected and tested for their anticancer activity in vivo in animal model of pancreatic tumors. In case of success our project shall result in new drug candidates of unique mechanism of action. Another important outcome will be substantial increase in our knowledge on cell biology in cancer.