Title: **Mathematical modeling of cancer evolution and response to radio- and immunotherapy**

High plasticity of cancer cells is one of the major reasons for limited efficacy of currently available anti-cancer drugs. Continuous accumulation of both genetic and epigenetic changes during tumor growth, together with high heterogeneity of tumor microenvironment, increase the chances for pre-existing or actively acquired therapy resistant subclones. In-depth understanding of the abovementioned processes and development of novel therapeutic strategies seems to be impossible without utilizing the tools of mathematical modelling. Such a tools allow to systematically recapitulate and simulate macroscopic cancer growth dynamics (in some level of detail) based on the gathered biological evidence.

The scientific achievement described in the habilitation application consists of a series of papers devoted to the broadly understood mathematical modeling of cancer development and anti-cancer therapeutic interventions. The series starts with two papers (*Poleszczuk et al., Plos Comp Biol, 2015 & Stem Cells Int, 2016*) in which we model evolution of several important traits of cancer cells, such as proliferation capacity and migration potential. The aim was to check which of those traits have the biggest impact on the speed of tumor growth and thus, which trait is the most promising target for therapeutic intervention. We have also shown that cancer cell plasticity is not always tumor growth promoter and in some cases it might also lead to the cancer population collapse, especially in the case of cytotoxic therapeutic intervention such as radiotherapy. The aforementioned therapy is considered in the next two papers of the series (*Poleszczuk et al., Cancer Res, 2016; Walker et al., Sci Rep, 2018*) in which we analyze the possibility of using ionizing radiation as a tool to boost systemic immune response against the tumor. We proposed and analyzed a clinical decision supporting system (Patent No.: US 9,990,715 B2) designed to help the clinicians to choose the tumor lesion for radiotherapy to maximize systemic immune response. Therapeutic benefits of harnessing the synergy between radiotherapy and immune system has been also shown in another paper from the series (*Poleszczuk et al., Breast Cancer Res, 2017*), in which a novel approach has been applied to analyze the SEER database (Surveillance, Epidemiology, and End Results; more than 8.5 mln of patients) in order to show the potential benefits of using pre-surgical radiotherapy compared to the common post-surgical approach. Most importantly, the synergy between the radiation and immune system can be significantly augmented by the currently available immunotherapies. Modeling tumor responses to various immunotherapies is a topic of the last two papers in the series (*Kather JN et al., Cancer Res 2017 & Cancer Res 2018*). In those papers we use histopathological data to create patient-specific computational models of tumor response to immunotherapy. We show that such a models can provide personalized survival predictions for various anticancer therapies.

Mathematical, computational and statistical models developed and presented throughout the abovementioned series of papers might find application in clinical practice as well as in basic research, ultimately leading to the development of novel, more effective, and highly personalized anticancer therapies.