Disclosing chromatin accessibility in brain tumor cells after treatment by cracking a 'nucleosomal code'

Our understanding of cancer has increased over the years and as a result personalized treatments became available. More recently pharmaceutics leading to changes in epigenetic profile, i.e. structures formed by DNA and corresponding proteins, gained attention as a promising targeted treatment, mostly to support other cancer therapies. One of the most successful strategy for combined cancer therapy is an increased response to immunotherapy by application of targeted epigenetic treatment. Although epigenetic alterations are effective in evaluation of disease risk, progression or clinical response, a precise correspondence between epigenetic treatment and chromatin response is not established for majority of pharmaceutics applied. We hypothesize that elucidating molecular mechanisms evoked by the stimulating epigenetic profile, will provide a key data for making progress in tumor and targeted therapies research. The main goal of this project is to provide a characterization of epigenetic changes involved in the response to particular treatments and form a framework for evaluating changes in chromatin accessibility for other stimuli.

The goals of the project will be achieved through the application of already established techniques which have not yet been combined to study chromatin response to epigenetic treatments. We will use our new method called MACC (Mieczkowski, J. et al. Nat. Commun. 2016) to analyse physical and biochemical properties of cell response to epigenetic stimuli. To provide additional mechanistic insights we will profile covalent modifications and variants of histones, a core part of fundamental structural unit of chromatin in eukaryotic organisms. We will perform systematic, computational analysis of the obtained profiles and recognize epigenetic maps of regions distinguishing between treated and untreated primary cell cultures. We will apply machine learning technics and a comprehensive analysis of all gathered types of data together with external resources which will provide a functional sense to the obtained results. Computational analysis will provide a set of genomic loci associated with response to epigenetic stimulation. After selection of genomic loci involved in the cell response we will check whether the chromatin state in the treated cells and/or response mechanisms are be characteristic for cancer cells and/or specific genetic background.

Direct analysis of the chromatin landscape in primary cultures of cancer cells will provide insights into epigenetic regulatory networks and profiles of chromatin physical properties associated with the response to the epigenetic treatment. Our project will constitute a novel approach, never before applied to study mechanisms of response to cancer treatment. Our results will provide new avenues to shape potential of cell responses, and better understand mechanisms standing behind success of combined therapies.