Malignant melanoma is a cancer that develops from pigment cells called melanocytes. Most melanomas occur on the skin, however it can also be found in gastrointestinal tract and in the eye. If cought at an early stage it is almost always curable with a minor surgical operation to remove the tumor. However, metastatic melanoma (spreading to the other parts of the body) in most cases cannot be cured, and unfortunately leads to the fatal end. The major problem with melanoma cells is high resistance to the commonly used approches including chemotherapy, which is generally used as palliative care to slow down the progression of the disease, and to control symptoms, reduce complications, and keep patients comfortable.

Drug resistance is unsolved pharmacological problem that cause failure of the many types of therapies including anti-cancer therapies. Drug resistance can be either pre-exisiting (intrinsic) or apparent after initial, positive theraupeutic response (aquired). Cancer cells aquire resistance by many different mechanisms that include: increased expression of antiapoptotic proteins, increased expression of membrane proteins that export drugs outside cell (e.g. from the ABC family), increased glutatione (GSH) level, increased DNA repair, mutations in drug's target genes, activation of some cellular pathways. Unfortunately, little is know about mechanisms mediating melanoma cells resistance and the question: why melanoma cells are relatively insensitive to chemotherapy in comparison to other non-melanoma cancer cells, still remains unanswered. However, there is hypothesis linking melnoma resistance with the physiological process of melanin production. Melanomas are formed from the melanocytes, pigment-containing cells in the skin. Malanoma cells similarily to melanocytes contain an unique organelles called melanosomes that create the environment for melanin (pigment) synthesis. The pigment production is a process generating many, highly cytotoxic compounds. This is why cells producing melanin need to develop protective mechanisms detoxifying endogenous melanogenic cytotoxicity (that is induced when intermediates leak from melanosomes to cytoplasm). However, these detoxifying mechanisms that are useful in normal cells are undesirable in cancer cells and might be stimuli and contributor of the intrinsic resistance of melanomas.

Our screening of chemical library for componds with potential anti-melanoma activity resulted in identification of AC-93253, SIRT2 inhibitor as a molecule exerting many desirable effects on melanoma cells including: cell cycle arrest, inhibition of proliferation, increase in apoptosis, sensitization to doxorubicin and dowregulation of many genes that are suspected to be involved in drug resistance and progression of melanomas. To our knowledge, this represents the first report linking SIRT2 with the regulation of genetic information in melanoma cells,potentially important from therapeutic point of view. The main purposes of our proposal are:

1. Identification in melanoma cells genetic information that is SIRT2-dependent.
2.Determination whether SIRT2 is good target for targeted therapies against malignant melanoma.

In other words, we want to identify SIRT2-dependent genetic program in melanoma cells and evaluate it as promising molecular target for anti-melanoma therapy. The research plan is organized in interconnected research tasks that include: search for genes regulated in SIRT2-dependent manner followed by mapping of genetic information responsible for melanoma cells progression followed by validation of identified markers. The scope of proposed analysis covers analysis changes in the modulation of melanoma genetic programs and correlation it with the phenotype of resistant cells.