High-grade gliomas are the most aggressive primary brain tumors that occur frequently in the central nervous system. Following diagnosis, the 5-year survival rate of patients with glioma is much worse than patients with most other types of malignancies. Current standard care consists of tumor resection, irradiation and chemotherapy, however cancer cells, especially gliomas, reprogram themselves in multiple ways to evade the effect of these therapies and gain so called *resistance* to drug treatment. The risk that tumors may acquire resistance to anticancer drugs remains a major clinical challenge in successful treatment of glioma patients.

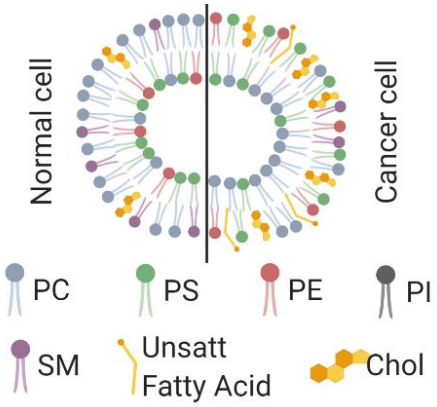

Figure 1. Schematic illustration of the differences in composition of normal cell membrane and cancer cell membrane.

A significant number of researches showed that biophysical properties of membrane lipids and the lipid profile of cells change during malignant transformation (*Figure 1*). The structural, biophysical and biochemical differences between cancer and normal cell membranes can enhance or inhibit drug activity and toxicity. Drugs will also have different effects on the membranes with different lipid and protein conformation, orientation, their packing and fluidity. **In addition, we hypothesize that lipid membranes composition and changes in lipid orientation during drug-resistance development as well as biochemical and biophysical properties of the cell membrane are significant contributors to acquired drug resistance.**

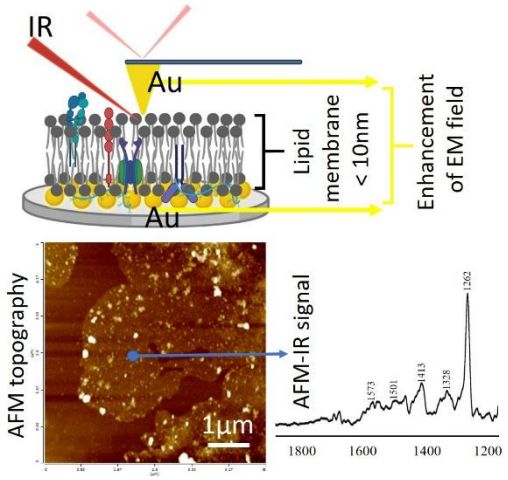

Figure 2. Schematic representation of AFM-IR setup for lipid membrane measurements using AFM (top panel) and topography of the membrane sample obtained from human skin fibroblasts and corresponding local absorption spectra (bottom panel).

In this research project we propose to study nanoscale structure and organization of native lipid membranes isolated from normal and cancer glioma cells as well as cancer cells that acquired drug resistance. We will achieve this using AFM-IR technique **that will allow for detailed nanoscale analysis of the native cell membranes.** Typically, atomic force microscopy (AFM) ensures topographic images of the samples with nanoscale precision, however their structural identification becomes unknown. On the other hand, infrared spectroscopy (IR) is a routine applied method for chemical discrimination of various kinds of materials, but the ~3 µm spatial resolution offered by this method is far from the resolution needed for the characterization of the nano-objects. AFM-IR, which combines the IR and AFM methods, achieves both goals, namely local chemical analysis of the sample and nanometer spatial resolution providing exploration of nanometer-size samples (*Figure 2*).

Therefore, the hypothesis guiding this project is that description of the relationship between nanoscale composition, structure and organization of the native cell membranes and effectiveness of the therapeutic drugs is critical to fully describe molecular mechanism of drug resistance. Understanding this relationship might also help in developing diagnostic tools to predict drug resistance in clinical settings.