1.The goal of the research proposal is to discover and to understand **what are structural determinants allowing for artificial optical signal transduction in cells: from elementary absorption of photons at artificial chromophores to proteins' activation and regulation of basic physiological processes such as insulin release or enhancement of glioma proliferation.** Recently (2005-2015) hundreds of papers have been published where numerous light-activated proteins (or other artificial systems) were used to study animal brain, animal behavior or cell metabolism. Optogenetics and optopharmacology are booming and contribute a lot to neuroscience. However, the detailed molecular mechanisms of signal transductions (i.e. a chain of conformational transitions leading from protein excitation to a physiological response) are missing in the literature. We want to fill this gap, at least for several model systems: (1) CT fluorescent probes embedded in protein cavities, (2) closing/opening of rectifying potassium channel Kir6.2 by light activated azobenzene sulfonylurea derivatives docked to SUR1 protein, (3) shedded by light soluble neuronal adhesive protein neuroligin sNLG3 which leads to an accelerated proliferation of glioma.

2. In this project we will mainly apply standard methods of quantum chemistry (QCh) (HF, DFT, TD DFT, CAS-CI) and molecular dynamics simulations (MD) to systems with increasing complexity. However, there is no standard classical method for performing MD simulations for proteins containing excited chromophores. Working on another project we are currently developing such a method. It is based on J. Tully surface hoping algorithm and **our new method will be applied for modeling excited proteins dynamics** in this study. For QCh calculations we will use standard packages Gaussian09 and Jaguar, for docking we plan to use Autodock Vina and Glide, for MD the NAMD/VMD package and our own scripts will be applied. We will use local clusters for setting up systems and Polish supercomputer centers (PCCS, Cyfronet, ICM, TASK) for >100ns MD simulations for complexes of 0.5-0.7 mln atoms. For analysis we will use local modern graphical workstations available at the Inst. of Physics/ICNT NCU. We will apply QCh to determine geometries, charges, MEPs, in selected chromophores such as azobenzene derivatives of sulfonylurea, CT fluorescent probes (ALADAN), non-standard fluorescent amino acids, etc.. TD DFT and SAC-CI will be applied to calculate electronic spectra of these compounds. Based on appropriate QCh estimates new classical force field (CHARMM27) parameters relevant for cis- and trans- forms and the excited states of the photoactive compounds will be determined. Bioinformatics methods and homology modelling will be used to determine the protein complexes structures if such experimental structures are missing (SUR1, sNLG3). Where appropriate, we will use our own memetic algorithms to determine classical ligand diffusion paths and collective variables suitable for description of photo-activation processes.

3. Pathways of optical signal transduction in majority of optogenetic systems are not know. **We will determine such pathways leading form absorption of photon through chromophore isomerization to protein conformational change and modification of its biological activity. This knowledge should help to develop new "intelligent" drugs for Type II Diabetes Mellitus.** Hopefully, in the future optical control of insulin release will be available also for humans, not only to lab animals as of today. Moreover, molecular details of proliferating activity of neuroligin 3 protein, determined in this project, **may help to fight glioma**.