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SUMMARY of
2015 RESEARCH RESULTS REPORT
For International Collaborative Research with IPR, Osaka University

Research Title		**Molecular foundations for optical control of insulin release**
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	Present Title	**Full Professor of Physics, Head of Theoretical Biophysics Group**
Research Collaborator (Host PI)		**Professor Haruki Nakamura**

Summary:

Optical control of living systems activity offers new fascinating possibilities both in research and biomedicine. Thus, optogenetics, developed in recent years is booming. Optically active proteins are inserted into living systems, like neurons and laser light allows for controlled activity of strictly localized cells. Our project is related to this new area and aims in better understanding of optical switches interaction with medically important proteins: EPAC2 and SUR1.

We studied computationally interactions of JB235 in both *trans*- and *cis*- conformations with both EPAC2 and SUR1 receptor proteins. These are large systems and using computational facilities available in IPR, Osaka University are critical for the project.

Consequently, the following results were obtained.

1. New classical Force Field parameters for the JB235 photoactive compound were developed in Torun, Poland. Polish group have good experience in such work, they have computational pipeline for developing new parameters, based on quantum chemistry.

2. For JB235 parameters were developed that should allow running molecular dynamics simulations in the electronic excited state. Such simulations are very rare in the literature, but quite appropriate in this problem.

3. The EPAC2 computer model was prepared based on existing X-ray structure.

4. For system SU1 there is no crystallographic structure determined yet. However, there are numerous (>12) similar ABC transporter proteins deposited in the PDB, so we created a homologous model of SUR1 for Mus Musculus and/or Homo Sapiens. However, we have found out shortcomings or problems with modeling of SUR1, due to a lack of a reliable mode of binding of SUR1 to Kir6.2 potassium channel.

5. Docking of the J235 to EPAC2 and SUR1 using existing codes. The best pose/poses was optimized.

6. Molecular dynamics studies were performed in total over 100 ns simulations for ground state (*trans*) and excited state (*cis*) conformations of the drug.

Based on graphical analysis of the above MD simulations of *trans* and *cis* conformers, the *cis* conformer is found to be more stable in IP pocket than the *trans* conformer.