Grenoble Alliance for Integrated Structural & Cell Biology

INTERNSHIP PROPOSAL

Institute and Group: Institute of Structural Biology, Membrane transporter Group

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Research project title: Structure and Mechanisms of Glutamate Transporters

5 Keywords to describe the project: membrane proteins, glutamate transporters, X-ray crystallography

Description of the project (aims, experimental techniques, recommended background):
Excitatory amino acid transporters (EAATs) are key elements of glutamate homeostasis in the mammalian central nervous system. In addition, they also function as anion channels. The glutamate transporters are essential for normal development and function, and are implicated in stroke, epilepsy and some neurodegenerative diseases. Eukaryotic glutamate transporter homologue from Pyrococcus horikoshii (GLTph) is used as a model protein to study structure and functional mechanisms of the EAATs. Since 2004 several seminal structural works on this protein have been published (Akyuz et al. *Nature*, 2013, PMID: 23792560; Reyes et al. *Nature*, 2009 PMID: 19924125; Boudker et al. *Nature,* 2007 PMID: 17230192; Yernool et al, *Nature*, 2004 PMID: 15483603). However, due too mainly not sufficient structural resolution some important features of glutamate transporter mechanisms are still lacking. Recently we obtained to date highest resolution structure (2.4 Å) Apo form of the transporter. The goal of the project is to elucidate high resolution structures of different functional states of the protein. It will allow us to understand a complete picture of molecular mechanisms of the transporter. In addition we plan to solve high resolution structure of medically relevant mutant (first crystals are available, however, they have provided only 3.6 Å resolution structure).

Justification that the internship's subject fits with the general theme of GRAL:
This project is related to structural studies of membrane proteins using X-ray crystallography. Also it requires molecular biology, biochemistry, biophysics approaches to protein production and functional tests of membrane proteins.

Relevant publications of the team:

Volkov O., K. Kovalev, V. Polovinkin, V. Borshchevskiy, Ch. Bamann, R. Astashkin, E. Marin, A. Popov, T. Balandin, D. Willbold, G. Büldt, E. Bamberg and V. Gordeliy. Structural Insights into Ion conduction by Channelrhodopsin 2. *Science* (2017), eaan8862. doi: 10.1126/science.aan8862.

Gushchin, I., Melnikov, I., Polovinkin, V., Ishchenko, A., Yuzhakova, A., Buslaev, P., Bourenkov, G., Grudinin, S., Round, E., Balandin, T., Borshchevskiy, V., Willbold, D., Leonard, G., Büldt, G., Popov, A. and V. Gordeliy, Mechanism of transmembrane signaling by sensor histidine kinases. *Science* **356,** eaah6345, doi: 10.1126/science.aah6345 (2017).

Moukhametzianov R.E., Klare J.P., Efremov R.G., Baeken C., Göppner A., Labahn J., Engelhard M. ,Büldt G. and V. Gordeliy . Development of the signal in sensory rhodopsin and its transfer to the related transducer. *Nature* (2006) 440, 115-119.