OIST SEMINAR

Ms Sabine Hessler

University of Sussex

DATE: **Tuesday, January 17th, 2017**

TIME: **10:00 – 11:00**

VENUE: **Meeting Room D015, Level D, Lab 1**

Effects of β-secretase BACE1 on KCNQ (Kv7) channels

Abstract:

The beta-secretase BACE1 is widely known for its pivotal role in the amyloidogenic pathway leading to Alzheimer's disease, but how its action on transmembrane proteins other than the amyloid precursor protein affects the nervous system and heart tissues is only beginning to be understood.

My data suggest that BACE1 regulates neuronal excitability through an unorthodox, nonenzymatic interaction with members of the KCNQ2-5 (Kv.7.2-7.5) family that give rise to the M-current, a noninactivating potassium current with slow kinetics. In hippocampal neurons from BACE1 null- mice, loss of M-current enhanced neuronal excitability. The diminished M-current was related to the previously reported epileptic phenotype of BACE1-deficient mice. In transfected HEK293T cells, BACE1 amplified reconstituted M-currents, altered their voltage dependence, accelerated activation, and slowed deactivation. Biochemical evidence strongly suggested that BACE1 physically associates with channel proteins in a beta-subunit-like fashion. These results establish BACE1 as a physiologically essential constituent of regular M-current function and elucidate a striking new feature of how BACE1 impacts on neuronal activity in the intact and diseased brain

BACE1 also serves as a novel interaction partner of KCNQ1, a potassium channel in cardiac myocytes. Using HEK293T cells as heterologous expression system to study the electrophysiological effects of BACE1 and KCNE1 on KCNQ1 in different combinations, BACE1 slowed the inactivation of KCNQ1 current producing an increased initial response to depolarizing voltage steps, activation kinetics of KCNQ1/E1 currents were significantly slowed in the presence of co-expressed BACE, and BACE1 impaired reconstituted cardiac IKs when cardiac action potentials were used as voltage commands, but interestingly augmented the IKs of ATP-deprived cells, suggesting that the effect of BACE1 depends on the metabolic state of the cell. Though our data show that BACE1 is present in heart tissue and in human iPSC-derived cardiomyocytes, we do not know yet whether BACE1 activity in heart tissue is also susceptible to pathophysiological conditions.

Please contact Prof. Kuhn (bkuhn@oist.jp) if you are interested in talking to the speaker.