Support letter from your supervisor or a senior co-worker explaining why you should be selected for this course

**Letter of recommendation for Aparna Malisetty**

As the main supervisor of the Master's thesis, I strongly recommend Aparna Malisetty as a partici­pant in the BioExcel Summer School on Biomolecular Simulations, which would be of great impor­tance to her and also for me and my entire research group.

I have known Aparna since mid-2019, when she was highly recommended by Angelika Lampert (Pro­fes­sor of Physiology, RWTH Aachen University) due to her excellent performance in the Biomedical Engineering M.Sc. programme at RWTH Aachen University. Due to her excellent computer skills (which are also evident from her CV), I was happy to offer Aparna a paid position as a student assis­tant. Her task was to use an existing high-resolution X-ray crystal structure to identify positions in the P2X3 receptor (a ligand-gated ion channel) that would allow insertion of the Myc-9E10 antibody epitope (10-residue recognition sequence: EQKLISEEDL) into the P2X3 polypeptide chains at positions that were as functionally silent as possible. Using the software Modeller, Aparna identified six poten­tially suitable positions. All six corresponding mutants were generated by Aparna using mole­cular biology methods she learned in my lab. All six mutants proved to be well expressed in *Xenopus laevis* oocytes, homotrimeri­zation competent and functional, but not necessarily silent for reasons that have not been clarified so far.

After an internship at LifeTec Group, Eindhoven, The Netherlands, as part of the M.Sc. programme, Aparna returned to write her Master's thesis in my research group. The aim of her master thesis is to structurally interpret data available to us by our previous extensive biochemical and functional alanine scanning mutagenesis study on the P2X1 receptor. Aparna’s initial analyses made evident to her that deeper insights into the available data require molecular dynamics simulations. This is because the alanine scanning mutations (in blocks of 4-5 residues each) not only influence the potential contact sites between the P2X1 subunits (as I had expected), but also the local folding of the polypeptide chain. As members of RWTH Aachen University, we are in principle entitled to computing time on a supercomputer (JUWELS) at the computing centre there. We are therefore basically confident that we can perform such calculations, but a comprehensive introduction to the basic knowledge required for this seems essential to us.

The enormous importance of this computer-based structure analysis for all areas of molecular medicine is beyond question. With the recent revolution of cryo-electron microscopic structural elucidation of membrane proteins, I believe we are at the very beginning of fascinating new insights into the biophysics of ion channels and their enormous therapeutic potential.

Thank you for your great course offer, which we are excited to apply for. For Aparna, the course would come at just the right time, having just familiarized herself with relevant, academically accessible programmes through her cleverness and perseverance. An exciting 1-ns molecular dynamics simulation, which she realized completely on her own on her desktop computer, shows a misfolding of the first transmembrane domain of the P2X1 receptor due to a 5-alanine residue substitution. This may explain the previously for us unexplainable biochemical observation of an aggregation of the P2X1 polypeptide in the absence of a physically relevant contact site.

I am convinced that participation in this course will give Aparna the decisive step forward to be able to make scientifically sound structural predictions according to the state-of-the-art.

With best regards

Please do not hesitate to contact me if further information is needed.

Günther Schmalzing

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University Professor of Pharmacology

RWTH Aachen University