2016 Jülich – OCPC – Programme
for the involvement of postdocs in bilateral collaboration projects

PART A

Title of the project: Multi-scale simulation based-structural predictions of human odorant receptors: The case of the OR7D4 receptor in complex with its agonists androstenone and androstadienone

Jülich's institute: Computational Biomedicine (IAS-5 / INM-9)

Project leader: Prof. Paolo Carloni, Dr. Alejandro Giorgetti

Web-address: http://www.fz-juelich.de/ias/ias-5/EN/Home/home_node.html

Description of the project (max. 1 page)[1]**:** see overleaf

Description of existing or sought Chinese collaboration partner institute (max. half page)**:**
We would be interested in possible collaborations with Chinese partner research groups involved in structural predictions of human G-protein coupled receptors.

Required qualification of the post-doc:

• PhD in Physics, Chemistry, Computational Biology, Bioinformatics
• Experience with protein structural bioinformatics and computational biophysics (MD simulations)
• Additional skills in docking techniques

PART B

Documents to be provided by the post-doc:

• Detailed description of the interest in joining the project (motivation letter)
• Curriculum vitae, copies of degrees
• List of publications
• 2 letters of recommendation

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[1]   Please add overleaf

PART C

Additional requirements to be fulfilled by the post-doc:

- Max. age of 33 years
- PhD degree not older than 5 years
- Very good command of the English language
- Strong ability to work independently and in a team

Description of the project:

Chemosensation –olfaction and taste- is the most ancient human sensory system[1,2]. Using an arsenal of more than 400 olfactory receptors (ORs), humans can discriminate possibly more than 1 trillion different odors[3]. ORs are also expressed in tissues other than the olfactory epithelium and are involved in a variety of key physiological and pathological processes[4]. Hence, unraveling the mechanism of activation of ORs at a molecular level may lead to an explanation of the effect of genetic variability on smell sensing and other physiological processes. It might also help design new drugs against ORs related to pathologies. Unfortunately, experimental structural information is lacking. Molecular modeling and multiscale simulations, in close combination with experimental data, is then the method of choice for structural predictions.

ORs belong to the human G-protein coupled receptors (GPCRs) family and thus the experimental structures of other GPCRs can be used as templates to generate structural models of ORs. However, their low sequence identity makes the generation of good models a daunting task. In our lab, we are using advanced bioinformatics techniques[5,6] along with multiscale molecular dynamics simulations, to predict the structural determinants of ligands/GPCRs complexes. In particular, our calculations have lead to successful predictions in the case of other GPCRs for which structural information is unavailable, i.e. the bitter taste receptors[7].

Here we will use our computational tools to move on to ORs. As pilot project, we will focus on the human OR7D4 receptor[8]. The receptor is currently one of the best characterized human ORs in terms of molecular biology experiments[8,9] making it an ideal system to start with. Our work will unravel the structural determinants for the binding of agonists such as the steroids androstenone and androstadienone. The calculations will be validated against available molecular biology experiments[8,9], as already successfully done for other GPCRs[7]. Comparison of sequence-similar receptors with different affinities for the aforementioned agonists (such as the phenotypically different human OR7D4 variants or the non-responsive mouse OR7D4 orthologue) or sequence-divergent receptors with similar ligand affinities (such as OR7C1, OR10A6 and OR2J2) will help to pinpoint the key protein residues for ligand binding and signal transduction. **In order to develop a robust and reliable protocol applicable in general to ORs, our approach could be ideally complemented by predicting tools other than those used here**. In China, there are several research groups involved in GPCR modeling, and we are seeking a collaboration with one of those for this project.

References

[1] Hoover, K. C. (2010). *Am. J. Phys. Anthropol.*, 143(S51), 63-74.
[2] Krusemark, E. A., et al. (2013). *J. Neurosci.*, 33(39), 15324-15332.

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[4] Flegel, C., et al. (2013). *PLoS One*, 8(2), e55368.

[5] Sandal, M. et al. (2013). *PLoS One*, 8(9), e74092.

[6] (a) Marchiori, A., et al. (2013). *PloS One*, 8(5), e64675; (b) Sandal, M., et al. (2015). *J. Chem. Theory Comput.*, 11(9), 4439-4449.

[7] Leguèbe, M., et al. (2012). *PLoS One*, 7(10), e47332.

[8] Keller, A. et al. (2007). *Nature*, 449(7161), 468-472.

[9] (a) Ohloff, G., et al.(1983). *Helv. Chim. Acta*, 66(1), 192-217; (b) Aronov, E. V., et al. (1993). *Chem. Senses*, 18(3), 229-243; (d) Pierce, J. D., et al. (1993). *Chem. Senses*, 18(3), 245-256; (e) Pierce, J. D., et al. (1996). *Chem. Senses*, 21(2), 223-237.