2017 Helmholtz – OCPC – Programme
for the involvement of postdocs in bilateral collaboration projects

PART A

Title of the project: Novel Probes for Neuroimaging in Parkinson's Disease

Helmholtz Centre and institute:
Forschungszentrum Jülich, Institute of Neuroscience - Molecular organization of the brain

Project leader: Prof. Dr. Andreas Bauer

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Description of the project:

Parkinson's disease (PD) is currently an incurable disease affecting about 1% of the population over the age of 65. Recently, PARKIN, a causal gene for autosomal recessive early-onset Parkinsonism, has been demonstrated to interact with the protein mitoNEET (mNT) in the mitochondria. mNT is therefore emerging as a potential therapeutic target for neurodegenerative diseases. The protein belongs to the recently discovered NEET family of iron-sulfur (FeS) proteins. These are defined by a unique CDGSH amino acid sequence in their FeS cluster-binding domain. Another protein, Miner 1 (NAF-1), belonging to the same NEET family, has been recently found to be over-expressed in the brain in the early stage of the neuronal development. Since iron and reactive oxygen species (ROS) accumulation in the brains of patients with neurodegenerative diseases is well documented and since the NEET proteins are highly expressed in these patients (our non-published results), it is safe to assume that the labile 2Fe-2S clusters of the NEET are a major source for the iron accumulation that promotes high ROS.

Project:
Here, we plan to use computational approaches coupled to in vitro, in vivo, and ex-vivo experiments to determine new effective ligands able to stabilize the NEET proteins clusters and thus avoiding the iron and ROS accumulation in the brains affected by neuro-degenerative diseases. Specifically we will predict the entire structure of the proteins embedded in the outer mitochondrial membranes (notably the helix packing of the transmembrane portion) by coarse grain and bioinformatics methods, such as homology modelling and evolutionary algorithms. We will use empirical force-field-based and hybrid quantum mechanics-molecular mechanics methods to characterize structural and dynamical features of apo- and holo-NEET proteins and - based on these molecular findings - design

analogues of the drugs by screening databases such as the ligand.info and Zinc. The ligands with the highest affinity will be purchased/synthesized and tested both in vitro (biochemically) and in vivo (animal model systems).

Contribution of a potential candidate:
A potential candidate will be involved in in vitro, ex vivo and in vivo testing (PET) of the new ligand. The most promising compounds will be screened for blood brain barrier (BBB) penetration and efflux transporter substrate qualities using in vitro cell layer BBB models. As a screening for selectivity, we will study the binding of target compounds (fluorescent or covalently coupled to fluorophores) to fresh native brain tissue sections, using fluorescence microscopy. The most appropriate candidates, fulfilling the Lipinski's rule of five will be tested in the established rotenone rodent model of mitochondrial dysfunction. Since Pioglitazone has been shown to relieve motor impairment and dopamine levels close to control levels, it will be used as positive comparator.

Time schedule (2 years):
1. In vitro testing of the binding characteristics of the ligands with in vitro quantitative autoradiography (both in vitro using brain slices and ex vivo) and establishing a metabolite analysis system for potential PET ligands – 6 months.
2. Most effective ligands are further tested for BBB penetration and for cerebral distribution characteristics in animal PET studies – 1 year.
3. Final drug candidates will be tested regarding their indicator functionality in a rodent PD model – 6 months.

The preceding steps for modelling the entire protein structure of mNT and NAF-1 and molecular dynamics simulations (including Hybrid Molecular Mechanics simulations and Force matching calculations) have already been started (in collaboration with the Institute for Computational Biomedicine (Prof. Paolo Carloni, FZJ/INM-9).

The post-doc project will therefore be ready to start in the second half of 2017.

Description of existing or sought Chinese collaboration partner institute:

An ideal partner institute has a brain imaging and/or pharmacological and/or neuroscientific background, since most of the post-doc program is referring to the preclinical evaluation of a potential ligand for magnetic resonance imaging (MRT) and positron emission tomography (PET).

Required qualification of the post-doc:

- PhD in nuclear medicine or pharmacology or animal health or neuroscience,
- Experience with animal experiments and/or PET instrumentation,
- Additional skills in behavioural animal testing and/or pharmacology and/or PET quantification/modelling.

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

PART C

Additional requirements to be fulfilled by the post-doc:

- Max. age of 35 years
- PhD degree not older than 5 years
- Very good command of the English language
- Strong ability to work independently and in a team