2026 Helmholtz – OCPC – Programme

for the involvement of postdocs in bilateral collaboration projects

PART A

Title of the project:

< Ligand residence time predictions via active learning and structure-informed modelling: the case of the ecto-5'-nucleotidase (CD73) as a pharmaceutical target >

Helmholtz Centre and/or institute:

Forschungszentrum Jülich GmbH, 52428 Jülich

Project leaders:

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Description of the project (max. 1 page):

Ligand Residence Times (RTs) are key pharmaceutical parameter. Unfortunately, determining drug–target RTs by either experimental kinetic measurements and/or molecular simulations are low-throughput and costly. Machine learning (ML) approaches could be much faster and cheaper in predicting RTs; yet the limited size of existing RT databases greatly limits the domain of their applications.

Here, the successful candidate will overcome these difficulties (i) by developing an uncertaintyware machine learning code to identify new ligand scaffolds, and (ii) by measuring RTs in the wet lab to build up a data base exploitable by machine learning techniques. We will focus on the ecto-5'-nucleotidase (CD73) pharmaceutical target, a key immunoregulatory enzyme involved in cancer progression and inflammation, making it an attractive therapeutic target. For this protein our collaborator, Prof. **C. E. Müller** (University of Bonn), (i) has set up a competition-association binding assay. This uses the novel tritiated radioligand [^{3}H]PSB-17230 to determine CD73 inhibitor RTs. (ii) has already measured more than two dozen RTs of different compounds from her own ligand library. These high-quality kinetic data, along with those measured by the candidate (about 70), will be then used to train the candidate's ML models. These will transcend traditional supervised learning approaches, which may fail to actively identify 'what the model does not know', resulting in low confidence and high error rates when predicting high-uncertainty molecules. Indeed, the candidate

will use Active Learning approaches, which have emerged as an efficient data sampling strategy that selects high-uncertainty compounds for further experimental testing. This enables the efficient exploration of chemical space while minimizing experimental costs. Metadynamics simulations of ligand unbinding from CD73, for which the PIs have large expertise, will be performed. They will provide the molecular basis of the measured RTs for selected ligands. Combining structure-informed molecular dynamics with data-driven predictions in an Active Learning cycle will further improve RT estimates for novel scaffolds. This approach leverages existing kinetic databases while actively expanding them through targeted sampling to address persistent data scarcity in ligand RTs. Over the course of a three-year project, the successful candidate will carry out structural analysis, develop active learning models, perform biomolecular simulations and conduct experimental benchmarking, ultimately identifying ligands with tailored residence times. This approach, which will pave the way for the development of more effective and durable CD73 inhibitors, will be readily extended to other pharmaceutical targets.

Description of existing or sought Chinese collaboration partner institute (max. half page)**:**

Shanghai Jiao Tong University (SJTU) is one of China's leading research universities, with strong international reputations in biomedical sciences, drug design, and artificial intelligence. The university offers an interdisciplinary research environment integrating experimental pharmacology, structural biology, and computational modeling. This makes SJTU an excellent partner for collaborative research on residence time-oriented drug discovery. This collaboration builds on **Prof. Shuguang Yuan**'s research group's expertise at SJTU in the molecular mechanisms of drug-target interactions, machine learning–based prediction of ligand residence times, and structure-kinetics relationships. This expertise closely aligns with the applicant's research focus on machine learning–based prediction of ligand residence time and data–driven modeling of drug–target kinetics for ecto–5'–nucleotidase (CD73). The collaboration between the applicant and Prof. Yuan is grounded in their shared scientific interest in understanding and predicting ligand residence times through integrative computational and experimental approaches. The planned research visit by Prof. Paolo Carloni will further strengthen this partnership by enabling close methodological integration, the coordinated development of structure-informed and active learning–based computational frameworks, and the joint supervision of the successful candidate. Beyond the immediate project, this collaboration is expected to develop into a long-term partnership that will support joint publications, future funding applications, and a sustained bilateral exchange between Forschungszentrum Jülich and Shanghai Jiao Tong University.

Required qualification of the postdoc:

<Sample text below>

- PhD in Physics, Chemistry, Biology
- Experience with Data Science, Machine Learning, biological databases
- Additional skills in wet chemistry lab, computational drug design
- Language requirement: Fluent in spoken and written English