Activation of the 20S Proteasome to Normalize Tau Homeostasis

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Country

USA

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1

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Research Abstract

Project Summary/Abstract. Microtubule-binding protein tau (MAPT/tau) accumulates to cause a family of fifteen progressive neurodegenerative disorders, incluing frontotemporal dementia (FTD), progressive supranuclear palsy (PSP) and some forms of Alzheimer’s disease (AD). The

common feature of these untreatable, fatal diseases is that tau homeostasis is imbalanced, resulting in its accumulation and aggregation. Thus, a potential way to treat them is to enhance the flux of tau through the proteasome. During aging, the capacity of the proteasome pathway appears to deteriorate, potentially creating conditions that favor abnormal tau accumulation. It has recently been observed that many cells, including neurons, contain substantial pools of 20S proteasome that are not fully activated. We hypothesize that these “latent” pools could be mobilized to enhance tau turnover. Indeed, it is already known that microinjection of active proteasome or over-expression of proteasome subunits speeds the clearance of tau. Now, we propose to develop small molecules that are potent and selective agonists of the 20S proteasome. Towards this goal, we have used structure-based methods to identify small molecules that bind to the allosteric sites on the 20S proteasome that are responsible for “gating” the entry of substrates. NMR studies showed that the lead molecules bind to the intended sites and EM studies show that, consistent with the design, they “open” the 20S proteasome. Strikingly, we found that these molecules stimulate proteasome activity between 8 to 20-fold in vitro. The lead molecule also accelerated turnover of disease-associated tau in cell-based models, consistent with the model. The next critical step in this project is to (SA1) pursue the structure-guided, hit-to-lead optimization of the chemical series and (SA2) characterize the relationships between the 20S proteasome and tau homeostasis. This work is significant because it will provide new chemical probes for use in understanding tau homeostasis, potentially validating the 20S as a new drug target for tauopathies. The work is innovative because it employs cutting-edge computational, structural and experimental approaches to generate allosteric agonists of an important enzyme.

Further information available at:

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Investments < €500k

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