**Dr. Stefanie Flohr, Novartis**

**December 9th, 2024, 5PM (Berlin time, CET)**

**Registration link:**

<https://us06web.zoom.us/webinar/register/WN_x8pQLUeESsSO568YgVhtQw>

**Identification and Optimization of Novel GPR126 Positive Allosteric Modulators - targeting a highly lipophilic cavity at the TM/lipid bilayer interface**

The adhesion receptor GPR126 has been reported to have a critical role in Schwann cell function during peripheral nerve regeneration [1]. To date, only agonistic tool compounds which allow to study function of the receptor have been reported.

In an HTS campaign with the Novartis compound collection, several positive allosteric modulators (PAMs) for GPR126 were identified, which are so far unprecedented in literature. These PAMs are characterized by high logD values (>5) which led to very low solubility and restricted their usefulness as in vivo tool compounds. Cryo-EM analysis of the HTS hit elucidated its binding site at the interface of TM5-7 to the lipid bilayer. Despite the high lipophilicity of the PAM binding site, efforts were made to reduce lipophilicity and plasma protein binding of the PAMs to identify compounds suitable for in vivo studies. A knowledge based computational analysis identified several hotspots for weakly polar groups in the PAM binding site. This information was used to further optimize the PAM series. In addition, we used the chromatographic %HSA as a surrogate [2], which proved to be a valuable parameter for efficiently monitoring changes in the highly lipophilic compound series.

By employing these approaches, we identified the first known orally in vivo active PAMs with nanomolar activity, high alpha shifts and logD values less than 4.

[1] J. Neurosci 2017; 37 (12) 3106-3108.

[2] J. Pharm. Sci. 2003; 92 (11), 2236-2248.

**Dr. Christina Lamers, University Leipzig**

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**Structure-activity and structural determinants of compstatins, first in class cyclic peptides complement C3 inhibitors**

Despite the growing recognition of aberrant complement activation as contributor to various clinical conditions, the arsenal of available complement therapeutics has long been limited. It was only in May 2021 that, with pegcetacoplan (Empaveli, Apellis), a second class of complement-specific drugs has been approved by the FDA. Pegcetacoplan is based on a second-generation analog (i.e., Cp05) of the peptidic C3 inhibitor compstatin, which was originally identified at the University of Pennsylvania in 1996. Meanwhile, the compstatin family has grown impressively and several derivatives have reached clinical development. Among those is Cp40 (AMY-101, Amyndas), a third-generation analog with prolonged target residence that omits the PEGylation used in pegcetacoplan.

In this study, we combined a newly resolved co-crystal structure of Cp40 in complex with C3b with molecular dynamics simulations and direct binding studies using a panel of compstatin derivatives to arrive at a detailed structure-activity-relationship profile. Using a surrogate of pegcetacoplan (i.e., Cp05-PEG-Cp05) we compared target binding modes of mono- and bivalent compstatin derivatives. Finally, we provide a more detailed insight into the mode-of-action of Cp40. The results of our study may guide the future development of a promising class of complement inhibitors.