**Dr. María Méndez Pérez**

**June 24th, 2025, 5PM (Berlin time, CET)**

**Registration link:**

<https://us06web.zoom.us/webinar/register/WN_TDmE49HdSSuFrlNZs6Nk_Q>

**Discovery and optimization of a new class of RIPK1 inhibitors enabled by late-stage photoredox catalysis**

Receptor Interacting Protein Kinase 1 (RIPK1) plays a crucial role in regulating necroptosis and inflammation and the potential therapeutic benefits of RIPK1 inhibitors are being investigated in several clinical trials.1 ,2 We will describe the discovery and optimization of a new series of highly potent and selective RIPK1 inhibitors, that were identified by combining structure-based approaches, free-energy perturbation (FEP+) and state-of-the-art machine learning approaches for property predictions. Using X-ray crystallography, we could confirm that the inhibitors bind as allosteric type III inhibitors, thereby not contacting the kinase hinge region. We will illustrate how a C(sp3)-C(sp2) photochemical transformation was a key enabler for the efficient SAR exploration and profile optimization.



Literature:

[1] Zhang. Y. et al. Eur. J. Med. Chem. **2024**, *265*, 116123. Lessene, G. et al. J. Med. Chem. **2023**, *66*, 2361. [2] He, S., Wang, X. RIP kinases as modulators of inflammation and immunity. Nat Immunol **2018**, 19, 912.