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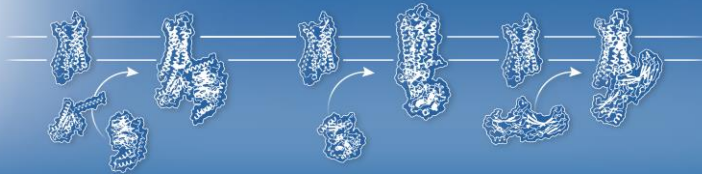
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Session 2:

Characterization of a novel orally bioavailable NPFF receptor antagonist for the treatment of opioid-induced hyperalgesia and analgesic tolerance

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Chronic pain is a major public health problem in humans for which current treatments often prove to be ineffective and display adverse side effects. In the United States, the massive use of opioids for the treatment of chronic pain led to more than 500 000 deaths by overdose over the last fifteen years highlighting the urgent need to develop new therapeutic strategies for pain relief. Neuropeptide FF receptors (NPFF1R and NPFF2R) and their endogenous ligand neuropeptide FF have been shown previously to display anti-opioid properties and to play a critical role in the adverse effects associated with chronic administrations of opiates. We describe here the design and optimization of a drug-like orally active NPFFR ligand called RF1359 that display nanomolar affinity and potent antagonist activity for NPFF1R subtype. It displays promising properties for future drug development in terms of metabolic stability, pharmacokinetic profile, solubility, selectivity and safety profile. In naïve mice, the pharmacological blockade of NPFF receptors with RF1359 efficiently prevents the development of morphine-induced hyperalgesia while preserving its analgesic effect over chronic administration. Moreover, when evaluated in two different clinically relevant models of pain, RF1359 significantly improved morphine-induced analgesia allowing to reduce morphine dose and thus potential adverse side effects associated with chronic morphine. Altogether, our data indicate that RF1359 represents a promising lead compound for the development of therapeutic agents that could improve opiates efficacy upon chronic administration and limit adverse side effects.