CYCLE DE CONFÉRENCES DE CHIMIE

Avec le concours de : Université Clermont Auvergne
INP Clermont Auvergne

Jeudi 16 décembre à 16 h

Amphi 9111 – Pôle Physique

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Discovery of first-in-class extracellular FLT3 inhibitors for the treatment of neuropathic pain: From hits to a clinical candidate

We recently identified the FLT3 receptor tyrosine kinase as a key target in triggering and maintaining chronic neuropathic pain [1]. A first in silico screening of 5 million commercially available compounds led us to identify the very first extracellular inhibitors of this receptor, which have been optimized by medicinal chemistry to BDT001, the first specific FLT3 negative allosteric modulator (NAM) able to completely reverse neuropathic pain in rodents [1]. To find potential back-ups to BDT001, we undertook the experimental screening of the French Compound Library (45000 compounds) thanks to an in vitro time-resolved FRET assay. The HTS assay yielded 110 hits from 10 different chemical series whose developability has been determined by early absorption-distribution-metabolism-excretion-toxicity (ADMET) studies of representative hits. Three chemical series, with a strong oral bioavailability potential, have been prioritized for medicinal chemistry hit to lead optimization. Like BDT001, these compounds are NAMs of the FLT3 receptor tyrosine kinase and exhibit anti-hyperalgesic properties in mice. Parallel optimization of potency, ADMET and early safety properties leads to BDT4046, a FLT3 NAM representing a first-in-class series of novel analgesic compounds to treat neuropathic pain with a long-lasting duration of action, a clear superiority to standard of cares (antiepileptics, antidepressants).

[1] Rivat et al. *Nat. Commun.*, 2018, **9**, 1042

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