56. CSF1-Receptor Inhibitors

(Lead Discovery Center)

Asset Overview

Product Type	Small molecule
Disease Area	Inflammation
Indication	Neuroinflammation and Inflammation
Current Stage	Lead Optimization
Target	CSF1-Receptor
MoA	CSF1R inhibition
Brief Description	• As a potential target for many indications, CSF1R inhibition results in a reduction of the CSF1R dependent kinase phosphorylation, proliferation, and pro-inflammatory cytokine production, e.g., in primary murine microglia • During inflammation, the CSF1-Receptor is upregulated in several preclinical murine models of neuroinflammation and neurodegeneration - NTNU & LDC primarily focus on (neuro)inflammation • Inflammation is a common neuropathological feature in several neurological disorders (e.g., ALS, TBI) • Objective: Generation of BBB permeable, potent, effective and selective CSF1R inhibitors to prevent neuroinflammation
Intellectual Property	-
Publication	-
Inventors	Bård Helge Hoff, Geir Bjørkøy, Eirik Sundby – Norwegian University of Science and Technology (NTNU), Trondheim/Norway Clare Pridans - University of Edinburgh (UoE), UK

Highlights

- Rational and structure-based inhibitor design resulted in very promising hit classes for H2L → ~170 analogues to date (co-crystal structure available)
- Ex vivo profiling in M-CSF induced macrophage pERK assay: 20 best compounds with IC50 values <200nM
- eADMET profiling: good stability and clearance values (human microsomes), no in vitro cytotoxic effects up to 30µM
- Binding mode identified: stabilization of inactive conformation – different MoA compared to active site competitors
  → Excellent selectivity profile (DiscoverX panel)
- In vivo PK studies revealed a frontrunner compound with an excellent brain penetration

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Key Data

CSF1-Receptor (CSF1R) Inhibitors