Lead Discovery Center LDC

NTNU

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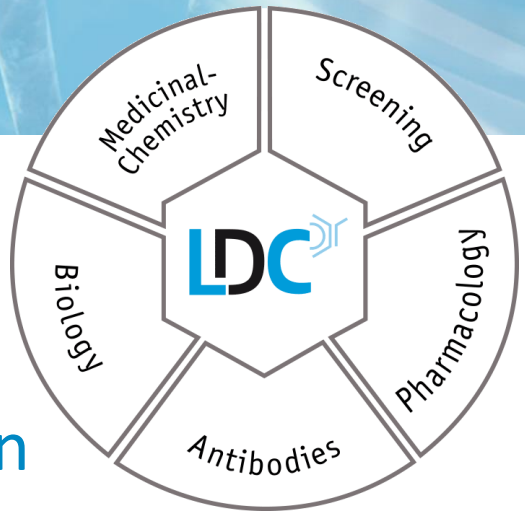
KHAN-I

CSF1-Receptor Inhibitors

Neuroinflammation and Inflammation



CSF1-Receptor (CSF1R) Inhibitors

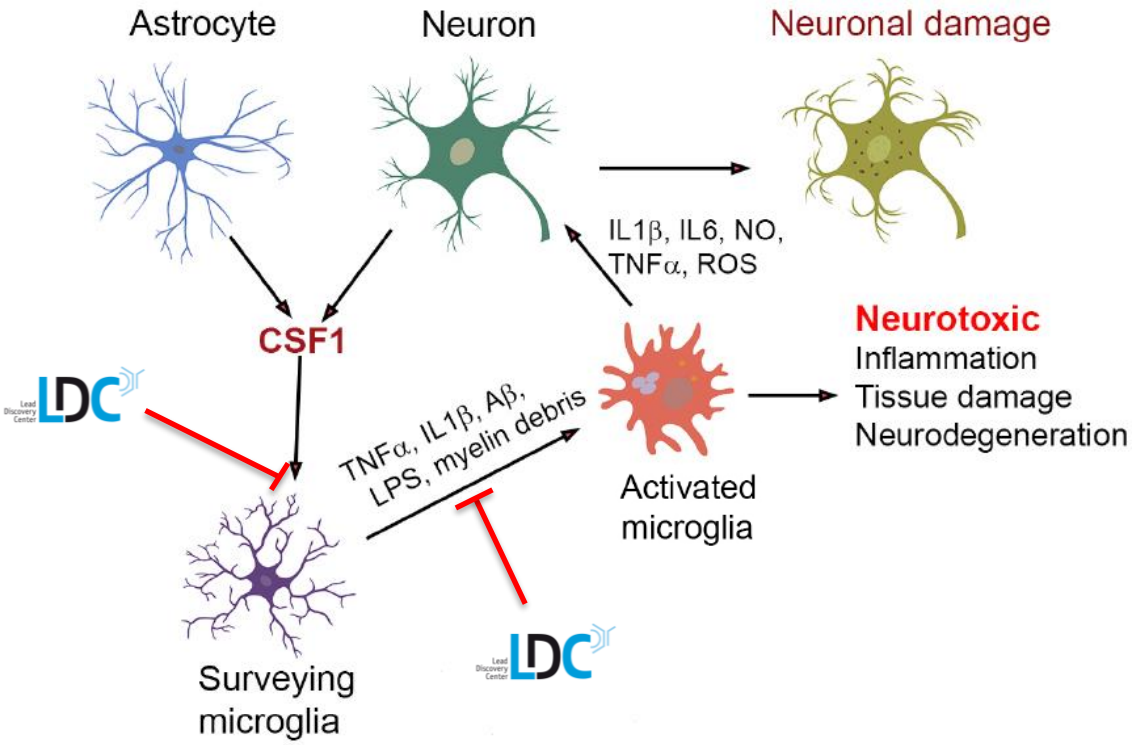


Fig. adapted from Bo et al. 2022, NRR., 17 (4)

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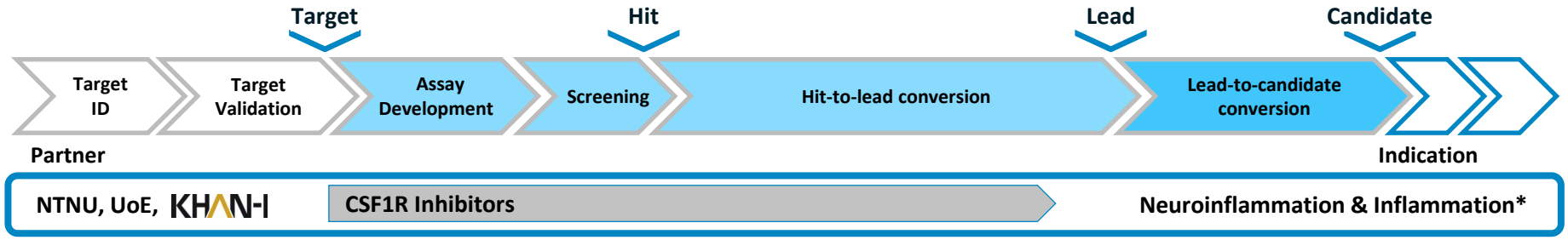
CSF1R Inhibitors: Executive Summary



** upside potential: osteoporosis, cancer, CMT1X*

- **Target rationale**
  - *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*
- **Key achievements & USPs**
  - *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 IC_{50} 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*
- **Current activities & next steps**
  - *In vitro efficacy on microglia viability, broad selectivity profiling, PoC in vivo model selection*

*** Geladaris et al., Int. J. Mol. Sci. 2021, 22(7), 3461.*

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