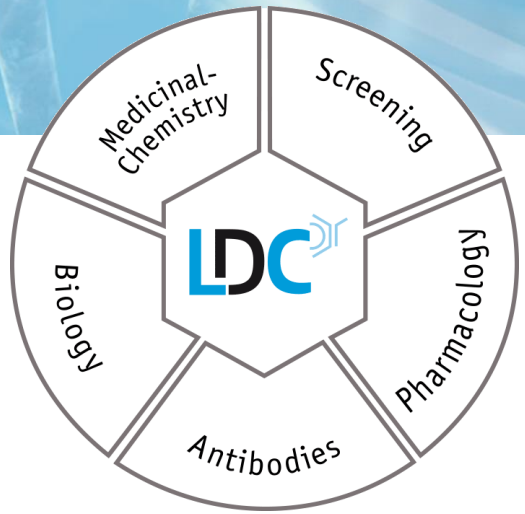
Lead Discovery Center LDC

MAX-PLANCK-GESELLSCHAFT

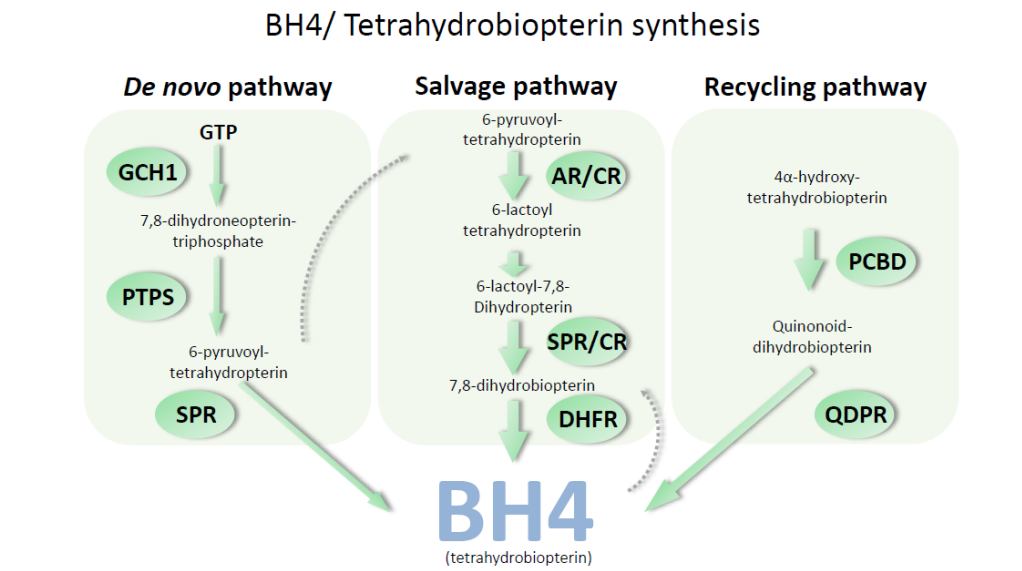
KHAN-I

PAVING THE WAY FOR INNOVATIVE MEDICINES

SPR-Inhibitors in the field of Neuropathic Pain with an upside in Inflammation/Autoimmune



SPR (BH4) – Inhibitors



GCH1: GTP cyclohydrolase I

PTPS: Pyruvoyl tetrahydrobiopterin synthase

SPR: sepiapterin reductase

AR: Aldose reductase

CR: Carbonyl reductase

DHFR: Dihydrofolate reductase

PCBD: Pterin-carbinolamine dehydratase

QDPR: quinoid dihydropteridine reductase

Partners:

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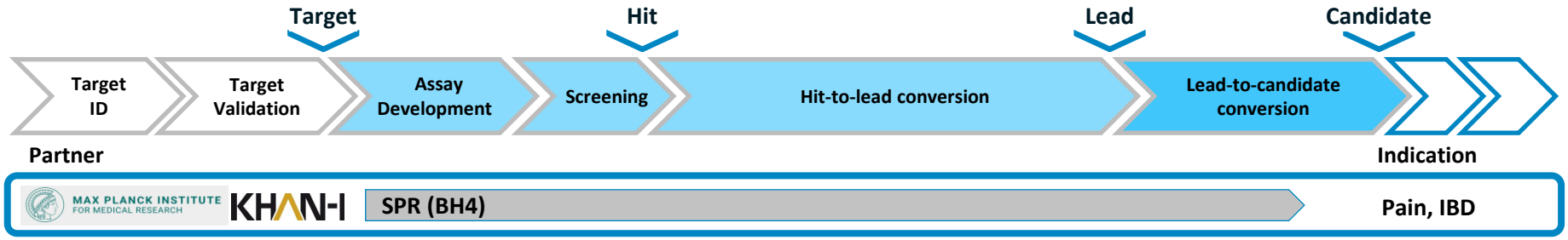
SPR Inhibitors: Executive Summary



- **Target rationale**
  - ***Basic principle**: Tetrahydrobiopterin (BH4) critically involved in nociceptive signalling*

  → humans: gene-variants of GTP cyclohydrolase 1 (rate-limiting step in BH4 synthesis) effectively modulates pain

  → (i) BH4 levels increased in injured sensory neurons, (ii) BH4 induces nitric oxide (NO) biosynthesis, (iii) NO important transmitter involved in nociceptive processes, (iv) blockade of sepiapterin reductase (SPR) effectively blocks BH4 production (in vitro & in vivo validation)
  - ***Objective**: Generation of next generation (peripherically restricted) SPR inhibitors*
- **Key achievements & USPs**
  - *Access to highly potent SPR inhibitors (lead optimization stage and compound series comprising ~2.000 cpds)*
  - *In-depth characterization of small selection of compounds: PK/PD, ADME, toxicology (mouse, rat, limited dog and NHP data)*
  - *Identification of peripherally restricted frontrunner leads from PK dog-study for candidate nomination experiments (tolerability, MTD, RDT, allometric scaling, etc.)*
  - *In vivo efficacy (Proof of concept) with next generation SPR inhibitors demonstrated in SNI and post-operative pain models*
- **Current activities & next steps**
  - *In vivo experiments to achieve preclinical candidate (PCC) nomination in progress*
  - *Exploration of other applications in the area of inflammation (e.g. IBD) in progress*

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