Kv1.3 inhibitors: en route to clinical trials
Stefan Tasler, Tobias Dreker, Ilga Krimmelbein, Svetlana Hamm
4SC Discovery GmbH, Am Klopferspitz 19a, 82152 Planegg-Martinsried, Germany

Screening for Kv1.3 inhibitors: vHTS and conventional E-Phys
- Two docking approaches (homology models using KcsA and Kv1.2), additional pharmacophore alignment
- Proprietary tool 4SC's Kv1.3 inhibitors are highly efficacious in autoimmune disease animal models (PIA, EAU, ACD)
  

Kv1.3 and autoimmune diseases
- Kv1.3 and IK-1 are crucial K+ channels in calcium signaling / proliferation of T-lymphocytes
- Activation state and type of T-cell subset define expression numbers for these K+ channels
- Targeting K+ channels should be effective in suppressing distinct subsets of activated T-cells
- Inhibition of Kv1.3 targets disease relevant Treg cells while leaving other immune responses intact
- Treatment of autoimmune diseases: multiple sclerosis, diabetes type 1, psoriasis, rheumatoid arthritis, uveitis

Efficacy in autoimmune disease animal models
- Pristane-induced arthritis (PIA): Class II vs. Class III
  - p.o. administration, 60 mg/kg for KV07, 45 mg/kg for KV07
  - readout: alteration of Arthritic Index (AI)

Data collection: Leads and Optimized Leads (OL)

Unique Selling Point
- KV07 (Class III): repeated oral dosing of 30 mg/kg once daily for 14 days or of 45 mg/kg twice daily for 31 days well tolerated
  - no injection was observed
- OL1 (Class II): repeated oral dosing of 80 mg/kg twice daily for 31 days well tolerated
  - no effect observed on clinical biochemistry [4]
- OL1 does not affect innate immunity and naive T-cells (= USP)

Safety
- OL1 (Class I):
  - Camp Safety Screen 44 @ 1 µM compound concentration
    - no effect on the viability of HEK293 cells
    - no effect on the viability of Caco2 cells
    - no effect on the viability of HepG2 cells
  - no effect on the viability of PBMCs
  - no effect on the viability of unstimulated PBMCs
  - no effect on the viability of unstimulated PMBCs

Well tolerated upon repeated oral administration
- Good to excellent selectivity towards a variety of different target classes
- OL1 does not affect innate immunity and naive T-cells (= USP)