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

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 4SCan®: Screening of virtual library of 6.6 Mio commercially available compounds
- Manual patch clamp assay (gold standard): high quality functional data, high temporal resolution
- High content information → state- and use-dependent block mechanisms

Data collection: Leads and Optimized Leads (OL)

- PK data, p.o. administration, male Wistar rat
- Compounds Class II

Kv1.3 homology model based on bacterial KcsA

Safety

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

Unique Selling Point

- OL1 (Class II): no inhibitory effect on activation of innate immune cells (marker CD69) and their cytokine release in response to pathogen-like stimulus (via TLR) [1,2]
- OL1 (Class II): repeated oral dosing of 30 mg/kg once daily for 15 days or of 45 mg/kg twice daily for 31 days was well tolerated
- Tolerability
  - Exacerbation study in rats: 10 mg, p.o., sid, 4 days = well tolerated
  - no effect observed on clinical and histopathological score

Efficacy in autoimmune disease animal models

- Pristane-induced arthritis (PIA): Class II vs. Class III
  - p.o. administration, 60 mg/kg for KV07
  - readout: alteration of arthritis index (AI)

- Experimental autoimmune uveitis (EAU): Class III
  - p.o. administration, 60 mg/kg, sid for KV07
  - readout: alteration of clinical and histopathological score

- Allergic contact dermatitis (ACD): Class II
  - topical application, 2% cream of KV08
  - readout: ear swelling

OL1 (Class II)

- Topical application, 2% cream of KV08
  - readout: ear swelling

4SC’s Kv1.3 inhibitors are highly efficacious in autoimmune disease animal models (PIA, EAU, ACD)
- Efficacious upon oral and topical application
- Dose-dependent effect
- Therapeutic treatment regimen as efficacious as prophylactic

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Kv1.3 inhibitors: en route to clinical trials