AMPD2. Using HEK293, surface AMPD2 expression was reduced after Golgi transport inhibition. AMPD2 surface expression was not accompanied by enhanced cell death. Expression of AMPD2 could be confirmed in membrane fractions of HEK293 using immunoblot of precipitated AMPD2 and mass spectrometry, respectively.

Conclusions: Here, we demonstrate for the first-time surface expression of AMPD2 on immune cells enabling these cells to extracellularly convert AMP into IMP constituting a shunt-like mechanism to control the levels of adenosine and extracellular ATP formed from adenine nucleotides thereby controlling immunomodulation.

Disclosure of Interest: None declared

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SAT0039

LL37 UP-REGULATION AND ANTI-LL37 REACTIVITY ARE SHARED BY PSORIASIS AND PSORIATIC ARTHRITIS PATIENTS

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Background: The antimicrobial peptide LL37 plays a pathogenic role in psoriasis (Pso) due to its adjuvant and auto-antigenic properties. At least a third of Pso patients develop psoriatic arthritis (PsA) but mechanisms that lead PsA development in Pso patients remain elusive.

Objectives: To understand the role of LL37 in PsA pathogenesis and its relationship with inflammatory molecules IFN α , GM-CSF, C5a.

Methods: Blood samples were collected from 32 biologic-naïve PsA, 12 active Pso (without PsA) patients and 8 healthy donors (HD). Synovial fluids (SF) were collected from 17 PsA and 12 osteoarthritis (OA) patients. Synovial biopsies from 3 biologic-naïve PsA patients were studied by confocal microscopy. Native-LL37 was synthesised and carbamylated LL37 (LL37carb) produced by incubating LL37 with 1 M potassium cyanate and verified by dot-blot assay. Antibodies to native-LL37/LL37carb and levels of LL37, GM-CSF, IFN α and complement C5a were measured by in-house and commercial ELISA tests, respectively, in SF and plasma.

Results: High LL37 levels were detectable in SF of PsA compared to OA. Anti-LL37 [24% in SF (4/17)] and anti-LL37carb antibodies [47% in SF (8/17), 46% in plasma (15/32)] were present in PsA but not in OA and HD. Anti-LL37carb antibodies [41% (5/12)] were also detectable in Pso plasma. IFN α was present in 37% of SF PsA (7/16; not detectable in OA) and correlated with C-reactive Protein (CRP); GM-CSF and C5a levels were significantly higher in SF PsA than in SF OA. Notably, GM-CSF was also detectable in 40% and 30% of PsA and Pso plasma, respectively, but not in HD; Plasma C5a levels were comparable between PsA and Pso and significantly higher than in HD. SF GM-CSF correlated with anti-LL37carb autoantibodies. Anti-LL37carb antibodies correlated with levels of C5a in Pso and PsA plasma. In synovial tissues of PsA the expression of the IFN-related gene MX1 was highly up-regulated in close proximity of neutrophil markers myeloperoxidase and LL37.

Conclusions: LL37 and, in particular, LL37carb is the target of autoantibodies that correlate with pro-inflammatory GM-CSF and C5a in both Pso and PsA, suggesting immunological pathways in common between psoriasis and psoriatic arthritis.

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SAT0040

SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF BCD-089, NOVEL MONOCLONAL ANTI-IL-6 RECEPTOR ANTIBODY: RESULTS FROM THE FIRST-IN-HUMAN SINGLE DOSE ESCALATION STUDY IN HEALTHY VOLUNTEERS

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Background: BCD-089 is a fully human monoclonal antibody targeting membrane-bound and soluble forms of IL-6R α , thereby blocking of IL-6 classic and trans- signalling. IL-6, a proinflammatory cytokine, plays a central role in the pathogenesis of many chronic inflammatory and autoimmune diseases. Thereby inhibition of IL-6 signalling is a promising approach in the treatment of immune-mediated pathology.

Objectives: To assess safety, immunogenicity, pharmacokinetics and pharmacodynamics of a single administration of BCD-089.

Methods: This was a phase I, open label, single ascending dose clinical study in healthy male volunteers, aged 22–37 years (n=19). In 1 st cohort, one «sentinel» volunteer received 0.006 mg/kg of BCD-089. Volunteers in cohorts 2–7 received single doses of BCD-089 0.3, 0.625, 1.0, 1.6, 2.2 and 2.9 mg/kg, respectively. Every next cohort was included after completed safety evaluation for the previous one. Safety, PK/PD and immunogenicity were assessed during 71 days follow up.

Results: All enrolled subjects have completed follow up period of 71 days. No withdrawals occurred. Single SC administration of BCD-089 was well tolerated and showed good safety profile at all tested doses: no grade 3/4 AEs, SAEs, DLTs or allergic reactions were reported in any cohort. None of the volunteers developed ADA to BCD-089. The only AEs reported were grade 1 or 2 laboratory abnormalities.

Abstract SAT0040 – Table 1. Subjects with abnormal test results, n (%). Table shows only cohorts where at least one abnormal test result was reported.

Adverse events	0.3 mg/kg (n=3)	0.625 mg/kg (n=3)	1.0 mg/kg (n=3)	2.2 mg/kg (n=3)	2.9 mg/kg (n=3)
Grade 1 WBC decrease	-	-	1 (33.3%)	2 (66.6%)	1 (33.3%)
Grade 1 neutropenia	-	-	1 (33.3%)	1 (33.3%)	-
Grade 2 neutropenia	-	-	-	1 (33.3%)	1 (33.3%)
Grade 2 t.bilirubin increase	-	1 (33.3%)	-	-	-
Grade 1 AST decrease	1 (33.3%)	-	-	-	-
Grade 1 Creatinine decrease	-	1 (33.3%)	-	-	-

Single SC administration of BCD-089 had a dose-dependent PK: the drug became detectable in the serum within the first 12 hour after injection for all tested doses (2–8 hour for doses>1.0 mg/kg). Serum concentration dose-proportionally increased and reached maximum at day 3 after administration, then gradually decreased. Elimination half-life showed significant inter-personal variability and dose-dependency, reflecting non-linear PK typical for drugs with target-mediated disposition.

Abstract SAT0040 – Figure 1. BCD-089(A), sIL6R(B), IL6(C) and CRP(D) serum concentration (Median and IQR).