Methods: The retrospective clinical characterisation of 14 male and 57 female SSc patients (26–82 years) included mRSS, organ involvement assessed by laboratory tests, spirometry and imaging such as CT-scan or echocardiography. 30/71 had active disease (EUSTAR activity score). Ab were measured by ELISA and normalised to a standard serum. Median ab levels from SSc were compared to HC (Mann Whitney Test). Ab patterns were analysed using different statistical approaches (factor analysis, principal component analysis (PCA), linear discriminant analysis (LDA), cluster analysis and biserial correlation).

Results: Clinical SSc subgroups (diffuse/limited cutaneous, male/female) differ in ab levels and form separate clusters (LDA method). Moreover, 5 resp. 7 latent factors group ab and clinical disease manifestations. Factor analysis reveals VEGFR2 and YBX1 ab to be more unique with the lowest communalities. The biserial correlation shows moderate associations between ab patterns and SSc specific symptoms such as Raynaud's, calcinosis or akroosteolysis but also unspecific symptoms such as polyneuropathy. Compared to association of ETAR ab with Raynaud's and skin sclerosis HGFR ab are inversely correlated. In HC most ab levels against GPCR and growth factors are higher than in SSc except for YBX1 which has the highest ab levels in SSc patients. In HC ab levels against YBX1 ab are associated with male sex and family history of rheumatic diseases. Yet, ADRB2 ab are linked to the absence of GI symptoms or depression and ab against ENG, ETAR, PAR2, PAR1 with normal troponine levels (absence of heart involvement).

Abstract OP0005 – Figure 1. (a) Projection of individuals (points) and variables (arrows), representing the measured proteins, in the space of the two principle components. The almost perfect separation between controls (cyan) and cases (orange) is explained by higher protein levels for almost all proteins in the HD groups against lower values in the SSc group. By contrast, only the YBI_P18 protein presents a tendency to be higher in the SSc group and lower in the other group. *M1* and *betaladr* proteins have lowest contributions for separating HG from SSc participants. (b) Dandelion plot displays 5 latent factors the cluster antibodies against GPCR and growth factors in SSc

Conclusions: We describe 31 new ab against GPCR and growth factors in SSc. Ab as well as SSc disease manifestations could be clustered by latent factors. Most ab titers in SSc were lower than in HC. Some ab were linked to the absence of SSc manifestations. Thus, we postulate that a dysbalance of functionally protective autoantibodies, that can be found in healthy individuals, and the appearance of SSc specific ab such as Scl70 contribute to its pathogenesis. Considering the preliminary character of our data, the functional impact of ab against GPCR and growth factors has to be validated *in vitro* and statistical correlations to be confirmed in a prospective independent patient cohort.

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OP0006

SAFETY AND EFFICACY OF LENABASUM (JBT-101) IN DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS SUBJECTS TREATED FOR ONE YEAR IN AN OPEN-LABEL EXTENSION OF TRIAL JBT101-SSC-001

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Background: Lenabasum (JBT-101) is a selective cannabinoid receptor type 2 agonist that activates resolution of innate immune responses in humans and reduces inflammation and fibrosis in animal models of SSc. It is a synthetic, oral, non-immunosuppressive small molecule. Lenabasum had acceptable safety and tolerability and showed evidence of clinical benefit in diffuse cutaneous SSc (dcSSc) in Phase 2 trial JBT101-SSC-001 (NCT02465437).

Objectives: The objective of this study was to provide long-term open-label safety and efficacy data in dcSSc subjects who received lenabasum in that trial.

Methods: Subjects who completed the double-blind placebo-controlled (DBPC) part of JBT101-SSC-001 were eligible to receive lenabasum 20 mg BID in an open-label extension (OLE).

Results: 36/38 (95%) eligible subjects enrolled in the OLE and 34/36 (94%) were on baseline immunosuppressive drugs. The mean interval off study drug from the end of DBPC dosing to the start of OLE dosing of 9.5 weeks (range 4.7 to 56 weeks). At the time of data cut-off, the duration of OLE dosing was median 51.4 weeks, mean 45 weeks (range 26, 418 weeks), and 19 subjects had completed Week 60. Three subjects discontinued, 2 for AEs and 1 for withdrawal of consent. Adverse events (AEs, n=171) occurred in 33/36 (92%) subjects in the OLE. By maximum severity, 1 (3%) subject had life threatening AE, 3 (8%) subjects had severe AEs, 21 (58%) subjects had moderate AEs and 8 (22%) had mild AEs. Seven (19%) subjects had AEs considered related to lenabasum. The AEs that occurred in ≥10% of subjects (n,% of subjects) were upper respiratory tract infection (8, 22%), urinary tract infection (5, 14%), diarrhoea (4, 11%) and skin ulcers (4, 11%). Mild intermittent dizziness occurred in 3 (8%) subjects. One subject developed renal crisis 7 days after starting 60 mg/day prednisone prescribed by a non-study physician and had 2 severe and 1 life-threatening/serious AEs related to the renal crisis and deemed unrelated to lenabasum. During the OLE, there was improvement in multiple efficacy outcomes from both the study start and the OLE start. For example, in the 25 subjects who had completed OLE Week 52 at the time of data cut-off, the mean (SE) improvements from study start were: ACR CRIS score=56% (9%); modified Rodnan Skin Score=-8.6 (1.5); HAQ-DI=-0.14 (0.11), Physician Global Assessment=-0.9 (0.5), and 5-D Itch Questionnaire=-2.3 (0.8). Forced vital capacity% predicted was stable from study start with mean (SE) change=0.4% (0.7%).

Conclusions: In OLE of Phase 2 trial JBT101-SSC-001, lenabasum continues to have acceptable safety and tolerability in dcSSc with no severe or serious AEs. Multiple efficacy outcomes improved, although open-label nature of dosing with lenabasum is acknowledged. These data support Phase 3 testing of lenabasum for treatment of dcSSc.

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Basic mechanisms of inflammation

OP0007

GROWTH DIFFERENTIATION FACTOR 11 ATTENUATES INFLAMMATORY ARTHRITIS THROUGH ANTAGONISING NF-KB SIGNALLING PATHWAY

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Background: It is well established that the tumour necrosis factor- α (TNF- α) plays a dominant role in rheumatoid arthritis (RA)¹ and other arthritis models.^{2,3} Growth Differentiation Factor 11 (GDF11) is recently reported to be closely

associated with various inflammatory diseases. However, whether GDF11 interacts with TNF- α and plays a role in RA still remains unknown.

Objectives: To investigate the potential role of GDF11 in development of RA, and to testify the underlying mechanisms involved.

Methods: NF- κ B-luciferase transgenic mice (Balb/c strain), DBA-1 mice, micro-CT, *in vivo* imaging system (IVIS), mice bone marrow-derived macrophages (BMDM), cell immunostaining, collagen induced arthritis model (CIA), collagen antibody induced arthritis model (CAIA), GDF11 recombinant protein, co-immunoprecipitation Co-IP, Western blot, real time PCR, Histology, immunohistochemistry, unpaired t-tests (Mann-Whitney), paired t-tests, and ANOVA.

Results: The interaction between GDF11 and TNFR1/TNFR2 in BMDM was implied by co-immunoprecipitation (Co-IP) (figure 1A-B). BMDM cells were cultured with stimulation of 10 ng/ml TNF- α , in the presence or absence of 10 μ g/ml GDF11. Inflammation-associated cytokines, including IL-1 β , IL-6 and inducible nitric oxide synthase (iNOS) were assessed at 12 hour time point through real time PCR (figure 1C-1E), and expression level of IL-1 β was assayed through ELISA at 72 hour time point (figure 1F). As a result, GDF11 suppressed TNF- α -induced expression of inflammatory cytokines. Every experiment was repeated for three times. Collagen-induced arthritis (CIA) mice model was established in DBA-1 mice, and intraperitoneal injection of GDF11 attenuated clinical score (figure 2A), synovitis, pannus and bone erosion (figure 2B-2D) compared with PBS control group (n=7 for each group). Representative pictures of the paw (figure 2E), micro-CT (figure 2F) as well as HE staining (figure 2G) revealed that GDF11 greatly suppressed joint destruction in CIA model. In addition, GDF11 inhibited TNF- α -induced expression of biomarkers for activation of NF- κ B signalling pathway, including NF- κ B2 (figure 3A), phosphorylation of I κ B α (figure 3B) and nuclear translocation of p65 (figure 3C) in BMDM, which were tested through real time PCR, Western blot and cell immunostaining, respectively. To testify the function of GDF11 in activation of NF- κ B signalling pathway *in vivo*, p-I κ B α expression was detected through immunohistochemistry in CIA model, and GDF11 diminished phosphorylation of I κ B α (figure 4A) compared with PBS group (n=5). Moreover, CAIA arthritis model was established in BALB/C strain-based NF- κ B luciferase mice, and GDF11 markedly repressed intensity of bioluminescence signal in the paws of CAIA model (figure 4B-4C). The values are the mean $\pm$ SD. *p<0.05, **p<0.01 and ***p<0.005 vs control group.

Conclusions: These results reveal GDF11 as potential antagonist for inflammatory function of TNF- α . Besides, GDF11 displays promising protective function in inflammatory arthritis mice models. In conclusion, GDF11 may shed light on treatment of inflammatory arthritis and provide a potential therapeutic instrument for RA in the future.

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OP0008 MODELLING AN AUTOINFLAMMATORY IMMUNOPROTEASOME DISEASE NAKAJO-NISHIMURA SYNDROME WITH HUMAN PLURIPOTENT STEM CELL-DERIVED MYELOID CELL LINES

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Background: Nakajo-Nishimura syndrome (NNS) is an immunoproteasome-associated autoinflammatory disorder caused by a mutation of PSMB8 gene.¹ Although dysfunction of immunoproteasome causes various cellular stresses attributed to the overproduction of inflammatory cytokines and chemokine in NNS, precise underlying mechanisms of autoinflammation are still largely unknown.

Objectives: We aim to investigate and understand the detailed mechanisms and signal pathways in NNS and to seek potential therapeutic candidates.

Methods: We established a panel of isogenic pluripotent stem cell (PSC) lines with the homozygous G201V mutation in PSMB8 gene using CRISPR/Cas9-mediated genome editing system. Myeloid cell lines (MLs) were established from each clone and used for functional analysis.^{2,3}

Results: Immunoproteasome activity of PSMB8-mutant PSC-derived MLs (MTMLs) reduced even without stimulation, compared to that of the isogenic wild-type counterparts. When stimulated, MT-MLs showed overproduction of inflammatory cytokines and chemokines, with elevated reactive oxygen species (ROS). The levels of phosphorylated p38 MAPK and STAT1 also increased. Treatment with a p38 MAPK inhibitor, a JAK inhibitor and anti-oxidants dose-dependently decreased the abnormal production of cytokines and chemokines in MT-MLs. Both unstimulated and stimulated MT-MLs showed distinct transcriptional profiles, indicating the ML-MLs were already in a 'primed' state before stimulation.