counts (α -SMA staining) and of 23 serum inflammatory cytokines/chemokines (Mouse-Cytokine-23-plex, Bio-Rad-Laboratories).

Results: 17-DMAG decreased dermal thickening by $53\pm 3\%$ ($p<0.001$) (nintedanib by $46\pm 2\%$, $p<0.001$), collagen content by $48\pm 5\%$ ($p=0.004$) (nintedanib by $50\pm 4\%$, $p=0.003$), myofibroblast counts by $42\pm 9\%$ ($p<0.001$) (nintedanib by $44\pm 7\%$, $p<0.001$), and levels of IL-1 α , IL-6, IL-12(p40), CXCL1, MCP-1, MIP-1 α/β , RANTES (in all: $p<0.05$) compared to vehicle-treated mice injected with bleomycin for 6w. Moreover, 17-DMAG also induced regression of pre-established fibrosis to below the levels of vehicle-treated mice injected with bleomycin for 3w and NaCl for 3w (dermal thickness by $14\pm 3\%$, collagen content by $20\pm 5\%$, myofibroblast counts by $13\pm 9\%$; whereas in nintedanib by $10\pm 3\%$, $21\pm 4\%$, $17\pm 7\%$, respectively; in all: $p<0.05$), and levels of IL-12(p40), CXCL1, MCP-1, MIP-1 β , RANTES (in all: $p<0.05$). No significant weight loss, decrease in activity or changes in fur texture were observed upon 17-DMAG treatment.

Conclusion: This is the first study on effects of Hsp90 inhibitor 17-DMAG in the treatment of established dermal fibrosis. We demonstrate that 17-DMAG effectively prevents the progression and induces regression of established bleomycin-induced dermal fibrosis, in an extent that was comparable to nintedanib in this study (which was recently FDA approved for slowing the rate of decline in lung function in adults with SSc-ILD). 17-DMAG was well tolerated without obvious clinical signs of toxicity. These data suggest that Hsp90 could be a novel potential target in the treatment of SSc dermal fibrosis.

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OP0136

THE INFLUENCE OF LONG-TERM EXERCISE AND IN VITRO EXERCISE-MIMICKING STIMULATION ON THE PRODUCTION OF MYOKINES AND CYTOKINES IN MYOTUBES OF PATIENTS WITH CHRONIC IDIOPATHIC INFLAMMATORY MYOPATHIES

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Background: It has been demonstrated several times that endurance exercise has beneficial effects on the condition of patients with idiopathic inflammatory myopathies (IIM). Muscle contraction during exercise is a major stimulus for the release of myokines that are supposed to take part in the beneficial adaption to exercise.

Objectives: The aim of this study was to find out how a six-month physiotherapy and *in vitro* exercise-mimicking treatment affect myokine and cytokine production in myotubes of IIM patients.

Methods: Seven patients with chronic IIM took part in a six-month physiotherapy (stretching and strengthening), which significantly improved their muscle strength and endurance. IIM patients ($n=7$) before and after the six months exercise and their respective healthy counterparts (HC, $n=9$) underwent a *musculus vastus lateralis* biopsy. Isolated skeletal muscle cells were grown, differentiated into myotubes, which were treated with a pharmacological cocktail: palmitate, forskolin and ionomycin (PFI) to mimic exercise-stimulated contractions *in vitro*. Myokine and cytokine concentrations produced by myotubes to the culture medium were analyzed with ELISA and the multiplex immunoassay, respectively. RT-PCR was used for the evaluation of myokine gene expression in the cultured myotubes.

Results: Compared to myotubes of healthy controls, myotubes of IIM patient released more myostatin and activin A into the medium. The myostatin gene was expressed significantly more in muscle cells of patients than in healthy controls' cells ($p<0.05$). After a six-month rehabilitation program, activin A secretion was four-fold reduced in myotubes of patients with IIM, while myostatin release

and gene expression remained unchanged. In myotubes of IIM patients, less follistatin and more follistatin like 3 were detected in the culture medium compared to HC myotubes. Myotubes derived from IIM patients after six months of rehabilitation secreted twice as much follistatin and half the amount of follistatin like 3 into the medium than myotubes derived from IIM patients prior to rehabilitation ($p<0.05$). There was no difference in secretion of interleukin (IL) 6, IL-17, tumor necrosis factor (TNF) and vascular endothelial growth factor (VEGF) between myotubes of IIM patients and myotubes of HC. However, six-month exercise significantly ($p<0.05$) reduced release of IL-6, TNF and VEGF in myotubes of IIM patients. Contrary to our expectation, stimulation of PFI had no effect on the release of myostatin, activin A, follistatin and follistatin like 3, or the expression of their genes. PFI treatment significantly ($p<0.05$) increased IL-6 secretion in myotubes from HC and IIM patients prior to six months of rehabilitation. On the other hand, it was observed that myotubes of HC and IIM patients exposed to the PFI cocktail secreted significantly less inflammatory cytokines IL-17, TNF and VEGF into the medium compared to unstimulated myotubes ($p<0.05$).

Conclusion: In conclusion, long-term exercise influenced the production of myokines and decreased release of inflammatory cytokines in myotubes of IIM patients. *In vitro* exercise-mimicking treatment increased the secretion of IL-6 and decreased the release of inflammatory cytokines as IL-17, TNF- α and VEGF in myotubes of patients with IIM and healthy individuals.

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OP0137

GENOME-WIDE WHOLE-BLOOD TRANSCRIPTOME PROFILING IN A LARGE EUROPEAN COHORT OF SYSTEMIC SCLEROSIS PATIENTS

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Background: The analysis of annotated transcripts from genome-wide expression studies data is of paramount importance to understand the molecular phenomena underlying the occurrence of complex diseases, such as systemic sclerosis (SSc).

Objectives: To perform whole-blood transcriptome and pathway analysis on whole-blood (WB) RNA collected in two cohorts of European SSc patients. Via a discovery and validation strategy we aimed at characterizing the molecular pathways that differentiate SSc from controls and that are reproducible in geographically diverse populations.

Methods: WB samples from 252 controls and 162 SSc patients were collected in RNA stabilizers. Patients were divided into a discovery ($n=79$; Southern Europe) and validation cohort ($n=83$; Central-Western Europe). RNA sequencing was performed by an Illumina assay. Functional annotations of Reactome pathways were performed with the FAIME algorithm. In parallel, a immunophenotyping analysis on 28 circulating cell populations was assessed. We then tested: the presence of differentially expressed genes or pathways and the correlation between absolute cell counts and RNA transcripts/FAIME scores in regression models. Results significant in both populations were considered as replicated.

Results: A total of 15224 genes and 1277 related functional pathways were available for analysis. Among these, 99 genes and 225 pathways were significant in both sets. The heatmap in figure shows the relative expression of replicated pathways and the distribution of cases and controls (red and green bars). Among the significant pathways we found a deregulation in: type-I IFN, TLR-cascade and signalling, function of the tumor suppressor p53 protein, platelet degranulation and activation. Correlation analysis showed that the count of several cell