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Figure.

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OP0019 **DEFINING SYSTEMIC LUPUS ERYTHEMATOSUS MOLECULAR TAXONOMY THROUGH DATA-DRIVEN RESTRATIFICATION AND IDENTIFICATION OF CLUSTER-TAILORED DRUGS FOR A PERSONALIZED MEDICINE APPROACH**

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Background: Systemic Lupus Erythematosus (SLE) is characterized by lack of treatment diversity, largely empirical treatment decisions, and paucity of novel compound development.

Objectives: We sought to stratify SLE patients based on their molecular phenotype and predict personalized therapeutic compounds, tailored to the molecular fingerprint of each subgroup.

Methods: We performed a co-expression analysis using our publicly available whole blood RNA-seq data of 120 SLE patients. Modules of commonly regulated genes were established and used to re-stratify patients through hierarchical clustering, in a data-driven, clinically independent, manner. Next, we established an in silico, subgroup signature-based, drug prediction pipeline. Investigated drugs included both those currently in practice and those who have been tested in

SLE clinical trials and are listed in the iLINCS prediction databases. Finally, drug repurposing analysis was performed, to identify novel perturbagens that counteract group-specific SLE signatures.

Results: Molecular taxonomy identified five distinct lupus molecular endotypes, each characterized by a unique gene module enrichment pattern. A group defined by strong neutrophilic signature encompassed almost exclusively patients with active nephritis, while a B-cell expression group included patients with severe lupus phenotype. Metabolic processes enrichment defined a group of patients with disease of moderate severity and serologic activity. Finally, patients with mild lupus features were distributed in two groups, which demonstrated enhanced basic cellular functions, myelopoiesis, and autophagy. The ability of different compounds to reverse the transcriptomic aberrancies observed in each patient group was examined. Bortezomib efficiently reversed disturbances in the "neutrophilic" cluster. Azathioprine and ixazomib might be a reasonable option for patients of the "B-cell" cluster, whereas fostamatinib appeared efficacious for the "Metabolism" patient subgroup.

Conclusion: The clinical spectrum of SLE encompasses distinct molecular endotypes, each defined by unique pathophysiologic aberrancies, which can be utilized to guide personalized care and direct novel compound development.

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OP0020 **HOMEBOX D TRANSCRIPTION FACTORS SHAPE DIFFERENTIAL JOINT ENVIRONMENT BETWEEN ANTERIOR FINGER JOINTS AND THUMB**

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Background: The expression of embryonic Homeobox (HOX) genes is tightly regulated based on anatomic location in human adult dermal and synovial fibroblasts. Previously, we showed that HOX-D10, -D11 and -D13 are higher expressed in synovial fibroblasts from small distal joints from the hands and feet, in particular in digits II-V and wrists compared to thumb and that this expression pattern is epigenetically imprinted¹. The consequences of the tightly restricted expression of these transcription factors are largely unknown.

Objectives: To elucidate the function of HOXD10, -D11 and -D13 in synovial fibroblasts.

Methods: Synovial tissues were isolated from paws of naïve C57BL/6 mice (n=8), from patients with rheumatoid arthritis (RA), osteoarthritis (OA) and from healthy controls. Synovial fibroblasts were cultured and transfected with GapmeR to silence HOXD10, -D11, and -D13, respectively or with control GapmeR. RNA sequencing was performed on the NovaSeq platform and pathway analysis was done using R packages and web-based tools (GSEA, EnrichR, Cytoscape). HOXD target gene expression was measured by qPCR (n=3-6).

Results: To confirm and further analyze the distinctive expression pattern of HOXD genes, we measured their expression in healthy synovial tissues of different joints of human feet and mouse paws. Similar to what we had found in hands, HOXD10, -D11 and -D13 were less abundant in the joints of the first digit of human feet compared to digits II-V (n=3-4 in each joint). Measurements in joints of mouse paws showed lower expression of HoxD10, -D11 and -D13 in distal interphalangeal joints compared to proximal interphalangeal joints and metacarpophalangeal (MCP) joints, respectively. Silencing of HOXD10, -D11 and -D13, affected the expression of 5333, 2217 and 7347 genes, respectively, in cultured RA synovial fibroblasts from human wrists (n=3).

There were more transcripts equally regulated by HOXD10 and -D13 (40% of all HOXD10 and 31% of all HOXD13 regulated transcripts), than by HOXD11 and either -D10 or -D13 (18% of all HOXD10 regulated genes and 16% of all HOXD13 regulated genes), suggesting most redundancy between HOXD10 and -D13 (Figure 1). Among genes differentially expressed in SF isolated from MCP II-V versus thumb joints, 19%, 4% and 33% were regulated by HOXD10, -D11 or -D13, respectively, supporting a role for HOXD13 in particular in shaping the joint specific environment. All three HOXD transcription factors regulated genes involved in cell cycle progression, demonstrating dependence of synovial fibroblasts on these HOX genes for cell division. Other enriched pathways were Toll-like receptor and integrin signaling pathways, regulation of unsaturated fatty acid synthesis and autophagy and extra-cellular matrix protein organization. We could

confirm several targets of HOXD10, -D11, and -D13 by qPCR, e.g. *NR4A1*, *ROR2*, *LIF*, *ATF3*.

Figure 1. Comparison of the genes which were differentially expressed after HOXD10-11-13 silencing

Conclusion: The expression of HOXD10, -D11 and -D13 in synovial fibroblasts and tissues strikingly overlaps with predilection sites for RA. Silencing experiments suggested that these embryonic HOX transcription factors have a crucial role in regulating fibroblast functions and might shape a joint specific environment that modulates the development and course of RA in specific joints.

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OP0021

IDENTIFICATION OF DIFFERENTIALLY EXPRESSED GENES IN EARLY RHEUMATOID ARTHRITIS PATIENTS RESPONDING TO TOCILIZUMAB

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Background: Tocilizumab (TCZ) is a monoclonal antibody that binds to the interleukin 6 receptor (IL-6R), inhibiting IL-6R signal transduction to downstream inflammatory mediators. TCZ has shown to be effective as monotherapy in early rheumatoid arthritis (RA) patients (1). However, approximately one third of

patients inadequately respond to therapy and the biological mechanisms underlying lack of efficacy for TCZ remain elusive (1). Here we report gene expression differences, in both whole blood and peripheral blood mononuclear cells (PBMC) RNA samples between early RA patients, categorized by clinical TCZ response (reaching DAS28 < 3.2 at 6 months). These findings could lead to identification of predictive biomarkers for TCZ response and improve RA treatment strategies.

Objectives: To identify potential baseline gene expression markers for TCZ response in early RA patients using an RNA-sequencing approach.

Methods: Two cohorts of RA patients were included and blood was collected at baseline, before initiating TCZ treatment (8mg/kg every 4 weeks, intravenously). DAS28-ESR scores were calculated at baseline and clinical response to TCZ was defined as DAS28 < 3.2 at 6 months of treatment. In the first cohort (n=21 patients, previously treated with DMARDs), RNA-sequencing (RNA-seq) was performed on baseline whole blood PAXgene RNA (Illumina TruSeq mRNA Stranded) and differential gene expression (DGE) profiles were measured between responders (n=14) and non-responders (n=7). For external replication, in a second cohort (n=95 therapy-naïve patients receiving TCZ monotherapy), RNA-seq was conducted on baseline PBMC RNA (SMARTer Stranded Total RNA-Seq Kit, Takara Bio) from the 2-year, multicenter, double-blind, placebo-controlled, randomized U-Act-Early trial (ClinicalTrials.gov identifier: NCT01034137) and DGE was analyzed between 84 responders and 11 non-responders.

Results: Whole blood DGE analysis showed two significantly higher expressed genes in TCZ non-responders (False Discovery Rate, FDR < 0.05): urotensin 2 (UTS2) and caveolin-1 (CAV1). Subsequent analysis of U-Act-Early PBMC DGE showed nine differentially expressed genes (FDR < 0.05) of which expression in clinical TCZ non-responders was significantly higher for eight genes (MTCOP12, ZNF774, UTS2, SLC4A1, FECH, IFIT1B, AHSP, and SPTB) and significantly lower for one gene (TND2P28M). Both analyses were corrected for baseline DAS28-ESR, age and gender. Expression of UTS2, with a proposed function in regulatory T-cells (2), was significantly higher in TCZ non-responders in both cohorts. Furthermore, gene ontology enrichment analysis revealed no distinct gene ontology or IL-6 related pathway(s) that were significantly different between TCZ-responders and non-responders.

Conclusion: Several genes are differentially expressed at baseline between responders and non-responders to TCZ therapy at 6 months. Most notably, UTS2 expression is significantly higher in TCZ non-responders in both whole blood as well as PBMC cohorts. UTS2 could be a promising target for further analyses as a potential predictive biomarker for TCZ response in RA patients in combination with clinical parameters (3).

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Adaptive immunity (T cells and B cells) in rheumatic diseases and Innate immunity in rheumatic diseases

OP0022

RHO EXPRESSION FACILITATES T CELL MIGRATION TO LYMPH NODES IN RESPONSE INFLAMMATION

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Background: Deficiency in geranylgeranyltransferase type I (GGTase-I) results in accumulation of active Rho family proteins RhoA, Rac1 and Cdc42, responsible for cell communication and migration. We reported that mice with GGTase-I deficient macrophages (GLC mice) develop a spontaneous and age-dependent arthritis, reproducing pathology of RA [1].

Objectives: We study how GGTase-I deficiency in Mφ changes T cell phenotype to facilitate their translocation to joints and the development of arthritis.