rheumatoid arthritis (RA) [2]. Therefore, neutralizing IL-17 might be a therapeutic option during the asymptomatic autoimmune prodromal phase in autoimmune diseases like RA, where TH17 cytokines orchestrate the emergence of a pro-inflammatory autoantibody response and the transition into active RA.

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AB0017

IMMUNE CHARACTERISTICS OF PERIPHERAL BLOOD IN SECONDARY SJOGREN'S SYNDROME PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Secondary Sjogren's Syndrome (sSS) is diagnosed when symptoms of SS coexist with other systemic connective tissue disease, often secondary to rheumatoid arthritis(RA).The occurrence of SS secondary with RA will worsen the course of disease and increase the high incidence and mortality of RA. At present, the immune characteristics of peripheral blood of sSS with RA are not clear.

Objectives: To observe the difference of immune Immune characteristics in peripheral blood between sSS secondary to RA, primary Sjogren's syndrome(pSS) and RA patients.

Methods: 20 sSS with RA patients, 20 pSS patients and 20 RA patients hospitalized in Shanxi medical university the second Hospital were enrolled. The percentage and absolute numbers of lymphocyte phenotypes and CD4+ T subsets in peripheral blood were examined by flow cytometry.

Results: As for the percentage and absolute number of total T, B, NK, CD4+T,CD8+ T and the ratio of CD4 + T to CD8+ T cells, there was no significant difference between the sSS with RA, RA, and SS group. There was also no statistical difference in the percentage of CD4+T subsets(Th1,Th2,Th17 and Treg) between the three groups. But the ratio of Th17 and Treg in sSS with RA group was increased than pSS group.About comparison of absolute number of CD4+T subsets, there was no statistical difference among the three groups except that the Th1 cells in RA group was significantly higher than SS group.

Conclusion: Elevated Th17/Treg may be an immunological feature that differentiates sSS with RA patients from pSS patients. In addition, in general, peripheral blood of patients with RA and SS have similar immune characteristics.

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Figure 1. The comparison about the lymphocyte phenotypes and CD4+ T subsets in peripheral blood of sSS with RA(n=20), pSS(n=20) and RA patients(n=20).(*p<0.05, **p<0.001, ***p<0.0001)

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AB0018

ACCUMULATION OF FUNCTIONALLY MATURE CD1c+ DENDRITIC CELLS CONTRIBUTES TO SYNOVIAL INFLAMMATION IN INFLAMMATORY ARTHRITIS

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Background: Myeloid Dendritic Cells (DC) are potent antigen presenting cells that can be subdivided into CD141 and CD1c+ DC. We have previously reported an unacknowledged role for CD141+ DC in the IA synovium. However, the identification and function of CD1c+ DC in the IA synovium has yet to be fully elucidated.

Objectives: To investigate if CD1c+ DC reside in the IA synovium and ascertain if they represent a unique population, distinct from peripheral CD1c+ DC and if they contribute to synovial inflammation.

Methods: Synovial tissue (ST) biopsies and synovial fluid mononuclear cells (SFMC) were obtained via arthroscopy and healthy control (HC) ST was obtained during ACL surgery. Synovial tissue single cells suspensions were generated following enzymatic and mechanical digestion. Single cell analysis of synovial tissue cell suspensions, along with PBMC and SFMC was performed by multicolour flow cytometry. CD1c+ DC were sorted from IA synovial fluid and peripheral blood and bulk RNA sequencing was performed. CD1c+ DC functionality and maturation was assessed using OVA DQ phagocytosis assays, multiplex ELISA and DC: T cell cocultures.

Results: Within the circulation the frequency of CD1c+ DC are significantly decreased in IA peripheral blood compared to HC (p<0.01) in addition to expressing significantly higher levels of the maturation markers CD80 (p<0.01) and CD40 (p=0.08). IA peripheral blood DC also express significantly higher levels of CXCR3 (p<0.01) and CCR7 (p<0.05) compared to HC - suggestive of DC migration from the periphery to the synovium. Following RNA-seq analysis, IPA and differentially expressed gene (DEG) analysis revealed an enrichment in genes involved in DC maturation, TLR signalling and chemokine signalling in IA peripheral blood compared to HC. In support of the hypothesis that DC migrate and accumulate in the IA synovium, CD1c+ DC were identified in IA ST and were significantly enriched compared to IA peripheral blood (p<0.01). IA ST CD1c+ DC express significantly higher levels of the activation marker CD80 compared to IA peripheral blood (p<0.05) or HC ST (p<0.05). Upon examination of IA synovial fluid, we report similar findings to ST, whereby CD1c+ DC are enriched in synovial fluid compared to PB (p<0.001). Moreover, RNA sequencing and PCA analysis of synovial versus blood CD1c+ DC revealed distinct transcriptional variation between both sites. Functionally, synovial CD1c+ DC express higher levels of the maturation markers CD80, CD83, CD40, PD-L1 and BTLA (all p<0.05) and have distinct coexpression of these maturation markers which is unique to the synovium. Synovial CD1c+ DC are less phagocytic compared to peripheral blood DC, have decreased production of MMP1 and MMP9 and importantly are still capable of additional activation *in-vitro*. Finally, synovial CD1c+ DC induce the proinflammatory cytokines TNFα, GMCSF, IL-17a and IFNγ from CD4+ T-cells in allogeneic DC: T cells cocultures.

Conclusion: Mature circulatory CD1c+ DC migrate and accumulate in the IA synovium. Synovial DC are present in the IA synovium in a mature state, have distinct tissue specific characteristics and can induce proinflammatory CD4+ T cell responses.

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AB0019

TREATMENT OF AUTOIMMUNE AND INFLAMMATORY SKIN DISEASES USING SKIN-TARGETING BIFUNCTIONAL ANTIBODIES: A LOCALIZED IMMUNOMODULATION APPROACH

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Background: Current treatment approaches for autoimmune conditions comprise primarily of systemic immunosuppressants or cytokine blockade. The concentration of therapeutic molecules to the tissues that are the sites of autoimmune and inflammatory diseases is a promising approach with the potential to induce therapeutic benefit and avert risks associated with systemic immunotherapies. Pandion Therapeutics is developing a bifunctional antibody platform that can drive localized immune modulation by combining a "tether antibody" that targets a tissue of choice and an "effector end" that activates specific regulatory immune pathways to restore immune-homeostasis.

Objectives: Here we report the engineering of a skin-tethered PD-1 agonist and a skin-tethered CD39 that inhibit T cell activation and function and deplete local ATP, respectively, modulating different arms of the immune system in a tissue specific manner.

Methods: Biophysical assays were performed to characterize Skin-tethered immune effectors for drug-like properties and *in vitro* and *in vivo* assays for target binding, cellular activity and tissue specific-localization. Moreover, these bifunctional molecules were tested in pathway-relevant preclinical models such as Vitiligo and Contact Hypersensitivity.

Results: Biophysical characterization of the bifunctional molecules showed desired drug like properties including specificity, stability, and manufacturability. The skin tethered bifunctionals showed effector activity in *in vitro* assays and selectively localized to the skin. Skin localization strikingly correlated with a tether-dependent efficacy compared to a non-tether control.

Conclusion: We believe that this therapeutic approach has the potential to drive the resolution of cutaneous inflammation, providing an opportunity for developing new targeted therapies for autoimmune and inflammatory skin diseases.

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AB0020 ACPA ILLUSTRATING THE IMPACT OF IGG FAB-GLYCOSYLATION ON TRANSPLENTAL TRANSFER OF ANTIBODIES AND THEIR BINDING TO THE NEONATAL FC-RECEPTOR (FCRN)

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Background: Fc neonatal receptor (FcRn) is crucial for IgG half-life and transplacental transport. Different sites of IgG carry glycans which may affect binding to FcRn. While the effect of Fc-glycans has been investigated, the impact of Fab-glycosylation (~14% IgG) on IgG-FcRn interaction remains unclear. Anti-citrullinated protein antibodies (ACPA) of rheumatoid arthritis patients exhibit remarkably high Fab-glycosylation (~90%). This makes ACPA an ideal model to investigate how Fab-glycosylation influences IgG-FcRn interaction.

Objectives: To investigate the potential impact of IgG Fab-glycosylation on IgG transplacental transfer and interaction with FcRn.

Methods: To investigate transplacental transport of ACPA and total IgG, serum of ACPA-positive RA patients (mothers) as well as of healthy mothers and their respective newborns was analyzed. IgG Fab- and Fc-glycosylation was investigated with liquid chromatography and mass-spectrometry. Furthermore, ACPA monoclonal IgG were produced and glycoengineered to acquire several variants of the same monoclonal antibody differing only in their glycosylation profile. These glycovariants were then used to investigate the impact of Fab-glycans on the affinity of IgG for FcRn. Surface plasmon resonance (SPR) and affinity chromatography were implemented.

Results: When measured in mothers' serum and cord blood samples, Fab-glycosylation of IgG antibodies was ~20% lower in newborns compared to their mothers, which was observed for ACPA IgG, non-ACPA IgG in RA patients and total IgG of healthy controls (Figure 1). This may indicate that transplacental transfer of Fab-glycosylated antibodies is impaired. SPR results suggested that presence of Fab-glycans slightly lowered the affinity of IgG for FcRn. However, presence of Fab-glycans did not have a significant effect on

the results of FcRn affinity chromatography. Together, these results suggest that Fab-glycans may impair association of IgG with FcRn, while dissociation likely stays intact.

Conclusion: Our results suggest that Fab-glycans inhibit IgG-FcRn binding which negatively affects the transplacental transfer of Fab-glycosylated IgG. The impact of Fab-glycosylation on IgG half-life requires further investigation.

Figure 1.

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AB0021 CHARACTERISATION OF AGE-ASSOCIATED B CELLS IN EARLY, DRUG NAÏVE RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease of immune dysregulation affecting the joints. While T cells play a recognised role in disease pathogenesis, the presence of autoantibodies years before the clinical onset of disease, and the efficacy of the B cell-depleting therapy rituximab, highlight a pathogenic role for these functionally diverse lymphocytes. A novel subset, termed age-associated B cells (ABCs), are described as CD19^{high} CD21⁺ CD11c⁺, with a high proportion expressing the transcription factor T-bet; they are elevated in murine models of autoimmunity and produce autoantibodies characteristic of autoimmune disease. A detailed characterisation of ABCs in early, drug naïve RA has not yet been conducted.

Objectives: We aimed to characterise peripheral blood (PB) and synovial fluid (SF) ABCs in patients suffering from early drug naïve RA. As a secondary objective we sought to determine whether this population differs between RA patients and age-matched early psoriatic arthritis (PsA; disease controls) and healthy controls.

Methods: Newly presenting early RA and other inflammatory arthritis patients, naïve to immunomodulatory treatment, were recruited from the Newcastle Early Arthritis Clinic. Patients with established RA (≥1 year duration on treatment and age-matched healthy controls were recruited in parallel. B cell subsets (naïve (CD19⁺IgD⁺CD27⁻), switched memory (CD19⁺IgD⁺CD27⁺) and ABC (CD19⁺CD21⁺CD11c⁺)) in PB and SF were characterised by flow cytometry. FACS sorted PB B cell subset gene expression profiles were assessed using a customised NanoString nCounter Human Immunology v2 Panel.

Results: Transcriptionally, ABC differed from both naïve and switched memory B cells. In keeping with published studies ABCs had an activated memory phenotype, exemplified by elevated expression of CD69, CD80, and CD86, as well as Ki67, HLA-DR, IgG and T-bet. Interestingly, ABC had high expression of the Fc Receptor Like (FcRL) family (FcRL1-5), and an inflammatory homing profile (high levels of CXCR3 and low levels of CXCR4 and CXCR5). We found no difference in the proportion of PB ABC between RA patients and control groups, and no association of ABC frequencies with age. Focussing on RA ABCs specifically, we observed elevated ABC frequencies in females, but no association with disease activity. In keeping with their chemokine receptor profile, cross-sectional analysis also demonstrated ABC enrichment in SF compared to PB, with SF frequencies higher in established than early disease. The transcriptome of ABCs from early RA patients differed from both age-matched disease controls and healthy donors (Figure 1 next page).

Conclusion: These data demonstrate that ABCs have a unique, activated, class-switched proliferative phenotype that is transcriptionally distinct from switched memory and naïve B cells. Interestingly, at the transcriptome level early RA ABCs differ to their counterparts in health and other inflammatory arthritides, suggesting they may differ functionally and contribute to pathogenesis. Of note,