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.

Methods: Biophysical assays were performed to characterize Skin-tethered bispecific antibodies for drug-like properties and in vitro and in vivo assays for target binding, cellular activity and tissue-specific localization. Moreover, these bifunctionals were tested in pathway-relevant preclinical models such as Vitiligo and psoriasis. Here we report the engineered 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.

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 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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ACPA ILLUSTRATING THE IMPACT OF IGG FAB-GLYCOSYLATION ON TRANSPLANTURAL 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-class-switched 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 or 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 monocular IgG were produced and glycengineered to acquire several variants of the same monocular antibody differing only in their glycosylation profile. These glycovariants were then used to investigate the impact of Fab-glycosylation on the affinity of IgG-FcRn interaction. Surface plasmon resonance (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 rate 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.

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

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Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease of joint structures, which affects the pannus and cartilage, with a reported prevalence in females of 30% and 10% in males. The initial presentation of RA is insidious, with increased risk of development in females, which negatively affects the transplacental transfer of Fab-glycosylated IgG. The novel subset, termed age-associated B cells (ABCs), are described as CD19high CD21low CD27dim and CD69+ using flow cytometry. 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.

Results: After measuring 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. Moreover, 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 rate stays intact.

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Figure 1

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