Targeting an IgA-CD89-Neutrophil Axis as a Therapeutic Strategy in Severe Rheumatoid Arthritis Patients

Kayla Walzer, Rebecca Fuchs, Haben Ghermazien, Bonny Alvarenga, Amber Pham, Hema Singh, Sharon Zhao, Jinjin Zhang, Jas Singh, Angelo Kaplan, Jenna Pappalardo, Nigel Walker, Matthew Walters, Connor Rosen

Arcus Biosciences, Inc., Hayward, CA USA

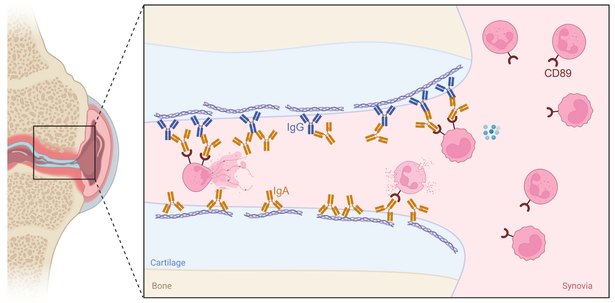
EULAR Congress 2026
June 3-6, London
Poster ID POS0892

Background

Background: Autoantibodies of the IgA isotype have been associated with severe disease and poor response to standard-of-care biologic therapies in patients with rheumatoid arthritis (RA). Immune complexes containing IgA antibodies trigger inflammatory reactions through the immune receptor CD89, which may underlie the specific disease manifestations associated with IgA autoantibodies.

Objectives: This study aimed to understand the expression and function of CD89 on human immune cell populations, as well as the association of IgA and CD89-expressing cell populations with clinical characteristics in RA patients.

Methods: Primary human immune cells were stimulated ex vivo with IgA immune complexes and the ability of an anti-CD89 antibody to block downstream responses was determined. Publicly available transcriptomic and proteomic datasets were examined for genes, proteins, and pathways associated with IgA production and immune cell responses. Synovial tissue biopsies were stained with specific antibodies for IgA and immune cell markers.



Results

CD89 is Expressed in Neutrophils and Myeloid Cells in RA Synovium

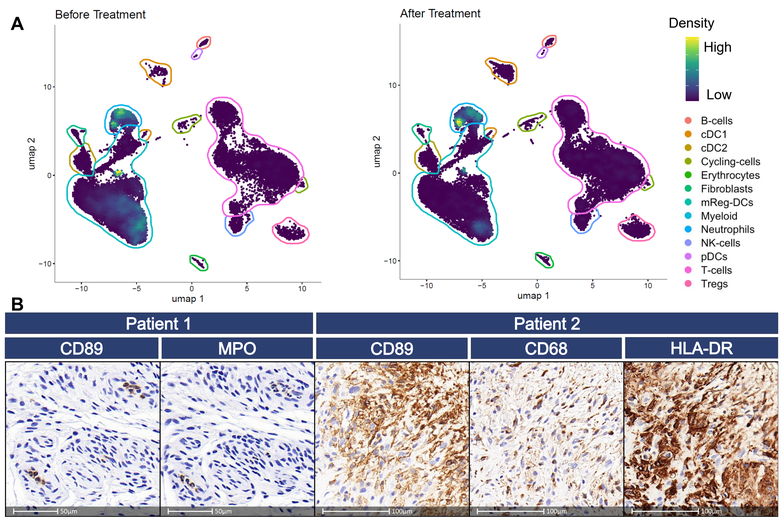


Figure 1: (A) scRNAseq data[1] from n=5 patients with pre- and post-treatment (4 weeks, adalimumab) samples were examined for *FCAR* expression. Neutrophils and myeloid cells with *FCAR* expression were detected in both pre- and post-treatment samples. **(B)** Serial sections from commercially obtained FFPE synovial tissue blocks derived from rheumatoid arthritis (RA) patients were stained for the indicated markers. CD89 expression was observed in regions enriched for neutrophils (MPO^+) and myeloid cells ($CD68^+$ and $HLA\text{-}DR^+$).

Results

IgA Induces CD89-Dependent NETosis in Neutrophils

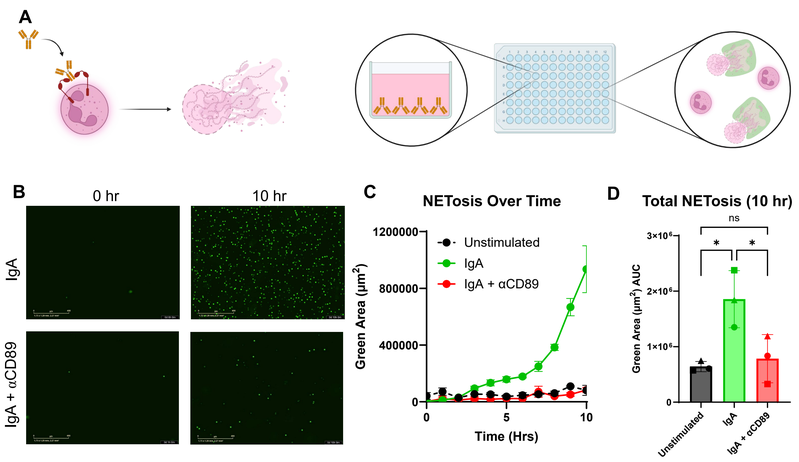


Figure 2: (A) Schematic of neutrophil activation by plate-bound IgA immune complexes. CD89 activation by IgA induces NETosis. Monoclonal IgA is coated on a plate, neutrophils are added, and NETosis is detected by fluorescence of cell-impermeable DNA dye Sytox Green using live-cell imaging. **(B)** Representative images from a single donor of Sytox Green fluorescence at the indicated timepoints with the indicated treatments. **(C)** Representative donor time course of NETosis (green fluorescent area) from the experiment shown in B. IgA induces time-dependent NETosis that is fully inhibited by an anti-CD89 antibody[2]. **(D)** Quantification of total NETosis across multiple donors from the experiments shown in B. IgA induces NETosis that is fully inhibited by an anti-CD89 antibody. * $p < 0.05$

Synovial IgA1 and CD89 Overlap in Areas of Tissue Damage

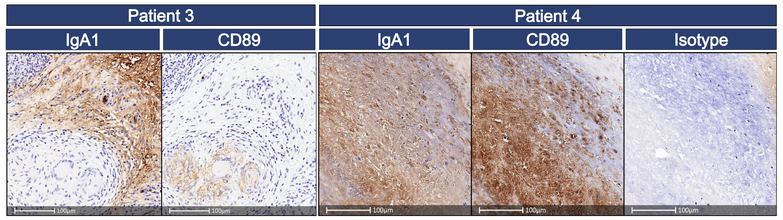


Figure 3: Serial sections from commercially obtained FFPE synovial tissue blocks derived from rheumatoid arthritis (RA) patients were stained for the indicated markers. Patient 3 (control) shows minimal colocalization, whereas Patient 4 exhibits prominent IgA1–CD89 overlap in regions of fibrinoid necrosis, consistent with collagen destruction and inflammatory injury.

IgA-CD89-Neutrophil Axis Activity is Detected in RA Synovium

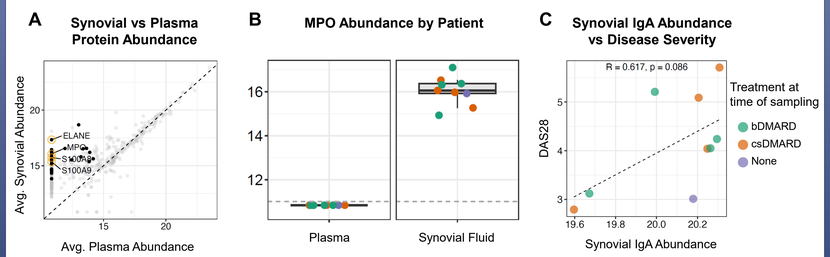


Figure 4: (A) Proteomic data[3] from synovial fluid and plasma from n=9 patients were analyzed for neutrophil proteins (black), which are specifically enriched in the synovial fluid. **(B)** All patients show detection of MPO in synovial fluid, regardless of treatment status, with plasma MPO levels below the limit of detection (dotted line). **(C)** Synovial IgA is weakly correlated with disease severity (Spearman correlation).

Results

Synovial Neutrophils are Associated with Disease Severity in Seropositive Patients

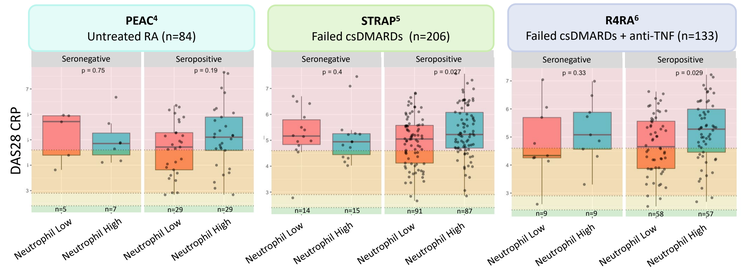


Figure 5: Analysis of synovial tissue bulk RNAseq[4-6] was used to stratify patients based on neutrophil gene signature[7] expression. High expression (based on median cut) of the neutrophil gene signature is associated with increased disease severity in patients from multiple cohorts representing different stages in RA treatment.

IgA-Expressing B Cell Clones can Expand in the RA Synovium

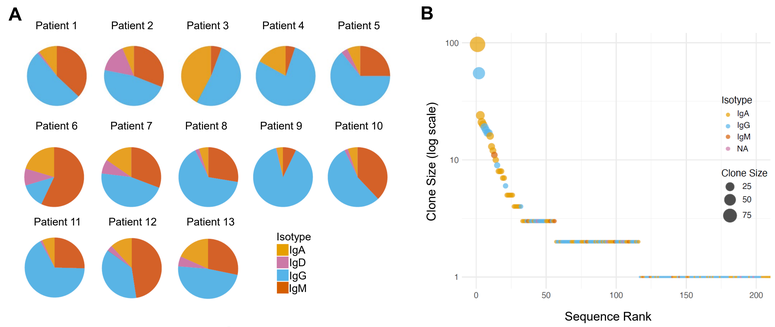


Figure 6: (A) scRNAseq data[8] from n=13 patients were examined for BCR sequences and classified by isotype. All patients show detectable IgA BCRs in the synovium, with several patients showing higher proportions of IgA. **(B)** Unique sequences ("clones") from Patient 3 were ranked according to the number of sequences identified from each clone. The top expanded clone, and a significant fraction of the expanded clones, were IgA.

Summary

Results: CD89 is highly expressed on synovial neutrophils and myeloid cells, but not on T cells, B cells, or NK cells. CD89 activation through IgA immune complexes strongly drives neutrophil activation and is fully inhibited with an anti-CD89 antibody. Synovial IgA-CD89 colocalization is associated with tissue destruction, and RA patients show evidence of neutrophil activation in synovial fluid regardless of prior treatment. RA patients with the highest levels of neutrophil infiltration and IgA protein in synovial fluid had the most severe disease. This difference was observed in both early and established RA patient cohorts. Together, these results demonstrate that the IgA-CD89-neutrophil axis is present in RA patient joints, is associated with disease severity, and does not appear to be addressed with current therapies.

Conclusions: CD89 is an immune receptor that activates neutrophils downstream of IgA immune complexes. Combined transcriptomic, proteomic, and histological measurements demonstrate a link between neutrophils, IgA, and disease activity in RA patients. These links are maintained in patients with advanced disease. Targeting this IgA-CD89-neutrophil axis may therefore provide clinical benefit in a patient population that is poorly responsive to standard-of-care therapies. Arcus is advancing a potent anti-CD89 antibody towards clinical evaluation.

References: 1) Xia 2025 *Sci Data* **2)** WHO Proposed INN List 133 **3)** Stork 2025 *Mol Cell Prot* **4)** Lewis 2019 *Cell Rep* **5)** Lewis 2025 *Nat Comms* **6)** Rivellese 2022 *Nat Med* **7)** Hong 2022 *iScience* **8)** Dunlap 2024 *Nat Comms* and DOI 10.7303/syn47090942.6 through ARK Portal. Introduction figure and Fig 2A generated with BioRender.