TH117

Synovial Expression Levels of PD-1, the Target of Rosnilimab, Correlate with Disease Activity and Persist Across Disease Stages and Lines of Therapy in Rheumatoid Arthritis

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BACKGROUND & OBJECTIVE

PD-1 Pathway is Dysregulated in Rheumatoid Arthritis (RA)

- Programmed cell death protein 1 (PD-1) is a coinhibitory receptor that reduces the activation status of T cells when engaged with its ligand PD-L1[1-3]
- There is over a two-fold increase in PD-1+ T cells in the periphery of RA patients compared to healthy controls[4]
- 80% of T cells in RA synovium are PD-1+[5]

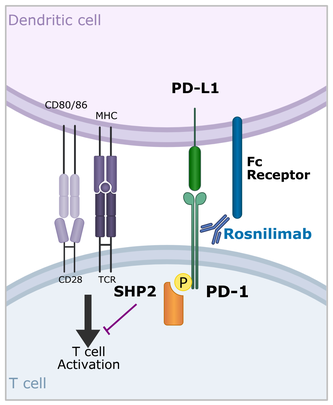

Figure 1. Proposed MoA of rosnilimab

Rosnilimab (PD-1 modulator, IgG1)

- Mechanism of action and proposed impact on PD-1+ T cells (**Fig. 1**)
  - Depletion of PD-1^{high} Teff, Tfh, and Tph cells and inhibition of remaining PD-1+ T cells resulting in:
    - Reduced pathogenic T cell migration, proliferation, and inflammatory cytokine secretion (e.g. IFNγ)
    - Reduced Tfh and Tph-derived cytokines (IL21 and CXCL13) preventing subsequent plasmablast and plasma cell generation and autoantibody levels
- Modulation through PD-1 may restore immune homeostasis in numerous autoimmune and inflammatory indications, including RA

Objective: Assess the therapeutic potential of PD-1 modulation using synovial tissue transcriptomic data from RA patients across different lines of therapy, including treatment naïve as well as inadequate responders to csDMARD and anti-TNF treatments

METHODS

Evaluation of PD-1 expression in RA patient synovial T cells

- PD-1 levels were evaluated across the single-cell synovial cell atlas from the Accelerating Medicines Partnership (AMP) Phase II Rheumatoid Arthritis study that includes data from 70 patients with various disease severities and treatment histories[6]
- T cell subsets were clustered into 24 subtypes of interest, annotated by the AMP consortium, and assessed for PD-1 expression via single-cell RNA-seq

Characterization of treatment naïve early RA patient synovial tissue

- The Pathobiology of Early Arthritis Cohort (PEAC) includes RNA-sequencing data from synovial tissue biopsied from 90 early RA patients naïve to therapy[7]
- The Gene View module on the QMUL PEAC RNA-seq Data shiny website was utilized to evaluate PD-1 and CXCL13 expression correlation with clinical phenotypes

Analysis of PD-1 levels and T cell activation status in RA patient synovium across different lines of therapy

- RNA-seq data across RA patient synovium (n=20)/cohort from three different study cohorts; PEAC, STRAP (csDMARD inadequate responders), and R4RA (TNF inadequate responders) were analyzed for CD3 expression and compared to PD-1 expression and markers of Tph and T cell activation
- Transcriptomic data of osteoarthritis (OA) patient synovial tissue (n=6) from GEO accession GSE254682 was analyzed and served as a control group

RESULTS

PD-1 was Highly Expressed on Tph/Tfh, Proliferating, and Memory T Cells in RA Patient Synovium

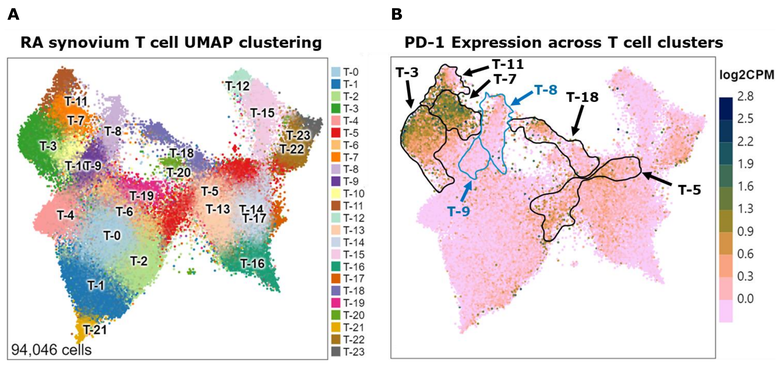

Figure 2. Uniform manifold approximation and projection (UMAP) clusters of T cells from RA patient synovium with arrows identifying Tph and Tfh/Tph cells, T-7 and T-3, respectively (A) and feature plot of PD-1 expression across T cell subtypes (B)

- AMP RA phase II patient-derived synovial T cells were clustered into 24 unique T cell subtypes via UMAP analyses (**Fig. 2A**)
- CD4+ Tph (T-7) and Tfh/Tph (T-3) cells demonstrated the highest PD-1 expression compared to other T cell subsets (**Fig. 2B**)
- Notably, high PD-1 expression was also observed across proliferating T cells (T-18) and several memory T cell subtypes, including CD4+ CD146+ memory (T-11) and CD4+ GZMK+ memory (T-5) T cells
- CD4+ CD25high and CD25low regulatory T cells (T-8 and T-9, respectively) demonstrated minimal PD-1 expression

RESULTS

PD-1 and CXCL13 Expression in RA Synovium was Significantly Correlated with RA Disease Activity

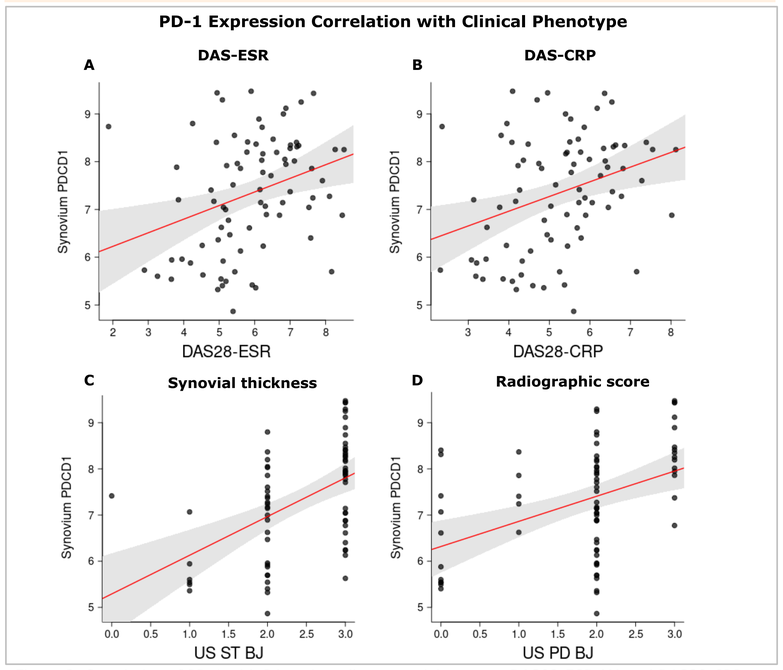

Figure 3. Correlation of PD-1 with RA patient disease activity scores DAS82-ESR (A) and DAS28-CRP (B), ultrasound synovial thickness (C) and total Sharp van der Heijde radiographic score (D)

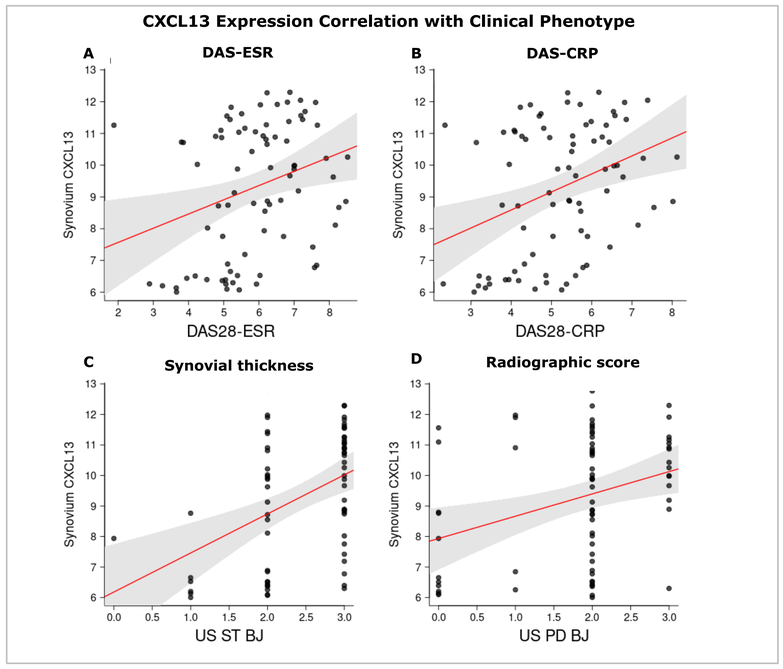

Figure 4. Correlation of CXCL13 with RA patient disease activity scores DAS82-ESR (A) and DAS28-CRO (B), ultrasound synovial thickness (C) and total Sharp van der Heijde radiographic score (D)

From treatment naïve early RA patient-derived synovial biopsy bulk RNA-seq (PEAC cohort):

- Both PD-1 and CXCL13 transcript levels showed significant positive correlations with disease activity scores (**Fig. 3A & 4A**) and DAS28-ESR (**Fig. 3B & 4B**)
- PD-1 and CXCL13 also both significantly correlated with ultrasound synovial thickness (US ST BJ **Fig. 3C & 4C**), and total Sharp van der Heijde radiographic scores (US PD BJ **Fig. 3D & 4D**)

Correlation P-values

	DAS-ESR	DAS-CRP	Synovial Thickness	Radiographic score
PD-1	$2.2x10^{-3}$	$4.8x10^{-3}$	$4.9x10^{-6}$	$7.8x10^{-5}$
CXCL13	$3.0x10^{-3}$	$1.9x10^{-3}$	$1.9x10^{-4}$	$1.2x10^{-2}$

RESULTS

PD-1 Levels in RA Synovium Persisted Across Lines of Therapy and PD-1+ T Cells were in an Activated State

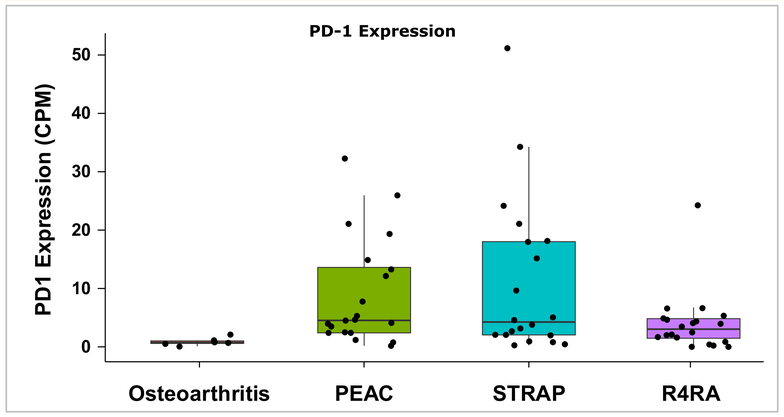

Figure 5. PD-1 expression across three different treatment cohorts compared to OA controls

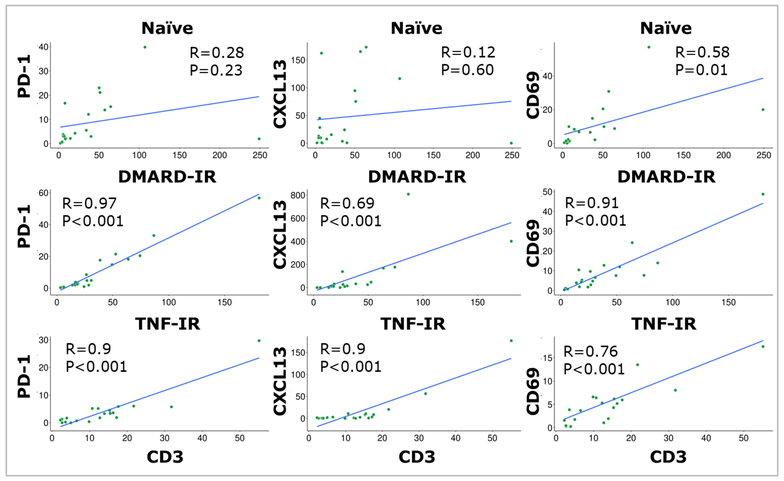

Figure 6. CD3 transcript level correlation with PD-1, CXCL13, and CD69 across three different treatment cohorts

- PD-1 transcript levels show upregulation in RA patients compared to OA controls, and maintained expression levels in patients post-treatment with csDMARD and anti-TNF therapies (**Fig. 5**)
- T cell activation markers (PD-1 and CD69) and CXCL13 expression levels closely correlated with CD3 expression across disease stages, indicating synovial T cells continue to exhibit an activated, Tph-like phenotype (**Fig. 6**)

CONCLUSIONS

- Synovial PD-1 and CXCL13 expression levels correlated with clinical markers of disease activity and joint inflammation
- PD-1+ T cells in RA synovium were observed to be preferentially in an activated state and persisted across naïve, DMARD-IR, and TNF-IR patients
- These data support the importance of PD-1 in RA disease pathogenesis and the biological rationale for developing rosnilimab as a potential treatment option following other lines of therapy
- RENOIR, an ongoing Phase 2 trial of rosnilimab in moderate-to-severe RA, includes biologic naïve and experienced patients that will provide additional insight on the therapeutic potential of rosnilimab (NCT06041269)

ACKNOWLEDGEMENTS

1. This research was funded by Anaptys
2. Cynthia Alexander of Anaptys provided significant contribution to the writing, content development, and poster design
3. Disclosures: ML, CC, FR, LFJ, and CP are consultants and received research grants from Anaptys. For ML, CC, FR, LFJ, and CP, additional disclosures available on request. All other authors are employees and stockholders of Anaptys

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