IPART

International Psoriasis & Arthritis Research Team

PROGRESS REPORT

As of April 30, 2025

INFRASTRUCTURE

The **International Psoriasis and Arthritis Research Team (IPART)** is a highly successful, international consortium of rheumatologists and dermatologists across Canada and the United States with expertise in genomics, inflammation, immunology and epidemiology. IPART was formed in 2007 and spearheaded by Dr. Dafna D. Gladman, its Principal Investigator.

IPART has six (6) core sites namely:

Toronto, Ontario, CANADA	**Dr. Dafna D. Gladman,** Division of Rheumatology, University of Toronto, Temerty Faculty of Medicine, Toronto Western Hospital **Dr. Vinod Chandran**, Division of Rheumatology, University of Toronto, Temerty Faculty of Medicine, Toronto Western Hospital **Dr. Denis Poddubnyy,** Division of Rheumatology, University of Toronto, Temerty Faculty of Medicine, Toronto Western Hospital **Dr. Cheryl F. Rosen**, Division of Dermatology, University of Toronto, Toronto Western Hospital
St. John's, Newfoundland,	**Dr. Proton Rahman** - Division of Rheumatology and Genetics, Memorial University of Newfoundland
Vancouver, British Columbia,	**Dr. Jan Dutz** - Divisions of Rheumatology and Dermatology, University of British Columbia, Vancouver
Ann Arbor, Michigan, USA	**Dr. James T. Elder** - Division of Dermatology, University of Michigan, Ann Arbor, MI, USA
Rochester, New York, USA	**Dr. Christopher Ritchlin** - Division of Rheumatology, University of Rochester, NY, USA **Dr. Norman Madsen**, University of Rochester Medical Center, Rochester, NY
Toronto, Ontario, CANADA (Site 2)	**Dr. Lihi Eder** - Division of Rheumatology, University of Toronto, Women's College Hospital

IPART has other active collaborating sites across Canada and internationally as follows:

1. London, Ontario (University of Western Ontario – **Dr. Sherry Rohekar and Dr. Tristan Boyd)**
2. Haifa, Israel (Carmel Medical Center – **Dr. Devy Zisman)**
3. Detroit, MI (Henry Ford Health System – **Dr. Qing-Sheng Mi and Dr. So Yeon Paek)**
4. India (Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS) – **Dr. Vikas Agarwal)**
5. Ottawa, Ontario (University of Ottawa – **Dr. Sibel Aydin)**
6. Vancouver, BC (ARTUS Health Center - **Dr. Jonathan Chan** joined our core site at the University of British Columbia – Dr. Jan Dutz)
7. Vellore, India – (Christian Medical College - **Dr. Ashish Matthew and Dr. Debashish Danda**)
8. Quebec City, Quebec (CHU de Quebec, Université Laval – **Drs. Paul Fortin and Louise Bessette)**

PROGRESS REPORT

DATABASE AND BIOBANKING UPDATE

DATABASE

	TWH	WCH	St. John's	Vancouver	Ann Arbor	Rochester	London	Winnipeg	Israel	Halifax	Argentina	Ottawa
PsA	1751	370	614	99	22	273	227	72	321	4	4	18
Psoriasis	750	400	82	44	69	218	5	193	31	21	9	0
Total	2501	770	696	143	91	491	232	265	352	25	13	18
Female (%)	45.2	55.7	53.2	51.1	47.6	56.9	43.1	50.6	54.5	36.0	92.3	55.6
Caucasian (%)	83.2	72.8	99.2	64.0	98.8	89.7	93.8	82.7	71.4	92.0	75.0	94.4
Visits Ps	3.9	2.4	1.0	1.7	2.6	1.8	1.0	3.7	1.3	1.4	1.0	N/A
Visits PsA	15.9	7.9	1.4	2.0	2.3	3.2	6.3	5.0	3.8	1.3	1.0	1.3
Age Ps	29.3	31.3	29.7	31.2	30.2	32.3	33.5	31.0	36.8	28.4	31.1	35.9
Age PsA	38.7	42.7	39.5	37.5	41.5	41.2	43.4	41.1	45.2	46.0	40.3	45.2
DD Ps	20.0	18.9	18.6	23.5	14.4	19.6	23.4	24.2	19.6	24.8	21.7	N/A
DD PsA	18.2	8.8	11.0	14.6	12.0	12.6	15.1	13.5	13.3	4.2	28.1	14.2

Number of patients within database as of April 1, 2025.

Ps = Psoriasis; PsA = Psoriatic arthritis; DD = disease duration at last visit

In summary:

	PsA	PsC	**TOTAL**
Number of patients	3775	1822	**5597**

IPART TORONTO BIOBANK

Here is the latest update of biospecimen samples stored in our facility:

	TWH PsA	**TWH PsC**	**Women's College**	**St. John's**	**London**	**Halifax**	**Winnipeg**
DNA	1426	697	652	168	217	26	223
SERUM	12462	1973	2061	490	563	35	264
RNA	9140	805	1063	41	592	35	169
SYNOVIAL FLUID	224		35				

Biospecimen samples are updated as of April 14, 2025.

RESEARCH UPDATE (2QTR 2024 – 1QTR 2025)

In the past years, IPART has made significant progress in its research program, particularly in the areas of clinical, genetic, and biomarker studies. The following projects are ongoing in all sites, utilizing IPART consented participants and datasets, directly or indirectly through various collaborations:

Progress Report by Drs. Dafna Gladman, Vinod Chandran, Denis Poddubnyy, and Cheryl Rosen
IPART Toronto Core Site – UHN – Toronto Western Hospital, Ontario, Canada

The following projects are spearheaded by **Dr. Dafna D. Gladman**, PI, Toronto Core site at UHN:

- **Chronic kidney disease (CKD) is a comorbidity in patients with psoriatic arthritis (PsA).** We wanted to determine the prevalence of CKD in our patients with PsA determine their long term outcomes and identify risk factors for the development of CKD in PsA patients. Of 1336 patients from the Toronto Cohort included in the study 123 (9.3%) were found to have CKD. Ninety-eight of the 123 patients developed CKD during follow-up at a median of 8.2 years from entry into the Cohort. In terms of outcomes, 18.3% of the 98 patients had doubling of their baseline serum creatinine and 50% had a sustained ≥ 40% reduction of baseline estimated glomerular filtration rate (eGFR). Only 2 patients developed a sustained eGFR of <15%. Multivariable analysis adjusted for age, sex and eGFR at baseline, revealed that Diabetes, kidney stones, radiographic damage, elevated uric acid and use of non-steroidal anti-inflammatory drugs were independent risk factors for CKD, while methotrexate use was protective (1).
- **We searched for candidate biomarkers for response to treatment in psoriatic disease**. Based on the literature we identified 5 candidate proteins and determined whether treatment with tumour necrosis factor inhibitors (TNFi) or interleukin 17 inhibitors (IL-17i) altered serum levels of CSCL10, MMP3, Sq00A8, ACP5 and CCL2, and whether baseline levels of these proteins predicted response to treatment with these therapies. We included 92 PsA patients treated with TNFi, 16 treated with IL-17i, 22 treated methotrexate and no biologics, and 75 were not treated with either conventional of biologic DMARDs. We also studied 28 psoriasis without arthritis (PsC) patients who were treated with biologics and 28 patients not on any systemic medications. These patients were matched on age, sex and disease duration. Serum was obtained from treated patients before initiating therapy and 3-6 months after. We found that CXCL10, MMP3, S100A8, ACP5 and CCL2 were significantly decreased in TNFi-treated patients, while ACP5 and CCl2 were significantly increased in the IL-17i-treated patients. When corrected for sex, reductions in protein levels were still significant for S100A8 and ACP5. Changes in MMP3 and S100A8 levels were significantly different between untreated PsA and matched biologic-treated PsA. MMP3 levels were also reduced in patients treated with methotrexate alone. In PsC patients there was no difference in serum levels of the biomarkers between biologics treated or non-treated patients. Baseline levels of CXCL10, MMP3, S100A8, and ACP5 had good predictive value (area under the curve > 0.80) for response to biologics in patients with PsA. Thus MMP3, S100A8, ACP5 and CXCL10 have potential use as serum biomarkers to predict response to treatment in PsA (2).
- **Smoking has been linked with impaired health status, pain, comorbidities, and limited physical function in patients with psoriatic disease, as well as reduced compliance and response to therapy.** The association between smoking and radiographic damage has been established in some inflammatory joint diseases, but not in psoriatic disease. We aimed to investigate this relationship in psoriatic arthritis (PsA). We analyzed radiographic data from 1736 patients with

PsA followed prospectively in the Toronto Cohort. Multivariate analysis revealed that increasing age, baseline swollen joint count, baseline dactylitis, baseline ESR and baseline radiographic damage are risk factors for progression of damage, while biologics or targeted synthetic DMARDs were protective, Smoking status does not affect time to progression of damage in PsA (3).

- **Among 264 patients treated with biologic therapy for PsA 94 (35.6%) developed secondary failure at a medium time to failure of 2.7 years.** The incidence rate of secondary failure was 5.96 per 100 person years. More complete clinical response, use of TNF-α inhibitors, and commencement as the first-ever biologic were associated with longer lasting efficacy (4).
- **We aimed to explore whether the time interval between the onset of psoriasis and PsA impacts the clinical phenotype at base line, as well as long-term outcomes**. 702 patients were included in the study. Three hundred and sixty-six (52.1%) presented with an early transition ≤ 9 years, while 336 (47.9%) developed PsA after 9 years of psoriasis. The late transition group was associated with a younger age at onset of psoriasis, older age at onset of PsA, higher body mass index, higher PASI and less frequent use of conventional synthetic DMARDs at baseline. Adjusting for HLA-B827 and HLA-C*6 did not impact the results. There was no significant difference with regards to outcomes (5).
- **Some 15% of patients with PsA present with joint manifestations before skin psoriasis.** We set out to evaluate the differences in demographic and disease characteristics as well as the impact on disease activity and structural damage in patients who develop PsA before psoriasis. Of 1702 PsA patients in the Toronto Cohort at the time of the study, 147 (8.6%) presented with PsA first. These patietns were younger at diagnosis of PsA and older at diagnosis of psoriasis. They had less nail lesions, but more erosive disease and clinical damage, higher HLA-B27 and lower frequency of HLA-C*06. These patients also experienced faster progression of radiographic damage (6).

PUBLICATIONS:

1. Kharouf F, Gao S, Al-Matar S, Cook RJ, Chandran V, Gladman DD. Chronic kidney disease in patients with psoriatic arthritis: a cohort study. RMD 2024;10(4):e004636.
2. Offenheim R, Cruz-Correa OF, Ganatra D, Gladman DD. Candidate Biomarkers for Response to Treatment in Psoriatic Disease. J Rheumatol. 2024;51:1176-86.
3. Kharouf F, Maldonado Ficco H, Gao S, Sheanne B, Pereira D, Cook R, Chandran V, Gladman D. The Association of Cigarette Smoking with Radiographic Progression in Psoriatic Arthritis [abstract]. Arthritis Rheumatol. 2024; 76 (suppl 9):2912-14.
4. Kharouf F, Gao S, Alhadri A, Pereira D, Cook R, Chandran V, Gladman D**.** Incidence and Predictors of Secondary Failure to Biologic Therapy in Patients with Psoriatic Arthritis [abstract]. Arthritis Rheumatol. 2024; 76 (suppl 9):2951-53.
5. Kharouf F, Mehta P, Gao S, Pereira D, Cook R, Gladman D, Chandran V. Does the Time Interval Between the Onset of Psoriasis and Psoriatic Arthritis Impact Disease Presentation and Outcomes? [abstract]. Arthritis Rheumatol. 2024; 76 (suppl 9):4163-65.
6. Kharouf F, Carrizo Abarza V, Gao S, Pereira D, Cook R, Chandran V, Gladman D. Do Patients That Develop PsA Before Psoriasis Have Different Disease Outcomes? [abstract]. Arthritis Rheumatol. 2024; 76 (suppl 9):4688-90.

Research activities spearheaded by **Dr. Vinod Chandran** are appended below:

- **We conducted a cross-sectional survey study using the Pain Quality Assessment Scale (PQAS) to better characterize the skin pain experience among patients with mild-moderate PsO and PsA**. We found that the most common pain qualities were "aching" (69.6%), "tender" (69.6%), "dull" (65.2%), "itchy" (65.2%), and "hot" (59.4%); "cold" (26.1%) was least common. Global intensity (3.96 ± 2.97) and/or unpleasantness (4.48 ± 3.31) scores were generally higher than any individual quality, and like previous studies, were significantly higher in females vs males (intensity P = .003; unpleasantness P = .004). Patients with scalp and palmoplantar PsO reported higher average "itchy" (3.38 ± 2.83) and "hot" (3.50 ± 2.65) scores respectively, while those with fibromyalgia reported higher scores across most pain qualities. Global skin pain measures significantly correlated with functional outcomes (SF36_BP, SF36_PCS ρ = 0.40-0.52), but not DLQI (ρ = 0.20-0.22) or PASI (ρ = 0.12-0.14). Disease Activity index for Psoriatic Arthritis (DAPSA) also significantly correlated with global skin pain measures (ρ = 0.56-0.57, P < .05), possibly suggesting a modulatory effect of PsA on overall skin pain burden. Conversely, "itchy" pain was moderately and weakly correlated with DLQI (ρ = 0.52) and PASI (ρ = 0.36), respectively, but lacked functional correlation. Body surface area did not correlate with any PQAS question.
- **Metabolic syndrome (MetS) is a known comorbidity of PsA and is associated with PsA disease activity**. We aimed to explore the association between MetS and radiographic features (peripheral and axial) in PsA. We included patients with PsA followed at our prospective observational cohort for the period between 1978 and 2024. We identified patients with MetS on longitudinal follow-up and used generalized estimating equations (GEE) analysis to define the radiographic features independently associated with MetS, adjusting for age, sex, PsA disease duration, calendar decade, and use of targeted disease-modifying antirheumatic drugs. MetS was not significantly associated with axial disease or radiographic damage to peripheral joints, assessed as the presence of syndesmophytes or sacroiliitis and the radiographic damaged joint count, respectively. On the other hand, MetS was significantly associated with calcaneal spurs, diffuse idiopathic skeletal hyperostosis, and degenerative disc disease.
- **We assessed the activation state of leukocyte populations, including polymorphonuclear neutrophils (PMNs) and monocyte/macrophages, in blood and synovial fluid (SF) by multicolour flow cytometry.** We also evaluated the correlation between leukocyte numbers and expression of activation markers with disease activity parameters. SF PMNs showed an elevated activation state compared with blood PMNs, but a reduced activation state compared with oral PMNs of non-arthritic controls. In vitro stimulation caused SF PMNs to become further activated, demonstrating that they retain a reserve capacity for activation in response to specific triggers. We found significant variability between patients in the expression of SF PMN CD activation markers, indicating a range of possible activation states across patients. However, PMN CD marker expression remained consistent over two sequential visits in a subset of patients, indicating patient-specific distinct inflammatory states during flares. We found that markers of disease activity increased with elevated SF macrophage numbers. Expression of several CD markers on blood or SF cells, for example, PMN expression of the high-affinity Fc-receptor CD64, correlated with disease activity markers, including pain score and Disease Activity index for Psoriatic Arthritis score.
- **We measured a broad panel of protease-mediated biomarkers reflecting inflammation and tissue remodeling in serum and synovial fluid (SF) obtained from PsA patients experiencing**

flares (acutely swollen joint[s], PsA-flare). In serum, biomarker levels assessed in PsA-flare patients were compared to controls and in early-diagnosed PsA patients not experiencing flares (referred to as PsA without flare). Furthermore, the biomarker levels assessed in SF from PsA-flare patients were compared to the levels in SF of osteoarthritis (OA) patients. In serum, levels of the PRO-C3 and C3M, reflecting formation and degradation of the interstitial matrix, were found significantly elevated in PsA-flare compared to controls and PsA without flare. The remodeling marker of the basement membrane, PRO-C4, was significantly elevated in PsA-flare compared to PsA without flare. The inflammation and immune cell activity related markers, CRPM, VICM, and CPa9-HNE were significantly elevated in PsA-flare patients compared to controls and PsA without flare. In addition, VICM (AUC = 0.71), CPa9-HNE (AUC = 0.89), CRPM (AUC = 0.76), and PRO-C3 (AUC = 0.86) showed good discriminatory performance for separating PsA-flare from PsA without flare. In SF, the macrophage activity marker, VICM, was significantly elevated whereas the type II collagen formation marker, PRO-C2, was significantly reduced in the PsA-flare compared to OA. The combination of five serum markers reflecting type III and IV collagen degradation (C3M and C4M, respectively), type III and VI collagen formation (PRO-C3 and PRO-C6, respectively), and neutrophil activity (CPa9-HNE) showed an excellent discriminatory performance (AUC = 0.98) for separating PsA-flare from PsA without flares. Thus, a serum biomarker panel of C3M, C4M, PRO-C3, PRO-C6, and CPa9-HNE reflecting synovitis, enthesitis, and neutrophil activity may serve as novel tool for quantitatively monitoring flares in PsA patients.

PUBLICATIONS:

1. Dienes S, Rahmani A, Gao S, Kashetsky N, Hanna S, Chandran V. Skin pain characteristics in psoriasis and psoriatic arthritis: A cross-sectional study. JAAD Int 2025;20:56-58.
2. Kharouf F, Gao S, Tunc SE, Ye JY, Pereira D, Gladman DD, Chandran V. Association Between Metabolic Syndrome and Radiographic Changes in Psoriatic Arthritis: A Cohort Study. Arthritis Care Res (Hoboken). 2025 Mar 2. doi: 10.1002/acr.25513.
3. Fine N, Glogauer M, Chandran V, Oikonomopoulou K. Characterisation of myeloid cells in circulation and synovial fluid of patients with psoriatic arthritis. RMD Open 2024;10:e004457.
4. Groen SS, Nielsen SH, Bay-Jensen AC, Rasti M, Ganatra D, Oikonomopoulou K, Chandran V. Investigating protease-mediated peptides of inflammation and tissue remodeling as biomarkers associated with flares in psoriatic arthritis. Arthritis Res Ther 2024;26(1):107

Research activities spearheaded by **Dr. Denis Poddubnyy** are detailed below:

- **AXIS Study – Axial Involvement in Psoriatic Arthritis.** The AXIS study, co-led by Dr. Denis Poddubnyy in collaboration with GRAPPA and ASAS, is focused on the clinical characterization and classification of axial involvement in psoriatic arthritis (axPsA). In 2024, significant progress was made in analyzing a comprehensive international dataset of over 400 patients with psoriatic arthritis. The team completed a detailed clinical and imaging characterization, which will serve as the foundation for the development of new classification criteria. These efforts involve both data-driven modeling and consensus methodologies, including Delphi exercises with international experts. The classification development phase is currently underway, aiming to provide a validated framework for identifying axPsA.

- **COMPOSITION Study – Comparison of a physician-based versus questionnaire-based approach to identify patients with a high probability of psoriatic arthritis among patients with psoriasis.** The COMPOSITION study as a new project supported by GRAPPA aims to determine whether structured musculoskeletal (MSK) evaluations conducted by dermatologists (as well as other non-rheumatologist healthcare professionals) can improve the referral quality and early diagnosis of psoriatic arthritis. In 2024, Dr. Poddubnyy's team finalized the study protocol, secured funding, completed site selection, and laid the groundwork for study activation. The study will assess the diagnostic value and practicality of incorporating a standardized MSK assessment into referral pathways from dermatology and primary care. The project is currently in the preparation phase, with the study kick-off expected in mid-2025.

PUBLICATIONS:

1. Rademacher J, Torgutalp M, Hempel CM, Proft F, Haibel H, Protopopov M, Spiller L, Poddubnyy D, Rios Rodriguez V. Biomarkers reflecting disturbed gut barrier under treatment with TNF inhibitors in radiographic axial spondyloarthritis. RMD Open. 2024;10(4):e004752.
2. Dorfner FJ, Vahldiek JL, Donle L, Zhukov A, Xu L, Häntze H, Makowski MR, Aerts HJWL, Proft F, Rios Rodriguez V, Rademacher J, Protopopov M, Haibel H, Hermann KG, Diekhoff T, Adams LC, Torgutalp M, Poddubnyy D, Bressem KK. Anatomy-centred deep learning improves generalisability and progression prediction in radiographic sacroiliitis detection. RMD Open. 2024;10(4):e004628.
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4. Rademacher J, Poddubnyy D, Rios Rodriguez V. [Microbial and genetic factors in the pathogenesis of spondyloarthritis]. Z Rheumatol. 2025 May;84(4):268-275. German.
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7. Gensler LS, Jans L, Majumdar S, Poddubnyy D. Unmet Needs in Spondyloarthritis: Imaging in Axial Spondyloarthritis. J Rheumatol. 2024;51(12):1241-1246. Review.
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9. Reich A, Weiß A, Lindner L, Baraliakos X, Poddubnyy D, Zinke S, Stille C, Strangfeld A, Regierer AC. Correction: Depressive symptoms are associated with fatigue, poorer functional status and less engagement in sports in axSpA and PsA: an analysis from the RABBIT-SpA cohort. Arthritis Res Ther. 2024;26(1):177. No abstract available.
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12. Busch F, Bressem KK, Suwalski P, Hoffmann L, Niehues SM, Poddubnyy D, Makowski MR, Aerts HJWL, Zhukov A, Adams LC. Open Access Data and Deep Learning for Cardiac Device Identification on Standard DICOM and Smartphone-based Chest Radiographs. Radiol Artif Intell. 2024;6(5):e230502.
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A Progress Report by Dr. Proton Rahman

IPART Genetic Core Site – Memorial University of Newfoundland (MUN), St. John's, NL, Canada

The following projects are spearheaded by **Dr. Proton Rahman**, at MUN:

Completed Two Mendelian Randomization Studies:

- First, we performed a bidirectional two-sample MR to investigate the complex causal relationship between depression and psoriatic arthritis (PsA) or psoriasis (Tang et al.). Although there appeared to be a positive association between depression and both PsA and psoriasis, the association for PsA did not reach statistical significance, while a significant causal effect was found for psoriasis. There was no evidence of reverse causation indicating that psoriasis leads to depression, although a significant reverse causation from PsA to depression was observed. The absence of a significant and consistent causal link between depression and PsA suggests that the relationship seen in observational studies may be due to confounding factors and potential biases. However, a causal association between depression and psoriasis appears to exist.
- In another study, we evaluated the causal association between immunological characteristics and conditions such as ankylosing spondylitis (AS), psoriatic arthritis (PsA), and psoriasis (PsV) using a bidirectional, two-sample Mendelian randomization approach (Li et al.). This study identified several immune cell types associated with spondyloarthritis (SpA) phenotypes. Some of these cell types, including HLA-DR on CD14-CD16+ monocytes and double-negative T cells (CD4-CD8), have already been implicated in the pathogenesis of SpA. Further analysis of the data could link specific immune cell subtypes to immune-mediated disorders, identify potential causal genes, determine the direction of effects, and enhance our understanding of the disease's pathogenesis.

Participated in three multicenter studies in spondyloarthritis:

- One of the studies found that the average diagnostic delay for axial SpA among Canadian patients was approximately nine years (Rahman et al.). This significant diagnostic delay was associated with a high number of healthcare provider visits before diagnosis, increased usage of nonsteroidal anti-inflammatory drugs (NSAIDs), and marked functional limitations in daily life, illustrating the complicated journey of axSpA patients. This study was facilitated by Novartis.
- We also quantified the residual disease activity and burden of disease in Canadian patients with PsA (Gladman et al.). This study revealed a substantial burden and unmet need for improved therapies for Canadians with PsA, alongside notable regional variations in outcomes that require further investigation. This study was facilitated by AbbVie.
- Finally, we participated in a large multinational meta-analysis of genome-wide association studies (GWAS) in PsA. In collaboration with JT Elder and others, this meta-analysis of 18 GWAS

identified 109 distinct psoriasis susceptibility loci, including 46 that had not been previously reported (Dand et al.).

PUBLICATIONS:

1. Dand N, et al., GWAS meta-analysis of psoriasis identifies new susceptibility alleles impacting disease mechanisms and therapeutic targets. Nat Commun. 2025 Feb 28;16(1):2051. doi: 10.1038/s41467-025-56719-8.
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A Progress Report by Dr. James T. Elder
IPART Core Site - University of Michigan, Ann Arbor, MI, USA

The following projects are led by **Dr. James T. Elder,** at the University of Michigan, Ann Arbor, MI, USA:

- We recently carried out the largest GWAS meta-analysis of psoriasis to date, through an international collaboration involving 18 different datasets, with 36,466 cases and 458,078 controls after QC. Effective sample size increased 3.4-fold (103,614 vs. 30,597) compared to our previously most powerful PsV GWAS [1]. We identified 168 signals, including 28 linkage disequilibrium (LD) blocks with 2 or more independent loci, and 2 LD blocks with 4 or more loci, including 25 loci in the MHC. This analysis nearly doubled the number of EUR psoriasis loci, compared to our most recent report [2]. Relative to the largest previous analysis [2], the expanded GWAS provided a marked (~2-fold) increase in genetic resolution to narrow down the causal variants: a 2.0-fold reduction in median number of variants per BCS (8 vs. 16), a 2.0-fold reduction in median length of BCS (23.9 kb vs. 46.8 kb), a 2.1-fold increase in median posterior probability (PP) for the best candidate causal variant in the BCS (0.404 vs. 0.188), a 2.1-fold increase in number of loci with ≤ 5 variants in the BCS (25 vs. 12), and a 2.3-fold increase in number of BCS with best candidate causal variant having PP > 0.50 (23 vs. 10). We also conducted a transcriptome-wide association study to identify regulatory effects of psoriasis susceptibility variants and cross-referenced these against single cell expression profiles in psoriasis-affected skin [3], highlighting roles for the transcriptional regulation of hematopoietic cell development and epigenetic modulation of interferon signaling in psoriasis pathobiology. These results have been published in Nature Communications [1].

- In an effort to understand the molecular basis of our psoriasis meta-GWAS signals, we generated and sequenced nine PBMC-derived cell fractions (~50,000 cells each): CD1c+ mDC, four fractions of unstimulated CD3+CD45RO+ memory T cells (CD4+CLA-, CD4+CLA+, CD8+CLA-, CD8+CLA+) and the same four T-cell fractions after 24 hr of stimulation of CD1c- cells (consisting mainly of T-cells) with anti-CD3/anti-CD28 beads. We have completed flow-sorting, RNA-seq library formation and sequencing, as well as high-density genotyping, followed by imputation using the TOPMed reference panel [4]. These efforts have generated an unprecedented resource for genetic analysis of gene expression, consisting of up to 153 genotyped individuals with both RNA-seq and ATAC-seq data (ranging from 117 to 153 depending upon cell type) yielding 1,190 and 1,230 post-QC libraries, respectively (MQ30, 25M reads/sample). In a recent SID abstract [5], we reported a preliminary analysis of the RNA-seq and ATAC-seq data from these 153 individuals. Principal components analysis (PCA) revealed clear separations on the basis of activation, CD8/CD4, and skin homing status. Our data also highlighted marked up-regulation of Th17 "signature genes" *IL17A*, *IL17F*, *IL21* and *CCL22*, as well as key energy-generating glycolysis genes *ENO1*, *PKM1* and *LDHA* after 24h of CD3/CD28 stimulation. We further revealed 88 DEGs in T-cells of psoriatics vs. controls (71 up vs. 17 down, $p = 2 \times 10^{-9}$ for the up/down difference, exact binomial test). *IL17A* and *IL17F* were the only two interleukin transcripts overexpressed in activated T-cells from psoriasis cases vs. controls (each 1.9-fold, $p_{adj} = 4.7 \times 10^{-4}$ for CD4 and CD8 combined). Moreover, scRNA-seq of psoriatic skin revealed overexpression of *IL17A* in skin-homing (*FUT7*+) vs *FUT7*- T-cells (2.2-fold, p= 0.003). Chromatin accessibility and gene expression were most strongly correlated in activated T-cells and declined over ±0.3 Mb from the transcription start site. Besides prominent increases in AP-1 family transcription factor (TF) binding with activation, TF footprinting revealed that activation of CLAP T-cells had little effect on TF occupancy, consistent with their history of prior activation in the skin. These results reveal a psoriasis-relevant nexus between T-cell activation and expansion of T17-polarized CLAP T-cells, and suggest that skin-homing T-cells retain a chromatin-embedded memory of their prior activation *in vivo*. These results have been presented in abstract form [5] and are in the final stages of submission for publication.
- We conducted an eQTL analysis for over 6.3M common (minor allele frequency [MAF] ≥ 0.05) well-imputed markers and RNA-seq data for each immunocyte type from the experiment outlined just above, encompassing 153 individuals. We overlapped the cis-eQTLs with 64 lead non-MHC psoriasis-associated variants from [6] (+/- 1.0 Mb from each gene's TSS). Reminiscent of our earlier results in skin and lymphoblastoid cells [7], SNP rs27432 regulating *ERAP1* and *ERAP2*, which encode aminopeptidases involved in HLA Class I antigen presentation, was the most highly significant eQTL in all four CD4 T-cell conditions (and also highly significant in all four CD8 T-cell conditions), In contrast, *KLRC4*/ rs11053802 was among the top three most significant eQTLs in all four CD8+ T-cell conditions, but was not significant in CD4+ T-cells (Fisher exact *p = 0.029*). These results highlight our ability to link psoriasis genetic signals to cell type-dependent gene regulation.
- **Transcriptome-wide association studies (TWAS) of long noncoding (lnc) RNAs.** Employing 727 genotyped RNA-seq samples of sun-exposed and non-sun-exposed skin from GTEx, we used PrediXcan [8] to model the genetically regulated component of expression for 10,809 coding genes and 1,712 skin-expressing lncRNAs. We applied the resulting models to impute genetically regulated transcriptomes for 24,147 genotyped samples (10,033 psoriatic cases and 14,114

controls) from 6 cohorts, using well-imputed markers. We identified 43 non-MHC genes having imputed expression significantly correlated (Bonferroni $p < 3.1x10^{-6}$) with disease status. These genes map to 18 psoriasis susceptibility loci, with 7 of them pointing to only one candidate. This work has been published recently. [9]

- **Psoriasis associations in accessible chromatin.** Our previous work showed that psoriasis genetic signals overlap significantly with active enhancers in T-cells [2]. We utilized our ATAC-seq results to profile chromatin accessibility patterns of resting and 24h CD3/CD28-activated T-cell subsets from 153 individuals (86 cases and 67 controls). We identified 8,516,230 common (MAF > 1%) biallelic variants mapping to open chromatin regions with good read mappability from 1,227 ATAC-seq samples. Utilizing GATK [10] to count the number of reads for each allele, we measured allele-specific accessibility (ASA) for genetic variants mapping to the 95% BCS of potentially causal psoriasis variants (within +/- 100 kb of the best signal for each locus), and identified 862 sites with heterozygous genotypes that mapped to accessible chromatin in 1,184 ATAC-seq samples. Among 67 EUR psoriasis GWAS signals, up to 16 markers from the BCS regions overlapped with heterozygous sites in open chromatin regions encompassing markers exhibiting significant (FDR $\leq$ 10%) ASA in CD3/CD28-activated, but not resting T-cells, including *IFNLR1*, *IL23A*, *ZNF365*, and *PTGER4*.

- **Hi-C mapping**. High-throughput chromosome conformation capture (Hi-C) is a tool for capturing long-range 3D chromatin interactions [11]. We generated Hi-C libraries from the aforementioned nine cell types for two individuals, and sequenced them to a depth of $\geq$1 billion paired reads per library (0.94 $\pm$ 0.14, mean $\pm$ SD). We identified 13,186 ± 2,857 Hi-C loops per library, ranging from 30 to 1,980 kb long. About half of the identified loops have at least one end overlapping a transcription start site (TSS). We identified 27 ± 6 loops per library that linked promoters to known psoriasis signals, defined by the 95% BCS generated from our recent transethnic GWAS [12]. Of 47 target genes involved in such loops, we found 8 previously suggested gene targets for psoriasis: *ANXA6, ELMO1, ETS1, FASLG, MBD2, IFI44, PTGER4* and *STARD6*. Among them, *ANXA6, ETS1, FASLG* and *IFI44* were present only in T cells, while the rest were seen in both T-cells and mDC. We further revealed other psoriasis gene candidates including *KAT5, NHLRC3/PROSER1,* and *SUCO*.

- **scRNA-seq.** We have generated a substantial scRNA-seq dataset from normal (NN) vs. uninvolved (PN) vs. lesional (PP) psoriatic skin, providing a resource for establishing disease relevance by identifying the cell types in which psoriasis-associated genes are expressed. 33 skin biopsies were used to make 10X Genomics scRNA-seq libraries. We delineated multiple cell types using their gene expression signatures, demonstrating altered gene expression signatures for PP vs. NN / PN skin for KC, FB, T-cells, DC, endothelial cells, and several others. This work has been published in Nature Communications [3].

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Articles Submitted for Publication:

1. Feng BJ, Carroll C, Tejasvi T, Tsoi LC, Nair RP, Goldgar DE[1], Callis Duffin K, Orbai AM, Stuart PE, Elder JT, Walsh JA, Krueger GG: Exome-Guided Proteomic Analysis Identifies Early Biomarkers for the Progression from Psoriasis to Psoriatic Arthritis. Lancet Rheumatology, submitted 2024
2. Shaked G, Zhang H, Zhang Z, Gudjonsson JE, Elder JT, Patrick M, Tsoi LC: Loopsim: Enrichment Analysis of Chromosome Conformation Capture with Fast Empirical Distribution Simulation. Nucleic Acids Research Genomics and Bioinformatics, submitted.

A Progress Report by Drs. Christopher Ritchlin and Norman Madsen
IPART Core Site - University of Rochester, Rochester, NY, USA

The IPART registry has proven to be an invaluable resource for the Rochester lab to address fundamental questions related to psoriatic disease and ongoing projects depend on its coordination with IPART. The following projects of **Drs. Christopher Ritchlin and Norman Madsen** are ongoing:.

- **Humanized Mouse Model of Psoriatic Disease.** At the IPART Meeting last May 2024, we presented our data on findings in the SGM-GM3 humanized mouse model in which we demonstrated that phenotypic features of psoriasis or musculoskeletal disease were phenocopied in this model following injection of PBMC and sera from individual patients. We published our results in JCI Insight following that presentation. We are now: 1) exploring the

histopathology and molecular landscape of the disease in the axial skeleton and uveal tract of these mice; 2) injecting mice with sera and PBMC from TNFi Inadequate responders and treating them with different biologics to better understand the signature of inadequate response and determining which are the most effective treatments.; 3) examining the autoantigen that is driving the response in the serum; 4) determining if the recapitulation of the human phenotype in the mice is in part, driven by trained innate immunity. Data from these experiments will be submitted to the ACR 2025 Meeting.

- **RANKL expression by keratinocytes in PsA psoriatic plaques.** In 2023, we presented data at the 2023 IPART scientific meeting showing that PsA but not PsO plaques express RANKL. We have gone on to demonstrate that the RANKL is expressed by keratinocytes in response to both TNF and IL-17 stimulation. In addition, supernatants from these keratinocytes, following exposure to IL-17 and TNF, drive osteclastogenesis when cultured with human monocytes. These data provide another site of pre-osteoclast activation which may account for the elevated frequency of osteoclast precursors in human PsA. This manuscript is submitted for publication.
- **AMP-AIM Progress.** Dr. Ritchlin is the MPI for the ELLIPSS Team of the AMP-AIM Project. We are recruiting PsA and PsO patients at 8 sites and performing skin and synovial biopsies and microbiome analysis of the skin and stool along with extensive immune and genetic profiling of blood specimens. We collected synovium and skin from 12 PsO and PsA patients with early disease (biologic naïve) and these specimens have been analyzed using the Xenium spatial transcriptomics platform and scRNAseq technologies along with repertoire analyses. The data are currently being analyzed at BWH in Boston and University of Michigan. We should have these data by the 3rd quarter of 2025.
- **PAMPA Program.** The PAMPA Study is a multi-site study with centers in Canada (Toronto, St Johns) and the US (NYU, Rochester, Utah, Boston). We are recruiting psoriasis patients with no joint pain and screening them with MSK ultrasound. Patients who meet an ultrasound threshold, with no MSK pain are recruited to one of 3 arms: guselkumab, placebo, observation for patients on topicals or phototherapy. After 6 months, the placebo arm receives guselkumab. The two primary outcome measures are the development of PsA and the change in ultrasound score at 6 months. We have recruited over 100 patients to date to the study.
- **Obesity Program at URMC.** Obesity is a major barrier to treatment response in our patients and we have worked very hard at our center to address weight challenges with our patients. The emergence of GLP-RA represents a major treatment advance that will greatly help out patients lose weight. However, medicines alone are not the answer. We are committed to helping our patients take on lifestyle changes that will allow them to maintain a more optimal week either without medications or after the GLP-RA is stopped. We responded to a Lilly RFA to develop a Q/I Project that will facilitate efficient and accurate measurement of BMI coupled by structural changes in the office (larger chairs and gowns) and the establishment and documentation of referral strategies to our Center for Community Health and Prevention. This center, with 7 dieticians, works with patients on life-style changes using self-determination theory methods. We recently submitted this application but if funded, we plan to start the study in the next quarter. This project is headed by Dr. Norman Madsen. In collaboration with Lilly, we also prepare a review on obesity that will be informative for caregivers in rheumatology.

- **Clinical trials.** Drs. Madsen and Ritchlin are engaged in clinical trials that examine the efficacy and safety of biologic agents in PsA. We have carried out studies over the last year that assess the following medications in phase trials that include bimekizumab and deuravacitinib . We have also carried out post-hoc analyses for guselkumab, tofacitinib and bimekizumab. Dr. Madsen will be leading trials this year to assess the efficacy and safety of sonelokimab and tirzepatide in PsA.

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A Progress Report by Dr. Jan Dutz

IPART Core Site – University of British Columbia (UBC), Vancouver, Canada

The following clinical studies are ongoing in the Vancouver core site spearheaded by **Dr. Jan Dutz**:

- **Small molecule inhibitors for treatment of biologic refractory psoriasis or psoriatic arthritis (In progress).** Roflumilast is a PDE4 inhibitor which has been approved for treatment of COPD. Oral roflumilast has recently been shown to be safe and effective for psoriasis (Lancet Reg Health Eur. 2023 Apr 21;30:100639). We hypothesize that oral administration may have a beneficial effect for patients with psoriatic arthritis in a similar fashion as apremilast. Advantages of roflumilast therapy would include once daily dosing and decreased cost. We currently have a series of patients with psoriatic arthritis, where we have used roflumilast in addition to IL-23 or IL-17 inhibition (similar to J Clin Rheumatol. 2022 Mar 1;28(2):e626-e628), followed in our clinics and are compiling for publication. Two recent case series suggest that TYK2 inhibitors may be added to biologic therapy to enhance response in either the skin (PMID 38754982) or the joints (PMID 38011328). We have designed a pilot trial to test the hypothesis that the addition of either roflumilast (A PDE4 antagonist) or a Tyk2 Inhibitor to patients on single biologic agent therapy and ongoing disease activity will improve disease in multiples domains (enthesitis, dactylitis, peripheral arthritis, nail disease, skin disease, axial disease) and that this improvement may relate to control of aberrant type 1 interferon signaling.
- **Improving therapy for patients with psoriasis and psoriatic arthritis (in progress).** Many patients have benefited from therapy with biologic response modifying medications. A common side effect is pain with injection and injection site reaction (ISR). We hypothesize that these reactions may be in part mediated by innate immune activation within the skin. We are collecting a series to patients who have tried applying clobetasol to the injection site 1 day prior to each dose to see if that improves injection pain, swelling, and erythema. We currently have a series of 10 patients treated for ISR (with citrate product and without citrate product) and are planning mechanistic studies in a subsequent series of patients.
- **Psoriasis induced pigmentation.** Persistent dyspigmentation is an underappreciated consequence of psoriasis. Lentiginous hyperpigmentation is a unique phenomenon in zones previously affected by plaques of psoriasis following treatment, noted in 14% of patients in one cohort (J Am Acad Dermatol. 2020 Oct;83(4):1188-1191). Multiples publications associate this effect with topical or systemic treatment. We have noted this phenomenon in patients after as little as 1 month of disease. We are reviewing our patient cohort to determine the role of skin pigmentation, ethnicity, and therapy, on this side effect.

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A Progress Report by Dr. Lihi Eder
IPART Toronto (2) Core Site – Women's College Hospital, Toronto, ON, Canada

The following projects are ongoing at the Toronto Site 2 – Women's College Hospital spearheaded by **Dr. Lihi Eder**.

- **Sex differences in serum proteomic profiles in psoriatic arthritis**

  ***Background*:** Sex-related differences exist in the clinical presentation and treatment outcomes of patients with psoriatic arthritis (PsA). While males and females are equally susceptible to developing PsA, the underlying biological mechanisms driving the sex-related differences remain unknown.

  Objective: We conducted an untargeted proteomic study to identify sex-specific serum proteins and biological pathways in males and females with PsA.

  ***Methods*:** We measured 6402 unique serum proteins in 50 male and 50 female patients with active PsA and 50 age- and sex-matched non-psoriatic controls. We conducted differential expression and pathway enrichment analysis to compare PsA vs. controls overall and by sex, and PsA males vs. PsA females. Differentially expressed proteins (DEPs) were defined as false discovery rate p-value < 0.05 and an absolute fold change ≥ 1.2. Pathway enrichment was performed on the DEPs using pathDIP v5 and visualized as protein-pathway networks using NAViGaTOR v3. Machine learning classifiers were used to develop sex-specific multi-biomarker models to distinguish PsA from controls. Random forest models highlighted proteins with the highest predictive performances.

  Results: The differential analysis revealed over 20 times more sex-specific DEPs in PsA males vs. controls (n=741) than in PsA females vs. controls (n=31). The enriched pathways among DEPs in PsA males vs. PsA females were related to intracellular signalling, vascular function, cytokine signalling, and immune cell functions (NETosis, phagocytosis). Classification models were able to discriminate PsA from controls for both sexes with an area under the curve of 0.85-0.99. Variable importance analysis identified leukotriene A-4 hydrolase as a significant predictor in PsA females vs. controls, and IL-36 alpha, NEK7, and PIK3CA/PIK3R1 were significant predictors in PsA males vs. controls.

  ***Conclusion*:** We identified significantly more deregulated proteins and biologic pathways in males than in females with PsA. These findings offer new insights into the sex-specific biological pathways implicated in PsA. Further exploration in this area may lead to more personalized and effective therapeutic interventions tailored to the unique characteristics of male and female patients.

- **The incidence and risk factors of brady -and tachy-arrhythmia in patients with psoriatic arthritis.**

  ***Background*:** Patients with psoriatic arthritis (PsA) have been found to be at higher risk for developing diabetes, hypertension, and obesity. These conditions are considered traditional risk factors for development of irregular heart rhythm, and therefore patients with PsA are suspected to be at higher risk.

  ***Objective*:** To assess the incidence rate and risk factors for cardiac tachy- and brady- arrhythmias in patients with PsA. We hypothesize the incidence will be high and that disease control patients will have less arrhythmia.

  ***Methods*:** This was a retrospective cohort analysis using study data from the IPART study cohort, including patients who reported having an arrythmia event in their clinic visit documentation. We evaluated the association between the presence of any arrhythmia and psoriatic arthritis through multivariable regression models. We adjusted for age, sex, BMI, use of cardiac or biological systemic medications, disease severity. We then explored the effects of time-dependent covariates, (time-varying risk factors: PASI score, TJC and SJC, damaged joint count, pain score, HAQ score, MDA, CRP level, and ESR). We calculated hazard ratio for atrial fibrillation/ flutter, ventricular fibrillation, ventricular tachycardia, MobitzII 2nd degree heart block, complete heart block and sick sinus syndrome.

  ***Results*:** A total of 1670 patients with PsA were analyzed (80 atrial tachyarrhythmias, 17 bradyarrhythmias/pacemakers and 11 ventricular tachyarrhythmias). By age 70, the CIRs were 7.82%, 0.67% and 0.45% for atrial, ventricular and bradyarrhythmia, respectively. In multivariable analysis, remission/low vs. high disease activity state was associated with lower risk of atrial tachyarrhythmia (current HR 0.49, 95% CI 0.26, 0.92; adjusted-mean HR 0.46, 95% CI 0.23, 0.91). Along the same line, higher 3-item Visual Analog Scale (3-VAS) was associated with higher risk of atrial tachyarrhythmia (current level HR 1.18, 95% CI 1.04, 1.33; adjusted-mean HR 1.22, 95% CI 1.04, 1.44).
  ***Conclusions*:** Higher PsA disease activity is associated with higher atrial tachyarrhythmia risk. These findings reinforce the importance of controlling inflammation in PsA to optimize cardiac health.

- **Association of Contextual Factors with Sonographic Inflammatory and Structural Phenotypes in Psoriatic Arthritis Patients: A Cross-sectional Study**

  Objective: Ultrasound can enhance psoriatic arthritis (PsA) disease activity assessment, but the impact of contextual factors on sonographic findings in PsA remains unclear. This study examines how demographic and clinical factors affect sonographic lesions in active PsA.

  Methods: Cross-sectional study of 115 active PsA patients from the IPART cohort who underwent US evaluation for synovitis, enthesitis, peritenonitis, tenosynovitis, bone erosion, and new bone formation (NBF). Lesions were scored semi-quantitatively with B-mode and Doppler using a 64-joint, 16-enthesis, and 34-tendon ultrasound protocol. Total scores were analyzed using t-tests and linear regression by age, sex, body mass index, diabetes, alcohol, smoking, disease duration, and biological/target-synthetic disease-modifying anti-rheumatic drug (b/tsDMARDs) exposure.

***Results**:* Patients (mean age 47.1, 47.8% females) had a mean Disease Activity in Psoriatic Arthritis of 22.6 (SD 12.87) and mean sonographic scores for synovitis and enthesitis of 35.6 (SD 22.94) and 30.1 (SD 22.12), respectively. Older patients showed significantly higher enthesitis, bone erosion, and NBF scores. Multivariable analysis revealed that age ≥ 60 was linked to significantly higher inflammatory and structural enthesitis (adjusted β 6.37 and 14.6, respectively), bone erosion (β 2.53), and NBF (β 13.7), and that b/tsDMARDs-exposure correlated with significantly higher synovitis (β 12.8) and tenosynovitis scores (β 5.95).

***Conclusion*:** Older age correlated with more severe inflammatory and structural lesions, reflecting either a more severe PsA phenotype or overlap with age-related changes. Higher synovitis and tenosynovitis scores in b/tsDMARDs-exposed patients likely reflect disease severity rather than a direct effect of treatment. Incorporating contextual factors into sonographic assessments can improve personalized PsA management.

- **The Association Between Glucose Intolerance and Psoriatic Arthritis Features**

***Background*:** Patients with psoriatic arthritis (PsA) have a higher prevalence of diabetes mellitus (DM) compared to the general population, and PsA activity has been found to be associated with a higher risk of developing DM. The bidirectional relationships between glucose intolerance and PsA disease activity and duration remain unclear. Our study evaluated the association between glucose intolerance, measured by HbA1c, and PsA measures of disease activity and duration in patients without known DM.

Methods: We analyzed HbA1c data from 278 patients (1524 visits) from the IPART cohort. Patients were excluded from the analysis if they had a prior diagnosis of DM or used anti-DM drugs or if they used systemic corticosteroids.

Results: 24.7% and 0.6% of visits met the criteria for pre-diabetes and DM, respectively. Age ($r=0.41$) and BMI ($r=0.34$) were cross-sectionally associated with HbA1c levels ($p<0.05$ for both). We assessed the association between measures of PsA disease activity and the HbA1c trajectory as a function of age using linear mixed models adjusting for sex, BMI and PsA duration. Longer PsA duration (≥5 years vs. < 5 years) was associated with a positive upward trajectory in HbA1c as a function of age, independent of BMI and sex (adjusted β for HbA1c slope 0.005, $p<0.0001$). This finding suggests that prolonged PsA disease duration is associated with a more rapid decline in glucose tolerance and progression towards DM that is independent of age and BMI. No association was found between HbA1c and PsA measures of disease activity (e.g. joint count, psoriasis severity, patient reported outcomes and c-reactive protein) in terms of both absolute levels or its trajectory over time after adjusting for BMI, age, sex and medication use.

Conclusion: Overall, the main finding was that prolonged PsA duration is associated with more rapid progression towards DM. While no direct link was found between PsA measures of disease activity and glucose intolerance, our findings highlight a potential "window-of-opportunity" that exists in the immediate period following PsA diagnosis for the prevention of progression towards DM. The results emphasize the importance of early metabolic screening and interventions following PsA diagnosis to prevent progression towards DM.

Future research should focus on elucidating shared metabolic and inflammatory pathways to inform targeted strategies that address both PsA and metabolic comorbidities, ultimately improving long-term outcomes for this patient population. Ultimately, this knowledge could

identify shared metabolic and inflammatory mechanisms and inform targeted interventions to improve outcomes.

- **Higher levels of high-sensitivity CRP is associated with future development of Psoriatic Arthritis in Psoriasis: A prospective cohort study**

  Objective: We aimed to assess whether high sensitivity c-reactive protein (hsCRP) could predict the development of psoriatic arthritis (PsA) in patients with psoriasis.

  Methods**:** We analyzed data from a prospective cohort of patients with psoriasis without PsA at enrollment. Participants were assessed annually by a rheumatologist for signs and symptoms of PsA. Information on patient demographics, psoriasis features, medications and musculoskeletal symptoms was collected. hsCRP levels were measured in serum samples collected at baseline using standard commercial assays. The association between hsCRP levels and risk of development of PsA was assessed using multivariable Cox proportional hazards model adjusted for age, sex, psoriasis severity and duration, nail lesions, body mass index (BMI), fatigue, and medication use.

  Results**:** A total of 589 patients with psoriasis followed from 2006 to 2019 were analyzed. 57 patients developed PsA during the follow up period. Mean level of hsCRP was 3.1±5.5 mg/L (hsCRP levels in incident PsA cases: 5.4±13.1). Significantly higher levels of hs-CRP at baseline were found in patients with arthralgia, obesity and in females. Higher hs-CRP levels were associated with future development of PsA in multivariable analysis (hazard ratio (HR) 1.04, 95% confidence interval (CI) 1.01, 1.07, p=0.007). Similar effect size was seen in males and females. No significant interaction was found between hsCRP and sex or BMI.

  Conclusion: Higher levels of systemic inflammation, as measured by hsCRP, are associated with future development of PsA.

- **Combination of Biological and Targeted Synthetic Disease-Modifying Antirheumatic Drugs in Psoriatic Arthritis**

  Background/Purpose**:** Psoriatic arthritis (PsA) is a complex inflammatory disease where achieving remission remains challenging despite multiple approved biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs). The low remission rates have spurred interest in combining b/tsDMARDs. Given the paucity of data on such combinations, this case series aims to describe the outcomes of combined b/tsDMARD therapy, providing insights into its effectiveness and safety.

  Methods: Case series within a prospective PsA cohort (IPART), identifying patients on combined b/tsDMARD therapy (two drugs from TNF inhibitors, JAKi, TYK2i, IL17i, IL23i, IL-12/23i). Apremilast (APR) and b/tsDMARD combinations were analyzed separately for safety.

  Demographic and clinical data were collected prospectively and supplemented retrospectively via electronic records. Safety outcomes, including infections and non-infectious events, were reviewed.

  Treatment response was assessed through changes in disease activity scores from baseline to follow-ups at 3-6 and 6-12 months. Measurements included tender and swollen joint counts (TJC / SJC), Disease Activity in PsA (DAPSA), psoriasis area and severity index (PASI), body surface area (BSA), and patient-reported outcomes (numerical rating scale for pain, skin, and patient global).

Results: We identified 9 patients that used combined JAK/TYK2i and bDMARD, detailed in Table 1. Most failed multiple csDMARDs (range 2-5) and b/tsDMARDs (range 2-8). The majority were obese (median BMI 31.2). The primary reason for combination therapy was active skin and musculoskeletal inflammation. Median duration on this combination therapy was 259 days. The IL17i + JAK/TYK2 was used in 5 patients (duration range of 214-1751 days), with one infectious stomatitis being observed. Four patients used IL23i + JAK/TYK2i combination (189-424 days), with one episode of folliculitis after addition of deucravacitinib. The TNFi + JAK/TYK2i combination was used 1 patient (324 days), with no side effects. Numerical improvement was seen across several measures of disease activity (Table 2 and Figure 2). Only 1 patient who was using ixekizumab plus deucravacitinib discontinued the therapy at the first follow-up due to worsening of the peripheral arthritis (the patient was previously using ixekizumab plus methotrexate).

We identified 15 patients using combinations of b/tsDMARDs with APR, with a median duration of 735 days. In the APR combination group, various therapies were used over different durations, with some patients having several different drugs combined with APR over time. IL12/23i or IL-23i + APR in 9 patients (360-1,890 days), IL17i + APR in 9 patients (90-2,790 days), TNFi + APR in 7 patients (180-2,340 days), and JAKi + APR in 1 patient (540 days). There were two episodes of diarrhea, with no infections.

Conclusion: This case series provides preliminary data demonstrating a favorable safety profile. Furthermore, short-term response was observed, with improvements in both musculoskeletal and skin domains. However, as this is an observational study with a short-term follow-up, there is a need for randomized clinical trials to further explore and validate these findings.

- **Sex differences in cellular immune profiles in psoriatic arthritis**

Background**:** Males and females are equally susceptible to developing psoriatic arthritis (PsA), yet differences exist in their clinical presentation and treatment outcomes. Males with PsA are 2-3 times more likely to respond positively to their treatments, while females often discontinue their drug treatments sooner due to poor effectiveness and increased side effects. A meta-analysis of randomized controlled trials in PsA found that males were more likely to respond positively to treatments overall and by drug class, including tumor necrosis factor inhibitors (TNFi), interleukin-17 inhibitors (IL-17i), and IL-12/23i. However, no differences were seen for males and females on JAKi and TYK2i. The biological mechanisms driving the sex-related treatment outcome differences remain unclear.

Hypothesis & Objective**:** We hypothesize that cells from the immune system differ between male and female PsA patients, which partially contributes to the differences in treatment responses. Thus, we aim to measure differences and changes in the immune system cells in males and females with PsA before and after starting drug therapy to explain the varying treatment responses.

Methods**:** We will use patient clinical information and peripheral blood mononuclear cells (PBMCs) from the IPART database and biobank. We have identified 26 patients for TNFi (11 males, 15 females), 32 for IL-17i (15 males, 17 females), and 19 for healthy controls (7 males, 12 females). We will use suspension mass cytometry (CyTOF) to characterize the cellular immune profiles of patient PBMC samples before and three months after initiating their drug treatment. Immune cells are stained with the Maxpar Direct Immune Profiling Assay (MDIPA, Standard

BioTools). The assay is a pre-titrated, dried-down, 30-marker metal-tagged antibody cocktail optimized for CyTOF. The assay identifies 37 immune populations, including many relevant to PsA pathophysiology. We supplemented the core panel with antibodies targeting co-stimulation and exhaustion markers for deeper phenotyping and functional characterization.

Unsupervised clustering analysis will be applied to identify and compare immune cell phenotypes among all patients with PsA (general) and separately in males and females (sex-specific). Clinical and imaging parameters will be compared across the identified clusters to determine the clinical relevance of any identified sex-specific immune profiles. We will use regression models to compare the levels of the following parameters across the identified immune clusters: tender and swollen joint count, psoriasis severity, patient-reported outcomes, DAPSA, and ultrasound inflammatory scores. We will assess the association between individual sex-specific and general immune clusters and treatment responses from the models. Lastly, we will use supervised classification models to predict treatment response by the different drug classes and compare the predictive capabilities using receiver operating curves

***Progress to date*:** We have completed our pilot study to identify optimal antibody concentrations for the main experiment. We are currently staining and acquiring our PsA patient and control samples.

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A Progress Report by Dr. Devy Zisman

IPART Israel Collaborating Site – Carmel Medical Center, Haifa, Israel

The following projects are ongoing at the *Carmel Medical Center, Haifa, Israel* spearheaded by **Dr. Devy Zisman.**

- **Biologic switching in psoriatic arthritis: Insights from real-world data and key risk factors**

  Background: Psoriatic arthritis (PsA) is a chronic, heterogeneous inflammatory condition requiring personalized treatment strategies. Biologic therapy switching reflects the disease's dynamic nature and aims to optimize disease control while balancing efficacy, safety, and patient-specific factors.

  Objective: To analyze real-world switching patterns of biologic disease-modifying antirheumatic drugs (bDMARDs) in PsA patients, identify associated risk factors, and provide insights into predictors of mode-of-action switching.

  Methods: This retrospective cohort study utilized the Clalit Health Services database (2005-2023), encompassing 9607 PsA patients in Israel. Patients initiating bDMARDs were tracked for therapy switches. Clinical, demographic, and socioeconomic variables were extracted, and statistical analyses compared characteristics between switchers and non-switchers. Patterns of switching were stratified by the number of switches and study periods (2005-2014, 2015-2023).

  Results: Among 3851 patients initiating bDMARDs, 1848 (48 %) switched therapy at least once. Anti-TNF therapy was the dominant first-line choice, but switching to anti-IL17 therapy became prevalent as the first switch in both single-switch and multi-switch scenarios. Subsequent switches often involved cycling back to anti-TNF or transitioning to other modes of action, such as anti-IL23 or JAK inhibitors. Switching patterns remained consistent across study periods. Switchers were more likely to be female (56.5 vs. 50.6 %, $p < 0.001$), obese (28.1 vs. 22.6 %, $p < 0.001$), smokers (41.6 vs. 37.1 %, $p = 0.005$), and from lower socioeconomic backgrounds (34.1 vs 31.4 %, $p = 0.04$). These factors were all independently associated with switching in mechanism of action on multivariate analysis.

  Conclusion: Cross class biologic switching is common in PsA management (48 %) and influenced by patient demographics and comorbidities. Switching patterns were consistent across time periods despite expanding therapeutic options.

- **Coexistence of Familial Mediterranean Fever with Psoriatic arthritis- A Retrospective case control cohort analysis**

  Background & Objective: Familial Mediterranean Fever (FMF) is an autosomal recessive autoinflammatory disease, associated with various inflammatory conditions. FMF may share some mechanistic pathways with Psoriatic Arthritis (PsA). However, data on the association of FMF with PsA is scarce. We aimed to assess this association using data from a large population database.

  Methods: A retrospective cohort study based on data from a large healthcare provider was conducted between January 2010 and December 2023. Patients with FMF treated with colchicine without history of PsA were identified and frequency matched by age and sex to 10 healthy controls and followed until the occurrence of PsA, death or end of follow-up. Cox proportional hazard regression analysis was used to assess the association between FMF and PsA adjusting for demographic factors and comorbidities.

Results: The FMF cohort included 9,736 subjects, of whom 51.2% were females, with a mean age of 32.0±19.7 years, matched by age and sex to 97,360 controls. During the follow-up, 43 patients in the FMF group developed PsA compared to 119 in the controls, resulting in a hazard ratio of 3.52 (95% CI 2.48-5.0) adjusted to demographics and clinical characteristics. No significant differences were observed between patients with PsA and FMF vs. PsA without FMF in terms of demographics, comorbidities and treatment with conventional or biologic disease modifying anti-rheumatic drugs. **Conclusions:** FMF is associated with increased risk of developing PsA. The positive association between FMF and PsA may point to common pathogenetic pathways that could influence treatment choices.

- **Angiogenesis markers in difficult to treat psoriatic arthritis patients**

  Background: Angiogenesis plays a key role in the pathogenesis of psoriatic arthritis (PsA), but the mechanism is not fully elucidated. We have previously shown that CD147/extracellular matrix metalloproteinase inducer (EMMPRIN) can induce the expression of the pro-angiogenic factors vascular endothelial growth factor (VEGF) and matrix metallopeptidase 9 (MMP-9) in a co-culture of the human HT1080 fibrosarcoma and U937 monocytic-likecell lines. Relative to single cultures, the co-culture of these cells not only enhanced pro-angiogenic factors but also decreased the antiangiogenic factors endostatin and thrombospondin-1 (Tsp-1), generally increasing the angiogenic potential as measured by a wound assay. Using anti-CD147 antibody, CD147 small interfering RNA (siRNA), and recombinant CD147,we demonstrate that CD147 hormetically regulates the generation of endostatin but has no effect on Tsp-1. Since endostatin is cleaved from collagen XVIII (Col18A), we applied different protease inhibitors and established that MMP-9 and proteasome 20S, but not cathepsins, are responsible for endostatin generation. MMP-9 and proteasome 20S collaborate to synergistically enhance endostatin generation, and in a non-cellular system, CD147 enhanced MMP-9 activity and hormetically regulated proteasome 20S activity. Serum samples obtained from RA patients and healthy controls mostly corroborated these findings, indicating clinical relevance. These findings suggest that secreted CD147 mediates a possibly allosteric effect on MMP-9 and proteasome 20S activities and can serve as a switch that turns angiogenesis on or off, depending on its ambient concentrations in the microenvironment. Difficult to treat (D2T) psoriatic arthritis (PsA) presents a state of active inflammatory disease manifestations despite therapy with two mode of action of biologic DMARDS(b-DMARDS) or target synthetic-DMARDS(ts-DMARDS).

  Objectives: To assess the levels of pro- and anti-angiogenic factors in patients with D2T PsA patients compare to non-D2T PsA patients from our IPART site database.

  Methods: We will determine the serum levels of the pro-angiogenic factors EMMPRIN/CD147, VEGF, and MMP-9 activity, and anti-angiogenic factor endostatin and Thrombospondin-1 (Tsp-1) as well as proteasome 20S, cathepsins levels and levels of IL -17, IL-23, IL-12 in D2T-PsA patients and in and non-D2T control groups of patients treated with biologic-DMARDS (b-DMARDS) and /or conventional-DMARDS (c-DMARDS). In vitro assessment of the angiogenesis will be performed by wound assay test. Each patient with D2T-PsA will be matched with at least one non-D2T patient with similar age and disease duration. The serum of the visit with the highest scores of articular and skin manifestations in the database will be evaluated.

  Progress to date: We have identified all D2T PsA patients in our IPART database and matched them with non-D2T patients with similar age and disease duration. We are currently evaluating the levels of the different factors and will present our preliminary results at the meeting.

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UPCOMING INITIATIVE

INTERNATIONAL PSORIASIS AND ARTHRITIS RESEARCH TEAM (IPART) PHASE 2

Background

One of the limitations in identifying the genes and other laboratory biomarkers associated with psoriatic disease (PsD) outcomes is the large number of patients with the disease required to do these types of studies. No single doctor's office, clinic or hospital has a sufficient number of patients to conduct these investigations independently. It is for this reason that IPART was established in 2006.

Phase 1 (the original protocol) of IPART's research operation was approved by the University Health Network (UHN) Research Ethics Board (REB) in 2008 as identified by **CAPCR ID 08-0630**. The first five years (2007-2012) was funded by the Canadian Institutes of Health Research (CIHR) New Emerging Team grant, followed in subsequent years by other grants from The Arthritis Society, NIH, CIHR, etc., as well as multi-industry support, which has sustained its operations until present. Numerous findings have emerged from the original IPART protocol as outlined in detail in the progress reports released to its stakeholders during IPART's annual scientific meetings. However, significant questions we set out to answer remain. Apart from the related sub-projects included in this report, most research components in phase 1 have been achieved and/or completed except for the genetic and biomarker studies which are continuing and form part of the new phase 2 protocol.

Phase 2

In mid-2024, the IPART core and collaborating site investigators developed the protocol for the next phase of IPART's research entitled: "**INTERNATIONAL PSORIASIS AND ARTHRITIS RESEARCH TEAM (IPART) - PHASE 2: PREDICTION OF DISEASE OUTCOMES IN PSORIASIS AND PSORIATIC ARTHRITIS USING CLINICAL, IMAGING AND BIOMARKER DATA – A LONGITUDINAL COHORT STUDY**" which has now been approved by the UHN REB docketed as **CAPCR ID# 24-5640.** It is expected that conditional institutional approval (IA) will be obtained at UHN by mid-year, allowing UHN to begin re-consenting existing IPART participants at UHN and enrolling new patients under the Phase 2 protocol. Thereafter, all core and collaborating sites will facilitate their respective institutional ethics approvals and execute the associated data/ materials transfer agreements in order to collaboratively perform the projects included in phase 2. Full IA will be obtained at UHN once all site agreements have been finalized.

It is anticipated that some phase 2 projects may begin in early 2026 as IA is obtained across sites, and all aims will be completed over a period of approximately ten (10) years.

- **Primary Objectives**

  The overall goal of IPART is to make advances that will lead to significant improvement in outcomes for patients with psoriasis without arthritis (PsC) or psoriatic arthritis (PsA). To achieve this goal, it is imperative that we continue to build the database of carefully phenotyped PsC and PsA patients.

  The database will be used to address the following specific aims in phase 2:

  1. Identify patients with psoriasis destined to develop psoriatic arthritis using clinical features as well as genetic, other soluble biomarkers and imaging modalities (e.g. ultrasound);
  2. Determine whether psoriasis patients treated with biologic therapy are protected from developing psoriatic arthritis;
  3. Identify predictors for drug response and persistence in PsA using imaging and laboratory biomarkers;
  4. Identify predictors for developing co-morbidities (e.g. cardio-metabolic, cancer, infections) among patients with psoriasis and PsA and assess the impact of co-morbidities on disease outcomes using clinical, laboratory and imaging data;
  5. Evaluate the relationship between clinical, laboratory and imaging biomarkers and identify predictors for progression of radiographic damage among patients with psoriatic arthritis;
  6. Evaluate whether the addition of small molecule inhibitors to patients with incomplete response to biologic therapy lead to improved clinical outcomes (effect of combination therapies);
  7. Assess the effect of weight loss on response to biologic therapy in psoriatic disease;
  8. Genetics and disease expression in PsA;
  9. Study sex and gender differences in psoriasis and PsA disease course and response to treatment; and study the underlying mechanisms of these sex/gender differences using clinical and biomarkers data.

EDUCATION, TRAINING & ADVOCACY COMPONENTS

IPART will continue to collaborate with the **Gladman-Krembil Psoriatic Disease Research Program,** UHN-Toronto Western Hospital, likewise spearheaded by Drs. Dafna D. Gladman (Director) and Vinod Chandran (Co-Director) with the following initiatives:

- **PsA Patient Advisory Committee** – The Psoriatic Arthritis Clinic at the UHN-Toronto Western Hospital (TWH), being the core patient resource of the IPART Research Program, is dedicated to patient care and research in psoriasis and PsA. Its mandate is to ensure that the knowledge learned from this research be made available to the patients of the clinic, their families and other interested lay groups. In the past, dissemination pathways were limited to newsletters and annual patient symposiums. The Toronto site investigators spearheading the Psoriatic Arthritis Clinic at TWH deemed it crucial to obtain feedback and participation from its patients and therefore, the Patient Advisory Committee has been formed in 2012, which now has approximately 8 members in the group. They have actively been involved in 1) reviewing educational materials from a patient perspective, 2) provide suggestions and ideas on patient symposium formats, and 3) determine how to effectively spread information on psoriatic disease updates and the latest trend on new therapies for psoriatic diseases.

  Delegates from the Patient Advisory Committee will henceforth be invited to the annual IPART scientific meetings.

- **Psoriatic Arthritis Patient Forum** – Annually, the Gladman-Krembil Psoriatic Disease Research Program takes the lead in conducting educational symposiums for patients with psoriasis and PsA registered in the program for the last almost 20 years; IPART collaborates in these events. The goal for these events is to provide patient education related to psoriatic diseases as well as share information on ongoing and planned research activities in psoriasis and PsA, providing updates on newer clinical management approaches and therapies for these conditions. These educational forums also feature other important related topics like diet, physiotherapy and exercise, skin, stress and pain management, and patient advocacy.

- **Fellows Training** – Training of fellows is an important activity in the program, increasing potential future recruitment of rheumatologists. These fellows contribute significantly into the program and stipends paid for each annually, solicited from various sources. These fellows take active roles in the execution of the various projects ongoing in the IPART and Gladman-Krembil Psoriatic Disease Research Program. Several of these have resulted in the publications described above.

- **Studentship** – Through the Gladman-Krembil Psoriatic Disease Research Program and IPART, medical students likewise take part in projects and core activities as outlined above. The program normally accepts 4-6 students each year and we have several productive summer students investigating our patients.

- **IPART Annual Scientific and Investigator Meetings** – The IPART core investigators, collaborating site investigators and its key coordinators meet annually as one of its medium of dissemination to its stakeholders, to coordinate research activities and unveil new discoveries.

  For 2025, the scientific meeting will be held in-person and is scheduled for **May 16, 2025 from 8:00 AM to 12:00 PM** at the BMO Education and Conference Centre, Krembil Discovery Tower, UHN – Toronto Western Hospital, 60 Leonard Ave., Toronto, Ontario MM5T 2S8.

- **Knowledge Transfer and Exchange** - Knowledge transfer occurs at several levels i.e. presentations

at professional meetings and publications as described in the previous pages. Another aspect of knowledge translation is with other stakeholders, which include patients and their involvement in disseminating information, assistance during grant submissions, etc.

FUNDING STATEMENT

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At present, IPART is funded by multi-industry support from **ABBVIE, PFIZER, UCB, FRESENIUS KABI,** and **ELI LILLY** granted through the IPART Toronto core site at the University Health Network, Toronto Western Hospital.

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