PROGRESS REPORT

As of April 30, 2024

PROGRESS REPORT

DATABASE AND BIOBANKING UPDATE

DATABASE

	TWH	WCH	St. John's	Vancouver	Ann Arbor	Rochester	London	Winnipeg	Israel	Halifax	Argentina	Ottawa
PsA	1725	354	614	99	22	276	211	75	285	4	4	19
Psoriasis	738	404	82	44	69	221	5	193	31	21	9	0
Total	2463	758	696	143	91	497	216	268	316	25	13	19
Female (%)	45.3	56.6	53.2	51.1	47.6	56.9	42.1	50.6	54.7	36.0	92.3	55.6
Caucasian (%)	83.5	73.1	99.2	64.0	98.8	89.7	93.8	82.7	70.9	92.0	75.0	94.4
Visits Ps	3.9	2.2	1.0	1.7	2.6	1.8	1.0	3.7	1.3	1.4	1.0	N/A
Visits PsA	15.4	7.0	1.4	2.0	2.3	3.2	6.1	5.0	3.9	1.3	1.0	1.3
Age Ps	29.2	31.3	29.7	31.2	30.2	32.3	33.2	31.0	36.7	28.4	31.1	35.9
Age PsA	38.6	42.8	39.5	37.5	41.5	41.2	43.0	41.1	45.5	46.0	40.3	45.2
DD Ps	20.0	18.6	18.6	23.5	14.4	19.6	22.7	24.2	19.2	24.8	21.7	N/A
DD PsA	18.0	8.1	11.0	14.6	12.0	12.6	14.9	13.5	13.4	4.2	28.1	14.2

Number of patients within database as of April 12, 2024.

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

In summary:

	PsA	PsC	**TOTAL**
Number of patients	3688	1817	**5505**

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	1405	690	625	168	194	26	223
Serum	11558	1958	1790	490	500	35	264
RNA	9097	797	1021	41	530	35	169
Synovial Fluid	205		31				

Biospecimen samples are updated as of April 11, 2024.

RESEARCH UPDATE (2QTR 2023 – 1QTR 2024)

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 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:

We analyzed the prevalence and predictors of musculoskeletal surgery among the IPART patients registered at the Toronto Western Hospital Psoriatic Arthritis Clinic. We found that 11.8% of our patients underwent musculoskeletal surgery. The predictors for undergoing surgery were the total number of damaged joints, tender and/or swollen joints, presence of nail lesions, higher HAQ scores, elevated acute phase reactants, and HLA-B27 positivity. Higher Psoriasis Area Severity Index (PASI) scores were "protective" (1).

The Toronto Western Hospital component of the IPART database was included in the CanSpA study aimed describing real world retention and effectiveness of Secukinumab among Canadian patients with psoriatic arthritis. The overall retention was 73% at 12 months, with 15.5% being in Disease Activity of Psoriatic Arthritis (DAPSA) remission while 14.4% were in remission based on the Psoriatic Arthritis Disease Activity Score (PASDAS) at 12 months. PASI score improved by 65.8% and tender and swollen joint counts by 65.5% and 73.7% respectively (2).

We analyzed trends in biologic use at the Toronto Western Hospital IPART cohort. Among 571 patients who initiated biologic therapy between January 2000 and July 2020 the highest 3-year persistence probability was observed with certolizumab when used as first biologic while interleukin 17 inhibitors (IL-17i) had the lowest probability. When used as a second medication, certolizumab had the lowest probability of survival. Depression/Anxiety were associated with a higher rate of drug discontinuation due to all causes while having a higher education was associated with lower rates. Higher tender joint count was also associated with a higher rate of discontinuation sue to all causes. Older age at the start of first biologic treatment was associated with a higher rate of discontinuation due to side effects, while obesity had a protective role (3).

We carried out genome wide DNA methylation study to identify markers that can predict which patients with psoriasis will develop psoriatic arthritis. We identified a set of 36 highly relevant methylation markers across 15 genes and several intergenic regions. A classification model based on these markers identified converter and non-converters with an area under the receiver operating curve (AUC) of 0.96 (4)

Using the Toronto Western Hospital IPART psoriasis cohort, we derived a predictive model for the development of psoriatic arthritis for 1 and 5 years. The risk of developing psoriatic arthritis within one year of enrollment into the cohort included younger age, male sex, and family history of psoriasis. Back stiffness, nail pitting, joint stiffness, use of biologic medications patient global health and pain severity with an AUC of 72.3. The risk of developing psoriatic arthritis within 5 years was associated with morning stiffness, psoriatic nail lesions, psoriasis severity, fatigue, pain and use of systemic non biologic medication or phototherapy with an AUC of 74.9 (5).

PUBLICATIONS:

1. Kwok TSH, Sutton M, Cook RJ, Pereira D, Chandran V, **Gladman DD**. Musculoskeletal Surgery in Psoriatic Arthritis: Prevalence and Risk Factors. J Rheumatol 2023;50:497-503.

2. **Gladman D**, Choquette D, Khraishi M, Inman R, Hussein S, Neish D, Leclerc P. Real-world retention and clinical effectiveness of secukinumab for psoriatic arthritis: Results from the CanSpA Research Network. J Rheumatol 2023;50:641-648.
3. Rida MD, Lee KA, Chandran V, Cook RJ, **Gladman DD**. Persistence of Biologics in the Treatment of Psoriatic Arthritis: Data From a Large Hospital-Based Longitudinal Cohort. Arthritis Care & Res 2023;75:2174-2181.
4. Cruz-Correa OF, Pollock RA, Machhar R, **Gladman DD**. Prediction of psoriatic arthritis in patients with psoriasis using DNA methylation profiles. Arthritis Rheumatol 2023;75:2178-2184.
5. Eder L, Lee KA, Chandran V, Widdifield J, Drucker AM, Ritchlin C, Rosen CF, Cook RJ**, Gladman DD**. Derivation of a multivariable psoriatic arthritis risk estimation tool (PRESTO): a step towards prevention. Arthritis Rheumatol online 2023/08/09.

Research activities spearheaded by **Dr. Vinod Chandran,** Co-Investigator – Toronto core site, have focused on identifying biomarkers for psoriatic arthritis, particularly metabolomics, as well as investigating immune response to COVID-19 vaccines.

A Solid-Phase Microextraction-Liquid Chromatography-Mass Spectrometry Method for Analyzing Serum Lipids in Psoriatic Disease

Approximately 25% of psoriasis patients have an inflammatory arthritis termed psoriatic arthritis (PsA). There is strong interest in identifying and validating biomarkers that can accurately and reliably predict conversion from psoriasis to PsA using novel technologies such as metabolomics. Lipids, in particular, are of key interest in psoriatic disease.

We sought to develop a liquid chromatography-mass spectrometry (LC-MS) method to be used in conjunction with solid-phase microextraction (SPME) for analyzing fatty acids and similar molecules. A total of 25 chromatographic methods based on published lipid studies were tested on two LC columns. As a proof of concept, serum samples from psoriatic disease patients (n = 27 psoriasis and n = 26 PsA) were processed using SPME and run on the selected LC-MS method. The method that was best for analyzing fatty acids and fatty acid-like molecules was optimized and applied to serum samples.

A total of 18 tentatively annotated features classified as fatty acids and other lipid compounds were statistically significant between psoriasis and PsA groups using both multivariate and univariate approaches. The SPME-LC-MS method developed and optimized was capable of detecting fatty acids and similar lipids that may aid in differentiating psoriasis and PsA patients.

Classifying Patients with Psoriatic Arthritis According to their Disease Activity Status using Serum Metabolites and Machine Learning

Psoriatic arthritis (PsA) is a heterogeneous inflammatory arthritis, affecting approximately a quarter of patients with psoriasis. Accurate assessment of disease activity is difficult. There are currently no clinically validated biomarkers to stratify PsA patients based on their disease activity, which is important for improving clinical management.

We aimed to identify metabolites capable of classifying patients with PsA according to their disease activity.

An in-house solid-phase microextraction (SPME)-liquid chromatography-high resolution mass spectrometry (LC-HRMS) method for lipid analysis was used to analyze serum samples obtained from patients classified as having low (n = 134), moderate (n = 134) or high (n = 104) disease activity, based on psoriatic arthritis disease activity scores (PASDAS). Metabolite data were analyzed using eight machine learning methods to predict disease activity levels. Top performing methods were selected based on area under the curve (AUC) and significance.

The best model for predicting high disease activity from low disease activity achieved AUC 0.818. The best model for predicting high disease activity from moderate disease activity achieved AUC 0.74. The best model for classifying low disease activity from moderate and high disease activity achieved AUC 0.765. Compounds confirmed by MS/MS validation included metabolites from diverse compound classes such as sphingolipids, phosphatidylcholines and carboxylic acids.

Several lipids and other metabolites when combined in classifying models predict high disease activity from both low and moderate disease activity. Lipids of key interest included lysophosphatidylcholine and sphingomyelin. Quantitative MS assays based on selected reaction monitoring, are required to quantify the candidate biomarkers identified. Identifying

Serum Metabolomic Markers Associated with Skin Disease Activity in Patients with Psoriatic Arthritis

Psoriatic arthritis (PsA) is a chronic, systemic, immune-mediated inflammatory disease causing cutaneous and musculoskeletal inflammation that affects 25% of patients with psoriasis. Current methods for evaluating PsA disease activity are not accurate enough for precision medicine. A metabolomics-based approach can elucidate psoriatic disease pathogenesis, providing potential objective biomarkers.

With the hypothesis that serum metabolites are associated with skin disease activity, we aimed to identify serum metabolites associated with skin activity in PsA patients.

We obtained serum samples from patients with PsA (n = 150) who were classified into mild, moderate and high disease activity groups based on the Psoriasis Area Severity Index. We used solid-phase microextraction (SPME) for sample preparation, followed by data acquisition via an untargeted liquid chromatography-mass spectrometry (LC-MS) approach. Disease activity levels were predicted using identified metabolites and machine learning algorithms.

Some metabolites tentatively identified include eicosanoids with anti- or pro-inflammatory properties, like 12-Hydroxyeicosatetraenoic acid, which was previously implicated in joint disease activity in PsA. Other metabolites of interest were associated with dysregulation of fatty acid metabolism and belonged to classes such as bile acids, oxidized phospholipids, and long-chain fatty acids. We have identified potential metabolites associated with skin disease activity in PsA patients.

Pharmacodynamic Effects of Filgotinib Treatment Driving Clinical Improvement in Patients with Active Psoriatic Arthritis Enrolled in the EQUATOR Trial

The goal of this study was to identify protein and transcriptional biomarkers and pathways associated with baseline disease state, the effect of filgotinib (FIL) treatment on these biomarkers, and to investigate the mechanism of action of FIL on clinical improvement in patients with active PsA.

The phase II EQUATOR (NCT03101670) trial evaluated the efficacy of FIL, a Janus kinase 1-preferential inhibitor, in patients with PsA. Peripheral protein and gene expression levels in association with clinical state at baseline and post-treatment were assessed in 121 patients using linear mixed effects models for repeated measures analyses. Mediation analysis and structural equation modelling (SEM) were performed to investigate the mechanism of action of FIL at week 4 on downstream clinical improvement at week 16.

Baseline analyses showed that markers of inflammation were significantly associated with multiple PsA clinical metrics, except for Psoriasis Area and Severity Index (PASI), which corresponded to Th17 markers. FIL treatment resulted in sustained transcriptional inhibition of immune genes and pathways, a sustained increase in B-cell fraction and mature B-cells in circulation, and a transient effect on other cell fractions. Mediation analysis revealed that changes in B cells, systemic inflammatory cytokines and neutrophils at week 4 were associated with changes in clinical metrics at week 16. SEM suggested that FIL improved PASI through reduction of IL-23 p19 and IL-12 p40 proteins.

Our results revealed that FIL treatment rapidly downregulates inflammatory and immune pathways associated with PsA disease activity corresponding to clinical improvement in PsA.

Third and Fourth Vaccine Doses Broaden and Prolong Immunity to SARS-CoV-2 in Adult Patients with Immune-Mediated Inflammatory Diseases

Previous studies have reported impaired humoral responses after SARS-CoV-2 mRNA vaccination in patients with immune-mediated inflammatory diseases (IMIDs), particularly those treated with anti-TNF biologics. We previously reported that IMID patients diagnosed with inflammatory bowel disease, psoriasis, psoriatic arthritis, ankylosing spondylitis, or rheumatoid arthritis exhibited greater waning of Ab and T cell responses than healthy control subjects after SARS-CoV-2 vaccine dose 2. Fewer data are available on the effects of third and fourth doses.

This observational cohort study collected plasma and PBMCs from healthy control subjects and untreated or treated patients with IMIDs prevaccination and after one to four doses of SARS-CoV-2 mRNA vaccine (BNT162b2 or mRNA-1273). SARS-CoV-2-specific Ab levels, neutralization, and T cell cytokine release were measured against wild-type and Omicron BA.1 and BA.5 variants of concern. Third vaccine doses substantially restored and prolonged Ab and T cell responses in patients with IMIDs and broadened responses against variants of concern. Fourth-dose effects were subtle but also prolonged Ab responses. However, patients with IMIDs treated with anti-TNF, especially patients with inflammatory bowel disease, exhibited lower Ab responses even after the fourth dose. Although T cell IFN-γ responses were maximal after one dose, IL-2 and IL-4 production increased with successive doses, and early production of these cytokines was predictive of neutralization responses at 3-4 mo postvaccination.

Our study demonstrates that third and fourth doses of the SARS-CoV-2 mRNA vaccines sustain and broaden immune responses to SARS-CoV-2, supporting the recommendation for three- and four-dose vaccination regimens in patients with IMIDs.

When Should I Get My Next COVID Vaccine? Data from the SUrveillance of responses to COVID-19 vaCcines in systEmic immunE mediated inflammatory Diseases (SUCCEED) Study

Our objective was to determine how serologic responses to COVID vaccination/infection in immunemediated inflammatory disease (IMID) are affected by time since last vaccination and other factors.

Post-COVID-19 vaccination, data and dried blood spots/sera were collected from adults with rheumatoid arthritis, inflammatory bowel disease, systemic lupus, ankylosing spondylitis/spondylarthritis and psoriasis/psoriatic arthritis. First sample was at enrolment and then 2-4 weeks and 3, 6, and 12 months after latest vaccine dose. Multivariate generalized estimating equation regressions (including medications, demographics, and vaccination history) evaluated serologic response, based on log-transformed anti-RBD IgG titres; we also measured anti-nucleocapsid IgG.

Positive associations for log-transformed anti-RBD titres were seen with female sex, number of doses, and self-reported COVID infections in 2021-2023. Negative associations were seen with prednisone, anti-TNF agents, and rituximab.Over 2021-2023, most (94%) of anti-nucleocapsid positivity was associated with a self-reported infection in the 3 months prior. From March 2021 to Feb 2022, anti-nucleocapsid positivity was present in 5-15% of samples and was highest in the post-Omicron era, with anti-nucleocapsid positivity trending to 30-35% or higher as of March 2023. Anti-nucleocapsid positivity in IMID remained lower than Canada's general population seroprevalence (>50% in 2022 and >75% in 2023).Time since last vaccination was negatively associated with log-transformed anti-RBD titres, particularly after 210 days.

Ours is the first pan-Canadian IMID assessment of how vaccine history and other factors affect serologic COVID-19 vaccine responses. These findings may help individuals personalize vaccination decisions,

including consideration of additional vaccination when >6 months has elapsed since last COVID vaccination/infection.

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2. Bowdish DME, Chandran V, Hitchon CA, Kaplan GG, Avina-Zubieta JA, Fortin PR, Larché MJ, Boire G, Gingras AC, Dayam RM, Colmegna I, Lukusa L, Lee JLF, Richards DP, Pereira D, Watts TH, Silverberg MS, Bernstein CN, Lacaille D, Benoit J, Kim J, Lalonde N, Gunderson J, Allard-Chamard H, Roux S, Quan J, Hracs L, Turnbull E, Valerio V, Bernatsky S; SUCCEED investigative team. When Should I Get My Next COVID Vaccine? Data from the SUrveillance of responses to COVID-19 vaCcines in systEmic immunE mediated inflammatory Diseases (SUCCEED)study. J Rheumatol. 2024 Apr 15:jrheum.2023-1214.
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5. Koussiouris J, Looby N, Kotlyar M, Kulasingam V, Jurisica I, Chandran V. Classifying patients with psoriatic arthritis according to their disease activity status using serum metabolites and machine learning. Metabolomics. 2024 Jan 24;20(1):17.
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A Progress Report by Dr. Proton Rahman, PI
IPART Genetic Core Site – Memorial University of Newfoundland, St. John's, NL, Canada

The following projects are spearheaded by **Dr. Proton Rahman,** at the Memorial University of Newfoundland (MUN); the results of which will be orally presented in details during the scientific meeting:

Epidemiology of Psoriasis in the Canadian province of Newfoundland and Labrador

Co-Investigators: Dr Alison K Wright, Prof Darren M Ashcroft, Prof Christopher E M Griffiths, Dr. Julia-Tatjana Maul, Prof Wayne P Gulliver

This study aimed to determine the incidence and prevalence of psoriasis in Newfoundland and Labrador between 2001 and 2020. It examined the onset of psoriasis by age, gender, ethnicity, and rural secretariat region, as well as the impact of social determinants of health data on the regional prevalence of psoriasis and psoriatic arthritis. The study used two databases from the Newfoundland and Labrador Centre for Health Information (NLCHI): the Provincial Discharge Abstract Database (PDAD) and the Newfoundland and Labrador Medical Care Plan (MCP) Fee-for-Service (FFS) Physician Claims Database. Additionally, census subdivision (CSD) data will be captured from the Master Geography File database. The study population consisted of all individuals contributing to the databases between 1 January 2001 and 31 December 2020.

Impact of Multiple IMIDs (IBD and psoriatic disease) (study funded by Janssen)

This study aimed to describe the natural history of concomitant inflammatory musculoskeletal diseases (IMIDs), such as psoriatic disease and inflammatory bowel disease (IBD). It compared the disease course and co-morbid illness of single vs. multiple IMIDs, identified predictors of subsequent IMIDs, and compared single vs. multiple IMIDs regarding mortality, cardiovascular, mental health, fee for service, and hospitalization cost.

Comparison of Pediatric vs Adult Psoriasis: (study funded by Janssen)

This study compared the epidemiology, disease characteristics, co-morbidities, mortality, and costs of pediatric-onset psoriasis to adult-onset psoriasis. The study used a control group matched based on the sex and the onset age of pediatric psoriasis patients. The study population consisted of 1540 patients whose psoriasis was first noted before age 18.

PUBLICATIONS:

1. Gladman DD, Chandran V, Rosen CF, Rohekar S, Boyd T, Eder L, **Rahman P**, Dutz J, Chan J, Haydey RP, Barac S, Laliberté MC, Girard T, Fournier PA, Sutton M, Pereira D, Chim T, Coupal L, Choquette D. Residual Disease Activity in Canadian Patients With Psoriatic Arthritis Treated With Advanced Therapies: Results From a Multiregistry Analysis (UNISON-PsA). J Rheumatol. 2024 May 1;51(5):479-487. doi: 10.3899/jrheum.2023-0716. PMID: 38359937.
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A Progress Report by Dr. James T. Elder
IPART Core Site - University of Michigan, Ann Arbor, MI, USA

GENETIC STUDIES

International meta-GWAS

Our new, greatly enlarged international meta-GWAS of psoriasis (UK, USA, Canada, Germany, Norway, Estonia) has been reviewed by Nature Communications (NCOMMS), and we have nearly finished our revisions in response to critique. The article was reviewed favorably overall but revisions were requested, which are now nearly complete and ready for re-submission. The article has been submitted to MedRxiv (2023.10.04.23296543, doi: 10.1101/2023.10.04.23296543). The submitted abstract is as follows:

> "Psoriasis is a common, debilitating immune-mediated skin disease. Genetic studies have identified biological mechanisms of psoriasis risk, including those targeted by effective therapies. However, the genetic liability to psoriasis is not fully explained by variation at robustly identified risk loci. To move towards a saturation map of psoriasis susceptibility we meta-analysed 18

GWAS comprising 36,466 cases and 458,078 controls and identified 109 distinct psoriasis susceptibility loci, including 45 that have not been previously reported. These include susceptibility variants at loci in which the therapeutic targets IL17RA and AHR are encoded, and deleterious coding variants supporting potential new drug targets (including in *STAP2*, *CPVL* and *POU2F3*). We 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, highlighting roles for the transcriptional regulation of haematopoietic cell development and epigenetic modulation of interferon signalling in psoriasis pathobiology."

Transethnic GWAS

Because transethnic analysis may facilitate prioritization of causal genetic variants, we performed a genomewide association study (GWAS) of psoriasis in South Asians (SAS), consisting of 2,590 cases and 1,720 controls. Comparison with our existing European-origin (EUR) GWAS showed that effect sizes of known psoriasis signals were highly correlated in SAS and EUR (Spearman $\rho = 0.78$; $p < 2 \times 10^{-14}$). Transethnic meta-analysis identified two non-MHC psoriasis loci (1p36.22 and 1q24.2) not previously identified in EUR, which may have regulatory roles. We also conducted a fine-mapping of MHC psoriasis associations in SAS and EUR. HLA-C*06 was the top-ranking MHC locus in both populations but was even more prominent in SAS based on odds ratio, disease liability, model fit and predictive power. Transethnic modeling also substantially boosted the probability that the HLA-C*06 protein variant is causal. Secondary MHC signals included coding variants of HLA-C and HLA-B, but also potential regulatory variants of these two genes as well as HLA-A and several HLA class II genes, with effects on both chromatin accessibility and gene expression. This study was published in 2022 [1], and has been cited 18 times. In other HLA-related genetic studies, we collaborated in the generation of a high-resolution HLA reference panel capturing global population diversity, which was published in Nature Genetics [2].

TDMA and MR Studies

We continue to participate in trans-disease meta-analyses (TDMA) and Mendelian Randomization (MR) studies involving psoriasis and PsA, revealing relationships between psoriasis and COVID-19 [3] and Type II diabetes [4].and exploring potential genetic relationships between psoriasis/PsA and other diseases, including osteoporosis [5], body mass index [6], adiposity [7], and periodontitis [8].

Rare Variants for Prediction of PsC to PsA Conversion

We (at the University of Michigan) are collaborating with the Utah Psoriasis Initiative (UPI) headed by Gerald Krueger, Bingjian Feng and colleagues in Salt Lake City to analyze exome sequencing data generated by Regeneron Genetics Center from Michigan and Utah DNA samples. We had hoped to include IPART DNA samples in this study but an agreement between UHN and Regeneron could not be worked out. These data have been used to nominate proteins which may be biomarkers for progression to PsA. Three candidate protein biomarkers have been identified in plasma and tested at Utah. Once the paper is published, IPART samples will form a valuable genetic and proteomic replication set based on time-to event as well as case-control analysis.

FUNCTIONAL GENETIC/GENOMIC STUDIES

CD3/CD8-stimulated PBMC as an Endophenotype for Th17 Expansion in Psoriasis

Psoriasis has a polygenic basis, as shown by genome-wide association studies (GWAS) [9]. Overall, 80-90% of GWAS signals appear to be regulatory in nature [10-15], requiring new datasets and tools for analysis of genetic regulation of gene expression in disease-relevant cell types. The regulatory milieu of blood [16] and other tissues [17-19] varies in a cell type-specific fashion, which is dependent upon the activation status of immunocytes including monocytes [20] and T-cells [21-23]. To address these dependencies, we generated ATAC-seq and RNA-seq datasets from subsets of peripheral blood mononuclear cells (PBMC) in a sample

of 153 individuals, with the ultimate goal of understanding the regulatory effects of psoriasis-associated genetic variation. We chose PBMC not only due to their ready accessibility from large numbers of subjects, but also for the known enrichment of psoriasis genetic signals in innate and acquired immune-related functions and in regulatory elements from different T-cell subsets [24].

We[25] and others[26-29] have shown that the ability of T-cells in CD3/CD28-stimulated peripheral blood mononuclear cell (PBMC) cultures to manifest Th17 expansion is restricted to memory T-cells, is strongly monocyte-dependent, and requires monocyte-T-cell contact. We flow-sorted 4 memory T-cell subsets (CD4 / CD8 x CLA+ / CLA-) from PBMC of 153 individuals (86 cases, 67 controls), either with (Day 1) and without (Day 0) 24h of CD3/CD28 activation using anti-CD3/anti-CD28 Dynabeads **(Fig. 1)**. Analysis of bulk RNA- seq data from the 8 different T-cell fractions indicated (a) admixture of monocytes in the CLA+ T-cell fractions at Day 0, and (b) marked reduction in the expression of monocyte signature genes (e.g. *CD14*, *CD93*, *CD163*, *S100A8*, *S100A9*, and *S100A12)* within 24h of CD3/CD28 activation. We confirmed both of these findings by standard flow cytometry for CD45RO, CD3, and CD14, as well as imaging flow cytometry (IFC) for CD3 and CD14 (data not shown).

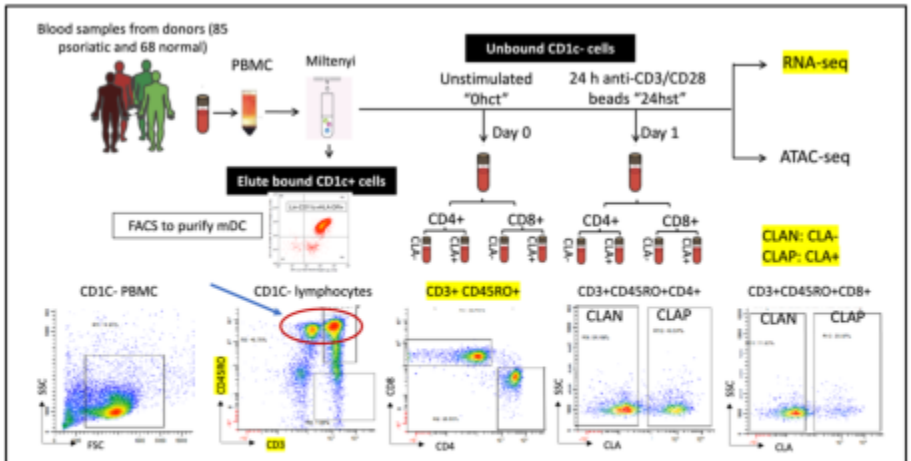

Fig. 1. Summary of flow sorting experiment. Flow sorts are from unstimulated PBMC from a single individual. Note overlap between CD45RO+CD3^{lo} and CD45RO+CD3^{hi} cells in the CD1c- lymphocytes (arrow).

Regarding monocyte admixture in T-cell populations: As shown in **Fig.1,** we found overlap between CD45RO+CD3^{lo} and CD45RO+CD3^{hi} cells during the cell sorting procedure, which was somewhat variable from subject to subject. This would be expected based on our flow sorting protocol because monocytes and skin-homing T-cells are both CD45RO+[30] and CLA+[31]. Thus, it appears that our efforts to maximize the number of sorted T-cells cells appears to have led to the observed monocyte admixture, as the only factor separating the two populations was cell surface expression of CD3. Interestingly, IFC revealed the presence of many extracellular particles carrying RNA and DNA and acquisition of well-demarcated CD14-bright "specks" both as intercellular particles and within T-cells, even in freshly isolated PBMC without CD3/CD28 activation. As shown in **Fig. 2**, the percentage of CD14+ specks in the CD3^{hi} population increases as the overall CD14 signal intensity increases.

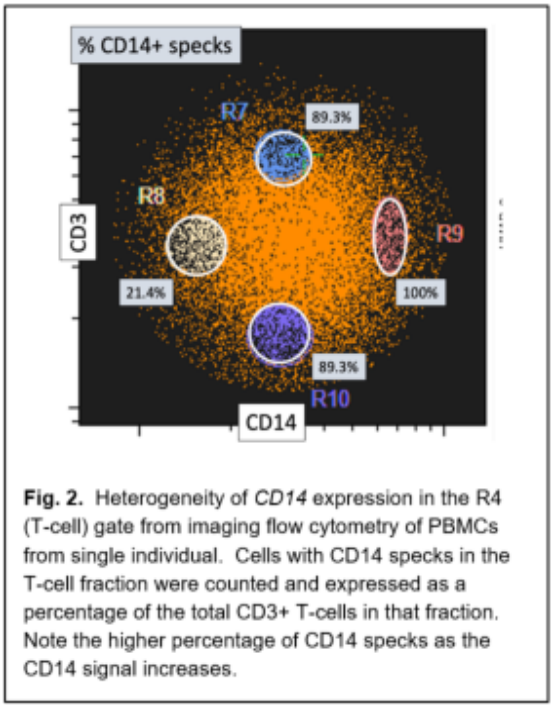

Fig. 2. Heterogeneity of *CD14* expression in the R4 (T-cell) gate from imaging flow cytometry of PBMCs from single individual. Cells with CD14 specks in the T-cell fraction were counted and expressed as a percentage of the total CD3+ T-cells in that fraction. Note the higher percentage of CD14 specks as the CD14 signal increases.

Regarding loss of monocytes after T-cell activation: We found that the loss of monocytes varies from 85 to 90% after 24 hr ($p < 0.001$). Monocyte losses in PBMC cultures have been reported in older studies [32-35], as well as in our own work[25] and in a recent CITE-seq study[36]. Many of the older studies claimed that monocytes were being killed by cytotoxic T-cells. To better understand the phenomenon of monocyte loss in this system, we performed time-lapse microscopy (TLM) of purified monocytes, non-monocytes, and mixtures of the two over 24 hr, which showed that monocytes die under our culture conditions whether or not non-monocytes (i.e., T-cells, B-cells, and NK cells) are present. Based on our studies, we now suspect that this phenomenon of CD14+ specks in the $CD3^{hi}$ population mentioned above represents efferocytosis of monocyte apoptotic bodies by T-cells and/or NK cells.

In February 2023, we submitted an NIH R01 application based on the above observations. We **hypothesized** that: (a) CD14+ particles are monocyte-derived apoptotic bodies **(MonABs)**, which are formed in both resting and TCR-activated PBMCs; (b) MonABs are formed due to oxidative stress and DNA damage occurring under laboratory conditions; (c) MonABs can replace the monocyte contact requirement for Th17 expansion to elicit Th17 responses; (d) MonAB-derived nucleic acids gain access to host cells and trigger innate responses by interacting with psoriasis-associated double-stranded RNA (dsRNA) sensors, leading to Th17/Tc17 (T17) induction. Unfortunately, this application was not discussed. Nevertheless, substantial genetic and genomic information related to how genetic variation affects gene expression and chromatin accessibility during T-cell activation has emerged from this study.

Despite these complexities, the CD3/CD28-stimulated PBMC system has provided detailed information about the gene expression and chromatin accessibility profiles induced by CD3/CD28 activation, due to the large number of individuals sampled (153). Analysis of the RNA-seq data revealed that activation-related differentially expressed genes (DEGs) included strongly upregulated Th17 signature mRNAs (*IL17A*, *IL17F*, *IL22*, and *CCL22*) along with the Th1 cytokine *IFNG.* Thus, we found 109- and 1,052-fold changes in *IL17A* and *IL17F* mRNAs in activated vs resting T-cells, with an additional 4.4- fold change in activated CLA+ vs. CLA-. Very similar results were seen for other T17 signature genes including *IL22* and *CCL20* upon T-cell activation (146-fold and 87-fold, respectively). There was a corresponding induction of IL-17A and IL-22 proteins as detected by flow cytometry. Stratified analysis of skin-homing in CD3/CD28-activated cells revealed 2.9 to 12.1-fold upregulation of *IL17A*, *IL17F*, *IL22*, and *CCL22* in CLA+ vs CLA-, without a corresponding difference in *IFNG*. *IL17A* and *IL17F* were overexpressed in activated T-cells from psoriatics vs. controls (1.9-fold, $p=4.7x10^{-4}$). As revealed by scRNA-seq of psoriatic skin[37], *IL17A* was overexpressed (2.2-fold, p= 0.003) in skin-homing (*FUT7*+) vs. *FUT7*- T-cells, whereas *IFNG* was not.

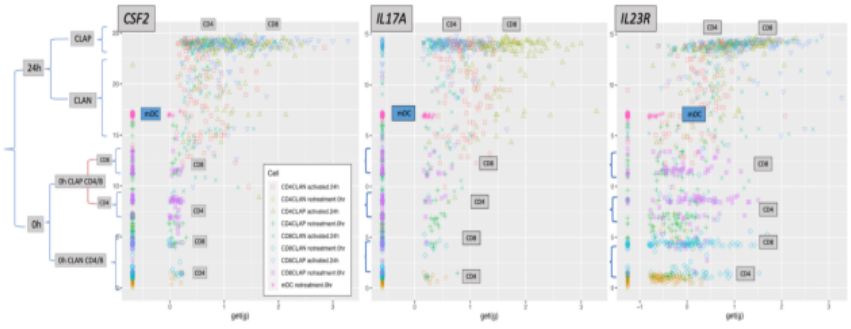

Fig. 3. Pseudotime (y-axis) of CSF2, IL17A, and IL23R in resting vs. activated, skin homing vs. non-skin homing memory T-cells in flow-sorted PBMC subsets. The x-axis is a measure of normalized gene expression. Cell key applies to all 3 panels. CLAP, CLA-positive. CLA-, CLA-negative.

Of particular relevance to the findings about the behavior of the CD3/CD28-stimulated PBMC system described above, we found that T-cell activation markedly up-regulated expression of (a) *CSF2* mRNA encoding GM-CSF, and (b) *IL23R* mRNA, encoding the IL-23-specific subunit of the IL-23 receptor (IL-23R). As illustrated by pseudotime trajectory analysis[38], which quantifies cell lineage and biological trajectory of the bulk RNA-seq data emerging from the flow-sorted PBMC dataset, we found a 262-fold increase in *CSF2* mRNA encoding GM-CSF in activated vs resting T-cells, with an additional 2.2-fold change in activated CLA+ vs. CLA-. **(Fig. 3).**

T-cell activation also induced a 6-fold expression of *IL23R*, whose regulation we have shown to be directly impacted by psoriasis-associated genetic variation**.** Thus, we **hypothesize** that the small fraction of myeloid cells that persist in the PBMC cultures after activation are protected from death by CM-CSF produced by the activated T-cells. In turn, activation upregulates IL23R on T-cells, rendering them responsive to IL-23 produced by inflammatory myeloid dendritic cells. Together, these factors could explain the remarkable clustering of T-cells and dendritic-shaped monocyte-derived cells that we observe by time lapse microscopy.

Integration of Genetic and Genomic Data

As the ultimate goal of this work, the integration of psoriasis disease association data from the expanded meta-GWAS with the ATAC-seq, RNA-seq, and genotyping information from these 153 individuals is ongoing **(Fig. 4)**. Using Bayesian techniques, we have found that the number of strong candidates for being a causal variant is increasing from 3 to 8-fold by incorporating gene expression and chromatin accessibility data.

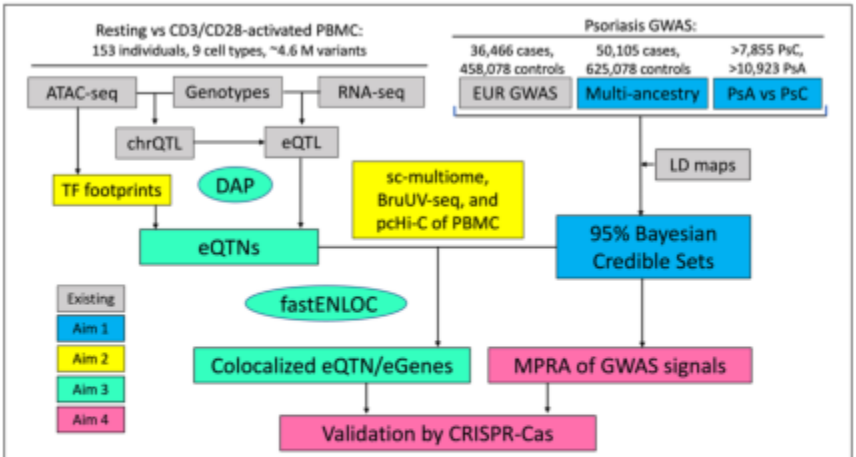

Fig. 4. Plan for integration of GWAS, ATAC-seq, RNA-seq, BruUV-seq, and pcHi-C data. In our Linkage Analysis of Familial Psoriasis grant application, Aims are color coded, gray indicates data complete.

Funding Status

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A Progress Report by Dr. Christopher Ritchlin
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. We have four ongoing projects that depend on coordination with IPART.

Elevated RANKL Expression Skin Plaques of PsA Compared to PsO Patients

We previously demonstrated that osteoclast precursors are elevated in the circulation in PsA patients. We also identified increased RANKL expression in the synovium of PsA patients. It is known that keratinocytes in psoriasis can express RANKL but the comparative expression of RANKL in psoriatic plaques vs PsA plaques has not been examined. We found RANKL expression was significantly higher in the epidermis and dermis of PsA compared to PsO patients. Moreover, DC-STAMP+ monocytes (osteoclast precursors) were significantly higher in PsA plaques. Lastly keratinocytes from psoriatic plaques (PsO and PsA) demonstrated marked upregulation of RANKL when exposed to TNF plus IL-17 compared to either cytokine alone.Over the past year, we deeply phenotyped the patients and demnstrated that supernatants from keratinocytes produce RAKNKL These studies provide support for the concept that the skin in PsA patients may drive monocytes toward an osteoclast phenotype and suggest the possiblity that the skin may serve as an arthritis marker in patients with psoriasis. This abstract was an oral presentation at the ACR in 2023 and we are submitting a manucript to Clinical Immunology the end of this month. (1)

Development of a Humanized Mouse Model of Psoriasis and PsA

Dr. Luz Garcia-Hernandez, a scientist in my lab developed a humanized mouse model of PsO and PsA that recapitulates the phenotype of the patient. Mice develop psoriatic lesions when injected with PBMC and sera from psoriasis patients and arthritis and psoriasis following injection of PBMC and sera from a PsA patient. The mice also develop dactylitis if the patient has dactylitis features. We extracted thje cells from the joints and skin and performed transcriptic analysis demonstrating chemokines and cytokines expressed by these cells. We are now injecting the mice with PBMC and sera from TNFI non responders to examine which pathways remain active. This is an excellent model to examine mechansisms of non-response and provides a highly personalized model to examine novel therapies. We demonstrated that we can recapitulate the axial phenotype in these mice and we are studying inadeqaute responders and testing various therapies in this model (2-4). A manuscript describing this research was just accepted by JCI Insight.

Recruitment of Patients for Clinical Trials

My Team is engaged in a number of clinical trials, two of which Jose Scher and I designed (AFFINITY, PAMPA)and we recruit patients through IPART. We are also engaged in trials examining effiacy of biologics and JAKi and depend on IPART to recruit patients.(5) The AFFINITY TRIAL is fully enrolled and we are reviewing the data from the trial next week.

AMP-AIM Study

The University of Rochester Medical Center is the lead site for the Psoriatic Disease Team in the AMP AIM Study. This innovative collaboration between industry, FNIH and academic centers will recruit patients with psoriasis and PsA and examine skin, synovium and blood with advanced technologies such as scRNA-seq, spatial transcriptomics,metabolomics and epigenomics performed on blood, synovial tissue and skin samples. We completed all the background work to establish the consortium and we will begin recruitng patients next week. Two manuscripts were published by members of our team and we contributed samples from the IPART patients to NYU and Dr. Castillo. Dr. Gudjonsson is an MPI on our AMP AIM ELLIPSS Psoriasis and Psoriatic Arthritis Team. (6,7)

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2. Garcia-Hernandez M, Rangel-Moreno J, Paine A, Bhattacharya S, Fox J, Meyer E, Isett B, Bao R, Bruno T, Ritchlin C. Psoriatic Arthritis Disease Subtypes Mediated by CD8 T Cells Are Phenocopied in a Novel Humanized Murine Model of Psoriasis and Arthritis [abstract]. *Arthritis Rheumatol.* 2022; 74 (suppl 9).
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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**:

Roflumilast a PDE4 Inhibitor for Treatment of Mild/Moderate Psoriasis and 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.

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.

PUBLICATIONS:

1. A. M. Drucker et al., Top Ten Research Priorities for Psoriasis, Atopic Dermatitis and Hidradenitis Suppurativa: The SkIN Canada Priority Setting Initiative. J Cutan Med Surg 27, 133-139 (2023).
2. D. D. Gladman et al., Residual Disease Activity in Canadian Patients With Psoriatic Arthritis Treated With Advanced Therapies: Results From a Multiregistry Analysis (UNISON-PsA). J Rheumatol 51, 479-487 (2024).
3. P. Nash et al., Systematic literature review and network meta-analysis of therapies for psoriatic arthritis on patient-reported outcomes. BMJ Open 13, e062306 (2023).
4. K. A. Papp et al., Use of Systemic Therapies for Treatment of Psoriasis in Patients with a History of Treated Solid Tumours: Inference-Based Guidance from a Multidisciplinary Expert Panel. Dermatol Ther (Heidelb) 13, 867-889 (2023).

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**:

Prediction of Psoriatic Arthritis Tool (PRESTO): Development and performance of a new scoring system for psoriatic arthritis risk.

Background: A simple, scalable tool that identifies psoriasis patients at high risk for developing psoriatic arthritis (PsA) could improve early detection and facilitate early intervention for this condition. However, no such prediction tool currently exists.

Objective: Our overall objective is to develop an accurate risk prediction model for the development of PsA and to assess its performance among patients with psoriasis.

Methods: In this longitudinal cohort study we analyzed data from the International Psoriasis and Arthritis Team (IPART) study, a prospective cohort of psoriasis patients without PsA at the time of enrollment. The

participants were followed prospectively from 2006 to 2019, and their PsA status was assessed annually by a rheumatologist. Information about their demographics, psoriasis characteristics, co-morbidities, medications, and musculoskeletal symptoms was used to develop prediction models for PsA. Penalized binary regression models were used for variable selection while adjusting for psoriasis duration; the stacked LASSO with equal weights was adopted to deal with multiple imputed datasets for incomplete data. Risks of developing PsA over 1- and 5-year time horizons were estimated. Internal validity was assessed using 5-fold cross-validation. Model performance was assessed by the area under the curve (AUC), and calibration plots.

Results: A total of 635 psoriasis patients were analyzed (mean duration of follow up 7.7 years). 51 and 71 patients developed PsA during the 1-year and 5-year periods, respectively. The risk of developing PsA within 1 year was associated with younger age, male sex, family history of psoriasis, back stiffness, nail pitting, level of stiffness, use of biologic medications, patient global assessment of health and pain severity (AUC 72.3, 95% confidence interval (CI) 65.5, 79.1, Figure 1A). The risk of developing PsA within 5 years was associated with morning stiffness, psoriatic nail lesion, psoriasis severity (by PASI), fatigue severity (by FACIT-fatigue), pain severity and use of systemic non-biologic medication or phototherapy (AUC 74.9, 95% CI 69.3, 80.5, Figure 1B). Calibration plots showed reasonable agreement between predicted and observed probabilities. The sensitivity and specificity for a 2.5% probability of PsA onset within 1 year were 54.5% and 75%, respectively. The sensitivity and specificity for a 5% probability of PsA onset within 5 years period were 61.1% and 77%, respectively.

Conclusion: The development of PsA within clinically meaningful time frames can be predicted with reasonable accuracy for psoriasis patients. Additional work is underway to validate these models in external cohorts of psoriasis patients.

Reference: Eder L, Lee KA, Chandran V, Widdifield J, Drucker AM, Ritchlin C, Rosen CF, Cook RJ, Gladman DD. Derivation of a Multivariable Psoriatic Arthritis Risk Estimation Tool (PRESTO): A Step Towards Prevention. Arthritis Rheumatol. 2023 Aug 9. doi: 10.1002/art.42661. Epub ahead of print. PMID: 37555242.

Experiences and Perspectives of Patients with Psoriatic Arthritis Participating in a Randomized Controlled Trial of Dietary Interventions

Background/Purpose: Dietary Interventions in psoriatic arthritis (DIPSA) is a randomized controlled trial (RCT) assessing the efficacy of dietary modifications in patients with psoriatic arthritis (PsA). Ideally, the design of an adjunct therapy trial and the intervention itself should engage patients in a positive experience. We aimed to describe patients' experience participating in a dietary RCT in a rheumatology setting.

Methods: DIPSA (NCT04180904) compares the efficacy of the Mediterranean diet and DASH-low caloric diet as adjunct therapy to the standard of care in PsA. Patients with moderately active PsA (DAPSA > 10) who were overweight or obese (BMI 25-40) were enrolled into the trial for 24 weeks. The trial design is shown in Figure 1. At the end of the trial, participants underwent a semi-structured interview regarding their participation including challenges faced, positive aspects of the trial, and recommendations for a future intervention and/or trial. Interviews lasted 20-30 min and were carried out by trained research coordinators. The interviews of first 50 participants who completed the trial (out of intended 90) were analyzed using modified grounded theory by two research coordinators with input from the two PIs.

Results: The mean age of the participants was 54.8 years (SD 12.3 years) and 66% were females. Key themes identified included the benefit of increased wellness from healthy diet, structured intervention, support from dietitian and other staff, self-awareness, barriers to dietary changes, and other lifestyle changes (Figure 2). The themes, subthemes and a few representative quotes are included in Table 1.

Patients found advice regarding healthy eating habits, setting personal goals, incorporating or avoiding particular food items in the diet to be beneficial for their overall health and well-being. However, most wished for a well-organized and structured diet in the form of recipes, menus, or a booklet. Support from the staff, phone calls from a dietitian and daily text messages motivated participants to adhere to the diet. Participants became more cognizant of the effect of diet on their pain and arthritis which led to higher confidence in controlling pain through dietary modification. Our study identified some important barriers to dietary change in PsA. Psychological barriers included reluctance to change the diet because of taste and habit, and difficulty adhering during times of stress and fatigue. Social issues arose when eating out, traveling or dining with others. Other barriers to healthy eating were related to time constraints and affordability. Finally, participants expressed a desire to continue beneficial dietary changes as well as to commit to other healthy lifestyle choices, e.g., increased physical activity, mindfulness and meditation.

Conclusion: Patients with PsA found the DIPSA interventions to be feasible and valuable. Support from a multidisciplinary team, especially dietitian advice, was deemed crucial. Psychosocial barriers, cost and time constraints prevent patients from implementing healthy dietary changes. Finally, focusing on dietary change had carryover, helping patients to make healthy choices in other aspects of life.

Reference: Eder L, Tarannum S, Bush K, Cohen S, Compher C, Emanoilidis H, Gillespie S, Gladman D, Chandran V, Scher J, Ogdie A. Experiences and Perspectives of Patients with Psoriatic Arthritis Participating in a Randomized Controlled Trial of Dietary Interventions [abstract]. Arthritis Rheumatol. 2023; 75 (suppl 9).

Derivation and Internal Validation of a Disease-specific Cardiovascular Risk Prediction Model for Patients with Psoriatic Arthritis and Psoriasis.

Background/Purpose: Cardiovascular risk in patients with psoriatic disease (PsD) may be underestimated by conventional scoring systems. We derived and internally validated a 5-year disease-specific cardiovascular risk prediction model for patients with PsD.

Methods: Participants from a longitudinal PsD cohort without a prior history of cardiovascular events who were followed from 1992 to 2020 were analyzed. Data on cardiovascular risk factors, and PsD-related features that included measures of musculoskeletal and skin inflammation, patient-reported outcomes and medications were obtained from the cohort's database. The study outcome included a composite cardiovascular event including any of the following: angina, myocardial infarction, congestive heart failure, transient ischemic attack, stroke, revascularization procedures and cardiovascular death. Using time-varying covariates, we fit models to predict cardiovascular events within a 5-year time period. A base prediction model including traditional cardiovascular risk factors was first assessed, followed by an expanded model that included the base model and PsD-related features. Model performance was assessed using measures of discrimination and calibration, and sensitivity and specificity.

Results: A total of 1,336 patients (92% with psoriatic arthritis) were analyzed (mean age 48 ± 12.9 years, 46.8% female) (Table 1). During a mean follow-up of 6.8 years, 85 (6.4%) patients developed incident cardiovascular events. Discriminative ability of the base model (with traditional cardiovascular risk factors alone) was excellent, with an AUC of 85.5 (95% CI 81.9-89.1) (Figure 1). An expanded model that included traditional cardiovascular risk factors and the number of damaged joints did not improve risk discrimination compared to the base model (AUC 85.5, 95% CI 82.0-89.1). All models were well calibrated and appeared to be an accurate estimate of the observed number of cardiovascular events (Figure 2). Sensitivity and specificity of the 10% cut-off point for cardiovascular risk was 49% and 92%, respectively. When considering the total number of cardiovascular events, depending on the model, up to 53% of events occurred in patients who were classified as 'intermediate risk' (< 10%).

Conclusion: A prediction model that includes traditional cardiovascular risk factors alone is accurate in predicting cardiovascular risk in patients with PsD, showing excellent discrimination and calibration in this patient population.

Reference: Colaco K, Lee KA, Akhtari S, Winer R, Chandran V, Harvey P, Cook RJ, Piguet V, Gladman DD, Eder L. Derivation and Internal Validation of a Disease-Specific Cardiovascular Risk Prediction Model for Patients With Psoriatic Arthritis and Psoriasis. Arthritis Rheumatol. 2024 Feb;76(2):238-246. doi: 10.1002/art.42694. Epub 2023 Dec 19. PMID: 37691498.

Sex Dysmorphism of Immune and Imaging Profiles in Psoriatic Arthritis

Background: Psoriatic arthritis (PsA) affects males and females equally, but the clinical manifestations, disease course, and response to treatment differ. Limited information exists on the relationship between sex dimorphisms in biological pathways and the severity of sonographic inflammation and damage in PsA.

Objectives: We seek to clarify how sex, as a biological factor, determines the course of PsA and influences response to advanced therapies. Thus, we aim to identify sex-specific biological pathways in PsA by integrating serum proteomic and ultrasound data in male and female patients with active PsA compared to matched controls.

Methods: We analyzed 100 age-matched patients with active PsA (1:1 sex ratio) and 50 age- and sex-matched healthy controls. All patients had active PsA and were about to start systemic therapy. The levels of >7000 serum proteins were assessed using the aptamer-based SomaScan assay. Differentially expressed proteins (DEPs) were identified using the limma package and defined as false discovery rate p-value less than 0.05 and an absolute fold change greater than 1.2 between PsA and healthy controls (overall and by sex). Multivariable machine learning classifiers were used to identify the best-performing protein signatures for disease status and disease severity (overall and by sex) from the proteins. Pathway analysis was performed with pathDIP5 using literature-curated pathways.

Progress to date: A total of 809 upregulated DEPs and 132 downregulated DEPs were identified in PsA males vs. control males, and 144 upregulated DEPs and 82 downregulated DEPs in PsA females vs. control females. There were 741 unique DEPs in PsA males, 31 in PsA females, and 200 shared between the sexes. Pathway analysis is ongoing to identify unique and shared biological pathways between the sexes using protein-protein interactions from the Integrated Interactions Database (IID). Multivariable machine learning classifiers were employed to predict disease status. We aim to create a single, consolidated list of proteins ranked by importance and frequency of selection across the different predictive models in the samples. Afterwards, we will identify important proteins to predict disease severity overall and by sex.

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 a 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 will be a retrospective cohort analysis using study data from the International Psoriasis and Arthritis Research Team (IPART) study cohort, including patients who reported having an arrythmia event in their clinic visit documentation. We will then evaluate the association between the presence of any arrhythmia and psoriatic arthritis through multivariable regression models. We will adjust for age, sex, BMI, use of cardiac or biological systemic medications, disease severity. We will then explore 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 will calculate hazard ratio for atrial fibrillation/ flutter, ventricular fibrillation, ventricular tachycardia, MobitzII 2nd degree heart block, complete heart block and sick sinus syndrome.

Progress to date: We have completed data collection for this study. Data sources include the CIHI data extract (containing hospitalization information for cardiac events, including arrhythmia events, between 1994 and 2017 based on ICD9 and ICD10 codes), IPART clinic visit identifying arrhythmias, and paper and electronic chart review. We classified arrhythmia events to three groups for the purpose of analysis: 1- atrial arrhythmia (this group includes atrial fibrillation and supraventricular tachycardia events), 2- ventricular arrhythmia (this group include ventricular tachycardia and ventricular fibrillation events), and 3- bradyarrhythmia group (this group include second- or third-degree heart blocks as well as those with permanent pacemaker or ICD implanted). We found 154 unique arrhythmia incident events in 132 patients. 111 in atrial arrhythmia group, 15 events in ventricular arrhythmia group and 28 events in brady arrhythmia group. Next, we will be preparing for data analysis by merging the spreadsheet containing arrhythmia events with the IPART extract on psoriatic arthritis disease activity, demographic, cardiovascular and medications used.

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3. Husni ME, Kaur R, Armstrong AW, **Eder L.** GRAPPA 2022 Trainee Symposium: A Summary of Oral and Poster Presentations. J Rheumatol. 2023 Jul 15:41-46. doi: 10.3899/jrheum.2023-0526. Epub ahead of print. PMID: 37453732.
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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.**

Epidemiological Trends in Psoriatic Arthritis: A Comprehensive Population-Based study

Background: Psoriatic arthritis (PsA) is a chronic, potentially debilitating inflammatory arthritis often associated with psoriasis. Understanding the epidemiology of PsA across diverse populations can provide valuable insights into its global burden and the role of genetic and environmental factors. This study aimed to estimate PsA's temporal trends, prevalence, and incidence, while assessing variations in age, gender, and ethnicity in Israel from 2016 to 2022.

Methods: Data were sourced from the Clalit Health Services (CHS) database, covering over half of the Israeli population. Algorithm-based definitions for PsA and psoriasis cases were used. Demographic factors, including age, gender, socioeconomic status (SES), ethnicity, urban/rural residence, BMI, and smoking status, were analyzed. Standardized prevalence and incidence rates were calculated. Logistic regression analyses examined associations of sociodemographic variables with PsA.

Results: In 2022, the prevalence of PsA was 0.221%, with an incidence rate of 13.54 per 100,000 population. This prevalence has tripled since 2006, reflecting a rising trend in PsA over time. Females exhibited a higher prevalence (1.15; 95%CI 1.09-1.21), and PsA was more common in Jewish individuals (1.58; 95%CI 1.45 – 1.71) those with higher SES (1.4; 95% CI 1.31, 1.5) , and those with obesity (2.17; 95%CI 2.04-2.31).

Conclusions: This comprehensive population-based study pointed to an increase prevalence of PsA, emphasizing the rising healthcare demands and economic burden faced by this patient population. Further research is essential to delve into the factors driving these trends.

Progress to date: Accepted for publication

The Risk Factors for Uveitis among Psoriatic Arthritis Patients: A Population-based Cohort Study.

Background: There is a wide range of prevalence reported for uveitis in PsA in different publications, ranging from 0.2% [5] to 25% [6]. Notably, to date, scarce data exists regarding the prevalence of uveitis following the introduction of biological disease modifying anti-rheumatic drugs (bDMARDs), especially anti-tumor necrosis factor-alpha (anti-TNFα) agents. Unlike the fusion protein composed of the soluble TNFα receptor antagonist etanercept, monoclonal anti-TNFα agents are known to be effective therapies for uveitis [7, 8]. Therefore, one might presume that these agents are able to prevent the occurrence of uveitis flares in this population, but little data currently exists to support this supposition. The aim of our study was to evaluate the incidence of uveitis within a large cohort of PsA patients compared to a healthy control group and to evaluate any effect that bDMARDs might have on this incidence.

Objective: To examine the association between psoriatic arthritis (PsA) and uveitis, and to identify risk factors for uveitis among patients with PsA in the era of biologics.

Methods: A retrospective matched cohort study was conducted within the database of a large healthcare provider. Newly diagnosed 6,147 adult PsA patients between 2005 and 2020 were matched by the index date of PsA diagnosis, age, sex and ethnicity to 23,999 randomly selected controls. This cohort was used to examine the association between PsA and uveitis. An additional analysis was conducted within the PsA group to identify uveitis risk factors, using two analytic approaches: a retrospective cohort study, and a nested case-control study.

Results: Uveitis was diagnosed in 107 patients in the PsA group (1.7%) vs 187 (0.8%) patients in the control group (adjusted HR, 2.39, 95% CI 1.81-2.15, p<0.005), and was similar when the analysis was confined to patients without past uveitis.

Uveitis was diagnosed more in females (2.1% vs 1.3%, HR 1.61, 95% CI 1.09-2.40, p<0.05), and was acute in all cases. Anterior uveitis was documented in 41.1% of the cases, 64.5% unilateral, 9.3% bilateral. In the PsA group, using nested case control approach, only past uveitis [adjusted-OR 136.4 (95% CI 27.38-679.88), p<0.005], and treatment with etanercept [adjusted-OR 2.57 (95% CI 1.45-4.57, p=0.001] were independently associated with uveitis.

Conclusion: PsA is associated with increased risk of uveitis. Past uveitis and treatment with etanercept were associated with higher risk of uveitis.

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Shared Decision Making and Treatment Adherence in the Management of Psoriatic Arthritis Patients: A Prospective study

Background: Shared decision making (SDM) is a process by which patients and clinicians work together to create a treatment plan that integrates evidence-based information, clinician experience, and patient

preferences, values and goals for their care. In recent years, the concept of SDM has become a central component of high-quality medical care and is considered an overarching principle of the disease-specific treatment guidelines recommended by the American College of Rheumatology (ACR). A recent scoping review by Morrison et al. identified an unmet need in rheumatology for generating effective tools for SDM especially in those rheumatologic conditions such as PsA that have yet to be studied with regard to SDM. Adherence to the treatment regimen is often associated with improved outcomes in chronic conditions such as diabetes mellitus, as well as with reduced health expenditures (8-10). Treatment adherence may be facilitated through SDM in various chronic conditions, and therefore, may lead to improved patient outcomes. However, the association between SDM and treatment adherence among PsA patients is scarcely investigated.

Aims and hypotheses: 1. To investigate the association between SDM and treatment adherence. 2. To investigate the association between sociodemographic factors and SDM, and their joint effect, in turn, on treatment adherence.

Methods: Study design and setting: A prospective, 1-year study, to be carried out at the Rheumatology Outpatient clinics at Lin, Zvu'lun, and Naharyia. Study population: Patients>18 years old, previously diagnosed with PsA based on the Casper Criteria, who are able to sign informed consent forms in Hebrew or Arabic and part of IPART data Base .

Primary outcome: Treatment adherence, as reflected by medication consumption (derived from Electronic Medical Records) and patients' reporting.

Secondary outcome: Patient assessed disease activity (Scale of 1-10).

Study tools: In order to assess SDM, we will use the Hebrew translated version of the 9-item SDM Questionnaire (SDM-Q-9) previously validated in primary care patient samples. In order to assess disease activity, physician and patient questionnaires will be used to obtain the composite measure DAPSA score. Treatment adherence will be evaluated by a patient questionnaire (the eight-item Morisky Medication Adherence Scale - MMAS-8) and documented medication refills in the Clalit Heath Services (CHS) database.

Study procedure and data collection: Patients will be recruited during their usual follow-up visit at their rheumatology clinic. They will be asked to complete the study questionnaires immediately after the medical encounter. A follow-up questionnaire will be completed during their next follow-up visit, on average 4-6 months following the study recruitment visit. In case of a later follow-up visit, the follow-up questionnaire will be completed via phone call, to comply with study's timeline. Demographic and clinical information will also be collected on each patient, including age, sex, ethnicity (Jewish/Arab), smoking history, past medical history, disease status (active/remission), co-morbidities, and medications.

Progress to date: We prepared the needed CRF including the Hebrew versions of the questionnaires and all the logistics procedures and will start recruiting patients shortly.

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EDUCATION, TRAINING & ADVOCACY COMPONENTS

IPART will continue to collaborate with the **Gladman-Krembil Psoriatic Disease Research Program,** *formerly* PSARP (Psoriatic Arthritis 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 8 members in the group. They have actively been involved in reviewing educational materials from a patient perspective, and provide suggestions and ideas on patient symposium formats, and how to effectively spread information on psoriatic disease updates and the latest trend on new therapies for psoriatic diseases.
- **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.

  For 2024, the in-person patient forum event is scheduled for **December 4, 2024** at the **BMO Conference Center, Krembil Discovery Tower, UHN-Toronto Western Hospital, 60 Leonard Ave., Toronto, ON M5T 2S8**.
- **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 2024, the scientific meeting will be held in-person and is scheduled for **May 10, 2024 from 8:00 AM to 12:00 PM at the DOUBLE TREE by Hilton, 108 Chestnut St., Toronto, Ontario M5G 1R3**
- **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.

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.

Originally, IPART has five core sites namely:

Toronto, Ontario, CANADA	**Dr. Dafna D. Gladman,** Division of Rheumatology, University of Toronto, Toronto Western Hospital **Dr. Cheryl F. Rosen**, Division of Dermatology, University of Toronto, Toronto Western Hospital **Dr. Vinod Chandran**, Division of Rheumatology, 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, CANADA	**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, Michigan
Rochester, New York, USA	**Dr. Christopher Ritchlin** - Division of Rheumatology, University of Rochester, New York

During the IPART core meeting of April 25, 2024, the Toronto (2) site a Women's College Hospital has been elevated as a new core site in IPART, details as follows:

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)**

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

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