PROGRESS REPORT

As of June 30, 2023

PROGRESS REPORT

DATABASE AND BIOBANKING UPDATE

DATABASE

	TWH	WCH	St. John's	Vancouver	Ann Arbor	Rochester	London	Winnipeg	Israel	Halifax	Argentina	Ottawa
PsA	1663	306	609	99	22	276	195	75	254	4	4	19
Psoriasis	716	394	82	44	69	221	5	193	29	21	9	0
Total	2379	700	691	143	91	497	200	268	283	25	13	19
Female (%)	44.7	55.6	53.2	51.1	47.6	56.9	42.0	50.6	56.8	36.0	92.3	55.6
Caucasian (%)	83.9	73.3	99.2	64.0	98.8	89.7	93.8	82.7	73.2	92.0	75.0	94.4
Visits Ps	4.0	1.9	1.0	1.7	2.6	1.8	1.0	3.7	1.2	1.4	1.0	N/A
Visits PsA	15.2	6.3	1.4	2.0	2.3	3.2	5.7	5.3	4.0	1.3	1.0	1.3
Age Ps	29.1	31.8	29.7	31.2	30.2	32.3	33.0	31.0	36.8	28.4	31.1	35.9
Age PsA	38.5	42.6	39.5	37.5	41.5	41.2	42.8	41.1	46.3	46.0	40.3	45.2
DD Ps	20.1	16.9	18.1	23.2	14.2	18.9	18.1	24.0	18.7	23.5	18.4	N/A
DD PsA	17.8	7.7	10.7	14.4	11.8	12.6	15.1	13.2	13.3	3.0	10.9	13.9

Number of patients within database as of June 12, 2023.

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

In summary:

	PsA	PsC	**TOTAL**
Number of patients	3526	1783	**5309**

IPART TORONTO BIOBANK

Here is the latest update of biospecimen samples stored in our facility as of June 26, 2023:

	TWH PsA	TWH PsC	Women's College	St. John's	London	Halifax	Winnipeg
DNA	1393	668	590	168	175	26	223
Serum	10773	1928	1461	490	418	35	264
RNA	9056	772	965	41	448	35	169
Synovial Fluid	195		28				

RESEARCH UPDATE (2QTR 2022 – 1QTR 2023)

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**:

A Progress Report by Dr. James T. Elder
IPART Core Site - University of Michigan, USA

GENETIC AND GENOMIC DISSECTION OF PSORIATIC ARTHRITIS

This project has been funded from September 2012 until now by the National Institutes of Health (NIH), National Institutes of Arthritis and Musculoskeletal and Skin Diseases, Grant Award No. R01AR063611 to the University of Michigan (Dr. James T. Elder, PI), and Sub-award No. 3002567461 to the University Health Network -IPART Research Program (Dr. Dafna Gladman, PI).

GENETIC STUDIES

Our international meta-GWAS of psoriasis (UK, USA, Canada, Germany, Norway, Estonia) is now written up and being circulated among the 83 authors. To move towards a saturation map of psoriasis susceptibility we meta-analysed 18 GWAS comprising 36,466 cases and 458,078 controls and identify 45 psoriasis susceptibility loci for the first time. 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. 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 psoriatic skin, highlighting roles for the transcriptional regulation of haematopoietic cell development and epigenetic modulation of interferon signalling in psoriasis pathobiology. This analysis nearly doubled the number of EUR psoriasis loci, compared to our most recent report [1]. Relative to the largest previous analysis [1], 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). Sixty regions map to psoriasis susceptibility loci reported previously in European populations. Thirty of these (excluding MHC) include multiple independent association signals; a few, notably at *IL12B* and *TYK2*, include many such signals. These results have been presented in abstract form[2] and will soon be submitted for publication.

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. For these two loci, the transethnic GWAS provided higher genetic resolution and reduced the number of potential causal variants compared to using the EUR sample alone. We then explored multiple strategies to develop reference panels for accurately imputing MHC genotypes in both SAS and EUR populations and conducted a fine-mapping of MHC psoriasis associations in SAS and the largest such effort for 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 highlights the shared genetic basis of psoriasis in SAS and EUR populations and the value of transethnic meta-analysis for discovery and fine-mapping of susceptibility loci. These studies were published in 2022 [3]. 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 [4].

We continue to participate in trans-disease meta-analyses and Mendelian Randomization studies involving psoriasis, revealing relationships between psoriasis and COVID-19 [5] and Type II diabetes [6].and exploring potential genetic relationships between psoriasis/PsA and other diseases, including osteoporosis [7], body mass index [8], adiposity [9], and periodontitis [10].

EPIGENOMIC STUDIES

CD3/CD8-stimulated PBMC as an endophenotype for Th17 expansion in psoriasis

We[11] and others[12-15] 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 CLAP / CLAN) from PBMC of 153 individuals (86 cases, 67 controls). Activation-related differentially expressed genes (DEGs) strongly upregulated Th17 signature mRNAs (*IL17A*, *IL17F*, *IL22*, and *CCL22*) along with the Th1 cytokine *IFNG*, with a corresponding induction of IL-17A and IL-22 proteins by flow cytometry. These findings were confirmed by cluster analysis of single-cell (sc)RNA-seq libraries of CD3/CD28-activated PBMC (n=4). 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, *IL17A* was overexpressed (2.2-fold, p= 0.003) in skin-homing (*FUT7*+) vs. *FUT7*- T-cells, whereas *IFNG* was not.

As reported in older literature[16-19] and a recent CITE-seq study[20], our bulk and scRNA-seq experiments confirmed disappearance of monocytes within 24h of CD3/CD28. activation, which we confirmed by imaging flow cytometry (IFC) and time-lapse microscopy (TLM). Correspondingly, we also observed the rapid formation of many extracellular particles carrying RNA and DNA and acquisition of well-demarcated CD14-bright "specks" both as particles and on the surface of T-cells, even in freshly isolated PBMC without CD3/CD28 activation.

Based on these observations, we hypothesize 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. In February, we submitted a new NIH R01 application on this project.

Over the past year, we have conducted imaging flow cytometry (IFC) and time-lapse microscopy (TLM) experiments to explore these hypotheses. Some of the TLM experiments were performed on cells stained with CellTracker Green and CellTracker Red vital dyes to stain monocytes and non-monocytes, respectively (non-monocytes consist of B-cells and NK cells in addition to T-cells). These populations were separated from PBMC using the Miltenyi Pan Monocyte Isolation Kit. We stained the monocytes with CellTracker Green and non-monocytes with CellTracker Red, recombined them at a 2:1 ratio of non-monocytes to monocytes, and subjected them to activation with anti-CD3/CD28 beads. While these experiments confirmed the dramatic early loss of monocyte, they also revealed a subset of monocytes "re-appearing" after 4-8 hours in the vicinity of clusters of red stained cells, which appeared to be proliferating T-cells. This suggested that the remaining monocytes were being supported by the activated T-cells and vice versa. To visualize this phenomenon, we generated time-lapse videos for submission over a ~12 hr time interval. Starting at about 4 hours after CD3/CD28 activation, increased numbers and size

of clusters containing both red and green cells were evident. We believe that this reflects the release of factors supporting proliferation, survival, and chemotaxis of monocytes when T-cells are activated by the beads. One such example is *CSF2*, a gene mapped to a psoriasis locus whose expression increases by 262-fold in bead-activated vs. non-activated PBMC in our bulk RNA-seq dataset.

In a related project as part of our ongoing work on "Linkage Analysis of Familial Psoriasis", formerly R01AR04742, now R01AR082336-01A1, we utilized the U-M Flow Cytometry Core to generate 9 cell fractions from PBMC: myeloid dendritic cells (mDC), four fractions of unstimulated CD3+CD45RO+ memory T cells (CD4+CLA-, CD4+CLA+, CD8+CLA-, CD8+CLA+) and the same 4 fractions after 24 hours of stimulation of the CD1c- column flow-through (primarily T-cells) with anti-CD3/anti-CD28 beads. While characterizing this culture system, we found that CD14+ monocytes remained with the T-cells in the flow-through after magnetic bead capture of CD1c+ cells. As noted above for whole activated PBMC, these CD14+ monocytes were rapidly lost from the CD3-CD28 activated cultures, as demonstrated by (a) markedly reduced expression of the monocyte signature genes CD14, CD36, S100A8, S100A9, and S100A12 at 24h vs. 0 h of CD3/CD28 activation, (b) by flow cytometric demonstration of marked reduction in CD14+CD3- cells after CD3/CD28 activation, and (c) by an independent set of single-cell RNA-seq (scRNA-seq) experiments performed on CD3/CD28-activated vs. non-activated PBMC (unpublished data). This is important because previous work by ourselves [11] and others (Evans et al., Proc Natl Acad Sci U S A 104: 17034, 2007) demonstrated a stringent requirement for monocytes for Th17 polarization of memory T-cells in CD3/CD28-activated PBMC.

We have completed flow-sorting, RNA-seq and ATAC-seq library formation and sequencing, as well as high-density genotyping using Illumina Infinium Omni5Exome-4 arrays containing ~4.6 million whole-genome and functional exonic variants, followed by imputation using the TOPMed reference panel. These experiments generated an unprecedented collection of 153 individuals (86 psoriasis cases and 67 healthy controls) for genetic analysis of gene expression. We generated 1,057 RNA-seq and 1,090 ATAC-seq libraries from these 153 subjects, derived from 8 flow-sorted T-cell subsets (defined by CD4/CD8, CLA+/CLA-, and 0/24h CD3/CD28 stimulation). Effects of activation and skin-homing were analyzed by DESeq2, using a Wald test to assess true main effects with significance criteria of FDR < 0.05 and $|\log2\ FC| \geq 0.585$) to identify differentially expressed genes (DEGs) and differentially accessible regions (DARs).

RNA-seq: From the RNA-seq libraries, we identified 2,795, 3,629, and 10,673 genes for CD8/CD4, CLA+/CLA-, and resting vs. activated T-cells, respectively. CD4/CD8 DEGs revealed top KEGG enrichment for "Cytokine-cytokine receptor interaction (CCRI)" (FDR = 8.3e-19) and included "Th17 cell differentiation" (FDR = 7.8e-03), with up-regulation of *IL17A* (3.2-fold), *IL17F* (1.8-fold), and *IL22* (2.9-fold) in CD4. CLA+/CLA- DEGs also revealed top enrichment for "CCRI" (FDR=2.4e-18), with up-regulation of *IL17A* (3.3-fold), *IL17F* (2.2-fold), and *IL22* (1.9-fold) in CLA+. Activation-related DEGs were also enriched for "CCRI" (FDR = 2.1e-04), with dramatic up-regulation of *IL17A* (109-fold), *IL17F* (1052-fold), and *IL22* (146-fold) at 24 h. Examination of two-way interactions between skin-homing and activation using DESeq2 followed by functional enrichment analysis using KEGG revealed top enrichment for "Th17 cell differentiation".

ATAC-seq: After peak calling, 78,234 consensus peaks were present in ≥ 30 ATAC-seq libraries. A Wald test identified 9,072, 3,934, and 21,174 consensus peaks as differentially accessible regions (FDR < 0.05, $|\log2\ FC| \geq 0.585$) in CD4 vs CD8, CLA+ vs CLA-, and resting vs. activated T-cells, respectively. For functional annotation, DARs were assigned to the closest genes using ChIPseeker. CD4/CD8 DARs were most significantly enriched for the KEGG pathway "Th17 cell differentiation" (FDR=2.4e-07). CLA+/CLA- DARs were most enriched for "MAPK signaling pathway" (FDR=1.5e-06) and included "Th17 cell differentiation" (FDR=4.1e-04). Activation-responsive (0/24h) DARs were most enriched for "T cell receptor signaling pathway" (FDR = 1.0e-07) and included "Th17 cell differentiation" (FDR=2.3e-06). We next performed an analysis of differentially bound transcription factor (TF) binding motifs (DBMs) utilizing CENTIPEDE (Pique-Regi et al., Genome Res 21, 447-455, 2011), highlighting a marked and highly significant increase in accessibility corresponding to binding of AP-1 family TFs after 24 hr of CD3/CD28 stimulation. These

results have been presented in abstract form at recent SID meetings [21-23] and are currently being written up for publication.

BIOMARKER STUDIES

EBV Associations

Progress of biomarker studies has been significantly hampered by COVID-related restrictions on longitudinal patient sampling. At present, we are utilizing GWAS-based analytical tools such as Regulatory Element Locus Intersection (RELI) (Nat Genet 50:699, 2018) to explore the potential role of Epstein-Barr virus (EBV) encoded TFs in shaping the landscape of psoriasis-associated regulatory signals. Of the 121 SNPs listed in GWAS catalog in 2018, we identified 61 independent loci by linkage disequilibrium pruning. We applied RELI to determine whether the binding of transcription factors (TFs) and coactivators were concentrated at the 61 psoriasis risk loci. We evaluated 1,535 human and 52 virally encoded TF ChIP-seq (chromatin immunoprecipitation with DNA sequencing) datasets. We found that Epstein-Barr nuclear antigen leader protein (EBNALP), EBNA3C and EBNA2 occupied 32 (52.5%), 22 (36.0%), 17 (27.9%) of the 61 psoriasis loci with 11.3, 6.6 and 5.2-fold enrichment and with $p=3.2*10^{-12}$, $p=1.6*10^{-09}$ and $p=2.5*10^{-6}$ after Bonferroni correction, respectively. The viral (n=3) and human TFs (n=38) cluster together in an optimal subset of ~30 of the 61 psoriasis loci at $p=1.1*10^{-178}$. More than 75% of the most highly associated viral and human TF ChIP-seq datasets were collected from EBV transformed B cell lines in the EBV Latency III expression program of viral expression. These as-yet-unpublished results nominate EBV for a role in the pathogenesis of psoriasis by a mechanism operating in transformed B cells through the EBV Latency III program of viral expression. However, we also completed serological studies on EBMA-1 positivity in ~200 subjects with psV (906 PsC, 1,082 PsC), and 1071 controls. While we did find a relationship between disease status and EBNA-1 titers these studies were confounded by the fact that age was strongly associated with anti-EBNA-1 titer and positivity. After controlling for age and gender covariates, disease status was weakly associated with anti-EBNA-1 titer for PsV-control and PsA-control but not PsC-control or PsA-PsC phenotype comparisons. Taken together, these epigenetic and serologic findings do not provide much in the way of evidence for an association similar to that observed between EBV and other autoimmune diseases including systemic lupus erythematosus.

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.

PUBLICATIONS:

1. Tsoi LC, Stuart PE, Tian C, Gudjonsson JE, Das S, Zawistowski M, Ellinghaus E, Barker JN, Chandran V, Dand N, Duffin KC, Enerback C, Esko T, Franke A, Gladman DD, Hoffmann P, Kingo K, Koks S, Krueger GG, Lim HW, Metspalu A, Mrowietz U, Mucha S, Rahman P, Reis A, Tejasvi T, Trembath R, Voorhees JJ, Weidinger S, Weichenthal M, Wen X, Eriksson N, Kang HM, Hinds DA, Nair RP, Abecasis GR, Elder JT. Large scale meta-analysis characterizes genetic architecture for common psoriasis associated variants. Nat Commun. 2017;8:15382. PubMed PMID: 28537254; PMCID PMC5458077.
2. Dand N, Tsoi LC, Barker JN, Simpson M, Elder JT, International-Psoriasis-GWAS-Consortium. Expanded GWAS meta-analysis offers novel insights into psoriasis biology (abstract). J Invest Dermatology 2022:131.

3. Stuart PE, Tsoi LC, Nair RP, Ghosh M, Kabra M, Shaiq PA, Raja GK, Qamar R, Thelma BK, Patrick MT, Parihar A, Singh S, Khandpur S, Kumar U, Wittig M, Degenhardt F, Tejasvi T, Voorhees JJ, Weidinger S, Franke A, Abecasis GR, Sharma VK, Elder JT. Transethnic analysis of psoriasis susceptibility in South Asians and Europeans enhances fine-mapping in the MHC and genomewide. HGG Adv. 2022;3(1). Epub 2021/12/21. PubMed PMID: 34927100; PMCID PMC8682265.
4. Luo Y, Kanai M, Choi W, Li X, Sakaue S, Yamamoto K, Ogawa K, Gutierrez-Arcelus M, Gregersen PK, Stuart PE, Elder JT, Forer L, Schonherr S, Fuchsberger C, Smith AV, Fellay J, Carrington M, Haas DW, Guo X, Palmer ND, Chen YI, Rotter JI, Taylor KD, Rich SS, Correa A, Wilson JG, Kathiresan S, Cho MH, Metspalu A, Esko T, Okada Y, Han B, Consortium NT-OfPM, McLaren PJ, Raychaudhuri S. A high-resolution HLA reference panel capturing global population diversity enables multi-ancestry fine-mapping in HIV host response. Nat Genet. 2021;53(10):1504-16. Epub 2021/10/07. PubMed PMID: 34611364.
5. Patrick MT, Zhang H, Wasikowski R, Prens EP, Weidinger S, Gudjonsson JE, Elder JT, He K, Tsoi LC. Associations between COVID-19 and skin conditions identified through epidemiology and genomic studies. J Allergy Clin Immunol. 2021;147(3):857-69 e7. Epub 2021/01/25. PubMed PMID: 33485957; PMCID PMC7825803.
6. Patrick MT, Stuart PE, Zhang H, Zhao Q, Yin X, He K, Zhou XJ, Mehta NN, Voorhees JJ, Boehnke M, Gudjonsson JE, Nair RP, Handelman SK, Elder JT, Liu DJ, Tsoi LC. Causal Relationship and Shared Genetic Loci between Psoriasis and Type 2 Diabetes through Trans-Disease Meta-Analysis. J Invest Dermatol. 2021;141(6):1493-502. Epub 20201230. PubMed PMID: 33385400; PMCID PMC8154633.
7. Xia J, Xie SY, Liu KQ, Xu L, Zhao PP, Gai SR, Guan PL, Zhao JQ, Zhu YP, Tsoi LC, Stuart PE, Nair RP, Yang HQ, Liao YT, Mao K, Qiu MC, Ying ZM, Hu B, Yang ZH, Bai WY, Zhu XW, Cong PK, Elder JT, Ye ZM, Wang B, Zheng HF. Systemic evaluation of the relationship between psoriasis, psoriatic arthritis and osteoporosis: observational and Mendelian randomisation study. Ann Rheum Dis. 2020;79(11):1460-7. Epub 2020/08/02. PubMed PMID: 32737104.
8. Budu-Aggrey A, Brumpton B, Tyrrell J, Watkins S, Modalsli EH, Celis-Morales C, Ferguson LD, Vie GA, Palmer T, Fritsche LG, Loset M, Nielsen JB, Zhou W, Tsoi LC, Wood AR, Jones SE, Beaumont R, Saunes M, Romundstad PR, Siebert S, McInnes IB, Elder JT, Davey Smith G, Frayling TM, Asvold BO, Brown SJ, Sattar N, Paternoster L. Evidence of a causal relationship between body mass index and psoriasis: A mendelian randomization study. PLoS Med. 2019;16(1):e1002739. Epub 2019/02/01. PubMed PMID: 30703100; PMCID PMC6354959.
9. Martin S, Tyrrell J, Thomas EL, Bown MJ, Wood AR, Beaumont RN, Tsoi LC, Stuart PE, Elder JT, Law P, Houlston R, Kabrhel C, Papadimitriou N, Gunter MJ, Bull CJ, Bell JA, Vincent EE, Sattar N, Dunlop MG, Tomlinson IP, Bell JD, Frayling TM, Yaghootkar H. Disease consequences of higher adiposity uncoupled from its adverse metabolic effects using Mendelian randomisation. Elife. 2022;11. Epub 2022/01/26. PubMed PMID: 35074047; PMCID PMC8789289.
10. Baurecht H, Freuer D, Welker C, Tsoi LC, Elder JT, Ehmke B, Leitzmann MF, Holtfreter B, Baumeister SE. Relationship between periodontitis and psoriasis: A two-sample Mendelian randomization study. J Clin Periodontol. 2022. Epub 2022/04/02. PubMed PMID: 35362630.
11. Lambert S, Hambro CA, Johnston A, Stuart PE, Tsoi LC, Nair RP, Elder JT. Neutrophil Extracellular Traps Induce Human Th17 Cells: Effect of Psoriasis-Associated TRAF3IP2 Genotype. J Invest Dermatol. 2019;139(6):1245-53. Epub 2018/12/12. PubMed PMID: 30528823.
12. Evans HG, Suddason T, Jackson I, Taams LS, Lord GM. Optimal induction of T helper 17 cells in humans requires T cell receptor ligation in the context of Toll-like receptor-activated monocytes. Proc Natl Acad Sci U S A. 2007;104(43):17034-9. PubMed PMID: 17942669; PMCID PMC2040448.
13. Olliver M, Hiew J, Mellroth P, Henriques-Normark B, Bergman P. Human monocytes promote Th1 and Th17 responses to Streptococcus pneumoniae. Infect Immun. 2011;79(10):4210-7. Epub 20110725. PubMed PMID: 21788380; PMCID PMC3187264.

14. Desel C, Murray PJ, Lehmann CHK, Heger L, Christensen D, Andersen P, Mack M, Dudziak D, Lang R. Monocytes Elicit a Neutrophil-Independent Th1/Th17 Response Upon Immunization With a Mincle-Dependent Glycolipid Adjuvant. Front Immunol. 2022;13:880474. Epub 20220502. PubMed PMID: 35585969; PMCID PMC9108773.
15. Duraisingham SS, Hornig J, Gotch F, Patterson S. TLR-stimulated CD34 stem cell-derived human skin-like and monocyte-derived dendritic cells fail to induce Th17 polarization of naive T cells but do stimulate Th1 and Th17 memory responses. J Immunol. 2009;183(4):2242-51. Epub 20090722. PubMed PMID: 19625644.
16. Pryjma J, Zembala M, Baran J, Ernst M, Flad HD. Elimination of monocytes from cultures activated with recall antigens. Immunol Lett. 1995;46(3):229-35. PubMed PMID: 7590940.
17. Ashany D, Song X, Lacy E, Nikolic-Zugic J, Friedman SM, Elkon KB. Th1 CD4+ lymphocytes delete activated macrophages through the Fas/APO-1 antigen pathway. Proc Natl Acad Sci U S A. 1995;92(24):11225-9. PubMed PMID: 7479970; PMCID PMC40604.
18. Kaplan MJ, Ray D, Mo RR, Yung RL, Richardson BC. TRAIL (Apo2 ligand) and TWEAK (Apo3 ligand) mediate CD4+ T cell killing of antigen-presenting macrophages. J Immunol. 2000;164(6):2897-904. PubMed PMID: 10706675.
19. Jagger AL, Evans HG, Walter GJ, Gullick NJ, Menon B, Ballantine LE, Gracie A, Magerus-Chatinet A, Tiemessen MM, Geissmann F, Rieux-Laucat F, Taams LS. FAS/FAS-L dependent killing of activated human monocytes and macrophages by CD4+CD25- responder T cells, but not CD4+CD25+ regulatory T cells. J Autoimmun. 2012;38(1):29-38. Epub 20111224. PubMed PMID: 22197557.
20. Lawlor N, Nehar-Belaid D, Grassmann JDS, Stoeckius M, Smibert P, Stitzel ML, Pascual V, Banchereau J, Williams A, Ucar D. Single Cell Analysis of Blood Mononuclear Cells Stimulated Through Either LPS or Anti-CD3 and Anti-CD28. Front Immunol. 2021;12:636720. Epub 20210317. PubMed PMID: 33815388; PMCID PMC8010670.
21. Zhang X, Tsoi LC, Nair RP, Stuart PE, Wen X, Elder JT. Differential gene expression and chromatin accessibility reveals Th17 polarization in skin-homing T cells [abstract]. J Invest Dermatol. 2020.
22. Zhang Z, Tsoi LC, Nair RP, Stuart PE, Pique-Regi R, Wen R, Elder JT. Differential chromatin accessibility in skin-homing vs. non-skin homing CD4+ T cells [abstract]. J Invest Dermatol. 2019;139(5).
23. Zhang Z, Zhao Y, Tsoi LC, Nair RP, Stuart PE, Wen X, Elder JT. Differential gene expression in psoriatic vs. normal T-cells is enhanced by CD3-CD28 activation [abstract]. J Invest Dermatol. 2021.

A Progress Report by Dr. Christopher Ritchlin
IPART Core Site - University of Rochester, 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.

Metabolomic changes in the transition from psoriasis to PsA

We sampled sera from estabished PsO and PsA patients and individuals who transitioned from PsO to PsA before and after onset of disease. We found that secondary bile acids were decreased in patients at risk to develop arthritis along with low levels of butyrate a short chain fatty acid. None of these patinets were on anti-inflammatory therapy when these labs were drawn. These data underscore the strong influence of secondary bile acids on inflammation and open new avenues of investiation and therapy [1].

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. 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. We are submitting this work for publication in the next 2 weeks.

Development of a humanized mouse model of psoriasis and PsA

Dr. Luz Garcia-Hernandez, a scientist in the Rochester 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[2].

Recruitment of patients for clinical trials

The Rochester team is engaged in a number of clinical trials, two of which Drs. Jose Scher and Christopher Ritchlin 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, 7, 9].

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.

PRESTO: a prediction tool for the devlopment of PsA

We collaborated with Dr. Eder to develop PRESTO. Please see details under her section [10].

PsA treatment [8]

Spatial transcriptomic analysis of psoriasis [6]

PUBLICATIONS:

1. Paine A, Brookes PS, Bhattacharya S, Li D, De La Luz Garcia-Hernandez M, Tausk F, Ritchlin C. Dysregulation of Bile Acids, Lipids, and Nucleotides in Psoriatic Arthritis Revealed by Unbiased Profiling of Serum Metabolites. Arthritis Rheumatol. 2023 Jan;75(1):53-63. doi: 10.1002/art.42288. Epub 2022 Nov 25. PMID: 35818333

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).
3 Haberman RH, MacFarlane KA, Catron S, Samuels J, Blank RB, Toprover M, Uddin Z, Hu J, Castillo R, Gong C, Qian K, Piguet V, Tausk F, Yeung J, Neimann AL, Gulliver W, Thiele RG, Merola JF, Ogdie A, Rahman P, Chakravarty SD, Eder L, Ritchlin CT, Scher JU. Efficacy of guselkumab, a selective IL-23 inhibitor, in Preventing Arthritis in a Multicentre Psoriasis At-Risk cohort (PAMPA): protocol of a randomised, double-blind, placebo controlled multicentre trial. BMJ Open. 2022 Dec 23;12(12):e063650. doi: 10.1136/bmjopen-2022-063650. Erratum in: BMJ Open. 2023
4 Meer E, Merola JF, Fitzsimmons R, Love TJ, Wang S, Shin D, Chen Y, Xie S, Choi H, Zhang Y, Scher JU, Ritchlin CT, Gelfand JM, Ogdie A. Does biologic therapy impact the development of PsA among patients with psoriasis? Ann Rheum Dis. 2022 Jan;81(1):80-86. doi: 10.1136/annrheumdis-2021-220761. Epub 2021 Oct 6. PMID: 34615
5. Coates LC, McInnes IB, Merola JF, Warren RB, Kavanaugh A, Gottlieb AB, Gossec L, Assudani D, Bajracharya R, Coarse J, Ink B, Ritchlin CT. Safety and Efficacy of Bimekizumab in Patients With Active Psoriatic Arthritis: Three-Year Results From a Phase IIb Randomized Controlled Trial and Its Open-Label Extension Study. Arthritis Rheumatol. 2022 Dec;74(12):1959-1970. doi: 10.1002/art.42280. Epub 2022 Nov 18. PMID
6. Castillo RL, Sidhu I, Dolgalev I, Chu T, Prystupa A, Subudhi I, Yan D, Konieczny P, Hsieh B, Haberman RH, Selvaraj S, Shiomi T, Medina R, Girija PV, Heguy A, Loomis CA, Chiriboga L, Ritchlin C, Garcia-Hernandez ML, Carucci J, Meehan SA, Neimann AL, Gudjonsson JE, Scher JU, Naik S. Spatial transcriptomics stratifies psoriatic disease severity by emergent cellular ecosystems. Sci Immunol. 2023 Jun 8;8(84):eabq7991. doi: 10.1126/sciimmunol.abq7991.
7. Ritchlin CT, Deodhar A, Boehncke WH, Soriano ER, Kollmeier AP, Xu XL, Zazzetti F, Shawi M, Jiang Y, Sheng S, Helliwell PS. Multidomain Efficacy and Safety of Guselkumab Through 1 Year in Patients With Active Psoriatic Arthritis With and Without Prior Tumor Necrosis Factor Inhibitor Experience: Analysis of the Phase 3, Randomized, Placebo-Controlled DISCOVER-1 Study. ACR Open Rheumatol. 2023 Mar;5(3):149-164. doi: 10.1002/acr2.11523.
8. Leung YY, Kavanaugh A, Ritchlin CT. Expert Perspective: Management of the Psoriatic Arthritis Patient After Failure of One Tumor Necrosis Factor Inhibitor. Arthritis Rheumatol. 2023 Mar 16. doi: 10.1002/art.42498. Epub ahead of print. PMID: 36924066.
9. Bawany F, Ryan Wolff J, Ritchlin CT, Tausk F. Home Phototherapy Improves Access to Dermatologic Care: A Novel Stakeholder Alliance to Facilitate Its Implementation. Clin Cosmet Investig Dermatol. 2023 May 2;16:1175-1180. doi: 10.2147/CCID.S408323. PMID: 37159611; PMCID: PMC10163900.
10 Eder,L. Chandran, V. Widdifield V, Drucker, AM, Ritchlin C, Rosen C, Cook RJ, Gladman DD. Derivation of a psoriatic arthritis risk estimation tool (PRESTO): a step towards prevention. Arthritis Rheumatology (2023 in press).

A Progress Report by Dr. Proton Rahman
IPART Genetic Core Site – Memorial University of Newfoundland, Canada

The following projects are ongoing at the genetic core site in Newfoundland:

Excess auto-inflammatory missense mutations were noted in PsA and AS compared to psoriasis and RA

AS and PsA display a footprint of autoimmune and autoinflammatory features. We screened for genetic variants associated with known autoinflammatory disease in patients with AS and PsA and compared it to rheumatoid arthritis (RA) and psoriasis (Ps), which were all identified from the UK Genome Biobank. 886 PsA, 1264 AS, 5,567 Ps, and 5361 RA patients were identified. Autoinflammatory genes were selected from the Blueprint Autoinflammatory Syndrome Panel, and all missense mutations were identified from

these 47 autoinflammatory genes in all four cohorts. We noted an overabundance of autoinflammatory variants in AS and PsA compared to RA and Ps. The average number of auto-inflammatory variants per patient was 0.88 in PsA, 0.741 in AS, 0.362 in psoriasis, and 0.388 in RA. CARD14, MEFV, and SLC29A3 were the mostly autoinflammatory genes with missense mutations in PsA.

Evidence of a Causal Relationship between Hyperlipidemia and Psoriasis and Psoriatic Arthritis: A Mendelian Randomization Study

Recent Norwegian studies suggest that lipid changes may drive psoriatic disease, independent of obesity, as analyses of the separate components of metabolic syndrome showed an increased risk of psoriasis for high total cholesterol, triglycerides, and HDL (remained after adjusting for BMI). So we used Mendelian randomization (MR) to assess the causal effect of total cholesterol by measuring the variation of genes of known function.

Our study cohorts were identified from the FinnGen Biobank. Hyperlipidemia was identified by code E4_HYPERLIPNAS, psoriasis by code L12_PSORIASIS, and psoriatic arthritis by code M13_PSORIARTH. The single-nucleotide polymorphisms (SNPs) were used as instrumental variables (IV) to identify the potential causal effect. An inverse variance weighted (IVW) model was used to estimate causality for each IV in this two-sample MR study. The MR was performed in both directions to explore the possibility of reverse causality. Based on their ID, 4535 patients with hyperlipidemia, 4510 psoriasis, and 1553 PsA patients were identified from the FinnGenn Biobank. The control patients ranged from 147,221 to 212,242, depending on the cohort being compared.

Genetic instruments comprising 5 SNPs for hyperlipidemia, 16 SNPs for psoriasis and 4 SNPs for PsA were used for this two-sample MR. A significant causal effect was noted in the following: Hyperlipidemia leading to psoriasis (OR 1.26 (95% CI 1.10-1.44; $p < 0.0009$); Hyperlipidemia leading PsA (OR 1.35 (95% CI 1.08-1.68; p=0.007). No causal effect was noted in the reverse direction.

Our two-sample MR study genetically predicted that hyperlipidemia has a potential causal association with psoriatic disease, which leads to a higher risk of psoriasis and PsA. Further

validation and molecular studies are required to understand this relationship.

Pharmacogenomic study in PsA through transcript profiling of CD8+ T cells.

At the IPART scientific meeting, we hope to provide an update of our pharmacogenetic study to see if cell type-specific transcriptomic data obtained at baseline can predict response to TNF and IL-17 inhibitors at 3 months and whether it can help to identify pathways associated with response to biologics. We just completed CD8+ T cell transcriptomes of 40 PsA patients treated with TNFi and IL-17Ai, at baseline and three months after treatment and are currently analyzing this data. A preliminary report of this analysis will be provided.

PUBLICATIONS:

1. Allard-Chamard H, Li Q, Rahman P. Emerging Concepts in Precision Medicine in Axial Spondyloarthritis. Current Rheumatology Reviews. In Press
2. Maksymowych, WP.; Inman, R; Bessette, L; Rahman, P; Rampakakis , E; Asin-Milan, O; Rachich, M; Marrache, A ; Lehman, A. Clinical Metrics Associated with Sustained Low Functional Impairment in Axial Spondyloarthritis (axSpA). Arthritis Care and Research
3. Kavanaugh A, Baraliakos B, Gao S, Chen W, Sweet K, Chakravarty SD, Song Q, Shawi M, Rahman P. Genetic and molecular distinctions between axial psoriatic arthritis and radiographic axial spondyloarthritis: post hoc analyses from four phase 3 clinical trials. Advances in Therapy, In press
4. Ritchlin CT, Coates LC, Mease PJ, van der Heijde D, Song J, Jiang Y, Shawi M, Kollmeier AP, Rahman P. The effect of guselkumab on inhibiting radiographic progression in patients with active psoriatic arthritis: study protocol for APEX, a Phase 3b, multicenter, randomized, double-blind, placebo-controlled trial. Trials. 2023 Jan 10;24(1):22. doi: 10.1186/s13063-022-06945-y.
5. Haberman RH, MacFarlane KA, Catron S, Samuels J, Blank RB, Toprover M, Uddin Z, Hu J, Castillo R,

Gong C, Qian K, Piguet V, Tausk F, Yeung J, Neimann AL, Gulliver W, Thiele RG, Merola JF, Ogdie A, Rahman P, Chakravarty SD, Eder L, Ritchlin CT, Scher JU. Efficacy of guselkumab, a selective IL-23 inhibitor, in Preventing Arthritis in a Multicentre Psoriasis At-Risk cohort (PAMPA): protocol of a randomised, double-blind, placebo controlled multicentre trial. BMJ Open. 2022 Dec 23;12(12):e063650. doi: 10.1136/bmjopen-2022-063650. PMID: 36564123.

6. Inman RD, Garrido-Cumbrera M, Chan J, Cohen M, de Brum-Fernandes AJ, Gerhart W, Haroon N, Jovaisas AV, Major G, Mallinson MG, Rohekar S, Leclerc P, Rahman P. Work-related Issues, Physical and Psychological Burden in Canadian Axial Spondyloarthritis Patients. Results From the International Map of Axial Spondyloarthritis. J Rheumatol. 2022 Dec 1:jrheum.220596. doi: 10.3899/jrheum.220596. Epub ahead of print. PMID: 36455954.
7. Liu M, Zhang H, Xie Z, Huang Y, Sun G, Qi D, Furey A, Randell EW, Rahman P, Zhai G. Glutathione, polyamine, and lysophosphatidylcholine synthesis pathways are associated with circulating pro-inflammatory cytokines. Metabolomics. 2022 Sep 30;18(10):76. doi: 10.1007/s11306-022-01932-5. PMID: 36180605.
8. Liu M, Huang Y, Zhang H, Aitken D, Nevitt MC, Rockel JS, Pelletier JP, Lewis CE, Torner J, Rampersaud YR, Perruccio AV, Mahomed NN, Furey A, Randell EW, Rahman P, Sun G, Martel-Pelletier J, Kapoor M, Jones G, Felson D, Qi D, Zhai G. Restricting Branched-Chain Amino Acids within a High-Fat Diet Prevents Obesity. Metabolites. 2022 Apr 7;12(4):334. doi: 10.3390/metabo12040334.
9. Costello CA, Rockel JS, Liu M, Gandhi R, Perruccio AV, Rampersaud YR, Mahomed NN, Rahman P, Randell EW, Furey A, Kapoor M, Zhai G. Individual participant data meta-analysis of metabolomics on sustained knee pain in primary osteoarthritis patients. Rheumatology (Oxford). 2022 Sep 19:keac545. doi: 10.1093/rheumatology/keac545. Epub ahead of print. PMID: 36124971.
10. Badaiki W, Penney M, Pyper E, Lester K, Skeard J, Shin J, Fisher B, Hew H, Gulliver S, Gulliver W, Rahman P. Laying the Foundation for Real-World Evidence Studies in Newfoundland and Labrador. J Cutan Med Surg. 2022 Sep-Oct;26(5):494-501.
11. Badaiki W, MD, Pyper E, Lester K, Skeard J, Penney M, Shin J, Fisher B, Hew H, Gulliver S, Gulliver W, Rahman P. Laying the Foundation for Real-World Evidence Studies in Newfoundland and Labrador. International Journal of Population Data Science, In Press
12. Eder L, Li Q, Rahmati S, Rahman P, Jurisica I, Chandran V. Defining Imaging Sub-phenotypes of Psoriatic Arthritis: Integrative Analysis of Imaging Data and Gene Expression in a PsA Patient Cohort. Rheumatology (Oxford). 2022 Nov 28;61(12):4952-
13. Etchegary H, Pullman D, Simmonds C, Rahman P. Public interest in unexpected genomic findings: a survey study identifying aspects of sequencing attitudes that influence preferences. J Community Genet. 2022 Jan 21. doi: 10.1007/s12687-022-00577-0.

A Progress Report by Dr. Jan Dutz, PI

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

The following clinical studies are ongoing in the Vancouver core site:

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. Roflumilast has recently been shown to have activity against psoriatic skin lesions when applied topically (N Engl J Med. 2020 Jul 16;383(3):229-239). We hypothesize that oral administration may have a beneficial effect for patients with mild/moderate psoriasis and psoriatic arthritis in a similar fashion as apremilast. Advantages of roflumilast therapy would include once daily dosing and decreased cost. We have collected a number of

patients who would be good candidates for apremilast but who do not have extended benefits for coverage of apremilast. With their consent, we have tried using roflumilast for some success for treating their disease. We currently have a series of over 10 patients with psoriasis 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 8 patients treated for ISR (with citrate product and without citrate product) and are planning mechanistic studies in a subsequent series of patients.

Online screening tool for the early identification of psoriatic arthritis (in progress)

Roughly, a third of patients with psoriasis will develop psoriatic arthritis. Most of the time the psoriasis occurs initially and some studies have suggested up to 15% of patients may have undiagnosed psoriatic arthritis at dermatology offices. We created an online website utilizing a modified PEST questionnaire (included questions to screen for axial involvement). Patients from Dr. Jan Dutz's clinic were used as a pilot to see whether the website ran smoothly and collected adequate information. Each patient was mailed a letter asking them to log onto the website. Additionally, there was a link from the UBC skin care center directing them to this page. Patients were given a unique PIN to identify how many individuals had accessed the site. In this initial pilot, 16 patients have filled out the questionnaire and 9 scored positive on the PEST. We are incorporating USS and developing an infrastructure to enable USS screening prior to assessment by the IPART clinic.

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. T. Khosravi-Hafshejani *et al.*, Small plaque psoriasis re-visited: A type of psoriasis mediated by a type-I interferon pathway. *Exp Dermatol* 31, 753-763 (2022).
3. L. E. Kristensen *et al.*, Ixekizumab Demonstrates Consistent Efficacy Versus Adalimumab in Biologic Disease-Modifying Anti-rheumatic Drug-Naïve Psoriatic Arthritis Patients Regardless of Psoriasis Severity: 52-Week Post Hoc Results from SPIRIT-H2H. *Rheumatol Ther* 9, 109-125 (2022).
4. E. Lubrano *et al.*, Management of Axial Disease in Patients With Psoriatic Arthritis: An Updated Literature Review Informing the 2021 GRAPPA Treatment Recommendations. *J Rheumatol* 50, 279-284 (2023).
5. K. A. Papp *et al.*, Use of Systemic Therapies for Treatment of Psoriasis in People Living with Controlled HIV: Inference-Based Guidance from a Multidisciplinary Expert Panel. *Dermatol Ther (Heidelb)* 12, 1073-1089 (2022).
6. K. A. Papp *et al.*, Practical and Relevant Guidelines for the Management of Psoriasis: An Inference-Based Methodology. *Dermatol Ther (Heidelb)* 12, 253-265 (2022).
7. 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).
8. M. Shurey, A. Yip, O. Ziouzina, J. Chan, J. P. Dutz, Combination Therapy With Tofacitinib and IL-12/23, IL-23, or IL-17A Inhibition for the Treatment of Refractory Psoriatic Arthritis: A Case Series. *J Clin Rheumatol* 28, e626-e628 (2022).

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

The following projects are ongoing at the IPART core lead site at University Health Network (UHN):

CLINICAL STUDIES

With Dr. Lihi Eder, we completed a study on incidence and risk factors for venous thromboembolic events in our patients with psoriasis and PsA. The study showed that the incidence rate was low ranging from 6-12/10,000. Risk factors identified were older age, diabetes and use of corticosteroid [1].

We investigated the prevalence and risk factors associated with osteoporosis and low bone mineral density in PsA. We found that osteopenia and osteoporosis occurred in the same frequency as the general population, although the presence of polyarticular disease may be associated with worse bone mineral density [2].

We investigated the utility of the ToPAS 2 in identifying psoriasis and found that the skin related questions were discriminatory [3].

We found that Cannabis was used in about a third of the patients, mostly for pain relief. However, the pain levels in those who did not did not take Cannabis were similar. Serum levels of IL-23 levels were statistically significantly higher in non-users than in users [4].

With Dr. Lihi Eder, we studied heart failure in our patients with psoriasis and PsA. The incidence rate of first heart failure event was 2.85 per 1,000 patient-years. Independent risk factors for heart failure events were ischemic heart disease, adjusted mean tender joint count, adjusted mean swollen joint count, adjusted mean erythrocyte sedimentation rate, adjusted mean C-reactive protein level, and physical function, while achieving minimal disease activity (MDA) was protective [5].

We found that depression and anxiety prevented patients with PsA from achieving MDA state [6].

With Dr. Lihi Eder, we identified cardiac biomarkers for cardiac outcomes in our patients with psoriasis and PsA [7].

Analyzing our patients with enthesitis, we found that the enthesitis improved within a year regardless of which medication was used [8].

We compared patients with isolated axial PsA to those with ankylosing spondylitis and found that the phenotype is different. Axial PsA patients are older, have less inflammatory back pain and a lower frequency of HLA-B27. Isolated axial PsA is rare and the majority of the patients develop peripheral joint disease as well [9].

We studied musculoskeletal surgery in our patients with PsA.

PUBLICATIONS:

1. Damian AC, Colaco K, Rohekar S, Boyd T, Chandran V, Gladman DD, Cook R, Eder L. The incidence and risk factors for venous thromboembolic events in patients with psoriasis and psoriatic arthritis. Semin Arthritis Rheum 2022;53:151960.

2. Kwok TSH, Sutton M, Yang Ye J, Pereira D, Chandran V, Gladman DD. Prevalence and factors associated with osteoporosis and bone mineral density testing in psoriatic arthritis. Arthritis Care Res (Hoboken) 2022;74:1006-1012.
3. Taylor JH, Deo M, Sutton M, Chandran V, Shanmugarajah S, Pereira D, Gladman DD, Rosen CF. Assessment of the Toronto Psoriatic Arthritis Screen 2 as a Screening Tool for Psoriasis. J Cutaneous Med Surg 2022;26:237-242.
4. Tsang J, Silverberg O, Machhar R, Pollock R, Pereira D, Sutton M, Gladman DD, Rosen CF. Exploring cannabis use and perspectives among psoriatic disease patients. Clin Rheumatol 2022;41:1431-1437.
5. Koppikar S, Colaco K, Harvey P, Akhtari S, Chandran V, Gladman DD, Cook R, Eder L. Incidence of and risk factors for heart failure in patients with psoriatic disease - A cohort study. Arthritis Care Res 2022;74:1244-1253.
6. Wong A, Ye JY, Cook RJ, Gladman DD, Chandran C. Depression and anxiety reduce the probability of achieving a state of sustained minimal disease activity in patients with psoriatic arthritis. Arthritis Care Res 2022;74:1430-1434.
7. Colaco K, Lee KA, Akhtari S, Winer R, Welsh P, Sattar N, McInnes IB, Chandran V, Harvey P, Cook RJ, Gladman DD, Piguet V, Eder L Association of cardiac biomarkers with cardiovascular outcomes in patients with psoriatic arthritis and psoriasis: a longitudinal cohort study. Arthritis Rheumatol 2022;74:1184-1192.
8. Mathew AJ, Sutton M, Pereira D, Gladman DD, Chandran V. Effectiveness of disease modifying anti-rheumatic drugs for enthesitis in a prospective longitudinal psoriatic arthritis cohort. J Rheumatol. 2022;49:1020-1025.
9. Kwok TSH, Sutton M, Pereira D, Cook RJ, Chandran V, Haroon N, Inman RD, Gladman DD. Isolated axial disease in psoriatic arthritis and ankylosing spondylitis with psoriasis. Ann Rheum Dis 2022;81:1678-1684.
10. Kwok TSH, Sutton M, Cook RJ, Pereira D, Chandran V, Gladman DD. Musculoskeletal Surgery in Psoriatic Arthritis: Prevalence and Risk Factors. J Rheumatol. Online 2022/11/15.

METABOLOMICS

Exploring the Serum Metabolome for Potential Diagnostic Markers of Psoriatic Arthritis

Background: Psoriatic arthritis (PsA) is an inflammatory immune-mediated musculoskeletal skin disease that affects approximately 25% of psoriasis patients causing progressive disability. As a heterogeneous disease, with sometimes subtle manifestation, accurate assessment of PsA is difficult. As such, there is a need for early detection diagnostic tests for PsA. A liquid chromatography – high resolution mass spectrometry (LC-HRMS) general untargeted metabolomics analysis following solid phase microextraction (SPME) was applied to serum samples collected from patients with PsA and psoriasis without PsA (PsC), to perform discovery analysis to investigate potential diagnostic markers of PsA.

Methods: Serum samples were obtained from a biobank of carefully phenotyped PsC (n=100) and PsA (n = 101) patients who had no history of cancer, had no active infection nor received previous treatment with biologics. Novel high throughput technique – SPME – was used to prepare all samples simultaneously followed by LC-HRMS analysis.

Data (pre)processing and feature identification was performed using 2 workflows - Compound Discoverer 3.3 and an independent Rscript. Supervised multivariate analysis and various Machine Learning (ML) algorithms including logitboost, adaptive boosting, support vector machine (SVM), logistic regression, and random forest (RF), were used for predictive feature analysis. Area Under the Receiver Operating Characteristic (AUROC) was then used to evaluate the performance of these features. Only features in models with an area under the curve (AUC) of 0.85 or greater were considered as candidate biomarkers.

Results: A minimum of ten features and a maximum of eighty features from the adaptive boost models produced an AUC of 0.896 and 0.921 respectively. All other models with feature numbers ranging between

twenty to eighty produced AUC between 0.891 and 0.915. Several small molecules could be validated via MS Level 2 spectral database matching. Trihydroxyoctadecenoic acid and N-nervonoyl cysteine contributed significantly to the multivariate supervised analysis and performed well according to high AUROC scores. Interestingly, lipids such as docosahexanoyl-sn-gylcerophosphocholine were identified via MS level 2, but there were several other features that were found to be significant that could only be tentatively identified as glycero-lipids and fatty acids. Results from this metabolomics workflow were integrated with top-down multi-omics data for the same patients. Data integration revealed that confirmed and tentatively identified features like glycero- and phospholipids overlapped differentially expressed pathways from the transcriptome.

Conclusion: SPME-LC-HRMS based untargeted metabolomic analyses have identified small molecules (lipids) with excellent discriminative ability between PsA and PsC. Thus, the development of quantitative targeted assays for these metabolites and subsequent validation may provide diagnostic markers for PsA.

Identifying Serum Metabolomic Markers Associated with Psoriasis Skin Disease Activity

Background: Psoriasis is a chronic, immune-mediated inflammatory skin disease that affects over 2.5% of the global population. Approximately 25% of psoriasis patients also have a form of inflammatory arthritis called psoriatic arthritis (PsA). Current methods for evaluating skin disease activity, like Psoriasis Area and Severity Index (PASI), are subjective and prone to intra- and inter-rater variability. A metabolomics-based approach can elucidate psoriatic disease pathogenesis and provide potential objective biomarkers. Therefore, we aimed to use solid phase microextraction (SPME) with liquid chromatography coupled with mass spectrometry (LC-MS) with the hypothesis that serum metabolites are associated with skin disease activity.

Methods: Serum samples from PsA patients (n=151) with active skin disease and a range of PASI scores were selected. Patients were classified into 3 groups of psoriasis activity based on PASI- low (PASI 1-4.8) n=56, moderate (PASI 5-9.8) n=45, and High (PASI 10.1-54.6) n=40. SPME devices were prepared in-house and used to conduct the sample preparation, followed by positive and negative ion mode data acquisition via an untargeted approach using LC-MS. Associations between the levels of each metabolite and PASI scores was evaluated using 8 Machine learning (ML) models including support vector machine (SVM), random forest, and Naïve Bayes (NB) with varied feature sizes of 1-80. These models were summarised using Area Under Receiver Operator Characteristic curves (AUROC) for performance. Statistically significant metabolite features were tentatively identified.

Results: ML models were able to distinguish between low and high PsA severity with Area Under Curve (AUC) score as low as 0.745 for 10 features, and as high as 0.813 for 40 features. Trends were similar for other disease activity comparisons. A SVM model with 10 features were able to predict between low and high severity PsA with AUC = 0.862, and p-value < 0.05. The features of interest used in best performing models were associated with dysregulation of fatty acid metabolism when predicting between low PASI versus moderate or high PASI. 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 tentatively identified features belong to classes such as bile acid metabolites, oxidized phospholipids, N-acrylamide, and long-chain fatty acids.

Conclusion: An untargeted metabolomics approach was employed to analyze potential differences in serum metabolome of PsA patients of varying skin disease activity. Confirmation and validation of the tentatively identified circulating metabolites should be conducted to reveal potential biomarkers of PsA disease activity.

Exploring Metabolite Markers Associated with Treatment Response of Biologic Disease Modifying Antirheumatic Drugs in Psoriatic Arthritis Patients

Background: The use of biologic disease-modifying anti-rheumatic drugs (bDMARDS) is the current standard of care for severe diseases like psoriatic arthritis (PsA) which affects approximately 25% of

psoriasis patients. However, randomized controlled trials demonstrate a difference in the ACR20 response rate of only 20-30% in patients receiving treatment vs placebo. Thus, choosing the appropriate type of bDMARDS to administer targeted therapy of PsA remains challenging. Predictive biomarkers may help facilitate precision medicine. The objective of this study was to apply a global metabolomics approach to identify small molecules associated with treatment efficacy in PsA patients treated with either tumour necrosis factor inhibitors (TNFi) or Interleukin 17A inhibitors (IL-17Ai).

Methods: Serum samples were obtained from PsA patients satisfying the CASPAR criteria. Patients were treated with either TNFi (n = 20; infliximab, adalimumab, etanercept, certolizumab or golimumab) or IL-17Ai (n = 20; secukinumab or ixekizumab). Patients were evaluated at baseline and 3 months post-therapy and determined as responders or non-responders based on the Disease Activity Index for PsA (DAPSA) wherein responders had DAPSA < 14. Solid phase microextraction (SPME), a novel high throughput technique was used to prepare all samples simultaneously followed by liquid chromatography – high-resolution mass spectrometry (LC-HRMS) analysis.

Data processing and feature identification was performed using 2 platforms – Metaboanalyst R and Compound Discoverer 3.3 respectively. Various Machine Learning (ML) algorithms including Naïve-Bayes (NB), logit boost, adaptive boosting, linear regression, support vector machine (SVM), linear discriminant analysis (LDA), and random forest (RF), was used for predictive feature analysis. Only features in models with an area under the curve of 0.7 or greater were considered as candidate metabolite markers.

Results: 7/20 (35%) of patients treated with TNFi and 13/20 (65%) of patients treated with IL17Ai were responders. As little as 5 features from an SVM model produced an AUROC value of 0.732, while as many as 20 features using NB produced a value of 0.812 between responders and non-responders for both treatments combined at baseline. When considering a single treatment option (TNFi or IL-17Ai only), less than 5 features were required to produce AUROC scores of > 0.9 in both positive and negative mode data. Several exposome-related metabolites were identified via MS level 2 spectral matching including cotinine, adipic acid, toluic acid, monobutylphthalate and tridecylic acid. Glycochenodeoxycholic acid, an endogenous metabolite was also identified.

Conclusion: The identification of cotinine – a metabolite found in tobacco, could indicate that a risk behaviour such as smoking, or an exposure to second hand smoke as well as glycochenodeoxycholic acid – a metabolite that stimulates the mitochondrial pathway to cell death, may indicate that multiple mechanisms of action affects response to treatment. Validation of these results is required.

DIAGNOSTIC BIOMARKERS

Combining Clinical, Genetic and Protein Markers Provide Fair but Unsatisfactory Discrimination between Psoriatic Arthritis and Psoriasis

Background/Purpose: Psoriatic Arthritis (PsA) is an inflammatory arthritis present in a quarter of patients with cutaneous psoriasis. Early diagnosis of PsA remains a challenge. The performance of screening questionnaires have been disappointing. Specific clinical features have been noted to be associated with PsA in patients with psoriasis. We have previously developed a panel of 'PsA-enriched' SNPs as well as a panel of proteins that differentiates PsA patients from those with psoriasis without PsA (PsC). However, these markers individually did not have a high discriminant value in differentiating PsA from PsC. With the hypothesis that a combination of clinical features, genetic variants and protein biomarkers will better differentiate PsA from PsC, we aimed to develop diagnostic signatures.

Methods: Patients with PsA (n=102) and PsC (n=100) were identified from a database of a cohort of patients with psoriatic disease, and group matched for age, sex and psoriasis duration. Demographic and clinical information (age, sex, psoriasis duration, psoriasis area and severity index [PASI], nail disease, and BMI) collected at the time of assessment were retrieved. Serum and DNA samples were retrieved from the linked biobank. 42 single-nucleotide polymorphisms (SNPs) of 19 genes weighted towards PsA

(TNFRSF9, IL23R, PTPN22, LCE3A, REL, 5q31, IL13, TNIP1, IL12B, HLA-B, HLA-C, MICA, TRAF3IP2, TNFAIP3, IL23A, FBXL19, TYK2, ZNF816A, and KIR2DS2) were genotyped. 15 proteins (TNFSF14, S100A8/9, COMP, CRP, M2BP, OPG, DEFA, ITGB5, RANKL, CXCL10, Leptin, MMP3, OPN, Periostin, and SOST) were assayed using ELISA. Association between clinical, genetic and protein markers and PsA were determined and models developed to discriminate PsA from PsC using machine learning algorithms (Random Forest, Support Vector Machines (SVM), AdaBoost, DecisionTree, NaiveBayes, LogitBoost, Logistic Regression, and Linear Discriminant Analysis (LDA)).

Results: When combining features, clinical and demographic features had poor value in distinguishing PsA from PsC (best performing model (sex and PASI)- AdaBoost, AUROC 0.607, $p<0.0045$). SNPs (FBXL19 (rs10782001), TNFAIP3 (rs9321623), IL13 (rs1800925), HLA-B (rs9266242), IL23R (rs2201841 and rs4655683), TN1P1 (rs146571698), HLA-B*3906 (rs2844603) and on 5q31 (rs715285)) and proteins (S100A8/9, Leptin, ITGB5, CRP, CXCL10, OPG, SOST, OPN, Periostin, and RANKL) had fair value in discriminating PsA from PsC with best performing model SVM, (AUROC 0.69, $p<0.001$) and logistic regression (AUROC 0.694, $p<0.001$), respectively. When combined, proteins, SNPs and clinical features provided better discriminatory value (40 features, best performing model- Random Forest, AUROC 0.733, $p <0.001$).

Conclusion: Combining previously identified clinical, genetic and protein markers have only a fair ability to differentiate PsA from PsC; better diagnostic signatures need to be identified.

PUBLICATIONS:

1. Cheung MW, Dayam RM, Shapiro JR, Law JC, Goeteguer RL, Chao GYC, Stempak J, Pereira D, Croituru D, Acheampong L, Rizwan S, Lee JD, Ganatra D, Law R. Rodriguez VE, Delgado-Brand M, Mailhot G, Piguet V, Chandran, V Silverberg MS, Watts TH, Gingras AC. Third and fourth vaccine doses broaden and prolong immunity to SARS-CoV-2 in adult patients with immune-mediated inflammatory diseases. The Journal of Immunology. 2023 May 30. In Press. Impact Factor 5.43.
2. Rida MA, Lee KA, Chandran V, Cook RJ, Gladman DD. Persistence of biologics in the treatment of psoriatic arthritis (Psa): Data from a large hospital based longitudinal cohort. Arthritis Care Res (Hoboken). 2023 Mar 13. Impact Factor 5.178.
3. Nazri JM, Oikonomopoulou K, de Araujo ED, Kraskouskaya D, Gunning PT, Chandran V. Histone deacetylase inhibitors as a potential new treatment for psoriatic disease and other inflammatory conditions. Critical Reviews in Clinical Laboratory Sciences. 2023 Feb 27;60:300-320. Impact Factor 7.721.
4. Bassini A, Sartoretto S, Jurisica L, Magno-França A, Anderson L, Pearson T, Razavi M, Chandran V, Martin L 3rd, Jurisica I, Cameron LC. Sportomics method to assess acute phase proteins in Olympic level athletes using dried blood spots and multiplex assay. Scientific Reports. 2022 Nov 18;12:19824. Impact Factor 4.997..
5. Kwok TSH, Sutton M, Cook RJ, Pereira D, Chandran V, Gladman DD. Musculoskeletal surgery in psoriatic arthritis: Prevalence and risk factors. Journal of Rheumatology. 2022 Nov 15;50:497-503. Impact Factor 5.346.
6. Kwok TSH, Sutton M, Pereira D, Cook RJ, Chandran V, Haroon N, Inman RD, Gladman DD. Isolated axial disease in psoriatic arthritis and ankylosing spondylitis with psoriasis. Annals of the Rheumatic Diseases. 2022 Aug 16;81(9):1678-1684. Impact Factor 28.003.
7. Park S, Silverberg OM, Moez E, Chandran V, Gladman DD. Investigation into the wait time for consultation in the psoriatic arthritis program. Clinical Rheumatology. 2022 Jul 22;41(12):3753-3757. Impact Factor 3.65.

8. Wong A, Ye JY, Cook RJ, Gladman DD, Chandran V. Depression and anxiety reduce the probability of achieving a state of sustained minimal disease activity in patients with psoriatic arthritis. Arthritis Care Res (Hoboken). 2022 Jun 8;74(9):1430-1434. Impact Factor 5.178. Sen
9. Mathew AJ, Sutton M, Pereira D, Gladman DD, Chandran V. Effectiveness of Disease-Modifying Antirheumatic Drugs for Enthesitis in a Prospective Longitudinal Psoriatic Arthritis Cohort. Journal of Rheumatology. 2022 Jun 1;49(9):1020-1025. Impact Factor 5.348.
10. Koppikar S, Colaco K, Harvey P, Akhtari S, Chandran V, Gladman DD, Cook R, Eder L. Incidence of and risk factors for heart failure in patients with psoriatic disease - a cohort study. Arthritis Care Res (Hoboken). 2022 May 10;74(8):1244-1253. Impact Factor 5.178.
11. Dayam RM, Law JC, Goetgebuer RL, Chao GY, Abe KT, Sutton M, Finkelstein N, Stempak JM, Pereira D, Croitoru D, Acheampong L, Rizwan S, Rymaszewski K, Milgrom R, Ganatra D, Batista NV, Girard M, Lau I, Law R, Cheung MW, Rathod B, Kitaygorodsky J, Samson R, Hu Q, Hardy WR, Haroon N, Inman RD, Piguet V, Chandran V, Silverberg MS, Gingras AC, Watts TH. Accelerated waning of immunity to SARS-CoV-2 mRNA vaccines in patients with immune mediated inflammatory diseases. JCI Insight. 2022 Apr 26;7(11):e159721. Impact Factor 9.484.
12. Kwok TSH, Sutton M, Yang Ye J, Pereira D, Chandran V, Gladman DD. Prevalence and factors associated with osteoporosis and bone mineral density testing in psoriatic arthritis. Arthritis Care Res (Hoboken). 2022 Mar 25;74(6):1006-1012. Impact Factor 5.178.
13. Colaço K, Lee KA, Akhtari S, Winer R, Welsh P, Sattar N, McInnes IB, Chandran V, Harvey P, Cook RJ, Gladman DD, Piguet V, Eder L. Association of Cardiac Biomarkers with Cardiovascular Outcomes in Patients with Psoriatic Arthritis and Psoriasis: A Longitudinal Cohort Study. Arthritis & Rheumatology. 2022 Mar 8;74(7):1184-1192. Impact Factor 15.483.
14. Eder L, Li Q, Rahmati S, Rahman P, Jurisica I, Chandran V. Defining imaging sub-phenotypes of psoriatic arthritis: Integrative analysis of imaging data and gene expression in a PsA patient cohort. Rheumatology (Oxford). 2022 Feb 14;61:4952-4961. Impact Factor 7.046.

COLLABORATING SITES' REPORTS

Progress Report by Dr. Lihi Eder

IPART Toronto (2) Collaborating Site – Women's College Hospital, Toronto, Ontario, Canada

The following projects are ongoing at the Toronto Site 2 – Women's College Hospital:

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 timeframes can be predicted with reasonable accuracy for psoriasis patients. Additional work is underway to validate these models in external cohorts of psoriasis patients.

Metabolic Disorders and Abnormal Dietary Patterns and Their Association with Psoriatic Arthritis Activity: The Dietary Intervention in PsA (DIPSA) Study.

Background: Psoriatic Arthritis (PsA) is associated with obesity and its related metabolic abnormalities. The role of diet as an adjunct therapy in PsA remains unclear.

Objectives: We aimed to describe the prevalence of cardiometabolic abnormalities and adherence with healthy eating recommendations among patients participating in the DIPSA study and asses their association with measures of disease activity.

Methods: DIPSA is a randomized controlled trial (NCT04180904) that aims to compare the efficacy of Mediterranean diet and DASH-low caloric diet vs. standard of care as adjunct therapy in patients with PsA who are overweight or obese (BMI>25). Study participants must have Disease Activity in Psoriatic Arthritis (DAPSA) score >10 and be on stable therapy. Baseline information on the first 32 patients enrolled in the study (out of expected 90 patients) was analyzed. The presence of cardiometabolic abnormalities was assessed based on medical history, physical examination and laboratory tests. All participants completed a 24-h dietary recall of foods/beverages consumed during 3 separate weekdays. Healthy Eating Index (HEI) 2015, a diet quality score which evaluates adherence to dietary guidelines for Americans, was calculated. The score includes 13 food components (9 components encouraged, 4 to limit) with a range of 0 (low) to 5 or 10 (high). We describe the baseline cardiometabolic abnormalities and adherence with healthy diet scores and assess their correlation with PsA disease activity measures.

Results: The mean age of study participants was 53.3 years (71.9% females). The mean DAPSA, tender and swollen joint counts were 23.6, 6.6 and 1.1, respectively. A significant proportion of the patients had obesity (71.9%) and related metabolic abnormalities such as dyslipidemia (41.9%), hypertension (37.5%) metabolic syndrome (46.9%). Mean HEI-2015 was 59.3 with higher adherence scores (HEI2015>50; 25%Q1) found in females than males (91% vs. 57%, respectively, pp<0.05). No differences in HEI-2015 scores were found between age and level of education groups. Of the individual HEI-2015 food groups, the lowest adherence scores were found for whole grain and total sodium consumption (Table 1). Significant correlation was found between lower added sugar and both lower fatigue and lower PSAID scores (Figure 1), and correlation between greater whole fruit consumption and lower swollen joint count. Additionally, a correlation was found between the unsaturated than saturated fatty acids and higher enthesitis score.

Conclusion: High prevalence of metabolic abnormalities was found in patients with PsA starting a diet intervention study. Adherence with healthy diet eating recommendations at baseline was higher in female patients and individual foods, particularly sugar and whole fruit consumption, were associated with PsA measures of disease activity. The DIPSA study will determine the role of dietary interventions as adjunct therapy in PsA.

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.

SUMMARY OF SITE NUMBERS

- Participants recruited to date: 684
- Participants recruited in the last year: 34
- Distribution of participants by disease status (PsA/PsC): 299/385

PUBLICATIONS:

1. Eder L, Tony HP, Odhav S, Agirregoikoa EG, Korkosz M, Schwartzman S, Sprabery AT, Gellett AM, Park SY, Bertram CC, Ogdie A. Responses to Ixekizumab in Male and Female Patients with Psoriatic Arthritis: Results from Two Randomized, Phase 3 Clinical Trials. Rheumatol Ther. 2022 Jun;9(3):919-933. doi: 10.1007/s40744-022-00445-w.
2. Colaco K, Lee KA, Akhtari S, Winer R, Welsh P, Sattar N, McInnes IB, Chandran V, Harvey P, Cook RJ, Gladman DD, Piguet V, Eder L. Association of Cardiac Biomarkers With Cardiovascular Outcomes in Patients With Psoriatic Arthritis and Psoriasis: A Longitudinal Cohort Study. Arthritis Rheumatol. 2022 Jul;74(7):1184-1192. doi: 10.1002/art.42079.

3. Sarabia S, Farrer C, Yeung J, Jerome D, Cook RJ, Eder L. Comparative Efficacy of Different Triage Methods for Psoriatic Arthritis: Results From a Prospective Study in a Rapid Access Clinic. Arthritis Care Res (Hoboken). 2022 Aug;74(8):1254-1262. doi: 10.1002/acr.24570.
4. Kuriya B, Akhtari S, Movahedi M, Udell JA, Lawler PR, Farkouh ME, Keystone EC, Hanneman K, Nguyen E, Harvey PJ, Eder L. Statin Use for Primary Cardiovascular Disease Prevention Is Low in Inflammatory Arthritis. Can J Cardiol. 2022 Aug;38(8):1244-1252. doi: 10.1016/j.cjca.2022.04.002.
5. Koppikar S, Colaco K, Harvey P, Akhtari S, Chandran V, Gladman DD, Cook R, Eder L. Incidence of and Risk Factors for Heart Failure in Patients With Psoriatic Disease: A Cohort Study. Arthritis Care Res (Hoboken). 2022 Aug;74(8):1244-1253. doi: 10.1002/acr.24578.
6. Tarannum S, Leung YY, Johnson SR, Widdifield J, Strand V, Rochon P, Eder L. Sex-and gender-related differences in psoriatic arthritis. Nat Rev Rheumatol. 2022 Sep;18(9):513-526. doi: 10.1038/s41584-022-00810-7.
7. Eder L, Li Q, Rahmati S, Rahman P, Jurisica I, Chandran V. Defining imaging sub-phenotypes of psoriatic arthritis: integrative analysis of imaging data and gene expression in a PsA patient cohort. Rheumatology (Oxford). 2022 Nov 28;61(12):4952-4961. doi: 10.1093/rheumatology/keac078. PMID: 35157043; PMCID: PMC9707284.
8. Eder L, Mathew AJ, Carron P, Bertheussen H, Cañete JD, Azem M, Sedie AD, Salvarani C, Ranza R, Elliott A, Turkiewicz A, de Toledo RA, Bukulmez H, Stoenoiu MS, Mandelin AM 2nd, Koehm M, Lindsay CA, Siegel E, Mease PJ. Management of Enthesitis in Patients With Psoriatic Arthritis: An Updated Literature Review Informing the 2021 GRAPPA Treatment Recommendations. J Rheumatol. 2023 Feb;50(2):258-264. doi: 10.3899/jrheum.220312.
9. Tarannum S, Widdifield J, Wu CF, Johnson SR, Rochon P, Eder L. Understanding sex-related differences in healthcare utilisation among patients with inflammatory arthritis: a population-based study. Ann Rheum Dis. 2023 Feb;82(2):283-291. doi: 10.1136/ard-2022-222779.
10. Eder L, Croxford R, Drucker AM, Mendel A, Kuriya B, Touma Z, Johnson SR, Cook R, Bernatsky S, Haroon N, Widdifield J. Understanding COVID-19 Risk in Patients With Immune-Mediated Inflammatory Diseases: A Population-Based Analysis of SARS-CoV-2 Testing. Arthritis Care Res (Hoboken). 2023 Feb;75(2):317-325. doi: 10.1002/acr.24781. Epub 2022 Sep 27. PMID: 34486829; PMCID: PMC8653048.
11. Eder L, Gladman DD, Mease P, Pollock RA, Luna R, Aydin SZ, Ogdie A, Polachek A, Gruben D, Cadatal MJ, Kinch C, Strand V. Sex differences in the efficacy, safety and persistence of patients with psoriatic arthritis treated with tofacitinib: a post-hoc analysis of phase 3 trials and long-term extension. RMD Open. 2023 Mar;9(1):e002718. doi: 10.1136/rmdopen-2022-002718. PMID: 36958766; PMCID: PMC10030648.

Progress Report by Dr. Devy Zisman
IPART Israel Collaborating Site – Carmel Medical Center, Haifa, Israel

The following projects are ongoing at the Israel Site – Carmel Medical Center:

Treatment Persistence of Apremilast Among Patients with Psoriatic Arthritis

Background: Persistence in drug therapy is a measure of real world treatment effectiveness and tolerability.

Objective: To estimate the persistence of apremilast prescribed to patients with psoriatic arthritis (PsA), identify causes and characteristics associated with treatment discontinuation of apremilast in the real-world setting.

Methods: Patients with PsA from a large health care provider database with a dispensed prescription of apremilast, that was indicated and approved for PsA (DMARDs) as of January 1st, 2016 on failure to at least 2 disease-modifying anti-rheumatic drugs , were identified and followed until medication stop date or the end of observation period(June 30th, 2021). Persistence was assessed by examining the distribution of time until the first apremilast discontinuation. We defined discontinuation events as a lack in filling the prescription within a 90 grace days period. Treatment changes were based on physician decisions and patient preferences. Causes of treatment discontinuation were manually retrieved by reviewing each patient medical record in the database. Demographic data including age, sex, body mass index(BMI), ethnicity and socioeconomic status as well as Charlson comorbidity index were retrieved. Data regarding use of conventional and biologic DMARDs were also extracted. Descriptive statistics, including means (standard deviations) for continuous variables and frequencies (%) for categorical variables, were used. Persistence estimates were derived using non-parametric survival analysis using Kaplan-Meier functions, with treatment discontinuations as failure events.

Results: 568 PsA patients treated with aprimilast were identified. The mean age of the study population was 55.3±14.0 years, of whom 332 (58.5%) were females, 38.4% were obese (BMI>30), 75.2% had a Charlson comorbidity index>1, 24.1% were on concomitant treatment with methotrexate, and 72.4% were biologic naïve. Socioeconomic status was estimated as low, medium and high at 29.8, 43.0 and 27.2%, respectively. The median persistent period was 6.1 95%CI (5.2-6.9) months in which only 16.9% remained persistent on apremilast. No difference was found with regards to age, sex. Socioeconomic status, ethnicity and obesity between patients who were persistent compared to patients who discontinued apremilast. Concomitant treatment with methotrexate and prior history of biologic therapy did not affect drug persistency (log rank P=0.957 and 0.082 , respectively). Causes for treatment discontinuation were due to lack of skin efficacy in 19.4%, lack of joint efficacy in 33.3%, combined skin and joint inefficacy at 2.3%, side effects in 23.9%, other reasons in 12.4%.

Conclusion: In this large observational cohort studied in the era of apremilast therapy, a relatively low drug persistence was observed. Treatment discontinuation was mainly for joint inefficacy. Concomitant use of methotrexate and prior biologics use didn't have any impact on persistency, advocating for more studies for proper patient selection to assure treatment effectiveness and persistency.

COVID-19 Vaccine Efficacy Among Patients with Psoriatic Disease: A Population-based Study

Background: Little information is available on the effectiveness of COVID-19 mRNA vaccination in patients with psoriatic disease (PsD) including psoriasis (PsO) and psoriatic arthritis (PsA)

Objective: To assess the efficacy of COVID-19 vaccination series in preventing SARS-CoV2 infection and COVID-19-related hospitalizations in patients with PsD and non-psoriatic controls and the association of immune-modulating medications on these COVID-19-related outcomes.

Methods: A population-based study was performed using the Clalit Health Services database. For the comparison of PsD and non-psoriatic controls, we assembled a cohort of patients with diagnoses of PsO and/or PsA and matched them by age, sex-, and clinic location (1:5 ratio). For assessment of vaccine effectiveness, the following 2 periods were analyzed separately: Period 1 which corresponded to initiation of COVID-19 vaccination until initiation of booster (third) vaccines (December 2020-August 2021); Period 2 corresponded to initiation of booster vaccines to end of study (August 2021-December 2021). Study outcomes included: SARS-CoV2 PCR positivity and hospitalization for COVID-19. For assessment of the association of medications and COVID-19 related outcomes, we performed a matched nested case-control study within the PsD cohort in which each case (SARS-CoV2 infection and COVID-19 hospitalization) was matched with 10 controls (negative for these outcomes). Vaccine efficacy was assessed using regression models with time varying covariates for vaccination status adjusted for demographics, comorbidities and medication use.

Results: A total of 128,754 PsD patients and 600,439 controls positive for SARS-CoV2 (5,934 vs 26,292, with 315 vs 1,127 hospitalized, respectively) were identified in the database. Vaccine efficacy for SARS-

CoV2 infection was similar among patients with PsD (HR for 2nd vaccine: 0.20) vs controls (HR for 2nd vaccine: 0.20). Vaccine efficacy for COVID-19 hospitalization was also similar among PsD patients (HR for 2nd vaccine: 0.15) vs controls (HR for 2nd vaccine: 0.08). Booster vaccines remained effective in reducing risk of infections (HR for of 3rd vaccine: 0.41) and hospitalization (HR for of 3rd vaccine <0.01) among patients with PsD. When the analysis was restricted to patients with PsD and adjusted for use of systemic therapies, vaccine efficacy for SARS-CoV2 infections (OR period 1: 2nd vaccine: 0.19; OR period 2: 3rd vaccine: <0.01) and hospitalizations (OR period 1: 2nd vaccine: 0.01; OR period 2: 3rd vaccine: 0.17) remained high. Use of etanercept was associated with higher risk of SARS-CoV2 infection and Janus Kinase inhibitors use was associated with higher risk of hospitalizations. PsA status was not associated with higher risk of both SARS-CoV2 infection and hospitalizations compared to patients with PsO alone.

Conclusion: COVID-19 vaccine has similar efficacy in patients with PsD to that seen in non-psoriatic controls. Risk of COVID-19 hospitalization among PsD patients may be influenced by certain immune-modulating therapies.

Incidence of Herpes Zoster events after each of three doses of the BNT162b2 mRNA vaccine in patients with spondyloarthritis (SpA)

Background: The importance and efficacy of mRNA COVID-19 vaccination in coping with the pandemic are well established, but inconsistencies remain in the data regarding side effects, especially in patients with rheumatic diseases treated with immunosuppressive therapy.

Objective: We aimed to assess the incidence of Herpes Zoster (HZ) in patients with psoriatic arthritis (PsA) and ankylosing spondylitis (AS) after each of the three doses of the BNT162b2 mRNA vaccine compared to HZ incidence in a similar time period two years prior to vaccination, and the effect of immunosuppressive therapy on this incidence.

Methods: The database of Clalit Health Services, the largest health care provider of approximately 4.7 million members in Israel, was retrospectively analyzed for patients with a diagnosis of PsA and AS starting from 12/2018 and who later received 3 doses of the BNT162b2 mRNA vaccine in a national vaccination campaign from 12/2020-12/2021. For each individual, data on demographic, socioeconomic, and selected chronic comorbidities, as well as use of glucocorticosteroids, conventional/ biologic/ targeted-synthetic disease modifying anti-rheumatic drugs (c/b/ts DMARDs) and previous HZ vaccination status were retrieved. The incidence of HZ events was calculated during the 6 weeks following each of the three mRNA COVID-19 vaccine doses and compared to a similar time period within this group of patients two years prior by McNemar test, and also relative to fully-vaccinated controls from the general population matched by sex and age at 1:10 ratio. Multivariable logistic regression was used to assess for any association between DMARD use within 3 months prior HZ event in spondyloarthropathy (SpA) patients.

Results: The study population consisted of 6460 spondyloarthropathy (SpA) patients, 4648 (70.7 %) with PsA, 1812 (27.6%) with AS and 115 (1.7%) with both PsA and AS with a mean age of 57.6±15.0 years, of whom 3107 (48.1%) male. The incidence of HZ events was higher among SpA patients in comparison to the general population both pre- (p=0.004) and post- (p=0.027) mRNA COVID-19 vaccination, even after controlling for multiple covariates, with no significant difference in HZ reactivation occurring in the PsA vs AS subgroups pre- and post mRNA vaccination. The number of HZ events was not increased in SpA patients on DMARDs of any type in comparison to SpA patients not on these medications.

Conclusion: The risk of HZ after each one of the three BNT162b2 mRNA vaccine doses was not increased in PsA and AS patients compared to a similar time period two years prior to vaccination, and was not influenced by the type of DMARD used.

PUBLICATIONS:

1. Furer V, Zisman D, Kibari A, Rimar D, Paran Y, Elkayam O. Herpes zoster following BNT162b2 mRNA Covid-19 vaccination in patients with autoimmune inflammatory rheumatic diseases: a case series. Rheumatology (Oxford). 2021 Oct 9;60(SI):SI90-SI95.

2. Furer V, Eviatar T, Zisman D, Peleg H, Paran D, Levartovsky D, Zisapel M, Elalouf O, Kaufman I, Meidan R, Broyde A, Polachek A, Wollman J, Litinsky I, Meridor K, Nochomovitz H, Silberman A, Rosenberg D, Feld J, Haddad A, Gazzit T, Elias M, Higazi N, Kharouf F, Shefer G, Sharon O, Pel S, Nevo S, Elkayam O. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicenter study. Ann Rheum Dis. 2021 Oct;80(10):1330-1338.
3. Furer V, Eviatar T, Zisman D, Peleg H, Braun-Moscovici Y, Balbir-Gurman A, Paran D, Levartovsky D, Zisapel M, Elalouf O, Kaufman I, Broyde A, Polachek A, Feld J, Haddad A, Gazitt T,Elias M, Higazi N, Kharouf F, Pel S, Nevo S, Elkayam O. Predictors of Immunogenic Response to theBNT162b2 mRNA COVID-19 Vaccination in Patients with Autoimmune Inflammatory Rheumatic Diseases Treated with Rituximab. Vaccines (Basel). 2022 Jun 6;10(6):901
4. Furer V, Eviatar T, Freund T, Peleg H, Paran D, Levartovsky D, Kaufman I, Broyde A, Elalouf O, Polachek A, Feld J, Haddad A, Gazitt T, Elias M, Higazi N, Kharouf F, Gertel S, Pel S, Nevo S, Hagin D, Zisman D, Elkayam O. Immunogenicity induced by two and three doses of the BNT162b2 mRNA vaccine in patients with autoimmune inflammatory rheumatic diseases and immunocompetent controls: a longitudinal multicentre study. Ann Rheum Dis. 2022 Nov;81(11):1594-1602
5. Gazitt T, Eviatar T, Shear J, Meidan R, Furer V, Feld J, Haddad A, Elias M, Hijazi N, Stein N, Shaked Mishan P, Zetser A, Peleg H, Elkayam O, Zisman D. Development of Autoantibodies Following BNT162b2 mRNA COVID-19 Vaccination and Their Association with Disease Flares in Adult Patients with Autoimmune Inflammatory Rheumatic Diseases (AIIRD) and the General Population: Results of 1-Year Prospective Follow-Up Study. Vaccines (Basel). 2023 Feb 17;11(2):476
6. Kharouf F, Eviatar T, Braun M, Pokroy-Shapira E, Brodavka M, Zloof Y, Agmon-Levin N, Toledano K, Oren S, Lidar M, Zisman D, Tavor Y, Amit-Vazina M, Sabbah F, Breuer GS, Dagan A, Beshara-Garzuzi R, Markovits D, Elias M, Feld J, Tayer-Shifman O, Gazitt T, Reitblatt T, Rubin L, Haddad A, Giryes S, Paran D, Peleg H, Molad Y, Elkayam O, Mevorach D, Balbir-Gurman A, Braun-Moscovici Y A deep look into the storm: Israeli multi-center experience of coronavirus disease 2019 (COVID-19) in patients with autoimmune inflammatory rheumatic diseases before and after vaccinations. . Front Immunol. 2023 Mar 13;14:1064839

Progress Report by Dr. Sibel Aydin

IPART Collaborating Site – University of Ottawa, Ottawa, Ontario, Canada

The Ottawa site is doing a pilot study on **Identification of Bone-Forming Phenotype through Genotype in Spondyloarthritis (SpA).** This is a study in collaboration with Dr. Lihi Eder and Dr. Proton Rahman. The group's aim is to generate pilot data in SpA to conduct a multicenter study linking the bone-forming phenotype with genotype a) enabling a sample size calculation, b) determining the SNPs to be tested, c) improving definitions of new bone forming phenotype to be used as a study outcome. Within 112 patients being recruited, 6 different definitions of new bone forming phenotype is tested, including radiographs of the spine and ultrasound of the peripheral entheses. In parallel, 42 SNPs have been investigated. All data collection is completed for the study and further analysis in ongoing. The preliminary results will be presented at the IPART annual scientific meeting on June 30, 2023.

EDUCATION, TRAINING & ADVOCACY COMPONENTS

IPART will continue to collaborate with the **Psoriatic Arthritis Research Program (PsARP),** 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 more than 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, IPART collaborates with PsARP, the latter taking the lead in conducting educational symposiums for patients with psoriasis and PsA registered in the Psoriatic Arthritis Program for the last 18 years. 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 2023, PsARP will be conducting an in-person patient forum event scheduled for **October 15, 2023 from 1-5PM at the Courtyard Marriott Downtown Toronto**.
- **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 PsARP programs. Several of these have resulted in the publications described above.

  In collaboration with the **Spondyloarthritis Research Consortium of Canada (SPARCC**), PsA fellows, as part of their mandatory training initiatives, will take part in the SPARCC Fellows Training Day scheduled for **September 8, 2023 at the BMO Conference Centre, UHN-TWH, Krembil Tower**.
- **Studentship** – Through the PsARP and IPART programs, medical students likewise take part in projects and core activities as outlined above. The program normally accepts 4-6 students each year and presently, 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 2023, the scientific meeting will be in virtual format scheduled for **June 30, 2023 from 1:00 – 5:00 PM eastern standard time**.
- **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

BACKGROUND

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.

CORE SITES

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

COLLABORATING SITES

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) Toronto, Ontario (Women's College Hospital – **Dr. Lihi Eder)**
3) Haifa, Israel (Carmel Medical Center – **Dr. Devy Zisman)**
4) Detroit, MI (Henry Ford Health System – **Dr. Qing-Sheng Mi and Dr. So Yeon Paek)**
5) India (Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS) – **Dr. Vikas Agarwal)**
6) Ottawa, Ontario (University of Ottawa – **Dr. Sibel Aydin)**
7) Vancouver, BC (ARTUS Health Center - **Dr. Jonathan Chan** joined our core site at the University of British Columbia – Dr. Jan Dutz)
8) Vellore, India – (Christian Medical College - **Dr. Ashish Matthew and Dr. Debashish Danda**)
9) 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, ELI LILLY, UCB and FRESENIUS KABI** granted through the IPART Toronto core site at the University Health Network, Toronto Western Hospital.

At the IPART Ann Arbor core site, a grant renewal has been extended by the **National Institutes of Health (NIH), National Institutes of Arthritis and Musculoskeletal and Skin Diseases,** Prime Award No. 5R01AR063611-08 to the University of Michigan (Dr. James T. Elder, PI), and Sub-award No. SUBK00010328 to the University Health Network -IPART Research Program (Dr. Dafna Gladman, PI).

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