IPART
International Psoriasis & Arthritis Research Team

## 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. It has five core sites namely:

| | |
|---|---|
| Toronto, Ontario, CANADA | **Dr. Dafna D. Gladman,** Division of Rheumatology, University of Toronto, Toronto Western Hospital<br>**Dr. Cheryl F. Rosen**, Division of Dermatology, University of Toronto, Toronto Western Hospital<br>**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 |

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) Winnipeg, Manitoba (Winnipeg Clinic – **Dr. Snezana Barac and Dr. Richard Haydey**)
3) Toronto, Ontario (Women's College Hospital – **Dr. Lihi Eder and Dr. Jensen Yeung**)
4) Haifa, Israel (Carmel Medical Center – **Dr. Devy Zisman**)
5) Detroit, MI (Henry Ford Health System – **Dr. Qing-Sheng Mi and Dr. So Yeon Paek**)
6) India (Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS) – **Dr. Vikas Agarwal**)
7) Ottawa, Ontario (University of Ottawa – **Dr. Sibel Aydin**)
8) Vancouver, BC (ARTUS Health Center - **Dr. Jonathan Chan** joining our core site at the University of British Columbia – Dr. Jan Dutz)
9) Vellore, India – (Christian Medical College - **Dr. Ashish Matthew and Dr. Debashish Danda**)

Recently, a new site has joined IPART from the University of KwaZulu Natal, Durban, South Africa with **Dr. Ajesh Maharaj** leading the group as Head Rheumatologist in the Department of Internal Medicine, Prince Mshiyeni Memorial Hospital Umlazi, Nelson R. Mandela School of Medicine. The site has obtained institutional approval at the University Health Network (lead site) in Toronto, and is now completing ethics submission and other institutional formalities in South Africa to officiate its collaboration.

IPART was a recipient of the CIHR New Emerging Team (NET) grant (Gladman-CIHR IIN 84039 over a period of five (5) years from July 2007 and ended in June 2012) that focused on the biologic basis of PsC (cutaneous psoriasis) and PsA (psoriatic arthritis), and the overall goal underlying this research network is make advances that will lead

to the significant improvement in outcomes for patients with psoriasis and PsA. IPART's objectives are 1) to develop a database of cohorts of carefully phenotyped patients with PsC and PsA, 2) to identify susceptibility factors for PsA among patients with PsC, and 3) to identify risk factors for disease severity among patients with PsC and PsA using the database. While IPART continued heavily on its genetics and biomarker research since the end of the CIHR – NET grant in 2012, it has evolved into a major engine for research in psoriasis and PsA, making significant advances in the field.

**At present, IPART is funded by multi-industry support from ABBVIE, AMGEN, NOVARTIS, CELGENE, UCB, PFIZER, and ELI LILLY.**

## DATABASE AND BIOBANKING UPDATE

### DATABASE

IPART has the largest collection of well characterized patients with PsD (psoriatic diseases) followed longitudinally in the world. It has successfully established a large multicenter cohort of well phenotyped patients with PsC and PsA, tracked on a web-based database which includes clinical, laboratory, and imaging information, linked to biologic specimens.

| Update 15 March 2019 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | TWH | WCH | St. John's | Vancouver | Ann Arbor | Rochester | London | Winnipeg | Israel | Halifax | Argentina |
| PsA | 1578 | 173 | 579 | 78 | 15 | 219 | 160 | 43 | 159 | 4 | 4 |
| Psoriasis | 684 | 339 | 81 | 43 | 67 | 206 | 5 | 170 | 6 | 21 | 9 |
| Total | 2262 | 512 | 660 | 121 | 82 | 425 | 165 | 213 | 165 | 25 | 13 |
| Female* | 44.1 | 57.2 | 57,8 | 47.1 | 48.8 | 56.8 | 42.1 | 50 | 56.7 | 36 | 92.3 |
| Caucasian* | 86 | 76.2 | 99.6 | 66.2 | 98.8 | 89.4 | 94.6 | 84.2 | 83.3 | 92 | 75 |
| Visits Ps | 4.0 | 1.9 | 1.0 | 1.7 | 2.5 | 1.8 | 3.9 | 1.9 | 1.8 | 1.4 | 1.0 |
| Visits PsA | 12.8 | 4.8 | 1.5 | 1.9 | 2.2 | 3.2 | 3.9 | 2.7 | 4.8 | 1.3 | 1.0 |
| Age Ps | 28.8 | 31.7 | 34.8 | 31.4 | 30.2 | 32.1 | 32.8 | 31.1 | 35.6 | 28.4 | 31.1 |
| Age PsA | 38.2 | 43.7 | 44.7 | 38.1 | 41.5 | 40.5 | 42.1 | 41.5 | 45.6 | 46.0 | 40.3 |
| DD Ps | 19.7 | 17.1 | 15.5 | 23.1 | 17.1 | 16.8 | 22.0 | 18.5 | 19.4 | 19.7 | 21.2 |
| DD PsA | 16.7 | 9.2 | 5.6 | 14.1 | 12.5 | 9.4 | 8.8 | 6.2 | 9.8 | 4.7 | 28.1 |
| *=%, Ps =Psoriasis; PsA=Psoriatic arthritis; DD=disease duration at presentation | | | | | | | | | | | |

In summary:

| | PsA | PsC | total |
|---|---|---|---|
| Number of patients | 3012 | 1631 | 4643 |

Establishing a common clinical database has been a significant achievement for the IPART network and checks off a major goal from the original proposal. The database has been a foundational asset we developed from which all projects and activities have stemmed. It is the database which has allowed us to address our objectives; 1) identify susceptibility factors for PsA among patients with PsC and 2) to identify risk factors for disease severity among patients with PsC and PsA.

New functionality has been added to DADOS to import lab results from external sources (Lifelabs) and internal databases. This is has streamlined the process of adding data to the database and improved quality.

## IPART TORONTO BIOBANK

The IPART biobank continues to grow and expand as our research endeavors progress. We have built a biobank that contains the world's largest collection of biosamples that is matched with detailed clinical phenotype and molecular data for Psoriatic Arthritis and Psoriasis only cohorts.

The core laboratory is based at Toronto Western Hospital and receives the majority of IPART biosample collection with several of the core collaborating sites also maintaining local biobanks for IPART. Vancouver, Rochester, Ann Arbor and St. John's all maintain biorepositories for IPART. The core IPART laboratory is accredited for biosafety standards and continues to maintain high standards for consistent sample processing and handling, with standard operating procedures and quality control. We have also adopted ethical guidelines; have privacy protocols and a governance structure which ensures our biobank is operating within industry standards.

With substantial biobanking as part of our program we are now able to better manage the large number of samples with full auditing and tracking capabilities. Every single aliquot will be monitored and tracked for collection, storage, allocation and use. The system even sends alerts for when more samples are required to replenish depleting stocks which is very useful in the use of our DNA biobank. This is one of the ways in which we have improved our biobanking practice.

The implementation of biobank sample management software, **CaTissue,** is almost complete with the final upload due very soon. The system has been linked to our clinical database which enables us to search data sources from biological samples available and matching clinical data.

Here is the latest update of biosamples stored in our facility:

| | TWH PsA | TWH PsC | Women's College | St. John's | London | Halifax | Winnipeg |
|---|---|---|---|---|---|---|---|
| **DNA** | 1274 | 649 | 447 | 376 | 171 | 25 | 289 |
| **Serum** | 8635 | 1786 | 781 | 479 | 498 | 32 | 262 |
| **RNA** | 6044 | 496 | 496 | 113 | 492 | 32 | 219 |
| **Synovial Fluid** | 101 | | 12 | | | | |

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# RESEARCH UPDATE (2018-2019)

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 on-going:

***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 to September 2018 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) active through September 2017.

*We are pleased to announce that our competing renewal application received a percentile score of 4.0 from t NIH ACTS study section as of February 19, 2019, and hence is very likely to be funded for the next five years.*

**Genetic Studies**

A 2014 paper described differential genetic associations of PsA vs. PsC (PsC is here defined as patients that do not have arthritis symptoms after 10 years of psoriasis diagnosis) in the MHC (1). This paper found an amino acid residue in HLA-B that efficiently discriminated PsA from PsC. The second paper, (2), describes differential associations between PsA vs. PsC at non-MHC loci. We carried out a genome-wide association study (GWAS) of 1430 PsA cases and 1417 unaffected controls. Meta-analysis of this study with three other GWAS and two targeted genotyping studies, encompassing a total of 9293 PsV cases, 3061 PsA cases, 3110 PsC cases and 13,670 unaffected controls of European descent, detected 10 regions associated with PsA and 11 with PsC at genome-wide (GW) significance. We firmly established several of these regions as PsA loci (IL28RA, IFIH1, NFKBIA) or PsC loci (TNFRSF9, LCE3C/B, TRAF3IP2, IL23A, NFKBIA) for the first time. After replication, we also identified a newly GW significant PsV locus near CDKAL1 (rs4712528, odds ratio (OR) = 1.16, P = 8.4 × 10-11). Among identified psoriasis risk variants, three were more strongly associated with PsC than PsA (rs12189871 near HLA-C, P = 5.0 × 10-19; rs4908742 near TNFRSF9, P = 0.00020; rs10888503 near LCE3A, P = 0.0014), and two were more strongly associated with PsA than PsC (rs12044149 near IL23R, P = 0.00018; rs9321623 near TNFAIP3, P = 0.00022). The PsA-specific variants were independent of previously identified psoriasis loci near IL23R and TNFAIP3. We also found multiple independent susceptibility loci in the IL12B, NOS2, and IFIH1 regions. Most recently, we developed a computational pipeline to identify and use independent genetic signals for distinguishing PsV vs. normal controls, and PsA vs. PsC , with the objective of generating an innovative way to predict those ~25% of incident PsV cases that are at risk for PsA (3). In the largest PsA/PsC study to-date (4), consisting of 6 cohorts with >7,000 genotyped PsA and PsC patients, we increased the numbers of PsA and PsC samples with GWAS coverage by 40% and 97%, respectively, compared to our previous meta-analysis (2). This was achieved by including an additional cohort (Exomechip) and re-phenotyping the samples to incorporate recent PsA diagnoses. Additionally, the density and diversity of genetic and amino acid markers was raised substantially through genetic and HLA

imputation and by combining the Haplotype Reference Consortium (HRC) and the 1,000 Genomes Project (1KG) as reference panels. We identified 9 new loci for psoriasis or its subtypes, and observed that active enhancers in lymphocytes are highly enriched among subtype-specific loci. We achieved 0.82 area under the receiver operator curve (AUROC) in distinguishing PsA vs. PsC, and >90% precision for PsA prediction among psoriatic patients with the greatest genetic load.

The search for rare variants underlying PsA has been greatly enhanced by combining our efforts with a parallel exome array effort undertaken by our European colleagues with the support of the International Psoriasis Council (IPC). The latter effort is termed the IPC Exome Consortium [IEC]). A manuscript has been published in the American Journal of Human Genetics (5). The GWAS aspect of this study was enhanced by addition of ~15,000 psoriasis cases and ~280,000 controls for whom GWAS data was available through 23andMe, and by the framework GWAS available on the Affymetrix Core Exome chip. We conducted the largest meta-analysis of genome-wide association studies (GWAS) for psoriasis to date, including data from eight different Caucasian cohorts, with a combined effective sample size >39,000 individuals. We identified 16 additional psoriasis susceptibility loci achieving genome-wide significance, increasing the number of identified loci to 63 for European-origin individuals. Functional analysis highlighted the roles of interferon signaling and NFκB cascade, and we showed that the psoriasis signals are enriched in regulatory elements from different T cells (CD8+ T-cells and CD4+ T-cells including TH0, TH1, and TH17). The identified loci explain ~28% of the genetic heritability and generate a discriminatory genetic risk score (AUC = 0.76 in our sample) that is significantly correlated with age at onset ($p = 2 \times 10\text{-}89$). Analysis of these datasets has been published in Nature Communications (6) .

We have also entered into a collaboration with Drs. Anne Barton, John Bowes, and colleagues to undertake an expanded meta-analysis of rare and common variants associated with PsA. As part of this collaboration, a manuscript on rare variants focusing on *IFIH1* was recently published in the Annals of Rheumatic Diseases (7). Dr. Barton and her colleagues are also participating in an expanded meta-GWAS of psoriasis involving 30,599 cases and 152,461 controls. This meta-analysis combines case-control cohorts from the U.S., U.K. (England/Scotland), Canada (Toronto/Newfoundland), Germany, Estonia, and Sweden. All psoriasis cases are physician diagnosed, and a substudy includes individuals with rheumatologist-diagnosed psoriatic arthritis.

Finally, we are pleased to report that the U-M and Regeneron Genetics Center have recently reached an agreement under which all psoriasis DNA samples collected at Michigan to date (both case-control and the family sample) will be subjected to a uniform GWAS (to aid in quality control) and, most importantly, to exome sequencing, in the context of a scientific collaboration with Regeneron taking the form of a public-private partnership. There are no restrictions on publication of these data, which we have estimated will cost approximately $6 million to perform, hence representing very substantial leverage of NIH investment in this project. This agreement could provide an template to extend this study to other IPART investigators, if they are interested in doing so.

**Biomarker Studies**

Current activities in the Elder lab are centered on identification and validation of genetic and genomic biomarkers for PsA development. *Genetic biomarkers:* Using an extended version of our dataset with improved phenotyping

for PsA, we generated a computational pipeline for predicting PsA among psoriasis patients using data from six cohorts with >7000 genotyped PsA and PsC patients (8). We identified 9 new loci for psoriasis or its subtypes and achieved 0.82 area under the receiver operator curve in distinguishing PsA vs. PsC when using 200 genetic markers. Among the top 5% of our PsA prediction we achieve >90% precision with 100% specificity and 16% recall for predicting PsA among psoriatic patients. Combining statistical and machine-learning techniques, we showed that the underlying genetic differences between psoriasis subtypes can be used for individualized subtype risk assessment.

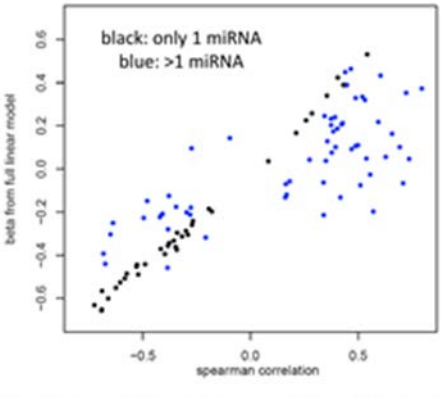


**Fig. 1.** Correlations between DE miRNA and mRNA levels in all samples (pre- and post-conversion). Note highly correlated behavior in mRNAs targeted by only a single miRNA (black dots), compared to mRNAs targeted by multiple miRNAs (blue dots).

*Genomic Biomarkers:* Based on IPART-supported discussions between research centers, we have conducted mRNA and micro-RNA (mi-RNA) transcriptome experiments utilizing blood samples stored at study entry, which were paired with additional blood samples from incident PsA cases at the onset of PsA development. We analyzed 65 pairs of converters from PsC to PsA at 3 centers (U-M, UHN, and Rochester, 19, 36, and 10 pairs, respectively). The time from initial PsC ascertainment to PsA conversion varied from 112 to 3,187 days (median 1,087 days). Pre- and post-conversion blood samples were collected in RNA stabilization tubes and stored at $-80^{o}$, RNA was isolated, separate mRNA and miRNA libraries were generated using Illumina mRNA and small RNA kits, and the libraries were sequenced at the Kiel Genome Center. For miRNAs, we used GenBoree (http://genboree.org/site/) for alignment and read counts, and limma/voom for paired differential expression (DE) analysis. We analyzed 311 miRNAs with a mean abundance of ≥1 read per sample. For mRNAs, we used STAR/HTSeq for alignment and expression quantification (9, 10), and the limma/voom pipeline with quantile normalization for paired DE analysis (11). These analyses yielded 60 miRNAs and 1,516 mRNAs meeting the DE criteria of FDR < 10% and $|\log2FC| \geq \log2(1.5)$. Using miRDB (12) to relate miRNAs and their mRNA targets that were expressed in our datasets, we identified 28,829 relationships involving 282 miRNAs targeting 4,525 genes. 54 of these miRNAs were DE (27 up and 27 down in PsA), and they targeted 1,580 mRNAs, 55 of which were also DE (44 up, 11 down, avg ~4-fold). Among the 23 mRNA targets of "up" miRNAs, 16 mRNAs were increased and 7 were decreased (avg ~2-fold) in PsA samples. Among the 35 targets of "down" miRNAs, 31 target mRNAs were increased and 4 were decreased (avg ~8-fold). Most (37) of the 55 DE mRNAs were targeted by only one DE miRNA, with the other mRNAs ranging from 2 to 8 miRNAs. For the mRNAs targeted by only one miRNA, there was a strong correlation between the expression of DE miRNAs and their DE mRNA targets, as assessed by linear modeling **(Fig. 1)**. While all DE mRNAs and miRNAs are of interest as potential biomarkers, these highly correlated DE mRNA / miRNA pairs, and DE miRNAs relevant to T-cell and OC biology, are strong candidates for mechanistic investigation.

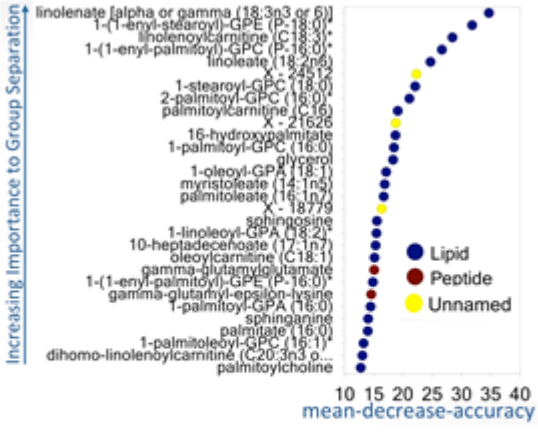


**Fig. 2.** Biochemical importance plot for metabolites altered in PsC→PsA converters. The plot shows the top 30 Mean Decrease Accuracy values calculated for comparison of PsC and PsA, where higher value indicates greater group-differentiating contribution.

*Metabolomic Biomarkers:* We performed a metabolomic analysis of PsC-to-PsA converters on the Metabolon platform, involving 50 pairs of serum samples from PsC-to-PsA converters from Michigan, Toronto, and Rochester (31, 10, and 9 pairs, respectively). Median time to conversion was 1,087 days (range 112 - 3,187). Metabolomic profiling of these samples revealed multiple biochemical signatures related to the pathophysiology of the disease. Following log transformation and imputation of missing values with the minimum observed value, 293 out of 1,299 biochemicals were significantly ($p<0.05$ by matched pairs t-test) altered in PsA vs. PsC (275 up in PsA, 18 down), with another 110 altered at $0.05<p<0.1$ (104 up, 6 down). For example, numerous metabolic indications of increased inflammation were observed in the affected cohort with significant elevations in inflammatory lipid mediators, free fatty acids, endocannabinoids, and sphingolipids. Converters also exhibited evidence of perturbed energetics, both from lipid oxidation, as well as a switch to Warburg metabolism with a dependence on glutaminolysis. Elevated oxidative stress was accompanied by an altered antioxidant status (notably increased taurine, suggestive of a protective role against neutrophil- and macrophage [MΦ]-derived oxidants) (13). The metabolism results are collectively consistent with the broader T-cell pathobiology of psoriasis since a large body of evidence shows that T-cells switch from oxidative phosphorylation to less efficient aerobic glycolysis when activated (Warburg metabolism) (14). Random forest analysis was used to identify metabolites that differentiated between PsC and PsA groups, resulting in a predictive accuracy of 74% (compared to 50% by random chance), demonstrating that individual metabolites were able to classify the two groups with a good degree of confidence **(Fig. 2)**. The metabolites with greatest effects on classification were largely lipids, including polyunsaturated fatty acids, lysoplasmalogens, lysophospholipids, and metabolites associated with glutamate metabolism (e.g. gamma-glutamylglutamate). Collectively, these results point to several avenues for both follow- up biomarker and mechanistic studies, as well as therapeutic opportunities. Additionally, the Toronto site performed a pilot metabolomic analysis of serum from ten PsC→PsA converters on a locally-developed platform utilizing solid phase microextraction for sample preparation. Identified metabolites were associated with intercellular matrix macromolecules (elastin and collagen fragments), as well as those associated with lipid, carbohydrate and purine metabolism.

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## PUBLICATIONS

Recent publications from our genetics and genomics research are listed below. Because of the nature of our research, these studies have been partially supported by other awards to Dr. Elder and colleagues.

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

The IPART Registry is an essential resource for our research efforts at URMC. To date, we have recruited psoriasis patients as well as PsA patients. We have now linked our patients to stored biospecimens and omics data in our Biologic Lab Informatics Server (BLIS) developed at our institution. This resource allows to link patient demographics with stored serum, PBMCs, skin, synovial tissues and bone marrow samples in the lab. In addition, the samples are linked to flow and omics data both raw and transformed and to raw and interpreted imaging data. To date, we have worked only with the samples at our site but we look forward to expanding these studies to our co-investigators in IPART. Here are the several ongoing projects at URMC:

**Transcriptomic and Metabolomic pathways associated with the transition from psoriasis to PsA**

We analyzed whole blood RNA for changes in coding and long non-coding RNAs in psoriasis patients and those that developed PsA before and after the development of musculoskeletal disease. We have preliminary data on 9 patients with psoriasis who converted to PsA. These analyses are still in progress but to date we have found the following. First, we performed gene expression profiling on whole blood collected from healthy controls (HCs) (n=10) and a subset of Ps (n = 19) patients who either have (n=10) or have not transitioned (n = 9) to PsA using Clariom D microarray which assesses both coding and noncoding gene expression. Our in-depth analysis of global transcriptomic profiles generated from whole peripheral blood collected from both Ps and PsA patients, as well as HCs has enabled us to identify a number of coding (IGHA1, ATP5D, VAMP2, CHEK2, ADIPOR2, NDUFAF3, ABCG2, TESC) and noncoding (SNORD24, PCED1B-AS1, RP11-713C19.2, SNORA14B) genes that are differentially expressed in patients who developed PsA compared to those who did not develop PsA and healthy controls (Figure 1). Further confirmatory studies are required to explore the potential of the newly identified differentially expressed genes as biomarkers for diagnosing PsA or identifying psoriasis patients at increased risk for arthritis. Second, our pathway analysis of the differentially expressed genes identified in our transcriptomic data indicated marked dysregulation of metabolic pathways and mitochondrial function. Therefore, to further identify key metabolic differences between Ps, and PsA patients, we performed unbiased global metabolic profiling of serum samples collected from a subset of Ps (n=9) and PsA (n=9) patients in our biorepository. Our preliminary analysis of these serum samples indicated that many inflammatory lipid mediators (including 12-HEPE, 14-HDoHE, and 13-HODE) were significantly elevated in PsA compared to Ps. Similarly, our metabolomic data indicated increased lipid turnover, altered glutamate, and tryptophan metabolism in PsA compared to Ps patients. While our preliminary metabolomic analysis of patients' samples provided initial valuable insights, the small dataset requires additional samples from patients with psoriatic disease and other immune medicated disorders. Unlike our transcriptomic analysis, we were unable to analyze serum samples from healthy subjects or compare serum metabolites of the same set of Ps patients (who eventually developed arthritis) collected before and after the arthritis. Thus, moving forward, we plan to analyze additional serum samples collected from Ps and PsA patients (20 each), heathy subjects, RA patients (n= 20) and OA patients (n=20) to provide complementary datasets that will increase our chances to identify specific metabolomic biomarkers for PsA. We submitted a biomarker discovery grant to the NPF to secure additional funding for these studies.

**Cutaneous RANKL expression as a marker of psoriasis in psoriasis**

To test the hypothesis that RANKL expression in the dermis and epidermis of psoriatic skin is a marker of arthritis, we are collecting skin biopsies from psoriasis patients and patients who have PsA (untreated). To date, we have collected 20 samples from psoriasis and 7 samples from PsA patients. We plan to obtain skin biopsies from 3 more PsA patients and we will then analyze the tissues for immunohistochemistry focusing on RANKL expression and also perform RT-PCR and Western blot analysis for RANKL in all the tissues. We expect that the RANKL expression will be higher in PsA and that will correlate with circulating osteoclast precursor frequency. These studies are funded by an NPF Discovery Grant.

**Thy1 expression as a measure of new bone formation in PsA**

We found that Thy1, a membrane expressed molecule on cells of many lineages including mesenchymal cells promotes osteoblast differentiation. To date the mechanisms underlying pathologic new bone formation are unknown. Indeed, this effect on bone was most strongly observed in obese vs WT mice. This effect is likely acting through the Wnt signaling pathway. We are now planning to measure Thy1 protein in the serum of psoriasis patients, PsA patients without new bone formation and those with pathlogic new bone findings. These studies are about to commence. We are also crossing Thy1-/- mice with TNF Tg mice to determine if the erosive phenotype in these mice is more extreme in the absence of Thy1.

**Ultrasound findings and OCP frequency in psoriasis patients and healthy controls**

US studies and serologic assessment for OCP and OCP subsets were performed on Ps patients and HC. Ps was confirmed by a dermatologist. 150 patients were screened at the University of Rochester and regional dermatology practices. 78 Ps patients (mean age 49.5; mean BMI 31.9; mean disease duration 20 years; f, n=42; m, n=36) and 25 HC (mean age 43; mean BMI 27.3; f, n=17; m, n=8) were enrolled. No subject had symptoms or physical findings of PsA. Complete OCP data were available for 74 Ps and 20 HC subjects. US assessments were obtained in all HC and 75/78 Ps subjects. A wide range of imaging abnormalities were noted in almost 50% of psoriasis patients without musculoskeletal symptoms and these was significantly higher than in healthy controls. These findings included synovitis, enthesitis and increased Doppler signals. In addition, the frequency of OCP was significantly higher in psoriasis patients than controls and most elevated in patients with US findings. Serum levels of 14-3-3h were not increased in patients or controls. The combination of US findings and elevated OCP have potential to identify Ps patients at risk to develop PsA.

**Lipidomics in PsA**

We are collaborating with Monica Guma to study prostaglandin metabolites in Ps and PsA patients. We are providing serum samples to her site.

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

**Real World Evidence Studies**

In collaboration with Janssen, we have engaged the Newfoundland and Labrador Center for Health Information (NLCHI) and four rheumatologists and two dermatologists for this RWE study. Through the NLCHI administrative database we have identified over 14,000 individuals that have been coded for psoriasis. These patients can be linked to other administrative databases thru a unique identified. Through clinic charts we have ~ 4,500 psoriasis patients and ~ 1000 PsA patients. These patients have disease specific information available along with medication use. We are now in the process of conducting RWE studies on mortality, cost utilization and other outcomes.

**Heritability of PsA**

We estimated the heritability in University of Michigan (UM) database (3117 unaffected controls, 715 PsA patients,1155 PsC patients, 2938 PsV patients). The UM data was genotyped on custom Affy-metrix exome chip with 461,092 autosomal SNPs. The stringent quality control (QC) was performed and we filtered out genetic markers that had high missing rate (>1%), low minor allele frequency (<5%), significant deviation from Hardy-Weinberg equilibrium ($p<0.001$). Finally, 230k SNPs were kept for the heritability estimation.

The heritability of PsC, PsV and PsA were estimated by interrogating 715 PsA, 1155 PsC, ,2938 PsV patients and 3117 unaffected controls of European ancestry. The samples were genotyped on a custom Axiom Biobank plus genotyping array and core GWAS chip with 461,092 autosomal SNPs. Further imputation led to 1.3M well-imputed SNPs based on the autosomal reference panel of the HapMap Phase 3 (HM3) CEU cohort. The heritability of PsC, PsV and PsA were estimated using the following three methods- Linkage Disequilibrium Adjusted Kinships (LDAK) and GCTA which relies on the restricted maximum likelihood algorithm (ReML). Sex and the top 5 principal components were used as covariates to control for gender effect and population stratification in each analysis. Parallel analyses were performed after removing SNPs from the MHC region. The prevalence also was used to adjust the heritability estimation. SNP based heritability estimates suggest greater or equal heritability for PsC as compared to PsA. Common environmental factors may need to be

considered to account the strong recurrence rate of PsA over psoriasis among first degree relatives reported in previous epidemiological studies.

**Pharmacogenomics in PsA**

We are actively recruiting psoriatic arthritis patients that are initiating biologic therapy (TNFi, IL12/23, IL-17 or JAK 1,3 inhibitor). Along with baseline clinical data and patient report outcome collection, peripheral blood is being collected for (a) serum (b) DNA (c) RNA and (d) PBMC isolation. At 12 weeks after starting biologic treatment, disease activity including ACR50 response is being assessed for PsA patients and categorized into responders and non-responders. Adverse events are also documented. Clinical data will be combined with genetic and other omics data to develop a model for personalizing optimal choice of biologic therapy. Patients enrolled in the discovery phase will be followed for 2 years for long- term data collection. If patients do not respond to treatment they will be switched to another biologic, in keeping with current standard clinical practice. Blood sample for serum, DNA and RNA will again be collected for a new biologic start. To date ~ 25 patients have been collected.

**Identification of rare variants for extreme phenotype**

We preformed next generation sequencing (whole exome sequencing) for 7 probands with mutilans and their parents, Their exome was sequenced with Average Read Depth – 68X. With input from Quan Li and Igor Jurisca, Sara Rahmati led the informatic analysis. After applying Varscan and Tridenovo methods to detect pathogenic SNVand DNAcopy to infer CNV across the seven trios, three gene sets were identified. Performing conventional pathway enrichment analysis highlighted pathways related to WNT, NOTCH, NOTCH1 and Autophagy implicating these pathways in severe PsA.

**SNP based algorithm to identify psoriasis patients at risk of PsA**

We developed ~ 40 SNP based test comprising of PsA weighted targets as compared to psoriasis. Multiplexing, laboratory validation, and genotyping in the discovery cohort has been completed. Initial sensitivity, specificity, positive / negative predictive values and AUC has been imputed. We are now in process of validating our findings in a larger cohort.

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

**Early Diagnosis of PsA**

Our clinical phenotyping and bio-repository have been the foundation for early diagnosis research. We continue to recruit new patients through our PsA clinic, Dermatology clinics and referrals from family medicine. The new patients usually have early disease status which enables us to focus on their specific characteristics and determine new and better approaches on identification.

Soluble biomarkers -The early PsA detection biomarker panel project is almost complete. The laboratory testing is complete and the data analysis continues with the biostatisticians who will help develop a prediction model that has potential to be used in a clinical setting.

We had previously reported on an exciting find with chemokine CXCL10, and found the elevated levels seem to indicate transformation from PsC to PsA. We are continuing to look at the fluctuation in the levels of this molecule over time to determine how it relates to disease progression.

We are continuing to look for novel biomarkers which will add to the precision of the prediction model.

**Global Biomarker Profiling**

Genetics - In our collaboration with colleagues at the Henry Ford Hospital in Detroit and the University of Michigan Ann Arbor, we have been able to examine gene expression profiles from patients with early disease. We have done this utilizing next generation RNA sequencing on patients who have early disease or appear to be pre-disease. This RNA expression signature will also be compared with miRNA expression profiles in collaboration with IPART. So far we have completed the RNAseq and miRNA component and have a large dataset to analyse. Using these advanced transcriptomic techniques, we hope to find genetic signatures of patients with psoriasis who will develop PsA and also response patterns to therapeutics.

We also looked closely at –21 HLA Class I dimorphisms and how these differentiate PsA from PsC patients. With HLA typing data from our lab we found psoriasis and control groups had significantly lower prevalence of –21M compared to those with PsA. This provides insight to the role of natural killer cells in PsA pathogenesis and a genetic marker that distinguishes PsA from PsC. This work will be presented by Dr. Chandran at a plenary session at the ACR.

Epigenetics - Previous findings from our study of epigenetic variants in sperm showed us that aberrant methylation of IL-22, a pro inflammatory cytokine produced by natural killer and T cells, in sperm of PsA patients compared to PsC patients. We are now continuing to collect buccal cells and peripheral blood mononuclear cells to test if IL-22 is also aberrantly methylated in those tissues as well – which could mean a new biomarker of PsA.

Another project looking at whole blood methylation profiling aims to discover predictive epigenetic biomarkers associated with PsA. Currently the DNA samples have been sent for testing and we expect data to be returned very soon, which will enable the analysis to begin and continue over the next several months.

Proteomic Studies – We have identified a number of proteins that distinguished between PsA and PsC. Daniela Cretu completed her PhD and demonstrated that CD5L, ITGbeta5, M2BP, MPO, MMP-3, and CRP level are markers for PsA. The combination of ITGbeta5, M2BP, and CRP level differentiates PsA from PsC, and performs better than CRP level alone. This paper is published in Arthritis Care and Research 2018.

The collection of novel PsA biomarkers has been reviewed and identified through proteomic studies. This review was published in Proteomes 2018.

Functional Studies – We are currently looking at protein and peptide expression in the synovial fluid. We expect to learn more about the signaling pathways and key modulators of disease.

Verification and validation of these candidates is underway.

Microbiome - In our efforts to characterize the microbiome of the skin in PsA and PsC patients we are currently at 80% of the target patient recruitment number and expect to finish collection in 1-2 months. Dr. Yerushalmi, a PhD student has completed the systematic review and is currently writing a paper on microbiome methodology. These have been presented at several conferences and research days.

The stool microbiome also has potential to learn new insights about PsA. We are currently reviewing the literature to determine the approach we will take and hope to set up our lab, so we can process the samples required. We are now looking at analysis of the microbiome and the metabolome of the stool.

**Disease Expression**

Disease Activity - Our biostatisticians are currently analyzing our data from biomarker studies and combining it with our clinical data to identify measures of disease activity. We hope to quantify disease activity which

will help initiate and guide appropriate therapy by looking for relationships between marker signals and pre and post drug treatment.

Definition and biomarkers for disease pattern – Colleagues in Newfoundland are examining the extreme phenotype of PsA, the analysis is underway as we look at the mutilans form of PsA. We tested the association of 28 SNPs within the TRPV4 gene with 113 arthritis mutilans patients in our cohort (versus 432 non-mutilans PsA patients). We discovered a significant association with alleles and genotypes of two SNPs (rs10850830 and rs1861812) with arthritis mutilans, as well as a significant interaction between TRPV4 SNPs and HLA-B27. An abstract for this project has been submitted to the CRA.

We also analyzed data from our own cohort and compared it with an ankylosing spondylitis cohort to determine if there were overlaps in patient characteristics and disease differentiation. By looking at demographic, genetic, clinical and radiographic data, we were able to determine they are different populations, despite the many features in common. A paper has been submitted for publication.

The clinical data for PsA patients with axial disease was also reviewed to define what constitutes axial PsA since there is no universally accepted definition. Looking at the progression of disease in the sacroiliac joints she found that the New York Criteria for sacroiliitis is an appropriate definition for axial PsA. She also found that young patients with a short disease duration and elevated ESR are at increased risk of progressing. A paper has been submitted for publication.

Definition and predictors of remission – We are defining remission with clinical, serological and radiographic information. When defined as a state of no clinical activity, we found 18% of patients with PsA achieved remission at least once and 11% were able to sustain it for 1 year. We also found that a high body mass index (BMI) reduced the chance of sustained remission while the use of biologic therapies increased the chance of remission. An abstract has been accepted to the ACR with a manuscript has been drafted.

Systems Biology – AI4A Artificial Intelligence for Arthritis project – Our efforts here are to construct a network of psoriatic disease using GWAS and other 'omics data - a Masters Student has been accepted to initiate this project and will work with Dr. Proton Rahman in Newfoundland and Dr. Igor Jurisica at the Krembil Research Institute.

**Defining Outcomes**

Malignancy – We have completed an analysis on prevalence of malignancy in our cohort and specifically whether biologic therapy is a malignancy risk in PsA. We found the incidence of malignancy is not increased in PsA patients compared to the general population, and no predictors of malignancy could be identified. We also found there was no increased risk associated with biologic use. for a poster will be presented at the ACR and a manuscript is in preparation.

Mortality – We have completed an analysis of mortality data and determined the frequency of death and risk of death compared to the general population. We also looked at predictors for death including clinical features, therapies use, acute phase reactants, imaging and other biomarkers. We found the overall standardized mortality ratio was similar to the general population, with an elevation among patients who were younger at presentation. This is an improvement compared with our previous mortality studies, suggesting that we are

indeed making a difference to the outcomes of patients with PsA. A poster will be presented at the ACR and the manuscript is in preparation.

Surgical Interventions – We want to review the last 25 years' data to see if there is a difference in surgical interventions and predictors requiring surgery. This project is in the initiation phase.

Cardiovascular Complications – Currently a systematic review in underway, with classification and verification of cardiovascular events along with biomarkers in our dataset will be analyzed. We have demonstrated that elevated high sensitivity Troponin-I is associated with more pronounced atherosclerosis in patients with psoriatic disease independently of usual cardiovascular disease risk factors.

Anxiety and Depression- We looked at the effects of depression and anxiety on the minimal disease activity score. We found the presence of anxiety and/or depression reduces the probability of achieving sustained MDA in those with PsA. A poster will be presented at the ACR and the manuscript is now in preparation.

Test a new patient reported outcome in PsA – We evaluated the PsAID questionnaire – Psoriatic Arthritis Impact of Disease, to determine whether it could replace any of the questionnaires we currently give patients. We found that the PsAID score could not replace any of our current measures. We also found that the PsAID could replace the Health Assessment Questionnaire in the Minimal Disease Activity criteria. The study has been completed and a poster was presented at EULAR 2018. A poster will be presented at the ACR and a manuscript has been written.

Economic impact of PsA - We have examined the data to determine the economic impact, cost effectiveness and work productivity, and have a manuscript in preparation.

**Therapeutic Interventions**

We evaluated the literature with regards to therapeutics in PsA. Effective therapies for treating PsA have emerged over the last 15 years and newer agents continue to be discovered, allowing greater therapeutic options for controlling psoriatic disease activity and preventing joint damage and disability. Personalized therapy for patients with PsA is now a possibility. This paper was published in Current Rheumatology Reports 2018.

We reviewed the available evidence on the efficacy and effectiveness of methotrexate in psoriatic arthritis and its role in treating psoriatic arthritis to target, as well as in combination with biologic agents. These findings were published in Drugs 2018.

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1. Johnson K, Ye J, Chandran V, Gladman DD. A novel role for the Psoriatic Arthritis Impact of Disease Questionnaire (PsAID). J Rheumatol 2018 July (In press)

2. Machhar RA,Ye J, Chandran V, Gladman DD. miR 21-5p as a biomarker of psoriatic arthritis and response to treatment. J Rheumatol 2018 July (In press)
3. Zhou AL, Muntyanu A, Szeto VG, Ye J, Chandran V, Gladman DD. Lost-to-follow investigation in psoriatic arthritis. J Rheumatol 2018 July (In press)
4. Szeto VG, Ye JY,l Zhou AL, Chandran V, Gladman DD, Rosen CF. The link between psoriasis, psoriatic arthritis and the onset of diabetes. J Rheumatol 2018 July (In press)
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## TORONTO SITE ON-GOING NEW STUDIES - 2019

In **2019**, the following projects are underway in the Toronto core site utilizing the IPART detailed data and

biosamples:

- **Project Title: "MOLECULAR PROFILING AND PHARMACOGENOMICS OF PSORIATIC ARTHRITIS PATIENTS"**

  Background: Epigenomics is the study of heritable changes in gene expression that does not involve changes to the underlying DNA sequence. DNA methylation is an epigenetic silencing mechanism, which occurs at the 5'-carbon of cytosine residue within the CpG dinucleotides by DNA methyltransferases. Although studies of genome-wide DNA methylation in PsA patients are lacking, numerous genome-wide DNA methylation studies have been performed in psoriasis.

  Metabolomics, the systematic study of the unique chemical fingerprints that specific cellular processes leave behind, belongs to the family of "-omics" science. With advanced profiling technology, it is now possible to rapidly measure thousands of metabolites simultaneously from only minimal amounts of sample (body fluid, tissue, etc.), bringing new energy to broad unbiased approaches to the field. Through the study of metabolomics, it is possible to define the current status of the tissue, organ, and the organism, as a result of environmental exposure and genetic predisposition that is not otherwise predictable by genomics and/or proteomic characterizations.

  Objective: The objective and key elements of this sub-study are to identify new biomarkers for treatment response, aligned with the primary and dominant goal underlying the IPART research network to make advances that will lead to significant improve in outcomes for patients with psoriatic diseases. In this sub-study, we hypothesize that an integrated omic profile in PsA patients prior to starting treatment with biologic agents (TNFi or IL-17i) can be used as biomarkers to predict response to treatment at follow-up visits.

  This project will be completed over a two-year period (January 2019 to December 2020). We aim to include 40 PsA patients in each drug category (TNFi or IL-17i) from the PsA clinic. Samples will be drawn at baseline and after one month and three months of follow up. Isolation of cell subsets from PBMCs as well as deep sequencing and analysis and quantification of the results will be done in the laboratory of Dr. Proton Rahman at Memorial University in Newfoundland.

- **Project Title: "MUSCULOSKELETAL SURGERY IN PSORIATIC ARTHRITIS: PREVALENCE AND RISK FACTORS"**

  Background and Objectives: The primary objective of this study is to determine the prevalence of musculoskeletal surgery in patients with PsA, both in terms of all musculoskeletal surgery regardless of indication as well as musculoskeletal surgery specifically pertaining to the PsA disease process. Secondary objectives include determining clinical, radiographical and laboratory risk factors associated with the need for musculoskeletal surgery in this patient population. We hypothesize that the need for musculoskeletal surgery is a relative proxy for sub-optimally controlled disease activity in PsA patients. As such, we theorize that the same factors associated with clinical disease progression in PsA patients will be associated with a higher chance of requiring musculoskeletal surgery. Hence, we predict that evidence of significant inflammation including number of active joints, elevated inflammatory markers, radiographical evidence of joint disease, and escalating medication needs including steroid use will be associated with the need for musculoskeletal surgery.

  Methods: Patients report at time of consultation and follow-up visits to have had a musculoskeletal surgical intervention are recorded as such in the database. These patients will be identified and their

charts reviewed to confirm the type of surgery performed. The surgical procedure will also be cross-referenced to the patients' clinical records by a physician researcher to determine if the intervention was related to the patient's underlying PsA. The following variables at initial consultation as well as at the visit closest to the surgery will also be retrieved for analysis: age of diagnosis, sex, disease duration based on the time of diagnosis, BMI, clinical pattern, inflammatory markers, American Rheumatism Association (ARA) functional class, symmetry, nail changes, number of actively inflamed joints, and number of joints of each of the 4 grades of the Steinbrocker radiological grading system, NSAID use, DMARD use, biologics use, peripheral and/or axial involvement, number of inflamed entheses, physician global assessment scores, patient global assessment scores, body surface area of psoriasis, Psoriasis Area Severity Index (PASI) score, number of affected nails, Health Assessment Questionnaire (HAQ) score, physical component summary score (SF-PCS) and mental component score (SF-MCS). The variables will then be compared between patients who underwent musculoskeletal surgery and those who did not to determine associated risk factors for musculoskeletal surgery.

This is a retrospective analysis of prospectively collected data in a cohort study of psoriatic arthritis followed in the PsA clinic at UHN-TWH through the IPART research program. This project will be completed over a period of 2 years from July 1 2019 to June 30 2020.

- **Project Title: "ASSESSING SPINAL DISEASE IN PSORIATIC ARTHRITIS"**

  This is a retrospective review study using prospectively collected clinical data from the IPART database.

  Background: PsA is an inflammatory arthritis that affects 30 percent of patients with psoriasis. PsA has several domains, including peripheral arthritis, axial disease, dactylitis, enthesitis, skin and nail disease. The CASPAR criteria are highly sensitive and specific for classifying PsA. Radiographic assessment helps diagnose PsA. Unique radiographic features include fluffy periostitis around the joints, new bone formation at the site of enthesitis, asymmetric sacroiliitis, paravertebral ossification, cervical spine involvement, and nonmarginal and asymmetrical syndesmophytes.

  Although axial disease has been recognized as a domain of PsA (AxPsA), it has been difficult to define it as other concurrent pathologies from natural degeneration are challenging to distinguish on radiograph. Patients with PsA do not have as much pain as patients with the prototypic inflammatory arthritis of the back, ankylosing spondylitis (AS), thus radiographic assessment is required.

  The aim of the current investigation is to identify all patients whose radiographs have not been scored according to mSASSS, obtain the radiographs, and score them. Also to determine whether the presence of degenerative disc disease affects the scoring of radiographs in patients with PsA. In addition will also determine whether anti-TNF agents use is associated with less progression of mSASSS scores compared to conventional DMARDs.

  Method: This study is carried out by a second-year medical student with graduate training who obtains the radiographs, organize reading sessions with the staff, and enter the scores into the database. The presence of degenerative disc disease is recorded, and an analysis will be performed to determine whether it affects the score. The scores will be compared against anti-TNF use using the University of Toronto PsA Clinic's research database. The information on the mSASSS will be added to the PsA database, and information from the database will be included in the analysis of the data. This is part of the longitudinal cohort study, which has REB approval. Patient have already had their x-rays, and in this project, the x-rays that have already been read by the team will be reread with more details of the back involvement.

## 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** - One of our mandates as a research program is to ensure that the knowledge learned from this research is made available to our patients, their families and other interested lay groups. This is achieved by way of newsletters and annual patient symposiums. A PsA patient advisory committee has been formed to help in reviewing educational materials and provide feedback and suggest for the format of symposiums and bring forth ideas for other formats of disseminating information to patients.
- **Psoriatic Arthritis Patient Forum** – Annually, PsARP and IPART jointly conduct a PsA patient forum that highlights presentations about causes of the diseases, recent advances in treatment of psoriasis and PsA, comorbidities, etc. These educational forums also feature other important related topics like diet, physiotherapy, skin, stress reduction and patient advocacy.
- **Fellows Training** – Training of fellows is an important activity in the program, increasing potential future recruitment of rheumatologists. These fellows contribute significantly into the program and stipends are paid for each annually solicited from various sources. These fellows take active roles in the execution of the various projects on-going in the IPART and PsARP programs.
- **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.
- **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 2019, the meeting is taking place at the **Intercontinental Toronto Centre Hotel on April 12, 2019.** At which time, IPART's research updates and progress report will be unveiled.
- **Knowledge Transfer and Exchange** - For knowledge transfer, a strategic partnership of patient-advocates and researchers will be critical for ensuring that new knowledge is translated into action. This initiative will be discussed and deliberated upon during the annual scientific meeting as mentioned above.

IPART
International Psoriasis & Arthritis Research Team

## ACKNOWLEDGMENT

**We would like to thank our valued sponsors for their continued support to the IPART Research Program.**

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