PROGRESS REPORT

(Period ending January 31, 2018)

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. 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.

The IPART team 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

IPART has other 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)

DATABASE AND BIOBANKING UPDATE

IPART is a unique research group which has been successful in establishing 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. This is the largest collection of well characterized patients with PsD (psoriatic diseases) followed longitudinally in the world.

PATIENT RECRUITMENT IN IPART

	Toronto	Vancouver	WCH	Ann Arbor	St.John's	Rochester	Argentina	London	Halifax	Winnipeg	Israel
PsA	1519	49	126	15	579	194	4	112	4	44	143
Psoriasis	667	35	264	67	80	189	9	3	21	164	3
Total	2186	84	390	82	659	383	13	115	25	208	146

DATABASE

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.

Research data collection has evolved from hard copy clinical binders to a robust and sophisticated web based application that facilitates the clinical process and enables capture of data in a reliable and consistent manner. Our dataset provides such highly detailed information about PsD that our scope of research questions to be answered is extremely wide.

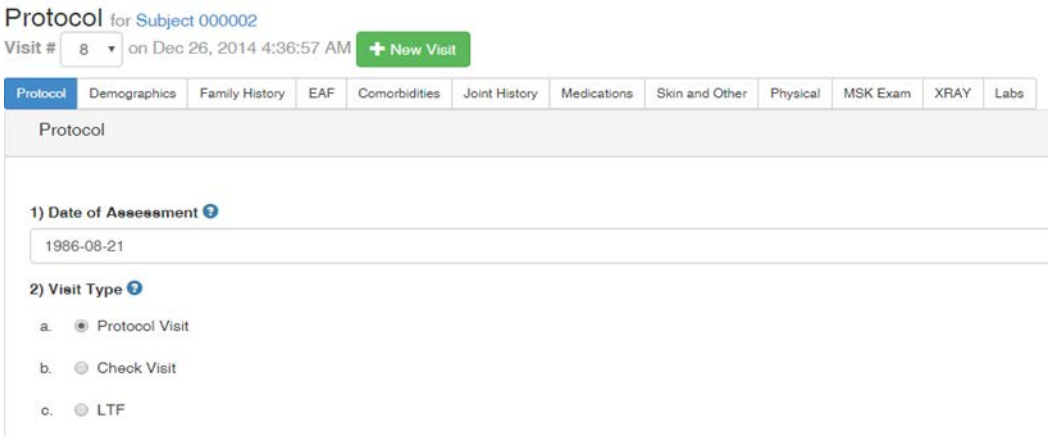
In 2015, we began a transfer of IPART data onto a new platform called DADOS. This application was originally developed at Duke University and made available as open source. The TECHNA team, a University Health Network (UHN) institute focused on technology in health, has implemented DADOS as the single web interface application for research. It is fully compliant with privacy regulations (HIPAA/PIPEDA) and has been enhanced with additional privacy features such as audit logging, role-based permissions and source document linkage. This program was designed to cater for multi-center studies.

Our adoption of this application has included development of additional features that are customized specifically for rheumatology and also facilitate the process of collecting such detailed data from each patient encounter. The IPART protocol is long and in terms of time required to capture such detail and record it has been a challenge to operationalize and maintain follow up. The balance of physician time with patients, physician-patient interactions and obtaining detailed data that is both accurate and of high quality are often at odds. It is essential for technology to step in and help to resolve this problem.

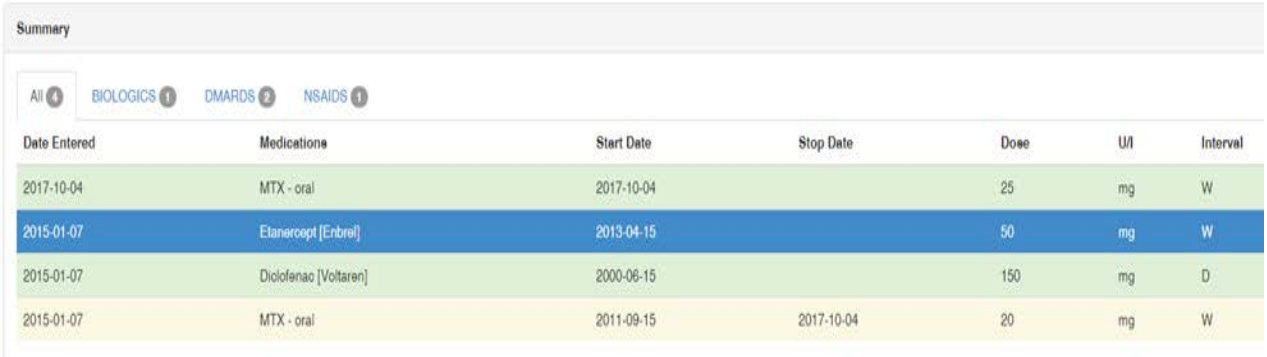
With help from our industry sponsors, we have been able to develop components of DADOS that will address some of these challenges. The components we have created are:

1. **Image spot tap** – we can upload any image and create hot spots that can be tapped on to indicate a score or clinical feature.

2. **Unscheduled visit data capture** – we can add visits at any time point.

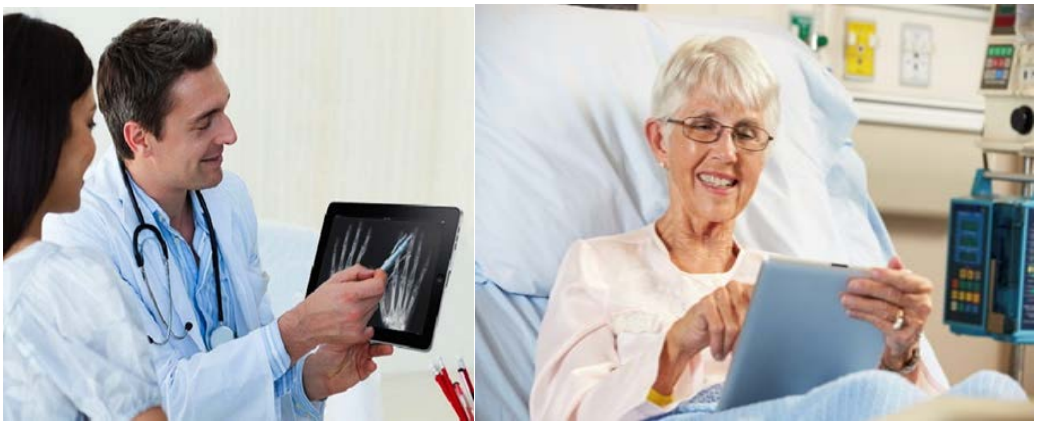


3. **Medications tracking** – tracking all Biologics, DMARDS and NSAIDS use, start and stop dates, dosages, stop reasons and side effects.



Date Entered	Medications	Start Date	Stop Date	Dose	U/I	Interval
2017-10-04	MTX - oral	2017-10-04		25	mg	W
2015-01-07	Etanercept [Enbrel]	2013-04-15		50	mg	W
2015-01-07	Diclofenac [Voltaren]	2000-08-15		150	mg	D
2015-01-07	MTX - oral	2011-09-15	2017-10-04	20	mg	W

4. **iPAD devices in clinics for both patients and physicians** – patients enter quality of life questionnaires at each visit on an iPAD in the clinic, physicians can complete the protocol on an iPAD during the encounter with the patient.



5. **DADOS Connect** – an external portal set up for patients to complete questionnaires from home.

Next, we plan to automate the importation of laboratory results from both UHN data warehouses and also from external laboratories such as Lifelabs. This will increase the data quality and also make our data capture more efficient.

Recently DADOS has become federated with our biobanking program, **CaTissue**, which links our clinical database to the biobank samples. Research staff can direct query the system to rapidly identify samples available for specific subsets of patients, make a request and distribute samples to their project. This is extremely useful when proposing research questions and checking for feasibility.

IPART TORONTO BIOBANK

	TWH		Women's College	St. Johns	London	Halifax	Winnipeg
	PsA	PsC					
DNA	1239	646	284	376	127	25	289
Serum	7500	1605	380	479	356	32	262
RNA	4898	697	313	103	343	32	219
Synovial Fluid	84		6				

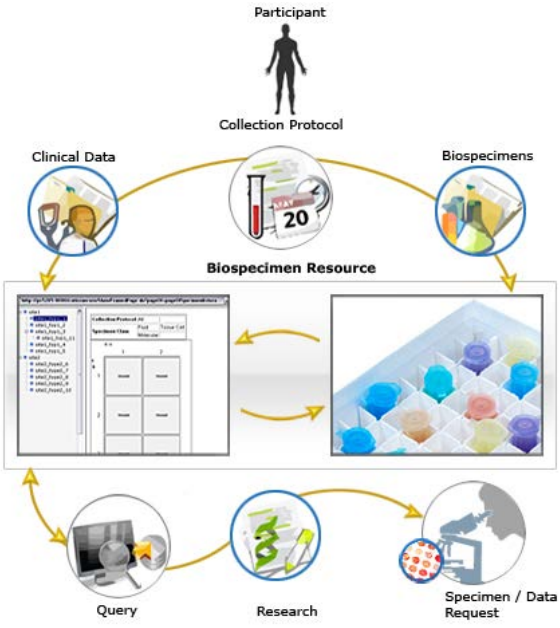
The IPART biobank continues to grow and expand as our research endeavors progress. We have built a biobank that contains the world's largest collection of biosamples that is matched with detailed clinical phenotype and molecular data for Psoriatic Arthritis and Psoriasis only cohorts.

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.

In the past 6 months, we have been working on implementing caTissue to our biobank. CaTissue is an open source application originally developed as part of the US government program caBIG. UHN have implemented caTissue across the institute and provide support and access to researchers and clinicians. CaTissue offers our program a biorepository tool for sample inventory management, tracking and annotation. It is a web-based application with several large scale biobanks at UHN utilizing the system such as; SPARCC and AS Team, Orthopedics, GU Biobank, multi-organ transplant biobank, cardiovascular team, leukemia biobank, living biobank and infectious diseases. It supports both internal and external users, which facilitates network programs such as ours.

CaTissue is linked to UHN data repositories which build a connection between demographic and clinical data, research clinical data and the biosamples collected from each patient. Using SAP software, we are able to query across multiple data platforms to identify data of interest.

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.



caTissue Suite

RESEARCH UPDATE - 2017

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. Christopher Ritchlin and Dr. Francisco Tausk
IPART Core Site - University of Rochester, USA

OCP STUDIES

This project entitled "**IDENTIFYING PSORIATIC ARTHRITIS EARLY AMONGST PATIENTS WITH PSORIASIS**" was funded by The Arthritis Society Strategic Operating Grant SOG-12-002 (October 2012 – September 2015, extended through March 30, 2016) and spearheaded by Dr. Dafna D. Gladman in Toronto, with a sub-grant extended to the University of Rochester (Dr. Christopher Ritchlin).

Transition from Psoriasis to PsA

We recruited 44 psoriasis patients with either a duration of psoriasis of 5 years or >10% body surface area of psoriasis. All patients completed the PASE questionnaire and were examined by a rheumatologist for the presence of MSK involvement. Those patients who had no MSK symptoms or signs underwent scintigraphy and an MRI of the most affected joint on scintigraphy, if present and power Dopper ultrasound of the entheses and joints. The patients had blood drawn for OCP, serum biomarkers, RNA and DNA. They were followed prospectively with the primary endpoint the diagnosis of PsA by CASPAR Criteria. 9 patients developed PsA over 4 years. The variables associated with progression to PsA were elevated OCP and PDUS characterized by positive Doppler signals at the entheses and erosions. Metabolomic analyses of these patients before and after transition were carried out and are described above. Transciptome analysis is currently in progress and we will be sharing sera with the Toronto site to perform analysis of CXCL10 levels in the sera. The patients in this study are all in the IPART Registry and this project was funded by Amgen.

PDUS findings in psoriasis patients and controls

To better understand the MSK findings in psoriasis patients by PDUS, 75 psoriasis patients and 20 healthy controls underwent PDUS of the joints and entheses. 7 psoriasis patients and 3 controls had bone marrow aspirates performed as well and OCP frequencies were measure and sera was collected as well as RNA and DNA. To date, PDUS have been analyzed using PSASon scoring.

Assessment of DC-STAMP as an early response marker in PsA

This study was based on the hypothesis that a change in monocyte DC-STAMP expression at 2 weeks will predict long-term response to TNFi. To test this hypotheses, DC-STAMP expression in monocytes from PsA patients were assessed and Power Doppler Ultrasound (PDUS) of inflamed joints performed at baseline, 2 weeks and 6 months after starting a TNFi. The primary outcome measure will be the change in the Disease Activity Score 28 (DAS28)-CRP at 6 months. We examined if the change in DC-STAMP^{+}CD14^{+} expression at 2 weeks correlates with the change in the DAS-28CRP and DPUS score at 6 months. We collected data on 28 PsA patients as outlined above and these data are currently being analyzed.

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

GENETIC AND BIOMARKER STUDIES:

This project entitled "**GENETIC AND GENOMIC DISSECTION OF PSORIATIC ARTHRITIS**" is funded by 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); (September 2012 – 2017).

Genetic Studies

We are pleased to report that, the exome array variation experiment that we undertook with Affymetrix proved to be more comprehensive and more cost-effective than we anticipated. By combining previous and newly-collected data, we have produced two manuscripts that we consider to be of high impact. The first, published in 2014, describes differential associations with PsA vs. PsC in the MHC (Okada et al, Am J Hum Genet 95(2):162-72, 2014). This paper found an amino acid residue in HLA-B that efficiently discriminated PsA from PsC. The second paper, which is now published the American Journal of Human Genetics (Stuart et al, Am J Hum Genet 97(6):816-36, 2015), 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, $P = 8.4 \times 10^{-11}$). Among identified psoriasis risk variants, three were more strongly associated with PsC than PsA (rs12189871 near *HLA-C*, $P = 5.0 \times 10^{-19}$; 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. These results provide novel insights into the pathogenetic similarities and differences between PsC and PsA.

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]). Genotyping and a manuscript has been in the American Journal of Human Genetics (Dand et al, AJHG 2017). 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. Analysis of these datasets has now been published in Nature Communications (Tsoi et al., Nat Comms 2017).

We have also entered into collaboration with Drs. Anne Barton 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. After considerable discussion with Dr. Barton and her colleagues, and unfortunately, we remain in a very preliminary stage of our planned collaboration. We would appreciate support from

IPART team members to encourage Dr. Barton and her colleagues to move forward on this analysis, which has now been planned for more than two years, but not executed as yet.

Biomarker Studies

Early diagnosis of inflammatory arthritis is the key to preventing joint damage, improving health outcomes and reducing health care costs. Psoriatic arthritis (PsA), an inflammatory arthritis associated with psoriasis, provides a unique opportunity for early diagnosis since most patients develop PsA after the onset of cutaneous psoriasis. There is high prevalence of undiagnosed PsA among patients with psoriasis. Dermatologists play a pivotal role in preventing joint destruction in psoriasis patients by screening for PsA and referring patients to rheumatologists when appropriate. A valid screening tool will facilitate appropriate referral to rheumatologists. Unfortunately, the performances of screening questionnaires have been disappointing. No biomarkers for PsA have been validated, although pilot studies show promise. We believe that in a disease such as PsA that is more auto-inflammatory than autoimmune, potential biomarkers are overexpressed in inflamed target tissues (joints and skin) and subsequently enter systemic circulation. Using quantitative proteomic methods we have identified candidate markers for PsA. The most promising of these proteins as well as proteins identified as important after literature review will be sought in serum using a targeted approach. Hypothesizing that a serum biomarker-based predictive model will identify patients with PsA from those with psoriasis without PsA (PsC), a predictive model for PsA will be developed.

Based on genetic, clinical, and biological markers, our goal is to develop a user friendly and robust prediction model for PsA for dermatologists that will enable dermatologists to make better referral decisions and positively influence early diagnosis of PsA, resulting in improved quality of life and function. In the future we will further validate the tool and explore the clinical utility, acceptance by stakeholders, cost effectiveness and the most appropriate means for the ethical introduction of this model into the clinic. We are in a unique position to perform these studies as our research team includes clinicians, experts in proteomics, biostatistics, KTE, and ethical, legal, and social issues related to biomarker research with access to a large cohort of well-phenotyped patients with PsA and PsC and a linked biobank.

In this regard, our ***current activities*** are centered on identification and validation of biomarkers for PsA development, disease subtypes, drug responsiveness, and co-morbidities in PsV patients. We are in an excellent position to coordinate protein-level and transcriptome level information for blood and skin samples. 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. In initial quality control (QC) experiments planned at the previous IPART meeting, we assessed cross-platform validation and established appropriate QC measures. The results, which will be presented at our upcoming meeting, identify a group of conversion-related miRNA transcripts, many of which are correlated (directly or inversely) with conversion-related mRNA transcripts.

Very recently, we have also performed a metabolomic analysis of PsC-to-PsA converters on the Metabolon platorm, involving 65 longitudinally-documented coverters from PsC to PsA from Toronto, Rochester, and Michigan. The preliminary results indicate the emergence of several sytemic inflammatory processes as PsA develops.

Statistical Comparisons	
Matched Pairs t-Test	
Statistically Significant Biochemicals	PsC PsA
Total biochemicals p≤0.05	293
Biochemicals (↑↓)	275 | 18
Total biochemicals 0.05<p<0.10	110
Biochemicals (↑↓)	104 | 6

The preliminary **conclusions**, which we have received as a service report from Metabolon, are as follows:

Metabolomic profiling of serum from individuals who converted from cutaneous psoriasis (PsC) to psoriatic arthritis (PsA) revealed multiple biochemical signatures related to the pathophysiology of the disease. 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. Furthermore, elevated oxidative stress was also observed in PsA subjects, along with an altered antioxidant status. Collectively, these results point to several avenues for both follow up mechanistic studies, as well as therapeutic opportunities. It may also be informative to comparing these findings to other inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus (SLE) to gain insight into both similarities and differences to help identify unique candidate biomarkers of disease. Based on these developments, we are currently preparing the competing renewal application.

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. Proton Rahman

IPART Genetic Core Site – Memorial University of Newfoundland, Canada

Much of the time in 2017 was spent in seeking for large scale funding to maintain the genetics program at Memorial. Two large operating grants were submitted both to federal agencies. One was sent to Genome Canada and the other to Atlantic Innovation Fund. The objectives of the operating grants were to facilitate early identification of persons with SpA or at-risk of SpA, identify biomarkers of disease activity and progression, and accurately identify patients who are likely to benefit from specific treatment modalities, through improved prognostic stratification and prediction of treatment response. The deliverables include:

1. Genetically-guided screening algorithms and new models of care for AxSpA and PsA targeted at primary care health practitioners;

2. Novel endophenotypes in SpA using high dimensional molecular phenotypes to facilitate prognostic stratification and pharmacogenetics of SpA by musculoskeletal (MSK) specialists; and

3. Implementation of a novel screening tool by quantifying clinical benefits and harms, as well as cost consequences in comparison with the current standard of care, and to clarify specific psychosocial and ethical aspects

We were not successful in the Genome Canada grant but were successful for the AIF grant and received 3.5 million dollars over the next three years to maintain our genetics program. We also were awarded an equipment grant from the Atlantic Canada Opportunities Fund for 2.5million dollars to purchase a NovaSeq for exome and full genome sequencing.

The following studies are presently ongoing related to IPART:

1. Full exome sequencing of a multiplex family – this has identified a potential functional candidate. The candidate gene identified is being verified using Sanger Sequencing;
2. Genome wide epigenetic study of a multiplex family – this led to identification of a small number of CpG sites that can distinguish PsA cases from unaffected relatives and health controls. We are validating this to see if the markers have any utility outside this family;
3. Genome wide CNV analysis imputed from previous GWAS data. This did not identify any significant CpG sites after corrections for multiple testing was completed;
4. Deep sequencing for PsA concordant and discordant twins, looking to see if rare variants can explain the difference;
5. Developing a SNP based PsA panel to identify PsA among psoriasis patients;
6. Developing and optimizing a procedure for preparing circulating miRNA libraries for sequencing with Ion Torrent Technology; and
7. Assessing our circulating miRNA library preparation, circulating miRNA sequencing, and circulating miRNA differential expression data analyses in a PGx-PsA patient cohort as an exploratory investigation of these methodologies.

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

CLINICAL FEATURES

We found that certain clinical features at baseline identify patients with psoriasis who subsequently develop psoriatic arthritis (PsA). Baseline arthralgia (in women), heel pain, high fatigue score and high stiffness score predicted the development of PsA during follow-up (1).

We identified 42 pregnancies among 29 PsA women. The outcome of pregnancy was excellent with 95% live births. Arthritis improved, or was stable low activity in 58.5% of pregnancies. However, during the postpartum period 40% had either worse or stable high disease activity. On the other hand, the skin activity during pregnancy either improved or was low in 88% of the pregnancies. A logistic regression analysis revealed a favourable skin disease course during the pregnancy period in the pregnant group compared to the control group, but not in joint disease (2).

We found that obesity is linked with late-onset psoriasis and PsA, while normal weight is associated with the presence of the HLA-B*27 allele and an earlier onset of the disease. These results highlight the differential risk factors that may drive the inflammatory process in psoriatic disease (3).

Clinical enthesitis was detected in 35% of the patients with an annual incidence of 0.9%. Enthesitis usually involves only 1 or 2 sites simultaneously. The most common tender enthesitis sites are at the insertions of the Achilles tendon, plantar fascia, and the lateral epicondyles. More active disease and more pain are associated with enthesitis (4). The Madrid Sonographic Enthesis Index (MASEI) was used to measure enthesitis in 223 patients with PsA. The study found that a higher MASEI score, which reflects more severe enthesitis, is associated with severity of peripheral radiographic joint damage as measured by mSS. Furthermore, the severity of enthesitis was associated with proliferative and erosive features of joint damage including joint ankylosis, arthritis mutilans and periostitis. Additionally, a higher enthesitis score was associated with features of axial radiographic damage, including syndesmophytes and sacroiliitis (5).

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COMORBIDITIES

The incidence of diabetes is higher in PsA than in the general population. Risk factors for developing diabetes among patients with PsA include actively inflamed joints and elevated sedimentation rate over time (1).

Patients with psoriatic disease have poor sleep quality. Poor sleep is associated with fatigue, anxiety, and lower EQ-5D. In patients with PsA, poor sleep is associated with active joint Inflammation (2).

We have previously shown that patients with PsA have a higher prevalence of subclinical atherosclerosis demonstrated by carotid ultrasound. We recently demonstrated that anti-TNF□ agents reduce the risk of progression of subclinical atherosclerosis among patients with PsA (3).

An investigation into patients' recognition that comorbidities are being evaluated by their physicians revealed that overall; patients documented being moderately well screened for most comorbidities and were most unsure about having their blood sugar and cholesterol levels monitored. There was a discrepancy between patient recognition and chart confirmation of comorbidities, suggesting that patients need to be educated on how their comorbidities are being assessed (4)

Hyperuricemia was detected in 32% of the patients with PsA. Comparing patients with and without hyperuricemia (matched on age and sex demonstrated that patients with hyperuricemia had more concurrent co-morbidities including cardiovascular disease (CVD) and metabolic diseases, as well as higher prevalence of kidney stones and higher creatinine. Over the follow-up, 163 of the 318 patients had persistent hyperuricemia for more than 2 visits. These patients developed more myocardial infarction, heart failure, and renal impairment. Multivariate analysis showed an association between persistent hyperuricemia, disease duration and obesity (5).

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ASSESSMENT OF DAMAGE

One hundred and twenty five PsA patients underwent 168 MRI (magnetic resonance imaging) (135 axial and 33 peripheral). The predominant indications were for suspected inflammatory (51.1%) or degenerative (24.4%) disease. Magnetic resonance imaging revealed inflammatory and/or structural change in 34.1% versus 54.8% with degenerative changes. In MRI axial inflammation (n = 25), the majority (48%) had sacroiliac joint involvement, whereas 28% had inflammation at 2 or more sites. Of the periphery, 60.6% of scans were on hands and 21.2% were on feet alone. The main indications were for suspected subclinical synovitis (78.8%). Inflammatory arthritis was the MRI diagnosis in 72.7%.MRI findings influenced treatment change in 56.3%, but were insufficient to effect treatment change without clinical findings (1).

Having demonstrated that the available methods for assessing inflammatory spinal disease are reliably in PsA, we set out to determine whether these scores are sensitive to change. Two sets of 105 PsA spinal radiographs at two time points at least 2 years apart were read by 3 rheumatologists who were blinded to the time points using several methods were used: the Bath Ankylosing Spondylitis Radiology Index (BASRI), the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS), the Radiographic Ankylosing Spondylitis Spine Score (RASSS), and the PsA Spondylitis Radiology Index (PASRI). A fourth rheumatologist who was aware of the time points and was considered the gold standard indicated whether there was progression. Logistic regression analyses showed that an increase of 1 point in the respective scores was associated with the following odds ratios for identifying true progression: BASRI-s 3.0, mSASSS 5.27, RASSS 3.70, and PASRI 3.06. It was concluded that the available scoring systems for quantifying radiographic axial PsA have moderate sensitivity but high specificity for detecting true change (2).

References for Damage Assessment

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PROTEOMIC AND METABOLOMIC BIOMARKERS

In addition to genomic, transcriptomic and metabolomic approaches for early detection of PsA, we have continued to evaluate biomarkers identified using a proteomic approach. We have identified biomarkers from proteomic analysis of synovial fluid and skin biopsies. A study based on four high-priority markers (M2BP, CD5L, MPO, and ITGB5) indicate that protein biomarkers are likely to identify PsA in patients with psoriasis. We found that CD5L, ITGB5, M2BP, MPO, MMP3 and CRP are markers for PsA. Combination of ITGB5, M2BP and CRP differentiate PsA from PsC, and performs better than CRP alone. Further investigations on a larger panel of protein biomarkers are currently underway.

Another unmet need is identifying markers for PsA disease activity. We have conducted solid phase microextraction (SPME) sample preparation followed by global metabolomics analysis on the mass spectrometer in our laboratory on 10 healthy controls, 10 patients each with mild, moderate and severe PsA. By performing this analysis in-house, we have demonstrated the capability and quality of our proposed approach. The sample extracts were run randomly on a high resolution mass spectrometer (Q-Exactive). The subsequent data was processed using XCMS, XCMS Online, and Metaboanalyst. The pooled QC clustered very tightly, strongly suggesting instrument stability during the run. There was a clear separation between healthy controls vs patients with severe PsA. Interestingly, the majority of patients with mild PsA clustered closer to the controls while those classified as moderate were distributed across the plot. Further data analysis of the positive ion mode and negative ion mode RAW data is on-going but the initial analysis strongly suggests that there are very different metabolic pathways dysregulated in PsA.

In addition, we currently hold a 1-year CIHR-IMHA catalyst grant funded study to compare the serum metabolomic profiles of patients with psoriasis prior to developing PsA to that after PsA onset to identify pathways and markers associated with arthritis development (n = 20). Initial analyses have provided us results similar to that reported by Dr. Elder above.

TORONTO SITE ON-GOING STUDIES

Furthermore, the following projects have evolved in the Toronto core site utilizing the IPART detailed data and biosamples since 2016. Most of these projects have obtained ethics approval and are now on-going:

- **Project Title: "COMORBIDITIES AND THEIR MANAGEMENT IN PSORIASIS AND PSORIATIC ARTHRITIS"**

  Background: Psoriasis is a chronic skin condition that affects 2-3% of the population of which about 30% will go on to develop psoriatic arthritis. Patients with psoriasis and psoriatic arthritis are known to have increased risk for other conditions such as cardiovascular disease, depression, obesity, diabetes, and hypertension. Our previous studies have shown that despite the increased occurrence

of these conditions patients have little knowledge and risk awareness of these conditions. We hypothesized that patients with psoriatic disease are not routinely screened for comorbidities by their primary care physicians, and therefore not treated for these comorbidities. The aim of this study is to determine how physicians managing these patients identify and address these co-existing conditions in the clinic setting.

Method: A questionnaire was developed and completed by both psoriasis and psoriatic arthritis patients followed in the University of Toronto Psoriatic Disease Program through IPART. This questionnaire will determine whether they have had their standard screening tests performed for these conditions such as blood pressure, blood sugar, cholesterol, and weight by their primary care physicians or any other physician, and whether they are being treated for those conditions. Charts will be reviewed from the PsA and psoriasis clinics to determine whether the comorbidities are mentioned and addressed. An analysis of the data collected will be carried out to determine how many patients have either their primary physician or specialist manage the comorbidities with the help of the biostatistician.

Knowing the extent of current patient knowledge and physician management of these co-existing conditions in psoriatic disease will allow us to develop improved education and better approaches to limit the development and serious outcomes that these conditions can lead to.

- **Project Title: "MINIMALLY IMPORTANT DIFFERENCE OF THE PSORIATIC ARTHRITIS DISEASE ACTIVITY SCORE (PASDAS) IN PATIENTS UNDERGOING TREATMENT WITH BIOLOGICS AND METHOTREXATE"**

  Background: Psoriatic arthritis (PsA) is an inflammatory arthritis that affects people with psoriasis, a chronic skin condition. It is often difficult for clinicians taking care of patients with PsA to assess how active the disease is. Recently, a new method of assessing PsA disease activity called the Psoriatic ArthritiS Disease Activity Score (PASDAS) was developed through an international effort. The score ranges from 0-10 and was shown to improve with treatment. However, we do not know how much change in the PASDAS score patients suffering from PsA perceive as important. Finding this is important since change of the PASDAS score equal to or more than this value would necessitate a change in treatment provided there are no troublesome side-effects or excessive costs.

  Method: Through the proposed study on patients attending the largest and best characterized patients with PsA in Canada, we intend to determine this important value by comparing the change in PASDAS scores in patients who improve or worsen on treatment with anti-TNF agents as well as methotrexate. The results will help the clinicians treating patients with PsA to better interpret the change in PASDAS score. This will lead to better management of patients with PsA and further lead to better outcomes and limit side effects of treatment.

- **Project Title: "UNRAVELLING THE PHENOTYPIC HETEROGENEITY OF PSORIATIC ARTHRITIS: ROLE OF THE CUTANEOUS MICROBIOME"**

  Background: The primary and dominant goal of the IPART research network is to make advances that will to lead to significant improvement in outcomes for patients with psoriatic arthritis (PsA) and cutaneous psoriasis (PsC). This will be achieved through improved understanding of the biological basis of PsA and PsC with an emphasis on identifying risk factors for disease severity among patients with PsA and PsC. Identification of these determinants may aid in disease diagnosis, prediction of prognosis and therapeutic outcomes.

Psoriasis is a common inflammatory skin disease affecting 1-3% of the Canadian population. Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis that affects 30% of psoriasis patients. PsA is remarkably heterogeneous in its presentation. Owing in part to its genetic heterogeneity, PsA varies widely in its clinical features and outcomes. Features such as axial involvement, severity of cutaneous psoriasis and the time interval between the onset of psoriasis and PsA have been linked to genetic factors (HLA alleles and haplotypes), suggesting that genetic heterogeneity at least partially drives phenotypic heterogeneity. Yet, differences in several other disease manifestations remain unexplained by this genetic heterogeneity. Evidence supporting varying severities of psoriatic disease between these phenotypes prompts an investigation of the role of an important cutaneous factor: the microbiome. The growing interest in the role of the human microbiome in health and disease, afforded by advances in sequencing methods in recent years, has enabled scientists to characterize the cutaneous microbiota associated with psoriasis. A pilot study further investigated the cutaneous microbiome differences between PsC and PsA. Yet, no study to date has investigated for its role in the sub-phenotypic heterogeneity of PsA.

In this study, we aim:

1. To characterize the cutaneous microbiome of psoriatic plaques, and compare it to that of an unaffected, contralateral site and a matched site in a control subject.
2. To Investigate for correlation between cutaneous microbiome diversity and disease severity:
   a. Extent and severity of skin disease and cutaneous microbiome in psoriasis and PsA patients.
   b. Extent (including axial vs. peripheral phenotype) of joint disease and cutaneous microbiome in PsA patients.
3. To investigate for a correlation between the microbiome diversity findings with the patient's genotype (specifically, HLA-C*06 and HLA-B*27).

- **Project Title: "THE PREDICTIVE VALUE OF MSK ULTRASOUND FOR DISEASE OUTCOMES IN EARLY PSORIATIC ARTHRITIS: A LONGITUDINAL MULTICENTER COHORT STUDY"**

Background: Ultrasound is widely used in rheumatology practice. It has a potential of serving as an adjunct to the clinical assessment and affecting treatment decisions in patients with psoriatic arthritis (PsA). However, there is limited information about the utility of musculoskeltal ultrasound in assessing disease activity and predicting long term outcomes in patients with PsA. We hypothesize that the extent of musculoskeletal inflammation detected by ultrasound predicts subsequent long-term outcomes in patients with PsA, including the achievement of minimal disease activity and the development of structural damage. We aim to investigate these hypotheses in a longitudinal study in patients with early PsA.

Methods: In this prospective cohort study 70 patients with early PsA with active peripheral arthritis from the IPART cohort study will be recruited. The patients will be assessed at baseline, 6 months, 1 year and 2 years. Medical history will be obtained and musculoskeletal and skin assessments will be performed at each visit. The achievement of a minimal disease activity state will be determined at 1 year. Ultrasound scanning of 42 joints and 14 entheseal sites will be performed at baseline, and 6 months. These sites will be scored for the presence and degree of synovitis and enthesitis. The presence of bone erosion will also be recorded. Structural damage progression will be assessed using radiographs of the hands and feet. Radiograph of the hand and feet will be obtained at baseline and 2 years. Two main outcomes will be considered: 1) the achievement of a minimal disease activity state at 12 months; 2) progression of structural damage at 24 months. The association between the degree of musculoskeletal inflammation detected by ultrasound at baseline

and the probability of achieving the various outcomes will be assessed using logistic regression analysis

- **Project Title: "ASSESSMENT OF THE PSORIATIC ARTHRITIS IMPACT OF DISEASE (PsAID) QUESTIONNAIRE"**

  Background: Psoriatic arthritis is an inflammatory musculoskeletal disease that affects patients with psoriasis. The disease presents with different manifestations that include arthritis in the peripheral joints (hands, feet, knees, and ankles), arthritis in the joints of the spine, inflammation in the insertion of tendons and ligaments into bone, inflammation of a whole digit, skin psoriasis and nail psoriasis. These manifestations have an impact on patients' quality of life and function. Currently a number of questionnaires are used to record the impact of the disease on patients. However, the majority of these were developed for patients with rheumatoid arthritis. Recently, a new questionnaire was developed specifically for patients with psoriatic arthritis.

  Method: The Psoriatic Arthritis Impact of Disease (PsAID) will be compared with other instruments that assess quality of life and function. Moreover, we shall test whether the PsAID can replace other instruments used in composite measures that assess disease activity in psoriatic arthritis. If we can demonstrate that the PsAID is better than the other instruments, patients will need to complete fewer questionnaires during their clinic visit. Composite measures which include the PsAID may function better than those using questionnaires that were not specifically developed for psoriatic arthritis.

- **Project Title: "UNDERSTANDING DYNAMIC PSORIASIS PHENOTYPES THROUGH METABOLOMICS**".

  This is a retrospective non-interventional investigator-initiated study, in collaboration with the University of Waterloo. This study has just been awarded the CIHR Catalyst Grant: Musculoskeletal Health and Arthritis on March 2017.

  Background: The objective of this study is to use an innovative sample extraction technology called solid phase microextraction (SPME; pioneered in Waterloo, ON) coupled to a high resolution mass spectrometer (Q-Exactive) to perform global/untargeted metabolomics profiling on psoriasis patients who subsequently develop psoriatic arthritis (PsA; converters) and on those who remain PsA free (non-converters). We hypothesize that serum metabolome profiling will identify key pathways involved in psoriasis progression, including the development of PsA in patients with cutaneous psoriasis.

  Method: In order to accomplish this objective, we have developed the following strategy:

  1. Identify differences in serum metabolomic profiles between patients with chronic plaque psoriasis who subsequently develop PsA (converters), patients with chronic plaque psoriasis who do not develop PsA (non-converters), and healthy controls. Serum samples will be obtained at "baseline; time 0" for this analysis among the 3 groups of subjects.

  2. Identify metabolite profiles associated with the transition from a purely cutaneous psoriasis to psoriasis with PsA (converters), and profiles associated with a stable phenotype (non-converters). Serum samples will be obtained at "baseline; time 0" and at "time x" when the diagnosis of PsA is made in one of the cohorts, and a matched time point in the other.

  3. Use the metabolite profiles from Aim 1 and 2 to identify pathways and networks associated with psoriasis progression, including the development of PsA.

We believe that the longitudinal study will provide insights into the pathogenesis of psoriatic disease (PsD) such that we will be able to 1) identify key pathways that lead to PsA in patients with psoriasis which may be targets of (preventive) therapy, and 2) identify clinically useful biomarkers for stable, as well as, transitioning psoriasis phenotypes.

- **Project Title: "THE LINK BETWEEN PSORIASIS AND DIABETES: DO PSORIATIC PATIENTS WITH TYPE 2 DIABETES HAVE A HIGHER RISK OF DEVELOPING PSORIATIC ARTHRITIS?**

  Background: Psoriasis is a chronic immune-mediated skin condition that affects more than 125 million people in the world. About 30% of the patients with psoriasis develop psoriatic arthritis. Individuals with psoriasis are also at a higher risk of developing chronic comorbidities such as cardiovascular disease, Crohn's disease and Type 2 Diabetes (T2D).

  T2D is currently a serious public health problem which may have severe complications, including increased mortality. Research has shown a higher incidence of T2D in people with psoriasis. The environmental and genetic link between psoriasis and diabetes is fully understood. We speculate that the inflammatory nature of psoriasis increases the risk of patients developing diabetes which may then drive the development of psoriatic arthritis. Therefore the aim of this project is to determine whether individuals with psoriasis who have T2D are at a greater risk of developing psoriatic arthritis than people with psoriasis alone.

  If we are able to demonstrate a higher incidence of psoriatic arthritis in patients with both psoriasis and T2D, it would suggest that physicians treating patients with psoriasis should screen patients early in their course for the presence of T2D. The physician should also follow those patients with both psoriasis and T2D closely in order to diagnose and treat psoriatic arthritis early.

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 2017 – 2018, the meeting is taking place at the **Marriott Toronto Downtown Eaton Centre Hotel on February 9, 2018.** 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.

PUBLICATION LIST

For the period covering the **4th quarter of 2016 through the end of December 2017,** IPART investigators have made a number of advances, resulting in the following publications, collectively as an IPART team and individually using IPART datasets:

1. Eder L, Wu Y, Chandran V, Cook R, Gladman DD. Incidence and predictors for cardiovascular events in patients with psoriatic arthritis. Ann Rheum Dis 2016;75:1680-1686.
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ACKNOWLEDGMENT

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