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## Seminars in Arthritis and Rheumatism

# Advancing research paradigms and pathophysiological pathways in psoriatic arthritis and ankylosing spondylitis: Proceedings of the 2017 Platform for the Exchange of Expertise and Research (PEER) meeting

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## Introduction − Dr. Sonya Abraham

The seronegative spondyloarthropathies, including psoriatic arthritis (PsA) and ankylosing spondylitis (AS), are characterized by varied clinical symptoms, severity, and disease course [1,2]. Diagnosis and monitoring can be challenging because there is no definitive laboratory biomarker for reliably measuring inflammation or other disease processes associated with spondyloarthropathies. Over time, many patients with PsA and AS eventually experience significant disability and impaired quality of life [1,2]. This may be partially

accounted for by delays in diagnosis and subsequent treatment [3], as well as the presence of comorbidities.

In recent years, research efforts aimed at identifying risk factors for PsA, including clinical, imaging, genetic, and laboratory assessments, have yielded major advances. The Platform for the Exchange of Expertise and Research (PEER) was formed to facilitate the exchange of research insights, sharing of expertise, and discussion of unmet needs in rheumatology research.

The objective of the current report is to provide an overview of the 2017 PEER meeting, which was held on May 19−20, 2017, in London, UK, and highlighted the most up-to-date research findings regarding PsA and AS pathophysiology, early detection, comorbidities, and treatment.

## Development of psoriatic arthritis in patients with psoriasis: insights from a prospective cohort − Dr. Lihi Eder

The majority of patients with PsA initially develop skin disease, with joint disease following approximately 7−13 years later [4,5]. A delayed diagnosis of PsA is associated with worse outcomes than when the diagnosis is made earlier in the disease course [3]. In order to identify patients at risk for PsA, and increase early diagnosis and

treatment, the ongoing Toronto Psoriasis Cohort Study aims to evaluate the genetic and environmental risk factors associated with PsA development; enrolled patients with psoriasis are followed on a yearly basis until they develop PsA (Fig. 1) [6].

The study has suggested that the incidence of PsA is higher than previously estimated [6]. Based on the data collected, a prediction model estimated that over 20 years of follow-up, approximately 35% of the cohort patients were predicted to develop PsA [6]; this contrasts with only 5% cumulative prevalence among psoriasis patients described in a previous report of a Rochester, Minnesota, cohort [7]. In the Toronto Psoriasis Cohort Study, clinical factors (including psoriasis severity), presence of nail lesions or uveitis, lower level of patient education, and use of retinoids to treat psoriasis were predictors of PsA development [6,8]. A related body of research has also identified trauma as a significant predictor of PsA development [9–11]. By contrast, trauma is not associated with onset of rheumatoid arthritis (RA) [9].

Other factors associated with PsA development in the Toronto cohort as well as a UK cohort include higher body mass index; presence of nonspecific musculoskeletal symptoms, including pain, fatigue, and stiffness, among psoriasis patients, even in the absence of distinct arthritis on physical examination; and certain biomarkers [6,12]. C-X-C motif chemokine 10 (CXCL10) was found at higher levels in the serum of patients with psoriasis who subsequently developed PsA and may be a potential biomarker for predicting PsA [13,14]. Subclinical enthesitis, as detected by magnetic resonance imaging (MRI) or ultrasound, is often present in patients with psoriasis and observed at the nail and joints; the clinical significance of this finding requires further investigation [8,15].

Overall, the findings derived from the Toronto cohort and other related investigations indicate that it may be possible to identify a subset of psoriasis patients who may be at higher risk for the development of PsA than other psoriasis patients. Based on the Toronto cohort analyses discussed above, PsA risk factors include trauma, higher body mass index, severe skin psoriasis, nail lesions, uveitis, and nonspecific musculoskeletal symptoms, as well as higher serum levels of CXCL10. Use of these findings in the clinic may give rise to a new model of care in which certain psoriasis patients flagged as at high risk for PsA could obtain treatment at a substantially earlier stage of PsA disease development. Prompt identification of risk factors for PsA and earlier treatment initiation could potentially prevent the development of full-blown PsA.

## PROMPT research program: an overview and update – Professor Neil Mchugh

The ongoing UK National Institute for Health Research (NIHR)-funded program grant for applied research, "early detection to imPRove OutcoMe in people with undiagnosed Psoriatic arthriTis" (PROMPT), encompasses a series of research activities aimed at facilitating accurate and early detection of PsA in UK primary care. An additional aim of the study is to develop patient-completed outcome measures of early disease that are relevant to patients with PsA and not adequately captured by currently available assessments.

The PROMPT research program includes focus groups examining what patients perceive to be important patient-reported outcome measures to enhance early screening, detection, and diagnosis in the primary care setting and in clinical treatment of PsA [16,17]. PROMPT draws upon findings from the ongoing Epidemiology of Psoriatic Arthritis (EPIC) study, which is based on analysis of the Clinical Practice Research Datalink database for epidemiological factors associated with PsA. It also encompasses ongoing research into cost-effectiveness, screening questionnaires, and barriers to PsA diagnosis.

To date, focus group studies have demonstrated that pain and fatigue are rated as most important by patients, yet neither of these conditions is adequately captured in current composite measures for PsA [16,17]. Moreover, a substantial proportion of patients are diagnosed with PsA within 13 years of the onset of cutaneous psoriasis [5]. The interval between onset of psoriasis and PsA appears to have a genetic basis, with human leukocyte antigen (HLA)-C*06 being associated with a prolonged delay in PsA development and HLA-B*27 being associated with very short interval or contemporaneous onset of psoriasis and PsA [18,19]. The PROMPT study further indicated that uveitis and Crohn's disease, but not ulcerative colitis, are more common in patients with PsA than in those with psoriasis alone [20]. The Total bUrDen of psORiasis (TUDOR), an ongoing randomized, controlled study, is central to PROMPT in evaluating enhanced surveillance of PsA compared with standard primary care. TUDOR is the first study to prospectively examine the impact of early diagnosis on long-term outcomes in PsA (Fig. 2); with a planned 5-year duration, outcomes are expected to become available in 2021.

## The ongoing quest for early diagnosis and biomarker discovery in ankylosing spondylitis – Dr. Raj Sengupta

Goals for improving outcomes in AS include earlier detection and treatment, which represents a major challenge and unmet need. In 1999, the time between symptom onset and diagnosis was a median of 5 years, which had not improved in 2013, based on analysis of clinical data at 2 large UK secondary care centers [21].

As with PsA, delay in diagnosis is associated with worse outcomes, including poor function and mobility and increased risk of work disability [22,23]. When AS is diagnosed and treated earlier, the Bath Ankylosing Spondylitis Metrology Index score tends to be
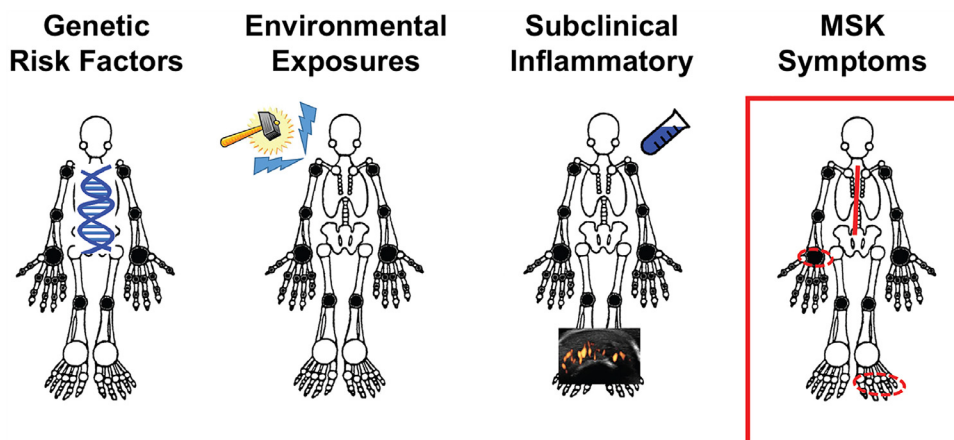


**Fig. 1.** The pre-clinical phases of PsA [6]. MSK, musculoskeletal psoriatic arthritis. Risk factors shown are based on data from the Toronto Psoriasis Cohort Study, a long-term prospective observational study assessing the development of psoriatic arthritis in patients with psoriasis.
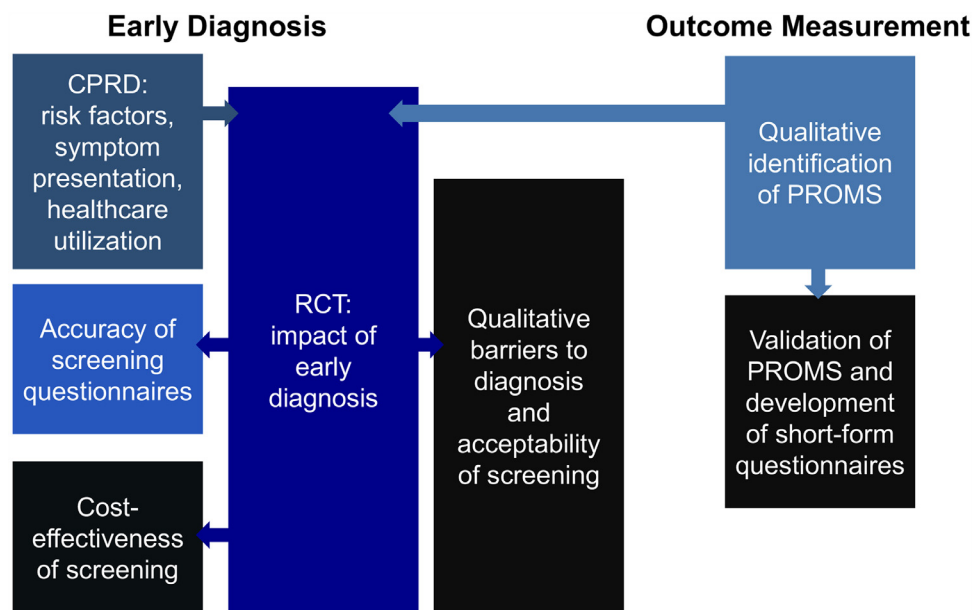
## Early Diagnosis

## Outcome Measurement



**Fig. 2.** Overview of the PROMPT investigative plan. CPRD, UK Clinical Practice Research Datalink; PROMPT, "early detection to imPRove OutcoMe in people with undiagnosed Psoriatic arthriTis"; PROMS, patient-reported outcome measure; RCT, randomized controlled trial.

maintained, indicating that patient mobility remains stable and does not deteriorate [24]. In 1 study, a higher proportion of patients with early disease (< 5 years) responded to adalimumab treatment compared with patients with later disease (≥ 5 years) [25]. Another study demonstrated that following initiation of tumor necrosis factor (TNF) inhibitor treatment, radiographic progression was significantly slower in early disease patients than in later disease patients [26].

Among the emerging biomarkers for early detection of AS are approximately 41 genes, including those that encode major histocompatibility complex (MHC) class 1 proteins; related genes such as *ERAP1, UBE2E3, UBE2L3*, and those involved in CD8 + T-cell function; microbial sensing genes; and those involved in other immune functions that are not clearly understood [27,28]. However, the usefulness of these biomarkers in the clinical setting is not yet well developed.

Other inflammatory markers, such as C-reactive protein, erythrocyte sedimentation rate, and vascular endothelial growth factor, are not sufficiently specific and sensitive to differentiate patients with AS from either healthy controls or those with other arthropathy. Some patients with AS may exhibit normal values, and elevations of these markers are seen in other arthropathies [29,30]. IL-17 and IL-23, however, have been found to be more consistently elevated in patients with AS compared with healthy controls [31]. Markers of bone turnover, such as Wnt-3a, sclerostin, monocyte chemoattractant protein-1, and calprotectin, are promising because they tend to be higher in patients with AS compared with healthy controls [30,32,33]. Among these, only monocyte chemoattractant-1 has demonstrated the capability to distinguish AS patients from healthy controls or those with mechanical low back pain [33]. Likewise, while anti-flagellin antibodies and diagnostic biomarkers (e.g., autoantibodies against protein phosphatase magnesium-dependent 1A) are also elevated in patients with AS, only autoantibodies against protein phosphatase magnesium-dependent 1A have shown promise in helping to distinguish between patients with AS vs. healthy controls or patients with RA or PsA, given that they correlate with baseline disease severity and vary according to changes in disease severity related to clinical response to TNF-α inhibitor treatment [34,35]. These findings, however, require further validation in an independent patient cohort.

Major challenges in the use of biomarkers for AS diagnosis include a lack of consistent results across studies, large variation among patients due to the heterogeneous nature of AS, and questions around the reliability of the assays. Large studies in well-defined patient cohorts are needed to bring use of these biomarkers to the bedside. To address some of these challenges, the PROgnostic Markers In Spondyloarthritis (PROMISE) study is under way, with a planned enrollment to include 250 patients with axial SpA or AS, with assessments to identify prognostic markers in SpA, including patient-reported outcomes and radiograph, MRI, biomarker, and genetic analyses. In the meantime, Web-based tools aimed at healthcare providers and patients with the intention of improving early AS detection are available, including the Spondyloarthritis Diagnosis Evaluation (SPADE) tool for the global provider community (http://www.spadetool.co.uk/), Back in Focus website for primary general practitioners (https://www.axialspabackinfocus.co.uk, sponsored by AbbVie), and Don't Turn Your Back on It website for patients (http://www.dontturnyourbackonit.co.uk).

### Subclinical enthesopathy and development of psoriatic arthritis – Professor Dennis McGonagle

Enthesitis is inflammation occurring in tissue that connects ligament to bone, driving cytokine-mediated immunobiologic response at sites in the body that otherwise lack an immune response [36]. It is a common hallmark of the spondyloarthropathies, including PsA and AS [36]. Ongoing work has revealed how both mechanical stress and the genes responsible for the interleukin (IL)-12 and IL-23 inflammatory pathway have been associated with the development of enthesitis [37].

In murine models of spondyloarthritis (SpA), entheseal-resident IL-23 receptor-positive T cells have been shown to be critical to SpA pathogenesis [37]. In human entheseal tissue, IL-23R-positive innate type 3 lymphoid cells are present and show elevated levels of transforming growth factor-β1 and TNF-α transcripts [38]. Moreover, patients with SpA and PsA exhibit microdamage at ligament and tendon attachment sites associated with MHC type 1-linked signals, including HLA-B*27 [39,40]. Clinically asymptomatic patients often have enthesopathy observed on ultrasound [41,42] and preliminary studies have shown that the presence of subclinical enthesitis may predict the development of PsA [43]. Enthesopathy is also linked to nail disease, which in turn is linked to PsA development [7,44]. In patients with psoriasis, barrier dysfunction may contribute to adaptive MHC-1-associated immune responses that drive enthesopathy and PsA development (Fig. 3) [45].
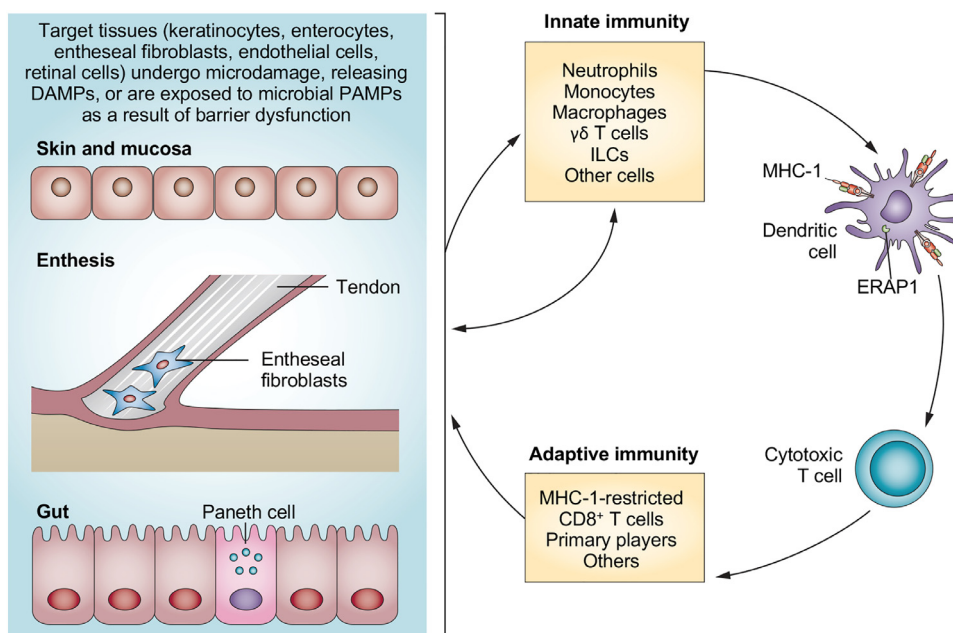
**Fig. 3.** Enthesopathy in psoriasis: Adaptive immune priming [45]. DAMP, damage-associated molecular pattern; DC, dendritic cell; ERAP1, endoplasmic reticulum aminopeptidase 1; NK, natural killer cell; PAMP, pathogen-associated molecular pattern.

Systemic treatment aimed at psoriasis, including methotrexate, the anti-TNFs, and ustekinumab [46], as well as anti-IL-17s and apremilast, may help to resolve subclinical enthesitis because these agents also have licensed indications for treating clinical arthritis. In a study using methotrexate (with or without a concomitant TNF inhibitor) in patients with psoriasis or PsA, the number of entheses with inflammatory abnormalities based on ultrasound was significantly decreased with 6 months of treatment [46]. The enthesis may be useful for ultrasound screening for early or preclinical PsA, as well as a treatment target; likewise, the systemic treatment of psoriasis has the potential to prevent development of arthritic lesions [43,46].

## Superb microvascular imaging: novel Doppler ultrasound technology and its application in rheumatic diseases – **Professor Adrian Lim**

With the availability of new imaging techniques, the potential exists to diagnose PsA earlier and to better understand disease progression. Well-established imaging techniques that have been used to assess vascular flow include color/power Doppler ultrasound (PDUS) and some advanced dynamic flow ultrasound technologies. PDUS is cost-effective compared with contrast-enhanced MRI and useful for assessing inflammation in joints or tendons [47,48]. It is the current accepted gold standard to denote active inflammation in joints and tendons.

Superb microvascular imaging (SMI) is an emerging and novel ultrasound technology that allows visualization of the microvasculature without the need for ultrasound contrast. SMI uses filters and a unique algorithm to selectively detect and remove random clutter without compromising the clinical data of interest. SMI, utilizing 24 MHz power, can distinguish slower flowing vessels within the microvasculature, which may help to identify sites of active inflammation (Fig. 4). In a study directly comparing the ability of SMI to detect inflammation in tendons and joints vs. PDUS, SMI revealed vascularity that was not detected by PDUS in a significant number of cases ($P = 0.007$); in cases where vascularity was detected by both PDUS and SMI, vascularity scores were significantly greater with SMI ($P < 0.001$) [49].

Three-dimensional ultrasound imaging is also on the horizon. While the technology is available, its use requires training on how to properly manipulate the images. Images are currently of low resolution; however, algorithms are improving. Three-dimensional ultrasound has potential uses in measuring and quantifying vascularity in combination with SMI, as well as imaging cartilaginous surfaces. In addition to its potential usefulness in screening and diagnosis, future studies may include SMI to measure changes in vascularity during treatment.

## Psoriatic arthritis and immune-metabolic interactions – **Dr. Stefan Siebert**

PsA is associated with comorbid diabetes, hypertension, and cardiovascular disease, as well as hyperuricemia [50,51]. Accumulating evidence demonstrates that metabolic dysfunction underlying these comorbid conditions is a key component of the PsA disease process
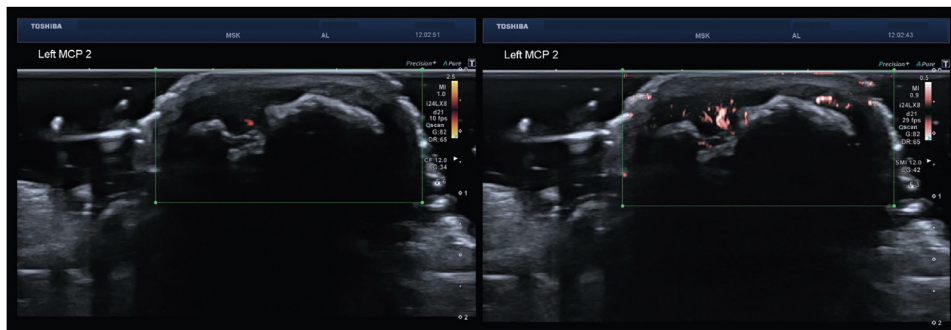


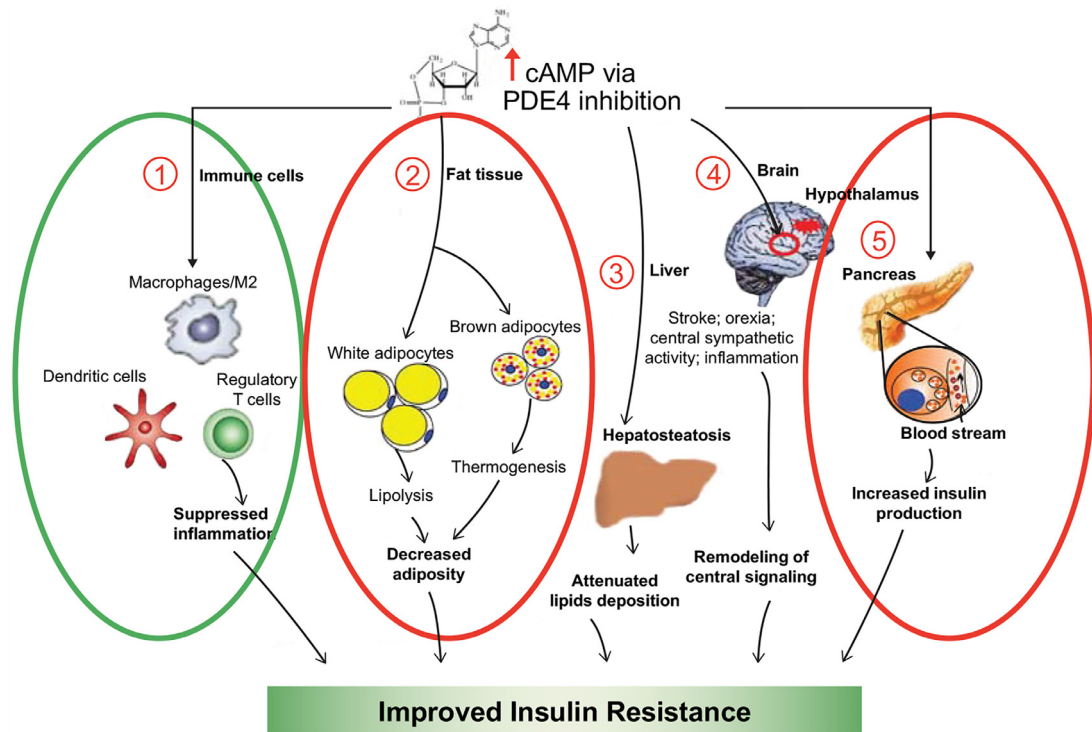**Fig. 4.** Superb microvascular imaging of the index finger in a patient with psoriatic arthritis.

**Fig. 5.** Targeting PDE4 suppresses inflammation and decreases adiposity. Reprinted with permission from Wu C and Rajagopalan S. Phosphodiesterase-4 inhibition as a therapeutic strategy for metabolic disorders. Obes Rev 2016;17:429–41 [58], © John Wiley and Sons. cAMP, cyclic adenosine monophosphate; PDE4, phosphodiesterase 4.

itself and is not fully accounted for by lifestyle factors. Patients with PsA are more likely to have metabolic syndrome, as well as a greater number of metabolic syndrome components, than patients with RA or other, non-inflammatory conditions [52−54].

PsA patients also are more likely to be obese than the general population and to have a higher body mass index than patients with RA [52,55]. Additionally, psoriasis patients who are overweight or obese are more likely to develop PsA [55,56]. Obesity may play a role in the development of PsA and may influence treatment response. The release of adipokines from fat cells can drive metabolic dysfunction as well as pro-inflammatory pathways (Fig. 5), potentially leading to increased PsA risk [57,58]. Obesity is also associated with decreasing likelihood of optimal clinical response to therapy in PsA [59,60], while weight loss is associated with increased likelihood of achieving good outcomes with TNF inhibitor therapy [61].

The metabolic component of PsA may be influenced by the treatment prescribed. One study showed that PsA and RA patients who were receiving TNF inhibitors or hydroxychloroquine were at lower risk for developing diabetes than patients who were receiving methotrexate [62]. However, certain disease-modifying anti-rheumatic drugs, including TNF inhibitors, are associated with weight gain or an increase in percentage of body fat [63,64]. Phosphodiesterase 4 inhibitors have been associated with weight loss as well as reduction in hemoglobin A1c and may decrease insulin resistance [58,65−67] (Fig. 5). The ongoing Immune Metabolic Associations in Psoriatic Arthritis (IMAPA) study in Glasgow, UK, is investigating the effects of phosphodieasterase 4 inhibition on immune-metabolic interactions in PsA using the phosphodiesterase 4 inhibitor apremilast (ClinicalTrials.gov identifier: NCT03399708).

**New insights into the genetics of psoriatic arthritis – Professor Anne Barton**

PsA is a complex disease that has environmental and strong genetic components that contribute to susceptibility [68]. Identifying PsA susceptibility genes can aid in predicting disease development,

helping to indicate suitable preventive strategies, as well as in the design of more targeted drug therapies. In a genome-wide association study, variants of the TRAF3IP2 gene were associated with PsA and psoriasis [69]. In a more recent case-control association analysis, while PsA-associated loci exhibited extensive overlap with known psoriasis-susceptibility loci, the 5q31 locus was specific to PsA [70]. Within the 5q31 locus, fine mapping analysis of single nucleotide polymorphisms revealed SLC22A5 to be a likely candidate causal gene associated with PsA, with rs715285 or rs10065787 being the possible causal variant [70]. This association is independent of the IL-13 association with psoriasis.

Another gene known to be very important in the development of psoriasis and PsA encodes the IL-23 receptor (IL-23R) [70]. However, distinctly different variants on the IL-23R gene are associated with psoriasis vs. PsA; the gene associated with psoriasis encodes a non-synonymous variant and may impact gene function, while the PsA-associated variant is located in the IL-23R promoter region and may impact gene expression, although that has yet to be experimentally confirmed (Fig. 6) [71].

Variants linked to PsA appear more often to co-localize with epigenetic markers of open chromatin in CD8 + memory T cells. Genes encoding HLA subtypes have been strongly associated with psoriasis and PsA [70]. HLA-C*0602 is strongly associated with both conditions and yet it counterintuitively has been reported to be protective for PsA compared with psoriasis [70,72]. However, after controlling for age at onset of psoriasis, HLA-C*0602 has been shown to be primarily associated with skin (psoriasis) rather than joint (PsA) disease [73]. By contrast, variants at HLA-B (amino acid position 97) are associated with PsA and AS. The specific amino acid residue at position 97 may mediate which disease develops, and individuals with an associated serine residue are at risk for PsA but not for AS; those with an associated asparagine residue are at risk for both PsA and AS [73,74].

While an extensive overlap has been seen among the genes associated with psoriasis and PsA, a distinct set of genes uniquely contribute to the risk of PsA. Ongoing work encompassing genome-wide association studies, analysis of rare gene variants, and analyses of
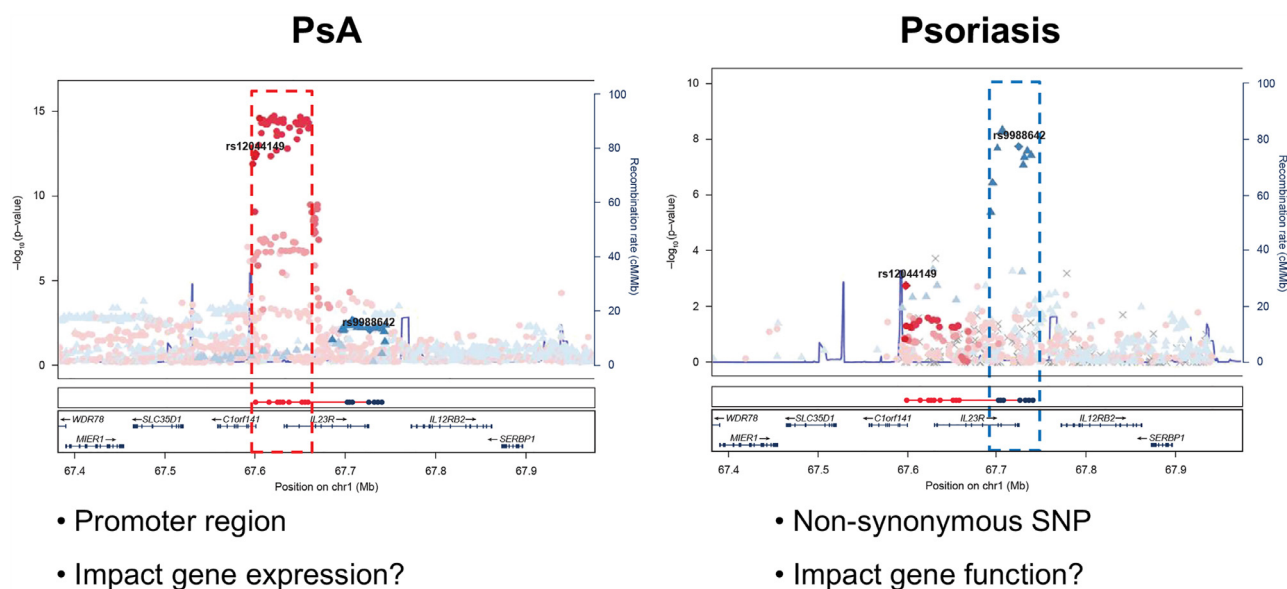
**Fig. 6.** Different IL-23R gene variants are associated with PsA vs. psoriasis [71]. PsA, psoriatic arthritis; SNP, single nucleotide polymorphism.

genes that may contribute to PsA-associated risk factors, such as nail pitting, uveitis, and severe psoriasis, are required to fully understand the genetic background to PsA.

## Arthropathies under a proteomic spotlight – Professor Stephen Pennington

The entire set of proteins expressed by an organism or an organ system may be evaluated using mass spectrometry-based proteomics [75]. In an era of increased understanding of disease complexity, such a proteomic approach forms the cornerstone of studies into the identification and measurement of panels of protein biomarkers that correlate with presence or severity of a certain condition [76,77]. Such protein biomarker panels or signatures may be used to improve disease diagnosis or treatment and to better support personalized medicine. This approach and process (using antibody-based assays) has yielded some success in the setting of RA, with approval and clinical adoption of the Vectra® DA test (Crescendo Bioscience, Inc., South San Francisco, CA, USA), which examines 12 biomarkers associated with RA disease activity [78].

For rheumatic diseases such as PsA and AS, a wide variety of treatments are available; however, only a small proportion of patients respond to any single treatment. Because rheumatic diseases are so physiologically heterogeneous, systems-driven proteomics may be a valuable approach toward predicting patient response to treatment by allowing personalized treatment decisions based on a unique profile or signature of proteins detected in a patient's tissue, synovial fluid, or blood [79−81]. Ongoing proteomic projects in PsA include examination of the pathophysiologic role of the IL-17 receptor and its adaptor protein ACT-1, biomarkers that predict response to TNF inhibitor treatment, biomarkers that predict joint damage, and biomarkers that aid PsA diagnosis [82−86].

The proteomic strategy begins with unbiased protein discovery, followed by assay development. The use of multiple reaction monitoring (MRM) mass spectrometry for multi-protein assays supports rapid assay development and analytical validation. Following clinical evaluation, the assays are then subjected to regulatory approval and adoption in the clinical setting (Fig. 7).

With regard to developing a similar test for PsA, several key questions remain unanswered. We do not fully understand the biologic mechanisms underlying bony changes that occur in PsA. Moreover, no biomarker test clearly differentiates PsA from RA, and no known predictors have been linked to response to a given treatment. To address these challenges, the ongoing Health Research Board (Ireland)-funded study (PAPRICA) aims to evaluate approximately 140 target candidate proteins considered to be involved in PsA pathophysiology using MRM assays on blood samples obtained from patients enrolled in a number of clinical studies. It is hoped that the impending findings may be calibrated to address a variety of clinical questions and issues, including differential PsA/RA diagnosis, predicting disease progression or prognosis, and predicting treatment response.

## Genetics and immunology of ankylosing spondylitis – Professor Paul Bowness

AS and the related spondyloarthritides are a group of diseases that share common genetic and clinical features, including inflammation that involves IL-23- and IL-17-driven signaling, enthesitis, and new bone formation [87]. Phenotypically, SpA and AS are considered immune-mediated inflammatory diseases, somewhere on a spectrum between autoimmune diseases and autoinflammatory diseases. AS is associated with a major hereditary component; the presence of HLA-B*27 accounts for approximately 30% of the hereditary variation, while *ERAP1, IL-23R, IL-12B*, and other genes linked to Th17 responses play lesser roles (> 100 loci have been linked to AS in large genetic analyses) [87,88].

HLA-B*27 is an MHC class 1 molecule that is present on most cells of the body. It functions by presenting peptide antigens to CD8+ T cells [87]. Each HLA-B*27 molecule carries a specific peptide antigen and is capable of initiating a corresponding immune response. The role of HLA-B*27 in AS pathogenesis is not completely understood; however, several hypotheses (i.e., arthritogenic, unfolded protein response, and free heavy chain) are being studied (Fig. 8). According to the arthritogenic hypothesis, HLA-B*27 might present "arthritogenic" peptides (e.g., from joints) to CD8 + T cells, hence triggering inflammation [87]. Alternatively, the unfolded protein response hypothesis proposes that inappropriate HLA-B*27 folding or trafficking might also occur due to malfunctioning *ERAP1*, which normally acts to trim the peptides bound to HLA-B*27 molecules and therefore facilitates cell surface egress [87]. The free heavy chain hypothesis posits that HLA-B*27 might malfunction due to the presence of an unpaired cysteine residue at position 67, which can cause it to form homodimers by pairing with another HLA-B*27 residue. HLA-B*27
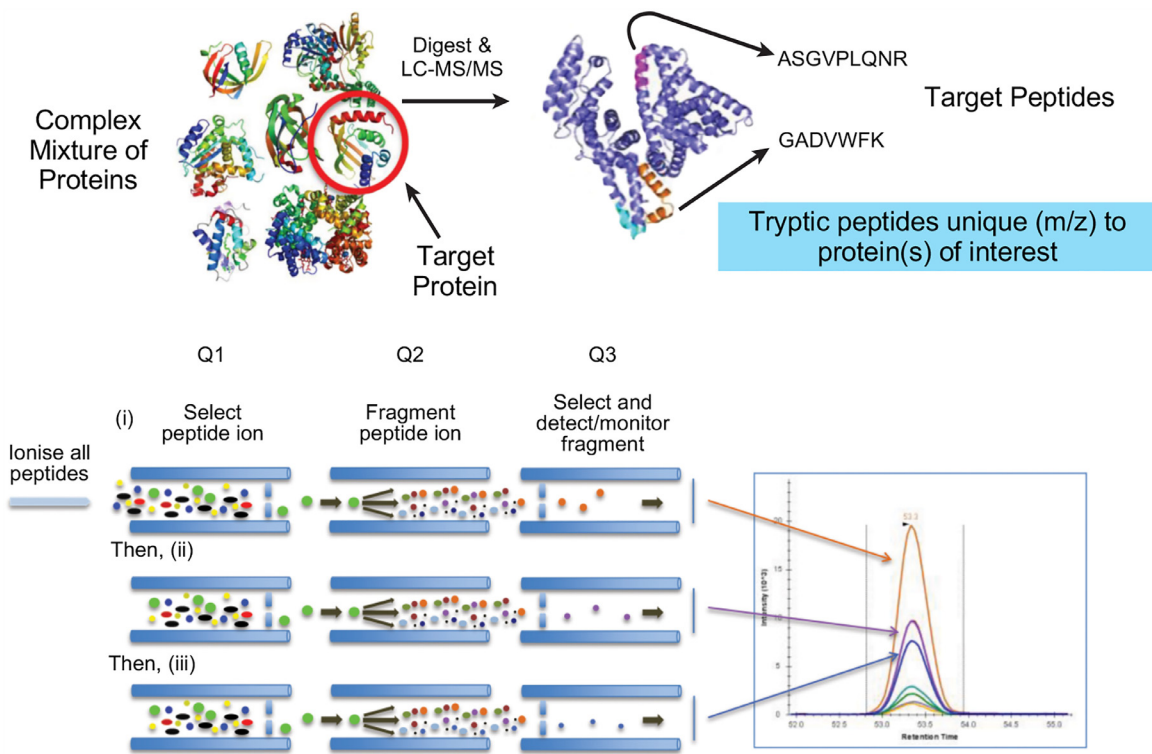
**Fig. 7.** Multiple reaction monitoring development. LC-MS/MS, liquid chromatography−mass spectrometry.

homodimers can form inside cells but also can be expressed on the cell surface, where they can then bind to several immune receptors, triggering aberrant immune responses, including Th17 responses [87]. Th17 cells in turn produce a number of ILs, including IL-17, IL-21, IL-22, and IL-23. CD4 cells, including Th17 cells that express the KIR3DL2 receptor, which can bind strongly to HLA-B*27 homodimers, are increased in patients with AS and are increased in the joints of patients with SpA [89]. Currently, immunotherapy for AS includes TNF inhibitors and biologic therapies targeting IL-17/23. Future treatments may include small molecule inhibitors that target components of the Th17 inflammatory responses, such as HLA-B*27 signaling, transcription factors, and *ERAP1*.

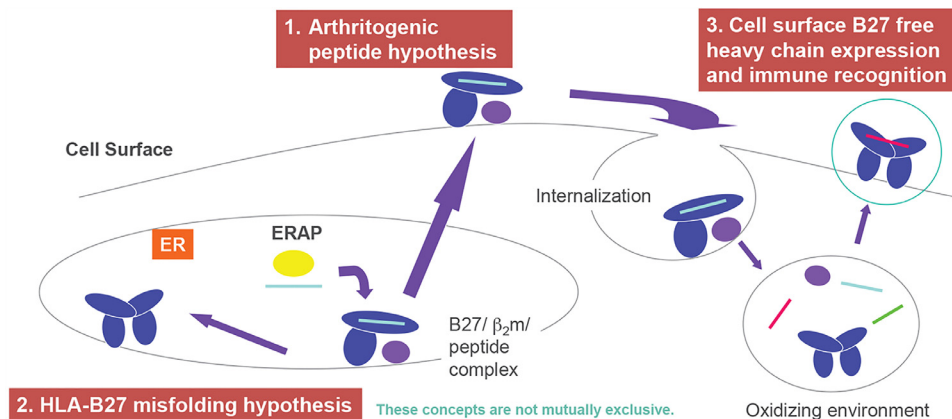**Fig. 8.** Overview of hypotheses explaining the role of HLA-B*27 in spondyloarthritis pathogenesis. HLA, human leukocyte antigen.

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