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**Chasing the Target: reports from the Advances in Targeted Therapies meeting, 2025**

Kevin L. Winthrop,[1] Andreas Kerschbaumer,[2,x] John D Isaacs,[3] Philip Mease,[4] Xenofon Baraliakos,[5] Mary K. Crow,[6] Maya Buch,[7] Stefan Siebert,[8] Neil Basu,[8] Philip Conaghan,[9] Margreet Kloppenburg,[10] Oliver Distler,[11] Robert Landewe,[12] Dana E. Orange,[13,6] Kevin Wei,[14] Daniel Aletaha,[2] Iain B McInnes,[15] Thomas Huizinga,[10] Reinhard Voll,[16] Ellen M. Gravallese,[17] Ferdinand C Breedveld,[10] and Josef S. Smolen[2]

[1]Oregon Health and Science University, Portland, OR, USA;

[2]Division of Rheumatology, Department of Medicine, Medical University of Vienna, Vienna, Austria

[3]Division of Immunology and Rheumatology, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA

[4]Translational and Clinical Research Institute, Newcastle University and Musculoskeletal Unit, Newcastle Hospitals, Newcastle upon Tyne, UK;

[5]Swedish Medical Center; University of Washington, Seattle, WA, USA;

[6]Rheumazentrum Ruhrgebiet, Ruhr University Bochum, Herne, Germany

[7]Mary Kirkland Center for Lupus Research, Hospital for Special Surgery, New York, NY, USA

[8]Centre for Musculoskeletal Research, Division of Musculoskeletal and Dermatological Sciences, The University of Manchester, Manchester, UK

[9]School of Infection and Immunity, University of Glasgow, Scotland, UK

[10]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Biomechanical Reserch Centre, Leeds, UK

[11]Department of Rheumatology, University of Leiden, Leiden, Netherlands;

[12]Department of Immunology and Rheumatology, University Hospital Zürich, Switzerland

[13]Department of Rheumatology, Amsterdam University Medical Center, The Netherlands

[14]Rockefeller University, New York, NY, USA

[15]Division of Rheumatology, Inflammation, and Immunity, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

[16] MVLS College Office, University of Glasgow, Glasgow, UK and School of Infection, and Immunity, University of Glasgow, Glasgow, UK

[17]Department of Rheumatology and Clinical Immunology, University of Freiburg, Freiburg, Germany;

[18]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Corresponding author: Kevin L Winthrop M.D., M.P.H., OHSU, School of Public Health, 3181 SW Sam Jackson Park Rd, Mail Code GH104, Portland, OR 97239; +1 (503) 494-5496 phone, +1 (503) 346-8277 (fax), e-mail: Winthrop@ohsu.edu.

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## Abstract

### Background

The Advances in Targeted Therapies annual meeting brings together immunology and rheumatology experts, from basic scientists to clinicians, to discuss and debate scientific updates and unmet needs within the field.

### Objectives

This article simed to articulate the most important unmet scientific needs in rheumatology.

### Methods

At the 25th Advances in Targeted Therapies (ATT) meeting, over 100 investigators joined disease-focused breakout groupsrheumatoid arthritis (RA), psoriatic arthritis (PsA), axial

spondyloarthritis (axSpA), systemic lupus erythematosus (SLE), Systemic Sclerosis (SSc), and osteoarthritis (OA). Each group, led by a facilitator and rapporteur, mapped (i) key unmet needs, (ii) promising mechanistic or therapeutic approaches, and (iii) near-term priorities for research and trials. This report synthesises the consensus highlights

**Results**

Six disease-focused groups(RA, PsA, axSpA, SLE, SSc, and OA)identified convergentpriorities: earlier detection and interception; validated molecular and clinical endotypes to guide therapy; strategies for immune reset and short-course induction combinations with strict safety oversight; metabolic modifiers; precision targets in axSpA and fibroblast-directed approaches in RA; phenotype-driven therapeutic development and intra-articular options in OA;and pragmatic trial designs that include pregnant persons and very early disease

**Conclusions**

Across immune-mediated diseases, progress will hinge on validated endotypes, practical interception strategies, and trials that reflect real-worldpopulations.The immediate agenda is to de-risk immune reset and induction approaches, standardise tissue and digital bio- markers, and close evidence gaps for refractory disease. Prevention—and ultimatelycure— remains the horizon.

## Background

The Advances in Targeted Therapies meeting (ATT) has met annually for 25 years, typically in Europe. The gathering convenses leaders in many aspects of auto-immune inflammatory diseases including rheumatologists/immunologists, infectologists, public health experts and epidemiologists, as well as clinical scientists from different fields of medicine. For 3.5 days, these experts deliver scientific talks with udpates in their respective areas of expertise, discuss potential scientific collaborations, as well as debate and prioritize the unmet research needs in the field.[1]

## Methods

On day 2 of the meeting, we divided conference participants into break-out groups according to their areas of expertise and interest. Attendees from Europe, North America, and Asia particapted. The disease specific interests groups were similar to previous years: Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), axial Spondyloarthritis (axSpA), Systemic Lupus Erythematous (SLE), Systemic Sclerosis (SSc), and osteoarthritis (OA). A facilitator lead each groups, and a rapporteur recorded the guided discussion within the areas of translational science, clinical care, and therapeutic development. Thisgroup-specific record served as the basis for each section within the current manuscript, with both facilitator and rapporteur together developing a section-specific draf for the manuscript.We asked the facilitator to guide its group in discussion regarding current unmet needs within these clinical areas. While rapporteurs captured this dialogue, the highlighted unmet needs described herein are only a selection of those discussed.

## Results

### Rheumatoid Arthritis

*Defining and Characterizing Refractory RA*

Refractory RA was highlighted by the group as a major unmet need. [2] Difficult-to-treat RA (D2T RA) is multifactorial: while many RA patients have complicating factors (e.g. comorbid chronic pain, fibromyalgia, depression) that amplify symptom burden, others exhibit persistently active synovitis driven by ongoing inflammation despite immunosuppressive therapies targeting distinct pathways and cell types. The distinction between non-inflammatory drivers versus truly refractory immune-mediated disease was felt to be one of the most critical aspects by the group.

At the same time, there is a recognized need for predictive biomarkers and stratification tools to predict which patients will become refractory and to guide personalized management for this challenging subgroup. In summary, the panel emphasized refining the definition and early identification of refractory RA, acknowledging it as a heterogeneous entity requiring both multidisciplinary management and novel therapeutic strategies.[3]

*Identifying biomarkers of refractory RA*

The timing of interventions in RA emerged as a pivotal theme. Delays in achieving disease control might predispose to develop difficult-to-treat disease. Notably, a recent multicenter study demonstrated that failure to start methotrexate within 3 months of diagnosis and prolonged corticosteroid use beyond 6 months were early predictors of later D2T RA,[4] in line with findings of a very long lag period until DMARD-start in patients with refractory RA.(REF) These findings reinforce the "window of opportunity" concept – early, aggressive treatment can prevent the establishment of refractory disease.[5] Beyond early therapy, understanding the temporal evolution of RA at the molecular level is a growing focus. Advanced profiling techniques, including serial synovial biopsies, single-cell RNA sequencing, and spatial transcriptomics, are being applied to characterize RA disease heterogeneity over time. Such studies reveal significant cellular and molecular heterogeneity in the synovial tissue: distinct cellular communities (spanning multiple immune cell subsets and stromal cells) dominate at different disease stages.[6] These distinct RA Cell Type Abundance Phenotypes, or CTAPs, represent a strategy for personalized therapy.[7] For example, molecular signals preceding a flare might prompt preemptive treatment adjustments. The group highlighted that integrating longitudinal molecular profiling data with clinical decision-making could enable truly adaptive, precision treatment in RA, adjusting therapy not just to current disease activity, but also where the patient is coming

from to where the patient is headed on the disease timeline.[8] Ongoing initiatives were noted, including prospective studies following individuals from pre-clinical autoimmunity through disease progression, but also consortia focusing on identifying tissue and blood biomarkers to predict response to future therapies in D2T patients, which will be crucial to validate biomarkers and novel targets for early intervention.

Further challenges arise in the context of molecular remission. For example, which joint should be biopsied if none are symptomatic? While there is great enthusiasm for molecular phenotyping of patients using synovial biopsy, this assessment remains difficult to integrate into routine care due to concerns about indemnification, training, infrastructure, and the immediate actionability of results. Recent advances in deep molecular profiling of formalin-fixed, paraffin-embedded (FFPE) tissue sections enable studies using historical samples, which could be informative.[9] A sufficiently large number of high-quality FFPE biopsies could facilitate Machine learning (ML)/ artificial intelligence (AI) -driven stratification approaches.[10]

The introduction of whole-body imaging approaches, such as multiplex PET tracers, could help address this biopsy question and revolutionize trial outcome measures.[11] These techniques, evolving in oncology, could be adapted to assess inflammation across all joints by labeling targets such as complement, fibroblast activation protein (FAP), or other immunoinflammatory markers. Molecular study data could also inform the development of novel PET tracers for joint imaging.

ML and AI continue to develop rapidly,[12] with the ability to detect complex, non-linear patterns in large datasets that may exceed human analytical capabilities. In addition to direct clinical, biological, and genetic data, routinely collected ‘metadata’, such as demographics, blood counts,

and biochemical tests—may contain valuable, underutilized insights. A significant challenge remains the need for high-quality, expertly curated datasets. If pharmaceutical and biotech companies agreed to pool data—such as from placebo arms of clinical trials—this could yield powerful results. Similar data-sharing models have been implemented previously, though not specifically in the context of AI.[13] Such datasets could be useful diagnostically, prognostically, or even theragnostically.

*Fibroblast-Targeted Strategies*

There is growing interest in therapies directed at the synovial stroma, particularly synovial fibroblasts, which are central drivers of chronic inflammation and joint damage in RA.[14] To date, no fibroblast-specific treatment has been approved and current DMARDs primarily target immune cells, cytokines or cytokine-activated signal transduction pathways. The group discussed how this represents a major unmet need, especially given evidence that many refractory cases often have a fibroblast-dominated synovial tissue pathotype. Patients who experience an insufficient response to multiple biologics can exhibit a "pauci-immune" synovial phenotype, with few infiltrating lymphocytes but an abundance of activated fibroblasts. This points to pathogenic fibroblasts as key perpetuators of disease in these cases. Recent single-cell and spatial transcriptomic studies have delineated discrete synovial fibroblast subsets in RA joints (e.g., pro-inflammatory $THY1^+$ sublining fibroblasts versus tissue-destructive lining fibroblasts), providing specific targets for intervention.[15] Strategies to target fibroblasts were in focus of the discussions. One approach is to selectively deplete or modify pathogenic fibroblasts by exploiting unique surface markers – for example, fibroblast activation protein (FAP) is being investigated as a target for imaging and directed therapies in RA synovium. Another strategy is to block critical fibroblast signaling pathways (such as cadherin-11 or Notch3, implicated in fibroblast activation

and joint invasion). The group underscored that intervening at the stromal level, particularly early in disease, could disrupt the feed-forward loop of inflammation and damage.[16] Unlike broad immunosuppression, targeting fibroblasts might quell local joint pathology with fewer systemic effects, though specificity is a challenge since fibroblasts are ubiquitous in tissues. Ongoing preclinical work and early-phase trials (e.g., of FAP-targeted agents or inhibitors of fibroblast survival pathways) were noted. Overall, there was optimism that fibroblast-targeted therapies will complement immune-directed therapies, especially for patients in whom immune cell–targeted drugs have proven insufficient.[17]

*Immune Reset and Combination Approaches*

For patients with refractory RA, the session explored more intensive therapeutic paradigms, including combination therapies and immune system "reset" strategies. The concept of combination therapy involves hitting multiple inflammatory pathways concurrently to overcome redundancy. In practice, combining biologic DMARDs is rare due to infection risk, but emerging case reports suggest it can be effective in selected cases. The group noted that, moving forward, clinical trials could explore short-term combination induction therapy in refractory RA, with tight safety monitoring. In parallel, an even more ambitious approach is an "immune reset" – "rebooting" the patient's immune system to a tolerant state. Autologous hematopoietic stem cell transplantation (AHSCT) was an early example, aiming to eradicate autoreactive immune cells and reconstitute a new immune repertoire. While AHSCT achieved drug-free remission in some RA patients, its use has been limited by procedural risks and toxicity.[18] A modern twist on immune resetting is emerging from the field of cell therapy: notably, chimeric antigen receptor (CAR) T-cell therapy. In 2022, a landmark study demonstrated that a one-time infusion of anti-CD19 CAR T cells (to ablate B cells) induced prolonged drug-free remission in a case series of

patients with severe refractory SLE.[19] Treated individuals showed resolution of disease activity and re-emergence of naïve B cells months later, essentially achieving an autoimmune "reset". This striking result was discussed as proof-of-concept that resetting immunity is feasible in autoimmunity. For RA, which shares pathogenic B cell involvement (especially in seropositive RA), similar strategies could be transformative, with only few cases being reported until now.[20] The prospect of CAR T-cell therapy (or CAR-modified regulatory T cells) or Bispecific T-cell Engagers (BITEs) in RA was raised, alongside antigen-specific tolerizing therapies (such as peptide vaccines to induce immune tolerance to citrullinated proteins). These approaches remain experimental, but they illustrate the paradigm of aiming for sustained remission or cure in refractory RA by deep immune intervention. The experts cautioned that such approaches carry significant risks and will require careful clinical evaluation. Nonetheless, the success in lupus has galvanized interest in exploring whether difficult-to-treat RA might be overcome by therapies that reboot or retrain the immune system rather than continually suppressing it.

Advances in molecular technologies, imaging, and data science are opening new avenues for personalized management and trial design in RA. However, integration into clinical practice remains limited by workforce constraints, data interpretation challenges, and infrastructure needs. Collaborative efforts, including data sharing and investment in scalable tools, will be essential to fully realize the promise of precision rheumatology.

**Psoriatic Arthritis**

Now that we are 25 years into the use of bDMARDs and tsDMARDs in the treatment of the complex, multi-clinical domain condition PsA, we are encountering an increasing number of

patients who have “tried everything” but still have evidence of active disease and/or troublesome symptoms. This is a phenomenon common across immune mediated inflammatory disease conditions. Many of these patients have had serial treatments, often for years, with advanced immunomodulatory drugs with different mechanisms of action (MOAs): tumor necrosis factor alpha inhibitors (TNFi), interleukin (IL)-17Ai, IL-17A/Fi, IL-12/23i, IL-23i, phosphodiesterase 4 inhibitor (PDE)-4i, janus kinase inhibitors (JAKi) and abatacept targeting CD80/CD86. Some have been cycling through these drugs since they first became available and are now at a juncture where they have tried at least one or more drugs from each MOA. Working groups to create a consensus-based definition of “Difficult to Treat” (D2T) and “Complex to Manage” (C2M) PsA are near completion of criteria development,[21-24] similar to the work that has been done RA[2] and axSpA.[25,26] The RA group has a unitary definition of D2T, requiring inadequate response or intolerance of several drugs along with objective evidence of ongoing active joint disease. The PsA and axSpA groups have adopted a slightly different approach.[21-26] D2T or “Treatment Refractory” is applied to a patient who has had adequate trials and subsequent inadequate response or intolerance to several MOAs and has active inflammation/progressive damage in relevant domains including arthritis, enthesitis, dactylitis, spondylitis, skin and/or nail disease, objectively verified by physical exam, imaging, and/or laboratory variables. For this patient, switching medicines or trying dual therapy with more than one immunomodulatory drug may be warranted. Studies of several large cohorts of patients with established PsA and axSpA have shown that between 10 and 30% of patients fall into this category and in PsA have shown that factors such as presence of spinal disease, skin disease, and obesity increase the risk for this state.[27-30] It is these criteria that can be used by clinical trial designers for the inclusion criteria for dual or novel therapy trials, by regulatory agencies to understand the unmet need for

therapies with new MOAs and dual therapy trials, and by payors to appreciate the need for more complex and costly therapy for this group of patients. C2M PsA and axSpA criteria subsume all patients in the D2T category, but also include patients who demonstrate apparent moderate to high disease activity as measured by composite measures that include subjective elements such as pain, joint tenderness, patient global, and physical function despite lack of evidence of inflammation or progressive structural damage. For example, a patient with concomitant fibromyalgia or osteoarthritis may have residual pain in the absence of active PsA. Other contributing factors may be comorbidities such as obesity, cardiovascular disease, diabetes, or depression. However, as already stated in the treat-to-target recommendations almost a decade ago, “The choice of the target and of the disease activity measure should take comorbidities, patient factors and drug-related risks into account”; in other words, if certain comorbidities exist, the rheumatologist needs to think about which measure is appropriate to determine disease activity and which one is needed to look at the comorbid condition. One confounder is the inclusion of physical function into disease activity instruments, since physical function will become irreversible in long standing disease due to joint damage and, therefore, determination of clinical remission using such scoring may be blunted by virtue of an erratic instrument. Identification of these confounding factors and adherence to pertinent recommendations is important to avoid unnecessary switching of immunomodulatory medicines. Also somewhat different, in poor access to care and other socioeconomic and sociocultural aspects also have to be taken into account.REF For D2T criteria, it is clear that the development of new drugs with different MOA, such as TYK2 or TL1A inhibitors and clinical trials of dual therapy are needed. In addition to trials, collecting information about dual therapy from large observational registries can be done using these standardized criteria. If confounding factors lead to C2M state, other

strategies beyond immunomodulatory therapies need to be considered and tested. For example, for concomitant nociplastic pain, improved and practical methods to identify this pain mechanism, which may respond to neuromodulatory and other modes of therapy, are needed. Addressing obesity with diet and exercise, and possibly weight loss drugs (trials ongoing), will likely be beneficial for C2M PsA outcomes in this group.

Current trials of therapies for PsA now almost completely address the multi-domain nature of the disease, with single and composite measures addressing arthritis, enthesitis, dactylitis, skin and nail disease, pain, fatigue, physical function, mental health, and quality of life.[31] However, not all clinical manifestations of psoriatic disease may respond well to the same therapeutic principle, as is also the case in SLE and systemic sclerosis (see below). Thus, response of arthritis should be in the forefront of the rheumatologists' strives to improve outcomes in PsA. The spondylitis aspect of PsA, axial PsA (axPsA), is not reliably or accurately assessed in most clinical trials, although we are now beginning to see studies devoted specifically to axPsA.[32,33] Several potentially confounding issues which may influence PsA treatment outcomes have been identified, including sex,[34] weight,[30] concomitant nociplastic pain,[35] and depression.[36] Additionally, it is now being recognized that background use of weight loss medications, such as GLP-1 receptor agonists, and neuromodulatory medicines, may influence treatment outcomes and potentially should be considered in stratification and other strategies to mitigate the effect of these potential confounding factors on treatment outcomes.

Accurate diagnosis of axPsA remains a problem. The AXIS study, a collaborative research project between GRAPPA and ASAS, has completed enrollment and preliminary analysis. Pending is development of axPsA classification criteria from the study. In over 400 PsA patients, after careful evaluation by investigators, and then re-evaluation after central imaging reading,

27% were considered to have axPsA.[37,38] There are genetic, clinical, and imaging features that are different in axPsA than axSpA.[39] Thus, evidence for therapeutic effectiveness of drugs trialed in axSpA may not be equally applicable for axPsA. We encourage more specific axPsA trials such as MAXIMISE and STAR,[32,33] incorporating new classification criteria, to more reliably determine effectiveness of different drugs/mechanisms in this clinical domain of PsA.

The question as to whether the transition from psoriasis alone to the appearance of concomitant PsA can be "intercepted", i.e. prevented or diminished in severity, remains open. In particular, the question as to whether achievement of remission or low disease activity in psoriasis, by one or more therapeutic mechanisms, can prevent the appearance of PsA is being actively pursued. There have been mixed results in observational studies regarding aggressive psoriasis treatment in preventing PsA.[40,41] An example of a prospective trial to more reliably address this question, using an IL-23 inhibitor, the PAMPA trial, is underway.[42]

We expect expanding use of digitally acquired data, such as weekly or daily patient reported measures, as well as inputs about function and motion from wearable devices, in order to provide more granular assessment in clinical trials.[43] This may also be used more commonly in clinical practice, along with support from artificial intelligence, in tracking and documenting patient health longitudinally, including between scheduled clinic appointments.

Global projections indicate there will be too few rheumatologists to face the need for rheumatology care in years to come.[44] One approach to addressing this gap is an increase in number, especially in the US, of "advanced practice practitioners" – nurse practitioners and physician assistants – who have consultative and prescriptive authority.[44,45] There needs to be increased effort toward education, and increased acceptance as in other countries, of this echelon of rheumatology clinicians to support service delivery. An alternative may be to make becoming

a rheumatologist more attractive by including more elaborate techniques for optimal patient care into the curriculum.

**Advanced Therapeutic Strategies in Axial Spondyloarthritis**

AxSpA is a chronic inflammatory disease primarily affecting the sacroiliac joints and the spine. On top of non-steroidal anti-inflammatory drugs, biological therapies such as TNFi and IL-17i, have provided relief for many patients. Recent research has unveiled novel targets that potentially promise alternative, more precise and effective interventions.

One of the most novel targets is the T-cell receptor (TCR) repertoire. A Russian study identified antibodies against TCRVβ5 as potential modulators of the immune response in axSpA.[46] These antibodies supposedly selectively influence specific T-cell subsets, that would offer a more targeted approach to treatment. In line with this, a recently reported Phase 2 clinical trial, published in 2024 in Russian language only, highlighted the possible role of TCRVβ9 in the pathogenesis of axSpA.[47] A confirmatory Phase 3 randomized control trial (RCT) is currently awaited.

Because of the relation between the major histocompatibility complex class I molecule HLA-B27 and axSpA, autoreactive B27-restricted CD8+ T-cell clones have been a focus of interest in axSpA-research for decades. A 2022 paper by Yang et al demonstrated in vitro the existence of these T-cells with restricted TCR repertoire and identified candidate peptides (bacterial) that could be drivers of the inflammatory processes characteristic of the disease.[48] Their research

suggests that targeting CD8+ T-cells could mitigate inflammation and prevent disease progression. However, in recent review paper it was noted that these B27-restricted CD8+ T-cell clones account for only a small part of the entire population supposedly deleted by the above mentioned antibodies, and a lot of experimental work has to  done to better understand the role of such restricted CCD8+clones in driving inflammation in axSpA.[49]

Beyond cellular targets, the gut microbiome may play a crucial role in axSpA. Research suggests that gut dysbiosis—an imbalance in the gut microbial community—is associated with increased disease activity and impaired physical function in axSpA patients.[50-52] Studies have found that patients with axSpA exhibit a higher frequency of gut dysbiosis, as compared to healthy controls, with interesting correlations to disease activity measures, such as the Ankylosing Spondylitis Disease Activity Score (ASDAS), and measures of physical function, such as the Bath Ankylosing Spondylitis Functional Index (BASFI).  These findings underscore the importance of the gut-joint axis in the pathogenesis of axSpA and open up new therapeutic possibilities.

Obviously, genetic factors contribute to the development of axSpA. The HLA-B27 gene is a well-established risk factor, and its interaction with endoplasmic reticulum aminopeptidase 1 (ERAP1) has been shown to influence disease susceptibility and severity.[53-55] ERAP1 plays a pivotal role in processing peptides for presentation by MHC class I molecules. The contribution of certain ERAP-1 polymorphisms in affecting the peptide repertoire presented by HLA-B27 is under debate.[56] This interaction may lead to the activation of autoreactive T-cells, initiating inflammatory processes in the axial and peripheral joints. Understanding these genetic interactions may open the door to more personalized medicine approaches in axSpA treatment.

In conclusion, the evolving landscape of axSpA therapy emphasizes precision medicine, targeting specific immune pathways and genetic factors. Advancements in understanding the roles of TCRVβ5, TCRVβ9, CD8+ T-cells, gut microbiota, and HLA-B27-ERAP1 interactions offer promising avenues for developing more effective and individualized treatments. As research progresses, these insights may lead to novel therapeutic strategies that may further improve patient outcomes in axSpA.

**Systemic Lupus Erythematosus**

This year's SLE related discussions adopted a more optimistic approach. After a brief discussion around the potential for immune-reset therapy (i.e. CAR-T), the group choose to consider the recent successes in the field and then reflected upon the ingredients which subserved them with the goal of motivating even greater future advances.

The shift, several years ago, of translational science towards specific SLE target discovery rather than perpetual repurposing of therapeutic agents from RA has been a major contributor to the relatively rapid growth of successful therapeutic development programs.[57,58] Patients are only now beginning to reap the rewards of this reorientation. The investigator community now needs to devote similar energy to molecular endotyping and ultimately personalized medicine.[59,60]

Another parallel factor in recent successes has been productive modifications to trial design, especially in relation to the minimization of background glucocorticoids within protocols.[61] It is hoped that the community will now feel more confident to take the next step and aspire to support tapering protocols which aim for the complete elimination of glucocorticoids. Similarly, as familiarity grows with novel interventions and their safety profiles, it is hoped that deeper and

more potent modulation of their underlying targets will be embraced with a view to enhancing efficacy, and possibly even immune reset.

It is equally important not to overlook established therapies. Mycophenolate Mofetil (MMF), for example, has been an undoubted success for many and yet we still do not fully understand its molecular mechanism of action. It was recommended that studies defining the transcriptional profiles modulated by MMF in relation to clinical response could provide critical new insights into disease mechanisms and perhaps identify new therapeutic targets.[62] By harnessing such knowledge, we may derive superior drugs. However, one always has to keep in mind that concomitant glucocorticoid therapy (at different doses potentially different), let alone other treatment modalities may confound the results and, therefore, "clean" populations should be sought for these analyses. These may also be broad in their mechanisms and ultimately inform a combinatorial targeted approach.

Regardless of the therapy, new or old, there is a consistent disconnect between patient and physician perception of what treatment success looks like. Specifically, the patient priorities of fatigue and cognitive fog are poorly managed with existing tools, often fueling poor compliance.[63] This dimension is considered a major unmet need, and more work to understand underlying neuroimmune mechanisms may ultimately lead to new solutions which could complement existing treatment strategies.

Engagement of the rheumatology and dermatology investigator communities with regulatory authorities, along with contributions from voluntary organizations and patients, has shown progress in recognizing the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) as an outcome measure for clinical trials.[64] A similar advancement regarding measures important to SLE patients, such as fatigue, could be similarly transformational.

Last but not least, heightened prioritization of SLE among several industry partners has contributed greatly to the growing SLE armamentarium. Current areas in need of further progress are precision medicine biomarker discovery, pediatric trials, and inclusion of pregnant subjects and those with early disease.[65-67] These can be very feasibly addressed if the patient, physician, academic and industry communities continue to agilely grow their existing partnerships with the shared goal of transforming SLE outcomes.

**Systemic Sclerosis**

This year's discussion focused on key requirements to advance therapeutics of SSc and the discussions included two associated treatment paradigms.

Align trials to predominant major organ involvement: As with other RMDs, a particular challenge in the management of SSc is its multiple manifestations and the heterogeneity across patient populations. This has implications on the design of trials. A point of discussion was whether the aim of treatment intervention trials should be to target all (possible) or specific major organ involvement. Heterogeneous temporal associations make it challenging to address totality of organ involvement. Much progress has been made in the treatment landscape for SSc-PAH and more recently, SSc-ILD. Consensus amongst the group was therefore to align trials to predominant major organ involvement, meaning SSc-ILD remains a principal focus of trials, but these should ensure other organ complications are captured in (key) secondary endpoints. This allows study of more homogeneous patient cohorts, to use FDA- approved endpoints (FVC) and known pathways to approval of medications by agencies. Following this concept, SSc disease

modifying medications would then need to show clinically significant effects on several organ endpoints. Combined indices like revised CRISS were also discussed. It was noted that revised CRISS needs enrichment criteria other than for example, ILD enriched cohorts. Combined indices are promising but need definition of minimally clinically important difference. Performance might depend on the recruited population in each specific clinical trial. Revised CRISS is currently used in clinical trials which will allow further validation.

Target the pre-damage disease stage: The second paradigm discussed was stage of disease. Most clinical trials focus on early diffuse cutaneous SSc (typically, less than 5 to 7 years from the onset of the first non-Raynaud symptom of SSc)[68] to address the SSc subgroup and stage associated with greatest risk for major organ involvement. Nevertheless, an over-riding feeling was the need to target disease at the earliest stages and not only focus once damage/fibrosis is established (e.g. we don't wait for erosions in RA but have a disease activity score to identify active inflammation). To do this, we need to understand how to identify relevant (future diffuse) disease early as VEDOSS criteria do not enable this. Similarly, pre-stage SSc-ILD needs further study and identification of risk factors.[69]

Recognize organ involvement and impact with longer disease duration: The group this year also highlighted the importance of not dismissing longer disease duration, especially, with data demonstrating variable disease course and later onset ILD[70] and cardiac involvement.[69]

Refine the target of treatment to reflect disease activity: The group agreed that optimal disease activity scores need to be developed to address the ability of therapies to abrogate disease activity and progression. Current activity scores often define activity as a progression in recent damage. This assumes that recent activity places patients at higher risk of ongoing activity, which is not the case in SSc.[71]

The clinical trial priorities identified and associated unmet needs were:

(i) Very early, pre damage SSc: this also means we need to know how to identify this stage of disease (defining disease activity in the absence of fibrosis that the VEDOSS criteria do not enable and similar for pre-stage SSc-ILD) and to recognise the sweet spot when considering risk vs benefit of targeted therapeutics.

(ii) Sequencing of therapies: how and when to use predominant immune and fibrosis targeted agents was picked up from 2023 meeting discussions and remains unaddressed. Arguably, this may be relevant in mitigating development of a refractory population. It was noted that differentiating therapies as immune or fibrosis-targeting might no longer be adequate as these targets overlap, such as with emergent therapies like nerandomilast.

(iii) Post MMF, RTX and/or TCZ inefficacy: The group also raised the treatment gap for individuals whose disease progresses despite currently available therapeutics. This population is perhaps akin to the 'difficult to treat' populations that have emerged in RA and PsA although a tailored definition is warranted for SSc.

The above priorities were set against continued support of trials in limited cutaneous disease where there is ongoing research activity by the international community. The group emphasised that designing such trials is contingent on understanding the right trial populations and developing companion diagnostics to support a precision medicine approach. The group also acknowledged the increasing challenges in recruitment to trials now that treatments for SSc are available.

In addition to the disease stages targeted for clinical trials, the group supported development of treatments for specific manifestations of SSc with a high unmet need. SSc is associated with the

greatest risk of cardiovascular involvement across the autoimmune diseases.[72] SSc-primary heart involvement has benefitted from recent consensus definitions and management strategies but gaps in understanding of mechanisms, natural history and a lack of validated endpoints outside of MACE limit the ability to develop specific therapeutic strategies and trials. As included in the 2023 discussion, other manifestations were discussed that associate with poor quality of life - calcinosis, gastrointestinal involvement (upper and lower GI) and musculoskeletal involvement (including contractures). Discussion focussed again on the need to appreciate the underlying mechanisms and gain a better understanding of prevalence and natural history before dedicated trials can be considered. The challenge in feasibility of trials for such manifestations was also highlighted with prevalence of for example calcinosis, approximately 5%, contrasting with ILD (50%). Also needed are better tools for assessment, such as joint involvement and disease activity, as simply borrowing from diseases such as RA, is not appropriate. Here, data show DAS28/similar activity measures employed in RA are likely inadequate as will be influenced by SSc skin involvement. Furthermore, the assumption that RA targeted therapies would be effective similarly in joint involvement of other RMDs including SSc is not implicit, with notably, sc-RNA sequencing studies in SSc suggesting synovial pathology is remarkably different from RA. An additional area highlighted was sexual/erectile dysfunction that receives little to no attention. Peripheral vasculopathy/Raynaud's Phenomenon, although almost universally present in SSc and managed with vasodilators (CCB and PDE5i) remains sub optimally treated and associated with poor quality of life. Optimal strategies for using current therapies and development of novel treatments are needed.

**Osteoarthritis**

Treatment options for osteoarthritis (OA) remain very limited, so unmet therapeutic need is very high for this massive global problem. Because of lack of success in clinical trials for a range of therapies, there has been increasing focus on better defining phenotypes, or more appropriately, the underpinning molecular endotypes, that might enable enrichment at trial inclusion.[73,74]

Current phenotypes employed in clinical trials have been very broad. Modern studies commonly use a 'pain phenotype' in that they enroll for sustained moderate to severe pain at baseline in the target joint and usually exclude widespread pain. Such inclusions have been based on historic factors that influence the responsiveness of pain outcomes, rather than targeting, for example, people with a specific type of pain, such as peripheral nociceptive pain. Also, methodological issues such as regression to the mean may influence pain measurement. A recent study applied 2 pain inclusion criteria, based on both WOMAC pain and average daily pain from a pre-trial run-in period, as well as standard exclusions for widespread pain, and still reported substantial placebo responses.[75] Despite the limitations of current inclusion criteria, preliminary reports from this Phase 2 RCT of a novel neurotrophin-3 inhibitor, demonstrated analgesic efficacy compared with placebo at all 3 doses tested. Joint safety events were seen infrequently with previous neurotrophin inhibitors (anti-nerve growth factor therapies) but at least in the follow up to 30 weeks after 16 weeks of treatment, there was no increased incidence of joint safety events (including rapidly progressive OA) compared with placebo.[75] Larger trials with longer follow up will now be required.

An 'inflammatory phenotype,' using MRI-determined synovitis, was included in a recent RCT of methotrexate in hand OA.[76] At a dose of 20mg weekly, this study demonstrated clinically meaningful analgesic response at 6 months, though with limited benefits on function. Another study of methotrexate (aiming for 25mg weekly) in knee OA, also demonstrated meaningful

reduction in NRS pain at 6 months.[77] Synovitis was not an inclusion in the latter trial, but MTX did not demonstrate reduction in synovitis. Instead, better analgesic responses were seen in patients with elevated highly sensitive CRP (hsCRP), suggesting a systemic anti-inflammatory benefit on knee pain. Clinical trials like this, that incorporate some exploration of mechanism of action, are essential for better phenotype or endotype delineation.

Methotrexate has broad anti-inflammatory and anti-cytokine actions. Targeting a single cytokine, interleukin-1, has not been considered effective in previous OA clinical trials.[78] However, an analysis from a large RCT of cardiovascular patients treated with anti-IL1 demonstrated a substantial benefit from active therapy in reducing rates of joint replacement.[79] The patients in this study had high rates of diabetes and obesity with elevated hsCRP and were treated for over 3.5 years. Another cardiovascular RCT with large patient numbers compared low dose colchicine for over 2 years versus placebo and similarly showed a substantial reduction in joint replacement for the colchicine-treated arm.[80] Colchicine works by inhibiting the inflammasome and IL-1, but again previous OA trials had not shown analgesic benefit. These studies may be giving insights into an inflammatory phenotype and/or a metabolic phenotype.

Targeting IL-1 has also been the focus of novel intra-articular gene therapies, a new direction for OA therapeutics. Two such therapies aiming to provide increased expression of IL-1 receptor antagonist have recently reported preliminary phase 1 results, demonstrating acceptable safety and some evidence to support proof of principle.[81,82] Steroid pretreatment will likely be required with these therapies to improve tolerability but also vector transduction.

Obesity is a common component of metabolic syndrome. Weight loss has previously been reported to reduce OA pain, but the advent of novel weight loss therapies offers opportunity to capitalize on their significant weight loss benefits, both systemically and at joint level. Bliddal

and colleagues recently reported the results of a large RCT of the GLP-1 receptor agonist semaglutide in a large knee OA trial, where 75.4% of participants had BMI ≥ 35kg/m$^2$.[83] They demonstrated substantial weight loss and clinically meaningful reduction in pain over 68 weeks.

Another agent with effects on weight, glucose production and insulin resistance is metformin, which has also demonstrated anti-inflammatory effects. A recent RCT in knee OA randomised 107 non-diabetic overweight or obese patients to metformin or placebo and demonstrated a meaningful reduction in pain compared to placebo after 6 months of therapy.[84] Such trials indicate that targeting a 'metabolic phenotype' with weight loss and likely systemic anti-inflammatory effects, will be an interesting future direction for OA management. However, more knowledge on the impact of these drugs on OA structural pathology and pain is awaited, as well as understanding of potential side effects, including muscle loss with GLP-1 receptor agonists.

**Summary**

The 25$^{th}$ annual ATT meeting discussed and identified the most important unmet research needs in the field of rheumatology (**Table 1**). Novel immune reset strategies such as CAR T-cell therapy, the potential of GLP1 agonists as adjunctive therapy, and the further development of targeted therapies, particularly for those with advanced or refractory disease, were prominent in discussions across disease states. The need for cure or prevention of disease remains as the ultimate target.

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