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A Report from the Psoriasis: From Gene to Clinic 10th International Congress

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SUMMARIZING SESSIONS WITH A FOCUS ON PSORIASIS

INTRODUCTION

The Psoriasis: From Gene to Clinic 10th International Congress took place in London from Thursday, December 5, to Saturday, December 7, 2024. This triennial event brought together leading experts, researchers, and clinicians to discuss advances in psoriasis research and clinical care. The Congress featured keynote lectures, invited speaker sessions, free communications, and a sponsored lecture addressing genetic foundations, clinical features, and evolving therapeutic approaches for psoriasis. This blog post highlights key discussions and presentations from the meeting. **Download the full Gene to Clinic Congress Report** for a comprehensive review, or continue reading for session highlights.

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Dissecting the Psoriasis Transcriptome: From Molecular Endotypes to Treatment Resistance

Michel Gilliet, MD, IPC Councilor
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Professor Michel Gilliet started the talk by looking back at the history of the translational revolution, which began with the application of immunohistochemistry during the early 1900s and continued until the recent use of spatial transcriptomics. The knowledge of immune pathways in skin diseases has widely expanded with the application of transcriptomic analysis, providing diagnostic and treatment stratification on different immune-mediated diseases (Table 1).

Table 1. Immune pathways in skin diseases and therapeutic implications.

Skin disease	Immune pathway	Treatment
Psoriasis	Th17	Anti-IL-23, Anti-IL-17
Eczema	Th2	Anti-IL4R, Anti-IL-13
Lichen planus	Th1	JAK1/2i
Lupus erythematosus	IFN-α/β	Anti-IFNAR
Neutrophilic diseases	IL-1/IL-36	Anti-IL36R, Anti-IL-1R

This application of transcriptomic studies leads to precision medicine, wherein module matching for treatment choice can be used for patients resistant to treatment. This module-based profiling approach by Prof. Gilliet can be summarized with the following key points:

- Powerful diagnostic support based on dominant expression
- Dominant matching enhances response rates in both naïve and non-responding patients
- Subdominant modules exist within a disease
- Switches of subdominant modules into dominance may drive therapy resistance.

Different module expressions across psoriasis phenotypes can be stratified into three groups: IFN-I, TH17, and Neutrophilic expressions that correspond to acute/inflammatory, chronic plaque, and pustular psoriasis, respectively.

Plasmacytoid dendritic cells (pDC) initiate psoriasis through IFN-alpha.[1] The resistance to anti-IL-23 and anti-IL-17 therapies among some patients with psoriasis is linked to dominant type I IFN expression. Interestingly, it has been shown that C1q inhibits type I IFNs induced by pDC, while C1q suppression is observed in resistant psoriasis. In conclusion, therapeutic failure is observed in IFN-I shift to dominance and is related to suppressed C1q. Therapies targeting IFN-I and pDC (and potentially C1qBP) should be considered.

Reference:

1. Nestle FO, Conrad C, Tun-Kyi A, et al. Plasmacytoid predendritic cells initiate psoriasis through interferon-alpha production. *J Exp Med*. 2005;202(1):135-143.

Challenges of Managing Psoriasis in Low and Middle Income Countries

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The challenges in managing psoriasis in middle- and low-income countries are summarized into issues related to the government, physicians, payers, and patients.

Limited access to healthcare services	Psychosocial impact
High cost of treatment	Environmental & lifestyle factors
Lack of awareness and education	Limited research and data constraints
Poor adherence to treatment	Policy & funding constraints
Limited access to treatment	

The limitation to healthcare services is primarily due to the inadequate healthcare infrastructure, shortage of dermatologists/specialists, and limited access to specialized care and advanced treatment.

Treatment cost entails a significant burden, especially since biologics are expensive and unaffordable to most patients. Subsidized or public healthcare programs are limited, while patients mostly pay out of pocket. Furthermore, supply chain disruption is an issue in these areas that affects the availability of these medications. In some regions, tar or other conventional topical generic agents are the only available treatment.

Poor adherence to treatment is an outcome of financial constraints among patients. This leads to intermittent or incomplete follow-up and treatment. This also leads to barriers in applying international guidelines wherein the prescription of the medications is based on economic grounds, not medical grounds. In addition, guidelines and clinical trials lack data on skin color, early intervention, and tapering of biologics that usually reflect the real-world scenario in these regions. Indeed, a delay in diagnosis represents a problem with the absence of guidelines for each specific region.

The color of the skin also represents a problem in diagnosis in this part of the world, with varied clinical characteristics of the disease, severity, and different comorbidities in patients with skin of color. The classification of psoriasis severity uses the psoriasis area and severity index, which uses erythema as one of its indices. This poses a challenge in detecting erythema in patients with skin of color as these may have a dark brown or violaceous hue instead of the pink or red color seen among patients with lighter skin complexions.[1]

Reference:

1. Alexis AF, Blackcloud P. Psoriasis in skin of color: epidemiology, genetics, clinical presentation, and treatment nuances. *J Clin Aesthet Dermatol*. 2014;7(11):16-24.

Psoriasis: Past, Present, and Future

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Professor Mark Lebwohl had an overview of the psoriasis therapeutics developed over the past decades. The era of biologics started with the initial discovery and understanding of the immunopathogenesis of psoriasis. Currently, more than ten biologics vary in terms of efficacy, speed of onset, durability of response, safety, usage in pregnancy, efficacy for psoriatic arthritis, and cost. More biologics have an increasing percentage of patients achieving PASI 100, while some may even provide clearance of lesions within 72 hours. Safety Boxed warnings were often seen in conventional systemic agents such as methotrexate, with bone marrow suppression as a common cause of mortality, In contrast to a safer profile with the newer biologics and oral systemic agents, such as deucravacitinib and apremilast. Obesity is a common comorbidity among patients with psoriasis and shall have varied dose adjustments in infliximab and ustekinumab, while IL-17 and IL-23 inhibitors have shown good data among this patient population. Prof. Lebwhol also expressed the benefit of using glucagon-like peptide 1 (GLP-1) receptor agonists among this patient population. A recent review showed that 4 of 5 clinical studies of GLP-1 receptor agonists among patients with psoriasis demonstrated significant improvements in psoriasis area severity index and weight/body mass index with no major adverse events.[1]

Oral medications have also been developed for psoriasis, and multiple upcoming and novel treatments targeting tyrosine kinase 2, IL-17, and IL-23 are in development. Despite all these breakthroughs, there are still unmet needs for better treatment options (e.g., psoriatic arthritis, palmoplantar psoriasis, nail psoriasis, and palmoplantar pustulosis), cost, and more effective topical therapy.

The ability to clear the skin with novel therapeutics and research has dramatically improved in recent years, with hopes for an even better result soon.

Reference:

1. Karacabeyli D, Lacaille D. Glucagon-Like Peptide 1 Receptor Agonists in Patients With Inflammatory Arthritis or Psoriasis: A Scoping Review. *J Clin Rheumatol*. 2024;30(1):26-31.

Redefining Psoriasis Severity and the Need for Systemic Therapy

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The terms “mild,” “moderate,” and “severe” that currently define psoriasis severity have been proposed to be changed into a more simplified and succinct categorization, according to Dr. Bruce Strober. While “moderate-severe” classification has been proposed to be defined as:

- High-impact sites: psoriasis in critical areas
- Treatment resistance: when topicals fail
- Psoriatic arthritis: When present, suggests greater severity
- Quality of life impact: Pronounced effects on well-being and symptoms

The traditional classification of psoriasis severity is guided by body surface area (BSA) and psoriasis area and severity index (PASI). These are variably standardized across many definitions and are often complex or time-consuming to calculate. In addition, adhering to mainly BSA or PASI alone for the classification of severity can significantly lead to undertreatment. Thus, applying the term “high impact sites” can avoid this problem and elevate treatment necessity. This has been further substantiated by real-world surveys and registries of psoriasis patients, which indicate that high-impact site involvement, regardless of BSA, translates into lower quality of life.[1] A recent study also reported a high disease burden, including patients with limited skin involvement, and this should serve as an opportunity to align patient and dermatologist perceptions to optimize the management of psoriasis and psoriatic arthritis.[2]

Treatment guidelines are now adapting to reflect these clinical realities. Previously, there was mismatch/misclassification between rigid clinical trials derived cutoffs (e.g., PASI >12) and real-world practice. This rigid threshold for biologics or trial inclusion omits vital groups of patients and does not reflect the real-world experience of physicians and patients. This also led to having scant information on the efficacy and safety of these specific populations (e.g., patients with high-impact areas) and reimbursement refusal (off-label use). The elimination of terms such as "mild," "moderate," and "severe" therefore allows the delivery of safe and effective therapy to patients who historically were not studied in traditional psoriasis clinical trials. Finally, current trials on psoriasis should prioritize disease impact over BSA/PASI.

References:

1. Nicolescu AC, Ionescu MA, Constantin MM, et al. Psoriasis Management Challenges Regarding Difficult-to-Treat Areas: Therapeutic Decision and Effectiveness. *Life (Basel)*. 2022;12(12):2050.
2. Lebwohl M, Langley RG, Paul C, et al. Evolution of Patient Perceptions of Psoriatic Disease: Results from the Understanding Psoriatic Disease Leveraging Insights for Treatment (UPLIFT) Survey [published correction appears in Dermatol Ther (Heidelb). 2022 Jan;12(1):79.

Harnessing the Power of Technology in Transforming Psoriasis Care

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Dr. Justin Ko proposes the use of technology that can augment high-value care through the following:

- Democratize access and expertise
- Enhance quality
- Improve efficiency
- Augment clinicians
- Engage patients
- Fuel discovery

He stressed that technology is not a solution but a tool we can apply positively and negatively. The proper use of technology enhances the well-being of physicians, reaching more patients in underserved environments and maintaining the patients in care.

Artificial intelligence (AI) revolutionized the diagnosis and management of psoriasis. Al algorithms can analyze vast datasets to pinpoint novel mechanisms associated with psoriasis clinical diagnosis, severity quantification, biomarker identification, and treatment response.[1] Al-powered tools are being developed for remote patient monitoring, predicting disease flares, and providing personalized patient education and engagement. At the same time, teledermatology lowers the cost of care, improves patient experience, increases access to care, and offers better care coordination.[2]

Integrating this technology into clinical practice is a major leap in delivering care to our patients. Deep clinician engagement and leadership are needed to ensure a fair, equitable, and responsible tech-enabled future of dermatology care.

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1. Smith P, Johnson CE, Haran K, et al. Advancing Psoriasis Care through Artificial Intelligence: A Comprehensive Review. *Curr Dermatol Rep*. 2024;13(3):141-147.
2. Kim GE, Afanasiev OK, O'Dell C, Sharp C, Ko JM. Implementation and evaluation of Stanford Health Care store-and-forward teledermatology consultation workflow built within an existing electronic health record system. *J Telemed Telecare*. 2020;26(3):125-131.

Changing Paradigms in the Science and Practice of Generalised Pustular Psoriasis

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Generalized pustular psoriasis (GPP), first described by Dr. von Zumbusch, has been explored further with recent discoveries in the genetic and immunological pathways involved in GPP.

GPP is a rare, potentially life-threatening auto-inflammatory disease characterized by unpredictable recurrent flares of widespread painful erythema studded with sterile pustules and lakes of pus. This often presents with systemic manifestations and may be complicated by sepsis and organ failures, with reported mortality rates ranging from 2% to 16%.[2]

The IL-36 pathway plays a critical role in GPP's pathogenesis, contrasting this from the IL-23/17 pathway found generally with psoriasis vulgaris. This vital discovery opens the development of biologic therapies that directly target the IL-36 pathway and offer a more precise, effective, and safe treatment for GPP.[3] Based on the EFFISAYIL 1 trial, sposilimab treatment shows fast clearance of pustule as early as 24 hours while maintaining a good safety profile.

Early and accurate diagnosis is essential in this rare form of psoriasis. Hence, an international consensus definition and diagnostic criteria for GPP using the modified Delphi method was initiated by the International Psoriasis Council's Generalized Pustular Psoriasis Working Group.[4] The creation of this international consensus shall serve as a reference point for clinicians and researchers that will further change the paradigm in the science and practice of GPP.

References:

1. Zumbusch L. Psoriasis und pustulöses Exanthem. *Archiv für Dermatol Syph*. 1910;99:335–346.
2. Balato A, Ambrogio F, Burlando M, et al. Commentary: Unmet Needs in Generalized Pustular Psoriasis in Clinical Practice. *Dermatol Ther (Heidelb)*. 2024;14(1):5-13.
3. Bachelez H, Choon SE, Marrakchi S, et al. Trial of Spesolimab for Generalized Pustular Psoriasis. *N Engl J Med*. 2021;385(26):2431-2440.
4. Choon SE, van de Kerkhof P, Gudjonsson JE, et al. International Consensus Definition and Diagnostic Criteria for Generalized Pustular Psoriasis from the International Psoriasis Council. *JAMA Dermatol*. 2024;160(7):758-768.

Stratifying Biologics Based on Real World Evidence

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According to Professor Lone Skov, stratifying patients with the corresponding biologics treatment will lead to optimal treatment for each patient, lower costs, and change the disease trajectory. Numerous highly efficacious biologic treatments for psoriasis have led to long-term remission. However, some patients may not have this optimal response initially nor may eventually lose effectiveness after an initial response. A real-world study has also provided characteristics of 'super responders'(SR) and 'super non-responders' (SNR) to the first biologic monotherapy for psoriasis.[1] Female sex, shorter study follow-up, higher DLQI, high frequency of adalimumab, lower frequency of ustekinumab at registration, and higher number of comorbidities were associated with SNRs compared with SRs. Also, proactive adalimumab therapeutic drug monitoring (TDM) has positively benefited patients with psoriasis based on data from a national registry. TDM has yet to be implemented in routine clinical care, but this may bridge the biomarker research-to-practice gap.[2] Recent studies have indicated that genetic markers such as HLA-C*06:02, the initial treatment response, and drug concentration levels post-initiation can predict treatment response.[3] Regarding safety, real-world evidence has similar data to clinical trials, and biologics have no safety concerns. The incidence of atrial fibrillation and major adverse cardiovascular events has no substantial difference after the initiation of ustekinumab versus tumor necrosis factor inhibitors.[4]

All this real-world evidence provides better personalized treatment plans for our patients. With personalized medicine, we can improve treatment response, identify response markers, and better patient safety outcomes.

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1. Mason K, Alabas O, Dand N, et al. Characteristics of 'super responders' and 'super non-responders' to first biologic monotherapy for psoriasis: a nested case-control study. *Br J Dermatol*. 2024.190(3):441–444.
2. Raharja A, Arkir Z, Rinaldi G, et al. Real-World Implementation and Outcomes of Adalimumab Therapeutic Drug Monitoring in Psoriasis: A National Specialized Center Experience. *J Invest Dermatol*. 2023;143(9):1708-1716.e4.
3. Dand N, Duckworth M, Baudry D, et al. HLA-C*06:02 genotype is a predictive biomarker of biologic treatment response in psoriasis. *J Allergy Clin Immunol*. 2019;143(6):2120-2130.
4. Lee MP, Desai RJ, Jin Y, Brill G, Ogdie A, Kim SC. Association of Ustekinumab vs TNF Inhibitor Therapy With Risk of Atrial Fibrillation and Cardiovascular Events in Patients With Psoriasis or Psoriatic Arthritis. *JAMA Dermatol*. 2019;155(6):700-707.

Higher IL-10+ T Cell and Treg Cell Counts in Psoriatic Skin are Associated with Super-Response to Guselkumab: Data from the Phase 3b GUIDE trial

Khusru Asadullah, Julianty Angsana, Kristen Kohler, Jocelyn Sendecki, Monica WL Leung, Sarah Tabori, Nenja Krüger, Sven Wegner, Yvonne Personke, Robert Sabat, Kerstin Wolk, Andreas Pinter, Peter Weisenseel, Knut Schäkel, Kilian Eyerich

Interleukin-10 (IL-10) and regulatory T (Treg) cells play key roles in autoimmunity, and the increased presence of these cells is believed to counter-regulate pathogenic tissue-resident memory (TMR) and T-helper (Th) 17 cells in psoriasis.

The Phase 3b GUIDE trial (NCTO3818035) examines the clinical and immunological impact of an extended guselkumab (an interleukin [IL]-23p19 subunit inhibitor) dosing interval in patients with moderate to severe plaque-type psoriasis. Patients who achieved a Psoriasis Area and Severity Index [PASI]=0 at both Week [W]20 and W28 with guselkumab treatment were defined as super-responders (SRes). In the sub-study of GUIDE, the comparison of immunological differences among SRes versus non-SRes was determined from non-lesional and lesional skin cells from 63 patients.[1]

The IL-10+ T cell counts at baseline were higher in both non-lesional and lesional skin of SRes versus non-SRes (with an SRe to non-SRe ratio of 3.1:1 in non-lesional skin and a 3.0:1 ratio in lesional skin; $P<0.05$). This was sustained in lesional skin after treatment with guselkumab, with higher IL-10+ T cell counts observed in SRes than non-SRes at W4 (with an SRe to non-SRe ratio of 4.6:1; $P<0.05$) and at W28 (with a ratio of 4.4:1; $P<0.05$). Meanwhile, Treg cell (CD4+CD25+FoxP3+) counts were also higher in SRes at W4 and W28 (with an SRe to non-SRe ratio of 3.1:1 at W4 and a ratio of 2.9:1 at W28; $P<0.05$). Further analysis of effector T cell subsets showed that CD8+ TRM and IL-17A+ T cell counts in lesional skin were reduced by guselkumab up to W68.

In summary, this data suggests that higher IL-10+ T cell and Treg cell counts and faster normalization of CD8+ TRM and IL-17A+ T cell counts characterize super-responders. Biomarkers in patients with moderate to severe plaque-type psoriasis can be a prospect, with higher IL-10+ T cell and Treg cell counts as positive predictors for better response to guselkumab.

Reference:

1. Angsana J, Kohler K, Sendecki J, et al. 587 Higher IL-10+ T cell and Treg cell counts in psoriatic skin are associated with super-response to guselkumab: Data from the phase 3 guide trial. *J Invest Dermatol. 2023;143(5)*: S101.

High Induction Dosing of Risankizumab in Patients with Moderate to Severe Plaque Leads to Marked Suppression of Resident Memory T Cell Number and Function in Resolved Psoriatic Skin

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Resident memory T cells (Trm) are non-circulating memory T cells that can develop within tissues in response to infection with certain pathogens. These are recently found in skin previously affected by active psoriasis and are believed to be responsible for the recurrences of psoriasis at sites of previously healed plaques.[1]

Risankizumab, a humanized monoclonal antibody that inhibits IL-23, is approved to treat moderate to severe plaque psoriasis. The objectives of the KNOCKOUT study evaluated the number of lesional Trm with the treatment of higher-than-approved Risankizumab induction doses (300mg and 600mg).[2] Twenty adult patients with moderate to severe plaque psoriasis were randomized 1:1 to receive either the 300mg or 600 mg dose given subcutaneously at weeks 0, 4, and 16, with no further dosing. The change in Trm number from lesional and non-lesional skin biopsies was evaluated at weeks 0 and 52 as the primary endpoint.

In lesions of patients receiving the higher dose (600 mg) of risankizumab, the number of CD8+ tissue-resident memory T cells was markedly reduced, with more marked suppression of the intercellular communication network between TRM and keratinocytes compared to the lower dose (300 mg) group. A shift towards increased crosstalk between Tregs and TRM was noted, particularly in the 600 mg dose group.

Static Physician's Global Assessment (sPGA) was monitored throughout the study and reported here with modified non-responder imputation. At Week 16, 94.4% (n=17, 95% C [72.7, 99.91) of all patients achieved sPGA 0/1, and 66.7% (n=12, 95% CI [41.0, 86.7]) achieved sPGA 0. At Week 52, 36 weeks after the last dose, sPGA 0/1 and sPGA 0 responses were achieved by 61.1% (n=11, 95% Cl [35.7, 82.71) and 44.4% (n=8, [95% C| 21.5, 69.21) of all patients, respectively.

In conclusion, this higher dosing regimen reduced Trm cell count, possibly supporting the high and prolonged therapeutic clinical responses noted among patients.

References:

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2. Blauvelt A, Gudjonsson JE, Matheson R, et al. High Induction Dosing of Risankizumab in Patients with Moderate-to-Severe Plaque Psoriasis: 52 Week Results from the Phase 2 KNOCKOUT Study. Abstract presented at: American Academy of Dermatology (AAD) 2024 Annual Meeting. March 7-12, 2024. San Diego, CA.

Boehringer Ingelheim Sponsored Lecture Targeting the IL-36 pathway in GPP: From Gene to Clinic

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The discovery of the IL36RN gene raised awareness of the central nature of the IL-36 pathway in generalized pustular psoriasis (GPP). IL-36 is a member of the IL-1 superfamily, a primary mediator of innate immunity and inflammation.[1] The dysregulation of the IL-36 pathway leads to dysregulated signaling and inflammation. This pathway can become dysregulated by a difunctional IL-36Ra protein and/or by the expression of very high levels of IL-36 cytokines.[2]

GPP was initially thought to be a severe variant of plaque psoriasis. However, a different inflammatory pathway that drives GPP differs from plaque psoriasis. IL-36 pathway is preferentially involved in GPP, in contrast to the IL-23/IL-17 axis in plaque psoriasis.[3]

This development in the understanding of the immunopathogenesis of GPP has led to the development of agents that block IL-36R signaling. This approach has shown efficacy and safety for the treatment of GPP. In the EFFISAYIL 1 trial, treatment with spesolimab was associated with rapid pustular and skin clearance within one week versus placebo in patients experiencing GPP flare.[4] This treatment has also decreased the expression of pathogenic genes associated with GPP and the IL-36 pathways associated with clinical improvement in GPP.

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