Tribunal Session Summary

Session: conclave-20260514-223445-identify-the-principal-scientific-f6c1

Depth: T6

Advocates: 6 | Judges: 5 | Cost: $5.5106 | Time: 26m 40s

THE PROMPT: Identify the principal scientific discovery that significantly enhanced the efficacy of psoriasis therapy in the last five years. Include evidence supporting its impact and any key mechanisms involved. Don't be overly scientific.

THE RULING: The principal scientific advances in psoriasis therapy over the last five years are dual IL-17A/F blockade and IL-23p19-selective inhibition, which together represent a co-leadership model: one redefining the ceiling of skin clearance, the other enabling the first credible pathway to drug-free remission. The strongest evidence is the BE-RADIANT trial, which proved dual IL-17A/F inhibition (bimekizumab) significantly raises complete skin clearance (PASI 100) rates compared to IL-17A inhibition alone, and the GUIDE trial, which demonstrated for the first time that early-treated patients can maintain clearance after stopping IL-23p19 inhibitors. The main caveat is that no direct head-to-head trial exists between these two classes, so a definitive hierarchy cannot be established.

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Core Analysis

The Dual-Axis Breakthrough in Psoriasis Therapy

The last five years have not been defined by a single discovery, but by the maturation of two complementary therapeutic strategies that have transformed psoriasis from a chronic, relapsing disease into one where near-total or complete clearance and even drug-free remission are realistic goals for many patients. These advances—dual IL-17A/F blockade and IL-23p19-selective inhibition—represent distinct but equally transformative axes of efficacy: **depth of clearance** and **durability of response**.

1. Dual IL-17A/F Blockade: Shattering the Efficacy Ceiling

The principal discovery on the depth-of-clearance axis is the clinical validation that neutralizing both IL-17A and IL-17F (dual IL-17A/F blockade) produces significantly higher rates of complete skin clearance than blocking IL-17A alone. This was conclusively demonstrated in the **BE-RADIANT trial**, a phase 3b, double-blind, head-to-head randomized controlled trial (RCT) published in *The Lancet* in 2021.

- **Evidence**: The trial compared bimekizumab (dual IL-17A/F inhibitor) to secukinumab (IL-17A inhibitor) in patients with moderate-to-severe plaque psoriasis. At the primary endpoint of week 16, **62% of patients treated with bimekizumab achieved PASI 100 (complete skin clearance)**, compared to **49% of those treated with secukinumab**. This 13-percentage-point advantage was statistically significant ($p<0.001$). The superiority was sustained at week 48, with **67% vs. 46% achieving PASI 100**.

- **Mechanism**: IL-17A and IL-17F are sister cytokines that are co-expressed in psoriatic skin lesions and signal through the same receptor (IL-17RA/RC) on keratinocytes. While IL-17A is a potent inflammatory signal, IL-17F is more abundant. Prior therapies that blocked only IL-17A left IL-17F active, allowing a residual "inflammatory leak" that prevented complete healing. Bimekizumab, by shutting down both signals, silences the entire inflammatory cascade to the skin, enabling a higher proportion of patients to achieve completely clear skin.
- **Impact**: This discovery redefined the therapeutic goal. For decades, "clear skin" was a rare outcome. The BE-RADIANT trial proved that a majority of patients could achieve PASI 100, establishing complete clearance as a new, attainable standard of care. This is a direct, within-window (2021) validation of a new efficacy mechanism—IL-17F's non-redundant role—that significantly enhanced therapeutic outcomes.

2. IL-23p19-Selective Inhibition: Enabling Disease Modification

The principal discovery on the durability and disease-modification axis is that selectively blocking the IL-23 p19 subunit (IL-23p19 inhibition) can produce sustained, near-total clearance and, in a defined patient population, enable drug-free remission. This represents a paradigm shift from lifelong suppression to the potential for a cure-like state.

- **Evidence**: The **LIMMitless trial**, a 5-year open-label extension study of risankizumab, demonstrated that **approximately 85% of initial responders maintained PASI 90 (90% or greater improvement)** through 256 weeks (nearly 5 years). This level of sustained efficacy is unprecedented. More significantly, the **GUIDE trial** provided the first peer-reviewed evidence of drug-free remission. In this phase 3b, randomized, double-blind, placebo-controlled withdrawal study, early-treated patients with moderate-to-severe plaque psoriasis who achieved a super-response (PASI 90/100) on guselkumab were randomized to continue treatment or switch to placebo. A substantial proportion of these super-responders maintained their clearance for up to 48 weeks after completely stopping the drug.
- **Mechanism**: IL-23 sits upstream in the inflammatory cascade, acting as the master regulator that drives the survival and expansion of pathogenic Th17 cells. By selectively targeting the p19 subunit unique to IL-23, these drugs (e.g., risankizumab, guselkumab) intercept the disease at its source. This upstream blockade is believed to deplete the pool of pathogenic tissue-resident memory T (TRM) cells in the skin, which are responsible for disease recurrence. By reducing this "immune memory," the skin can heal and remain clear even after the drug is withdrawn, a phenomenon not observed with downstream inhibitors like IL-17 blockers.
- **Impact**: This discovery fundamentally changes the treatment goal. Instead of managing a flare, the aim is to modify the disease course. The ability to achieve drug-free remission, even in a subset of patients, is a revolutionary advance, transforming psoriasis from a chronic burden into a potentially modifiable condition.

3. Co-Leadership: The Synthesis of Two Transformative Advances

The evidence does not support a single "principal discovery" because the two classes excel on different, patient-meaningful dimensions of efficacy.

- **Dual IL-17A/F blockade (bimekizumab)** is the leader in **speed and depth of clearance**, achieving the highest rates of PASI 100. This is the breakthrough for patients whose primary goal is to have completely clear skin as quickly as possible.
- **IL-23p19 inhibition (risankizumab, guselkumab)** is the leader in **long-term durability, safety, and disease modification**. It offers the most favorable safety profile (with a lower risk of oral candidiasis and

inflammatory bowel disease flares compared to IL-17 inhibitors) and the only proven pathway to drug-free remission. This is the breakthrough for patients who prioritize long-term stability and the possibility of stopping treatment.

The lack of a direct, head-to-head RCT comparing bimekizumab and an IL-23p19 inhibitor in plaque psoriasis means that claims of overall superiority by either side are inferential, not proven. The convergence of the debate on a co-leadership model is not a compromise but an epistemic necessity based on the available evidence. The two discoveries are complementary, not competitive, and together they have redefined the therapeutic landscape.

4. Rejection of Alternative Claims

- **Reversible Epigenetic Scarring**: While an intriguing hypothesis, the claim that this is the principal discovery was rejected due to a lack of primary, peer-reviewed evidence. The data cited (e.g., from the STEPIn trial) were based on conference summaries and news articles, not a published, prespecified clinical trial linking epigenetic reversal to superior clinical outcomes. It remains a plausible supporting mechanism for why early treatment works, but it is not a therapeutic discovery in its own right.
- **IL-23/Th17 Pathway Understanding**: The claim that the understanding of this pathway is a recent discovery was dismissed as it predates the five-year window by at least 15 years. The pathway was characterized in the mid-2000s and is textbook immunology. The recent advance is not the understanding of the pathway, but the clinical maturation of drugs that target it with high precision and durability.

Fact-Check Summary

Claim	Evidence Quality	Verdict	Notes
Bimekizumab superior to secukinumab on PASI 100 (BE-RADIANT)	PEER_REVIEWED	✓ Verified	*Lancet* 2021, p<0.001
IL-23p19 inhibitors maintain ~85% PASI 90 at 5 years (LIMMitless)	PEER_REVIEWED	✓ Verified	*Br J Dermatol* 2023
IL-23p19 inhibition enables drug-free remission (GUIDE)	PEER_REVIEWED	✓ Verified (subset-limited)	*JAMA Dermatol* 2023–2024
IL-17F is a non-redundant co-driver	PEER_REVIEWED	✓ Verified	*Sci Transl Med* 2018
Bimekizumab maintains >70% PASI 100 at Year 4 (BE-BRIGHT)	SECONDARY	■ Unverifiable	Open-label extension; no peer-reviewed NRI analysis
Reversible epigenetic scarring is the principal discovery	ANECDOTAL	✗ Rejected	No primary peer-reviewed evidence

How We Got Here

Scorecard

Judge	Claude Opus 4.7	Grok 4	Magistral Medium	Gemini 3.1 Pro	GPT-5	DeepSeek V4 Pro	Winner
GPT-OSS 120B	REJECT	REJECT	REJECT	REJECT	REJECT	**ACCEPT**	DeepSeek V4 Pro
Zhipu GLM-5	REJECT	REJECT	REJECT	REJECT	**ACCEPT**	PARTIAL ADOPT	GPT-5
Mistral Large 3	REJECT	REJECT	REJECT	REJECT	REJECT	**ADOPT**	DeepSeek V4 Pro
Qwen 3 235B (Cerebras)	REJECT	REJECT	REJECT	REJECT	**ADOPT**	**ADOPT**	DeepSeek V4 Pro
DeepCogito v2.1 671B	REJECT	REJECT	REJECT	**ACCEPT**	REJECT	REJECT	Gemini 3.1 Pro

Convergence Assessment

The convergence was **epistemic**, driven by verifiable corrections and logical refutations. Key evidence includes:

- **Claude Opus 4.7** conceded the misattribution of the STEPIn trial data (an IL-17A study) to support IL-23 efficacy.
- **Gemini 3.1 Pro** conceded that the BE BOLD trial, which it cited for superiority, was in psoriatic arthritis and not relevant to plaque psoriasis.
- **DeepSeek V4 Pro** conceded that its reliance on the BADBIR registry for drug survival was premature due to limited bimekizumab follow-up.
- **Grok 4** fully conceded its original position on epigenetic scarring after challenges exposed the lack of primary evidence.

These were not shifts in opinion due to social pressure, but direct responses to falsifiable claims being disproven, confirming that the convergence was evidence-driven.

Closing Statements

GPT-5: My final position is that the principal discovery is the clinical validation of IL-17F as a non-redundant co-driver, proven by the BE-RADIANT trial's superiority of bimekizumab over secukinumab on PASI 100. This is a discrete, within-window efficacy lift. I acknowledge IL-23p19 inhibitors as co-leaders on durability and tolerability, but the clearest new mechanism-driven efficacy gain is dual IL-17A/F blockade. My strongest evidence is the head-to-head RCT, the mechanistic concordance of IL-17A/F signaling, and the large gains over prior standards.

DeepSeek V4 Pro: My final position is that the principal discovery is the clinical maturation of IL-23p19 inhibitors, demonstrated by the LIMMitless 5-year durability data and the GUIDE trial's drug-free remission. This is a paradigm shift from suppression to modification. I refined my position to focus on remission in super-responders after challenges. My strongest evidence is the GUIDE trial's controlled remission data, the LIMMitless NRI-based durability, the coherent upstream mechanism, and the clean safety profile.

Gemini 3.1 Pro: I entered the debate believing dual IL-17A/F blockade was the sole breakthrough, but adversarial testing forced me to adopt a co-leadership model. The principal discovery is twofold: dual IL-17A/F for absolute clearance (BE-RADIANT) and IL-23p19 for disease modification (GUIDE). My strongest evidence is the BE-RADIANT trial proving IL-17F's necessity, the BE-BRIGHT extension showing sustained PASI 100, and the GUIDE trial as the necessary co-pillar that defeated my exclusive claims.

Claude Opus 4.7: The principal advance is the demonstration that IL-23p19 inhibition can produce disease modification—drug-free remission in early-treated super-responders. Bimekizumab is a co-leader for short-term PASI 100. My position evolved from "durable clearance" to "disease modification" after Gemini 3.1 Pro's challenge on BE-BRIGHT data. My strongest evidence is the GUIDE trial, the asymmetry on drug-free remission, the TRM-cell mechanism, and the framing distinction between "ceiling" and "paradigm."

Reality Checks

Claim	Challenge	Result
Claude Opus 4.7: "Targeting IL-23 specifically works better than targeting IL-17 downstream of it."	**Gemini 3.1 Pro:** "You are using the efficacy data of an IL-17 drug (STEPIn) to argue for the superiority of an IL-23 drug. Explain."	Full concession. Claude Opus 4.7 admitted the misattribution and withdrew the ordinal ranking of IL-23 as superior.
Gemini 3.1 Pro: "The BE BOLD trial shows bimekizumab defeated risankizumab head-to-head in active psoriatic disease."	**DeepSeek V4 Pro:** "BE BOLD was a psoriatic arthritis trial with a different endpoint (ACR50). You cannot extrapolate a joint result to skin clearance."	Full concession. Gemini 3.1 Pro retracted the use of BE BOLD as evidence for plaque psoriasis superiority.
Grok 4: "The principal discovery is reversible epigenetic scarring in skin cells."	**Claude Opus 4.7:** "You cite a single Nature news article summarizing conference data. Explain why this should be considered definitive evidence."	Full concession. Grok 4 retracted the claim, stating the evidence was not primary peer-reviewed data.

Next Steps

Next Step	Why It Matters	Confidence
Conduct a direct head-to-head RCT comparing bimekizumab and an IL-23p19 inhibitor (e.g., risankizumab) in plaque psoriasis.	This is the only way to resolve the co-leadership model and determine if one class is superior on both PASI 100 and durability.	90%
Perform a peer-reviewed, NRI-adjusted analysis of the BE-BRIGHT open-label extension data for bimekizumab.	To verify the claim that >70% of patients maintain PASI 100 at Year 4 under intention-to-treat conditions, addressing concerns about attrition bias.	60%
Launch a prospective RCT to determine if drug-free remission can be achieved with dual IL-17A/F blockade.	To test if the disease-modification advantage of IL-23p19 is unique or if it can be replicated with a different mechanism.	40%
Validate the clinical utility of epigenetic markers (e.g., DNA methylation) as predictors of treatment response and remission.	To determine if early intervention based on these markers can improve long-term outcomes, potentially unifying the timing and mechanism hypotheses.	50%

Dissenting Opinions

No dissenting opinions were filed in this session.

Glossary

Term	Definition
ACR50	A measure of improvement in psoriatic arthritis, indicating a 50% reduction in disease activity.
BE-RADIANT	A phase 3b, double-blind, randomized controlled trial that compared bimekizumab to secukinumab in plaque psoriasis.
BE BOLD	A phase 3b head-to-head trial that compared bimekizumab to risankizumab in active psoriatic arthritis.
BE BRIGHT	An open-label extension study of bimekizumab that assessed long-term safety and efficacy.
BE-SURE	A phase 3 trial that compared bimekizumab to adalimumab in patients with moderate-to-severe plaque psoriasis.
BE-VIVID	A phase 3 trial that compared bimekizumab to ustekinumab in patients with moderate-to-severe plaque psoriasis.
Candidiasis	A fungal infection, often oral thrush, which is a known side effect of IL-17 inhibitors.
Deucravacitinib	An oral TYK2 inhibitor approved in 2022 for the treatment of psoriasis.
Epigenetic scarring	A hypothesized persistent change in gene expression in skin cells that may contribute to psoriasis chronicity.
Guttate psoriasis	A form of psoriasis often triggered by a streptococcal infection, characterized by small, drop-like lesions.
GUIDE	A phase 3b, randomized, double-blind, placebo-controlled withdrawal trial of guselkumab in plaque psoriasis.
IL-17A	A pro-inflammatory cytokine that plays a key role in the pathogenesis of psoriasis.
IL-17F	A sister cytokine to IL-17A that signals through the same receptor and contributes to psoriatic inflammation.
IL-23	A pro-inflammatory cytokine that drives the survival and expansion of pathogenic Th17 cells.
IL-23/Th17 axis	The central immunological pathway in psoriasis, where IL-23 activates Th17 cells to produce inflammatory cytokines.
LIMMitless	A 5-year open-label extension study of risankizumab that assessed long-term safety and efficacy.
mNRI	Modified Non-Responder Imputation, a statistical method in clinical trials where patients who drop out are counted as treatment failures.

Term	Definition
Network Meta-Analysis (NMA)	A statistical method that compares multiple treatments using both direct and indirect evidence from different trials.
PASI	Psoriasis Area and Severity Index, a standardized score used to measure the severity of psoriasis.
PASI 90	A 90% or greater improvement in the Psoriasis Area and Severity Index score.
PASI 100	A 100% improvement in the Psoriasis Area and Severity Index score, indicating completely clear skin.
p19 subunit	The unique protein subunit of the IL-23 cytokine that is targeted by selective inhibitors like risankizumab and guselkumab.
Psoriatic arthritis	A form of inflammatory arthritis that affects some people with psoriasis.
Secukinumab	A biologic drug that inhibits IL-17A, approved in 2015 for the treatment of psoriasis.
STEPIn	A clinical trial that evaluated secukinumab in patients with early-onset moderate-to-severe plaque psoriasis.
Tissue-resident memory T (TRM) cells	Immune cells that permanently reside in the skin and are believed to play a key role in psoriasis relapse.
ustekinumab	A biologic drug that inhibits IL-12 and IL-23, approved in 2009 for the treatment of psoriasis.

How The Conclave Works

The Conclave is a structured multi-model deliberation system. Instead of asking one AI model a question and trusting its answer, the Conclave convenes a panel of independent models, forces them to argue, and subjects their conclusions to judicial review. The process is adversarial by design — consensus must be earned through evidence, not assumed through agreement.

Advocates are independent AI models (e.g., Claude, GPT-5, Gemini, DeepSeek) that each receive the same question and produce a sealed submission without seeing each other's work. Each submission must include a falsifiable hypothesis, tagged evidence with reasoning type (deductive/inductive/abductive), provenance labels for any frameworks cited, and an honest self-assessment.

Challenges follow submissions. Each advocate reads all other submissions and directly attacks weak points — not polite reviews, but pointed cross-examination. They must identify the single factual crux that would settle each disagreement.

Debate Rounds (1–7 depending on depth) force advocates to defend, concede, or revise their positions under pressure. The system tracks position stability across rounds to detect sycophantic drift — when models change their stance to agree with others without citing new evidence.

Judges (called Justices on The Bench) are separate models that never participated as advocates. They evaluate the full record: submissions, challenges, and debate transcripts. They fact-check claims, audit framework provenance, assess whether convergence was epistemic (evidence-driven) or affective (social pressure), and render a verdict: ACCEPT one position, SYNTHESIZE the best elements, or REMAND for further debate.

Depth levels control rigor: T1/Spot Check (submissions only), T2/Standard Review (1 debate round, 1 judge), T3/Deep Review (3 rounds, 3 judges), T4/Full Panel (5 rounds, full panel), T5/Stress Test (5 rounds + Fresh Eyes review), T6/Red Team (7 rounds + mid-debate judicial checkpoint).

The system is deterministic code — it cannot be sycophantic. It dispatches prompts, collects responses, and enforces the adversarial structure. The models argue; the code referees.