Tribunal Session Summary

Session: conclave-20260514-203332-what-was-the-principal-bdee

Depth: T6

Advocates: 5 | Judges: 5 | Cost: $2.7038 | Time: 31m 09s

THE PROMPT: What was the principal scientific discovery that significantly improved the efficacy of psoriasis therapy over the past 25 years? Please explain the discovery, mechanism, and its impact on treatment approaches, focusing on how it changed clinical practices and patient outcomes.

THE RULING: The principal scientific discovery was the elucidation of the IL-23/Th17 immune axis, with IL-23—specifically via its p19 subunit—as the upstream, non-redundant survival factor for pathogenic Th17 cells, and IL-17 as a key downstream effector. This hierarchical discovery redefined psoriasis as an IL-23-driven disease, enabled the development of biologics targeting IL-23p19 or IL-17, and led to superior clinical outcomes in efficacy, durability, and safety.

The Prompt

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The Ruling

The principal scientific discovery was the elucidation of the IL-23/Th17 immune axis, with IL-23—specifically via its p19 subunit—as the upstream, non-redundant survival factor for pathogenic Th17 cells, and IL-17 as a key downstream effector. This hierarchical discovery redefined psoriasis as an IL-23-driven disease, enabled the development of biologics targeting IL-23p19 or IL-17, and led to superior clinical outcomes in efficacy, durability, and safety.

The strongest evidence is the convergence of biochemical, genetic, and clinical data: the 2000 discovery of the IL-23p19 subunit, GWAS identifying *IL23R* and *IL12B* as top psoriasis risk loci, and head-to-head trials (ECLIPSE, IMMerge) showing IL-23p19 inhibitors outperform IL-17 inhibitors on sustained PASI 90 and drug survival. The main caveat is that the long-term safety of IL-23p19 inhibition beyond 10 years remains under study.

Core Analysis

The Discovery: From Th1 to IL-23/Th17 Axis

Prior to 2000, psoriasis was widely believed to be a Th1-mediated disease, with TNF-α and IFN-γ considered central drivers. The paradigm shift began with the **discovery of the IL-23p19 subunit** (Oppmann et al., *Immunity*, 2000), which distinguished IL-23 (p19/p40) from IL-12 (p35/p40). This biochemical identification revealed that IL-23, not IL-12, was the cytokine responsible for stabilizing and maintaining pathogenic T-helper 17 (Th17) cells.

This was followed by the **definition of the Th17 lineage** (Harrington et al., *Nature Immunology*, 2005; Langrish et al., *JEM*, 2005), which established that IL-23 promotes the survival and expansion of Th17 cells that produce IL-17A, IL-17F, and IL-22—cytokines directly implicated in keratinocyte hyperproliferation, neutrophil recruitment, and epidermal inflammation.

Genome-wide association studies (GWAS) from 2007 onward (Cargill et al., *Nature*, 2007; Nair et al., *Nature Genetics*, 2009) provided human genetic validation, showing strong enrichment of risk variants in *IL23R* and *IL12B* (which encodes the p40 subunit shared by IL-12 and IL-23), but not in Th1-related genes. This convergence of biochemical, cellular, and genetic evidence established the **IL-23/Th17 axis** as the central pathogenic circuit in psoriasis.

Mechanism: Hierarchical Signaling and Therapeutic Implications

The axis operates as a **hierarchical pathway**: **IL-23 (via p19/p40)** → **Th17 cell survival/expansion** → **IL-17/IL-22 production** → **epidermal inflammation and plaque formation**.

This hierarchy explains the differential clinical performance of biologics:

- **IL-23p19 inhibitors** (e.g., guselkumab, risankizumab) block the upstream survival signal for pathogenic Th17 cells, leading to functional depletion of tissue-resident memory T cells (TRMs) in the skin. This results in **superior durability**, with median time to relapse after withdrawal reaching **~295 days** (IMMhance trial, *Lancet*, 2020).
- **IL-17 inhibitors** (e.g., secukinumab, ixekizumab) block the downstream effector cytokines, achieving **rapid symptom relief** and high PASI 75/90 rates (~70–80% at 12 weeks), but with **shorter drug survival** and higher relapse rates.
- **p40 inhibitors** (e.g., ustekinumab) block both IL-12 and IL-23, offering intermediate efficacy, confirming that **IL-23—not IL-12—is the dominant driver**.

The mechanistic distinction is critical: targeting the upstream survival factor (IL-23) disrupts the chronicity of disease by depleting TRMs, while targeting downstream IL-17 controls inflammation but does not eliminate the source.

Impact on Clinical Practice and Patient Outcomes

The discovery directly led to a **stepwise improvement in therapeutic outcomes**:

- **Efficacy benchmarks shifted** from PASI 75 (achieved by ~35–50% with TNF inhibitors) to **PASI 90 and PASI 100** as routine goals. IL-23p19 inhibitors achieve **PASI 90 in ~75–85%** and **PASI 100 in ~50%** of patients by week 52.
- **Drug survival rates are highest** for IL-23p19 inhibitors, with >80% of patients remaining on therapy at 2 years (PSOLAR, BADBIR registries), surpassing IL-17 and TNF inhibitors.
- **Dosing intervals extended** to every 8 weeks (some even 12 weeks), improving adherence and quality of life.
- **Safety profiles diverged**: IL-17 blockade is associated with **exacerbation of inflammatory bowel disease (IBD)**, whereas IL-23p19 inhibition is **neutral or beneficial** in IBD, making it preferable for patients with comorbidities.

Clinical guidelines (e.g., AAD-NPF, EDF) now reflect this hierarchy, with IL-23p19 inhibitors often recommended as first-line biologics for moderate-to-severe psoriasis.

Why the Axis—Not Just IL-17 or p19 Alone—is the Principal Discovery

While **Gemini 3.1 Pro** correctly emphasized the **p19 subunit as the optimal therapeutic target**, and **Magistral Medium** rightly noted **IL-17's clinical importance**, the **principal discovery was the integrated, hierarchical model**—not any single node in isolation.

- The **p19 discovery** (2000) was necessary but not sufficient; it was the **context of the Th17 lineage and its dependence on IL-23** (2005) that revealed p19's therapeutic significance.
- The **IL-17 discovery** was downstream and did not explain why blocking IL-23 yields longer remissions.
- Only the **full axis model** predicted both therapeutic classes, explained their differential durability, and aligned with genetic and histologic evidence.

Thus, the breakthrough was not merely identifying a molecule, but **mapping a pathogenic circuit and identifying its rate-limiting node**—a hallmark of transformative science.

How We Got Here

Scorecard

Judge	Gemini 3.1 Pro	Grok 4	Magistral Medium	DeepSeek V4 Pro	GPT-5	Winner
GPT-OSS 120B	ACCEPT	ACCEPT	REJECT	ACCEPT	ACCEPT	DeepSeek V4 Pro
Zhipu GLM-5	REJECT	REJECT	REJECT	REJECT	ACCEPT	GPT-5
Qwen 3 235B (Cerebras)	REJECT	REJECT	REJECT	REJECT	ACCEPT	GPT-5
DeepCogito v2.1 671B	REJECT	REJECT	REJECT	ACCEPT	REJECT	DeepSeek V4 Pro
MiniMax M2.7	REJECT	REJECT	REJECT	ACCEPT	REJECT	DeepSeek V4 Pro

Convergence Assessment

Convergence was epistemic, driven by verifiable corrections and new evidence. Magistral Medium's major revision—from claiming IL-17 as the principal discovery to acknowledging the upstream role of IL-23—was triggered by overwhelming evidence from GWAS and head-to-head trials. GPT-5's (GPT-5) refinement to center the axis on the p19 subunit was driven by data on drug survival and relapse kinetics. No advocate changed their position due to social pressure; all shifts were evidence-based.

Closing Statements

Magistral Medium My final position is that the principal scientific discovery is the elucidation of the IL-23/Th17 immune axis, with IL-23 as the upstream survival factor and IL-17 as the downstream effector cytokine. I initially focused narrowly on IL-17's role, but the debate forced me to appreciate the crucial importance of IL-23 as the upstream regulator. The strongest surviving evidence is the genetic enrichment at IL23R/IL12B loci, lesional overexpression of IL-23 subunits, and the clinical superiority of p19 inhibitors on sustained endpoints. I also concede that ustekinumab represented an important functional first step, not a fundamental flaw, and that the biological reality is more nuanced than I initially claimed.

Gemini 3.1 Pro My final position is that the discovery of the IL-23p19 subunit is the principal scientific breakthrough. I entered the debate arguing for the broad "IL-23/Th17 axis" but emerged advocating for the specific biochemical isolation of the p19 subunit. The clinical reality punishes broad axis targeting and strictly rewards precise p19 targeting. My strongest surviving evidence is the foundational isolation of p19 (Oppmann et al., 2000), the clinical divergence of the IL-23/Th17 nodes (p19 inhibitors avoid IBD flares and candidiasis), and unmatched drug survival with a median relapse-free interval of 295 days. I concede that ustekinumab was a functional first step and that IL-17 blockade provides rapid onset, but the p19 subunit remains the apex discovery.

Grok 4 My final position is that the principal scientific discovery is the elucidation of the IL-23/Th17 axis with IL-23p19 as the non-redundant upstream survival factor. The axis framework predicted both IL-17 and IL-23 therapies and explained their differential performance. My strongest surviving evidence is the head-to-head and withdrawal trials (ECLIPSE, IMMerge, IMMhance) showing p19 superiority, the genetic and histologic data converging on IL-23p19, the selective p19 agents isolating the pathogenic driver, and the real-world drug-survival meta-analyses ranking p19 inhibitors highest. I concede that p40 blockade was a feasibility benchmark and that the axis is hierarchical, not indivisible.

GPT-5 My final position is that the principal scientific discovery is the elucidation of the IL-23/Th17–IL-17 axis, with IL-23 as the upstream, non-redundant survival factor for pathogenic Th17 cells. This framework predicted both therapeutic classes and their hierarchy. My strongest surviving evidence is the convergent human biology centering on IL-23 upstream of IL-17, the head-to-head and withdrawal data demonstrating upstream durability superiority, the axis framework predicting safety divergences, the practice transformation metrics aligning with the axis discovery, and the expansive predictive power beyond a single node. I refined my position to acknowledge that p19 is the keystone of the axis and that IL-17 blockade has value for rapid onset.

DeepSeek V4 Pro My final position is that the principal scientific discovery is the identification of the IL-23/Th17 immune axis as the central pathogenic circuit. The axis model, consolidated between 2005 and 2009, rests on three pillars: the demonstration that IL-23 is the master survival factor for Th17 cells, lesional profiling linking the pathway to human disease, and GWAS placing variants in *IL12B* and *IL23R* among the strongest risk loci. My strongest surviving evidence is the genetic anchoring of the IL-23 pathway, the monotonic efficacy gradient across axis-targeting therapies, the safety differentiation that the axis alone explains, and the paradigm shift in treatment goals from PASI 75 to PASI 90/100. I refined my argument to acknowledge that the p19 subunit is the most elegant destination on the map, but the axis is the principal discovery.

Reality Checks

Claim	Challenge	Result
Gemini 3.1 Pro: The identification of the unique IL-23p19 subunit corrected a fundamental flaw in the understanding of psoriasis pathogenesis.	**Grok 4:** Ustekinumab (p40 blockade) achieved PASI 75 rates of ~66–70% in PHOENIX trials by 2008—well before any selective p19 agent—and remains effective today, showing the p40 model was never a “fundamental flaw” but a functional first step.	Gemini 3.1 Pro conceded that the "fundamental flaw" phrasing was hyperbolic and factually incorrect, revising to acknowledge ustekinumab as a functional first step.
Gemini 3.1 Pro: IL-23p19 inhibitors demonstrate PASI 100 rates of 50–60% at 16 weeks.	**GPT-5:** Phase 3 data place PASI 100 at week 16 closer to 36–51% for risankizumab (UltIMMa-1/2) and ~35–45% for guselkumab (VOYAGE), not a consistent 50–60%.	Gemini 3.1 Pro conceded the overstatement, revising to reflect accurate trial statistics.
DeepSeek V4 Pro: TNF-α inhibitors achieve PASI 75 ≈35% at week 12.	**GPT-5:** The same trial reported higher PASI 75 for the 50 mg BIW arm (~49% at week 12); selectively quoting the lower-dose arm understates the TNF benchmark.	DeepSeek V4 Pro conceded the cherry-picking, revising to acknowledge the higher dose response.

Next Steps

Next Step	Why It Matters	Confidence
Determine the long-term safety profile (>10 years) of IL-23p19 inhibition compared with IL-17 blockade.	Informs optimal first-line biologic choice, especially for patients with comorbidities (e.g., IBD, infection risk).	~60%
Investigate whether combination targeting of IL-23 and IL-17 (dual-axis blockade) provides additive benefit, or does it increase adverse events?	Could further improve refractory disease but may raise safety concerns.	~55%
Understand how IL-23 blockade leads to the functional depletion of pathogenic tissue-resident memory T cells (TRMs).	Could enable therapies that induce long-term remission or "functional cures."	~70%
Identify upstream regulators (e.g., innate lymphoid cells) that could yield even more durable remission.	May open a new therapeutic class beyond IL-23.	~40%

Dissenting Opinions

No dissenting opinions were filed in this session.

Glossary

Term	Definition
AAD-NPF guidelines	Clinical practice guidelines for psoriasis treatment issued jointly by the American Academy of Dermatology and the National Psoriasis Foundation.
DLQI	Dermatology Life Quality Index, a standardized questionnaire measuring the impact of skin disease on a patient's quality of life, with scores of 0–1 indicating no impact.
ECLIPSE trial	A head-to-head phase 3 trial comparing guselkumab (IL-23p19 inhibitor) to secukinumab (IL-17A inhibitor) in moderate-to-severe plaque psoriasis.
GWAS	Genome-wide association study, a method that scans markers across the complete sets of DNA of many individuals to find genetic variations associated with a particular disease.
IBD	Inflammatory bowel disease, a group of disorders that cause chronic inflammation of the digestive tract, including Crohn's disease and ulcerative colitis.
IL-17	Interleukin-17, a pro-inflammatory cytokine produced by Th17 cells that plays a key role in autoimmune diseases like psoriasis.
IL-23	Interleukin-23, a cytokine composed of p19 and p40 subunits that promotes the survival and expansion of pathogenic Th17 cells.
IMMhance trial	A phase 3 trial evaluating the efficacy and safety of risankizumab, an IL-23p19 inhibitor, in patients with moderate-to-severe plaque psoriasis, including a withdrawal phase.
IMMerge trial	A head-to-head phase 3 trial comparing risankizumab (IL-23p19 inhibitor) to secukinumab (IL-17A inhibitor) in moderate-to-severe plaque psoriasis.
PASI	Psoriasis Area and Severity Index, a standardized tool used to measure the severity of psoriasis based on the area and severity of plaques.
PASI 75	A clinical endpoint indicating a 75% improvement in the Psoriasis Area and Severity Index score from baseline.
PASI 90	A clinical endpoint indicating a 90% improvement in the Psoriasis Area and Severity Index score from baseline.
PASI 100	A clinical endpoint indicating complete clearance of psoriasis, with no measurable disease.
p19 subunit	The unique protein subunit of the IL-23 cytokine that pairs with the p40 subunit; its discovery allowed for selective targeting of IL-23.
p40 subunit	A protein subunit shared by both IL-12 and IL-23 cytokines; targeting p40 inhibits both cytokines.

Term	Definition
Th17 cells	T-helper 17 cells, a subset of T cells that produce IL-17 and are involved in autoimmune and inflammatory diseases.
TRMs	Tissue-resident memory T cells, a subset of T cells that persist in tissues after infection and can contribute to chronic inflammation in autoimmune diseases like psoriasis.
ustekinumab	A monoclonal antibody that targets the p40 subunit shared by IL-12 and IL-23, used to treat psoriasis and other autoimmune conditions.

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.