

Validating the "Bat Engine" for Target Discovery: PS-1001, a First-in-Class Pan-Inflammasome Inhibitor Inspired by Evolutionary Biology

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The Paratus Discovery Engine: Decoding Evolution to Discover First-in-Class Targets

Bats: Nature's Model for Disease Resilience

Across millions of years, natural selection has shaped bats to survive extremes of physiology and environment, producing adaptations that regulate immunity, metabolism, cellular stress responses, and longevity. By decoding these solutions at genomic scale across hundreds of bat species, Paratus translates evolutionary advantage into first-in-class therapeutic targets.

Inflammation without damage: Strong antiviral defenses with precision-controlled inflammation

Metabolic resilience: Flight-driven extreme metabolism without the cardiac or metabolic damage that drive human disease

Longevity under stress: Bats maintain cellular health and tissue integrity across long lifespans despite intense physiological demands

AI-Driven Discovery Engine

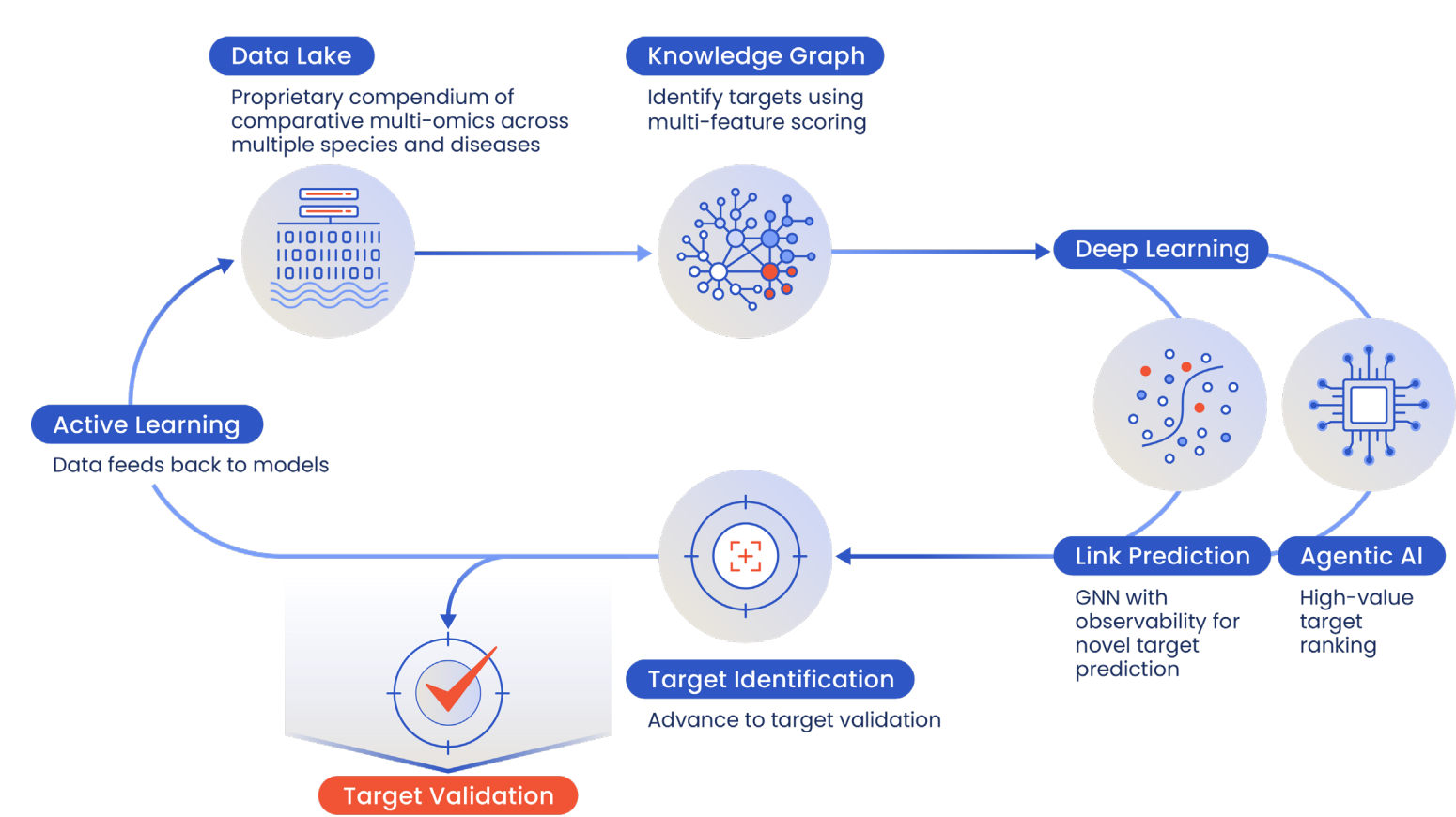


Fig. 1 The Paratus Discovery Engine connects a proprietary multi-omics data lake to knowledge graph-based target prediction and agentic AI triage—a closed-loop pipeline from evolutionary signal to validated target.

Active focus areas: Immunology & Inflammation - Cardiometabolic Disease

- Scale and Breadth:** The Knowledge Graph integrates proprietary multi-omic data across species and diseases, surfacing hundreds of candidates unconstrained by prior hypotheses or expert bandwidth.
- Speed:** Agentic AI triages candidates by disease relevance, druggability, competitive landscape, and evolutionary fit—compressing months of expert review into weeks.
- Continuous Improvement:** Experimental results feed back into model retraining each cycle via lab-in-a-loop, making the platform progressively faster and more accurate.

ASC: An Evolutionarily Validated Inflammasome Target

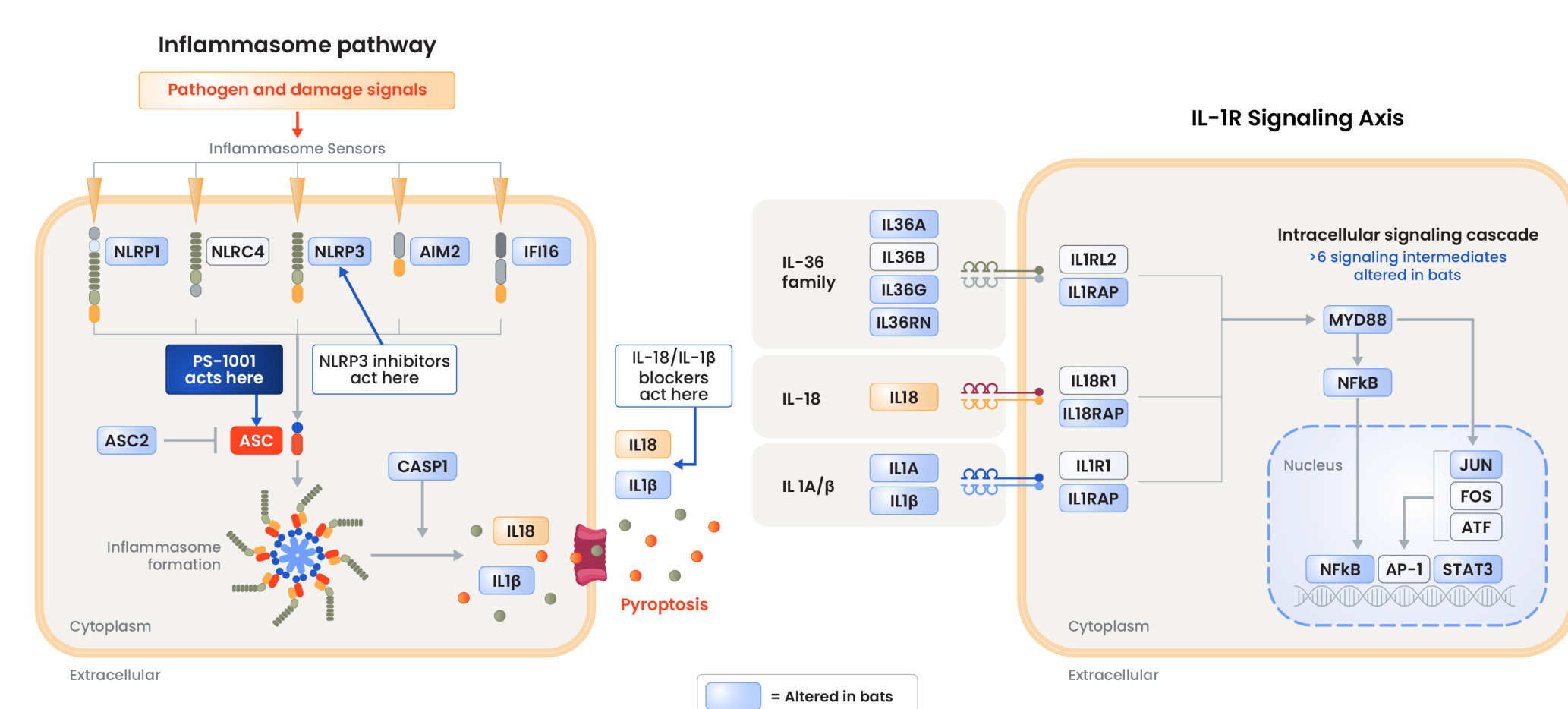
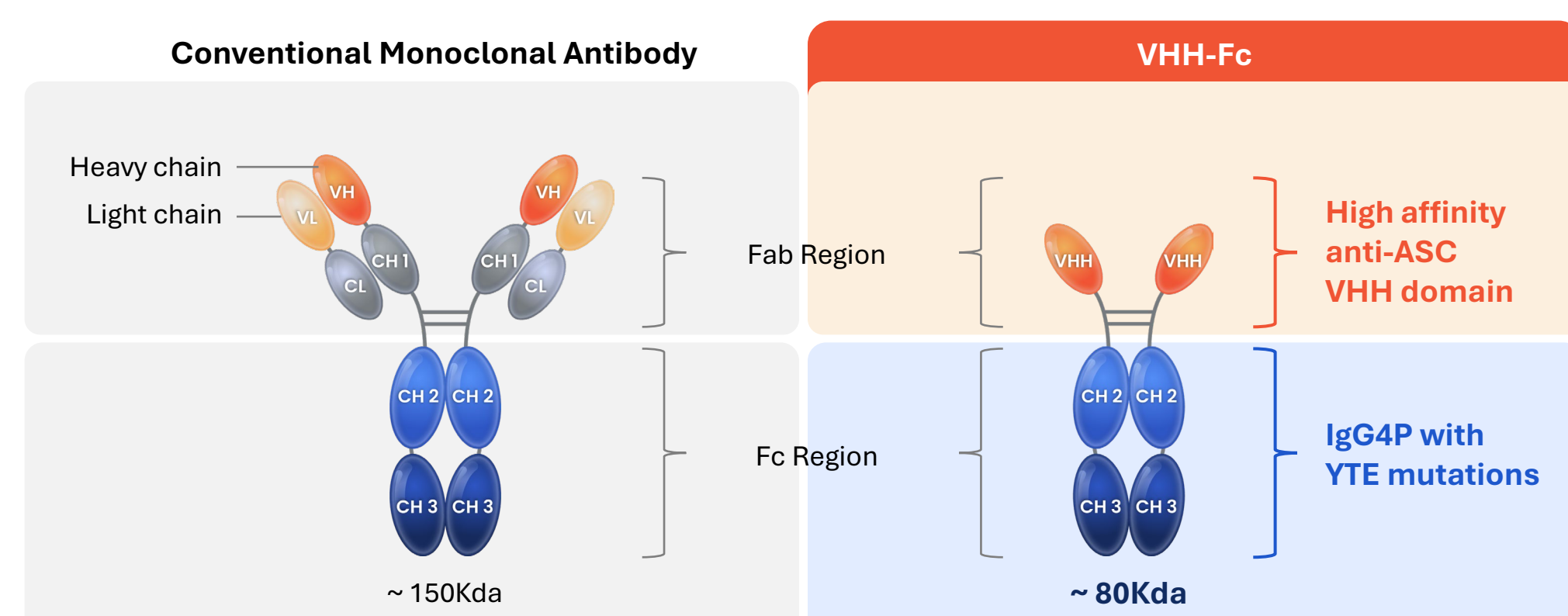


Fig. 2 Bat genomes show extensive evolutionary adaptations across inflammasome and IL-1R signaling axes. ASC emerged as the highest confidence therapeutic node at the convergence of the bat evolutionary signature.

- Evolutionary signal:** Bat genomes carry gain-of-function mutations in ASC2 and widespread adaptations across the IL-1 superfamily—convergent evidence identifying ASC as a high-confidence target. (Ahn et al., Cell 2023)
- Central regulatory node:** ASC governs the release of both IL-1β and IL-18 across all major inflammasome sensors—inhibiting ASC offers pan-inflammasome control.
- Platform proof-of-concept:** ASC is the basis for PS-1001, validating the platform's capacity to generate first-in-class therapeutic hypotheses.

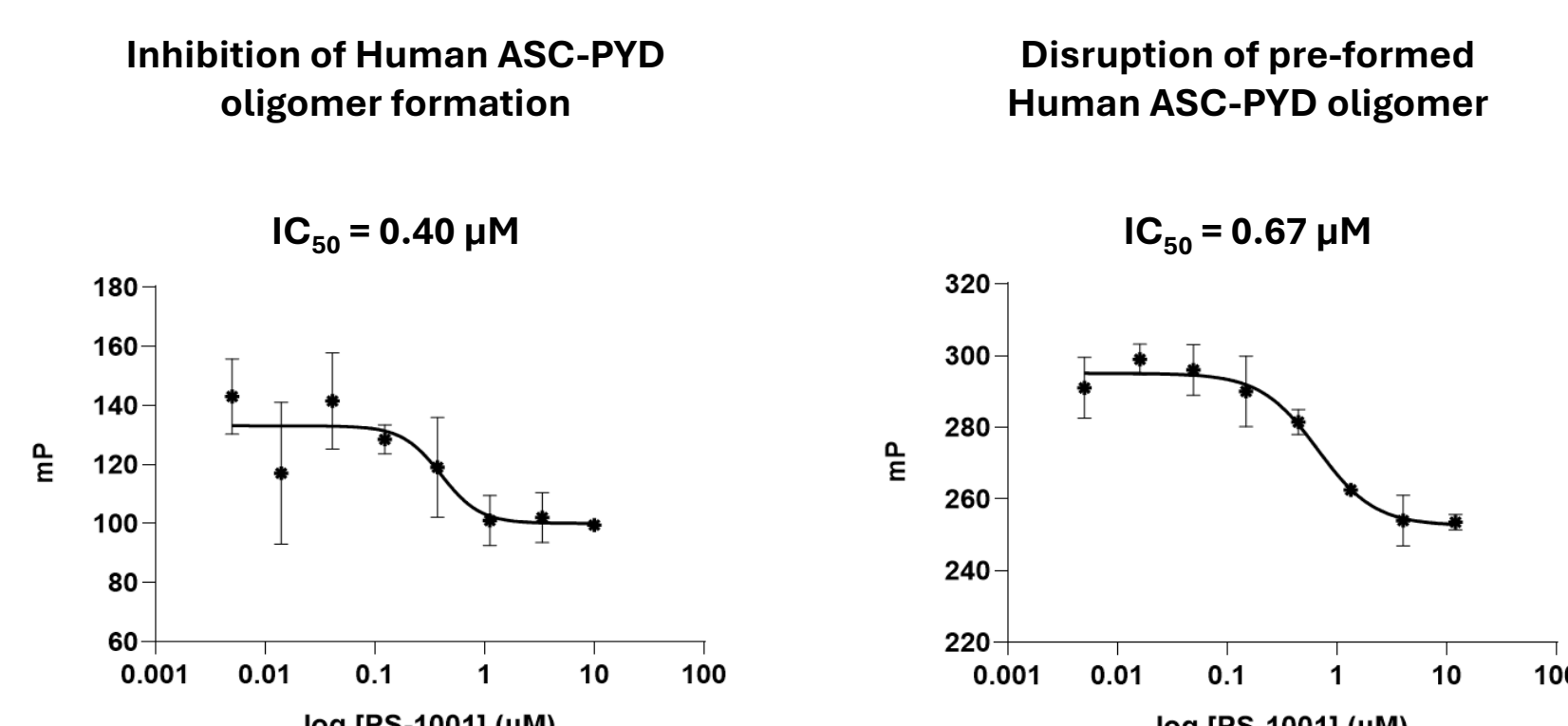
PS-1001 Molecular and Pharmacologic Profile

PS-1001 Molecule Profile



- Structure:** PS-1001 is a bivalent VHH-Fc fusion protein (80 kDa) consisting of a high affinity anti-ASC VHH domain fused to a human IgG4P Fc backbone engineered with half-life extending mutations.
- Tissue Penetration:** Smaller format than conventional antibodies facilitates deep tissue penetration.
- Intracellular Delivery:** PS-1001 was engineered for intracellular uptake and cellular potency, ensuring potent target engagement.

Dual Mechanism of Action

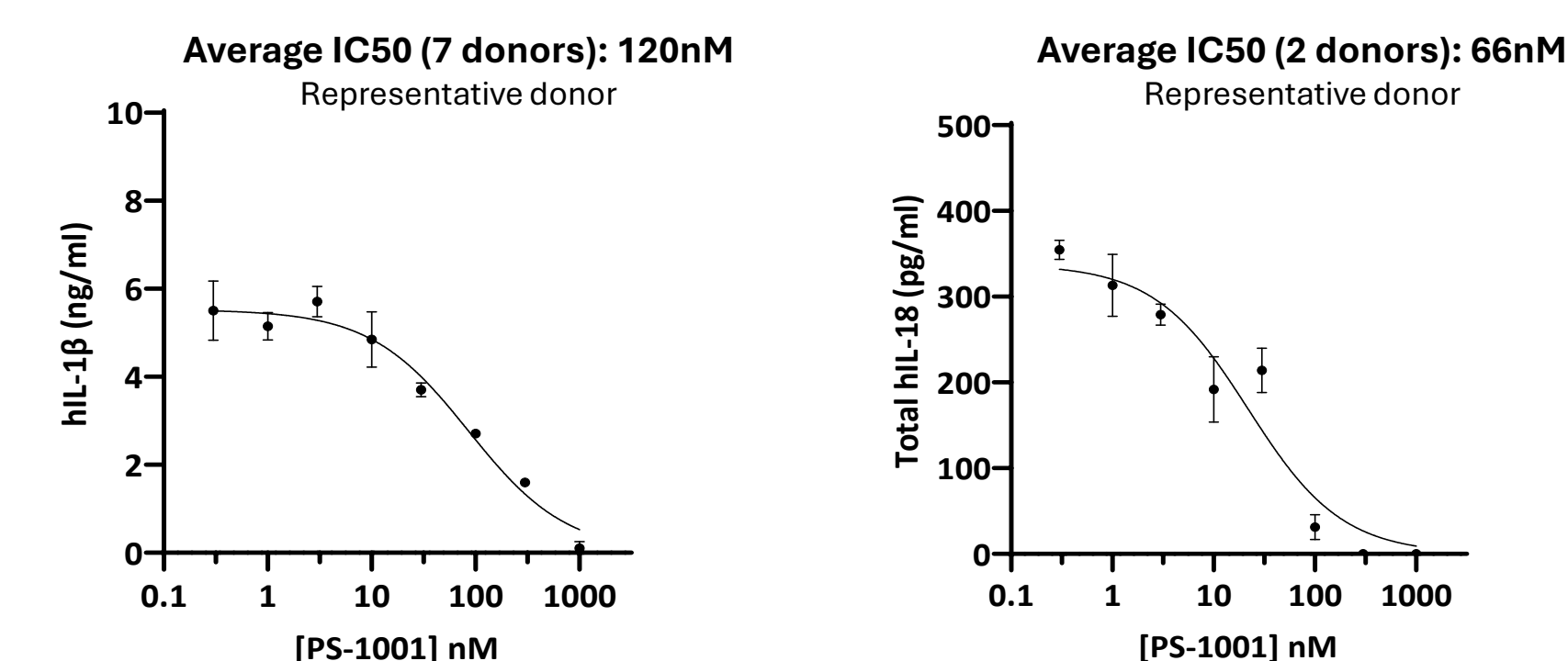


PS-1001 inhibits the inflammasome via two distinct mechanisms:

- Inhibition of Speck Formation:** Inhibits nucleation of productive ASC filament formation, preventing inflammasome activation, pyroptosis, and cytokine release.
- Disruption of Pre-formed Specks:** Actively disassembles existing ASC filaments—both intracellular and extracellular—dampening the spread of inflammation.

Potent Cellular Activity

PS-1001 potently inhibits IL-1β and IL-18 release in inflammasome-activated (LPS:ATP) human PBMCs.

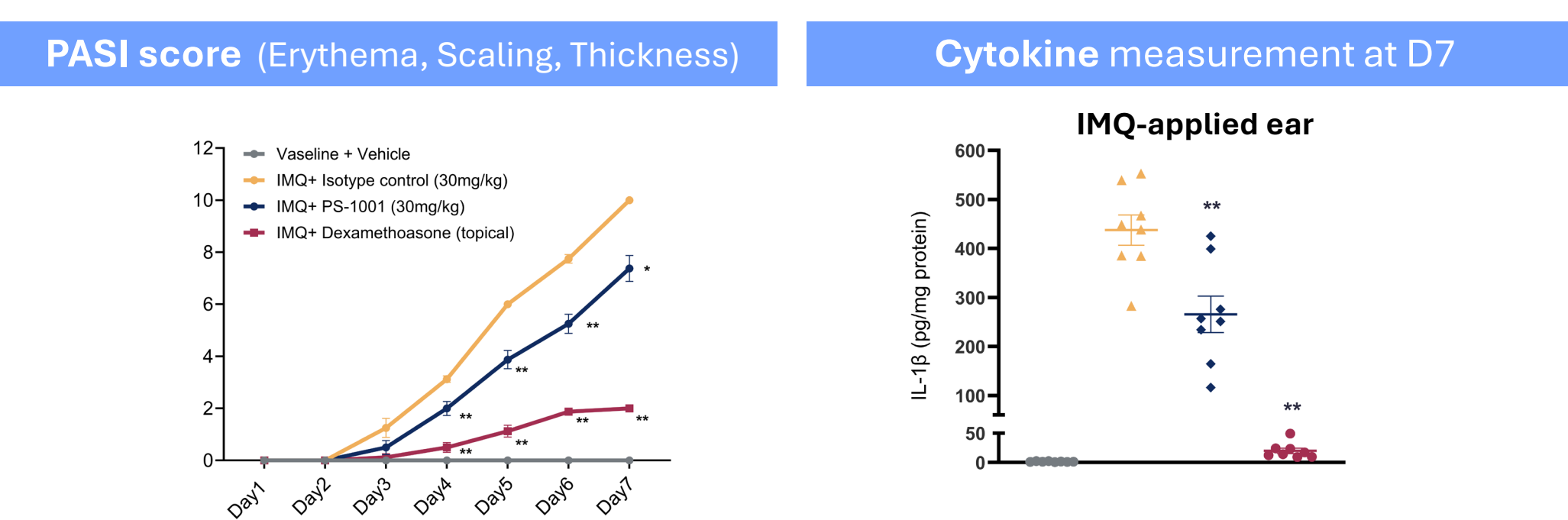


	Mechanism	Limitation
Single cytokine blockers	Single cytokine (IL-1β or IL-18)	Misses the other cytokine
NLRP3 inhibitors	Single inflammasome sensor	NLRP1, NLRP4, AIM2, Pyrin pathways remain active
PS-1001 (ASC)	Pan-inflammasome, blocks all sensors, IL-1β + IL-18	

In Vivo and Translational Proof-of-Concept

Efficacy in Murine Inflammatory Models

In Vivo Efficacy: PS-1001 significantly reduced disease pathology and inflammation in the Imiquimod (IMQ)-induced psoriasis model.

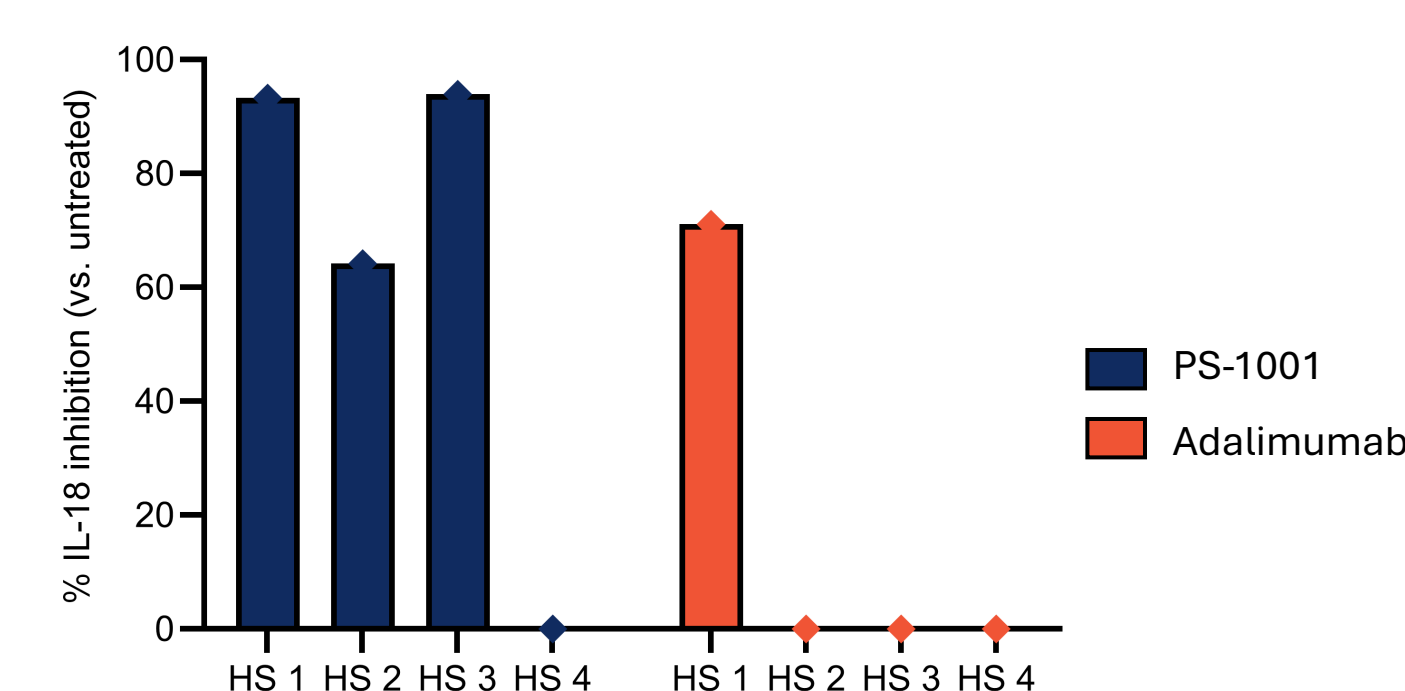


Photographs of back skin at D7



- Broad Activity:** Robust efficacy was also demonstrated in murine Gout and Colitis models, confirming broad anti-inflammatory activity across disease contexts.

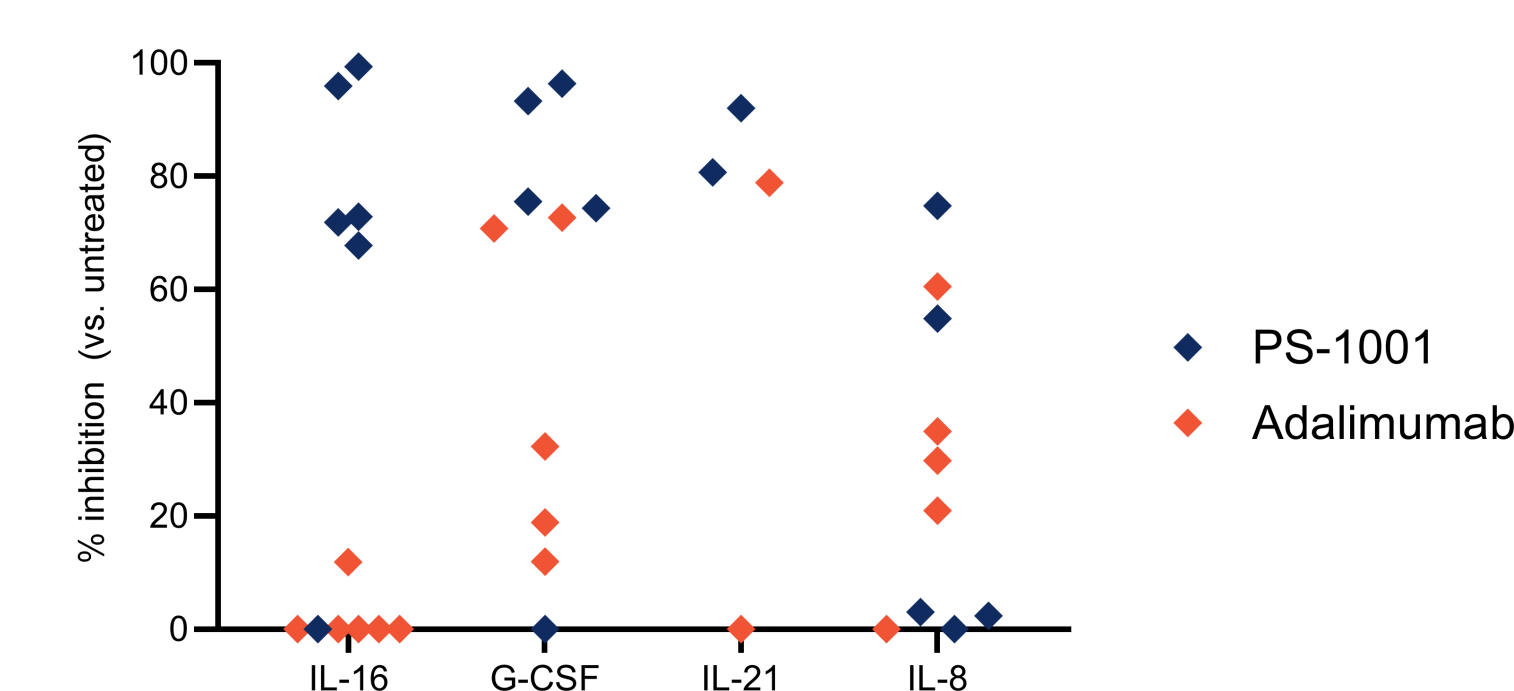
Potent IL-18 Inhibition in HS Patient-Derived Skin



- Robust Response:** PS-1001 achieved a >60% reduction in IL-18 secretion compared to vehicle in 3/4 patient donors.
- Target Engagement:** Significant IL-18 suppression confirms tissue penetration and target engagement in HS lesional skin.
- Distinct Mechanism:** IL-18 is a key inflammatory driver in HS that is not addressed by IL-1 inhibitors or approved biologics.

Preclinical Proof-of-Concept in Hidradenitis Suppurativa (HS): PS-1001 was evaluated in the HS 3D-SeboSkin model, an ex vivo system derived directly from lesional skin of HS patients that preserves the native immune architecture and inflammatory milieu of the disease (Zouboulis et al., Pharmaceuticals 2023).

Broad Innate and Adaptive Axis Suppression in HS

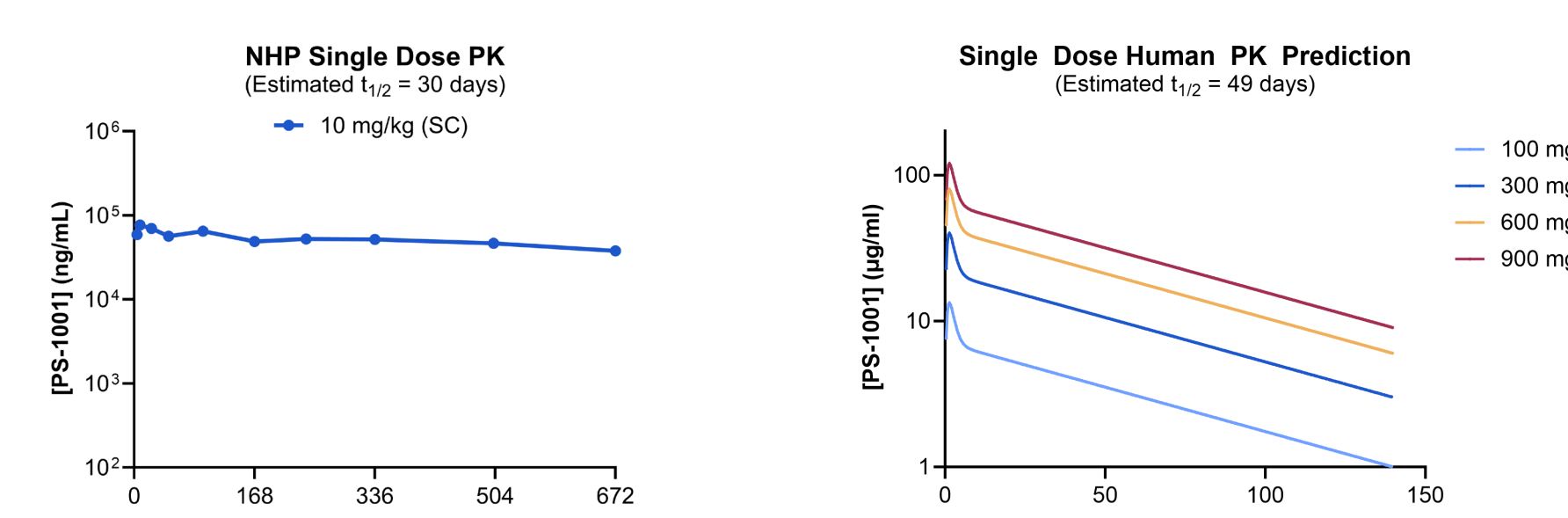


- Upstream vs Downstream:** PS-1001 suppresses a broader repertoire of pro-inflammatory cytokines than adalimumab's single downstream TNF-α blockade.
- Neutrophil axis (IL-8, G-CSF):** Suppression of key chemoattractants limits neutrophil infiltration, a central driver of abscess formation and purulence in HS.
- Chronicity signals (IL-21, IL-16):** Disrupts T-cell recruitment and the Th17-driven persistence mechanism underlying chronic HS lesions.
- Th1/IFN-γ axis (IL-18):** Direct IL-18 suppression disrupts IFN-γ production and the self-perpetuating Th1 inflammatory loop.

Safety, PK & Clinical Readiness

- Non-Clinical Safety:** PS-1001 was well tolerated following two SC doses in NHP (40 and 160 mg/kg), with no adverse findings over a 20-day recovery period.
- CMC and Developability:** High-concentration (>100 mg/mL) liquid formulation with low viscosity and excellent stability supports a low-volume SC autoinjector presentation. Clinical-grade drug substance manufactured at scale and released for GLP toxicology studies.
- Immunogenicity Risk:** Favorable profile observed in *in vitro* assays (50 donors), demonstrating low T-cell activation potential comparable to approved biologics.

Predicted Human PK Supports Infrequent Dosing



- Modeling Strategy:** PK-PD modeling supports a maintenance dosing interval of up to once every three months (Q3M).
- Half-Life Extension:** Engineered Fc backbone confers a predicted human half-life (t_{1/2}) of ~49 days, enabling infrequent SC maintenance dosing suited to chronic inflammatory disease.

Conclusion

- Paratus Discovery Engine:** Evolutionary biology, deep multi-omic data, and agentic AI decode nature's most resilient mechanisms, generating first-in-class therapeutic targets.
- Discovery of ASC:** Bat biology identified ASC as an evolutionarily validated target, a central regulatory node governing pan-inflammasome activity across the IL-1 superfamily.
- PS-1001** is a first-in-class pan-inflammasome inhibitor translating bat biology into human pharmacology, delivering simultaneous IL-1β and IL-18 suppression across all sensors—a profile not achievable with single cytokine blockers or NLRP3 inhibitors.
- Path to Clinic:** PS-1001 is a potent, long-acting ASC inhibitor with a predicted dosing interval of up to Q3M, supporting treatment of multiple inflammatory diseases. Toxicology studies are underway and First-in-Human trials are planned for early 2027.