PS-1001, a Novel Pan-Inflammasome Inhibitor Targeting the Adaptor Protein ASC: A Platform Candidate for Inflammasome-Driven Inflammatory Diseases

Nisha Padmanabhan[1], Edwin K. Lim[1], Abigail YT Loh[1], Qihui Seet[1], Amir M. Hossini[2,3], Christos C. Zouboulis[2,3,4], **Ganesh M. Mugundu[5]**, Mark Cockett[5], Lewis Z. Hong[1]

[1] Paratus Sciences, Singapore, [2] Departments of Dermatology, Venereology, Allergology and Immunology, Staedtisches Klinikum Dessau, Dessau, Germany, [3] Brandenburg Medical School Theodor Fontane and Faculty of Health Sciences Brandenburg, Neuruppin, Germany, [4] Department of Dermatology, Venereology and Immunology, Universitaetsklinikum Ruppin-Brandenburg, Neuruppin, Germany, [5] Paratus Sciences, Boston, USA

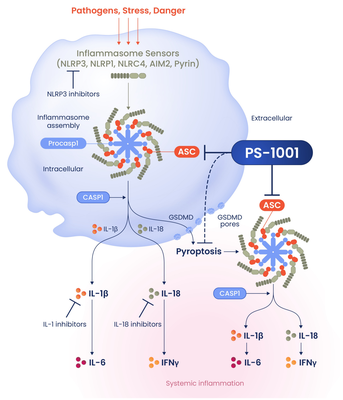
1. PS-1001 Mechanism

ASC Inhibition: Novel Mechanism to Achieve Pan-Inflammasome Inhibition

Overcoming the Limitations of Single Cytokine and Single Sensor Blockade

WHERE ALL SENSORS CONVERGE

ASC has Resisted Small-Molecule Drug Discovery to Date; PS-1001 is a Biologic Engineered to Reach it.



Genetically & Clinically Validated Pathway

Gain-of-function mutations cause severe autoinflammatory disease
NLRP1 → skin disorders[1] · NLRP3 → CAPS[2] · NLRC4 → MAS[3–5]

Complete CASP1 loss-of-function is compatible with life
Eight individuals reached adulthood and had children, with no excess infection risk[6]

Blocking inflammasome output already delivers clinical efficacy
Approved IL-1 pathway blockade validates the pathway, but does not address IL-18 & pyroptosis

1. Zhong et al, Cell (2016) 2. Booshehri and Hoffman, J Clin Immunol (2019)
3. Canna et al, Nat Genet (2014) 4. Kitamura et al, J Exp Med (2014)
5. Romberg et al, Nat Genet (2014) 6. Dominy et al, J Allergy Clin Immunol (2026)

2. Molecular Profile

PS-1001: A First in Class, Potent and Long-Acting Pan-Inflammasome Inhibitor

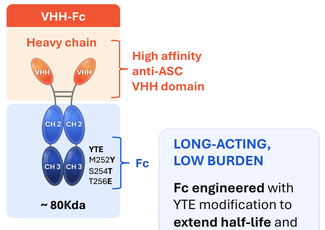
DIFFERENTIATED MECHANISM

Intracellular and extracellular ASC inhibition, dual-MoA action with **disease-modifying potential**

POTENT ANTI-ASC INHIBITOR

Pan-inflammasome control ASC is the convergence point for NLRP3, NLRP1, AIM2, NLRC4 and Pyrin

PS-1001 inhibits production of IL-1β and IL-18



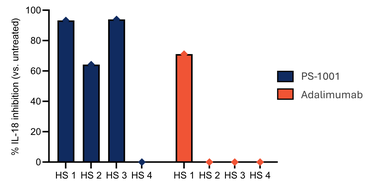
LONG-ACTING, LOW BURDEN

Fc engineered with YTE modification to **extend half-life** and **enable longer dosing intervals**

Preclinical data; further evaluation ongoing. VHH-Fc = anti-ASC single-domain (VHH) binder on a human IgG4P Fc with YTE (M252Y/S254T/T256E) half-life extension

4. *Ex Vivo* PD

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.

Human *Ex Vivo* PD 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., Pharmaceutics 2023)*.

5. *In Vivo* Efficacy

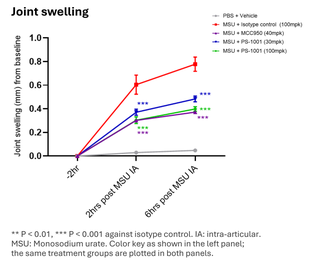
Efficacy Demonstrated In Mouse and Non-Human Primate Models

Blockade at ASC translates into disease-level effect *in vivo*, **matching an NLRP3 inhibitor in gout and an anti-IL-17 antibody in NHP psoriasis**. Reduced disease activity was also seen in mouse psoriasis and colitis models.

Mouse Gout MSU-INDUCED

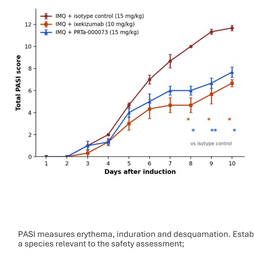
Reduced joint swelling and improved pain sensitivity, PS-1001(IV) at 30 and 100 mg/kg comparable to MCC950 (IP) at 40mg/kg.

Joint swelling



NHP Psoriasis IMQ-INDUCED

PASI score with a representative ASC VHH-Fc (PRTa-000073) comparable to ixekizumab, an approved anti-IL-17.



MSU: Monosodium urate. Color key as shown in the left panel; the same treatment groups are plotted in both panels.

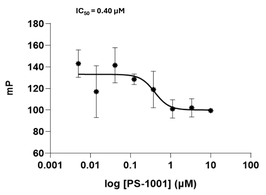
** P < 0.01, *** P < 0.001 against isotype control. IA: intra-articular.

PASI measures erythema, induration and desquamation. Establishes PD in a species relevant to the safety assessment;

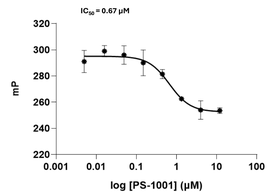
3. Pharmacology: *In vitro* and Human PBMC Data

Dual Mechanism of Action

Inhibition of Human ASC-PYD oligomer formation



Disruption of pre-formed Human ASC-PYD oligomer

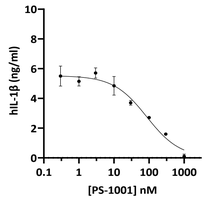


PS-1001 inhibits the inflammasome via two distinct mechanisms:

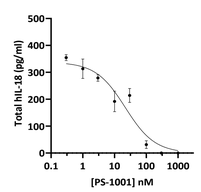
- **Inhibition of Speck Formation:** Inhibits nucleation of productive ASC filament formation, preventing inflammasome activation, pyroptosis, and cytokine release (IL-1β and IL-18).
- **Disruption of Pre-formed Specks:** Actively disassembles existing ASC filaments—both intracellular and extracellular—dampening the spread of inflammation.

Potent Cellular Activity

Average IC50 (7 donors): 120nM
Representative donor



Average IC50 (2 donors): 66nM
Representative donor



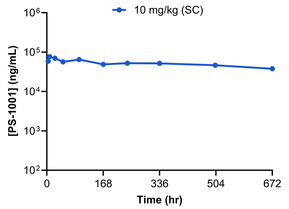
PS-1001 potently inhibits IL-1β and IL-18 release in inflammasome-activated (LPS:ATP) human PBMCs.

	Mechanism	Limitation
Single cytokine blockers	Single cytokine (IL-1β or IL-18)	Misses the other cytokine
NLRP3 inhibitors	Single inflammasome sensor	NLRP1, NLRC4, AIM2, Pyrin pathways remain active
PS-1001 (ASC)	Pan-inflammasome, blocks all sensors, IL-1β + IL-18	

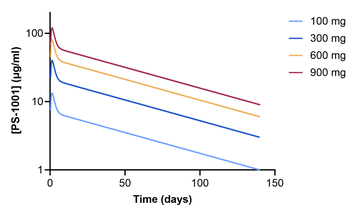
6. Predicted Human PK

Long Half-Life Supports Maintenance Dosing of Every 3 Months

NHP Single Dose PK
(Estimated $t_{1/2}$ = 30 days)



Single Dose Human PK Prediction
(Estimated $t_{1/2}$ = 49 days)



- **Half-Life Extension:**
  Engineered Fc backbone confers a predicted human half-life (t1/2) of ~49 days, enabling infrequent SC maintenance dosing suited to chronic inflammatory disease.
- **Infrequent Dosing:**
  PK-PD modeling supports a maintenance dosing interval of up to **once every three months (Q3M).**

7. Favorable Safety and Clinical Readiness

A Strong Foundation for Clinical Development

- **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 .GLP Tox study is ongoing.
- **CMC and Developability:**. Clinical-grade drug substance manufactured at scale and released for GLP toxicology studies.
- **Lower Immunogenicity Risk:** Favorable profile observed in *in vitro* assays (50 donors), demonstrating low T-cell activation potential comparable to approved biologics.

Conclusion

- **PS-1001 is a first-in-class, potent pan-inflammasome inhibitor targeting ASC.**
- **Activity demonstrated across multiple inflammasome-driven *in vivo* models and broad suppression of inflammatory mediators in human *ex vivo* tissue.**
- **The integrated preclinical package supports advancement into IND-enabling studies, with priority focus on genetically and mechanistically defined autoinflammatory syndromes where IL-1β and IL-18 co-dysregulation drives pathology.**