IL-1A Report

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With Gemini 3.5 as Research Assistant

Introduction & Biological Mechanism

Interleukin-1 alpha (IL-1α) is a foundational, dual-function pro-inflammatory cytokine and primary "alarmin" belonging to the Interleukin-1 cytokine superfamily. Unlike its sister cytokine Interleukin-1 beta (IL-1β)—which requires cleavage by the NLRP3/Caspase-1 inflammasome to achieve biological activity—IL-1α is unique because its precursor protein is constitutively expressed and biologically active in its intact form within healthy epithelial tissues, keratinocytes, vascular endothelial cells, and mucosal barrier linings. When cells experience ischemia, mechanical trauma, toxic exposure, or necrotic cell death, intact precursor IL-1α is immediately released into the extracellular microenvironment. In this context, IL-1α functions as a classic damage-associated molecular pattern (DAMP) or "alarmin," sending an instantaneous signal to neighboring immune and stromal cells that barrier integrity has been compromised. In addition to its secreted and membrane-bound forms, precursor IL-1α can translocate to the nucleus, where it acts as a transcriptional regulator to amplify cellular stress responses.
Upon extracellular release or surface presentation, IL-1α binds to the cell-surface Interleukin-1 Receptor Type 1 (IL-1R1). Receptor binding recruits the IL-1 Receptor Accessory Protein (IL-1RAcP) to form a high-affinity signaling complex. This intracellular complex recruits the adapter protein MyD88, IRAK family kinases, and TRAF6, initiating downstream activation of nuclear factor kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs). This cascade triggers transcription of a secondary inflammatory wave, including Tumor Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), Cyclooxygenase-2 (COX-2), matrix metalloproteinases (MMPs), and neutrophil-attracting chemokines such as IL-8 (CXCL8).

Signs, Symptoms, and Associated Diseases

Because epithelial barriers and vascular structures serve as massive storage reservoirs for preformed IL-1α, dysregulated IL-1α activity drives severe cutaneous, fibrotic, vascular, and systemic inflammatory disorders.

Associated Clinical Diseases

- **Dermatological & Barrier Inflammatory Disorders:** Skin tissue contains high concentrations of constitutive IL-1α. Uncontrolled IL-1α signaling drives chronic, destructive skin pathologies including Hidradenitis Suppurativa (HS), Psoriasis, Atopic Dermatitis (Eczema), and severe nodulocystic Acne Vulgaris.

- **Systemic Sclerosis (Scleroderma) & Fibrotic Conditions:** IL-1α binds with higher affinity than IL-1β to IL-1R1 on dermal and pulmonary fibroblasts. Overproduction of IL-1α induces a persistent cycle of fibroblast activation, collagen deposition, vascular endothelial damage, and microthrombi formation, contributing to lung and skin fibrosis in Systemic Sclerosis.

- **Vascular Pathology and Atherosclerosis:** Endothelial cell-surface IL-1α bridges circulating platelets to vascular walls, promoting leukocyte recruitment, arterial plaque instability, and chronic vasculopathy.

- **Oncology & Tumor-Mediated Inflammation:** In advanced solid tumors—such as colorectal, pancreatic, and non-small cell lung cancers—tumoral IL-1α drives tumor angiogenesis, local invasion, metastatic spread, and systemic cancer cachexia (severe muscle wasting and anorexia).

- **Rheumatoid Arthritis (RA) & Joint Destruction:** Synovial cell necrosis releases IL-1α into joint spaces, stimulating chondrocytes and synovial fibroblasts to secrete collagenases and RANKL, accelerating cartilage breakdown and periarticular bone erosion.

- **Neuroinflammation & Central Sensitization:** In the central nervous system, IL-1α released by injured astrocytes and primed microglia drives persistent neuroinflammation, underlying central sensitization in Fibromyalgia, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), and Long COVID.

‘Associated Physical Signs and Symptoms

Patients with chronic elevated IL-1α production typically present with severe inflammatory cutaneous lesions (painful nodules, sinus tracts, and scaling plaques), persistent localized burning and pruritus, joint morning stiffness and synovitis, profound debilitating physical fatigue, unrefreshing sleep, cognitive dysfunction ("brain fog"), low-grade systemic fevers, and elevated serum inflammatory markers, such as high-sensitivity C-reactive protein (hs-CRP) and erythrocyte sedimentation rate (ESR).

Targeted Pharmacological Interventions & Biological Therapeutics

‘Therapeutics designed to block the IL-1α pathway include highly specific anti-IL-1α monoclonal antibodies as well as broad IL-1 receptor antagonists that inhibit both IL-1α and IL-1β.

1. **Specific Anti-IL-1α Monoclonal Antibodies**

- **Bermekimab (JNJ-77474462 / MABp1 / Xilonix):** A first-in-class, fully human IgG1k monoclonal antibody engineered to specifically bind and neutralize human IL-1α. By targeting IL-1α selectively, Bermekimab blocks IL-1R1 engagement by IL-1α without interfering with IL-1β activity. Bermekimab has demonstrated efficacy in Phase II clinical trials for Hidradenitis Suppurativa, Systemic Sclerosis, Atopic Dermatitis, and advanced metastatic cancers.

2. Dual IL-1α / IL-1β Receptor Blockers & Traps

- **Anakinra (Kineret):** A recombinant human Interleukin-1 receptor antagonist (rIL-1Ra). Anakinra competitively binds to IL-1R1 on cell membranes, blocking receptor assembly with IL-1RAcP and inhibiting signaling downstream of both IL-1α and IL-1β. It is FDA-approved for Rheumatoid Arthritis, Neonatal-Onset Multisystem Inflammatory Disease (NOMID), and Deficiency of IL-1Ra (DIRA).

- **Rilonacept (Arcalyst):** A dimeric soluble fusion protein ("IL-1 trap") that incorporates the extracellular binding domains of IL-1R1 and IL-1RAcP linked to the Fc portion of human IgG1. It acts as a circulating sink that binds both IL-1α and IL-1β with high affinity before they can reach cell-surface receptors.

Comparative Effectiveness, Costs, and Potential Side Effects

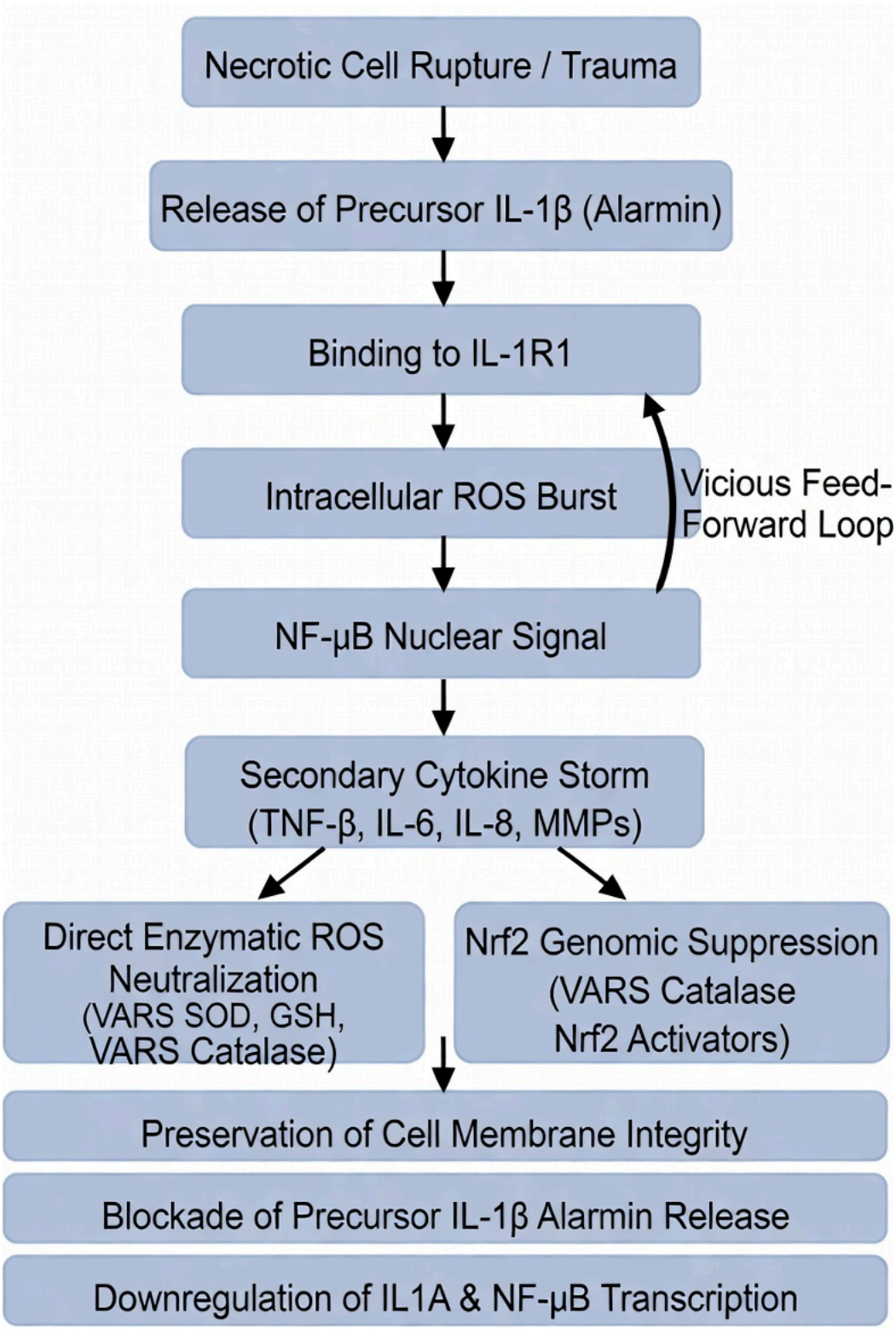
Therapy	Primary Indication / Mechanism	Clinical Effectiveness	Estimated Cost	Potential Side Effects & Drawbacks
Bermekimab (Selective mAb)	Hidradenitis Suppurativa, Systemic Sclerosis, Cancer; direct IL-1α neutralization.	High efficacy in clinical trials; achieved significant reductions in abscesses, pain scores, and skin/lung fibrosis scores.	High ($30,000–$60,000+ per year in trial settings).	Injection-site reactions, upper respiratory tract infections, headache, fatigue, variable late-phase endpoints in specific dermatologic al trials.

Therapy	Primary Indication / Mechanism	Clinical Effectiveness	Estimated Cost	Potential Side Effects & Drawbacks
Anakinra (Recombinant IL-1Ra)	RA, CAPS/NOMID, systemic autoinflammatory conditions; competitive IL-1R1 blockade.	High efficacy in systemic autoinflammation and febrile syndromes; rapid onset but requires daily subcutaneous injections.	High ($40,000–$60,000 annually).	Injection-site reactions (occurring in up to 70% of patients), risk of severe bacterial infections, neutropenia, headache.
Rilonacept (Soluble IL-1 Trap)	Recurrent Pericarditis, Cryopyrin-Associated Periodic Syndromes (CAPS); dual IL-1α/β trap.	Highly effective in suppressing disease flares and chronic chest/joint pain; weekly dosing schedule.	Very High ($150,000–$200,000+ annually).	Upper respiratory infections, injection-site erythema, minor lipid profile elevations, risk of serious opportunistic infections.

The VARS Triad as Adjuvant or Stand-Alone Therapy

For patients seeking targeted non-pharmaceutical options, controlling IL-1α-driven systemic inflammation requires addressing two cellular vulnerabilities: intracellular reactive oxygen species (ROS) production and necrotic cell membrane rupture. When extracellular IL-1α binds IL-1R1, it triggers immediate NADPH oxidase (NOX) activation, generating intracellular ROS that sustain NF-κB nuclear signaling. Furthermore, oxidative stress compromises cell membrane integrity, causing necrotic cell lysis that releases stored precursor IL-1α alarmins into circulation.

The **VARS Triad**—comprising **VARS Glutathione**, **VARS Superoxide Dismutase (SOD)**, and **VARS Catalase** (fortified with super active **Nrf2 enhancers**)—provides a comprehensive enzymatic and genomic defense to break this self-sustaining alarmin release loop.



Advanced Biochemical & Genomic Mechanisms Against IL-1α Pathophysiology

- **VARS Superoxide Dismutase (SOD):** Rapidly converts superoxide radicals ($O_2^{\cdot -}$)—generated downstream of IL-1R1 receptor ligation—into hydrogen peroxide (H_2O_2). By neutralizing superoxide, SOD prevents its reaction with nitric oxide to form peroxynitrite ($ONOO^-$), preserving microvascular endothelial function and preventing inflammatory vascular damage.

- **VARS Catalase (with Super Active Nrf2 Enhancers):** Delivers a dual-action defense against IL-1α alarmin signaling:

    1. *Direct Enzymatic Neutralization:* Converts hydrogen peroxide (H_2O_2) into water (H_2O) and molecular oxygen (O_2). This stops Fenton-reaction-induced hydroxyl radical ($OH^{\bullet}$) generation, preventing lipid peroxidation of epithelial and keratinocyte cell membranes. Preserving cell membrane integrity keeps preformed precursor IL-1α trapped inside intact cells, preventing its release as an extracellular alarmin.

    2. *Potent Nrf2 Genomic Induction:* Active Nrf2 enhancers incorporated within VARS Catalase induce nuclear translocation of Nrf2 and binding to Antioxidant Response Elements (ARE). Active Nrf2 directly represses NF-κB transcription, downregulates *IL1A* gene transcription, decreases secondary cytokine expression, and restores cellular antioxidant homeostasis.

- **VARS Glutathione (GSH):** Functions as the primary intracellular thiol antioxidant and electron donor. Sustained IL-1α signaling rapidly depletes intracellular reduced GSH. Restoring reduced GSH buffers against oxidative stress, maintains mitochondrial inner membrane potential, prevents necrotic cell death, and stops the release of intracellular IL-1α alarmins.

Clinical Application: Adjuvant vs. Stand-Alone Protocols

- **As an Adjuvant Therapy:** When combined with targeted biologicals (such as Bermekimab or Anakinra), the Nrf2-enhanced VARS Triad operates synergistically. While pharmacological agents block extracellular receptor sites or trap circulating cytokines, the VARS Triad quenches intracellular oxidative stress, stabilizes cell membranes to prevent further alarmin leakage, and downregulates inflammatory gene expression via Nrf2 induction.

- **As a Stand-Alone Therapy for "Natural Option" Patients:** For patients who decline synthetic pharmaceuticals or biological injectables due to cost, injection-site side effects, or infection risks, the VARS Triad offers an effective non-pharmaceutical approach. By protecting cellular membrane integrity and inducing Nrf2 antioxidant defense pathways, the triad halts the feed-forward

inflammatory loops driving chronic IL-1α activity without inducing systemic immunosuppression.

- **Tolerability and Safety:** Unlike biological receptor blockers, the VARS Triad does not cause systemic immune suppression or increase susceptibility to severe bacterial or opportunistic infections. It is well-tolerated, cost-effective relative to biological injectables, highly bioavailable, and maintains an exceptionally favorable clinical safety profile.

Conclusion

Interleukin-1 alpha functions as a critical epithelial and endothelial alarmin that drives cutaneous disease, systemic fibrosis, vascular inflammation, and tumor-associated pathology. While targeted biological agents—such as the anti-IL-1α antibody Bermekimab and the receptor antagonist Anakinra—provide effective extracellular blockade, their broad clinical application is restricted by high treatment costs, daily injection burdens, and immunosuppressive risks. The Nrf2-enhanced VARS Triad (Glutathione, SOD, and Nrf2-fortified Catalase) provides a targeted biochemical and genomic protocol to protect cell membrane integrity, quench intracellular ROS, and downregulate *IL1A* gene transcription, serving as a reliable adjuvant or stand-alone therapy.

References

1. Dinarello CA. Overview of the IL-1 family in innate inflammation and adaptive immunity. *Immunol Rev*. 2018;281(1):8-27.
2. Di Paolo NC, Shayakhmetov DM. Interleukin 1α and the inflammatory process. *Nat Immunol*. 2016;17(8):906-913.
3. Kokolakis G, Sabat R, Boer J, et al. Bermekimab in patients with hidradenitis suppurativa: a phase 2, open-label, multicenter study. *J Am Acad Dermatol*. 2020;83(5):1311-1318.
4. Karonis M, Kanni T, Baziaka F, et al. A randomized clinical trial of bermekimab treatment for clinical improvement of systemic sclerosis. *iScience*. 2023;26(9):107626.
5. Cavalli G, Dinarello CA. Suppression of inflammation and acquired immunity by IL-1α and IL-1β blockade. *Front Immunol*. 2021;12:667086.
6. Tonelli C, Chio IIC, Tuveson DA. Transcriptional regulation by Nrf2. *Antioxid Redox Signal*. 2018;29(17):1727-1745.
7. Rider P, Voronov E, Dinarello CA, Apte RN, Cohen I. Alarmins: feel the stress. *FEBS J*. 2017;284(16):2572-2586.