

# IL-17A (rs2275913) Report

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With Gemini 3.5 as Research Assistant

## Introduction & Biological Mechanism

Interleukin-17A (IL-17A) is the signature pro-inflammatory homodimeric cytokine produced predominantly by specialized CD4<sup>+</sup> T helper 17 (Th17) cells, as well as gamma-delta ( $\gamma\delta$ ) T cells, innate lymphoid cells (ILC3s), neutrophils, and invariant natural killer T (iNKT) cells. IL-17A plays an indispensable role in mucosal host defense against extracellular bacterial and fungal pathogens (such as *Candida albicans*). However, when overexpressed, IL-17A acts as a potent driver of tissue destruction, neutrophil recruitment, and chronic autoimmune pathology.

The single nucleotide polymorphism (SNP) designated **rs2275913** (commonly referred to as **-197G>A** or **G197A**) is a critical genetic variant situated in the promoter region of the *IL17A* gene on chromosome 6p12.2. Functional genomic analyses demonstrate that the substitution of guanine (G) with adenine (A) at position -197 significantly alters the transcriptional regulation of IL-17A. Specifically, the **197A (A)** variant allele creates an enhanced binding motif for Nuclear Factor of Activated T cells (NFAT), a major transcription factor governing *IL17A* gene expression downstream of T-cell receptor (TCR) activation.

Consequently, individuals carrying the risk **A allele** (GA or AA genotypes) exhibit significantly higher binding affinity for NFAT, resulting in elevated *IL17A* promoter activity, increased mRNA transcription, and markedly elevated secretion of circulating and local IL-17A protein compared to wild-type GG homozygotes.<sup>5</sup> Once secreted, IL-17A binds to the heterodimeric Interleukin-17 Receptor complex (IL-17RA/IL-17RC) expressed on keratinocytes, synovial fibroblasts, chondrocytes, endothelial cells, and microglial cells. Receptor engagement triggers the recruitment of the adapter protein Act1 and TRAF6, activating nuclear factor kappa B (NF- $\kappa$ B), mitogen-activated protein kinase (MAPK), and C/EBP signaling cascades. This drives excessive release of secondary inflammatory mediators, matrix metalloproteinases (MMPs), and neutrophil-attracting CXC chemokines (such as CXCL1, CXCL2, and IL-8/CXCL8).

## Signs, Symptoms, and Associated Diseases

Genetically determined hyper-expression of IL-17A driven by the *IL17A* rs2275913 risk allele promotes persistent systemic, cutaneous, osteoarticular, and neuroinflammatory disorders.

### Associated Clinical Diseases

- **Psoriasis & Psoriatic Arthritis (PsA):** High local concentrations of IL-17A stimulate keratinocyte hyperproliferation and chemokine production, recruiting neutrophils to form epidermal microabscesses. In joint structures, IL-17A fuels synovial inflammation, enthesitis, and bone erosion.
- **Ankylosing Spondylitis (AS) & Axial Spondyloarthritis:** IL-17A is a primary mediator of inflammation at enthesal insertion sites, accelerating pathological osteoblast activation, syndesmophyte formation, and spinal ankylosis.
- **Rheumatoid Arthritis (RA):** Synovial IL-17A works synergistically with TNF- $\alpha$  and IL-1 $\beta$  to induce synovial fibroblast proliferation, osteoclastogenesis via RANKL expression, and articular cartilage degradation by matrix metalloproteinases.
- **Systemic Lupus Erythematosus (SLE):** Meta-analyses demonstrate that the rs2275913 AA and GA genotypes are significantly associated with increased susceptibility to SLE, where elevated IL-17A promotes B-cell hyperreactivity, autoantibody production, and renal tissue injury.<sup>6</sup>
- **Inflammatory Bowel Disease (IBD - Ulcerative Colitis):** While basal IL-17A contributes to mucosal integrity, dysregulated overproduction driven by the rs2275913 promoter variant exacerbates intestinal mucosal ulceration and chronic systemic inflammation in ulcerative colitis.<sup>5</sup>
- **Neuroinflammation, Central Sensitization & Fibromyalgia:** Microglial cells and astrocytes express functional IL-17RA receptors. Overexpression of IL-17A compromises blood-brain barrier integrity, primes microglial cells, and enhances central pain processing, directly contributing to Fibromyalgia, Long COVID, ME/CFS, and neurodegenerative decline.

## Associated Physical Signs and Symptoms

Patients harboring the rs2275913 risk variant who present with elevated IL-17A levels routinely exhibit erythematous scaling skin plaques, enthesitis (tendon-bone insertion pain, such as Achilles tendonitis), severe morning joint stiffness, chronic spinal rigidity, deep muscular allodynia, widespread neuropathic pain, unrefreshing sleep, debilitating physical fatigue, cognitive dysfunction ("brain fog"), and elevated serum markers including high-sensitivity C-reactive protein (hs-CRP) and erythrocyte sedimentation rate (ESR).

## Targeted Pharmacological Interventions & Biological Therapeutics

Given the foundational role of IL-17A in tissue inflammation, targeted monoclonal antibodies blocking IL-17A or its receptor subunit have transformed the treatment landscape for autoimmune and inflammatory conditions.

### 1. Selective Anti-IL-17A Monoclonal Antibodies

- **Secukinumab (Cosentyx):** A fully human IgG1k monoclonal antibody that selectively binds to and neutralizes circulating IL-17A homodimers, preventing engagement with the IL-17RA/IL-17RC receptor complex. It is FDA-approved for moderate-to-severe plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis.<sup>1</sup>
- **Ixekizumab (Taltz):** A humanized IgG4 monoclonal antibody engineered with high affinity to selectively bind and neutralize both IL-17A and IL-17A/F heterodimers, blunting Th17-mediated tissue destruction.<sup>2</sup>

## 2. Dual IL-17A/F & IL-17 Receptor Blockers

- **Bimekizumab (Bimzelx):** A humanized monoclonal antibody designed to dual-inhibit both IL-17A and IL-17F isoforms, providing broader blockade of the IL-17 signaling axis in plaque psoriasis and psoriatic arthritis.<sup>3</sup>
- **Brodalumab (Siliq):** A human monoclonal antibody that binds to the IL-17RA receptor subunit itself, blocking the biological signaling of IL-17A, IL-17F, IL-17A/F, IL-17C, and IL-17E (IL-25).<sup>4</sup>

## Comparative Effectiveness, Costs, and Potential Side Effects

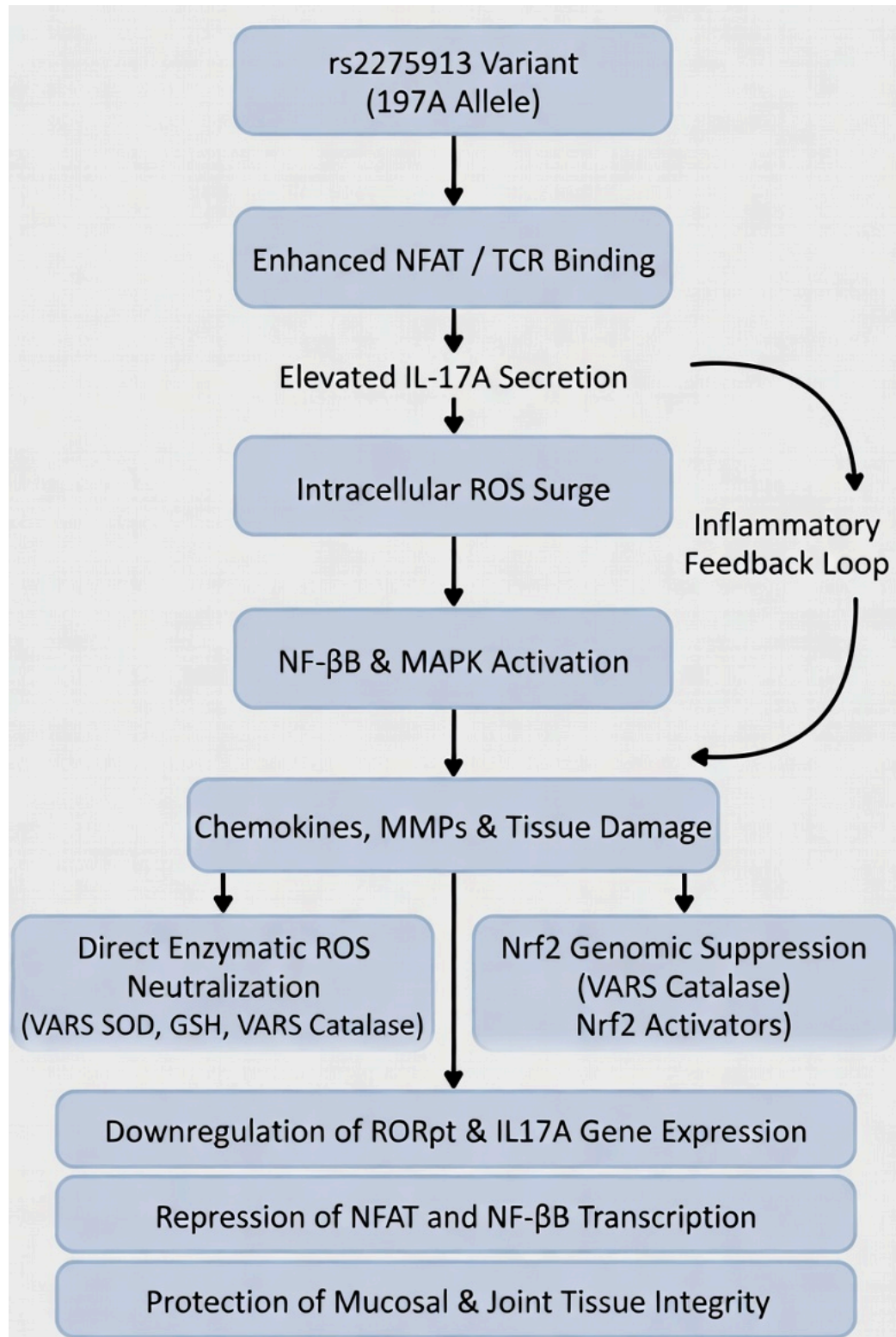
| Therapy                       | Primary Indication / Mechanism                                                   | Clinical Effectiveness                                                                                                  | Estimated Cost                      | Potential Side Effects & Drawbacks                                                                                                                                 |
|-------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|-------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Secukinumab (Cosentyx)</b> | Psoriasis, PsA, Ankylosing Spondylitis; selective IL-17A inhibitor. <sup>1</sup> | High efficacy (PASI 90 achieved in 70–80% of psoriasis patients; marked reduction in spinal inflammation). <sup>1</sup> | High (\$60,000 –\$80,000 annually). | Upper respiratory tract infections, mucocutaneous candidiasis (fungal overgrowth), neutropenia, potential exacerbation of Inflammatory Bowel Disease. <sup>1</sup> |

| Therapy                      | Primary Indication / Mechanism                                                | Clinical Effectiveness                                                                                          | Estimated Cost                     | Potential Side Effects & Drawbacks                                                                                                                      |
|------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Ixekizumab (Taltz)</b>    | Plaque Psoriasis, PsA, Axial Spondyloarthritis; anti-IL-17A mAb. <sup>2</sup> | High clearance rates (PASI 90/100 in up to 80–90% of patients); rapid onset of action. <sup>2</sup>             | High (\$65,000–\$85,000 annually). | Injection-site reactions (common), oral/cutaneous candidiasis, neutropenia, elevated risk of upper respiratory infections. <sup>2</sup>                 |
| <b>Bimekizumab (Bimzelx)</b> | Severe Plaque Psoriasis, PsA; dual IL-17A & IL-17F inhibitor. <sup>3</sup>    | Superior clinical clearance compared to selective IL-17A blockers in head-to-head clinical trials. <sup>3</sup> | High (\$70,000–\$90,000 annually). | Increased incidence of oral candidiasis (~10–15% of patients due to dual IL-17A/F blockade), mild neutropenia, upper respiratory symptoms. <sup>3</sup> |
| <b>Brodalumab (Siliq)</b>    | Severe Plaque Psoriasis; broad IL-17RA receptor antagonist. <sup>4</sup>      | High clearance in recalcitrant psoriasis cases; rapid disease suppression. <sup>4</sup>                         | High (\$40,000–\$60,000 annually). | Boxed Warning for suicidal ideation/behavior, severe mucocutaneous candidiasis, neutropenia, Crohn's disease exacerbation. <sup>4</sup>                 |

## The VARS Triad as Adjuvant or Stand-Alone Therapy

For patients with the *IL17A* rs2275913 risk polymorphism who seek non-pharmaceutical options or wish to avoid the infection risks associated with monoclonal antibodies, controlling IL-17A activity requires targeting both the genomic promoter drive and the intracellular redox loops that maintain Th17 differentiation and NF-κB/NFAT activation.

The **VARs Triad**—comprising **VARs Glutathione**, **VARs Superoxide Dismutase (SOD)**, and **VARs Catalase** (fortified with super active **Nrf2 enhancers**)—delivers a multi-targeted enzymatic and genomic strategy to downregulate IL-17A expression and quench downstream tissue damage.



## Advanced Biochemical & Genomic Mechanisms Against IL-17A Pathophysiology

- **VARs Superoxide Dismutase (SOD):** Rapidly dismutates the superoxide radical ( $O_2^{\cdot-}$ )—produced downstream of IL-17RA receptor ligation in keratinocytes, endothelial cells, and synovial fibroblasts—into hydrogen peroxide ( $H_2O_2$ ). Clearing superoxide prevents its interaction with endothelial nitric oxide to form peroxynitrite ( $ONOO^-$ ), preserving microvascular barrier integrity and blunting neutrophil recruitment.
- **VARs Catalase (with Super Active Nrf2 Enhancers):** Delivers a dual-action biochemical and genomic defense against IL-17A overproduction:
  1. *Direct Enzymatic Catalysis:* Converts hydrogen peroxide ( $H_2O_2$ ) into water ( $H_2O$ ) and molecular oxygen ( $O_2$ ). This eliminates the substrate for Fenton-reaction hydroxyl radical ( $OH^\bullet$ ) formation, preventing lipid peroxidation and matrix degradation in joint cartilage and skin tissue.
  2. *Potent Nrf2 Genomic Induction:* The high-potency Nrf2 activators incorporated within VARs Catalase promote Nrf2 nuclear translocation and ARE binding. Active Nrf2 directly represses the master Th17 lineage transcription factor ROR $\gamma$ t (RAR-related orphan receptor gamma t) and inhibits NFAT and NF- $\kappa$ B activity. By counteracting the hyperactive NFAT binding created by the rs2275913 (197A) promoter variant, Nrf2 activation directly suppresses *IL17A* gene transcription at the genomic level.<sup>7</sup>
- **VARs Glutathione (GSH):** Serves as the central intracellular thiol antioxidant. Intracellular GSH balance is critical for maintaining T-cell redox homeostasis; GSH depletion skews naïve T-cell differentiation toward the pro-inflammatory Th17 phenotype. Restoring intracellular reduced GSH pools inhibits aberrant Th17 differentiation, quenches intracellular oxidative stress, and protects cellular proteins from oxidative damage.

## Clinical Application: Adjuvant vs. Stand-Alone Protocols

- **As an Adjuvant Therapy:** When combined with biological therapeutics (such as Secukinumab or Ixekizumab), the Nrf2-enhanced VARs Triad works synergistically. While biological antibodies neutralize circulating IL-17A ligands extracellularly, the VARs Triad operates intracellularly to quench downstream oxidative cascades, prevent mucosal barrier breakdown, and downregulate genomic *IL17A* transcription through Nrf2 pathways. Crucially, the VARs Triad supports mucosal cellular health without suppressing host immune defense against opportunistic pathogens.
- **As a Stand-Alone Therapy for "Natural Option" Patients:** For patients harboring the rs2275913 risk allele who decline injectable biologicals due to cost, fear of immunosuppression, or history of recurrent infections, the VARs Triad provides a non-pharmaceutical approach. By combining direct ROS

neutralization with Nrf2-mediated transcriptional repression of ROR $\gamma$ t, NFAT, and *IL17A*, the triad systematically dampens the IL-17A axis without causing systemic immune suppression.

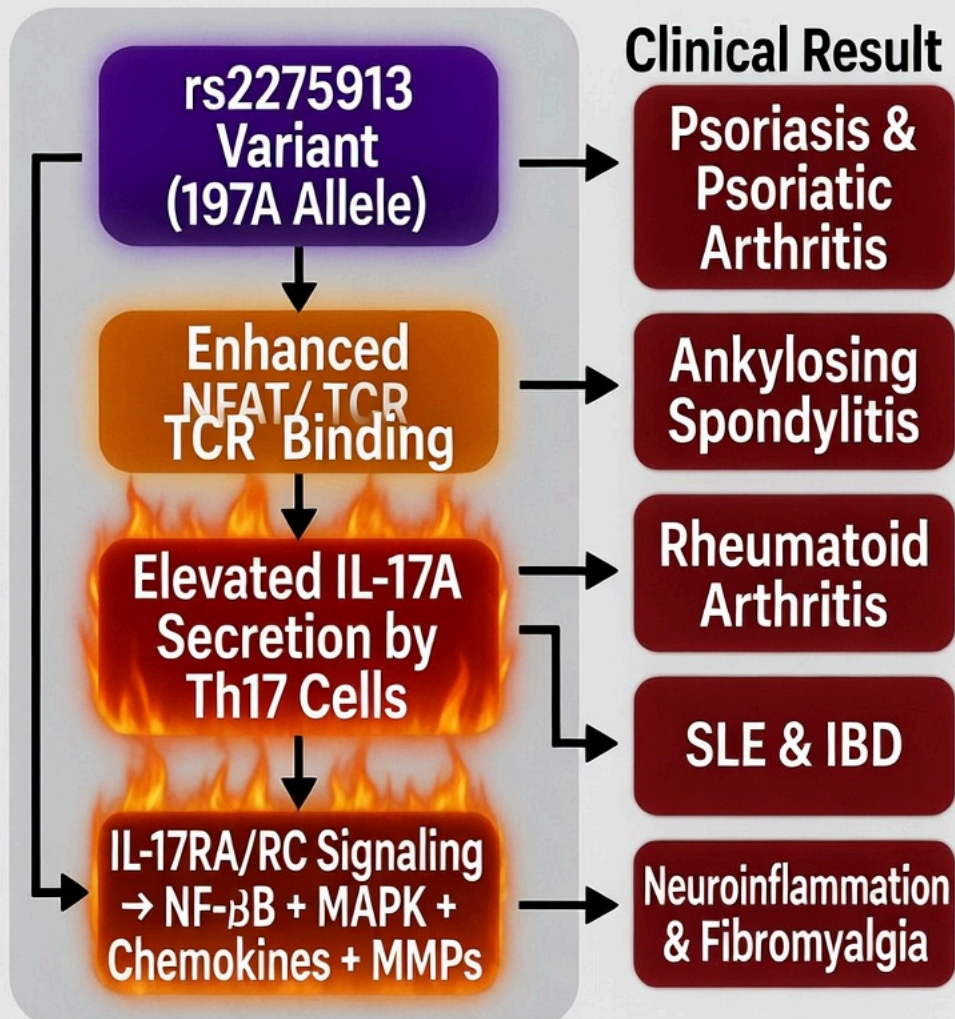
- **Tolerability and Safety:** Unlike injectable biologicals, the VARS Triad does not increase susceptibility to serious bacterial or fungal infections, neutropenia, or inflammatory bowel disease flares. It is highly bioavailable, cost-effective relative to biological injectables, well-tolerated, and carries an exceptionally favorable safety profile.

## Conclusion

The *IL17A* rs2275913 (G197A) single nucleotide polymorphism represents a functional genetic variant where the 197A risk allele enhances NFAT transcription factor binding, driving elevated IL-17A production. This genetic hyper-expression fuels chronic autoimmune diseases including psoriasis, ankylosing spondylitis, rheumatoid arthritis, lupus, and neuroinflammatory chronic pain syndromes. While targeted monoclonal antibodies (Secukinumab, Ixekizumab, Bimekizumab) provide potent extracellular neutralization, high annual costs, injection burdens, and risks of candidiasis limit their universal application. The Nrf2-enhanced VARS Triad (Glutathione, SOD, and Nrf2-fortified Catalase) offers a targeted biochemical and genomic intervention that quenches downstream ROS, restores Th17 redox balance, and represses *IL17A* gene transcription, serving as an effective adjuvant or stand-alone natural therapy.

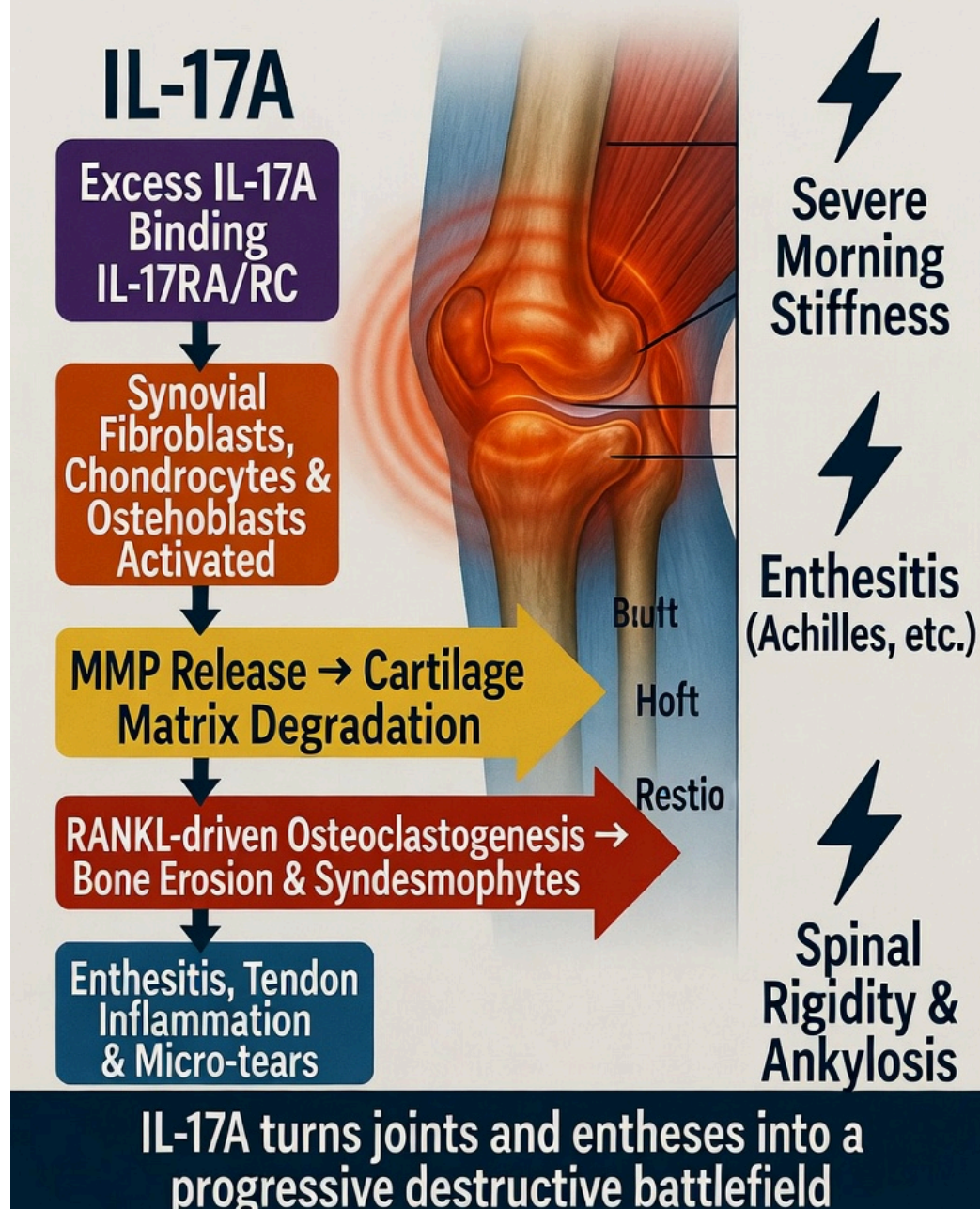
## Diagrams

# IL-17A rs2275913: THE 197A ALLELE FIRESTORM



**Genetic promoter variant locks  
IL-17A in permanent overdrive**

# HOW IL-17A ATTACKS BONES, TENDONS & CARTILAGE



## TREATMENT OPTIONS: BIOLOGICS vs VARS TRIAD

### Anti-IL-17 Biologics

(Cosentyx, Taltz, Bimzelx, Siliq)

#### Mechanism:

Upstream Cytokine or Receptor Blockade

**\$40,000 – \$90,000  
per year**

#### Side Effects



Mucocutaneous candidiasis, Neutropenia, Serious infections, IBD exacerbation, Suicidal ideation risk (Brodalumab), Immunosuppression

### VARs TRIAD –

Downstream Redox & Genomic Circuit Breaker

**VARs SOD → Quenches Superoxide →  
Blunts Neutrophil Recruitment**

**VARs Catalase + Nrf<sub>2</sub> →  
Converts H<sub>2</sub>O<sub>2</sub> + Represses ROR<sup>γt</sup> / NFAT / IL17A**

**VARs Glutathione →  
Restores Th17 Redox Balance + Protects Tissue**

**Only \$529 per month**

- No immunosuppression • Zero serious side effects
- Directly downregulates IL-17A gene •
- Protects cartilage, bone & mucosa •
- Rapid reduction in inflammation & pain

**VARs Triad restores redox balance, represses IL-17A at the genomic level, and protects joints without the massive cost or risks of biologics.**

## References

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