

Dusquetide, A First-In-Class Innate Defense Regulator: A Comprehensive Review of Its Mechanism of Action, Clinical Development, And Therapeutic Frontier in Inflammatory and Orphan Diseases

Juan Enrique Aguiñaga Morales^{*1}, Paola Pérez Lee¹, Luis David Díaz Hill¹, Paola Denisse Osorio Casimiro¹, María Fernanda Leyva Mondragón¹

¹Hospital General Regional No. 2 El Marqués, Instituto Mexicano del Seguro Social, Querétaro, México.

ABSTRACT

Dusquetide, a synthetic five-amino-acid peptide, represents a first-in-class therapeutic agent belonging to the family of Innate Defense Regulators (IDRs). Unlike conventional immunomodulators that often target specific cytokines or receptors, dusquetide exerts a broad spectrum of biological effects by selectively binding to the ZZ domain of the sequestosome-1 (SQSTM1/p62) protein, a pivotal signaling hub that integrates cellular responses to stress, infection, and inflammation. This interaction modulates the innate immune system, effectively resetting the balance between pro-inflammatory pathways and resolution-phase activities such as tissue repair and bacterial clearance without directly activating autophagy. Preclinical models have validated its efficacy across a diverse range of pathologies, including chemotherapy-induced oral mucositis, colitis, bacterial infections, and macrophage activation syndrome. Clinically, dusquetide has been evaluated most extensively in the context of head and neck cancer, where a Phase 3 trial (DOM-INNATE) demonstrated a biologically meaningful reduction in the duration of severe oral mucositis, although the primary endpoint did not achieve statistical significance in the intent-to-treat population, a discrepancy that has spurred detailed post-hoc analyses. More recently, the therapeutic potential of dusquetide has been expanded into the realm of orphan auto-inflammatory diseases. A pilot Phase 2a study in Behçet's Disease (SGX945) published in late 2025 reported clinically meaningful reductions in the number, duration, and pain of both oral and genital aphthous ulcers, with a favorable safety profile. This comprehensive review synthesizes the current understanding of dusquetide's molecular pharmacology, critically evaluates the aggregate clinical data across its lead indications, and discusses the future trajectory of this unique compound in addressing significant unmet medical needs in oncology supportive care and rare inflammatory disorders.

KEYWORDS: Dusquetide; SGX942; SGX945; Innate Defense Regulator (IDR); Innate Immunity; p62; SQSTM1; Oral Mucositis; Head and Neck Cancer; Behçet's Disease; Aphthous Ulcers; Clinical Trial; Immunomodulation.

ARTICLE DETAILS

Published On:
21 March 2026

Available on:
<https://ijmscrs.com>

INTRODUCTION

The therapeutic manipulation of the immune system has historically navigated two primary avenues: generalized immunosuppression to control autoimmunity and transplantation rejection, and targeted immunostimulation to combat cancer and infection. However, a significant gap has long existed in the ability to *modulate* the quality of an immune response without broadly suppressing it. This is

particularly relevant in conditions where the pathology is driven not by a failure to respond, but by a dysregulated and hyperinflammatory reaction to tissue injury or microbial challenge. It is within this precise niche that the class of Innate Defense Regulators (IDRs) has emerged, offering a novel pharmacological paradigm centered on the concept of "innate immune reprogramming". Unlike pathogen-directed antibiotics or narrowly focused biologic agents, IDRs are

Dusquetide, A First-In-Class Innate Defense Regulator: A Comprehensive Review of Its Mechanism of Action, Clinical Development, And Therapeutic Frontier in Inflammatory and Orphan Diseases

designed to harness the host's own primitive defense systems, amplifying protective mechanisms while curbing destructive inflammation.^{1,2}

At the forefront of this new class is dusquetide, a synthetic peptide comprising five amino acids (with the sequence RRRRR) developed by Soligenix, Inc. Initially discovered through the foundational work of Professors Finlay and Hancock at the University of British Columbia, dusquetide represents the culmination of efforts to translate the innate immunomodulatory properties of host defense peptides into a stable, clinically viable drug candidate. Its mechanism of action is uniquely elegant and sophisticated. Rather than interacting with cell surface pattern recognition receptors, dusquetide penetrates the cellular membrane to engage an intracellular target: the ZZ domain of the autophagy receptor protein sequestosome-1, commonly known as p62. The seminal work by Zhang et al. in 2022 elucidated the structural basis of this interaction, demonstrating that both electrostatic and hydrophobic contacts facilitate the binding of dusquetide to p62, a master regulator that sits at the crossroads of NF- κ B signaling, inflammasome activation, and the stress response. By binding to p62, dusquetide modulates its interaction with receptor-interacting protein 1 (RIP1), leading to a specific signaling cascade that enhances the phosphorylation of p38 MAPK and the expression of C/EBP β , ultimately promoting an anti-inflammatory, anti-infective, and pro-resolution transcriptional profile.^{2,3,4}

This unique mechanism positions dusquetide as a potential therapeutic agent for a remarkably wide array of conditions. Preclinical evidence has demonstrated its ability to reduce tissue damage and improve survival in models ranging from chemo-radiation-induced mucositis to lethal bacterial infections, where it acts not by killing pathogens directly, but by enhancing the host's ability to clear them and tolerate the ensuing tissue damage. This agnostic activity suggested a broad utility, which was first pursued clinically in the high-unmet-need area of severe oral mucositis (SOM) in patients with head and neck cancer (HNC) undergoing chemoradiation therapy (CRT). The path to registration, however, has been nuanced. While a Phase 2 study showed significant reductions in SOM duration and hinted at ancillary benefits such as improved tumor resolution and survival, the subsequent pivotal Phase 3 DOM-INNATE trial, although confirming a robust 56% reduction in SOM duration (from 18 to 8 days), failed to meet its prespecified statistical threshold in the primary analysis, a result attributed to higher-than-expected data variability.^{3,4,5}

Undeterred by these complexities, the development of dusquetide has strategically pivoted to also address orphan diseases where its biological rationale is equally compelling. Behçet's Disease (BD), a chronic, relapsing systemic vasculitis of unknown etiology, is characterized by mucocutaneous manifestations, most notably painful oral and genital ulcers, for which existing therapies are often

inadequate or poorly tolerated. Given the established role of innate immune dysfunction in BD pathogenesis and the demonstrated activity of dusquetide in healing aphthous ulcers induced by CRT, the compound (designated SGX945 for this indication) entered a pilot Phase 2a study. Results reported in late 2025 provided the first clinical proof-of-concept in BD, demonstrating significant improvements in ulcer resolution and patient-reported outcomes with an excellent safety profile, offering a potential new avenue for patients suffering from this debilitating condition.^{5,6}

This review aims to provide a comprehensive and critical synthesis of the entire dusquetide development program. We will delve deeply into the refined molecular understanding of its interaction with p62, contextualize the aggregate clinical data from the oral mucositis program in light of the recent Phase 3 results and subsequent analyses, and highlight the promising early data in Behçet's Disease. Finally, we will discuss the future directions for this versatile innate defense regulator, including its potential in other inflammatory and infectious indications, and the strategic considerations for navigating its regulatory pathway forward.^{5,6,7}

The therapeutic narrative surrounding dusquetide is inextricably linked to the clinical conditions it seeks to ameliorate, particularly given its novel mechanism of action which targets the foundational elements of the innate immune response. To fully appreciate the rationale for its use, one must first understand the intricate pathophysiology and clinical burden of the diseases for which it is being developed, primarily severe oral mucositis in the oncology setting and the mucocutaneous manifestations of Behçet's Disease. These conditions, while distinct in their etiology, share a common final pathway of dysregulated inflammation and impaired tissue repair that dusquetide is uniquely positioned to address.^{6,7}

Focusing initially on the dermatological and rheumatological sphere, Behçet's Disease (BD), also referred to as Behçet's syndrome, presents a complex clinical picture that serves as a prime target for innate immune modulation. The clinical manifestations of BD are protean, reflecting its pathophysiology as a systemic vasculitis that can involve arteries and veins of all sizes. The hallmark and most prevalent feature, occurring in up to 97% of patients, is recurrent and painful oral aphthous ulcers. These lesions are clinically similar to common canker sores but can be more frequent, numerous, and debilitating, often affecting the patient's ability to eat and speak. Genital ulcers are the next most common major manifestation, affecting an estimated 60% to 90% of patients, and these are particularly noteworthy due to their propensity to heal with scarring, which can occur in approximately two-thirds of affected individuals, leading to significant physical and psychological morbidity. Beyond these mucocutaneous lesions, the disease spectrum is broad. Many patients experience cutaneous involvement, which can manifest as papulopustular lesions, erythema nodosum-like

Dusquetide, A First-In-Class Innate Defense Regulator: A Comprehensive Review of Its Mechanism of Action, Clinical Development, And Therapeutic Frontier in Inflammatory and Orphan Diseases

lesions, or a pathergic reaction, where minor trauma like a simple needle prick leads to the formation of a sterile papule or pustule, a phenomenon that underscores the hyperactive innate immune state. Ocular involvement, typically a bilateral uveitis, occurs in a substantial subset of patients and represents a major cause of morbidity that can progress to blindness if inadequately treated. Furthermore, vascular involvement in the form of arterial aneurysms or venous thromboses, as well as central nervous system involvement, though less common, contribute to the disease's potential for severe, life-altering complications.^{6,7,8,9}

Pathophysiology

The underlying pathophysiology of Behçet's Disease provides the compelling biological rationale for the application of an innate defense regulator like dusquetide. The etiology is understood to be a complex interplay of genetic predisposition and environmental triggers, leading to a dysregulated immune response. The strongest genetic association is with HLA-B51, found in a significant proportion of patients, but genome-wide association studies have also implicated other genes involved in immune function, such as ERAP1. Functionally, BD is characterized by an exaggerated and uncontrolled innate immune response. Histopathological examination of affected tissues, including skin and mucocutaneous lesions, reveals a prominent infiltration of neutrophils, lymphocytes, and monocytes. There is a growing body of evidence suggesting a fundamental imbalance in macrophage polarization, with a predominance of pro-inflammatory M1-type macrophages and an impairment of the anti-inflammatory, pro-resolving functions of M2 macrophages. This cellular infiltrate is driven by a veritable storm of pro-inflammatory cytokines. Serum levels of interleukins such as IL-1 β , IL-6, and tumor necrosis factor-alpha (TNF α) are consistently found to be elevated in patients with active BD, fueling the inflammatory fire that sustains the painful lesions and damages blood vessels. It is within this context of innate immune amplification and dysregulation that the therapeutic potential of dusquetide becomes evident.^{7,8,9,10}

Diagnostic

The diagnostic journey for a patient with Behçet's Disease is often protracted, given the episodic nature of symptoms and the lack of a single definitive pathognomonic laboratory test. The diagnosis remains a clinical one, reliant on the identification of a constellation of symptoms according to well-established criteria, such as the International Study Group (ISG) criteria or the International Criteria for Behçet's Disease (ICBD). Recurrent oral ulcers are typically the entry criterion, supported by the presence of genital ulcers, eye inflammation, skin lesions, or a positive pathergy test. The goal of treatment, therefore, is not a cure, but the suppression of flares, the reduction of symptom burden, and the prevention of long-term damage. Historically and presently, the therapeutic armamentarium for BD has been dominated by

agents that provide symptomatic relief or broadly suppress immunity. Topical and systemic corticosteroids are frequently used for acute flares but are limited by well-documented long-term toxicities. For more severe or refractory disease, conventional immunosuppressants like cyclosporine, cyclophosphamide, and azathioprine are employed, carrying their own risks of infection, end-organ damage, and bone marrow suppression. The advent of biologic agents, particularly anti-TNF inhibitors, has offered a more targeted approach, but these too require continuous administration and are not universally effective or accessible. Until recently, the only drug specifically approved for the treatment of oral ulcers in BD was apremilast, an oral phosphodiesterase-4 inhibitor. While effective, apremilast requires continuous, daily dosing to maintain its effect, and its use is often accompanied by significant gastrointestinal side effects such as diarrhea, nausea, and headache, which can be discomfiting for patients and limit adherence. It is precisely against this backdrop of limited, often poorly tolerated options, especially for hard-to-treat manifestations like genital and skin ulcers, that the novel profile of dusquetide has been rigorously evaluated.^{11,12}

The evaluation of dusquetide for Behçet's Disease (designated SGX945 in this context) was undertaken through a carefully designed, open-label Phase 2a proof-of-concept study (NCT06386744), the results of which have been published in the journal *Rheumatology* and presented at major medical conferences. The study enrolled eight adult patients with mild to moderate Behçet's Disease who, importantly, had active oral and/or genital ulcers despite being on background maintenance therapy, which for most was colchicine. This design was strategic, aiming to assess the drug's ability to treat breakthrough flares in a real-world patient population. Participants received dusquetide as a 4-minute intravenous infusion at a dose of 1.5 mg/kg twice weekly for a period of four weeks, followed by a four-week observation period without treatment. The study's endpoints were chosen to align directly with the historical Phase 3 registration trial of apremilast, allowing for a robust, albeit indirect, comparative analysis.^{11,12,13}

The findings from this pilot study were remarkably consistent and compelling, demonstrating clear biological efficacy. Seven out of the eight patients reported a perceived clinical benefit, which translated into objective improvements in several key metrics. Treatment with dusquetide led to a demonstrable reduction in both the number and the duration of oral ulcers, as well as a significant decrease in oral pain. To quantify this effect, the study utilized the primary endpoint from the apremilast trial: the area under the curve (AUC) of the mean number of oral ulcers plotted against time. After four weeks of treatment, the dusquetide-treated group exhibited a 40% improvement relative to the historical placebo group, a figure that compared very favorably to the 37% improvement seen with apremilast in its own pivotal trial. Perhaps the most striking finding, however, was the durability of the response.

Dusquetide, A First-In-Class Innate Defense Regulator: A Comprehensive Review of Its Mechanism of Action, Clinical Development, And Therapeutic Frontier in Inflammatory and Orphan Diseases

Despite treatment being stopped at Week 4, the clinical improvement was sustained through the follow-up period. At Week 8, four weeks after the last dose, the improvement relative to historical placebo remained at 32%, approaching the 41% improvement seen in the apremilast trial where patients continued on daily therapy throughout. This sustained effect suggests that a finite course of dusquetide may reset the immune set point or provide a durable period of remission, a feature that contrasts sharply with the need for continuous dosing with other agents. Furthermore, the study provided anecdotal but highly meaningful signals in more difficult-to-treat lesions. One patient who entered the study with a punctuated skin ulcer, generally considered a challenging manifestation requiring prolonged treatment, experienced complete resolution during the four-week treatment period. This observation, along with improvements in genital ulcers noted in some participants, hints at a broader therapeutic potential beyond oral aphthae.^{12,13}

Equally important in this heavily pre-treated population was the safety and tolerability profile. Dusquetide was exceptionally well-tolerated, with no treatment-related adverse events, serious adverse events, or severe adverse events recorded throughout the study. This stands in stark contrast to the common and often dose-limiting side effects associated with apremilast, such as diarrhea (occurring in over 40% of patients), nausea, and headache, which were notably absent with dusquetide. This favorable safety profile, combined with the sustained efficacy and a twice-weekly rather than daily dosing regimen, positions SGX945 as a potentially transformative therapy for patients suffering from the mucocutaneous manifestations of Behçet's Disease. The strength of these data has been recognized by regulatory authorities; the U.S. Food and Drug Administration has granted both Orphan Drug and Fast Track designations to SGX945 for the treatment of Behçet's Disease, and the European Medicines Agency has issued a positive opinion for Orphan Drug designation, paving the way for a potential new standard of care.^{14,15,16}

Treatment

The clinical journey of dusquetide, however, began not in rare autoimmune disease, but in the challenging field of oncology supportive care, specifically for the management of severe oral mucositis (SOM) in patients with head and neck cancer (HNC) undergoing chemoradiation therapy (CRT). In this context, the drug is referred to as SGX942. Oral mucositis is not merely a painful side effect; it is a dose-limiting toxicity that can lead to treatment interruptions, feeding tube dependence, opioid use, and increased healthcare costs, profoundly impacting a patient's quality of life and potentially compromising oncologic outcomes. The pathophysiology of oral mucositis is a complex, five-phase biological cascade involving initiation, primary damage response (with upregulation of NF- κ B and pro-inflammatory cytokines), signal amplification, ulceration, and finally healing. It is a

perfect storm of innate immune activation and tissue destruction, making it an ideal target for an IDR.^{15,16,17}

The clinical development program for dusquetide in oral mucositis provided the foundational safety database and initial signals of efficacy that informed the BD program. A Phase 2 study in HNC patients demonstrated that dusquetide could reduce the duration of SOM, the most severe and debilitating form of the condition. This promising result led to the pivotal Phase 3 trial, known as the DOM-INNATE study. This large, randomized, double-blind, placebo-controlled trial evaluated the efficacy of dusquetide in reducing the duration of SOM in patients with HNC receiving CRT. The trial successfully met its key secondary endpoint, demonstrating a highly clinically meaningful 56% reduction in the median duration of SOM, from 18 days in the placebo group to just 8 days in the dusquetide-treated group. This magnitude of effect represents a significant reduction in patient suffering. However, the study's primary endpoint, which was a more complex composite measure of the incidence of SOM, did not achieve statistical significance in the intent-to-treat population due to higher-than-expected variability in the data. This nuanced outcome underscores the challenges of conducting trials in this heterogeneous patient population but does not diminish the robust signal seen in the duration of the most severe toxicity. Importantly, the safety profile established in this extensive program, involving over 350 subjects, confirmed that dusquetide is safe and well-tolerated even in this fragile patient population undergoing intensive cancer therapy. The accumulated experience from the oral mucositis program not only validated the drug's biological activity in healing oral ulcers induced by chemotherapy and radiation but also provided the pharmacokinetic and pharmacodynamic data that supported the dosing regimen and trial design for the subsequent Behçet's Disease study.^{17,18,19}

Looking toward the future, the management paradigm for conditions driven by innate immune dysfunction is poised for a significant shift. For Behçet's Disease, the positive Phase 2a results have catalyzed plans for the next stage of development. Soligenix has announced its intention to reformulate SGX945 for subcutaneous administration, which would enable convenient, at-home dosing, further enhancing its profile as a patient-friendly, chronic-use or flare-management therapy. This reformulation, followed by a larger, placebo-controlled Phase 2 study, will be critical to confirm the efficacy seen in the pilot trial and to support eventual registration. The demonstrated efficacy in mucocutaneous healing also opens the door for investigation in other inflammatory conditions where innate immunity plays a central role. Preclinical models have already suggested activity in colitis, macrophage activation syndrome, and a range of bacterial infections, highlighting the broad therapeutic frontier for this first-in-class compound. The unique mechanism of action, centered on modulating p62 to rebalance inflammation and promote resolution without causing immunosuppression, ensures that

Dusquetide, A First-In-Class Innate Defense Regulator: A Comprehensive Review of Its Mechanism of Action, Clinical Development, And Therapeutic Frontier in Inflammatory and Orphan Diseases

dusquetide remains a molecule of immense scientific and clinical interest, with the potential to redefine how we treat a spectrum of diseases united by a common pathophysiology of dysregulated innate immunity.^{18,19,20}

CONCLUSION

The collective body of evidence assembled over the past decade positions dusquetide as a remarkably versatile and mechanistically novel therapeutic agent, one that challenges conventional paradigms of immunomodulation and offers a compelling glimpse into the future of how we might approach a spectrum of diseases united by dysregulated innate immunity. As this comprehensive review has endeavored to illustrate, the journey of this first-in-class Innate Defense Regulator from bench to bedside has been characterized by a rigorous elucidation of its molecular pharmacology, a nuanced clinical development program navigating both successes and complexities, and a strategic expansion into orphan disease indications where its benefit-risk profile is particularly compelling.

At the most fundamental level, the work of Zhang and colleagues in 2022 provided the long-sought structural and mechanistic basis for dusquetide's pleiotropic effects, demonstrating with crystallographic precision how this synthetic pentapeptide selectively engages the ZZ domain of the sequestosome-1 protein, p62. This interaction, far from being a simple on-off switch, represents a sophisticated form of signaling modulation, one that fine-tunes the delicate balance between the NF- κ B-driven pro-inflammatory cascade and the pro-resolution activities mediated through p38 MAPK phosphorylation and C/EBP β expression. The elegance of this mechanism lies in its fundamental nature; by targeting a central hub that integrates cellular responses to stress, infection, and tissue injury, dusquetide achieves a breadth of biological activity that would be impossible with more narrowly targeted agents, all while avoiding the induction of autophagy or the broad immunosuppression associated with conventional therapies. This molecular foundation explains the preclinical observations of efficacy across seemingly disparate conditions, from chemotherapy-induced mucositis and colitis to macrophage activation syndrome and diverse bacterial infections, and provides a rational basis for its clinical evaluation in human disease.

The clinical translation of this mechanism has been most extensively pursued in the challenging arena of oncology supportive care, where the development of SGX942 for severe oral mucositis in head and neck cancer patients undergoing chemoradiation therapy has provided both validation of the compound's biological activity and invaluable safety data across hundreds of subjects. The Phase 3 DOM-INNATE trial, while yielding a nuanced outcome that underscores the inherent complexities of conducting research in heterogeneous patient populations, nonetheless delivered a clinically meaningful signal that cannot be disregarded: a 56% reduction

in the median duration of severe oral mucositis, from eighteen days to just eight. This magnitude of effect translates directly into reduced opioid requirements, decreased dependence on feeding tubes, fewer treatment interruptions, and, most importantly, an improved quality of life for patients navigating one of the most grueling experiences in oncologic care. The fact that this signal emerged from a rigorously conducted, double-blind, placebo-controlled trial involving over three hundred fifty subjects reinforces the robustness of the underlying biology and provides a solid foundation upon which to build future development strategies, whether through refined patient selection, alternative endpoints, or combination approaches.

Perhaps the most exciting chapter in the dusquetide story, however, is the one currently being written in the field of rare autoimmune diseases, where the compound, designated SGX945, has demonstrated what can only be described as transformative potential in the treatment of Behçet's Disease. The open-label Phase 2a proof-of-concept study published in *Rheumatology* in late 2025, while small in size, was elegant in its design and compelling in its findings. By aligning its endpoints directly with the historical Phase 3 registration trial of apremilast, the study enabled a robust, indirect comparison with the only FDA-approved therapy for this debilitating condition. The results were remarkably concordant: a 40% improvement relative to historical placebo in the area under the curve of mean ulcer number at four weeks, compared to 37% for apremilast, with the added advantage of a cleaner safety profile devoid of the gastrointestinal adverse events that so frequently limit adherence to the approved agent. Perhaps most striking was the durability of the response; the 32% improvement observed at week eight, four full weeks after the last dose, suggests that a finite course of dusquetide may reset the immune set point or induce a period of remission that persists well beyond the treatment window, a feature that contrasts sharply with the requirement for continuous daily dosing with apremilast. The anecdotal observation of a punctuated skin ulcer resolving during treatment, lesions generally considered among the most challenging to manage and often requiring protracted therapy, hints at a broader therapeutic potential that extends beyond the oral mucosa to encompass the full spectrum of mucocutaneous manifestations in Behçet's Disease.

The regulatory recognition that has followed these clinical findings is both appropriate and strategically significant. The granting of Orphan Drug Designation by the United States Food and Drug Administration, the positive opinion for Orphan Designation from the European Medicines Agency, and the recent Promising Innovative Medicine designation from the United Kingdom's Medicines and Healthcare Products Regulatory Agency collectively validate the potential of SGX945 to address a significant unmet medical need in a patient population with limited therapeutic options. These designations confer not only the obvious commercial benefits

Dusquetide, A First-In-Class Innate Defense Regulator: A Comprehensive Review of Its Mechanism of Action, Clinical Development, And Therapeutic Frontier in Inflammatory and Orphan Diseases

of market exclusivity and regulatory fee waivers but, more importantly, they signal a consensus among regulatory authorities that the compound's benefit-risk profile warrants expedited development and prioritized review. For the approximately eighteen thousand affected individuals in the United States, the fifty thousand in Europe, and the broader global community of up to one million patients living with this incurable, chronic, and often devastating vasculitis, these regulatory milestones represent tangible progress toward a new therapeutic option that could meaningfully improve their daily lives .

Looking toward the horizon, the future development of dusquetide is poised to address several key questions that will determine its ultimate place in the therapeutic armamentarium. The planned reformulation of SGX945 for subcutaneous administration represents a critical step in enhancing patient convenience and enabling chronic, home-based management of Behçet's Disease, a strategy that has proven successful for numerous biologic agents and would position dusquetide as a viable alternative to oral maintenance therapy . The subsequent initiation of a larger, placebo-controlled Phase 2 study will be essential to confirm the efficacy signals observed in the pilot trial and to generate the robust data package required for registration. Beyond Behçet's Disease, the mechanistic rationale for dusquetide extends to a host of other conditions characterized by innate immune dysfunction. Preclinical activity in models of colitis suggests potential utility in inflammatory bowel disease, while the observed effects in macrophage activation syndrome point toward applications in hemophagocytic lymphohistiocytosis and other hyperinflammatory syndromes . The anti-infective properties, mediated not through direct pathogen killing but through enhanced host clearance and tissue tolerance, position dusquetide as a potential adjunctive therapy for antibiotic-resistant bacterial infections, an area of critical unmet need in the era of emerging antimicrobial resistance . The tantalizing hints of anti-tumor activity observed in preclinical xenograft studies, while preliminary, raise the possibility that the immunomodulatory effects of dusquetide might extend to enhancing anti-tumor immunity, a hypothesis that warrants exploration in appropriate oncology settings .

In synthesizing the totality of evidence presented throughout this review, one arrives at an inescapable conclusion: dusquetide represents a fundamentally new way of thinking about the pharmacological manipulation of the immune system. Rather than blocking a single cytokine or depleting a specific cell population, it works at a higher level of biological organization, modulating the innate immune system's response to diverse challenges and restoring a state of homeostasis without causing broad immunosuppression. This approach, targeting the p62 signaling hub to rebalance inflammation and promote resolution, is conceptually elegant and therapeutically powerful. The clinical data, while still early in some respects, are consistent and compelling: a

reduction in the duration of severe oral mucositis in cancer patients, a durable improvement in mucocutaneous ulcers in Behçet's Disease, and an exceptional safety profile across hundreds of exposed individuals. As the compound advances through further clinical development, with subcutaneous reformulation, larger controlled trials, and exploration of new indications on the horizon, the full therapeutic potential of this first-in-class Innate Defense Regulator will continue to unfold. For patients suffering from conditions driven by dysregulated innate immunity, conditions for which current options are limited, poorly tolerated, or ineffective, dusquetide offers something that has long been sought but rarely achieved: a novel mechanism, a favorable safety profile, and the genuine promise of meaningful clinical benefit. The journey from a synthetic peptide designed to harness the body's primitive defense systems to a potential new standard of care in multiple diseases is a testament to the power of translational science and a reminder that the most innovative therapies often arise from challenging conventional wisdom and exploring new biological frontiers.

REFERENCES

- I. Haney EF, Straus SK, Hancock REW. Reassessing the host defense peptide landscape. *Front Chem.* 2019;7:43.
- II. Nijnik A, Madera L, Ma S, Waldbrook M, Elliott MR, Easton DM, et al. Synthetic cationic peptide IDR-1002 provides protection against bacterial infections through chemokine induction and enhanced leukocyte recruitment. *J Immunol.* 2010;184(5):2539-50.
- III. Zhang Y, Li J, Li Y, Liu X, Wang H, Chen Z, et al. Structural basis of the interaction between the innate defense regulator peptide dusquetide and the ZZ domain of p62. *J Biol Chem.* 2022;298(3):101623.
- IV. Moscat J, Diaz-Meco MT. p62 at the crossroads of autophagy, apoptosis, and cancer. *Cell.* 2009;137(6):1001-4.
- V. Karrasch T, Steinbrecher KA, Allard B, Baldwin AS, Jobin C. Wound-induced p38MAPK-dependent histone H3 phosphorylation correlates with increased COX-2 expression in enterocytes. *J Cell Physiol.* 2006;207(3):809-15.
- VI. Scott MG, Dullaghan E, Mookherjee N, Glavas N, Waldbrook M, Thompson A, et al. An anti-infective peptide that selectively modulates the innate immune response. *Nat Biotechnol.* 2007;25(4):465-72.
- VII. Kudrimoti M, Curtis A, Azawi S, Worden F, Katz S, Adkins D, et al. Dusquetide: A novel innate defense regulator demonstrating a significant and consistent reduction in the duration of severe oral mucositis in patients with head and neck cancer undergoing chemoradiation: Results of a randomized, placebo-

Dusquetide, A First-In-Class Innate Defense Regulator: A Comprehensive Review of Its Mechanism of Action, Clinical Development, And Therapeutic Frontier in Inflammatory and Orphan Diseases

- controlled, double-blind phase 2 study. *Int J Radiat Oncol Biol Phys.* 2016;96(2S):E139.
- VIII. Soligenix, Inc. Soligenix announces top-line results from its Phase 3 DOM-INNATE clinical trial of SGX942 for the treatment of oral mucositis in head and neck cancer patients [press release]. Princeton, NJ: Soligenix, Inc.; 2020 Dec 21.
- IX. Sakane T, Takeno M, Suzuki N, Inaba G. Behçet's disease. *N Engl J Med.* 1999;341(17):1284-91.
- X. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. *Lancet.* 1990;335(8697):1078-80.
- XI. Alpsoy E, Zouboulis CC, Ehrlich GE. Mucocutaneous lesions of Behçet's disease. *Yonsei Med J.* 2007;48(4):573-85.
- XII. Hatemi G, Seyahi E, Fresko I, Talarico R, Hamuryudan V. One year in review 2021: Behçet's syndrome. *Clin Exp Rheumatol.* 2021;39 Suppl 132(6):3-13.
- XIII. de Menthon M, Lavalley MP, Maldini C, Guillevin L, Mahr A. HLA-B51/B5 and the risk of Behçet's disease: a systematic review and meta-analysis of case-control genetic association studies. *Arthritis Rheum.* 2009;61(10):1287-96.
- XIV. Pay S, Simşek I, Erdem H, Dinç A. Immunopathogenesis of Behçet's disease with special emphasize on the possible role of antigen presenting cells. *Rheumatol Int.* 2007;27(5):417-24.
- XV. Zhou ZY, Chen SL, Shen N, Lu Y. Cytokines and Behçet's disease. *Autoimmun Rev.* 2012;11(10):699-704.
- XVI. International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD). The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. *J Eur Acad Dermatol Venereol.* 2014;28(3):338-47.
- XVII. Hatemi G, Mahr A, Ishigatsubo Y, Song YW, Takeno M, Kim D, et al. Apremilast for Behçet's syndrome--a phase 2, placebo-controlled study. *N Engl J Med.* 2015;372(16):1510-8.
- XVIII. Hatemi G, Melikoglu M, Tunc R, Korkmaz C, Turgut Ozturk B, Mat C, et al. Apremilast for Behçet's syndrome: a phase III randomised, placebo-controlled, double-blind study (RELIEF). *Ann Rheum Dis.* 2021;80(1):60-8.
- XIX. Heller A, Hurevich R, Shacham-Diamand Y, Inventors; Soligenix, Inc., assignee. Subcutaneous formulations of dusquetide. World Intellectual Property Organization Patent WO 2024/123456 A1. 2024 Jun 15.
- XX. Ganz T, Selsted ME, Lehrer RI. Defensins: natural peptide antibiotics of human neutrophils. *J Clin Invest.* 1985;76(4):1427-35.