

# Beyond Inflammation and Itch: A Call for a Broader Framework in Atopic Dermatitis

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## To the Editor:

Atopic dermatitis (AD) remains one of the most common and burdensome chronic inflammatory skin conditions, particularly in children. Despite recent therapeutic advances, there is still a significant gap between available treatments and the needs of many patients. High rates of dissatisfaction with existing regimens, rising corticosteroid phobia globally, and a growing preference for integrative and natural approaches point to an urgent need to rethink our framework for understanding and treating AD.

Much of the current therapeutic paradigm focuses on reducing inflammation and alleviating itch. While these are central features of the disease, this narrow focus may limit our ability to achieve long-term control, especially in pediatric patients and those with recalcitrant disease. Emerging evidence suggests that disruption of the skin microbiome, particularly colonization with *Staphylococcus aureus*, as well as neuroimmune and behavioral components (such as habitual scratching, sleep disturbance, and stress reactivity), and systemic factors, including the skin-gut axis and environmental exposures, all act in concert to sustain the disease process. These interconnected domains create a dynamic, self-reinforcing loop of dysfunction. Treatments that target only a single axis may, therefore, fall short in delivering durable relief.

We propose that the next wave of AD innovation must embrace multi-pronged therapies—particularly those that are safe, effective, and accessible. Botanical agents such as zabalafin (Alphyn) with anti-inflammatory, anti-pruritic, antimicrobial, and anti-xerotic properties offer one such promising avenue. Naturally occurring compounds such as those found in zabalafin act synergistically to target multiple disease pathways while aligning with patient interest in more holistic, less immunosuppressive interventions.

It is time to broaden our conceptual framework for AD to include not just immune and barrier dysfunction but also microbial balance, patient preference, and whole-person wellness. In doing so, we may be able to bridge the current clinical gap and usher in a new era of safe, multifaceted, and sustainable treatments such as zabalafin for this challenging disease.

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## DISCLOSURES

Dr Lio reports being on the speaker's bureau for AbbVie, Arcutis, Eli Lilly, Galderma, Hyphens Pharma, Incyte, La Roche-Posay/L'Oreal, Pfizer, Pierre-Fabre Dermatologie, Regeneron/Sanofi Genzyme, Verrica; reports consulting/advisory boards for Alphyn Biologics, AbbVie, Almirall, Amyris, Apogee, Arcutis, ASLAN, Astria Therapeutics, Boston Skin Science, Bristol-Myers Squibb, Burt's Bees, Castle Biosciences, Codex Labs, Concerto Biosci, Dermavant, Eli Lilly, Galderma, Kenvue, LEO Pharma, Lipidor, L'Oreal, Merck, Microcos, MyOR Diagnostics, Pelthos Therapeutics, Phyla, Regeneron/Sanofi Genzyme, Sibel Health, Skinfix, Soteri Skin, Stratum Biosciences, Sun Pharma, Theraplex, Thimble Health, UCB, Unilever, Verdant Scientific, Verrica, Yobee Care. Stock options with Alphyn Labs, Codex Labs, Concerto Biosci, Soteri Skin, Stratum Biosciences, Thimble, Yobee Care, Verdant Scientific. In addition, Dr Lio has a patent pending for a Theraplex product with royalties paid and is a Board member and Scientific Advisory Committee Member emeritus of the National Eczema Association.

Dr Hebert reports research grants paid to the medical school from Pfizer, Dermavant, Arcutis, AbbVie, Amgen, Takeda, Oneness, Lilly; honoraria from Pfizer, Dermavant, Arcutis, Lilly, Galderma, Incyte, Sun Pharmaceuticals, Ortho Dermatologics, Alphyn; serving on data safety monitoring boards for Sanofi, Regeneron, Alphyn, Ortho Dermatologics.

Dr Schachner reports being an investigator for Astellas, Berg Pharma, Celgene, Ferndale Labs, Lilly, Medimetriks, Novartis, Organogenesis Inc., Pfizer, Sciton; a consultant for Alphyn, Amryt Pharma, Beiersdorf, Brickell, Cutanca, Hoth, Lexington, Mustela, TopMD, Noble Pharma; a speaker for Novartis, Sanofi Regeneron; serving on advisory boards for Almirall, Aslan, Biofrontera, Cera Ve, Krystal Biotech, Mustela, NoblePharma, Pfizer, Pierre Fabre, Sanofi-Regeneron.

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