

# Vitamin D, Estrogen May Be Key to New SLE Tx

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Denver Bureau

SNOWMASS, COLO. — Vitamin D and estrogen may provide the basis for a new generation of nonimmunosuppressive therapies for systemic lupus erythematosus, Dr. Betty Diamond predicted at a symposium sponsored by the American College of Rheumatology.

Systemic lupus erythematosus (SLE) is characterized by both autoreactivity and a

degree of intrinsic immunodeficiency. Immunosuppressive therapies invariably compound problems on the immunodeficiency side—and all current SLE therapies are quite immunosuppressive, as are the biologic agents now generating considerable excitement as the next-generation lupus therapies.

For this reason, the biologics should be viewed as no more than a way station on the road to more completely restorative therapies, argued Dr. Diamond, head of

the Center for Autoimmune Diseases at the Feinstein Institute for Medical Research in Manhasset, N.Y.

“We need to move forward with the next generation of lupus therapies, but at the same time we should be thinking about the following generation, where I believe we can do better,” she said.

Her optimism is grounded in part on lessons provided by mouse models of SLE, which have shown that many different cellular pathways lead to lupus. The key will

be to target multiple pathways in order to decrease autoreactivity while avoiding immunosuppression—and perhaps even improving immunocompetence.

Vitamin D regulates immune homeostasis. In vitro, vitamin D suppresses maturation of dendritic cells, which are deeply involved in the inflammatory response in lupus. Presenting vitamin D to cultured SLE dendritic cells inhibits expression of interferon-inducible genes, thereby decreasing the pro-immunogenic inflammatory cascade that is a hallmark of the disease.

The precise way in which vitamin D regulates dendritic cells is unclear, but one potential mechanism hinges upon the vitamin's ability to suppress transcription of NF-kappaB, upon which dendritic cell activation depends.

Vitamin D also promotes expression of regulatory T cells, suppresses interleukin-12, and balances Th1 and Th2 T-cell re-

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DR. DIAMOND

sponses. Vitamin D deficiency is highly prevalent in patients with SLE, and serum vitamin D levels correlate inversely with SLE Disease Activity Index scores.

Dr. Diamond and her coinvestigators are about to step beyond the preclinical stage by launching a clinical trial of vitamin D supplementation in patients with mild lupus. The goal will be to see if, as in vitro, vitamin D inhibits induction of the interferon signature.

Turning to estrogen as a potential therapeutic target in SLE, Dr. Diamond said her interest was initially piqued by the epidemiology of the disease.

“The greatest risk factor for lupus is being female, that's for sure. And that's not just a matter of having two X chromosomes, but is in fact partly mediated by hormones.” And “before puberty the ratio of girls to boys who get lupus is about 3:1, after puberty it's 9:1, and after menopause it goes down to 2:1. So at the time when hormones are most active the female predisposition to lupus is highest,” she noted.

In mouse models of lupus, physiologic titers of estradiol alter the B-cell repertoire by promoting rescue of pathogenic high-affinity DNA-reactive B cells while impairing maturation of low-affinity DNA-reactive B cells.

This is accomplished through increased expression of B-cell activating factor (BAFF). The high-affinity DNA-reactive B cells generate antibodies which form proinflammatory immune complexes. This work suggests antiestrogenic therapies might provide a way to reduce the risk of lupus in women in their reproductive years to a level comparable to that of prepubertal girls or postmenopausal women.