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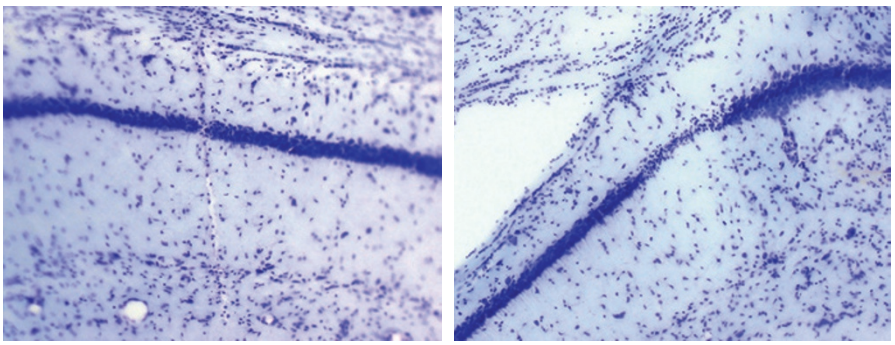
CONNECTIVE TISSUE DISEASES

A small molecule that blocks antibody-mediated tissue damage—a new type of therapy for SLE?

Myriad autoantibodies are implicated in the pathogenesis of systemic lupus erythematosus (SLE), in particular species that recognize DNA and crossreact with tissue antigens. Now, a molecule designed to mimic a key self epitope has been shown to block damaging autoantibody binding *in vitro*, in human sera, and in mice. Crucially, the agent seems to lack the immunogenicity that haunts candidate biological therapies. As Betty Diamond *et al.* report in *Proceedings of the National Academy of Sciences*, the work offers hope that orally-delivered, specific, and well-tolerated therapies for SLE can now be developed.

Kidney disease, a major cause of death in patients with SLE, involves nephrotoxic anti-DNA autoantibodies that crossreact with tissue antigens, forming complexes that elicit aberrant immune responses. Diamond and colleagues previously discovered that the tissue target of a subset of such autoantibodies—found in approximately 40% of patients with SLE—is a pentapeptide consensus sequence, DWEYS, that forms part of the NR2A and NR2B subunits of human *N*-methyl *D*-aspartate receptor (NMDAR). Besides nephrotoxicity, as the investigators later found, NMDAR-reactive autoantibodies also mediate neurotoxicity. As we reported in January (see Further reading), the action of these antibodies might underlie neuropsychiatric manifestations of SLE.

"We've been studying these antibodies for 10 years and have shown their neurotoxicity in mice and patients," says Diamond, "so we wanted to develop a therapeutic." The researchers previously blocked anti-NMDAR activity in experimental models using an unnatural DWEYS peptide made from amino acids of D chirality. The peptide itself is not orally absorbed, and although various couplings of it with antibodies have shown some success in treating lupus-prone mice, the reagents are complicated to produce and administer, and immunogenic *in vivo*.



Mouse coronal brain tissue stained with cresyl violet, at 10X magnification, shows that microinjection of FISLE-412 (left), in comparison with control peptide (right), blocks binding of a microinjected anti-dsDNA antibody. Such a result is the first step in screening a potential peptidomimetic for efficacy. Image supplied courtesy of Bruce T. Volpe.

To circumvent these issues, Diamond and colleagues designed molecular scaffolds to create a compound predicted to mimic the neutralizing action of the DWEYS peptide. Once synthesized, the molecule (FISLE-412) was shown in competitive ELISAs to neutralize mouse and human monoclonal autoantibodies with anti-DNA and anti-NMDAR crossreactivity. Furthermore, polyclonal reactivity present in sera from patients with SLE was also substantially inhibited by FISLE-412, in most but not all samples tested. Far less of the compound was needed than of DWEYS peptide to block autoantibody binding in the assays.

The next step was to test FISLE-412 in tissues. In glomeruli isolated from mouse kidneys, the peptidomimetic was again effective at blocking binding by the monoclonal antibodies, and effective to different degrees against the polyclonal reactivity of sera from different patients.

Finally, the researchers tested whether FISLE-412 would remain neutralizing in the complex environment of whole tissues and organs. Hippocampal injection of the monoclonal antibodies into living mice caused, as expected, neuronal apoptosis. Pretreatment of the antibodies with FISLE-412 entirely abrogated this effect.

"We just showed that FISLE-412 protects kidneys as proof of principle of its potential efficacy," explains Diamond, continuing, "the most significant finding is that small molecules can block antibody-mediated tissue damage." This result, she adds, is "totally novel."

"This work is exciting," agrees Maria Dall'Era, Director of the Lupus Clinic and Research Center at the University of California, San Francisco, "because it offers the hope that a therapeutic might be developed that can treat neuropsychiatric manifestations in some of our SLE patients." She cautions that neurological symptoms of SLE are multifactorial in etiology, but adds that the study "represents a step forward in the development of a therapeutic for those patients whose mechanism of neurologic involvement is the production of a pathogenic anti-DNA antibody that crossreacts with the NMDA receptor."

Diamond *et al.* hope to test the molecule in a clinical trial, and might develop peptidomimetics of other autoantigens.

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Original article Bollm, O. *et al.* Generation of a unique small molecule peptidomimetic that neutralizes lupus autoantibody activity. *Proc. Natl Acad. Sci. USA* **108**, 10255–10259 (2011)

Further reading Leah, E. Neurons excited to death by SLE autoantibodies. *Nat. Rev. Rheumatol.* **7**, 1 (2011)