Neutralizing lupus autoantibodies

By Tim Fulmer, Senior Writer

Although several classes of autoantibodies have been identified in lupus, efforts to target them have so far been unsuccessful. Now, researchers at **The Feinstein Institute for Medical Research** have designed a peptidomimetic small molecule that accomplished the task in mouse models of the disease.¹ The researchers believe the molecule could help treat lupus nephritis as well as neuropsychiatric symptoms that occur in about a third of all lupus patients.

Moreover, the compound does not interact with immune cells, which could avoid immunosuppressive side effects that have been an issue with lupus therapies.

Lupus is a chronic autoimmune disease characterized by excess production of autoantibodies and proinflammatory cytokines that cause severe damage to multiple organs, including the skin, joints, kidneys and CNS.

One class of autoantibodies, those against double-stranded DNA (dsDNA), correlates with disease severity² and exerts its effects by cross-reacting with multiple protein antigens, leaving deposits in tissues and triggering inflammatory cascades.

Previously, Betty Diamond and colleagues showed that two of these antigens were the NR2A and NR2B subunits of the NMDAR in the kidneys and CNS. Binding of anti-dsDNA antibodies to the subunits contributed to neuropsychiatric symptoms of lupus.³⁻⁵ Diamond is head of the institute's Center for Autoimmune Diseases and Musculoskeletal Disorders.

Thus, the researchers hypothesized that inhibiting interactions between the autoantibodies and the receptor could decrease formation of autoantibody deposits that cause organ dysfunction. The result, they expected, would be an inhibitor that would treat lupus nephritis as well as the neuropsychiatric symptoms of the disease that occur in 30%–40% of lupus patients.⁶

To create an inhibitor, Diamond and Yousef Al-Abed used a five-amino-acid sequence on the autoantibody-binding site of the NMDAR as a template for generating a small molecule that mimicked the binding site. Al-Abed is head of the institute's Laboratory of Medicinal Chemistry.

This peptidomimetic small molecule, FISLE-412, blocked anti-dsDNA autoantibodies *in vitro* with 30-fold more potency than a peptide derived from the original five-amino-acid sequence. The compound also inhibited the reactivity of anti-dsDNA autoantibodies in sera from lupus patients.

In *ex vivo* mouse kidney glomeruli, FISLE-412 lowered deposition of lupus autoantibodies compared with vehicle. Finally, in the hippocampus of live mice, FISLE-412 blocked autoantibody-induced neurotoxicity compared with vehicle.

The findings were published in the *Proceedings of the National Academy of Sciences*.

Optimize and test

The only other lupus therapy targeting anti-dsDNA autoantibodies had a rocky time in the clinic. In 2009, and based on an unfavorable interim efficacy analysis, **La Jolla Pharmaceutical Co.** discontinued the last of a series of Phase III trials of its Riquent abetimus, an oligonucleotide carrier complex that binds anti-dsDNA antibodies on the surface of B cells.

Despite sharing anti-dsDNA autoantibodies as a common target, Riquent and FISLE-412 differ in their mechanisms of action. The former targets autoantibodies on B cells, whereas the latter targets autoantibodies deposited in tissues and organs.

Thus, FISLE-412 is less likely to alter the function of B cells that may be important for host immunity. Moreover, by directly targeting autoantibody-antigen interactions, FISLE-412 potentially can decrease or even prevent the antibody-antigen deposits thought to cause multiorgan failure.

Diamond said FISLE-412 may also have advantages over targeted biologics for lupus. First, the compound is not immunosuppressive—it blocks a single autoantibody-antigen interaction rather than proinflammatory cytokines and/or families of immune cells. Second, FISLE-412 is orally available.

The only marketed targeted lupus therapy, Benlysta belimumab from **Human Genome Sciences Inc.** and **GlaxoSmithKline plc**, is an injectable mAb that targets BLyS (BAFF), which plays a key role in the differentiation and survival of B cells. The drug was associated with serious and sometimes fatal infections during its three clinical trials, as well as side effects including nausea, diarrhea, headache and skin rashes.

Moving forward, Diamond and Al-Abed will continue to collaborate. Al-Abed said he will focus on optimizing FISLE-412's pharmacokinetics, whereas Diamond is planning additional testing of the optimized compound in mice before testing in patients.

Dimitrios Boumpas, professor of rheumatology and clinical immunology at the **University of Crete School of Medicine**, suggested looking at FISLE-412 in mouse models of lupus nephritis to confirm that inhibiting deposition of autoantibodies in the kidneys of live animals reduces tissue injury sufficiently to have a real therapeutic benefit.

Boumpas would also like to see evidence in lupus patients that deposition of dsDNA autoantibodies in tissues is a key driver of lupus pathology in humans.

Diamond said the team's latest findings are covered by patents and available for licensing from the Feinstein Institute.

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