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Identification of candidate T-cell epitopes and molecular mimics in chronic Lyme disease.

Hemmer B, Gran B, Zhao Y, Marques A, Pascal J, Tzou A, Kondo T, Cortese I, Bielekova B, Straus SE, McFarland HF, Houghten R, Simon R, Pinilla C, Martin R.

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Elucidating the cellular immune response to infectious agents is a prerequisite for understanding disease pathogenesis and designing effective vaccines. In the identification of microbial T-cell epitopes, the availability of purified or recombinant bacterial proteins has been a chief limiting factor. In chronic infectious diseases such as Lyme disease, immune-mediated damage may add to the effects of direct infection by means of molecular mimicry to tissue autoantigens. Here, we describe a new method to effectively identify both microbial epitopes and candidate autoantigens. The approach combines data acquisition by positional scanning peptide combinatorial libraries and biometric data analysis by generation of scoring matrices. In a patient with chronic neuroborreliosis, we show that this strategy leads to the identification of potentially relevant T-cell targets derived from both Borrelia burgdorferi and the host. We also found that the antigen specificity of a single T-cell clone can be degenerate and yet the clone can preferentially recognize different peptides derived from the same organism, thus demonstrating that flexibility in T-cell recognition does not preclude specificity. This approach has potential applications in the identification of ligands in infectious diseases, tumors and autoimmune diseases.

Publication Types:

- Case Reports

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Neurology. 2003 Jun 24;60(12):1916-22. Related Articles, Links

Comment in:

- Neurology. 2003 Jun 24;60(12):1888-9.

Cognitive function in post-treatment Lyme disease: do additional antibiotics help?

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BACKGROUND: It is controversial whether additional antibiotic treatment will improve cognitive function in patients with post-treatment chronic Lyme disease (PTCLD). OBJECTIVE: To determine whether antibiotic therapy improves cognitive function in two randomized double-blind placebo-controlled studies of patients with PTCLD. METHODS: A total of 129 patients with a physician-documented history of Lyme disease from three study sites in the northeast United States were studied. Seventy-eight were seropositive for IgG antibodies against Borrelia burgdorferi, and 51 were seronegative. Patients in each group were randomly assigned to receive IV ceftriaxone 2 g daily for 30 days followed by oral doxycycline 200 mg daily for 60 days or matching IV and oral placebos. Assessments were made at 90 and 180 days after treatment. Symptom severity was measured from the cognitive functioning, pain, and role functioning scales of the Medical Outcomes Study (MOS). Memory, attention, and executive functioning were assessed using objective tests. Mood was assessed using the Beck Depression Inventory and Minnesota Multiphasic Personality Inventory. RESULTS: There were no significant baseline differences between seropositive and seronegative groups. Both groups reported a high frequency of MOS symptoms, depression, and somatic complaints but had normal baseline neuropsychological test scores. The combined groups showed significant decreases in MOS symptoms, higher objective test scores, and improved mood between baseline and 90 days. However, there were no significant differences between those receiving antibiotics and placebo. CONCLUSION: Patients with post-treatment chronic Lyme disease who have symptoms but show no evidence of persisting Borrelia infection do not show objective evidence of cognitive impairment. Additional antibiotic therapy was not more beneficial than administering placebo.

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- Clinical Trial
- Multicenter Study
- Randomized Controlled Trial

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Two controlled trials of antibiotic treatment in patients with persistent

symptoms and a history of Lyme disease.

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BACKGROUND: It is controversial whether prolonged antibiotic treatment is effective for patients in whom symptoms persist after the recommended antibiotic treatment for acute Lyme disease. METHODS: We conducted two randomized trials: one in 78 patients who were seropositive for IgG antibodies to Borrelia burgdorferi at the time of enrollment and the other in 51 patients who were seronegative. The patients received either intravenous ceftriaxone, 2 g daily for 30 days, followed by oral doxycycline, 200 mg daily for 60 days, or matching intravenous and oral placebos. Each patient had well-documented, previously treated Lyme disease but had persistent musculoskeletal pain, neurocognitive symptoms, or dysesthesia, often associated with fatigue. The primary outcome measures were improvement on the physical- and mental-health-component summary scales of the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36)--a scale measuring the health-related quality of life--on day 180 of the study. RESULTS: After a planned interim analysis, the data and safety monitoring board recommended that the studies be discontinued because data from the first 107 patients indicated that it was highly unlikely that a significant difference in treatment efficacy between the groups would be observed with the planned full enrollment of 260 patients. Base-line assessments documented severe impairment in the patients' health-related quality of life. In intention-to-treat analyses, there were no significant differences in the outcomes with prolonged antibiotic treatment as compared with placebo. Among the seropositive patients who were treated with antibiotics, there was improvement in the score on the physical-component summary scale of the SF-36, the mental-component summary scale, or both in 37 percent, no change in 29 percent, and worsening in 34 percent; among seropositive patients receiving placebo, there was improvement in 40 percent, no change in 26 percent, and worsening in 34 percent (P=0.96 for the comparison between treatment groups). The results were similar for the seronegative patients. CONCLUSIONS: There is considerable impairment of health-related quality of life among patients with persistent symptoms despite previous antibiotic treatment for acute Lyme disease. However, in these two trials, treatment with intravenous and oral antibiotics for 90 days did not improve symptoms more than placebo.

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New Tool Provides Major Advance for Understanding Chronic Lyme Disease and Other Illnesses

One of the most frustrating puzzles of Lyme disease is why some people develop debilitating chronic complications despite receiving recommended treatment. Now scientists have developed a new method to explore if these arthritic and neurologic symptoms result from the body's immune system turning against itself. Knowing the answer is key to developing better ways to diagnose Lyme disease, and to treat and possibly prevent its complications.

A report describing this research, led by scientists at the National Institutes of Health (NIH), appears in the December issue of *Nature Medicine*.

"This finding is a major advance for Lyme disease researchers and their patients," notes Anthony S. Fauci, M.D., director of the National Institute of Allergy and Infectious Diseases (NIAID). "We now have a powerful new tool to investigate what role autoimmune mechanisms play in the development of chronic symptoms associated with Lyme disease. We also can use this strategy to study other infectious and immunologic diseases."

Adriana Marques, M.D., of NIAID's Laboratory of Clinical Investigation, heads one of the Institute's two large studies of chronic Lyme disease and co-authored the new report.

The new technique, developed by Roland Martin, M.D., of the National Institute of Neurological Disorders and Stroke (NINDS), Richard Simon, Ph.D., of the National Cancer Institute (NCI), together with Clemencia Pinilla, Ph.D., of the Torrey Pines Institute for Molecular Studies, San Diego, was tested on a sample taken from a patient in the NIAID study. The patient has chronic central nervous system disease and a strong immune response against the Lyme agent, *Borrelia burgdorferi*, in both his spinal

fluid and blood. Their technique identified the specific bits of the Lyme agent his T cells recognized when they mounted an immune response against the bacterium. Equally important, it pinpointed candidate self-antigens, snippets of his own cells that mimicked those recognition sites on the bacterium.

The existence of these microbial mimics does not prove they cross-react with the immune system and cause the body to turn on itself, but it is a major step in investigating that possibility. Dr. Marques and her collaborators at NIH and Tufts University's Mark Klempner, M.D., leader of the other large NIAID-supported chronic Lyme disease study, are now planning to use this method to check samples from other patients to see if they have similar autoantigen profiles. If those results look promising, further investigations can be done, including trying to recreate the autoimmune disease model in small animals.

According to the study team, their strategy opens up new avenues for understanding the immune response involved in a variety of diseases where the causative agent has not yet been identified, such as rheumatoid arthritis, diabetes or inflammatory bowel disease. It also can be used to help design novel vaccines against infectious agents and tumors, and to identify candidate self-antigens and develop ways to turn off unwanted immune responses they might generate. "We are already using this technique in our study of multiple sclerosis," notes Dr. Martin.

For the research reported here, the scientists used the T cells found in the patient's spinal fluid to probe for what might be triggering the immune response causing his disease. First, they grew T cells that reacted against a mixture of all the bacterium's proteins. Then they tested that T-cell clone against a library of 200 mixtures of peptides, small pieces of proteins made from combinations of the 20 known amino acids. Each peptide was 10 amino acids in length; one amino acid was held constant while the other nine were randomized. Next, they numerically ranked each amino acid according to the strength of the immune response it generated at each position in the peptide. Finally, they performed a computer search of three databanks-the human genome, *B. burgdorferi* and all known viral proteins-to find any peptide sequences that matched their most reactive peptides. This search enabled them to identify candidate antigens and self-antigens potentially implicated in the disease.

The team found that the T-cell clone recognized multiple peptides, including some derived from viruses, as well as human autoantigens potentially important in the chronic Lyme disease process. While the response of the T-cell clone to *B. burgdorferi* peptides was strongest, its reactivity with multiple human proteins indicates that these T cells may be continuously stimulated either by the bacterium or by the human proteins, possibly leading to autoimmune tissue damage.

The report's other co-authors are Dr. Bernhard Hemmer (now at the University of Marburg, Germany); Drs. Bruno Gran, Abraham Tzou, Takayuki Kondo, Irene Cortese, Bibiana Bielekova and Henry F. McFarland from NINDS; Dr. Yingdong

Zhao from NCI; Dr. Stephen Straus from NIAID; and Drs. Jeannick Pascal and Richard Houghten from Mixture Sciences and the Torrey Pines Institute for Molecular Studies.

NIAID, NINDS and NCI are components of the National Institutes of Health (NIH). NIAID conducts and supports research to prevent, diagnose and treat illnesses such as HIV disease and other sexually transmitted diseases, tuberculosis, malaria, asthma and allergies. NINDS is the nation's leading supporter of research on the brain and nervous system, and a lead agency in the congressionally designated Decade of the Brain. NIH is an agency of the U.S. Department of Health and Human Services.

Press releases, fact sheets and other NIAID-related materials are available on the NIAID Web site at http://www.niaid.nih.gov.

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