The year that shaped the outcome of the OspA vaccine for human Lyme disease

Raymond J. Dattwyler and Maria Gomes-Solecki

The expansion of Lyme borreliosis endemic areas and the corresponding increase of disease incidence have opened the possibility for greater acceptance of a vaccine. In this perspective article, we discuss the discovery of outer surface protein A (OspA) of B. burgdorferi, and the subsequent pre-clinical testing and clinical trials of a recombinant OspA vaccine for human Lyme disease. We also discuss in detail the open public hearings of the FDA Lyme disease vaccine advisory panel held in 1998 where concerns of molecular mimicry induced autoimmune to native OspA were raised, the limitations of those studies, and the current modifications of recombinant OspA to develop a multivalent subunit vaccine for Lyme disease.

LYME DISEASE AND OUTER SURFACE PROTEIN A (OSPA) OF B. BURGDORFERI

The skin lesion erythema migrans is the classic clinical marker of early Lyme disease. The first well documented case of erythema migrans acquired in the United States was reported in 1970 in Wisconsin1. In 1976, Mast and Burrows described a cluster of cases of erythema migrans in Southeastern Connecticut2. A year later, others described a cluster of patients with large joint arthritis in the area of Old Lyme, Connecticut3, and named this condition Lyme arthritis. After retrospective analysis, it became apparent that most of these patients previously had erythema migrans and some had heart block, facial nerve palsy, or meningitis. At that point, the name of the illness was changed from Lyme arthritis to Lyme disease4.

Borrelia burgdorferi was identified as the etiologic agent of this illness after a spirochete was isolated from ixodes dammini ticks5 (currently named I. scapularis) and from blood of patients with Lyme disease6. The earliest reference to an outer surface protein of Borrelia burgdorferi that associated with bacterial agglutination dates to 19847. In vitro culture8 and immunochemical analysis of this spirochete soon followed7, as did subsequent recombinant cloning of the ospa gene9. OspA was proposed as a vaccine candidate for Lyme borreliosis after anti-OspA antibodies10,11 and immunization with recombinant OspA protein (rOspA)12 protected mice from challenge with several strains of cultured B. burgdorferi. Additional studies showed that B. burgdorferi was eliminated from infected nymphal ticks feeding on rOspA vaccinated mice and monkeys13,14. Following rOspA vaccination, blockage of transmission of the spirochete from the tick vector to the host15 and the ability of anti-rOspA antibody to agglutinate B. burgdorferi16 suggested a bactericidal mediated mechanism of action. However, the titer of anti-rOspA antibody required to eliminate B. burgdorferi from ixodes ticks was 2 Logs higher than the titer required to block transmission17,12. Although B. burgdorferi attachment within feeding ticks was dependent on OspA18 and a receptor for OspA (TROSPA) was found in the I. scapularis midgut, blocking TROSPA resulted in a diminished but persistent B. burgdorferi colonization of the tick midgut19. Further studies using OspA-specific monoclonal antibodies showed that even low concentrations of antibody blocked transmission despite the presence of many live spirochetes in the tick20. Thus, the mechanism of action mediated by bactericidal-independent OspA antibody that results in blockage of transmission of B. burgdorferi still needs to be clarified.

The clinical picture of Lyme disease has changed over the past 30 years. Lyme arthritis was emphasized as the key manifestation of late disease in North America and it may have been more common in the 1980s, but it is not common now. With early diagnosis and more effective treatment protocols the incidence of true Lyme arthritis dropped dramatically21–23. Although arthritic manifestations are still frequently reported, subjective joint pain (arthralgias) and true arthritis are conflated, which leads to an overestimation of Lyme arthritis incidence. In a recent Canadian study of 1230 patients reported to have Lyme disease, the overall incidence of arthritis was 0.028%. Of the 475 cases reported to have late Lyme disease only 35 (7.4%) manifested true arthritis, while 440 (92.6%) had arthralgias24. If we consider the estimate that about 10% of patients who develop Lyme arthritis will develop treatment-resistant Lyme arthritis (i.e., antibiotic-refractory Lyme arthritis)25 an objective estimate of current (2021) treatment-resistant Lyme arthritis incidence in Lyme disease patients would be about 0.0028%.

In the mid-1990s, when recombinant OspA (rOspA) was being tested in clinical trials as a potential vaccine candidate for human use it was unknown if this protein was involved in the pathogenesis of treatment-resistant Lyme arthritis. In a retrospective study of the antibody response to infection with B. burgdorferi, significant levels of anti-Ospa/OspB antibodies were not present in patients with erythema migrans or meningitis; in contrast, in patients with prolonged disease, some of which were previously treated with antibiotics and later developed Lyme arthritis, 71% had measurable antibodies to native OspA and OspB26. Another study reported that OspA reactive Th1 cells were detectable in synovial fluid of treatment-resistant Lyme arthritis patients years after antibiotic treatment but were not detectable in the joints of patients with treatment-responsive Lyme arthritis27. Although spirochetal DNA was found in the joint before most Lyme arthritis patients underwent antibiotic treatment, no spirochetal DNA was found in the joints of patients after...
mimicry hypothesis is that co-infections or other inflammatory syndromes may lead to increased production of IFNγ by Th1 cells in the joint that will upregulate enhanced presentation of self-peptides that amplify local inflammatory responses. Whether differences in OspA natively expressed in *B. burgdorferi* and recombinant OspA produced in expression systems could account for differences in inflammation needs further investigation.

### CLINICAL TRIALS OF THE RECOMBINANT OSPA (ROSPA) VACCINE FOR LYME DISEASE PREVENTION

The results of a Phase II clinical trial were published in 1994. It reported on the safety and immunogenicity of recombinant OspA (rOspA) with and without adjuvant in 36 healthy adult volunteers. The researchers found that both vaccine compositions induced high-titer of anti-rOspA antibodies that neutralized *B. burgdorferi* in vitro, with the most common adverse reactions being pain and tenderness at the site of inoculation. The safety and immunogenicity of the rOspA vaccine was again tested in 30 healthy volunteers who had been previously diagnosed with Lyme disease. In that study, reported in 1995, 93% of subjects developed high titer of antibody to rOspA and transient systemic side effects were recorded with three subjects also reporting mild arthralgias that lasted 24 h. Between January of 1995 and March of 1998 two Phase III efficacy studies were done in which two slightly different compositions of recombinant OspA were tested. In one study, a chemically lipidated full length recombinant OspA protein was adsorbed to aluminum hydroxide (L-rOspA with adjuvant, LYMErixTM, SmithKline Beecham (SKB), Pittsburgh, PA, now GlaxoSmithKline—GSK) and tested in a placebo-controlled trial: 5469 subjects received the vaccine and 5467 subjects received a non-OspA placebo. In the other study, also a placebo-controlled trial, full length recombinant OspA lipoprotein was tested without adsorption to any adjuvant (ImuLymeTM, PasteurMérieux-Connaught, Swiftwater, PA). In that study, 5156 subjects received the vaccine and 5149 subjects received a non-OspA placebo. In the first study, two IM inoculations of adjuvanted L-rOspA vaccine (LYMErixTM) prevented Lyme disease with 49% efficacy in the first year, and a third IM inoculation a year later prevented infections with 76% efficacy. In the second study, two IM inoculations of non-adjuvanted rOspA lipoprotein (ImuLymeTM) prevented Lyme disease with 68% efficacy in the first year, and a third IM inoculation prevented infections with 92% efficacy in the second year. It is possible that differences in efficacy of both vaccines could be due to differences in the composition. The immune response to OspA has been shown to be dependent on lipid modification of this protein. The lower efficacy rate of LYMErixTM compared to ImuLymeTM may have been related to the chemical lipidation process of the purified protein. In contrast, the ImuLymeTM composition was purified as a lipoprotein and was used without adsorption to adjuvant. In both LYMErixTM and ImuLymeTM clinical trials, a thorough analysis of adverse effects was performed. In both, administration of the vaccine was associated with mild to moderate local and systemic reactions that lasted 3–7 days and there was no significant increase in the frequency of arthralgias, arthritis, or neurologic events in vaccine recipients in comparison to placebo controls. Although causality was not shown, a later case report highlighted that transient symmetrical polyarthritis was observed in two males over 40 years of age as a possible adverse event of rOspA vaccination. In both cases, the adverse event was successfully treated with a 5-day course of ibuprofen. In the meantime, researchers found that rOspA vaccine efficacy was dependent on the maintenance of high antibody titers in serum over time. Furthermore, others found that vaccine-induced immune responses to rOspA did not replicate the sequence of events needed in natural infection to induce treatment-resistant Lyme arthritis. More recent systematic reviews and meta-analysis
of published data have found that reported adverse events were not different between vaccinated and placebo groups.\textsuperscript{16,47}

**THE FIRST MEETING OF THE FDA LYME DISEASE VACCINE ADVISORY PANEL: MAY 1998**

SmithKline Beecham (SKB) decided to move forward with the LYMErix vaccine for the prevention of Lyme disease and submitted an application to the FDA. In May of 1998, the FDA officers reviewing the application along with a panel of selected FDA advisers, the Vaccines and Related Biological Products Advisory Committee, participated in a public, FDA-sponsored meeting to discuss the LYMErix vaccine. A transcript of the meeting is available.\textsuperscript{48} A pre-meeting package included details on the vaccine clinical study carried out by SKB. The company's representatives gave an overview of the study including the study design, efficacy, and safety data. During the safety discussion, the study's lead investigator presented previously undisclosed data suggesting that *B. burgdorferi* entry into the joint could induce autoimmune arthritis in genetically susceptible individuals due to molecular mimicry between a dominant T cell epitope in *B. burgdorferi* native outer surface protein A and the human leukocyte function-associated antigen 1 within the pro-inflammatory milieu of the joint.\textsuperscript{49} Because the members of the advisory panel had not been briefed on these new scientific developments, they did not have an opportunity to gather evidence beforehand to help the panel understand the issue. Although it was reinforced that natural infection, not vaccination with rOspA, may play a role in treatment-resistant Lyme arthritis in a very small percentage of genetically predisposed individuals, the suggestion that there could be cross-reactivity between a human integrin and OspA raised concerns, there were discussions of unanticipated potential risks of LYMErix, as well as a need for greater caution and continued testing. The consensus of the panel was that the study data did not show significantly different safety issues among subjects in the vaccine and in the placebo groups, and that a Lyme disease vaccine would benefit public health. Thus, the panel recommended to the FDA that LYMErix should be approved. Other factors that diminished the enthusiasm for the vaccine were the low efficacy rate of LYMErix in the first year, the need for continued booster doses to maintain sufficient titer of neutralizing antibodies, the availability of effective treatment and that children were not included.\textsuperscript{50} In January of 2001, another FDA meeting was held. A perspective on that meeting is discussed elsewhere.\textsuperscript{49} The FDA never withdrew the SKB license to commercialize the OspA vaccine.

Editorial reviews on the demise of the Lyme disease vaccine have been written,\textsuperscript{49–55} two of which discuss risk communication and policy implications. We agree that scientific evidence and best patient care practices should guide the ethics of Lyme disease activism. However, we also acknowledge that unclear, sometimes contradictory scientific terminology may have led to confusion that drove health care professionals' vaccine hesitancy and subsequent public skepticism.

**CURRENT RECOMBINANT OSPA (ROSPA) BASED VACCINES**

After the 1998 Vaccines and Related Biological Products Advisory Committee FDA meeting, researchers started working on strategies to re-engineer rOspA as a vaccine candidate. The objective was to modify the epitope in rOspA identified as a putative mimic of hLFA1 while preserving the integrity and immunogenicity of the protein. Some modified the epitope by site directed mutagenesis, while others swapped the putative sequence with the same region of another genospecies such as *B. afzelii*. In both cases, the mutated rOspA protected mice from needle\textsuperscript{56} and tick transmitted\textsuperscript{57} *B. burgdorferi* infection. rOspA chimeras containing different sequences of Borrelia genospecies were constructed with the ultimate goal of developing a vaccine applicable to both the US and the European market.\textsuperscript{58} The intellectual property covering sequence substitutions in the C terminus of full length rOspA with the equivalent sequences from *B. garinii* and *B. afzelii* was eventually licensed by Stony Brook University to Baxter.\textsuperscript{58} This license then originated the multivalent six serotype rOspA compositions further developed by Baxter scientists. Results of the Baxter Phase I and Phase II clinical trials published in 2013 showed that the updated formulation was both safe and immunogenic.\textsuperscript{59} Subsequently, Valneva Austria GmbH applied a similar strategy to produce a composition containing only the modified C-terminus domains\textsuperscript{60} of 6 serotypes of rOspA to develop a subunit multivalent broadly protective vaccine (VLA15).\textsuperscript{61} VLA15 is currently undergoing two Phase II clinical trials to determine the best dose (573 subjects) and schedule of immunization (246 subjects) for human use.\textsuperscript{62} VLA15 technology was acquired by Pfizer in April of 2020 and both companies are collaborating to codevelop and commercialize their Lyme disease vaccine. Other strategies to use rOspA based prevention measures have been described elsewhere.\textsuperscript{64–66}

**CONCLUSIONS**

Two recombinant OspA vaccines have been proven efficacious for human use and new candidates are in development. The initial hypothesis that native *B. burgdorferi* OspA may contribute to the development of treatment-resistant Lyme arthritis was scientifically questionable, but it raised safety concerns regarding recombinant OspA vaccines. Nearly two decades after the Lyme disease vaccine was withdrawn from the market, there continues to be a lack of evidence that recombinant OspA induces clinically significant cross-reactivity with the human hLFA-1 epitope.

**DATA AVAILABILITY**

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Received: 13 December 2020; Accepted: 15 December 2021; Published online: 27 January 2022

**REFERENCES**

1. Scirranti, R. J. Erythema chronicum migrans. Arch. Dermatol. 102, 104–105 (1970).
2. Mast, W. E. & Burrows, W. M. Erythema chronicum migrans and “Lyme arthritis”. *JAMA* 236, 2392 (1976).
3. Steere, A. C. et al. Lyme arthritis: An epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. *Arthritis Rheum.* 20, 7–17 (1977a).
4. Steere, A. C. et al. Erythema chronicum migrans and Lyme arthritis. The enlarging clinical spectrum. *Ann. Intern. Med.* 86, 685–698 (1977).
5. Burgdorfer, W. et al. Lyme disease–a tick-borne spirochetosis? *Science* 216, 1317–1319 (1982).
6. Benach, J. L. et al. Spirochetes isolated from the blood of two patients with Lyme disease. *N. Engl. J. Med.* 308, 740–742 (1983).
7. Barbour, A. G. Immunochemoanalysis of Lyme disease spirochetes. *Yale J. Biol. Med.* 57, 581–586 (1984).
8. Barbour, A. G. Isolation and cultivation of Lyme disease spirochetes. *Yale J. Biol. Med.* 57, 521–525 (1984).
9. Howe, T. R., Mayer, L. W. & Barbour, A. G. A single recombinant plasmid expressing two major outer surface proteins of the Lyme disease spirochete. *Science* 227, 645–646 (1985).
10. Schlaib, U. E. et al. Monoclonal antibodies specific for the outer surface protein A (OspA) of Borrelia burgdorferi prevent Lyme borreliosis in severe combined Immunodeficiency (scid) mice. *Proc. Natl Acad. Sci. USA* 87, 3768–3772 (1990).
11. Schlaib, U. E., Kramer, M. D., Wallich, R., Tran, T. & Simon, M. M. Experimental Borrelia burgdorferi infection in inbred mouse strains: Antibody response and association of H-2 genes with resistance and susceptibility to development of arthritis. *Eur. J. Immunol.* 21, 2397–2405 (1991).
12. Fikrig, E., Barthold, S. W., Kantor, F. S. & Flavell, R. A. Protection of mice against the Lyme disease agent by immunizing with recombinant OspA. Science 250, 553–556 (1990).

13. Fikrig, E. et al. Elimination of Borrelia burgdorferi from vector ticks feeding on OspA-immunized mice. Proc. Natl Acad. Sci. USA 89, 5418–5421 (1992).

14. Philipp, M. T. et al. The outer surface protein A (OspA) vaccine against Lyme disease: Efficacy in the cynomolgus monkey. Vaccin. Rev. 15, 1872–1887 (1997).

15. de Silva, A. M., Telford, S. R. 3rd, Brunet, L. R., Barthold, S. W. & Fikrig, E. Borrelia burgdorferi OspA is an arthropod-specific transmission-blocking Lyme disease vaccine. J. Exp. Med. 183, 271–275 (1996).

16. Sadziene, A., Thompson, P. A. & Barbour, A. G. In vitro inhibition of Borrelia burgdorferi by peptides recognized by T cells from Lyme disease vaccinated mice. J. Immunol. 157, 4546–5502 (1996).

17. Delmar, C. A., Shapiro, E. D., Burke, G. S., Parcells, V. J. & Bell, G. L. Lyme disease in children in southeastern Connecticut. Pediatric Lyme Disease Study Group. N. Engl. J. Med. 335, 1270–1274 (1996).

18. Lu, L. Lyme arthritis. Infect. Dis. Clin. North Am. 19, 947–961 (2005).

19. Fikrig, E. et al. A critical appraisal of “chronic Lyme disease.” N. Engl. J. Med. 357, 1422–1430 (2007).

20. Johnson, K. O. et al. Clinical manifestations of reported Lyme disease cases in Ontario, Canada: 2005–2014. PLoS One 13, e0198509 (2018).

21. Steere, A. C. & Thompson, K. M. The Lyme vaccine: A cautionary tale. Epidemiol. Infect. 135, 1–8 (2007).

22. Sigal, R. S. Misconceptions about Lyme disease: Confusions hindering best-choosen terminology. Ann. Intern. Med. 153, 413–419 (2000).

23. Poland, G. A. Vaccines against Lyme disease: What happened and what lessons can we learn? Clin. Infect. Dis. 52, 2525–2528 (2011).

24. Plotkin, S. A. The rise and fall of the Lyme disease vaccines: a cautionary tale. J. Med. Ethics 37, 68–73 (2011).

25. Aronowitz, R. A. The rise and fall of the Lyme disease vaccine study consortium. J. Immunol. Today 21, 163–168 (1998).

26. Maier, B. et al. Multiple cross-reactive self-antigens for Borrelia burgdorferi-specific HLA-DR-restricted T cells. Eur. J. Immunol. 30, 448–457 (2000).

27. Steere, A. C. & Baxter-Lowe, L. A. Association of chronic, treatment-resistant Lyme arthritis with rheumatoid arthritis (RA) allelithes. Arthritis Rheum. 41, 581 (1998).

28. Schumacher, R. et al. Safety and immunogenicity of a recombinant outer surface protein A vaccine for Lyme disease. J. Infect. Dis. 172, 1324–1329 (1995).

29. Steere, A. C. et al. Vaccination against Lyme disease with recombinant Borrelia burgdorferi outer-surface lipoprotein A with adjuvant. Lyme Disease Vaccine Study Group. N. Engl. J. Med. 339, 209–215 (1998).

30. Sigal, L. H. et al. A vaccine consisting of recombinant Borrelia burgdorferi outer-surface protein A to prevent Lyme disease. Recombinant outer-surface protein A Lyme disease vaccine consortium. N. Engl. J. Med. 339, 216–222 (1998).

31. Weis, J. J., Ma, Y. & Erdile, L. F. Biological activities of native and recombinant Borrelia burgdorferi outer surface protein A: Dependence on lipid modification. Infect. Immun. 62, 4632–4636 (1994).
ACKNOWLEDGEMENTS
Throughout many years, research in this area was supported in part by the Intramural and Extramural Research Programs of the National Institutes of Health (NIH) and Centers for Disease Control and Prevention (CDC). The authors’ salary was supported in part by the following PHS grants: R01 AI139276 (MGS) and R44 AI150060 (RJD). The funders played no role in the conceptualization, design, decision to publish, or preparation of this manuscript.

AUTHOR CONTRIBUTIONS
R.J.D. was a member of the Vaccines and Related Biological Products Advisory Committee and attended the FDA meeting in 1998; M.G.S. wrote the manuscript; both authors edited the final manuscript.

COMPETING INTERESTS
The authors declare the following competing interests: M.G.S. (stocks, patents), R.J.D. (stocks, patents). M.G.S. and R.J.D. have no financial interests in Valneva/Pfizer and were not commissioned by any private or public sources to write this manuscript.

ADDITIONAL INFORMATION
Correspondence and requests for materials should be addressed to Raymond J. Dattwyler or Maria Gomes-Solecki.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/

© The Author(s) 2022