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COMMENTARY

Better drugs for Lyme disease: focus on the spirochete

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Abstract: Twenty-five years ago, the AIDS epidemic was wreaking havoc around the world. Although "HIV denialists" threatened to undermine research efforts to combat the epidemic, development of targeted antiviral therapy eventually provided effective treatment for the disease. Now the Lyme disease epidemic is wreaking havoc around the world, and "Lyme denialists" are undermining efforts to combat the epidemic. Drawing on our experience with the AIDS epidemic, there is a significant need to develop targeted therapy to control the Lyme disease epidemic.

Keywords: HIV/AIDS, Lyme disease, *Borrelia burgdorferi*, tick-borne disease, designer drugs

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It was 1993. The AIDS epidemic was in full swing with nearly 25,000 new cases diagnosed annually in the USA.[1] Repurposed chemotherapy drugs such as zidovudine (AZT) and other nucleoside analogs were failing to control the HIV-induced disease, and in the absence of effective therapy, over 80% of AIDS patients were using alternative and complementary treatments in a desperate attempt to keep their shattered lives going.[2] Citing flawed concepts of retroviral pathology, a small group of "HIV denialists" was whispering that HIV was not the cause of AIDS and that the medical community should turn away from antiretroviral therapy and look elsewhere for better AIDS treatment.[3]

Amid this cacophony, the voice of AIDS researcher David Ho helped to refocus the attack against AIDS.[4] In a memorable quote, Ho stated his case quite simply: "It's the virus, stupid!" The emphasis on targeting HIV encouraged the pharmaceutical industry to redouble its efforts to develop better antiretroviral therapy. Within 3 years, pharmaceutical giants Roche Holding AG (Basel, Switzerland), Merck & Co. (Kenilworth, NJ, USA) and Abbott Laboratories (Chicago, IL, USA) had produced highly active antiretroviral protease inhibitors, and the reversal of AIDS mortality had begun.[1] The rest is history.

Fast forward 25 years to 2018. The Lyme disease epidemic is in full swing with more than 300,000 new cases diagnosed annually in the USA.[5] Early-generation antibiotics such as tetracyclines and penicillins are failing to control the tick-borne disease, and in the absence of effective therapy more than two-thirds of Lyme disease patients are using alternative and complementary treatments in a desperate attempt to put their shattered lives back together.[6] Citing flawed studies of antibiotic therapy, a small group of "Lyme denialists" has proclaimed that *Borrelia burgdorferi*, the spirochetal agent of Lyme disease, is not the cause of persistent symptoms in the growing number of patients suffering from chronic illness.[7] Confronted with the controversy over chronic Lyme disease, the pharmaceutical industry has turned its back on suffering patients

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and their doctors who are trying to fight the disease. In the absence of more effective therapy, health care organizations and insurers have become complacent about inadequate treatment for Lyme disease.[6,8]

Amid this medical disaster, two recent reports should help to refocus the attack against the Lyme spirochete. The report by Cabello et al[9] highlights the ability of *Borrelia* "sleeper cells" to survive for extended periods in both the tick vector and vertebrate host using a "stringent response" that has been described in other bacterial infections.[10] The stringent response in *Borrelia* is mediated by an "alarmone", (p)ppGpp, that is postulated to be the master regulator of this function in the Lyme spirochete, and the complex metabolic and morphologic changes involved in the *Borrelia* stringent response allow the spirochete to cope with otherwise lethal nutritional deprivation, antimicrobial therapy, and host immunological defenses.[9] The detailed adaptive functions described by Cabello et al help to explain tolerance to antibiotics in *Borrelia* "persister cells" studied in vitro by other researchers,[11,12] and recognition of "sleeper cells" supports the likelihood of persistent *Borrelia* infection in patients who suffer from chronic Lyme disease symptoms despite conventional antibiotic therapy.[13]

The second report by Middelveen et al[14] demonstrates that Lyme disease patients are infected with viable *Borrelia* spirochetes that can be cultured from various body fluids, even if the patients are taking conventional antibiotic therapy. To address skepticism from "Lyme denialists,"[15] *Borrelia* cultures were tested in a blinded manner in laboratories located in Canada, Australia, and the USA using different molecular techniques, and the results were validated in a completely independent laboratory.[14] The study confirms and extends similar reports of viable *Borrelia* spirochetes in treated nonhuman primates[16] and in Lyme disease patients with persistent symptoms from Europe[17,18] and the USA,[19–21] and the results emphasize the ability of *Borrelia* spirochetes to evade antibiotic therapy under clinical conditions.[14,22] The finding of live *Borrelia* spirochetes in semen and vaginal secretions is particularly disturbing because it suggests that Lyme disease could be sexually transmitted in a manner similar to syphilis, chlamydia, HIV, Ebola, and Zika virus.[23–27]

What does this mean? It is time for the pharmaceutical industry to train its sights on *Borrelia burgdorferi* in the same way that it has attacked HIV and hepatitis C virus (HCV). Because a safe and effective Lyme disease vaccine is presently out of reach for technical reasons,[28,29] we need targeted designer drugs to treat the Lyme spirochete, and we can use the HIV and HCV models to develop these drugs.[8] Designer drugs would avoid the overuse of 60-year-old antibiotics that are marginally effective to begin with, and targeted therapy would provide more rational treatment for the tick-borne disease. Development of designer drugs for *Borrelia* would also open the door for research into more effective treatment for tick-borne bacterial, protozoal, and viral coinfections.[30–32] Furthermore, if *Borrelia* is proven to be sexually transmitted, targeted drug therapy would theoretically be more effective in preventing the spread of the spirochete, given the success with preexposure and postexposure prophylaxis for HIV disease.[33,34]

To paraphrase David Ho, "It's the spirochete, stupid!" We must find better ways to kill the Lyme spirochete with targeted designer drugs.

Disclosure

The authors report no conflicts of interest in this work.

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