Araim's Cibinetide in Inflammatory and Autoimmune Diseases: Increasing Evidence for Immune Modulation and Pleiotropic Benefit

TARRYTOWN, NY, May 16, 2018. Cibinetide, the lead compound of **Araim Pharmaceuticals, Inc.,** a clinical stage biotechnology company pioneering the development of innate repair receptor (IRR) activator platform technology, has recently been shown to have a profound immune cell modulation, anti-inflammatory, and disease modifying activity in animal models of two major human immune-mediated diseases: inflammatory bowel disease and systemic lupus erythematosus. Cibinetide is one of a library of peptides that activates cellular repair via IRR agonism.

In the first set of experiments, Nairz and colleagues[1] studied cibinetide's potential immune-modulatory and disease modification effect in the dextran sodium sulfate (DSS)-colitis mouse model of inflammatory bowel disease (IBD). Intestinal lamina propria macrophages, a key mediator of chronic inflammation in IBD, were shown to express IRR, and mice treated with cibinetide following disease initiation demonstrated significant improvement in disease activity and survival. Cibinetide-treated mice were found to have preserved intestinal lamina propria tissue integrity due to reduced infiltration of myeloid cells, and diminished production of pro-inflammatory disease mediators including cytokines, chemokines and nitric oxide synthase-2. Cibinetide effects were dependent on IRR and JAK2 functionality and were mediated via inhibition of NF-κB subunit p65 activity, a ubiquitous pro-inflammatory transcription factor that typically initiates and amplifies inflammatory processes.

Utilizing two different animal disease models for systemic lupus erythematosus **(**SLE), a significant human autoimmune disease, Huang and colleagues[2] evaluated the efficacy of cibinetide (a.k.a. ARA 290) for disease amelioration in both a pristane-induced SLE mouse model and an MRL/lpr genetic SLE mouse model. In both disease models, cibinetide reduced signs of systemic inflammation associated with disease activity. One of the most definitive markers for SLE is an increase in antinuclear antigen (ANA) autoantibodies in the serum, and another hallmark of SLE is the deposition of autoantibodies as immune complexes in the kidney, leading to inflammation and destruction of the glomeruli. Cibinetide treatment decreased ANAs and anti-dsDNA autoantibodies, suppressed the expression of pro-inflammatory cytokines/chemokines, increased anti-inflammatory cytokines, promoted clearance of cellular debris, and reduced the number of apoptotic cells. Overall, cibinetide significantly improved kidney function in both models of SLE.

Cibinetide works via binding to the IRR which becomes expressed in response to pro-inflammatory molecules at a site of injury. Receptor binding leads to activation of

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[1] Nairz, M., et al., *Cibinetide dampens innate immune cell functions thus ameliorating the course of experimental colitis.* Sci Rep, 2017. **7**(1): p. 13012.

[2] Huang, B., et al., *Non-erythropoietic erythropoietin-derived peptide protects mice from systemic lupus erythematosus.* J Cell Mol Med, 2018.

multiple intracellular signaling pathways that suppress damage while simultaneously activating cellular and tissue repair. This pathway has been demonstrated by a plethora of academic researchers to improve outcomes in a wide variety of disease models. Anthony Cerami, founder of Araim, stated "The compilation of results from many independent groups shows that this class of compounds could possibly be transformative to the treatment of inflammatory autoimmune and other chronic inflammatory diseases."

About Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the colon and small intestine, the most prevalent being Crohn's disease and ulcerative colitis, with serious effects on quality of life and morbidity. The exact causes of IBD remain unknown, but immune system malfunction is considered central, and diet and stress as strong contributing factors. Treatments aimed at suppressing inflammatory activity include corticosteroids, which have frequent side effects, and more recently, biologics such as anti-TNF therapies. However, approximately 30% of patients do not respond to anti-TNF therapy, and an additional 30% do not maintain efficacy [3]. The goal of achieving optimal long-term outcomes has not been satisfied in most patients and additional treatments or co-treatments is desirable [4].

About Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown cause characterized by multi-system involvement with significant morbidity and increased mortality. The rates of SLE mortality have decreased overall but remain high relative to the general population [5]. The disease can affect virtually every organ. Immunologic abnormalities, particularly the production of a number of antinuclear antibodies, are a prominent feature of the disease. While immunosuppressive therapy has positively impacted the prognosis of SLE, many patients still do not respond to traditional therapy. Furthermore, conventional immunosuppressive treatments for SLE are associated with a high risk of side effects. One challenge in caring for patients with SLE is a paucity of approved therapeutics for treatment of the diverse disease manifestations. In the last 60 years, only one drug, belimumab, has been approved for SLE treatment, thus, active SLE disease remains a significant problem[6].

About Araim Pharmaceuticals, Inc.

Araim Pharmaceuticals, Inc. is a private clinical stage biopharmaceutical company with a library of peptides that activate the body's own immune system to repair the damage of chronic disease and slow the aging process. We are focused on delivering novel

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[3] Ben-Horin, S., U. Kopylov, and Y. Chowers, *Optimizing anti-TNF treatments in inflammatory bowel disease.*Autoimmun Rev, 2014. **13**(1): p. 24-30.
[4] Neurath, M.F., *Current and emerging therapeutic targets for IBD.* Nat Rev Gastroenterol Hepatol, 2017. **14**(5): p. 269-278.
[5] Yen, E.Y., et al., *46-Year Trends in Systemic Lupus Erythematosus Mortality in the United States, 1968 to 2013: A Nationwide Population-Based Study.* Ann Intern Med, 2017. **167**(11): p. 777-785.
[6] Mahieu, M.A., et al., *A critical review of clinical trials in systemic lupus erythematosus.* Lupus, 2016. **25**(10): p. 1122-40.

therapies that slow, stop, and reverse chronic conditions. Through an extensive pre-clinical program, Araim's library of IRR agonists have demonstrated in a wide-array of disease conditions to activate the endogenous system to reduce inflammation, stop the spread of injury, and activate healing and regeneration. Our most advanced program, cibinetide, has completed Phase 2 trials in Diabetic Neuropathy and Sarcoid Neuropathy with demonstrated nerve regeneration. http://www.araimpharma.com/

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