Silencing cytokines

By Michael J. Haas, Senior Writer

A group led by **Resolvyx Pharmaceuticals Inc.** cofounder Charles Serhan has shown that the endogenous bioactive lipid resolvin D2 improves symptoms in sepsis.[1] The findings could expand the number of indications addressed by Resolvyx, which is developing resolvins for inflammatory indications, although the company has not disclosed how it will utilize the findings.

Resolvins are lipid mediators produced through the oxygenation of the ω-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). In multiple inflammatory conditions, resolvins manage the immune response.

Resolvyx began operations in late 2005 after exclusively licensing a patent portfolio of endogenous resolvins and their analogs from **Brigham and Women's Hospital**, where Serhan is director of the Center of Experimental Therapeutics and Reperfusion Injury. He is also a professor of anesthesiology at **Harvard Medical School**.

The company's most advanced compounds are based on resolvin E1 (RvE1), which is derived from EPA. Studies by Serhan and colleagues in 2007 and 2008 demonstrated the potential of RvE1 to treat acute inflammation and airway inflammation, respectively.[2,3] Since then Serhan has been investigating the therapeutic potential of resolvin D2 (RvD2), which is derived from DHA.

"It took us some time to establish the complete stereochemistry for RvD2 and begin to appreciate the broad basis of its actions in mammalian systems," Serhan told *SciBX*.

In mouse models of surgery-induced microbial sepsis, his latest team has now shown that RvD2 treatment reduced levels of proinflammatory cytokines associated with poor outcomes in sepsis and inhibited excessive leukocyte infiltration into the peritoneum compared with vehicle treatment. The compound achieved both effects without blocking the pathways that activate immune cells and thus stimulated endogenous pro-resolution mechanisms without exerting an immunosuppressive effect.

RvD2 also recruited phagocytes to increase the clearance of bacteria from the peritoneum and blood and increased mouse survival compared with that of controls.

"Our experiments show that RvD2 is a master regulator of the cytokine storm" associated with sepsis, said Serhan. "Our data suggest that RvD2 silences the outflow of all cytokines from macrophages as they're eating infected cells. The exciting part about this biology is that it goes against the grain of current therapeutic strategies of treating excessive inflammation with immunosuppression."

In contrast, he said, "RvD2 facilitates the resolution of inflammation."

Results were reported in *Nature*. The team included researchers from Barts and the London School of Medicine and Dentistry, which is part of **Queen Mary, University of London**, and the **University of Southern California**.

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> ***—Philip Vickers, Resolvyx Pharmaceuticals Inc.***

Indications of resolution

Serhan said RvD2 potentially could be combined with existing antibiotics to treat sepsis. He said the combination might reduce the required dose of antibiotic and thus the potential for antibiotic resistance.

"Our RvD2 study is a demonstration of a new type of endogenous molecule that acts on the effector immune system to enhance the killing of bacteria but is not an antibiotic" and so is not properly described as an anti-infective, Serhan said. "It requires a new word that I haven't found yet."

He also thinks RvD2 might have a protective effect in situations in which bowel mucosal damage could lead to sepsis, such as GI surgery or radiation therapy used for treating cancer or during bone marrow transplant.

Serhan acknowledged that more work with the surgical models of sepsis would be needed to determine how many types of bacterial infections RvD2 could clear. "But this is beyond the capability of an academic lab to test," he said.

Resolvyx CSO Philip Vickers said the findings by Serhan and colleagues underscore the potential of resolvins to treat diverse inflammatory indications without suppressing the immune system. "This is especially important in an inflammatory indication with an underlying infection—like sepsis—where immunosuppression would be counterproductive," he said.

"The *Nature* paper shows that resolvin D2 promotes active clearance of the infection to decrease bacterial load," said Vickers. "It doesn't provide just passive protection from inflammation."

Thus, Vickers has added indications such as periodontitis, oral mucositis and acute respiratory distress syndrome (ARDS) to the list of possible indications where RvD2 might be effective. But he declined to say whether the company planned to pursue them.

Resolvyx has DHA-derived resolvins in preclinical development to treat asthma, arthritis and inflammatory bowel disease (IBD).

Resolvyx's RX-10045, an isopropyl ester prodrug of a synthetic RvE1 analog formulated as a topical solution, completed a Phase I/II study to treat dry eye early this year.

Vickers said that RX-10001, an oral solution of synthetic RvE1, has just completed Phase I testing to treat asthma, arthritis and IBD.

The company plans to take the compounds into Phase III and Phase II testing, respectively, in 2010.

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