The worm turns

By Tim Fulmer, Senior Writer

U.K. researchers have shown that ES-62, a glycoprotein secreted by parasitic worms, prevents and treats septic shock in mice.¹ The group now is developing small molecule mimics of the protein for septic shock as well as inflammatory diseases such as asthma, arthritis and lupus.

In previous work, the group reported that ES-62 from *Acanthocheilonema viteae* bound toll-like receptor 4 (TLR4), thereby blocking the proinflammatory response of multiple mouse immune cells such as macrophages, dendritic cells (DCs) and mast cells.^{2,3}

Based on those findings, the team hypothesized that ES-62 might have utility in treating bacterial septic shock, which is triggered by excessive levels of multiple inflammatory mediators and can lead to vascular leakage, tissue injury, organ failure and death.

First, the researchers looked at the effects of ES-62 on immune cells *in vitro*. ES-62 blocked proinflammatory signaling in neutrophils and macrophages from sepsis patients.

In a mouse model of shock caused by the endotoxin lipopolysaccharide (LPS), pretreatment with ES-62 led to 100% survival compared with no survival for mice given vehicle control ($p < 0.01$). ES-62 also protected against shock in a mouse model of infectious sepsis caused by ligation and puncture of the intestinal cecum.

ES-62 also was able to treat established sepsis. Survival rates in mice receiving the compound 3 and 6 hours after ligation and puncture were 80% and 70%, respectively, whereas all control animals died ($p < 0.01$).

Finally, to get a better idea of how the compound would be used in the clinic, the researchers combined ES-62 with the broad-spectrum antibiotic amoxicillin, which is the first-line treatment for septic shock. In the mice, the combination conferred 100% survival at 6 hours after ligation and puncture.

Data were published in *Nature Immunology*, and the team was led by Alirio Melendez, professor of molecular and clinical pharmacology in the MRC Centre for Drug Safety Science at the **University of Liverpool**; William Harnett, professor of molecular immunology at the **University**

of **Strathclyde**; and Margaret Harnett, professor of immune signaling at the **University of Glasgow**.

The authors concluded that ES-62 and its synthetic small molecule analogs “might offer a suitable new therapeutic tool for the treatment of septic shock as well as other microbe-mediated diseases in humans, in whom out-of-control inflammation can lead to a fatal outcome.”

Mimicking ES-62

Corresponding author Melendez told *SciBX* he is continuing to work with the Harnetts to develop small molecule analogs of ES-62 that mimic the glycoprotein's anti-inflammatory effects in sepsis.

“For the past 30 years, sepsis treatment has largely been by administration of antibiotics and maintenance of blood flow. Despite those treatments, mortality rates for patients with severe illness, who experience multiorgan damage and septic shock, remain as high as 50%,” said Melendez. “By suppressing and limiting catastrophic inflammatory responses while allowing bacterial clearance to occur, ES-62

has the ability to enhance recovery in septic shock” versus antibiotics alone.

Xigris drotrecogin alfa, a recombinant form of human activated protein C (APC) from **Eli Lilly and Co.**, is the only approved drug to treat sepsis in the U.S. However, the drug's label contains a warning of an increased risk of serious bleeding events due to the drug's antithrombotic mechanism of action, limiting its use to severely septic patients at high risk of death.

Based on other preclinical studies, William Harnett suggested that an ES-62 mimic might also be useful for treating inflammatory diseases, including asthma, arthritis and lupus.

According to Melendez, the paper's findings are covered by patent applications. The licensing status is undisclosed.

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COMPANIES AND INSTITUTIONS MENTIONED

Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
University of Glasgow, Glasgow, U.K.
University of Liverpool, Liverpool, U.K.
University of Strathclyde, Glasgow, U.K.

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