**Supplemental Digital Content**

**Cecal ligation and puncture**

Cecal ligation and puncture was performed as previously described by Rittirsch et al (1). After mouse anesthesia, the abdomen was opened; then the caecum was exteriorized. A ligature was done on the proximal part of the caecum just after the ileocecal valve and then the caecum was perforated from side to side with a 21G needle to produce a severe cecal ligation and puncture-induced sepsis. The cecum was gently squeezed to extrude a small amount of feces through the perforation holes. The caecum was then returned into the peritoneal cavity and the abdominal wall was closed with a suture. Just after surgery, saline (1.2 ml/100g body weight), and buprenorphine (5ng/100g body weight) were administrated. Two hours after the cecal ligation and puncture, each animal was blindly administered either CSL111 (40 mg apolipoproteinA1/kg) or saline. The injection was done through the caudal vein and was repeated at 24h and 48h after the cecal ligation and puncture. Sham-operated mice (n=16) underwent the same surgical procedure but the caecum was neither ligated nor perforated.

**Intraperitoneal injection of bacteria (IP model)**

This second model of sepsis induced a peritonitis characterized by a rapid intravascular transfer of bacteria (2). *Escherichia coli* IAI76 strain bacteria were IP-injected. To determine the optimal bacterial concentration, a correlation curve between optical density (OD) at 600 nm of the bacterial solution and the number of colony forming unit developed on Luria-Bertani agar was performed. Bacteria were cultured in Luria-Bertani culture medium at 37°C for 20 hours. Bacteria were washed twice with saline by centrifugation (3000g for 15 minutes). Dilutions were then realized in order to seed culture media that were subsequently incubated at 37°C for 24 hours before colony forming unit count. The concentration of bacteria was estimated by spectrophotometry (Optic density 600 nm). 4.10^7 colony forming unit/ml were injected into the intraperitoneal cavity in a volume of 400 μL of saline. To choose this dose, a pilot experiment was performed with injection of different concentrations of bacteria, in order to reach a severe but not 100% lethal infection (70% of mortality). Briefly, after mouse anesthesia (n=10), different concentrations of E. coli were IP-injected (from 10^7 to 10^8 colony forming unit/ml). 4.10^7 colony forming unit /ml concentration was chosen because the mortality rate at 36 hours was 80%. (figure S6). In conclusion, a concentration of 4.10^7 colony forming unit/ml of *Escherichia coli* IAI76 strain bacteria was injected into the intraperitoneal cavity in a volume of 400 μL of saline.

After injection of bacteria, each animal was blindly administered either CSL111 (40 mg/kg) or saline. Injections were done in retro-orbital vein. Sham-operated mice underwent an abdominal surgery without any bacterial injection.

**Pseudomonas aeruginosa pneumonia model (pneumonia model)**

The bacterial strain ATCC 27853 was grown to mid-logarithmic phase in a Brain heart infusion for 24 hours at 37 °C. Bacteria were then washed twice and diluted in a phosphate buffered saline solution to a final concentration of 4 x 10^8 colony forming unit /ml. Our protocol was approved by our local ethic committee (20938-2019031114427274). C57Bl/6 mice (8-10 weeks) were anaesthetized with 2% inhaled isoflurane and Buprenorphine (0.05mg/kg SC) and placed in supine position. The cervical region was sterilized and a 1 cm midline skin incision was made just cranial to the thoracic inlet. The trachea was visualized by blunt dissection and was then cannulated with a 22 gauge intravenous catheter. 50µl of *Pseudomonas aeruginosa* solution or 50µl of saline were then instilled in the trachea through the catheter. Skin was sutured and animals were left for recovery in a warm cage. Analgesia and hydration were performed with buprenorphine and saline injection. Until anesthesia recovery, animals were maintained at 37° C in their cages and afterward were housed in a temperature- and light-controlled room with free access to water and food. Two hours after the pneumonia model, each animal was administered either CSL111 (40 mg apolipoproteinA1/kg) or saline. The injection was done through the caudal vein.

**Plasma and histological analyses**

Twenty-four hours after surgical procedure, the animals were sacrificed.

*Collection of plasma and organ samples:* Four hours before the cecal ligation and puncture, 300μL of blood were sampled on EDTA from the retro-orbital vein. The blood was centrifuged at 2000g at 20°C for 10 minutes, the plasma (supernatant) was centrifuged a second time (2000g, 20°C, 10 minutes) and stored at -80°C. Whole blood was also sampled for determining bacterial concentration.

In the 24-hour study, mice were exsanguinated by cardiac puncture after a thoracotomy (about 500 μl of EDTA-blood was collected). The same procedure of centrifugation and storage as described above was performed. After ligation of the right lung, the left lung was inflated with optimal cutting temperature and 60% sucrose solution (ratio 1/1) at a pressure of 25cmH2O, placed in optimal cutting temperature solution before freezing in liquid nitrogen and subsequent sectioning at 6μm. The remaining part of the lung was divided in 2: One part was weighted and incubated with Roswell Park Memorial Institute medium (without phenol red) for 24 hours at 37°C and then stored at -20°C. The other part was stored at -20°C in a Trizol solution for RNA extraction. For histological studies, liver, right lung, spleen and kidney samples were also stored at -20°C in optimal cutting temperature solution.

In the pneumonia model, at 24 hours, mice were exsanguinated by cardiac puncture after a thoracotomy (about 500 μl of EDTA-blood were collected). A bronchoalveolar lavage was performed in the right lung. In brief, after ligation of the left lung, the trachea was cannulated with a 22 gauge catheter. 1ml of precold sterile phosphate buffered saline was slowly injected into the lung and aspiration repeated three times. The lavage fluid was then collected and centrifuged at 1500g at 4°C for 10 minutes. The supernatant was collected and stored at -80°C. After ligation of the right lung, the left lung was inflated with optimal cutting temperature solution at a pressure of 25cmH2O, placed in optimal cutting temperature solution before freezing in liquid nitrogen and subsequent sectioning at 6μm. Liver was also stored at -20°C in optimal cutting temperature solution.

*Plasma cell-free DNA measurement*

Circulating DNA may result from neutrophil overactivation (NETosis or production of extracellular traps) leading to the release of their genetic material, but also from the all potentially dying cells including endothelial cells (3).

The concentration of cell-free DNA was determined in 10 μL of plasma using the Quant-iTTM high-sensitivity DNA assay kit and a QubitH fluorometer (Invitrogen, Carlsbad, CA, USA) following the manufacturer’s instructions. After the production of a standard curve with thymus calf DNA, plasma samples (10 μL) were disposed in a 96 well-plate, diluted with 90 μL of Tris-EDTA and a fluorescent reagent (100 μL) was added protected from the light. The fluorescence was then measured (λ excitation=485nm, λ emission= 535nm).

*Cytokine and endothelial marker measurement*

Cytokine levels were measured using the Milliplex cytokine magnetic kit (Merck Millipore® France). The concentrations of pro-inflammatory cytokines Interleukin-1ß and Tumor Necrosis Factor α as well as anti-inflammatory cytokine Interleukin-10 were determined in plasma obtained 4 hours before and 24 hours after the cecal ligation and puncture using a sequential enzyme-linked immunosorbent assay method. Endothelial markers were measured by multiplexed enzyme-linked immunosorbent assay using a cardiovascular panel (Merck Millipore® France). for Intercellular adhesion molecule-1, Vascular cell adhesion molecule-1, E-selectin, Matrix metallopeptidase-9 and Plasminogen activator inhibitor-1 were measured in plasma obtained 4 hours before and 24 hours after the cecal ligation and puncture.

In the pneumonia model, the concentration of Interleukin-6 cytokine was determined in the bronchoalveolar lavage fluid and in plasma using the same enzyme-linked immunosorbent assay method.

*RNA isolation and Real-Time Quantitative Polymerase Chain Reaction*

Lung is a major organ that becomes dysfunctional in sepsis. We tested the hypothesis that CSL111 may limit or delay the mortality by controlling lung inflammation via inhibition of lung pro-inflammatory molecule expression. Lung slice were homogenized in Trizol reagent and RNA was isolated using the Qiagen RNeasy kit (Qiagen, Hilden, Germany). In total, 1μg of RNA was reverse transcribed and Real-Time Quantitative Polymerase Chain Reaction using an Applied Biosystems 7700 Polymerase Chain Reaction machine (Foster City, CA, USA) was performed. In all samples, the mRNA transcript levels of Tumor Necrosis Factor α, Interleukin-6, and the adhesion molecules E-selectin and Intercellular adhesion molecule-1, Vascular cell adhesion molecule-1 were determined.

*Histological analysis of the lung*

Lungs were perfused with optimal cutting temperature medium in situ and removed before snap freezing with liquid nitrogen. Ten-micron frozen sections were fixed with acetone for 10 minutes for immuno-histofluorescence and with 4% paraformaledehyde for hematoxylin/eosin staining. Anti-human apolipoproteinA1 (#178422, 1.4 mg/mL) and anti-mouse CD68 (#HM1070 100 µg/mL) antibodies were applied for 1h30 after blocking non-specific sites with 10% bovine serum albumin in Phosphate-buffered saline for 30 minutes. Appropriate secondary antibodies conjugated with Alexa 488 and Alexa 594 respectively were incubated for 1h30 at room temperature. Each step was separated be 3 washes with 0.05 % Triton X100-phosphate buffered saline. The sections were mounted in Dako fluorescence mounting medium before analysis with NanoZoomer S60 digital slide scanner (Hamamatsu).

An observer blinded to the experimental conditions performed histological analysis quantification. Positivity for CD68 and ApolipoproteinA1 immunostaining and cells counting were determined by using ImageJ® software.

*Bacteria count*

High-density lipoproteins have been shown to bind lipopolysaccharide and to promote its clearance. We tested whether CSL111 may limit the effects of sepsis by reducing the concentration of circulating bacteria.

In the cecal ligation and puncture model, serial dilutions of whole blood were performed in saline and 100 μL of these solutions were seeded in Luria-Bertani Agar culture medium. After a 24h incubation at 37°C, the colony forming unit were counted in order to evaluate the bacterial concentration. The same protocol was carried out with tissue homogenates from liver, lung, spleen and kidney in order to determine the number of colony forming unit.

In the pneumonia model, a bacterial count was also performed (liver and lung). Tissues were homogenized using an Ultra-Turrax® device and then diluted in phosphate buffered saline 1X (1mg of tissue for 20 ml of phosphate buffered saline 1X). After centrifugation at 400g for 5’ in order to discar tissue debris, the supernatant was diluted in brain heart infusion broth (10µl of the solution + 90µl of brain heart infusion broth) before incubation at 37°C in a 96-well microplate. The plate was then incubated at 37°C. An automated spectrophotometer (Bioscreen C, ThermoLifeScience®) was used to monitor growth curves. Optical density was read at 600 nm at T0, T2, T4, and T16 hours.

1. Rittirsch D, Huber-Lang MS, Flierl MA, Ward PA. Immunodesign of experimental sepsis by cecal ligation and puncture. *Nat Protoc*. 2009;4(1):31–6.

2. O’Dwyer MJ, Starczewska MH, Schrenzel J, Zacharowski K, Ecker DJ, Sampath R, Brealey D, Singer M, Libert N, Wilks M, Vincent JL. The detection of microbial DNA but not cultured bacteria is associated with increased mortality in patients with suspected sepsis-a prospective multi-centre European observational study. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis*. 2017 Mar;23(3):208.e1-208.e6.

3. Brinkmann V, Zychlinsky A. Beneficial suicide: why neutrophils die to make NETs. *Nat Rev Microbiol*. 2007 Aug;5(8):577–82.