Investigational Agent Reparixin and IL-8 Signal Inhibition in CAP and ARDS

Inflammatory responses during CAP and ARDS can contribute to significant morbidity and mortality

Community-acquired pneumonia (CAP)

- CAP is a lower respiratory tract infection caused by bacterial or viral pathogens (e.g., *Streptococcus pneumoniae*, influenza)[1]
- Dysregulation of the resulting inflammatory response can lead to severe CAP, cytokine storm, ALI, and sepsis[2,3]
- Severe CAP accounts for nearly 6% of ICU admissions; ICU mortality in CAP is nearly 35%[4]

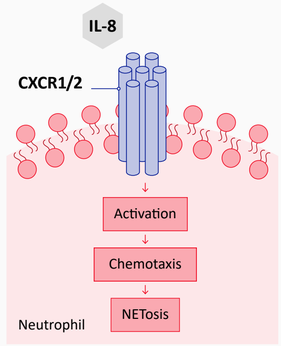
Acute respiratory distress syndrome (ARDS)

- ARDS is an acute inflammatory lung injury characterized by hypoxemia; common etiologies include sepsis and pneumonia[5,6]
- The hyperinflammatory phenotype of ARDS is characterized by an influx of neutrophil activity leading to tissue injury[6]
- ARDS accounts for 10% of ICU admissions and 23% of patients requiring mechanical ventilation; ICU mortality exceeds 40% in severe ARDS[7]

IL-8 is a proinflammatory cytokine implicated in the pathogenesis and progression of CAP and ARDS

- IL-8 is a proinflammatory cytokine associated with high inflammation potential during severe lung inflammation and infection[6]
- IL-8 mediates its biological effects through CXCR1 and CXCR2 binding, which induces chemotaxis and neutrophil activation[6]
- Activated neutrophils can elicit a hyperdriven immune response by releasing granule proteins and chromatin to form NETs through a process called NETosis[6]
- Excessive NETosis can produce toxic events for the host cell and contribute to disease pathogenesis[6]

IL-8 activates neutrophils



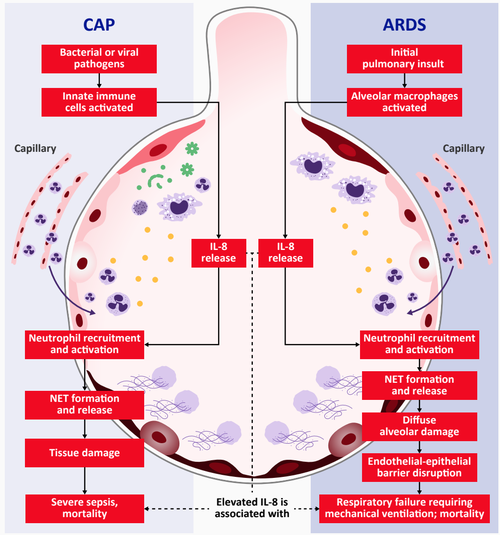
CAP

- During CAP pathogenesis, innate immune cells detect bacterial or viral pathogens, triggering IL-8 secretion[2]
- IL-8 stimulates neutrophil infiltration and activation and induces NET formation, leading to pulmonary tissue injury[2,8]
- Elevated IL-8 in CAP is associated with complications such as severe sepsis and mortality[9,10]

ARDS

- In ARDS, an initial pulmonary insult activates alveolar macrophages, inducing IL-8 secretion and neutrophil recruitment into the lungs[5,11]
- Excessive neutrophil accumulation and IL-8–mediated NET formation cause diffuse alveolar damage and endothelial–epithelial barrier disruption[5,11]
- Elevated IL-8 in ARDS is associated with longer time on mechanical ventilation, prolonged ICU stays, multiple organ failure, and increased risk of mortality[12–14]

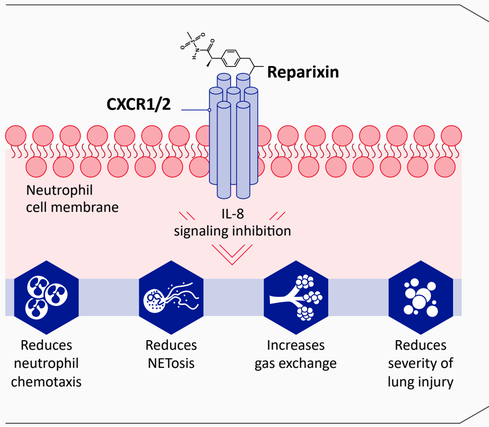
IL-8 in CAP and ARDS

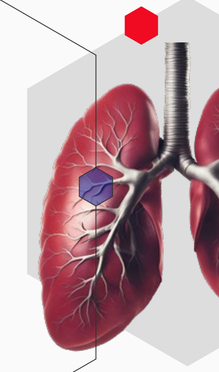


Reparixin is an investigational agent targeting IL-8–mediated hyperinflammation in CAP and ARDS

- Reparixin is an investigational, potent, noncompetitive allosteric inhibitor of the IL-8 receptors CXCR1 and CXCR2[15]
- Reducing IL-8 signaling with reparixin may attenuate inflammatory responses and improve associated clinical outcomes in severe CAP and ARDS by reducing neutrophil recruitment and NET formation[8,16]
- Reparixin is currently being evaluated in adults hospitalized with CAP (REPAVID-22; Phase 3) and moderate-to-severe ARDS (RESPIRATIO; Phase 2)[17,18]
- Reparixin add-on therapy was well tolerated and associated with fewer clinical events and fewer ICU admissions in Phase 2/3 trials in severe COVID-19 pneumonia[19,20]

Potential mechanism of action[8,16]





Abbreviations: ALI, acute lung injury; COVID-19, coronavirus disease 2019; CXCR, CXC chemokine receptor; ICU, intensive care unit; IL-8, interleukin 8; MoA, mechanism of action; NET, neutrophil extracellular trap; SARS-COV-2, severe acute respiratory syndrome coronavirus 2.

References: 1. Brown JS. *Clin Med (Lond)*. 2012;12(6):538-543. **2.** Kumar V. *Front Immunol*. 2020;11:1722. **3.** Ramirez JA. *Univ Louisville J Respir Infect*. 2018;2(2):4-6. **4.** Woodhead M, et al. *Crit Care*. 2006;10(suppl 2):S1. **5.** Han S, Mallampalli RK. *J Immunol*. 2015;194(3):855-860. **6.** Cesta MC, et al. *Front Pharmacol*. 2021;12:808797. **7.** Bellani G, et al. *JAMA*. 2016;315(8):788-800. **8.** Alsabani M, et al. *Br J Anaesth*. 2022;128(2):283-293. **9.** Aliberti S, et al. *Pneumonia (Nathan)*. 2016;8:8. **10.** Wu CL, et al. *J Formos Med Assoc*. 2006;105(1):49-55. **11.** Matthay MA, et al. *Nat Rev Dis Primers*. 2019;5(1):18. **12.** Parsons PE, et al. *Crit Care Med*. 2005;33(1):1-6; discussion 230-232. **13.** Hildebrand F, et al. *Cytokine*. 2007;37(3):192-199. **14.** Cartin-Ceba R, et al. J Crit Care. 2015;30(1):219.e1-7. **15.** Bertini R, et al. *Proc Natl Acad Sci U S A*. 2004;101(32):11791-11796. **16.** Zarbock A, et al. *Br J Pharmacol*. 2008;155(3):357-364. **17.** ClinicalTrials.gov. NCT05254990. Accessed April 8, 2024. https://clinicaltrials.gov/study/NCT05254990. **18.** ClinicalTrials.gov. NCT05496868. Accessed April 8, 2024. https://clinicaltrials.gov/study/NCT05496868. **19.** Landoni G, et al. *Infect Dis Ther*. 2022;11(4):1559-1574. **20.** Piemonti L, et al. *Infect Dis Ther*. 2023;12(10):2437-2456.

Images provided by Freepik.

For more information, contact Dompé at usmedinfo@dompe.com

Dompé

MED-US-RPX-2400006. Date of preparation April 2024.