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Treatment of Sepsis and Acute Respiratory Distress Syndrome (ARDS)

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The problem to be solved:
Unmet clinical needs Sepsis and ARDS

Sepsis

- > 19 000 000 cases/year
- Mortality: 30%
- Uncontrolled systemic inflammation initiated by infections

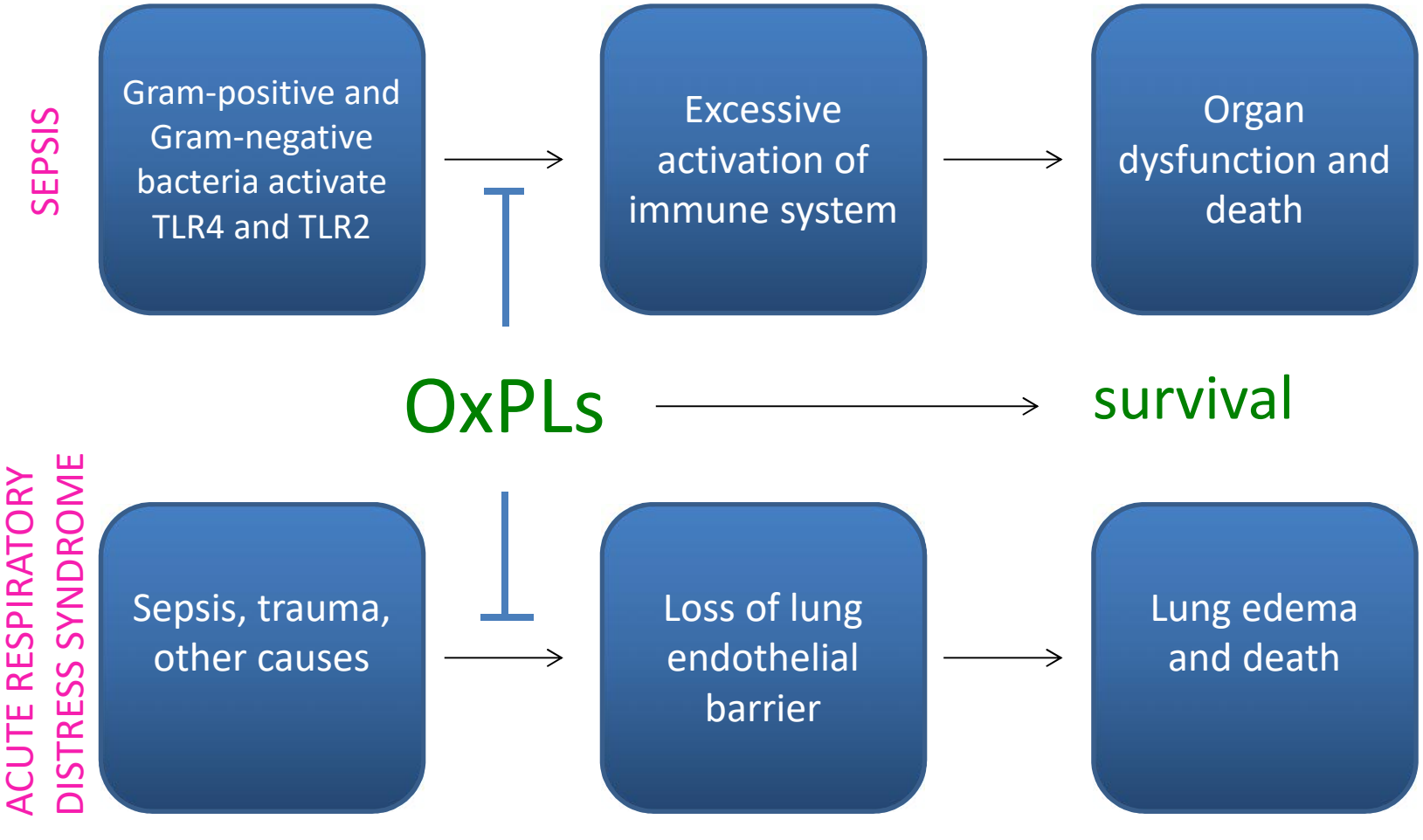
Acute Respiratory Distress Syndrome (ARDS)

- 1 000 000 cases/year
- Mortality: 40%
- Lung endothelial barrier disruption
- > 30% result from sepsis

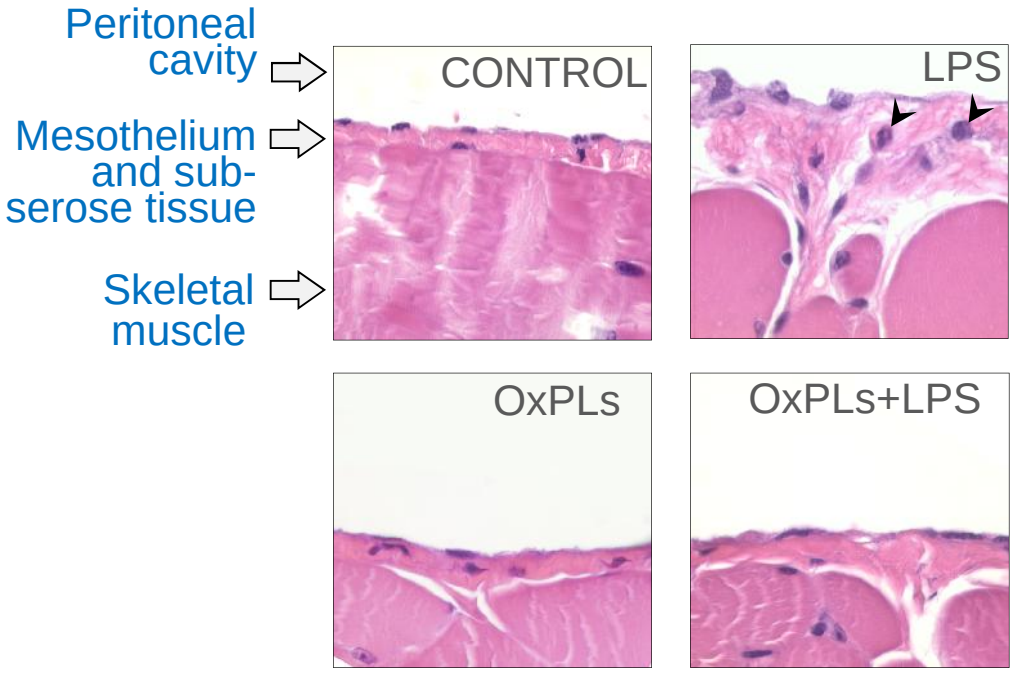
✓ Severe clinical conditions
✓ High incidence
✓ Often observed in the same patient
✓ No effective drug treatment

Our solution to the problem: Novel class of biologically active lipids

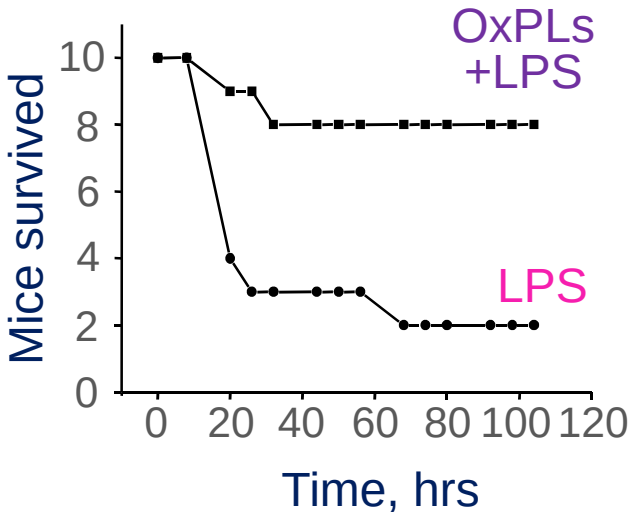
- Oxidized phospholipids: nonenzymatic oxidation of PL-esterified PUFAs



Oxidized phospholipids (OxPLs) reduce lethality in an animal model of sepsis

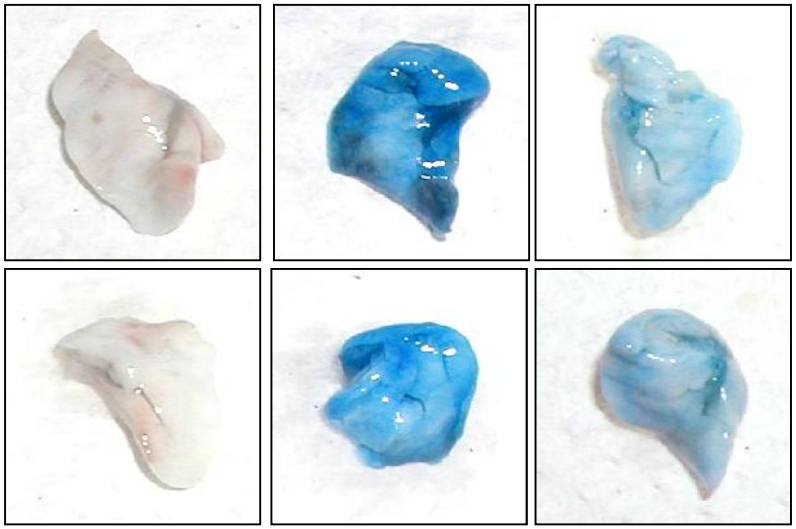


LPS = bacterial lipopolysaccharide, a ligand for TLR4

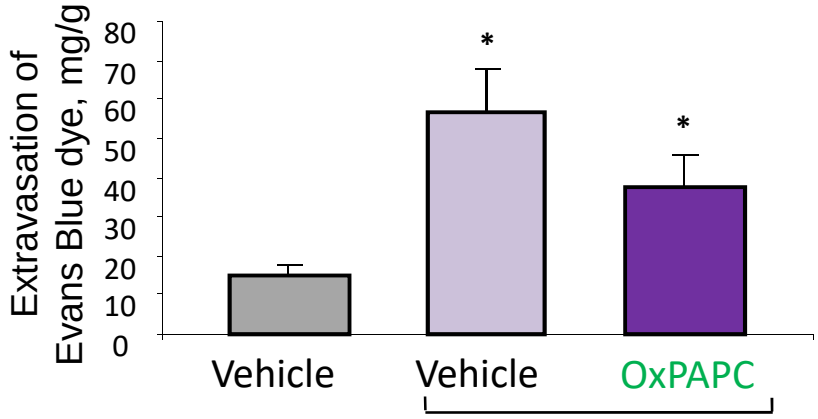


Oxidized phospholipids (OxPLs) reduce lung edema in an animal model of acute respiratory distress syndrome *(co-inventor: Prof. K. Birukov, Univ. of Chicago)*

High volume lung ventilation
(mechanical + oxidative lung damage)



Extravasation of Evans Blue dye

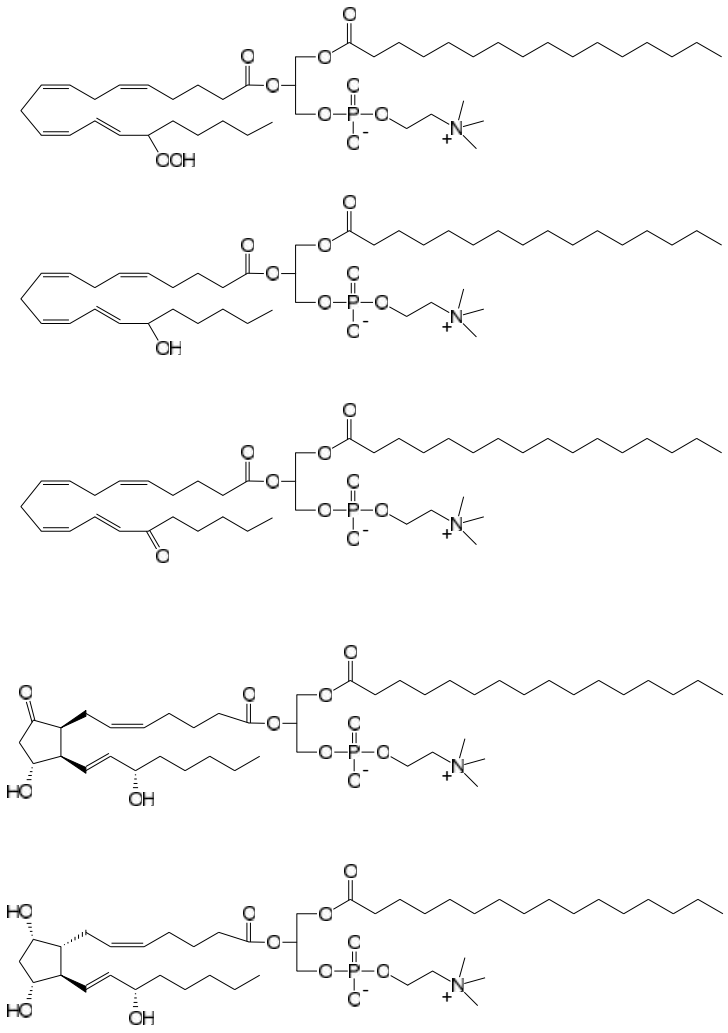


Oxidized phospholipids protect against edema induced by:

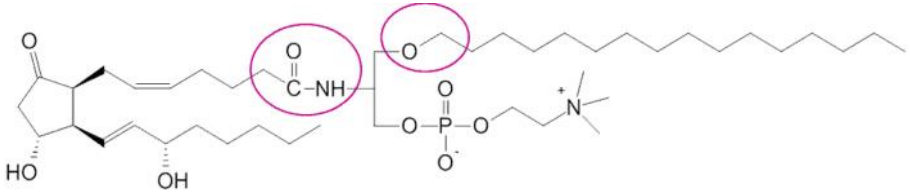
- High ventilation volume
- Gram-positive bacteria (stimulate TLR2)
- Gram-negative bacteria (stimulate TLR4)

Active molecules

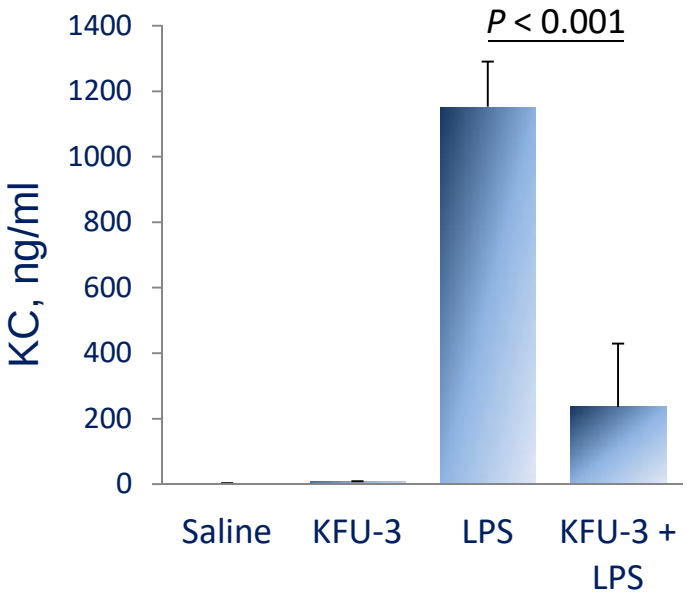
Naturally occuring oxidized phospholipids



Fully synthetic hit *KFU-3*



Inflammatory cytokine KC in mouse plasma

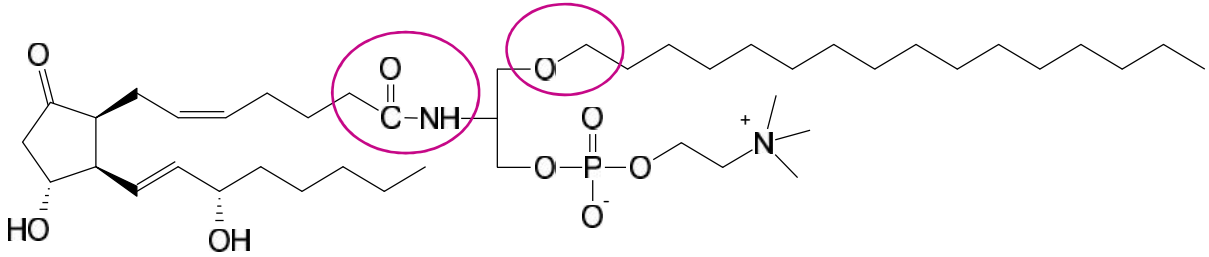


Advantages of OxPL-based hit compounds: unique polypharmacology

- Double antagonists of TLR4 and TLR2: inhibit inflammation
- Increase lung endothelial barrier through stimulation of EP4 and surface GRP78 receptors: prevent edema
- This double protective effect may be especially beneficial in combined clinical cases of sepsis and ARDS

Development status

- Several pharmacological hits active in common preclinical models of sepsis and ARDS
- First attempts to improve structure were successful:
  - Enhanced stability to major PL-degrading enzymes such as phospholipase A2
  - Modified scaffold allowing faster synthesis of derivatives as compared to physiological phospholipids
  - Non-electrophilic species: lower toxicity



Commercial opportunity and contact

Technology offered for:

- Licensing
- Collaboration for preclinical / clinical development

IP:

- priority application US 15/667,893 (filed on 3/8/2017) [not published yet]
- protected are the compounds themselves and their use

Freedom-to-operate:

- no other patents are known this time that might harm a commercialization

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