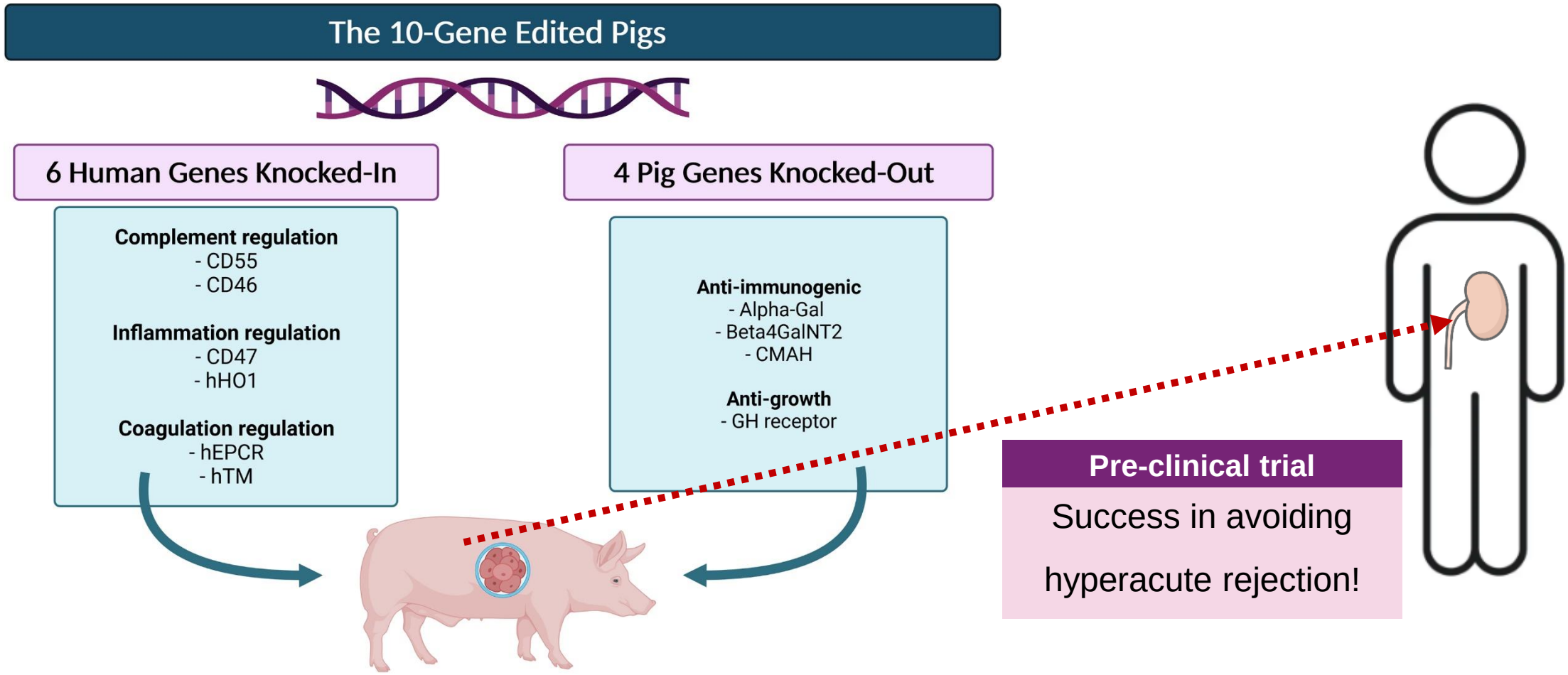
Suppression of innate immune-induced rejection by a membrane-type human surfactant protein-A in xenotransplantation

Soichi Matsumura[1], Akira Maeda[2], Shota Fukae[1], Ryo Tanaka[1], Shigeaki Nakazawa[1], Kazuaki Yamanaka[1], Yoichi Kakuta[1], Shuhei Kogata[2], Chiyoshi Tomiyama[2], Hirosi Eguchi[2], Hiroomi Okuyama[2], Shuji Miyagawa[2], Norio Nonomura[1]

1Department of Urology, Osaka University Graduate School of Medicine
2Pediatric Surgery, Osaka University Graduate School of Medicine

Xenotransplantation



Alpha-Gal = α-1,3-galactosyltransferase; Beta4GalNT2 = β1,4-N-acetylgalactosyltransferase; CMAH = CMP-N-acetylneuraminic acid hydroxylase; GH = growth hormone; hEPCR = human endothelial protein C receptor; hHO1 = human hemeoxygenase-1.

Boulet J, et al. JACC Basic Transl Sci . 2022

Overcoming innate immunity is essential for long-term graft survival in xenotransplantation.

→ Novel genetic modifications

Background and Objective

- ✓ One major issue in xenotransplantation for clinical application is the inadequate control of innate immune cells. Further genetic modifications are considered necessary for the control of innate immune cells.

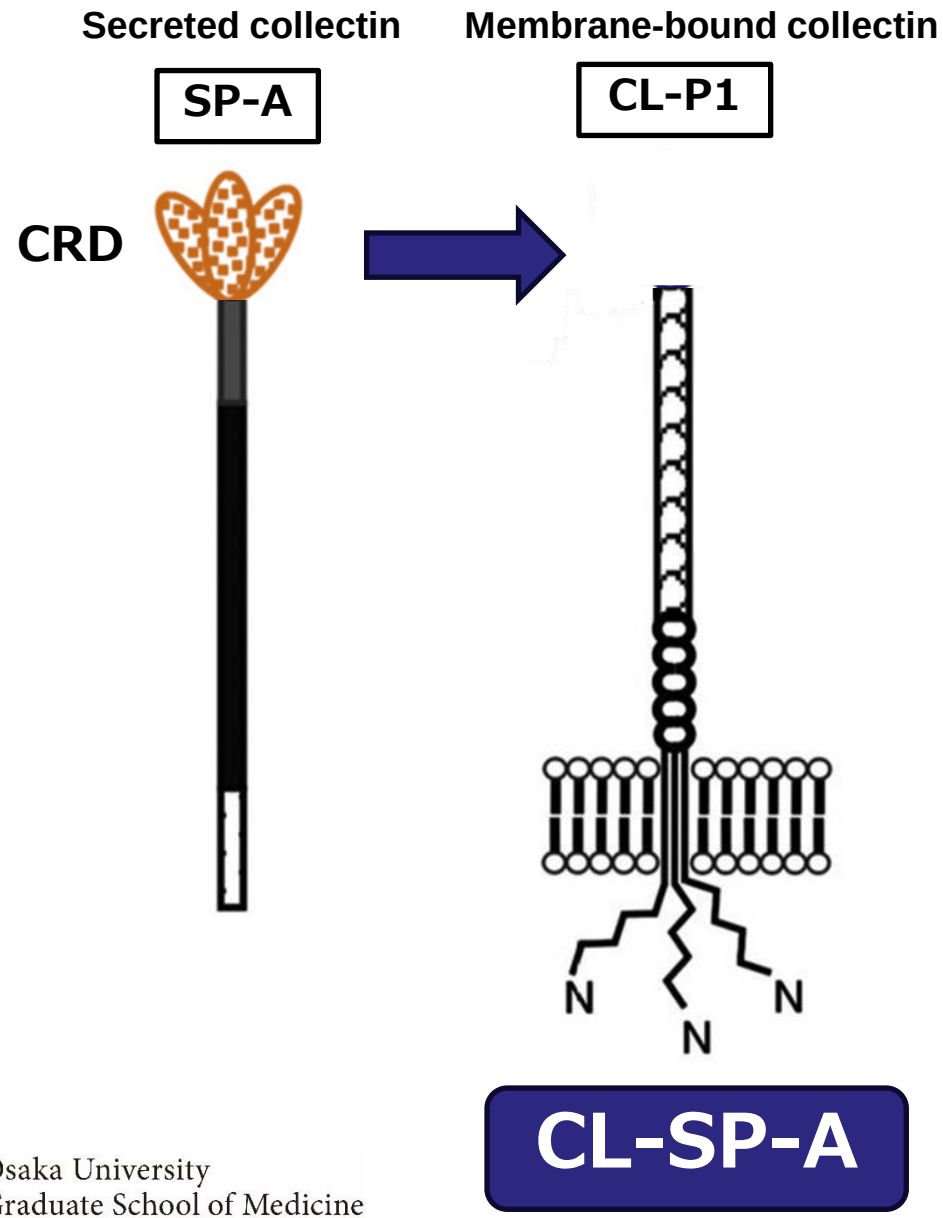
  Loupy A, et al. Lancet . 2023

- ✓ Signal-regulatory protein-α (SIRPα) is known as a receptor that exerts inhibitory effects on the effector functions of macrophages and neutrophils.

- ✓ The CRD (carbohydrate recognition domain) portion of surfactant protein-A (SP-A), a regulator of innate immunity, interacts with signal regulatory protein α (SIRPα), initiating suppressive signals via ITIM to deliver negative signals.

  Yokohira M et al. J Toxicol Pathol. 2014

Background and Objective

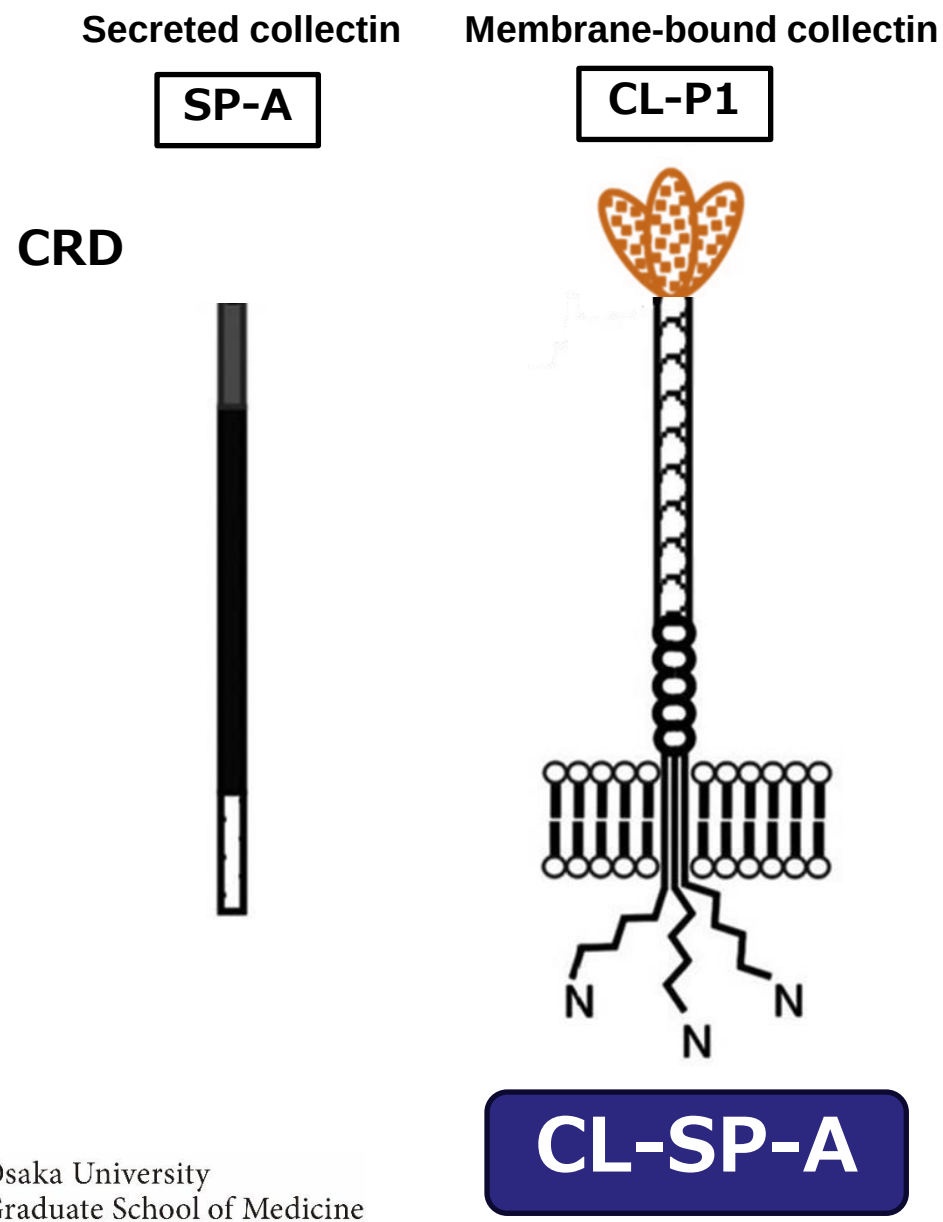


- ✓ To express the characteristic carbohydrate recognition domain (CRD) portion of SP-A on the endothelium of the graft's pig vasculature, a novel collectin called CL-SP-A was created by replacing the CRD portion of SP-A with that of the membrane-type collectin CL-P1.

＊SIRPα:Signal-regulatory protein-α, CRD:Carbohydrate recognition domain, SP-A: Surfactant protein A

Yokohira M et al. J Toxicol Pathol. 2014

Background and Objective



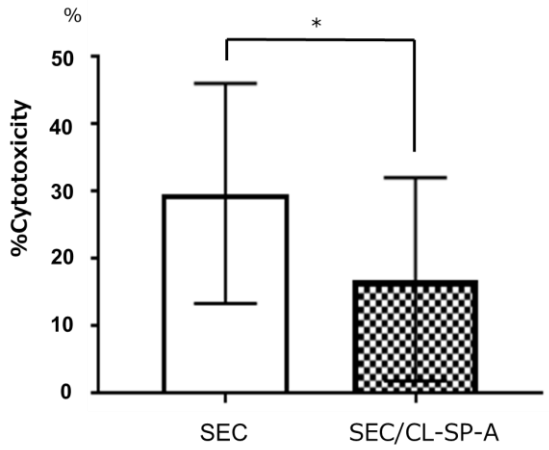
- ✓ To express the characteristic carbohydrate recognition domain (CRD) portion of SP-A on the endothelium of the graft's pig vasculature, a novel collectin called CL-SP-A was created by replacing the CRD portion of SP-A with that of the membrane-type collectin CL-P1.
- ✓ By expressing CL-SP-A on swine endothelial cells (SEC), the inhibitory effect of human macrophages and neutrophils on xenogeneic rejection reactions is to be investigated.

＊SIRPα:Signal-regulatory protein-α, CRD:Carbohydrate recognition domain, SP-A: Surfactant protein A

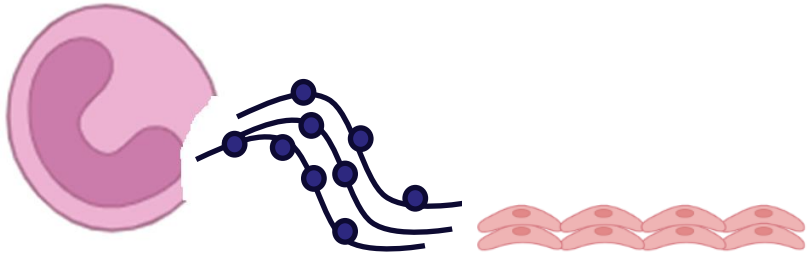
Yokohira M et al. J Toxicol Pathol. 2014

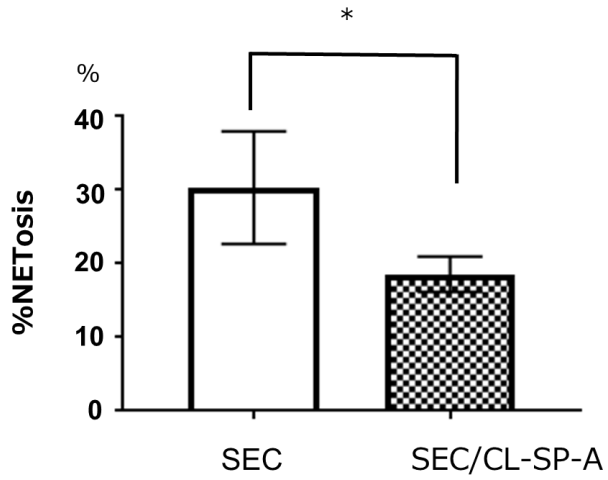
Result

Swine Endothelial Cells

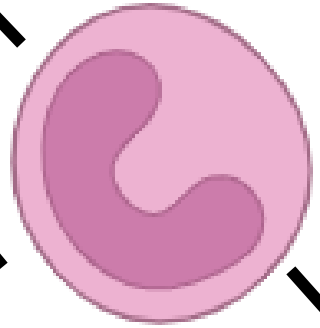


NETosis

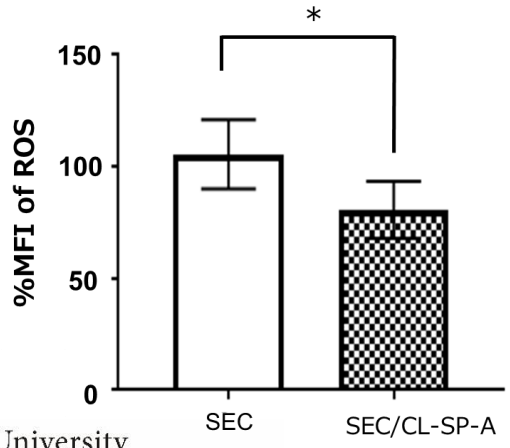




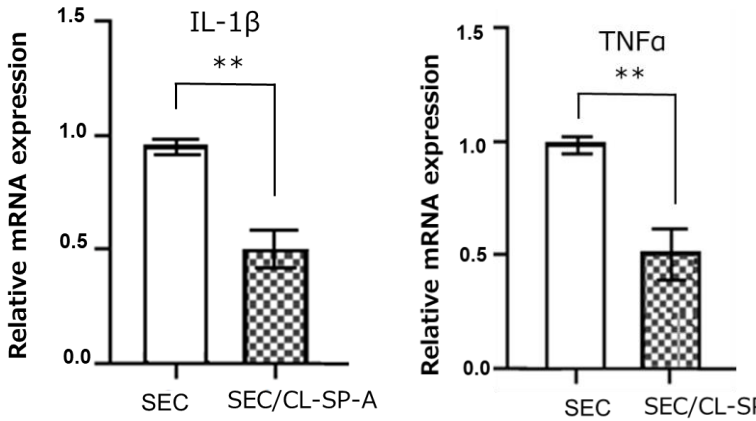
Neutrophil



ROS



Produce inflammatory cytokines

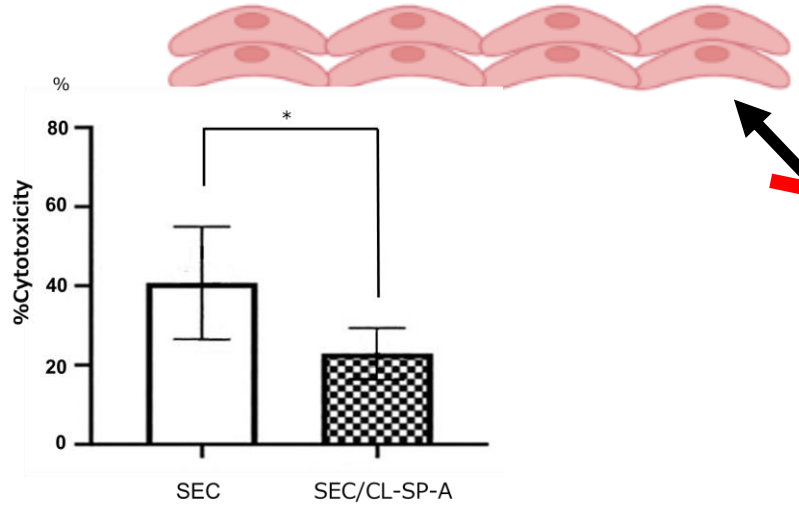


* p<0.05

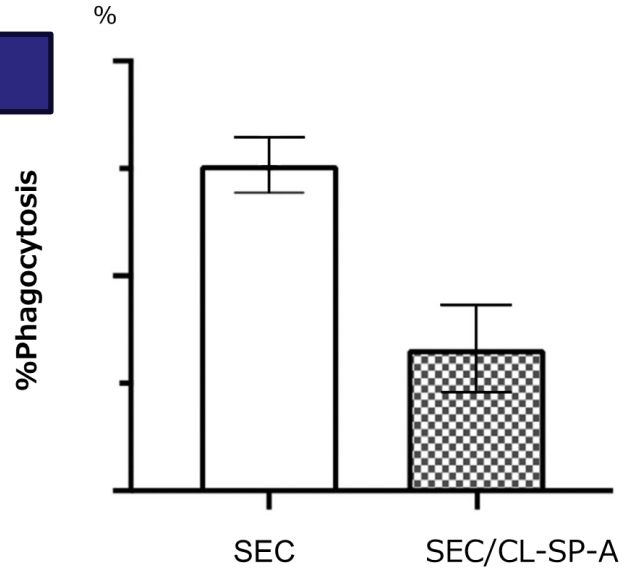
** p<0.01

Result

Swine Endothelial Cells

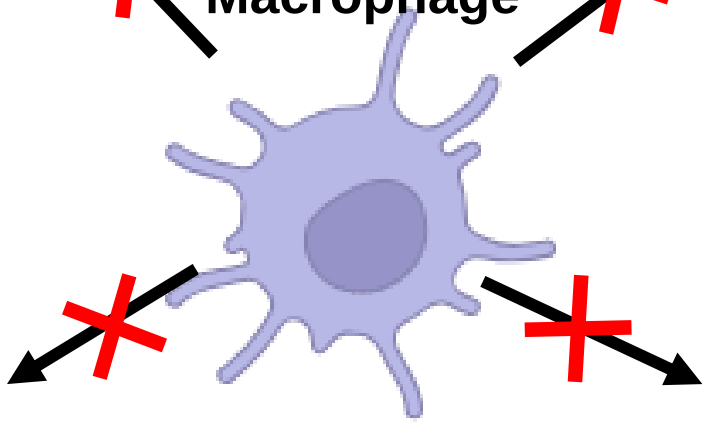


Phagocytosis

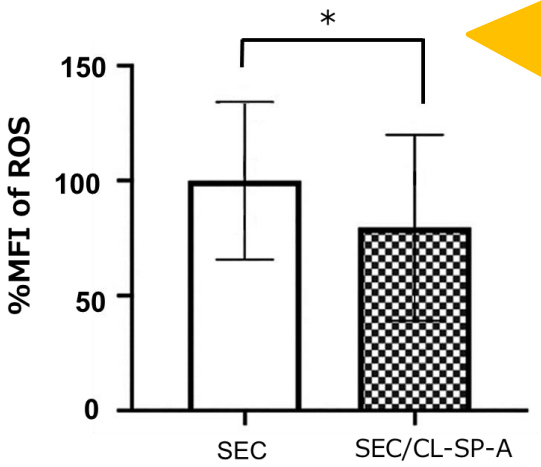


*** p < 0.001

Macrophage



ROS



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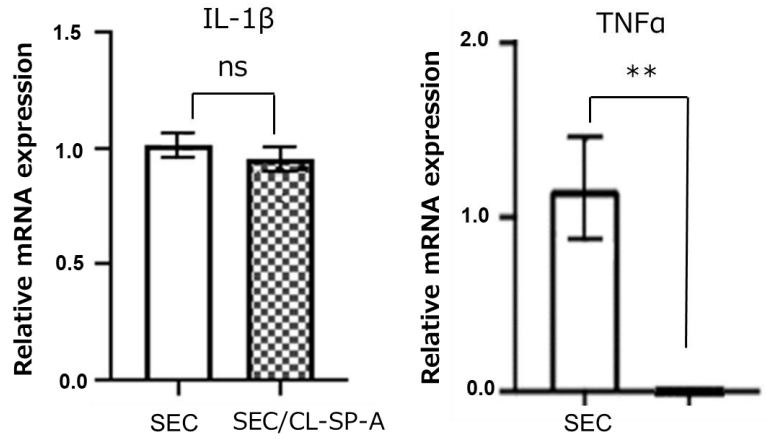

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CL-SP-A suppressed human macrophage and neutrophil-mediated xenogeneic responses