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Auxora™ for the Treatment of AKI
24 June 2025
1:45 pm

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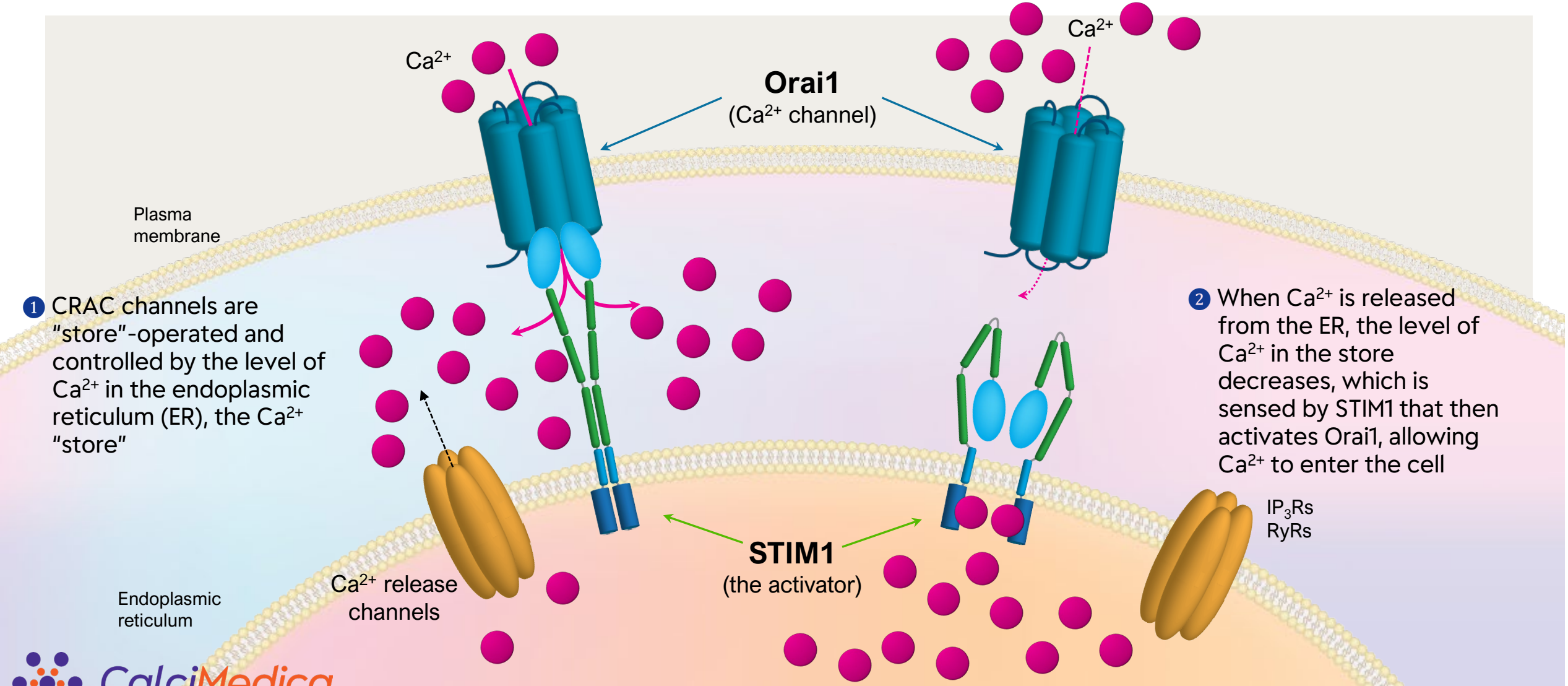
Background
Orai1

CRAC Channels and Store Operated Calcium Entry



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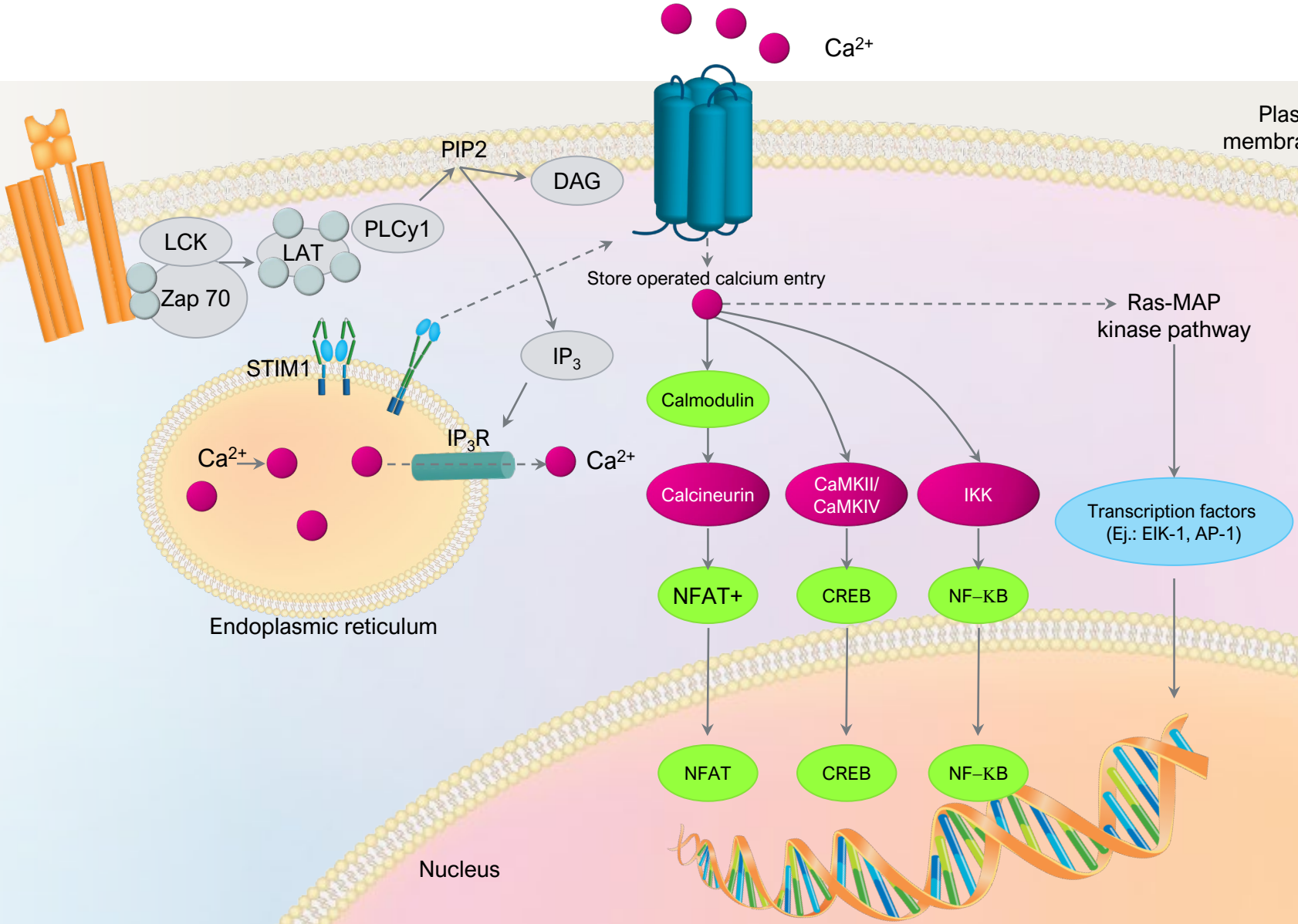
Adapted from Roos,...Stauderman, J. Cell Bio. 2005; Zhang...Stauderman, Cahalan, Nature, 2005; Zhang...Stauderman, Cahalan, PNAS, 2006.

Role of CRAC Channels in the Adaptive Immune Response

- Antigen binding to the T cell receptor causes Ca2+ release from the ER through IP3R, activating STIM1 and opening CRAC channels
- Ca2+ entering the cell through open CRAC channels activates the calcineurin/NFAT pathway, and other pathways, resulting in cytokine expression and release
- CRAC channel inhibitors modulate the downstream calcium-dependent pathways, most notably the calcineurin/NFAT pathway



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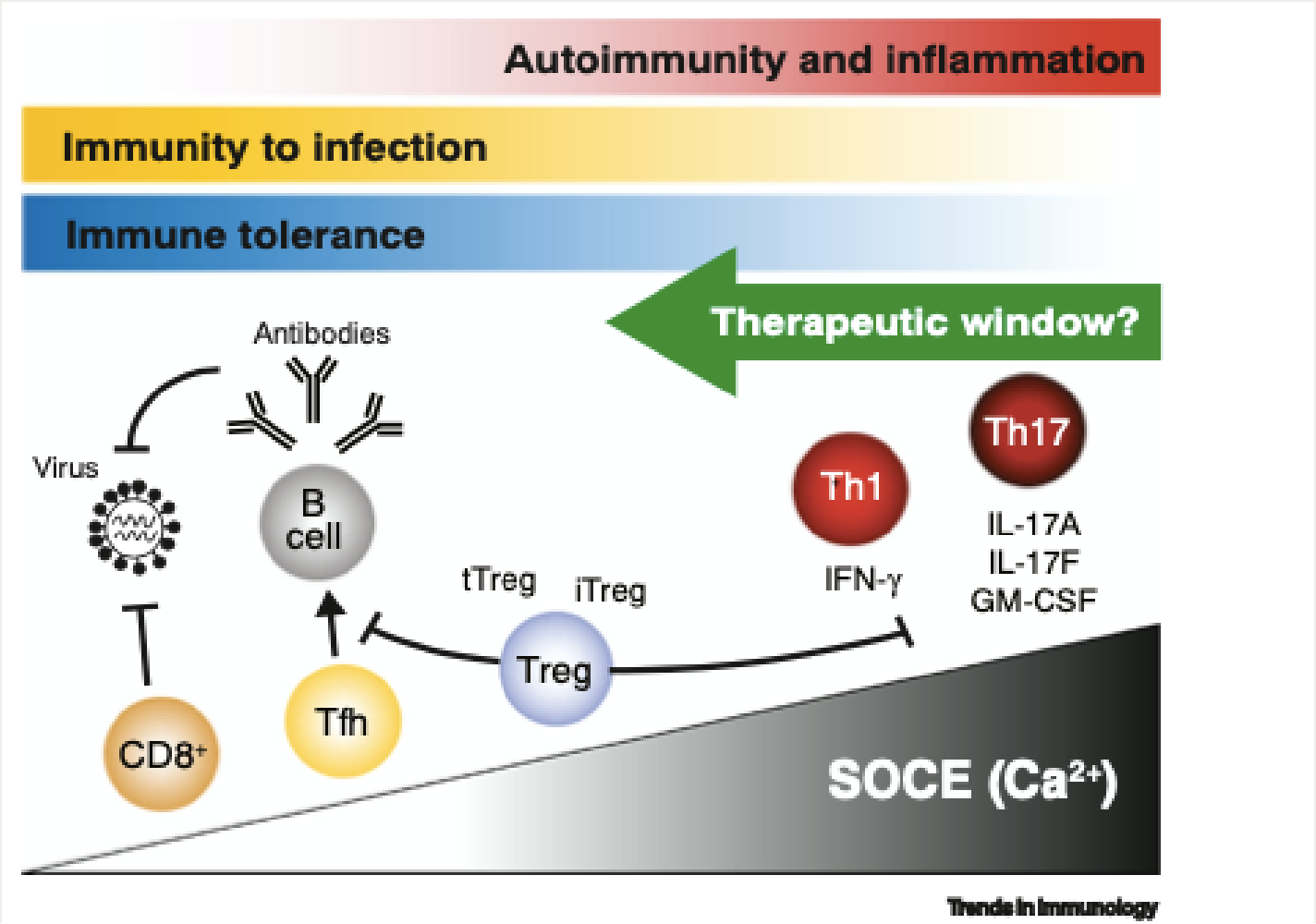
Adapted from Feske, Nat Rev Immunol, 2007

Partial Inhibition of SOCE Provides Therapeutic Window to Treat Acute Critical Illnesses Without Increasing Risk of Infection



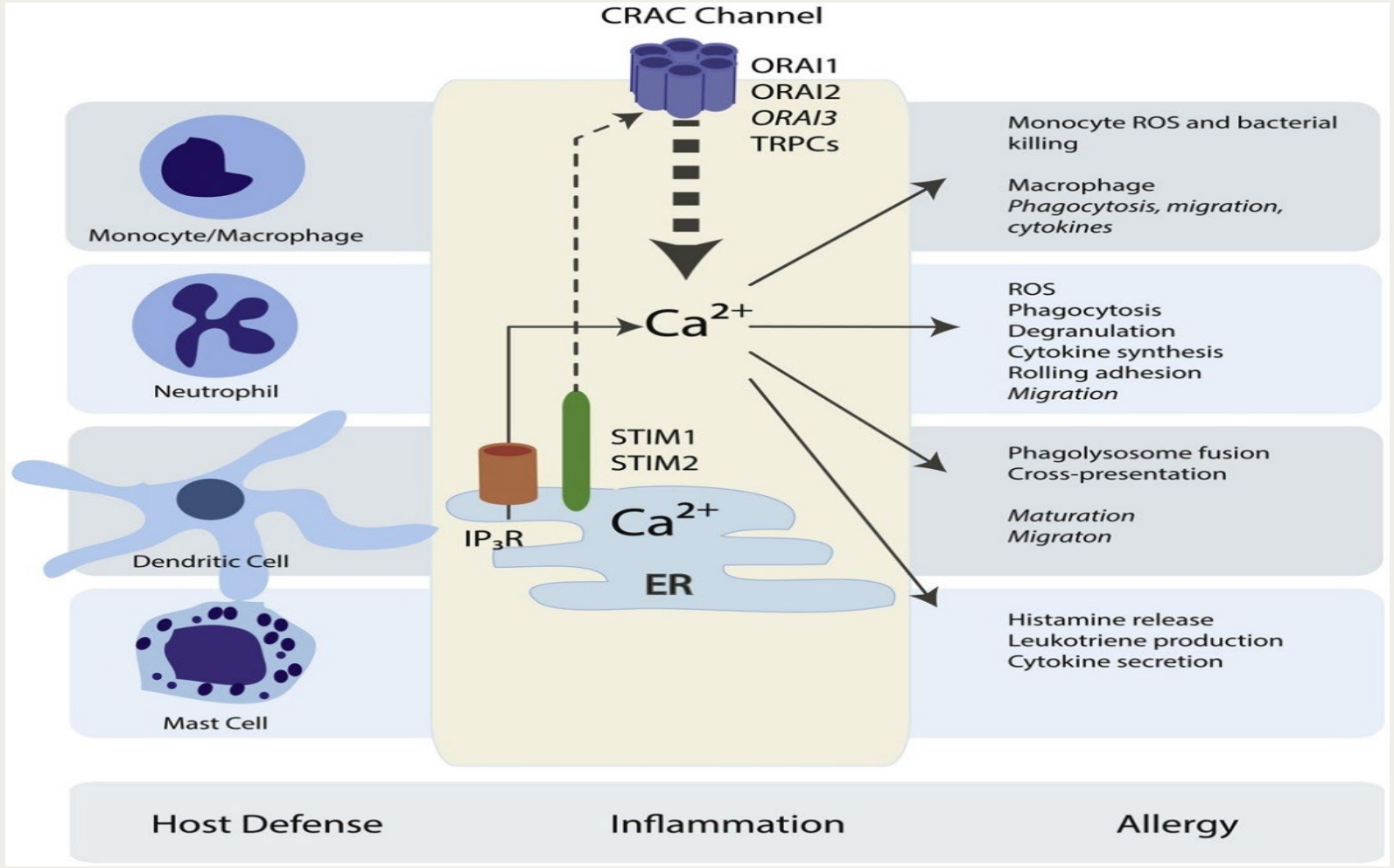
Vaeth, Martin, Sascha Kahlfuss, and Stefan Feske. "CRAC channels and calcium signaling in T cell-mediated immunity." Trends in immunology 41.10 (2020): 878-901.

Demonstration of a Therapeutic Window

PBMC Cytokines	Zegocractin Mean IC_{50} in nM
IL-2	59
IL-17	120
IL-6	135
IFNγ	138
TNFα	225
IL-10	303
IL-4	879

Human PBMCs stimulated with plate-bound anti-CD3/anti-CD28 in buffer +10% serum for 48 hrs.
Released cytokines measured by Luminex at Millipore.

Role of CRAC Channels in Innate Immune Response



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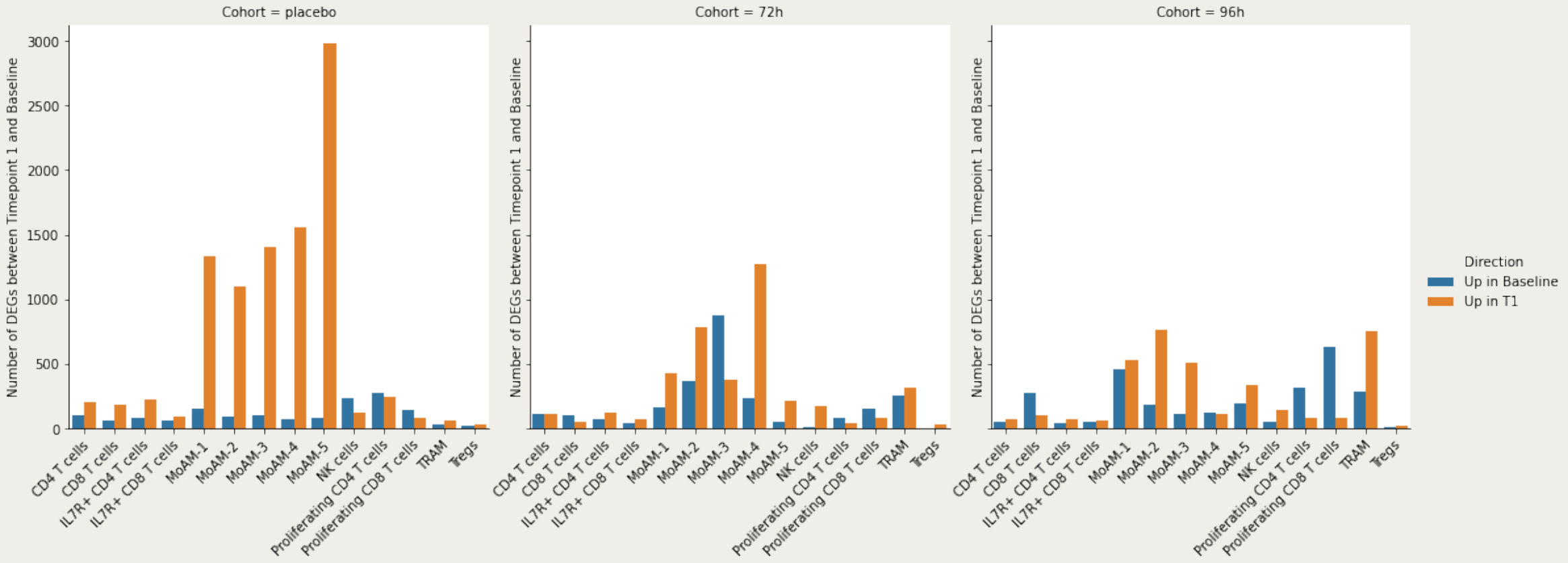
Clemens, Regina A., and Clifford A. Lowell. "CRAC channel regulation of innate immune cells in health and disease." Cell Calcium 78 (2019): 56-65.

Auxora Downregulates Inflammatory Gene Expression Across T Cells and Macrophages in the Lung

Conclusion: Auxora is a potent and selective CRAC channel inhibitor that induces global repression of cytokines in T cells and monocyte-derived macrophages (MDM) in the lungs of patients with COVID-19.



DEG: Differential Gene Expression MoAM: Monocyte-derived alveolar macrophages
Unpublished. Courtesy of Dr. Misharin, Northwestern University

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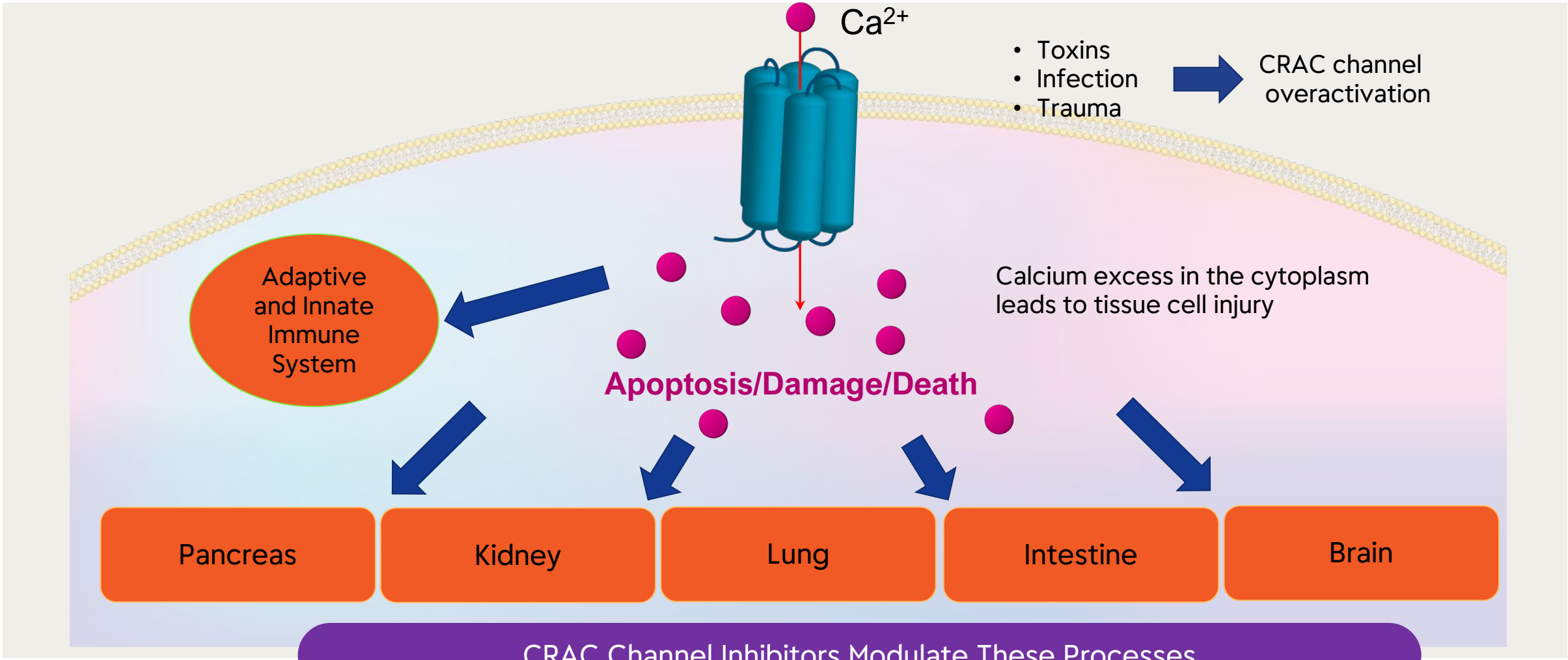
Orai1 in AHRF and AKI

CRAC Channel Overactivation Directly Injures Tissues



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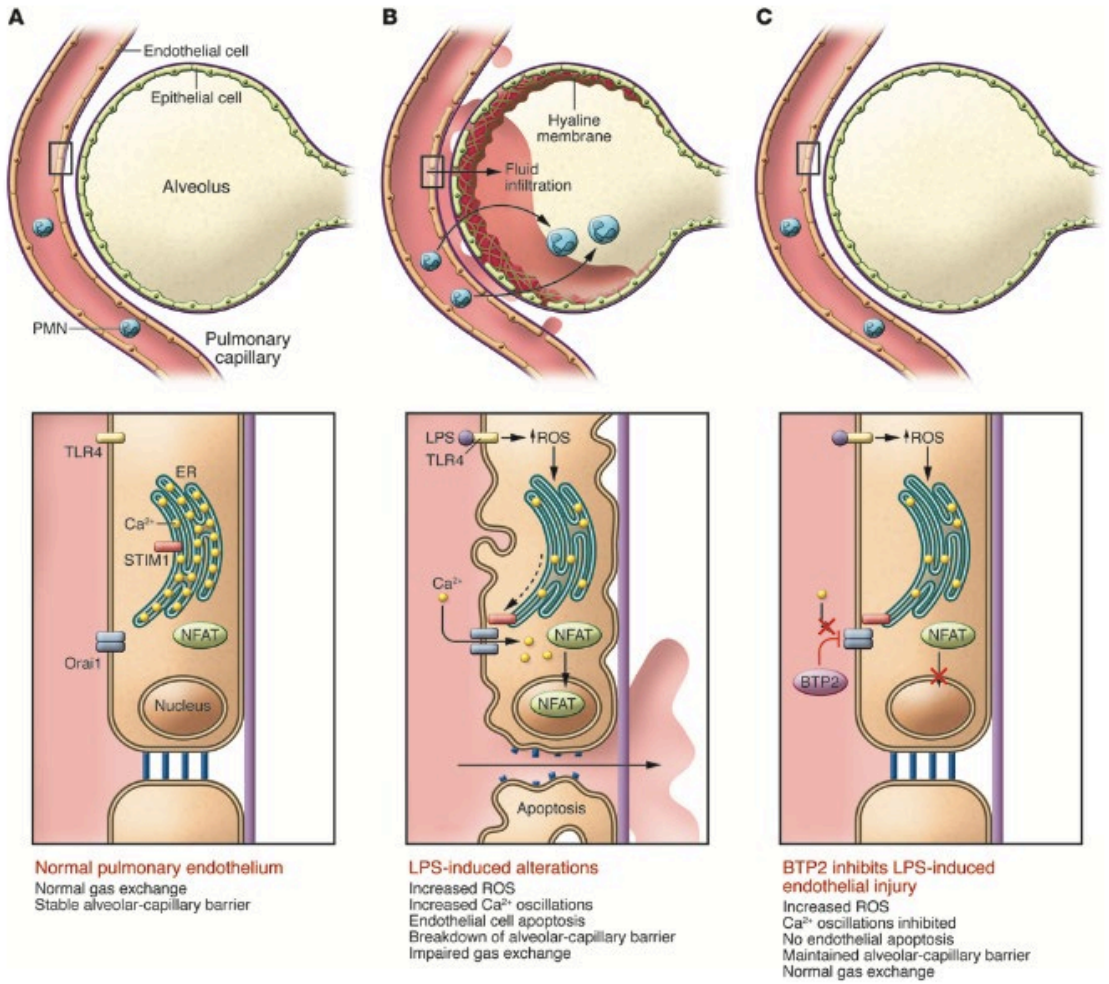
CRAC Channel Overactivation Results in Endothelial Dysfunction



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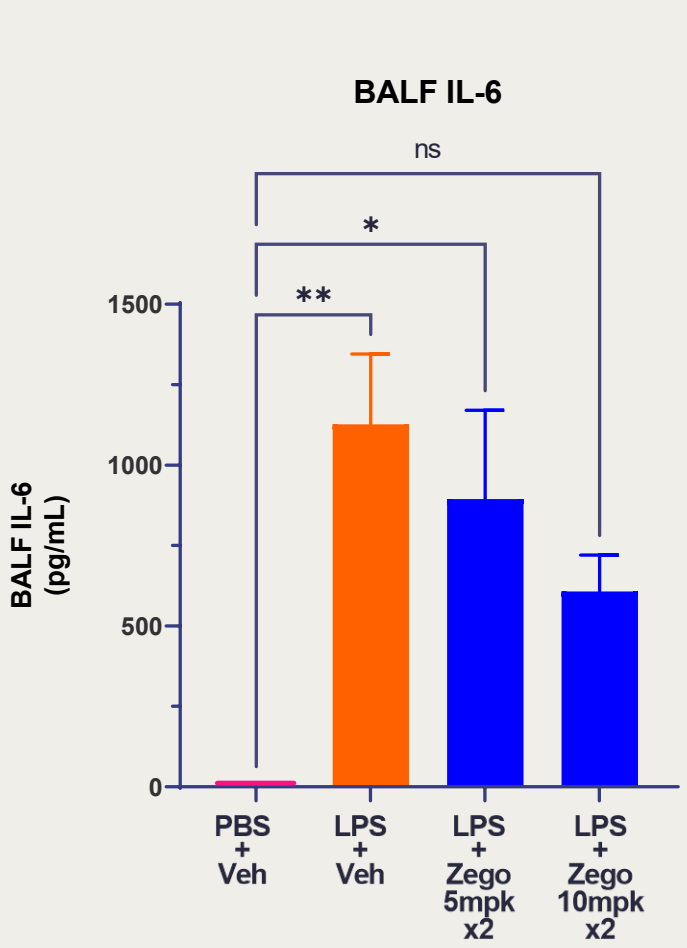
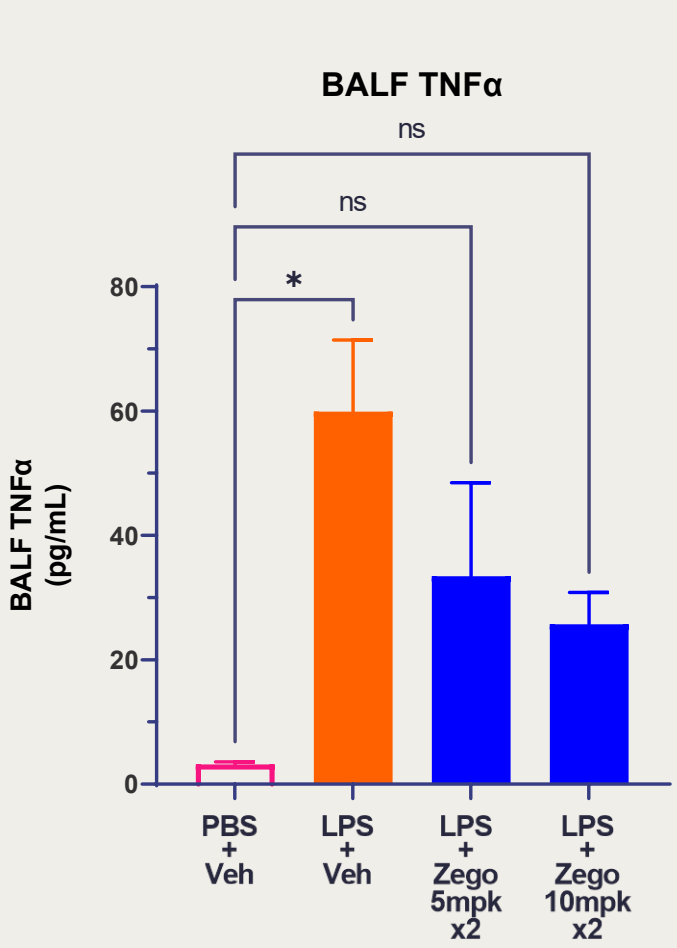
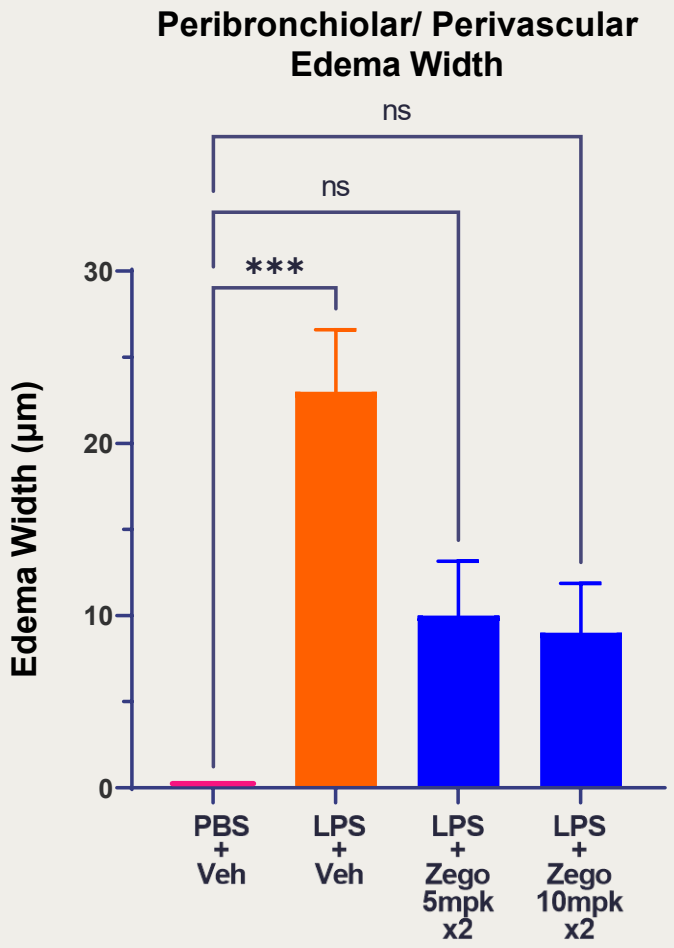
Gandhirajan, Rajesh Kumar, et al. "Blockade of NOX2 and STIM1 signaling limits lipopolysaccharide-induced vascular inflammation." The Journal of clinical investigation 123.2 (2013).
Seeley, Eric J., Paul Rosenberg, and Michael A. Matthay. "Calcium flux and endothelial dysfunction during acute lung injury: a STIMulating target for therapy." The Journal of clinical investigation 123.3 (2013): 1015-1018.

Zegocractin Decreased Alveolar Inflammation and Peribronchiolar/ Perivascular Edema in a Mouse Model of LPS

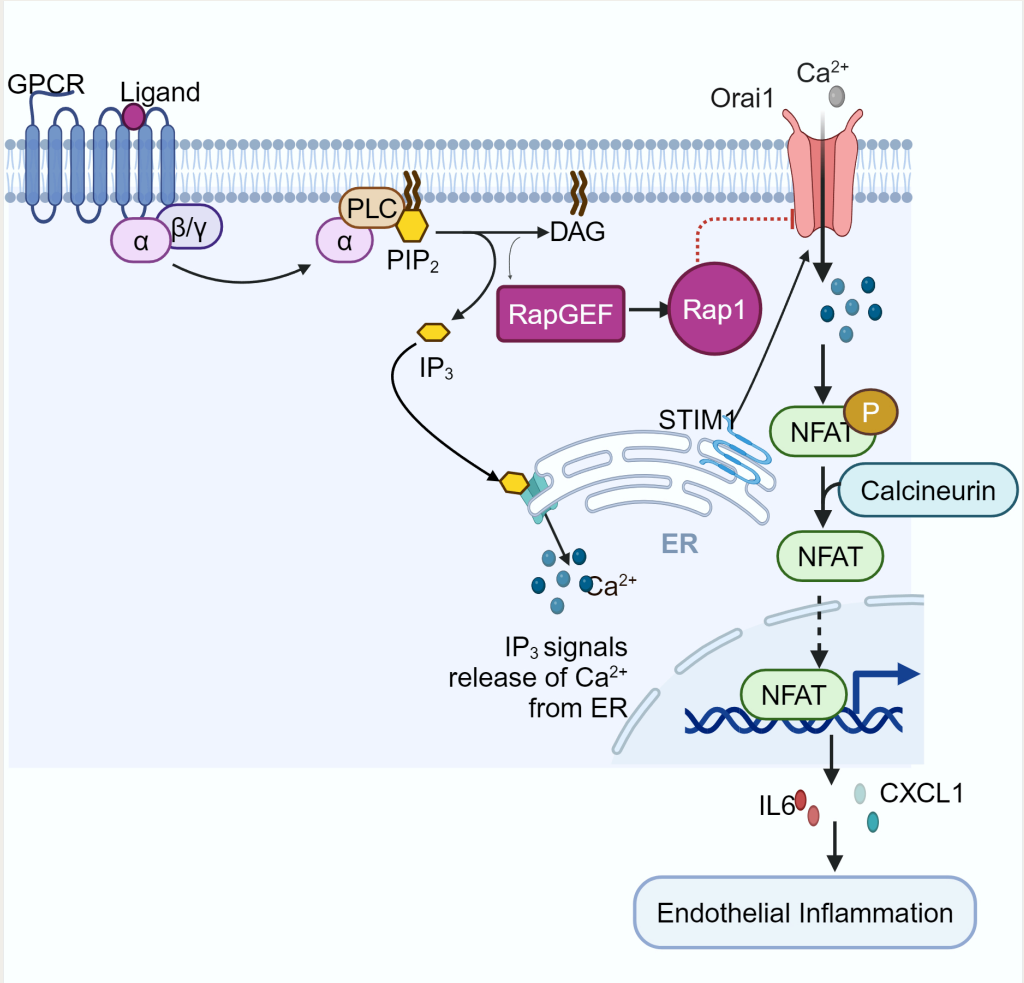






BALF: Bronchioalveolar Lavage Fluid
Statistical analysis performed by ANOVA with Dunnet's multiple comparisons post-test; ***p<0.001, **p<0.01, *p<0.05
PBS - phosphate buffered saline, LPS - lipopolysaccharide, Veh - vehicle, Zego - Zegocractin, mpk - milligrams per kilogram, x2 - given twice at 5-hour intervals

Orai1 Downregulation Promotes Recovery of Endothelial Cells



- Rapi1A is a master regulator of endothelial barrier restoration and studies have highlighted Rap1's role in restoring lung endothelial barrier integrity and aiding recovery from acute lung injury,
- Rap1A limits Orai1 expression to regulate Ca2+ entry and EC permeability to restore barrier integrity.

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Martín-Aragón Baudel, Miguel, Madeline Nieves-Cintrón, and Manuel F. Navedo. "Rap1 Brings the A Game to Control Lung Endothelium." Arteriosclerosis, Thrombosis, and Vascular Biology 44.11 (2024): 2288-2290.
Kosuru, Ramoji, et al. "Rap1A modulates store-operated calcium entry in the lung endothelium: a novel mechanism controlling NFAT-mediated vascular inflammation and permeability." Arteriosclerosis, Thrombosis, and Vascular Biology 44.11 (2024): 2271-2287.

Preclinical Study of I/R Injury Model of AKI in Rat

Measure GFR
MediBeacon

→ 40 minutes bilateral kidney IRI

→ 2 hours

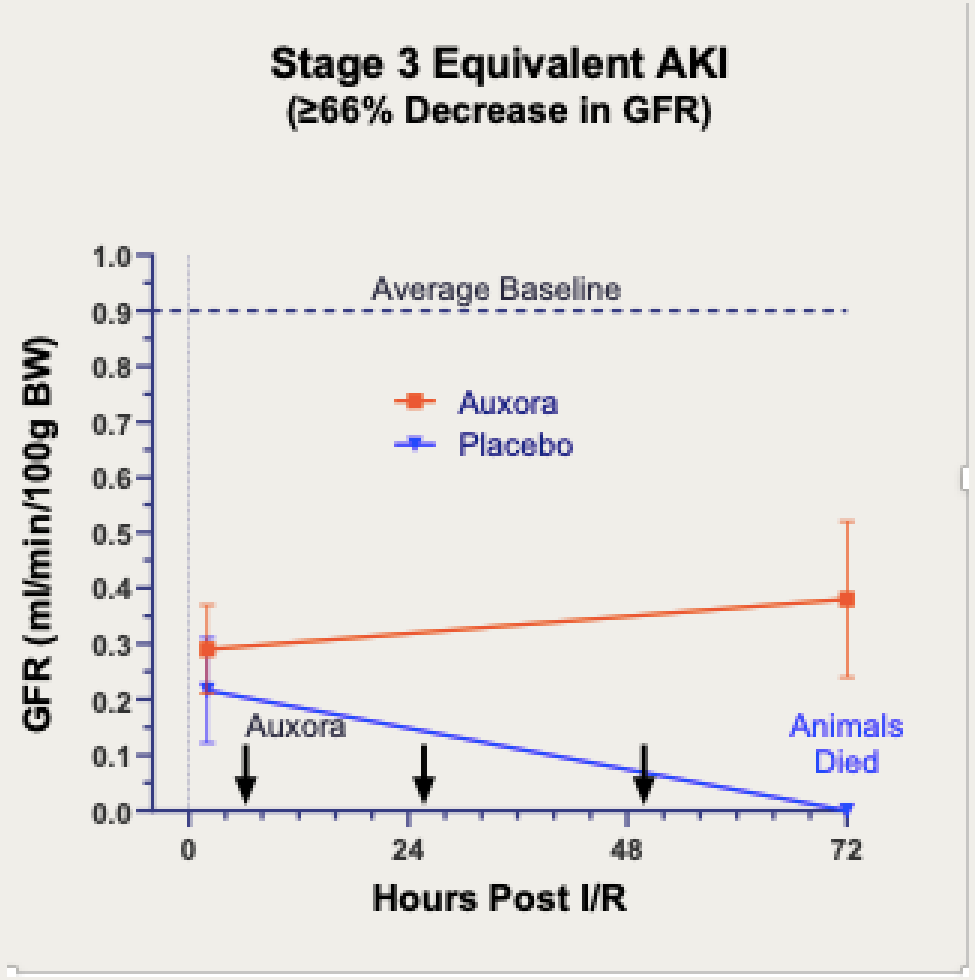
→ Measure GFR
MediBeacon

→ 4 hours

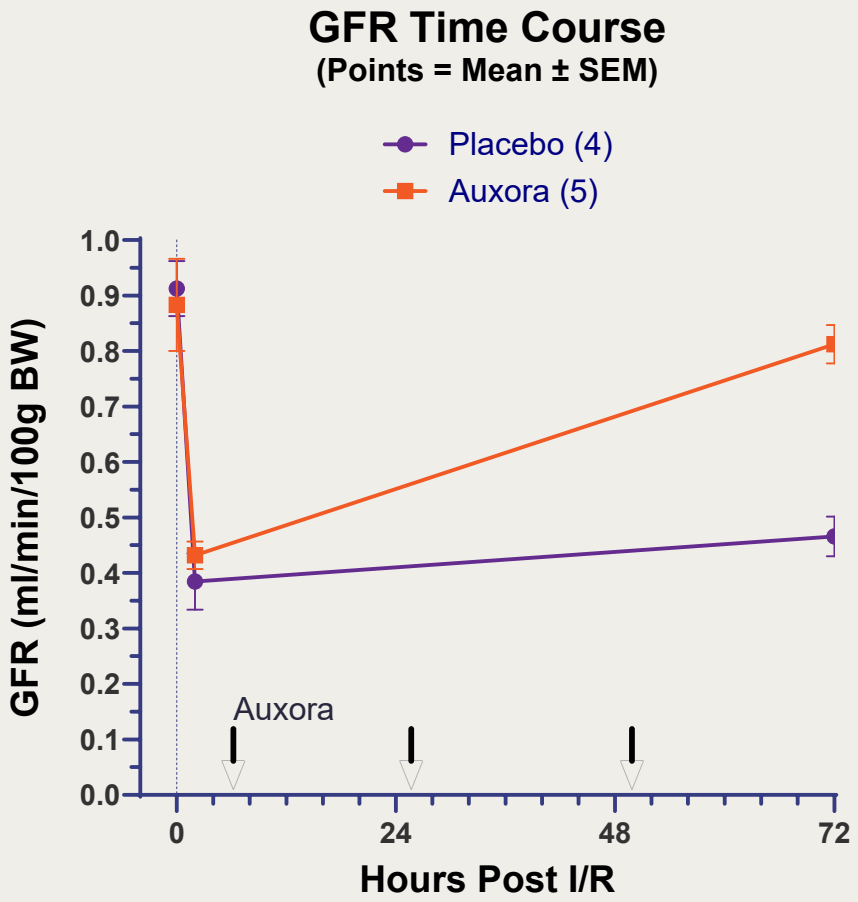
→ Balance GFR between 2 groups

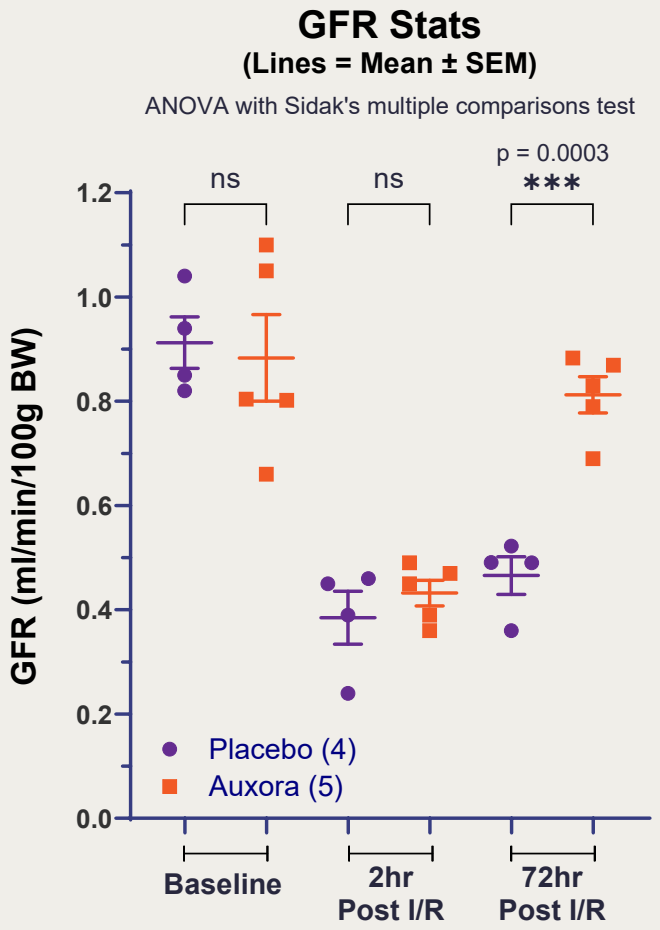
→ Rx with Auxora or Placebo q24 hours x3

Rats with Severe AKI



Rats with Moderately Severe AKI





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