THE 30TH INTERNATIONAL CONFERENCE ON
ADVANCES IN CRITICAL CARE NEPHROLOGY
AKI & CRRT 2025
MARCH 3-6, 2025 MANCHESTER GRAND HYATT SAN DIEGO, CALIFORNIA
Jointly Provided by
UC San Diego SCHOOL OF MEDICINE
and
CRRT, INC.

# Changing Paradigms in Acute Kidney Injury: From Mechanisms to Management

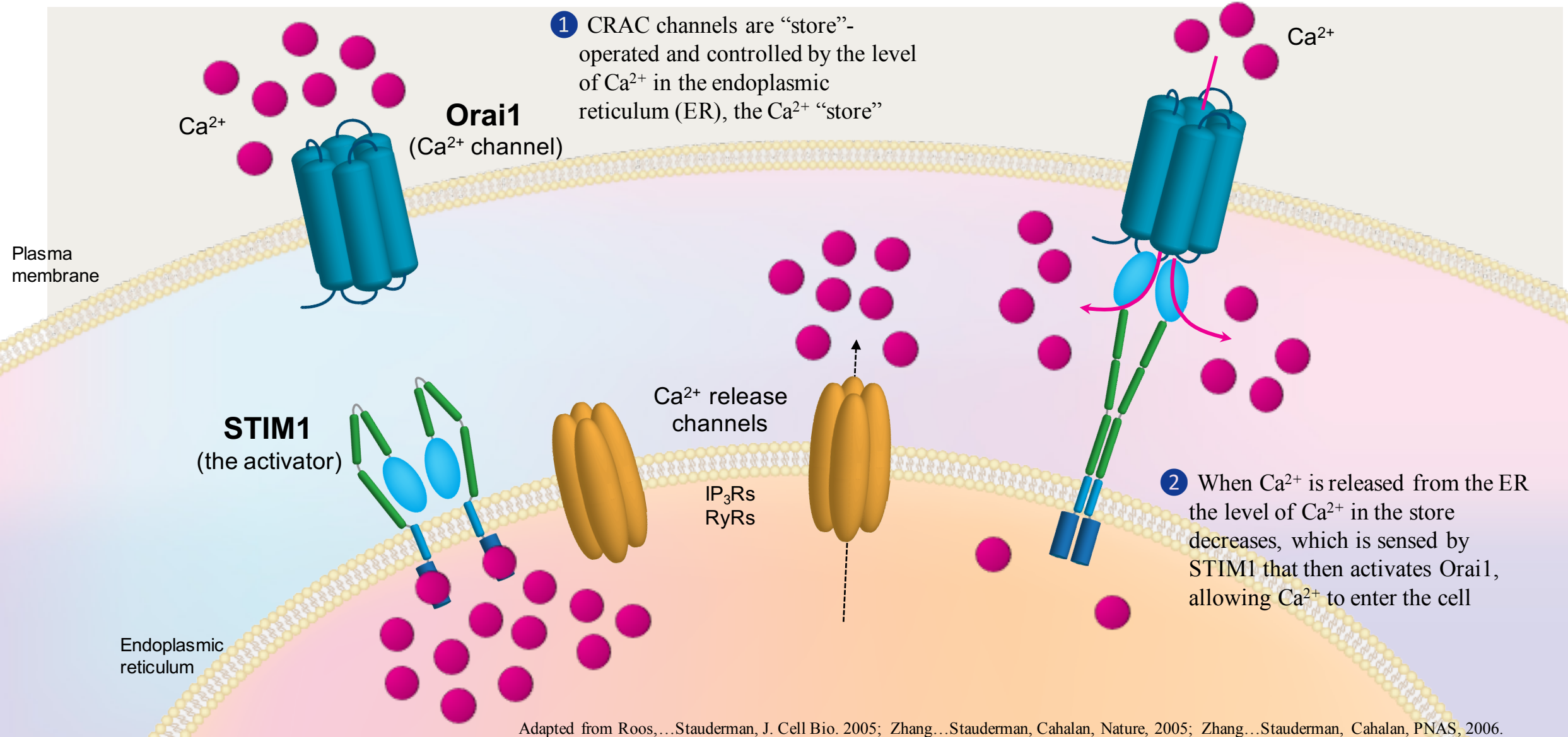
# The Role of Orai-1 in AKI

**Sudarshan Hebbar MD**
**Chief Medical Officer, CalciMedica Inc.**

CalciMedica

# Background
# Orai1

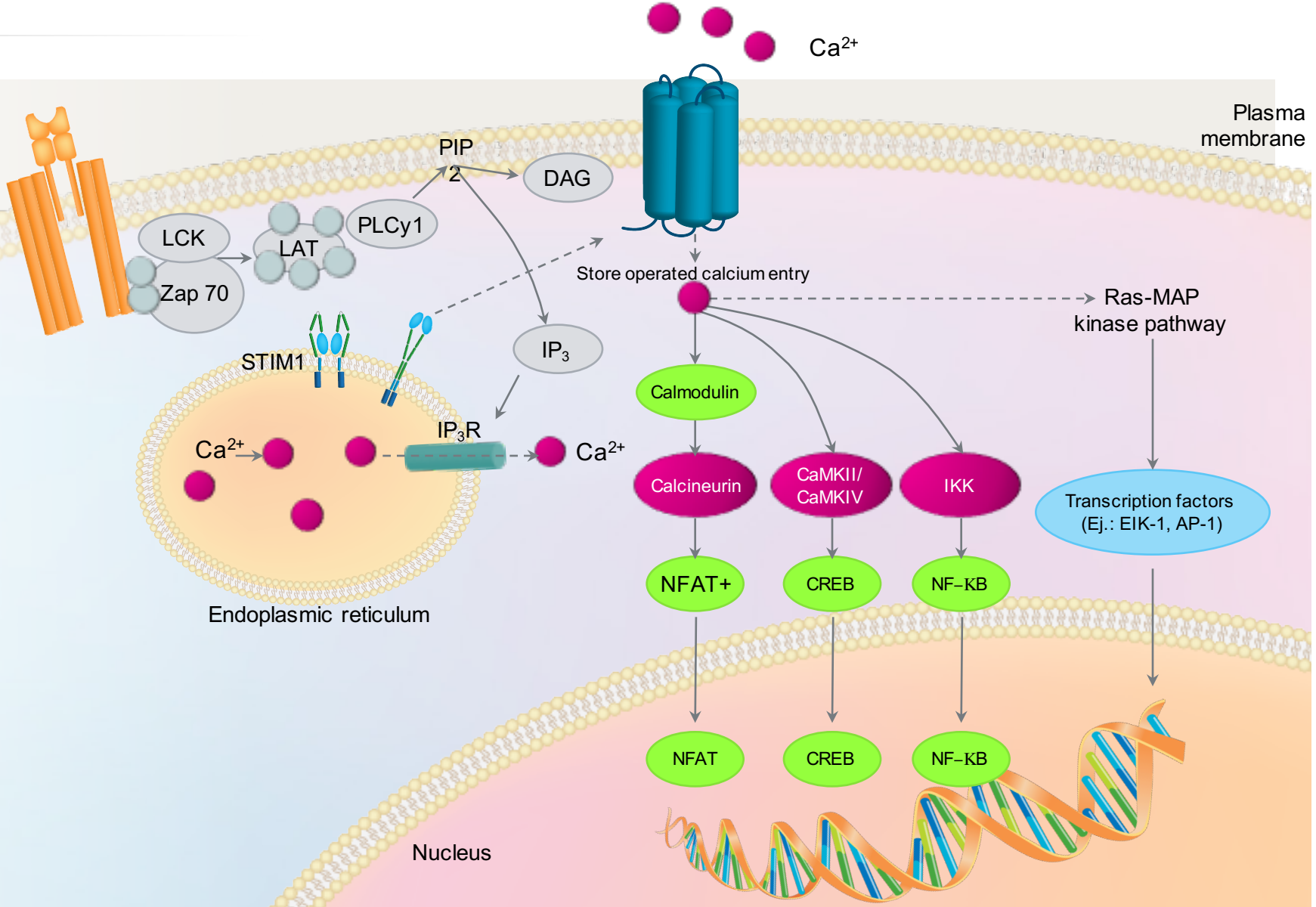
# $Ca^{2+}$ Release-activated $Ca^{2+}$ (CRAC) Channels Require Two Proteins: Orai1 and STIM1




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

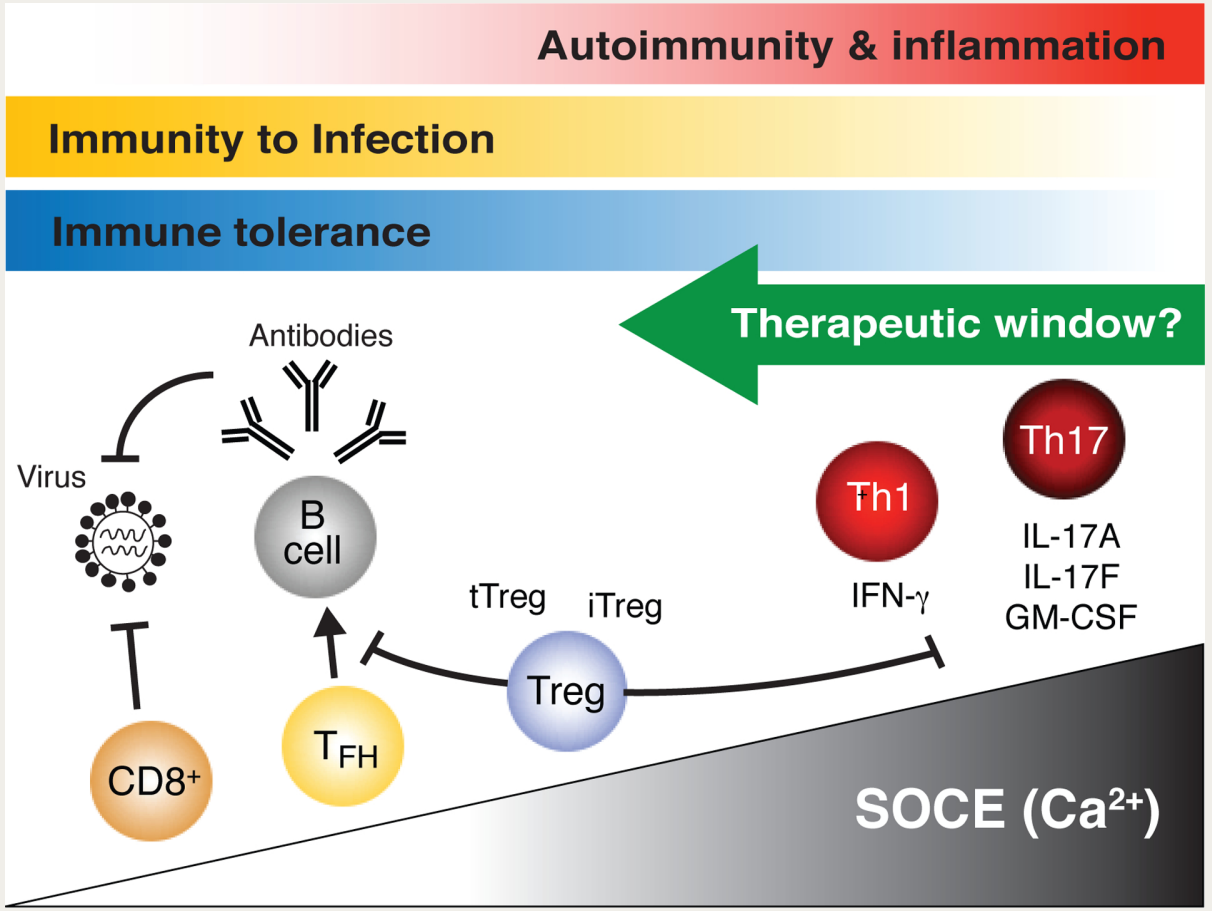
- Antigen binding to the T cell receptor causes Ca2+ release from the ER through IP3R, activating STIM1 and opening CRAC channels
- Ca2+ entering the cell through open CRAC channels activates the calcineurin/NFAT pathway, and other pathways, resulting in cytokine expression and release




CalciMedica

Adapted from Feske, Nat Rev Immunol, 2007

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




CalciMedica

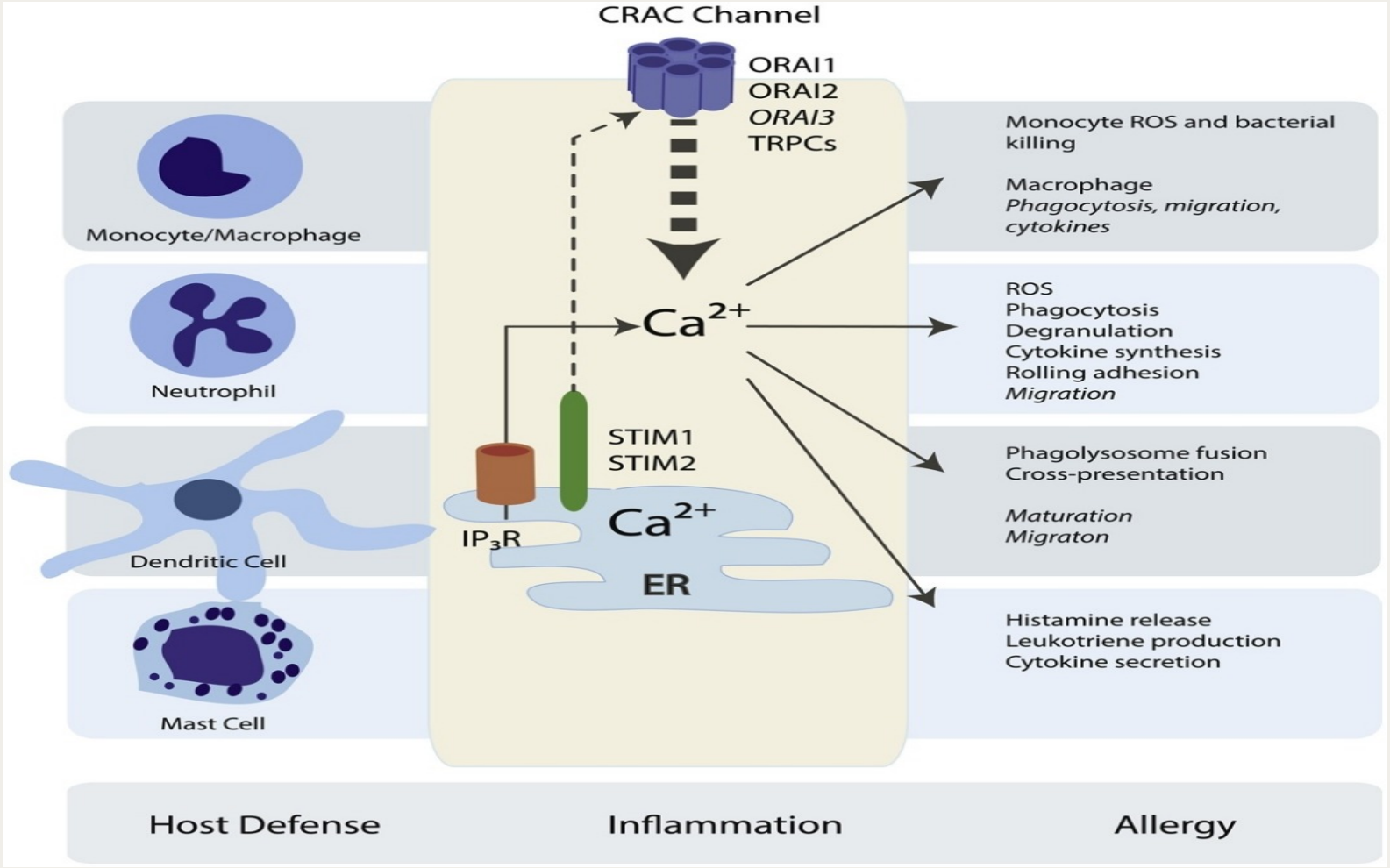
Vaeth, Martin, Sascha Kahlfuss, and Stefan Feske. "CRAC channels and calcium signaling in T cell-mediated immunity." Trends in immunology 41.10 (2020): 878-901.

# 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.

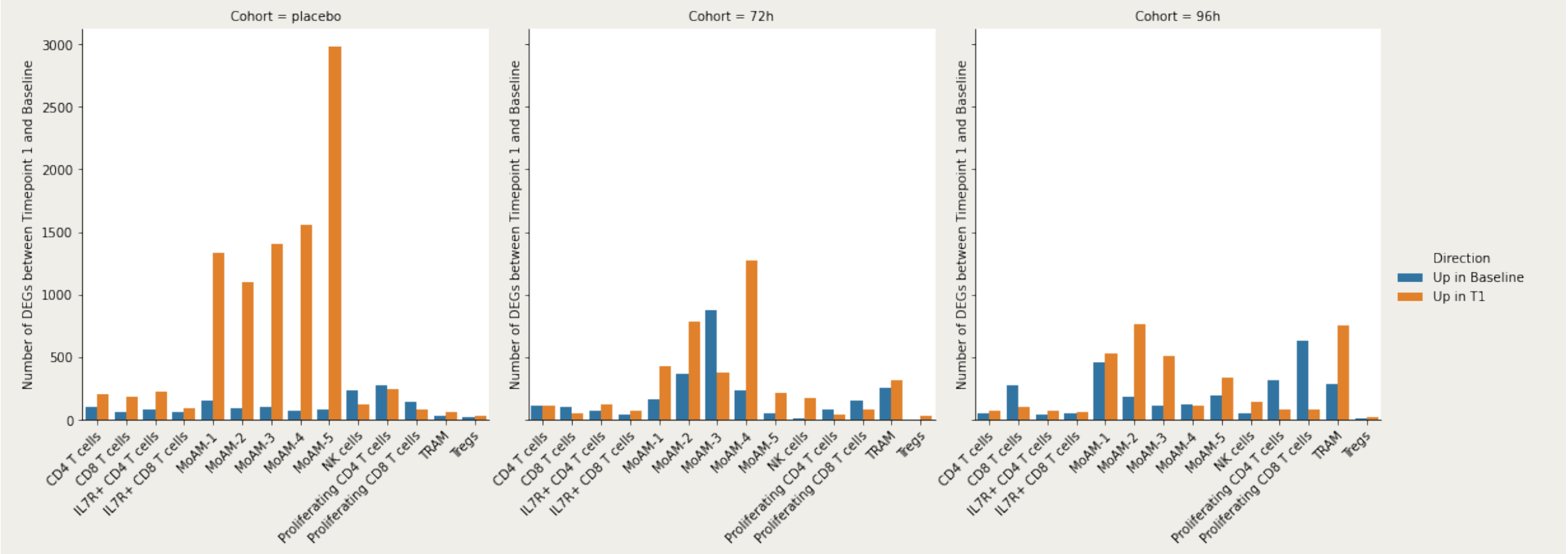
# Role of CRAC Channels in Innate Immune Response






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

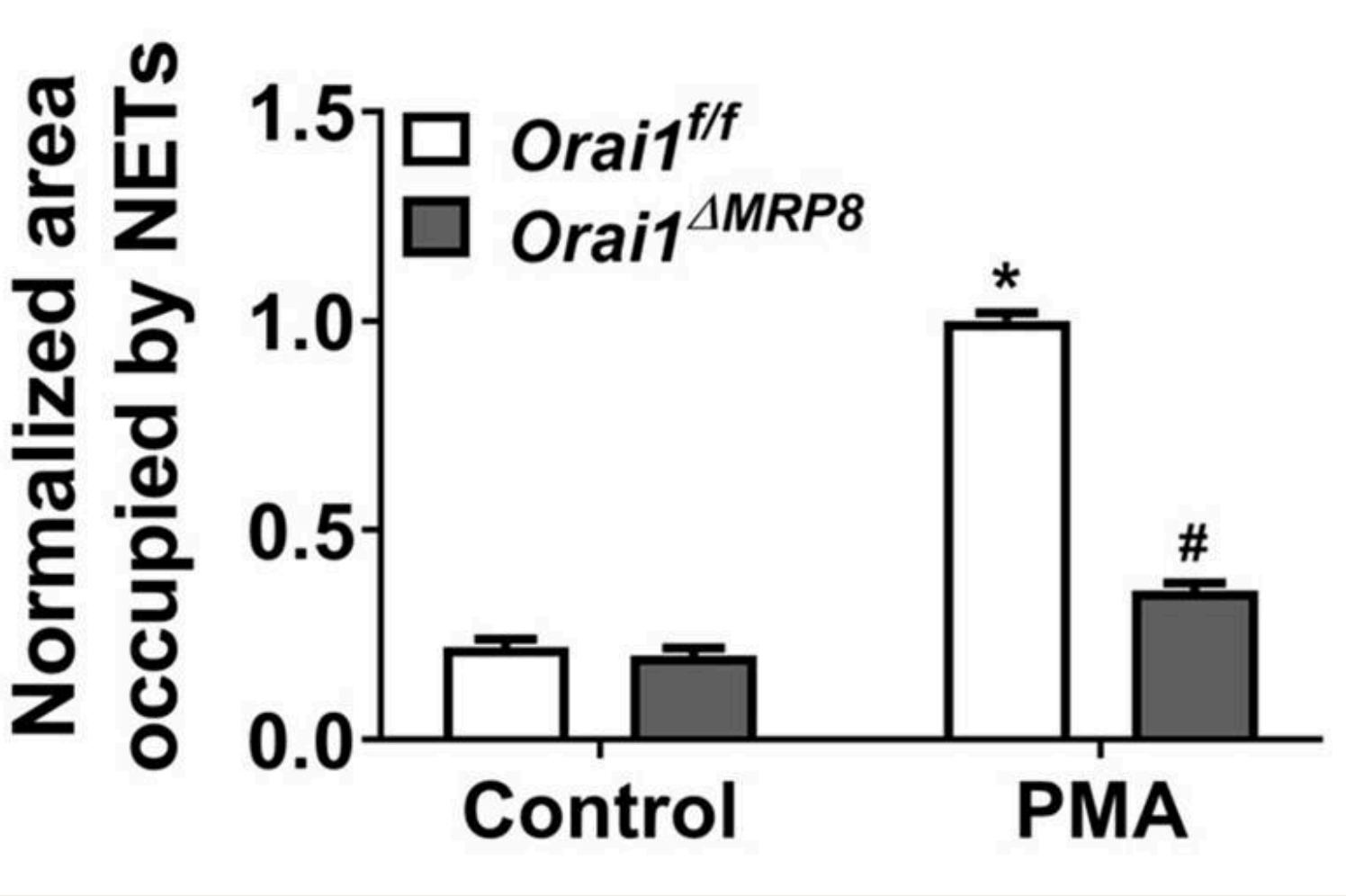
# Auxora Downregulates Inflammatory Gene Expression Across T Cells and Macrophages in the Lung




**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

# Orai1 Deletion in Neutrophils Protects Against NET Formation and Acute Lung Injury



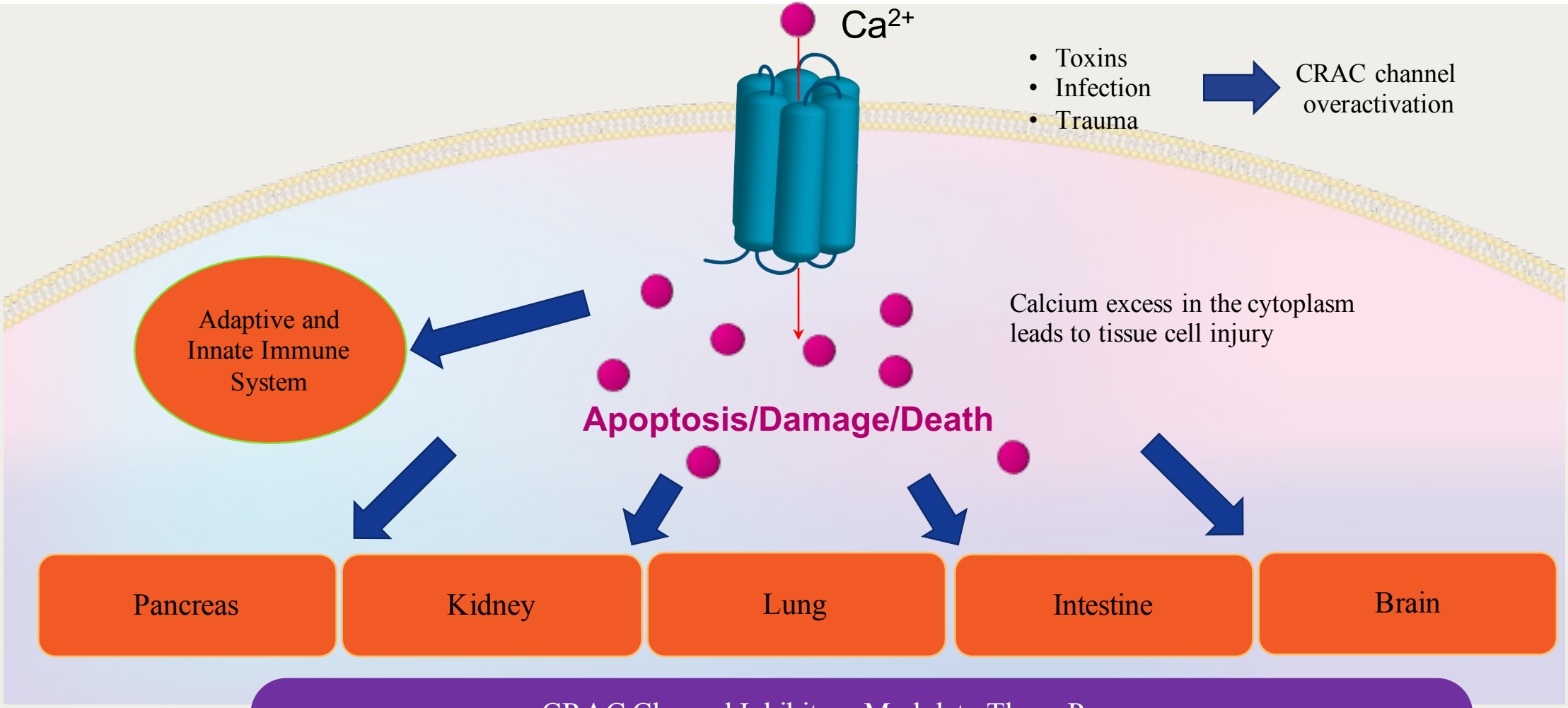

phorbol 12-myristate 13-acetate (PMA)

Niu, Mengya, et al. "Neutrophil-specific ORAI1 calcium channel inhibition reduces pancreatitis-associated acute lung injury." Function 5.1 (2024): zqad061.

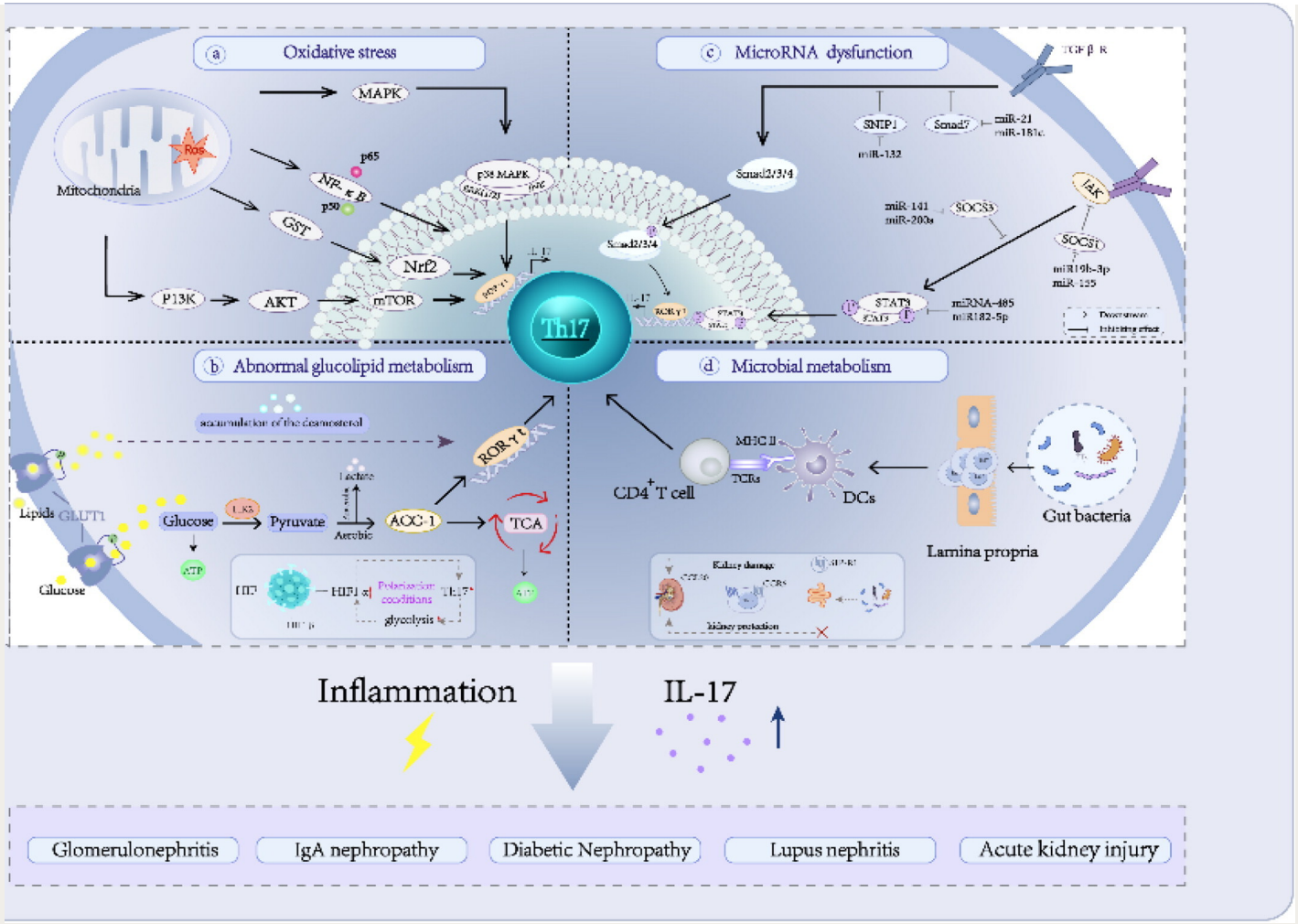
CalciMedica

# Background
# Orai1 Role in AKI

# CRAC Channel Overactivation Activates Immune Response and Directly Injures Tissues



# TH17 Cells Play an Important Role in Kidney Disease




Zhang, Tao, et al. "Th17 cells: A new target in kidney disease research." *International Reviews of Immunology* (2024): 1-17.

# Markedly Elevated IL-17 Levels Associated with Severe AKI

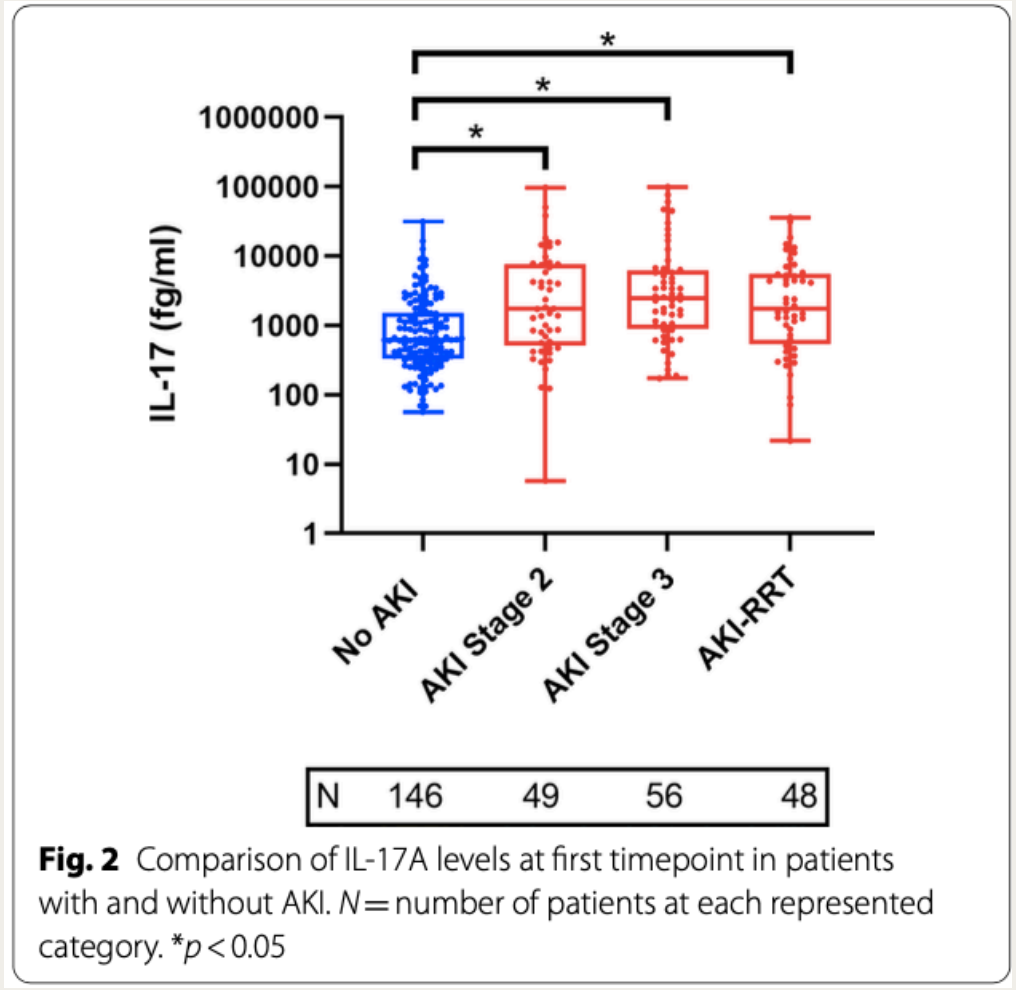
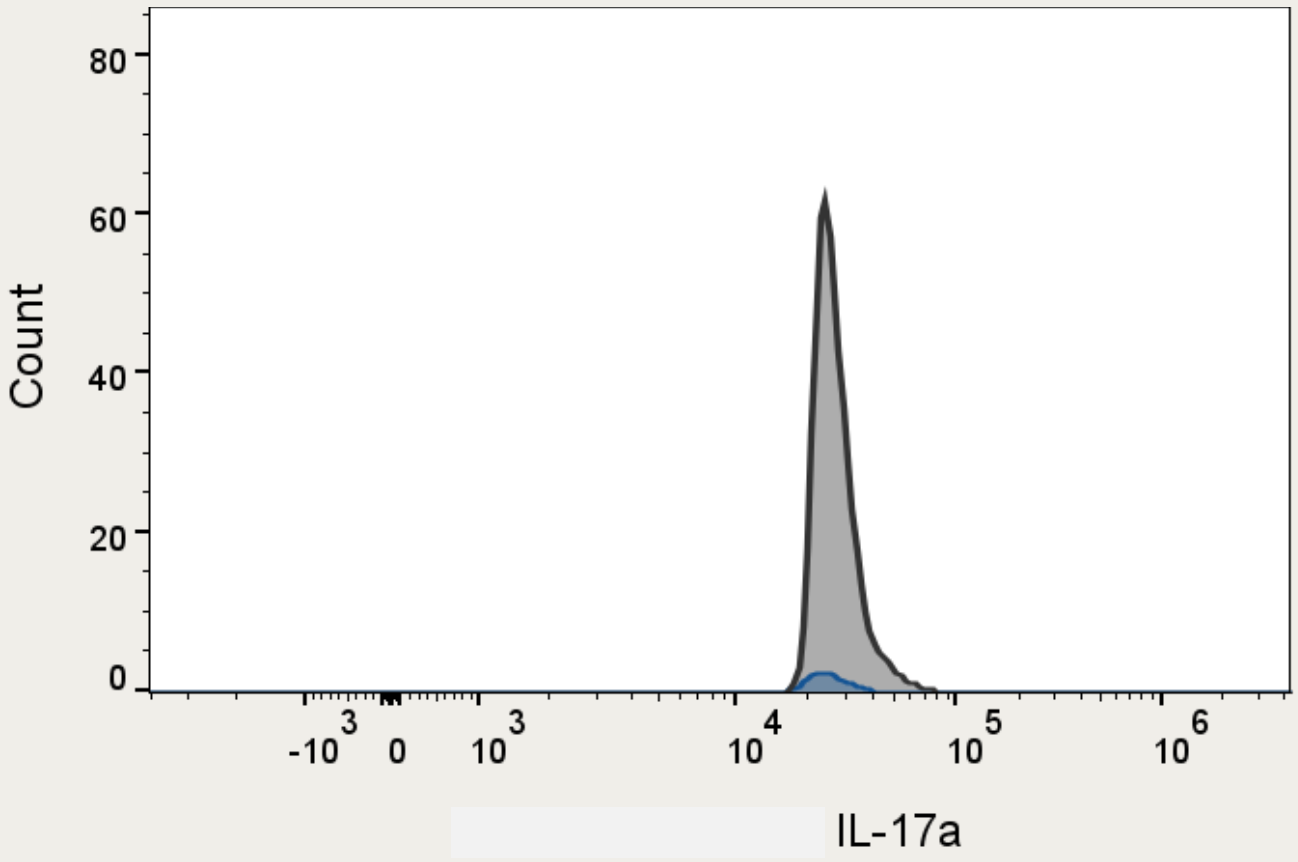



**Fig. 2** Comparison of IL-17A levels at first timepoint in patients with and without AKI. *N* = number of patients at each represented category. *$p < 0.05$



Collett, Jason A., et al. "Serum IL-17 levels are higher in critically ill patients with AKI and associated with worse outcomes." Critical Care 26.1 (2022): 1-9.

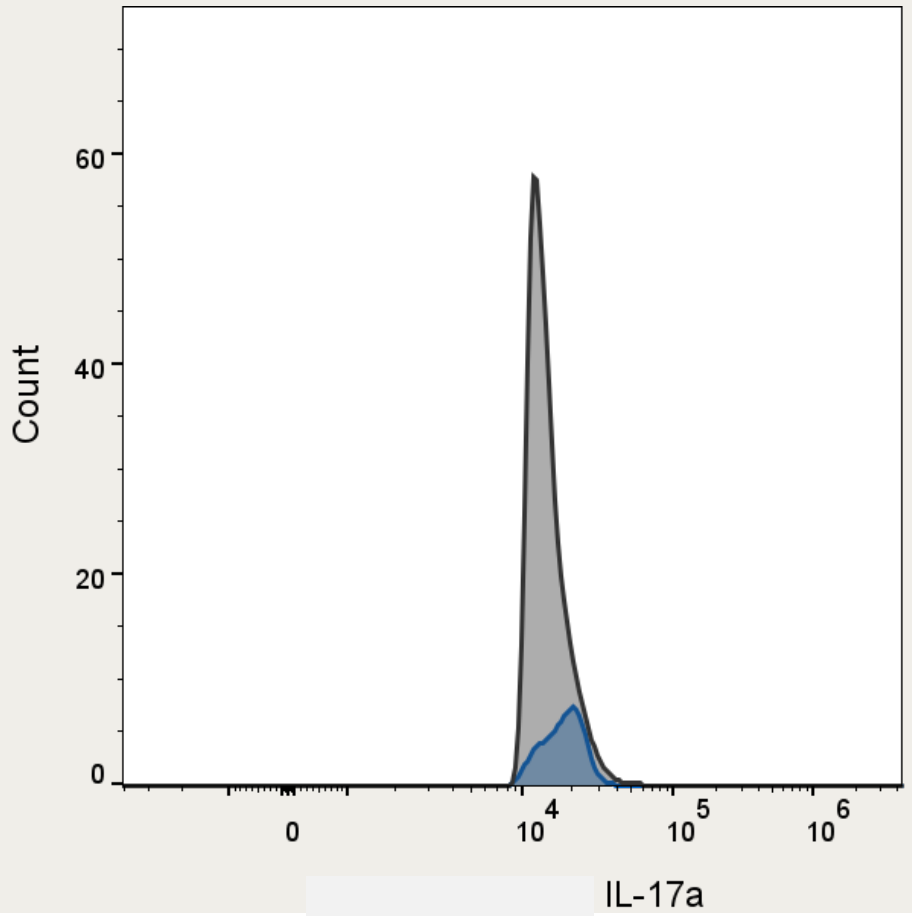
# Kidney IL-17 response to Kidney IRI (CD4 gated)




| | Sample Name |
|---|---|
| IR | 6459 L.MNC.fcs |
| Sham | 6460 L.MNC.fcs |

Unpublished. Courtesy of Dr. Basile Indiana University

# Lung IL-17 response to Kidney IRI (CD4 gated)




| | Sample Name |
|---|---|
| IR | 6459 L.MNC.fcs |
| Sham | 6460 L.MNC.fcs |



Unpublished. Courtesy of Dr. Basile Indiana University

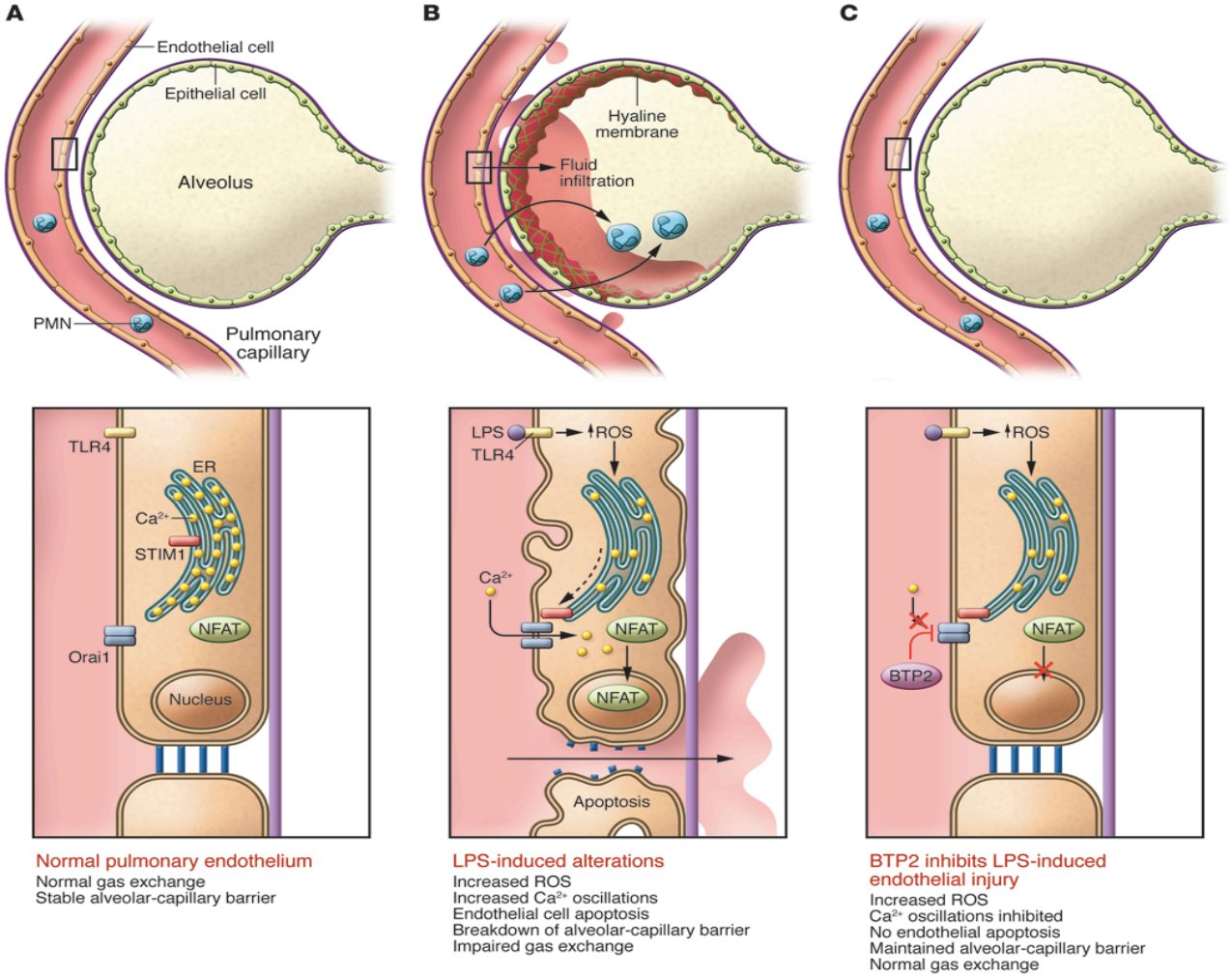
# Two Phenotypes of AKI Based on Levels of Angiopoietin 2 and 1

- Two phenotypes previously recognized in AKI: AKI-SP1 and AKI-SP2
  - Angiopoietin 2/Angiopoietin 1 ratio much higher in AKI-SP2 than AKI-SP1
- AKI-SP2 has higher risk of AKI Stages 2 and 3, non recovery, and mortality

**These findings suggest endothelial dysfunction plays an important role in AKI outcomes**

-Bhatraju, Pavan K., et al. "Identification of acute kidney injury subphenotypes with differing molecular signatures and responses to vasopressin therapy." American journal of respiratory and critical care medicine 199.7 (2019): 863-872.
-Sack, Kelsey D., John A. Kellum, and Samir M. Parikh. "The angiopoietin-Tie2 pathway in critical illness." Critical care clinics 36.2 (2020): 201-216.

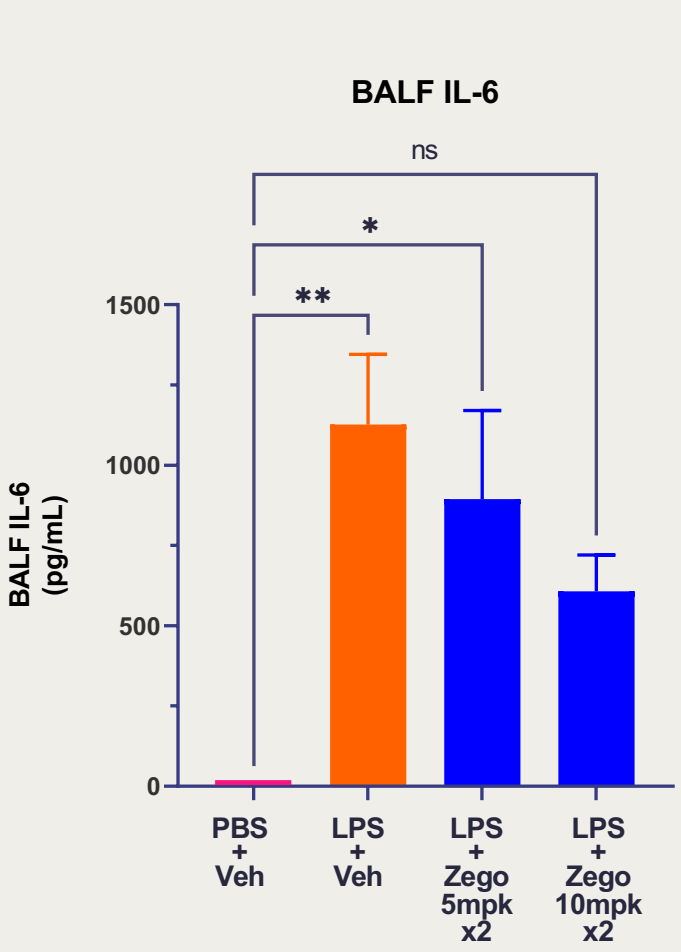
# CRAC Channels: Central Role in Endothelial Dysfunction

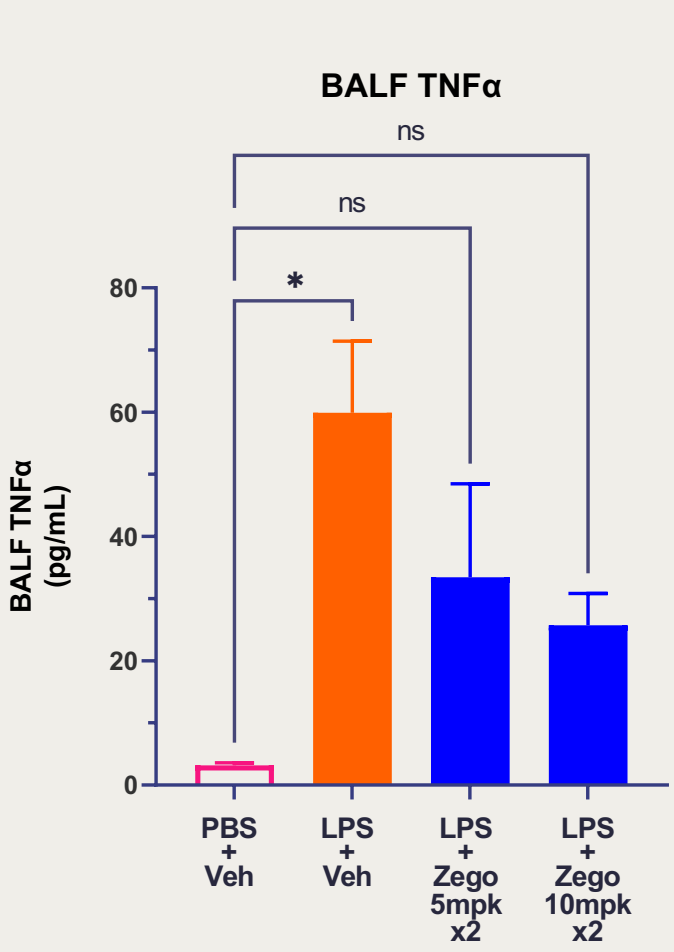


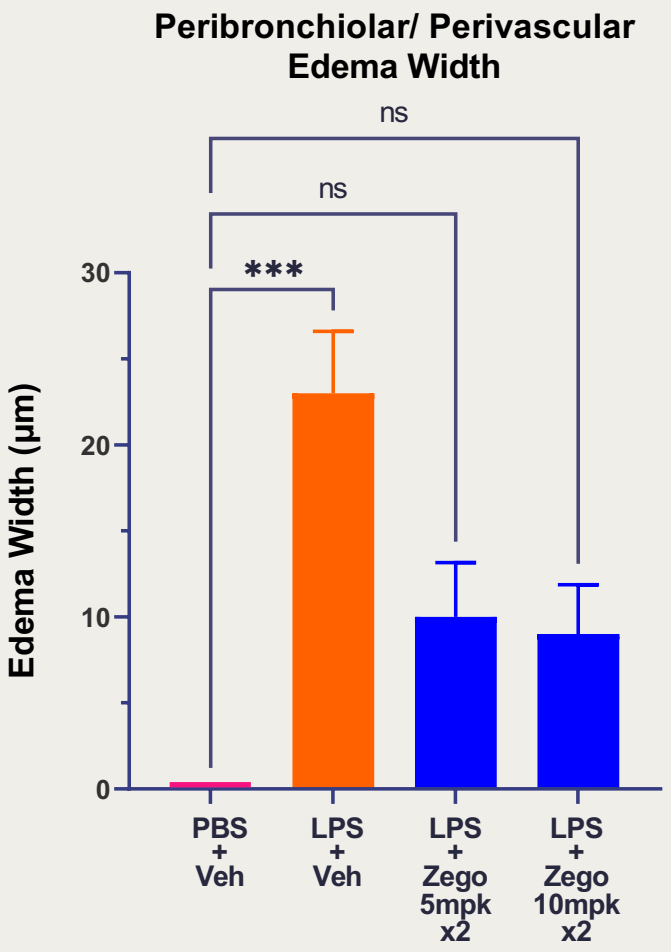

CalciMedica

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

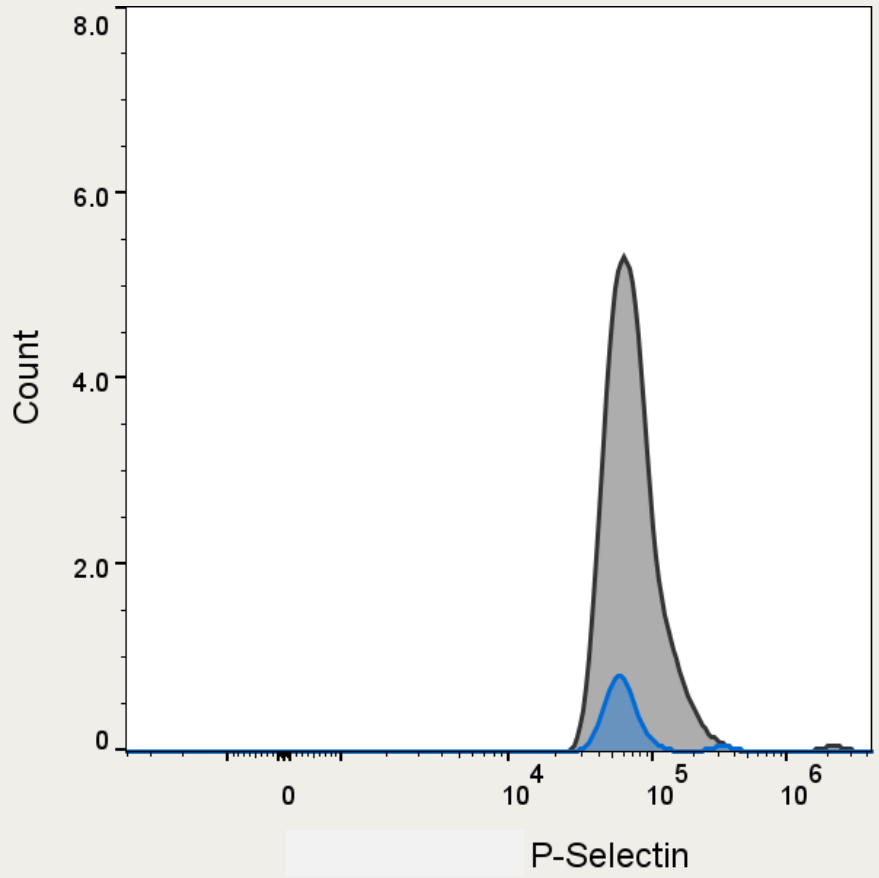



BALF: Bronchioalveolar Lavage Fluid
Statistical analysis performed by ANOVA with Dunnet's multiple comparisons post-test; ***p<0.001, **p<0.01, *p<0.05
PBS - phosphate buffered saline, LPS - lipopolysaccharide, Veh - vehicle, Zego - Zegocractin, mpk - milligrams per kilogram, x2 - given twice at 5-hour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

# Kidney Endothelial P-selectin Response to Kidney IRI (CD31+/CD45- gated)




| | Sample Name |
|---|---|
| IR | 6459 L.MNC.fcs |
| Sham | 6460 L.MNC.fcs |

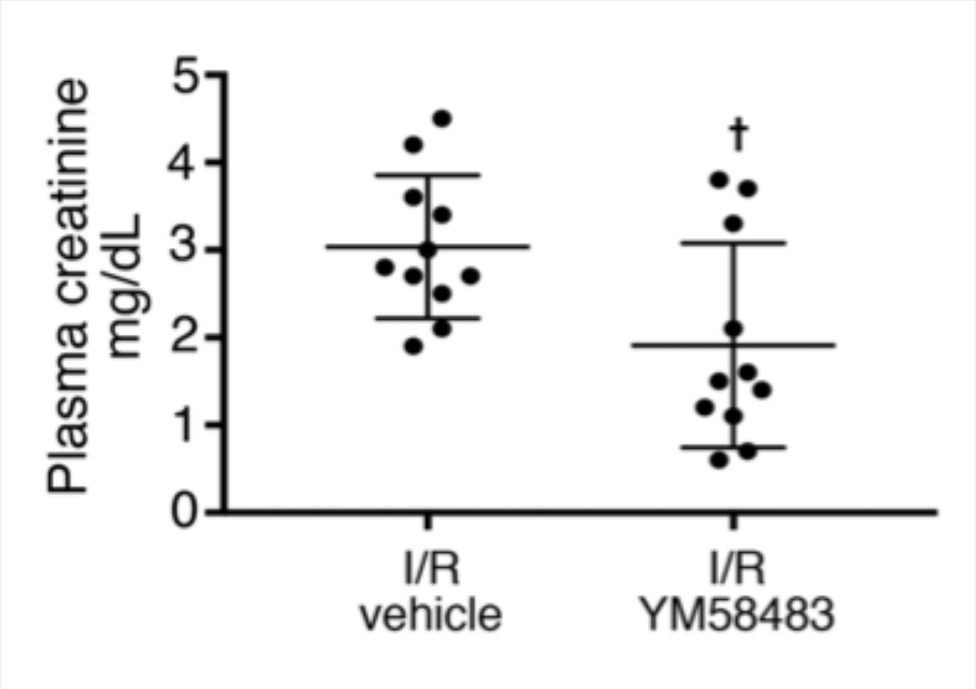

Unpublished. Courtesy of Dr. Basile Indiana University

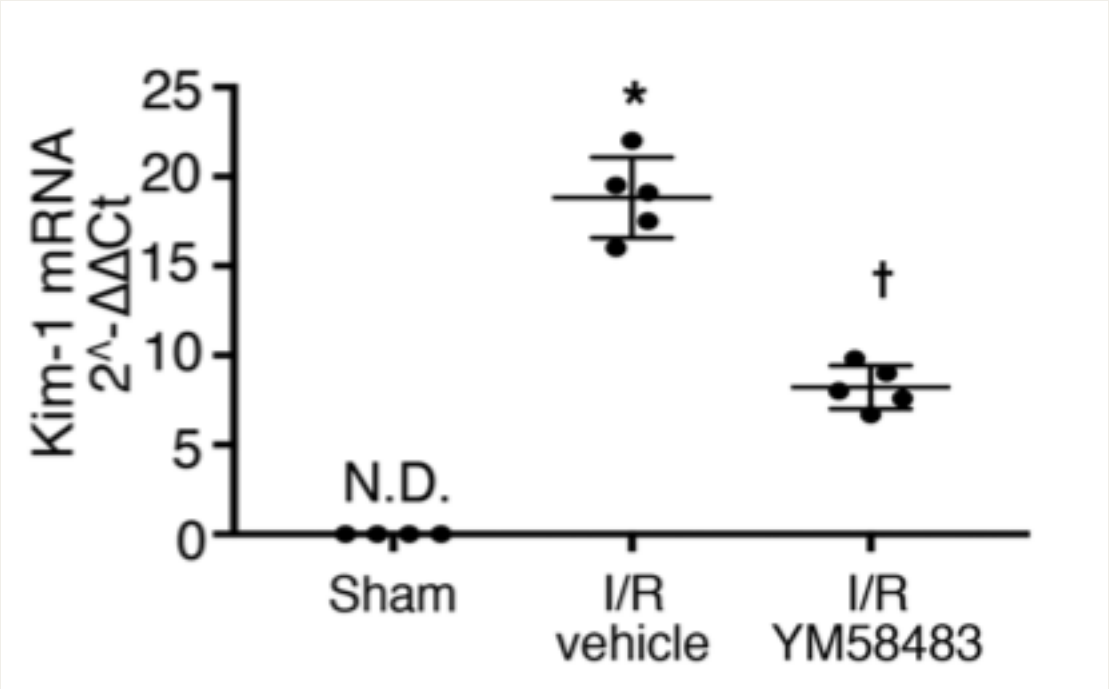
CalciMedica

# Preclinical Testing of CRAC Channel Inhibitors in AKI

# AKI Prevented by Administration of a CRAC Channel Inhibitor

Rats were dosed orally with BTP2 (a CRAC channel inhibitor) 2-3 hours prior to 40 minutes of ischemia/reperfusion (I/R) injury

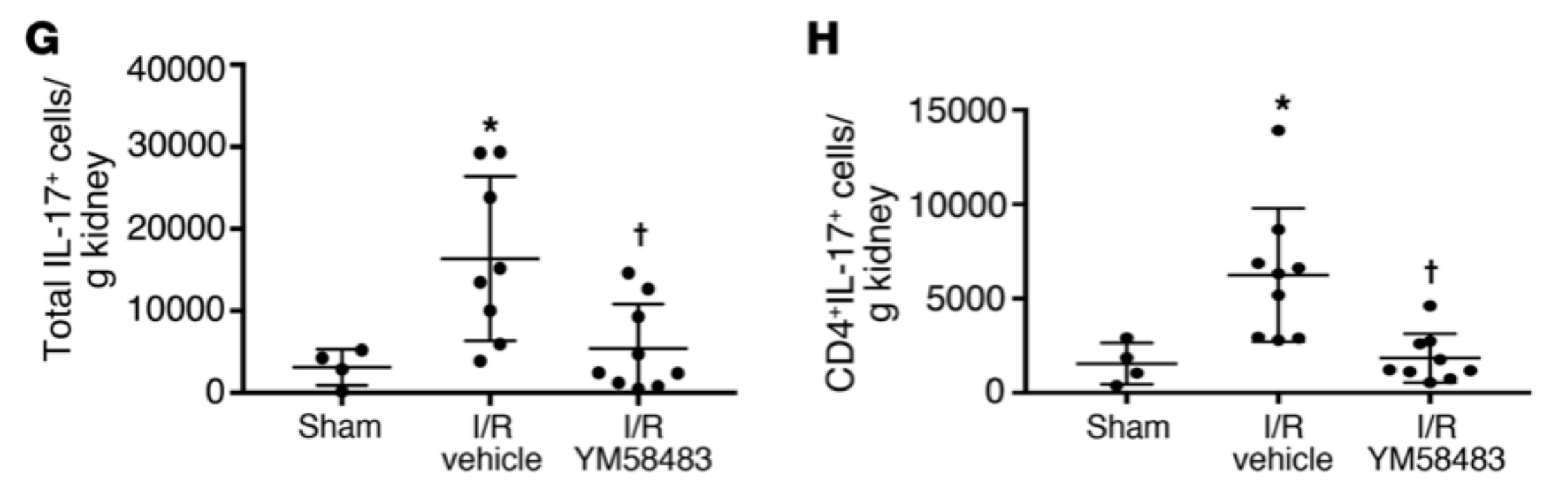



CalciMedica

Mehrotra, Purvi, et al. "Calcium channel Orai1 promotes lymphocyte IL-17 expression and progressive kidney injury." The Journal of clinical investigation 129.11 (2019): 4951-4961

# BTP2 Decreased $CD4^{+}IL\text{-}17^{+}$ Cells After I/R Injury




CalciMedica

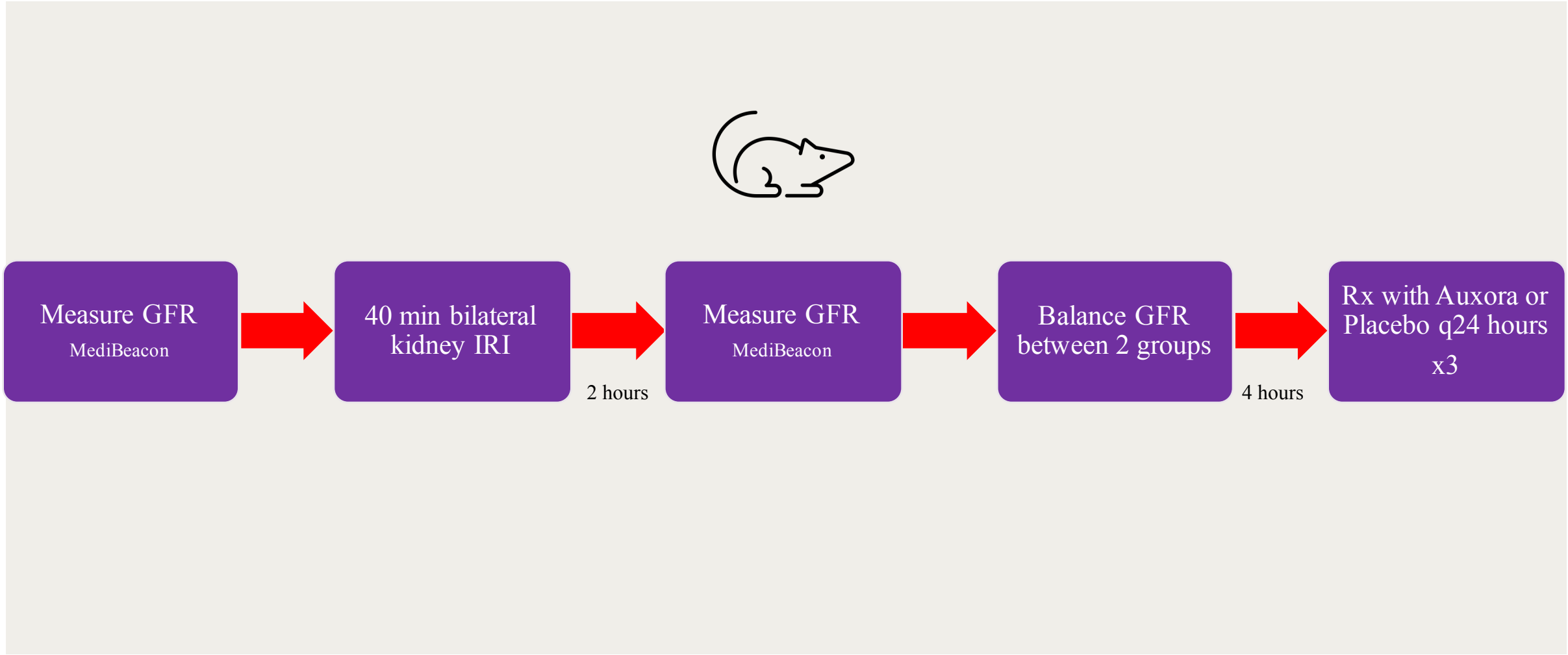
Mehrotra, Purvi, et al. "Calcium channel Orai1 promotes lymphocyte IL-17 expression and progressive kidney injury." The Journal of clinical investigation 129.11 (2019): 4951-4961

# Buttressing The Results

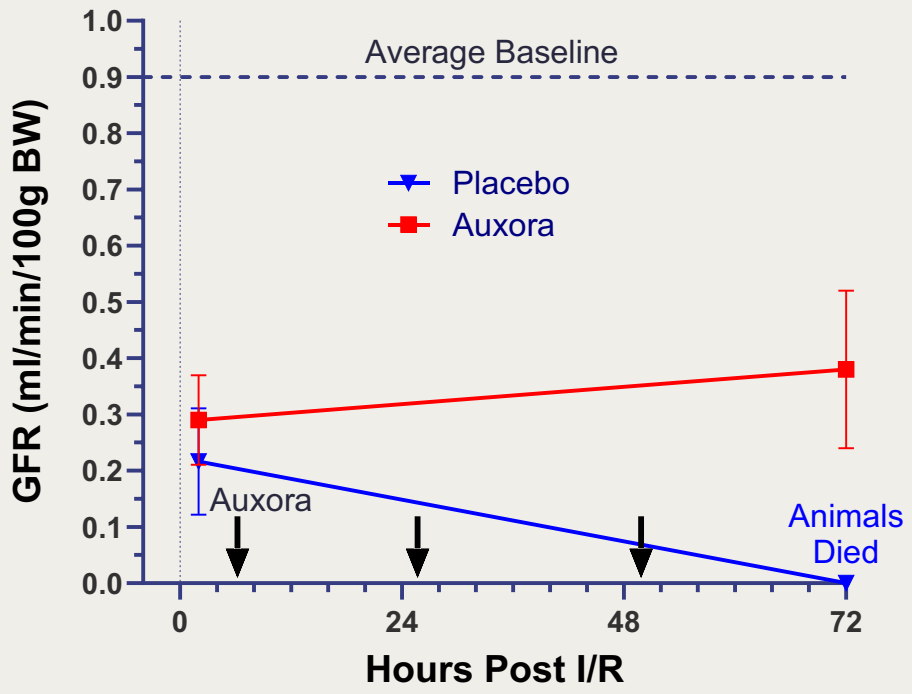
Preventative trial, not a treatment trial

Use of creatinine; No actual measure of GFR

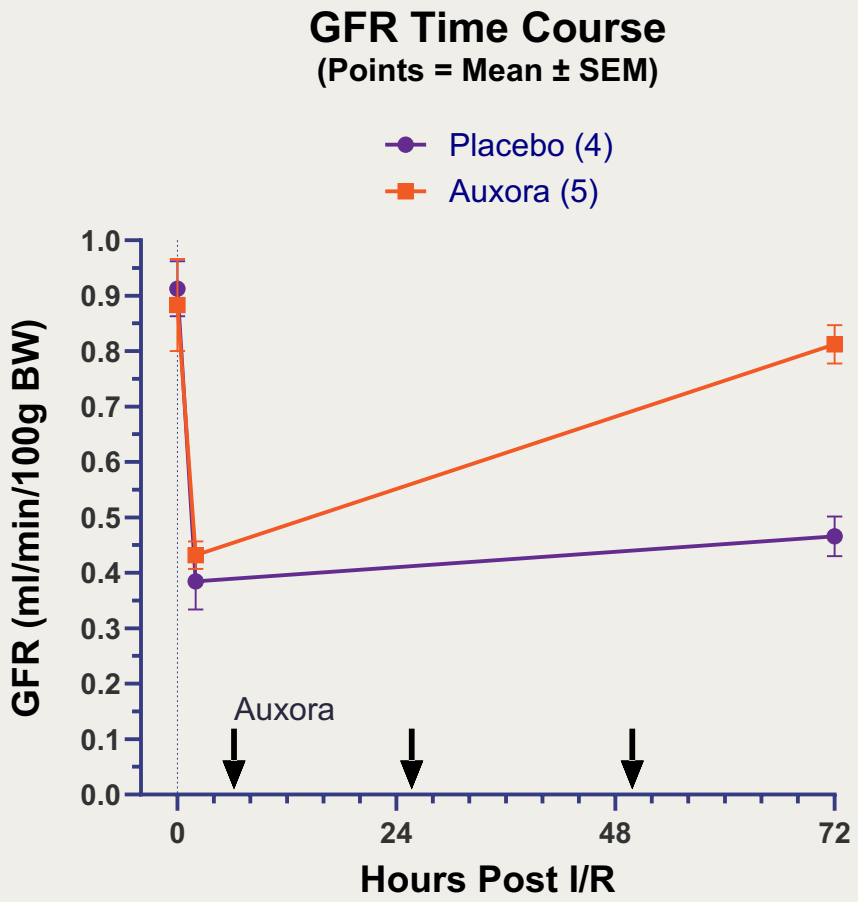
# Preclinical Study of I/R Injury Model of AKI in Rat

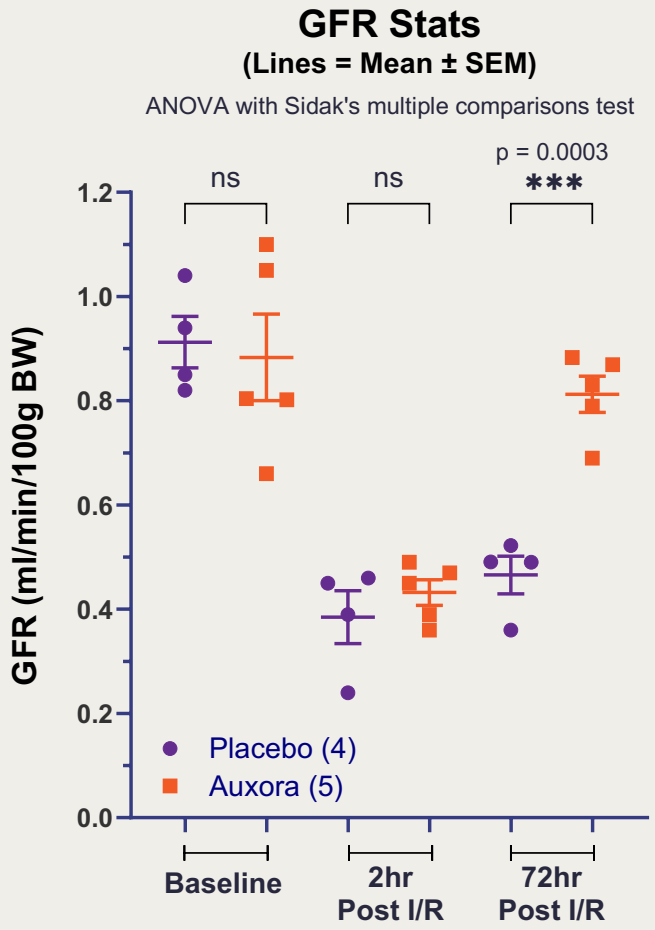


# Rats with Severe AKI



# Rats with Moderately Severe AKI



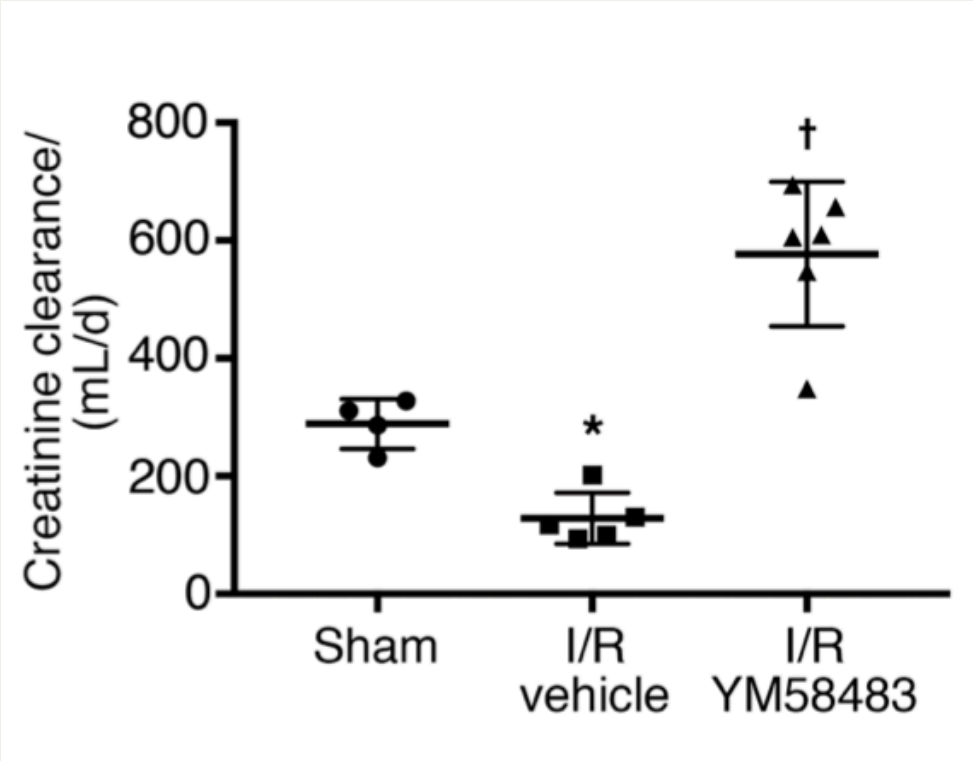

CalciMedica

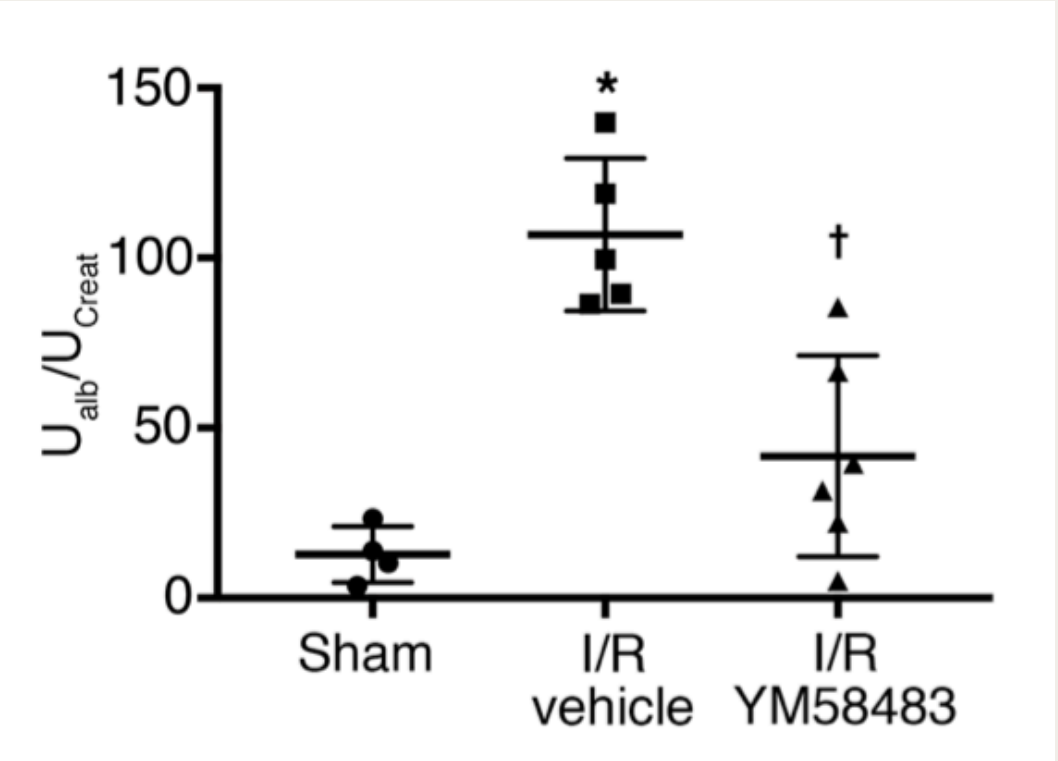
CalciMedica

# Background
# Orai1 Role in AKI to CKD Transition

# CRAC Channel Inhibition Attenuates Progressive Renal Damage After AKI

The effect of BTP2 on Th17 activation by high-salt diet following AKI was evaluated in rats subjected to unilateral renal I/R followed by contralateral nephrectomy and transition to high-salt diet

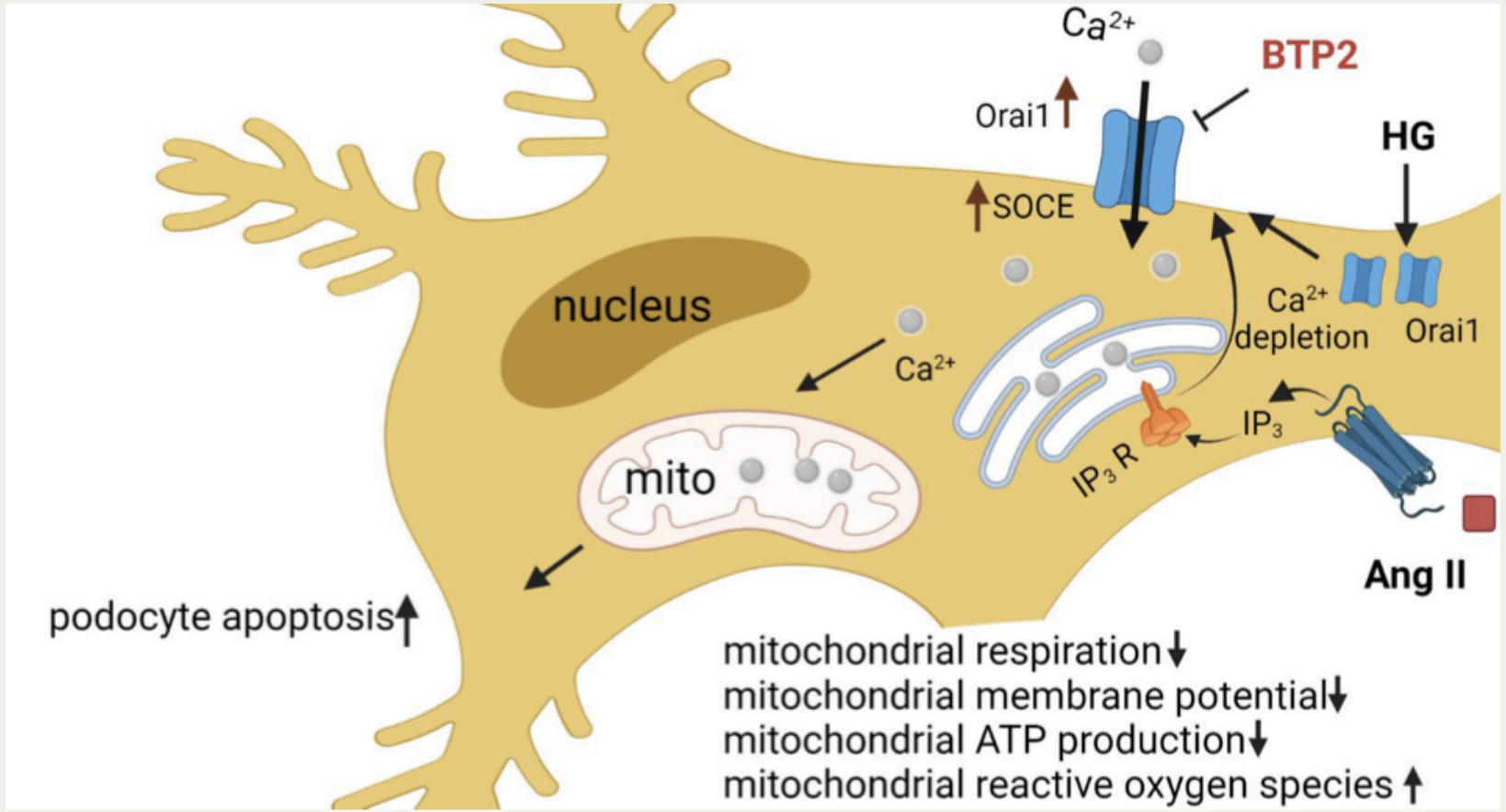



CalciMedica

Mehrotra, Purvi, et al. "Calcium channel Orai1 promotes lymphocyte IL-17 expression and progressive kidney injury." The Journal of clinical investigation 129.11 (2019): 4951-4961

# ORAI1 Mediates Podocyte Injury from High Glucose and Angiotensin II




**CONCLUSION: SOCE mediates HG and Ang II-induced podocytes apoptosis and mitochondria damage**

Tao, Yu, et al. "Store-operated Ca2+ entry inhibition ameliorates high glucose and ANG II-induced podocyte apoptosis and mitochondrial damage." American Journal of Physiology-Renal Physiology 324.5 (2023): F494-F504..

# CRAC Channel Inhibition Decreases Podocyte Injury from High Glucose and Angiotensin II

- In cultured human podocytes, both high glucose and Ang II treatment induced podocyte apoptosis, which was significantly blunted by an SOCE inhibitor, BTP2.
- Seahorse analysis showed that podocyte oxidative phosphorylation in response to high glucose and Ang II was impaired. This impairment was significantly alleviated by BTP2.
- BTP2, but not TRPC6 channel inhibitor, significantly blunted the damage of podocyte mitochondrial respiration induced by Ang II treatment.
- Furthermore, BTP2 reversed impaired mitochondria membrane potential (MMP), ATP production, and enhanced mitochondria superoxide generation induced by HG treatment.
- Finally, BTP2 prevented overwhelming Ca2+ uptake in HG treated podocytes.

Tao, Yu, et al. "Store-operated Ca2+ entry inhibition ameliorates high glucose and ANG II-induced podocyte apoptosis and mitochondrial damage." American Journal of Physiology-Renal Physiology 324.5 (2023): F494-F504..

# CRAC Channel Inhibition Prevents Epithelial to Mesenchymal Transition

- Renal fibrosis induced by a high fat diet or unilateral urinary obstruction was associated with increased expression of Orai1 in the kidney cortex.
- In cultured human proximal tubule epithelial cells (HK2), knockdown of Orai1 $Ca^{2+}$ channel with adenovirus–Orai1–short hairpin RNA markedly inhibited TGF-β1 induced intracellular $Ca^{2+}$ influx and phosphorylation of smad2/3.
- Knockdown or blockade using a CRAC channel inhibitor SKF96365 of the Orai1 $Ca^{2+}$ channel in HK2 cells also prevented epithelial-to-mesenchymal transition induced by TGF- β1.

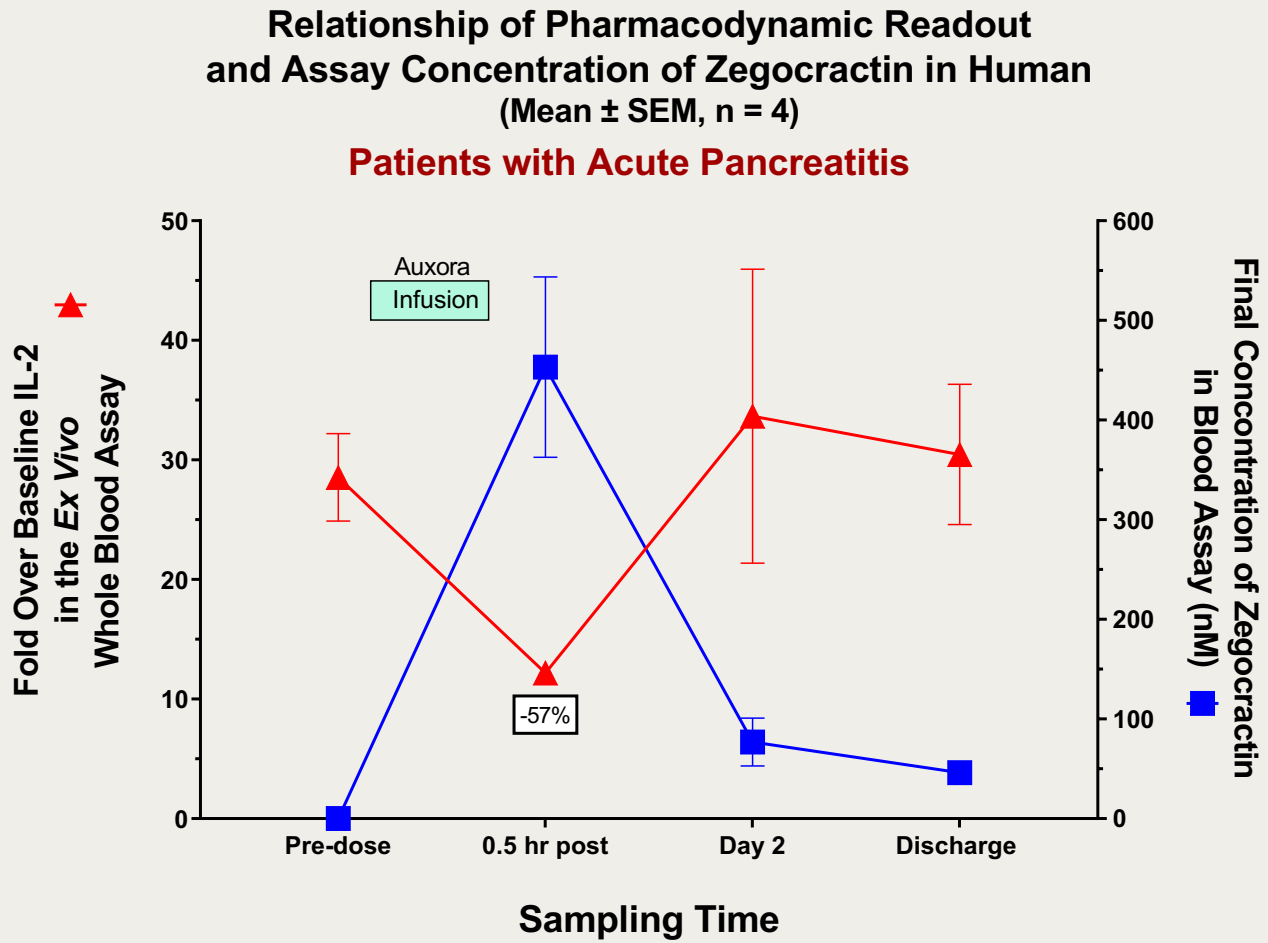


Mai, Xiaoyi, et al. "Blockade of Orai1 store-operated calcium entry protects against renal fibrosis." Journal of the American Society of Nephrology 27.10 (2016): 3063-3078.

CalciMedica

# Clinical Development of Auxora

# Auxora™ : Immunomodulator with an On Off Switch



# Completed and Currently Conducted Human Studies of Auxora
# Significant Experience of Testing Auxora in Critically Ill Patients

| Study | Population | Intervention | Comparison | Results |
|---|---|---|---|---|
| CM4620-201 | Acute Pancreatitis Accompanied by SIRS and Hypoxemia | Auxora (mg/kg) infused over 4 hours<br>High Dose Regimen: 2.08, 2.08, 1.6, 1.6 (6 patients)<br>Low Dose Regimen: 1.0, 1.4, 1.4, 1.4 (8 patients) | Standard of Care<br>(7 patients) | Both the low dose and high dose regimens were well tolerated with AEs reported comparable with respect to frequency, severity, and type.<br>Rapid improvement in multiple patient outcomes |
| CM4620-202 | Acute Pancreatitis | Auxora single 2.08 mg/kg infusion over 4 hours<br>(7 patients) | None | Auxora was well tolerated. Demonstrated target engagement of CRAC channels in peripheral lymphocytes |
| CARPO<br>CM4620-203 | Acute Pancreatitis Accompanied by SIRS | Auxora (mg/kg) infused over 4 hours<br>High Dose Regimen: 2.0, 2.0, 2.0 (54 patients)<br>Middle Dose Regimen: 1.0, 1.0, 1.0 (54 patients)<br>Low Dose Regimen 0.5, 0.5, 0.5 (54 patients) | Matching Placebo<br>(54 patients) | The high and middle doses of Auxora decreased the rate of new onset severe respiratory failure in patients with acute pancreatitis presenting with ≥2 SIRS criteria. Win ratio integrating key endpoints and mGMCP modeling of food tolerance and organ failure identified high dose level as best dose.<br>Auxora was well tolerated. |
| CRSPA<br>St. Jude's<br>(underway) | Asparaginase Induced Acute Pancreatitis | Auxora infused over 4 hours<br>Regimen: 30 mg/m$^2$ x 1 day, 42 mg/m$^2$ x 3 days<br>(14 pediatric patients) | Historical Controls | Preliminary results indicate Auxora is well tolerated<br>Improvement in clinical symptoms and 30-day outcomes compared to historical controls |
| CARDEA<br>CM4620-204 | Covid-19 with Respiratory Failure on LFO2 and HFNC | Auxora (mg/kg) infused over 4 hours<br>Dose levels (mg/kg): 2.0, 1.6, 1.6<br>(Part 1 20 patients)<br>(Part 2 143 patients) | Standard of Care (Part 1 10 patients)<br>Matching Placebo (Part 2 141 patients) | Auxora was well tolerated<br>Improvement in multiple patient outcomes<br>Statistically significant decrease in mortality at Day 30 |
| CM4620-205 | Covid-19 with Respiratory Failure on IMV | Auxora (mg/kg)<br>Cohort 1: 2.0, 1.6, 1.6 infused over 4 hours (2)<br>Cohort 2: 2.0, 2.0, 1.6, 1.6 infused over 4 hours (2)<br>Cohort 3: 2.0 infused over 4 hours, 1.6 infused over 24 hours x4 (1) | Matching Placebo<br>(2 patients) | Auxora reduced inflammatory gene expression in alveolar macrophages and T cells without a change in the relative abundance of either population. Auxora inhibits CRAC channel activation in T cells to attenuate their activation of monocyte derived alveolar macrophages and reduce lung injury after viral pneumonia. |

# CARDEA Post-Hoc Analysis of All-Cause Mortality Patients with Severe COVID-19 Pneumonia and AKI

| | Number of Patients | Placebo 131 | Auxora 129 | Absolute Reduction | Relative Reduction | Difference (95% CI)[a] |
|---|---|---|---|---|---|---|
| Day 30 | 260 | 23 (17.6%) | 10 (7.7%) | 9.9% | 56.3% | -9.86 (-17.80, -1.93) |
| Day 60 | 260 | 27 (20.6%) | 18 (13.8%) | 6.8% | 33.0% | -6.75 (-15.75, 2.24) |
| **Post-Hoc Analysis** | | | | | | |
| Days 30 & 60 | 38 with likely AKI* | 7/15 (46.7%) | 4/23 (17.4%) | 29.3% | 62.7% | |

eGFR <60 at screening; no known CKD



Bruen C, Al-Saadi M, Michelson EA, Tanios M, Mendoza-Ayala R, Miller J, Zhang J, Stauderman K, Hebbar S, Hou PC. "Auxora vs. placebo for the treatment of patients with severe COVID-19 pneumonia: a randomized-controlled clinical trial." Critical Care 26: 1-11 (2022)

# CARDEA D-Dimer Analysis

Decrease in D-dimer levels in patients treated with Auxora

| D-Dimer | Placebo (N=131) | Auxora (N=130) | Auxora v. Placebo |
|---|---|---|---|
| Mean Baseline Value, mg/L (SD) | 2.05 (3.9) (n=122) | 2.61 (7.4) (n=119) | |
| Mean 72-hour Value, mg/L (SD) | 2.15 (3.8) (n=82) | 1.35 (1.2) (n=78) | |
| Change LS Mean, mg/L (95% CI) | 0.04 (-0.59, 0.67) | -0.88 (-1.52, -0.23) | -0.92 (-1.82, -0.02) |
| P-Value | 0.8990 | 0.0082 | 0.0460 |

# CARDEA Angiopoietin1 and 2 Analysis

Increases in Angiopoietin-1 and decreases in Angiopoietin-2 in patients treated with Auxora

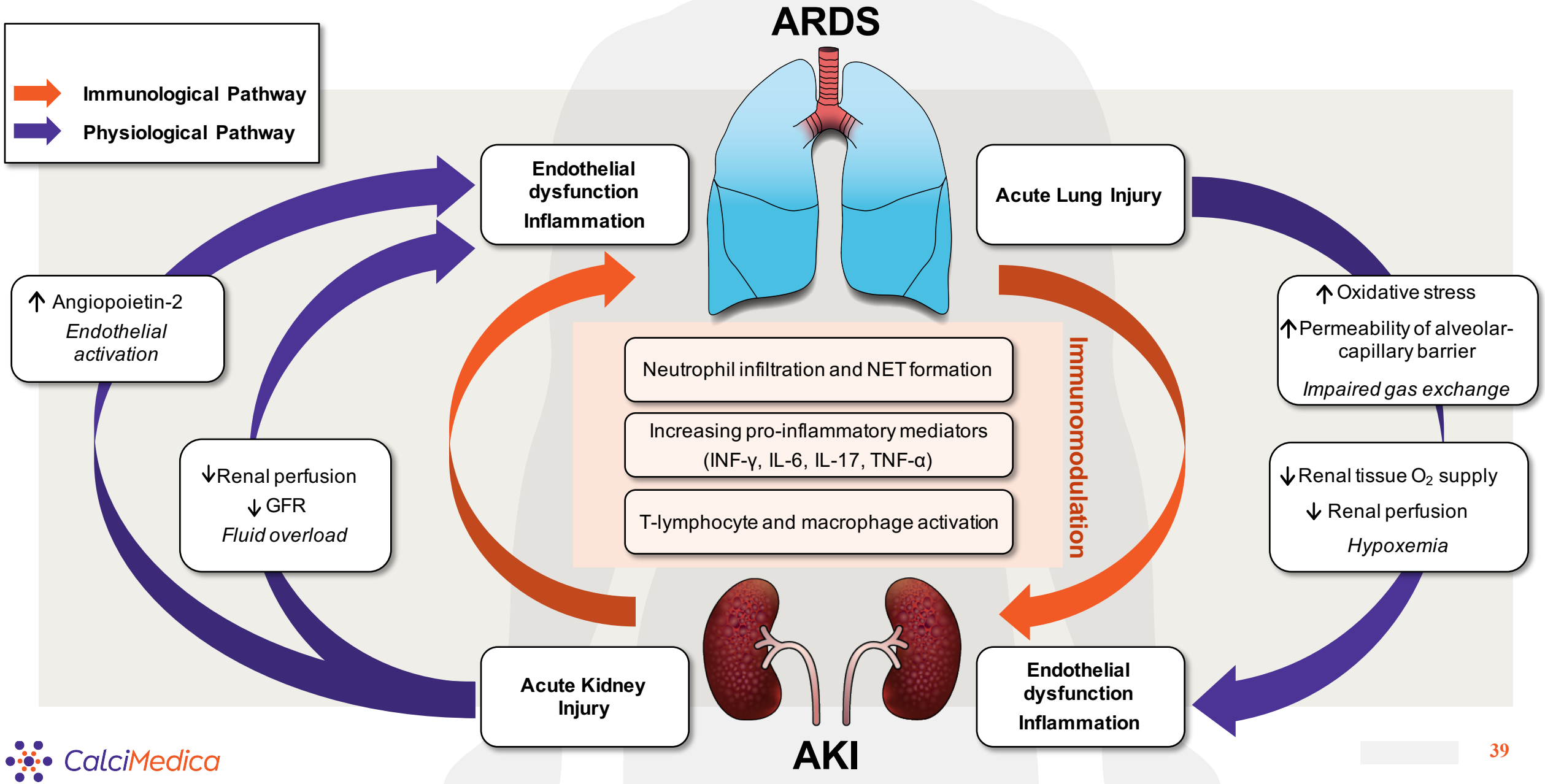
| Angiopoietin-1 | Auxora (N=96) |
|---|---|
| Mean Baseline Value, pg/mL (SD) | 38395.45 (16408.26) (n=81) |
| Mean 96-hour Value pg/mL (SD) | 41651.42 (15876.91) (n=70) |
| Change LS Mean (95% CI) | 4832.61 (1212.69, 8452.54) |
| P-Value | 0.0093 |

| Angiopoietin-2 | Auxora (N=96) |
|---|---|
| Mean Baseline Value, pg/mL (SD) | 2963.65 (1713.513) (n=76) |
| Mean 96-hour Value pg/mL (SD) | 2423.96 (1342.434) (n=67) |
| Change LS Mean (95% CI) | -636.49 (-1122.52, -150.46) |
| P-Value | 0.0107 |

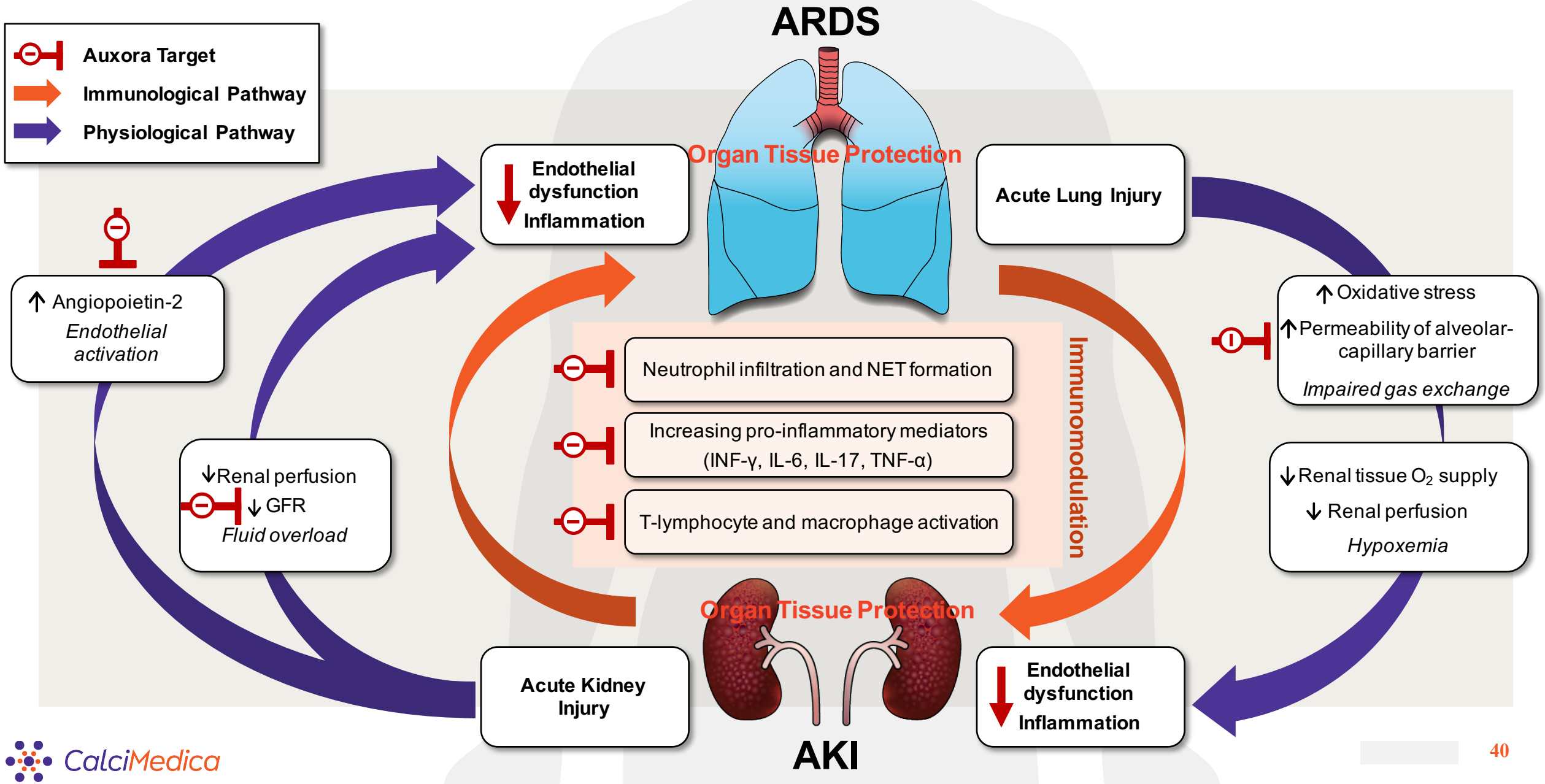
CalciMedica

# Conclusion

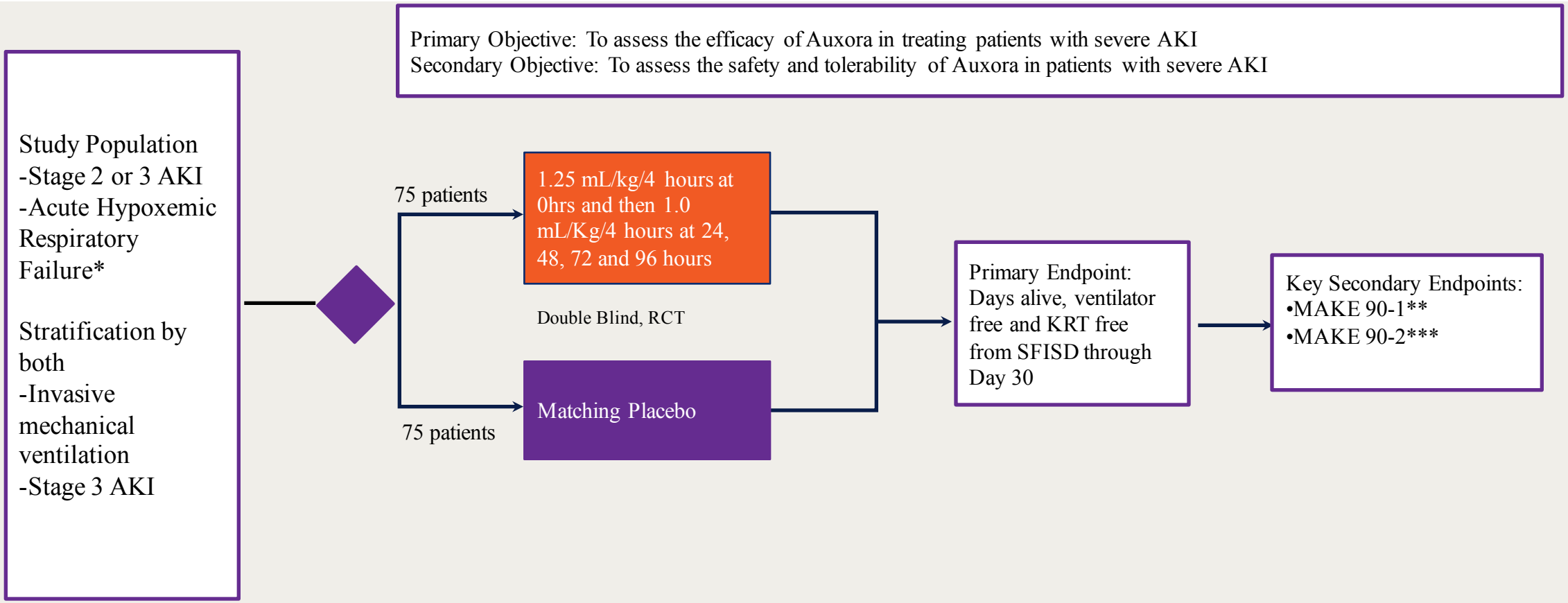
# Multiple Injury Pathways Activated in ARDS/AKI Crosstalk



# Auxora Targets Multiple Injury Pathways Activated in ARDS/AKI



# Auxora for the Treatment of AKI and Modulation of Injurious "Crosstalk" with the Lung: A Randomized Control Trial (KOURAGE) NCT06374797




*AHRF will be defined as a P/F ≤300 that has been determined by either an arterial blood gas or imputed from the oxygen saturation (SpO2) recorded using pulse oximetry and is being treated with high flow nasal cannula with minimum flow rate ≥ 30 liters/min, or non-invasive mechanical ventilation, or invasive mechanical ventilation

**MAKE 90-1: ≥ 25% decline in eGFR from baseline, incident KRT, and all-cause mortality at 90 days

***MAKE 90-2: ≥ 35% decline in eGFR from baseline, incident KRT, and all-cause mortality at 90 days

CalciMedica