



Murine Models and Immune Therapy

What Can Mice Teach Us About AIN?

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DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INELIGIBLE COMPANIES

- Nothing to disclose

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Nothing to disclose

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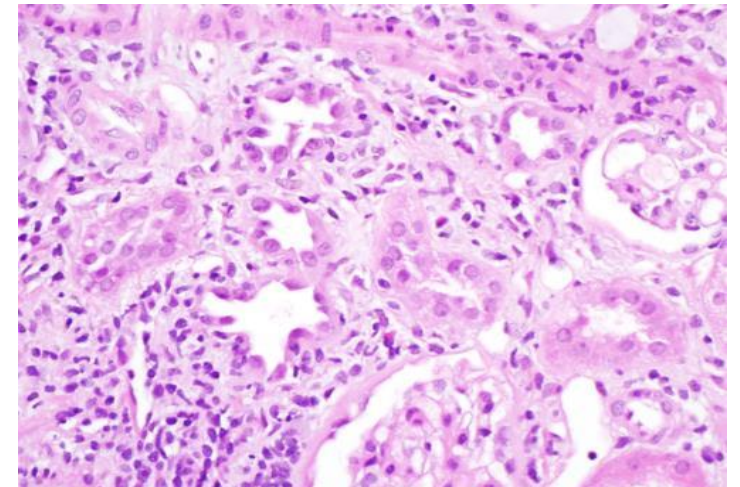
Learning Objectives

Review immune mechanisms of immune checkpoint associated acute interstitial nephritis (ICI-AIN)

- Understand available murine models
- Discuss ICI-AIN
- Evaluate strengths and limitations of the mouse models
- Identify future directions for translational research

ICI-induced Acute Interstitial Nephritis

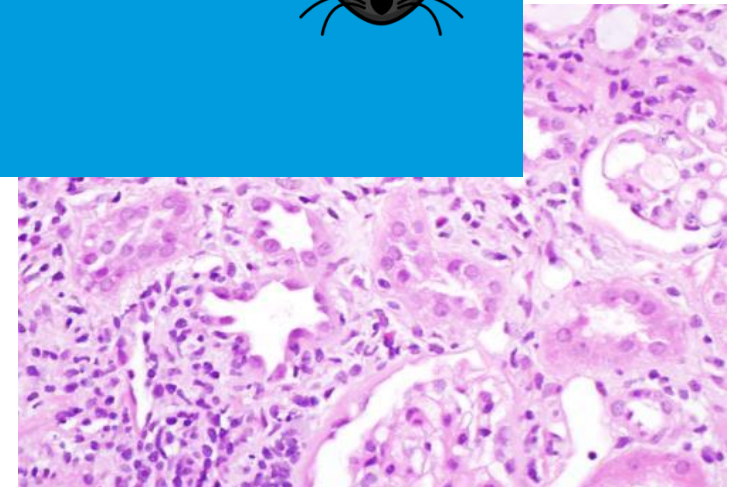
- ICI-AIN is the most common renal immune-related adverse event(irAE), accounting for >80-90% of kidney biopsies in ICI-treated patients. Incidence ranges from 1-5% depending on regimen, with combination anti-PD-1/anti-CTLA-4 conferring the highest risk.
- Histopathologically predominantly CD4⁺ T-cell interstitial infiltrate, tubulitis, occasional granulomas.
- Human kidney biopsies provide only a single time point and mechanisms remain poorly understood.
- Mouse models permit:
 - Temporal analysis
 - Immune-cell tracking
 - Mechanistic studies
 - Therapeutic testing

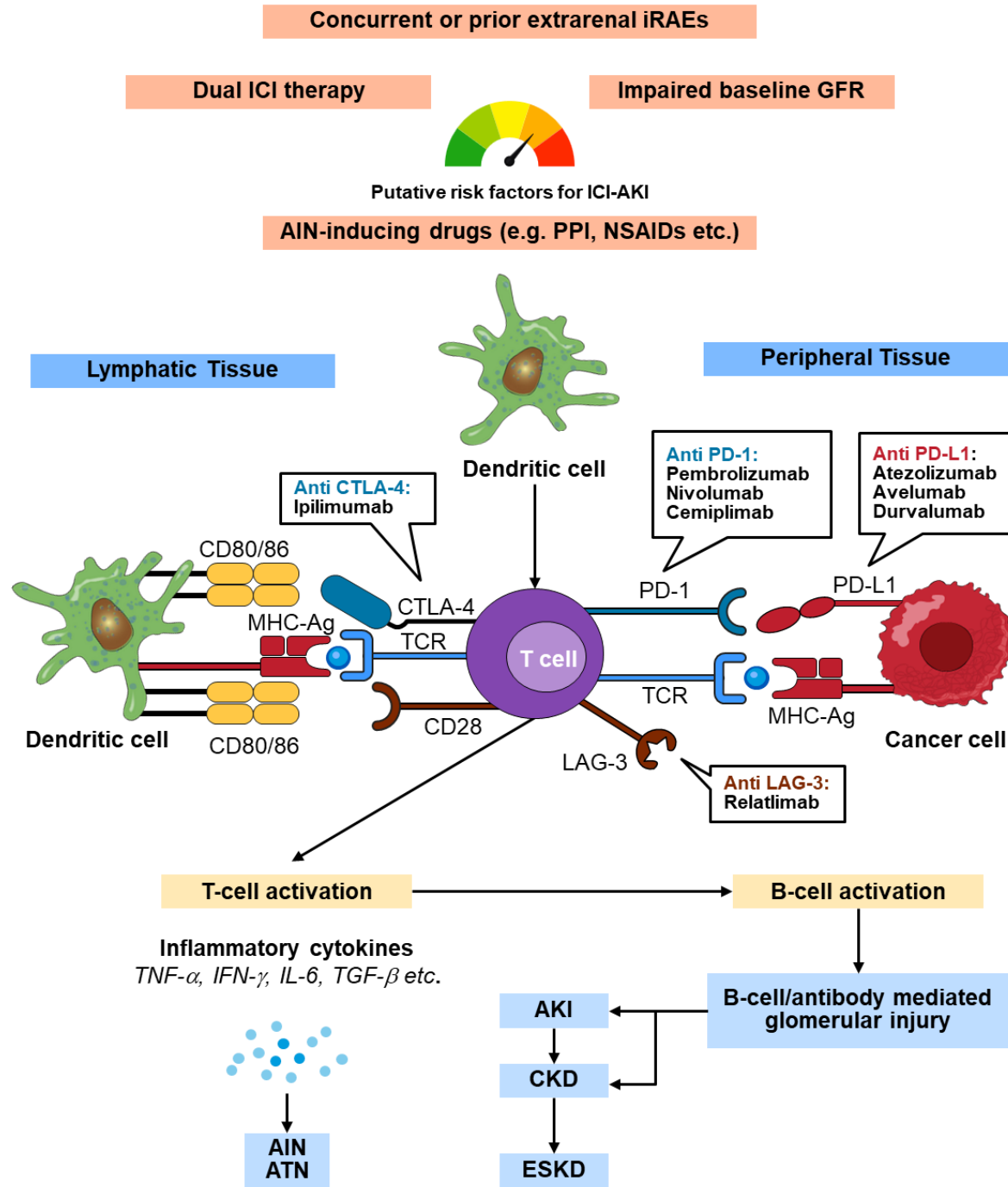


ICI-induced Acute Interstitial Nephritis

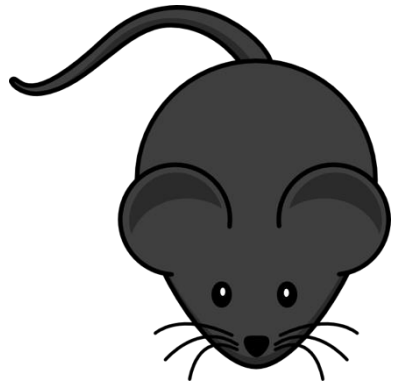
- ICI-AIN is the most common renal immune-related adverse event(irAE), accounting for >80-90% of kidney biopsies in ICI-treated patients. Incidence ranges from 1-50% depending on regimen, with combination anti-PD-1/anti-CTLA-4 regimens showing the highest incidence.
- Histopathology: acute tubulointerstitial nephritis (tubulitis)
- Human mechanistic studies
- Mouse models
 - Temporal analysis
 - Immune-cell tracking
 - Mechanistic studies
 - Therapeutic testing

The challenge has been creating a model that resembles human ICI-AIN





Pathogenesis and Risk Factors of Immune Checkpoint Inhibitor (ICI) – Induced Acute Kidney Injury



Mouse Models

Advantages

- Controlled genetics
- Knockout strains
- Immune manipulation
- Longitudinal studies
- Tissue collection
- Therapeutic testing

Challenges

- Species differences
- Drug metabolism
- Limited spontaneous AIN

Murine Models of ICI-AIN

Mechanism	Model(s)	Key Findings	References
Human immune system-driven interstitial nephritis & vasculitis	HIS-BRGS (controls were non-humanized)	Nivolumab ± ipilimumab induced significant interstitial nephritis and vasculitis/periarteritis; combination therapy → more extensive pathology with T-helper cell accumulation; non-humanized controls showed no nephritis, requiring human immune system requirement	Asby et al. KI, 2025
Resident macrophage-driven inflammation	Anti-PD-1 C57BL/6 Cx3cr1CreER/+;R26Td mice (small n= max 4)	↑ CD8 +T cells and Macrophages upregulate CXCL9 and MMP12 and depletion alleviates injury without compromising tumor therapy	Ma et al. Adv Sci, 2025
TNF-α/IFN-γ synergy	Humanized PD-1/PD-L1	↑CD4+ and CD8+T cells. Proinflammatory cytokines synergize with ICIs; TNF-α blockade is protective. Single-cell RNA-seq identified shifts in immune cell populations and key genes	Cuenca Narvaez et al. JCI Insight, 2026
IL-21-CXCL13-autoantibody axis	Aged C57BL/6 + anti-PD-1	CD4 ⁺ T-cell IL-21 drives CXCL13 and IgG deposition; B-cell depletion protective	Tsukamoto et al. PNAS, 2022
Two-hit hypothesis (ICI + nephrotoxin)	ICI + cisplatin	ICIs potentiate cisplatin tubular injury via inflammatory amplification	Tascón et al.



Translating Human Renal Immune Related Adverse Events into Experimental Model

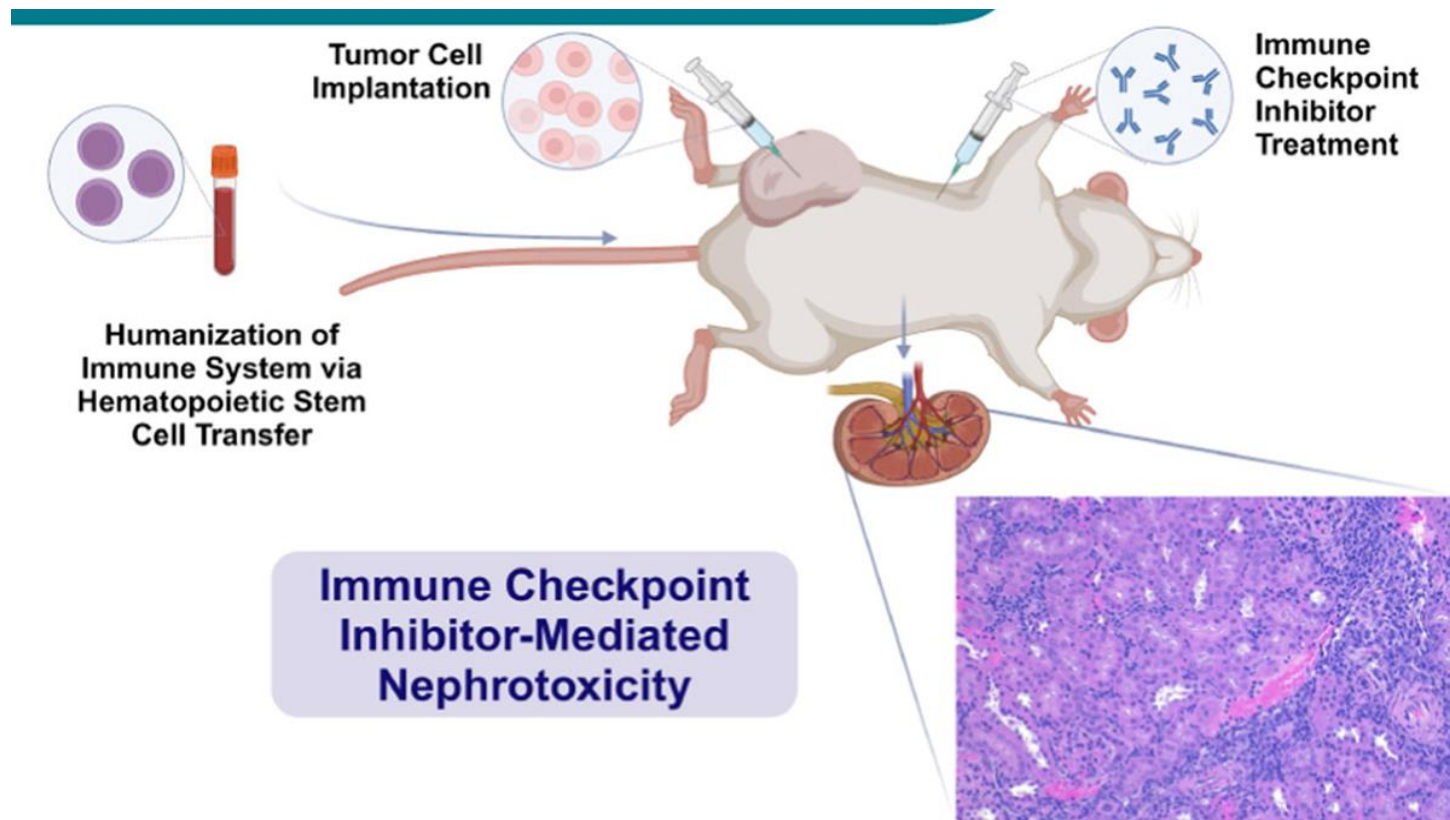
Pathological findings of immunotherapy-induced nephrotoxicity in a humanized immune system mouse model



Sarah C. Asby¹, Lauren E. Thompson¹, Michael Goedken², Scott M. Lucia^{3,4,5}, Adrian T. Dominguez⁴, Adwitiya Kar⁴, Todd M. Pitts⁴, Katja Kiseljak-Vassiliades⁴, Julie Lang⁴, Lauren M. Aleksunes⁶ and Melanie S. Joy^{1,4,5}

¹Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Aurora, Colorado, USA; ²Research Pathology Services, Rutgers University, Piscataway, New Jersey, USA; ³Department of Pathology, University of Colorado, Aurora, Colorado, USA; ⁴Cancer Center, University of Colorado, Aurora, Colorado, USA; ⁵Renal Division, University of Colorado, Aurora, Colorado, USA; and ⁶Department of Pharmacology and Toxicology, Rutgers University, Piscataway, New Jersey, USA

Pathological Findings of Immunotherapy-Induced Nephrotoxicity in a Humanized Immune system Mouse Model



Conclusion: A novel humanized immune system tumor-bearing mouse model recapitulates some of the key features of ICI-induced kidney injury observed in the clinical setting

Pathological findings of immunotherapy-induced nephrotoxicity in a humanized immune system mouse model

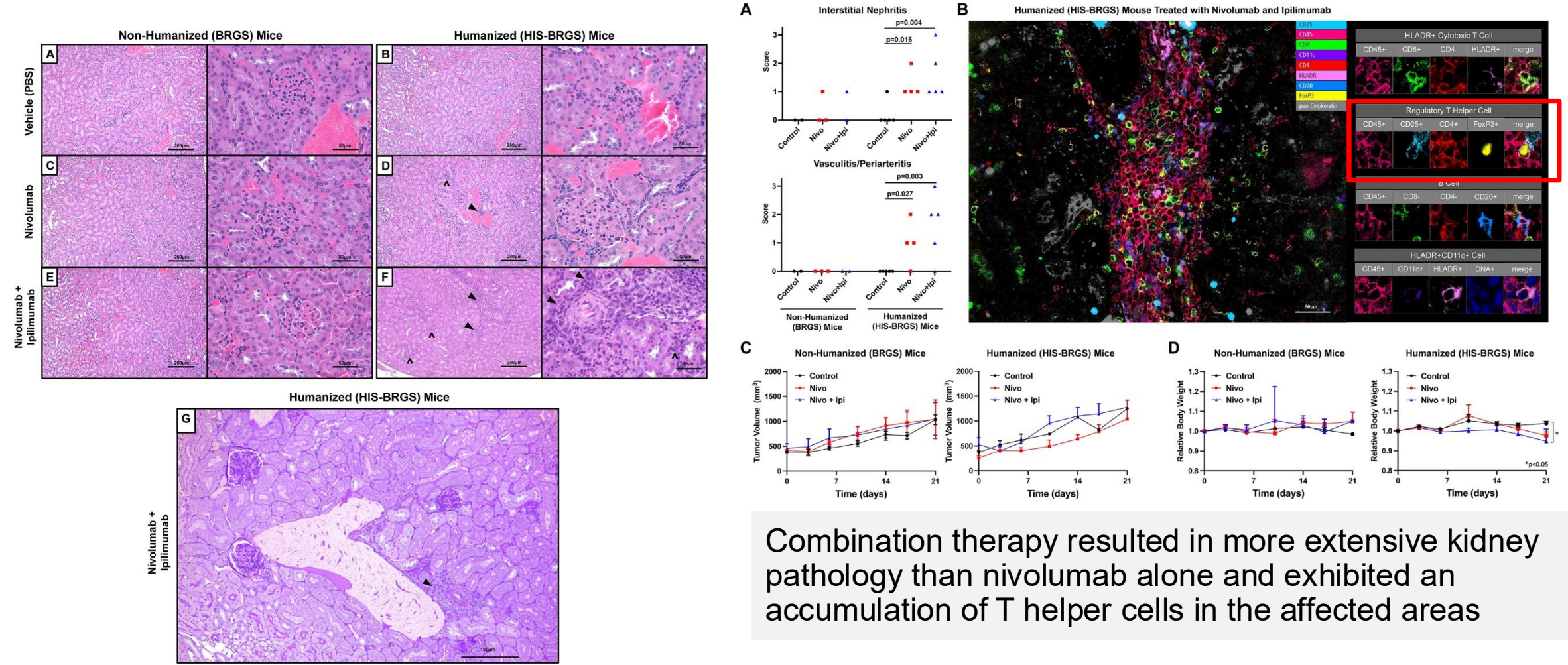


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- HIS-BRGS mice with human breast cancer xenografts treated with nivolumab ± ipilimumab for 4 weeks
- ICI-treated humanized mice developed predominantly vasculitis/periarteritis, closely resembling human ICI nephritis
- Dual ICI: Nivolumab + ipilimumab induced more severe renal inflammation than nivolumab alone
- Renal infiltrates were dominated by CD4+ helper T cells, supporting a T cell-mediated pathogenesis

Histopathologic Analysis of Kidneys from Tumor-bearing Non-Humanized BRGS and Humanized Immune System (HIS) – BRGS Mice after ICI Treatment

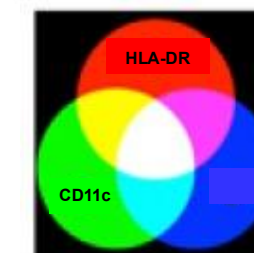
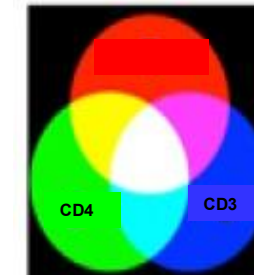
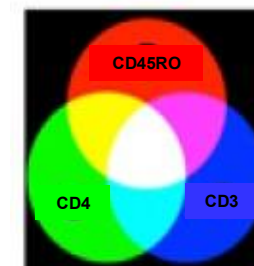
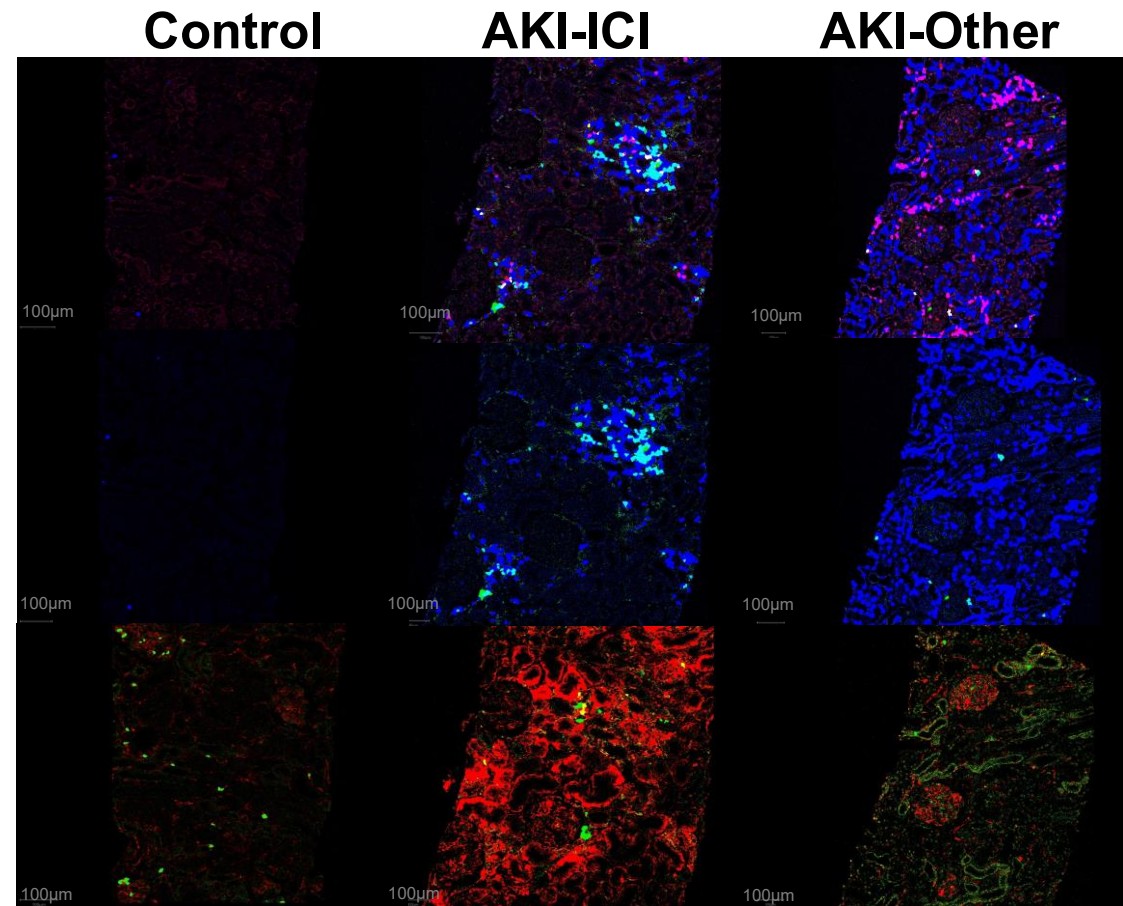


Human Kidney Tissue Immunophenotyping by Imaging Mass Cytometry (CYTOF)

→ **CD4
Memory
Cells**
CD3 + CD4 + CD45RO

→ **T Helper
Cells**
CD3 + CD4

→ **Dendritic
cells**
CD11c + HLA-DR



Pitfalls

- Limited immune-cell characterization: Infiltrating populations were not fully characterized by flow cytometry, and immune composition differed from human kidney biopsies as in this model there was predominantly vasculitis/periarteritis(up to 25% of tissue in most animals)
- Complex and costly model: Human immune system reconstitution requires several months and substantial resources, limiting scalability
- While highly translational, the model represents an early-stage and simplified version of human ICI nephritis and requires further validation for chronic injury, biomarkers, and therapeutic testing
- Short-term model (up to 4 weeks) may not reflect chronic ICI exposure

Resident Macrophage-Orchestrated Immune and Fibroblast Interactions in Immune Checkpoint Inhibitor-Associated Nephrotoxicity

Yanhong Ma, Yang Chen, Qinfan Yao, Yuxi Wang, Nan Ouyang, Fei Han, Guzong Wang, Meifang Wang, Yuan Yuan, Jianghua Chen, Jianzhen Shan, and Dajin Chen**

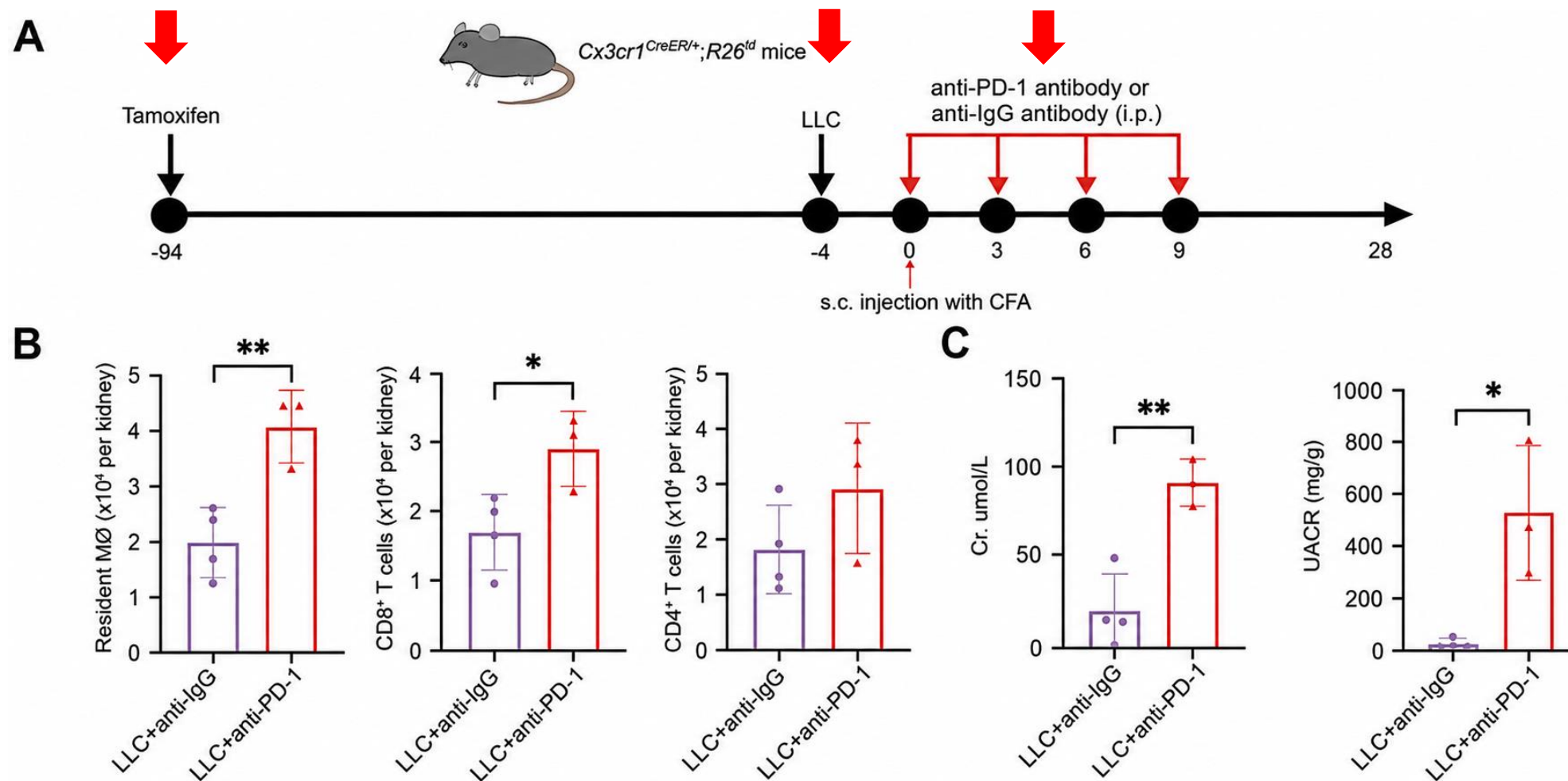
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- Human ICI-AN biopsies demonstrated increased resident macrophages, fibroblasts, CD4⁺ and CD8⁺ T cells compared to healthy controls
- Resident macrophages emerged as the key orchestrators of immune-fibroblast interactions
- Macrophages showed enhanced CXCL9 and MMP12 signaling, linking inflammation and fibrosis
- Elevated expression of TNF- α , IL-1 β , and the proliferation marker Ki-67, correlating with tissue injury severity

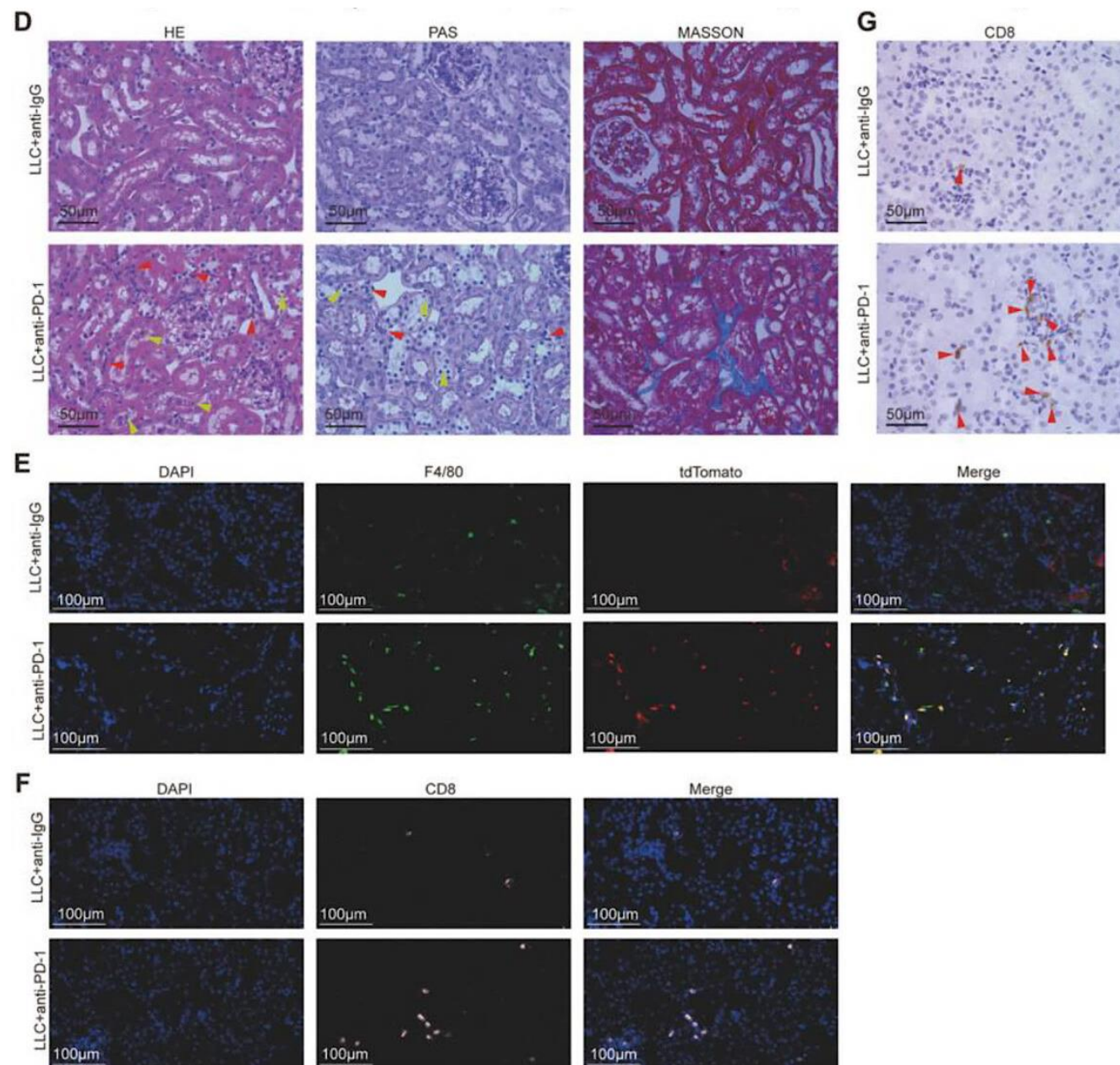
ICI-Induced Nephrotoxicity in With Tamoxifen-induced TD

Tomato Labeling of CX3CR1⁺ Resident Macrophage



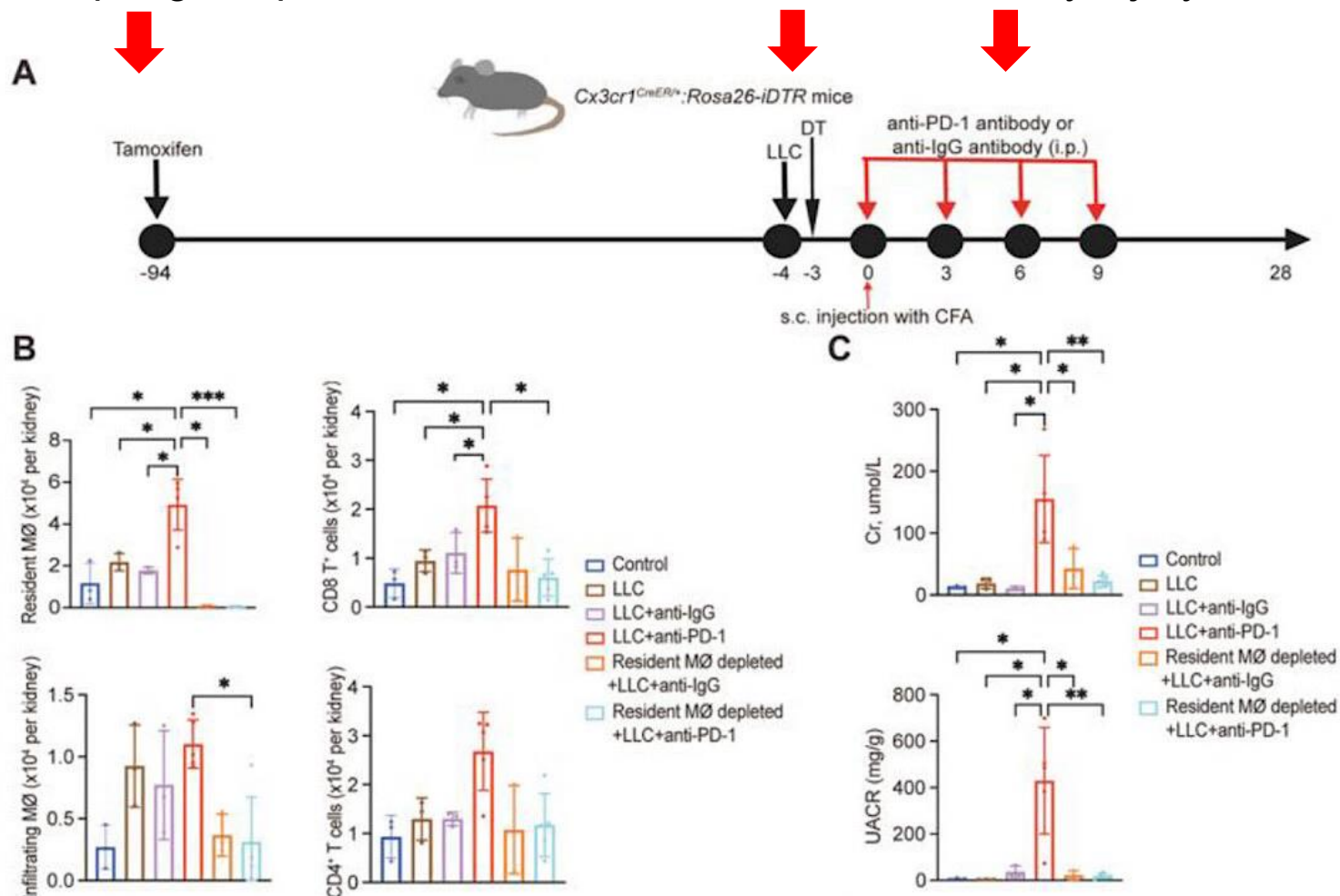
ICI-Induced Nephrotoxicity in With Tamoxifen-induced TD

Tomato Labeling of CX3CR1⁺ Resident Macrophage (cont)



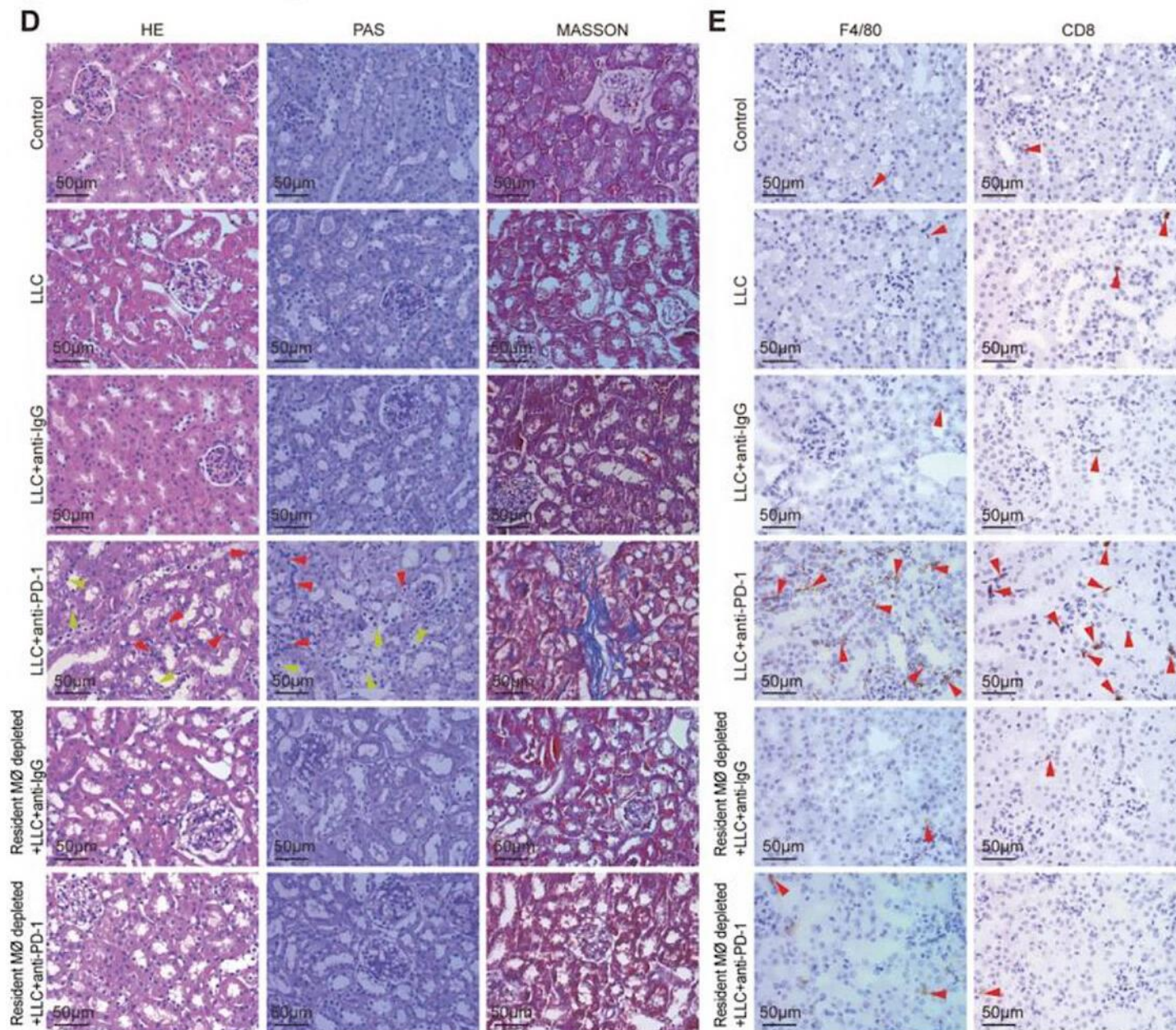
Resident Macrophage-Orchestrated Immune and Fibroblast Interactions in ICI-Associated Nephrotoxicity

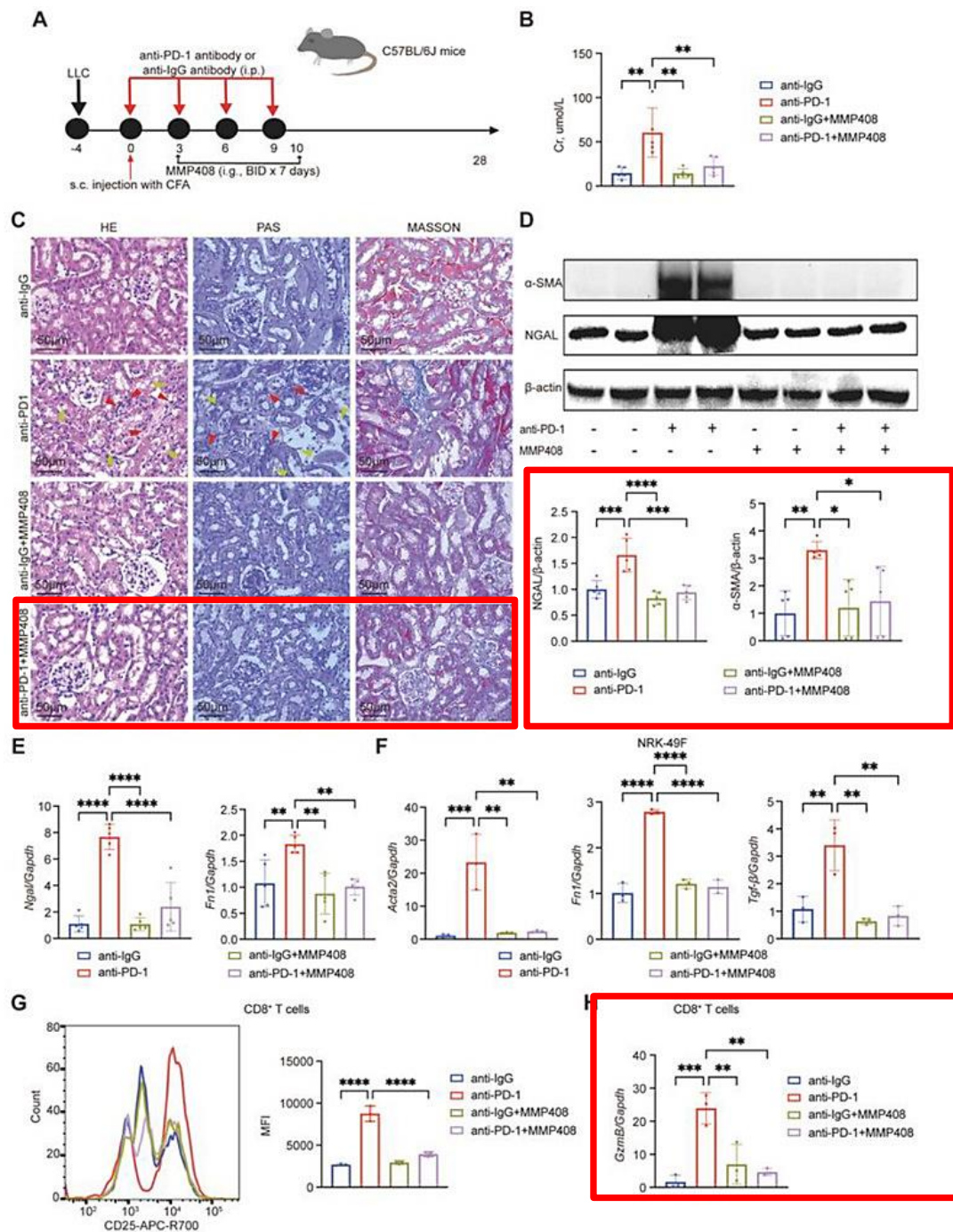
Macrophage depletion reduced anti-PD-1–induced kidney injury without affecting tumor size



Resident Macrophage-Orchestrated Immune and Fibroblast Interactions in ICI-Associated Nephrotoxicity

Macrophage depletion reduced anti-PD-1–induced kidney injury without affecting tumor size





MMP12 Inhibition and CXCL9 Neutralization Mitigate Renal Injury and Immune Activation in ICI-AN

- Blocking MMP12 (MMP408) reduced kidney injury and fibrosis
- Blocking CXCL9 reduced CD8⁺ T-cell activation and inflammation
- Overall: targeting MMP12/CXCL9 protected the kidney from anti-PD-1 toxicity

Pitfalls

- Complete Freund's Adjuvant(CFA) may artificially amplify immune activation
- Lewis Lung Cancer (LLC) tumors show limited PD-1 responsiveness
- Short-term model (28 days) may not mimic chronic ICI exposure
- Primarily reproduces AIN but not all the full spectrum of ICI nephrotoxicity (e.g., GNs)
- Murine immune and stromal biology limits translatability

TNF- α blockade mitigates immune checkpoint-related nephritis in a humanized mouse model

Victor D. Cuenca Narvaez,¹ Coraima Nava Chavez,¹ Omar Al Refai,¹ Johanna E.J. Jacobs,² Luis E. Gutierrez,¹ Song Zhang,² Xiaoyan Li,^{1,3} Jacob B. Hirdler,⁴ Michael F. Romero,^{1,5} Joerg Herrmann,² Xiaogang Li,^{1,3} Haidong Dong,^{4,6} Alfonso Eirin,^{1,2} and Sandra M. Herrmann¹

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TNF- α blockade mitigates immune checkpoint-related nephritis in a humanized mouse model

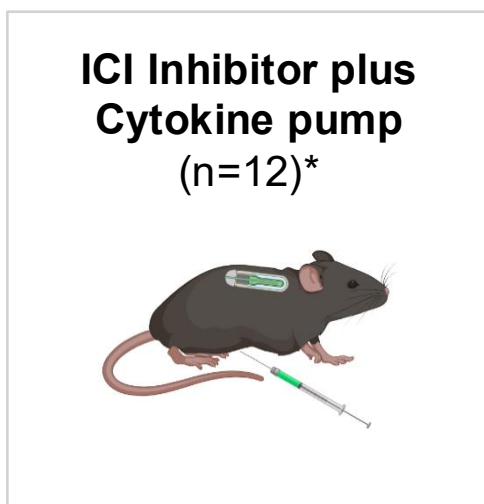
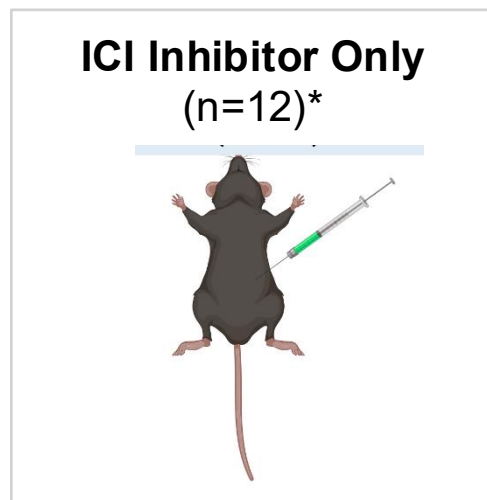
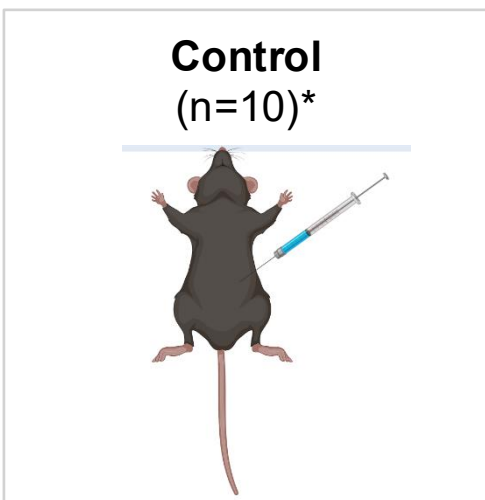
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- Humanized PD-1/PD-L1 mouse model reproduced key features of ICI-associated nephritis
- ICIs increased renal CD4⁺/CD8⁺ T-cell infiltration and inflammatory cytokine expression
- TNF- α /IFN- γ co-stimulation worsened kidney inflammation and injury
- TNF- α blockade reduced nephritis, inflammatory cytokines, and T-cell infiltration
- scRNA-seq identified immune pathways and therapeutic targets supporting TNF- α inhibition as a potential preventive strategy

Methods: Humanized PD-1/PD-L1

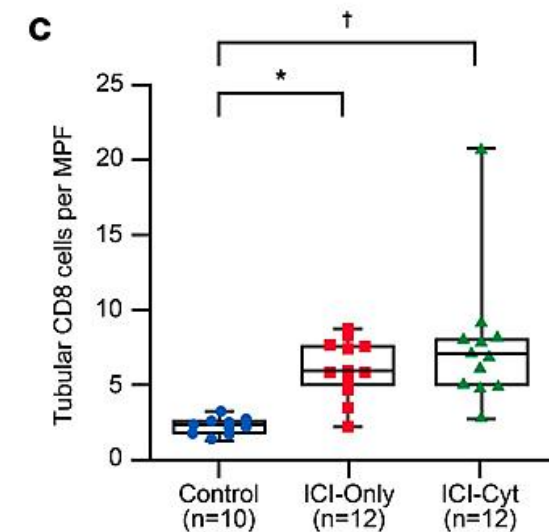
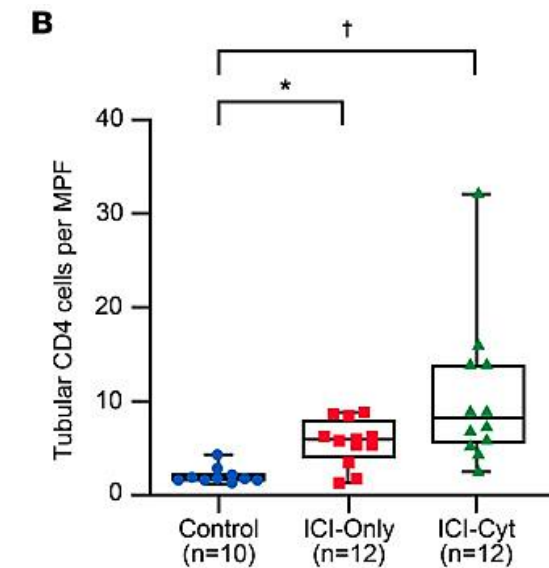
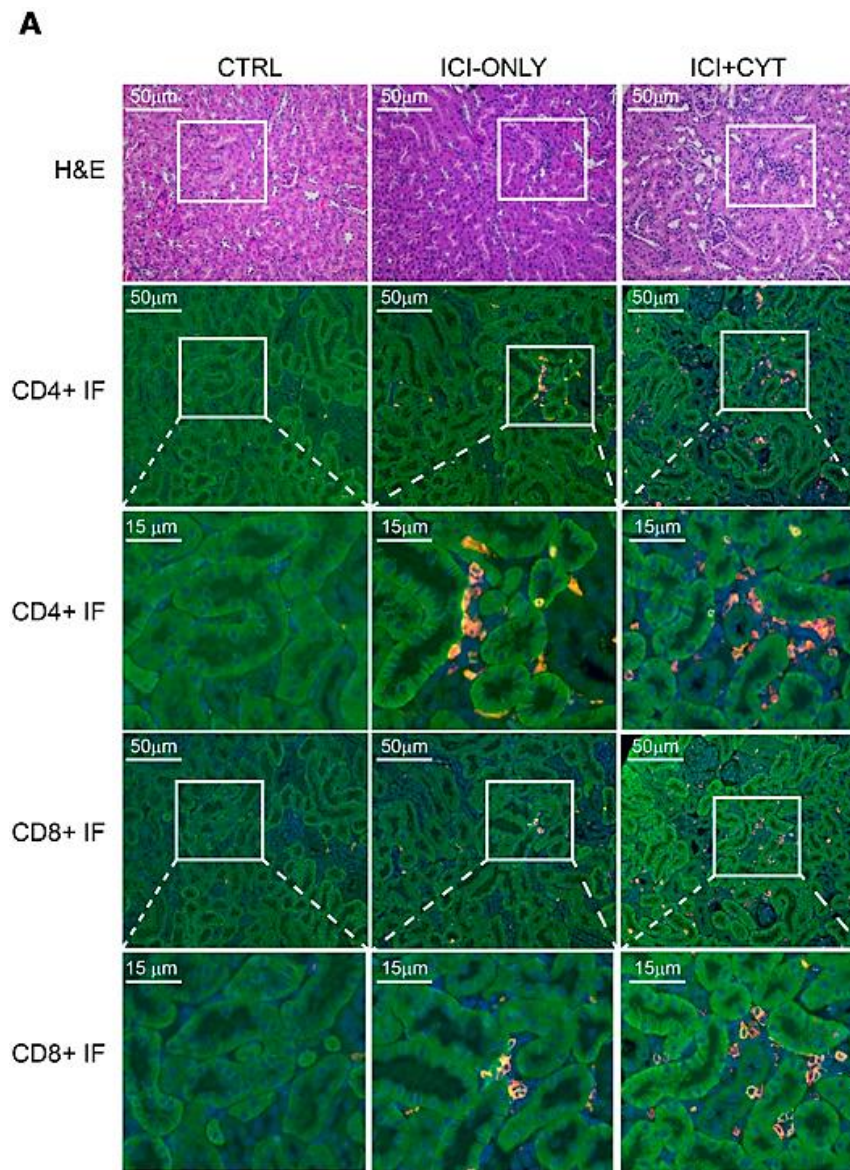


Control
Saline

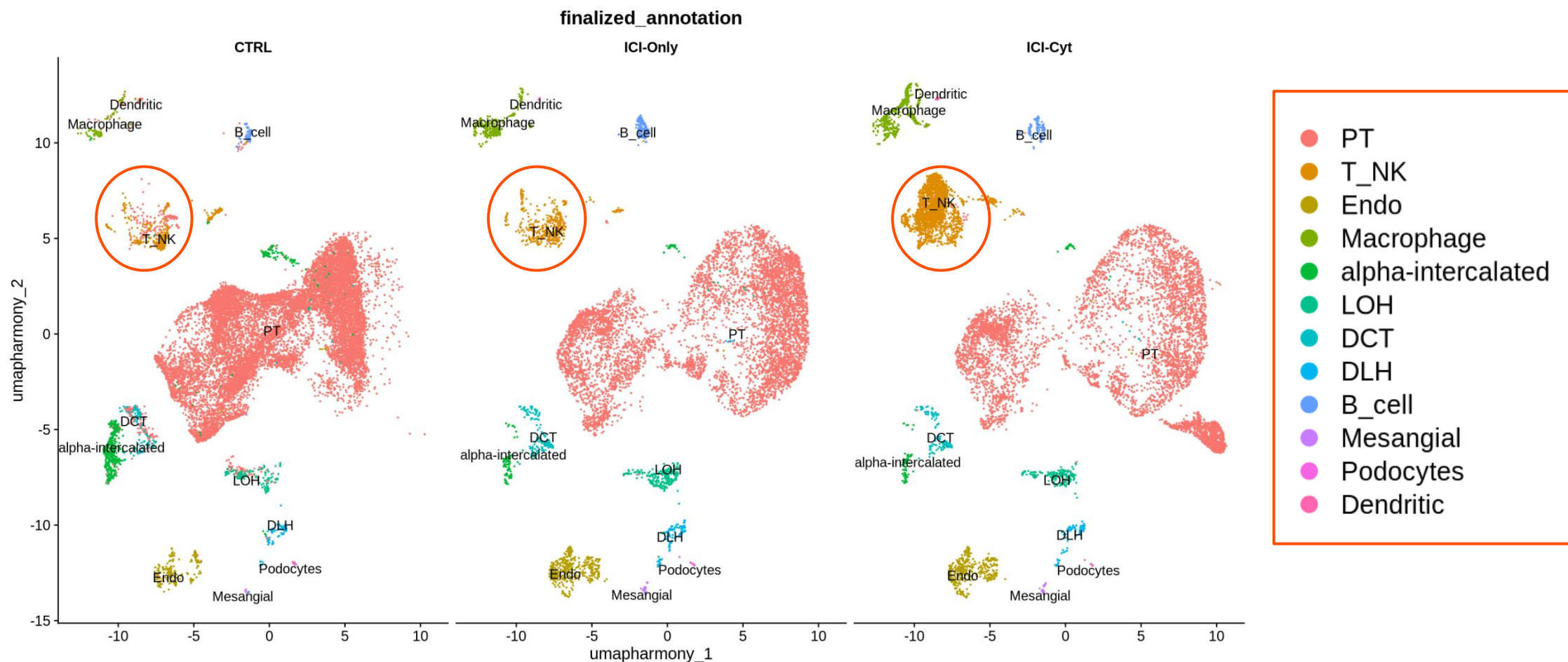
ICI-Only
Pembrolizumab plus anti-mouse-CTLA-4

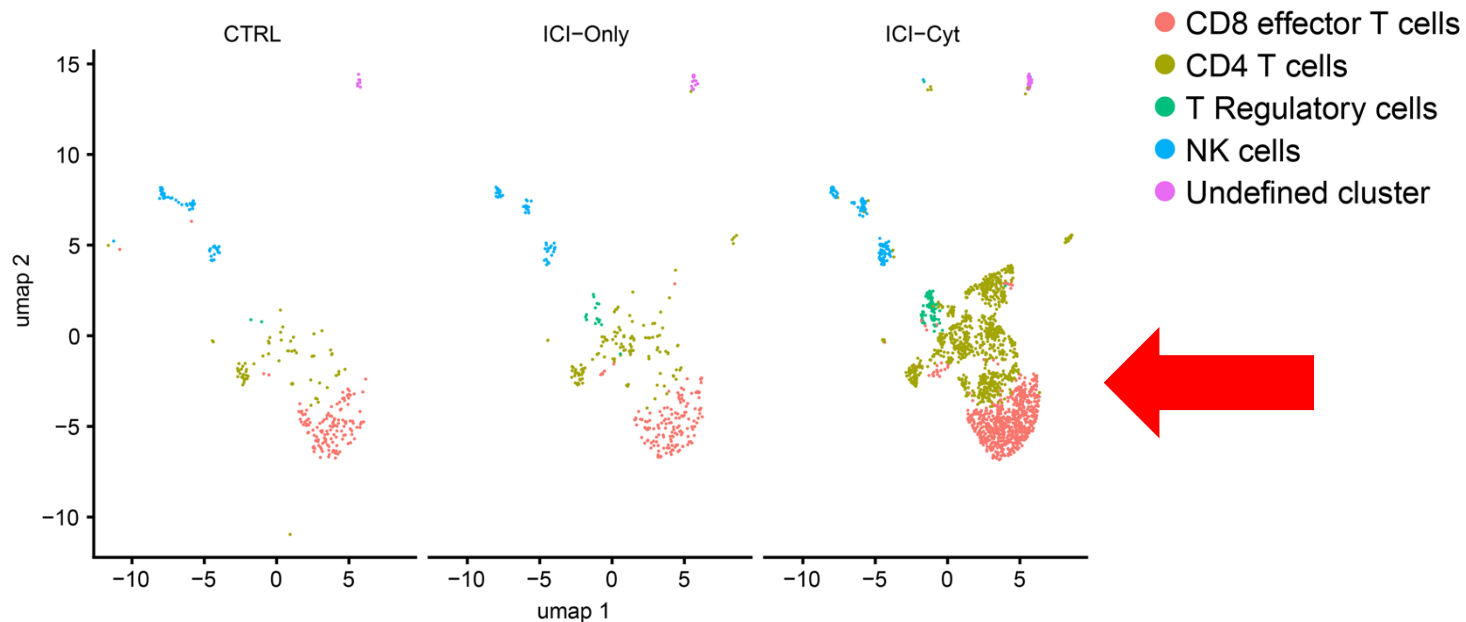
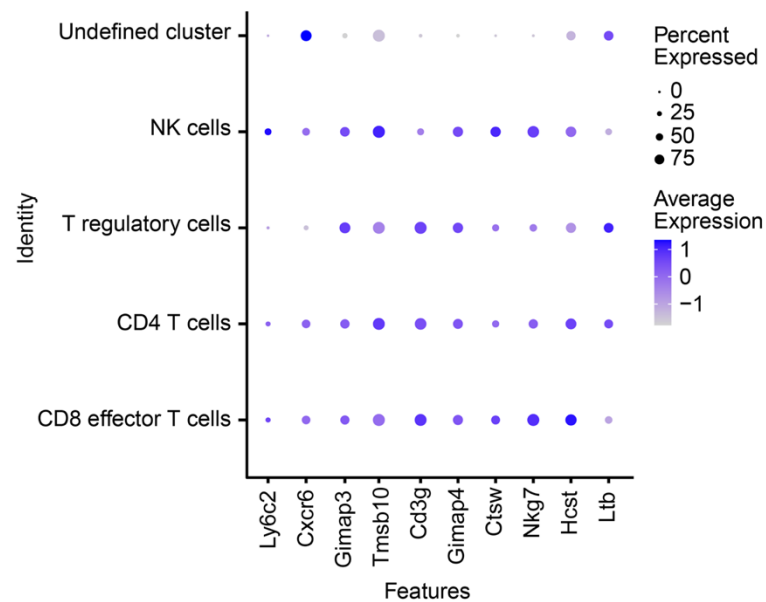
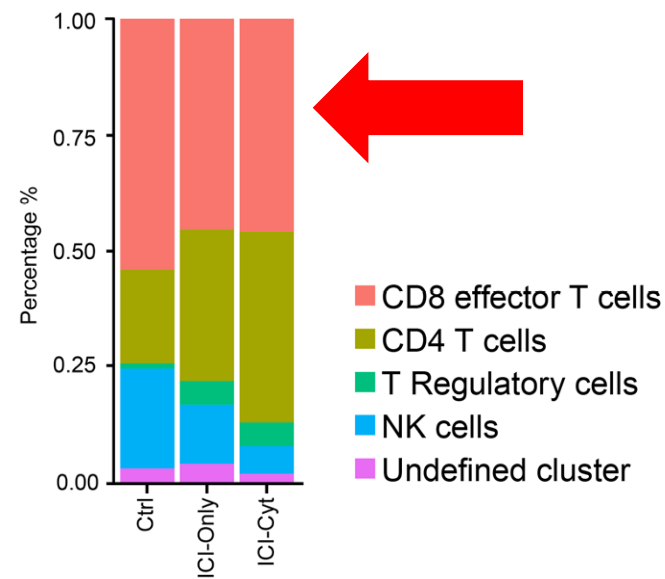
ICI-Cyt
ICIs plus Cytokine Pump (TNF- α and IFN- γ)

CD4+ and CD8+ Tubular T Cell Number by Immune Checkpoint Inhibitor Treatment Regimen

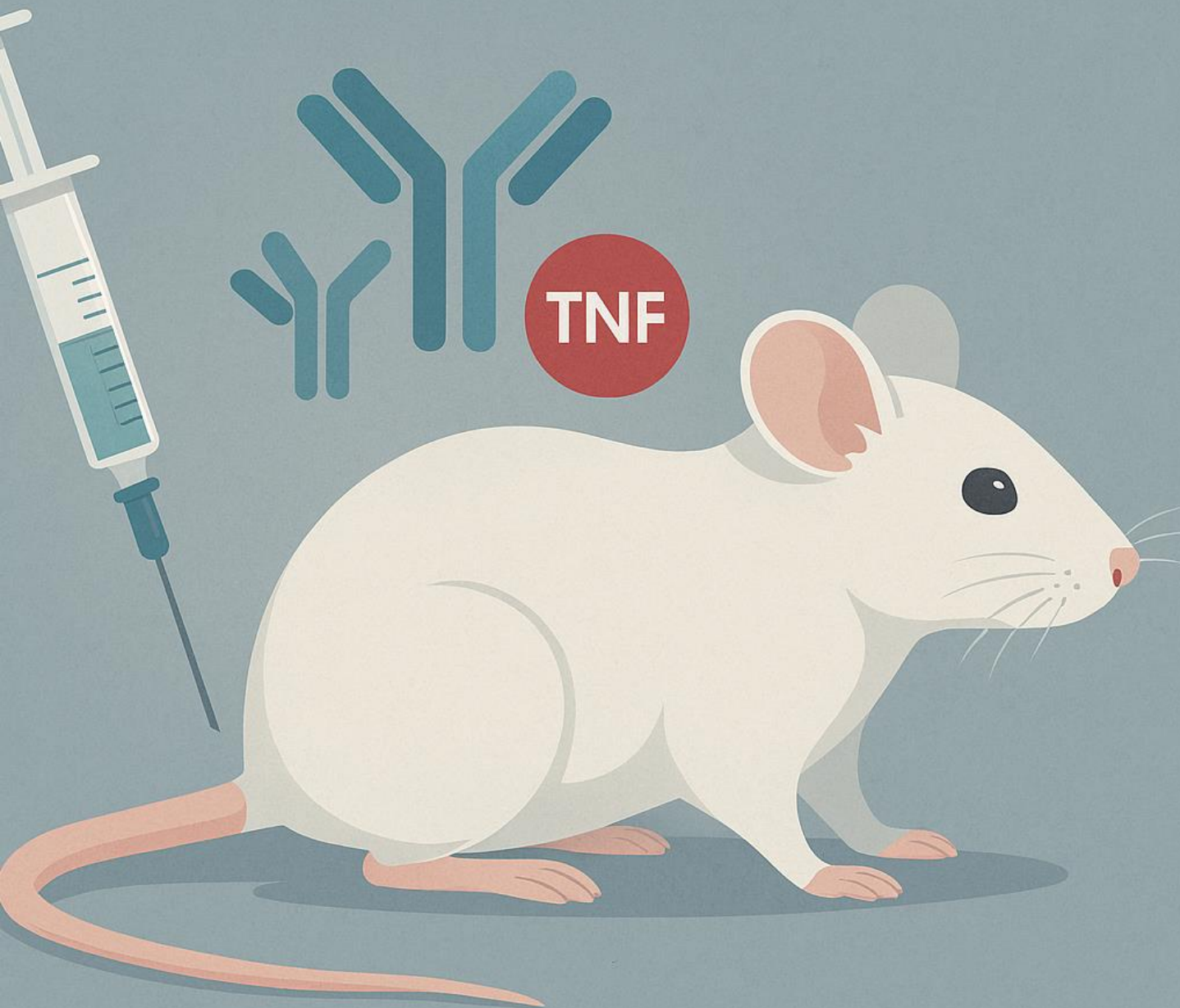


Treatment-Dependent Changes in Kidney Cell Clusters Revealed by Single-Cell Transcriptomics



A**B****C**

Single-cell Transcriptomic Profiling of Kidney Tissue Across Immune Checkpoint Inhibitor Treatment Groups



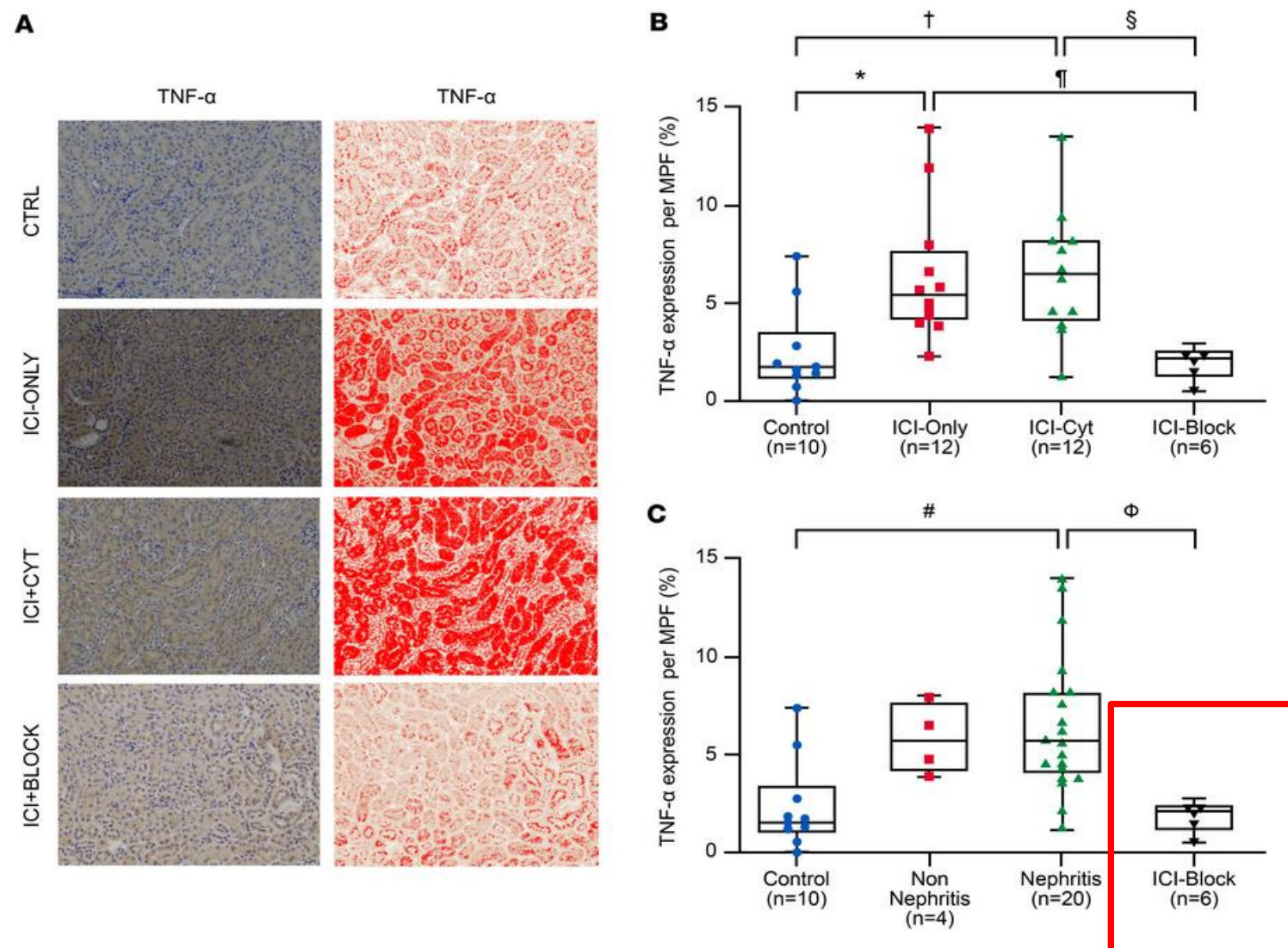
TNF- α Blockade Immune for Mitigation of ICI- associated Acute Interstitial Nephritis

Plasma Concentration of Cytokines by Treatment Group and Nephritis Status Including TNF- α Blockade

Cytokine (pg/mL)	Control	ICI-only	ICI-Cyt	ICI-block	P
pIL-6	5.91 (1.18, 13.38)	89.39 (31.49, 189.12)A	45.55 (19.54, 206.12)B	10.71 (4.75, 33.43)	0.002
pTNF- α	4.93 (3.20, 12.22)	912.52 (304.49, 8430.90)A,C	1250.64 (418.81, 9644.14)B,D	12.37 (4.62, 20.49)	<0.001
pMCP-1	53.00 (33.62, 77.28)	1878.07 (1111.09, 4366.45)A†	2225.60 (1342.33, 3469.33)B,D	107.15 (80.40, 185.97)	<0.001
Cytokine (pg/mL)	Control	Nonnephritis	Nephritis	ICI-block	P
pIL-6	5.91 (1.18, 13.38)	36.45 (11.70, 125.47)	69.99 (30.14, 208.58)E	10.71 (4.75, 33.43)	0.001
pTNF- α	4.93 (2.36, 12.82)	714.16 (307.52, 9320.60)F	1061.26 (51.66, 10000.00)E,G	12.37 (4.62, 20.49)	0<.001
pMCP-1	53.00 (33.62, 77.28)	1790.42 (1179.22, 5351.43)F,H	2099.01 (1212.37, 3469.33)E,G	107.14 (80.40, 185.97)	<0.011

ICI, immune checkpoint inhibitor; p, plasma. Summary statistics for nonnormal distributed samples reported median (IQR), P values derived from Kruskal-Wallis followed by Dunn's multiple-comparison test for post hoc analysis. P values in bold denote statistical significance at the 0.05 α level. AP < 0.05 for group ICI-Only versus Control in post hoc test adjusted for multiple comparisons. BP < 0.05 for group ICI-Cyt versus Control in post hoc test adjusted for multiple comparisons. CP < 0.05 for group ICI-Only versus ICI-Block in post hoc test adjusted for multiple comparisons. DP < 0.05 for group ICI-Cyt versus ICI-Block in post hoc test adjusted for multiple comparisons. Nephritis groups: EP < 0.05 for group Nephritis versus Control in post hoc test adjusted for multiple comparisons. FP < 0.05 for group Non-Nephritis versus Control in post hoc test adjusted for multiple comparisons. GP < 0.05 for group Nephritis versus ICI-Block in post hoc test adjusted for multiple comparisons. HP < 0.05 for group Non-Nephritis versus ICI-Block in post hoc test adjusted for multiple comparisons.

TNF- α Expression in Renal Tubular Compartments During ICI and TNF- α Blockade

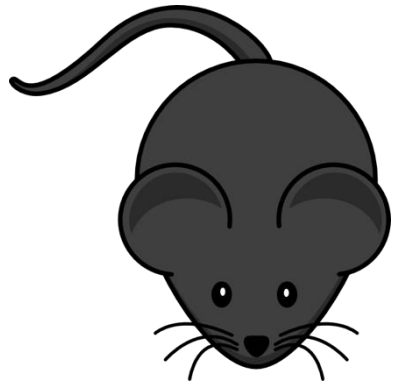


Summary

- ICI therapy promotes kidney inflammation with increased CD4⁺ and CD8⁺ T-cell infiltration
- Inflammatory cytokines, especially TNF- α and IFN- γ , contribute to ICI-associated nephritis
- Blocking TNF- α reduced kidney inflammation and inflammatory cytokine signaling
- The humanized PD-1/PD-L1 mouse model reproduces key features of ICI nephritis and may help test strategies to prevent kidney toxicity

Pitfalls

- Incomplete recapitulation of the human immune system
- Cytokine-enhanced inflammatory environment may overestimate disease severity
- Primarily reproduces AIN rather than the full spectrum of ICI nephrotoxicity (not GNs, etc)
- Short-term model (up to 8 weeks may not reflect chronic ICI exposure)



Translational Insights

Mouse findings informing humans

- Biomarkers
- Urinary cytokines
- CXCL9
- CXCL10
- IFN signatures

Potential therapies

- Steroids
- TNF blockade
- IL-17 inhibition
- Regulatory T-cell approaches
- Precision immunomodulation



Limitations of Murine Models

- Different immune repertoire
- Different microbiome
- Short lifespan
- Artificial disease induction
- Limited diversity
- Difficulty reproducing human drug exposure
- Models are not perfect but are useful

Future Directions

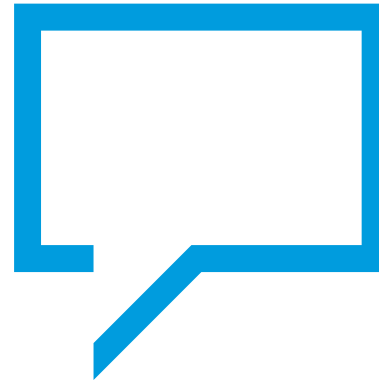
- Better ICI-associated AIN models
- Humanized immune systems
- Biomarker validation
- Precision therapeutics
- Reverse translation from patients to mice

Take-Home Messages

- AIN is primarily an immune-mediated disease
- Mouse models reveal mechanisms impossible to study in humans
- T-cells and innate immune cells cooperate to drive renal injury
- Murine studies are guiding biomarker and therapeutic development
- Continued refinement of models will improve translation to patient care

Thank you

**Questions
& answers**



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