



Animal Model Workshop

Autologous Humanized PDX-TIL Models for Precision Medicine in RCC

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Kidney Cancer Program

UT Southwestern Medical Center

September 11-13, 2025

Session #: 7 Humanized Models

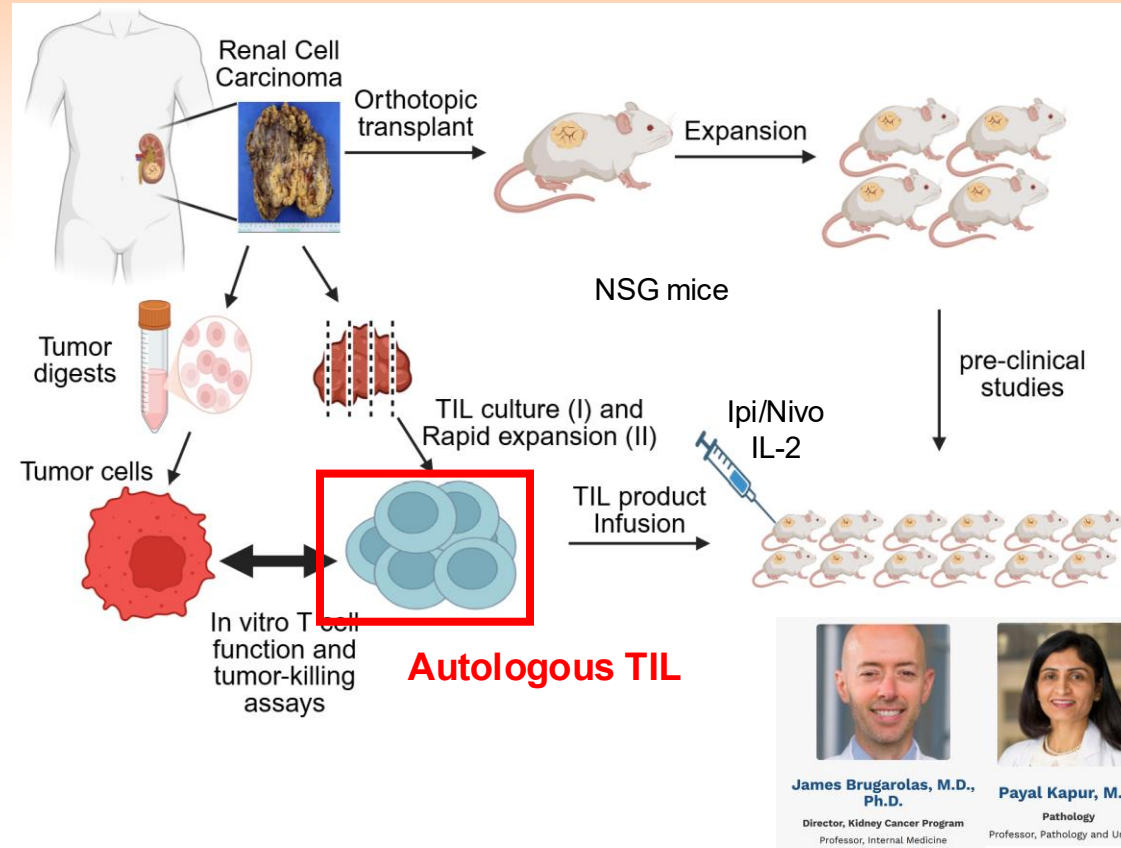


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Patient-Matched Autologous PDX/TILs Model development



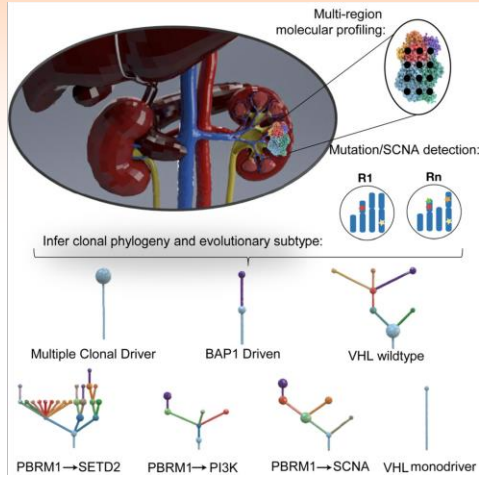
Pros:

- Preserves physiological relevance
- Captures patient-specific immunogenicity
- Enables personalized therapy testing
- Improves translational predictability
- Supports biomarker discovery
- Allows mechanistic studies of resistance

(Supported by Drs. Brugarolas and Kapur)

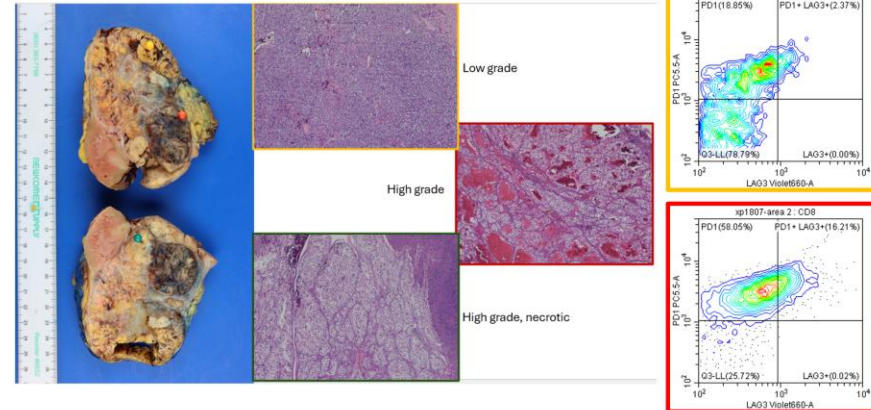
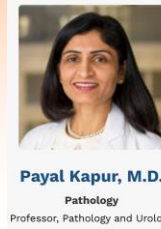
Exploring Intra-Tumor Heterogeneity of TILs

Clinicopathological Characteristics



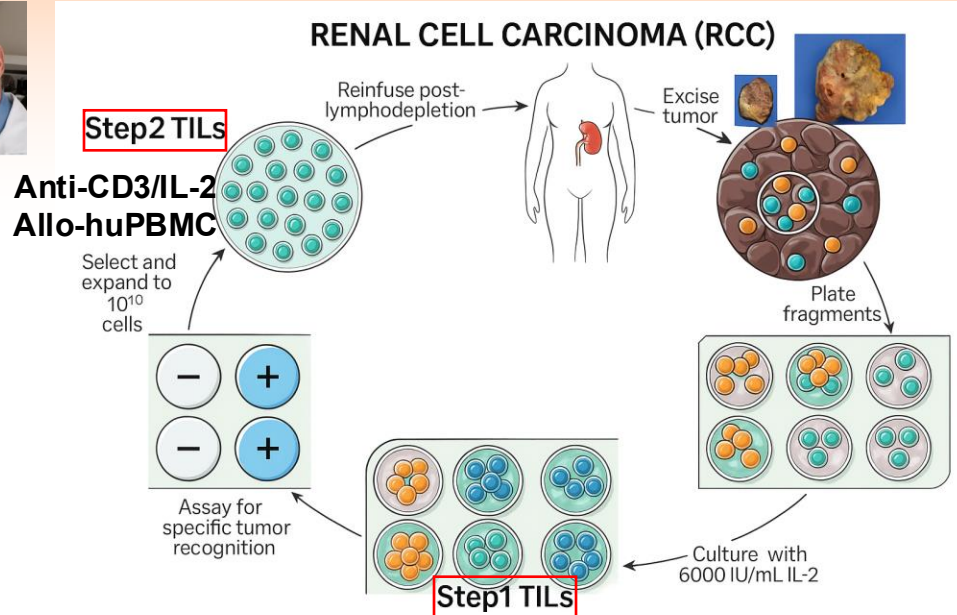
Turajlic et al., Cell, 2018

Variable	Category	Measure, N (%)
Total	Patients	13 (100.0)
Specimen	Kidney, Left	5 (38.5)
	Kidney, Right	8 (61.5)
Diagnosis	ccRCC	12 (92.3)
	Unclassified RCC	1 (7.7)
Size (cm)	Median (IQR)	10.5 (9.2–13.2)
	G2	1 (7.7)
	G3	7 (53.8)
Grade	G4	5 (38.5)
	N	11 (84.6)
	Y	2 (15.4)
Sarcomatoid	N	10 (83.3)
	Y	2 (16.7)
Rhabdoid	N	12 (92.3)
	Y	1 (7.7)
Necrosis	N	13 (100.0)
	pT3	6 (46.2)
	pNx	6 (46.2)
pT stage	pN0	1 (7.7)
	pN1	4 (30.8)
	pMx	3 (27.3)
Metastasis	pM1	8 (72.7)
	Loss	8 (88.9)
	Intact	1 (11.1)
BAP1 IHC	Positive	1 (11.1)
	Negative	
CA IX IHC	Positive	
	Negative	

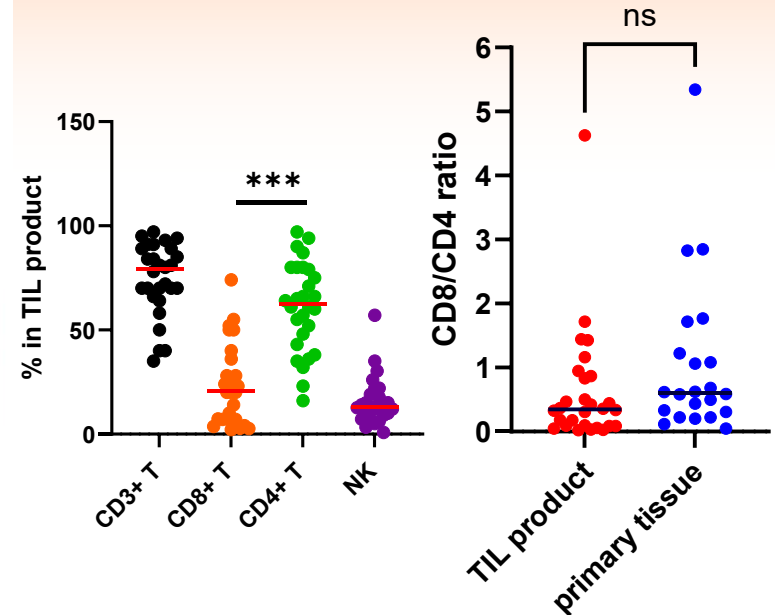


Summary: A total of 28 TIL lines were generated from 13 patients, and 5 PDX/TIL mouse lines were established.

Schematic of Tumor Fragment Culture and TIL expansion



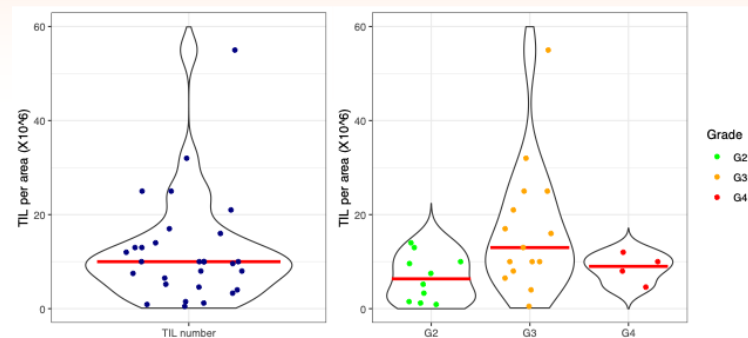
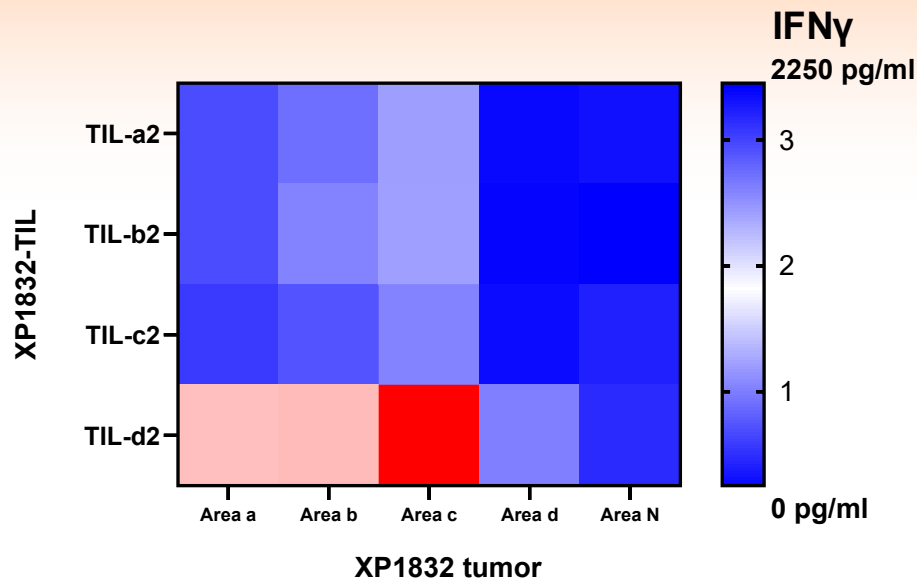
Modified from SAR, Science, 2015



* TIL products maintain CD8/CD4 ratios in tumor tissue.



Distinct Tumor Regions Yield TILs with Differential Antitumor Activities



>50% of the samples yield 1×10^7 or more TILs and correlated with presence of aggressive features in flanking sections

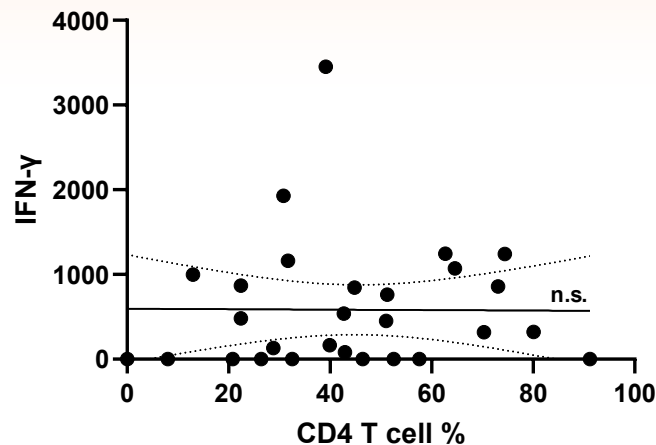
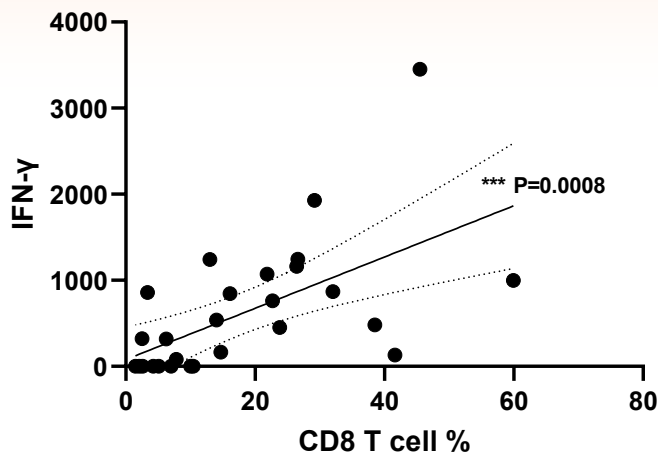
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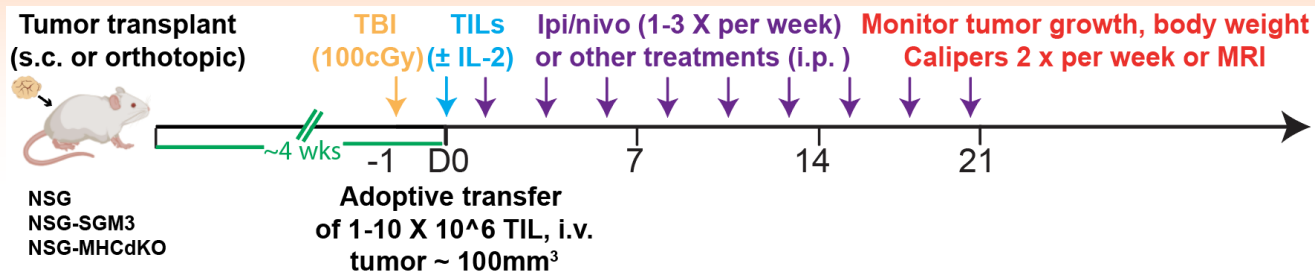
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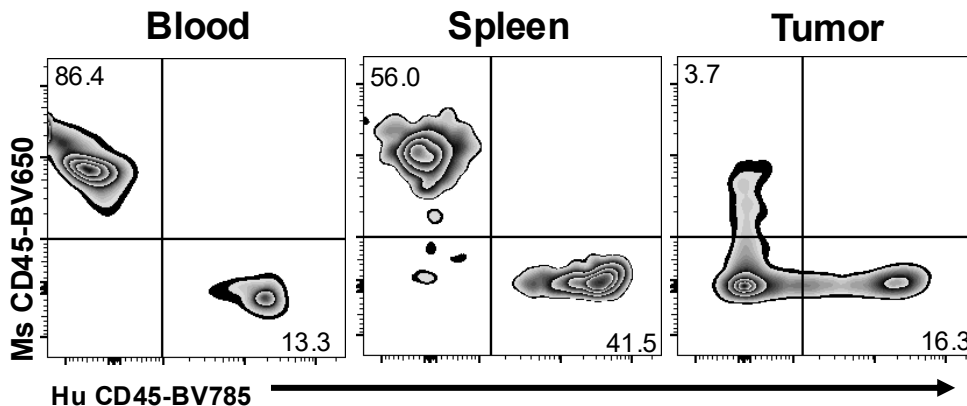
CD8⁺ T Cell Numbers, but Not CD4⁺ T Cells, Correlate with Anti-Tumor Activity in TIL Products



Workflow and Characterization of Patient-Matched PDX-TIL Models



PDX-TIL Line: #5



Ipi/nivo Treatment Inhibited Tumor Growth and Prolonged Survival in PDX-TIL Models.

Patient:

Age: 75 Sex: female

Principle diagnosis:

Right sided clear-cell renal cell carcinoma,

Genomics:

Mutations: VHL pathogenic mutation (hallmark of ccRCC); SETD2 and ATM pathogenic mutations; BAP1 variant.

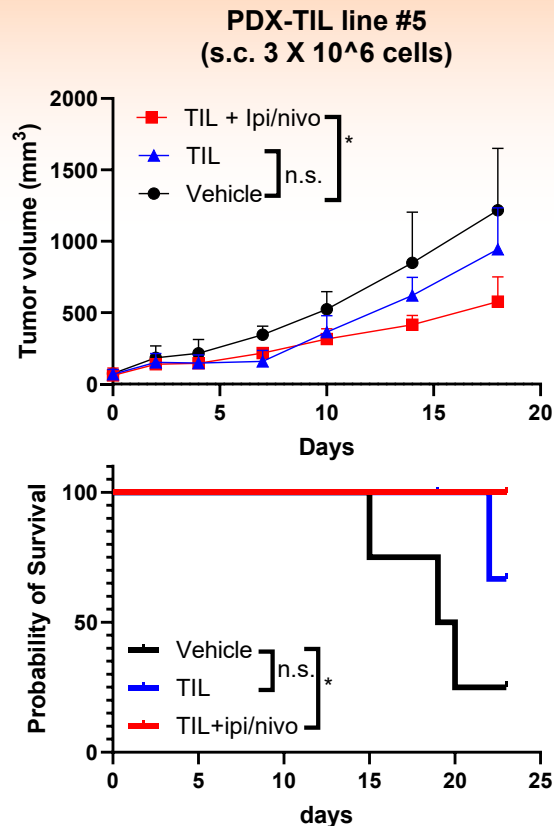
Microsatellite stable

Tumor Mutational Burden: 3 mutations/Mb
(quiet mutational landscape)

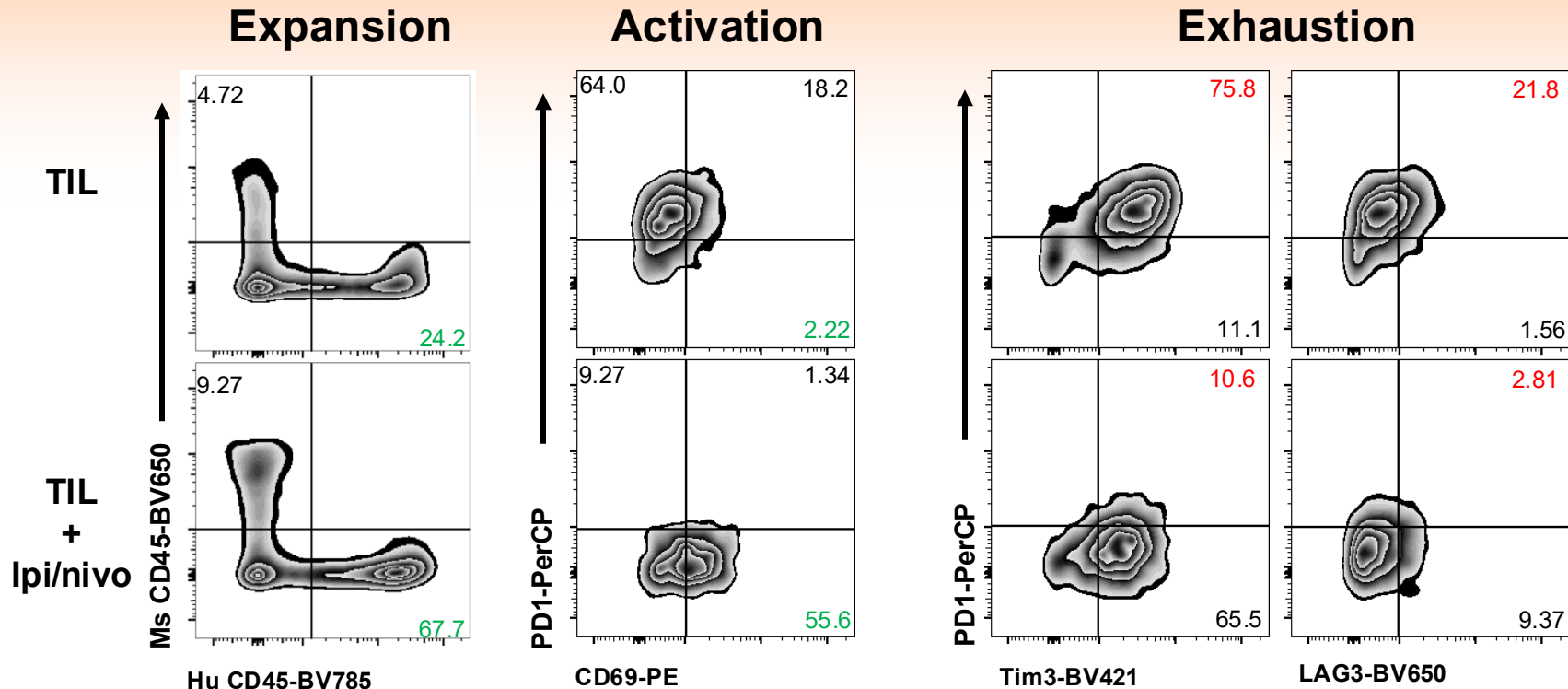
Treatment History:

9/2024-Present: anti-PD1

currently no evidence of recurrence or residual disease.



Ipi/nivo treatment expanded tumor-infiltrating lymphocytes and promoted T cell activation in autologous PDX-TIL models.



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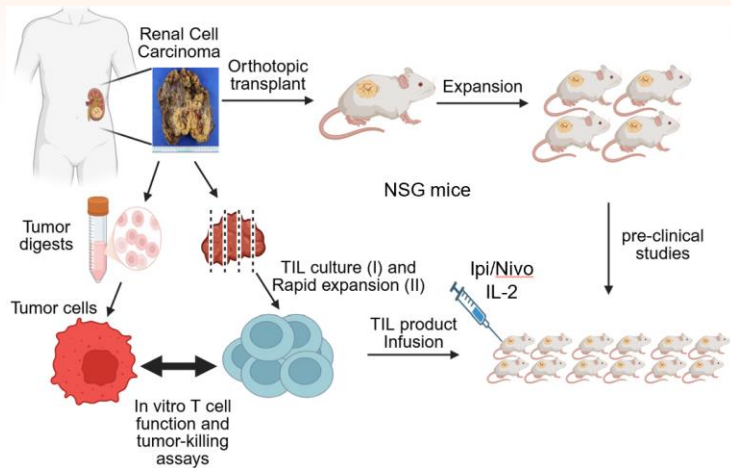


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Current Challenges

Autologous PDX/TILs models

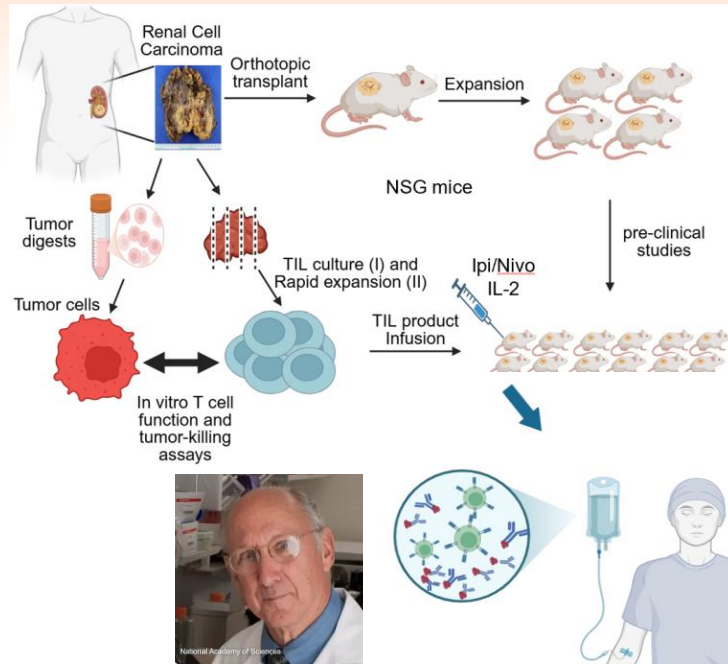


Cons:

- Limited cell number
- Expansion challenges
- Variable quality across patients
- Label- and time- intensive
- Model complexity and cost
- Immune compartment incompleteness
- Engraftment variability

Future Directions

Autologous PDX/TILs models



- Optimize TIL expansion protocols
- Broaden immune compartment reconstitution
- Humanized cytokine support
- Single-cell and spatial multi-omics integration
- High-throughput immunotherapy testing
- Gene editing of TILs
- Clinical correlation pipelines

“Super” TIL product for RCC

Acknowledgements

Yue Lab members:

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Angel Lopez
Aimee Hsu



Ning Cai, MD, PhD
Postdoc Researcher



Angel Lopez, B.S.
Research Technician



Aimee Hsu
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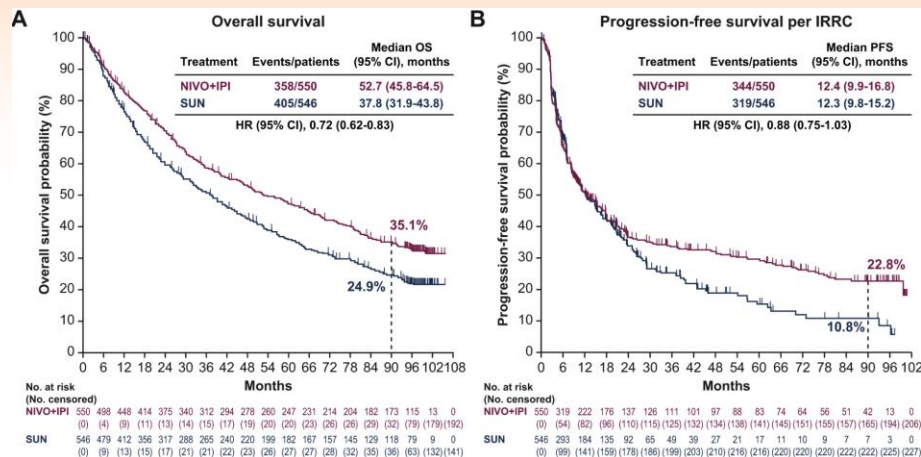
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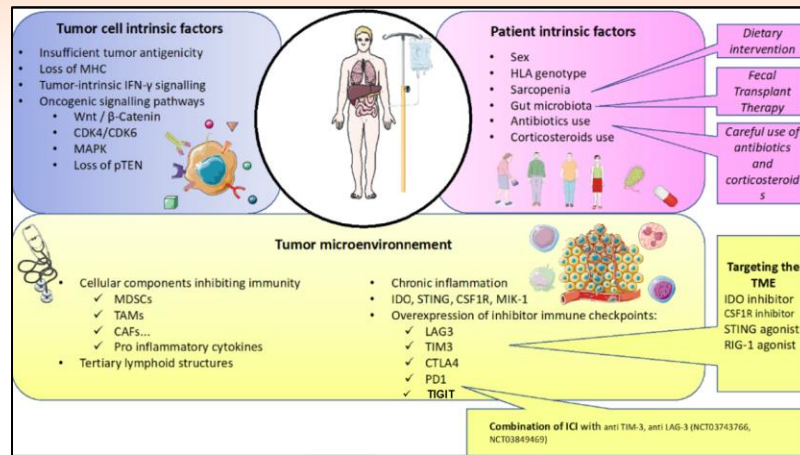


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Immunotherapy Resistance in Renal Cell Carcinoma



Tannir et al., Ann Oncol, 2024



Modified Cancer Drug Resistance, 2020

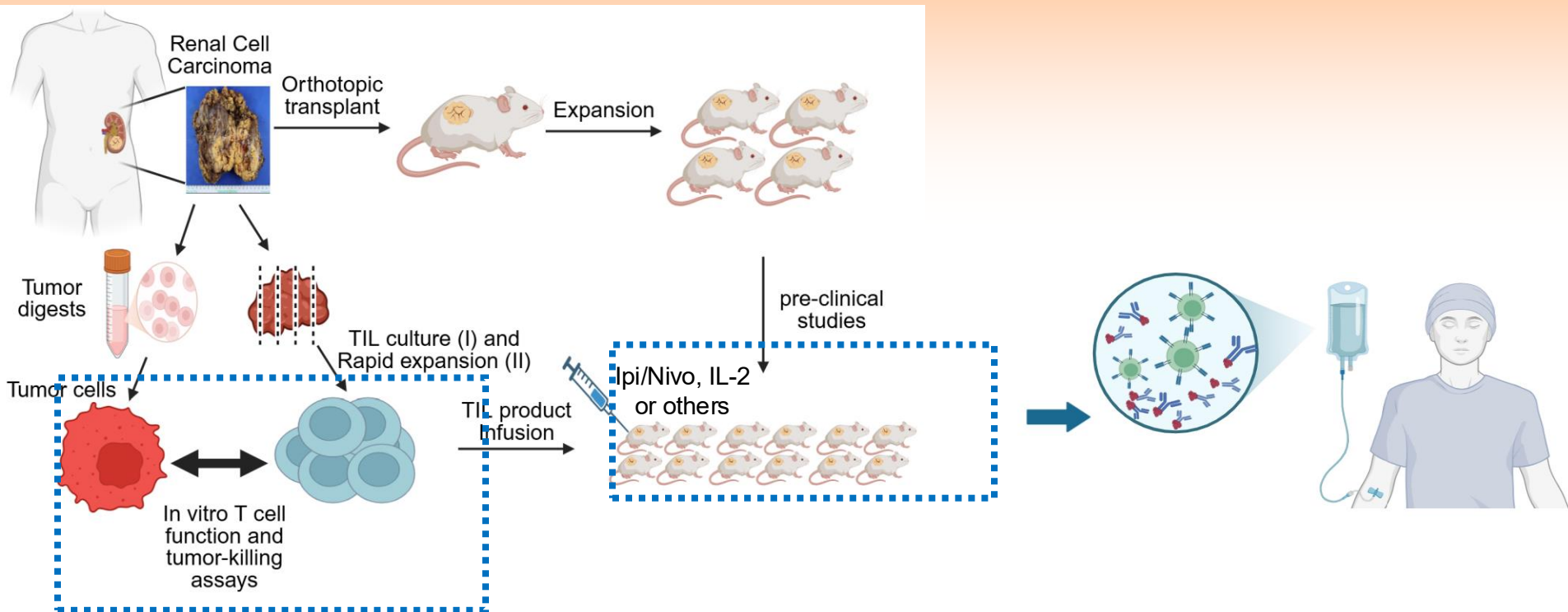
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Combining in vitro and in vivo immune assays for “super” TILs



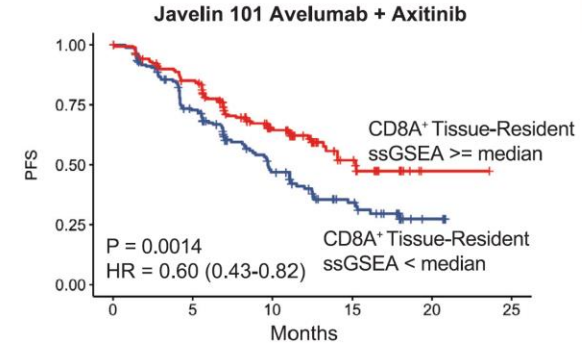
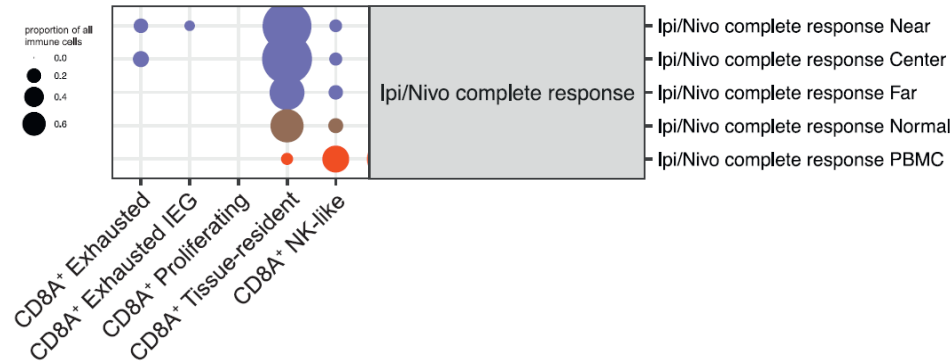
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Tumor-infiltrating CD8+ T cells markedly increased in patients responsive to immunotherapies



Krishna et al, Cancer Cell, 2021