



**ROGEL CANCER CENTER**  
MICHIGAN MEDICINE

# Evaluating TIME in lung cancer

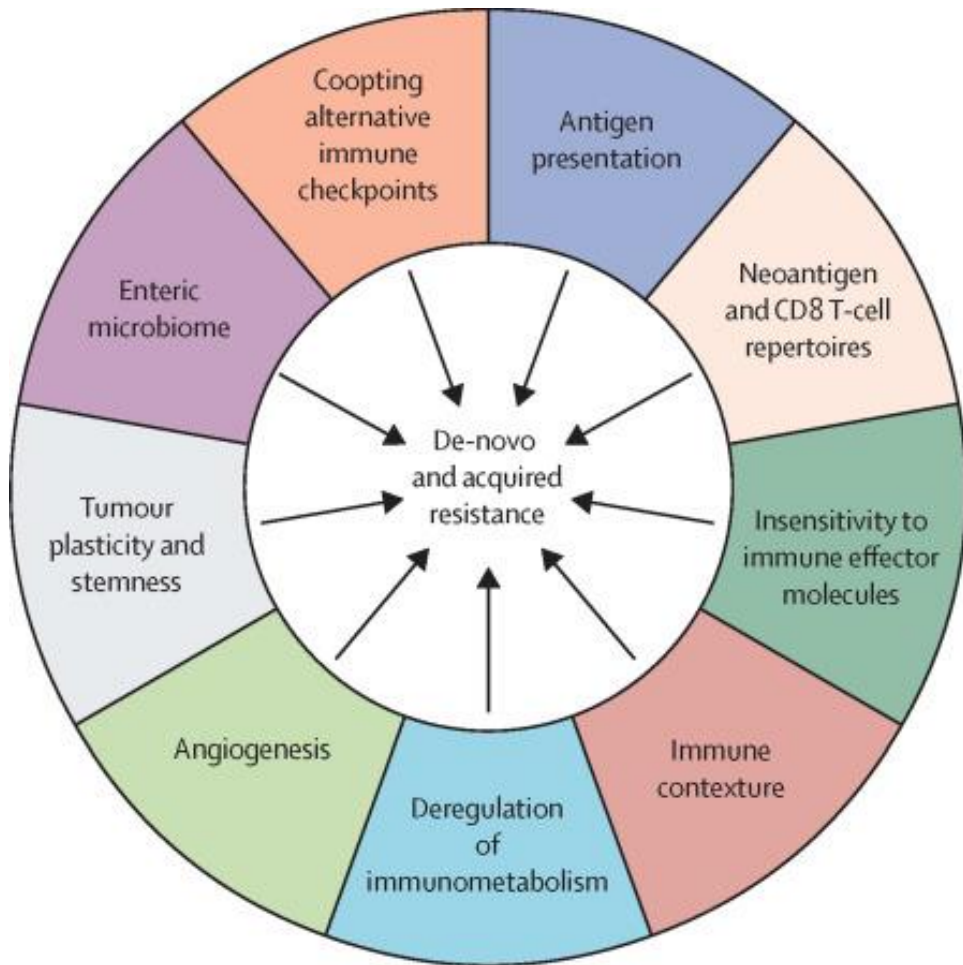
Rogel Cancer Center Basic Science Retreat 6-19-2019

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Center for Molecular Imaging (CMI),  
Rogel Cancer Center

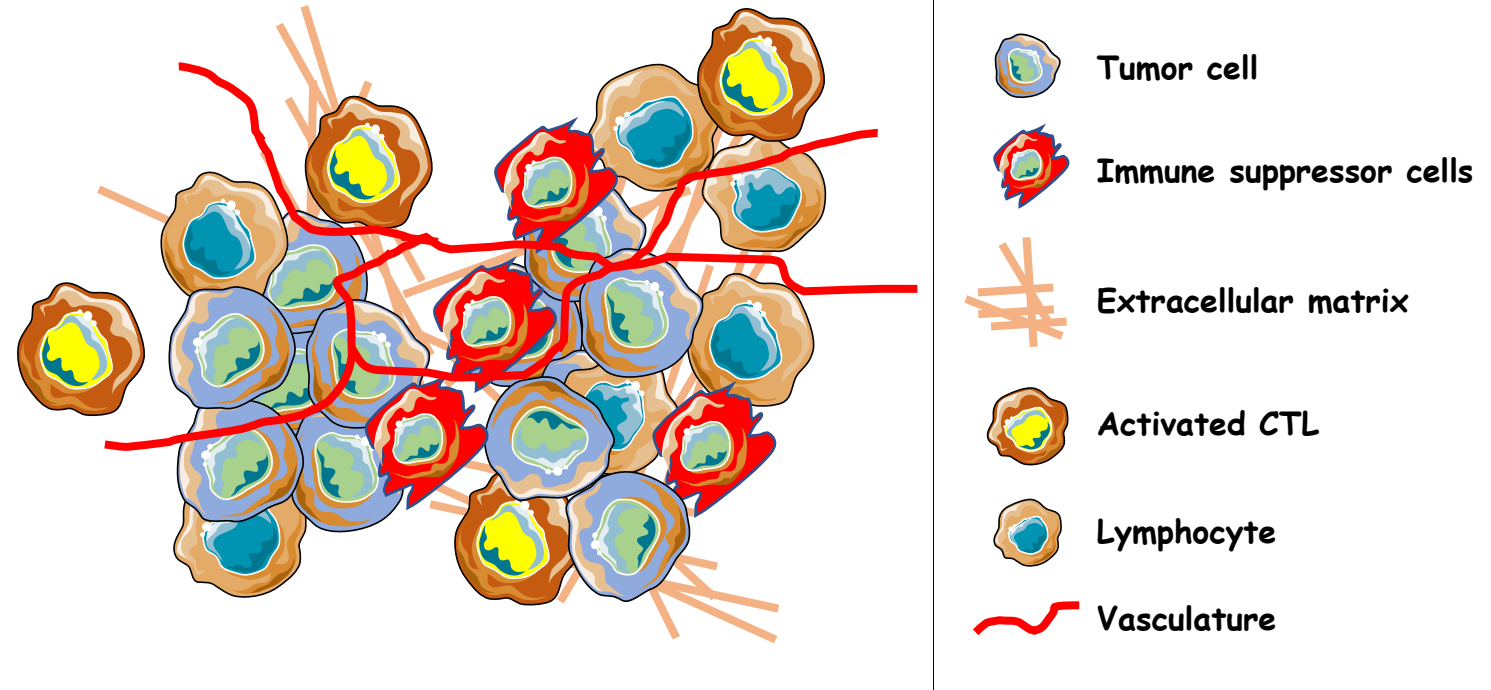


# Insight into the pathobiology of lung cancer by understanding the Tumor immune microenvironment (TIME)

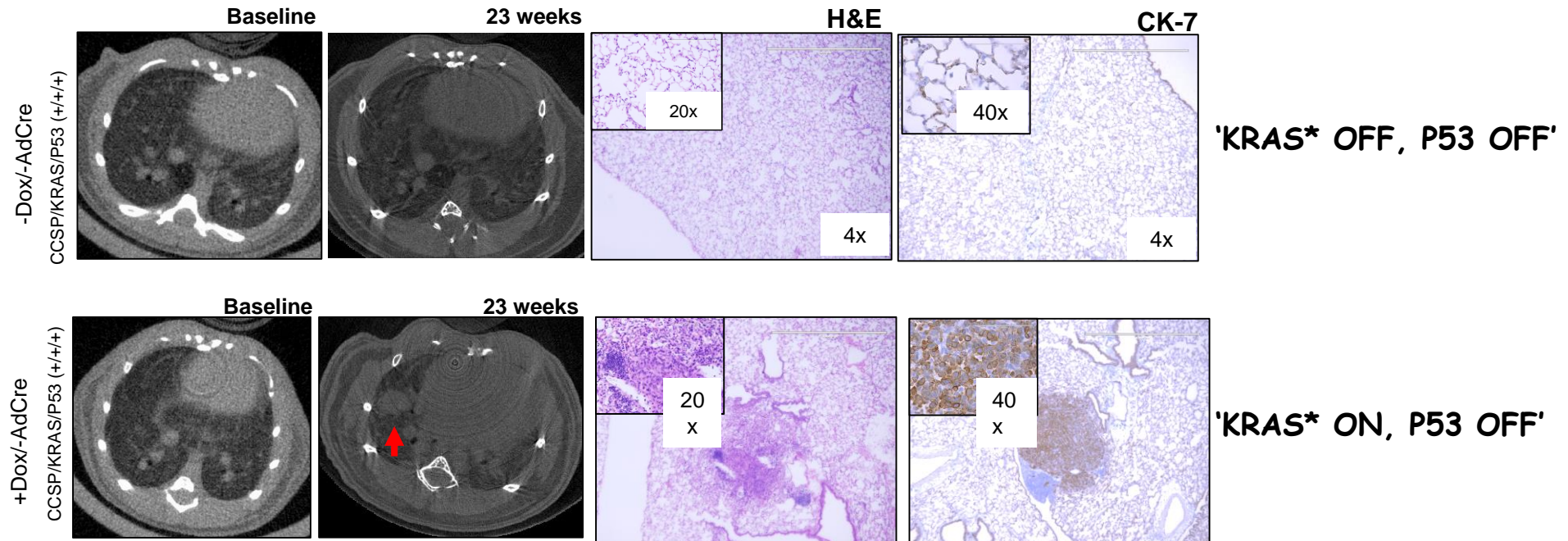
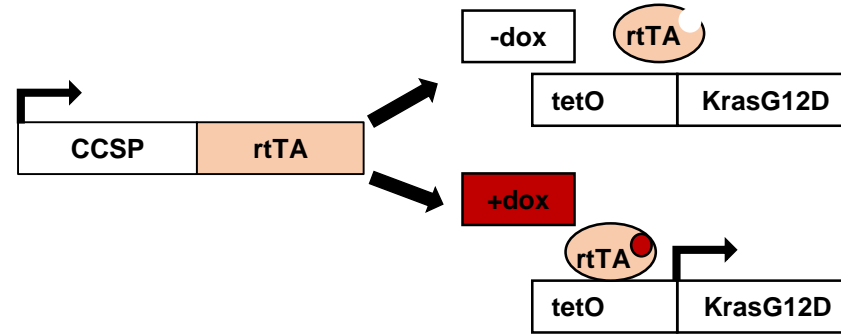


Enhancing efficacy of ICI therapy by understanding the immune contexture and immune metabolism

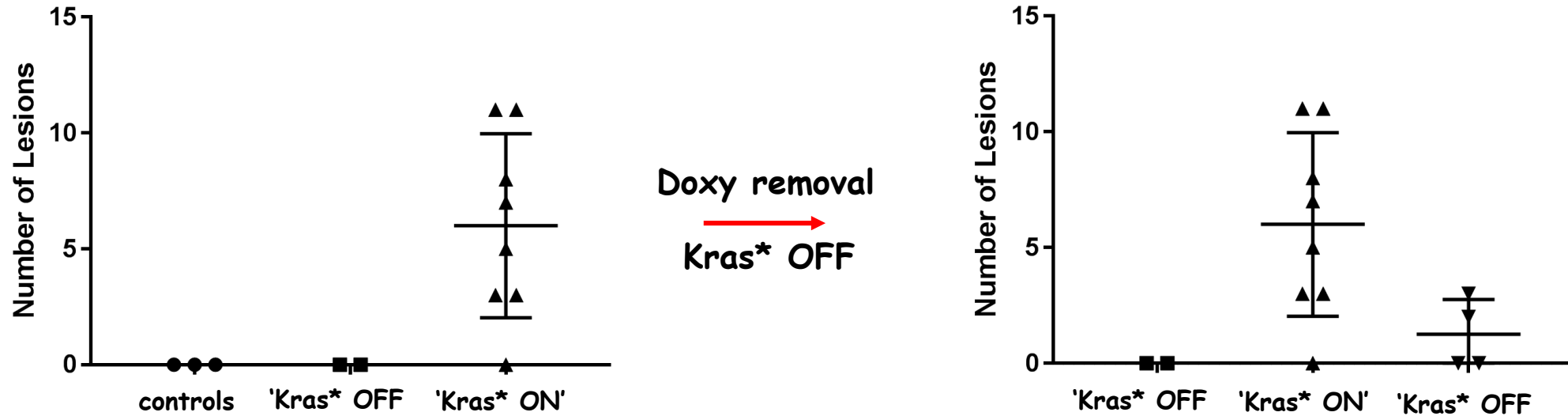
Differential response to Immunotherapy depends on the established tissue-specific microenvironment



# Inducible *Kras*\* lung cancer model

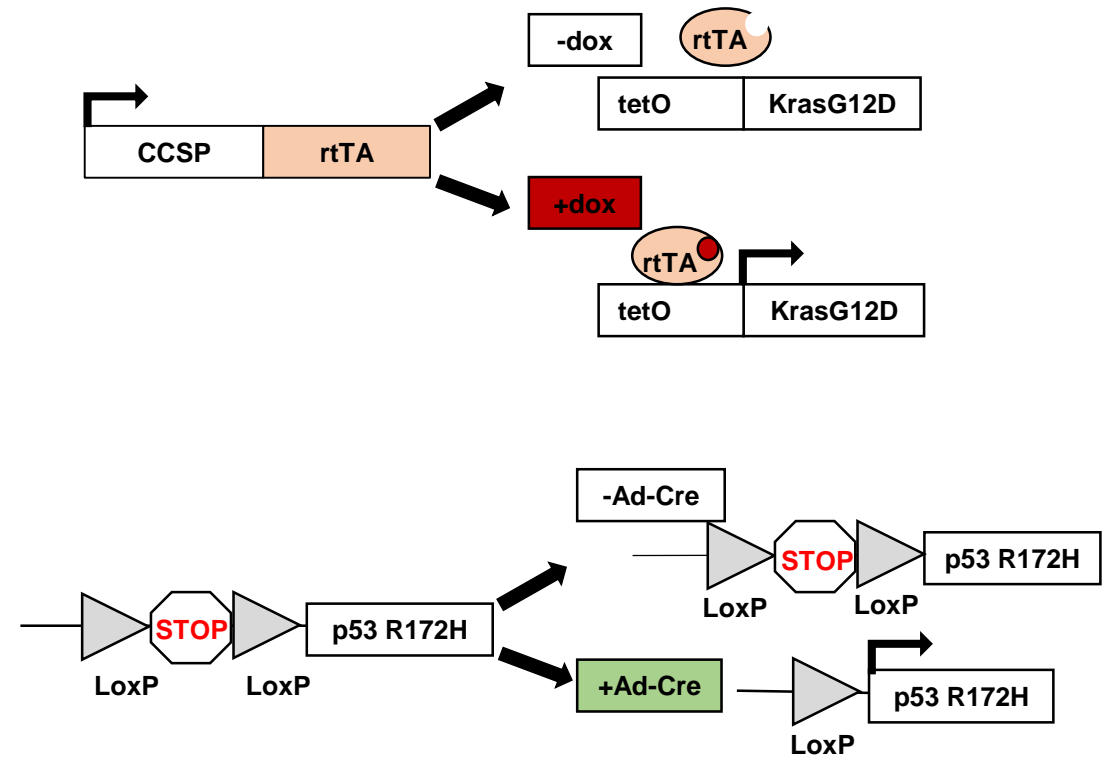
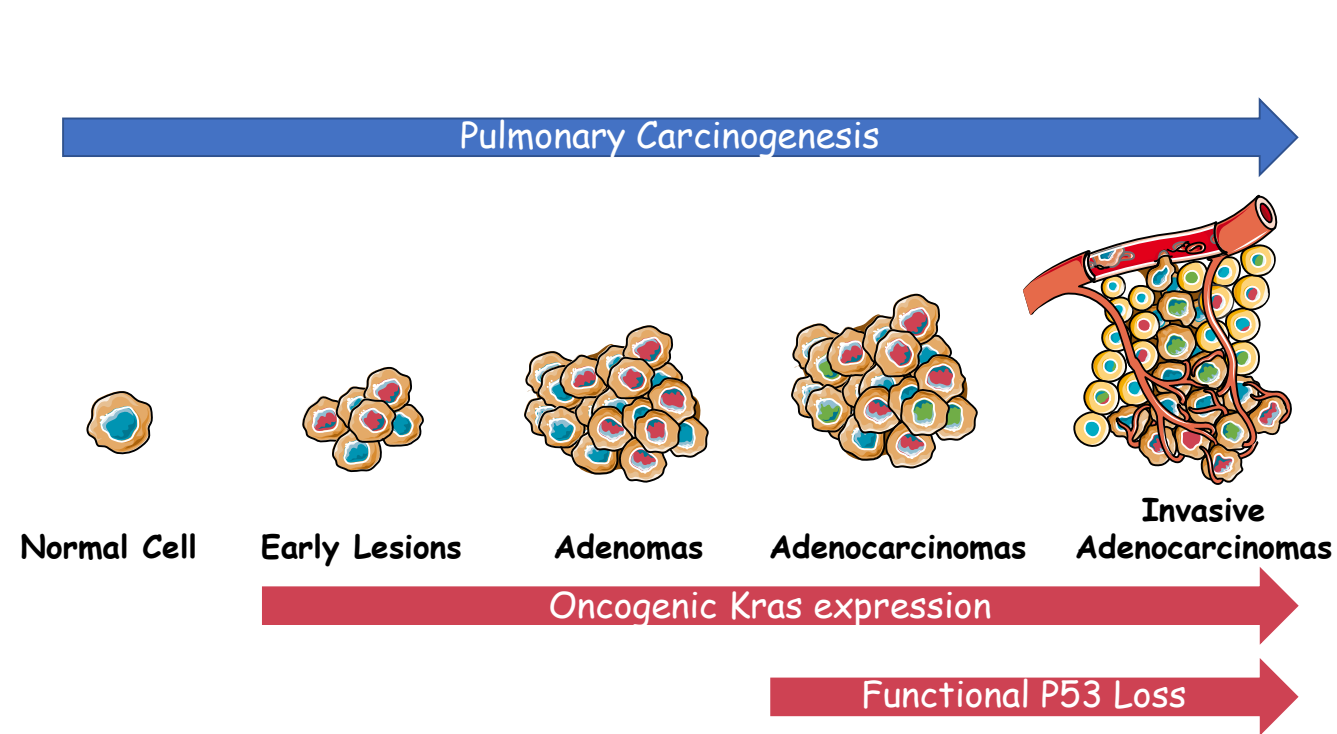


# Oncogenic Kras\* is required for tumor maintenance



Controls: single transgenic mice on doxycycline

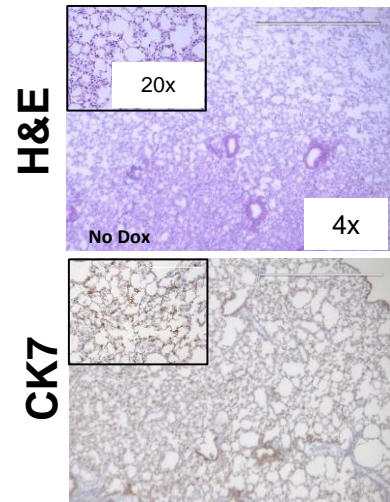
# Inducible *Kras*\* and mutant p53 lung cancer model



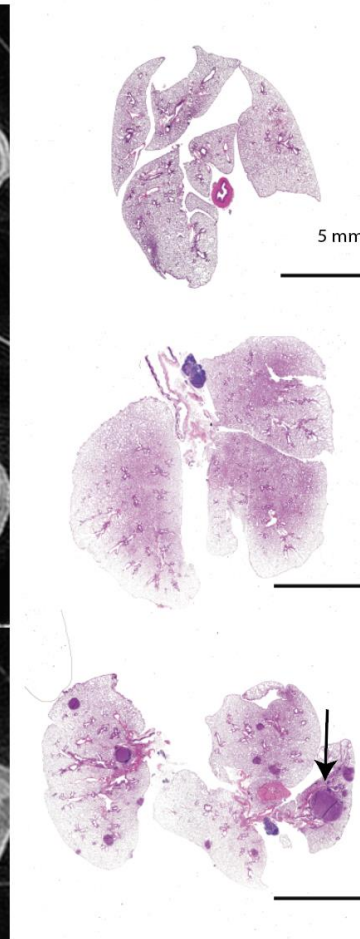
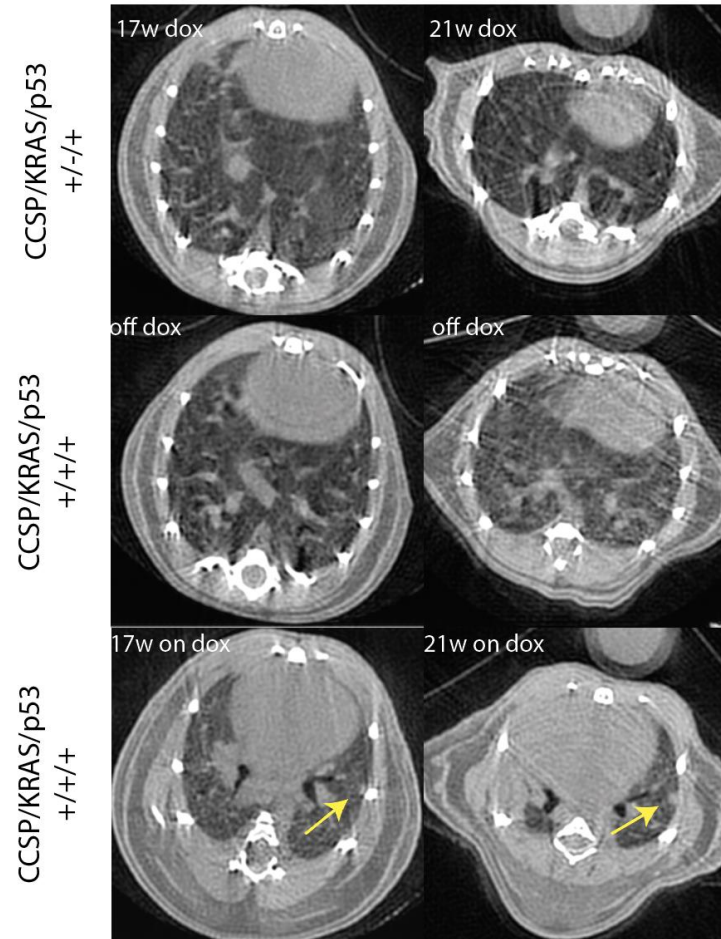
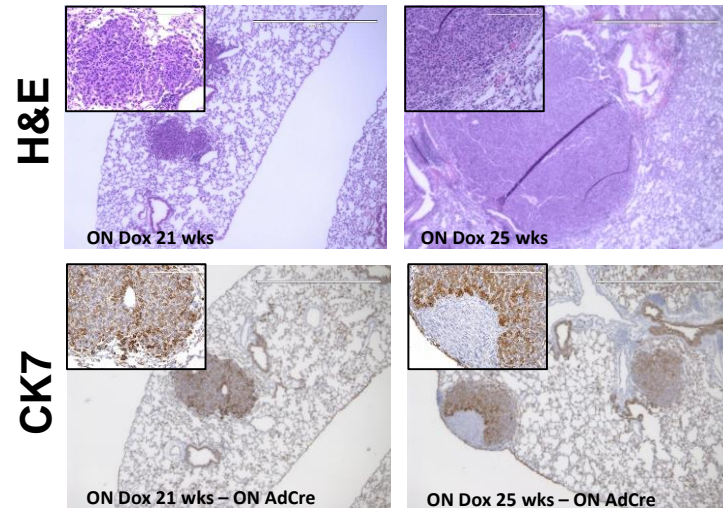


# Simultaneous activation of Kras\* and p53R172H leads to adenocarcinomas

'Kras\* OFF, P53 OFF'



'Kras\* ON, P53 ON'



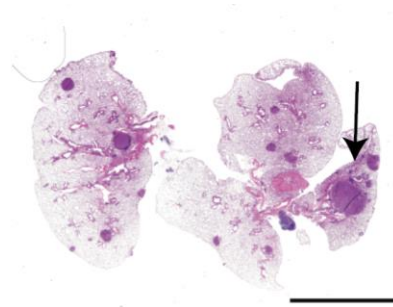
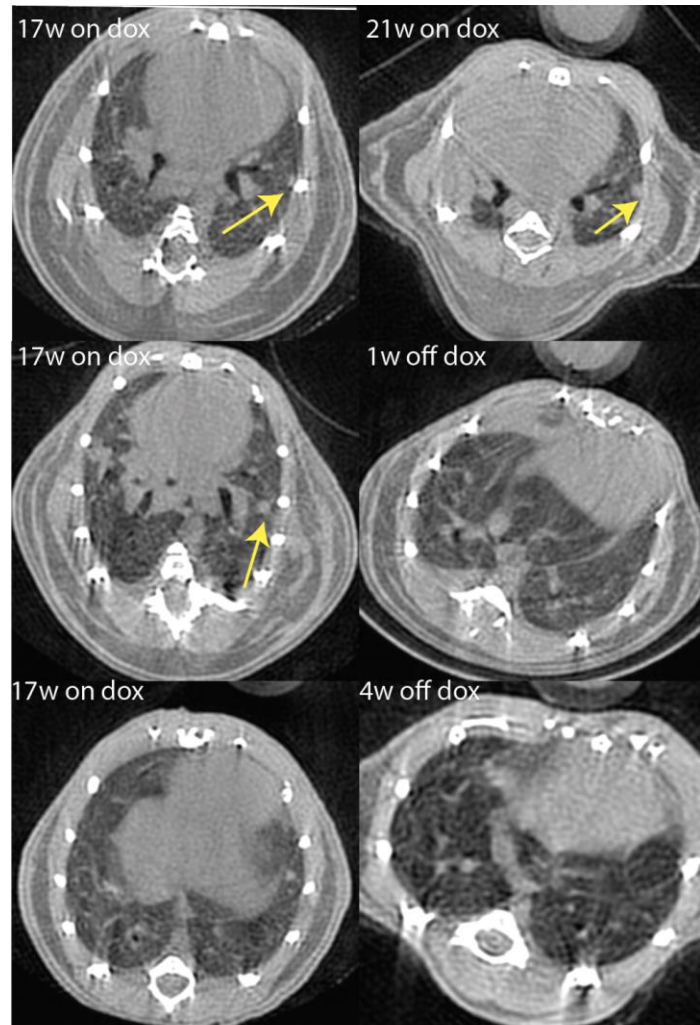
controls

'KRAS\* OFF, P53 OFF'

'KRAS\* ON, P53 ON'

Controls: single transgenic mice on doxycycline

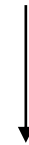
# Kras\* is required for tumor maintenance of adenocarcinomas



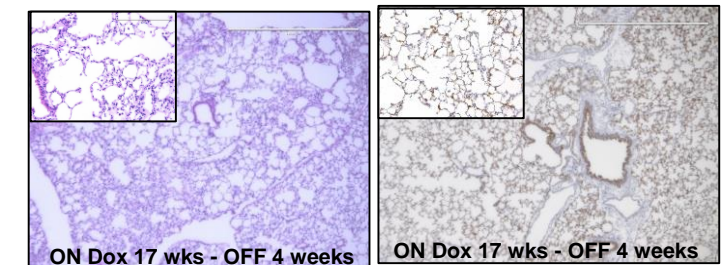
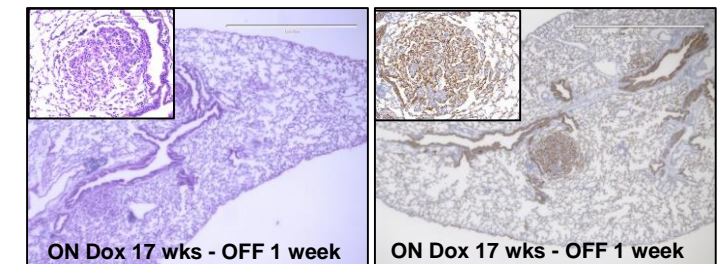
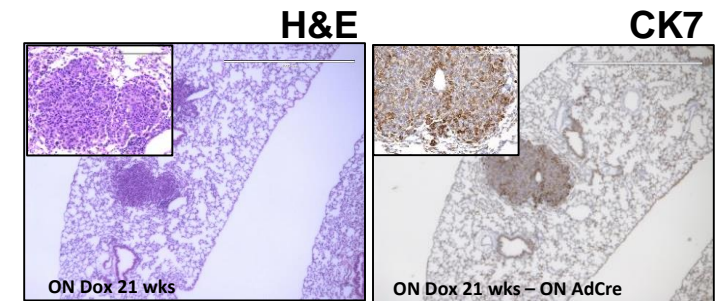
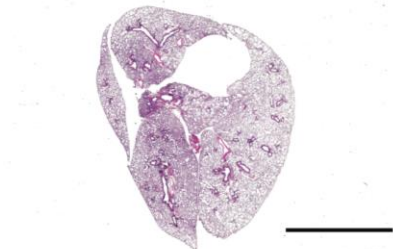
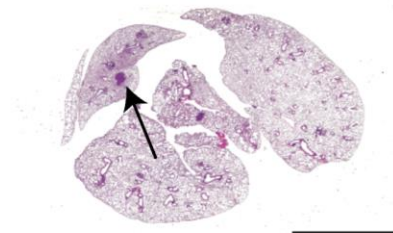
'KRAS\* ON, P53 ON'



KRAS\* OFF, P53 ON  
1 week OFF

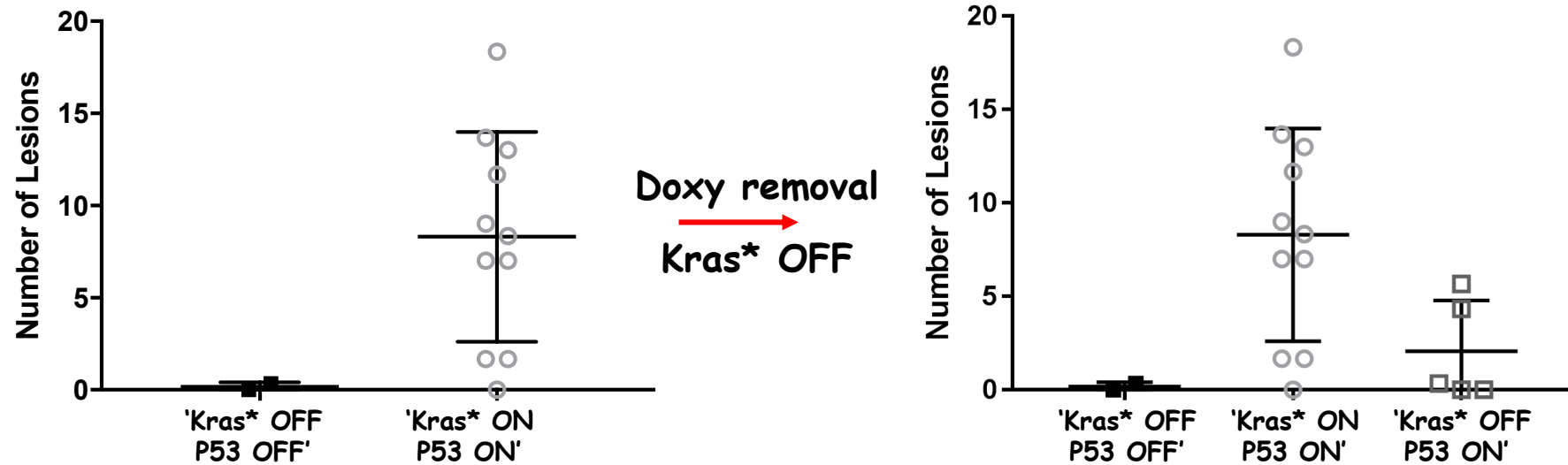


'KRAS\* OFF, P53 ON'  
4 week OFF



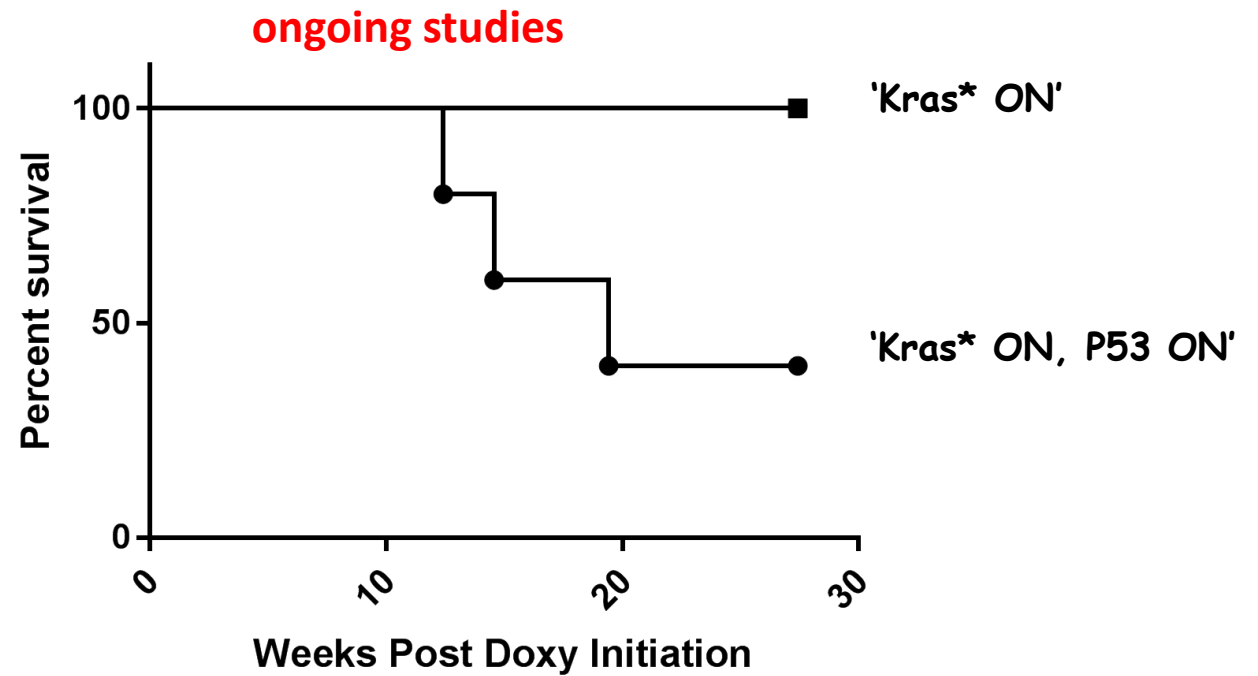
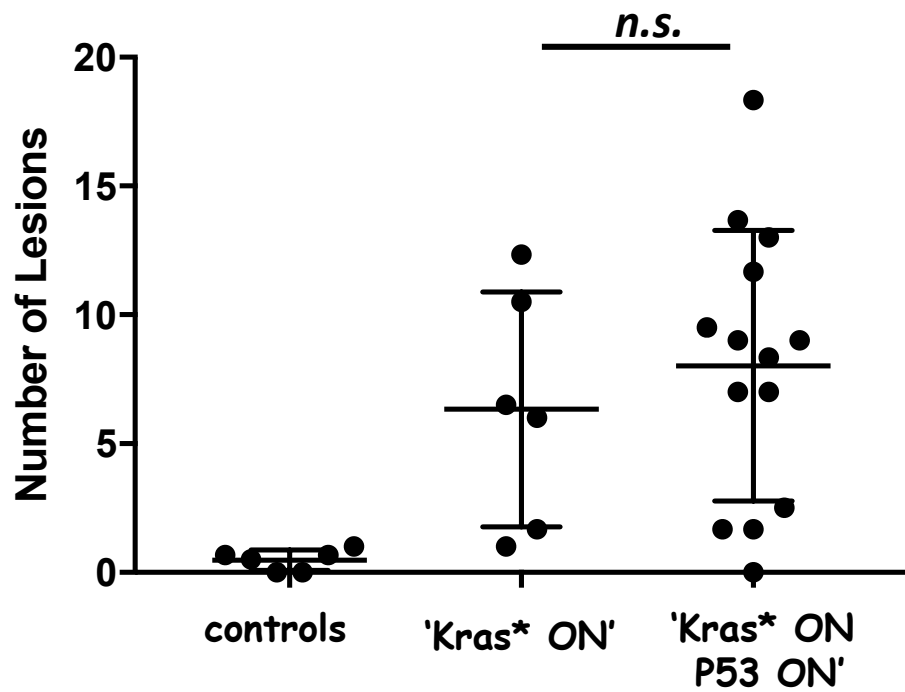


# Oncogenic Kras\* is required for tumor maintenance in p53 mutant adenocarcinomas





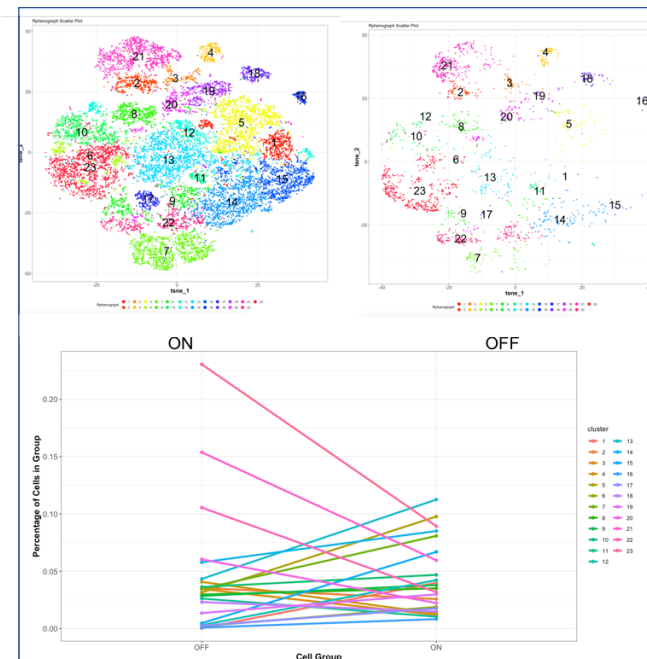
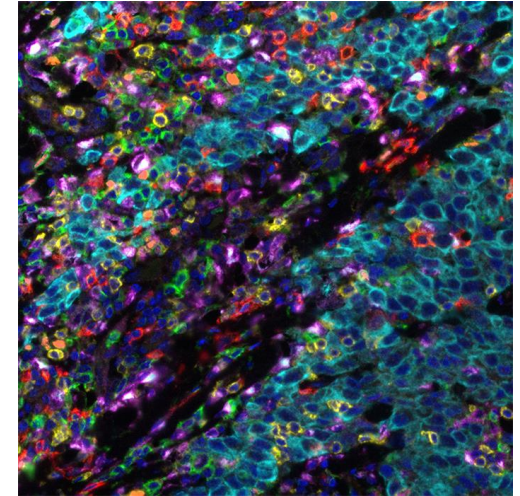
# Number of lesions is similar between 'Kras\* ON' an 'Kras\* ON, P53 ON' mice



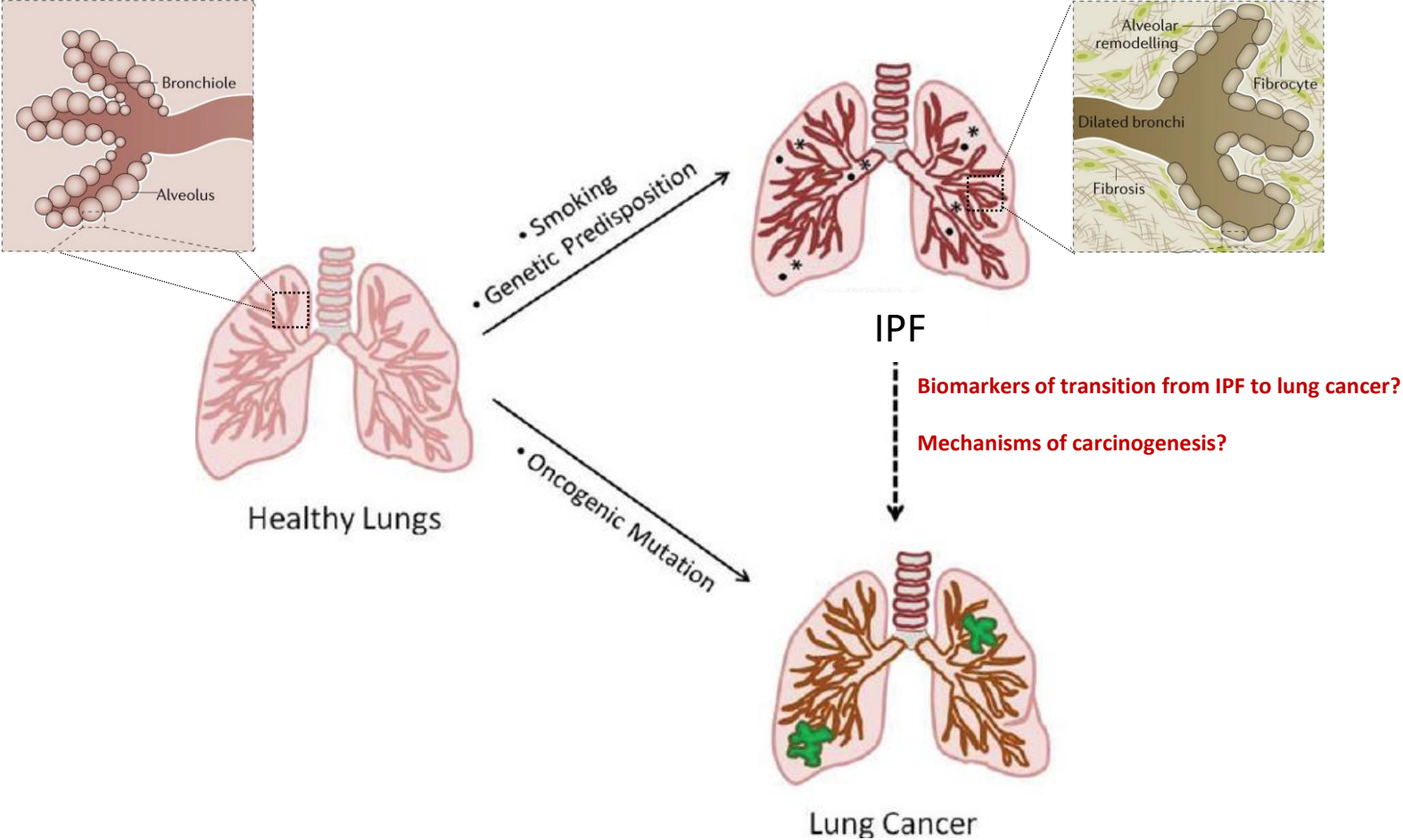
Controls: single transgenic mice on doxycycline

# Future directions

- Comparison between 'Kras\* ON' and 'Kras\*ON P53 ON' groups to determine: **lesion size, lesion location, cell of origin, metastases to brain and liver.**
- Use multiplex immunohistochemistry (OPAL) to characterize immune and tumor cells allowing visualization and analysis of cellular interactions within the tumor microenvironment (ongoing studies with Dr. Frankel's lab).
- Immune Profiling by CYTOF with Dr. Marina Pasca di Magliano's group



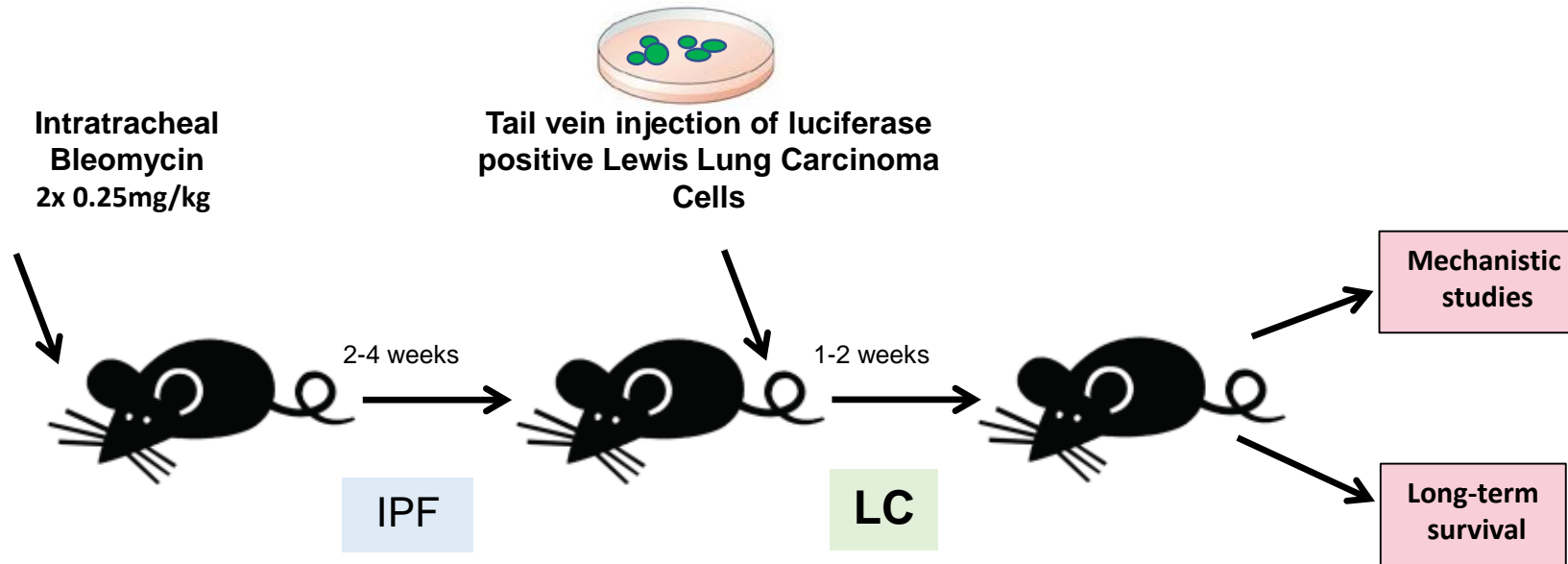
# Understanding of the link between pulmonary disease and lung cancer



Adapted from Balla et al, J.Radiation and Cancer Research, 2018, Vol (9), Page 165-176 and Nature reviews.



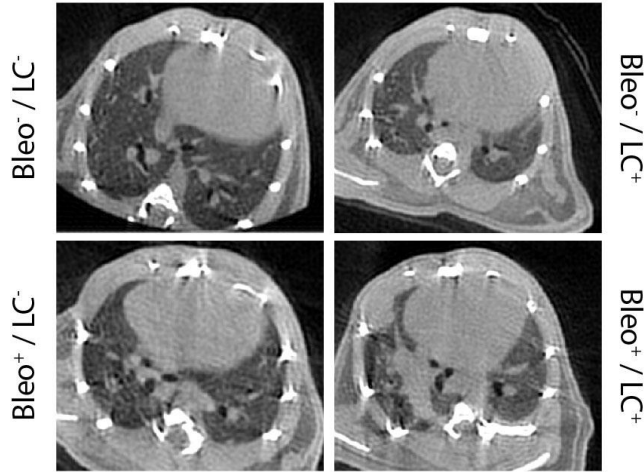
# Development of a Syngeneic Mouse Model for Idiopathic pulmonary associated-Lung Cancer



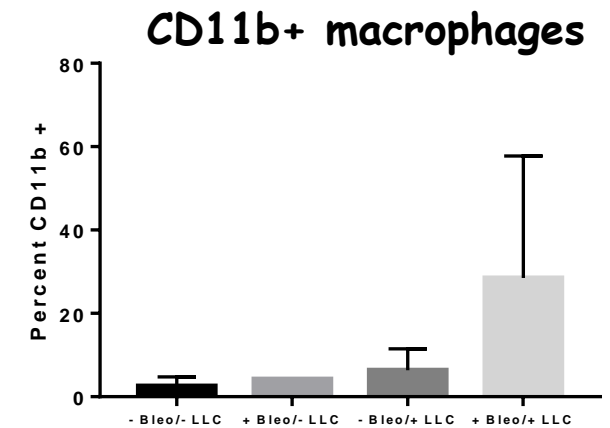
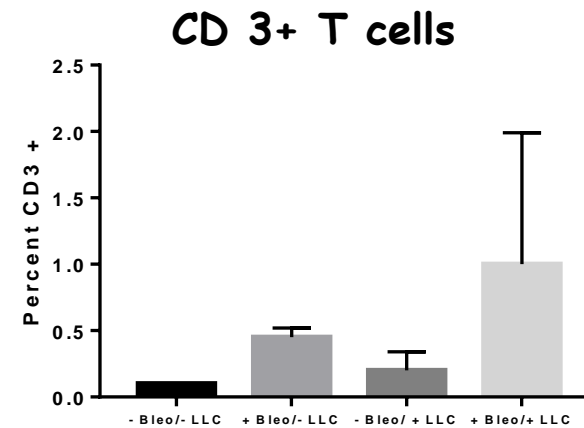
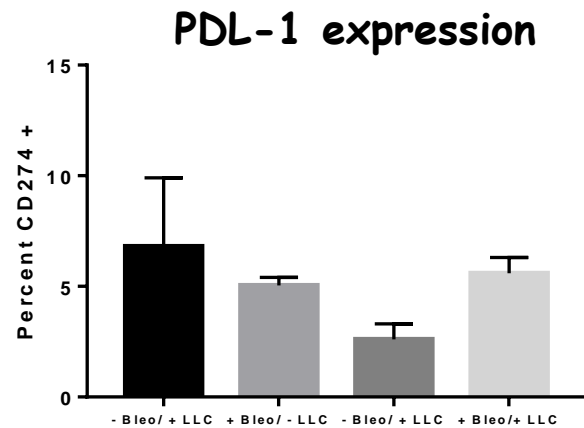
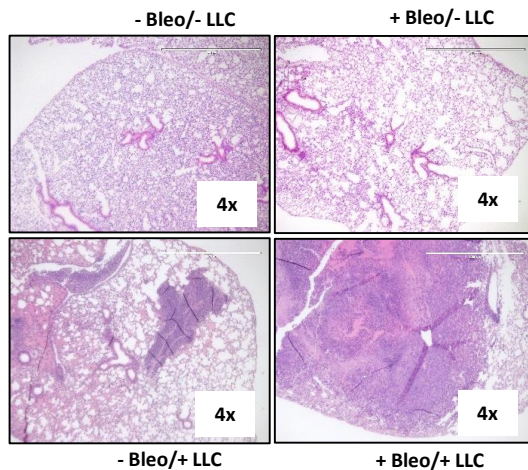
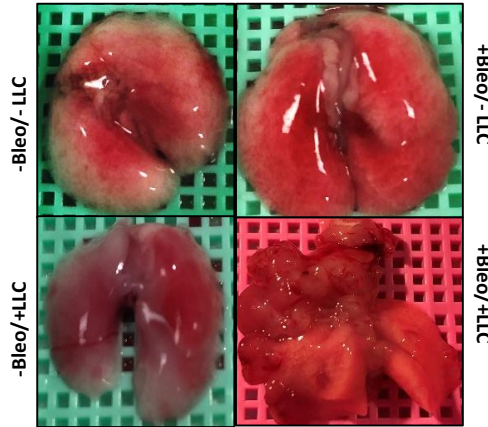
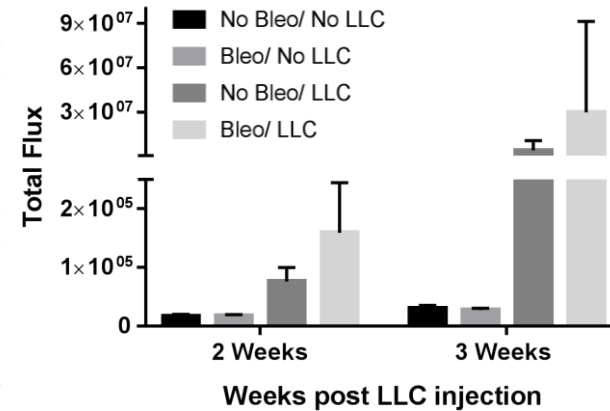
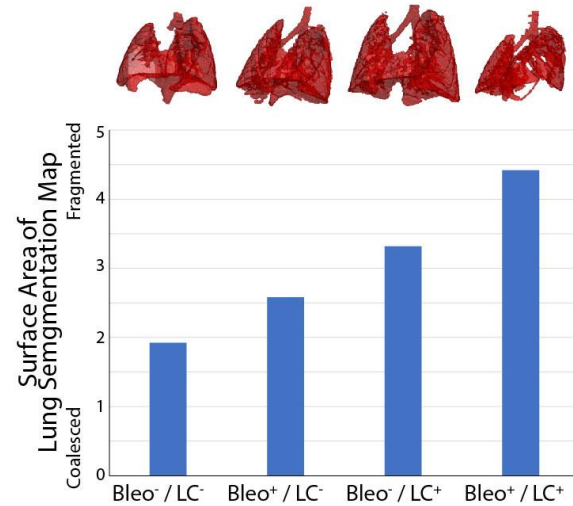
Groups	Inducer	Doses
Healthy lung	-bleo/-LLC-1 luc	Vehicle controls
Fibrotic lung	+bleo/-LLC-1 luc	0.5 mg/kg bleomycin
Lung cancer	-bleo/+LLC-1 luc	1x10 <sup>6</sup> LLC-1 luciferase expressing cells
Fibrous and cancerous lung	+bleo/+LLC-1 luc	0.5 mg/kg bleo/1x10 <sup>6</sup> cells

# Tumor Progression Correlates With CD11b+ Macrophages in Lungs of IPF-LC mice

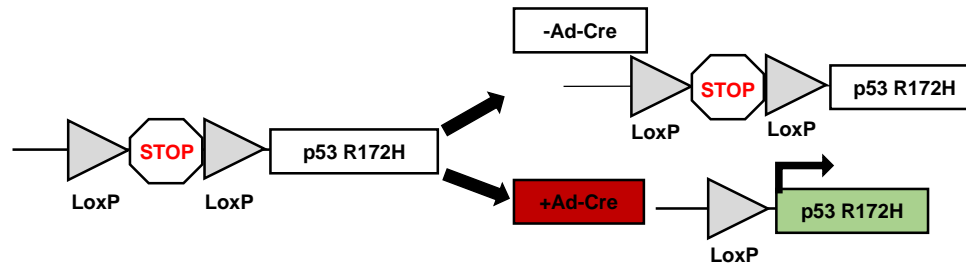
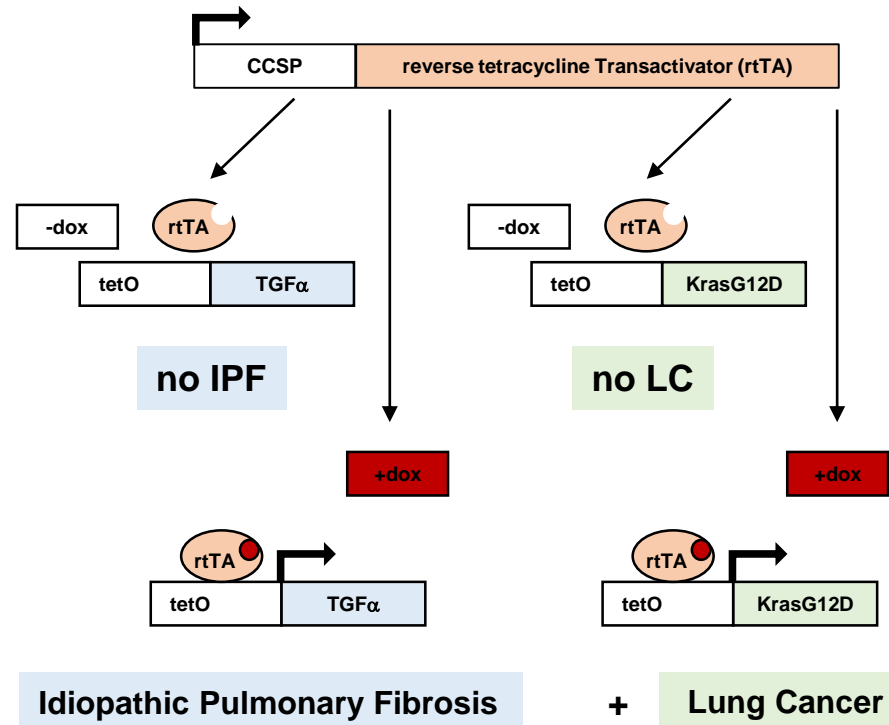
Preclinical Computed Tomography Scan



Lung Redering



# Development of an Inducible IPF-associated Lung Cancer Mouse Model

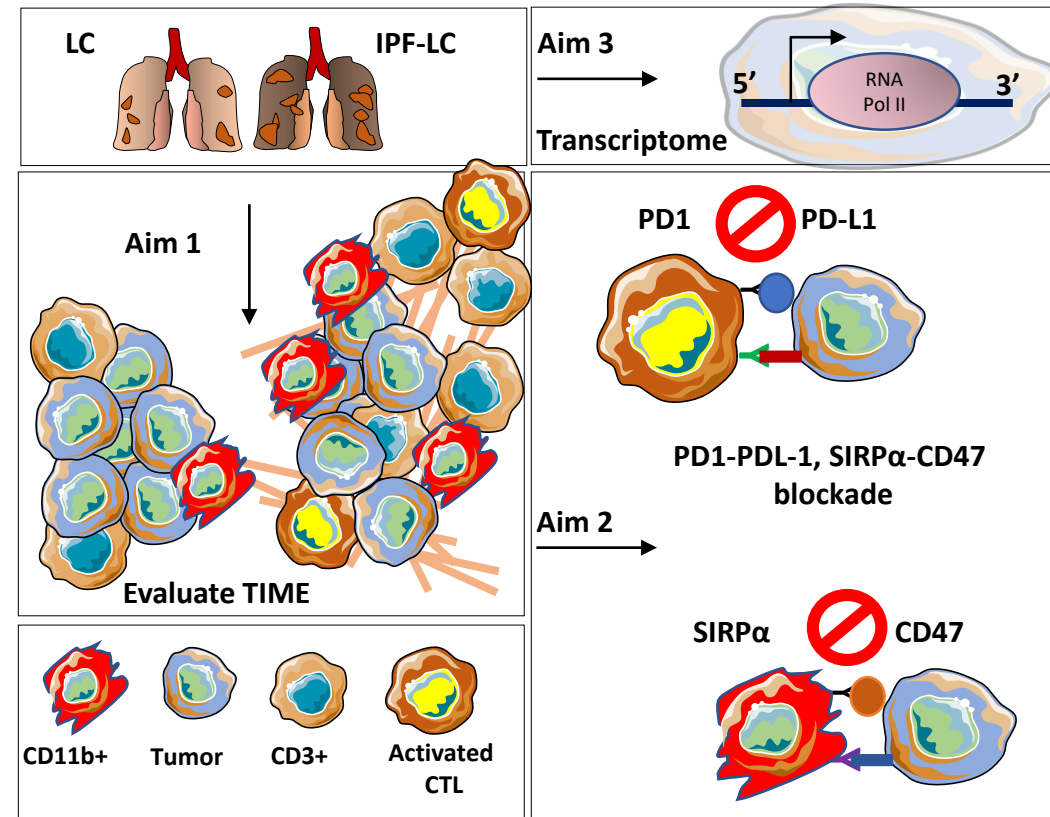




# Future Directions

- generate IPF-LC GEM mouse model
- Determine the tumor immune microenvironment and metabolomic landscape of IPF-LC.
- Evaluate immune check point-based therapies.
- Determine transcriptomic profiles of murine IPF-LC and patient IPF associated lung cancer tissue.

## TIME Promotes Tumors in IPF-LC



# Acknowledgements

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Kara Monchamps  
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