ROGEL CANCER CENTER
MICHIGAN MEDICINE

Understanding the mechanistic link between idiopathic pulmonary fibrosis and lung cancer

Cancer Biology/Cancer Genetics Program Meeting 7-11-2019

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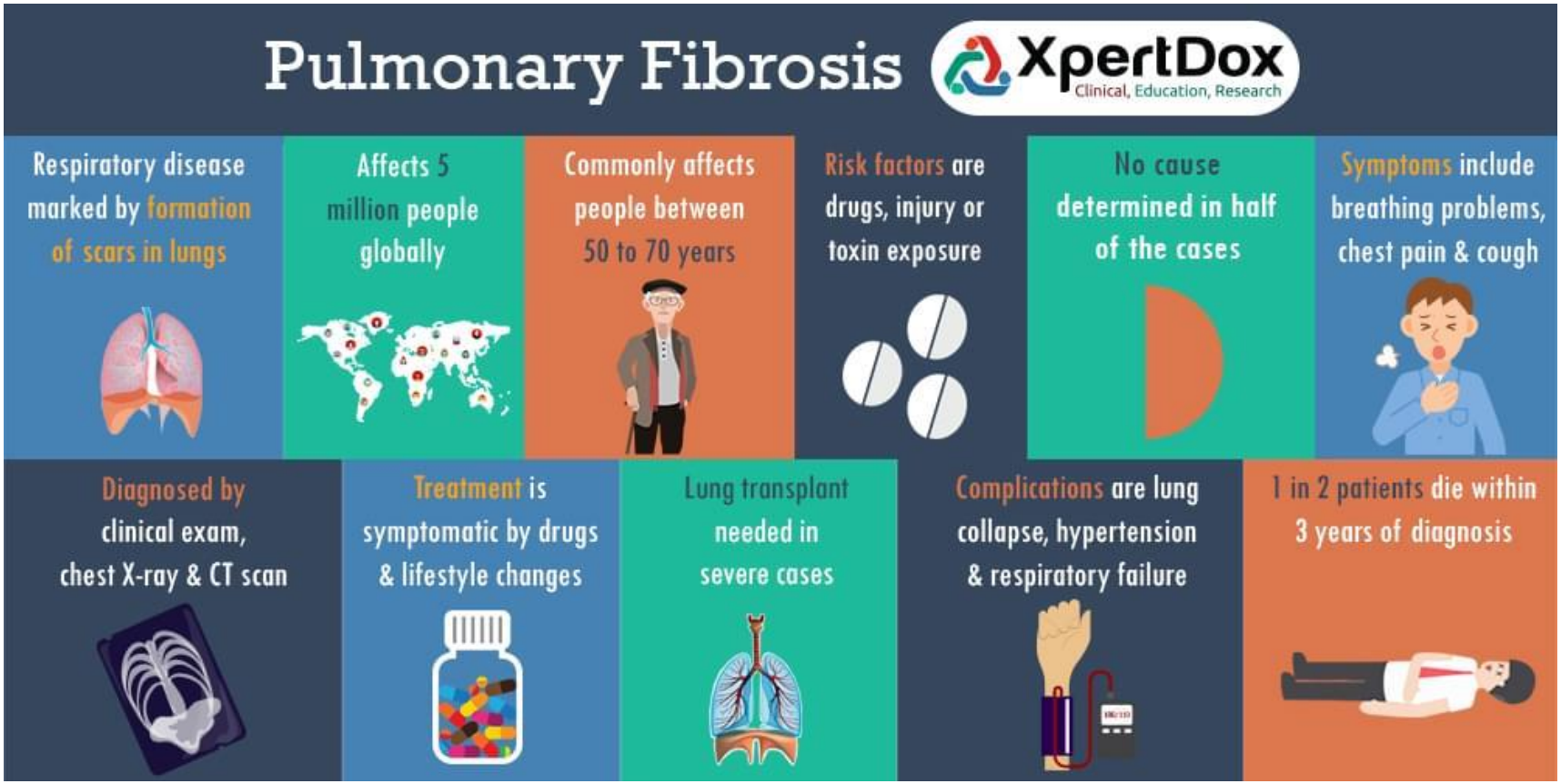
Department of Radiology Michigan Medicine,
Center for Molecular Imaging (CMI),
Rogel Cancer Center

Smoking remains the biggest risk factor for Idiopathic Pulmonary Fibrosis (IPF)



IPF results in Irreversible Lung Damage

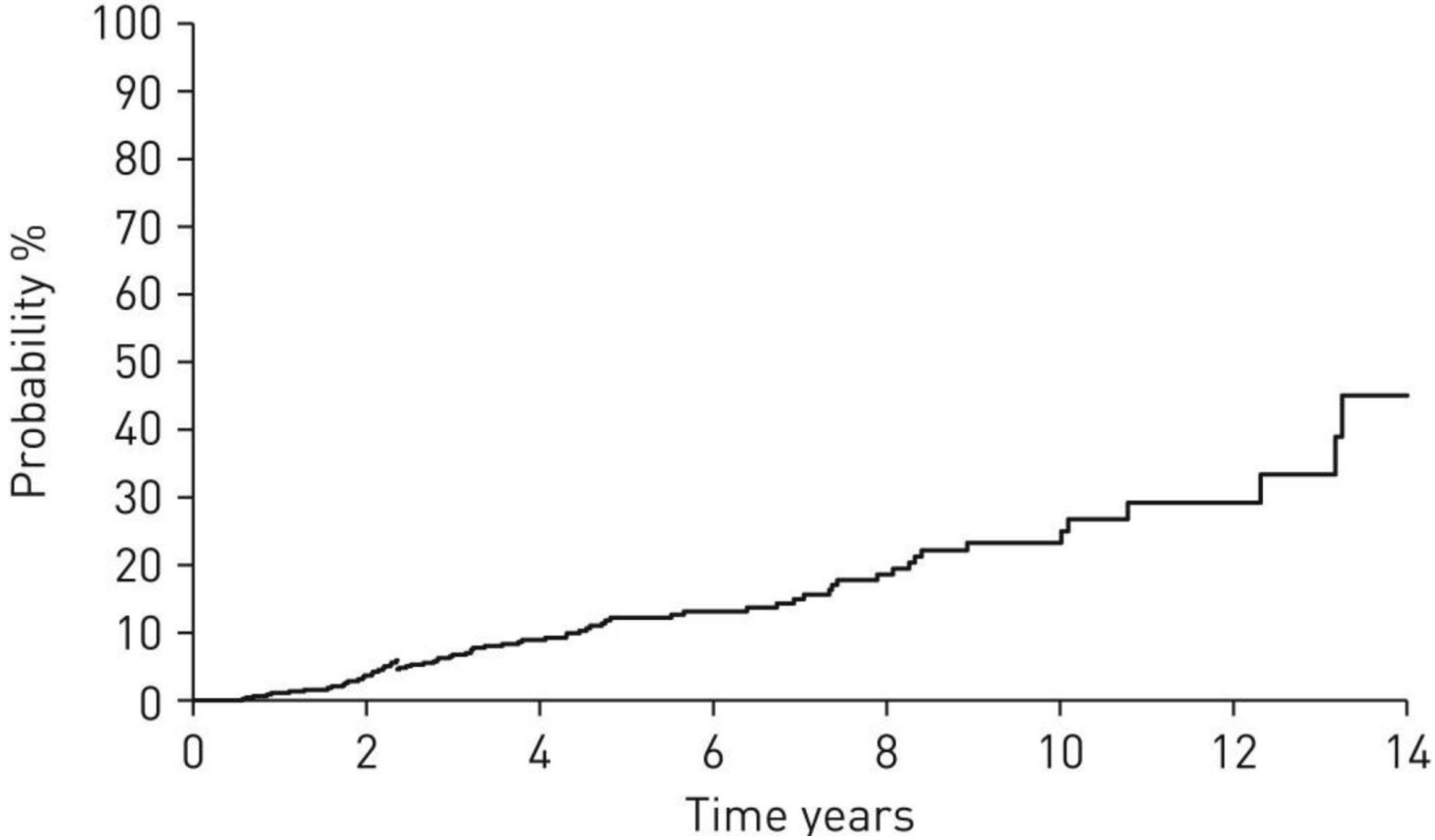
Normal healthy lung tissue is soft and flexible, allowing easy breathing

In IPF, the lung tissue is damaged, becoming scarred over time. This process is called fibrosis

As IPF gets worse, scarring spreads through the lungs which makes breathing more difficult. Once the lung tissue is damaged from progressive scarring, unfortunately it doesn't recover

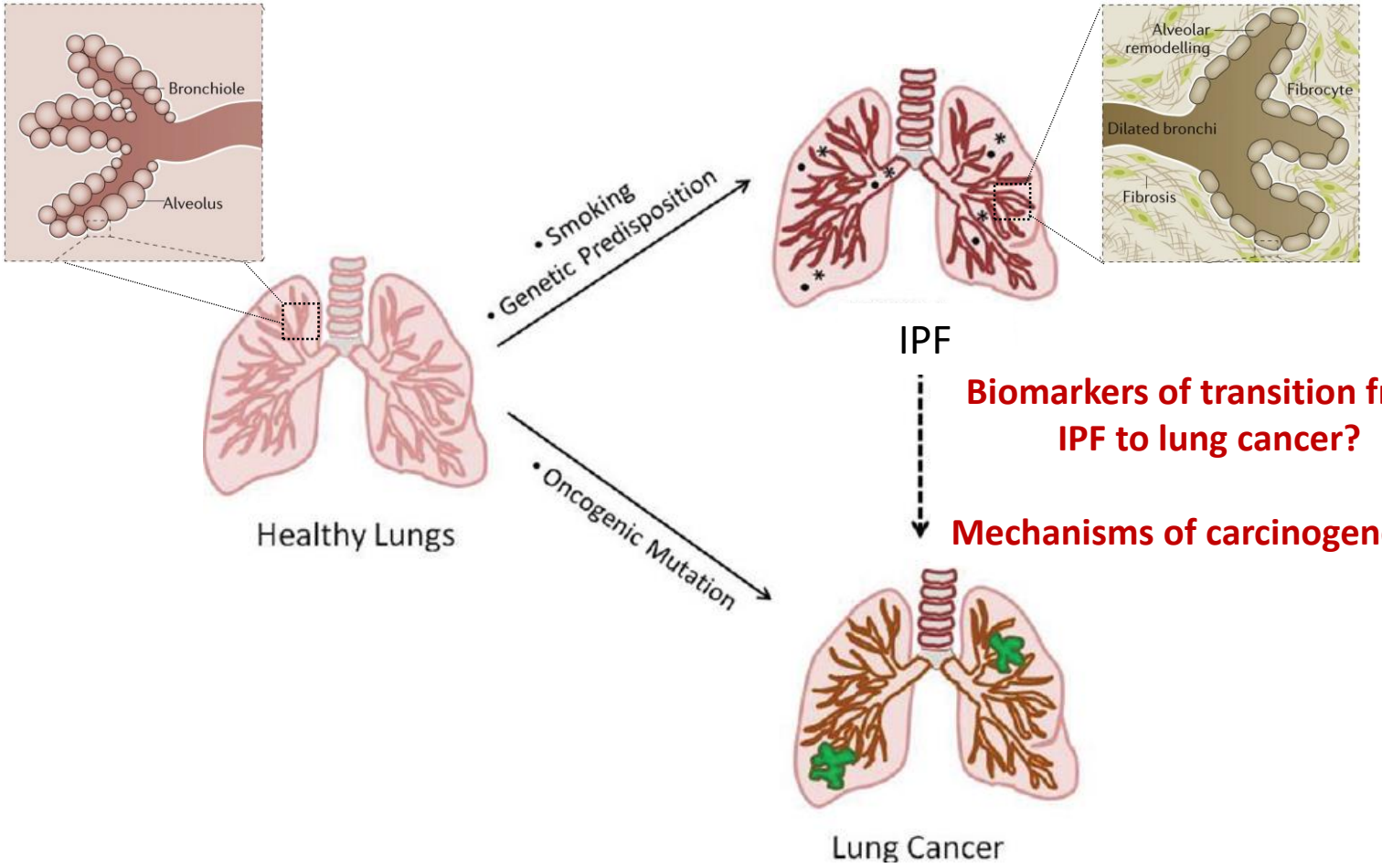
EU-IPFF
EUROPEAN IDIOPATHIC PULMONARY FIBROSIS & RELATED DISORDERS FEDERATION

Around 20% of IPF patients develop lung cancer within 10 years of diagnosis



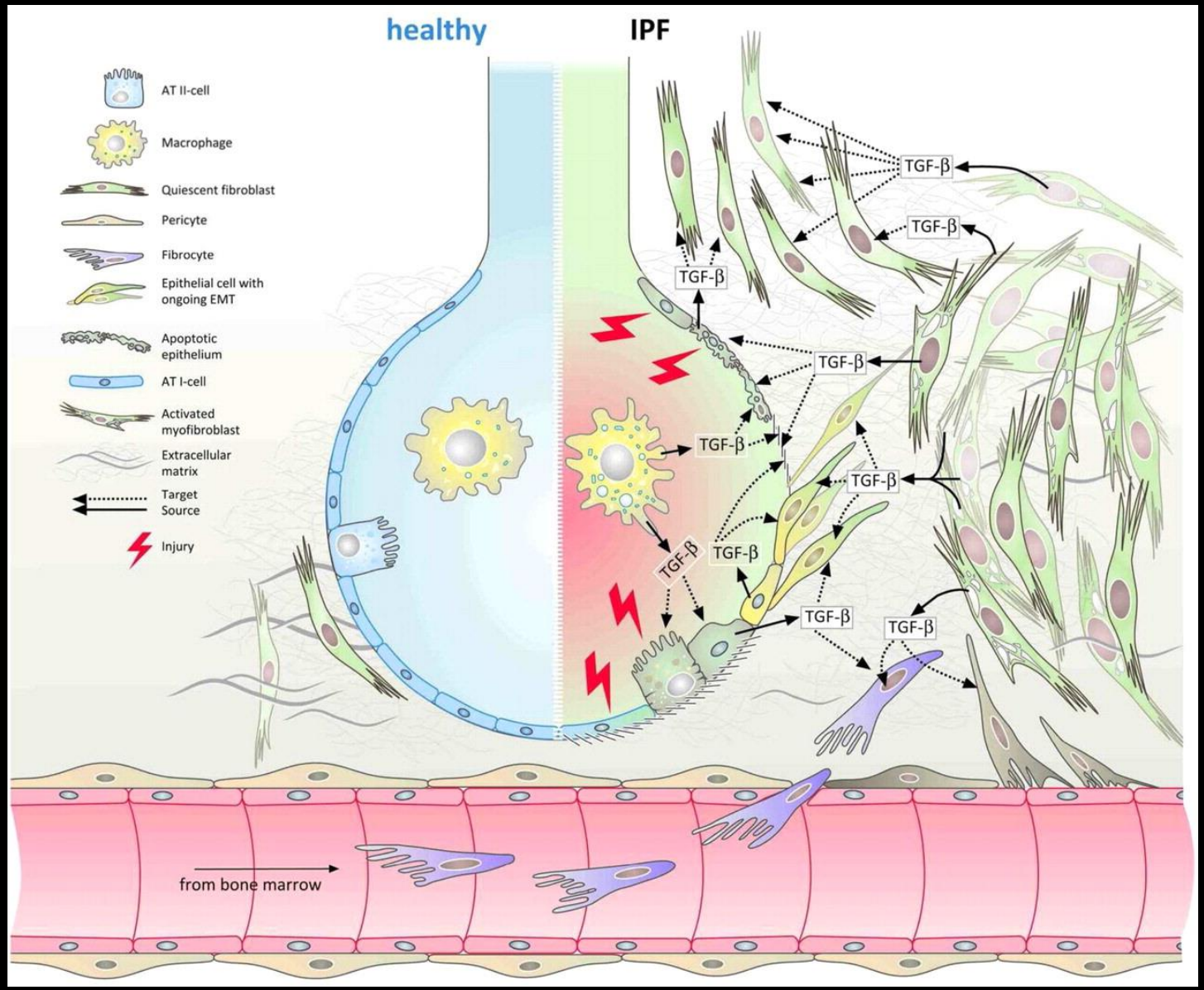
Kato et al, ERJ Open Res. 2018 Jan; 4(1): 00111-2016.

Identification of the mechanistic links between IPF and lung cancer



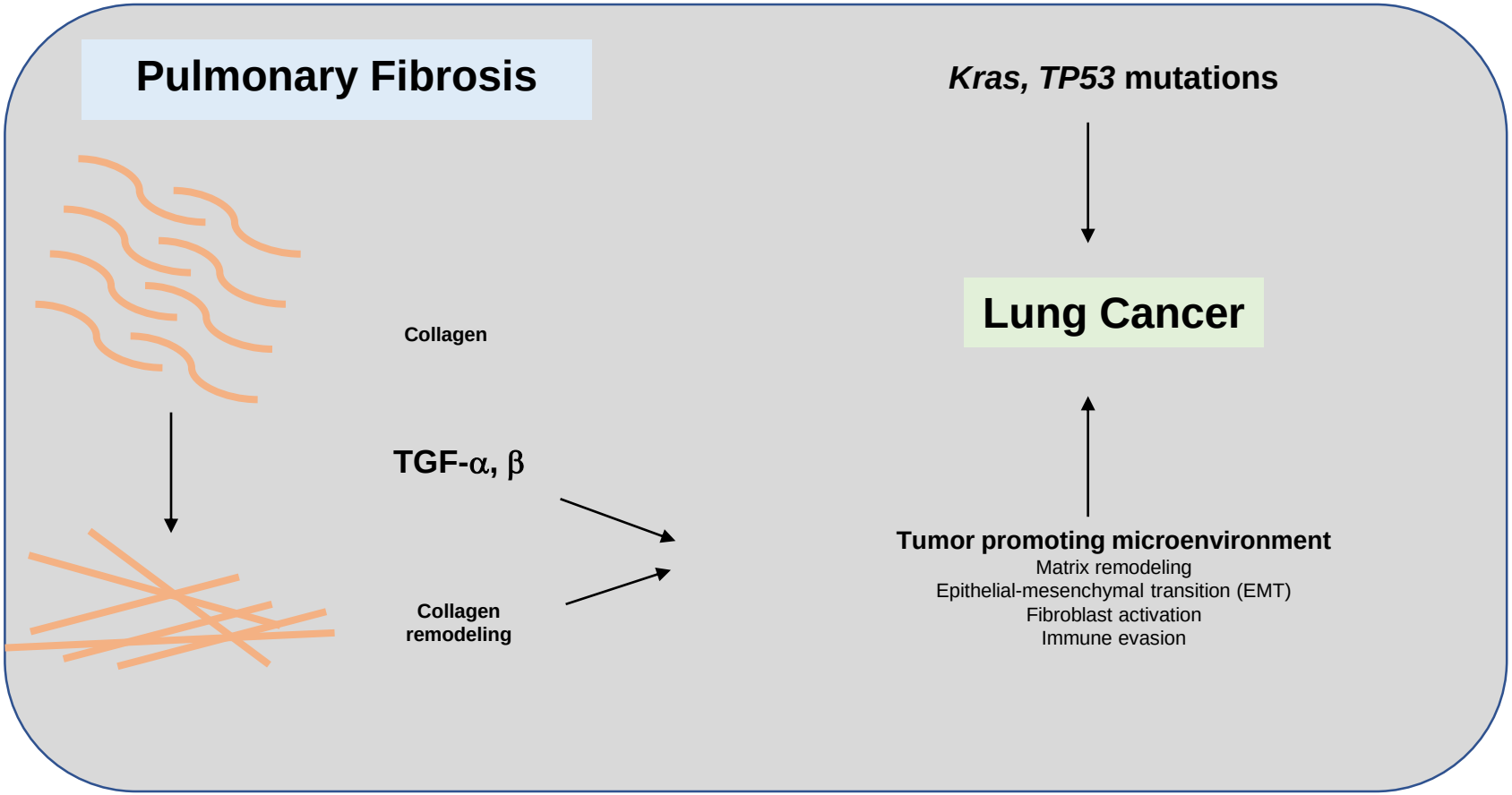
Adapted from Balla et al, J.Radiation and Cancer Research, 2018, Vol (9), Page 165-176 and Nature reviews.

TGF-β in Lung Fibrosis

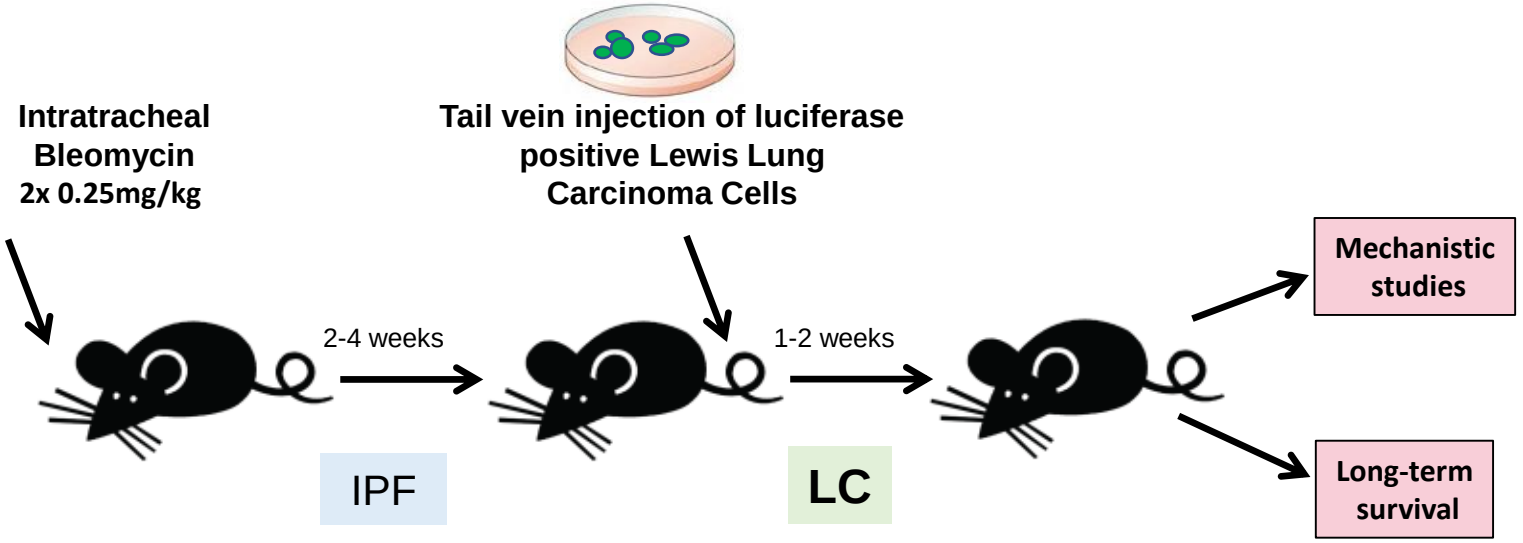


Isis E. Fernandez et al, ATS, Vol. 9, No. 3 | Jul 15, 2012

Tumor Promoting Milieu in IPF?

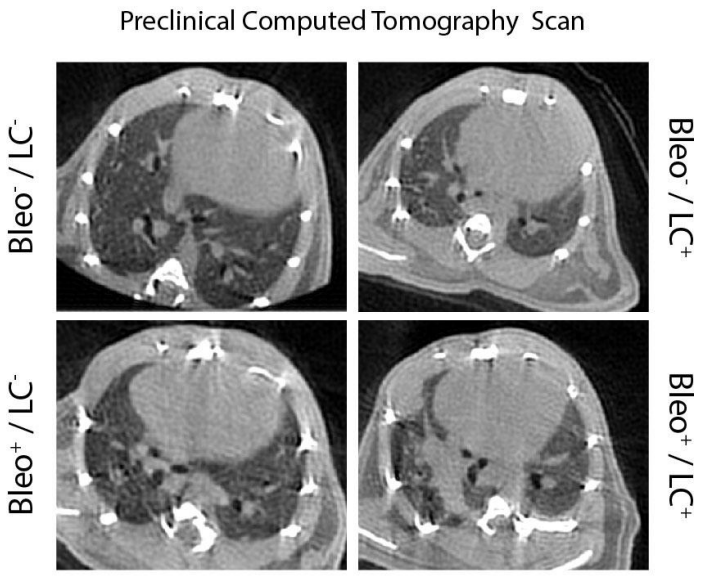


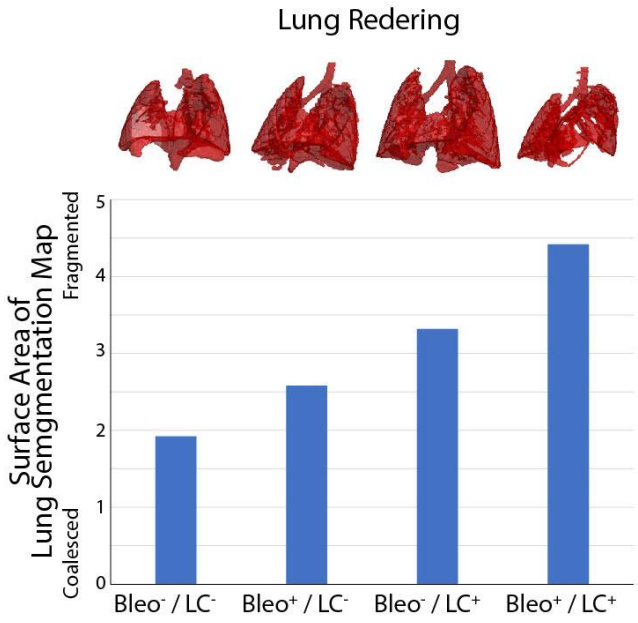
Idiopathic Pulmonary Fibrosis associated Lung cancer (IPF-LC) Mouse Model



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	1x10^6 LLC-1 luciferase expressing cells
Fibrous and cancerous lung	+bleo/+LLC-1 luc	0.5 mg/kg bleo/1x10^6 cells

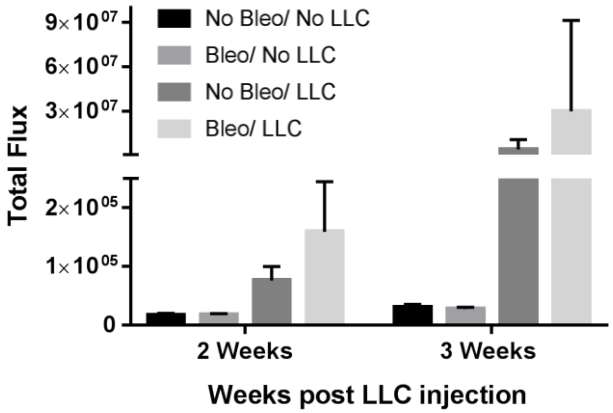
Quantitative assessment of lung structure with disease by micro CT

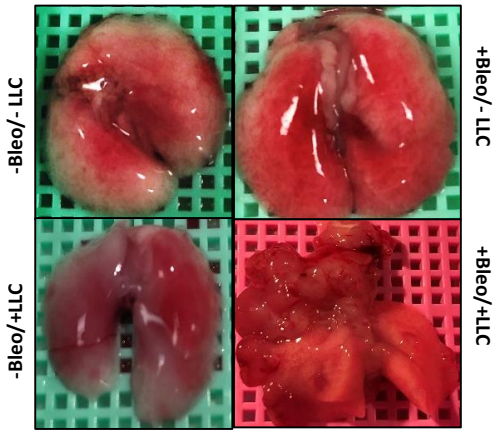


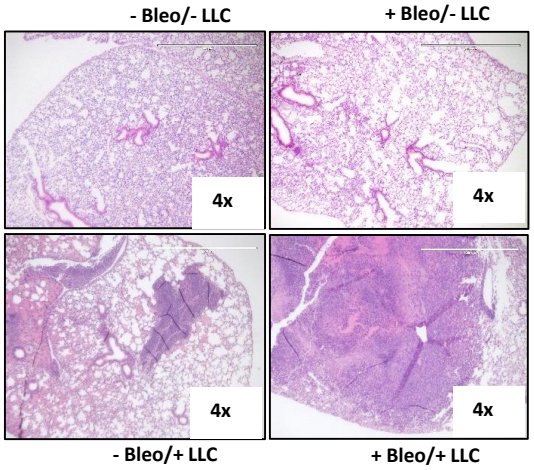


Collaboration with Craig Galban's group

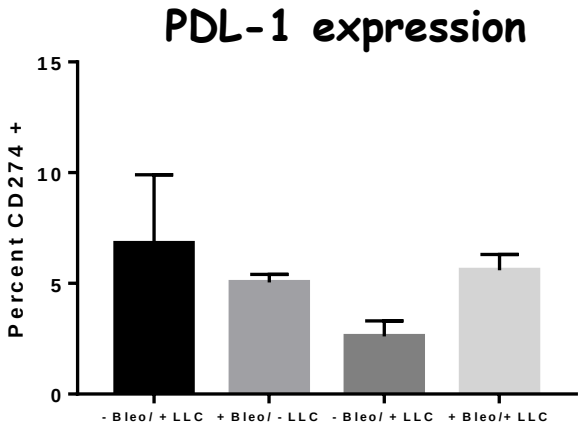
Increased severity of lung cancer in fibrous lungs

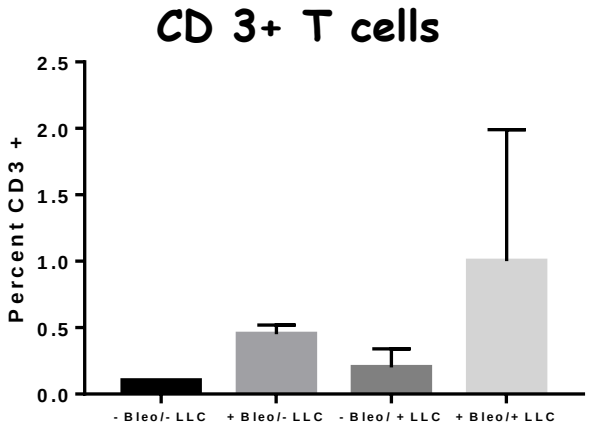


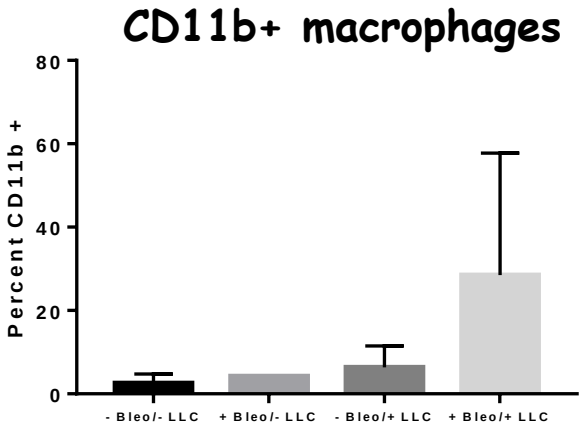




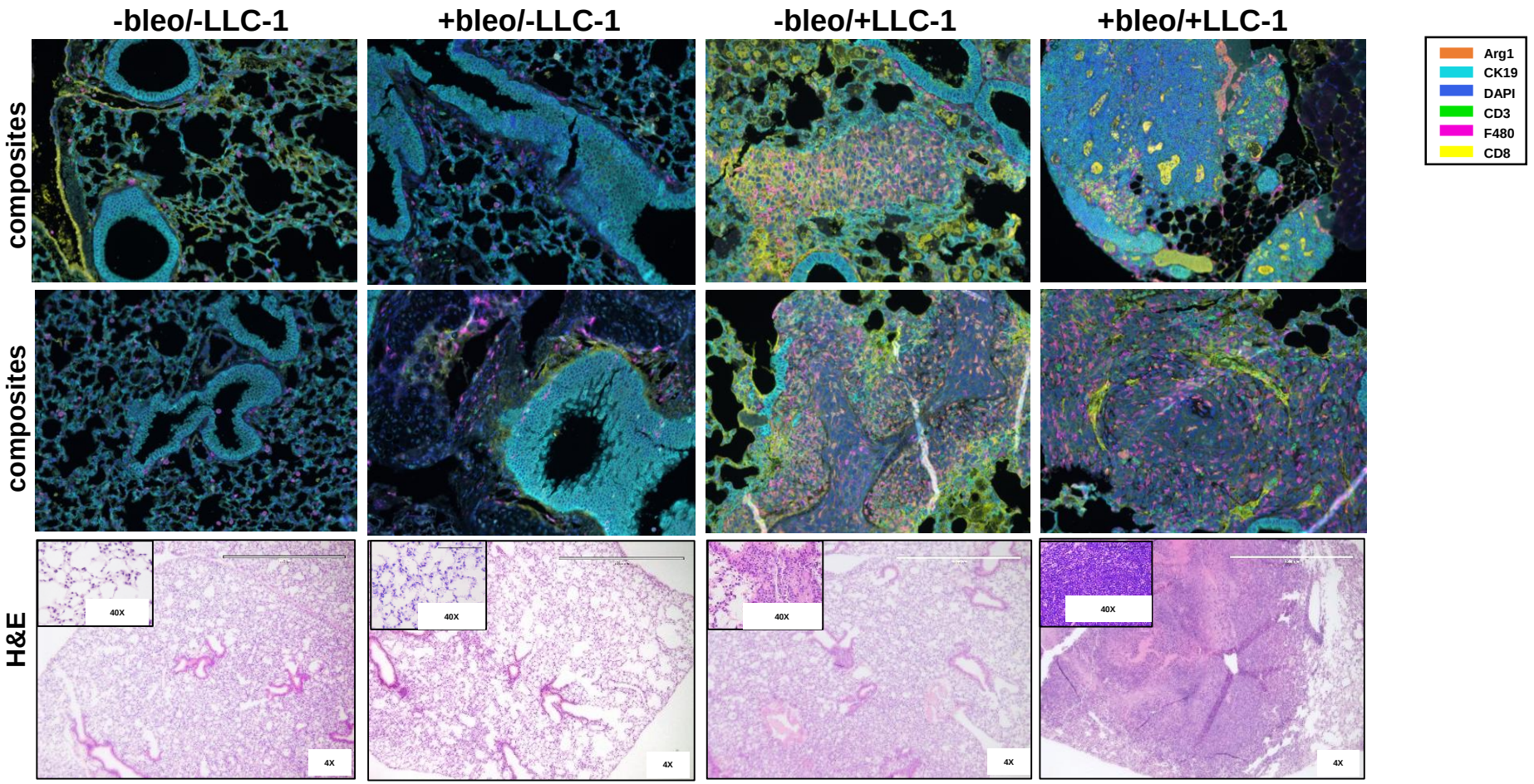
Tumor Progression Correlates With CD11b+ Macrophages in Lungs of IPF-LC mice







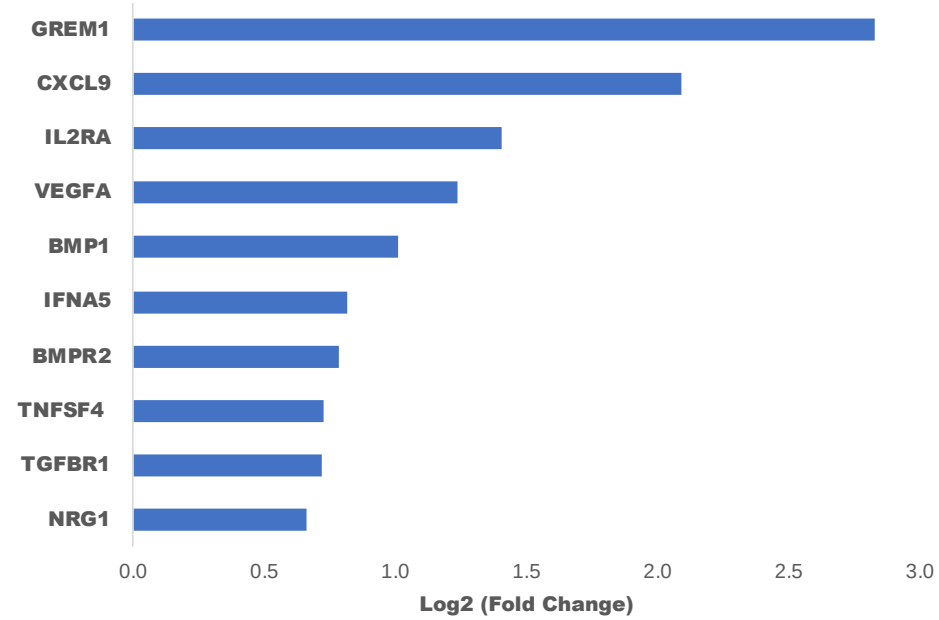
Analyzing TIME in IPF-LC

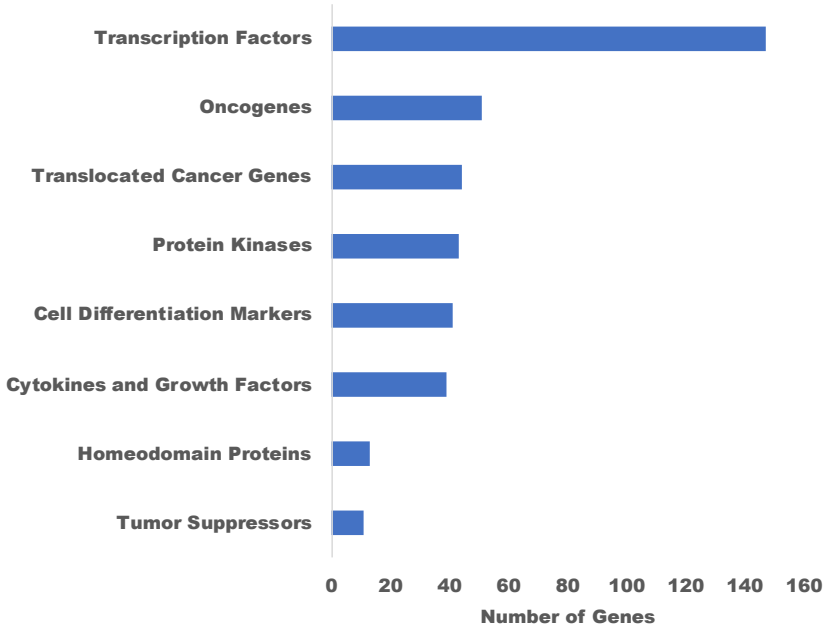


Collaboration with Drs. Pasca di Magliano and Frankel

Transcriptome changes in COPD-associated lung cancer

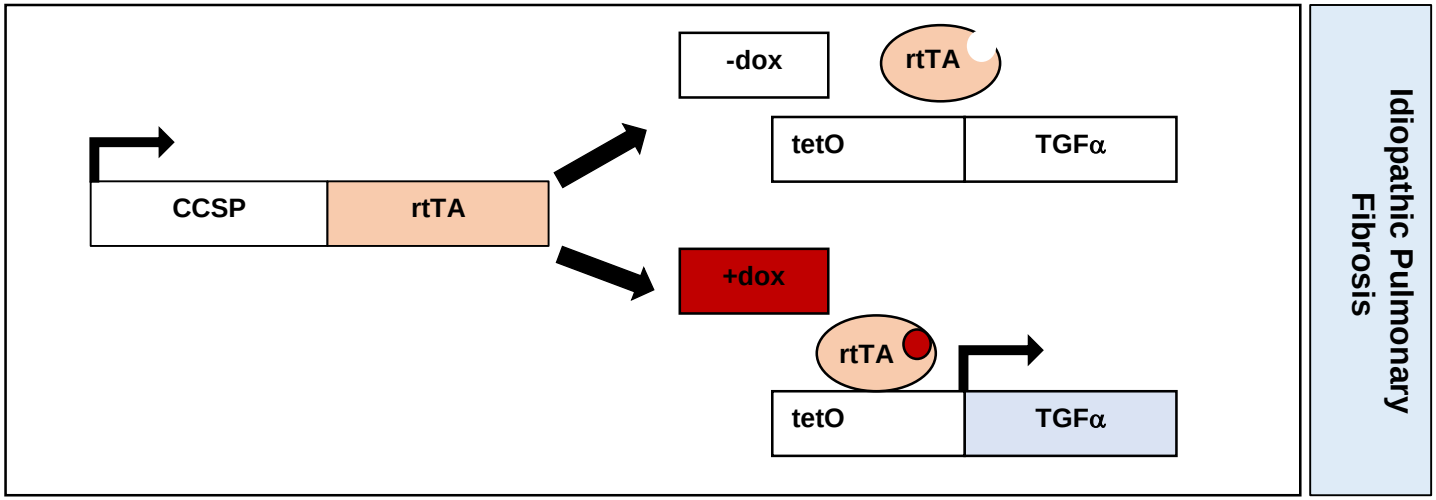
Highly enriched genes **upregulated** in COPD associated lung cancer compared to COPD ($p<0.05$)





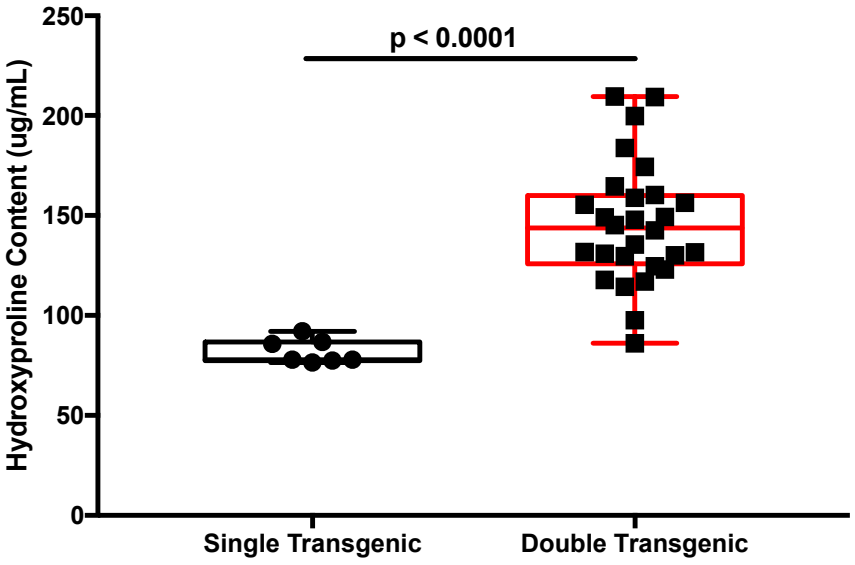
Collaboration with David Beer

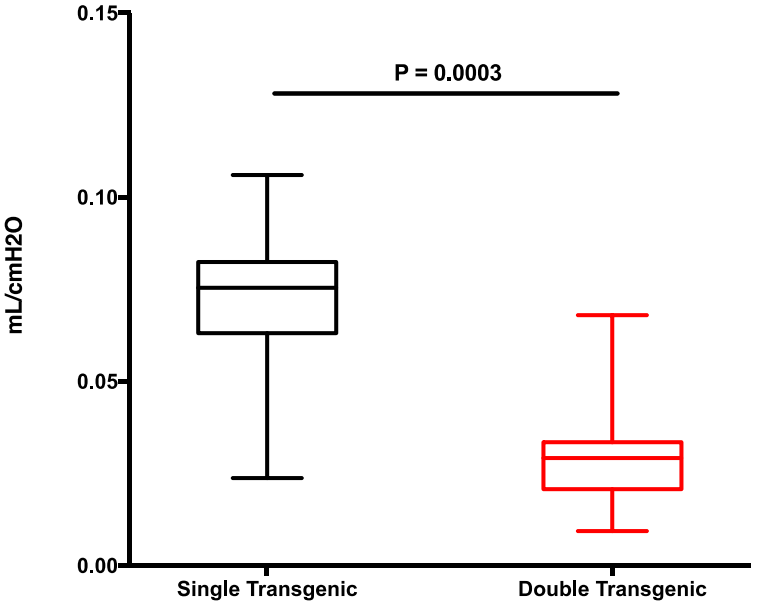
Transgenic mouse model for idiopathic pulmonary fibrosis (IPF)



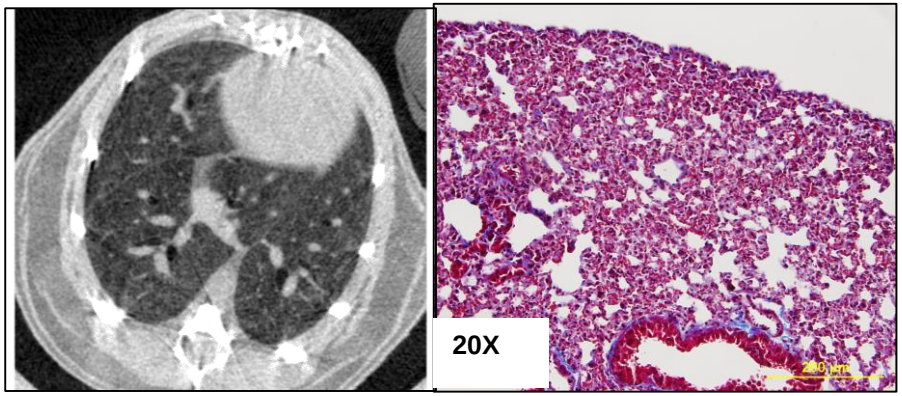
Hardie et al, Am J Physiol Lung Cell Mol Physiol 286: L741-L749, 2004.

TGF-alpha inducible IPF mouse model recapitulates human disease

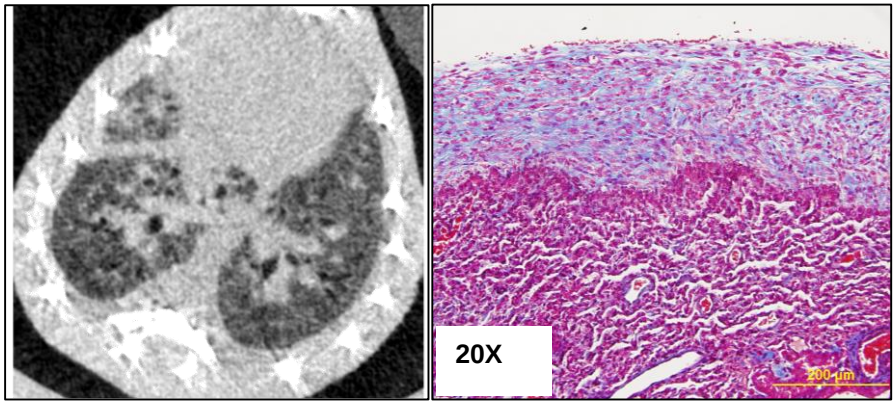




Pleural fibrosis

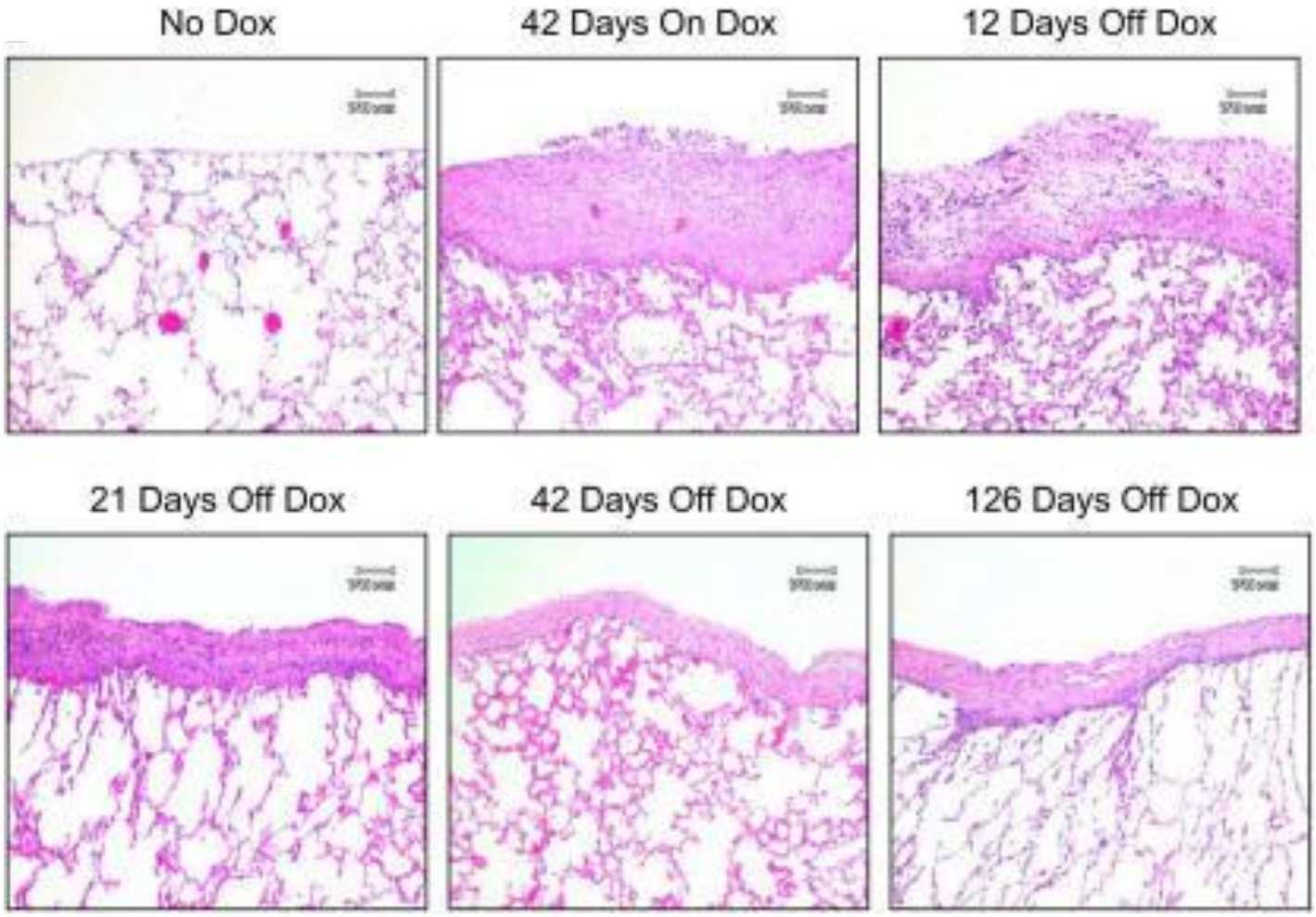


CCSP-rtTA$^{+/-}$
or TGF-α$^{+/-}$



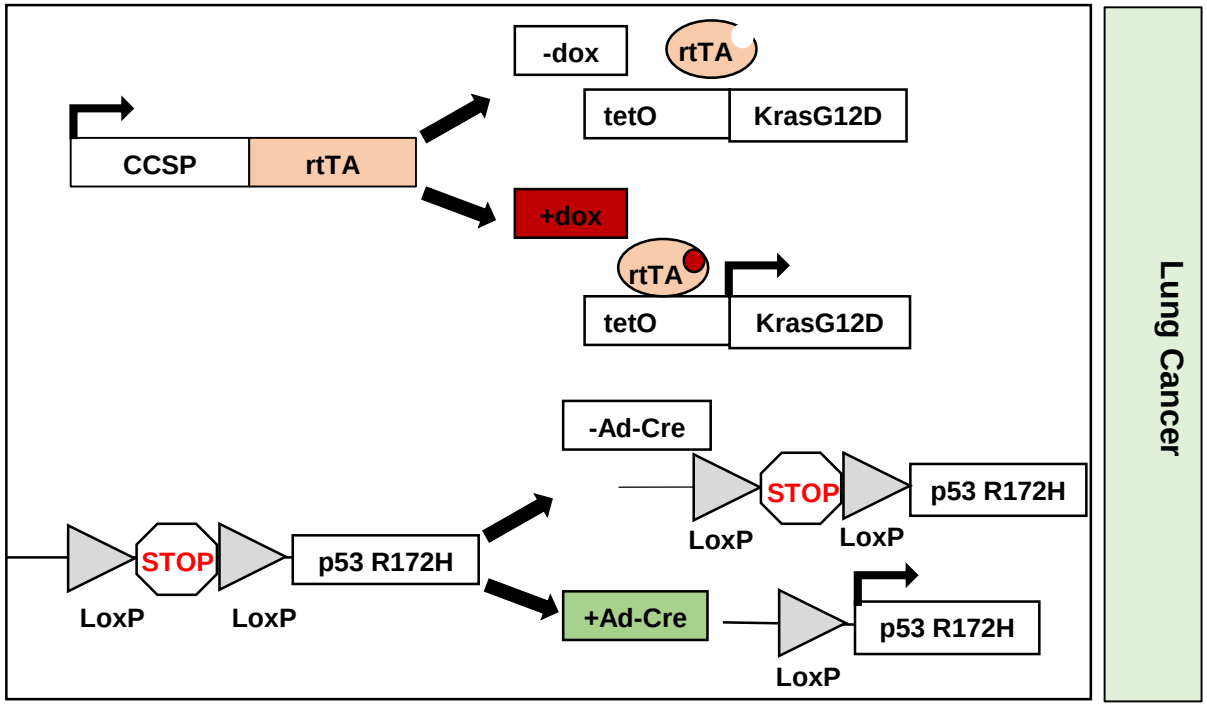
CCSP-rtTA$^{+/-}$/TGF-α$^{+/-}$

Reversibility of TGF-alpha-induced pulmonary fibrosis



Hardie WD et al, Am J Respir Cell Mol Biol. 2007 Sep; 37(3): 309–321.

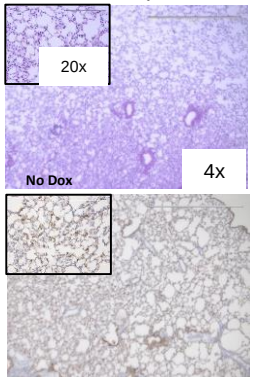
Inducible *Kras** and mutant p53 lung cancer model



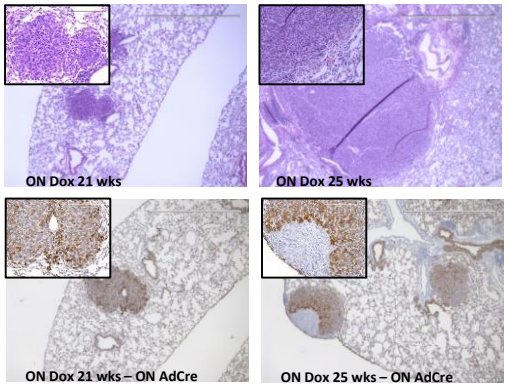
Fisher et al, Genes Dev. 2001 Dec 15; 15(24): 3249-3262.

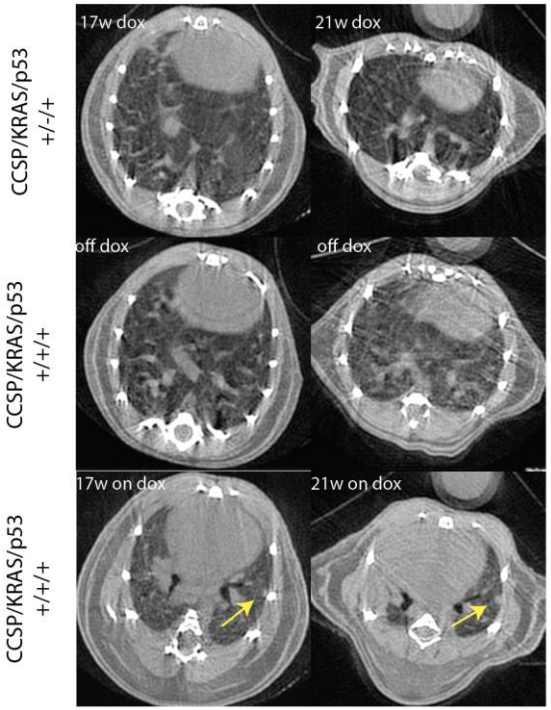
Simultaneous activation of Kras* and p53R172H leads to adenocarcinomas

'Kras* OFF, P53 OFF'



'Kras* ON, P53 ON'





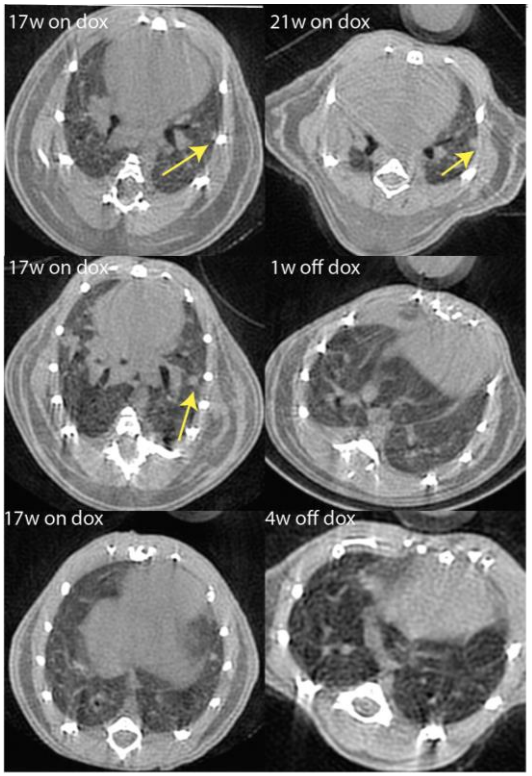
controls

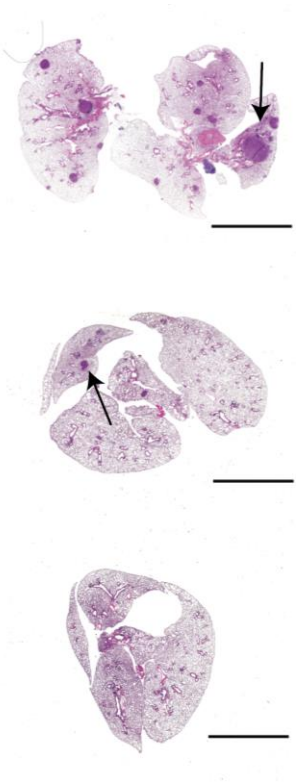
'KRAS* OFF, P53 OFF'

'KRAS* ON, P53 ON'

Controls: single transgenic mice on doxycycline

Kras* is required for tumor maintenance of adenocarcinomas

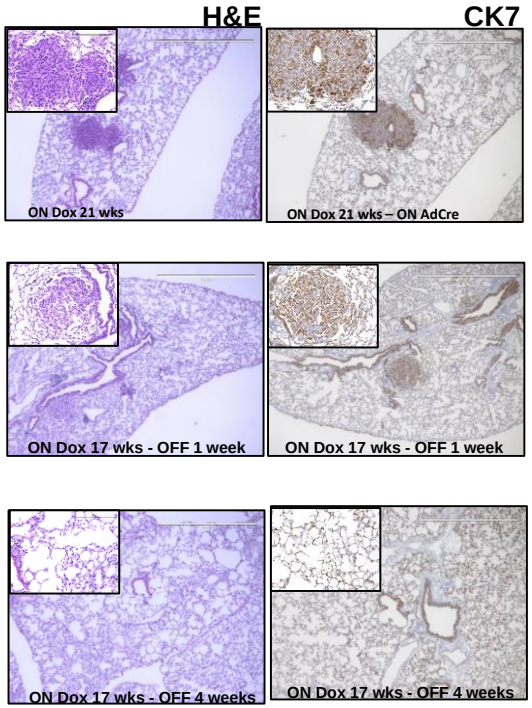


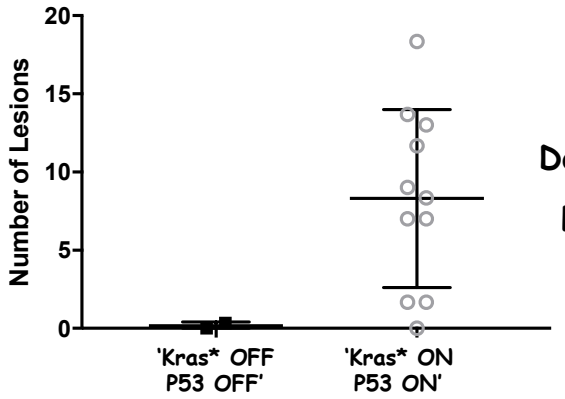


'KRAS* ON, P53 ON'

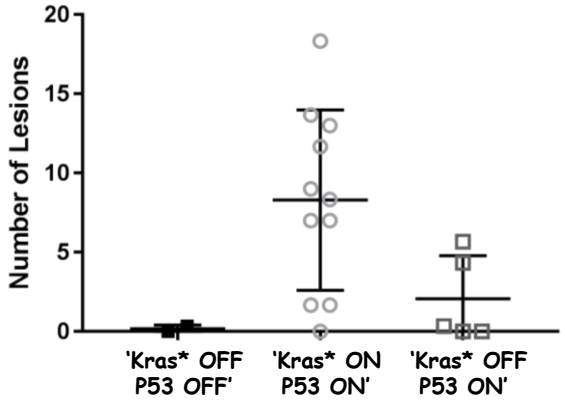
KRAS* OFF, P53 ON
1 week OFF

'KRAS* OFF, P53 ON'
4 week OFF

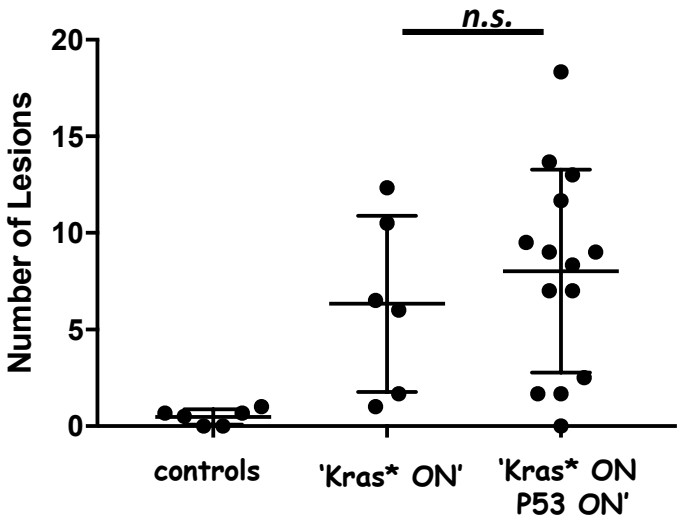




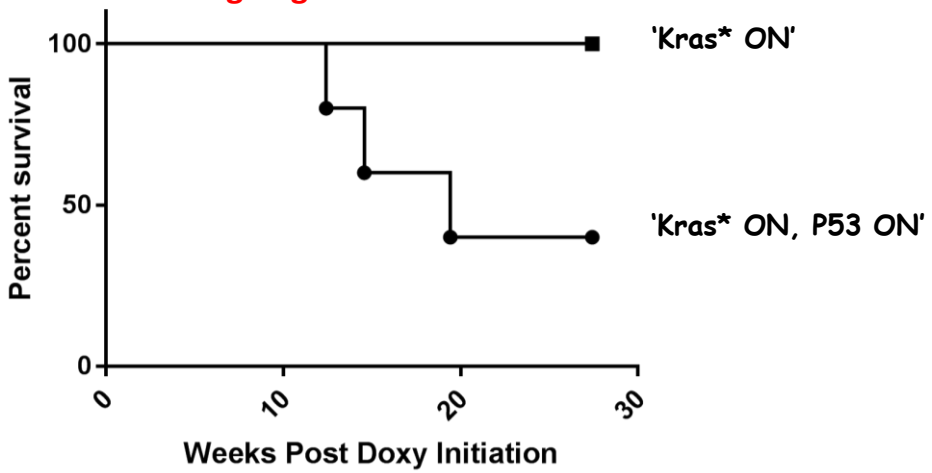
Doxy removal
Kras* OFF



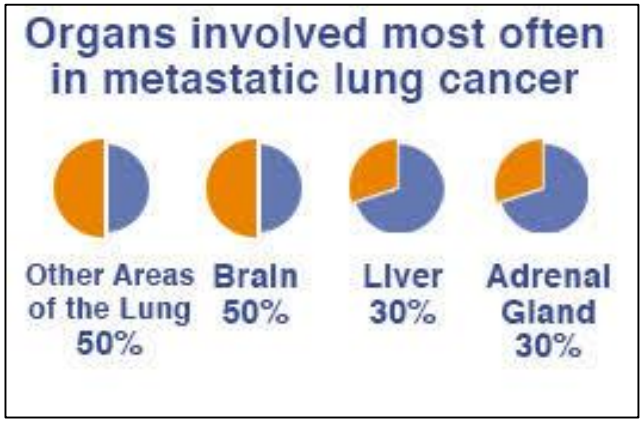
Number of lesions is similar between 'Kras* ON' an 'Kras* ON, P53 ON' mice



ongoing studies

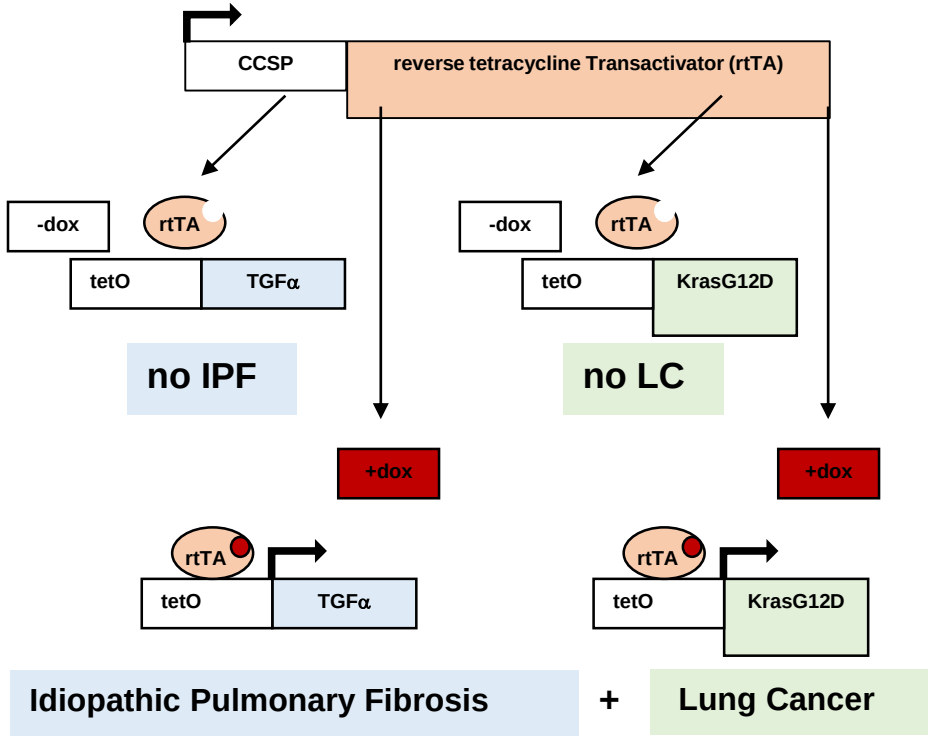


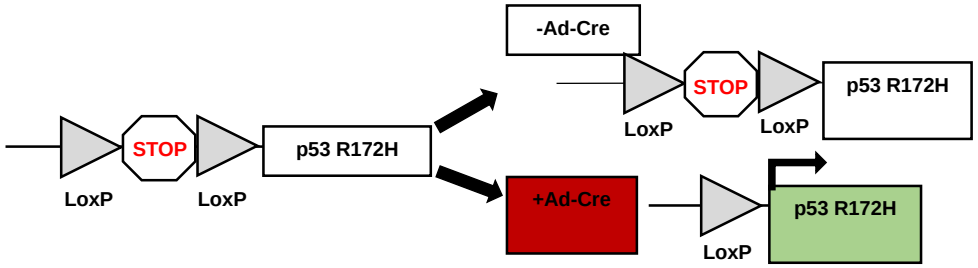
Survival disadvantage due to development of metastases?



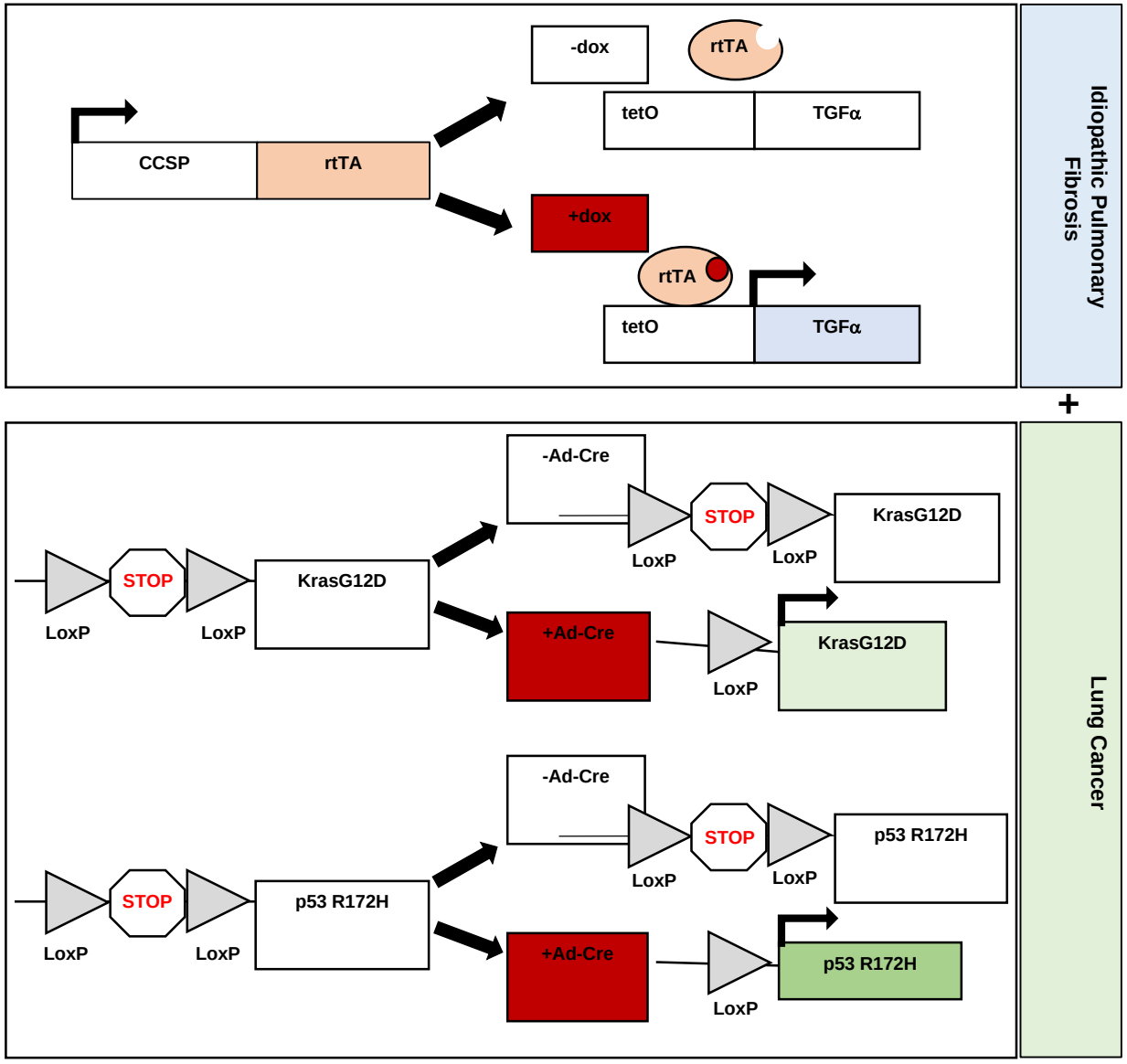
Controls: single transgenic mice on doxycycline

Development of an Inducible IPF-associated Lung Cancer Mouse Model





Genetic makeup of the 'consecutive IPF-LC' mouse model



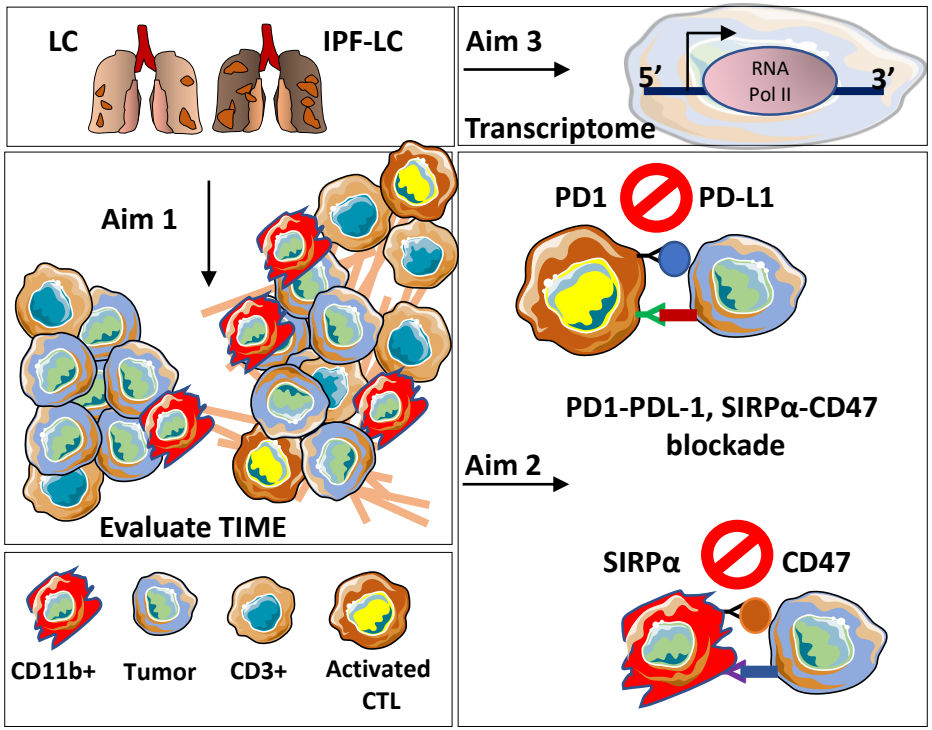
Summary and Future Directions

- Developed IPF-LC mouse models
- Evaluated the lung microenvironment

- Determine the tumor immune microenvironment and metabolomic landscape of IPF-LC.

- Evaluate immune check point-based therapies.

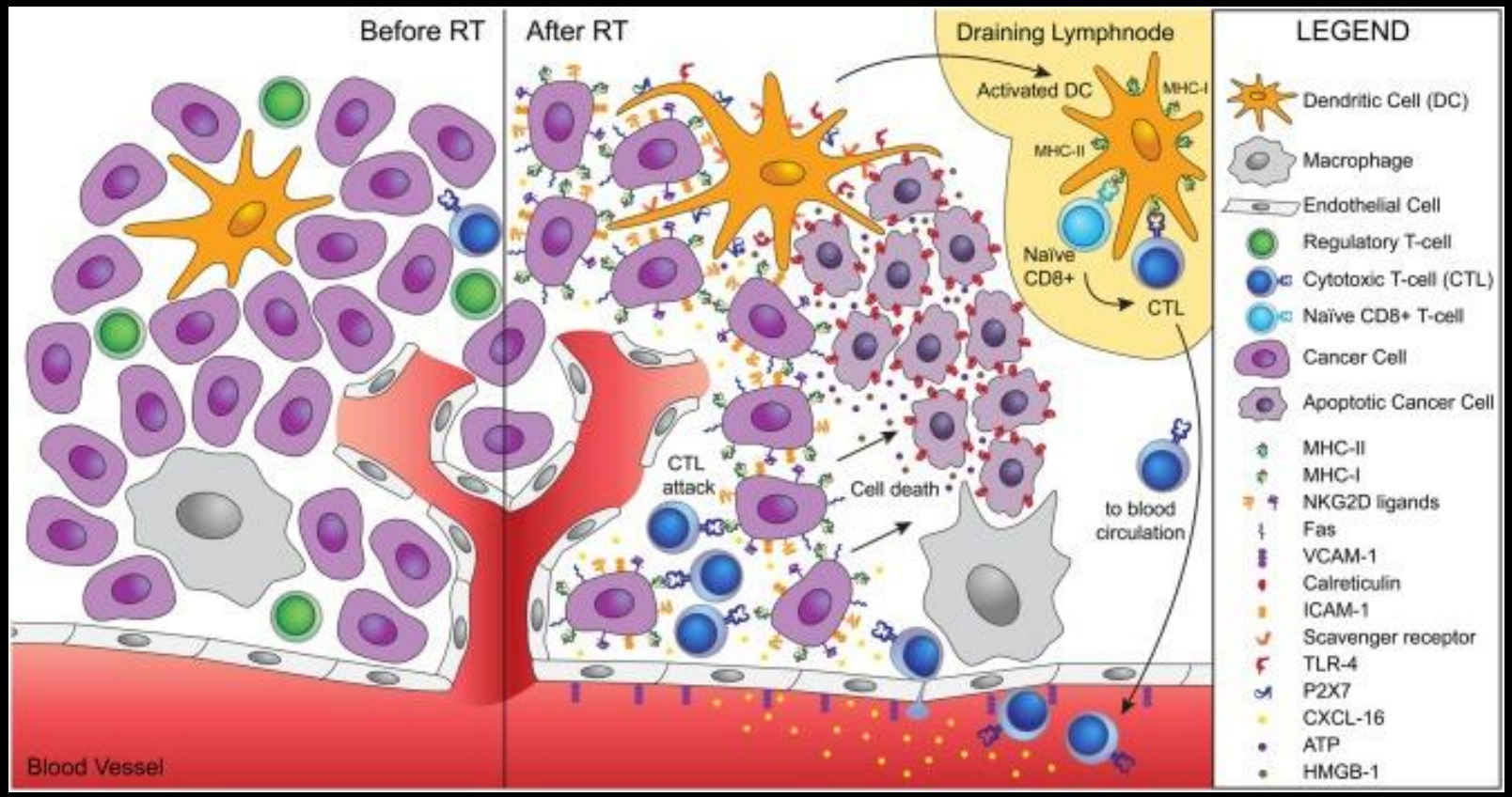
- Determine transcriptomic profiles of murine IPF-LC and patient IPF associated lung cancer tissue.



TIME Promotes Tumors in IPF-LC

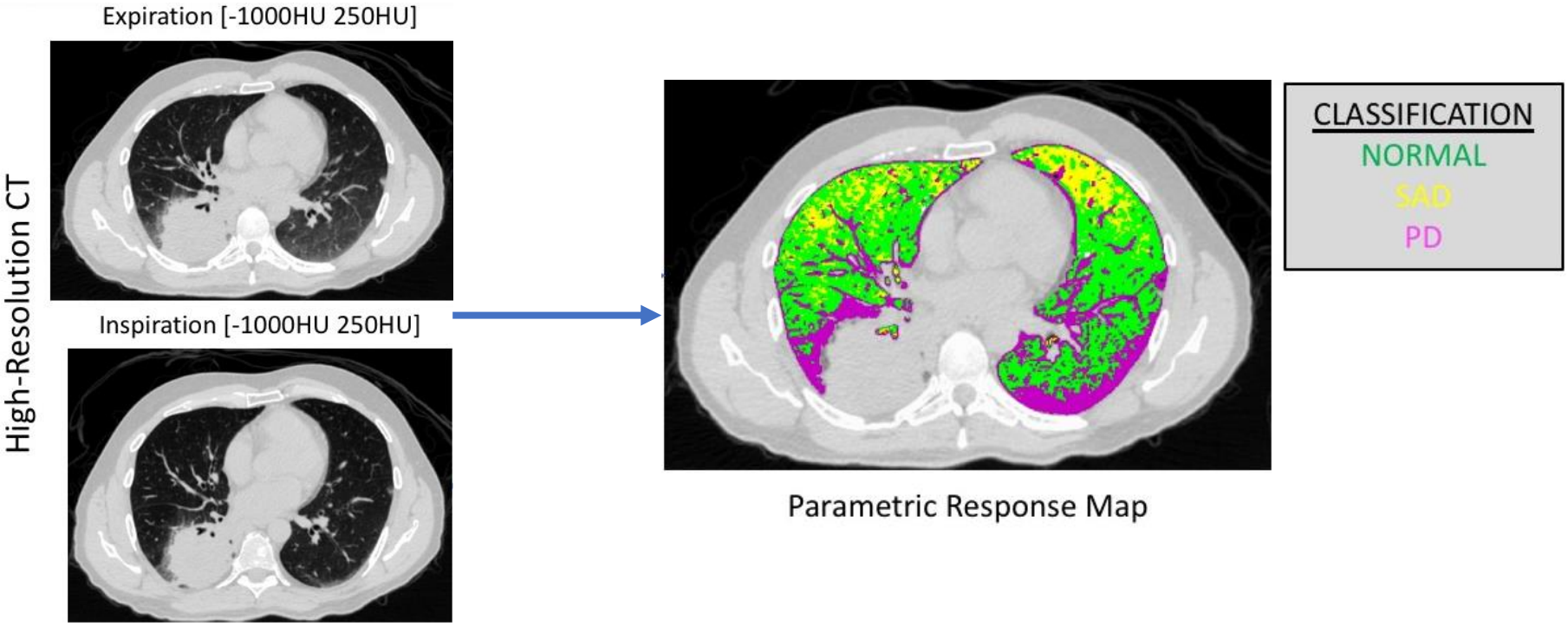
Radiation induced lung toxicity (RILT)

Radiation induces pneumonitis



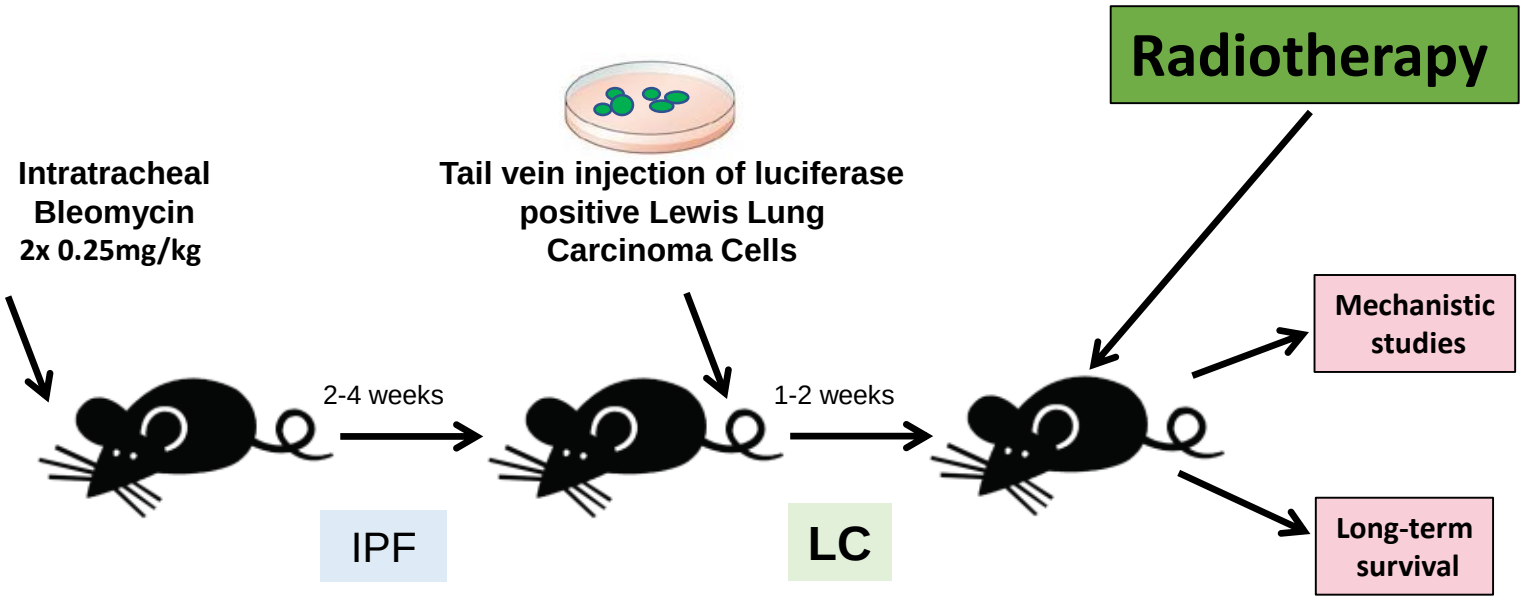
Demaria et al, Frontiers in Oncology, August 2012, Volume 2, Article 95

Pre-existing fibrosis exacerbated RILT



Collaboration with Craig Galban, Rocky Owen, Martha Matuszak, Caitlin Schonewolf, Shruti Jolly.

Evaluate the mechanisms of pre-existing inflammation in RT in mouse lung cancer model



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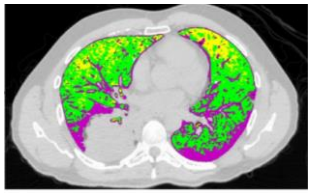
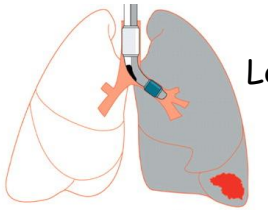
Assess pre-RT serum- and tissue based inflammatory markers as indicators of pre-existing co-morbidity



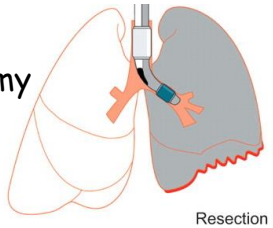
Parametric Response Map



Tumour

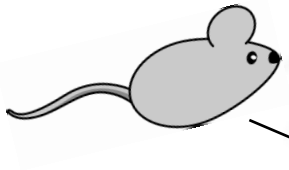
Before surgery

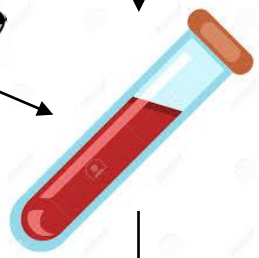
Lobectomy



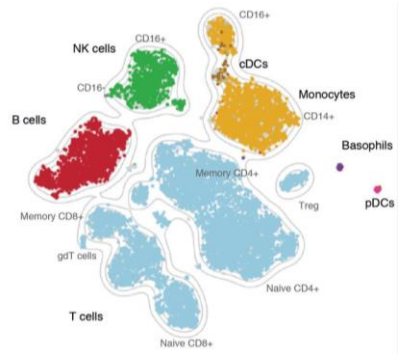
Resection

After surgery

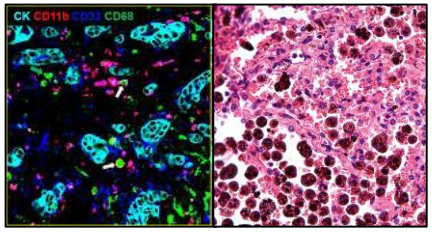




Cytokine/
Luminex

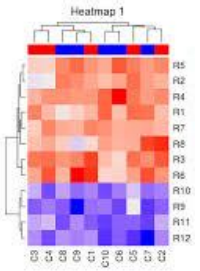


CyTOF



Histology

FACS



RNA seq

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Nneka Mbah

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Shruti Jolly

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Craig Galban
Aleksa Fortuna
Sundaresh Ram

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Rogel Cancer Center Research Grant

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THANK YOU!