

# Emphysema Induces Lung-Specific Autoantibodies that Exacerbate Ischemia Reperfusion Injury Post-Lung Transplantation

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# Adult Lung Transplants

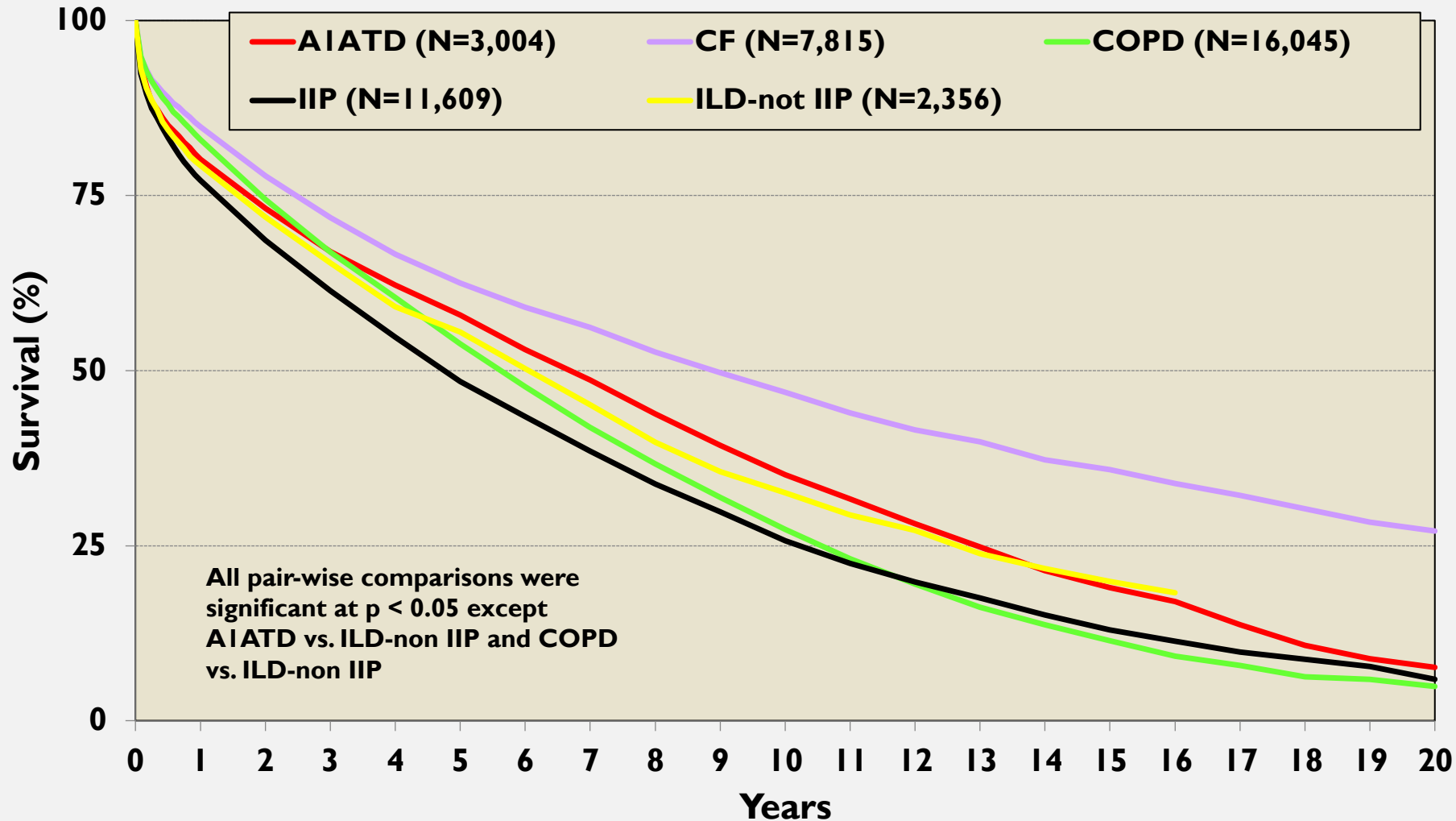
## Indications (Transplants: January 1995 – June 2015)

Diagnosis	Detailed diagnosis	N (%) (N=36.237)
COPD	COPD/EMPHYSEMA	10,462 (28.9%)
	OTHER SPECIFY	1 (<0.05%)
AIATD	ALPHA - 1 - ANTITRYPSIN DEFICIENCY	1,350 (3.7%)
IIP	DESQUAMATIVE INTERSTITIAL PNEUMONITIS (DIP)	11 (<0.05%)
	IIP:ACUTE INTERSTITIAL PNEUMONIA	2 (<0.05%)
	IIP: BOOP/COP	50 (0.1%)
	IIP: DESQUAMATIVE INTERSTITIAL PNEUMONIA	10 (<0.05%)
	IIP: IDIOPATHIC PULMONARY FIBROSIS (IPF)	9,655 (26.6%)
	IIP: LYMPHOCYTIC INTERSTITIAL PNEUMONIA (LIP)	11 (<0.05%)
	IIP: NONSPECIFIC INTERSTITIAL PNEUMONIA	189 (0.5%)
	IIP: RESPIRATORY BRONCHIOLITIS	2 (<0.05%)
	USUAL INTERSTITIAL PNEUMONITIS	106 (0.3%)
	ILD-not IIP	ALVEOLAR PROTEINOSIS
AMYLOIDOSIS		3 (<0.05%)

# Adult Lung Transplants

## Kaplan-Meier Survival by Diagnosis

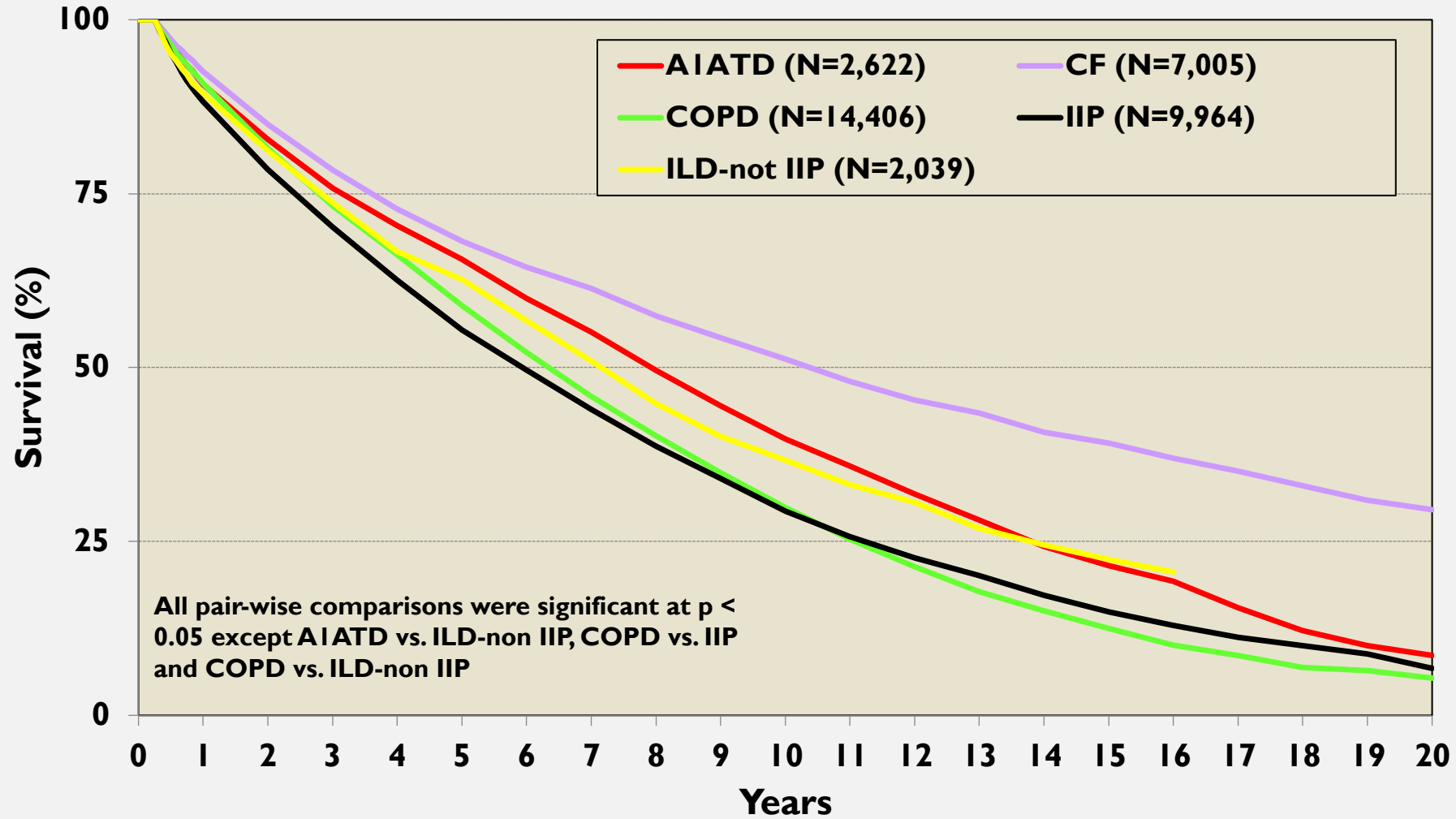
(Transplants: January 1990 – June 2014)



**Median survival (years):**  
AIATD: 6.7  
CF: 8.9  
COPD: 5.6  
IIP: 4.8  
ILD-not IIP: 6.1

# Adult Lung Transplants

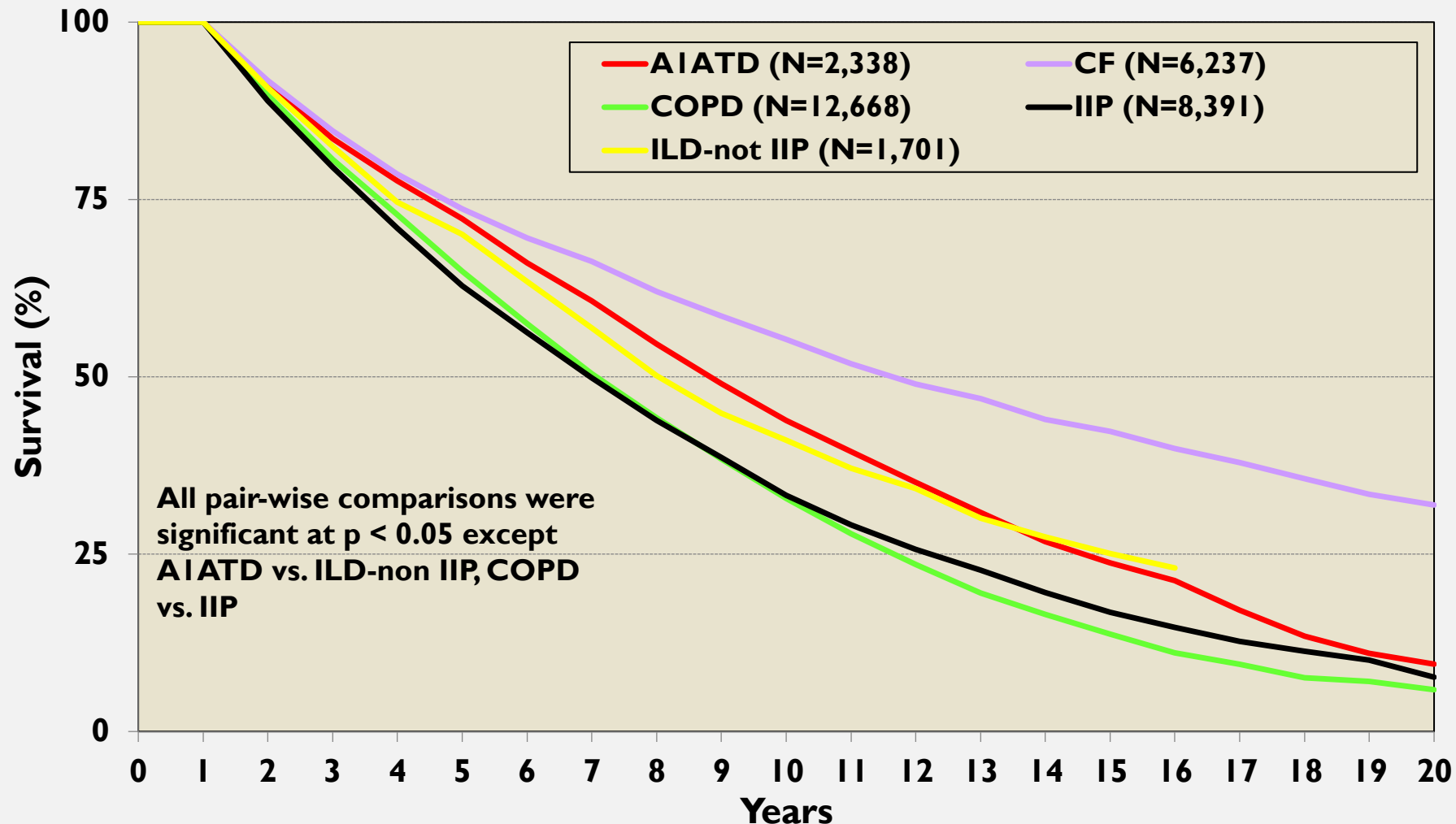
## Kaplan-Meier Survival by Diagnosis Conditional on Survival to 3 Months (Transplants: January 1990 – June 2014)



Median survival (years):  
**AIATD: 7.9**  
**CF: 10.3**  
**COPD: 6.3**  
**IIP: 5.9**  
**ILD-not IIP: 7.1**

# Adult Lung Transplants

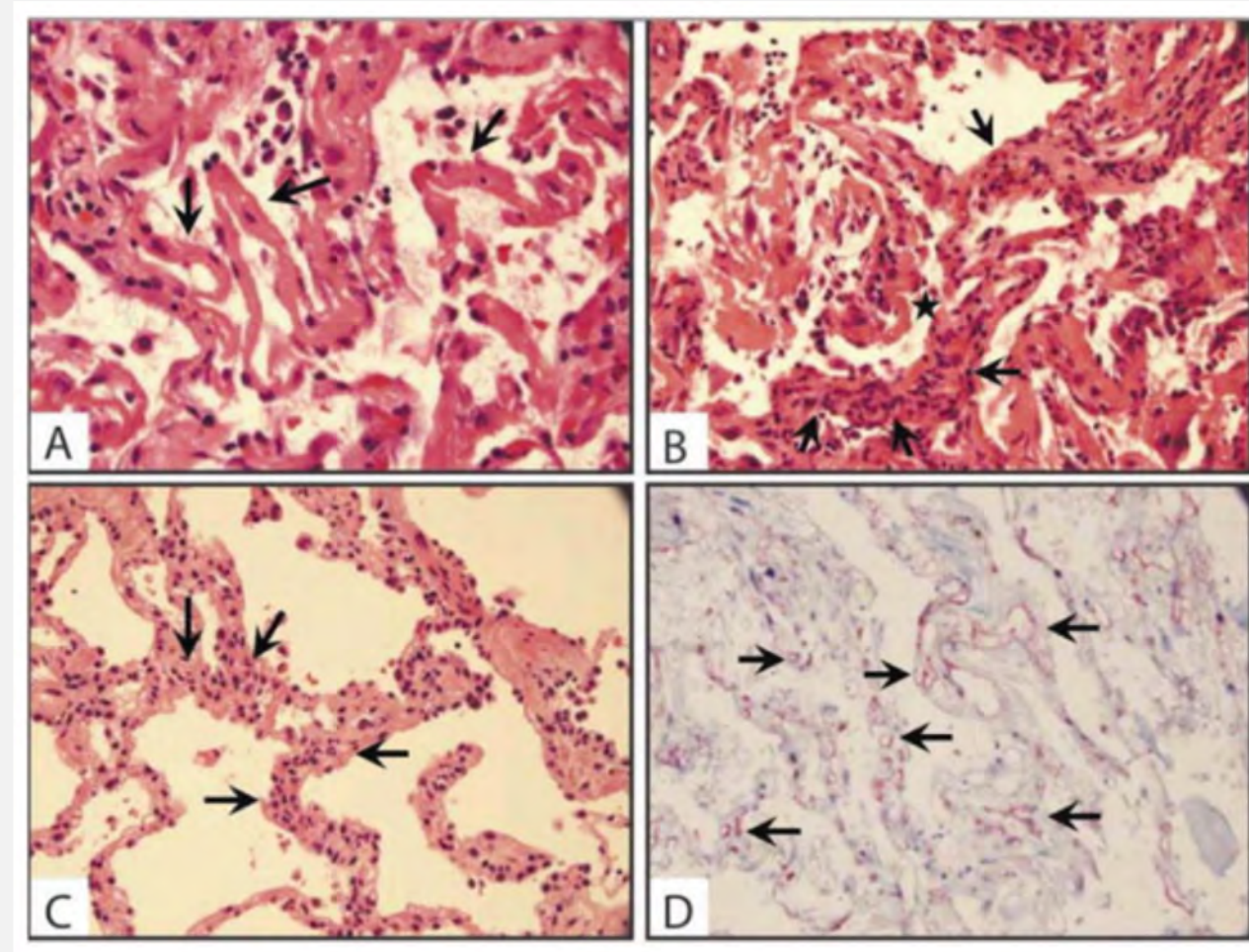
## Kaplan-Meier Survival by Diagnosis Conditional on Survival to 1 Year (Transplants: January 1990 – June 2014)



Median survival (years):  
 AIATD: 8.9  
 CF: 11.7  
 COPD: 7.1  
 IIP: 7.0  
 ILD-not IIP: 8.0

# OUTCOME DISCREPANCIES

- Recognition of antibody mediated injury in LTx is on the rise
- Pre-transplant autoantibodies are associated with worse PGD.<sup>1</sup>
  - 88% vs 54%
- Ab depletion in patients with DSA post-LTx lowers the risk for chronic rejection<sup>3</sup>
  - But not effective for all patients
- Where do COPD fit in?



# AUTOANTIBODIES IN COPD

- Increase in B cell follicular formations as disease progresses

*Brussels et al. Lancet. 2011 Sep 10;378(9795):1015-26*

- Increase autoantibodies following chronic smoke exposure

- Epithelial cells, endothelial cells, extracellular matrix proteins, modified proteins

Brandsma et al. BMC Pulmonary Medicine 2010, 10:64

Rinaldi Thorax. 2012 Aug;67(8):694-700

Lee et. al. Nat Med. 2007 May;13(5):567-9

Low et al. Pulm Med. 2011;2011:826160. doi: 10.1155/2011/826160

Greene et al. Am J Respir Crit Care Med. 2010 Jan 1;181(1):31-5

# ANTIBODIES IN EMPHYSEMA

- Collagen I
- Elastin
- Decorin
- Rheumatoid factor (RF)
- Cyclic citrullinated peptides (CCPs)
- HSP70



# NON-HLA AUTOANTIBODIES IN LT<sub>x</sub>

- Abs against Non-HLA self Antigens implicated in worse short- and long-term outcomes
  - Development has largely been noted to occur post-transplantation
- K-alpha Tubulin
- Collagen V
- Collagen I

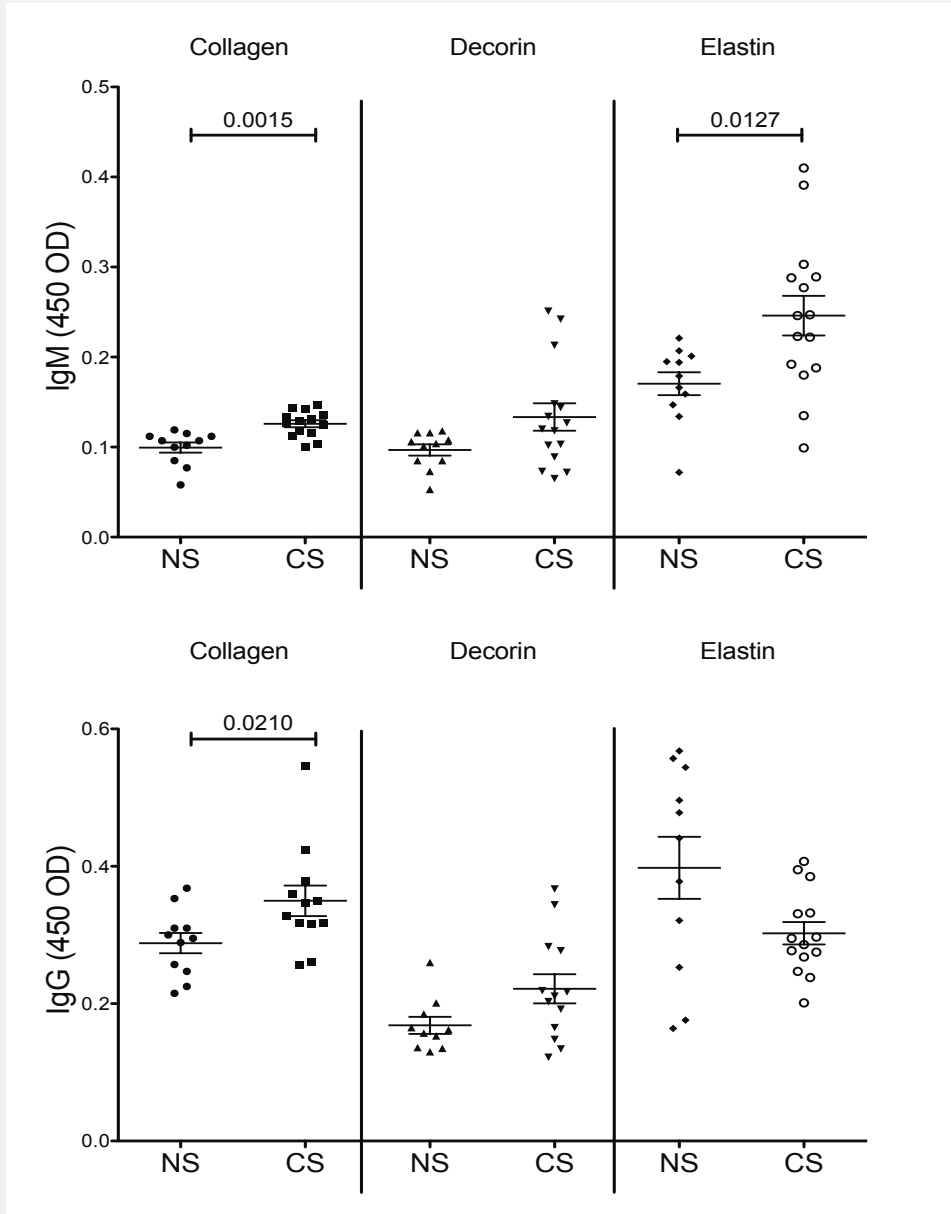
DO COPD-RELATED AUTOANTIBODIES  
HAVE SIGNIFICANCE FOR LT<sub>x</sub>?

# EMPHYSEMA MOUSE MODEL

- Cigarette smoke exposure
  - 5 hours a day
  - 5 days a week
  - 6 months

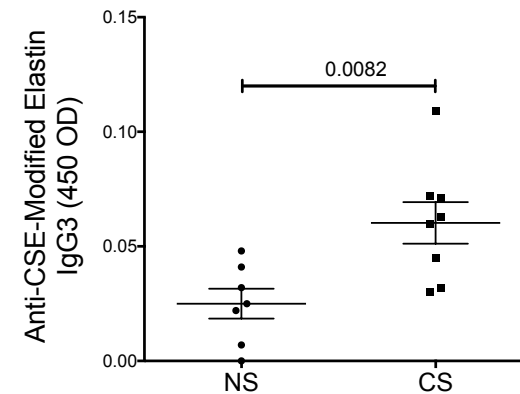
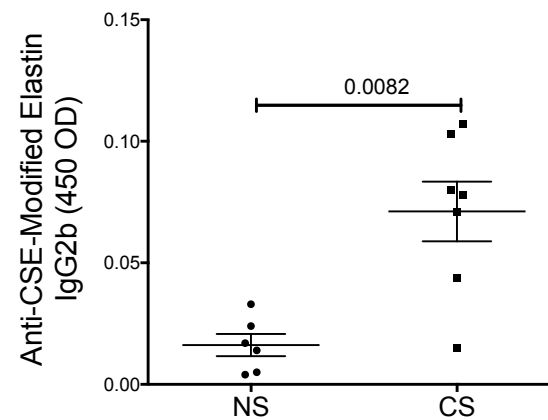
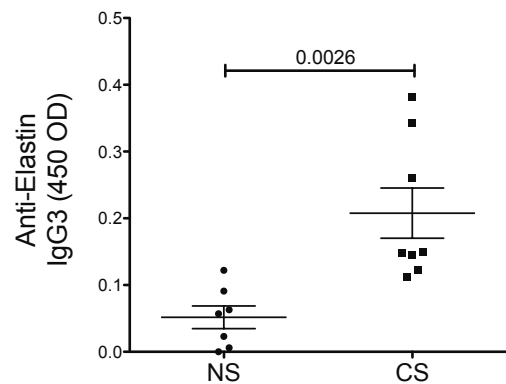
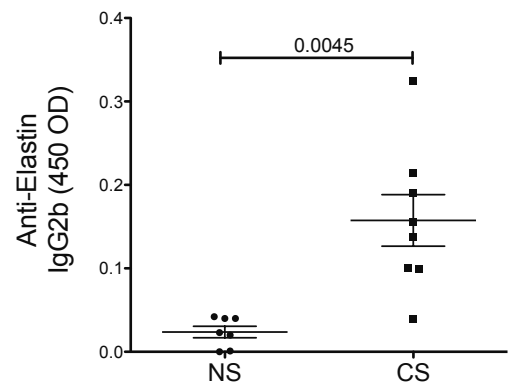
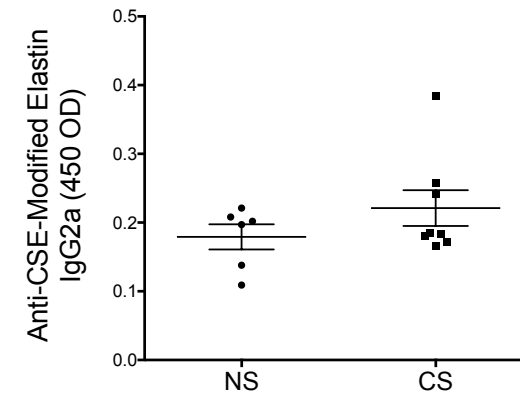
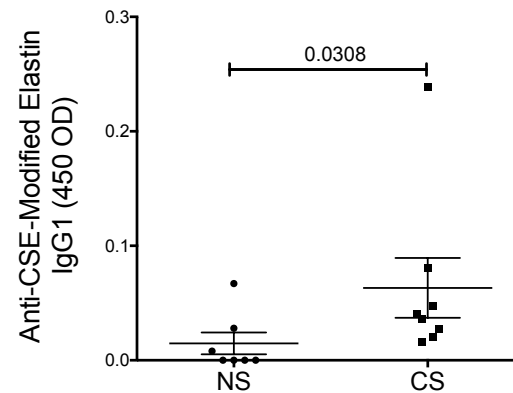
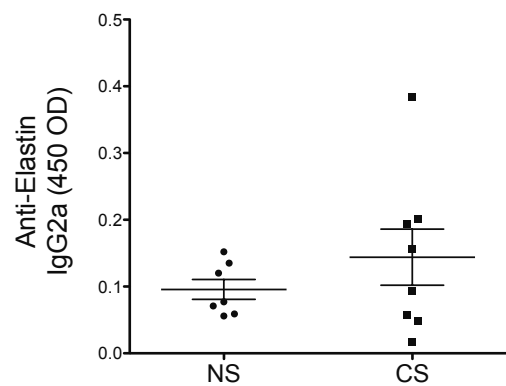
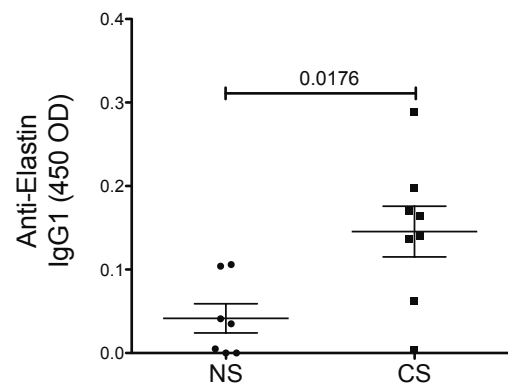


# Serum Ab Elisa to self extracellular matrix proteins



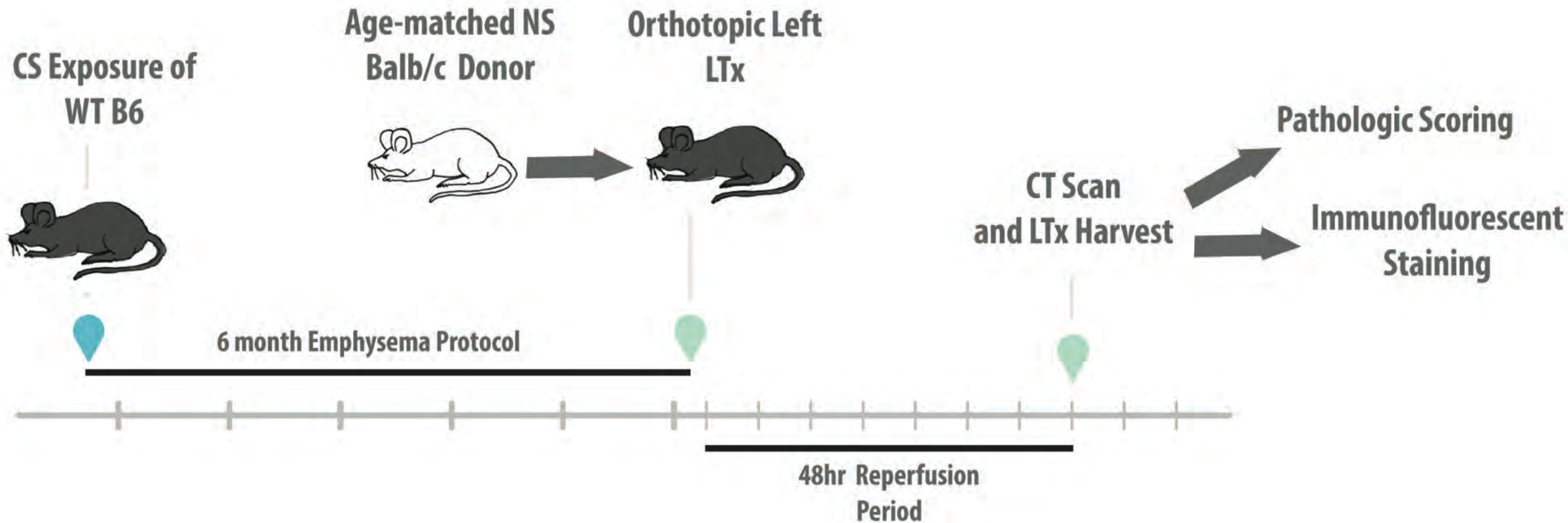
**ELASTIN AND COLLAGEN  
AUTOREACTIVE ABS EXIST  
IN MOUSE MODEL  
AND CORRELATE WITH  
SMOKE EXPOSURE**

# CS-MODIFIED ELASTIN INDUCES IgG RESPONSE OF COMPLEMENT FIXING SUBTYPES



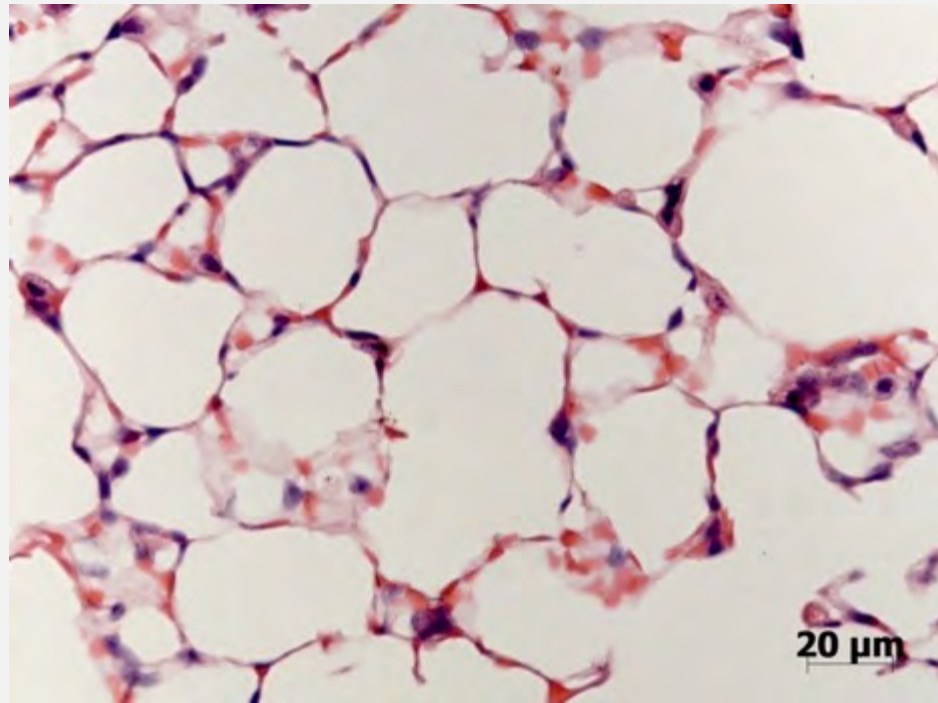
**DOES PRE-EXISTING AUTO-REACTIVITY  
IMPACT POST TRANSPLANT  
OUTCOMES?**

# TRANSPLANT MODEL

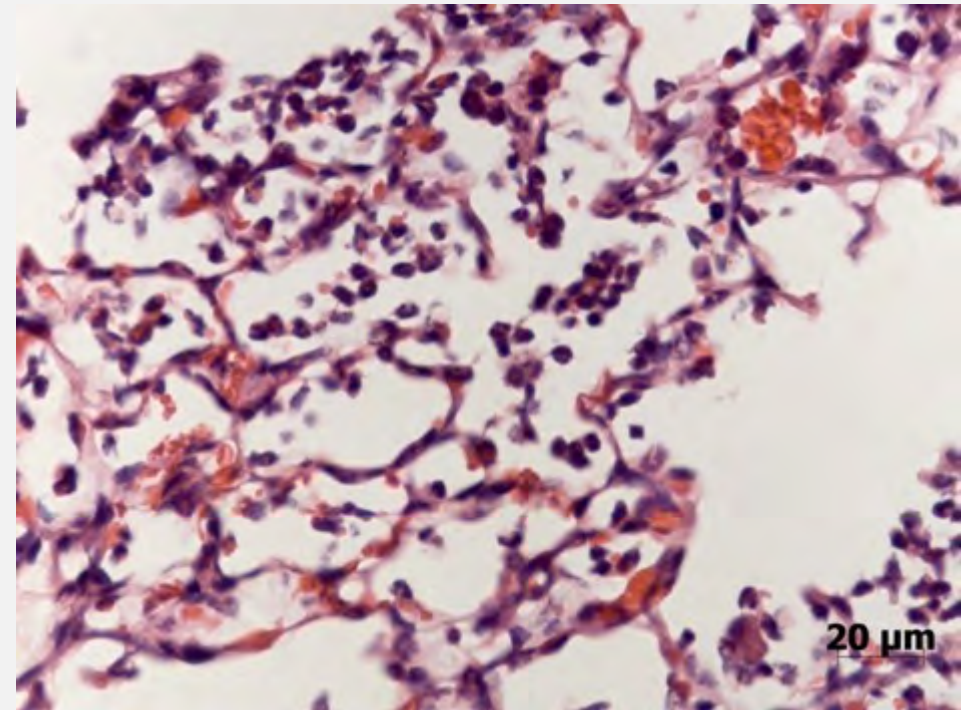


# RECIPIENT CS EXPOSURE EXACERBATES IRI

NS CONTROL

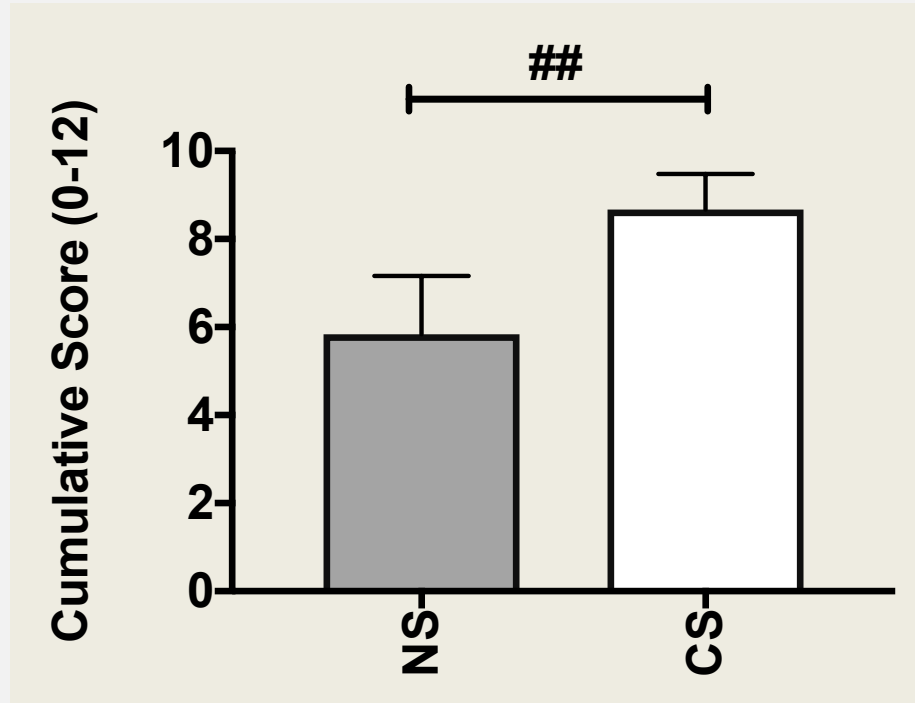


CS RECIPIENT

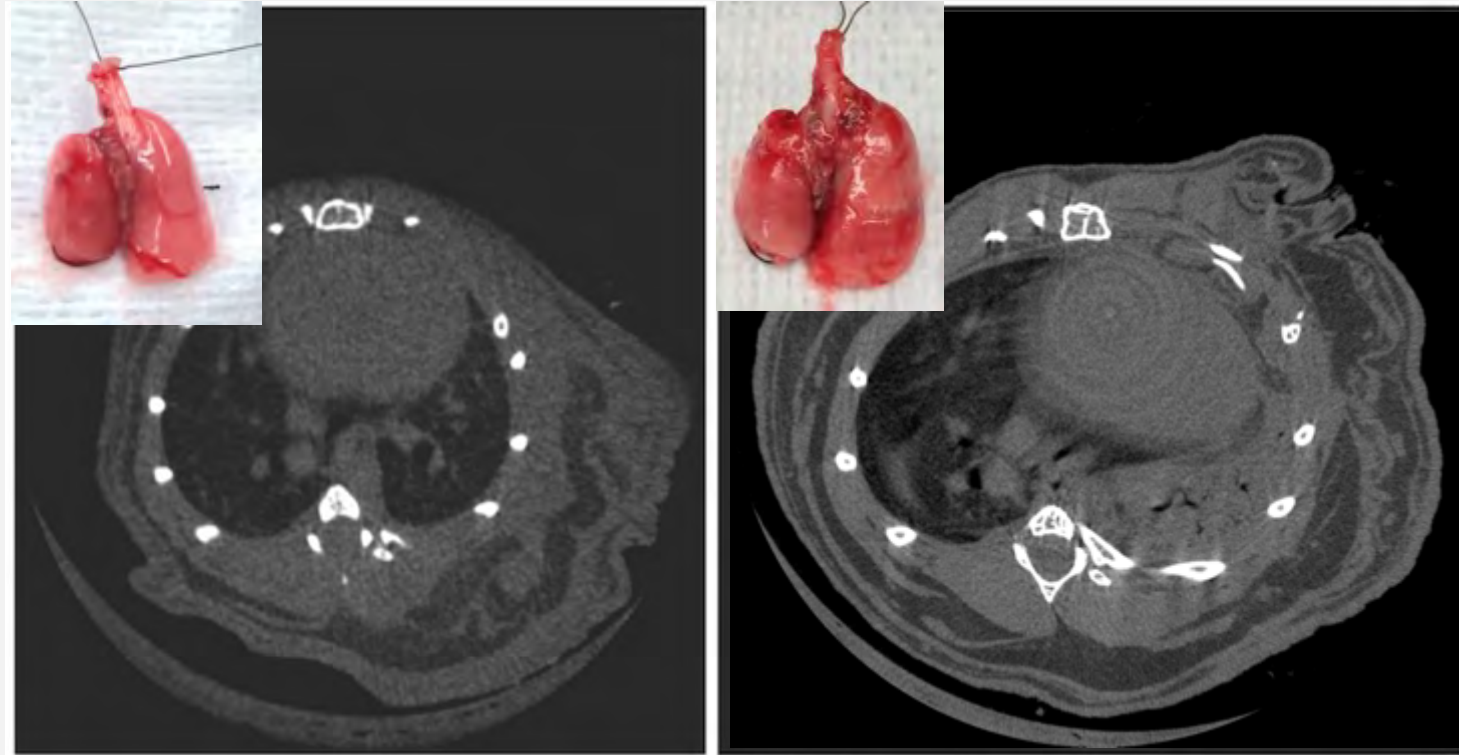




# RECIPIENT CS EXPOSURE EXACERBATES IRI



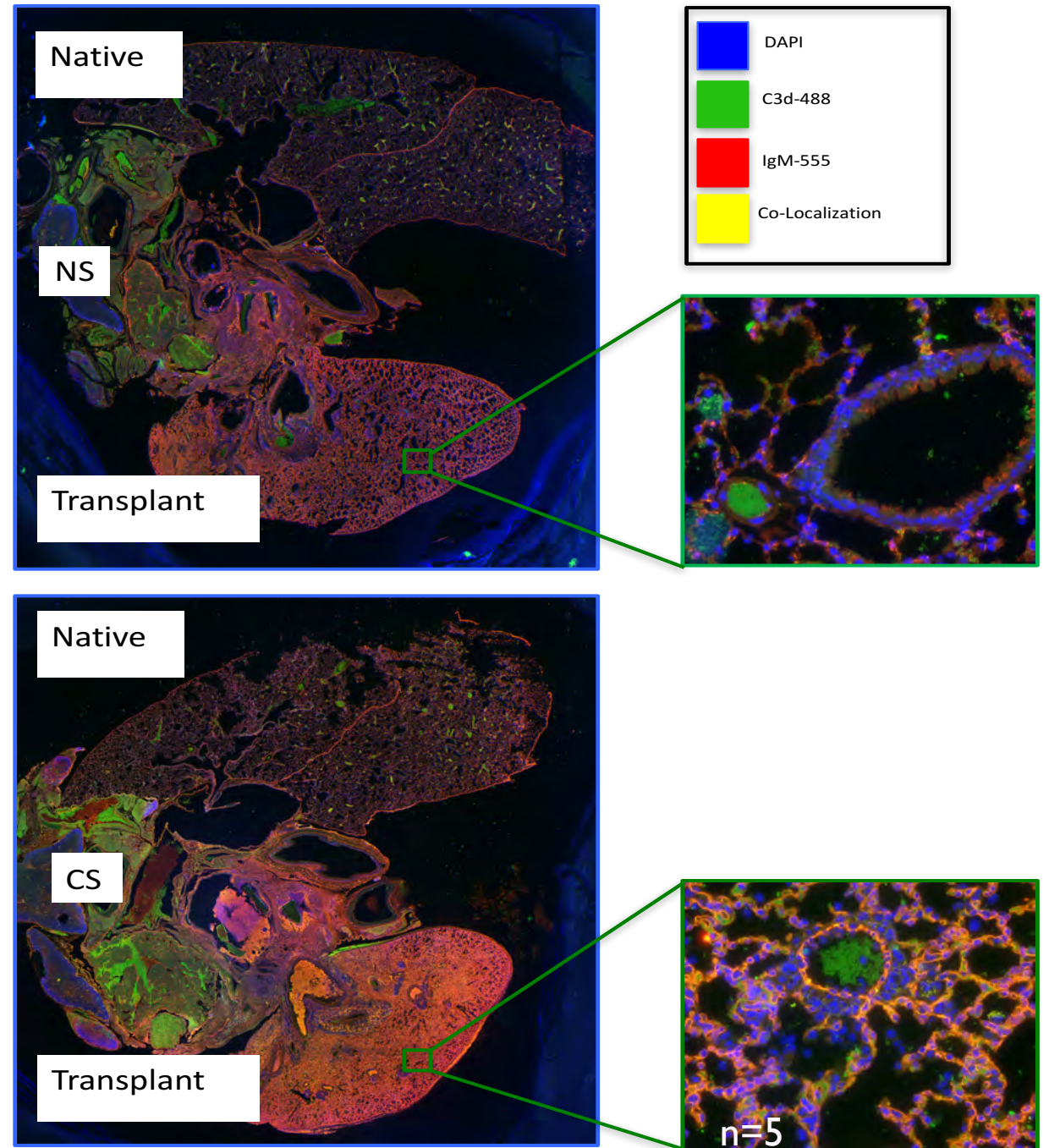
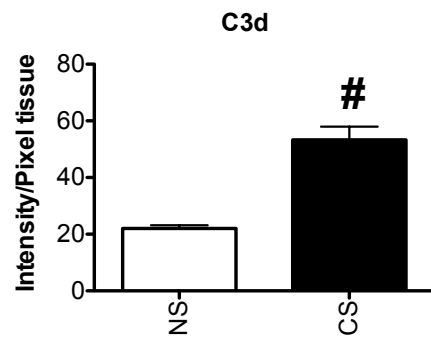
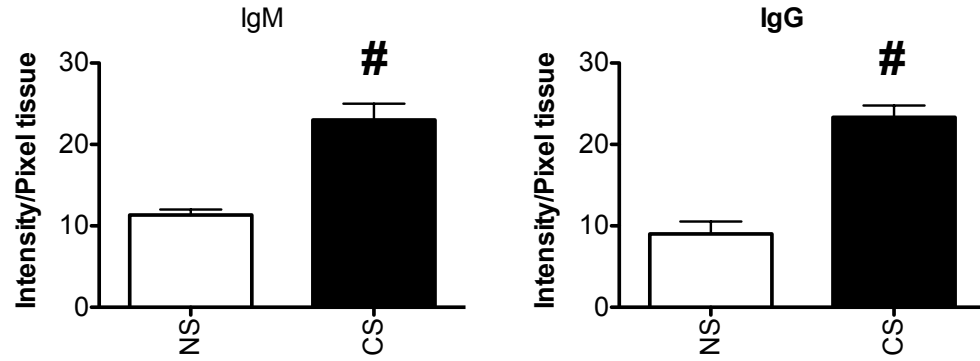
##p<0.001. n=5



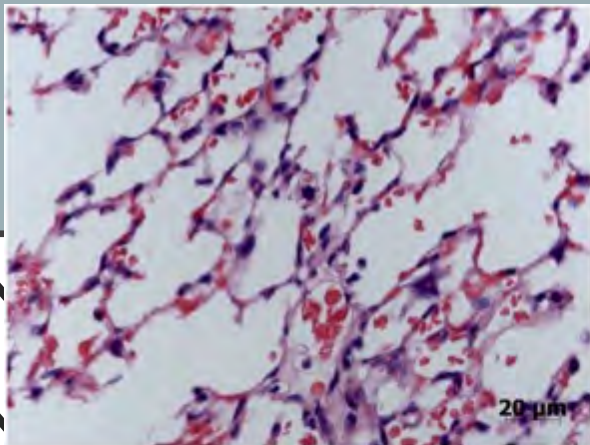
NS

CS

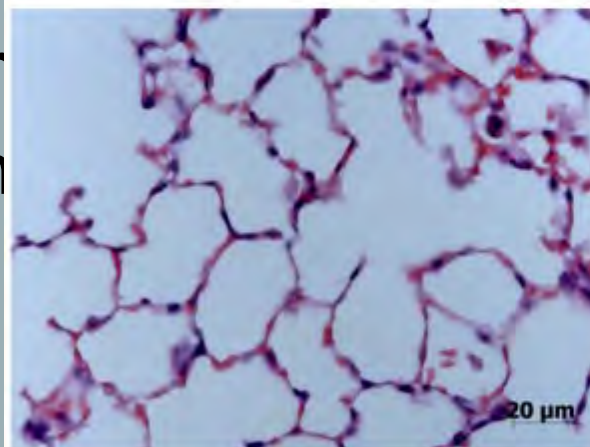
# COMPLEMENT DEPOSITION AND IgM/IgG SIGNIFICANTLY INCREASED IN CS VS NS



# SYNGENEIC TRANSPLANT



Rag1+CS

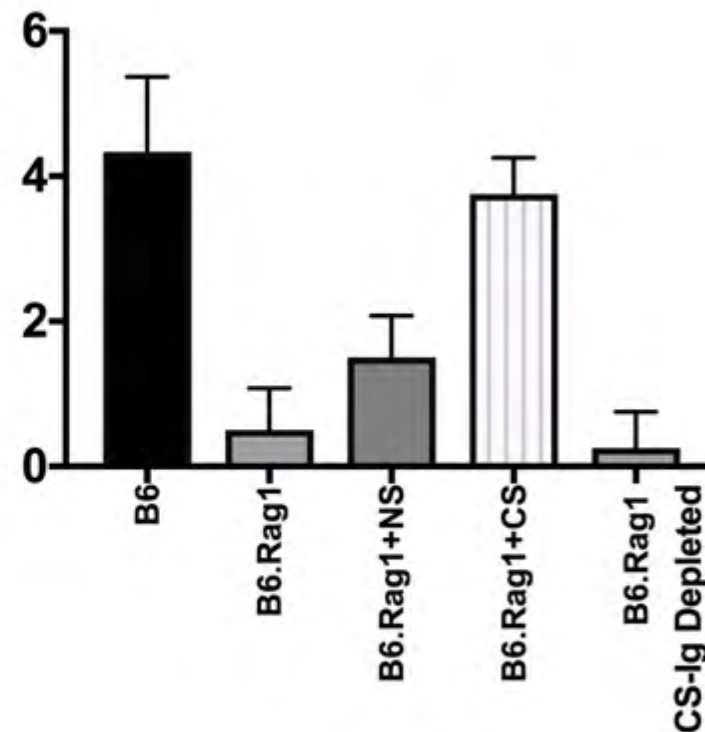


Rag1+  
CS-Ig Depleted

Recipients received  
serum from  
immediately

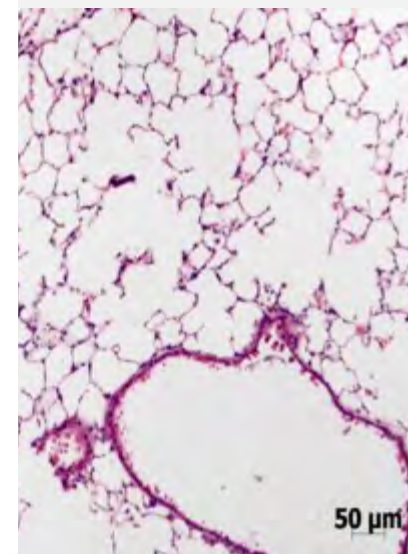
Analyzed 6h

Cumulative Histology Score 0-12

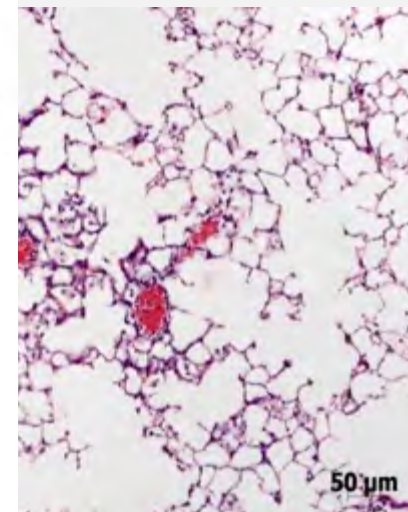


D6 Rag1-D6

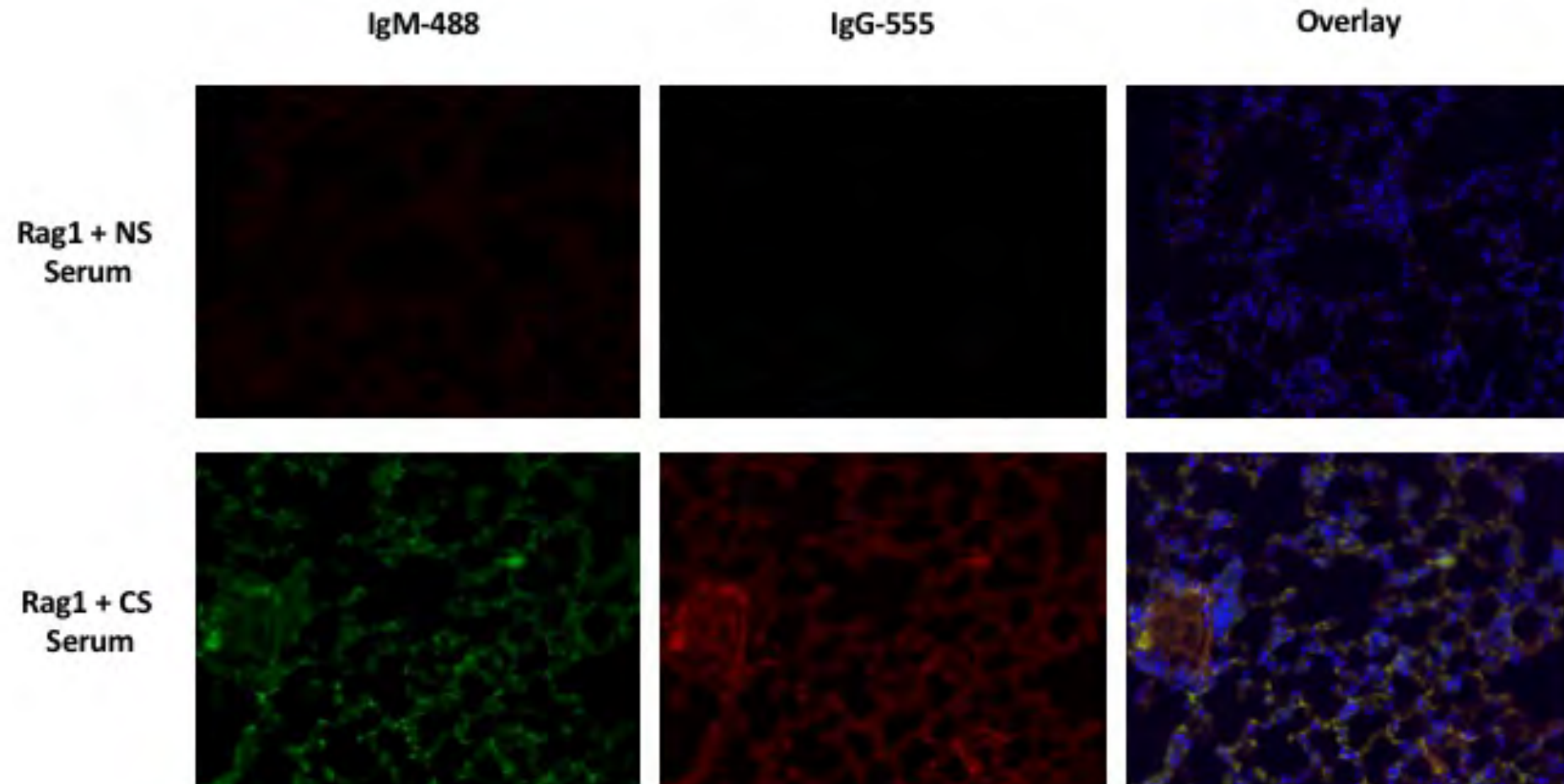
D6 Rag1-B6.Rag1



Rag1-B6.Rag1  
+CS serum



# ANTIBODY DEPOSITION IN CS- RECONSTITUTED RAG LT<sub>x</sub> IS SIGNIFICANTLY INCREASED



# CONCLUSIONS

- Recipient autoreactivity primes for IRI
- CS exposure induces the development of lung specific autoantibodies that can exacerbate IRI and even drive IRI in the absence of alloimmunity
- Complement-fixing subtypes of antibodies are upregulated and may represent an appropriate therapeutic target
- Recipient CS exposure associated with worsened acute rejection
  - Implications for current LTx research and the animals models of LTx presently employed