

Tissue-specific, Auto-reactive CD4+CD28null cells in Explanted COPD Lungs

Diplomarbeit
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Diagnosis and Regeneration

unter der Anleitung von
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Chronic inflammation of the lung tissue
caused by:

Tobacco Smoking

In- and Outdoor air pollution

Occupational exposures

Genetic Factors



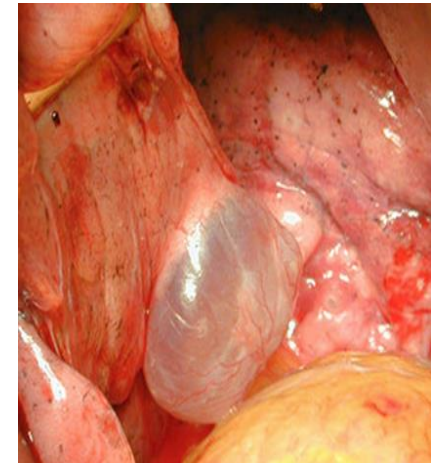
Continual decline in airflow

Classification according to the Global Initiative for
Chronic Obstructive Lung Disease in GOLD I - IV

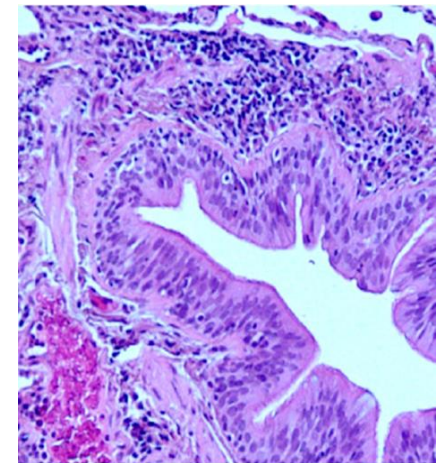
Global Initiative for Chronic
Obstructive
Lung
Disease



Changes in the lung:
pulmonary emphysema
inflammatory infiltrate
air trapping
exacerbations



Systemic changes:
elevated pro-inflammatory cytokines & CRP
- $TNF-\alpha$, $IL-6$, $IL-8$
higher prevalence of cardiovascular disease,
diabetes, lung cancer
weight loss



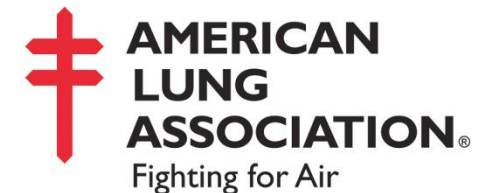
WHO Fact Sheet October 2013

Worldwide 64 million people affected by COPD

In 2011, it ranked as the fourth leading cause of death

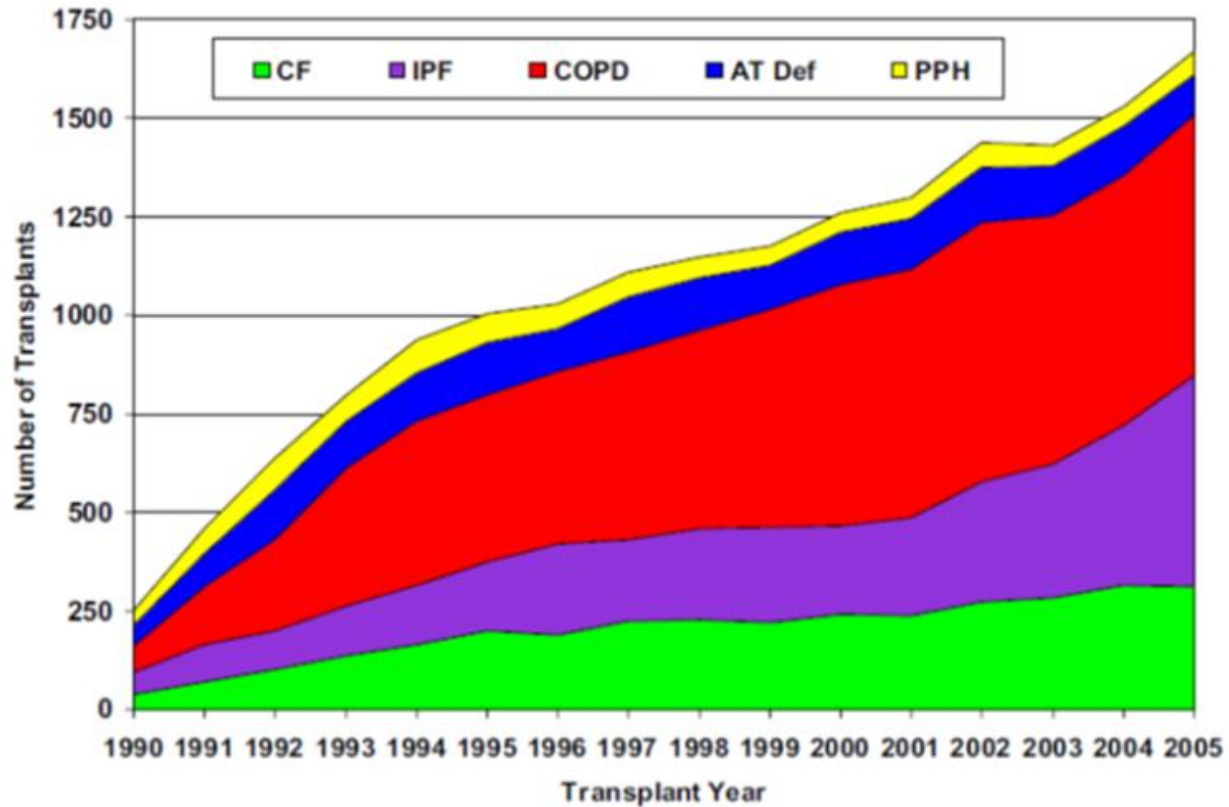
The disease now affects men and women almost equally, due in part to increased tobacco use among women in high-income countries

COPD is not curable, but treatment can slow the progress of the disease





Background



Trigger mechanism

Inflammation of lung tissue

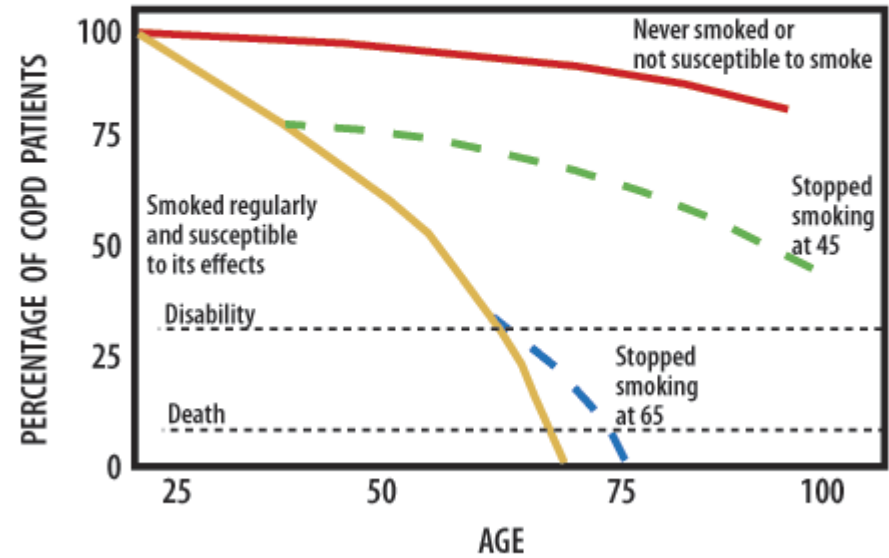
Predisposition

Yes

No

Progression of immune response / COPD/ accelerated decline of lung function

Normal decline of lung function



Reprinted with permission from O'Donnell et al.⁴

Hypothesis: Does COPD have an autoimmune component?

A Agustí, W MacNee, K Donaldson, M Cosío

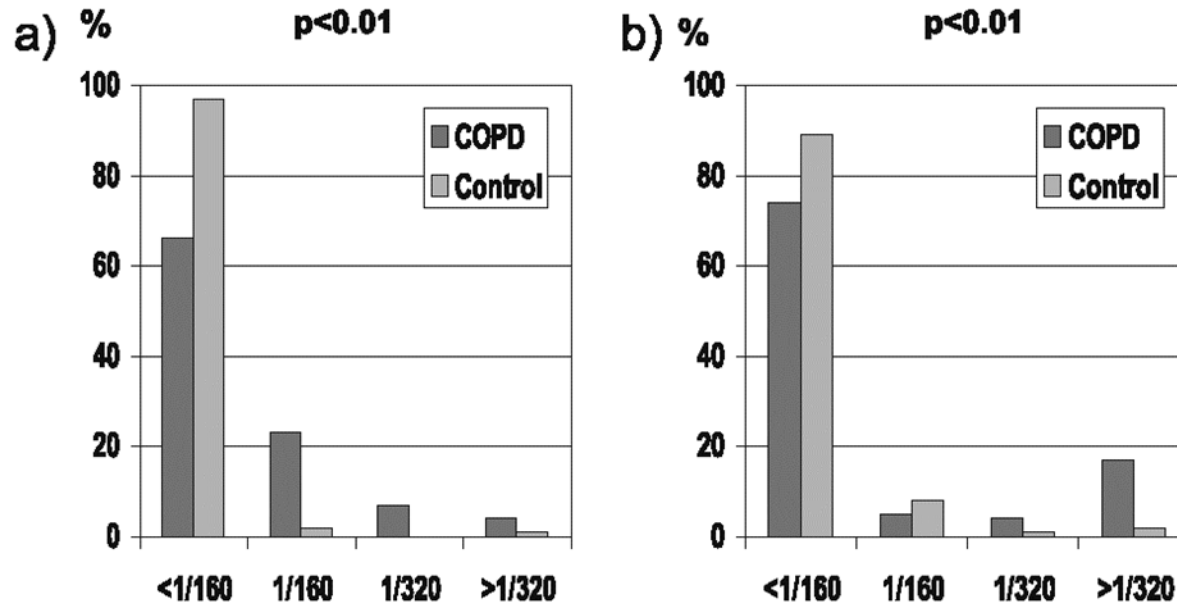
A new hypothesis that considers the role of the immune system in the pathogenesis of COPD is explored which, if true, will generate new therapeutic opportunities in this condition.

Thorax 2003;**58**:832-834

Only small percentage of smokers reach the later stages of COPD

Persistence despite smoking cessation

Smokers have increased levels of antigen-presenting cells



Autoantibody titers

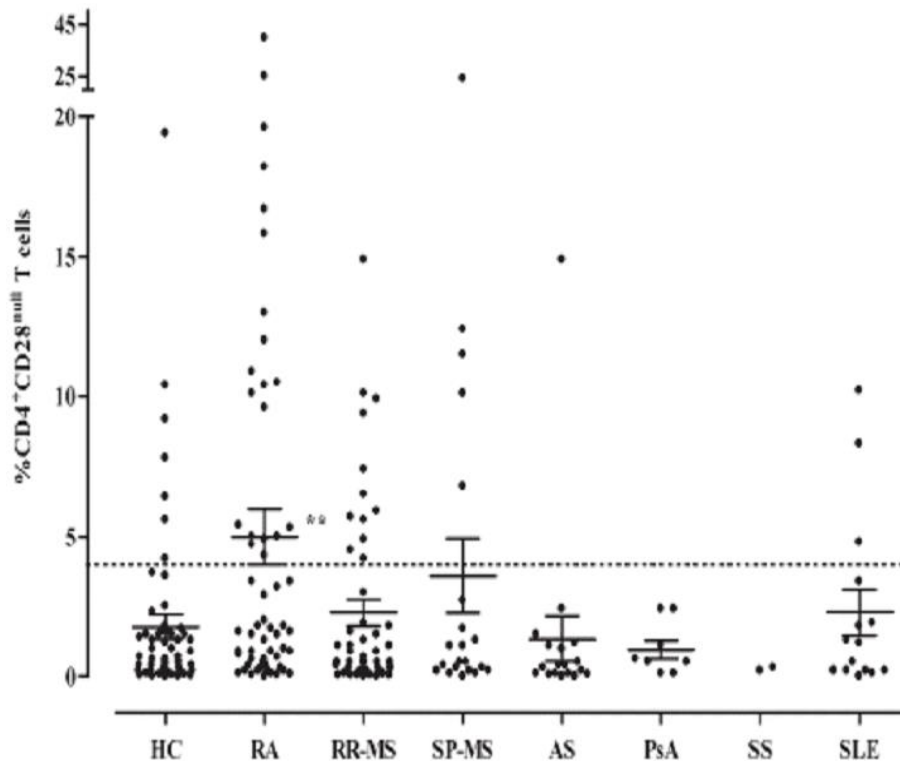
a) antinuclear antibody (ANA)

b) anti-tissue antibody (AT)

Analyses of immunosenescent markers in patients with autoimmune disease

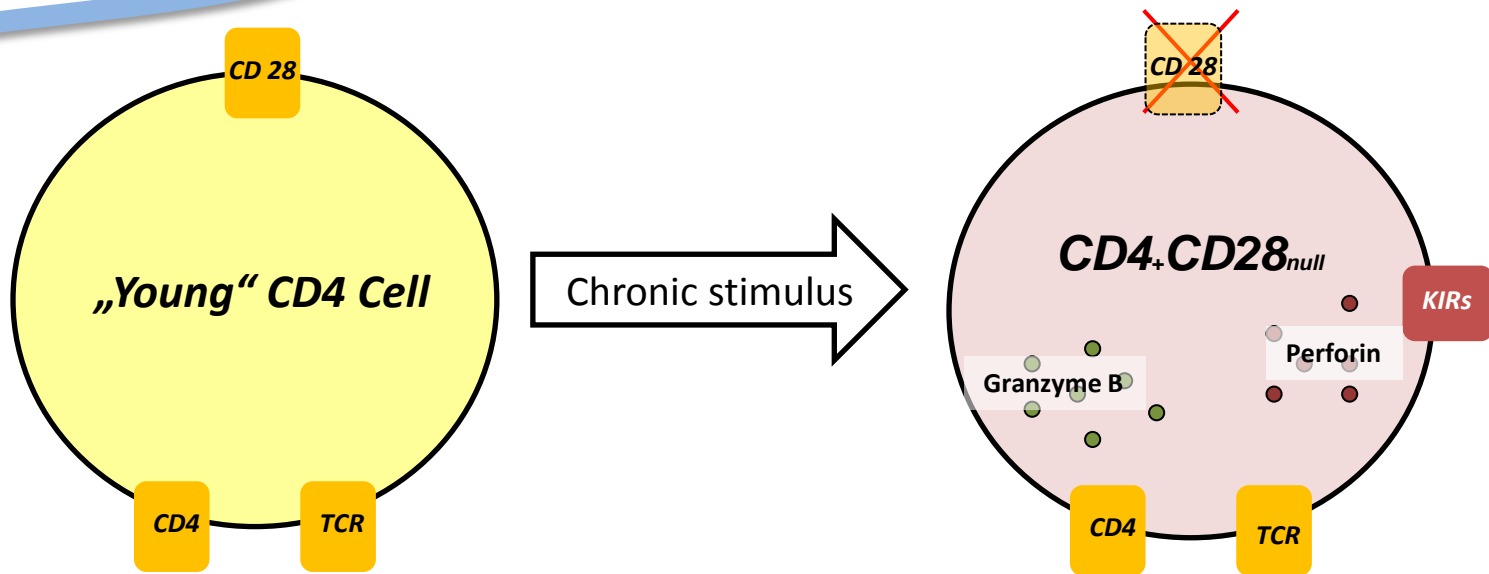
Marielle Thewissen ^a, Veerle Somers ^a, Koen Venken ^a, Loes Linsen ^a, Pieter Van Paassen ^b, Piet Geusens ^a, Jan Damoiseaux ^b, Piet Stinissen ^{a,*}

Clinical Immunology (2007) 123, 209–218



CD4+CD28null

Rheumatoid arthritis
Wegener's granulomatosis
Ankylosing spondylitis
Multiple sclerosis
Inflammatory bowel disease
etc.



Ability to lyse target cells

High levels of perforin and granzyme B

Expression of Killer immunoglobulin-like receptors (KIRs)

Elevated expression of Bcl-2

Clinical & Experimental Immunology
The Journal of Translational Immunology

British Society for immunology

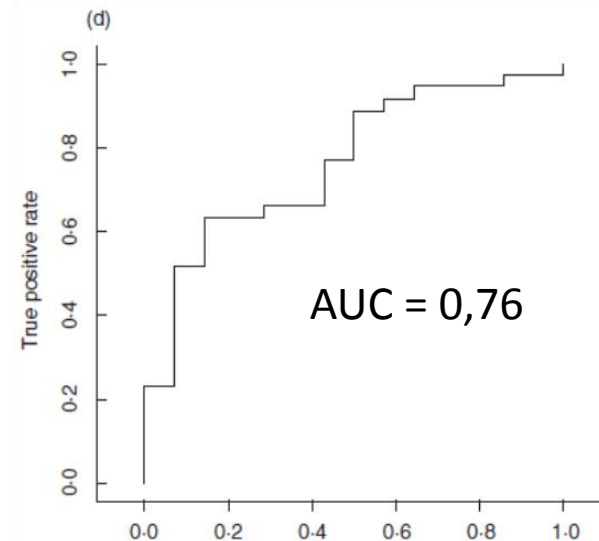
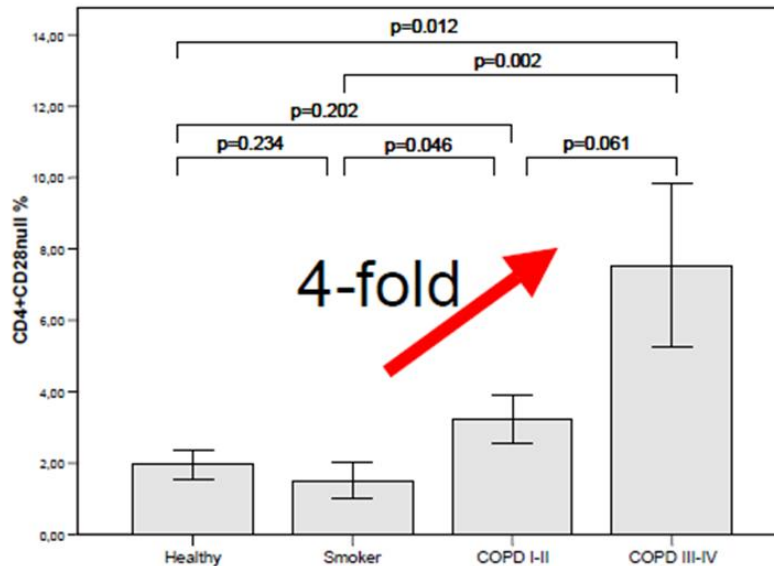
Clinical and Experimental Immunology

ORIGINAL ARTICLE

doi:10.1111/j.1365-2249.2008.03835.x

T cell senescence and contraction of T cell repertoire diversity in patients with chronic obstructive pulmonary disease

C. Lambers, S. Hacker, M. Posch, K. Hoetzenecker, A. Pollreisz, M. Lichtenauer, W. Klepetko and H. Jan Ankersmit



Can CD4+CD28null cells be found in explanted endstage COPD lungs?

Do CD4+CD28null cells appear in the lungs in levels comparable to systemic levels?

Do those cells have auto-reactive properties?

2 study groups

- COPD GOLD IV (n=13)
- Healthy controls (n=5)

**Flow cytometry – Blood
CD4+ cells**

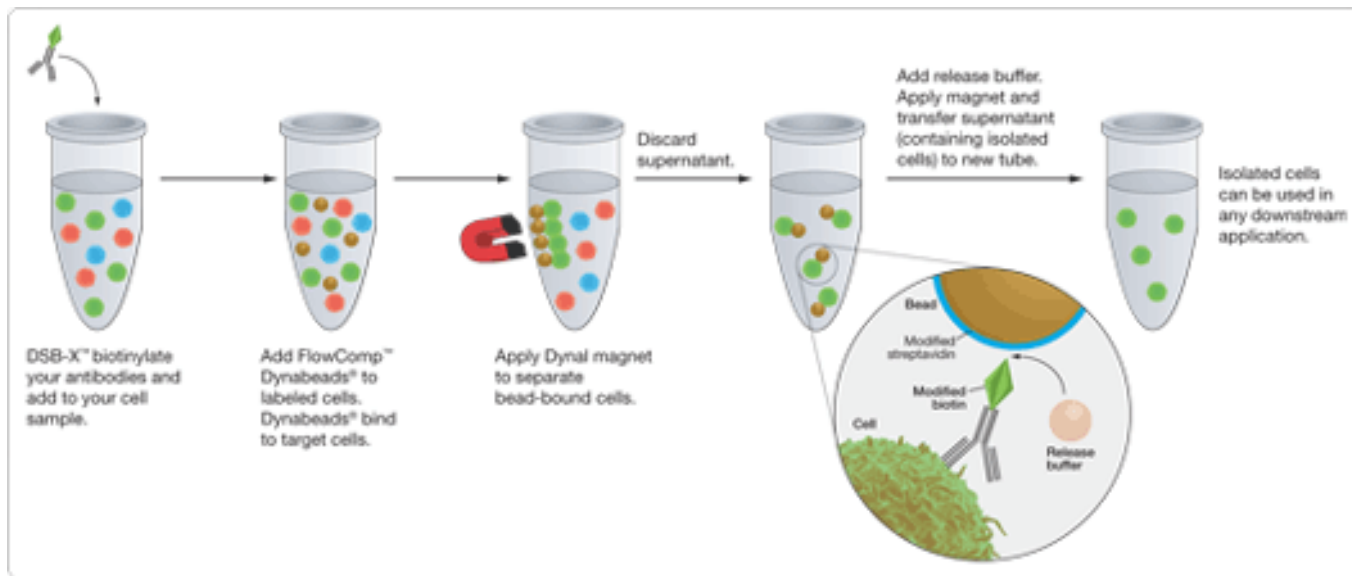


Proliferation Assay - incubated with:

- Elastin soluble
- Elastin peptide
- Collagen peptide
- BSA
- IL-2

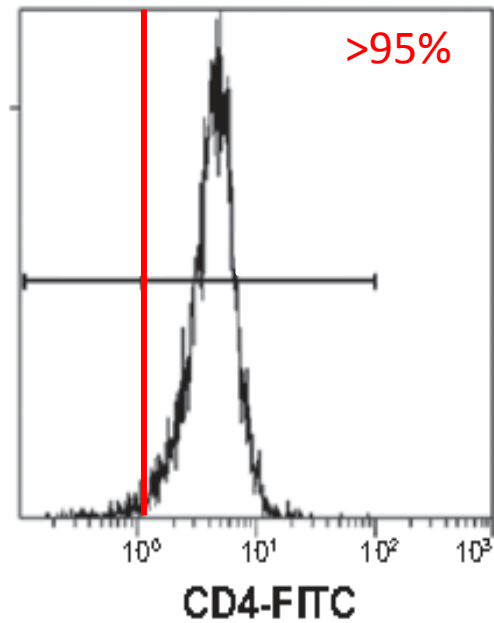
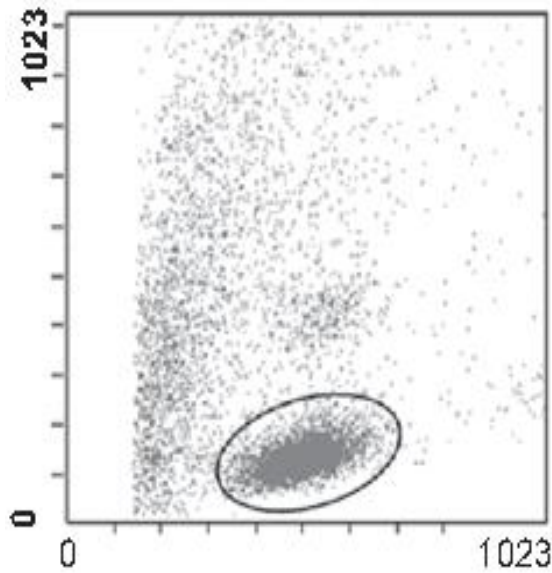


Dynabeads separation

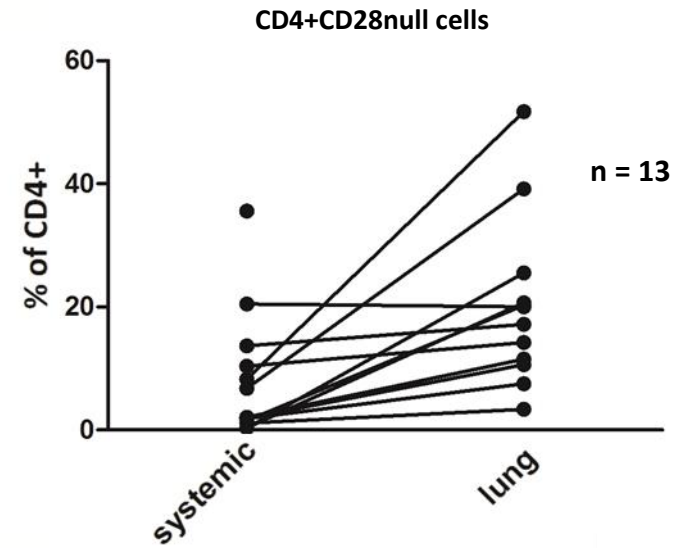
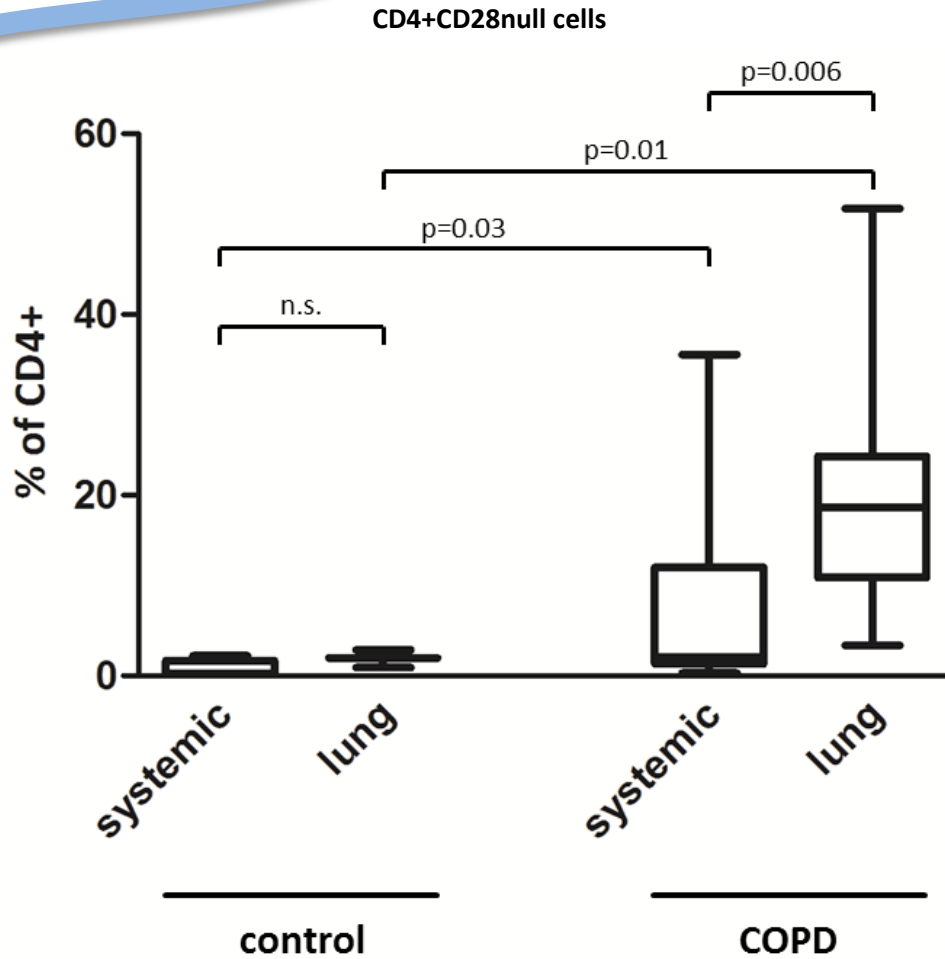


	Gender	Age	FEV1 %	FEV1 % VCmax	TLC	Medication	Smoker/PY
Patient 1	M	52	29	55	131	Th, ACH, BA, INH-C	Yes/25
Patient 2	M	49	28	39	189	Th, ACH, BA, INH-C	Yes/65
Patient 3	F	65	30	52	141	Th, ACH, BA, INH-C, syst-C	Yes/40
Patient 4	F	57	31	48	160	Th, ACH, BA, INH-C	Yes/30
Patient 5	F	58	15	57	107	Th, ACH, BA, INH-C, syst-C	Yes/38
Patient 6	F	62	13	50	171	Th, ACH, BA, INH-C	Yes/37
Patient 7	F	55	28	62	131	Th, ACH, BA, INH-C, syst-C	Yes/35
Patient 8	F	48	14	47	129	Th, ACH, INH-C, syst-C	Yes/30
Patient 9	M	63	15	36	160	ACH, BA, INH-C	Yes/40
Patient 10	M	58	23	34	132	ACH, BA, INH-C	Yes/100
Patient 11	M	59	23	37	130	ACH, BA, INH-C, syst-C	Yes/50
Patient 12	F	54	17	43	148	Th, ACH, BA, INH-C	Yes/90
Patient 13	F	39	36	51	125	Th, ACH, BA, INH-C, syst-C	No
Control 1	M	61	71	83	120	BA	Yes/80
Control 2	M	87	75	87	109	/	Yes/75
Control 3	M	18	Spontaneous pneumothorax—no lung function available			/	No
Control 4	F	79	61	81	111	/	No
Control 5	M	48	95	93	115	/	No

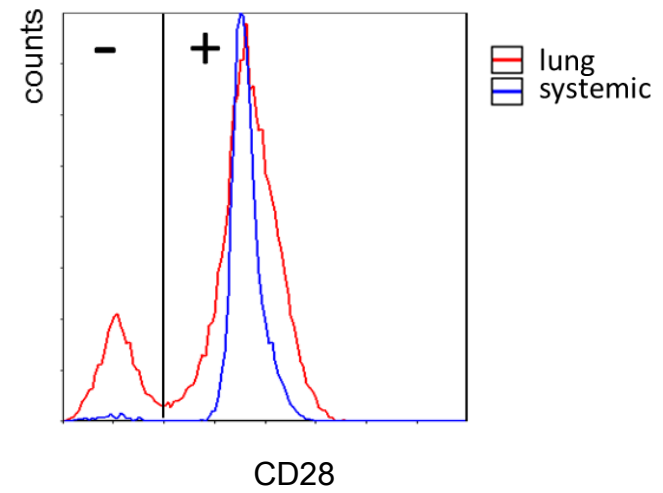
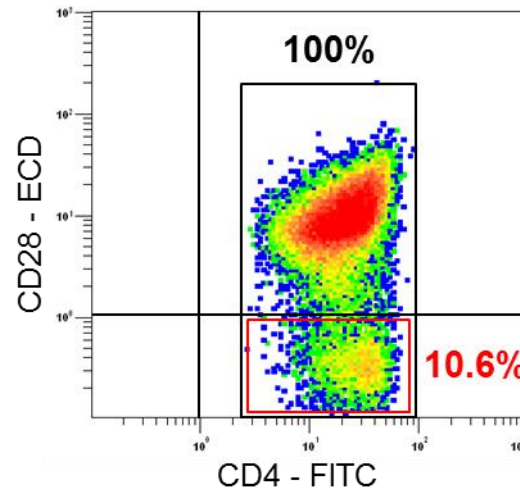
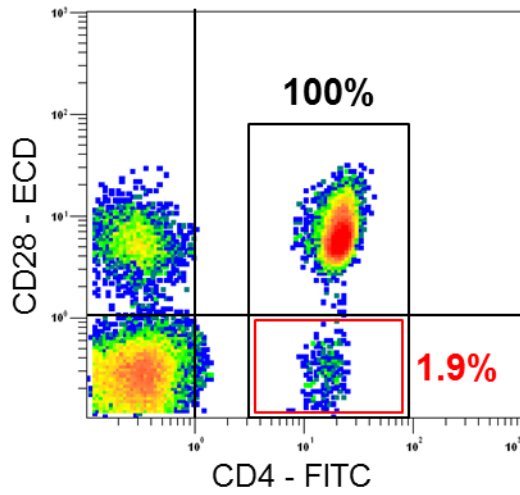
Results



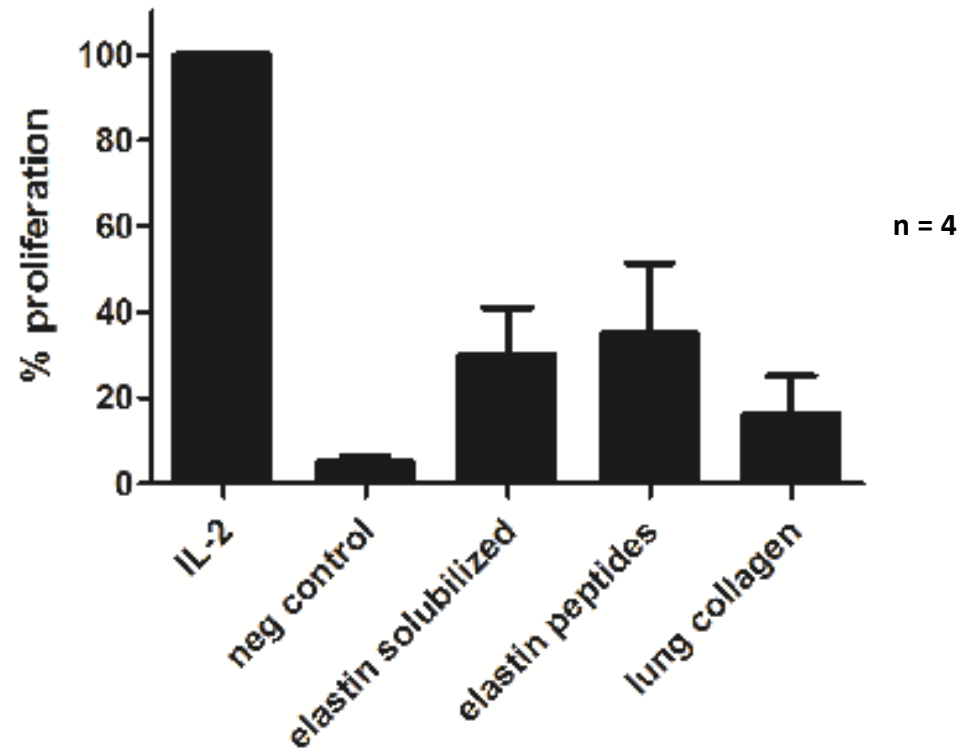
Results



Results



CD4+ proliferative response



CD4+CD28null cells

- are systemically increased in COPD when compared to healthy controls
- are in higher numbers in lung tissue than in the circulation from end-stage COPD patients
- show proliferative response when in contact with components of the extracellular matrix

These findings suggest that CD4+CD28null cells that are resident in the lung play a role in the pathomechanism of COPD

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