Rôle de la sénescence cellulaire dans les maladies respiratoires chroniques

Implication dans le cancer du poumon

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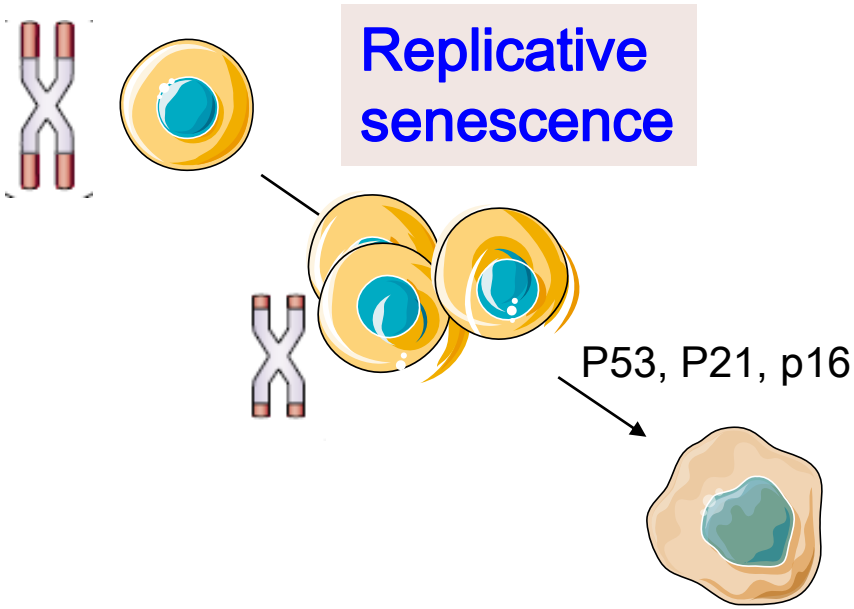
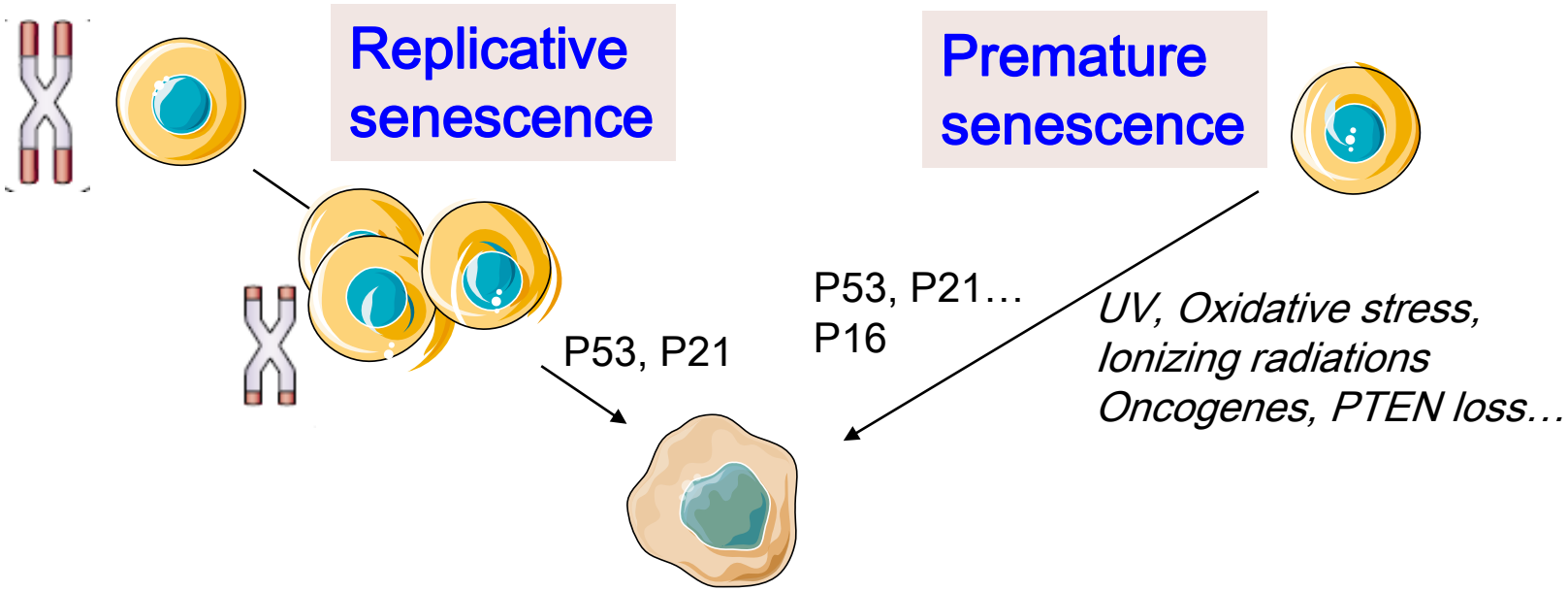
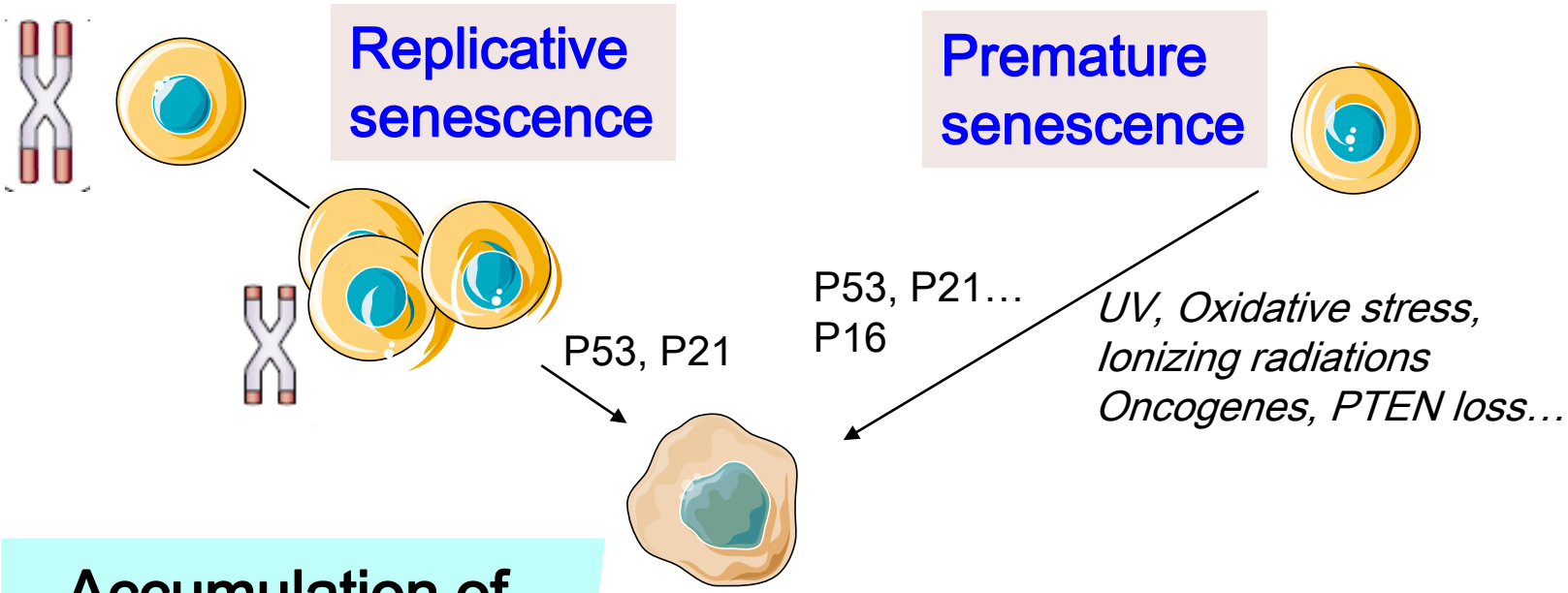
Cell senescence: a target for lung aging and diseases



Cell senescence: a target for lung aging and diseases



Cell senescence: a target for lung aging and diseases

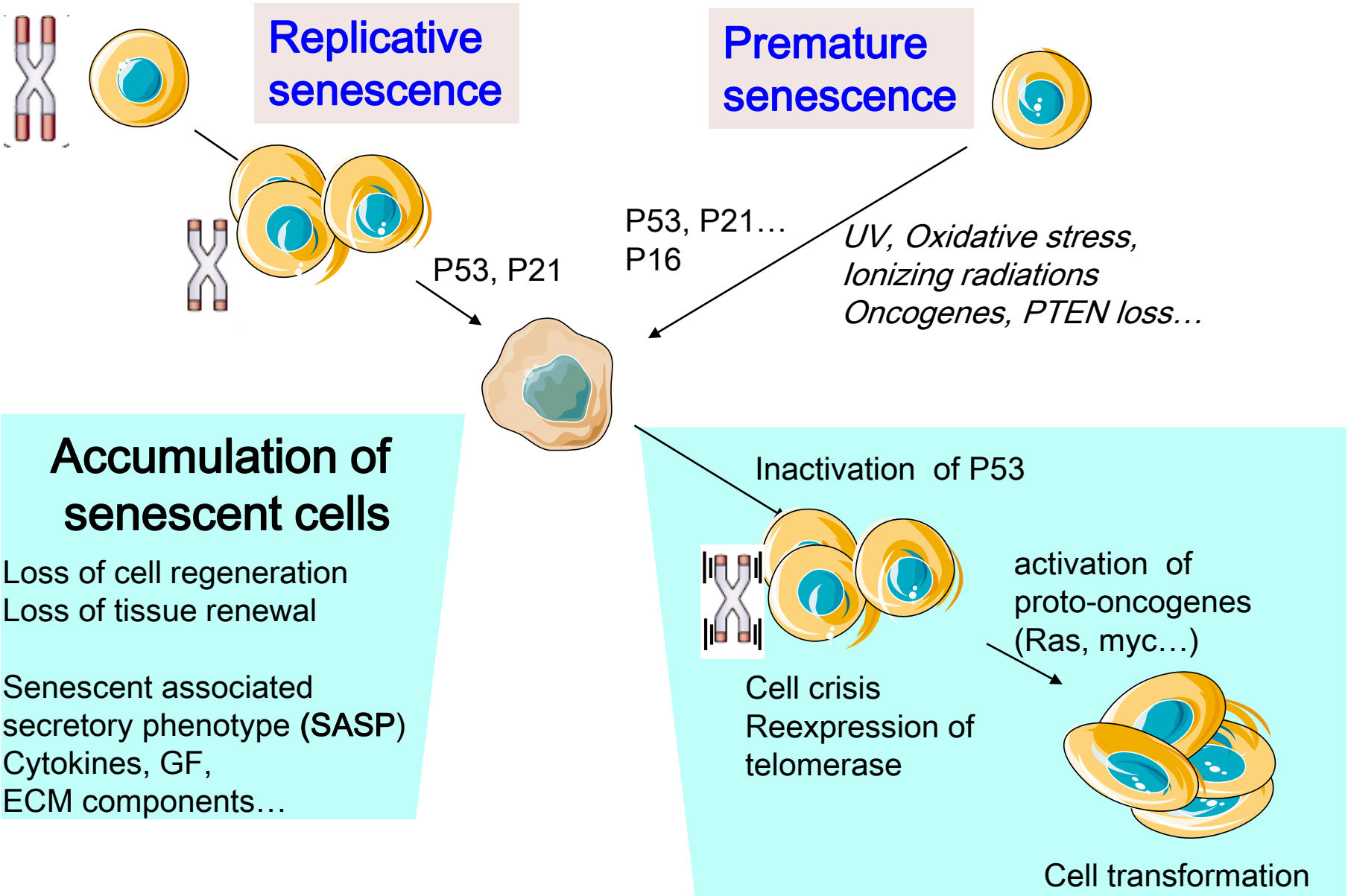


Accumulation of senescent cells

Loss of cell regeneration
Loss of tissue renewal

Senescent associated secretory phenotype (SASP)
Cytokines, GF,
ECM components…

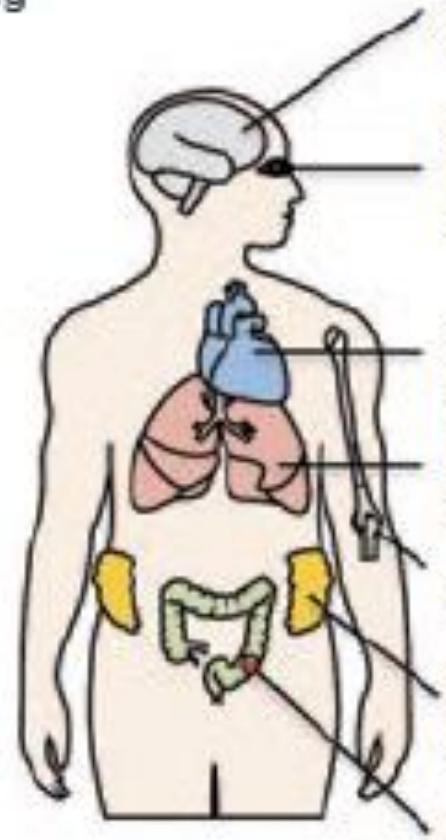
Cell senescence: a target for lung aging and diseases



Cellular senescence,
A common denominator of age-related diseases ?

Universal aging traits

Impaired wound healing
Weak immune system
Reduced hearing
Osteoporosis
Sarcopenia
Hair graying
Skin wrinkling
Poor vision



Age-related diseases

Alzheimer's disease
Parkinson's disease

Cataracts
Macular degeneration
Glaucoma

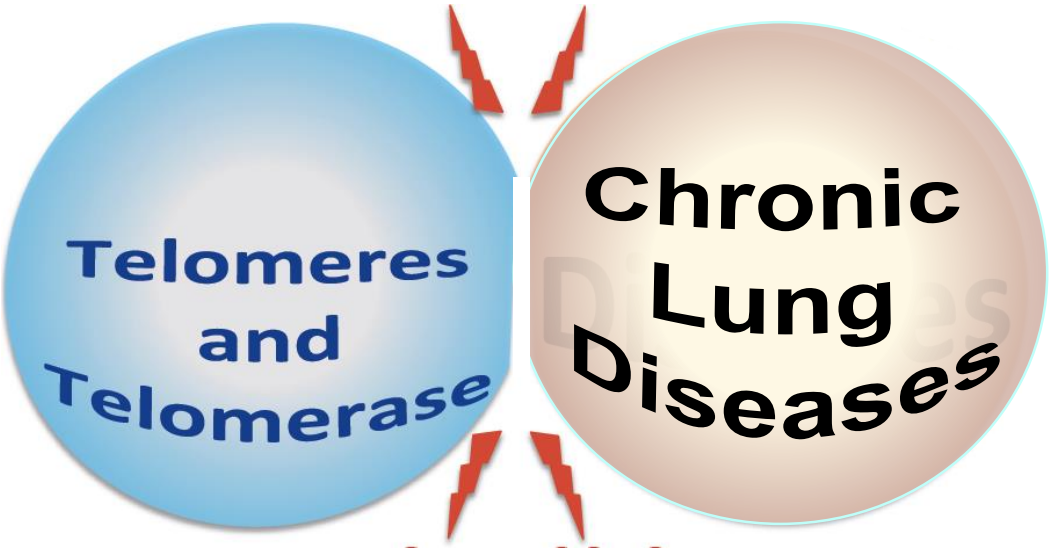
Atherosclerosis
Hypertension

IPF
COPD

Osteoarthritis

Type 2 diabetes
(obesity, fat dysfunction)

Cancer
Treatment-related disability


Telomeres
and
Telomerase
Chronic
Lung
Diseases

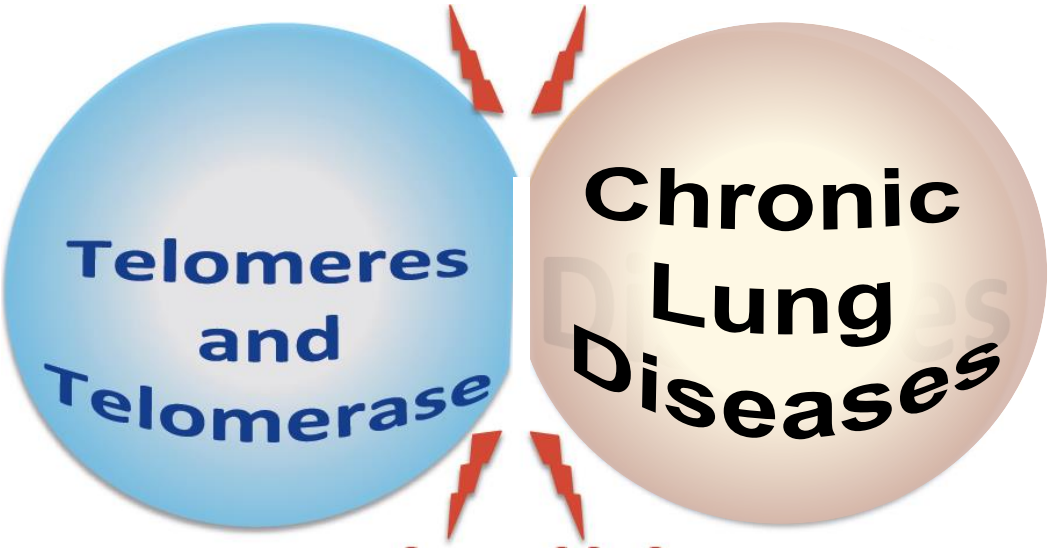
Lung fibrosis

Age-related disease

Rare disease

Chronic obstructive pulmonary disease (COPD)

Frequent, age-related degenerative disease



Lung fibrosis

Age-related disease

Rare disease

Chronic obstructive pulmonary disease (COPD)

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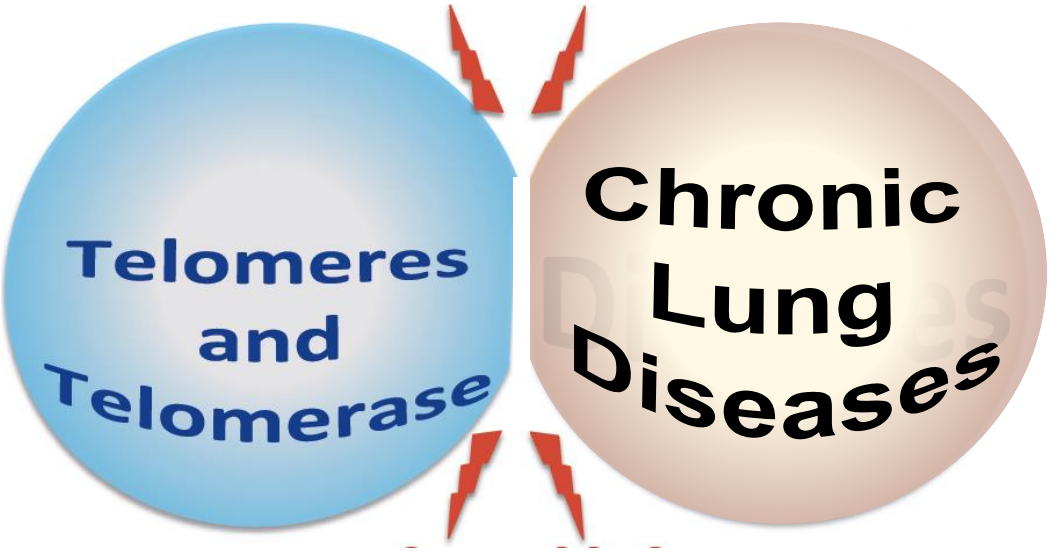
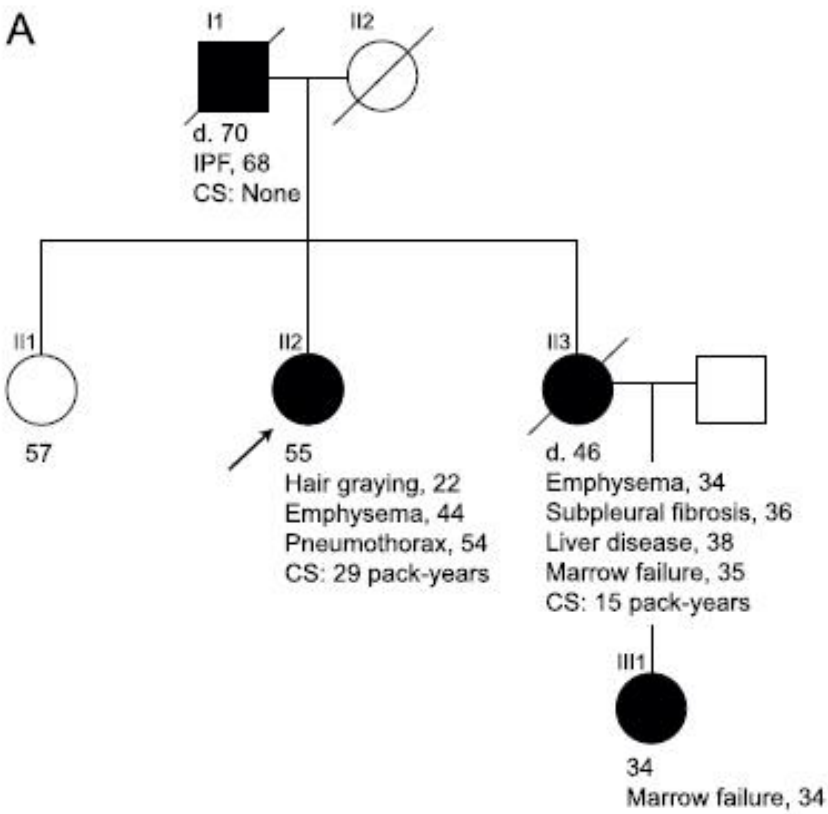
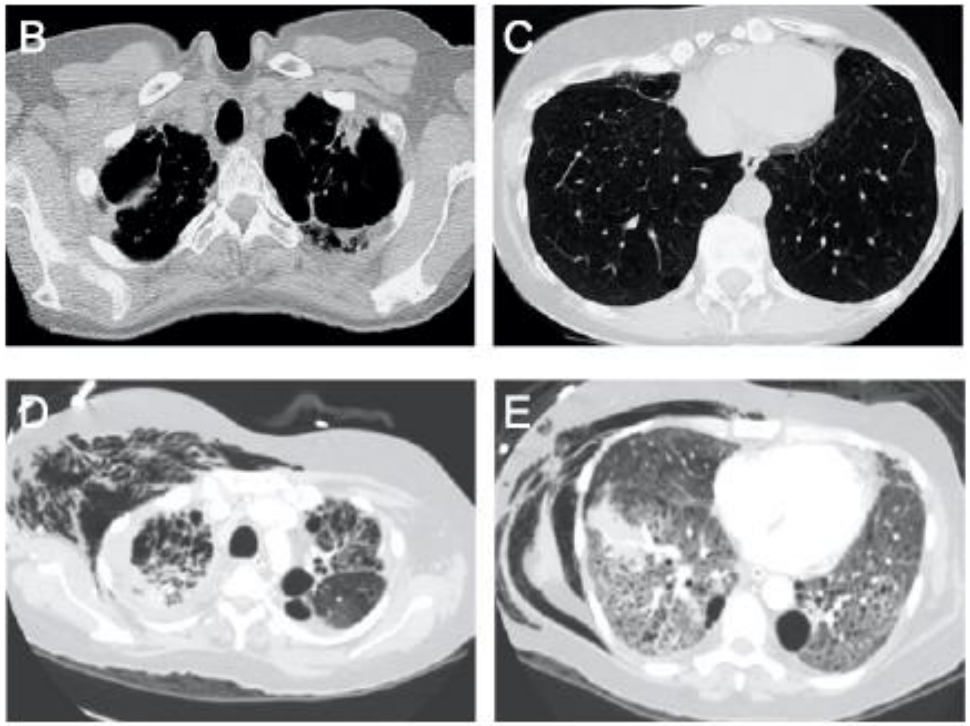


Lung diseases are the most prevalent manifestations of mutant telomere genes

Armanios M, Blackburn E, Nature Genetics, 2012

Telomase mutation is associated with lung fibrosis and/or emphysema susceptibility



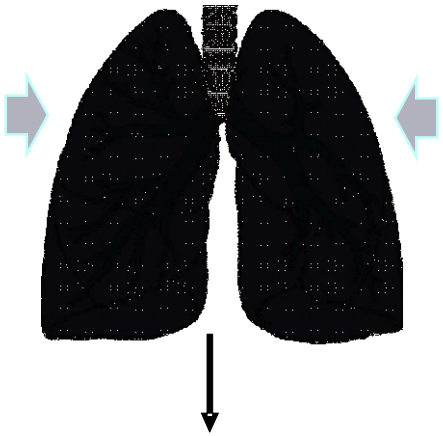


Alder JK et al, AJRCCM, 2011
Stanley SE et al, J Clin Invest, 2014

Cellular senescence and human lung disease

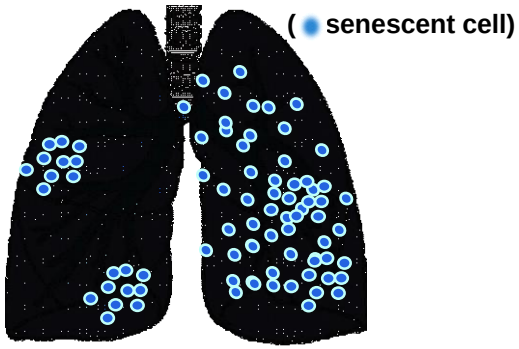
Aging : telomere shortening

Genetic factors :
- Inheritable short telomeres
- Telomerase deficiency



Environmental factors
Smoke, stress
Infection

Lung accumulation of senescent cells



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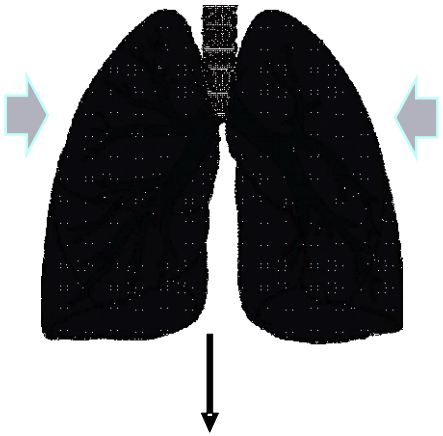

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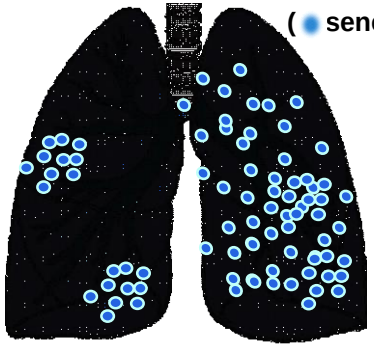
Decline in lung function

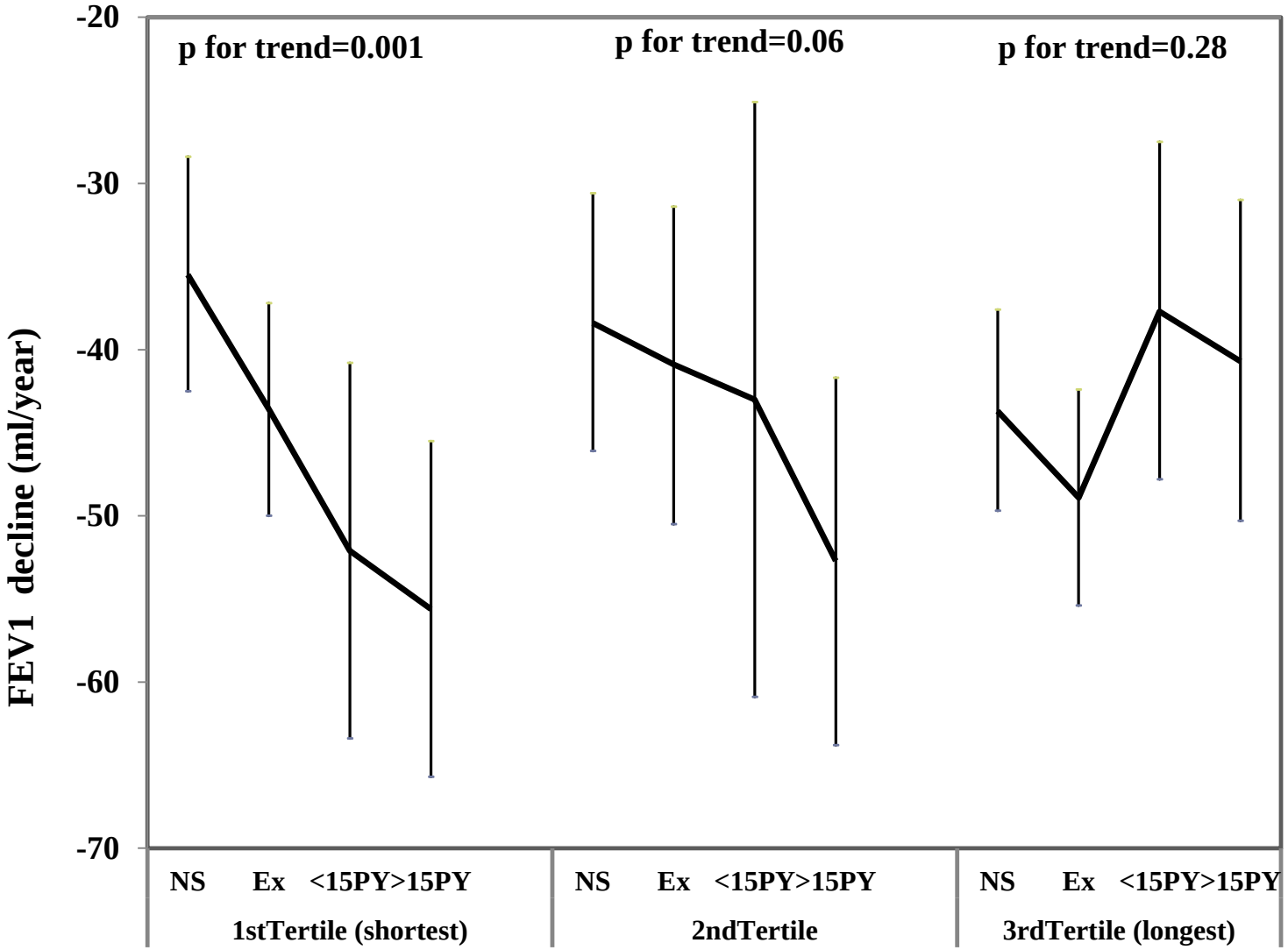


Increased susceptibility to diseases

Emphysema
Lung fibrosis
Inflammation, COPD,

Lung cancer *(p53 mutation)*

Telomere length determines the decline in lung function (448 participants, 11 year follow-up)

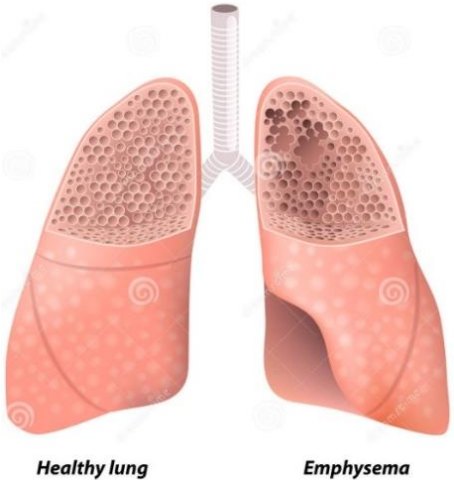


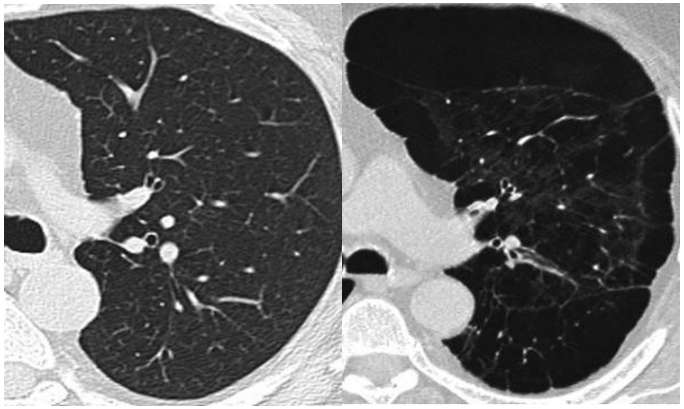
Andujar P et al, Thorax, 2017
Savale L et al, Am J Respir Crit Care Med, 2009

Chronic Obstructive Pulmonary Disease

COPD : frequent disease (3rd leading cause of death worldwide)

- Age related disease
- Etiology :Tobacco intoxication : 80-90%, chronic inflammation
- Definition : Airway obstruction : FEV1/ VC < 70%
- Pathology : Chronic bronchitis and emphysema



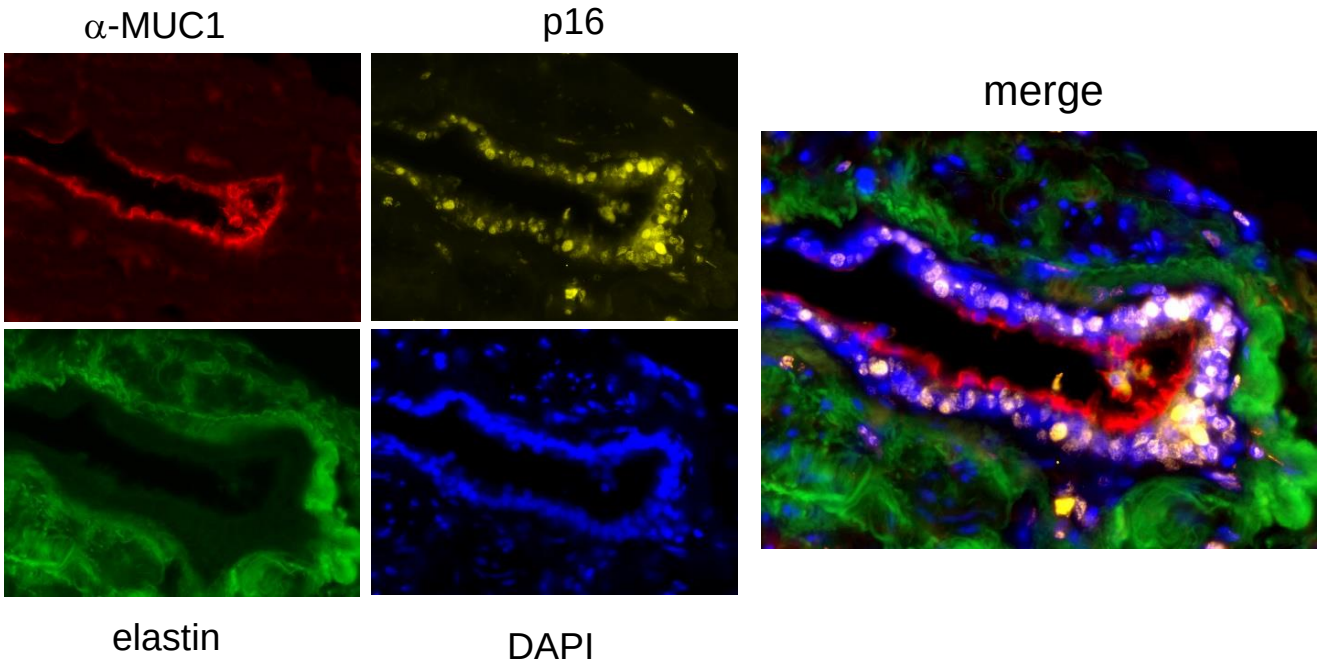


Major causes of death in COPD

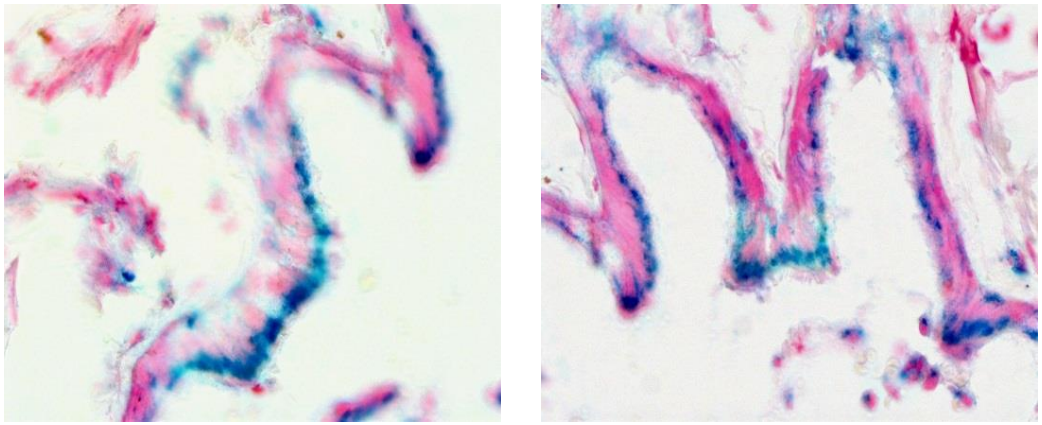
- Respiratory failure (1/3)
- Lung cancer (1/3)
- Co-morbidities (cardiovascular events,1/3)

COPD : senescent bronchial epithelial cells

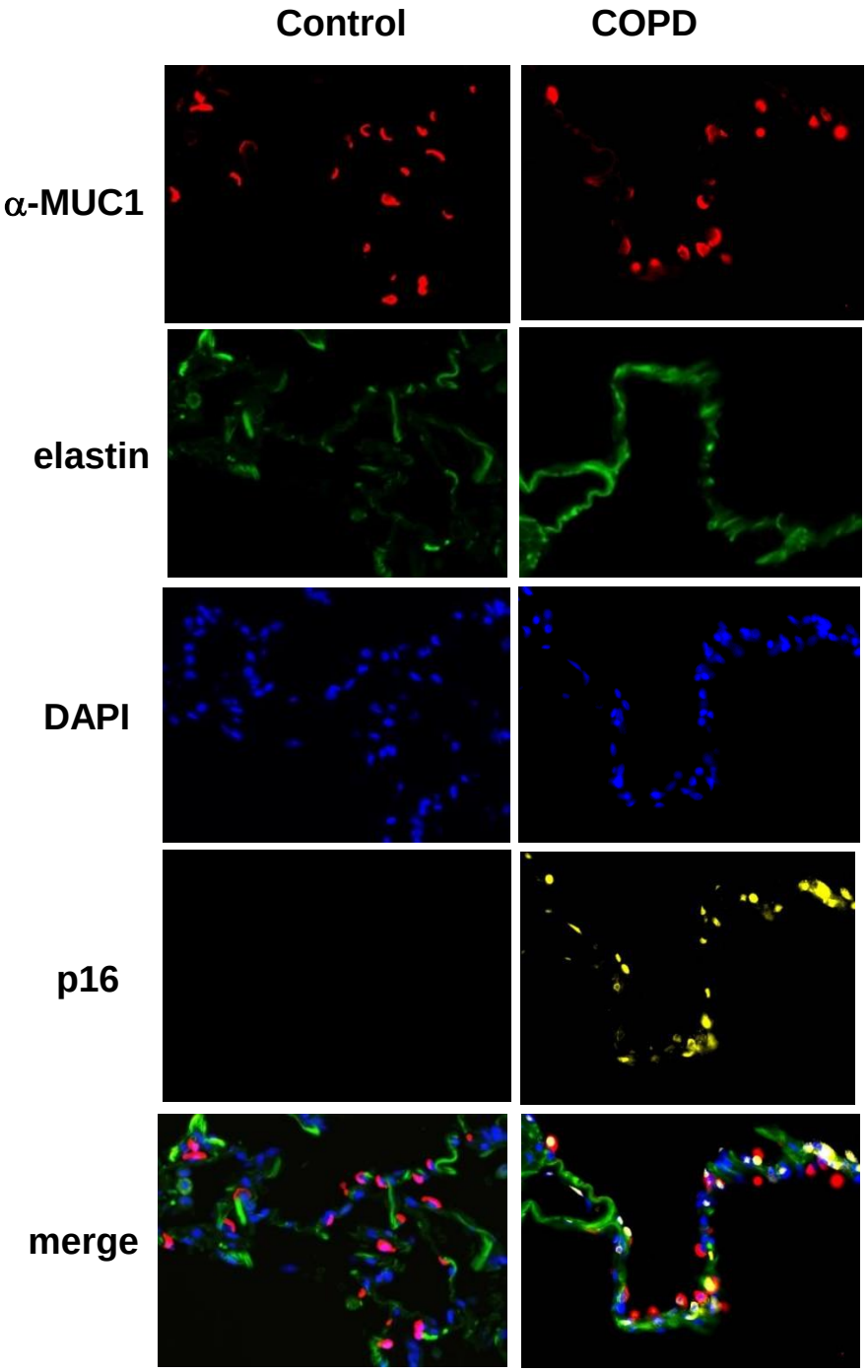
Immunofluorescence



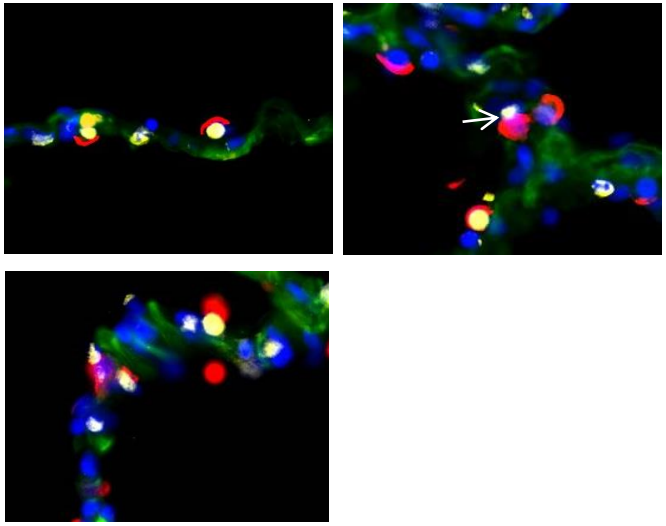
Immunohistochemistry



COPD
Senescent alveolar epithelial cells

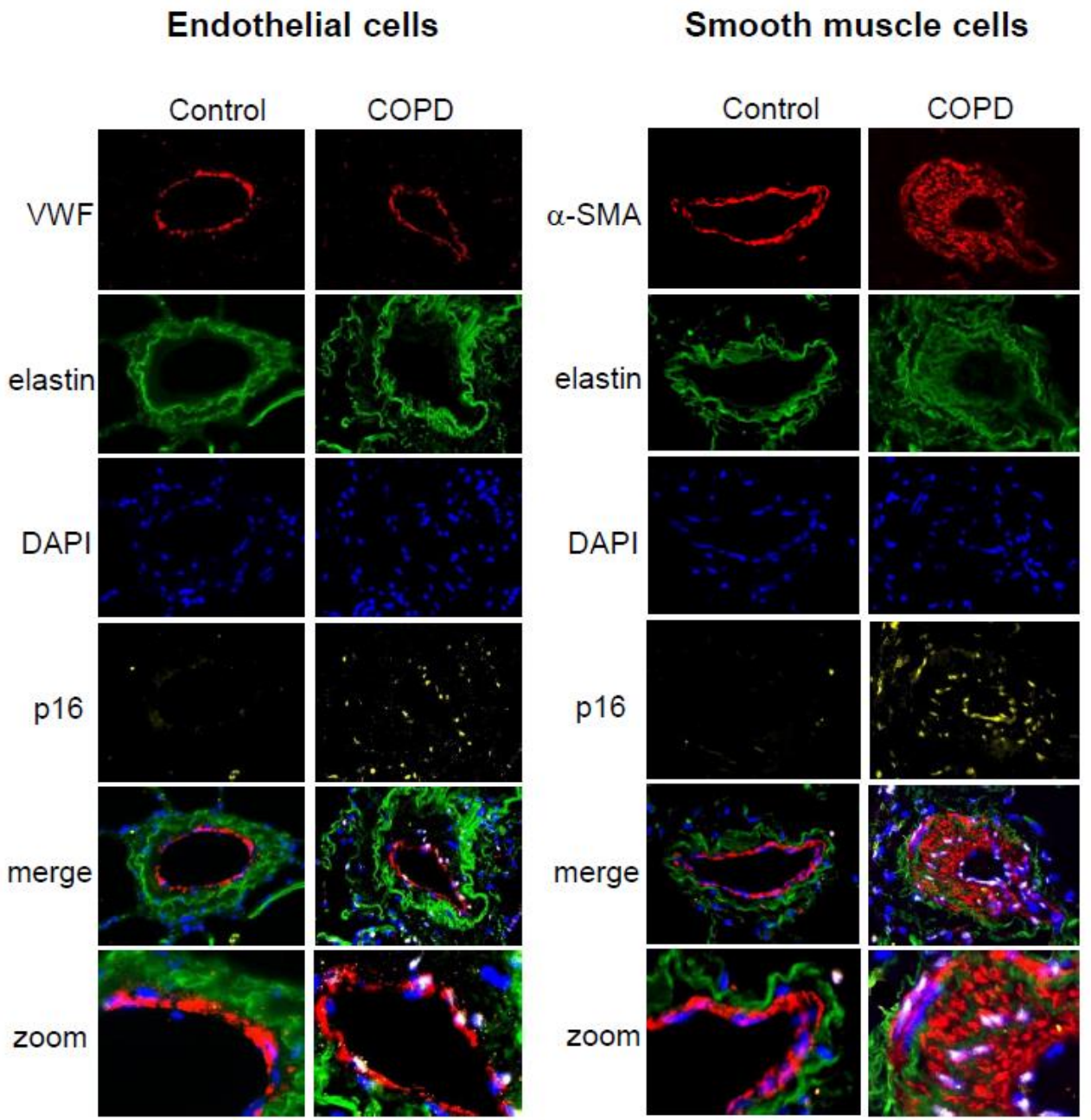


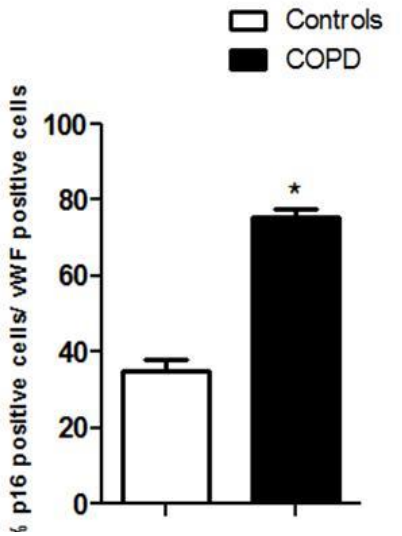
zoom

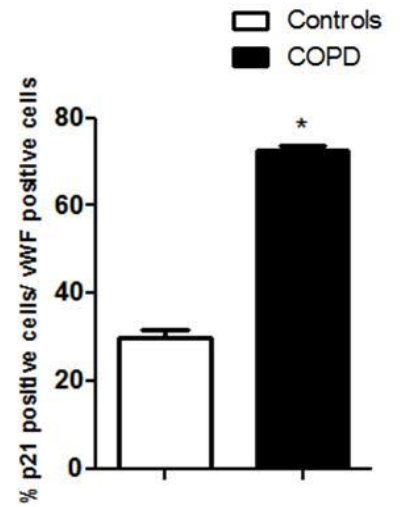


Amsellem V, AJRCCM, 2011
Noureddine H, Circ Res, 2011
Dagouassat m, AJRCCM, 2013

COPD : senescent endothelial and smooth muscle cells







Amsellem V, AJRCCM, 2011
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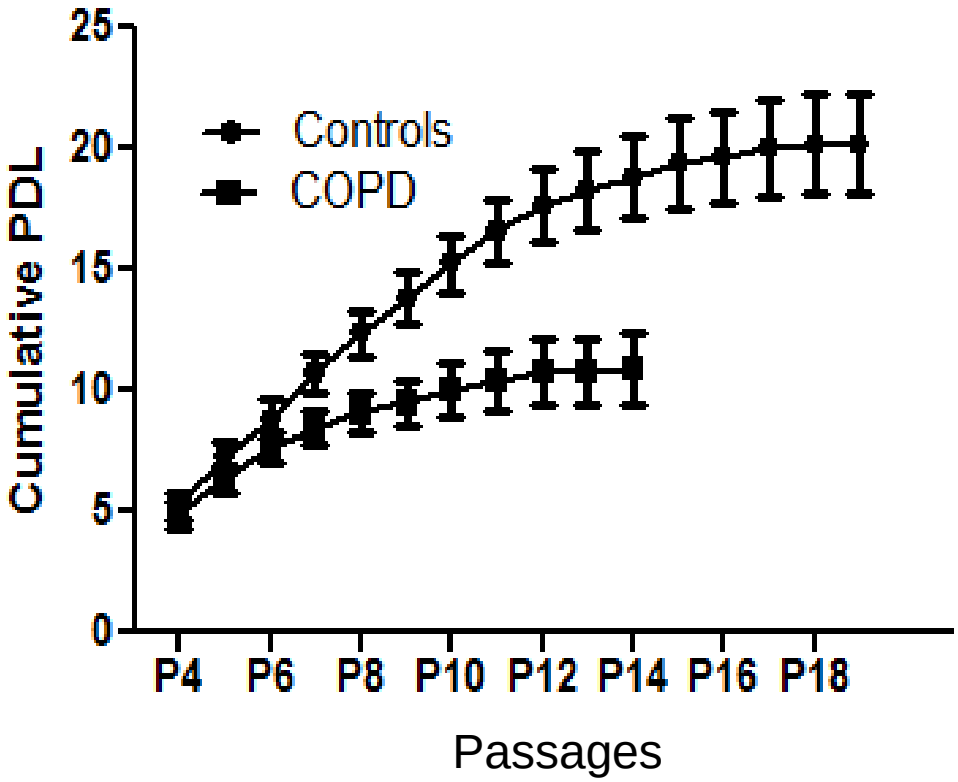
Early replicative senescence of cultured P-EC from patients with COPD



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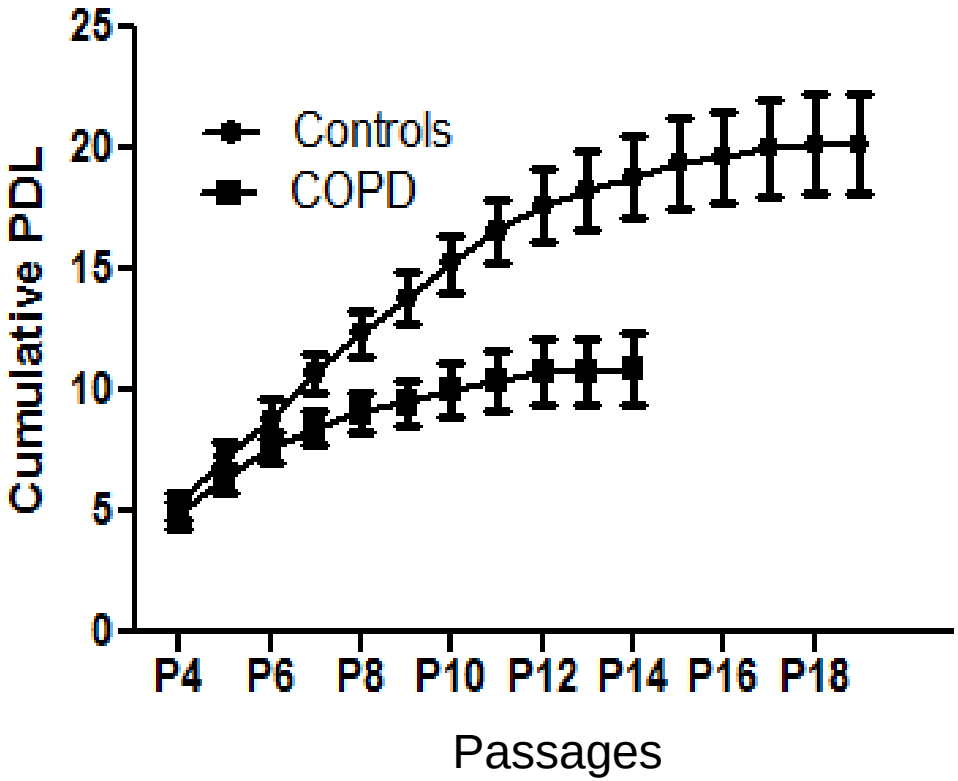
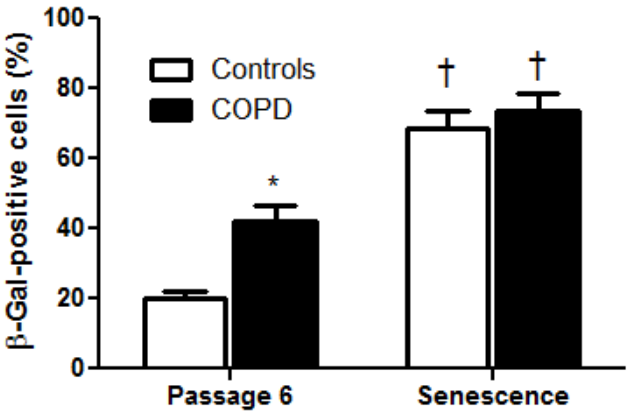
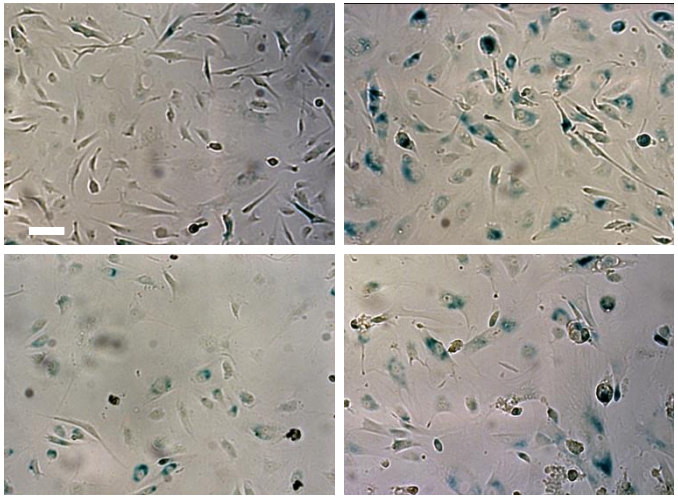
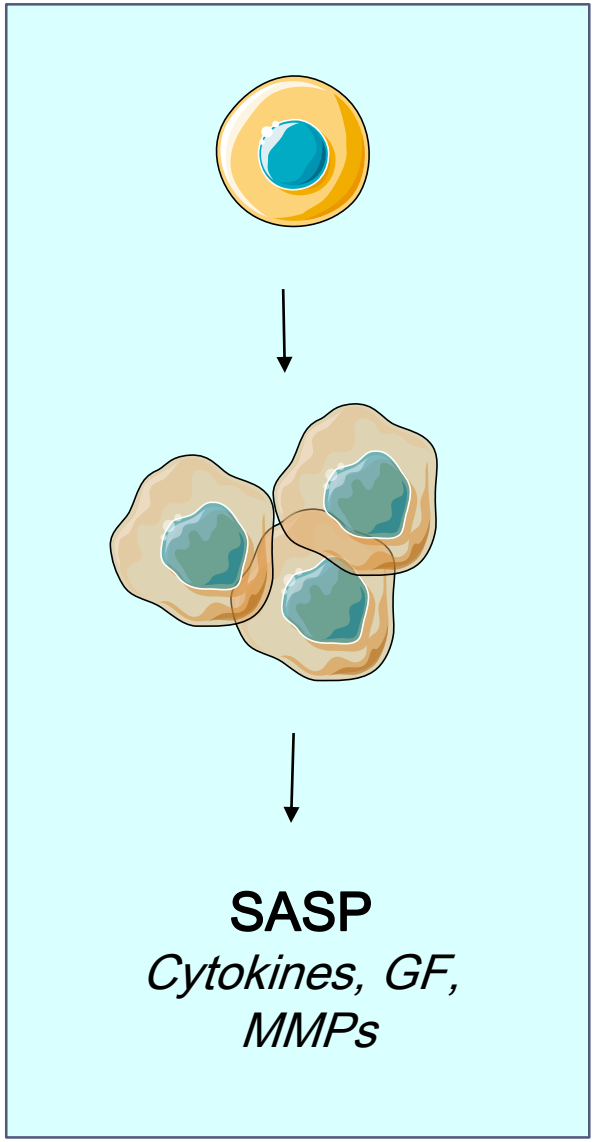


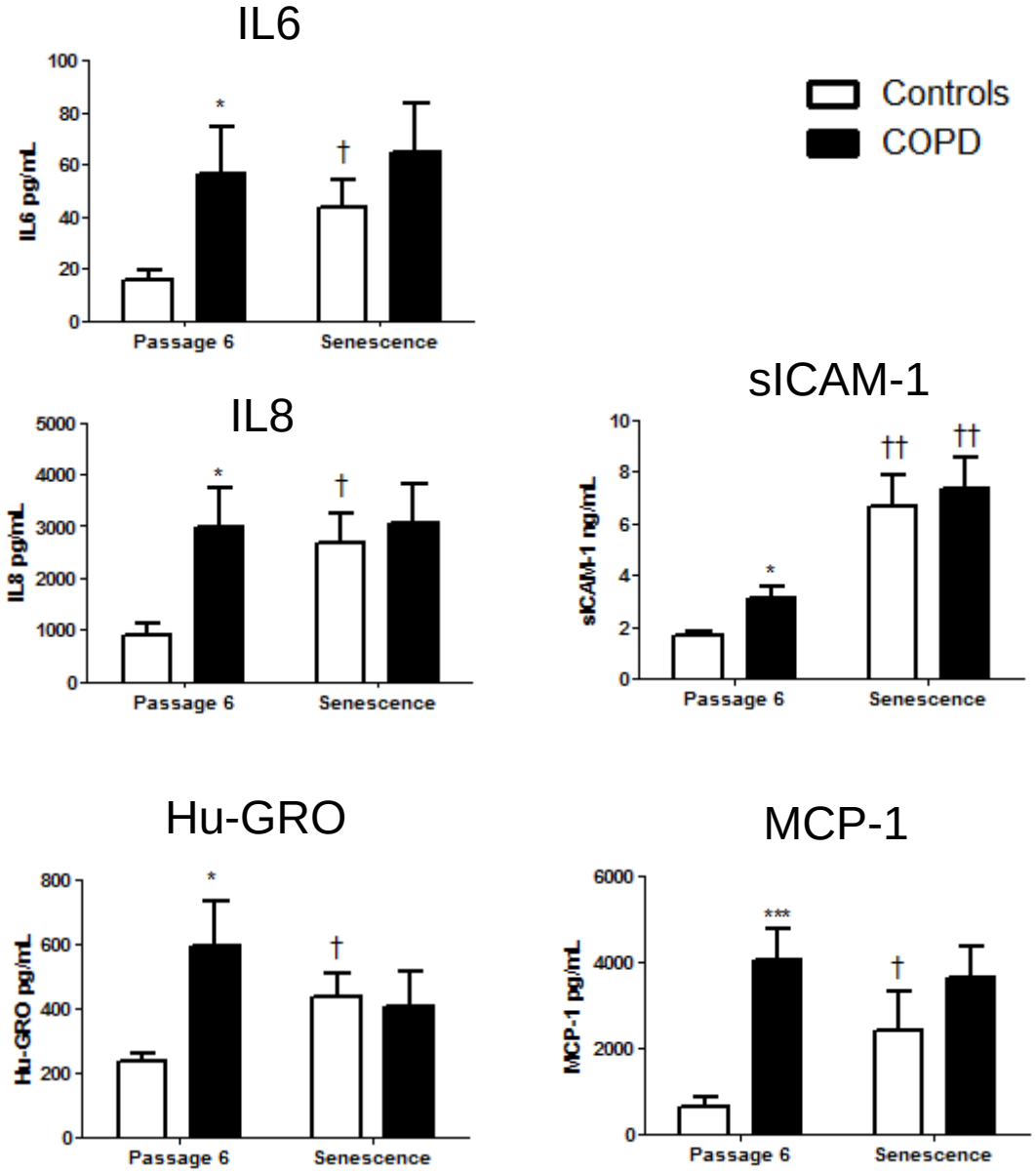




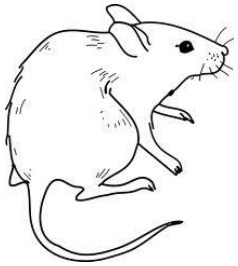
Amsellem V et al, AJRCCM, 2011

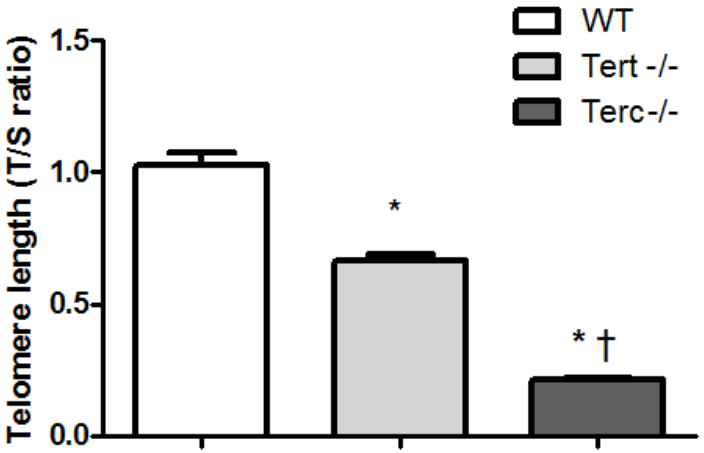
Mediators released from P-ECs in patients with COPD and controls

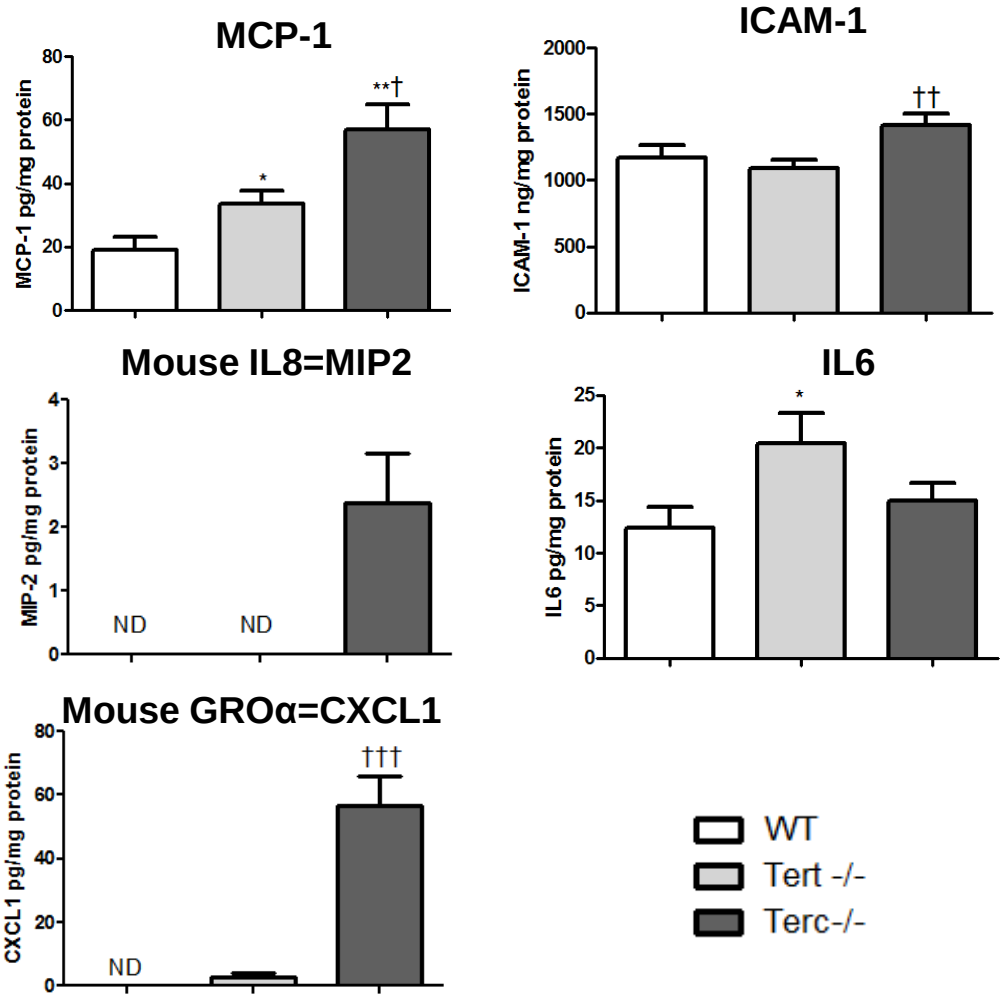




Telomere length and cytokine levels in lungs from TERT-/- and TERC-/- mice





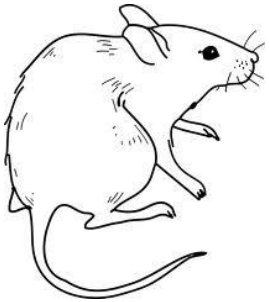


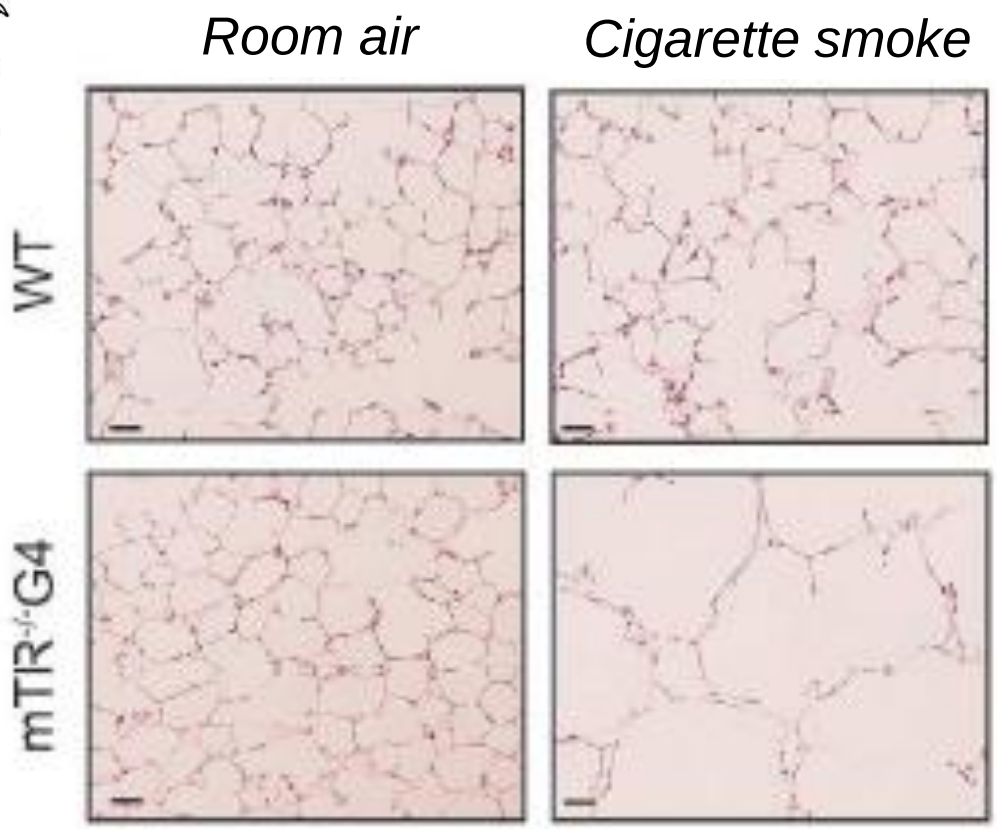
TERT-/-: Generation 3

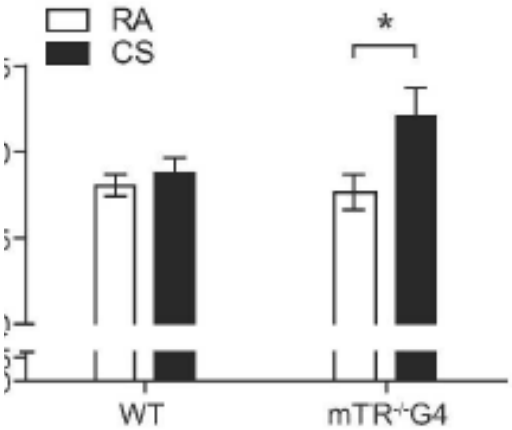
TERC-/-: Generation 2

Amsellem V et al, AJRCCM, 2011

Telomere length is a determinant of emphysema suceptibility





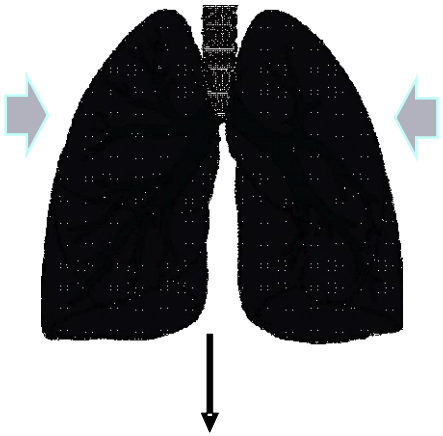


Alder JK et al, AJRCCM, 2011

Cellular senescence and lung aging

Aging : telomere shortening

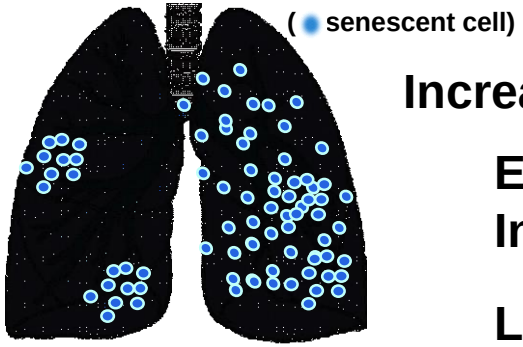
Genetic factors :
- Telomerase deficiency
- Inheritable short telomeres



Environmental factors
Smoke, stress
Infection

Lung accumulation of senescent cells

Decline in lung function



Increased susceptibility to diseases

Emphysema
Inflammation, COPD,

Lung cancer

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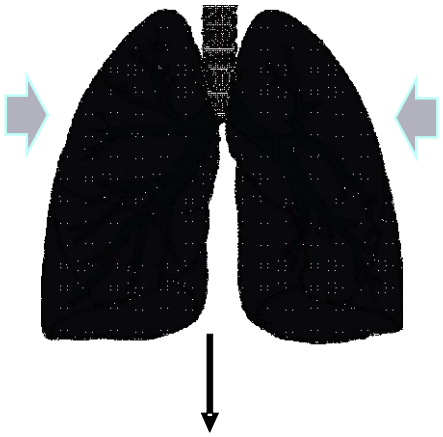

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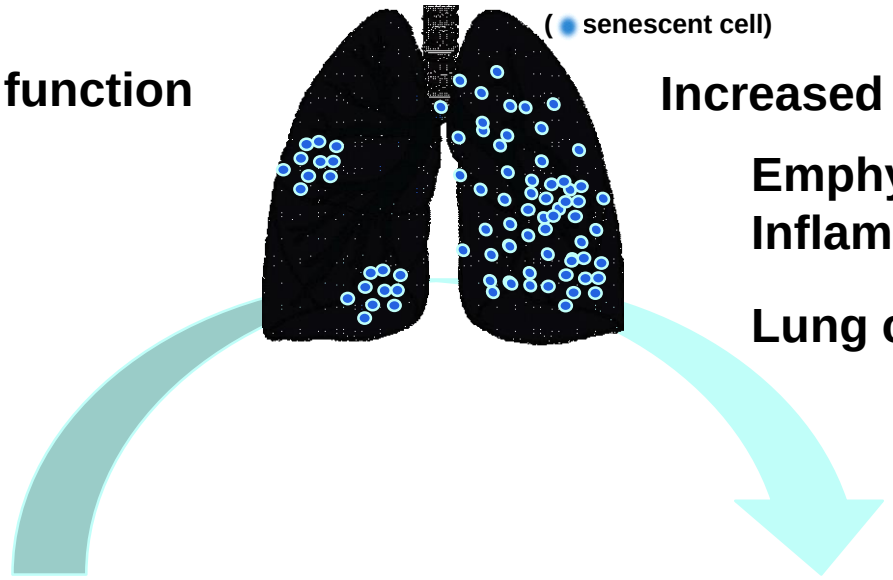

Decline in lung function

Increased susceptibility to diseases

Emphysema
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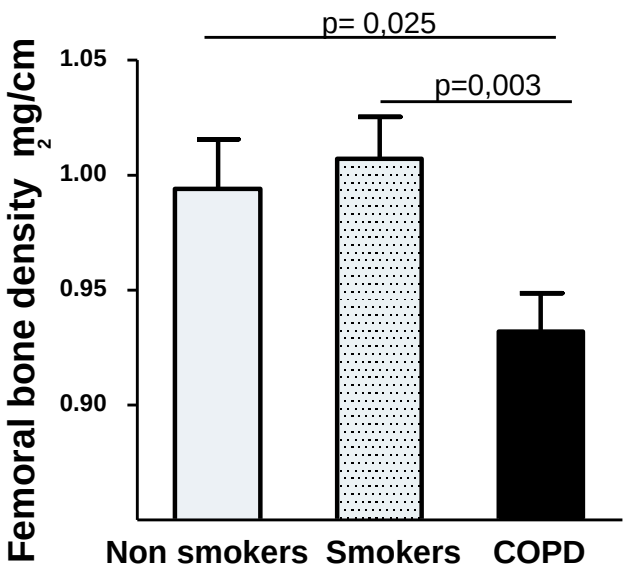
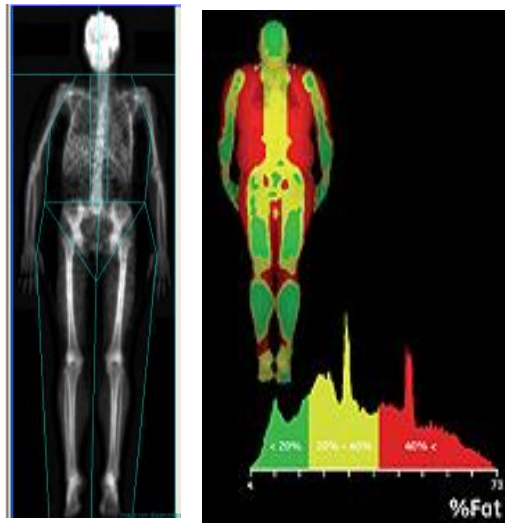
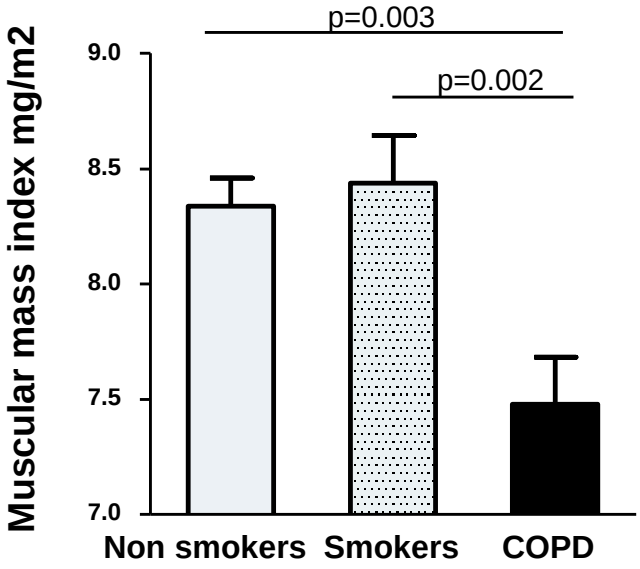
Lung cancer

Systemic aging

Decreased bone density and Muscular mass in patients with COPD

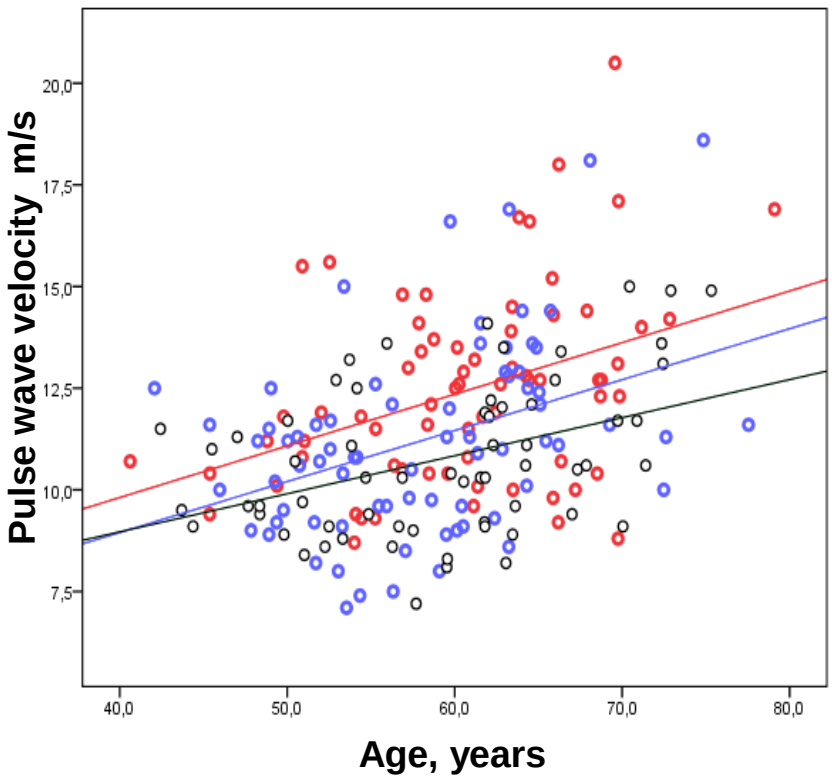


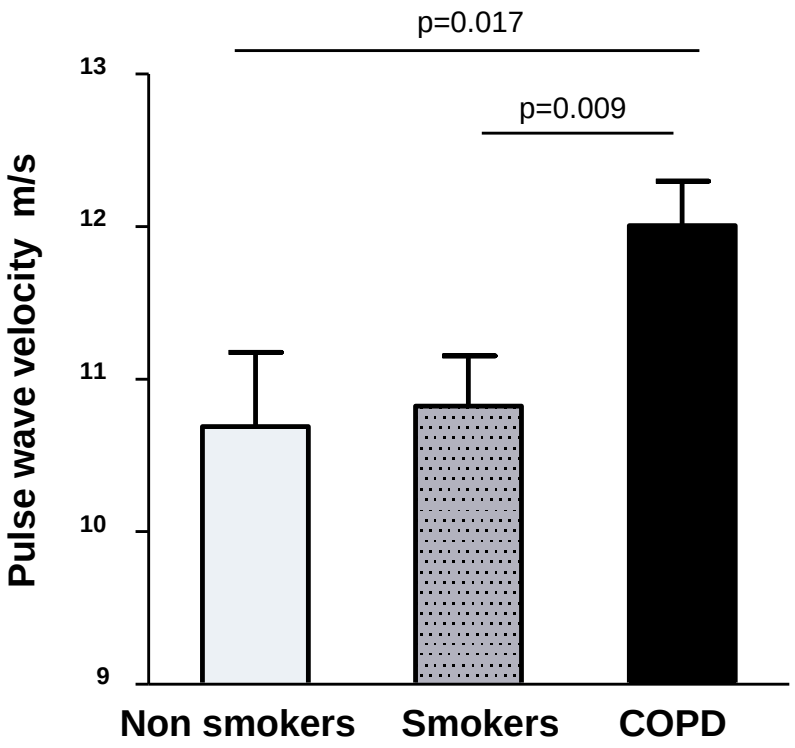




Boyer L et al, 2015

Increased arterial stiffness in patients with COPD compared to age-matched controls





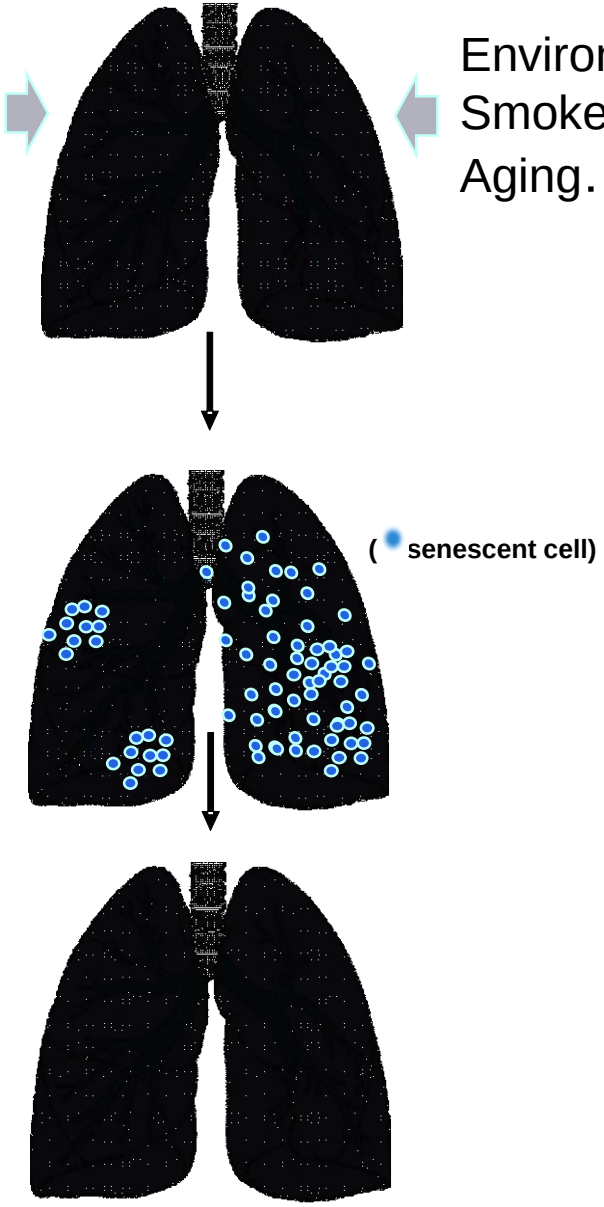
Boyer L et al, 2015

Therapeutic interventions ?

Genetic factors :

telomerase deficiency
Inheritable short telomeres

Environmental factors
Smoke, stress
Aging….



Decline in lung function
COPD,
Emphysema
Inflammation
Systemic manifestations

HEALTHY LUNG

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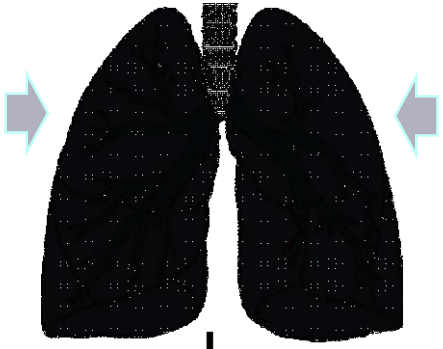
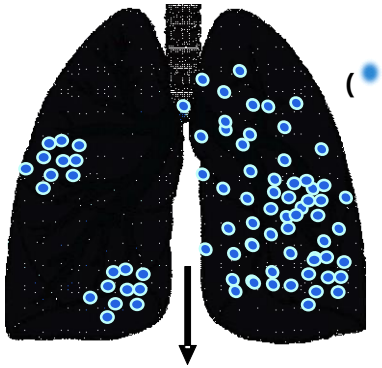


Environmental factors
Smoke, stress
Aging….

Halting the cell senescence process

Decline in lung function
COPD,
Emphysema
Inflammation
Systemic manifestations



(• senescent cell)

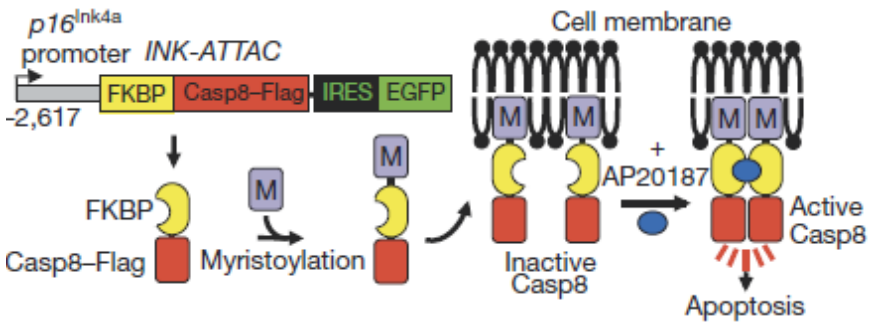
Eliminating senescent cells

Suppressing the SASP

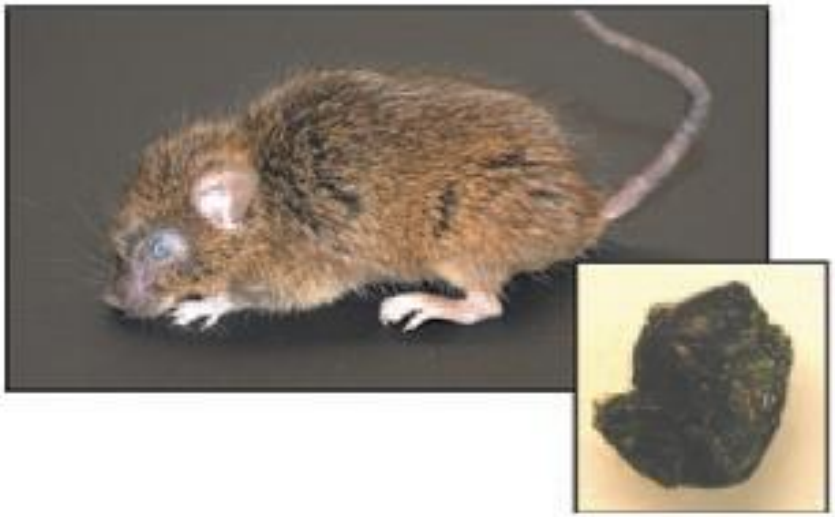
HEALTHY LUNG

p16^{INK4a} promoter, a senescence-sensitive driver of a killer gene

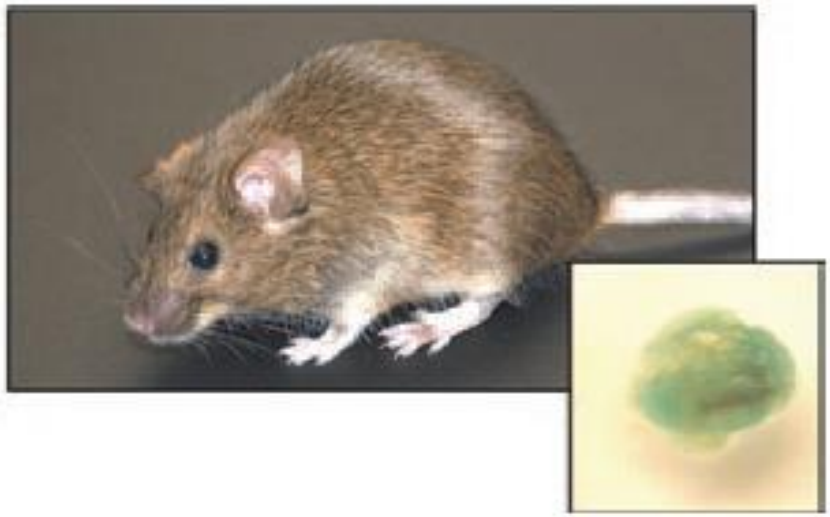
p16$^{INK\text{-}ATTAC}$ mice



BubR1 progeroid mouse

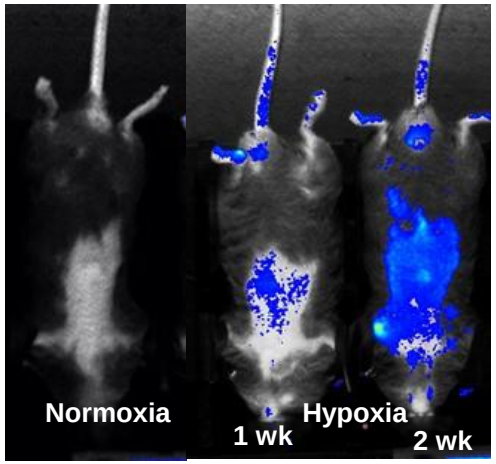


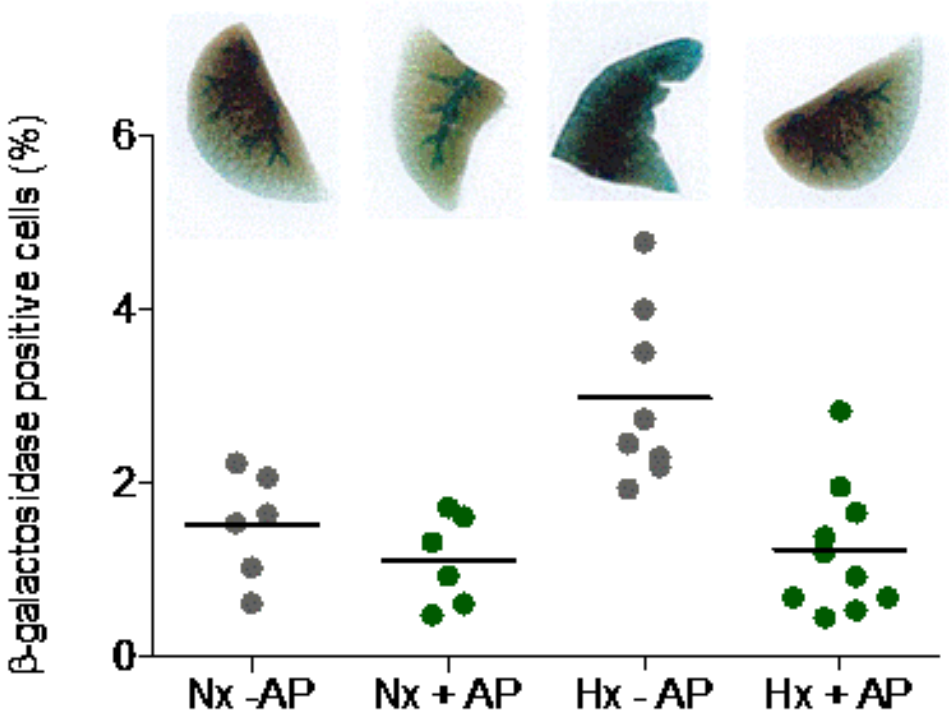
BubR1 progeroid mouse lacking *p16*^{Ink4a}

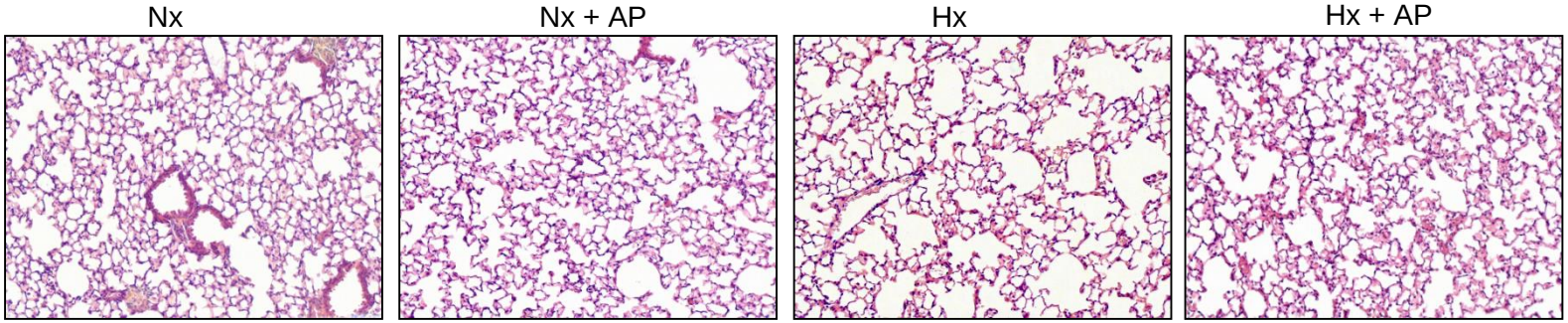


Baker DJ et al, Nature, 2011

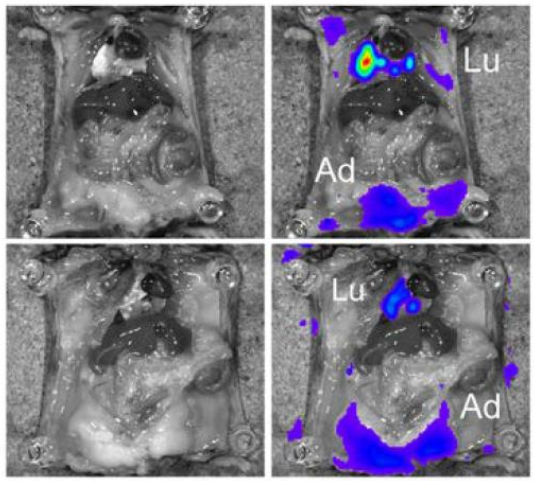
P16-luc and p16-ATTAC mice exposed to chronic hypoxia

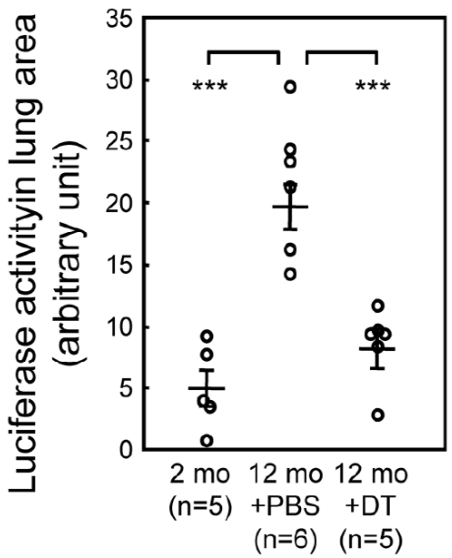


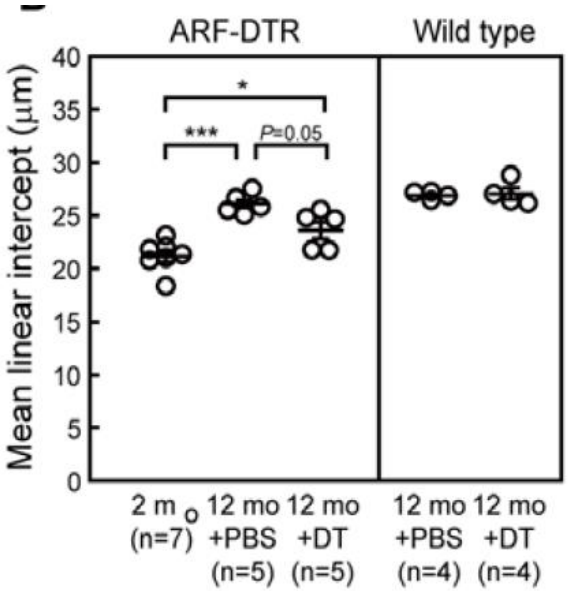


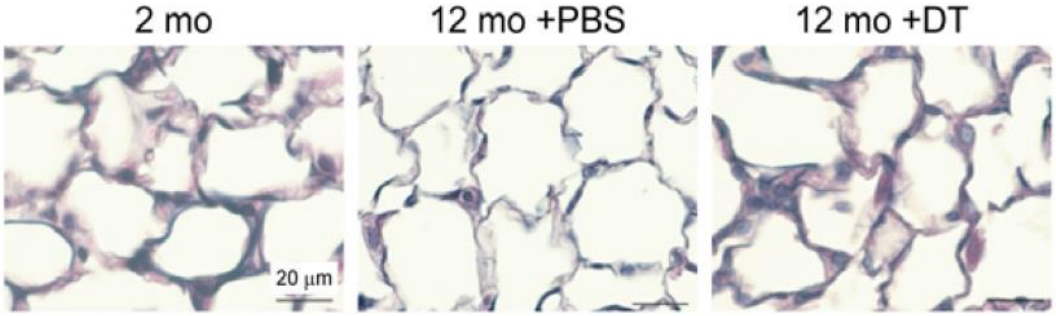


Elimination of p19ARF-expressing cells enhances pulmonary function in mice









Hashimoto M et al, JCI insight, 2016

Senescent cells clearance in non progeroid mice

Naturally occurring p16^{Ink4a}–positive cells shorten healthy lifespan

Darren J. Baker[1], Bennett G. Childs[2], Matej Durik[1], Melinde E. Wijers[1], Cynthia J. Sieben[2], Jian Zhong[1], Rachel A. Saltness[1], Karthik B. Jeganathan[1], Grace Casaclang Verzosa[3], Abdulmohammad Pezeshki[4], Khashayarsha Khazaie[4], Jordan D. Miller[3] & Jan M. van Deursen[1,2]

Baker DJ et al, Nature, 2016

22 m (BL/6)

Increased lifespan (20%)

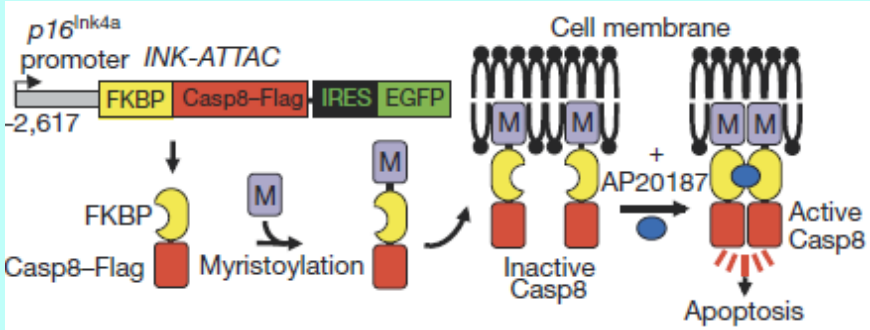
Decreased tumorigenesis

Reduced natural aging

glomerulosclerosis
cardiomyocyte hypertrophy
arteriosclerosis
cataract formation….

Senolysis : eliminating senescent cells

p16$^{INK\text{-}ATTAC}$ mice



Baker DJ et al, Nature, 2011

Baker DJ et al, Nature, 2016

Senolytics :

Senolytic agents based on drug screening: quercetin, dasatinib

Zhu Y, Aging Cell, 2016

Senolytic agents based on targeting antiapoptotic systems

Navitoclax, ABT-737 (suppression of Bcl2 inhibition)

FOXO4dr peptide….

Tse C, Cancer Res 2008

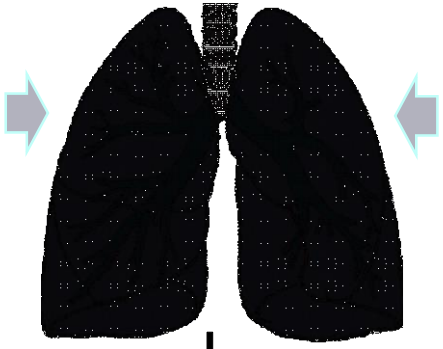
Zhu Y, Aging Cell, 2016

Baar MP et al, Cell, 2017

Therapeutic interventions ?

Genetic factors :

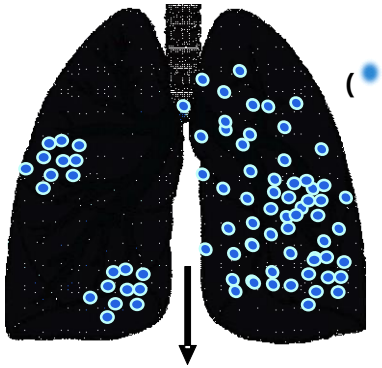
telomerase deficiency
Inheritable short telomeres



Environmental factors
Smoke, stress
Aging….

Halting the cell senescence process

Decline in lung function
COPD,
Emphysema
Inflammation
Systemic manifestations



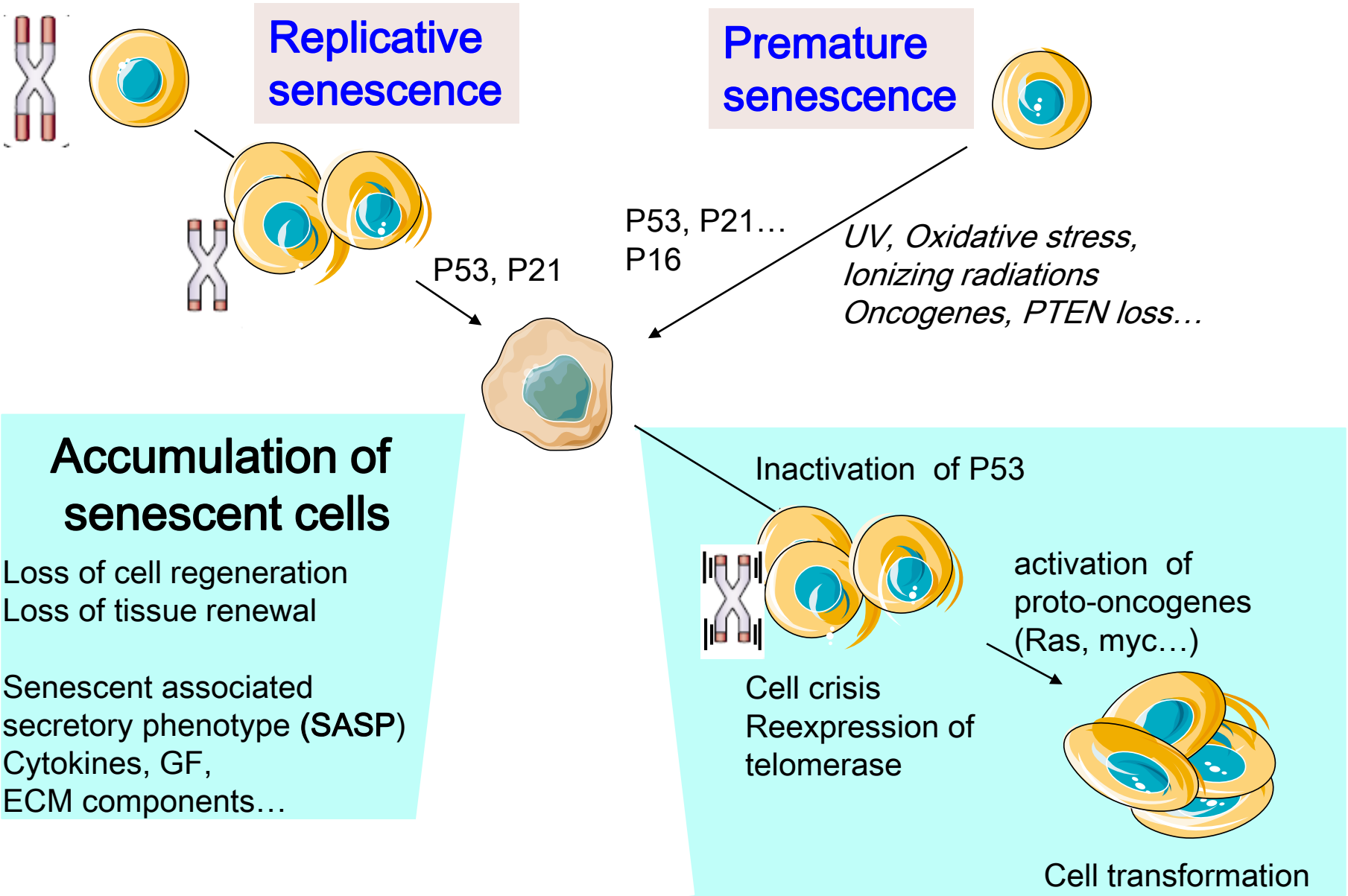
(• senescent cell)

Eliminating senescent cells

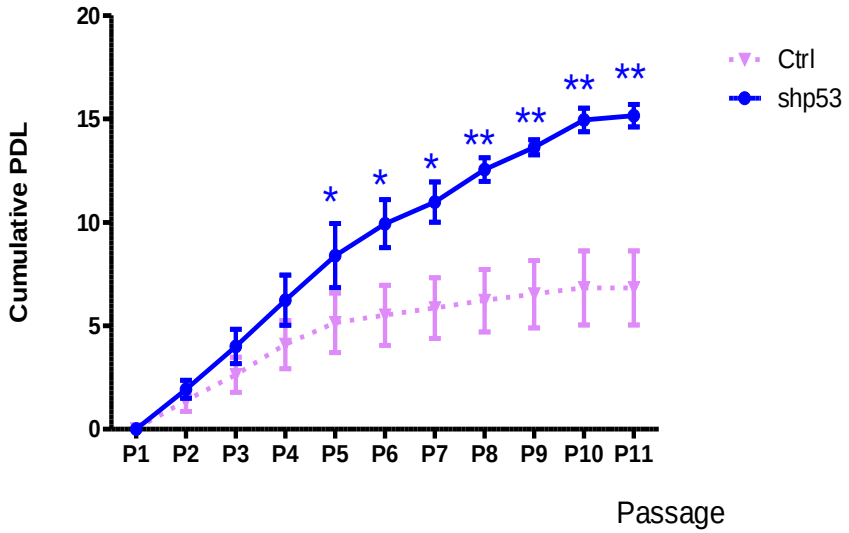
Suppressing the SASP

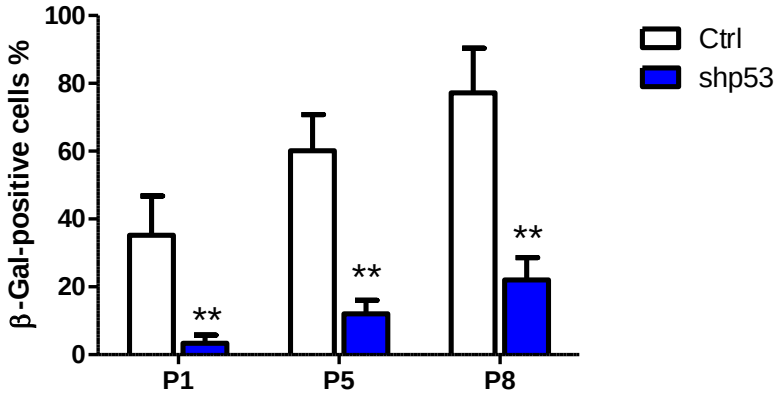
HEALTHY LUNG

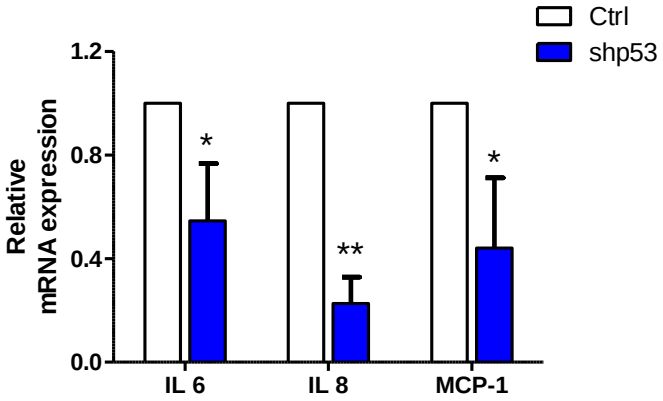
Cell senescence: a target for lung aging and diseases

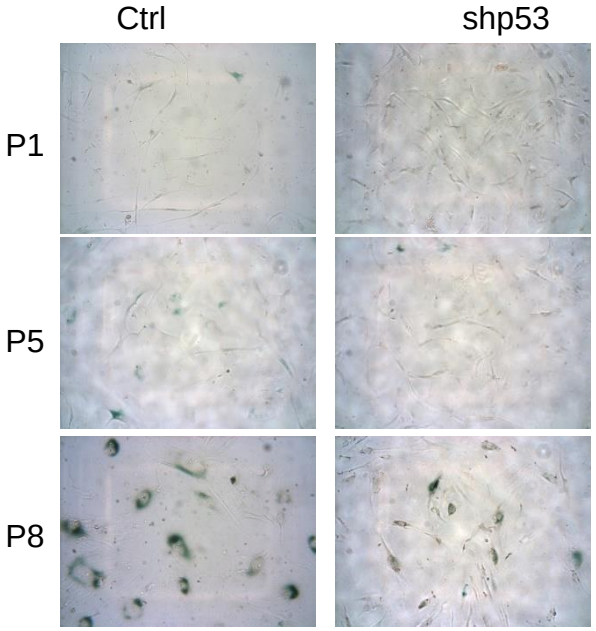


Cell senescence in COPD depends on the p53 pathway

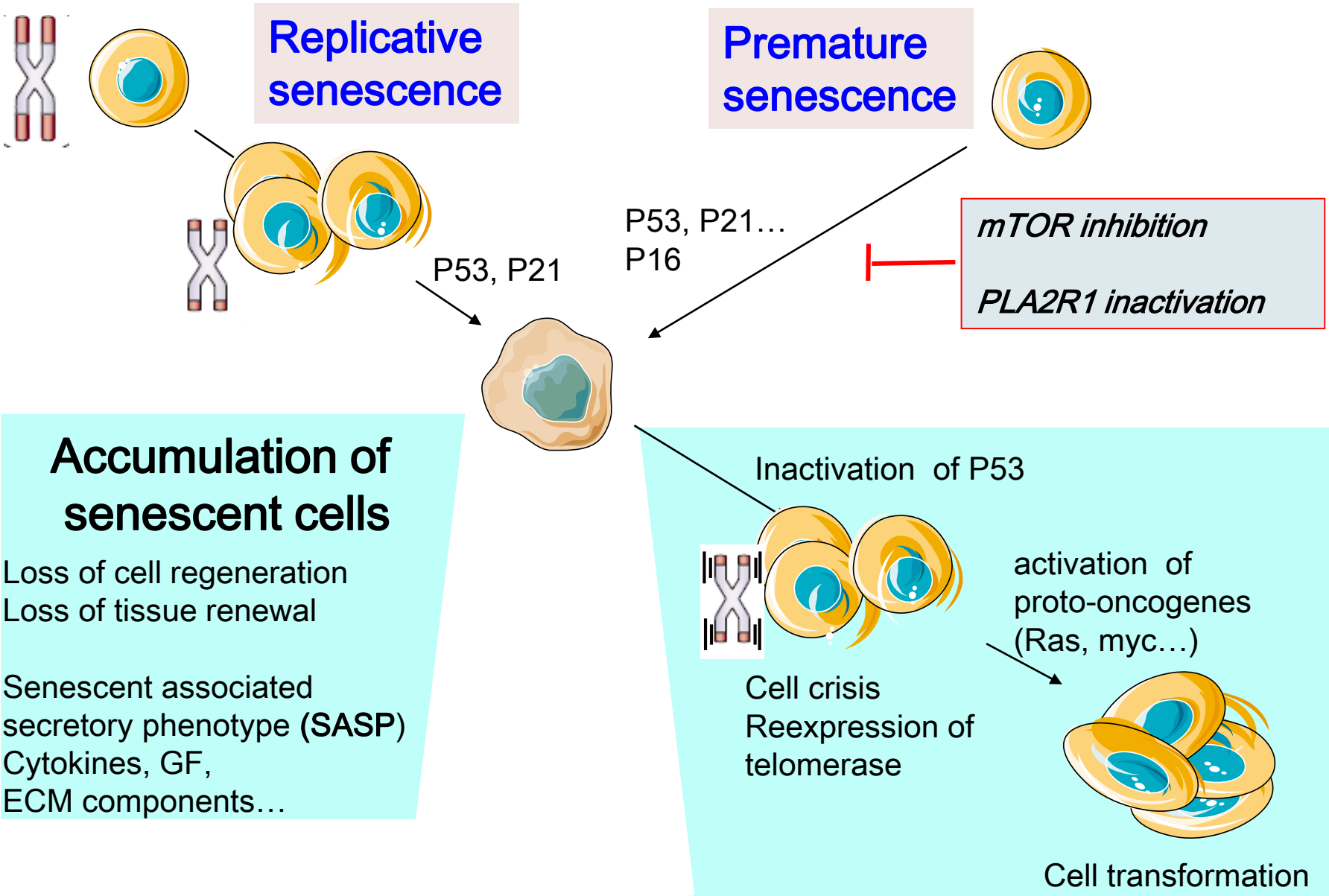


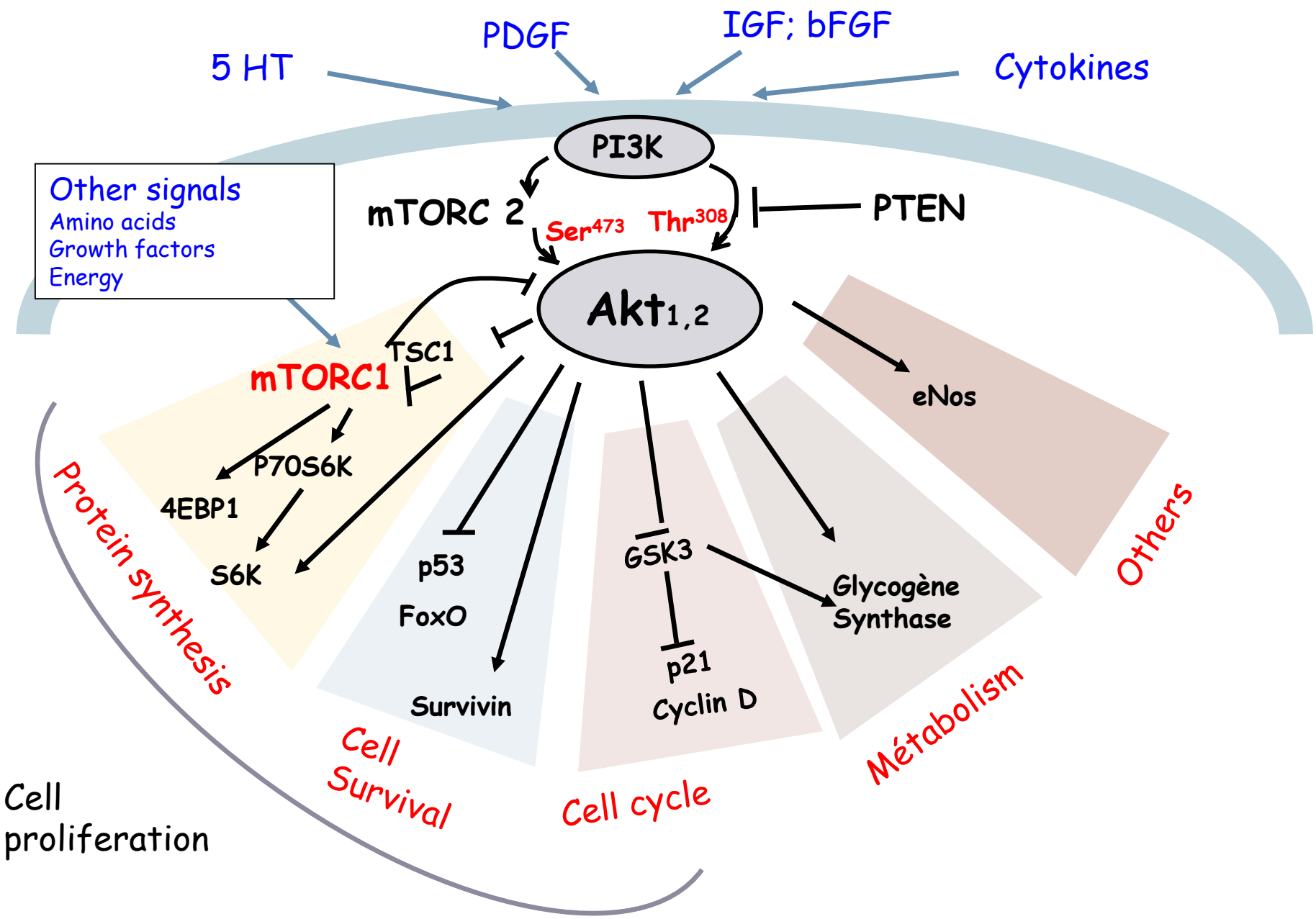




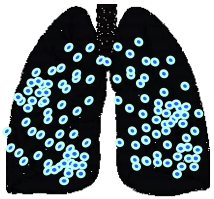


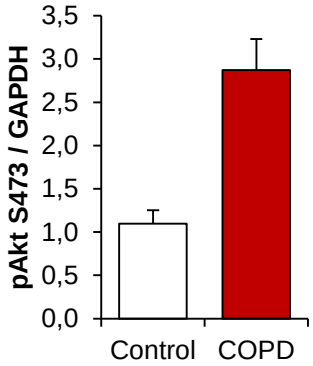
Cell senescence: a target for lung aging and diseases

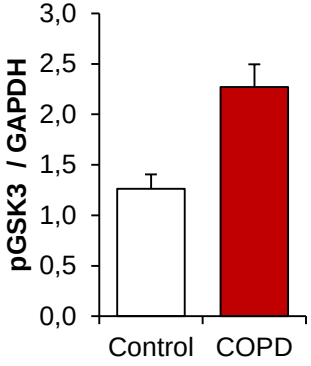


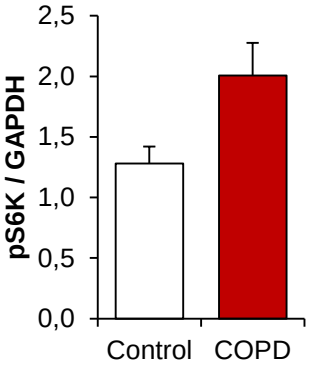

5 HT
PDGF
IGF; bFGF
Cytokines
PI3K
mTORC 2
Ser473
Thr308
PTEN
Other signals
Amino acids
Growth factors
Energy
Akt1,2
TSC1
mTORC1
P70S6K
4EBP1
S6K
p53
FoxO
Survivin
GSK3
p21
Cyclin D
Glycogène
Synthase
eNos
Protein synthesis
Cell
Survival
Cell cycle
Métabolism
Others
Cell
proliferation

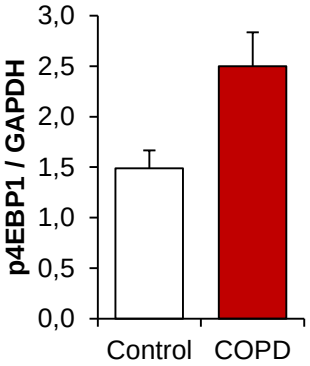
Activation of the Akt/mTOR pathway in lungs from patients with COPD

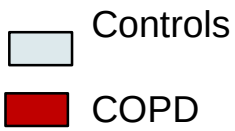


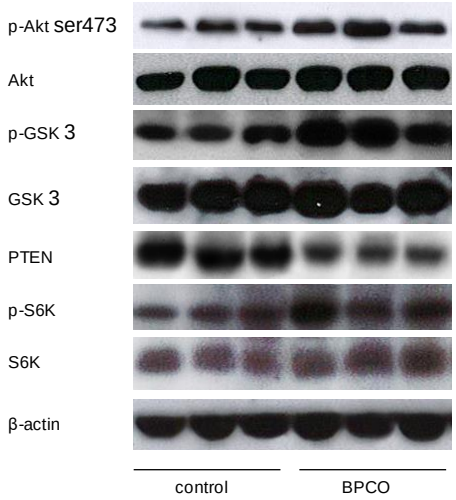


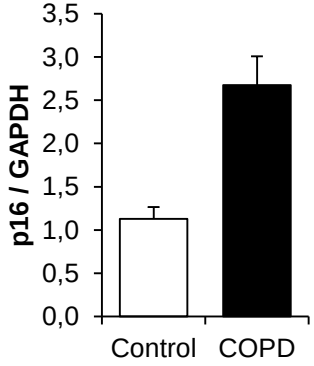


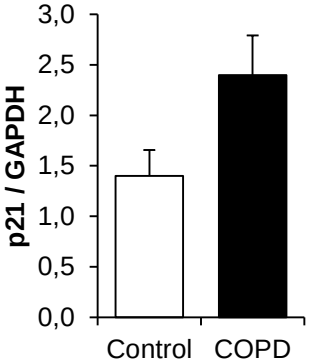


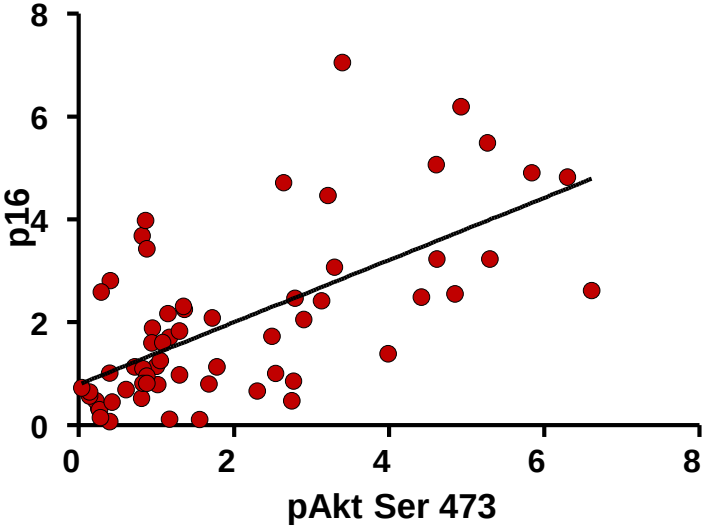




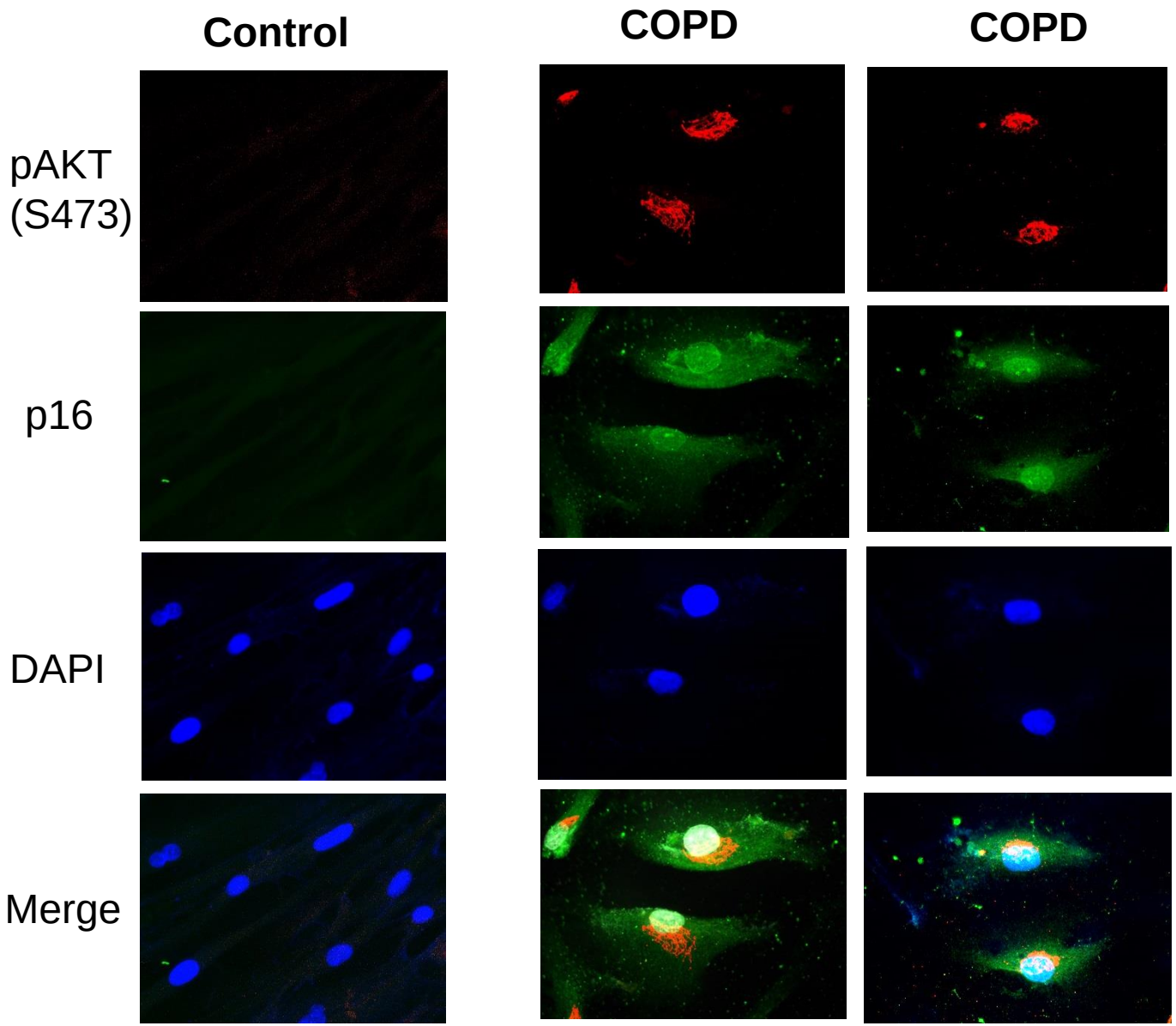


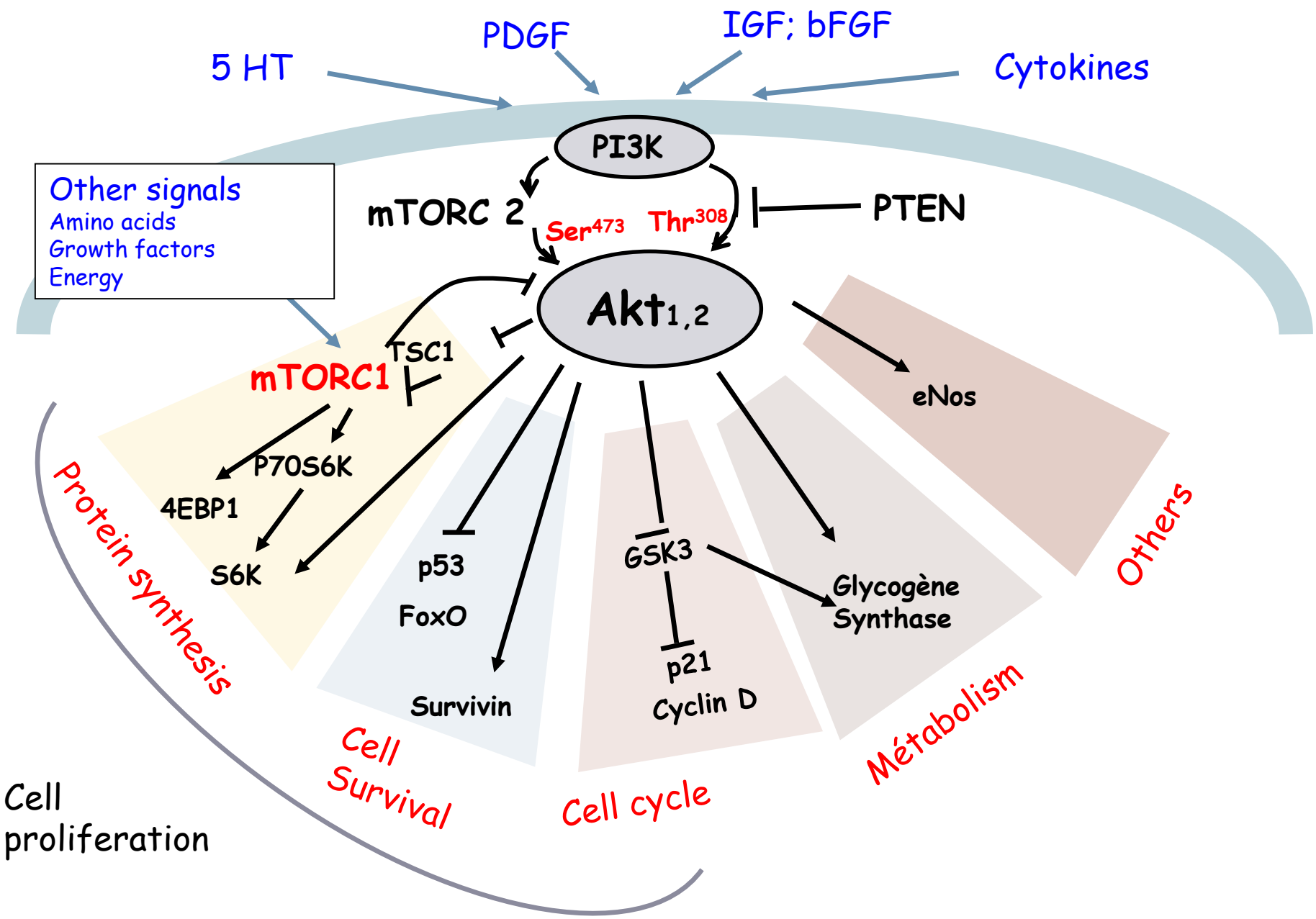




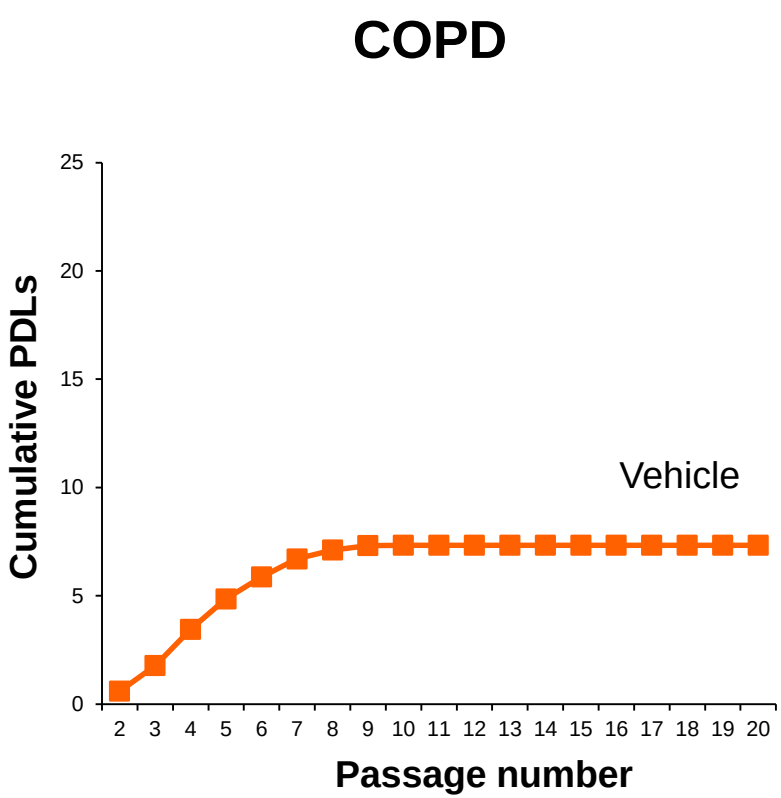


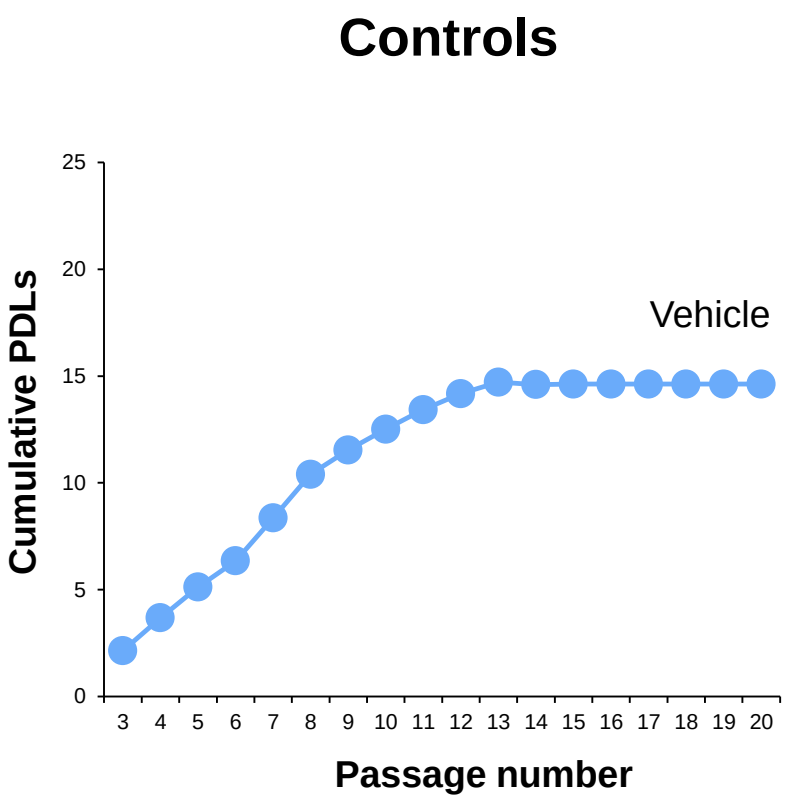
Activation of the Akt/mTOR pathway in cells from patients with COPD



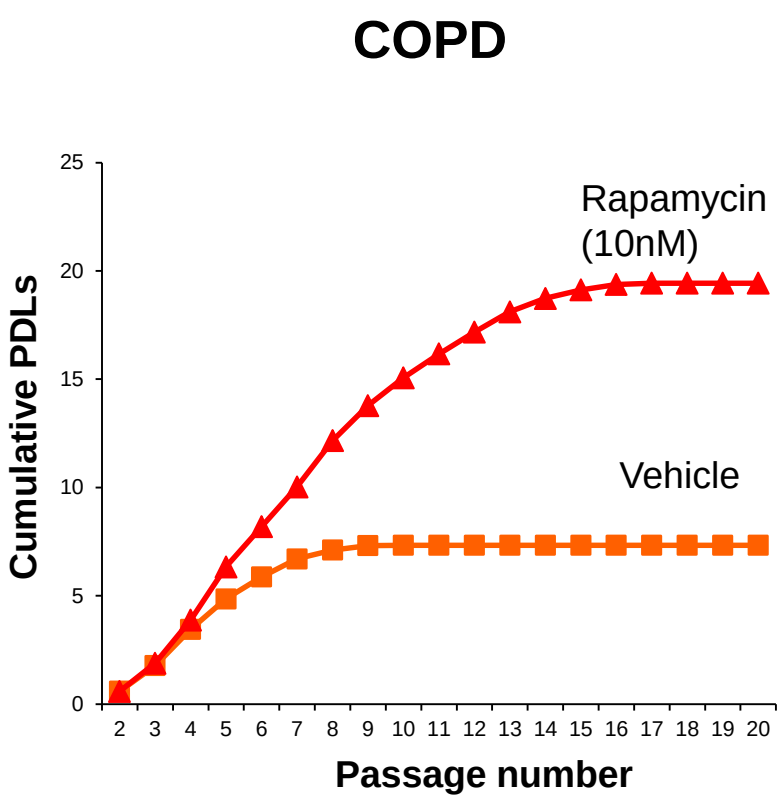

5 HT
PDGF
IGF; bFGF
Cytokines
PI3K
mTORC 2
Ser473
Thr308
PTEN
Other signals
Amino acids
Growth factors
Energy
Akt1,2
TSC1
mTORC1
P70S6K
4EBP1
S6K
p53
FoxO
Survivin
GSK3
p21
Cyclin D
Glycogène
Synthase
eNos
Protein synthesis
Cell
Survival
Cell cycle
Métabolism
Others
Cell
proliferation

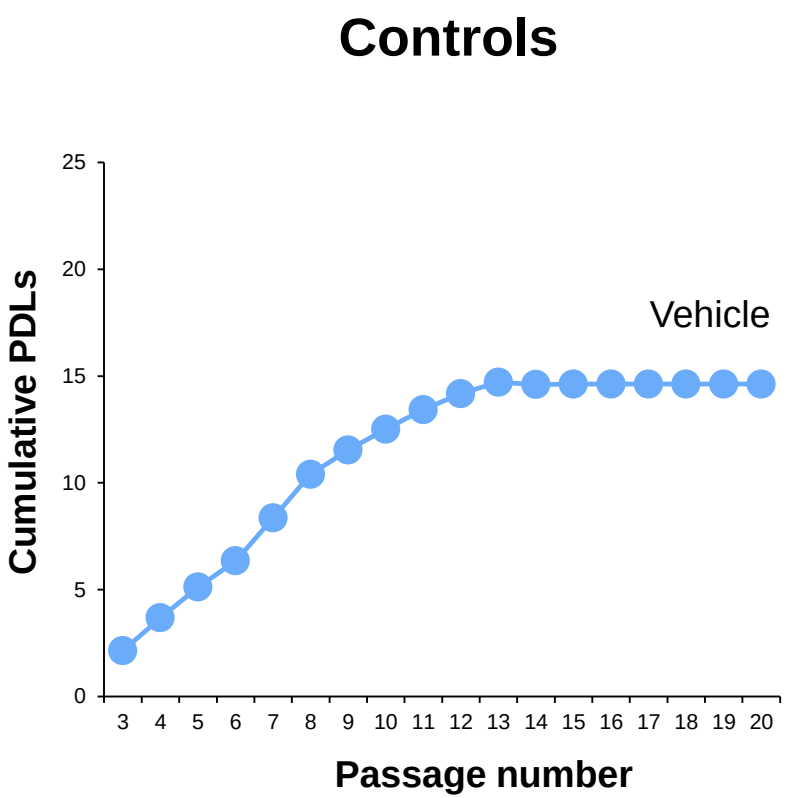
Effects of rapamycin on cell senescence in COPD Endothelial cells





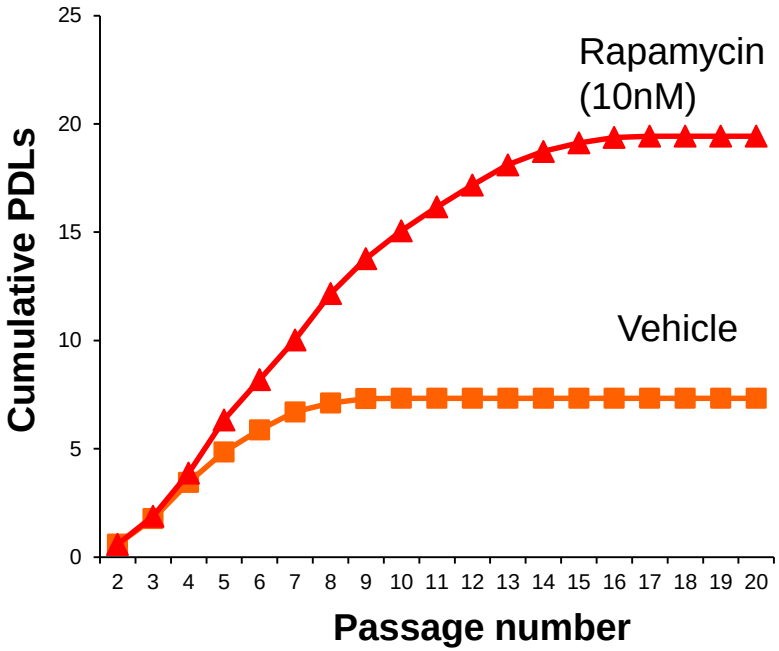
Effects of rapamycin on cell senescence in COPD Endothelial cells



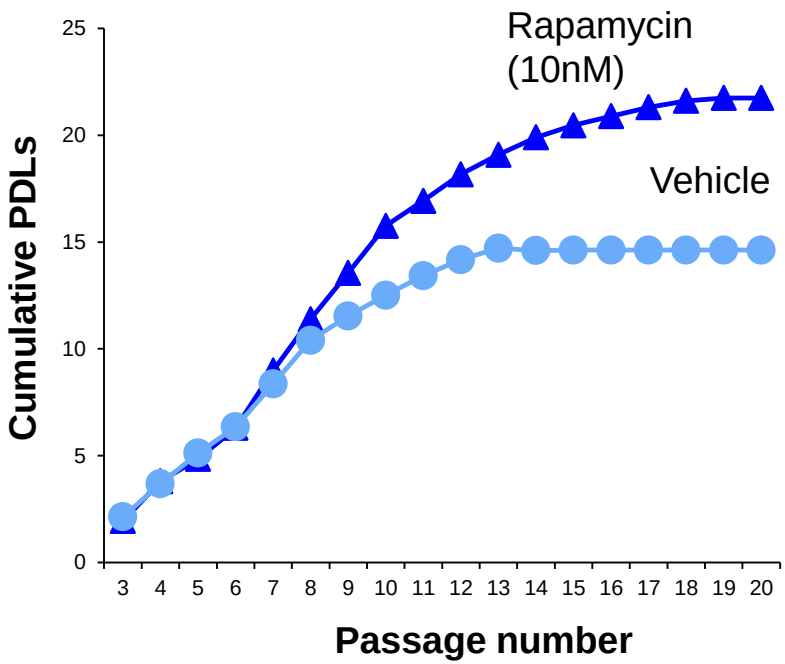


Effects of rapamycin on cell senescence in COPD Endothelial cells

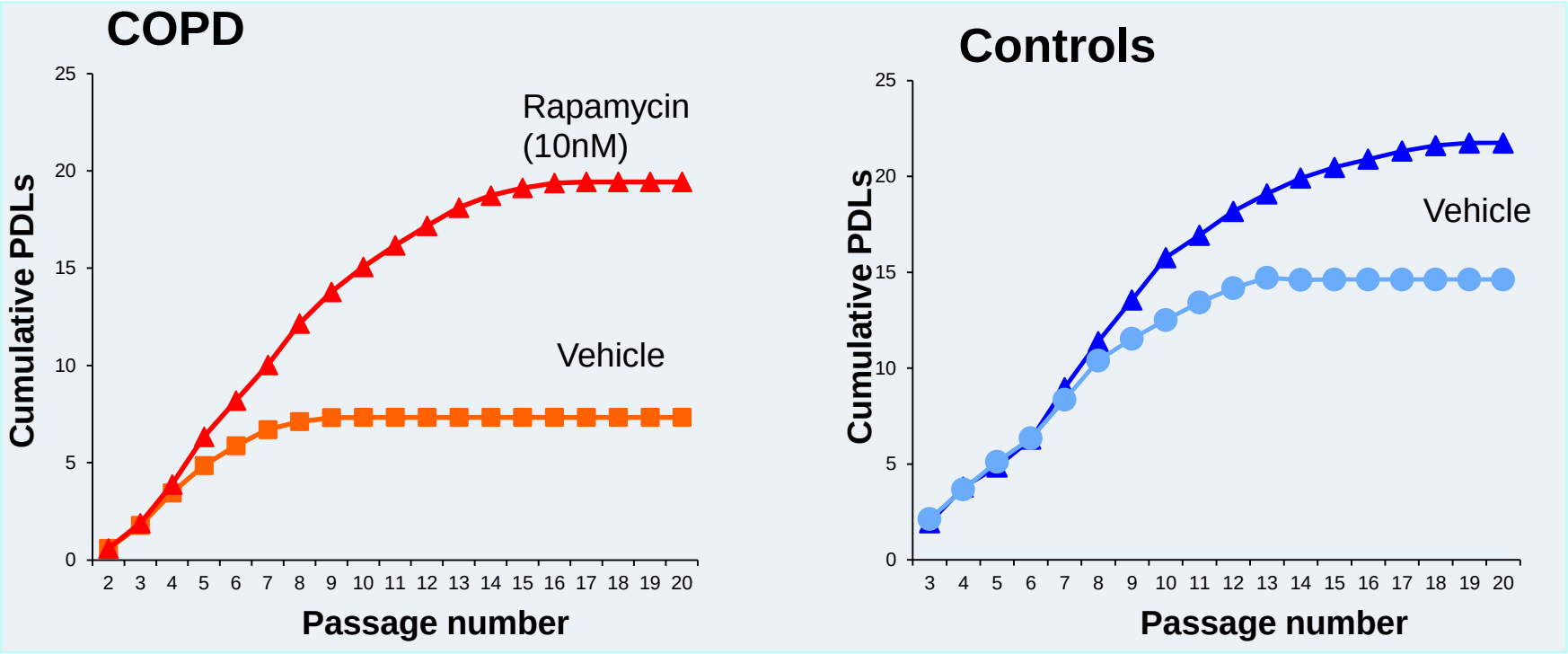
COPD

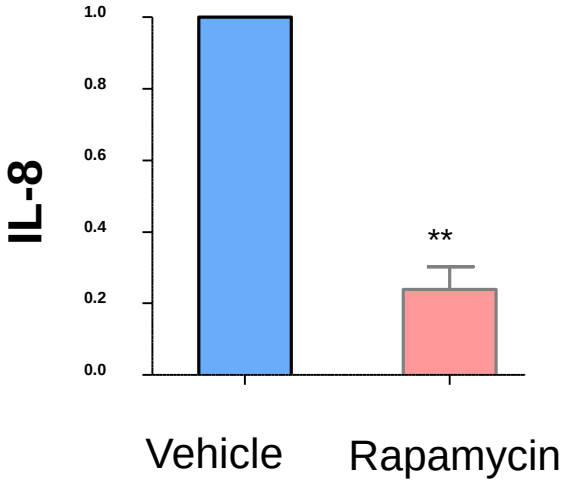


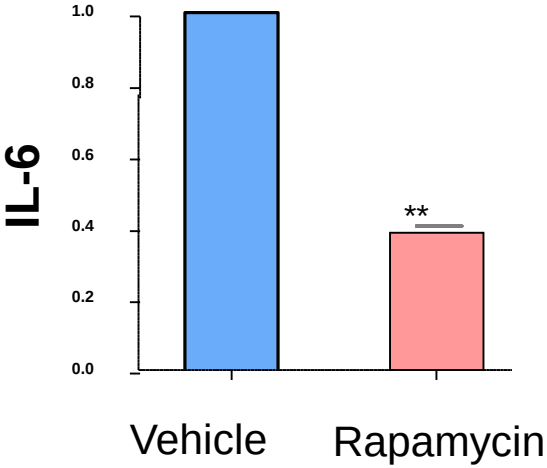
Controls



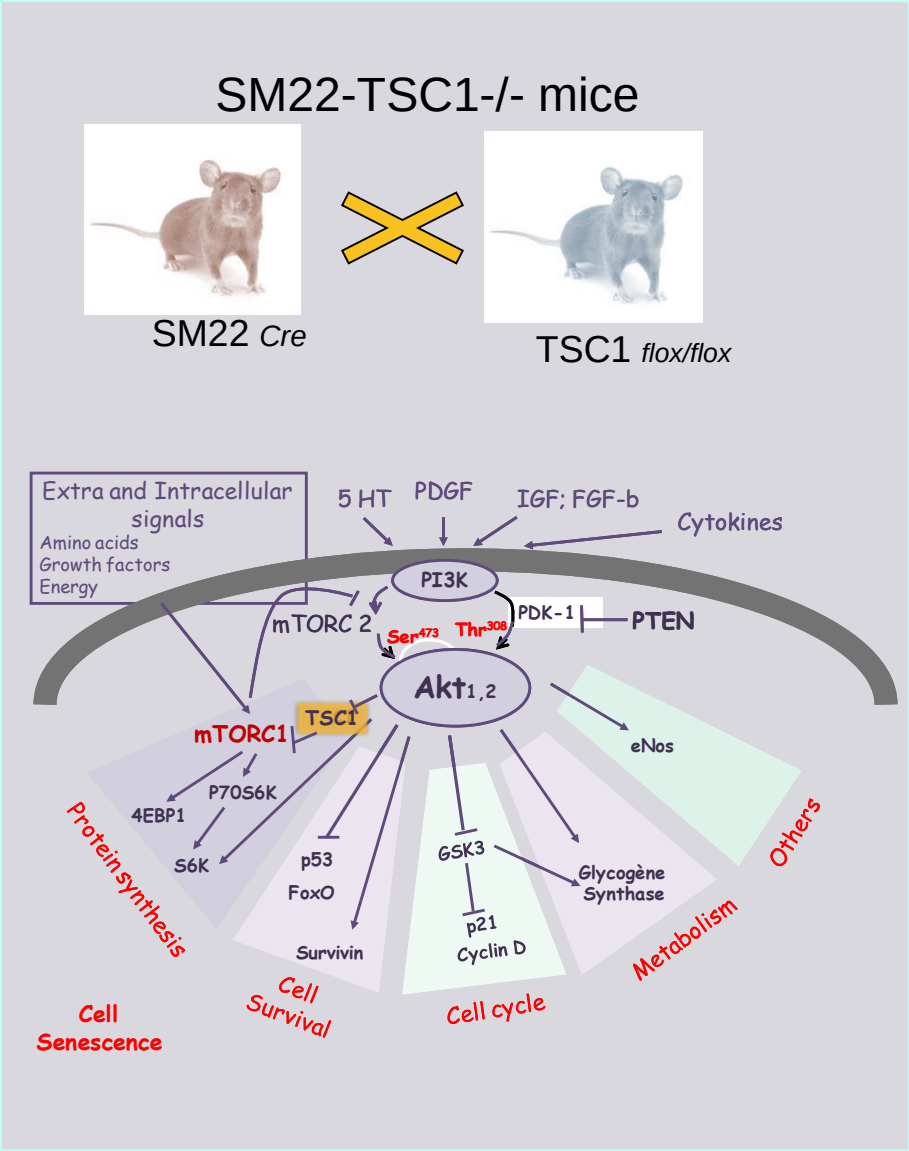
Effects of rapamycin on cell senescence in COPD

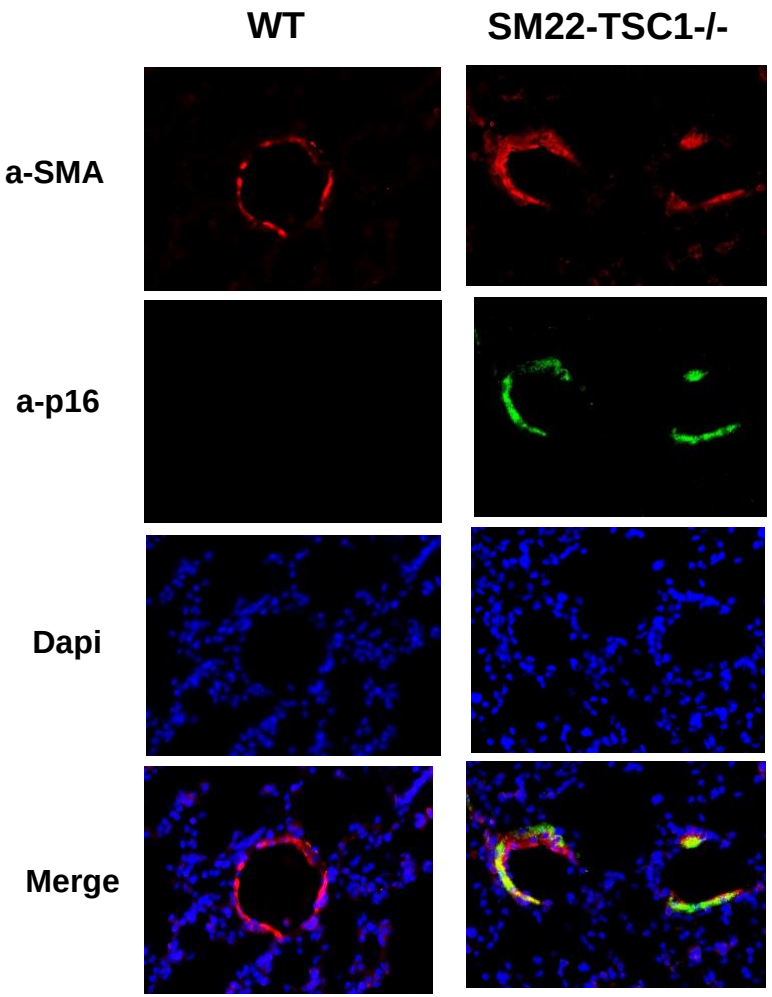




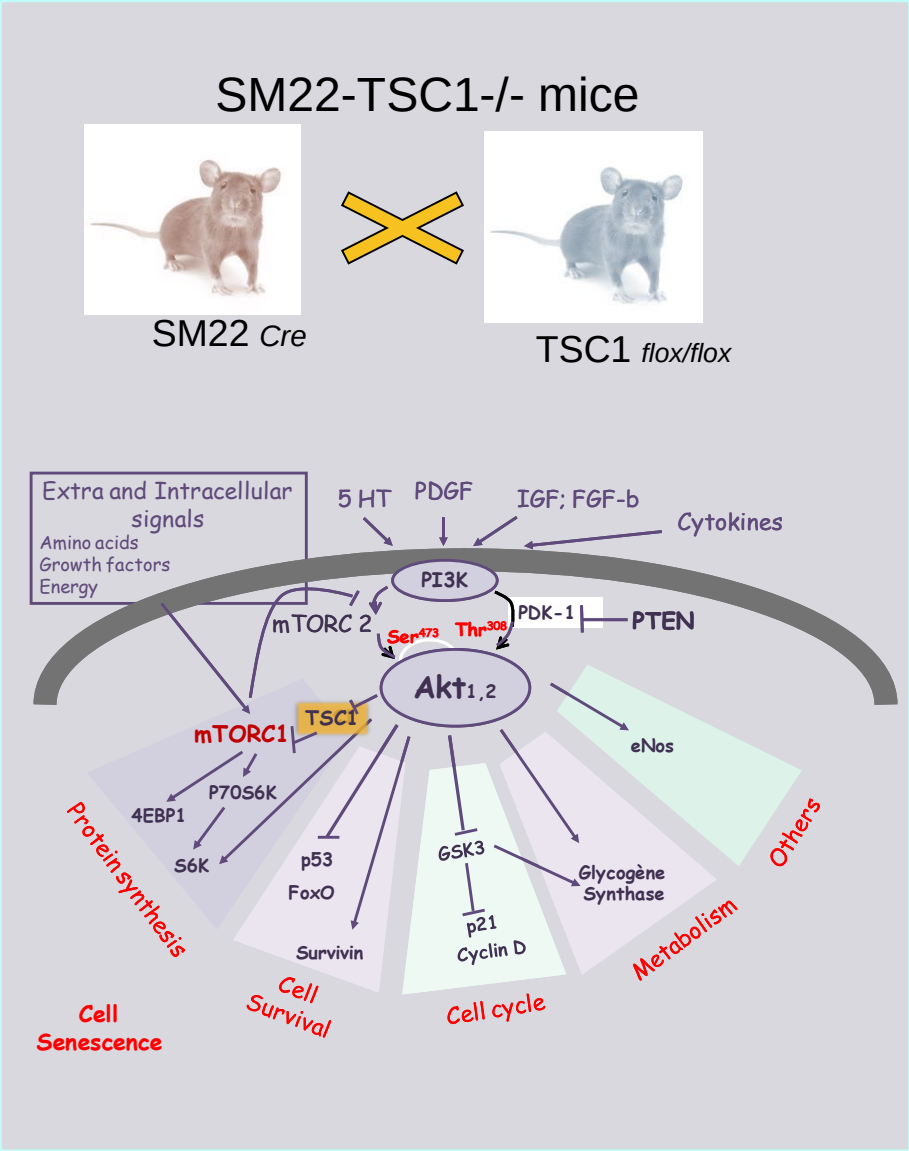


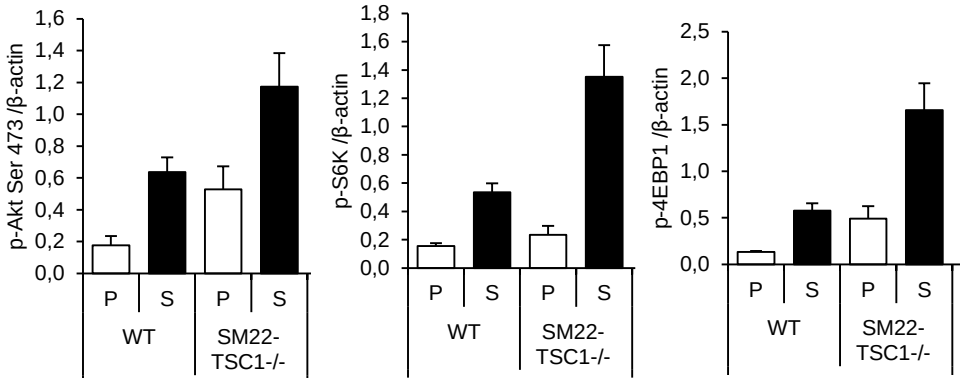
PASMC senescence in SM22-TSC1-/- mice

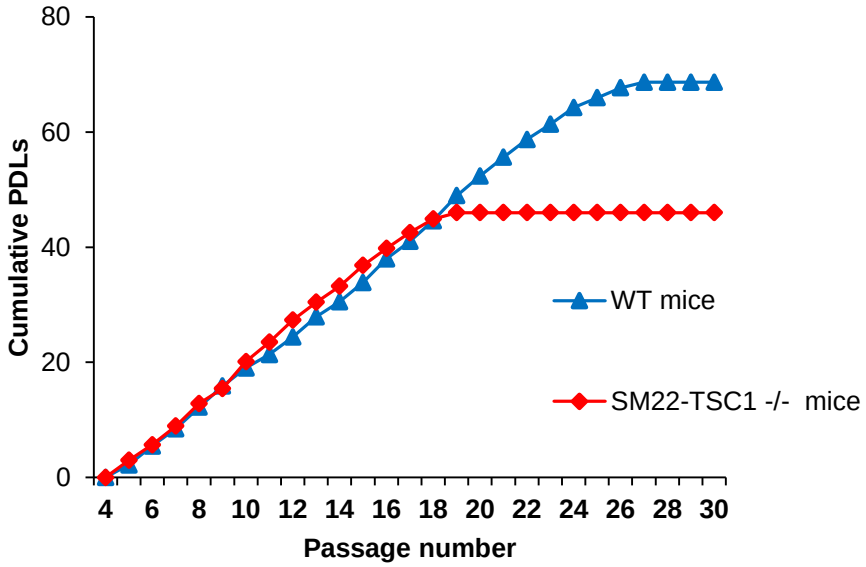




Replicative PASMC senescence in SM22-TSC1-/- mice





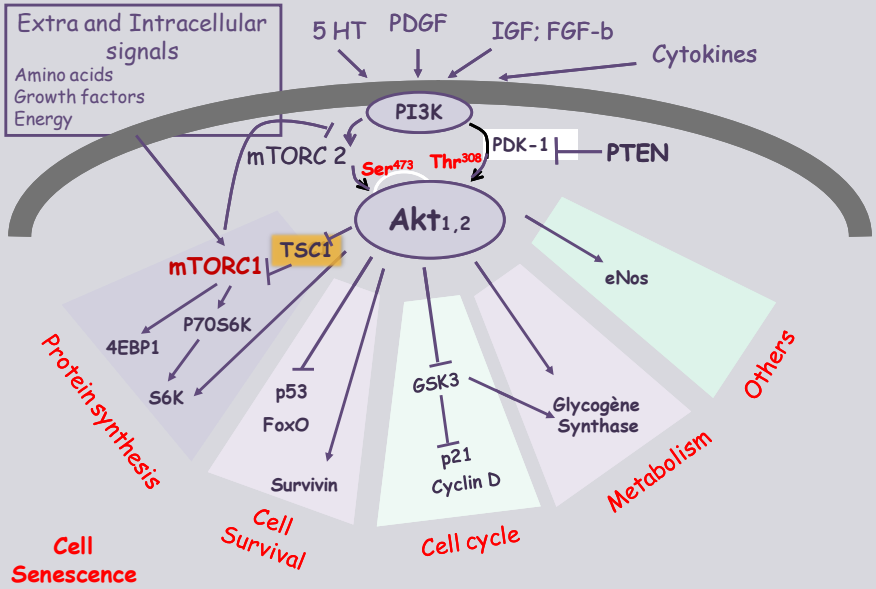


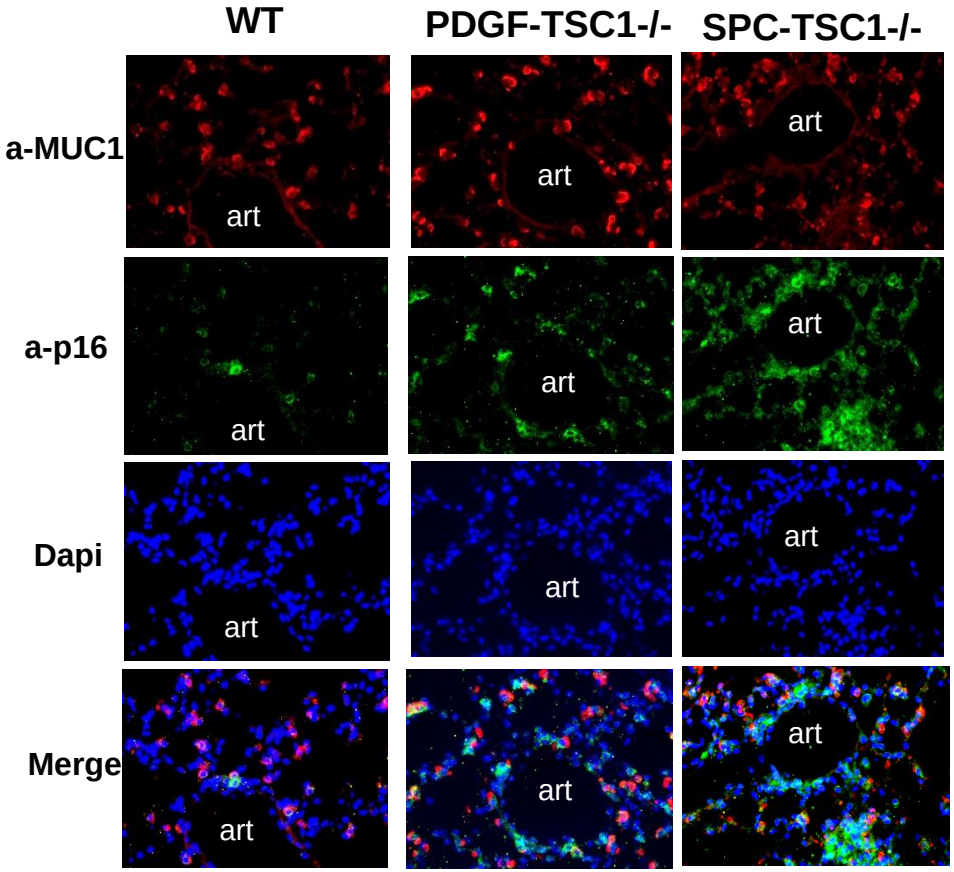
Cell senescence in SPC-TSC1-/- and PDGF-TSC1-/- mice

PDGF-TSC1-/- mice
SPC-TSC1-/- mice

SPC *Cre*
PDGF *Cre*

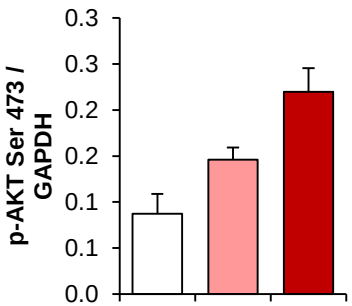
TSC1 *flox/flox*

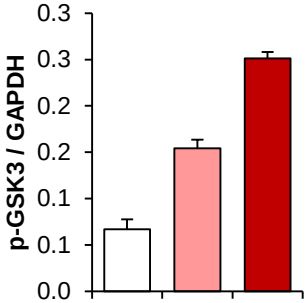


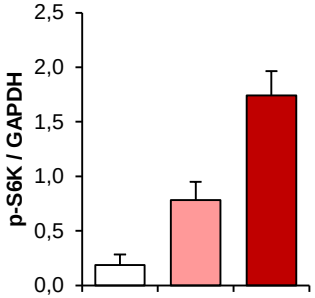


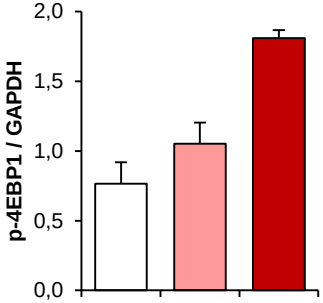
PDGF-TSC1 -/- mice : condition deletion of TSC1 in endothelial cells

1-3-6 Months









- Tamoxifen

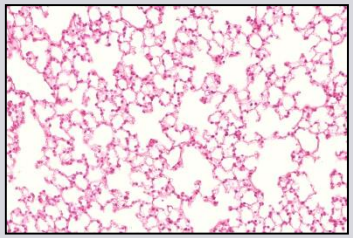
+ Tamoxifen

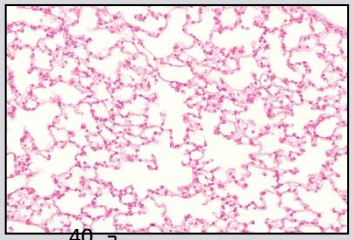
WT

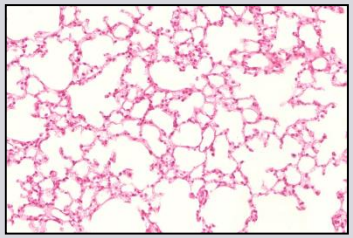
PDGF-TSC1 -/-

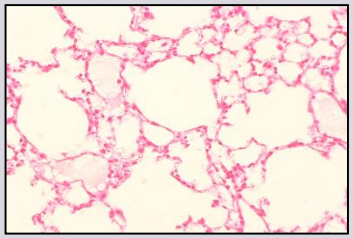
PDGF-TSC1 -/- 3 months

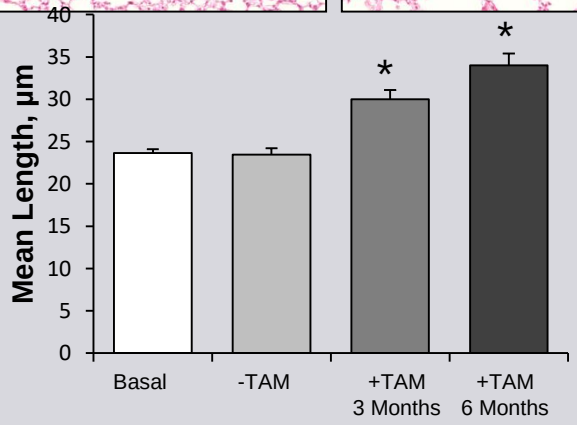
PDGF-TSC1 -/- 6 months





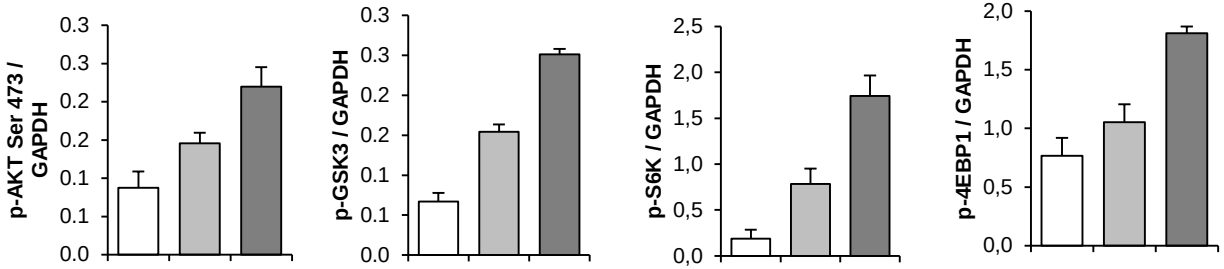


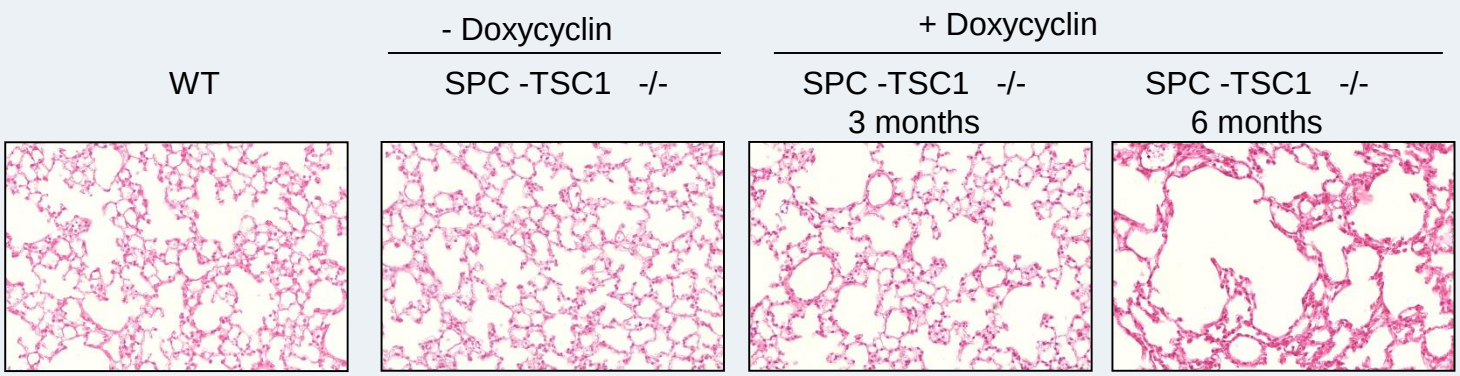


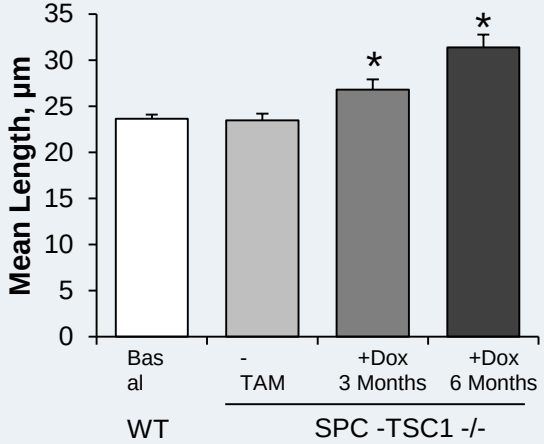


SPC-TSC1 -/- mice : deletion of TSC1 in alveolar type II cells

3 –6 Months

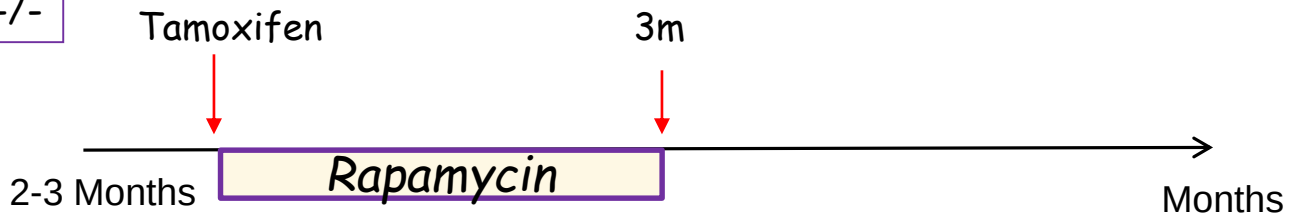




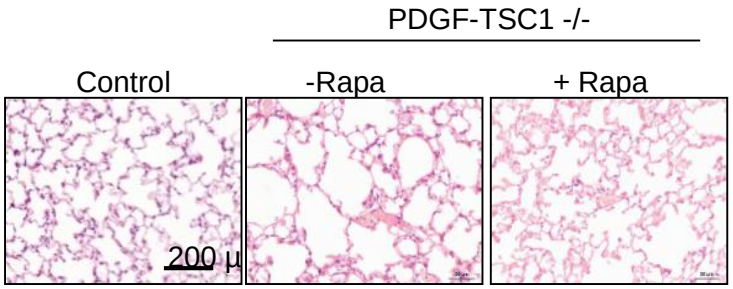


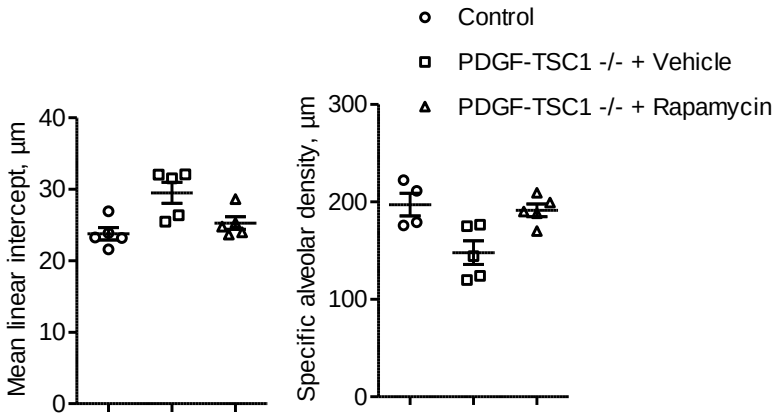
Rapamycin protects against emphysema and PH development

PDGF-TSC1 -/-

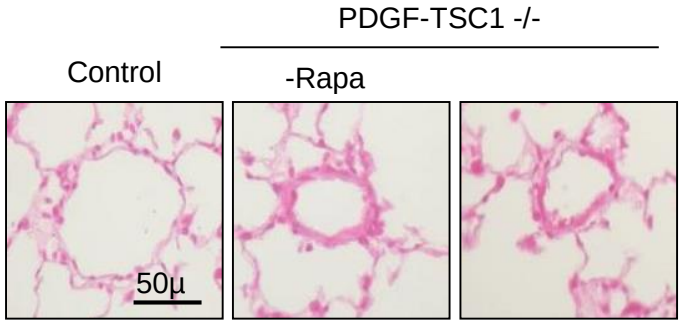


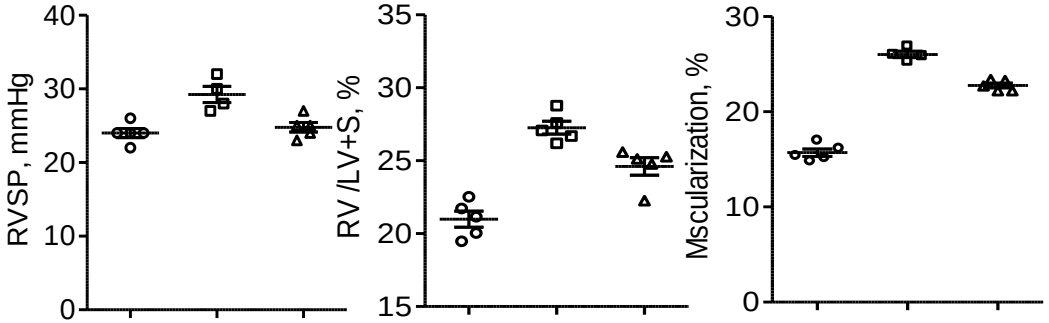
➢ Emphysema



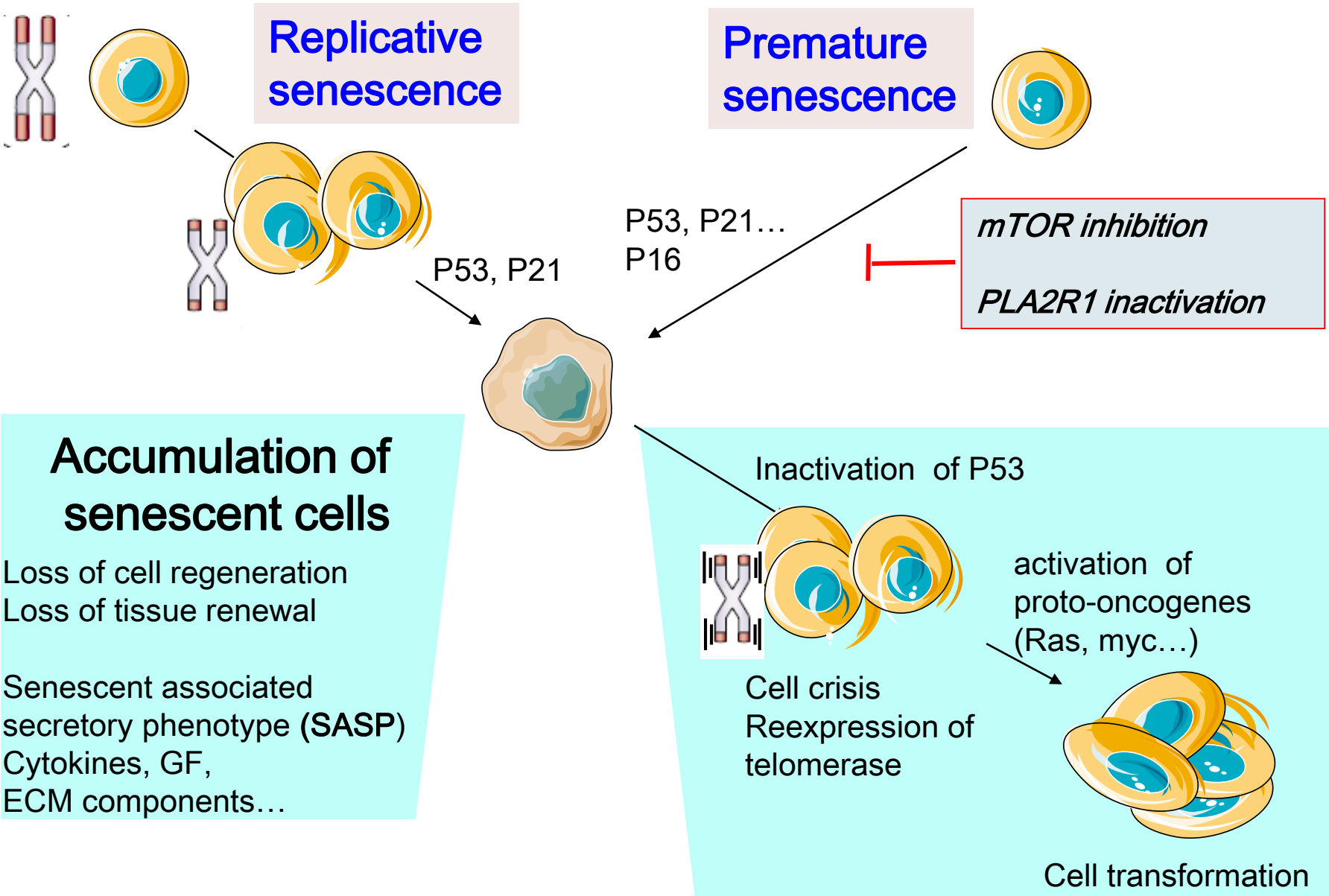


➢Pulmonary Hypertension





Cell senescence: a target for lung aging and diseases

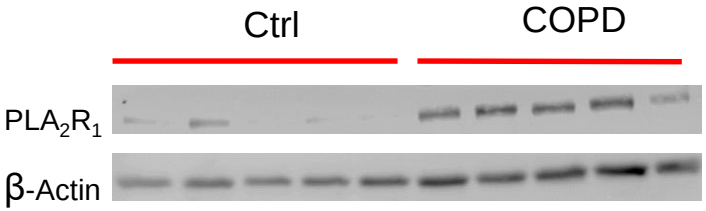


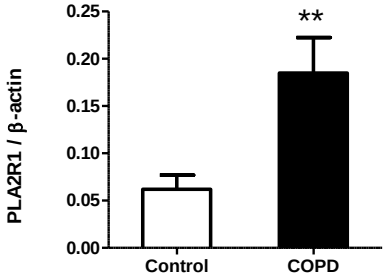
Signaling pathways involved in cellular senescence

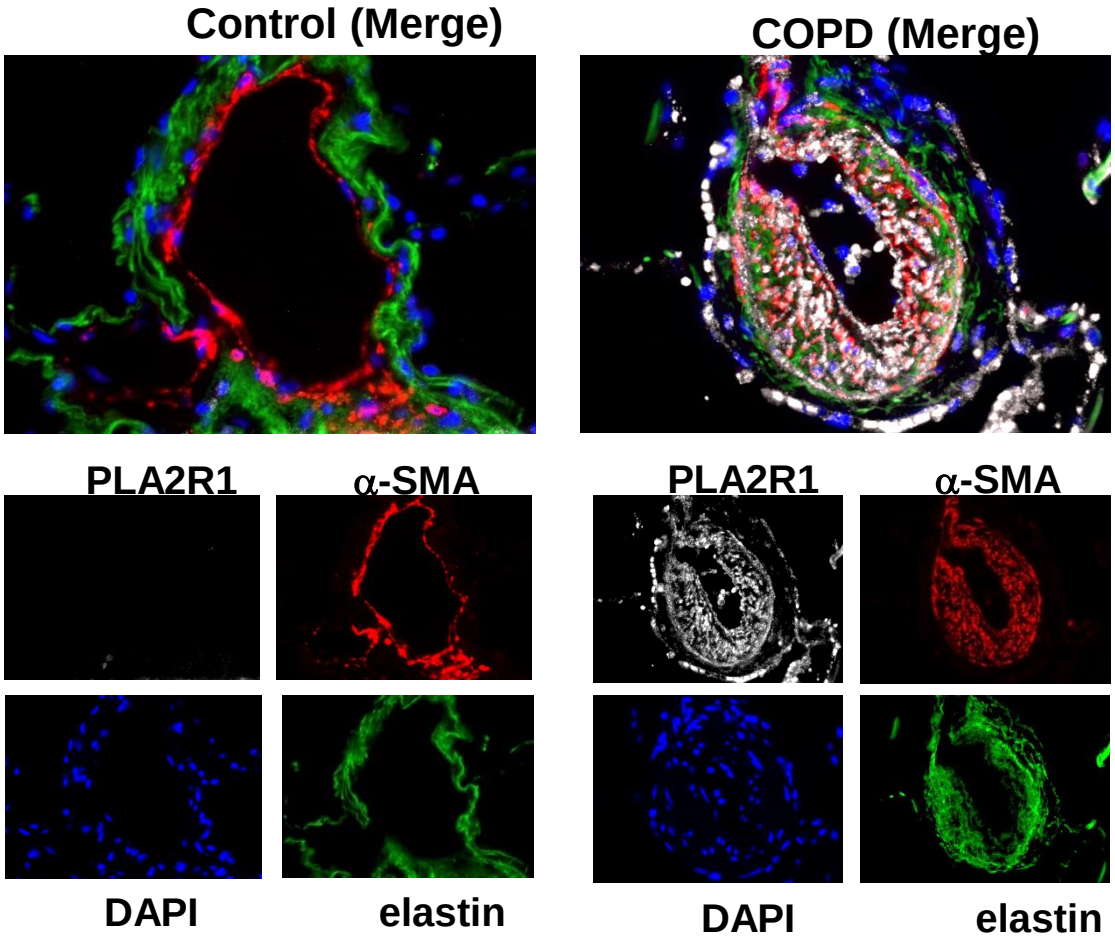
The M-type receptor PLA2R regulates senescence through the p53 pathway

EMBO Rep. 2009 Mar;10(3):271-7

Arnaud Augert[1], Christine Payré[2], Yvan de Launoit[1], Jesus Gil[3], Gérard Lambeau[2] & David Bernard[1+]

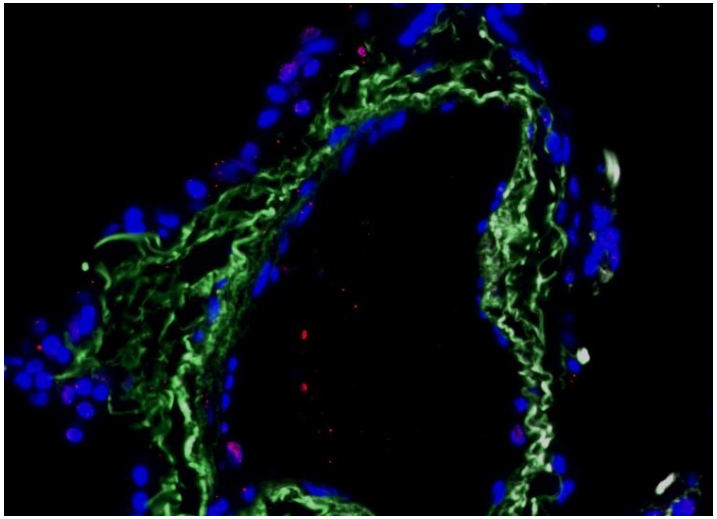




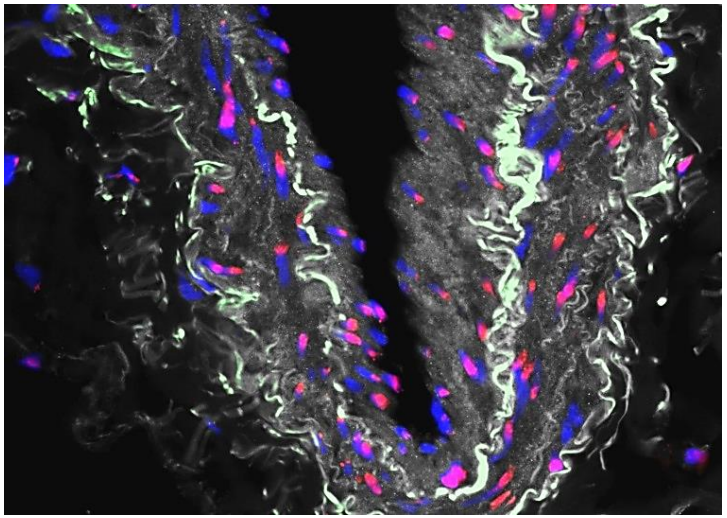


PLA2R1 expression in p16 stained cells in lungs from control and COPD patients.

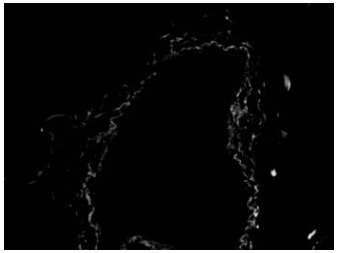
Control (Merge)



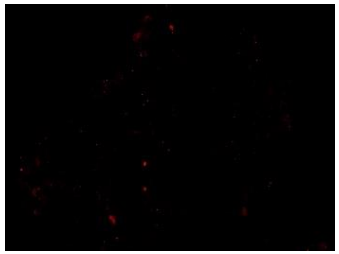
COPD (Merge)

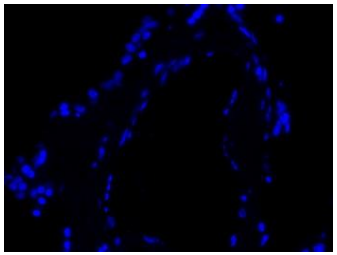


PLA2R1

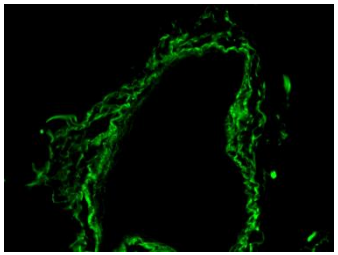


p16



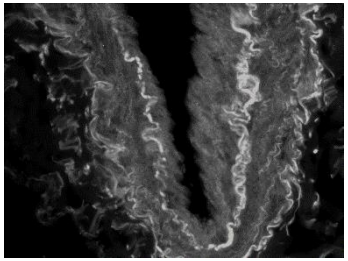


DAPI

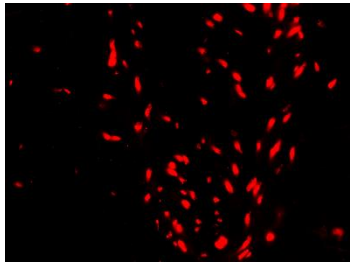


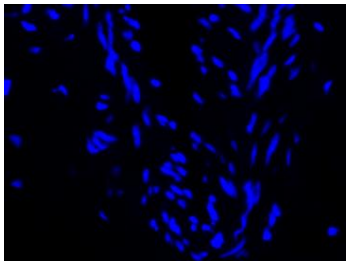
elastin

PLA2R1



p16





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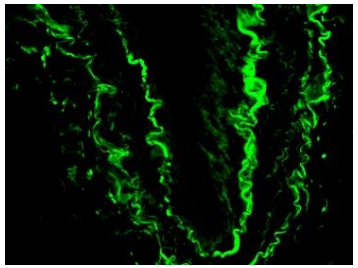
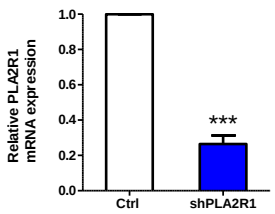
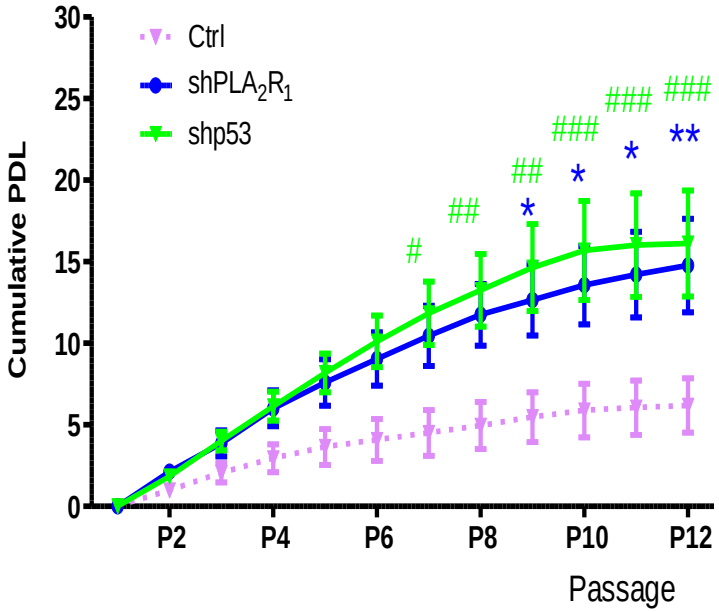


elastin

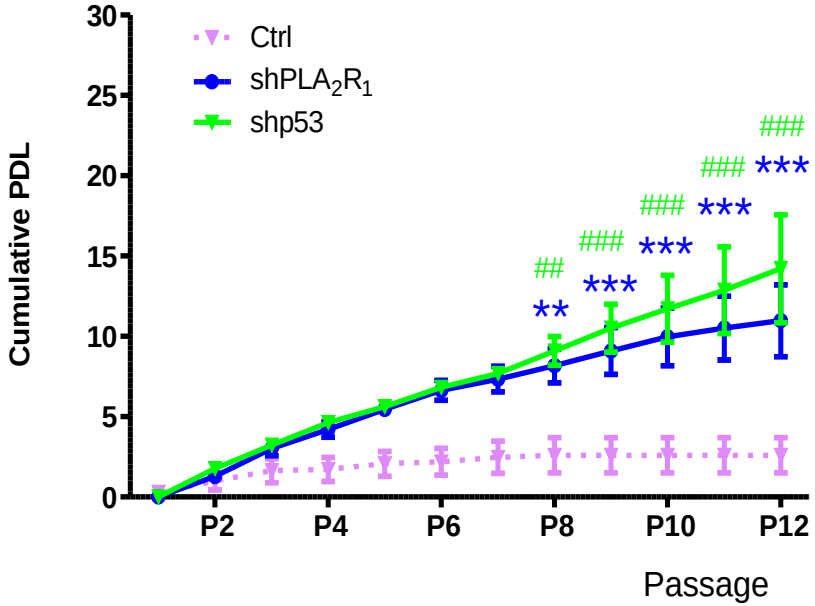
PLA2R1 knockdown inhibits senescence of pulmonary vascular smooth muscle cells from patients with COPD



Control

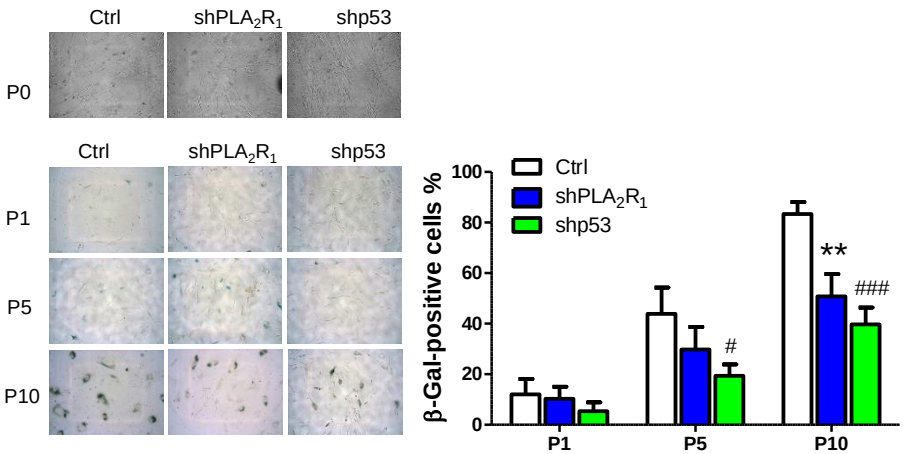


COPD

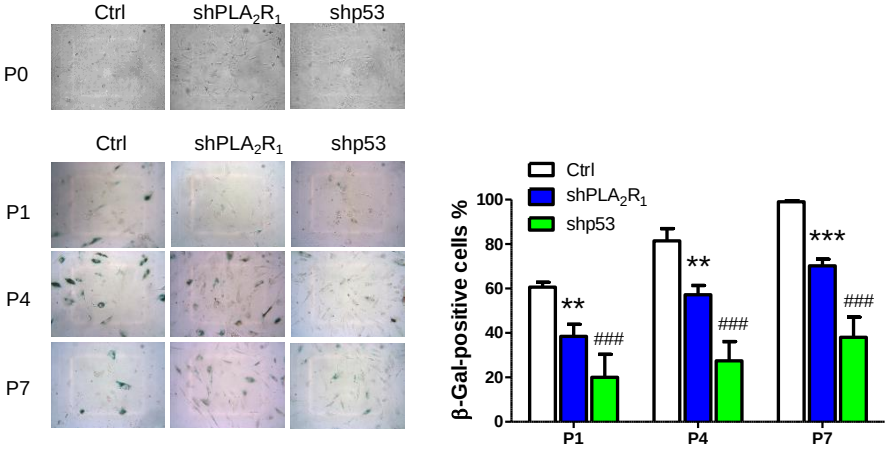


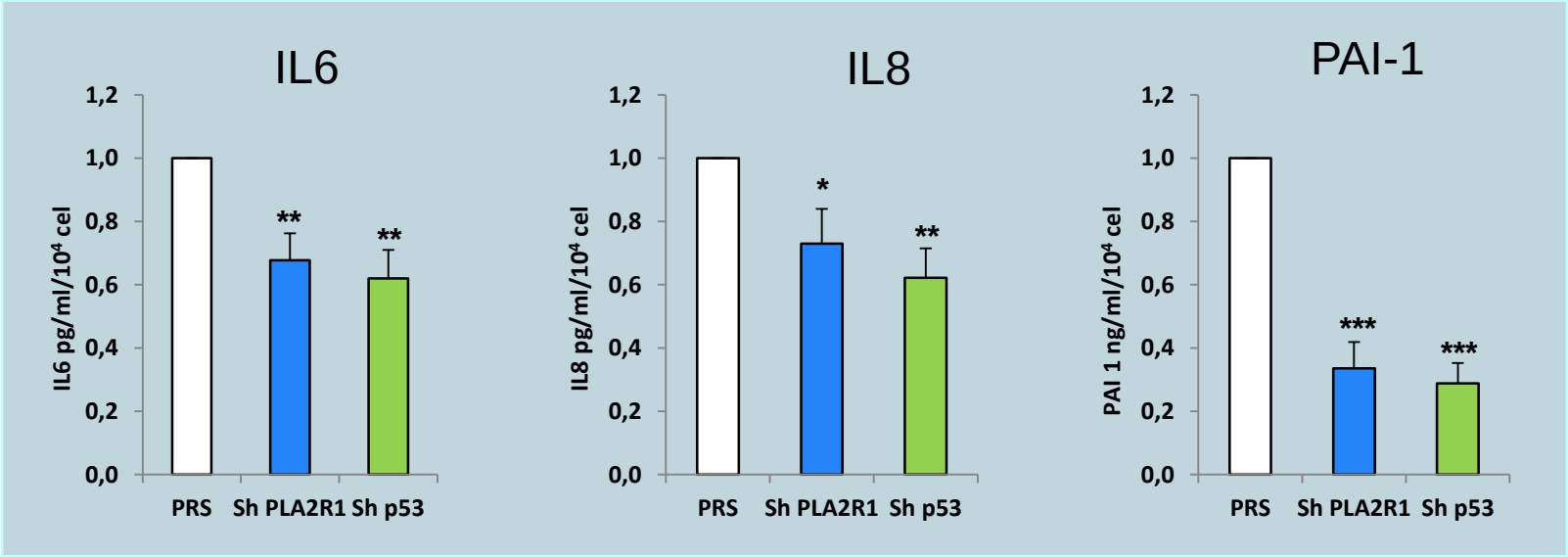
PLA2R1 knockdown: effects on β-gal activity and SASP members in PA-SMCs from patients with COPD

Control

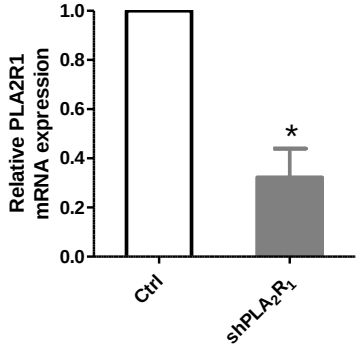


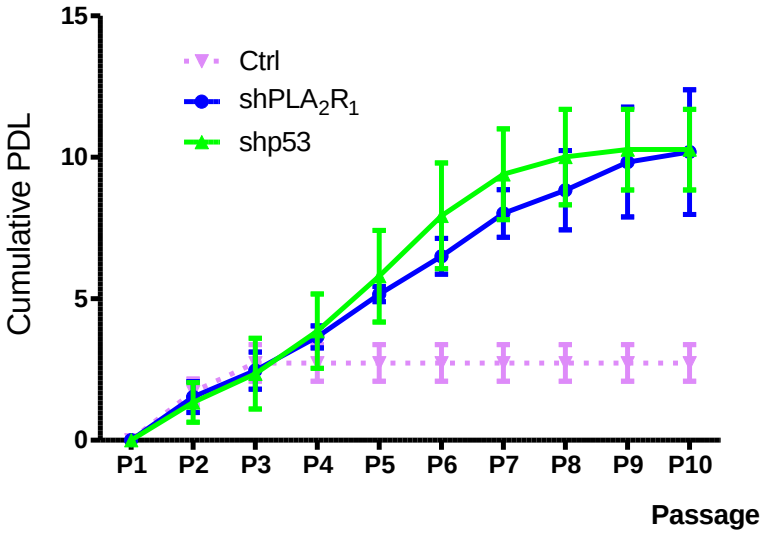
COPD

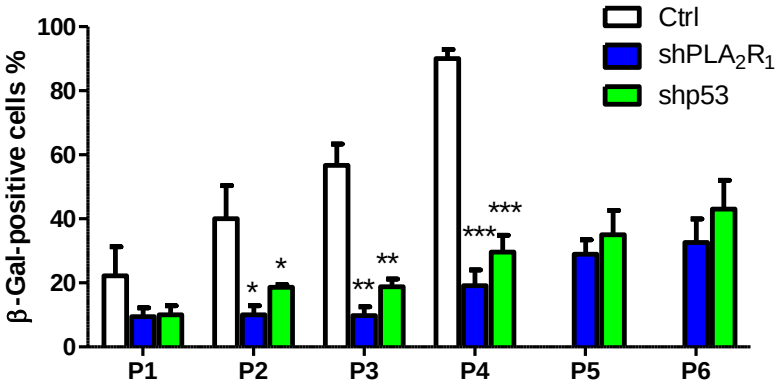


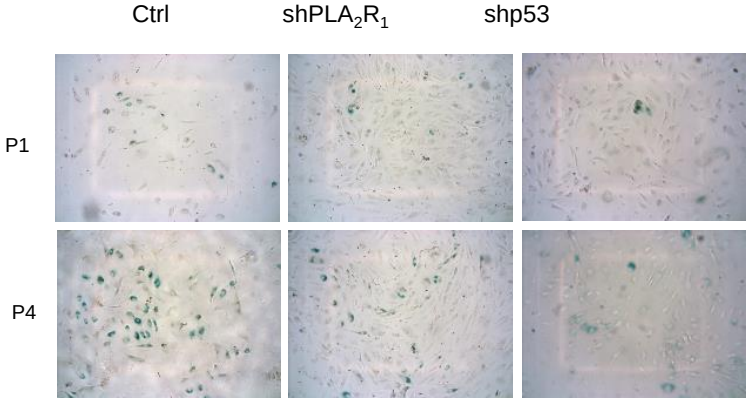


PLA2R1 knockdown inhibits senescence of pulmonary vascular endothelial cells from patients with COPD





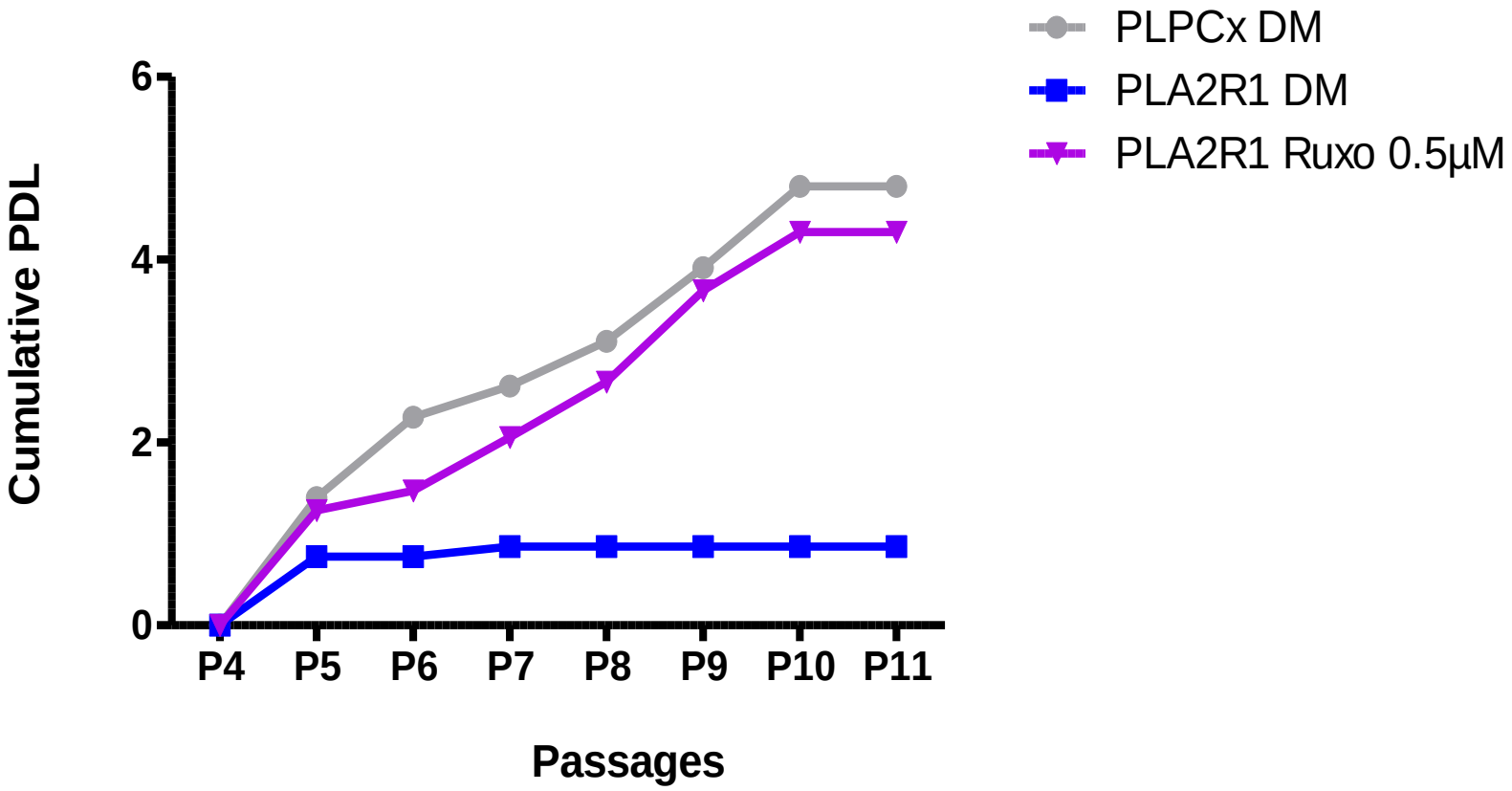




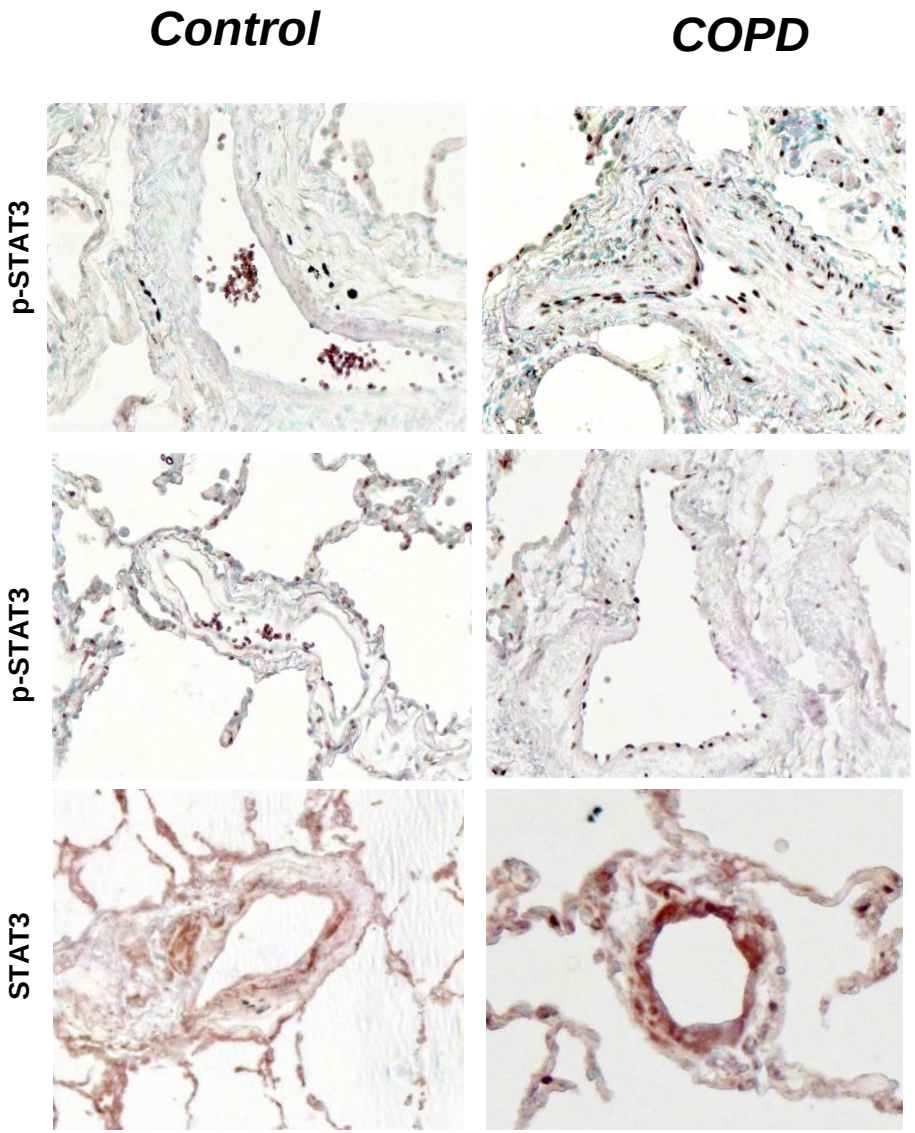
PLA2R1 gene transduction induces cell senescence
Inhibition by the JAK ½ inhibitor Ruxolitinib

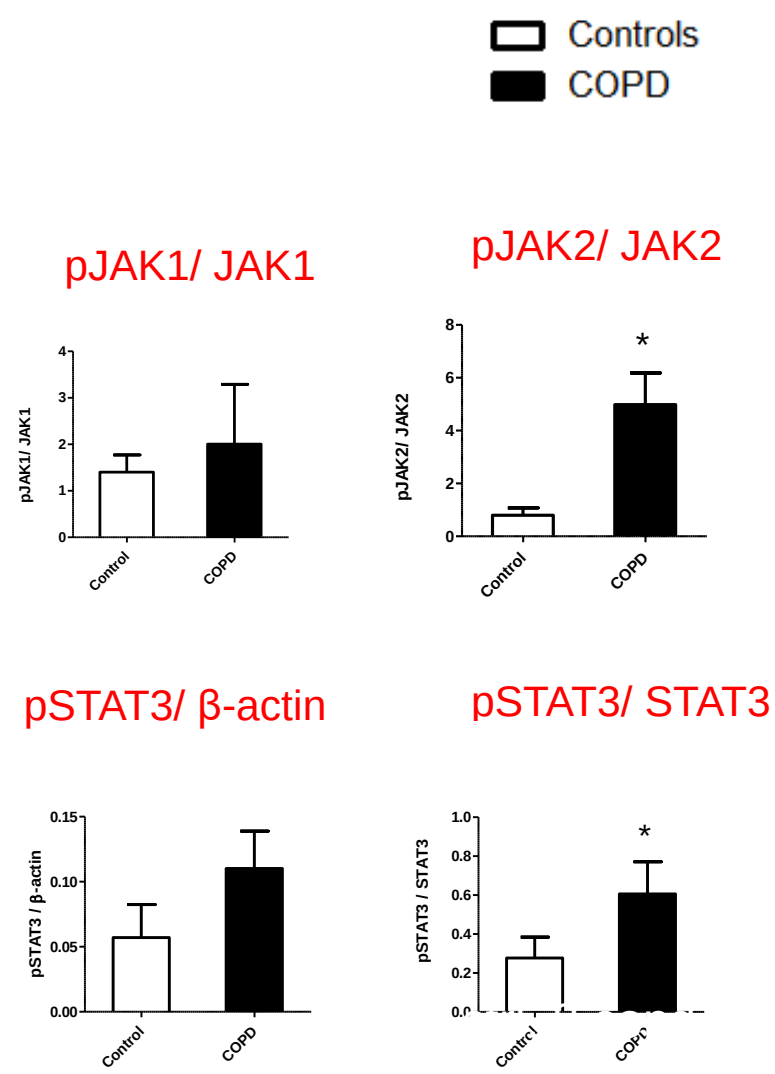
PLA2R1 mediates tumor suppression by activating JAK2

Vindrieux D et al, Cancer Res, 2013

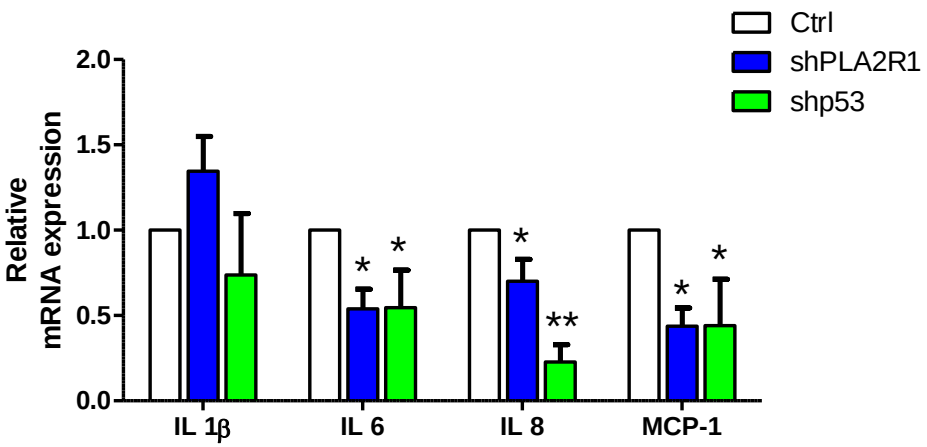


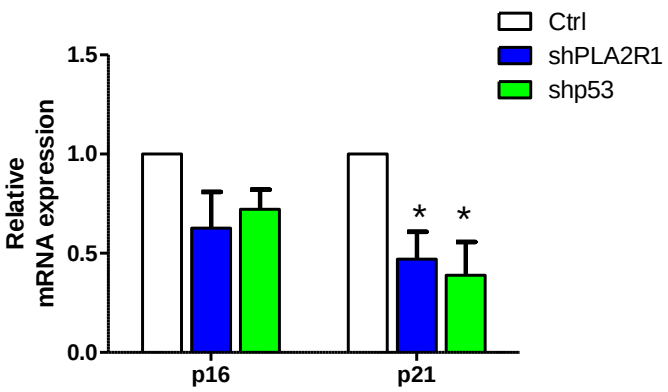
Activation of the JAK/Stat pathway in lungs and cells from Patients with COPD

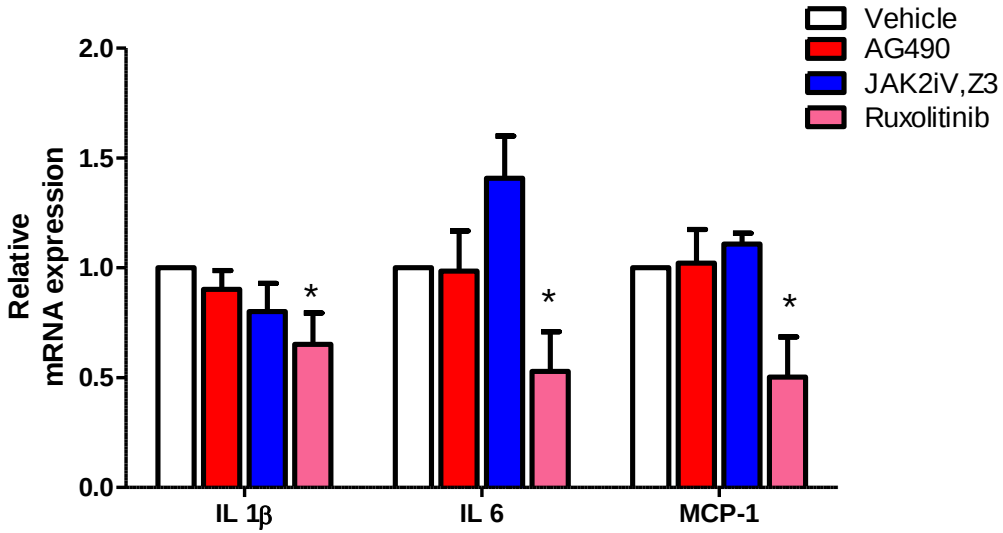




Inhibition of the SASP by PLA2R1 knockdown or by JAK1 inhibitors



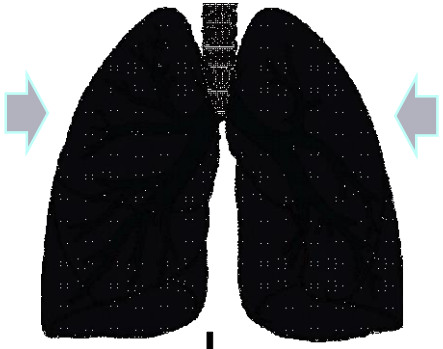




Therapeutic interventions ?

Genetic factors :

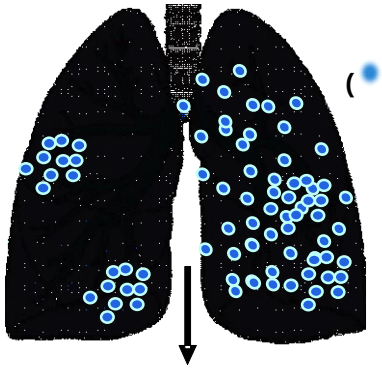
telomerase deficiency
Inheritable short telomeres



Environmental factors
Smoke, stress
Aging….

Halting the cell senescence process

Decline in lung function
COPD,
Emphysema
Inflammation
Systemic manifestations



(• senescent cell)

Eliminating senescent cells

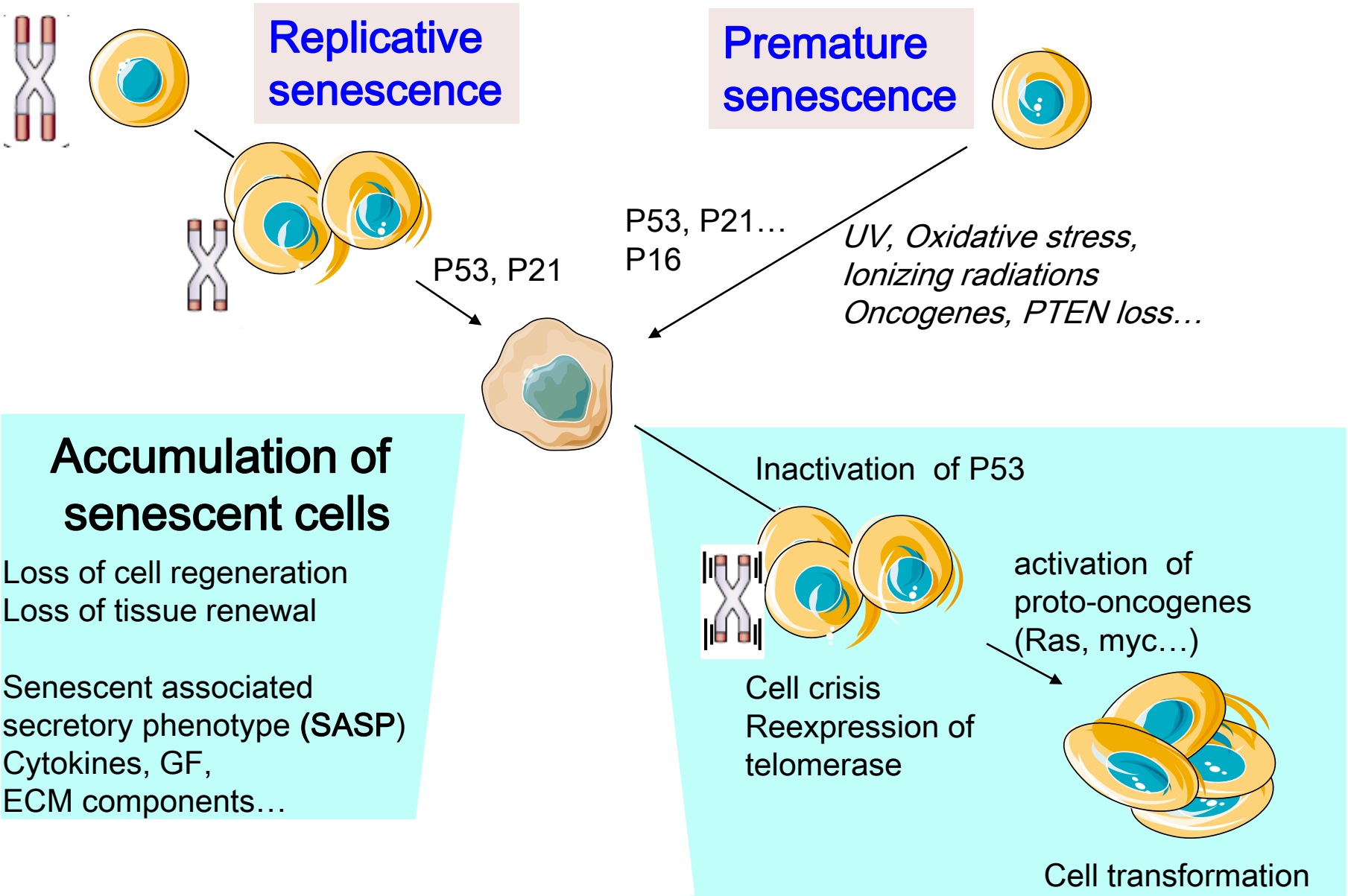
Suppressing the SASP

HEALTHY LUNG

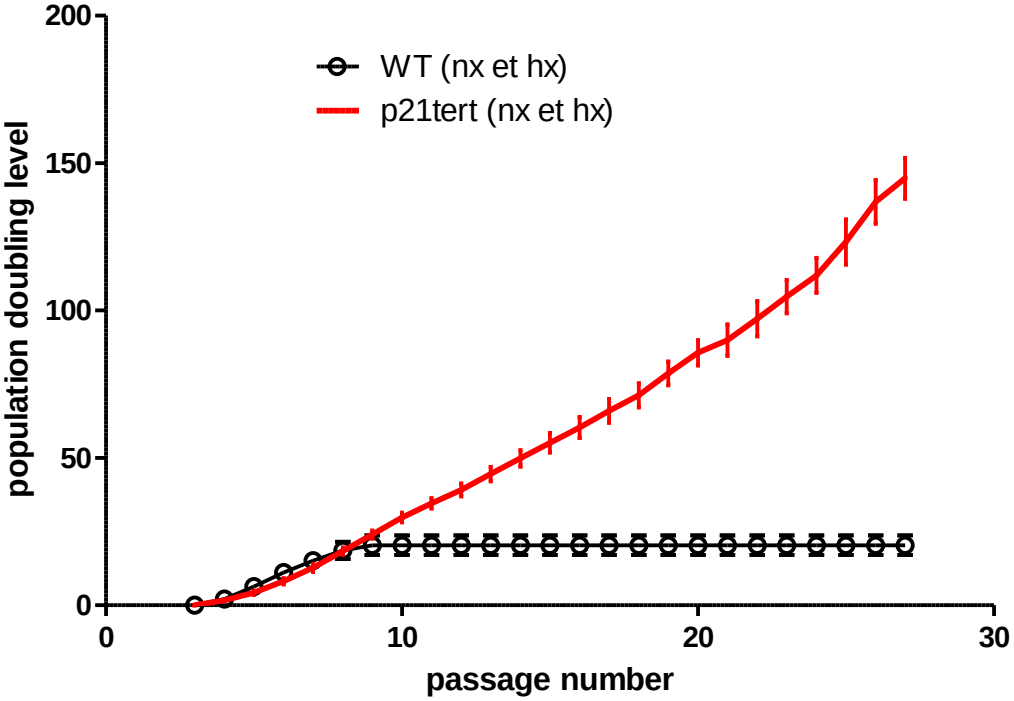
Targeting specific age-related diseases is the most suitable approach to test the effectiveness of agents that target cell senescence

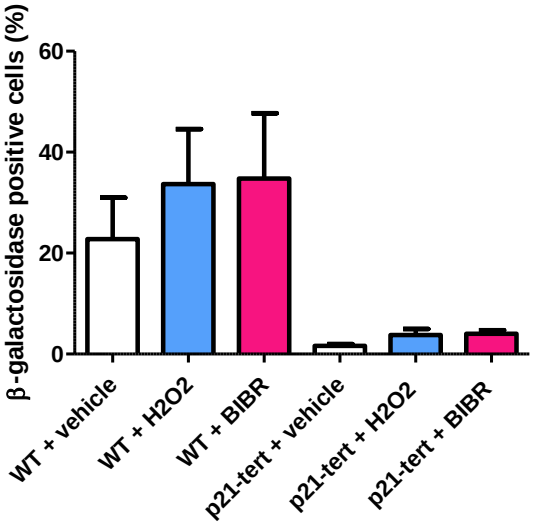
COPD
An optimal disease for clinical trials

Cell senescence: a target for lung aging and diseases

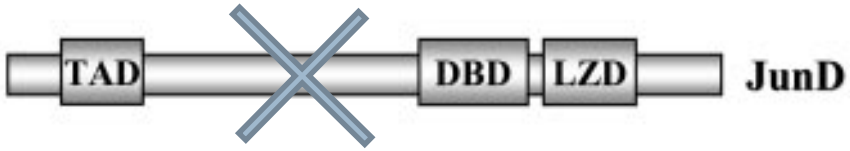


Telomerase expression under the control of p21



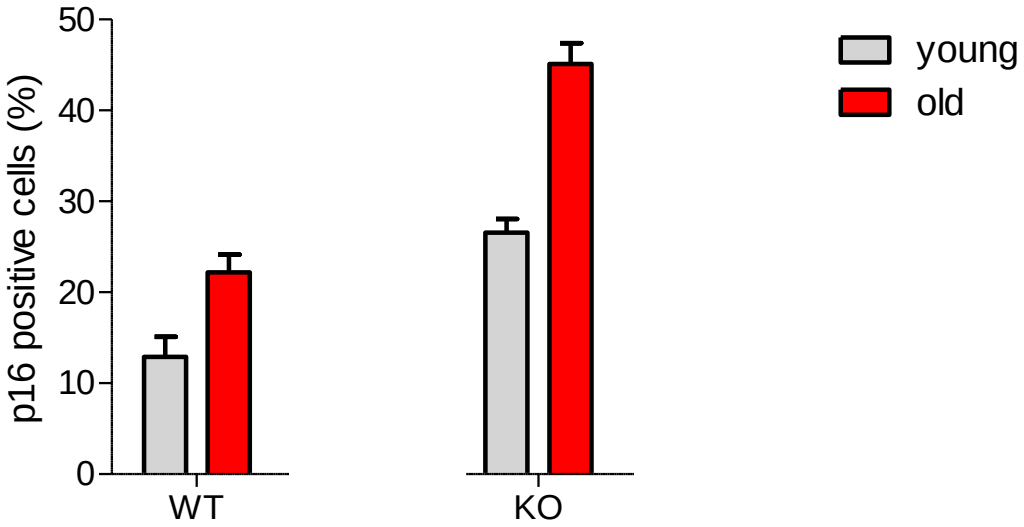


Effect of oxidative stress-induced cell senescence in the lung

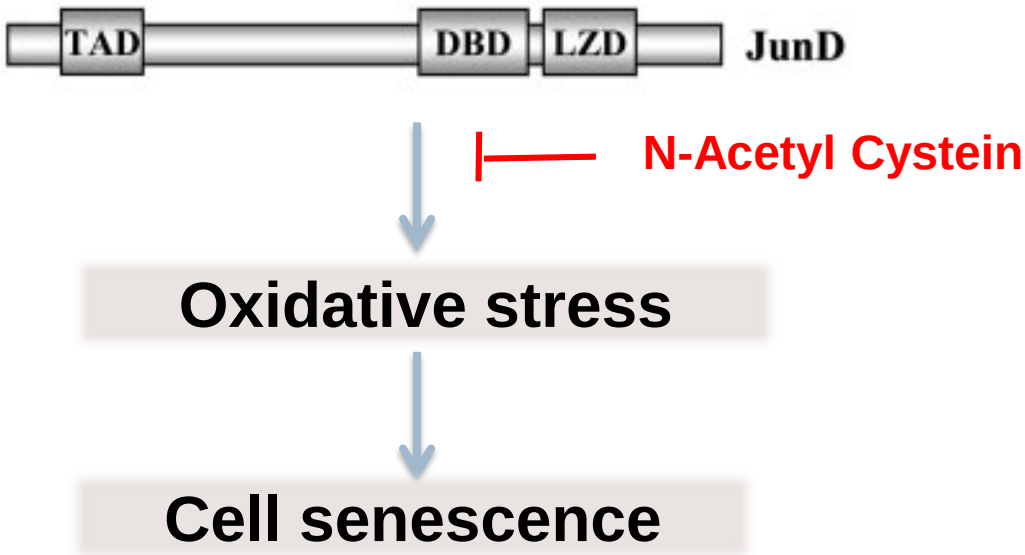


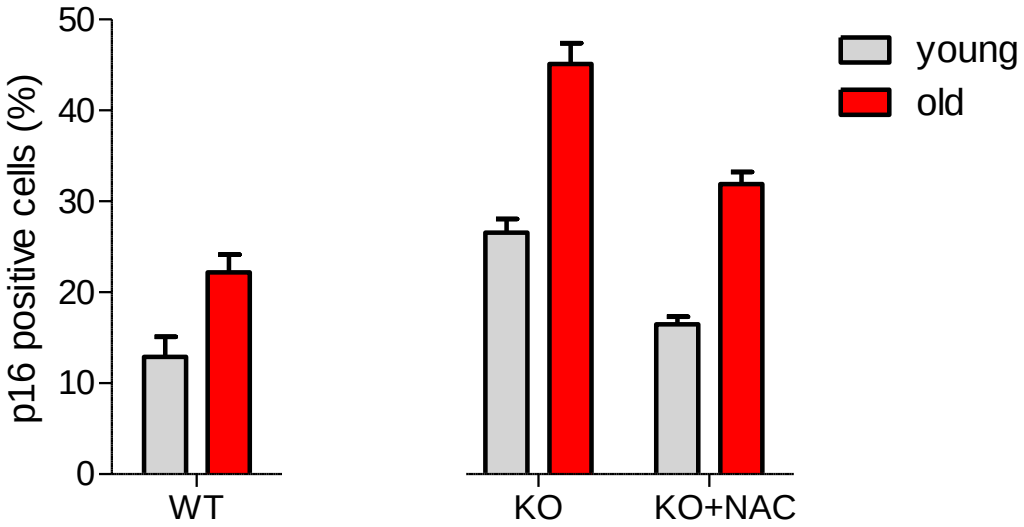
Oxidative stress

Cell senescence

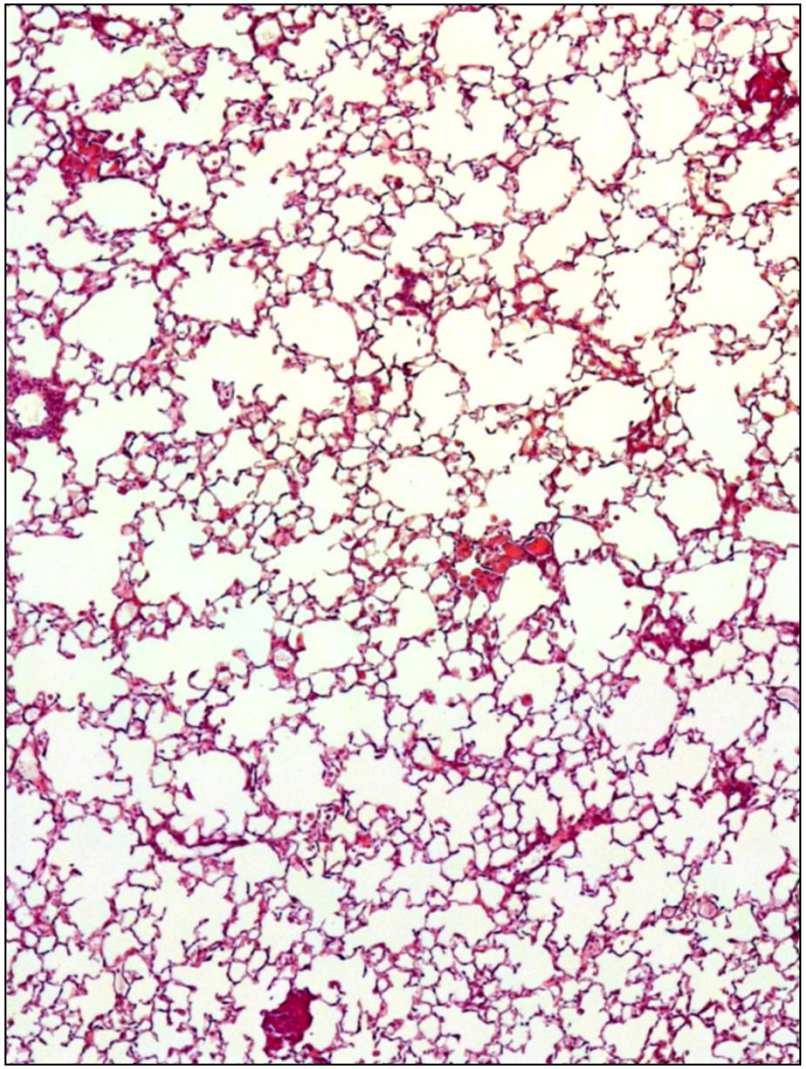


Effect of oxidative stress-induced cell senescence in the lung

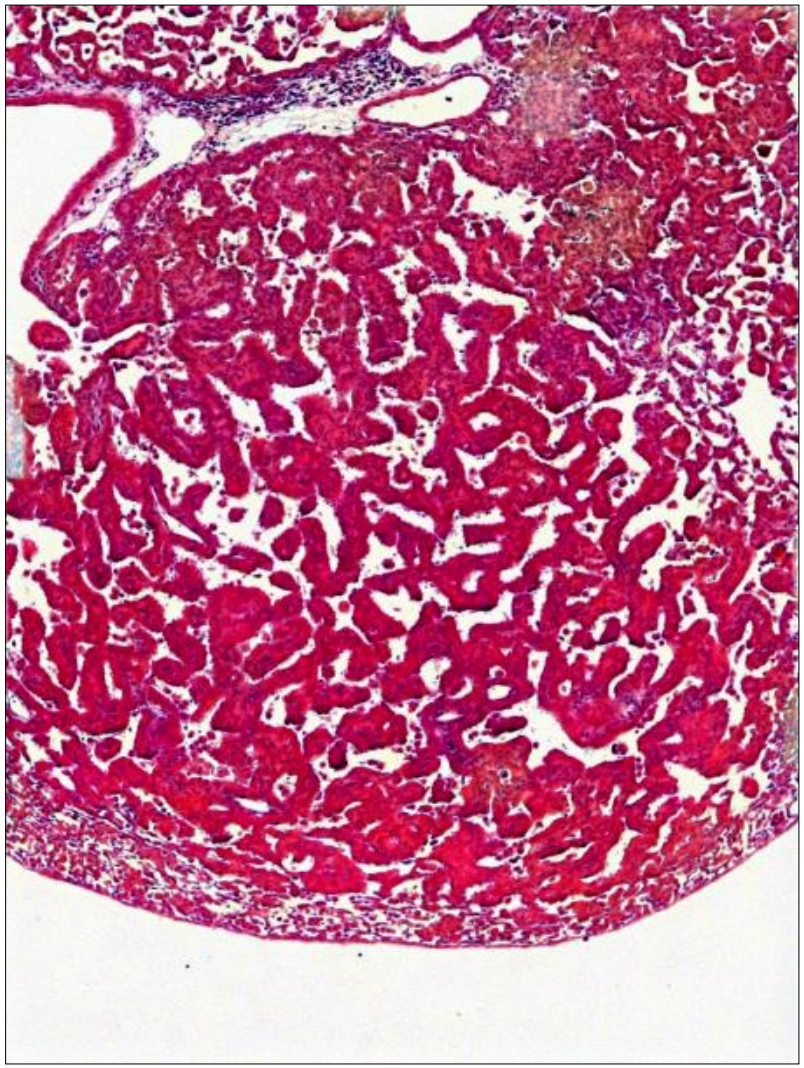




Lungs from junD-/- mice



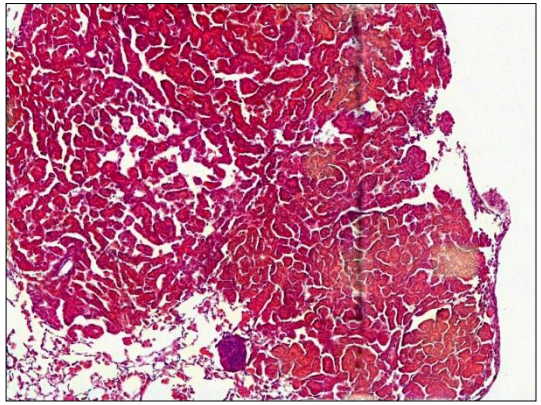
JunD KO mice, old

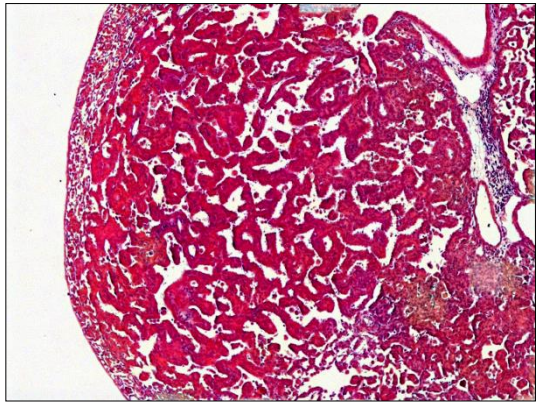


JunD KO mice, old
+ NAC

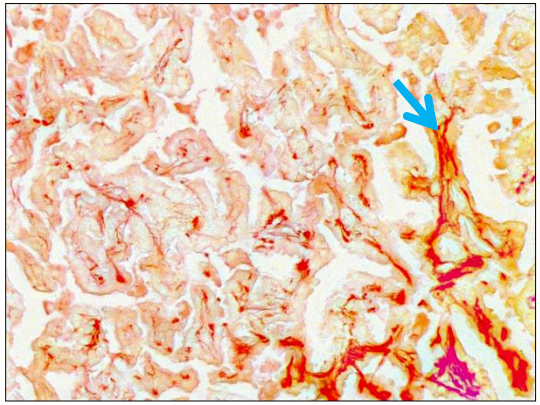
Lung adenocarcinoma development

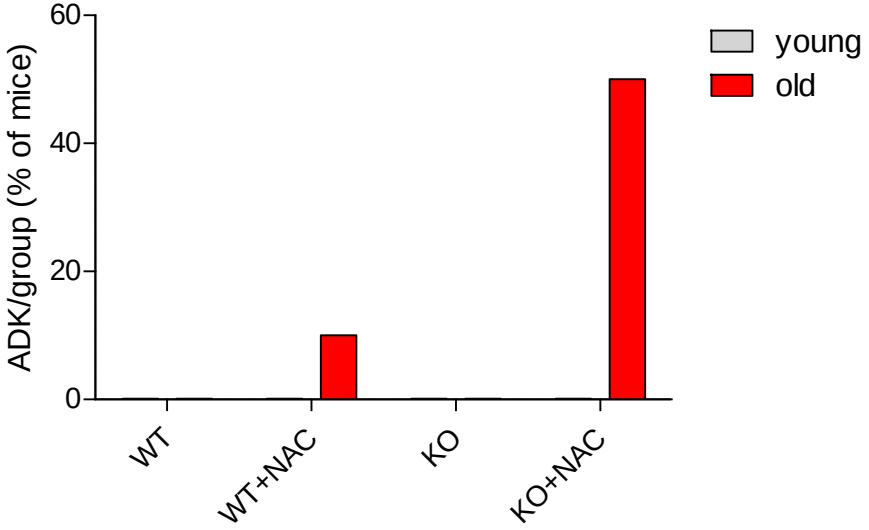
H&E coloration





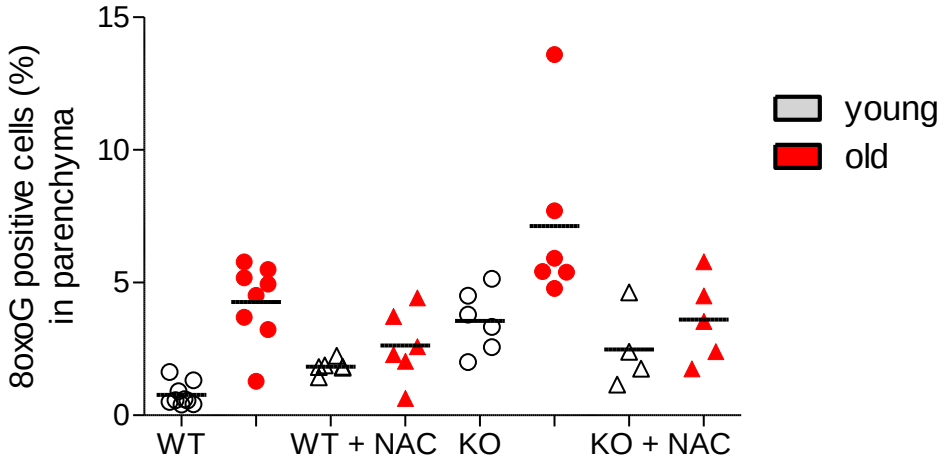
Sirius red coloration

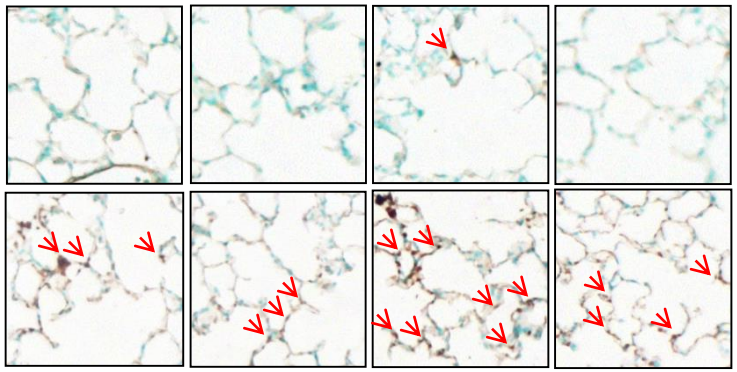




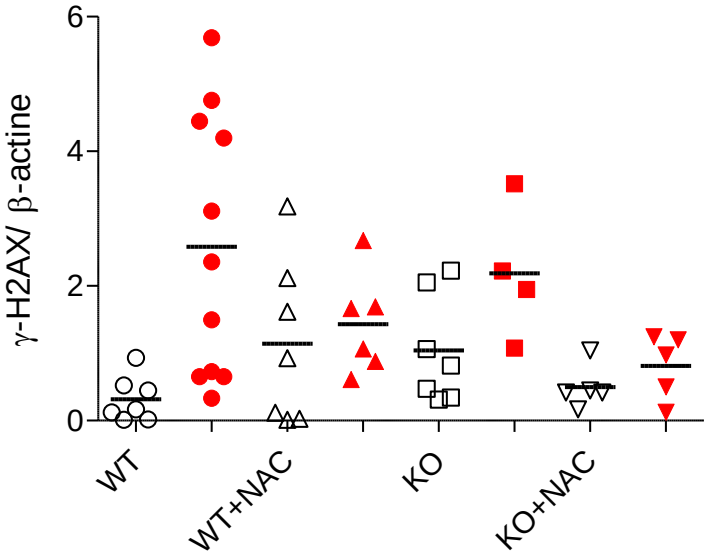
Oxidative stress signature assessment

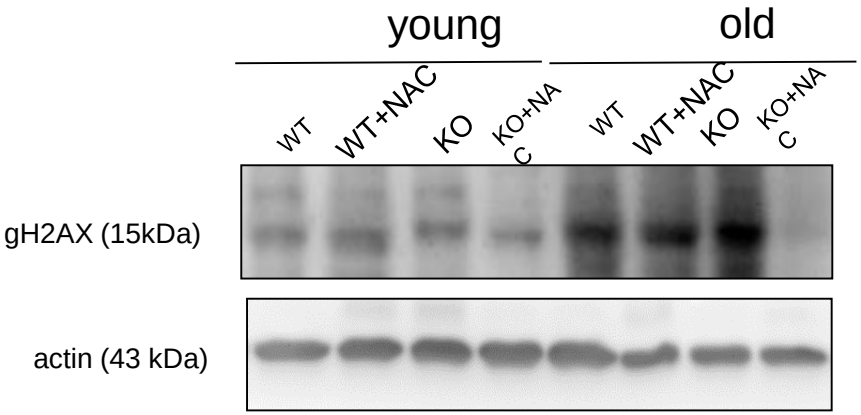
DNA oxidation: 8-oxoguanine staining



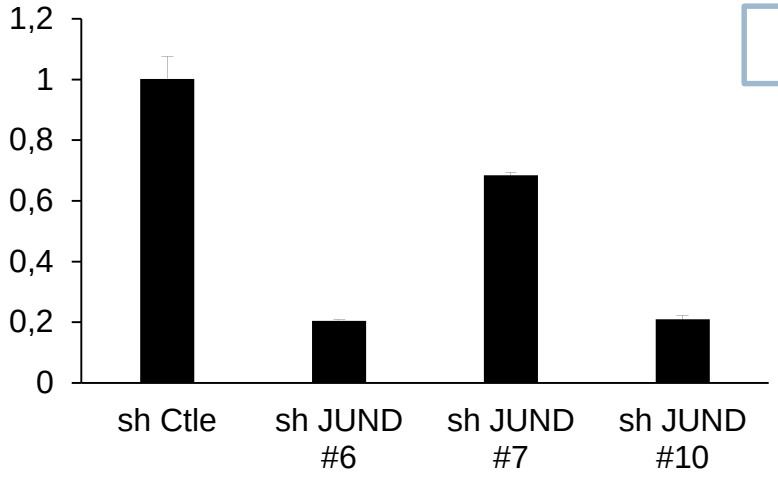


dsDNA breaks: gamma-H2AX assessment

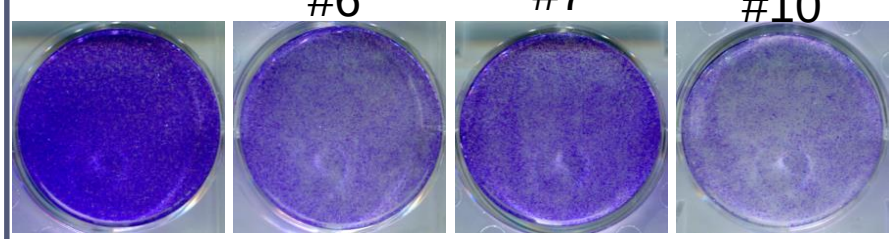


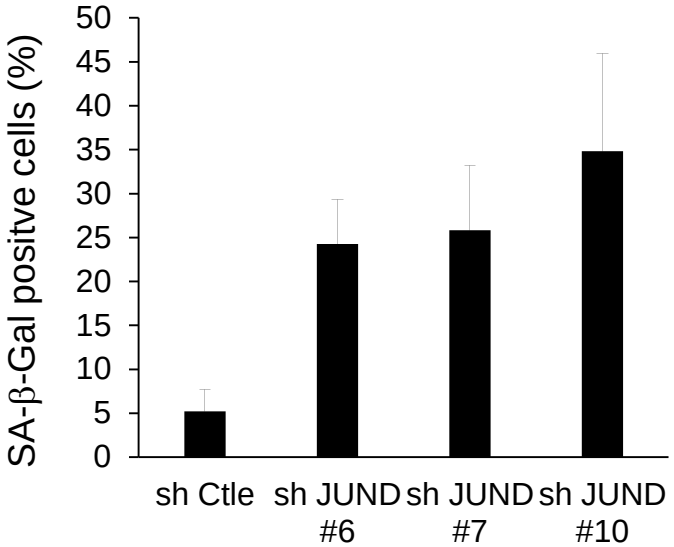


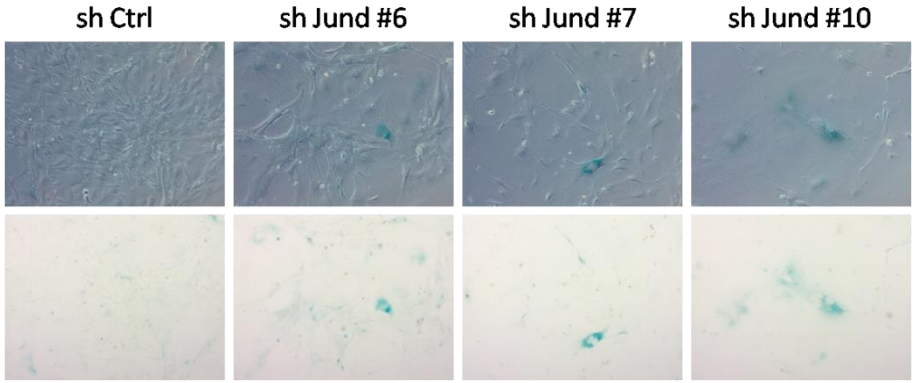
MEF studies



MEFs (pas immortalisés)

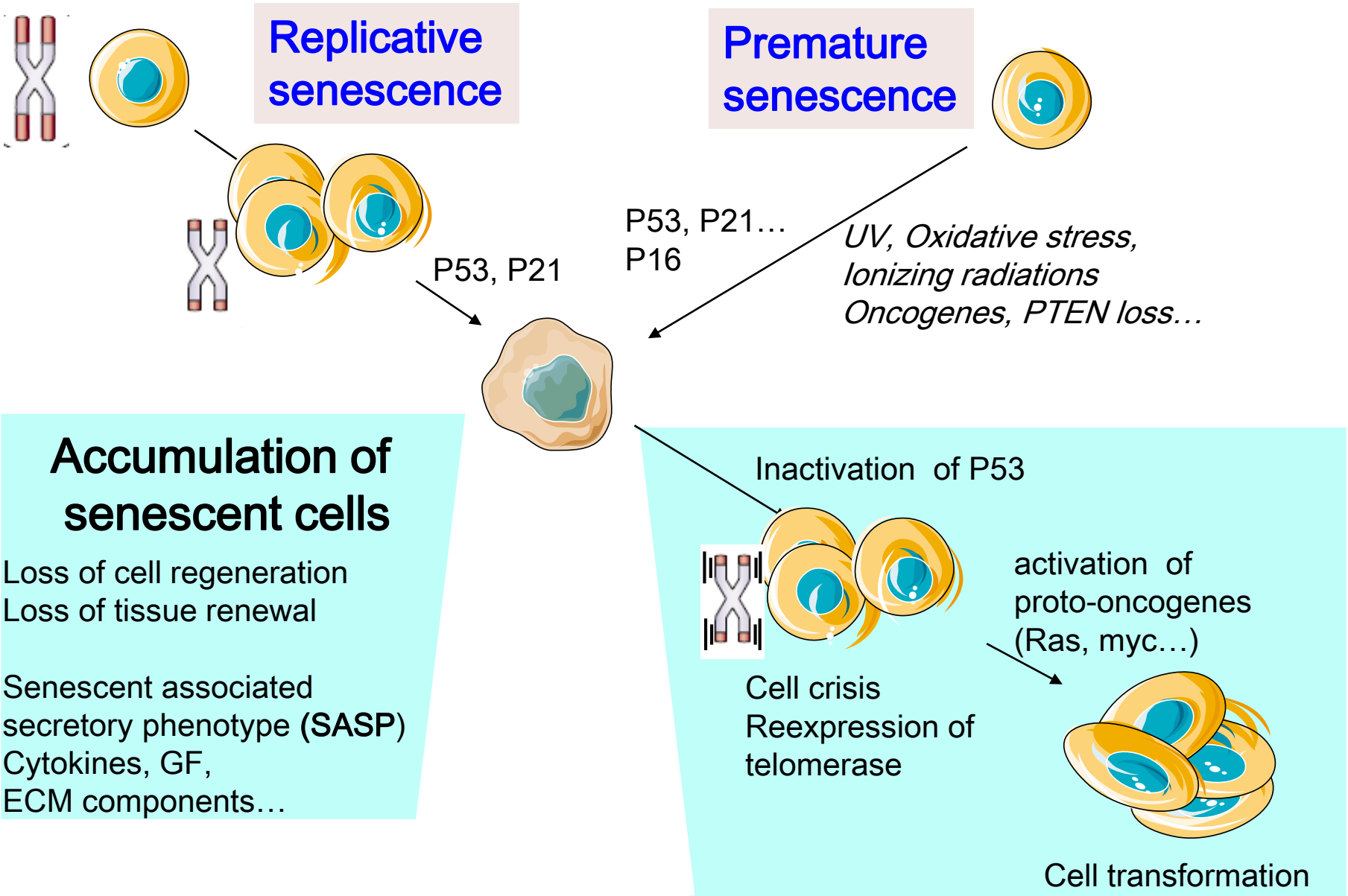




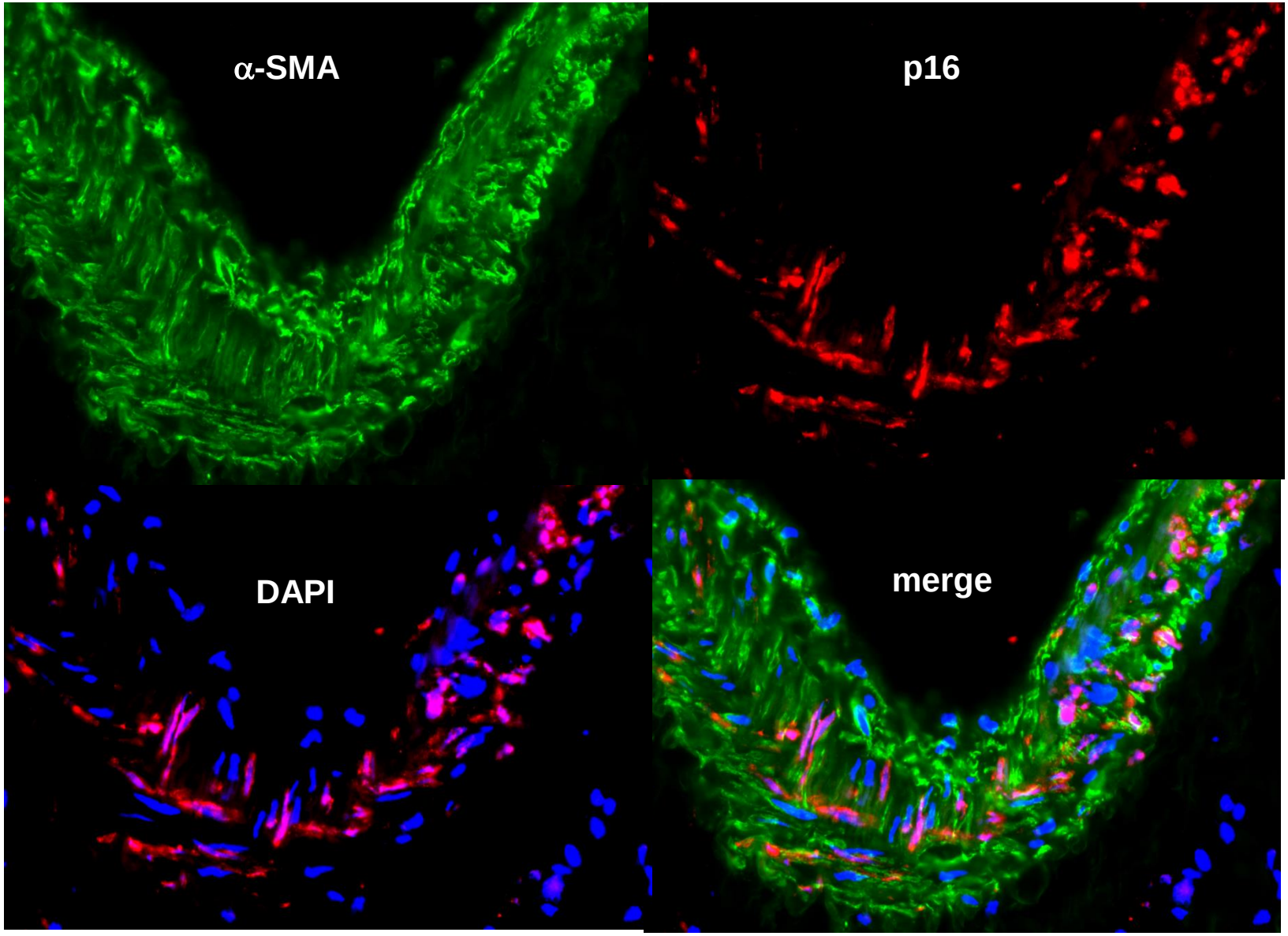


David Bernard Team:
Guillaume Collin

Cell senescence: a target for lung aging and diseases



Remodeled pulmonary vessels in cystic fibrosis



Thank you for your attention

INSTITUT MONDOR DE RECHERCHE BIOMÉDICALE

Association pour la Recherche sur le Cancer

FONDATION RECHERCHE MÉDICALE

Agence Nationale de la Recherche ANR

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ERS EUROPEAN RESPIRATORY SOCIETY
every breath counts

HelmholtzZentrum münchen
German Research Center for Environmental Health

Silke Meiners

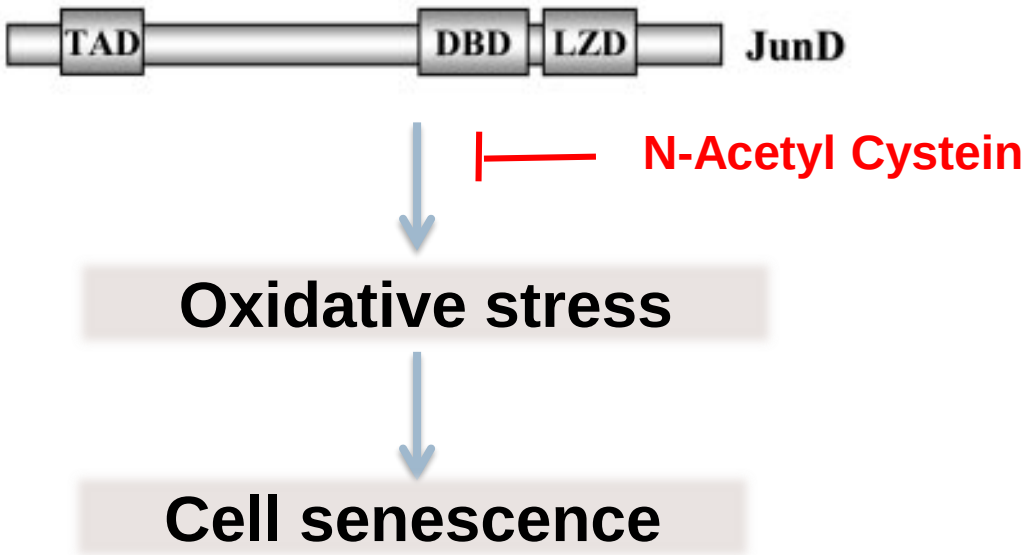
CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

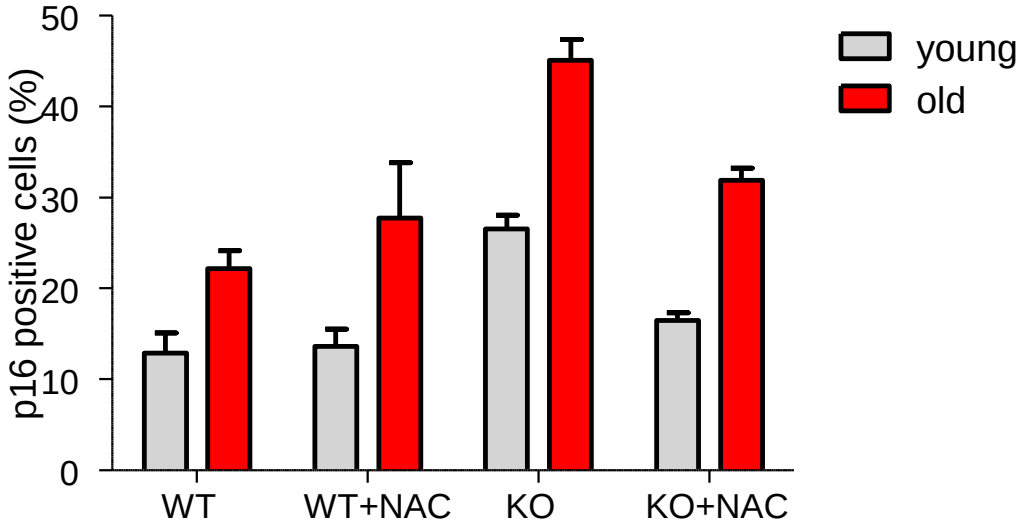
David Bernard

EFPA et Imagerie

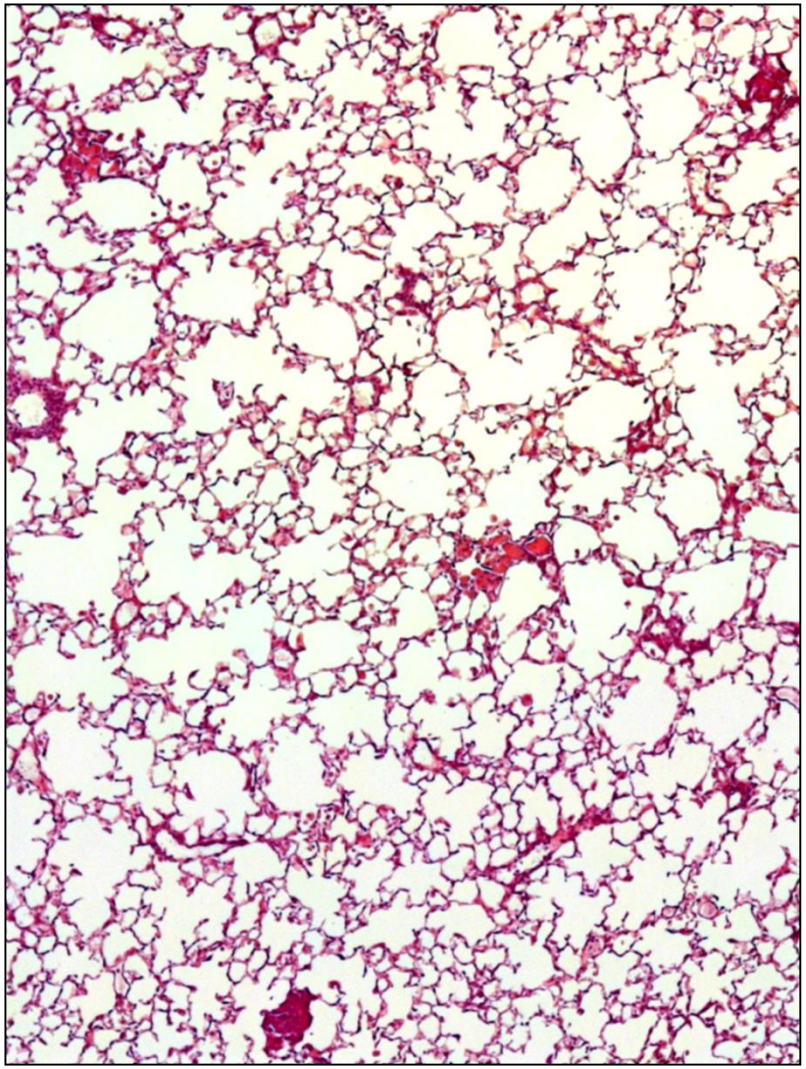
Rachid Souktani
Xavier Decrouy
Christelle Micheli
Catherine Boisnier

Effect of oxidative stress-induced cell senescence in the lung



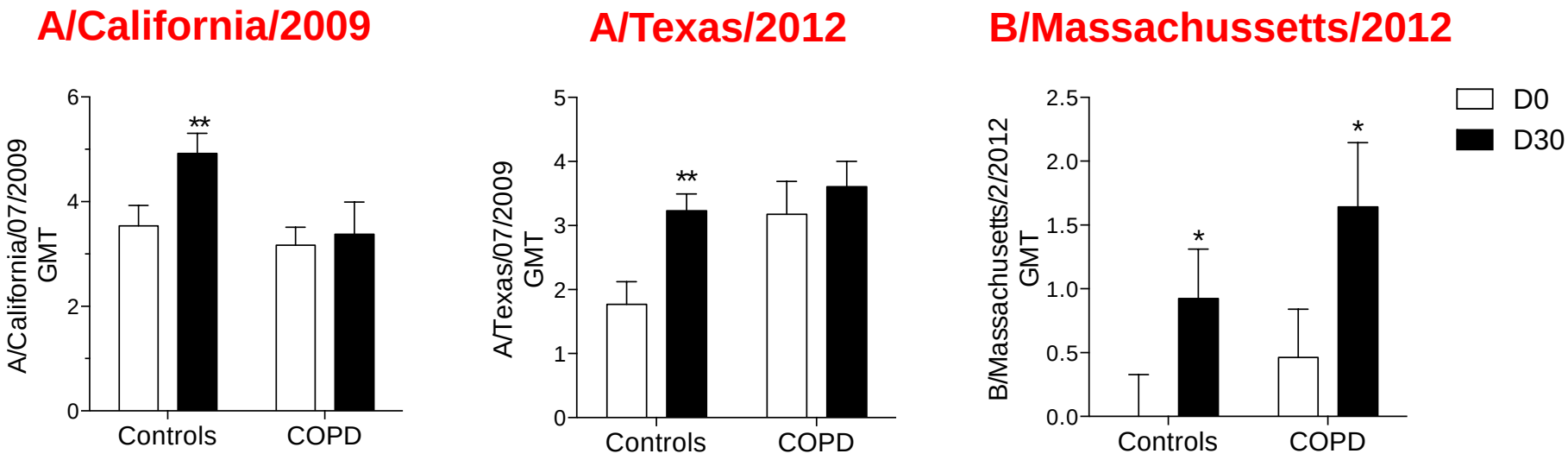


Lungs from junD-/- mice



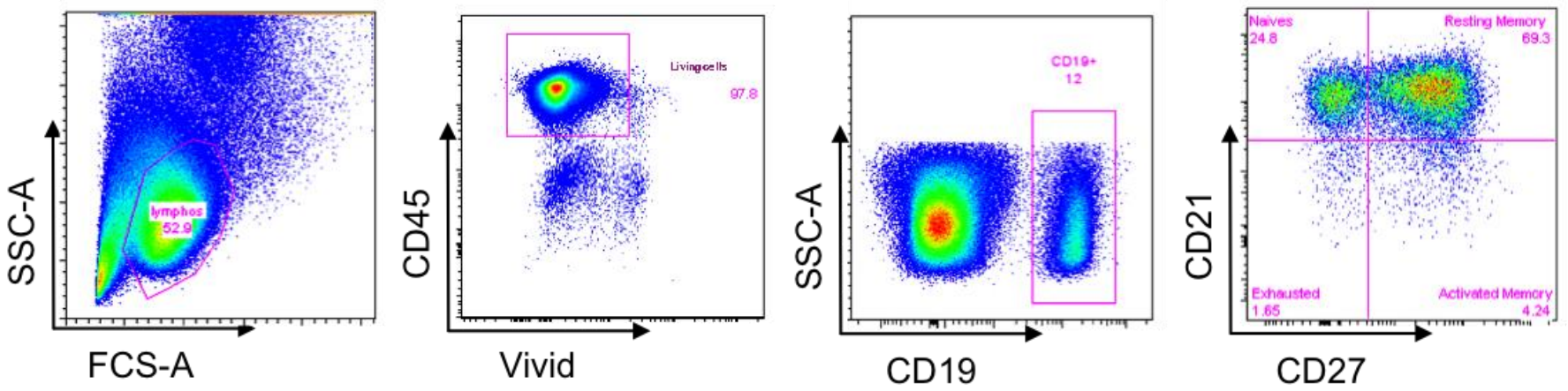
JunD KO mice, old

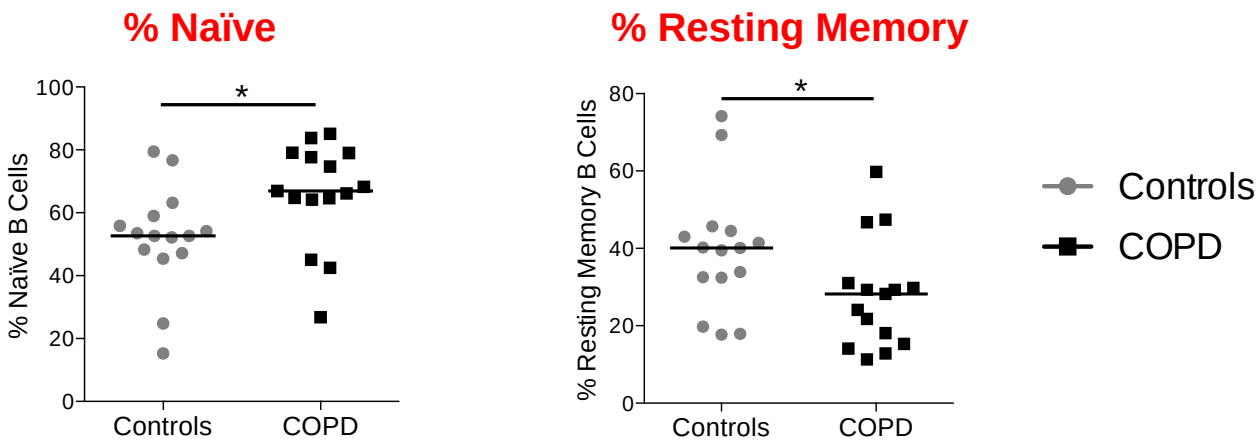
Impaired humoral immune response to influenza vaccine



	Séroconversion Contrôles	Séroconversion BPCO
A/California/7/2009	30.8%	14.3%
A/Texas/50/2012	46.2%	28.6%
B/Massachusetts/02/2012	21.4%	23.1%

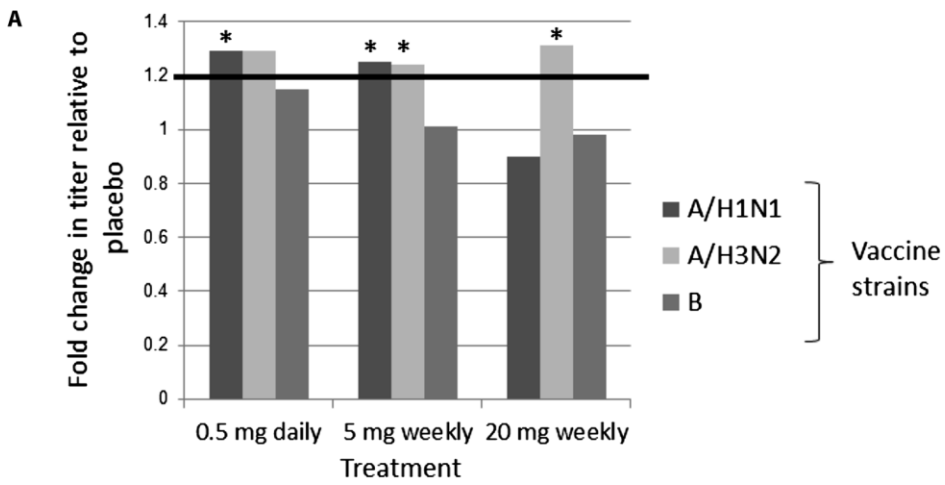
Patients with COPD had higher percentages of naive B cells and lower percentages of resting memory B cells

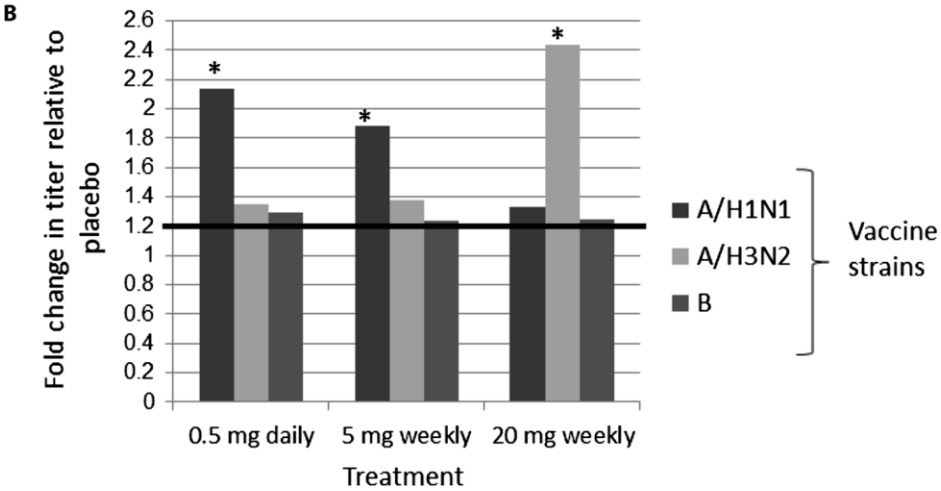




mTOR inhibition improves immune function in the elderly

*Joan B. Mannick,[1]*et al; Science Transl Med, 2014*





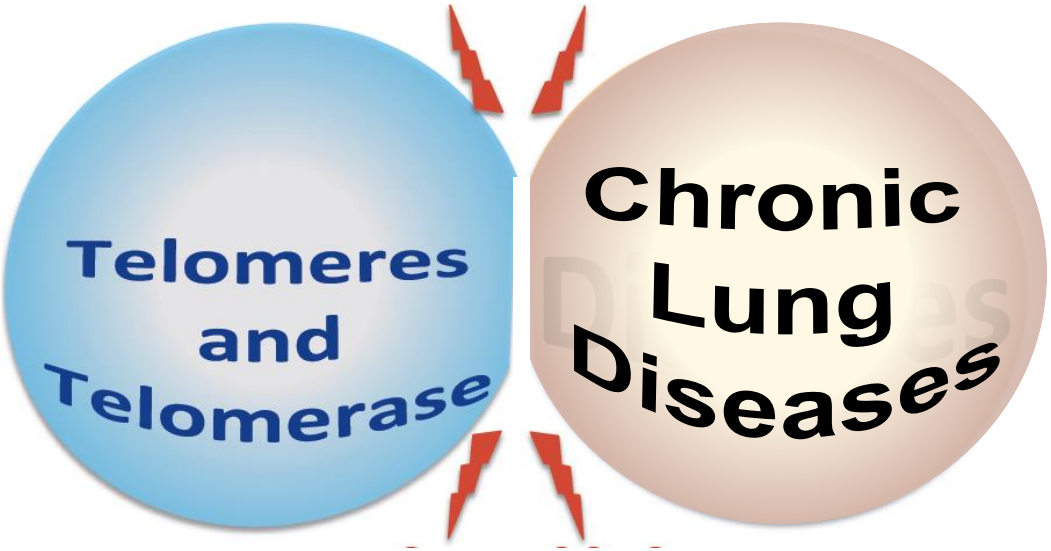
Lung fibrosis

Age-related disease

Rare disease

Chronic obstructive pulmonary disease (COPD)

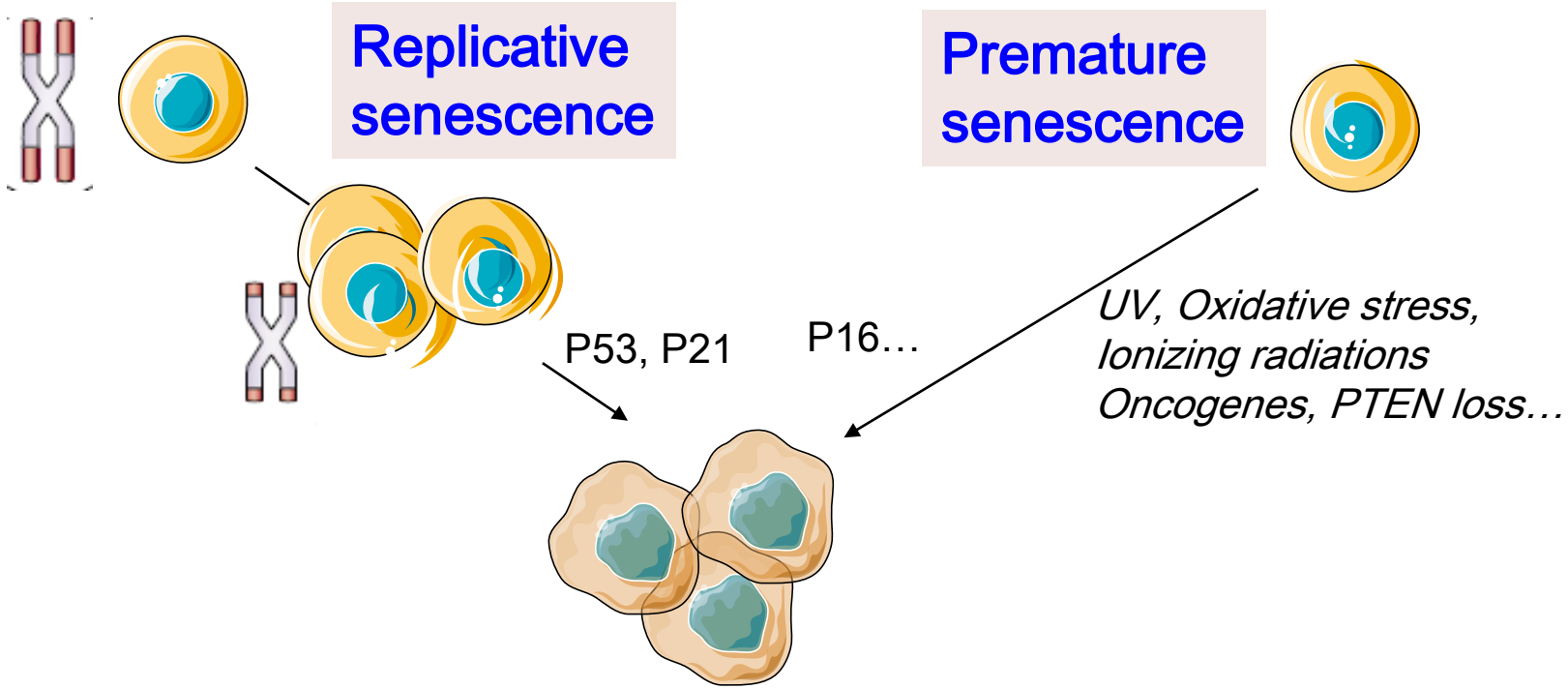
Frequent, age-related degenerative disease



Pulmonary hypertension

Remodeling of pulmonary vessels

Cell senescence: a common denominator for lung diseases



Accumulation of lung senescent cells: AEC, EC, SMC, fibroblasts

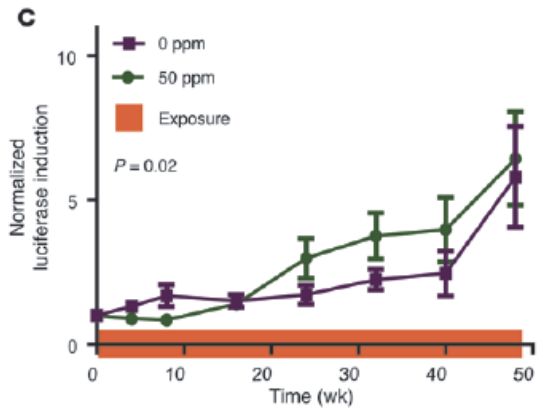
Loss of lung tissue renewal
Cessation of cell regeneration

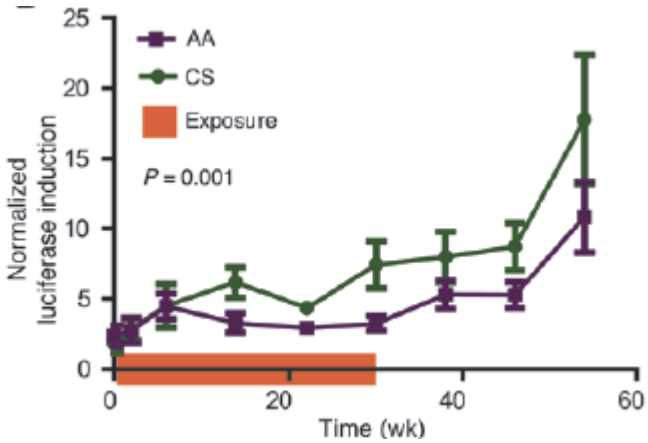
SASP : Release of mediators
Cytokines, GF, MMPs..

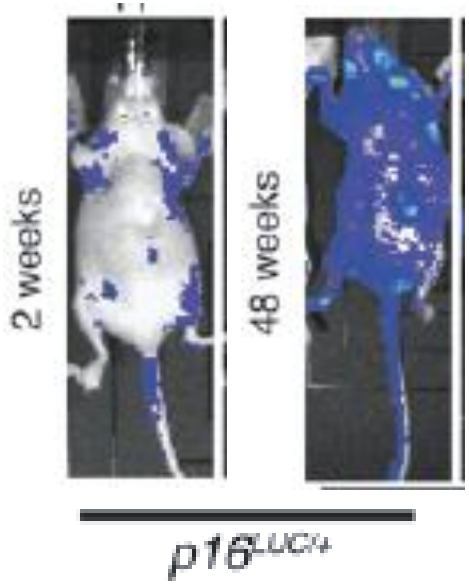
Lung tissue remodeling, fibrosis, emphysema, inflammation

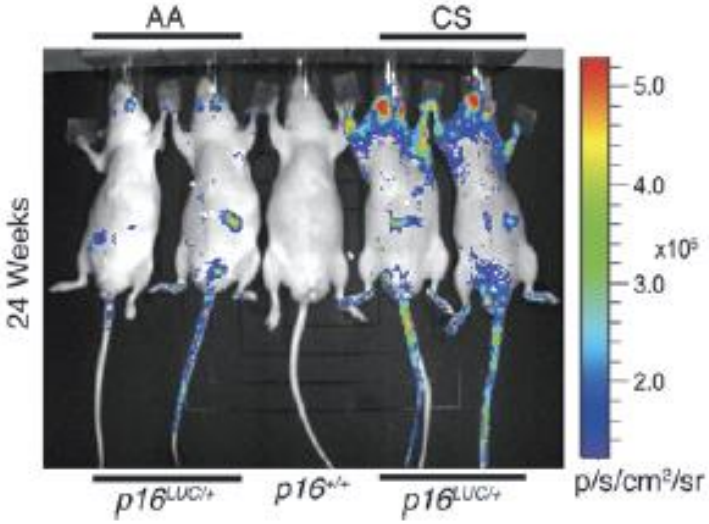
$p16^{INK4a}$ promoter, a senescence-sensitive driver of a reporter gene

$p16^{LUC/+}$ mice



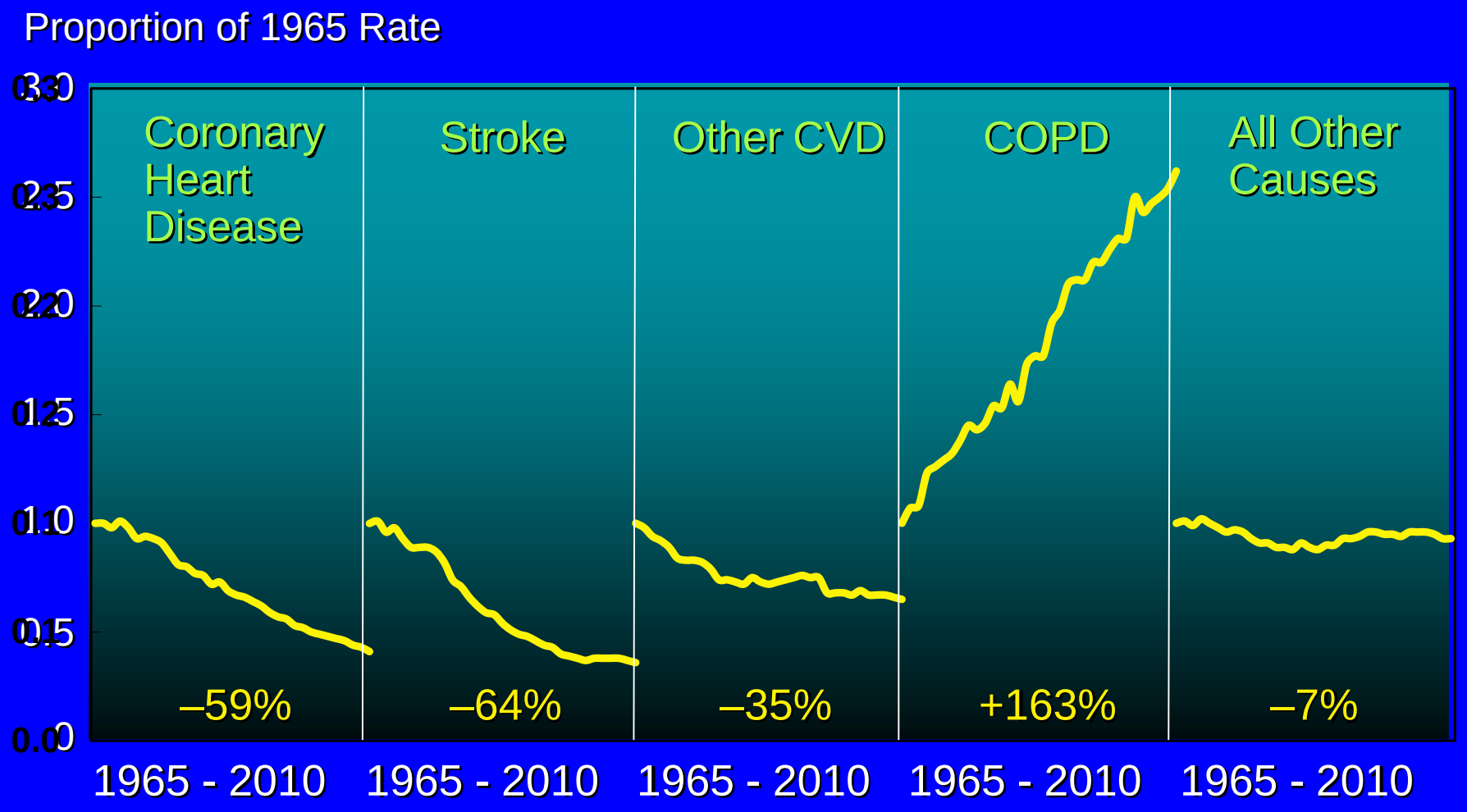


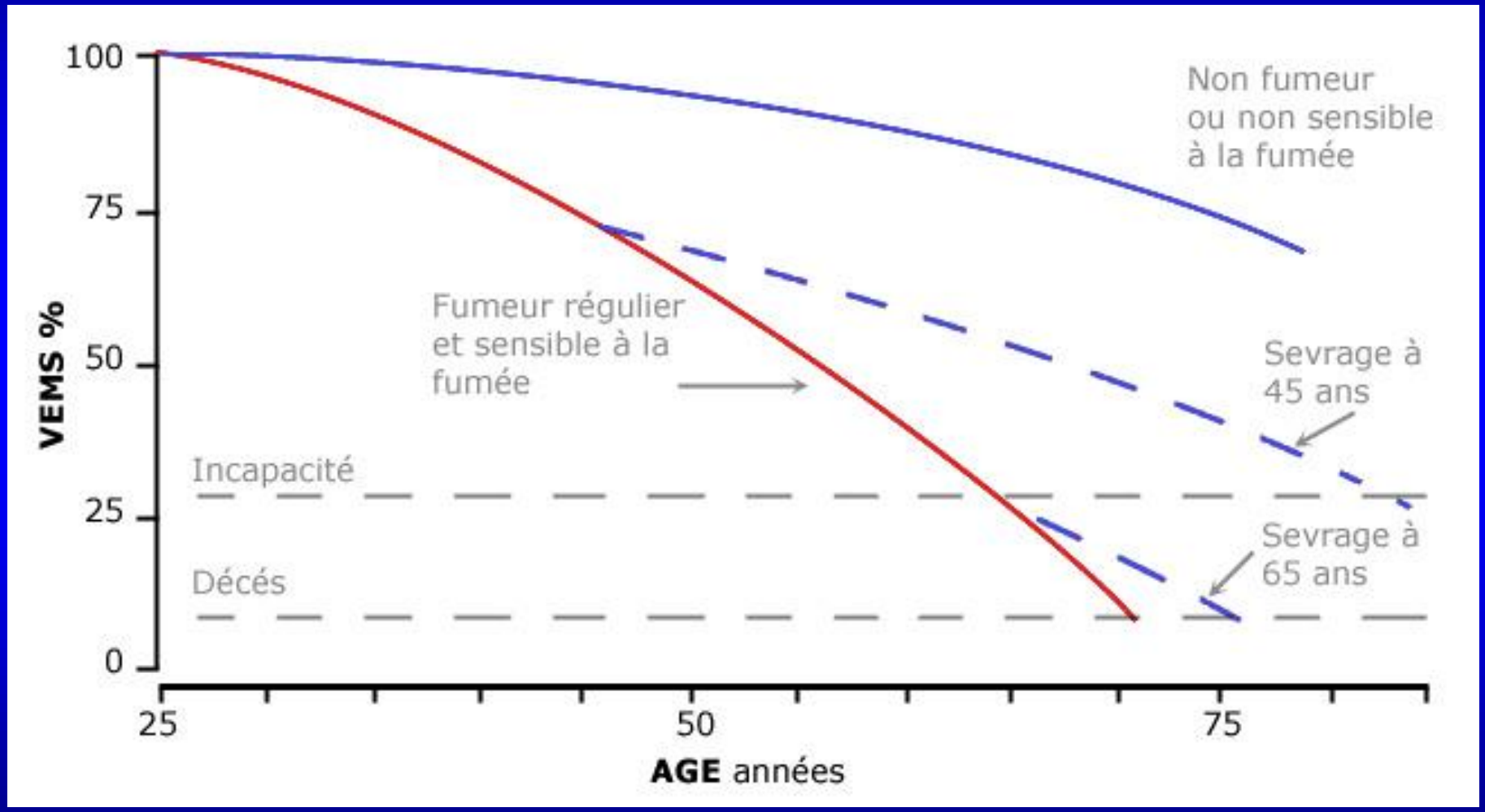




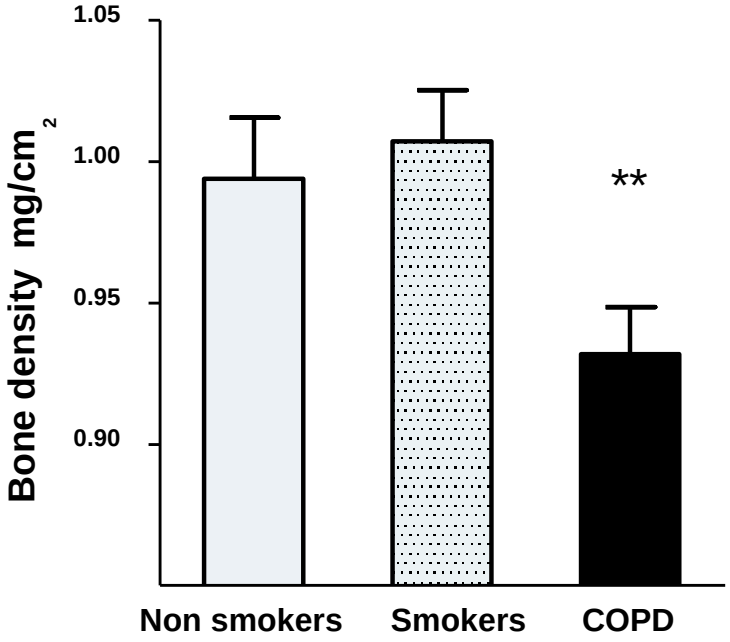
Sharpless, N E, J Clin Invest, 2014

Percent Change in Age-Adjusted Death Rates, U.S., 1965-1998



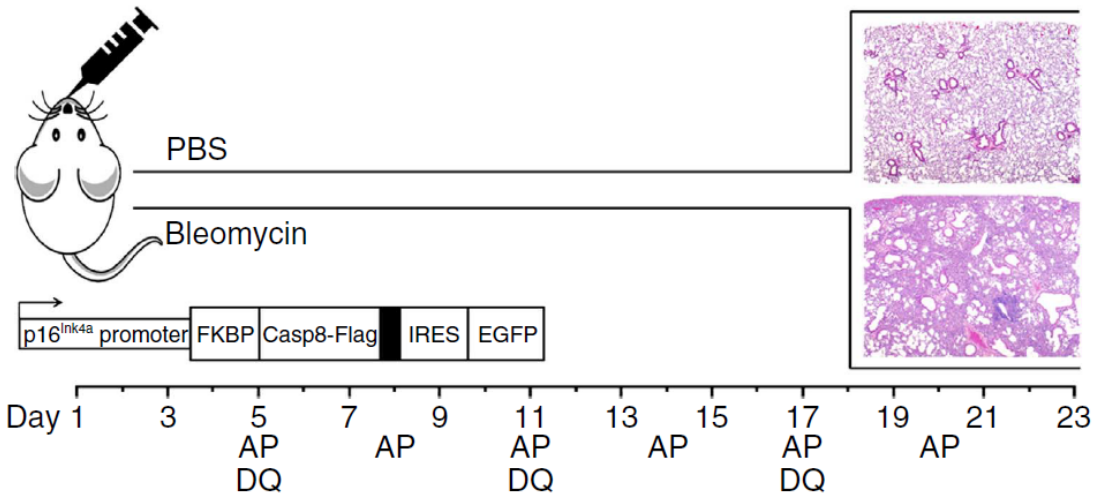

100
75
50
25
0
VEMS %
Non fumeur
ou non sensible
à la fumée
Fumeur régulier
et sensible à la
fumée
Sevrage à
45 ans
Incapacité
Sevrage à
65 ans
Décés
25
50
75
AGE années

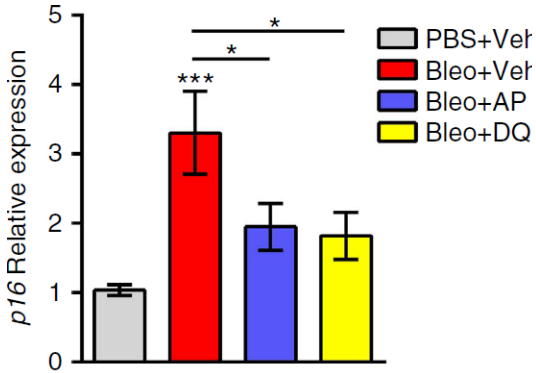
Premature aging in smokers ?

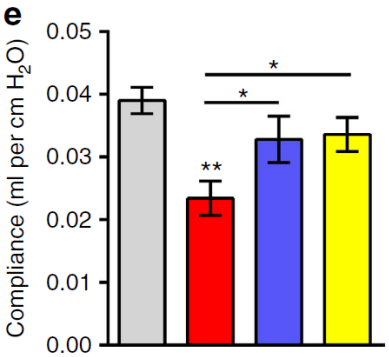


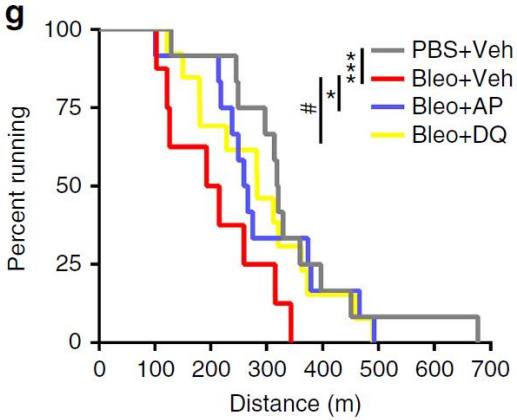
Boyer L et al, 2015

Inhibition of bleomycin-induced lung fibrosis by eliminating senescent cells









Shafer MJ et al, Nat Commun, 2017

Telomerase expression under the control of p21