Cell therapy from cardiac to pulmonary diseases

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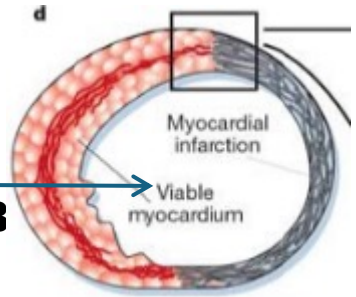
AFMP 2025 - BOLOGNE

Cell therapy - Target population

AMI



BONAMI trial

Acute/LV dysfunction/B

Roncalli et al. EHJ 2011

BONAMI trial | **EXCELLENT trial**

Ischemic Heart Failure

MESAMI program 1-2

Chronic/MSC

Trophic properties
Secretion of bioactive factors and cytokines

Neovascularization
Cardiac regeneration

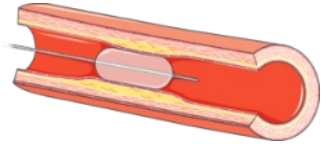
Effects
- **Pro-angiogenic**
- **Anti-apoptotic**
- **Chemo-attractive**
- **Anti-fibrotic**
- **Anti-inflammatory**

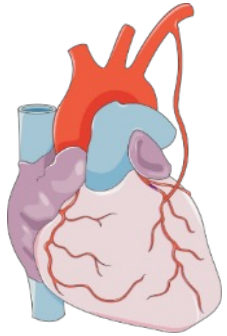
MESAMI

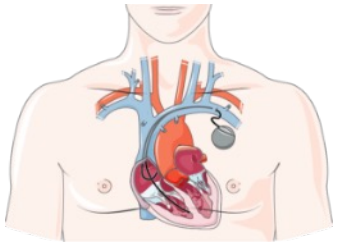
Increasing prevalence of HF:
- ❖ Aging population
- ❖ Advances in treatment (CAD)
- ❖ Medical need !

Public Health problem

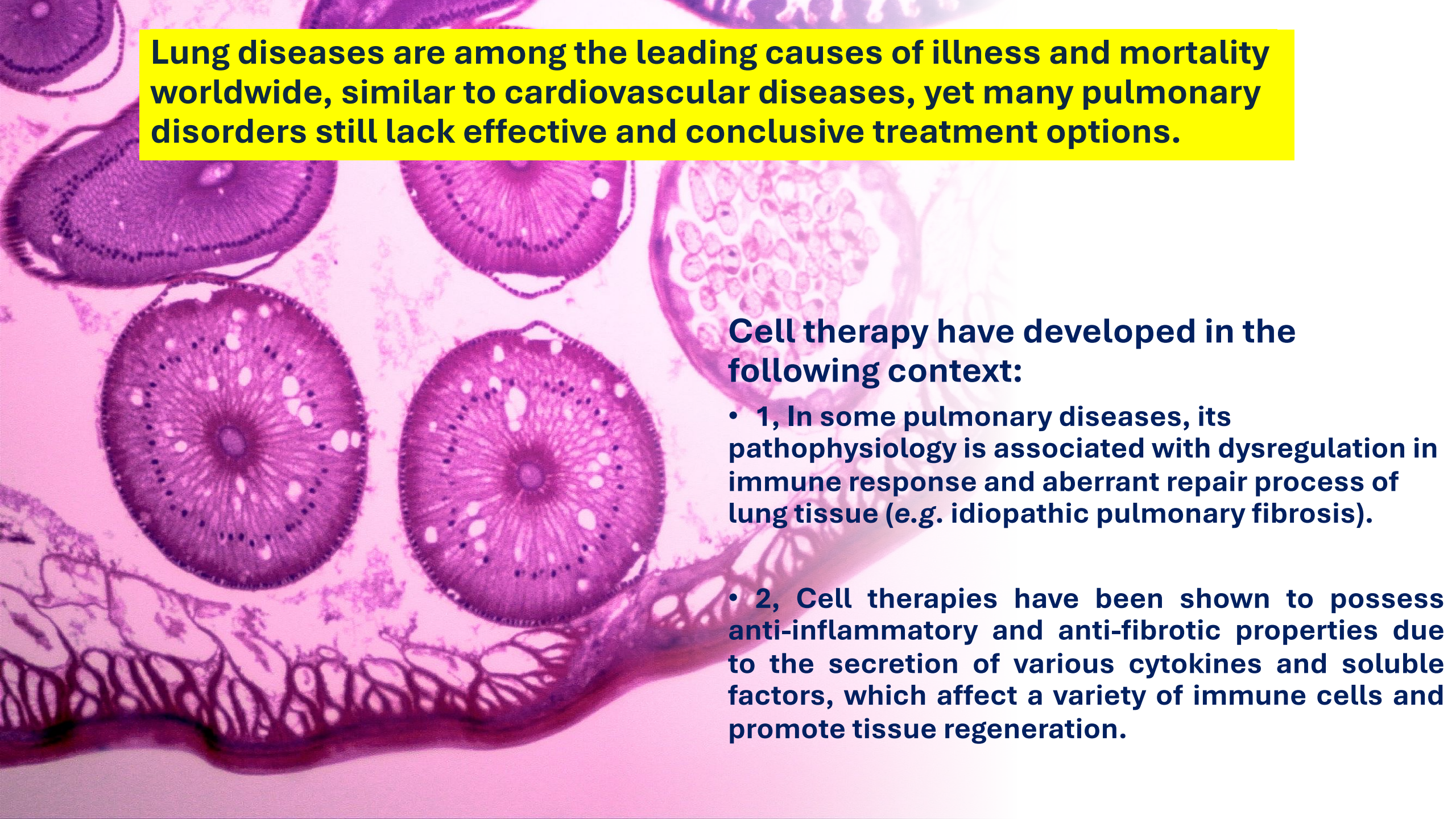
Heart Failure







Severe prognosis: 1 in five patients will die within a year of their diagnosis, 5-year death rate > 50%.

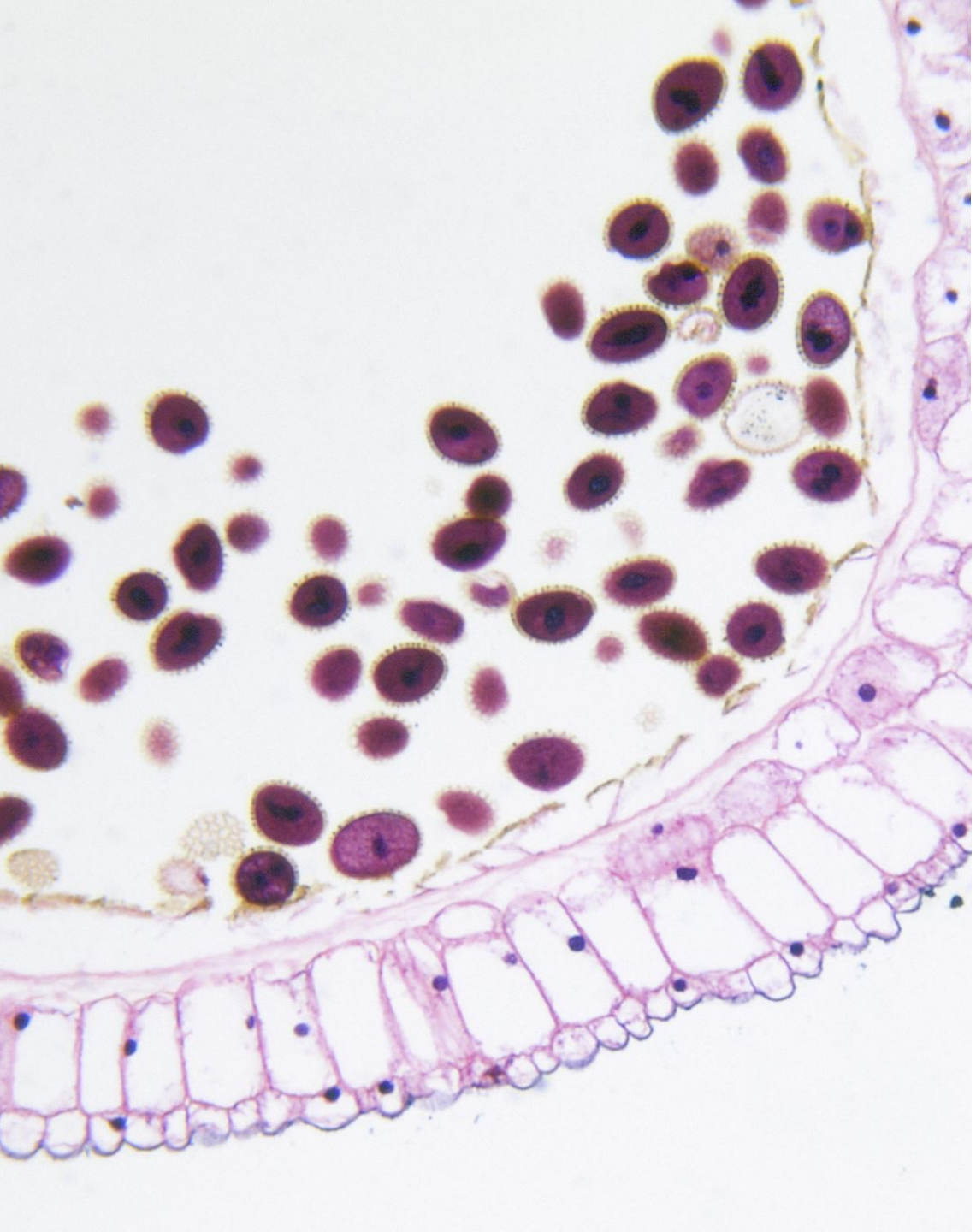


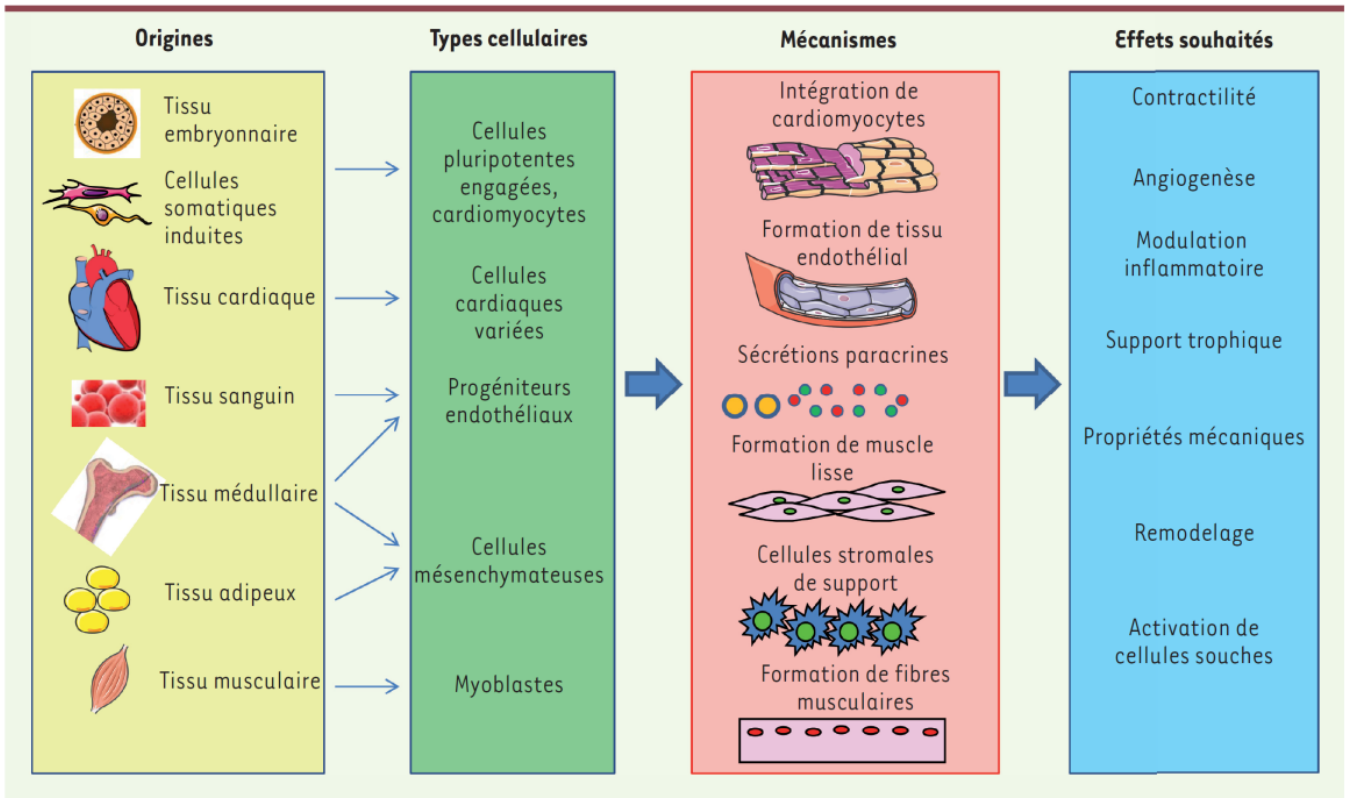
Lung diseases are among the leading causes of illness and mortality worldwide, similar to cardiovascular diseases, yet many pulmonary disorders still lack effective and conclusive treatment options.

Cell therapy have developed in the following context:

- 1, In some pulmonary diseases, its pathophysiology is associated with dysregulation in immune response and aberrant repair process of lung tissue (*e.g.* idiopathic pulmonary fibrosis).

- 2, Cell therapies have been shown to possess anti-inflammatory and anti-fibrotic properties due to the secretion of various cytokines and soluble factors, which affect a variety of immune cells and promote tissue regeneration.





- **Among the many types of stem cells, mesenchymal stem cells (MSCs) are the most studied cell products.**

- **Easy isolation**
- **Immunomodulatory effect**
- **Safety**
- **No ethical concerns**
- **Rapid localization to the lungs after infusion**

Mesenchymal stem cells

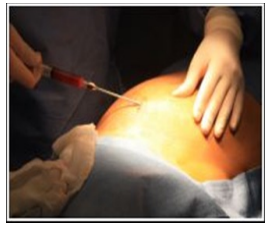
Razeghian-Jahromi *et al. Stem Cell Research & Therapy* (2021) 12:361
https://doi.org/10.1186/s13287-021-02443-1

Stem Cell Research & Therapy

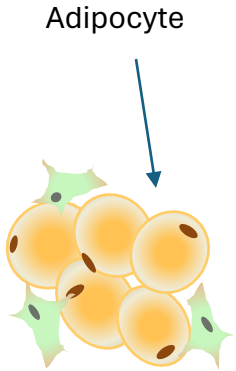
REVIEW Open Access

Surfing the clinical trials of mesenchymal stem cell therapy in ischemic cardiomyopathy

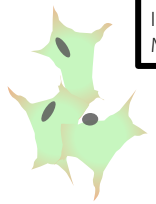
Iman Razeghian-Jahromi[1], Anthony G. Matta[2,3], Ronan Canitrot[2], Mohammad Javad Zibaeenezhad[1], Mahboobeh Razmkhah[4], Anahid Safari[5], Vanessa Nader[2,6] and Jerome Roncalli[2,7*]



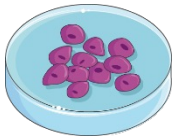
Adipose Tissue

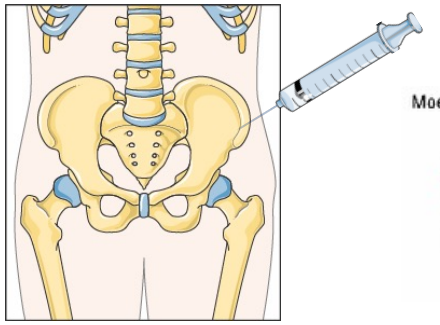


Selection then multiplication of cells in culture

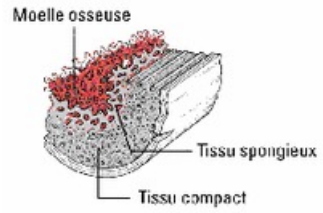


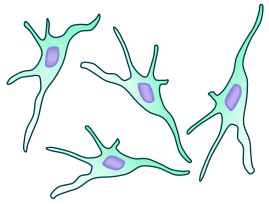
Adipose Derived Stem cells



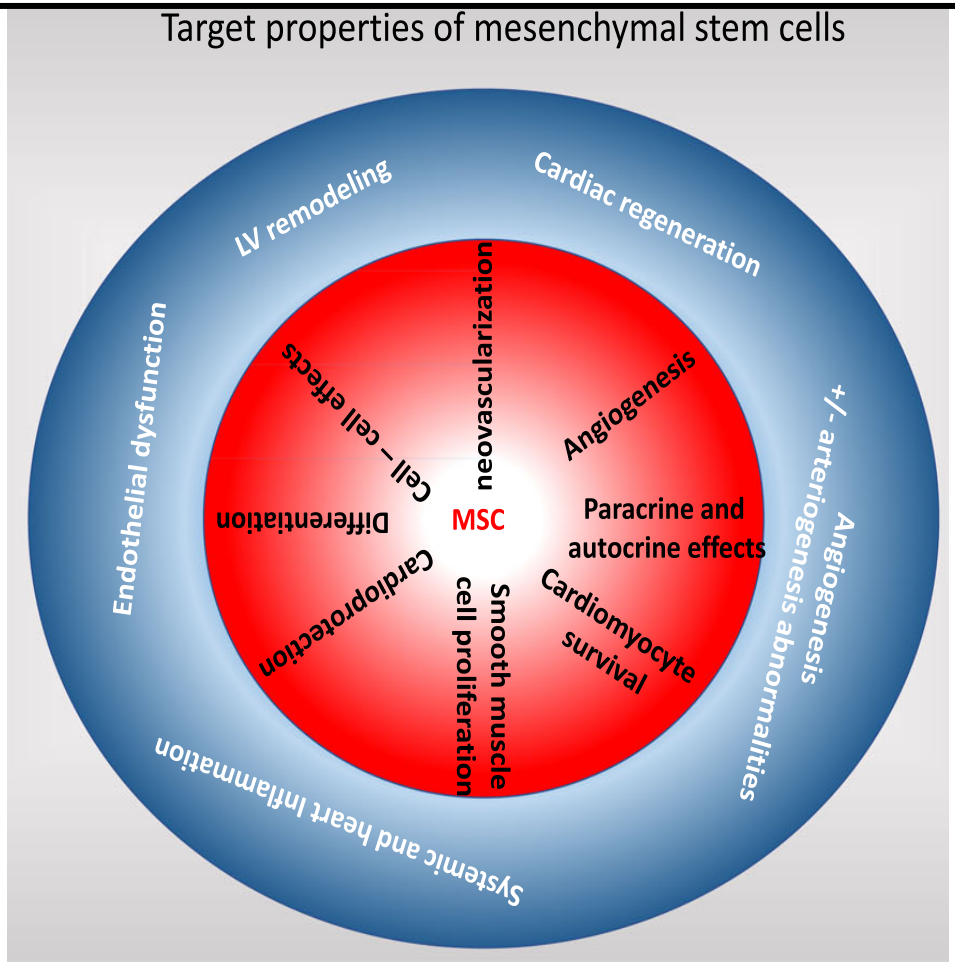


Bone Marrow

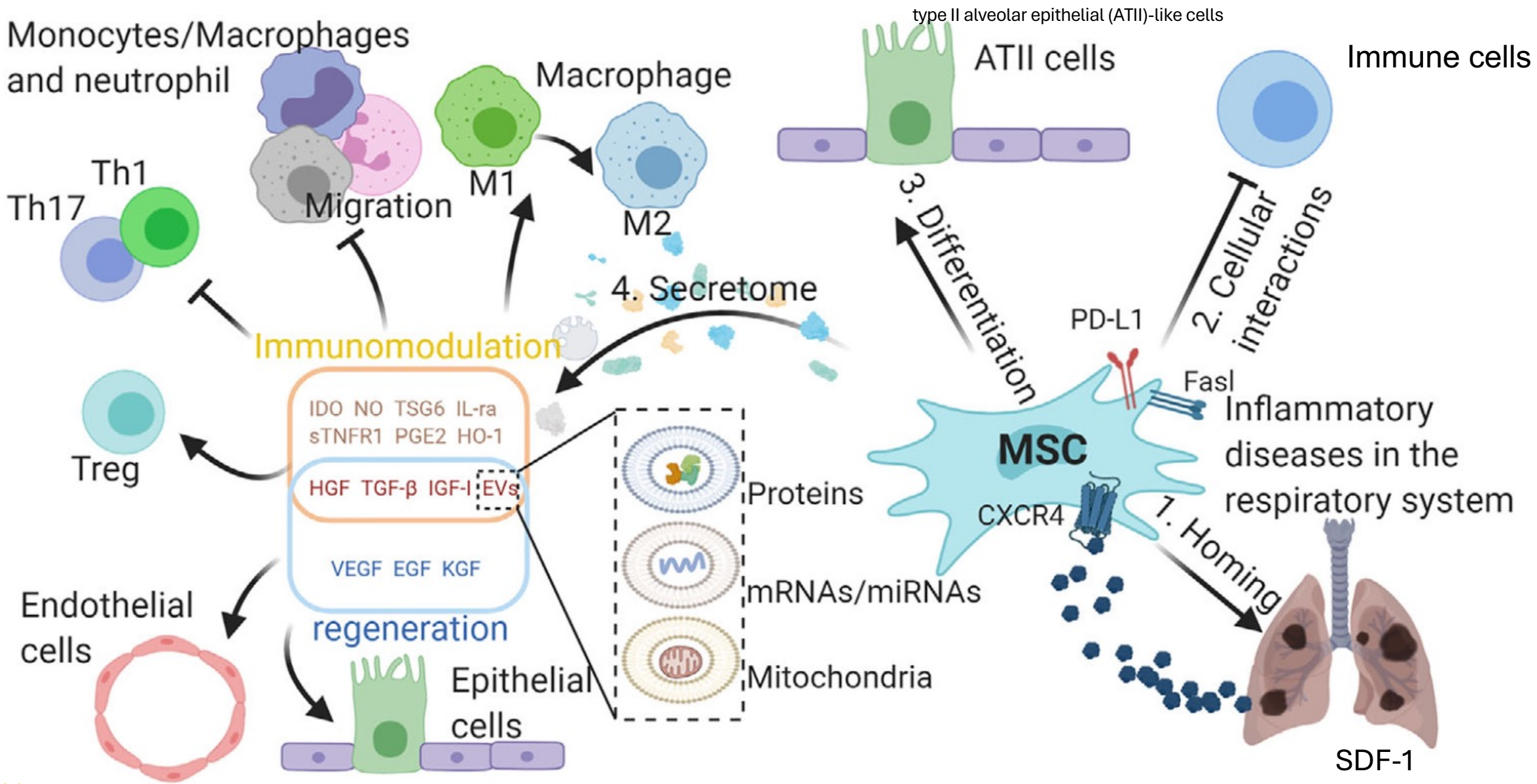




Mesenchymal stem cells



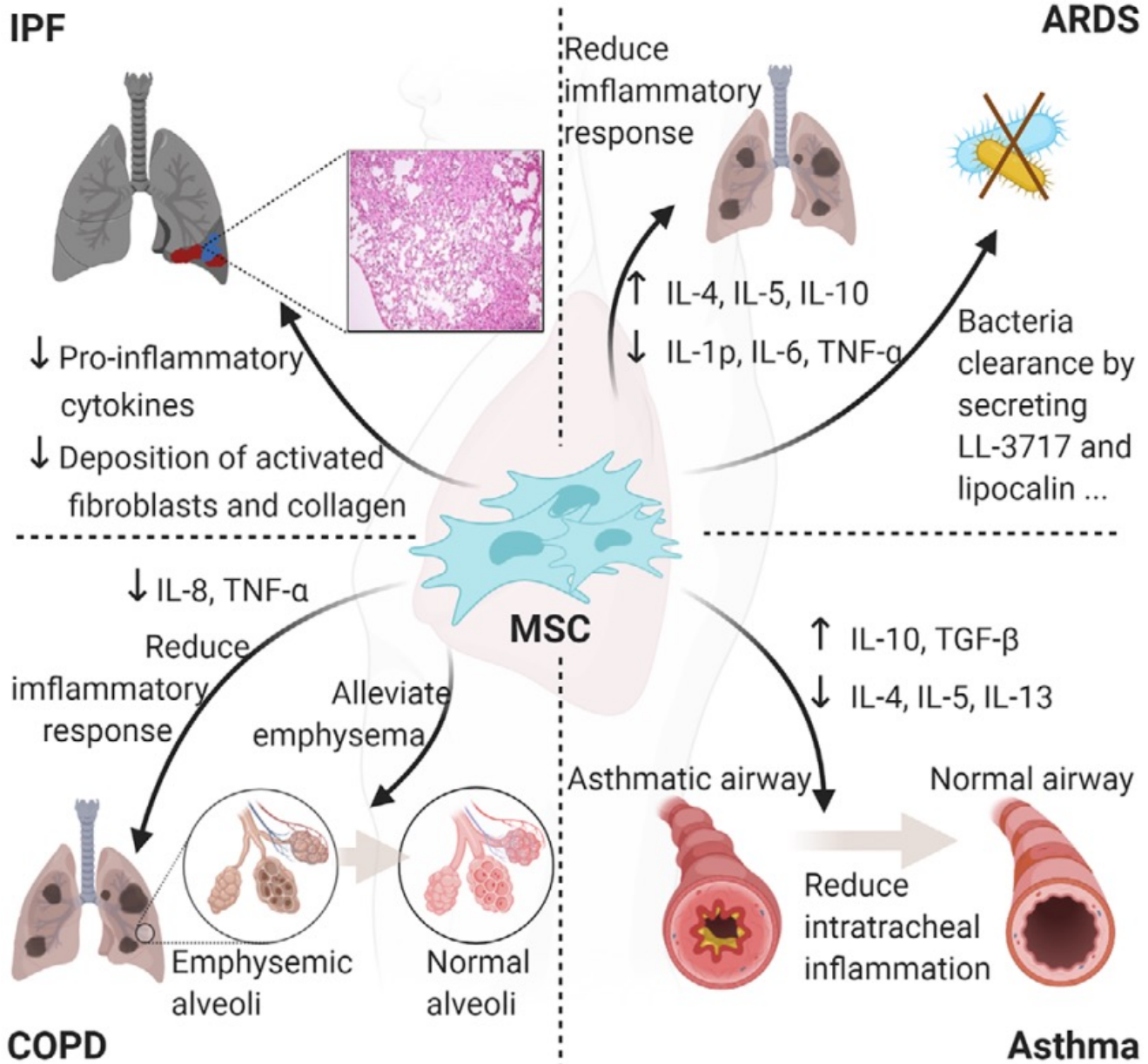
[Properties of MSC in inflammatory diseases in respiratory system]



anti-inflammatory factors
growth factors

MedComm 2020; 2: 351-380.

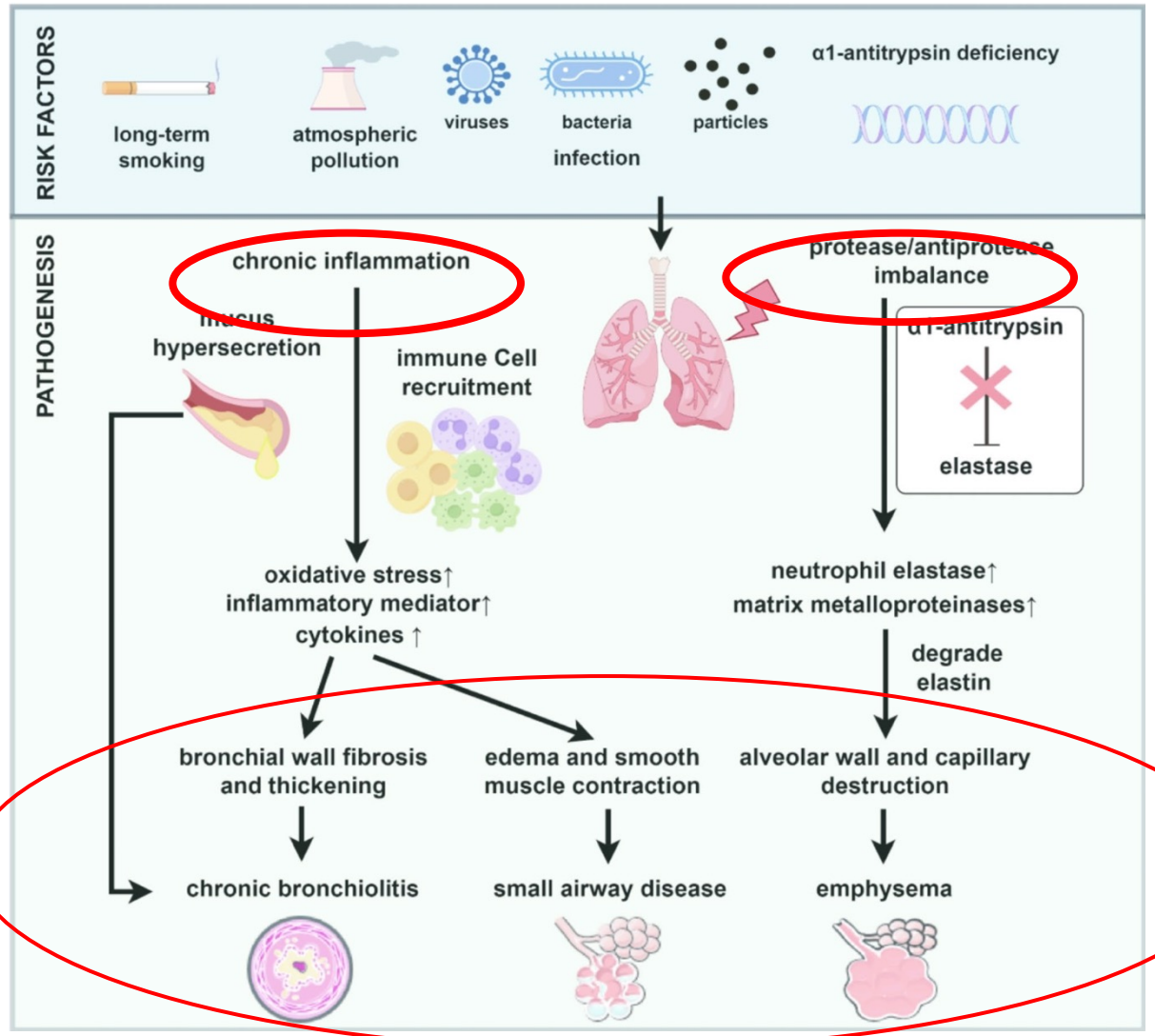
[Representative pulmonary diseases for which cell therapies are studied as a treatment option]



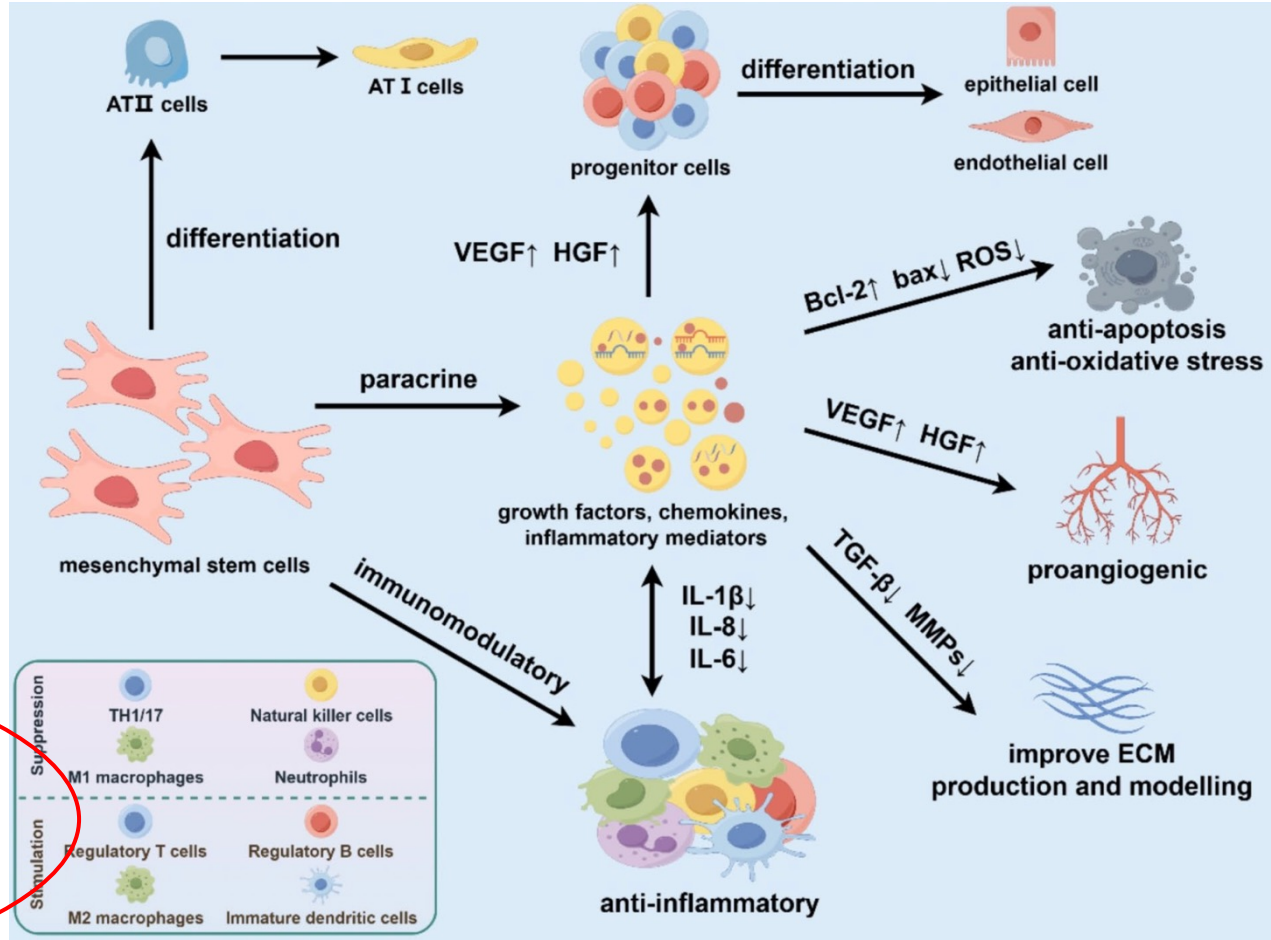
MedComm 2020; 2: 351-380.

[Chronic obstructive pulmonary disease (COPD)]

Chronic inflammation

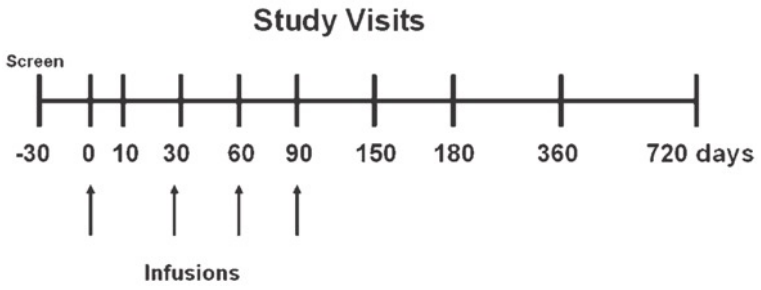


Immunomodulation via paracrine effect of MSC



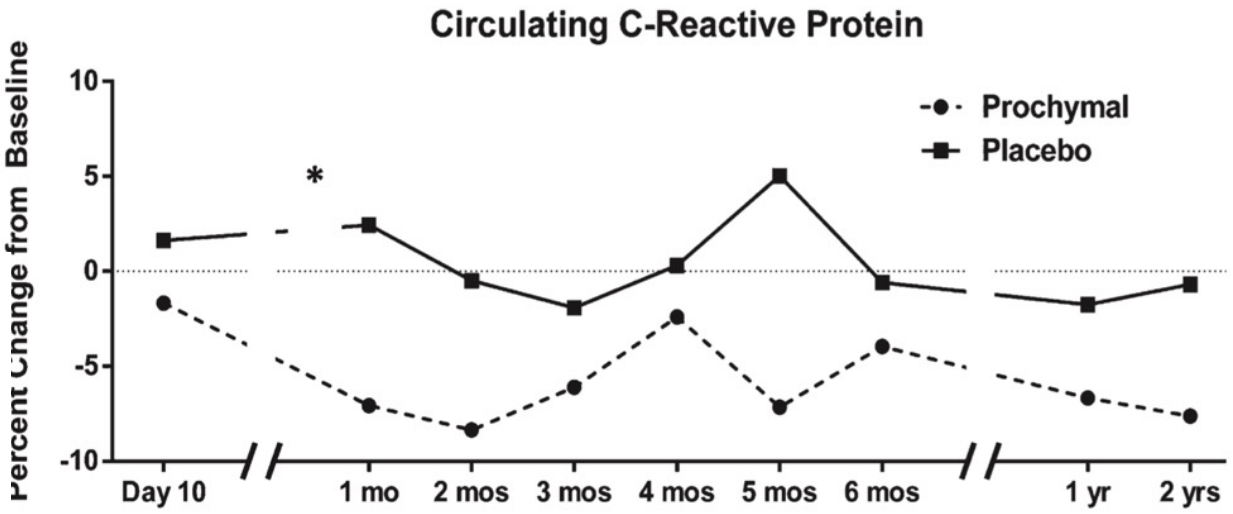
Stem cell Res Ther 2024; 15: 312.

[Chronic obstructive pulmonary disease (COPD)] Phase 2 TRIAL

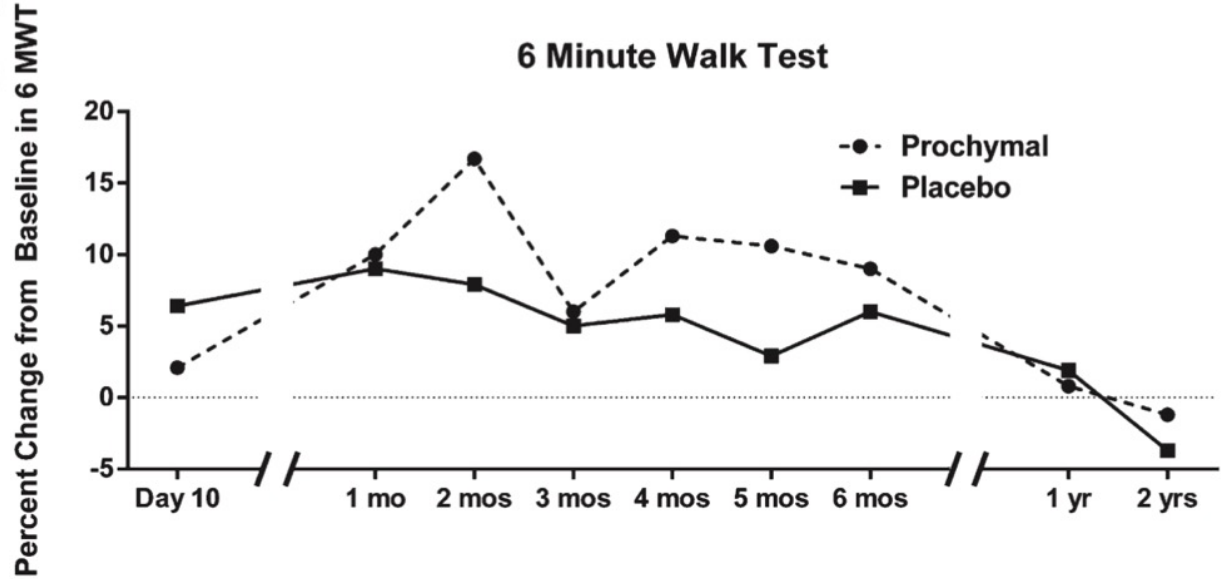


Screened (94)

	Prochymal	Placebo
Intention to Treat [1]	30 (100%)	32 (100%)
Received Study Treatment (4 Infusions)	30 (100%)	32 (100%)
Per-protocol set [2]	29* (96.7%)	32 (100%)
Safety set [3]	30 (100%)	32 (100%)
Completed Study [4]	19 (63.3%)	27 (84 %)
Did not complete study [5]	11 (36.7%)	5 (16%)
Lost to follow-up	2 (18.2%)	0 (0%)
Death	3 (27.3%)	2 (20%)**
Withdrew consent or authorization to use PHI	5 (45.5%)	3 (60%)
Physician Decision	1 (9.1%)	1 (20%)



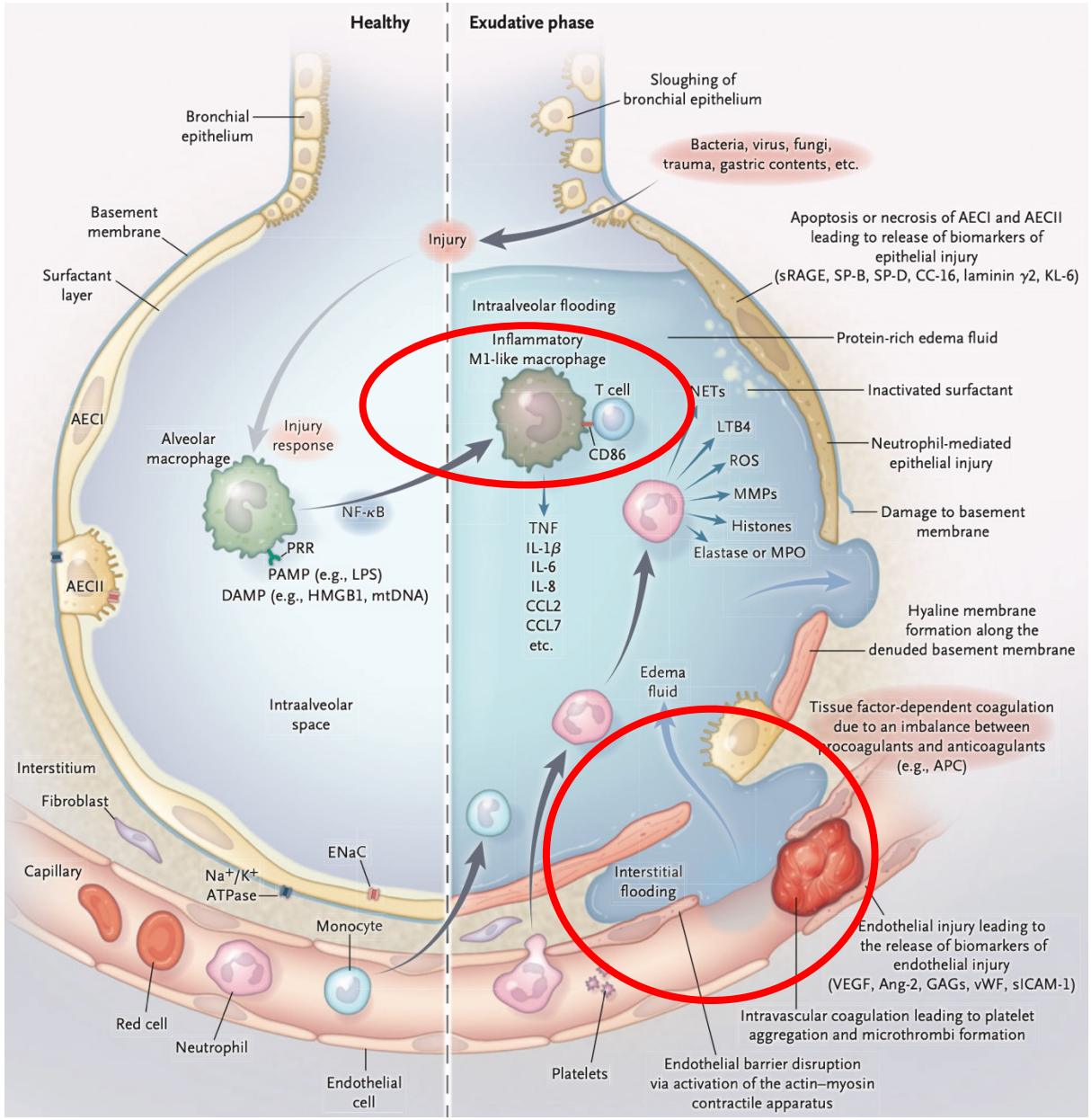
decrease in CRP levels, suggesting a possible improvement in the inflammatory process



Chest 2013; 143: 1590-8.

[Acute lung injury / Acute respiratory distress syndrome (ALI/ARDS)]

The main pathological feature of ALI/ARDS is diffuse injury of pulmonary capillary endothelial cells and pulmonary epithelial cells accompanied by alveolar hyaline membrane formation, increased pulmonary vascular permeability and inflammatory hemorrhagic infiltrate of alveolar space.



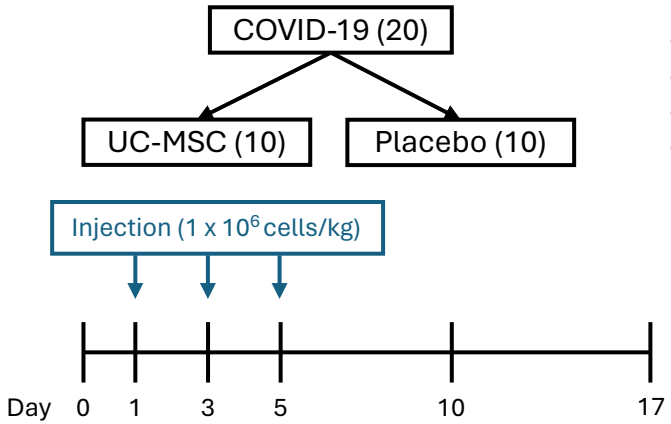
New Engl J Med 2017; 377: 562-572.

Release of inflammatory factors and the aggregation of inflammatory cells

↓

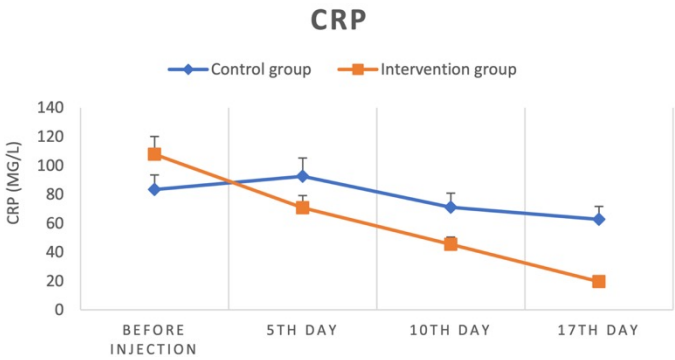
allogenic mesenchymal stem cells, which when infused into the body can slow down an immune response and prevent the body from damaging itself.

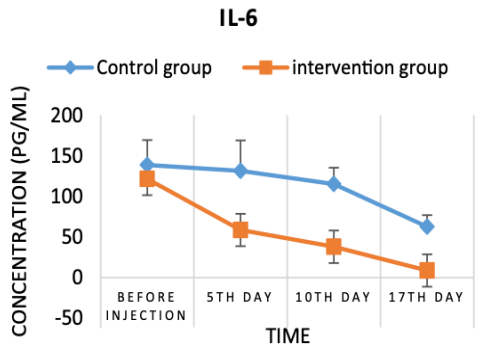
[Acute lung injury / Acute respiratory distress syndrome (ALI/ARDS)]

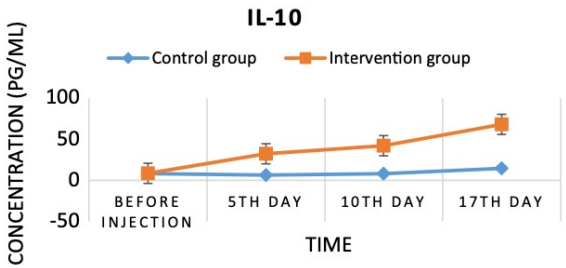


Inclusion criteria

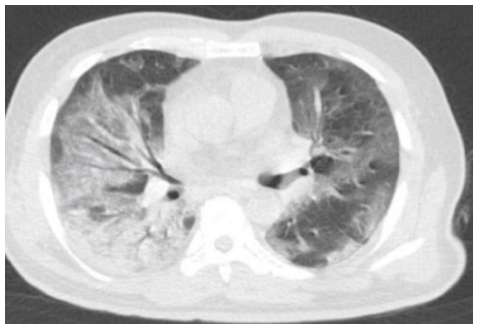
- 18 to 75 years old
- Confirmed COVID-19
- Non-severe ARDS ($120 \leq SpO_2/FiO_2 \leq 315$)
- Required supplemental oxygen



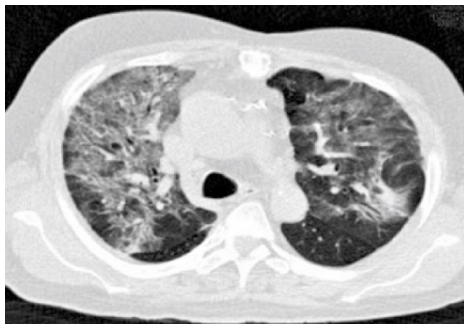




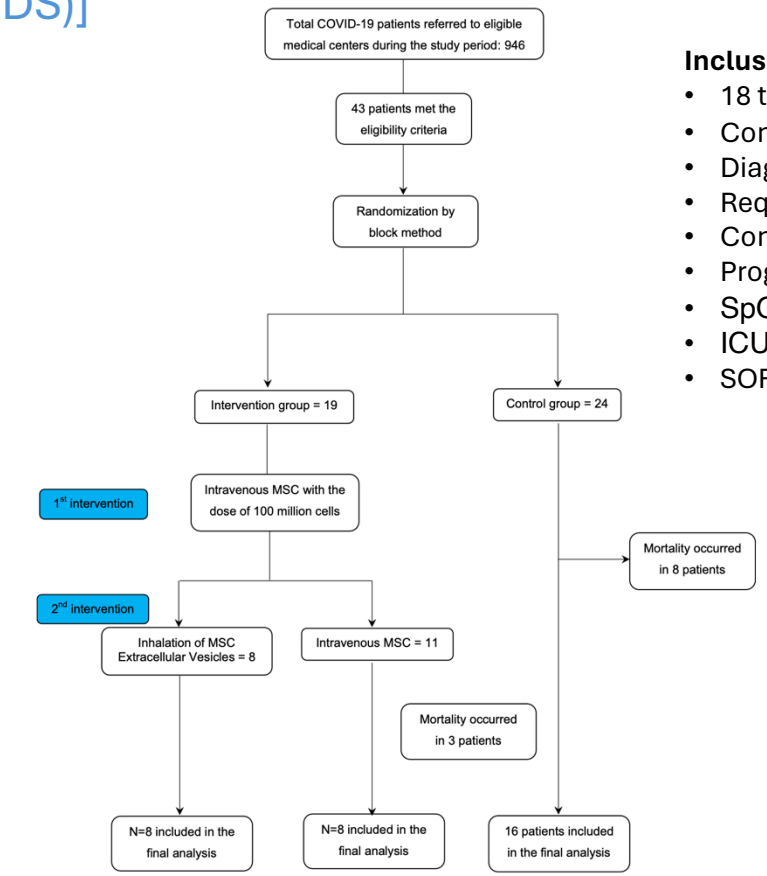
Placebo



UC-MSC



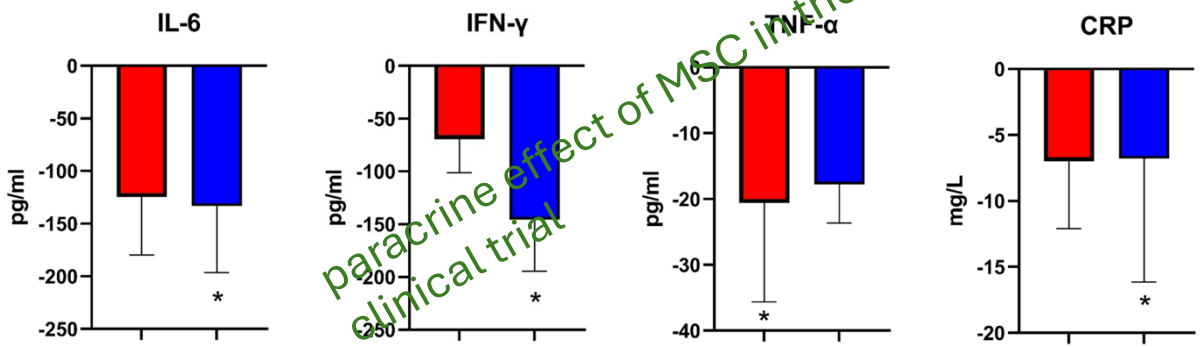
Stem Cell Res Ther 2022; 13: 283.



Inclusion criteria

- 18 to 65 years old
- Confirmed COVID-19
- Diagnosis of ARDS by Berlin criteria
- Required supplemental oxygen
- Confirmation of pneumonia
- Progressive status (>50% in 24-48h)
- $SpO_2/FiO_2 \leq 300$ mmHg
- ICU admission < 48 h
- SOFA score between 2 and 3

Phase 2 TRIAL

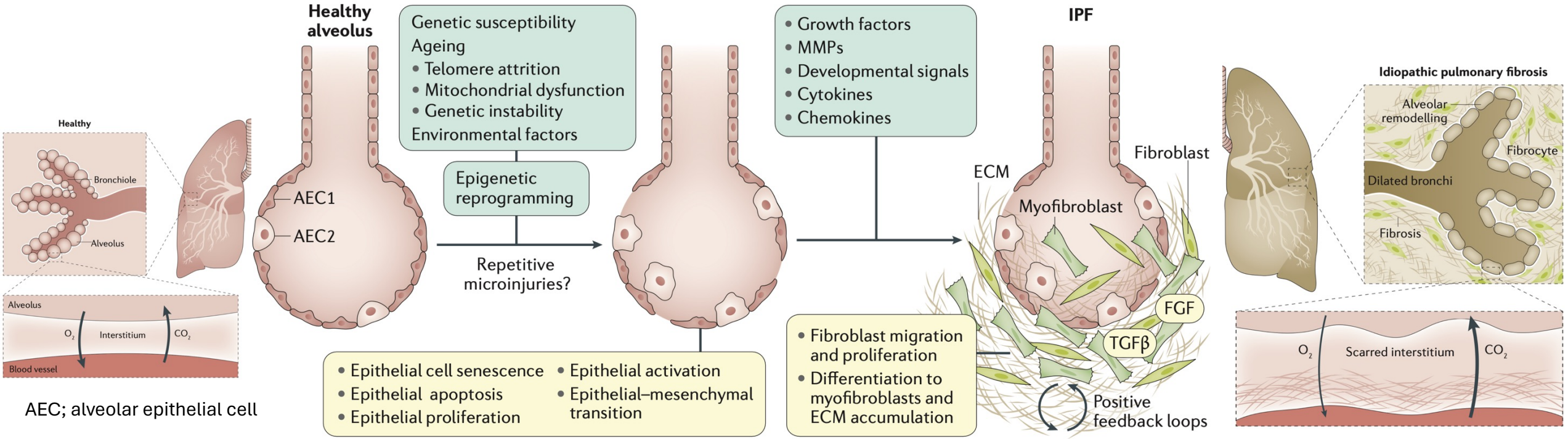


paracrine effect of MSC in the clinical trial

Red; MSC alone
Blue; MES-EV

Stem Cell Res Ther 2023; 14: 169.

[Idiopathic pulmonary fibrosis (IPF)]



AEC; alveolar epithelial cell

Nat Rev Dis Primers 2017; 3: 17074.

MSC

Paracrine effects

Immunomodulation & Anti-inflammation
- Inflammatory cytokines ↓
- Cell infiltration ↓
- M2 macrophage ↑

Anti-fibrosis
- ECM ↓
- Collagen deposition ↓
- Fibronectin ↓
- MMP ↑

Tissue regeneration
- AT2 senescence ↓
- AT2 proliferation ↑

Stem Cell Res Ther 2022; 13: 492.

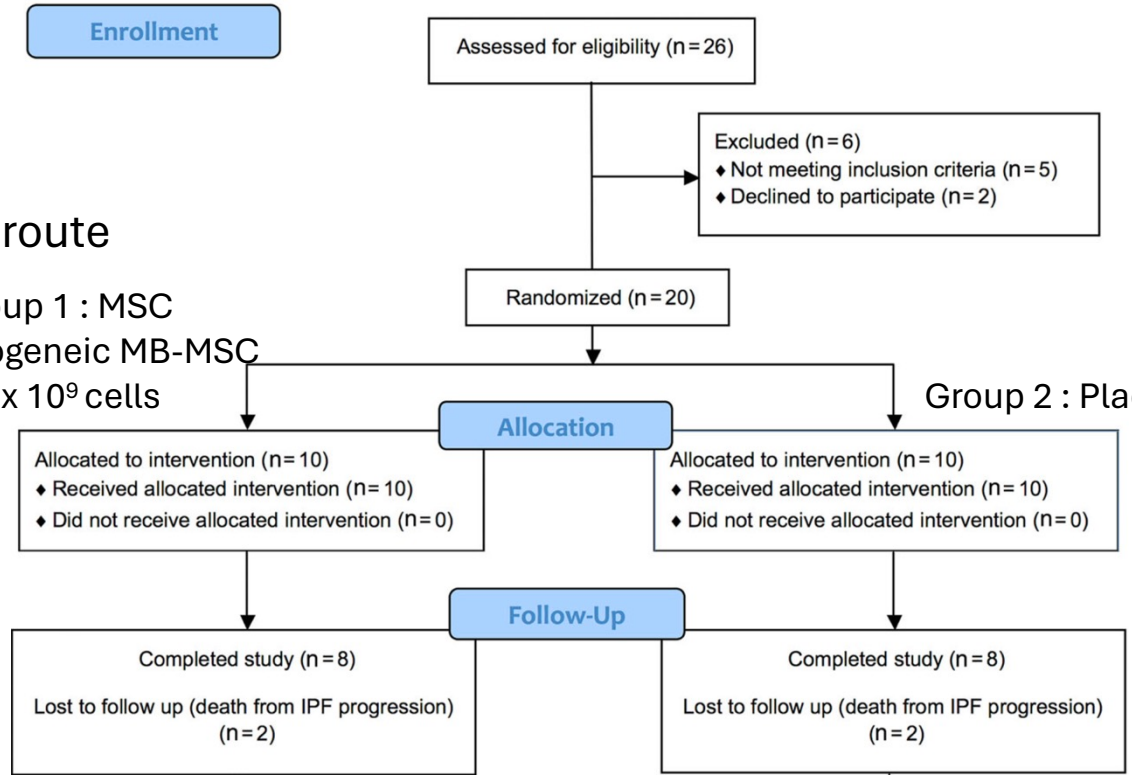
[Clinical trial for IPF using MSCs]

Allogeneic bone marrow MSC

IV route

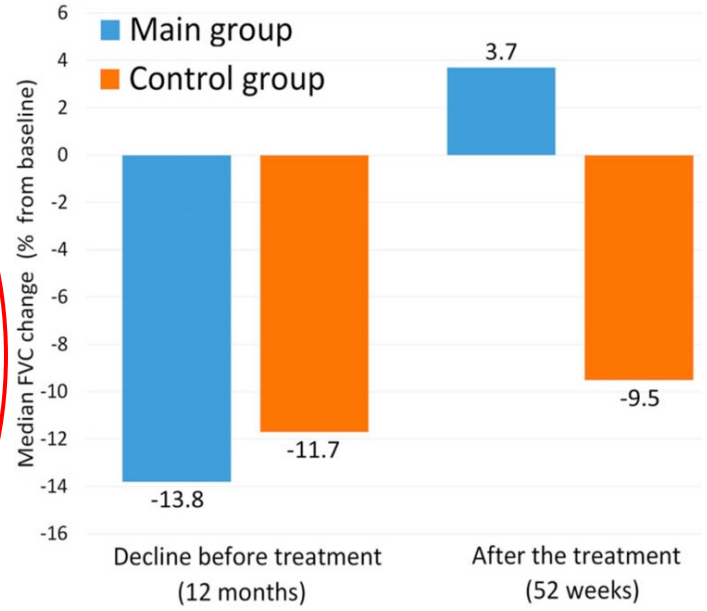
Group 1 : MSC
Allogeneic MB-MSC
1.6 x 10^9 cells

Group 2 : Placebo



Events	1 MSC (n = 10)	2 Placebo (n = 10)	Total (n = 20)	*P* value
All AEs	8 (80.0) / 28	7 (70.0) / 16	15 (75.0) / 44	>.999 ^
Death	2 (20.0) / 2	2 (20.0) / 2	4 (20.0) / 4	>.999 ^
Transient fever	4 (40.0) / 6	1 (10.0) / 1	5 (25.0) / 7	.303 ^
Weakness	4 (40.0) / 4	1 (10.0) / 1	5 (25.0) / 5	.303 ^
Cough	2 (20.0) / 2	2 (20.0) / 2	4 (20.0) / 4	>.999 ^
Headache	2 (20.0) / 4	2 (20.0) / 2	4 (20.0) / 6	>.999 ^
LRTI	2 (20.0) / 2	2 (20.0) / 2	4 (20.0) / 4	>.999 ^
Nausea	2 (20.0) / 2	2 (20.0) / 2	4 (20.0) / 4	>.999 ^
URTI	2 (20.0) / 3	2 (20.0) / 2	4 (20.0) / 5	>.999 ^
Chill	2 (20.0) / 2	0 (0.0) / 0	2 (10.0) / 2	.474 ^
IPF exacerbation	0 (0.0) / 0	1 (10.0) / 1	1 (5.0) / 1	>.999 ^
Ischemic stroke	1 (10.0) / 1	0 (0.0) / 0	1 (5.0) / 1	>.999 ^
Skin rash	0 (0.0) / 0	1 (10.0) / 1	1 (5.0) / 1	>.999 ^

MSCs, Placebo	12 months before	Baseline	13th week	26th week	39th week	52nd week
FVC (% of predicted)						
MSCs	60.0 (52-72)	51.5 (43-67)	46.5 (41-62)	51.5 (44-67)	56* (43-69)	55.5* (42-68)
Placebo	58.0 (55-68)	51.0 (48-61)	49.0 (45-56)	49.5 (45-57)	49.0 (44-53)	48.0 (43-52)
DLCO (% of predicted)						
MSCs	29.0 (26-42)	28.0 (22-33)	28.5 (24-34)	29.0* (25-36)	28.0 (22-34)	28.0* (24-34)
Placebo	30.0 (27-40)	29.5 (24-35)	27.5 (22-34)	28.5 (24-34)	27.5 (23-31)	26.5 (22-29)
6MWDT distance (m)						
MSCs	ND	271.0 (150-381)	340* (240-390)	360** (261-423)	366.5** (270-404)	373.5** (273-429)
Placebo	ND	247.5 (197-346)	289 (229-377)	287 (223-370)	277 (220-362)	267.5 (212-359)

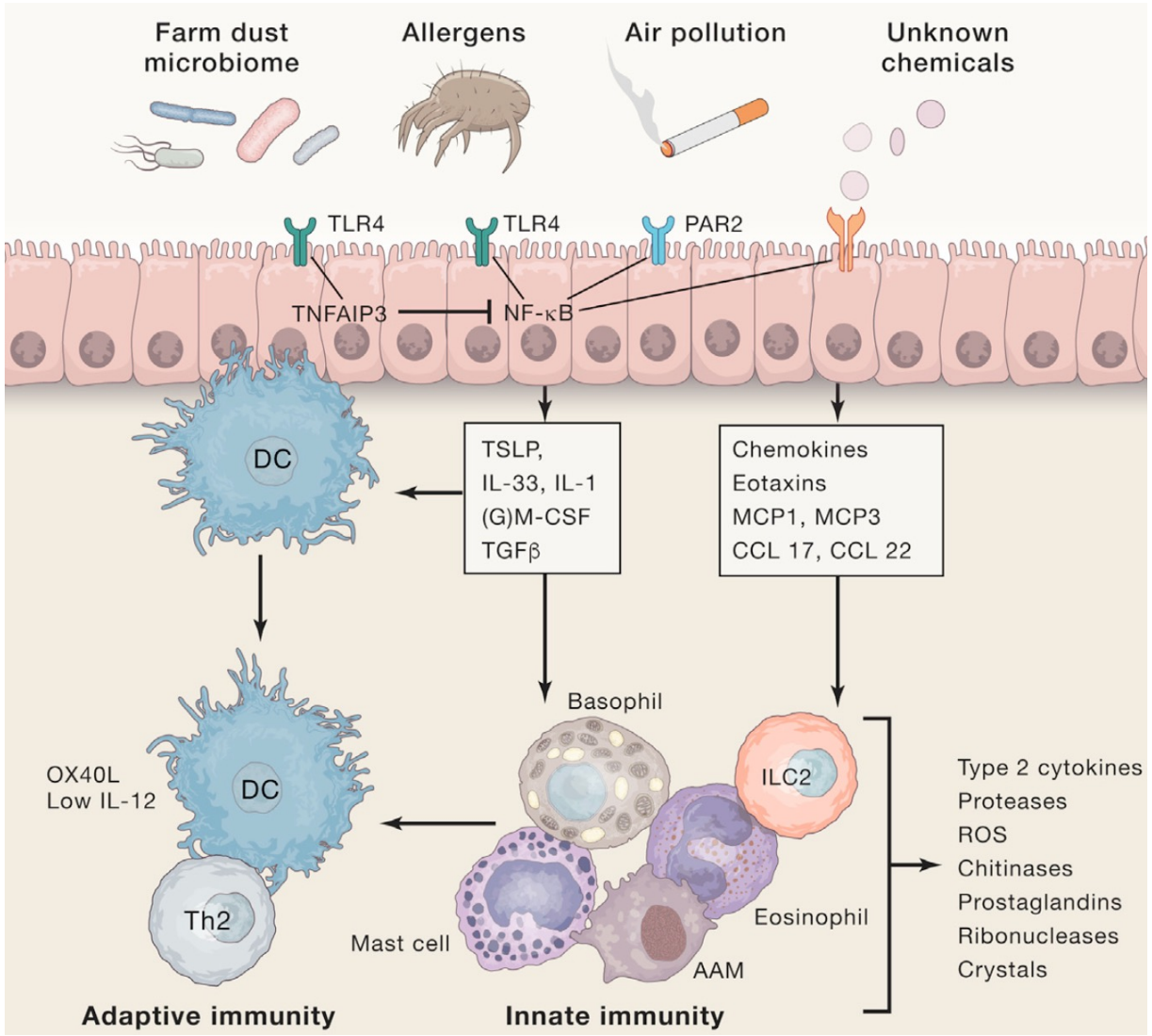


Pulmonary function: FVC: forced vital capacity; DLco: diffusing capacity of carbon monoxide

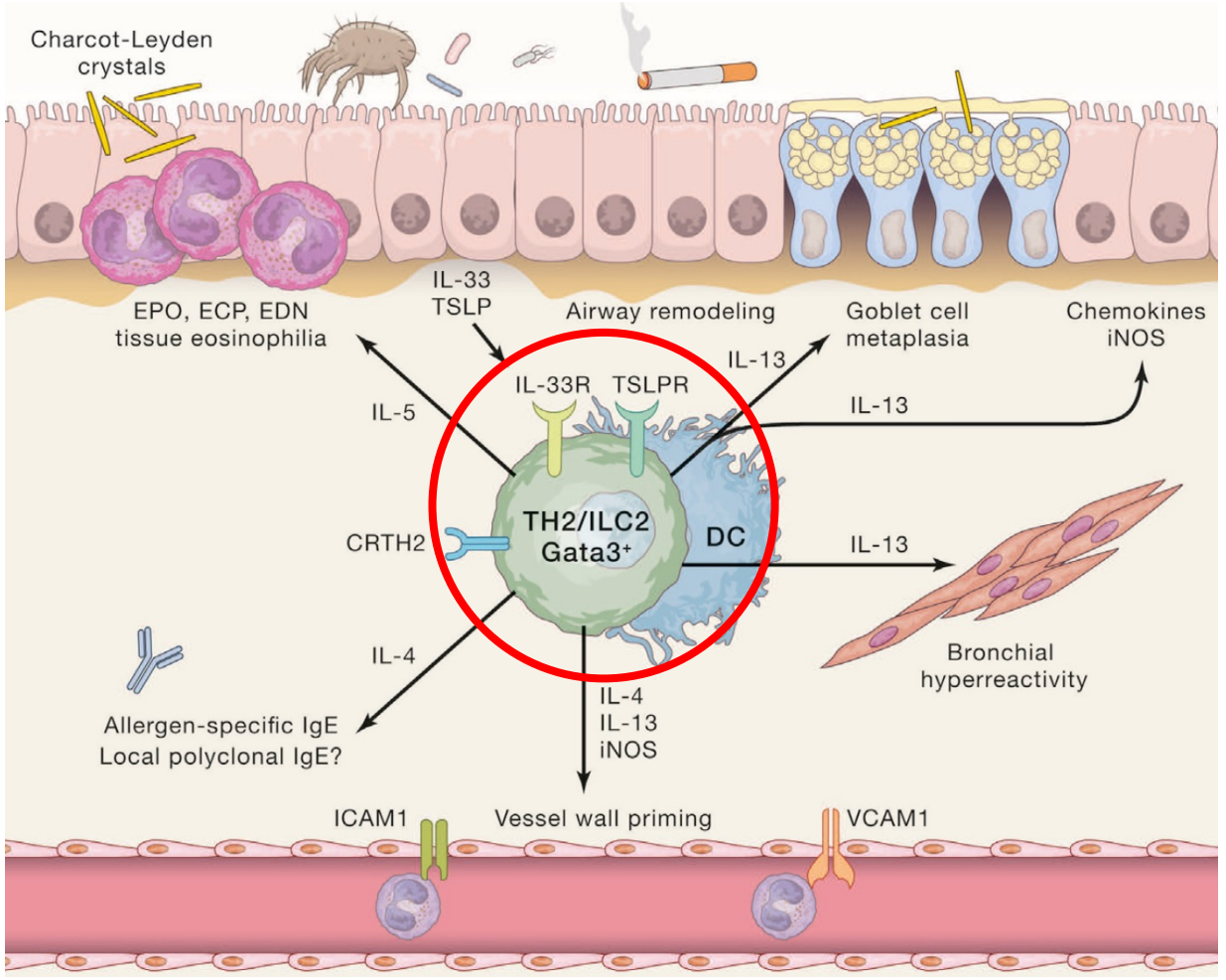
Stem Cells Transl Med 2020; 9: 6-16.

[Asthma]

Chronic inflammation of the airway wall, characterized by the infiltration and activation of immune cells



DC: Dendritic cells

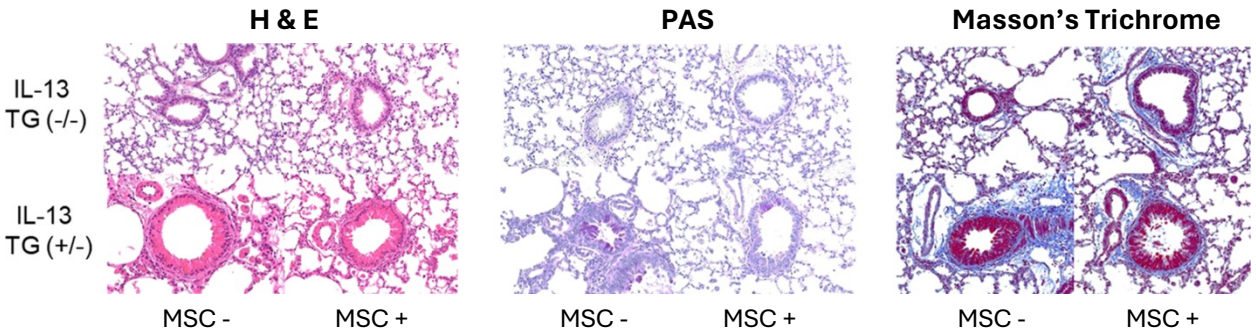


many mediators that contribute to airway inflammation

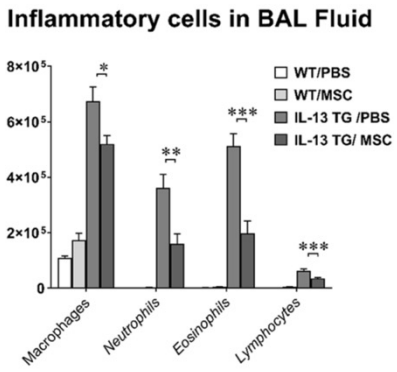
Cell 2021; 184: 1469-1485.

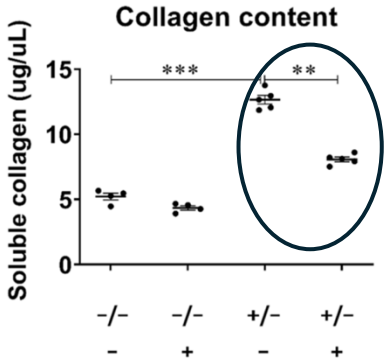
[Asthma]

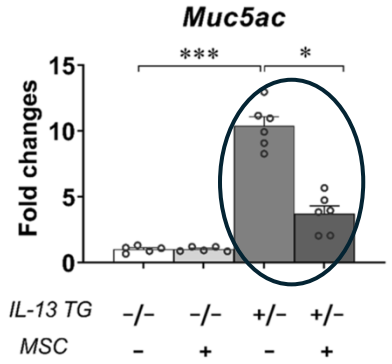
intratracheally route; hUC-MSC



decrease of inflammatory cell recruitment





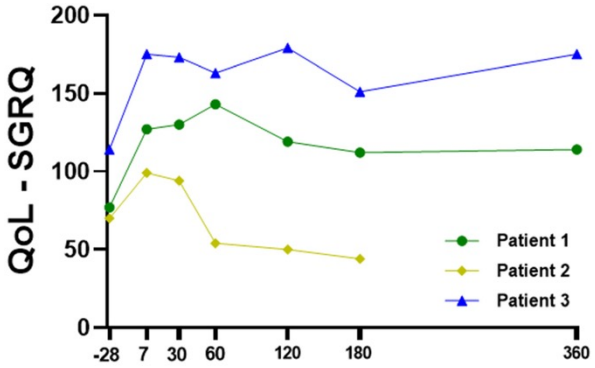


Mucus secretion

CD markers	Phenotype	Percentage
$CD45^{low}CD34^{high}SSC\downarrow$	Hematopoietic stem cells	0.88
$CD45^{low}CD34^{+}CD19^{+}$	B cell progenitors	3.26
$CD45^{+}CD34^{-}CD64^{+}CD14^{-}$	Promonocytes	0.88
$CD105^{+}CD90^{high}CD73^{+}CD45^{-}CD34^{-}$	Mesenchymal stromal cells	0.1
$FSC\downarrow SSC\downarrow CD45^{-}CD71^{+}CD36^{+}$	Erythroblasts	8.1
$CD45^{+}CD34^{-}CD64^{+}CD14^{+}$	Monocytes	2.92
$CD45^{+}CD34^{-}CD3^{+}$	T lymphocytes	14.13
$CD45^{+}CD3^{+}CD4^{+}$	Helper T cells	5.16
$CD45^{+}CD3^{+}CD8^{+}$	Cytotoxic T cells	4.33
$CD45^{+}CD3^{-}CD19^{+}$	B cells	3.2
$CD45^{+}CD56^{+}$	NK cells	1.2
$CD45^{low}SSC\uparrow$	Neutrophils	69.56

Patient	Parameters	Visit (days) D–28 (baseline)	D + 360
1	FVC (L)	2.23	1.89
	FVC (%)	76	65
	FEV_1, pre-BD (L)	1.5	1.46
	FEV_1 (%)	62	61
	6MWT (m)	273	294
2	FVC (L)	1.99	1.77
	FVC (%)	74	66
	FEV_1, pre-BD (L)	0.88	0.66
	FEV_1 (%)	41	31
	6MWT(m)	412	324
3	FVC (L)	1.89	1.86
	FVC (%)	64	64
	FEV_1, pre-BD (L)	0.83	0.85
	FEV_1 (%)	35	37
	6MWT (m)	354	390

IV BM-MNC



Only safety

Sci Rep 2022; 12: 9811.

Stem Cell Res Ther 2020; 11: 167.

CONCLUSION

Future perspectives for stem cell therapies

- Inflammation & Fibrosis – Paracine effects
- Treatment timing, severity of the disease
- Stem cell selection, cell free
- Cell delivery route
- Appropriate dose - Frequency of administration
- Further Clinical trials

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