Societat Catalanobalear de Transfusió Sanguínia

Medicina Transfusional i Teràpia cel·lular en temps de pandèmia

Cèl·lules en front de la COVID

4 de Maig de 2021

Dr. Sergi Querol.
Cap dels Serveis de Teràpia Cel·lular i Avançada
Banc de Sang i Teixits

Salut/

bancsang.net

Cèl·lules en front de la COVID

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1) COVID19 i Trasplantament de progenitors

(amb Dr Jesús Fernandez)

2) Teràpia cel·lular i avançada i COVID19

(amb Dr Joaquim Delgadillo)

Impacte de la pandèmia al TPH

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Recommendation during Covid-19 pandemic

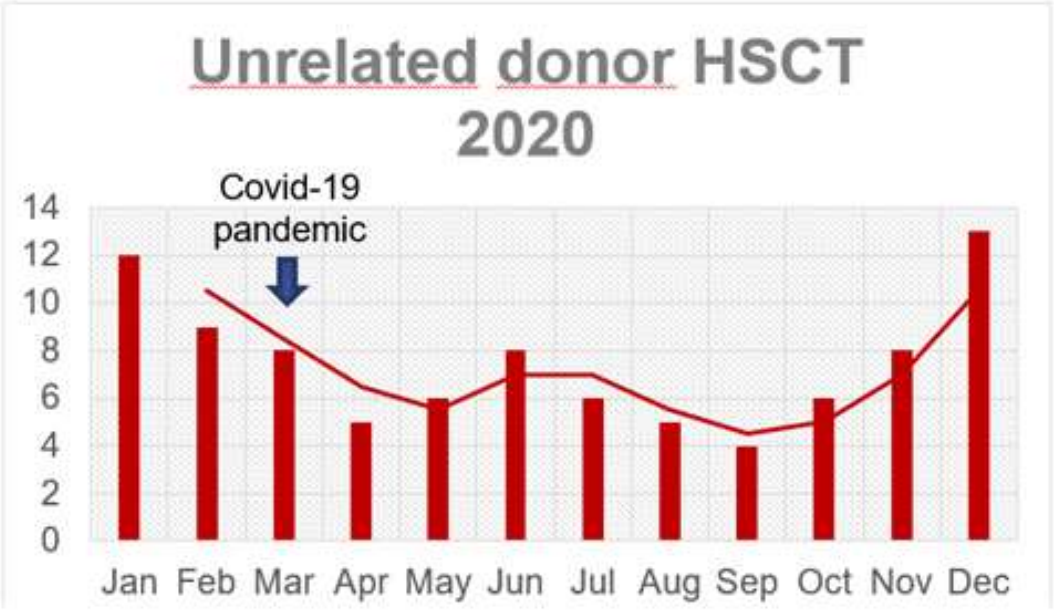
- ***Spanish Bone Marrow Donors Registry (REDMO)*** March 5th 2020:
- Cryopreservation
- "Cryo-quarantine" or SARS-COV-2 donor result
- Consider deferring transplantation, use Spanish donors, haploidentical donor or CBU, prevent using bone marrow

- **EBMT** March 23th 2020
- Cryopreservation
- Defer non-urgent transplant

- **WMDA** May 4th 2020
- Cryopreservation
- Assuring product's quality before starting conditioning

Cryopreservation was recommended by the Spanish Registry and international organizations

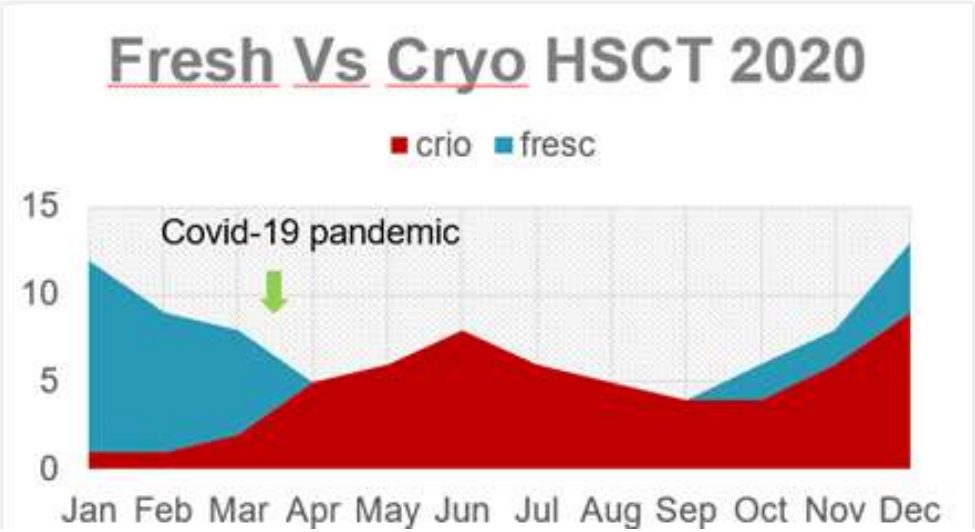
Activitat de TPH durant la pandèmia



- Trend to decreasing activity months after onset pandemic and recovery ending 2020

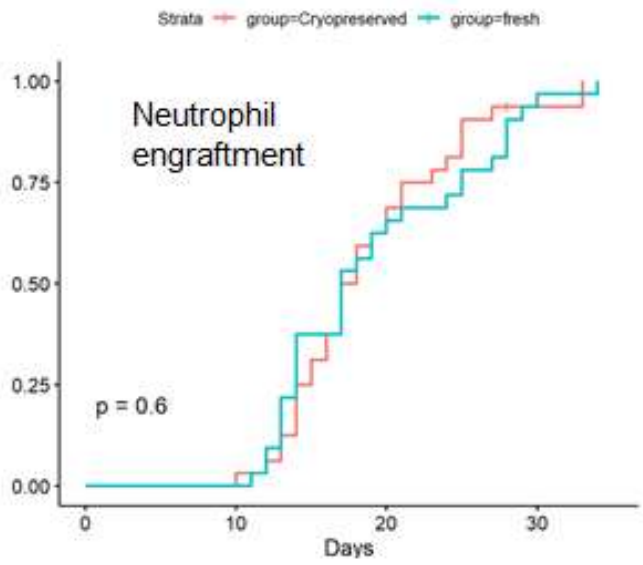
Reference: Garcia-Lopez J, et al. SARS-Cov-2/COVID-19 pandemic: first wave, impact, response and lessons learnt in a fully integrated Regional Blood and Tissue Bank. A narrative report. Blood Transfus. 2021 Jan 15. doi: 10.2450/2021.0259-20. Epub ahead of print. PMID: 33539280.

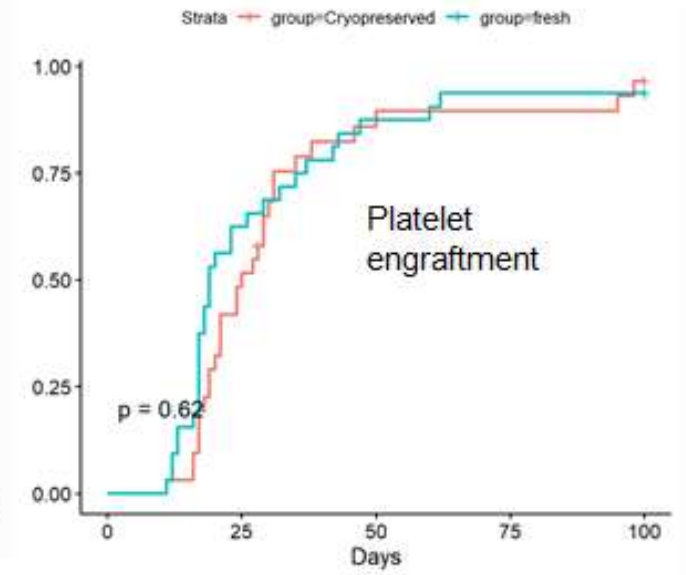
Conseqüencies pel Laboratori de Teràpia Cel·lular

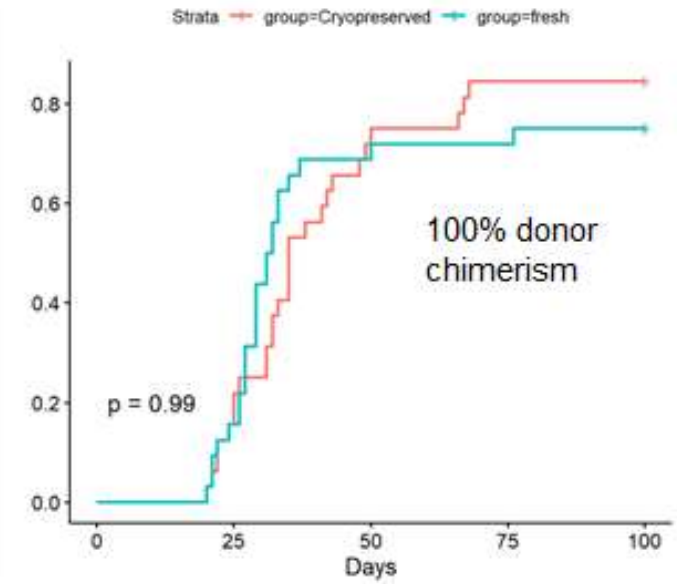


Almost all grafts (87%) have been cryopreserved during Covid-19 pandemic

Impacte en l'empelt

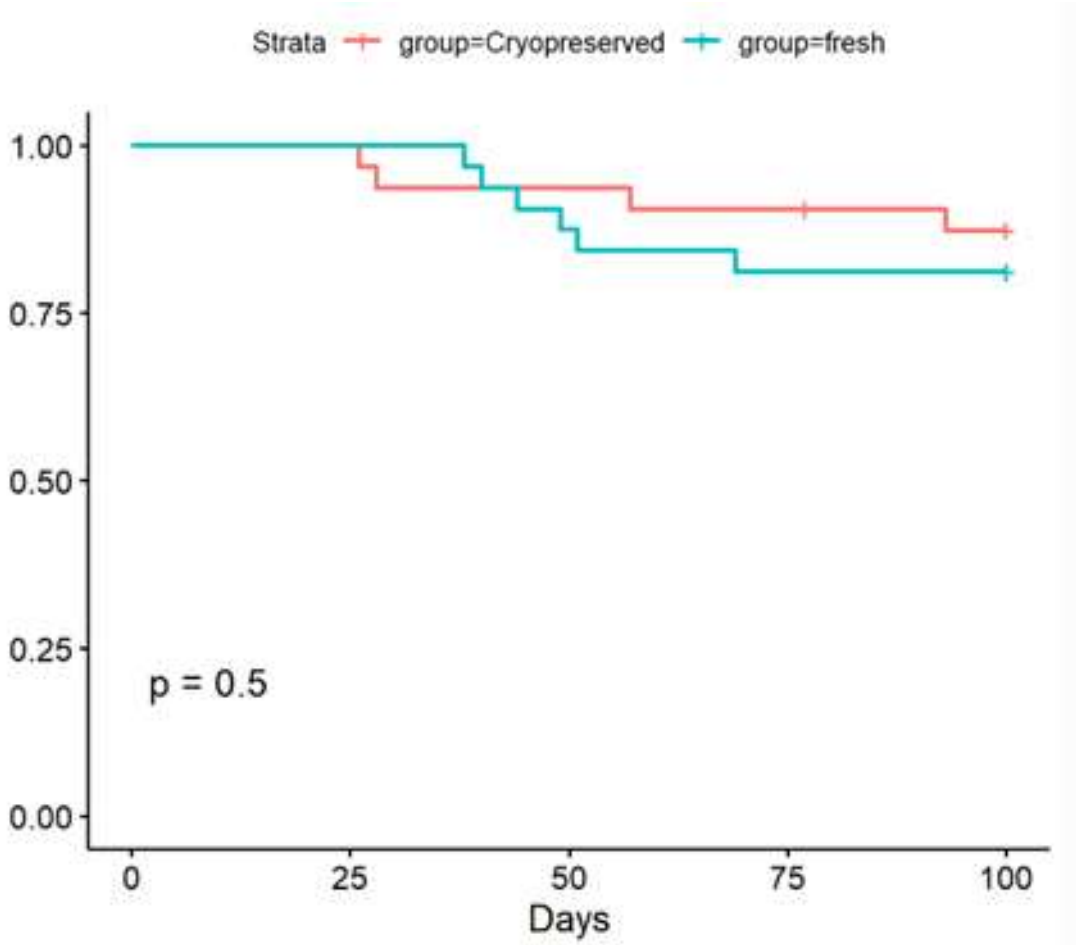






No statistical difference regarding hematological recovery and full donor chimerism
One patient experimented graft failure in cryopreserved group

Impacte en la supervivència



No statistical difference regarding overall survival until day +100

Efectes col·laterals

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13% unrelated cryopreserved grafts were not infused as of February 1rst 2021

REASON	NUMBER OF PATIENTS
Relapse/Progression of patient's disease	3
HLA-mismatch detected after BM donor collection	1
Donor-specific anti-HLA antibodies (DSA)	1
Patient decision	1

- DKMS experience **5-10%** will eventually not be infused

Reference: Schmidt AH, Buk D, Platz A, van den Brink MRM. Cryopreservation for All Is No Option in Unrelated Stem Cell Transplantation. Comment on Dholaria B, et al. Securing the Graft During Pandemic: Are We Ready for Cryopreservation for All? Biol Blood Marrow Transplant. 2020;26:e145-e146. Biol Blood Marrow Transplant. 2020 Nov;26(11):e298-e299. doi: 10.1016/j.bbmt.2020.08.011. Epub 2020 Aug 18. PMID: 32822844; PMCID: PMC7434475.

Sumari

Trasplantament de Progenitors Hemopoètics

- La criopreservació és un procés segur per garantir la disponibilitat de productes de cèl·lules mare hematopoètiques en el moment del condicionament:
  - No hi ha diferències estadístiques en quant a la supervivència global fins al dia 100

- Els empelts criopreservats que acaben sense infusió presenten un problema ètic.
  - L'afèresi i la recollida de medul·la òssia són segures, però no del tot exemptes de riscos.

- Començar el condicionament immediatament després de la recepció
  - Els resultats dels controls de qualitat poden estar disponibles a les 48 h després de la criopreservació

Cèl·lules en front de la COVID

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Virus respiratori "especial"

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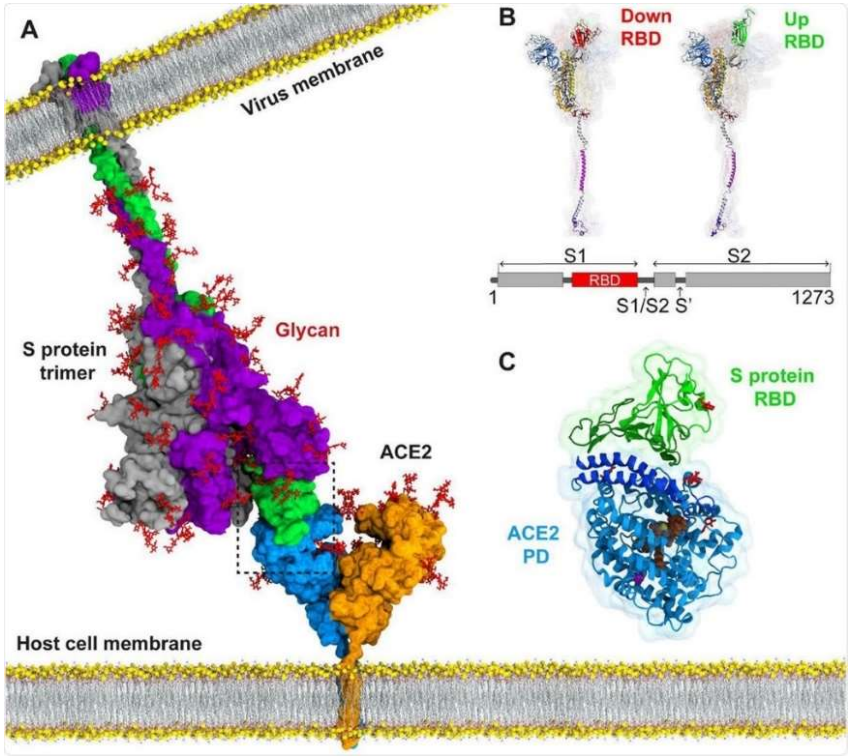
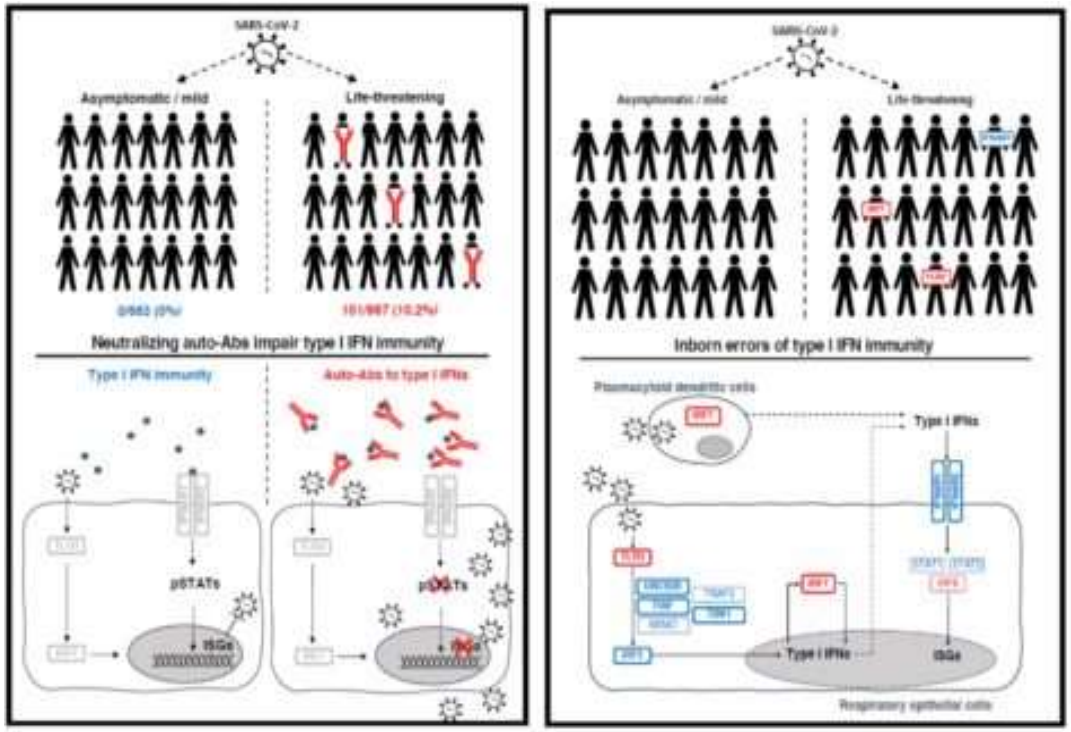
ACE2 + Interferó de tipus I



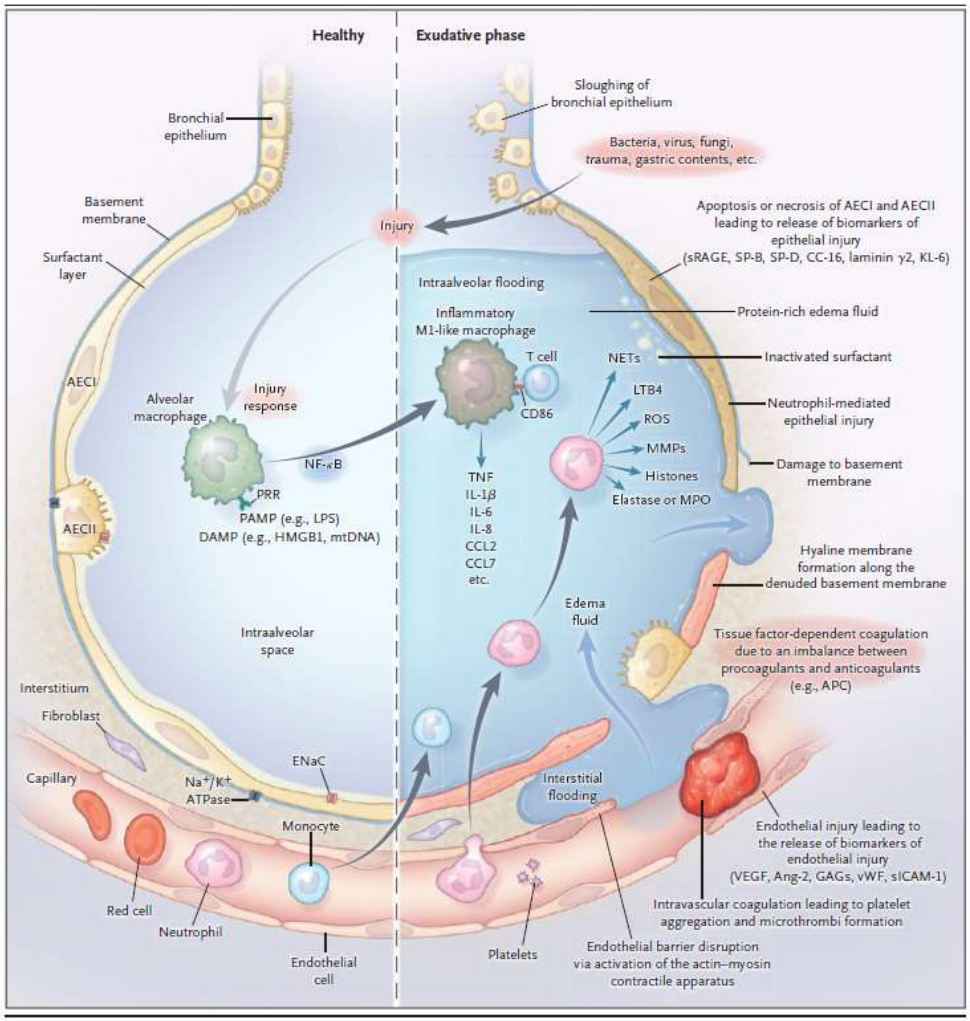
Alvèol pulmonar
Endoteli



Susceptibilitat individual i genètica

Síndrome del distrés respiratori agut

Ràpida evolució



Thompson T et al. NEJM 2017; 377: 562-573; Horie S et al. J Thorac Dis 2018;10: 5607-5620; Carsana L, et al. medRxiv preprint doi: https://doi.org/10.1101/2020.04.19.20054262

- Mediana inici a malaltia severa-critica: 10 dies (8%)
- Mediana inici a mort: 16 dies (0,92%)

- Lesió pulmonar severa pel virus
- **Secreció de citocines pro-inflamatòries**
- Edema i invasió cel·lular de l'espai alveolar (**limfopènia**)
- Dany alveolar difús
  - hemorràgia i edema intra-alveolar
  - formació de membranes hialines
  - atelèctasis
  - edema intersticial
  - lesió i disrupció barrera endotelial
- **Infecció endotelial**, congestió capil·lar, microtrombosi

Tractaments biològics per a la COVID19

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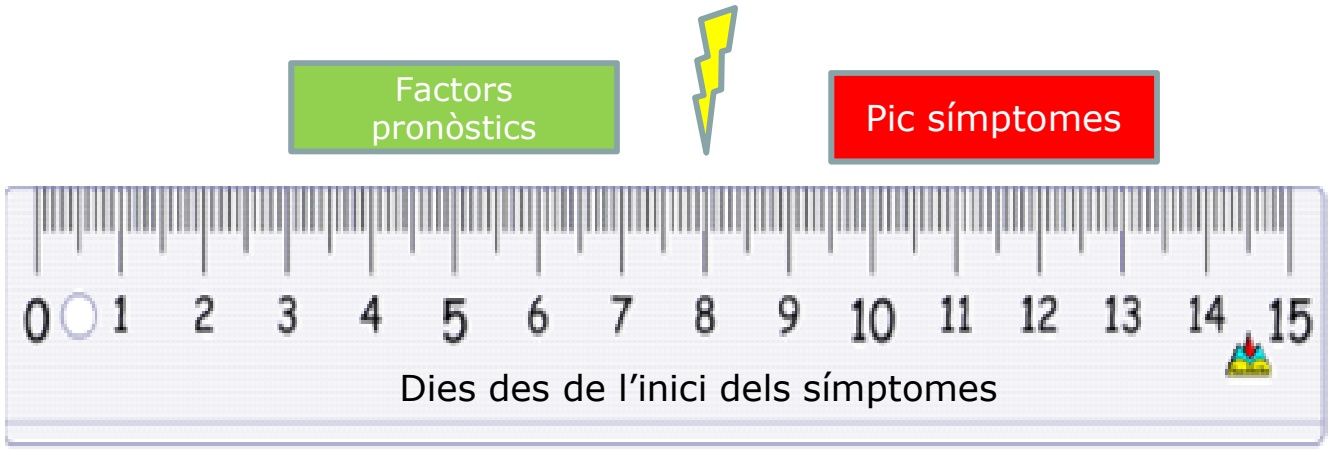
Dosis viral
Memòria prèvia



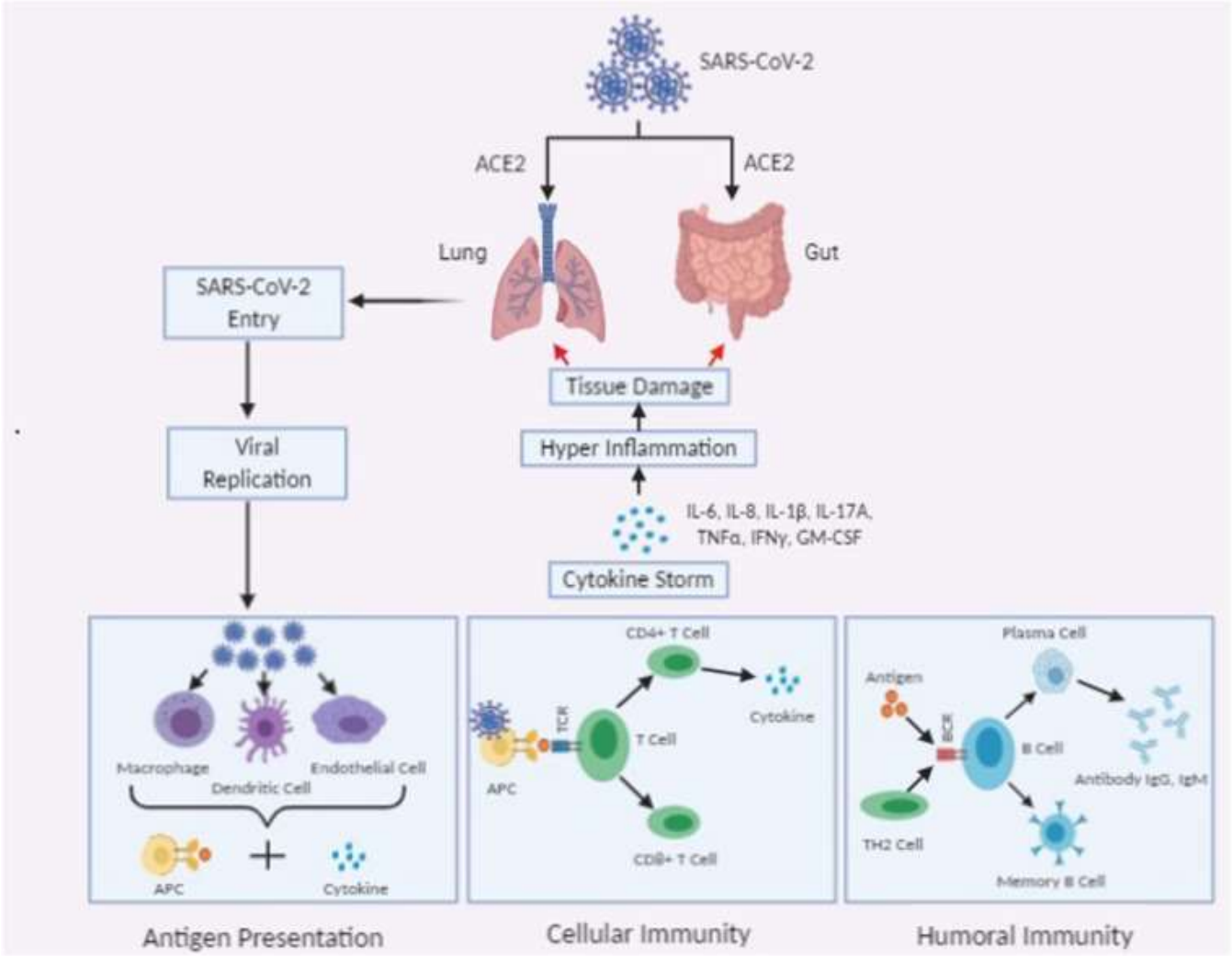
Mortalitat
Gravetat
Dies d'ingrés
Seqüeles

TRACTAMENTS BIOLÒGICS

- Immunoglobulines
  - Plasma Convalescent (BST)
  - Sèrum Hiperimmune (Grifols)
  - Anticossos específics (REGN-Cov2)
- Bloqueig IL6
  - Corticoides
- MSC
- Virus T específics

Luo XH, Zhu Y, Mao J, Du RC. T-cell immunobiology and cytokine storm of COVID-19. Scand J Immunol. 2020 Oct 28:e12989.

Temps de resposta i híperinflamació



<u>IMMUNITAT HUMORAL:</u>
IgA: Pic dia 7-20

IgM: Pic dia 10-20

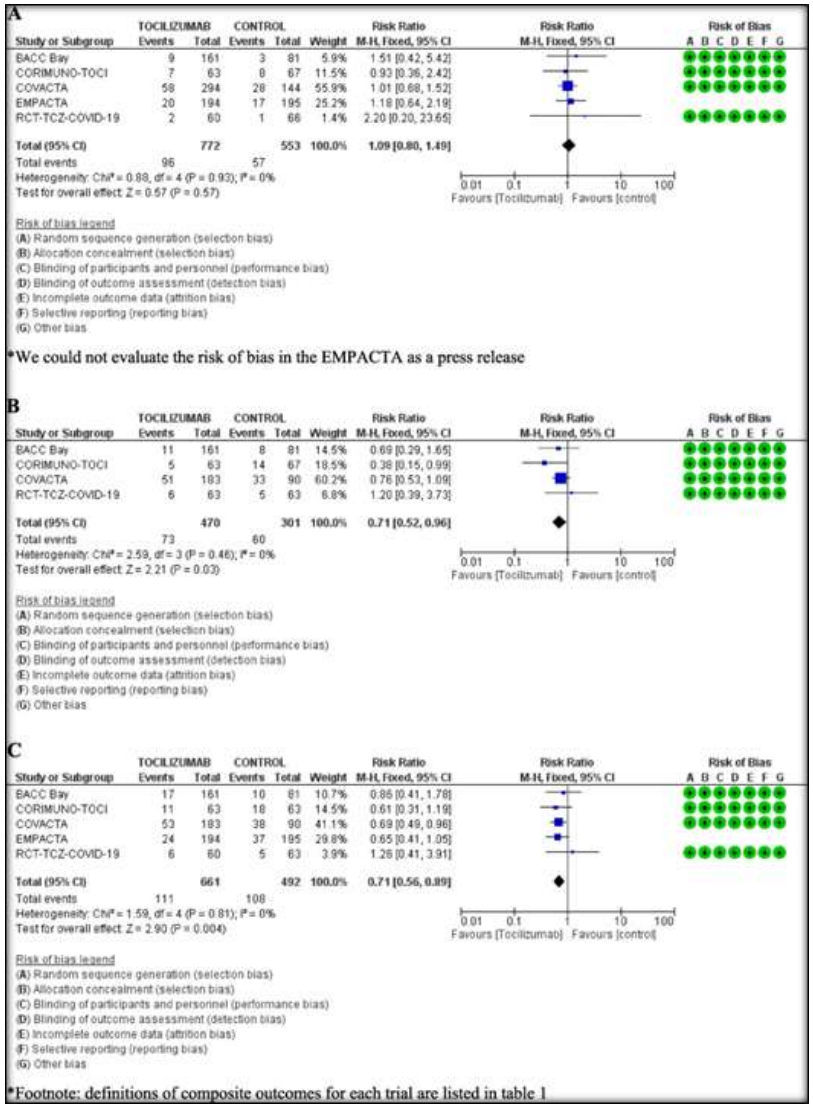
IgG: Pic dia 21-60

<u>IMMUNITAT CEL·LULAR:</u>
Linfos T: Pic 10-20

Chatterjee SK, Saha S, Munoz MNM. Molecular Pathogenesis, Immunopathogenesis and Novel Therapeutic Strategy Against COVID-19. Front Mol Biosci. 2020 Aug 11;7:196.

Tractament de la hiperinflamació

ANTI-IL6 NO ES SUFICIENT



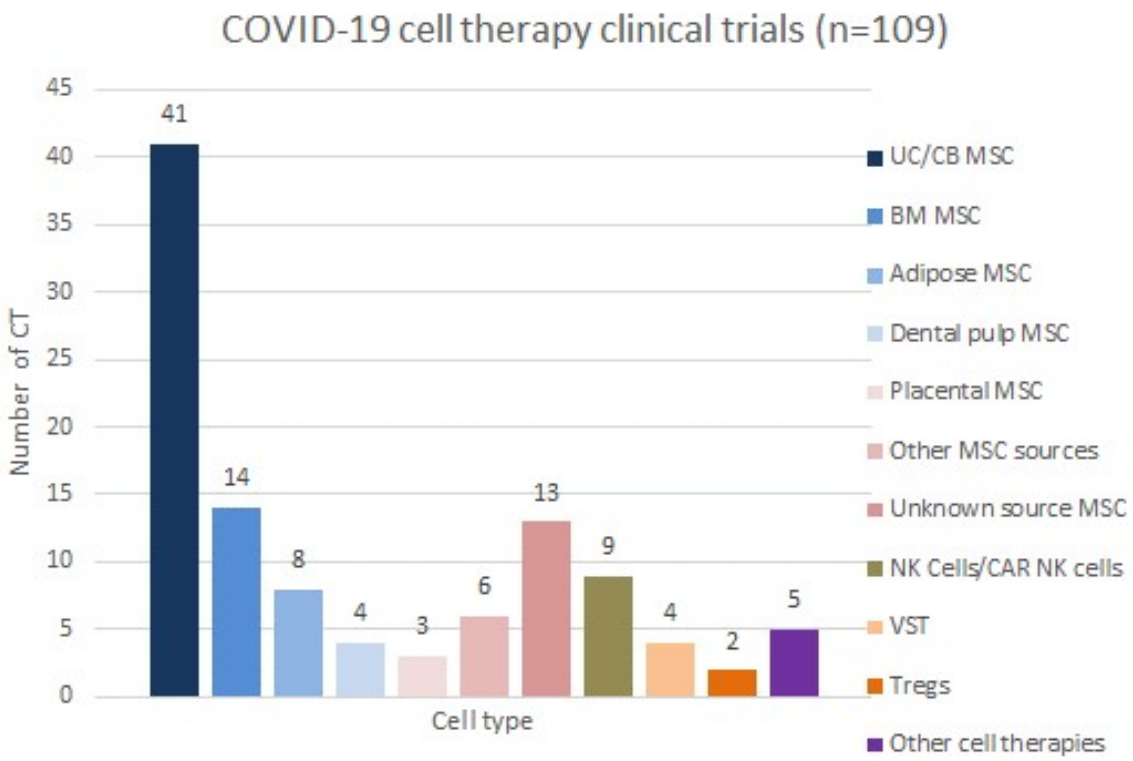
effect of tocilizumab on 28-30 days **mortality**

effect of tocilizumab on **risk for mechanical ventilation**

effect of tocilizumab on 28-30 days **composite outcome**

Tleyjeh IM, et al. Efficacy and safety of tocilizumab in COVID-19 patients: A living systematic review and meta-analysis. Clin Microbiol Infect. 2020 Nov 5:S1198-743X(20)30690-X.

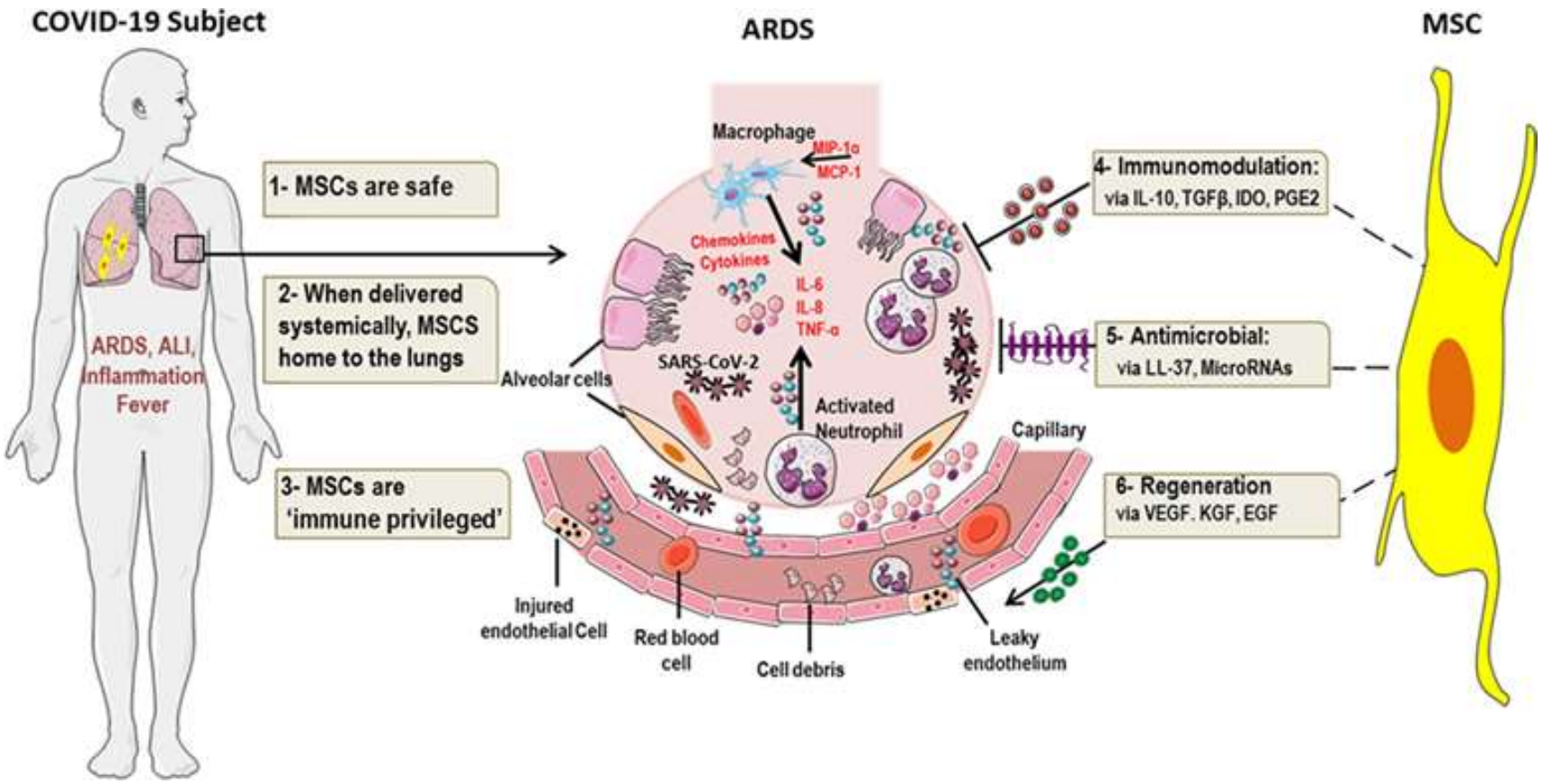
Teràpia cel·lular i COVID19



- 81% phase 1 or 2
- 26 countries
  - China & US 45%
- Mean 43 (±279) patients to enrol
  - 62% ≤30 patients

CellTrials.org COVID-19 Clinical Trials by Cell Trials Data Team (CT registered up to Oct 2020)

Mesenquimals i SDRA



Durand N et al. Regen Med 2020. https://doi.org/10.1038/s41536-020-00105-z

Evidencies clíniques amb mesenquimals

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Author	Study type	Total n (MSC/Ctrl)	MSC source	MSC cells/kg (frequency)	Route	Main outcomes
[1]Leng et al, 2020	Phase I non randomized	10 (7/3)	NR* (UC)	1 x 10^6 (1 dose)	IV	• No treatment related AEs or SAEs • Improvement in symptoms, pulmonary function, inflammatory cells and biomarkers
[2]Meng et al, 2020	Phase I non randomized	18 (9/9)	UC	30 x 10^6** (3 doses)	IV	• No serious infusion associated AEs • Trend in improvement of symptoms, pulmonary function and inflammatory biomarkers
[3]Shu et al, 2020	Phase I/II randomized	41 (12/29)	UC	2 x 10^6 (1 dose)	IV	• Significant differences in time to clinical improvement; clinical improvement at days 7 and 14; score on 7-category scale at day 7 and inflammatory cells and biomarkers at day 15
[4]Lanzoni et al, 2020	Phase I/II Randomized, placebo controlled	24 (12/12)	UC	1 x 10^{6**} (2 doses)	IV	• No SAEs related to MSCs • Significant differences in survival, time to recovery and inflammatory biomarkers
[5]Guo et al, 2020	Observational	31 (31/)	UC	1 x 10^6 (1 dose: 11 pts) (2 doses: 9 pts) (3 doses: 11 pts)	IV	• No treatment related AEs or SAEs • Improvement in pulmonary function, inflammatory cells and biomarkers
[6]Sanchez Guijo et al, 2020	Observational	13 (13/)	AT	1 x 10^6 (1 dose: 2 pts) (2 doses: 10 pts) (3 doses: 1 pts)	IV	• No treatment related AEs or SAEs • Improvement in pulmonary function, inflammatory cells and biomarkers

1 Leng Z et al. Aging and disease 2020. https://doi.org/10.14336/AD.2020.0228

2 Meng F et al. Sig Transduct Target Ther 2020. https://doi.org/10.1038/s41392-020-00286-5

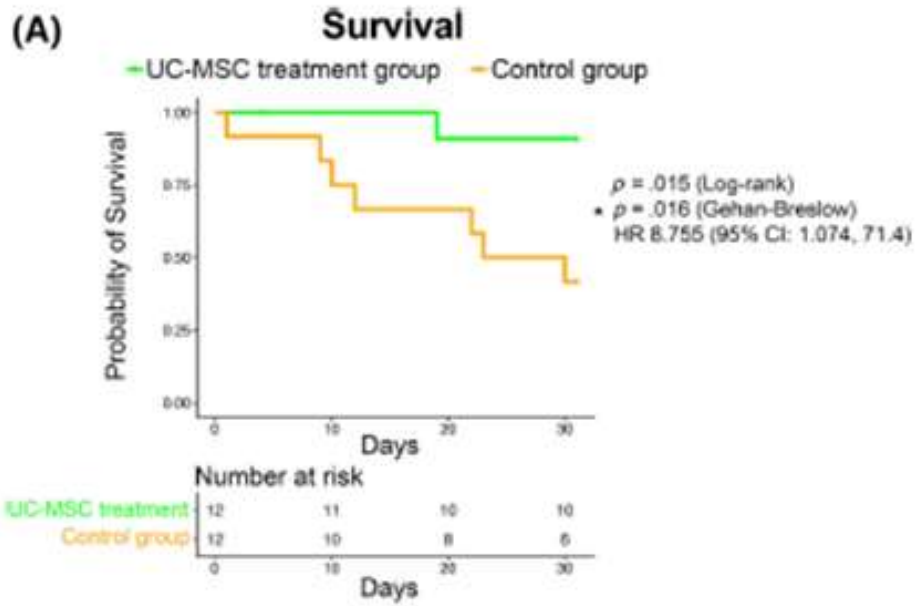
3 Shu et al. Stem Cell Res Ther 2020. https://doi.org/10.1186/s13287-020-01875-5

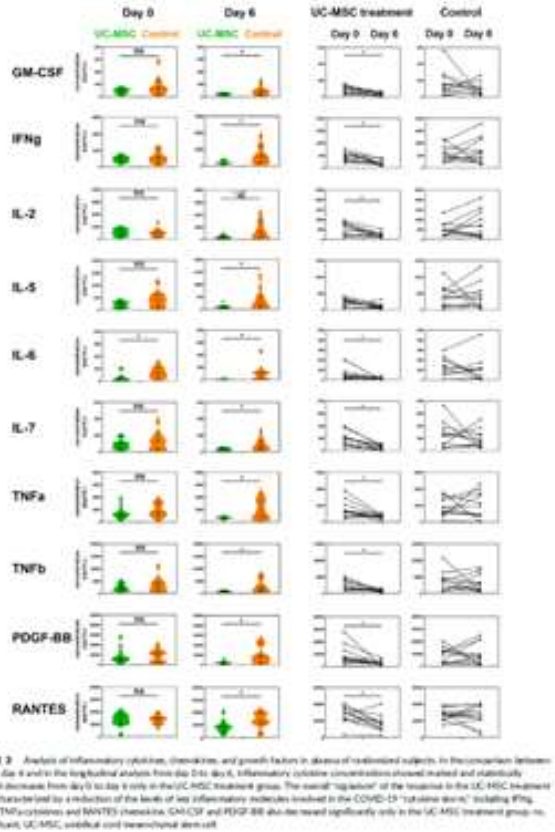
4 Lanzoni et al. STEM CELLS Transl Med 2021. https://doi.org/10.1002/sctm.20-0472

5 Guo et al. Crit Care 2020. https://doi.org/10.1186/s13054-020-03142-8

6 Sanchez-Guijo F et al. EClinicalMedicine 2020. https://doi.org/10.1016/j.eclinm.2020.100454

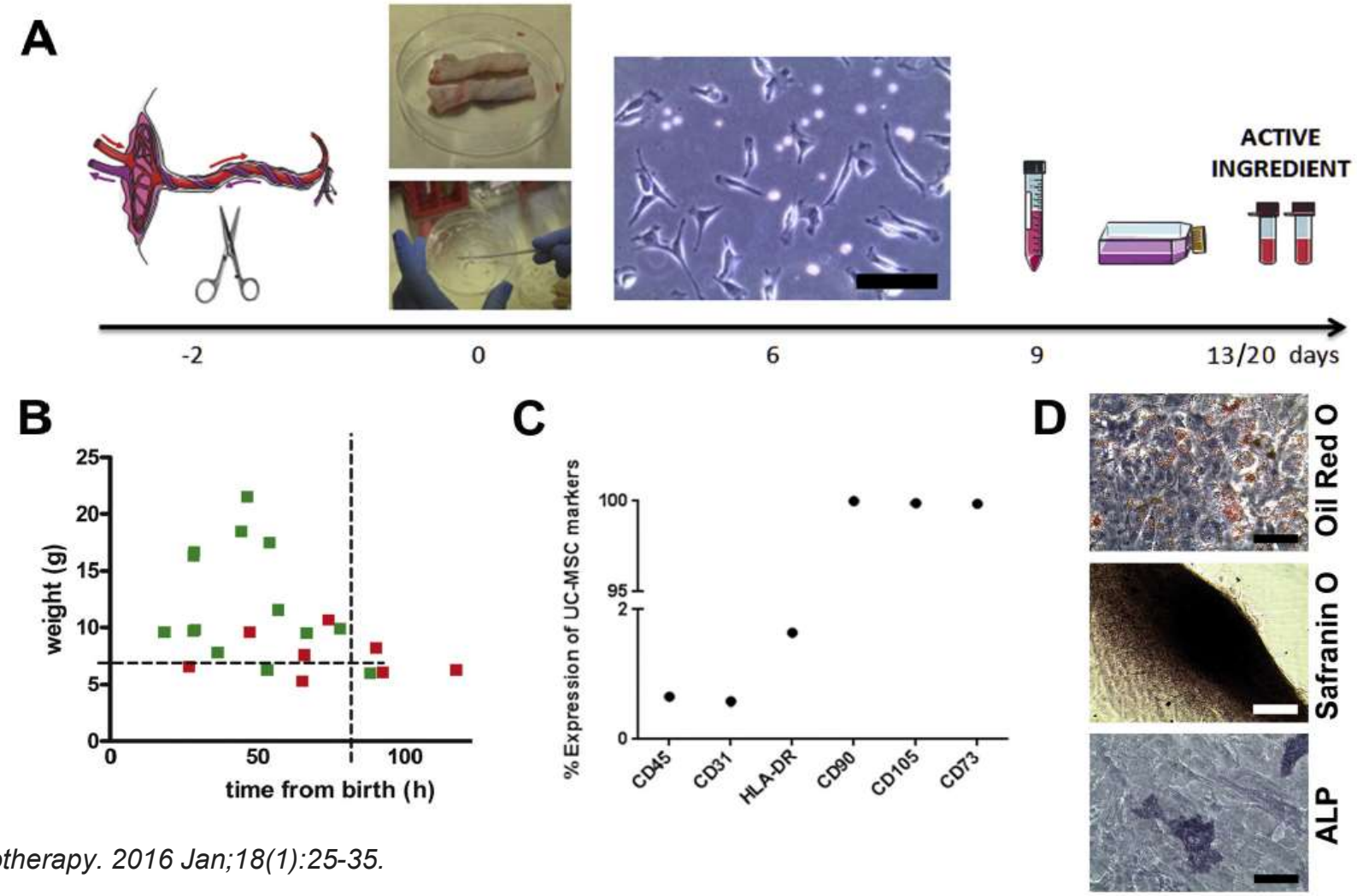
Evidencies clíniques amb mesenquimals





Lanzoni et al. STEM CELLS Transl Med 2021. https://doi.org/10.1002/sctm.20-0472

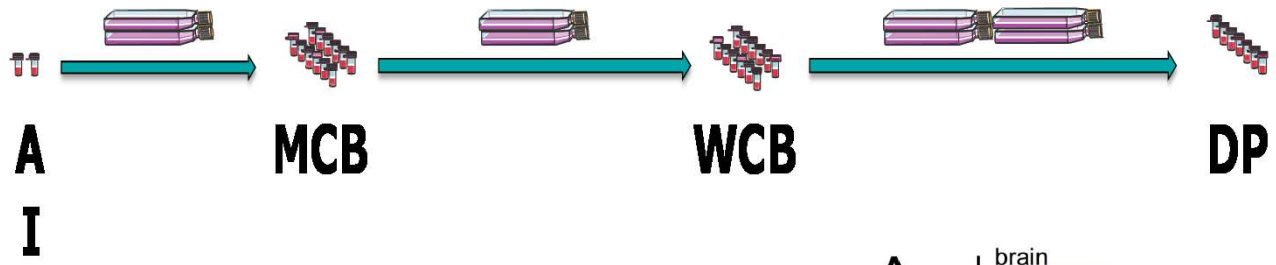
Selection , validation and GMP production (1)

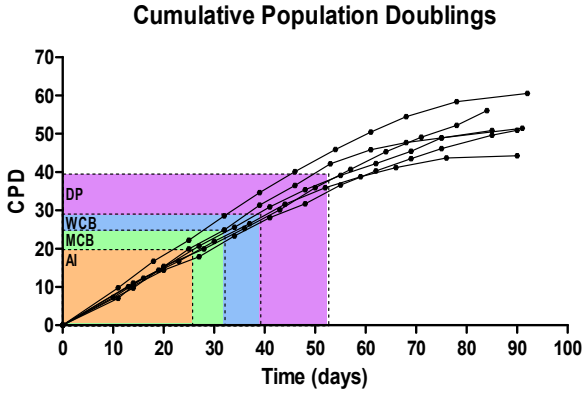


Oliver-Vila I, Cytotherapy. 2016 Jan;18(1):25-35.

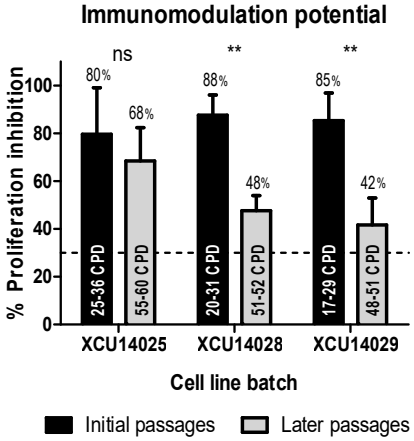
Figure 1. Derivation of UC-MSCs from Wharton's jelly. (A) Schematic depicting the derivation of UC-MSCs. Medium was changed every 3–4 days, and cultures were passaged normally on the ninth day, thus yielding the AI from days 13 to 20. (B) A minimum of 80% success rate (green dots represent success; red dots represent failure) in the derivation of UC-MSCs was achieved when using tissue fragments of at least 7 g and processed within 80 h from extraction at birth. (C) Immunophenotype of the AI. (D) Multi-potentiality of UC-MSCs was assessed for adipogenesis (oil red O staining), chondrogenesis (safranin O staining) and osteogenesis (alkaline phosphatase [ALP] staining). Portion A of the figure is from the Medical Art Gallery (Les Laboratoires Servier). Scale bars = 100 μm.

Selection , validation and GMP production (2)





Most of the cumulative population doublings (CPD) occurred in the generation of the Active Ingredient and the Drug Product.
The Drug Product contains approximately 40 CPD.



UC-MSC have the ability to inhibit lymphocyte proliferation response after polyclonal stimulation.
Although this ability decreases along cell expansion in culture, it is maintained above 30% (lymphocyte proliferation inhibition), which is the cut-off for acceptance of the drug product.

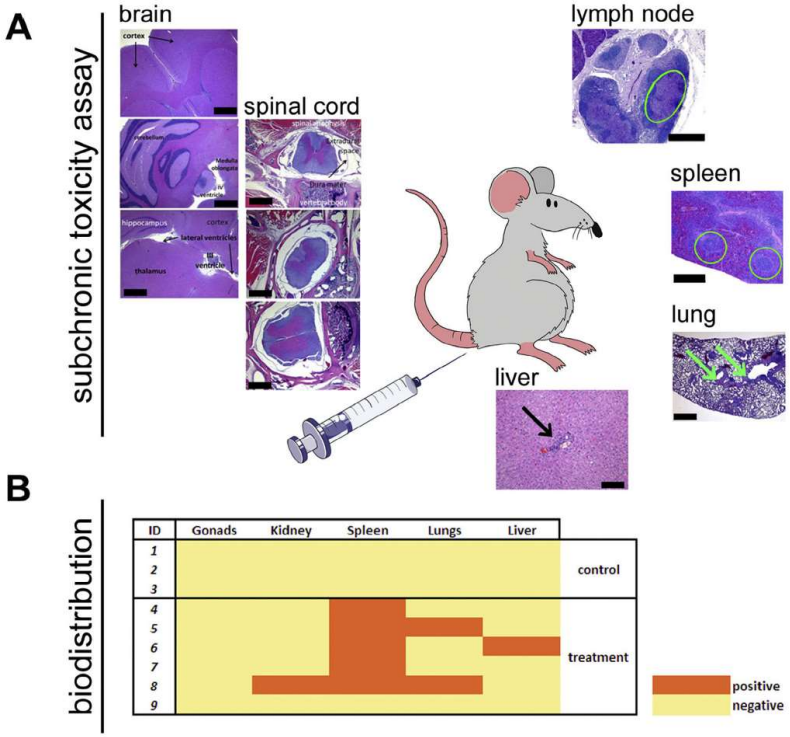


Figure 4. Assessment of subchronic toxicity and biodistribution of UC-MSCs in immunodeficient rats. Athymic rats were administered with 1×10^6 MSCs intravenously and culled at 3 months posttreatment. (A) Both the structure of the brain and spinal cord (analyzed at the cervical, thorax and lumbar levels) appeared normal in all animals. As expected in immunodeficient animals, the spleen of all animals presented T-cell depletion in the lymphoid follicles (highlighted with green circles) and the submandibular lymph node presented T-cell depletion (highlighted with a green circle) in the paracortical areas. Non–clinically relevant findings observed in other organs regardless of the experimental group included hyperplasia of BALT (bronchial associated lymphoid tissue) in the lungs with accumulation of lymphoplasmacytic cells and macrophages in the bronchovascular compartment (green arrows), mild hepatitis with presence of lymphoplasmacytic cells and macrophages in the portal area (black arrow). (B) Biodistribution analyses by semiquantitative PCR for the amplification of human *CART1* gene sequence evidenced persistence of UC-MSCs preferentially in the spleen, although presence of human genetic material was also detected in lungs, liver and kidney. Scale bars = 1000 μm, except for spleen (500 μm) and liver (100 μm).

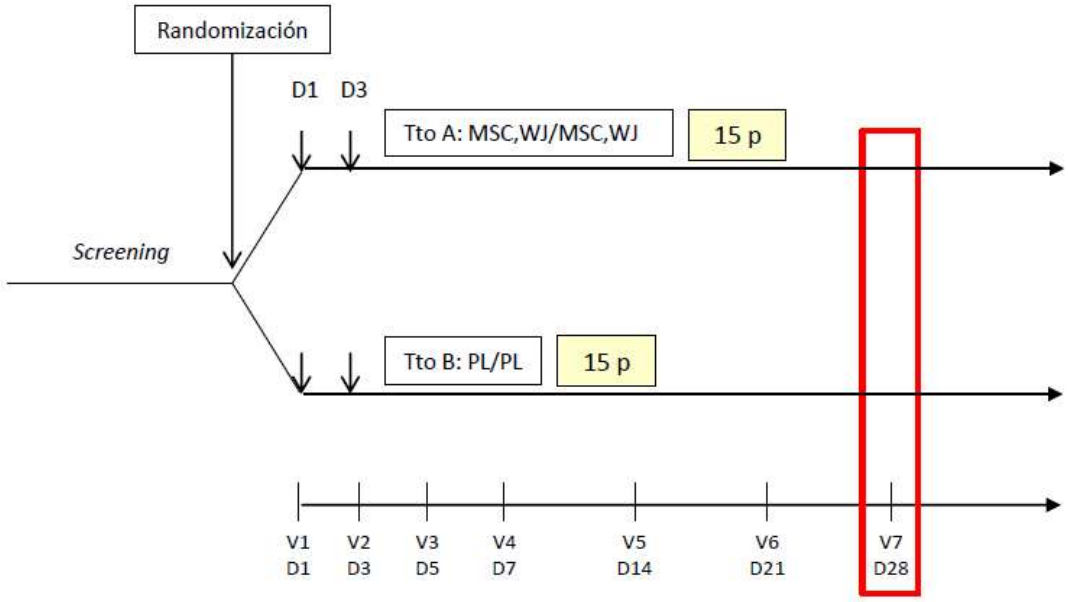
Oliver-Vila I, Cytotherapy. 2016 Jan;18(1):25-35.

Assaig COVIDMES

Banc de Sang i Teixits

Assaig clínic pilot prospectiu, doble cec, randomitzat, paral·lel i controlat amb placebo per a l'avaluació de la **seguretat i eficàcia de dues dosis de MSC, WJ** en pacients amb síndrome de distrés respiratori agut secundari a infecció per SARS-CoV-2

Esquema Estudio COVIDMES

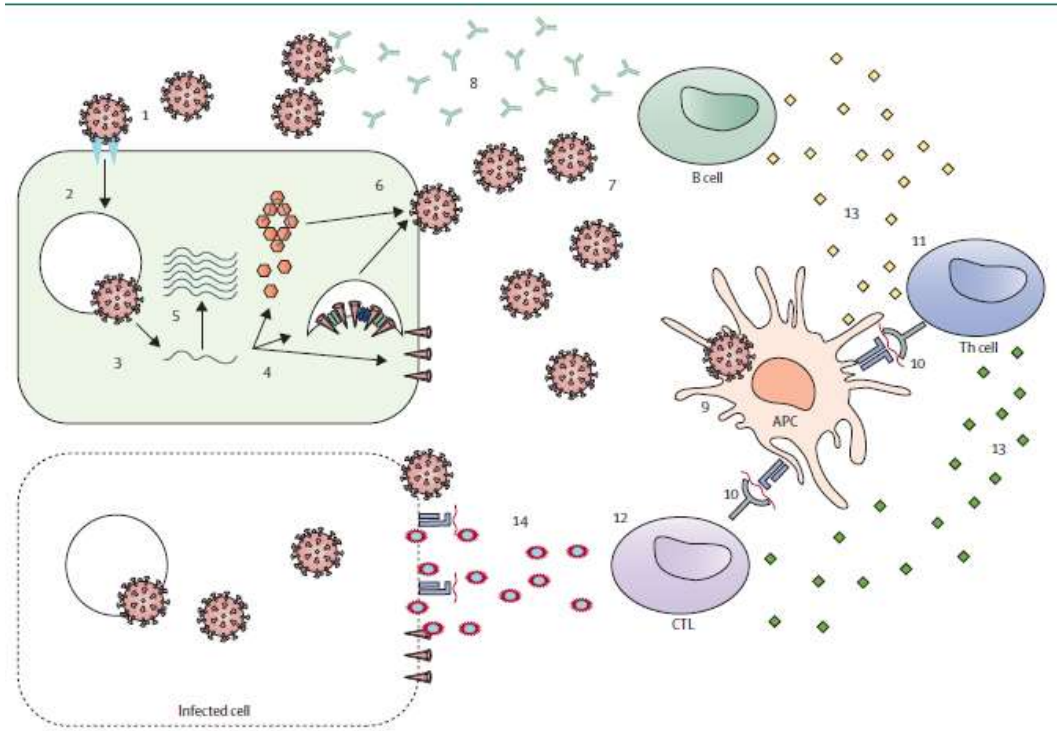


Reclutament a Març 2021

Centro hospitalario	IP	Fecha inicio reclutamiento	Pacientes incluidos
Hospital Clínic	Dr. P. Castro	13/05/2020	3
Hospital Bellvitge	Dr. R. Mañez	18/05/2020	-
Hospital del Mar	Dra. J. Marín-Corral	13/05/2020	9
Hospital Vall d'Hebron	Dr. R. Ferrer	12/06/2020	-
Mútua Terrassa	Dr. J. Trenado	21/05/2020	1
Moisès Broggi	Dr.R.Lafuente	03/02/2021	2
H. Sagrat Cor	Dr.L.Morales	28/01/2021	2
Cl. Sagrada Familia	Dra.P.Duran	pendiente	
TOTAL			17/30

Codi estudi: BST-COVID-01; EUDRACT: 2020-001505-22

Limfòcits i COVID19



- Profunda limfopènia T, resposta innata desregulada / excessiva (Fathi i Rezaei, 2020)
- Paper important de la immunitat adaptativa de les cèl·lules T en la protecció i l'eliminació del virus (Braun et al., 2020), amb respostes contra S, M, N (Grifoni et al., 2020)
- Models preclínics d'infecció per SARS-CoV-1, VST adoptius eren curatives en ratolins infectats

Poland GA, Ovsyannikova IG, Kennedy RB. SARS-CoV-2 immunity: review and applications to phase 3 vaccine candidates. Lancet. 2020 Nov 14;396(10262):1595-1606.

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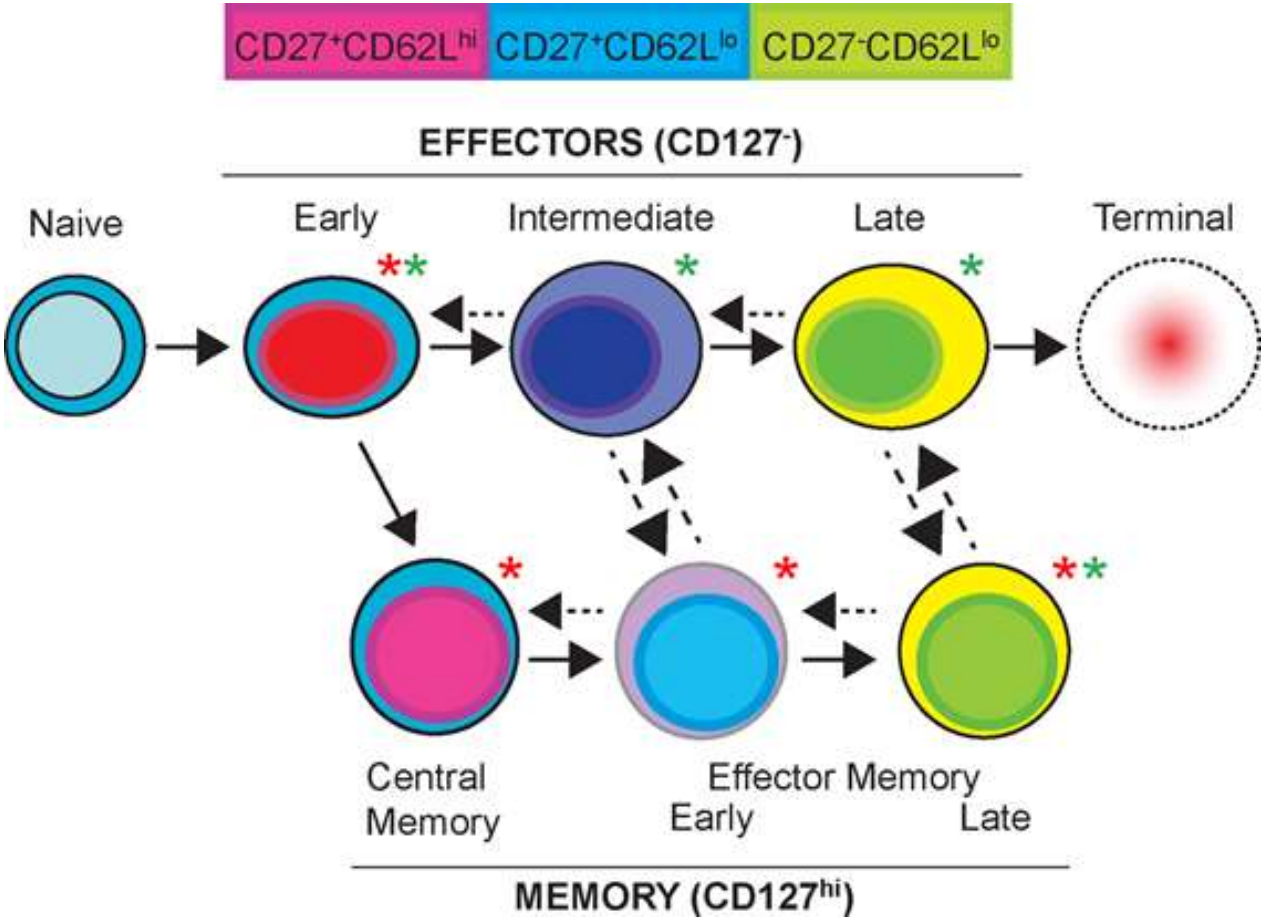
Accelerar el temps de resposta ex vivo



Generation of glucocorticoid resistant SARS-CoV-2 T-cells for adoptive cell therapy. bioRxiv 2020 Sep 15:2020.09.15.298547. Basar R et al, MD Anderson, Houston, USA

SARS-CoV-2 specific memory T lymphocytes from COVID-19 convalescent donors: identification, biobanking and large-scale production for Adoptive Cell Therapy. bioRxiv 2020 Oct 26. Ferreras C et al, Hospital La Paz, Madrid, Spain

ACT4COVID: Donants convalescents de cèl·lules

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REDOCEL

TCELBANC

EXPANSIÓ

SELECCIÓ DIRECTA

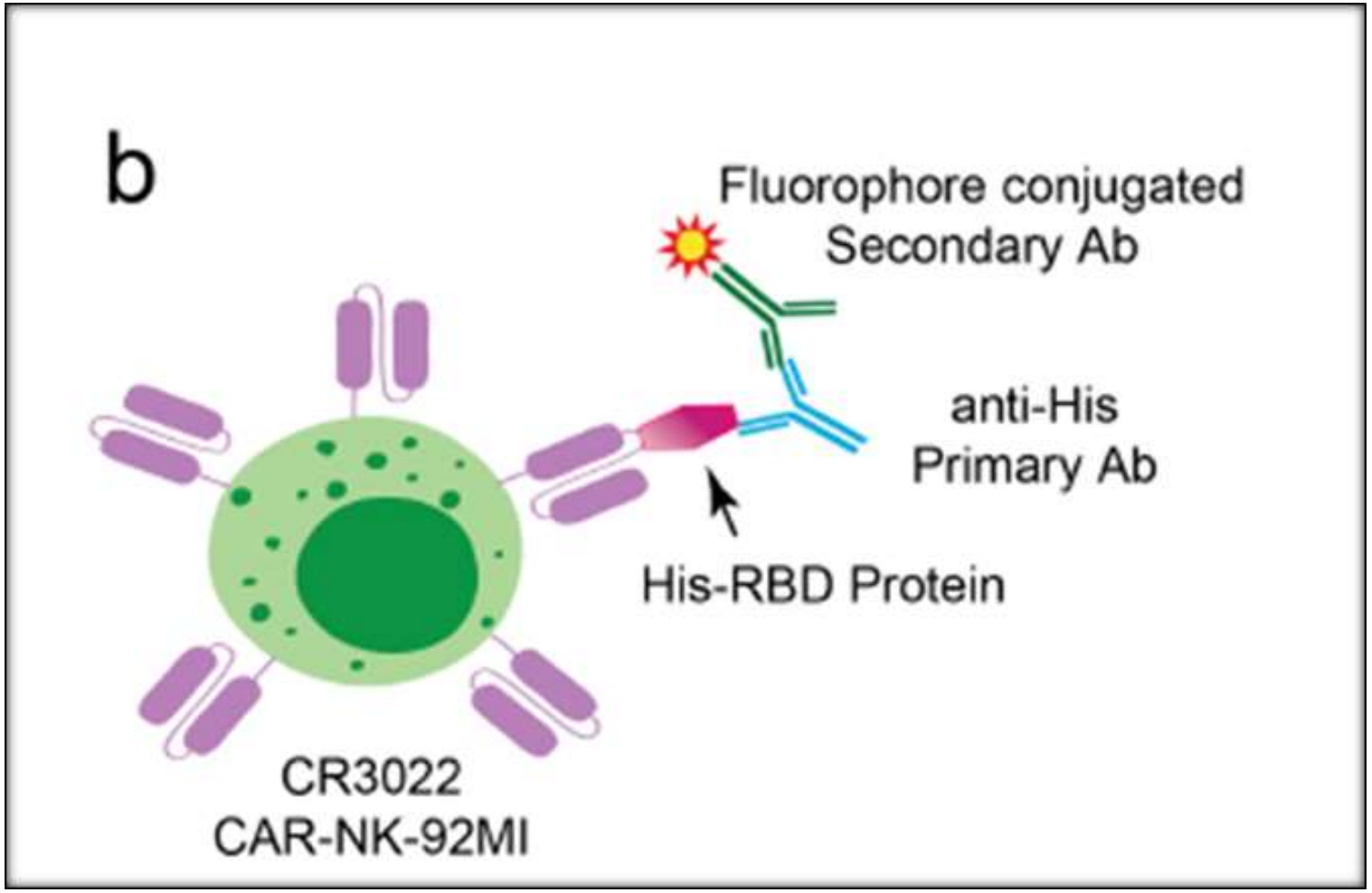
VIROTCEL

CLÍNIC BARCELONA Hospital Universitari

SARS-COV-2 CAR-NK CELLS

Banc de Sang i Teixits

CR3022-CAR-NK cells can specifically bind to RBD of SARS-CoV-2 and pseudotyped SARS-CoV-2 S protein



Ma M, Badeti S, Geng K, Liu D. Efficacy of Targeting SARS-CoV-2 by CAR-NK Cells. bioRxiv [Preprint]. 2020 Aug 12:2020.08.11.247320.

Sumari

Teràpies cel·lulars i avançades

- Afectació pulmonar i endotelial
- Dis-regulació immunitària
- Síndrome del distrés respiratori agut
- Finestra d'oportunitats
- Teràpies immunològiques
  - Fàrmacs
  - Anticossos
  - Cèl·lules
- Model per a altres malalties

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