Traitement par cellules stromales mésenchymateuses dans le syndrome de détresse respiratoire aiguë associé au SARS-CoV-2

Pr Antoine Monsel (Paris)

Conflits d'intérêt

Base Transparence Santé

Accueil • Recherche par bénéficiaire • Résultats •

Résultats des déclarations par bénéficiaire

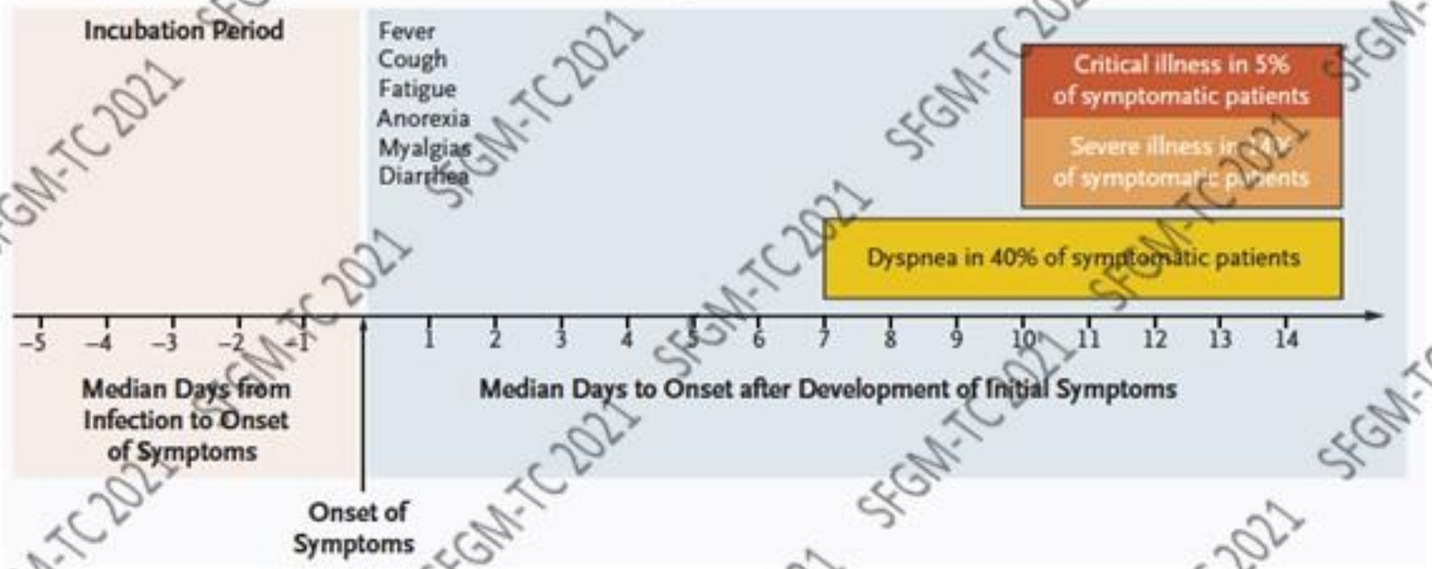
Afficher les Avantages | Afficher les Conventions | Afficher les Rémunérations

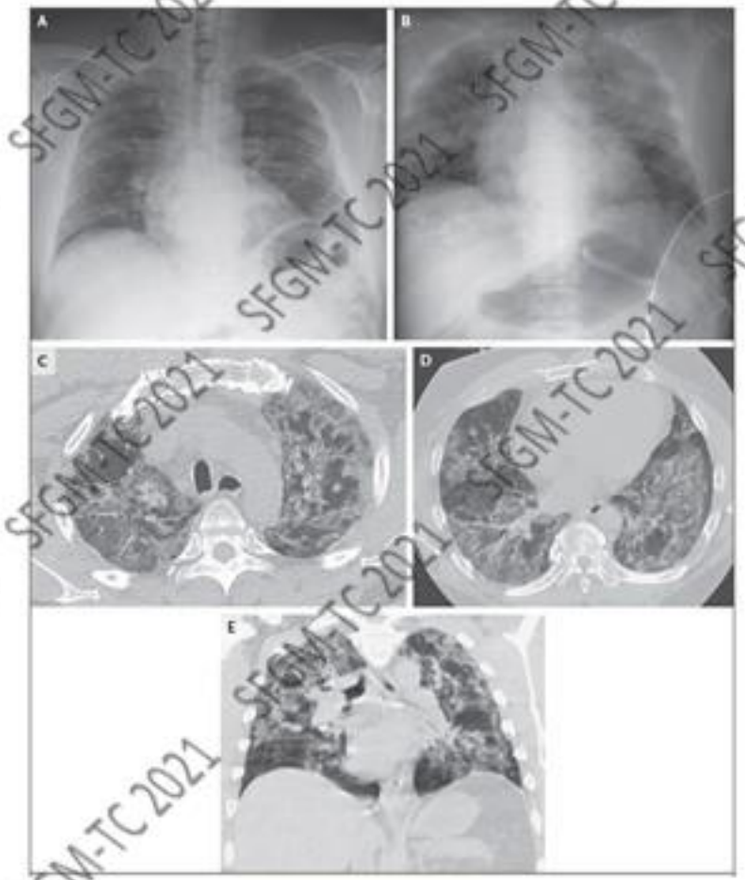
4 Avantage(s) correspondant à votre sélection

Bénéficiaire	Type de bénéficiaires	Entreprise	Date	Nature	Montant	
MONSEL ANTOINE	Médecin	GILEAD SCIENCES	13/04/2016	REPAS	25 €	Détail
MONSEL ANTOINE	Médecin	MSD France	13/01/2016	INSCRIPTION	390 €	Détail
MONSEL ANTOINE	Médecin	FRESENIUS KABI FRANCE	24/01/2018	Inscription	630 €	Détail
MONSEL ANTOINE	Médecin	FRESENIUS KABI FRANCE	24/01/2018	Inscription	630 €	Détail

Pandémie COVID-19 et SDRA associé

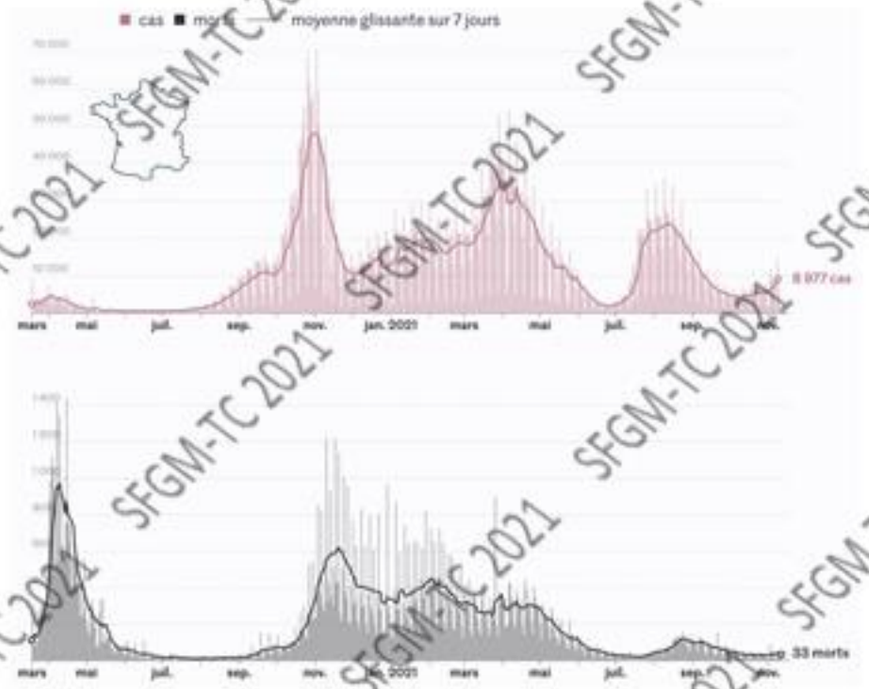
- *Monde*: 253 millions de personnes touchés – **5,1 millions de morts**
- *France*: 7,3 Millions de cas confirmés – **120 000 morts**
- COVID-19: 5-10% de cas critiques
- **SDRA dans 60-70% des cas**
- **Mortalité 25-40%**





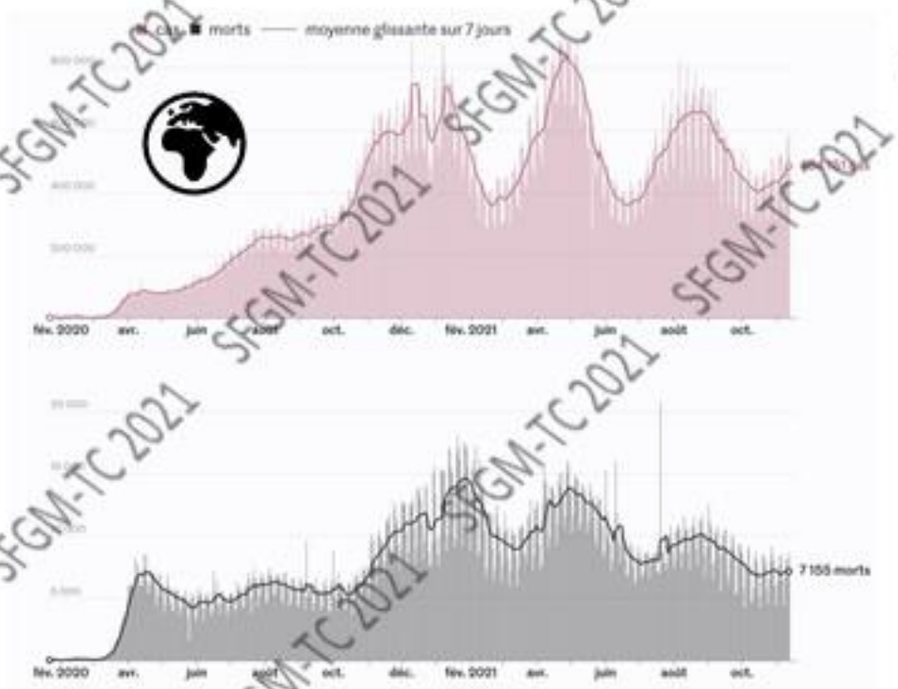
Pandémie COVID-19 et SDRA associé

- Vaccins: épuisement de la réponse et variants
- Corticoïdes / Anticorps monoclonaux / Anti-IL6 R
- **Support ventilatoire et « réanimation d'organes »**

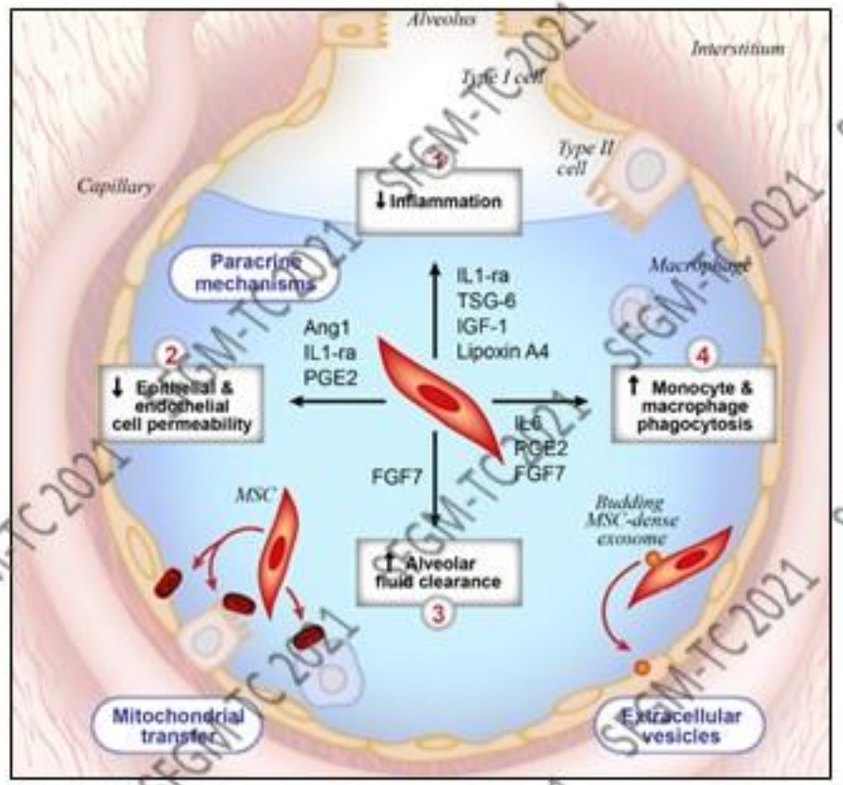


cas

décès

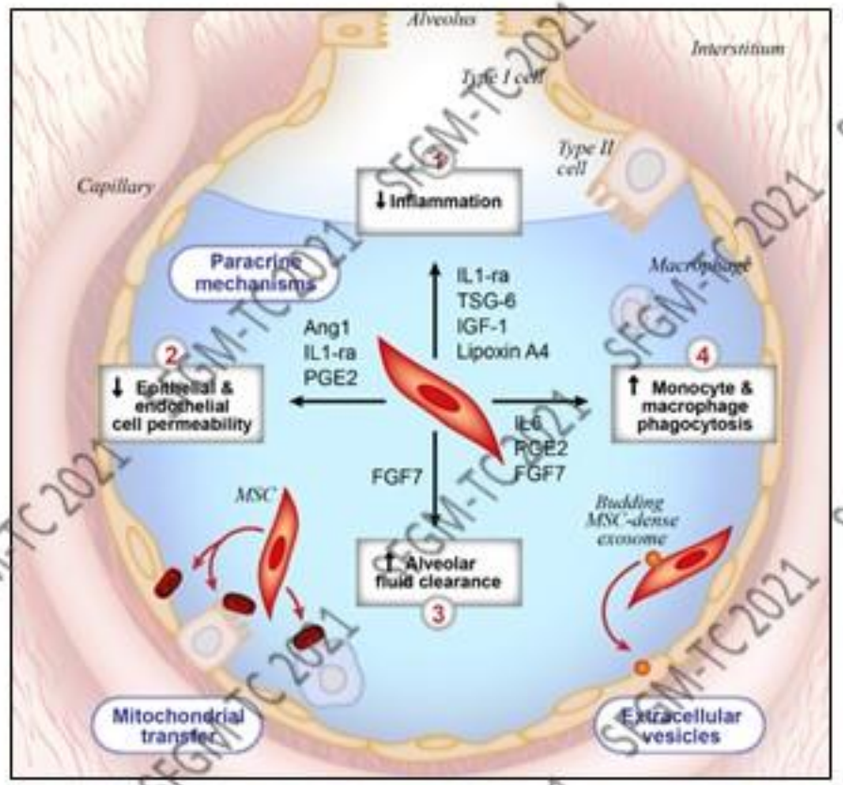


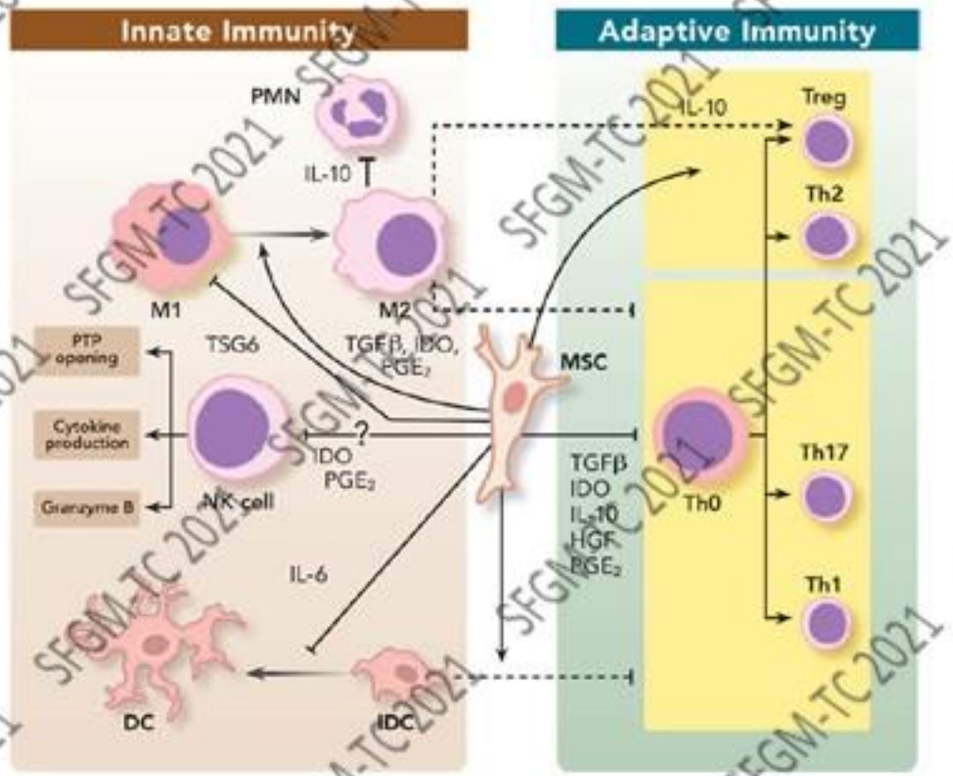
Rationnel des CSM dans le SDRA



Huppert et al. *Semin Resp Crit Care*, 2019

Rationnel des CSM dans le SDRA





Monsel et al. *Anesthesiology*, 2014

CSM: études publiées dans le SDRA

- **7 études publiées** dans le SDRA en réanimation: **160 patients**
- **Dont 4 études publiées de phase I / IIa** dans le SDRA en réanimation

Years	Author	Country	Phase	Indications	MSCs source	MSC dose per kg	Frequency	Route of delivery	Total enrolments (patents=n)	Mortality MSCs (death/n)	Mortality in control (death/n)	Outcome
2014	Guoping Zheng	China	Controlled trial	Pneumonia, aspiration	Allogeneic AD-MSCs	1×10^6 cells/kg	A single-dose	Intravenous	25(12)	6(0)	6(0)	Safety
2014	Youjin Chang	South Korea	Case report	Pneumonia	UCB-MSCs	1×10^6 cells/kg	A single-dose	Intravenous	1(1)	1(1)	N/A	With risk
2015	Jennifer G Wilson	USA	Phase 1	Pneumonia, aspiration	Allogeneic BM-MSCs	1、5 and 10 × 10^6 cells/kg	A single-dose	Intravenous	9(9)	9(0)	N/A	Safety
2015	Oscar E Simonson	Sweden	Case series	Infection	Allogeneic BM-MSCs	2×10^6 cells/kg	N/A	Intravenous	2(2)	2(0)	N/A	Potential safety
2019	Michael A Matthay	USA	Phase 2a	Pneumonia, aspiration	Allogeneic BM-MSCs	10×10^6 cells/kg	A single-dose	Intravenous	1038(60)	40(1)	20(0)	Safety
2020	Hon-Kan Yip	Taiwan	Phase 1	Pneumonia	UC-MSCs	1、5 and 10 × 10^6 cells/kg	A single-dose	Intravenous	9(9)	9(3)	N/A	Safety
2020	Jiajia Chen	China	N/A	H7N9	Allogeneic MB-MSCs	1×10^6 cells/kg	Multiple infusion	Intravenous	61(61)	17(3)	44(24)	Safety

Matthay et al. *Lancet Respir Med*, 2018
Wilson et al. *Lancet Respir Med*, 2015
Zheng et al. *Respir Res*, 2014

CSM: études publiées dans le SDRA

- **7 études publiées** dans le SDRA en réanimation: **160 patients**
- **Dont 4 études publiées de phase I / IIa** dans le SDRA en réanimation
  - Bonne tolérance clinique (>100 patients)

- **Bonne tolérance clinique** chez le patients de réanimation en SDRA
- **Impact sur quelques biomarqueurs** de l'inflammation

Matthay et al. *Lancet Respir Med*, 2018
Wilson et al. *Lancet Respir Med*, 2015
Zheng et al. *Respir Res*, 2014

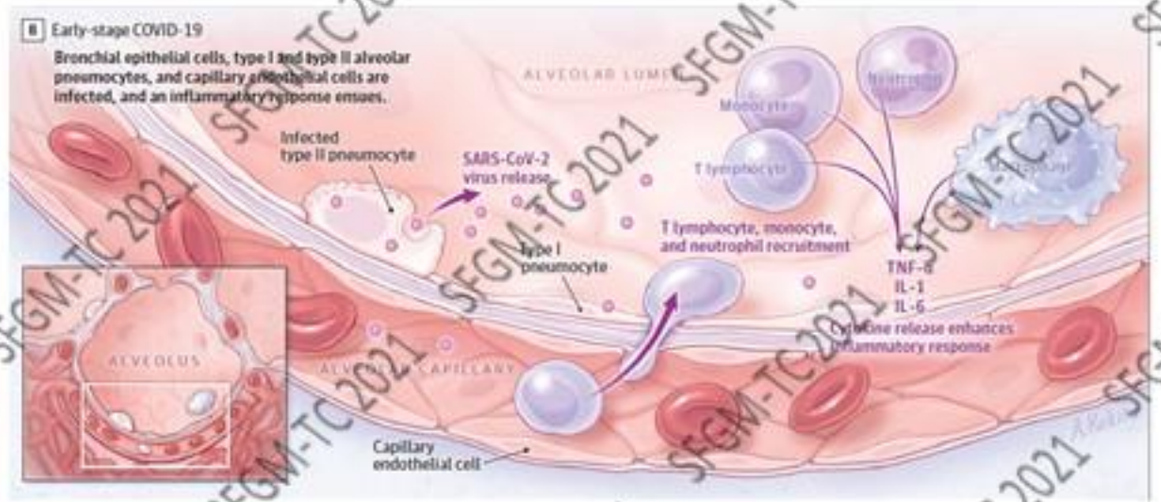
Rationnel des CSM dans le SDRA SARS-CoV-2

COVID-19: consider cytokine storm syndromes and immunosuppression

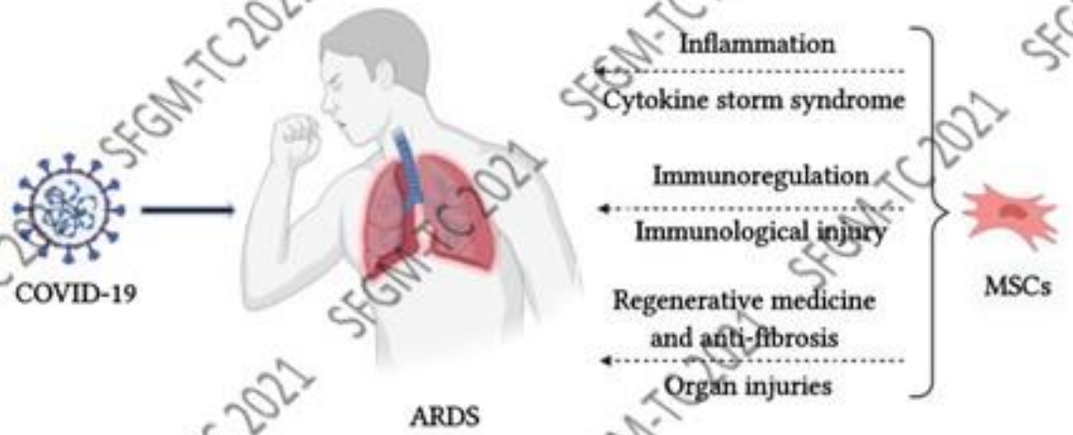
*Puja Mehta, Daniel F McAuley, Michael Brown, Emilie Sanchez, Rachel S Tattersall, *Jessica J Manson, on behalf of the HLH Across Speciality Collaboration, UK*
Jessica.manson@nhs.net

Mehta et al. *Lancet*, 2020

Capacités immunomodulatrices des cellules stromales mésenchymateuses (CSM)



Wiersinga et al. *JAMA*, 2020



Raza et al. *Cytotherapy*, 2020

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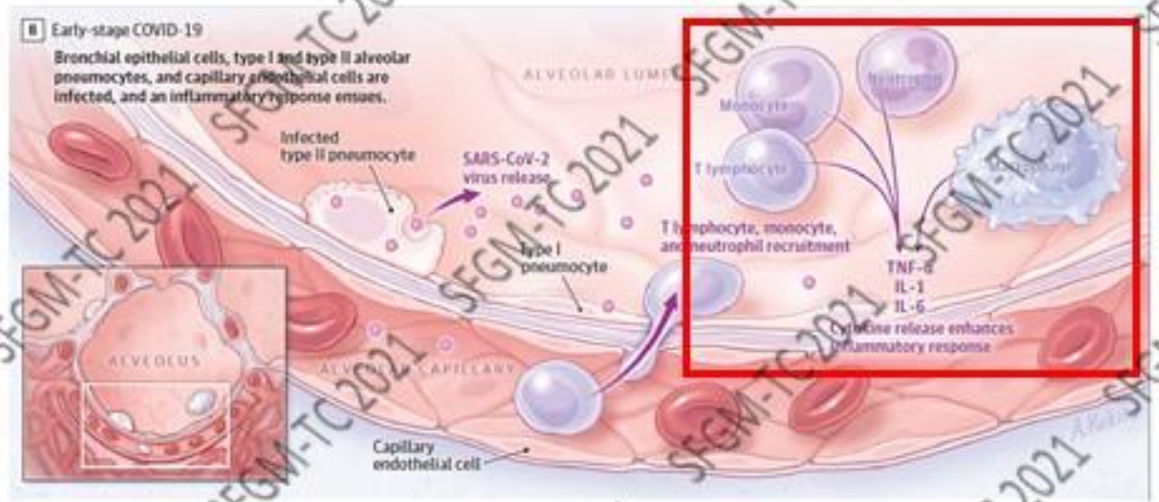
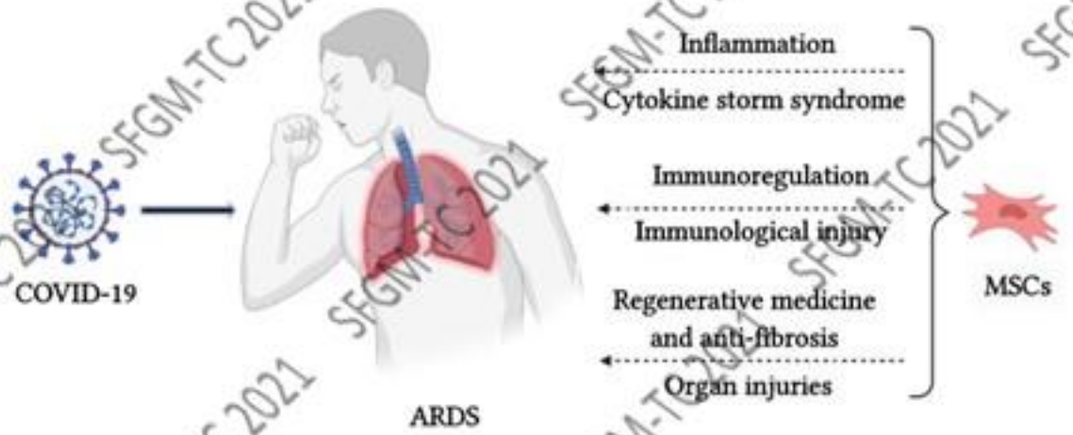


Wiersinga et al. *JAMA*, 2020



Raza et al. *Cytotherapy*, 2020

CSM dans le SDRA SARS-CoV-2

- **7 études (non RCT)** publiées dans le SDRA SARS-CoV-2
  - > 100 patients
  - Étude de Guo et al. (Crit Care 2020) N = 32
  - Bonne tolérance clinique

2020	Lei Shu	China	Controlled trial	COVID-19	UC-MSCs	2×10^6 cells/kg	A single-dose	Intravenous	47(41)	12(0)	29(3)	Safety	42
2020	Lingling Tang	China	Controlled trial	COVID-19	Allogeneic, MB-MSCs	N/A	Multiple infusion	Intravenous	2(2)	2(0)	N/A	Safety	43
2020	Yingxin Zhang	China	Case report	COVID-19	UCWJ-MSCs	1×10^6 cells/kg	N/A	Intravenous	1(1)	1(0)	N/A	Safety	44
2020	Bing Liang	China	Case report	COVID-19	UC-MSCs	5×10^7 cells	3 times	Intravenous	1(1)	1(0)	N/A	Safety	45
2020	Leng Z	China	Controlled trial	COVID-19	N/A	1×10^6 cells/kg	A single-dose	Intravenous	10(10)	7(0)	3(0)	Safety	27
2020	Fan ping Meng	China	Phase 1	COVID-19	UC-MSCs	3×10^7 cells	3 times	Intravenous	18(18)	9(0)	9(0)	Safety and well tolerated	46

CSM dans le SDRA SARS-CoV-2

- **7 études (non RCT)** publiées dans le SDRA SARS-CoV-2
  - > 100 patients
  - Étude de Guo et al. (Crit Care 2020) N = 32
  - Bonne tolérance clinique

- **2 RCT publiées (UC-MSC)**
  - Mortalité élevée (50%-60%)
  - Sévérité des patients
  - Timing: phase tardive ou inconnue
  - Pas de biomarqueurs
  - Caractérisation du MTI

Lanzoni et al. *Stem Cell Transl Med*, 2021
Dilogo et al. *Stem Cell Transl Med*, 2021

Essai STROMA-CoV-2

- Essai clinique randomisé contrôlé en double aveugle
  - Phase IIb
  - DGOS/ANR
  - 10 centres

- Inclusion
  - > 18 ans
  - PCR COVID+
  - SDRA (Berlin) dans les 96 premières heures (phase hyper-inflammatoire)
  - N= 21 traités (CSM) versus 21 placébo
  - Délai d'inclusion: 3 mois
  - Délai de suivi: 1 an

1.10^6 UC-MSC/kg (max = 80.10^6) J1 – J3±1 – J5±1
voie intraveineuse

Essai STROMA-CoV-2

- Essai clinique randomisé contrôlé en double aveugle
  - Phase IIb
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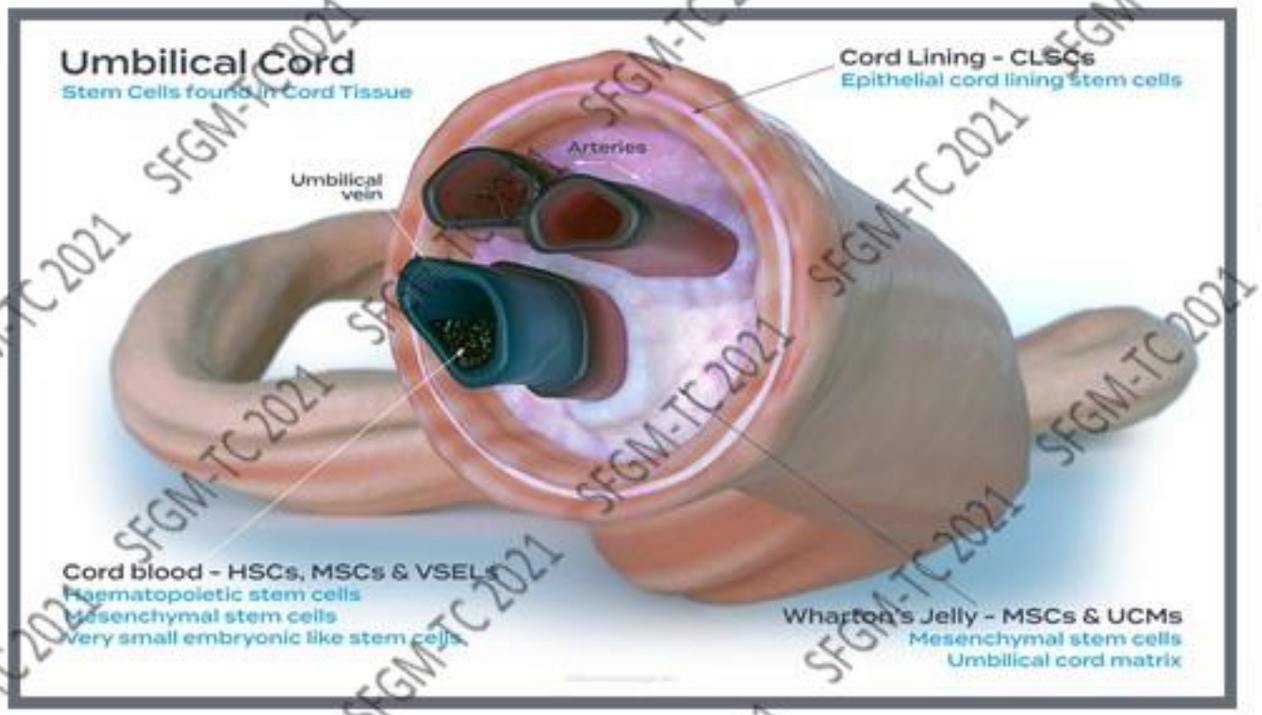
Critère de jugement I^aire^:
Variation PaO_2/FiO_2 entre J0 et J7

Essai STROMA-CoV-2

Cellules stromales mésenchymateuses issues de cordon ombilical (CSM-CO)

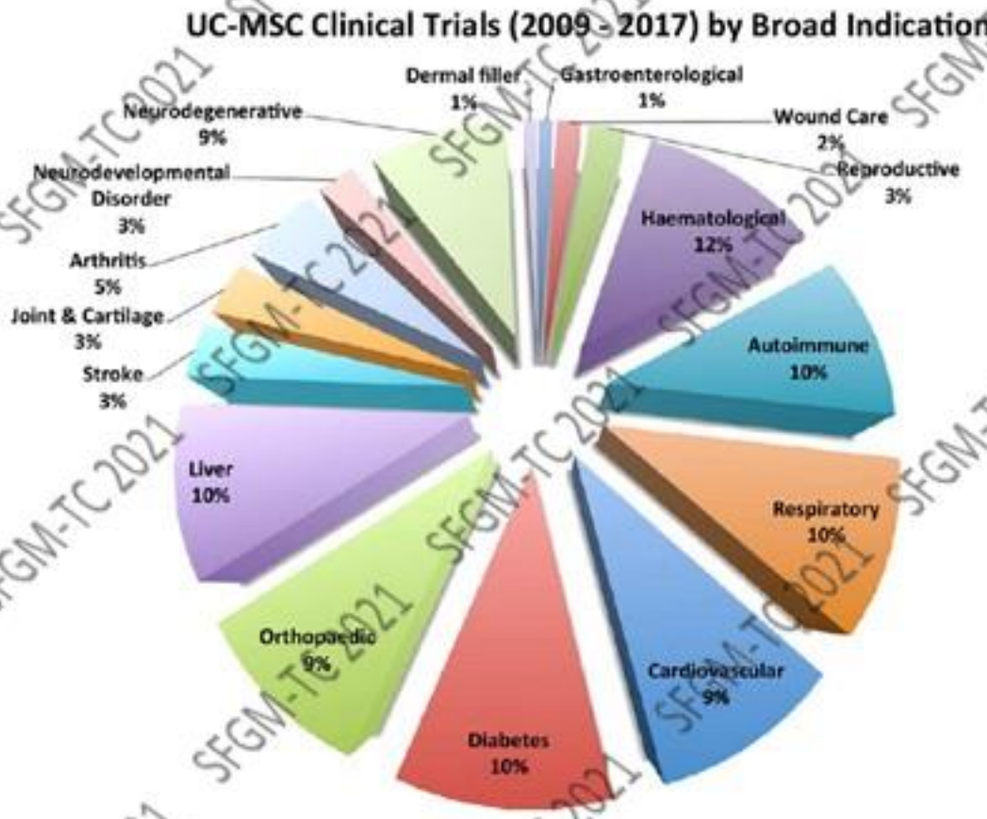


Essai STROMA-CoV-2

Cellules stromales mésenchymateuses issues de cordon ombilical (CSM-CO)

- Avantages des CSM issues de cordon
  - Bioactivité supérieure
  - Absence d'immunogénicité
  - Fort potentiel de prolifération en culture
  - Risque néoplasique minimal
  - Pas de problématique éthique
  - Accessibilité des cellules +++

- Sécurité



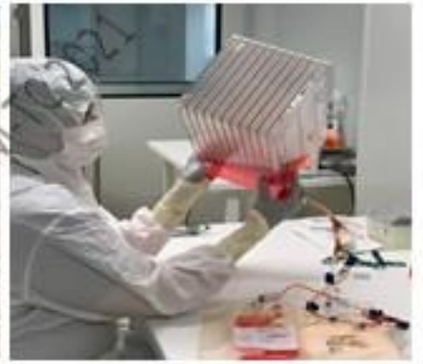
Davies et al. *Stem Cells Transl Med* 2017

Faisabilité en Mars 2020: plateforme MEARY

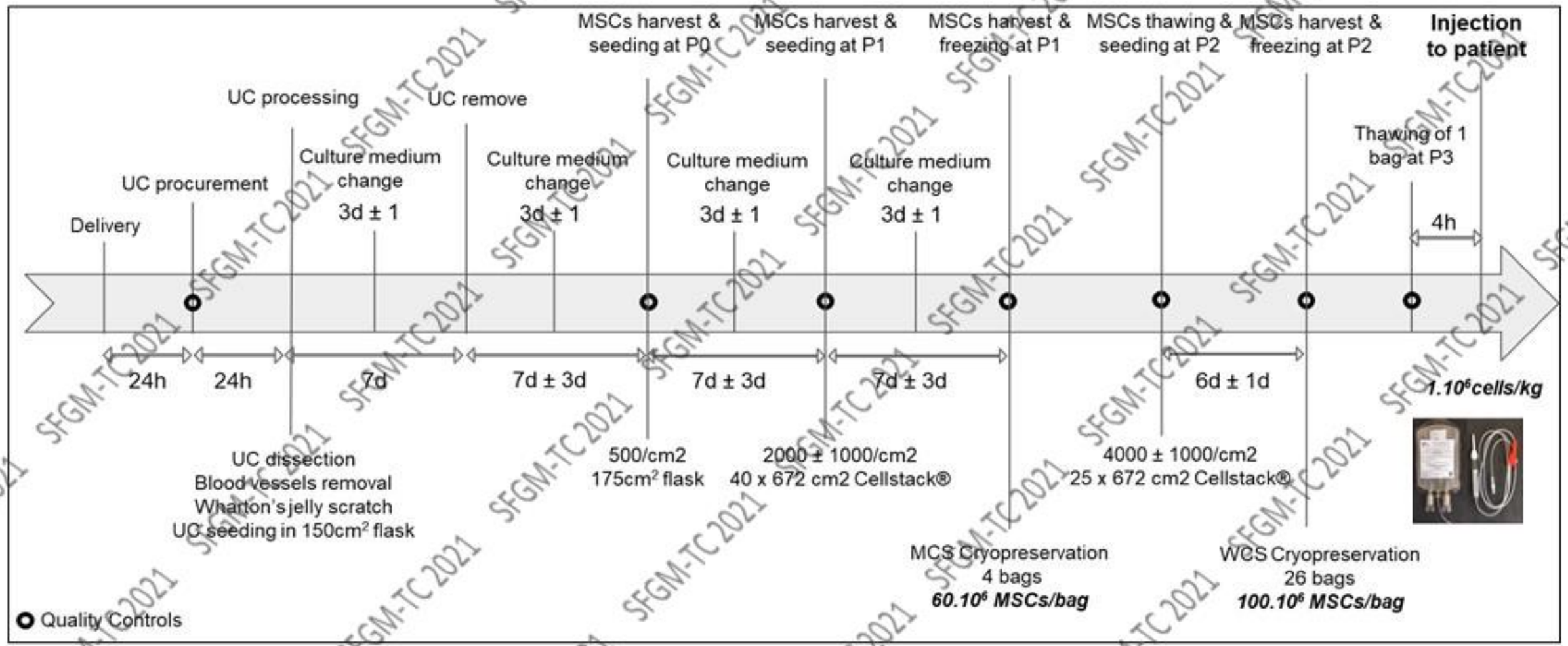
- Production selon les conditions GxP
  - GMP: good **manufacturing** practice
  - GCP: good **clinical** practice
  - GLP: good **laboratory** practice
  - GSP: good **storage** practice
  - GDP: good **distribution** practice
  - GRP: good **review** practice

- CSM issues de cordon
  - en cours d'essai

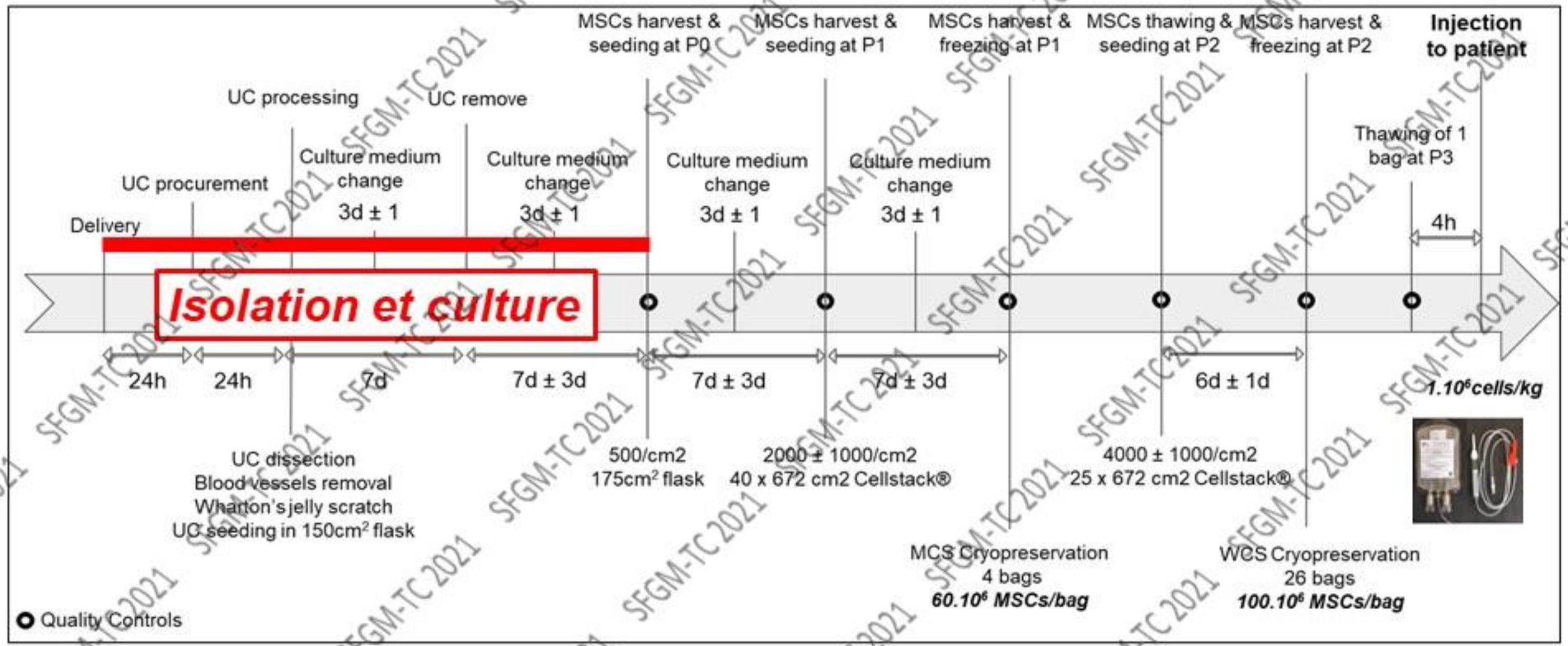
MEARY CENTER
Medical Engineering and Research in cell & gene therapy



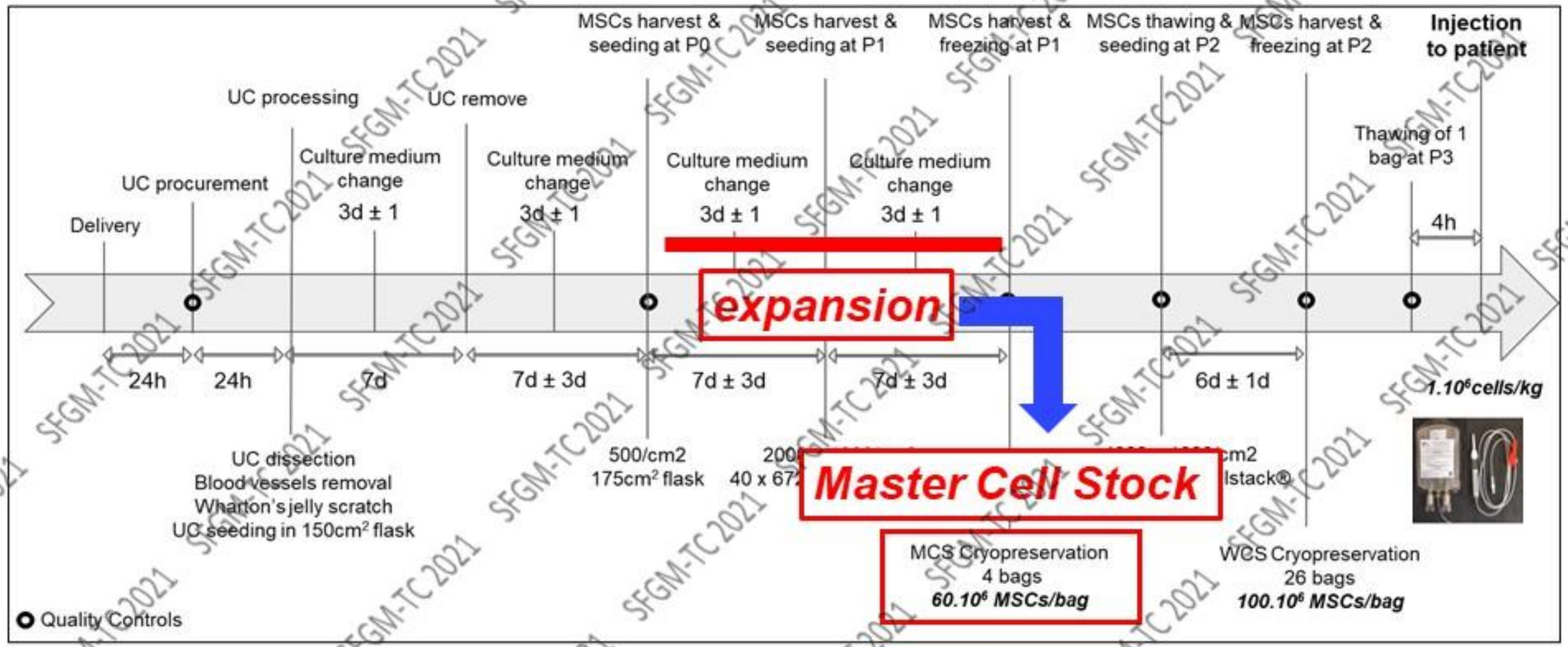
Faisabilité en Mars 2020: plateforme MEARY



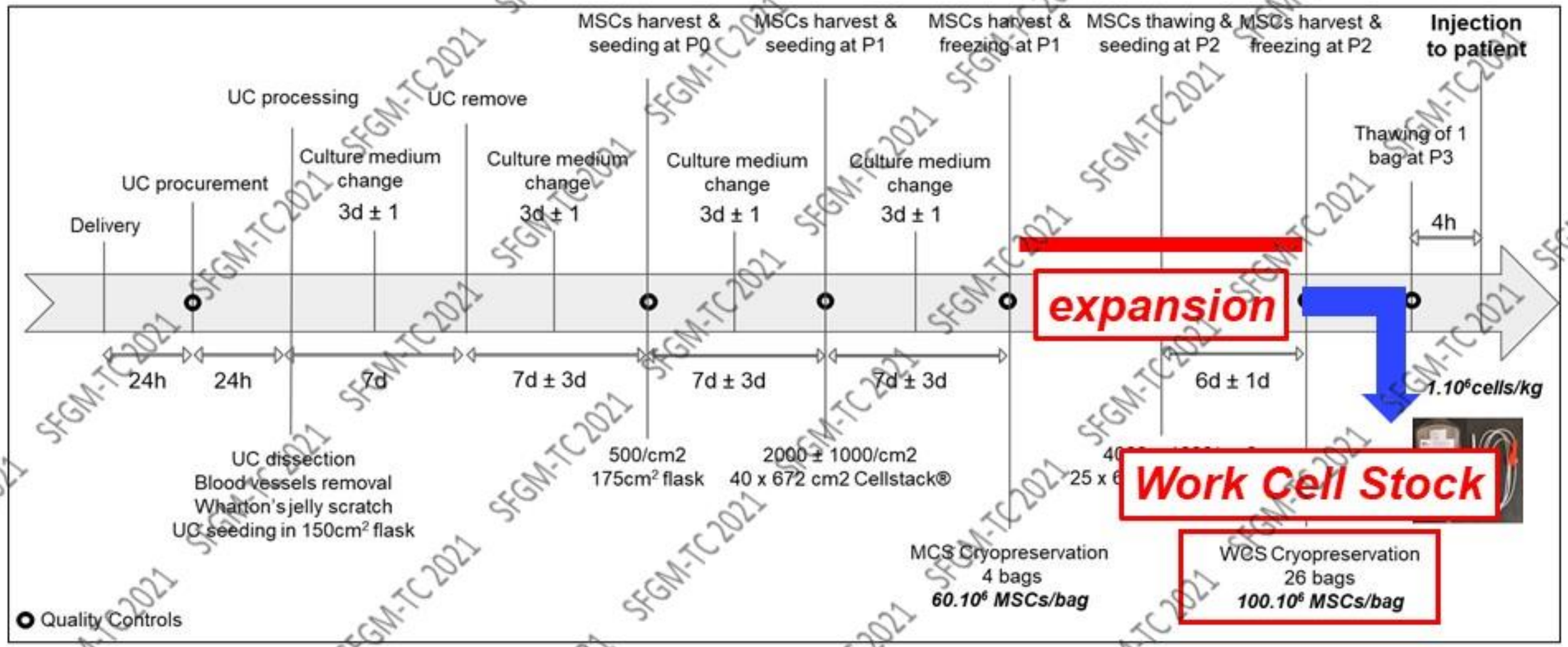
Faisabilité en Mars 2020: plateforme MEARY



Faisabilité en Mars 2020: plateforme MEARY

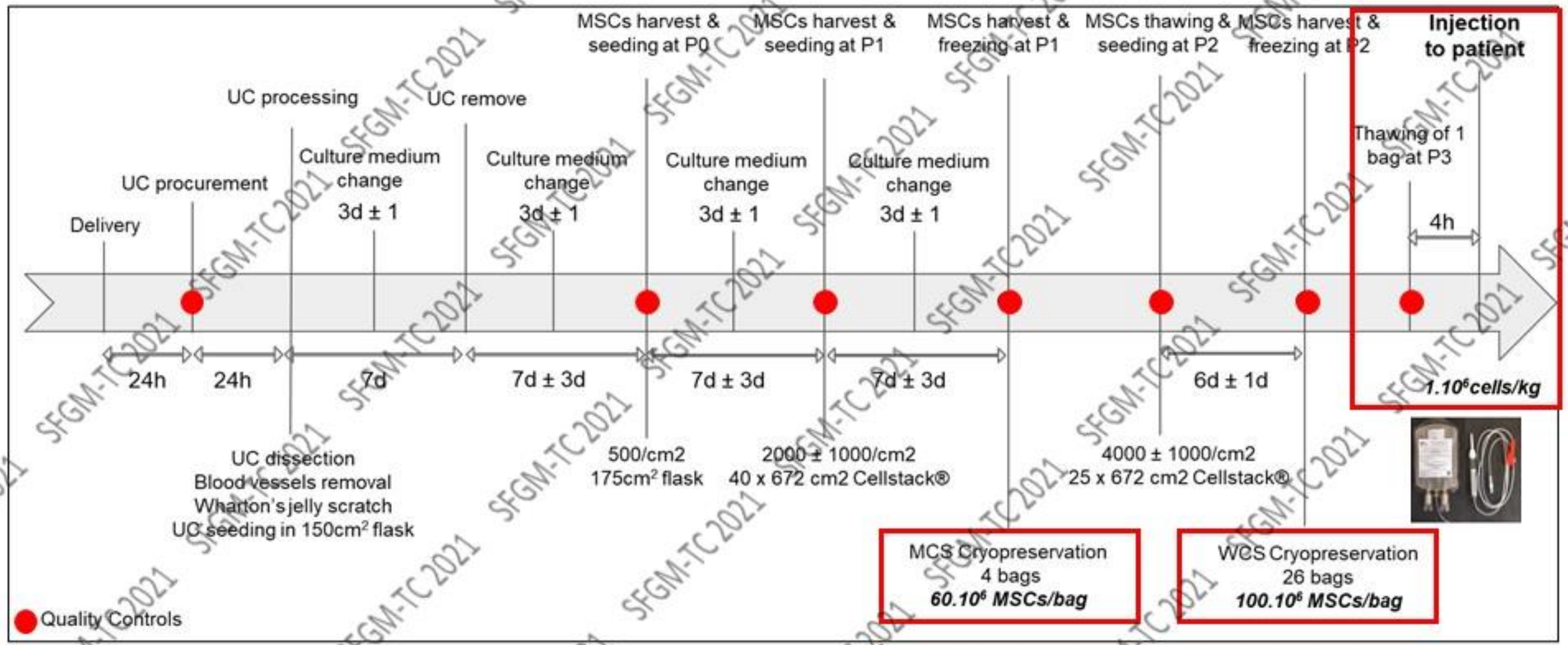


Faisabilité en Mars 2020: plateforme MEARY

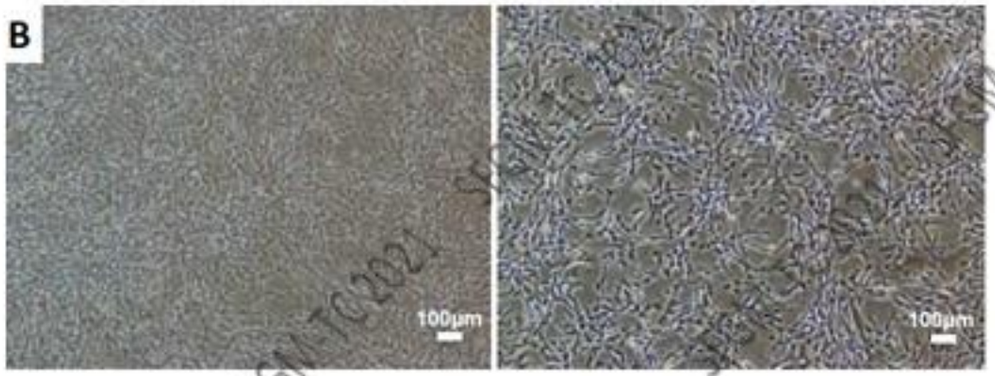


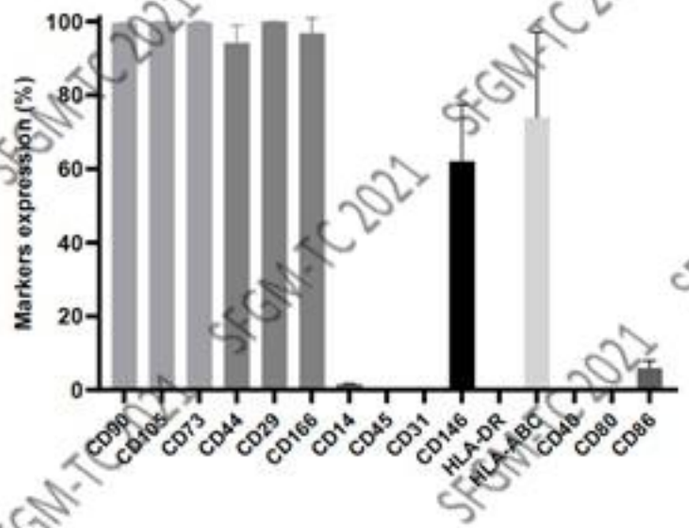
Mebarki et al. *Stem Cell Res Ther*, 2021

Faisabilité en Mars 2020: plateforme MEARY



Caractérisation du MTI



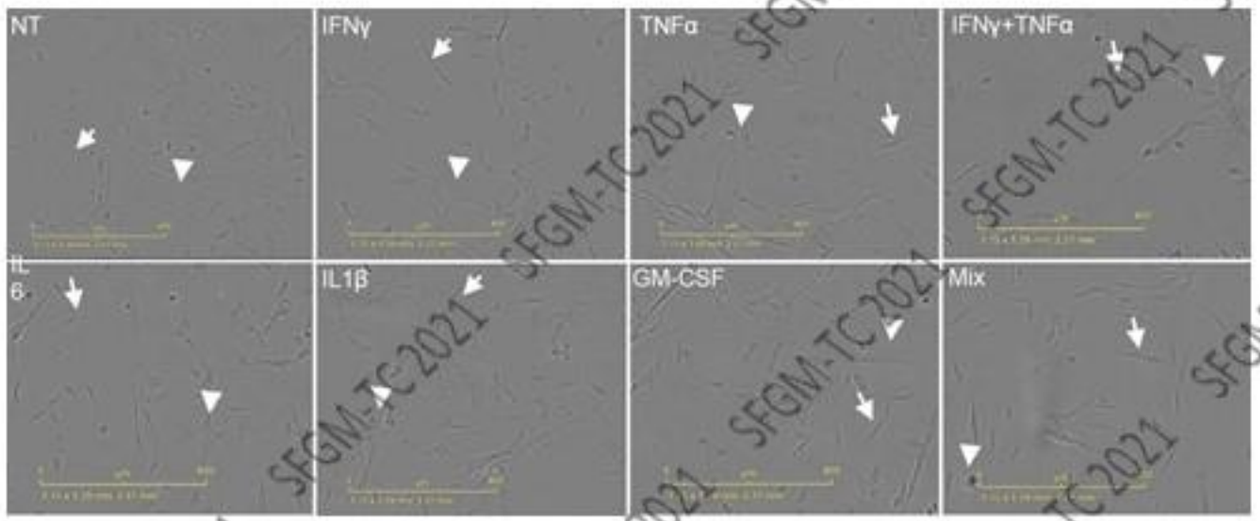


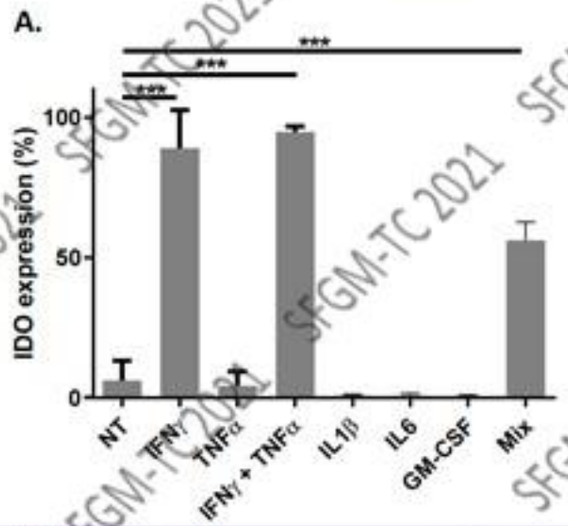
- Contrôles qualité
- Caractérisation
- Sécurisation
- « Potency assay »

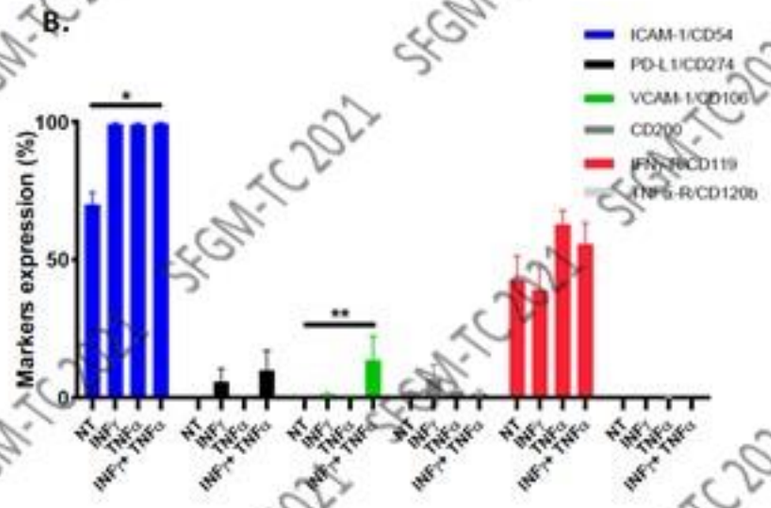
Quality controls	Results		Specifications
	MCS	WCS	
Viability (%)	94.0 ± 4.2	90.3 ± 2.1	≥ 80
CD90 (%)	99.5 ± 0.0	99.8 ± 0.2	≥ 90
CD73 (%)	99.9 ± 0.1	99.9 ± 0.0	≥ 90
CD105 (%)	96.8 ± 1.6	98.4 ± 1.6	≥ 90
CD45/CD34/CD11b/CD19/HLA-DR (%)	0.4 ± 0.1	0.9 ± 0.5	≤ 2
CFU-F (%)	> 1	> 1	> 1
MLR (AUC)	NA	0.15 ± 0.01	NA
Microbiology	Negative		Negative
Endotoxins	< 2 EU/mL		< 2 EU/mL
Mycoplasmas	< 10 UFC/mL		< 10 UFC/mL
Karyotype	46 XY		46 XY or XX

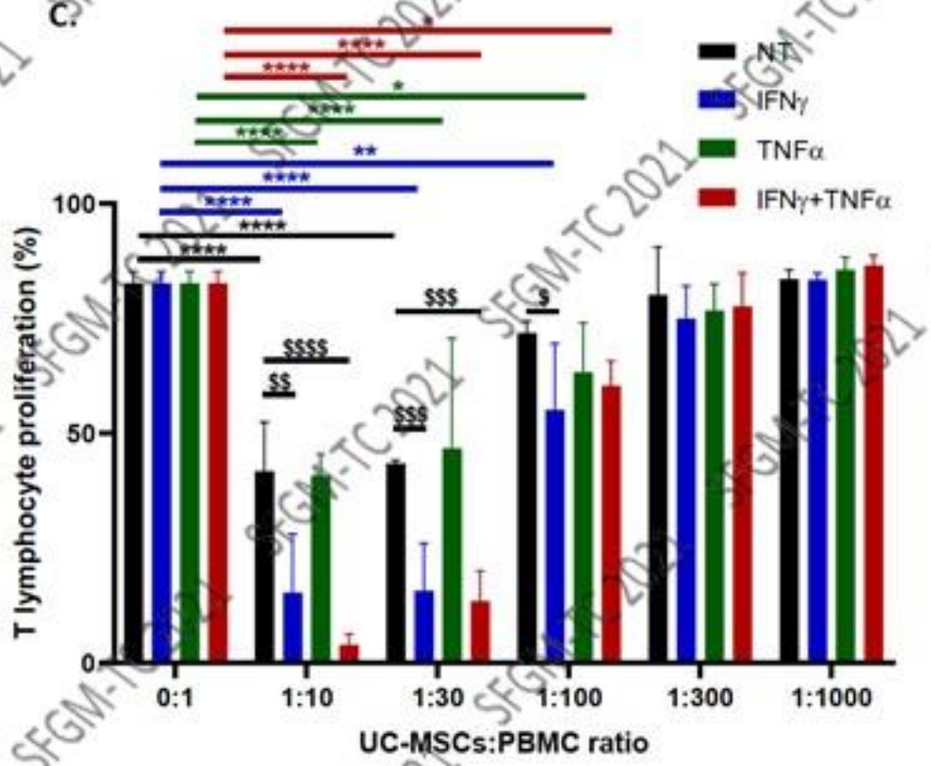
Mebarki et al. *Stem Cell Res Ther*, 2021

Caractérisation du MTI



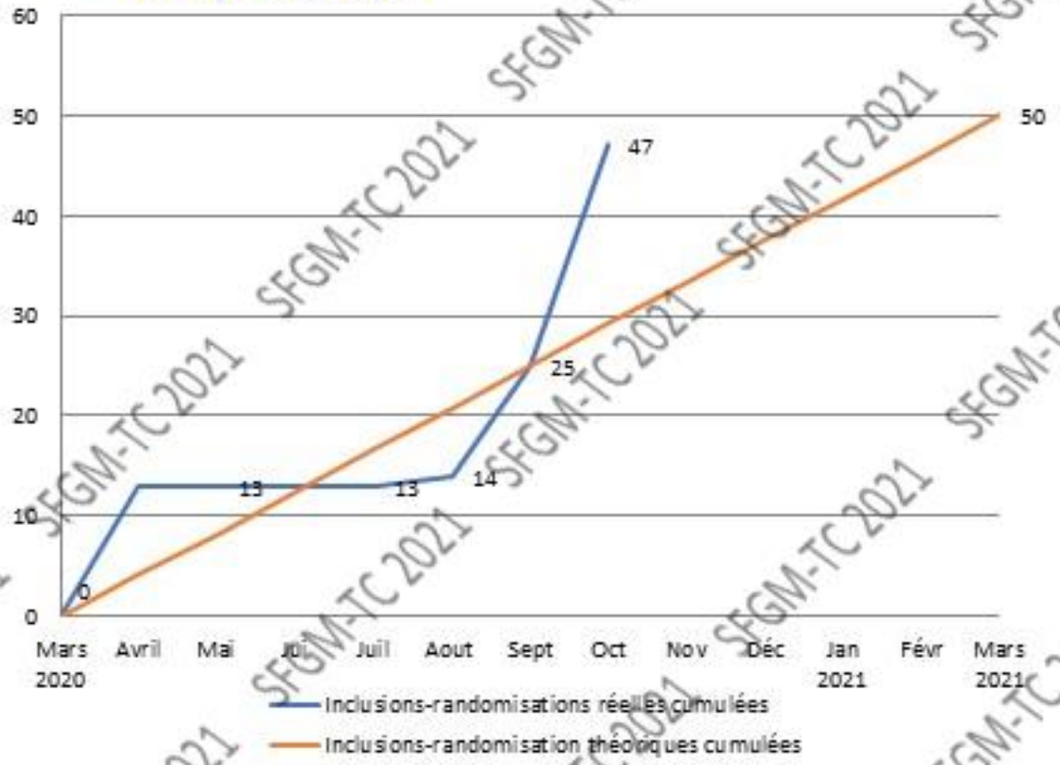


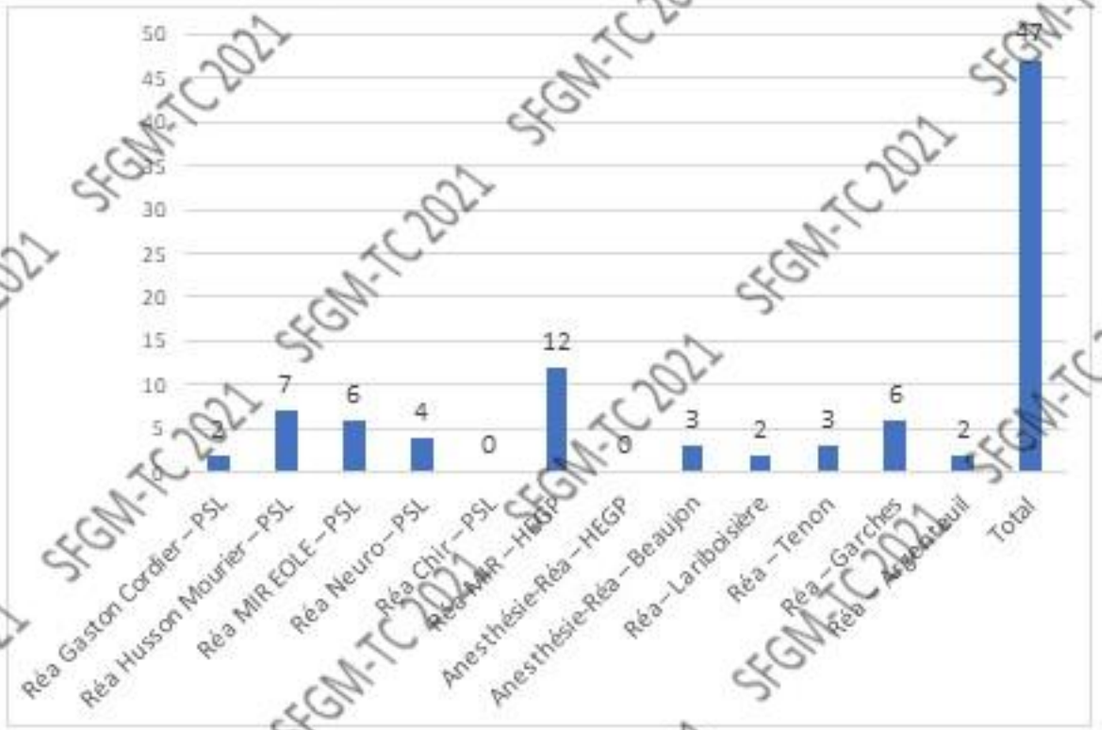




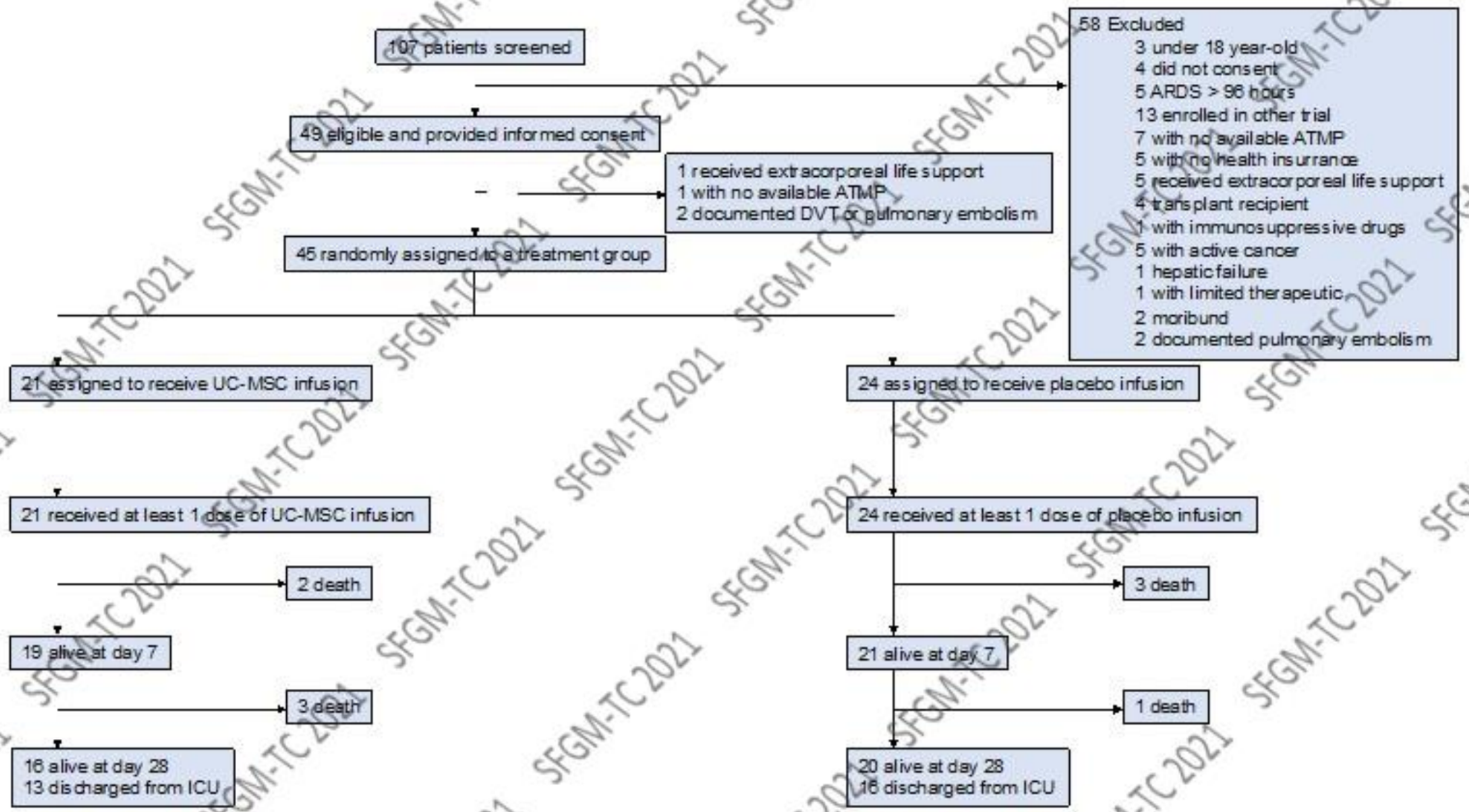
2 vagues d'inclusion

- 2 vagues d'inclusions: Avril et Septembre
- 10 centres inclueurs
- 49 patients





Flow chart



Démographie

Table 1. Baseline characteristics.

Patients'characteristics	UC-MSC n = 21	placebo n = 24
Age (years)	64 (10.4)	63.2 (11.4)
Male sex	17 (81%)	20 (83.3%)
Body mass index	28.6 (3.5)	28 (5.5)
Obesity	7 (33.3%)	6 (25%)
Sepsis-related Organ Failure Assessment score	5.5 (2.7)	5.9 (2.7)
Mean arterial pressure (mmHg)	91.3 (18.3)	81.5 (16.9)
Vasopressors at the time of inclusion	5 (23.8%)	14 (58.3%)
Comorbidities		
Chronic obstructive pulmonary disease	0 (0%)	1 (6.7%)
Active smoking	0 (0%)	0 (0%)
Chronic heart failure	0 (0%)	0 (0%)
Atrial fibrillation	2 (13.3%)	0 (0%)
Hypertension	11 (73.3%)	10 (66.7%)
Coronary artery disease	2 (13.3%)	2 (13.3%)
Stroke	2 (13.3%)	1 (6.7%)
Chronic obstructive pulmonary disease	20 (35%)	18 (35%)
Immunodeficiency	0 (0%)	0 (0%)
Active neoplasia	0 (0%)	0 (0%)
Corticosteroids (chronic intake)	0 (0%)	0 (0%)
Immunomodulatory drugs	2 (11.7%)	0 (0%)

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Démographie

Respiratory characteristics	UC-MSC	placebo
Ventilatory support (NIV and/or HFNO)	10 (31.2%)	4 (12.5%)
Invasive mechanical ventilation	11 (52.4%)	20 (83.3%)
Tidal volume (mL/kg PBW)	6.2 (0.7)	6.3 (0.8)
Plateau airway pressure (cmH_2O)	21.8 (4.2)	24.8 (5.1)
PEEP	10.8 (2.9)	11.2 (3.2)
Driving pressure	11.3 (4.3)	13.2 (3.9)
Compliance (mL/cmH_2O)	45.2 (27.8)	35.2 (14.9)
SpO_2 (%)	94.6 (3.4)	96.0 (3.0)
PaO_2:FiO_2 (mmHg)	156.2 (68.2)	171.2 (72.9)
Lung injury score	3.0 (0.7)	2.8 (0.5)
$PaCO_2$ (mmHg)	40 (8.5)	43.2 (9.8)
pH	7.41 (0.1)	7.37 (0.1)
Neuromuscular blocking agents	6 (28.6%)	16 (66.7%)
Ventilation mode		
Volume control	11 (100%)	19 (95%)
Pressure control	0 (0%)	0 (0%)
Pressure support	0 (0%)	1 (5%)

Démographie

Respiratory characteristics	UC-MSC	placebo
Ventilatory support (NIV and/or HFNO)	10 (31.2%)	4 (12.5%)
Invasive mechanical ventilation	11 (52.4%)	20 (83.3%)
Tidal volume (mL/kg PBW)	6.2 (0.7)	6.3 (0.8)
Plateau airway pressure (cmH_2O)	21.8 (4.2)	24.8 (5.1)
PEEP	10.8 (2.9)	11.2 (3.2)
Driving pressure	11.3 (4.3)	13.2 (3.9)
Compliance (mL/cmH_2O)	45.2 (27.8)	35.2 (14.9)
SpO_2 (%)	94.6 (3.4)	96.0 (3.0)
PaO_2:FiO_2 (mmHg)	156.2 (68.2)	171.2 (72.9)
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Traitements reçus

Table 3. Doses of treatment received and corticosteroids administration from day 0 to day 7.

	UC-MSC	placebo
Number of doses received over 7 days	2.7 (0.6)	2.7 (0.5)
One single dose received	2 (9.5%)	1 (4.2%)
Two doses received	2 (9.5%)	4 (16.7%)
Three doses received	17 (80.9%)	19 (79.2%)
Corticosteroids administration over 7 days	15 (71.4%)	16 (66.7%)

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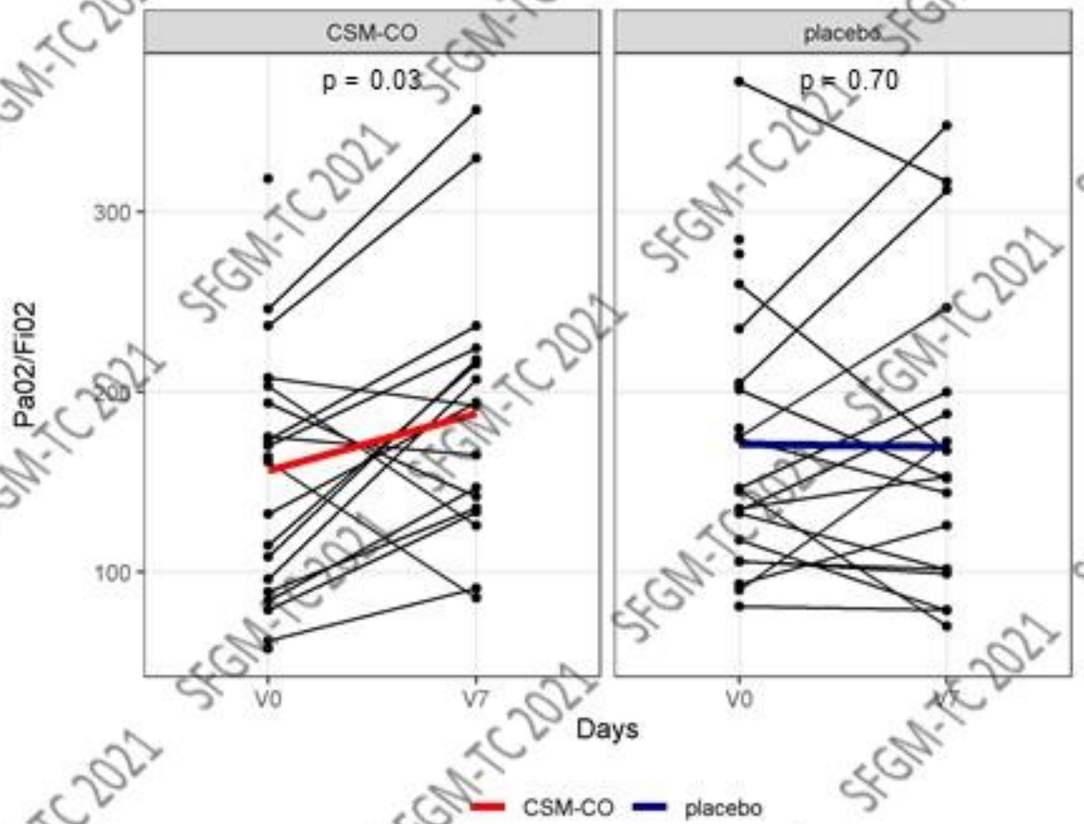
Critère de jugement primaire

Table 4. Main clinical outcomes.

	UC-MSC n = 21	placebo n = 24	Odds ratio or median difference (95% CI)	P value
Primary endpoint				
PaO_2:FiO_2 ratio change from day 0 to day 7 (principal analysis)	54.3 [-15.5-93.3]	25.3 [-33.3-104.6]	7.4 [-44.7-59.7]	0.77
PaO_2:FiO_2 ratio change from day 0 to day 7 (sensitivity analysis)	54.3 [-15.5-93.3]	25.3 [-33.3-83.1]	12.5 [-33.8-56.7]	0.59
PaO_2:FiO_2 ratio change from day 0 to day 7 (per protocol analysis)	54.3 [-16.3-93.3]	32.7 [-35.3-94.7]	8.2 [-45.1-61.6]	0.76
PaO_2:FiO_2 ratio change from day 0 to day 7 (per protocol with sensitivity analysis)	54.3 [-10.5-93.3]	32.7 [-35.3-83.7]	10.3 [-38.4-58.9]	0.67

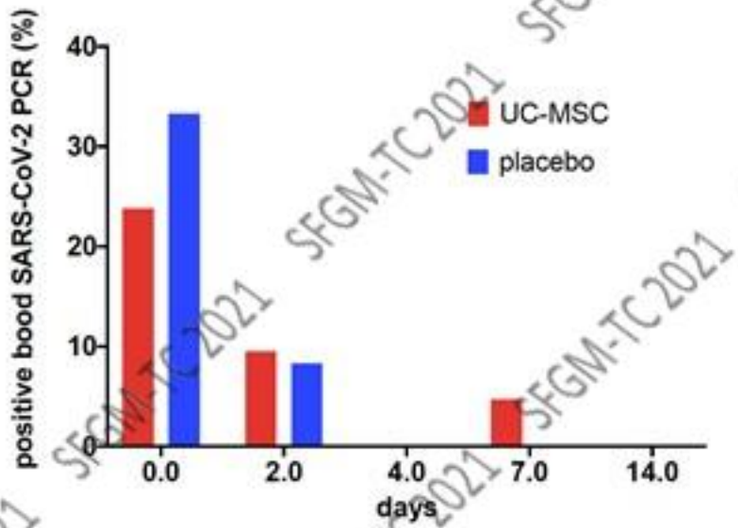
Critère de jugement primaire

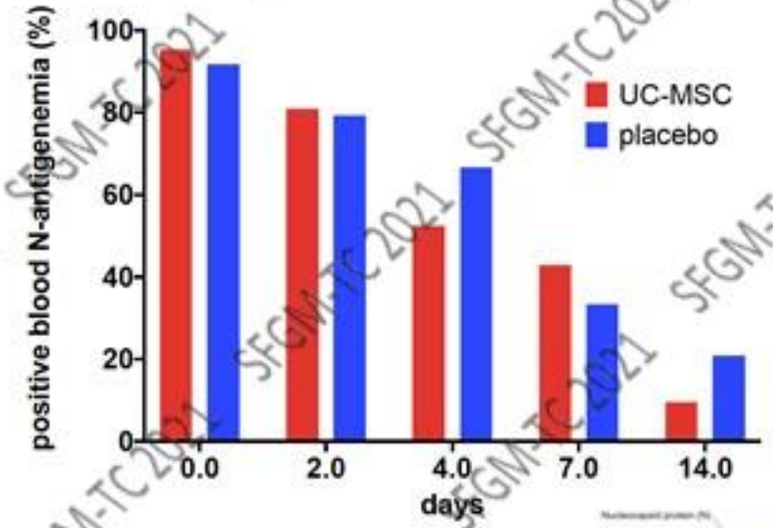


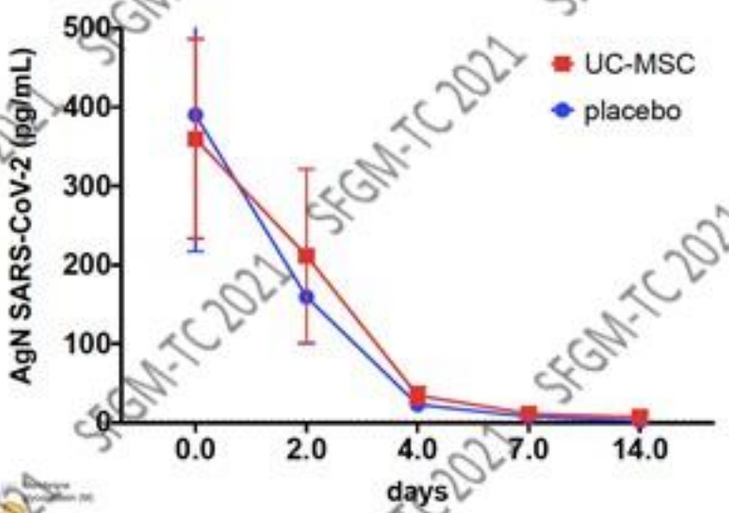
Critères de jugement secondaires

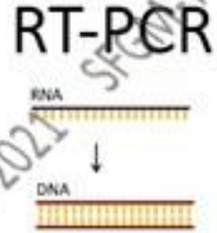
Secondary endpoints	UC-MSC	placebo	Median difference (95% CI) or Hazard ratio or Sub hazard ratio	
PaO_2:FiO_2 ratio change from day 0 to day 14	11.0 [-39-72.7]	28.2 [-1-67.3]	1.69 [-82.1-90.7]	1
Number of ventilation-free days to day 28	17.0 [0-25]	12.0 [0-19.7]	0.5 [-3.0-8.0]	0.61
Duration of ventilation to day 28	9.0 [3-20]	10 [5.7-20.0]	-2.5 [-8.0-3.0]	0.38
SOFA change from day 0 to day 7	-1.5 [-2-0.75]	-2 [-3.2-0.2]	0.5 [-2-3]	0.60
SOFA change from day 0 to day 14	-0.5 [-1.2-1]	-3.0 [-3--1]	1.5 [-1-5]	0.12
Number of organ-failure-free days to day 14	3.0 [0.0-6.0]	2 [0-9.0]	-0.5 [-4.0-3.0]	0.96
Number of organ-failure-free days to day 28	16[2-20]	15 [0.75-23]]	-0.5 [-7.0-4.0]	0.68
Time to reach PaO_2:FiO_2 ratio > 200	5.0 [5.0-7.0]	2.5 [0-5.2]	1.4 [0.6-2.9]	0.44
Time to reach PaO_2:FiO_2 ratio < 300	8.0 [6.0-14.0]	7.0 [3.7-15.5]	0.9 [0.4-2.0]	0.87
Time to ICU discharge	13.4 (8.5)	13.1 (9.4)	1.2 [0.6-2.5]	0.59
Time to weaning	19.1 (9.8)	17.1 (10.3)	1.6 [0.6-4.3]	0.37
Compliance change from day 0 to day 7	-3.6 [-11.8-4.7]	-0.1 [-4.5-2.4]	0.4 [-24.7-25.5]	1
Compliance change from day 0 to day 14	-3.0 [-3.0--3.0]	2.5 [-0.9-11.7]	-5.52 [-35.41-1.11]	0.8
Driving pressure change from day 0 to day 7	0.5 [-3.2-4.2]	0.5 [-1.2-2.2]	0 [-13-13]	1
Driving pressure change from day 0 to day 14	1.0 [1.0-1.0]	-1.5 [-2.0-0.2]	2.5 [-3.0-3.0]	0.8
Mortality to day 28	5 (26.3%)	4 (18.2%)	2.0 [0.5-8.5]	0.36

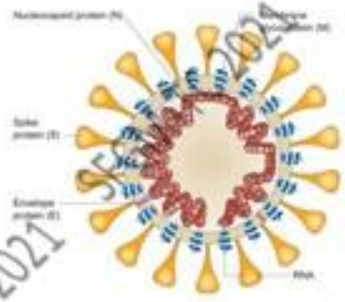
virologie











Sécurité: évènements indésirables

Table 5. Summary of adverse events for randomized subjects.

Topics	UC-MSC n = 21	placebo n = 24	Total	P
Adverse events from day 0 to day 14				
Number of subjects with AEs	18 (85.7%)	18 (75%)	36 (80%)	0.47
Number of AEs reported	51 (51.5%)	48 (48.5%)	99 (100%)	0.15
Number of subjects with SAEs	6 (28.6%)	6 (25%)	12 (26.7%)	0.79
Number of SAEs reported	12 (23.5%)	6 (12.5%)	18 (18.2%)	0.15
Number of AEs by severity				0.93
Mild	16 (31.4%)	15 (31.2%)	31 (31.3%)	
Moderate	24 (47.1%)	24 (50%)	48 (48.5)	
Severe	11 (21.6%)	9 (18.7%)	20 (20.2)	
Number of AEs by grade[a]				0.11
Grade 1	19 (38.8%)	10 (20.8%)	29 (29.9%)	
Grade 2	15 (30.6%)	19 (39.6%)	34 (35.0%)	
Grade 3	9 (18.4%)	16 (33.3%)	25 (25.8%)	
Grade 4	6 (12.2%)	3 (6.2%)	9 (9.3%)	
Number of AEs by relatedness to treatment				0.41
Possible	1 (2%)[b]	0 (0%)	1 (1.0%)	
Other treatment	4 (8.0%)	2 (4.3%)	6 (6.2%)	
Other disease	1 (2.0%)	1 (2.1%)	2 (2.1%)	
COVID-19 progression	30 (60.0%)	37 (78.2%)	67 (69.1%)	
Other causes	3 (6.0%)	2 (4.3%)	5 (5.1%)	
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Sécurité: pré-immunisation et immunogénicité

- **DSA préformés (J0)**
  - **6/21 (29%) 80% HLA-1**
  - 1/21 (5%) avec MFI>5000 (A32)
  - 5/21 avec MFI entre 500 et 2000
    - A2/A32/cW12/cW7/DQ7

- **DSA de novo (J14)**
  - **3/21 (14%) 100% HLA-2**
  - DQ2, MFI = 3500
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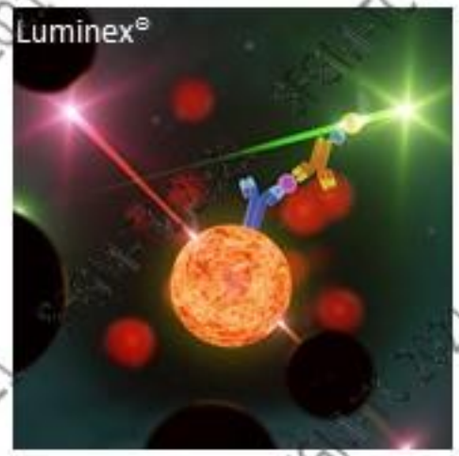
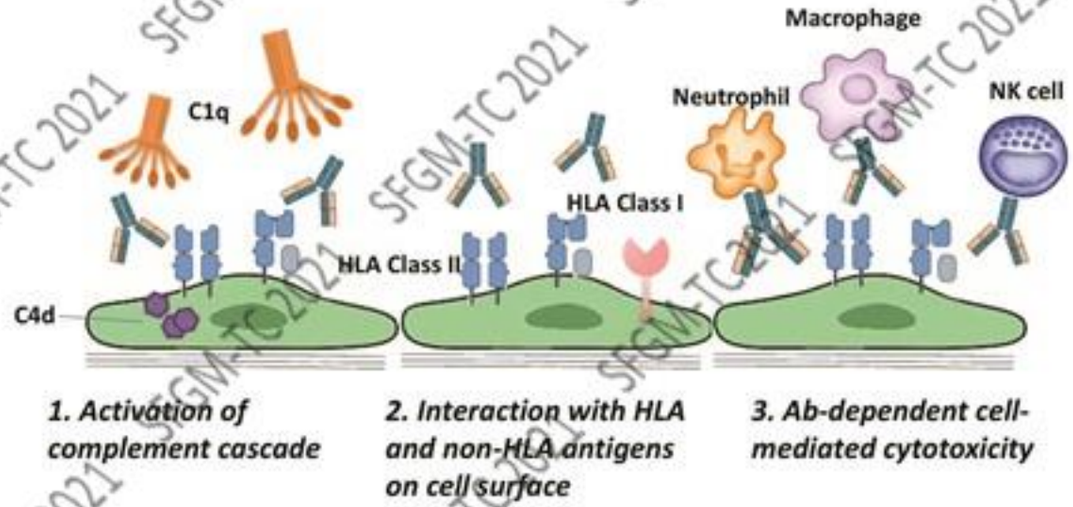
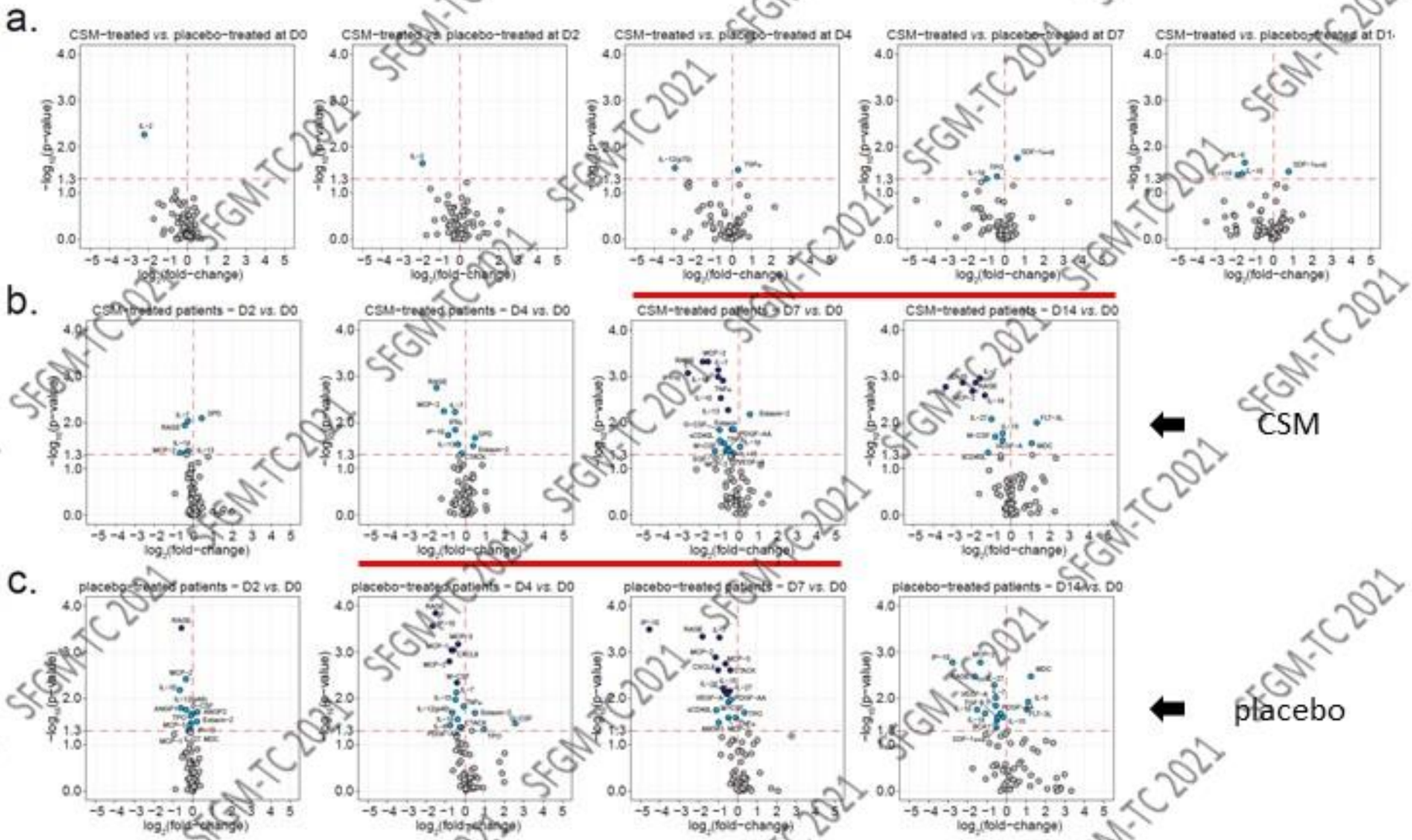
  - DP4, MFI = 681





Biomarqueurs plasmatiques

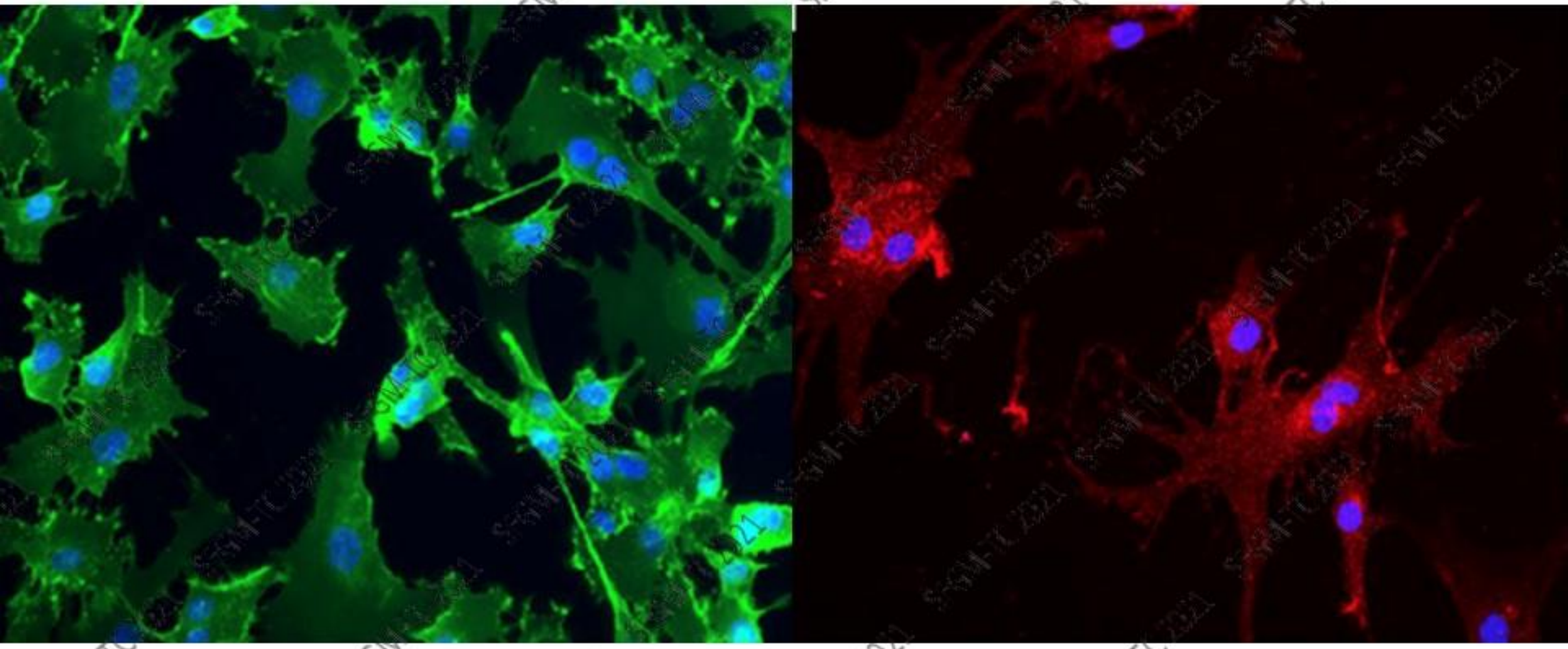


Essai STROMA-CoV-2: conclusions

- NS sur le critère primaire et les critères secondaires
- Augmentation significative du P/F (J0-J7) dans le groupe CSM (sans imputation) et pas dans le groupe placébo
- Sécurité d'emploi confirmée
- 30% des patients avec DSA préformés sur HLA-1: impact?
- 14% des patients avec DSA de novo J14: immunisation?
- Biomarqueurs:
  - Cinétique dans les 2 groupes
  - Décalage de la cinétique dans le groupe CSM → signature ?

Essai STROMA-CoV-2: conclusions

- une des premières études de phase II française
- possibilité de méta-analyses avec les études françaises, espagnoles, brésiliennes et américaines
- données M6 et M12
- points forts
  - design
  - phénotype « pur » de SDRA (pneumonie virale, même virus, même sévérité, précoce)
  - CSM produites en GxP – caractérisation – sécurisation – potency
  - critères secondaires M6 et M12: qualité de vie et EFR
- limites
  - mortalité élevée
  - traitements partiels, 2 cordons, variabilité entre les batch
  - 2 vagues: DEXAMETHASONE et de prise en charge entre les 2 vagues
  - 2 vagues: sévérités diffèrent avec plus de VM lors de la première vague



Merci de votre attention