Post COVID : de la clinique à l'essai

Dr. Mayssam Nehme
mayssam.nehme@hcuge.ch

20 mars 2023

CoviCare, CoviBoard, RAFAEL

Service de médecine de premier recours
Hôpitaux Universitaires de Genève

Pr. Idris Guessous
Idris.guessous@hcuge.ch

Hôpitaux Universitaires Genève

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

POST-COVID

- Prévalence du post-COVID estimée à 10% (revue de la littérature 2023)
- Pourcentage de personnes qui développent des symptômes similaires au syndrome de fatigue chronique
- Retentissement sur la capacité fonctionnelle
- Risque avec réinfections
- Risque d'augmentation des co-morbidities

Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol. 2023 Jan 13:1–14. doi: 10.1038/s41579-022-00846-2. Epub ahead of print.

Nehme M, Braillard O, Chappuis F, Courvoisier DS, Guessous I; CoviCare Study Team. Prevalence of Symptoms More Than Seven Months After Diagnosis of Symptomatic COVID-19 in an Outpatient Setting. Ann Intern Med. 2021 Sep;174(9):1252-1260. doi: 10.7326/M21-0878. Epub 2021 Jul 6.

Nehme M, Braillard O, Chappuis F, Courvoisier DS, Kaiser L, Soccal PM, Reny JL, Assal F, Bondolfi G, Tardin A, Graf C, Zekry D, Stringhini S, Spechbach H, Jacquerioz F, Salamun J, Lador F, Coen M, Agoritsas T, Benzakour L, Favale R, Genevay S, Lauper K, Meyer P, Poku NK, Landis BN, Baggio S, Grira M, Sandoval J, Ehrsam J, Regard S, Genecand C, Kopp G, Guerreiro I, Allali G, Vetter P, Guessous I; CoviCare Study Team. One-year persistent symptoms and functional impairment in SARS-CoV-2 positive and negative individuals. J Intern Med. 2022 Jul;292(1):103-115. doi: 10.1111/joim.13482. Epub 2022 Mar 31

Nehme M, Chappuis F, Kaiser L, Assal F, Guessous I. The Prevalence, Severity, and Impact of Post-COVID Persistent Fatigue, Post-Exertional Malaise, and Chronic Fatigue Syndrome. J Gen Intern Med. 2022 Nov 10:1–5. doi: 10.1007/s11606-022-07882-x. Epub ahead of print.

Nehme M, Braillard O, Chappuis F; CoviCare Study Team, Guessous I. The chronification of post-COVID condition associated with neurocognitive symptoms, functional impairment and increased healthcare utilization. Sci Rep. 2022 Aug 25;12(1):14505. doi: 10.1038/s41598-022-18673-z.

Bowe B, Xie Y, Al-Aly Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. Nat Med. 2022 Nov;28(11):2398-2405. doi: 10.1038/s41591-022-02051-3. Epub 2022 Nov 10

DeVries A, Shambhu S, Sloop S, Overhage JM. One-Year Adverse Outcomes Among US Adults With Post–COVID-19 Condition vs Those Without COVID-19 in a Large Commercial Insurance Database. JAMA Health Forum. 2023;4(3):e230010. doi:10.1001/jamahealthforum.2023.0010

www.rafael-postcovid.ch

Collaboration multicentrique et multidisciplinaire – Aspects médicaux, sociaux et professionnels

Colloques CoviBoard, coordination des soins

Consultation spécialisée: Evaluation complète et multidisciplinaire

Coordination par médecin traitant

Investigations, suivi par médecin traitant

Prise en charge par médecin traitant

Dépistage & Prise en charge

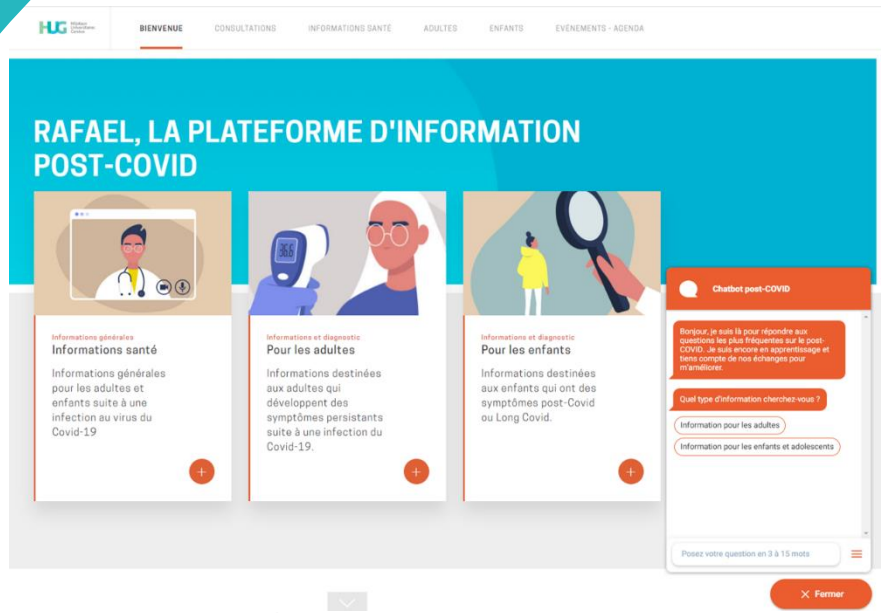
Prévention – Information – Echange citoyen.ne.s- communauté

Symptômes très invalidants, pas d'amélioration, complexité sociale ou médicale

Symptômes persistants fréquents ou multiples

Symptômes persistants

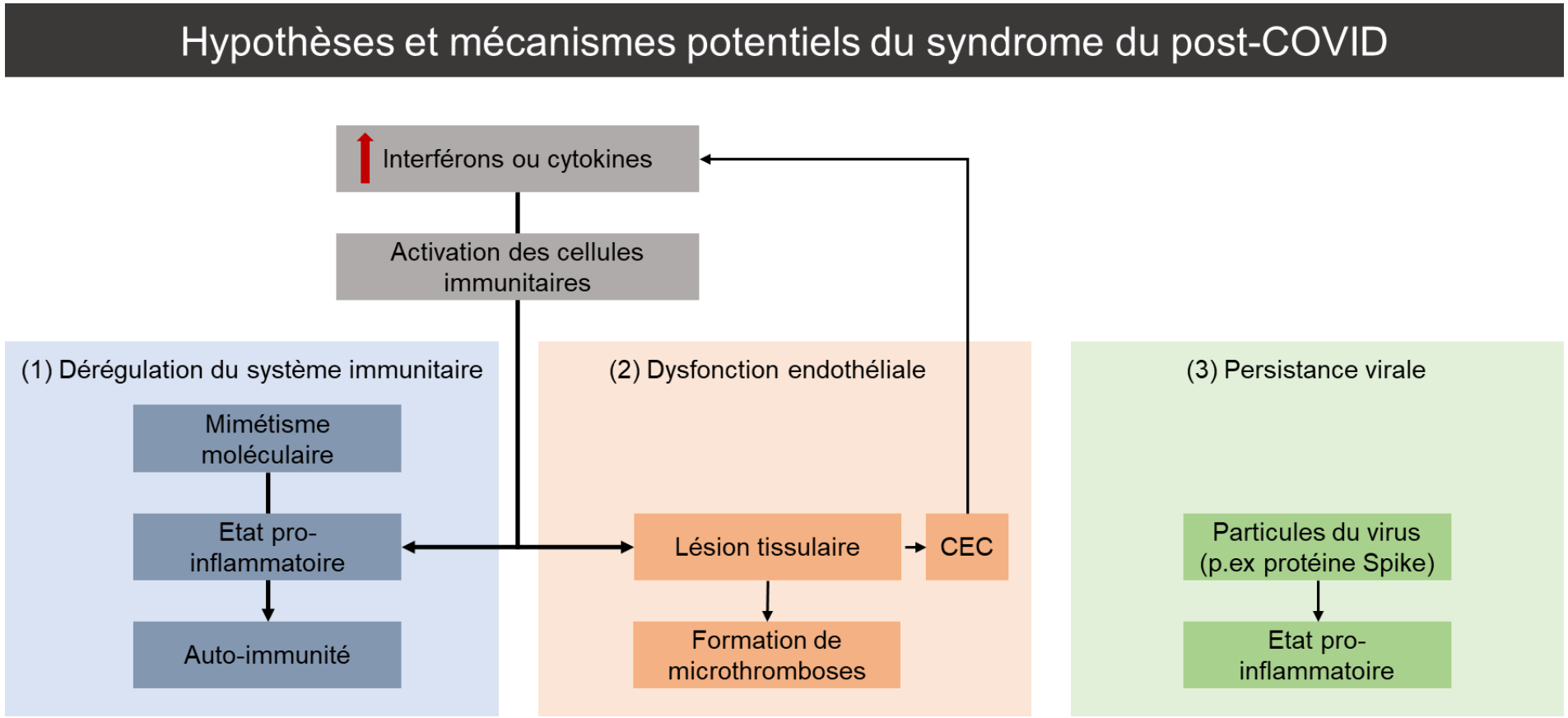
Population générale



Hôpitaux Universitaires Genève

HUG Hôpitaux Universitaires Genève · CHUV Centre hospitalier universitaire vaudois · CICR · Hôpital du Valais Spital Wallis · Hôpital Riviera-Chablais Vaud-Valais · Réseau Delta · Ligue pulmonaire genevoise · TX · MVPHysio · unisanté · Hôpital du Jura · UNHCR The UN Refugee Agency · SGAIM SSMIG SSGIM · Long Covid Schweiz Suisse Svizzera Switzerland · medX romandie · pédiatrie suisse · Espoirs

PATHOPHYSIOLOGIE



Nehme M, Ducrot A, Salmon D, Guessous I. Post-Covid : nouveautés 2022 et prochaines étapes. Rev Med Suisse 2023 ; 19 : 160-6 | DOI : 10.53738/REVMED.2023.19.812.160

Etude européenne menée par les HUG

Nous conduisons avec GeNeuro une étude clinique qui a pour but de tester un traitement chez des personnes atteintes de fatigue/troubles de concentration après une infection au SARS-CoV-2

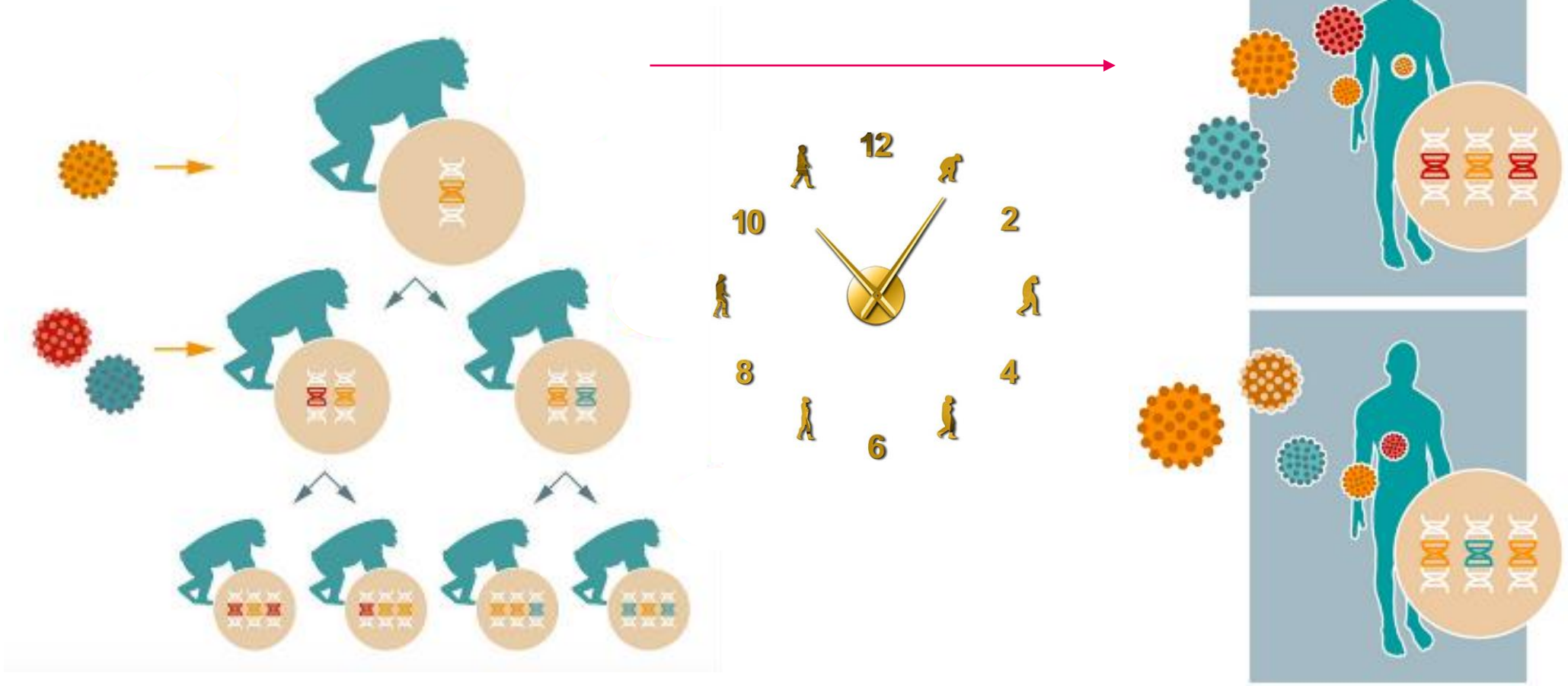
Il s'agit du *Temelimab*, une molécule qui cible une protéine (HERV-W ENV) identifiée chez une partie des personnes touchées par le COVID et le post-COVID

Cette protéine (HERV-W ENV) produit une inflammation et a été retrouvée dans des affections notamment neurologiques avant le COVID

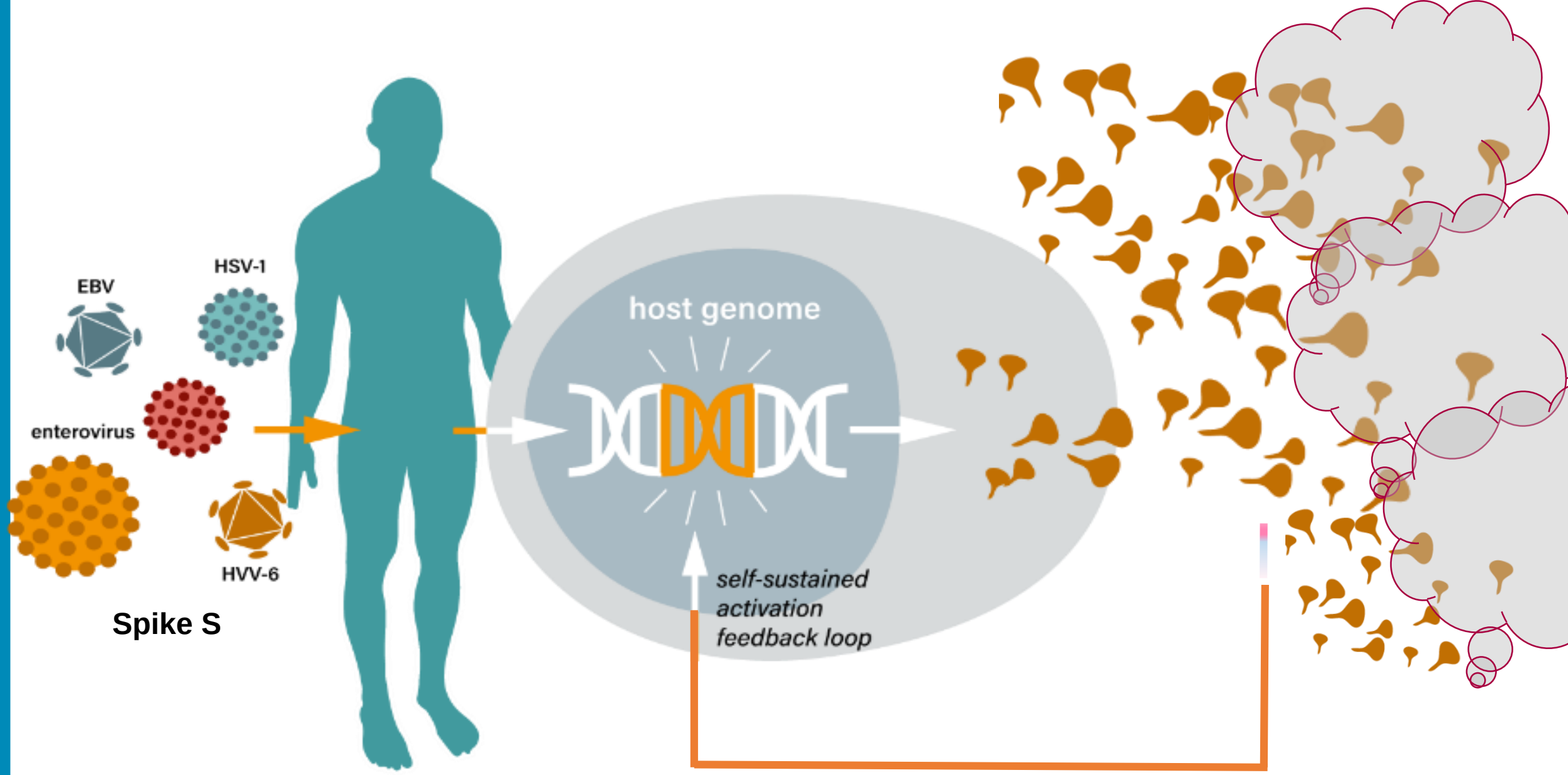
Cette protéine est activée après une exposition au SARS-CoV-2 et contribue à l'inflammation

Incorporation de rétrovirus dans le génome de l'hôte

8% de l'ADN humain



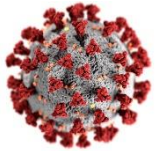
Hôpitaux Universitaires Genève



Hôpitaux Universitaires Genève

W-ENV le lien entre le SARS-CoV-2 et le post-COVID?

SARS-CoV-2



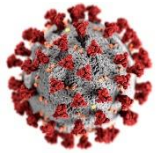
» » » » ? » » » »

Post-COVID

Fatigue
Troubles de la concentration
Dépression et anxiété
Troubles du sommeil
Troubles de la fonction motrice
Problèmes sensoriels/moteurs
Engourdissement et picotements, spasmes musculaires, raideur et faiblesse

W-ENV le lien entre le SARS-CoV-2 et le post-COVID?

SARS-CoV-2

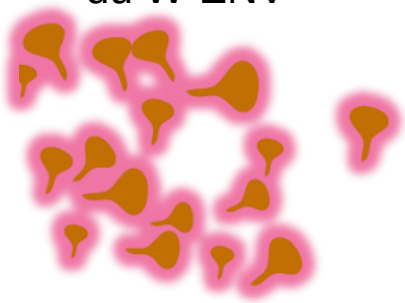


Spike S

Expression de W-ENV chez certains individus

La production de W-ENV peut continuer longtemps après l'infection aigue

Propriétés pro-inflammatoires et pathogèniques du W-ENV



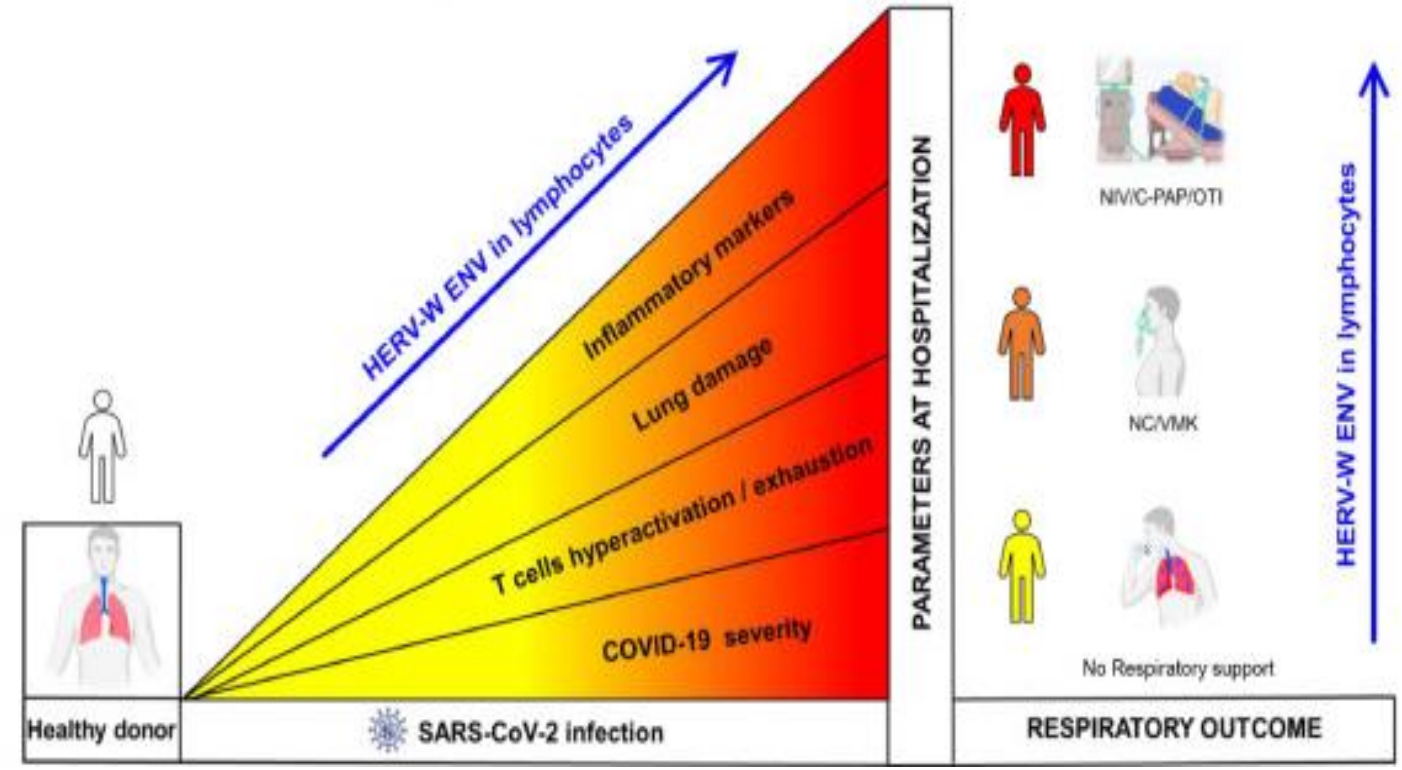
- Lymphocytes
- Tissu du cerveau
- Vaisseaux sanguins

Post-COVID

Fatigue
Troubles de la concentration
Dépression et anxiété
Troubles du sommeil
Troubles de la fonction motrice
Problèmes sensoriels/moteurs
Engourdissement et picotements, spasmes musculaires, raideur et faiblesse

Hôpitaux Universitaires Genève

GeNeuro a développé un test permettant de détecter W-ENV dans le sérum

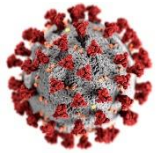


https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00134-1/fulltext

W-ENV a été détecté chez 25 à 50% des patients avec COVID

W-ENV le lien entre le SARS-CoV-2 et le post-COVID?

SARS-CoV-2

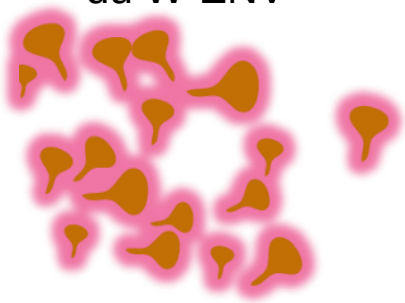


Spike S

Expression de W-ENV chez certains individus

La production de W-ENV peut continuer longtemps après l'infection aigue

Propriétés pro-inflammatoires et pathogèniques du W-ENV



- Lymphocytes
- Tissu du cerveau
- Vaisseaux sanguins

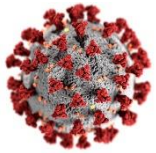
Post-COVID

Fatigue
Troubles de la concentration
Dépression et anxiété
Troubles du sommeil
Troubles de la fonction motrice
Problèmes sensoriels/moteurs
Engourdissement et picotements, spasmes musculaires, raideur et faiblesse

Hôpitaux Universitaires Genève

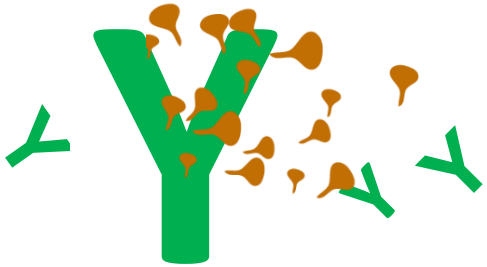
Etude européenne menée par les HUG

SARS-CoV-2



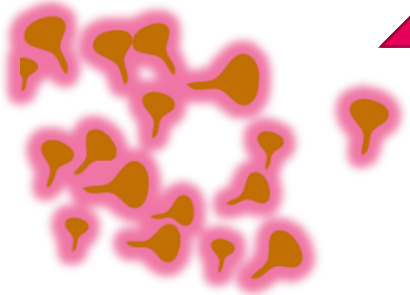
Spike S

Expression de W-ENV chez certains individus



La production de W-ENV peut continuer longtemps après l'infection aigue

Propriétés pro-inflammatoires et pathogèniques du W-ENV



- Lymphocytes
- Tissu du cerveau
- Vaisseaux sanguins

Post-COVID

Fatigue

Troubles de la concentration

Dépression et anxiété

Troubles du sommeil

Troubles de la fonction motrice

Problèmes sensoriels/moteurs

Engourdissement et picotements, spasmes musculaires, raideur et faiblesse

Hôpitaux Universitaires Genève

- Infection SARS-CoV-2
- Fatigue, troubles cognitifs
- Temelimab vs Placebo
- 6m 1x/m +

examens neuropsy,

prises de sang etc.

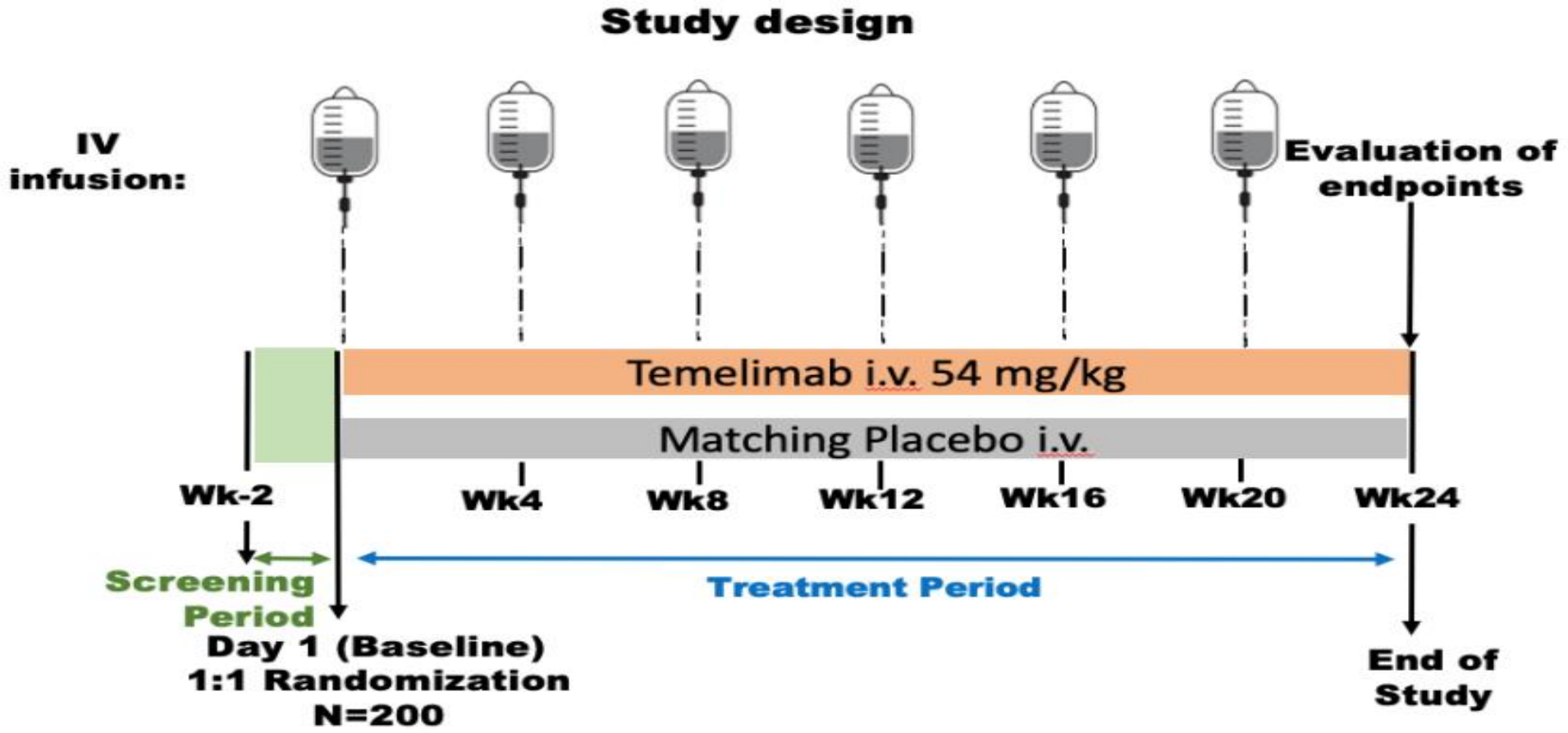
etude.longcovid@hcuge.ch

Tel: 022 372 1151

Hôpitaux Universitaires Genève

Hôpitaux Universitaires Genève

Etude européenne menée par les HUG



Hôpitaux Universitaires Genève

Etude européenne menée par les HUG
Pour qui?

- 18 ans ou plus

- Ayant été testées positives au COVID-19 (PCR, antigénique ou sérologie)

- Symptômes persistants au moins 3 mois après leur infection
tels que la fatigue, la perte de mémoire, le manque de concentration

- Positives à la protéine HER-W ENV (ce critère est vérifié à l'aide d'une prise de sang lors de l'étude)

Case study

- Août-Sept 2022

Hôpitaux Universitaires Genève

Case study

- Août-Sept 2022

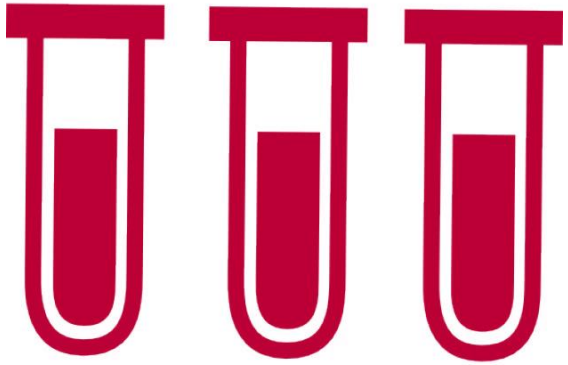
Hôpitaux Universitaires Genève

Case study

- Août-Sept 2022
- Revoir processus

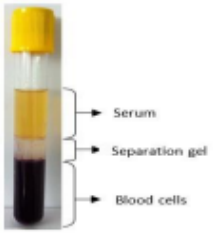
Case study

- Août-Sept 2022
- Revoir processus
- Batchs-Lots



WWCT / GeNeuro GNC-501

Flowchart version date: 21-Jun-2022

Testing	Collection Tubes	Processing	Sample Aliquot and Shipping	Tube label
HERV-W ENV Protein Serum **At Visits:** • Screening • Week 12 • Week 24	 1x 5.0 mLGold top Serum Separator Tube **[BD Vacutainer® SST™ II Advance with Hemogard™ tube] yellow gold tips** Ref **367955** **Specific instruction for collection tube:** • Should be stored between 4°C to 25°C. • Should not be exposed to direct light. • Should be handle with precaution due to potential breakage risks. • Should not be re-used. • Tubes should be disinfected with a solution of 70% ethanol Fig. a  After centrifugation, any tube not showing the three layers (serum, separation gel and blood cells) as shown in the above picture (a) must be rejected.	• Collect 2 mL of blood within the SST tube: • Gently invert the tube by hand 4-5 times. Vigorous mixing can cause hemolysis which is not suitable. • Let stand upright at room temperature for 30 min to allow blood to clot. **Note: For good and standardized results, do not store the tube for more than 2h after blood sampling until centrifugation**. • Use a temperature-controlled centrifuge pre-cooled at +4°C (including the rotor).After centrifuge equilibration, centrifuge the tube at 2000 g during 10 minutes at +4°C. **Keep the centrifuge brake off.** • When the centrifuge stops, carefully remove the tube without disturbing the pellet. 3 layers should be seen in the tube as per the figure "a." **Preparation of serum samples – aliquoting** **If possible, work under the laminar flow disinfected with a solution of 70% ethanol.** • Using serological pipette, slowly and carefully collect the serum, leaving few mm above the interface with the separation gel to avoid aspiring gel or clotted debris. • Transfer the serum into a 15 mL Falcon tube (ref 352096).  • Gently vortex the serum using the slowest speed. • Make 3 aliquots of 250 µL of serum into 1.5 mL pre-labelled Eppendorf tubes • Store immediately the serum aliquots at -80°C, vertically, in dedicated storage boxes. **Continued on next page….**	1.5 mL Eppendorf ref 0030120086  **3 x 250 µl**	**Serum (HERV-W 1)** **Serum (HERV-W 2)** **Serum (HERV-W 3)**

Hôpitaux Universitaires Genève

WWCT / GeNeuro GNC-501

Flowchart version date: 21-Jun-2022

IMPORTANT NOTES BEFORE SAMPLE COLLECTION

General:

- All transport tubes are pre-labelled. Please select the correct tube.
- Samples must be collected in the order listed in this Flowchart.
- Make sure you complete Requisition Form /Fetch EzRF for all samples collected.
- Ensure the kits are stored at ambient temperature (15°C to 25°C)

Study Specific:

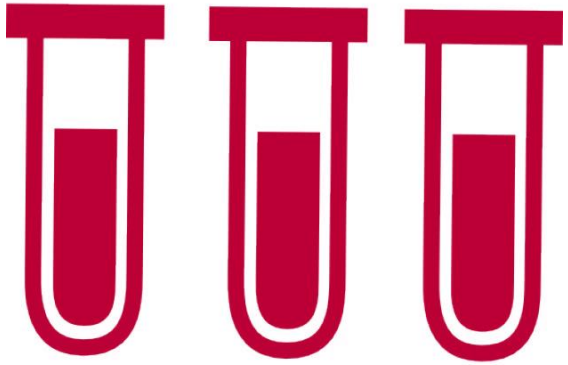
- Volumes mentioned are minimum volumes required to perform all required analysis. Please make sure required volume is transferred to the transport tubes.

For all Biomarker samples:

- Subjects should be partially or fully sitting in bed with legs extended.
- Same posture should be ensured for all visits. Patients should be calm and quiet before and during the sample collection.
- Samples should be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein from the contralateral side used for study drug infusion.

Case study

- Août-Sept 2022
- Revoir processus
- Batchs-Lots



- Monitoring de la T°C

Hôpitaux Universitaires Genève

Etude européenne menée par les HUG

- Prévalence +
- Inclusion de participant.e.s

etude.longcovid@hcuge.ch
Tel: 022 372 1151

Commission directrice	Centres
Commission Cantonale d'éthique de la recherche Genève (CCER)	Principal investigator Idris Guessous, , Geneva

Commission(s) locale(s)	Centres
BE	PD Dr.med. Robert Hoepner, Department of Neurology, Inselspital Bern, University Hospital Bern, CH-3010 Bern
BS	Dr. med. Margret Hund-Georgiadis, REHAB Basel, Clinic for Neurorehabilitation and Paraplegiology, 4055 Basel
VD	Prof. Dr.med. Pierre-Olivier Bridevaux, Pulmology Department, Valais Hospital, 1951 Sion
ZH	Dr. med. Gregory Fretz, Policlinic, Kantonsspital Graubünden, 7000 Chur

HUG Hôpitaux Universitaires Genève

Merci

Dr. Mayssam Nehme
mayssam.nehme@hcuge.ch

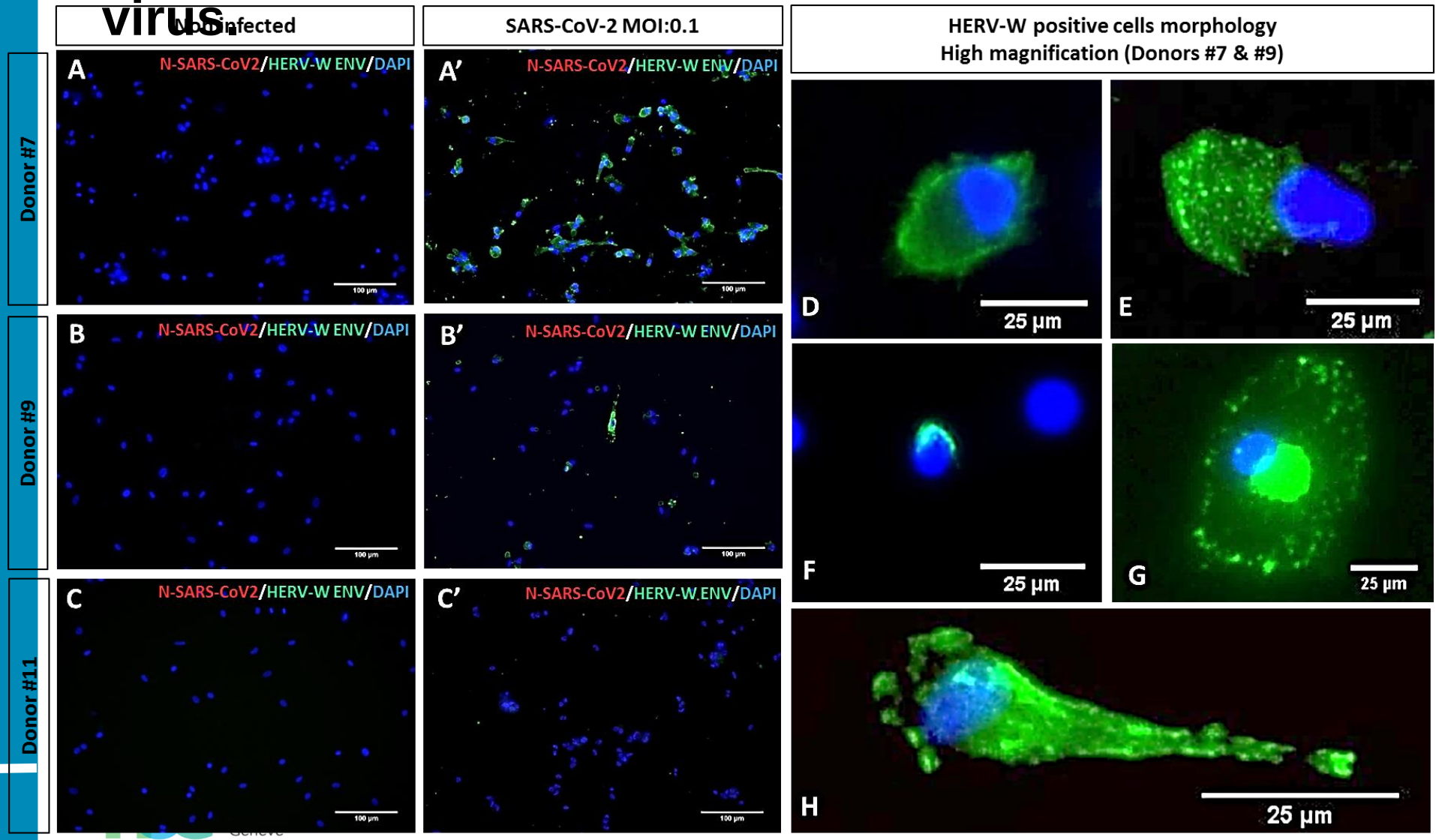
Service de Médecine de Premier Recours
Hôpitaux Universitaires de Genève

Pr. Idris Guessous
Idris.guessous@hcuge.ch

Hôpitaux Universitaires Genève

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

HERV-W ENV immunodetection in primary PBMC cultures from healthy blood donors with and without SARS-CoV-2 infectious virus.



PBMCs from healthy blood donors were inoculated (A'-C') or not (A-C) with SARS-CoV-2 virus (MOI*: 0.1) and collected after 3 or 7 days. For each culture, GN_mAb_Env01 and anti-N-SARS-CoV-2 antibodies were respectively used to detect HERV-W ENV (green labelling) and Nucleocapsid protein of SARS-CoV-2 (red labeling).

The 3 donors presented here show responding PBMC cultures with few positive cells: Donor # 7 at day 7 (A, A') and Donor # 9 at day 3 (B, B') and a non-responding culture from Donor # 11 at day 7 (C, C'). The different morphological aspects of HERV-W ENV positive cells are presented with high magnifications (D-H). DAPI was used to stain nuclei (blue staining).

Source: https://www.researchsquare.com/article/rs-301236/v1

*Multiplicity Of Infection

SARS-CoV-2 infection triggers the expression of HERV-W ENV, found in hospitalized patients and associated with disease severity

HERV-W ENV is present in blood circulation of **COVID-19 patients** and is associated with disease severity

- SARS-CoV-2 induces *in vitro* HERV-W ENV expression in human blood cells of >20% of healthy volunteers, suggesting an induvial susceptibility

  https://www.medrxiv.org/content/10.1101/2022.01.18.21266111v2

- HERV-W ENV is detected in the blood of all of hospitalized COVID-19 patients, not in controls
- Evidence of a correlation between HERV-W ENV expression levels and evolution of disease severity

  https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00134-1/fulltext

- "This might represent an excellent opportunity to conduct a randomized controlled clinical study in patients with COVID-19", Editorial Commentary by Dr Avindra Nath, Intramural Clinical Director of NINDS

  https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00156-0/fulltext

Hôpitaux Universitaires Genève

Primary endpoint – Week 24 vs Baseline

improvement in cognitive impairment

- measured by an increase of ≥0.5 z-scores in the Token Motor Test,

OR

improvement in fatigue

- measured by a decrease of ≥3 points in the Patient-Reported Outcomes Measurement Information System Fatigue Short Form 7a (PROMIS Fatigue SF 7a) score

Secondary objective

- To evaluate the efficacy of treatment with temelimab plus local SoC treatment versus local SoC alone over 6 months on measures of cognition, fatigue, anxiety, depression, functional impairment/disability and quality of life in PASC patients

- To evaluate safety and tolerability of temelimab in PASC patients

Procedure	Screening period*	Treatment						End of Study
Study Day	**Up to 21**	**1**	**28 W4**	**56 W8**	**84 W12**	**112 W16**	**140 W20**	**168 W24**
Allowable Window		**0**	**±5 Days**	**±5 Days**	**±5 Days**	**±5 Days**	**±5 Days**	**±5 Days**
Informed Consent[a]	X							
Eligibility Assessment[b]	X	X						
Randomization		X						
Demographics	X							
Medical History	X							
Physical Examination[c]	X	X			X			X
Weight	X	X	X	X	X	X	X	X
SARS-CoV-2 Test[d]		X[d]						
HERV-W Env[e]	X				X			X
PROMIS Fatigue SF 7a	X	X			X			X
Token Motor Test (from BAC)	X	X			X			X
Tower of London (from BAC)		X						X
Verbal Memory Test (from BAC), Digit Sequencing Test (from BAC) and Semantic and Letter Fluency (from BAC)		X			X			X
SDMT		X			X			X
PDQ-20	X	X			X			X
GAD-7		X			X			X
PHQ-9		X			X			X

Hôpitaux Universitaires Genève

Procedure	Screening period*	Treatment						End of Study
Study Day	**Up to 21**	**1**	**28 W4**	**56 W8**	**84 W12**	**112 W16**	**140 W20**	**168 W24**
Allowable Window		**0**	**±5 Days**	**±5 Days**	**±5 Days**	**±5 Days**	**±5 Days**	**±5 Days**
SDS		X			X			X
EQ5D-5L	X	X			X			X
PCFS		X			X			X
M.I.N.I	X**							
Vital Signs[f]	X	X	X	X	X	X	X	X
12-lead ECG[g]	X				X			X
Pregnancy Test[h]	X	X	X	X	X	X	X	X
Serological infection markers: HIV 1/2, HBsAg, anti-HBsAb, anti-HBcAb, and HCV	X							
Hematology[i]	X				X			X
Serum Chemistry[j]	X				X			X
Coagulation[k]	X				X			X
Urinalysis	X				X			X
Study Drug Infusion		X	X	X	X	X	X	
Biomarkers (incl. NfL)[l]		X			X			X
PK (Temelimab Serum Concentration)		X	X	X	X	X	X	X
Anti-drug Antibodies		X	X	X	X	X	X	X
Adverse Events/Serious Adverse Events	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X

Hôpitaux Universitaires Genève