

**The polarity and specificity of SARS-CoV2 -specific T lymphocyte
responses as a biomarker of disease susceptibility**

FIELD OF THE INVENTION

The present invention relates to the field of antiviral vaccination. More
5 particularly, the invention provides immunogenic compositions for vaccination against
SARS-CoV-2 and methods for *in vitro* determining if an individual is likely to resist to an
infection by SARS-CoV-2.

BACKGROUND OF THE INVENTION

The emergence and spread of severe acute respiratory syndrome
10 coronavirus-2 (SARS-CoV-2), the causative agent of coronavirus disease 2019, have
resulted in devastating morbidities and socioeconomic disruption. The development of
community protective immunity relies on long-term B and T cell memory responses to
SARS-CoV-2. This can be achieved through viral infection [1] or by vaccination [2–4].
Reports on rapidly decreasing spike- and nucleocapsid-specific antibody titers post-
15 COVID-19 infection [5] or reduced neutralizing capacity of vaccine-induced antibodies
against viral escape variants compared to the ancestral SARS-CoV-2 strain [6,7] have
shed doubts on the importance of humoral immunity as a standalone response. In
contrast, T cell immunity was identified as an important determinant of recovery and
long-term protection against SARS-CoV-1, even 17 years after infection [8–11].

20 The TH1 versus TH2 concept suggests that modulation of the relative
contribution of TH1 or TH2 cytokines regulates the balance between immune protection
against microbes and immunopathology [12–14]. TH1 cells (as well as cytotoxic T cells
with a similar cytokine pattern referred to as Tc1 cells) produce IFN γ , IL-2, and TNF α ,
promote macrophage activation, antibody-dependent cell cytotoxicity, delayed type
25 hypersensitivity, and opsonizing and complement-fixing IgG2a antibody production [12]
Therefore, TH1/Tc1 cells drive the phagocyte-dependent host response and are pivotal
for antiviral responses [13,14]. In contrast, TH2 (and Tc2) cells produce IL-4, IL-5, IL-10
and IL-13, providing optimal help for both humoral responses and mucosal immunity,
through the production of mast cell and eosinophil growth and differentiation factors, thus
30 contributing to antiparasitic and allergic reactions. Naïve T cell differentiation to distinct
TH fates is guided by inputs integrated from TCR affinity, CD25 expression,
costimulatory molecules, and cytokines [15].

SARS-CoV-2-specific T cell immunity plays a key role during acute
COVID-19, and up to eight months after convalescence [16–20]. Indeed, functional T cell

responses remain increased in both frequency and intensity up to six months post-infection [5]. They are mainly directed against spike, membrane and nucleocapsid proteins, and have been studied in greater detail by single cell sequencing in a limited number of patients [21]. Memory TH1/Tc1 T cells specific for SARS-CoV-2 and follicular T helper cells (TFH) cells have been detected in mild cases [21]. However, cases of reinfection have been reported [22], raising questions on the clinical significance of T cell polarization and peptide repertoire specificities against current viral variants. Moreover, pioneering reports suggest that, before SARS-CoV-2 became prevalent (i.e., before 2020), some individuals exhibit immune responses, mainly among CD4⁺ T cells, against SARS-CoV-1 nucleocapsid (NC) and ORF1a/b, or common cold coronaviruses (CCC) spike and nucleocapsid proteins that are cross-reactive with SARS-CoV-2 [9,23–25]. However, the relevance of CCC or SARS-CoV-1-specific memory T cells for effective protection against the current pandemic remains questionable [21,26]. The current study was designed to correlate T cell responses to clinical protection against COVID-19, in healthy individuals and cancer patients, who are more susceptible to severe infections, and by extension to reinfection and breakthrough infection post-vaccination.

In the Example 1 below, the inventors studied SARS-CoV-2 –specific T cell responses in 382 cancer-bearing or cancer-free subjects, and prospectively followed up 227 COVID-free individuals to understand which T cell polarity and peptide repertoire may convey resistance to COVID-19. They found that a SARS-CoV-2-specific IL-2/IL-5 lymphokine ratio < 1 conferred susceptibility to COVID-19 infection or reinfection in both health care workers (HCW) and cancer patients, coinciding with defective TH1/Tc1 recognition of the receptor binding domain (RBD) of the spike protein, likely affecting viral evolution by selecting for new antigenic variants. Moreover, T cell immunity against the S1-RBD reference strain tended to decrease with time and in cancer patients, and crossreacted to some degree with the RBD sequences of viral variants of concern.

SUMMARY OF THE INVENTION

In the Example 1 below, the inventors characterized the polarity and specificity of circulating SARS-CoV-2-specific T cell responses against whole virus lysates and 186 unique peptides derived from the SARS-CoV-1 or SARS-CoV-2 ORFomes to determine T cell immune correlates with spontaneous (crossreactive), virus-elicited or vaccine-induced protection against COVID-19 infection or reinfection in healthy individuals and in a more vulnerable population composed of cancer patients. Irrespective of the presence of malignant disease, a high ratio between the prototypic T helper 1 (TH1)/ T cytotoxic type 1 (Tc1) cytokine, interleukin-2 (IL-2), and the prototypic

T helper 2 (TH2) cytokine, interleukin-5 (IL-5), released from SARS-CoV-2-specific memory T cells measured in early 2020, among SARS-CoV-2-negative persons, was associated with low susceptibility of these individuals to develop PCR-detectable SARS-CoV-2 infection in late 2020 or 2021. Of note, T cells from individuals who recovered
5 after SARS-CoV-2 reinfection spontaneously produced elevated levels of IL-5 and secreted the immunosuppressive TH2 cytokine interleukin-10 in response to SARS-CoV-2 lysate, suggesting that TH2 responses to SARS-CoV-2 are maladaptive. Moreover, individuals susceptible to SARS-CoV-2 infection, reinfection or breakthrough infection post-vaccination exhibited a selective deficit in the TH1/Tc1 peptide repertoire affecting
10 the highly mutated receptor binding domain (RBD) amino acids (331-525) of the spike protein. The inventors thus deduced that a SARS-CoV-2-specific IL-2/IL-5 lymphokine ratio < 1 conferred susceptibility to COVID-19 infection or reinfection in both health care workers (HCW) and cancer patients, coinciding with defective TH1/Tc1 recognition of the receptor binding domain (RBD) of the spike protein, likely affecting viral evolution by
15 selecting for new antigenic variants.

Current vaccines triggered anti-S1-RBD specific TH1/Tc1 responses in most healthy subjects, albeit with reduced efficacy in cancer patients. T cell immunity against the S1-RBD reference strain tended to decrease with time and in cancer patients, and crossreacted to some degree with the RBD sequences of viral variants of concern.
20 T cell immunity against the RBD sequences of viral variants of concern was reduced in vaccinees independently of age, gender and cancer. These findings indicate that COVID-19 protection relies on TH1/Tc1 cell immunity against SARS-CoV-2 S1-RBD, which in turn likely drives the phylogenetic escape of the virus.

The inventors then found that the most important response for being
25 protected against a circulating strain of SARS-CoV-2 is a TH1 response against the RBD (amino acids 331-525 of the spike protein) of said circulating strain. For example, a high TH1 response against the S1-RBD of the reference (Wuhan) strain was not only insufficient to protect against infection by the omicron strain, but it could even facilitate this infection.

30 The next generation of COVID-19 vaccines should elicit high-avidity TH1/Tc1 (rather than TH2)-like T cell responses against the RBD domain of current and emerging viral variants, while booster vaccinations should be guided by prior T cell assays.

According to a first aspect, the present invention thus pertains to a method
35 for *in vitro* determining whether an individual is likely to resist to an infection by SARS-CoV-2, comprising:

- (i) generating dendritic cells (DC) from monocytes obtained from said individual;
- (ii) loading said DC with a SARS-CoV-2 lysate or SARS-CoV-2 antigens;
- 5 (iii) contacting peripheral blood lymphocytes (PBL) from said individual with the DC obtained in step (ii), in appropriate conditions to activate said PBL;
- (iv) following the PBL activation, measuring the expression of at least one cytokine secreted by Th1 cells, selected from the group consisting of IL-2, IFN γ and TNF α , and measuring the expression of at least one cytokine secreted by Th2 cells,
- 10 selected from the group consisting of IL-5, IL-4, IL-9, IL-10 and IL-13; and
- (v) from the results of step (iv), assessing the Th1/Th2 polarization of SARS-CoV-2-specific memory T cell response in said individual,
- wherein a Th1 polarization indicates that the individual is likely to resist to an infection by SARS-CoV-2, and a Th2 polarization indicates that the individual is
- 15 susceptible to an infection by SARS-CoV-2.

The invention also pertains to another method for *in vitro* determining whether an individual is likely to resist to an infection by SARS-CoV-2, comprising:

- (i) incubating T lymphocytes from said individual with a mix of antigenic peptides from SARS-CoV-2, under conditions appropriate to stimulate Th1
- 20 and/or Th2 lymphocytes specific for said peptides; and
- (ii) assessing the presence of Th1 and/or Th2 lymphocytes;
- wherein the presence of Th1 lymphocytes specific for said peptides indicates that the individual is likely to resist to an infection by SARS-CoV-2, and/or the absence of Th1 lymphocytes and/or the presence of Th2 lymphocytes specific for said
- 25 peptides indicates that the individual is susceptible to an infection by SARS-CoV-2.

A method for monitoring the efficacy of a vaccination against SARS-CoV-2 in an individual, comprising performing any of the above methods with a biological sample from said individual, is also part of the present invention.

- Another aspect of the invention is also the use of one of the above
- 30 methods for *in vitro* assessing the susceptibility or resistance status of an individual after vaccination, to monitor the efficacy of a vaccination against SARS-CoV-2 in an individual or in a population.

- The invention also relates to an immunogenic composition comprising, in one or several polypeptides, the epitopes present in a sequence corresponding to amino
- 35 acids 331 to 525 of a SARS-CoV-2 spike protein, as well as, optionally, the epitopes present in a sequence corresponding to amino acids 1 to 165 of a SARS-CoV-2 spike protein.

A nucleic acid molecule encoding the above-defined polypeptides is also part of the invention, as well as an immunogenic composition comprising the same.

The present invention also relates to a vaccine comprising an immunogenic composition as described above, as well as a pharmaceutically acceptable excipient and/or adjuvant.

Another aspect of the present invention is an immunogenic composition comprising a polypeptide comprising or consisting of the sequence LDSKVGGNY (SEQ ID No: 262), or a nucleic acid encoding the same, for use in the treatment of cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure Legends

Figure 1. SARS-CoV-2 TH1/Tc1 responses in COVID-19 and unexposed individuals.

A. Graphical representation of the prospective patient cohorts used for the study (refer to Table 1 to 3). **B.** First experimental in vitro stimulation assay of peripheral blood lymphocytes (PBL) using crosspresentation of viral lysates by autologous dendritic cells (DC). Twelve plex flow cytometric assay to monitor cytokine release in replicates. **C.** Mean fold changes ($\log_2$, F.C) between SARS-CoV-2-specific cytokine secretions of acute COVID-19 patients or convalescent COVID-19 individuals and controls (also refer to S1C). **D.** Ratios of cytokine secretion between PBL stimulated with DC pulsed with SARS-CoV-2 (or the other CCC lysates) *versus* VeroE6 (or *versus* CCC respective control cell lines), at the acute or convalescent phases of COVID-19. One typical example is outlined in Figure S1A of Fahrner *et al.*, 2022 [100]. Each dot represents the mean of replicate wells for one patient (Controls, n=304; Convalescent COVID-19, n=54; Acute COVID-19, n=24). Asterisks indicate statistically significant differences in comparison to the control group determined using two-sided Wilcoxon-Mann-Whitney test (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$). **E.** Spearman correlations between SARS-CoV-2-specific IL-2 release and anti-NC IgG antibody titers (Controls, n=63; Convalescent, n =16). **F.** Spearman correlations between SARS-CoV-2-specific IL-5 release and anti-NC IgG antibody titers (Controls, n=63; Convalescent, n=16).

Figure 2. Unexposed individuals susceptible to COVID-19 exhibited a SARS-CoV-2 specific TH2 profile during the first surge of the pandemic.

A-B. Upper scheme: Outline of the prospective collection of blood samples used to identify COVID-19 resistant (light grey) *versus* susceptible (black) cancer patients (A, upper panel, Table 1, Tables 4&5) and pie chart indicating the absolute numbers (and %) of patients reported as contact (resistant) or infected (susceptible) or unexposed (grey)

during one-year follow-up (B). Lower scheme: Outline of the prospective collection of blood samples used for the comparison of T cell responses in the cohort of cancer-free individuals who lived in the same household with family members tested positive for COVID-19 during the 2020 lock down (Table 4). C. Number of positive cytokines released by SARS-CoV-2-specific PBL during the crosspresentation assay (Figure 1B) in each group (Unexposed, n=159; Resistant, n=48; Susceptible, n=22). D-E. SARS-CoV-2-specific IL-2 (left panel) and IL-5 (right panel) secretion contrasting resistant (light grey) *versus* infected (black) cancer cases. Each dot represents the ratio (D) of the replicate wells in one individual and the box plots indicate medians, 25th and 75th percentiles for each cancer patient subset. The bar plots (E) represent the percentage of positive patients (resist., n=41; suscept., n=19). Fisher exact test to compare the number of cytokine positive patients across groups (* $p < 0.05$). F. SARS-CoV-2-specific IL-2/IL-5 ratios (means $\pm$ SEM) in the different subsets of healthy and cancer individuals presented in panel A. Refer to Figure 7 for the waterfall plots to visualize variations in the percentages of individuals with IL-2/IL-5 ratios $>$ or $<$ 1 according to subject category. All group comparisons were performed using two-sided Wilcoxon-Mann-Whitney test and asterisks indicate statistically significant differences. G. CCC (OC43 and 229E)-specific IL-2 ratio (left panel) or IL-5 secretion ratio (right panel) contrasting contact (resistant, light grey dots, n=34) versus infected (susceptible, black dots, n=11) cases. H. Spearman correlations between OC43 and SARS-CoV-2-specific IL-2 (left panel) and IL-5 (right panel) secretions in 156 controls. I. Anti-spike IgG titers (means $\pm$ SEM) specific of seasonal betacoronaviruses in contact (resist., light grey dots, n=34) versus infected (suscept., black dots, n=11) cases. J-K. SARS-CoV-2-specific T cell reactivity monitored by IL-5 and IFN γ -ELISA (J) or IFN γ ELISpot (K) before and after Dupilumab in 9 patients diagnosed with atopic dermatitis. Each line represents the mean of two experimental replicates that are shown for n=3 samples before Dupilumab, and for n=7 samples after Dupilumab, including 7/9 in COVID-19 convalescence, only one patient had paired samples pre- and post-Dupilumab. Wilcoxon signed rank test for paired comparisons of clustered data (J) or linear mixed model (K) were used to compare experimental groups. L. Scheme detailing the two groups of cancer-free individuals from the same hospital with opposite clinical phenotypes (multi-exposed individuals (n=12) versus patients reinfected with SARS-CoV-2 (n=17) patients) (K, left panel). Results of the crosspresentation assay against SARS-CoV-2 for IL-10 (K, right panel) and IL-2. IL-5 levels at baseline and after TCR cross-linking are depicted in the middle panel. Each dot represents the mean of two replicates for one patient. All group comparisons were performed using two-sided Wilcoxon-Mann-Whitney test and asterisks indicate statistically significant differences (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$).

Figure 3. Peptide recognition patterns in all distinct subsets of individuals: repertoire breadth of peptide does not predict resistance to COVID-19.

A. Experimental setting for the 185 peptide-based *in vitro* stimulation assays. B-C. Percentages of positive peptides in individuals from the pre-COVID19 era (n=24) *versus* contemporary controls (n=97) (B, right panel) and in cancer (n=111) *versus* cancer free contemporary individuals (n=10) (B, left panel) and in uninfected (control (contemporary), n=97) *versus* convalescent (recovery, n=27) (C, left panel) and resistant individuals (non-infected contact cases (n=44) *versus* susceptible (infected, n=18) individuals (C, right panel). Group comparisons were performed using two-sided Wilcoxon-Mann-Whitney test and asterisks indicate statistically significant differences (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$).

Figure 4. Spike Receptor Binding Domain (S1-RBD)-directed TH1/Tc1 recall responses predict resistance to COVID-19.

A. Volcano plot showing statistical significance (p values) and magnitude of change in odd ratios of IFN γ secretion in response to SARS-CoV-1 (sarbecovirus) and SARS-CoV-2 peptides belonging to distinct viral proteins (each scatterplot) between susceptible *versus* resistant individuals. B-D. Percentages of patients recognizing at least one of the 11 S1-RBD peptides in the IFN γ ELISA of the peptide IVS assay across patients' groups described in Figure 2A (B) or convalescent *versus* reinfected patients (C) or vaccinees experiencing breakthrough infection (D). E. Percentages and absolute numbers of mutations contained in our S1-RBD peptide list reported in the current SARS-CoV-2 variants (refer to Table S12 of Fahrner *et al.*, 2022). The difference of the probability of mutation in S1-RBD region and in other regions was evaluated using logistic regression (Odd Ratio=0.21, 95% confidence interval [0.06; 0.68], $p=0.01$). F, H. High-throughput screening T cell assay using the Enzyme Linked Fluorescent Assay technique in an automatic platform monitoring IFN γ levels in whole blood samples from several independent cohorts of HCW (F) or cancer patients (H) with or without COVID-19 history (F), pre- and/or per (after 1 immunization, Day 21) and/or post vaccination (Day 90, Day 180) using different peptide pools (Table 12,). Monitoring of IFN γ release (F, H lower panels) and percentages of individuals with IFN γ levels > threshold of detection (upper panels). G. Influence of covariates (refer to Subtables S13a and S13b of Fahrner *et al.*, 2022 for statistics). Specimen were not systematically paired in the kinetic study. The log₁₀ normalized IFN γ secretions for all peptide stimulation were pooled to model simultaneously their dynamics from the first vaccine to day 180 using linear mixed effect regression adjusted for the patient age, sex, cancer status, COVID history, and vaccine schedule (cf statistical method section for more details). The Forest plot depicts the impact of the different variables on the PEPwtRBD IFN γ secretion levels (a positive or

negative coefficient indicating increase or decrease of IFN γ IU/ml respectively) (G).
 I. Paired analysis of the differential magnitude of TH1/Tc1 reactivity against PEP_{wtRBD}
 versus PEP_{mutRBD} in 343 cancer-free HCW vaccinees with no history of COVID-19. Each
 line represents one patient sample. Group comparisons were performed using two-sided
 5 paired Wilcoxon-Mann-Whitney test and asterisks indicate statistically significant
 differences (* p <0.05, ** p <0.01, *** p <0.001, **** p <0.0001).

Figure 5. Detailed SARS-CoV-2 and CCC-specific cytokine release for convalescent COVID-19 patients compared with unexposed individuals.

A. Percentage and number of patients in each cohort (Pre-COVID19 era (yes (+)/no(-)),
 10 Cancer (yes (+)/no(-) and COVID-19 (yes (+)/no(-)) who had a SARS-CoV-2-specific
 cytokine release (for the 5 statistically significant cytokines at the convalescent phase)
 compared with VeroE6 (Control, n=304; Convalescent, n=54). B-C. Idem as in Figure
 1D comparing frequencies of patients with CoV-2/VeroE6 ratios>2 for the most relevant
 cytokines in cancer versus cancer-free control individuals, taking into account cancer
 15 staging (C). Asterisks indicate statistically significant differences of SARS-CoV-2-
 specific cytokine release proportions between two groups determined using Fisher exact
 test (* p <0.05).

Figure 6. TH1/Tc1 differentiation patterns in susceptible versus resistant individuals.

20 A-B. Unsupervised hierarchical clustering of SARS-CoV-2-specific cytokine release.
 Heatmap of cytokine release in the crosspresentation assay performed during the first
 surge of the pandemic in unexposed individuals (n=60), aligning cytokines in the two
 subject categories, susceptible (persons who got infected during the second or the third
 surge of the pandemic) versus resistant (contact) individuals. Group comparisons were
 25 performed using a two-sided Wilcoxon-Mann-Whitney test. C. Dynamic study of the
 stability of the TH1/TH2 profile in individuals that were followed up at two time points.
 Ratio of cytokine release at the acute and convalescent phase (left panel) and
 corresponding IL-2/IL-5 ratio (right panel) in 5 cancer patients. Two-sided Wilcoxon-
 Mann-Whitney test did not reveal significant difference between both time points.
 30 D. Validation cohort of 2A with 8 additional HCW from Hospices Civils de Lyon (HCL)
 and 10 cancer patients from Gustave Roussy (D). E. Percentages of SARS-CoV-2
 specific TH1 or TH2 cell responses determined by dual Elispot assay (CoV2/VeroE6
 >1.5 increase in IFN γ (left) or IL-5 $^{+}$ (middle) SFC respectively). Calculation of the IFN γ
 /IL-5 $^{+}$ SFC ratio per individual in VeroE6 or SARS-CoV-2 condition, and percentages of
 35 patients with an increased (>2) ratio in the SARS-CoV-2 condition, in both Resist versus
 Suscep. Groups (right panel). Fisher's exact test to compare the number of patients
 positive for each category between groups (* p <0.05, ** p <0.01).

Figure 7. Waterfall plots indicating the IL-2/IL-5 ratio in all patient or individual groups.

Waterfall plot between IL-2 and IL-5 ratio of cytokine release in the Figure 1B IVS assay in all patients during the first surge of the pandemic depicting cancer (grey) versus cancer free (black) COVID-19+ convalescent patients (D), resistant (grey) versus susceptible (black) (A), locked down (or unknown) subjects (B, n=301) and healthy individuals in contact with their COVID-19+ family members (C). Each bar represents one patient. Proportion of patients exhibiting an IL-2/IL-5 ratio superior or inferior to 1 is indicated in each panel. Clinical conditions are annotated as 0, +, ++, +++ for asymptomatic, mild, moderate, and severe COVID-19 severity, respectively. Refer to Figure 2F where percentages are compared inbetween groups.

Figure 8. Crosspresentation assays using viral variants.

A. Percentage and number of patients in Fig2L right panel who had a SARS-CoV-2-specific IL-2 release. Of note, only 4 reinfected patients could be tested because DC could not be differentiated into monocytes in the others to allow the crosspresentation assay. **B.** Cytokine ratio in the crosspresentation assay detailed in Figure 1B, using the original strain IHUMI846 (early 2020 episode) (CoV-2 in (A)), versus the Danish mink (B.1.160, 20A.EU2, GH) and North African (B1.367, 20C, GH) strains in 25 control individuals. Statistical comparisons were performed using paired two-sided Wilcoxon-Mann-Whitney test and the asterisks indicate statistically significant differences (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$).

Figure 9. Logistic regression analyses identifying cohort -specific fingerprints of T cell repertoires.

A. Statistically significant peptide signatures in the peptide-based IVS assay (Figure 3A) using a multivariable logistic regression analysis adjusted for period (pre-COVID-19 era or contemporary patients), COVID-19 history and cancer (refer to Tables 2 and 3). The left column shows variables, and the x axis indicates the significant peptides ($p_{val} < 0.05$). The magnitude of the log (Odd Ratio) is indicated in the red/blue color code while that of the p-value is represented by the circle size. **B-C.** Log10 of the p value of the Fisher exact test comparing two groups of 101 individuals, based on their reactivity to PEP_{wIRBD} (yes/no) for each HLA allele (B), followed by selection of the most significant allele with its relative proportion among RBD reactive or areactive vaccinees (C).

DETAILED DESCRIPTION

According to a first aspect, the present invention pertains to a method for *in vitro* determining whether an individual is likely to resist to an infection by SARS-CoV-2, comprising:

- 5 (i) generating dendritic cells (DC) from monocytes obtained from said individual;
- (ii) loading said DC with a SARS-CoV-2 lysate or SARS-CoV-2 antigens;
- (iii) contacting peripheral blood lymphocytes (PBL) from said individual with the DC obtained in step (ii), in appropriate conditions to activate said PBL;
- (iv) following the PBL activation, measuring the expression of at least one cytokine
10 secreted by Th1 cells, selected from the group consisting of IL-2, IFN γ and TNF α , and measuring the expression of at least one cytokine secreted by Th2 cells, selected from the group consisting of IL-5, IL-4, IL-9, IL-10 and IL-13; and
- (v) from the results of step (iv), assessing the Th1/Th2 polarization of SARS-CoV-2-specific memory T cell response in said individual,
- 15 wherein a Th1 polarization indicates that the individual is likely to resist to an infection by SARS-CoV-2, and a Th2 polarization indicates that the individual is susceptible to an infection by SARS-CoV-2.

An individual "susceptible" to an infection by SARS-CoV-2 is one having little resistance to such an infection, and therefore capable of being infected.

- 20 In the above method, a "SARS-CoV-2 lysate" preferably refers to a lysate of a SARS-CoV-2 circulating strain, against which the resistance status of the individual is sought, or a lysate of a strain genetically close to said circulating strain.

- Similarly, "SARS-CoV-2 antigens" preferably refers to antigens of a SARS-CoV-2 circulating strain, against which the resistance status of the individual is sought, or antigens of a strain genetically close to said circulating strain. According to a
25 particular embodiment, the SARS-CoV-2 antigens comprise or consist of a SARS-CoV-2 Spike protein or a fragment thereof comprising the receptor binding domain (RBD) of the Spike protein (corresponding to amino acids 331-525 of the spike protein of the reference Wuhan strain). Preferably, the Spike RBD present in the antigen(s) used for
30 loading the dendritic cells is identical to that of the circulating strain, or has at least 80%, preferably at least 90% and more preferably at least 95% identity with the RBD of the Spike protein of the circulating strain.

- According to a particular embodiment of the above method, the expressions of IL-2 and IL-5 are measured in step (iv), and the ratio IL2/IL-5 is calculated
35 in step (v). A ratio IL2/IL5>1 indicates that the individual is likely to resist to an infection

by SARS-CoV-2, and $IL2/IL5 \leq 1$ indicates that the individual is susceptible to an infection by SARS-CoV-2.

According to another embodiment, the present invention relates to a method for *in vitro* determining whether an individual is likely to resist to an infection by SARS-CoV-2, comprising:

- (i) incubating T lymphocytes from said individual with a mix of antigenic peptides from SARS-CoV-2, under conditions appropriate to stimulate Th1 and/or Th2 lymphocytes specific for said peptides; and
 - (ii) assessing the presence of Th1 and/or Th2 lymphocytes;
- wherein the presence of Th1 lymphocytes specific for said peptides indicates that the individual is likely to resist to an infection by SARS-CoV-2, and/or the absence of Th1 lymphocytes and/or the presence of Th2 lymphocytes specific for said peptides indicates that the individual is susceptible to an infection by SARS-CoV-2.

While the experimental part illustrates this method with an incubation time of several days, the skilled person can of course modify the protocol to shorten this incubation time and/or automate the whole process, for example by using techniques disclosed in WO2018/202864 and in references cited therein.

In the above method, the "mix of antigenic peptides from SARS-CoV-2" preferably comprises peptides comprising epitopes of the RBD of the Spike protein of a circulating strain, or epitopes able to trigger an immune reaction cross-reacting with the RBD of a SARS-CoV-2 circulating strain, against which the resistance status of the individual is sought.

According to a particular embodiment, the mix of antigenic peptides comprises at least five peptides of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from a sequence consisting of aminoacids 331 to 555 of a SARS-CoV-2 spike protein (preferably identical or having at least 80%, at least 90% and preferably at least 95% identity with the aminoacids 331 to 555 of the SARS-CoV-2 spike protein of a circulating strain). As already mentioned, in the present text, the aminoacid positions are those of the proteins of the reference strain (Wuhan), which are disclosed in GenBank (MN908947.3).

According to another particular embodiment, the mix of antigenic peptides used to perform the above method comprises:

- at least five peptides of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from a sequence consisting of aminoacids 331 to 555 of a SARS-CoV-2 spike protein; and
- at least one, preferably at least two or at least three peptides of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from a SARS-CoV-2 nucleocapsid protein.

As described in the experimental part below, the inventors identified the subregions of the spike proteins which are of particular importance in the immune response against the virus. Thus, according to another particular embodiment, the mix of antigenic peptides used to perform the above method comprises:

- 5 - at least five peptides of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from a sequence consisting of aminoacids 361 to 555 of a SARS-CoV-2 spike protein, wherein at least one or two of said peptides are preferably from a sequence consisting of aminoacids 361 to 495 of a SARS-CoV-2 spike protein and at least one or two of said peptides are preferably from a sequence consisting of aminoacids 466 to 555 of a SARS-
10 CoV-2 spike protein; and
- at least two, preferably at least 3 peptides of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from a sequence consisting of aminoacids 1 to 135 of a SARS-CoV-2 spike protein.

According to yet another particular embodiment, the mix of antigenic
15 peptides used to perform the above method comprises:

- at least one, preferably at least two or at least three peptides of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from a sequence consisting of aminoacids 1 to 270 of a SARS-CoV-2 nucleocapsid protein; and/or
- at least one, preferably at least two or at least three peptide of 9 to 50 aminoacids,
20 preferably 12 to 25 aminoacids, from a sequence consisting of aminoacids 331 to 419 of a SARS-CoV-2 nucleocapsid protein; and/or
- one peptide of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from a SARS-CoV-2 ORF3a_AB protein, preferably consisting of or encompassing a sequence consisting of aminoacids 244 to 258 of said SARS-CoV-2 ORF3a_AB protein; and/or
- 25 - at least two peptides of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from a sequence consisting of aminoacids 856 to 1050 of a SARS-CoV-2 spike protein.

According to yet another particular embodiment, the mix of antigenic peptides used to perform the above method comprises:

- at least one peptide of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from
30 a sequence consisting of aminoacids 1 to 165 of a SARS-CoV-2 spike protein; and/or
- at least one peptide of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from a SARS-CoV-2 ORF10 protein; preferably from a sequence consisting of aminoacids 1 to 22 of a SARS-CoV-2 ORF10 protein and/or
- at least one peptide of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from
35 a SARS-CoV-2 ORF8 protein, preferably from a sequence consisting of aminoacids 1 to 36 or 99 to 121 of a SARS-CoV-2 ORF8 protein.

When performing the above method, step (i) can be performed by incubating T lymphocytes with the mix of antigenic peptides from SARS-CoV-2 in the presence of IL-2 and IL-15 to stimulate Th1 and/or Th2 lymphocytes specific for said peptides; in step (ii), the presence of Th1 lymphocytes can then be assessed by measuring the production of IFN γ and/or the presence of Th2 lymphocytes can be assessed by measuring the production of at least one cytokine selected from IL-5, IL-4, IL-6, IL-9 IL-10 and IL-13.

Alternatively, the stimulation of Th1 and/or Th2 lymphocytes in step (i) can be done by incubating T lymphocytes with the mix of antigenic peptides from SARS-CoV-2 in the presence of low doses of IL-2 or IL-15, or PMA/ionomycin, or low dose of anti CD3/anti CD28 antibodies to sensitize the TCR, in addition to IL-4 and/or anti-IL12 antibodies; then, in step (ii), the presence of Th2 lymphocytes can be assessed by measuring the production of at least one cytokine selected from IL-5, IL-9 IL-10 and IL-13.

According to a particular embodiment, the above method can be performed using at least one recipient that contains a mix of peptides which are common to all known strains of SARS-CoV-2 or induce cross-reactive immunity.

Alternatively or additionally, the above method is performed using at least one recipient that contains a mix of peptides which encompass the RBD region of circulating strain(s) of SARS-CoV-2 or induce cross-reactive immunity against this region in circulating strain(s).

According to a particular embodiment of the above method, the mix of peptides is dispatched in several recipients for performing the method, wherein at least one recipient contains a mix of peptides which are specific for one or more SARS-CoV-2 variant(s). The skilled person can thus establish a detailed profile of the individual or of a population, for example to assess the prevalence or the dynamics of a given strain.

According to a particular embodiment of the above method, the mix of peptides is dispatched in several recipients for performing the method, wherein at least one recipient contains a mix of peptides which are common to all known strains of SARS-CoV-2 or induce cross-reactive immunity, and at least another recipient comprises a mix of peptides which are specific for one or more SARS-CoV-2 variant(s).

When the above method is performed with a recipient that contains a mix of peptides which are common to all known strains of SARS-CoV-2 or induce cross-reactive immunity, detection of Th1 lymphocytes in said recipient indicates that the individual is likely to resist to an infection by any SARS-CoV-2 strain.

Conversely, when the method is performed with a mix of peptides comprising only peptides present in the proteins of a given variant strain of

SARS-CoV-2, the result indicates whether the individual is likely to resist to an infection by this variant strain of SARS-CoV-2.

According to a particular embodiment of the above method, the Th1 response is assessed using a first mix of peptides comprising at least 3, 4, 5, 6 or more peptides relevant for assessing Th1 response against SARS-CoV-2 and the Th2 response is assessed using a second mix of peptides comprising at least 3, 4, 5, 6 or more peptides relevant for assessing Th2 response against SARS-CoV-2.

The skilled person can chose the peptides present in the first and/or second mixes of peptides so that they comprise at least one peptide described in Table 12. According to a particular embodiment, several peptides are selected amongst those of Table 12. These two mixes of peptides can be identical or partially or totally different.

According to a particular embodiment, the first and second mixes of peptides are present in separate recipients/tubes.

When performing the above method, the presence of Th1 lymphocytes can be assessed in step (ii) by measuring the production of IFN γ in the recipient comprising the first mix of peptides and the presence of Th2 lymphocytes can be assessed by measuring the production of at least one cytokine selected from IL-5 in the recipient comprising the second mix of peptides.

In the absence of Th1 after incubation of the T lymphocytes with a mix of peptides covering a sequence comprising amino acids 331 to 525 and/or amino acids 329 to 521 and/or amino acids 391 to 555 of a SARS-CoV-2 spike protein (under conditions appropriate to stimulate Th1), the skilled person performing the method can deduce that the individual is susceptible to an infection by SARS-CoV-2 and its variants.

The same interpretation can be deduced if the results show the presence of a Th2 response combined to the absence or weak presence of Th1 after incubation of the T lymphocytes with a mix of peptides covering a sequence comprising amino acids 331 to 525 and/or amino acids 329 to 521 and/or amino acids 391 to 555 of a SARS-CoV-2 spike protein indicates that the individual is susceptible to an infection by SARS-CoV-2 and its variants (under conditions appropriate to stimulate Th1/Th2).

Conversely, the presence of Th1 after incubation of the T lymphocytes with a mix of peptides covering a sequence comprising amino acids 331 to 525 and/or amino acids 329 to 521 and/or amino acids 391 to 555 of a SARS-CoV-2 spike protein indicates that the individual is likely to resist to an infection by SARS-CoV-2 and its variants, at least to an infection by a SARS-CoV-2 strain having a RBD sequence with a high level of identity (at least 80%, 90%, 95% or 99%) with the sequences used to perform the method.

The inventors identified that the most important target for a protective Th1 response is that of the RBD of the spike protein. If this region is not tested or elicits a poor Th1 response, the presence of Th1 after incubation of the T lymphocytes with a mix of peptides comprised in a sequence consisting of amino acids 1 to 135 of a SARS-CoV-2 spike protein indicates that the individual is likely to resist to an infection by SARS-CoV-2 and its variants, only if a Th1 response has also been obtained against another part of the virus, e.g. against peptides of the nucleocapsid.

According to another of its aspects, the present invention pertains to a method for monitoring the efficacy of a vaccination against SARS-CoV-2 in an individual, comprising performing a method as those described above with a biological sample from said individual (after vaccination).

This method can advantageously be used to assess the efficacy of a vaccine for inducing a protective immune response against one or several new variant(s). For example, using peptides specific for said new variant(s) to stimulate Th1 and/or Th2 lymphocytes after vaccination (prime or boost) of the individual with a vaccine based on the Wuhan strain, a skilled person can assess whether the individual has become resistant to said new variant(s) thanks to this vaccination. Doing so in a representative cohort would provide information useful for dynamically establishing a correct vaccination policy in a population, depending of the population (age, ...) and the time (circulating and/or emerging strains).

Of course, at the individual level, this method can be used to monitor the efficacy of a vaccination against SARS-CoV-2 in an individual.

Another aspect of the present invention is an immunogenic composition comprising, in one or several polypeptides, the epitopes present in a sequence corresponding to amino acids 331 to 525 of a SARS-CoV-2 spike protein; such an immunogenic composition can additionally comprise, in the same or in different polypeptides, the epitopes present in a sequence corresponding to amino acids 1 to 165 of a SARS-CoV-2 spike protein.

According to a particular embodiment such an immunogenic composition comprises a first polypeptide sequence comprising amino acids 331 to 525 of a SARS-CoV-2 spike protein, and a second polypeptide sequence comprising amino acids 1 to 165 of a SARS-CoV-2 spike protein, wherein said first and second polypeptide sequences are in the same polypeptide molecule or in separate polypeptides which are distinct from a natural spike protein.

According to an example of such an immunogenic composition, the first polypeptide sequence consists of amino acids 331 to 525 of a SARS-CoV-2 spike

protein, and/or the second polypeptide sequence consists of amino acids 1 to 165 of a SARS-CoV-2 spike protein.

According to another example of such an immunogenic composition, the first polypeptide sequence consists of amino acids 331 to 600 of a SARS-CoV-2 spike protein or a fragment thereof, and/or the second polypeptide sequence consists of amino acids 1 to 270 of a SARS-CoV-2 spike protein or a fragment thereof.

As already mentioned, the above amino acid positions are those of the reference Wuhan strain, it being clearly understood that the immunogenic composition can comprise sequences originating from one or several other SARS-CoV-2 strain, for example from circulating variant(s) of concern.

In addition to the polypeptides mentioned above, an immunogenic composition according to the invention can further comprise a polypeptide sequence comprising amino acids 1 to 270 of a SARS-CoV-2 nucleocapsid protein, and/or a polypeptide sequence comprising amino acids 244 to 258 of a SARS-CoV-2 ORF3a_AB protein, and/or a polypeptide sequence comprising amino acids 29 to 92 of a SARS-CoV-2 ORF8 protein, and/or a polypeptide sequence comprising amino acids 22 to 38 of a SARS-CoV-2 ORF10 protein, wherein said additional polypeptide sequence(s) are in the same polypeptide molecule as the first and/or second polypeptide sequences or are in one or several separate polypeptide(s).

As shown in Example 2, the inventors also tested tumor infiltrating lymphocytes (TIL) from patients in the pre-pandemic time, and during the pandemic, to identify potential T-cell cross-reactivity between SARS-CoV-2 and self or viral proteins. By doing so, they identified cross-reactivity with SARS-CoV-1 but not with other circulating Coronaviral species, as well as a possible cross-reactivity to non-mutant or mutant human 'self proteins'. TIL are an interesting source to screen for potential autoimmunity in viral targets because they invade tissues.

Positive reactivity against SARS-CoV-2 peptides, based on the cytokine production pattern, can thus indicate an increased risk for autoimmune diseases upon exposure to the viral pathogen, or an increased pathogenicity upon viral infection due to an overt immune response (unproductive inflammation in the lung and other organs). To avoid such reaction and possible resulting organ-specific damage (such as myocarditis or damage of olfactory receptors for example), immunogenic compositions designed for being administered to humans should thus be devoid of sequences which could be recognized by T-cells also recognizing non-mutant human tissue.

Hence, according to a particular embodiment, the immunogenic composition according to the invention does not comprise the peptide sequence LVRDLPQGFSALE (SEQ ID No: 377).

5 According to another particular embodiment, the immunogenic composition according to the invention does not comprise the peptide sequence DVRVVLDFI (SEQ ID No: 178).

According to another particular embodiment, the immunogenic composition according to the invention does not comprise the peptide sequence LLNKHIDAY (SEQ ID No: 275).

10 According to another particular embodiment, the immunogenic composition according to the invention does not comprise the peptide sequence IELCVDEAG (SEQ ID No: 305).

According to another particular embodiment, the immunogenic composition according to the invention does not comprise the peptide sequence MKFLVFLGI (SEQ ID No: 308).

15 According to another particular embodiment, the immunogenic composition according to the invention does not comprise the peptide sequence MKFLVFLGIITTV (SEQ ID No: 378).

20 Of course, the immunogenic compositions according to the invention can be administered as polypeptide(s), or in the form of a nucleic acid molecule encoding the same. Such a nucleic acid molecule encoding the polypeptide(s) present in immunogenic compositions defined above are thus also part of the present invention, as well as an immunogenic composition comprising the same such as, for example, a viral vector comprising the same.

25 According to a preferred embodiment, the nucleic acid molecule according to the invention is a RNA molecule.

Another aspect of the present invention is a vaccine composition against SARS-CoV-2. In a particular embodiment, such a vaccine composition comprises an immunogenic composition as any one of those described above, as well as a pharmaceutically acceptable excipient and/or adjuvant.

30 Preferred adjuvants are those that favor a Th1 response. Examples of adjuvants which are appropriate for being included in a vaccine composition according to the invention thus include TLR4 agonists, TLR3 ligands/ agonists, TLR7-8 agonists and TLR9 agonists.

35 More particularly, a vaccine composition according to the invention can advantageously comprise at least one adjuvant selected from the group consisting of lipopolysaccharides, MPL: 3-O-desacyl-4'-monophosphoryl lipid A derived from

Salmonella minnesota LPS, poly A :U, poly I :C, IMIQUIMOD, CpG DNA and CpG ODNs.

5 Surprisingly, the inventors also identified a sequence in the spike protein of SARS-CoV-2 that shares antigenic sites with an antigen that is specific for certain forms of cancers. Due to this antigenic mimicry, an infection by SARS-CoV-2 could elicit an immune response ameliorating the patients' antitumor response.

The present invention thus pertains to an immunogenic composition comprising a polypeptide comprising a sequence selected amongst LDSKVGGNY (SEQ ID No: 262), NSNNLDSKV (SEQ ID No: 263) and NSNNLDSKVGGNY (SEQ ID No: 10 379), or a nucleic acid encoding the same, for use in the treatment of cancer.

According to a preferred embodiment, such an immunogenic composition is used in the treatment of a cancer overexpressing Tensin-1.

Such an immunogenic composition according to the invention is particularly useful for immunotherapy of a pancreas adenocarcinoma or a colon 15 adenocarcinoma.

Other characteristics of the invention will also become apparent in the course of the description which follows of the experimental assays which have been 20 performed in the framework of the invention and which provide it with the required experimental support, without limiting its scope.

EXAMPLES**Example 1: The polarity and specificity of SARS-CoV2 -specific T lymphocyte responses determine disease susceptibility****5 Material and methods**

Patient and cohort characteristics. All clinical studies were conducted after written informed consent in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. Cohorts' and subsets' characteristics are detailed in Tables 1 to 8, 10 and 14, and Figure 1A. Two cohorts of cancer patients (from
 10 the pre-COVID-19 era and from the COVID-19 era) and three cohorts of healthy volunteers (from the pre- COVID-19 era and from the COVID-19 period including three cohorts of vaccinees (HCL, GR, cancer/cancer free) were exploited to set up the translational research analyses. Peripheral blood mononuclear cells (PBMC) were provided by Gustave Roussy Cancer Campus (Villejuif, France) and IHU Méditerranée
 15 Infection (Marseille, France) (see Blood analyses section). The type of ancillary studies is detailed in Table 1.

Contemporary clinical studies (COVID-19 era): 1/ ONCOVID clinical trial and regulatory approvals.

20 Principles. The protocol NCT04341207 is available on the clinicaltrials.gov website. Gustave Roussy Cancer Center sponsored the trial named `ONCOVID` and collaborated with the academic authors on the trial design and on the collection, analysis, and interpretation of the data. Sanofi provided trial drugs. Protocol approval was obtained from an independent ethics committee (ethics protocol number EudraCT No: 2020-
 25 001250-21). For details, refer to previous report [32]. **Samples for translational research.** PMBCs were isolated less than 8 hours after the blood collection (at patient inclusion and at every hospital visit) and kept frozen at -80°C. **2/ PROTECT-Cov clinical trial and regulatory approvals. Principles.** IHU Méditerranée Infection sponsored the trial named `PROTECT-Cov` and collaborated with the academic authors on the trial
 30 design and on the collection, analysis, and interpretation of the data. Protocol approval was obtained from an independent ethics committee (ethics protocol number ANSM No: 2020-A01546-33). The trial was conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. All patients provided written informed consent. **Subjects.** PROTECT-Cov eligible subjects were members of the
 35 same family/home composed of two or more people and selected from the microbiology laboratory register on SARS-Cov-2 tests performed between March 23 and April 10, 2020. **Trial design.** Members of the same family/home who had at least one

(a)symptomatic COVID-19 + case (RT-qPCR <35 Ct values for SARS-CoV-2 on nasopharyngeal swabs) and at least one member with negative RT-qPCR for SARS-CoV-2 (≥ 35 Ct) were screened. A telephone interview was conducted in order to confirm and complete the list of family circles in connection with the positive case. The compliant subjects finally selected were invited to come back to the IHU Méditerranée Infections hospital where they were included in the trial and had a blood test. **3/ COVID-SER clinical trial and regulatory approvals. Principles.** At the "Hospices Civils de Lyon", France was conducted the trial named COVID-SER. Protocol approval was obtained from an independent ethics committee (the national review board for biomedical research, Comité de Protection des Personnes Sud Méditerranée, ID-RCB-2020-A00932-37). The clinical study was registered on ClinicalTrial.gov (NCT04341142). For details, refer to Mouton et al. [43]. Written informed consent was obtained from all participants and the study. Blood sampling was performed before vaccination and 4 weeks after receiving 1 or 2 doses of vaccine for naive and convalescent health care workers respectively. According to French procedures, a written non-opposition to the use of donated blood for research purposes was obtained from healthy volunteers. The donors' personal data were anonymized before transfer to our research laboratory. We obtained approval from the local ethical committee and the French ministry of research (DC-2008-64) for handling and conservation of these samples. Human biological samples and associated data were obtained from NeuroBioTec (CRB HCL, Lyon France, Biobank BB-0033-00046) and Virginie Pitiot. **4/ COV3AP-HP clinical trial and regulatory approvals. Principles** BioMérieux S.A is the promotor of the trial "COV3AP-HP" approved by the local ethical committee (number N° ID-RCB : 2021-A00304-37). The trial was conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki at Gustave Roussy and Cochin Institute, France. All subjects provided written informed consent. **5/ Dupilumab for atopic dermatitis translational study.** This trial was conducted at the Department of Dermatology, Center of Excellence in Eczema Laboratory of Inflammatory Skin Diseases, Icahn School of Medicine at Mount Sinai New York, NY, USA with Regeneron sponsorship after ethical committee approval (STUDY-20-00682-MOD001).

Clinical studies from the Pre-COVID-19 era: 1/ Series of patients with cancer: This cohort is composed of different IGR clinical trials. Patients were included and blood was collected and banked between 1999 and 2018 (Pre-COVID-19 era). **Clinical studies** have been described in previous reports [29,31,77] (CALEX protocol, n1 ID RCB 2007-A01074-49, date 29 February 2008). (Study code « Dex2 »: NCT01159288, date 19 December 2005) (Study code « LUD 99 003 »: N-CSET : 99/090/752, date 1 December 1999) (Phase I IMAIL-2 trial approved by the Kremlin Bicêtre Hospital Ethics Committee

[no 07–019] and the Agence Française de Sécurité Sanitaire des Produits de Santé [no A70385–27; EudraCT N°:2007–001699–35 in 2007]. **2/ Series of patients without cancer** : Peripheral blood was obtained from healthy volunteers at the *Etablissement Français du Sang* (EFS, Paris France, n 18EFS031 date 24 September 2018).

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Blood analyses. Blood samples (for serum and PBL) were drawn from patients enrolled in the different cohorts presented in the cohort description section above. Whole human peripheral blood was collected into sterile vacutainer tubes. **Anti-SARS-CoV-2 immunoglobulins measurements.** Serum was collected from whole blood after centrifugation at 600 g for 10 min at room temperature and transferred to -80°C freezer to await analysis. Serological analysis SARS-CoV-2 specific IgA, IgM and IgG antibodies were measured in 119 serum samples from 87 patients with The Maverick™ SARS-CoV-2 Multi-Antigen Serology Panel (Genalyte Inc. USA) according to the manufacturer's instructions. The Maverick™ SARS-CoV-2 Multi-Antigen Serology Panel (Genalyte Inc) is designed to detect antibodies to five SARS-CoV-2 antigens: nucleocapsid, Spike S1 RBD, Spike S1S2, Spike S2 and Spike S1 or seasonal HCoV -NL-63 nucleocapsid, -OC-43, -229E and -HK-U1 Spike in a multiplex format based on photonic ring resonance technology. This system detects and measures with good reproducibility changes in resonance when antibodies bind to their respective antigens in the chip. The instrument automates the assay. Briefly, 10µl of each serum samples were added in a sample well plate array containing required diluents and buffers. The plate and chip are loaded in the instrument. First the chip is equilibrated with the diluent buffer to get baseline resonance. Serum sample is then charged over the chip to bind specific antibodies to antigens present on the chip. Next, chip is washed to remove low affinity binders. Finally, specific antibodies of patients are detected with anti-IgG or -IgA or -IgM secondary antibodies. **Isolation of peripheral blood mononuclear cells (PBMCs) from fresh blood sampling.** Venous blood samples (10ml to 30ml) were collected in heparinized tubes (BD Vacutainer® LH 170 U.I., Dutscher, UK). On the same day, blood was processed in a biosafety level 2 laboratory at Gustave Roussy Institute, Villejuif, France, or in IHU Méditerranée Infection, Marseille, France. Peripheral blood mononuclear cells (PBMCs) were freshly isolated by LSM, Lymphocyte Separation Medium (Eurobio Scientific, France) density gradient centrifugation according to manufacturer's instructions. (Leucosep tubes, Greiner; Biocoll, Bio&SELL). PBMCs were then collected, washed once with phosphate-buffered saline solution (PBS) and aliquoted in 1ml of cryopreservation medium (CryoStor®, STEMCELLS Technologies, USA) in cryovials (two cryovials per patient). Cryovials (Cryotube™ vials ThermoFisher Scientific, Denmark) were conserved for 24h at -80°C in a cryo-freezing container

(Mr.Frosty™, Thermo Fisher Scientific) before storage in liquid nitrogen. ***Serum and serologies.*** Specific anti-SARS-CoV-2 IgG antibodies were detected by the Liaison XL automated chemiluminescent immunoassay (CLIA) (Diasorin Inc., Saluggia, Italy) according to the manufacturer's recommendations. Seroneutralization was performed as
5 already described [78].

Reagents: culture media, cytokines, ELISA and multiplex assays. PBMC isolation.
Blood samples were collected in heparinized tubes BD Vacutainer® LH 170 U.I., from
Dutscher (catalog reference: 367526), diluted in PBS 1X purchased from Eurobio
10 Scientific (catalog reference: CS3PBS01-01) and transferred in Leucosep™ - 50mL
purchased from Greiner Bio-One (catalog reference: 227290). Blood was centrifuged
using MF48-R Centrifuge from AWEL Industries (catalog reference: 20023001). PBMC
were collected in Centrifuge tube 50mL TPP from Dutscher (catalog reference: 91050),
washed with PBS 1X, resuspended in CryoStor® CS10 purchased from STEMCELL™
15 technologies (catalog reference: 5100-0001) and transferred in Cryotube™ vials from
ThermoFisher Scientific (catalog reference: 377267). Samples were finally conserved for
24h at -80°C in a cryo-freezing container Mr.Frosty™ from Thermo Fisher Scientific
before storage in liquid nitrogen. ***Crosspresentation assay or peripheral blood
lymphocyte stimulation with autologous monocyte derived- dendritic cells (DC).***
20 Frozen PBMCs were thawed, washed and resuspended in RPMI Medium 1640 (1X)
purchased from GIBCO (catalog reference: 31870-025). Counting and viability were
evaluated using Vi-CELL™ XR Cell Viability Analyzer from Beckman Coulter (catalog
reference: AV13289). To separate adherent and non-adherent cell populations, PBMC
were transferred in 6 or 24 well flat bottom Sterile tissue culture testplate TPP purchased
25 from Dutscher (catalog reference: 92006 / 92024) and cultured in complex medium
(Complex Medium 1) containing human AB serum (catalog reference: 201021334),
purchased from Institut de Biotechnologies Jacques Boy France), RPMI Medium 1640
(1X) (catalog reference: 31870-025), Sodium Pyruvate (catalog reference: 11360-039),
Penicillin /Streptomycin (catalog reference: 15140-122), L-Glutamine (200mM) (catalog
30 reference: 25030-024) HEPES Buffer Solution (catalog reference: 15630-056), MEM
NEAA (catalog reference: 1140-035), purchased from GIBCO/ThermoFisher Scientific.
The Non-adherent fraction was cultured in another complex medium (Complex Medium
2) containing human AB serum, Iscove's Modified Dulbecco's Medium (catalog
reference: I3390), from Sigma-Aldrich, Sodium Pyruvate (catalog reference: 11360-039),
35 Penicillin/Streptomycin (catalog reference: 15140-122), L-Glutamine (200mM) (catalog
reference: 25030-024) HEPES Buffer Solution (catalog reference: 15630-056), MEM
NEAA (catalog reference: 1140-035) from GIBCO/ThermoFisher Scientific and

Recombinant Human IL-2 (PHAR000306) from Gustave Roussy Institute pharmacy. The adherent fraction was differentiated into monocyte derived- dendritic cells (mo-DC) in a mo-DC differentiating media constituted with Complex Medium 1 supplemented with Recombinant Human GM-CSF Premium purchased from Miltenyi (catalog reference: 130-093-867) and human IFN α -2b (Introna) purchased from MSD (France) (catalog reference: PHAR008943). For activation and maturation, DCs were stimulated with LPS purchased from Invivogen (catalog reference:) and GM-CSF purchased from Miltenyi Biotec (catalog reference: 130-093-867). PBL and mo-DC were finally co-cultured into 96 well V bottom Sterile Nunc™ plate, VWR purchased from Dutscher (catalog reference: 92097). For positive control, PBL were stimulated with Dynabeads™ Human T-Activator CD3/CD28 purchased from GIBCO / ThermoFisher Scientific (catalog reference: 11131D). All cell cultures were performed at 37°C, 5% CO₂ into Heraus® incubator purchased from Kendro Laboratory Products, ThermoFisher Scientific (catalog reference: BB 6220) And supernatants were transferred into 96 well V bottom Sterile Nunc™ plate, VWR purchased from Dutscher (catalog reference: 734-0491) and frozen.

Peptide-based assay. 96 well V bottom Sterile Nunc™ plate were coated with peptides at 2 μ g/mL in RPMI Medium 1640 (1X) (catalog reference: 31870-025) supplemented with 1% Penicillin/Streptomycin (catalog reference: 15140-122) and conserved at -80°C. PBMCs were then thawed and plated in plate containing peptides in RPMI Medium 1640 (1X) (catalog reference: 31870-025) supplemented with 1% Penicillin/Streptomycin (catalog reference: 15140-122) supplemented with Recombinant Human IL-15 Premium grade from Miltenyi biotec (catalog reference: 130-095-765) and Recombinant Human IL-2 (PHAR000306) from Gustave Roussy Hospital. For positive, PBMC were stimulated with functional grade CD3, OKT3 purchased from ThermoFisher Scientific (catalog reference: 16-0037-85). Cell cultures were then supplemented with human AB serum (catalog reference: 201021334) purchased from Institut de Biotechnologies Jacques Boy (France) and cultured at 37°C, 5% CO₂.

Cytokines monitoring. Supernatants from cultured cells from Crosspresentation assay were monitored using the MACSPlex Cytokine 12 Kit human purchased from Miltenyi Biotec (catalog reference: 130-099-169). Acquisitions and analyses were performed on CytoFLEX S purchased from Beckman Coulter (catalog reference: B75442)/FACS Aria Fusion purchased from BD biosciences and FlowJo Software from Treestar respectively. Whereas Supernatants from cultured cells from peptide-based assay were monitored using ELISA tests purchased from BioLegend: ELISA MAX™ Deluxe Set Human IFN- γ (catalog reference: 430104) ELISA MAX™ Deluxe Set Human IL-17 (catalog reference: 433914) and ELISA MAX™ Deluxe Set Human IL-9 (catalog reference: 434705).

Viral studies. Biosafety levels for in vitro experiments. Frozen PBMCs from patients with a confirmed negative RT-qPCR for SARS-CoV-2 genome at the time of blood drawing were processed in a biosafety level 2 laboratory at Gustave Roussy Institute, Villejuif, France. All samples from patients with positive RT-qPCR were processed in a biosafety level 3 laboratory at Henri Mondor Hospital, Créteil, France. When a patient was sampled at different timepoints, samples were processed together in the same laboratory. **RT-qPCR analysis.** SARS-CoV-2 diagnostic testing of clinical nasopharyngeal swabs or other samples by RT-qPCR was conducted from 14 March to 23 March 2020 at an outside facility using the Charité protocol. From the 23th March 2020 testing was performed internally at the Gustave Roussy. The cycle thresholds were collected only for assays performed at Gustave Roussy. Nasopharyngeal swab samples were collected using flocked swabs (Sigma Virocult) and placed in viral transport media. SARS-CoV-2 RNA was detected using one of two available techniques at Gustave Roussy: the GeneFinder COVID-19 Plus RealAmp kit (ELITech Group) targeting three regions (*RdRp* gene, nucleocapsid and envelope genes) on the ELITe InGenius (ELITech Group) or the multiplex real-time RT-PCR diagnostic kit (the Applied Biosystems TaqPath COVID-19 CE-IVD RT-PCR Kit) targeting three regions (ORF1ab, nucleocapsid and spike genes) with the following modifications. Nucleic acids were extracted from specimens using automated Maxwell instruments following the manufacturer's instructions (Maxwell RSC simplyRNA Blood Kit; AS1380; Promega). Real-time RT-PCR was performed on the QuantiStudio 5 Dx Real-Time PCR System (Thermo Fisher Scientific) in a final reaction volume of 20 µl, including 5 µl of extracted nucleic acids according to the manufacturer instruction. **Viral lysates and their production.** SARS-CoV-2 IHUMI2, IHUMI845, IHUMI846, IHUMI847 (early 2020 episode), IHUMI2096 (20A.EU2, B.1.160) and IHUMI2514 (20C, B.1.367) [25] IHUMI3076 (20I/501Y.V1, B.1.1.7), IHUMI3147 (20H/501Y.V2, B.1.351) and IHUMI3191 (20J/501Y.V3, P.1) strains were isolated from human nasopharyngeal swab as previously described [25] and grown in Vero E6 cells (ATCC CRL-1586) in Minimum Essential Medium culture medium (MEM) with 4% fetal calf serum (FCS) and 1% L-glutamine. Influenza strains H1N1 (0022641132) and H3N2 (8091056304) were isolated then produced from human nasopharyngeal swab in MDCK cells (ATCC CCL-34) in MEM with 10% FCS and 1% L-glutamine. All these clinical isolates were characterized by whole viral genome sequencing from culture supernatants. Coronavirus OC43 (ATCC vr-1558) was grown in HCT8 cells (ATCC CCL-244) in RPMI with 10% FCS. Coronavirus 229E (ATCC vr-740) was grown in MRC5 cells (ATCC CCL-171) in MEM with 10% FCS. All reagents for culture were from ThermoFisher Scientific and all cultures were incubated at 37°C under 5% CO₂ without antibiotics. All viral strains were

produced in 125 cm² cell culture flasks. When destruction of cell monolayer reached approximately 80%, between 2 to 7 days according to cell line and viral strain, culture supernatant was harvested. After low -speed centrifugation to remove cells and debris (700 x g for 10 min.) supernatants were filtered through 0.45 then 0.22 µm pore-sized filters. These viral suspensions were then inactivated for 1 hour at 65°C before use. BaTches of scrapped control uninfected cells were rinsed twice in PBS, and then finally resuspended in 5 ml of PBS at 5.10⁵ cells/ml. All cells and antigens were tested negative for Mycoplasma before use.

In vitro stimulation assays. Crosspresentation assay or peripheral blood lymphocyte stimulation with autologous monocyte derived- dendritic cells (DC).

Frozen PBMCs were thawed, washed and resuspended in RPMI 1640 media (GIBCO). Viability and count were evaluated using a Vi-Cell XR Cell Counter (Beckman Coulter, Brea). PBMC were then cultured in RPMI 1640 supplemented with 10% human AB serum, 1mM Glutamine, 1% sodium pyruvate, 1% HEPES, 1% penicillin/streptomycin at a cell density of 0.5M cells/cm² for 2 hours at 37°C, 5% CO₂ and separated into adherent and non-adherent cell populations. Non-adherent cells, containing Peripheral Blood Lymphocytes (PBL), were collected and cultured 4 days at 37°C, 5% CO₂ in IMDM medium (Sigma-Aldrich, UK), supplemented with 10% human AB serum (Institut de Biotechnologies Jacques Boy, France), 1mM Glutamine (GIBCO/ThermoFisher Scientific, UK) 1% Sodium Pyruvate (GIBCO/ThermoFisher Scientific, UK), 1% HEPES (GIBCO/ThermoFisher Scientific, UK), 1% penicillin/streptomycin (GIBCO/ThermoFisher Scientific, UK) and 200 UI/mL rhIL-2 (Miltenyi, Germany). The adherent cell population was cultured for 3 days, at 37°C, 5% CO₂, in a mo-DC differentiating media containing RPMI 1640 supplemented with 10% human AB serum, 1mM Glutamine, 1% sodium pyruvate, 1% HEPES, 1% penicillin /streptomycin, 1000UI/mL rhGM-CSF (Miltenyi) and 250UI/mL human IFNα-2b (Introna, MSD France). At day 3, adherent cells were slowly detached by pipetting after 20 minutes of incubation at 4°C and 20.000 cells were seeded in 96 well round bottom plate and were pulsed, or not (control condition), overnight, at 37°C, 5% CO₂, with 1/10 heat inactivated viral lysates, or their respective control (see viral lysates production section). Spinoculation (800g for 2h, Centrifuge 5810R, Eppendorf, Germany) was next performed to ensure synchronized capture of the viral particles by mo-DCs. For activation and maturation, adherent cells were stimulated with LPS (10 ng/mL, Thermofisher) and GM-CSF (1000UI/mL). After 6h, mo-DCs were washed twice to remove LPS from the media and 100 000 PBL/well were seeded onto mature mo-DCs. PBL alone served as negative control, and PBL stimulated with anti-CD3 and anti-CD28 microbeads (1µL/mL, Dynabeads T-Activator, InVitrogen) as a positive control. moDC-PBL co-culture was

incubated at 37°C, 5% CO₂ for 48h and supernatants were harvested and stored at -20°C.

Multiplex Cytokine Analysis or bead-based multiplex assays. moDC-PBL co-culture supernatants were analyzed using bead-based multiplex kit assays (MACSplex cytokine 12 human, Miltenyi) according to the manufacturer protocol. Briefly, 50uL of supernatant were used with a MACSPLEX Cytokine12 Capture Beads (Miltenyi, France) to measure the concentration of 12 cytokines (GM-CSF, IFN- α , IFN- γ , IL-10, IL-12, IL-17A, IL-2, IL-4, IL-5, IL-6, IL-9, TNF- α). Bead fluorescence was acquired on a CytoFLEX flow cytometer (Beckman Coulter) for samples processed at Gustave Roussy Institute and on a FACS Aria Fusion (Becton Dickinson) for samples processed in the biosafety level 3 laboratory at Henri Mondor Hospital. FlowJo (Treestar, Ashland, OR, USA) software was used for analysis. **Positivity threshold determination for cytokine concentration using multiplex assays and commercial ELISA assays.** For multiplex assays (or ELISA), a 4 parameter logistic regression was fitted for each cytokine based on the APC mean fluorescent intensity (or Optical Density) of standard dilution samples using nlpr(v0.1-7). This model was then used to calculate the concentration of each sample of unknown concentration. For multiplex assays, a ratio was computed for each cytokine using the cytokine concentration measured in response to each virus (SARS-CoV-2, HCoV-229E, HCoV-OC43) divided by the median concentration of their respective biological controls (Vero 81, MRC5, HCT8). A positivity threshold was set up based on the ratio for each cytokine. A ratio of above 1.5 minimum was requested to consider the supernatant "positive" for a cytokine. When necessary, a higher threshold was set up as such, median cytokine concentration of the biological controls + 2 times the standard deviation of the biological control concentrations divided by the median concentration. For ELISA assays, a ratio was computed as the concentration of the sample divided by the mean concentration of the negative controls.

ELISpot assay. The enumeration of antigen-specific IFN γ and IL-5 producing T cells was performed using the ImmunoSpot human IFN γ /IL-5 double-color enzymatic ELISPOT kit (Cellular Technology Limited (CTL), Germany). Peripheral blood lymphocytes were stimulated with autologous monocyte derived- dendritic cells loaded with SARS-CoV-2 lysates or their respective controls (see cross presentation assay section). After 48 hours, cells were resuspended in serum-free testing medium (CTL, Germany) containing 1 mM GlutaMAX (Gibco) and 1% penicillin/streptomycin (GIBCO) at a final volume 200 μ L/well and seeded in a 96-well nitrocellulose plate coated with human IFN γ and IL-5 capture antibody. Plates were incubated for 18h at 37 °C in 5% CO₂. ELISPOT assays were then performed according to manufacturer's instructions. Spots were counted by CTL ImmunoSpot Analyzer using ImmunoSpot software.

- Flow cytometric analyses. Sample preparation.** Cells from the crosspresentation assays (PBL+DC loaded with viral lysates or VeroE6 supernatants) were stained for viability with Zombie Aqua (BioLegend Cat#423102) for 20 min at +4°C, then washed in staining buffer (PBS 1X, BSA 2%, 2mM EDTA). Then, cells were stained with a panel of antibodies (as indicated in table for supplementary methods below) for 20 min at room temperature in staining buffer with Brilliant Strain Buffer (BD, Cat#563794). Cells were then washed, fixed and permeabilized (Foxp3/Transcription Factor Staining Buffer Set eBiosciences Cat#00-55-23-00) for 40 min at +4°C before being stained with intracellular antibodies for 30 min at +4°C. **Data Acquisition.** Samples were acquired on a BD LSRFortessa™ X-20 Flow Cytometer. **Data analysis.** Analysis was performed with FlowJo software (Tree Star).

Table for supplementary methods:

Channel	Target	Clone	Reference	Company
BUV496	CD8	RPA-T8	612942	BD
BUV737	CCR7/CD197	2-L1-A	749676	BD
BUV805	CD4	SK3	612887	BD
BUV396	CD3	UCHT1	563546	BD
PE-Cy7	CCR4/CD194	1G1	557864	BD
FITC	CXCR3/CD183	G025H7	353704	BioLegend
APC-R700	CCR6/CD196	11A9	565173	BD
PE-CF594	4-1BB/CD137	4B4-1	309826	BioLegend
BV605	CD25	2A3	562660	BD
BV650	OX40/CD134	ACT35	563658	BD
BV786	CD45RA	HI100	563870	BD
BV711	CD69	FN50	310944	BioLegend
BV510	CD14	M0P9	563079	BD
BV510	CD19	SJ25C1	562947	BD
BV421	Ki67	B56	562899	BD
BB700	GATA3	L50-823	566642	BD
PE	T-bet	eBio4B10	12-5825-82	eBiosciences

- Whole-transcriptome RNA-sequencing.** PBL from eleven resistant and 7 susceptible patients as well as 8 and 10 patients for whom crosspresentation assays revealed an IL-2/IL-5 ratio > and <1 respectively were used for the RNA sequencing of PBLs at 48 hrs after incubation with DC loaded with viral lysates. Cells from 18 wells post-stimulation with SARS-CoV-2 or VEROE6 were analyzed. The RNA integrity (RNA Integrity Score ≥ 7.0) was checked on the Agilent 2100 Bioanalyzer (Agilent) and quantity was determined using Qubit (Invitrogen). SureSelect Automated Strand Specific RNA Library Preparation Kit was used according to manufacturer's instructions with the Bravo Platform. Briefly, 30 to 100 ng of total RNA sample was used for poly-A mRNA selection using oligo(dT) beads and subjected to thermal mRNA fragmentation. The fragmented mRNA samples

were subjected to cDNA synthesis and were further converted into double stranded DNA using the reagents supplied in the kit, and the resulting dsDNA was used for library preparation. The final libraries were bar-coded, purified, pooled together in equal concentrations and subjected to paired-end sequencing (2 x 100 bp) on Novaseq-6000
 5 sequencer (Illumina) at Gustave Roussy.

Peptide-based assays.

Rationale of peptide selection and peptide synthesis (Refers to Table 9). Peptide
 10 selection and synthesis: the peptides from the spike and nucleocapsid proteins were selected by dividing the sequences of the SARS-CoV-2 spike protein (RefSeq ID QHD43416.1) and of the nucleocapsid protein (RefSeq ID QHD43423.2) in non-overlapping 15 amino acid segments. The peptides from the membrane protein were selected by dividing the sequence of 2 potential immunogenic regions of the SARS-CoV-
 15 2 (RefSeq QHD43422.1) membrane protein in overlapping 15 amino acid segments. The peptides from the ORF8 and ORF10 proteins were selected by dividing the sequences of the SARS-CoV-2 ORF8 protein (RefSeq ID QHD43422.1) and of the ORF10 protein (RefSeq ID QHI42199.1) in overlapping 15 amino acid segments. The peptides from ORF3 and some for ORF8 were selected based on a previous study⁷⁹. The SARS-CoV-
 20 1peptides were peptides found to be immunogenic in previous reported studies [11,54,80,81,82,83,84]. The peptides were synthesized by peptides&elephants GmbH (Berlin, Germany). The peptide pools for the controls for Influenza, EBV and CMV were acquired from peptides&elephants GmbH (Berlin, Germany) order numbers LB01774, LB01361 and LB01232 respectively.

186-Single peptide in 96 well plates. Lyophilized peptides were dissolved in sterile water and used at 2µg/mL in RPMI 1640 glutamax media (GIBCO) supplemented with 1% penicillin/streptomycin (GIBCO). 185 single peptides were plated in duplicates in 96 well round bottom TPP treated culture plates. Peptide plates were then stored at -80°C
 30 until use. The day of the experiment, peptide plates were thawed at room temperature. Frozen PBMCs were thawed, washed and resuspended in RPMI 1640 media (GIBCO). Viability and count were evaluated using a Vi-Cell XR Cell Counter (Beckman Coulter, Brea). PBMCs were then plated in RPMI 1640 glutamax media (GIBCO) supplemented with 1% penicillin/streptomycin (GIBCO), with 200UI/mL rhIL-2 (Miltenyi) and 200UI/mL
 35 rhIL-15 (Miltenyi) at a cell density of 10x10³ cells and incubated with each peptide at 37°C, 5% CO₂. PBMCs were stimulated with 60 ng/mL OKT-3 antibody (ThermoFisher Scientific, clone OKT3) or with 10µg/mL phytohemagglutinin as positive controls and

PBMCs alone served as negative controls. After 6 hours, 20µL of human AB serum was added to each well and plates were incubated at 37°C, 5% CO₂ for 6 additional days. On day 7, supernatants were harvested and frozen at -80°C. Concentration of IFN γ , IL-9, IL-5 and IL-17A in the culture supernatant was determined using a commercial ELISA kit (ELISA Max Deluxe set human IFN- γ , Biolegend).

Peptide pools and COVID IGRA Biomérieux assay utilized for the COVID-SER clinical trial vaccinees [43]. Fresh blood collected in heparanized tubes was stimulated for 22 hours at 37°C under 5% of CO₂ with peptide pools targeting RBD (46 peptides) (bioMérieux, France) diluted in IFA solution (bioMérieux, France). The IFA solution was used as a negative control and a mitogen was used as a positive control. The peptides (15-mer) encompassed the whole RBD protein sequence and overlapped by 5-residues. The concentration of IFN γ in the supernatant was measured using the VIDAS automated platform (VIDAS® IFN γ RUO, bioMérieux). The positivity range was 0.08 -8 IU/mL and IFA positivity thresholds were defined at 0.08 IU/mL. The IFN γ response was defined as positive when the IFN γ concentration of the test was above threshold and the negative control was below threshold or when the IFN γ concentration of the test minus IFN γ concentration of the negative control was above threshold. All positive controls were $\geq$ 8 IU/mL. **Peptide pools and high throughput screening T cell assay with COVID IGRA Biomérieux assay utilized for the COV3AP-HP clinical trial vaccinees** [43]. Same process but using different peptides pools that are detailed in Figure 5C of Fahrner *et al.*, 2022 and Table 12.

Generating TH2 cell lines.

Generating SARS-CoV-2 lysates specific clones. 10 million peripheral blood lymphocytes from a healthy donor with history of SARS-CoV-2-specific IL-5 release (refer to Figure 1D) were stimulated with autologous monocyte derived- dendritic cells loaded with SARS-CoV-2 lysates (see cross presentation assay section). After 18 hours, cells were harvested and CD137⁺ cells were isolated using CD137 MicroBead Kit, human (Miltenyi, France) according to manufacturer's instructions. Limiting dilution of CD137⁺ cells was performed by seeding 100µL of CD137 positive cellular suspension at a 10 cells/mL concentration in 96 round bottom well plates in sterile conditions. Feeder cells were generated by isolating CD14 positive cells using CD14 MicroBead Kit, human (Miltenyi, France). Isolated feeder cells were co-cultured with CD137 positive cells at a 1000:1 ratio and cultivated in IMDM medium (Sigma-Aldrich, UK), supplemented with 10% human AB serum (Institut de Biotechnologies Jacques Boy, France), 1mM Glutamine (GIBCO/ThermoFisher Scientific, UK), 1% Sodium Pyruvate

(GIBCO/ThermoFisher Scientific, UK), 1% HEPES (GIBCO/ThermoFisher Scientific, UK), 1% penicillin/streptomycin (GIBCO/ThermoFisher Scientific, UK), supplemented with 100UI/mL IL-7 (Miltenyi, France) and 100UI/mL IL-15 (Miltenyi, France). Medium was changed every 2-3 days. Clones were screened for IFN- γ and IL-5 secretion by quantification of the accumulation of these cytokines in supernatants between day 7 and day 13 using commercial ELISA kits. 93 clones of interest were identified and screened for specificity against SARS-CoV-2 lysates by quantifying IFN- γ and IL-5 secretion after restimulation with autologous monocyte-derived dendritic cells loaded with SARS-CoV-2 lysate or its respective control at day 21. Three rounds of IVS were performed over 3 weeks. Clones were starved in a cytokine free media two days before restimulation. Six SARS-CoV-2 specific cell lines could be identified and their MHC-I/MHC-class II recognition dependency was assessed by monitoring IFN- γ and IL-5 production after stimulation with autologous monocyte derived- dendritic cells loaded with SARS-CoV-2 lysate or its respective control in the presence or absence of neutralizing anti-HLA-ABC and HLA-DR, DP, DQ antibodies (W6/32 & Tü39) at day 28. Flow cytometric determination of CD4, CD8, T-bet, GATA3 was performed on the IL-5 producing SARS-CoV-2 specific cell lines according to methods already reported [32].

Generating Spike 25- specific cell lines.

PBMC from an healthy donor with previous history of breakthrough COVID-19 infection after complete vaccination were stimulated using 186 peptides spanning the ORFome of SARS-CoV-2 (Figure 3A). IFN γ and IL-5 were monitored in supernatants after 7 days of culture using commercial ELISA kits to identify IL-5 -restricted reactivity. One Spike 25 -specific IL-5 producing (but IFN γ negative) T cell line was identified and further expanded using monocyte derived -dendritic cells (DC) pulsed with Spike 25 for one week (at a concentration of 1 μ g/mL in RPMI supplemented with 10% human AB serum (Institut de Biotechnologies Jacques Boy, France), 1mM Glutamine (GIBCO/ThermoFisher Scientific, UK), 1% Sodium Pyruvate (GIBCO/ThermoFisher Scientific, UK), 1% penicillin/streptomycin (GIBCO/ThermoFisher Scientific, UK), IL-2 200UI/mL (Miltenyi) and IL-15 (Miltenyi). After the 3rd week, the T cell line was restimulated with Spike 25 -loaded DC in the presence or absence of neutralizing anti-HLA-ABC and HLA-DR, DP, DQ antibodies (W6/32; Tü39) in duplicate wells to monitor cytokine release using the 12 plex assay and stained with CD3, CD4, CD8, GATA3, T-bet, -specific antibodies to assess phenotypical characteristic by flow cytometry (refer to flow cytometric analyses).

Statistical analyses. All calculations, statistical tests, and data visualization were performed using R v4.0.3. All analyses were performed on independent samples, excepting when the presence of replicates is mentioned. The associations between continuous variables were evaluated using Spearman correlation. Group comparisons were performed using non-parametric test with the `wilcox.test` R function: the Wilcoxon-Mann-Whitney test for independent samples, and the Wilcoxon signed rank test for paired samples. When the number of replicates was unbalanced between the individuals, the Wilcoxon signed rank test for paired comparisons of clustered data was performed with the `clusWilcox.test` function of the R package `clusrank`. The comparison of categorical data was performed using the Fisher exact test with the `fisher.test` R function. Hierarchical clustering was performed with the package `hclust`, using the Euclidean distance. Linear and logistic regressions were performed with respectively the `lm` and the `glm` R base functions. A peptide set enrichment analysis was performed with the R package `fgsea` (version 1.14.0), using as statistic the t-value of the coefficient of univariable linear regressions of the logarithm-normalized IL-2 secretion on the different peptides. All hypothesis tests (including those of regression coefficients) were two-sided and considered as statistically significant when $p < 0.05$. Graphical illustrations were drawn using the standard R packages dedicated to the data visualization (`ggplot2`, `ggpubr`, `corrplot`, `complexheatmap`, `circlize`, and `Hmisc`). *RNA-seq data analysis.* Quality control were made on raw FastQ files with FastQC (v0.11.9) [85]. Quality reports were gathered with MultiQC (v1.9) [86]. Abundance estimation was performed with Salmon (v0.9.0) [87] using GENCODE (GRCh38, v34) annotation [88]. Quantification results were aggregated with tximport (v1.14.0), and differential gene analysis was performed with DESeq2 (v1.30.0), according to the Soneson et al. [89] procedure. The whole pipeline was powered by both Snakemake [90] and SnakemakeWrappers. Gene set enrichment analysis on DESeq2 results was performed with GSEA software (v4.1.0, pre-ranked based on Wald test statistic, 1000 permutations, weighted enrichment statistic) and immunologic signature gene sets coming from MSigDB (C7, v7.4) [91]. *Multivariate analyses of peptide pool -specific T cell responses according to co-variables* (Figure 4, Subtables S13a and S13b of Fahrner et al., 2022). We pooled the log10 normalized IFN γ secretion measurements obtained with the three peptide pools to model simultaneously their dynamics from the first shot of vaccine using linear mixed effect regression adjusted for the patient age, sex, cancer status (yes/no), COVID history, and vaccine schedule. To identify the differences between the dynamics of each panel, we adjusted the model for the peptide pool (representing baseline differences), and added interaction terms between the peptide pool and each covariable (including the time since the first vaccine). The intra-patient and intra-panel correlation were considered by adding patient-peptide

random effect for the intercept. A statistically significant interaction indicates that the covariable has an impact on the peptide-specific IFN γ measurement that is statistically different from its impact on the reference peptide pool (Subtables S13a and S13b of Fahrner *et al.*, 2022).

Table 1. Overview of all subgroups and cohorts.

COHORTS							CROSS- Presentation*		PEPTIDES	
NAME	Cancer		Covid		Vaccinees		Elisa	ELISPOT°	7 day-long IVS (Single peptide)**	22hr ex vivo (Pool)****
	Yes	No	Yes	No	Yes	No				
ONCOVID	X		X	X	X	X	X	X		
PROTECT-CoV		X		X		X	X			
HCW-HCL		X	X	X	X	X		X	X	X
CoV3APHP		X	X	X	X	X		X	X	X
Re-infected (2nd covid)		X	X			X	X	X		
Breakthrough infection		X	X	X	X			X		
Dupilumab							X	X		

* Refer to Figure 1B
** Refer to Figure 3A
*** Refer to Figure 5C of Fahrner *et al.*, 2022
° Refer to Figure 6C

Table 2. Characteristics of cancer patients and healthy individuals (ONCOVID and others)

		Controls (n=320)		Acute COVID-19 (n=40)		P.value*	Convalescent COVID-19 (n=69)		P.value #
		n	%	n	%		n	%	
Years	2000 - Nov. 2002	7	2	-	-	< 0.01	-	-	< 0.01
	Nov. 2002 - 2018	61	19	-	-		-		
	Unknown	2	1	-	-		-		
	2020 - 2021	250	78	40	100		69	100	
Age (years)	Median	61		63		0.13	56		0.02
	[Range]	[18-89]		[20-90]			[21-85]		
Gender	Male	124	45	22	55	0.31	28	41	0.05
	Female	150	55	18	45		41	59	
	Unknown	46	-	-	-		-	-	
Malignancy	Yes	257	80	40	100	< 0.01	40	58	< 0.01
	No	63	20	0	0		29	42	

Refers to available samples described in table S1
* : statistical analyses between controls and aAcute COVID-19;
: statistical analyses between controls and convalescent

Table 3. Clinical characteristics of vaccinated cancer patients.

Vaccinated cancer patients (n=92)			
Age (years)	Median	57	
	[Range]	[20-86]	
		n	%
Gender	Male	34	37
	Female	57	63
	Unknown	1	
Type of cancer	Solid tumors	73	80
	Hematologic tumors	18	20
	Unknown	1	
Cancer spread	Localized	10	11
	Locally advanced	18	20
	Metastatic	62	69
	Unknown	2	
Patients under cancer treatment before sampling (windows of 2 months)	All	87	96
	Unknown	1	
Cancer treatment	Chemotherapy	45	49
	Immunotherapy	30	33
	Radiotherapy	5	5
	Others	28	31
	Unknown	1	

Table 4. Characteristics of family members during the 2020 lockdown (PROTECT-CoV).

		Total		Contact (n=22)		Convalescent (n=29)		P.value
Age (years)	Median	46		39		49		0.69
	[Range]	[17-75]		[17-75]		[20-62]		
		n	%	n	%	n	%	
Gender	Male	26	51	13	59	13	45	0.40
	Female	25	49	9	41	16	55	
Number of contacts per case within the family								
1-3				5	23	1	3	< 0.01
4-6				14	64	15	52	
7-9				1	5	8	28	
10-12				2	9	0	0	
> 12				0	0	5	17	
Number of SARS-CoV-2 positive individuals in the family								
0				4	18	0	0	< 0.01
1-3				18	82	18	62	
4-6				0	0	5	17	
7-15				0	0	6	21	
Household size								
0				2	9	0	0	< 0.01
1-2				0	0	5	17	
3-5				18	82	16	55	
6-8				2	9	8	28	
Household living space (m ²)								
< 70				7	32	6	21	0.16
70-100				3	14	11	38	
> 100				12	55	12	41	
Number of rooms in the household								
2-3				10	45	7	24	0.22
4-5				6	27	14	48	
6-8				6	27	8	28	
Number of individuals using personal protective equipment								
				13	59	18	62	1
Number of individuals respecting barriers gestures								
				16	73	22	76	1

Table 5. Characteristics of contact (resistant) and infected (susceptible) cancer patients and corresponding swimmer plot.

		Resistant (n=54)		Susceptible (n=22)		P.value
Age (years)	Median	54		53		0.9
	[Range]	[19-81]		[22-80]		
		n	%	n	%	
Gender	Male	17	31	11	50	0.2
	Female	37	69	11	50	
Malignancy	Yes	54	100	22	100	1.0
	No	0	0	0	0	
Type of cancer	Solid tumors	52	96	19	86	0.1
	Hematologic tumors	2	4	3	14	
Cancer spread	Localized	25	46	4	18	0.07
	Locally advanced	8	15	5	23	
	Metastatic	21	39	13	59	

Table 6. Characteristics of contact (resistant) and infected (susceptible) cancer patients and corresponding swimmer plot.

		Resistant (n=9)		Susceptible (n=9)		P.value
Age (years)	Median	50		44		0.452
	[Range]	[28-71]		[28-82]		
		n	%	n	%	
Gender	Male	4	44	2	22	1.000
	Female	5	56	7	78	
Malignancy	Yes	5	56	3	33	1.000
	No	4	44	6	67	
Type of cancer	Solid tumors	5	100	3	100	1.000
	Hematologic tumors	0	0	0	0	
Cancer spread	Localized	1	20	1	33	1.000
	Locally advanced	0	0	1	33	
	Metastatic	4	80	1	33	

Results

1.1. Effector and memory T cell responses against coronaviruses during COVID-19 infection

5 We conducted a cross-sectional analysis of the functional T cell responses across several cohorts of healthy individuals and cancer patients enrolled during the first surge of the pandemic (Figure 1A, Figure 2A) with the final aim of determining T cell correlates with clinical protection against COVID-19 diagnosed until March 2021 (Tables 1-6) [27]. First, we focused on the quality of SARS-CoV-2-specific
10 T cell responses detected in 215 cancer patients who stayed COVID-19-free between mid-March and September 2020, that we compared to 24 and 28 cancer patients in the acute and convalescence phase of SARS-CoV-2 infection respectively (Tables 2&3, Figure 1A). In parallel, we analyzed 22 COVID-19-free healthy volunteers (HV) from 15 distinct families at the same time as their family members who were in convalescent
15 phase for COVID-19 (n=26) (Figure 2A, Table 4). A third cohort of 67 individuals from the pre-COVID-19 era (leukocytes frozen between 1999 and 2018) were either HV from the blood bank (n=38) or cancer patients (n=29) recruited in the context of clinical trials (Figure 1A) [28–31].

T cell responses directed against viral lysates from the reference SARS-
20 CoV-2 strain IHUM1846 (CoV-2) isolated in early 2020 or two endemic common cold coronaviruses (CCC), OC43 and 229E, were evaluated by an *in vitro* stimulation assay (IVS, Figure 1B). Autologous monocyte derived-dendritic cells (DC) were differentiated for each individual and pulsed with heat-inactivated viral lysates before exposure to LPS. The specific viral lysates were compared to supernatants from cell lines permissive for
25 viral replication (such as VeroE6 for SARS-CoV-2, Figure S1A of Fahrner *et al.*, 2022). Peripheral blood lymphocytes (PBL) were then stimulated for 48hrs by viral lysate-loaded DC (Figure 1B). The cytokines accumulating in the supernatants were analyzed by means of a 12-plex flow cytometry-based bead assay (Figure S1A of Fahrner *et al.*, 2022). In this crosspresentation assay, SARS-CoV-2-related cytokine release from PBL
30 depended on MHC class I and MHC class II molecules, as shown using specific neutralizing antibodies (Figure S1B of Fahrner *et al.*, 2022). We calculated the ratio of cytokine release by dividing interleukin concentrations following exposure to viral lysates by those obtained with the respective control supernatants, to ascribe the specificity of the reactivity to SARS-CoV-2 or to common cold coronaviruses (CCC) antigens for each
35 subject. First, we characterized the intensity and the quality of PBL responses elicited at the acute phase of SARS-CoV-2 infection (day of symptom onset and/or first positive qPCR of the oropharyngeal swab and/or serology), between mid-March and mid-May

2020 in 24 interpretable tests performed on COVID-19⁺ subjects compared to a cohort of 304 controls (Tables 2&3). Robust SARS-CoV-2 specific IL-2 and IFN γ release, most likely caused by TH1/Tc1 cells, and the secretion of IL-4, IL-5 and IL-10, most likely mediated by TH2/Tc2 effector T cells, were detectable (Figure 1C, Figure 1D). Of note, COVID-19 infection did not reactivate CCC-specific T cell responses (Figure 1D, Figure S2A of Fahrner *et al.*, 2022). We next examined the polarization of SARS-CoV-2-specific memory T cell responses between May and September 2020 in 54 convalescent COVID-19 individuals (median time lapse between PCR negative and T cell assay: 85 days, range: 13-106 days) compared with contemporary controls (Figure 1A, Figure 1C-D, Figure S1C, S2A-B of Fahrner *et al.*, 2022, Figure 5, Tables 2&3). A mixed SARS-CoV-2-specific memory TH1/TH2 response was observed in most convalescent subjects within the next 2-3 months after acute infection. Differences in memory T cell responses between unexposed controls and COVID-19⁺ individuals could not be attributed to age, gender or cancer status as they were still statistically significant for IL-2, IL-5 and TNF- α in a separate analysis matching 51 convalescent patients to 51 control patients using a propensity score adjusting for age, gender and cancer status (Figure S1C of Fahrner *et al.*, 2022). More specifically, SARS-CoV-2 -specific IL-2 and IL-5 secretion levels were comparable in cancer and cancer-free COVID-19 patients during the recovery phase. Flow cytometric analyses of SARS-CoV-2-reactive T cells revealed central memory (TCM) TH1 (CD3⁺CD4⁺CD45RA⁻CCR7⁺T-bet⁺GATA3⁻CD69⁺Ki67⁻) and effector/effector memory (TEM) Tc1 (CD3⁺CD8⁺CD45RA⁻CCR7⁻T-bet⁺CD25⁺Ki67⁺) phenotypes (Figure S1D of Fahrner *et al.*, 2022). Of note, SARS-CoV-2 specific IL-2 release at recovery correlated with an increase in the frequency of circulating non-activated TFH cells (Figure S1E of Fahrner *et al.*, 2022) 32. In some of these patients, we performed double-color IFN γ /IL-5 ELISpot assays which were consistent with ELISA-based cytokine measurements (Figure S3B of Fahrner *et al.*, 2022). Moreover, the frequency of IFN γ -secreting cells correlated with the percentage of CD4⁺T-bet⁺TEM, and the frequency of IL-5-secreting cells was associated with the proliferation of CD8⁺CCR4⁺T-bet⁺ in the crosspresentation assay (Figure S3C of Fahrner *et al.*, 2022). Finally, SARS-CoV-2 specific IL-2 secretion was the only parameter correlating with anti-SARS-CoV-2 nucleocapsid (NC) antibody titers (reported to be stable for 8 months 5) but not with IgG and IgA antibodies targeting the S1 domain of the SARS-CoV-2 spike protein including the RBD (Figure 1E-F).

As previously described [21,23,24,33,34], contemporary COVID-19 negative subjects also harbored spontaneous (cross-reactive) SARS-CoV-2 specific-polyfunctional TH1/Tc1 memory responses that appear to pre-exist in cancer patients and healthy individuals whose blood was drawn in the pre-COVID-19 era, including prior

to outbreaks of SARS-CoV-1 and MERS (Figure S2A-B of Fahrner *et al.*, 2022 and Figure 2A). The unsupervised hierarchical clustering considering 12 cytokines monitored in 358 subjects did not segregate pre-COVID-19 from contemporary unexposed individuals nor convalescent patients (Figure S2A of Fahrner *et al.*, 2022).
5 Preexisting frequencies of SARS-CoV-2-specific IL-2⁺ and IL-5⁺ T cell responses were comparable (about 15%) in individuals with or without cancer, with no impact of the cancer staging (Figure 5B-C).

Hence, while TH1 and TH2 cell responses were elicited during the acute phase of COVID-19, preexisting and SARS-CoV-2-induced memory responses leading to IL-2 and IL-5 release were similarly detectable in healthy subjects and cancer patients.
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1.2. Clinical relevance of the IL-2/IL-5 ratio to predict COVID-19 infection

We next determined the clinical significance of these memory T cell responses monitored in unexposed individuals during the first surge of COVID-19 (mid-March to mid-May 2020) to decipher the nature of memory T cells contributing to susceptibility or resistance to the successive surges of this viral pandemic in fall 2020 and winter 2021. We phoned 229 patients to discover that 22 individuals had developed COVID-19 infections (diagnosed by qPCR or serology) with different degrees of severity according to WHO criteria (Figure 2A, Table 5). Indeed, about one third of the initially COVID-19-free individuals became contact cases (n=70) and 29% among these contact cases were diagnosed with COVID-19 infection by specific RT-qPCR or serology (n=22, Figure 2B, Tables 5&6). The unsupervised hierarchical clustering of the T cell secretory profiles in these 70 individuals failed to correctly segregate resistant (contact) from susceptible (infected) cases (Figure 6A). In addition, the polyfunctionality of T cell responses failed to segregate the two categories of cancer patients (Figure 2C, Figure 6B). However, IL-2 and IL-5 secreted by memory T cells responding to SARS-CoV-2 correlated with resistance and susceptibility to SARS-CoV-2, respectively (Figure 2D-E). Indeed, the levels of IL-2 in the recall response and the proportions of individuals exhibiting IL-2 polarized T cell memory responses were both associated with resistance to COVID-19 (Figure 2D, $p=0.01$, two-sided Wilcoxon-Mann-Whitney test, Figure 2E, $p=0.049$, Fisher exact test). In contrast, IL-5 levels in recall responses were associated with increased susceptibility to COVID-19 (Figure 2D, $p=0.057$, two-sided Wilcoxon-Mann-Whitney test). Of note, the intra-individual variability of the spontaneous SARS-CoV-2 -specific recall TH1 or TH2 responses were negligible over time (Figure 6C).
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Next, we analyzed the clinical significance of the ratio between SARS-CoV-2-specific IL-2 and IL-5 release. Indeed, the IL-2/IL-5 recall response ratio was significantly higher in cancer patients who were SARS-CoV-2-resistant (Figure 2F) and
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in convalescent patients (Figure 7A). The vast majority (15 out of 19) of cancer patients doomed to be infected with SARS-CoV-2 exhibited an IL-2/IL-5 ratio ≤ 1 , with the two severe COVID-19 cases displaying an IL-2/IL-5 ratio < 10 (Figure 7B). Moreover, the transcription profile of PBL in the crosspresentation assays leading to IL-2/IL-5 ratios > 1 performed in 18 patients (8 with an IL-2/IL-5 ratio > 1 and 10 with an IL-2/IL-5 ratio < 1) was enriched in genes expressed in TH1/Tc1 (e.g. IFN γ & GRZMB) versus TH2/Tc2 (e.g. CXCR5 & CD79A), respectively (Figure S3D of Fahrner *et al.*, 2022). In contrast, CCC-specific T cell reactivities did not allow to discriminate susceptible from resistant individuals (Figure 2G), although IL-5 (not IL-2) stood out as the strongest correlate between SARS-CoV-2 and OC43-specific T cell responses among 156 individuals (Figure 2H). Of note, titers of IgG antibodies directed against the spike of the seasonal betacoronaviruses OC43 and HKU1 (but not the alphacoronavirus 229E and NL63) were higher in individuals susceptible to SARS-CoV-2 compared to resistant individuals (Figure 2I).

The SARS-CoV-2-specific IL-2/IL-5 recall response ratio was also clinically significant in the cohort of cancer-free individuals that were locked down together with their COVID-19-positive family members (Figure 2A, Table 4, Figure 7C-D). Individuals who did not get infected harbored IL-2/IL-5 ratios > 1 reaching mean values comparable to those achieved in convalescent individuals (Figure 2F, Figure 7A) at higher frequencies than the overall population (Figure 7C). We next utilized the double-color IFN γ /IL-5 ELISpot assay to enumerate cytokine-producing T cells in blood from cancer patients (n=8) and HCW (n=10) drawn in March 2020 and followed up for 12 months for the COVID-19 diagnosis (Figure 6D, Figure 2I of Fahrner *et al.*, 2022, Table 6). While 6 out 9 resistant subjects (who did not develop COVID-19) exhibited a SARS-CoV-2 specific 2 fold increase in IFN γ^+ /IL-5 $^+$ spot ratios, none of the 9 susceptible subjects (who developed asymptomatic or mild COVID-19) did so (Figure 6E).

Of note, Dupilumab, a monoclonal antibody blocking IL-4R α signaling that reduces the severity of COVID-19 in rodents and patients with allergy [35], improved the IFN γ /IL-5 balance of the SARS-CoV-2-specific response in a group of 9 patients suffering from atopic dermatitis (Table 7). Thus, injections of Dupilumab inhibited SARS-CoV-2-specific IL-5 release but stimulated SARS-CoV-2-specific IFN γ secretion (Figure 2J, K).

Table 7. Characteristics of atopic dermatitis patients treated (or not) with dupilumab during the pandemic.

Allergic patients (n=9)											
SUBJECT #	Age	Gender	Type of Allergy	Severity of the Allergy	Other atopic conditions	Treatment	Date of Start	Date of blood sampling	COVID-19	Date of COVID-19 diagnosis	COVID-19 symptoms
1	56	Female	Atopic Dermatitis	Moderate	None	Dupilumab	25/05/2017	22/06/2020	Control	NA	NA
2	27	Male	Atopic Dermatitis	Moderate	Food allergies, seasonal allergies	Dupilumab	21/11/2017	07/07/2020	Control	NA	NA
3	46	Male	Atopic Dermatitis	Severe	None	Dupilumab	06/03/2019	25/06/2020	Convalescent	29/03/2020	Unk
4	54	Male	Atopic Dermatitis	Moderate	Food allergies	Dupilumab	Unk/03/2019	15/07/2020	Acute	Asymptomatic, 15/07/2020	No
5	56	Male	Atopic Dermatitis	Severe	Seasonal allergies, history of asthma	Dupilumab	23/03/2018	21/08/2020	Convalescent	Unk/03/ 2020	Unk
6	30	Male	Atopic Dermatitis	Severe	None	Dupilumab	Unk/04/2017	07/01/2021	Acute	07/01/2021	No
7	27	Female	Atopic Dermatitis	Moderate	Food allergies, seasonal allergies	No systemic treatment	NA	27/07/2020	Acute	27/07/2020	No
8	34	Female	Atopic Dermatitis	Moderate	Seasonal allergies	No systemic treatment	NA	16/11/2020	Acute	16/11/2020	Yes
9	41	Female	Atopic Dermatitis	Moderate	Seasonal allergies	No systemic treatment	NA	Sample 1: 21/01/2021 Sample 2: 13/05/21	Acute	21/01/2021	No

NA: not applicable

Unk: unknown

Table 8. Characteristics of multi-contact and re-infected cancer-free individuals.

		Re-infected (n=17)		Multi-exposed cases (n=12)		P.value
Age (years)	Median	37		48		0.08
	[Range]	[16-78]		[28-69]		
		n	%	n	%	
Gender	Male	7	41	6	50	0.72
	Female	10	59	6	50	
Comorbidities	Yes	5	31	-	-	-
	No	11	69	-	-	
	Unknown	1	-	-	-	
Type of comorbidities	Asthma	3	60	-	-	-
	Obesity	2	40	-	-	
	Type 2 diabetes	2	40	-	-	
	Cancer		20	-	-	
	HIV*	1	20	-	-	
	HBP**	2	40	-	-	
Time to reinfection (mo.)	< 03	2	17	-	-	-
	03 - 06	7	58	-	-	
	> 06	3	25	-	-	
	Unknown	5	-	-	-	
Second surge variants	B.1.177	1	-	-	-	-
	B.1.160	6	-	-	-	
	B.1.351	1	-	-	-	
	B.1.1.7	2	-	-	-	
	Unknown	7	-	-	-	

Refers to eligible patients described in Table S1

*Human Immunodeficiency Virus

**High Blood Pressure

- Given that 15-25% of individuals exhibit a TH2/Tc2 memory response to SARS-CoV-2 (Figure 7D), we wondered whether such individuals would be at higher risk to get reinfected by SARS-CoV-2 variants. Hence, we analyzed PBMCs in a series of
- 5 individuals (n=17) who were diagnosed with COVID-19 during the first surge of the SARS-CoV-2 pandemic and then were reinfected with viral variants prevailing during the later outbreak occurring in fall 2020 or winter 2021, comparing them to HCW who, in spite of multi-exposure and multiple oropharyngeal PCR tests, remained SARS-CoV-2-negative (n=12) (Table 8, Figure 2L). Surprisingly, monocytes could be differentiated into

DC only in 4 out of 17 reinfected patients. Unstimulated PBL from reinfected and re-convalescent subjects spontaneously secreted much higher levels of IL-5 than did PBL from multi-exposed cases, reaching similar ranges as those obtained after TCR crosslinking (Figure 2L, middle panel). After specific restimulation with SARS-CoV-2 lysates, IL-10 was markedly increased in recall responses from reinfected but not multi-exposed cases (Figure 2L, right panel), and IL-2 was undetectable (Figure 8A). In this small cohort of multi-contact individuals, the recognition pattern of the United Kingdom (UK) (IHUMI3076, B.1.1.7), South Africa (IHUMI3147, B.1.351) and Brazil (IHUMI3191, P.1)[25] strains were rather variable, some individuals losing the TH1/Tc1 or acquiring a TH2/Tc2 profile, depending on the strain (Figure S4A of Fahrner *et al.*, 2022). We next compared the immunogenicity of the lysates derived from the original SARS-CoV-2 strain (IHUMI846) with that of the Danish (IHUMI2096, 20A.EU2, B.1.367, GH) and North African (IHUMI2514, 20C, B.1.160, GH) strains isolated at the end of 2020 [25]. Of note, T cells lost their capacity to produce IL-2 in response to the IHUMI2096 and IHUMI2514 viral variants while IL-17 release tended to increase ($p=0.0857$, Figure 8B).

We conclude that an imbalanced TH1/Tc1 *versus* TH2/Tc2 polarity of SARS-CoV-2 specific-memory T cell responses determines susceptibility to infection, an IL-2/IL-5 ratio >1 indicating resistance to COVID-19.

1.3. Defects in the Th1 repertoire residing in SARS-CoV-2 RBD in susceptible individuals

In hosts affected by viral infections or cancer, the breadth of T cell epitope recognition is a prerequisite for protective immunity [36–38]. We analyzed the diversity of SARS-CoV-2 T cell responses by single peptide mapping using 186 peptides with 9 to 51 amino acids corresponding to 146 non-overlapping or poorly overlapping epitopes of the SARS-CoV-2 ORFeome (among which 25 epitopes were shared with SARS-CoV-1), encompassing membrane, nucleocapsid, spike, ORF3a, ORF8 and ORF10 proteins, plus 41 epitopes covering the SARS-CoV-1 ORFeome of immunological relevance (among which 8 epitopes were shared with SARS-CoV-2), as well as a series of positive controls, namely epitopes from influenza virus, Epstein Barr virus (EBV) and cytomegalovirus (CMV), phytohemagglutinin (PHA), and anti-CD3 ϵ (OKT3) antibody (Table 9). IFN γ responses against the 186 peptides were evaluated in 148 individuals (121 unexposed individuals, 27 convalescent COVID-19-positive patients, 18 reinfected patients). To enable the detection of low-frequency SARS-CoV-2 peptide-specific T cells, we used an in vitro 7 day-long, IL-2+IL-15 enriched IVS assay in the presence of each individual peptide (Figure 3A). We chose to monitor IFN γ , a proxy for TH1/Tc1 responses, as opposed to IL-2, in the 7 day- coculture supernatants by ELISA because recombinant human IL-2 was already added to the IVS assay to maintain T cell viability

(Figure 3A). The overall recognition patterns of these peptides across various patient populations, and their individual frequencies are detailed in Figure 3B, 3C and S5 of Fahrner *et al.*, 2022. About 10% convalescent individuals recognized more than 15% of our peptide selection within the SARS-CoV-2 ORFeome. T cell responses in unexposed patients, in particular in the pre-COVID-19 era, covered large specificities, as suggested by previous reports [9,21,24] (Figure 3B, right panel and Figure 3C of Fahrner *et al.*, 2022). In accord with the literature [9,24], the T cell repertoire of convalescent COVID-19 patients was larger than that of unexposed individuals, mainly directed against spike, membrane, and nucleocapsid (NC) and, to a lower extent, against ORF3a, ORF8, and ORF10 (Figure 3B, 3D left panel). The breadth of the peptide recognition coverage tended to be reduced in cancer patients compared with others (Figure 3B left panel, Figure 3B of Fahrner *et al.*, 2022). In a limited number of individuals, we measured not only IFN γ but also IL-5, IL-9 and IL-17 by ELISA. The recognition profile specific to the spike (and more specifically the RBD) as well as ORF8 was more geared toward TH1/Tc1 (IFN γ) than TH2 (IL-5), TH9 (IL-9) or TH17 (IL-17) production (Figure S6A-C of Fahrner *et al.*, 2022). The membrane- and NC-specific repertoire was strongly TH17 oriented (Figure S6B of Fahrner *et al.*, 2022).

Using logistic regression analyses, we determined the TH1/Tc1 peptide recognition fingerprint significantly associated with each patient category (Figure 9A). The hallmark repertoire of the pre-COVID-19 era consisted in a stretch of peptides covering part of the SARS-CoV-1 genome (spike, membrane, ORF3a, NC), some peptide residues sharing high or complete homology with SARS-CoV-2, as well as numerous ORF8 sequences (Table 9). Of note, the recognition pattern of these SARS-CoV-1 epitopes highly correlated with responses directed against ORF8 peptides. In contrast, the COVID-19-associated blueprint encompassed many nucleocapsid peptides (NC_1 (residues 1-15), NC_6-7 (residues 76-105), NC_8 (residues 106-120) sharing 93% and 100% homology with OC43 and HKU1, respectively, the HLA-A2- restricted nonamer (RLNQLESKV) NC_226-234 from SARS-CoV-1 (sharing high structural homology with the SARS-CoV-2 epitope RLNQLESKM) and another SARS-CoV-1 NC nonamer peptide (NC_345-361), three peptides residing in ORF8, two epitopes belonging to the RBD region ("SPIKE29") found at high frequency across subjects (23.5%), as well as a peptide from the C terminal portion of spike ("SPIKE84", residues 1246-1260) (Figure 9A). Cancer patients tended to lack some specificities, yet with no prototypical signature (Figure 9A).

Table 9. SARS-CoV-1 and CoV-2 orfeome peptide list: sequences and positions.

Peptide name	Peptide sequence	SEQ ID	Virus	Protein	Similar sequence in SARS-CoV-2	SEQ ID	SARS-CoV-2 1st pos	SARS-CoV-2 last pos	SARS-CoV-1 1st pos	SARS-CoV-1 last pos
Spike1	MFVFLVLLPLVS SQC	1	SARS-CoV-2	Spike			1	15		
Spike2	VNLTTRTQLPP AYTN	2	SARS-CoV-2	Spike			16	30		
Spike3	SFTRGVVYPDK VFRS	3	SARS-CoV-2	Spike			31	45		
Spike4	SVLHSTQDLFLP FFS	4	SARS-CoV-2	Spike			46	60		
Spike5	NVTWFHAIHVS GTNG	5	SARS-CoV-2	Spike			61	75		
Spike6	TKRFDNPVLPF NDGV	6	SARS-CoV-2	Spike			76	90		
Spike7	YFASTEKSNIR GWI	7	SARS-CoV-2	Spike			91	105		
Spike8	FGTLDSTQTS LLIV	8	SARS-CoV-2	Spike			106	120		
Spike9	NNATNVIKVCE FQF	9	SARS-CoV-2	Spike			121	135		
Spike10	CNDPFLGVYH KNK	10	SARS-CoV-2	Spike			136	150		
Spike11	SWMESEFRVYS SANN	11	SARS-CoV-2	Spike			151	165		
Spike12	CTFEYVSPFL MDLE	12	SARS-CoV-2	Spike			166	180		
Spike13	GKQGNFKNLRE FVFK	13	SARS-CoV-2	Spike			181	195		
Spike14	NIDGYFKIYSKH TPI	14	SARS-CoV-2	Spike			196	210		
Spike15	NLVRDLPQGFS ALEP	15	SARS-CoV-2	Spike			211	225		

Spike16	LVDLPIGNIIRF QT	16	SARS-CoV-2	Spike				226	240		
Spike17	LLALHRSYLTPG DSS	17	SARS-CoV-2	Spike				241	255		
Spike18	SGWTAGAAAYY VGYL	18	SARS-CoV-2	Spike				256	270		
Spike19	QPRTELLKYNE NGTI	19	SARS-CoV-2	Spike				271	285		
Spike20	TDVDCALDPL SETK	20	SARS-CoV-2	Spike				286	300		
Spike21	CTLKSFTVEKGI YQT	21	SARS-CoV-2	Spike				301	315		
Spike22	SNFRVQPTESIV RFP	22	SARS-CoV-2	Spike				316	330		
Spike23	NITNLCPFGEVF NAT	23	SARS-CoV-1 + SARS- CoV-2	Spike				331	345	318	332
Spike24	RFASVYAWNRRK RISN	24	SARS-CoV-2	Spike				346	360		
Spike25	CVADYSVLVNS ASFS	25	SARS-CoV-2	Spike				361	375		
Spike26	TFKCYGVSPSTK LNDL	26	SARS-CoV-2	Spike				376	390		
Spike27	CFTNVYADSFVI RGD	27	SARS-CoV-2	Spike				391	405		
Spike28	EVRQIAPGQTG KIAD	28	SARS-CoV-2	Spike				406	420		
Spike29	YNYKLDDFTG CVIA	29	SARS-CoV-2	Spike				421	435		
Spike30	WNSNNLDSKV GGNYN	30	SARS-CoV-2	Spike				436	450		
Spike31	YLYRLFRKSNLK PFE	31	SARS-CoV-2	Spike				451	465		
Spike32	RDISTEIQAGS TPC	32	SARS-CoV-2	Spike				466	480		
Spike33	NGVEGFNCYFP LQSY	33	SARS-CoV-2	Spike				481	495		

Spike34	GFQPTNGVGY QPYRV	34	SARS-CoV-2	Spike			496	510		
Spike35	VLSFELLHAPA TVC	35	SARS-CoV-2	Spike			511	525		
Spike36	GPKKSTNLVKN KCVN	36	SARS-CoV-2	Spike			526	540		
Spike37	FNFNGLTGTGV LTES	37	SARS-CoV-2	Spike			541	555		
Spike38	NKKFLPFQFG RDIA	38	SARS-CoV-2	Spike			556	570		
Spike39	DTTDAVRDPQT LEIL	39	SARS-CoV-2	Spike			571	585		
Spike40	DITPCSFQGV VITP	40	SARS-CoV-2	Spike			586	600		
Spike41	GTNTSNQVAVL YQDV	41	SARS-CoV-2	Spike			601	615		
Spike42	NCTEVPVAIHAD QLT	42	SARS-CoV-2	Spike			616	630		
Spike43	PTWRVYSTGSN VFQT	43	SARS-CoV-2	Spike			631	645		
Spike44	RAGCLIGAEHV NNSY	44	SARS-CoV-2	Spike			646	660		
Spike45	ECDIPGAGICA SYQ	45	SARS-CoV-2	Spike			661	675		
Spike46	TQTNSPRRARS VASQ	46	SARS-CoV-2	Spike			676	690		
Spike47	SIAYTMSLGAE NSV	47	SARS-CoV-2	Spike			691	705		
Spike48	AYSNNIAIPTN FTI	48	SARS-CoV-2	Spike			706	720		
Spike49	SVTTEILPVSMT KTS	49	SARS-CoV-2	Spike			721	735		
Spike50	VDCTMYICGDS TECS	50	SARS-CoV-2	Spike			736	750		
Spike51	NLLQYGSFCT QLNR	51	SARS-CoV-1 + SARS-CoV-2	Spike			751	765	733	747

Spike52	ALTGIAVEQDKN TQE	52	SARS-CoV-2	Spike			766	780		
Spike53	VFAQVKQYKTP PIK	53	SARS-CoV-2	Spike			781	795		
Spike54	DFGGFNSQILP DPS	54	SARS-CoV-2	Spike			796	810		
Spike55	KPSKRSFIEDLL FNK	55	SARS-CoV-2	Spike			811	825		
Spike56	VTADAGFIKQY GDC	56	SARS-CoV-2	Spike			826	840		
Spike57	LGDIARDLICA QKF	57	SARS-CoV-2	Spike			841	855		
Spike58	NGLTVLPPLLTD EMI	58	SARS-CoV-2	Spike			856	870		
Spike59	AQYTSALLAGTI TSG	59	SARS-CoV-2	Spike			871	885		
Spike60	WTFGAGAALQI PFAM	60	SARS-CoV-1 + SARS- CoV-2	Spike			886	900	868	882
Spike61	QMAYRFNGIGV TQNV	61	SARS-CoV-1 + SARS- CoV-2	Spike			901	915	883	897
Spike62	LYENQKLIANQF NSA	62	SARS-CoV-2	Spike			916	930		
Spike63	IGKIQDSLSSSTA SAL	63	SARS-CoV-2	Spike			931	945		
Spike64	GKLQDVVNQNA QALN	64	SARS-CoV-1 + SARS- CoV-2	Spike			946	960	928	942
Spike65	TLVKQLSSNFG AISS	65	SARS-CoV-1 + SARS- CoV-2	Spike			961	975	943	957
Spike66	VLNDILSRLDKV EAE	66	SARS-CoV-1 + SARS- CoV-2	Spike			976	990	958	972
Spike67	VQIDRLITGRLQ SLQ	67	SARS-CoV-1 + SARS- CoV-2	Spike			991	1005	973	987
Spike68	TYVTQQLIRAAE IRA	68	SARS-CoV-1 + SARS- CoV-2	Spike			1006	1020	988	1002
Spike69	SANLAATKMSE CVLG	69	SARS-CoV-1 + SARS- CoV-2	Spike			1021	1035	1003	1017

Spike70	QSKRVDFCGKG YHLM	70	SARS-CoV-1 + SARS-CoV-2	Spike				1036	1050	1018	1032
Spike71	SFPQSAPHGW FLHV	71	SARS-CoV-2	Spike				1051	1065		
Spike72	TYVPAQKNFT TAPA	72	SARS-CoV-2	Spike				1066	1080		
Spike73	ICHDGKAHFPR EGVF	73	SARS-CoV-2	Spike				1081	1095		
Spike74	VSNQTHWFTQ RNFY	74	SARS-CoV-2	Spike				1096	1110		
Spike75	EPQIITDNTFV SGN	75	SARS-CoV-2	Spike				1111	1125		
Spike76	CDVIGIVNNTV YDP	76	SARS-CoV-2	Spike				1126	1140		
Spike77	LQPELDSFKEEL DKY	77	SARS-CoV-1 + SARS-CoV-2	Spike				1141	1155	1123	1137
Spike78	FKNHTSPDVL GDIS	78	SARS-CoV-1 + SARS-CoV-2	Spike				1156	1170	1138	1152
Spike79	GINASVWNIQKE IDR	79	SARS-CoV-1 + SARS-CoV-2	Spike				1171	1185	1153	1167
Spike80	LNEVAKNLNES LIDL	80	SARS-CoV-1 + SARS-CoV-2	Spike				1186	1200	1168	1182
Spike81	QELGKYEQYIK WFWY	81	SARS-CoV-1 + SARS-CoV-2	Spike				1201	1215	1183	1197
Spike82	IWLGFAGLIAIV MV	82	SARS-CoV-2	Spike				1216	1230		
Spike83	TIMLCMTSCC SCLK	83	SARS-CoV-2	Spike				1231	1245		
Spike84	GCCSCGSCCKF DEDD	84	SARS-CoV-2	Spike				1246	1260		
Spike85	SEPVKGVKLH YT	85	SARS-CoV-1 + SARS-CoV-2	Spike				1261	1273	1243	1255
Nucleocapsid_1	MSDNGPQNQR NAPRI	86	SARS-CoV-2	Nucleocapsid				1	15		
Nucleocapsid_2	TFGGPSDSTGS NQNG	87	SARS-CoV-2	Nucleocapsid				16	30		

Nucleocapsid_3	ERSGARSKQRR PQGL	88	SARS-CoV-2	Nucleocapsid			31	45		
Nucleocapsid_4	PNNTASWFTAL TQHG	89	SARS-CoV-1 + SARS-CoV-2	Nucleocapsid			46	60	47	61
Nucleocapsid_5	KEDLKFRGQG VPIN	90	SARS-CoV-2	Nucleocapsid			61	75		
Nucleocapsid_6	TNSSPDDQIGY YRRA	91	SARS-CoV-2	Nucleocapsid			76	90		
Nucleocapsid_7	TRRIRGGDGKM KDLS	92	SARS-CoV-2	Nucleocapsid			91	105		
Nucleocapsid_8	PRWYFYLTGT PEAG	93	SARS-CoV-2	Nucleocapsid			106	120		
Nucleocapsid_9	LPYGANKDGIW VAT	94	SARS-CoV-2	Nucleocapsid			121	135		
Nucleocapsid_10	EGALNTPKDH GTRN	95	SARS-CoV-1 + SARS-CoV-2	Nucleocapsid			136	150	137	151
Nucleocapsid_11	PANNAIVLQLP QGT	96	SARS-CoV-2	Nucleocapsid			151	165		
Nucleocapsid_12	TLPGFYAEGS RGGS	97	SARS-CoV-1 + SARS-CoV-2	Nucleocapsid			166	180	167	181
Nucleocapsid_13	QASSRSSRSR NSSR	98	SARS-CoV-2	Nucleocapsid			181	195		
Nucleocapsid_14	NSTPGSSRGTS PARM	99	SARS-CoV-2	Nucleocapsid			196	210		
Nucleocapsid_15	AGNGGDAALAL LLLD	100	SARS-CoV-2	Nucleocapsid			211	225		
Nucleocapsid_16	RLNQLESKMSG KGQQ	101	SARS-CoV-2	Nucleocapsid			226	240		
Nucleocapsid_17	QQGQTVTKKSA AEAS	102	SARS-CoV-1 + SARS-CoV-2	Nucleocapsid			241	255	242	256
Nucleocapsid_18	KKPRQKRTATK AYNV	103	SARS-CoV-2	Nucleocapsid			256	270		
Nucleocapsid_19	TQAFGRRGPEQ TQGN	104	SARS-CoV-1 + SARS-CoV-2	Nucleocapsid			271	285	272	286
Nucleocapsid_20	FGDOELIRQGT DYKH	105	SARS-CoV-2	Nucleocapsid			286	300		

Nucleocapsid_21	WPQIAQFAPSA SAFF	106	SARS-CoV-1 + SARS-CoV-2	Nucleocapsid			301	315	302	316
Nucleocapsid_22	GMSRIGMEVTP SGTW	107	SARS-CoV-1 + SARS-CoV-2	Nucleocapsid			316	330	317	331
Nucleocapsid_23	LTYTGAIKLDDK DPN	108	SARS-CoV-2	Nucleocapsid			331	345		
Nucleocapsid_24	FKDQVILLNKHI DAY	109	SARS-CoV-2	Nucleocapsid			346	360		
Nucleocapsid_25	KTFPPTPEPKD KKKK	110	SARS-CoV-1 + SARS-CoV-2	Nucleocapsid			361	375	362	376
Nucleocapsid_26	ADETQALPQRQ KKQQ	111	SARS-CoV-2	Nucleocapsid			376	390		
Nucleocapsid_27	TVTLPAADLDD FSK	112	SARS-CoV-2	Nucleocapsid			391	405		
Nucleocapsid_28	QLQQSMSSADS TQA	113	SARS-CoV-2	Nucleocapsid			406	419		
Membrane_1	MADSNGTITVE ELKK	114	SARS-CoV-2	Membrane			1	15		
Membrane_2	ITVEELKKLEQ WNL	115	SARS-CoV-2	Membrane			8	22		
Membrane_3	KKLLEQWNLVI GFLF	116	SARS-CoV-2	Membrane			15	29		
Membrane_4	EQWNLVIGFLFL TWI	117	SARS-CoV-2	Membrane			22	36		
Membrane_5	LLESELVIGAVIL RG	118	SARS-CoV-2	Membrane			133	147		
Membrane_6	IGAVILRGHLRIA GH	119	SARS-CoV-2	Membrane			140	154		
Membrane_7	HLRIAGHHLGR CDIK	120	SARS-CoV-2	Membrane			148	162		
SARS_2016.05.006	LLNKHIDAYKTF P	121	SARS-CoV-1 + SARS-CoV-2	Nucleocapsid			352	364	353	365
SARS_10.1128_1	PLQASLPFGWL VIGV	122	SARS-CoV-1	ORF3a	PIQASLPFGW LIVGV	188	36	50	36	50
SARS_10.1128_2	NYNKYRYLRG KLRF	123	SARS-CoV-1	Spike	NYNLYRLFR KSNLKP	189	448	464	435	451

SARS_10.1128_3	AGCLIGAEHVD TSYECDI	124	SARS-CoV-1	Spike	AGCLIGAEHV NNSYECDI	190	647	664	633	650
SARS_10.1128_4	GETALALLDR LNQ	125	SARS-CoV-1	Nucleocapsid	GDAALALL DRLNQ	191	215	229	216	230
SARS_10.1128_5	GHLRMAGHSLG RCDI	126	SARS-CoV-1	Membrane	GHLRIAGHIL GRCDI	192	147	161	146	160
SARS_10.1128_6	NFNGLTGTGLV TPSSKRF	127	SARS-CoV-1	Spike	NFNGLTGTGV LTSNKKF	193	542	559	528	545
SARS_10.1128_7	DIPIGAGICASY HTVSL	128	SARS-CoV-1	Spike	DIPIGAGICAS YQTQINS	194	663	680	649	666
SARS_10.1128_8	SWFITQRNFFS PQII	129	SARS-CoV-1	Spike	HWFTQRNF YEPQII	195	1101	1115	1083	1097
SARS_HLA-A*02:01_1	FIAGLIAIV	130	SARS-CoV-1 + SARS-CoV-2	Spike			1220	1228	1202	1210
SARS_HLA-A*02:01_2	LITGRLOSL	131	SARS-CoV-1 + SARS-CoV-2	Spike			996	1004	978	988
SARS_HLA-A*02:01_3	RLNEVAKNL	132	SARS-CoV-1 + SARS-CoV-2	Spike			1185	1193	1167	1175
SARS_HLA-A*02:01_4	ILPDPLKPT	133	SARS-CoV-1	Spike	ILPDPSPKS	196	805	813	787	795
SARS_HLA-A*02:01_5	VVFLHVTYV	134	SARS-CoV-1 + SARS-CoV-2	Spike			1060	1068	1042	1050
SARS_HLA-A*02:01_6	KLPDDFMGCV	135	SARS-CoV-1	Spike	KLPDDFTGCV	197	424	433	411	420
SARS_HLA-A*02:01_7	VLNDILSRL	136	SARS-CoV-1 + SARS-CoV-2	Spike			976	984	958	966
SARS_HLA-A*02:01_8	LLLDRLNQL	137	SARS-CoV-1 + SARS-CoV-2	Nucleocapsid			222	230	223	231
SARS_HLA-A*02:01_9	RLNQLESKV	138	SARS-CoV-1	Nucleocapsid	RLNQLESKM	198	226	234	227	235
SARS_HLA-A*02:01_10	GMSRIGMEV	139	SARS-CoV-1 + SARS-CoV-2	Nucleocapsid			316	324	317	325
SARS_HLA-A*02:01_11	WLTTHGAIKLD DKDPQF	140	SARS-CoV-1	Nucleocapsid	WLTTHGAIKL DDKDPNF	199	330	346	331	347
SARS_HLA-A*02:01_12	QFKDNVILLNKH IDAYK	141	SARS-CoV-1	Nucleocapsid	NFKDQVILLN KHIDAYK	200	345	361	346	362
SARS_HLA-A*02:01_13	MASGGGETALA LLLLDRLNQLES KV	142	SARS-CoV-1	Nucleocapsid	MAGNGGDA LALLDRLN QLESKM	201	210	234	211	235

SARS_HLA-A*02:01_14	TWLT ^L YHGAIKLD DKDPQFKDNVIL	143	SARS-CoV-1	Nucleocapsid	TWLT ^L YHGAIK LDDKDPNFKD QVILL	202	329	353	330	354
SARS_HLA-A*02:01_15	GETALALLL	144	SARS-CoV-1	Nucleocapsid	GDAALALLL	203	215	224	216	225
SARS_HLA-A*02:01_16	LVIGFLFLAWIM LLQFAYSNRNR F	145	SARS-CoV-1	Membrane	LVIGFLFLTWI CLLQFAYANR NRF	204	22	45	21	44
SARS_HLA-A*02:01_17	VLAAYVRINWV TGGIAIACIV GLMW	146	SARS-CoV-1	Membrane	VLAAYVRINWI TGGIAIACIL VGLMW	205	66	92	65	91
SARS_HLA-A*02:01_18	ILLNVPLRGTVT RPLMESELVIG	147	SARS-CoV-1	Membrane	ILLNVPLHGTI LTRPLESEL VIG	206	116	141	117	140
SARS_HLA-A*02:01_19	IGNYKLNTDHA GSNDNIALLV	148	SARS-CoV-1	Membrane	IGNYKLNTDH SSSDNIALLV	207	199	221	200	220
SARS_HLA-A*02:01_20	GHLRMAGHPLG RCDI	149	SARS-CoV-1	Membrane	GHLRIAGHIL GRCDI	192	147	161	146	160
SARS_HLA-A*02:01_21	PLQASLPFGWL VIGV	150	SARS-CoV-1	ORF3a	PIQASLPFGW LIVGV	188	36	50	36	50
SARS_01026-X	DVNCTDVSTAIH ADQLTPAWR	151	SARS-CoV-1	Spike	DVNCTEVPVA IHADQLTPTW R	208	614	634	600	620
SARS_01025-8_1	KDKKKKTDEAQ PLPQRQKKQ	152	SARS-CoV-1	Nucleocapsid	KDKKKKADET QALPQRQKK Q	209	370	389	371	390
SARS_01025-8_2	QRQKKQPTVTL LPAADMDDFSR Q	153	SARS-CoV-1	Nucleocapsid	QRQKKQQTIV TLLPAADLDD FSKQ	210	384	406	385	407
SARS_HLA-DR0401_1	NAFNCTFEYISD AFSLDV	154	SARS-CoV-1	Spike					155	172
SARS_HLA-DR0401_2	YISDAFSLDVSE KSGNFK	155	SARS-CoV-1	Spike					163	180
SARS_HLA-DR0401_3	YLRHGKLRPFE RDISNVP	156	SARS-CoV-1	Spike					442	459
SARS_HLA-DR0401_4	RPFERDISNVPF SPDGK	157	SARS-CoV-1	Spike					449	465

SARS_3726.2005_1	MADNGTITVEEL KQLLEQWNLVI GFLFLAWI	158	SARS-CoV-1	Membrane	MADNGTITV EELKKLLEQW NLVIGFLFLTW I	211	1	32	1	31
SARS_3726.2005_2	LMESELVIGAVII RGHLRMAGHPL GRCDIK	159	SARS-CoV-1	Membrane	LLESELVIGAV ILRGHLRIAGH HLGRCDIK	212	133	162	132	161
SARS_5314.2004_1	NNNAATVLQLP QGTTLPGFYA EGSR	160	SARS-CoV-1	Nucleocapsid	ANNAIVLQL PQGTTLPGF YAEGSR	213	152	175	153	176
SARS_5314.2004_2	KTFPTEPKKD KKKKTDEAQL PQRQKKQPTVT LLPAADMDDFS RQLQNSM	161	SARS-CoV-1	Nucleocapsid	KTFPTEPKK DKKKKADETQ ALPQRQKKQ QTVTLPAAD LDDFSKQLQQ SM	214	361	411	362	412
ORF8_1	MKFLVFLGIITV AA	162	SARS-CoV-2	ORF8			1	15		
ORF8_2	GIITVAAFHQE CSL	163	SARS-CoV-2	ORF8			8	22		
ORF8_3	AFHQECSLQSC TQHQ	164	SARS-CoV-2	ORF8			15	29		
ORF8_4	LQSCCTQHQPYY VDDP	165	SARS-CoV-2	ORF8			22	36		
ORF8_5	QPYWDDPCPI HFYS	166	SARS-CoV-2	ORF8			29	43		
ORF8_6	PCPIHFYSKWYI RVG	167	SARS-CoV-2	ORF8			36	50		
ORF8_7	SKWYIRVGARK SAPL	168	SARS-CoV-2	ORF8			43	57		
ORF8_8	GARKSAPLIELC VDE	169	SARS-CoV-2	ORF8			50	64		
ORF8_9	LIELCVDEAGSK SPI	170	SARS-CoV-2	ORF8			57	71		
ORF8_10	EAGSKSPIQYIDI GN	171	SARS-CoV-2	ORF8			64	78		

ORF8_11	IQYIDIGNYTVS CLP	172	SARS-CoV-2	ORF8			71	85	
ORF8_12	NYTVSCLPFTIN CQE	173	SARS-CoV-2	ORF8			78	92	
ORF8_13	PFTINCQEPKLG SLV	174	SARS-CoV-2	ORF8			85	99	
ORF8_14	EPKLGSLVRC SFYE	175	SARS-CoV-2	ORF8			92	106	
ORF8_15	VVRCSFYEDFL EYHD	176	SARS-CoV-2	ORF8			99	113	
ORF8_16	EDFLEYHDRV VLDF	177	SARS-CoV-2	ORF8			106	120	
ORF8_17	DVRVWLDLFI	178	SARS-CoV-2	ORF8			113	121	
ORF10_1	MGYINVFAPFT IYS	179	SARS-CoV-2	ORF10			1	15	
ORF10_2	AFPFTIYSLLLC RMN	180	SARS-CoV-2	ORF10			8	22	
ORF10_3	SLLLCRMNSRN YIAQ	181	SARS-CoV-2	ORF10			15	29	
ORF10_4	NSRNYIAQVDV VNFN	182	SARS-CoV-2	ORF10			22	36	
ORF10_5	QVDVVFNFILT	183	SARS-CoV-2	ORF10			29	38	
ORF8_A	GNYTVSCSPFTI NCQ	184	SARS-CoV-2	ORF8			77	91	
ORF8_BC	GNYTVSCLPFTI NCQ	185	SARS-CoV-2	ORF8			77	91	
ORF3a_AB	VQIHTIDGSSGV VNP	186	SARS-CoV-2	ORF3a			244	258	
ORF3a_C	VQIHTIDVSSGV VNP	187	SARS-CoV-2	ORF3a			244	258	

SARS-CoV-2 Refseq ID: QHD43416.1 (Spike); QHD43423.2 (nucleocapsid); QHD43419.1 (membrane); QHD43417.1 and QHZ00380.1 (Orf3a); QHD43422.1 (Orf8); QHI42199.1 (Orf10); **SARS-CoV-1 Refseq ID:** AAP41037.1 (Spike); AAP41047.1 (nucleocapsid); AYV99779.1 (membrane); AYV99776.1 (Orf3a); (Orf8); (Orf10)

Next, we investigated the ORFeome peptide repertoire associated with SARS-CoV-2-specific IL-2 (supposedly protective) memory responses in 118 unexposed individuals by means of linear regression analysis (Figure 4B of Fahrner *et al.*, 2022, left panel). Among the 9 peptides associated with a positive contribution to IL-2 secretion, one
 5 nonamer (KLPDDFMGCV in SARS-CoV-1 genome and KLPDDFTGCV in the SARS-CoV-2 genome) resided in the RBD region that constitutes the binding site for its cellular receptor angiotensin-converting enzyme 2 (ACE2) 39 while, conversely among the 13 peptides associated with a hole in the TH1 response, 5 resided within the RBD of the spike glycoprotein. More specifically, there was a statistically significant enrichment of RBD-
 10 related peptides within this TH1/Tc1 hole (Figure 4B of Fahrner *et al.*, 2022, right panel).

In order to validate the clinical significance of the TH1/Tc1 repertoire hole and the assumption that a defect in the TH1/Tc1 recognition pattern of the RBD sequence could be a risk factor for COVID-19, we annotated the presence of at least one positive peptide selected from the RBD region spanning aminoacid 331-525 residues (called
 15 "SPIKE23" to "SPIKE35" in Table 9), *versus* other regions of the Orfeome in each of the 83 individuals who were comprehensively explored in the peptide-based IVS assay, 37 resistant (contact) individuals, 14 infected persons (susceptible) as well as 32 controls (unexposed lockdown and/or unknown) using the IFN γ ELISA (Figure 4A). The Volcano plot assigning significant odd ratios of TH1/Tc1 reactivities to different SARS-CoV1/CoV2
 20 aminoacid sequences between susceptible *versus* resistant individuals, highlighted that anti-S1-RBD TH1/Tc1 reactivity best correlated with resistance to infection (Figure 4A). In accordance with the immunodominance of S1-RBD, the other signatures indicated by our logistic regression analysis (Figure 9A), namely the convalescent or the pre-COVID-19 era-related blueprints were not significantly associated with COVID-19 resistance (Figure 4E-
 25 F of Fahrner *et al.*, 2022). While susceptible individuals exhibited a significant defect in the RBD-related TH1/Tc1 repertoire (Figure 4B), up to 25% of the resistant individuals harbored robust TH1/Tc1 responses to the 331-525 aminoacid residues of RBD (Figure 4B, $p=0.049$, Fisher exact test). Secondly, the RBD-specific TH1/Tc1 responses were almost undetectable in patients who got infected twice with SARS-CoV-2 (Table 8), while they
 30 could be measured in 50% convalescent COVID-19 patients (Figure 4C, $p=0.011$, Fisher exact test) in accordance with a recent report highlighting the immunodominance of the S346-365 region (corresponding to our "SPIKE24" epitope) in convalescent individuals [40]. Thirdly, patients diagnosed with COVID-19 breakthrough infections more than one month after complete vaccination (Table 10) harbored a major defect in S1-RBD-specific TH1/Tc1
 35 cell responses (Figure 4D). Of note, neutralizing antibody titers were above the detection limit in 66% of COVID-19 patients infected once *versus* 40% of reinfected patients. In contrast, in vaccinees experiencing breakthrough infection, IgG antibody titers against

trimeric Spike assessed within 2 months post-2nd vaccine were comparable to levels measured in unaffected vaccinees (Figure S6D of Fahrner *et al.*, 2022). Thus the cellular anti-S1-RBD TH1/Tc1 response might be a better predictor of protection against SARS-CoV-2 infection than the humoral response against trimeric Spike.

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Table 10. Characteristics of vaccinees experiencing a breakthrough infection.

		Breakthrough infection				p value
		No (n=20)		Yes (n=9)		
Age (years)	Median	48		67		0.004
	[Range]	[21-77]		[51-88]		
		n	%	n	%	
Gender	Male	4	20	6	67	0.032
	Female	16	80	3	33	
Malignancy	Yes	7	35	1	11	0.372
	No	13	65	8	89	
Obesity	Yes	0	0	1	11	
	No	0	0	8	89	-
	Unknown	20	0	0	0	
Asthma	Yes	0	0	3	33	
	No	0	0	6	67	-
	Unknown	20	0	0	0	
Days from second vaccination and COVID-19 first symptoms	Median	NA		41		
	[Range]			[9-69]		-
	Unknown			2		
COVID-19 variant	Alpha	NA		9	100	-

IFN γ and IL-5 T cell responses to S1-RBD peptides were evaluated in 81 patients. Less than 10% individuals harbored S1-RBD-specific TH2/Tc2 responses (Table 11). Long-lived TH2 clones could be derived from two patients exhibiting robust spontaneous or breakthrough COVID19-induced SARS-CoV-2 or SPIKE25 -specific IL-5 release (Figure S7A-F of Fahrner *et al.*, 2022). Of note, there was a robust concordance of the polarization status of patients between the two (cross-priming and peptide-based) IVS assays ($p=2.2e-16$ for the TH1/Tc1 cytokines IL-2 and IFN γ release; $p < 1e-16$ for the TH2/Tc2 factor IL-5, McNemar test).

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Table 11. Peptide-specific T cell polarisation determined by IL-5 or IFN- γ quantification.

Spontaneous immunity	SARS-CoV-2 protein		n*	IL-5 ⁻ /IFN γ ⁻	IL-5 ⁺ /IFN γ ⁻	IL-5 ⁻ /IFN γ ⁺	IL-5 ⁺ /IFN γ ⁺	P.value
	Membrane	Resistant	35	20	3	1	1	0.76
		Susceptible		10	0	0	0	
	Nucleocapsid	Resistant	42	17	3	7	3	0.58
		Susceptible		9	0	3	0	
	S1	Resistant	36	15	0	9	4	0.34
		Susceptible		7	0	1	0	
	S1-RBD	Resistant	36	15	3	10	0	0.06
		Susceptible		8	0	0	0	
	S2	Resistant	23	8	0	7	1	0.75
		Susceptible		5	0	2	0	
	ORF8	Resistant	22	11	0	5	0	1.00
		Susceptible		4	0	2	0	
	ORF10	Resistant	23	15	0	1	0	0.53
		Susceptible		6	0	1	0	
	ORF3a	Resistant	22	14	0	1	0	1.00
		Susceptible		7	0	0	0	
Vaccine-induced immunity	Peptide pool	Vaccinated	n	IL-5 ⁻ /IFN γ ⁻	IL-5 ⁺ /IFN γ ⁻	IL-5 ⁻ /IFN γ ⁺	IL-5 ⁺ /IFN γ ⁺	P.value
	PEP _{orf}	No	15	6	2	6	1	0.003
		Yes	30	3	0	26	1	
	PEP _{wtrBD}	No	15	12	0	3	0	0.020
		Yes	68	30	0	38	0	
	PEP _{mutBD}	No	15	14	0	1	0	0.167
		Yes	30	20	1	9	0	

*The numbers correspond to the enumeration of patients who were positive for at least one of the epitopes of each protein listed in Table 9.

- Given that immunoselection may drive antigenic drift of viruses as well as the evolution of viral phylogeny, we analyzed the coincidence of mutations (mutations occurring in at least 75% of emergent variant or predicted to decrease antibody neutralizing activity) in the SARS-CoV-2 ORFeome41 with T cell memory patterns of clinical significance (Table S12 of Fahrner *et al.*, 2022). Significantly higher mutation frequencies were detected within the S1-RBD-specific TH1 response (62%) compared with other regions of the SARS-CoV-2 orfeome (25.5%) (odds ratio = 0.21, 95% confidence interval [0.06; 0.68], $p=0.01$, Figure 4E).

During the course of this study, SARS-CoV-2 mRNA and DNA vaccines were approved by FDA and EMA based on reports that they prevent COVID-19 infection with an efficacy of >90%.^{3,42} Using a simple 22hr-whole blood stimulation assay allowing the quantitative measurement of IFN γ using the Enzyme Linked Fluorescent Assay technique in an automated platform (VIDAS® IFN γ RUO, 43 we analyzed RBD-specific T cell reactivities before and/or after dual vaccination with BNT162b2 mRNA (BioNTech/Pfizer) and/or AZD1222 adenovirus (Astrazeneca) in 233 unexposed HCW and 92 cancer patients, as well as in 69 convalescent individuals before and/or after one vaccine. Firstly, using a pool of 42 overlapping peptides spanning the S1-RBD sequence, we observed 90% reactivity in naive (cancer-free, no COVID-19 infection) HCW (n=70) 3 weeks after the second immunization, as well as in convalescent patients (n=14) after the sole vaccination (not shown). Secondly, we reduced the S1-RBD 42 peptide pool to our collection of 11 non overlapping peptides ("PEP_{wIRBD}") (Figure 5C of Fahrner *et al.*, 2022, Tables 9 and 12). PBL reactivities to both of these peptide pools were MHC class I and class II dependent (Figure S8 of Fahrner *et al.*, 2022). As a positive control of memory responses against SARS-CoV-2 [44], we used a pool of eighteen 15-mer epitopes "PEP_{Orf}" comprising not only different stretches of overlapping S1-RBD peptides but also peptides spanning Spike S1 and S2, membrane and nucleocapsid sequences (Figure 5C of Fahrner *et al.*, 2022, Table 12). At day 90 post-vaccine initiation, 75% of HCW (with no history of COVID-19 nor cancer) mounted PEP_{wIRBD} -specific TH1/Tc1 responses while >90% responded to PEP_{Orf}, reaching similar levels as individuals with a history of COVID-19 or one course of vaccination with an impact of gender and time of sampling (Figure 4F, upper panel, Table 13). The magnitude of PEP_{wIRBD} -specific IFN γ release post-vaccination was maintained up to day 180 in both patient subsets (Figure 4F, lower panel). Multivariate analyses confirmed that administration of two vaccines or COVID-19 infection followed by one vaccine elicited significant TH1/Tc1 immune responses against S1-RBD independently of age, gender, cancer and time of sampling (Figure 4G). Of note, the titers of IgG S1-RBD antibodies poorly correlated with PEP_{wIRBD}-specific T cell IFN γ secretions in 176 HCW vaccinees without a history of COVID-19 (Figure 5G of Fahrner *et al.*, 2022, R=0.17, p=0.025).

Table 12. Epitope sequences for PEPorF, PEPwtRBD, PEPmut RBD, PEPovRBD.

Peptide pools name	Peptide sequence	Seq ID No	Virus	Protein	SARS-CoV-2 position	
					1 st	last
PEPorf	SASFSTFKCYGVSP	215	SARS-CoV-2	Spike	371	385
PEPorf	YKLPDDFTGCVIAWN	216	SARS-CoV-2	Spike	423	437
PEPorf	NNLDSKVGGNYNYLY	217	SARS-CoV-2	Spike	439	453
PEPorf	SKVGGNYNYLYRLFR	218	SARS-CoV-2	Spike	443	457
PEPorf	YLYRLFRKSNLKPFE	31	SARS-CoV-2	Spike	451	465
PEPorf	SNLKPFRDISTEIY	219	SARS-CoV-2	Spike	459	473
PEPorf	CTFEYVSQPFLMDLE	12	SARS-CoV-2	Spike	166	180
PEPorf	NIDGYFKIYSKHTPI	14	SARS-CoV-2	Spike	196	210
PEPorf	LMDLEGKQGNFKNLR	220	SARS-CoV-2	Spike	176	190
PEPorf	NFSQILPDPSKPSKR	221	SARS-CoV-2	Spike	801	815
PEPorf	NLLLQYGSFCTQLNR	51	SARS-CoV-2	Spike	751	765
PEPorf	LLWPVTLACFVLAHV	222	SARS-CoV-2	Membrane	56	70
PEPorf	CLVGLMWLSYFIASF	223	SARS-CoV-2	Membrane	85	99
PEPorf	RGHLRIAGHHLGRCD	224	SARS-CoV-2	Membrane	146	160
PEPorf	YRINWITGGIAIAMA	225	SARS-CoV-2	Membrane	71	85
PEPorf	KEITVATSRTLSTYYK	226	SARS-CoV-2	Membrane	166	180
PEPorf	LLESELVIGAVILRG	118	SARS-CoV-2	Membrane	133	147
PEPorf	PSGTWLTYTGAIKLD	227	SARS-CoV-2	Nucleocapsid	326	340
PEPwtRBD	CVADYSVLYNSASFS	25	SARS-CoV-2	Spike	361	375
PEPwtRBD	TFKCYGVSPTKLNDL	26	SARS-CoV-2	Spike	376	390
PEPwtRBD	CFTNVYADSFVIRGD	27	SARS-CoV-2	Spike	391	405
PEPwtRBD	EVRQIAPGQTGKIAD	28	SARS-CoV-2	Spike	406	420
PEPwtRBD	YNYKLPDDFTGCVIA	29	SARS-CoV-2	Spike	421	435
PEPwtRBD	WNSNNLDSKVGGYN	228	SARS-CoV-2	Spike	436	450
PEPwtRBD	YLYRLFRKSNLKPFE	31	SARS-CoV-2	Spike	451	465
PEPwtRBD	RDISTEIYQAGSTPC	32	SARS-CoV-2	Spike	466	480
PEPwtRBD	NGVEGFNCYFPLQSY	33	SARS-CoV-2	Spike	481	495
PEPwtRBD	GFQPTNGVGYQPYRV	34	SARS-CoV-2	Spike	496	510
PEPwtRBD	VVLSFELLHAPATVC	35	SARS-CoV-2	Spike	511	525
PEPmutRBD	CVADYSFLYNSASFS	229	SARS-CoV-2	Spike	361	375
PEPmutRBD	EVRQIAPGQTGNIAD	230	SARS-CoV-2	Spike	406	420
PEPmutRBD	EVRQIAPGQTGTIAD	231	SARS-CoV-2	Spike	406	420
PEPmutRBD	WNSKNLDSKVGGNYN	232	SARS-CoV-2	Spike	436	450
PEPmutRBD	WNSKNLDSKVGGNYN	233	SARS-CoV-2	Spike	436	450
PEPmutRBD	YRYRLFRKSNLKPFE	234	SARS-CoV-2	Spike	451	465
PEPmutRBD	RDISTEIYQVGSTPC	235	SARS-CoV-2	Spike	466	480
PEPmutRBD	RDISTEIYQAGNTPC	236	SARS-CoV-2	Spike	466	480
PEPmutRBD	RDISTEIYQAGSKPC	237	SARS-CoV-2	Spike	466	480

PEPmutRBD	NGAEGFNCYFPLQSY	238	SARS-CoV-2	Spike	481	495
PEPmutRBD	NGVKGFNCYFPLQSY	239	SARS-CoV-2	Spike	481	495
PEPmutRBD	NGVQGFNCYFPLQSY	240	SARS-CoV-2	Spike	481	495
PEPmutRBD	NGVEGFNCYFPLRSY	241	SARS-CoV-2	Spike	481	495
PEPmutRBD	GFQPTYGVGYQPYRV	242	SARS-CoV-2	Spike	496	510
PEPovRBD	SASFSTFKCYGVSPST	243	SARS-CoV-2	Spike	371	385
PEPovRBD	YKLPDDFTGCVIAWN	244	SARS-CoV-2	Spike	423	437
PEPovRBD	NNLDSKVGGNYNYLY	245	SARS-CoV-2	Spike	439	453
PEPovRBD	SKVGGNYNYLYRLFR	246	SARS-CoV-2	Spike	443	457
PEPovRBD	YLYRLFRKSNLKPFE	31	SARS-CoV-2	Spike	451	465
PEPovRBD	SNLKPFERDISTEY	247	SARS-CoV-2	Spike	459	473
PEPovRBD	LLWPVTLACFVLAIV	248	SARS-CoV-2	Membrane	56	70
PEPovRBD	CLVGLMWLSYFIASF	249	SARS-CoV-2	Membrane	85	99
PEPovRBD	RGHLRIAGHHLGRCD	250	SARS-CoV-2	Membrane	146	160
Spike28_a2	EVQRQIAPGQTGPDIAD	251	SARS-CoV-2	Spike	406	420
Spike23 G339D	NITNLCPFDEVFNAT	252	SARS-CoV-2	Spike	331	345
Spike25 S371L	CVADYSVLYNLASFS	253	SARS-CoV-2	Spike	361	375
Spike25 S373L	CVADYSVLYNSALFS	254	SARS-CoV-2	Spike	361	375
Spike25 S375F	CVADYSVLYNSASFF	255	SARS-CoV-2	Spike	361	375
Spike32 T478K	RDISTEYQAGSKPC	237	SARS-CoV-2	Spike	466	480
Spike33 E484A	NGVAGFNCYFPLQSY	256	SARS-CoV-2	Spike	481	495
Spike34 G496S	SFQPTNGVGYQPYRV	257	SARS-CoV-2	Spike	496	510
Spike34 Q498R	GFRPTNGVGYQPYRV	258	SARS-CoV-2	Spike	496	510
Spike34 Y505H	GFQPTNGVGHQPYRV	259	SARS-CoV-2	Spike	496	510

The percentages and magnitude of these responses were reduced in 92 cancer patients who were mostly under therapy (Tables 2&3) as compared to 187 cancer-free individuals (adjusted p value for differences in percentages of PEP_{Off} positivity=0.016, adjusted p value for differences in IFN γ levels upon stimulation with PEP_{wtRBD}=0.027, Figure 4H).

The binding affinity of S1-RBD peptides to MHC class I and class II proteins was calculated using the NetMHCpan algorithm. This approach predicted strong binding to MHC class I HLA-A, -B and -C alleles for the RBD epitopes "SPIKE25" (residues 361_375), "SPIKE27" (residues 391-405), "SPIKE31" (residues 451-465). In contrast, "SPIKE33" (residues 481_495) was estimated to have a low affinity for HLA-B and no affinity for HLA-C alleles (Subtable S13a of Fahrner *et al.*, 2022). Only "SPIKE24", "SPIKE25" and

"SPIKE31 were predicted to bind with a high affinity to MHC class II HLA-DR alleles (Subtable S13b of Fahrner *et al.*, 2022) as already reported for the immunodominant S346-365 region [40]. To investigate potential links between the lack of spontaneous or vaccine-induced S1-RBD-specific TH1 responses and HLA genotypes, we analyzed the distribution of HLA-I and HLA-II alleles in 101 individuals, 53 vaccinees and 48 cancer patients prior to vaccination, of which 45% presented anti-S1-RBD TH1 responses (Figure 9B-C). As already reported in severe COVID19 in an Indian population [45], we found that HLA-DPB1*04:01 was significantly associated with RBD areactivity (Figure 9B-C). This is in line with the observation that none of the RBD peptides were predicted to be strong binders for this allele (Subtable S13b of Fahrner *et al.*, 2022). Moreover, the HLA-DQA1*01:02 allele paired with the DQB1*05:02 allele was significantly associated with RBD areactivity (14% *versus* 0% in RBD areactive *versus* reactive respectively, $p=0.042$, Figure 9B).

Finally, we analyzed T cell responses directed against S1-RBD sequences of the viral variants of concern (VOC) that were recently renamed by WHO as Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1) and Delta (B.1.617.2). Indeed, these strains predominantly mutate in the S gene compared with the reference (Wuhan) strain and more precisely within the S1-RBD peptide residues of the "PEP_{wtrBD}" pool. Therefore, we generated a fourth peptide pool "PEP_{mutRBD}" encompassing the 14 mutations described within the S1-RBD sequences of VOC (Table S12 of Fahrner *et al.*, 2022) that we tested in 343 individuals. TH1/Tc1 cell reactivity was higher against PEP_{wtrBD} than PEP_{mutRBD} in univariate analyses ($n=33$ positive/48 (68%) vs 18/38 (47%) at D90, p value=0.051, $n=43$ positive/94 (46%) vs 23/82 (28%) at D180, p value=0.019), coinciding with a drop in the magnitude of IFN γ secretion levels in cancer free individuals (Figure 4F, Figure 4I). The multivariate analysis indicated that this difference was independent from age, gender and time of sampling (Table 13). The difference of T cell reactivity between PEP_{wtrBD} and PEP_{mutRBD} cannot be ascribed to non mutated peptide residues missing in PEP_{mutRBD} pool (such as the immunodominant spike 29, which was recognized in <3% of vaccinees when tested separately in this high-throughput screening T cell assay ($p=0.4$, Figure S8G of Fahrner *et al.*, 2022).

Table 13a. Multivariate analyses for vaccine or infection-induced IFN γ release.

PEPorf		Multivariate analysis	P.value
Sampling time		-0.001 (-0.003 to 0.000)	0.049
Age (years)		0.003 (-0.001 to 0.006)	0.180
Gender	Male	-0.117 (-0.213 to -0.019)	0.020
Cancer	Yes	-0.161 (-0.307 to -0.020)	0.030
Covid history and vaccine rounds	No COVID-19 history ; 1 round	0.334 (0.209 to 0.460)	<0.001
	No COVID-19 history ; 2 round	0.685 (0.484 to 0.900)	<0.001
	Convalescent ; no round	0.411 (0.247 to 0.574)	<0.001
	Convalescent ; 1 round	0.875 (0.689 to 1.069)	<0.001

Table 13b. Multivariate analyses for vaccine or infection-induced IFN γ release.

PEPwtRBD		Multivariate analysis	P.value
Sampling time		-0.001 (-0.002 to 0.000)	0.251
Age (years)		0.001 (-0.003 to 0.004)	0.697
Gender	Male	-0.042 (-0.120 to 0.030)	0.317
Cancer	Yes	-0.179 (-0.342 to -0.002)	0.028
Covid history and vaccine rounds	No COVID-19 history ; 1 round	0.101 (-0.004 to 0.215)	0.066
	No COVID-19 history ; 2 round	0.310 (0.123 to 0.507)	0.001
	Convalescent ; no round	-0.028 (-0.163 to 0.109)	0.678
	Convalescent ; 1 round	0.397 (0.242 to 0.566)	<0.001

Table 13c. Multivariate analyses for vaccine or infection-induced IFN γ release .

PEPmutRBD versus PEPwtRBD		Multivariate analysis	P.value
PEPmutRBD		0.152 (-0.055 to 0.378)	0.149
Sampling time		0.001 (-0.001 to 0.003)	0.153
Age (years)		-0.002 (-0.006 to 0.003)	0.507
Gender	Male	-0.046 (-0.167 to 0.078)	0.452
Cancer	Yes	0.216 (-0.026 to 0.454)	0.065
Covid history and vaccine rounds	No COVID-19 history ; 1 round	-0.104 (-0.260 to 0.042)	0.188
	No COVID-19 history ; 2 round	-0.336 (-0.620 to -0.037)	0.014
	Convalescent ; no round	-0.023 (-0.215 to 0.153)	0.812
	Convalescent ; 1 round	-0.358 (-0.617 to -0.151)	0.002

Altogether, these results suggest that defects in the TH1 repertoire affecting the recognition of SARS-CoV-2 S1-RBD are associated with susceptibility to infection or reinfection by SARS-CoV-2 or failure of Spike-based vaccines. T cell responses against

S1-RBD from VOCs appear to be reduced in vaccinees as of August 2021, commensurate with the fact that this antigenic region mutates more than other regions of the SARS-CoV-2 orfome.

5 Discussion

Identifying immune correlates of protection from SARS-CoV-2 is critical to predict the efficacy of existing and future vaccines and to follow a potential decay in immune protection imposing repeated immunizations. Thus the titers of neutralizing antibodies that correlate with IgG antibodies against trimeric S or RBD represent a good proxy of protection against breakthrough infections [46,47]. The landscape of prevalence and immunodominance of SARS-CoV-2 T cell epitopes - supposedly associated with protection during the acute phase - has been thoroughly investigated [48]. Using 40-mer peptide pools covering regions of membrane, nucleocapsid, ORF3a, ORF7/8, and spike proteins, Tan *et al.* observed a statistically significant correlation between the early appearance of SARS-CoV-2 peptide-reactive cells and shorter duration of infection [49]. Here, we unravel the first prospective correlation between preexisting (before the first surge) SARS-CoV-2-specific TH2/Tc2 immune responses and susceptibility to infection with SARS-CoV-2 or reinfection with viral variants, based on 3 independent cohorts and two different methods to monitor TH1/Tc1 and TH2/Tc2 cytokines (ELISA and ELISpot). Both in healthy individuals and cancer subjects, the best immunological correlate for the susceptibility to infection with SARS-CoV-2 was undistinguishably a recall response characterized by a low ratio of TH1/TH2 lymphokines (and more precisely an IL-2/IL-5 ratio <1) secreted upon exposure to the reference SARS-CoV-2 viral strain. The IL-5 memory response coincided with a hole within the TH1/Tc1 cell repertoire affecting the RBD of the spike protein. Five lines of evidence argue in favor of the clinical significance and protective effect against the infection of TH1/Tc1 immune responses directed against anti-S1-RBD for the current pandemic. TH1/Tc1 responses were undetectable i) in individuals from the pre-vaccine era who are susceptible to infection by SARS-CoV-2, ii) in reinfected persons, and iii) in subjects manifesting breakthrough infections after vaccination, and iv) were somehow reduced against the S1-RBD mutated sequences from VOC in vaccinated HCW. Finally, given the high rate of mutations residing in the immunologically and clinically relevant sequence of interest (331-525 aminoacid residues of the spike protein), we are tempted to conclude that an immune-driven selection process of viral phylogeny is currently occurring, as already discussed [50,51].

Reportedly, CD4⁺ TH1 and TH2 responses are induced during the primary phase of viral infection, and both TH1 and TH2 can generate an anamnestic response upon rechallenge with the same virus [52]. Survivors from SARS-CoV-1 infection developed

polyfunctional T cells producing TH1 cytokines and long-term CD8⁺ T cell responses as late as 11 years post-infection [9]. The TH1 cytokine IL-2 (which correlated with circulating non-activated TFH cells in convalescent patients in our study) was the pivotal factor distinguishing susceptible from resistant individuals. Signaling *via* the high-affinity IL-2 receptor (which requires CD25/IL-2R α expression) favors the generation of CXCR5-T effector cells, and this is associated with TH1 responses sustained by the transcription factor TBX21. Moreover, the development of IFN γ producing effector memory T cells depends upon CD25.15 Accordingly, upon infection with lymphocytic choriomeningitis (LCMV), CD25-deficient CD4⁺ T cells largely fail to form IFN γ producing T effector cells in secondary lymphoid organs and to generate lung tissue resident memory T cells [53]. In contrast, increased TH2 cytokine release correlated with poor outcome in patients, a finding corroborated in mouse studies of SARS-CoV-1 [54,55] and SARS-CoV-2 [35]. During SARS-CoV-2 infection, TH2-associated blood markers, such as eosinophilia and circulating IL-5, IL-33, eotaxin-2 and eotaxin-3 correlate with COVID-19 severity [56]. In fact, Dupilumab, an anti-IL-4R α antibody blocking IL-13 and IL-4 signaling [57] protected against inflammatory and severe COVID-19 in two retrospective cohorts [35]. We found that Dupilumab boosts SARS-CoV-2-specific TH1 responses, supporting the rationale of current Phase II trials that evaluate this antibody in the prevention of severe COVID-19 lung infection.

TCR signaling plays a major role in CD4⁺ polarization and can vary according to the TCR affinity, the amount of peptide/MHC-II complexes perceived by a TCR, or the length of time a T cell spends proofreading peptide/MHC-II complexes [15]. Of note, the RBD-specific TH1/Tc1 responses against spike regions 361-375 and 391-405 exhibited robust binding capacities across all MHC class I alleles. Several authors reported cross-reactivities between CCC and SARS-CoV-2 [9,20,23,24,33,34,58,59]. However, such cross-reactive T cells may correlate with poor clinical outcome [60–65]. Indeed, according to one report [21], preexisting CCC-specific memory CD4⁺ T cells exhibit low TCR avidity in almost all unexposed individuals, and are strongly expanded in severe but not mild COVID-19. Moreover, CCC/SARS-CoV-2-cross-reactive T cell clones shared among convalescent and infected individuals harbored lower functional avidity than non-cross-reactive clones, suggesting antigenic imprinting of the TCR repertoire by previous exposure to CCC [26,66]. Of note, these spike-specific cross-reactive CD4⁺ T cells might not only re-expand during infection but also following vaccination. In line with this possibility, we detected a strong positive correlation between CCC and SARS-CoV-2-specific IL-5 release by memory T cells in unexposed individuals. Moreover, CCC-specific IgG titers were higher in susceptible compared to resistant individuals. Finally, the SARS-CoV-1 and ORF8-specific T cell repertoire prevailing in the pre-COVID-19 era failed to be clinically relevant for the

avoidance of COVID-19 and such a repertoire was frequently detected in reinfected individuals during their convalescence phase. Of note, we generated S1-RBD-specific IL-4 or IL-5 producing T cell lines and CD4⁺CD8⁺ T cell clones from one HCW presenting a breakthrough infection after vaccination. Hence, we cannot rule out the possibility that a preexisting TH2 immunity, for instance directed against S1-RBD sequences shared by sarbecoviruses9 could increase the susceptibility to, and severity of, SARS-CoV-2 infection [54–56,67].

Our data fuel the theory that i) robust TH1 memory immune responses against RBD might restrain viral infection, thus exerting a selective pressure on the virus, obliging it to generate escape variants by mutation of RBD, ii) preexisting TH2 antiviral responses might not only be incapable of eliminating SARS-CoV-2-infected cells but actually favor (re)infection with SARS-CoV-2, ultimately increasing the viral reservoir, thus favoring the emergence of viral variants. Hence, immunization strategies should aim at triggering TH1/Tc1 (rather than TH2/Tc2) responses against S1-RBD. The efficacy of cellular immune response relies on three components, (i) the antigen, (ii) the adjuvant and (iii) the dynamics of viral evolution [68]. Immunization with inactivated SARS-CoV-1 or with the whole spike (S) protein, caused eosinophilic infiltration following viral re-exposure in mice [69,70]. Unfortunately, the efficacy of the vaccines composed of inactivated virus produced by Sinovac Biotech (CoronaVac) and Sinopharm (BBIBP-CorV) against VOC have not yet been reported. In contrast, at least in the case of SARS-CoV-1, immunization with RBD induced neutralizing antibodies in the absence of TH2/Tc2 responses [71]. Vaccine adjuvants can stimulate TH1/Tc1-favorable innate immunity, as this is the case for multiple viral vectors, virus-like particles and mRNA containing nanoparticles [66,72]. Finally, virus adaptation to the host has to be outcompeted. One might infer from our data that the currently protective immunodominant regions generating a TH1/Tc1 profile may be the focus of the future antigenic drift of SARS-CoV-2, in which case vaccines would have to be updated regularly [73]. Therefore, to win the race against emerging variants, an expedited world-wide vaccination rollout ensuring an immunization *en masse* against relevant epitopes (and in particular the entire RBD region of the former or current VOCs and Sarbecovirus [67] with vaccine formulations ensuring TH1/Tc1 (rather than TH2/Tc2) responses should outwit the COVID-19 pandemic. In countries of broad vaccine coverage, it may be advantageous to screen the population for IFN γ responses against S1-RBD and hence to determine the need of each individual for booster vaccination. Finally, current efforts to decipher HLA haplotypes associated with maladaptive S1-RBD TH1 responses may open an avenue for personalized vaccine design [74–76].

Example 2: Tumor infiltrating lymphocytes (TIL) as a source to predict tissue resident reactivity to epitopes within viral species that give rise to increased risk to autoimmunity, increased protection or overt, non-productive inflammation.

- 5 The clinical characteristics of the patients and multicontact cases from whom the results below are derived are shown in Example 1 (Tables 1, 8) and in Table 14.

Table 14: Clinical characteristics of indexed and contaminated

Patients' characteristics		Index (n=54)		Contaminated (n=22)		P.value
Age (years)	Median	56		54		0.86
	[Range]	[21-83]		[23-82]		
		n	%	n	%	
Gender	Male	17	31	11	50	0.21
	Female	37	69	11	50	
Malignancy	Yes	54	100	22	100	1.0
	No	0	0	0	0	
Symptoms	Yes	51	94	7	32	0.54
	No	-	-	7	32	
	Unknown	3	6	8	36	
Clinical course	Day hospital (Mild)	-	-	5	72	<0.001
	Hospitalization (Moderate)	-	-	1	14	
	Admission to ICU (Severe)	-	-	1	14	

ICU: Intensive care unit

10

Peptide selection

The final version of the genome of the SARS-CoV-2 virus was released on January 17th 2020 (RefSeq ID MN908947.3). On March 6th 2020 there was no information regarding the immunogenicity of SARS-CoV-2 proteins, from the publicly available sequence data we synthesized peptides covering the entire spike (RefSeq ID QHD43416.1) and nucleocapsid proteins (RefSeq ID QHD43423.2).

From the membrane protein the peptides were selected to cover 2 potential immunogenic regions of the SARS-CoV-2 membrane protein (RefSeq QHD43419.1); these regions had immunogenic potential because there is a similar region in the SARS-CoV-1 membrane protein.

We also selected peptides covering the entire ORF8 (RefSeq ID QHD43422.1) and ORF10 (RefSeq ID QHI42199.1) proteins, these peptides were chosen because these two proteins

20

do not exist in the SARS-CoV-1 and might reveal to be interesting immunogenic targets due to their uniqueness of being non-shared with SARS-CoV-1, and not to be present in other Coronaviruses. They will also aid to differentiate between vaccination and exposure since they are not shared between other Coronavirus-species.

- 5 Other SARS-CoV peptides were peptides found to be immunogenic in previous reported studies (92-99).

In addition, the selected peptides do not have any exact match with the other human coronaviruses.

Results

- 10 TIL (tumor infiltrating lymphocytes) are T-cells, mostly CD4⁺ and CD8⁺ T-cells that home preferentially into malignant tissue. They have a particularly homing mechanism and are believed to derive about 10% from immune cells from peripheral blood and from 90% from tissue-resident immune cells: cells that home into tissues and rarely or never leave the tissue. The reactivity of TIL – that are harvested from tumor lesions during surgery – allows
15 a unique view into tissue-reactive T-cells. It also allows to examine potential autoimmune reactivity, since – in principle – anti-cancer directed cellular immune responses are in fact very focused auto-immune responses.

TIL reactivity therefore reflects i) an anti-cancer response, and ii) autoimmune response in general.

- 20 TIL were expanded *ex vivo* from tumor specimens from patients with different cancer lesions and tested for reactivity to the 187 peptides derived from the SARS-CoV-2 targets. Reactivity was determined by IFN-gamma production in 10e4 TIL / peptide species or as IL-17 production / 10e4 TIL / peptide target.

- TIL were tested from two different populations: patients who underwent surgery for tumors
25 in the pre-pandemic time, *i.e.*, starting in 2017 till early 2019 in Lisbon, Portugal, and patients during the pandemic time (as shown in Tables 15 and 16). T-cell reactivity resided in the SARS-CoV-2 Spike protein, in the nucleocapsid protein, as well as in viral proteins whose functions are still ill-defined (e.g. ORF8). The SARS-CoV2 peptide selection allowed to identify cross-reactivity with SARS-CoV-1 but not with other circulating Coronaviral
30 species. Cross-reactivity to non-mutant or mutant human 'self proteins' is possible.

1. IFN production.

- Table 15:** SARS-2016.05.006 (similarity to human proteins and to bacterial species, identified in **Table 17**), Spike peptide 30 (human tissue proteins, e.g. Tensin which is responsible for driving tissue remodeling in lung tissue and other organs, extracellular
35 matrix formation) and the nucleocapsid 12 (no similarities found) are recognized in TIL harvested from patients in the pre-pandemic and in the pandemic timeframes.

Reactivity to SARS-2016.05.006, to the spike peptide 30 and nucleocapsid 12 in the pre-pandemic period (e.g. 2017, 2018, early 2019).

Cross-reactivity between human proteins and SARS-CoV are responsible for the recognition defined by IFN production in the pre-pandemic and can also drive the T-cell responses in the pandemic time frame.

The Spike protein 15 is preferentially recognized in the post-pandemic time frame (human proteins and / or bacteria, implying that cross-reactivity does not only pre-exist in the immune repertoire but T-cells can be stimulated and expanded upon exposure to SARS-CoV-2 that also recognize human proteins. The ORF8-9 in the pre-pandemic time frame (similar to human Myocilin, a protein that is normally secreted into the aqueous humor of the eye), is recognized in the pre-pandemic time frame, yet less in the pandemic, suggesting T-cell anergy or clonal deletion. Exposure to the virus may eliminate these T-cells or keep them non-functional.

2. Other cytokines.

Not only IFN-gamma (a strongly inflammatory cytokine associated with immune protection and also with overt, i.e. too strong immune responses), yet other cytokines, such as IL-17, that particularly drives autoimmune responses, are detected in the pre-pandemic time frame against peptides that derived from SARS-CoV-2 (**Table 16**). For instance peptide ORF8-1 that shares homology to human proteins or bacterial species. Exposure of the immune system to SARS-CoV-2 would allow for activation and expansion of SARS-CoV-2 specific T-cell responses that would also recognize human. Also ORF8-17 is recognized from T-cells prior to the pandemic time (in October 2017) in tumor infiltrating T-cells. This peptide does not share homology to human proteins or bacterial species and shows that the human T-cell receptor repertoire did not delete anti-SARS-CoV-2 directed T-cell responses during thymic education, i.e. the individual development of the human immune system. IL-17 productive T-cells that are pre-existing against SARS-CoV, can augment anti-viral responses and induce overt inflammation or induce autoimmune responses in case of similarities between viral targets and human proteins.

3. The spike 30 peptide that represents a target for T-cells in the pre-pandemic and pandemic time frame defined by IFN gamma production – that would also be able to drive autoimmune response due to the cross-reactivity to the peptide species listed in **Table 17** is also affected by mutations in the spike protein. Such cross-reactive T-cells may also be protective or drive overt tissue damaging immune responses.

Potential protection / design of future vaccines

Tumor infiltrating T-cells are a source of tissue resident T-cells that enable to detect autoimmune responses (e.g. reactivity against non-mutant) self proteins that can be screened for reactivity against viral targets. TIL are a superior source as compared to immune cells from blood to screen for potential autoimmunity in viral targets since they are able to invade tissues and since anti-cancer immune responses are a certain form of autoimmune responses.

Positive reactivity against SARS-CoV-2 peptides or viral targets in general in TIL, based on the cytokine production pattern, may indicate i) increased risk for autoimmune diseases upon exposure to the viral pathogen, ii) increased protection (since the virus-reactive T-cells are already present), and/or iii) increased pathogenicity upon viral infection due to an overt immune response (unproductive inflammation in the lung and other organs). Organ-specific damage is therefore not only a bystander effect of the cellular immune response, it is associated with the presence of T-cells that recognize both the viral pathogen and non-mutant human tissue. The reactivity pattern is quite consistent in TIL from patients in the pre-pandemic time frame.

TIL are therefore a source to predict increased risk for autoimmunity, increased protection or non-productive inflammation. Screening should be made with different cytokines: IFN-gamma indicates inflammation, peptide targets eliciting IL-17 may indicate increased risk for autoimmune responses since IL-17 is in general associated with autoimmunity.

Such peptide species may be eliminated from vaccine candidates.

→ Examples eliciting IFN-gamma responses:

- Spike15: NLVRDLPQGFSALEP (SEQ ID No: 15)
preferentially pandemic period
Crossreactivity to tissue and bacteria
- Spike30: WNSNNLDSKVGGNYN (SEQ ID No: 30)
pre and pandemic periods
Crossreactivity to tissue and bacteria
- nucleocapsid_12: TLPKGFYAEGSRGGS (SEQ ID No: 97) (SARS-CoV1/2)
pre and pandemic periods
No hits found
- SARS_2016.05.006: LLNKHIDAYKTFP (SEQ ID No: 121) (SARS-CoV1/2)
pre and pandemic periods
Crossreactivity to tissue and bacteria
- ORF8_9: LIELCVDEAGSKSPI (SEQ ID No: 170)
preferentially pre-pandemic
Cross-reactivity to tissue

→ Examples eliciting IL-17 responses:

- ORF8_1: MKFLVFLGIITTVAA (SEQ ID No: 162)
Crossreactivity to tissue and bacteria
- ORF8_17: DVRVVLDFI (SEQ ID No: 178)

5

No hits identified

Table 15

COVID PEPTIDES	D1 TILs (metastasis pancreas adenocarci noma INFg pg 10000 cells	D11 TILs (metastasis pancreas adenocarci noma) INFg pg 10000 cells	D13 TILs (metastasis pancreas adenocarci noma) INFg pg 10000 cells	D126 TILs (pancreas adenocarci cinoma) INFg pg 10000 cells	D303 TILs (rectum adenocarci cinoma) INFg pg 10000 cells	D306 TILs (pancreas adenocarci noma) INFg pg 10000 cells	D309 TILs (pancreas adenocarci cinoma) INFg pg 10000 cells	D310 TILs (colon adenocarci noma) INFg pg 10000 cells	D311 TILs (colon adenocarci cinoma) INFg pg 10000 cells	D1209 PBMCs (pancreas adenocarci noma) INFg pg 10000 cells
SARS_HLA- A*02:01_1	0,0	137,00	101,66	54,9	32,3	166,5	5,6	9,3	303,1	0,0
SARS_HLA- A*02:01_2	0,0	0,00	11,48	3,3	19,2	0,0	2,0	5,4	128,9	0,0
SARS_HLA- A*02:01_3	0,0	0,00	51,79	2,0	4,5	0,0	4,5	0,0	123,9	0,0
SARS_HLA- A*02:01_4	0,0	0,00	0,00	0,2	11,3	0,0	3,6	3,6	134,3	0,0
SARS_HLA- A*02:01_5	0,0	0,00	0,00	5,1	0,0	0,0	20,0	0,0	74,1	0,0
SARS_HLA- A*02:01_6	0,0	0,00	48,30	32,0	0,9	0,0	3,7	0,0	74,2	0,0
SARS_HLA- A*02:01_7	0,0	0,00	95,26	23,5	2,9	0,0	21,8	7,5	128,1	0,0
SARS_HLA- A*02:01_8	0,0	129,08	32,70	69,7	0,4	209,3	6,6	23,0	144,7	0,0
SARS_HLA- A*02:01_9	0,0	0,00	0,00	46,6	0,0	0,0	3,0	0,0	157,7	0,0
SARS_HLA- A*02:01_10	0,0	0,00	0,00	4,5	0,0	0,0	4,9	0,0	96,2	0,0
SARS_HLA- A*02:01_11	0,0	0,00	1,58	147,5	0,0	0,0	1,4	0,0	81,5	0,0
SARS_HLA- A*02:01_12	0,0	0,00	0,00	0,0	0,0	0,0	1,8	0,0	76,2	0,0
SARS_HLA- A*02:01_13	0,0	0,00	57,80	0,0	0,0	0,0	8,6	0,0	49,4	0,0

SARS_HLA-A*02:01_14	0,0	0,00	18,74	0,0	0,0	0,0	0,0	3,7	0,0	97,7	0,0
SARS_HLA-A*02:01_15	0,0	0,00	0,00	0,0	0,0	0,0	0,0	0,7	0,0	91,0	0,0
SARS_HLA-A*02:01_16	0,0	8,36	14,17	54,3	2,8	0,0	0,0	10,2	0,0	137,8	0,0
SARS_HLA-A*02:01_17	0,0	0,00	0,00	9,0	0,9	0,0	0,0	10,3	12,2	138,0	0,0
SARS_HLA-A*02:01_18	0,0	0,00	0,00	0,0	0,0	0,0	0,0	0,2	0,0	137,4	0,0
SARS_HLA-A*02:01_19	0,0	0,00	0,00	0,0	0,0	0,0	0,0	6,7	0,0	56,8	0,0
SARS_HLA-A*02:01_20	0,0	0,00	0,00	0,0	0,0	0,0	0,0	2,1	0,0	81,5	0,0
SARS_HLA-A*02:01_21	0,0	0,00	0,00	0,0	0,0	0,0	0,0	0,4	0,0	43,0	0,0
SARS_10.1128_1	0,0	0,00	0,00	0,0	0,0	0,0	0,0	1,0	0,0	75,7	0,0
SARS_10.1128_2	0,0	0,00	56,67	0,0	0,0	0,0	0,0	5,7	0,0	90,1	0,0
SARS_10.1128_3	0,0	0,00	36,61	17,8	0,0	0,0	0,0	4,0	0,0	138,9	0,0
SARS_10.1128_4	0,0	0,00	69,16	7,5	0,9	0,0	0,0	8,6	0,0	107,2	0,0
SARS_10.1128_5	0,0	0,00	0,00	0,0	0,0	0,0	0,0	1,7	0,0	83,8	0,0
SARS_10.1128_6	0,0	0,00	0,00	0,0	0,0	0,0	0,0	0,6	0,0	75,4	0,0
SARS_10.1128_7	0,0	0,00	28,08	0,0	0,0	0,0	0,0	0,6	0,0	78,9	0,0
SARS_10.1128_8	0,0	0,00	63,26	0,0	0,0	0,0	0,0	3,2	0,0	68,2	0,0
SARS_HLA-DR0401_1	0,0	0,00	0,00	0,0	0,0	0,0	0,0	31,3	0,0	104,6	0,0
SARS_HLA-DR0401_2	0,0	0,00	0,00	0,0	0,0	0,0	0,0	5,3	0,0	39,7	0,0

SARS_HLA- DR0401_3	0,0	21,84	10,43	28,7	118,3	0,0	4,3	5,8	130,9	0,0
SARS_HLA- DR0401_4	0,0	5,41	0,00	0,0	0,0	0,0	6,5	3,0	219,3	0,0
SARS_3726.20 05_1	0,0	0,00	0,00	5,8	0,0	0,0	9,4	0,0	129,4	0,0
SARS_3726.20 05_2	0,0	0,00	0,00	0,0	0,0	0,0	3,8	0,0	109,5	0,0
SARS_5314.20 04_1	0,0	0,00	90,98	0,0	0,0	0,0	0,5	0,0	83,8	0,0
SARS_5314.20 04_2	0,0	0,00	0,00	0,0	0,0	0,0	3,6	0,0	85,8	0,0
SARS_01025- 8_1	0,0	0,00	32,33	1,6	0,0	0,0	3,0	0,0	93,2	0,0
SARS_01025- 8_2	0,0	0,00	151,43	0,0	0,0	0,0	0,0	0,0	83,1	0,0
SARS_01026- X	0,0	0,00	27,36	14,6	0,0	0,0	3,9	2,9	122,9	0,0
SARS_2016.05 .006	0,0	145,37	179,35	117,6	11,2	261,2	4,9	14,6	322,3	0,0
membrane_1	0,0	0,00	0,00	24,0	0,0	0,0	2,7	1,3	169,8	0,0
membrane_2	0,0	0,00	15,32	160,6	0,0	0,0	3,9	0,0	153,6	0,0
membrane_3	0,0	0,00	0,00	166,1	0,0	0,0	2,3	0,0	154,1	0,0
membrane_4	0,0	0,00	0,00	1,9	0,4	0,0	4,0	0,0	157,0	0,0
membrane_5	0,0	0,00	0,00	103,9	0,0	0,0	3,1	0,0	139,0	0,0
membrane_6	0,0	0,00	209,89	128,1	0,0	0,0	4,5	4,5	111,2	0,0
membrane_7	0,0	35,79	155,66	68,6	4,9	16,3	4,5	25,6	276,7	0,0
Spike1	0,0	176,71	0,00	21,8	7,2	0,0	3,0	54,7	327,9	0,0
Spike2	0,0	0,00	0,00	0,0	4,2	0,0	2,0	5,1	125,3	0,0
Spike3	0,0	0,00	0,00	0,0	0,0	0,0	5,5	2,6	164,5	0,0
Spike4	0,0	0,00	0,00	0,0	0,0	0,0	3,7	0,0	160,3	0,0
Spike5	0,0	0,00	0,00	0,0	5,8	0,0	2,5	9,7	122,8	0,0
Spike6	0,0	0,00	0,00	0,0	0,0	0,0	3,1	0,0	137,1	0,0
Spike7	0,0	0,00	0,00	0,0	10,4	0,0	7,1	0,0	165,4	0,0
Spike8	0,0	0,24	0,00	213,8	23,0	21,7	2,8	1,5	285,8	0,0

Spike9	0,0	12,96	189,32	0,0	2,6	0,0	0,0	21,6	8,4	204,3	0,0
Spike10	0,0	0,00	32,66	0,0	0,0	0,0	0,0	2,8	0,0	94,2	0,0
Spike11	0,0	0,00	0,00	0,0	0,0	0,0	0,0	0,0	0,0	127,4	0,0
Spike12	0,0	0,00	0,00	0,0	0,0	0,0	0,0	0,0	0,0	59,0	0,0
Spike13	0,0	0,00	0,00	0,0	9,0	0,0	0,0	3,1	0,0	75,4	0,0
Spike14	0,0	0,00	0,00	0,0	0,0	0,0	0,0	2,8	0,0	69,1	0,0
Spike15	0,0	0,00	0,00	0,0	0,0	0,0	0,0	1,2	0,0	141,6	0,0
Spike16	0,0	0,00	0,00	0,0	0,0	0,0	0,0	10,4	0,0	176,1	0,0
Spike17	0,0	0,00	0,00	0,0	0,0	0,0	0,0	8,9	0,0	241,4	0,0
Spike18	0,0	0,00	0,00	0,0	0,0	0,0	0,0	1,8	0,0	69,9	5,0
Spike19	0,0	0,00	0,00	0,0	0,0	0,0	0,0	1,3	0,0	87,5	0,0
Spike20	0,0	0,00	0,00	0,0	0,0	0,0	0,0	1,5	0,0	79,7	0,0
Spike21	0,0	0,00	0,00	0,0	0,0	0,0	0,0	1,1	0,0	114,5	0,0
Spike22	0,0	0,00	0,00	0,0	0,0	0,0	0,0	3,4	0,0	82,5	0,0
Spike23	0,0	0,00	0,00	0,0	0,0	0,0	0,0	4,3	0,0	63,3	0,0
Spike24	0,0	15,63	0,00	0,0	0,0	0,0	0,0	4,6	0,0	147,6	0,0
Spike25	0,0	0,00	47,33	0,0	0,0	0,0	0,0	2,6	0,0	259,9	0,0
Spike26	0,0	0,00	0,00	39,7	0,0	0,0	0,0	0,0	0,0	127,3	0,0
Spike27	0,0	0,00	0,00	65,1	0,0	0,0	0,0	0,5	0,0	57,3	0,0
Spike28	0,0	0,00	0,00	0,0	0,0	0,0	0,0	0,7	0,0	131,7	0,0
Spike29	0,0	0,00	158,41	0,0	0,0	0,0	0,0	0,0	0,0	83,1	0,0
Spike30	0,0	0,00	69,14	36,8	0,0	0,0	0,0	0,9	0,0	131,1	0,0
Spike31	0,0	0,00	0,00	0,0	0,0	0,0	0,0	15,0	0,0	61,0	0,0
Spike32	0,0	160,05	21,95	0,0	0,0	25,2	0,0	2,3	1,6	167,0	0,0
Spike33	0,0	0,00	0,00	31,9	0,0	0,0	0,0	3,0	0,0	201,2	0,0
Spike34	0,0	0,00	0,00	0,0	0,0	0,0	0,0	2,9	0,0	104,5	0,0
Spike35	0,0	0,00	0,00	0,0	0,0	2,4	0,0	1,1	0,0	101,0	0,0
Spike36	0,0	0,00	0,00	99,7	0,0	0,0	0,0	0,0	0,0	103,4	0,0
Spike37	0,0	0,00	0,00	0,0	0,0	0,0	0,0	0,5	0,0	113,0	0,0
Spike38	0,0	0,00	0,00	0,0	0,0	0,0	0,0	0,0	0,0	165,5	0,0
Spike39	0,0	0,00	0,00	0,0	0,0	0,0	0,0	1,7	0,0	146,5	0,0
Spike40	0,0	0,00	0,00	21,0	0,0	0,0	0,0	2,0	0,0	205,5	0,0
Spike41	0,0	105,07	0,00	55,0	0,0	442,7	0,0	3,0	100,6	206,2	0,0
Spike42	0,0	0,00	0,00	31,9	0,0	0,0	0,0	1,9	2,9	164,5	0,0
Spike43	0,0	0,00	0,00	6,2	0,0	0,0	0,0	0,0	0,0	104,2	0,0

Spike44	0,0	0,00	0,00	0,00	0,0	0,0	0,0	0,0	26,5	1,4	0,0	158,1	0,0
Spike45	0,0	139,74	0,00	0,00	1,9	0,0	0,0	0,0	0,0	21,8	0,0	99,9	0,0
Spike46	0,0	0,00	0,00	0,00	0,0	0,0	0,0	0,0	0,0	9,7	0,0	103,7	0,0
Spike47	0,0	0,00	0,00	0,00	29,4	0,0	0,0	0,0	0,0	0,0	0,1	123,4	0,0
Spike48	0,0	0,00	0,00	0,00	45,7	0,0	0,0	0,0	0,0	2,4	137,3	205,5	0,0
Spike49	0,0	112,71	27,08	73,0	0,0	6,0	0,0	30,8	0,2	24,9	261,3	0,0	0,0
Spike50	0,0	0,00	0,00	0,00	0,0	0,0	0,0	0,0	0,7	0,0	144,5	0,0	0,0
Spike51	0,0	0,00	11,90	0,00	0,0	0,0	0,0	0,0	13,9	8,1	154,4	0,0	0,0
Spike52	0,0	0,00	13,42	0,00	0,0	0,0	0,0	0,0	0,0	0,0	122,9	0,0	0,0
Spike53	0,0	0,00	0,00	0,00	0,0	0,0	0,0	0,0	0,0	0,0	89,1	0,0	0,0
Spike54	0,0	0,00	0,00	0,00	0,0	0,0	0,0	0,0	6,1	0,0	149,6	0,0	0,0
Spike55	0,0	0,00	0,00	0,00	0,0	0,0	0,0	0,0	1,7	24,0	66,1	0,0	0,0
Spike56	0,0	97,90	15,25	80,9	0,0	0,0	200,4	1,9	40,2	247,9	0,0	0,0	0,0
Spike57	0,0	2,64	0,00	0,00	0,0	3,1	0,0	0,6	0,0	230,5	0,0	0,0	0,0
Spike58	0,0	0,00	0,00	0,00	0,0	0,0	0,0	0,0	0,0	102,3	0,0	0,0	0,0
Spike59	0,0	0,00	0,00	0,00	0,0	0,0	0,0	0,0	0,0	165,9	0,0	0,0	0,0
Spike60	0,0	0,00	0,00	0,00	0,0	0,0	0,0	0,3	0,0	83,8	0,0	0,0	0,0
Spike61	0,0	0,00	0,00	0,00	0,0	0,0	0,0	0,0	0,0	73,1	0,0	0,0	0,0
Spike62	0,0	0,00	0,00	0,00	0,0	0,0	0,0	0,0	0,0	86,3	0,0	0,0	0,0
Spike63	0,0	0,00	0,00	0,00	0,0	0,0	0,0	0,0	0,0	66,4	0,0	0,0	0,0
Spike64	0,0	0,00	0,00	0,00	0,0	2,9	0,0	2,2	4,5	169,5	0,0	0,0	0,0
Spike65	0,0	0,00	337,93	0,00	0,0	0,0	0,0	0,5	8,9	190,7	0,0	0,0	0,0
Spike66	0,0	0,00	186,03	0,00	0,0	0,0	0,0	1,5	0,0	145,2	0,0	0,0	0,0
Spike67	0,0	0,00	160,38	0,00	0,0	0,0	0,0	0,0	0,0	83,3	0,0	0,0	0,0
Spike68	0,0	0,00	0,00	0,00	0,0	0,0	0,0	1,0	0,0	72,9	0,0	0,0	0,0
Spike69	0,0	0,00	411,14	0,00	0,0	0,0	0,0	5,7	0,0	83,9	0,0	0,0	0,0
Spike70	0,0	0,00	0,00	0,00	0,0	0,0	0,0	0,1	0,0	47,1	0,0	0,0	0,0
Spike71	0,0	0,00	284,52	0,00	0,0	0,0	0,0	0,0	0,0	59,2	0,0	0,0	0,0
Spike72	0,0	228,65	37,46	0,00	0,0	5,6	31,2	0,3	0,5	189,7	0,0	0,0	0,0
Spike73	0,0	0,00	39,74	0,00	0,0	0,0	0,0	0,2	1,7	182,9	0,0	0,0	0,0
Spike74	0,0	0,00	68,17	0,00	0,0	0,0	0,0	9,0	0,0	80,7	0,0	0,0	0,0
Spike75	0,0	0,00	0,00	0,00	0,0	0,0	0,0	12,6	0,0	92,7	0,0	0,0	0,0
Spike76	0,0	0,00	0,00	0,00	0,0	0,0	0,0	2,9	0,0	125,6	0,0	0,0	0,0
Spike77	0,0	0,00	0,00	0,00	0,0	0,0	0,0	2,4	0,0	97,5	0,0	0,0	0,0
Spike78	0,0	0,00	0,00	0,00	0,0	0,0	0,0	0,6	0,0	94,2	0,0	0,0	0,0

nucleocapsid_15	0,0	0,00	111,54	0,0	69,6	0,0	8,0	19,0	240,4	0,0
nucleocapsid_16	0,0	110,92	32,61	0,0	24,0	0,0	1,7	0,0	175,3	0,0
nucleocapsid_17	0,0	67,01	0,00	0,0	10,7	0,0	1,7	0,0	120,4	0,0
nucleocapsid_18	0,0	0,00	269,10	0,0	45,8	0,0	2,5	0,0	198,4	0,0
nucleocapsid_19	0,0	25,74	184,16	37,4	49,7	0,0	9,3	80,0	334,4	0,0
nucleocapsid_20	0,0	0,00	20,79	0,0	0,0	0,0	3,7	4,6	184,4	0,0
nucleocapsid_21	0,0	0,00	73,90	0,0	0,0	0,0	0,0	0,0	60,2	0,0
nucleocapsid_22	0,0	0,00	177,89	0,0	0,0	0,0	1,8	0,0	125,0	0,0
nucleocapsid_23	0,0	0,00	0,00	0,0	0,0	0,0	0,3	0,0	92,6	0,0
nucleocapsid_24	0,0	0,00	46,80	0,0	0,0	0,0	0,0	0,0	92,5	0,0
nucleocapsid_25	0,0	0,00	0,00	0,0	0,0	0,0	1,1	0,0	75,8	0,0
nucleocapsid_26	0,0	0,00	8,29	0,0	0,0	0,0	0,6	0,0	114,8	0,0
nucleocapsid_27	0,0	48,34	83,05	0,0	0,0	0,0	3,5	0,0	240,9	0,0
nucleocapsid_28	0,0	128,71	0,00	0,0	149,1	0,0	2,3	44,7	195,6	0,0
ORF8_1	0,0	284,71	0,00	0,0	0,0	0,0	1,1	6,2	8,3	0,0
ORF8_2	0,0	0,00	0,00	0,0	0,0	0,0	1,2	0,0	0,0	0,0
ORF8_3	0,0	0,00	0,00	0,0	0,0	0,0	6,4	0,0	3,5	0,0
ORF8_4	0,0	0,00	76,94	0,0	0,0	0,0	4,0	0,0	1,3	0,0
ORF8_5	0,0	146,76	62,95	0,0	0,0	0,0	0,0	0,0	0,0	0,0
ORF8_6	0,0	204,83	0,00	0,0	0,0	0,0	2,0	0,0	0,0	0,0
ORF8_7	0,0	217,82	94,47	0,0	0,0	0,0	0,0	0,0	0,0	0,0

ORF8_8	0,0	69,59	37,50	0,0	0,0	0,0	0,0	1,9	4,6	28,1	0,0
ORF8_9	0,0	112,66	251,07	9,2	0,0	0,0	0,0	1,6	0,0	1,8	0,0
ORF8_10	0,0	0,00	0,00	0,0	0,0	0,0	0,0	0,7	0,0	0,0	0,0
ORF8_11	0,0	0,00	0,00	0,0	0,0	0,0	0,0	2,8	0,0	0,0	0,0
ORF8_12	0,0	0,00	83,89	0,0	0,0	0,0	0,0	1,0	0,0	0,0	0,0
ORF8_13	0,0	0,00	19,58	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
ORF8_14	0,0	0,00	0,00	0,0	0,0	0,0	0,0	0,9	0,0	0,0	0,0
ORF8_15	0,0	0,00	0,00	0,0	0,0	0,0	0,0	2,7	0,0	0,0	0,0
ORF8_16	0,0	38,17	100,81	0,0	0,0	0,0	0,0	5,6	0,0	0,0	0,0
ORF8_17	0,0	139,79	0,00	89,0	45,1	0,0	0,0	1,4	2,5	9,3	0,0
ORF10_1	0,0	41,30	0,00	7,8	8,7	0,0	0,0	0,5	0,0	0,0	0,0
ORF10_2	0,0	45,48	0,00	5,9	21,5	0,0	0,0	1,1	0,0	0,0	0,0
ORF10_3	0,0	19,81	0,00	0,1	16,3	0,0	0,0	1,2	0,0	0,0	0,0
ORF10_4	0,0	29,29	0,00	2,2	23,9	0,0	0,0	2,7	0,0	0,0	0,0
ORF10_5	0,0	30,02	0,00	0,0	21,7	0,0	0,0	3,1	0,0	0,0	0,0
ORF8_A	0,0	48,99	0,00	0,0	15,9	0,0	0,0	1,3	0,0	0,0	0,0
ORF8_BC	0,0	129,49	60,03	46,8	26,6	277,2	2,5	2,5	17,3	0,0	0,0
ORF3a_AB	0,0	265,83	0,00	151,3	1,4	133,5	6,2	6,2	116,2	6,9	0,0
ORF3a_C	0,0	130,79	0,00	14,4	0,0	32,3	16,2	16,2	8,9	6,8	0,0
VIRUS (SARS-CoV-2)	No Data	254,69	0,00	7,6	No Data	No Data	No Data	No Data	No Data	No Data	0,0
OKT3	0,0	28,20	27,76	175,3	24,0	407,6	497,8	497,8	320,1	724,7	0,0
PHA	0,0	337,76	0,00	0,0	39,7	113,0	552,2	552,2	325,6	64,4	0,0
EBNA	0,0	0,00	0,00	0,0	0,0	0,0	1411,0	1411,0	3594,0	9,3	1,0
CMV	0,0	0,00	0,00	0,0	9,0	0,0	1207,0	1207,0	3446,0	19,5	0,0
CMV Pool	No Data	140,66	0,00	65,0	No Data	No Data	No Data	No Data	No Data	No Data	0,0
M1	0,0	166,14	16,49	0,4	1,1	82,4	4,5	4,5	0,0	0,0	0,0

Table 16

	Pre Pandemic	Post Pandemic			
COVID PEPTIDES	D1 TILs (metastasis pancreas adenocarcinoma) IL17 pg 10000 cells	D303 TILs (rectum adenocarcinoma) IL17 pg 10000 cells	D306 TILs (pancreas adenocarcinoma) IL17 pg 10000 cells	D309 TILs (pancreas adenocarcinoma) IL17 pg 10000 cells	D311 TILs (colon adenocarcinoma) IL17 pg 10000 cells
SARS_HLA- A*02:01_1	0,0	59,4	0,0	0,0	43,3
SARS_HLA- A*02:01_2	0,0	77,9	0,0	0,0	16,7
SARS_HLA- A*02:01_3	0,0	48,1	0,0	0,0	24,9
SARS_HLA- A*02:01_4	0,0	57,3	0,0	0,0	20,9
SARS_HLA- A*02:01_5	0,0	99,5	0,0	0,0	39,7
SARS_HLA- A*02:01_6	0,0	30,5	0,0	0,0	20,5
SARS_HLA- A*02:01_7	0,0	78,1	4,3	0,0	25,9
SARS_HLA- A*02:01_8	0,0	130,5	12,4	0,0	35,3
SARS_HLA- A*02:01_9	0,0	35,2	0,0	0,0	33,4
SARS_HLA- A*02:01_10	0,0	21,1	0,0	0,0	14,2
SARS_HLA- A*02:01_11	0,0	16,3	0,0	0,0	24,4
SARS_HLA- A*02:01_12	0,0	32,3	0,0	0,0	18,7

SARS_HLA-A*02:01_13	0,0	35,8	0,0	0,0	11,6
SARS_HLA-A*02:01_14	0,0	22,8	0,0	0,0	12,1
SARS_HLA-A*02:01_15	0,0	24,5	0,0	0,0	15,6
SARS_HLA-A*02:01_16	0,0	49,9	0,0	0,0	22,3
SARS_HLA-A*02:01_17	0,0	40,6	0,0	0,0	27,6
SARS_HLA-A*02:01_18	0,0	18,0	0,0	0,0	12,6
SARS_HLA-A*02:01_19	0,0	13,4	0,0	0,0	16,9
SARS_HLA-A*02:01_20	0,0	31,1	0,0	0,0	11,4
SARS_HLA-A*02:01_21	0,0	16,3	0,0	0,0	16,7
SARS_10.1128_1	0,0	27,7	0,0	0,0	14,5
SARS_10.1128_2	0,0	21,9	0,0	0,0	18,9
SARS_10.1128_3	0,0	44,1	0,0	0,0	18,2
SARS_10.1128_4	0,0	36,5	0,0	0,0	28,8
SARS_10.1128_5	0,0	26,6	0,0	0,0	9,7
SARS_10.1128_6	0,0	12,3	0,0	0,0	15,8
SARS_10.1128_7	0,0	18,1	0,0	0,0	11,5
SARS_10.1128_8	0,0	5,3	0,0	0,0	17,9
SARS_HLA-DR0401_1	0,0	20,5	0,0	0,0	11,5
SARS_HLA-DR0401_2	0,0	20,2	0,0	0,0	26,7
SARS_HLA-DR0401_3	0,0	44,4	0,3	0,0	18,1

SARS_HLA- DR0401_4	0,0	57,5	0,0	0,0	29,9
SARS_3726.2005_1	0,0	20,2	0,0	0,0	11,5
SARS_3726.2005_2	0,0	7,2	0,0	0,0	17,3
SARS_5314.2004_1	0,0	24,2	0,0	0,0	16,5
SARS_5314.2004_2	0,0	36,8	0,0	0,0	18,1
SARS_01025-8_1	0,0	27,3	0,0	0,0	12,1
SARS_01025-8_2	0,0	31,4	0,0	0,0	20,2
SARS_01026-X	0,0	58,8	0,0	0,0	16,7
SARS_2016.05.006	0,0	141,3	38,8	0,0	43,0
membrane_1	0,0	30,7	0,0	0,0	15,0
membrane_2	0,0	40,3	0,0	0,0	21,6
membrane_3	0,0	60,6	15,7	0,0	33,4
membrane_4	0,0	73,7	22,7	0,0	59,6
membrane_5	0,0	65,4	7,1	0,0	26,5
membrane_6	0,0	44,5	0,0	0,0	30,5
membrane_7	0,0	143,4	15,7	0,0	27,7
Spike1	0,0	134,7	6,8	0,0	33,5
Spike2	0,0	52,2	0,0	0,0	15,5
Spike3	0,0	38,8	0,0	0,0	17,1
Spike4	0,0	38,4	3,0	0,0	27,0
Spike5	0,0	89,3	14,6	0,0	43,9
Spike6	0,0	69,5	11,4	0,0	42,0
Spike7	0,0	67,6	0,0	0,0	11,1
Spike8	0,0	254,5	17,1	0,0	16,9
Spike9	0,0	50,9	0,0	0,0	30,4
Spike10	0,0	31,0	0,0	0,0	6,3
Spike11	0,0	26,2	0,0	0,0	11,6
Spike12	0,0	28,5	0,0	0,0	17,9
Spike13	0,0	68,2	9,8	0,0	39,1
Spike14	0,0	36,6	0,0	0,0	31,4
Spike15	0,0	32,5	0,0	0,0	10,6

Spike16	0,0	56,7	0,0	0,0	0,0	11,6
Spike17	0,0	58,3	0,0	0,0	0,0	19,7
Spike18	0,0	23,6	0,0	0,0	0,0	13,2
Spike19	0,0	29,7	0,0	0,0	0,0	11,6
Spike20	0,0	27,5	0,0	0,0	0,0	8,0
Spike21	0,0	29,4	1,6	0,0	0,0	21,7
Spike22	0,0	15,7	0,0	0,0	0,0	7,5
Spike23	0,0	27,8	0,0	0,0	0,0	6,8
Spike24	0,0	62,4	0,0	0,0	0,0	11,8
Spike25	0,0	55,4	0,0	0,0	0,0	14,2
Spike26	0,0	23,7	0,0	0,0	0,0	5,5
Spike27	0,0	29,6	0,0	0,0	0,0	9,0
Spike28	0,0	28,3	0,0	0,0	0,0	6,2
Spike29	0,0	31,1	0,0	0,0	0,0	7,7
Spike30	0,0	26,6	0,0	0,0	0,0	15,0
Spike31	0,0	30,0	0,0	0,0	0,0	12,2
Spike32	0,0	74,6	0,0	0,0	0,0	9,5
Spike33	0,0	98,6	0,8	0,0	0,0	20,5
Spike34	0,0	26,5	0,0	0,0	0,0	10,3
Spike35	0,0	25,3	0,0	0,0	0,0	12,1
Spike36	0,0	30,9	0,0	0,0	0,0	12,9
Spike37	0,0	63,0	0,0	0,0	0,0	8,8
Spike38	0,0	28,3	0,0	0,0	0,0	15,3
Spike39	0,0	31,1	0,0	0,0	0,0	9,4
Spike40	0,0	75,6	0,0	0,0	0,0	13,4
Spike41	0,0	118,4	17,8	0,0	0,0	37,3
Spike42	0,0	44,4	0,0	0,0	0,0	15,7
Spike43	0,0	50,0	0,0	0,0	0,0	10,3
Spike44	0,0	47,3	0,0	0,0	0,0	13,4
Spike45	0,0	76,4	5,3	0,0	0,0	8,9
Spike46	0,0	28,9	0,0	0,0	0,0	18,8
Spike47	0,0	61,5	0,0	0,0	0,0	12,8

Spike48	0,0	62,1	0,0	0,0	0,0	16,9
Spike49	5,7	121,9	0,0	0,0	0,0	37,7
Spike50	0,0	95,3	0,0	0,0	0,0	17,7
Spike51	0,0	66,9	0,0	0,0	0,0	22,7
Spike52	0,0	74,0	12,1	0,0	0,0	19,3
Spike53	0,0	96,6	0,0	0,0	0,0	17,3
Spike54	0,0	70,9	0,0	0,0	0,0	14,8
Spike55	0,0	98,9	0,0	0,0	0,0	10,1
Spike56	0,0	149,0	21,3	0,0	0,0	31,3
Spike57	0,0	105,2	0,0	0,0	0,0	20,3
Spike58	0,0	50,0	0,0	0,0	0,0	5,4
Spike59	0,0	17,9	0,0	0,0	0,0	17,6
Spike60	0,0	32,5	0,0	0,0	0,0	3,8
Spike61	0,0	36,2	0,0	0,0	0,0	8,5
Spike62	0,0	49,3	0,0	0,0	0,0	8,3
Spike63	0,0	41,3	0,0	0,0	0,0	10,8
Spike64	0,0	70,5	0,0	0,0	0,0	18,3
Spike65	0,0	83,5	0,0	0,0	0,0	21,6
Spike66	0,0	33,7	0,0	0,0	0,0	4,1
Spike67	0,0	26,4	0,0	0,0	0,0	12,8
Spike68	0,0	32,9	0,0	0,0	0,0	10,9
Spike69	0,0	38,7	0,0	0,0	0,0	14,7
Spike70	0,0	31,5	0,0	0,0	0,0	11,7
Spike71	0,0	29,8	0,0	0,0	0,0	8,7
Spike72	0,0	56,3	0,0	0,0	0,0	15,0
Spike73	0,0	82,5	0,0	0,0	0,0	21,8
Spike74	0,0	38,8	0,0	0,0	0,0	9,0
Spike75	0,0	32,6	5,9	0,0	0,0	10,6
Spike76	0,0	26,0	0,0	0,0	0,0	7,7
Spike77	0,0	43,0	0,0	0,0	0,0	19,1
Spike78	0,0	28,1	0,0	0,0	0,0	11,7
Spike79	0,0	30,9	0,0	0,0	0,0	7,3

Spike80	0,0	69,0	0,0	0,0	0,0	14,1
Spike81	0,0	99,1	0,0	0,0	0,0	31,4
Spike82	0,0	45,0	0,0	0,0	0,0	5,9
Spike83	0,0	29,6	0,0	0,0	0,0	0,0
Spike84	0,0	34,6	0,0	0,0	0,0	3,6
Spike85	0,0	35,7	0,0	0,0	0,0	12,0
nucleocapsid_1	0,0	38,7	0,0	0,0	0,0	10,2
nucleocapsid_2	0,0	31,4	0,0	0,0	0,0	6,8
nucleocapsid_3	0,0	187,2	0,0	0,0	0,0	5,5
nucleocapsid_4	0,0	49,7	0,0	0,0	0,0	0,0
nucleocapsid_5	0,0	53,1	0,0	0,0	0,0	0,0
nucleocapsid_6	0,0	104,9	0,0	0,0	0,0	21,7
nucleocapsid_7	0,0	65,4	0,0	0,0	0,0	2,6
nucleocapsid_8	0,0	65,4	0,0	0,0	0,0	0,4
nucleocapsid_9	0,0	68,3	0,0	0,0	0,0	0,0
nucleocapsid_10	0,0	127,7	0,0	0,0	0,0	7,1
nucleocapsid_11	0,0	81,9	0,0	0,0	0,0	19,5
nucleocapsid_12	69,0	84,7	0,0	0,0	0,0	31,4
nucleocapsid_13	0,0	59,6	0,0	0,0	0,0	15,2
nucleocapsid_14	0,0	35,8	0,0	0,0	0,0	14,0
nucleocapsid_15	51,9	63,6	0,0	0,0	0,0	26,2
nucleocapsid_16	0,0	49,8	0,0	0,0	0,0	12,2
nucleocapsid_17	0,0	35,1	0,0	0,0	0,0	15,2
nucleocapsid_18	0,0	47,8	0,0	0,0	0,0	19,8
nucleocapsid_19	37,1	77,5	0,0	0,0	0,0	62,3
nucleocapsid_20	11,6	13,1	0,0	0,0	0,0	29,3
nucleocapsid_21	0,0	1,1	0,0	0,0	0,0	7,9
nucleocapsid_22	0,0	4,8	0,0	0,0	0,0	2,4
nucleocapsid_23	0,0	6,1	0,0	0,0	0,0	13,4
nucleocapsid_24	0,0	0,6	0,0	0,0	0,0	12,6
nucleocapsid_25	0,0	2,4	0,0	0,0	0,0	11,7
nucleocapsid_26	0,0	7,4	0,0	0,0	0,0	24,9

nucleocapsid_27	0,0	27,4	0,0	0,0	0,0	32,8
nucleocapsid_28	0,0	22,0	0,0	0,0	0,0	25,9
ORF8_1	14,5	44,1	0,0	0,0	0,0	0,0
ORF8_2	0,0	0,0	0,0	0,0	0,0	0,0
ORF8_3	0,0	5,0	0,0	0,0	0,0	0,0
ORF8_4	0,0	5,2	0,0	0,0	0,0	0,0
ORF8_5	0,0	10,0	0,0	0,0	0,0	0,0
ORF8_6	0,0	5,9	0,0	0,0	0,0	0,0
ORF8_7	0,0	11,0	0,0	0,0	0,0	0,0
ORF8_8	0,0	30,3	4,7	0,0	0,0	0,0
ORF8_9	0,0	79,2	0,0	0,0	0,0	1,2
ORF8_10	0,0	33,9	0,0	0,0	0,0	0,0
ORF8_11	0,0	44,3	0,0	0,0	0,0	0,0
ORF8_12	0,0	59,3	0,0	0,0	0,0	0,0
ORF8_13	0,0	47,7	0,0	0,0	0,0	0,0
ORF8_14	0,0	37,7	0,0	0,0	0,0	0,0
ORF8_15	0,0	29,5	0,0	0,0	0,0	0,0
ORF8_16	0,0	38,9	0,1	0,0	0,0	0,0
ORF8_17	80,7	105,2	0,0	0,0	0,0	0,0
ORF10_1	0,0	84,2	1,8	0,0	0,0	0,0
ORF10_2	0,0	82,2	3,7	0,0	0,0	0,0
ORF10_3	0,0	88,4	0,0	0,0	0,0	0,0
ORF10_4	0,0	88,0	0,0	0,0	0,0	0,0
ORF10_5	0,0	87,3	0,0	0,0	0,0	0,0
ORF8_A	0,0	76,7	0,0	0,0	0,0	0,0
ORF8_BC	0,0	76,9	0,0	0,0	0,0	7,4
ORF3a_AB	6,9	55,4	40,9	0,0	0,0	0,0
ORF3a_C	0,0	67,1	13,4	0,0	0,0	0,0
Virus (SARS-CoV-2)	No Data	No Data	No Data	No Data	No Data	No Data
OKT3	1101,0	17,8	92,5	0,0	0,0	205,1
OKT3	1186,7	30,3	67,5	0,0	0,0	177,7

OKT3	No Data	11,2	97,4	0,0	128,9
OKT3	No Data	91,0	0,0	0,0	2,0
PHA	1033,7	17,4	0,0	0,0	0,0
PHA	1132,7	23,6	0,0	0,0	0,0
PHA	No Data	26,1	0,0	0,0	0,0
PHA	No Data	92,0	0,0	0,0	0,0
EBNA	0,0	23,6	0,0	0,0	1,0
CMV	0,0	18,0	0,0	0,0	6,0
M1	2,2	68,0	1,0	0,0	0,0

Table 17

IA3:G80L-5 Signature	Peptide	Virus Sequence	SEQ ID	Potential Cross Reactive Sequence	SEQ ID	Protein Name
	Spike27	No Hits		No Hits		
	Spike28	RQIAPGQTG	260	REIAPGLTG	310	Activating molecule in BECN1-regulated autophagy protein 1
		EVRQIAPGQ	261	ELRQGAPGQ	311	SUN domain-containing protein 2
		EVRQIAPGQ	261	EVRQAAPEQ	312	Protein translocase subunit SecA Protein translocase subunit SecA [Bacteroides thetaiotaomicron VPI-5482]
		EVRQIAPGQ	261	EVRQAAPEQ	312	Protein translocase subunit SecA [Bacteroides fragilis NCTC 9343]
	Spike29	No Hits		No Hits		
	Spike30	LDSKVGNY	262	LKSKHGGNY	313	Tensin-1
		NSNLDISKV	263	NSYNLNSKV	314	Probable cell division protein WhiA [Clostridium botulinum A str. Hall]
		LDSKVGNY	262	LGSKVGNNY	315	Uridine permease [Saccharomyces cerevisiae S288C]
	Spike31	YRLFRKSNL	264	YMLFRKYNL	316	THUMP domain-containing protein 1
		LYRLFRKSN	265	LWRLFRKKN	317	Protein O-linked-mannose beta-1,2-N-acetylglucosaminyltransferase 1
		LYRLFRKSN	265	LYNLFTKSN	318	Probable G-protein coupled receptor 82
		LYRLFRKSN	265	LYRDFRKEN	319	Zinc finger protein with KRAB and SCAN domains 2
		LYRLFRKSNL	266	LFRLFRHSNL	320	Protein transport protein sec1 [Schizosaccharomyces pombe 972h-]
	Spike32	STEIQAGS	267	STQIQAVS	321	Phospholipid-transporting ATPase ABCA1
		DISTEIQQA	268	DISTGIYKA	322	CDK-activating kinase [Saccharomyces cerevisiae S288C]
		ISTEIQAG	269	IATEIYGAG	323	Formyltetrahydrofolate synthetase [Campylobacter curvus 525.92]

Spike33	GFNCYFPLQ S	270	GFNIYFPLMS	324	FXNA-like protease [Schizosaccharomyces pombe 972h-]
	EGFNCYFPL	271	ENFNCMFPL	325	ABC-transporter-regulating transcription factor [Aspergillus oryzae RIB40]
ORF8_5	No Hits		No Hits		
nucleocapsid_8	FYYLGTGPE	272	FYYLGS GRE	326	Xyloside xylosyltransferase 1
	PRWYFYVLG TGPEA	273	PRWYFYVLG TGPHA	327	Human coronavirus OC43
	PRWYFYVLG TGP	274	PRWYFYVLG TGP	274	Human coronavirus HKU1
SARS_2016.05.006	LLNKHIDAY	275	LLYKAIDAY	328	Voltage-dependent L-type calcium channel subunit alpha-1F
	LLNKHIDAY	275	LLNKNIDVY	329	Menaquinone biosynthesis protein MenD [Staphylococcus aureus RF122]
	LNKHIDAYK	276	LPKHIDAFK	330	Methenyltetrahydrofolate cyclohydrolase [Pediococcus pentosaceus ATCC 25745]
Spike2	RTQLPPAYT	277	RTQSPPVYT	331	Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 1
	TQLPPAYTN	278	TQTPPAYIN	332	E3 ubiquitin-protein ligase TTC3
	VNLTTRTQL	279	VELTTKTQL	333	Transcription termination/antitermination protein NusG [Mycoplasma pneumoniae M129]
	LTTRTQLPP	280	LVVRTQLPP	334	Quinic acid utilization activator [Neurospora crassa OR74A]
	NLTTRTQLP	281	NLTTRIALP	335	RNase Y [Helicobacter pylori 26695]
Spike3	No Hits		No Hits		
Spike15	LVRDLPQGF	282	LVQDLAQGF	336	Tryptophan--tRNA ligase, mitochondrial
	LVRDLPQGF S	283	LVRDLVTGFS	337	U11/U12 small nuclear ribonucleoprotein 35 kDa protein
	LPQGFSALE	284	LAQGFSGLE	338	UDP-N-acetylmuramate dehydrogenase [Pseudomonas fluorescens Pf0-1]
Spike21	KSFTVEKGI	285	KTFTVQKGI	339	Desmoglein-3

IL-2 Signature	ORF10_4	No Hits		No Hits		
	ORF10_5	No Hits		No Hits		
	Spike51	NLLQYGSF	286	NLLQIGSF	340	DNA translocase FtsK [[Haemophilus] ducreyi 35000HP]
	Spike56	LADAGFIQ	287	LADRGFIQ	341	CHS5 SPA2 rescue protein 2 [Saccharomyces cerevisiae S288C]
		VTLADAGFI	288	VALQDAGFI	342	MetRS [Burkholderia lata]
	Spike57	LGDIARDLI	289	LGDIARDAI	343	SNF-related serine/threonine-protein kinase
		LGDIARDL	290	LGDKAVRDL	344	Tonsoku-like protein
		LGDIARDL	290	LGDLAARQL	345	Major membrane protein I [Mycobacterium avium]
		LGDIARDL	290	LGEAAARDL	346	DXPS [Leptospira borgpetersenii serovar Hardjo-bovis str. JB197]
	Spike84	GCCSCGSCC	291	GCCSGGGCC	347	Late cornified envelope protein 4A
Ex-Positive Patients		SCGSCCKFD	292	SYGKCKKFD	348	ABN B [Aspergillus fumigatus A1163]
		SCGSCCKFD	292	SYGKCKKFD	348	ABN B [Aspergillus fischeri NRRL 181]
	Spike85	VLKGVKLHY	293	VLKGSKLHF	349	Kinesin-like protein KIF14
		SEPVKGVK	294	SEAVLDGVK	350	WD repeat-containing protein 87
		EPVLKGVKL	295	EPVLKGLNL	351	ECF transporter A component CbiO [Salmonella enterica subsp. enterica serovar Typhi]
		EPVLKGVKL	295	EPVLKGLNL	351	ECF transporter A component CbiO [Salmonella enterica subsp. enterica serovar Paratyphi A str. ATCC 9150]
	SARS_HLA-A*02:01_14	QFKDNVILL	296	QIKDRVILL	352	Olfactory receptor 52Z1
		AIKLDDKDPQ	297	AIKLDDKAPE	353	TdRPase [Klebsiella pneumoniae subsp. pneumoniae MGH 78578]
		GAIKLDDKD	298	GSIKLEDKD	354	Oligopeptide transport ATP-binding protein AppD [Bacillus subtilis subsp. subtilis str. 168]
		DPQFKDNVIL	299	DGQFEDNVIL	355	Alpha-glucosiduronase [Aspergillus flavus NRRL3357]
Non significant controls		QFKDNVILL	300	QYKQVILL	356	Protein SPA2 [Saccharomyces cerevisiae S288C]

SARS_HLA-A*02:01_15	ETALALLLL	301	DTALDLLLL	357	Sorting nexin-19
	GETALALL	302	GAAALALL	358	Torsin-1B
	GETALALL	302	GAAALALL	358	Peroxiredoxin-like 2A
	ETALALLLL	301	ETTPALLLL	359	Protocadherin-16
	ETALALLLL	301	EIALKLLLL	360	SCAN domain-containing protein 3
	ETALALLLL	301	ETALLFL	361	Protein PHTF1
	ETALALLLL	301	ESALAKLLL	362	Transmembrane protein 176A
	ETALALLLL	301	QTALAVLLL	363	Cellulose synthase 2 regulatory subunit [Komagataeibacter xylinus]
	ETALALLLL	301	QTALAVLLL	363	Cellulose synthase 3 regulatory subunit [Komagataeibacter xylinus]
	GETALALLLL	144	GATLLALLLL	364	C4-dicarboxylate transport sensor protein DctB [Pseudomonas aeruginosa PAO1]
	GETALALL	302	GETARALL	365	Uncharacterized lipoprotein TP_0449 [Treponema pallidum subsp. pallidum str. Nichols]
	GETALALL	302	GETAFAMLL	366	Purine nucleotide synthesis repressor [Yersinia enterocolitica subsp. enterocolitica 8081]
	GETALALL	302	GETAFAMLL	366	Purine nucleotide synthesis repressor [Yersinia pestis Antiqua]
	GETALALL	302	GETAFAMLL	366	Purine nucleotide synthesis repressor [Yersinia pestis Pestoides F]
	ETALALLLL	301	ETAVALLVL	367	Manganese transporter pdt1 [Schizosaccharomyces pombe 972h-]
	GETALALLLL	144	GITILALLLL	368	Glycoprotein 21 [Human T-lymphotropic virus 2]
	ETALALLLL	301	EAALQLLLL	369	RF-1 [Bordetella pertussis Tohama I]
	ETALALLLL	301	EAALQLLLL	369	RF-1 [Bordetella parapertussis 12822]
SARS_HLA-A*02:01_16	VIGFLFLAW	303	VISFLFAW	370	Uncharacterized transporter C11D3.18C [Schizosaccharomyces pombe 972h-]
	LVIGFLFLAW	304	LVTGFLALAW	371	Glycoprotein 41 [HIV-1 M:F1_V1850]
nucleocapsid_12	No Hits		No Hits		

	ORF8_9	IELCVDEAG	305	IDLAVDEAG	372	Myocilin	
	ORF8_1	LVFLGIIT	306	LVFLGIVVT	373	Zinc finger protein 90	
		FLVFLGIIT	307	FLVFLFIVT	374	OATP-RP4	
		MKFLVFLGI	308	MKILSFLGI	375	PC1-like 2 protein	
		VFLGIITTV	309	VFAGILTTV	376	Fibrinoligase	
	ORF8_17	No Hits		No Hits			

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CLAIMS

1. A method for *in vitro* determining whether an individual is likely to resist to an infection by SARS-CoV-2, comprising:
- 5 (i) generating dendritic cells (DC) from monocytes obtained from said individual;
- (ii) loading said DC with a SARS-CoV-2 lysate or SARS-CoV-2 antigens;
- (iii) contacting peripheral blood lymphocytes (PBL) from said individual with the DC obtained in step (ii), in appropriate conditions to activate said PBL;
- 10 (iv) following the PBL activation, measuring the expression of at least one cytokine secreted by Th1 cells, selected from the group consisting of IL-2, IFN γ and TNF α , and measuring the expression of at least one cytokine secreted by Th2 cells, selected from the group consisting of IL-5, IL-4, IL-9, IL-10 and IL-13; and
- 15 (v) from the results of step (iv), assessing the Th1/Th2 polarization of SARS-CoV-2-specific memory T cell response in said individual,
- wherein a Th1 polarization indicates that the individual is likely to resist to an infection by SARS-CoV-2, and a Th2 polarization indicates that the individual is susceptible to an infection by SARS-CoV-2.
- 20
2. The method of claim 1, wherein in step (iv), the expressions of IL-2 and IL-5 are measured, and in step (v), the ratio IL2/IL-5 is calculated, wherein IL2/IL5 > 1 indicates that the individual is likely to resist to an infection by SARS-CoV-2, and IL2/IL5 $\leq$ 1 indicates that the individual is susceptible to an infection by SARS-CoV-2.
- 25
3. A method for *in vitro* determining whether an individual is likely to resist to an infection by SARS-CoV-2, comprising
- (i) incubating T lymphocytes from said individual with a mix of antigenic peptides from SARS-CoV-2, under conditions appropriate to stimulate Th1 and/or Th2 lymphocytes specific for said peptides; and
- 30 (ii) assessing the presence of Th1 and/or Th2 lymphocytes;
- wherein the presence of Th1 lymphocytes specific for said peptides indicates that the individual is likely to resist to an infection by SARS-CoV-2, and/or the absence of Th1 lymphocytes and/or the presence of Th2 lymphocytes specific for said peptides indicates that the individual is susceptible to an infection by SARS-CoV-2.
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4. The method of claim 3, wherein the mix of antigenic peptides comprises:
- at least five peptides of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from a sequence consisting of aminoacids 331 to 555 of a SARS-CoV-2 spike protein; and
 - 5 - at least one, preferably at least two or at least three peptides of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from a SARS-CoV-2 nucleocapsid protein.
5. The method of claim 3 or claim 4, wherein the mix of antigenic peptides comprises:
- 10 - at least five peptides of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from a sequence consisting of aminoacids 361 to 555 of a SARS-CoV-2 spike protein, wherein at least one or two of said peptides are preferably from a sequence consisting of aminoacids 361 to 495 of a SARS-CoV-2 spike protein and at least one or two of said peptides are preferably from a
 - 15 sequence consisting of aminoacids 466 to 555 of a SARS-CoV-2 spike protein; and
 - 20 - at least two, preferably at least 3 peptides of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from a sequence consisting of aminoacids 1 to 135 of a SARS-CoV-2 spike protein.
6. The method of any of claims 3 to 5, wherein the mix of antigenic peptides further comprises:
- 25 - at least one, preferably at least two or at least three peptides of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from a sequence consisting of aminoacids 1 to 270 of a SARS-CoV-2 nucleocapsid protein; and/or
 - 30 - at least one, preferably at least two or at least three peptide of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from a sequence consisting of aminoacids 331 to 419 of a SARS-CoV-2 nucleocapsid protein; and/or
 - 35 - one peptide of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from a SARS-CoV-2 ORF3a_AB protein, preferably consisting of or encompassing a sequence consisting of aminoacids 244 to 258 of said SARS-CoV-2 ORF3a_AB protein; and/or
 - at least two peptides of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from a sequence consisting of aminoacids 856 to 1050 of a SARS-CoV-2 spike protein.

7. The method of any of claims 3 to 6, wherein the mix of antigenic peptides further comprises:
- at least one peptide of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from a sequence consisting of aminoacids 1 to 165 of a SARS-CoV-2 spike protein; and/or
 - at least one peptide of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from a SARS-CoV-2 ORF10 protein; preferably from a sequence consisting of aminoacids 1 to 22 of a SARS-CoV-2 ORF10 protein and/or
 - at least one peptide of 9 to 50 aminoacids, preferably 12 to 25 aminoacids, from a SARS-CoV-2 ORF8 protein, preferably from a sequence consisting of aminoacids 1 to 36 or 99 to 121 of a SARS-CoV-2 ORF8 protein.
8. The method of any of claims 3 to 7, wherein in step (i), T lymphocytes are incubated with the mix of antigenic peptides from SARS-CoV-2 in the presence of IL-2 and IL-15; and in step (ii), the presence of Th1 lymphocytes is assessed by measuring the production of IFN γ and/or the presence of Th2 lymphocytes is assessed by measuring the production of at least one cytokine selected from IL-5, IL-4, IL-6, IL-9 IL-10 and IL-13.
9. The method of any of claims 3 to 7, wherein in step (i), T lymphocytes are incubated with the mix of antigenic peptides from SARS-CoV-2 in the presence of low doses of IL-2 or IL-15, or PMA/ionomycine, or low dose of anti CD3/anti CD28 antibodies to sensitize the TCR, in addition to IL-4 and/or anti-IL12 antibodies; and in step (ii), the presence of Th2 lymphocytes is assessed by measuring the production of at least one cytokine selected from IL-5, IL-9, IL-10 and IL-13.
10. The method of any of claims 3 to 9, wherein the method is performed in at least one recipient that contains a mix of peptides which are common to all known strains of SARS-CoV-2 or induce cross-reactive immunity.
11. The method of any of claims 3 to 10, wherein the mix of peptides is dispatched in several recipients for performing the method, wherein at least one recipient contains a mix of peptides which are common to all known strains of SARS-CoV-2 or induce cross-reactive immunity, and at least another recipient comprises a mix of peptides which are specific for one or more SARS-CoV-2 variant(s).

12. The method of claim 10 or claim 11, wherein detection of Th1 lymphocytes in said at least one recipient containing a mix of peptides which are common to all known strains of SARS-CoV-2 indicates that the individual is likely to resist to an infection by any SARS-CoV-2 strain.
13. The method of any of claims 3 to 12, for assessing whether an individual is likely to resist to an infection by a variant strain of SARS-CoV-2, wherein the method is performed with a mix of peptides comprising only peptides present in the proteins of said variant strain.
14. A method for monitoring the efficacy of a vaccination against SARS-CoV-2 in an individual, comprising performing the method of any of claims 1 to 13 with a biological sample from said individual.
15. Use of the method according to any one of claims 1 to 14, to monitor the efficacy of a vaccination against SARS-CoV-2 in an individual.
16. An immunogenic composition comprising, in one or several polypeptides, the epitopes present in a sequence corresponding to amino acids 331 to 525 of a SARS-CoV-2 spike protein, as well as the epitopes present in a sequence corresponding to amino acids 1 to 165 of a SARS-CoV-2 spike protein.
17. The immunogenic composition of claim 16, comprising a first polypeptide sequence comprising amino acids 331 to 525 of a SARS-CoV-2 spike protein, and a second polypeptide sequence comprising amino acids 1 to 165 of a SARS-CoV-2 spike protein, wherein said first and second polypeptide sequences are in the same polypeptide molecule or in separate polypeptides.
18. The immunogenic composition of claim 17, wherein said first polypeptide sequence consists of amino acids 331 to 525 of a SARS-CoV-2 spike protein, and/or the second polypeptide sequence consists of amino acids 1 to 165 of a SARS-CoV-2 spike protein.
19. The immunogenic composition of claim 16 or claim 17, wherein the first polypeptide sequence consists of amino acids 331 to 600 of a SARS-CoV-2 spike protein or a fragment thereof, and/or the second polypeptide sequence consists of amino acids 1 to 270 of a SARS-CoV-2 spike protein or a fragment thereof.

20. The immunogenic composition of any of claims 17 to 19, further comprising a 3rd polypeptide sequence comprising amino acids 1 to 270 of a SARS-CoV-2 nucleocapsid protein, and/or a 4th polypeptide sequence comprising amino acids 244 to 258 of a SARS-CoV-2 ORF3a_AB protein, and/or a 5th polypeptide sequence comprising amino acids 29 to 92 of a SARS-CoV-2 ORF8 protein, and/or a 6th polypeptide sequence comprising amino acids 1 to 36 of a SARS-CoV-2 ORF8 protein, and/or a 7th polypeptide sequence comprising amino acids 22 to 38 of a SARS-CoV-2 ORF10 protein, wherein said 3rd, 4th, 5th, 6th and/or 7th polypeptide sequences are in the same polypeptide molecule as the first and/or second polypeptide sequences or are in one or several separate polypeptide(s).
21. The immunogenic composition of any of claims 16 to 20, which does not comprise the peptide LVRDLPQGFSALE (SEQ ID No: 377).
22. The immunogenic composition of any of claims 16 to 21, which does not comprise the peptide DVRVVLDFI (SEQ ID No: 178).
23. The immunogenic composition of any of claims 16 to 22, which does not comprise the peptide LLNKHIDAY (SEQ ID No:275).
24. The immunogenic composition of any of claims 16 to 23, which does not comprise the peptide IELCVDEAG (SEQ ID No:305).
25. The immunogenic composition of any of claims 16 to 24, which does not comprise the peptide MKFLVFLGIITTV (SEQ ID No: 378).
26. A nucleic acid molecule encoding the polypeptides defined in any of claims 16 to 25.
27. The nucleic acid molecule, which is a RNA molecule.
28. An immunogenic composition comprising the nucleic acid molecule of claim 26 or claim 27.
29. The immunogenic composition of claim 28, comprising a viral vector.

30. A vaccine, comprising the immunogenic composition of any of claims 16 to 26 and 28 to 29, as well as a pharmaceutically acceptable excipient and/or adjuvant.
- 5 31. The vaccine of claim 30, comprising at least one adjuvant selected from the group consisting of TLR4 agonists, TLR3 ligands/ agonists, TLR7-8 agonists and TLR9 agonists.
- 10 32. The vaccine of claim 30 or 31, comprising at least one adjuvant selected from the group consisting of lipopolysaccharides, MPL: 3-O-desacyl-4'-monophosphoryl lipid A derived from *Salmonella minnesota* LPS, poly A :U, poly I :C, IMIQUIMOD, CpG DNA and CpG ODNs.
- 15 33. An immunogenic composition comprising a polypeptide comprising the sequence LDSKVGGNY (SEQ ID No: 262), or a nucleic acid encoding the same, for use in the treatment of cancer.
- 20 34. The immunogenic composition of claim 33, for use in the treatment of a cancer overexpressing Tensin-1.
- 35 35. The immunogenic composition of claim 34, for the use of claim 33 or 34, wherein said cancer is a pancreas adenocarcinoma or a colon adenocarcinoma.
- 25 36. The immunogenic composition of claim 33, for the use of claims 33 to 35, wherein said polypeptide comprises the sequence NSNNLDSKVGGNY (SEQ ID No: 379).
- 30 37. The method of any of claims 3 to 13, wherein the Th1 response is assessed using a first mix of peptides comprising at least 3, 4, 5, 6 or more peptides relevant for assessing Th1 response against SARS-CoV-2 and the Th2 response is assessed using a second mix of peptides comprising at least 3, 4, 5, 6 or more peptides relevant for assessing Th2 response against SARS-CoV-2.
- 35 38. The method of claim 37, wherein said first and second mixes of peptides are present in separate recipients/tubes.

39. The method of claim 37 or claim 38, wherein in step (ii) of the method, the presence of Th1 lymphocytes is assessed by measuring the production of IFN γ in the recipient comprising the first mix of peptides and the presence of Th2 lymphocytes is assessed by measuring the production of at least one cytokine selected from IL-5, IL-4, IL-9, IL-10 and IL-13 (preferable IL-5) in the recipient comprising the second mix of peptides.
40. The method of any of claims 3 to 13 and 37 to 39, wherein the absence of Th1 after incubation of the T lymphocytes with a mix of peptides covering a sequence comprising amino acids 331 to 525 and/or amino acids 329 to 521 and/or amino acids 391 to 555 of a SARS-CoV-2 spike protein indicates that the individual is susceptible to an infection by SARS-CoV-2 and its variants.
41. The method of any of claims 3 to 13 and 37 to 40, wherein the presence of a Th2 response combined to the absence or weak presence of Th1 after incubation of the T lymphocytes with a mix of peptides covering a sequence comprising amino acids 331 to 525 and/or amino acids 329 to 521 and/or amino acids 391 to 555 of a SARS-CoV-2 spike protein indicates that the individual is susceptible to an infection by SARS-CoV-2 and its variants.
42. The method of any of claims 3 to 13 and 37 to 41, wherein the presence of a Th1 response after incubation of the T lymphocytes with a mix of peptides covering a sequence comprising amino acids 331 to 525 and/or amino acids 329 to 521 and/or amino acids 391 to 555 of a SARS-CoV-2 spike protein indicates that the individual is likely to resist to an infection by SARS-CoV-2 and its variants.
43. The method of any of claims 3 to 13 and 37 to 42, wherein the presence of a Th1 response after incubation of the T lymphocytes with a mix of peptides comprised in a sequence consisting of amino acids 1 to 135 of a SARS-CoV-2 spike protein indicates that the individual is likely to resist to an infection by SARS-CoV-2 and its variants, only if a Th1 response has also been obtained against another part of the virus, e.g. against peptides of the nucleocapsid.