PHRC-20-0375

Porteur de projet Mr Guy GOROCHOV

Profession :

doctor

Ville :

PARIS

Site hospitalier d'exercice :

HU PITIE SALPETRIERE APHP

1 Porteur de projet/Project coordinator

1.1.1 . Civilité/Civility :

M.

1.1.2 . Nom/Last Name :

GOROCHOV

1.1.3 . Prénom/First name :

Guy

1.1.4 . Ville/City :

Paris

1.1.5 . Courriel/Email :

guy.gorochov@aphp.fr

1.2.1 . Profession du porteur de projet/Profession :

Médecin

1.2.2 . Si 'Autre' préciser laquelle/If 'other', please specify which one :

1.2.3 . Domaine/Domain :

Immunologie / Allergologie

1.2.4 . Spécialité/Speciality :

Immunologie Biologique

1.3.1 . Financements antérieurs obtenus par le porteur de projet dans le cadre des appels à projet de la DGOS (PHRC national, régionaux, inter régionaux, PRT, PRT K, PRC, STIC, PREQHOS, PREPS, PHRIP, PRME) :/Previous funding obtained by the project leader for institutinal projects (national, regional or inter-regional PHRC, PRT, PRT K, PRC, STIC, PREQHOS, PREPS, PHRIP, PRME) :

Oui

1.3.2 . Si oui, préciser (année de soumission, type d'appel à projets, investigateur-coordinateur, n°, état d'avancement: en instruction, mis en œuvre, en cours, phase d'analyse, publication princeps, abandonné)/If yes, please specify (year of submission, type of call for proposals, coordinator, number, progress: in instruction, implemented, in progress, analysis phase, original publication, terminated) :

PHRC régional 2009: “Corrélation Phénotypes Cliniques / Cellules T Régulatrices au cours de la Sarcoidose”. 140 000€ pour 2 ans. Terminé et publié: Miyara et al. Immunity, 30: 899-911. 2009.

2 Structures/Organizations

2.1 . Etablissement de santé ou GCS coordonnateur gestionnaire des fonds/Affiliated institution responsible for the budget from the ministry of health :

ASSISTANCE PUBLIQUE-HOPITAUX DE PARIS / 75184 / PARIS 4E ARRONDISSEMENT / 3 AVENUE VICTORIA

2.2 . Nom du correspondant gestionnaire financier/Financial manager :

[APHP-GesFin] Yannick VACHER

2.3 . Structure responsable de la gestion de projet/Organization responsible for project management :

URC Pitié-Salpêtrière

2.4 . Structure responsable de l’assurance qualité /Organization responsible for quality inssurance :

URC Pitié-Salpêtrière

2.5 . Structure responsable de la gestion de données et des statistiques/Organization responsible for data management and statistics :

URC Pitié-Salpêtrière

2.6 . Nombre prévisionnel de centres d’inclusion (NC)/Planned number of recruiting centres (NC) :

1

3 Projet de recherche/Research project

3.01.1 . Titre du projet FR/Project title FR :

Stratification de la sévérité des patients COVID-19 hospitalisés par la quantification des cytokines sérique par SIMOA

3.01.2 . Titre du projet UK/Project title EN :

Stratification of hospitalized COVID-19 patients for severity using multiparametric single-molecule array digital ELISA quantification of serum cytokines

3.01.3 . Acronyme (sans espace)/Acronym (w/o space) :

Digital Covid

3.02.1 . Première soumission de ce projet à un appel à projet DGOS/First submission to DGOS calls for proposals :

Oui

3.02.2 . Si non, préciser (année, programme, numéro, Acronyme, Porteur)/If non, please specify (edition, program, number, Acronym, coordinator) :

3.03 . Domaine du projet de recherche/Field of study :

3.03.1 . Le projet concerne-t-il le domaine de l'oncologie ?/Does the project concern the field of oncology? :

Non

3.03.2.1 . Le projet concerne-t-il une maladie rare ?/Does the project concern a rare disease ? :

Non

3.03.2.2 . Si oui, préciser son code ORPHA/If yes, please specify the ORPHA number :

3.03.2.3 . et le nom de la maladie rare/If yes, specify the rare disease name :

3.03.3 . Discipline principale/Main :

Infectiologie / Biologie des agents infectieux / Hygiène

3.03.4 . Discipline secondaire/Secondary :

Immunologie / Allergologie

3.03.5 . Discipline libre/Other :

3.03.6 . Mots clés libres/Free keywords :

coronavirus, pronostic, stratification, biomarqueurs

3.04.1 . Priorité(s) thématique(s)/Thematic priority(ies) :

Soins primaires

3.04.2 . Plan de santé publique/Public health plan :

Projet non concerné par les plans de santé publique listés ici

3.05 . Ages concernés de la population cible/Ages of studied population :

Adulte et gériatrie

3.06 . Chirurgie/Surgery :

Non

3.07 . Rationnel (contexte et hypothèses)/Rational (context and hypothesis) :

Corona virus infections in the past have been characterized by the onset of a cytokine storm, an uncontrolled inflammatory response, aggravating viral sepsis, acute respiratory distress syndrome, respiratory failure, shock, organ failure, and death. Virus-induced inflammation associated with a cytokine storm begins at the infection site and and spreads throughout the body via the systemic circulation. The hallmark of a cytokine storm is an abnormal regulation and uncoordinated release of several pro-inflammatory cytokines at inappropriate time intervals during infection, such as interleukin (IL)-6, IL-?, Tumor necrosis factor (TNF-?) and Interferon (IFN)-? (2). It is of note that the location of the initial infection does not seem to be a decisive factor for the severity of local and systemic cytokine storms. For example, influenza viruses infect and destroy the ciliated epithelial cells of the conducting airways, whereas SARS-CoV infects type II pneumocytes in the alveolar walls, yet both lead to indistinguishable clinical syndromes of acute lung injury with respiratory failure and sepsis. In this respect, the measurement of the above-mentioned pro-inflammatory cytokines may provide a rather accurate picture reflecting the cytokine profile at the location of the initial infection the magnitude of which is associated with the severity of the clinical condition of the infected patient. We hypothesize that cytokine levels and combinations thereof determined with this new standardized assay would represent a biomarker of COVID-19-related severity. Therefore, the primary objective of this study is to characterize the relationship between a broad panel of digital ELISA-determined cytokine concentrations at hospital admission and clinically assessed severe subsequent evolution. Using our previous approach, we shall then determine among the panel of cytokines tested, which

cytokine or which combination of cytokines, is the best predictor of clinical deterioration.

3.08 . Originalité et caractère Innovant/Originality and innovative aspects :

No simple or standardized assay is available to quantify directly in serum reliably inflammatory cytokines in routine clinical practice, particularly in the context of an epidemics. Single-molecule–array (Simoa) digital enzyme-linked immunosorbent assay (ELISA) technology enables direct cytokine quantification at fg/mL concentrations. The technique requires no sample preparation and results can be obtained within hours.

3.09 . Description des bénéfices attendus pour les patients et/ou pour la santé publique/Expected benefit for patients or public health :

It is of crucial importance to screen patients for severity in order preferentially admit future severe patient in intensive care units. Based on our previous studies and those of others, direct serum-cytokine determination with a highly sensitive assay might improve prediction of clinical severity and possibly provide clues for potential treatments (anti-cytokine biotherapies). We indeed recently demonstrated the clinical superiority of the latter technology over bioassays and Quantiferon technology to quantify IFN-? and IFN-gamma, respectively. These studies highlight the potential of this technology to avoid false negatives and to stratify patients according to clinical evolution (see attached refs by Mathian et al.).

3.10 . Objet de la recherche/Focus of research :

3.10.1 . Technologie de santé/Health technology :

Autre (Autre produit de santé, autre acte, etc).

3.10.2 . Préciser lequel ou lesquels/please specify which one(s) :

Prognosis

3.10.3 . Dispositif médical : le cas échéant, date de marquage CE (JJ/MM/AAAA)/Date of CE marking :

3.10.4 . Médicament : le cas échéant, date d'AMM (JJ/MM/AAAA)/Date of market authorization :

3.10.5 . RIHN : le cas échéant, code acte et libellé/RIHN (uncovered innovative procedures list) : number and name :

3.11 . Phase ou équivalent pour les dispositifs médicaux/Phase or equivalent for medical devices :

Non Applicable

3.12 . Niveau de maturité de la technologie de santé (TRL)/Technology readiness level :

4A

3.13.1.1 . Type d'objectif principal (1)/Main objective (1) :

Description d’hypothèses

3.13.1.2 . Type d'objectif principal (2)/Main objective (2) :

Pronostic

3.13.2 . Description de l'objectif principal/Main objective description :

The primary objective of the study is to assess the diagnostic performance of a combination of cytokine levels measured in serum by multiparametric digital ELISA to efficiently stratify COVID-19 infected patients at hospital admission.

3.13.3 . Description des objectifs secondaires/Secondary objectives description :

The secondary objective of the study is to assess the diagnostic performance of isolated cytokine levels measured by digital ELISA to efficiently stratify COVID-19 infected patients at hospital admission.

3.14 . Critères d'évaluation/End points :

3.14.1 . Critère d’évaluation principal (en lien avec l’objectif principal)/Primary end point (linked to main objective) :

Prediction power for death and/or ventilation at inclusion following hospital admission

3.14.2 . Critères d’évaluation secondaires (en lien avec les objectifs secondaires)/Secondary end points (linked to secondary objectives) :

Prediction power for death and/or ventilation at inclusion following hospital admission

3.15 . Population de l'étude/Study population :

3.15.1 . Principaux critères d’inclusion/Main inclusion criteria :

Patients admitted to a referenced health-care facility with confirmed infection with SARS-CoV-2

3.15.2 . Principaux critères de non inclusion/Main exclusion criteria :

- Refusal by the patient, his or her relative or legal representative (depending on the situation) to participate in the study - Patients being kept under judicial safeguard

4 Méthodologie et inclusions/Methodology and inclusions

4.1 . Méthodologiste/Methodologist :

4.1.1 . Civilité/Civility :

Mme

4.1.2 . Nom/Last name :

TUBACH

4.1.3 . Prénom/First name :

Florence

4.1.4 . Ville/City :

Paris

4.1.5 . Tél./Phone number :

01 42 16 05 88

4.1.6 . Courriel/Email :

florence.tubach@aphp.fr

4.2 . Méthodologie du projet/Methodology :

4.2.1 . Plan expérimental/Experimental design :

Etude cas-témoins

4.2.2 . Si 'Autre plan expérimental' préciser quel type/If 'other', please specify :

4.2.3 . Description du plan expérimental/Experimental design description :

Our study is a nested case-control study that will rely on available Peripheral blood mononuclear sample and serum samples from the longitudinal French COVID-19 cohort organized by the REACTing consortium (Coordinator PR. Yazdan YAZDANPANAH). Study design, severe patients and control stable patients : Serum samples will be obtained from 120 patients divided in two groups: i) Patients admitted for surveillance remaining clinically stable at day 15 after admission, and i) patients admitted for surveillance with subsequent clinical deterioration requiring ventilation and/or leading to death. The participating centers are French Reference Health Institutions (ESRs), health facilities that are set-up to receive patients infected with SARS-CoV-2. Each SRS has an infectious disease unit with at least one negative pressure isolation room, as well as an isolation room. Infectious disease departments as well as resuscitation units of French ESRs will be the recruiting centers for research. Digital ELISA Cytokines and chemokine concentrations, expressed in fg/mL,

were will be determined with Simoa, digital ELISA technology (Quanterix SimoaTM Lexington, MA, USA), using the HD-1 Analyzer (QuanterixTM. A cytokine profile will be determined by through multiparametric analysis of GM-CSF, IFN-?, IFN-?, IL-1?, IL-2, IL-6, IL-8, IL-10, IL-15, IL-17A, IP10, MCP1, TNF-?, IL-22 and IL-28A. A total volume of 1mL of serum per patients will be requested from the REACTing and APHP biobanks. Statistical analyses Differences between patient groups will tested. Principal Componant Analysis will be used to determine the best cytokine combination required to stratify patients. The diagnostic performances of such a short list panel of cytokines measured by digital ELISA to predict clinical severity will then be investigated by analyzing receiver operating characteristics (ROC) curves, with death and/or ventilation as the gold standard for those analyses.

4.2.4 . Si groupe comparateur: description du groupe expérimental/Experimental group description :

Patients admitted for surveillance with subsequent clinical deterioration requiring ventilation and/or leading to death.

4.2.5 . Si groupe comparateur: description du groupe contrôle/Control group description :

Patients admitted for surveillance remaining clinically stable at day 15 after admission

4.3 . Inclusions/Enrollment :

4.3.1 . Le projet comporte-t-il des inclusions de sujets (ou autres participations) ?/Does the project inclued enrollment or participation ? :

Oui

4.3.2.1 . Durée de la participation de chaque sujet ou participant (durée)/Duration of participation (duration) :

30

4.3.2.2 . Durée de la participation de chaque sujet ou participant (unité de temps)/Duration of participation (unit of duration) :

Jour(s)

4.3.3 . Durée prévisionnelle de recrutement (DUR) (en mois)/Anticipated duration of recruitment (DUR) (in month) :

2

4.3.4 . Nombre de sujets ou observations prévu(e)s à recruter (NP)/Total number of scheduled participants to be recruited or observations to be collected (NP) :

120

4.3.5 . Justification de la taille de l'échantillon/Sample size justification :

60 cases and 60 controls will be included in the study. These numbers were chosen to allow sensitivity and specificity to be estimated in a sufficiently informative manner, that is, with sufficient precision to determine the future relevance of their use in clinical practice. Thus, under the assumption of a real sensitivity/specificity of 80%, the confidence interval will provide an accuracy of 10-12% (48/60, 80%, IC95 = [67.7%; 89.2%]), and an accuracy of the order of 6%-10.5% (54/60, 90%, IC95 = [79.5%; 96.2%]) for a real sensitivity/specificity of 90%.

4.3.6 . Nombre de sujets ou observations prévu(e)s à recruter/ mois / centre ((NP/DUR)/NC) : Valeur calculée (cf. document liste des centres coinvestigateurs)/Number of participants to be recruited or observations to be collected per month per centre ((NP/DUR)/NC) (cf. sub-investigators centers file) :

10

4.3.7 . (NP/DUR)/NC) : Justification si le chiffre est supérieur à 2/If more than 2, please justified :

Rapid evolution of the epidemics, centers will receive more than ten patients per month

5 Médico-économie/Health-economics

5.1 . Economiste de la santé/Health economist :

5.1.1 . Un économiste de la santé participe-t-il au projet?/Is a health economist involved in the project? :

Non

5.1.2 . Civilité/Civility :

5.1.3 . Nom/Last name :

5.1.4 . Prénom/First name :

5.1.5 . Ville/City :

5.1.6 . Tél./Phone number :

5.1.7 . Courriel/Email :

5.2 . Analyse médico-économique/Health economic analyse :

5.2.2 . Analyse médico-économique/Health economic analyse :

5.2.3 . Description de l'analyse médico-économique/Health economic analyse description :

6 Financement/Funding

6.1 . Niveau approximatif de financement DGOS demandé, en euros/Approximate level of required DGOS (MoH) funding, in euros :

-135500

7 Références bibliographiques/Bibliographic references

7.1 . Référence 1 (PMID, année, revue, titre, auteurs)/Reference 1 (PMID, year, review, title, authors) :

PMID: 21688259, 2011, Eur. J. Immunol. 41:2596-605, Multiparameter grouping delineates heterogeneous populations of human IL-17 and/or IL-22 T-cell producers that share antigen specificities with other T-cell subsets, Larsen M, Arnaud L, Hié M, Parizot C, Dorgham K, Shoukry M, Kemula M, Barete S, Derai D, Sauce D, Amoura Z, Pène J, Yssel H, Gorochov G.

7.2 . Référence 2 (PMID, année, revue, titre, auteurs)/Reference 2 (PMID, year, review, title, authors) :

2012, Ann Rheum Dis 71:1227-34. Activated and resting regulatory T cell exhaustion concurs with high levels of interleukin-22 expression in systemic sclerosis lesions. Mathian A, Parizot C, Dorgham K, Trad S, Arnaud L, Larsen M, Miyara M, Hié M, Piette JC, Frances C, Yssel H, Amoura Z, Gorochov G.

7.3 . Référence 3 (PMID, année, revue, titre, auteurs)/Reference 3 (PMID, year, review, title, authors) :

PMID: 29720448, 2018, Sci Transl Med 2018 10. pii: eaan1217. Microbial ecology perturbation in human IgA deficiency. Fadlallah J, El Kafsi H, Sterlin D, Juste C, Parizot C, Dorgham K, Autaa G, Gouas D, Almeida M, Lepage P, Pons N, Le Chatelier E, Levenez F, Kennedy S, Galleron N, de Barros JP, Malphettes M, Galicier L, Boutboul D, Mathian A, Miyara M, Oksenhendler E, Amoura Z, Doré J, Fieschi C, Ehrlich SD, Larsen M, Gorochov G.

7.4 . Référence 4 (PMID, année, revue, titre, auteurs)/Reference 4 (PMID, year, review, title, authors) :

PMID: 30507062, 2019 Arthritis Rheumatol. 2019 71:756-765. Monitoring Disease Activity in Systemic Lupus Erythematosus With Single-Molecule Array Digital Enzyme-Linked Immunosorbent Assay Quantification of Serum Interferon-?. Mathian A, Mouries-Martin S, Dorgham K, Devilliers H, Barnabei L, Ben Salah E, Cohen-Aubart F, Garrido Castillo L, Haroche J, Hie M, Pineton de Chambrun M, Miyara M, Sterlin D, Pha M, Lê Thi Huong D, Rieux-Laucat F, Rozenberg F, Gorochov G, Amoura Z.

7.5 . Référence 5 (PMID, année, revue, titre, auteurs)/Reference 5 (PMID, year, review, title, authors) :

PMID: 31570366, 2019, Ann Rheum Dis 78:1669-1676. Ultrasensitive serum interferon-? quantification during SLE remission identifies patients at risk for relapse. Mathian A, Mouries-Martin S, Dorgham K, Devilliers H, Yssel H, Garrido Castillo L, Cohen-Aubart F, Haroche J, Hié M, Pineton de Chambrun M, Miyara M, Pha M, Rozenberg F, Gorochov G, Amoura Z.

8 Informations pour les évaluateurs/Information related to the assessment of the project

8.1 . Eléments liés à la mise en œuvre/Elements ensuring feasibility :

8.1.1 . Participation d'un réseau de recherche/Research network participation :

We obtained confirmation from the REACTing consortium (Coordinator Pr Yazdan YAZDANPANAH) that serum samples will be made available for the study.

8.1.2 . Participation de partenaires industriels/Industry participation :

No

8.1.3 . Autres éléments garantissant la faisabilité du projet/Other aspects ensuring feasibility :

The REACTing consortium has previously obtained emergency ethical approval for virological and immunological studies on COVID-19-infected patients. Our team played a pioneering role in the field of clinical digital ELISA translational research (see above listed refs by Mathian A. et al.), and is also well trained in general for translational research and complex data analysis and modelling (see refs to Larsen et al and Fadlallah et al.).

8.2 . Expertises antérieures et commentaires/Previous expert comments :

8.2.1 . Expertises et commentaires du jury antérieurs /Previous expert and jury comments :

8.2.2 . Réponse aux expertises et commentaires du jury antérieurs /Previous expert and jury comments replies :

8.3.1 . Autre(s) commentaire(s)/Other comment(s) :

8.4 . Caractéristique du champ d'expertise du rapporteur/Field of expertise of the rapporteur :

8.4.1 . Domaine du rapporteur suggéré/Suggested rapporteur's domaine :

Immunologie / Allergologie

8.4.2 . Mot-clé libre lié au domaine des évaluateurs/Domain related keyword :

cytokines, anti-viral immunity

8.4.3 . Ages concernés/Ages of studied population :

Adulte et gériatrie

8.4.4 . Chirurgie/Surgery :

Non

9 Observations sur le formulaire/Template improvements

9.0 . Commentaires utilisateur de la plateforme Innovarc-3 (préciser votre rôle)/Innovarc-3 user feedback (specify your role: expert, investigator,manager, delegate or rapporteur.) :

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