CONSORTIUM AGREEMENT

Project title: *Understanding the two faces of the COVID-19 immune response to predict the clinical course and define strategies for early and late phase intervention.*

ZonMw file N°: **10430012010024.**

THIS CONSORTIUM AGREEMENT (the "**Agreement**") is based on the General Terms and Conditions Governing Grants of ZonMw, version 1st July 2013 and the decision of ZonMw to award the Grant for this Project as communicated to the Main Applicant in a Grant Letter dated 14 July 2020 with ZonMw file number 10430012010024 and shall come into effect on the date of last signature (the "**Effective Date**")

BY AND BETWEEN:

1. **Universitair Medisch Centrum Utrecht**, a public legal entity (*publiekrechtelijke rechtspersoon*) existing under Dutch law, Division Imaging & Cancer Center**,** having its principle place of business at Heidelberglaan 100, 3584 CX, Utrecht, the Netherlands, in this matter legally represented by Prof (10)(2e), and (10)(2e) hereinafter referred to as "**UMC Utrecht"**;

2. **Stichting VUmc**, a private legal entity, established under the laws of The Netherlands, having its registered office at De Boelelaan 1117, 1081 HV, Amsterdam, The Netherlands, in this matter duly represented by (10)(2e) hereinafter referred to as "**VUmc**";

3. **The State of the Netherlands,** represented by its Minister of Health, Welfare and Sport, on behalf of the Minister represented by mrs. dr. (10)(2e) Immunologie van Infectieziekten en Vaccins) of the National Institute for Public Health and the Environment RIJKSINSTITUUT VOOR VOLKSGEZONDHEID EN MILIEU (RIVM), having its home office at Antonie van Leeuwenhoeklaan 9, 3721 MA Bilthoven, the Netherlands, and registered with the Dutch Chamber of Commerce under number 30276683, hereinafter referred to as "**RIVM**";

hereinafter referred to, individually or jointly, as "Party" or "Parties".

WHEREAS

- The Parties, having considerable experience in the field of Immunology, have submitted a Full Project Proposal for the Project entitled *Understanding the two faces of the COVID-19 immune response to predict the clinical course and define strategies for early and late phase intervention* (hereinafter referred to as the "**Project**") to the funder ZonMw as part of the ZonMw call "BOTTOM-UP"
  This Agreement is based upon the decision of ZonMw to award the Grant for this Project as communicated to the Main Applicant in a Grant Letter with ZonMw file number 10430012010024 dated 14 July 2020
- The Parties intend to execute the Project as detailed in the Full Project Proposal attached as Annex 1 and in accordance with the with the General Terms and Conditions Governing the Grants of ZonMw, version 1st July 2013 and the specific conditions of the ZonMw Decision to award the Grant;
- The Parties wish to specify their respective rights and obligations in relation to the Project and wish to lay down general rules concerning the organization of the work, the management of the Project, and the use and dissemination of the Results;

PARTIES HEREBY AGREE AS FOLLOWS

1. Definitions

The definitions in the ZonMw General Terms and Conditions Governing Grants of ZonMw, applicable as from 1st July 2013 and attached to this agreement in Annex 2 (hereinafter "**General Terms and Conditions Governing Grants of ZonMw"**), apply to this Agreement unless stated otherwise.
The terms hereafter shall have the following meaning:

a. **Affiliates:** any company or other legal entity, of which a Party now or hereafter owns or controls directly or indirectly more than 50 % of the voting shares or by which the Party now or hereafter is owned or controlled directly or indirectly by more than 50 % of the voting shares, or any company or other legal entity which is under common control with a Party, but any such company shall be deemed to be an affiliated company only so long as such ownership or control exists;

b. **Background IP:** all data, know-how, knowledge, techniques, methods, models, discoveries, Materials, designs, software, trade secrets and other information, which is held by a Party prior to its accession to this Agreement or generated by that Party independently of the Project and made available by that Party for use in the Project in accordance with the terms and conditions of this Agreement and listed in Annex 3 of this Agreement which may be amended from time to time;

c. **Budget**: the budget in the Full Project Proposal providing an estimate of the total cost to carry out the Project, including an overview of the Contributions of each Party, attached as Annex 1;

d. **Consortium:** the group of organizations as described in the Full Project Proposal that participate in the Project;

e. **Contribution**: the total In Cash Contribution and the monetary equivalent of the total In-Kind Contribution of a Party according to the Project Budget of the Full Project Proposal;

f. **Coordinator**: means the Party identified in this Agreement who, in addition to its obligations as a Party, is obliged to carry out the specific coordination tasks provided for in this Agreement on behalf of the Parties to the Agreement, also referred to as "**Main Applicant**" or "**Grant Recipient**";

g. **Decision:** the formal written decision rendered by ZonMw in response to the application for the Grant indicating that the application has been successful;

h. **Foreground IP:** means the intellectual property rights and knowhow arising directly from the performance of the Project, including patents, copyrights or other intellectual property rights pertaining to such results following applications for, or the issue of patents, designs, supplementary protection certificates or similar forms of protection, excluding Background IP;

i. **Full Project Proposal** ("**Uitgewerkte Aanvraag**") the description of the research activities, including the milestones, the deliverables and the budget ("**Project Budget**") as attached to this Agreement as Annex 1;

j. **Funding Agency**: Netherlands Organisation for Health Research and Development, also referred to as '**ZonMw**';

k. **Grant Letter**: the ZonMw letter that contains the Decision with respect to the award of the Grant for this Project;

l. **In Cash Contribution**: the in cash contribution of a Party to this Project according to the Project Budget;

m. **In-Kind Contribution**: the in-kind contribution of a Party to this Project according to the Project Budget;

n. **Materials**: means the samples, such as but not limited to antibodies, DNA, micro-organisms or samples, as specified in Annex 3 as well as the non-modified derivatives obtained directly or indirectly from the original material such as subunit, progeny or descendant, fraction, and any composition containing the same;

o. **Project:** the project described in the Full Project Proposal;

p. **ZonMw Funding Conditions**: the General Terms and Conditions Governing Grants of ZonMw, applicable as from 1st July 2013 and the ZonMw Decision to award the Grant for this Project;

2. Purpose of the Agreement

The Parties agree to set up a Consortium for the purpose of as further detailed in the Full Project Proposal. The purpose of this Agreement is to specify the relationship among the Parties in relation to the Project in particular concerning the organisation of the research activities as outlined in the Full Project Proposal, the management of the Project and the rights and obligations of the Parties in relation to the Foreground IP.

Nothing in this Agreement shall be deemed to create a partnership or agency or any formal business organization or legal entity among the Parties. This Consortium does not have the purpose to exploit the Foreground IP commercially as a differentiated legal entity.

3. Cooperation within the Project

Each Party who participates in this Project remains solely responsible for carrying out its relevant part of the Project. Each Party will take part in the efficient implementation of the Project, and will cooperate, perform and fulfil, promptly and on time, all of its obligations in this Project under the ZonMw Funding Conditions and this Agreement as may be reasonably required from it and in a manner of good faith as prescribed by Dutch law.

The allocation of work to be performed within the Project is described in the Full Project Proposal. The Parties commit themselves to perform the work in accordance with the Full Project Proposal, including its timelines, and to notify the Project Leader in case of any problems that might occur and may have an impact on the timely execution of the Project. Each Party will, at the Project Leader's first request, promptly provide all information needed by the Project Leader/Coordinator to fulfil its obligations towards ZonMw.

Each Party will cooperate in good faith with the Project Leader in his efforts to fulfil his obligations resulting from this agreement and the ZonMw Funding Conditions in a timely and proper manner.

Each Party will take reasonable measures to ensure the accuracy of any information (including Background IP and Foreground IP) or material it supplies to the other Parties.

4. Project governance

4.1 Structure
The organizational structure of the Consortium shall comprise the following consortium bodies:

a. The project leader ("Project Leader");
b. The general assembly ("General Assembly").

4.2 The Coordinator and Project Leader
The Main Applicant of the Project and hence the Coordinator is UMC Utrecht. The Parties appoint dr. S. Nierkens to represent the Coordinator as the Project Leader for the term of this Agreement.

The Project Leader will act as an intermediary between the Parties and ZonMw. The Project Leader is furthermore tasked with:

a. Keeping accounts of the funds distributed to the Project by ZonMw and any other funding organisation and the distribution of these funds to the Parties;
b. Keeping accounts of the In-Kind Contributions and the In Cash Contributions of the Parties for the purpose of the Project;
c. Notifying the Parties of any official notifications from ZonMw in relation to the Project;

The Coordinator shall not be entitled to act or to make legally binding declarations on behalf of the other Parties.

4.3 The General Assembly
The General Assembly will be chaired by the Coordinator, unless decided otherwise by the General Assembly.

The General Assembly will consist of one representative of each Party ("Member").

The General Assembly is responsible for strategic and scientific management of the Project and will review, discuss and decide on all relevant decisions regarding the Project, including:

a. Changes to the Full Project Proposal;
b. Changes to the Budget;
c. Changes to the Agreement;
d. Additions to the list of Background IP as set out in Annex 3;
e. Withdrawal of a Party;
f. Termination of the participation of a defaulting Party
g. Termination of the Project and the Agreement.

Any changes to the Full Project Proposal, the Budget or this Agreement as discussed in the General Assembly might require prior written consent of the Funding Agency.

4.4 Decision making and conflict resolution

Each Member has one vote. A Party may not vote with regard to the decision relating to its identification to be in breach of its obligations nor to its identification as a defaulting Party.

Decisions shall be taken by a majority of the votes validly cast at a meeting.

The General Assembly will identify a defaulting Party. It will formally notify the defaulting Party (served personally or sent by mail with recorded delivery or telefax with receipt acknowledgement) of its failure to perform its obligations under the Agreement and give it 30 days to cure the breach. If the breach is not cured within that term or if the breach cannot be cured or the defaulting Party notifies the General Assembly that it cannot or will not cure the breach, the General Assembly will vote on termination of the defaulting Party and decide within the General Assembly on the re-allocation of tasks and funds to a new party.

A Party that is declared a defaulting Party shall bear all actual and reasonable costs incurred by the other Parties under the Project as a result of the defaulting Party's breach of obligations.
The General Assembly is further entitled to recover any payments already paid to the defaulting Party until the effective date of the declaration of the Party as a defaulting Party.

A non-defaulting Party may request the General Assembly to terminate its participation in the Project and to this Agreement. A Party leaving the Consortium will, upon request of the Project Leader, promptly transfer any unspent and uncommitted part of the funding to the Party that is ultimately responsible for the application and use of the funding.

Termination or withdrawal by a Party will not affect any rights or obligations of that Party incurred prior to the date of termination or withdrawal. This includes the obligation of that Party to make its Background IP and, if applicable, its Foreground IP, available to the Parties for the performance of the Project.

4.5 Meetings

The General Assembly will meet 6-monthy either in a telephone conference or in person, at dates determined by the Project Leader after consultation with other Members, or as often as necessary if requirements from this Agreement would necessitate more frequent meetings. Members will be noticed at least 30 days before the date about the meeting and its agenda.

Any Member shall use its best efforts to be present or represented at any meeting and may appoint a substitute or a proxy to attend and vote at any meeting and shall participate in a cooperative manner in the meetings.

The Project Leader shall produce written minutes of each meeting which shall be the formal record of all decisions taken. He shall send draft minutes to all Members within 14 (fourteen) calendar days of the meeting.

The minutes shall be considered as accepted if, within 14 (fourteen) calendar days from sending, no Member has objected in writing to the Project Leader with respect to the accuracy of the draft of the minutes.

All relevant email, letter and fax communication between the Parties will also be sent to the Project Leader.

The minutes of additional meetings between some or all of the Parties will be sent to the Project Leader.

4.6 The Principal Investigator

1. Each Party appoints its lead scientist on the Project as principal investigator ("**Principal Investigator**").
2. The Principal Investigator of each Party is responsible for supervision and direction of the Project at the Party's organisation.
3. The Principal Investigator is responsible for:
   a. Communication with the other Principal Investigators and the Project Leader;
   b. Reporting the progress of the research under the Project to the Project Leader on a six-monthly basis and at the General Assembly;
   c. The timely and proper preparing of the ZonMw progress reports and final report;
   d. Hosting the ZonMw site visit.

4. Involvement of third parties

Parties may not sub-contract any part of their research activities under the Full Project Proposal except with the prior written approval of the other Parties.

The Party engaging a third party in the execution of its share of the research activities under the Full Project Proposal is responsible for the execution of those activities by the third party and for the third party's compliance with the provisions of this Agreement and the obligations of the parties resulting from the ZonMw Funding Conditions.

The Party engaging a third party in the execution of its share of the research activities under the Full Project Proposal will ensure that the third party will assign any rights to the Results it has generated.

6. Duration and termination

This Agreement will go into effect on the Effective Date and will continue in effect up and until the termination or completion of the Project but no later than 24 months after the Effective Date.

Each Party may terminate this Agreement in relation to another Party prior to the termination date in the event of that other Party's bankruptcy (*faillissement*) or a moratorium of payments (*surseance van betaling*) or entering into a debt rescheduling arrangement (*schuldsaneringsregeling*) immediately upon the occurrence of the relevant event.

In case of breach of a Party of its substantial obligations as provided in the Agreement, the termination of the participation of the such defaulting Party will take place in accordance with the provisions of Clause 4.4 (*Decision making and conflict resolution*).

This Agreement shall automatically terminate without any further demand and without liability of any Party to the others upon the first to occur of the following events:

- in case no Decision is awarded by the Funding Agency;
- termination of the entire Decision by the Funding Agency.

Neither Party shall by reason of withdrawal or termination be relieved from:

- its responsibilities under this Agreement or the Decision in respect of that part of that Party's work package which has been carried out (or which should have been carried out) up to the date of withdrawal or termination; or
- any of its obligations or liabilities arising out of such withdrawal or termination.

The provisions of the clauses of this Agreement relating to liability, confidentiality (with five (5) years), intellectual property rights and publications shall survive the term or termination of this Agreement for any reason whatsoever to the extent needed to enable the Parties to pursue the remedies and benefits provided for in those Clauses. For the avoidance of doubt, termination or withdrawal shall not affect any rights or obligations incurred prior to the date of the termination.

7. Force Majeure

If the performance by either Party of any of its obligations under this Agreement (except a payment obligation) is delayed or prevented by circumstances not reasonably foreseeable at the time of the signing of this agreement and beyond its reasonable control (*Force Majeure*), that Party will not be in breach of this Agreement because of that delay in performance.

The Party concerned will give written notice to the other Parties without undue delay, describing the Force Majeure event(s), its anticipated duration and use of reasonable efforts to resume performance as soon as possible.

If the delay in performance is more than 3 months, the other Parties may terminate this Agreement with immediate effect by giving written Notice to the other Party. Where applicable, the transfer of tasks of such Party – if any – to a new Party shall be considered and decided upon by the General Assembly. Such decision should be subject to the agreement of the Funding Agency, which shall be duly informed, and object of the signature of a specific addendum to all relevant agreements.

8. Financial provisions

The Party responsible for the application and use of the Grant will make the funds available for the Project to the Parties upon receipt from ZonMw, according to the Budget.

Each Party is responsible for justifying its costs in accordance with generally accepted accounting and management principles and practices.

Each Party will be refunded based on actual and duly justified costs.

9. Liabilities of the parties

9.1 *No warranties*
Any information or advice, including Confidential Information, Materials, Data, Background IP and Foreground IP, made available for the Project under this Agreement, is made available "as is", and each Party understands and agrees that such is experimental in nature and is made available without any representation or warranty, express or implied, including any implied warranty as to the merchantability, satisfactory quality or fitness for any particular purpose, or, except as expressly provided for herein, any warranty that the use of the same will not infringe or violate any patent or other proprietary rights of any party.

9.2 Limitation and exclusion of contractual liability
No Party will be responsible to any other Party for any indirect or consequential loss or similar damage such as, but not limited to, loss of profit, loss of revenue or loss of contracts, provided such damage was not caused by a willful act.

The total aggregate liability of each Party to all other Parties for all losses, damages, or injuries of any kind arising out of or relating to this Agreement or its subject matter is limited to EUR 500,000 (five hundred thousand euro), except for and to the extent that such loss or damage is directly caused by a willful act (opzet) or gross negligence (bewuste roekeloosheid) of that Party and cannot be restricted or excluded by applicable law.

10. Intellectual Property.

10.1 Ownership of Background IP
Each Party shall remain the owner and shall retain control of the Background IP owned by it. The Parties must – on a royalty-free basis – give access to the other Parties to Background necessary for their research activities under this Agreement.

10.2 Ownership of Foreground IP

Foreground IP shall be owned by the Party whose employee(s) generated such Foreground IP, or on whose behalf such Foreground IP have been generated.

10.3 Protection, maintenance and costs of Foreground IP
Each Party is responsible for the application, acquisition and / or maintenance of its own Foreground IP and shall bear the costs relating to it.

In the event Parties jointly generate the Foreground IP and where their respective share of the invention or the work as the case may be cannot be ascertained (hereafter: „**Joint Foreground IP**"), the Parties concerned together are responsible for the application, acquisition and / or maintenance of that Joint Foreground IP. These Parties shall own such Joint Foreground IP in equal parts and contribute in equal parts to the costs of application, acquisition and / or maintenance of the Joint Foreground IP.

In the event of Joint Foreground IP, Parties shall make additional arrangements with regard to strategy, tasks and costs of application, acquisition and / or maintenance of that Joint Foreground IP and may designate a lead Party considering the circumstances. The lead Party shall timely discuss with the other Party or Parties applications, reports etc. in order to give the other Party or Parties the opportunity to comment thereon.

In the event of Joint Foreground IP each Party shall, and shall ensure that its employees, researchers, research fellows, individuals equivalent to those persons, give full cooperation and shall execute all documents, deeds and so forth as may reasonably be required in connection with the registration, protection and / or maintenance of that Joint Foreground IP.

10.4 Access rights Background IP

Parties hereby grant each other non-transferrable, non-exclusive, royalty free, fully paid up access rights to the Background IP contributed by it for the duration of the Project to the extent needed to enable the performance of the Project and to the extent each Party is authorized to grant such access rights.

10.5 Access rights Foreground IP
Parties hereby grant each other non–transferrable, non-exclusive, royalty free, fully paid up access rights to the Foreground IP, to the extent necessary to enable the performance of the Project and to the extent each Party is authorized to grant such access rights.

10.6 Access rights (Joint) Foreground IP
Parties hereby grant to each of the Parties non–transferable, non-exclusive, royalty free, fully paid up access rights for research and educational purposes for non-commercial use to their Foreground IP and Joint Foreground IP.

10.7 Transfer rights Foreground IP
If for the commercial use of its Foreground IP, a Party needs access rights to Background IP, or another Party's part in such Party's Foreground IP, the owning Party or Parties, as the case may be, may grant that Party access rights on market terms and conditions as applicable in the relevant international market to be further determined in good faith at that time.

10.8 Transfer rights Joint Foreground IP
In the event of Joint Foreground IP, neither Party is entitled to grant access rights or transfer or assign or make available in any other way any Joint Foreground IP to any third party without prior written consent of the other owning Party, which shall not be unreasonably withheld. The Parties owning the Joint Foreground IP shall in good faith determine and negotiate the terms and conditions to grant access rights or transfer or assign or make available in any other way any Joint Foreground IP to that third party.

The aforementioned terms and conditions with that third party shall include arrangements with regard to publication, remuneration at international market conditions, research and educational license for each of the Parties and the obligation to further develop and / or commercialize the Joint Foreground IP.

11. Materials

During the Project, Parties may provide to each other Materials. Each Party receiving Material from another Party ("Recipient" and "Provider") will conform to the following terms and conditions:

a. Provider will retain all intellectual property rights in and to Materials provided under this Agreement;
b. Recipient shall use the Materials solely for the purposes of carrying out the Project;
c. Recipient will not use Materials in humans or for testing of humans for any purpose;
d. to the extent required by applicable laws and regulations, Provider shall maintain, document and retain records of informed consent from each study participant or the participant's legally authorized representative in accordance with applicable laws and regulations;
e. Recipient acknowledges that in case of human samples the individual concerned shall at all times have the right to request Provider to destroy their Material. In the event of such a request, Recipient shall promptly destroy the Material in an approved manner, unless the patients' Material has been fully de-identified;
f. the Parties acknowledge that in case of a finding, (an unsought and unsuspected result of the research), Recipient shall provide all relevant information to Provider to allow Provider to inform the individual concerned;
g. Recipient shall not sell or transfer received Materials to any other person or entity or bring it in the public domain. Recipient shall keep and treat the Material confidential. Recipient may only disclose non-individually identifiable information regarding the Material in a summary form that aggregates more than one individual's clinical information for scientific journal publication, in all events to the extent permitted under applicable laws and regulations.
h. Parties shall comply with all applicable laws and regulations in the use of received Materials;
i. Within 30 days of completion of the Project or termination of this Agreement, whichever is earlier, Recipient shall discontinue its use of, and shall, at the sole discretion of Provider, return or destroy the Material.

12. Data Protection

During the Project, Parties may provide to each other research data, which may constitute Personal Data ("**Data**"). Each Party receiving Data, as described in Annex 3, from another Party ("Recipient" and "Provider") will conform to the following terms and conditions:

a. Provider will retain all intellectual property rights in and to the Data provided under this agreement;
b. Parties shall comply with all applicable requirements of the GDPR including all local implementing legislation and shall give all reasonable assistance to each other where appropriate or necessary to comply with such duties;
c. Parties are data controllers in respect of all Personal Data processed pursuant to this agreement;
d. Recipient shall use received Personal Data solely for the purposes of carrying out the Project;
e. any transfer of Personal Data to countries that are not recognized as providing adequate protection measures for Personal Data processing outside the EU or the EEA will only be allowed if Parties have agreed on adequate safeguards;
f. each Party ("**Indemnitor**") shall indemnify the other Party or Parties and hold them harmless for any claims or actions by third parties and for any fines imposed by the data protection authorities directly arising from (i) an attributable shortcoming on the part of Indemnitor or its processors in the fulfilment of its obligations under this Article, or (ii) any violation by Indemnitor or its processors of the applicable legislation governing the processing of Personal Data;
g. within 30 days of completion of the Project or termination of this agreement, whichever is earlier, Parties shall destroy any received Personal Data in their possession or control.

13. Publication procedure

After the parties have discussed their specific contribution to the project, the intention is to publish in collaboration, as further provided in the following clauses. Exemption to this is the already – before the start of the Project - generated data using the parties corresponding materials which can be published without previous consultation.

Parties acknowledge that the Project is a collaborative effort, and that a joint publication is anticipated to be authored by the participating researchers. Parties shall not independently publish any results of the Project before other than in accordance with this clause.

In case no joint publication has been made within 12 months of completion of the Project and a Party wishes to publish inwritten form, oral presentation or make public in any other form, information relating to the Background IP, Foreground IP or any other information regarding the Project – confidential or not – will submit in writing to the Project Leader the intended publication 45 days before the intended publication date or before the date of submission for disclosure to review the publication. The intended publication will clearly state the intended publication date.

The Project Leader will promptly make the intended publication available to the other Parties.

The intended publication is Confidential Information and as such protected in the manner this Agreement provides for.

The Parties will have 45 days to review the intended publication. If the Parties do not response within this term, the publishing party is free to proceed with the intended publication or presentation without further delay.

The Parties can, by giving written notice to the Project Leader, raise an objection with regard to the inclusion of their Confidential Information or may request a delay for a maximum of 90 days after receipt of the first written notice by the Project Leader, in order to seek patent or similar protection for the Results that are proposed to be published.

During the period for review mentioned above, the Parties may comment on the scientific content of the proposed publication. The publishing party agrees that all reasonable comments made by the Party in relation to a proposed publication or presentation will be incorporated into the publication or presentation. Furthermore, the Parties may cause the publishing party to remove from the projected publication any Confidential Information received by it that are not constituted results of the Project. The publishing party shall not unreasonably withhold or delay its consent to the reasoned request from such Party.

All publications will be in accordance with international recognized scientific and ethical standards concerning publications and authorship, including the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, established by the International Committee of Medical Journal Editors. Copyrights concerning Publications of the Clinical Trial remain with the authors of the Publication, regardless of any other provisions regarding intellectual property rights.

14. Confidentiality

For the purpose of this Agreement, confidential information ("**Confidential Information**") means:

a. any information disclosed in writing or other tangible form by one Party ("**Disclosing Party**") to another Party ("**Receiving Party**") for use in the Project and marked as CONFIDENTIAL,
b. or, any information initially disclosed orally and then summarized and confirmed in writing as CONFIDENTIAL within 30 days after the date of oral disclosure.

The Receiving Party may not disclose the Confidential Information to any of the other Parties or to a third Party, except with explicit written consent of the Disclosing Party.

The Confidential Information includes, without limitation:

a. the Full Project Proposal;
b. any and all Background IP listed in Annex 3 of this Agreement and made available by a Disclosing Party to a Receiving Party for use in this Project;
c. the Results of the Parties.

Confidential Information does not include information that:

a. is known or open to the public or otherwise in the public domain at the time of disclosure;
b. becomes part of the public domain by any means other than breach of this Agreement by a Receiving Party;
c. is already known to the Receiving Party at the time of disclosure and is free of any obligations of confidentiality;

d. is obtained by the Receiving Party, free of any obligations of confidentiality, from a third party that has a lawful right to disclose it.

If disclosure of Confidential Information other than as expressly permitted under this Agreement is required by law, that disclosure does not constitute a breach of this agreement so long as the Receiving Party:

a. notifies the Disclosing Party in writing at the earliest possible date of the disclosure so as to allow the Disclosing Party to take legal action to protect its Confidential Information,
b. discloses only that Confidential Information required to comply with the legal requirement, and
c. continues to maintain the confidentiality of this Confidential Information with respect to the other Parties and third Parties.

These obligations of non-use and non-disclosure of Confidential Information survive termination of this agreement and continue for a period of five (5) years after termination.

15. Applicable law

This Agreement affecting the rights and obligations between the Parties will be construed in accordance with and governed by Dutch Law.
In the event the Parties have been unable to amicably resolve any dispute arising out of this Agreement the competent court of Midden-Nederland, location Utrecht, the Netherlands, shall have exclusive jurisdiction.

16. Inconsistencies

In case of an ambiguity or inconsistency between the ZonMw Conditions r on the one hand and this Agreement on the other hand, ZonMw Conditions will take precedence of this Agreement.

17. Notices

All formal notices ("**Notices**") given by one Party to another Party pursuant to this Agreement will be in writing and will be delivered to the Contact Person of the other Party by (i) personal delivery, (ii) registered mail, (iii) registered courier, (iv) fax or (v) electronic mail, and in the latter two confirmed by mail, at the Party's address specified in this Agreement as listed in Annex 4.

18. Assignment

Except as specifically provided for in this Agreement, the rights and obligations arising from this Agreement shall not be assigned to third parties (including Affiliates) without the prior written approval of the other Parties.

19. Amendment

Amendments and modifications to the text of this Agreement require a separate written agreement to be signed between all Parties.

Signatures follow on next page

This Agreement has been agreed and signed by:

Signature

For: Universitair Medisch Centrum Utrecht

Name: (10)(2e)

Place:

Date:

Signature

For: Universitair Medisch Centrum Utrecht

Name: (10)(2e)

Place:

Date:

Signature

For: RIVM, on behalf of the Minister of Health, Welfare and Sport

Name: Dr. (10)(2e), (10)(2e)

Place: Bilthoven

Date:

Signature

For: VuMC

Name:

Place:

Date:

Annex 1

Full project proposal and the project budget

AANVRAAGFORMULIER

UITGEWERKTE SUBSIDIEAANVRAAG – BOTTOM-UP RONDE

COVID 19 programma

II. **Deadline voor indiening: 15 juni 2020 (14:00 u)**

LEES ALSTUBLIEFT ALLE INSTRUCTIES IN BIJLAGE "TOELICHTING INDIENING SUBSIDIEAANVRAAG" VAN DE OPROEPTEKST ZORGVULDIG!

Wanneer u het formulier heeft ingevuld:

1. **Zet het formulier om naar een PDF file en controleer de details**
2. **Upload het complete formulier als een bijlage bij uw indiening in Projectnet (Let op: dit zijn twee verschillende links, gebruik maar 1 van de 2!)**

ProjectNet: Aandachtsgebied 1 (voorspellende diagnostiek en behandeling)

BASISGEGEVENS (voorpagina)

1. NAAM VAN DE HOOFDAANVRAGER:

Dr. (10)(2e)

ORGANISATIE:

University Medical Centre Utrecht

2. ENGELSE PROJECTTITEL:

Understanding the two faces of the COVID-19 immune response to predict clinical course and define strategies for early and late phase intervention

NEDERLANDSE PROJECTTITEL:

Het begrijpen van de twee gezichten van de COVID-19 afweer respons om het ziekteverloop te voorspellen en betere therapeutische strategieën te ontwikkelen

ONDERZOEKSVOORSTEL **max 8 pagina's A4** (inclusief literatuurreferenties)	(voorpagina met basisgegevens niet meegerekend - font type Arial 10 pts)

1. PROBLEEMSTELLING, URGENTIE EN DOELSTELLING(EN)

Onderbouw probleemstelling, urgentie en doelstelling. Maak doelstelling SMART.

Relevance

The current corona virus disease 2019 (COVID-19) leaves us in the dark about the exact mechanisms of disease development and treatment options. Although the acute respiratory distress syndrome (ARDS) in COVID-19 patients is also observed in SARS and influenza infection, some clinical characteristics as well as heterogeneity in disease course and underlying immune dysregulation among COVID-19 patients are unique. This poses challenging questions as how to successfully overcome severe SARS-CoV-2 infections and how to predict severe disease course as timely targeted treatment may reduce the burden of disease. Central to the clinical outcome of COVID19-infected patients is the dual role of the immune system[1]. On the one hand an effective immune response is essential for clearing the virus. On the other hand, there is compelling evidence demonstrating that hyper-activation of the immune system plays a crucial role in the pathogenesis of organ injury and mortality due to off-target toxicity[2]. For instance, ARDS seems to be strongly linked to hyper-inflammation, also known as Cytokine Release Syndrome (CRS)[3-5]; a systemic inflammatory response that can be triggered by a variety of factors, including infection[6]. Importantly, although the far majority of patients with a severe disease course are over 55 years of age and present with multiple comorbidities, the observation that young and otherwise healthy subjects can develop lethal complications, suggests that unknown genetic susceptibility factors are involved.

The clinical challenge is now to therapeutically balance off-target immune toxicity and immunosuppression to improve outcomes in COVID-19 patients. To address this question, we require a deeper understanding of the functional evolution of both innate and adaptive immune responses over the course of the illness. This will enable informed decision making in the clinical handling of severe COVID-19 patients.

In this collaborative proposal between **UMC Utrecht, RIVM, and Amsterdam UMC – location Vumc** *(as encouraged by the ZonMw COVID-19 reviewing committee)*, we will perform a longitudinal immunological assessment of patients during the course of mild to severe illness (samples already available) to determine whether distinct clinical presentations are driven by differential immune responses. Besides providing a model of the underlying immune response, our approach will provide (i) prognostic biomarkers, (ii) potential targets for personalized treatment, and (iii) insights in the optimal timing for immune-mediated interventions.

3. Hypothesis

Activation of the innate immune response against SARS-CoV-2 is undisputed, although some reports suggest that activation might be suboptimal in the initial phase. The fight against the virus is intensified by the adaptive immune system, with production of SARS-CoV-2-specific antibodies and T cell–mediated responses being essential for clearing the virus and maintaining long-term immunity. In severe COVID-19 patients however, the virus is not cleared sufficiently, and it seems that persistent antigenic activation of T cells ultimately drives a nonresponsive cell state known as T cell "exhaustion". In the face of an insufficiently controlled virus infection this is double bad news: Besides the crucial role in the generation of specific anti-viral responses, functional T cells actively suppress innate immune over-activation to prevent severe immunopathology. The importance of the adaptive immune response in viral clearance suggests that in persisting and/or severe COVID-19 disease the virus either evades or suppresses effective adaptive immunity and that there may be a predisposition in some individuals[7]. Defective T cell immunity could be delayed or present from the beginning, but another possibility may be an overzealous T cell activation leading to exhaustion and T cell apoptosis. This is supported by the deep lymphopenia that is observed in severe COVID-19 patients. We hypothesize that:

1) *T cell dysfunction, characterized by exhaustion and apoptosis, contributes to SARS-CoV-2 persistence and hyper-inflammation.*
2) *Clinical outcome of COVID-19 patients can be predicted based on their genetic predisposition, functional immune profiles, and circulating analytes.*

4. Aims/work packages

To understand the order and interaction of immune events and link it to the disease course we propose the following work-packages:

WP I: Characterization of innate and adaptive immune responses across the COVID-19 disease course.
WP II: Identification of dysregulated networks of the circulating proteome over time.

WP III: Identification of genetic variants predisposing to severe COVID-19 disease.

WP IV: Multilayer data integration, selection and validation of relevant biomarkers, and development of a comprehensive prognostic model for clinical use.

2. LOPEND ONDERZOEK

Beschrijf beknopt gepubliceerd onderzoek EN lopend nationaal (en waar mogelijk internationaal) onderzoek op dit gebied en wat uw project daaraan toevoegt. Zie hier een lijst met mogelijke portals.

A sufficient T response is crucial for viral clearance. Interestingly, lymphopenia is associated with COVID- 19 severity: in 95-100%% of the ICU patients there is a significant decrease in total $CD4^+$ T cells and $CD8^+$ T cells[2,8,9], which may be attributed to T cell exhaustion resulting in apoptosis[7]. T cell exhaustion markers PD-1 and Tim-3 were indeed found to be increased on $CD8^+$ and $CD4^+$ T cells of COVID-19 patients[8]. In addition, elevated TNF-α levels in COVID-19 patients[10] may also contribute to T cell apoptosis directly through interaction with TNF receptor 1 (TNFR1). Interestingly, because aged T cells have considerable elevated expression of TNFR1, these T cells are more susceptible to apoptosis[11]. Based on the literature and preliminary data obtained in the UMCU and Amsterdam UMC–location VUmc, we propose that a defective T cell response leads to a sustained viral load, and development of severe and long-lasting disease accompanied by hyper-inflammation. Our preliminary research in severe COVID-19 patients (artDECO cohort, Amsterdam UMC – Location VUmc) revealed a massive remodelling of their CD4 and CD8 memory compartments (Fig. 1) during their stay at the ICU in an up to 4 weeks follow up with increased exhaustion marker expression and terminal memory differentiation. In addition, in a first pilot with the UMCU cohort we found strongly increased expression of the death receptor FAS on CD8 T cell of severe COVID-19 patients compared to healthy controls, indicating increased apoptosis (Fig. 2). Together our data support the hypothesis that severe COVID-19 is associated with terminal differentiation and severe loss of T cells. The questions we are addressing in the project include (1) what happens in an early phase of the disease, (2) can cellular parameters predict disease course and outcome, and (3) are cellular immune responses associated with hyper-inflammation?

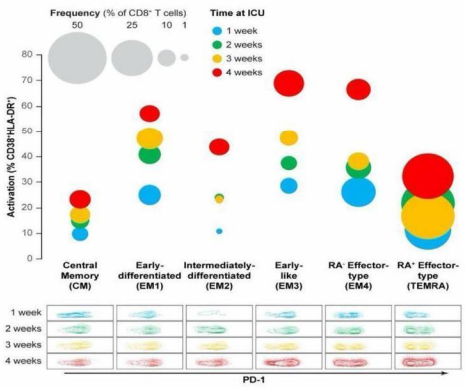

Fig. 1. *Characterization of the CD8 memory compartment in severe COVID-19 patients over their 4 weeks stay at ICU (N=32). $CD8^+$ cells were classified according to the expression of CD45RA, CD27, CD28, and CCR7. Subset frequency is proportional to bubble size and the Y axis indicates the proportion of activated ($CD38^+HLA\text{-}DR^+$) cells per subset. Underneath each $CD8^+$ T cell memory subset, the expression level of the activation/exhaustion marker PD- 1 is provided for the corresponding $CD38^+HLA\text{-}DR^+$ memory subset.*

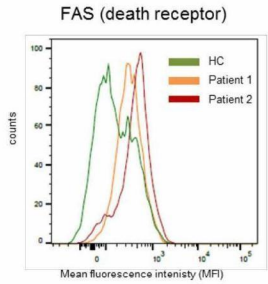

Fig. 2. *FAS (death receptor) expression on CD8 T cells from 2 severe COVID-19 patients (orange and red) compared to healthy control (green)*

Hyper-inflammation, also called CRS is characterized by a clear elevation in cytokine and chemokine levels. COVID-19 patients that require ICU administration showed increased levels of IP10, MCP1, granulocyte colony-stimulating factor (GCSF), macrophage inflammatory protein 1-α (M1P1α) and TNFα compared to non-ICU patients[2]. Another study observed elevated levels of IL-2R, IL-6, TNF-α and IL-10 in severe cases compared to moderate cases[10]. Important points that still need to be addressed are (1) heterogeneity of patients, (2) prognostic value of genetic, protein and cellular biomarkers, (3) possible targets and timing of immune-suppression, and (4) underlying mechanisms of the hyperinflammation/CRS- like phenomenon. These aspects will be addressed in the current project.

We combine the following unique aspects:

- Longitudinal follow-up of COVID-19 patients ranging from a-symptomatic to severe and from children to elderly (>1000 longitudinal samples (plasma and cells) have already been stored).
- Functional dynamics of both innate and adaptive immune response during the disease course.
- Specialized phenotypic and functional assays on neutrophils have already been performed (assays require fresh (<1-hour post blood draw) samples.
- Integration data-layers of circulating proteins, cellular responses, and genetics.
- Pipeline of biomarker discovery towards diagnostic implementation.
- Multidisciplinary team of translational immunologists, clinicians, medical immunologists, and computational biologists.

3. PLAN VAN AANPAK (ONDERBOUW KEUZES)

THEORETISCHE EN/OF EMPIRISCHE ONDERBOUWING

Because of the knowledge gaps discussed above (the lack of longitudinal functional data, from a-symptomatic to severe and from children to elderly), in this collaborative proposal between the UMC Utrecht, RIVM, and Amsterdam UMC-location VUmc (as was encouraged by the ZonMw COVID-19 reviewing committee), we will perform longitudinal assessment of patients during the course of mild to severe illness (samples already available) to determine whether distinct clinical presentations are driven by differential immune responses

STUDIE POPULATIE/DATABRONNEN

To address our questions, we will use three longitudinal patient cohorts (cohort overview in Fig. 3, demographics in Table 1). The **UMCU** and **VUmc** cohorts consist of patients with moderate to severe disease with a considerable proportion requiring ICU admission. For the UMCU cohort there is also ICU follow-up. The **RIVM** cohort consists of families with at least 1 confirmed SARS-CoV-2-infected family member and longitudinal sampling of both parents and children. This cohort includes controls, non-symptomatic to mild disease and, due to the unique set-up, also allows for pre- symptomatic monitoring of the immuneresponse. **Longitudinal** blood samples (plasma and cells) and clinical data have already been collected and stored from 150 UMCU COVID-19 patients, 55 RIVM families, and 113 VUmc COVID-19 patients and further collection is ongoing. As control groups we have collected blood from age and sex-matched healthy controls ("VITAL study", RIVM (n=25)), confirmed SARS-CoV-2 negative family members from the RIVM study (n=100), and historic plasma samples of severe influenza pneumonia patients and age-matched ARDS patients without infection (n=200, MARS biorepository, disease control groups).

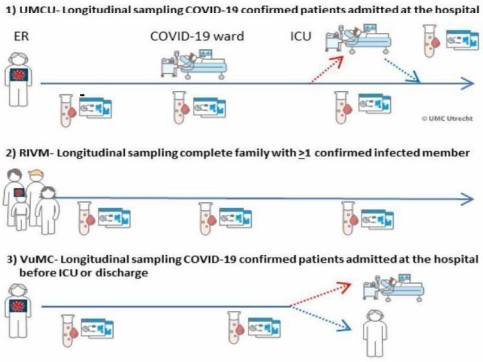

***Fig. 3**. Study design.*

	UMCU *Ward*	VUmc *Ward*	UMCU *ICU*	RIVM *Community*
Confirmed COVID19 (N)	150	113	95	67 out of 174
Age (years, IQR)	65.4, 55-74	64.4	66, 57-73	2, 61
Male gender (N, %)	79, 54	58, 51	59, 62	26, 39
BMI (median, IQR)	27.9, 25-31	n.a.	28, 26-31	n.a.
Lentgh of stay (days, median, IQR)	15, 7-24	n.a.	n.a.	n.a.
ICU indication (N, %)	42, 40.8	24, 21.2	n.a.	0, 0
ICU admission (N, %)	26, 30	n.a.	n.a.	0, 0
Invasive mechanical ventilation (N, %)	NA	NA	89, 94	NA
Ventilation time (days, median, IQR)	NA	NA	15, 8-25	NA
ICU stay (days, median, IQR)	NA	NA	16, 9-26	NA
Acute kidney injury (requiring RRT, N, %)	NA	NA	16, 17	NA
Deceased (N, %)	26, 18.7	19, 16.8	17, 18	0, 0

Table 1. Demographics of collected patient cohorts (NA, not applicable; n.a., not available). 26 of the UMCU ICU patients have been transferred from the UMCU ward. The other ICU patients have been referred from other centers

VERWACHTE UITKOMST

1) Novel insights into the mechanisms underlying the anti-Sars-CoV-2 response.
2) Immunological and genetic biomarkers/biomarker-profiles for patient stratification and patient monitoring.
3) Targets for early and late intervention.
4) Prediction model of the disease course based on immune parameters and genetics.

DATA-ANALYSE

WP I: Characterization of innate and adaptive immune responses across the COVID-19 disease course To understand COVID19 dynamics and disease heterogeneity it is particularly important to assess both **immune cell set abundance as well as function**.

(1) Neutrophils are one of the first innate cells to respond to pathogens, but their function can only be determined on freshly isolated cells. In the UMCU cohort neutrophil phenotype and function has already been assessed with stimulation assays and functional markers determined by automated flow cytometry within 1 hour after the blood draw (required for reliable neutrophil assessment).
(2) Deep immunophenotyping will be performed on cryopreserved PBMCs using a state-of-the-art spectral flow cytometry panel capable of determining the relative frequency and phenotype of more than 30 known innate and adaptive immune cell subsets, including major

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subpopulations of B cells, T cells, iNKT and NK cells, plasmacytoid DCs and cDCs, and classical and non-classical monocytes. Importantly this panel includes also activation markers and will give an overview of the total immune landscape and its activation status. This assay will be performed on 100 patients selected from the VUmc, UMCU and RIVM cohorts and 25 age-matched healthy/disease controls.

(3) To define activation or exhaustion of the adaptive immune response, T cell re-stimulation assays will be performed and activation markers, cytokine production (function), proliferation, exhaustion, tissue homing, and regulatory function will be assessed in 100 selected patients from the VUmc, UMCU, and RIVM cohorts and 25 age-matched healthy/disease controls. Additionally, COVID-19 specific immune responses will be assessed in a subset of patients by re-stimulation of PBMC with a mix of SARS-CoV- 2 specific proteins and IFN-γ production by T cells as a read-out.

(4) In all patients we will determine longitudinal anti-SARS-CoV-2 antibody development by Multiplex Immuno Assay detecting S1, RBD and N protein-specificity (developed by the RIVM) and neutralizing capacity with *in vitro* testing.

Together these data will provide a deep understanding of the dynamics and quality of the innate and adaptive immune response in different COVID-19 disease phases, as well as severity- and age-categories.

WP II: Identification of dysregulated networks of the circulating proteome over time.

Systemic inflammation may contribute to multiple pathophysiological processes that are associated with COVID-19, including vascular dysfunction and coagulation. The key mechanistic drivers of the observed dysregulated processes remain to be identified. To understand the dynamics of dysregulated protein networks related to the immune response but also to vascular function, angiogenesis, and hematological processes, the circulating proteome will be analyzed using Olink (UMC Utrecht is the only official service provider in the Netherlands) on ±1000 samples from all three cohorts plus healthy and disease controls. We will select 2 different panels (92 markers per panel) to measure markers associated with inflammation and vascular dysfunction based on a small pilot study that is currently being performed. To ensure fast initial data before a potential second wave of COVID-19, we will directly validate our findings in the VUmc cohort.

WP III: Identification of genetic variants predisposing to severe COVID-19 disease.

We will genotype common DNA polymorphisms using Illumina genome-wide genotyping arrays in 200 COVID-19 patients and will: (a) compare patients with population controls genotyped previously; this will identify human genetic variants predisposing to COVID-19; (b) compare mild and severe COVID-19patients; this will help to find genetic determinants of severe COVID-19; and (c) compare COVID-19 patients with and without CRS, aiming to find its genetic determinants. Given that SARS-CoV-2 is a new pathogen with only a short period of adaptation to humans, common genetic variation in humans can be expected to have relatively large effects detectable even in several hundred patients. Our findings will reveal subjects at high genetic risk of CRS and severe COVID-19. In the future, such high-risk subjects could be identified by population screening and then receive special care for targeted prevention of severe COVID-19. Furthermore, finding responsible genes and integrating them with our immunological data will help to understand the pathogenesis leading to these severe manifestations of COVID-19.

WP IV: Multilayer data integration, selection and validation of relevant biomarkers, and development of a comprehensive prognostic model for clinical use. To develop a model for the different trajectories of the anti-COVID-19 response and disease course, multi-layer data of cellular function, circulating proteome and genetics will be integrated with scripts developed in-house by the CTI-Computational Immunology group. Clinical data will be obtained from the UMCU Research Data Platform, MARS biorepository, and RIVM database and will be linked to antibody-responses, functional immune cell data and circulation proteome. For the validation of single circulating

biomarkers, and fast application the clinical setting, Luminex technology will be used. The UMCU has 200 customized single markers available for measurement and we can easily add novel markers discovered using Olink screening. The prognostic model will be validated in the VUmc cohort. To perform advanced multilayer integration of data and cohorts we have budgeted a postdoc with expertise in computational immunology.

5. Data-handling

Together we will use our developed and validated methods for acquiring, combining, and understanding the data, with the ultimate end of a better understanding of the immunopathophysiology of COVID19. We will use this information to gain a better understanding of the progression of disease and the biological determinants of severe COVID19 to improve patient care. To maximise sharing and reuse of data between project partners and, ultimately, the wider research community, a data management plan will be developed using the FAIR data principles. Data will be stored at the ICT platforms of VUmc, UMCU, and RIVM. Where relevant, any ethical aspects with respects to the sharing and publication of patient data both within and outside the project will be addressed by the data stewards. Data will be linked to the outcome database (https://covidpredict.nl/), making it easy to connect outcomes and other therapy and demographic parameters to the biobank data. We will integrate our findings continuously with other real-word data using COVID-19 Data Portal (https://www.covid19dataportal.org). This portal will be the primary entry point into the functions of a wider project, the European COVID-19 Data Platform.

(5)

POWERBEREKENING (indien van toepassing)

6. Sample size and power calculation for immune phenotyping

We expect a 40% increase in cytokine production by T cells during COVID-19 production and 40% increase in exhaustion phenotype in severe COVID-19 patients. This is based on our pilot results in COVID-19 patients. With a variation of 30% between individuals, an alpha of 0,05, and power of 0,8 this means a minimum group size of 18 patients per group (a-symptomatic/mild –severe – ICU). To also be able exclude confounding factors such as sex and age differences we will include at least 25 patients/group for all immune phenotyping, with 100 patients in total.

7. Sample size and power calculation for Olink measurements

To compute the population size for multivariate principal components the rule of thumb is five times the number of independent variables measured[12]. From published literature[13] and our own experience we know that analytes often highly correlate to one and another. The number of independent variables describes the unique analytes that do not correlate with any other analyte. Our unpublished results and those of Ghebre *et al*[13] suggest that with 150 analytes about 20 unique independent variables may be found, resulting in a required samples size for the discovery step when measuring 2 Olink panels (175 potential biomarkers) of 120 patients ((175*20/150)x5) when applying the rule of thumb[12].

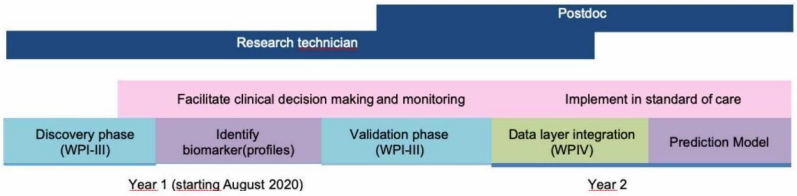
8. Sample size and power calculation for GWAS

Our main goal is to identify polymorphisms associated with severe COVID-19. Given that about 50% of COVID-19 patients in our cohorts had an indication for ICU admission, our study will include approximately 100 severe and 100 non-severe COVID-19 cases. This sample size allows ~80% statistical power to detect odds ratio (OR) = 3.5 for common DNA polymorphisms (minor allele frequency 30%) at a genome-wide significance level ($P = 5 \times 10^{-8}$). In contrast to other infectious diseases caused by ancient pathogens, where genetic effects predisposing to disease are small, SARS-CoV-2 started to infect humans only recently. Hence, there was no time for adaptation and human genetic variants in critical genes can strongly predispose to severe COVID-19. Therefore, it is not unrealistic to expect genetic effects as large as OR 3.5- 4. Moreover, only polymorphisms with such strong effects would be useful as genetic biomarkers predictive of severe COVID-19, and the

discovery of such polymorphisms is the main purpose of our GWAS. Nevertheless, finding DNA polymorphisms that confer weaker susceptibility may be also informative, because such polymorphisms could point at biologically-relevant genes and highlight novel pathways involved in disease pathogenesis. To find such weaker genetic effects we will combine our dataset with similar datasets from other countries.

4. PLAN VAN AANPAK (ONDERBOUW KEUZES)

TIJDSSCHEMA (maak daarbij duidelijk wanneer de eerste resultaten worden verwacht)



MOTIVATIE HAALBAARHEID

The UMCU currently has included 154 patients with proven SARS-CoV-2-positive PCR and follow-up samples, 113 patients are present at the VUmc with proven SARS-CoV-2-positive PCR and follow-up samples, and 55 families have been included in the RIVM cohort with at least one proven SARS-COV-2- positive family member. All samples, including historic disease controls, are stored in the biobank and we have obtained ethical approval to use the samples and clinical data. The proposed assays have been optimized and are ready-to-use and a pipeline of biomarker discovery towards diagnostic implementation has been established. The neutrophil assays on fresh blood samples, initial phenotyping and cell counts have already been performed. To ensure robust data integration, interpretation and translation to the clinic, we work with a multidisciplinary team of experts including virologists, intensivists, (medical and clinical) immunologists, infectious disease specialists, acute medicine specialist, pulmonologists, epidemiologists, and computational biologist. Since we have included both discovery analyses and validation in our project, **we aim to implement the first relevant biomarkers before the end of 2020 for clinical use and clinical trial monitoring.**

RECRUTERINGSSTRATEGIE (indien van toepassing)

All samples for analyses in the proposed study have already been collected.

5. RELEVANTIE

OPROEP SPECIFIEKE RELEVANTIE CRITERIA

Our project will give insights in the dynamics of the protective versus pathogenic role of the immune system in mild to severe COVID-19 infection. This is of crucial importance as we urgently need fast-responsive biomarkers, desirably available for point-of-care technologies to predict the disease course of the patients and assign the patients at risk for developing ARDS for an appropriate treatment modality. This will reduce disease burden and consequently the burden for IC units.

Immunosuppressive drugs are considered as candidates for treatment and some of these drugs have already been introduced to patients or will be tested in trials, such as REMAP-CAP. One of the

dilemmas here is that introducing immune suppression may also interfere with an effective anti-viral immune response. Furthermore, it remains unclear whether the immune responses in patients who rapidly develop respiratory failure upon hospital admission are distinct from those in patients who develop respiratory failure 7–10 d after hospital admission. A recent clinical trial showed improvement in only 33% of patients treated with anti-IL6, indeed suggesting differential disease courses in different patients[4]. **Together our data will provide: (i) selected dominant immune pathways that may be targeted by immunosuppressive drugs, (ii) prognostic immunologic and genetic biomarkers to stratify patients for optimal treatment options, and (iii) insights in the optimal timing of immune-related interventions and appropriate design of clinical trials**. Our data will not only be relevant for COVID-19 but also other (emerging) infections.

ZONMW ALGEMENE RELEVANTIE CRITERIA

Within the project diversity is an important theme as we have included patients with a wide age range and taking along age-matched controls. We will also zoom in on the sex differences since women seem to be less susceptible than men to develop severe COVID-19.

6. PROJECTGROEPLEDEN EN HUN ROLLEN

Onderbouw dat in de projectgroep relevante disciplines met de juiste expertise en beoogde einddoelgroep(en) zijn vertegenwoordigd. Maak helder welke deelnemers aan de projectgroep welke rol hebben. Geef bij voorkeur werkpakketten aan. * included in the ZonMw project-team list

We have composed a multidisciplinary project group, with experts from 3 different centres:

- (10)(2e) is a human T cell and inflammation specialist and (10)(2e) (VUmc) is an immunologist and expert in immune phenotyping and biomarker discovery. Together they will be leading the project and ensure integration of the different work-packages (I-IV)
- (10)(2e) and (10)(2e) (RIVM) are experts in innate immunity and host-pathogen interactions (WPI)
- (10)(2e) are specialized in the immune response against viruses (WP I)
- (10)(2e) is a medical immunologist and expert in disease-overarching immune-monitoring and biomarker research from exploration to clinical implementation (WP I, II & IV).
- (10)(2e) is an expert in genetic susceptibility to infectious diseases responsible for WP III
- (10)(2e) (VUmc) are infectious disease specialists and directly involved in clinical research care of COVID-19 patients. Together with (10)(2e) (10)(2e), an intensivist and leader of the MARS cohort and clinical immunologist (10)(2e) (10)(2e) they will interpret the clinical data and play a crucial role in patient stratification and translation of findings into the clinical setting (WP II and IV)
- (10)(2e) a computational and network immunologist that will be supervising integration of the data- layers (WP IV)

7. KENNISOVERDRACHT, IMPLEMENTATIE, BESTENDIGING

Beschrijf hoe u de kennis opgedaan in uw project gaat delen, en hoe u de resultaten en/of producten verder gaat brengen richting implementatie, bijvoorbeeld door toepassing in de praktijk, of bij het vormen van beleid.

- We will publish our findings in peer reviewed journals. We will also participate in appropriate scientific and non-scientific fora for the dissemination of the information generated in this project. Last, but not least, our team is heavily involved in the education of Biomedical and Medical students of the University of Utrecht, the Free University of Amsterdam, and the University of Amsterdam; which will ensure that new generations of researchers will be up to date on cutting-edge research on COVID19.
- Clinical immunologist (10)(2e) is part of the European REMAP-COVID leadership team, a REMAP- CAP affiliated platform for non-ICU COVID-19 patients. All relevant findings and

biomarkers will be directly implemented in these trials.

- Medical immunologist [redacted] will ensure fast implementation of relevant biomarkers into clinical diagnostics using an established discovery and validation pipeline.
- The RIVM will use the data and insights to advice policymakers as well as the general public.
- Cytek Biosciences BV, manufacturer of the instrument enabling the advanced immunophenotyping (Aurora 5 laser), provides *in kind* support, including a set of antibodies for panel optimization as well as technical support for data unmixing and QC. The technical innovations introduced in collaboration with Cytek will not only advance the current project, but also set a new state-of-the-art to monitor immune responses in severe infections, chronic inflammatory diseases, and immune therapies.

8. DEELNAME VAN DE STAKEHOLDER(S)/EINDDOELGROEPEN

Beschrijf welke partijen (die mogelijk geen mede-aanvrager zijn, bijvoorbeeld patiënten, zorgprofessionals) op welke manier bij uw project worden betrokken.

- [redacted] s a clinical immunologist and member of our team who will also be part of the European REMAP-COVID leadership team, a REMAP-CAP affiliated platform for non-ICU COVID-19 patients. All relevant findings and biomarkers will be directly implemented in these trials.
- Infectious disease specialists [redacted], intensivist [redacted] clinical immunologist [redacted] pulmonologist [redacted] and virologist [redacted] are directly involved in COVID-19 patient care as well as the project.
-

The RIVM will use tge data and insights to advice policymakers as well as the general public

9. LITERATUURREFERENTIES:

Vermeld hier de referenties die uw aanvraag inhoudelijk onderbouwen en vermijd opsommingen van publicaties van uw projectgroep(leden).

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Annex 2

ZonMw General Terms and Conditions Governing Grants of ZonMw, applicable as from 1st July 2013

By reference only

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Annex 3

Background IP

If applicable, Materials made available by each Party for use in the Project:

UMC Utrecht:

Material: Samples (plasma and/or cells)

VUmc:

Material: Samples (plasma and/or cells)

RIVM:

Material: Samples (serum and/or cells)

If applicable, Data made available by each Party for use in the Project:

UMC Utrecht

Proteomics and phenotypic and functional data acquired by flow cytometry

VUmc

Phenotypic data acquired by spectral flow cytometry

RIVM

Phenotypic data acquired by flow cytometry

Antibody levels in serum/plasma

ZonMw

Annex 4

List of contact persons and addresses for formal notices

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