nr	Dossiernummer	Hoofdaanvrager	Organisatie	Titel	Samenvatting	Looptijd (mdn)	Startdatum	Aangevraagd ZonMw Budget SA (€)	Thema	Prioscore tekst	Prioscore	Prioscore uitslag vergadering (eerste gedeelte)
1	50-56300-98-104	(10)(2e)	Radboudumc	Integrative analysis of multi-omics longitudinal data to **identify effective strategies for the prediction and treatment** of COVID-19	The currently ongoing world-crippling pandemic with the new SARS-CoV2 virus shows the desperate and urgent need for better strategies to predict and treat Coronavirus disease 2019 (COVID-19). A subset of COVID-19 patients develop very severe respiratory symptoms, whereas others experience mild flu-like symptoms. Although it is evident that the host genetic and non-genetic factors, in interaction with new SARS-CoV2 virus, can determine variability in COVID-19 outcome, the underlying molecular mechanisms of patient-specific (COVID-19) outcome are unknown. We have recently observed a striking time-dependent variability in immune response among COVID-19 patients, where 50% of the ICU patients showed immune response patterns similar to non-ICU patients. This suggests that instead of single layers of omics data measured cross-sectionally, we need longitudinal measurements of multi-omics to predict severity and to obtain biological/molecular explanations to the variability. To determine how individual variation in molecular response affects COVID-19 severity and outcome we will use a unique and a largest cohort to date of COVID-19 patients in the Netherlands to profile longitudinal multi-omics data. We will then characterize: 1) the role of plasma metabolites, inflammatory markers and circulatory proteome variability in explaining COVID-19 outcome; 2) pinpoint causal molecular networks using dynamic changes in host multi-omics data; and 3) provide the genetic support for multi-omics variability that determine COVID-19 outcome in a prospective independent cohort. By conducting systematic longitudinal systems biology analyses, we will be able to establish causal relationships between omics-networks and COVID-19 clinical phenotypes. This will increase our understanding of the pathogenesis of COVID-19 and help to sub-group patients based on their response pattern so that treatment strategies can be adapted to individual patient categories.	24	01-09-2020	(10)(2b)	4. virus, immuniteit, immuunrespons en pathogenese	Zeer relevant-Zeer goed	1	1

2	50-56300-98-120	(10)(2e)	Universitair Medisch Centrum Utrecht	Understanding the two faces of the COVID-19 immune response to predict clinical course and define strategies for early and late phase intervention	ONDERZOEKSVRAAG Het afweersysteem speelt een opvallende dubbelrol bij COVID-19, de ziekte veroorzaakt door het nieuwe coronavirus SARS-CoV-2. Een effectieve afweerrespons zorgt dat het virus aangevallen en opgeruimd wordt, maar als dat niet goed lukt, lijkt een hyper-activatie van het afweersysteem te ontstaan dat juist tot ernstige problemen leidt. We moeten dus **weten hoe en wanneer de afweer ontspoort en hoe we dit gericht zouden kunnen monitoren en behandelen**. URGENTIE Op dit moment is het onmogelijk om te voorspellen wie een milde of ernstige vorm van COVID-19 zal ontwikkelen. Bovendien tasten we in het duister over wat er precies misgaat in de afweer bij patiënten met een ernstig verloop en hoe we hen het best kunnen behandelen. Het gebruik van afweer-onderdrukkende medicatie is een van de mogelijke strategieën. HYPOTHESE Bij chronische en ernstige vormen van COVID-19 lijkt het virus niet goed te worden opgeruimd. Omdat de afweer hierbij een cruciale rol speelt hebben wij de volgende hypotheses: 1) Uitputting en ontregeling van T-lymfocyten draagt bij aan het persisteren van SARS-CoV-2, met hyper-inflammatie als gevolg. 2) COVID-19 patiënten kunnen worden ingedeeld op basis van eiwitten die vrijkomen in het bloed bij die ontregeling en door het meten van de functie (activiteit, uitputting, ontregeling) van de afweercellen. PLAN VAN AANPAK In een samenwerking tussen het UMC Utrecht en het RIVM brengen we in twee longitudinale COVID-19 patiënt cohorten de afweer in kaart. De samples zijn al verzameld, inclusief gezonde, en ziektecontroles. Door het meten van functionele afweer en circulerende eiwitprofielen in patiënten van verschillende leeftijden en met een zeer breed spectrum van ziekte-ernst ontwikkelen we een model van de onderliggende afweerrespons in verschillende fases van COVID-19. Daarnaast zullen we voorspellende biomarkers identificeren en valideren en inzicht geven in mogelijke targets voor interventie en optimale timing voor specifieke interventies.	24	15-07-2020	(10)(2b)	4. virus, immuniteit, immuunrespons en pathogenese	Zeer relevant-Zeer goed	1	1

3	50-56300-98-127	(10)(2e)	Amsterdam UMC - locatie AMC	ReCOVer: A randomized controlled trial testing the efficacy of cognitive behavioural therapy for preventing chronic postinfectious fatigue among patients diagnosed with COVID-19 disease	ONDERZOEKSVRAAG To investigate whether delivering timely **internet-based cognitive behavioural therapy** [iCBT], an evidence-based treatment for chronic fatigue, is effective in preventing the development of **post-COVID-19 chronic fatigue**. URGENTIE A substantial subgroup of COVID-19 patients is expected to develop post-COVID-19 chronic fatigue, i.e. severe fatigue persisting for more than 6 months with accompanying detrimental effects on patient functioning, quality of life and societal participation. Quickly gathering evidence on the efficacy of iCBT to prevent post-COVID-19 chronic fatigue and its possible consecutive implementation is a unique opportunity to help to alleviate the pandemic's negative impact on patient health and on the wider society. HYPOTHESE It is hypothesized that timely offering iCBT for fatigue, i.e. 3 to 6 months after COVID-19 diagnosis or hospital admission, will lead to a significant and clinically relevant reduction in fatigue (primary outcome) following the intervention (T1), will reduce the proportion of patients who progress to chronic fatigue at follow-up (T2) and foster patients' work ability, physical and social functioning as compared to care as usual. PLAN VAN AANPAK We propose a 2-arm Randomized Controlled Trail in which patients who have recovered from acute COVID-19 but suffer from ongoing severe and debilitating fatigue are randomized to either internet-based CBT or care as usual. The project will be conducted within 24 months. Primary outcome is patients' fatigue severity, as assessed with the CIS-fatigue at T1. A sample of 114 patients (57 in each arm) will provide sufficient power to identify clinical relevant differences in fatigue. Recruitment will be conducted within existing COVID-19 cohorts, among patients visiting outpatient clinics of participating hospitals, from referrals of general practitioners or self-referrals. Online delivery will allow offering CBT within the current preventive measures of social distancing.	24	30-07-2020	(10)(2b)	1a. behandeling	Zeer relevant-Goed	2	1

4	50-56300-98-128	(10)(2e)	Universitair Medisch Centrum Utrecht	BCG vaccination to minimise COVID-19 disease severity and duration	ONDERZOEKSVRAAG What is the **impact of BCG vaccination** compared to placebo vaccination on: 1) COVID-19 incidence, severity, and duration; 2) development and longevity of SARS-CoV-2-specific antibodies and on the immune system more generally; 3) the nasopharyngeal microbiome; and 4) participant-reported upper respiratory tract symptoms that were not due to COVID-19. URGENTIE We vaccinated healthcare workers in 9 Dutch hospitals at the start of the first epidemic wave, and plan to follow participants in 3 hospitals (UMCU, Radboud, and LUMC) at 12 and 24 weeks post-vaccination. We require funding to enable laboratory-confirmed outcome assessments now that testing materials and serology tests have become available. If beneficial, BCG vaccination could be implemented rapidly to protect key populations until SARS-CoV-2-specific vaccines become available. Because its effects are nonspecific, BCG vaccination could also serve as a first response in future pandemics caused by novel pathogens. HYPOTHESE Our primary hypothesis is that SARS-CoV-2 incidence will be similar in the two arms given the high infectiousness of the virus, but that disease severity and duration are reduced in the BCG arm. PLAN VAN AANPAK Vaccinations have been completed. Participants are reporting clinical data on an ongoing basis via a mobile phone app. SARS-CoV-2 RT-PCR testing was done at the time of symptom-reporting as part of routine hospital procedures; test results and stored nasopharyngeal swabs will be retrieved. Serum and saliva specimens will be collected at the 12- and 24-week post-vaccinations visits, and will be tested for IgG/IgA antibodies against SARS-CoV-2 and against all coronaviruses. The neutralising capacity of SARS-CoV-2 antibodies will be assessed in a subsample. Nasopharyngeal swabs and blood samples from participants who were exposed to BCG and SARS-CoV-2, BCG only, SARS-CoV-2 only, or neither will be assessed for parameters of trained innate immunity and the nasopharyngeal microbiome.	24	01-08-2020	(10)(2b)	4. virus, immuniteit, immuunrespons en pathogenese	Zeer relevant-Zeer goed	1	1

5	50-56300-98-148	(10)(2e)	Amsterdam UMC - locatie AMC	Therapeutic inhibition of excessive lung inflammation induced by anti-SARS-CoV-2 antibodies	RESEARCH QUESTION Severely ill COVID-19 patients often show **excessive lung inflammation** and acute respiratory distress syndrome leading to multiorgan failure and eventually death. Here, we will study the **underlying cause of these excessive inflammatory responses** and how to specifically counteract them. URGENCE Current treatment options for the devastating hyperinflammatory responses in COVID-19 patients are very limited. Since the development and distribution of a vaccine will take long (1-2 years), there is an urgent need for treatment of the most severely ill patients. HYPOTHESIS We hypothesize that the IgG antibodies that are generated against the Spike protein of CoV-2 cause excessive lung inflammation and tissue damage in the most severe cases of COVID-19. It has been shown that the virus leading to SARS, SARS-CoV, causes severe inflammation and lung injury through anti-Spike IgG antibodies, by converting wound-healing lung macrophages into very pro-inflammatory cells. Our preliminary data demonstrates that in COVID-19 patients anti-SARS-CoV-2 IgGs very similarly break the wound-healing phenotype of human lung macrophages and airway epithelium. We identified that it is not only caused by the early rise and high titer of anti-Spike IgGs, but also because the anti-Spike IgGs of severe patients are intrinsically more pathogenic. Moreover, our data demonstrate that we can specifically counteract this hyperinflammation, using the FDA/EMA-approved therapeutic small molecule inhibitor Fostamatinib. APPROACH We will (1) unravel how anti-SARS-CoV-2 IgGs drive excessive inflammation by human lung macrophages and airway epithelium, and (2) test small molecule inhibitors that can be repurposed to counteract this. Combined, we will provide proof-of-concept for novel treatments of the most severely ill COVID-19 patients.	12	01-08-2020	(10)(2b)	4. virus, immuniteit, immuunrespons en pathogenese	Zeer relevant-Zeer goed	1	1

6	50-56300-98-151	(10)(2e)	Amsterdam UMC - locatie AMC	Immunity against SARS-CoV-2 in immune-suppressed patients: increased risk of insufficient immunological memory or sufficient protection against re-infection?	Understanding of the **maintenance** of SARS-CoV-2-specific **immunity after primo-infection (SIAP) is pertinent to address the risk of re-infection**. However, it is unknown how long adaptive SIAP will last. This uncertainty is even more pressing for a large group of vulnerable immune-suppressed patients (ISP) who are at risk for severe disease when immunological memory is insufficient, as these patients may have less SIAP than healthy controls. In addition, there is a chance that the much-awaited national vaccination program against SARS-CoV-2 to protect the individual persons and to pursue herd immunity will be less effective in these patients, based on previous vaccinations against other pathogens. The objective of this study is to elucidate whether the course of SARS-CoV-2-specific immunity over time differs in ISP compared to healthy persons and whether the efficacy of SARS-CoV-2-targeted vaccination is reduced in these patients. We will thus provide valuable insights in the normal course of humoral and cellular immunity in healthy people and ISP, making the comparative results relevant for the whole society. To achieve this we will use the unique platform of our T2B consortium, a well-established close collaboration and infrastructure of 6 different academic hospitals, RIVM and Sanquin Blood Supply Foundation. We will build on several clinical studies already initiated by our clinical T2B partners to perform in-depth analysis of the humoral and cellular infection-induced and vaccine-induced immunity against SARS-CoV-2. In this prospective observational study we will collect longitudinal clinical data and samples that will be used to stratify for determining the vaccination efficacy, in ISP and healthy controls, with and without previous SARS-CoV-2 infection. Our data aim to provide guidance on medication adjustments to optimize SIAP and vaccination efficacy and to specify need for social distancing measures, not only for the vulnerable, but for the whole community.	24	01-08-2020	(10)(2b)	4. virus, immuniteit, immuunrespons en pathogenese	Zeer relevant-Zeer goed	1	1

7	50-56300-98-187	(10)(2e)	Nationale Intensive Care Evaluatie	Identification of COVID-19 patients with high Risk of mortality at ICU admiSsion – IRIS-study	Het doel van dit project is **patiënten kenmerken bij IC-opname** te identificeren die geassocieerd zijn met ongewenste uitkomst, t.w., extreem lange behandelduur en **sterfte** (IC en ziekenhuissterfte, als ook 90, 180 dagen sterfte). [URGENTIE] Ondanks dat de piek van COVID-19 patiënten op de IC achter ons ligt, worden dagelijks nog nieuwe COVID-19 patiënten opgenomen op de Nederlandse IC's. De zorg voor niet-COVID-19 patiënten start ook weer op, waardoor de druk op de IC capaciteit hoog blijft zeker bij een volgende golf COVID-19 infecties. Het is voor triage uitermate belangrijk om patiënten te identificeren waarvoor IC opname mogelijk niet van toegevoegde waarde is omdat zij een zeer hoge sterftekans of extreem lange behandelduur hebben. Deze prognostische informatie is belangrijk bij het 'samen beslissen'-proces waarin intensivisten en andere specialisten samen met de patiënt en naasten een afweging over IC-opname maken. Bestaande triage protocollen werden onder druk van een mogelijk tekort aan bedden aangescherpt o.b.v. expertkennis en zonder objectieve data te gebruiken m.b.t. uitkomsten van IC patiënten met en zonder COVID-19. [HYPOTHESE] Inzicht in determinanten voor ongewenste uitkomst en identificatie van hoog-risico patiënten ondersteunen en verbeteren het triage proces. [PLAN VAN AANPAK] In deze observationele studie gebruiken we drie reeds beschikbare en continue geüpdatet datasets: de NICE registratie, CovidPredict.org dataset en Vektis. Tezamen omvat dit alle IC-patiënten in Nederland, inclusief gedetailleerde en lange termijn uitkomstinformatie van COVID-19 patiënten. We passen statistische en machine learning technieken toe om prognostische modellen voor individuele patiënten te ontwikkelen en hoog-risico groepen te identificeren. Hoe deze predictiemodellen in de praktijk gebruikt kunnen worden t.b.v. 'samen beslissen', wordt geëvalueerd met intensivisten, andere specialisten en een panel met ex-IC patiënten met en zonder COVID-19.	24	27-07-2020	(10)(2b)	3. risicoanalyse en prognostiek	Zeer relevant-Zeer goed	1	1

8	50-56300-98-203	(10)(2e)	Sanquin Research	Establishment and duration of protective immunity against SARS-CoV-2, in relation to severity of SARS-CoV-2 infection.	ONDERZOEKSVRAAG In de meeste mensen is na een COVID-19 ziekte een immuunrespons tegen SARS-CoV-2 aan te tonen. Hoe lang deze immuunrespons blijft bestaan en of het een volledige of gedeeltelijke bescherming zal geven tegen een re-infectie is nog niet bekend. URGENTIE **Inzicht in de duur en de kwaliteit van de specifieke immuniteit, met name na infecties met nauwelijks of geen symptomen, is cruciaal voor de epidemiologische modellen en voor de "open-up" maatregelen.** HYPOTHESE Het is te verwachten dat de kwaliteit en duur van de specifieke immuniteit verschilt tussen mensen en deels samenhangt met de ernst van de doorgemaakte ziekte. PLAN VAN AANPAK Sanquin kan deze onderzoeken uitvoeren door gebruik te maken van regelmatige bloedafnames van >300.000 bloeddonoren, van wie van elke afname plasma gedurende 2 jaar wordt bewaard. Bij de start van het project in juli zullen wij 500 anti-SARS-CoV-2-positieve donoren hebben geïdentificeerd die verschillende mate van COVID-19 ziekte hebben doorgemaakt (asymptomatisch, milde, ernstige en kritische ziekte). In deze groepen zullen we gedurende 2 jaar het verloop van SARS-CoV2 antistoffen, en (in een subgroep) T- en B-celresponsen analyseren. Alle assays om dit onderzoek uit te voeren hebben wij al ontwikkeld. Dit onderzoek zal inzicht geven in de dynamiek van de immuunrespons in relatie tot de ernst van de doorgemaakte ziekte. In hoeverre deze immuunrespons beschermend is tegen re-infectie zullen wij in een prospectief cohort van 2000 geseroconverteerde donors vervolgen. Daarnaast zullen wij van alle personen die vanaf september 2020 COVID19-PCR positief getest worden, nagaan in hoeverre zij bloeddonor zijn, en dan retrospectief het opgeslagen plasma op seroconversie testen. VERWACHTE RESULTATEN Dit onderzoek zal inzicht geven in de duur en kwaliteit van SARS-CoV-2-specifieke immuniteit, en mogelijk tevens leiden tot biomarkers die de mate van bescherming tegen het virus voorspellen.	24	09-07-2020	(10)(2b)	4. virus, immuniteit, immuunrespons en pathogenese	Zeer relevant-Zeer goed	1	1
9	50-56300-98-255	(10)(2e)	Leids Universitair Medisch Centrum	COVID-19 and ischemic stroke - How to tame a dozing monster	COVID-19 pneumonia is complicated by a high risk of thrombotic complications, occurring with a cumulative incidence of 49% in intensive care unit (ICU) patients. These thrombotic complications are strongly associated with poor clinical outcome and death. Pulmonary embolism is the most common complication, but an emerging problem is the **increase in number of reported ischemic strokes of currently unknown magnitude and impact**. Our hypothesis is that the ischemic stroke is either caused by intensive coagulation-induced local thrombosis and intracranial vessel wall inflammation, and/or the result of a paradoxical embolism through a patent foramen ovale. In three work packages we will: 1) get an accurate estimate of the incidence of symptomatic ischemic stroke in all COVID-19 ICU patients (admitted to 15 Dutch hospitals as well as the prevalence of silent brain lesions as detected by MRI in a random sample of COVID-19 ICU survivors (n=100); 2) unravel its causes and impact on the basis of imaging studies, biomaterial and measures of functional outcomes, anxiety and depression; and 3) establish the optimal prevention of this unwanted thrombotic complication in COVID-19 patients by comparing incidences of ischemic stroke under different thrombosis prophylaxis strategies. Our multidisciplinary team, with complementary key expertise in all relevant aspects of the field, who were the first to report on the very high risk of thrombotic COVID-19 complications, is very capable of rapidly addressing this urgent problem of ischemic stroke in COVID-19.	24	15-07-2020	(10)(2b)	1a. behandeling	Zeer relevant-Zeer goed	1	1

10	50-56300-98-257	(10)(2e)	Maastricht Universitair Medisch Centrum+	WikiPathways as a platform for COVID-19 biological pathway models	Research question: The pandemic coronavirus disease 2019 (COVID-19), caused by the **SARS-CoV-2 virus**, is causing far-reaching problems worldwide. We aim to understand differences in COVID-19 severity from asymptomatic to deadly cases, what the **underlying molecular mechanisms** are that contribute to these differences and how appropriate treatment strategies can be discovered. Urgency: It is key to have comprehensive molecular maps of the virus-host interactions, host immune response and other affected processes to be able to predict disease progression and develop stratified treatment strategies. While this pandemic brought experts together from around the world in the COVID-19 Disease Map project, it also highlighted missing features in software tools and data analysis. Hypothesis: WikiPathways, a popular knowledge platform founded and co-maintained by Maastricht University, is central to allow the community to curate up-to-date molecular pathway models with captured provenance and connects to a scala of analysis tools which enable us to identify underlying molecular reasons for diversity in disease progression, support the drug development process for the different stages of COVID-19 and provide a knowledge resource for scientific and educational purposes. Action plan: We identified three aspects to support the fight against COVID-19 and future outbreaks: (1) Extension of WikiPathways as a resource for COVID-19 pathway models and to share and collaborate on all COVID-19 research. (2) Advancements of the software tools to allow more accurate representation of the current state of knowledge on relevant COVID-19 molecular processes in machine-readable pathway models. (3) To react to the constant influx of new knowledge, experiments and clinical data, we will develop automated, continuously updated data analysis pipelines to study the link between virus-host interactions, downstream processes and effects of different phenotypes to better predict disease progression.	24	30-07-2020	(10)(2b)	4. virus, immuniteit, immuunrespons en pathogenese	Zeer relevant-Zeer goed	1	1

11	50-56300-98-261	(10)(2e)	Erasmus MC	Identifying pathogenesis of COVID-19 pathology in the Dutch population and unravelling differences in pathogenetic mechanisms in high- and low-risk groups.	COVID-19 wordt gekenmerkt door een opvallende variatie in uiting en ernst van ziekte tussen patiënten, en is sterk tijdsafhankelijk. Het is tot dusverre onvoldoende duidelijk welke weefselreacties en pathogenetische processen aan deze variatie ten grondslag liggen. Dit beperkt zowel de ontwikkeling van specifieke diagnostische middelen als ook van gepersonaliseerde therapie voor individuele patiënten. Studie van het weefsel van door COVID-19 betroffen patiënten kan in dit opzicht verhelderend zijn, omdat in het weefsel een onderscheid kan worden gemaakt tussen direct door het virus veroorzaakte beschadiging, auto-immuniteit en de inmiddels vanuit de kliniek bekende stollingsfenomenen, die mogelijk allen een andere behandeling behoeven. Wij stellen voor om het in Nederland **beschikbare en geschikte weefsel** voornamelijk van obducties, maar ook van resectiepreparaten, en zo mogelijk biopten van met SARS-CoV-2 geïnfecteerde patiënten te organiseren in een **virtuele biobank** waarin deze vragen kunnen worden gesteld en beantwoord. Dit gebeurt op initiatief van het Dutch COVID-19 Pathology Consortium, dat reeds enkele weken actief is op het gebied van de informatievoorziening t.a.v. van COVID-19 in de pathologiepraktijk. Specifieke vragen die worden gesteld zullen betrekking hebben op 1) immuunreacties in het weefsel die voorspellen hoe de ziekte zich zal gaan ontwikkelen , wat de onderliggende pathogenetische mechanismen zijn en wat een mogelijke behandeling hiervoor kan zijn; 2) de relatieve aanwezigheid van voor COVID-19 belangrijke eiwitten in het weefsel, specifiek in relatie tot bekende risicogroepen; 3) de betrokkenheid van het centraal zenuwstelsel bij COVID-19; en 4) de lange termijn effecten van COVID-19 op het weefsel van overlevers van de acute fase van de ziekte. Deze data zullen naar verwachting leiden tot verbeterd begrip van de ontstaansgeschiedenis en variabiliteit van deze ziekte en leiden tot gepersonaliseerde behandeling, en derhalve hopelijk overleving.	24	13-07-2020	(10)(2b)	4. virus, immuniteit, immuunrespons en pathogenese	Zeer relevant-Zeer goed	1	1
12	50-56300-98-262	(10)(2e)	Spaarne Gasthuis	SARSLIVA and utility of saliva in diagnosis for wide scale testing, including viral and SARS-CoV-2 antibody detection in pre- and asymptomatic persons and follow-up of infections in COVID-19 patient; a house hold study	Saliva is an obvious source for SARS-CoV-2 detection. The virus's ability to infect and actively reproduce in the upper respiratory tract was shown last month by Wendtner et al, who reported on experiments that virus from the throats of nine people with COVID-19 could be cultured, showing that the virus is actively reproducing and infectious there. Saliva gland ducts also express the ACE2 receptor for the virus in rhesus macaques. High viral loads were already present in the saliva of COVID-19 patients at the onset of disease, which could account for the fast-spreading nature of this epidemic. Also, SARS-CoV-2 infection appears to shed viral particles from the throat into saliva even before symptoms start. Pre-symptomatic transmission was estimated to contribute to up to 60% of COVID-19 cases in China. Saliva may therefore be the obvious tool to detect a-symptomatic and pre-symptomatic individuals before actual symptoms present. **When saliva proves to detect low viral loads, COVID-19 patients, who may remain symptomatic for weeks to months, can be followed to see whether they still spread the virus.** To validate saliva for these purposes, we propose a study where we 1. Follow confirmed COVID-19 patients with home self -sampling of saliva for 4-6 weeks and at least two weeks after symptoms have stopped. 2. Follow household members for 4-6 weeks to detect potentially pre-symptomatic and a-symptomatic SARS-CoV-2 infected individuals. 3. Follow emerging IgA and IgG anti-SARS-COV-2 antibodies in saliva over time 4. Detect other respiratory viruses present in relation to symptoms of infection. The study is a close collaboration between the Spaarne hospital, Streeklaboratorium Haarlem, and the RIVM where viral diagnostics will be performed and mucosal SARS-CoV-2 antibody emergence. If we can use saliva for early detection, and at low viral loads in the course of infection, containment of viral spread is made easier and allows for improved policies in this pandemic.	16	10-04-2020	(10)(2b)	2. diagnostiek besmetting	Zeer relevant-Zeer goed	1	1

13	50-56300-98-265	(10)(2e)	Amsterdam UMC - locatie AMC	A virus-free high-throughput platform for studying coronavirus replication inhibitors	The COVID-19 crisis demonstrates our under-preparedness for the emergence of novel pandemic viruses. Because vaccine development is time consuming, antivirals are our fastest defense against new viruses. However, current SARS-CoV-2 antiviral screens require live virus experiments in a BSL3 facility. **Here we propose a screening method for inhibitors of SARS-CoV-2 that can be used in a standard tissue culture setting**. This method relies on the expression of the SARS-CoV-2 replicase proteins that are responsible for viral genome replication and transcription. A viral genome mimic that results in the expression of luciferase or GFP will be used as a reporter for the activity of SARS-CoV-2 replicase activity, which provides an easy, inexpensive and high-throughput read-out. We will us an available Antiviral Compound Library to start our screens. Potential hits will be validated using a cell-free in vitro assay and virus infection experiments using both conventional lung cell lines as well as the differentiated primary airway-epithelial culture system, a highly relevant ex vivo model established within our project team, limiting the need for animal experiments. Further screens will be performed together with current international industrial partners In addition to screening for novel or improved drug candidates, the platform can be used for studies into how SARS-CoV-2 induces activation of the innate immune system, which plays an important role in COVID-19 disease outcome. Overall, this system will advance our antiviral strategies and understanding of COVID-19.	12	01-08-2020	(10)(2b)	4. virus, immuniteit, immuunrespons en pathogenese	Zeer relevant-Zeer goed	1	1
14	50-56300-98-283	(10)(2e)	Sanquin Bloedvoorziening	Altered IgG fucosylation driving pathologies in COVID-19: Relevance for diagnosis and therapeutics	IgG antibodies are crucial for protection against invading pathogens. A highly conserved N-linked glycan within the IgG-Fc-tail, essential for IgG function, shows variable composition in humans. Afucosylated IgG variants are already used in anti-cancer therapeutic antibodies due to elevated binding and killing activity through Fc receptors (Fc?RIIIa). Here, we show that afucosylated IgG which are of minor abundance in humans (~6% of total IgG) are specifically formed against surface epitopes of enveloped viruses, including the S-protein of COVID-19. Furthermore, a large gap segregates intensive care patients from convalescent blood bank donors with mild symptoms and resolving symptoms unaided. **This strongly suggests altered anti-COVID-19 IgG-glycosylation to be responsible for the aggravated immune response and being for morbidity** and mortality. This mechanism of antibody-dependent enhancement of disease has been described by us earlier in pregnancy responses, and for Dengue virus by others, another enveloped virus with typical clinical exacerbation of immune responses leading to strong morbidity and mortality due to overactive antibody-mediated immune-responses. Here we will determine the full clinical course in hospitalized patients with relationship to outcome, link this to functional readouts, develop diagnostic tools, that can be used to **optimize convalescent antibody treatment (Plasma or IVIg)** of both health workers and patients.	24	30-07-2020	(10)(2b)	4. virus, immuniteit, immuunrespons en pathogenese	Zeer relevant-Zeer goed	1	1

15	50-56300-98-430	(10)(2e)	University of Twente	Measuring, understanding & reducing respiratory **droplet spreading**	To mitigate the Covid-19 pandemic, it is key to slow down the spreading of the deadly Corona virus. This spreading occurs through virus-laden droplets expelled at sneezing, coughing, singing, shouting, screaming, speaking, or even breathing. Unfortunately, surprisingly little is known on the characteristics and fate of such droplets. Such knowledge however is vital to reduce contamination and the reproduction factor R of Covid-19. Key questions are all intimately related to fluid dynamics and flow physics: How many droplets are actually expelled at above events? What is their initial size distribution? What is the lifetime of these respiratory droplets and how does it depend on humidity and temperature? How do the aerosol droplets distribute, in particular indoors, and what are ventilation concepts to get rid of them? How and to what degree do face masks reduce the input of the respiratory droplets into the environment? The answers to all of these questions are key to reduce the further spreading of Covid-19. Up to now, without sufficient answers to above questions, the authorities attempt to reduce the spreading with the so-called 'distance rule'. The distance between people should not be less than one and a half meters. However, this rule is based on a theory from the 1930 which long is outdated. The objective of the proposed work is to measure and understand the release and spreading of respiratory droplets through sneezing, coughing, singing, shouting, screaming, speaking, and breathing. We want to elucidate the flow physics of these droplets, in order to be able to take suitable countermeasures against the spread of the corona virus and thus to reduce the reproduction factor R. In particular, we would like to test how much face masks can reduce the release of respiratory droplets into the (indoor) environment. Our results will have an immediate impact on the regulations on where and when to use face masks and what quality requirements they must fulfill.	24	01-08-2020	(10)(2b)	4. virus, immuniteit, immuunrespons en pathogenese	Zeer relevant-Zeer goed	1	1

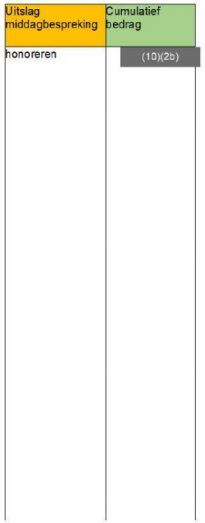
16	50-56300-98-102	(10)(2e)	Universitair Medisch Centrum Groningen	Prospective **cohort study of non-hospitalised COVID-19 patients**: determining length of isolation and patient clinical development at home (COVID-HOME study)	URGENCE Guidelines on COVID-19 management are developed as we learn from this pandemic. Most research is on hospitalised patients but, the impact on non-hospitalised ones, their clinical evolution, infectiousness, spreading routes and isolation length is not well understood. Studies are scarce, have small sample sizes and contradictory results. A better understanding is needed to properly manage patients isolated at home and improve biosafety guidelines. RESEARCH QUESTIONS 1. To measure the duration and routes of viral shedding, genetic diversity, and development of immunity of non-hospitalised COVID-19 individuals to improve guidelines for biosafety and patient isolation 2. To establish guidelines for the management of COVID-19 patients at home, including early detection of clinical and laboratory predicting factors for severity HYPOTHESIS 1. We expect viral shedding to last longer than 14 days (and differ by specimen) but virus viability to be shorter. They will differ by age and depend on immunity. 2. We expect to predict mild versus more severe clinical evolution using clinical and (changes in) laboratory parameters APPROACH PLAN A prospective longitudinal study of non-hospitalised COVID-19 patients began on 19/03/2020. We expect to enrol 200 individuals during 9 months (including 4 months before funds granted). Consenting people are visited weekly at home to obtain clinical data, a blood sample for laboratory parameters; and a nasopharyngeal/throat swab plus urine, stool and sperm or vaginal secretion to test for SARS-CoV-2 by RT-PCR. Blood samples are tested for key parameters related to disease severity. Patients are followed on days 7, 14 and 21 after confirmed infection, and if still PCR positive, invited to continue weekly sampling until negative. Household members of infected individuals are invited to join the study. We hope to obtain funds for a further 7 months to perform further sampling, serology, viral genotyping, viral culture and data analysis.	11	19-03-2020	(10)(2b)	3. risicoanalyse en prognostiek	Zeer relevant-Goed	2	2

17	50-56300-98-140	(10)(2e)	University Medical Center Groningen	**Obesity as an amplifier of inflammation and organ injury** in SARS-CoV-2 infected patients: prognostic potential and therapeutic target	The clinical course of COVID-19 infection varies from mild symptoms to severe respiratory failure which is poorly understood. We observed that the majority of COVID-19 patients admitted to our ICU with respiratory failure had central obesity. Recently, COVID-19 mortality was shown to be associated with obesity severity independent of age, sex, diabetes and hypertension. Excess adipose tissue and adipose-tissue secreted mediators must therefore play an important role in the progression toward respiratory failure in patients with COVID-19. Within the first 6 months of this project, we will analyse serial plasma samples from patients with mild symptoms and severe lung failure in order to determine whether adipose-tissue mediators are increased in COVID-19 patients identifying their potential as stratification markers. Moreover, unique organ biopsies from COVID-19 patients will enable us to swiftly unravel the as yet unknown pathophysiological mechanisms of organ failure which we will relate to plasma adipose-tissue mediators and biomarkers determining their prognostic potential. Adipose-tissue derived mediators are generally proinflammatory and prothrombotic which, in combination with COVID-19 infection, might amplify the thrombotic events observed in severe COVID-19 patients. We will therefore investigate how these adipose-tissue derived mediators in combination with the COVID-19 virus disrupt the integrity of the inner lining of blood vessels underlying aberrant organ microvascular responses. These studies are urgently needed in order to understand why obese individuals have severe disease manifestations, and to determine whether lipid-lowering interventions will reduce the number of patients developing respiratory failure. Our multidisciplinary team of experienced clinicians and researchers are dedicated to finding solutions for COVID-19 patients in order to reduce mortality, and alleviate the immense strain on medical staff in intensive care units worldwide.	24	15-07-2020	(10)(2b)	3. risicoanalyse en prognostiek	Zeer relevant-Goed	2	2
18	50-56300-98-145	(10)(2e)	Amsterdam UMC - locatie VUmc	The COUNTER-COVID study: Oral imatinib to reverse pulmonary vascular leak and disease burden in COVID-19	The COVID-19 pandemic has an unprecedented impact on global health, carrying a high burden for the individual patient and at society level. An important driver of this burden is hypoxemic respiratory failure (described as 'severe' COVID19), resulting from damage to the alveolocapillary barrier, excessive vascular leakage and pulmonary edema. Current management is supportive, and there is still no direct therapy available to treat severe Covid19. In the last decade we and other groups have shown that the clinically available Abl kinase inhibitor imatinib protects vascular integrity and can be used to treat vascular leak and pulmonary edema. Of note, imatinib was also shown to have antiviral properties, among others in SARS and MERS. Based on these properties we hypothesize that **imatinib can reduce disease burden and health resource consumption in patients with severe Covid19**. To test this hypothesis we initiated a randomized, placebo-controlled clinical trial to test a 10-day course of **oral imatinib in patients with severe Covid19**, aiming to reduce the need for oxygen and ventilatory support. This trial has obtained IRB approval and has thus far included >80patients in 10 centers in the Netherlands, thereby being one of the largest investigator-driven Covid19 intervention studies in the Netherlands. With the current proposal we aim to further increase the network of participating centers to 20 centers, to sustain the inclusion rate and **finish the trial end 2020**. As national referral center for pulmonary vascular disease, we will use an established large network of referring non-academic hospitals to realize this. If proven effective in this trial, it can be integrated swiftly in Covid19 management, also in low-income countries given the fact that oral imatinib is generically available. Future perspectives include application of imatinib beyond Covid19, for other diseases characterized by pulmonary vascular leak.	24	01-04-2020	(10)(2b)	RCT REMAP-CAP	Zeer relevant-Goed	2	2

19	50-56300-98-158	(10)(2e)	Radboudumc	A phase-2-study, pivotal for clinical development of **lanadelumab** for treatment of COVID-19 to prevent ARDS	Within the current COVID-19 Public Health Emergency of International Concern, understanding the effectiveness of treatment strategies in patients with proven infection that focus on reduction of virus-induced clinical complications is urgently needed. Patients with COVID-19 can present with pulmonary edema early in disease. We have proposed that this is due to a local vascular problem because of activation of bradykinin 1 receptor (B1R) and B2R on endothelial cells in the lungs, with this angioedema being kinin-dependent. We have already conducted a proof of concept study with B2R antagonist icatibant, providing evidence for the involvement of the kallikrein-kinin system. However, icatibant has some shortcomings. Now, we hypothesize that targeting the kallikrein-kinin system by inhibiting plasma kallikrein with lanadelumab has the potential to prevent acute respiratory distress syndrome in patients hospitalized with symptomatic COVID-19. We will conduct a proof of concept study to investigate whether intravenous lanadelumab can lower oxygen need and prevents resurgence of oxygen need during COVID-19 infection and is safe in COVID-19 patients. Moreover, we will study the effects of plasma kallikrein inhibition on immunological and kinin specific signatures and perform PK/PD of intravenous lanademulab in COVID-19 patients. Finally, we will provide a rationale and data on lanadelumab to implement this strategy in REMAP-CAP globally. This study must be considered as an experimental domain for REMAP-CAP. If we deliver the proof of concept of lanadelumab, the applicants of this proposal can introduce the strategy in REMAP-CAP globally.	12	01-07-2020	(10)(2b)	RCT REMAP-CAP	Zeer relevant-Goed	2	2
20	50-56300-98-234	(10)(2e)	Erasmus MC	**BTK inhibitie** als therapie voor hyper-inflammatoir syndroom in COVID-19 patiënten	Onderzoeksvraag: Welke moleculaire mechanismen zijn verantwoordelijk voor het therapeutische effect van Bruton's tyrosine kinase (BTK) inhibitie bij COVID-19 patiënten? Urgentie: SARS-CoV-2 infectie leidt bij ~5% van de patiënten tot IC opname door hyperinflammatie in de longen. Deze studie beoogt te onderzoeken hoe BTK-inhibitie een zeer ernstig klinisch beloop met langdurige IC opname kan voorkomen tijdens de acute fase van COVID-19 in het ziekenhuis en mogelijk ook verpleeghuizen. Hypothese: Onze hypothese is dat BTK inhibitie in COVID-19 patiënten hyperinflammatie en IC opname kan voorkomen en chronische longschade en mortaliteit kan verminderen door activatie en influx van monocyten in longen te remmen. Dit is gebaseerd op het volgende: - BTK is een intracellulair signaleringsmolecuul dat cruciaal is voor de activatie en productie van pro-inflammatoire cytokines door B cellen, monocyten, dendritische cellen (DCs) en neutrofielen. Juist deze cellen en cytokines zijn ontregeld in hyperinflammatie in COVID-19 patiënten. - COVID-19 symptomen lijken aanzienlijk verminderd in XLA patiënten (die een aangeboren defect hebben in het BTK gen) en in patiënten die met BTK inhibitors worden behandeld. - BTK inhibitors hebben beperkte bijwerkingen en hebben geen effecten op T en NK cellen die nodig zijn voor virusklaring. Plan van aanpak: Door aansluiting bij een internationale prospectieve fase III studie met de BTK small molecule inhibitor **acalabrutinib** onderzoeken we of deze behandeling leidt tot versneld herstel bij COVID-19 patiënten, met de volgende doelstellingen: 1. Identificatie van de rol van BTK en de genoom-brede effecten van BTK remmers in geactiveerde monocyten, macrofagen, DCs en B cellen. 2. Ontrafelen van de moleculaire en cellulaire mechanismen van de effecten van behandeling met BTK remmers op diverse immuun cellen bij COVID-19 patiënten. 3. Identificatie van correlaties tussen moleculaire effecten van BTK remming en klinische responsen bij COVID-19	24	30-07-2020	(10)(2b)	1b. behandeling	Zeer relevant-Goed	2	2

21	50-56300-98-269	Dr. (10)(2e)	Erasmus MC	**Clinical prediction models for COVID-19**: development, international validation and use	Approximately 20% of patients hospitalized with covid-19 require intensive care (ICU). Guiding clinicians and patients facing decisions on ICU admission requires an accurate forecast based on individual characteristics. Clinical prediction models provide such forecasts of ICU admission or mortality. A number of clinical prediction models appeared in the literature, but none were developed using high methodological rigor or were extemally validated. The aim of this study is to: 1) develop clinical prediction models that impact clinical care through guiding treatment decisions by predicting: i) need for ICU admission in patients hospitalized with covid-19; ii) mortality in hospitalized patients; iii) mortality in ICU patients; 2) assess the validity and generalizability of these models across different international datasets; 3) engage stakeholders to develop guidance for best use of these clinical prediction models in the care of covid-19 patients. We will retrospectively include over 4000 consecutive covid-19 patients presenting to the emergency departments of 10 Dutch hospitals. We will consider a broad set of predictors based on literature and expert knowledge that are routinely measured in the emergency department and use a competing risk framework with cox proportional hazards regression. For validation we have access to USA databases including over 10.000 patients. We will convene a multi-stakeholder panel including patients; relatives; hospitals physicians; GPs; nurses; and ethicists to create a cycle of continual stakeholder feedback that results in clinical decision support tools that are more useful when implemented in clinical care. The results of this project will improve care for covid patients since i)we develop transparent models with predictors that are available in clinical practice, ii)use state of the art methods, iii)perform multicenter international validation, iv)engage stakeholders, and v)the first models will be available within 3 months.	12	01-07-2020	(10)(2b)	3. risicoanalyse en prognostiek	Zeer relevant-Goed	2	2

22	50-56300-98-276	(10)(2e)	Netherlands Heart Institute	the PRAETORIAN-COVID study: A double-blind, placebocontrolled randomized clinical trial with valsartan for PRevention of Acute rEspiraTORy distress syndrome in hospitAlized patieNts with SARS-COV-2 Infection Disease	ONDERZOEKSVRAAG De SARS-CoV-2 pandemie veroorzaakt een hoge morbiditeit en mortaliteit doordat een SARS-CoV-2 infectie gecompliceerd kan gaan met het acute respiratory distress syndrome (ARDS).Het renine-angiotensine-systeem(RAS), een bekende cardiovasculaire cascade, blijkt ook een rol te spelen bij de ontwikkeling van ARDS. Angiotensine-II (ANG-II) en het ACE2 enzyme spelen een belangrijke rol in deze cascade. Het SARS-CoV-2 virus verbruikt ACE2 waardoor er minder ACE2 activiteit is. Deze verlaging in ACE2 activiteit en ophoping van ANG-II kan uiteindelijk tot ARDS leiden. Er zijn voldoende observationele en mechanistische data die suggereren dat **Angiotensine Receptor Blokkers (ARBs)** de ontwikkeling van een ARDS beeld kunnen remmen. Het onderzoeken van de rol van ARBs in de preventie van ARDS is van belang omdat: 1) ARBs wereldwijd op grote schaal beschikbaar zijn 2) ARBs slechts weinig bijwerkingen hebben die goed gekend zijn 3) ARBs goedkoop zijn (nl ca. 20 cent per dag). URGENTIE Gezien de discussie in de literatuur, de ernst van het ziekteteeld en de potentiele werking van ARBs is er een hoge urgentie om het nut van ARBs in SARS-CoV-2 te onderzoeken.Een positief profylactisch effect leidt niet alleen tot een verlaging van ziektelast en vermindering in zorgdruk maar is ook zeer snel kosteneffectief doordat minder patienten IC-verpleegbehoeftig worden, er minder exposure is voor personeel en minder verbruik van barrière-materiaal. HYPOTHESE De hypothese is dat angiotensine receptor blokkers de ontwikkeling van ARDS in gehospitaliseerde SARS-CoV-2 geïnfecteerde patiënten kunnen voorkomen. PLAN VAN AANPAK Een dubbelblinde, placebo-gecontroleerde 1:1 gerandomiseerde klinische internationale studie binnen het REMAP-CAP consortium om het effect van valsartan bij 651 volwassen gehospitaliseerde SARS-CoV-2 patiënten op het optreden van een primair endpoint (IC-opname, mechanische ventilatie of overlijden) binnen 14 dagen te onderzoeken.	24	7/1/2020	(10)(2b)	RCT REMAP-CAP	Zeer relevant-Zeer goed	1	1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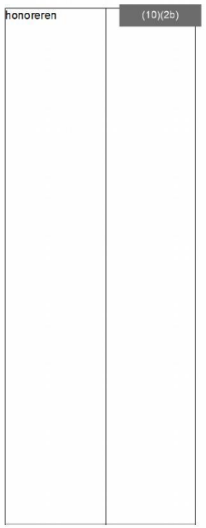
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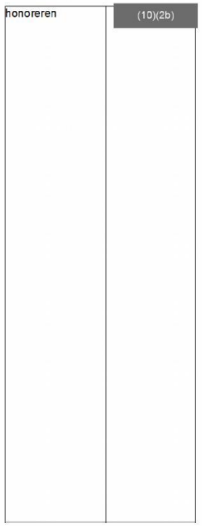
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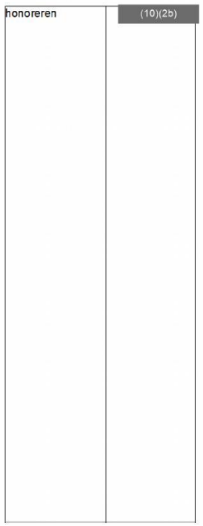
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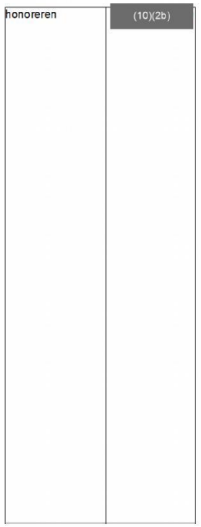
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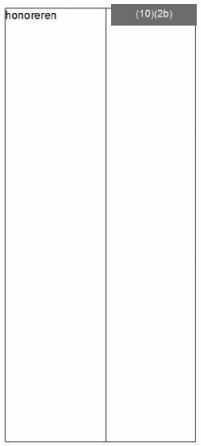
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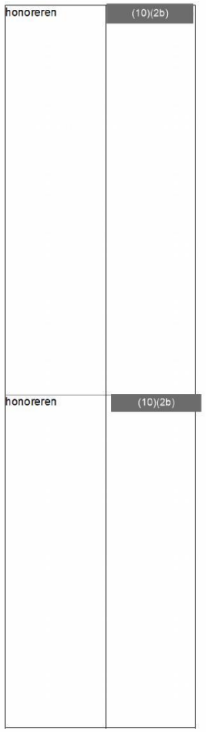
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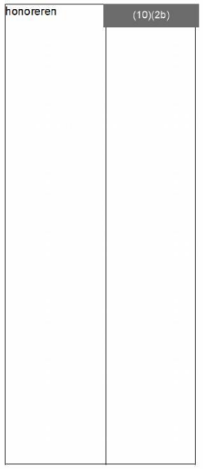
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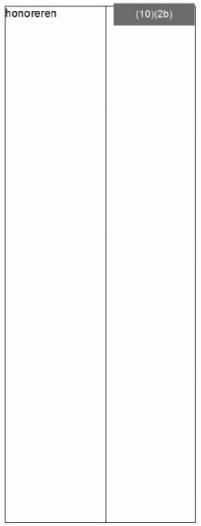
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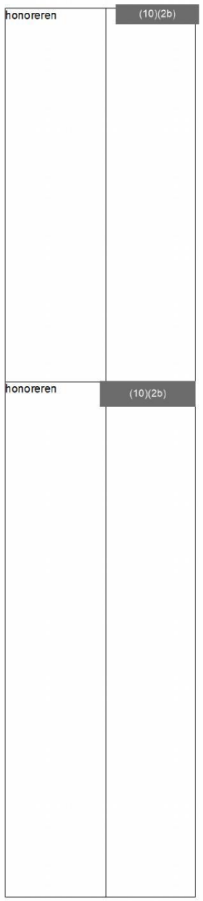
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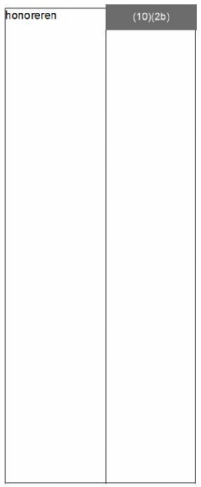
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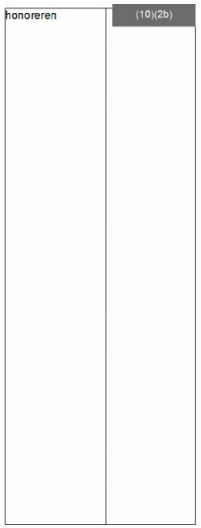
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