2011..... this article can't be found anywhere now !!!
This amazing lady kept it all these years

Share the arse out of this ❤️❤️❤️

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4 Page Special! Pages 13-16

Depopulation Through Forced Vaccination: *The Zero Carbon Solution!*

By Rachel Windeer

Image Courtesy of www.deesillustration.com

On April 26th, the Irish Independent published an article titled 'Concern for Children's Health as Parents ignoring vaccines'. Edel Kennedy, you should be ashamed of yourself! This is nothing less than an attempt by government, through their puppets in the media, to remove the rights of parents to determine the life choices of their offspring and removes any doubt that we now live in a dictatorship.

This is an OUTRAGEOUS insult to every parent in the country who has the common sense to research the efficacy of vaccines themselves by simply looking at the historical record rather than trust politicians whose lies in the media, including those perpetrated by the Dept. of Health under Mary Harney regarding the farce of 'swine flu' and the dangerous myth of HPV vaccination, have led the country into the abyss of utter poverty and sold the country into the communist grasp of European bureaucrats whose sole aim is the destruction of every member nation's sovereignty leaving them clutching at the bailout begging bowl of the IMF.

Vaccines are a fraud; pure and simple! The historical record PROVES this for anyone with a little patience and the courage to investigate the FACTS for themselves, and it does take courage, especially for those in the medical profession whose careers will be at risk if they dare expose this danger to our children. It also shatters their illusions that they're part of an organisation which is far from beneficial to those they believe they're protecting from illness.

However, their hypocratic oath should compel them to investigate such wild claims put out by pharmaceutical giants and their drug dealer sales representatives instead of taking the word of an industry well known as being utterly corrupt and ruthless in its business practices.

The Irish haemophiliac scandal, where patients were knowingly infected with HIV through contaminated blood products should be enough to convince anyone of Big Pharma's murderous intent.

This brings us to the real reasons for vaccinations. I'm not even going to prove to readers that they don't work. I'll simply urge you to look up the historical record. One simple example is the demise of measles.

The measles death rate had declined by 98% from 1915-1958 prior to any vaccination being introduced. In 1988 and 1989, 69% and 89% for measles cases in American school-aged children had been vaccinated! In 1995 56% of ALL measles cases in America were vaccinated.

These figures come from medical journals.

Those 3 simple examples PROVE that unvaccinated children are less likely to contract measles, and that the vaccine

Continued on page 10 >>

10 Facts That Prove The Bin Laden Fable Is a Contrived

PARENTS, TAXPAYERS AND ALL CONCERNED CITIZENS SHOULD BEWARE THE HIDDEN TRAPS IN THE *CHILDREN'S REFERENDUM.*
The Government has promised to put a Referendum on Children's Rights to the people later this year to amend the Constitution in order to give the State increased power over our children. **VOTE NO!!**
By Kathy Sinnot - ***Page 3***

OPEN ACCESS Freely available online

PLoS one

Immunization with SARS Coronavirus Vaccines Leads to Pulmonary Immunopathology on Challenge with the SARS Virus

Chien-Te Tseng[1,2], Elena Sbrana[1], Naoko Iwata-Yoshikawa[1,2], Patrick C. Newman[1], Tania Garron[1], Robert L. Atmar[3,4], Clarence J. Peters[1,2], Robert B. Couch[3,4]*

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Abstract

Background: Severe acute respiratory syndrome (SARS) emerged in China in 2002 and spread to other countries before brought under control. Because of a concern for reemergence or a deliberate release of the SARS coronavirus, vaccine development was initiated. Evaluations of an inactivated whole virus vaccine in ferrets and nonhuman primates and a virus-like-particle vaccine in mice induced protection against infection but challenged animals exhibited an immunopathologic-type lung disease.

Design: Four candidate vaccines for humans with or without alum adjuvant were evaluated in a mouse model of SARS, a VLP vaccine, the vaccine given to ferrets and NHP, another whole virus vaccine and an rDNA-produced S protein. Balb/c or C57BL/6 mice were vaccinated IM on day 0 and 28 and sacrificed for serum antibody measurements or challenged with live virus on day 56. On day 58, challenged mice were sacrificed and lungs obtained for virus and histopathology.

Results: All vaccines induced serum neutralizing antibody with increasing dosages and/or alum significantly increasing responses. Significant reductions of SARS-CoV two days after challenge was seen for all vaccines and prior live SARS-CoV. All mice exhibited histopathologic changes in lungs two days after challenge including all animals vaccinated (Balb/C and C57BL/6) or given live virus, influenza vaccine, or PBS suggesting infection occurred in all. Histopathology seen in animals given one of the SARS-CoV vaccines was uniformly a Th2-type immunopathology with prominent eosinophil infiltration, confirmed with special eosinophil stains. The pathologic changes seen in all control groups lacked the eosinophil prominence.

Conclusions: These SARS-CoV vaccines all induced antibody and protection against infection with SARS-CoV. However, challenge of mice given any of the vaccines led to occurrence of Th2-type immunopathology suggesting hypersensitivity to SARS-CoV components was induced. Caution in proceeding to application of a SARS-CoV vaccine in humans is indicated.

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Short Communication

First case of postmortem study in a patient vaccinated against SARS-CoV-2

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ABSTRACT

A previously symptomless 86-year-old man received the first dose of the BNT162b2 mRNA COVID-19 vaccine. He died 4 weeks later from acute renal and respiratory failure. Although he did not present with any COVID-19-specific symptoms, he tested positive for SARS-CoV-2 before he died. Spike protein (S1) antigen-binding showed significant levels for immunoglobulin (Ig) G, while nucleocapsid IgG/IgM was not elicited. Acute bronchopneumonia and tubular failure were assigned as the cause of death at autopsy; however, we did not observe any characteristic morphological features of COVID-19. Postmortem molecular mapping by real-time polymerase chain reaction revealed relevant SARS-CoV-2 cycle threshold values in all organs examined (oropharynx, olfactory mucosa, trachea, lungs, heart, kidney and cerebrum) except for the liver and olfactory bulb. These results might suggest that the first vaccination induces immunogenicity but not sterile immunity.

In short, the conclusion is, we made a big mistake. We didn't realize it until now. We thought the spike protein was a great targeted antigen. We never knew the spike protein itself was a toxin and was a pathogenic protein. So by vaccinating people we are inadvertently inoculating them with a toxin. [For] some people this gets into circulation and when that happens, in some people that can cause damage especially in the cardiovascular system and I have many other, I don't have time, but many other legitimate questions about the long-term safety there for this vaccine. For example, with that accumulating in the ovaries, one of my questions is, will we be rendering young people infertile? Some of them infertile. So I'll stop there. I know it's heavy-hitting.

— Dr. Byram Bridle, Professor on Viral Immunology at the University of Guelph, On Point with Alex Pierson, Published May 27th 2021

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Pharmacology | Free Access

Single intratracheal exposure to SARS-CoV-2 S1 spike protein induces acute lung injury in K18-hACE2 transgenic mice

Pavel Solopov, Ruben Colunga Biancatelli, Elizabeth Sharlow, John Lazo, John Catravas

First published: 14 May 2021 | https://doi.org/10.1096/fasebj.2021.35.S1.04183

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Abstract

The SARS-CoV-2 pandemic has infected more than 85,900,000 people and provoked the death of more than 1.9 million worldwide. Therapeutic options remain limited, and vaccines may exhibit narrow efficacy, due to short supplies, delays in distribution and the emergence of new resistant strains. It is mandatory to study new therapeutic approaches that modulate the strong inflammatory response observed in the lung, prevent respiratory failure and improve outcomes. The study of SARS-CoV-2 pathogenicity *in vivo* is challenging due to the necessary biosafety laboratory regulations. Thus, we developed an acute lung injury model by intratracheally instilling the S1 subunit of SARS-CoV-2 Spike S protein (400 μg/kg, 2 ml/kg body weight) in K18-hACE2 transgenic mice that overexpress the human receptor for SARS-CoV-2 Spike protein S, ACE2, and investigated outcomes 72 hours later. Mice exhibited an acute decline in body weight during the first 48 hours following instillation, compared to saline-instilled controls. At 72 hours, bronchoalveolar lavage fluid demonstrated a dramatic increase in white blood cell content, particularly neutrophils, and marked proteinosis compared to controls. Histologic examination of lung tissue revealed hyaline membranes, alveolar septal thickening, and a large number of neutrophils in the interstitial and alveolar spaces of Spike protein S exposed mice. We propose that a single exposure of K18-hACE2 mice to SARS-CoV-2 Spike Protein S subunit S1 may represent a valid model of COVID-19, allow the study of the molecular mechanisms of SARS-CoV-2 induced lung injury and be useful in the investigation of potential new therapeutic approaches to the management of COVID-19 as well as future coronavirus-dependent respiratory diseases.

SARS-CoV-2 Spike Protein Impairs Endothelial Function via Downregulation of ACE 2

Yuyang Lei,* Jiao Zhang,* Cara R. Schiavon, Ming He, Lili Chen, Hui Shen, Yichi Zhang, Qian Yin, Yoshitake Cho, Leonardo Andrade, Gerald S. Shadel, Mark Hepokoski, Ting Lei, Hongliang Wang, Jin Zhang, Jason X.-J. Yuan, Atul Malhotra, Uri Manor,† Shengpeng Wang,† Zu-Yi Yuan,† John Y-J. Shyy†

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection relies on the binding of S protein (Spike glycoprotein) to ACE (angiotensin-converting enzyme) 2 in the host cells. Vascular endothelium can be infected by SARS-CoV-2,[1] which triggers mitochondrial reactive oxygen species production and glycolytic shift.[2] Paradoxically, ACE2 is protective in the cardiovascular system, and SARS-CoV-1 S protein promotes lung injury by decreasing the level of ACE2 in the infected lungs.[3] In the current study, we show that S protein alone can damage vascular endothelial cells (ECs) by downregulating ACE2 and consequently inhibiting mitochondrial function.

We administered a pseudovirus expressing S protein (Pseu-Spike) to Syrian hamsters intratracheally. Lung damage was apparent in animals receiving Pseu-Spike, revealed by thickening of the alveolar septa and increased infiltration of mononuclear cells (Figure [A]). AMPK (AMP-activated protein kinase) phosphorylates ACE2 Ser-680, MDM2 (murine double minute 2) ubiquitinates ACE2 Lys-788, and crosstalk between AMPK and MDM2 determines the ACE2 level.[4] In the damaged lungs, levels of pAMPK (phospho-AMPK), pACE2 (phospho-ACE2), and ACE2 decreased but those of MDM2 increased (Figure [B], i). Furthermore, complementary increased and decreased phosphorylation of eNOS (endothelial NO synthase) Thr-494 and Ser-1176 indicated impaired eNOS activity. These changes of pACE2, ACE2, MDM2 expression, and AMPK activity in endothelium were recapitulated by in vitro experiments using pulmonary arterial ECs infected with Pseu-Spike which was rescued by treatment with N-acetyl-L-cysteine, a reactive oxygen species inhibitor (Figure [B], ii).

We next studied the impact of S protein on mitochondrial function. Confocal images of ECs treated with S1 protein revealed increased mitochondrial fragmentation, indicating altered mitochondrial dynamics (Figure [C], i). To examine whether these mitochondrial changes were due, in part, to the decreased amount of ACE2, we overexpressed ACE2 S680D (ACE2-D, a phospho-mimetic ACE2 with increased stability) or S680L (ACE2-L, a dephospho-mimetic with decreased stability)[4] in ECs. As shown in Figure [C], ii, ECs with ACE2-L had a higher number of fragmented mitochondria when compared to those with ACE2-D. Performing oxygen consumption rate and extracellular acidification rate assays, we found that ECs overexpressing ACE2-L had reduced basal mitochondrial respiration, ATP production, and maximal respiration compared to ECs overexpressing ACE2-D (Figure [D], i). Moreover, ACE2-L overexpression caused increased basal acidification rate, glucose-induced glycolysis, maximal glycolytic capacity, and glycolytic reserve (Figure [D], ii). Also, ECs incubated with S1 protein had attenuated mitochondrial function but increased

Key Words: angiotensin-converting enzyme 2 ■ endothelium ■ SARS-CoV-2

Meet the First Author, see p 1239

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For Sources of Funding and Disclosures, see page 1324.

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SARS-CoV-2 spike proteins disrupt the blood-brain barrier, new research shows

Potentially raising risk of neurological damage in COVID-19 patients

Date: October 29, 2020

Source: Temple University Health System

Summa... New research shows that the spike proteins that extrude from SARS-CoV-2 promote inflammatory responses on the endothelial cells that form the blood-brain barrier. The study shows that SARS-CoV-2 spike proteins can cause this barrier to become 'leaky,' potentially disrupting the delicate neural networks within the brain.

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Original Contribution

Endothelial cell damage is the central part of COVID-19 and a mouse model induced by injection of the S1 subunit of the spike protein☆

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ABSTRACT

Neurologic complications of symptomatic COVID-19 are common. Brain tissues from 13 autopsies of people who died of COVID-19 were examined. Cultured endothelial and neuronal cells were incubated with and wild type mice were injected IV with different spike subunits. In situ analyses were used to detect SARS-CoV-2 proteins and the host response. In 13/13 brains from fatal COVID-19, pseudovirions (spike, envelope, and membrane proteins without viral RNA) were present in the endothelia of microvessels ranging from 0 to 14 positive cells/200× field (mean 4.3). The pseudovirions strongly co-localized with caspase-3, ACE2, IL6, TNFα, and C5b-9. The surrounding neurons demonstrated increased NMDAR2 and neuronal NOS plus decreased MFSD2a and SHIP1 proteins. Tail vein injection of the full length S1 spike subunit in mice led to neurologic signs (increased thirst, stressed behavior) not evident in those injected with the S2 subunit. The S1 subunit localized to the endothelia of microvessels in the mice brain and showed co-localization with caspase-3, ACE2, IL6, TNFα, and C5b-9. The surrounding neurons showed increased neuronal NOS and decreased MFSD2a. It is concluded that ACE2+ endothelial damage is a central part of SARS-CoV2 pathology and may be induced by the spike protein alone. Thus, the diagnostic pathologist can use either hematoxylin and eosin stain or immunohistochemistry for caspase 3 and ACE2 to document the endothelial cell damage of COVID-19.

nature neuroscience

ARTICLES

https://doi.org/10.1038/s41593-020-00771-8

The S1 protein of SARS-CoV-2 crosses the blood–brain barrier in mice

Elizabeth M. Rhea[1,2], Aric F. Logsdon[1,2], Kim M. Hansen[1,2], Lindsey M. Williams[1], May J. Reed[2], Kristen K. Baumann[1], Sarah J. Holden[3], Jacob Raber[3,4], William A. Banks[1,2] ✉ and Michelle A. Erickson[1,2]

It is unclear whether severe acute respiratory syndrome coronavirus 2, which causes coronavirus disease 2019, can enter the brain. Severe acute respiratory syndrome coronavirus 2 binds to cells via the S1 subunit of its spike protein. We show that intravenously injected radioiodinated S1 (I-S1) readily crossed the blood–brain barrier in male mice, was taken up by brain regions and entered the parenchymal brain space. I-S1 was also taken up by the lung, spleen, kidney and liver. Intranasally administered I-S1 also entered the brain, although at levels roughly ten times lower than after intravenous administration. *APOE* genotype and sex did not affect whole-brain I-S1 uptake but had variable effects on uptake by the olfactory bulb, liver, spleen and kidney. I-S1 uptake in the hippocampus and olfactory bulb was reduced by lipopolysaccharide-induced inflammation. Mechanistic studies indicated that I-S1 crosses the blood–brain barrier by adsorptive transcytosis and that murine angiotensin-converting enzyme 2 is involved in brain and lung uptake, but not in kidney, liver or spleen uptake.

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Pathogenic priming likely contributes to serious and critical illness and mortality in COVID-19 via autoimmunity

James Lyons-Weiler

The Institute for Pure and Applied Knowledge, USA

ARTICLE INFO

Keywords:
SARS-CoV-2
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Pathogenic priming
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ABSTRACT

Homology between human and viral proteins is an established factor in viral- or vaccine-induced autoimmunity. Failure of SARS and MERS vaccines in animal trials involved pathogenesis consistent with an immunological priming that could involve autoimmunity in lung tissues due to previous exposure to the SARS and MERS spike protein. Exposure pathogenesis to SARS-CoV-2 in COVID-19 likely will lead to similar outcomes. Immunogenic peptides in viruses or bacteria that match human proteins are good candidates for pathogenic priming peptides (similar to the more diffuse idea of "immune enhancement"). Here I provide an assessment of potential for human pathogenesis via autoimmunity via exposure, via infection or injection. SAR-CoV-2 spike proteins, and all other SARS-CoV-2 proteins, immunogenic epitopes in each SARS-CoV-2 protein were compared to human proteins in search of high local homologous matching. Only one immunogenic epitope in a SARS-CoV-2 had no homology to human proteins. If all of the parts of the epitopes that are homologous to human proteins are excluded from consideration due to risk of pathogenic priming, the remaining immunogenic parts of the epitopes may be still immunogenic and remain as potentially viable candidates for vaccine development. Mapping of the genes encoding human protein matches to pathways point to targets that could explain the observed presentation of symptoms in COVID-19 disease. It also strongly points to a large number of opportunities for expected disturbances in the immune system itself, targeting elements of MHC Class I and Class II antigen presentation, PD-1 signaling, cross-presentation of soluble exogenous antigens and the ER-Phagosome pathway. Translational consequences of these findings are explored.

Uncanny similarity of unique inserts in the 2019-nCoV spike protein to HIV-1 gp120 and Gag

Prashant Pradhan[$1,2], Ashutosh Kumar Pandey[$1], Akhilesh Mishra[$1], Parul Gupta[1], Praveen Kumar Tripathi[1], Manoj Balakrishnan Menon[1], James Gomes[1], Perumal Vivekanandan*[1]and Bishwajit Kundu*[1]

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Abstract:

We are currently witnessing a major epidemic caused by the 2019 novel coronavirus (2019-nCoV). The evolution of 2019-nCoV remains elusive. We found 4 insertions in the spike glycoprotein (S) which are unique to the 2019-nCoV and are not present in other coronaviruses. Importantly, amino acid residues in all the 4 inserts have identity or similarity to those in the HIV-1 gp120 or HIV-1 Gag. Interestingly, despite the inserts being discontinuous on the primary amino acid sequence, 3D-modelling of the 2019-nCoV suggests that they converge to constitute the receptor binding site. The finding of 4 unique inserts in the 2019-nCoV, all of which have identity /similarity to amino acid residues in key structural proteins of HIV-1 is unlikely to be fortuitous in nature. This work provides yet unknown insights on 2019-nCoV and sheds light on the evolution and pathogenicity of this virus with important implications for diagnosis of this virus.

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Microbiology & Infectious Diseases

COVID-19 RNA Based Vaccines and the Risk of Prion Disease

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ABSTRACT

Development of new vaccine technology has been plagued with problems in the past. The current RNA based SARS-CoV-2 vaccines were approved in the US using an emergency order without extensive long term safety testing. In this paper the Pfizer COVID-19 vaccine was evaluated for the potential to induce prion-based disease in vaccine recipients. The RNA sequence of the vaccine as well as the spike protein target interaction were analyzed for the potential to convert intracellular RNA binding proteins TAR DNA binding protein (TDP-43) and Fused in Sarcoma (FUS) into their pathologic prion conformations. The results indicate that the vaccine RNA has specific sequences that may induce TDP-43 and FUS to fold into their pathologic prion confirmations. In the current analysis a total of sixteen UG tandem repeats (ΨGΨG) were identified and additional UG (ΨG) rich sequences were identified. Two GGΨA sequences were found. Potential G Quadruplex sequences are possibly present but a more sophisticated computer program is needed to verify these. Furthermore, the spike protein, created by the translation of the vaccine RNA, binds angiotensin converting enzyme 2 (ACE2), a zinc containing enzyme. This interaction has the potential to increase intracellular zinc. Zinc ions have been shown to cause the transformation of TDP-43 to its pathologic prion configuration. The folding of TDP-43 and FUS into their pathologic prion confirmations is known to cause ALS, front temporal lobar degeneration, Alzheimer's disease and other neurological degenerative diseases. The enclosed finding as well as additional potential risks leads the author to believe that regulatory approval of the RNA based vaccines for SARS-CoV-2 was premature and that the vaccine may cause much more harm than benefit.

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Letter to the Editor

Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases

Since the outbreak of COVID-19 caused by SARS-CoV-2, we tested 5 different blood specimens that were confirmed positive for SARS-CoV-2 IgG and IgM antibodies [1]. The measurements were for anti-nuclear antibody (ANA), anti-extractable nuclear antigen (ENA), anti-double-stranded DNA (dsDNA), actin antibody, mitochondrial antibody, rheumatoid factor (RF), and C1q immune complexes. We were surprised to find out that 3 of the 5 specimens had significant elevations in ANA, ENA, actin and mitochondrial antibodies, but not against dsDNA or RF. This prompted us to investigate patterns of cross-reactivity between SARS-CoV-2 and autoimmune target proteins.

Vaccine-induced autoimmunity from autoimmune cross-reactivity is associated with narcolepsy, Guillain-Barré syndrome, multiple sclerosis, demyelinating neuropathies, systemic lupus erythematosus, and postural orthostatic tachycardia syndrome in susceptible subgroups as reported by Segal and Shoenfeld [2]. Due to the significant red flags for the potential cross-reactive interactions with the current COVID-19 pandemic, we studied the relationships between spike and nuclear proteins of SARS-CoV-2 and autoimmune target proteins.

Commercially available mouse monoclonal antibody made against virus can in fact affect the body from head to toe, including the nervous [4], cardiovascular [5], immune [6], and digestive systems [7].

Is it possible that some of the extensive organ, tissue, and cellular damage done by SARS-CoV-2 is due to viral antigenic mimicry with human tissue?

If the answer is yes, then we may face an increase in the rates of autoimmune disease in the future, because any factor that causes chronic inflammation in the body can potentially induce autoimmune disease.

Because SARS-CoV-2 attacks the respiratory system first, in a very interesting letter [8] Kanduc and Shoenfeld suggested that because the SARS-CoV-2 spike glycoprotein and lung surfactant proteins shared 13 out of 24 pentapeptides, the immune response following infection with SARS-CoV-2 may lead to cross-reactions with pulmonary surfactant proteins, followed by SARS-CoV-2-associated lung disease [8]. Based on their findings, they warned against the use of the entire SARS-CoV-2 antigens in the vaccines and cautioned that perhaps the use of only unique peptides would be the most effective way to fight the SARS-CoV-2 infection. Very similar suggestions were made by Razim et al., in

nature microbiology

PERSPECTIVE

https://doi.org/10.1038/s41564-020-00789-5

Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies

Wen Shi Lee[1], Adam K. Wheatley[1,2], Stephen J. Kent[1,2,3]✉ and Brandon J. DeKosky[4,5,6]✉

Antibody-based drugs and vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are being expedited through preclinical and clinical development. Data from the study of SARS-CoV and other respiratory viruses suggest that anti-SARS-CoV-2 antibodies could exacerbate COVID-19 through antibody-dependent enhancement (ADE). Previous respiratory syncytial virus and dengue virus vaccine studies revealed human clinical safety risks related to ADE, resulting in failed vaccine trials. Here, we describe key ADE mechanisms and discuss mitigation strategies for SARS-CoV-2 vaccines and therapies in development. We also outline recently published data to evaluate the risks and opportunities for antibody-based protection against SARS-CoV-2.

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Cytokine Storm

David C. Fajgenbaum, M.D., and Carl H. June, M.D.

THE SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-COV-2) pandemic has reminded us of the critical role of an effective host immune response and the devastating effect of immune dysregulation. This year marks 10 years since the first description of a cytokine storm that developed after chimeric antigen receptor (CAR) T-cell therapy[1] and 27 years since the term was first used in the literature to describe the engraftment syndrome of acute graft-versus-host disease after allogeneic hematopoietic stem-cell transplantation.[2] The term "cytokine release syndrome" was coined to describe a similar syndrome after infusion of muromonab-CD3 (OKT3).[3] Cytokine storm and cytokine release syndrome are life-threatening systemic inflammatory syndromes involving elevated levels of circulating cytokines and immune-cell hyperactivation that can be triggered by various therapies, pathogens, cancers, autoimmune conditions, and monogenic disorders.

From the Department of Medicine, Division of Translational Medicine and Human Genetics, Center for Cytokine Storm Treatment and Laboratory (D.C.F.), and the Center for Cellular Immunotherapies and the Parker Institute for Cancer Immunotherapy (C.H.J.), Perelman School of Medicine, University of Pennsylvania, Philadelphia. Address reprint requests to Dr. Fajgenbaum at davidfa@pennmedicine.upenn.edu or to Dr. June at cjune@upenn.edu.

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Worse Than the Disease? Reviewing Some Possible Unintended Consequences of the mRNA Vaccines Against COVID-19

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ABSTRACT

Operation Warp Speed brought to market in the United States two mRNA vaccines, produced by Pfizer and Moderna. Interim data suggested high efficacy for both of these vaccines, which helped legitimize Emergency Use Authorization (EUA) by the FDA. However, the exceptionally rapid movement of these vaccines through controlled trials and into mass deployment raises multiple safety concerns. In this review we first describe the technology underlying these vaccines in detail. We then review both components of and the intended biological response to these vaccines, including production of the spike protein itself, and their potential relationship to a wide range of both acute and long-term induced pathologies, such as blood disorders, neurodegenerative diseases and autoimmune diseases. Among these potential induced pathologies, we discuss the relevance of prion-protein-related amino acid sequences within the spike protein. We also present a brief review of studies supporting the potential for spike protein "shedding", transmission of the protein from a vaccinated to an unvaccinated person, resulting in symptoms induced in the latter. We finish by addressing a common point of debate, namely, whether or not these vaccines could modify the DNA of those receiving the vaccination. While there are no studies demonstrating definitively that this is happening, we provide a plausible scenario, supported by previously established pathways for transformation and transport of genetic material, whereby injected mRNA could ultimately be incorporated into germ cell DNA for transgenerational transmission. We conclude with our recommendations regarding surveillance that will help to clarify the long-term effects of these experimental drugs and allow us to better assess the true risk/benefit ratio of these novel technologies.

COVID-19 Vaccination

Product Info by US Vaccine

Clinical Care

COVID-19 Vaccines

Managing Anaphylaxis

Myocarditis and Pericarditis Considerations

Lab Tests After Severe Allergic Reaction

Vaccinating Homebound Persons

Jurisdictions: Vaccinating Older Adults and People with Disabilities

Vaccination Sites: Vaccinating Older Adults

Clinical Considerations: Myocarditis and Pericarditis after Receipt of mRNA COVID-19 Vaccines Among Adolescents and Young Adults

Summary

Since April 2021, increased cases of myocarditis and pericarditis have been reported in the United States after mRNA COVID-19 vaccination (Pfizer-BioNTech and Moderna), particularly in adolescents and young adults. There has not been a similar reporting pattern observed after receipt of the Janssen COVID-19 Vaccine (Johnson & Johnson).

In most cases, patients who presented for medical care have responded well to medications and rest and had prompt improvement of symptoms. Reported cases have occurred predominantly in male adolescents and young adults 16 years of age and older. Onset was typically within several days after mRNA COVID-19 vaccination, and cases have occurred more often after the second dose than the first dose. CDC and its partners are investigating these reports of myocarditis and pericarditis following mRNA COVID-19 vaccination.

CDC continues to recommend COVID-19 vaccination for everyone 12 years of age and older given the risk of COVID-19 illness and related, possibly severe complications, such as long-term health problems, hospitalization, and even death.

Dall'Italia Politica italiana

Approvato il DDL defibrillatori al Senato. IRC: "Creare una più rapida catena del soccorso"

"Su 400.000 arresti cardiaci registrati ogni anno in Europa si stima che solo nel 58% dei casi chi assiste intervenga con le manovra salvavita (massaggio cardiaco, ventilazioni) e nel 28% dei casi con il defibrillatore"

Di **ITALIAN TRIBUNE** - Giugno 19, 2021

Pochi giorni fa é stato approvato dal Senato il disegno di legge 1441. Il **DDL defibrillatori** era passato alla fine di maggio in Commissione Igiene e Sanità del Senato ed aveva ottenuto già il lasciapassare alla Camera nel 2019.

"Disposizioni in materia di utilizzo dei defibrillatori semiautomatici e automatici", questo il titolo definitivo del disegno di legge 1441 che introduce misure importanti per rafforzare il primo soccorso in caso di arresto cardiaco.

Sono previsti dunque:

- uno stanziamento di 10 milioni di euro al fine di sistemare i defibrillatori automatici esterni (DAE) nei prossimi cinque anni nei luoghi molto frequentati (aeroporti, stazioni ferroviarie, porti, scuole e università e sui mezzi di trasporto come aerei, treni, navi,

The BMJ

pdoshi@bmj.com

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http://dx.doi.org/10.1136/bmj.m4037

Published: 21 October 2020

Will covid-19 vaccines save lives? Current trials aren't designed to tell us

The world has bet the farm on vaccines as the solution to the pandemic, but the trials are not focused on answering the questions many might assume they are. Peter Doshi reports

Peter Doshi *associate editor*

As phase III trials of covid-19 vaccines reach their target enrolments, officials have been trying to project calm. The US coronavirus czar Anthony Fauci and the Food and Drug Administration leadership have offered public assurances that established procedures will be followed.[1-4] Only a "safe and effective" vaccine will be approved, they say, and nine vaccine manufacturers issued a rare joint statement pledging not to prematurely seek regulatory review.[5]

But what will it mean exactly when a vaccine is declared "effective"? To the public this seems fairly obvious. "The primary goal of a covid-19 vaccine is to keep people from getting very sick and dying," a National Public Radio broadcast said bluntly.[6]

Peter Hotez, dean of the National School of Tropical Medicine at Baylor College of Medicine in Houston, said, "Ideally, you want an antiviral vaccine to do two things . . . first, reduce the likelihood you will get severely ill and go to the hospital, and two, prevent infection and therefore interrupt disease transmission."[7]

Yet the current phase III trials are not actually set up to prove either (table 1). None of the trials currently under way are designed to detect a reduction in any serious outcome such as hospital admissions, use of intensive care, or deaths. Nor are the vaccines being studied to determine whether they can interrupt transmission of the virus.

MedCrave
Step into the World of Research

International Journal of Vaccines and Vaccination

New Quality-Control Investigations on Vaccines: Micro- and Nanocontamination

Abstract

Vaccines are being under investigation for the possible side effects they can cause. In order to supply new information, an electron-microscopy investigation method was applied to the study of vaccines, aimed at verifying the presence of solid contaminants by means of an Environmental Scanning Electron Microscope equipped with an X-ray microprobe. The results of this new investigation show the presence of micro- and nanosized particulate matter composed of inorganic elements in vaccines' samples which is not declared among the components and whose unduly presence is, for the time being, inexplicable. A considerable part of those particulate contaminants have already been verified in other matrices and reported in literature as non biodegradable and non biocompatible. The evidence collected is suggestive of some hypotheses correlated to diseases that are mentioned and briefly discussed.

Keywords: Vaccine; Disease; Contamination; Protein corona; Biocompatibility; Toxicity; Nanoparticle; Immunogenicity; Foreign body; Environment; Industrial process; Quality control

Research Article

Volume 4 Issue 1 - 2017

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CHOOSING YOUR COVID-19 VACCINE

FACTS YOU NEED TO KNOW

Pfizer	**Pfizer:** $4.7 billion in fines for false claims, drug and medical equipment safety violations, off-label promotion, corrupt practices, kickbacks, and bribery.
moderna	**Moderna:** Has never brought a vaccine to market since its founding, despite fielding 9+ vaccine candidates, none of which made it through phase 3 clinical trials.
Johnson & Johnson	**Johnson & Johnson:** Named in hundreds of thousands of lawsuits for toxic and/or dangerous products, including drugs, shampoos, medical equipment, and asbestos-contaminated baby powder.
AstraZeneca	**AstraZeneca:** Suspended by two dozen European countries due to severe, lethal adverse reactions, like blood clots.

Don't worry, you're in safe hands!

If you're vaccinated, remember to wear a mask and socially distance because you can still spread COVID-19. Trust The Science™

Positive association between COVID-19 deaths and influenza vaccination rates in elderly people worldwide

Christian Wehenkel

Instituto de Silvicultura e Industria de la Madera, Universidad Juárez del Estado de Durango, Durango, Mexico

ABSTRACT

Background: The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an ongoing global health crisis, directly and indirectly impacting all spheres of human life. Some pharmacological measures have been proposed to prevent COVID-19 or reduce its severity, such as vaccinations. Previous reports indicate that influenza vaccination appears to be negatively correlated with COVID-19-associated mortality, perhaps as a result of heterologous immunity or changes in innate immunity. The understanding of such trends in correlations could prevent deaths from COVID-19 in the future. The aim of this study was therefore to analyze the association between COVID-19 related deaths and influenza vaccination rate (IVR) in elderly people worldwide.

Methods: To determine the association between COVID-19 deaths and influenza vaccination, available data sets from countries with more than 0.5 million inhabitants were analyzed (in total 39 countries). To accurately estimate the influence of IVR on COVID-19 deaths and mitigate effects of confounding variables, a sophisticated ranking of the importance of different variables was performed, including as predictor variables IVR and some potentially important geographical and socioeconomic variables as well as variables related to non-pharmaceutical intervention. The associations were measured by non-parametric Spearman rank correlation coefficients and random forest functions.

Results: The results showed a positive association between COVID-19 deaths and IVR of people ≥65 years-old. There is a significant increase in COVID-19 deaths from eastern to western regions in the world. Further exploration is needed to explain these findings, and additional work on this line of research may lead to prevention of deaths associated with COVID-19.

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Additional Information and Declarations can be found on page 15

DOI 10.7717/peerj.10112

Subjects Epidemiology, Global Health, Immunology, Infectious Diseases, Public Health
Keywords SARS-CoV-2, Global health crisis, Risk factors, Virus interference, Geographical longitude, Lockdown, Face mask use

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Vaccine Breakthrough Infections with SARS-CoV-2 Variants

Ezgi Hacisuleyman, Ph.D., Caryn Hale, Ph.D., Yuhki Saito, Ph.D., Nathalie E. Blachere, Ph.D., Marissa Bergh, B.S.N., Erin G. Conlon, Ph.D., Dennis J. Schaefer-Babajew, Ph.D., Justin DaSilva, M.S., Frauke Muecksch, Ph.D., Christian Gaebler, M.D., Richard Lifton, M.D., Ph.D., Michel C. Nussenzweig, M.D., Ph.D., Theodora Hatziioannou, Ph.D., Paul D. Bieniasz, Ph.D., and Robert B. Darnell, M.D., Ph.D.

SUMMARY

Emerging variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are of clinical concern. In a cohort of 417 persons who had received the second dose of BNT162b2 (Pfizer–BioNTech) or mRNA-1273 (Moderna) vaccine at least 2 weeks previously, we identified 2 women with vaccine breakthrough infection. Despite evidence of vaccine efficacy in both women, symptoms of coronavirus disease 2019 developed, and they tested positive for SARS-CoV-2 by polymerase-chain-reaction testing. Viral sequencing revealed variants of likely clinical importance, including E484K in 1 woman and three mutations (T95I, del142–144, and D614G) in both. These observations indicate a potential risk of illness after successful vaccination and subsequent infection with variant virus, and they provide support for continued efforts to prevent and diagnose infection and to characterize variants in vaccinated persons. (Funded by the National Institutes of Health and others.)

SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-COV-2) IN-

From the Laboratory of Molecular Neuro-oncology (E.H., C.H., Y.S., N.E.B., M.B., E.G.C., R.B.D.), the Laboratory of Molecular Immunology (D.J.S.-B., C.G., M.C.N.), the Laboratory of Human Genetics and Genomics (R.L.), the Laboratory of Retrovirology (J.D., F.M., T.H., P.D.B.), and the Howard Hughes Medical Institute (M.C.N., P.D.B., R.B.D.), Rockefeller University, New York. Address reprint requests to Dr. Darnell at the Laboratory of Molecular Neuro-oncology, Rockefeller University, 1230 York Ave., New York, NY 10065-6307, or at darnelr@rockefeller.edu.

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DOI: 10.1056/NEJMoa2105000

“Vaccine-Induced Covid-19 Mimicry” Syndrome:Splice reactions within the SARS-CoV-2 Spike open reading frame result in Spike protein variants that may cause thromboembolic events in patients immunized with vector-based vaccines

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Research Article

Keywords: Vector-based vaccines, CVST, SVT, thrombosis, splicing, Spike protein

DOI: https://doi.org/10.21203/rs.3.rs-558954/v1

MERCK

Merck Discontinues Development of SARS-CoV-2/COVID-19 Vaccine Candidates; Continues Development of Two Investigational Therapeutic Candidates

January 25, 2021 6:45 am ET

KENILWORTH, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the company is discontinuing development of its SARS-CoV-2/COVID-19 vaccine candidates, V590 and V591, and plans to focus its SARS-CoV-2/COVID-19 research strategy and production capabilities on advancing two therapeutic candidates, MK-4482 and MK-7110. This decision follows Merck's review of findings from Phase 1 clinical studies for the vaccines. In these studies, both V590 and V591 were generally well tolerated, but the immune responses were inferior to those seen following natural infection and those reported for other SARS-CoV-2/COVID-19 vaccines. Merck continues to advance clinical programs and to scale-up manufacturing for two investigational medicines, MK-7110 and MK-4482 (molnupiravir); molnupiravir is being developed in collaboration with Ridgeback Bio.

"We are grateful to our collaborators who worked with us on these vaccine candidates and to the volunteers in the trials," said Dr. Dean Y. Li, president, Merck Research Laboratories. "We are resolute in our commitment to contribute to the global effort to relieve the burden of this pandemic on patients, health care systems and communities."

https://www.astrazeneca.com ▶ media centre ▶ 15 June 2021: update on azd7442 storm chaser trial

Update on AZD7442 STORM CHASER trial in post-exposure prevention of symptomatic COVID-19

15 June 2021 07:00 BST

AstraZeneca today announced results from the STORM CHASER trial assessing the safety and efficacy of AZD7442, a long-acting antibody (LAAB) combination, for the prevention of symptomatic COVID-19 in participants recently exposed to the SARS-CoV-2 virus. The trial did not meet the primary endpoint of post-exposure prevention of symptomatic COVID-19 with AZD7442 compared to placebo.

Trial participants were unvaccinated adults 18 years and over with confirmed exposure to a person with a case of the SARS-CoV-2 virus within the past eight days. In the overall trial population, AZD7442 reduced the risk of developing symptomatic COVID-19 by 33% (95% confidence interval (CI): -26, 65) compared to placebo, which was not statistically significant (Table 1).

The trial included 1,121 participants in a 2:1 randomisation AZD7442 to placebo, with 23 cases of symptomatic COVID-19 accrued in the AZD7442 arm (23/749) and 17 cases accrued in the placebo arm (17/372). All participants had a negative SARS-CoV-2 antibody test on the day of dosing to exclude prior infection, and a nasopharyngeal swab was also collected and subsequently analysed for SARS-CoV-2 by RT-PCR to detect virus.

Given the importance of finding therapies for COVID-19 and to help interpret trial results during the pandemic, additional analyses were performed and are being communicated (Table 1).

In a pre-planned analysis of SARS-CoV-2 PCR positive (detectable virus) and PCR negative (no detectable virus) participants, AZD7442 reduced the risk of developing symptomatic COVID-19 by 73% (95% CI: 27, 90) compared with placebo, in participants who were PCR negative at time of dosing. In a post-hoc analysis, in participants who were PCR negative at baseline, AZD7442 reduced the risk of

Table 1: STORM CHASER analyses

Baseline subgroup	Onset of case post dose	Number of cases / number of participants		Relative risk reduction (95% confidence interval)
		AZD7442 (300mg IM)	Placebo	
All participants (Primary analysis)	All cases	23 / 749	17 / 372	33% reduction[a] (-26 to 65)
PCR-negative[b] (Pre-planned subgroup analysis)	All cases	6 / 715	11 / 358	73% reduction (27 to 90)
PCR-negative[b] (Post hoc subgroup analysis)	≤7 days	5 / 715	5 / 358	51% reduction (-71 to 86)
	>7 days	1 / 710	6 / 353	92% reduction (32 to 99)

a: Not statistically significant.
b: Includes 974 participants (15 cases) confirmed PCR negative at baseline and 99 participants (2 cases) with PCR status missing at baseline.
48 participants were confirmed PCR positive at baseline with 23 cases (AZD7442: 17/34; placebo: 6/14).

https://www.curevac.com/en/2021/06/16/curevac-provides-update-on-phase-2b-3-trial-of-first-generation-covid-19-vaccine-candidate-cvncov/

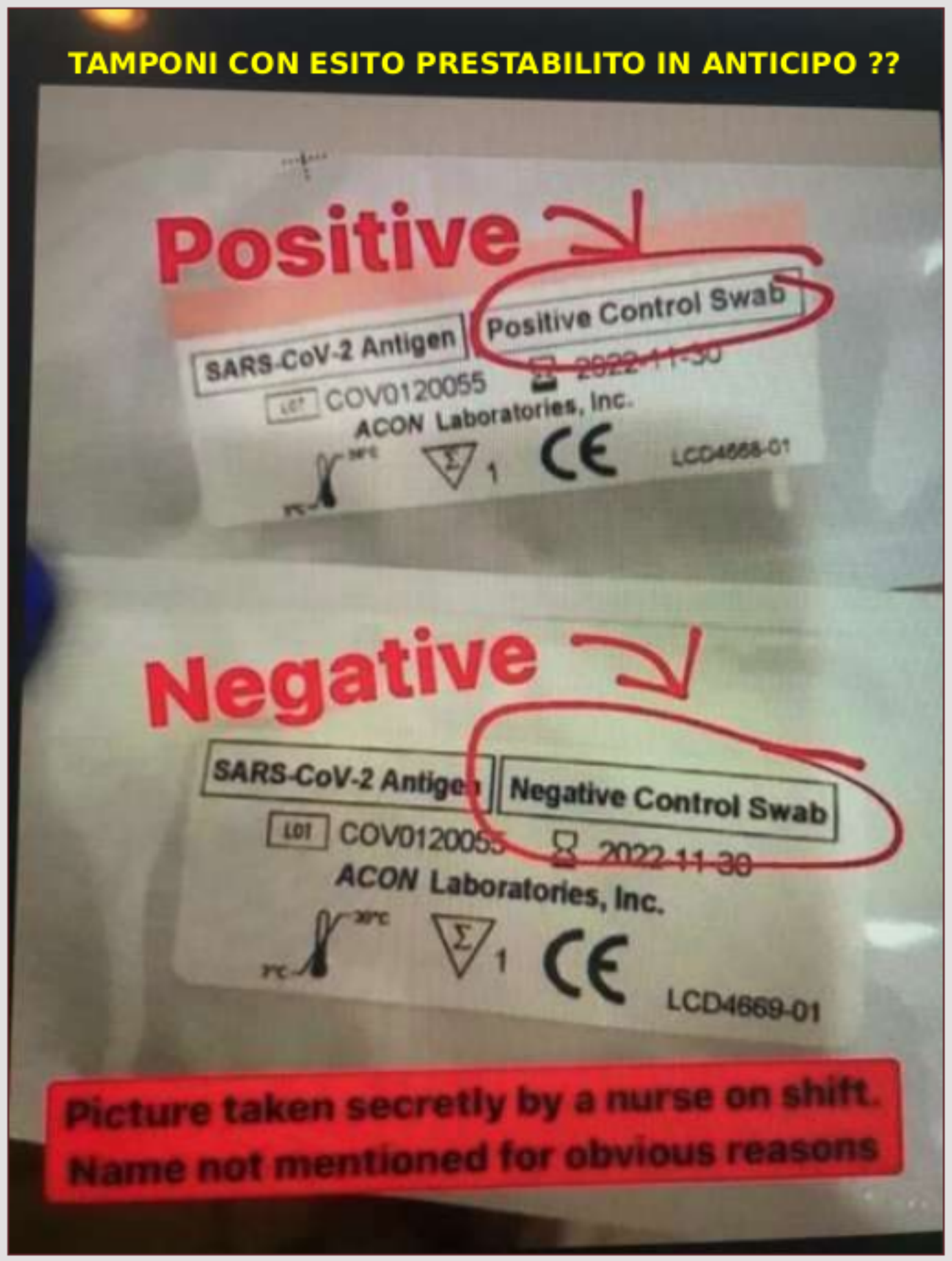
Press Release

June 16, 2021

CureVac Provides Update on Phase 2b/3 Trial of First-Generation COVID-19 Vaccine Candidate, CVnCoV

- Pivotal study conducted in 10 countries in fast changing environment of at least 29 COVID-19 variant strains; original strain almost completely absent
- At second interim analysis, statistical success criteria not met. Favorable safety profile confirmed
- Initial analyses show trend for age and variant dependent efficacy
- Results communicated to EMA, study progressing to final analysis within the next few weeks

TÜBINGEN, Germany / BOSTON, USA – June 16, 2021
CureVac N.V. (Nasdaq: CVAC), a clinical-stage biopharmaceutical company developing a new class of transformative medicines based on messenger ribonucleic acid ("mRNA"), today announced results of the second interim analysis of its international pivotal Phase 2b/3 study in approximatively 40,000 subjects (the HERALD study) of CureVac's first-generation COVID-19 vaccine candidate, CVnCoV. In the unprecedented context of at least 13 variants circulating within the study population subset assessed at this interim analysis, CVnCoV demonstrated an interim vaccine efficacy of 47% against COVID-19 disease of any severity and did not meet prespecified statistical success criteria. Initial analyses suggest


TAMPONI CON ESITO PRESTABILITO IN ANTICIPO ??
Positive
SARS-CoV-2 Antigen
Positive Control Swab
LOT COV0120055
2022-11-30
ACON Laboratories, Inc.
1
LCD4668-01
Negative
SARS-CoV-2 Antigen
Negative Control Swab
LOT COV0120055
2022-11-30
ACON Laboratories, Inc.
1
LCD4669-01
Picture taken secretly by a nurse on shift.
Name not mentioned for obvious reasons

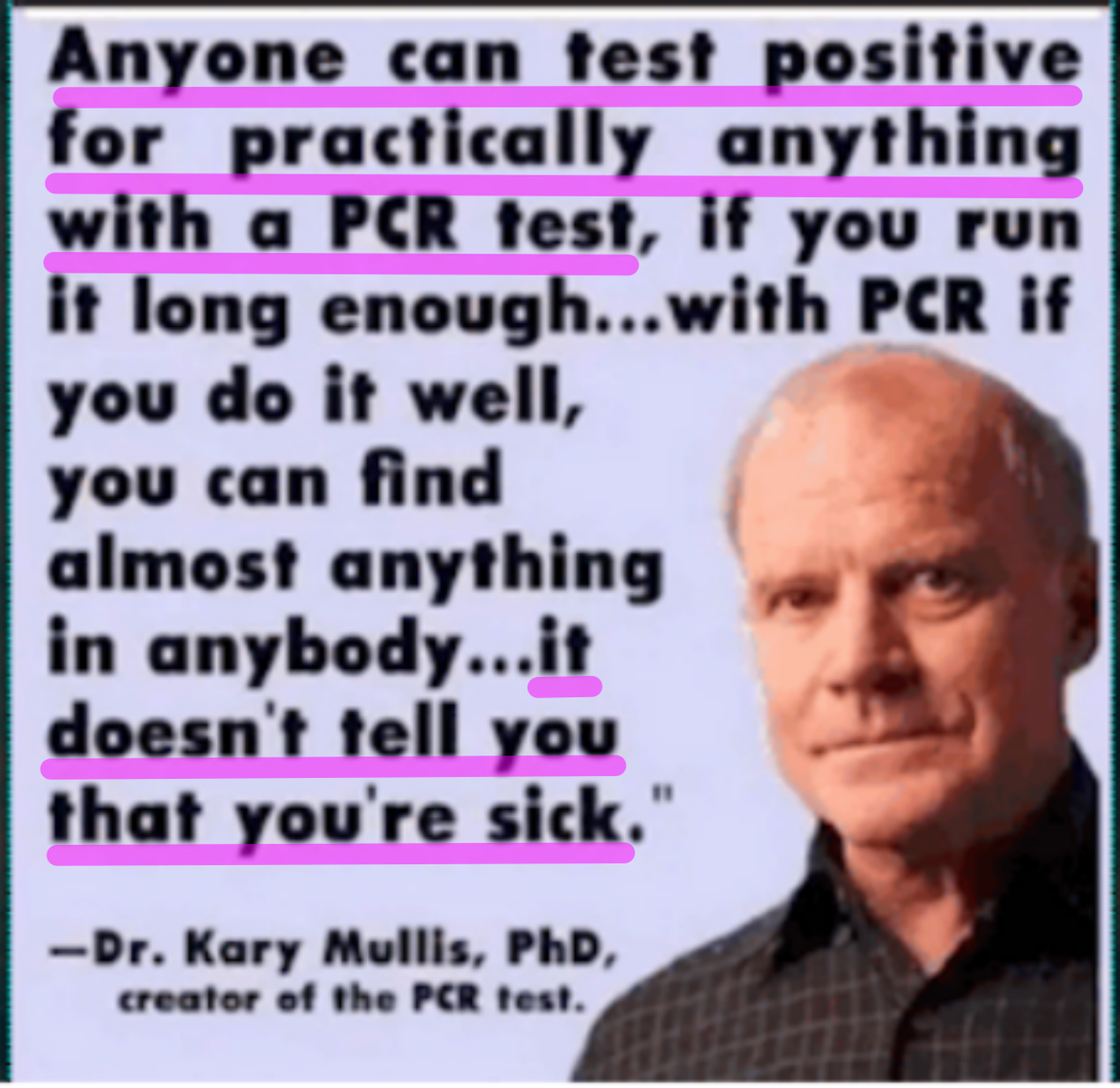
How convenient that Dr. Kary Mullis, inventor of the PCR test died suddenly in 2019—just prior to the advent of the scamdemic.

Dr Kary Banks Mullis

nato il 28 dicembre 1944, morto il 7 agosto **2019**
inventore del test **PCR** (usato nel tampone **covid**)

con il test PCR, diceva Mullis, chiunque può risultare positivo a tutto.. non **ha alcun valore diagnostico**

Mullis è morto poco prima della "pandemia" covid19



https://doi.org/10.1038/s41467-020-19802-w OPEN

Post-lockdown SARS-CoV-2 nucleic acid screening in nearly ten million residents of Wuhan, China

Shiyi Cao[1,11], Yong Gan[1,11], Chao Wang[1,11], Max Bachmann[2], Shanbo Wei[3], Jie Gong[4], Yuchai Huang[1], Tiantian Wang[1], Liqing Li[5], Kai Lu[6], Heng Jiang[7,8], Yanhong Gong[1], Hongbin Xu[1], Xin Shen[1], Qingfeng Tian[9], Chuanzhu Lv[10]✉, Fujian Song[2]✉, Xiaoxv Yin[1]✉ & Zuxun Lu[1]✉

Stringent COVID-19 control measures were imposed in Wuhan between January 23 and April 8, 2020. Estimates of the prevalence of infection following the release of restrictions could inform post-lockdown pandemic management. Here, we describe a city-wide SARS-CoV-2 nucleic acid screening programme between May 14 and June 1, 2020 in Wuhan. All city residents aged six years or older were eligible and 9,899,828 (92.9%) participated. No new symptomatic cases and 300 asymptomatic cases (detection rate 0.303/10,000, 95% CI 0.270–0.339/10,000) were identified. There were no positive tests amongst 1,174 close contacts of asymptomatic cases. 107 of 34,424 previously recovered COVID-19 patients tested positive again (re-positive rate 0.31%, 95% CI 0.423–0.574%). The prevalence of SARS-CoV-2 infection in Wuhan was therefore very low five to eight weeks after the end of lockdown.

ARTICLES
https://doi.org/10.1038/s41593-020-00758-5

nature neuroscience

Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19

Jenny Meinhardt[1,25], Josefine Radke[1,2,3,25], Carsten Dittmayer[1,25], Jonas Franz[4,5,6], Carolina Thomas[4,6], Ronja Mothes[1], Michael Laue[7], Julia Schneider[8], Sebastian Brünink[8], Selina Greuel[9], Malte Lehmann[10], Olga Hassan[1], Tom Aschman[1], Elisa Schumann[1,3], Robert Lorenz Chua[11], Christian Conrad[11], Roland Eils[11,12], Werner Stenzel[1], Marc Windgassen[13], Larissa Rößler[13], Hans-Hilmar Goebel[1], Hans R. Gelderblom[7], Hubert Martin[1], Andreas Nitsche[7], Walter J. Schulz-Schaeffer[14], Samy Hakroush[15], Martin S. Winkler[16], Björn Tampe[17], Franziska Scheibe[18,19], Péter Körtvélyessy[18,20], Dirk Reinhold[21], Britta Siegmund[10], Anja A. Kühl[22], Sefer Elezkurtaj[9], David Horst[9], Lars Oesterhelweg[13], Michael Tsokos[13], Barbara Ingold-Heppner[23], Christine Stadelmann[4], Christian Drosten[8], Victor Max Corman[8], Helena Radbruch[1,26] and Frank L. Heppner[1,2,19,24,26] ✉

The newly identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19, a pandemic respiratory disease. Moreover, thromboembolic events throughout the body, including in the CNS, have been described. Given the neurological symptoms observed in a large majority of individuals with COVID-19, SARS-CoV-2 penetrance of the CNS is likely. By various means, we demonstrate the presence of SARS-CoV-2 RNA and protein in anatomically distinct regions of the nasopharynx and brain. Furthermore, we describe the morphological changes associated with infection such as thromboembolic ischemic infarction of the CNS and present evidence of SARS-CoV-2 neurotropism. SARS-CoV-2 can enter the nervous system by crossing the neural–mucosal interface in olfactory mucosa, exploiting the close vicinity of olfactory mucosal, endothelial and nervous tissue, including delicate olfactory and sensory nerve endings. Subsequently, SARS-CoV-2 appears to follow neuroanatomical structures, penetrating defined neuroanatomical areas including the primary respiratory and cardiovascular control center in the medulla oblongata.

Polθ reverse transcribes RNA and promotes RNA-templated DNA repair

Gurushankar Chandramouly[1†], Jiemin Zhao[2†], Shane McDevitt[1†], Timur Rusanov[1], Trung Hoang[1], Nikita Borisonnik[1], Taylor Treddinick[1], Felicia Wednesday Lopezcolorado[3], Tatiana Kent[1], Labiba A. Siddique[1], Joseph Mallon[1], Jacklyn Huhn[1], Zainab Shoda[1], Ekaterina Kashkina[1], Alessandra Brambati[4], Jeremy M. Stark[3], Xiaojiang S. Chen[2], Richard T. Pomerantz[1]*

Genome-embedded ribonucleotides arrest replicative DNA polymerases (Pols) and cause DNA breaks. Whether mammalian DNA repair Pols efficiently use template ribonucleotides and promote RNA-templated DNA repair synthesis remains unknown. We find that human Polθ reverse transcribes RNA, similar to retroviral reverse transcriptases (RTs). Polθ exhibits a significantly higher velocity and fidelity of deoxyribonucleotide incorporation on RNA versus DNA. The 3.2-Å crystal structure of Polθ on a DNA/RNA primer-template with bound deoxyribonucleotide reveals that the enzyme undergoes a major structural transformation within the thumb subdomain to accommodate A-form DNA/RNA and forms multiple hydrogen bonds with template ribose 2′-hydroxyl groups like retroviral RTs. Last, we find that Polθ promotes RNA-templated DNA repair in mammalian cells. These findings suggest that Polθ was selected to accommodate template ribonucleotides during DNA repair.

INTRODUCTION

Polymerase θ (Polθ) is a unique DNA polymerase-helicase fusion protein in higher eukaryotes whose A-family polymerase domain evolved from Pol I enzymes (Fig. 1A) (*1*, *2*). However, contrary to most Pol I enzymes, Polθ is highly error-prone and promiscuous (*3*–*6*), performs translesion synthesis (TLS) opposite DNA lesions (*3*, *7*, *8*), and facilitates microhomology-mediated end-joining (MMEJ) of double-strand breaks (DSBs) by extending partially

RESULTS

Polθ exhibits RNA-dependent DNA synthesis activity

We tested whether the polymerase domain of Polθ (herein referred to as Polθ) reverse transcribes RNA like HIV RT using a DNA primer annealed to a RNA template (DNA/RNA). Polθ exhibits a similar rate of RT activity as HIV RT under identical conditions using substoichiometric amounts of enzyme relative to template (Fig. 1, B and C). Previous studies indicated that human Polη has

LETTER

https://doi.org/10.1038/s41586-018-0465-8

Widespread intronic polyadenylation inactivates tumour suppressor genes in leukaemia

Shih-Han Lee[1,5], Irtisha Singh[2,3,5], Sarah Tisdale[1], Omar Abdel-Wahab[4], Christina S. Leslie[2] & Christine Mayr[1]*

DNA mutations are known cancer drivers. Here we investigated whether mRNA events that are upregulated in cancer can functionally mimic the outcome of genetic alterations. RNA sequencing or 3′-end sequencing techniques were applied to normal and malignant B cells from 59 patients with chronic lymphocytic leukaemia (CLL)[1–3]. We discovered widespread upregulation of truncated mRNAs and proteins in primary CLL cells that were not generated by genetic alterations but instead occurred by intronic polyadenylation. Truncated mRNAs caused by intronic polyadenylation were recurrent ($n = 330$) and predominantly affected genes with tumour-suppressive functions. The truncated proteins generated by intronic polyadenylation often lack the tumour-suppressive functions of the corresponding full-length proteins (such as DICER and FOXN3), and several even acted in an oncogenic manner (such as CARD11, MGA and CHST11). In CLL, the inactivation of tumour-suppressor genes by aberrant mRNA processing is substantially more prevalent than the functional loss of such genes through genetic events. We further identified new candidate tumour-suppressor genes that are inactivated by intronic polyadenylation in leukaemia and by truncating DNA mutations in solid tumours[4,5]. These genes are understudied in cancer, as their overall mutation rates are lower than those of well-known tumour-suppressor genes. Our findings show the need to go beyond genomic analyses in cancer diagnostics, as mRNA events that are silent at the DNA level are widespread contributors to cancer pathogenesis through the inactivation of tumour-suppressor genes.

dataset to validate our CLL-IPA events[3] (Fig. 1c). We verified up to 71% of testable IPAs by this independent method and dataset (Extended Data Fig. 1d). For further analysis, we combined the datasets ($n = 59$ CLL samples) and focused only on CLL-IPAs that were present in more than 10% of the sample cohort resulting in 330 CLL-IPAs, derived from 306 genes (Fig. 1d, Supplementary Table 1). Although CLL-IPAs were detected in all CLL samples, one-third of the samples had a significantly higher number of CLL-IPAs (Fig. 1e, Extended Data Fig. 1e).

To investigate whether CLL-IPAs express truncated proteins, we performed western blots on 13 candidates. Whereas normal B cells only expressed the full-length proteins, the malignant B cells also expressed truncated proteins, the size of which was consistent with the predicted size of IPA-generated proteins (Fig. 2a, Extended Data Figs. 3 and 4).

To rule out that proteolytic cleavage truncates the proteins, we validated the presence of the IPA-generated truncated mRNAs (Extended Data Fig. 5a). Moreover, we were able to induce IPA isoform expression through the downregulation of splicing factors or through the inhibition of 5′ splice site recognition using an antisense oligonucleotide, indicating that deregulated mRNA processing can cause the expression of a truncated protein[11,12] (Extended Data Fig. 5b).

Many of the truncated proteins generated by CLL-IPAs are markedly similar to the predicted protein products produced by TR mutations, suggesting that CLL-IPAs may functionally mimic the outcome of genetic mutations (Fig. 2b, Extended Data Fig. 6a). To test this, we investigated the functional consequences of the expression of IPA and full-length protein isoforms of four candidates in malignant B cells.