Vaccination of elite athletes against SARS-CoV-2 and broader implications for public health policy

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Abstract

SARS-CoV-2, a human β -coronavirus implicated as the causative agent in the COVID-19 pandemic, has been the subject of the most globally intensive vaccine development effort in recorded history. The spectrum of SARS-CoV-2 vaccine candidates, deployed globally, demonstrates an expansive diversity in regards to both design philosophy and immunological mechanisms of action. In the context of an aging, physically de-conditioned, overweight global population, which finds itself heavily burdened by a high prevalence of non-communicable chronic disease; elite strength, power and endurance athletes represent a minority population comprised of extreme physiological outliers. This report explores the molecular toxicity and pathophysiology of the SARS-CoV-2 spike protein, design and immunological strategies embodied by the global spectrum of SARS-CoV-2 vaccine candidates, and the intersection of these phenomena with the demographic, lifestyle and physiological characteristics of elite athletes; so as to inform vaccination strategies against SARS-CoV-2 which most protect this outlying minority population.

Overview

SARS-CoV-2 β -coronavirus

The viral genome of a β -coronavirus typically encodes four classes of structural proteins: spike glycoproteins, envelope proteins, membrane proteins, and nucleocapsid proteins ⁽¹⁾. β -coronaviruses utilize a homo-trimeric spike glycoprotein (spike protein), consisting of two primary sub-units: a S1 sub-unit (S1) and a S2 sub-unit (S2) ⁽³⁾. SARS-CoV-2 spike proteins are instrumental in the process of virion cell entry and the subsequent development of COVID-19 infection ^(3,5). The SARS-CoV-2 spike protein receptor binding domain (RBD), located on S1, binds to human angiotensin converting enzyme 2 (hACE2), and subsequently induces the dissociation of S1 from hACE2, triggering S2 of the spike protein to adopt the more stable post-fusion conformation ^(1,3,4). Adoption of the post-fusion conformation by the SARS-CoV-2 spike protein is required for SARS-CoV-2 virion fusion with target cell membranes and the subsequent infection of said target cells by SARS-CoV-2 ^(1,3,4,5). Patients diagnosed with COVID-19 have demonstrated that SARS-CoV-2 spike proteins, as well as, constituent components of spike proteins, such as S1, are subject to enzymatic cleavage from SARS-CoV-2 virion ⁽¹²⁾. Enzymatic cleavage liberates SARS-CoV-2 spike proteins and/or spike protein constituent components and results in detectable plasma concentrations of isolated spike proteins and/or isolated S1 ^(12, 136). Isolated SARS-CoV-2 spike proteins, isolated S1 and isolated RBD of the SARS-CoV-2 spike protein are able to strongly interact with hACE2 ^(1,3,4,5). SARS-CoV-2 spike proteins and/or spike protein constituent components, such as S1, have demonstrated an exquisitely potent and multifaceted molecular toxicity ^(4,5,9,12). Plasma concentrations of isolated S1 have been found to strongly correlate with COVID-19 disease severity ⁽¹²⁾. The likelihood of admission to the intensive care unit (ICU) for COVID-19 patients with plasma concentrations of isolated S1 greater than 50 pg/mL (3.01×10^{10} kDa/ml) was found to be 77% ⁽¹²⁾. Further, 100% of patients demonstrating S1 plasma concentrations of greater than 50 pg/mL were intubated within one day of hospital admission ⁽¹²⁾.

SARS-CoV-2 spike protein toxicity

Isolated SARS-CoV-2 spike proteins and/or isolated spike protein constituent components, such as S1, have been observed to exert a profound and multifaceted molecular toxicity within a wide range of cell and tissue types ^(4,5,9,10,13,14,15,19). Manifestations of the molecular toxicity inherent to isolated SARS-CoV-2 spike proteins and/or isolated spike protein constituent components, such as S1, include, but are not limited to: lung and endothelial cell damage ^(5,8), thickening of the alveolar septa ⁽⁵⁾, increased tissue infiltration of mononuclear cells ⁽⁵⁾, impairment of acetylcholine-induced, endothelium-dependent vasodilation ⁽⁵⁾, altered mitochondrial dynamics, increased mitochondrial fragmentation, impaired mitochondrial function & compensatory increases in glycolysis- (also known as metabolic reprogramming) ⁽⁵⁾, down-regulation of angiotensin converting enzyme 2 (hACE2) ^(3,4,5,7,8,112), up-regulation of angiotensin converting enzyme (hACE) ^(3,4,5,7,8,112), increased levels of angiotensin II ^(3,4,5,7,8,112), increased levels of reactive oxygen species (ROS) generation and accompanying oxidative stress ^(3,4,5,7,8,112), increased platelet aggregation in response to agonists such as adenosine diphosphate (ADP) ⁽⁴⁾, increased platelet dense granule secretion in response to agonists such as ADP ⁽⁴⁾, induction of platelet integrin α IIb β 3 activation, induction of platelet P-selectin expression, markedly accelerated spreading of platelets across fibrinogen-coated surfaces ⁽⁴⁾, acceleration of clot retraction upon exposure to agonists such as ADP ⁽⁴⁾, increased thrombus formation ^(4,22,23,24), stimulation of platelets to release both Factor V and Factor XIII ⁽⁴⁾, stimulation of

platelet secretion of α -granule inflammatory cytokines: PF4, TNF- α , IL-8, and IL-1 β ⁽⁴⁾, increased formation of leukocyte-platelet aggregates (CD45+, CD41+) ⁽⁴⁾, increased formation of monocyte-platelet aggregates (CD14+ CD41+) ⁽⁴⁾, increased formation of neutrophil-platelet aggregates (CD65+ CD41+) ⁽⁴⁾, increased formation of neutrophil extracellular trap (NET) via platelet IL-8 secretion ^(4,25), induction of an inflammatory secretome by cardiac pericytes which resembles the phenomena of cytokine storm and includes: TNF α , IL-6, MCP1, and IL-1 β ^(7,9), activation of Toll-like receptor 4 (TLR4)/myeloid differentiation factor-2 (MD-2) signaling in cardiomyocytes ⁽¹⁰⁾, activation of NF- κ B signaling in cardiomyocytes subsequent to TLR4/MD-2 signaling ⁽¹⁰⁾, cardiac inflammation, cardiac hypertrophy and reduced cardiac systolic function ⁽¹⁰⁾, induction of hyper-inflammatory responses in human macrophages ^(13,14), induction of the NLRP3 inflammasome/caspase-1 pathway in human peripheral blood mononuclear cells ^(10,15), induction of the p38 MAPK pathway human peripheral blood mononuclear cells ^(10,15), induction of the NF- κ B pathway in human peripheral blood mononuclear cells ^(10,15), exaggerated production of TNF α , IL-6, IL-1 β and IL-8 by human peripheral blood mononuclear cells ^(10,15), significant degradation of blood-brain barrier properties ⁽¹⁹⁾, a loss of blood-brain barrier integrity ⁽¹⁹⁾, induction of pro-inflammatory cascades in cerebral endothelial cells ⁽¹⁹⁾, induction of immune infiltration into the CNS ⁽¹⁹⁾, up-regulation of cerebral endothelial cell matrix metalloproteinase expression ^(19,113), induction of micro-thrombi in the vasculature of the CNS ⁽¹¹⁴⁾, onset of acute hemorrhagic necrotizing encephalopathy ^(115,116,117), seeding of toxic neural protein aggregates ^(20,21), onset of neurodegeneration and associated cognitive decline ^(20,21), inhibition of BRCA1 recruitment to sites of DNA damage ⁽¹⁴⁸⁾, inhibition of 53BP1 recruitment to sites of DNA damage ⁽¹⁴⁸⁾, and significant inhibition of double-strand DNA damage repair mechanisms ⁽¹⁴⁸⁾.

Vaccine strategies against SARS-CoV-2

The spectrum of vaccine candidates deployed globally against SARS-CoV-2 demonstrates tremendous diversity in regards to both design philosophy and immunological mechanisms of action. Inactivated-virus vaccines, such as BBV152/Covaxin, CoviVac, BBIBP-CorV and CoronaVac can be viewed as constituting one end of this spectrum. Inactivated-virus vaccines represent the most enduring form of legacy vaccination technology, issuing forth from the most primordial attempts at vaccination. In the context of an aging, overweight, physically de-conditioned global population, heavily burdened by non-communicable chronic disease, public health policies involving the deployment of inactivated-virus vaccines against SARS-CoV-2 have not received significant support in many geopolitical jurisdictions. Individuals with obesity, chronic renal disease, type 2 diabetes mellitus (DM2) and those over 65 years of age are examples of conditions and/or population demographics, which correlate with significantly reduced levels innate immunity, as well as, very poor immune responses to vaccination with an inactivated-virus vaccines ^(45,46,47).

Where inactivated-virus vaccines can be viewed to constitute one extreme of the spectrum comprising SARS-CoV-2 vaccine candidates, nucleotide vaccines against SARS-CoV-2 can be viewed to constitute the polar opposite end of this spectrum. Where inactivated-virus vaccines constitute legacy vaccination technology, nucleotide vaccines comprise bleeding-edge vaccination technology ^(73,74). Where inactivated-virus vaccines present a non-functional, but molecularly complete, virion to the immune system of a recipient patient, nucleotide vaccines against SARS-CoV-2 introduce a

genetic template, which compels the protein synthetic apparatus of a recipient patient to self-generate a vaccine-induced synthetic viral antigen (73,74). Where the strength of an immune response resulting from an inactivated-virus vaccine depends on the competency of the immune system of a recipient patient, SARS-CoV-2 nucleotide vaccines forcefully compel the self-generation of synthetic viral antigens, so as to constitute an overwhelming barrage of antigenic signaling, thus, even severely immune compromised populations, such as the very old and very ill, are capable of extraordinarily high rates of seroconversion (45,46,47,77,91). Nucleotide vaccines against SARS-CoV-2 utilize DNA or mRNA genetic templates to compel self-generation of a vaccine encoded viral antigen (73,74). Current nucleotide vaccines against SARS-CoV-2 utilize a viral vector or an ionized lipid vehicle for the delivery of the vaccine's genetic template (73,103). Examples of nucleotide vaccines against SARS-CoV-2 include: BNT-162b2, mRNA-1273, Ad26.COV2.S, ChAdOx1 nCov-19/AZD1222 and Gam-COVID-Vac/Sputnik V. The deployment of nucleotide vaccines against SARS-CoV-2 have received high praise, generated great enthusiasm and have gained wide-spread acceptance on account of the high levels of seroconversion observed within populations comprising traditionally poor vaccine responders, such as but not limited to: individuals with: obesity, end-stage renal disease, DM2, cancer and those over 65 years of age (77,91).

Demographic, lifestyle and physiology traits of elite strength, power and endurance athletes

Elite strength, power and endurance athletes constitute an age demographic that is almost exclusively comprised of individuals under the age of 50 years old. Elite strength, power and endurance athletes engage in resistance exercise training (RT), endurance training (ET) and sprint training (ST) with great regularity, at high levels of intensity, for extended durations (119,120,121,122,123). Elite strength, power and endurance athletes have been found to exhibit more complete nutritional intake and correspondingly, fewer nutritional deficiencies than lesser-performing athletes and sedentary controls (27). A primary contributor to the dietary proficiency exhibited by elite athletes, is the greater extent to which this population utilizes nutritional supplementation compared to both lesser-performing athletes and sedentary controls (26). Protein and amino acid supplementation (protein/AA) constitutes the primary component of the supplementary nutritional regimen in a significant majority of elite strength, power and endurance athletes (26,27,28). In combination with RT, protein/AA has been observed to demonstrate a robust, dose-dependent increase in the rate of skeletal muscle protein synthesis (MPS) (29). The combination of RT and protein/AA triggers both mammalian target of rapamycin complex 1 (MTORC1) dependent and MTORC1 independent signaling cascades, which culminate in increased ribosomal biogenesis, increased translational capacity and increased translational efficiency (27,28,29,30,31,33,34,35,36,124,125,126,133,134). A sanity check calculation based on the observed differences in rates of MPS between populations of elite athletes actively engaged in RT while supported by protein/AA and populations of sedentary athletes in a protein-fed state, provides a highly conservative minimum difference in rates of MPS between populations of actively resistance-training elite athletes (supported by protein/AA), and the general population, at any given point within a 24-hour period, of time of 129% (29,30,35,36). The significantly greater rate of MPS observed in populations of actively-training elite athletes supported by protein/AA, can in large part be explained by the development of a robust mRNA translation apparatus within the skeletal muscle tissue of elite athletes (29,30,35,36). In addition to providing a potent stimulus for both the MTORC1

dependent and mTORC1 independent signaling cascades, thereby driving mRNA translational capacity and efficiency within the skeletal muscle tissue of elite athletes, intense and/or extensive RT and/or ET and/or ST also results in markedly increased plasma levels of ADP (27,28,29,30,31,33,34,35,36,44,124,125,126,128,132,133,134). Elite strength, power and endurance athletes engage in RT, ST and ET with markedly greater intensity and frequency relative to the general population (118,119,120,121,122,123). Therefore, elite athletes can also be expected to possess markedly higher average and peak plasma concentrations of ADP at any given point over a 24-hour period of time, when compared to members of the general population (44,130,132). Additionally, RT alone or in combination with ET results in increased skeletal muscle fiber cross-sectional area (CSA) (133). The observed increase of skeletal muscle fiber CSA observed within populations of actively training athletes is accompanied by an expansion of the accompanying skeletal muscle capillary network (133). Elite athletes possess enhanced endothelial-dependent vasodilative function, relative to healthy, but sedentary, age-matched controls (129). Reports indicate that, among populations of elite athletes, regular exposure to high-intensity RT and/or ET and/or ST reduces the ratio of AngII: Ang1-7, thus reducing ROS generation and oxidative stress, which subsequently reduces inflammation (131). Despite the fact that populations of actively training elite athletes demonstrate enhanced vasodilative function relative to healthy, sedentary controls; elite athletes have no enhanced ability to protect against platelet aggregation induced by ADP and arachidonic acid relative to healthy sedentary controls (129). Conversely, intensive RT and/or ET and/or ST may excessively increase platelet aggregation, thus promoting the risk of thrombotic events (130, 132). High-intensity and/or long duration RT and/or ET and/or ST has been found to dramatically increase plasma concentrations of ADP (44,130,132). Elevated plasma concentrations of ADP promote a prothrombotic state, manifesting in phenomena such as, increased platelet activation and thrombocytosis (44,128,132). This is supported by the fact that plasma from intensely exercising athletes has been found to demonstrate significantly up-regulated expression of P-selectin (44).

Emergent properties arising from the intersection of SARS-CoV-2 spike protein toxicity, SARS-CoV-2 vaccination technology and the demographic, lifestyle and physiological traits of elite athletes

Unlike large swaths of the population who demonstrate poor immune responses to inactivated-virus vaccines, elite athletes have demonstrated enhanced immune responses upon vaccination with inactivated-virus vaccines (45,46,47,37,38). Elite athletes generate immune responses to inactivated-virus vaccines that are approximately twice as great as immune responses to inactivated-virus vaccination observed within the general population (37). Additionally, the immune response generated by elite athletes upon vaccination with an inactivated-virus vaccine has been reported to be far more enduring than the immune responses generated, in response to inactivated-virus vaccines, within populations of obese individuals (47). Despite demonstrating superior immune responses to inactivated-virus vaccines, populations of elite athletes appear to incur no additional risk of vaccine-induced adverse events, relative to the general population, as a result of the observed enhanced responsiveness to inactivated-virus vaccines (39). Vaccination with inactivated-virus vaccines has been reported to inflict minimal disruptions to the training and competition regimes of elite athletes (39). Reports of populations of actively training elite athletes which demonstrate enhanced immunity coupled with a negligible prevalence of vaccine-induced training disruptions, reinforces the significant body of evidence which extols the effectiveness of

intense physical activity as a functional adjuvant to vaccination with inactivated-virus vaccines (40,41,42,43).

Therefore, the benefits of administering inactivated-virus vaccines against SARS-CoV-2 to elite strength, power and endurance athletes include, but are not limited to: 1) the formation of a robust and enduring antibody response against the comprehensive landscape of SARS-CoV-2 antigenic epitopes (55,56,57,65,67,68,69,70) 2) no requirement for elite athletes to reduce scheduled physical training and/or competitions following immunization (since exercise functions as a well recognized adjuvant to vaccination with an inactivated-virus vaccine 40,41,42,43); and there is no increased mechanistic risk of thrombogenesis and/or thromboembolism incurred by populations of actively training elite athletes following vaccination with an inactivated-virus SARS-CoV-2 vaccine (56). The maintenance of low levels of isolated spike proteins and/or isolated S1 following vaccination of elite athletes against SARS-CoV-2 are crucially important, due to the fact that actively training elite athletes are inherently predisposed to an elevated exercise-induced risk of thrombogenesis and thromboembolism, and isolated spike protein and/or isolated S1 acts to dramatically enhance this risk by facilitating coagulation and thrombogenesis in the context of exercise-induced elevations of plasma ADP (4,44,128,132). Inactivated-virus vaccines against SARS-CoV-2 introduce a fixed quantity of SARS-CoV-2 virion into the body of an elite athlete. For example, a 6mcg dose of an inactivated-virus vaccine, such as BBV152/Covaxin, introduces approximately 3.61×10^9 inactivated SARS-CoV-2 viral particles, where each virion expresses 25-50 spike proteins (147). SARS-CoV-2 spike proteins delivered via inactivated-virus vaccines, possess a limited ability to interact with hACE2 and/or TLR4 secondary to the fact that inactivated-virus vaccines present a very limited copy number of the complete SARS-CoV-2 virion to the immunosurveillance mechanisms of a recipient patient. Furthermore, SARS-CoV-2 spike proteins delivered as components of inactivated-virus SARS-CoV-2 vaccines, possesses a near-zero probability of entering the nucleus of even a single cell, belonging to a recipient patient, while structurally intact. SARS-CoV-2 spike protein-mediated inhibition of DNA double-strand break repair mechanisms requires that an intact spike protein be localized to the nucleus (148).

Conversely, vaccination of a population of elite strength, power and endurance athletes against SARS-CoV-2 with nucleotide vaccines exposes the athletes to clear and profound mechanistic risks of increased vaccination-induced adverse events. The basis of the heightened degree of mechanistic risk incurred by elite athletes, upon exposure to SARS-CoV-2 nucleotide vaccines, can be found to issue forth from the confluence of several well-established principles:

- 1) The demographic, nutritional, lifestyle and training characteristics of elite strength, power and endurance athletes drives the creation of a physiological phenotype which dramatically enhances MPS capacity and efficiency in the context of an expanded skeletal muscle capillary network.
- 2) Nucleotide vaccines against SARS-CoV-2 are administered via intramuscular injection, where the expanded capillary network of actively training elite athletes facilitates greater uptake of SARS-CoV-2 nucleotide vaccine particles, relative to segments of the population with less developed skeletal muscle vasculature. Subsequently, the DNA or mRNA genetic templates, delivered by SARS-CoV-2 nucleotide vaccines, forcibly compels the enhanced protein synthetic apparatus possessed by populations of actively training elite athletes, to self-generate SARS-CoV-2 spike

proteins in a *non-throttleable manner*, primarily within the skeletal muscle. Nucleotide vaccines, such as BNT-162b2 and mRNA-1273, introduce genetic templates, encoding for SARS-CoV-2 spike proteins, which have been subjected to codon optimization ⁽⁷⁵⁾. Optimized mRNA genetic templates, such as demonstrated by BNT-162b2 and mRNA-1273, compel the self-synthesis of SARS-CoV-2 spike proteins far more effectively than wild-type SARS-CoV-2 genomes encoding the SARS-CoV-2 spike protein ⁽⁷⁵⁾. 3) SARS-CoV-2 spike proteins and constituent components of SARS-CoV-2 spike proteins, such as S1, demonstrate a profound and multifaceted molecular toxicity, independent of SARS-CoV-2 infection ^(4,5,9,10,13,14,15,19). 4) SARS-CoV-2 nucleotide vaccine-induced, self-generated spike proteins are subject to enzymatic cleavage and are not constrained to a trans-membrane anchored existence at the site of synthesis ⁽¹³⁶⁾. SARS-CoV-2 nucleotide vaccines result in detectable plasma concentrations of isolated spike proteins and/or isolated spike protein constituent components, such as S1 ⁽¹³⁶⁾. SARS-CoV-2 nucleotide vaccine-induced, self-generated spike proteins are capable of exerting a systemic toxic effect via circulatory distribution and systemic interactions with tissue receptors such as, but not limited to hACE2 and TLR4. Manifestations of the interactions of vaccine-induced, self-synthesized SARS-CoV-2 spike proteins and/or spike protein constituent components, such as S1, include, but are not limited to, pathological events such as thrombogenesis, endothelial dysfunction and myocarditis ⁽¹⁵⁴⁾. Additionally, vaccine-induced, self-generated SARS-CoV-2 spike proteins may remain within the cell of origin and become localized to the nucleus, where inhibition of double stranded DNA repair mechanisms may occur ⁽¹⁴⁸⁾.

A temporal sequence can be described which characterizes the events which occur beginning with the administration of a SARS-CoV-2 nucleotide vaccine and ending with the generation of an antibody response of sufficient quality and/or quantity to neutralize the vaccine-induced, self-generated SARS-CoV-2 spike proteins and/or spike protein constituent components, such as S1. Such a temporal sequence is described by: the administration of a SARS-CoV-2 nucleotide vaccine (Time₁)-> the incorporation of the vaccine-provided genetic template into at least one cell of the recipient patient (Time₂)-> the onset of translation of the vaccine-provided genetic template encoding SARS-CoV-2 spike protein antigens (Time₃)-> the successful self-synthesis of SARS-CoV-2 spike protein antigens by the protein synthetic apparatus of the recipient patient (Time₄)-> the extracellular expression of vaccine-induced, self-generated synthetic SARS-CoV-2 spike protein antigens (Time₅)-> and the subsequent generation of an antibody response of sufficient quality and/or quantity as to neutralize the vaccine-encoded, self-generated SARS-CoV-2 spike protein antigens and/or spike protein constituent components, such as S1 (Time₆).

Given that the interval which exists between Time₄ and Time₆ must constitute a non-zero value, this interval must also, therefore, constitute a period of increased mechanistic risk, where vaccine-induced, self-generated SARS-CoV-2 spike proteins and/or spike protein constituent components are free to exert an inherent molecular toxicity within the cells, tissues and organ systems of a recipient patient in an unopposed fashion. It has been demonstrated that Time₄ begins as early as 1 day following the administration of an initial dose of SARS-CoV-2 nucleotide vaccine and Time₆ has been demonstrated to occur not before approximately 16 days following the administration of an initial dose of a SARS-CoV-2 nucleotide vaccine ⁽¹³⁶⁾. Members of the general population have demonstrated mean peak plasma concentrations of isolated S1 at 68 pg/ml or 4.09×10^{10} kDa/ml

between day 1 and day 15, following an initial dose of a SARS-CoV-2 nucleotide vaccine ⁽¹³⁶⁾. 4.09×10^{10} kDa/ml equates to a whole-body peak plasma concentration of isolated S1 measuring approximately 1.12×10^{14} kDa between day 1 and 15, following an initial dose of a SARS-CoV-2 nucleotide vaccine ⁽¹³⁶⁾. In stark contrast, following a 6mcg dose of a SARS-CoV-2 inactivated-virus vaccine, such as BBV152/Covaxin, the maximum potential whole-body load of S1 is only 1.036×10^6 kDa (considering a S1 mass of 76.5 kDa and a mean of 35 spike proteins per SARS-CoV-2 virion). Additionally, the maximum potential per/ml plasma concentration of S1 following a 6mcg dose of an inactivated-virus SARS-CoV-2 vaccine is only 376.93 kDa/ml.

As a result of the enhanced capacity and efficiency for translation of mRNA into protein that is found within the skeletal muscle tissue of actively training elite athletes, this population faces a profoundly increased level of mechanistic risk upon exposure to SARS-CoV-2 nucleotide vaccines. That is, vaccine-induced, self-generated SARS CoV-2 spike proteins and/or spike protein constituent components, such as S1, will be generated in greater magnitudes and/or at greater rates, compared to non-elite athletes. The resultant plasma concentrations of self-generated spike proteins and/or spike protein constituent components, such as S1, will be markedly elevated in populations of actively training elite athletes relative to plasma concentrations found in the general population following administration of a SARS-CoV-2 nucleotide vaccine. Subsequently, vaccine-induced, self-generated spike proteins and/or spike protein constituent components, such as S1, will exert a proportionally heightened level of molecular toxicity upon the cells, tissues and organ systems of actively training elite athletes. The inherent toxicity of vaccine-induced, self-synthesized SARS-CoV-2 spike proteins and/or spike protein constituent components, such as S1, provides a cogent explanation as to why nucleotide vaccines against SARS-CoV-2 have consistently been observed to induce class-specific adverse events in the form of myocarditis/pericarditis/myopericarditis (myocarditis) and thrombosis/thromboembolism/thrombocytopenia (thrombosis), whereas, inactivated-virus SARS-CoV-2 vaccines have not. Moreover, occurrences of post-SARS-CoV-2 nucleotide vaccine myocarditis and thrombosis are not evenly distributed within the population ^(86,87,88,92,93,94,95,100,135). Young males and females, respectively, are disproportionately afflicted by myocarditis and thrombosis following administration of SARS-CoV-2 nucleotide vaccines ^(100,135). The inherent toxicity of vaccine-induced, self-generated SARS-CoV-2 spike proteins and/or spike protein constituent components, such as S1, combined with the highly proficient protein synthetic apparatus characteristic of youth, creates a scenario of extreme mechanistic risk. The *non-throttleable* flogging of a highly competent protein synthetic apparatus, found in highly anabolic populations such as elite athletes, by vaccine-delivered, codon-optimized genetic templates, results in greater plasma concentrations of vaccine-induced, self-generated SARS-CoV-2 spike proteins and/or spike protein constituent components, such as S1, relative to less anabolic segments of the population. Thus, the high prevalence of SARS-CoV-2 nucleotide vaccine class-specific adverse events, such as myocarditis and thrombosis, disproportionately afflicts the most anabolic members of the population. That those members of the population who possess the most proficient protein synthetic apparatus frequently suffer pathology secondary to the toxicity of vaccine-induced, self-generated spike proteins and/or spike protein constituent components, such as S1, should not be viewed as rare, nor unexpected occurrences, but rather, an increased mechanistic risk for

thrombosis and/or myocarditis should be fully recognized as an entirely logical and expected outcome issuing forth from the application of vaccination technology that is capable of flogging the protein synthetic apparatus of recipient patients, in a non-throttleable manner so as to generate very high rates of seroconversion amongst even the most catabolic segments of the population, exemplified, as such, by patients with end-stage renal disease ⁽⁹¹⁾.

The significantly increased mechanistic risk incurred by populations of elite strength, power and endurance athletes upon vaccination with SARS-CoV-2 nucleotide vaccines provides a stark contrast to the impressively benign risk: reward ratio afforded to populations of elite athletes by inactivated-virus vaccines ^(37,39,47,56,100,135). The desirable risk profile of inactivated-virus SARS-CoV-2 vaccines in populations, such as elite athletes, with highly competent protein synthetic apparatus, expanded skeletal muscle capillary networks and high levels of physical activity are exemplified by the fact that individuals receiving inactivated-virus vaccines against SARS-CoV-2 are devoid of injuries and deaths resulting from myocarditis and thrombosis ⁽⁵⁶⁾. Inactivated-virus vaccines against SARS-CoV-2 provide highly immunocompetent populations, such as elite athletes, with a robust immune response against the comprehensive landscape of SARS-CoV-2 antigenic epitopes, while imposing no additional mechanistic risks of adverse outcomes relative to the general population. Conversely, SARS-CoV-2 nucleotide vaccines only stimulate populations of elite athletes to generate an immune response against a hyper-narrow SARS-CoV-2 antigenic epitope at the cost of incurring incredible mechanistic risk of class-specific, vaccine-induced adverse outcomes including but not limited to thrombosis and/or myocarditis.

The vaccination of elite strength, power and endurance athletes against SARS-CoV-2

The use of SARS-CoV-2 nucleotide vaccines should be avoided within the minority population of actively training elite strength, power and endurance athletes. Rather, inactivated-virus vaccines against SARS-CoV-2 should be considered first-line therapy and the gold standard for vaccination of populations of actively training elite strength, power and endurance athletes. Moreover, elite athletes contemplating vaccination against SARS-CoV-2 should receive detailed counseling and education as to the significant differences in mechanistic risk which exists between the various SARS-CoV-2 vaccine candidates, as it pertains to young, highly anabolic and intensely physically active populations.

In the event that an elite athlete has a known incompatibility with components of all known inactivated-virus vaccines against SARS-CoV-2, alternatives such as live-attenuated and sub-unit vaccines against SARS-CoV-2 should be considered as alternatives, due to their lower inherent mechanistic risk relative to SARS-CoV-2 nucleotide vaccines. The lower level of inherent mechanistic risk possessed by live-attenuated and/or sub-unit SARS-CoV-2 vaccines, relative to SARS-CoV-2 nucleotide vaccines, stems from the introduction of a fixed-dose of SARS-CoV-2 spike proteins and/or spike protein constituent components, such as S1.

It is crucially important to consider the extreme physiology and psychology, which characterizes elite athletes, in the context of the global population, when weighing what constitutes an acceptable risk of vaccine-induced adverse outcomes. The World Health Organization (WHO) defines disability as “any restriction or lack (resulting from any impairment) of ability to perform an

activity in the manner or within the range considered normal for a human being”. While elite strength, power and endurance athletes comprise an exceedingly small minority of the global population, the extreme physiology, psychology and accompanying limit-testing physical performances exemplified by this minority population must be acknowledged, respected and ultimately considered “normal” by healthcare professionals and government officials, for this group of human beings. Therefore, when contemplating the vaccination of elite athletes against SARS-CoV-2, not only should the avoidance of unnecessary serious injury and death be a driving factor in selecting appropriate SARS-CoV-2 vaccine candidates, but additionally, the avoidance of any adverse outcomes which result in restrictions or the lack of ability to perform at the highest levels of elite sport, regardless of how minor or insignificant such adverse events might appear from the perspective of members of the general global population, particularly physicians and officials.

In a great many geopolitical jurisdictions, there are no regulatory obstacles to the implementation of policies and practices, which would elevate the administration of inactivated-virus SARS-CoV-2 vaccines, in populations of actively training elite athletes, to the status of first-line therapy. China, Russia, India, Argentina, Bahrain, Brazil, Chile, Egypt, Indonesia, Iran, Morocco, Pakistan, Peru, Philippines, the United Arab Emirates, Turkey and countries participating within the WHO’s COVAX program are examples of some of the global geopolitical jurisdictions where inactivated-virus SARS-CoV-2 vaccines are readily available to populations of elite athletes and the healthcare professionals who care for them. However, considerable global inequity does exist among elite athletes, as it pertains to the availability of inactive-virus SARS-CoV-2 vaccines. Inactivated-virus SARS-CoV-2 vaccines are not available in a great many geopolitical jurisdictions. For example, inactivated-virus SARS-CoV-2 vaccines have not been made available in geopolitical jurisdictions such as, but not limited to: the United States of America and its territories, Canada, Australia, Japan, the United Kingdom and most Western European nations. The global disparity in the access of elite athletes to inactivated-virus SARS-CoV-2 vaccines represents an existential threat to fair and equitable global sport, to a degree that dwarfs the threat posed by doping. The threat to the integrity of sport is especially poignant, when viewed in the context of SARS-CoV-2 vaccine mandates a requirement for travel and/or training and/or competition. Universal access to inactivated-virus SARS-CoV-2 vaccines is not merely an issue of sport integrity it constitutes a bioethical dilemma of monumental proportions. Despite the fact that a PMC search of the US National Library of Medicine for the terms “individualized medicine” return over 370,000 relevant search results, little to no resources have been dedicated to examining the intersection of the molecular toxicity of the SARS-CoV-2 spike protein, the various characteristics of globally deployed SARS-CoV-2 vaccine candidates and those characteristics of immune competent and high anabolic populations. Elite athletes who live and/or compete within geopolitical jurisdictions that impose SARS-CoV-2 vaccine mandates as a condition of participation in training and/or competition, but do not concurrently make available (or recognize the validity) of inactivated-virus SARS-CoV-2 vaccines are made subject to most the despicable forms of prejudice, discrimination, injury and violations of basic human rights.

Mechanistically, it is likely that other highly anabolic populations, such as infants, children, adolescents, young adults, pregnant women and healthy adults, also would likely benefit from the

avoidance of *non-throttleable*, epitopically hyper-narrow SARS-CoV-2 nucleotide vaccines, in favor of vaccines which present a limited exposure to SARS-CoV-2 spike protein antigens in combination with a complete landscape of SARS-CoV-2 antigenic epitopes, where such vaccines include inactivated-virus vaccines against SARS-CoV-2. Additionally, the preferred use of inactivated-virus SARS-CoV-2 vaccines among highly anabolic segments of the global population may have a profound effect on reducing the number and severity of SARS-CoV-2 variants, as immunocompetent and highly anabolic individuals are likely to form a bulwark against the accelerated evolution of SARS-CoV-2 via enduring and robust immunologic responses against the comprehensive landscape of SARS-CoV-2 antigenic epitopes. The question of whether or not vaccination against SARS-CoV-2 is warranted in populations of elite strength, power and endurance athletes, or in any population for that matter, exceeded the scope of this report.

Etiology and ontology of post-SARS-CoV-2 nucleotide vaccination new-onset myocarditis, pericarditis and myopericarditis

As a consequence of examining the pathophysiology and molecular toxicity of the SARS-CoV-2 spike protein and spike protein constituent components, such as S1 in the context of the vaccination of actively training elite athletes against SARS-CoV-2, this report presents a novel hypothesis for the etiology and ontology of post-SARS-CoV-2 nucleotide vaccination new-onset myocarditis, pericarditis and myopericarditis.

SARS-CoV-2 spike protein molecular pathophysiology

(1.1) Introduction

SARS-CoV-2, a human β -coronavirus implicated as the causative agent in the COVID-19 pandemic is one of seven coronaviruses known to infect humans ^(1,10). MERS-CoV and SARS-CoV-1 comprise β -coronaviruses known to cause severe respiratory disease in humans, while SARS-CoV-2 infection has been widely associated with the onset of atypical-severe acute respiratory distress syndrome (ARDS)^(1,2). The etiology of SARS-CoV-2 associated ARDS may be rooted in the fact that SARS-CoV-2 infected individuals have been frequently observed to suffer critical cardiovascular complications, even among individuals without a prior history of cardiovascular disease ^(2,4). 20–40% of patients hospitalized for SARS-CoV-2 infection manifest a wide spectrum of symptoms related to heart injury, including, but not limited to: mild chest discomfort, palpitations, arrhythmias, cardiogenic shock and even fulminant heart failure ⁽²⁾. Myocardial injury has been reported in the majority of deceased SARS-CoV-2 infected patients, and approximately 7% of all SARS-CoV-2 related deaths have been directly linked to concurrent myocarditis ⁽²⁾.

Patients with SARS-CoV-2 infection, manifesting as severe COVID-19 disease, have commonly been observed to experience endothelial injury and rheological disturbances as evidenced by the prevalence of thrombotic disorders, sepsis, and disseminated intravascular coagulation (DIC)⁽⁴⁾. Studies of large populations of COVID-19 patients have reported that anywhere between 18.8% and 36.2% of patients infected with SARS-CoV-2 demonstrate thrombocytopenia on hospital admission ⁽⁴⁾. It has also been reported that the incidence of thrombotic complications for SARS-CoV-2 infected patients admitted to the intensive care unit (ICU) was 31%, while, in comparison, the incidence of thrombotic complications was reported at only 1.3% for non-SARS-CoV-2 infected admissions to the ICU ⁽⁴⁾.

β -coronaviruses are enveloped viruses with a single positive-stranded RNA genome approximately 26–32 kb in length ⁽¹⁾. Typically, the viral genome of β -coronaviruses encodes four classes of structural proteins: spike proteins, envelope proteins, membrane proteins, and nucleocapsid proteins ⁽¹⁾. Additionally the viral genome of β -coronaviruses may encode several non-structural proteins and multiple unique accessory proteins ⁽¹⁾. β -coronaviruses utilize a homo-trimeric spike glycoprotein (spike protein), consisting of two primary sub-units: the S1 sub-unit (S1) and the S2 sub-unit (S2) ^(1,3). SARS-CoV-2 spike proteins protrude from the envelope protein of virion and function to bind to target-receptors located on potential host cells ⁽³⁾. Cryo-electron microscopy studies of the interaction between SARS-CoV-1 spike proteins and human angiotensin converting enzyme 2 (hACE2), a component of the renin-angiotensin system (RAS), have demonstrated that spike protein $\leftrightarrow$ hACE2 interaction was an essential requirement for SARS-CoV-1 infection of target cells ⁽³⁾. Similarly to SARS-CoV-1, it has been widely reported that SARS-CoV-2 spike protein interactions with hACE2 are essential to SARS-CoV-2 virion cell entry ^(3,5). The importance of the SARS-CoV-2 spike protein $\leftrightarrow$ hACE2 interaction is highlighted by the fact that cells not expressing hACE2 are typically protected from infection by SARS-CoV-2 ^(3,5). The SARS-CoV-2 spike protein receptor-binding domain (RBD) is located on S1 of the SARS-CoV-2 spike protein ^(3,5). Reports examining binding between SARS-CoV-2 spike protein $\leftrightarrow$ hACE2 illustrate that the RBD binds to hACE2 with an affinity in the low nanomolar range, strongly indicating that the RBD is the key component of the SARS-CoV-2 spike protein responsible for the binding of hACE2 ^(3,5). Binding of the SARS-CoV-2 spike protein RBD to hACE2 triggers a resultant cascade of molecular events that, in the case of live virion, leads to the fusion between SARS-CoV-2 virion and target cell membranes ^(3,5). The spike protein of SARS-CoV-2, as well as spike protein constituent components, such as S1, are found within the blood plasma of COVID-19 patients in isolated forms, completely dissociated from whole SARS-CoV-2 virion ⁽¹²⁾. A strong correlation has been reported between high plasma concentrations of isolated S1 and the rate of ICU admission for patients with COVID-19 ⁽¹²⁾. Additionally, COVID-19 patients with plasma concentrations of isolated S1 greater than 50 pg/ml demonstrated a 100% likelihood of being intubated within one day of hospital admission ⁽¹²⁾. Beyond playing a crucial role during viral entry of target cells, SARS-CoV-2 spike proteins and S1 demonstrate a profound, inherent molecular toxicity ^(4,5,9). Isolated SARS-CoV-2 spike proteins and/or isolated S1 may exist in the circulation of COVID-19 patient where such isolated spike proteins and/or isolated S1 are capable of binding with hACE2 expressed by a variety of tissues and cell types ^(1,3,4,5,9,12). The interaction between hACE2 and isolated SARS-CoV-2 spike proteins occurs with the spike proteins existing in the pre-fusion conformation ^(1,3,4,5,9,12). The RBD of isolated SARS-CoV-2 spike proteins or isolated S1, upon interacting with hACE2, induces a number of molecular signaling cascades, the nature of which may vary depending on the cell and/or tissue type expressing hACE2 ^(1,3,4,5,10,12). The binding of hACE2 with the RBD of isolated SARS-CoV-2 spike proteins and/or isolated S1 culminates in the observed tissue-specific molecular toxicity associated with isolated spike proteins and isolated S1 ^(1,3,4,5,10,12).

(1.2) SARS-CoV-2 spike protein mediated hypercoagulation

Reports demonstrate that human platelets express hACE2 and transmembrane protease serine 2 (TMPRSS2) ⁽⁴⁾. Additionally, it has been demonstrated that isolated SARS-CoV-2 spike proteins directly bind to platelet expressed hACE2 ⁽⁴⁾. Incubation of washed human platelets, from healthy

donors, with isolated SARS-CoV-2 spike proteins, were found to potentiate platelet aggregation and dense granule secretion, in a dose-dependent fashion, upon exposure to collagen, thrombin and adenosine diphosphate (ADP)⁽⁴⁾. Additionally, incubation of washed human platelets, from healthy donors with isolated S1, were found to potentiate a dose-dependent increase in platelet aggregation and dense granule secretion in response to collagen, thrombin and ADP exposure⁽⁴⁾. Isolated SARS-CoV-2 spike proteins have been reported to induce integrin $\alpha\text{IIb}\beta 3$ activation and P-selectin expression, in the absence of any agonist⁽⁴⁾. Furthermore, isolated SARS-CoV-2 spike proteins and isolated S1, have been reported to enhance both integrin $\alpha\text{IIb}\beta 3$ activation and P-selectin expression among platelets from healthy human donors in the presence of agonists such as collagen, thrombin and ADP⁽⁴⁾.

While both isolated SARS-CoV-2 spike proteins, and isolated S1, are capable of initiating increased platelet aggregation, platelet dense granule secretion, induction of integrin $\alpha\text{IIb}\beta 3$ and P-selectin expression, isolated S2, appears uninvolved in these processes⁽⁴⁾. Reports demonstrate that the incubation of washed human platelets, from healthy donors, with isolated S2, was not found to alter or potentiate platelet aggregation, dense granule secretion, nor alter integrin $\alpha\text{IIb}\beta 3$ activation. No alterations of P-selectin expression in response to collagen, thrombin or ADP was reported following incubation of washed human platelets from healthy donors, with isolated S2^(3,4). Following incubation with isolated SARS-CoV-2 spike proteins, platelets from healthy human donors displayed markedly accelerated spreading across fibrinogen-coated surfaces⁽⁴⁾. Platelets from healthy human donors exposed to isolated SARS-CoV-2 spike proteins are reported to demonstrate enhanced clot retraction induced by agonists such as collagen, thrombin or ADP⁽⁴⁾. Additionally, after incubation with isolated S1, platelets from healthy human donors displayed markedly accelerated spreading across fibrinogen-coated surfaces and clot retraction induced by agonists⁽⁴⁾. Isolated SARS-CoV-2 spike proteins have also demonstrated the potential for thrombosis in vivo⁽⁴⁾. Platelets from wild-type mice were injected into thrombocytopenic wild-type (tcp-wt) mice, where these tcp-wt mice were then simultaneously administered isolated SARS-CoV-2 spike proteins intravenously⁽⁴⁾. No effects on thrombus formation were observed following mesenteric arteriole injury in tcp-wt mice transfused with platelets from wild-type mice⁽⁴⁾. However, when platelets from transgenic mice bearing hACE2 were injected into tcp-wt mice and said tcp-wt mice were simultaneously intravenously administered isolated SARS-CoV-2 spike proteins, thrombus formation was indeed observed to be potentiated⁽⁴⁾. It has been well established that mitogen-activated protein kinase (MAPK) participates in platelet activation and thrombosis^(16,17,18). Furthermore, hACE2 activation of MAPK has been demonstrated to mediate the potentiating effects of isolated SARS-CoV-2 spike proteins and/or isolated S1 on the activation of human platelet aggregation and dense granule secretion⁽⁴⁾. Isolated SARS-CoV-2 spike proteins, were found to phosphorylate hACE2, Erk, p38, and JNK in human platelets⁽⁴⁾. Platelets from healthy human donors were pre-treated with isolated SARS-CoV-2 spike proteins, where the spike proteins stimulated platelet hACE2 phosphorylation at 3 min, while MAPK (Erk, p38, and JNK) were phosphorylated subsequently to hACE2 phosphorylation⁽⁴⁾. Furthermore, the inhibition of Erk, p38, and JNK phosphorylation by the treatment of platelets with MAPK inhibitors: PD98059, SB203580, and SP600125 abolished the pro-thrombotic effects of isolated SARS-CoV-2 spike proteins, on human platelets⁽⁴⁾. The accelerated clot retraction elicited by the exposure of healthy human

platelets to isolated SARS-CoV-2 spike proteins, was also prevented by administration of MAPK inhibitors: PD98059, SB203580, and SP600125 ⁽⁴⁾.

Isolated SARS-CoV-2 spike proteins, have been observed to directly induce the release of coagulation factors, inflammatory cytokines, as well as catalyze the formation of leukocyte-platelet aggregates ⁽⁴⁾. Isolated SARS-CoV-2 spike proteins, were shown to stimulate platelet release of both Factor V and Factor XIII coagulation factors, at levels of release comparable to those observed via thrombin stimulation ⁽⁴⁾. Exposure of platelets, from healthy human donors, to isolated SARS-CoV-2 spike proteins, stimulated platelet secretion of α -granule inflammatory cytokines PF4, TNF- α , IL-8, and IL-1 β ⁽⁴⁾.

(1.3) SARS-CoV-2 spike protein induced endothelial dysfunction

Isolated SARS-CoV-2 spike proteins have been shown to induce endothelial cell damage independent of SARS-CoV-2 infection of said endothelial cells ⁽⁵⁾. Pulmonary artery endothelial cells exposed to isolated SARS-CoV-2 spike proteins have demonstrated impairment of acetylcholine-induced, endothelium-dependent vasodilation ⁽⁵⁾. Conversely, endothelium-independent vasodilation, induced by sodium nitroprusside, was not altered by exposure to isolated spike proteins ⁽⁵⁾. In addition to the demonstrated impairment of vasodilatory actions within populations of endothelial cells, isolated S1 has also demonstrated the ability to interact with endothelial hACE2 and elicit deleterious molecular sequelae ^(3,4,5). Endothelial cells exposed to isolated S1 demonstrated altered mitochondrial dynamics, increased mitochondrial fragmentation, impaired mitochondrial function, compensatory increases in glycolysis, down-regulation of hACE2 expression along with increased levels of oxidative stress ⁽⁵⁾.

hACE2 functions as a carboxypeptidase, cleaving a single residue from angiotensin I (AngI), generating Ang1–9 and cleaving a single residue from angiotensin II (AngII) to generate Ang1–7 ^(110,111). Angiotensin converting enzyme (hACE), in contrast to hACE2, cleaves AngI into AngII ^(110,111). Therefore, SARS-CoV-2 spike proteins upon binding to hACE2 induce a subsequent down-regulation of hACE2 expression, resulting in an increased rate and/or magnitude of AngII production ^(110,111). AngII is a vasoactive peptide that facilitates vasoconstriction, however, AngII also impacts many aspects of cellular function unrelated to vasoconstriction ⁽¹¹¹⁾. AngII binding to AT₁R causes AT₁R interaction with heterotrimeric G proteins, which subsequently trigger second messenger signaling via arachidonic acid, and ROS ⁽¹¹¹⁾. Arachidonic acid and ROS signaling, subsequently leads to downstream activation of phospholipases C, A, and D ⁽¹¹¹⁾. Additionally, AngII is known to stimulate nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (Nox) to produce superoxide and H₂O₂ ⁽¹¹¹⁾. Therefore, a mechanism exists, where SARS-CoV-2 spike proteins and/or S1 stimulate increased ROS production via AngII-induced expression of Nox family proteins ⁽¹¹¹⁾. A down-regulation of hACE2 expression subsequent to interactions of hACE2 with SARS-CoV-1 spike proteins and/or spike protein constituent components, such as S1, was observed to alter the stability of the RAS and resulted in a subsequent increase of AngII ⁽¹¹⁰⁾. Spike protein induced increases of AngII, secondary to downregulation of hACE2 expression, were reported to have been a major contributor to the phenomena of cytokine storm observed in SARS-CoV-1 infection ⁽¹¹⁰⁾. Reports strongly suggest that, like SARS-CoV-1, isolated spike proteins and/or isolated S1 of SARS-CoV-2 interact with and subsequently induce a down-regulation of hACE2 ^(5,112).

Acute coronary syndromes (ACS) have been associated with exposure to isolated SARS-CoV-2 spike proteins and isolated S1 (2,7). Physiological mechanisms contributing to ACS, (other than pro-thrombotic events such as: increased platelet aggregation, the formation of leukocyte-platelet aggregates and platelet release of coagulation factors), include the interaction of endothelial cells and/or cardiac pericytes, which express abundant hACE2, with isolated SARS-CoV-2 spike proteins and/or isolated S1 circulating in the plasma (7,12,136). Isolated SARS-CoV-2 spike proteins and/or isolated S1 may interact with hACE2 and subsequently initiate a down-regulation of hACE2 (5,7,12,136). As previously noted, a down-regulation of hACE2 results in reduced synthesis of Ang1-7 and a compensatory increase of AngII (5,7). Ang1-7 is associated with a well-regulate inflammatory response, reduced markers of oxidative stress, and endothelium-dependent vasodilation (5,7,8). Down-regulation of hACE2, secondary to SARS-CoV-2 spike protein binding, leads to lower Ang1-7 levels and correspondingly higher levels of AngII, resulting in increased ROS generation, inflammation, vasoconstriction, and endothelial dysfunction (5,7,8). Endothelial dysfunction induced via inflammatory processes and ROS-inflicted molecular damage, is associated with the release of von Willebrand factor (vWf), and the production of thromboxane and plasminogen activator inhibitor-1 (PAI-1) (8). Therefore, the existence of multiple, non-platelet driven, pro-thrombotic mechanisms are associated with the exposure of endothelial cells to isolated SARS-CoV-2 spike proteins and/or isolated S1.

Endothelial cells perform an immunosurveillance function within the context of a broader vascular immune response. Activation of the endothelium results in the recruitment and mobilization of immune cells to vascular beds and the tissues, which they perfuse (19). Normally functioning endothelium is able to limit oxidative stress via the expression of antioxidant mechanisms such as, superoxide dismutase and glutathione (8). However, dysfunctional endothelium, such as that which occurs upon down-regulation of hACE2, secondary to interactions with isolated SARS-CoV-2 spike proteins or isolated S1; actively promotes the generation of superoxide anions, which contribute to the enhancement of local oxidative stress (8). Increased levels of local oxidative stress have been associated with a higher risk of ACS (8). Additionally, a dysfunctional endothelium demonstrates enhanced production of endothelin-1, a potent vasoconstrictor and pro-thrombotic agent, thus contributing to an even further imbalance between vasodilation and vasoconstriction signaling (8). In addition to enhanced vasoconstriction, increased secretion of endothelin-1 promotes platelet aggregation and pathological sequelae, which may include myocardial ischemia (8). Endothelial dysfunction, resulting from isolated SARS-CoV-2 spike protein and/or isolated S1-induced down regulation of hACE2, manifests as increased inflammation, oxidative stress and vasoconstriction. This triad of factors can induce atheromatous plaque erosion and/or rupture, resulting in coronary thrombosis and ACS (8). ACS, such as myocardial infarction with non-obstructive coronary arteries (MINOCA) has been associated with exposure to SARS-CoV-2 spike proteins (8).

(1.4) SARS-CoV-2 spike protein induced cardiac pericyte dysfunction

Cardiac pericytes are pleiotropic cells associated with the coronary microvasculature (7,9). Cardiac pericytes have been demonstrated to support the integrity of coronary artery endothelial cells, facilitate vascular remodeling, facilitate repair of cardiac tissue, and modulate inflammation within

cardiac tissue ⁽⁹⁾. Dysfunctional cardiac pericytes have been observed in patients with severe myocardial disease ⁽⁹⁾. Additionally, dysfunctional cardiac pericytes have been observed to worsen ACS events, for example, in the case of myocardial infarction, cardiac pericytes are reported to remain persistently contracted, thus impeding circulation through coronary microvasculature and contributing to onset and/or worsening of thrombosis and ischemia ⁽⁹⁾. Cardiac pericytes surrounding the coronary microvasculature have been found to express hACE2, TMPRSS2 and extracellular matrix metalloproteinase inducer (CD147) ^(7,9). Cardiac pericytes exposed to isolated SARS-CoV-2 spike proteins were found to possess significantly increased levels of phospho-Erk1/2 ⁽⁹⁾. Antibodies against CD147 were found to abolish the observed increased phosphorylation of Erk1/2 resulting from cardiac pericyte exposure to isolated SARS-CoV-2 spike proteins ⁽⁹⁾. Anti-hACE2 antibodies were not found to abolish the increased phosphorylation of Erk1/2 in cardiac pericytes upon exposure to isolated SARS-CoV-2 spike proteins ⁽⁹⁾. Exposure to isolated SARS-CoV-2 spike proteins has been observed to trigger cardiac pericytes to generate a pro-inflammatory secretome resembling the phenomena of cytokine storm ⁽⁹⁾. Ten pro-inflammatory factors in cardiac pericytes were demonstrated to be significantly up regulated as a result of exposure to isolated SARS-CoV-2 spike proteins, including potent pro-inflammatory cytokines TNF α , IL-6, and MCP1 ⁽⁹⁾. Cardiac pericytes exposed to isolated SARS-CoV-2 spike proteins were observed to secrete increased levels of IL-1 β and unlike the phosphorylation of Erk1/2, the introduction of anti-CD147 neutralizing antibodies failed to prevent isolated SARS-CoV-2 spike proteins from stimulating cardiac pericytes to generate said pro-inflammatory secretome ⁽⁹⁾. Isolated SARS-CoV-2 spike proteins have been demonstrated to cause molecular and functional changes in human cardiac pericytes, both dependent and independent of the CD147 receptor ⁽⁹⁾. Exposure to isolated SARS-CoV-2 spike proteins activate the Raf/MEK/Erk signal transduction pathway in human cardiac pericytes, and phosphorylation of the Erk1/2 signaling pathway is instrumental to the induction of cyclooxygenase-2 (COX-2), a key prostaglandin synthase involved in inflammation ⁽⁹⁾. Isolated SARS-CoV-2 spike proteins may remain engaged with cellular receptors for a longer duration than the whole SARS-CoV-2 virion, resulting in prolonged stimulation of intracellular signaling ⁽⁹⁾.

(1.5) SARS-CoV-2 spike protein induced cardiomyocyte dysfunction

HCoV-NL63 (NL63) is an α -coronavirus known to infect humans and cause moderately severe respiratory tract symptoms ⁽¹⁰⁾. NL63 possesses spike proteins, that like the spike proteins of SARS-CoV-2, engage target cell hACE2 for virus entry ⁽¹⁰⁾. However, it has been demonstrated that SARS-CoV-2 spike proteins but not NL63 spike proteins interact with Toll-like receptor 4 (TLR4) ⁽¹⁰⁾. TLR4 is a crucial pattern recognition receptor, responsible for detecting pathogens and initiating innate immune responses ⁽¹⁰⁾. SARS-CoV-2 has been associated with the phenomena of cytokine storm, whereas NL63 has not been reported to be associated with the phenomena of cytokine storm ⁽¹⁰⁾. TLR4 possesses three essential domains: an extracellular leucine rich repeat domain (LRR), a transmembrane domain (TM) and an intracellular Toll/Interleukin-1 receptor like domain (TIR) ⁽¹⁰⁾. It has been demonstrated that experimental constructs expressing TLR4-LRR but not TLR4-TIR interact with SARS-CoV-2 spike protein S1 ⁽¹⁰⁾. Therefore, direct interactions of S1 with the LRR domain of TLR4, likely serves as an alarmin signaling pathway, that when activated subsequently induces host innate immune responses directed through TLR4 mediated pathways

(10). Reports demonstrate that S1 of the SARS-CoV-2 spike protein also directly interacts with myeloid differentiation factor-2 (MD-2), a critical co-receptor for TLR4 signaling (10). Direct interaction of S1 with TLR4 and MD-2 has been reported to subsequently activate nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling in cardiomyocytes (10). Additionally, cardiomyocytes have been reported possess endogenous innate immune mechanisms (10). The activation of cardiomyocyte innate immune pathways, particularly at high levels, is a known cause of cardiac inflammation and myocardial damage (10). The TLR4/MD-2->NF-κB axis is among the most prominent of innate immune pathways, as such, TLR4/MD-2->NF-κB signaling has been reported to be a potent driver of cardiac inflammation and hypertrophic remodeling (10). Activation of cardiomyocyte TLR4 has been reported to result in impaired cardiomyocyte contractility as well as the induction and expression of genes regulating pro-inflammatory cytokines (10). Conversely, in conditions such as septic shock and myocardial infarction, depletion of TLR4 in cardiomyocytes has been observed to reduce cardiac damage (10). Reported data suggests that SARS-CoV-2 spike protein S1 activation of NF-κB signaling via TLR4, comprises a pro-inflammatory, ROS generating and potentially cytotoxic mechanism, which functions independent of and in addition to: spike protein/S1 induced down regulation of hACE2 (5,10,112). Cardiomyocytes, exposed to membrane-localized SARS-CoV-2 spike protein S1, have demonstrated activation of TLR4/MD-2->NF-κB signaling of sufficient intensity to induces cardiac inflammation, cardiac hypertrophy and reduced cardiac systolic function (10). Additionally, it has been found that both glycosylated and non-glycosylated S1 activates TLR4 signaling and subsequently induces hyper-inflammatory responses among human macrophages (13,14).

(1.6) SARS-CoV-2 spike protein induced immune system hyper-activation

In addition to S1 stimulated TLR4/MD-2->NF-κB signaling, which results in the induction of hyper-inflammatory responses in human macrophages, exposure of human peripheral blood mononuclear cells (PBMCs) to isolated S1 has been demonstrated to activate: the NLRP3 inflammasome/caspase-1 pathway, the p38 MAPK pathway and the NF-κB pathway; resulting in the exaggerated production of TNFα, IL-6, IL-1β and IL-8 (10,15). Isolated SARS-CoV-2 spike proteins have been demonstrated to increase the proportion of leukocyte-platelet aggregates, namely CD45+ and CD41+ aggregates (4). Monocyte-platelet aggregates (CD14+ CD41+) and neutrophil-platelet aggregates (CD65+ CD41+) have been found to be significantly increased after incubation of platelets, from healthy human donors, with isolated SARS-CoV-2 spike proteins (4). These observations support reports that intra-tracheal exposure of K18-hACE2 transgenic mice, which over-express hACE2, to isolated S1 resulted in profound alveolar inflammation characterized by the infiltration of monocytes, macrophages, and neutrophils (112).

Neutrophils typically comprise the largest circulating population of white blood cells and play a pivotal role in innate immunity (25). Neutrophil activation is regulated by chemokines such as IL-8 (25). Neutrophil activation by IL-8, released by platelets in response to exposure to isolated SARS-CoV-2 spike proteins, has been observed to promote the formation of neutrophil extracellular trap (NET), platelet aggregation, and cytotoxicity (4,25). Neutrophils play a crucial role in the pathogenesis of endothelitis observed in SARS-CoV-2 infected COVID-19 patients where the cellular adhesion of mononuclear infiltrates caused by SARS-CoV-2 spike protein/hACE2 interactions induce genetic expression of IL-8 (5,6,25).

(1.7) SARS-CoV-2 spike protein induced central nervous system dysfunction

hACE2 is ubiquitously expressed throughout the vasculature of the frontal cortex⁽¹⁹⁾. hACE2 is found in both the capillary networks of the frontal cortex, as well as, the larger caliber vessels of the frontal cortex⁽¹⁹⁾. It has been demonstrated that introduction of isolated SARS-CoV-2 spike proteins to models of the human blood-brain barrier (hBBB) results in a significant degradation of hBBB properties⁽¹⁹⁾. Additionally, it has been found that isolated SARS-CoV-2 spike protein S1 promotes a loss of barrier integrity in an advanced 3D microfluidic model of the hBBB⁽¹⁹⁾. Evidence suggests that isolated SARS-CoV-2 spike proteins and/or isolated S1 and/or isolated S2 and/or isolated RBD induce pro-inflammatory responses in cerebral endothelial cells^(19,113,114).

Inflammation, ROS generation and endothelial dysfunction resulting from isolated SARS-CoV-2 spike protein and/or isolated S1 interactions with hACE2 expressed by cerebral endothelial cells response may contribute to deterioration of hBBB function⁽¹⁹⁾.

Reports demonstrate that upon exposure to isolated S1 at [10 nM], the presence of hBBB permeability, in the direction of the lumen->parenchymal compartment, was clearly evident as early as 2 hours post-S1 exposure⁽¹⁹⁾. These results suggest that isolated spike proteins and/or isolated S1 can induce hBBB permeability shortly following exposure and without the need for concomitant SARS-CoV-2 infection of cerebral endothelial cells⁽¹⁹⁾. Additionally, primary human brain microvascular endothelial cells exposed to isolated RBD, isolated S1 and isolated S2, of the SARS-CoV-2 spike protein, demonstrated elevated expression of the cell adhesion molecules (ICAM-1, VCAM-1), leukocyte chemotaxis factors (CXCL10, CCL5 (RANTES), and pro-inflammatory cytokines (IL-1 β , IL-6)⁽¹⁹⁾.

Given that isolated S1, isolated S2 and isolated RBD have been observed to exert similar deleterious effects on hBBB strongly suggests that isolated SARS-CoV-2 spike proteins and/or isolated constituent-components of spike proteins do not exclusively exert a deleterious effect on hBBB function purely via interaction with hACE2 expressed by cerebral endothelial cells⁽¹⁹⁾. Rather, the interaction of isolated SARS-CoV-2 spike proteins and/or isolated spike protein constituent-components with the hBBB, spans a multifocal array of interactions involving more than one species of receptor and/or signaling cascades⁽¹⁹⁾. Reported findings demonstrate that isolated SARS-CoV-2 spike proteins and/or isolated spike protein constituent-components reduce hBBB tightness, as indicated by the elevated expression of ICAM-1, VCAM-1, CXCL10, CCL5, IL-1 β and IL-6 by brain endothelial cells exposed to isolated S1, isolated S2 and isolated RBD⁽¹⁹⁾. The combination of reduced hBBB integrity and stimulation of chemotactic, inflammatory and cell adhesion molecules strongly indicates the potential for isolated SARS-CoV-2 spike proteins and/or isolated constituent-components of spike proteins to induced immune cell infiltration of the CNS, even in the absence of active SARS-CoV-2 infection⁽¹⁹⁾.

Isolated SARS-CoV-2 spike proteins and/or isolated constituent-components of spike proteins have been demonstrated to trigger very specific pro-inflammatory responses upon interaction with brain endothelial cells, where said inflammatory responses include up-regulation of matrix metalloproteinases (MMP) expression⁽¹⁹⁾. MMPs constitute a family of zinc-dependent extracellular matrix (ECM) remodeling endopeptidases, with the capacity to degrade almost every component of the ECM⁽¹¹³⁾. Primary human brain microvascular endothelial cells exposed to isolated S1 for 24 hours resulted in elevated expression of MMP3, MMP9 and MMP12⁽¹⁹⁾. MMP3

has been reported to contribute to the degradation of tight junction proteins, resulting in the development of breaches within the hBBB ^(19,113). MMP12 has been reported to contribute to the extravasation of immune cells as well as the enhanced migration of said immune cells into brain tissue ^(19,113). MMP9 has been reported to play a role in the disruption of the hBBB via microglia activation as well as through the enhanced migration of inflammatory cells into brain tissue ^(19,113). Isolated SARS-CoV-2 spike proteins, have demonstrated an ability to induce the formation of microclots within the vessels of the CNS ⁽¹⁹⁾. Corroboration of the pro-thrombotic characteristics of isolated SARS-CoV-2 spike proteins and/or isolated constituent-components of spike proteins, exists in the fact that histological examination of the CNS at autopsy of 20 individuals deceased from COVID-19, revealed the widespread presence of microthrombi and acute infarction ⁽¹¹⁴⁾. Six of twenty autopsy cases subject to histological examination of the CNS revealed that the distribution of vascular infarcts was variable in some regards, ranging from large cerebral artery territory infarcts to more consistently prevalent, small, patchy peripheral and deep parenchymal ischemic infarcts ⁽¹¹⁴⁾. Additionally, some instances of hemorrhagic, deep gray matter structures were observed, with concomitant global anoxic brain injury ⁽¹¹⁴⁾. All six cases of reported CNS vascular infarcts demonstrated a notable and consistent abnormality in the form of microthrombi, often being associated with small, patchy infarctions ⁽¹¹⁴⁾. On histological examination, all six cases demonstrated vascular congestion, which appeared disproportionately increased relative to findings typically observed during routine neuropathological evaluation ⁽¹¹⁴⁾. Abnormally increased vascular congestion was reported, on occasion, be accompanied by the presence of acute parenchymal microhemorrhages, which were observed with higher prevalence in the necrotic areas of infarction ⁽¹¹⁴⁾. Prominent acute parenchymal microhemorrhages localized within zones of infarction-induced necrosis was reported as suggestive of vascular damage and reperfusion injury ⁽¹¹⁴⁾.

The reported pro-thrombotic effects of isolated SARS-CoV-2 spike proteins and/or isolated constituent-components of spike proteins, combined with the reported isolated: spike protein/S1/S2/RBD- insults to vascular endothelium and accompanying breakdown of the hBBB, presents a highly tangible explanation for the high incidence of acute ischemic stroke observed in COVID-19 patients younger than 50 years old ⁽¹⁹⁾. Acute hemorrhagic necrotizing encephalopathy (ANE) is a condition related to increased levels of intracranial pro-inflammatory cytokines, which in-turn, leads to a deterioration of the hBBB ^(115,116,117). ANE has been reported to affect SARS-CoV-2 infected individuals, with often devastating neurological effects ^(115,116,117). Isolated SARS-CoV-2 spike protein/isolated spike protein constituent-component-induced breakdown of the hBBB, combined with isolated SARS-CoV-2 spike protein and/or isolated spike protein constituent-component-induced inflammation via mechanisms such as, TLR4/NF-kB signaling and hACE2 down-regulation, present a highly tangible explanations for the occurrence of ANE in COVID-19 patients, particularly in the absence of detectable SARS-CoV-2 viral load ^(115,116,117).

Long-term neurological COVID-19 complications have been reported to include neurodegeneration and cognitive decline ⁽²⁰⁾. The onset of both post-COVID-19 neurodegeneration and cognitive decline may, at least in part, be the result of isolated SARS-CoV-2 spike protein and/or isolated spike protein constituent-component-induced aggregation of misfolded neuro-proteins ⁽²⁰⁾. Isolated S1 has been observed to bind to heparin and heparin binding proteins (HBPs) present in brain tissue ⁽²⁰⁾. The resultant S1/heparin/HBPs complexes have been reported to be prone to

spontaneously undertaking the processes of self-assembly, aggregation, and fibrillation ⁽²⁰⁾. Isolated S1 has been reported to possess a greater propensity to the formation of protein aggregations than any other prior art acknowledged aggregation-prone protein ⁽²⁰⁾. Therefore, isolated S1 is highly pre-disposed to act as a functional amyloid and initiate the formation of toxic protein aggregates ⁽²⁰⁾.

Protein-protein docking studies examining the binding affinity of isolated S1 towards the amyloid-forming proteins: amyloid beta (A β), α -synuclein (α -Syn), Tau, prion and TDP-43 RNA-recognition motif (RRM) reported that the formation of S1/amyloid-protein complexes are energetically favored ⁽²¹⁾. The RBD, localized on S1, demonstrated protein-protein docking scores of varying affinity, thus indicating a graduated propensity, for the formation of S1/amyloid-forming protein complexes ⁽²¹⁾. Protein-protein docking scores enabled the ranking of RBD binding with known amyloid forming proteins in the following order: prion/RBD > A β /RBD > Tau/RBD > RRM/RBD > α -Syn/RBD ⁽²¹⁾. The RBD has been observed to possess a very strong docking affinity with heparin ⁽²¹⁾. A reported docking score of -282.57, revealed an affinity between heparin and RBD binding in excess of the propensity of RBD to bind to all other amyloid-forming proteins studied, with the exception of the binding affinity between prion protein and RBD ⁽²¹⁾. Amyloid forming HBP/heparin interactions were compared to RBD/heparin binding, and ranked on the basis of docking scores ⁽²¹⁾. RBD/heparin > prion/heparin > RRM/heparin > A β /heparin > Tau/heparin > α -Syn/heparin ⁽²¹⁾. The complex formed subsequent to RBD/heparin interaction, was examined for its affinity of to form subsequent complexes with HBPs ⁽²¹⁾. RBD/heparin complexes were found to possess greater affinity, on the basis of protein-protein docking scores, for binding HBPs, compared to the affinity of RBD for binding HBPs directly ⁽²¹⁾. Reported findings suggest, that the complex which results from the binding of heparin to RBD, possesses a strong ability to catalyze the formation of amyloid complexes with all examined HBPs ⁽²¹⁾. The reported ability of RBD/heparin complexes to function as a seed for neuro-protein aggregates is therefore greater than that demonstrated by RBD alone ⁽²¹⁾. Reported protein-protein docking scores indicate that α -Syn binds most strongly to RBD/heparin complexes followed by RRM > A β > Prion > Tau ⁽²¹⁾. Reports indicate that a general decrease in binding affinity occurs between RBD/heparin/HBP complexes with increasing temperature ⁽²¹⁾. As temperatures increased from 25 to 40 C, α -Syn appeared to have the strongest binding affinity for RBD/heparin complexes, followed by Prion > A β > RRM > Tau protein ⁽²¹⁾. The predicted binding affinities for RBD/heparin complexes with α -Syn and Tau were less affected as the temperature increased from 25C to 40C, relative to RBD/heparin complexes with prion, RRM, and A β ⁽²¹⁾. Decreased affinity between RBD/heparin/HBP complexes with increasing temperature can be explained via a mechanism in which increasing temperature disrupts the non-covalent interactions between the components of a RBD/heparin/HBP complex ⁽²¹⁾. While the explanation rooted in the disruption of non-covalent interactions remains plausible for RBD/heparin complexes with prion, RRM and A β ; the persistence of RBD/heparin/ α -Syn and RBD/heparin/Tau complexes suggests a high likelihood for the formation of stable and robust complexes, which are capable of serving as nucleation sites for neuro-protein aggregation under physiological conditions ⁽²¹⁾. Some amyloid proteins, such as A β 1-42, have been observed to bind, with a preferentially high affinity, to isolated S1 and hACE2 concomitantly ⁽²²⁾. The binding A β 1-42 to isolated S1 and hACE2 was observed to primarily occur through the C-terminal residues of A β 1-42 ⁽²²⁾. The interaction of A β 1-42 with S1 and hACE2, was also reported to strengthen the binding of S1 to hACE2 ⁽²²⁾. A

surrogate mouse model, treated with an intravenous inoculation of A β 1-42, showed that the clearance of A β 1-42 was reduced when intravenous administration of isolated SARS-CoV-2 spike proteins occurred simultaneously, thus demonstrating a synergistic binding between A β 1-42, S1 and hACE2 ⁽²²⁾. A β 1-42, secondary to the cooperative binding of hACE2 and S1, has been observed to drive an increased production of IL-6 ⁽²²⁾. IL-6 has been found to mediate thrombocytosis, platelet hyperreactivity, and accelerated thrombus development ^(23,24). An elevation in IL-6 has been reported to be associated with increased mortality in COVID-19 patients ⁽²⁴⁾. COVID-19 patients expressing increased IL-6 signaling have been observed to suffer multiple organ system damage via T-cell maturation, while also demonstrating increased expression of vascular endothelial growth factor (VEGF), increased vascular permeability, and decreased myocardial contractility ⁽²⁴⁾. IL-6 plays a significant role in the pathogenesis of venous thromboembolism observed in COVID-19 patients ⁽²⁴⁾. A direct association has been observed between an increased concentration of plasma IL-6 and fibrinogen levels among COVID-19 patients, thus reinforcing the link between inflammation, thrombotic events and SARS-CoV-2 spike protein molecular pathophysiology ⁽²⁴⁾.

(1.8) SARS-CoV-2 spike protein induced inhibition of DNA repair mechanisms

SARS-CoV-2 spike proteins are capable of being localized to the nucleus in significant quantities, as isolated SARS-CoV-2 spike proteins have been detected within chromatin-bound cell fractions ⁽¹⁴⁸⁾. Nuclearily localized, spike proteins have been reported to significantly impair double-strand DNA break (DSB) repair pathways, with reductions DSB repair activity reaching approximately 90% ⁽¹⁴⁸⁾. Isolated SARS-CoV-2 spike proteins localized to the nucleus were found to directly inhibit the non-homologous end joining (NHEJ) repair pathway ⁽¹⁴⁸⁾. Isolated spike proteins localized to the nucleus were found to markedly inhibit the formation of 53BP1 foci, a key checkpoint protein for NHEJ repair ⁽¹⁴⁸⁾. Additionally, nuclear localized, isolated spike proteins were found to directly inhibit the homologous recombination (HR) repair pathway ⁽¹⁴⁸⁾. Isolated spike proteins localized to the nucleus were found to markedly inhibit the formation of BRCA1 foci, a key checkpoint protein for HR repair ⁽¹⁴⁸⁾. NHEJ and HR constitute two of the major DNA repair pathways essential for the continuous protection of genome integrity ⁽¹⁴⁸⁾. Neither isolated S1 nor isolated S2 were found to impair NHEJ and HR to the extent full-length spike proteins inhibited DSB repair pathways ⁽¹⁴⁸⁾. Isolated spike proteins were found to inhibit DSB repair following cellular exposure to ionizing radiation, H₂O₂ and doxorubicin ⁽¹⁴⁸⁾. Collectively, these findings demonstrate that isolated SARS-CoV-2 spike proteins are localized to the nucleus, where DSB repair is inhibited via prohibition of DNA repair protein recruitment in both the NHEJ and HR pathways ⁽¹⁴⁸⁾.

Physiological and lifestyle characteristics of elite athletes

(2.1) Elite athletes possess enhanced translational capacity and efficiency relative to the general populace

Elite strength, power and endurance athletes rigorously employ meticulously designed approaches to physical training, nutrition, recovery, sleep and other lifestyle factors, in order to achieve physical performances that register at the extreme echelons of human physiology. Elite athletes have been found to utilize dietary supplements to a higher degree than lesser-performing athletes ⁽²⁶⁾. A significant majority of elite athletes regularly consume protein and/or amino acid

supplementation (protein/AA) as the most prominent component of a nutritional supplementation regime (26,27,28). High performance athletes who utilize nutritional supplements demonstrate a more complete daily nutrient intake, and present fewer nutritional deficiencies compared to lesser-performing athletes and sedentary controls alike (27). Protein/AA, in combination with resistance training (RT), has demonstrated a dose-dependent ability to increase the rate of skeletal muscle protein synthesis (MPS) (29). Given the robust level of evidence in support of RT towards improved performance among highly trained individuals, nearly all elite strength and power athletes engage, with great regularity, in physical training sessions wholly or partly comprised of RT (122). Elite strength and power athletes also regularly engage in frequent RT sessions of great intensity. Elite endurance athletes, including, but not limited to, long-distance runners and triathletes, also regularly engage in RT sessions despite some controversy as to whether maximal RT directly improves endurance sport performance (118,119,120,121). Elite endurance athletes are often found to engage in RT, despite any uncertainty that may exist surrounding the potential benefits of maximal RT to endurance sport performance, for the purpose of injury avoidance and the maintenance of musculoskeletal balance (123).

The up-regulation of MPS secondary to activation of mammalian target of rapamycin complex 1 (mTORC1) signaling is well-established response to RT (29,30,35). RT combined with protein/AA, has been reported to increase mTORC1 signaling beyond that observed from RT conducted in a fasted or carbohydrate only fed state (29,30,35). mTORC1 signaling, subsequently activated in response to RT, induces the phosphorylation of p70 ribosomal protein S6 kinase 1 (S6K1) (29,30).

Phosphorylation of S6K1 subsequently induces the phosphorylation of 40S ribosomal protein S6 (rpS6) and eukaryotic translation initiation factor 4B (eIF4B) (29,30,35). S6K1-induced phosphorylation of rpS6 and eIF4B culminate in up-regulation of ribosomal biogenesis and enhanced mRNA translational capacity (29,30,35). Ribosomal biogenesis involves the production of approximately 80 ribosomal proteins and four ribosomal RNAs (rRNAs), namely: 28S, 18S, 5S, and 5.8S rRNAs (126). Ribosomal biogenesis is tightly regulated at many of the hundreds of control nodes, which exist within the ribosomal synthetic process (126). Control nodes involve elements of transcription, translation, synthesis, assembly, and transport of the ribosome end product (126). The production of rRNA constitutes a major rate-limiting step in ribosomal biogenesis (126). Further evidence supporting RT as a potent stimulus for rRNA production, and therefore ribosomal biogenesis, is supplied by reports indicating that even among elderly adults, with significant skeletal muscle atrophy, hypertrophic myofibrillar responses, increased total muscle RNA content and increased amounts of phosphorylated S6K1, within the first 24 h following an initial bout of RT are observed (126). Given that approximately 85% of RNA present in skeletal muscle is rRNA, it is suggestive that RT facilitates rRNA stockpiling and thereby allows rapid rates of ribosomal biogenesis (126). Enhanced ribosomal biogenesis thus contributes to the phenomena of RT-induced increases of MPS and skeletal muscle hypertrophy (126).

Endurance training (ET) has also been reported to enhance MPS and elevate mTOR signaling in human skeletal muscle (127). While extensive and/or high frequency ET has been demonstrated to result in attenuated adenosine mono-phosphate (AMP)-activated protein kinase (AMPK) and mTOR signaling, acute bouts of ET result in elevated rates of AMPK and mTOR phosphorylation (127).

AMPK activation, in combination with, reduced rates of phosphorylation of eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) have been demonstrated to contribute to the inhibition of

MPS in the midst of RT bouts ⁽¹²⁷⁾. Conversely, increased activation of PKB, mTOR, S6K1 and eEF2 are observed during the first 1 to 2 hours of post-RT recovery and correlate with increased MPS ⁽¹²⁷⁾. Reports demonstrate that mTORC1 signaling increases the phosphorylation of 4E-BP1, which suppresses the ability of 4E-BP1 to bind and inhibit eukaryotic translation initiation factor 4E (eIF4E) ⁽³⁵⁾. The mTORC1-induced phosphorylation of 4E-BP1 allows eIF4E to directly bind the 5' end of mRNA molecules, thus forming an active eIF4F complex, a rate limiting step in the initiation of mRNA translation ⁽³⁵⁾.

PKB/Akt, a Ser-Thr phosphatidylinositol-regulated kinase, and its downstream targets, glycogen synthase kinase (GSK3) and mTOR, are critical regulators of protein synthesis in both skeletal and cardiac muscle ⁽³⁶⁾. Akt-mediated phosphorylation of GSK3 leads to the inhibition of GSK3 activity and an enhancement of the activity of eukaryotic initiation factor 2B (eIF2B) ^(29,30,35,36). eIF2B, a guanine nucleotide exchange factor, mediates the exchange of guanine diphosphate (GDP) for guanine triphosphate (GTP) on eukaryotic translation initiation factor F2 (eIF2) ⁽³⁶⁾. Once activated, eIF2-GTP complexes with initiator methionyl transfer RNA (met-tRNA_i), where the newly formed eIF2-GTP/met-tRNA_i complex subsequently binds to the 40S ribosomal subunit ^(29,30,35,36). Activation of eIF2B results in an enhanced rate of mRNA translation, mRNA proliferation and ultimately, increased mRNA translational efficiency ^(29,30).

RT combined with protein/AA, as practiced by elite athletes, induces mTORC1-mediated phosphorylation of S6K1/4E-BP1, and has demonstrated greater rates of both mRNA translational capacity and mRNA translational efficiency, relative to RT conducted with a post-RT recovery interval in either a fasted state or carbohydrate-only fed state ^(29,30). Male and female elite athletes respond equally well to the combination of RT and protein/AA, as neither MPS nor mTORC1 signaling has been reported to differ between cohorts of male and female athletes ⁽²⁹⁾. The combination of RT with protein/AA, has been reported to result in a post-RT enhancement of MPS of 138% for myofibrillar proteins, relative to a protein-fed, sedentary-state ⁽²⁹⁾. The combination of RT with protein/AA has been reported to result in a post-RT enhancement of MPS of 54% for sarcoplasmic proteins, relative to a protein-fed, sedentary-state ⁽²⁹⁾. The combination of RT with protein/AA, has been reported to result in a post-RT enhancement of MPS of 100% for mitochondrial proteins, relative to a protein-fed, sedentary-state ⁽²⁹⁾. RT combined with protein/AA, has been reported to result in a post-RT enhancement of MPS of 78% for mixed-skeletal muscle proteins, relative to a protein-fed, sedentary-state ⁽²⁹⁾. RT combined with protein/AA, has been reported to result in a post-RT enhancement of MPS of 170% for 2- or 3-pool models of MPS, (stable-isotopic mathematical models- arterial and venous limb balance methods), when compared to a protein-fed, sedentary-state ⁽²⁹⁾. Therefore, an average post-RT enhancement in the rate of MPS of 129% can be attributed to RT combined with protein/AA, across all post-exercise time periods and skeletal muscle protein species, relative to rates of MPS observed during a protein-fed, sedentary-state ⁽²⁹⁾.

The reported enhancements in the rates of MPS resulting from RT in combination with protein/AA, have been found to be subject to further optimization when specific strategies are utilized pertaining to protein/AA volume, composition and frequency ^(29,30,31). Optimization of a regimen

combining RT with protein/AA is reported to occur when of the ingestion of at least twenty grams of protein/AA, where said protein/AA contains at least 2 grams of leucine per serving, is consumed every three hours post-RT training stimuli; and where the total protein consumption is at least 80 grams (29,31). In highly-trained athletes this strategic regimen of RT and protein/AA has been reported to result in greater levels of MPS, relative to an equal amount of total protein/AA ingested, but where said ingested protein/AA, either: contained less than 2 grams of leucine per serving, and/or was consumed in either doses less than 20 grams and/or the interval between doses exceeded three hours (29,31).

The high degree of utilization of RT with protein/AA among elite athletes, where protein/AA is consumed in the context of an optimized volume<->composition<->frequency strategy (protein/AA_{optimized}), culminates in regularly and significantly elevated MPS, via activation of signaling pathways that include but not limited to, mTORC1 signaling pathways and down-stream effectors (27,28,29,30,31). mTORC1, constitutes a master growth regulator of mRNA translation initiation and elongation (27,28,29,30,31). Intense, high-frequency activation of mTORC1 signaling, via RT and protein/AA-optimized, allows elite athletes to sustain far greater levels of MPS for an entire 24-hour post-RT interval, compared to those rates of MPS observed in a largely-sedentary general population (27,28,29,30,31). Collectively, the intersection of the nutritional and physical training routines of elite strength, power and endurance athletes vigorously stimulates the formation of translation initiation complexes, promoting enhanced translational capacity and improved rates of global MPS (29,30,35,36).

In addition to mTORC1-mediated signaling, elite athletes have been found to possess more than twice the level of serum nerve growth factor (NGF) relative to control populations (34). NGF has been found to increase eIF2B activation (33). NGF induction of eIF2B is only partially dependent upon mTOR signaling, and therefore, the physiology of elite athletes demonstrates yet another molecular mechanism, separate from mTORC1 signaling, that stimulates greater rates of mRNA translation, mRNA proliferation and ultimately, increased mRNA translational efficiency relative to the general population (30,33,34).

Concentric and eccentric loading of skeletal muscle induces mechanosensory regulation of MPS, which involves focal adhesion kinase (FAK) proteins (35,124). FAK proteins are trans-membrane receptors that act as protein tyrosine kinases (35,124). FAK proteins are key elements for the transmission of contractile force through the skeletal muscle architecture and represent a central component of integrin signaling (35,124). The expression and activity of FAK in skeletal muscle tissue can activate MPS through both mTOR-dependent and mTOR-independent mechanisms (35). In addition to concentric and eccentric loading-induced mechanosensory regulation of skeletal MPS regulated by FAK proteins; ATP-turnover, calcium flux, redox balance, ROS generation, and intracellular oxygen pressure have all been implicated in the activation of signal transduction cascades regulating skeletal MPS (35).

Insulin sensitivity is characterized by the degree of cellular responsiveness to insulin-mediated glucose uptake. A primary driver of skeletal muscle insulin mediated glucose uptake is glucose

transporter 4 (GLUT4) ⁽¹²⁵⁾. ET and ST, both of which constitute core elements of elite strength, power and endurance athlete training programs, have been reported to result in an increased skeletal muscle expression of GLUT4, as well as, increased localization of GLUT4 to the perimembrane periphery of skeletal muscle cells ⁽¹²⁵⁾. These observations indicate that both ET and ST improve insulin sensitivity; and result in further enhancement of mRNA translational capacity and translational efficiency among populations of actively training elite athletes ^(30,125).

Translation of mRNA is primarily regulated at the initiation step, while the rate of protein synthesis has been observed to increase linearly with initiation rate ⁽³²⁾. Rates for the initiation of translation in eukaryotic cells have been found to vary significantly between individual mRNAs ⁽³²⁾. It has been reported that the time between initiation events for individual mRNAs in eukaryotic cells, representing the 5th to 95th percentile, spans a range between 4 and 293 seconds ⁽³²⁾. Protein synthesis rates have been observed to increase linearly with the ribosome allocation over the entire range of mRNAs ⁽³²⁾. Correspondingly, the density and the flux of ribosomes on mRNAs, strongly correlates to the rate of protein synthesis ⁽³²⁾. However, a small cluster of mRNA open reading frames (ORFs) have been reported to not demonstrate conformity to the broader relationship between ribosome allocation and the resultant rate of protein synthesis ⁽³²⁾. This minority population of mRNA ORFs almost exclusively encodes for ribosomal proteins, and demonstrates distinctly lower protein outputs relative to nearly all other mRNA ORFs ⁽³²⁾. Reports indicate that ribosome allocation is largely a function of the copy number and length of mRNA ORFs ⁽³²⁾. In this regard, the primary structure of a peptide, encoded via mRNA ORFs, has been reported to be a determinant of translation elongation rate, as negatively charged proteins are synthesized on average, at up to 2-fold higher rates relative to mRNA ORFs encoding positively charged amino acid sequences ⁽³²⁾. Additionally, non-polar amino acids with small side chains are associated with faster rates of elongation, whereas non-polar amino acids with bulkier side chains are associated with slower rates of elongation ⁽³²⁾. Reports indicate that physical training programs comprised of both ET and RT induce ribosomal biogenesis, measured via the abundance of externally and internally transcribed spacers of the 45-s pre-rRNA (ETS), (ITS), at a slightly more pronounced rate than physical training programs comprised only of RT ⁽¹³³⁾. The resultant increase in rates of ribosomal biogenesis, and the subsequent expansion of mRNA translational capacity, manifests as enhanced rates of muscle fiber hypertrophy, as illustrated by increased muscle fiber cross-sectional area (CSA) ⁽¹³³⁾.

(2.2) Elite athletes possess enhanced skeletal muscle vascularization relative to the general populace

An increase of skeletal muscle fiber CSA has been observed to accompany an expansion of the capillary network surrounding skeletal muscle fibers, which demonstrate increased CSA ⁽¹³³⁾. An expansion of the capillary networks surrounding both the type I and II skeletal muscle fibers, has been reported to occur following exposure to ET and RT ⁽¹³³⁾. Microvascular adaptations culminating in an expanded capillary network appear to occur as a result of cell signaling triggered by: increased muscle fiber CSA, higher rates of skeletal muscle perfusion and exposure to increased levels of vascular shear stress ⁽¹³³⁾. The reported link between muscle fiber CSA and the perfusing capillary network is further reinforced when the similarity of the time course of skeletal muscle

hypertrophy and angiogenesis is explored ⁽¹³⁴⁾. The existence of extensive cross talk between capillaries and skeletal muscle satellite cells provides support for the concept that an extensive vascular network may represent a factor of greater importance, in regards to the promotion of skeletal muscle hypertrophy, than solely the abundance of satellite cells ⁽¹³⁴⁾. Conversely, muscle tissue demonstrating reduced capillary density may also be subject to an attenuation of the hypertrophic response to training stimuli, despite sufficient satellite cell density ⁽¹³⁴⁾. Capillary rarefaction and endothelial apoptosis have been demonstrated to precede muscle atrophy during age-related sarcopenia and chronic heart failure ⁽¹³⁴⁾. Elite athletes have been reported to possess enhanced endothelial vasodilative function, as demonstrated by the higher values of flow-mediated dilation (FMD) observed in professional athletes relative to sedentary, healthy young men aged 18-40 ⁽¹²⁹⁾. However, the enhanced endothelial vasodilative function observed in elite athletes was reported to not be the result of increased nitric oxide (NO) biosynthesis relative to sedentary controls ⁽¹²⁹⁾. RT, ET and ST, conducted on a regular basis, increases blood flow parameters and shear stress experienced by elite athletes ⁽¹²⁹⁾. The increased blood flow and resultant changes in hemodynamic and rheological parameters that occur during regular, high-intensity physical training seems to provide a stimulus for both, acute and chronic changes in the vascular function of elite athletes, culminating in the reported positive effects on endothelial function ⁽¹²⁹⁾.

(2.3) Elite athletes possess a RAS balance favoring ACE2 over ACE and Ang1-7 vs AngII

Reports indicate that regular, high-intensity physical training augments the activity of RAS, leading to a reduction of the vascular Ang II: Ang1-7 ratio, as well as, ROS generation, oxidative stress and inflammation ⁽¹³¹⁾. Reported observations indicate that the vascular Ang II: Ang1-7 ratio contributes to the maintenance of cardiovascular homeostasis ⁽¹³¹⁾. Under conditions of hACE->Ang II over activity, the AT₁ receptor axis predominates, thus encouraging vasoconstriction, hypertrophic signaling and pro-inflammatory processes to also predominate ⁽¹³¹⁾. Whereas, under conditions when activity of the hACE2->Ang1-7 dominance, the Mas receptor axis predominates, typically with concomitant ACE and AT₁ inhibition, with subsequent promotion of vasodilation, anti-trophic signaling and anti-inflammatory processes ⁽¹³¹⁾. Despite the fact that elite athletes demonstrate enhanced endothelial vasodilative function relative to sedentary, healthy controls; elite athletes have not been found to possess significant differences in adenosine di-phosphate (ADP)-induced platelet aggregation, nor arachidonic acid-induced platelet aggregation relative to sedentary, healthy controls ⁽¹²⁹⁾. Rather, the intensive RE, ET and ST, regularly undertaken by elite athletes, may excessively increase platelet aggregation, thus promoting the risk of thrombotic events ^(130,132). New-onset occurrences of thrombotic events have been reported both during and immediately following athletic events such as, but not limited to: marathon and triathlon ⁽¹³⁰⁾.

(2.4) Elite athletes are regularly exposed to hypercoagulative and prothrombotic states

High intensity and/or long-duration RT, ET, and ST, the type routinely engaged in by elite athletes, has been found to increase plasma concentrations of ADP ^(44,130,132). Elevated plasma ADP concentrations promote a prothrombotic state, manifesting in platelet activation and thrombocytosis ^(44,128,132). Plasma from exercising athletes was found to significantly up-regulate the expression level of the platelet activation marker P-selectin ⁽⁴⁴⁾. P-selectin is a key adhesion molecule that mediates the interaction between platelets and leukocytes via P-selectin glycoprotein

ligand 1 (P-selectin GP1) ^(4,44). In response to the prothrombotic state induced by intense physical exercise, athletes up-regulate the serum concentrations of two soluble nucleotide-inactivating enzymes, nucleotide pyrophosphatase/phosphodiesterase (NPP) and nucleoside triphosphate diphosphohydrolase (NTPDase) ⁽⁴⁴⁾. Serum NPP and NTPDase activities rise during maximal exercise by 20–25% and 80–100%, respectively, and then decline after 30 minutes of recovery ⁽⁴⁴⁾. Despite the dramatic increase in serum NPP and NTPDase activities during intensive exercise, the ADP-induced prothrombotic state triggered by intensive exercise is only partially counteracted, as plasma ADP levels are observed to increase up to 2.5 fold ^(44,128). Crucially, the activity vascular NTPDase is diminished under conditions of inflammation or oxidant stress, thereby causing profound shifts in vascular permeability and local procoagulant responses ^(Robson et al. 2005 as cited in 44). These findings are consistent with observations of a well-recognized period of inflammation and prothrombotic risk that accompanies physical training in respect to variables such as intensity, duration and frequency. The risk to elite athletes of incurring a thrombotic event as a consequence of engaging in high-intensity and/or long-duration physical training, can be magnified by exposure to factors such as high altitude, trauma, immobilization, or dehydration induced hemoconcentration ⁽⁴⁸⁾. Further, elite athletes who are subjected to brief exposures of very high G-force loads and/or lower, but sustained G-force loads, also incur heightened risk of suffering thrombotic events ⁽¹⁴⁹⁾. Such athletes include but are not limited to: motorsport athletes, aeronautical athletes, full-contact and combat sports athletes, and members of high-performance military units which maintain high-levels of physical fitness and are also regularly exposed to G-loads.

Vaccines against SARS CoV-2

(3.1) Introduction

Immune responses have traditionally varied widely among different vaccine types and target pathogens ⁽⁴⁵⁾. For example, live-attenuated vaccines have been observed to usually induce high vaccine responses leading to life-long protection, often after just one dose ⁽⁴⁵⁾. Traditionally, inactivated, subunit, or toxoid vaccines usually require several doses, including booster doses, to achieve similar protection afforded by live-attenuated vaccines ⁽⁴⁵⁾. Responses to different classes of vaccines also vary greatly depending upon the characteristics of the recipient patient population ⁽⁴⁵⁾.

(3.2) Live-attenuated SARS-CoV-2 vaccine candidates

COVI-VAC (CDX-005), developed by Codagenix, is the leading live-attenuated SARS-CoV-2 vaccine candidate currently in clinical development ⁽⁴⁹⁾. The CDX-005 live-attenuated vaccine was developed via insertion of synonymous sub-optimal codon pairs (codon-pair de-optimization) ⁽⁴⁹⁾. Codon de-optimization introduced 283 silent point-mutations into the SARS-CoV-2 genome ⁽⁴⁹⁾. Additionally, the furin cleavage site typically present within wild-type SARS-CoV-2 spike proteins was deleted from the CDX-005 genome for added safety of the vaccine strain ⁽⁴⁹⁾. With the exception of the furin cleavage site deletion, the CDX-005 and the wild-type SARS-CoV-2 amino acid sequences are identical, thus ensuring, that all viral proteins can fully engage with the immune system of vaccine recipients ⁽⁴⁹⁾. A variety of different mechanisms collaborate in the attenuation of SARS-CoV-2 by codon-pair deoptimization, including but not limited to: a reduced rate of translation, protein misfolding, changes in mRNA secondary structures, altered regulatory signals, increased numbers of 3'-Cp5'-G or 3'-Up5'-A dinucleotides linking two codons ⁽⁴⁹⁾. One or all of

these processes may contribute to an impairment of genome replication in CDX-005⁽⁴⁹⁾. Additionally, it has been reported that many codon-pair-deoptimized viral genomes acquire a temperature sensitive phenotype at 37 °C, a fact by itself, that can be a major contributor to restricted virus proliferation in vivo⁽⁴⁹⁾. The attenuated CDX-005 virus presents every viral antigen present within wild-type SARS-CoV-2 virion, providing the potential for the generation of a broad immune response and making it likely to retain efficacy even if there is genetic drift in the target strain⁽⁴⁹⁾. Similar to live-attenuated vaccines approved for other pathogens, CDX-005, is being investigated for its ability to provide protective immunity against SARS-CoV-2 from a single dose^(45,49).

Additional live-attenuated SARS-CoV-2 vaccines under investigation constitute chimeric and/or recombinant vaccines. YF-S0, is a candidate vaccine that uses live-attenuated yellow fever 17D vaccine as a vector to express a noncleavable prefusion form of the SARS-CoV-2 spike antigen⁽⁵⁰⁾. YF-S0 has been reported to possess a robust safety profile⁽⁵⁰⁾. YF-S0 has been observed to induce high levels of SARS-CoV-2 neutralizing antibodies in hamsters (*Mesocricetus auratus*), mice (*Mus musculus*) and macaques (*Macaca fascicularis*), as well as, generating concomitantly protective immunity against yellow fever virus⁽⁵⁰⁾. Humoral immunity induced by YF-S0, may be enhanced, as a result of a significant cellular immune response, given that a beneficial T helper 1 polarization has been observed in mice⁽⁵⁰⁾. YF-S0 prevents infection with SARS-CoV-2 in a hamster and macaque models⁽⁵⁰⁾. Observations have been reported that a single dose of YF-S0 conferred protection from SARS-CoV-2 lung disease in the majority of vaccinated hamsters within as little as 10 days⁽⁵⁰⁾. Further live-attenuated SARS-CoV-2 vaccines under investigation include: a modified vaccinia Ankara vaccine (MVA) vector expressing membrane-anchored pre-fusion stabilized SARS-CoV-2 spike proteins but not secreted S1 subunits, a Newcastle disease virus vaccine (NDV) vector expressing SARS-CoV-2 spike protein in a membrane-anchored format and lacking the polybasic cleavage site as well as, a measles virus vaccine vector expressing SARS-CoV-2 spike protein, including the S1 subunit receptor binding domain (RBD)^(51,52,53). Chimeric and/or recombinant live-attenuated vaccine candidates, do not possess the full landscape of SARS-CoV-2 antigenic epitopes with which the immune system of recipient patients may engage to mount an immune response characteristic of classical live-attenuated vaccines. Therefore, chimeric and/or recombinant live-attenuated SARS-CoV-2 vaccine candidates should be viewed in a different context relative to whole-virion SARS-Cov-2 live-attenuated vaccine candidates, such as, but not limited to: CDX-005.

(3.3) Inactivated-virus SARS-CoV-2 vaccine candidates

Due to decades of familiarity with the industrial production of inactivated-virus vaccinations, the ability to scale-up production, the resultant relatively low cost of production, and low risk of adverse events, inactivated-virus vaccinations comprised some of the earliest candidates to populate the SARS-CoV-2 vaccine landscape^(68,69). BBIBP-CorV, an inactivated-virus SARS-CoV-2 vaccine, was developed from the isolation of three SARS-CoV-2 strains from bronchoalveolar lavage samples and/or throat swabs of three hospitalized patients during the COVID-19 outbreak⁽⁵⁴⁾. Samples from COVID-19 patients were utilized to develop preclinical *in vitro* neutralization and challenge models for an inactivated SARS-CoV-2 vaccine candidate⁽⁵⁴⁾. The three SARS-CoV-2 strains utilized were 19nCoV-CDC-Tan-HB02 (HB02), 19nCoV-CDC-Tan-Strain03 (CQ01), and

19nCoV-CDC-Tan-Strain04 (QD01) ⁽⁵⁴⁾. HB02, CQ01 and QD01 were observed to be scattered on a SARS-CoV-2 phylogenetic tree constructed from all viral sequences available at the time ⁽⁵⁴⁾. The three-pronged strategy was reportedly undertaken to ensure coverage of the main SARS-CoV-2 populations ⁽⁵⁴⁾. The viral strains utilized for BBIBP-CorV were isolated from Vero cells, which were infected via the throat swabs of patients to prevent possible mutations during viral culture and isolation ⁽⁵⁴⁾. A randomized, double-blind, placebo-controlled, trial examined the effectiveness of BBIBP-CorV in healthy people aged 18–80 years, who were negative for serum-specific IgM/IgG antibodies against SARS-CoV-2 at the time of screening ⁽⁵⁵⁾. BBIBP-CorV was found to induce neutralizing antibody responses, against SARS-CoV-2, in all vaccine recipients by day 42 ⁽⁵⁵⁾. Immunization with BBIBP-CorV, utilizing two doses of 4 µg of vaccine on days 0 and 21 or days 0 and 28, resulted in higher neutralizing antibody titers than administration of a single 8 µg dose or 4 µg dose on days 0 and 14 ⁽⁵⁵⁾. BBIBP-CorV, was determined to be safe and well tolerated at all tested doses in healthy individuals aged 18-80 years ⁽⁵⁵⁾. A prospective study involving 406 healthcare workers who received two doses of BBIBP-CorV, 21 days apart, was conducted to examine the potential for increased risk of thrombosis following vaccination with BBIBP-CorV ⁽⁵⁶⁾. Blood samples were taken from study subjects once before vaccination and again four weeks after the second vaccination ⁽⁵⁶⁾. The pre and post-vaccination blood samples were used to evaluate prothrombotic autoantibodies, including: anticardiolipin (aCL), anti-β2 glycoprotein I (aβ2GP1), anti-phosphatidylserine/prothrombin (aPS/PT), and anti-PF4-heparin ⁽⁵⁶⁾. The seroconversion rate of SARS-CoV-2 specific antibodies was 95.81% (389/406) four weeks after vaccination with BBIBP-CorV ⁽⁵⁶⁾. None of the subjects had spontaneous thrombosis or thrombocytopenia during the minimum follow-up period of eight weeks ⁽⁵⁶⁾. There was no significant difference found in any of the ten auto-antibodies samples collected pre and post-vaccination ⁽⁵⁶⁾. Notably, seven cases presented with anti-PF4-heparin antibodies (range: 1.18-1.79 U/mL) after vaccination, and none of them exhibited any sign of post-vaccination thrombotic disorder ⁽⁵⁶⁾. It was concluded that inactivated-virus SARS-CoV-2 vaccine BBIBP-CorV does not influence the profile of antiphospholipid antibody and anti-PF4-heparin antibody, nor increase the risk of thrombosis and thrombocytopenia ⁽⁵⁶⁾.

CoviVac, is a Vero cell propagated, β-propiolactone-inactivated whole virion vaccine, where the vaccine concentrate is found to contain mainly SARS-CoV-2 spike and nucleocapsid proteins ⁽⁵⁷⁾. CoviVac was evaluated for general acute toxicity in mice, guinea pigs and marmosets, and tests for chronic toxicity were conducted in mice and guinea pigs ⁽⁵⁷⁾. Additionally, CoviVac was evaluated for hypersensitivity reactions in guinea pigs ⁽⁵⁷⁾. No pathological changes were observed in vaccinated animals in comparison with the placebo groups and all tested parameters were within the physiological norm for the respective species ⁽⁵⁷⁾. Data from experiments involving Wistar rats indicated that multiple immunizations with the CoviVac inactivated-virus vaccine, before or during pregnancy did not have a negative effect on the prenatal development of the offspring or affect the development of the offspring in the postnatal period. Therefore, it was concluded that the potential reproductive toxicity of the SARS-CoV-2 spike protein delivered in multiple doses of an inactivated-virus vaccine preparation was low ⁽⁵⁷⁾. Mice and marmosets were assessed for the long-term immunogenicity studies of CoviVac ⁽⁵⁷⁾. The appearance of antibodies to different regions of the SARS-CoV-2 spike protein, namely the RBD and partial spike protein, were detected in mice on days 7-28 post-vaccination, where mice receiving two doses of either 1.5 µg/dose, 3 µg/dose or 6

µg/dose 14 days apart ⁽⁵⁷⁾. Antibodies to partial spike protein were observed starting from day 7 in the group of mice receiving a 6 µg/dose, and antibodies to RBD were observed beginning on day 21 post-vaccination ⁽⁵⁷⁾. On days 21 and 28, no differences were found between the titers of antibodies to partial spike protein and RBD in groups of mice receiving a 6 µg/dose, 3 µg/dose and 1.5 µg/dose ⁽⁵⁷⁾. Antibodies to nucleocapsid of SARS-CoV-2 were detected in vaccinated mice beginning on day 21 post-vaccination in all vaccinated animals ⁽⁵⁷⁾. Neutralizing antibody (NAb) titers then rose to a peak at 12 weeks post-vaccination and over the course of one year, did not demonstrate a significant decrease in NAb titers ⁽⁵⁷⁾. The mice and marmosets receiving two doses of 6 µg/dose, 14 days apart, demonstrated significantly higher NAb titers over a 52 week period of observation ⁽⁵⁷⁾.

CoronaVac is a Vero cell propagated, β-propiolactone inactivated whole-virion SARS-CoV-2 vaccine with aluminium hydroxide as the adjuvant ⁽⁵⁸⁾. Each dose of CoronaVac contains 3 µg of SARS-CoV-2 antigen in a 0.5mL aqueous suspension for injection with 0.45mg/mL of aluminium hydroxide ⁽⁵⁸⁾. CoronaVac inactivated-virus vaccine is prepared from SARS-CoV-2 strain CZ02 and is delivered as two, 3 µg doses administered by intramuscular injection 14 days apart ⁽⁵⁸⁾. As of April 28, 2021, CoronaVac has been approved in 22 countries for emergency use and has been utilized by the World Health Organization's COVAX program ^(58,59). A phase 3 trial of CoronaVac among 10,214 participants, aged 18–59 (median age of the participants was 45 years), yielded a vaccine efficacy of 83.5% for the prevention of PCR-confirmed symptomatic COVID-19 and demonstrated an efficacy of 100% for the prevention of COVID-19-related hospitalization ⁽⁵⁸⁾. In the phase 3 trial 50.8% of participants were older than 45 years, 57.8% of participants were male, 42.2% were female, 36.0% of participants were health-care workers, and 15.6% of participants were obese ⁽⁵⁸⁾. During the phase 3 trial, CoronaVac demonstrated a safety profile, which did not include any grade 4 adverse events or deaths during the study period ⁽⁵⁸⁾. 18.9% of participants in the vaccine group and 16.9% of participants in the placebo group, reported adverse events during the study period, which resolved in a median interval of 1 day ⁽⁵⁸⁾. Among all adverse events, 90.2% were grade 1 and 87.5% occurred within 7 days after injection ⁽⁵⁸⁾. The most common adverse event was inoculation site pain, which occurred significantly more frequently in the vaccine group (2.4%) than in the placebo group (1.1%) ⁽⁵⁸⁾. Other adverse events, included erythema, paraesthesia, and swelling, which occurred more rarely, and did not differ significantly in incidence between the vaccine and placebo groups ⁽⁵⁸⁾. The frequency of systemic adverse events was significantly higher in the vaccine group (17.7%) than in the placebo group (16.0%) ⁽⁵⁸⁾. Adverse events reported more frequently in the vaccine group than in the placebo group included fatigue, myalgia, chill, and nausea ⁽⁵⁸⁾. 0.1% of participants had serious adverse events during the study period, and one serious adverse event in the vaccine group, requiring hospitalization, was reported to have a causal relationship with the vaccine ⁽⁵⁸⁾. A vaccine group participant had a grade 3, systemic allergic reaction, which occurred more than 24 h after the administration of the first dose of vaccine and resolved uneventfully in the following 24 h ⁽⁵⁸⁾. CoronaVac effectiveness against symptomatic SARS-CoV-2 infection was observed to decline with increasing age 14 days or more after the second dose: CoronaVac was 59.0% effective among those aged 70–74 years, 56.2% effective among those aged 75–79 years, and 32.7% effective among those aged ≥80 years ⁽⁶⁰⁾. CoronaVac effectiveness against symptomatic SARS-CoV-2 infection did not differ by sex, reported cardiovascular disease, or regions of residence ⁽⁶⁰⁾. Elderly individuals with DM2, however, had lower protection than age-

matched individuals without DM2 ⁽⁶⁰⁾. CoronaVac vaccine effectiveness was found to be 32.6% for individuals with DM2 vs 50.5% for individuals without DM2 ⁽⁶⁰⁾. CoronaVac effectiveness against hospital admission was observed to decline with increasing age, 14 days or more after the second dose: CoronaVac effectiveness was 77.6% among those aged 70-74 years, 66.6% among those aged 75-79 years, and 38.9% among those aged ≥80 years ⁽⁶⁰⁾. Acute left hemiparesis was reported in a 24 year-old female fifteen minutes after her first dose of CoronaVac ⁽⁶¹⁾. It was reported the patient developed visual disturbances characterized by bright flashing lights in both eyes that lasted 5 min, followed by marked nausea and vomiting ⁽⁶¹⁾. Twenty minutes later, the patient noticed a tingling sensation over the fingers in her left hand, followed by numbness and weakness of the left arm ⁽⁶¹⁾. Brain computed tomography (CT) showed no evidence of infarction ⁽⁶¹⁾. A magnetic resonance imaging (MRI) showed no abnormalities ⁽⁶¹⁾. Five days after vaccination and symptom onset, the numbness and weakness gradually resolved ⁽⁶¹⁾. The presence of migraine-like headaches and the complete resolution of all symptoms without evidence of structural brain abnormalities strongly supported the diagnosis of hemiplegic migraine ⁽⁶¹⁾. Researchers theorized that the aluminum hydroxide adjuvant of CoronaVac was responsible for the disruption of the glutamate → nitric oxide → cGMP pathway, which resulted in the release of increased levels of nitric oxide and activation of the nitric oxide system ⁽⁶¹⁾. Subsequent to the activation of NMDA receptors via glutamate→nitric oxide→cGMP signaling, prolonged aura occurred ⁽⁶¹⁾. Researchers theorized that nitric oxide played a crucial role in inducing the onset of migraine aura and headache, as well as, the prolongation of the aura later in the course of the adverse event ⁽⁶¹⁾. A 23-year-old woman presented for treatment with a swollen, painful left knee joint, which had occurred for the past 18 days ⁽⁶²⁾. She had been inoculated with her first dose of CoronaVac 18 days prior and her second dose of CoronaVac occurred 4 days prior ⁽⁶²⁾. A diagnosis of reactive arthritis (ReA) after vaccination with CoronaVac was made and treatment was administered as a single intra-articular injection of betamethasone ⁽⁶²⁾. The swelling and pain was reported to be resolved 2 days post treatment and at follow-up one month later, the condition of the joint was found to be normal ⁽⁶²⁾. A 78-year old woman presented for treatment with tetraparesis, paresthesias of bilateral upper extremities, and urinary retention of one-day duration ⁽⁶³⁾. Three weeks before symptom onset, the patient had been vaccinated with CoronaVac ⁽⁶³⁾. Spine magnetic resonance imaging showed longitudinally extensive transverse myelitis (TM) from the C1 to the T3 spinal cord segment ⁽⁶³⁾. An extensive diagnostic workup was performed to exclude other possible causes of TM ⁽⁶³⁾. Researchers suggested that onset of longitudinally extensive TM may have been associated with CoronaVac vaccination in this case ⁽⁶³⁾. A 41-year-old woman with no cardiovascular risk factors who was admitted the emergency department with flushing, palpitation, dyspnea, and chest pain 15 min after being vaccinated with an initial dose of CoronaVac ⁽⁶⁴⁾. Electrocardiogram (ECG) showed V4-6 T wave inversion, and echocardiography revealed left ventricular wall motion abnormalities ⁽⁶⁴⁾. Troponin-I level on arrival emergency department was elevated ⁽⁶⁴⁾. Coronary angiography showed no sign of coronary atherosclerosis and the patient was diagnosed with type 1 Kounis syndrome, a rare clinical condition defined as the co-existence of acute coronary syndromes and allergic reactions ⁽⁶⁴⁾. The patient's symptoms resolved and the patient was discharged from hospital in good condition ⁽⁶⁴⁾.

Covaxin (BBV152) is a Vero cell propagated, β-propiolactone inactivated whole-virion vaccine, utilizing the NIV-2020-770 strain of SARS-CoV-2 which contains the Asp614Gly mutation,

characterized by an aspartic acid to glycine shift at the 614 position of the SARS-CoV-2 spike protein ^(65,67). BBV152 is formulated with the adjuvant Algel-IMDG, which is comprised of a Toll-like receptor (TLR) 7/8 agonist, an imidazoquinoline molecule (IMDG), adsorbed on aluminum hydroxide gel (Algel) ^(65,66,67). The phase 2 clinical trial of BBV152 resulted in neutralizing antibody titers that were similar in effect to a panel of SARS-CoV-2 convalescent serum samples ⁽⁶⁷⁾. All elicited cytokine responses to BBV152 were biased to Th1 cells ⁽⁶⁷⁾. The vaccine was well tolerated in 6 µg/dose and 3 µg/dose groups with no serious adverse events ⁽⁶⁷⁾. Long-term follow-up of phase 1 trial participants showed that neutralizing antibody titers persisted, and T-cell memory responses were more pronounced in the 6 µg with Algel-IMDG adjuvant group compared with pre-vaccination samples ⁽⁶⁷⁾. The Algel-IMDG adjuvant has been used to augment cell-mediated responses and both the 3 µg and 6 µg BBV152 formulations ⁽⁶⁷⁾. Algel-IMDG induced responses that were biased to a Th1 phenotype, with IgG1:IgG4 ratios >1 ⁽⁶⁷⁾. The ratio of Th1:Th2 cytokines was strongly biased to a Th1 response, with increased IFN γ generation ⁽⁶⁷⁾. BBV152 was also found to induce T-cell memory responses, which was shown by an increased frequency of antigen-specific CD4⁺ T cells expressing the memory phenotype marker CD45RO⁺ ⁽⁶⁷⁾. The increase in the CD4⁺CD45RO⁺CD27⁺ T-cell population also indicated the activation of the co-stimulatory marker CD27, and confirmed the antigen recall memory T-cell response ⁽⁶⁷⁾. The effector functions of T-cells were supported by Th1 cytokine secretions, which were observed in ex-vivo responses after stimulation of PBMCs for 3 days. The results of the BBV152 phase 2 clinical trial further corroborated the results of the phase 1 trial and demonstrated an increased frequency of CD4⁺ T cells producing IFN γ in study participants who received BBV152 ⁽⁶⁷⁾. BBV152 vaccination induced antibody generation that was found to bind SARS-CoV-2 spike glycoprotein and nucleocapsid protein epitopes ⁽⁶⁷⁾. As a component of the long-term follow-up to the BBV152 phase 1 trial, the secretion of anti-SARS-CoV-2 spike glycoprotein IgG antibodies at day 104 post-vaccination was observed, which demonstrates the long-lasting T-cell memory response generated by BBV152 vaccination ⁽⁶⁷⁾. Similar findings relative to anti-SARS-CoV-2 spike glycoprotein IgG antibodies and T-cell memory response, in support of long-term immunity, have been reported in convalescent patients who had previously had COVID-19 ⁽⁶⁷⁾. It has been demonstrated that a reduction in NAb titers, against Beta and Delta variants of SARS-CoV-2 occurs relative to NAb titers against other SARS-CoV-2 variants, within recipient patients post-BBV152 vaccination ⁽⁶⁸⁾. The neutralization potential of BBV152 vaccination has been reported to be well established and effective against Beta and Delta variants of SARS-CoV-2 ⁽⁶⁸⁾. The broad coverage of antigenic epitopes inherent to an inactivated-virus vaccine induces an immune response against the whole virion, which decreases the magnitude of reduced neutralization against emerging variants ⁽⁶⁸⁾. The most common adverse event in the BBV152 phase 2 clinical trial was pain at the injection site, followed by headache, fatigue, and fever. No severe or life-threatening (ie, grade 4 and 5) adverse events were reported ⁽⁶⁷⁾. After either 6µg or 3µg doses, the combined incidence of local and systemic adverse events in this study was lower than that of other SARS-CoV-2 vaccine platform candidates, and similar to that of other inactivated SARS-CoV-2 vaccine candidates ⁽⁶⁷⁾.

In general, inactivated-virus SARS-CoV-2 vaccinations appear to be well tolerated, with post-vaccination injection site pain being the most prominent adverse event, effecting 9% of recipients ⁽⁶⁹⁾. Post-vaccination injection site pain was rated mild to moderate in severity ⁽⁶⁹⁾. Inactivated-virus SARS-CoV-2 vaccinations, such as BBV152, have been reported to generate protective levels of

neutralizing antibodies in the majority of the recipient patients to evolving SARS-CoV-2 variants (68,70).

(3.4) SARS-CoV-2 peptide sub-unit vaccine candidates

Peptide sub-unit vaccines against SARS-CoV-2 include NVX-CoV2373 and EpiVacCorona (71). NVX-CoV2373 is a recombinant SARS-CoV-2 nanoparticle vaccine constructed from the full-length, wild-type SARS-CoV-2 spike glycoprotein, 5µg/dose (71). NVX-CoV2373 was designed with Matrix-M, (50µg/dose), an adjuvant based on saponin extracted from *Quillaja saponaria* (Molina tree) (71). Matrix-M has been found to induce high and long-lasting levels of broadly reacting antibodies supported by a balanced type TH1 and TH2 response (71). Matrix-M adjuvant promotes rapid and profound effects on cellular drainage to local lymph nodes creating a milieu of activated cells including T cells, B cells, Natural Killer cells, neutrophils, monocytes and dendritic cells (71). Vaccine studies utilizing Matrix-M as an adjuvant, have demonstrated a significant dose-sparing effect and an acceptable safety profile (71). In a Phase 1-2 clinical trial, a two-dose regimen, administered 21 days apart, of NVX-CoV2373 elicited immune responses at 35 days post-vaccination that exceeded NAb levels found in COVID-19 convalescent serum (71). Interim Phase 3 trial results for NVX-CoV2373 demonstrated 100% efficacy in preventing severe disease, while overall efficacy was 96.4% (71). NVX-CoV2373, comprised of 5 µg of a recombinant nanoparticle spike protein plus 50 µg of Matrix-M adjuvant, when administered as a two-dose regimen 21 days apart was 89.7% effective against symptomatic SARS-CoV-2 infection caused by both B.1.1.7 and non-B.1.1.7 variants (72).

Vaccination with NVX-CoV2373 demonstrated an efficacy of 96.4% against non-B.1.1.7 SARS-CoV-2 strains (72). The efficacy of vaccination with NVX-CoV2373 against non-B.1.1.7 SARS-CoV-2 variants compares favorably with the reported 95.0% efficacy against these SARS-CoV-2 strains for the Pfizer BNT161b2 messenger RNA (mRNA) vaccine, as well as, the efficacy of 94.1% reported for the Moderna mRNA-1273 vaccine (72). Injection-site tenderness and pain, fatigue, headache, and muscle pain were the most commonly reported local and systemic adverse events (72). Most adverse events were reported being grade 1 or 2 in severity and of a short mean duration (1.6, 1.6, and 1.8 days, respectively, after the first dose and 2.0, 1.8, and 1.9 days, respectively, after the second dose) (72). Grade 4 systemic adverse events were reported in 3 vaccine recipients (72). Two participants reported a grade 4 fever (>40 °C), one after the first dose and the other after the second dose (72). A third participant was found to have had positive results for SARS-CoV-2 on PCR assay at baseline (72). Five days after dose 1, this participant was hospitalized for Covid-19 symptoms and subsequently had six grade 4 events: nausea, headache, fatigue, myalgia, malaise, and joint pain (72). Systemic adverse events were reported more often by younger vaccine recipients than by older vaccine recipients and more often after the second dose than after the first dose (72). One serious adverse event comprised of myocarditis was reported in a vaccine recipient, 3 days after the second dose and was considered to be a potentially immune-mediated condition (72). The participant had a full recovery after 2 days of hospitalization (72). No episodes of anaphylaxis or vaccine-associated enhanced Covid-19 were reported (72).

EpiVacCorona is a subunit vaccine containing chemically synthesized peptide immunogens corresponding to selected protective epitopes of SARS-CoV-2 spike protein, conjugated to recombinant SARS-CoV-2 nucleocapsid protein and adjuvanted with aluminum hydroxide (71).

The Phase 1-2 trials demonstrated that a 2-dose vaccination scheme induced the production of antibodies specific to the antigens that make up the vaccine in 100% of the volunteers (71). No serious adverse events have been reported (71).

(3.5) SARS-CoV-2 nucleotide vaccine candidates

Nucleotide vaccines have recently been introduced onto the landscape of vaccine options (73,74). Nucleotide vaccines constitute an engineered nucleotide template, comprised of either mRNA or DNA, where said genetic template encodes for an engineered viral antigen (73,74). Vaccination with a SARS-CoV-2 nucleotide vaccine introduces the genetic template encoding for an engineered SARS-CoV-2 viral antigen into the cellular protein synthetic apparatus of a recipient patient via a delivery vehicle or vector. Upon delivery of the vaccine encoded genetic template the cellular protein synthetic apparatus of the recipient patient is compelled to self-synthesize the engineered viral antigen (73,74). Upon successful self-synthesis of the vaccine-encoded SARS-CoV-2 engineered viral antigen, the immune system of the recipient patient subsequently engages the self-synthesized viral antigen, culminating in a protective immune response (73,74). The majority of SARS-CoV-2 nucleotide vaccines, fielded globally, have utilized a nucleotide sequence encoding either: the complete wild-type (wt) SARS-CoV-2 spike protein, the complete SARS-CoV-2 spike protein engineered to be stable in the typically meta-stable pre-fusion conformation, or a SARS-CoV-2 spike protein S1 subunit homologue. Two general classes of SARS-CoV-2 nucleotide vaccines are currently utilized globally: viral vector nucleotide SARS-CoV-2 vaccines and mRNA nucleotide SARS-CoV-2 vaccines (73). Viral vector nucleotide vaccines currently deployed against SARS-CoV-2 utilize adenovirus viral vectors to introduce a DNA genetic template encoding for a SARS-CoV-2 antigen (73,103). The structure of a DNA nucleotide template is more robust than that of mRNA templates, thus allowing longer storage-life at higher temperatures (73,103). Additionally, the protein coat of the adenovirus vector provides protection to the DNA template as well as facilitating cellular entry of the vaccine genetic material (103). Characteristics of the adenovirus vaccine platform also include mimicry of the natural course of the infection, potentially resulting in the expression of vaccine-encoded antigens in the cell (73). The adenovirus vector of SARS-CoV-2 viral vector nucleotide vaccines may exert adjuvant effects, as adenoviruses target innate immune cells and macrophages, stimulating innate immune responses via pattern-recognition receptors (103). Activated innate immune cells and macrophages are induced to release type I interferon, thereby propagating both an antigenic and inflammatory signaling to T cells in lymph nodes draining the site of vaccine administration (103). More pronounced humoral and cytotoxic immune responses are thought to be induced by viral-vector SARS-CoV-2 nucleotide vaccines, compared to the humoral and cytotoxic immune responses induced via mRNA nucleotide vaccines, which possess an ionized-lipid delivery vehicle (73). However, pre-existing patient immunity against an adenovirus viral-vector may reduce effectiveness with which the nucleotide template encoding the synthetic SARS-CoV-2 viral antigen is delivered to the protein synthetic apparatus of a recipient patient (73). Upon administration of a SARS-CoV-2 viral vector nucleotide vaccine, DNA, which encodes the nucleotide template for the synthetic viral antigen, must first enter into the nucleus of the cell in order to produce the encoded viral antigen via mRNA molecules (103). Conversely, SARS-CoV-2 nucleotide vaccines which utilize mRNA, in an ionized-lipid vehicle, must simply introduce the mRNA encoding for SARS-CoV-2 viral antigens directly into the cytosol, where the mRNA template can immediately interact with

ribosomes and begin to generate vaccine-encoded viral antigens ⁽⁷³⁾. The possibility of integration of the DNA genome of SARS-CoV-2 viral vector nucleotide vaccines, into the genome of recipient patients has not been excluded ⁽¹⁰³⁾.

mRNA SARS-CoV-2 nucleotide vaccine candidates

Pfizer/BioNTech's BNT-162b2 vaccine introduces mRNA templates encoding for a SARS-CoV-2 spike protein, which differ from the spike protein in the reference SARS-CoV-2 genome (NC_045512) by two amino acids ⁽⁷⁵⁾. The SARS-CoV-2 spike protein encoded by BNT-162b2 replaces amino acids KV, found at sites 986 and 987 in NC_045512, with amino acids PP in order to stabilize the encoded spike protein in the typically meta-stable pre-fusion conformation ⁽⁷⁵⁾. The immunological bio-design rationale that drove the effort to stabilize the encoded spike protein in the pre-fusion conformation was a desire to train the host immune system to recognize the SARS-CoV-2 virion before membrane fusion and entry into host cells ⁽⁷⁵⁾. Translation initiation is typically the rate limiting step in the process of mRNA translation, and its efficiency depends heavily on how rapidly the 5'-UTR can load ribosomal protein onto the mRNA undergoing translation ^(32,75). During instances where mRNA translation initiation is highly efficient, elongation of the resultant amino acid sequence becomes the rate-limiting factor. Despite the fact that both BNT-162b2 and Moderna's mRNA-1273 nucleotide vaccine utilize the same SARS-CoV-2 spike protein antigen, with a PP substitution at sites 986/987 relative to NC_045512, the design of the vaccine delivered mRNA template varies considerably between BNT-162b2 and mRNA-1273, in respect to, the structure of: 5'-UTR, 3'-UTR and codon optimization ⁽⁷⁵⁾. One aspect of codon optimization can be termed within-family optimization ⁽⁷⁵⁾. Two strategies of within-family codon optimization have been used in the development of mRNA nucleotide vaccines against SARS-CoV-2 ⁽⁷⁵⁾. One approach, which can be termed the "fundamentalist strategy", consists of replacing all wild-type codons with the major codon ⁽⁷⁵⁾. Determination of the major codon depends on two criteria, 1) the codon is preferred by highly expressed gene(s), 2) the codon is decoded by the most abundant tRNA(s) ⁽⁷⁵⁾. A second approach to within-family codon optimization can be termed the "liberal strategy", which comprises a less extreme version of the fundamentalist strategy, which only replaces all synonymous wild-type codons with the optimal codon ⁽⁷⁵⁾. For example, consider a hypothetical synonymous codon family comprising NN(R), with NNG decoded by tRNA-1 and NNA decoded by tRNA-2 ⁽⁷⁵⁾. Furthermore, consider that tRNA-1 is twice as abundant as tRNA-2 and that highly expressed genes favor NNG codon over NNA codon ⁽⁷⁵⁾. An example of the fundamentalist strategy is to replace all codons with NNG ⁽⁷⁵⁾. Whereas an exemplary embodiment of the liberal strategy, based on the rationale that when a cell is full of mRNA with NNG codons, tRNA-1 will be under such a high demand that it may become less available than tRNA-2, even though there are twice as many tRNA-1 molecules in the cell compared to tRNA-2; therefore, it may be optimal to maintain a population of some NN(R) codons that are NNA so that they might be decoded by tRNA-2 ⁽⁷⁵⁾.

The liberal strategy has been consistently applied to the within-family codon optimization of the BNT-162b2 mRNA template ⁽⁷⁵⁾. Human cells are known to attack unmodified exogenous RNA, therefore BNT-162b2 features substitutions of all uridines (U) nucleotides with N1-methylpseudouridine ⁽⁷⁵⁾. The wild-type SARS-CoV-2 spike protein encoded by the reference genome NC_045512 contains 42 Arg residues, of which 30 are encoded by AGR codons, with the remaining 12 encoded by CGN codons ⁽⁷⁵⁾. Additionally, human genes use CGN mRNA codons more

frequently than AGR codons for encoding Arg ⁽⁷⁵⁾. For example, human ribosomal protein genes 33 RPS and 50 RPL, known for possessing high rates of expression, encode 64.2% of Arg residues via CGN codons ⁽⁷⁵⁾. BNT-162b2 features a reduction of 8 Arg residues encoded by AGR codons and a corresponding replacement by CGN codons encoding for Arg ⁽⁷⁵⁾. Potential risks of codon optimization via the substitution of Arg encoding AGR codons with CGN codons include the possibility that host zinc finger antiviral proteins (ZAP), which target CpG dinucleotides in viral RNA and recruit cellular RNA degradation complexes to degrade the viral RNA genome, may result in rapid degradation of the BNT-162b2 mRNA via ZAP mediated RNA degradation pathway ⁽⁷⁵⁾. However, BNT-162b2 is intended for delivery, via injection, into muscle tissue and the near absence of ZAP in human muscle cells suggests that BNT-162b2 mRNAs will not be subject to ZAP-mediated RNA degradation ⁽⁷⁵⁾.

Codon optimization, as applied to BNT-162b2, results in a much increased codon adaptation index (CAI) and index of translation efficiency (ITE) for the BNT-162b2 mRNA template relative to wild-type SARS-CoV-2 mRNA encoding spike proteins ⁽⁷⁵⁾. Wild-type SARS-CoV-2 spike proteins, from natural coronavirus variants, possess CAIs of < 0.7 for mRNAs encoding spike proteins, whereas, the codon-optimized mRNA encoding SARS-CoV-2 spike protein for BNT-162b2 has CAI equal to 0.94925 ⁽⁷⁵⁾. ITE can be viewed as a generalized CAI, taking into consideration background mutation bias, the ITE value of the mRNA delivered by BNT-162b2 is 0.8989, where the ITE for wild-type SARS-CoV-2 strain NC_045512 mRNA encoding spike protein, is only 0.5616 ⁽⁷⁵⁾. The maximum CAI and ITE values are 1 ⁽⁷⁵⁾. BNT-162b2 administration has demonstrated an estimated effectiveness, during a period beginning 7 days after administration of the second dose of BNT-162b2 at: 92% against documented SARS-CoV-2 infection, 94% against symptomatic SARS-CoV-2 infection, 87% against hospitalization, and 92% against severe SARS-CoV-2 infection ⁽⁷⁶⁾. Estimated effectiveness of BNT-162b2 after one dose was 46% against documented SARS-CoV-2 infection, 57% against symptomatic SARS-CoV-2 infection, 74% against hospitalization and 62% against severe SARS-CoV-2 infection ⁽⁷⁶⁾. BNT-162b2 has been widely hailed for stimulating the production of a significant neutralizing anti-body response in high-risk populations, such as but not limited to: those over the age of 65 years, overweight and obese individuals, patients DM2 and patients requiring renal dialysis ^(77,91). For example, it has been reported that IgG seropositivity against SARS-CoV-2 was found to be significantly lower among individuals with DM2, chronic diseases and those aged 60 years or older when vaccinated with CoronaVac, inactivated-virus vaccine, compared to those vaccinated with BNT-162b2 ⁽⁷⁷⁾. In terms of the production of a neutralizing anti-body response, BNT-162b2 vaccination of elderly, overweight/obese and DM2 populations can be viewed as having significantly reduced healthcare disparity, as these populations have typically demonstrated diminished immune responses to legacy vaccination technology ^(45,46,47,77). Reports suggest that the incidence of Bell's palsy or facial nerve palsy following vaccination with BNT-162b2 may be equivalent or slightly less than the incidence of facial nerve palsy attributed to influenza vaccines and CoronaVac ^(78,79).

The onset of venous thromboembolic events are a potential risk following vaccination with BNT-162b2, reports include thousands of documented occurrences of: cerebral venous thrombosis (CVT), deep vein thrombosis (DVT), pulmonary thromboembolism (PE), and portal vein thrombosis (PVT) ^(80,81,82,83,84,85). In addition to a risk of venous thromboembolic events, thousands of occurrences of thrombocytopenia and arterial thromboembolic events have been confirmed

following vaccination with BNT-162b2 ⁽⁸⁵⁾. Reports confirm that sequelae of thrombocytopenia and thromboembolic events such as, ischemic stroke, myocardial infarction, and sequelae of arterial thrombotic events such as, but not limited to, retinal artery occlusion and death, are a risk following vaccination with BNT-162b2 ⁽⁸⁵⁾. New-onset of myopericarditis following BNT-162b2 vaccination has been reported by health authorities in a multitude of countries ⁽⁸⁶⁾. Reported cases of post-BNT-162b2 myopericarditis predominately occur in younger adult men within 14 days following the second dose of the vaccine, however, cases have been reported in older males and females, as well as following the first dose of BNT-162b2 ^(86,87,88). New-onset cases of myasthenia gravis (MG) are reported to have occurred after administration of BNT-162b2 vaccine ⁽⁸⁹⁾. New-onset of multiple sclerosis (MS) has been reported as a potential consequence of vaccination with BNT-162b2 ⁽⁸⁹⁾. New-onset cases of nephrotic syndrome are reported to have occurred following vaccination with BNT-162b2 ⁽⁹⁰⁾. New onset cases of crescentic glomerulonephritis have been reported after administration of BNT-162b2, where kidney biopsies from effected individuals demonstrated IgA nephritis and anti-glomerular basement membrane (anti-GBM) disease ⁽⁹⁰⁾.

Moderna's mRNA-1273 nucleotide vaccine, like BNT-162b2, introduces a mRNA template encoding for a SARS-CoV-2 spike protein, which differs from the spike protein in the reference SARS-CoV-2 genome (NC_045512) by two amino acids ⁽⁷⁵⁾. The SARS-CoV-2 spike protein encoded by mRNA-1273 replaces amino acids KV, found at sites 986 and 987 in NC_045512, with amino acids PP, in order to stabilize the vaccine encoded spike protein in the pre-fusion conformation ⁽⁷⁵⁾. Also, in a fashion similar to BNT-162b2, all U in mRNA-1273 was replaced by N1-methylpseudouridine in order to decrease the likelihood of host-cell attack against mRNA-1273 ⁽⁷⁵⁾. However, where BNT-162b2 features a reduction of 8 Arg residues encoded by AGR codons in NC_045512 and a corresponding replacement of those AGR codons by CGN codons, mRNA-1273's developers have reduced AGR codons by 28, and replaced said AGR codons with CGN codons ⁽⁷⁵⁾. Despite possessing four times the number of CGN codons encoding for Arg relative to BNT-162b2, it is unlikely that mRNA-1273 will be subject to ZAP-mediated RNA degradation, as mRNA-1273 is administered via intramuscular injection, and ZAP has almost no reported presence in human muscle cells ⁽⁷⁵⁾. Additionally, Moderna applied the fundamentalist strategy of within-family codon optimization, for all codon families found in mRNA-1273 ⁽⁷⁵⁾. The codon optimization applied to mRNA-1273 has resulted in a CAI and an ITE for mRNA-1273 encoded spike protein mRNA that is much higher those possessed by wild-type spike protein genome from SARS-CoV-2 virion ⁽⁷⁵⁾. SARS-CoV-2 strain NC_045512 possesses a CAI of 0.68767 and an ITE of 0.5616, whereas, mRNA-1273 possesses a CAI of 0.97939 and an ITE of 0.9569 ⁽⁷⁵⁾. It is of note that the maximum CAI and ITE values are 1 and the CAI of BNT-162b2 is 0.94925, while the ITE of BNT-162b2 is 0.8989 ⁽⁷⁵⁾. Like BNT-162b2, mRNA-1273 has received far-reaching acclaim for the ability to generate significant NAb responses in high-risk populations, which have traditionally demonstrated poor response to legacy vaccination technology. In some reported instances, mRNA-1273 not only out-performed inactivated-virus SARS-CoV-2 vaccines, but also out-performed BNT-162b2 in the context of highly "at-risk" populations. For example, vaccination with mRNA-1273 has been reported to induce rates of seroconversion in 97% of dialysis patients and 49% of renal transplant patients ⁽⁹¹⁾. Comparatively, vaccination with BNT162b2 induced seroconversion in only 88% of dialysis patients and only 26% of renal transplant patients ⁽⁹¹⁾. IgG antibodies directed specifically against the SARS-CoV-2 spike

protein RBD were reported to be significantly higher in dialysis patients vaccinated by mRNA-1273 compared to dialysis patients vaccinated with BNT162b2 ⁽⁹¹⁾.

Reports have confirmed the onset of cases of acute myocarditis/pericarditis/perimyocarditis (myocarditis) following administration of mRNA-1273 ^(92,93,94,95). While most reported cases of new-onset myocarditis following administration of mRNA-1273 have involved otherwise healthy men under the age of 30, cases of myocarditis post-mRNA-1273 vaccination have been reported in females as well as older males ^(92,93,94,95). Presentation of new-onset cardiovascular disease post-mRNA-1273 vaccination may present with symptoms demonstrating a striking similarity to gastrointestinal illness or most interestingly, COVID-19 infection ⁽⁹³⁾. For example, new-onset myocarditis, post-mRNA-1273 administration has been reported to include presenting symptoms such as nausea, vomiting and diarrhea of one-day duration, acute severe gastroenteritis with dehydration and hypotension ⁽⁹³⁾. New-onset myocarditis, post-mRNA-1273 vaccination, has been reported to include echocardiography (ECG) findings consistent with pericarditis showing diffuse ST elevation and short PR interval ⁽⁹³⁾. Additionally, signs of severe ventricular dysfunction on ECG, demonstrating decreases in right and left ventricular function, reductions of ejection fraction (EF), pericardial effusion and signs of impending cardiac tamponade, have been reported as components of post-mRNA-1273 vaccination new-onset myocarditis ⁽⁹³⁾. Patients experiencing new-onset myocarditis post-mRNA-1273 vaccination do not always experience mild or self-limiting consequences ⁽⁹³⁾. For example, post-mRNA-1273 vaccination new-onset myocarditis can progress to hemodynamic instability, hypovolemic shock, obstructive shock and cardiogenic shock, MI, acute kidney injury, multi-organ failure, deranged liver function and DIC ⁽⁹³⁾. New-onset cases of nephrotic syndrome have been reported to occur following vaccination with mRNA-1273 ⁽⁹⁰⁾. New onset cases of crescentic glomerulonephritis have been reported after administration of mRNA-1273, where kidney biopsies from effected individuals demonstrated the presence of anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis, IgA nephritis and anti-glomerular basement membrane (anti-GBM) disease ⁽⁹⁰⁾. The mechanism of *de novo* ANCA-associated vasculitis post-mRNA-1273 vaccination may derive from a neutrophilic immune response to the vaccine-induced, patient-synthesized SARS-CoV-2 spike proteins or S1 fragments ⁽⁹⁰⁾. It is possible that mRNA-1273-induced spike proteins and/or S1 leads recipient patients to generate inflammatory cytokines such as TNF and interleukin-1B, which prime neutrophils leading to formation of NETs ⁽⁹⁰⁾. Persistent NETs and prolonged exposure to their contents can lead to disruption of tolerance and formation of antibodies to myeloperoxidase and proteinase 3, thus triggering an episode of ANCA-associated vasculitis ⁽⁹⁰⁾. As previously noted in this report, exposure of platelets, from healthy human donors, to isolated SARS-CoV-2 spike proteins, stimulated platelet secretion of α -granule inflammatory cytokines PF4, TNF- α , IL-8, and IL-1 β ⁽⁴⁾. Neutrophil activation is regulated by chemokines such as IL-8 ⁽²⁵⁾. Neutrophil activation by IL-8, released by platelets in response to exposure to isolated SARS-CoV-2 spike proteins, promotes the formation of neutrophil extracellular trap (NET), platelet aggregation, and cell damage ⁽²⁵⁾. Vaccination with mRNA-1273 has been reported to be associated with risk of post-vaccination thrombotic complications ⁽⁹⁶⁾. Post-mRNA-1273 vaccination thrombotic complications include reported instances of venous thromboembolism, such as DVT, CVT and PE ^(96,97,98).

Viral vector SARS-CoV-2 nucleotide vaccine candidates

Viral vector nucleotide vaccine Ad26.COV2.S, produced by Jansen, (Johnson & Johnson), introduces a DNA genetic template that encodes for a SARS-CoV-2 spike protein with furin cleavage site mutations and PP amino substitutions to stabilize the spike protein in pre-fusion conformation via a serotype 26 human adenovirus vector ^(73,103). Human adenovirus serotype 26 (Ad26) exhibits lower seroprevalence in humans compared to other adenovirus strains, thus allowing Ad26 to bypass the significant pre-existing immunity against other adenoviruses, such as but not limited to, adenovirus serotype 5 (Ad5) ⁽⁷³⁾. Ad26.COV2.S is administered as a single dose containing 5×10^{10} viral particles, and can be stored for up to 2 years in a standard freezer and up to 3 months at refrigerator temperatures ⁽⁹⁹⁾. A study of 19,630 patients who received Ad26.COV2.S reported COVID-19 disease onset, of moderate to critical severity at least 28 days after vaccination, totaling 66 cases among members of the vaccine group and 193 cases were reported in the placebo group, culminating in a vaccine efficacy of 66.1% ⁽⁹⁹⁾. Venous thromboembolic events were reported over three times more often in the Ad26.COV2.S vaccine group relative to the placebo group ⁽⁹⁹⁾.

Instances of post-vaccination seizure and tinnitus were reported more frequently in the Ad26.COV2.S group relative to the placebo group ⁽⁹⁹⁾. Guillain-Barré syndrome was also reported in the Ad26.COV2.S group but not found in the placebo group ⁽⁹⁹⁾. Serious adverse events reported after the administration of Ad26.COV2.S include: thrombotic and thromboembolic events occurring in the lower extremities, chest, and cerebral vasculature, including transverse sinus thrombosis with cerebral hemorrhage ^(99,100). New-onset myocarditis has also been reported post-vaccination with Ad26.COV2.S ⁽¹⁰⁰⁾. As a result of higher than expected occurrence of serious events, particularly in those under the age of 29, the United States FDA amended the Emergency Use Authorization (EUA) for Ad26.COV2.S on April 23, 2021 limiting distribution to individuals 18 years of age and older ⁽¹⁰⁰⁾.

ChAdOx1 nCov-19 vaccine (AZD1222), produced by Oxford-AstraZeneca, utilizes the replication-deficient chimpanzee adenovirus ChAdOx1 as a viral vector for the delivery of a DNA genetic template encoding for an unmodified wild-type SARS-CoV-2 spike protein antigen ^(73,101,103). AZD1222's use of ChAdOx1 is significant, because of the low level of pre-existing immunity in the human population against the virus, thus minimizing immune system interference with cellular delivery of AZD1222's genetic template ⁽⁷³⁾. AZD1222 is administered in a two-dose regimen, where two doses of 5×10^{10} viral particles are administered 28 days apart ⁽¹⁰¹⁾. AZD1222 has been evaluated in at least four clinical trials administered over three continents, where AZD1222 demonstrated vaccine efficacy, against symptomatic COVID-19 disease, of 70.4% after two doses and 64.1% after at one dose of 5×10^{10} viral particles ⁽¹⁰²⁾. Acute transverse myelitis (ATM) has been reported at a higher than expected rate following vaccination with AZD1222 ⁽¹⁰⁴⁾. Thrombotic-thrombocytopenia, resultant hemorrhage and sequelae such as ischemic stroke and death have been reported after vaccination with AZD1222 ^(105,106,107).

Gam-COVID-Vac (Sputnik V) is a SARS-CoV-2 viral vector nucleotide vaccine, which utilizes a hybrid approach to viral delivery of a DNA template encoding SARS-CoV-2 spike protein ^(73,103). The Sputnik V vaccine, produced by the Gamaleya Institute in St. Petersburg Russia, utilizes a viral vector based on Ad26 for the first dose (rAd26-S) and adenovirus serotype 5 (rAd5-S) for the second dose, in an attempt to maximize the advantages of the two vectors, while minimizing the deleterious nature of pre-existing immunity against either of the vaccine's viral vectors ^(73,108). Both, rAd26-S and rAd5-S

of Sputnik V introduce $1.0 \pm 0.5 \times 10^{11}$ viral particles per dose, via a 0.5 ml intramuscular injection administered 21-days apart ⁽¹⁰⁸⁾. Sputnik V has been reported to be 91.6% efficacious against COVID-19 disease, 21 days from the administration of the rAd26-S dose ⁽¹⁰⁸⁾. It has been reported that Sputnik V demonstrated 100% efficacy against severe COVID-19 disease ⁽¹⁰⁸⁾. It has been reported that the Sputnik V vaccine is well tolerated, with 0.3% of vaccinated patients reporting serious adverse events ⁽¹⁰⁸⁾. Reports from Argentina have not documented any cases of post-Sputnik V vaccination thrombocytopenia and/or thrombotic events, despite Argentina administering over four million doses of the Sputnik V ⁽¹⁰⁹⁾. Additionally, Serbia, which has been utilizing Sputnik V to vaccinate large segments of the population, has not reported cases of thrombocytopenia and/or thrombotic events ⁽¹⁰⁹⁾. However, significant controversy exists within the global research community in regards to the reported safety and effectiveness of Sputnik V ⁽¹⁵⁰⁾.

Emergent properties: the intersection of elite athlete physiology and lifestyle with SARS-CoV-2 spike protein molecular pathophysiology and SARS-CoV-2 vaccination technology.

(4.1) Introduction

Elite strength, power and endurance athletes, either male or female, who engage in regular intense RT and/or ET and/or ST, often in bouts of 4-6 hours per day, while supported by protein/AA_{optimized} can be said to possess far-greater magnitudes and/or rates of MPS relative to the general population at any given point within a 24-hour period ^(29,30,31). While it is difficult to determine a relatively exact magnitude for the degree of difference in MPS that exists between elite strength, power and endurance athletes and the level of MPS existing within the general population, a highly conservative lower limit of the difference between these divergent populations can be reasonably derived. Elite athletes, actively engaged in RT supported by protein/AA, demonstrate a 24-hour, post-RT rate of MPS that is on average 129% greater than the rate of MPS demonstrated by non-training athletes in a protein fed-state over the same 24-hour period ^(29,30,31). Therefore, the claim that populations of elite strength, power and endurance athletes actively engaged in RT, supported by protein/AA, demonstrate MPS that is at a minimum, 129% greater than the rate of MPS existing within the general population, is a highly-conservative, yet tenable position ^(29,30,31). As a consequence of regularly undertaking intense bouts of RT and/or ET and/or ST, supported by protein/AA, elite athletes demonstrate enhanced MPS via greater mRNA translational capacity and greater mRNA translational efficiency. The prolific rates of mRNA translation demonstrated by elite athletes originate from multiple signaling adaptations that converge to increase: ribosome biogenesis, skeletal muscle cellular inventory of ribosomal proteins and cellular inventory of ribosomal RNA ^(29,30,32,34,35). The sheer-multitude of signaling pathways anabolic towards MPS which are activated via elite level RT and/or ET and/or ST, when supported by protein/AA, and coupled with a youthful demographic, underscores the profound physiological drive that ultimately ensures the markedly elevated rates of MPS observed within actively-training populations of elite strength, power and endurance athletes ^(29,30,33,34,35).

(4.2) The impact of enhanced skeletal muscle protein synthesis on SARS-CoV-2 vaccination

The profound physiological drive toward MPS anabolism, present within actively training populations of elite athletes supported by protein/AA; eliminates barriers to protein synthesis encountered by members of the general population. For example, given the disproportionately

longer times required to translate mRNA ORFs that are responsible for encoding for ribosomal proteins themselves, the abundant skeletal muscle inventories of ribosomal proteins, rRNA and ribosomes, effectively provides actively-training elite athletes a significant “head-start” in regards to the translation of any mRNA or DNA template encoding SARS-CoV-2 spike proteins ⁽³²⁾. Possession of a large skeletal muscle inventory of ribosomal proteins is one mechanism which directly contributes to the massively greater rates of MPS found in actively-training elite athletes, relative to MPS observed within a sedentary general population ⁽³²⁾. Therefore the enhanced MPS reported in populations of actively training elite athletes, is a very likely contributor to the superior immunological responses observed in populations of actively training elite athletes in response to legacy vaccination technology, such as inactivated-virus vaccines ⁽³⁷⁾. Elite athletes have been observed to generate nearly twice the levels of vaccine-reactive CD4 T-cells, compared to non-athletes, following a dose of tetravalent influenza vaccine ⁽³⁷⁾. Following vaccination with a tetravalent influenza vaccine, the resultant cytokine profiles, in both elite athletes and non-athlete controls, were observed to change from multi-functional T-cells co-producing IFN γ , IL-2 and TNF α to T-cells with restricted cytokine expression ⁽³⁷⁾. The observed change in T-cells with restricted cytokine expression was observed to be associated with a significant increase in CTLA-4 expression, and this expression was significantly more pronounced in athletes relative to the control group ⁽³⁷⁾. Elite athletes were also found to mount a significantly greater neutralizing antibody response to a dose of tetravalent influenza vaccine, compared to the antibody response observed within non-athlete controls ⁽³⁷⁾. Elite athletes have been reported to generate an immune response with a protection rate of greater than 70% against all antigens contained in a repeated-dose, trivalent, inactivated-virus, split influenza vaccine, comprised of different antigenic content ⁽³⁸⁾.

The enhanced immune response to legacy vaccination technology observed within populations of actively-training elite strength, power and endurance athletes, stands in stark contrast to the immunological response observed among large swaths of the current global population. For example, immunological responsiveness to legacy vaccine technology in populations over the age of 65 years, are characterized by significantly diminished production of neutralizing antibodies ⁽⁴⁵⁾. Additionally, older populations demonstrate a more rapid waning of antibodies generated in response to legacy vaccination technology ⁽⁴⁵⁾. Populations of individuals over the age of 65 years have demonstrated lower antibody-generating immunological responses to diphtheria, hepatitis A (HepA), hepatitis B (HepB), pneumococcal polysaccharide vaccine (PPV23), tick-borne encephalitis (TBE) and tetanus vaccinations ⁽⁴⁵⁾. Adults with DM2 have been observed to generate a lower antibody response to HepB vaccination, compared to age-matched controls without DM2 ⁽⁴⁵⁾. Adults with chronic renal failure, who require hemodialysis, have been reported to generate markedly reduced antibody responses to diphtheria, HepB and tetanus vaccinations ⁽⁴⁵⁾. Patients with chronic renal failure, who require hemodialysis, have also been reported to demonstrate accelerated waning of vaccination-induced antibodies, which is especially magnified when hemodialysis patients concomitantly suffer from DM2 ⁽⁴⁵⁾. Vaccination of adult populations has demonstrated that increased body mass index (BMI) is inversely correlated with antibody responses to HepA and HepB vaccinations ^(45,46). Obesity seems to impair the ability of individuals to mount a protective immune response upon vaccination with legacy vaccination technology ^(45,46). Compared with influenza-vaccinated populations of non-obese adults, influenza-vaccinated obese

adults demonstrate twice the risk of influenza or influenza-like illness despite serological responses to vaccination which are equivalent to those generated by non-obese populations (47). The decreased effectiveness of legacy vaccination-induced antibodies, among obese individuals, appears to be the result of obesity related phenomena culminating in an impairment of the innate immune response (47).

While no vaccine, nor any medical treatment for that matter, is devoid of risk. Actively training elite athletes do not appear to incur any extra margin of mechanistic risk from inactivated-virus vaccines in exchange for the enhanced immunological responsiveness demonstrated by this population (39).

Elite athletes have been found to tolerate inactivated-virus vaccines exceedingly well. Reports indicate that 2.2% of athletes receiving a trivalent inactivated-virus influenza vaccination missed a total of only 0.7% of training sessions as a result of adverse post-vaccination effects (39). 5.9% of athletes receiving inactivated-virus vaccination were reported to require modifications to a total of only 1.7% of training sessions conducted within the first 2 days following vaccination (39). The most commonly reported post-vaccination adverse events, following administration of inactivated-virus vaccines to actively training athletes, were inoculation site pain, swelling and stiffness (39). The low prevalence and severity of adverse events following vaccination of elite athletes with inactivated-virus vaccines, combined with demonstrably superior immunological responses reported within populations of actively training elite athletes; are consistent with reported observations that physical exercise, both chronic and acute, constitutes a potent functional adjuvant (40,41,42,43). Therefore, the regular, intense and extensive physical training, which comprises a key component of the lifestyle of elite strength, power and endurance athletes, functions as a potent vaccine adjuvant, increasing the immunological response of athletes to inactivated-virus vaccines, live-attenuated virus vaccines and toxoid vaccines (40,41,42,43).

Standing in stark contrast to legacy vaccination technology, both in terms of novelty and the demonstrated ability to generate profound immunological responses in individuals over the age of 65, individuals with co-morbid conditions such as, but not limited to: obesity, DM2, renal disease requiring dialysis and renal transplant, are SARS-CoV-2 nucleotide vaccines (74,75). Both viral-vector nucleotide vaccines and mRNA nucleotide vaccines against SARS-CoV-2 have demonstrated high levels of seroconversion in populations over the age of 65 and possessing serious co-morbid conditions (74,75). The degree of seroconversion demonstrated within high-risk populations, by SARS-CoV-2 nucleotide vaccines, are far greater than the degree of seroconversion demonstrated within high-risk populations by inactivated-virus vaccines against SARS-CoV-2 (60,72,91).

Nucleotide vaccines against SARS-CoV-2 share many of the most common post-vaccination adverse events with inactivated-virus vaccines against SARS-CoV-2, including fever and injection site pain, edema and stiffness. Additionally, more severe post-vaccination complications have been observed to occur among recipients of nucleotide vaccines against SARS-CoV-2 and inactivated-virus vaccines against SARS-CoV-2 with similar frequency, including complications such as, but not limited to, Bell's palsy (78,79).

Nucleotide vaccines against SARS-CoV-2, as a class, feature unique post-vaccination adverse events not shared by inactivated-virus vaccines against SARS-CoV-2. Post-vaccination adverse events unique to nucleotide SARS-CoV-2 vaccines include thrombosis and myocarditis

(80,81,82,83,84,85,86,97,88,92,93,94,95,,99,100,105,106,107). As previously noted in this report, post-SARS-CoV-2

nucleotide vaccination adverse events categorized as thrombosis and/or myocarditis have occurred in males and females, the very young and very old. However, occurrences of post-SARS-CoV-2 nucleotide vaccination adverse events comprising thrombosis and/or myocarditis are not evenly distributed among the population.

A review of reported cases of post-SARS-CoV-2 nucleotide vaccination, new-onset myocarditis, revealed that while only 31.8% of all individuals vaccinated were below the age of 40 years old, this age group constituted 80.7% of all incidences of new-onset, post-SARS-CoV-2 nucleotide vaccination myocarditis ⁽¹⁰⁰⁾. Among individuals below the age of 29 years old, the observed cases of myocarditis were significantly in excess of the number of statistically expected cases ⁽¹⁰⁰⁾. The expected number of cases, based on an annual background incidence rate of 1–10 per 100,000 person-years in the USA and assuming presentation 30 days post vaccination, for individuals aged 6–17 years was found to be 5–52 cases of myocarditis, but as of July 4, 2021, 218 cases were reported to the VARES database ⁽¹⁰⁰⁾. The expected number of cases for individuals aged 18–29 years was found to be 9–94 cases of myocarditis, but as of July 4, 2021, 410 cases were reported to the VARES database ⁽¹⁰⁰⁾. Separately, of a reported 81 cases of post-SARS-CoV-2 nucleotide vaccination new-onset myocarditis, 77 of the cases involved male patients with a mean age of less than 30 years ⁽¹⁰⁰⁾. Instances of post-SARS-CoV-2 nucleotide vaccination new-onset myocarditis were observed following administration of both mRNA and viral vector SARS-CoV-2 nucleotide vaccines ⁽¹⁰⁰⁾. Onset of myocarditis was noted in 87.7% of occurrences following a second dose of mRNA SARS-CoV-2 nucleotide vaccines ⁽¹⁰⁰⁾. 11.7% of instances of post-SARS-CoV-2 nucleotide vaccination new-onset myocarditis, involving males with an average age of less than 30 years, developed following administration of an initial dose of a mRNA SARS-CoV-2 nucleotide vaccine ⁽¹⁰⁰⁾. Among males with a mean age under 30 years, who developed new-onset myocarditis following an initial dose of mRNA SARS-CoV-2 nucleotide vaccines, 78% of afflicted individuals had experienced a prior diagnosis of COVID-19 ⁽¹⁰⁰⁾.

A review of reported cases of post-SARS-CoV-2 nucleotide vaccine adverse events, comprised of thrombosis, revealed that nearly all cases of post-SARS-CoV-2 vaccination thrombocytopenia were reported to have occurred in women aged 18–48 years within 6–13 days after vaccination ⁽¹³⁵⁾. A review of reported cases of post-SARS-CoV-2 nucleotide vaccine thrombosis revealed that over 60% of end-organ sequelae, such as cerebrovascular accidents (CVA), myocardial infarction and pulmonary embolism occurred in women ⁽¹³⁵⁾. That the demographic distribution of myocarditis and/or thrombosis, disproportionately occurs within younger segments of the population should not be dismissed as an “exceedingly rare” artifact, but rather acknowledged and embraced as both logical and entirely-expected outcomes of applying nucleotide vaccination technology to potentially toxic synthetic SARS-CoV-2 spike protein antigens, via non-throttleable mechanisms, within a population of individuals possessing highly proficient protein synthetic capabilities.

The emergence of post-SARS-CoV-2 nucleotide vaccine myocarditis and/or thrombosis, predominately in younger segments of the population, represents the proverbial “other side of the coin” relative to the incredible rates of seroconversion stimulated by SARS-CoV-2 nucleotide vaccines in high-risk populations, such as renal dialysis patients, individuals with DM2, obese individuals and individuals over the age of 65. This double-edged sword aspect of SARS-CoV-2 nucleotide vaccine technology represents a novel emergent property arising from the following constituent elements: 1) isolated SARS-CoV-2 spike protein and isolated spike protein constituent

components, such as S1, demonstrate a potent and multi-faceted molecular toxicity independent of SARS-CoV-2 infection, 2) SARS-CoV-2 nucleotide vaccines leverage the translational capacity and translational efficiency inherent to the skeletal muscle protein synthetic apparatus of recipient patients and subsequently magnifies this capability via mechanisms which include but are not limited to: within family codon optimization and sophisticated delivery vehicles, thereby compelling the self-synthesis of highly toxic SARS-CoV-2 spike proteins in a manner that is entirely *non-throttleable*, 3) SARS-CoV-2 nucleotide vaccines induce the self-generation of SARS-CoV-2 spike protein antigens which are subject to enzymatic cleavage, thus becoming, isolated SARS-CoV-2 spike protein and/or isolated spike protein constituent components, including but not limited to S1, 4) isolated SARS-CoV-2 spike protein and/or isolated spike protein constituent components, such as S1, can and do permeate the circulatory system of vaccinated patients, where these potentially toxic, self-synthesized antigens are free to interact with a broad spectrum of cells and tissues, including those expressing hACE2 and TLR4 ⁽¹³⁶⁾.

Following an initial 100 µg dose of mRNA-1273, detectable levels of isolated S1 were observed in the plasma of 85% of recipient patients from the general population, as early as one day after inoculation ⁽¹³⁶⁾. Isolated S1 was detected from day one to day 14 following the initial dose of mRNA-1273 ⁽¹³⁶⁾. Peak plasma concentrations of isolated S1 levels were detected on average five days after inoculation ⁽¹³⁶⁾. The mean peak plasma concentration of isolated S1 was reported at 68 pg/mL ± 21 pg/mL ⁽¹³⁶⁾. Following an initial 100 µg dose of mRNA-1273 isolated SARS-CoV-2 spike proteins were detected in 23% of recipient patients, an average of 15 days after vaccination ⁽¹³⁶⁾. The mean isolated SARS-CoV-2 spike protein peak level detected was 62 pg/mL ± 13 pg/mL ⁽¹³⁶⁾. Following administration of the second dose of mRNA-1273, no isolated S1 or isolated spike protein was detectable in the plasma of vaccinated patients beginning two days after administration of the second dose ⁽¹³⁶⁾. An examination of the plasma of patients for SARS-CoV-2 nucleocapsid antigen, following receipt of an initial dose of mRNA-1273, was conducted to rule out concomitant SARS-CoV-2 infection ⁽¹³⁶⁾. Nucleocapsid antigens were undetectable in patients following an initial 100 µg dose of mRNA-1273 ⁽¹³⁶⁾. A negative finding for nucleocapsid antigen confirmed that isolated S1 and/or isolated SARS-CoV-2 spike protein detected in the plasma of vaccinated patients, following an initial dose of mRNA-1273, was indeed the result of vaccination with mRNA-1273 and the subsequent self-synthesis and enzymatic cleavage of SARS-CoV-2 spike protein antigens and/or constituent components, such as S1 ⁽¹³⁶⁾.

In comparison, it has been reported that the plasma of patients diagnosed with COVID-19 infection, via positive SARS-CoV-2 NP RT-PCR, where all plasma samples were obtained within the first ten days of the initial positive NP RT-PCR test result, demonstrated detectable levels of isolated S1 and/or isolated SARS-CoV-2 spike protein and/or nucleocapsid antigen ⁽¹²⁾. Plasma concentrations of isolated S1 demonstrated a higher correlation with clinical severity of COVID-19 disease than the plasma concentration of nucleocapsid antigens ⁽¹²⁾.

COVID-19 patients with plasma concentrations of isolated S1 greater than 50 pg/mL demonstrated a 77% likelihood of admission to the ICU ⁽¹²⁾. COVID-19 patients with plasma concentrations of isolated S1 between 6 pg/mL and 50 pg/mL demonstrated a 52% likelihood of admission to the ICU ⁽¹²⁾. Only 30% of COVID-19 patients were admitted to the ICU when demonstrating an isolated S1 concentration of less than 6 pg/mL ⁽¹²⁾. The difference in “time to intubation”, an interval measured

from the time of hospital admission until the time of intubation, was reported to be highly significant between COVID-19 patients with plasma concentrations of isolated S1 greater than 50 pg/mL and COVID-19 patients with plasma concentrations of isolated S1 of less than 6 pg/mL ⁽¹²⁾. 100% of COVID-19 patients, with plasma concentrations of isolated S1 greater than 50 pg/mL, were intubated within one day of hospitalization ⁽¹²⁾.

Following vaccination with a SARS-CoV-2 nucleotide vaccine, isolated S1 and/or isolated SARS-CoV-2 spike proteins circulate freely within the plasma of vaccinated patients ⁽¹³⁶⁾. Circulating, isolated S1 and/or isolated SARS-CoV-2 spike proteins are capable of interacting with a broad range of cells and tissues, including those expressing hACE2 and/or TLR4. Vaccine-induced, self-generated SARS CoV-2 spike proteins and/or S1 may interact with hACE2 and/or TLR4 to initiate changes within hematological and/or circulatory parameters of a recipient patient, via platelet, endothelial cell and immune cell mediated mechanisms triggered by the inherent molecular toxicity of SARS-CoV-2 spike proteins and spike protein constituent components, such as S1 ^(4,5,13,14).

The magnitude of the resultant plasma concentrations of isolated S1 and/or isolated SARS-CoV-2 spike proteins, subsequent to vaccination with a SARS-CoV-2 nucleotide vaccine, may be dramatically elevated if a recipient patient demonstrates an enhanced capacity for MPS capability and/or an expanded skeletal muscle capillary network, such as is found in populations of actively training elite athletes. Altered hematological properties induced by isolated S1 and/or isolated SARS CoV-2 spike proteins include: platelet aggregation in response to agonists such as ADP, increased platelet dense granule secretion in response to agonists such as ADP, markedly accelerated platelet spreading, enhanced thrombus formation, induced clot retraction, increased platelet P-selectin expression, increased formation of leukocyte-platelet aggregates, impairment of acetylcholine-induced, endothelium-dependent vasodilation, altered endothelial cell mitochondrial dynamics, increased endothelial cell mitochondrial fragmentation, impaired endothelial cell mitochondrial function, compensatory increases of endothelial cell glycolytic rate, down-regulation of hACE2 expression, increased levels of oxidative stress, inflammatory signalling and mononuclear cell invasion ^(3,4,5,110,111). Elite strength, power and endurance athletes frequently engage in multiple sessions of extensive and/or intensive RT and/or ET and/or ST daily. Sessions of intense physical activity are known to increase plasma ADP levels at least 2.5 fold ⁽⁴⁴⁾. ADP is an agonist known to induce thrombus formation upon binding of isolated S1 and/or isolated SARS-CoV-2 spike proteins to hACE2 ⁽⁴⁾. Actively training elite strength, power and endurance athletes, supported by protein/AA, demonstrate superior MPS and therefore this population possesses enhanced mRNA translational capacity and efficiency relative to the general populous. Peak plasma concentrations of isolated S1, ranging from 47 pg/mL to 89 pg/mL, were observed in members of the general population subsequent to receiving an initial dose of SARS-CoV-2 nucleotide vaccine, mRNA-1273 ⁽¹³⁶⁾. In light of the greater translational capacity and efficiency observed among actively training elite athletes, supported by protein/AA, this population should be expected to generate mean peak plasma concentrations of isolated S1, in response to vaccination with a SARS-CoV-2 nucleotide vaccine such as mRNA-1273, which corresponds to the rate of MPS for this population, which is conservatively estimated to be at least 129% greater than the rate of MPS found within the general populous. Therefore, a population of actively training elite athletes, supported by protein/AA, can conservatively be expected to generate mean peak plasma concentrations of isolated S1, in

response to an initial dose of a SARS-CoV-2 nucleotide vaccine such as mRNA-1273, which measures 156 pg/mL. Thus, populations of actively training elite athletes supported by protein/AA, are conservatively estimated to demonstrate mean peak plasma concentrations of vaccine-induced, self-generated isolated S1, at more than three times the 50 pg/mL concentration which is associated with severe COVID-19 disease outcomes, such as a 77% likelihood of ICU admission and a 100% likelihood of intubation within one day of ICU admission ⁽¹²⁾. Vaccine-induced, self-generated plasma concentrations of isolated S1 at levels of 156 pg/mL or greater, creates potentially catastrophic circumstances for elite strength, power and endurance athletes, given the frequency and magnitude of RT and/or ET and/or ST-induced elevations of plasma ADP ^(4,44). Resultingly, populations of actively training elite strength, power and endurance athletes incur an extreme level of enhanced mechanistic risk for suffering post-SARS-CoV-2 nucleotide vaccine thrombotic complications relative to members the general populous.

(5.1) Hypothesis: the bi-phasic etiology and ontology of post-SARS-CoV-2 nucleotide vaccination new-onset myocarditis is rooted in a pronounced, sexually dimorphic monocyte/macrophage response to vaccine-induced, self-generated SARS-CoV-2 spike protein antigens and/or constituent components of self-generated spike protein antigens, such as S1.

Key temporal and demographic characteristics of post-SARS-CoV-2 nucleotide vaccination new-onset myocarditis include: the high prevalence of onset for myocarditis following a dose of SARS-CoV-2 nucleotide vaccine that is not the initial dose, except in cases where a previous diagnosis of COVID-19 exists, the high prevalence of affected individuals demonstrating an age of under 49 years old, and the high prevalence of male individuals within afflicted populations. This report postulates that post-SARS-CoV-2 nucleotide vaccination new-onset myocarditis is the result of a bi-phasic process where the first dose of vaccination or prior COVID-19 disease causes: 1) stimulation of monocyte production in bone marrow, egress of monocytes from bone marrow, recruitment and migration of monocytes to cardiac tissue and the staging of a significant monocyte/macrophage resident population within cardiac tissue; and the formation of neutralizing antibody response to vaccine-induced, self generated SARS-CoV-2 spike protein antigens and/or constituent components of self-generated spike protein antigens, such as S1; 2) a subsequent dose of a SARS-CoV-2 nucleotide vaccine, (or an initial dose in the case of prior COVID-19 disease), triggers the self-synthesis and trans-membrane expression of vaccine-induce SARS-CoV-2 spike protein antigens, which stimulates the activation of the pre-staged resident population monocytes/macrophages directly against components of the cardiac milieu including, but not limited to, endothelial cells, cardiac pericytes and cardiomyocytes and manifesting as myocarditis. Following an initial dose of SARS-CoV-2 nucleotide vaccine, SARS-CoV-2 spike proteins are self-generated by the protein synthetic apparatus of a recipient patient, where the self-synthesized spike protein antigens subsequently proceed to stimulate a neutralizing antibody response from the immune system of a recipient patient ⁽¹³⁶⁾. A percentage of vaccine-induced, self-generated SARS-CoV-2 spike proteins undergo enzymatic cleavage and enter circulation as isolated spike proteins or isolated S1, prior to the generation of a neutralizing antibody response; during which time interactions may occur between self-generated isolated spike protein antigens and/or isolated S1 and receptor targets such as, but not limited to hACE2 and TLR4 ⁽¹³⁶⁾. A percentage of isolated S1 and/or isolated spike

proteins, conveyed via vascular and lymphatic circulation, perfuse cardiac tissue subsequently interacting with receptors such as hACE2 and TLR4 expressed by cells and tissue of the cardiac milieu. Interaction of isolated SARS-CoV-2 spike proteins and/or isolated S1 with hACE2 expressed by cells and tissue of the cardiac milieu, initiates a down-regulation of hACE2 expression within cardiac milieu. A down-regulation of hACE2 leads to a shift in the balance of hACE: hACE2 favoring the prevalence of hACE and subsequently resulting in an increased concentration of AngII. An increased prevalence of AngII, leads to increased ROS generation. The generation of ROS, such as superoxide, is associated with an inflammatory secretome of signaling molecules, such as TNF α and monocyte chemoattractant protein-1 (CCL2) ⁽¹³⁸⁾. The secretion of TNF α and CCL2, have been demonstrated to increase the expression of TLR4 ⁽¹³⁸⁾. Increased expression of TLR4 provides an increased target receptor density in the cardiac milieu with which isolated spike proteins and/or isolated S1 may interact. CCL2 signaling also stimulates bone marrow monocyte production, monocyte egress, monocyte/macrophage chemotaxis and infiltration of the cardiac milieu ⁽¹³⁹⁾. Therefore, the initial dose of a SARS-CoV-2 nucleotide vaccine, (or previously diagnosed COVID-19 disease), builds the molecular and histological foundation upon which a future bout of post-SARS-CoV-2 nucleotide vaccination new-onset myocarditis is built, via recruitment and staging of a resident cardiac population of monocytes/macrophages in parallel with the generation of a neutralizing antibody response to vaccine-induced, self-generated SARS-CoV-2 spike protein antigens.

Following the administration of a subsequent dose of a SARS-CoV-2 nucleotide vaccine, (or in the case of a previous diagnosis of COVID-19, an initial dose), self-generated SARS-CoV-2 spike proteins are generated via the protein synthetic apparatus of a recipient patient. Membrane-localization of self-generated SARS-CoV-2 spike proteins occurs within cardiomyocytes and/or resident populations of cardiac monocytes/macrophages and/or cardiac pericytes and/or cardiac endothelial cells ^(9,10,14). Membrane-localized spike proteins and/or S1 interact with an expanded population of TLR4 and MD-2 receptors, whose expression has been dramatically increased as a result of RAS balance having been shifted towards hACE/AngII and away from hACE2/Ang1-7, as a consequence of the self-generated spike proteins caused by initial dose of a SARS-CoV-2 nucleotide injection (or previous COVID-19 disease) ⁽¹⁰⁾. Reports demonstrate spike protein and/or S1 binds to TLR4/MD-2 receptors and subsequently activates NF-kB signaling in cardiomyocytes and/or monocytes/macrophages ^(10,13,14). Activation of NF-kB by TLR4/MD-2 signaling in cardiomyocytes, monocytes/macrophages, has been found to be of sufficient intensity so as to induce cardiac inflammation and cardiac hypertrophy, culminating in reduced cardiac systolic function ^(10,13,14). Therefore, a subsequent dose of a SARS-CoV-2 nucleotide vaccine, (or an initial dose in the case of prior COVID-19 disease), initiates cardiac inflammation via exaggerated TLR4->NF-kB signaling in cardiomyocytes and resident cardiac populations of monocytes/macrophages, which in-turn, were recruited and staged in cardiac tissue by actions of previous doses of SARS-CoV-2 nucleotide vaccine (or prior COVID-19 disease). Activation of the innate immune mechanisms of cardiomyocytes, as well as resident populations of cardiac monocytes/macrophages via TLR4->NF-kB signaling triggers cytotoxic innate immune activity and culminates in the onset of myocarditis.

Sexual dimorphism of monocyte/macrophage inflammatory secretomes

The demographic prevalence of post-SARS-CoV-2 nucleotide vaccination myocarditis in young males can be explained to a large extent by the fact that male-derived monocytes/macrophages, produce larger amounts of potent inflammatory cytokines, such as TNF α and IL-1 β , compared to female-derived monocytes/macrophages ⁽¹⁴⁰⁾. In the face of significant sexual dimorphism associated with the inflammatory secretomes of monocytes/macrophages, it is not surprising that testosterone treatment has been observed to induce inflammatory responses in human and mouse monocytes ⁽¹⁴⁰⁾. Monocyte-driven diseases, such as: amebiasis, leishmaniasis, and hepatocellular carcinoma, are more prominent in male humans and mice ⁽¹⁴⁰⁾. Among human patients suffering from hepatic amebiasis caused by *Entamoeba histolytica*, >80% of individuals who develop amebic liver abscess (ALA) are male, despite overall higher rates of *Entamoeba histolytica* infection being documented in females ⁽¹⁴⁰⁾.

Monocytes may be grouped based on expression of types of CD14 and CD16 markers as either, classical: CD14⁺CD16⁻, intermediate: CD14⁺CD16⁺, and non-classical: CD14⁻CD16⁺ ⁽¹⁴⁰⁾. Monocytes may be further classified according to expression of motifs such as, CCR2, (a CCL2 receptor) and CX₃CR1 ⁽¹⁴⁰⁾. CCR2 and CX₃CR1 have been reported to play an important role during monocyte recruitment and endothelial cell adhesion ⁽¹⁴⁰⁾. Yet another chemokine induced by TNF α , is C-X-C motif ligand 1 (CXCL1) ⁽¹⁴¹⁾. TNF α secretion induces CCL2 and CXCL1 production by endothelial cells, as well as a multitude of other cell types within injured and/or inflamed tissues ^(140,141). CCL2 induces egress of CCR2⁺ classical monocytes from the bone marrow, thereby enabling migration to sites of inflammation ⁽¹⁴⁰⁾. CCL2 is known to be present at higher concentrations in men than in women, while CXCL1 has also been demonstrated to be highly inducible via androgen signaling ⁽¹⁴⁰⁾. The extraordinary influence of androgen signaling on monocyte function is underscored by the fact that, monocytes obtained from a cohort of individuals undergoing female to male gender re-assignment demonstrated significantly enhanced inflammatory activity and potency following the onset of androgen therapy ⁽¹⁴⁰⁾.

This reports surmises that the etiology and ontology of post-SARS-CoV-2 nucleotide vaccination new-onset myocarditis issues forth as a result of the intersection of the significant sexual dimorphism which exists within monocyte molecular physiology and a biphasic exposure to the potent and multifaceted toxicity of SARS-CoV-2 spike proteins and/or spike protein constituent components. Phase 1, the priming stage, is initiated as a result of the administration of an initial dose of a SARS-CoV-2 nucleotide vaccine, (or previous bout of COVID-19 disease), which compels the self-generation of vaccine-induced SARS-CoV-2 spike protein antigens. Subsequent membrane expression and enzymatic cleavage of self-generated SARS-CoV-2 spike proteins gives rise to→ isolated spike proteins and/or isolated S1 permeating the vascular tree→ where said isolated spike proteins and/or isolated S1 binds to hACE expressed by cardiomyocytes and/or cardiac endothelial cells→ spike proteins/S1 binding to hACE2 causes a shift in hACE: hACE2 balance leading to increased AngII relative to Ang 1-7→ increased cardiomyocyte and/or endothelial levels of AngII results in subsequent ROS generation, TNF α secretion, TLR4 up-regulation, CXCL1 secretion and CCL2 secretion→CCL2 then induces egress of CCR2⁺ classical monocytes from the bone marrow→ facilitating chemotaxis of monocytes to cardiac tissue, thus establishing a resident cardiac monocyte/macrophage population.

Phase 2, activation, proceeds from the administration of a subsequent dose of a SARS-CoV-2 nucleotide vaccine, (or an initial dose in the case of prior COVID-19 disease), which compels a corresponding subsequent surge in the self-generation of vaccine-induced spike proteins→ vaccine-induced, self-generated spike proteins and/or S1 are membrane expressed and/or enzymatically cleaved, thus becoming isolated spike proteins or isolated S1→ membrane-localized spike proteins/S1 and/or isolated spike proteins/isolated S1 have demonstrated the ability to activate TLR4/NF-κB signaling→ vaccine-induced, self-generated spike proteins/S1 activate TLR4/NF-κB signaling in cardiomyocytes and/or the previously accumulated cardiac monocyte/macrophage population and/or cardiac pericytes and/or cardiac endothelial cells→ activation of monocytes/macrophages, localized within cardiac milieu, leads to cardiac inflammation, cardiac hypertrophy and reduced cardiac systolic function(10). A bi-phasic etiology arising from monocyte/macrophage sexual dimorphism and leading to the onset of post-nucleotide vaccination myocarditis is further supported by the fact that patients who died of COVID-19 possess cardiac tissue demonstrating a greater number and distribution of CD11+, CD68+ macrophages compared with matched controls or cases of non-COVID-19 myocarditis (137,139).

Just as young athletes recovering from COVID-19, demonstrate cardiac MRI abnormalities consistent with myocarditis to a higher degree than is statistically predicted (137,142,143,146). Male elite strength, power and endurance athletes find themselves exposed to an elevated mechanistic risk for the onset of post-SARS-CoV-2 nucleotide vaccination myocarditis secondary to: 1) the potential for exceedingly high peak plasma concentrations of vaccine-induced, self-generated SARS-CoV-2 spike protein/S1 issuing forth from the highly proficient protein synthetic apparatus possessed elite athlete skeletal muscle tissue, 2) the expanded capillary network possessed by elite athletes, 3) the robust innate immune function of elite athletes caused in part by the higher testosterone levels possessed by elite athletes, relative to age-matched controls and lesser performing athletes (146). In addition to androgen stimulation, the innate immune function of elite athletes is enhanced as a result of regular, intense physical training, with monocyte/macrophage function being especially enhanced (142,143).

The enhanced mechanistic risk incurred by elite male athletes also extends to their female elite athlete counterparts. Female Olympic athletes have been found to possess lower second digit to fourth digit ratios (2D:4D) and higher serum androgen levels when compared to age and sex matched controls, as well as when compared to lesser performing female athletes (144,145,146). As demonstrated by cohorts of women undergoing androgen therapy as a component of female to male gender-reassignment, exposure to increasing concentrations of androgens enhances monocyte/macrophage reactivity (140). That elite female athletes demonstrate elevated androgen levels, relative to sex and age matched controls, directly results in this population incurring an increased mechanistic risk, relative to said age and sex matched controls, for the onset of post-SARS-CoV-2 nucleotide vaccine new-onset myocarditis (140,144,145,146).

Despite the fact that a search of the US National Library of Medicine PMC database for the terms “personalized medicine” returned over 370,000 relevant results, little to no scientific diablouge has occurred surrounding the intersection of the inherent potent and multifaceted molecular toxicity of the SARS-CoV-2 spike protein and/or constituent components, such as S1 with *non-throttleable*

SARS-CoV-2 nucleotide vaccine technology, as applied to populations with highly proficient protein synthetic apparatus. As a result, many members of the minority population comprised of elite strength, power and endurance athletes have been unnecessarily exposed to the risk of and/or the outright occurrence of SARS-CoV-2 nucleotide vaccine injuries. A blatant and entirely inappropriate politicization has occurred surrounding the use of SARS-CoV-2 nucleotide vaccine technology. SARS-CoV-2 nucleotide vaccine technology has undoubtedly enabled a dramatically higher percentage of the oldest and most ill members of the population to generate a neutralizing immune response, (albeit against a hyper-narrow SARS-CoV-2 antigenic epitope and where the immune response is of highly questionable efficacy and durability), compared to legacy vaccination technology such as inactivated-virus vaccines. However, the wide-spread and entirely inappropriate use of SARS-CoV-2 nucleotide vaccines in highly anabolic and intensely physically active populations, typified by elite strength, power and endurance athletes, has led to the unfortunate displacement of the use of inactivated-virus vaccines in this population. Elite strength, power and endurance athletes have demonstrated the ability to generate a robust immune response against a comprehensive landscape of antigenic epitopes, as presented by inactivated-virus vaccines. The displacement of inactivated-virus vaccines from the most anabolic and physically active members of the population results in two very clear outcomes: 1) the tragic loss of the opportunity for a highly immune competent segment of the global population to form a bulwark against accelerated SARS-CoV-2 mutation and virulence, secondary to the formation of a robust immune response against the comprehensive landscape of SARS-CoV-2 antigenic epitopes; and 2) the more tragic and entirely unnecessary infliction of diminished athletic performance and/or disabilities and/or injuries and/or deaths upon highly anabolic populations with high levels of physical activity.

The entirely inappropriate use of SARS-CoV-2 nucleotide vaccines, within highly anabolic populations with high levels of physical activity, seems to be rooted in a number of deeply held erroneous beliefs regarding SARS-CoV-2 nucleotide vaccine technology. These beliefs, seemingly enshrined within prominent popular-culture aspects of the media, political, medical and scientific communities, appear to be based on an apparent misunderstanding of immuno-surveillance design strategies employed by the developers of SARS-CoV-2 nucleotide vaccines. Designers of some vaccine-encoded SARS-CoV-2 spike protein antigens engineered the resultant spike protein to permanently stable, in the otherwise typically meta-stable, pre-fusion conformation ^(151, 152). The beliefs at issue conflate the fact that some nucleotide vaccines encode for a SARS-CoV-2 spike protein stabilized in the pre-fusion conformation, with the belief that vaccine-encoded, patient-synthesized SARS-CoV-2 spike proteins stabilized in the pre-fusion conformation are incapable of interacting with hACE2 and/or TLR4 and/or other elements of human tissue; and therefore nucleotide vaccine-induced, self-generated spike proteins lack the inherently potent and multifaceted molecular toxicity of wild-type SARS-CoV-2 spike proteins ^(151,152,153). Therefore, adherents to this belief, reach the conclusion that SARS-CoV-2 nucleotide vaccine-induced, self-generated spike proteins are incapable of initiating the well-characterized pathophysiological cascades attributed to wild-type SARS-CoV-2 spike proteins ^(151,152). However, in actuality, the SARS-CoV-2 spike protein is trimeric and the RBD in each S1 subunit can adopt two different conformations, referred to as either “up” or “down” ⁽¹⁵⁵⁾. When the RBD conformation is “up” or pre-

fusion conformation, SARS-CoV-2 spike proteins can interact with hACE2; spike proteins are unable to interact well with hACE2 when in the “down” or post-fusion conformation ⁽¹⁵⁵⁾. A second closely held and deeply erroneous belief, as it pertains to SARS-CoV-2 nucleotide vaccines, is that vaccine-induced, self-generated SARS-CoV-2 spike proteins are confined to a trans-membrane bound existence at the location of synthesis. For example *“We would like to highlight some key features of the mRNA vaccines which would protect from thrombosis compared to getting COVID-19 infection. One of the key features is that the spike protein produced by the mRNA vaccines are trans-membrane anchored and not released into the circulation like in active SARS-CoV-2 infection and hence does not have the potential to interact with systemic endothelial cells. Moreover, the spike protein produced through these vaccines have proline mutations which affects its capability to bind to hACE2 as is unable to adapt to its shape. The immune response with production of neutralizing antibodies against the spike protein will also be protective against any systemic effects of spike protein interactions with ACE2. [Rinkoo, et al]”* ⁽¹⁵³⁾. The conjecture that vaccine-induced, self-generated SARS-CoV-2 spike proteins are benign as a result of a membrane-bound existence, typified by Rinkoo et al, has become a foundational element in the establishment of a medico-political narrative surrounding the purported safety and effectiveness of SARS-CoV-2 nucleotide vaccines within highly anabolic and intensely physically active populations. Perhaps the most deeply troubling aspect of this narrative is found in the ease with which its core tenants are completely and utterly destroyed. Ogata, et. al. have clearly demonstrated that vaccination with SARS-CoV-2 nucleotide vaccines results in the high likelihood of the generation of a readily detectable plasma concentration of isolated spike proteins and/or isolated S1 prior to the establishment of a neutralizing antibody response ¹³⁶. Therefore, beliefs, practices and policy positions which hold that, SARS-CoV-2 nucleotide vaccine-induced, self-synthesized spike protein antigens are not capable systemic of interactions with hACE2 (or other pertinent targets of spike protein and/or S1, such as but not limited to TLR4), must be viewed as entirely unsupported and subsequently be wholly rejected. Since it must be recognized that SARS-CoV-2 nucleotide vaccines are capable of generating high concentrations (>50pg/ml) of isolated plasma spike proteins and/or isolated S1, it must also be recognized that SARS-CoV-2 nucleotide vaccine-induced, self-synthesized spike proteins and/or S1 must possess the inherent potent and multifaceted molecular toxicity of SARS-CoV-2 spike proteins; and exposure to said inherent toxicity may culminate in events including but not limited to: plasma ADP-triggered thrombogenesis, hBBB degradation, heparin-amyloid nucleation, thrombocytopenia, myocarditis, inhibition of DNA repair mechanisms and inhibition of mitochondrial function ⁽¹⁵⁴⁾.

Therefore, elite strength, power and endurance athletes should be the subjects of physiology specific, risk-stratified vaccine recommendations where inactivated vaccines against SARS CoV-2 constitute first-line therapeutic agents, by virtue of the combined potential for greater immunological effectiveness, (relative to non-elite athletes), and the greatly diminished mechanistic risk of vaccine-induced pathology. Populations of actively training elite athletes should avoid use of SARS-CoV-2 nucleotide vaccine technology which compels the protein synthetic apparatus of a recipient patient to self-generate SARS CoV-2 spike protein antigens and/or the S1 sub-unit of the SARS CoV-2 spike protein and/or the SARS CoV-2 spike protein antigen S1 sub-unit RBD, as a result of: 1) the known toxicity of SARS CoV-2 spike protein antigens and/or spike protein constituent components, such as S1 and RBD, 2) the non-throttleable nature of SARS-CoV-2 nucleotide vaccine

technology; and 3) the enhanced mRNA translational capacity and efficiency possessed by actively training elite athletes in the context of an expanded skeletal muscle capillary network. In the event that an elite athlete has a known incompatibility with components of all known inactivated-virus vaccines against SARS-CoV-2, alternatives such as live-attenuated and sub-unit vaccines against SARS-CoV-2 should be considered as alternatives, due to their lower inherent mechanistic risk relative to SARS-CoV-2 nucleotide vaccines. The lower level of inherent mechanistic risk possessed by live-attenuated and/or sub-unit SARS-CoV-2 vaccines, relative to SARS-CoV-2 nucleotide vaccines, stems from the introduction of a fixed-dose of SARS-CoV-2 spike proteins and/or spike protein constituent components, such as S1.

It is crucially important to consider the extreme physiology and psychology, which characterizes elite athletes, in the context of the global population, when weighing what constitutes an acceptable risk of vaccine-induced adverse outcomes. The World Health Organization (WHO) defines disability as “any restriction or lack (resulting from any impairment) of ability to perform an activity in the manner or within the range considered normal for a human being”. While elite strength, power and endurance athletes comprise an exceedingly small minority of the global population, the extreme physiology, psychology and accompanying limit-testing physical performances exemplified by this minority population must be acknowledged, respected and ultimately considered “normal” by healthcare professionals and government officials, for this group of human beings. Therefore, when contemplating the vaccination of elite athletes against SARS-CoV-2, not only should the avoidance of unnecessary serious injury and death be a driving factor in selecting appropriate SARS-CoV-2 vaccine candidates, but additionally, the avoidance of any adverse outcomes which result in restrictions or the lack of ability to perform at the highest levels of elite sport, regardless of how minor or insignificant such adverse events might appear from the perspective of members of the general global population, particularly physicians and officials.

In a great many geopolitical jurisdictions, there are no regulatory obstacles to the implementation of policies and practices, which would elevate the administration of inactivated-virus SARS-CoV-2 vaccines, in populations of actively training elite athletes, to the status of first-line therapy. China, Russia, India, Argentina, Bahrain, Brazil, Chile, Egypt, Indonesia, Iran, Morocco, Pakistan, Peru, Philippines, the United Arab Emirates, Turkey and countries participating within the WHO’s COVAX program are examples of some of the global geopolitical jurisdictions where inactivated-virus SARS-CoV-2 vaccines are readily available to populations of elite athletes and the healthcare professionals who care for them. However, considerable global inequity does exist among elite athletes, as it pertains to the availability of inactive-virus SARS-CoV-2 vaccines. Inactivated-virus SARS-CoV-2 vaccines are not available in a great many geopolitical jurisdictions. For example, inactivated-virus SARS-CoV-2 vaccines have not been made available in geopolitical jurisdictions such as, but not limited to: the United States of America and its territories, Canada, Australia, Japan, the United Kingdom and most Western European nations. The global disparity in the access of elite athletes to inactivated-virus SARS-CoV-2 vaccines represents an existential threat to fair and equitable global sport, to a degree that dwarfs the threat posed by doping. The threat to the integrity of sport is especially poignant, when viewed in the context of SARS-CoV-2 vaccine mandates a requirement for travel and/or training and/or competition. Universal access to

inactivated-virus SARS-CoV-2 vaccines is not merely an issue of sport integrity it constitutes a bioethical dilemma of monumental proportions. Elite athletes who live and/or compete within geopolitical jurisdictions that impose SARS-CoV-2 vaccine mandates as a condition of participation in training and/or competition, but do not concurrently make available (or recognize the validity of) inactivated-virus SARS-CoV-2 vaccines are made subject to most the despicable forms of prejudice, discrimination, injury and violations of basic human rights.

Mechanistically, it is likely that other highly anabolic populations, such as infants, children, adolescents, young adults, pregnant women and healthy adults, also would likely benefit from the avoidance of *non-throttleable*, epitopically hyper-narrow SARS-CoV-2 nucleotide vaccines, in favor of vaccines which present a limited exposure to SARS-CoV-2 spike protein antigens in combination with a complete landscape of SARS-CoV-2 antigenic epitopes, where such vaccines include inactivated-virus vaccines against SARS-CoV-2. Additionally, the preferred use of inactivated-virus SARS-CoV-2 vaccines among highly anabolic segments of the global population may have a profound effect on reducing the number and severity of SARS-CoV-2 variants, as immunocompetent and highly anabolic individuals are likely to form a bulwark against the accelerated evolution of SARS-CoV-2 via enduring and robust immunologic responses against the comprehensive landscape of SARS-CoV-2 antigenic epitopes. The question of whether or not vaccination against SARS-CoV-2 is warranted in populations of elite strength, power and endurance athletes, or in any population for that matter, exceeded the scope of this report.

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