COVID-19 White Paper – Emergex Vaccines

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Relevant Literature Highlights

1. As of December 2020, only one strain of SARS-2-CoV is circulating and phylogenetic analysis indicates that it is still in the pandemic phase where it is adapting to its host in contrast to the post-pandemic phase where immune responses will drive positive selection of escape variants. N.B. it appears important that viruses are permitted to evolve in the pandemic phase in order to purge pathotype variants. They become more transmissible, but less pathogenic [1].
2. No recorded transmission from asymptomatic individuals was found in the analysis of 10 million subjects in China [2].
3. It has been confirmed that SARS-coV-2 is a quasi-species virus, and each individual generates a unique variant cloud and this process extends to differences between upper and lower respiratory tract in the same individual [3].
4. The size of the infectious bottleneck has been determined (number of virions to transmit the virus) and it is ~ 1000 compared to flu which is 1-2 virions making SARS-coV-2 difficult to transmit in open spaces and requiring confined super-spreader events (i.e., households, restaurants, bars, sports arenas etc.) [4].
5. First description of potential antibody mediated enhancement (ADE) antibodies in patients with severe COVID-19. Similar mechanism as previous described for flu [5, 6].
6. Many studies now showing critical importance of T-Cell immunity in COVID-19 [7].
7. Antibody escape mutants, which can limit usefulness of current monovalent Spike vaccines, are being detected as random stochastic events linked to Founder populations or iatrogenic causes, such as treatments with passive antibody therapy [8-10].

I. VACCINE CONSTRUCTS FOR QUASI-SPECIES VIRUSES SUCH AS SARS-2-COV – LESSONS FROM FLU VACCINES

Natural infection with an RNA quasi species virus such as flu induces a different footprint of IgG epitope recognition patterns compared with inactivated subunit vaccines [11]. It follows that flu vaccination therefore will result in an altered response to subsequent infection with immunological consequences. For example, mice exposed to a natural infection with A/H3N3 are protected from subsequent infections and also have heterosubtypic immunity to lethal avian flu A/H5N1. In contrast if the animals are first immunized with an inactivated A/H3N2 vaccine they are protected against A/H3N2 influenza but are no longer protected against lethal A/H5N1 [12]. The pre-immunization resulted in high levels of serum antibodies against A/H3N2 but prevented the generation of virus specific CD8 T memory cells. These T-Cells were clearly responsible for the immunity against the lethal avian flu and are cross-reactive between A/H3N2 and A/H5N1. The experiment demonstrates that priming with a vaccine that only generates antibodies prevents the generation of T-Cells upon subsequent natural infection. This was borne out in a study on children that demonstrated that those vaccinated with inactivated flu vaccines do not generate viral specific T-Cells against flu in contrast to unvaccinated children that all have good T-Cell responses by the age of 10 as the result of natural infection [13]. Lack of heterosubtypic neutralizing antibody response against H5N1 and H7N9 has also been demonstrated in humans for all three US-licensed influenza vaccines manufactured by different platforms [14].

The consequence of the vaccine induced restriction and segregation of antibody and T-Cell response has had major consequences for flu vaccination programs. Following the H1N1/2009 flu pandemic the pandemic strain A/California was used in global flu vaccination programs without change from 2010 to 2017 [15]. This repetitive use of the same vaccine was based on testing circulating strains from these years by infecting ferrets and then looking to see if antibodies generated by the ferrets neutralized the original 2009 strain. Based on these studies it was concluded by PHE/CDC/WHO year after year that there was no antigenic change in the circulating pandemic strains and governments continued to report high efficacy rates [16]. However, the Ministry of Health in Israel observed for the 2015-2016 winter flu season there was zero efficacy of the vaccine [17]. Analysis of antibodies from vaccinated individuals confirmed that they contained antibodies against the vaccine strain but showed very little reactivity to the strains actually in circulation. This outcome demonstrated that the ferret IgG foot print to flu infection differed from the human IgG footprint in a significant functional manner and was giving a false efficacy readout. This result was subsequently confirmed by WHO and the vaccine strain for the 2017-2018 flu season was changed to A/Michigan/45/2015. This result obviously calls into question the methodology for epidemiological reporting of flu effectiveness during the preceding years since there was a clear mismatch between vaccine and circulating strains making meaningful efficacy doubtful.

It follows that inactivated vaccines that induce antibodies against a virus can produce off-target IgG responses. Pre-existing IgG towards pandemic H1N1 prior to vaccination exists in many individuals [11]. Proteome peptide microarrays can segregate IgG footprints between natural infection and flu vaccination responses. Importantly pre-existing epitopes can be found that are completely absent from the IgG-epitope recognition repertoire of flu infected individuals. These epitopes represent dominant IgG responses associated with repetitive vaccination. Rabbit antibodies against these epitopes fail to neutralize pandemic flu in vitro confirming these IgG specificities are functionally off target. This conclusion was further exemplified by the observation that yearly repetitive flu vaccination with same vaccine does not boost IgG affinity maturation in subsequent years leading to reduction in sero conversion upon repeat vaccination. The negative impact of repeated vaccination can lead to high titres of low avidity antibodies which are associated with ARDS in flu disease [14]. Finally, it has been demonstrated that effectiveness (test positive) of flu vaccination decreases at 16% per month. This outcome compares with no changes in test positive outcome for RSV in same individuals suggesting natural immunity to RSV was not waning but immunity to the flu vaccine was waning [18].

Conclusions:

Review of the scientific literature on flu (especially pandemic H1N1/2009), which like pandemic SARS-2 is a quasi-species RNA virus, provides guidance in vaccine construction and usage. The

quasi species nature of these viruses presents a challenge to the infected host and T-Cell immunity has evolved to deal with these types of viruses. It has been confirmed by deep sequencing of donor recipient pairs (transmission bottleneck analysis) that each influenza donor is infected with a unique influenza variant and each variant is separated by at least one unique non-synonymous difference [19]. Quasi-species analysis of a COVD-19 patient has shown that when analysed temporally a different set of variants was found during each day of infection and the quasi-species variants differed between anatomical sites with no overlap - suggesting independent replication – essentially two different simultaneous infections in lower and upper respiratory tract [3]. The above dynamics would leave little scope for antibody intervention in disease pathology once an infection has occurred. Indeed Dengue, Zika, Chikungunya, Ebola, Marburg, SARS, flu and a whole host of other RNA virus infections use IgG as a part of their pathogenesis (e.g., ADE, ARDS, etc). Given the similarities between flu and SARS-2 it would be expected that host responses to similar types of vaccine constructs would elicit similar immunological outcomes. In totally one can expect:

1. Antibody response to all of the COVID-19 vaccines in development will wane perhaps at a rate of 16% /month.
2. Attempts at boosting with the same vaccine could have pathological consequences since it will drive low affinity non neutralizing antibody generation.
3. Immunization per se will prevent resident T memory cell responses from being generated resulting in no long-term immunity and no protection against new strains that will evolve in the post pandemic period.
4. Antibody responses to just a single protein (Spike) could have major consequences since the polyclonal IgG footprint generated by natural infection will be distorted – original antigenic sin hypothesis.
5. Vaccination of individuals who already have had COVID-19 and natural immunity could lose their natural immunity as the boosting with only a single protein will generate a dominate response only to epitopes present on the Spike version of the vaccine. It is important to note that IgG responses are predominately to conformational epitopes on Spike and these may be very different between the Spike response (IgG footprint) to Spike present in the membrane of SAR-2 virion and Spike artificially expressed in the plasma membrane of a transfected human cell. Consequently, it is predicted that many of the IgG specificities of the vaccine will not have targets on Spike expressed in an actual infection. Finally, antibody escape mutants can easily be generated to SARS-2 Spike as already demonstrated in vitro [20].

II. RE-EXAMINATION OF HIGH EFFICACY RATES FOR MONOVALENT SPIKE COVID-19 VACCINES – WILL THESE TRANSLATE INTO EFFECTIVENESS?

The introduction of antibody generating vaccines to a single viral protein (SARS-2 Spike) for protection against an RNA quasi species infection such as SARS-2 has no historical precedent. Even with the low effectiveness seasonal flu vaccines, antibodies are generated against at least 2 proteins (H and N) and it is known that the vaccines contain other flu derived proteins in smaller amounts as carry-over contaminants [21]. It is critical to understand the basis of >90% efficacy claims for these COVID-19 constructs and what mid-term and long-term consequences these vaccines may induce in the adaptive immune system and natural evolution of SARS-2.

The phylodynamics of the H1N1/2009 influenza pandemic provides an excellent background to understanding the most probable natural short-term evolution of pandemic SARS-2 since no intervention to circulating H1N1/2009 occurred until after ~20 months of viral circulation on a global scale [22]. In contrast mammalian adaption of 1918 influenza virus provides clues to the longer-term fate of a pandemic virus in the total absence of vaccine intervention [23]. Here the data is clear that H1N1 pandemics if left to their only evolution resolve on ~50-year cycles.

As of 2017, the H1N1/2009 virus has undergone significant genetic changes resulting in the generation of eight genetic groups [24]. The first index case of H1N1/2009 influenza was in March 2009 and vaccine against the A/California/7/2009-like was not introduced until Oct/Nov of 2010 for the 2010-2011 flu season. In contrast, a vaccine intervention ~10 months after the first index cases of SARS-2 is now imminent that potentially could interfere in the natural evolution of the virus. Specifically, natural evolution of a quasi-species virus in the pandemic phase includes waves of

severe bottlenecks which drive down the virulence of the pathogen because of the stochastic loss of the most virulent pathotypes through a process analogous to Muller's ratchet [25].

Population genetics analysis of H1N1/2009 pandemic and post 2011 post-pandemic clearly demonstrated that a transition from host adaptation to immune -driven selection occurred from 2011 onwards [22]. Up to this point global phylogeny of the HA gene revealed a comb-like appearance indicative of a rapid increase in genetic diversity in the absence of strong selective pressure with virus spread determined by stochastic events and rapid transmission - as would be expected of a virus population infecting a predominately naïve human population. This is currently what is being observed for the spread of SARS-2 [1]. In contrast, post-pandemic H1N1/2009 viruses isolated since 2011 exhibited a ladder-like phylogeny characteristic of viruses subject to continuous antigenic drift [22] Essentially by 2011 a critical population size had acquired immunity to H1N1/2009 virus either through natural infection or ongoing vaccinations and antibody-mediated selection may have started to drive virus evolution.

On a global perspective, maximal genetic diversity in H1N1/2009 peaked in Dec/Jan 2010 but biannual peaks and then seasonal peaks were seen in a number of countries including Mexico (April and Dec 2009). The USA/Europe showing first peak in December 2009. So up to 2011 (pandemic phase) positive selection of mutations was driven by adaptation to the new human host while in the later post-pandemic period positive selection was directed towards the viruses escaping the host immune response [22]. For the case of H1N1/2009 influenzas, the virus had nearly 20 months to adapt to its new host and decrease its virulence prior to vaccine intervention. The bottleneck for flu virus transmission at the beginning of the pandemic (July-August 2009) was measured and shown to be approximately 100-220 contributing pathotypes which enabled the transmission of multiple lineages and antigenic variants [26]. In contrast, measurement of average bottleneck size in post-pandemic period (averaged over five flu seasons) was 1.75 pathotypes [27]. That is, with time the virus had adapted to it new host and transmission was highly efficient requiring only 1-2 virions for transmission [28]. With this estimate of bottleneck, the probability of transmission of a rare variant is only 1.7% for a variant at 1% frequency and 3.3% for a variant at 2%. However, as there are several million infected individuals each year, inefficient processes and rare events at the scale of individual hosts are likely to occur at a reasonable frequency on a global scale [27]. So once established, influenza evolution is dominated by stochasticity on a local scale and positive selection on global scale. Essentially positive selection (immune or adaptive) is rarely strong enough to drive a new mutation to a frequency above 2% over the course of several days. In the case of SARS-2 it has been shown that the virus is only transmissible for two days prior to symptoms and 5 days post symptoms [29]. A very short infection and transmission window. Also, COVID-19 typically resolves within weeks, before the full maturation of humoral immunity to SARS-2. Consequently, in the absence of long-term persistent infection neither the infected patient nor subsequently infected individuals impart an immunological pressure on the virus [30].

Multiple deletions have been reported in the Spike genome in immunosuppressed patients infected with SARS-2 [9]. Proofreading cannot correct deletions. Prevalent and recurrent deletions in the Spike protein have been found followed by human-to-human transmission of variants with altered antigenicity. Viral evolution in the immunosuppressed patients can foreshadow preferred avenues of adaptation in immune experienced population when they have a pre-existing anti-SARS-2 antibody at the time of an infection. Such a mechanism would lead to rapid generation of antibody escape mutants from ether a pre-existing therapeutic antibody (monoclonal or polyclonal), or anti-Spike antibody generated by a vaccine.[8-10]

SARS-2 is still in the comb-like stage (consistent with flu phylodynamic) and is still considered a single lineage. Mutations during this stage have not yet been linked to any transmissible phenotypes or viral fitness [1]. The mutations observed to date could be the consequence of human RNA-editing systems in contrast to copying errors that are characteristics of RNA quasi-species viruses. Coronavirus are known to have a proof-reading mechanism in contrast to other RNA viruses.

It has recently been reported that the bottleneck for SARS-2 pathotype transmission early in the outbreak (Austrian super spreader event of February 2019) was 1000 pathotypes [4]. This is an enormous value and highest bottleneck recorded in literature [31]Transmission is a key bottleneck in limiting inheritance of viral diversity but clearly having a bottleneck of 1000 provides a vast opportunity for transmission of even low frequency variants. This contrasts with flu which has a very small

bottleneck (1-2) but high mutation rate. It appears the low mutation rate of SARs-2 has compensation via a large bottleneck and also deletion mutations. In order to prevent flu transmission by sterilizing immunity (i.e. antibody), one essentially needs to block every virion – a very difficult task and perhaps borne out by low effectiveness of flu vaccines. In contrast with a bottleneck of 1000 required for transmission of SARS-2, there will be added requirement for multiple microdroplets of virus to be transmitted simultaneously and consequently even low efficiency antibody neutralization in the upper respiratory tract could lead to efficient transmission blockage. The early stages of the H1N1/2009 pandemic flu also had a large bottleneck which decreased with time by ~100 fold. If a similar pattern evolves for SARS-2, then the bottleneck (efficiency of transmission) will also decrease making the probability of antibody capture and neutralization less efficient.

Conclusions:

The high efficacy rates (>90%) being reported for the COVID-19 vaccines can only be explained by the early pandemic stage large bottleneck for pathotype transmission allowing low efficiency neutralization of virus in the upper respiratory track to prevent infection. As the infection moves from pandemic to post-pandemic phase, the antibodies will rapidly lose efficacy. The situation with COVID-19, however, is more complicated since, in the past, immune positive selection has only occurred after the virus has adapted to the host (during first 1-2 years) because vaccines have not been administered in the actual pandemic phase. During the pandemic phase, the genetic diversity is also at its highest and this factor is adapting the virus to the host and also decreasing virulence.

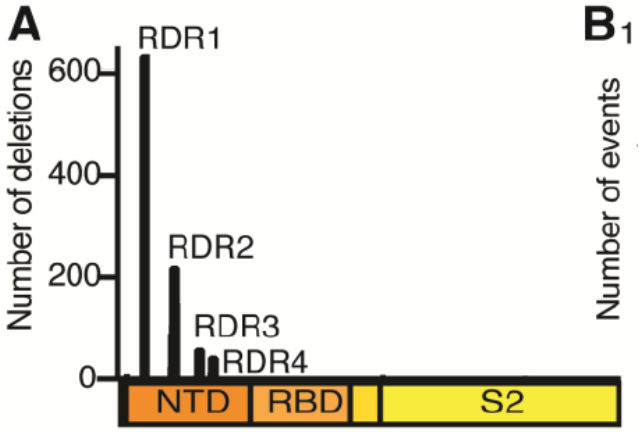
The early intervention of positive selection by pre-existing antibodies in individuals becoming infected with SARS-2 could interfere with the natural fluctuation in loose and tight bottlenecks that are purging the system of virulent pathotypes – that is, the virus could be being diverted into generating antibody escape mutants in contrast to mutation-selection as the result in fixation of non-virulent haplotypes in the global consensus sequence determined by quasi-species equilibrium.

III. URGENT AND CRITICAL NEED FOR T-CELL VACCINES

An unhappy truth: During a pandemic as a virus spreads to new geographic areas and to uninfected populations (including artificial islands of population previously in lockdown), spontaneous “Founder effects” will have significant impact on mutation frequencies [32].

COVID-19 typically resolves within weeks before full maturation of humoral immunity develops. It follows that, during a pandemic, neither the infected patient nor a subsequently infected individual imparts an immunologic pressure on the virus [32]. Stochastic events (random and probabilistic) generate selectively neutral mutations in frequency over time through the process of genetic drift. As of December 2020, there is no evidence for multiple strains of SARS-coV-2 [1]. To date none of the recurrent mutations in the SARS-CoV-2 population are statistically significantly associated with transmission. This assertion suggests that these mutations have evolved as neutral in the context of transmission (functional) and viral fitness. It follows that these mutations are not solely the result of errors by the viral RNA polymerase during viral replication but could also be the consequential result of human RNA-editing systems [1]. It is also important to note that these Founder effect events can occur repeatedly and independently (homoplasies) and also can be statistical artefacts since contact tracing can be a significant driver between detection and sequenced samples, leading to oversampling of particular genotypes and mutations [32].

The mutant termed VUI 202012/01 has recently been reported to be evolving in the UK and in various other locations [10]. These RDR deletion mutations have caused concern since they contain deletions in the NTD region as shown below.



The concern regarding deletion mutants of this type is based on the fact that they can affect antibodies binding to the NTD region that are involved in neutralization and, as such, could make current vaccines potentially less efficacious or totally obsolete. Current vaccines are all based on the Wuhan consensus sequence of January 2020. This reliance has been a predicted flaw with antibody generating vaccines since the beginning of the pandemic – that is, they will only have limited duration of action before antibody escape mutants evolve. What the deletion mutants (found in the UK and elsewhere) highlight is that these escape mutants are already circulating, having been formed many times stochastically by different Founders. With natural infection selective immune pressure would not generate the mutations and they should evolve under natural genetic drift. In contrast, the VUI 202012/01 variant it may have originated in a single immunosuppressed patient who had received passive antibody therapy. This immune selection, in contrast to natural genetic drift, resulted in a variant containing 17 mutant amino acid changes with 8 mutations in the Spike region. Based on the number and location of Spike protein mutations, it is very likely that some reduction in neutralization by antibodies will be seen, potentially increasing risk for reinfection or lower vaccine effectiveness.

The developers of most of the current vaccines in development, including those currently authorized under EUA, have claimed that, in addition to the generation of neutralizing antibodies to Spike, their vaccines also generate some form of T-Cell response. At best this T-Cell response would be limited to epitopes derived from Spike. Emergex' ligandome analysis of T epitopes generated in cells infected with SARS-coV-2 indicates a total of 3276 Class I CD8 epitopes (spread over 6 genotypes) from total viral protein with 415 epitopes in Spike (52 in RDRregion of Spike). These numbers are for total possible T-Cell targets so Spike at best could only contribute ~12.5% of the potential T-Cell response generated in a natural infection.

It is not yet clear how the heavily lipidic TLR 4/2 adjuvanted mRNA vaccines generate a T-Cell response [33]. However, use of chimeric mice has demonstrated that, upon intramuscular injection, the myocytes and not the antigen presenting cells (APCs) are transfected [34]. In order to stimulate a B-Cell (antibody) response the Spike protein must be made in a 3-D conformation which then binds to the Ig antigen receptors on the surface of a naïve B-Cell. This same cell must then take up some of the intact Spike (trogocytosis required) via internal immunoproteasome processing present in Class II receptors (on the same cell) that can interact with naive CD4 T-Cells [35]. Since the Spike protein coded is for the full-length membrane protein, the naive B-Cells need to interact directly with the surface of a myocyte expressing Spike. The myocyte inflammatory activity results in significant muscle pathology, including muscle necrosis [33]. The presenting myocytes will clearly be the target of cytotoxic CD8 T-Cells if such cells are generated.

The above discussion indicates that the antibody response must be mediated by B-Cells acting as APCs and this process will consequently generate CD4 T-Cells against Class II epitopes on Spike. However, B-Cells can also get activated in the absence of CD4 help, a process which occurs in many bacterial infections or via activation of the complement receptor C3d which can act as the second signal. The mRNA vaccines contain cationic lipids similar to endotoxin, so it is not clear whether or not these active lipids are providing the second signal and thus no CD4 T-Cells are actually generated.

Evidence that the mRNA vaccines (or adenovirus vectored vaccines) generate cytotoxic CD8 T-Cells is not robust. The assessment is made by stimulation of PBMCs from vaccinated individuals with overlapping pools of peptides and detecting the number of cells reactive to the entire pool for T-Cells that secrete IFN gamma. This process will be looking at only the CD29+ subset of CTLs since the CD38+ CTLs secrete IL-2. These pools can generate vast numbers of epitopes since the analysis is only performed after 20 hours of culture incubation, at which time extensive proteolysis will have taken place. This conclusion is experimentally evident from the observation that the CD4 specific control 15mers (to common infections) are all negative, presumably since the control peptides have been proteolytically cleaved [36]. Upon cleavage, these pools can generate ~10000 peptides between 8mer and 15mer. Further, it is well established that non-contiguous smaller peptides (i.e. 4mers etc) can combine either cis or trans to activate CD8 T-Cells in these types of assays [37].

So it is not surprising that some CD8 CTL activity is detected in these PBMC samples; however, the reactivity cannot be confirmed as being derived from Spike-related epitopes but could essentially be from any T memory cells present in the PBMCs stimulated by the vast pool of peptides. The absence of reactivity pre-immunization is not relevant since these vaccines contain potent adjuvants that will upregulate the background responses. Specifically, the mRNA vaccine trials did not use a control vaccine, but just PBS as placebo.

The long-term presence of the lipid adjuvants will result in a chronic inflammatory state in which the innate immune system will be activated. Viral non-specific vaccine effects will predominate, leading to false estimations of viral-specific vaccine action. This outcome is a well-documented and observed phenomena in the literature [38].

IV. CONCLUSIONS

As expected, antibody escape mutants are appearing (but unexpectedly via stochastic processes), even before any positive vaccine pressure to escape. However iatrogenic intervention appears to have generated the VUI 202012/01 variant. With millions of individuals being vaccinated with a univalent (Spike) vaccine, it will be expected that lots of vaccine-driven mutations will arise. As the vaccination coverage will drag over 2-3 years, there will be billions of mutation opportunities.

There is no compelling evidence that the current vaccines are generating any T-Cell responses and, if they do, that output will result in significant muscle pathology. With regards to T-Cell escape mutants, these have not been observed. It has been proposed that a series of cross-reactive clonotypes form a well-connected network that provides protection from virus-escape variants [39]. Specifically, it is shape that counts for the Class I T-Cell recognition and a single aa mutation will probably find a pre-existing repertoire ready to respond to it.

It is proposed that the adult T memory cell repertoires have evolved based on previous encounters. Temporal analysis of epitope specific clonotypes has demonstrated that the clonotype repertoire in acute viral infection is replaced in convalescence by an equally diverse “de novo” set of clonotypes with only ~9% of unique clonotypes detected in acute infection persisting into convalescence. Whilst the repertoires are individualized, there were prevalent and public usages of particular TCR families. [40].

TCR interactions determine CD8 T-Cell-mediated antiviral efficacy. It is estimated there are unique potential TCRαβ clonotypes. Recent advances in next generation deep sequencing has shed some light on the complexity of the system. In general, results show a highly diverse TCR repertoire is generated to a peptide-specific response [40]. Estimates of unique clonotypes range from several thousand to fifteen thousand/peptide. Importantly each individual has a unique TCR-repertoire (“private specificities”) to a viral epitope due to the stochastic nature of TCR formation.

The large pool of TCR clonotypes could provide resistance to viral escape mutants that are common in persistent virus infections or in viruses under vaccine-induced selection [39]. Different TCRs may activate antigen-specific cell functions differently, leading to a more functionally heterogenous pool of memory cells. Paradoxically T-Cell escape mutants favour the host – not the infectious agent. A critical point is that a consensus sequence provides no information as to the frequency of specific variant haplotypes and haplotype reconstruction is required to estimate frequencies [28]. That is, what specific mutations are actually found on a single variant? If 100 mutations are spread out over

100 variants, the immunological consequences are very different than if they are all together on the same variant.

Emergex has estimated that approximately 3000 T-Cell peptide targets are generated within a single individual upon infection. Each of these targets can potentially independently stimulate multiple naïve T-Cell clones, generating a vast army of poly-specific clonotypes; that is, there is a high degree of redundancy offered by T-Cell epitopes that buffers against escape mutations affecting antibody epitopes. A single T-Cell interaction can kill an infected cell. This biological context is a very different situation from antibody escape mutant whereby the 3-D structure of a single epitope targeted by a neutralizing antibody can be affected by multiple mutations, either at the epitope site or at a distant site. This outcome includes even glycosylation changes which are known to stabilize the 3-D structures of many proteins [41].

Emergex has confirmed that none of the mutations present in the recent VUI 202012/01 variant had any effect on documented T-Cell epitopes in the SARS-20CoV Class I ligandome library nor do they affect any of the epitopes on the Emergex current universal coronavirus vaccine (i.e., SARS-1 and SARS-2). This observation demonstrates the urgent need to clinically develop T-Cell vaccines that will provide broad spectrum protection against both the naturally occurring viral variants and also against the inevitable variants generated by the first generation use of monovalent Spike antibody vaccines.

It follows that unless T-Cell immunity was the basis for the current vast number of asymptomatic and mild cases of COVID-19 in the population, then the antibody escape mutants will create multiple waves of new pandemics including re-infection since the current antibody immunity is to the original Wuhan strain. To date, there is no evidence that the antibody vaccines prevent infection, but just mitigate disease – thus they will provide an unrelenting selective pressure for further mutations in contrast to the original intent of antibody-related vaccines to be sterilizing.

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