EMERGEX VACCINES

Scientific Rationale for the Use of T Cell Priming to Reduce R0 to Limit Spread of COVID-19 During Active Pandemic White Paper

In this White Paper we explore the scientific rationale for the use of T cell priming to reduce the basic reproduction number (R0) of SARs-CoV-2 to limit the spread of COVID-19 during active pandemic.

Emergex Vaccines is a company specifically set up to deal with emerging viral infections and resultant pandemics of existing endemic viral strains. Emergex has spent the last 5 years looking at the best prophylactic and therapeutic approaches to deal with events such as COVID-19. Emergex has triaged a vast amount of historical data going back to the beginning of the 20th Century to look at the positive factors (such as the live attenuated vaccines developed in the first half of the 20th Century) and negative/failed interventions that have been applied to previous pandemic and epidemic virus (e.g. flu, dengue, measles, RSV etc.). Importantly, Emergex has critically assessed the vaccine trials that have failed, with specific reference to trials intended to vaccinate against RNA virus: this class of virus is very different in its pathogenesis to DNA viruses and bacteria. **It is dangerous and inappropriate to apply a medical approach/technology that has worked for bacteria, or is in development for cancer vaccines, to RNA viral infectious diseases.**

There has been a hopeful, global movement to replace the annual "flu jab" with universal flu vaccines that are independent of seasonal serotype-based vaccines. Yet every vaccine proposed for COVID-19 can be summarized as "let's make a 'corona jab'". Lessons have not been learned from those failures or are being ignored for either expedience or for financial gain. Making a vaccine to be used in a pandemic is very different from making a vaccine that will have limited distribution, such as yellow fever vaccine for travellers. No country in the world would ever vaccinate an entire/extensive population with yellow fever vaccine as its inherent adverse events rate is too high to be used at the population level. "Flu jabs" have been able to hit 46% efficacy rates in a good year and zero in a bad year. Vaccines that do not work are not the problem – **the long-term vaccine-induced changes in the immune system should be the main public health concern**. A field has now grown up around "Vaccine Induced Disease". Atypical measles is a prime example of this concern.

Highly efficient flu jabs prevent influenza infectivity. Is this outcome a good thing? Population-based background immunity to endemic viruses depends on birth cohort imprinting. Children and young adolescents, if given flu jabs, do not develop cell-mediated lifetime protection against influenza, since cellular immunity requires infection by a replicating virus. Consider the consequences of a "*dengue jab*" in Brazil. Individuals living in dengue endemic regions are 80% seropositive by the time when they reach 20 years of age, due to natural exposure. They are only therefore at risk to dengue Haemorrhagic Fever [DHF] from the date of seroconversion since DHF occurs on secondary infection with a different strain – this outcome is obviously a much rarer event than exposure from the initial/endemic strain. DHF has never been reported in a primary dengue infection, whatever the serotype– except if a naive individual

was first given the *Dengvaxia* vaccine: a very sanguine message for the 734,000 children aged 9 and over vaccinated in the Philippines with this vaccine. In 1976, there was a refrigerator release of a previous H1N1 influenza strain that had last circulated in 1949. This accident caused a flu outbreak at US Army Fort Dix, New Jersey. The following year, despite no immediate recorded case of this strain outside of the Army base, a mass immunization of 25% of the US population was initiated against A/New Jersey/1976. This process had the unfortunate consequence of another disease by vaccination – Guillain-Barre Syndrome. "*Also, in early November, Albert Sabin published a New York Times editorial, "Washington and the Flu." He agreed with the decision to create the vaccine and be prepared for an outbreak but criticized the "scare tactics" used by Washington to achieve the goal. He suggested stockpiling the vaccine and having a wait-and-see strategy*". The Fort Dix strain continued to circulate (and was re-christened 'Russian Flu') until 2009 when it was finally replaced by Mexican/Swine Flu. Vaccinations are given at a population level to protect the few so they must also be safe for the many that provide the herd protection. 99.9% of children with polio did not get any neurologic complications. Therefore, to protect the afflicted 0.1%, a vast number of children were immunized and placed at risk of vaccine induced illness.

The other issue revolves around the use of serotype-specific vaccines that are antibody-mediated. For example, there are 66 flavivirus, like dengue, Zika and yellow fever, so is Emergex obliged to make 66 different "flavi jabs"? **Immunology over the last two decades has unambiguously demonstrated that cross-reactive immunity exists within a family of viruses at the Class I MHC expression level**. Brilliant and elegant experiments have shown that when an animal is immunized with different strains of a related virus, then the result is generation of a T Cell that is specific for the common epitopes of the virus family and strain-specific T Cells are removed from that mix. The human immune system has evolved to deal with the issue of 66 flavivirus, many of which co-circulate today, even to the extent that a single mosquito bite can contain more than one type of flavivirus.

The movement of SARS-CoV-2 around the world is what RNA viruses do. For example, within months of the index case of 2009 pandemic flu in Mexico, the new strain had spread around the world and, importantly, had completely eliminated the previous H1N1 strains that had been circulating since 1949. There was a 'new kid on the block' and competition for hosts was paramount. That process is what is happening today with **SARS-CoV-2: it is displacing the previous endemic coronavirus**. Perhaps the SARS of 2013 went endemic and is only now being displaced. T Cell dextramer analysis can resolve that issue.

Analysis of the age/death plots for flu and coronavirus are not different, except for a blip in the under-4 categories for flu. Bird flu, SARS, 2009 and 1957 pandemic flu, and COVID-19 all have similar pathology: death is via acute respiratory distress syndrome (ARDS). **This fatal outcome is not a cytokine storm pathology but is an immunological reaction to IgG called antibody-dependent-enhancement (ADE)**, a well-studied phenomenon. However, it appears that many antibody-based vaccine companies, now forced to deal with this issue because of regulatory concerns, do not understand ADE. Intrinsic ADE is a process whereby IgG immune complexes formed of virions bind to monocytes and macrophages and, via cytokine and other factors, suppress innate immunity and host defences, thus leading to increased infectious output by "previously-infected cells". It is not clear how this process can be avoided by any form of engineering of the antibody binding to COVID-19. Mesoscopic IgG clusters will still form, and it is these flocs that lead to ADE. One conclusion of the SARS epidemic was that ARDS should be treated with inhibitors of the complement cascade since activation of this system will quickly lead to lung oedema. Failure to appreciate this basic pathology probably contributed to the early 2020 deaths of the young doctors in China that were given glucocorticoids from Day Three. Acute viral infections will cause host-versus-transplant rejections and

allogenic stimulation of the immune system leads to heightened antiviral response. These biological phenomena are all related.

So how do we intervene in a pandemic? Basic math in elementary textbooks on epidemiology show that we need to get the R0<1. If less than 1, then a pandemic will die out naturally and the virus will become endemic. It will, however, not go away totally and could re-emerge in subsequent waves, as happened for the three waves of Spanish Flu, in which the third wave of infection was the most lethal. It is critical to allow herd immunity to proceed in a population, but that strategy can have consequences for the ability of a healthcare system to cope with the natural death rates that will be clustered as the viral wave moves through a population. In contrast, interfering with natural immunity for COVID-19 will re-create all the problems that mankind has previously caused following the introduction of flu vaccines in the 1950s. Emergex has learnt that lesson.

Thus, if antibodies (flu jabs) are to be avoided, what are the alternatives? Current regulatory issues make the introduction of a live attenuated vaccine impossible. **Vaccines that stimulate an increase in frequency of T effector cells (Cytotoxic T Lymphocytes or CTLs) and T memory cells, to common MHC epitopes of coronavirus in the absence of an existing infection, will prime that individual to respond immediately upon a subsequent viral infection** – in contrast to the normal 8-12 days required for T Cell expansion in a primary infection. It is a race between [i] the virus increasing its quasi-species diversity or "cloud" to a disease threshold from the initial bottleneck and [ii] the T Cells limiting that cloud growth by killing virally-infected cells. The "bottleneck" governing infectious disease transmission describes the size of the pathogen population transferred from the donor to the recipient host.

Narrow bottlenecks reduce the amount of viral genetic diversity that is transferred and, consequently, the rate in which the transferred virions can adapt to their new host. ***T Cells never look at or care about the intact virus – they only recognize a virally infected cell as a foreign element and thus eliminate it appropriately.*** The early arrival of the T Cells on the scene will have two consequences: [1] they reduce variant growth leading to subclinical disease (T Cells win) and [2] they also reduce the size of the viral donor population transmitted to a new recipient "bottleneck", both in time and magnitude, thereby reducing population spread. These events constitute a clear "prime-boost" strategy which is the approach taken by Emergex.

Viral challenge studies in animals vaccinated with antibodies show a very different pattern. Whilst diversity at amino acid level is found to be initially reduced, there is a dramatic rebound in increased amino acid diversity as the virus mutates rapidly in search of antibody escape variants. The initial loss in amino acid diversity is, however, matched by an increase in synonymous mutations. Synonymous mutations in subpopulations suggest that the phenotypes of the variant subpopulations are not different from the main subpopulation. This adaptation must therefore have importance in terms of evolution and adaptability. This context is clearly not something anyone wishes a vaccine to support. **Prior antibody immunization therefore increases viral bottleneck size in the recipient and presumably will lead to higher infectivity rates and could increase evolution and adaptability rates of the infecting virus.** This process is a rather underappreciated mechanism of antibody enhancement of disease. This outcome has clinically been observed in young adults who have had previous flu jabs and then later catch flu. They transmit great number of virions (6.3x) to recipients and can be considered super-spreaders when compared to unvaccinated individuals. A body of evidence is also appearing in the scientific literature that antibody escape mutants (under the pressure of monoclonal antibodies or in vivo immunization) can drive the development of more virulent viruses and also mutants can be generated that do not affect antibody binding but enhance the fusion ability of the virus.

The T Cell frequency enhancement by Emergex's T Chip vaccines results in the "prime" and the SARS-CoV-2 actual infection becomes the "boost". The early priming infection with replicating virus will allow natural immunity to evolve in the absence of clinical disease. **Importantly, the priming vaccination will cover any potential new coronavirus strains related to the current SARS-CoV-2 including 2013 SARS-1 due to heterologous immunity. Emergex's T Chip vaccines do not induce a CD4 response and thus do not contribute to IgE lung pathology in COVID-19.**

Transmitted/founder viruses can also rapidly escape from CD8+ T Cell responses. The rapid escape dynamics are associated with the higher-magnitude CD8+ T Cell responses – that is, the immunodominant T Cell responses. This "escape" actually could be detrimental to the virus since subdominant T Cell responses are thought to be critical in elimination of an infection and the dominant T Cell clones are involved in disease chronicity. However, there is a fundamental difference between the effect of antibody escape mutants and T Cell escape mutants. The T Cell escape mutants, whilst losing HLA binding affinity in an individual recipient (unique HLA type), will -- on subsequent transmission to a new recipient -- be reactive to a different HLA type in the population. Therefore, HLA heterogeneity in the population ensures that the T escape epitopes generated in one individual will be reactive in other members of the population as a whole.

Finally, **if there is no subsequent coronavirus infection, the priming vaccination is neutral – it only enters play at the time of an actual, later infection** – a very different pattern from live attenuated vaccines that give the patient a mild form of the illness at the outset. So, the Emergex 'prime-boost' pattern has the potential to replace live attenuated vaccines and become the new paradigm for control of RNA viral infections.

Emergex Vaccines Holding Ltd

Emergex Vaccines Holding Limited ("Emergex") is a private company based in Abingdon, Oxfordshire in the UK. Its primary focus is on the development of medicines for the prevention or reduction of viral-related illness as well as some intracellular bacteria-related diseases. Emergex has termed its therapeutic agents '**setpoint vaccines'**. The Company aims to develop setpoint vaccines that are population-based, inexpensive and can be delivered relatively quickly; thus, they will be capable of better intervening effectively in infectious outbreaks.

Emergex's setpoint vaccines enhance the body's natural immune response. They do not include any DNA or RNA and the components are entirely (100%) synthetic.

When a virus infects a cell, that infected cell reactively produces a peptide 'code' that is then expressed on the surface of the infected cell. This encrypted code is presented on the surface of the infected cell by HLA Class I molecules. In healthy uninfected cells, this internal code presented on the cell surface provides for recognition of "self" and prevents the immune system from eliminating that cell as foreign. For those infected cells, the viral 'code' however is recognized as foreign (not self) and the human immune system will kill and eliminate the infected cell via cytotoxic T lymphocytes (CTLs) called CD8+ T cells.

Instruction to the immune system regarding the viral antigens occurs via physical transfer of the viral peptides from the infected cell to the immune system. Emergex uses state-of-the art technologies to determine the exact antigens produced by a virus and then to deliver those antigens to the immune system via dendritic cells for CD8+ T cell programming….essentially programming and priming the immune system to perform its kill-and-clear functions.

CD8+ T cell programming prior to a viral infection changes the immune 'setpoint', such that upon first exposure to the infecting virus, the immune system is able to respond much faster. The increased speed of response limits disease progress, but still allows for primary infection, which drives lasting and long-term immunological memory (i.e. a consequence of natural infection and natural immunity). A proprietary gold nanoparticle system technology is used as the delivery system for transferring the peptide antigens to the correct immune system components.

Emergex has a growing pipeline of vaccine candidates including a coronavirus vaccine based on the post-convalescent T cell response from patients from the 2003 SARS epidemic and then modified to be cross-reactive with COVID-19. An MHC expression ligandome library is currently being determined experimentally that will define the "peptide" Class I expression library on human lung cells to insure a more precise second-generation construct.

The most advanced development programme focuses on the flavivirus family with an initial target indication of dengue fever. It is expected that immune 'setpoint' pre-programming will occur against other related flaviviruses, such as the Zika and Yellow Fever viruses, resulting in a single vaccine that targets multiple viruses within a single genetically conserved family of viruses. Applying the same principles, the Company also has programmes in development for a universal influenza (including pandemic flu) vaccine and for a universal filovirus (Ebola and Marburg, all strains) vaccine.

Discovery programmes include a yellow fever booster vaccine within Emergex's viral disease programmes and a vaccine against *Francisella tularensis* within Emergex's intracellular bacterial disease programmes. *Francisella tularensis* is the causative agent of tularemia, a form of pneumonia which is often lethal without treatment and is classified by the US government as a Tier 1 potential bioterrorist agent.

In June 2019, Emergex signed a development agreement with A*Star's Institute of Molecular and Cell Biology (IMCB) in Singapore to develop a vaccine for the highly contagious Hand, Foot & Mouth Disease. The agreement targets the development of a cross-therapeutic vaccine to protect against the group of viruses which are associated with HFMD, including enterovirus 71 (EV71) and coxsackievirus A16. EV71, a non-polio enterovirus, has recently been associated with paediatric acute flaccid myelitis (AFM) in the USA. AFM is a rare but serious condition. It affects the nervous system, specifically the area of the spinal cord called grey matter, which causes the muscles and reflexes in the body to become weak.

In 2019, Emergex announced that it had successfully secured a research and development (R&D) facility at Milton Park, Oxfordshire. This facility extends the Company's overall internal control of all its preclinical vaccine development programs. Key personnel at the site, who are highly experienced in the design, production and development of nanoparticles also joined Emergex, enhancing its internal resource of skills and expertise in vaccine development. In-house cGMP manufacturing facilities are also being established at Milton Park.

Precis of Emergex Technology and its Advantages

Emergex combines validated technologies, together with the very latest scientific insights to develop its set point vaccines:

- Emergex has successfully generated a 1st generation human specific MHC-Class I CD8 peptide ligandome library for Dengue, flu, Zika, Hepatitis B and *Francisella tularensis* for the most commonly occurring human alleles. The library contains encrypted peptide data to instruct

the immune system to alter the initial 'setpoint' of response on first exposure and potentially to reduce disease severity [but still allow natural immunity to provide long term protection]. Emergex's vaccines are self-adjuvant and also potentially limit or eliminate allergic, autoimmune or antibody mediated side effects of traditional vaccines.

- Where practical, blood samples of individuals with natural/acquired immunity to the pathogen are used to validate those peptide codes which were used to generate immunity in a natural infection.
- These validated peptides are combined with an extremely small (quantum) gold nanoparticle that can directly deliver to the naive immune system and then can program the immune system to eliminate pathogen-infected cells upon subsequent exposure and infection. It is the combination of these technologies that produces a set-point vaccine, capable of delivering the right peptides to the right place, in order to produce a strong T cell immune response that will target and kill infected cells.
- Emergex's vaccines are suited to be administered by novel microneedles technologies.

Emergex's vaccines are advantageous in numerous ways:

1. They should reduce viral disease to subclinical by priming a T cell mediated immune response.
2. Emergex's vaccines are self-adjuvant and limit or eliminate allergic, autoimmune or antibody mediated side effects of traditional vaccines. Emergex vaccines do not induce an antibody response [such as ADE].
3. They are 100% synthetic and also contain no RNA and DNA - do not use inactivated or live attenuated pathogens and therefore should be inherently safer to develop and use.
4. They replicate the cellular immune responses to highly conserved recognition elements of the pathogen often present in internal proteins in which selective pressure for mutation is minimal. An advantage of this approach is that these internal components are conserved within viral strains of the same virus superfamily, making feasible a broad/universal vaccine to tackle highly mutagenic viruses such as seasonal flu or COVID-19.
5. The current Emergex vaccines are designed to be delivered by novel microneedle technologies (for example a skin patch) which means that there is less need for primary healthcare providers to administer the vaccines, no need for travel to central health clinics, hence improved compliance – a major challenge to providing vaccination in crisis conditions or in developing-world settings. Future planned dry patch vaccines are stable at room temperature, thereby avoiding the need for refrigeration, which enables easy transportation to the crisis locations and to remote parts of the world where they are most needed.