CD8+ Priming as an Artificial Method for Inducing Herd Immunity into a Population White Paper

In this White Paper we explore CD8+ Priming as an artificial method for inducing herd immunity into a population.

First principles of immunology all point to CD8 + priming as the approach to deal with the COVID-19 pandemic. Blocking or preventing infection by antibodies (even if possible) is not an end game solution. Immunizing a population with a vaccine that induces seroconversion would also remove the possibility of using antibody testing to determine who has been infected. CD8+priming does not result in sero conversion. The antibody approach will not shorten the pandemic and could prevent herd and natural immunity from developing (for RNA viruses antibody approaches have never been shown to work – i.e. last 2 decades of HIV vaccine failures, Dengue, RSV, etc.). Only live attenuated vaccines have been shown to deal with RNA viruses (measles, polio, yellow fever etc.). Replication-diminishing vaccines and antivirals approaches would require precise knowledge of date of infection and dates of active virus activity (for example, VSVs-EBOV must be given within ten days of exposure or no effect). Acute respiratory distress syndrome (ARDS) is also thought to occur post-viral exposure so other palliative approaches are required such as the use of complement inhibitors. These approaches will make incremental changes at best but will not deal with the pandemic per se which clearly will return with multiple waves.

1. It is not about the platform – it is about what we want to do to a population to take R0 less than one. We have three groups in any population, naïve, post-convalescent, and infected. Any intervention must consider all three groups. Emergex called the Dengvaxia problem 18 months before it was reported by Sanofi, saying it would not work and it would cause problems. On Nov. 29, 2017 Sanofi admitted problems = 600 deaths, 3281 hospitalizations with severe Dengue almost all in “naïve” children. For clarity, no granting agency in the world would believe Emergex and we were not able to get a drop of finance for a new Dengue vaccine, based on different principles. Nevertheless, we proceeded to develop a T Cell prime vaccine for Dengue which was scheduled for clinical trial in the next several months of 2020 but has been put on hold with other non-corona trials. 2020 is dengue Deja vu as we have once again, we have been involved in producing White Papers – this time around regarding potential antibody dependent enhancement (ADE) issues of anti-spike protein vaccines for SARS-CoV-2

2. CD8+prime would have the following effect in different populations

   A. Naïve --- will have T Cells ready to go on day dpi0 rather than day dpi10 – critical paper showed that SAR 2 supresses gamma interferon innate immunity, so this is only way to overcome that defect. This is a prime-boost strategy where the actual infection is the boost. This is a one-shot procedure.

   B. Convalescent - prime will now act as the boost

C. Infected – like cancer, T Cell therapy increase ratio of T effector to infected target and also we add new T Cell specificities “to the resisting army” from subdominant clones. Vaccination can be better than natural infection.

3. ADE is a complicated process and totally misunderstood by the antibody vaccine companies who claim to have engineered it out. 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.… However, in SARS there was additional immune-complex complement pathology that occurred at the time of IgG seroconversion. This outcome is not ADE and is the result of released virions forming mesoscopic IgG latices in the lungs with the virions and thus setting off immune complex disease.

4. Herd immunity is not short-term immunity (like a flu jab), but long-term immunity, that is mediated by CD8+ T cell - not antibodies. Flu jabs give no long-term protection and only protect for 16% loss of efficacy/month. Society gives new flu jabs each year not because of serotype changes, but because the vaccine efficacy is short lived. CD4 memory is short term and peripheral whereas CD8 memory is long lived and central.

5. You do not want to interfere in herd immunity – if you block infection, you do not generate natural immunity and blocking herd immunity is putting vaccines at risk.

6. So, the only scientific, rational approach is [A] to change the immune set point in a population such that most, if not all, exposures to the virus result in subclinical disease and also [B] to reduce the transmission bottleneck size (number of pathogens transmitted from donor to recipient). That process reduces R0.

7. RNA quasi species – viral titres are meaningless numbers – to see what is happening, you need the Shannon Diversity Index – only obtained by deep sequencing. Specifically, it has been shown that in viral challenge into pre-vaccinated animals that fully clear the infection, the immune system diminishes variability of the quasi-species cloud even in the presence of increased viral load showing that loss of adaptability is the key to controlling RNA viruses. Animals that do not reduce viral diversity succumb to the virus.

8. (From Point 5 above) If antibodies are present at time of immunization, you force the virus to search its variant space for antibody escape mutants. When this is done in culture, you always get escape mutants and they can be more virulent than the initial infecting virus. These antibody escape mutants do not necessarily affect the person where they are generated but become part of the new donor cloud being passed to a new recipient. It should be added that blood viremia has not been reported in SARS 2, so it is not evident what antibodies in blood will do since no virus is present. These viruses are transmitted by cell to cell transmission, not released into blood and then spread. Antibody escape mutants can lead to more virulent and novel viral clouds.

9. (From point 5 above) Virus also can generate T escape mutants, but this problem was solved evolutionarily by our HLA system being heterogenous. We didn’t develop an heterogenous HLA system to make the lives of transplant surgeons difficult. The genetic heterogeneity provides a population buffer to deal with T Cell escape mutants. For example, if an individual is HLA A2

and there is a mutation in the HLA A2 T Cell epitope that makes it no longer bind to HLA A2 (escape) that is bad luck for the individual (i.e. the individual no longer recognize that epitope as foreign) but that mutant peptide (whose sequence change will makes it bind to a different HLA specificity e.g. HLA B7) changes HLA restriction - when passed to the heterogenous population containing all 800 or so HLA genotypes, the original escape mutant will now act as a protective epitope in individuals with HLA B7 tissue type. Critically T Cell escape mutants help to generate herd immunity amongst a population; otherwise we would end up with certain HLA types being more susceptible to an infection. In general, this outcome is not found.

10. The first thing that happens after infection is a strong innate immune reaction by NK cells and this reaction produces lots of natural antivirals. Viral load peaks at dpi2 co-incident with the peak of IFN gamma which then decline to zero on dpi4. The loss of the interferon-induced antiviral effect results in an increased availability of target cells to infection due to loss of their antiviral state. This loss of protection results in a second viral peak which then requires the adaptive immune response to clear it. Around dpi10, the T Cell system has expanded enough to now resolve the infection. In SARS, it was found that if sero conversion for IgG happened too early (before the T Cells cleared the virally infected cells), the patient developed ARDS. It is a three-way race, virus and antibodies are the bad guys and T effector cells are the good guys standing between resolution and lung pathology.

11. You need to know the viral signature on infected cells as they are the T Cell targets – no program can predict them. Also, if you generate a response against viral antigens in a cell which normally doesn't get infected, then that T Cell response will not match a naturally infected cell, so the T Cell response is off target. This is what recombinant adenovirus-vector based vaccines do. It is irrelevant to say "my vaccine generated a CD8 T Cell response" unless you show that response is relevant to infected Type II pneumocytes in SARS -2.

12. You can also gain insight from analysis of post convalescent blood samples to see what T Cell memory has evolved to protect them in the future: a good basis for a later, booster T Cell vaccine but might not be sufficient in the primary infection in which early-expressed, subdominant T Cell epitopes are expressed.

13. Once you have the library, you need to prime the naïve T Cells in an individual – this process requires mimicking the normal transmission of this information that occurs in a natural infection via one of three mechanisms, direct priming, cross-presentation and cross-dressing. Responding T Cell clones will increase in frequency by up to 1000-fold and generate T effector cells. If there is no virus present to fight, these cells will differentiate into T memory cells waiting for a future viral infection. This process is the immune "set point" cell programming and should not be confused with standard peptide vaccination.

In conclusion, CD8+ priming is an artificial method for inducing herd immunity into a population. Herd immunity is nothing more than changing the population set-point. This can be achieved by infection which can overload the health system or by pre-priming the population for herd immunity such that individuals that get infected have subclinical disease and resolve the infection more rapidly and those reducing chance of transmission and thus R0.