Salvagene GROUP

Business Unit: SARS-CoV-2 Task Force
Keynote: #50

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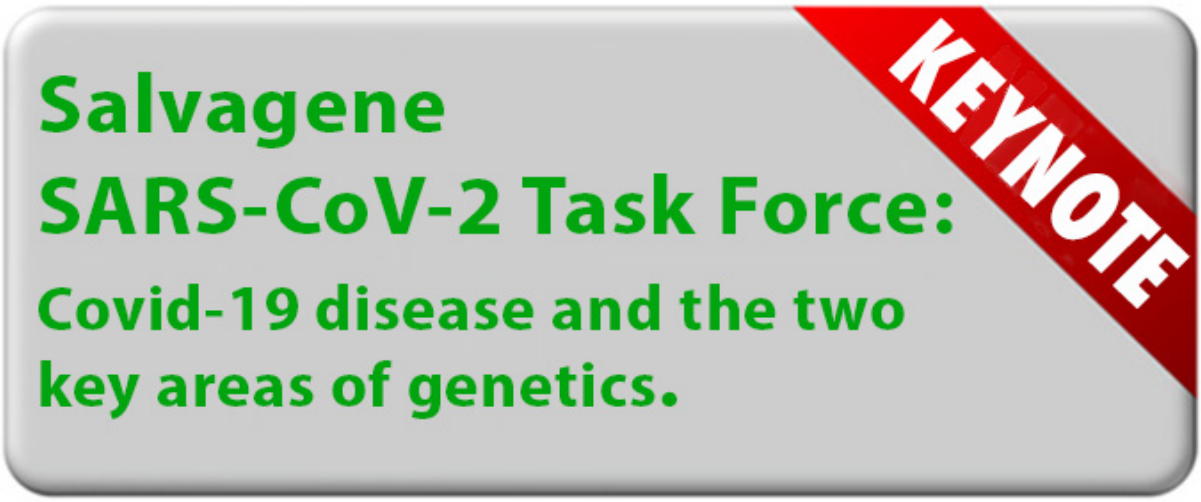

Dear Premium Customers,

We at Salvagene have been specializing in the field of genetics for more than 20 years, and it now constitutes our core competence. We are therefore looking at the coronavirus pandemic and the Covid-19 disease from a genetics-based perspective, and we regard it as a matter of utmost priority.

The two most important genetic aspects to be considered are our own human genome and the genome of the virus. Let us first of all take a look at the human genus which, as we have seen, has certain gene variants that are responsible either in part or in full for the Covid-19 disease taking more severe course. The risk of this may also be increased or reduced by the epigenetic status of certain genes at the time of infection. We will provide more detailed information on this in the next few days. However, we can already say that certain gene variants – so-called "genetic polymorphisms" – in the human genome are responsible either in part or in full for the disease taking a more severe course and that even absolutely healthy people in younger age groups with

no underlying conditions can also become ill or even die from a very severe course of the disease. This is of significance because, even if vaccines reduce the pandemic risk in the medium term, we believe that Covid-19 will keep us busy for many years to come. These gene variants therefore open up the scope for the development of C19 medications as well as the type of preventive medicine approach that we at Salvagene are pursuing.

Some genes have already been clearly identified, such as the TYK2 gene which makes immune cells highly aggressive and inflammatory. This can cause the immune response to go into overdrive, leading to a so-called "cytokine storm". DPP9 is another gene that we have long been familiar with – it also plays a major role in SARS-CoV2 infection in terms of inflammation. And then there is the OAS gene, which we have long had under observation. It has a protective role, because it helps prevent the virus from making copies of itself. The importance of interferons has also to be stressed (see Keynotes 36 and 37). Certain genes, such as IFNAR2, are responsible for the underproduction of interferon which not only functions as an alarm bell for the entire immune system but also generates an immediate immune response.

Our Salvagene Covid-19 Immunization Program has already taken a major practical step forward in this area, as we analyze the epigenetic states of the interferon receptors to see how quickly the immune system would respond to a SARS-CoV2 infection. We are paying particular attention to a cluster of genes on Chromosome 3, which has also been linked to very severe symptoms in patients suffering from Covid-19. Findings such as the above are constantly being incorporated into our Salvagene Covid-19 Immunization Program, as well as our Salvagene Premium Program, for example in our epigenetic analysis of interferons.

The second area of interest is the genome of the virus and its different variants and mutations, as we have reported in several previous Keynotes. Even though media coverage suggests that

SARS-CoV2 forms relatively few mutations, and even then only at a slow rate, we have always maintained that mutations are indeed occurring and that, to date, thousands have been identified. The important point here is not the relatively small number of mutations but rather the effects of the existing ones. The mutation we reported on at a very early stage, namely in June, is D614G, which we deduced was responsible for the significantly higher transmissibility of the virus, though not everyone agreed with this assessment at the time. We also expressed the opinion that D614G was associated with a reduced mortality rate, but because of the overall higher transmissibility, the total number of fatalities around the world has risen sharply nonetheless.

At the moment, we are preoccupied with the 50.1V2, a variant, that has come to the fore mainly in South Africa and which has been associated with far higher transmissibility and at the same time an increased likelihood of contracting the disease, including by younger people and those who do not have comorbidities. The rather rapid spread can possibly be explained by a higher binding capacity to the surface molecule on the target cell. Research is currently underway to ascertain whether the antibodies formed by natural infection or vaccination bind more poorly and are therefore less effective. This variant is relatively similar to the H69/V70 mutation which has now hit the headlines. It is found within the new B.1.1.7 variant which was first identified on 20th September in England and has now also spread to the Netherlands and Belgium. This has caused the Netherlands to impose an entry ban on all UK air passengers as of 6am yesterday (20th December). The EU Commission is holding an emergency session on 21st December to consider how the European Union as a whole will handle the issue of passenger arrivals from the UK. We confess that we are somewhat surprised that it is taken so long to publish details about this mutation. A similar flight and entry ban was already put in place a few weeks ago when the so-called “Cluster 5” mutation was discovered on mink farms in Denmark. This resulted in up to 28 million mink being culled in Denmark and Eastern European countries. Even after the mink had been buried, the virus got into the

groundwater, so the animal carcasses had to be dug up and disposed of by an alternative method. At that time, the UK had imposed a complete ban on entry from Denmark. Now the increased rate of infection, especially in south-east England, has led to the latest entry ban and the involvement of the WHO. Unfortunately, we believe that the time lag means that the mutation of the virus will have already reached not only the Netherlands but also the rest of the continent. Almost all health authorities practice genome surveillance, and this variant was already identified some time ago. Our current assessment is that this mutation is approximately twice as contagious as the original virus. The available data was published in the Covid-19 Genomics UK Consortium (COG-UK Consortium) a few days ago.

In terms of importance, most of the mutations are relatively harmless. The mutations that are of particular concern to us are those that are correlated with changes in the spike protein of the virus. The spike protein is located on the outer shell of the virus. The virus uses it to bind to certain receptors on human body cells, namely the ACE-2 receptors. The binding site of the spike protein is currently altered by three mutations within the B.1.1.7 variant. Firstly, the H69/V70 mutation – already an old acquaintance of ours observed in various parts of the world – which is able to strongly suppress the immune response. Secondly, the N501Y mutation which affects particularly important regions in the spike protein, increasing binding to the spike protein and making the virus more contagious and aggressive. Thirdly, we have P681H which can also cause considerable damage by means of the spike protein. The altered protein form involved has been analyzed by various research institutes, including the University of Cambridge, and the results suggest that it is about twice as infectious. Because the findings have so far only been published as a pe-print, we at Salvagene are unable to deliver any conclusive assessment at this stage.
These variants are further spread by infections, and our tools of analysis allow us to trace the lines of dissemination of SARS-CoV2 around the world. If this increased transmissibility is confirmed, then it could further complicate the containment of Covid-19. The big question we have already asked in previous Keynotes is

whether mutations can cause a vaccine to become less effective or even totally ineffective. It is a question which we have always answered with an unambivalent yes. Another question is whether mutations can also result from incorrect medication or, in particular, from poor-quality vaccines. We also answered in the affirmative to this a long time ago. This is why we always say here at Salvagene ”better no vaccine than a bad vaccine”. However, so far we only know of three changes in the spike protein and we are working on the assumption that these three changes are currently not enough to render a vaccine ineffective, but they may have the capacity to reduce its effectiveness.

However, it should be noted that, even if vaccines are unlikely to become ineffective due to single mutations, a combination of significant mutations in critical areas may eventually lead to this, as is the case with the flu vaccine. The result is, of course, that effectiveness drops away; in some seasons, it has even fallen below 50%. The consequences of this for the further course of the pandemic are grave. As with the flu vaccine, we would have to adjust the formula seasonally according to the incoming wave of SARS-CoV2 variants, a worrying scenario that we have to assume is becoming more and more likely.

We will continue to track these developments and include them as part of our advice on which vaccine to use at which juncture and whether vaccination makes sense at all as a criterion for our Salvagene Premium clients.

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