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THE NEXT QS-21 Stimulon™

Agenus' QS-21 is a Highly Effective and Widely Used Vaccine Adjuvant It Powers the World's Highly Successful Vaccine, SHINGRIX

QS-21 Has The Potential to Make a Pandemic Vaccine Highly Effective

The COVID-19 pandemic has infected almost 13 million people globally[1] and has claimed the lives of over half a million victims.[2] The current pandemic, as well as the risk of others in the future, has prompted a heightened state of readiness among governments, non-profit institutions and companies to rapidly develop vaccine countermeasures at scale. In this newsletter, we highlight recent advances by Agenus and our collaborator to produce the QS-21 Stimulon™ adjuvant at the cost and production capacity requirements of a global-pandemic-scale vaccine.

Access to a large scale supply of QS-21 Stimulon™, which is only possible through such a process, could be critical in alleviating public health crises. The ultimate path to ending a pandemic such as COVID-19 is the development of a highly efficacious vaccine that can offer durable protection against infection. QS-21 Stimulon™ is a proven adjuvant: it is a key component of GSK's shingles vaccine, Shingrix, with >90% efficacy.[3] Shingrix is one of the most successful vaccine launches in recent years, generating over $2.3 billion in revenue in just its second year of launch (2019). Prior to this, the only approved vaccine for shingles (Zostavax®) was ~50% efficacious.[4]

This precedence is noteworthy because the FDA recently set a similar bar of 50% efficacy for the approval of a COVID-19 vaccine. However, many experts and models, including the World Health Organization, have suggested that a vaccine with at least 70% effectiveness is needed to have a chance of stopping the spread of the virus.[5] Current COVID-19 vaccines in development will likely need help to meet these standards and be safe across different age groups. These are challenges for which QS-21 is well-suited. Importantly, QS-21 is compatible with all major vaccine technologies being pursued to combat COVID-19, including protein subunit, viral vector, mRNA and DNA vaccines.

In a preclinical study of the SARS-CoV virus (a virus highly related to COVID-19), a QS-21-containing vaccine was successful in protecting mice.[6] A follow-on study with a QS-21-containing vaccine showed protective effects in hamsters against SARS-CoV.[7] Further, QS-21 is one of a select few adjuvants that induce mucosal immunity, the body's first line of defense against respiratory viruses such as COVID-19.

QS-21 Vaccines Deliver Long Term Immunity And High Efficacy in the Elderly

The protection offered by QS-21 vaccines is highly durable. Shingrix has demonstrated sustained efficacy of more than 85% for the first four years after vaccination; additional follow-up is ongoing.[3] QS-21 is also highly effective in older individuals (≥70 years; see table in the next column),[8] who traditionally have a much poorer response to vaccines. High efficacy in the elderly is particularly important for vaccines targeting infections such as COVID-19 which has shown to inflict the elderly with a much higher risk of morbidity and mortality.

On a separate note, it is significant that GSK's QS-21 containing malaria vaccine, MOSQUIRIX™, has been used to protect pediatric populations. Thus, QS-21 containing vaccines are safe and effective for broad use across age groups, an important attribute to consider in the development of a pandemic vaccine.

Efficacy by Age[8]	Shingrix (QS-21)	Zostavax®
50 – 59 years	**97%**	70%
60 – 69 years	**97%**	64%
70 – 79 years	**91%**	41%
≥ 80 years	**91%**	18%

QS-21: Proven To Activate Critically Important Cellular Immune Responses; Recent Data Suggest Cellular Immune Response May Be Key to a Longer Lasting Vaccine-Induced Protection Against Covid-19[9]

Agenus' QS-21 Stimulon™ is a best-in-class adjuvant that significantly improves the immunogenicity and efficacy of vaccines by activating critically important cellular immune responses.[10, 11, 12]

QS-21's advantages relative to traditional vaccine adjuvants include:

- Broadened scope and increased titer of antibody responses
- Stimulation of T cell immune response
- A reduction of the antigen dose requirement to achieve optimal immune response; this is critical given limited supplies of pandemic vaccine antigens
- Enhancement of immune responses to notoriously weak antigens, including for viral, bacterial and parasitic pathogens

Well over 10 million people have been dosed with vaccines containing QS-21 Stimulon™, with demonstrated safety and efficacy in several indications. In addition to Shingrix, QS-21 Stimulon™ is a critical component in the first-ever malaria vaccine (GSK's MOSQUIRIX™), and a tuberculosis vaccine containing QS-21 Stimulon™ has recently successfully completed phase 2 trials with higher efficacy than other vaccines. Additional clinical trials have been conducted in hepatitis, HIV, and cancers such as melanoma and NSCLC. Preclinical data also support broad applicability across many indications, including for use in vaccines for anthrax, cancer, chlamydia, CMV, dengue, Ebola, group A streptococcus, H. pylori, hepatitis, HIV, HPV, HSV, influenza, Lyme, malaria, Moraxella catarrhalis, rotavirus, RSV, S. pneumoniae, SARS, smallpox, Staphylococcus aureus, tetanus, tuberculosis, and VZV. If current QS-21 supply and costs were not limiting, another important QS-21 application could be flu vaccines, which currently reduce the risk of illness by only 40-60%[13]. This represents another important and large market for QS-21.

THE CHALLENGE: Not Enough Raw Material To Make Billions of Doses Of QS-21

Currently the only source of QS-21 Stimulon™ is through Agenus' proprietary purification process to which only Agenus and GSK have access. This process uses bark extracts from the South American Quillaja saponaria tree from Chile. There are several limitations involved with this source. One is the quantity of this tree-derived raw material, which limits the availability of QS-21 to meet the demands of a pandemic or other high-volume vaccination needs[14]. This source is also heterogeneous, making the quality highly dependent on climate and environmental conditions. Finally, it is expensive; current costs are prohibitive for inclusion in high volume, low margin vaccines against pandemic pathogens, influenza, etc.

THE AGENUS SOLUTION: Proprietary Manufacturing From a Renewable Source

Agenus is pursuing a renewable raw material source, which along with our proprietary manufacturing process could yield high quantities of QS-21, potentially for billions of doses of vaccines. This would allow us to quickly scale production to meet the needs of pandemics or other high-volume vaccines. The process also results in a more consistent final product, reducing the variability associated with bark-extract material. Finally, Agenus' proprietary process with renewable raw material is expected to reduce manufacturing costs by more than 90% relative to the bark extract process. This highly pure, lower-cost product would enable much broader use of the QS-21 Stimulon™ adjuvant, including for critically important vaccines to fight today's and future pandemics.

Our data reveal that the QS-21 generated from this process is chemically and immunologically equivalent to QS-21 from bark extract, with equivalent T cell, innate immune and antibody responses. The program is now advancing to GMP scale-up.

Based on its attributes, QS-21 has the potential to serve as a key immune system activator for vaccines against future pandemic threats beyond COVID-19. To this point, 1.67 million unknown viruses exist in animal reservoirs and it is estimated that 631,000 to 827,000 of these viruses have the potential to be transmitted from animals to humans[15]. In the event of a future pandemic, our innovative, plant-cell-culture-based process for manufacturing QS-21 could make this critical adjuvant available at scale and with favorable economics for billions of people.

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