Fast Facts:
Vaxart's Oral COVID vaccine candidate: An easy pill to swallow

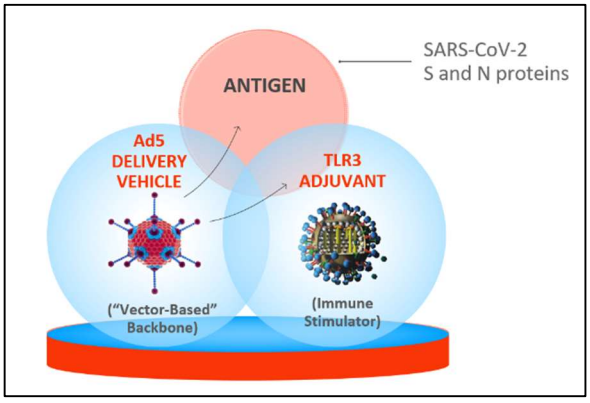
When Vaxart announced in January 2020 that it would be developing a COVID-19 vaccine, no one could have predicted the year that would follow. One year later, there would be 112 million cases, devastating numbers of hospitalizations and more than 2.5 million deaths globally due to the worldwide pandemic. A galvanized research community has developed numerous vaccine candidates at lightning speed, all while trying to attain high efficacy and safety.[1] Several vaccines have received authorization and approval for use globally.

Most of those efforts relied on traditional needle vaccines, but Vaxart is one of the few companies targeting an oral solution for COVID-19. Its VXA-CoV2-1 vaccine candidate is designed as a room temperature-stable tablet that may accelerate vaccine distribution efforts around the world by eliminating freezer requirements and the need for injections. At the heart of the design of this vaccine is a deep and acute understanding of the immune system and how it can be utilized to protect against a virus that has proven continuously complex to understand and contain.

VXA-CoV2-1 is the first oral COVID-19 tablet vaccine to be tested in humans in the U.S. If developed and distributed broadly, VXA-CoV2-1 holds the promise of solving the logistical challenge that allows the virus to hold billions of people worldwide in its thrall and a potential solution to mutating virus strains.

Understanding VXA-CoV2-1

Vaxart developed VXA-CoV2-1 using its proprietary technology called VAAST™ (Vector-Adjuvant-Antigen Standardized Technology), a platform that can be leveraged to develop vaccines for a range of diseases. The adenovirus type 5 virus (Ad5) delivery platform lies at the core of the technology. Ad5 is non-infectious and is used as a carrier for two critical components of the vaccine: the genes coding for "the antigen" and the "adjuvant." The antigen is a part of the target virus known to stimulate a protective immune response, specifically the SARS-CoV-2 Spike and Nucleocapsid proteins, and the adjuvant is a molecule that acts to boost the immune response, specifically a TLR3 immune stimulator.



The three components of VXA-CoV2-1

VXA-CoV2-1 is formulated into a tablet taken by mouth that delivers the antigen and adjuvant genes to the lining of the small intestine, known as the mucosa. When the vaccine encounters

the immune cells of the gastrointestinal mucosa, they are stimulated to produce an immune response against SARS-CoV-2.

The antigen in VXA-CoV2 is composed of the genes coding for **both** the SARS-CoV-2 spike (S) protein and the nucleocapsid (N) protein. Whereas the S protein is a common target for COVID-19 vaccines currently in use and in development, VXA-CoV2-1 is one of the first COVID-19 vaccine candidates that contains genes for both proteins.[2] This is key because the S protein has been prone to mutations over time, which may render vaccines targeting only this protein less effective. The N protein is largely conserved between emerging strains of the virus and may provide a long-term target for vaccine developers trying to broaden the responses against all strains of VXA-CoV-2-1.[3]

VXA-CoV2-1's Dual Immune Response

To better understand the immune response stimulated by VXA-CoV2-1, it's essential to have a basic understanding of the two main arms of the immune system. The immune system fights infections using antibodies produced by B-cells (humoral) and using T-cells (cell-mediated).

B-cells produce different types of antibodies, including IgA and IgG. IgA antibodies are primarily produced in places such as the gastrointestinal (GI) tract and the respiratory tract, where respiratory viruses first invade.[4] IgG antibodies are produced in the serum (blood). Traditional injectable vaccines work by inducing a strong IgG response in the blood, whereas oral vaccines induce an IgA response in the GI and respiratory tracts with some IgG responses in the blood as well. Because VXA-CoV2-1, like other Vaxart vaccines, triggers immunity in the respiratory and gastrointestinal tracts, it may be able to prevent infection and block transmission. People shed virus in the gastrointestinal track for a longer period of time,[5] which may mean that controlling virus at multiple mucosal sites could be beneficial.

Preclinical trials studying VXA-CoV2-1 in hamsters demonstrated that the vaccine led to a significant antibody response against SARS-CoV-2. The vaccine prevented lung damage, inflammation, and lung weight gain, compared to unvaccinated animals.

In addition, recently announced preliminary Phase 1 data (NCT04563702) showed strong safety for VXA-CoV2-1 and demonstrated that it led to a strong immune response stimulated by B-cells and T-cells. This two-pronged immune response has the potential to provide durable protection against SARS-CoV-2.

The data demonstrated IgA antibodies present in blood and/or nasal swab samples – the expected outcome – because the vaccine is administered orally and is absorbed in the GI tract. Because mucosal IgA can be more potent than serum IgG in neutralizing SARS-CoV-2,[6] it's possible that the infection could be prevented by even small quantities of IgA in the nose.[7,8]

The data also revealed that VXA-CoV2-1 resulted in a significant T-cell response to both the S and N proteins. Important anti-viral molecules (IFNγ and TNFα) were made when the cells from

Vaxart's subjects were given the SARS-CoV-2 proteins, at much higher levels than seen before immunization. As noted, although the S protein is vulnerable to mutation, the N protein is more conserved within the coronavirus family. This immune response against both antigens is an encouraging sign that VXA-CoV2-1 may be able to provide protection against multiple variants of the virus as the S protein mutates, a potential advantage over time. In addition, T-cell responses to SARs-CoV-1 (SARS), a close relative of SARs-CoV-2, have been found to last for 17 years after infection and could potentially be protective against SARs-CoV-2, demonstrating the potential of a robust T-cell response to provide durable immunity to a broad range of coronaviruses.[9]

Although many vaccine developers have focused on antibody production as the primary way to provide protection, there has been little focus on the role of T-cells, with a critical blind spot resulting in this area. VXA-CoV2-1 responds to this by marrying the B- and T-cell response to boost immunity and potentially provide durable efficacy.

The Logistical Benefits of an Oral COVID-19 Vaccine

Not only does VXA-CoV2-1 demonstrated important immunological responses, an oral COVID-19 vaccine provides other key advantages. Oral administration is quick and painless, providing an alternative to the many people who fear needles. Potential injection site reactions are also eliminated.

The preparation and administration of injections requires significant time and resources, which is limiting given healthcare systems' precarious – or in some places around the world, rudimentary -- state. A self-administered vaccine saves valuable time for many essential healthcare workers.

Perhaps most important, an approved VXA-CoV2-1 would be stable at room temperature, which is highly advantageous for storage and global distribution. Large communities in need with limited access to refrigeration could greatly benefit from an oral vaccine with a stable shelf-life.

Next Steps in the Study of VXA-CoV2-1

There continues to be a tremendous demand for safe and effective COVID-19 vaccines for various communities with differing needs. As injectable vaccines are rolled out in different countries, more needs to be done to assure that all communities are adequately protected. Oral vaccines have the potential to produce vaccine equity and greatly benefit underserved and vaccine-disadvantaged populations in the United States and around the world.

The advantages of an approved VXA-CoV2-1 are clear—it has the potential to give safe and broad durable immune protection with good tolerability. It is being developed so that it can be self-administered painlessly and quickly and stored/distributed at room temperature.

VXA-CoV2-1 will next be studied in a dose-ranging study in order to identify the ideal dose for a strong immunological response and safety profile. Then, VXA-CoV2-1 will enter an efficacy study with a large cohort of subjects in the hopes of distributing this vaccine globally shortly thereafter.

Literature Cited

1. Iwasaki, A. & Omer, S. B. Laskers 2020 Why and How Vaccines Work. (2020) doi:10.1016/j.cell.2020.09.040.

2. Moore, A. C. *et al.* Pre-clinical studies of a recombinant adenoviral mucosal vaccine to prevent SARS-CoV-2 infection. *bioRxiv* 2020.09.04.283853 (2020) doi:10.1101/2020.09.04.283853.

3. Dutta, N. K., Mazumdar, K. & Gordy, J. T. The Nucleocapsid Protein of SARS–CoV-2: a Target for Vaccine Development. *J. Virol.* **94**, (2020).

4. Corthésy, B. Multi-faceted functions of secretory IgA at mucosal surfaces. *Frontiers in Immunology* vol. 4 185 (2013).

5. Xu, Y. *et al.* Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nat. Med.* **26**, 502–505 (2020).

6. Sterlin, D. *et al.* IgA dominates the early neutralizing antibody response to SARS-CoV-2. *Sci. Transl. Med.* **13**, 2223 (2021).

7. Sterlin, D. *et al.* IgA dominates the early neutralizing antibody response to SARS-CoV-2. *Sci. Transl. Med.* **13**, 2223 (2021).

8. Russell, M. W., Moldoveanu, Z., Ogra, P. L. & Mestecky, J. Mucosal Immunity in COVID-19: A Neglected but Critical Aspect of SARS-CoV-2 Infection. *Front. Immunol.* **11**, 3221 (2020).

9. Le Bert, N. *et al.* SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. *Nature* **584**, 457–462 (2020).