Virus-like particles: A practical alternative to cultured rubella virus

The new candidate of choice for antibody discovery, vaccine development and diagnostics.

The diagnosis and management of infectious diseases is critical in the modern medical landscape. Factors such as emerging pathogens, mounting antimicrobial resistance, increasing world travel and changing lifestyles have added layers of complexity to controlling and containing infections.[1] In addition, drug development is a time- and resource-intensive process – with most candidates failing in clinical trials[2] – making effective preventative healthcare measures of the utmost importance to limit disease transmission.[3] The main challenge in addressing infectious diseases is finding efficient, cost-effective ways to enhance immunity, without jeopardizing the safety of vaccinated individuals.

In many countries, a routine immunization schedule now provides early protection to infants and children against infections that are most dangerous at a young age, with additional vaccinations offered throughout the lifespan to provide optimal benefits. Part of this schedule typically includes two doses of the measles, mumps and rubella (MMR) vaccine, a live attenuated vaccine that was introduced in 1988 to protect individuals from three serious and contagious viral diseases.[4] Of these three diseases, rubella virus is recognized as a major public health concern because of the teratogenic potential of infections acquired during pregnancy.[5] An increase in the uptake of vaccinations against rubella virus – and at least 28 other human diseases[6] – has had a significant impact on the number of preventable deaths that occur each year. In fact, between 2010 and 2017, improved vaccination coverage meant that the mortality rate for children under five years of age declined by nearly a quarter.[7]

Approaches to antibody discovery and vaccine development have progressed significantly in recent years, further accelerated by the demands of the COVID-19 pandemic. Immunization methods have shifted from vaccines based on inactivated or live attenuated viruses[3] to more modern approaches, such as mRNA- and vector-based vaccines and virus-like particles (VLPs). Non-infectious VLPs perfectly mimic the surface of infectious virus particles. This not only makes them a safe, efficient and scalable solution for vaccine development, but also means they hold great promise in the field of diagnostics, as they can bind and capture immunoglobulin M (IgM) antibodies that arise during primary infection. The aim of this whitepaper is to discuss the mechanisms, applications and benefits of VLPs in research and development, and the potential that these inactive virus particles hold for improving the diagnosis and prevention of rubella.

The whitepaper will cover:

- The background and evolution of virology;
- The production and mechanisms of VLPs;
- The Native Antigen Company's VLP portfolio;
- Potential applications of VLPs in research and development; and
- The specific application of VLPs for the diagnosis and management of rubella.

1. THE BACKGROUND AND EVOLUTION OF VIROLOGY

1.1. WHAT IS A VIRUS?

Viruses are sub-microscopic infectious agents that are dependent on the intracellular machinery of animal, plant or bacterial cells to multiply.[8] All viruses contain genetic material – either RNA or DNA encoding viral proteins – enclosed within a protective protein coat called a capsid, to form a nucleocapsid. Many virions replicating in eukaryotic cells also have an outer envelope, consisting of host lipids and viral glycoproteins, with some viruses incorporating host cell proteins into their envelopes.[8]

1.2. ADVANCES IN VIROLOGY

Virology – the scientific study of viruses and the diseases they cause – began with the discovery of tobacco mosaic virus by two independent researchers, Dmitri Ivanovsky and Martinus Beijerinck, in the 1890s.[9] These researchers classified viruses as distinct entities from other etiological agents and, since then, more than 5,000 viruses have been described in detail.[10] The evolution of virology has been marked by several significant milestones, including the development of methods to isolate and characterize viruses, recognition of the chemical properties of viruses, and the design and application of vaccines and therapeutics.[9] More recently, advances in virology and molecular biology have led to the development of platforms for the production of VLPs to replace traditional vaccines and diagnostic tools.

2. VIRUS-LIKE PARTICLES

2.1. INTRODUCTION TO VLPS?

VLPs are recombinant structures, built from one or several viral structural constituents, that mimic the outer shell of live virions perfectly – in terms of size, shape and molecular composition – but lack the genetic material required to productively infect host cells.[1,3] Despite being replication-defective and non-infectious, their similar conformation to natural viral particles means that VLPs mimic the antigenic epitopes of live viruses to elicit comparable immunogenic responses.[10,11,12] This makes them ideal candidates for the research and development of diagnostic tests and vaccines.[12]

2.2. MANUFACTURING EFFECTIVE VLPS

VLP production can be a complex and difficult procedure; it requires adequate yields of multiple viral structural proteins, correct assembly of these proteins into particles that imitate the conformation of the outer shells of the infectious virus, and expression of these particles in a system that is both safe and capable of producing multiple proteins on both a small scale (for testing), and on a larger scale (for manufacture).[13] Different types of viruses present different structures and levels of complexity, for example:

- Simple non-enveloped virions – such as parvoviruses and papillomaviruses – contain only nucleic acid encapsulated by one or two capsid proteins;
- Larger non-enveloped viral capsids – like reoviruses – have more than one protein layer, encoded by multiple RNA segments or generated from a single polyprotein;
- More complex viruses have a lipid envelope with viral glycoprotein spikes that act as receptors and membrane fusion agents. Influenza virus, HIV, hepatitis B and C and rubella virus fall into this category.[14]
- To date, a diverse range of VLPs have been synthesized in a variety of expression systems – including bacteria, yeast, mammalian, insect and plant systems – to mimic viruses with single or multiple capsid proteins, with or without lipid envelopes (Figure 1).[15]

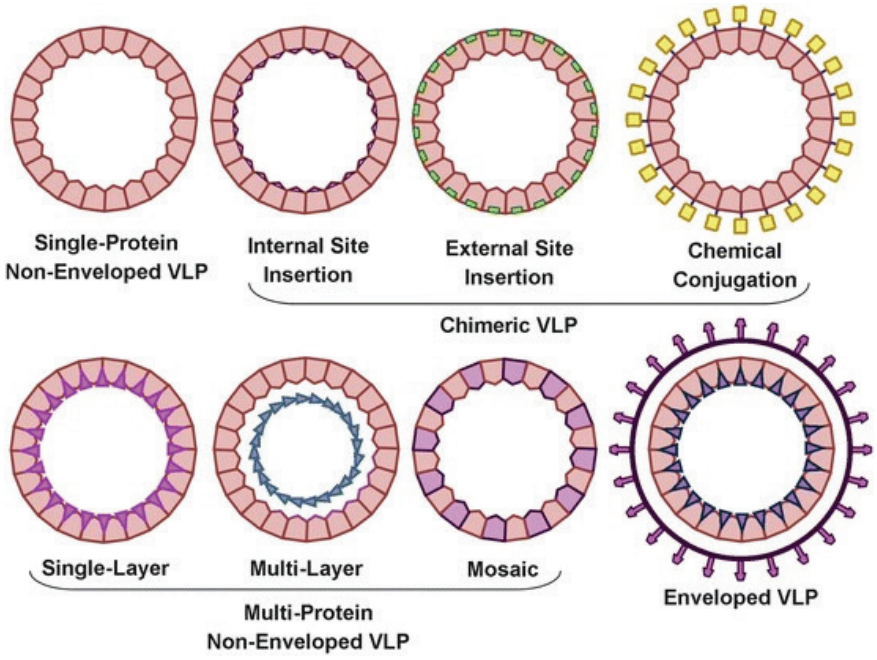

Figure 1: VLPs can be categorized based on their structural complexity, from single-protein particles with relatively simple structures to multi-protein VLPs with several distinct capsid layers.15 Examples of single-protein non-enveloped VLPs include those derived from caliciviruses, papillomaviruses and parvoviruses. Chimeric VLPs contain antigenic material from a target source, inserted as peptides into the VLP capsid protein or substructural secondary VLP proteins, or covalently coupled to the surface of a VLP (e.g. Q-beta phage). Multi-protein non-enveloped VLPs can be derived from infectious bursal disease virus, poliovirus and reoviruses. Rubella VLPs produced by The Native Antigen Company are an example of an enveloped VLP.

2.3. THE NATIVE ANTIGEN COMPANY'S VLP PORTFOLIO

The Native Antigen Company has developed a range of over 20 VLPs using a proprietary VirtuE™ (HEK293) mammalian cell line and insect cell expression systems. These VLPs are designed to display epitopes and glycosylation patterns identical to native viruses, while offering the additional benefit of being both non-infectious and safe to use. Their highly repetitive structural patterns make them ideal antigens for raising and capturing high affinity, high avidity antibodies, and they are also useful for the development of in vitro diagnostic assays and vaccines.

Our range of VLPs includes:

- Rubella VLPs;
- Chikungunya VLPs;
- Mayaro VLPs;
- O'nyong'nyong VLPs;
- Ross River VLPs;
- Dengue serotype 1-4 VLPs;
- Japanese Encephalitis VLPs;
- Ebola VLPs;
- Norovirus VLPs;
- Parvovirus VLPs;
- additional VLPs currently in development or early feasibility studies.

2.4. COMPARING THE STRUCTURE OF VLPS TO NATIVE VIRUSES

A key characteristic of VLPs is their ability to replicate the three-dimensional architecture of native virus particles, with spherical structure and uniform size distribution. Their structure and morphology can be visualized using transmission electron microscopy (TEM), an imaging method that was commonly used before the broad availability of whole genome and RNA sequencing to identify and quantify different viruses based on morphology.[11] The resulting images (Figure 2) demonstrate the close morphological resemblance of VLPs to the corresponding native virion particles.[16]

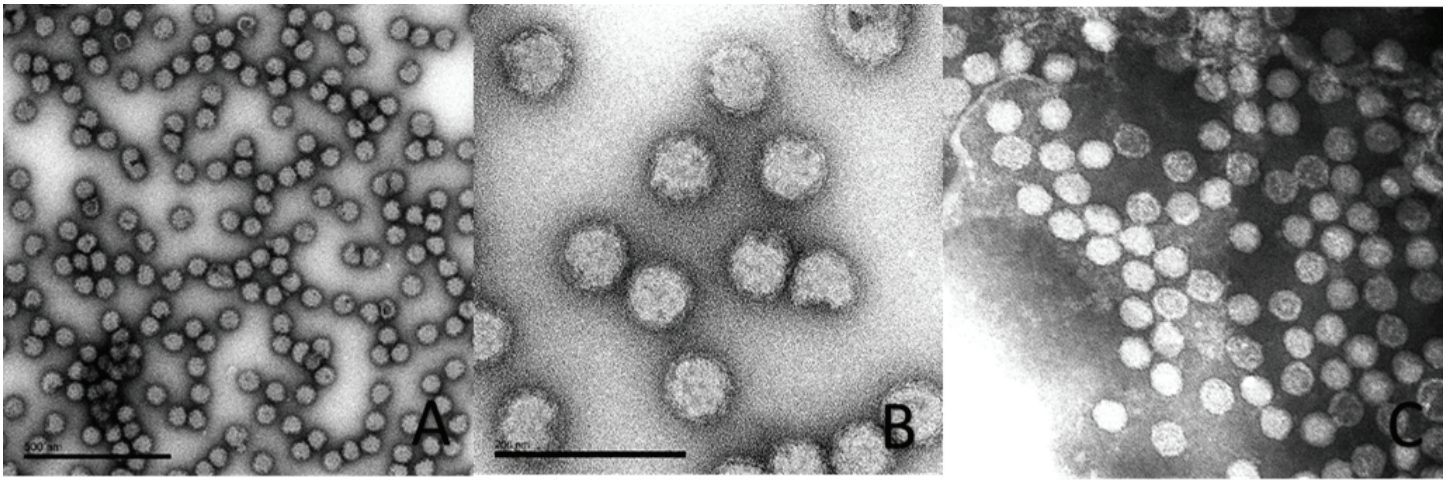

Figure 2: TEM images demonstrate that dengue virus VLPs (A and B) closely resemble native dengue virus particles (C).16,17

Correctly formed VLPs also imitate infectious virions in terms of epitope organization and other physicochemical features.[18] Metz et al. conducted an independent study comparing the similarities in antigenic features of The Native Antigen Company's synthetic VLPs and native virus particles using antibodies against conformational epitopes. The researchers compared four serotypes of live dengue virus particles with four serotypes of VirtuE™-expressed dengue VLPs. Study results confirmed that VLPs display comparable epitope presentation to native dengue virus.[18]

3. POTENTIAL APPLICATIONS OF VLPS IN RESEARCH AND DEVELOPMENT

By mimicking the structure and symmetry of pathogenic viruses, VLPs are recognized, taken up and processed by the immune system in the same way as live viruses, and are therefore effective as both vaccine candidates and as tools for developing in vitro diagnostic tests. They also offer a way to display antigenic epitopes and to deliver small molecules to cells and tissues, and have become important tools in the biomedical field, with a range of potential applications (Figure 1).

3.1. VLPS FOR ANTIBODY DETECTION AND DIAGNOSTICS

As soon as a virus is recognized by the immune system, immunoglobulins – glycoproteins that identify and bind to specific antigenic epitopes on the virion particle – are produced to aid its clearance.[19] As a result, viral serology measurements can be used to detect specific antibodies in serum of an infected human host, confirming present or past infection. The detection of IgM antibodies indicates a recent primary infection, while IgG antibodies can be detected in the later stages of infection, and even years after an infection has cleared.

IgM antibodies usually have low affinity for their targets – due to a lack of affinity maturation – but they present as pentamers when secreted, increasing their avidity for binding to repetitive structures, such as those on viral or bacterial surfaces. As a result, inactivated virus lysates – which include these repetitive structures – are traditional biological components of clinical diagnostic assays. However, to render virus particles safe for use in assay production, they must be exposed to heat and/or detergents, a process which may damage or destroy intact virions, reducing the quality and availability of potential antibody-binding epitopes. In contrast, VLPs do not require such potentially destructive treatment, offering a comparable immune response to native viruses to provide a safe and reliable platform for serology measurements and antibody detection.[20] In addition, their repetitive surfaces allow better binding of patient-derived IgM molecules compared to monomeric antigens and single recombinant proteins.[21]

In recent years, VLP-based enzyme immunoassays – tests that employ an enzyme linked to an antibody to detect antibody-antigen interactions – have been used to characterize immune responses to a variety of viral diseases.[22] In addition, VLPs and other nanoparticles – such as ferritin or heat-shock protein cages – can be modified to allow them to encapsulate the fluorescent dyes, magnetic nanoparticles and contrast agents widely used in diagnostic imaging methods.[23]

3.2. TRANSFORMING VACCINE DEVELOPMENT

Vaccination is one of the most cost-effective ways to control and prevent the spread of infectious diseases.[24] Vaccines introduce epitopes of a pathogen into the body, preemptively triggering a disease-specific protective immune response. During the COVID-19 pandemic, a new generation of vaccine types – which includes mRNA-, DNA- and vector-based vaccines, protein subunits and VLPs – were fast-tracked to approval. These novel vaccines remove whole viruses from the formulation altogether (Figure 3), reducing the risk of incomplete inactivation or reversion of virus particles to a more virulent form.[25,26,27]

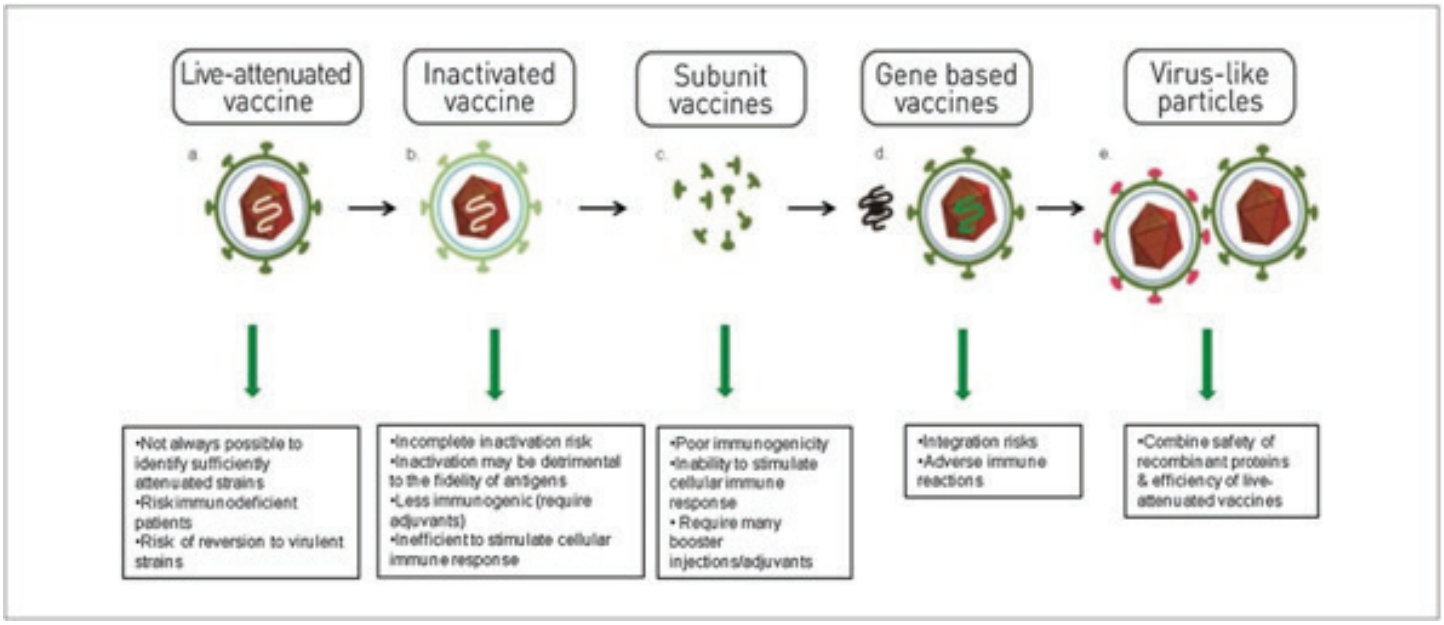

Figure 3: VLPs are part of a new generation of vaccines that remove whole viruses from the formulation, reducing the risk of incomplete inactivation or reversion to pathogenic forms.26

In comparison to other subunit vaccines, VLPs offer high potential as prophylactic and therapeutic vaccine platforms, because they can mimic viral antigenicity – activating strong cellular and humoral immune responses – without being pathogenic. As a result, they do not need to undergo potentially damaging deactivation steps, and therefore offer closer resemblance to their corresponding native virions, enhancing their immunogenicity and specificity.[15] They also offer a variety of additional benefits.

- VLPs have an organized, highly repetitive antigenic epitope array.
- They can be easily recognized and absorbed by antigen presenting cells due to their size (20 to 200 nm).[27]
- They can stimulate both humoral and cellular immune responses.[27]
- Multi-protein VLPs can contain several protein layers to resemble more complex virions, or even variant copies of the same protein derived from different viral strains, to confer multi-strain immunity.[15]
- Some particles can be loaded with immune-modulators – such as innate immune system stimuli – to provoke more effective immune responses.[13]
- VLPs can be generated in a range of production systems.[27]
- VLPs offer a much faster way of synthesizing subunit vaccines, taking as little as 12 to 14 weeks to prepare following the sequencing of an emerging viral strain[3] compared to up to 24 to 32 weeks for culturing and permanent deactivation of whole virus particles.
- The production process is both reproducible – reducing batch-to-batch variance that may be found in cultured viral strains – and scalable.[13]

3.3. OTHER APPLICATIONS

Aside from basic research, diagnostic and immunization purposes, VLPs can be repurposed to incorporate and deliver (a) exogenous oligonucleotides, (b) drug molecules or (c) small proteins to target organs and cells (Figure 4).[24]

a) Genomic information can be packaged into a VLP and delivered to target cells, resulting in expression of the viral gene products.[28] The most successful application of gene therapy to date trialed the use of retroviral vectors to treat X-linked severe combined immunodeficiency (X-SCID), a disease in which the patient lacks both cell-mediated immune responses and the ability to generate antibodies.[28]

b) Therapeutic molecules can be encapsulated by VLPs for delivery and released within host tissues.[29] Adenoviruses are the most commonly used viral vectors for drug delivery.[24]

c) VLPs can be used as carriers and engineered with targeting groups, by attaching a number of proteins or small molecules to their cell membrane, to enhance their specificity.[15,30] Often, these carrier VLPs are engineered to contain amino acids with reactive groups – such as cysteine or lysine groups – which enable easier binding to antigens.[31]

The success of VLPs as diagnostic tools and vaccine candidates has already been demonstrated for a range of viruses, including hepatitis B virus, human papillomavirus (HPV) and hepatitis E virus (HEV).24 Continued advances in the biomedical world will provide new possibilities for better management of numerous other contagious viral infections, including rubella virus.

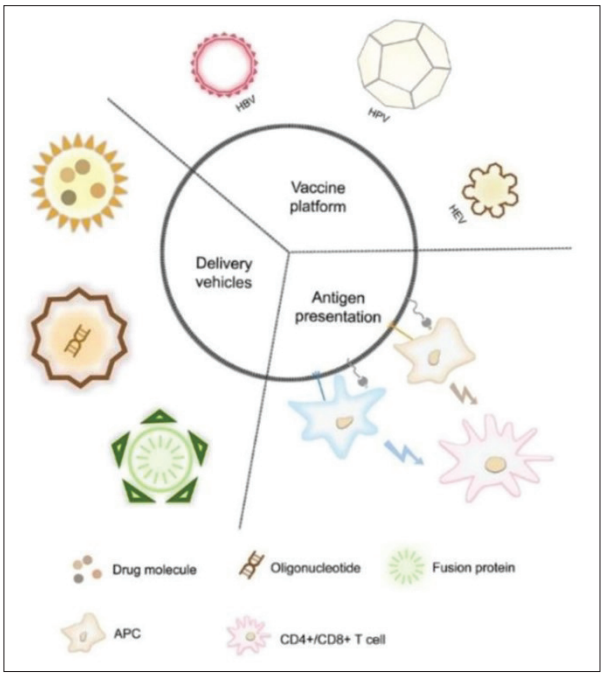

Figure 4: VLPs can be used to carry foreign antigens, to deliver therapeutic cargo, or as a vaccine platform.24

4. RUBELLA VLPS

4.1. CURRENT MANAGEMENT OF RUBELLA VIRUS

Rubella virus is a highly infectious human pathogen, also known as German measles, that is transmitted through the respiratory route and generally causes mild measles-like symptoms in children or adults. However, primary infection of pregnant women with the rubella virus, especially in the first trimester, can result in miscarriage or a collection of long-term birth defects – including incomplete organ development and intellectual disability – known as congenital rubella syndrome (CRS).[32]

Between 2000 and 2019, global uptake of rubella vaccination within routine immunization schedules increased from 99 countries 173 countries.[5] Most rubella vaccines – including MMR – use live attenuated virus, and have been successful in reducing the incidence of CRS.[5] In addition, every pregnant woman in the developed world is now screened for rubella virus antibodies in serum using a TORCH panel assay, which also detects antibodies against several other infectious diseases – including toxoplasmosis, cytomegalovirus and herpes simplex – that can complicate pregnancy.[33]

4.2. DISPLACING THE USE OF CULTURED RUBELLA VIRUS

Due to its prevalence and teratogenic potential, rubella virus is one of the most widely tested viruses on the planet. However, despite the prevalence of rubella testing in a healthcare setting, the virus is notoriously difficult to culture and extremely challenging to propagate at scale. It is therefore a very expensive reagent for diagnostic customers to obtain, and there are additional questions regarding the quality of cultured rubella strains; only the best batches can be used for the detection of early-stage viral infection (IgM), while lower quality batches can only be used for IgG diagnostics.

To overcome these issues, The Native Antigen Company offers rubella VLPs (Figure 5) as part of our portfolio of rubella virus reagents. This range also includes rubella E1 antigens, murine monoclonal IgG antibodies and recombinant human anti-rubella virus IgM antibodies for use in a wide range of research applications. Structurally, rubella virus is a small, enveloped, single-stranded RNA virus in the Matonaviridae family. Virions contain three major structural polypeptides: two membrane glycoproteins (E1 and E2) – which exist as a heterodimer and form the viral spike complexes on the virion surface – and a single non-glycosylated RNA-associated capsid protein (C).[34] Co-expression of all three structural proteins in HEK293 cells leads to the self-assembly and secretion of rubella VLPs,[32] offering a reliable and cost-effective source of reagents to help researchers achieve consistent and accurate results throughout immunoassay development and scale-up manufacturing.

4.3. IMPROVING RUBELLA RESEARCH AND PREVENTION

While vaccines against measles, mumps and rubella are widely used and effective, resurgences and outbreaks are still being reported. The World Health Organization has therefore developed the Measles and Rubella Strategic Framework, with the objective of achieving a world free from measles and rubella infections by 2030.[35] Challenges remain in controlling these diseases, and better vaccine coverage requires both social change and improvements in vaccination infrastructure, management and supply. However, due to the complex, costly and lengthy manufacturing process for current MMR vaccines – in addition to its outdated technology and resulting growth in vaccine hesitancy – it is difficult to respond to increasing requirements for immunization.[35] Therefore, rubella VLPs hold huge potential as a novel platform for rubella research and diagnostics, and offer a scalable, cost-effective route to immunization for vaccine developers.

*Information obtained via personal communications between the manufacturer and users of native rubella virus antigen.

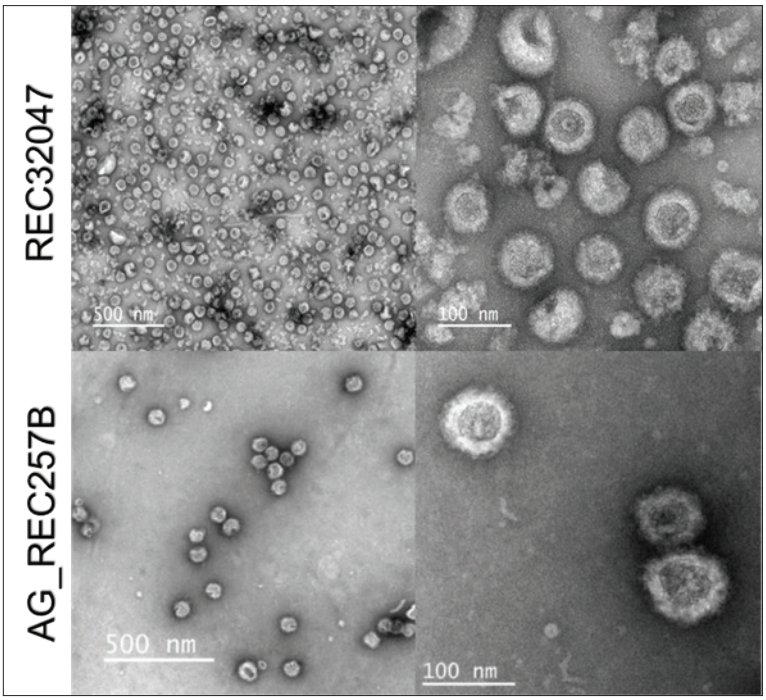

Figure 5: The Native Antigen Company supplies recombinant rubella (strain F-Therien) VLPs consisting of spike glycoprotein E1, spike glycoprotein E2 and capsid protein. These include sucrose-purified rubella VLPs (#REC32047) and sucrose- and ion exchange (IEX)-purified rubella VLPs (#AG_REC257B).

5. SUMMARY

Preventative management of viral infections is vital in the modern medical landscape, and this requires continual innovations in research, diagnostics and immunization approaches. Historically, antibody discovery and vaccine development were primarily based on inactivated or live attenuated viruses,3 but these techniques have their limitations. Instead, VLPs have emerged as part of a new generation of vaccines that offer a safer, more scalable solution. In addition, VLPs have multiple applications, ranging from immunization to drug delivery systems and molecular diagnostics. The success of VLPs has already been demonstrated for a range of viruses, and continuing biomedical advancements will provide new possibilities for better management of numerous other contagious infections, including rubella.

Find out more about our range of VLPs here: https://thenativeantigencompany.com/product-category/all/virus-like-particles/

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ABOUT US

The Native Antigen Company develops and manufacturers premium quality antigens and antibodies as well as offering a range of services to the diagnostic and biopharmaceutical industries. Our proprietary VirtuE™ expression system has been developed for the purpose of producing native-like proteins, which are widely adopted by leading in vitro diagnostic, vaccine and academic groups in cutting-edge R&D, where correct folding and glycosylation are vital. Our contract services range from antibody generation, to scale production of recombinant and native antigens, and bespoke assay development and QC.