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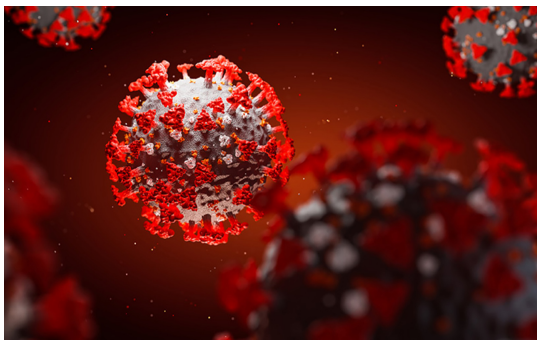
A Nanomaterial Path Forward for COVID-19 Vaccine Development



From mRNA vaccines entering clinical trials, to peptide-based vaccines and using molecular farming to scale vaccine production, the COVID-19 pandemic is pushing new and emerging nanotechnologies into the frontlines and the headlines.

Nanoengineers at UC San Diego detail the current approaches to COVID-19 vaccine development, and highlight how nanotechnology has enabled these advances, in a review article in *Nature Nanotechnology* published July 15.

“Nanotechnology plays a major role in vaccine design,” the researchers, led by UC San Diego Nanoengineering Professor Nicole Steinmetz, wrote. Steinmetz is also the founding director of UC San Diego’s Center for Nano ImmunoEngineering. “Nanomaterials are ideal for delivery of antigens, serving as adjuvant platforms, and mimicking viral structures. The first candidates launched into clinical trials are based on novel nanotechnologies and are poised to make an impact.”

Steinmetz is leading a National Science Foundation-funded effort to develop—using a plant virus— a stable, easy to manufacture COVID-19 vaccine patch that can be shipped around the world and painlessly self-administered by patients. Both the vaccine itself and the microneedle patch delivery platform rely on nanotechnology. This vaccine falls into the peptide-based approach described below.

“From a vaccine technology development point of view, this is an exciting time and novel technologies and approaches are poised to make a clinical impact for the first time. For example, to date, no mRNA vaccine has been clinically approved, yet Moderna’s mRNA vaccine technology for COVID-19 is making headways and was the first vaccine to enter clinical testing in the US.”

As of June 1, there are 157 COVID-19 vaccine candidates in development, with 12 in clinical trials.

Nanoengineering Professor Nicole Steinmetz is using a plant virus to develop a COVID-19 vaccine patch.

“There are many nanotechnology platform technologies put toward applications against SARS-CoV-2; while highly promising, many of these however may be several years away from deployment and therefore may not make an impact on the SARS-CoV-2 pandemic,” Steinmetz wrote. “Nevertheless, as devastating as COVID-19 is, it may serve as an impetus for the scientific community, funding bodies, and stakeholders to put more focused efforts toward development of platform technologies to prepare nations for readiness for future pandemics,” Steinmetz wrote.

To mitigate some of the downsides of contemporary vaccines—namely live-attenuated or inactivated strains of the virus itself—advances in nanotechnology have enabled several types of next-generation vaccines, including:

Peptide-based vaccines

Using a combination of informatics and immunological investigation of antibodies and patient sera, various B- and T-cell epitopes of the SARS-CoV-2 S protein have been identified. As time passes and serum from convalescent COVID-19 patients are screened for neutralizing antibodies, experimentally-derived peptide epitopes will confirm useful epitope regions and lead to more optimal antigens in second-generation SARS-CoV-2 peptide-vaccines. The National Institutes of Health recently funded La Jolla Institute for Immunology in this endeavor.

Peptide-based approaches represent the simplest form of vaccines that are easily designed, readily validated and rapidly manufactured. Peptide-based vaccines can be formulated as peptides plus adjuvant mixtures or peptides can be delivered by an appropriate nanocarrier or be encoded by nucleic acid vaccine formulations. Several peptide-based vaccines as well as peptide-nanoparticle conjugates are in clinical testing and development targeting chronic diseases and cancer, and OncoGen and University of Cambridge/DIOSynVax are using immunoinformatics-derived peptide sequences of S protein in their COVID-19 vaccine formulations.

An intriguing class of nanotechnology for peptide vaccines is virus like particles (VLPs) from bacteriophages and plant viruses. While non-infectious toward mammals, these VLPs mimic the molecular patterns associated with pathogens, making them highly visible to the immune system. This allows the VLPs to serve not only as the delivery platform but also as adjuvant. VLPs enhance the uptake of viral antigens by antigen-presenting cells, and they provide the additional immune-stimulus leading to activation and amplification of the ensuing immune response. Steinmetz and Professor Jon Pokorski received an NSF Rapid Research Response grant to develop a peptide-based COVID-19 vaccine from a plant virus: https://jacobsschool.ucsd.edu/news/news_releases/release.sfe?id=3005. Their approach uses the Cowpea mosaic virus that infects legumes, engineering it to look like SARS-CoV-2, and weaving antigen peptides onto its surface, which will stimulate an immune response.

Their approach, as well as other plant-based expression systems, can be easily scaled up using molecular farming. In molecular farming, each plant is a bioreactor. The more plants are grown, the more vaccine is made. The speed and scalability of the platform was recently demonstrated by Medicago manufacturing 10 million doses of influenza vaccine within one month. In the 2014 Ebola epidemic, patients were treated with ZMapp, an antibody cocktail manufactured through molecular farming. Molecular farming has low manufacturing costs, and is safer since human pathogens cannot replicate in plant cells.

Nucleic-acid based vaccines

For fast emerging viral infections and pandemics such as COVID-19, rapid development and large scale deployment of vaccines is a critical need that may not be fulfilled by subunit vaccines. Delivering the genetic code for in situ production of viral proteins is a promising alternative to conventional vaccine approaches. Both DNA vaccines and mRNA vaccines fall under this category and are being pursued in the context of the COVID-19 pandemic.

- DNA vaccines are made up of small, circular pieces of bacterial plasmids which are engineered to target nuclear machinery and produce S protein of SARS-CoV-2 downstream.
- mRNA vaccines on the other hand, are based on designer-mRNA delivered into the cytoplasm where the host cell machinery then translates the gene into a protein – in this case the full-length S protein of SARS-CoV-2. mRNA vaccines can be produced through in vitro transcription, which precludes the need for cells and their associated regulatory hurdles

While DNA vaccines offer higher stability over mRNA vaccines, the mRNA is non-integrating and therefore poses no risk of insertional mutagenesis. Additionally, the half-life, stability and immunogenicity of mRNA can be tuned through established modifications.

Several COVID-19 vaccines using DNA or RNA are undergoing development: Inovio Pharmaceuticals has a Phase I clinical trial underway, and Entos Pharmeuticals is on track for a Phase I clinical trial using DNA. Moderna's mRNA-based technology was the fastest to Phase I clinical trial in the US, which began on March 16th, and BioNTech-Pfizer recently announced regulatory approval in Germany for Phase 1/2 clinical trials to test four lead mRNA candidates.

Subunit vaccines

Subunit vaccines use only minimal structural elements of the pathogenic virus that prime protective immunity—either proteins of the virus itself or assembled VLPs. Subunit vaccines can also use non-infectious VLPs derived from the pathogen itself as the antigen. These VLPs are devoid of genetic material and retain some or all of the structural proteins of the pathogen, thus mimicking the immunogenic topological features of the infectious virus, and can be produced via recombinant expression and scalable through fermentation or molecular farming. The frontrunners among developers are Novavax who initiated a Phase I/II trial on May 25, 2020. Also Sanofi Pasteur/GSK, Vaxine, Johnson & Johnson and the University of Pittsburgh have announced that they expect to begin Phase I clinical trials within the next few months. Others including Clover Biopharmaceuticals and the University of Queensland, Australia are independently developing subunit vaccines engineered to present the prefusion trimer confirmation of S protein using the molecular clamp technology and the Trimer-tag technology, respectively.

Delivery device development

Lastly, the researchers note that nanotechnology's impact on COVID-19 vaccine development does not end with the vaccine itself, but extends through development of devices and platforms to administer the vaccine. This has historically been complicated by live attenuated and inactivated vaccines requiring constant refrigeration, as well as insufficient health care professionals where the vaccines are needed.

"Recently, modern alternatives to such distribution and access challenges have come to light, such as single-dose slow release implants and microneedle-based patches which could reduce reliance on the cold chain and ensure vaccination even in situations where qualified health

care professionals are rare or in high demand," the researchers write. "Microneedle-based patches could even be self-administered which would dramatically hasten roll-out and dissemination of such vaccines as well as reducing the burden on the healthcare system."

Pokorski and Steinmetz are co-developing a microneedle delivery platform with their plant virus COVID-19 vaccine for both of these reasons.

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"Advances in bio/nanotechnology and advanced nanomanufacturing coupled with open reporting and data sharing lay the foundation for rapid development of innovative vaccine technologies to make an impact during the COVID-19 pandemic," the researchers wrote. "Several of these platform technologies may serve as plug-and-play technologies that can be tailored to seasonal or new strains of coronaviruses. COVID-19 harbors the potential to become a seasonal disease, underscoring the need for continued investment in coronavirus vaccines

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