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The Buyer's Guide for Life Scientists

Technologies Reshaping Vaccine Research and Development

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The goal of most vaccinations is to stimulate the immune system to generate a protective response, enabling the host to deal with a potential threat it may encounter in the future. This was initially done by introducing a killed or attenuated, or perhaps related but less harmful, pathogen. The immune system would then learn to recognize associated immunogenic proteins and build up a defensive cache of cells and antibodies that allow it to neutralize the pathogen, before actually being susceptible to the effects of the pathogen itself.

Vaccine development typically took about 10 to 15 years. “COVID-19 and the immediate need for vaccines sparked a revolution in vaccine development, speeding up the process from years to months,” notes Steve Siembieda, Product Marketing Director—Biomolecular Analysis Division, Agilent Technologies.

In fact, CEPI (Coalition for Epidemic Preparedness Innovations) has as one of its missions for vaccines to be ready for initial authorization and production in just 100 days after a threat of a pandemic has been recognized, according to the global partnership’s website. They advocate having pipeline platforms ready to plug in the specifics of a new threat.

Getting started

“When it comes to vaccine design, the first thing we are always interested in is understanding what antibodies are typically generated by an infected person,” says Melanie Adams-Cioaba, Senior Director and General Manager of Pharma/BioTech for Electron Microscopy at Thermo Fisher Scientific. “That is the first question—so anything to do with antibody purification and characterization become really important techniques.”

Among these are plate-based ELISA methods, mass spectrometry, and other biophysical techniques such as surface plasmon resonance and interferometry measurements, to understand patients’ antibody repertoires in a high-throughput and fast manner. All of these technologies are important to help zero in on more high-resolution information about certain

antibodies and their interactions with specific viral antigens, like the SARS CoV-2 spike protein, for example, she notes.

In part, that allows for an understanding the "hot spots" of where populations of antibodies are binding. Once an epitope map is created, typically some of those epitopes are selected for more detailed, higher resolution, studies.

Structure

Rational design of vaccines should be guided by the immune system's response to pathogens. We want to know when the immune system generates broadly neutralizing antibodies. We also want to understand which proteins comprise the outer shell of the virus—the part that is most visible to the immune system—"not only what they are, but also what shape they take, and what are the properties of those shapes," Adams-Cioaba explains.

Structural-based techniques such as x-ray crystallography can generate very high-resolution images of antigens, as well as antigens bound to antibodies, at high throughput. But its associated challenges have led to the rise, over the past ten years, of cryo-electron microscopy (Cryo-EM). Cryo-EM is typically favored for systems that are very challenging to crystalize, such as highly dynamic systems and large systems. And because it allows for imaging without the need to crystalize, protein complexes can be imaged in solution or close to a native state, sometimes in hours.

"With Cryo-EM we can take a snapshot of millions and millions of particles and extract the different conformations from there—so, alternative snapshots of motion and dynamics," Adams-Cioaba says. "When we think of vaccine design in particular, a lot of these spike proteins and surface proteins undergo significant conformation changes. Where and when the antibodies bind is dependent on the shape and change of shape of these surface proteins."

As was done in the case of many of the vaccines against COVID 19, the most promising of these are proteins represented as mRNA to be transcribed and then translated by the host. "In the R&D phase, researchers can spend a lot of time iterating vaccine designs to optimize performance before moving downstream into scale-up and clinical testing," says Randy Dyer, VP of Marketing at Elegen. Use of the company's high-accuracy, linear, cell-free DNA template to make that mRNA alleviates some of the tedium and error-points of traditional cloning in bacteria, such as the potential for endotoxins, allowing development cycles to be accelerated. The sequence space for potential vaccine candidates can be broadened by using a cell-free chemical process that allows for DNA templates that are toxic to a bacterial host.

Delivery

Vaccines are not just immunogens that mimic or derive from pathogens. Increasingly, they can also leverage novel delivery platforms, such as lipid nanoparticles (LNPs), which can be complex to design and formulate. In addition to different lipid components themselves there are various

buffer or additive components. There are also differing methods to form those LNPs with their cargo (mRNA for example), with some groups preferring microfluidic mixing while others use more of a mix-and-incubate strategy, notes Adams-Cioaba.

Groups will form various LNPs using an assortment of methods, take samples of those, and use biophysical methods to estimate properties such as size, mass, consistency, homogeneity, and try to correlate these with formulations and strategies. “But it can be very difficult to distinguish if the LNP morphology is what you expect it to be: Is it spherical? Does it have the right outer- and inner structures associated with it? Does it exhibit a bleb, which almost looks like a conjoined twin of a blob? Are these morphologies stable over a course of freeze-thaw cycles?” she asks. “Really only direct imaging allows us to make sure that the LNPs are forming correctly.”

Along with LNPs, researchers are looking at variety of other delivery technologies including liposomes and outer membrane vesicles, organic and inorganic polymeric particles, and other immunostimulating complexes. Viral vector vaccines can be used to deliver genetic material, and subunit vaccines can deliver parts of a pathogen, to elicit an immune response, adds Siembieda.

And of course developing such formulations in the lab is just a precursor to determining their safety and efficacy, as well as their suitability for large-scale manufacturing.

AI and bioinformatics

With all the hype about AI of late, it should come as no surprise that neural network models of machine learning and bioinformatics have infiltrated nearly every aspect of vaccine design—from immunogen selection and delivery vehicle formulation to patient recruitment and the design of clinical trials—as well. It can deal with enormous datasets, taking disparate, complex inputs such as text, images, and sequence data and extract and classify features and patterns, allowing for the discovery and prediction of complex, non-linear relationships between and among them.

Examples include using AI to predict the amino acid sequences on a T cell receptor that will bind to a given peptide, and in what context. AI can help predict which epitope might be best to target a vaccine to a given population. And similarly, in the fields of cancer immunotherapy and autoimmune disease a patient’s specific omics data can be used to identify neoantigens and autoantigens, allowing for the design of personalized vaccines.