THE FRONT ROW
at Scripps Research



Controlling the where, when and how long of vaccine delivery

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ABOUT THE LECTURE

For vaccines to provide long-lasting protection from a disease, they must be optimized to promote specific, strong and durable immune responses. In his Front Row lecture, Scripps Research professor and Lita Annenberg Hazen Chair Darrell Irvine discussed chemical engineering approaches from his lab designed to steer the timing and location of vaccines and immunotherapies to enhance immune responses against HIV and cancer. Irvine emphasized how controlling these factors may be critical for next-generation immunotherapies and vaccines to reach their potential while remaining safe.

TOP TAKEAWAY POINTS

- Vaccines train the immune system to recognize specific threats and prepare to fight them if exposure occurs. They contain two key components: an antigen, which is the molecule the immune system recognizes and that prompts a protective response, and an adjuvant, which stimulates the innate arm of the immune system. Irvine emphasized how vaccines have transformed global health and saved millions of lives, causing cases of many severe diseases to plummet, including diphtheria, measles and meningococcus.

- Some diseases have been especially challenging to develop vaccines for. HIV, for example, has one protein on its surface that's the most common vaccine target—but this protein has only a few sites that don't constantly mutate to evade immune recognition. A promising strategy is to guide the immune system to produce broadly neutralizing antibodies (bnAbs), which bind to these stable sites. But immature B cells capable of producing bnAbs once mature are rare, and they must compete with other B cells that make less effective antibodies targeting unstable sites.

- Irvine's team discovered a way to help these rare, immature B cells develop toward producing bnAbs: by extending the vaccine dosing strategy. He showed that splitting the vaccine into six doses over a couple of weeks helped "load up" the antigen into B cell follicles in the lymph node, resulting in large increases in on-target B cells and antibody responses in preclinical models and early clinical testing.

- Despite these benefits, receiving six shots over multiple weeks for a single vaccination isn't a practical regimen. So, Irvine's team developed a way to mimic this extended dosing effect with a single shot by anchoring the HIV antigen to an adjuvant called alum, which slowly releases the antigen over time. In preclinical models, the engineered single-shot approach had similar effects to those of the extended dosing regimen, showing its potential as a practical delivery solution that maintains the benefits of extended dosing.

- Irvine described how this alum-anchoring technology is being applied to cancer. Every tumor accumulates different combinations of mutations, so to avoid needing to personalize a drug for each unique tumor, Irvine proposed an approach that uses antigens from the tumor itself. By adapting the alum-anchoring technology to hold IL-12 (a protein that activates immune cells) and injecting it directly into tumors, Irvine could stimulate the immune system to attack tumors in preclinical models. Ankyra Therapeutics, a spin-out company that Irvine co-founded, is now further developing the approach and testing it in clinical trials.

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