Scientists discover PVP-037, a potent vaccine adjuvant

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Many vaccines are only partially effective, have waning efficacy, or do not work well in the very young or the very old. For more than a decade, Ofer Levy, MD, Ph.D., and David Dowling, Ph.D., in the Precision Vaccines Program at Boston Children's Hospital, have tried improving vaccines by adding compounds known as adjuvants to boost vaccine

recipients' immune responses.

Now they've identified a new and promising adjuvant of their own, dubbed PVP-037. The finding is published in *Science Advances*.

"In principle, this compound can be added to any vaccine to enhance its action," says Levy, who directs the Precision Vaccines Program. "Adjuvants are like rocket fuel for the immune system. PVP-037 is one of the most active adjuvants we've discovered, and we think it induces a greater, more durable, and broader immune response to vaccines."

Robust innate immune responses

The researchers began by screening more than 200,000 small molecules from a Harvard Medical School library in human immune cells—specifically, in primary peripheral blood mononuclear cells, obtained from donors and cultured in their own plasma using a method developed within the Precision Vaccines Program. This yielded about 25 confirmed hits, with PVP-037 being the most active.

PVP-037 belongs to a family of molecules called imidazopyrimidines, which the study found to be active immunomodulators. PVP-037 and its analogs target the innate immune system, stimulating the pattern-recognition receptors TLR7 and TLR8 on antigen-presenting cells such as monocytes and dendritic cells.

"Screening small molecules against human primary cells is messier than using a homogenous cell line, because each individual is different," says Levy. "But that's the whole point: It's more reflective of human biology. A good adjuvant needs to be able to work across diverse populations. PVP-037 would not have been discovered by screening cell culture lines."

An optimized version of PVP-037 demonstrated broad innate immune activation in the donor immune cells, inducing NF-κB and production of TNF and other cytokines, signaling molecules that rally a wider immune response. Notably, PVP-037 did not provoke such a response in cultured cell lines. In live mice, it enhanced antibody responses against influenza and SARS-CoV-2 vaccine proteins.

Especially exciting to Levy and Dowling is that in addition to inducing robust immune activity, the compound is stable, easy to work with, and lends itself to chemical optimization for medical use. It can be formulated in most standardly-used drug delivery systems, such as oil-in-water emulsions.

"We did something special with the discovery of PVP-037," says Dowling. "Our work essentially condensed the full vaccine development pipeline—including analog optimization, establishing the mechanism of action, and creating an optimized formulation."

On tap: Tests against flu, whooping cough, and fentanyl

Boston Children's holds multiple patents on these discoveries, with Levy and Dowling as named inventors. They plan to assess PVP-037 across all age groups and test its ability to enhance immune responses to influenza and pertussis (whooping cough) vaccines as well as an opioid vaccine aimed at preventing fentanyl overdose deaths. The patents also cover potential uses of imidazopyrimidines as immunomodulatory compounds for allergy and cancer—additional future lines of research.

"Overall, we hope our precision vaccine approach will inspire others to adopt a similar innovation strategy for discovery and development of adjuvants and vaccines," says Dowling.

More information: Dheeraj Soni et al, From Hit to Vial: Precision discovery and development of an imidazopyrimidine TLR7/8 agonist adjuvant formulation, *Science Advances* (2024). DOI: 10.1126/sciadv.adg3747. www.science.org/doi/10.1126/sciadv.adg3747