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A vaccine that works in newborns? Promising compound may help protect babies during vulnerable window

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The underdeveloped immune systems of newborns don't respond to most vaccines, leaving them at high risk for infections like rotavirus, pertussis (whooping cough) and pneumococcus. Researchers at Boston Children's Hospital have identified a potent compound that activates immune responses in newborns' white blood cells substantially better than anything previously tested, and that could potentially make vaccines effective right at birth.

The ability to immunize babies at birth—rather than two months of age, when most current vaccination series begin—would be a triumph for global health. Worldwide, each year, infections kill more than 2 million infants under 6 months old. In resource-poor countries, birth may be the only time a child has contact with a health care provider.

While newborns lack most aspects of the immune response, researchers led by Ofer Levy, MD, PhD, of the Division of Infectious Disease at Boston Children's have shown that their white blood cells do have one receptor that responds strongly to stimulation, known as Toll-like receptor 8 (TLR 8). In their new work, published March 4 by the online open-access journal PLoS ONE, they tested a panel of synthetic small-molecule compounds that specifically target TLR8, known chemically as benzazepines.

The compounds, provided by VentiRx Pharmaceuticals (Seattle, WA),

potently stimulate the human immune system and are in clinical trials in patients with certain cancers.

Tested in Levy's lab, one benzazepine, VTX-294, produced a strong immune response in white blood cells from newborns (taken from cord blood samples) as well as whole blood from adults. It induced robust production of cytokines—chemicals that rally the immune response—and proved at least 10 times more potent than the best activator of TLR8 known previously.

"The response was not only equal to that in adults, but VTX 294 was sometimes actually more effective in newborns than adults," notes Levy, the study's senior investigator.

The compound also triggered production of so-called co-stimulatory molecules that enhance immune responses. Moreover, even very low concentrations of VTX-294 strongly activated antigen-presenting cells, a type of white blood cell whose activation induces immune memory—key to effective responses to vaccines.

Toll-like receptors (TLRs), first identified in humans about two decades ago, are part of the innate (rapid) immune response that provides our first defense against infections. Ten types of TLRs are known, and TLR stimulators have begun to be added to vaccines as adjuvants. The main one, monophosphoryl lipid A (MPLA), stimulates TLR4 and is used in the human papillomavirus vaccine Cervarix. However, in a recent clinical trial published in The New England Journal of Medicine, a malaria vaccine with MPLA failed to elicit a sufficient immune response in infants.

With encouraging results in cells from human newborns, Levy and colleagues now hope to formulate VTX 294 or a similar TLR8 stimulator for testing as a vaccine adjuvant in newborn primates, a

model in which the lab has expertise, and whose responses to TLR8 closely resemble humans'.

"This one receptor seems to lead to more adult-like responses—immediate, short-term responses that are more appropriate for fighting infections," says David Dowling, PhD, co-first author on the study. "We're excited about the benzazepines because they are already in the clinical pipeline. That advances the potential for using them in a clinical study in human newborns, once they have been proven safe in animal studies."

Provided by Children's Hospital Boston

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