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Elucidation of structural activity relationships of Lipid A-based TLR4 mimetic adjuvants in a bacterial subunit vaccine

***Jerilyn R. Izaca, Matthew E. Shermana, Etsuro Nanishib,c, Timothy R. O'Mearab,c, David J. Variscoa, Jocelynn Duvalla, Richard D. Smitha, Alison J. Scotta, David J. Dowlingb,c and Robert. K. Ernsta**

[a] *University of Maryland Baltimore, USA*
[b] *Boston Children's Hospital, USA*
[c] *Harvard Medical School, USA*

Background:

Immunoadjuvants are key components in vaccine formulations that enhance and shape immune responses to vaccines. We have previously demonstrated the ability to rapidly generate novel lipid A (LA) structures with potent adjuvant capabilities using Bacterial Enzymatic Combinatorial Chemistry (BECC). BECC utilizes expression or deletion of enzymes involved in the LA synthesis pathway for Gram-negative bacteria to purify TLR4 without further modifications. In this study, we evaluated 12 structurally different BECC molecules and tested their adjuvant capabilities in vitro and in in vivo models. All BECC molecules were tested for induction of NF-kb in immortalized murine and human cells and TNF-a, in pbmcs obtained from adult and elderly volunteers. To determine in vivo efficacy, C57BL/6 mice were vaccinated with each adjuvant and the recombinant Y. Pestis F1-V antigen in a prime-boost model. We also tested these adjuvants in an Influenza H1N1 challenge model using hemagglutinin as the antigen in BALB/c mice. Survival and weight loss were used to assess protective efficacy. Additionally, antibody levels and isotyping were measured to compare all adjuvant/ antigen combinations. Splenocytes were harvested in immunized mice and cytokine production was assessed via Luminex.

Results and Conclusions:

The most and least immunostimulatory molecules in vitro did not provide complete protection during challenge, demonstrating an optimal range of stimulation is needed for TLR4-mimetic adjuvants. Based on the splenocyte restimulation assay, different memory responses were produced depending on structure. The data from this study elucidates structure- activity mechanisms by evaluating adjuvant capability both in vitro and in vivo. Based on lipid A structure, we found significant differences in antibody production,

isotype generation, stimulation of pbmcs and in vitro cell lines, as well as protective efficacy that was structure dependent. Future research includes investigating these adjuvants in humanized mice that have been genetically engineered to have the htlr4/hmd-2 pathway.

Biography

Jerilyn R. Izac is currently working as a Microbiologist at National Institute of Standards and Technology (NIST), USA. She received her Post-Doctoral Degree from the University of Maryland Baltimore, USA. Her research mainly focusses on Microbiology and Immunology related areas.

Jizac@umaryland.edu