Innate immunity for biodefense: A strategy whose time has come

Catherine Amlie-Lefond, MD,[a] David A. Paz, BS,[a] Mary P. Connelly, BS,[a] Gary B. Huffnagle, PhD,[b] Kyle S. Dunn, BS,[c] Noel T. Whelan, MS,[a] and Harry T. Whelan, MD[a] *Milwaukee, Wis, Ann Arbor, Mich, and Washington, DC*

Defense against biothreat agents requires a broad-spectrum approach. Modulation of the innate immune system might fulfill this requirement. Hackett's previous review of innate immune activation as a broad-spectrum biodefense strategy identified several unresolved questions. The current article is a systematic approach to answering those questions with the focused participation of research groups developing this technology. Our team of academic and industry participants reviewed the promising agents and came to the following conclusions. It is feasible to construct a biodefense platform combining synergistic agents that activate the innate immune system against a broad range of pathogens on the basis of conserved microbial components by using a nasal spray for immune activation in the respiratory and gastrointestinal tracts because these are the most likely routes of attack. It might also be possible to include agents that inhibit molecular events leading to septic shock. Innate immune-activating agents designed to activate Toll-like and other receptors will probably provide protection against the biothreat pathogen spectrum for periods ranging from 2 to 14 days for IFNs up to 26 weeks for immunomodulatory oligonucleotides. Initial treatment is proposed on the first index case or biosensor alert. Boost doses would be required. Harmful inflammation is possible, but thus far, only transient fever has been observed. Autoimmune reaction and retroviral activation have not been seen thus far in preclinical and human trials of many of these compounds. Toll-like receptor agonists caused cytokine production in all subjects tested, but genetic polymorphism reduced the response to IFN in African American subjects. (J Allergy Clin Immunol 2005;116:1334-42.)

Key words: *Biodefense, immunomodulation, innate immunity, Toll-like receptors*

THE BIODEFENSE PROBLEM

A bioterror attack requires an immediate and effective response. Vaccines are limited by the inability to predict the pathogen and resistance to prophylactic vaccination. The inherent delay in adaptive immune response renders it inadequate for protection from bioterror attack. Innate immunity is an underexplored option for biodefense. Recent therapeutic advances suggest that innate immunomodulation holds the potential for improved survival after a bioterror attack with an infectious agent. Numerous products targeting various processes in the innate immune response are either currently available and moving toward human trials or in the initial stages of development.

In-depth investigation into opportunities offered by innate immunity for biodefense is currently lacking.

Innate immune cells use pathogen recognition receptors to recognize pathogen macromolecules to provide an immediate response with broad specificity. The pathogen-associated molecular pattern system of Toll-like receptors (TLRs) comprises cell-surface and endosomic receptors that recognize broadly conserved ligands unique to microorganisms. Currently, one TLR agonist is licensed for use in human subjects for certain viral infections and skin cancers, and other agonists are in advanced stages of clinical development. TLRs might be exploited against bioterrorism agents on the basis of their mechanism of action; however, excessive activation of the innate immune system can result in autoimmune disease and septic shock.[1] These issues are the focus of this investigation.

QUESTIONS ABOUT INNATE IMMUNITY FOR BIODEFENSE

In November 2004, a panel of invited experts met to consider the feasibility of innate immune modulation as

From [a]the Department of Neurology, Medial College of Wisconsin; [b]the Department of Internal Medicine and Microbiology and Immunology, University of Michigan; and [c]the Center for Technology and National Security Policy, National Defense University, Washington, DC.

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Reprint requests: Harry T. Whelan, MD, Bleser Professor of Neurology, Medical College of Wisconsin, 8701 Watertown Plank Rd, Milwaukee, WI 53226. E-mail: hwhelan@mcw.edu.

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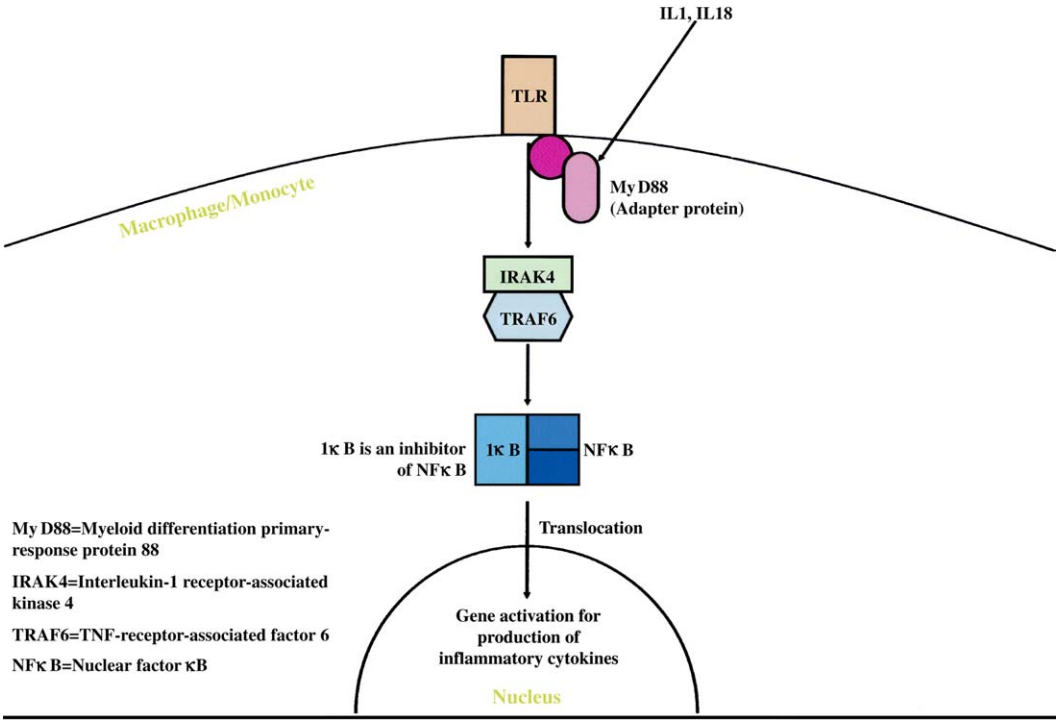

FIG 1. Common pathway used by TLRs for signal transduction.

Abbreviations used

BTA: Biothreat agent
DC: Dendritic cell
FDA: US Food and Drug Administration
HBV: Hepatitis B virus
HCV: Hepatitis C virus
HMGB1: High mobility group box 1
HPV: Human papillomavirus
HSV: Herpes simplex virus
IMO: Immunomodulatory oligonucleotide
IRM: Immune response modifier
NK: Natural killer
ODN: Oligodeoxynucleotide
TLR: Toll-like receptor

biodefense, including the risks in stimulating innate immunity, current resources, the time needed to develop and produce effective agents, and interfacing with regulatory agencies. At the conclusion of the meeting, technical documents describing the application of a particular product or technology to biodefense were requested.

In collaboration with independent reviewers, proposals were evaluated on compound–mechanism of action, potential activity, likelihood of product approval within 5 years, uniqueness, and overall grade. Criteria for evaluating this approach have been published by Hackett[1] and were applied to submitted technologies. Questions raised by Hackett include the following:

1. Which innate immune receptors stimulate effective prophylactic responses to the broadest range of bacterial and viral pathogens?
2. How long does protection last?
3. Could innate immune therapy trigger harmful inflammation?
4. Will innate immune stimulation promote autoimmune reactions or retroviral activation?
5. How important a factor is human genetic polymorphism within the innate immune system for innate immune therapy strategies?

ANSWERING THE QUESTIONS: PROS AND CONS TO FUTURE PATHS—INNATE IMMUNOMODULATION

Innate immune cells use pathogen recognition receptors to recognize pathogen macromolecules and promote rapid response. As mentioned above, TLRs are type I transmembrane and endosomically expressed proteins that are evolutionarily conserved and have been identified as the key pathogen recognition receptors in innate immunity. TLRs 1 through 10 are present on human innate immune cells and act through cellular signal cascade to augment host immune response through inflammation. TLR agonists can modify host inflammatory responses, potentially offering increased protection from infection. Currently, TLR agonists are licensed and being used in human subjects in the setting of microbial infection and cancer.