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Small Molecule Inhibitors of Toll-Like Receptor 3 for Treatment of Inflammatory and Infectious Diseases

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TECHNOLOGY
TRANSFER
OFFICE

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Boulder + Colo. Springs
4740 Walnut Street
Suite 100
Campus Box 589
Boulder, CO 80309

(303) 492-5647

———

Denver + Anschutz
Medical Campus
12635 E. Montview Blvd
Suite 350
Campus Stop F411
Aurora, CO 80045

303-724-0221

———

www.cu.edu/techtransfer

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Patent pending; available for exclusive or non-exclusive licensing.

Case Manager:
Molly Markley
molly.markley@cu.edu

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Background

Much of the research on immunomodulation has focused on targeting the cells and processes of the adaptive immune system, yet it is the innate immune system that provides the first line of defense against infection. The innate immune system is composed of various cells and mechanisms that play a critical role in initiating an immune response, and includes a family of proteins known as the Toll-like receptors (TLRs). TLRs are a class of transmembrane proteins that detect pathogen-associated molecular patterns (PAMPs) and elicit pathogen-specific immune responses. One of these receptors, Toll-like Receptor 3, (TLR3), is activated by double-stranded RNA (a form of genetic information found in some viruses) that is released from dying cells during inflammation or viral infection. Activation of TLR3 leads to the release of pro-inflammatory cytokines, triggering an immune response. Paradoxically, TLR3 activation can result in further infection and inflammation, and has been shown to contribute to morbidity and mortality in herpes simplex encephalitis and in certain viral infections, including the West Nile virus, phlebovirus, vaccinia, and influenza. Therefore, modulation of TLR3 pathways offers an attractive strategy to fight a variety of diseases.

Despite the significant potential, identification of small molecule inhibitors of TLR3 has been slow, due to the complexity of disrupting the protein-RNA contact.

Technology

A University of Colorado research group led by Hang (Hubert) Yin has developed a series of high-affinity small-molecule compounds that inhibit binding of double-stranded RNA to TLR3. In a multitude of assays, one compound (compound 4a, see JACS publication below) demonstrated potent antagonism to TLR3 signaling and inhibited expression of downstream pro-inflammatory signaling pathways mediated by the TLR3/dsRNA complex. This compound ("CU-CPT4a") exhibited high selectivity and low cytotoxicity in follow-up studies.

Data Update

Xenotropic murine leukemia-related virus (XMRV) is a recently discovered retrovirus that has been linked to human prostate cancer. Studies in human prostate cancer cell lines clearly indicated that TLR3 (along with TLR7) recognizes the retroviral genome of XMRV and evokes an anti-viral response. This suggests that at least a portion of the single-stranded RNA genome of retroviruses is capable of serving as a TLR3 ligand, likely through the formation of a higher order structure. Although XMRV was employed in this experiment, it is likely that the TLR3 recognition of retroviral genome applies to retroviruses in general, including HIV-1.

Key Documents

Modulators of TLR3/dsRNA Complex and Uses Thereof. PCT filed Jan 13, 2012.

Toll-Like Receptor 3 as a Surrogate Sensor of Retroviral Infection in Human Cells. Biochem. Biophys. Res. Commun. 2012 Aug;424(3):519-23. *PDF available upon request.*

Small-Molecule Inhibitors of the TLR3/dsRNA Complex. J Am Chem Soc. 2011 Mar 23;133(11):3764-7. *PDF available upon request.*