TLR4 Agonists and Antagonists

Corixa

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OVERVIEW

Corixa Corporation is developing a class of synthetic compounds that interact with a type of immune system cell-surface protein, known as a "toll-like receptor" (TLR). TLRs provide the body's first line of defense against a variety of pathogens by turning on or off critical aspects of the innate immune response. There are 10 kinds of TLRs, and each recognizes a different class of infectious agent based on common "molecular signatures."

Corixa's synthetic compounds mimic the molecular signatures that are recognized by toll-like receptor 4 (TLR4). Some of Corixa's TLR4 compounds act as **agonists**, or stimulants, of TLR4, and others act as **antagonists**, or deactivators, of TLR4. Pre-clinical research has demonstrated the ability of Corixa's TLR4 agonists to protect against viral, bacterial, fungal and parasitic infection by turning on the innate immune response. Additional research has shown that Corixa's TLR4 antagonists can function as anti-inflammatory agents by turning off the innate immune response.

MARKET OPPORTUNITY

Corixa plans to pursue various indications using its TLR4 compounds. Potential applications for TLR4 agonists include chronic obstructive pulmonary disease, upper airway resistance to biological warfare agents, seasonal or perennial rhinitis, allergies, and asthma. Potential applications for TLR4 antagonists include inflammatory bowel disease, rheumatoid arthritis, and inflammatory lung diseases such as cystic fibrosis.

In 2004, Corixa brought its first TLR4 compound into clinical development. A Phase I trial of TLR4 agonist CRX-675 is currently underway in patients suffering from seasonal allergic rhinitis (SAR). SAR is characterized by inflammation of the mucous membranes, and it occurs when allergens touch the lining of the nose. Results from the study are expected in the third quarter of 2005.

TLR4 AGONISTS

Corixa's TLR4 agonists have been successfully evaluated in viral, parasite and bacterial resistance models and have several promising clinical applications:

- **CRX-675.** In preclinical testing, allergic animals became non-responsive to allergen challenge of the airways after only one or two doses of CRX-675 administered in a nasal spray. In 2004, Corixa initiated a Phase I clinical trial with CRX-675 in patients with SAR.
- **CRX-527.** This TLR4 agonist is capable of stimulating nonspecific resistance to viral and bacterial pathogens at the mucosal and systemic level in preclinical models. Corixa intends to file an investigative new drug application for CRX-527 with the U.S. Food and Drug Administration in 2005 and will begin Phase I human clinical testing upon approval.
- **Other compunds.** Corixa is evaluating additional TLR4 agonists for use in the treatment of seasonal or perennial rhinitis, allergies, asthma, and upper airway resistance to biological warfare agents.

TLR4 ANTAGONISTS

Potential applications for TLR4 antagonists include therapies for inflammatory bowel disease, rheumatoid arthiritis and inflammatory lung diseases such as cystic fibrosis. The company is also exploring whether the antagonist compounds may be formulated and delivered orally.

SmithKline & Corixa R&D and our compounds

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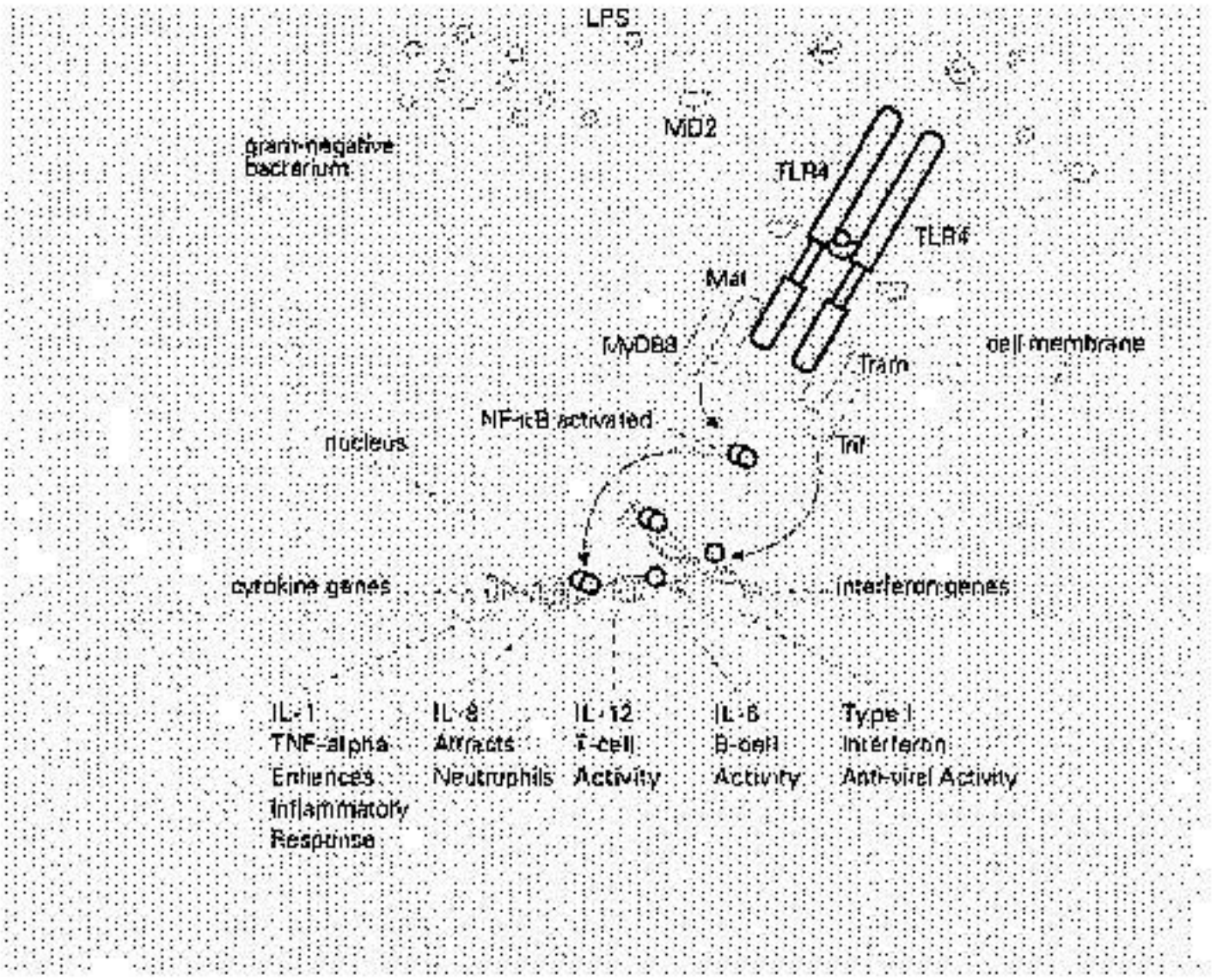
RECENT NEWS

April 26, 2004 – Corixa initiates a Phase I clinical trial of CRX-675 in patients with seasonal allergic rhinitis. This TLR4 agonist product is the first candidate to enter the clinic from Corixa's innate immunity program.

Jan. 5, 2004 – Corixa announces it has been awarded an $11.6 million, 5-year contract from the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health (NIH), to develop the company's proprietary synthetic molecules that act on TLR4. The contract is being funded by the Biodefense Partnership Program at the NIH.



TAKING TOLL

Toll-like receptors, made by many cells of the innate immune system, have been found to both direct an innate immune response and play a critical role in the adaptive response. TLR4 elicits these defenses when gram-negative bacteria begin to invade as shown above.

Ongoing studies show that TLR4 detects the attack by binding to a lipopolysaccharide (LPS), a sugar unique to gram-negative bacteria. LPS recognition in vivo is achieved by the cooperation of several molecules including LPS binding protein (LBP), CD14, MD2, and TLR4. The critical complex of TLR4, MD2, and LPS is what leads to activation of intracellular signaling pathways.

After recognizing the LPS complex, TLR4s signal to molecules (MyD88, Mal, Tram and Trif) inside the cell that trigger molecular interactions which induce innate immune responses and help to switch switch on T and B cells of the adaptive immune system.