Chemokine Signaling Antagonists as Therapeutics for Inflammatory Disease

BACKGROUND: Chronic inflammation causes the pain and tissue damage associated with many allergic and autoimmune diseases, including asthma, atherosclerosis, psoriasis, arthritis, and COPD. Millions of individuals suffer from these diseases. Treatment options are limited and clinicians often resort to prescribing steroids, which have significant side effects. Inflammation is caused by cells of the immune system entering tissues of the body in response to foreign invaders or tissue damage. The migrating cells secrete factors that kill the invaders and promote tissue healing. Thus, inflammation normally helps the immune system eliminate pathogens. Unfortunately, inflammation sometimes causes substantial collateral damage. The collateral damage can trigger additional inflammation, thereby initiating a feedback loop that results in chronic inflammation, pain and permanent tissue damage.

What is needed are safe and effective therapeutics for reducing chronic inflammation.

THE TECHNOLOGY: Discoveries at Trudeau Institute have resulted in issued and filed patents related to a novel pathway that controls inflammation by regulating the migration of immune cells.

One potential way to suppress chronic inflammation is to prevent immune cells from entering chronically inflamed tissues. A family of “chemokine” proteins controls the migration of immune cells. The chemokines are produced at sites of infection and damage. They function to recruit cells expressing chemokine receptors. Targeting single chemokine receptors may fail to provide clinical benefit since immune cells typically express multiple chemokine receptors. Trudeau Institute researchers discovered that CD38, an enzyme on the surface of immune cells, controls migration to multiple chemokines. They demonstrated that blockade of CD38-catalyzed reactions suppresses the migration of neutrophils, monocytes and dendritic cells to sites of inflammation.

One product of CD38-catalyzed reactions is the nucleotide ADPR (adenosine diphosphate ribose). ADPR activates TRPM2 (transient receptor potential cation channel M2), a channel that allows calcium to enter chemokine-activated cells. Working with collaborators from the University of Minnesota, Trudeau researchers designed, synthesized and tested novel analogs of ADPR. They produced analogs that selectively block TRPM2-regulated calcium responses, thereby blocking migration of cells to a subset of chemokines. The data indicate CD38 and TRPM2 antagonists constitute a new class of anti-inflammatory therapeutics.

APPLICATIONS:
• Provides a new means to prevent and treat inflammatory diseases
• Provides IP protection for methods for identifying new anti-inflammatory drugs
• Provides IP protection for the synthesis and use of novel compounds

BUSINESS OPPORTUNITY: Trudeau Institute is seeking partners to assist in the further development of this novel discovery. Partnership opportunities exist in the form of licensing and/or sponsored research.

PATENTS:
Title: Methods for Identifying Compounds that Inhibit CD38 Activity. U.S. Patent 6,955,884 (issued October, 2005).
Title: TRPM2-Specific Inhibitors. US application filed (priority date January, 2007).

PUBLISHED LITERATURE:
• Nature Medicine, 2001, 7:1209-16.
• The Journal of Experimental Medicine, 2007, 204:2705-2718.
• The Journal of Immunology, 2007, 179:7827-7839.

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HISTORY: The Trudeau Institute was founded in 1884 as a tuberculosis treatment and research facility. In 1964, the Institute was rededicated as an independent, nonprofit, biomedical research organization.

TODAY: The Trudeau Institute is a world-renowned leader in the effort to better understand the immune system for the purpose of preventing and treating human diseases. Our expertise and enthusiasm for modeling infection, immunity, vaccination, inflammation and sepsis have led to many pioneering discoveries. Mouse models currently studied at the Institute include influenza, parainfluenza, influenza-associated bacterial pneumonia, bacterial sepsis, pneumonic plague, tuberculosis, toxoplasmosis, schistosomiasis, and chronic herpesvirus infection. Our scientists are available for sponsored research, grant partnering and consulting.

MISSION: To make breakthrough discoveries that lead to improved human health.

FOCUS: Eradication of infectious and inflammatory disease through research aimed at the development of vaccines and immune-based therapeutics.

STAFF: Approximately 135 employees, including 12 Principal Investigators and 38 PhDs. The Scientist magazine consistently rates Trudeau Institute among the “Best Places to Work” for scientists and postdoctoral fellows.

FACILITIES: 42 acres in Saranac Lake, New York. 90,000 square feet of research and support space, including newly expanded BSL3 and ABSL3 facilities, and core facilities for animal breeding, imaging, and flow cytometry.

FINANCING: The Trudeau Institute is a nonprofit 501(c)(3) organization. The Institute’s $17M budget for 2009 was supported by federal grants (78%), donations from individuals and foundations (10%), and endowment funds (11%).