



SCIENCE FOR THE BENEFIT OF HUMANITY

Tari Suprpto, Ph.D.

Assistant Director

Technology Transfer

(212) 327-7095

tsuprpto@rockefeller.edu

Novel Targets for Anti-Inflammatory Agents

RU 202

Technology Summary

Inflammation is a normal response of the body to protect tissues from infection, injury or disease. The inflammatory response begins with the production and release of chemical agents by cells in the infected, injured or diseased tissue, which in turn induce the recruitment and binding of leukocytes to endothelium and the site of inflammation. This inflammatory reaction usually promotes healing; however, if uncontrolled, may harm the tissue. Inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, and Type 1 diabetes, affect more than 50 million Americans per year. New approaches are needed to discover and develop new drugs and treatments as well as to identify new targets for therapy.

The recruitment of leukocytes to the inflamed endothelium is a crucial step during the inflammation response. Leukocytes invade and pass through vascular endothelial tissue by a process in which a class of their surface protein called integrins, such as CR3, bind to their cognate receptors on the surface of endothelial cells. As a result, the junctions between the endothelial cells widen to permit the passage of the leukocytes. Inhibitors for such integrins should decrease leukocyte adhesion and would potentially be broad-spectrum anti-inflammatory agents.

Our scientists have found that filamentous hemagglutinin (FHA), a large protein of *Bordetella pertussis*, can recognize the CR3 integrin of leukocytes. The FHA is necessary for *B. pertussis* to adhere to ciliated respiratory epithelial cells during whooping cough. They have defined the regions for the binding of FHA to ciliated cells (CDR) and to CR3 (RGD) and produced peptides and antibodies (both polyclonal and monoclonal) against them. They have found that antibodies against RGD bind to endothelial cells, including those of the blood brain barrier (BBB), preventing adherence of leukocytes to endothelium and increasing BBB permeability. These antibodies are potentially suitable to produce therapeutics against meningitis or other diseases in which a inflammation could be dangerous. Moreover, they have found that peptides and antibodies against CDR affect the adherence of the bacteria to the respiratory tract. These peptides may be optimal vaccines for whooping cough caused by *B. pertussis* which provokes some 20–40 million cases and an estimated 200 000–400 000 fatalities each year.

Our researchers have also characterized domains of FHA that resemble C3bi and Factor X, which also bind to CR3 integrin. Antibodies against these regions bind to these natural molecules thus disrupting their function and decreasing the inflammatory response.

Area of Application

- **Research tools:** to study the binding and posterior recruitment of leukocytes through vascular endothelial cells.
- **Vaccines:** peptides and antibodies of the CDR region may be optimal vaccines for whooping cough caused by *Bordetella*.
- **Therapeutics:** peptides and antibodies of RGD would be powerful anti-inflammatory agents.

Stage of Development

Discovery.

Lead Inventor

Prof. Elaine Tuomanen

Patent Information

US Patent 5,932,217 (Issued on August 3, 1999).

US Patent 5,968,512 (Issued on October 19, 1999).

US Patent 6,015,560 (Issued on January 18, 2000).

References

Starzyk, et al. 2000. J Infect Dis. 181(1):181-7