



GRANT PROGRESS REPORT REVIEW

Grant: 01265: *Understanding Mechanisms Involved in Canine Autoimmune and Inflammatory Disorders*

Principal Investigator: Dr. Ronald Sluyter, Ph.D.

Research Institution: University of Wollongong

Grant Amount: \$48,730.00

Start Date: 1/1/2010 **End Date:** 12/31/2011

Progress Report: 6 month

Report Due: 6/30/2010 **Report Received:** 6/28/2010

Recommended for Approval: Approved

(Content of this report is not confidential. A grant sponsor's CHF Health Liaison may request the confidential scientific report submitted by the investigator by contacting the CHF office.)

Original Project Description:

Background: Autoimmune and inflammatory disorders have a major impact on the quality of life and lifespan of dogs. Studies in humans show an important role for an immune cell molecule (termed P2X7) in autoimmune and inflammatory disorders including inflammatory pain. P2X7 in these disorders has an ability to cause the release of key molecules (termed interleukins) that drive immunity and inflammation. Thus, P2X7 is attracting international interest as a therapeutic target in humans and currently undergoing clinical trials in patients with autoimmune or inflammatory disorders. The researchers have recently identified P2X7 on immune cells from dogs.

Objective: The researchers will study P2X7 on canine immune cells, and its role in canine immunity and inflammation. They will also study the P2X7 gene in various dog breeds to determine if P2X7 differs between breeds and whether these differences contribute to disease susceptibility. New information about canine P2X7 will enable the use of currently available compounds and the development of other compounds to target P2X7, and treat autoimmune and inflammatory disorders, as well as inflammatory pain in dogs.

Original Grant Objectives:

Objective 1: Characterize the cloned canine P2X7 receptor

Objective 2: Compare the P2X7 gene sequence and relative P2X7 receptor function between dog breeds

Objective 3: Determine if P2X7 receptor activation induces the maturation and release of IL-1? and IL-18 from canine monocytes and macrophages

Objective 4: Identify signalling events involved in the P2X7-mediated maturation and release of canine IL-1B and IL-18

Publications:

Report to Grant Sponsor from Investigator:

Autoimmune and inflammatory disorders have a major impact on the quality of life and longevity of dogs. Studies in humans highlight an important role for a molecule (termed P2X7), present on white blood cells, in autoimmune and inflammatory disorders including inflammatory-related pain. The role of P2X7 in these disorders is largely attributed to its ability to cause the release of key molecules (termed interleukins) that drive immunity and inflammation. Thus, P2X7 is attracting considerable international interest as a therapeutic target in humans, with a number compounds, able to block P2X7, currently undergoing clinical trials in patients with autoimmune or inflammatory disorders. We have recently identified P2X7 on white blood cells from dogs (English Springer spaniels). We propose to further study P2X7 on white blood cells from dogs, and its role in canine immunity and inflammation. We will also study the P2X7 gene in various dog breeds to determine if P2X7 differs between breeds and whether these differences contribute to disease susceptibility. New information about canine P2X7 will enable the use of currently available compounds and the development of other compounds to target P2X7, and treat autoimmune and inflammatory disorders, as well as inflammatory-related pain in dogs.

To date we have made (cloned) an artificial (recombinant) form of P2X7 from white blood cells obtained from an English Springer spaniel. This recombinant P2X7 will serve as a useful tool to study the role of P2X7 in dogs. Information from these studies may be used to develop drugs that can block canine P2X7. In addition, we have detected the expression of previously detected, as well as previously undetected immune/inflammatory-related molecules in white blood cells of dogs. These molecules may provide additional therapeutic targets in dogs. Finally, we have begun measuring the relative amounts of P2X7 in white bloods from various dog breeds and collecting genetic material from these same animals. This information will be used to determine if genetic differences contribute to susceptibility to autoimmune and inflammatory disorders in various breeds.