



**Canadian Arthritis Network  
International Partnership Initiative**

**International Research & Training Program  
LABORATORY/CLINIC PROFILE**

**Contact information of the principal investigator**

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**Please indicate if you are member or affiliate of one or more of the following  
International Partnership Initiative organizations:**

- AO Foundation – Biotechnology Advisory Board, Switzerland
- Arthritis Foundation, USA
- Arthritis Research Campaign, UK
- Canadian Arthritis Network, Canada
- Japan Society for the Promotion of Science, Japan
- Nuffield Foundation Oliver Bird Rheumatism Program, UK

**International Research & Training Program Opportunity**

**Please indicate which of the following international opportunities would be  
available at your laboratory/clinic.**

- Training Elective Rotation
- Research Mini-sabbatical
- Industry Training Rotation



**The International Research & Training Program will be available for trainee elective rotations and investigator mini-sabbaticals that commence on or before March 31, 2009. If you have any preferences regarding the dates when you can host an international trainee or investigator, please indicate this below.**

<b>Visit Length</b> (please indicate start and end dates if known):	
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**Please provide ten key words and a brief description of the research currently being conducted in your laboratory/clinic, including descriptions of any specialized equipment, methods or technologies employed at your facility.**

**10 key words**

<ol style="list-style-type: none"><li>1. Neutrophil</li><li>2. Adenosine</li><li>3. Phosphoinositol-3-kinase</li><li>4. Synoviocytes</li><li>5. Cytokines</li><li>6. Lysophosphatidic acid receptor</li><li>7. Sphingosine-1-phosphate receptor</li><li>8. Cell motility</li><li>9. Small GTPases</li><li>10. Secretion</li></ol>
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**Brief description** (up to ½ page)

Rheumatoid arthritis (RA) is a systemic autoimmune disorder in which joints are targeted by an inappropriate inflammatory response, eventually resulting in bone destruction and joint deformity. The pathogenesis of the disease and the underlying mechanisms remains rudimentary. Moreover, it remains a clinical challenge to effectively treat and manage the disease.

Angiogenesis, the formation of new blood vessels, and the recruitment of leukocytes to inflamed tissues are recognized to play critical roles in RA pathogenesis. Angiogenesis constitutes an early event of synovial hyperplasia that promotes the destruction of cartilage and bone. It also promotes persistence of synovial inflammation through the recruitment of leukocytes to the inflammatory site, creating the disease-specific microenvironment. It is worth mentioning that Autotaxin (ATX), a pro-angiogenic protein, is expressed at significantly higher levels in synoviocytes from patients with RA as compared to healthy donors. The mechanism through which ATX promotes angiogenesis and cell motility is dependent on its ability to catalyze the formation of lyso-phosphatidic acid (LPA) and sphingosine-1-phosphate (S1P) from lysophospholipids. This finding was a significant breakthrough since LPA is a bioactive lipid mediator that controls various cellular responses, such as cell proliferation, differentiation, survival and motility. LPA has been suggested to play a central role in a broad range of physiological and pathological processes.

The main objective of this research is thus to define the role of LPA in the pathogenesis of RA. We propose that LPA contributes to the pathogenesis of RA. Since LPA and S1P as well binds to G-protein coupled receptors that elicit diverse functional responses, we will determine whether LPA and S1P receptors are expressed by synoviocytes and whether the expression of those receptors is regulated in response to pro-inflammatory cytokines, such as TNF- $\alpha$ . Receptor functions will be investigated *in vitro* or *in vivo* using selective agonists or antagonists and the contribution of autotaxin and lysophospholipid receptors to the pathogenesis of RA will be analyzed in animal models.

**Key publications** (maximum 5 publications)

63. Boilard E., **Bourgoin S.G.**, Bernatchez C., Surette M. (2003) Identification of an autoantigen on the surface of apoptotic T-cells as a new ligand of inflammatory IIA phospholipase A<sub>2</sub>. *Blood*. 102:2901-2909.
68. Burelout C., Thibault N., Levasseur S., Simard S., Naccache P.H., **Bourgoin S.G.** (2004) Prostaglandin E<sub>2</sub> inhibits the phospholipase D pathway stimulated by formyl-Methionyl-Leucyl-Phenylalanine in human neutrophils. Involvement of EP<sub>2</sub> receptors and phosphatidylinositol 3-kinase  $\beta$ . *Mol. Pharmacol.* 66 (2): 293-301.
71. Hurtado-Lorenzo A., Skinner M., El Annan J., Futai M., Sun-Wada G.-H., **Bourgoin S.**, Casanova J., Wildeman A, Bechoua S, Ausiello D.A., Brown D., Marshansky V. (2006) V-ATPase Interacts with ARNO and Arf6 in Early Endosomes and regulates the protein degradative pathway *Nat. Cell Biology.* 8(2): 124-136.
72. Fortin A, Fernandes M., Borgeat P., **Bourgoin S.G.** (2006) Differential expression of adenosine receptors on human neutrophils and their up-regulation by specific inflammatory cytokines. *J. Leuk. Biol.* 79:574-585..
80. Zhao C., Fernandes M.J., Prestwich G.D., Turgeon, M., Di Battista J., Clair T., Poubelle P.E., **Bourgoin S.G.** (2007) Regulation of lysophosphatidic acid receptor expression and functions in human synoviocytes : Implications for rheumatoid arthritis. *Mol. Pharmacol.* Conditionnaly accepted.