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
x☐ 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.

x ☐ Training Elective Rotation

x ☐ 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.

Visit Length (please indicate start and end dates if known):	

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

1. chondrocytes
2. cartilage
3. TGF-beta
4. receptors
5.signaling
6. co-receptors
7. affinity labeling
8. western blot
9. RT-PCR
10. cell culture

Brief description (up to ½ page)

Regulation of TGF-β action in chondrocytes: Balance of signaling via two distinct type I receptors

Despite intense research efforts aimed at developing strategies for restoring diseased or injured cartilage, a successful treatment option for cartilage regeneration or repair remains elusive. Transforming growth factor-β (TGF-β) is unique in its ability to direct cartilage-specific matrix gene expression, prevent terminal hypertrophic differentiation, and maintain cartilage. Despite its chondroprotective effects, the clinical utility of TGF-β is compromised by side effects such as osteophyte formation and synovial fibroplasia. An alternative approach would be to target specifically those TGF-β responses that facilitate cartilage repair while inhibiting the responses responsible for its side effects. Our recent results suggest that it may be possible to selectively modulate distinct TGF-β responses by manipulating TGF-β action at the level of its receptors. TGF-β signals through a pair of receptors known as the type I (also known as activin receptor-like kinase 5 or ALK5) and the type II receptors. Our results demonstrate that in chondrocytes, in addition to ALK5, TGF-β also signals through a novel type I TGF-β receptor, ALK1. In addition, our data suggest that ALK1 pathway induces responses opposite to that of ALK5 pathway essential for cartilage maintenance. Identification of ALK1 as a critical regulator of chondrocyte differentiation and phenotype may provide unique avenues to improve disease outcome.

Hypotheses: (A) That ALK1 is a phenotypic marker in human articular chondrocytes, and plays a pivotal role in chondrocyte dedifferentiation and function, and therefore controls cartilage integrity; (B) That ALK1 opposes ALK5 signaling in chondrocytes and that TGF-β action in chondrocytes is regulated by a balance between their signaling activities; (C) That it is possible to manipulate chondrocyte differentiation and function by altering ALK1 versus ALK5 signaling activity, to promote cartilage repair.

Specific Objectives: ***(1) To demonstrate that ALK1 is a phenotypic marker and inducer of dedifferentiation in human articular chondrocytes; (2) To establish that ALK1 and ALK5 signaling induce opposing effects in chondrocytes and that endoglin plays a critical role in the balance between these two signaling pathways; (3) To identify ALK1 as a regulator of articular cartilage formation in vivo.***

Relevance: Osteoarthritis is a paramount medical problem affecting more than 50% of the population over 60 yrs of age, with no satisfactory treatments. Since TGF-β is a potent stimulator of cartilage repair, identification of molecules regulating TGF-β signaling and responses in chondrocytes may provide an avenue for the manipulation of TGF-β action in chondrocytes, and thus cartilage repair. The proposed studies are novel in that they may provide a basis for the development of a unique therapeutic approach in which novel proteins may be used to modulate TGF-β action locally to manipulate chondrocyte proliferation, phenotype, and matrix synthesis, and thus reparative capacity.

Key publications (maximum 5 publications)

1. Parker, W.L.*, Soe-Lin, H., Knaus, P., and **Philip, A.** Expression and function of TβRII-B, a variant of the type II TGF-β receptor, in human chondrocytes. Osteoarthritis and Cartilage 15: 442-453, 2006; doi:10.1016/j.joca.2006.10.006.

2. Finnson, K*, Tam, B*., Liu, K*., Marcoux, A*; Lepage P., Roy, S and **Philip, A.** Identification of CD109 as part of the TGF-β receptor system in human keratinocytes. FASEB Journal, 20: E780-E795, 2006; 20: 1525-1527, 2006

3. Cadot, C., Poirier, D., **Philip, A.** First synthesis of a steroid containing an unstable 19-nor-androsta-1,5-dien-3one system. Tetrahedron, 62: 4384-4392, 2006

4. Parker, W.L*., Goldring, M.B., and **Philip, A.** Endoglin is expressed on human chondrocytes and forms a heteromeric complex with betaglycan in a ligand and type II TGF-ß receptor independent manner. J. Bone Min. Res. 18: 289-302, 2003.

5. Tam, B*., Finnson, K*, and **Philip, A.** (2003) Glycosylphosphatidyl inositol-anchored proteins regulate TGF-ß signaling in keratinocytes. J. Biol. Chem. 278: 49610-617.