There is one thing even more vital to science than intelligent methods; and that is, the sincere desire to find out the truth, whatever it may be.

Charles Sanders Pierce
4. AIMS AND OBJECTIVE OF THIS STUDY

OPN, a member of SIBLING family of matrix associated protein has been considered as one of the potential biomarkers in varieties of cancer. OPN has been shown to promote tumor progression by interacting with multiple integrins and CD44 variants, which in turn regulates downstream kinases and transcription factors that ultimately augment the expression of various oncogenic and proangiogenic molecules like VEGF, MMPs, uPA and COX-2. Moreover, earlier studies demonstrated that OPN produced in senescent fibroblast promotes preneoplastic cell growth. Furthermore, it has been shown that OPN produced in the bone marrow compartment regulates hematopoietic stem cell pool size. Recently it has also been shown that targeting OPN either at RNA or protein level significantly attenuates tumor progression and metastasis in multiple cancer models. Andro, a bicyclic diterpenoid lactone, from medicinal plant called *Andrographis paniculata* is one of the potential anti-cancer agent which has not been studied in depth. Previous studies have focused on role of Andro with respect to anti-inflammatory effects and regulation of tumor cell proliferation, migration and invasion. Till date, the effects of Andro on tumor growth and angiogenesis remain to be elucidated. Therefore, first part of the study is aimed to delineate the anti-cancer property of Andro and the molecular mechanism underlying it. In the second part, role of stroma-derived OPN in melanoma progression and the molecular mechanism involved in the process has been addressed.

- To isolate, purify and characterize Andro from *Andrographis paniculata*.
- To study the effect of Andro on breast cancer and normal cell viability and motility.
- To investigate the effect of Andro in breast cancer cell cycle progression and apoptosis.
- To decipher the effect of Andro on breast tumor-endothelial cell interactions, *in vitro* angiogenesis and the mechanism underlying it.
- To ascertain the effect of Andro on the expressions of OPN and other angiogenic and tumorigenic genes in breast cancer cells.
- To investigate the role of Andro in *in vitro* as well as *in vivo* tumorigenicity in orthotopic breast cancer model and correlate the expression profiles of genes and proteins regulated by Andro in mice breast tumor specimens.
To analyze the effect of stromal/host-derived OPN in regulation of melanoma growth by using wild type and OPN-knockout mice.

To examine the role of host derived-OPN in metastasis in murine melanoma model.

To establish primary culture from the tumors generated in OPN wild type and knockout mice and to characterize these cells.

To re-examine the tumorigenicity and metastatic property of primary cells from the tumors generated in OPN wild type and knockout mice.

To study the effects of stromal derived-OPN on SP phenotype of B16F10 melanoma cells.

To investigate the signaling pathway and molecular mechanism involved in the regulation of stromal OPN induced SP phenotype in B16F10 cells.