

Research Projects: Julie Sharp

1. Evolution of mammary gland function by use of monotreme models.

Monotreme reproductive strategy consists of the animals laying eggs which are carried by the mother in an external skin flap or pouch where pouch secretions are predicted to keep the egg moist and protected against bacterial infection. The small and altricial hatchlings which emerge from small eggs are completely dependent on milk as the sole source of nutrition during the suckling period and undergo a significant amount of development during this stage. Analysis of milk composition and gene expression during the echidna lactation cycle will be undertaken and focus on identifying factors that may have biological activity to meet the needs of the developing young.

2. Transcriptome analysis, protein composition and endocrine regulation of protein expression in pigeon crops at hatching.

Many amniotes have developed a reproductive strategy of nurturing their young by producing milk rich in protein and nutrients. Some birds initially feed their hatchlings an exclusive diet of "crop milk" which is produced by regurgitation of a milk-like substance from the crop gland. Investigation of the composition of crop milk and endocrine regulation will develop our understanding of the crop gland and be used to draw analogies to the mammary gland. Transcriptome and protein composition studies of the crop gland and milk, respectively will be undertaken at different stages following hatching in order to identify expression of milk-like proteins and growth factors.

3. Identification of proteins in the placenta/omniote/colostrum/milk continuum.

Our recent studies have shown that a group of proteins are expressed in human placenta, amniotic fluid and milk providing a continuum for the infant. We have microarray data comparing gene expression profiles of human placenta, amniotic cells, colostrum cells and milk cells. Comparative analysis with wallaby and echidna milk cells; animals which both give birth to very immature young that rely solely on milk for development, will be undertaken to further identify proteins which may be involved in the continuum. The function of these proteins will be studied for their involvement in development of the young. In the future these may be used for treatment of pre-term babies and/or disease.

4. Investigation of the efficacy of milk proteins in reducing tumour size using mouse models of human breast cancer growth and metastasis.

We have recently identified a milk protein with apoptotic properties. Using cell biology and molecular biology techniques the apoptotic properties of this protein will be investigated by use of *in vitro* and *in vivo* models of breast cancer. These studies may develop this protein as a treatment for breast cancer treatment and prevention.

5. Mammary gland responses to mastitic infection in humans.

Infection of the mammary gland during lactation is common among breast feeding women. The response of the mammary gland to infection at this time will be studied by use of global gene expression analysis. A mastitis culture model using mammospheres, which resemble the 3 dimensional structure of the mammary gland alveolus, will be developed and enable testing of identified response factors.

6. Cell survival, innate immunity and the role of the extracellular matrix in the Cape fur seal mammary gland during lactation.

The fur seal has a unique lactation cycle allowing fur seal mothers to turn off lactation while they return to seal to forage for up to 3 weeks. Upon return to shore the mother reinitiates lactation, a process which is unique to fur seals. During extended time spent at sea foraging the fur seal mammary gland does not involute. In most mammals, periods of milk stasis renders the mammary gland vulnerable to infection resulting in mastitis, however, the fur seal mammary gland avoids infection and continues to produce milk once back on shore. We have developed a fur seal culture model where mammary cells are cultured *in vitro*, excrete their own matrix and produce mammospheres which, upon hormone induction express milk protein genes. This culture model will be used to investigate the innate immunity of the fur seal mammary cells, and the role of fur seal matrix in mammary gland survival.

7. Investigation of uncharacterized milk genes expressed in the Cape fur seal mammary gland.

In order to evaluate the global gene expression pattern of the Cape fur seal mammary gland 11, 232 EST's were sequenced and annotated, however several highly expressed EST's are currently unannotated and represent unknown and unstudied genes. The high expression of these genes during fur seal lactation suggests these genes have an important function. These genes will be studied for function in protection of the fur seal mammary gland from infection during milk stasis while at sea, and in the gut of the pup while it remains on shore for long

periods fasting while awaiting the return of the mother. These aspects will be studied by use of cell based assays.

8. Fur seal mammary stem cells – a model for examining LALBA function in the mammary gland.

We have recently shown that LALBA, a milk protein, is implicated in autocrine regulation of involution of the mammary gland. The Cape fur seal is unique in that it does not express this gene and therefore presents a naturally occurring gene knockout model. Stem cells from the fur seal mammary gland will be isolated and characterized. These cells will then be transplanted into mice mammary fat pads to generate LALBA knockout mammary glands. This model will then be used to examine LALBA function in involution of the mammary gland.