

## TITLE OF PROJECT

**Tumour development: a role for the enzyme sphingosine kinase**



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### Project Description

It is well described that blood vessel formation (angiogenesis) is critical for the development of tumours and their metastasis. There is now increasing evidence that the enzyme sphingosine kinase (SK)-1 regulates blood vessel development. Indeed, our own work demonstrates that SK-1 regulates the survival and activity of the cells which make up the blood vessels<sup>1</sup>. Furthermore, we and others have shown that mice injected with cells over-expressing SK-1 exhibit increased tumour development<sup>2</sup>. The mechanisms by which this occurs are still unknown.

**Aim 1: Do mice with genetically modified levels of SK-1 develop EL4 solid tumours and B16 metastases at the same rate?** We already have preliminary data to suggest that endothelial cells with high levels of SK-1 promote blood vessel formation and that fibroblasts over-expressing SK-1 injected into mice develop larger tumours (ref #1 Limaye et al and ref #2 Xia et al). Do these preliminary results correlate to a tumour development in mice expressing varied levels of SK-1 in the endothelial compartment alone? Does depletion of SK-1 reduce solid or metastatic tumour development?

**Aim 2: By what mechanisms does SK-1 mediate solid and metastatic tumour development?** Preliminary data from our collagen-induced arthritis model (derived from AEC # 81/04, manuscript in preparation) suggest that SK-1 mediates a subset of white blood cells (T and B lymphocytes) as well as disease specific antibody production. Are there similar mechanisms at play in solid or metastatic tumour development in the genetically altered mice?

Taken together, we will investigate the role of SK-1 in tumour development using the EL4 and B16 mouse models of solid and metastatic tumours in genetically modified mice to determine whether the enzyme SK-1 mediates the amount and type of antibody production against collagen as well as lymphocyte mobility and function. **We believe that by understanding the mechanisms in tumour development potential therapeutic targets can be generated.**

### References

1. Limaye V et al. Sphingosine kinase-1 enhances endothelial cell survival through a PECAM-1-dependent activation of the PI-3K/AKT pathway. *Blood* 2006, 105(8):3169-77.
2. Xia P, Gamble JR, Wang L, Pitson SM, Moretti PAB, Wattenberg BW, D'Andrea RJ, Vadas MA. An oncogenic role for sphingosine kinase. *Current Biology* 2000, 10: 1527-1530.