**FINAL PROJECT REPORT**

***Name:***

Dr Judith McKenzie

***Project Title:***

Function of Soluble CD83 in Chronic Lymphocytic Leukemia

**Please copy the "Outcome(s)" statement, entered on your application form, in the space below.**

Although currents treatments prolong the survival of CLL patients the majority still relapse and CLL remains largely incurable. It is clear that the immune system can, in some instances, mount a response against CLL cells and understanding how CLL cells and the immune system interact is essential for the development of new therapies. If this study indicates that release of sCD83 by CLL aids the progression of CLL then this will focus research onto methods to inhibit this release. Such methods will then need to be incorporated into therapeutic protocols. This will then allow the development of better therapies and increase the effectiveness of current therapies such as allogeneic SCT and autologous immunotherapy. The results of this study will be of considerable international research interest and will be likely to be accepted for publication in a high impact factor journal.

**Will your work contribute to this outcome(s) in the manner you envisaged? If not, what has changed?**

This study has made a number of novel findings with respect to sCD83 in CLL.
In particular we have demonstrated that CLL cells actively release sCD83, and that elevated levels of sCD83 in patient blood are associated with poor prognosis. As envisaged this work was of interest in the area of CLL and has been published in an international leukaemia journal.

**Please copy the "Specific Objective(s)" statement, entered on your application form, in the space below.**

Soluble CD83 (sCD83) is a potent inhibitor of immune responses, and animal studies have shown that its presence can increase tumour progression. Although levels of sCD83 are elevated in the blood of CLL patients, it has not been established whether CLL cells can release sCD83 and, if they do, whether it represents a mechanism by which they can escape immune surveillance. Understanding how CLL cells escape the immune system is critical for both the development of new therapies, and improving existing approaches such as allogeneic transplantation.
The aim of this research is to (i) Identify the optimal stimuli for inducing sCD83 release by CLL cells (ii) Determine the functional significance of sCD83 release by CLL cells (iii) Determine the exact level of CD83 expression by CLL cells before and after activation

**Briefly describe how successful you were in achieving the stated objective(s). If the objective(s) was not achieved, explain why that is the case and describe what you did manage to achieve.**

Aim (i)
We have successfully determined the optimal stimuli that induce the release of sCD83 from CLL cells.
Culture of the cells with a combination of IL-4 and solid phase anti-CD83 antibody for a period of three days significantly increases sCD83 release (23 – 117 fold, p=0.013), with levels of >1,000pg/ml observed in all preparations analysed.

Aim (iii)
We have successfully determined the effect of activation on CD83 expression.
Resting CLL cells lacked membrane CD83, but expressed low level cytoplasmic CD83. Activation with IL-4 alone up-regulated membrane CD83 expression, but did not induce release of sCD83. sCD83 release was only induced when both stimuli were present.

Aim (ii)
We were unable to determine the functional significance of sCD83, despite extensive investigation. The difficulties in obtaining sufficient purified material from CLL cells proved too problematic to overcome.
Because of this we attempted to address the issue of whether CD83 has a role in CLL progression using an alternative approach. We measured circulating CD83 levels in a cohort of Christchurch CLL patients and analysed the association between CD83 levels and clinical outcomes. We found that CLL patients with elevated sCD83 levels had significantly shorter treatment free survival, and in bivariate analysis sCD83 remained a significant independent prognostic factor.

**Please confirm delivery of the outputs listed on your application form. If these outputs were not to be delivered, please explain why.**

All of these results have been included in a paper published in the journal *Leukaemia Research* (see attached pdf), and also presented at the Australasian Immunology Society conference in December 2008.