

FINAL PROJECT REPORT

Date:

Name:

Dr Judith McKenzie

Project Title:

Analysis of immunosuppression by Chronic Lymphocytic Leukemia cells

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

Suppression of anti-cancer responses by Chronic Lymphocytic Leukaemia (CLL) cells is thought to facilitate disease progression. Overcoming this suppression may have therapeutic benefit. Green tea and the cancer drug Lenalidomide have shown promise in the treatment of CLL, but the mechanisms underlying these effects are unclear. The aims of this project are to (i) Determine the effect of green tea components and lenalidomide on CLL mediated suppression of both T cell and Natural Killer cell (NK) activity (ii) Analyse usage by CLL cells of known suppressive mechanisms and, in particular, whether the reported expression of HLA-G by CLL cells contributes to their immunosuppressive ability and (iii) determine whether green tea and lenalidomide modulate aspects of these inhibitory pathways. It is envisaged that sufficient patient samples to complete the project should be obtainable within a year.

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.

The development of a robust functional assay system has been a major (and unexpected) difficulty in this project- this has held up the planned, and relatively straight forward, screening of the effects of green tea and lenalidomide.

At the time of our last report (August/2012) we had, based on data published by other groups, developed an assay for measuring the suppressive capacity of CLL cells. However subsequently we found that a number of the published findings regarding CLL activity that underpinned our assay were incorrect. Although this caused some further time delays we were fortunate in that our findings enabled us to develop a improved assay that has significantly increased sensitivity (by 2-3 fold). This improved sensitivity increases our ability to both identify compounds that are capable of overcoming CLL suppressive activity and analyse the suppressive mechanisms utilised. We have previously optimised the concentrations of inhibitory compounds to be tested and all other additional assays and reagents required have also been fully developed. We are now therefore currently testing the effect of these inhibitory compounds in our assays. Finishing this work (ie completing the required number of replicate experiments, publications costs etc) will require a small amount of additional funding which will be applied for. We expect this work will be fully publishable even if the green tea and lenalidomde show no effect as the methodology used and the type of suppression observed is of considerable interest in its own right.

In summary the project has taken longer than initially envisaged – we are confident however that we have overcome all the barriers to this work and that we can finish the proposed study and submit a publication within this year

Briefly describe any interesting outcomes which might not have been considered in your original objectives (if any).

The development of a high sensitivity assay for CLL mediated suppression has given us the ability to analyse the effects of currently used chemotherapy drugs on CLL function. A project addressing this is currently being developed.

During this project we have as a by product set up and validated a range of assays that, although not effective in measuring CLL activity are effective at measuring suppressive activity by other cell types. This will be of considerable benefit in future projects as it will help avoid the methodological difficulties we encountered with this project.