FINAL PROJECT REPORT

Date: 22 December 2015

Name:

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Project Title:

Activated Chronic Lymphocytic Leukaemia cells: suppressive effects on T cell responses.

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

The interaction of Chronic Lymphocytic Leukaemia (CLL) cells with activated T cells in the leukaemic micro-environment provides signals important in CLL activation, progression and survival. CLL progression is associated with profound immunosuppression but it is unclear what effects T cell mediated activation has on the ability of CLL cells to suppress immune responses. We have developed an *in vitro* system for the stimulation of CLL cells by activated T cells that generates CLL cells able to suppress subsequent T cell responses. The aims of this project are to analyse these activated CLL cells and determine: (i) the phenotypic and functional changes induced during their activation (ii) the suppressive mechanisms they utilise (iii) the sensitivity of different T cell populations to their suppressive effects and (iv) the effect of current and newly developed chemotherapy drugs on their suppressive capacity. Understanding how activated CLL cells modulate the function of T cells and determining the effect of drug therapies on this process will help identify elements that could be targeted in order to improve treatments for this currently incurable disease.

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.

In this project we have been investigating the ability of CLL cells to suppress the body's anti - cancer response.

Objectives (i) and (iii) were completed last year, and demonstrated that the interaction of CLL cells with the immune system results in CLL cells which are increased in size and have up-regulated expression of activation markers. These activated cells then become capable of suppressing normal immune responses. We have also shown that both CD4 and CD8 T cell responses are affected. This work has now been published in the journal Leukemia Research.

We then used this model of CLL activation as a basis for investigating both the underlying mechanism of suppression and potential therapies that may overcome it (Objectives (ii) and (iv).

In order to examine the mechanism of suppression we utilised a very large panel of agents which block pathways which may potentially be involved, but had no success in reversing the suppressive activity, suggesting that none of these candidate mechanisms were involved.

In the last few months however we have identified two compounds that reverse the suppression induced by CLL cells. The first, ATRA, is already used clinically for the treatment of another form of leukaemia but to date little research has been done on its effects on CLL. The other compound, caffeine, inhibits a number of biochemical pathways that may induce suppression. Our studies have implicated one of those pathways which interestingly is also targeted by a recently developed drug (Idelalisib) which is showing considerable promise in clinical trials as a treatment for CLL. Much is unknown about how exactly Idelalisib

impacts on CLL progression and we have now made the novel finding that it can reverse CLL mediated suppression. We feel that we have achieved our stated objectives, and will shortly be preparing our more recent findings for publication.

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

The finding that ATRA and caffeine, which are not currently used for the treatment of CLL, were able to reduce CLL mediated suppression was an unexpected finding. Exactly how these compounds are affecting the CLL cells will be the subject of future study.