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Title of Project

Is selection pressure responsible for chronic refractory IBD? –Does steroid therapy ultimately lead to treatment failure by preferential selection of disease-propagating T cells?

Lay summary

For fifty years, glucocorticoids (steroids) have been one of the mainstay treatments in the management of IBD. However, 20-30% of IBD patients do not respond to steroid therapy. Some patients appear intrinsically unresponsive to steroids from the onset of their disease, while others appear to become tolerant to their effects. IBD results from an inappropriate activation of T lymphocytes and it is thought that GCs act via these cells. We have shown that specific subsets of these T cells (groups of clones) are associated with disease. However, it is not known whether GC resistance affects all T cells, or simply these disease-associated clones. If steroids influence specific T cell subsets in a different manner, then using steroids may lead to a greater preponderance of steroid resistant subsets.

We have shown that it is possible to determine a patient's clinical response, or non-response, to steroid therapy in the laboratory, by an *in vitro* method. Therefore, we propose that, because T cell-driven disease persists in GC-resistant patients, the mechanisms of resistance are focussed on disease-inducing T cell clones.

To address this hypothesis, we will isolate T cells from patients known to GC-resistant and determine whether GC resistance is restricted to particular clones. Firstly, we will determine whether steroids suppress all subsets of T cells, or whether some subsets are more, or less, steroid responsive than others. Secondly, we will examine the molecular basis of what the resistant T cell clones respond to, which will give an indication of their disease-inducing capability. Finally, we will determine whether the use of steroids lead to preferential growth of steroid resistance cells *in vitro* and *in vivo*, by studying GC resistance in relapsing patients.

This work will help us to understand why steroid therapy fails. More importantly, it will help us to understand whether 'over-use' of steroids leads to the propagation of chronic disease, by providing conditions which allow disease propagating T cells to flourish.