

Proposal for Bench to Bedside PhD project 2010

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**Rescuing antiviral T cells from replicative senescence in chronic hepatitis B virus infection**

**Project Summary:**

Persistent hepatitis B virus infection (HBV) is responsible for more than a million deaths a year worldwide. In patients who are unable to control this virus, the immune response is disabled by progressive CD8 T cell exhaustion, as recently characterised by the Maini group(1, 2). The Akbar group have highlighted the additional role for replicative senescence in limiting immune responses in the context of highly differentiated T cells (3). We hypothesise that the decades of extremely high antigen load in HBV infection may impair responding T cells by driving the dual processes of exhaustion and senescence through non-redundant molecular pathways. It is well-recognised that the outcome of HBV infection is adversely affected by increasing age; our preliminary data suggest this may be a result of premature senescence of antiviral T cells. This project will address the role of newly defined pathways of T cell senescence in persistent HBV infection. The specific aims will be to define the interaction between telomere erosion, p38 MAPkinase induction and dysregulated free radical production by mitochondria in highly differentiated T cells from patients with HBV infection. All these processes have been shown to be involved in the induction of cellular senescence in human T cells. In particular, we will determine whether blocking these processes using specific inhibitors of p38 activity or antioxidants, that neutralize free radicals, can functionally rejuvenate the T cells from HBV patients. This project therefore involves the study of a disease process in humans and the data generated may be instrumental in defining new therapeutic interventions.

**Training environment:**

The candidate will join two dynamic groups who are at the forefront of research in these cutting-edge, clinically important areas of human immunology. The joint supervisors of this project share a lab, and have a strong history of productive research collaboration (1, 4, 5) and of successful supervision of PhD students. Additional day-to-day supervision will be provided by experienced post-doctoral researchers within their groups.

Through the clinical responsibilities of Professor Maini, the candidate will also have the chance to visit out-patient clinics in viral hepatitis and learn more about the medical context of their research and of the samples they work on.

**Key references:**

1. Das, A., Hoare, M., Davies, N., Lopes, A. R., Dunn, C., Kennedy, P. T., Alexander, G., Finney, H., Lawson, A., Plunkett, F. J., *et al.* (2008) *The Journal of experimental medicine* **205**, 2111-2124.
2. Lopes, A. R., Kellam, P., Das, A., Dunn, C., Kwan, A., Turner, J., Peppas, D., Gilson, R. J., Gehring, A., Bertolotti, A., *et al.* (2008) *The Journal of clinical investigation* **118**, 1835-1845.
3. Henson, S. M., Franzese, O., Macaulay, R., Libri, V., Azevedo, R. I., Kiani-Alikhan, S., Plunkett, F. J., Masters, J. E., Jackson, S., Griffiths, S. J., *et al.* (2009) *Blood* **113**, 6619-6628.
4. Maini, M. K., Soares, M. V., Zilch, C. F., Akbar, A. N., & Beverley, P. C. (1999) *J Immunol* **162**, 4521-4526.

5. Soares, M. V., Borthwick, N. J., Maini, M. K., Janossy, G., Salmon, M., & Akbar, A. N. (1998) *J Immunol* **161**, 5909-5917.