Project title: Mechanism of the reduced cutaneous immunity in the old

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The average human life expectancy has almost doubled in the last 200 years and is still on the increase. It has been projected that up to 40% of the population in Europe and the U.S.A. will be over 60 years old in the year 2050. These demographic changes have profound implications in terms of morbidity and mortality, as well as huge resource implications for healthcare delivery. The incidence and severity of infectious diseases such as pneumonia, meningitis, sepsis, urinary tract infections, RSV and influenza is increased in elderly individuals. Furthermore, elderly individuals are more susceptible to infection by organisms to which they were previously immune, and to reactivation of dormant infectious agents such as Varicella-zoster virus (VZV), EBV and mycobacteria. Susceptibility to infections is further exacerbated by a decline in effective in response to vaccination.

Over the last 10 years we have developed a unique model to study human immune responses in the skin in vivo [1-3]. This model involves intradermal injection of antigen- such as PPD, candida or VZV into the forearm of young or old healthy volunteers and has been used to identify the kinetics of accumulation and disappearance of antigen-specific memory and regulatory T cell[2,3] populations in the skin. Furthermore using this model we have shown that the decrease observed in cutaneous immune responses in the older individuals result from a defect in the activation of the endothelium which leads to decreased migration of T cells into the site of antigen challenge. The reduced activation of endothelium correlates with decreased TNF-a production by macrophages present in the old skin. We proposed that the one possible explanation of this observation is accumulation of regulatory T cells in the skin of older donors.

The aims of this project are twofold: 1) To explore the early phases of the response and the interaction between the components of innate and adaptive immunity in the first 12 hours following the antigen challenge in order to better understand the basis for reduced TNF-a production and 2) to investigate the balance between different T cell populations during the course of the immune response in the skin: are Th1, Th17 and Treg cells accumulating and proliferating with different kinetics in young and old donors.

Changes we have identified are a normal part of the ageing process that contributes to disease and therefore reduced quality of life in older people. The more knowledge we have about healthy ageing, the better we get at preventing, managing and treating

diseases. Therefore a better understanding of the basis for the reduced immune response in the skin is expected to open up new ways to boost the immune system in older people to give them a better chance of fighting infection and reducing the risk of skin cancer. In addition, there is scope to extend this project to analyze changes in the cutaneous immunity during inflammatory (eczema, psoriasis) or malignant disease (melanoma, BCC).

Reference List

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(2) Vukmanovic-Stejic M, Agius E, Booth N et al. The kinetics of CD4Foxp3 T cell accumulation during a human cutaneous antigen-specific memory response in vivo. J Clin Invest. 2008;118:3639-3650.

(3) Reed JR, Vukmanovic-Stejic M, Fletcher JM et al. Telomere erosion in memory T cells induced by telomerase inhibition at the site of antigenic challenge in vivo. J Exp Med. 2004;199:1433-1443.