ImmunoTools IT-Box-Cy55M-Award 2013

Christian Markus Hüber

PhD Supervisor: Dr. Francesco Colucci

Department of Obstetrics & Gynaecology
University of Cambridge
Box 223, The Rosie Hospital
Robinson Way
Cambridge CB2 0SW, United Kingdom

Immunological memory and adaptive features of innate Natural Killer cells

Immunological memory is a hallmark of adaptive immunity, i.e. T and B cells. Recent evidence, however, suggests that also innate immunity may form memory and could produce long-lived cells. Long-lived Natural Killer (NK) cells form in mice in response to specific stimuli (i.e. viruses) and are more responsive to subsequent viral infections. Preliminary data from patients suggests that human NK cells too may form memory. Therefore characterization of memory NK cells may inform a new generation of vaccines and therapies. During my first year of the Wellcome Trust Infection and Immunity PhD Programme in Cambridge, I have successfully adapted and validated a new mouse model of cell fate mapping to study memory NK cells. I am therefore able to mark activated NK cells indelibly with a fluorescent marker for as long as they live by exploiting the cre/loxP system, which switches on a fluorescent reporter in activated NK cells. So, for example, I can carefully analyse the fate of activated NK cells after activation by viruses, but also other stimuli, such as tumour cells or invading fetal cells during pregnancy – indeed NK cells are key players in tumour immunity and in reproduction. Particularly relevant to tumour immunity is a population of cytokine-induced long-lived NK cells, which are, both in humans and mice, more powerful against cancer cells. Being in my second year, I am now studying the fate of marked NK cells in terms of life span and their residence in the mouse body. I will then be able to analyse the effector functions of long-lived NK cells upon restimulation with the same or a different stimulus.

Murine cytokines by ImmunoTools would help me studying how various cytokines shape memory NK cells. Using our unique model system we can map the function of specific cytokines and combinations of cytokines in shaping “memory” in NK cells ex vivo. As an example, we can link specific cytokines or combinations of cytokines to specific effector functions elicited in both “conventional” and memory NK cells. In addition, we will measure NK cell effector functions such as natural and antibody-dependent cellular cytotoxicity, as well as production of IFN-γ, GM-CSF, TNF-α and different chemokines. Having the opportunity to switch on or off and to amplify a particular effector function in order to adapt it to a clinical need would offer a great advantage in therapeutic settings that aim at manipulating the immune system. For example, during a liver infection it may be advisable to switch on IFN-γ production but not cytotoxicity of NK cells in order to avoid killing of infected hepatocytes. The results of our experiments may inform new NK cell-based therapies and help to

understand if and how memory NK cells can be exploited in next-generation vaccines based on innate immunity.