세미나 초록

발표주제	**Transcriptional and epigenetic regulation of immune cells for next generation biopharmaceutical medicine**
발표내용	Changes in cell state and cellular behaviour are driven by environmental signals that modulate intracellular pathways to alter gene transcription. As an example, tumour-infiltrating CD8+ T cells monitor tumour antigens (peptide-MHC complexes) and other surface signals on antigen-presenting cells through their T cell receptors and costimulatory or inhibitory receptors, and integrate these with responses to cytokines, chemokines, adhesion molecules, TNF superfamily proteins, sensors of extracellular metabolites such as ATP, and so on. Each of these signals activates intracellular pathways that are integrated at the transcriptional and post-transcriptional levels to produce distinct patterns of gene expression and hence distinct anti-tumour responses. Cooperative interactions among transcription factors are essential for gene transcription. We previously showed that NFAT and AP-1 (Fos-Jun) transcription factors cooperate to promote the effector functions of T cells, but that under conditions where it is unable to cooperate with AP-1, NFAT imposes a negative feedback programme of T cell hyporesponsiveness ("exhaustion"). Here we show that BATF and IRF4 cooperate to counter T cell exhaustion. Overexpression of Batf in CD8+ T cells expressing a chimeric antigen receptor (CAR) promoted the survival and expansion of tumour-infiltrating CAR T cells, increased their production of effector cytokines, decreased their expression of inhibitory receptors and the exhaustion-associated transcription factor TOX, and led to the generation of long-lived memory T cells that controlled tumour recurrence. These responses were dependent on the BATF-IRF interaction, since cells expressing a Batf mutant unable to interact with Irf4 did not survive in tumours and did not effectively delay tumour growth. We suggest that BATF overexpression is a therapeutically viable option for improving the anti-tumour responses of T cells, by skewing their phenotypes and transcriptional profiles away from exhaustion and towards increased effector function.