



## **TWO POSITIVE FEEDBACK LOOPS CONTROL FUNCTION AND MEMORY INDUCTION IN TYPE 1 T-HELPER LYMPHOCYTES**

Edda G. Schulz

*Developmental Epigenetics group, Institut Curie, Paris, France*

T-helper (Th) lymphocytes regulate adaptive immune responses. According to the nature of the pathogen, naïve Th lymphocytes can differentiate into either Th1 or Th2 cells. These differentiated cell types are critical for the establishment of immunological memory. In this work I aimed at understanding how the gene-regulatory network in Th1 cells integrates extracellular signals to control cellular function. I performed quantitative kinetic measurements to identify new interactions and construct a mathematical model for the expression dynamics of critical genes: (1) the Th1 lineage specifying transcription factor T-bet, (2) the receiver of the Th1 differentiation signal, IL-12 receptor, and (3) the Th1 effector cytokine Interferon- $\gamma$ . Model-driven experiments showed that instruction for Th1 differentiation is a two-step process. Initial T-bet induction through a sensitive Ifn- $\gamma$  dependent pathway accelerates the response of the slow feedback loop between T-bet and the IL-12 receptor, active late during differentiation. I have identified this slowly activated T-bet/IL-12R feedback as the critical determinant for the differentiation efficiency. Thus, specific modules within the gene-regulatory network can be associated with effector function and memory induction in Th1 cells, respectively.