Decoding cellular signals: irreversible commitment during hES cells differentiation

Silvia Santos
MRC-Imperial College London

During cell decision-making signal transduction networks dynamically change in time and space in response to cues, and thereby trigger different cellular states. Human embryonic stem cells (hESC) have the propensity to differentiate into the three germ layers (endoderm, mesoderm and ectoderm) and are therefore an ideal system to address *how extracellular cues are decoded in order to commit to a specific cell fate*. Bone morphogenetic protein 4 (BMP4) triggers hES cells differentiation towards mesoderm, via SMAD signaling.
We investigated how BMP4 signals are first decoded by SMAD signaling networks and drive hES cell differentiation. We found that irreversible commitment to differentiation in hES cells is an unexpectedly early event, which precedes changes in cell morphology, epigenetics and lineage specific gene expression. In my talk I will describe how we combined single cell imaging, RNAseq and mathematical modelling and found that a sustained, bistable and irreversible activation of SMAD signaling networks underlies early commitment to hESC differentiation. I will also show that commitment to differentiation is driven by commitment genes, which decode SMAD activation dynamics. Finally, I will discuss the implications of early committing to differentiation for plasticity in cell fate choices.
Our work is shedding light into how the pluripotency-differentiation switch is triggered by intracellular protein and gene networks and provides a simple mechanism for how commitment and fate-choice can be encoded during cell state transitions.