Speaker name: Ana Cvejic, University of Cambridge

Title: “Single Cell Analysis of Zebrafish Blood Development”

Short abstract:
Mammalian blood formation is the most intensely studied system of stem cell biology, with the ultimate aim to obtain a comprehensive understanding of the molecular mechanisms controlling fate-determining events. A single cell type, the haematopoietic stem cell (HSC), is responsible for generating more than 10 different blood cell types throughout the lifetime of an organism. This diversity in the lineage output of HSCs is traditionally presented as a stepwise progression of distinct, transcriptionally homogeneous populations of cells along a hierarchical differentiation tree. However, most of the data used to explain the molecular basis of lineage differentiation and commitment were derived from populations of cells isolated based on well-defined cell surface markers. An inherent problem with this approach is that the presence of specific cell surface markers does not directly reflect the transcriptional state of a cell.

Here we used a marker-free approach to computationally reconstruct the blood lineage tree in zebrafish and order cells along their differentiation trajectory, based on their global transcriptional differences. By reconstructing their developmental chronology computationally, we were able to place each cell along a continuum from stem cell to mature cell, refining the traditional lineage tree. Within the population of transcriptionally similar stem and progenitor cells our analysis revealed considerable cell-to-cell differences in their probability to transition to another, committed state. This suggested that although global transcriptional changes before and after the branching point were continuous, the probability of a cell progressing to any of the committed states was determined only by a subset of highly relevant genes. Therefore, cells that were transcriptionally similar overall could have a high probability of differentiation to distinct cell types. Once the cell fate decision was executed, the progression of cells along the continuum is characterised by a highly coordinated transcriptional program, displaying simultaneous suppression of genes involved in cell proliferation and ribosomal biogenesis and increased expression of lineage specific genes. Our comparative analysis between zebrafish, mouse and human across seven different haematopoietic cell types, including innate lymphocytes (ILCs), revealed a high level of conservation of blood cell type specific genes. The lowest conservation was observed for lymphocytes, possibly reflecting their adaptation to fish specific pathogens and virulence factors.

Short bio:
Ana Cvejic is a Faculty member at the Cambridge Stem Cell Institute and an Honorary Faculty member at the Sanger Institute. In 2008 Ana received her PhD in Biochemistry at the University of Bristol. She then moved to the University of Cambridge/Wellcome Trust Sanger Institute to start a Postdoctoral Fellowship, with Professor Willem Ouwehand. In 2012 Ana was awarded the CRUK Career Development Fellowship to start her independent group. In 2015 Ana was awarded ERC Starting Grant and in 2016 EMBO Young Investigator award. With the principal expertise and research interest in the

molecular regulation of blood stem cell fate choices Ana's research sits at the intersection of molecular biology, genetics and systems biology and it closely couples experimental approaches and "big" biological data analysis.

Link lab website: https://www.stemcells.cam.ac.uk/research/pis/cvejic and http://www.haem.cam.ac.uk/staff/senior-staff/dr-ana-cvejic/