BIOENGINEERING RECRUITING SEMINAR

“Quantitative Dissection of Protein Dynamics in the Immune System”

Thursday – April 23, 2015 – 3:00 p.m.
EPFL – room SV1717a

Marko Jovanovic, Ph.D.
Regev Lab, Broad Institute of MIT and Harvard, Cambridge, MA (USA)

host: Prof. B. Deplancke

Abstract

Gene expression is tightly controlled from transcription to protein degradation. Although the mammalian genome encodes >1500 RNA binding and translation-associated proteins (RBPs), most systematic approaches focused on changes in mRNA abundance. We developed new experimental and computational strategies to study the regulation of protein production in dynamic systems, and applied them to the response of primary dendritic cells (DCs) to pathogens. First, we combined measurements of protein production and degradation and RNA dynamics to build a quantitative, genome-scale model of the differential regulation of gene expression in LPS stimulated primary DCs. We found that upon LPS stimulation, changes in RNA abundance play a dominant role in determining most dynamic fold changes in protein levels. In contrast, the preexisting proteome of proteins performing basic cellular functions is remodeled primarily through changes in protein production or degradation. Next, to help determine which genes regulate such expression changes, we adapted the new CRISPR technology to develop a marker based genome-wide CRISPR screen in DCs from a new Cas9-transgenic mouse. In this screen, DCs are infected with a genome wide lentiviral library of sgRNAs, stimulated with LPS, and monitored by intra-cellular staining for the anti-inflammatory cytokine TNF-α. We successfully discover near-complete known pathways of the LPS response as well as many new candidates, especially in complexes regulating protein modification or chromatin biology not previously implicated in the response. This work provides a systematic framework to dissect gene expression regulation that I will leverage to understand the role of RBPs and the ribosome in protein production.

(Dr. Jovanovic is applying for a position in Bioengineering at the EPFL)

See current Bioengineering seminar calendar at http://bioengineering.epfl.ch/seminars