CANCER SCIENCE INSTITUTE OF SINGAPORE

# CANCER SYSTEMS BIOLOGY MINI-SYMPOSIUM

**Date:** Thursday, 26 November 2015
**Time:** 2pm - 4pm
**Venue:** #01-02 Learning Rm, Centre for Translational Medicine (MD6)
(14 Medical Drive, Singapore 117599)
**Host:** Dr. Pieter Eichhorn & Dr. Touati Benoukraf

## Lodewyk Wessels



**Professor and Group Leader, Computational Cancer Biology Group, The Netherlands Cancer Institute**

### Modeling Pharmacogenomic Interactions In Cancer

Systematic studies of cancer genomes are providing unprecedented insights into the molecular nature of human cancer. Using this information to guide the development and application of therapies in the clinic is challenging. Here we report how cancer-driving alterations identified in 11,289 tumors from 29 tissues (integrating mutations, copy-number alterations, methylation and gene expression) correlate with response to 265 compounds profiled in 1,001 human cancer cell-lines. We find that cell-lines faithfully recapitulate oncogenic aberrations identified in tumors, and that many of these associate with drug sensitivity or resistance. Logic-based modeling uncovers combinations of aberrations that specifically sensitize to drugs. *For most drugs, combinations of mutations explain the drug response better than single mutations.* Finally, projecting the identified markers back onto primary tumors captures their clinical relevance, in terms of prevalence in cancer patients. Our comprehensive analysis and associated datasets are rich resources to identify novel therapeutic options for selected cancer sub-populations.

## Laurence Calzone, Andrei Zinovyev





**Research Engineers, Institut Curie**

### Identifying the Interaction Between p53 And Notch pathway In Triggering Metastasis: From Maps To Models.

Cancerogenesis is driven by mutations leading to dysfunctioning of complex network of molecular interactions and affecting multiple cellular functions at the same time. Successful application of systems biology methods for analysis of high-throughput data requires detailed reconstructions of signalling networks amenable for computational analysis. Atlas of Cancer Signalling Network (ACSN) is a global map of molecular mechanisms implicated in cancer. The resource is combined with tools for map navigation and data visualization in the biological network context. Constructing and updating ACSN involves careful manual curation of molecular biology literature and participation of experts. The content of ACSN covers major mechanisms involved in cancer progression, including DNA Repair, Cell Survival, Apoptosis, Cell Cycle, EMT and Cell Motility. Cell signalling mechanisms are depicted in details, together creating a seamless 'geographic-like' map of molecular interactions frequently deregulated in cancer. The map is browsable using the Google Maps engine and semantic zooming principle. The associated web-blog provides a forum for commenting and curating the ACSN content. ACSN may help improving patient stratification, predicting treatment response and resistance to cancer drugs as well as proposing new treatment strategies. ACSN is available at http://acsn.curie.fr. Various roles of TP53 protein are presented in all maps of ACSN in different post-translational modifications. Using the information gathered in ACSN, we built a logical model focusing on metastasis. We will present how diverse alterations in the two pathways, the Notch and p53 pathways, can trigger metastasis. The model is able to reproduce previously published experimental results, and to formulate some predictions on the role of genes and pathways in the metastatic process. In this study, we have also developed two methods in order to: (1) predict genetic interactions and (2) match the transcriptomics data to the attractors of the logical model and validate the model on cell line experiments. The genetic interaction profile for our model reveals putative candidates for targeted therapy able to diminish the probability of metastasis. In particular, we have shown that the double mutation Notch gain-of-function and p53 loss-of-function has the highest probability to acquire metastasis. This result matches the hypothesis from our previous work, which was experimentally verified in mouse model of colon carcinoma (Chanrion et al, 2014, Nature Communications).