Master « In Silico Drug Design »
Second Year

INTERNSHIP OFFER

Academic Year 2016/2017

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Name of laboratory or company: Novartis, NIBR(Novartis Institute for Biomedical Research)

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Internship field : Research **Professional**

Few keywords to describe internship subject:

Cancer cell lines, chemotherapeutics , target genes , siRNA, efflux pumps, sensitivity profiles, off target effects , drug resistance

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Project Title : Reliability of RNAi data for predicting of response to compound data on cancer cell lines.

The internship subject is a first step towards a thesis : Yes - No

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Short description of project:

The aim of this project is to understand to what extent RNAi mediated viability screens on cancer cell lines can reliably predict compound sensitivity. To this effect two available datasets will be used:

1. A pooled short hairpin RNA (shRNA) screen across 390 cell lines from the Cancer Cell Line Encyclopedia (CCLE) with a library encompassing ~7500 genes. This effectively provides a sensitivity profile across cell lines upon gene knock-down.
2. A compound-mediated proliferation dataset performed on a subset of the same cell lines. The annotations for these compounds include among others the structure of the compound, the expected mechanism of action (MoA) as well as the expected main targets of the compound.

The integration of the datasets should in a first instance enable the investigation of compound vs gene profile correlations, i.e. the compound mediated sensitivity profile vs the gene-knock down sensitivity profile. **As a result multiple questions can then be asked:**

1. Is the gene with the strongest correlation to the compound profile also the expected target of the compound? i.e. can we predict the MoA of less well annotated compounds using gene knock-down sensitivity data?
2. If not can the deviation be explained by off-target effects? Is the combination of the main target gene profile in combination with its off-target profile a good predictor of the compound sensitivity profile?

Can further analysis be performed to inform on potential off-target effects of poorly annotated compounds?

3. What are the influences of the compounds' properties on the predictive value of the shRNA data? E.g. Is the compound a substrate of the efflux pump?

This study aims to tackle these questions. The analysis will be performed using the statistical computing environment R.

QSAR and structural analysis studies may also be performed on compound data for further comprehension of the relationship between their chemical properties and their biological effect (including target and off target effects)

As a result of this project we hope to gain a better understanding of compound sensitivities in cancer cell lines by leveraging the functional annotation provided by shRNA pooled screens as well as the available information on compound structure and expected MoA. If successful this study should provide impactful information for the drug discovery process by raising off-target flags early, helping propose new compound MoAs, or generally raise the level of understanding of compound mediated sensitivity in cell autonomous in vitro settings.

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