

Master Project internship

Project title	Classifying compounds according to mode-of-action through multiplexed automated-fluorescence microscopy assays
Laboratory	Biomolecular Screening Facility (http://bsf.epfl.ch/)
Head of Lab Assistant	Dr Gerardo Turcatti, MER Dr Fabien Kuttler
Contact	gerardo.turcatti@epfl.ch (021 693 96 66) fabien.kuttler@epfl.ch (021 693 16 28)
Starting date	2020

Background

High content analysis using automated fluorescence microscopy is widely applied at BSF-ACCESS for morphological profiling of cells upon interaction with screened drugs or chemical compounds tested. Highly informative data extracted from fluorescence microscopy imaging of cells allows identifying and classifying a certain number of phenotypes clustered according to the biological signature obtained (1).

Aim

In order to increase the level of information related to intracellular events provoked by chemical interference, the morphological profiling assay 'cell painting' (2) will be implemented. Briefly, in this multiplexed method, six fluorescent probes are used simultaneously for revealing cellular compartments or organelles under chemical perturbation. By automated image analysis and extraction of hundreds of features, and using machine learning algorithms, compounds will be clustered according to the phenotypic profile they trigger.

Following proper setting up, development and statistical assay validation, a screen will be performed using a training set of drugs with known mode of action from the ACCESS 'repurposing collection' (3), and fingerprints or signatures will be used for assignment of possible modes of action for new compounds. This will constitute a significant advancement in the early drug discovery process for characterizing hits and leads from our screens, for discovering new biological activities and/or determining potential off target effects. In addition, such predictive profiling approaches would be valuable for characterizing synergies in drug combination approaches.

For this multidisciplinary chemical biology project, experiments will initially be performed with one cell line at a fixed time point and at a single concentration. For deeper characterization and for few selected compounds, fluorescence-imaging time-lapse experiments can be envisioned for tracking the phenotypic evolution over time. Open source supervised machine learning software and solutions such as Cell profiler (4) or Cell cognition (5) will be used for image analysis and throughout the project.

References

1. Rappaz, B., Kuttler, F., Breton, B. and Turcatti, G. (2015) In Fang, Y. (ed.), *Label-Free Biosensor Methods in Drug Discovery*. Springer New York, pp. 307-325.
2. Bray, M.-A., Singh, S., Han, H., Davis, C.T., Borgeson, B., Hartland, C., Kost-Alimova, M., Gustafsdottir, S.M., Gibson, C.C. and Carpenter, A.E. (2016) Cell Painting, a high-content image-based assay for morphological profiling using multiplexed fluorescent dyes. *Nature Protocols*, **11**, 1757-1774.
3. Corsello, S.M., Bittker, J.A., Liu, Z., Gould, J., McCarren, P., Hirschman, J.E., Johnston, S.E., Vrcic, A., Wong, B., Khan, M. *et al.* (2017) The Drug Repurposing Hub: a next-generation drug library and information resource. *Nature Medicine*, **23**, 405-408.
4. Carpenter, A.E., Jones, T.R., Lamprecht, M.R., Clarke, C., Kang, I.H., Friman, O., Guertin, D.A., Chang, J.H., Lindquist, R.A., Moffat, J. *et al.* (2006) CellProfiler: image analysis software for identifying and quantifying cell phenotypes. *Genome biology*, **7**, R100-R100.
5. Held, M., Schmitz, M.H.A., Fischer, B., Walter, T., Neumann, B., Olma, M.H., Peter, M., Ellenberg, J. and Gerlich, D.W. (2010) CellCognition: time-resolved phenotype annotation in high-throughput live cell imaging. *Nature Methods*, **7**, 747-754.