Combining High Throughput Screening with Image-Based Phenotyping to advance APBD drug discovery

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Glycogen storage diseases (GSD) are caused by intracellular accumulation of insoluble inclusion bodies, chiefly composed of normal, or malconstructed glycogen. In the prototypical GSD Adult Polyglucosan Body Disease (APBD) the pathogenic glycogen accumulates in the cytosol of nerve cells as an aberrant, poorly branched form called polyglucosan. Polyglucosans are formed as a result of deficient activity of the glycogen branching enzyme (GBE).

We have developed a patient cell-based assay in order to identify small molecule inhibitors of polyglucosan body (PB) accumulation. Using this assay in a high throughput format, we have screened the DIVERSet-CL 10,080 compound library and discovered and validated 11 dose-dependent potential hits. Similarities between these hits and drugs interacting with docking targets of the hits have been found and most hits were similar to drugs interacting with the glycogen synthase (GS) activator protein phosphatase 1 (PP1).

We have also generated a novel, personalized analytical tool for assessing drug efficacy. This tool is image-based phenotyping (IBP): a global phenotypic fingerprint of patients' primary skin fibroblasts, which encompasses multiple cellular and subcellular features. IBP enables us to identify image based features within patient cells which may change in response to tested small molecules. This analysis has generated phenotypic signatures of APBD patients and control subjects. Using computational classification methods, we are able to define control and pathological global phenotypes in skin fibroblasts respectively derived from unaffected subjects and APBD patients. This analysis will be used to compare the effect of our 11 hits on cell status.

In summary, combining high throughput screening (HTS) with clustering analysis and especially with IBP constitutes an important upgrade to conventional HTS. As demonstrated in our work on APBD, obtaining as much information as possible on the cellular effects of tested drug candidates is crucial for their future development and will facilitate dealing with their prospective adverse effects.