New concept for treatment of glycogen storage disease Ib and diabetes mellitus type 2: small molecule compounds able to adjust glucose level through binding glucose-6-phospate translocase (GlucoAdjust)

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GlucoAdjust project aims to solve fast-growing health challenges important for the society, namely it will focus on discovery of new treatments for one rare disease glycogen storage disease type Ib (GSD Ib) and one common disease diabetes mellitus type 2 (DM type 2). We propose a completely new concept based on the identification of small molecule (SM) compounds able to directly bind to glucose-6-phospate translocase (G6PT) and thus fine-tune glucose level. To tackle these challenges, an interdisciplinary international team will screen large library of SMs combining in silico and in vitro approaches and identify SMs that directly bind to G6PT. SMs able to stabilize G6PT and increase its function thus correcting hypoglycemia are potential drugs for GSD Ib. On the other hand, SMs that inhibit G6PT may be used to induce hypoglycemia in DM type 2 treatment. To obtain highly functional results of testing SMs in vitro, human hepatocyte models for GSD Ib and DM type 2 as well as controls will be developed (differentiated from human healthy and GSD Ib iPSC and diabetic adipose stem cells). For the first time, whole transcriptome of human GSD Ib hepatocytes will be used to delineate molecular processes disturbed due to G6PT deficiency. As a result, RNA hallmarks of GSD Ib phenotype will be determined and used for evaluation of SMs' effect in both models. To be efficient for GSD Ib, SMs will have to revert GSD Ib phenotype into normal. The key to discover satisfactorily effective, yet sufficiently mild inhibitor for DM type 2 will be to avoid hallmarks representing GSD Ib phenotype. Thus, a revolutionary concept of using GSD Ib as a model of hypoglycemia to better optimize DM type 2 treatment is proposed here. Results will be openly disseminated to make a wide scientific, educational, social and economic impacts. GlucoAdjust anticipates innovative results with a potential to be further translated into drugs able to improve lives of people with GSD Ib and DM type 2 worldwide.