Poster

Glucokinase and structural-based drug discovery

D. Gasparikova[1], E. Pohl[1], R. Chikhale[2]

[1]Durham University, Lower Mount Joy, South Rd, Durham, DH1 3LE, United Kingdom [2]12 Union Road, Cambridge, CB2 1EZ, United Kingdom dorota.gasparikova@durham.ac.uk

Human *glucokinase* (GK) is a hexokinase isozyme (hexokinase IV) active in the liver and the pancreas [1]. In the beta cells of the pancreas, GK acts as a glucose sensor for insulin secretion, while in the liver it facilitates the transformation of glucose into glycogen, which allows glucose to be stored for later use (Fig. 1) [2]. The role of GK in the reduction of glucose levels in the body leads to the pharmacological desire to develop glucokinase binders with the potential to counterbalance the glycaemic imbalance related to type-2 diabetes [3]. Consequently, applying fragment-based methods to identifying fragment hits binding to GK can lead to the recognition of allosteric activators/inhibitors of GK, which can be used as lead compounds in the future. Furthermore, GK undergoes conformational changes depending on the presence of glucose and can therefore be 'closed', 'open' or 'super-open' [4]. Understanding the different conformations and their role in binding is very important for determining which binding poses are feasible. In combination with *docking* experiments using GOLD, X-ray crystallography and binding assays are allowing for more insight to be made into interactions of GK and a selection of potential GK binders.

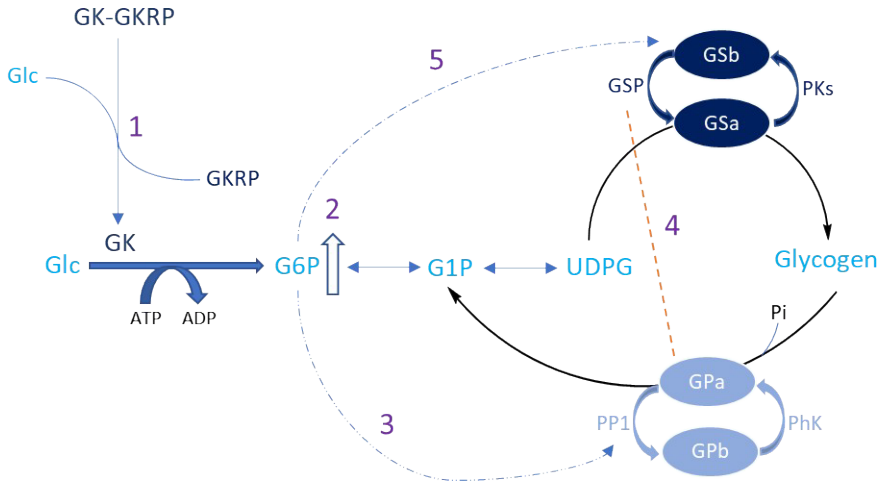

Figure 1. Diagram representing the steps involved in the conversion of glucose into glycogen in the liver. PKs stands for protein kinase and PhK stands for phosphorylase kinase.

[1] S. M. Sternisha and B. G. Miller, Molecular and cellular regulation of human glucokinase, Arch. Biochem. Biophys., 2019, 663, 199–213.

[2] Matschinsky, Franz M., and David F. Wilson. 2019. "The Central Role of Glucokinase in Glucose Homeostasis: A Perspective 50 Years after Demonstrating the Presence of the Enzyme in Islets of Langerhans." *Frontiers in Physiology* 10

[3] Z. S. Cheruvallath, S. L. Gwaltney, M. Sabat, M. Tang, J. Feng, H. Wang, J. Miura, P. Guntupalli, A. Jennings, D. Hosfield, B. Lee and Y. Wu, Design, synthesis and SAR of novel glucokinase activators, Bioorganic Med. Chem. Lett., 2013, 23, 2166–2171.

[4] P. B. Iynedjian, Molecular physiology of mammalian glucokinase, Cell. Mol. Life Sci., 2009, 66, 27–42.