EDITORIAL

Special issue of Mini-Reviews in Medicinal Chemistry dedicated to the memory of Nikos G. Oikonomakos (1945-2008).

Glycogenolysis is the phosphorolytic degradation of the storage polysaccharide glycogen to glucose-1-phosphate which, after subsequent transformations to glucose-6-phosphate and glucose, may serve as an energy source for the organism's cells. The rate determining phosphorylation step of the process is catalyzed by glycogen phosphorylases (GP). These enzymes belong to the most studied biocatalysts and archetypical phenomena like phosphorylative and allosteric regulation were described for the first time with GPs. The tissue specific GP isoenzymes are responsible for maintaining blood glucose levels (liver isoform) as well as for direct fuel supply of the given cells/tissues (muscle and brain isoforms). Because of the direct connection between blood sugar levels and elevated hepatic glucose output, and thereby liver GP, in type 2 diabetic patients inhibition of the enzyme was suggested as a possible base for an antidiabetic therapy. Though this is the most intensively investigated therapeutic field, several others e. g. treatment and/or prevention of early cardiac and cardiovascular disease in non-diabetics, stabilizing cardiac arrhythmias, protection against ischemic injury, preventing tumour growth have been suggested to be targeted by inhibitors of GP. Thus, finding good matches between the biological and chemical space represented by the binding sites of GP on one hand and the relevant parts of the small molecule universe on the other has attracted long standing interest in both academia and industry.

The roots of these investigations had been in Oxford (United Kingdom) where *L. N. Johnson*, *G. W. J. Fleet*, *N. G. Oikonomakos* and coworkers started to study glucose derived inhibitors of GP by combining methods of organic synthesis, enzyme kinetics, protein crystallography, and computational chemistry. The work was continued and extended by the Oikonomakos group in Athens (Greece) as part of a worldwide collaboration. Although the sudden and untimely passing of Nikos on Aug 31, 2008 brought about a slight break in this activity, the members of the group are carrying on the research. What else than this could demonstrate better how enthusiastic as a scientist, how collaborative as a colleague, and how efficient as an educator Nikos was.[*] The authors and the editor of this special issue pay a tribute to his memory by gathering the latest results of the title field.

The most accessed GP isolated from rabbit muscle is presented in the first paper by *Evangelia D. Chrysina* (Athens, Greece) describing the binding peculiarities of a range of glucose derivatives and analyzing the structure-activity relationships in structural terms supported by crystallographic results. The next survey by *Jean-Pierre Praly* and *Sébastien Vidal* (Lyon, France) gives an overview of the glycogen metabolism with its enzymes and regulation in the context of diabetes mellitus followed by a

[*]For a detailed biography, please, follow the link: http://www.eie.gr/nhrf/institutes/iopc/cvs/cv-oikonomakos-en.html

detailed description of syntheses and kinetic studies of glucose based and iminosugar type inhibitors disclosed in the past couple of years. *Thanasis Gimisis* (Athens, Greece) summarizes an extensive synthetic work supported by enzyme kinetics and crystallography to probe the catalytic site of GP by *N*-glucopyranosides of oxamic acid derivatives, L-α-amino acids and peptides, purine and pyrimidine nucleobases and related compounds. *Wendy A. Loughlin* (Brisbane, Australia) focuses on the allosteric inhibition of GP by a large array of compounds of extremely high chemical diversity and also discusses the question of isoform selectivity. The application of computational methods to the design of GP inhibitors is analyzed by *Joseph M. Hayes* and *Demetres D. Leonidas* (Athens, Greece) who present several examples on how computations may reduce experimental costs, cost effectiveness of molecular modelling and docking methods themselves, and what are the pros and cons of binding site predictions. Physiological investigations surveyed by *Loranne Agius* (Newcastle, United Kingdom) have been instrumental in revealing the ways of action of GP inhibitors and validating GP as a therapeutic target against type 2 diabetes. Last but not least, *Li Xu* and *Hongbin Sun* (Nanjing, China) raise and explain the possibility of a new non-antidiabetic application of inhibition of glycogenolysis in a therapeutic approach to cerebral ischemia.

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