

P022 Assessment of glucokinase activators on pancreatic beta cell function and viability

Niamh Mullooly¹, Dave Smith² and Philip Newsholme¹

¹UCD School of Biomolecular and Biomedical Science, Conway Institute, UCD Dublin, Ireland

²Pancreas Biology Section AstraZeneca 3S28A Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK

Type 2 diabetes is associated with failure of the pancreatic beta cell to secrete appropriate amounts of insulin in response to an increase in the circulating concentration of glucose. Recent research efforts have targeted mechanisms of diabetes associated beta cell failure with respect to insulin secretion. New beta cell therapies will follow discovery of new targets for cell based anti-diabetic agents. The glucose sensing enzyme glucokinase (GK) is one promising target. This enzyme catalyses a key early step in glycolysis - the phosphorylation of glucose to glucose-6-phosphate. The importance of this enzyme and its tissue selectivity, have led to the development of molecular activators of GK. We have tested GKA50, an Astazeneca produced potent activator of GK activity, with respect to clonal beta cell (BRIN-BD11) metabolism, insulin secretion and cellular integrity. This bio-engineered cell line has a high glucokinase-kexokinase ratio compared to other beta cell lines and exhibits bi-phasic glucose stimulated insulin secretion, consistent with normal beta cells. The metabolic and insulin secretory action of GKA50 was determined using basal (1.1mM) and stimulatory (16.7mM) glucose + alanine (10mM) conditions. The effects of GKA50 on cell growth and viability was assessed using the WST-1 cell viability assay. Glucose consumption and lactate production were also analysed. Results demonstrated that GKA50 enhanced insulin secretion in stimulatory conditions and that secretion was glucose dependant. This research may lead to development of novel enzyme based drugs for future therapy of type 2 diabetes.