STRESZCZENIE W JĘZYKU ANGIELSKIM

Tytuł w języku angielskim: Development of an innovative GPR40 agonist as a potential therapeutic in therapy of the type 2 diabetes.

Research on the interplay between non-esterified fatty acids and glucose, glucagon and insulin homeostasis dates to the 1960s and 1970s. At the beginning of the 21st century, a period of intense work began with the deorphanization of G-protein coupled receptor 40 (GPR40), also called the free fatty acid receptor 1 (FFAR1). As a result of these efforts, it turned out that synthetic analogs of natural GPR40 ligands may be utilized in the treatment of diabetes type 2. The activation of FFAR1, which is highly expressed on beta cells of pancreatic Langerhans islets, by medium-to long-chain endogenous free fatty acids, results in the stimulation of insulin release in a blood glucose concentration-dependent manner. The enthusiasm for new, orally dosed treatments for type 2 diabetes likely being free of the potential occurrence of hypoglycemia as some approved drugs, persisted until the Takeda company announced the withdrawal of their most promising GPR40 agonist drug candidate, TAK-875 (fasiglifam), from the Phase 3 clinical trials, due to some concerns about the liver safety. Independently, other companies stopped or slowed down their GPR40 agonist development programs as well. This fact has left an open space for new opportunities, but at the same time, many problems were raised regarding designing an effective and safe FFA1-based drug for the treatment of T2D.

CPL207280, an innovative compound designed and developed by Celon Pharma S.A., showed 3 times greater activity towards the receptor *in vitro* and exhibited similar pharmacological effects *in vivo* in diabetic animal models to that observed for TAK-875. CPL207280 showed 10 times reduced toxicity in hepatocytes, 10 times reduced inhibition of hepatic bile acid transporters and no interference with oxidative phosphorylation in mitochondria or mitochondria viability compared to TAK-875. More importantly, it showed no hepatotoxicity in toxicology studies in rats and monkeys. Therefore CPL207280 is ready for further clinical development as a potential innovative antidiabetic drug.