

Ultra-Long-Acting GLP-1 Analogue

Overview

Drug Name	P11				
Description	To achieve an ultra-long-acting and effective GLP-1 analogue of minimized side				
	effects, a unique GLP-1 protection technology was developed to prevent				
	degradation mediated by proteolytic enzymes. The modified GLP-1 analogues are				
	gradually released in vivo, prolonging the effective duration of treatment. The				
	commercially available Trulicity (developed by Eli Lilly) for treating diabetes is also				
	a GLP-1 analogue, also resulting in hypoglycemic weight loss. Our In vivo and in				
	vitro experiments have shown that applying our protection technology to Trulicity				
	leads to a more constant drug concentration in blood, significantly longer half-life,				
	and less side effects. In addition, the plan to develop a long-acting GLP-1/GIP dual				
	agonist using this protection technology has been proposed.				
Target	GLP-1 receptor				
Drug Modality	Fc fusion protein; Polypeptide				
Indication	Type 2 diabetes				
Product Category	GLP-1 analogue				
Mechanism of Action	As a GLP-1 analogue, P11 binds to GLP-1 receptors to activate intracellular				
	signaling pathways, achieving a unique hypoglycemic effect that can be prolonged				
	by this novel protection technology.				
Status	Preclinical				
Patent	Relevant patents submitted				

Collaboration Opportunity

Protheragen Inc. is actively seeking partnership to further develop P11. Potential collaboration can be strategic alliance, licensing, or marketing agreement. We look forward to hearing from you.

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Target

Glucagon-like Peptide 1 (GLP-1) Receptor

Introduction	Glucagon-like peptide-1 (GLP1) is a hormone derived from the preproglucagon			
	molecule (GCG; 138030) and is secreted by intestinal L cells. It is the most potent stimulator of glucose-induced insulin secretion and also suppresses in vivo acid secretion by gastric glands. GLP1 receptor (GLP1R) bind to GLP1 with high affinity			
	and the binding between the two activates adenylate cyclase. The receptor is 463			
	amino acids long and contains 7 transmembrane domains. Sequence homology is			
	found only with the receptors for secretin, calcitonin, and parathyroid hormone,			
	which together form a newly characterized family of G protein coupled receptors.			
Approved Name	Glucagon like peptide 1 receptor			
Official Symbol	GLP1R			
Gene Type	Protein coding			
Synonyms	GLP-1; GLP-1R; GLP-1-R			
Ensembl	ENSG00000112164			
Gene ID	2740			
mRNA Refseq	NM_002062			
Protein Refseq	NP 002053.3			
OMIM	<u>138032</u>			
UniProt ID	P43220			
Chromosome Location	6p21.2			
Clinical Resources				
Gene Function	This gene encodes a 7-transmembrane protein that functions as a receptor for			
	glucagon-like peptide 1 (GLP-1) hormone, which stimulates glucose-induced insulir			
	secretion. This receptor, which functions at the cell surface, becomes internalized			
	in response to GLP-1 and GLP-1 analogs, and it plays an important role in the			

signaling cascades leading to insulin secretion. It also displays neuroprotective effects in animal models. Polymorphisms in this gene are associated with diabetes. The protein is an important drug target for the treatment of type 2 diabetes and stroke. Alternative splicing of this gene results in multiple transcript variants.

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Pathway	MAPK signal pathway; cAMP signaling pathway		
Major Conditions	Diabetes; Cardiovascular disorders; Insulinoma; Myocardial infarction; etc.		

Indication

Type 2 Diabetes (T2D)

The International Diabetes Federation (IDF) estimated a global prevalence of 463 million adults living with diabetes in 2019, equivalent to 9.3% of the adult (20-79 years) world population, and projected that this number would increase to 700 million (10.9% of adults) by 2045. Diabetes is classified into four major subtypes: type 1, type 2, gestational, and other. Type 2 diabetes (previously designated non-insulin-dependent diabetes mellitus), or adult-onset diabetes, accounts for over 90% of the diabetic patient population in the Western world. Risk factors for type 2 diabetes include age, obesity, physical inactivity, family history of diabetes, prior history of gestational diabetes, impaired glucose tolerance, impaired fasting glucose, hypertension, polycystic ovary syndrome and race/ethnicity. Type 2 diabetes is strongly favored by genetic predisposition, although environmental factors also contribute significantly to its development. The objective of diabetes therapy is to achieve the best possible glycemic control while avoiding hypoglycemia, thus reducing the long-term risk of complications. Current treatment guidelines emphasize three major components of treatment of the patient with type 2 diabetes: diet and exercise, normalization of blood glucose levels, and aggressive management of cardiovascular risk factors to prevent micro- and macrovascular complications.

Mechanism of Action

Prolonging the Hypoglycemic Effect of GLP-1 Analogue Therapeutics by A Novel Protective Technology

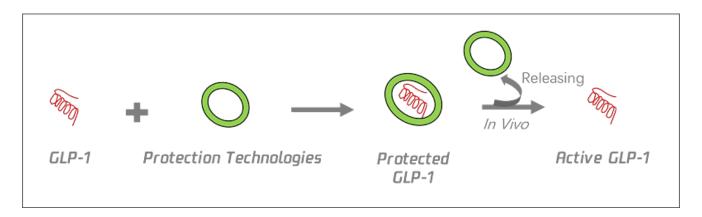
Glucagon-like peptide-1 (GLP-1) is a peptide hormone secreted by intestinal enteroendocrine L-cells, functioning through the combination with GLP-1 receptor. Such combination activates the cyclic adenosine monophosphate (cAMP) pathway and mitogen-activated protein kinase (MAPK) pathway. GLP-1 lowers glucose concentrations by augmenting insulin secretion and suppressing glucagon release. Additional effects of

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GLP-1 include retardation of gastric emptying, suppression of appetite and, potentially, inhibition of β -cell apoptosis. The main defects of GLP-1 analogue therapeutics are short duration of action and high incidence of adverse reactions. Ultra-long-acting and with fewer side effects, P11 was developed by applying our unique GLP-1 protection technology to Trulicity (a GLP-1 analogue drug developed by Eli Lilly).



• Prolonging GLP-1 half-life: Preventing degradation mediated by DPP-4 and other proteolytic enzymes.• Reducing drug side effects/keeping blood concentration constant/expanding application range: Special mechanism to gradually release active GLP-1.• Further modification of GLP-1: The modified GLP-1 can stimulate the generation of cAMP and stay on the cell surface longer, thus increasing the duration of action to stimulate insulin secretion and reducing the degradation of GLP-1 receptor.

Status

Status of P11

In vitro and in vivo data on P11 are available. Patent application of the protection technology has been submitted.

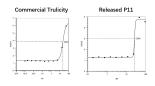
	Discovery/Optimization	Pre-clinical	Phase I	PhaseII	PhaseIII	
P11 •						

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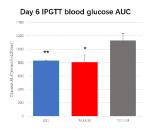


Data



cAMP Assay

The cAMP activity is the same between experiment (d-P11) and control (Trulicity) groups. EC50 values of the d-P11 and Trulicity are 26.9nM and 22nM, respectively.



Intraperitoneal Glucose Tolerance Test (IPGTT)

Trulicity and P11 were administered subcutaneously to C57BL mice at day 1(200 nmol/kg) and IPGTT was performed on Day 6. The results showed that P11 significantly reduced blood glucose on Day 6.

*: p<0.05, **: p<0.01

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