

1. V razvitih delih sveta, kjer imamo dovolj hrane je velik problem debelost. V zadnjih nekaj letih so izumili različna zdravila, ki pomagajo pri izgubi prekomerne teže. Eno izmed najbolj popularnih zdravil je Ozempic. Poišči to zdravilo v spletni bazi podatkov DrugBank.

V spletni brskalnik vpiši DrugBank in na njihovi spletni strani poišči Ozempic.

2. Kakšno je ime te učinkovine in kakšen je mehanizem delovanja?

The screenshot shows the DrugBank website interface. The top navigation bar includes the DrugBank logo and links for 'Explore', 'For Drug Discovery', 'For Clinical Software', and 'For Academic Research'. A search bar is located in the top right corner. The left sidebar contains a list of navigation options: Identification, Pharmacology, Interactions, Products, Categories, Chemical Identifiers, References, Clinical Trials, Pharmacoeconomics, Properties, Spectra, Targets (1), Enzymes (3), and Carriers (1). The main content area displays the profile for Semaglutide (DB13928). The 'Structure' tab is active, showing a chemical structure diagram. The 'Description' section states: 'A medication used to control blood sugar in diabetes, reduce weight, and prevent heart diseases in selected adults.' The 'DrugBank ID' is DB13928, and the 'Type' is Small Molecule. The 'US Approved' status is YES, and the 'Other Approved' status is YES. The 'Patents' count is 41, and the 'Indicated Conditions' count is 8. The 'Clinical Trials' section shows a table with columns for Phase 0, Phase 1, Phase 2, Phase 3, and Phase 4, with counts of 2, 168, 99, 145, and 66 respectively. The 'Therapeutic Categories' section lists Blood Glucose Lowering Agents, GLP-1 Agonists, and Incretin Mimetics. The 'Mechanism of Action' section is highlighted with a green circle and shows 'Glucagon-like peptide 1 receptor Agonist'. The 'IDENTIFICATION' section at the bottom provides a summary of Semaglutide, its brand names (Ozempic, Rybelsus, Wegovy), and its generic name (Semaglutide), which is also highlighted with a green circle. The DrugBank Accession Number is DB13928.

Tukaj najdeš generično ime učinkovine; semaglutide. Mehanizem delovanja pa je tak, da se veže na GLP1 receptor in ga aktivira, da se spodbudi izločanje inzulina in zniža krvni sladkor. Semaglutid sodi med agoniste receptorja za GLP-1.

3. V katero družino receptorjev spada protein, na katerega deluje to zdravilo?

Zapiši:

- Uniprot ID: P43220
- Dolžino proteina: 463 AKO
- Kaj je njegov ligand? GLP1 (glukagon like peptide-1)

P43220 · GLP1R_HUMAN

Protein¹ Glucagon-like peptide 1 receptor
Gene¹ GLP1R
Status¹ UniProtKB reviewed (Swiss-Prot)
Organism¹ Homo sapiens (Human)

Amino acids 463 (go to sequence)
Protein existence¹ Evidence at protein level
Annotation score¹ 100

Entry Variant viewer 463 Feature viewer Genomic coordinates Publications External links History

Tools · Download · Add · Add a publication · Entry feedback

Function¹
G-protein coupled receptor for glucagon-like peptide 1 (GLP-1) (PubMed:19861722, PubMed:26308095, PubMed:27196125, PubMed:28514449, PubMed:7517895, PubMed:8216285, PubMed:8405712).
Ligand binding triggers activation of a signaling cascade that leads to the activation of adenylyl cyclase and increased intracellular cAMP levels (PubMed:19861722, PubMed:26308095, PubMed:27196125, PubMed:28514449, PubMed:7517895, PubMed:8216285, PubMed:8405712).
Plays a role in regulating insulin secretion in response to GLP-1 (By similarity). (By similarity) (7 Publications)

- V katero družino receptorjev spada? V družino z G-proteinom sklopljenih receptorjev 2

Family & Domainsⁱ

Features
Showing features for regionⁱ.

Download

340 50 100 150 200 250 300 350 400 450 368

M C K T D I K C R L A K S T L T L I P L L G T H E V I F A

TYPE	ID	POSITION(S)	DESCRIPTION
Region		352-355	Important for allosteric inhibitor binding (1 Publication)

Sequence similaritiesⁱ
Belongs to the G-protein coupled receptor 2 family. (Curated)

- Kje v celici se nahaja? V celični membrani

UniProt BLAST Align Peptide search ID mapping SPARQL UniProtKB · Advanced · List · Search · Help

Function Names & Taxonomy Subcellular Location Disease & Variants PTM/Processing Expression Interaction Structure Family & Domains Sequence Similar Proteins

Subcellular Locationⁱ

Cell membrane
The cell membrane is the selectively permeable membrane which separates the cytoplasm from its surroundings. Known as the cell inner membrane in prokaryotes with 2 membranes.

UniProt

Cell membrane (7 Publications) Multi-pass membrane protein (1 Publication)

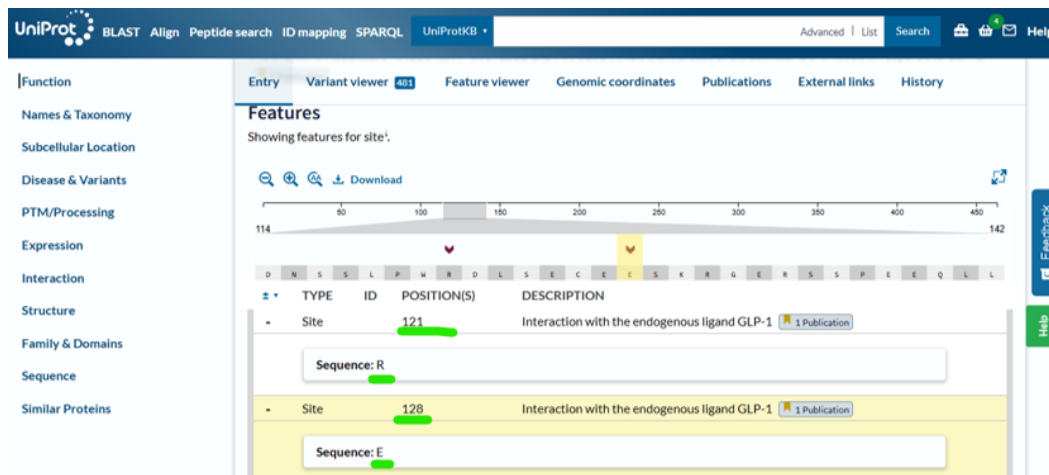


<http://www.uniprot.org/locations/SL-0029>

- f. Koliko in katere domene vsebuje? Vsebuje 2 domeni; ekstracelularna hormonska receptorska domena in rodopsinski 7-vijačni transmembranski proteini. Podatke najdeš na InterPro



- g. Na katero domeno se veže ligand? Ligand se veže na ekstracelularno hormonsko receptorsko domeno.
- h. S katerimi aminokislinskimi ostanki interagira ligand? R121 in E128

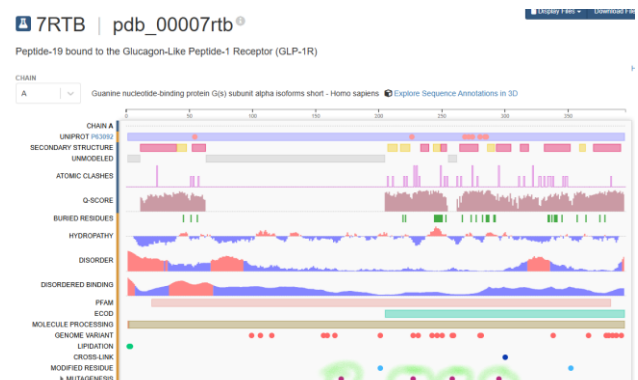


4. Zapiši PDB kodo eksperimentalno dobljene strukture receptorja z največ aminokislinskimi ostanki? S katero metodo je bila pridobljena struktura? Ali so bile za določitev strukture uvedene kakšne mutacije. Če ja, koliko jih je?

7RTB (22-463). Krioelektronska mikroskopija. Ja, 4 mutacije.

Structure

SOURCE	IDENTIFIER	METHOD	RESOLUTION	CHAIN	POSITIONS	LINKS
PDB	7R0B	EM	3.20 Å	R	24-422	PDB: RC.SB.PDB PDB: PDBsum Foldseek
PDB	7R0P	EM	2.90 Å	R	24-422	PDB: RC.SB.PDB PDB: PDBsum Foldseek
PDB	7RTB	EM	2.14 Å	R	22-463	PDB: RC.SB.PDB PDB: PDBsum Foldseek
PDB	7S15	EM	3.80 Å	R	24-422	PDB: RC.SB.PDB PDB: PDBsum Foldseek
PDB	7S1M	EM	2.41 Å	R	24-463	PDB: RC.SB.PDB PDB: PDBsum Foldseek




5. Ali obstaja AlphaFold model za ta receptor? Če ja, pojasni kaj pomenijo različne barve na proteinu.

AlphaFold model je večinoma obarvan s temno modro barvo, kar pomeni, da je velika verjetnost, da je pravilno konstruiran protein na tistem delu. Vsebuje tudi nekaj oranžnih delov, kar pomeni, da je slabša verjetnost napovedi.

UniProt

BLASTAlignPeptide searchID mappingSPARQLUniProtKB

AdvancedListSearch

 [Help](#)

Function

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History

PDB

8YW3


EM

2.68 Å

R

24-463

PDB · RCSB-PDB · PDBj · PDBsum

 Foldseek

PDB

9IVG


EM

3.00 Å

R

24-463

PDB · RCSB-PDB · PDBj · PDBsum

 Foldseek

PDB

9IVM


EM

3.22 Å

R

24-463

PDB · RCSB-PDB · PDBj · PDBsum

 Foldseek


AlphaFold

AF-P43220-F1

Predicted

1-463

AlphaFold

 Foldseek

3D structure databases

AlphaFoldDB

P43220

EMDB

EMD-20179

EMD-21147

SMR

P43220

ModBase

Search...

Feedback

Help

Mol* 3D Viewer

Sequence of AF-P43220-F1 Chain 1: Glucagon-like A

1 MAGAPGFLRLAILLLGNVGRAGPRPGATVSLWEIVQMRREYRQQRSLTDPFPATDLFNR
75 84 89 100 113 124 131
TFDEYACNPQGGPGSFVNVSCWYLFMASSVFGQHVTFCTAEGMLQKNSSLWRLSECEE
141 141 151 161 171 181 191
SGGSESSSPQQFLFVYIIVTGVALSFSALVIASRILLGFRLNCTRYNIHLNLFASFILRAL

Structure Tools

Structure

AF-P43220-F1

Type Model

Nothing Focused

Quick Styles

Default Illustrative Stylize Current

Components AF-P43220-F1

Preset + Add

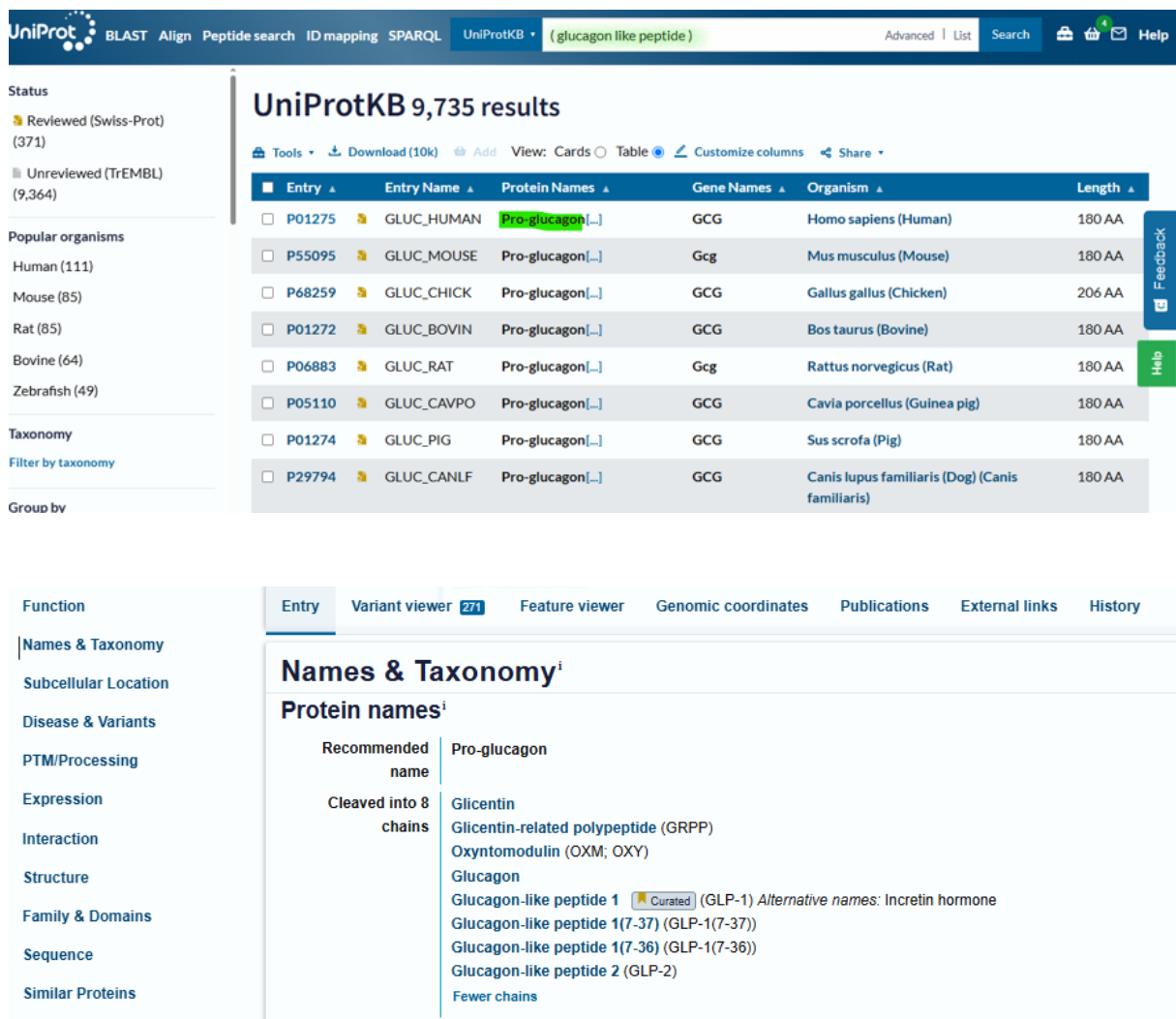
Polymer Cartoon

Measurements

+ Add

Model Confidence
AlphaMissense Pathogenicity
TED Domains

6. Naravni ligand tega receptorja nastane iz propeptida, ki se razcepi v več verig (ena izmed njih je ta ligand). Naštej še ostale peptide, ki nastanejo iz tega propeptida.



The screenshot shows the UniProtKB search results for 'glucagon like peptide'. The top table lists 9,735 results. Below it, the 'Names & Taxonomy' page for entry P01275 (Pro-glucagon) is displayed.

Entry	Entry Name	Protein Names	Gene Names	Organism	Length
P01275	GLUC_HUMAN	Pro-glucagon[...]	GCG	Homo sapiens (Human)	180 AA
P55095	GLUC_MOUSE	Pro-glucagon[...]	Gcg	Mus musculus (Mouse)	180 AA
P68259	GLUC_CHICK	Pro-glucagon[...]	GCG	Gallus gallus (Chicken)	206 AA
P01272	GLUC_BOVIN	Pro-glucagon[...]	GCG	Bos taurus (Bovine)	180 AA
P06883	GLUC_RAT	Pro-glucagon[...]	Gcg	Rattus norvegicus (Rat)	180 AA
P05110	GLUC_CAVPO	Pro-glucagon[...]	GCG	Cavia porcellus (Guinea pig)	180 AA
P01274	GLUC_PIG	Pro-glucagon[...]	GCG	Sus scrofa (Pig)	180 AA
P29794	GLUC_CANLF	Pro-glucagon[...]	GCG	Canis lupus familiaris (Dog) (Canis familiaris)	180 AA

Entry	Variant viewer	Feature viewer	Genomic coordinates	Publications	External links	History				
<h3>Names & Taxonomyⁱ</h3> <h4>Protein namesⁱ</h4> <table border="1"> <tr> <td>Recommended name</td> <td>Pro-glucagon</td> </tr> <tr> <td>Cleaved into 8 chains</td> <td> Glicentin Glicentin-related polypeptide (GRPP) Oxyntomodulin (OXM; OXY) Glucagon Glucagon-like peptide 1 Curated (GLP-1) <i>Alternative names:</i> Incretin hormone Glucagon-like peptide 1(7-37) (GLP-1(7-37)) Glucagon-like peptide 1(7-36) (GLP-1(7-36)) Glucagon-like peptide 2 (GLP-2) Fewer chains </td> </tr> </table>							Recommended name	Pro-glucagon	Cleaved into 8 chains	Glicentin Glicentin-related polypeptide (GRPP) Oxyntomodulin (OXM; OXY) Glucagon Glucagon-like peptide 1 Curated (GLP-1) <i>Alternative names:</i> Incretin hormone Glucagon-like peptide 1(7-37) (GLP-1(7-37)) Glucagon-like peptide 1(7-36) (GLP-1(7-36)) Glucagon-like peptide 2 (GLP-2) Fewer chains
Recommended name	Pro-glucagon									
Cleaved into 8 chains	Glicentin Glicentin-related polypeptide (GRPP) Oxyntomodulin (OXM; OXY) Glucagon Glucagon-like peptide 1 Curated (GLP-1) <i>Alternative names:</i> Incretin hormone Glucagon-like peptide 1(7-37) (GLP-1(7-37)) Glucagon-like peptide 1(7-36) (GLP-1(7-36)) Glucagon-like peptide 2 (GLP-2) Fewer chains									

Pod zavihkom Names and Taxonomy vidimo, da iz propeptida (proglukagona) nastanejo peptidi Glicentin, Glicentin-related polypeptide (GRPP), Oxyntomodulin (OXM; OXY), Glucagon, Glucagon-like peptide 1 Curated (GLP-1), Glucagon-like peptide 1(7-37) (GLP-1(7-37)), Glucagon-like peptide 1(7-36) (GLP-1(7-36)), Glucagon-like peptide 2 (GLP-2).

7. Naštej še tri molekule, ki aktivirajo GLP1 receptor.

Pod Disease & Variants imamo povezavo do učinkovin, ki delujejo na ta receptor. Klik na povezavo nas pripelje do strani DrugBank, kjer lahko preverimo, kako snov deluje. Trije agonisti tega GLP-1 receptorja so: albiglutide, dulaglutide, efpeglenatide, exenatide ... (poleg semaglutida).

UniProt BLAST Align Peptide search ID mapping SPARQL UniProtKB P43220 X Advanced | List Search Help

Function Entry Variant viewer Feature viewer Genomic coordinates Publications External links History

Names & Taxonomy MIM 138032 gene PharmGKB PA28725

Subcellular Location

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Similar Proteins

Miscellaneous

Pharos P43220 Tcin

Chemistry

ChEMBL CHEMBL1784

DrugBank DB09043 Albiglutide
DB09045 Dulaglutide
DB15650 Etepeglenatide
DB01276 Exenatide
DB00040 Glucagon
DB16697 Glutazumab
DB06655 Liraglutide
DB09265 Lixisenatide
DB13928 Semaglutide
DB14027 Taspoglutide
DB15171 Tirzepatide
Fewer DrugBank links

DrugCentral P43220
GuidetoPHARMACOLOGY 249

8. Eden izmed agonistov GLP-1 receptorja je albiglutid. Sintetiziran je tako, da je naravni agonist receptorja vezan na človeški albumin. Naravni agonist receptorja je občutljiv na proteolitično cepitev z dipeptidil peptidazo-4, ki peptidno vez cepi specifično med alaninom in glutamatom. V tem zdravilu so občutljivost na to peptidazo odpravili s točkovno mutacijo. Napiši kakšna je bila ta mutacija.

Namig: uporabi bazo DrugBank za iskanje zaporedja albiglutida.

Narediš globalno (lahko tudi lokalno) poravnavo aminokislinskega zaporedja albiglutida in GLP-1. Zaporedje GLP-1 dobiš iz Uniprot, kjer pogledaš zaporedje v proglukagonu:

PTM/Processing Features

Showing features for signal, peptide, modified residue, propeptide.

Download

TYPE All ID POSITIONS DESCRIPTION

Signal 1-20

Peptide PRO_000011254 21-50 Glucagon-related polypeptide [By similarity]

Peptide PRO_000011253 21-89 Glucagon [By similarity]

Peptide PRO_000011256 53-81 Glucagon [Publication]

Sequence: HSGQTFSDYSKYLDGRRAGDFVQVLMIT

Peptide PRO_000011255 53-89 Oryzanolide [By similarity]

Modified residue 54 Phosphoserine [By similarity]

Propeptide PRO_000011257 84-89 [Publication]

Peptide PRO_000011258 92-128 [Publication]

Sequence: HSGQTFSDYSKYLDGRRAGDFVQVLMIT

Peptide PRO_000011260 98-127 Glucagon-like peptide 1(7-36) [Publication]

Peptide PRO_000011259 98-128 Glucagon-like peptide 1(7-37) [Publication]

Modified residue 105 Phosphoserine [By similarity]

Modified residue 108 Phosphoserine [By similarity]

Modified residue 127 Arginine amide [Publication]

Propeptide PRO_000011261 131-145 [By similarity]

Peptide PRO_000011262 146-178 Glucagon-like peptide 2 [By similarity]

Modified residue 150 Phosphoserine [By similarity]

Modified residue 152 Phosphoserine [By similarity]

IDENTIFICATION

Summary Albiglutide is a GLP-1 agonist used to manage type 2 diabetes mellitus.

Generic Name Albiglutide DrugBank DB09043 Accession Number

Background Albiglutide is a glucagon-like peptide-1 agonist (GLP-1) biologic drug indicated in the treatment of type 2 diabetes. It is marketed under the brands Eperzan and Tanzeum by GSK (GlaxoSmithKline). It is a dipeptidyl peptidase-4-resistant glucagon-like peptide-1 dimer fused to human albumin. Albiglutide was approved on April 15, 2014 by the FDA.

Type Biotech Groups Approved, Withdrawn

Biologic Classification Protein Based Therapies; Fusion proteins

Protein Structure Representation of Albiglutide Protein Chemical Formula C₁₂₁₂H₂₀₂₂N₄₆₀O₄₂₁ Protein Average Weight 72970.0 Da

Sequences

Albiglutide (Protein)

HEGTFSDYSKYLDGRRAGDFVQVLMIT

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V globalni poravnavi vidimo, da je v albiglutidu namesto alanina pred glutamatom glicin. Mutacija, ki privede do odpornosti na peptidazo je torej A2G:

```
#
#
#=====
GLP-1      1 HDEFEHHEGTFSDYSKYLDGRRAGDFVQVLMIT 37
Albiglutide 1 HDEFEHHEGTFSDYSKYLDGRRAGDFVQVLMIT 44
GLP-1      38 ----- 37
Albiglutide 45 EGQAKEFIAMLVKGRHSEVARRFKDLGEENFKALVLTAFQYQQC 94
GLP-1      38 ----- 37
Albiglutide 95 PFEDHVKLVNEVEFAKTVADESAENCKDSLHTFGDKLCTVATRETY 144
GLP-1      38 ----- 37
Albiglutide 145 GEMADCCAKQEPERNECFQKHQDHPKLVLPVPEVQVCTAFHDMETTF 194
GLP-1      38 ----- 37
Albiglutide 195 LKKYLYEIAIRHPYFYAPELLFFAKRYKAFTCCQAQKACLLPKLDE 244
GLP-1      38 ----- 37
Albiglutide 245 LRDEGKASSAQRLKCALQKFGERAFKANAVARLSQRPKAEFAEYVKL 294
```

9. Doma imamo kužka, ki vedno prosi za priboljške in je že prekomerno debel. Ali imajo kužki podobne GLP1 receptorje kot ljudje, da bi mu lahko dala zdravilo semaglutide za zmanjšanje apetita?

V BLAST vstavi aminokislinsko zaporedje za človeški GLP-1 in išči podobno zaporedje pri kužkih (*Canis*).

The screenshot shows the NCBI BLAST search interface. The 'Enter Query Sequence' section contains the GLP-1 sequence: >GLP-1 HDEFERHAEGTFTSDVSSYLEGQAAKEFIAWLKGRG. The 'Choose Search Set' section shows 'Standard databases (nr etc.)' selected, with 'Non-redundant protein sequences (nr)' chosen. The 'Organism' is set to 'Canis (taxid:9611)'. The 'Program Selection' section shows 'blastp (protein-protein BLAST)' selected. The 'Query Length' is 37. The 'Other reports' section includes 'Distance tree of results', 'Multiple alignment', and 'MSA viewer'. The 'Compare these results against the new Clustered nr database' button is visible. The 'Sequences producing significant alignments' table shows four results for Canis lupus dingo and Canis lupus familiaris.

Description	Scientific Name	Max Score	Total Score	Query Cover	E value	Per. Ident	Acc. Len	Accession
pro-glucagon isoform X2 [Canis lupus dingo]	Canis lupus dingo	80.1	113	100%	1e-20	100.00%	179	XP_025326838.1
pro-glucagon isoform X1 [Canis lupus dingo]	Canis lupus dingo	80.1	113	100%	1e-20	100.00%	180	XP_025326837.1
pro-glucagon precursor [Canis lupus familiaris]	Canis lupus familiaris	80.1	113	100%	2e-20	100.00%	180	NP_001003044.1
preproglucagon, partial [Canis lupus familiaris]	Canis lupus familiaris	54.7	54.7	70%	5e-12	100.00%	26	BAM48567.1

Glede na podobnost, bi Ozempic lahko deloval tudi pri kužkih, vendar bi bilo potrebno izvesti veliko raziskav.

10. Je objavljen kakšen pregledni članek, v katerem bi se skupaj pojavili besedi "Ozempic" in "pets"?

Ne.

The screenshot shows the PubMed search interface. The search bar contains the query '(ozempic) AND (pets)'. The search results show 'No results were found.' The 'MY CUSTOM FILTERS' section shows 'PUBLICATION DATE' filters: 1 year, 5 years, 10 years, and Custom Range. The 'Filters applied: Review. Clear all' button is visible.

V zadnjem desetletju prejšnjega tisočletja se je endokrinolog dr. John Eng posvečal identifikaciji novih hormonov. Vznemirili so ga podatki raziskav, ki so kazali, da strupi iz nekaterih kač in kuščarjev povzročijo povečanje trebušne slinavke, kar je namigovalo, da te snovi na nek način stimulirajo ta organ. Ugotovil je, da je pošast glia (*Heloderma suspectum cinctum*) po dolgih obdobjih stradanja sposobna upočasniti svoj metabolizem in ohraniti konstantno raven sladkorja v krvi. Preučil je njen strup in odkril peptid, za katerega je kasneje presenečen ugotovil, da je po strukturi in funkciji podoben človeškemu hormonu GLP-1. Ta v trebušni slinavki takoj po obroku stimulira sintezo inzulina, a je aktiven zgolj 2 minuti. Novo odkriti peptid pa ostane aktiven več ur.


11. Poišči UniProt ID za ta peptid v organizmu pošasti glia (*Heloderma suspectum cinctum*). (Namig: uporabi BLAST in išči po zbirki UniProt). Dr. Eng je peptid, ki ga je odkril, tudi poimenoval - kako?

Uniprot ID: C6EVG1

Ime: Exendin-4

12. Sintetična oblika tega peptida - exenatide se danes pogosto predpisuje bolnikom s sladkorno boleznijo tipa 2, saj izboljša učinkovitost primarnega zdravljenja. Exenatid je agonist receptorja za GLP-1. Primerjaj peptid iz strupa glia pošasti z njegovim sintetičnim analogom exenatidom. V čem je razlika?

V bazi DrugBank poiščemo zaporedje za exenatid.

IDENTIFICATION			
Summary	Exenatide is a GLP-1 agonist used in the management of type 2 diabetes mellitus.		
Brand Names	Bydureon, Byetta		
Generic Name	Exenatide	DrugBank Accession Number	DB01276
Background	Exenatide is a glucagon-like peptide-1 (GLP-1) analog ¹ . It activates the GLP-1 receptor and increases insulin secretion, decreases glucagon secretion, and slows gastric emptying to improve glycemic control ² . Exenatide was given FDA approval on April 28, 2005 ³ . It is available as immediate- and extended-release formulations. ^{1,2} Bydureon, the brand name product of extended-release exenatide in an injectable suspension, was discontinued in 2021. Bydureon BCise, an auto-injector extended-release formulation, remains available. ⁴		
Type	Biotech	Groups	Approved, Investigational
Biologic Classification	Protein Based Therapies Hormones		
Protein Structure		Protein Chemical Formula	C ₁₃₄ H ₂₄₂ N ₅₀ O ₂₆ S
		Protein Average Weight	4186.6 Da
Sequences	<div> <div>Exenatide</div> <div> <div>MGFTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS</div> <div>Download FASTA format</div> </div> </div>		

Naredimo poravnavo exenatida z zaporedjem exendina-4, ki ga dobimo na UniProtu. Vidimo, da je exenatid res analog exendina-4, le da so ga skrajšali na N- (za 47 ostankov) in C- (za 1 ostanek) koncu.

Exendin-4	1	MKIIILWLCVFGFLFLATLFPISWQMPVESGLSSEDSASSESFASKIKRHGE	50
Exenatide	1	-----HGE	3
Exendin-4	51	GTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSG	87
Exenatide	4	GTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-	39

13. Zakaj misliš, da je exenatid bolj stabilen od GLP-1 in zato lahko učinkuje dlje časa?

Naredimo poravnavo GLP-1 in exenatida iz katere vidimo, da exenatid ne vsebuje mesta AE, zato ni občutljiv na dipeptidil peptidazo-4, tako kot GLP-1.

Exenatide	1	-----HGE	39
		. : .: .: .: . .	
hGLP-1	1	HDEFERHAE	37