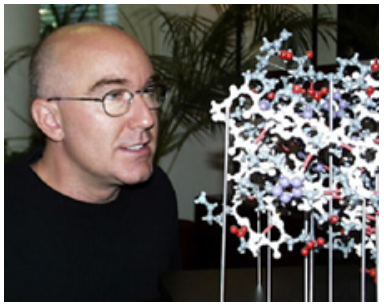
12. Peptidy a proteiny používané jako léčiva

„Druggability“

Druggability is a term used in drug discovery to describe a biological target (such as a protein) that is known to or is predicted to bind with high affinity to a drug. Furthermore, by definition, the binding of the drug to a druggable target must alter the function of the target with a therapeutic benefit to the patient.

Druggability, je schopnost nějakého proteinu být ovlivnitelný nějakým léčivem, tak že to má pozitivní efekt pro organismus.
Léčivem (drogou) se obvykle míní malá molekula („small-molecule“), ale může to být i protilátka.

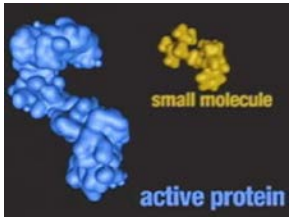


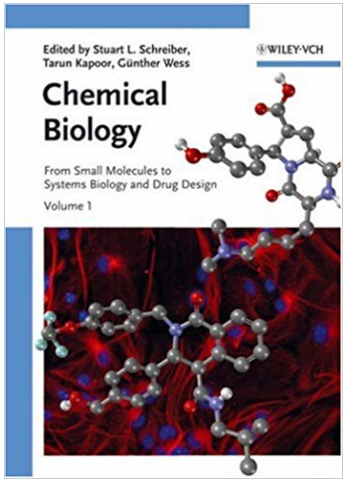
If a drug has already been identified for a target, that target is by definition **druggable**.
Jestliže byla pro daný protein již nalezena umělá látka, která jej ovlivňuje, tak je protein „druggable“.

Stuart L. Schreiber
Harvard University
Chemical Biology a „small-molecule concept“

Undruggable targets – Ty proteiny co nejsou ovlivnitelné léčivem

It is estimated that only 10-15% of human proteins are disease modifying while only 10-15% are druggable, meaning that only between 1-2.25% of disease modifying proteins are likely to be druggable. Hence, it appears that the number of new undiscovered drug targets is very limited.
Currently, about 2% of human proteins interact with approved drugs.



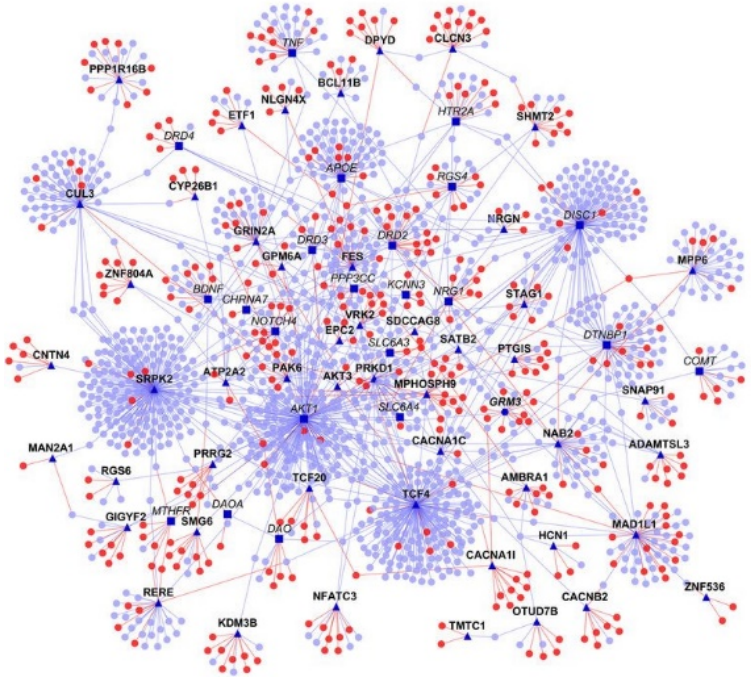


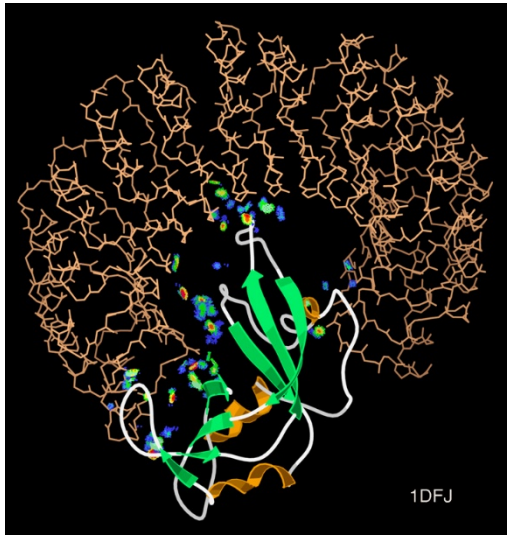
Typickými představiteli „**undruggable**“ molekul jsou proteiny účastnící se tzv. „**Protein-Protein Interactions** (PPI)“, tzn. **interakcí mezi proteiny**.

Důvodem je obtížná inhibice či napodobení (mimikování) těchto interakcí malými molekulami (small molecules).

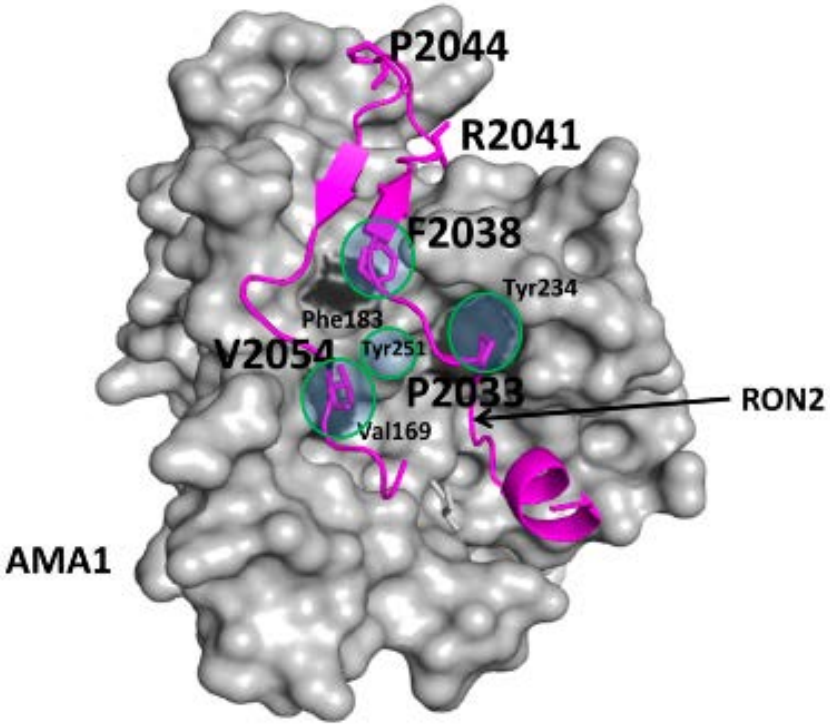
Protein–protein interactions (**PPIs**) are the physical contacts of high specificity established between two or more protein molecules as a result of biochemical events steered by electrostatic forces including the hydrophobic effect.

PPI zapojené do patogeneze schizofrenie





Ribonuclease + protein inhibitor.



Modulating PPIs with small-molecules is very difficult:

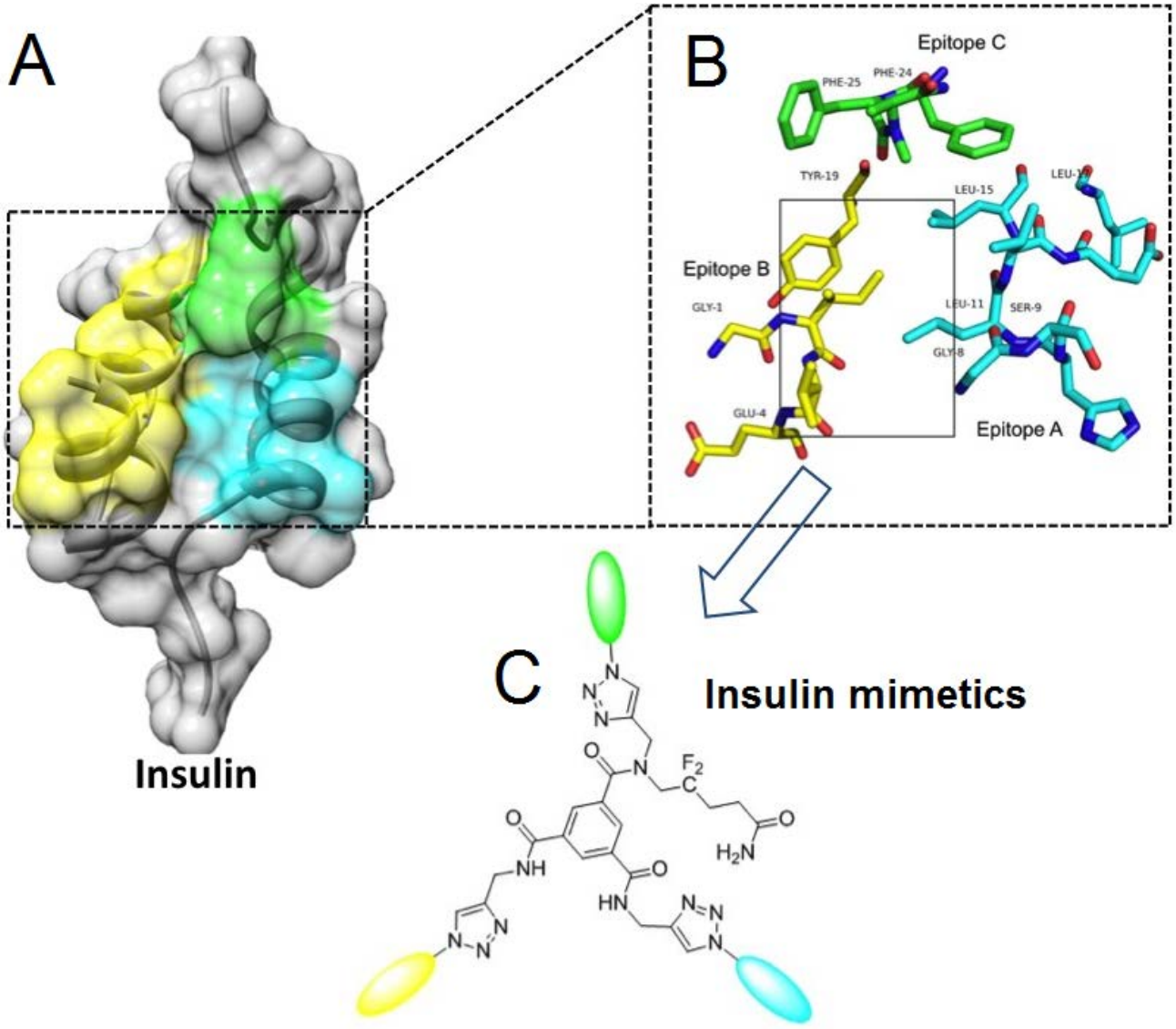
(i) the interfacial surface area for the specific recognition of two interacting proteins is usually large (1,500–3,000 Å^2) and exposed to solvent;

(ii) interaction surfaces are often shallow and featureless; and

(iii) binding regions in protein–protein interactions (PPIs) are often noncontiguous.

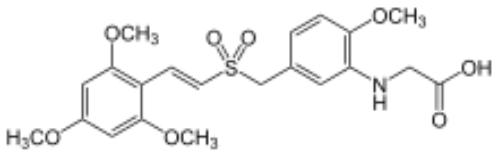
Hot-spots

However, the process can be simplified by using protein hot spots, which are groups of residues (ca. 600 Å^2) that confer to a majority of free energy for protein–protein association.


A
Insulin
B
Epitope C
PHE-25
PHE-24
TYR-19
LEU-15
Epitope B
GLY-1
LEU-11
SER-9
GLY-8
GLU-4
Epitope A
C
Insulin mimetics
O
N
F2
C
O
H2N
O
NH
O
HN
N
N
N
N
N
N

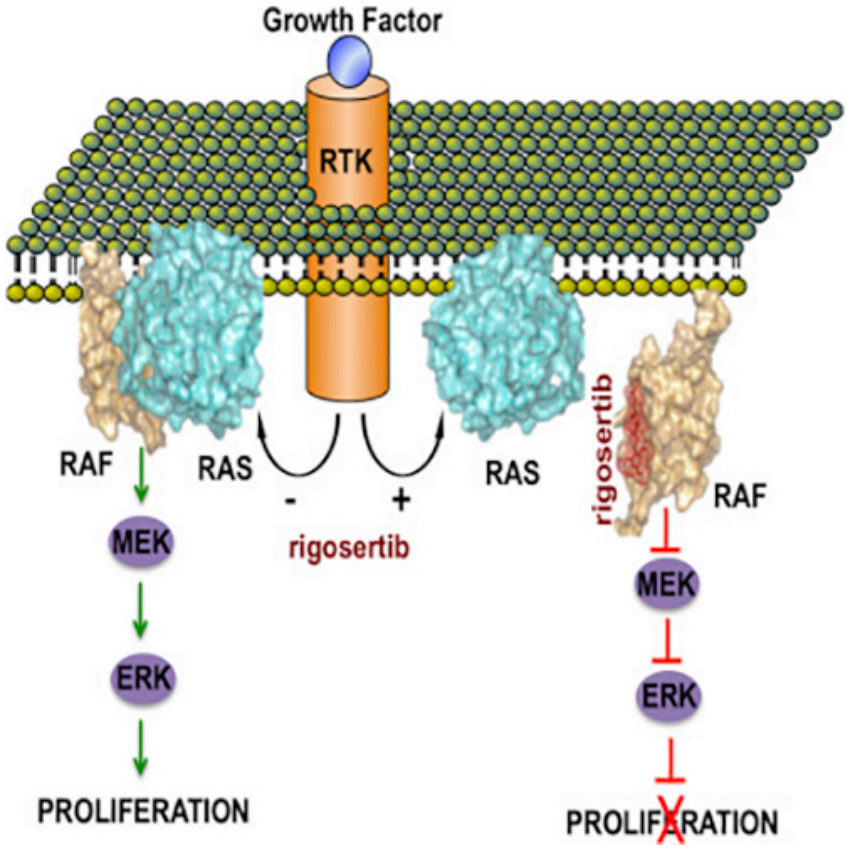
Úspěšný příklad „small molecule“ inhibitoru PPI, rok 2016 (Onconova Therapeutics)

Rigosertib is in phase III clinical trials for the treatment of chronic myelomonocytic leukemia.



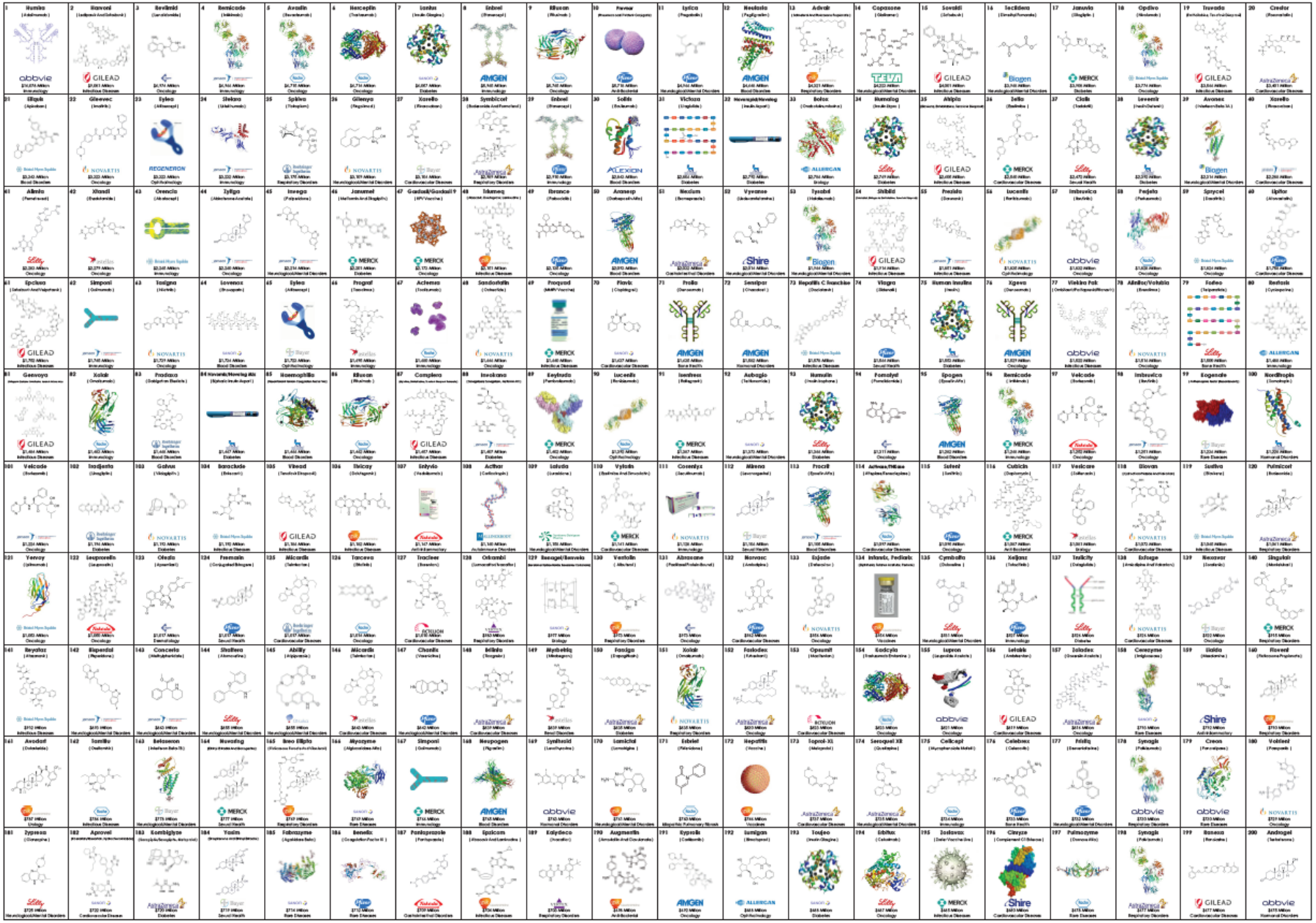
Rigosertib inhibuje interakci mutovaného RAS proteinu a PI3K/RAF v tumorech.

RAS proteiny byly považované za notoricky undruggable.



Top 200 Pharmaceutical Products by Retail Sales in 2016

Compiled and Produced by the Njardarson Group (The University of Arizona): David T. Smith, Michael D. Delost, Haziq Qureshi, Jón T. Njarðarson



1

Humira

(Adalimumab)

abbvie

$16,078 Million

Immunology

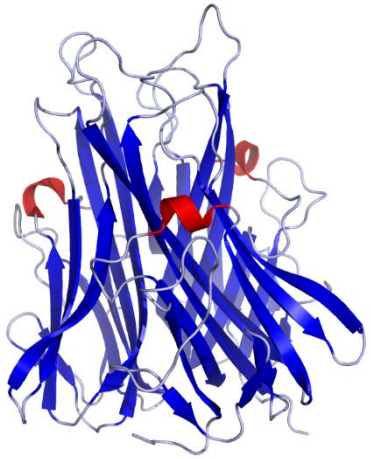
Adalimumab (Humira) je první lidská monoklonální protilátka jako léčivo.

Je používán pro potlačení zánětlivé reakce při autoimunních onemocněních jako *revmatická artritida, psoriatická artritida, Crohnova nemoc, chronická psoriáza a jiné.*

Váže se na tumor necrosis factor-alpha (TNFα),

a tím inhibuje jeho interakci s TNFα- receptorem,

který spouští zánětlivou reakci.



TNFα je produkován jako 233 AA membránový prekurzor v aktivovaných makrofázích.

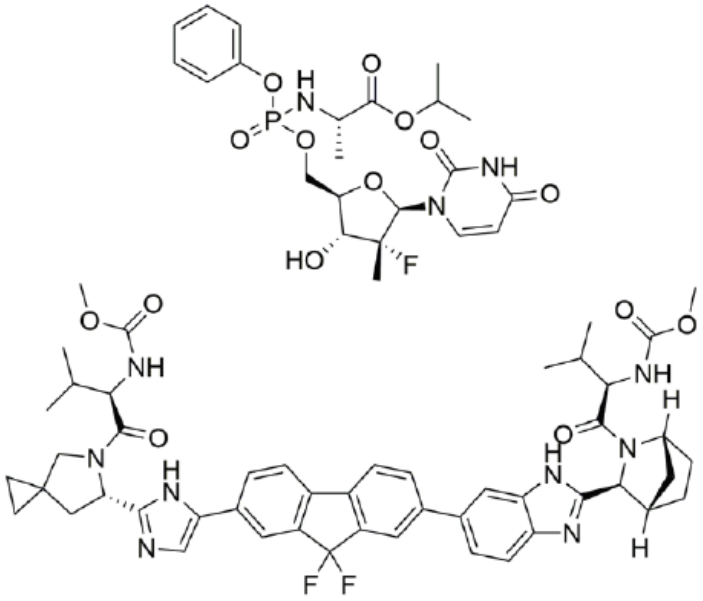
Aktivní 51kDa trimerní TNF je generován metalloproteázou TNF alpha converting enzyme (TACE či ADAM17).

Interaguje s receptory TNFα-R1 a R2, které jsou exprimované ve většině tkání.

subkutánní (s.c.) podání

2 Harvoni

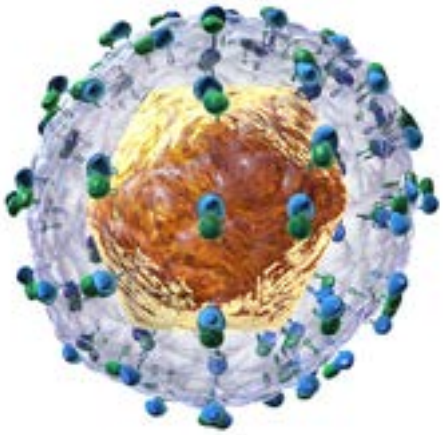
(Ledipasvir And Sofosbuvir)



GILEAD

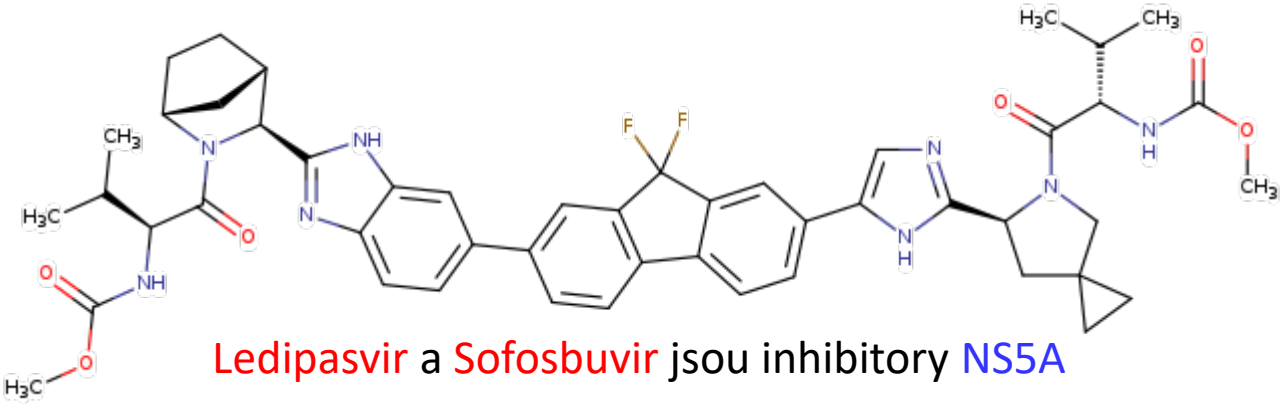
$9,081 Million

Infectious Diseases

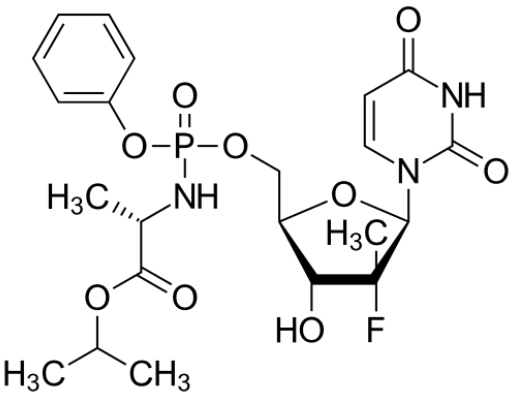


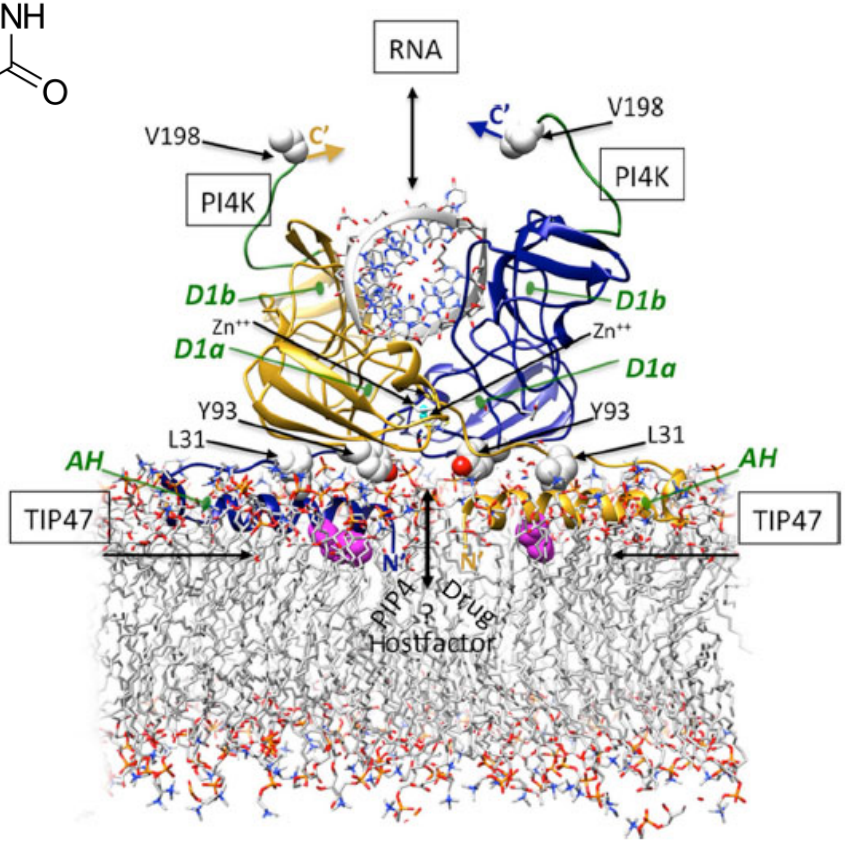
Hepatis C Virus (HCV)

Žloutenka typu C, je infekční onemocnění, které postihuje především játra. Toto onemocnění způsobuje virus hepatitidy C (HCV). Hepatitida C často není doprovázena žádnými příznaky, chronická infekce však může vést ke zjizvení jater a po mnoha letech až k cirhóze. V některých případech dochází u osob s cirhózou k selhání jater, rakovině jater či ke značnému zduření žil jícnu a žaludku, což může vést až k vykrvácení a smrti. Hepatitida C se přenáší primárně krví při nitrožilní aplikaci drog, používáním nesterilních pomůcek a krevní transfúzí. Na světě žije odhadem 130–170 miliónů osob infikovaných hepatitidou C. Dle české studie Univerzity Obrany trpí v ČR chronickou formou tohoto onemocněním cca 80 tisíc lidí.



Ledipasvir a Sofosbuvir jsou inhibitory NS5A



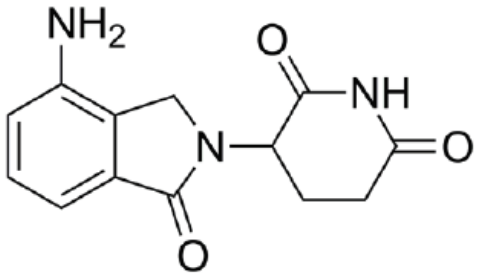


Nonstructural protein 5A (NS5A)

je zinc-binding a prolin-rich hydrofilní fosfoprotein který hraje klíčovou roli v replikaci RNA viru Hepatitidy C, je to asi transkripční aktivátor či RNA polymeráza.

3 Revlimid

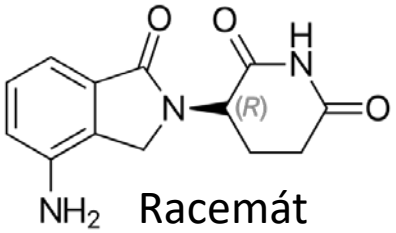
(Lenalidomide)



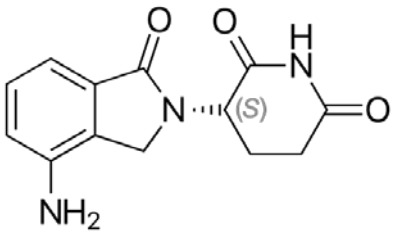
Celgene

$6,974 Million

Oncology



Racemát

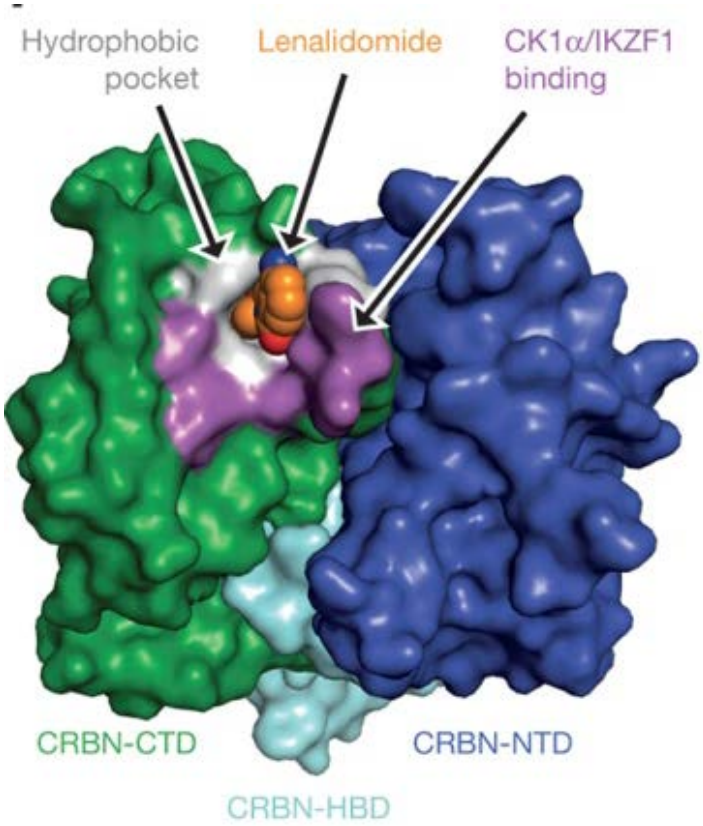


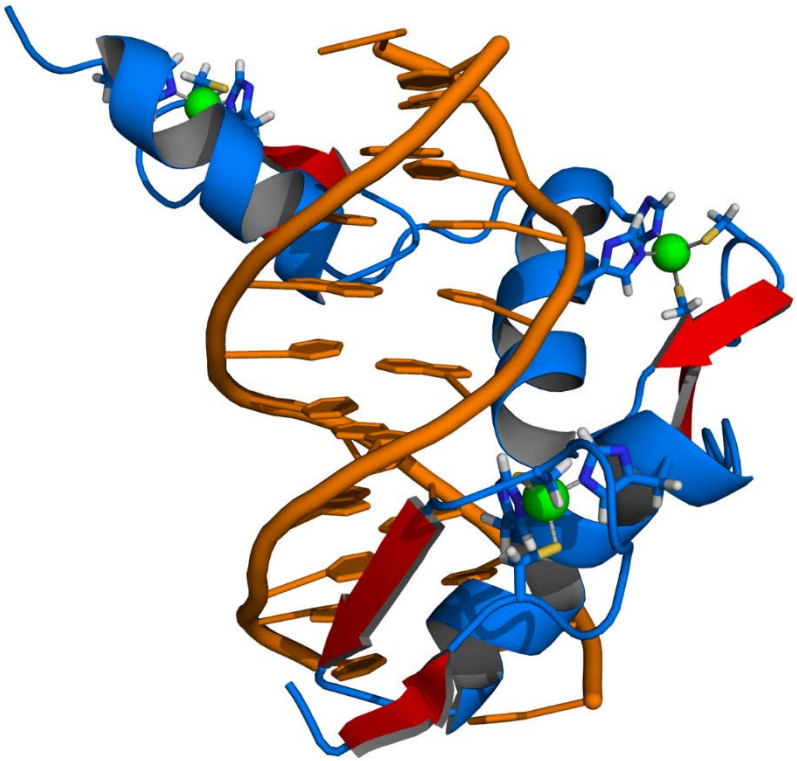
Revlimid či Lenalidomid je jedním z nejperspektivnějších léků v léčbě mnohočetného myelomu.

Je mimořádně účinný s akceptovatelným toxickým profilem a snadnou aplikací u nemocných, neboť jde o perorální lék.

Mnohočetný myelom, také Kahlerova nemoc (po Otto Kahlerovi), je maligní nádorové onemocnění plazmatických buněk, což je typ bílých krvinek za fyziologických podmínek produkující protilátky. Incidence této nemoci je 1 až 4 nemocní na 100 000 obyvatel za rok (10-40 v ČR).

Revlimid (lenalidomid) interaguje s E3 ligázou cereblon a „přeprogramovává“ tento enzym tak, aby degradoval tzv. transkripční faktory Ikaros (IKZF1 a IKZF3), což jsou důležité proteiny v hematopoetickém systému.

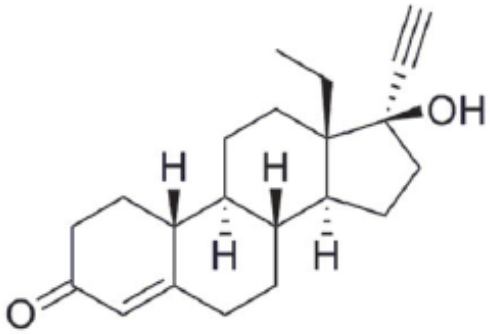




IKZF jsou tzv. „*zinc fingers*“ proteiny, které se vyznačují stabilizací struktury pomocí Zn^{2+} iotů.

112 Mirena

(Levonorgestrel)

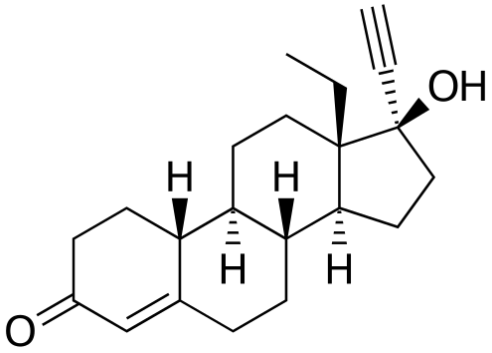


Bayer

$1,106 Million

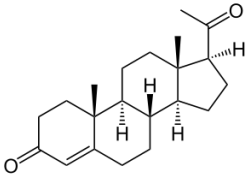
Sexual Health

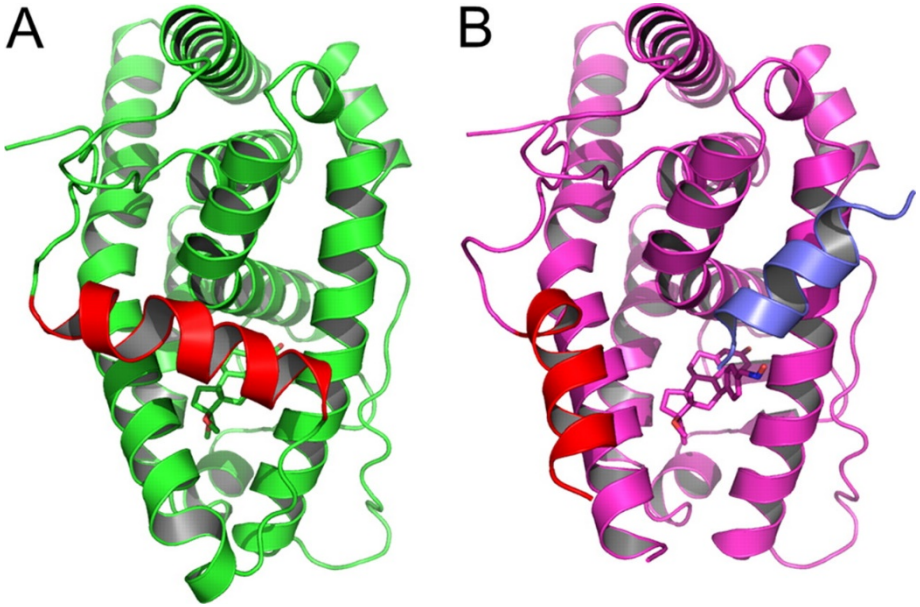
Levonorgestrel



Hormonální antikoncepce.
Bud‘ jako pilulka (120 h).
Nebo jako součást nitroděložního tělíska
ze kterého se hormon pomalu uvolňuje (Mirena).

Levonorgestrel je agonista receptoru progesteronu (PR), což je hlavní biologický cíl sexuálního hormonu progesteronu, ale váže se 3x lépe.



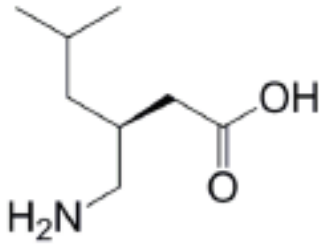


Progesteron je nezbytný k indukce exprese PR, jinak receptor sám inhibuje svou transkripci. Vazba hormonu strukturně inhibuje inhibici transkripce.
Po vazbě progesteronu na PR se komplex přesouvá do jádra a váže se na DNA, indukuje transkripci a formování mRNA a produkci specifických proteinů – inhibice ovulace.

11

Lyrica

(Pregabalin)

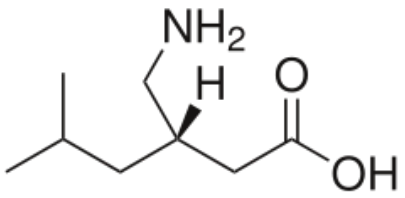


Pfizer

$4,966 Million

Neurological/Mental Disorders

Lyrica či Pregabalin

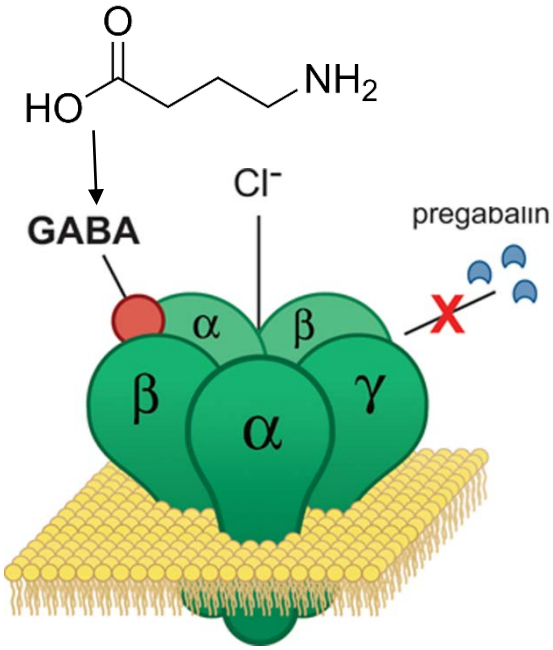


3-isobutyl GABA (3-isobutyl gama-aminomáselná)

Pregabalin se používá k léčení epileptických záchvatů, neuropatické bolesti a úzkostných poruch.

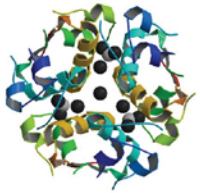
Je klasifikován jak analog GABA.
GABA se váže vysokou afinitou na „α2δ subunit-containing voltage-gated calcium channels (VDCC)“.

Pregabalin **zvyšuje extracelulární koncentraci GABA** v mozku tím, že zvyšuje hladiny L-Glutamic acid decarboxylázy (GAD), enzymu odpovědného za produkci GABA.



Pregabalin se NEVÁŽE na GABA receptory,
ale zvyšuje hladinu GABA.

7 Lantus
(Insulin Glargine)

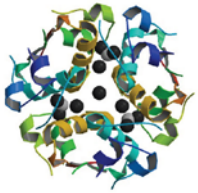


SANOFI
$6,057 Million
Diabetes

32 Novorapid/Novolog
(Insulin Aspart)

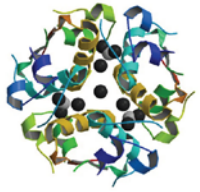
$2,792 Million
Diabetes

34 Humalog
(Insulin Lispro)



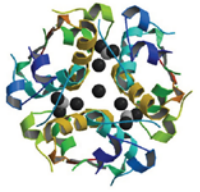
Lilly
$2,769 Million
Diabetes

38 Levemir
(Insulin Detemir)



$2,392 Million
Diabetes

75 Human Insulins
(Insulin)

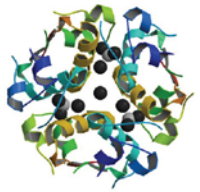


$1,553 Million
Diabetes

84 Novomix/Novolog Mix
(Biphasic Insulin Aspart)

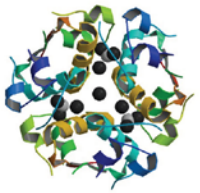
$1,467 Million
Diabetes

93 Humulin
(Insulin Isophane)



Lilly
$1,366 Million
Diabetes

193 Toujeo
(Insulin Glargine)



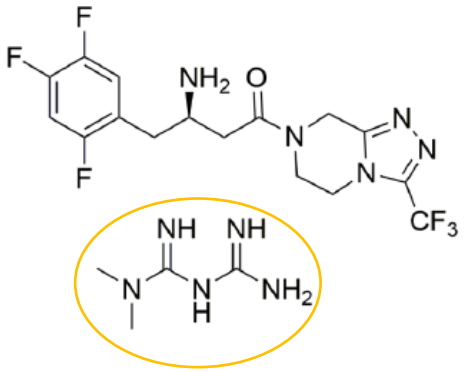
SANOFI
$688 Million
Diabetes

Insulin jeho analogy
pro diabetiky typu I a II

Metformin

46 Janumet

(Metformin And Sitagliptin)



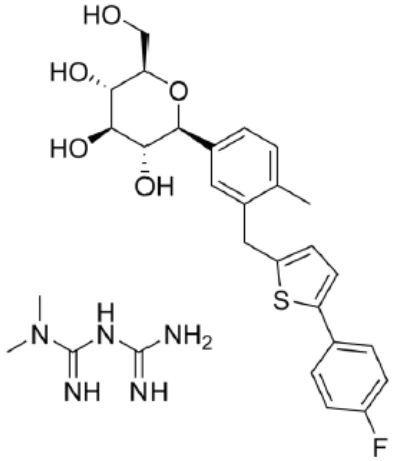
MERCK

$2,201 Million

Diabetes

88 Invokana

(Canagliflozin/Canagliflozin, Metformin HCl)



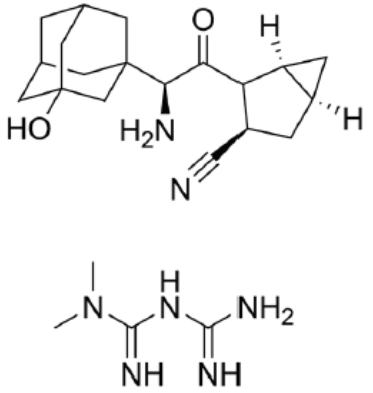
janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

$1,407 Million

Diabetes

183 Kombiglyze

(Saxagliptin/Saxagliptin, Metoprolol)



AstraZeneca

$720 Million

Diabetes

Poruchy v produkci insulinu a jeho působení

Diabetes mellitus - cukrovka

Diabetes typu 1 - pankreas neprodukuje insulin, autoimunitní destrukce β-buněk, vrozený, juvenilní diabetes

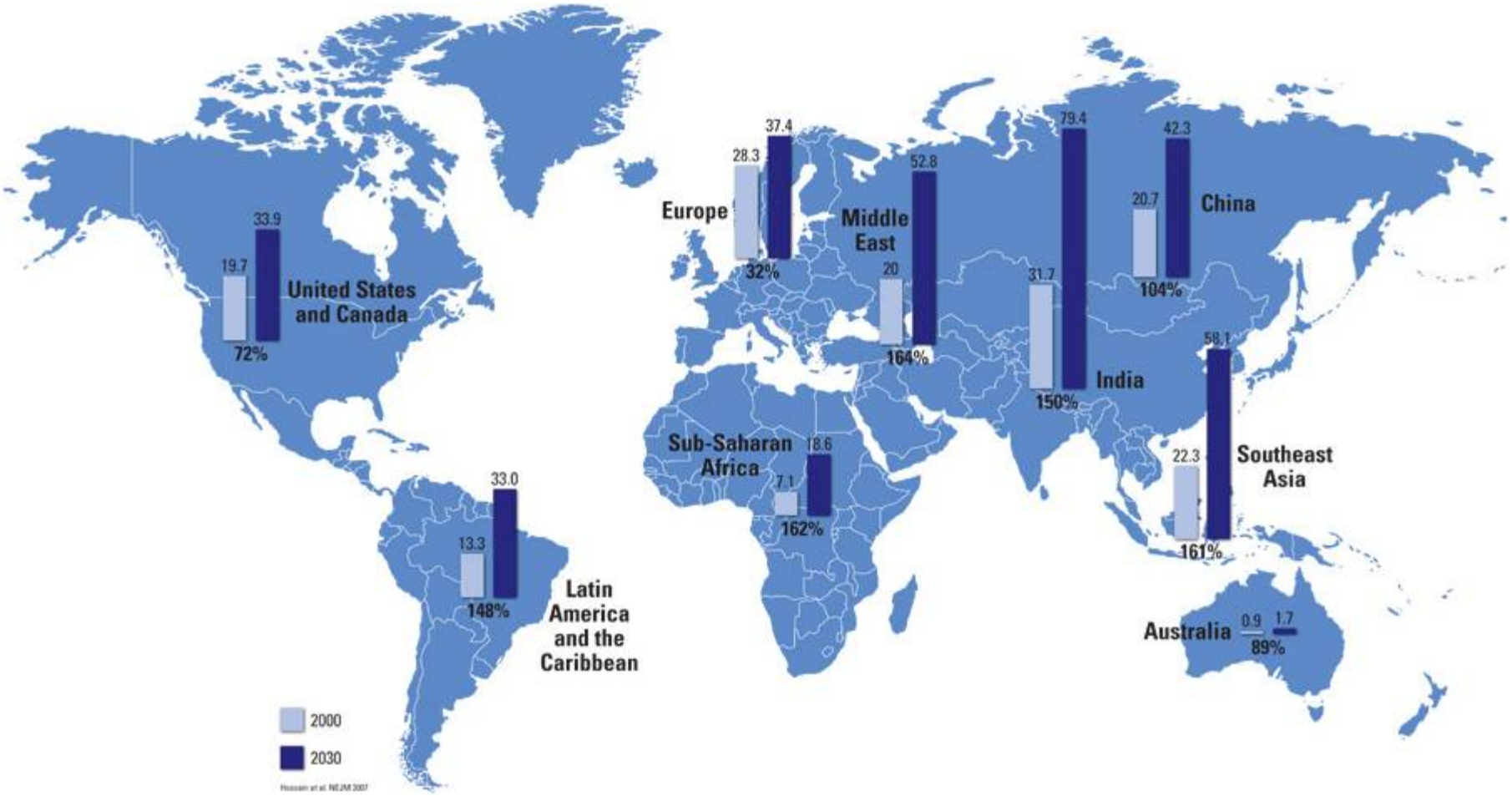
Diabetes typu 2 - produkce insulinu normální, snížená citlivost vůči insulinu, vyšší věk, obezita, civilizační choroba, mechanismus vzniku nejasný, nejspíše problém v metabolismu tuků, může přerůst v diabetes typu 1

Těhotenský diabetes - gestační, GDM, 4% těhotných žen

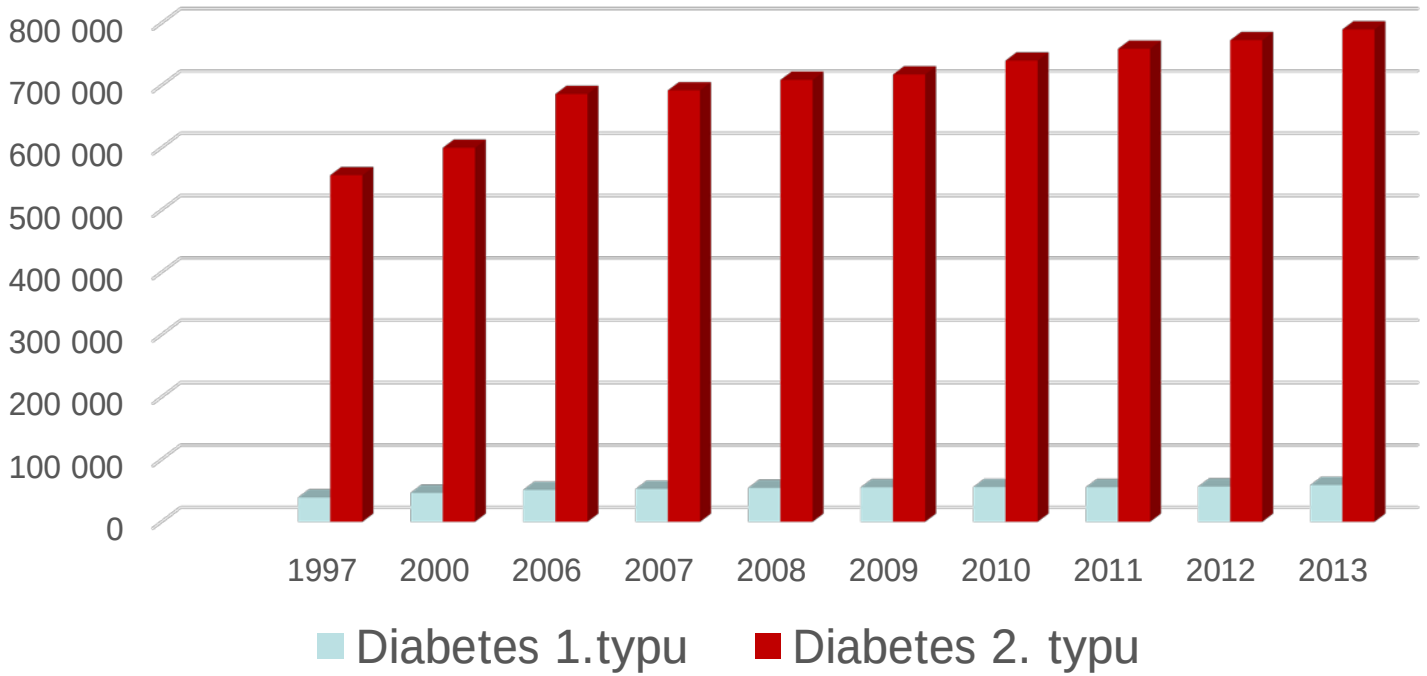
Ostatní specifické typy diabetu - sekundární, způsobené např. onemocněním pankreatu

V ČR asi 800 tisíc diabetiků (60 tisíc diabetiků typu 1), plus dalších 250 tisíc to neví.
Celosvětově 365 miliónů diabetiků (2011), 550 milionů v roce 2030.

Diabetes a obezita jsou epidemie 21. století



Počet diabetických pacientů v České republice



- každoroční nárůst je 55 tisíc diabetických pacientů
- na nemoci spojené s diabetem zemře každoročně 22 tisíc pacientů
- odhaduje se, že je přibližně v ČR 250 tisíc osob, u kterých nebyl zatím diabetes rozpoznán

Projevy diabetu

Akutní komplikace diabetu:

- hyperglykémie (>7 mM Glc) (žízeň, časté a vydatné močení, hubnutí, únava, poruchy vědomí)

- hyperglykémie s ketoacidózou (pH krve klesá)

- hypoglykémie (<3,3 mM Glc, díky léčbě insulinem)

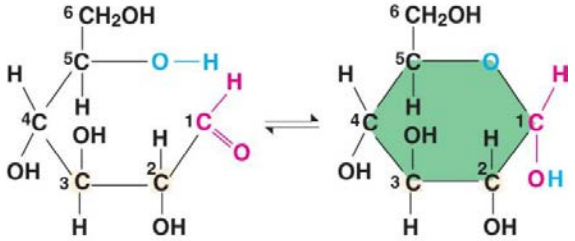
Projevy diabetu

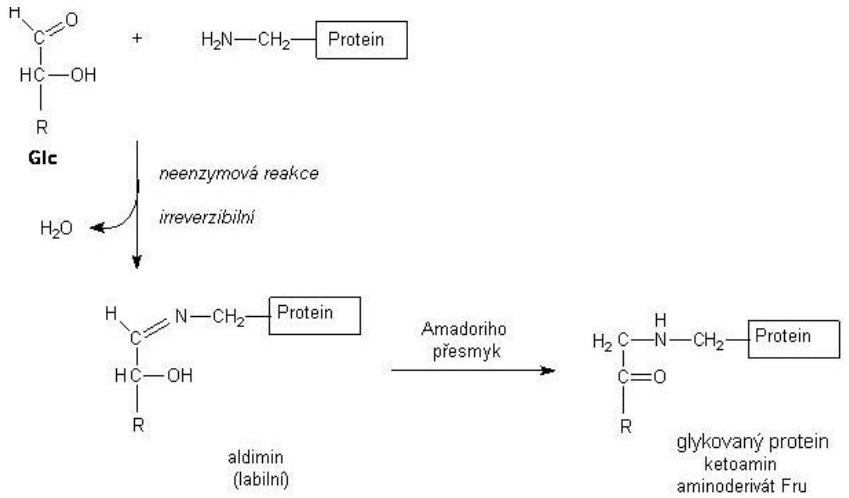
Pozdní komplikace diabetu: Díky nespecifickým glykacím proteinů krevní glukózou.

Účast Glu na tvorbě reaktivních radikálů.

Poškození proteinů cévních stěn a krevních proteinů.

Glykovaný hemoglobin (normálně 2,8-4%, 120 dní doba života erythrocytu)





Projevy diabetu

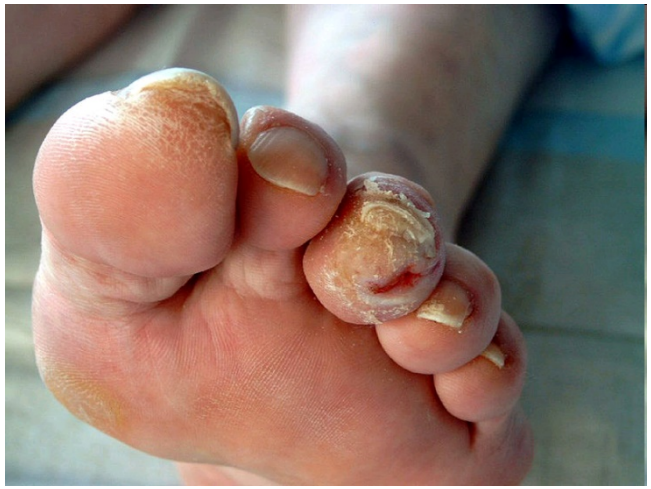
Pozdní komplikace diabetu:

- diabetická nefropatie
- diabetická retinopatie
- diabetická neuropatie
- diabetická makroangiopatie
- diabetická noha

Projevy diabetu

Pozdní komplikace diabetu:

- diabetická nefropatie
- diabetická retinopatie
- diabetická neuropatie
- diabetická makroangiopatie
- diabetická noha



Léčba diabetu

Velmi obtížně léčitelné onemocnění. Diabetes typu 1 je neléčitelný.

Transplantace pankreatu, Langerhansových ostrůvků, či β-buněk.

Snaha o udržení hladiny krevní glukózy na normální hladině (3.5-5.5 mM).

Dieta - hlavně diabetes typu 2, který je civilizačním onemocněním

Fyzická aktivita - vede k odbourávání glykogenu, který je doplňován z krevní Glc, pohyb zvyšuje vnímavost těla vůči insulinu

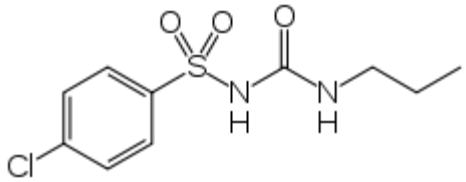
Medikace - léčba léky

Pravidelné kontroly hladiny krevního cukru glukometry

Léčba diabetu podáváním léků

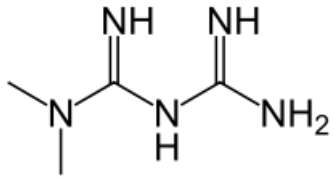
Orálně podávaná antidiabetika – diabetes typu 2

Látky zvyšující sekreci insulinu (secretagogues) – der. Sulfonyl močoviny (KATP channel)



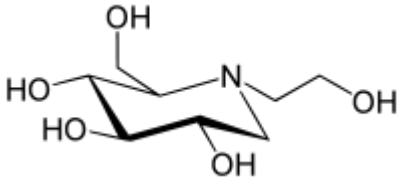
chlorpropamid

Látky zvyšující citlivost vůči insulinu (senzitizers) - biguanidy (Glc do periferií)

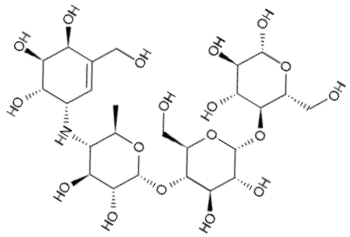


metformin

Inhibitory α-glukosidázy - zpomalují vstřebávání Glc ve střevech



miglitol

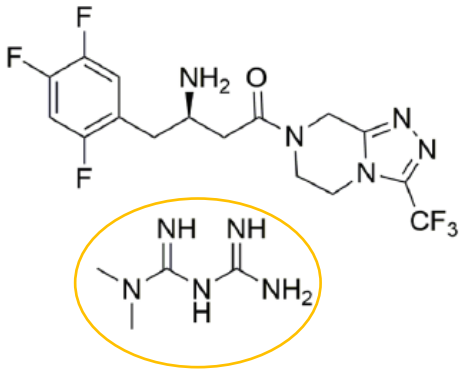


akarbóza

Metformin

46 Janumet

(Metformin And Sitagliptin)



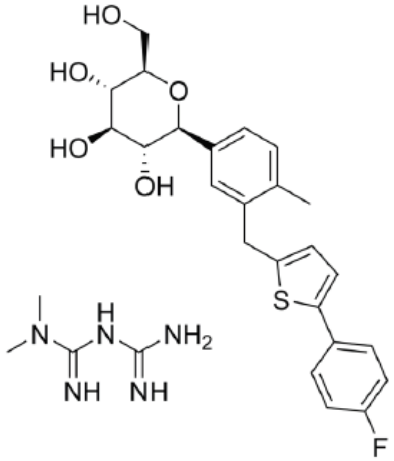
MERCK

$2,201 Million

Diabetes

88 Invokana

(Canagliflozin/Canagliflozin, Metformin HCl)



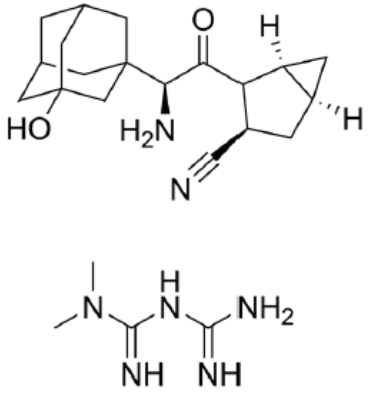
janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

$1,407 Million

Diabetes

183 Kombiglyze

(Saxagliptin/Saxagliptin, Metoprolol)

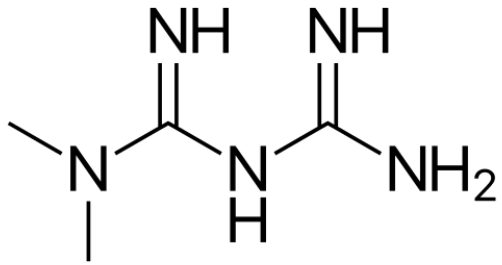


AstraZeneca

$720 Million

Diabetes

Metformin

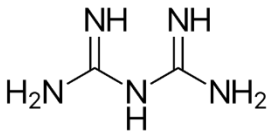


Orální lék „první volby“ pro léčbu diabetu typu 2, speciálně u obézních pacientů.
Je ale používán i pro léčbu cyst na vaječnících, a snižuje riziko kardiovaskulárních chorob a rakoviny při diabetu.

Metformin primárně blokuje produkci glukózy v játrech (glukoneogenezi), zvyšuje citlivost těla vůči insulinu a zvyšuje vstřebávání glukózy v periferiích.

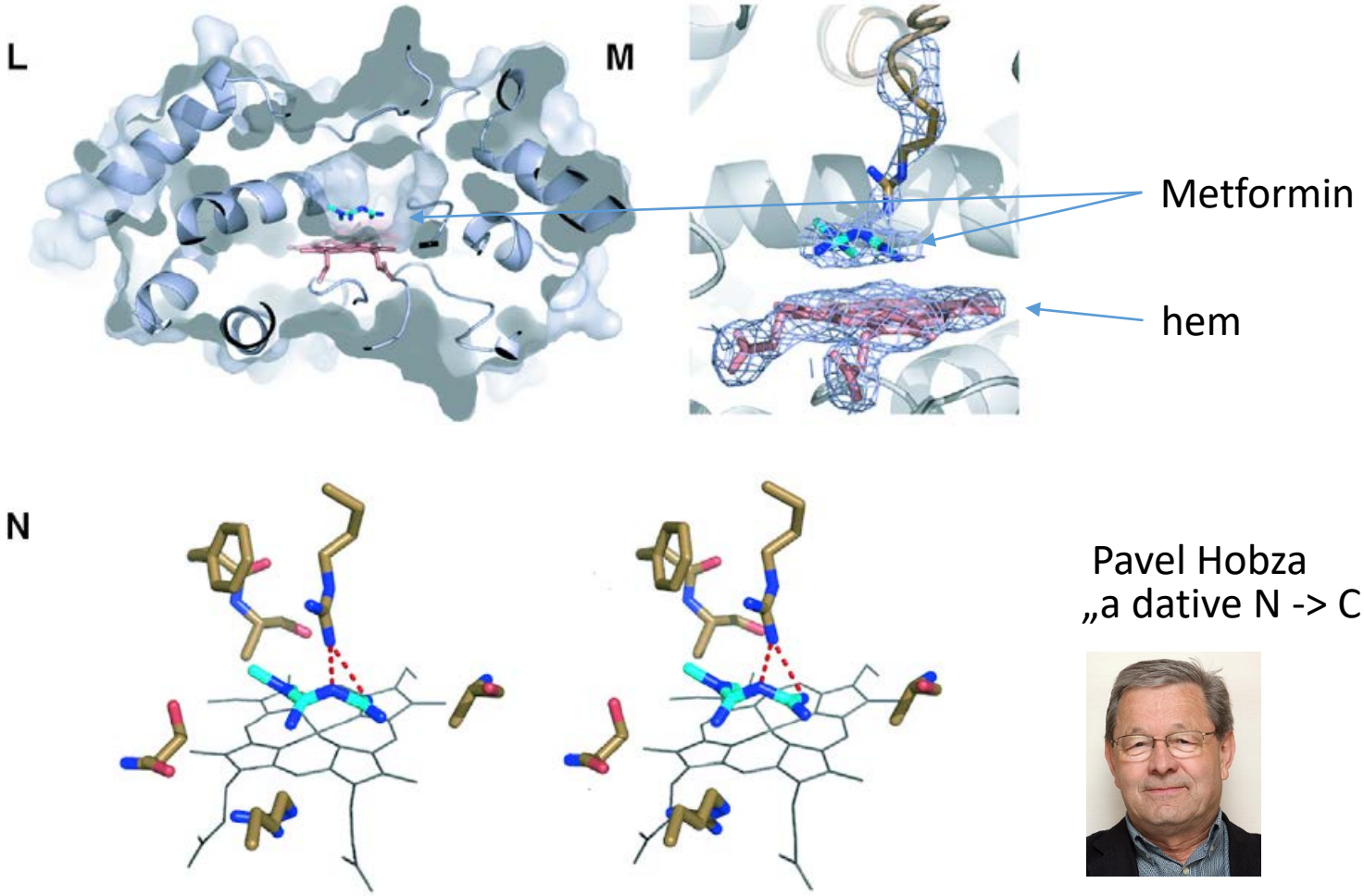
Mechanismus účinku není zcela přesně znám. Bylo navrženo, že metformin inhibuje mitochondriální komplex I, aktivuje AMP-aktivovanou protein kinasu (AMPK), inhibuje glucagonem indukované zvýšení cAMP, snižuje aktivaci protein kinasy A (PKA) a inhibuje mitochondriální glycerolfosfát dehydrogenasu.

Metformin patří mezi biguanidy, látky nacházející se i v rostlinách a používaných jako lidová léčiva.



Jestřabina lékařská
Galega officinalis

Metformin také inhibuje CYP3A4 monooxygenázu, která je zapojena do mechanismu vzniku rakoviny prsu. To by mohl být anti-rakovinný mechanismus působení metforminu.



Pavel Hobza
„a dative N -> C bond“

Cell Chem Biol. 2017 Oct 19;24(10):1259-1275
Heme Binding Biguanides Target Cytochrome P450-Dependent Cancer Cell Mitochondria.

Peptidy

Analogy glucagon-like peptidu 1 (GLP-1, inkretin), 44 aminokyselin

- zvyšují sekreci insulinu a snižují sekreci glukagonu
- **Exenatide** (Eli Lilly) či **Liraglutide** (Victoza, Novo Nordisk)

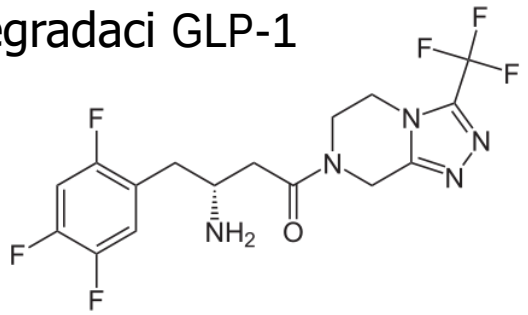
Analogy amylinu, 35 aminokyselin

- Snižují sekreci glukagonu
- Pramlintide

Další látky

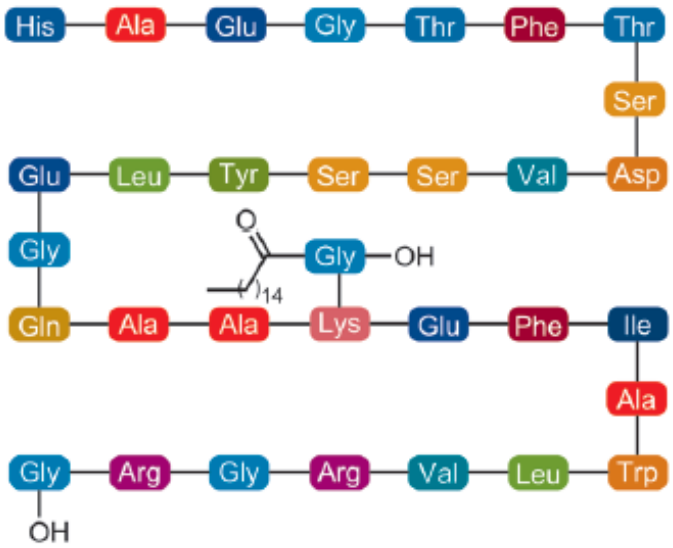
Inhibitory enzymu DPP-IV – zabraňují degradaci GLP-1

Sitagliptin



31 Victoza

(Liraglutide)



novo nordisk®

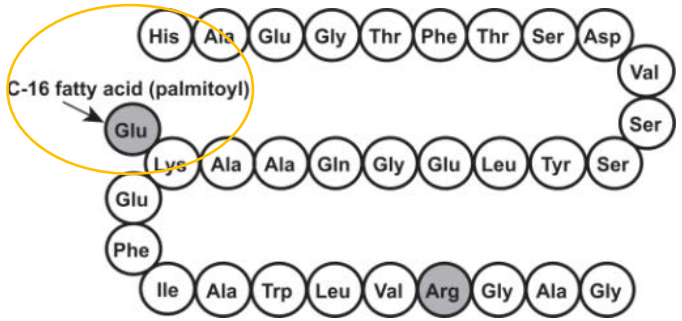
$2,806 Million

Diabetes

Liraglutide je analog GLP-1

(glucagon-like peptide 1), je to agonista, tzn.

váže se do stejného místa stejného receptoru.

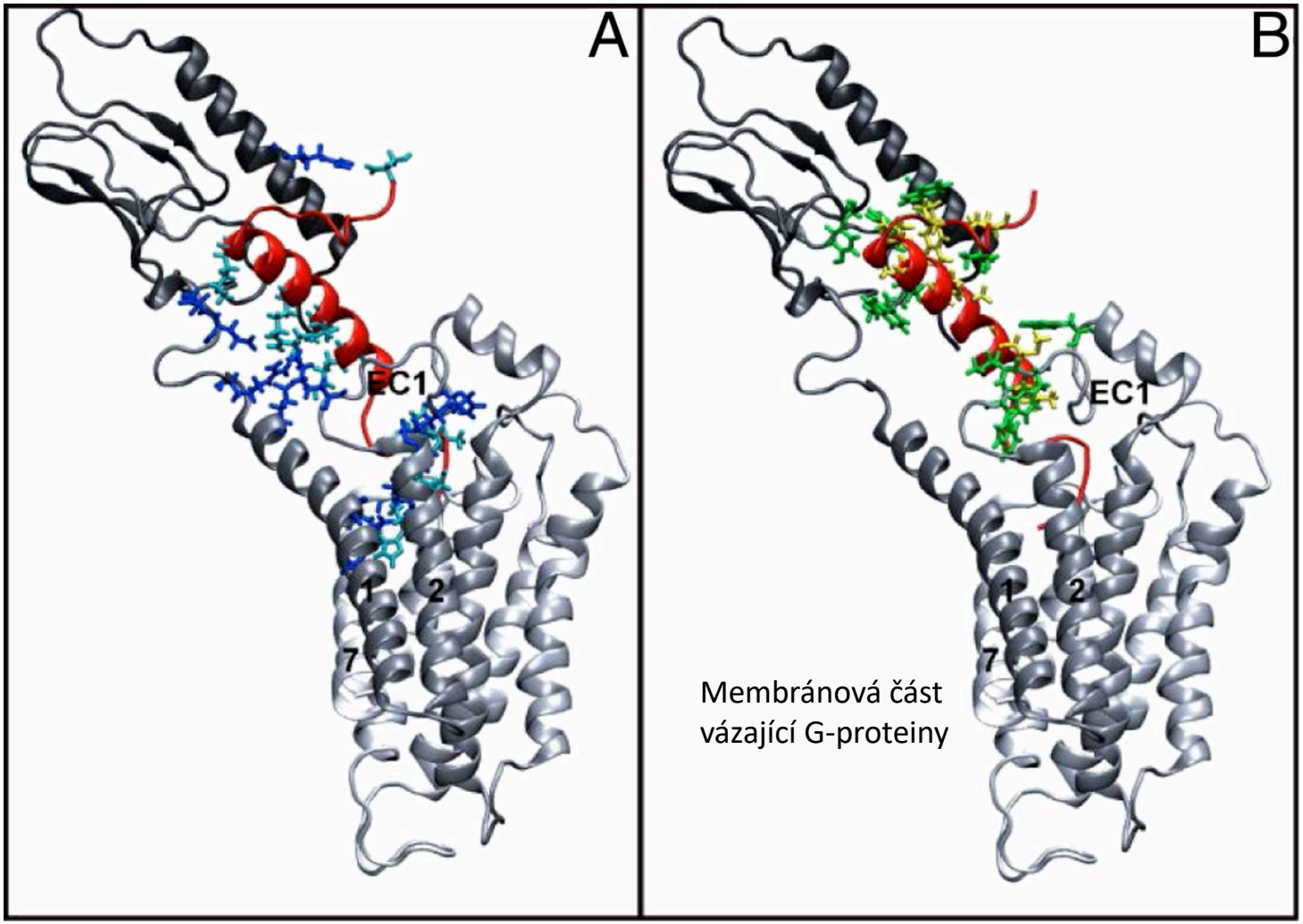


Liraglutid je podáván obézním diabetikům typu 2 injekčně, zvyšuje sekreci insulinu a zároveň snižuje sekreci glukagonu, a tím redukuje hyperglykémii.
Působí jen v závislosti na vysoké koncentraci glukózy, čímž snižuje riziko hypoglykémie.
Snižuje chuť k jídlu a tím i stimuluje ztrátu váhy, snižuje triacylglyceridy,
snižuje apoptózu a tak i regeneruje beta-buňky.

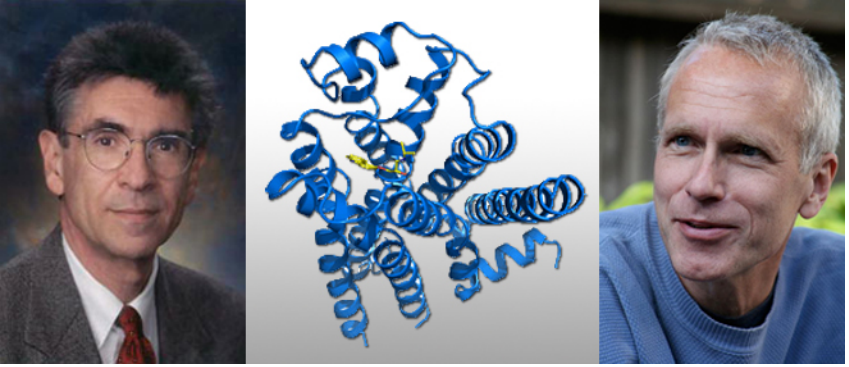
Glucagon-like peptide 1 receptor (GLP1R) se nachází v beta buňkách pankreatu.
Je členem rodiny tzv. **G protein-coupled receptorů (GPCR)**. Je to membránový protein.

L. Maletínská z ÚOCHB, analogy PRP, 2017 licence s Novo Nordisk, podobné efekty, jiný mechanismus účinku.

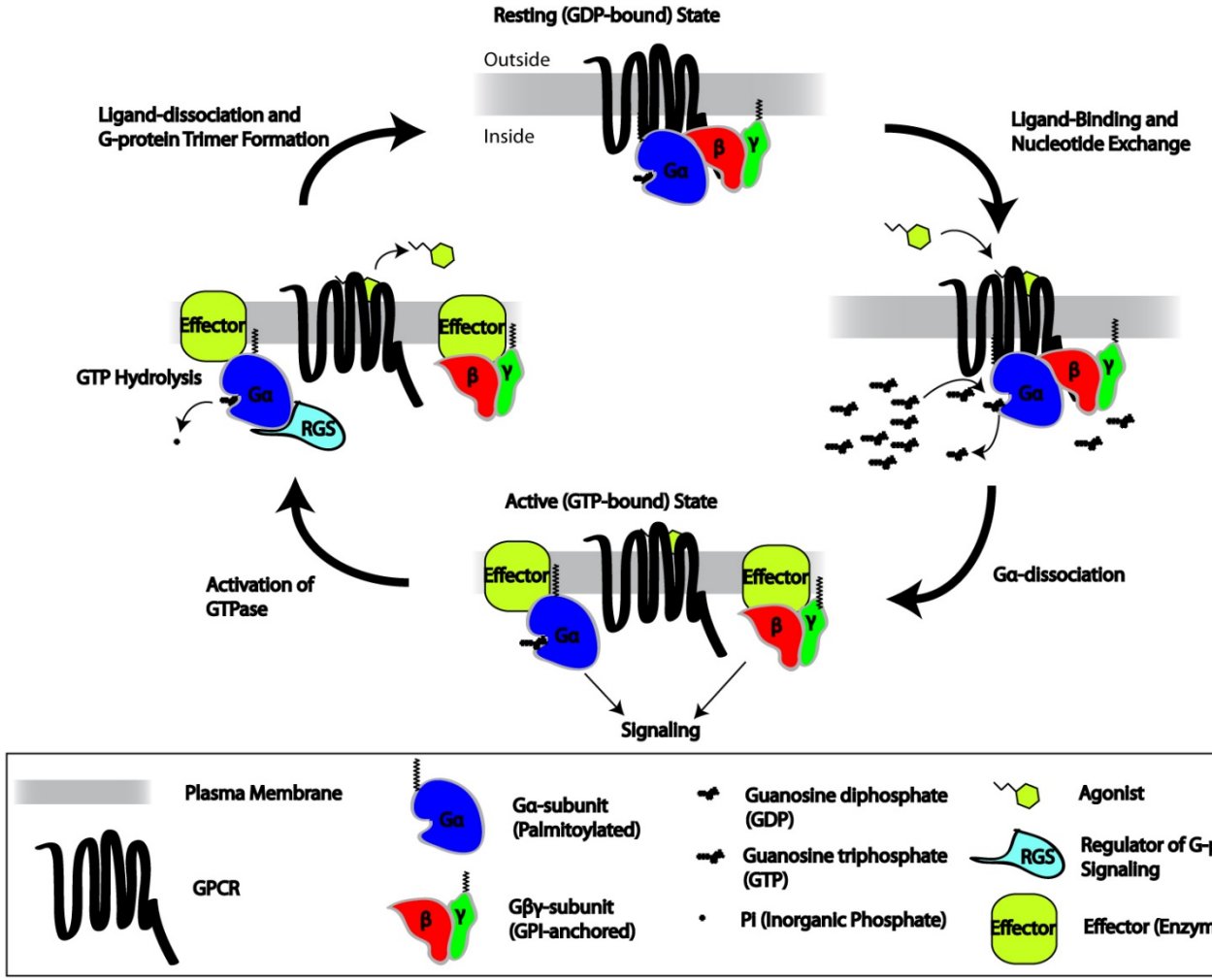
Overview of the GLP-1 ligand binding site's hydrophobic (A) and hydrophilic (B) interactions.



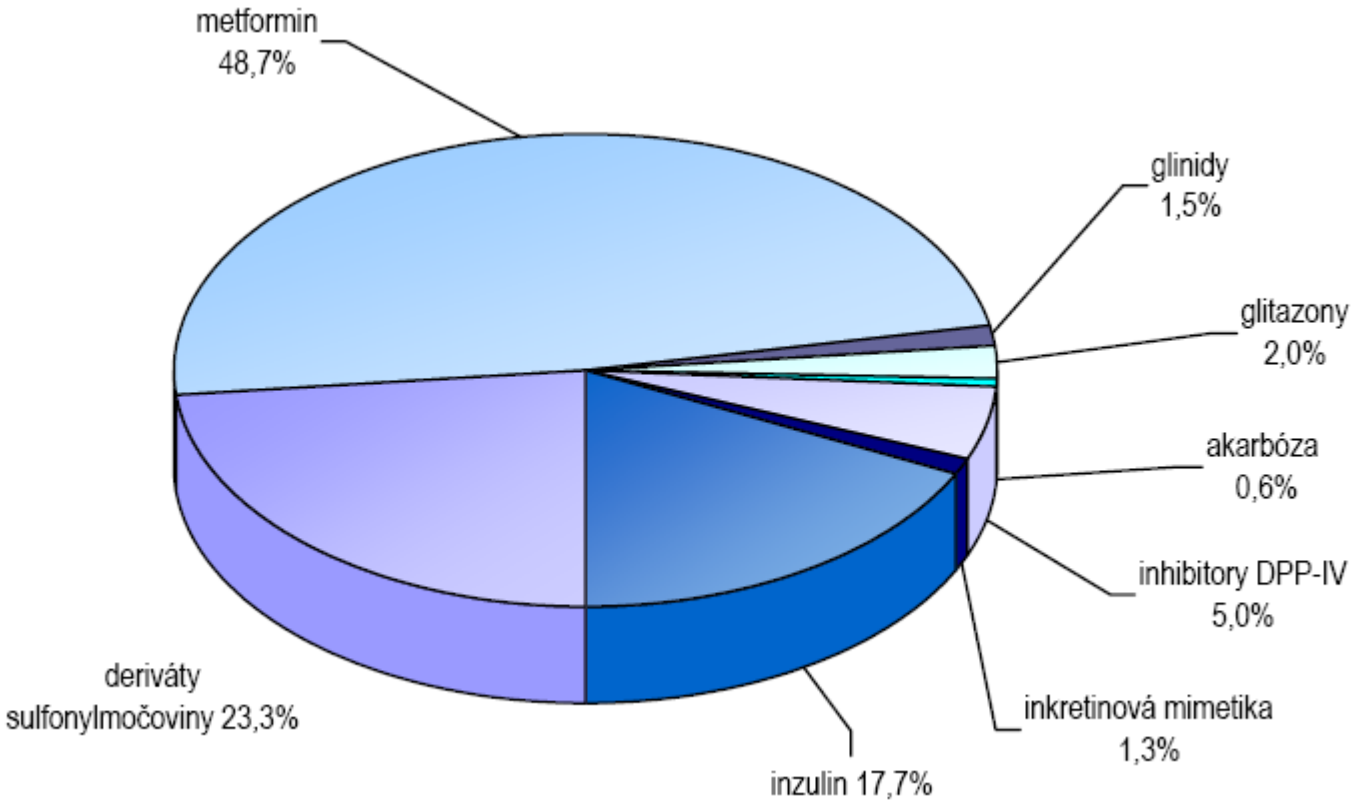
Andrea Kirkpatrick et al. PNAS 2012;109:19988-19993



Robert J. Lefkowitz (left) and Brian K. Kobilka (right) were awarded the 2012 Nobel Prize in chemistry for their work on G-protein coupled receptors, or GPCRs, shown at center.



Farmakologická léčba diabetiků 2. typu v ČR

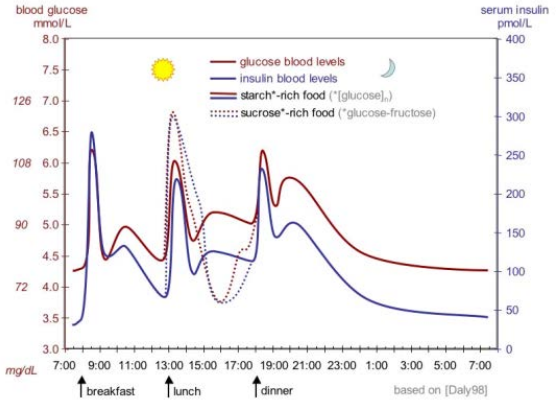


Diabetes 1. typu - Léčba insulinem

Léčba lidským insulinem - rekombinantní (v 2002, 70%)

Eli Lilly (1982, Humulin, *E. coli),* Novo Nordisk, Sanofi Aventis, Pfizer

10 miliard $ za rok (jen insulin), 30 miliard $ za rok (všechny léky)



Problémy léčby insulinem

Způsob podání

Výběr „správné dávky" a její načasování

Výběr vhodného preparátu insulinu (rychlost a délka účinku)

Přizpůsobení dávky příjmu potravy a fyzické aktivitě, stresu, nemoci atd.

Variabilita absorpce při s.c. podání

s.c. podání je nefyziologické ve srovnání s jemným dávkováním pankreatu

Obtížné a nepříjemné pro pacienty

Nebezpečí omylu – hypoglykémie (příliš mnoho insulinu)

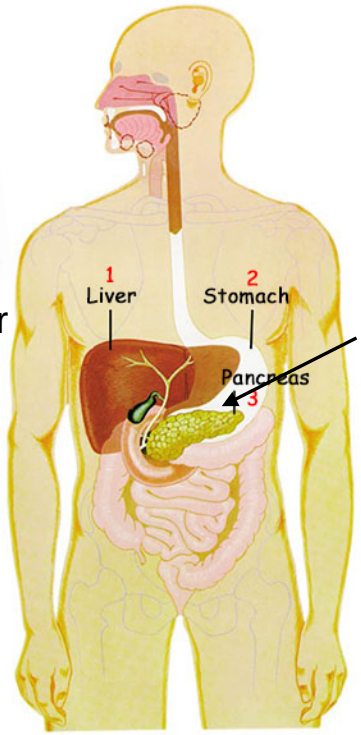
Insulin má nízký terapeutický index (poměr mezi toxickou dávkou a léčebnou dávkou)

Fyziologicky nejprve insulin (50%) působí v játrech kde inhibuje glukoneogenezi, až pak jde do periferií. Při s.c. podání je tomu naopak.

Differences in insulin administration

s.c. Administered insulin precipitates under skin and it is more or less slowly released to act first in the periphery.

Inhibition of glucose production in liver is delayed, which causes disbalances in glycaemia.

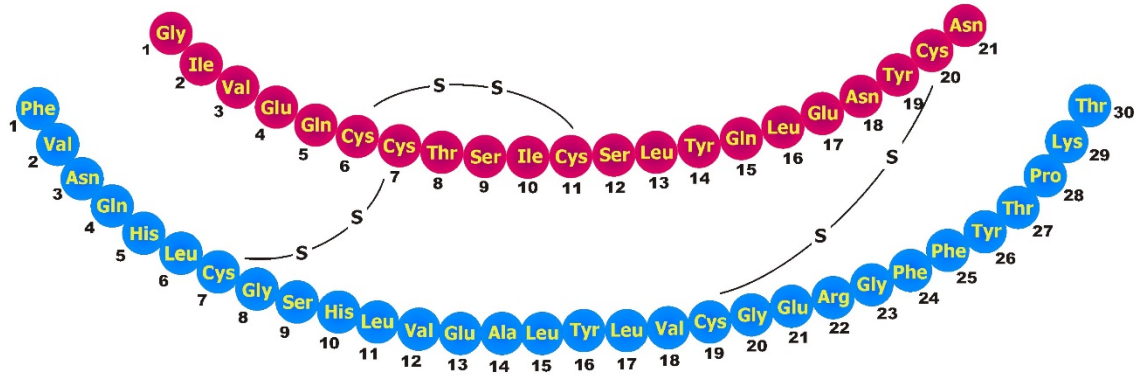


Endogenous insulin first acts in liver (95% IR-B), where it inhibits gluconeogenesis and glycogenolysis (50% of insulin).

Only thereafter, the rest of insulin goes to and acts in periphery (muscles and adipose tissue with cca 70% IR-B).

Léčba analogy insulinu

Pozměněné insuliny, analogy, nabízejí vyšší komfort pacientům



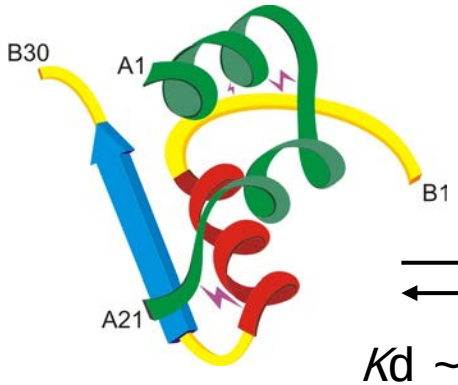
Principem účinku používaných analogů je
změna jejich rozpustnosti vzhledem k přirozenému insulinu
(nižší dimerizace, vyšší pI a tím nižší rozpustnost či vazba na sérové proteiny)

Oligomerizace insulinu

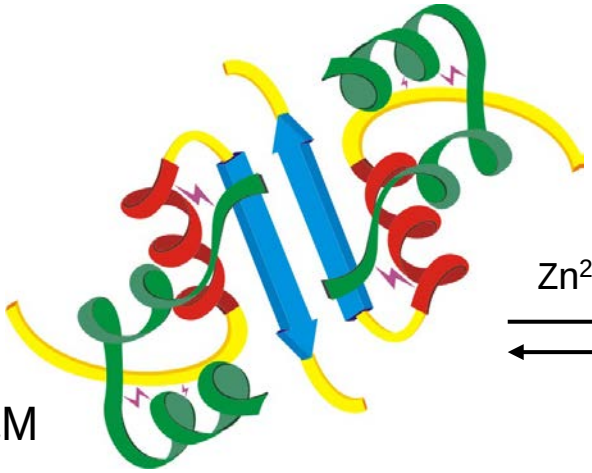
Monomer

Dimer

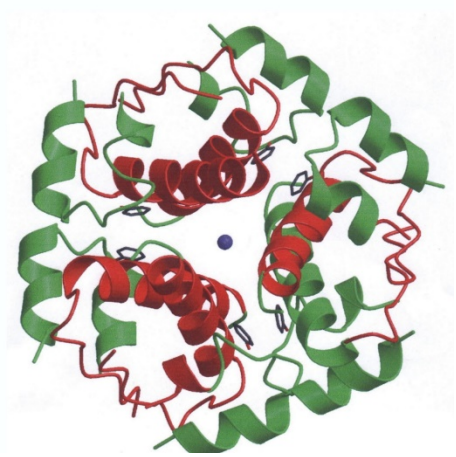
Hexamer



*K*d ~ 10 μM



Zn^{2+}

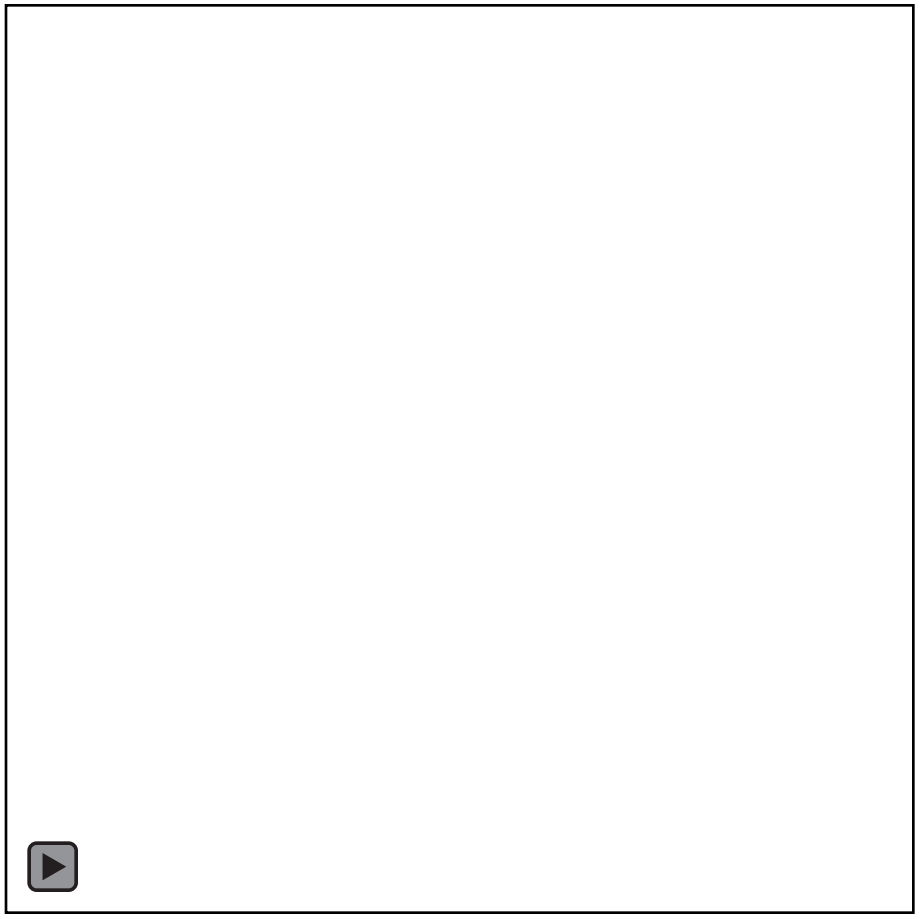


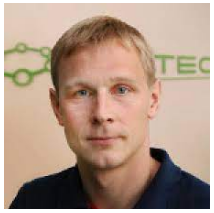
Aktivní forma insulinu

Koncentrace insulinu

Přítomnost Zn^{2+} (*K*d ~ 1 μM)

Cryo-TEM imaging
Electron diffraction tomography data (EDT)

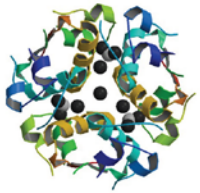




Jiří Nováček
CEITEC MUNI

Manuscript submitted

7 Lantus
(Insulin Glargine)

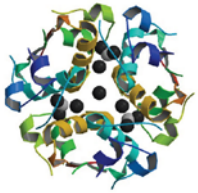


SANOFI
$6,057 Million
Diabetes

32 Novorapid/Novolog
(Insulin Aspart)

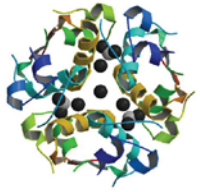
$2,792 Million
Diabetes

34 Humalog
(Insulin Lispro)



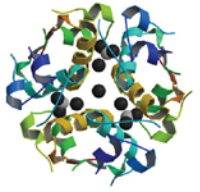
Lilly
$2,769 Million
Diabetes

38 Levemir
(Insulin Detemir)



$2,392 Million
Diabetes

75 Human Insulins
(Insulin)

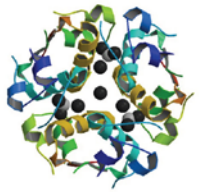


$1,553 Million
Diabetes

84 Novomix/Novolog Mix
(Biphasic Insulin Aspart)

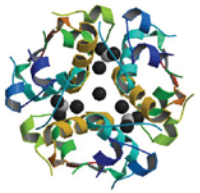
$1,467 Million
Diabetes

93 Humulin
(Insulin Isophane)



Lilly
$1,366 Million
Diabetes

193 Toujeo
(Insulin Glargine)



SANOFI
$688 Million
Diabetes

Insulin jeho analogy
pro diabetiky typu I a II

6 analogů v klinické praxi

Analogy s rychlým nástupem účinku

Lispro ([LysB28, ProB29]-insulin, Humalog), Eli Lilly

Aspart ([AspB28]-insulin, Novalog), Novo Nordisk

Glulisine ([LysB3, GluB29]-insulin, Apidra), Sanofi-Aventis

Analogy s prodlouženým účinkem

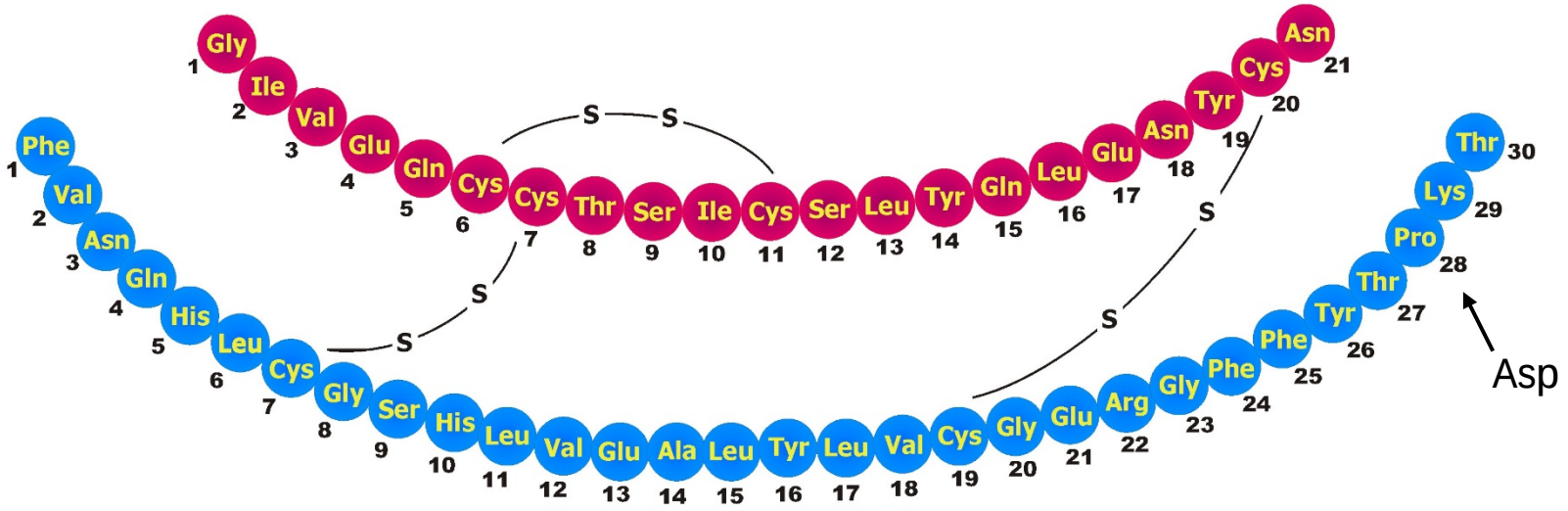
Glargine ([GlyA21, ArgB31, ArgB32]-insulin, Lantus), Sanofi-Aventis

Detemir (LysB29-bound myristic acid, Levemir), Novo Nordisk

Degludec (des-ThrB30)-LysB29-γ-glutamyl-hexadecanedioic acid, Tresiba), Novo Nordisk

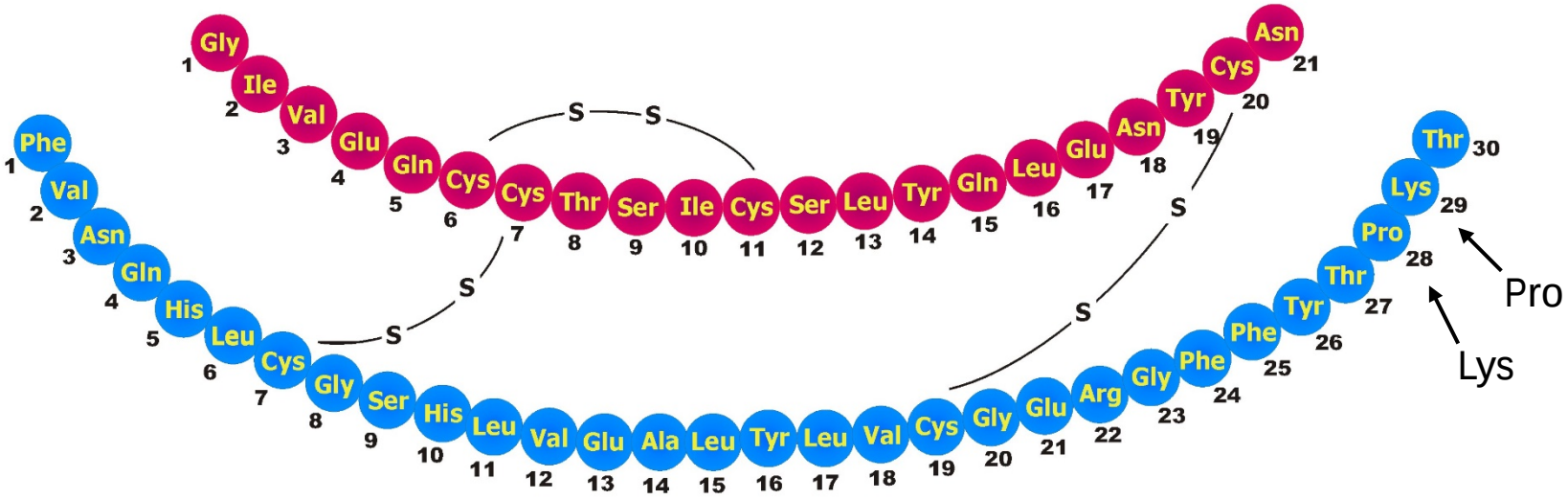
Analogy s rychlým nástupem účinku

Aspart
(nedimerizuje)



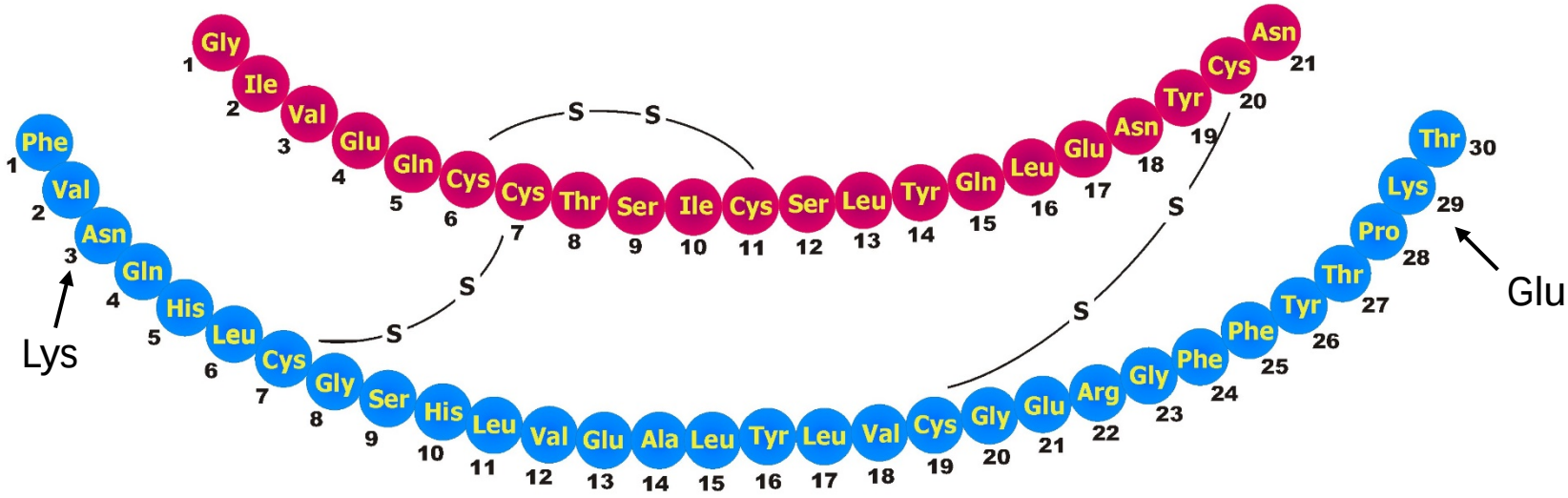
Analogy s rychlým nástupem účinku

Lispro
(nedimerizuje)



Analogy s rychlým nástupem účinku

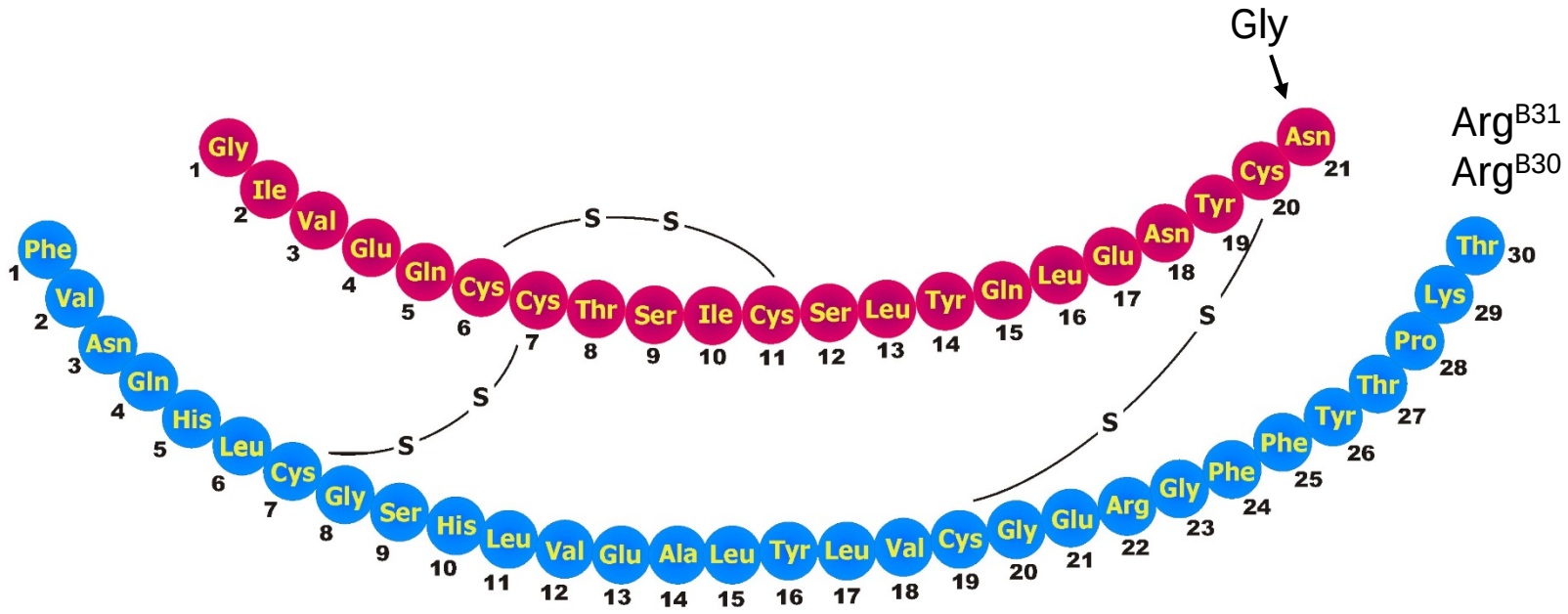
Glulisine
(pravděpodobně netvoří hexamery)



Analogy s prodlouženým účinkem

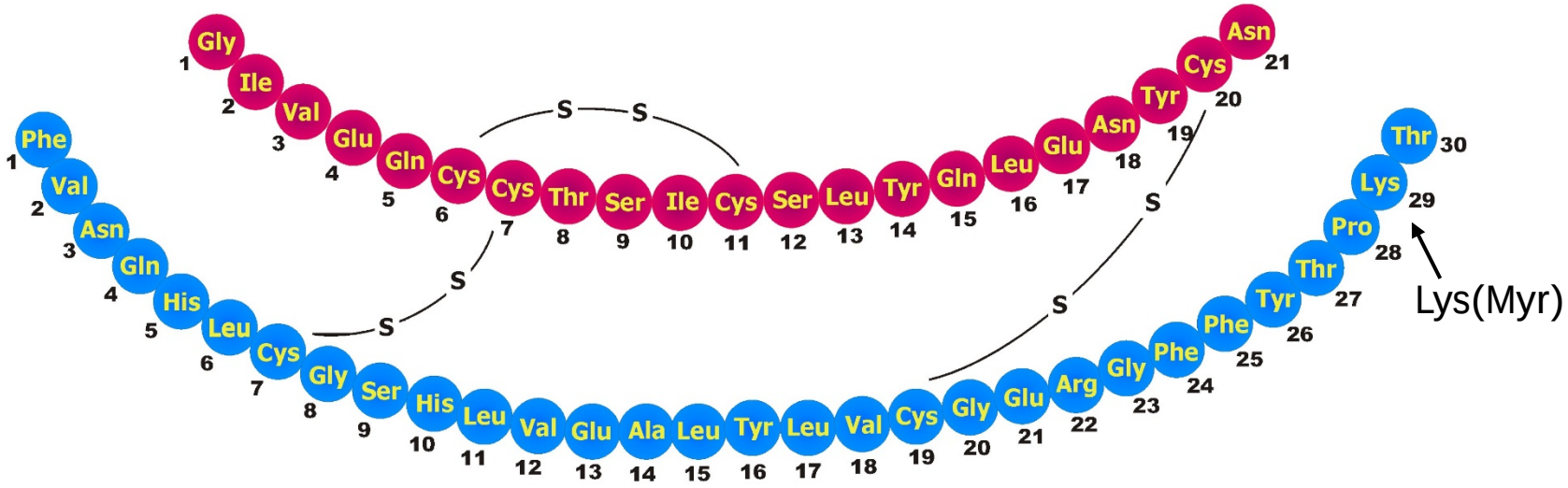
Glargine

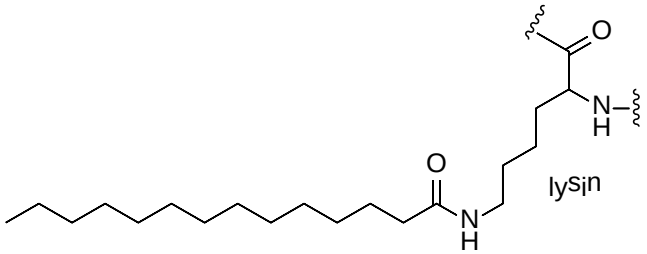
(špatně rozpustný, precipituje a váže se na sérové proteiny)



Detemir

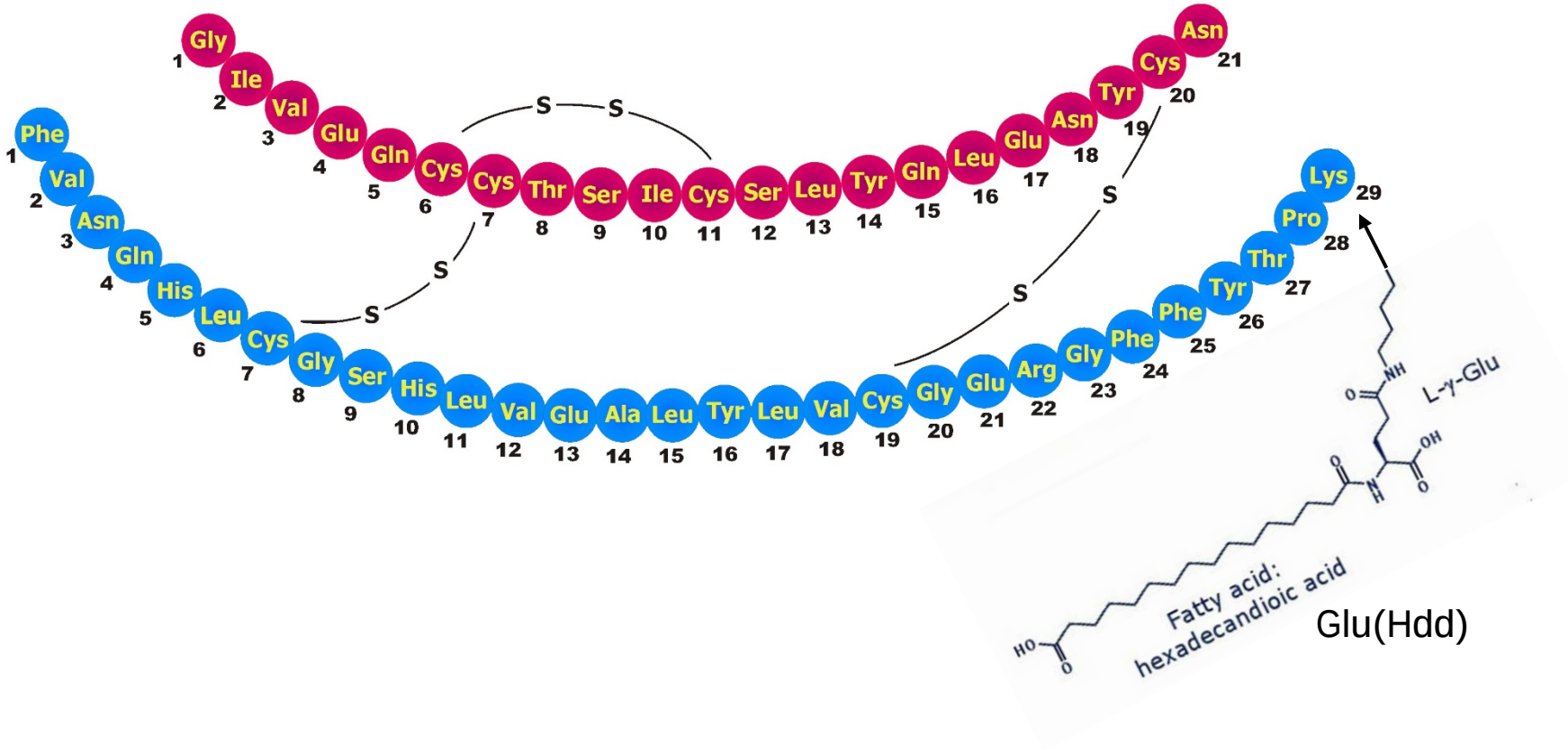
(váže se na sérové proteiny)

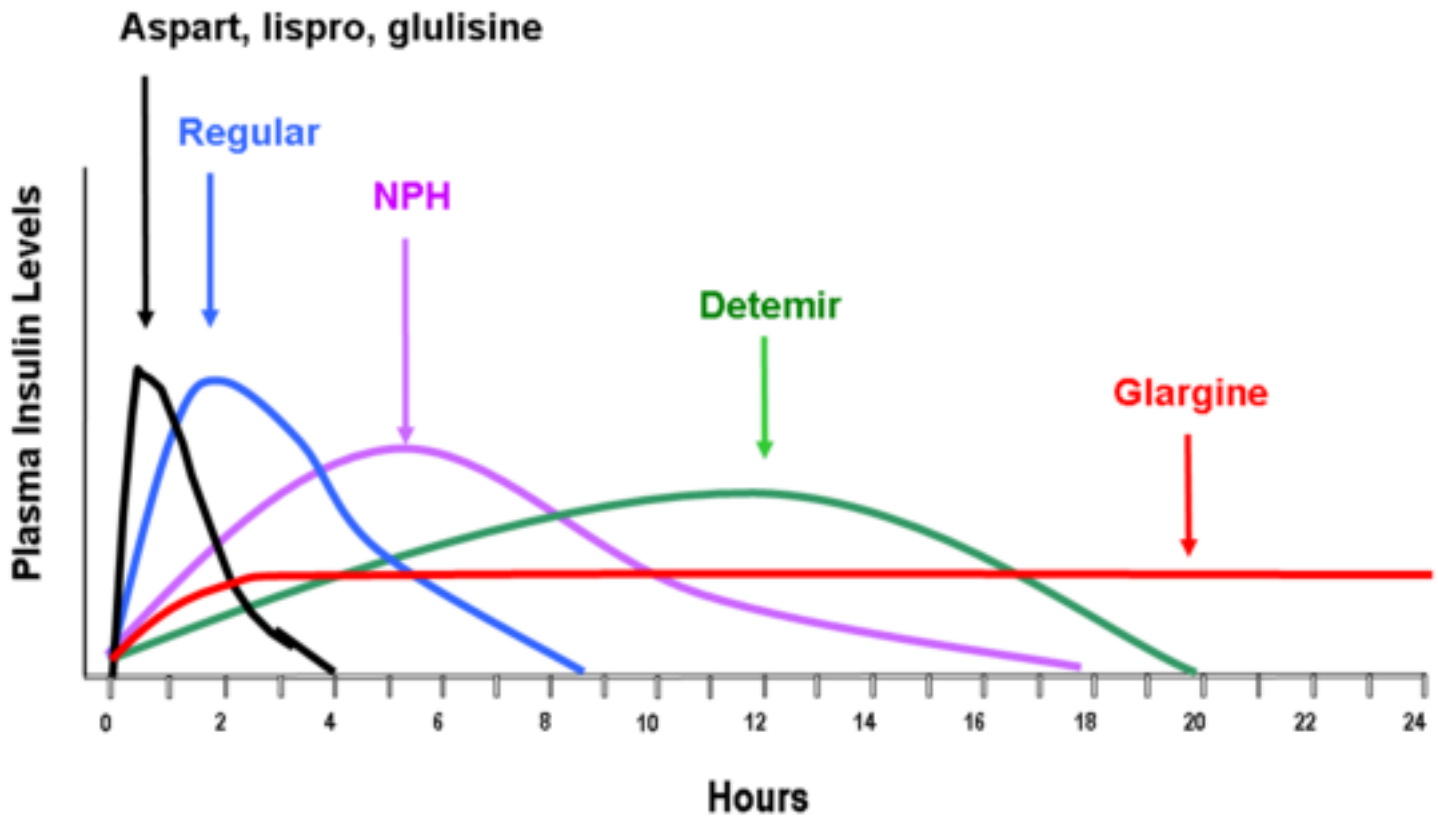




Analogy s prodlouženým účinkem

Degludec
(váže se na sérové proteiny)




Aspart, lispro, glulisine
Regular
NPH
Detemir
Glargine
Plasma Insulin Levels
0
2
4
6
8
10
12
14
16
18
20
22
24
Hours

Současnost je velmi plodné období pro léčiva diabetu

Degludec-Tresiba

Afrezza

Exubera (Pfizer), práškový insulin v inhalátoru, 2006 - 2007

Table 1 | **Selected insulin analogues that are recently approved or in development**

Name	Company	Description	Mechanism	Development phase	Refs
Insulin degludec (Tresiba)	Novo Nordisk	Fatty-acylated insulin analogue	Basal	• Approved in the EU in 2013 • Approved in the US in 2015	10, 175–178
Insulin peglispro (LY2605541)	Eli Lilly	Insulin lispro with 20 kDa PEG	Basal	Programme terminated	9,71, 180–182, 188
Afrezza	Sanofi	Insulin powder in thumb-size inhalation devices	Inhalation	Approved in 2014	112–114
Dance-501	Dance Biopharm	Solution-based formulation in pocket-size device	Inhalation	Phase II	189
ORMD-0801	Oramed Pharmaceuticals	Formulation using POD technology	Oral	Phase II	116,173
NN1953	Novo Nordisk	Formulation using GIPET technology	Oral	Phase II	69
NN1957	Novo Nordisk	Formulation using GIPET technology	Oral	Phase I	69
U-strip	Transdermal Specialties	Insulin patch with ultrasonic trigger	Transdermal	Not disclosed	190,191
AB101	AntriaBio	Insulin encapsulated in PLGA microspheres	Ultralong	Preclinical	61
TransCon insulin	Ascendis	Chemically-immobilized insulin on PEG hydrogel	Ultralong	Phase II	62,63
HM12470 (^{LAPS}Insulin115)	Hanmi	Fc–insulin conjugate	Ultralong	Phase I	64,65
PE0139 (Insumera)	Phase Bio	Elastin-like polypeptide fusion	Ultralong	Phase II	67,68
NN1436 (LAI287)	Novo Nordisk	Not disclosed	Ultralong	Phase I	69
NN1438 (LAI338)	Novo Nordisk	Not disclosed	Ultralong	Phase I	69
IDegLira (Xultophy)	Novo Nordisk	Liraglutide and insulin degludec combination	Co-therapy with GLP1	• Approved in the EU in 2014 • FDA submission	13,69, 192
BioChaperone lispro	Adocia	Lispro formulation	Rapid acting	Phase III	78
BIOD-123	Biodel	Formulation using Linjeta technology	Rapid acting	Phase II	77
LixiLan	Sanofi	Lixisenatide and insulin glargine combination	Co-therapy with GLP1	FDA submission	193, 194
Ryzodeg	Novo Nordisk	Insulin degludec and insulin aspart	Basal and fast acting	• Approved in the EU in 2013 • Approved in the US in 2015	69, 195–197
Insulin-327	Novo Nordisk	Hepatoselective insulin	Experimental	NA	11
INS-A and INS-B	Novo Nordisk	Receptor-selective analogues	Experimental	NA	12
PBA-insulin	MIT	Glucose-responsive insulin analogue	Experimental	NA	123

Fc, crystallisable fragment; FDA, US Food and Drug Administration; GIPET, gastro-intestinal permeation enhancement technology; GLP1, glucagon-like peptide 1; MIT, Massachusetts Institute of Technology; NA, not applicable; PEG, polyethylene glycol; PLGA, poly(lactic-co-glycolic acid); POD, protein oral delivery.

Zaykov, Mayer, DiMarchi, Pursuit of a perfect insulin
Nature Reviews Drug Discovery 15, 425, 2016

In 2013

Novo Nordisk to invest up to $3.7 billion on diabetes pills

COPENHAGEN Mon Oct 7, 2013 6:27pm IST

(Reuters) - Novo Nordisk plans to invest up to 20 billion Danish crowns ($3.65 billion) on developing diabetes tablets intended to replace traditional insulin injections, it said on Monday.

The Danish company said it planned to spend the money through to 2020 on six diabetes pills it has under development and that the sum included potential production facilities.

It estimates the global market for diabetes tablets could be worth more than 100 billion crowns a year from the beginning of the next decade, a spokesperson said, confirming a report in the Danish business newspaper Borsen.

In the conventional treatment, insulin has to be injected into the bloodstream, something that scares off many potential users in the early stages of diabetes.

The challenge for the tablet technology is to get the insulin through gastric acid and into the bloodstream.

Novo Nordisk, the world's largest insulin producer, aims to develop both an insulin and a so-called GLP-1 agonist in tablet form. The company has around 500 employees working on the development of the tablets, the spokesperson said.

It will spend around 1 billion crowns on the projects this year, with investment increasing towards possible product launches early next decade.

At 1235 GMT, Novo Nordisk shares were flat at 913.5 crowns.

Zastaveno o dva roky později pro finanční problémy

ÚOCHB AV ČR
IOCB PRAGUE

Future drugs (?)

Insulins in clinical trials

Table 1. Overview of cited clinical trials of novel insulins beyond the centennial

Insulin	Clinical trials registry identifiers[a,b] Refs	Trial Phase Population Number of individuals	Type of trial	Main objective Primary endpoint
Oral insulin				
Oral insulin 338 (OI338)	NCT02470039 [51]	II T2D 50	Randomized, double-blind, parallel, active-controlled	Efficacy and safety during 8 weeks of treatment with once-daily OI338 versus once-daily s.c. insulin glargine U100 Treatment difference in FPG at week 8
ORMD-0801	NCT00867594 [52]	II T1D 8	Single-arm pilot trial	Tolerability and glycemic stability during 10 days of treatment three times daily in conjunction with usual insulin therapy Safety and tolerability
ORMD-0801	NCT03467932 [53]	II T2D 354	Randomized, parallel, placebo-controlled	Efficacy during 12 weeks of treatment up to three times daily versus placebo Change in HbA_{1c} at week 12
ORMD-0801	NCT02653300 [58]	II T2D and NASH 8	Single-arm pilot trial	Safety, tolerability, and early effects on liver fat content during 12 weeks of once-daily treatment Change in liver fat at 12 weeks
Insulin tregopil	CTRI/2009/091/ 000479 [54]	II T2D 20	Open-label, single ascending dose trial	PK and glucodynamics when administered before a standard meal Postprandial glucose concentration
Insulin tregopil	CTRI/2008/091/ 000276 Summarized in [59]	III T2D 264	Randomized, double-blind, parallel, pfvlacebzo-controlled	Efficacy and safety during 24 weeks of treatment 4 times daily versus placebo Change in HbA_{1c} at week 24
Insulin tregopil	NCT03392961 [60]	I T2D 51	Randomized, open-label, crossover, placebo-controlled	Effect of premeal dosing time, between-meal interval, and meal composition on PK and PD of single-dose insulin tregopil $AUC_{0-180\ minutes}$
Once-weekly insulin				
BIF (LY320959)	NCT02942914 [64]	I T2D and healthy 57 and 16	Double-blind, first-in-human, single ascending dose trial	Safety and tolerability, PK, and PD after single dose Frequency of serious adverse reactions
BIF (LY320959)	NCT03367377 [64]	I T2D 33	Randomized, open-label, active-controlled, multiple ascending dose trial	Safety and tolerability, PK, and PD during 6 weeks of once-weekly treatment versus once-daily insulin glargine U100 Frequency of serious adverse reactions
BIF (LY320959)	NCT03736785 [66]	II T2D 399	Randomized, open-label, parallel, active-controlled	Efficacy and safety during 32 weeks of once-weekly treatment versus once-daily insulin degludec Change in HbA_{1c} at week 32
Insulin icodec	NCT02964104 [71]	I T2D 50	Randomized, double-blind, active-controlled, multiple ascending dose trial	Safety and tolerability, PK, and PD during 5 weeks of once-weekly treatment versus once-daily insulin degludec Number of adverse events
Insulin icodec	NCT03751657 [70]	II T2D 247	Randomized, double-blind, parallel, active-controlled	Efficacy and safety during 26 weeks of once-weekly treatment versus once-daily insulin glargine U100 Change in HbA_{1c} at week 26
Hepato-preferential insulin				
BIL	NCT01654380 [74]	I Healthy 8	Randomized, open-label, crossover, active-controlled	EGP and GDR during continuous i.v. infusion of BIL or insulin glargine U100 Suppression of EGP
BIL	NCT01481779 NCT01435616 NCT01454284 NCT01468987 NCT01582451 NCT01790438 NCT01792284 [75]	III T1D and T2D 1914 and 4297	Program of seven randomized, double-blind or open-label, parallel or crossover, active-controlled trials	Efficacy and safety during 26-78 weeks of once-daily treatment versus once-daily insulin glargine U100 or once- or twice-daily NPH insulin Change in HbA_{1c} at week 12-52
Glucose-sensitive insulin				
MK-2640	NCT02269735 [89]	I Healthy and T1D 36 and 16	Healthy: Open-label ascending dose trial T1D: Randomized, open-label, crossover, active-controlled	Safety, PK, and PD during i.v. infusion (versus regular human insulin in individuals with T1D) Frequency of adverse events

Oral insulins

„Once-weekly“ insulins

Hepato-preferential insulins

Glc-sensitive insulins

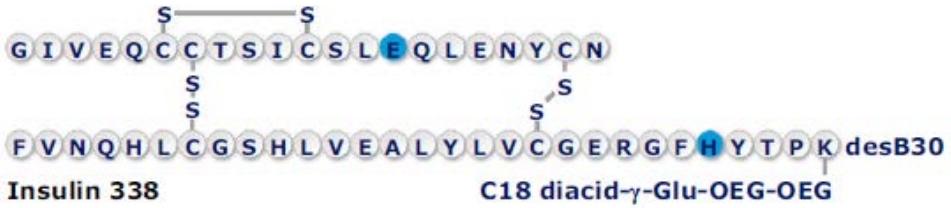
Kurzhals, P. et al., Trends Pharm. Sci., 42, 620-639 (2021)

Oral insulins

Oral insulin 338 (OI338)

Novo Nordisk, Phase 2, pill with Na-caprate,

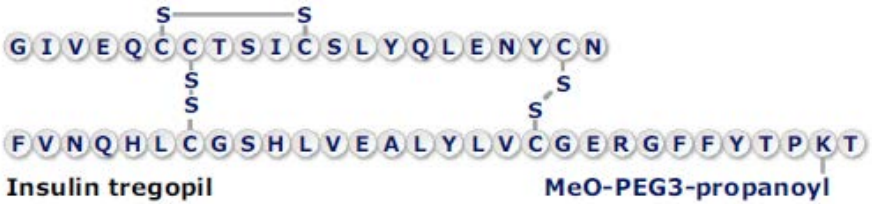
500x-lower IR binding, 2% bio-availability, halted



Insulin Tregopil

Biocon, Phase 3, pill with Na-caprate,

Rapid onset, in trials



ORMD-0801

Oramed Pharmaceuticals, Phase 2, insulin in a pill with oil, trypsin inhibitor, EDTA, in trials

Kurzhals, P. et al., Trends Pharm. Sci., 42, 620-639 (2021)

„Once-weekly“ insulins

BIF, LY3209590, Basal insulin Fc

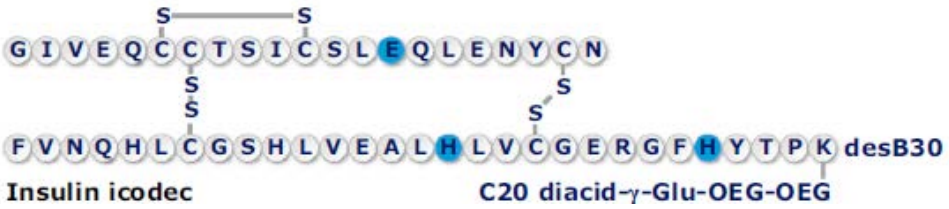
Eli Lilly, Phase 2, two single-chain insulins connected with IgG, 100x lower IR binding, plasma protein binding, in trials

Kurzhals, P. et al., Trends Pharm. Sci., 42, 620-639 (2021)

„Once-weekly“ insulins

Insulin Icodec

Novo Nordisk, Phase 2, mutated insulin, lipidized, plasma protein binding, low affinity, $t_{1/2}$ 196 h, in trials



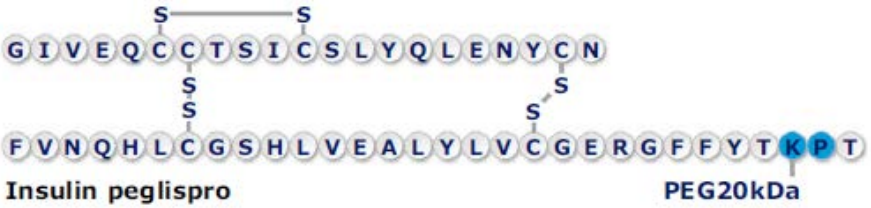
Kurzhals, P. et al., Trends Pharm. Sci., 42, 620-639 (2021)

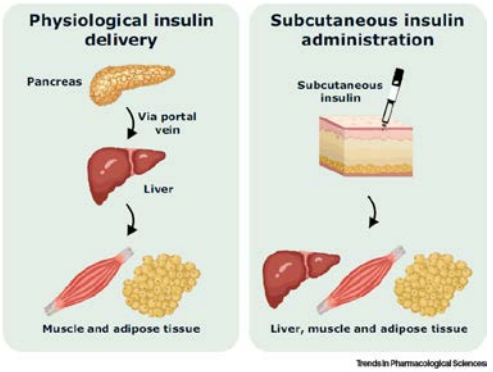
Hepato-preferential insulins

Insulin peglispro (BIL, LY2605541)

Eli Lilly, apparent Mr >70 Kda, large hydrodynamic radius causes preferential hepatic clearance after s.c.,

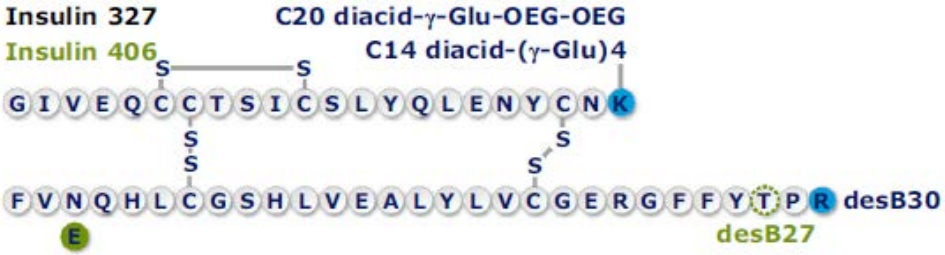
But higher aminotransferases, TAGs and fat liver, Phase 3 halted.





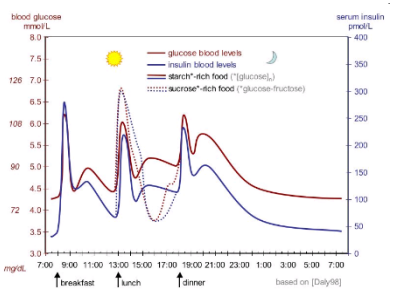
Insulin 327 a Insulin 406

Novo Nordisk, similar properties to peglispro, in studies



Kurzhals, P. et al., Trends Pharm. Sci., 42, 620-639 (2021)

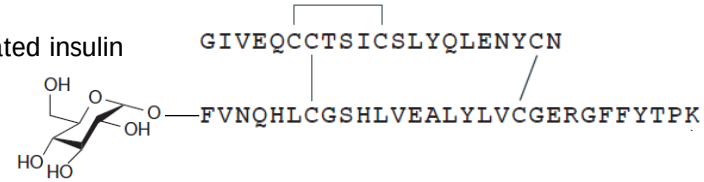
Glucose-sensitive insulins

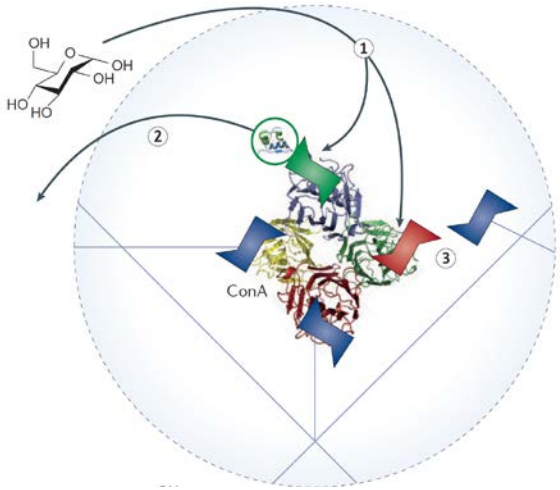


Danger of hypoglycemia.

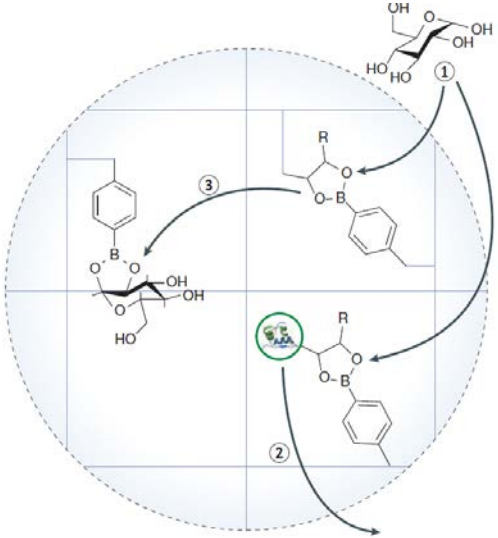
Insulin preparations able to auto-adjust its activity to glucose concentration.

Glycosylated insulin



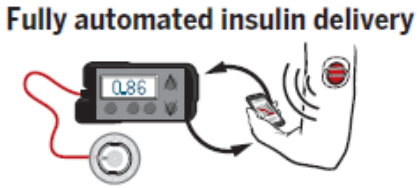


High glucose releases glycosylated insulin from polymer-bound lectin.



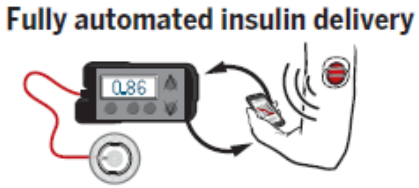
High glucose releases glycosylated insulin from polymer-bound phenylboronic acid.

Zaykov, A.N. et al., Nat. Rev. Drug. Discov., 15, 425-439, (2016)



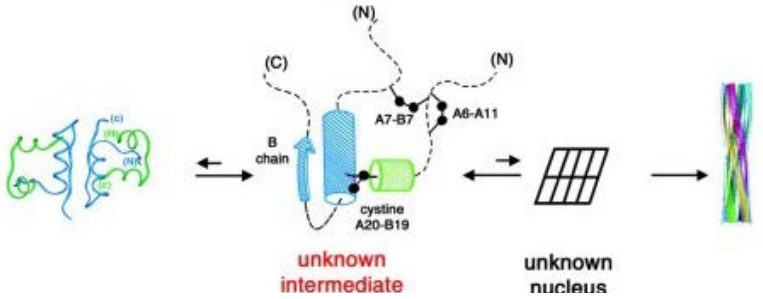
Artificial pancreas

„Closed-loop systems“



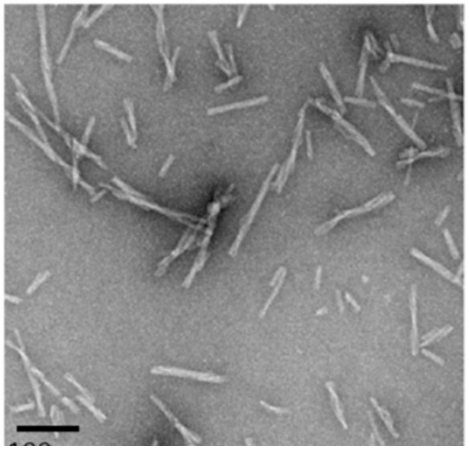
Artificial pancreas

„Closed-loop systems“



More thermally stable insulins

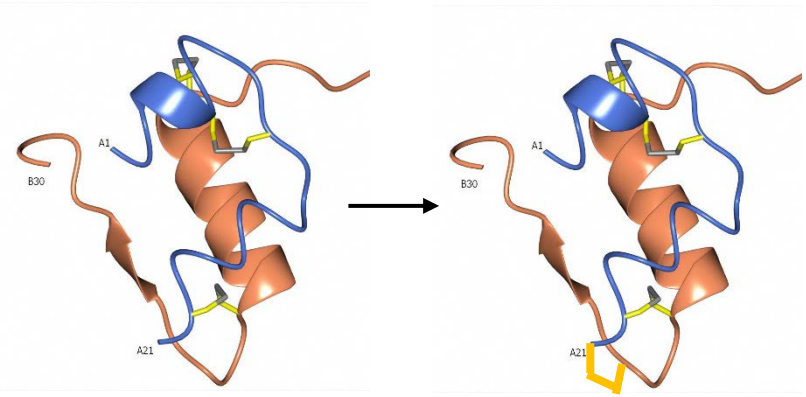
Insulin should be resistant towards formation of insoluble fibrils



Thermally more stable insulins

Xiong et al., Chem. Sci, 2020, 11, 195-200

Stabilization of insulin‘s 3-D structure by fourth disulphide bridge



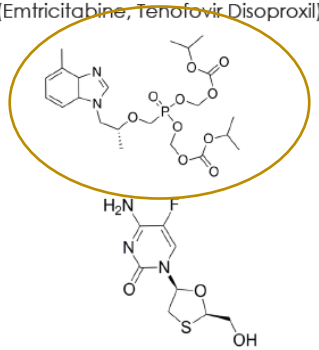
Hossain et al., J. Am. Chem. Soc., 2020, 142, 1164-1169

Glycosylation of insulin dramatically increased its thermal stability (at 50°C)

Tenofovir disoproxil fumarate
Gilead Sciences

19 Truvada

(Emtricitabine, Tenofovir Disoproxil)



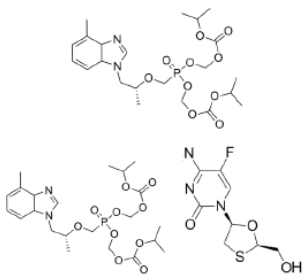
GILEAD

$3,566 Million

Infectious Diseases

35 Atripla

(Efavirenz, Emtricitabine, Tenofovir Disoproxil)



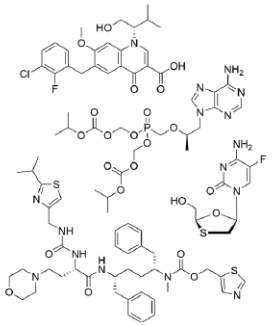
GILEAD

$2,605 Million

Infectious Diseases

54 Stribild

(Cobicistat, Elvitegravir, Emtricitabine, Tenofovir Disoproxil)



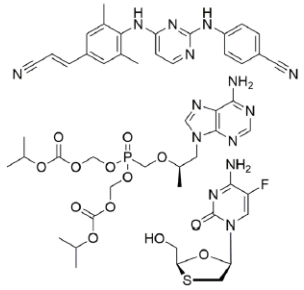
GILEAD

$1,914 Million

Infectious Diseases

87 Complera

(Rilpivirine, Emtricitabine, Tenofovir Disoproxil Fumarate)



GILEAD

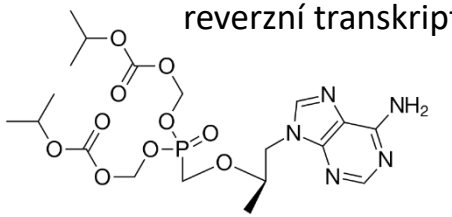
$1,457 Million

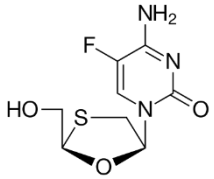
Infectious Diseases

Jedna pilulka denně

Truvada (2004) je látka pro léčbu AIDS, proti retrovirům jako je HIV

Tenofovir disoproxil
je inhibitor
reverzní transkriptázy



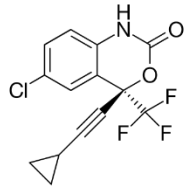


Emtricitabine
je inhibitor
reverzní transkriptázy

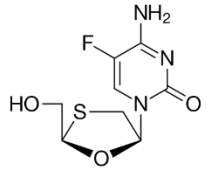
Patent doběhl v roce 2017.

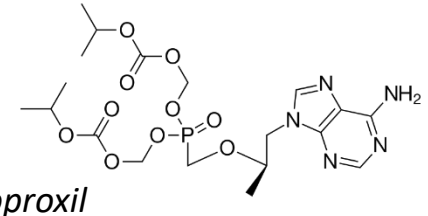
Atripla (2006) je látka pro léčbu AIDS, proti retrovirům jako je HIV

Efavirenz je inhibitor
reverzní transkriptázy



Emtricitabine
je inhibitor
reverzní transkriptázy





Tenofovir disoproxil
je inhibitor
reverzní transkriptázy

Tenofovir (Gilead) je acyklický nukleotidový inhibitor, Embricitabine (Gilead) je nukleosidový inhibitor a Efavirenz (Bristol-Myers Squibb) je ne-nukleosidový inhibitor reverzní transkriptázy.
Jejich součinnost je třeba aby se účinně blokoval virus HIV, který velmi snadno mutuje.

HIV-1 reverzní transkriptáza

A **reverse transcriptase** (RT) is an enzyme used to generate complementary DNA (cDNA)

from an RNA template, a process termed **reverse transcription**.

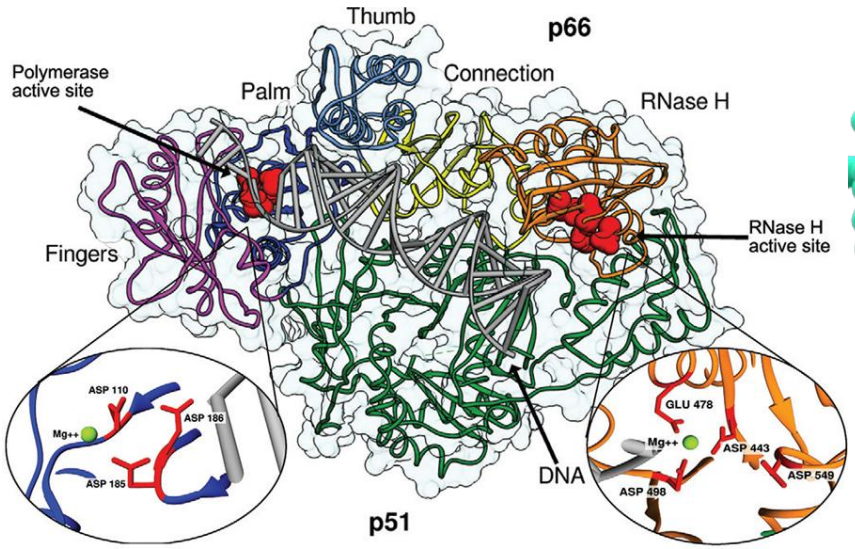
It is mainly associated with **retroviruses** (**HIV**). However, non-retroviruses also use RT (**the hepatitis B virus**)

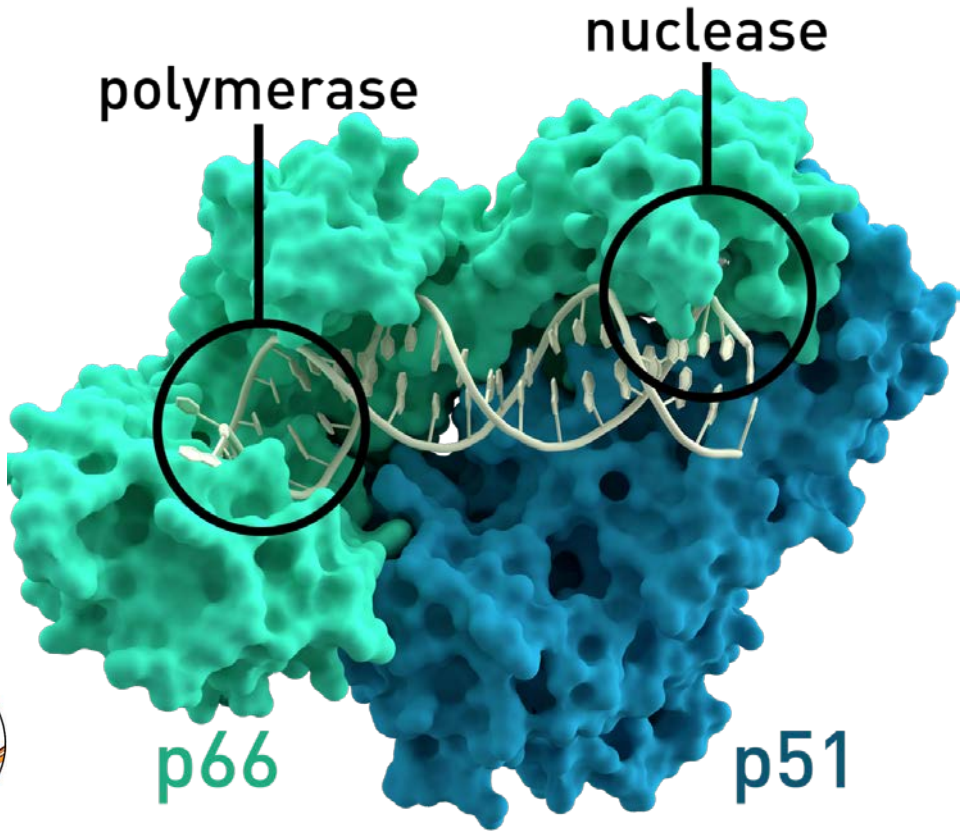
Retroviral RT has three sequential biochemical activities:

(a) RNA-dependent DNA polymerase activity,

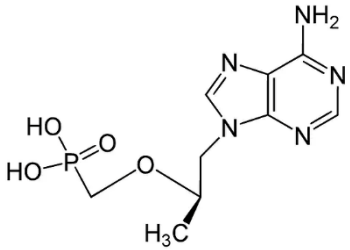
(b) ribonuclease H, and

(c) DNA-dependent DNA polymerase activity.

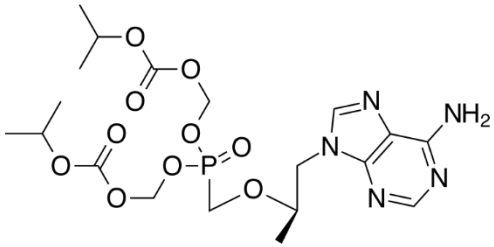




Tenofovir



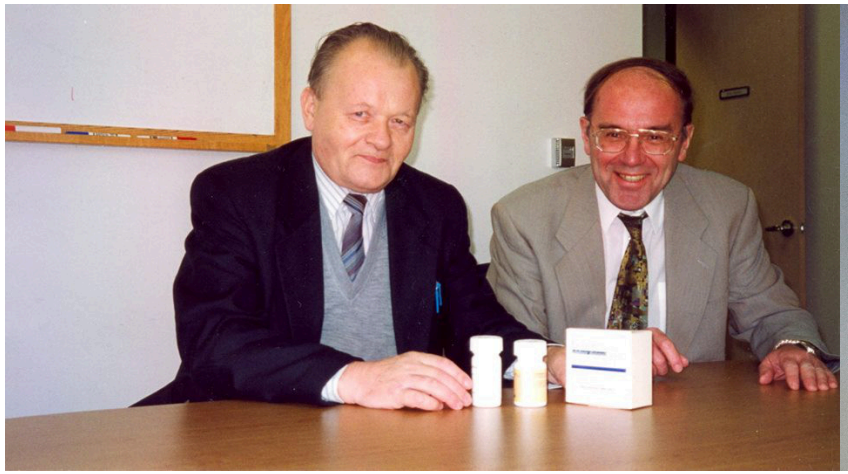
enzymy
esterázy



Tenofovir disoproxil
(chránící skupiny zvyšují lipofilicitu,tj. prodroga)

9-(2-Phosphonyl-methoxypropyly)adenine (PMPA)

The „Holy“ Trinity



Antonín Holý (ÚOCHB)
Ivan Rosenberg
Petr Alexander
Hana Dvořáková aj.

Chemie

První patent 1984

Erik De Clerq
Catholic University
of Leuven (Leuven, Belgium).

Biologické testy

První testy 1985

John C. Martin
Gilead Sciences, Ltd.
Foster City, CA

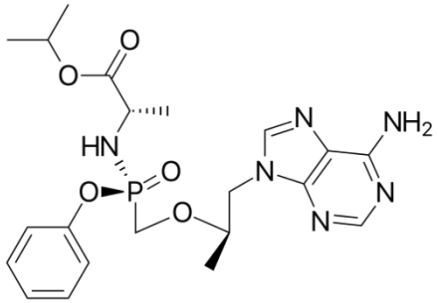
Komercializace

V Gileadu od roku 1990
předtím v Bristol-Myers Squibb

2001 FDA povolení na HIV, v 2008 na hepatitidu B


velký sál
KD Petra Bezruče
Petr Zelenka

Tenofovir alafenamide fumarate (TAF)



Vyvinul Gilead Sciences na základě tenofoviru.

Léčba HIV a Hepatitidy B.

Má vyšší aktivitu a lepší distribuci do lymfatických tkání

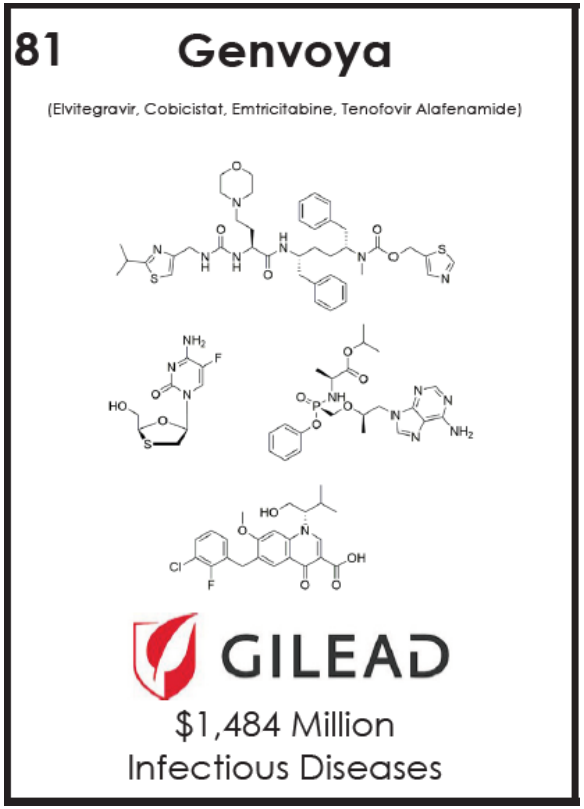
a nižší toxicitu než tenefovir disoproxil.

Gilead dostal souhlas FDA v 11/2016, prodává je jako Vemlidy**.**

Aplikuje se v kombinaci s jiným léky pod jmény

Genvoya, Descovy a Odefsey.

ÚOCHB má licenční práva.



za jeden rok…..