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AMINOKISLINE, PEPTIDI, PROTEINI, DELO S PROTEINI

AMINOKISLINE- ZGRADBA
LASTNOSTI

- Disociacija
- Polarnost
- Reaktivnost
- Spektroskopske lastnosti

PEPTIDNA VEZ

PEPTIDI, PROTEINI

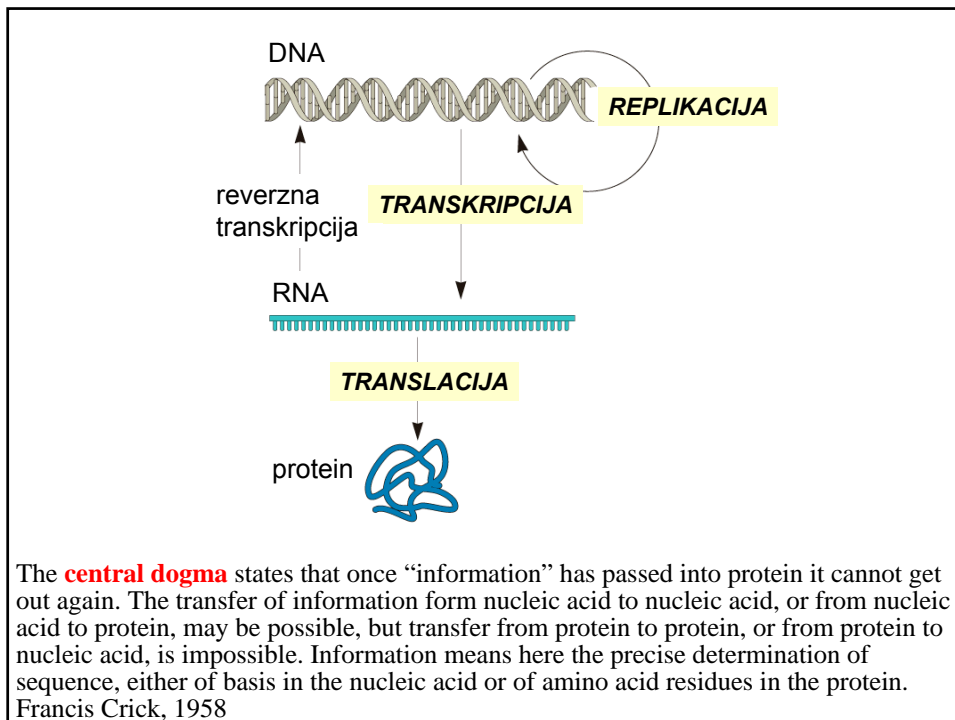
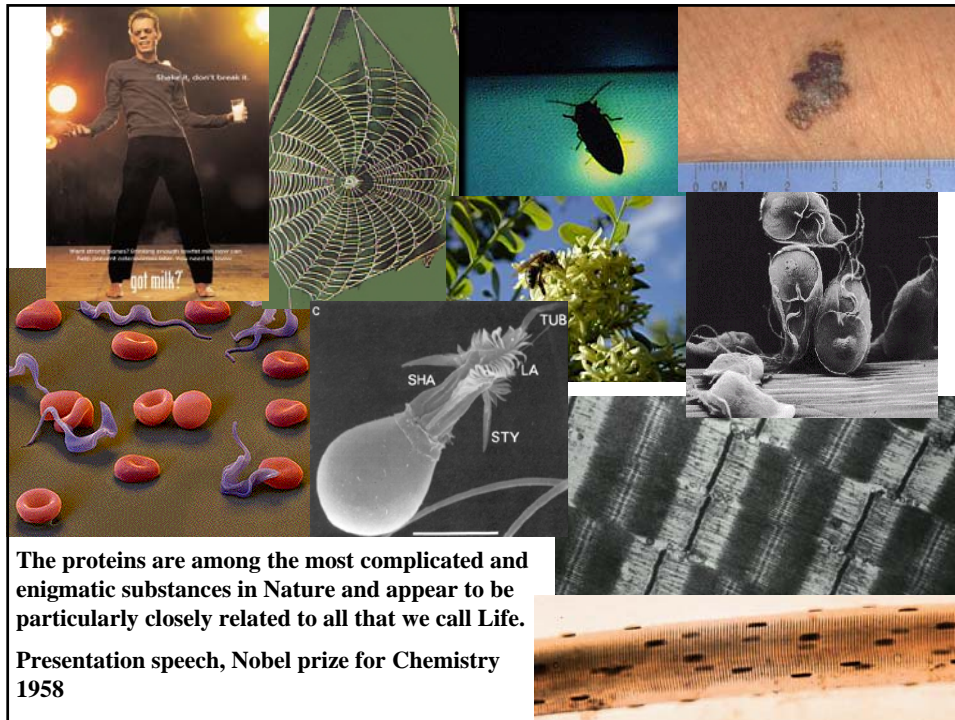
LASTNOSTI PROTEINOV

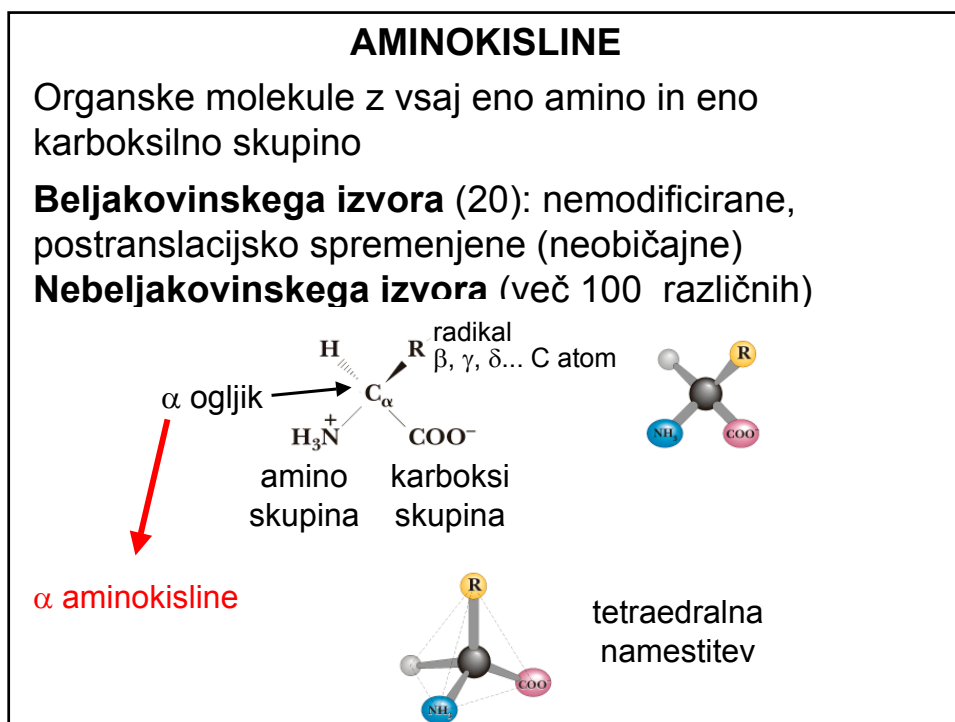
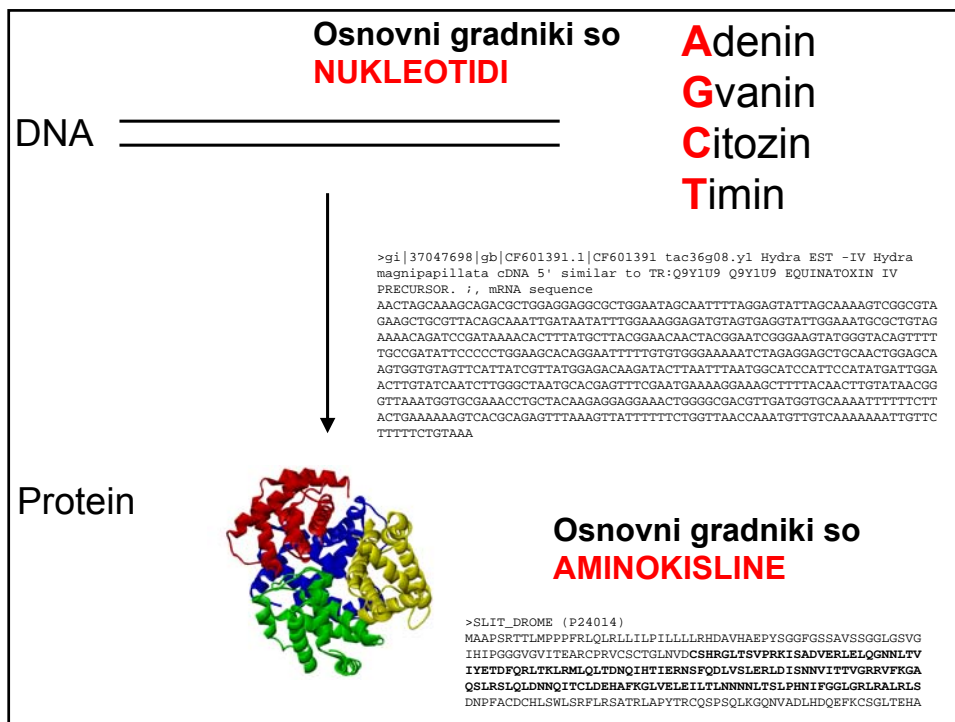
NIVOJI PROTEINSKE ZGRADBE

PRIMARNA ZGRADBA

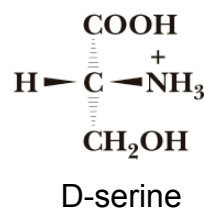
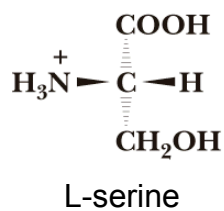
DOLOČEVANJE PRIMARNE ZGRADBE

ZAKAJ JE POMEMBNO POZNAVANJE PRIMARNE ZGRADBE





- asimetrični α ogljikov atom
- optično aktivne stereoizomere
- vse razen Gly so kiralne
- **L-aminokislina** prevladujejo v naravi
- D,L-nomenklatura zasnovana na D- in L-gliceraldehidu



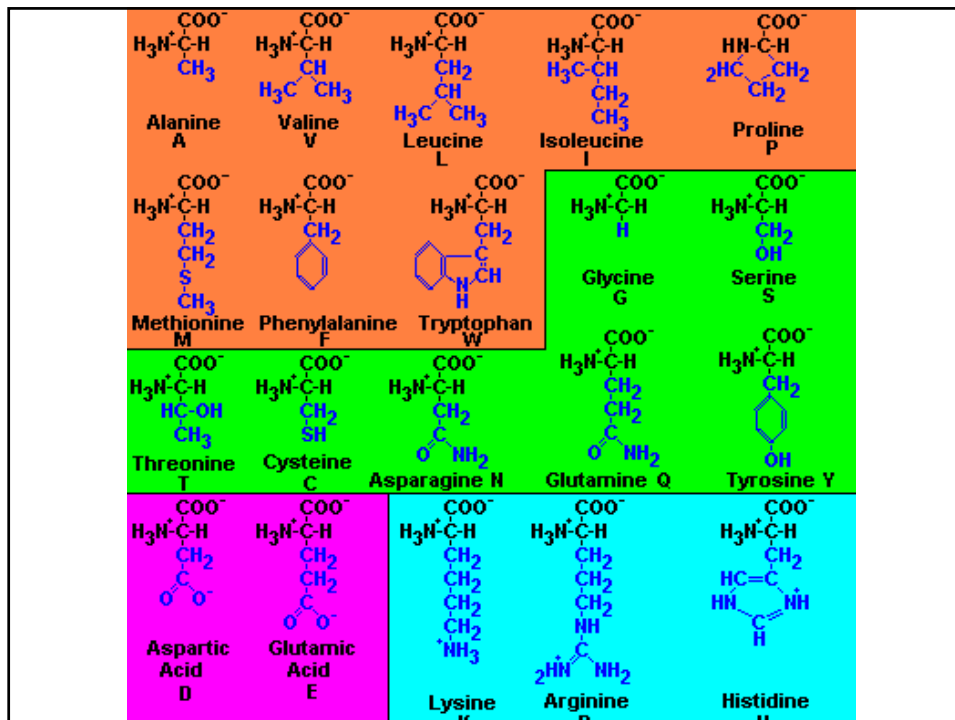
20 NARAVNIH AMINOKISLIN

enočrkovna koda, tričrkovna koda

podobnosti v lastnostih stranskih skupin, združevanje v skupine

delitev glede na polarnost stranske skupine

hidrofobne	polarne, nenabite	polarne, nabite
Gly G	Ser S	Asp D
Ala A	Thr T	Glu E
Val V	Cys C	Lys K
Leu L	Tyr Y	Arg R
Ile I	Asn N	His H
Pro P	Gln Q	
Met M		
Phe F		
Trp W		



Skupina 1- nepolarne stranske skupine

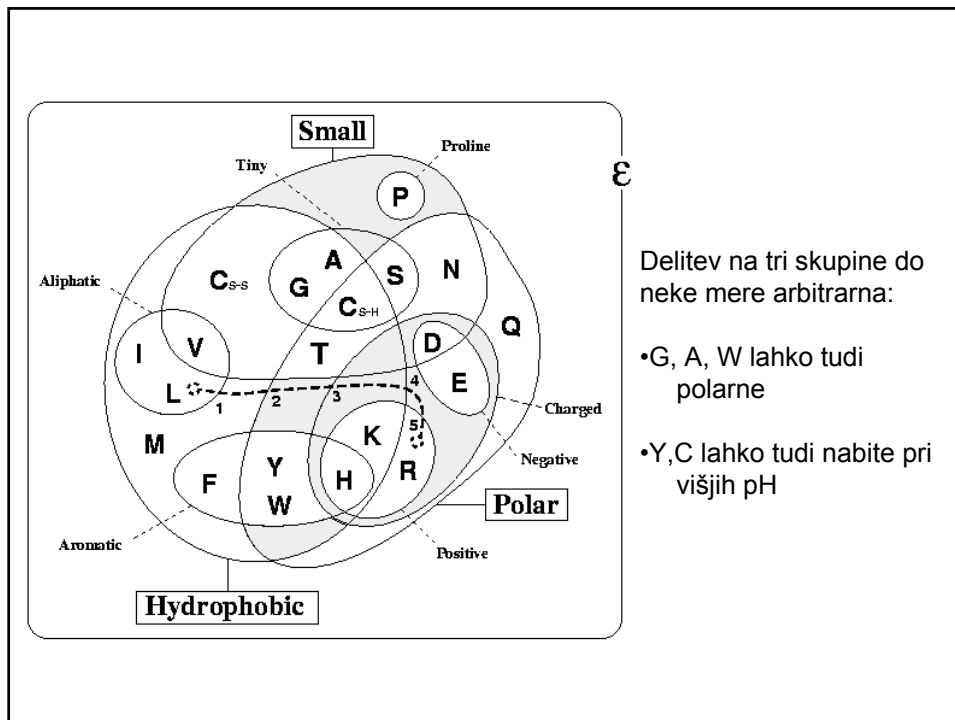
Gly, Ala, Val, Leu, Ile, Pro, Met, Phe, Trp
 alifatske ali aromatske stranske skupine- hidrofoben karakter.
 Nizka kemijska reaktivnost stranskih skupin. V notranjosti proteina, stran od vodne faze.

Skupina 2- polarne, nenabite

Ser, Thr, Cys, Tyr, Asn, Gln
 Različne funkcionalne skupine z enim heteroatomom (O, S ali N), ki ima elektronski par. Lahko tvori H-vezi z vodo ali drugimi skupinami. Cys- disulfidna kovalentna vez, pomembna za 3D zgradbo proteinov. Na površini proteinov.

Skupina 3- polarne, nabite pri fiziološkem pH

Asp, Glu, Lys, Arg, His
 Kisle ali bazične stranske skupine. Neto naboj Asp in Glu pri pH 7.4 je -1 , neto naboj Lys, Arg in His pa $+1$. Imidazolna skupina His ima pKa pri fizioloških pogojih, zato ima lahko neto naboj $+2$. Na površini proteinov.

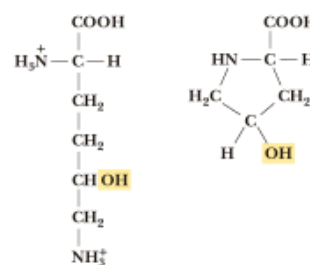


NEOBIČAJNE AMINOKISLINE- kemijsko spremenjene

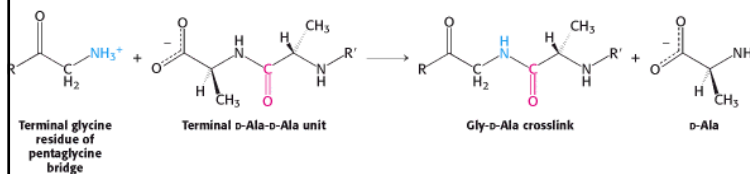
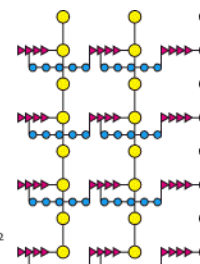
po translaciji, pomembno za funkcijo proteina

- 4-hidroksiprolin, 5-hidroksilizin v kolagenu
- histoni veliko metiliranih, acetiliranih, fosforiliranih
- N-formilmetionin pri biosintezi prokariotskih proteinov
- γ - karboksiglutaminska kislina pri proteinih, ki sodelujejo pri strjevanju krvi
- D-aminokislina komponente bakterijskih celičnih sten, antibiotikov (gramicidin A)

5-hidroksilizin 4-hidroksiprolin



sladkorji
tetrapeptidni
pentapeptidni
mostički



DERIVATI AMINOKISLIN Z BIOLOŠKO FUNKCIJO

γ -aminobutirična kislina (GABA)

dopamin

histamin (dekarboksiliran histidin)

tiroksin

INTERMEDIATI V METABOLIZMU

citrulin, ornitin

homocistein

S-adenozilmetionin

nevrottransmitter

nevrottransmitter

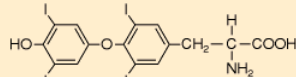
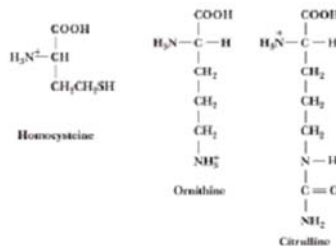
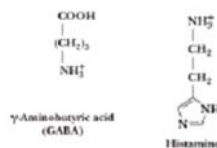
lokalni mediator alergijskih reakcij

tiroidni hormon, ki vsebuje jod

v metabolizmu uree

v metabolizmu aminokislin

donor metilne skupine



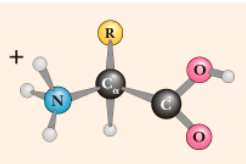
3,5,3',5'-Tetraiodothyronine (Thyroxine)

DISOCIACIJA AMINOKISLIN

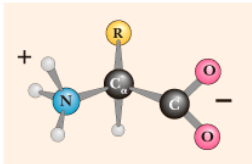
Netopne v organskih topilih (aceton, eter), dobro topne v vodi. Pri fiziološkem pH (7.4) obstajajo kot ioni dvojčki. **Amfoterne**.

Pomembno poznavanje naboja, ker določa lastnosti proteinov!

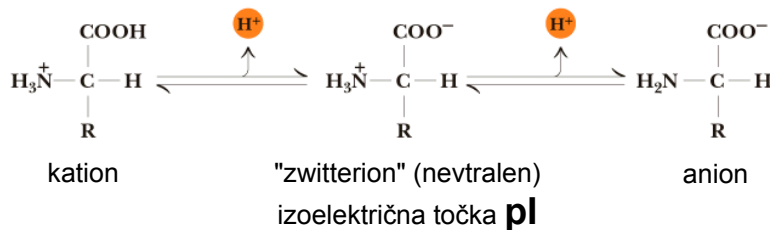
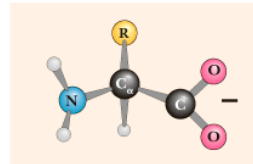
pH 1 neto naboj +1



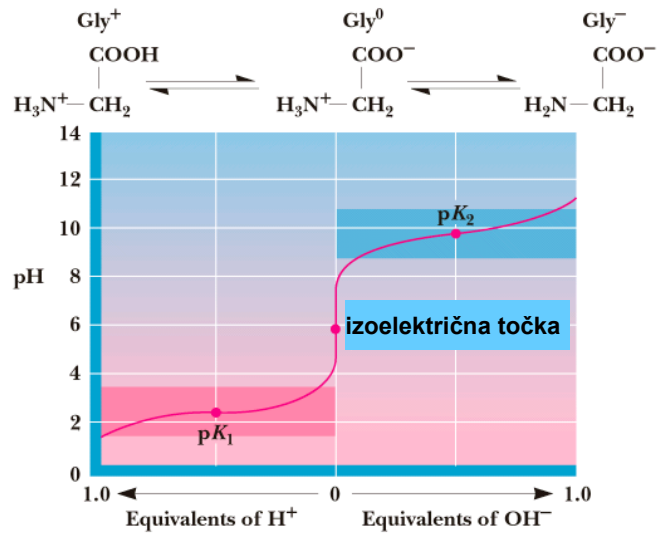
pH 7 neto naboj 0



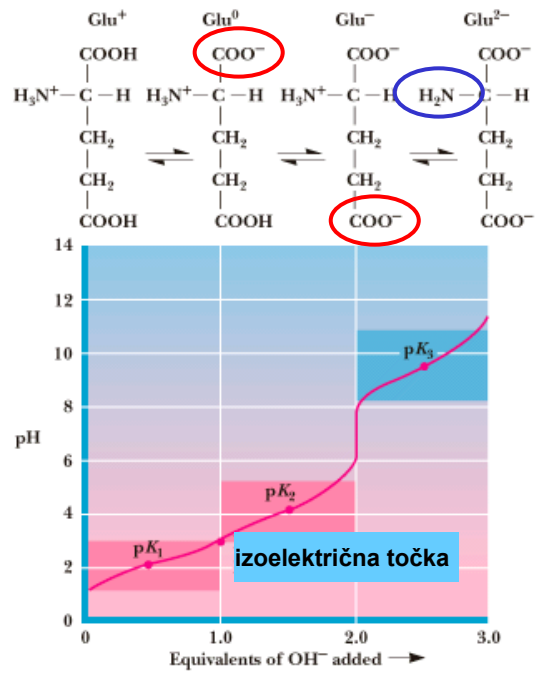
pH 13 neto naboj -1



TITRACIJA GLICINA



TITRACIJA GLUTAMINSKE KISLINE



pK_a vrednosti aminokislin

α-karboksilna skupina (-COOH): pK_a = 2

α-amino skupina (-NH₃⁺): pK_a = 9

Kisle aminokisljine

Aspartat, Asp, D pKa3 = 3.9

Glutamat, Glu, E pKa3 = 4.3

Bazične

Arginin, Arg, R pKa3 = 12.5

Histidin, His, H pKa3 = 6.0

Lizin, Lys, K pKa = 10.5

Cistein, Cys, C (-SH) pKa3 = 8.3

Serin, Ser, S (-OH) pKa = 13

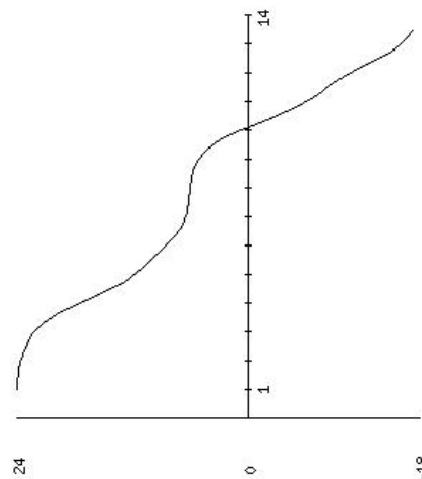
Treonin, Thr, T (-OH) pKa = 13

Tirozin, Tyr, Y (fenolna) pKa = 10.1

vrednosti so približne in odvisne od neposredne okolice stranske skupine

Ala (A)	4	3,12 %
Arg (R)	10	7,81 %
Asn (N)	9	7,03 %
Asp (D)	6	4,69 %
Cys (C)	8	6,25 %
Gln (Q)	7	5,47 %
Glu (E)	6	4,69 %
Gly (G)	5	3,91 %
His (H)	5	3,91 %
Ile (I)	3	2,34 %
Leu (L)	2	1,56 %
Lys (K)	8	6,25 %
Met (M)	5	3,91 %
Phe (F)	4	3,12 %
Pro (P)	7	5,47 %
Ser (S)	16	12,50 %
Thr (T)	8	6,25 %
Trp (W)	0	0,00 %
Tyr (Y)	5	3,91 %
Val (V)	10	7,81 %

TITRACIJA Ribonukleaze A



alpha-NH3 :	9,69	Asp :	3,86
alpha-COOH :	2,34	Glu :	4,25
Arg :	12,40	Cys :	8,33
Lys :	10,50	Tyr :	10,00
His :	6,00		

titracijska krivulja "zabrisana"
veliko število ionizabilnih aminokislin
3D struktura ⇒ pK se lahko premaknejo
do nekaj enot

REAKTIVNOST AMINOKISLIN

Karboksilne skupine	pretvorbe v estre, amide
Amino skupine	pretvorbe v amide, Schiffove baze
Hidroksilne skupine	pretvorbe v estre

Kemijske spremembe po translaciji

Imajo pomembno vlogo za strukturo in delovanje proteina

Fosforilacija tirozina, serina

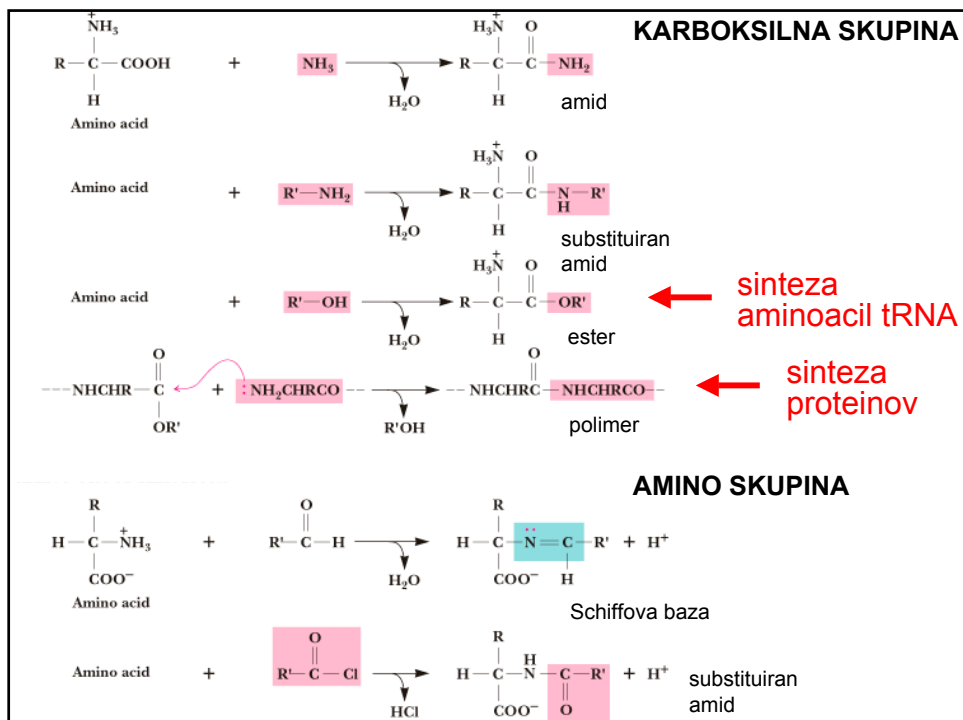
Cys- disulfidna vez, alkilacija, tvorba merkaptidov

Hidroksilirana oblika prolina in lizina v kolagenu

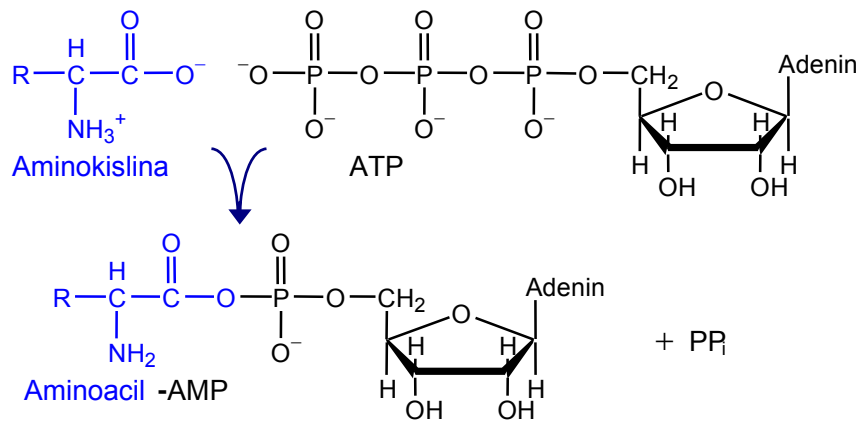
Kemijske reakcije za detekcije aminokislin in pri analizi proteinov

Ninhidrińska reakcija vijolična barva

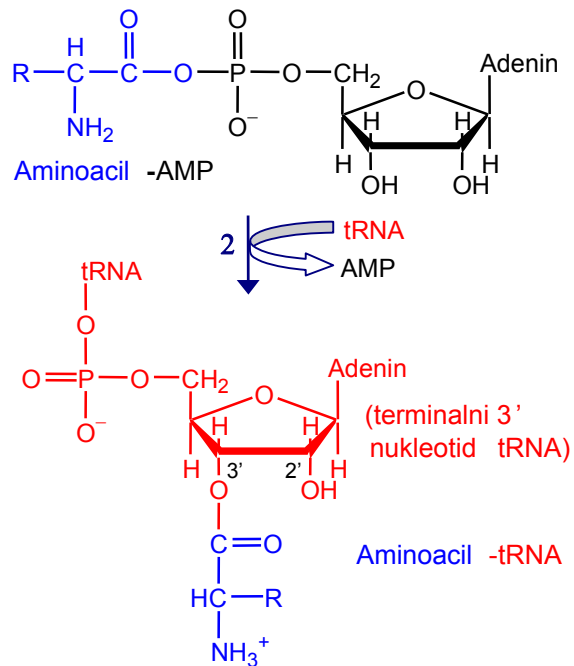
Sangerjeva reakcija rumena barva



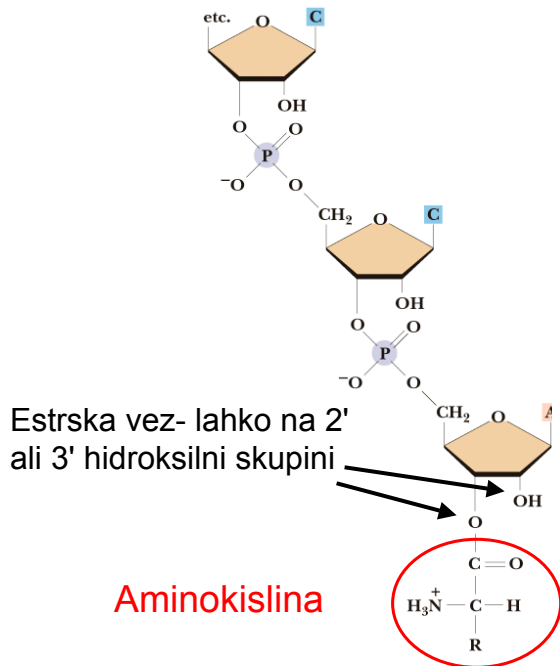
1. korak



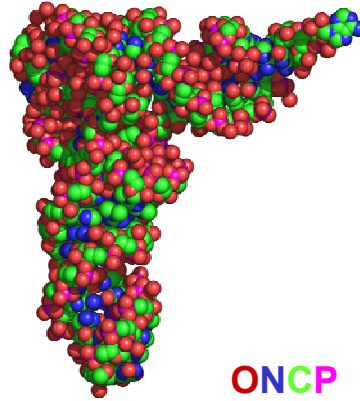
2. korak



CCA 3' KONEC



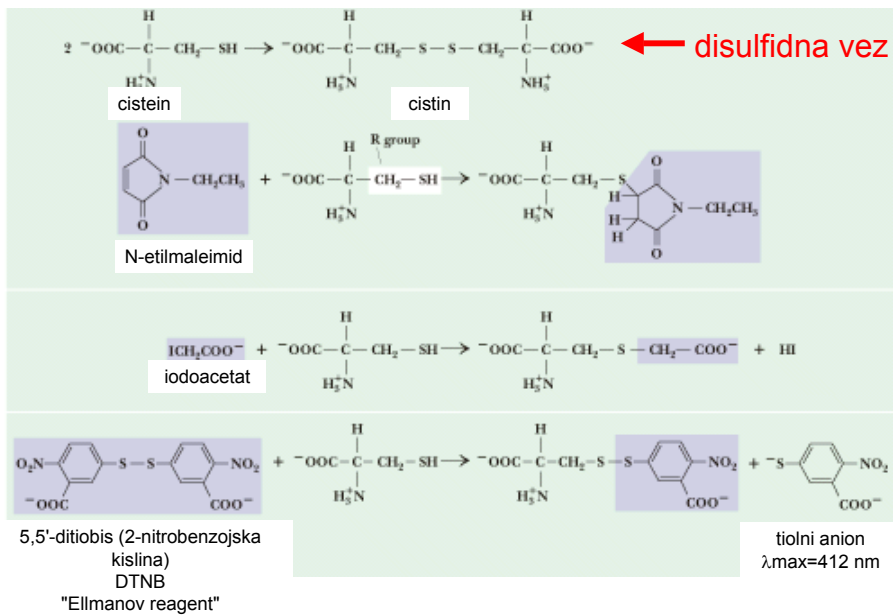
kvasna fenilalanin tRNA

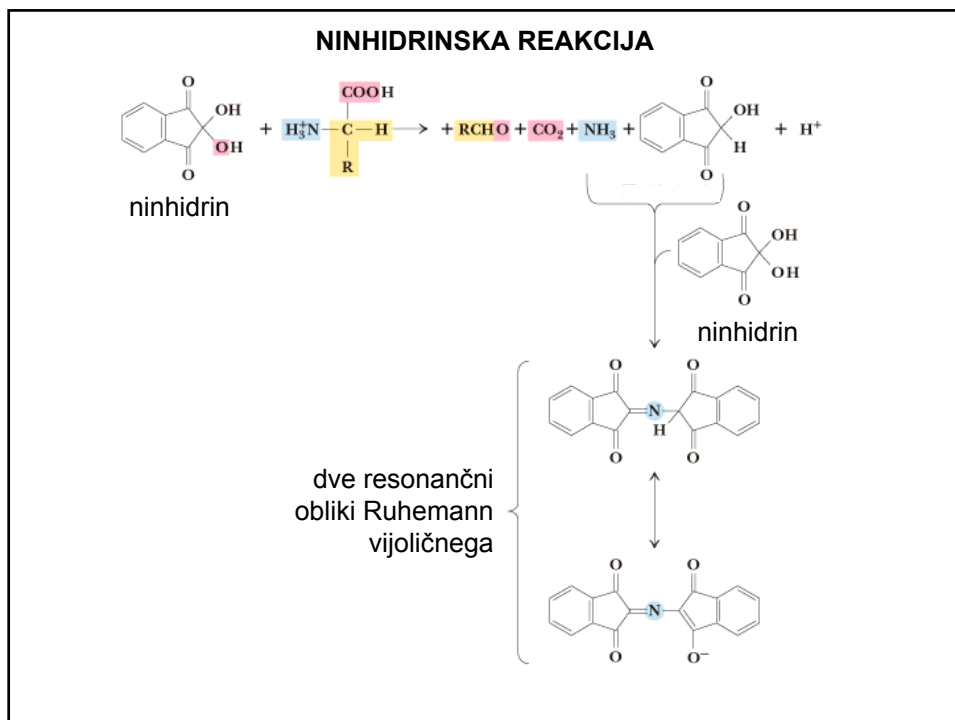


ONCP

H. Shi and P.B. Moore, *RNA* 6: pp. 1091, 2000

TIOLNA SKUPINA (Cys)

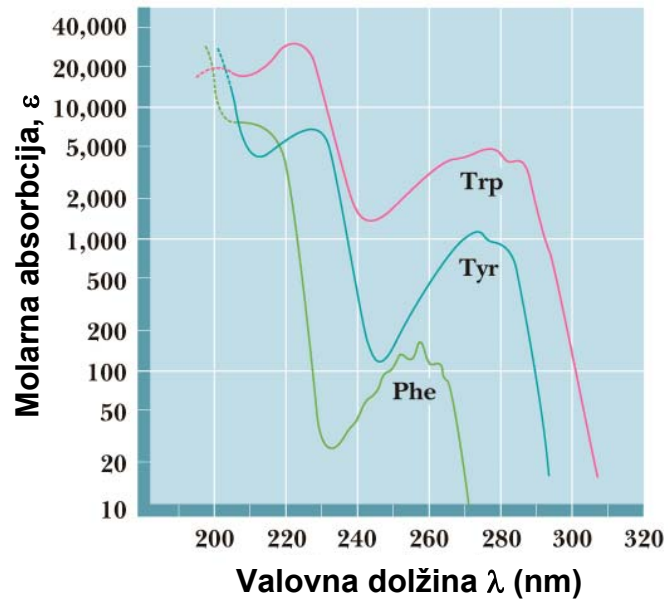




SPEKTROSKOPSE LASTNOSTI AMINOKISLIN

- Vse absorbirajo svetlobo v infrardečem območju
- Phe, Tyr in Trp absorbirajo UV
- Absorbpcija pri valovni dolžini 280 nm - pomoč za zasleditev aromatičnih aminokislin (Phe, Tyr in Trp) in določanje koncentracije proteinov
- NMR spektri – značilni za vsako aminokislino
- Asimetrične - sukajo ravnino polarizirane svetlobe (CD-spektroskopija)
- Označene aminokislino lahko ločujemo s HPLC (tekočinska kromatografija z visoko ločljivostjo)-pomembno pri določanju primarne zgradbe proteinov

ABSORPCIJSKI SPEKTRI AROMATSKIH AMINOKISLIN

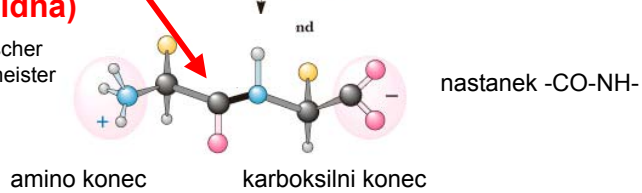


aminokisliline se lahko povezujejo s peptidno vezjo



**PEPTIDNA VEZ
(amidna)**

1902 Emil Fischer
& Franz Hofmeister



N-terminalni konec

ostanek "residue"

C-terminalni konec

Tyr Gly Gly Phe Leu **YGGFL**

2-9 ostankov peptidi: di-, tri-, tetra-, penta-, hekso-, hepta-, okta-, nona-
 10-100 ostankov oligopeptidi, polipeptidi
 nad 100 ostankov proteini

v celici 2-2000 ostankov (molekulska teža 220-220.000 Da)
 z 20 aminokislinami veliko možnosti

n=2	20 ² =400
n=3	20 ³ =8000
n=100	20 ¹⁰⁰ =1.27 × 10 ¹³⁰

biosinteza na ribosomih, glede na zaporedje nukleotidov
 razgradnja hidroliza z bazo, kislino ali encimi (proteinaze, proteaze, peptidaze; prebavni encimi v želodcu!)

BIOLOŠKO POMEMBNI PEPTIDI

Glutation tripeptid (Glu-Cys-Gly). Regulacija oksido-reduktivnih reakcij. Odstranitev prostih radikalov v celici.

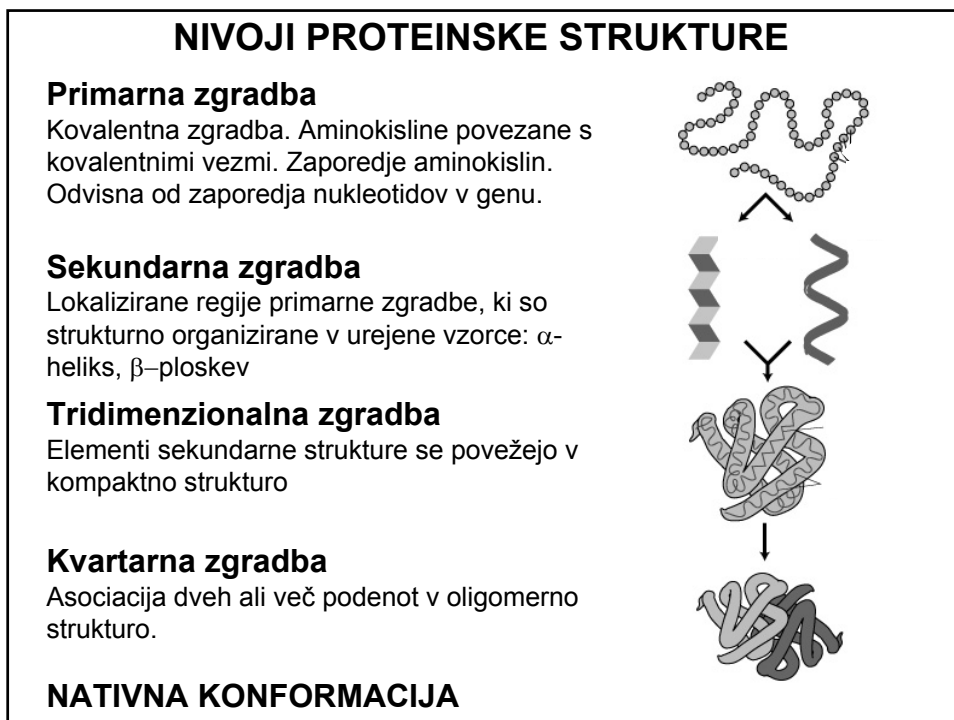
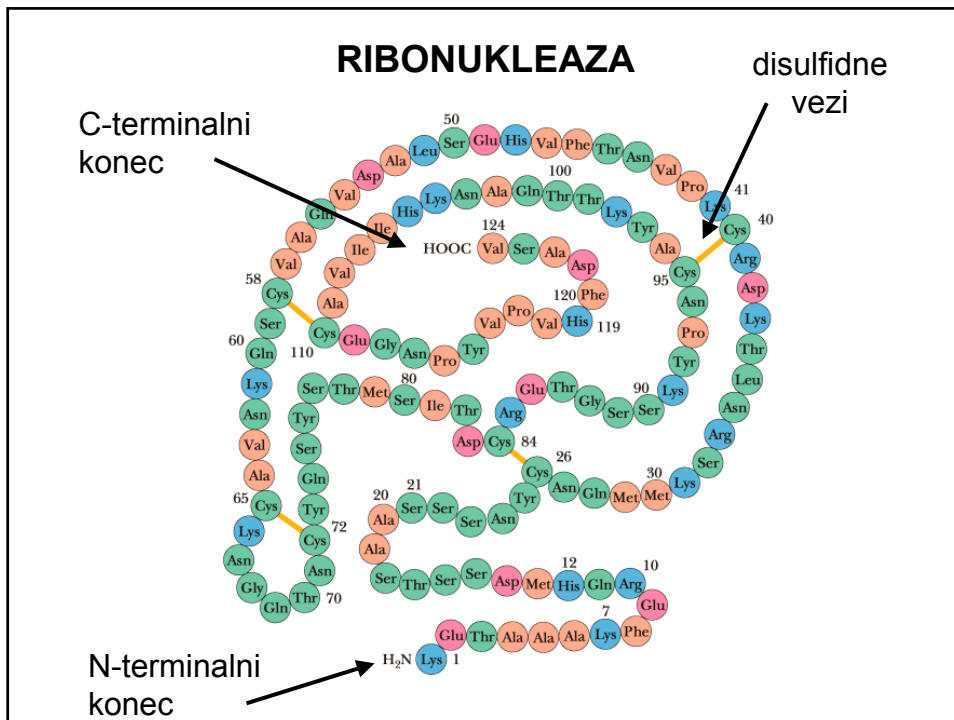
← GSH reduciran
 GSSG oksidiran

Oksitocin, vazopresin nonapeptidi. Ciklizirani z disulfidno vezjo.
G-L-P-C-N-Q-I-Y-C

Inzulin 51 ostankov. Regulira metabolizem glukoze.

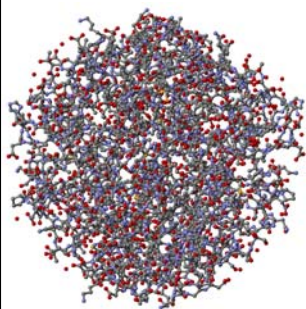
Enkefalini kontrolirajo bolečino.

Aspartam Sintetični peptid. L-Asp-L-Phe. Umetno sladilo.

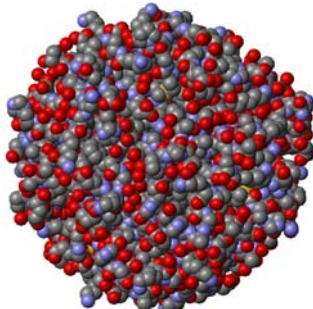


PRIKAZ PROTEINSKE STRUKTURE

>gi|122615|sp|P02023|HBB_HUMAN HEMOGLOBIN BETA CHAIN
 MVHLTPEEKSAVTALWGKVNVDVEVGGEALGRLLVVYPWTQRFFESFGDLSTPDAVMG
 NPVKAHGKKVLGAFSDGLAHLAHLNLRKGTFAFLSEHLHCDKHLHVDPENFRLLGNVLCVLA
 AHHFGKEFTTPVQAAAYQKVVAGVANALAHKYH



Vezi
(skeletni)



Atomi
(Van der Waalsov radii
atomov: Corey-Pauling-
Koltun - CPK model)



Shematsko
cilindri (α -heliks)
trakovi (β -ploskev)

VELIKOST PROTEINOV, SESTAVA, LASTNOSTI

Proteini se razlikujejo po

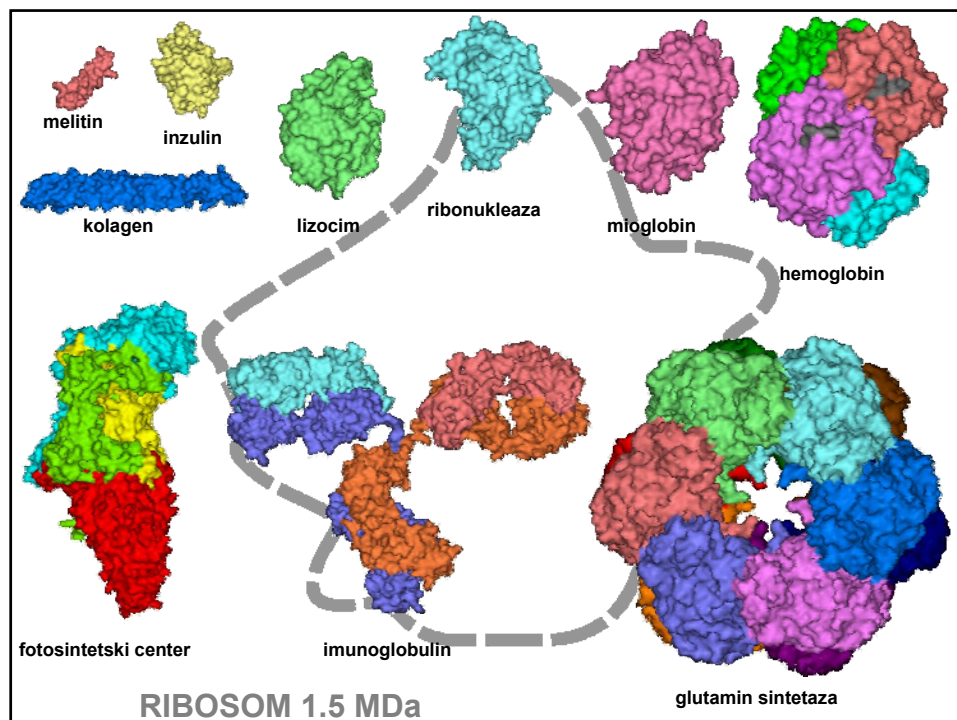
Lokaciji v celici	membranski, citosolni; v različnih organelih
Velikosti	število aminokislinskih ostankov (masi)
Obliki	globularni (bolj fleksibilni; dobro topni v vodi), fibrozni (kolagen, keratin; visoka natezna trdnost; slabše topni v vodi)
Zaporedju	zaporedje aminokislin (od N proti C koncu), ki gradi protein
Sestavi aminokislin	hidrofobni (membranski), polarni proteini
Številu podenot	monomerni, dimerni, tetramerni, oligomerni homo-oligomerni enake podenote hetero-oligomerni različne podenote
Dodanih skupinah	prostetične skupine. Enostavni, konjugirani glikoproteini, lipoproteini, nukleoproteini, fosfoproteini, metaloproteini (Ca^{2+} , Zn^{2+}), kromoproteini (hemoproteini, flavoproteini ...)

Tip proteina	Funkcija
GLOBULARNI	
inzulin	hormon
hemoglobin	transport (kisik)
mioglobin	skladiščenje (kisik)
ribonukleaza	encim (hidroliza RNA)
lizocim	encim (hidroliza bakterijske stene)
citokrom c	elektronski transport
imunoglobulin	obramba (protitelo)
aktin	premikanje (protein v mišicah)
FIBRILARNI	
kolagen	strukturni protein
keratin	strukturni protein
miozin	premikanje (protein v mišicah)
elastin	elastičnost
MEMBRANSKI	
laktorna permeaza	membranski kanalček
rodopsin	detekcija svetlobe

Funkcija		
Encimi	kataliza kemijskih reakcij	amilaza, polimeraza, nukleaza, proteinaza
Strukturni proteini	mehanska podpora celicam in organizmom	kolagen, keratin
Obramba	obramba pred vdorom tujkov, toksini	protitelesa, komplement, perforin
Transport	prenos snovi	hemoglobin, lipoproteini
Shranjevanje	shranjevanje snovi	ferritin
Regulacija	regulatorni proteini	transkripcijski faktorji, translacijski faktorji
Komunikacija	prenos signalov preko membrane	receptorji, G-proteini
Premikanje	kontrakcija mišic	miozin, aktin, dinein

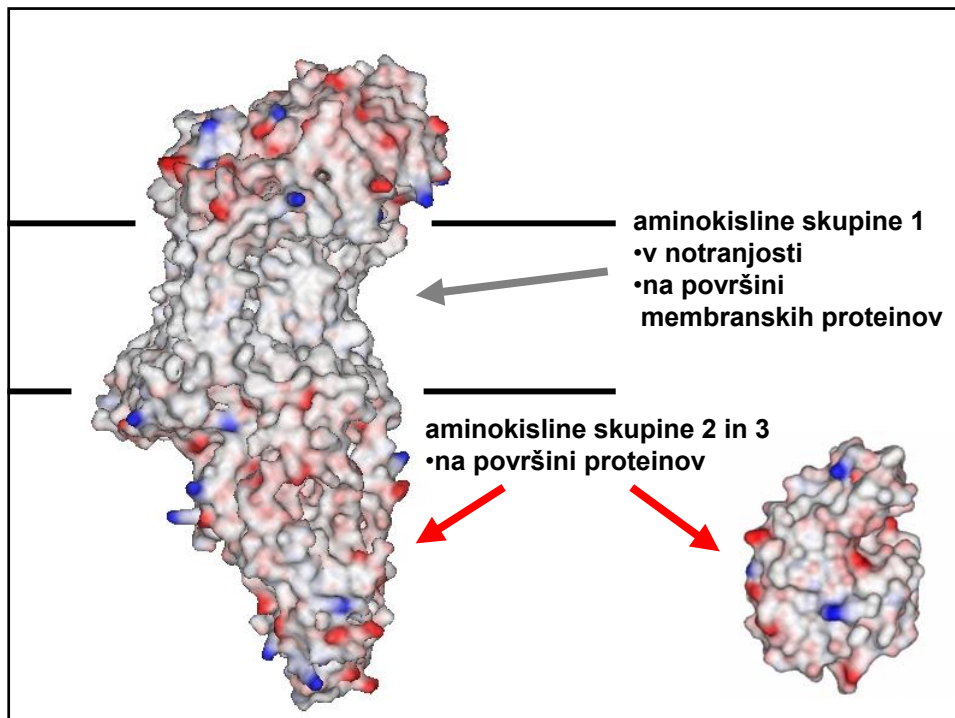
VELIKOST PROTEINOV nekaj primerov

Protein	Molekulska masa	Število aminokislin	Število podenot
Melitin (peptid-čebela)	3.000	26	1
Inzulin (goveji)	5.733	51	2
Citokrom C (human)	13.000	104	1
Ribonukleaza A (goveja)	13.700	124	1
Lizocim (jajčni beljak)	13.930	129	1
Mioglobin (mačji)	16.890	153	1
Kimotripsin (goveji)	21.600	241	3
Hemoglobin (človeški)	64.500	574	4
Fotosintetski center	132.200	1191	4
Imunoglobulin G (človeški)	145.000	1320	4
RNA polimeraza (<i>E.coli</i>)	450.000	4100	5
Feritin (mačji)	450.000	4100	24
Glutaminska sintetaza	600.000	5616	12
Glutamat dehidrogenaza (goveja)	1.000.000	8300	40



FUNKCIJA JE ODVISNA OD AMINOKISLINSKE SESTAVE

Aminokislina	ADH citosolni	Histon vezan na DNA	Kolagen strukturni	lac permeaza membranski
Ala	7.5	13.3	11.7	8.4
Arg	3.2	13.3	4.9	2.9
Asn	2.1	0.7	1.0	3.8
Asp	4.5	3.0	3.0	1.4
Cys	3.7	1.5	0	1.9
Gln	2.1	5.9	2.6	2.6
Glu	5.6	5.2	4.5	2.6
Gly	10.2	5.2	32.7	8.6
His	1.9	1.5	0.3	1.0
Ile	6.4	5.2	0.8	7.9
Leu	6.7	8.9	2.1	12.9
Lys	8.0	9.6	3.6	2.9
Met	2.4	1.5	0.7	3.4
Phe	4.8	3.0	1.2	13.4
Pro	5.3	4.4	22.5	2.9
Ser	7.0	3.7	3.8	7.0
Thr	6.4	7.4	1.5	4.6
Trp	0.5	0	0	1.4
Tyr	1.1	2.2	0.5	3.4
Val	10.4	4.4	1.7	7.0



IZOLACIJA IN ČIŠČENJE PROTEINOV

Kromatografske metode (preparativne)

- ionsko-izmenjevalna kromatografija po naboju
- gelska kromatografija po velikosti
- afinitetna kromatografija po afiniteti

Elektroforeze (analitske)

- NaDS-PAGE po velikosti
- izoelektrično fokusiranje po naboju
- nativna elektroforeza po velikosti, naboju, obliki

Ultracentrifugacija

velikost, oblika delcev

Kristalografija, NMR spektroskopija

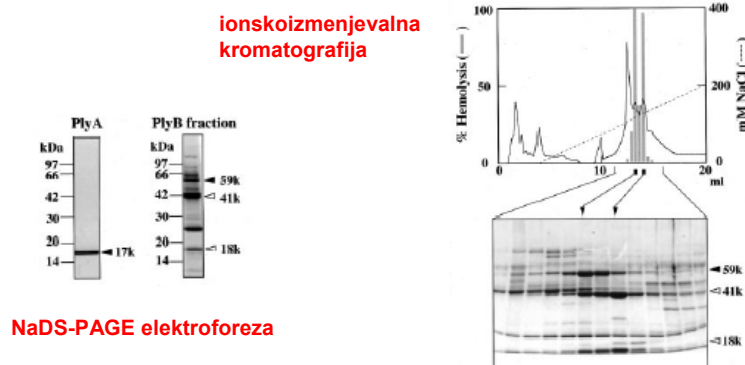
3D struktura

Masna spektroskopija (analitska)

masa, zaporedje proteina

VEČ NA VAJAH!!

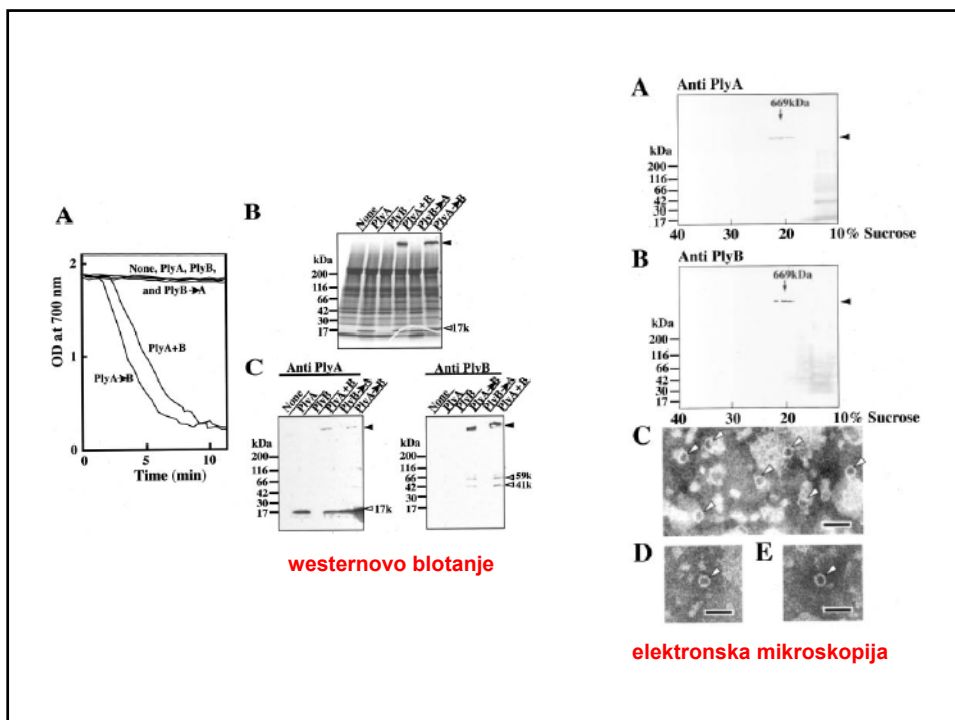
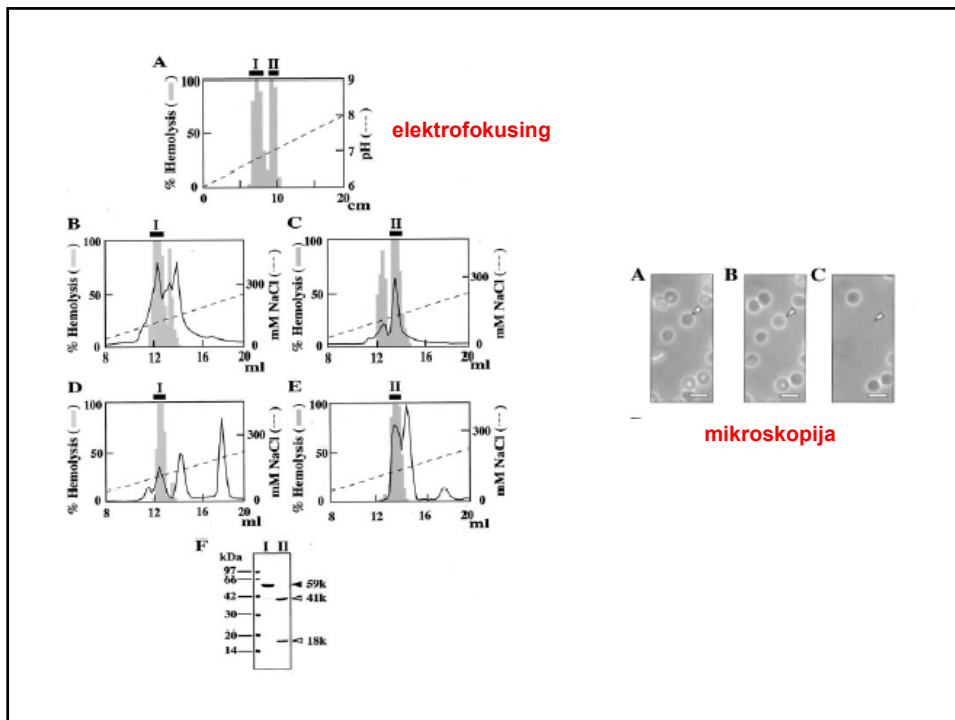
JOURNAL CLUB...



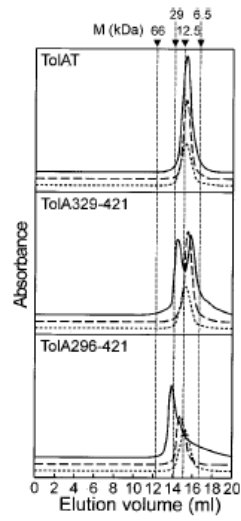
Toshio Tomita, Kayoko Noguchi, Hitomi Mimuro, Fumio Ukaji, Kiyoshi Ito, Noriko Sugawara-Tomita, and Yohichi Hashimoto

Pleurotolysin, a Novel Sphingomyelin-specific Two-component Cytolysin from the Edible Mushroom *Pleurotus ostreatus*, Assembles into a Transmembrane Pore Complex

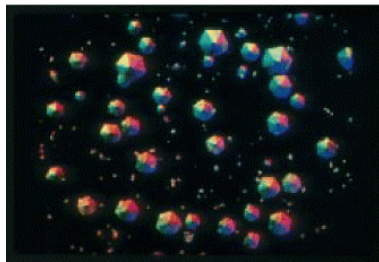
J. Biol. Chem., Jun 2004; 279: 26975 - 26982 ; 10.1074/jbc.M402676200



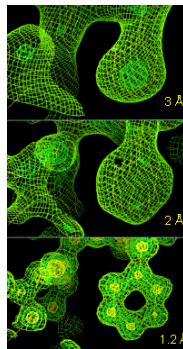
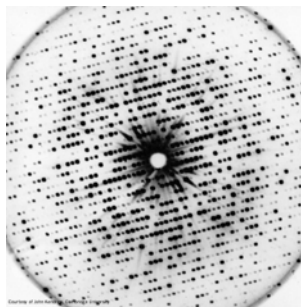
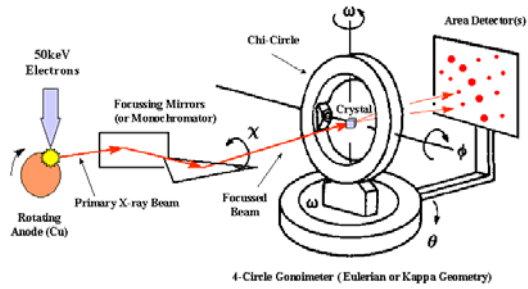
**gelska
kromatografija**



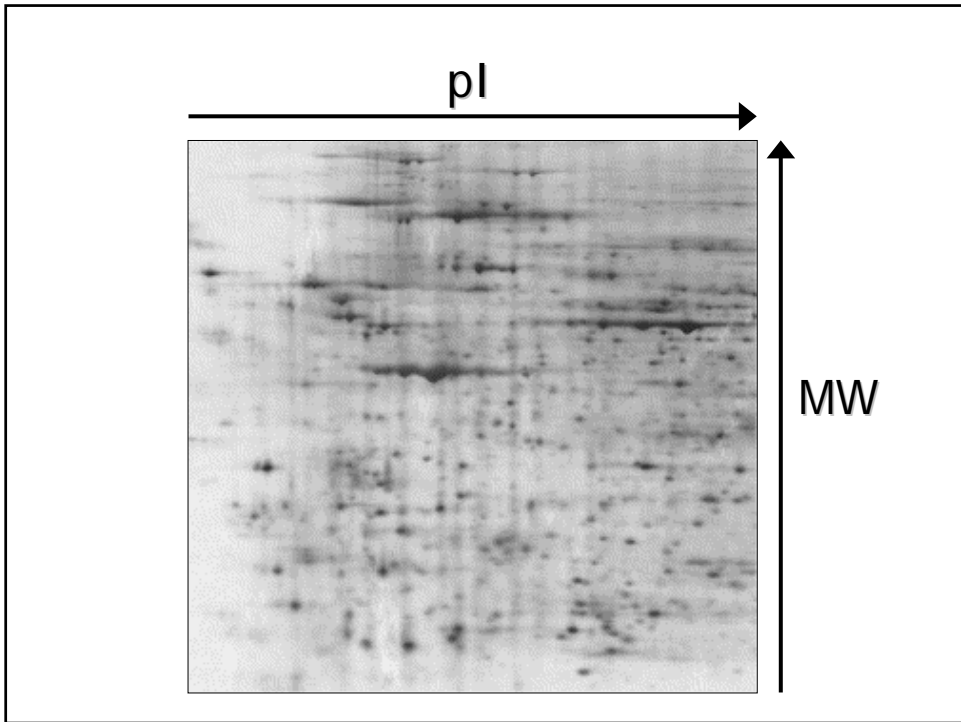
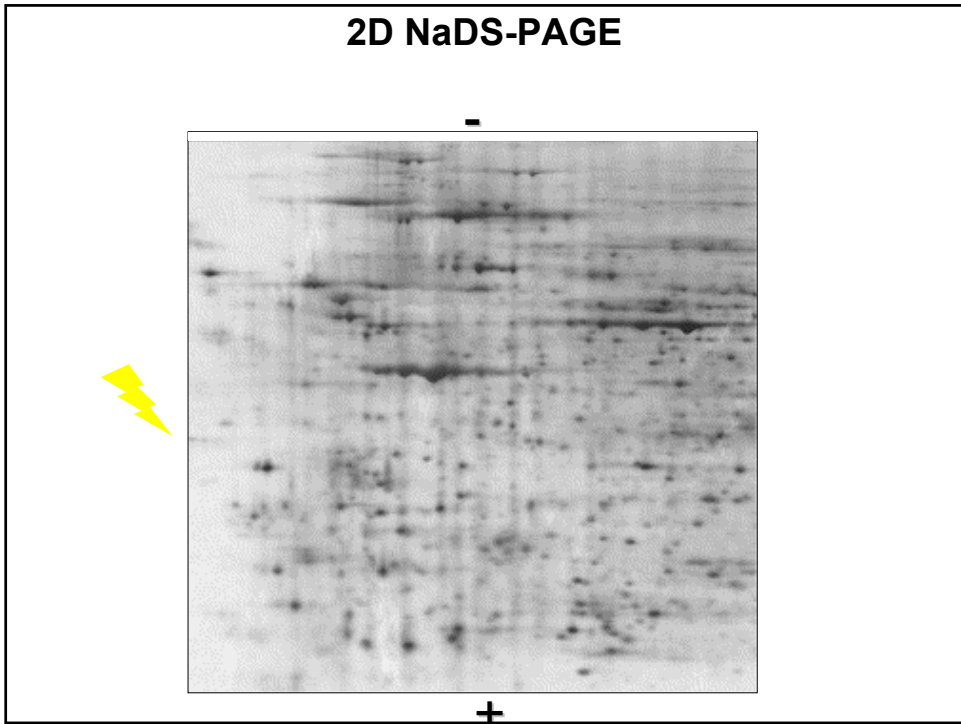
Gregor Anderluh, Isa Gökçe, and Jeremy H. Lakey
 A Natively Unfolded Toxin Domain Uses Its Receptor
 as a Folding Template
 J. Biol. Chem., May 2004; 279: 22002 - 22009 ;
 10.1074/jbc.M313603200

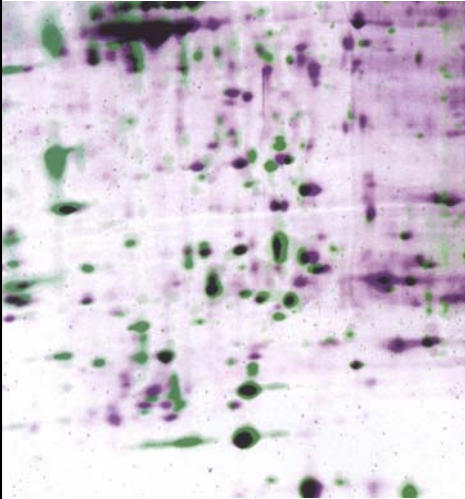


človeški inzulin



2D NaDS-PAGE





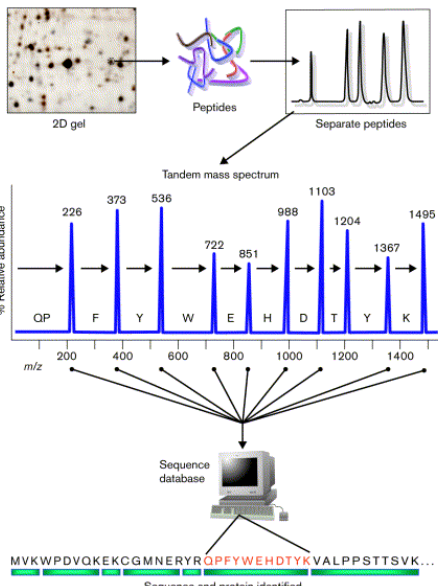
ZASLEDOVANJE DIFERENCIALNEGA IZRAŽANJA PROTEINOV

Proteini izraženi v:
 Normalnih jetrih vijolično
 Jetrnem tumorju zeleno
 Obeh črno

*Bioprobes 38, October 2001,
 Molecular Probes, Eugene, USA*

MASNA SPEKTROMETRIJA

- Uporablja se za identifikacijo proteinov
- Določeno proteinsko točko izrežemo iz 2DG
- Protein s proteazo (npr. tripsinom) razrežemo na peptide
- Po MS iz spektra mas peptidov poskušamo določiti protein
- Če ni primerne odgovora, določimo še aminokislinsko zaporedje enega od peptidov na tandemskem MS



The diagram illustrates the process of protein identification. It starts with a 2D gel showing protein spots. A specific spot is excised and digested into peptides. These peptides are then separated and analyzed by tandem mass spectrometry (MS/MS), resulting in a spectrum with peaks at various m/z values (226, 373, 536, 722, 851, 988, 1103, 1204, 1367, 1495). The spectrum shows relative abundance versus m/z. The identified sequence is **MVKWPDVQKEKGGMNERYRQPFYWEHDTYKVALPPSTTSVK...**, with the peptide **QPFYWEHDTYK** highlighted in red. The source is cited as *Current Opinion in Chemical Biology*.

DOLOČANJE ZAPOREDJA AMINOKISLIN

INZULIN (goveji)
 veriga A: 21 aminokislin
 veriga B: 30 aminokislin
 3 disulfidne vezi

Frederick Sanger 1953

- Sanger: vse molekule enega proteina imajo enako zaporedje aminokislin
- Zaporedje aminokislin proteinov lahko določimo na dva načina:
 - dejansko zaporedje aminokislin
 - zaporedje nukleotidov v genu (ali mRNA), ki določa protein
- Določitev aminokislinske sestave kislina in alkalna hidroliza do prostih aminokislin, kromatografija in določitev posameznih aminokislin
- Odločitev za način fragmentacije (vsebnost lizina, metionina itd.)

Sanger, F., Thompson, E.O.P. and Kitai, R. (1955) *Biochem. J.* **59**, 509

DOLOČANJE ZAPOREDJA AMINOKISLIN

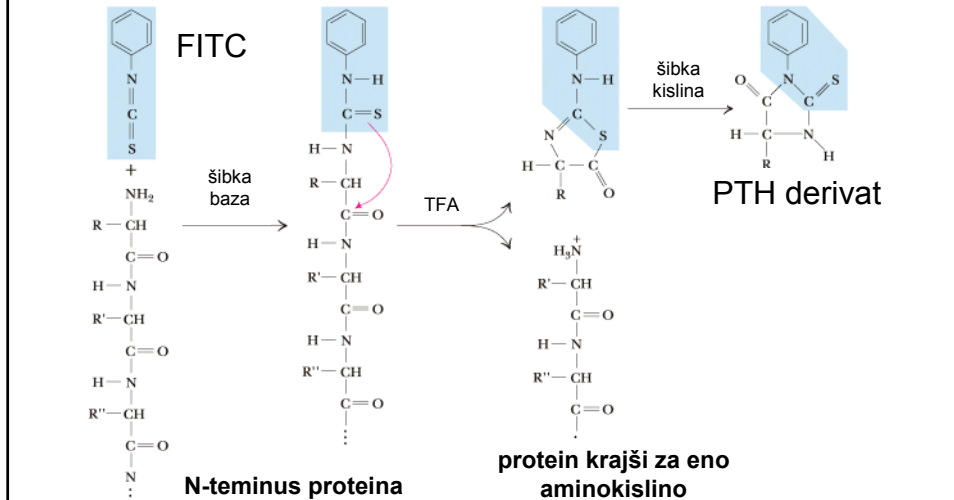
Postopek:

1. Če več polipeptidnih verig, ločitev.
2. Cepitev (redukcija) disulfidnih vezi
3. Določitev sestave vsake verige
4. Določitev N- in C-terminalnih ostankov
5. Cepitev vsake verige na manjše fragmente in določitev zaporedij za vsakega
6. Ponovitev koraka 5 z drugim načinom cepitve, da dobimo drugačen niz fragmentov.
7. Rekonstrukcija zaporedja proteina iz prekrivajočih se fragmentov
8. Določitev položaja disulfidnih vezi

IDENTIFIKACIJA N-TERMINALNIH OSTANKOV

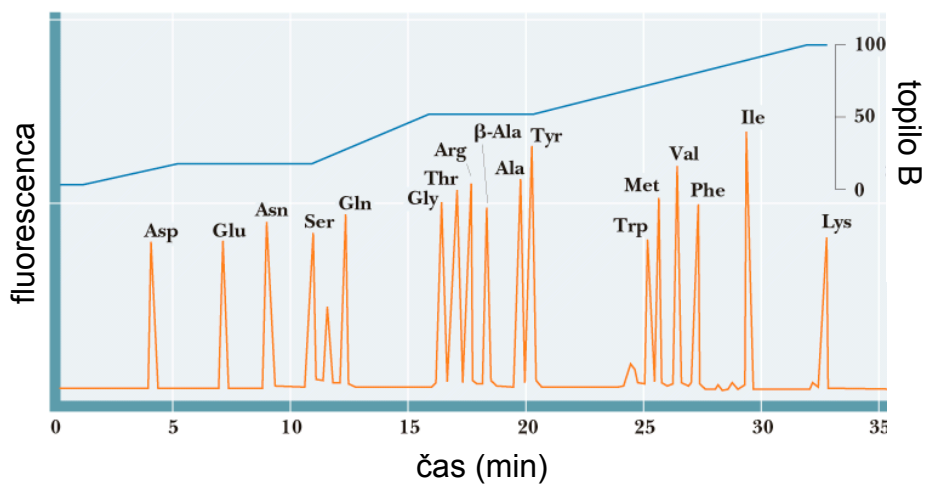
Edmanova degradacija:

- Fenil-izotiocianat (FITC)
- Derivati: feniltiohidantoini (PTH-derivati)



HPLC OZNAČENIH AMINOKISLIN

zaradi različne polarosti stranskih skupin se različno zadržujejo na nosilcu kolone



FRAGMENTACIJA VERIG

- *Encimska fragmentacija*
 - tripsin – cepitev peptidne vezi za Lys, Arg
 - kimotripsin – cepitev za Phe, Tyr, Trp
 - klostripain - kot tripsin, vendar za Arg bolj kot za Lys
 - stafilokokna proteaza
 - za Glu, Asp v fosfatnem pufru
 - specifično za Glu v acetatnem ali bikarbonatnem pufru
- *Kemijska fragmentacija*
 - cianogen bromid- cepitev za Met

REKONSTRUKCIJA CELOTNEGA ZAPOREDJA

- uporaba dveh ali več fragmentacijskih nizov peptidov
- določanje zaporedja vsem dobljenim peptidom (Edmanova degradacija)
- poravnava prekrivajočih se peptidnih zaporedij
 - Tripsinska cepitev
A-E-F-M-S-G-I-T-P-K **L-V-G-K**
 - Stafilokokno-proteazna cepitev
F-M-S-G-I-T-P-K **L-V-G-K-A-E**
 - cianogen bromidna cepitev
L-V-G-K-A-E-F-M **S-G-I-T-P-K**

Prekrivanje

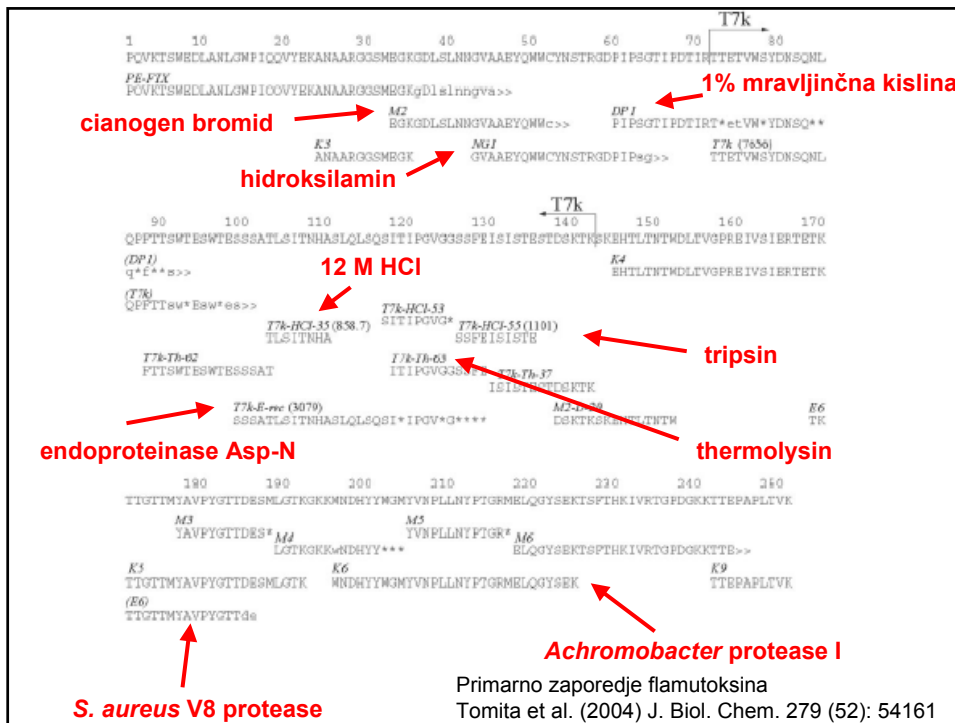
L-V-G-K A-E-F-M-S-G-I-T-P-K

L-V-G-K-A-E F-M-S-G-I-T-P-K

L-V-G-K-A-E-F-M S-G-I-T-P-K

Končno zaporedje

L-V-G-K-A-E-F-M-S-G-I-T-P-K



The Nobel Prize in Chemistry 1958

Frederick Sanger

"for his work on the structure of proteins, especially that of insulin"

Doctor Frederick Sanger. It sometimes happens that an important scientific discovery is made so to say "overnight" - if the time is ripe and the necessary background is there. Yours is not of that kind. The first successful determination of the structure of a protein is the result of many years of persistent and zealous work, in which the final solution of the problem has been approached step by step. You knew when you began to look into the structure of the insulin molecule 15 years ago that the problem was a formidable one.



The Nobel Prize in Chemistry 1980

Walter Gilbert

Frederick Sanger

"for their contributions concerning the determination of base sequences in nucleic acids"

Sanger is responsible for the **first complete determination of the sequence of a DNA molecule**. He has established the sequence of the 5375 building blocks in DNA from a bacterial virus called phi-X174.

Sequence investigations with the methods of Gilbert and Sanger together with the recombinant-DNA technique make excellent tools for continued investigations of the structure and function of the genetic material.

ZAKAJ JE POMEMBNO POZNAVANJE PRIMARNE STRUKTURE (ZAPOREDJA AMINOKISLIN):

1. Iskanje podobnih proteinov v podatkovnih zbirkah. Homologi- evolucijsko sorodni proteini, ki imajo lahko isto funkcijo. Zato je navadno primarna struktura zelo ohranjena.
2. Študij evolucijskih odnosov, tvorba filogenetskih dreves. citokrom c, globinska družina
3. Iskanje mutacij. Spremenjeno zaporedje gena se odraža v spremenjenem (in nefunkcionalnem) proteinu. Lažje je takšne spremembe detektirati z genetskimi metodami. srpastocelična anemija
4. Poznavanje zaporedja olajša sklepanje o 3D strukturi proteina. Omejeno število vzorcev zvitja.

ALPHA1	-MVHLSADKRNVRKAWGKVGAHAGEYCAEELERMFSSPTTKTYPHDLDSH-----G-SAQVNGHGKRVADALTNVAHVDDMPNA	80
ALPHA2	-MVHLSADKRNVRKAWGKVGAHAGEYCAEELERMFSSPTTKTYPHDLDSH-----G-SAQVNGHGKRVADALTNVAHVDDMPNA	80
THETA	-MAVLSAEDRALVRAWKKVGSNIGVYTTLEERFEAHPAKKTYSHLDLSP-----G-SSQVRAHGQVADALSDIVERADDPHA	80
GAMMA	MCHLTPEDKATLRSWQKVN--VEDAGGELGRLLVVYPWTPQRFESFGNLSASAIMGNPRVKAHGKRVVTSFGDLAHLNDLNGT	85
BETA	MVHLTPPEKSAVVALWQKVN--VDVGGELGRLLVVYPWTPQRFESFGDLSTPDVAVMGNPRVKAHGKRVVTSFGDLAHLNDLNGT	85
EPSILON	MVHLEAEPKAAVRSLSKMN--VEAGGELGRLLVVYPWTPQRFESFGNLSASAIMGNPRVKAHGKRVVTSFGDLAHLNDLNGT	85
DELTA	MVHLTPPEKSAVVALWQKVN--VDVGGELGRLLVVYPWTPQRFESFGDLSTPDVAVMGNPRVKAHGKRVVTSFGDLAHLNDLNGT	85
MYOGLOBIN	-MGSDDGEWQLVNLWQKVEADIPGHQGVVLRLEKGFPELEKEDKQKHKSEDEKASEDLKRGATVETALGGIKKKGHHEE	86

ALPHA1	LSALSDDEHAKRQVDPVNFKLLSHCLLVLAALPAEFTPAVHSLDQFLASVSVVLSKVR-----	142
ALPHA2	LSALSDDEHAKRQVDPVNFKLLSHCLLVLAALPAEFTPAVHSLDQFLASVSVVLSKVR-----	142
THETA	LSALSHDEACQLRVDPASPQLLGHCLLVLAALPAEFTPAVHSLDQFLASVSVVLSKVR-----	142
GAMMA	FAQLSELCCKLQVDPENFRLLGNVLLVLAALHFGKFFPEVQAAYQRVAVGAVNALAHKYH-----	147
BETA	FATLSELCCKLQVDPENFRLLGNVLLVLAALHFGKFFPEVQAAYQRVAVGAVNALAHKYH-----	147
EPSILON	FATLSELCCKLQVDPENFRLLGNVLLVLAALHFGKFFPEVQAAYQRVAVGAVNALAHKYH-----	147
DELTA	ESQLSELCCKLQVDPENFRLLGNVLLVLAALHFGKFFPEVQAAYQRVAVGAVNALAHKYH-----	147
MYOGLOBIN	IKPLAASHTAKHKIPVKYLEFISELILVQLQSKHPGDSGADAGMNAALBELFRKDLASNYKELGFGG	154

mioglobin β α

prednik hemoglobina

prednik globinov

	10	20	30	40	50	60			
Človek	MVHLTPPEKSAV	TALWQKVN	VDEVG	GGEALGRLL	VVYPWT	QRFESFGDLS	TPDVMGNP	59	
Šimpanz	MVHLTPPEKSAV	TALWQKVN	VDEVG	GGEALGRLL	VVYPWT	QRFESFGDLS	TPDVMGNPK	60	
Zajec	MVHLSSEKSAV	TALWQKVN	VDEVG	GGEALGRLL	VVYPWT	QRFESFGDLS	SANAVMNNPK	60	
Zlata ribica	-VEWDAERSA	IIGLWQKLN	PDEIG	QALARCL	LIVYPWT	QRYFAT	FGNLSSPA	IMGNPK	59
Lastovka	-VQWDAEKQL	ITGLWQKVN	VACCG	GEALARL	LIVYPWT	QRFESFGNLS	SPTAVLGNPK	59	
Krokodil	-ASFDPEKQL	IGDLWQKVN	VAHCC	GEALSRL	LIVYPWK	RRYFEN	FGDISNAQA	IMHNEPK	59

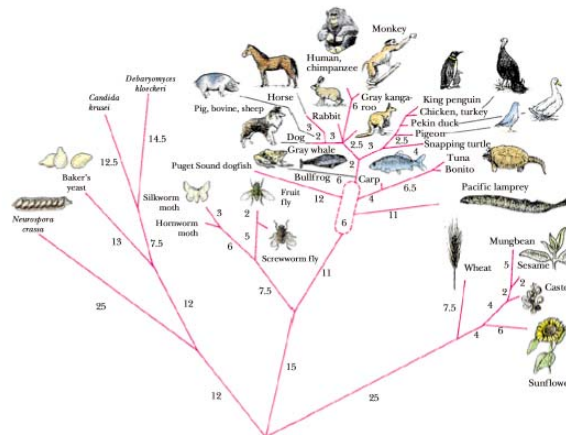
	70	80	90	100	110	120				
Človek	VKAHGKVKL	GAFSDEL	AHLNDL	KTFAFL	SELHCD	KLHVDP	ENFRLLGNV	LVCVLAHFFG	119	
Šimpanz	VKAHGKVKL	GAFSDEL	AHLNDL	KTFAFL	SELHCD	KLHVDP	ENFRLLGNV	LVCVLAHFFG	120	
Zajec	VKAHGKVL	AFAFSEGL	SHLDNL	KTFAFL	SELHCD	KLHVDP	ENFRLLGNV	LIVLSSHFFG	120	
Zlata ribica	VAAHGRV	VMGGLERA	TKNMDN	IKATY	APLSVM	HSEK	LHVDPD	NFRLLADCI	IVCAAMKFG	119
Lastovka	VQAHGKVL	TSGEAV	KNLDSIK	NIF	SQLS	ELHCD	KLHVDP	ENFRLLGDI	LIVVLAHFFG	119
Krokodil	VQAHGKVL	ASGEAV	CHLDG	IRAHF	ANLSK	LHCD	KLHVDP	ENFKLLGDI	LIVLAHFFG	119

	130	140		
Človek	-KEFTPPVQAAYQKVV	VAGVANALAHKYH	146	
Šimpanz	-KEFTPPVQAAYQKVV	VAGVANALAHKYH	147	
Zajec	-KEFTPPVQAAYQKVV	VAGVANALAHKYH	147	
Zlata ribica	PSGFNADVQEA	WQKFLSVV	SALCROYH	147
Lastovka	-KDFTPDCQAA	WQKLV	RVVAHALARKYH	146
Krokodil	-KDFGLECH	AAYQKLV	RVVAALAAEYH	146

Takšni proteini so homologi!

citokrom c- encim udeležen pri respiraciji
 znano zaporedje velikega števila vrst
 od okoli 100 aminokislin je

- 38 invariantnih (ista aminokislina na istem mestu) pri vseh vrstah
- 55 invariantnih med konjem in kvasovko
- 8 mest je hipervariabilnih
- zaporedje je identično pri konju, svinji, ovci, kravi



SRPASTOČELIČNA ANEMIJA MOLEKULARNA BOLEZEN- VZROK V SPREMEMBI ZAPOREDJA AMINOKISLIN

NCBI

MIM #603903
 Text
 Clinical Features
 Diagnosis
 Gene Therapy
 Animal Model
 History
 References
 Contributors
 Creation Date
 Edit History

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 Online Mendelian Inheritance in Man

All Databases PubMed Nucleotide Protein Genom

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All: 1

#603903
SICKLE CELL ANEMIA

TEXT

A number sign (#) is used with this entry because sickle cell anemia is the result of mutant beta globin (HBB; [141](#) mutation causes sickling of hemoglobin rather than reduced amount of beta globin which causes beta-thalassemia

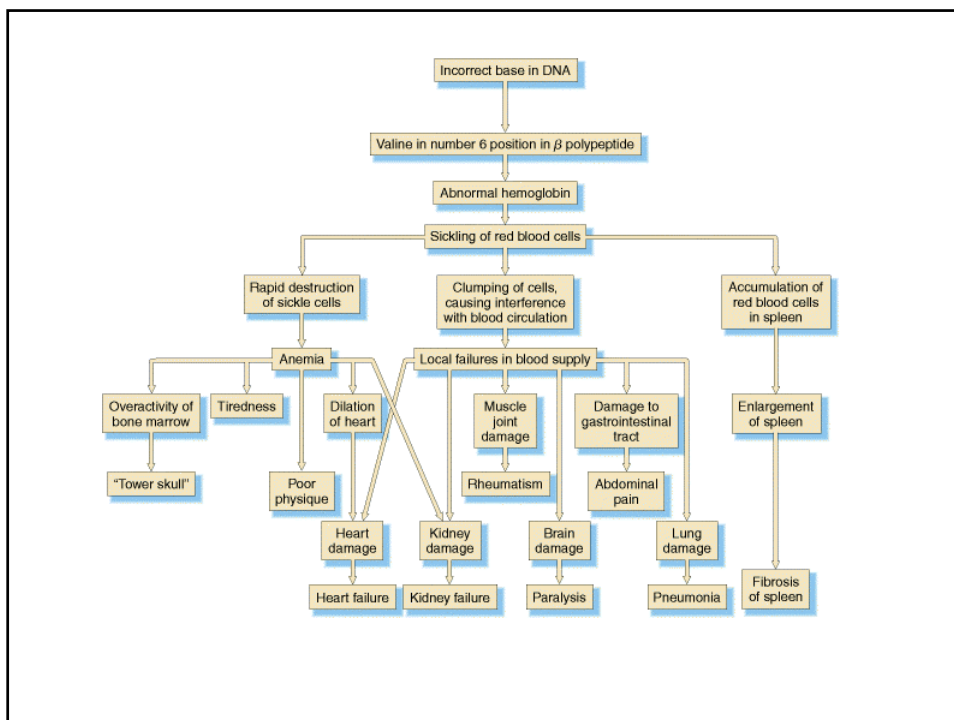
The most common cause of sickle cell anemia is Hb S ([141900.0243](#)), with SS disease being most prevalent in .

CLINICAL FEATURES

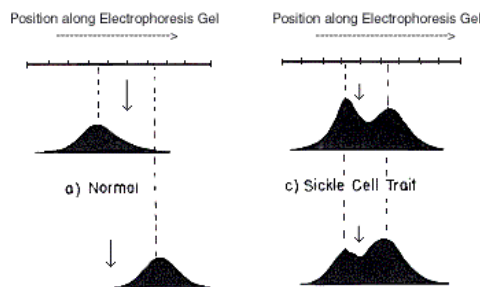
In many children with sickle cell anemia, functional asplenia develops during the first year of life and septicemia is

HISTORY

Noel, a first-year dental student at the Chicago College of Dental Surgery, was admitted to the Presbyterian Hospital in late 1904 where Ernest E. Irons, a 27-year-old intern, obtained a history and performed routine physical, blood, and urine examinations. He noticed that Noel's blood smear contained 'many pear-shaped and elongated forms' and alerted his attending physician, James B. Herrick, to the unusual blood findings. Irons drew a rough sketch of these erythrocytes in the hospital record. Herrick and Irons followed Noel over the next 2.5 years through several episodes of severe illness as he continued his dental studies. Thereafter, Noel returned to Grenada to practice dentistry. He died 9 years later at the age of 32.



1949 - Linus Pauling s sodelavci objavi "Sickle Cell Anemia, a Molecular Disease" v reviji Science. Članek pojasni uporabo proteinske elektroforeze pri pojasnitvi razlik med normalnim in hemoglobinom srpastih celic. Prvič so vzrok bolezni povezali s spremembo v strukturi proteina.



ZONE ELECTROPHORESIS AND THE MINOR HEMOGLOBIN COMPONENTS OF NORMAL HUMAN BLOOD

HENRY G. KUNKEL

Filter paper electrophoresis because of its simplicity and widespread availability has been of great value in elucidating the various abnormal hemoglobins. For population screening a simple technique of this type was essential. However, a number of limitations have gradually become apparent: adsorption in the path of migration, inequality of migration in different parts of the paper and poor adaptability to preparative isolation represent a few of these limitations.

As an alternative procedure we have been interested in the use of other supporting media such as potato starch and polyvinyl chloride particles, particularly for the isolation of various hemoglobin fractions. Both of these media, employed in the form of a thin slab, although possessing inherent limitations of their own, have been of some value for these purposes. The starch block technique has the disadvantage that extraneous materials from the starch itself frequently contaminate the purified hemoglobin fractions. The polyvinyl chloride supporting medium avoids this limitation. However, the ease of handling the starch, the homogeneity of migration, the low electroosmotic flow and the ready visibility of minor colored components against the white starch background have made this procedure more generally useful.

Fig. 1 illustrates a photograph taken with transmitted light on orthochromatic film of the red components of various normal and abnormal hemoglobins separated on a thin starch block. The separation is in general very

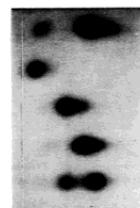


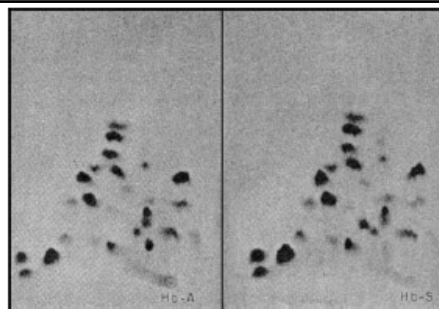
FIG. 1.—Comparison of different Hb separated on the same starch slab. Line at left is site of application. Anode is to the right. Barbitol buffer pH 8.6 T/2 0.05

- a. Normal Hb
- b. Homozygous C
- c. Sickle cell anemia
- d. Umbilical cord
- e. Sickle cell trait

157

1956 - Vernon Ingram in J.A. Hunt sta določila zaporedje hemoglobinu in odkrila, da je sprememba aminokislina v HbS vzrok za srpastocelično anemijo.

stanje leta 1962



	α Chain										
	1	2	16	30	57	58	68	116	141		
Hb I	Val.	Lys.	Lys.	Glu.	Gly.	His.	Asp.	NH ₂	Glu.	Arg.	
Hb G ₁ Honolulu								Glu.	NH ₂		
Hb Norfolk									Asp.		
Hb Boston									Tyr.		
Hb G ₂ Philadelphia									Lys.		
Hb O Ikonosie										Lys.	

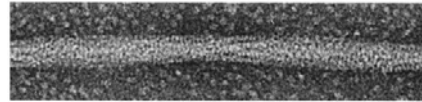
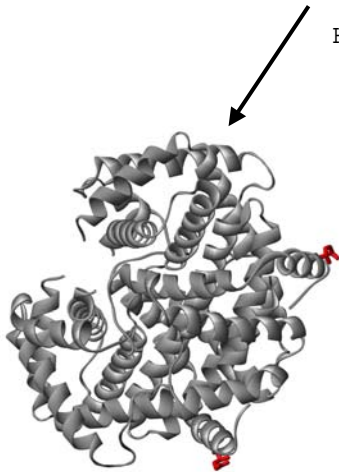
	β Chain										
	1	2	3	5	7	26	63	67	121	146	
Hb S	Val.	His.	Lys.	Glu.	Glu.	Glu.	His.	Val.	Glu.	Met.	
Hb C											
Hb G ₁ San Jose											
Hb E											
Hb G ₂ Goshute											
Hb M ₁ Milwaukee											
Hb D ₁ Puget (D ₁)											
Hb Zürich											
Hb O ₁ Osaka											

Vernon M. Ingram
Sickle-Cell Anemia Hemoglobin: The Molecular Biology of the First "Molecular Disease"—The Crucial Importance of Serendipity
Genetics, Vol. 167, 1-7

SRPASTOCELIČNA ANEMIJA

MVHLTP**E**EKSAVTALWGKVNVEVGGGALGRLLVVYPWTQRFFESFGDLSTPDAVMGNPVK
 AHGKKVLGAFSDGLAHLNLDNLKGT**F**ATLSELHCDKLHVDPENFRLLGNVLVCVLAHHFGKEF
 TPPVQAAYQKV**V**VAGVANALAHKYH

HbB	CCT	GAG	GAG
	P	E	E
HbS	CCT	GTG	GAG
	P	V	E



MVHLTP**E**EKSAVTALWGKVNVEVGGGALGRLLVVYPWTQRFFESFGDLSTPDAVMGNPVKAHGKKVLGAF
 SDGLAHLNLDNLKGT**F**ATLSELHCDKLHVDPENFRLLGNVLVCVLAHHFGKEFTPPVQAAYQKV**V**VAGVANALA
 HKYH

MVHLTP**V**EKSAVTALWGKVNVEVGGGALGRLLVVYPWTQRFFESFGDLSTPDAVMGNPVKAHGKKVLGAF
 SDGLAHLNLDNLKGT**F**ATLSELHCDKLHVDPENFRLLGNVLVCVLAHHFGKEFTPPVQAAYQKV**V**VAGVANALA
 HKYH

ASFD**P**HEKQLIGDLWHKVDVAHCGG**E**ALSRMLIVYPWKR**R**YFENFGDISNAQA**I**MHNEKVQAHGKKVLAS**F**
 GEAVCHLDG**I**RAHFANLSKLHCEK**L**HVDPENFKLLGD**I**I**I**IVLA**A**HYPKDFGLECH**A**AYQKLVRQ**V**AAALA
 A**E**YH

GLSDGEWQLVLNVWGK**V**EADIPGHGQ**E**VLIRLFK**G**HP**T**LEKFDKFKHLK**S**EDEM**K**ASEDLK**K**HGATV**L**TA
 LGGIL**K**KKGH**H**EAEIKPLAQSHAT**K**HKIPVK**Y**LEF**I**SE**C**I**I**QVLQSK**H**PGDFGADAQ**G**AMNKALEL**F**RK**D**M
 AS**N**YKEL**G**FQ**G**

MALEKSLV**R**LLLLLVL**I**LLVLG**V**WQPS**L**GK**E**SRA**K**FRQ**H**MDSD**S**SPSS**S**TYCNQ**M**RRR**N**MTQ**G**RCK**P**V
 N**T**FV**H**EPLVD**V**Q**N**VC**F**Q**E**K**V**TCK**N**GQ**G**NC**Y**KS**N**SS**M**H**I**TD**C**RL**T**NG**S**RY**P**NC**A**Y**R**T**S**PK**E**R**H**I**I**V**A**CE**G**SP
 Y**V**PH**F**DA**S**VE**D**ST

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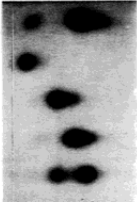
10      20      30      40      50      60      70      80
ALPHA1  -MVVSAADKNNVKAAMGKVGAHAGCYCAELERMFPSPTTKTVFPHDLSH----G-SAQVNGHGKRVADALTNVAHVDDMPNA  80
ALPHA2  -MVVSAADKNNVKAAMGKVGAHAGCYCAELERMFPSPTTKTVFPHDLSH----G-SAQVNGHGKRVADALTNVAHVDDMPNA  80
THETA   -MAVSAEDRALVRAAMKVGSNVGVYTTLEERFETAPPAKTVFPHDLSP----G-SSQVRAHGQVADALSDVERADDDIPNA  80
GAMMA   MCFEPEEDKATLRSVWGKVN--VEDAGGEALGRLLVVYPVTPQREFDSFGNLSASAIMGNPRVKAHGKRVVTSFGDAIKHLIDLKGT  85
BETA    MVHLTPEKSAVAVLWQKVN--VDVGGGALGRLLVVYPVTPQREFDSFGDLSTPDVAVMGNPRVKAHGKRVVTSFGDAIKHLIDLKGT  85
EPSILON MVHLTPEKAAVAVLWQKVN--VEDAGGEALGRLLVVYPVTPQREFDSFGNLSASAIMGNPRVKAHGKRVVTSFGDAIKMDLNLKPA  85
DELTA   MVHLTPEKAAVAVLWQKVN--VDVGGGALGRLLVVYPVTPQREFDSFGDLSTPDVAVMGNPRVKAHGKRVVTSFGDAIKHLIDLKGT  85
MYOGLOBIN -MGSDGGEWQLVNLVWQKVEADIPGHQGVVLRLEKGFPELEKEDKQKHKSEDEKASEDLKRGATVETALGGIKKKGHHEAE  86

90      100     110     120     130     140     150
ALPHA1  LSALSDDEHAKRQVDPVNFKLSHCLLVLAALPAEFTPAVHSLDQFLASVSVVITNSKVR----- 142
ALPHA2  LSALSDDEHAKRQVDPVNFKLSHCLLVLAALPAEFTPAVHSLDQFLASVSVVITNSKVR----- 142
THETA   LSALSHDEHACQVDPVDPFQLLGHCLLVLAALPAEFTPAVHSLDQFLASVSVVITNSKVR----- 142
GAMMA   EATLSELECDKLEVDPENFKLLGNVLLVLAHFGKQEPPEVQAAYORVIVGVAALAHKRYE----- 147
BETA    EATLSELECDKLEVDPENFKLLGNVLLVLAHFGKQEPPEVQAAYORVIVGVAALAHKRYE----- 147
EPSILON EATLSELECDKLEVDPENFKLLGNVLLVLAHFGKQEPPEVQAAYORVIVGVAALAHKRYE----- 147
DELTA   EATLSELECDKLEVDPENFKLLGNVLLVLAHFGKQEPPEVQAAYORVIVGVAALAHKRYE----- 147
MYOGLOBIN IKPLAASLHAKHHPVKYLEFISECLIQVLOSRRPGDGADAGMNAALDELFRKDLASNTKELGPGQ  154

```

Hemoglobin se pojavlja v več oblikah-1

odrasli	HbA ₁	$\alpha_2\beta_2$
odrasli	HbA ₂	$\alpha_2\delta_2$
fetalni	HbF	$\alpha_2\gamma_2$
embrionalni	Hb Gower-1	$\zeta_2\varepsilon_2$
embrionalni	Hb Portland	$\zeta_2\gamma_2$



OMIM - Online Mendelian Inheritance in Man - Microsoft Internet Explorer

Address: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=omim>

Search OMIM for hemoglobin

Display: Titles Show: 20 Send to: Text

All: 136

Items 1 - 20 of 136

1: [+141900](#)
HEMOGLOBIN--BETA LOCUS, HBB
BETA-THALASSEMIA, INCLUDED
Gene map locus [11p15.5](#)

2: [+141800](#)
HEMOGLOBIN--ALPHA LOCUS 1; HBA1
ALPHA-THALASSEMIA, INCLUDED
Gene map locus [16pter-p13.3](#)

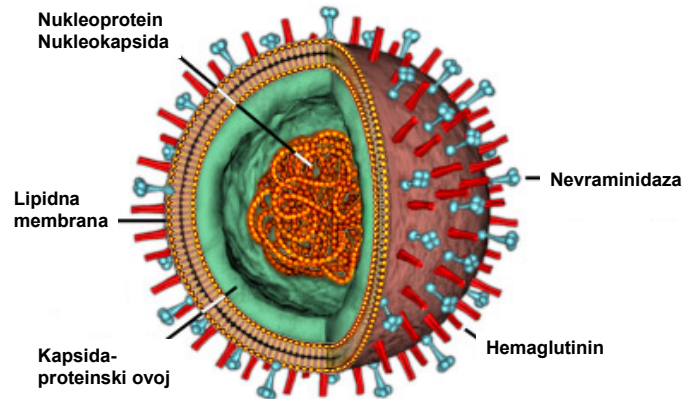
3: [*141850](#)
HEMOGLOBIN--ALPHA LOCUS 2; HBA2
Gene map locus [16pter-p13.3](#)

4: [*142250](#)
HEMOGLOBIN, GAMMA G, HBG2
Gene map locus [11p15.5](#)

531 variant β verige!

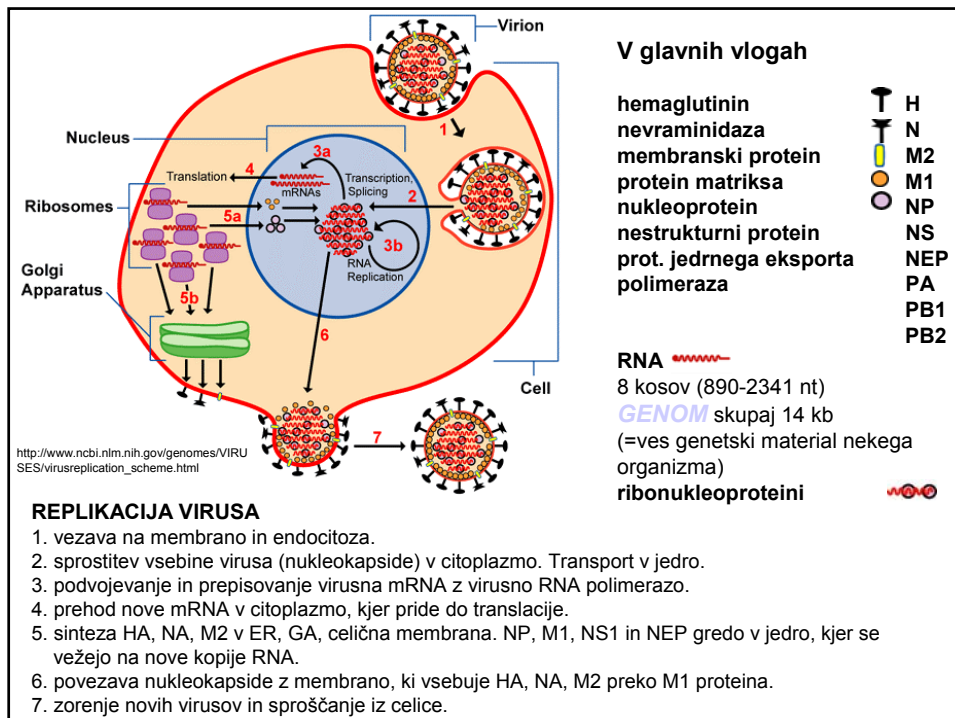
start | Internet | 12:28 ponedeljek 21.3.2005

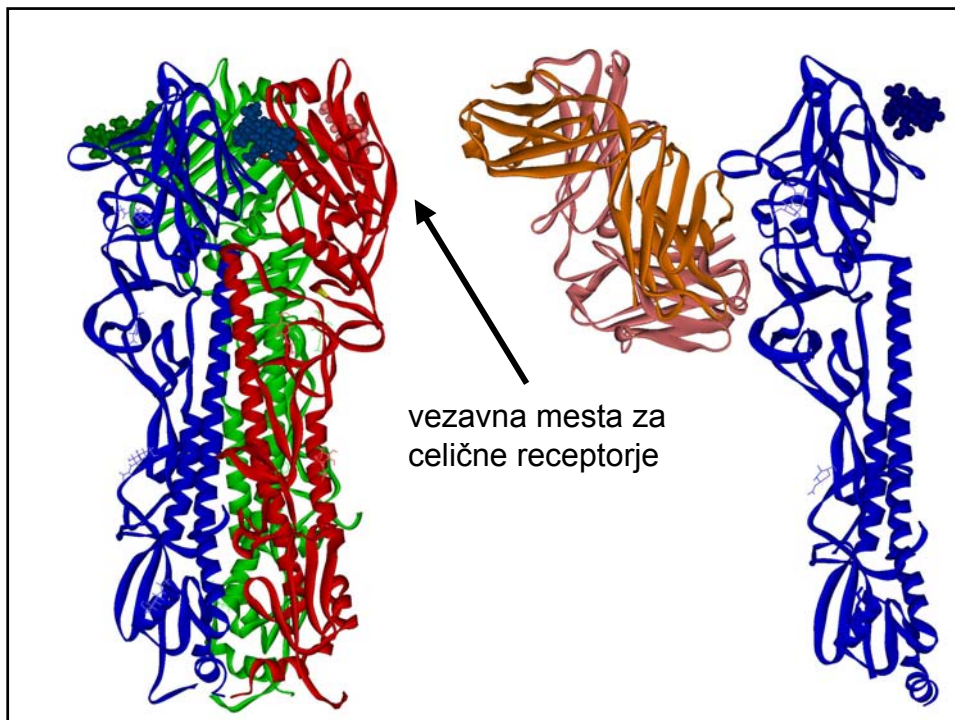
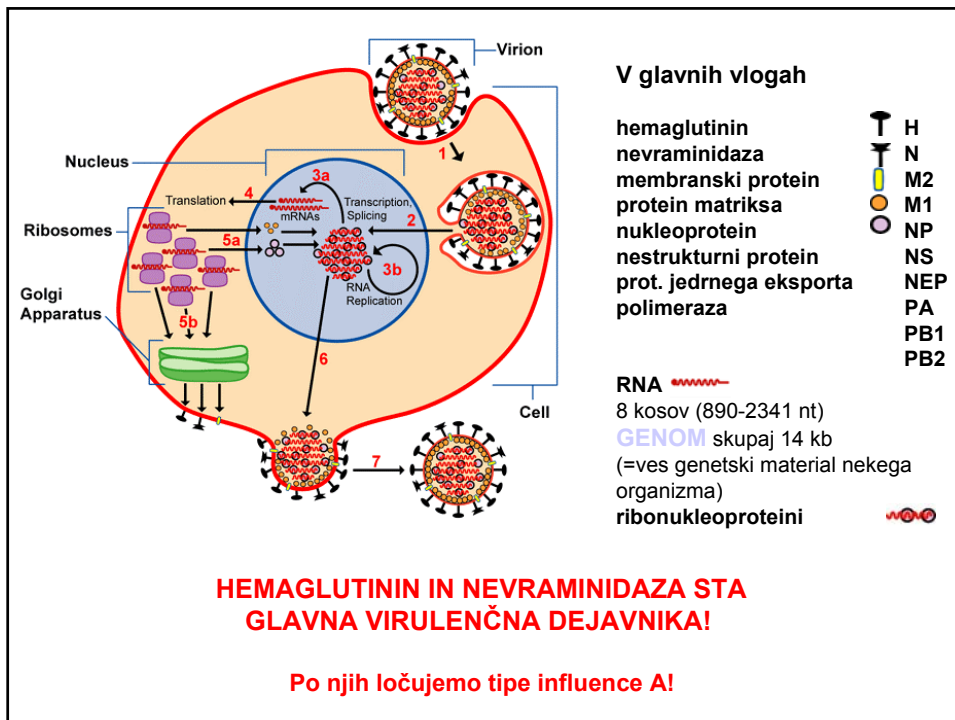
ZGRADBA VIRUSA INFLUENCE



<http://micro.magnet.fsu.edu/cells/viruses/influenzavirus.html>

En virusni delec tako vsebuje
 okoli 500 molekul **hemaglutinina (H; HA)**
 okoli 100 molekul **neuraminidaze (N; NA)**
 okoli 3000 molekul **proteina matriksa**
 8 molekul **RNA**
 na vsako molekulo RNA je vezano večje število **nukleoproteina (NP)**
 nekaj molekul **RNA polimeraze**, ki je sestavljena iz treh podenot
nestrukturni protein z neznano funkcijo





Tip A

16 tipov glede na hemaglutinin H1-H16
9 tipov glede na nevraminidazoN1-N9

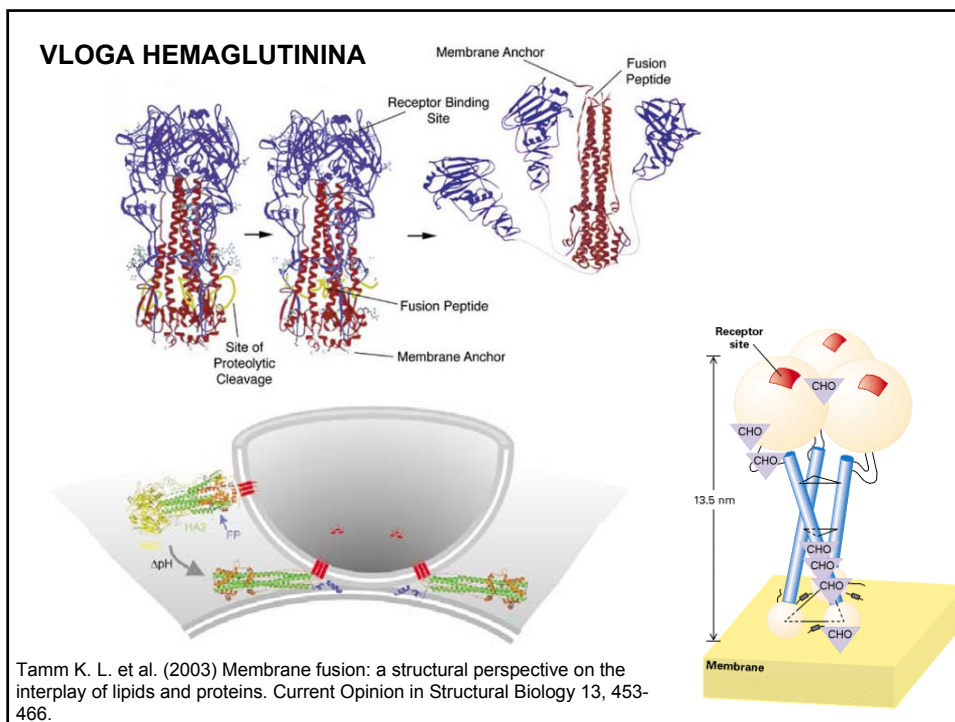
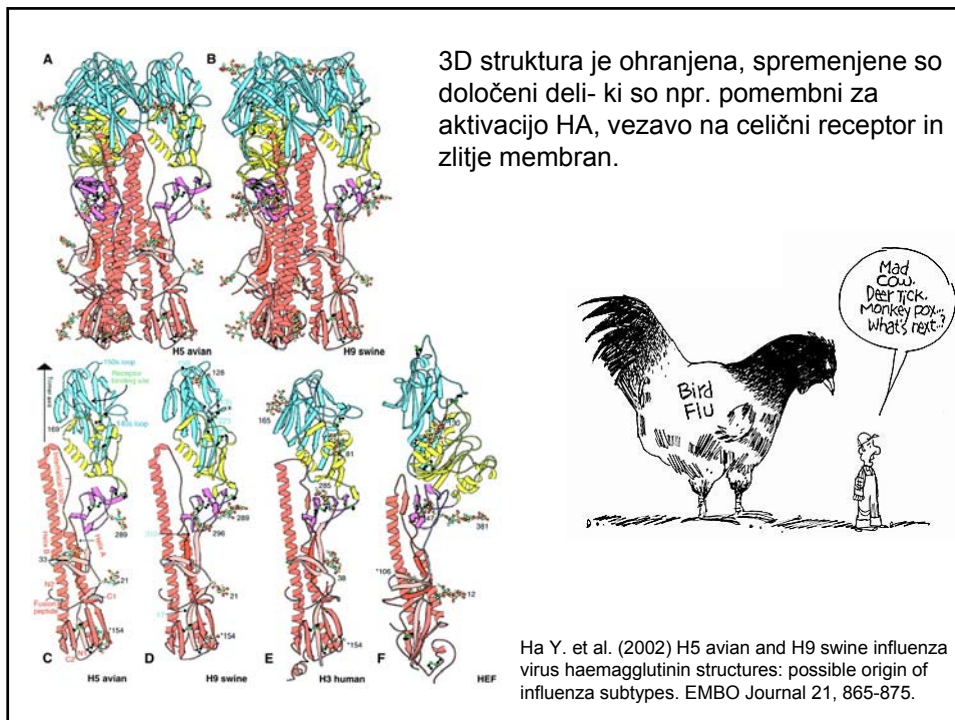
Divje ptice rezervoar za vse tipe tipa A (izvorne);
nekateri visoko patogeni, npr. H5 in H7

Prašiči so lahko okuženi s človeškimi in ptičjimi virusi. Lahko pride do
sočasne infekcije z obema

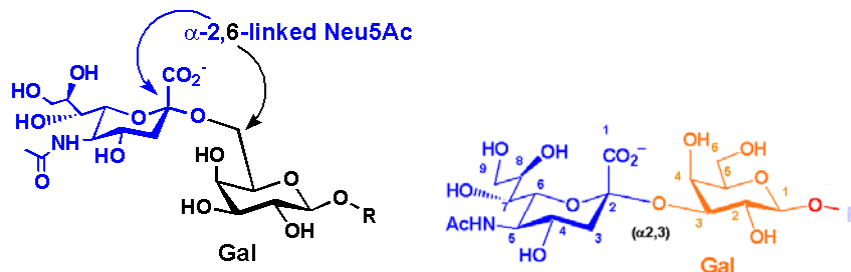
Človeški tipi so H1, H2, H3

1918	H1N1	????	Španska gripa	20-40 milijonov mrtvih
1957	H2N2	Ptiči	Azijska gripa	70.000 mrtvih v ZDA
1968	H3N2	Ptiči	Hong Kong	34.000 mrtvih v ZDA
1977	H1N1	Ptiči	Ruska gripa	
1997	H5N1	Ptiči	Hong Kong; Ptičja gripa	
2003	H7N7	Ptiči	Nizozemska; Ptičja gripa	1 mrtev

H1gi 12292	DDFHDSNWKNIYEKVKSQLNNNAKEIGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 530
H1gi 83658	DDFHDSNWKNIYEKVKSQLNNNAKEIGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 529
H1gi 12295	DDFHDSNWKNIYEKVKSQLNNNAKEIGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 530
H2gi 81940	DDFHDSNWKNIYDKVRSQQLNDNAKEIGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 533
H2gi 49357	DDFHDSNWKNIYDKVRSQQLNDNAKEIGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 533
H2gi 82020	DDFHDSNWKNIYDKVRSQQLNDNAKEIGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 526
H5gi 85062	DDFHDSNWKNIYDKVRSQQLNDNAKEIGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 532
H5gi 154402	DDFHDSNWKNIYDKVRSQQLNDNAKEIGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 532
H5gi 85701	DDFHDSNWKNIYDKVRSQQLNDNAKEIGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 532
H6gi 82032	DDMHDSNWKNIHEKVKSQLNDNANDIGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 531
H6gi 82032	DDMHDSNWKNIHEKVKSQLNDNANDIGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 531
H6gi 82032	DDMHDSNWKNIHEKVKSQLNDNANDIGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 531
H11gi 5642	DDLDHDSNWKNIHEKVRRLNDNAKDEIGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 529
H11gi 6813	DDLDHDSNWKNIHEKVRRLNDNAKDEIGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 529
H11gi 1228	DDLDHDSNWKNIHEKVRRLNDNAKDEIGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 529
H13gi 1229	DDMHDSNWKNIHEQVRRILNDNAIDEGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 530
H13gi 2322	DDMHDSNWKNIHEQVRRILNDNAIDEGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 530
H13gi 3242	DDMHDSNWKNIHEQVRRILNDNAIDEGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 529
H16gi 8201	DDLDHDSNWKNIHEQVRRILNDNAIDEGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 528
H16gi 8201	DDLDHDSNWKNIHEQVRRILNDNAIDEGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 528
H16gi 8201	DDLDHDSNWKNIHEQVRRILNDNAIDEGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 530
H8gi 12293	DDHDSNWKNIYDEKRRASPNIDAGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 528
H9gi 22131	DDHDSNWKNIYDEKRRASPNIDAGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 529
H12gi 1228	DDHDSNWKNIYDEKRRASPNIDAGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 528
H9gi 49357	DDHDSNWKNIYDEKRRASPNIDAGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 524
H9gi 28775	DDHDSNWKNIYDEKRRASPNIDAGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 524
H9gi 12293	DDHDSNWKNIYDEKRRASPNIDAGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 524
H3gi 82020	DDLDHDSNWKNIHEKVRRLNDNAIDEGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 530
H3gi 82010	DDLDHDSNWKNIHEKVRRLNDNAIDEGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 530
H3gi 52078	DDLDHDSNWKNIHEKVRRLNDNAIDEGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 530
H4gi 84028	DDLDHDSNWKNIHEKVRRLNDNAIDEGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 528
H4gi 23224	DDLDHDSNWKNIHEKVRRLNDNAIDEGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 528
H4gi 82021	DDLDHDSNWKNIHEKVRRLNDNAIDEGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 528
H14gi 1229	DDLDHDSNWKNIHEKVRRLNDNAIDEGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 532
H14gi 1229	DDLDHDSNWKNIHEKVRRLNDNAIDEGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 527
H7gi 82039	DDLDHDSNWKNIHEKVRRLNDNAIDEGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 524
H7gi 82035	DDLDHDSNWKNIHEKVRRLNDNAIDEGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 524
H7gi 12288	DDLDHDSNWKNIHEKVRRLNDNAIDEGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 527
H15gi 8202	DDLDHDSNWKNIHEKVRRLNDNAIDEGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 534
H15gi 8202	DDLDHDSNWKNIHEKVRRLNDNAIDEGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 534
H10gi 1229	DDLDHDSNWKNIHEKVRRLNDNAIDEGNGCEEFYVHRCDDICMSSVVRNGTYDYPKQSEESKLNREKIDGCVLDESIG-IYQI	: 525



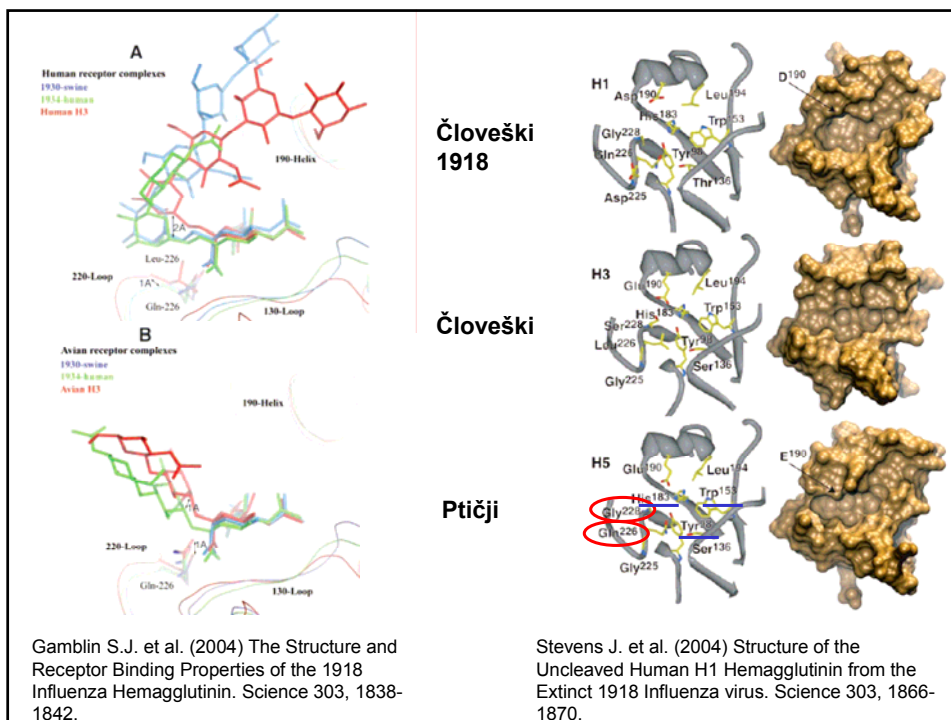
ZAKAJ PTIČJI VIRUS NE INFICIRA ČLOVEŠKIH CELIC?

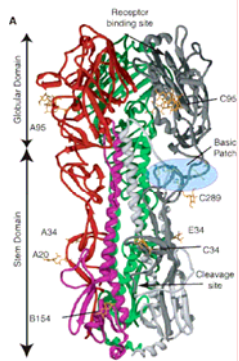


Hemaglutinin prepozna N-acetilneuraminsko kislino (sialna kislina) vezano na glikolipide in glikoproteine na celični površini.

Vsi HA **ptičjih virusov** prepoznajo sialno kislino vezano z α 2-3 vezjo na galaktozo. Vsi HA **človeških virusov** prepoznajo sialno kislino vezano z α 2-6 vezjo.

Okužba človeških celic s ptičjimi virusi zato zahteva **spremembe v vezavni specifičnosti**.





ZAKAJ SO TIPI H5 IN H7 TAKO INFEKTIVNI?

Gruča pozitivno nabitih aminokislin, ki tvorijo mesto cepitve, kar vodi do lažje aktivacije virusa.

Stevens J. et al. (2004) Structure of the Uncleaved Human H1 Hemagglutinin from the Extinct 1918 Influenza virus. *Science* 303, 1866-1870.

KAKŠEN JE VISOKO INFEKTIVEN VIRUS?

Mnogo (slabo poznanih) faktorjev omogoča virulenčnost virusov:

- HA za vezavo na celični receptor
- Interakcije virusnih proteinov med seboj in s komponentami celic
- Efektivnost replikacije
- Prilagojenost gostitelju
- Transmisibilnost

PB2	PB1	PA	NP	NA	M1	M2	NS1	NS2
T9N ^a	I179M	N27D	S27A	A18S	T218A	N23S	G71E	R87K
R340K	I469T	R262K	R77K	L23F	V219I	I51V	A82V	G26D
K389R	K586R	I332S	K98R	V30I		R56K	N143I	
G590S	D619N	V348I	R103K	H40Y				
V667I	V709I	V421I	M136I	C42F				
			I197V	G143V				
			I406T	R172K				
			I425V	K199E				
			E480D	G216V				
				I265T				
				V307I				
				K385N				
				E399D				
				W437L				

Holmes E.C. et al. (2004) Whole-Genome Analysis of Human Influenza A Virus Reveals Multiple Persistent Lineages and Reassortment Among Recent H3N2 Viruses. *Plos Biology* 3, 1579-1589.