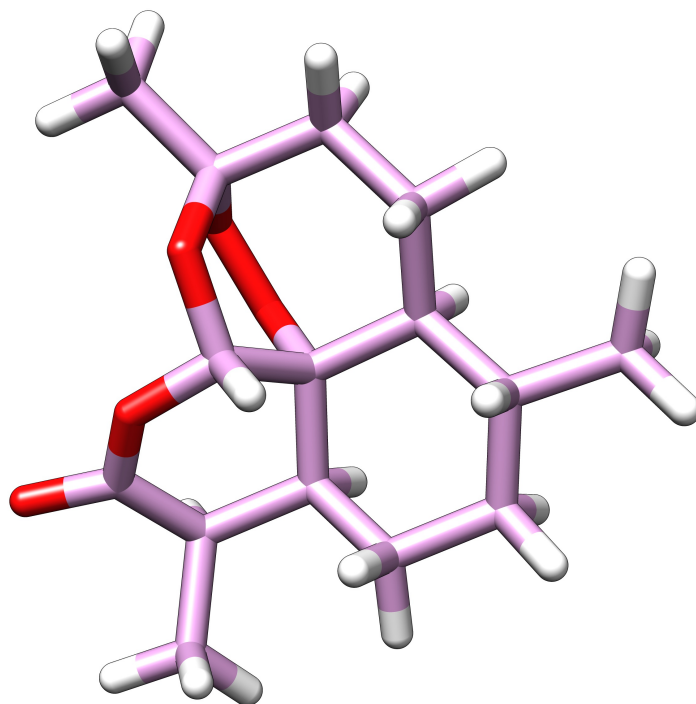


Proteiner som läkemedel

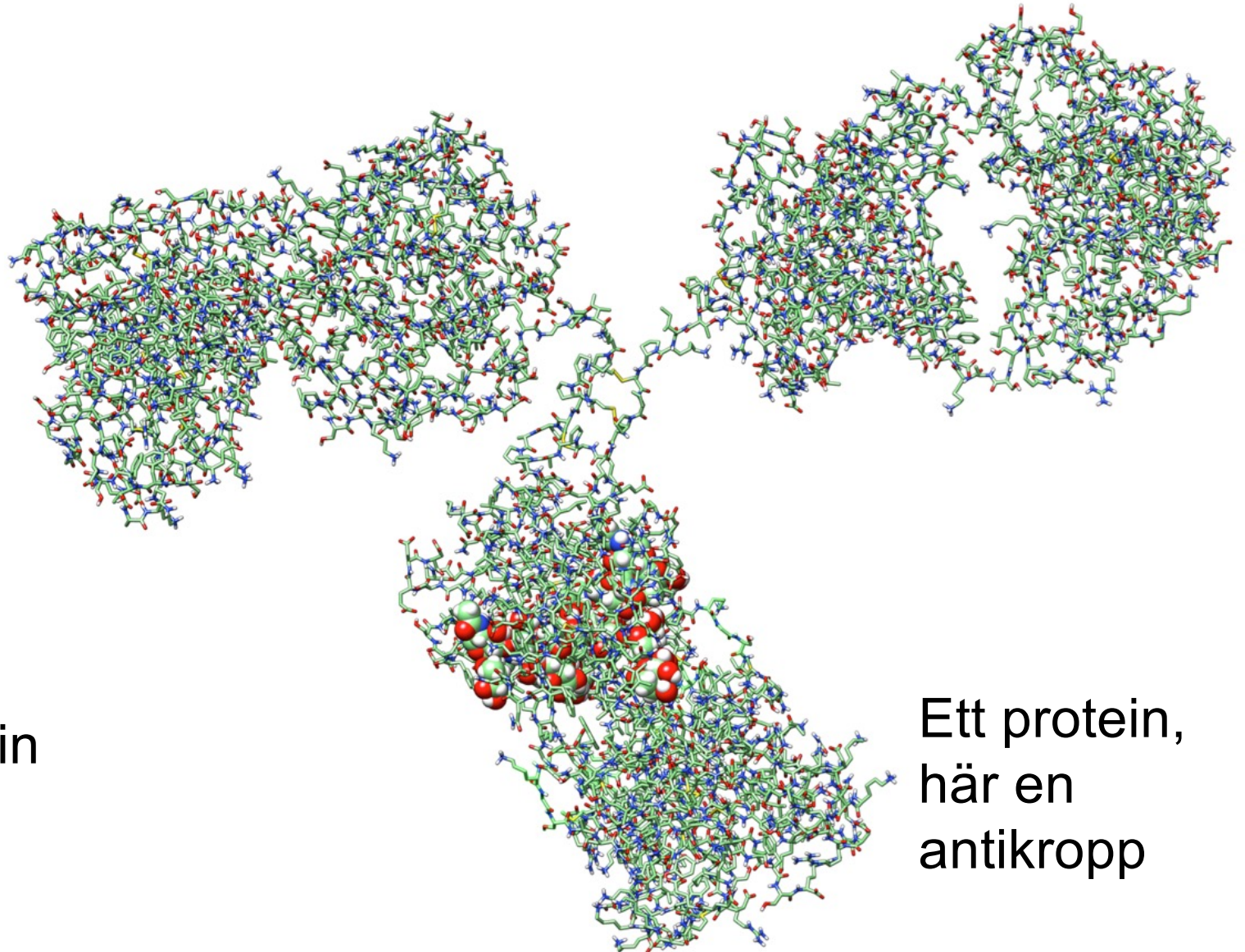
Ulf Göransson

ulf.goransson@fkog.uu.se



Artemisinin

Olika stora molekyler

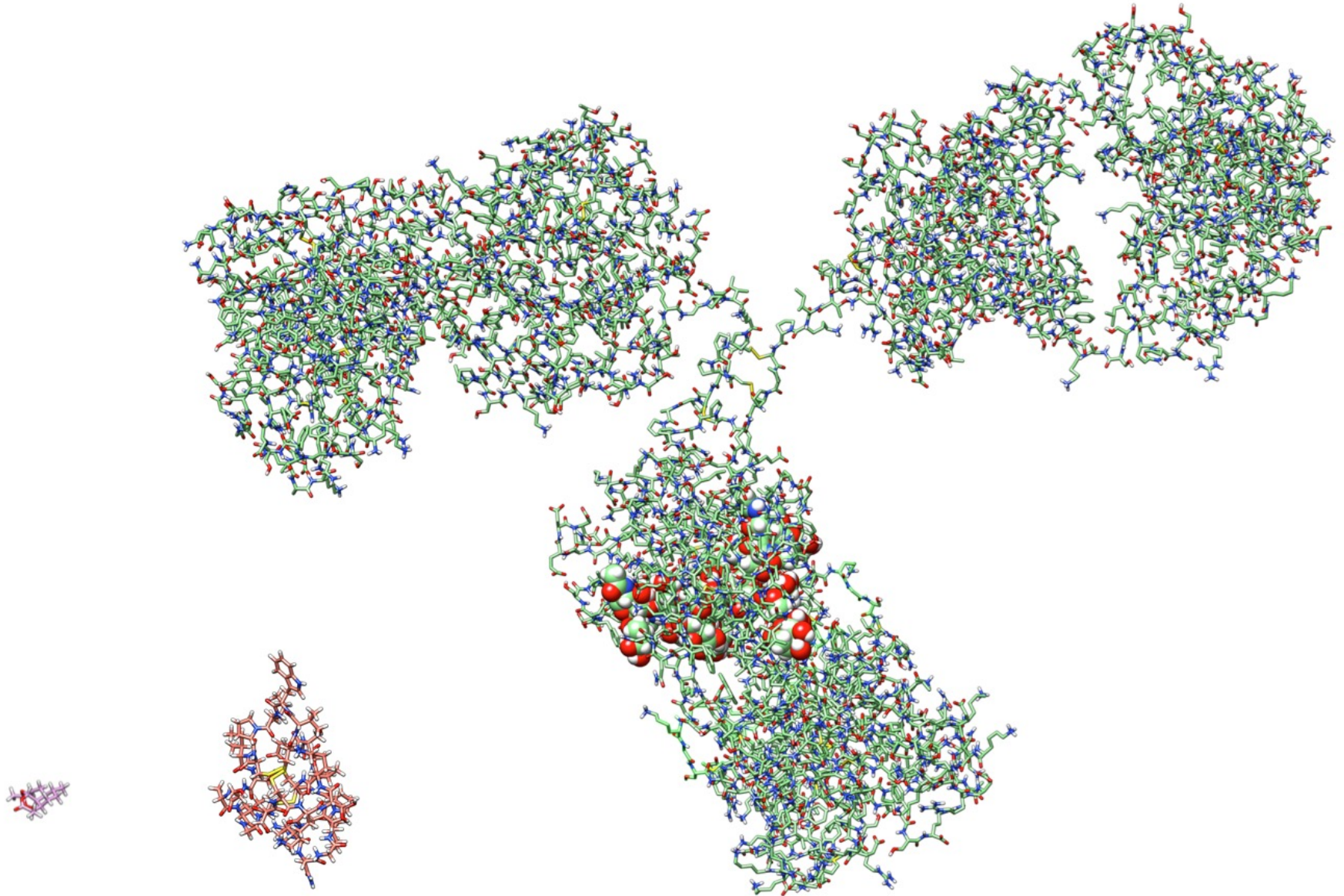


Artemisinin



Ett protein,
här en
antikropp

Peptider



Top 200 Pharmaceutical Products by US Retail Sales in 2012

Compiled and Produced by the Njardarson Group (The University of Arizona): Edon Vitaku, Elizabeth A. Iardi, Jón T. Njardarson

1 Neurim (Antidepressant) AstraZeneca	2 Abilify (Antipsychotic) AstraZeneca	3 Crestor (Lipid-lowering agent) AstraZeneca	4 Advair Diskus (Respiratory inhaler) Boehringer Ingelheim	5 Cymbalta (Antidepressant) Eli Lilly	6 Rumitek (Antidepressant) AbbVie	7 Enbrel (Anti-inflammatory) Amgen	8 Remicade (Anti-inflammatory) Centocor	9 Copaxone (Multiple sclerosis treatment) TEVA	10 Neulasta (Cancer treatment) Amgen	11 Singulair (Asthma treatment) Merck	12 Silvan (Antidepressant) Olanex Pharmaceuticals	13 Plavix (Blood thinner) Boehringer Ingelheim	14 Athalia (Antidepressant) Boehringer Ingelheim	15 Splice HandHaler (Antidepressant) Boehringer Ingelheim	16 OxyContin (Painkiller) Purdue Pharma	17 Januvia (Diabetes treatment) Merck	18 Avastin (Cancer treatment) Olanex Pharmaceuticals	19 Levon (Antidepressant) Olanex Pharmaceuticals	20 Tuvaso (Antidepressant) Gilead
21 Levamisole (Antiparasitic) Novartis	22 Spargan (Antiparasitic) Amgen	23 Sildenafil (Erectile dysfunction) Novartis	24 Lyrica (Painkiller) Pfizer	25 Lipitor (Lipid-lowering agent) Pfizer	26 Celebrex (Painkiller) Pfizer	27 Humalog (Insulin) Olanex Pharmaceuticals	28 Gleevec (Cancer treatment) Novartis	29 Nomidex (Antidepressant) Allergan	30 Actos (Diabetes treatment) Takeda	31 Locortin (Antidepressant) Olanex Pharmaceuticals	32 Vioxx (Painkiller) Shire	33 Suboxone (Painkiller) Purdue Pharma	34 SEQUEL (Antidepressant) AstraZeneca	35 Nasonex (Nasal spray) Merck	36 Zafra (Antidepressant) Merck	37 Methylphenidate (ADHD treatment) AbbVie	38 Androgel (Testosterone replacement) AbbVie	39 Invokadr (Diabetes treatment) Novartis	40 Elevar HCT (Diabetes treatment) Novartis
41 Lidoderm (Painkiller) Allergan	42 Abobotulin (Botulinum toxin) Allergan	43 Symbyax (Antidepressant) AstraZeneca	44 Humalog (Insulin) Olanex Pharmaceuticals	45 SEQUEL (Antidepressant) AstraZeneca	46 Ticor (Painkiller) AbbVie	47 Alimta (Cancer treatment) Eli Lilly	48 Bosulfin (Cancer treatment) Allergan	49 Novartis (Antidepressant) Allergan	50 Actos (Diabetes treatment) Takeda	51 Combivent (Respiratory inhaler) Boehringer Ingelheim	52 Viagra (Erectile dysfunction) Pfizer	53 Pack HFA (Respiratory inhaler) TEVA	54 Novartis (Antidepressant) Allergan	55 Nasonex (Nasal spray) Merck	56 Novartis (Antidepressant) Allergan	57 Novartis (Antidepressant) Allergan	58 Novartis (Antidepressant) Allergan	59 Novartis (Antidepressant) Allergan	60 Novartis (Antidepressant) Allergan
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Poster av Njardarson group, University of Arizona

1 Humira (Adalimumab)	2 Eliquis (Apixiban)	3 Keytruda (Pembrolizumab)	4 Revlimid (Lenalidomide)	5 Imbruvica (Venclextar)	6 Oncivy (Axicabtagene)	7 Eylea (Aflibercept)	8 Avelir (Novelir)	9 Ertacry (Enfortumab)	10 Xarelto (Rivaroxaban)	11 Rhuon (Rituximab)	12 Zimtra (Zoledronic acid)	13 Hercaplan (Hershey's)	14 Pervin 13 (Pervin 13)	15 Reticade (Reticade)	16 Ibrance (Exemestane)	17 Bikany (Bikany)	18 Tocifeine (Tocifeine)	19 Tuclytic (Tuclytic)	20 Xtandi (Enzalutamide)
21 Lactavis (Lactavis)	22 Sutro (Sutro)	23 Gempyr (Gempyr)	24 Oncivy (Axicabtagene)	25 Eylea (Aflibercept)	26 Gardasil (HPV vaccine)	27 Peptra (Peptra)	28 Lynce (Lynce)	29 Cemivy (Cemivy)	30 Januvia (Sitagliptin)	31 Impey (Impey)	32 Viloxin (Viloxin)	33 Jardiance (Empagliflozin)	34 Larix (Larix)	35 Gleny (Gleny)	36 Nexavis (Nexavis)	37 Xolite (Xolite)	38 Togivon (Togivon)	39 Rumex (Rumex)	40 Enlysta (Enlysta)
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81 Enfesto (Enfesto)	82 Jentivaco (Jentivaco)	83 Oncivy (Axicabtagene)	84 Predisa (Predisa)	85 Avonax (Avonax)	86 Oncivy (Axicabtagene)	87 Xym (Xym)	88 Lupras (Lupras)	89 Oncivy (Axicabtagene)	90 Sondastin (Sondastin)	91 Biltra (Biltra)	92 Crest (Crest)	93 Faviga (Faviga)	94 Amlur (Amlur)	95 Vimpal (Vimpal)	96 Capozone (Capozone)	97 Decary (Decary)	98 Tysol (Tysol)	99 Lorenza (Lorenza)	100 Myrtan (Myrtan)
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Varför?

Vilka fördelar har proteiner som
läkemedel?

Nackdelar?

Proteiner som läkemedel

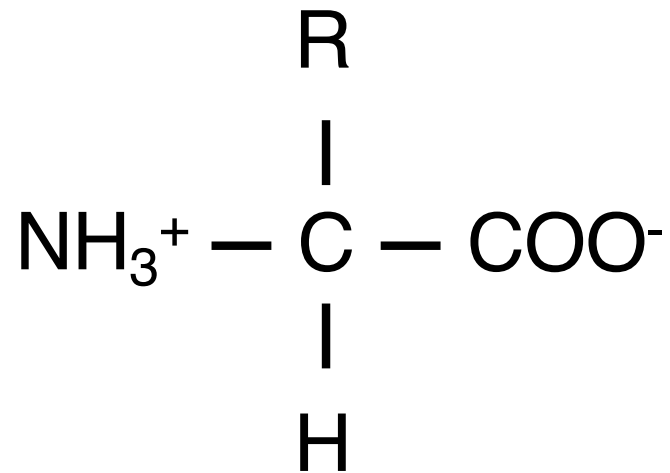
Kemin och biologin bakom

Tillverkning och produktion

Biologin och kemin bakom

- DNA-mRNA-protein (transkription/translation)
- Aminosyror byggstenarna i proteiner
- Amidbindningar/peptidbindningar
- Primär, sekundär, tertiär, kvartär struktur
- Posttranslationella modifieringar (PTM)

Byggstenen

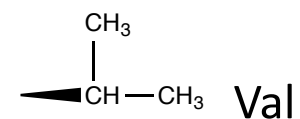
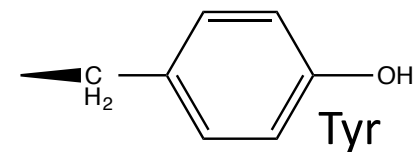
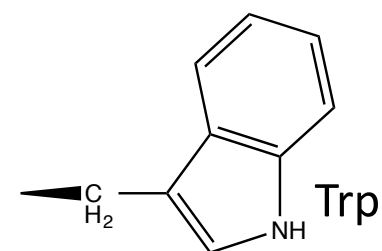
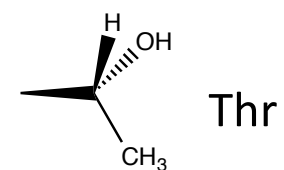
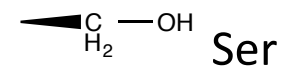
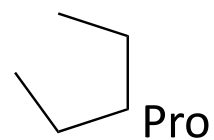
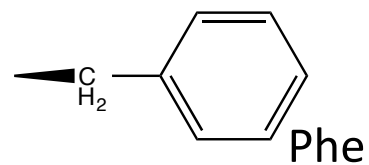
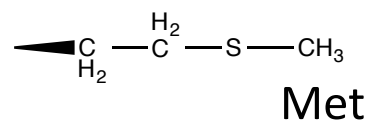
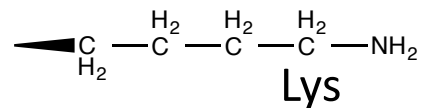
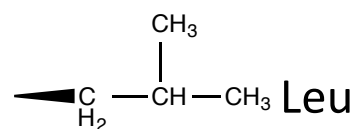
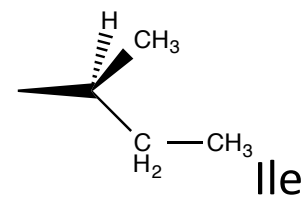
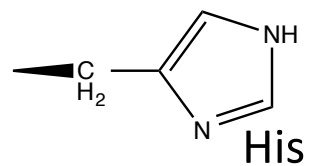
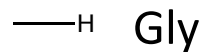
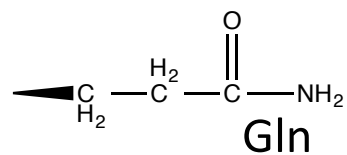
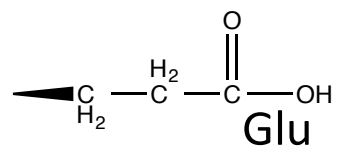
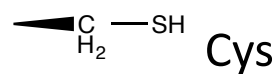
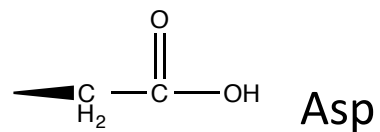
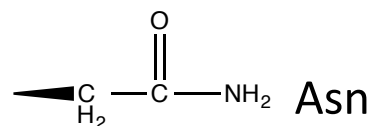
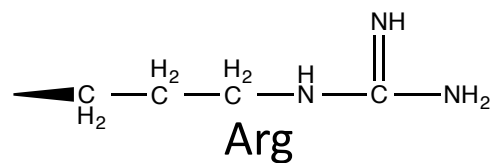
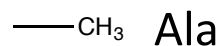


Alfa-kolet kiralt

Sekvens av aminosyror primärstruktur

Hydrofoba, hydrofila, laddade aminosyror beroende på sidokedjan

Sidogrupper



Post-translationella modifikationer

Glykosylering: N-eller O-bundet socker på Ser, Thr, Asn

Fosforylering: Reversibel fosforylering av Ser, Thr, Tyr

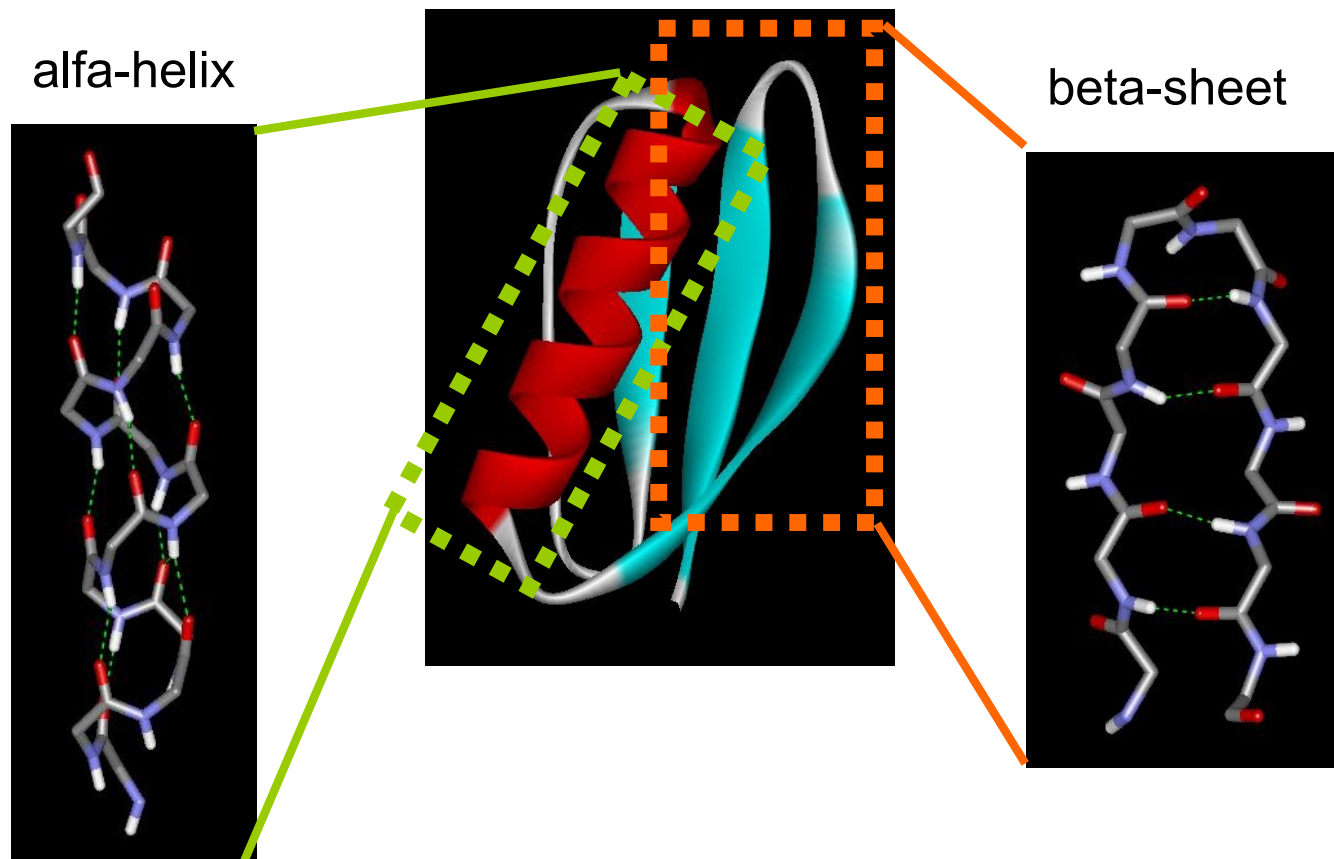
N-terminal acylering

C-terminal amidering

Disulfider (disulfidbryggor)

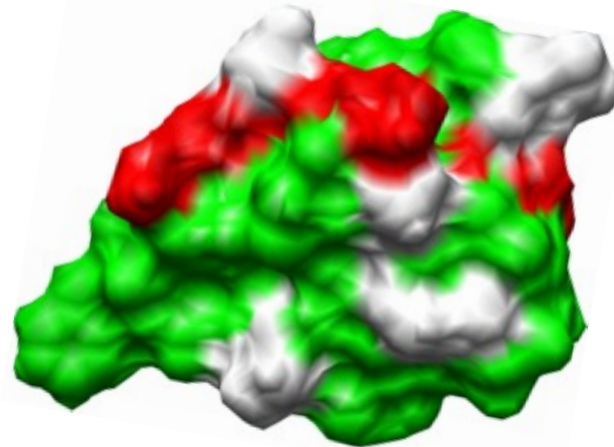
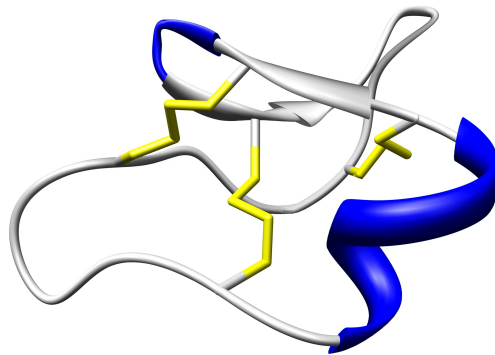
Veckning och struktur

Sekundärstruktur: alfa-helix, beta-sheet, loopar och svängar



Veckning och struktur

Tertiärstruktur: proteinets rymdstruktur. Presenteras ofta med bara skelettet (bara peptidbindningar) eller som rymdstruktur (ytan på strukturen)



Kvartärstruktur: flera peptider/proteiner struktur tillsammans

Veckning och struktur

Proteiner bara aktiva i sin rätta tertiära (tre-dimensionella) struktur

Aminosyrasekvensen kodar för detta, hur det går till är dock okänt i detalj

Oxidativ veckning – formering av disulfider

Tillverkning/Produktion

- Isolering från källan
- Kemisk syntes
- Rekombinanta tekniker



Upstream och Downstream

Studiebesök Testa

Exempel insulin

- Insulin
 - gen (inkl intron)
 - preproinsulin 110 aminosyror (24 aa exportsignal)
 - proinsulin (inkl 35 aa peptid C)
 - insulin
- Från pankreas av gris (1 aa skillnad) och nöt (3 aa skillnad)
 - sidoeffekter
- Konvertera insulin från gris till humant insulin
 - C-terminalt alanin ersätts med threonin med enzymatiska metoder
- Rekombinant uttryck
 - Först A och B separat
 - Sedan proinsulin
- Genteknik
 - Förändra sekvens för snabbare insulin
- Se Kapitel 3 i kursboken “Biotechnology for Beginners”

Produktionssystem rekombinanta proteiner

Prokaryoter:

Bakterier: hög koncentration, billigt, enkelt, skalbart, kan ej glykosylera och veckar ej som eukaryota. Ex E.coli

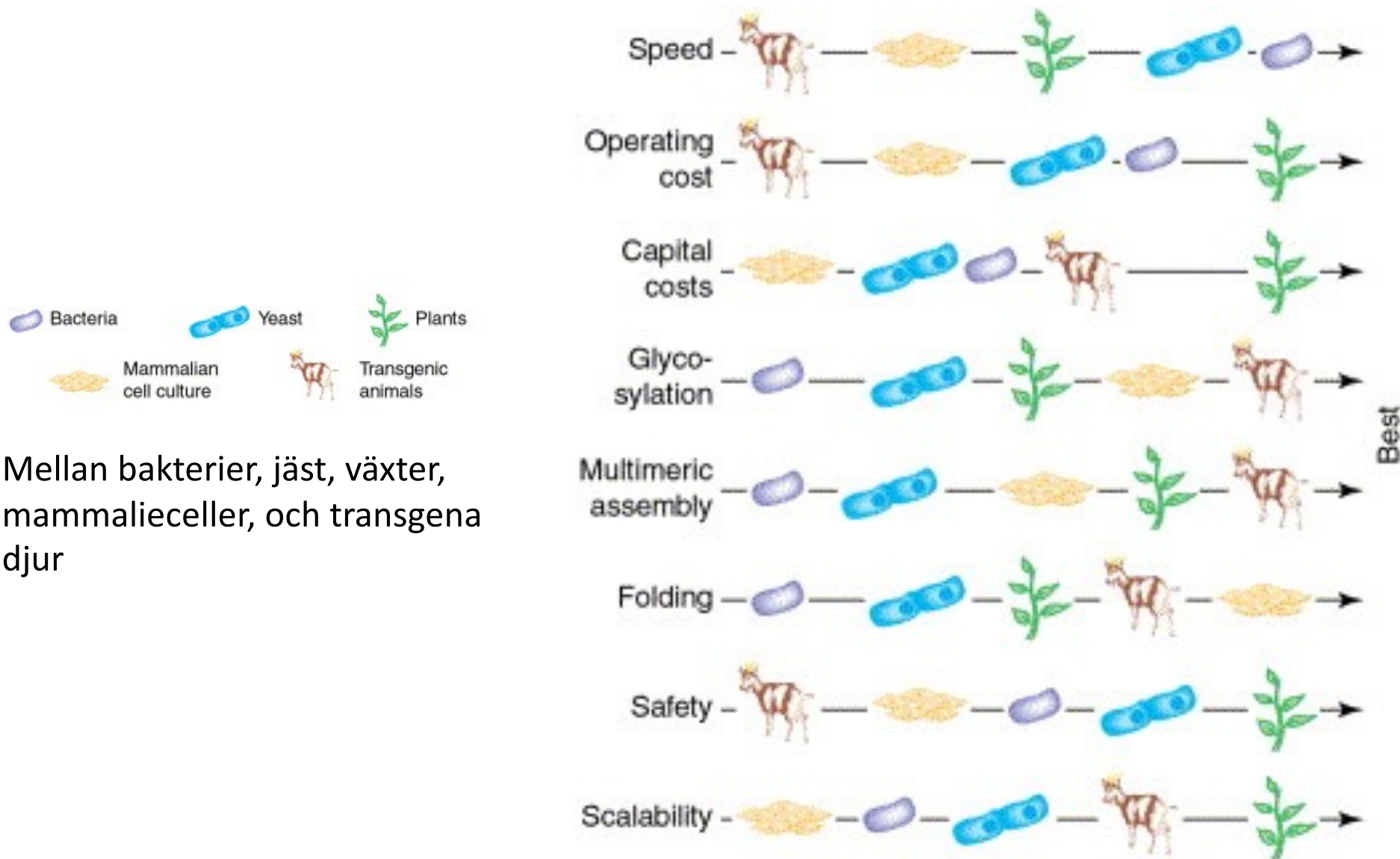
Eukaryoter:

Jäst: hög concentration; sekretion, disulfider, glykosylering och korrekt veckning möjlig

Mammalieceller: Korrekt veckning och PTM, teknikkrävande (dyrt och långsamt, låga utbyten. Chinese hamster ovary (CHO) cells); Transgena djur (Atryp®)

Växter: Korrekt veckning och PTM, skalbart, ingen risk för humana patogener, kan glykosylera liknande mammalieceller. Första läkemedlet Elvelyso™. Zmapp™.

Jämförelse produktionssystem



Mellan bakterier, jäst, växter, mammalieceller, och transgena djur

Isolering och rening av produkten

Filtrering/Koncentrering

Ta bort bulk/debris

Isolering av slutprodukt fri från kontaminanter
och varianter

Metoder för rening och analys

Kontaminationer

Värd-relaterade: virus, bakterier, värdrelaterade proteiner/DNA, PTM varianter, endotoxiner

Produkt-relaterade: substitutioner av aminosyror, denaturerat protein, isomera konformationer, dimerer/aggregat

Process-relaterade: komponenter från odlingsmedium och/eller upprening (tex hormoner, vitaminer), metaller, kolonnmaterial

Kvalitet och stabilitet

- Renhet >99%
- Möjliga problem
- Deamidering (Asn till Asp/betaAsp)
- Oxidation (Trp/Met)
- Omlagring av disulfidbryggor
- Aggregering
- Enzymatisk nedbrytning
 - Vilka aminosyror viktiga?

Hur kontrollera detta? Se Ytterbergs föreläsning

Läkemedel

Antikroppar, polyklonala och monoklonala antikroppar

Proteiner, tex HGH, FVIII (glykosylerat, chinese hamster ovary cells, CHO), antitrombin (Atryn®), transgena djur), taliglucerase alfa (Elelyso®), interleukiner, interferoner

Antikroppsutveckling

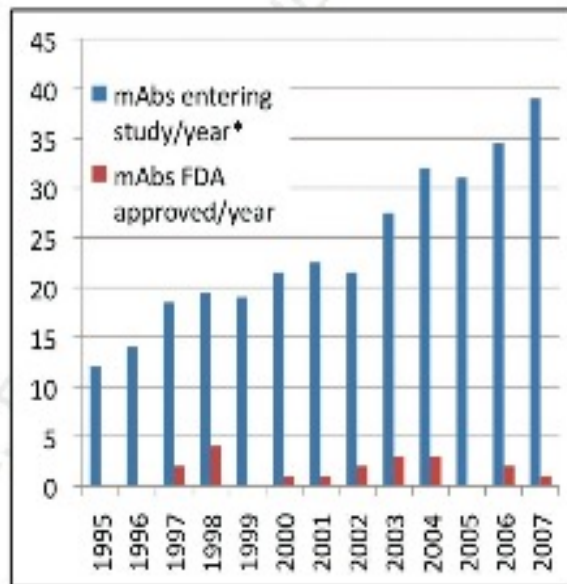


Figure 1. Therapeutic monoclonal antibodies entering clinical study or approved, 1995–2007. Data presented as two-year moving average
Source: Tufts Center for the Study of Drug Development

Reichert et al, mAbs, 2008

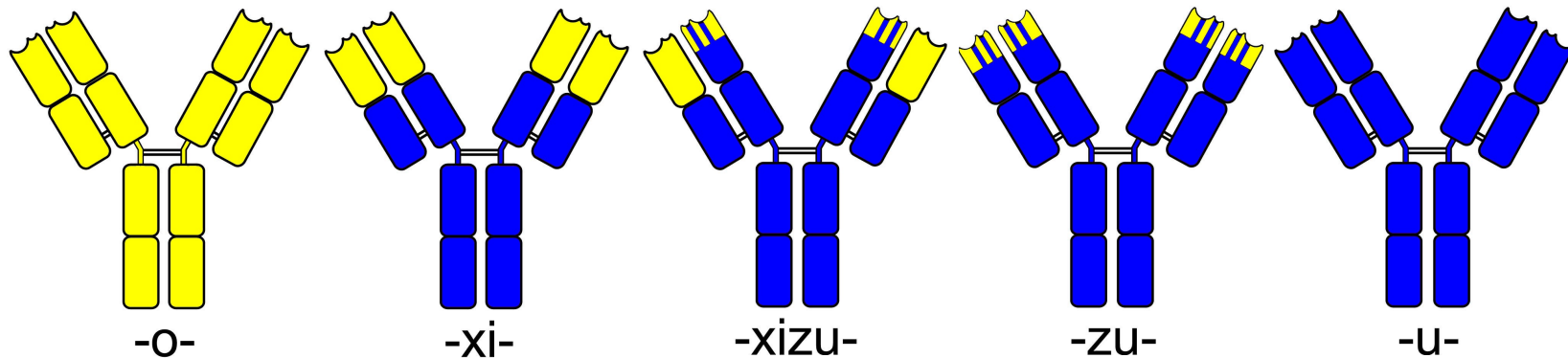
- relativt hög % godkännande från fas 1 till godkänd (ca 20%) (jfr med traditionella LM)
- Ca 50 godkända idag
- 2016, 6 nya godkända
- 2017 10 nya godkända
- 2018 12 nya godkända, 62 i sen klinisk fas, ca 600 i klinisk utveckling totalt

Biosimilarer, Antibody Drug Conjugates, Bispecifika...

Reference: **Antibodies to watch in 2020**. Kaplon H, Muralidharan M, Schneider Z, Reichert JM. *MAbs*. 2020;12(1):1703531. doi:10.1080/19420862.2019.1703531

Rituximab

- Ett av de första antikropps-läkemedlen (1998) MabThera, Rituxan Indikation: Non-Hodgkin lymphoma
- Målet CD20; uttrycks på B-celler. Antikroppsmolekylen blir en markör för NK celler
- Chimeric IgG1 – variabla domänen ej human (dvs mus)



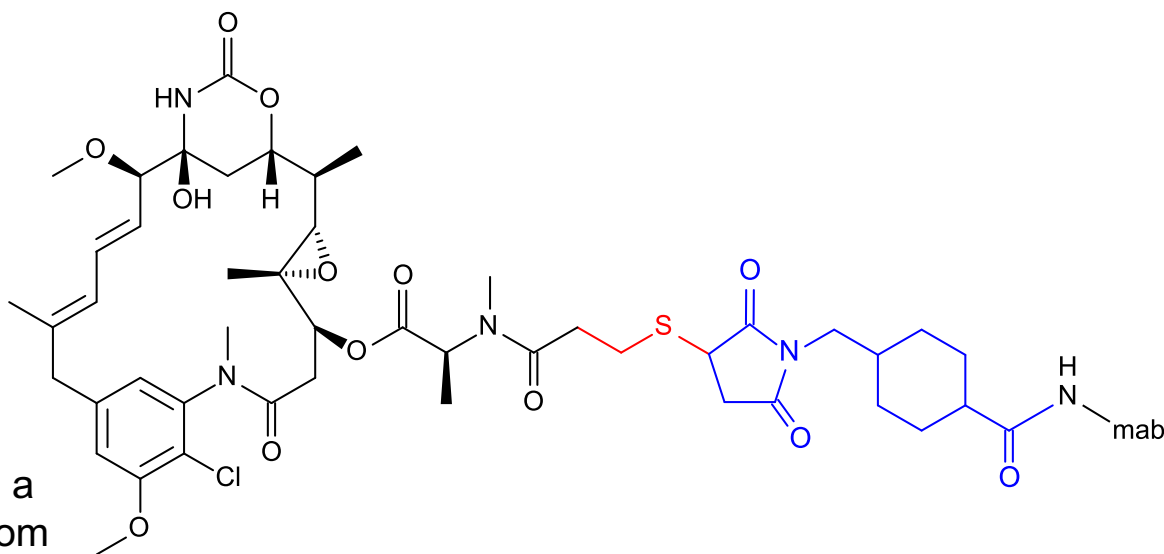
Human – blå (mörk)

Company name, Country	Product name	Stage of development
Amgen, USA	-	Biosimilar in active development
Biocad, Russia*	AcellBia	Non-originator biological approved in Russia
BioXpress Therapeutics, Switzerland	-	Biosimilar in pipeline
Boehringer Ingelheim, Germany	BI695500	Phase I and III trials
Celltrion/Hospira, South Korea/USA	CT-P10	Phase I trial completed. Phase III trials for RA and lymphoma
Dr Reddy's Laboratories, India*	Reditux	Reditux marketed in Bolivia, Chile, India and Peru
iBio, USA	-	Rituximab produced in non-transgenic green plants.
Intas Biopharmaceuticals, India*	MabTas	'Similar biologic' approved in India in February 2013
Laboratorio Elea, Argentina	Novex	<i>Medicamento biológico similar</i> approved in Argentina in October 2013
Mabion, Poland	MabionCD20	Phase III trial in lymphoma
Merck, USA	MK-8808	Phase I trials in RA and lymphoma completed
Oncobiologics/Viropro, USA	-	Biosimilar in development; one
Pfizer, USA	PF-05280586	Phase I/II study in RA completed, extension study and phase III study in lymphoma
Probiomed, Mexico*	Kikuzubam	Kikuzubam marketed in Bolivia, Chile, Mexico and Peru
Samsung BioLogics, South Korea	SAIT101	Phase III trial in RA halted in 2012
Sandoz, Switzerland	GP2013	Phase I trial in Japanese NHL patients, phase I/II trial in RA and phase III trial in lymphoma
Stada Arzneimittel, Germany	-	Made a deal with Gedeon Richter in 2011 for rituximab
Teva Pharmaceutical Industries/Lonza, Israel/Switzerland	TLO11	Phase III trial of TLO11 halted
Torrent Pharmaceuticals/ Reliance Life Sciences, India*	-	Exclusive licensing agreement announced in December 2014
Zenotech Laboratories, India*	Rituximab	'Similar biologic' approved in India in February 2013

Ado-trastuzumab emtansine

Kadcyla®, humaniserad IgG1; immunokonjugat, behandling av bröstcancer

Trastuzumab binder till HER2 (human epidermal growth factor receptor 2) och hindrar tillväxt av celler; konjugatet DM1, en tubulinhämmare tas upp av cellen och inducerar apoptos



Tumor inhibitors. LXXIII. Maytansine, a novel antileukemic ansa macrolide from *Maytenus ovatus*, Kupchan, et al *J. Am. Chem. Soc.*, 1972, 94 (4), pp 1354–1356

