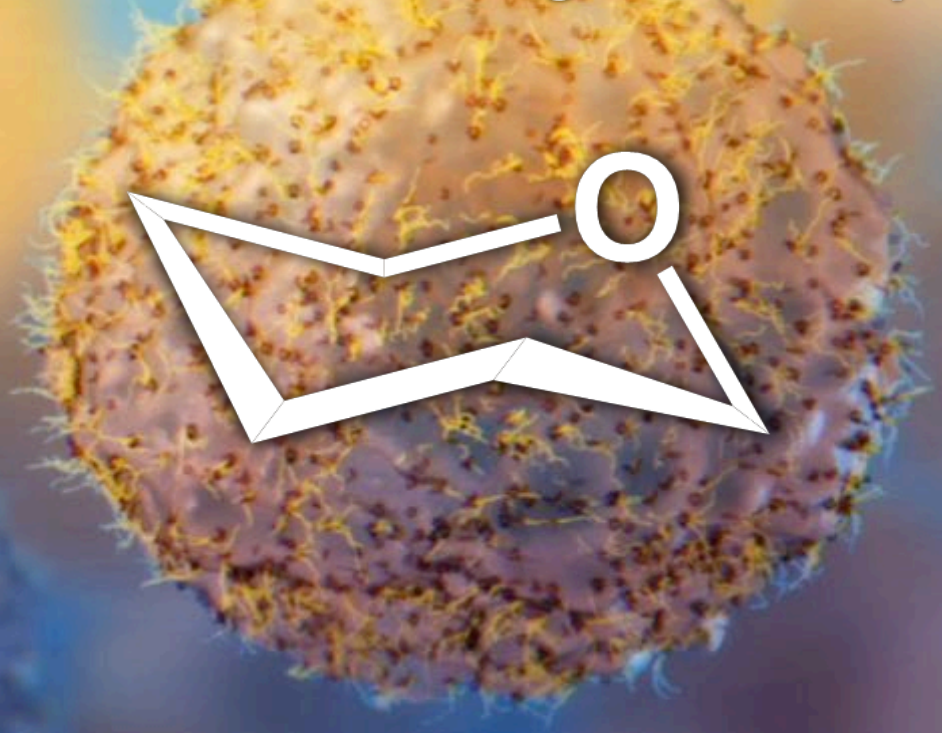
Is suiker altijd zoet?

Op onderzoek naar de suiker streepjescode op cellen met slim moleculair gereedschap



Utrecht University

Tom Wennekes

Imagination at work

Woudschoten Chemie Conferentie 2022

C3

Is suiker altijd zoet?

Op onderzoek naar de suiker streepjescode op cellen met slim moleculair gereedschap

Utrecht University

Tom Wennekes

Imagination at work

Woudschoten Chemie Conferentie 2022

C3

Is suiker altijd zoet?

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Imagination at work

Woudschoten Chemie Conferentie 2022

C3

Is suiker altijd zoet?

Inhoud van mijn lezing:

- **Introducties:** chemische biologie → mij → suikers
- **Onderzoek:** slimmer zijn dan het griep virus
- **Onderzoek:** de perfecte omhelsing van Cholera
- **In het nieuws:** Klik chemie is gaaf!
- **Echt gebeurd:** Zoet biomoleculair moord mysterie
- Chemie op de basisschool?

Utrecht University

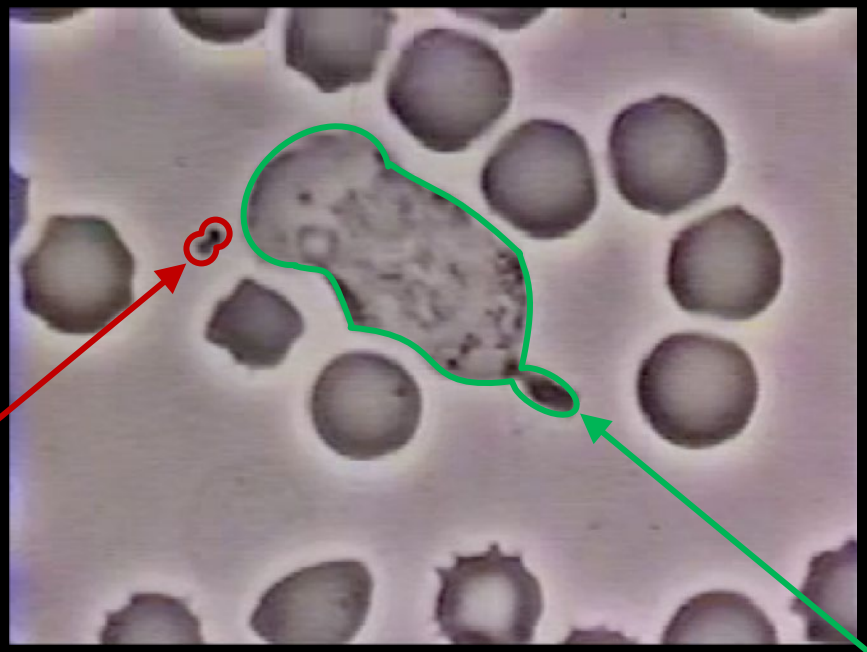
Tom Wennekes

Imagination at work

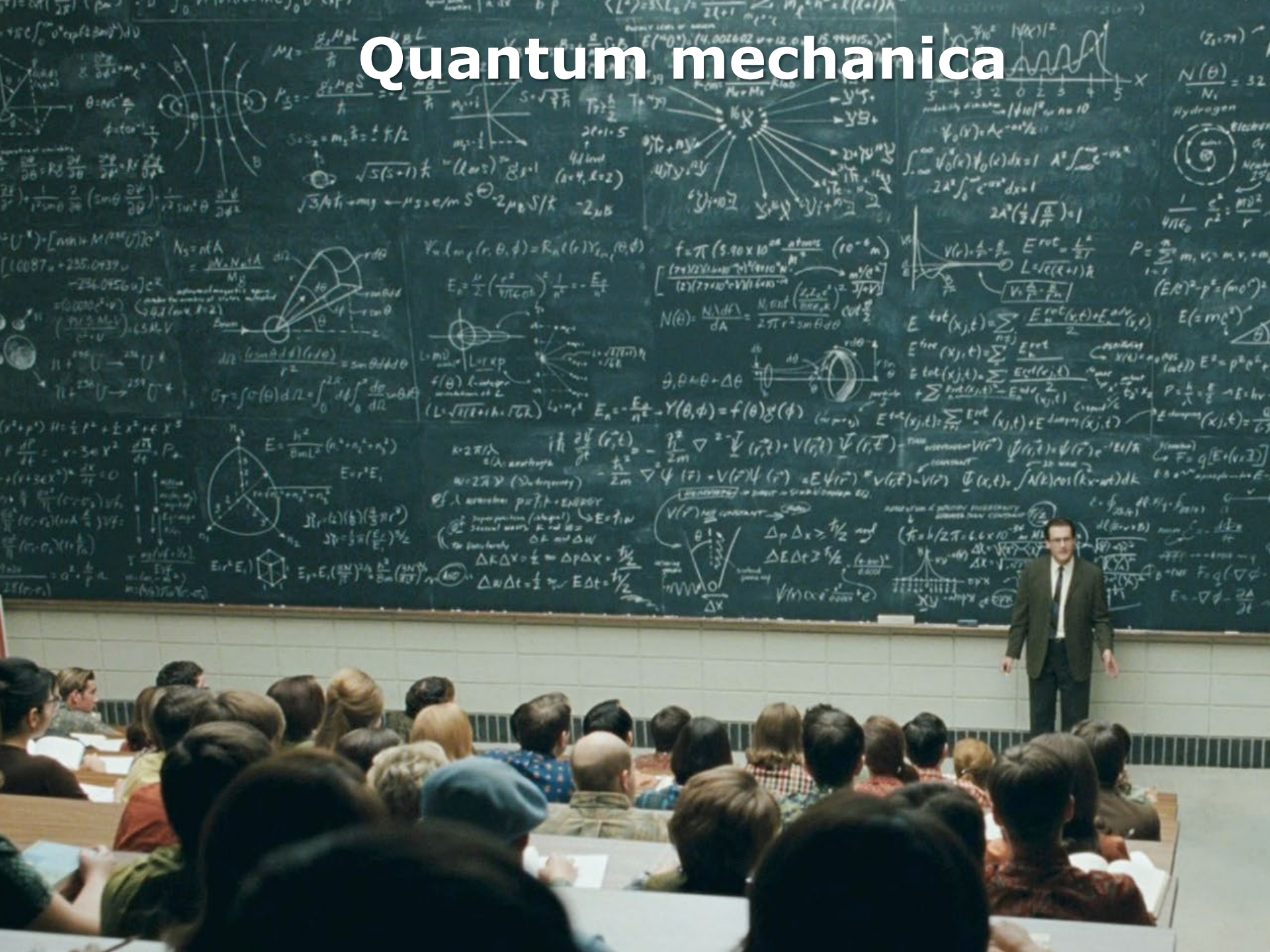
Woudschoten Chemie Conferentie 2022

C3

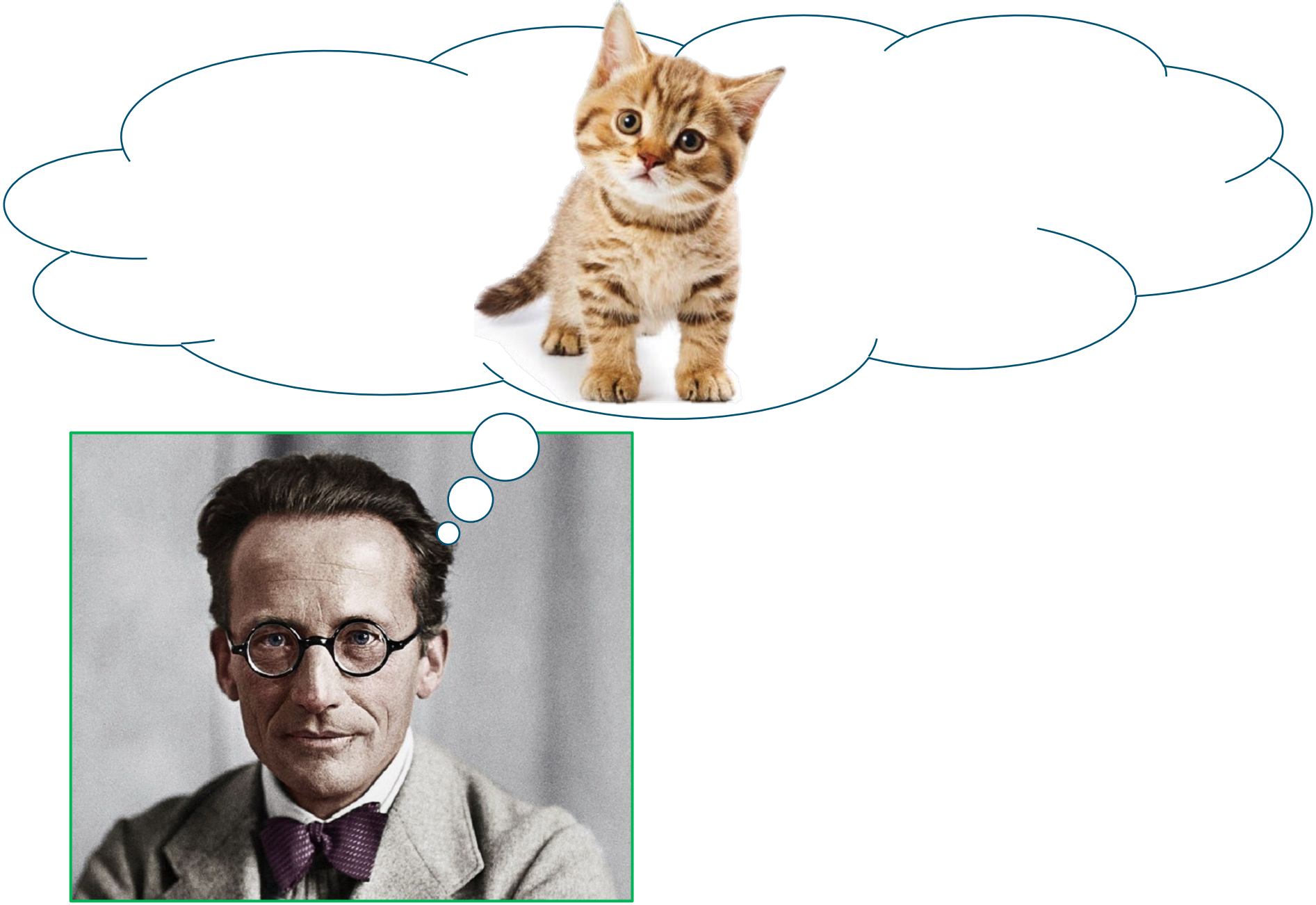
Hoe “jaagt” deze witte bloedcel op de bacterie?



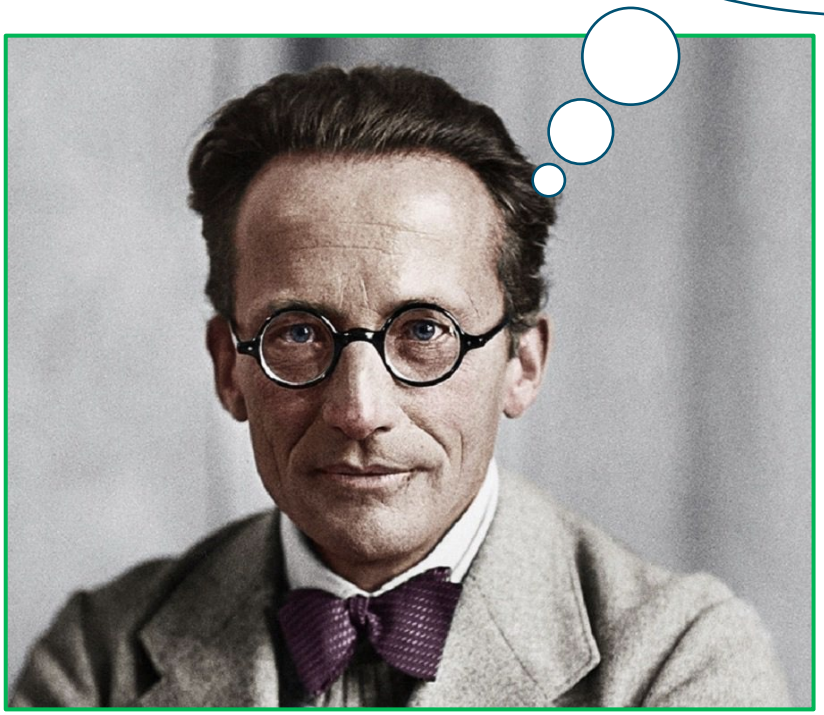
Quantum mechanica

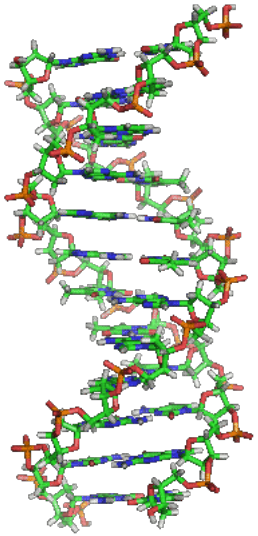


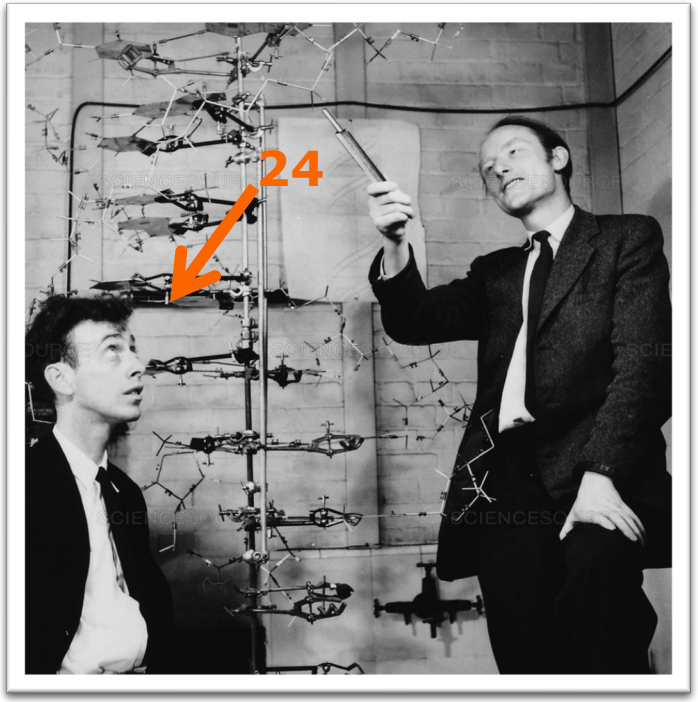
Erwin Schrödinger (1887 - 1961)



*"Alle gebeurtenissen in ruimte en tijd die zich afspelen binnenin een levend wezen kunnen verklaard worden door natuurkunde en **chemie!**"*







Erwin Schrödinger in zijn boek uit 1944 'Wat is Leven?'

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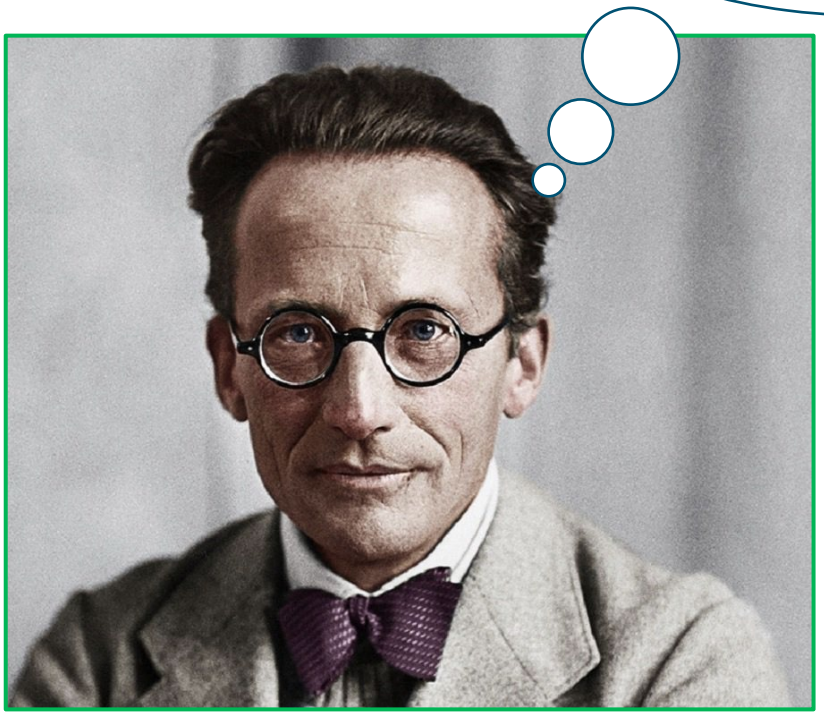

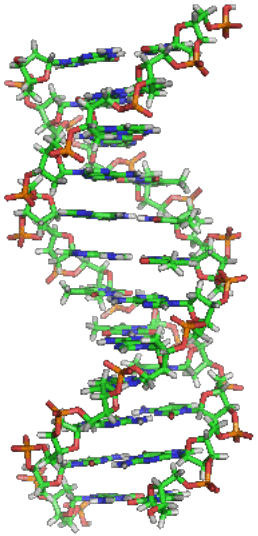

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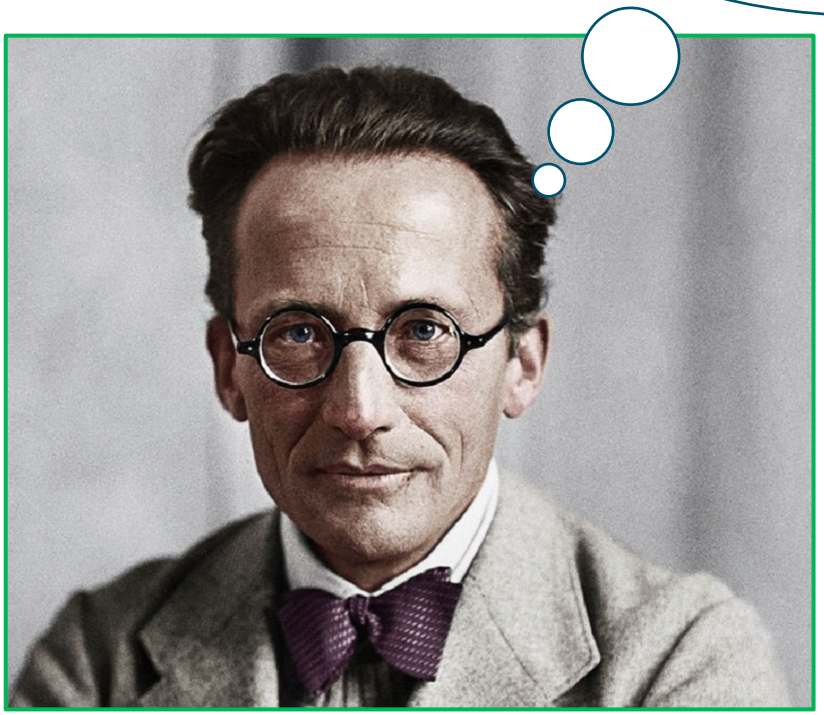
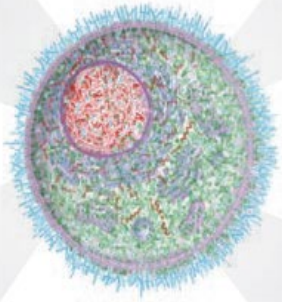


Alles in de natuur moet zich houden aan de regels van de chemie!

Chemische Biologie past de regels van de chemie toe op biologische systemen

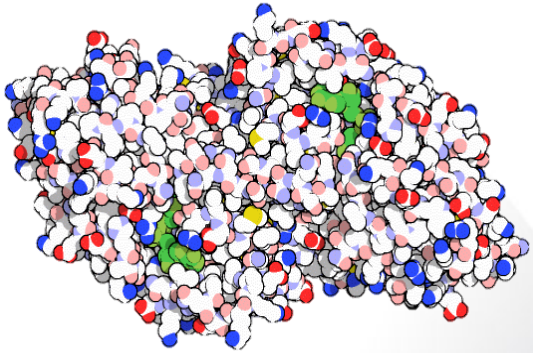
Erwin Schrödinger in zijn boek uit 1944 'Wat is Leven?'

vier essentiele bouwstenen van het leven

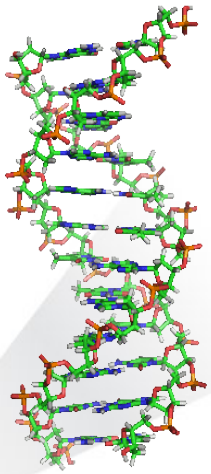


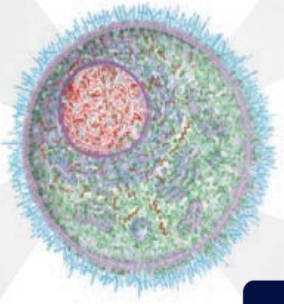
Biomoleculen

Eiwitten

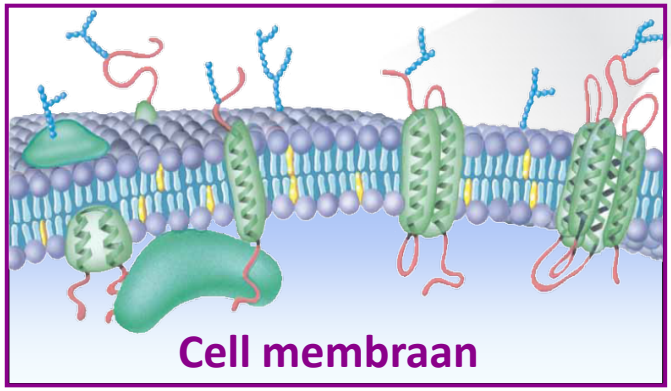


Nucleine zuren (DNA & RNA)

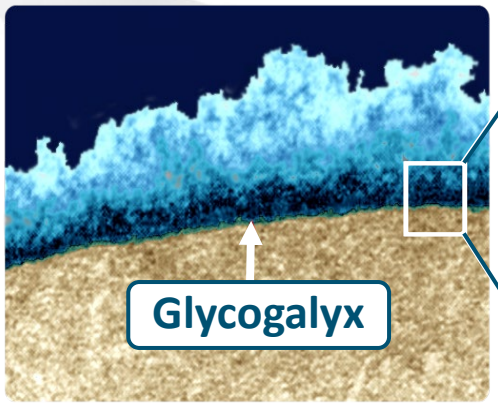


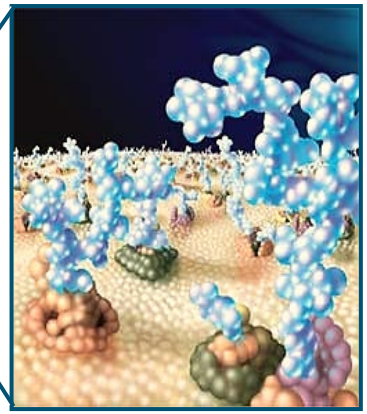


Lipiden



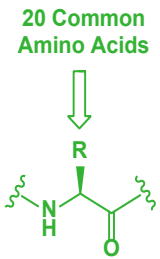
Koolhydraten (suikers)



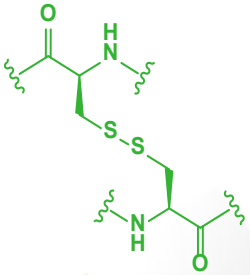


Biomoleculen

Eiwitten

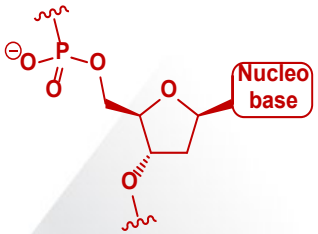


Proteins

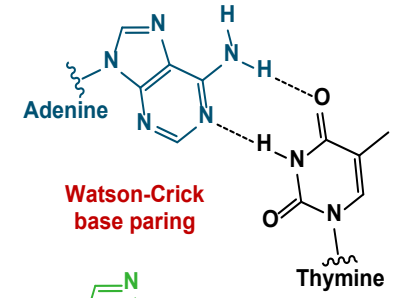


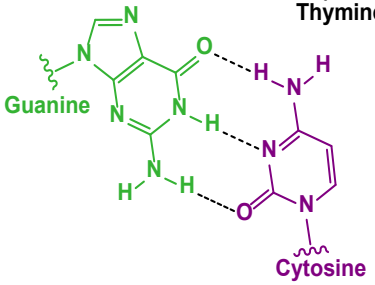
disulfide bond

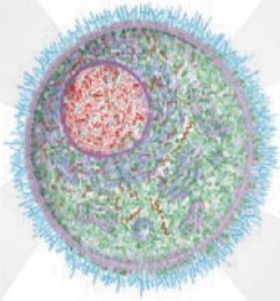
Nucleine zuren (DNA & RNA)



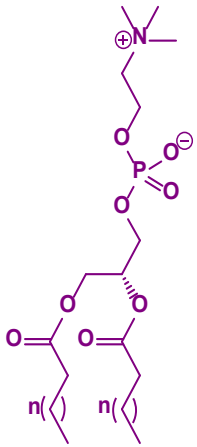
DeoxyriboNucleic Acid



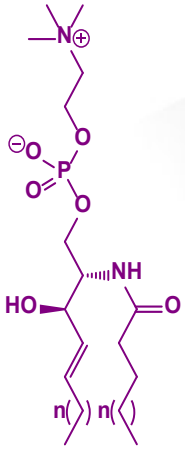




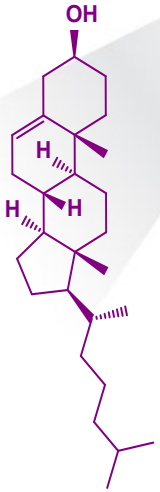
Lipiden



Phosphatidyl-
choline

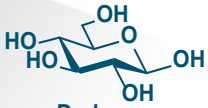


Sphingomyeline

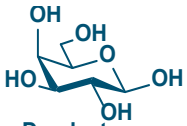


Cholesterol

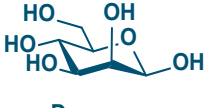
Koolhydraten (suikers)



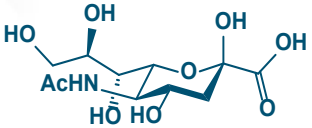
D-glucose



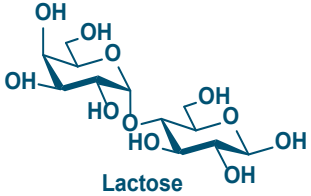
D-galactose



D-mannose



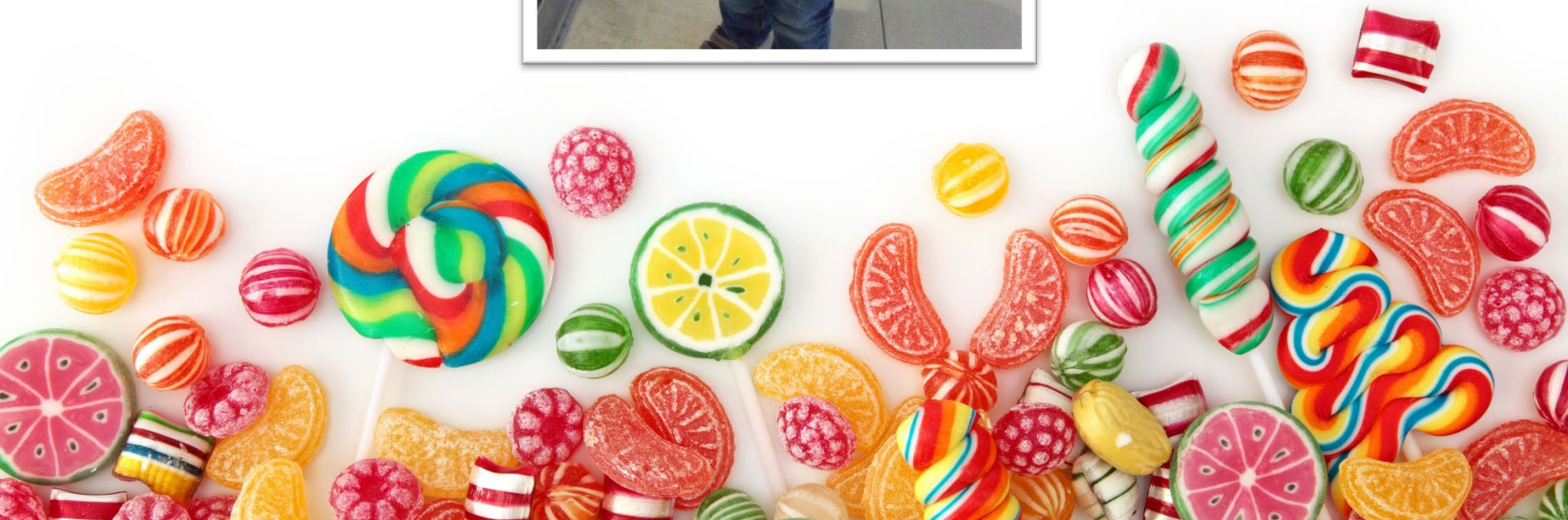
N-acetylneuraminic acid



Lactose

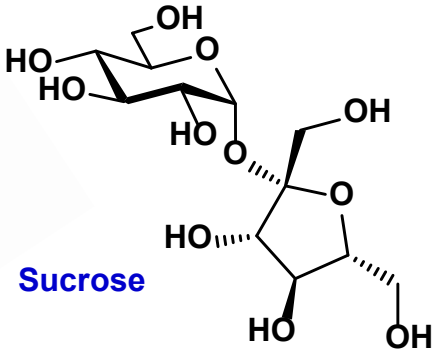
Mijn chemische geschiedenis

Tom Wennekes

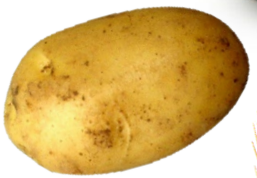


Percentage biomassa aarde = suikers?

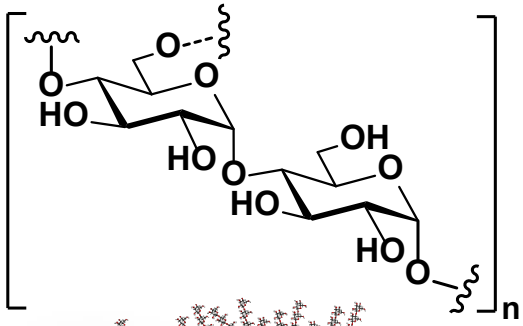
Suikers in je dagelijks leven…



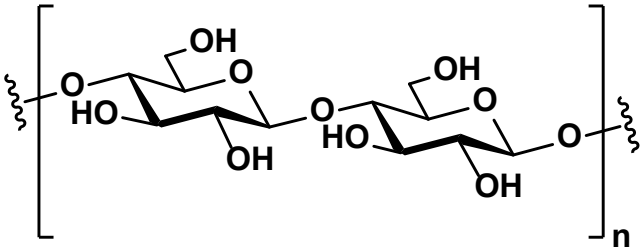
Sucrose



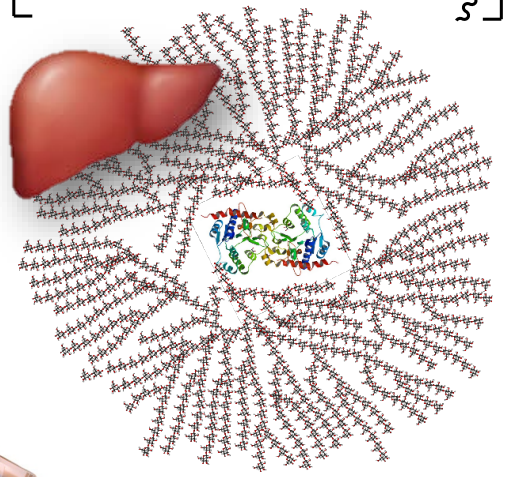
Zetmeel en Glycogeen

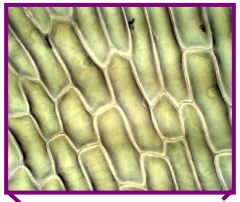


Cellulose

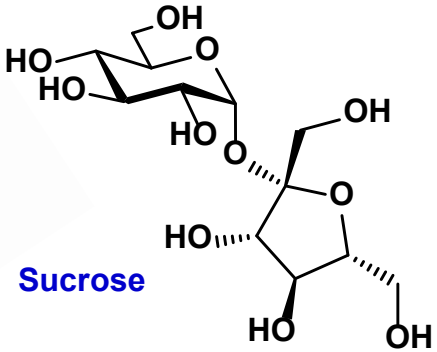


Energie & Structuur

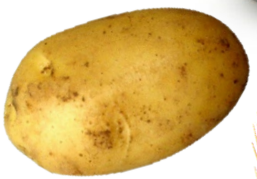




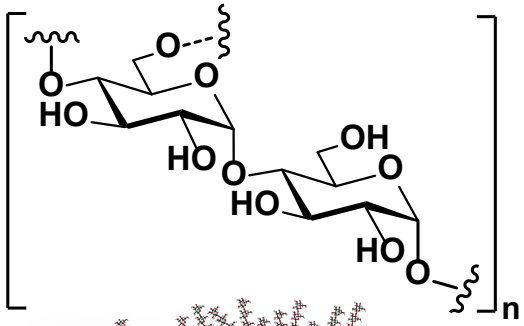
Suikers in je dagelijks leven…



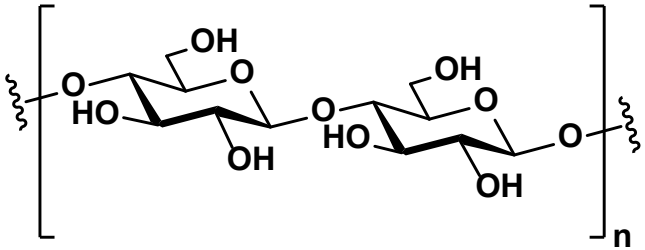
Sucrose



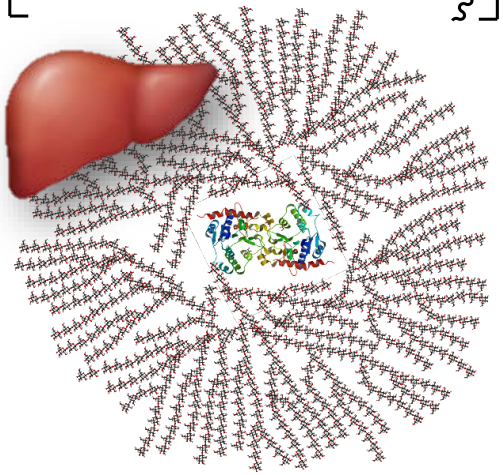
Zetmeel en Glycogeen

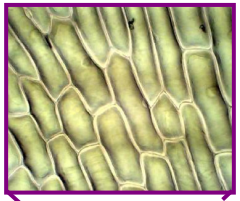


Cellulose

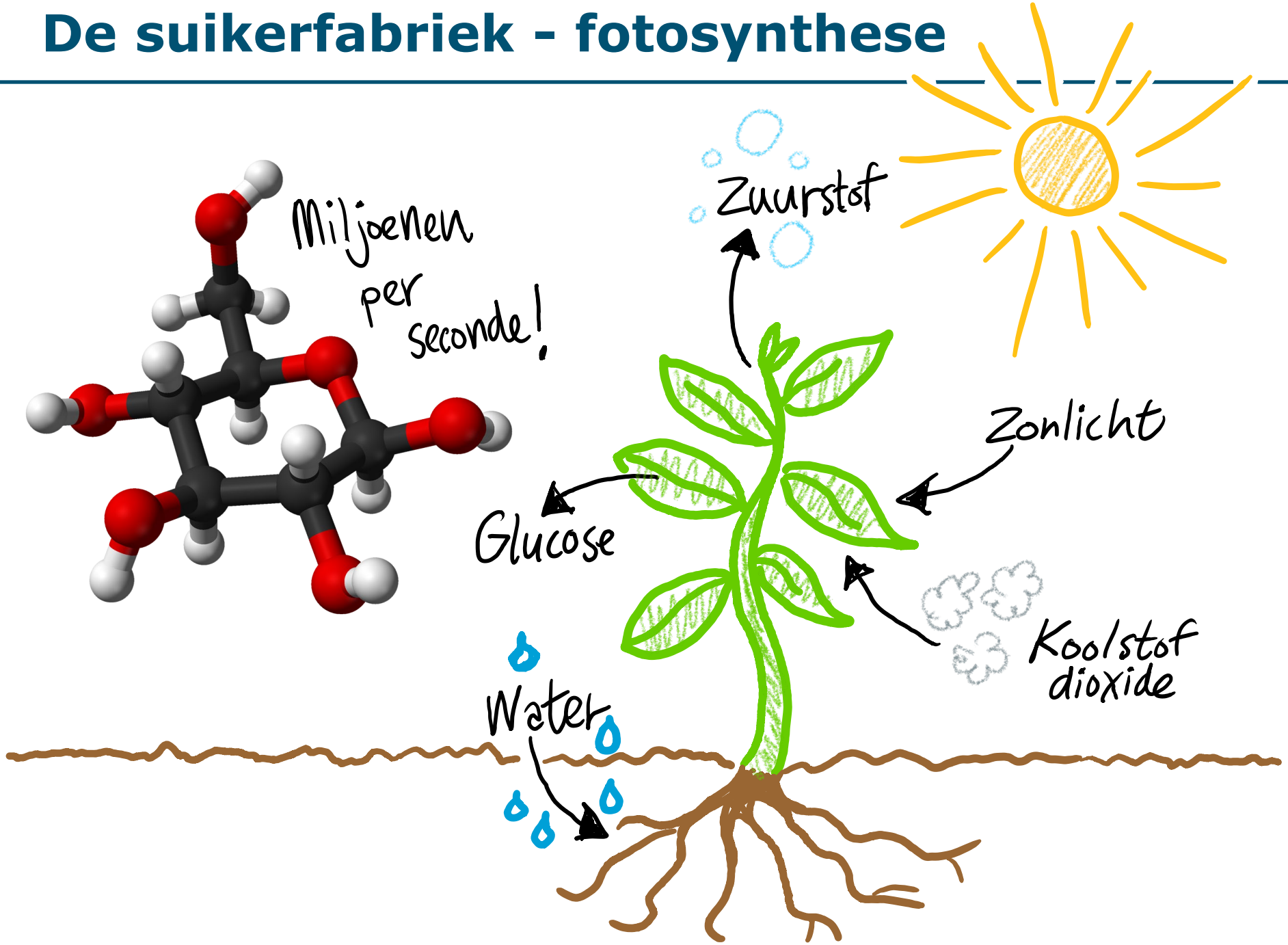


Energie & Structuur



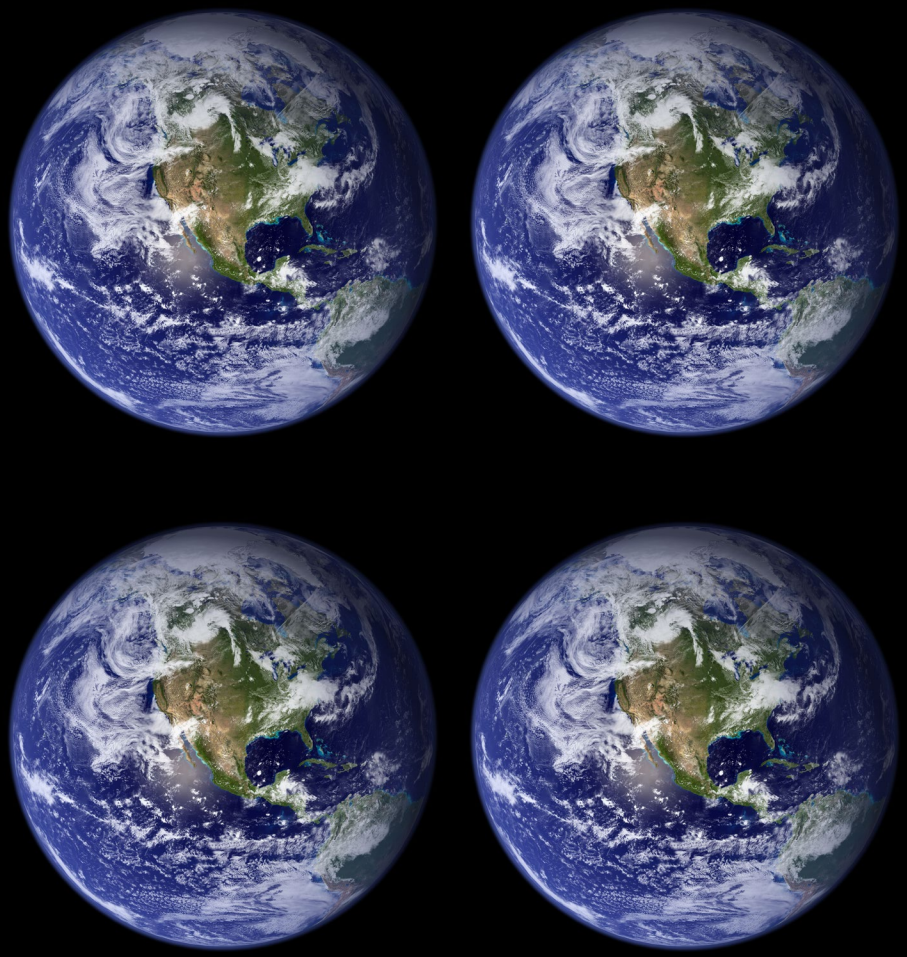


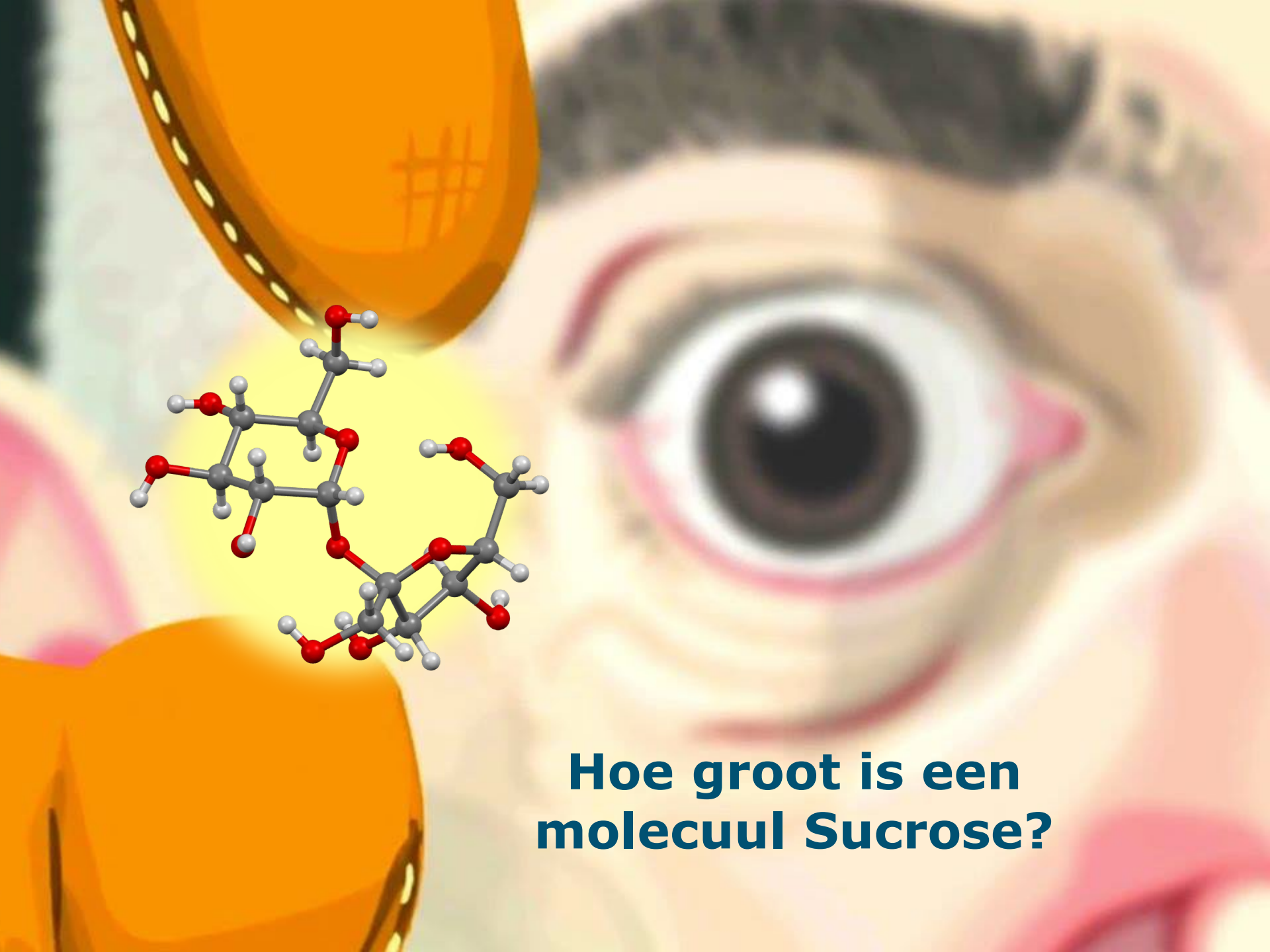
De suikerfabriek - fotosynthese



CO_2

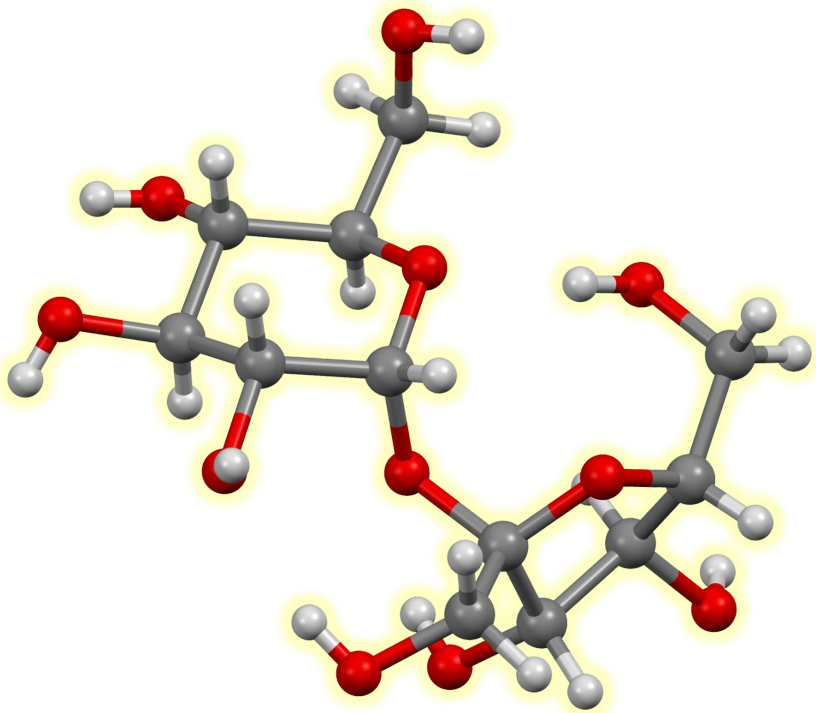
Before it's too late. wwf.org
WWF





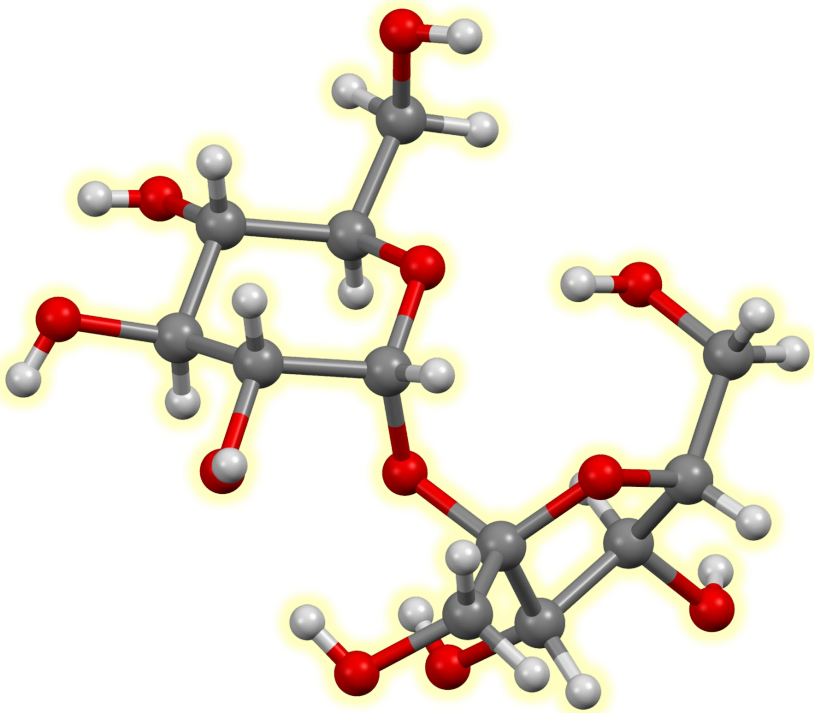
Hoe groot is een molecuul Sucrose?

Een Sucrose molecuul is erg klein! hoe klein?



Hoeveel keer kleiner dan een appel?

Een Sucrose molecuul is erg klein! hoe klein?

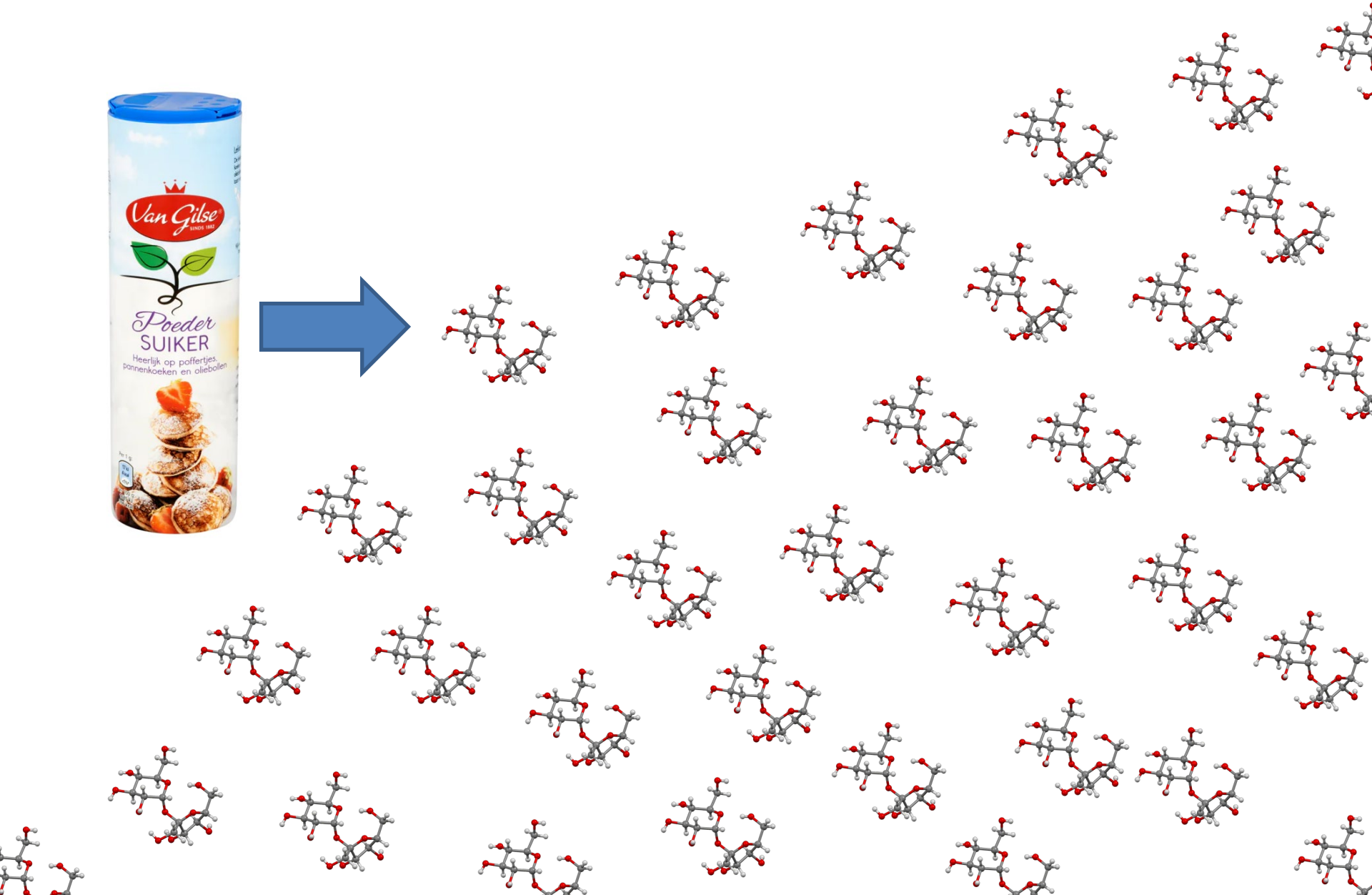


125 miljoen keer kleiner dan een appel

Als je een appel 125 miljoen keer vergroot?

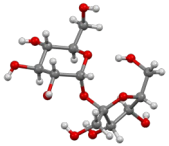
Dan wordt deze even groot als de aarde!

1 poeder suiker korrel ≈
hoeveel sucrose moleculen?

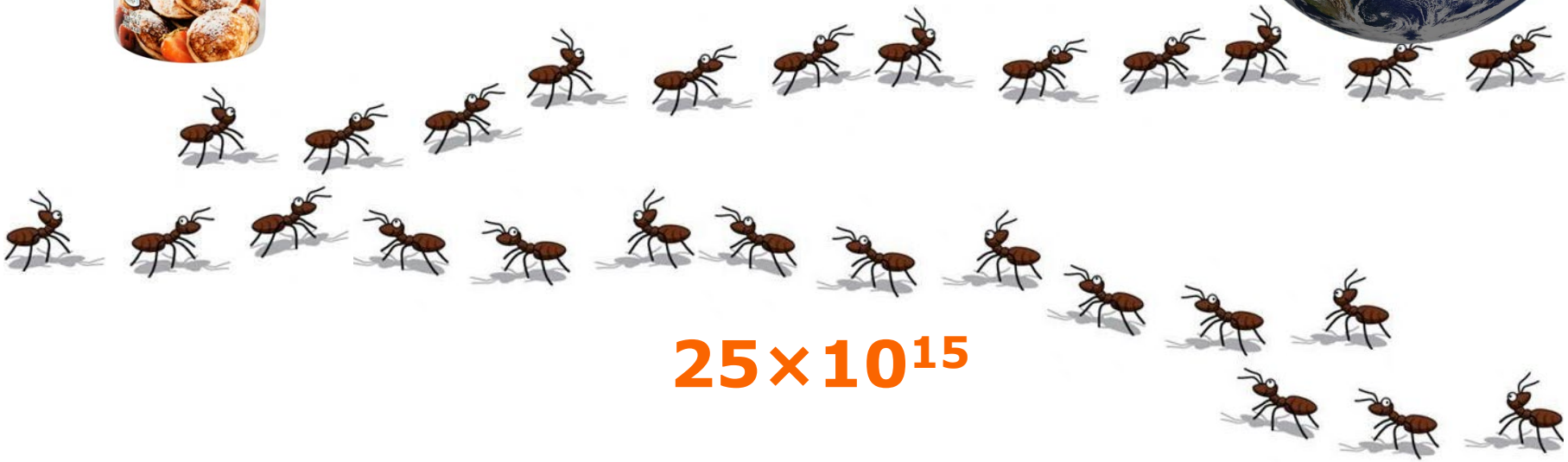


1 poeder suiker korrel ≈ 250000000000000000 Sucrose moleculen

250 biljard ≈ 10 x alle mieren op aarde



250×10^{15}



25×10^{15}

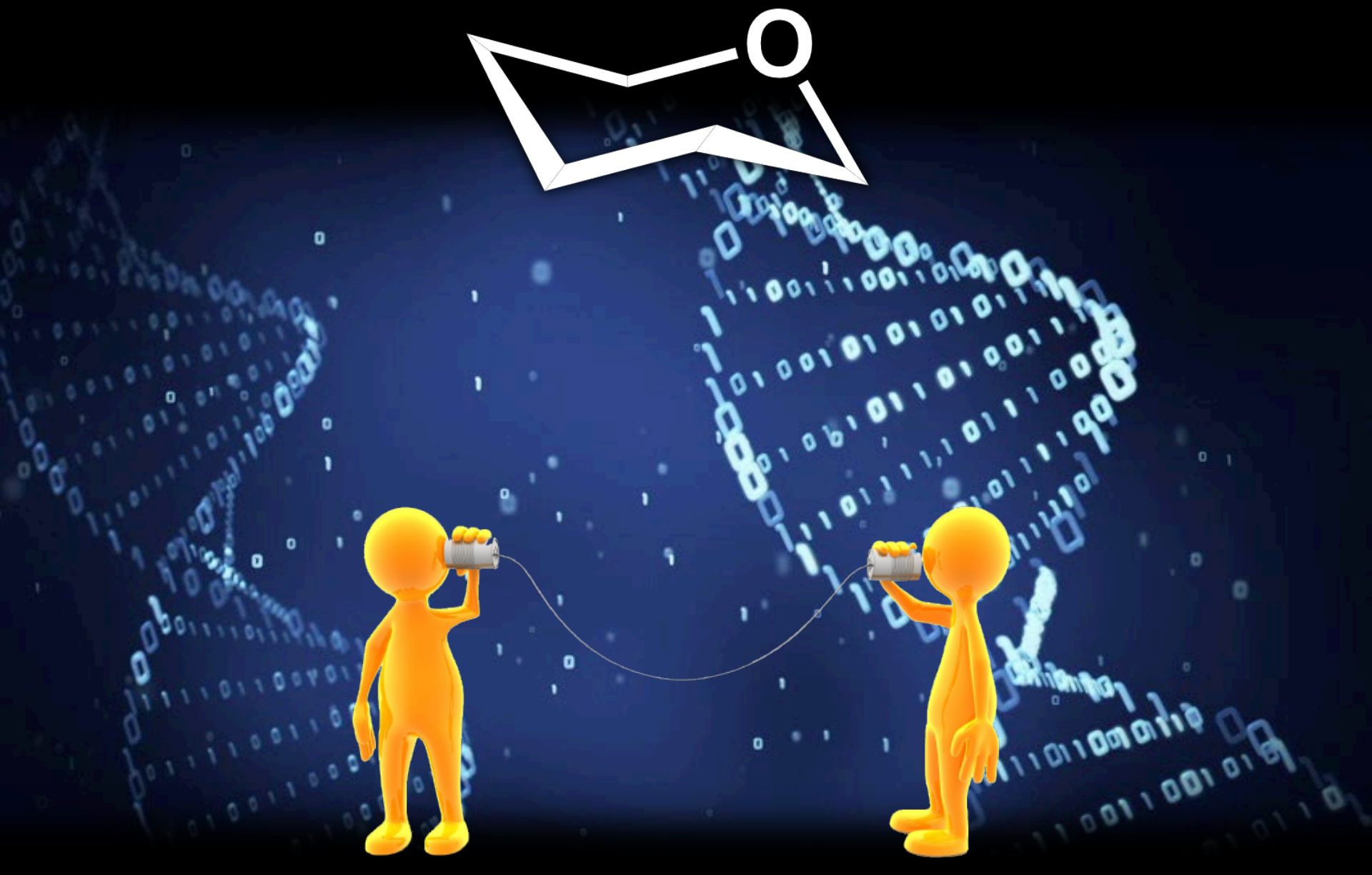
Suikers = Sachariden = Koolhydraten = Glycanen

kunnen ook “praten”

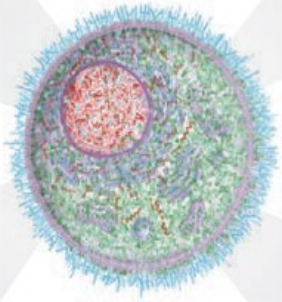
Opslag en overdracht van informatie

via een chemische structuur

Een suikercode



vier essentiele bouwstenen van het leven



Hoe zou je aan iemand op straat omschrijven hoe een cel eruitziet?

Cellen in biologie boeken zijn te kaal!

Alle cellen op aarde hebben
een uniek suiker laagje

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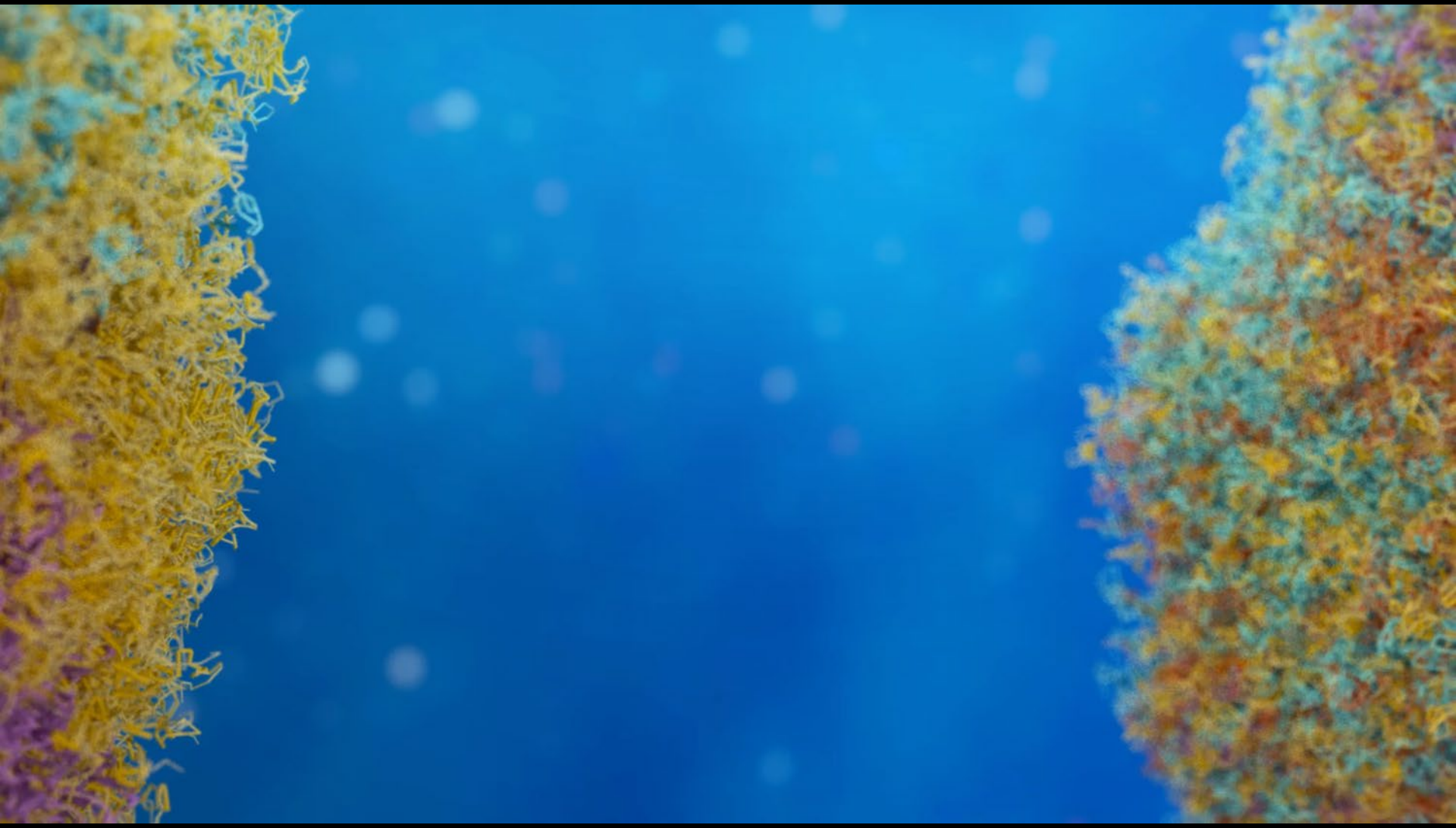
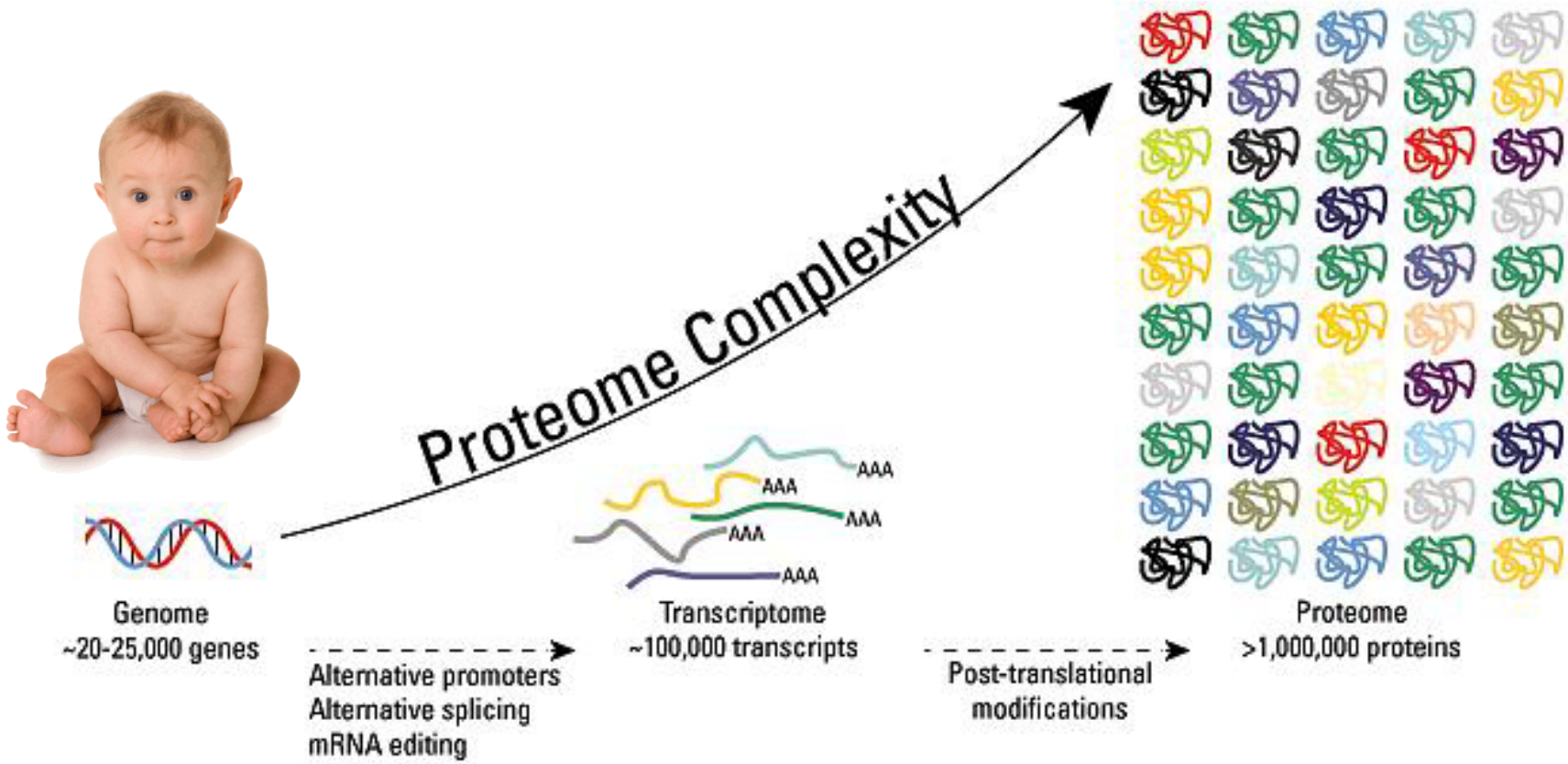
Een suikercode op de cel



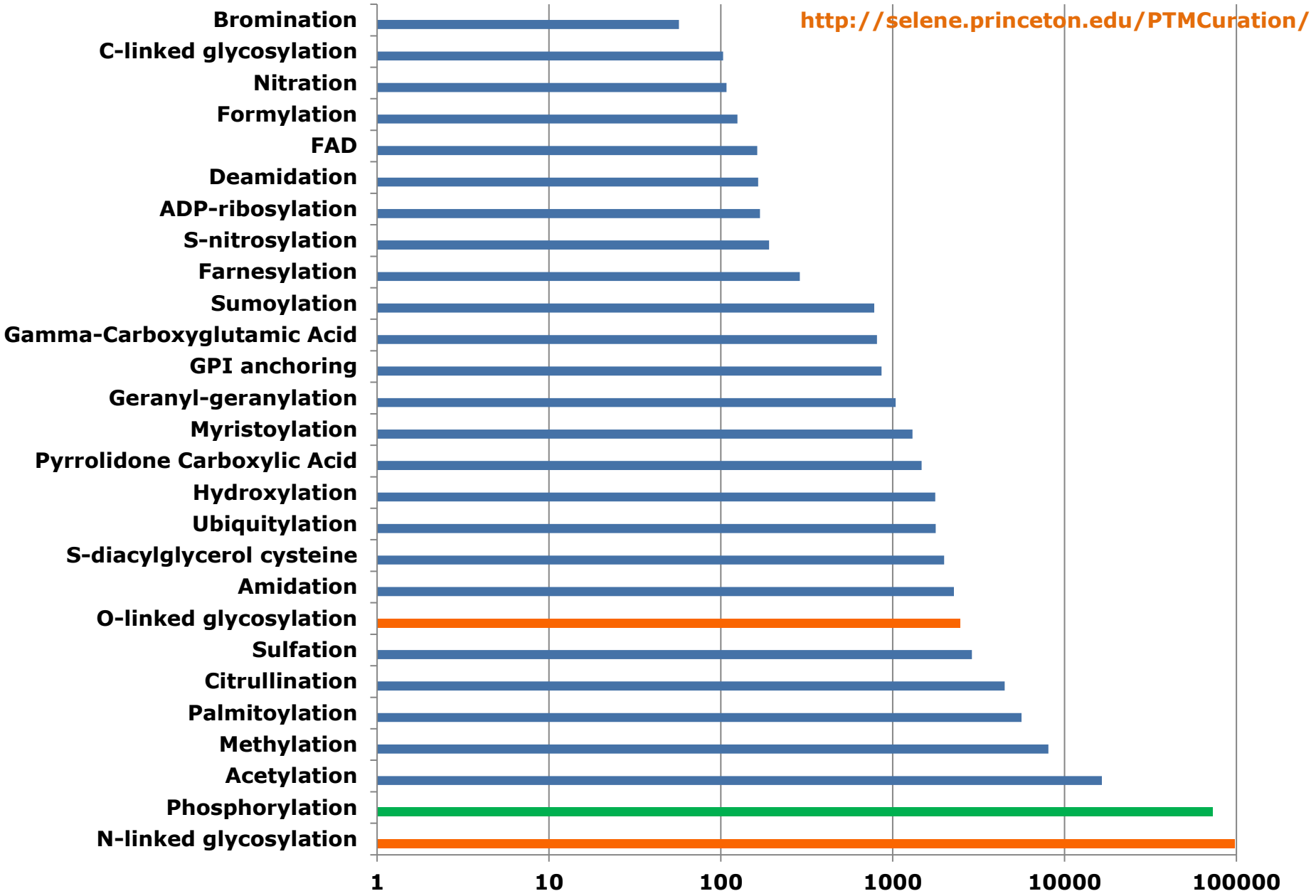
Waar zitten die suikers dan aan vast op de cel?

Welke heeft meer unieke onderdelen in het bouwplan?

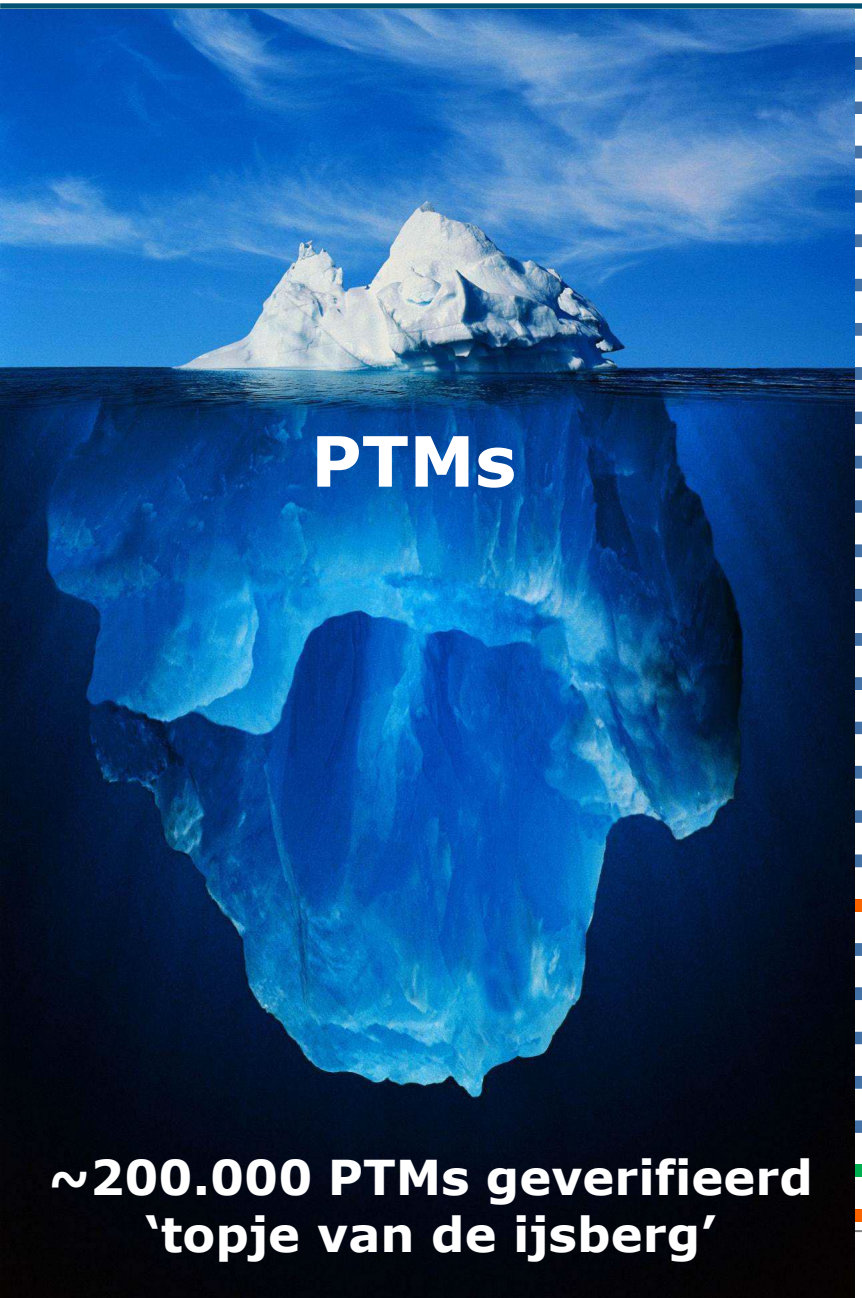
Post-translationele modificatie eiwitten

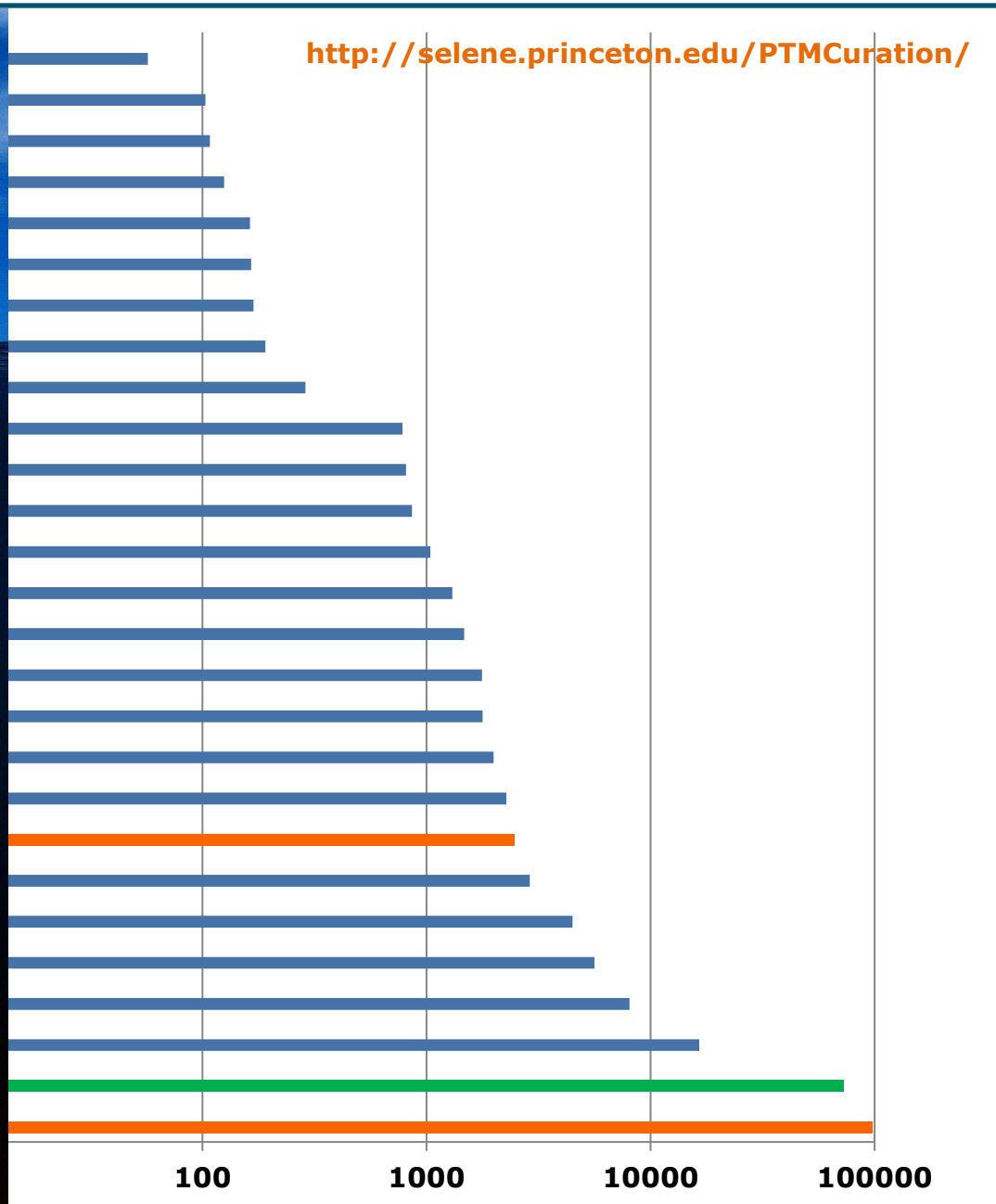


Post-translationele modificatie eiwitten

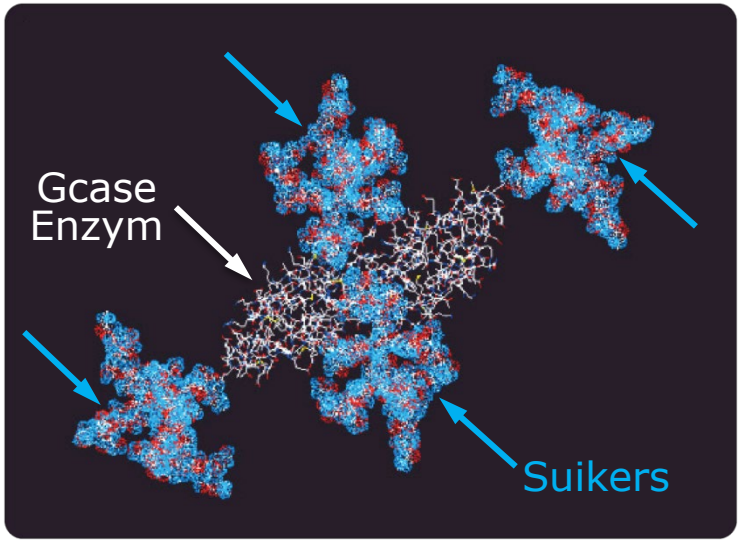


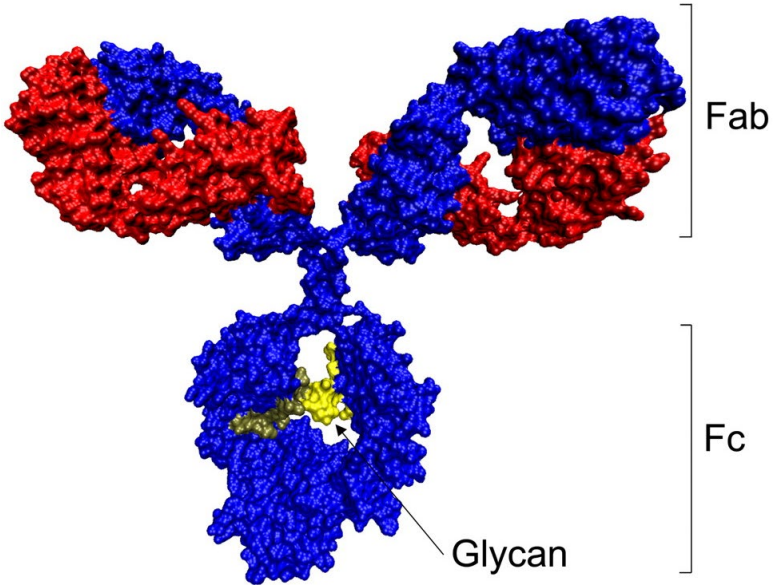
Post-translationele modificatie eiwitten





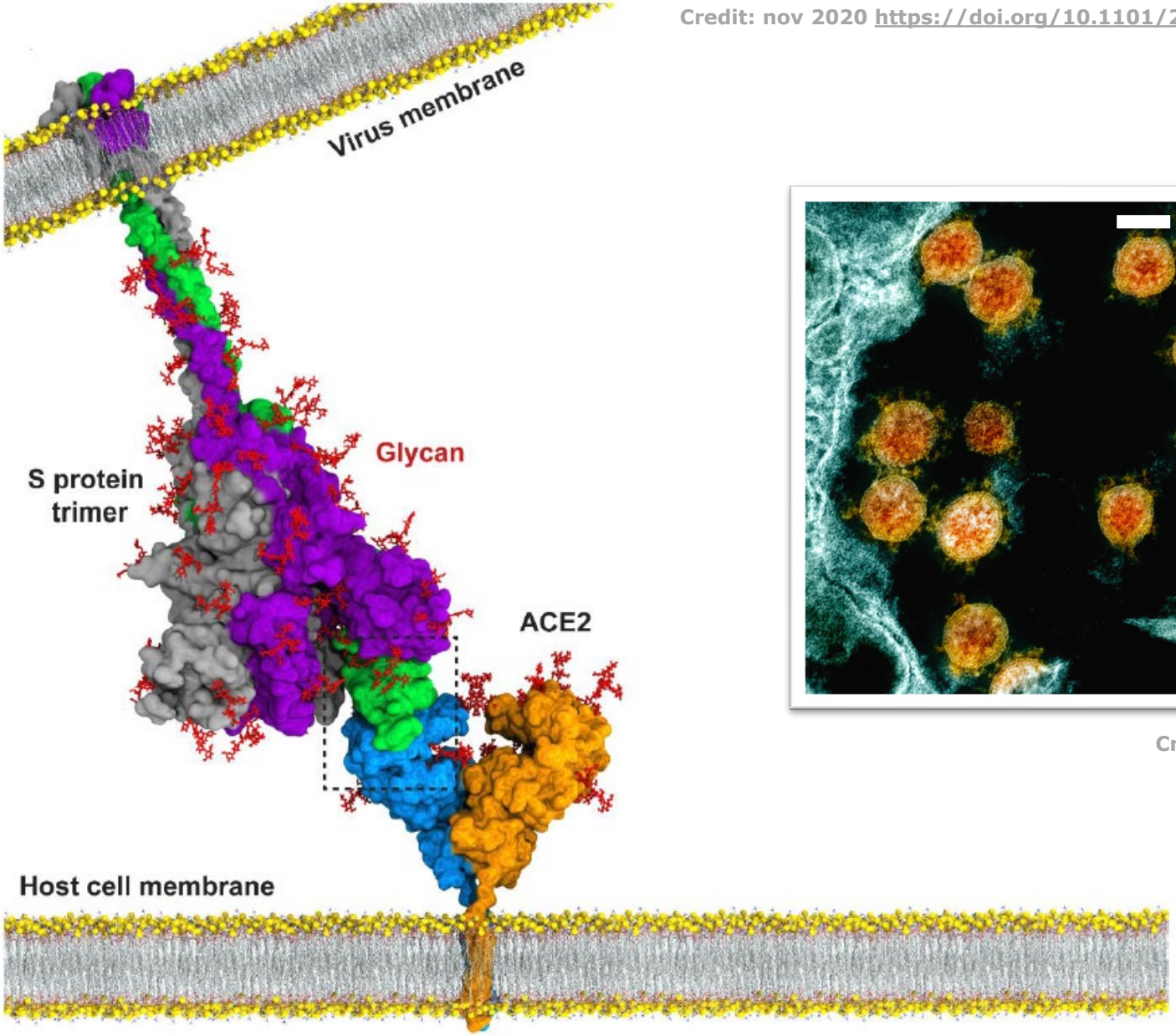
Suiker PTMs zijn vaak groot & complex

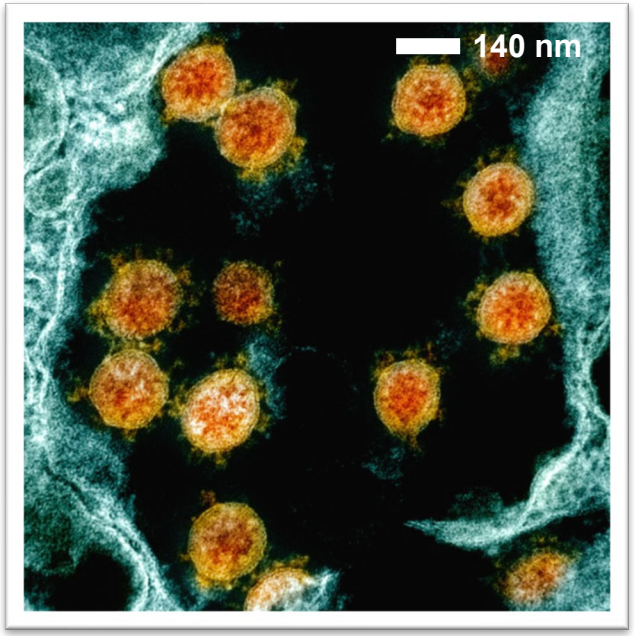




Het coronavirus is ook bedekt met suikers: belangrijk?

Credit: nov 2020 https://doi.org/10.1101/2020.09.21.305490



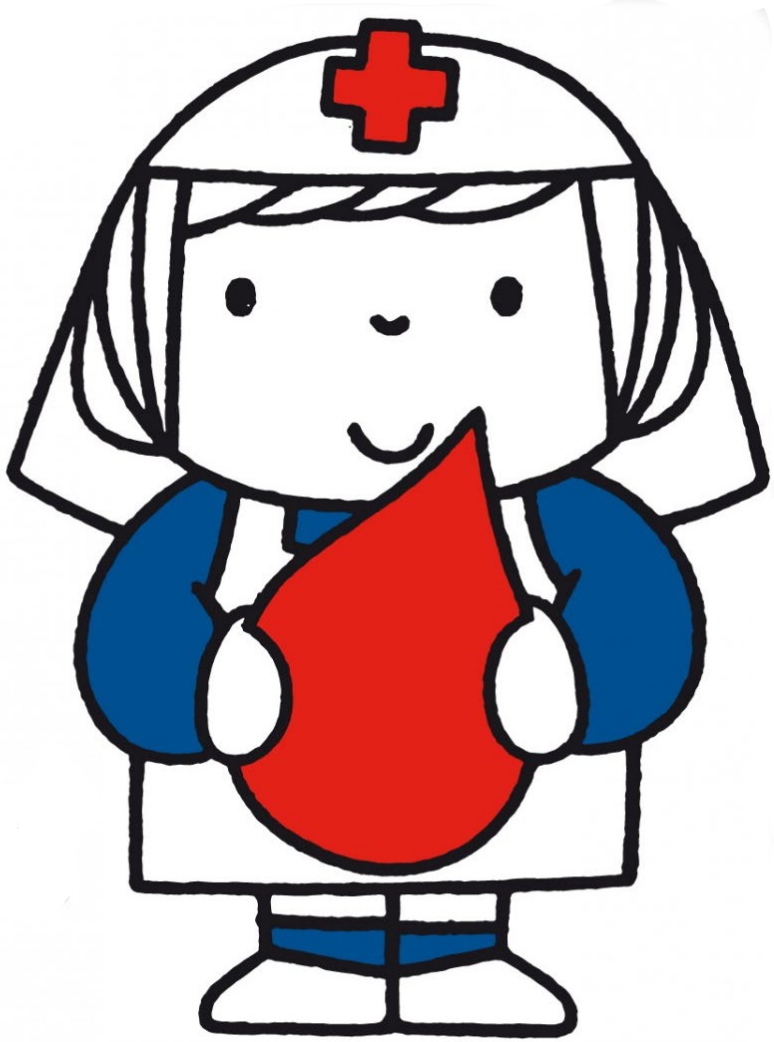


Credit: NIAID

Onze cellen ontmoeten & groeten

elkaar via een suikercode

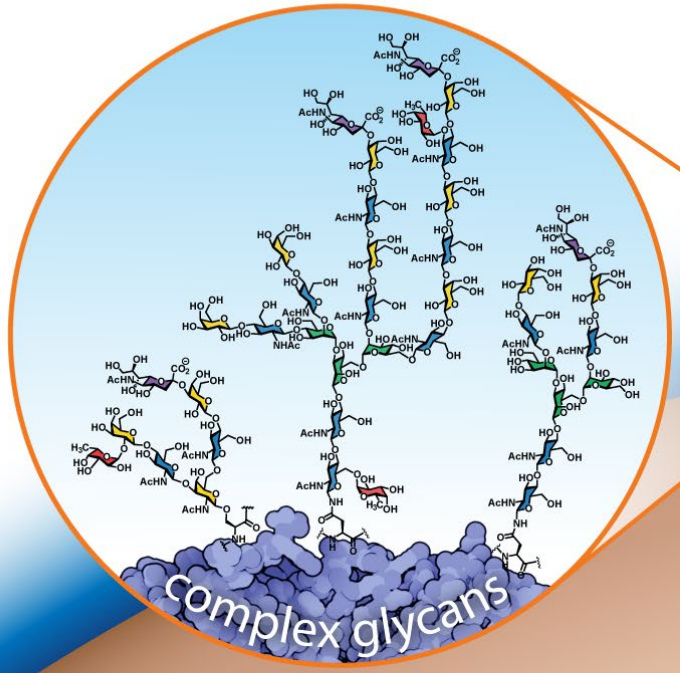
Wat is je bloedtype?

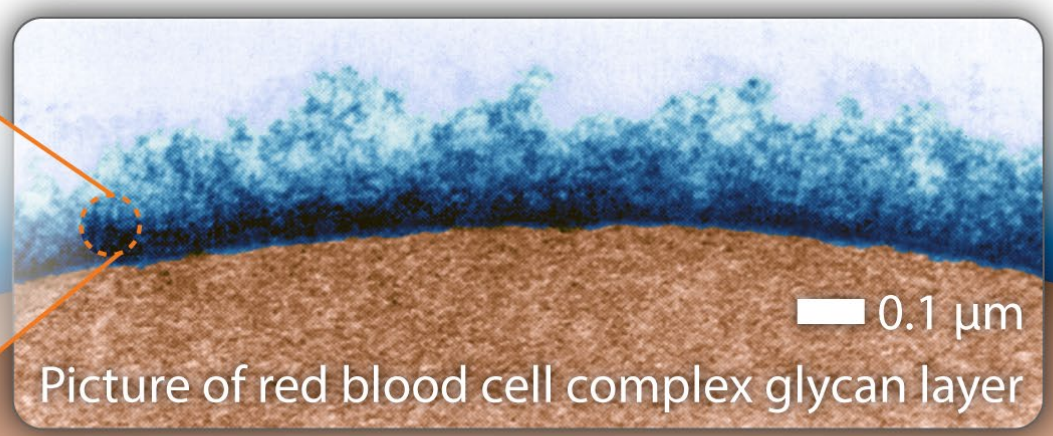


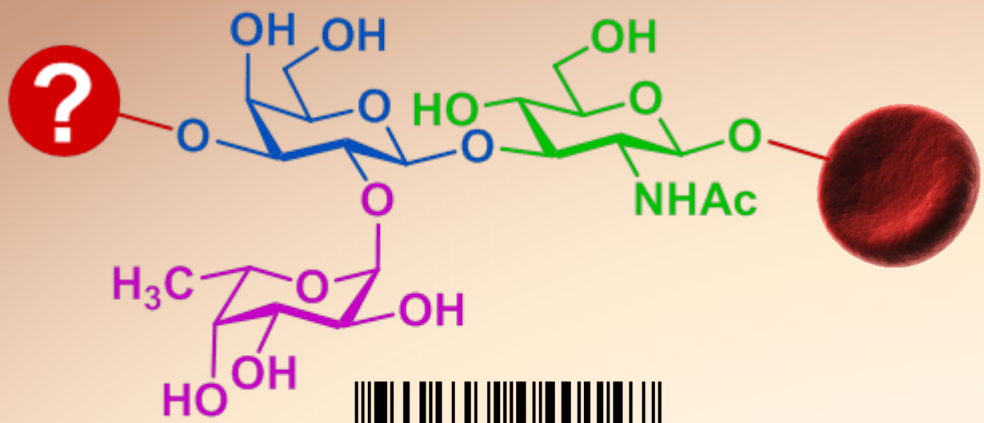
je bloed type is een suikercode

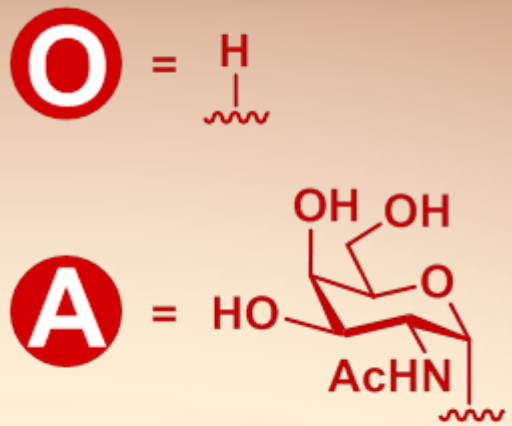
je bloed type is een suikercode

je bloed type is een suikercode









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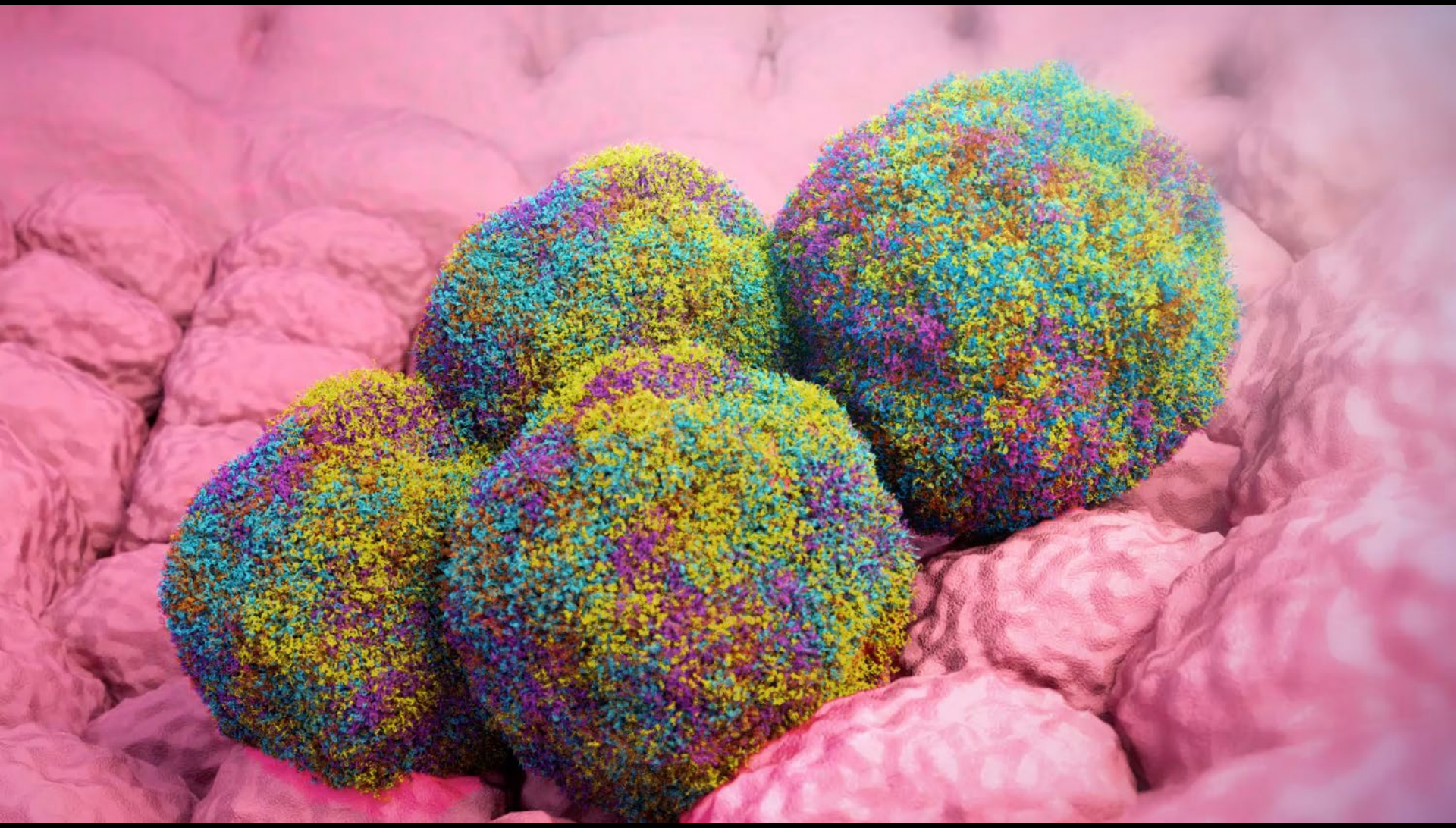
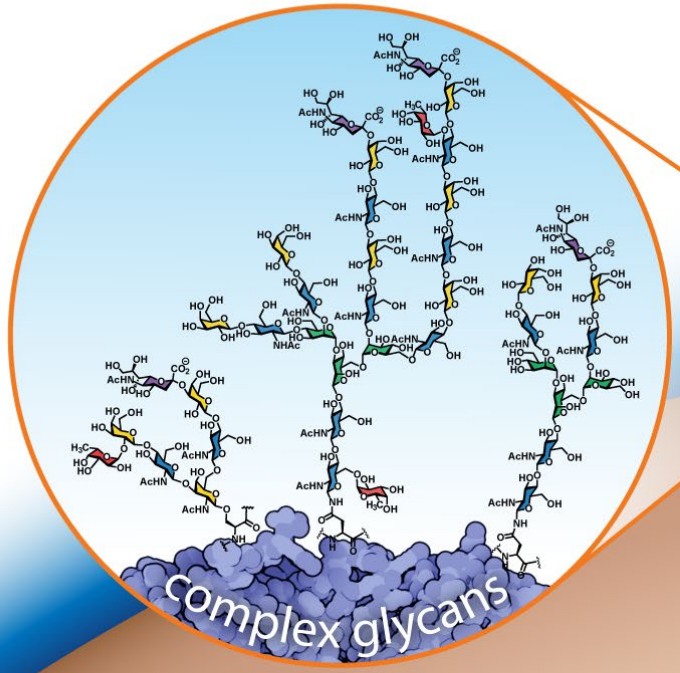
Kanker ontsnapt via de suikercode

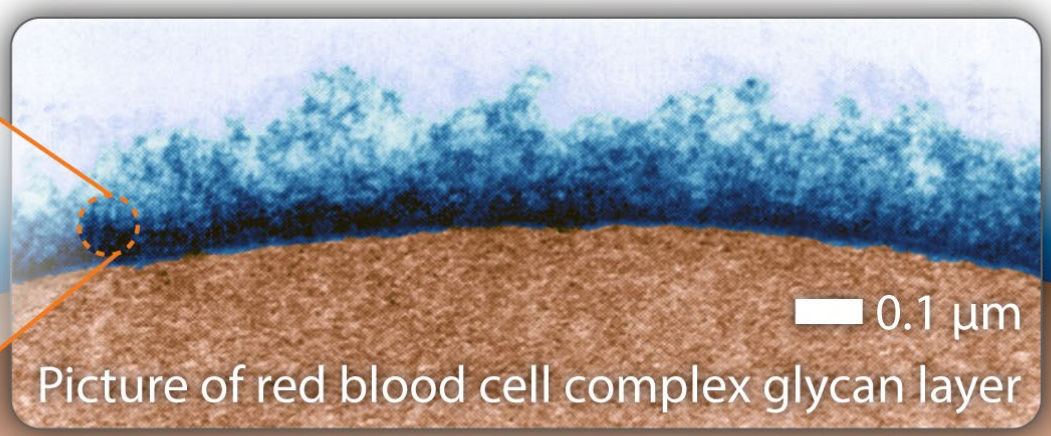


Onze cellen ontmoeten & groeten

elkaar via een suikercode

Waarom belangrijk? Cruciale suiker inzichten





- Alle cellen op aarde hebben een complexe laag suikers
- Genetisch elimineren van welke soort suiker dan ook is dodelijk
- Rol in de meeste interacties tussen ziekteverwekkers en ons
- Bij vrijwel elke ziekte in de mens spelen suikers een rol
- Afwijkende suiker codes zijn universeel in kanker
- Biofarmaceutische geneesmiddelen werken alleen met suikers erop

Onze cellen ontmoeten & groeten

elkaar via een suikercode

Studie van suikers is uitdagend

“De donkere materie van het biologisch universum”

Studie van suikers is uitdagend

⇒ **Structuur is niet linear en complex**

⇒ **Suikercodes niet genetisch vastgelegd**

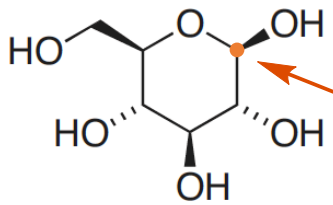
Studie van suikers is uitdagend

Aantal theoretisch mogelijke oligomeren		
Oligomeer groote	DNA	Aminozuren
1	4	20
2	16	400
3	64	8.000
4	256	160.000
5	1024	3.200.000
6	4.096	64.000.000

⇒ Structuur is niet linear en complex

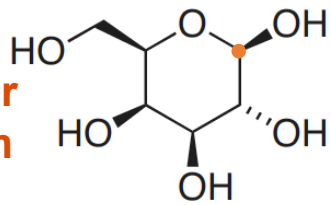
⇒ Suikercodes niet genetisch vastgelegd

Bouwstenen: 10 soorten essentiële suikers

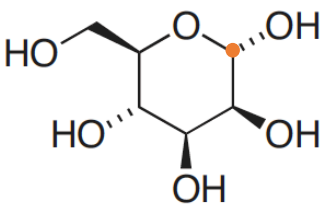


anomeer centrum

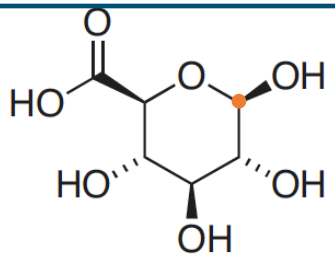
β-D-glucose
(Glc)



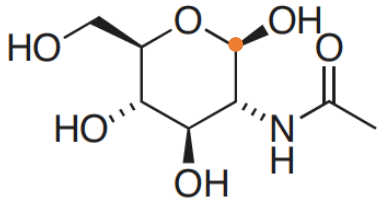
β-D-galactose
(Gal)



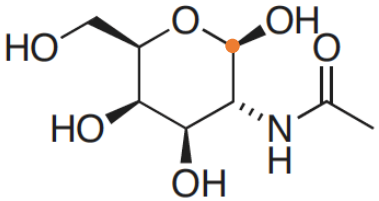
α-D-mannose
(Man)



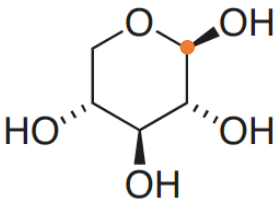
β-D-glucuronic acid
(GlcA)



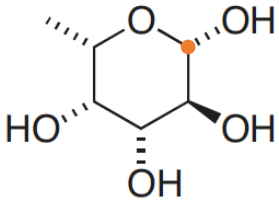
β-*N*-acetyl-D-glucosamine
(GlcNAc)



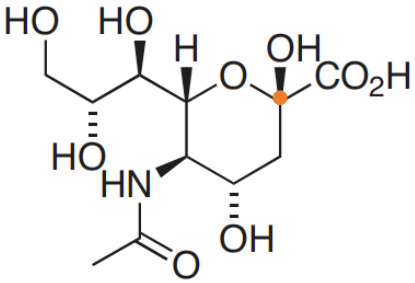
β-*N*-acetyl-D-galactosamine
(GalNAc)



β-D-xylose
(Xyl)

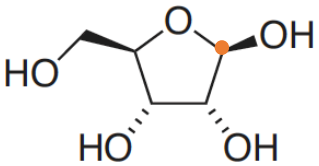


β-L-fucose
(Fuc)



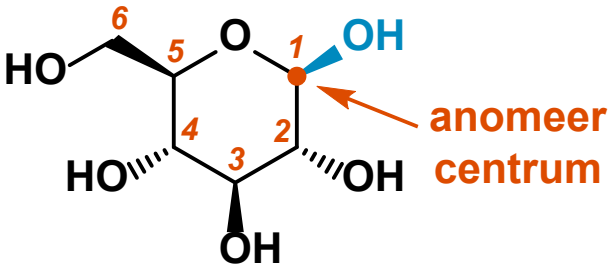
β-*N*-acetyl-D-neuraminic acid
(Neu5Ac)

Suikers met een hexagon-ring hebben een stoel conformatie

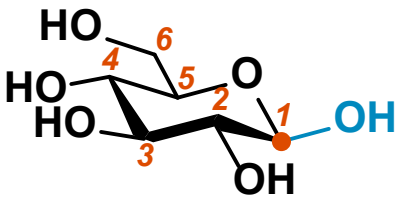


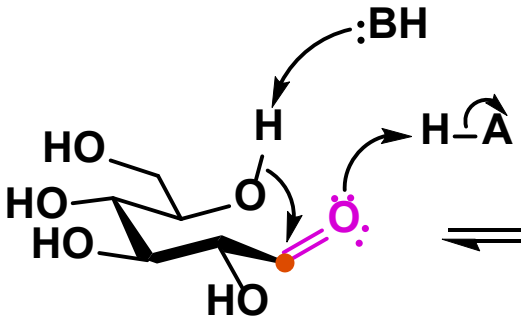
β-D-ribose
(Rib)

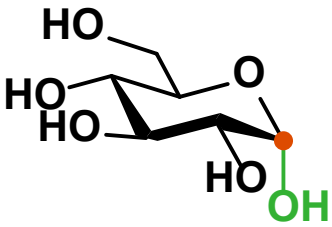
Bouwstenen: 10 soorten essentiële suikers x2



de twee anomeren van D-glucose



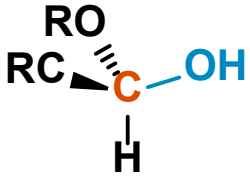




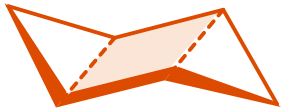
β-anomeer (37%)
hemiacetaal (sp^3)

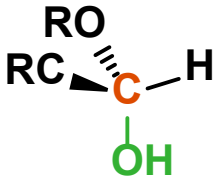
open keten (<<1%)
aldehyde (sp^2)

α-anomeer (63%)
hemiacetaal (sp^3)



R-chiraal centrum





S-chiraal centrum

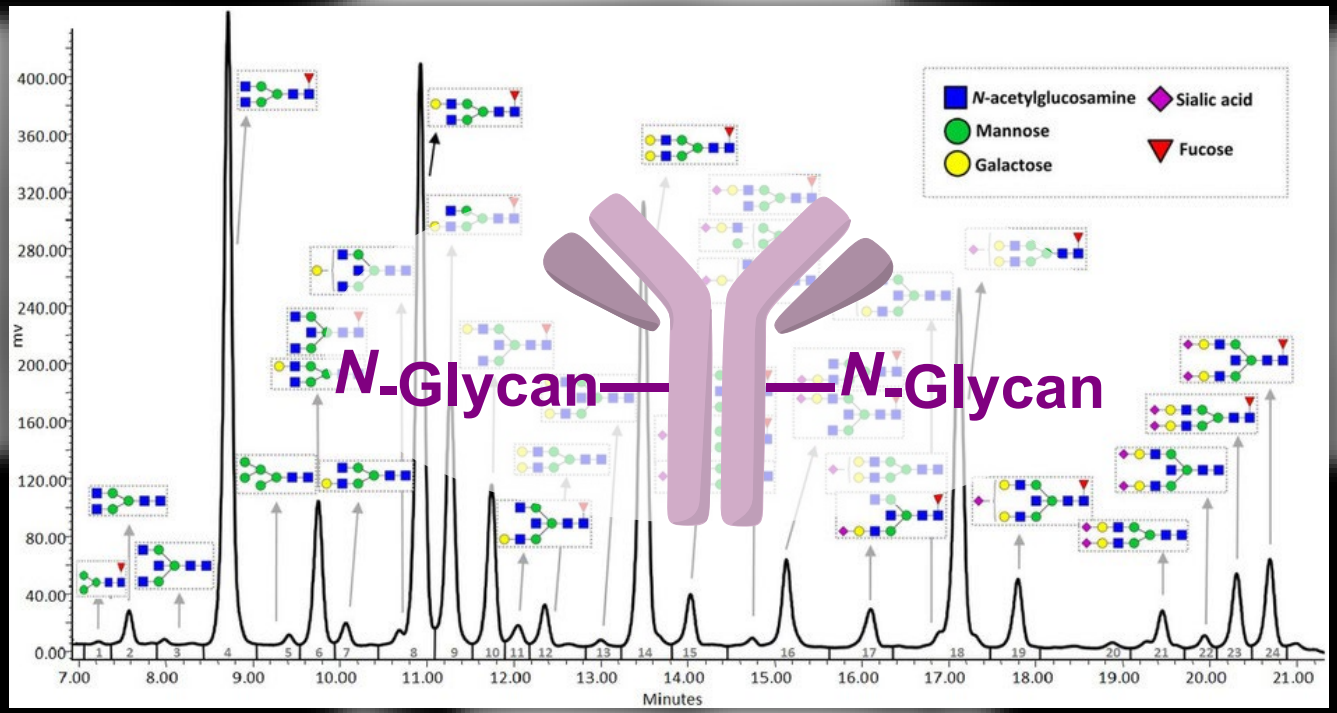
Studie van suikers is uitdagend

Aantal theoretisch mogelijke oligomeren			
Oligomeer groote	DNA	Aminozuren	Suikers
1	4	20	20
2	16	400	1360
3	64	8.000	126.080
4	256	160.000	13.495.040
5	1024	3.200.000	1.569.745.920
6	4.096	64.000.000	192.780.943.360

⇒ **Structuur is niet linear en complex**

⇒ **Suikercodes niet genetisch vastgelegd**

Studie van suikers is uitdagend



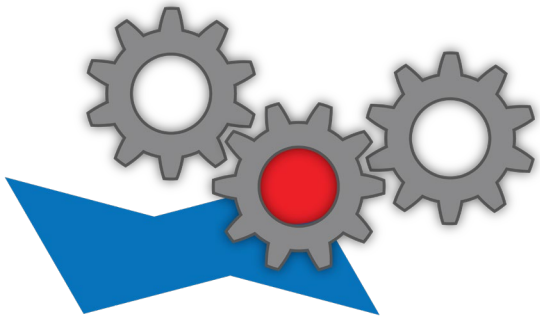
⇒ **Structuur is niet linear en complex**

⇒ **Suikercodes niet genetisch vastgelegd**

Hoe bestuderen? Chemische Biologie

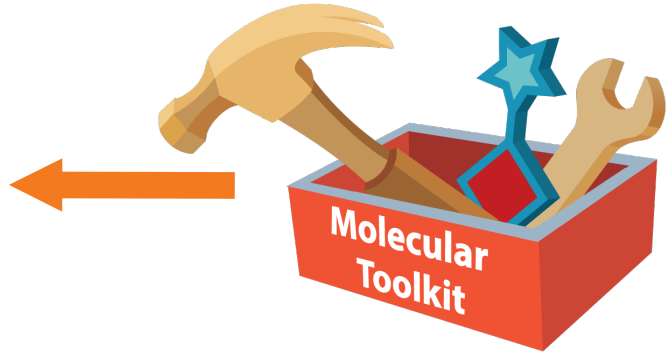
Biologisch probleem:

Gezondheid & Ziekte



Rol van suikercode op moleculair niveau

Chemische aanpak:

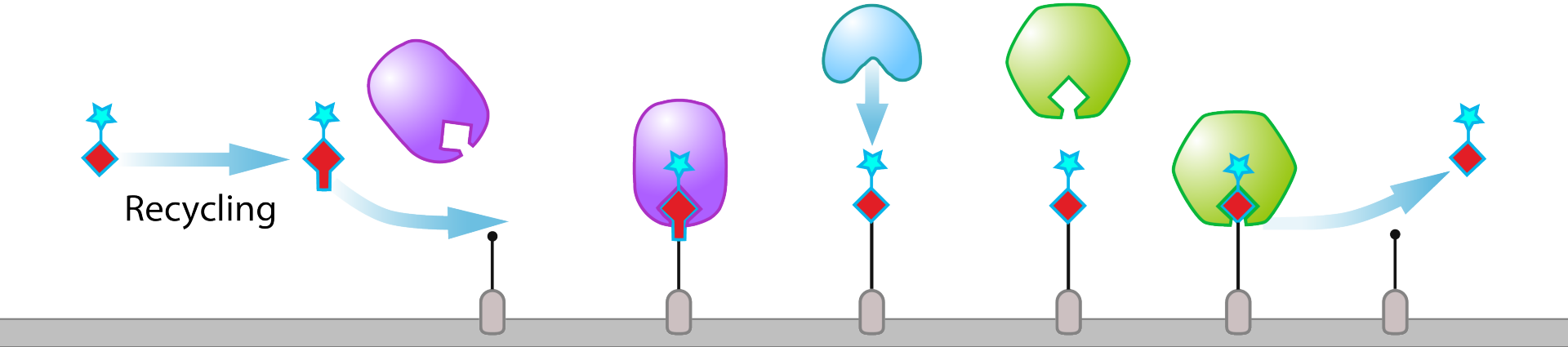


Op maat gemaakt moleculair gereedschap

Productie door
suiker schrijver:
glycosyltransferase

Herkenning door
suiker lezer:
lectine & antilichaam

Afbraak door
suiker wisser:
glycosidase



Onze cellen ontmoeten & groeten

elkaar via een suikercode

Veel ziekteverwekkers misbruiken

de suikercode op onze cellen

Is suiker altijd zoet?

Inhoud van mijn lezing:

- **Introducties:** chemische biologie → mij → suikers
- **Onderzoek:** slimmer zijn dan het griep virus
- **Onderzoek:** de perfecte omhelsing van Cholera
- **In het nieuws:** Klik chemie is gaaf!
- **Echt gebeurd:** Zoet biomoleculair moord mysterie
- Chemie op de basisschool?

Utrecht University

Tom Wennekes

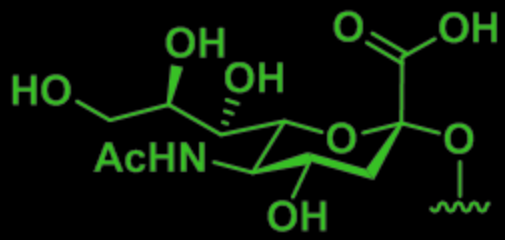
Imagination at work

Woudschoten Chemie Conferentie 2022

C3

Slimmer zijn dan het griep virus

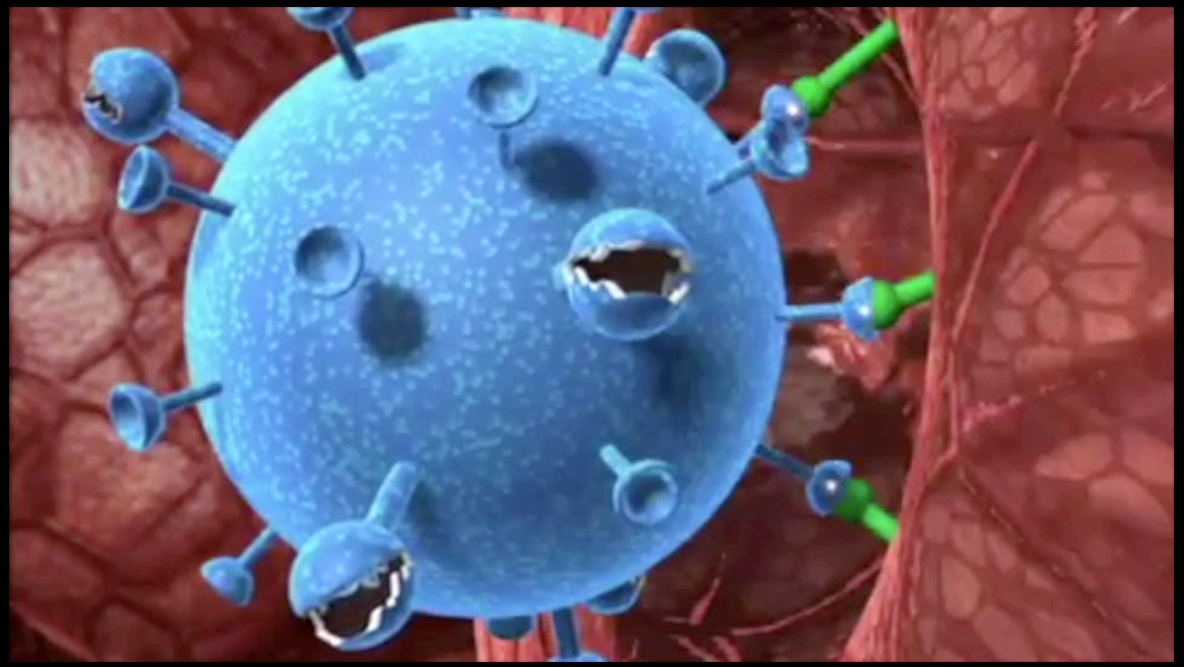
Doelwit virus: onze suikercode

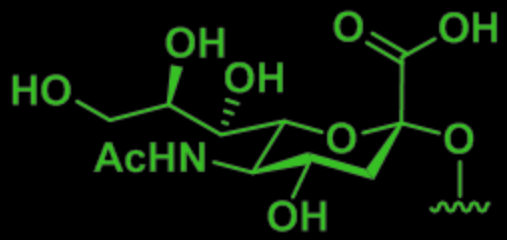


suiker molecuul

moleculair klitteband

infecteren & vermenigvuldigen

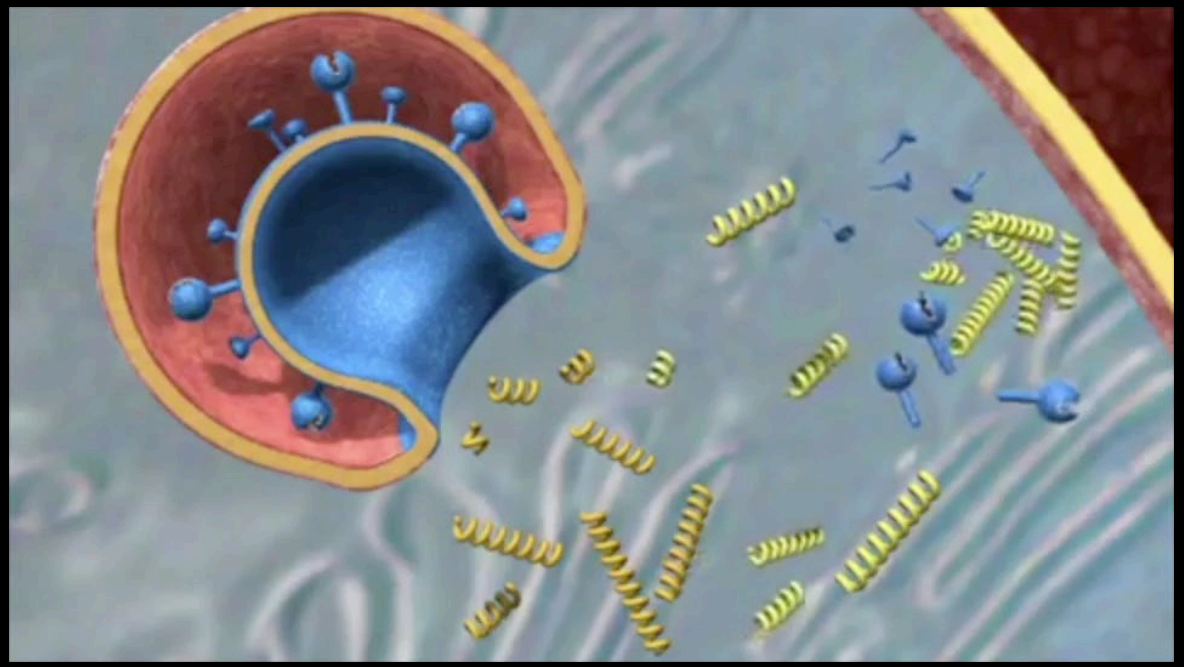


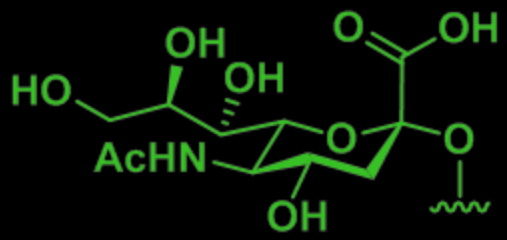


suiker molecuul

moleculair klitteband

ontsnappen & infectie verspreiden

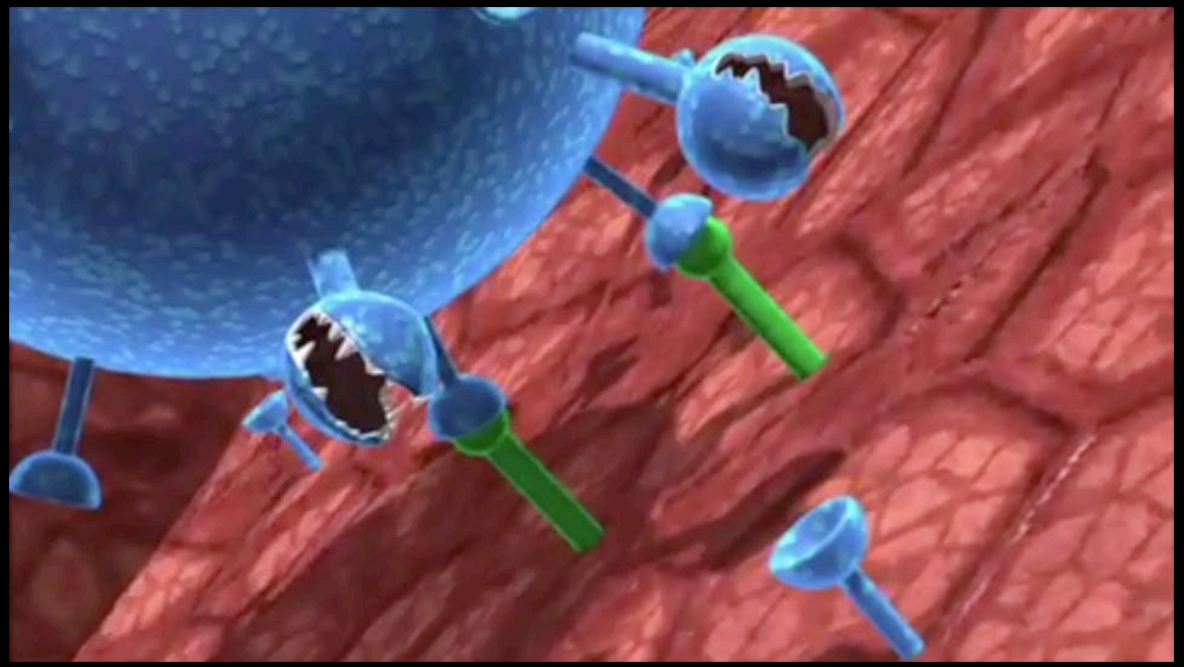




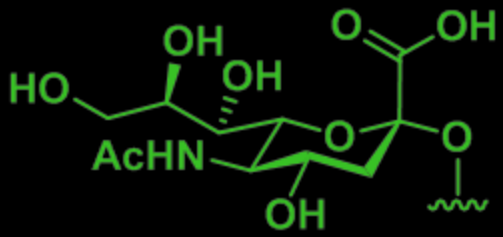
suiker molecuul

moleculaire schaar

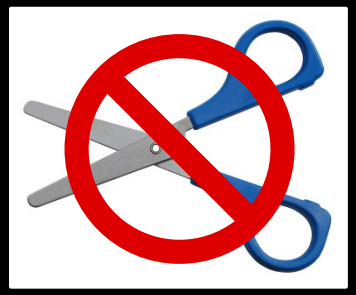
Het virus misleiden



Antiviraal middel



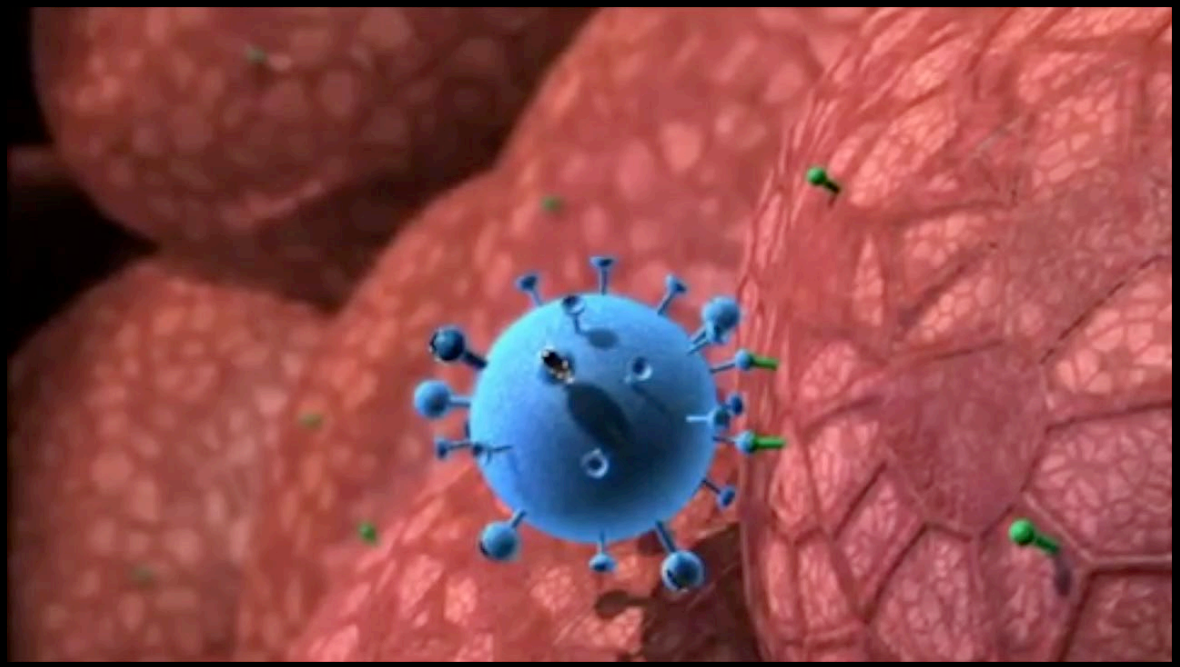
suiker molecuul



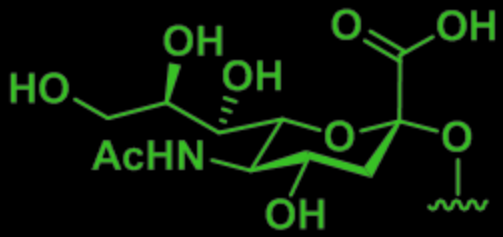
moleculaire schaar

Ontwerp & synthese

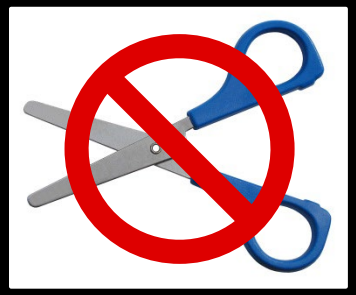
Chemische Biologie in actie



Antiviraal middel



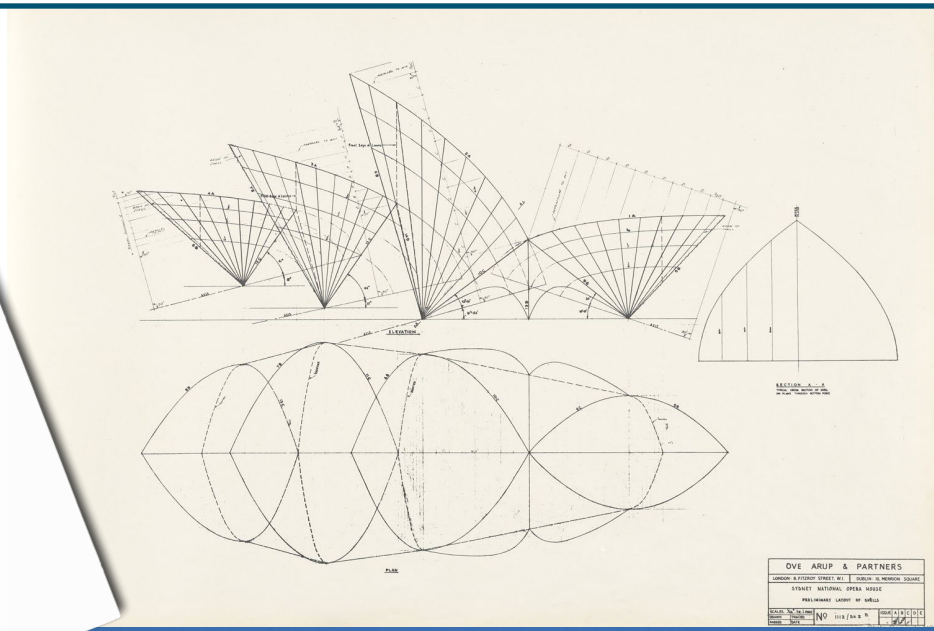
suiker molecuul



moleculaire schaar

Ontwerp & synthese

Op maat gemaakt: idee→ontwerp→maken→ testen



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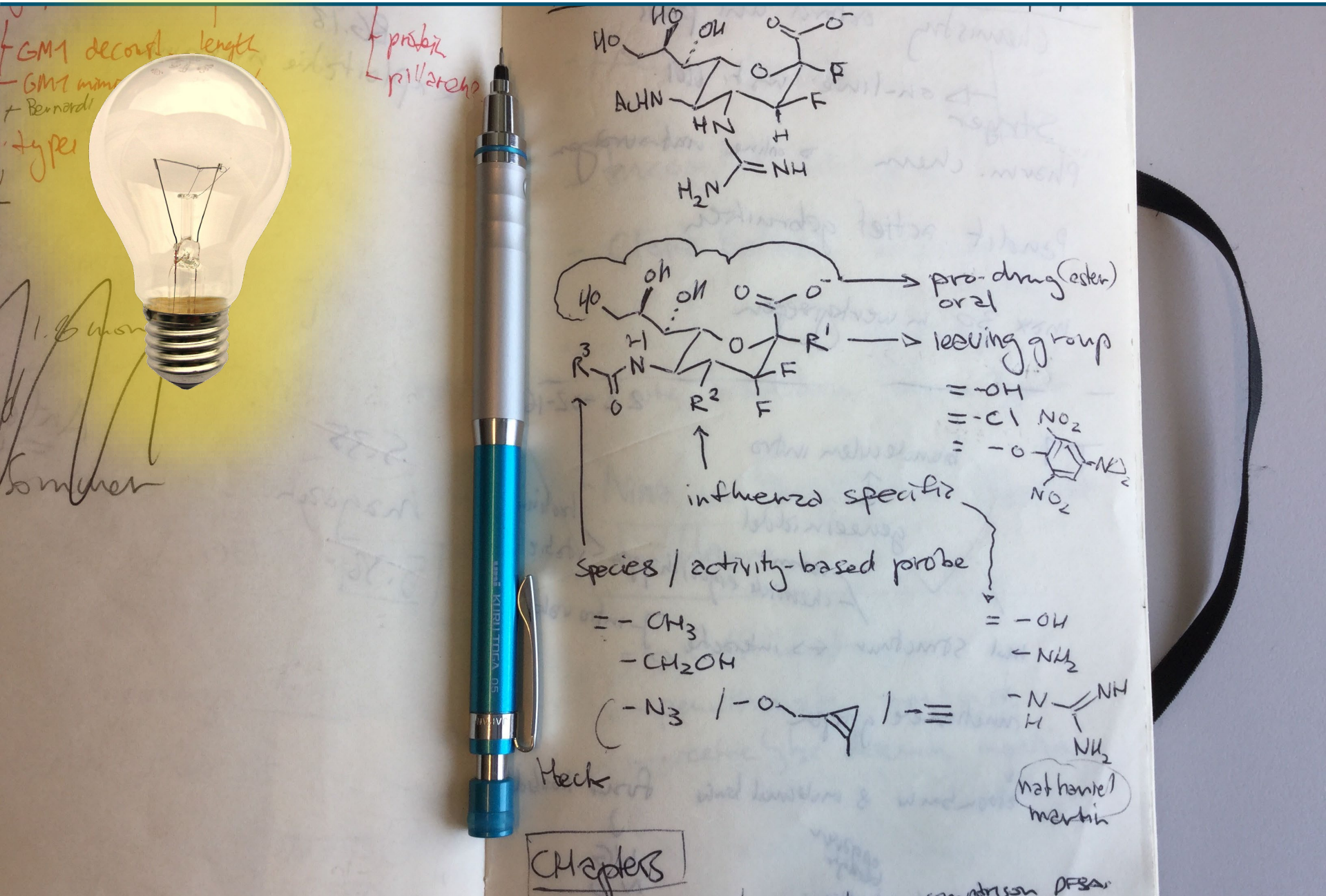

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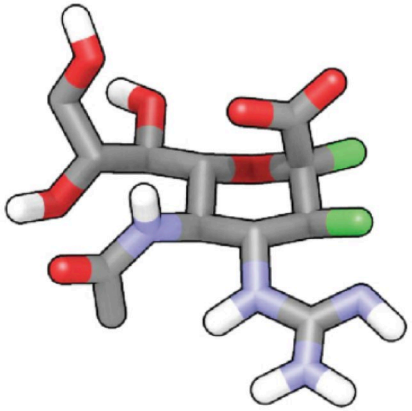

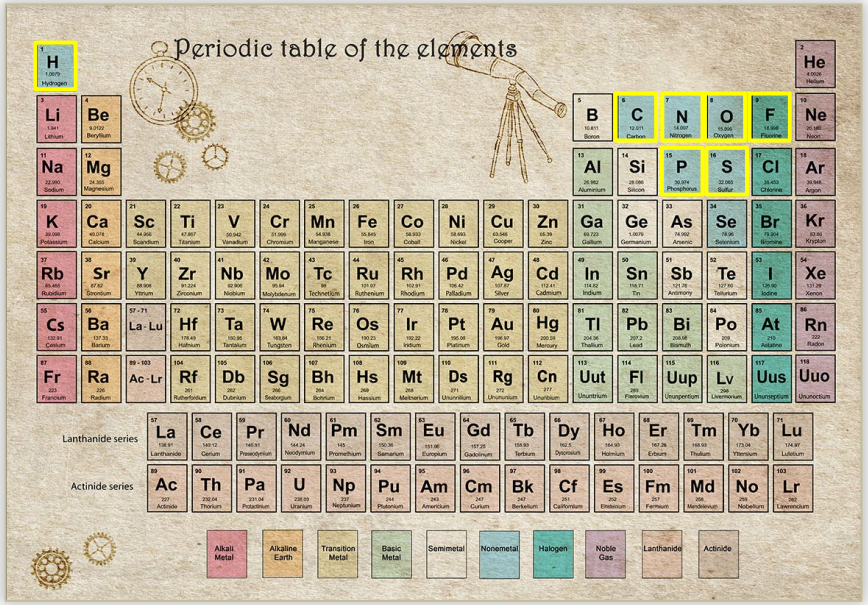

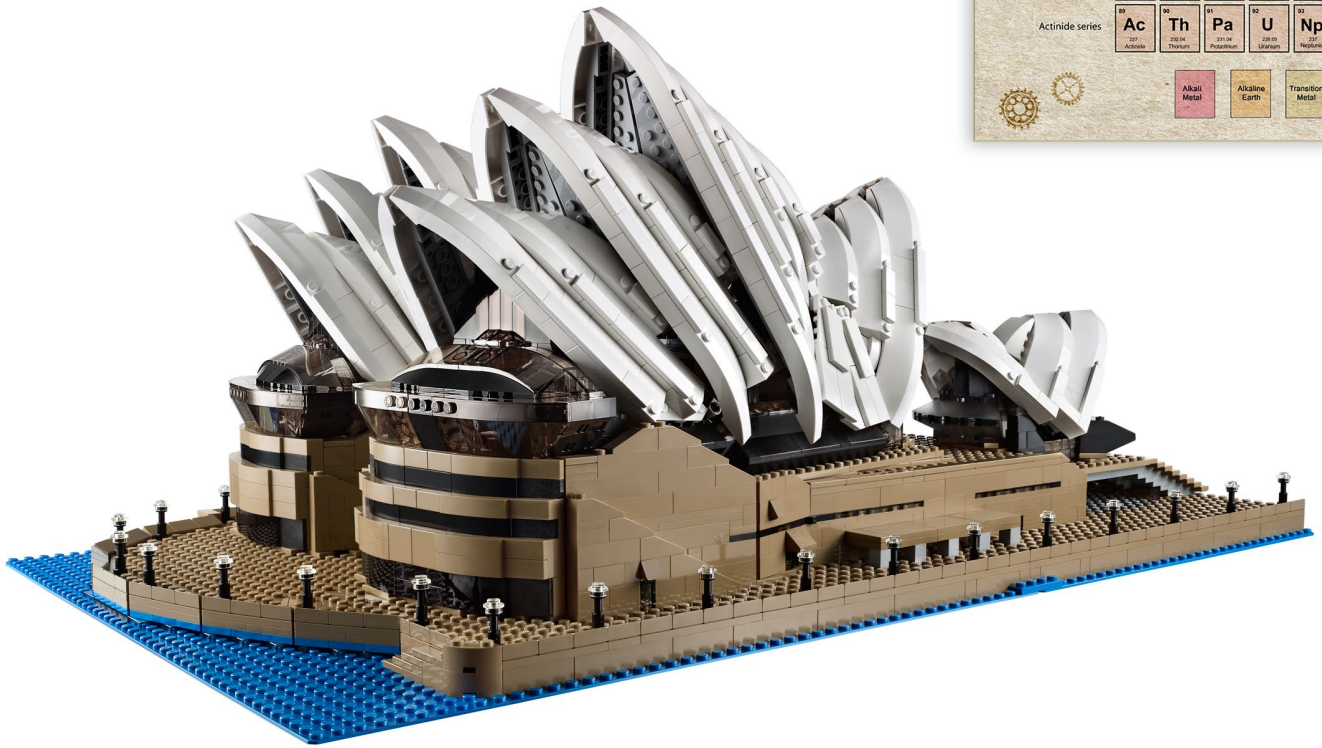

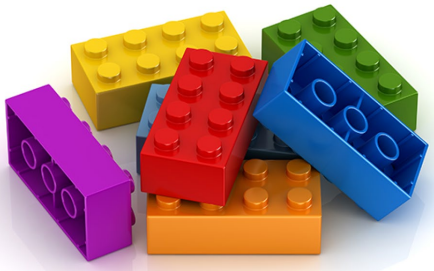

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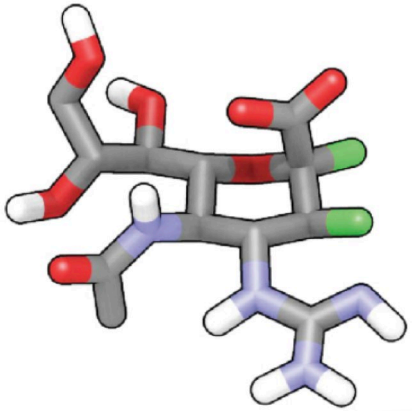
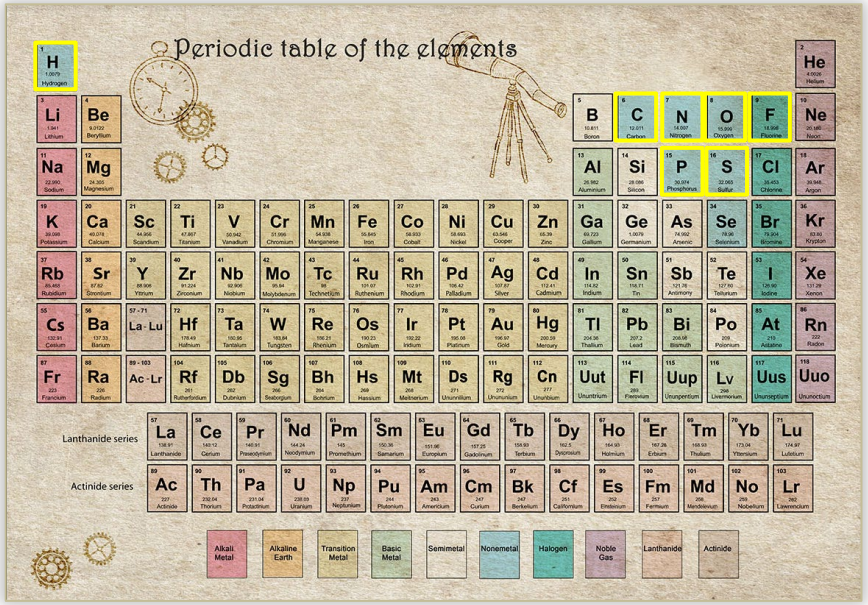
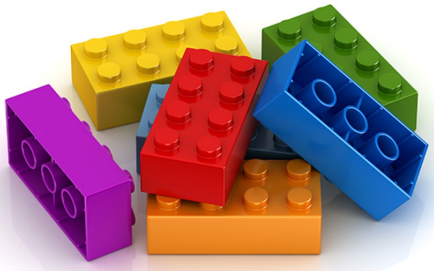
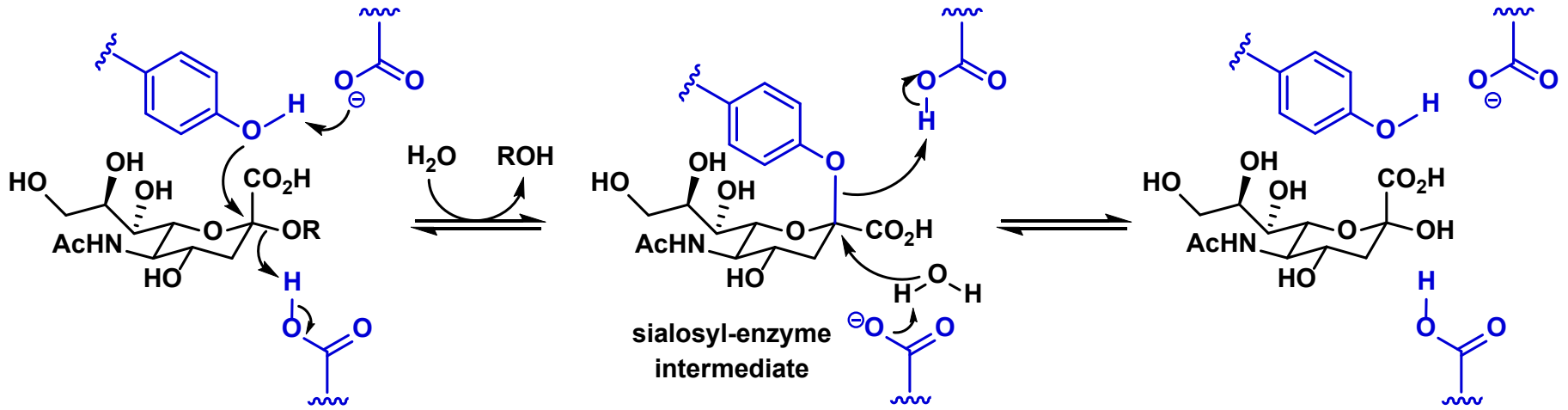




Hoe bedenk je zo'n ontwerp?



Reactie mechanisme neuraminidase enzym



Vastzetten van het covalente intermediair in het enzyme door:

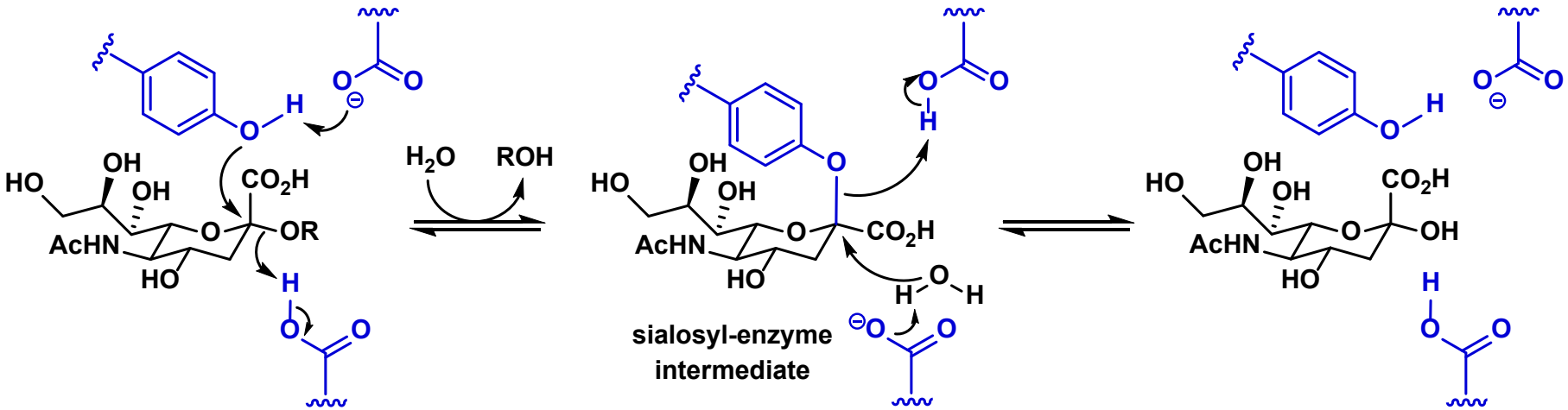
1: Sterke herkenning = lijken op natuurlijk substraat

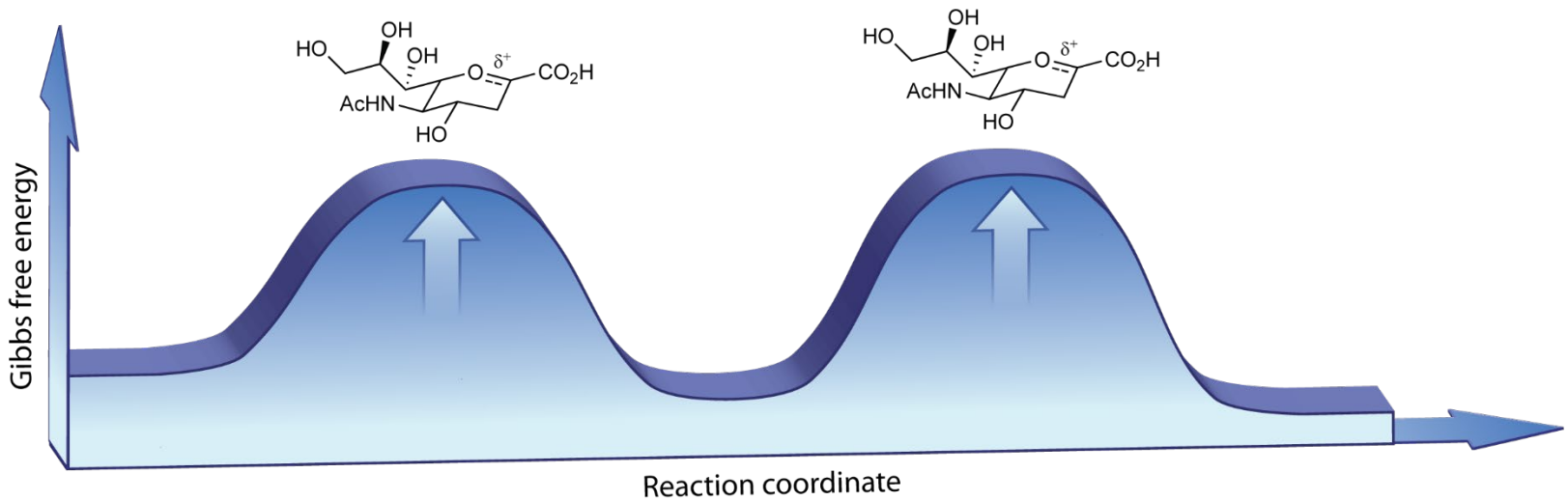
2: Aanpassen van snelheid vorming↑ en hydrolyse↓ intermediair

Doel: Een heel langzaam substraat

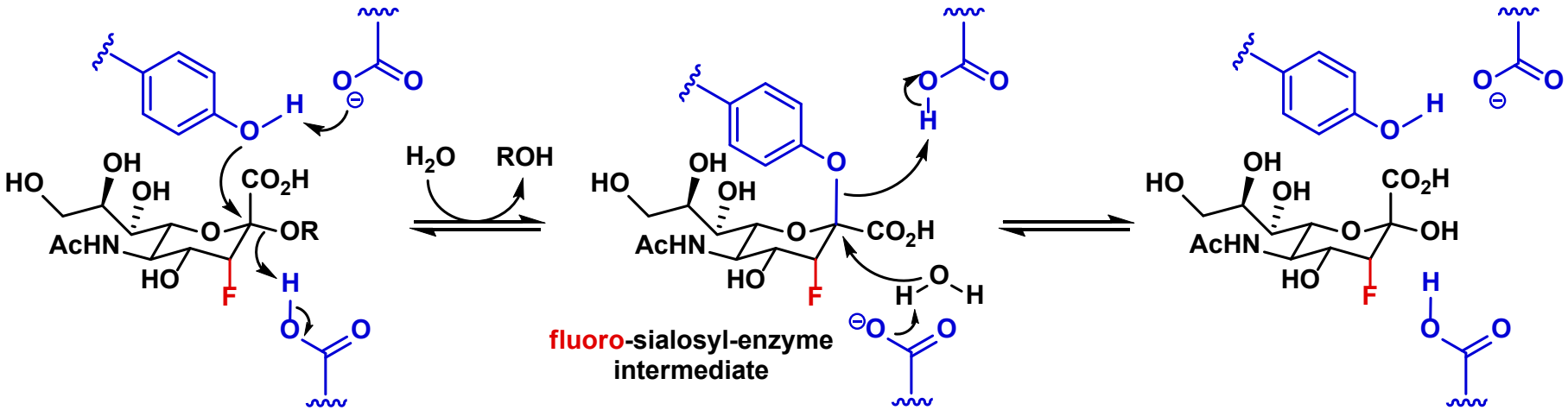
Wither's fluorosugars: J. Biol. Chem. **1988**, p7929 JACS, **2003,** p7532

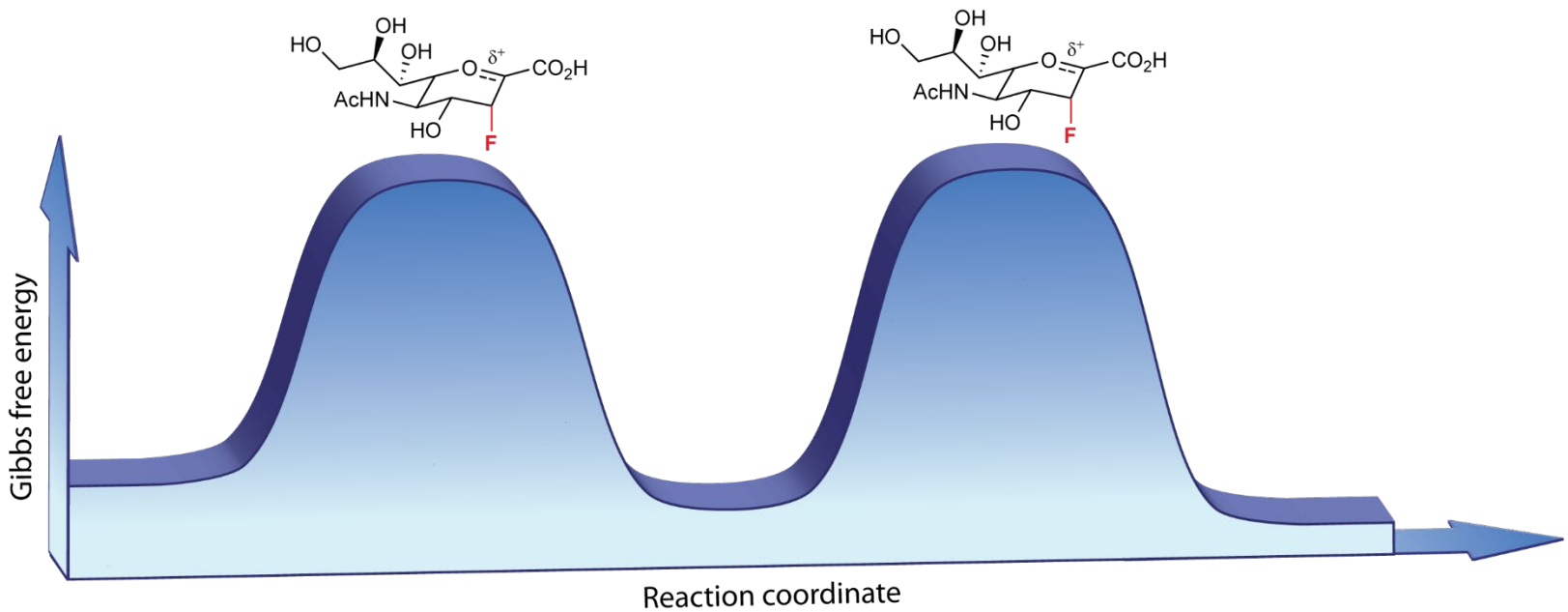
Reactie mechanisme neuraminidase enzym



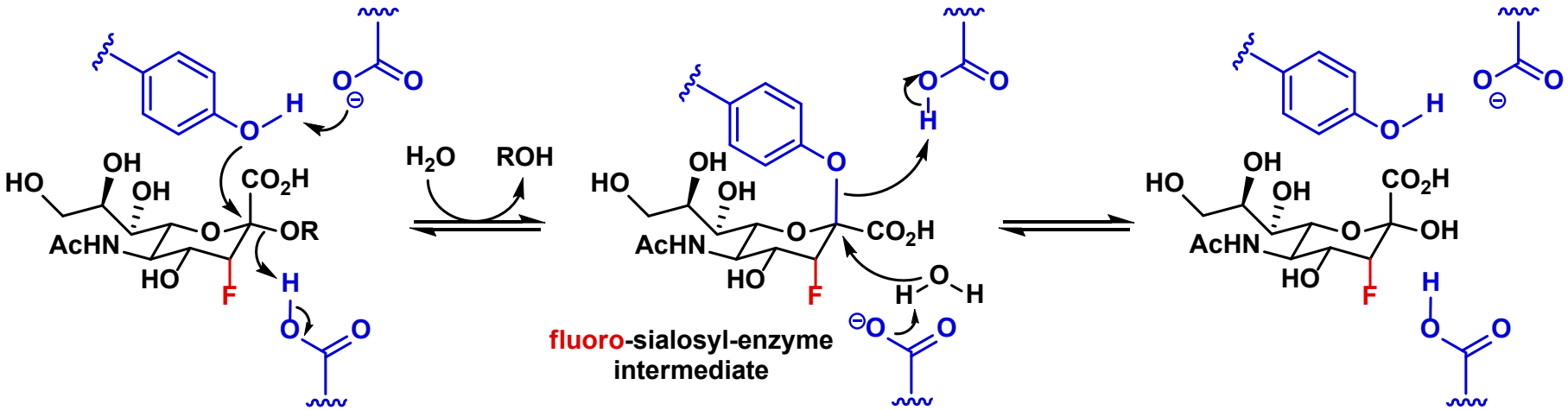


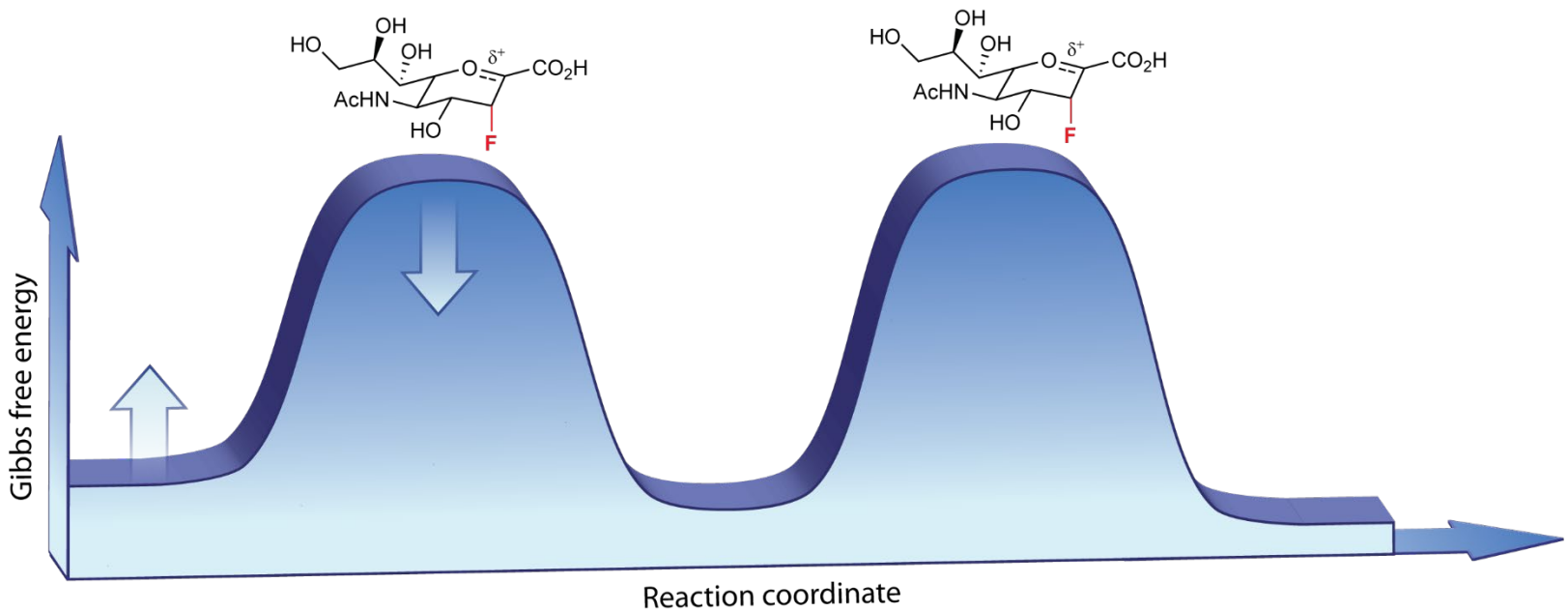
Fluor atoom op C-3 destabiliseerd



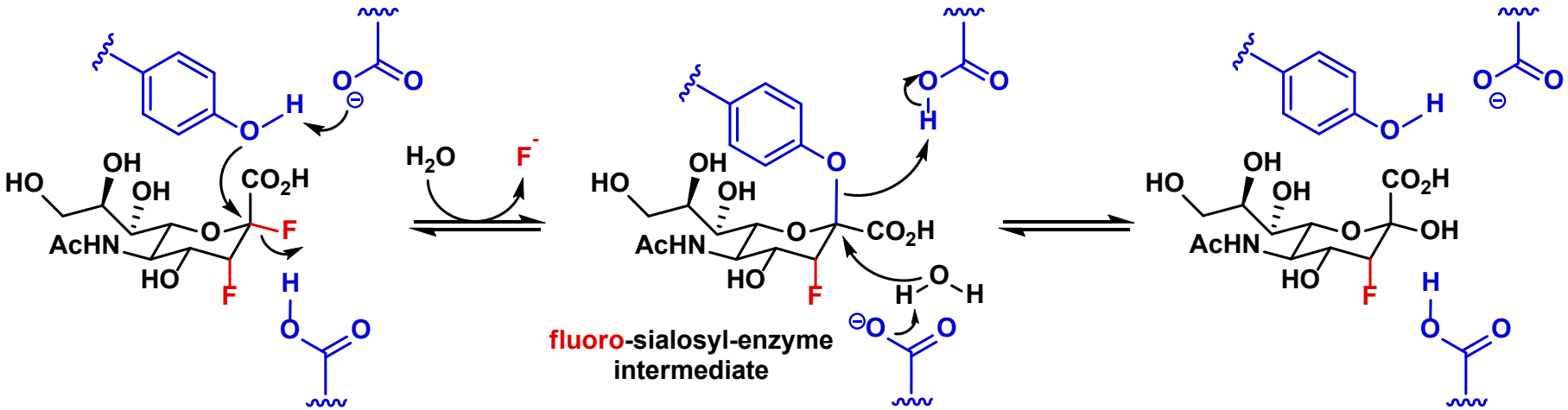


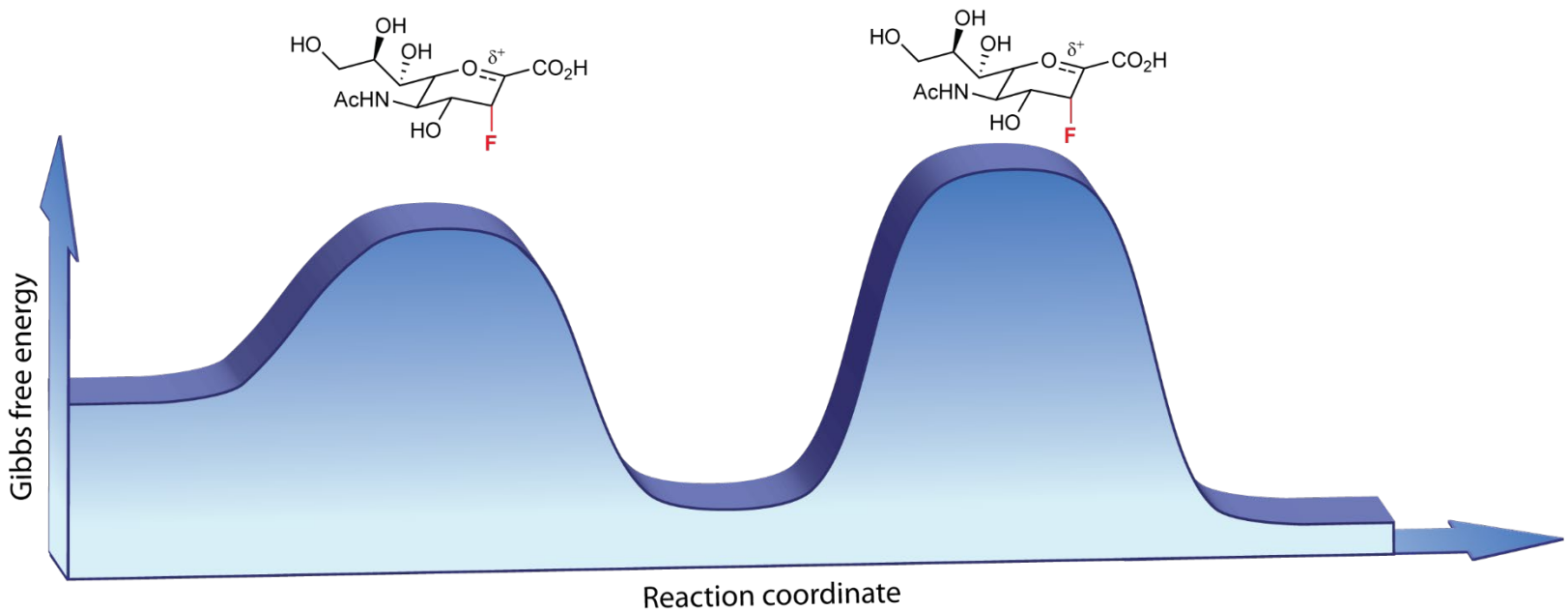
Covalent intermediair vastzetten



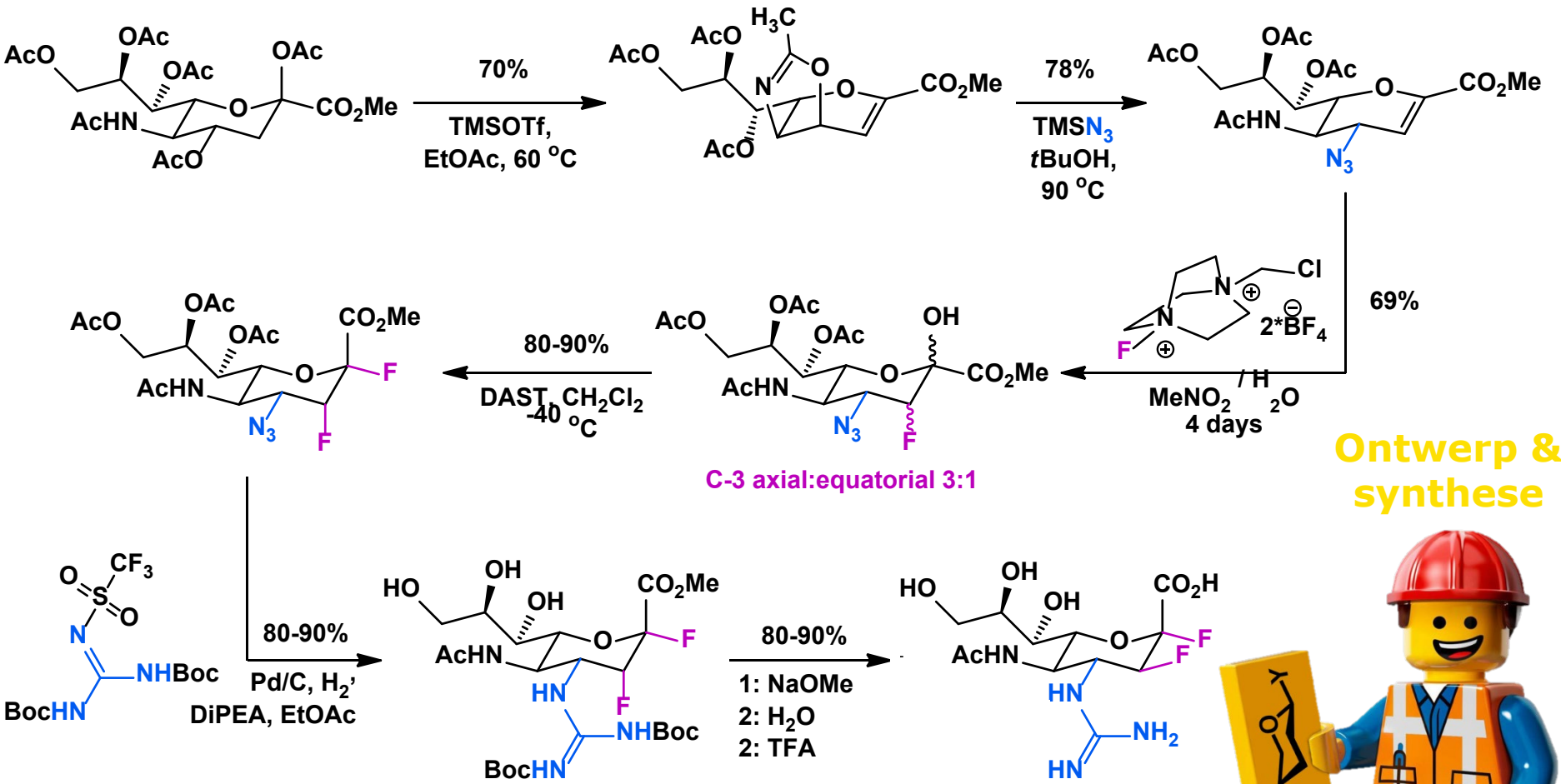


Covalent intermediair vastzetten





Op maat gemaakt met Organische Chemie

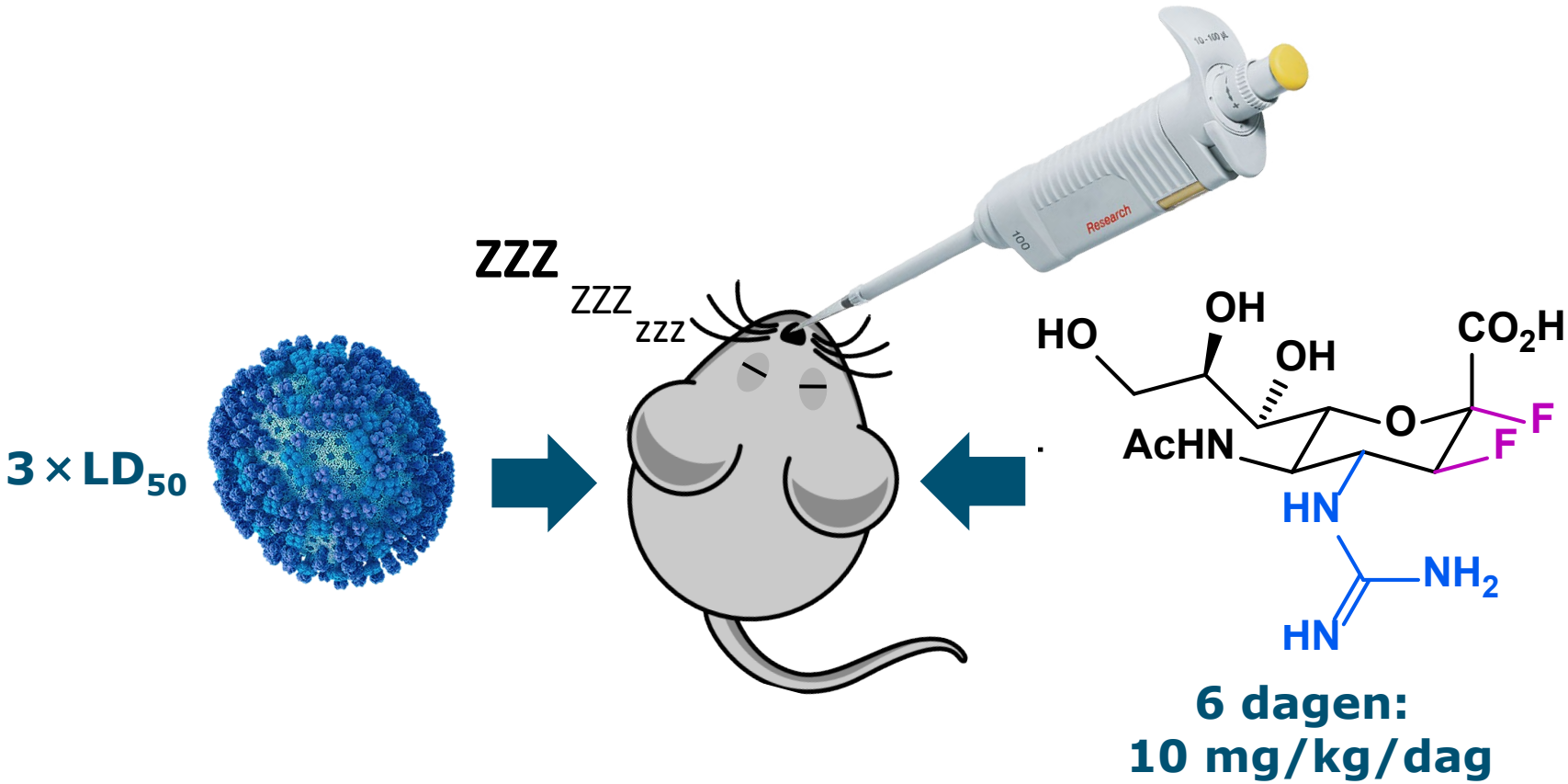


Ontwerp & synthese

Science **2013,** 340, p71

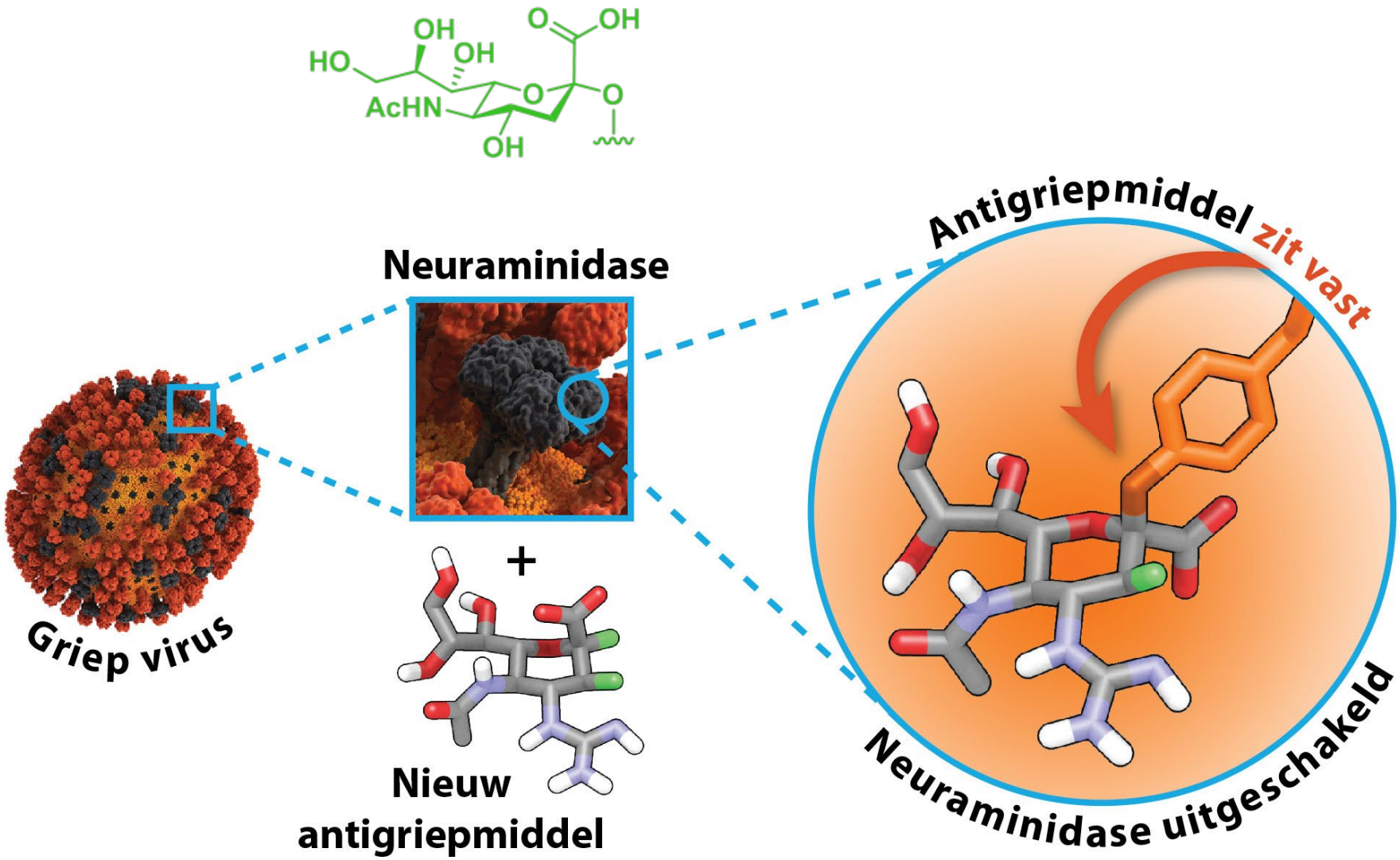
DS-65
18.6 mL H2O
1.6 mL
1.7.6
2.9
10.75
8 mL DCM

Op maat gemaakt: idee→ontwerp→maken→ testen



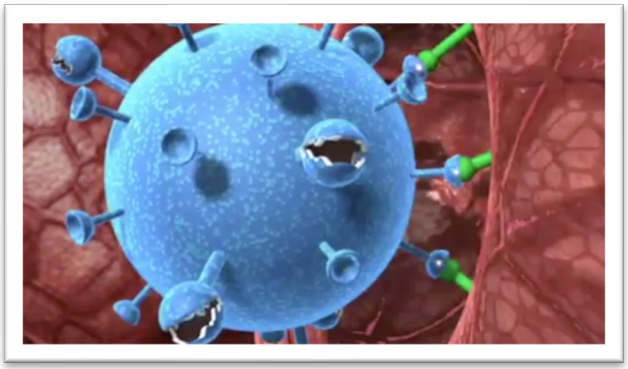
Science **2013,** 340, p71

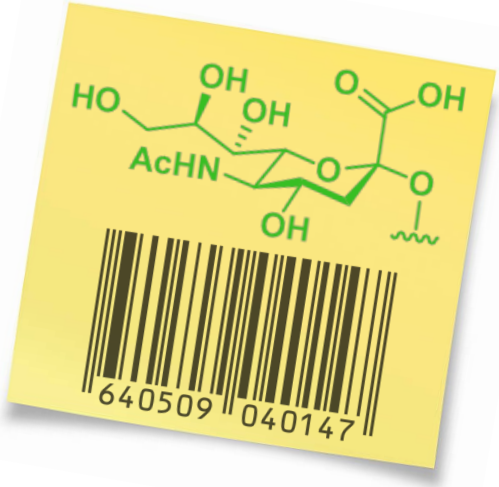
Chemische Biologie: ”slim” antigriepmiddel

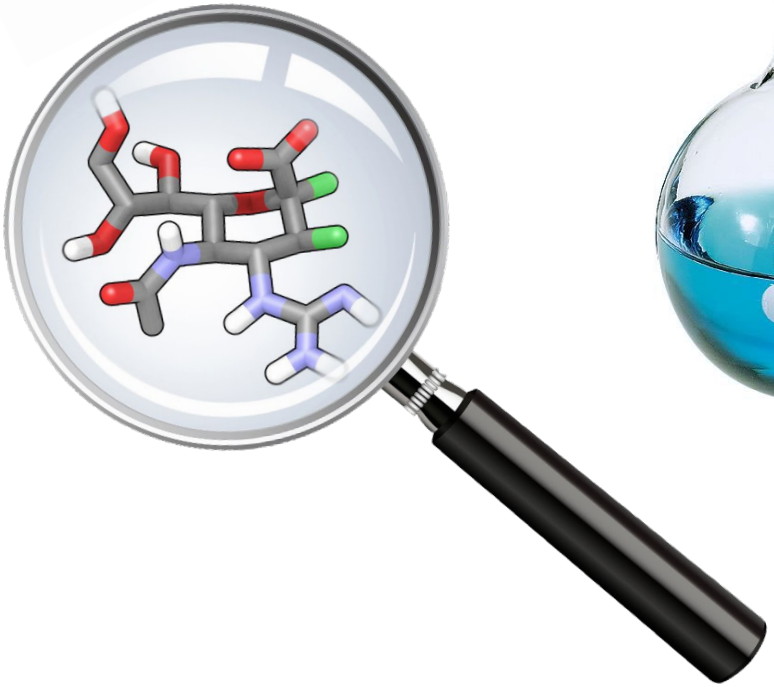


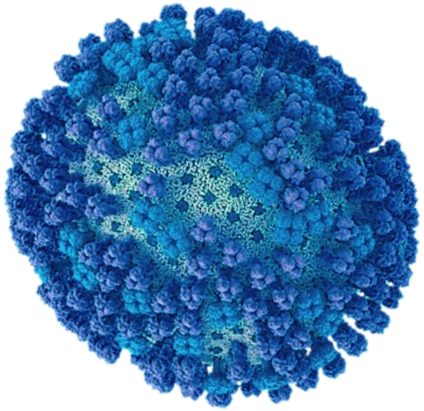
Science **2013,** 340, p71

Chemische Biologie: ”slim” antigriepmiddel









Op maat gemaakt antiviraal suiker molecuul

Is suiker altijd zoet?

Inhoud van mijn lezing:

- **Introducties:** chemische biologie → mij → suikers
- **Onderzoek:** slimmer zijn dan het griep virus
- **Onderzoek:** de perfecte omhelsing van Cholera
- **In het nieuws:** Klik chemie is gaaf!
- **Echt gebeurd:** Zoet biomoleculair moord mysterie
- Chemie op de basisschool?

Utrecht University

Tom Wennekes

Imagination at work

Woudschoten Chemie Conferentie 2022

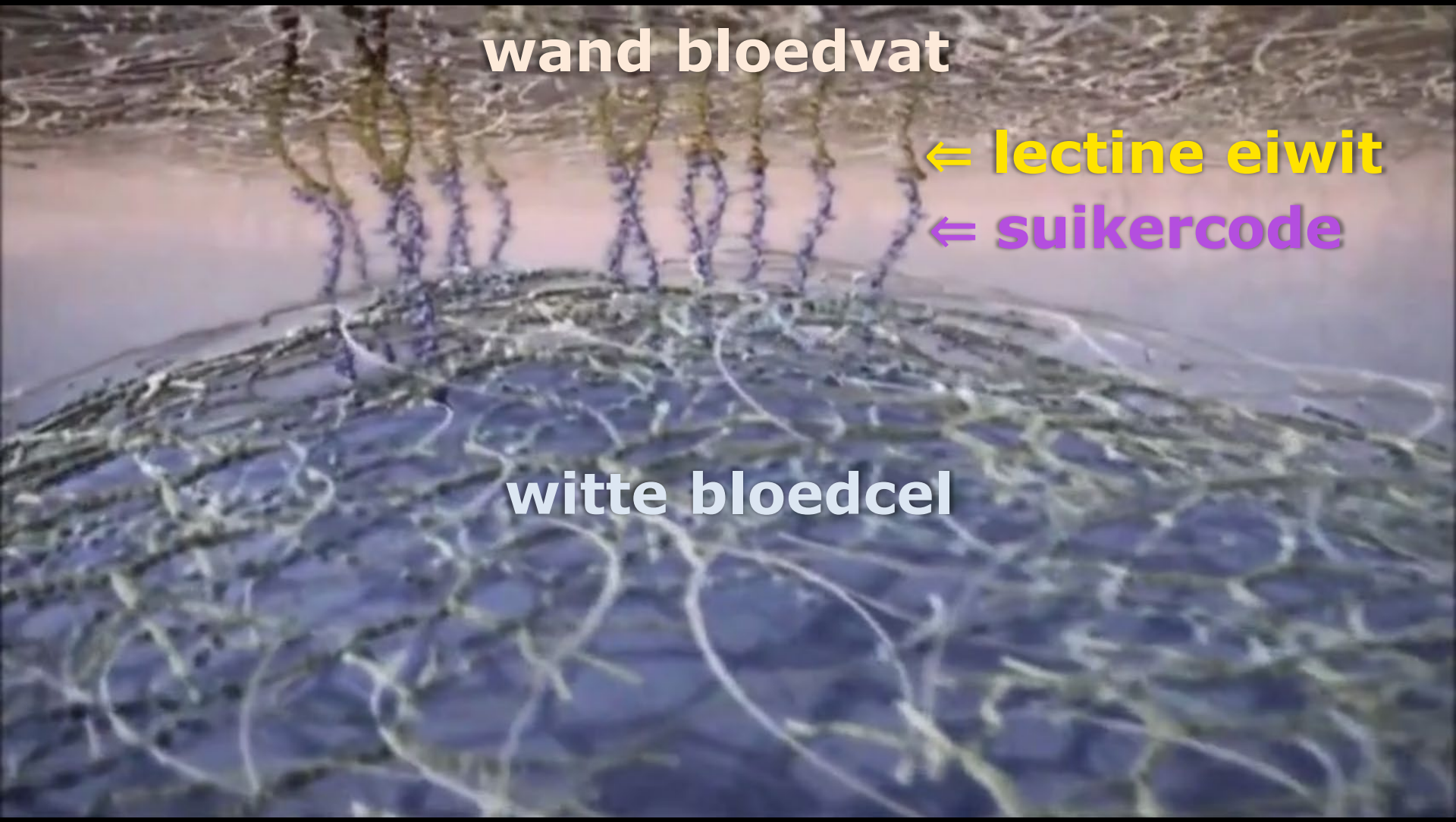
C3

Meervoudige interacties zijn cruciaal

voor sterke binding en specifieke herkenning van suikers

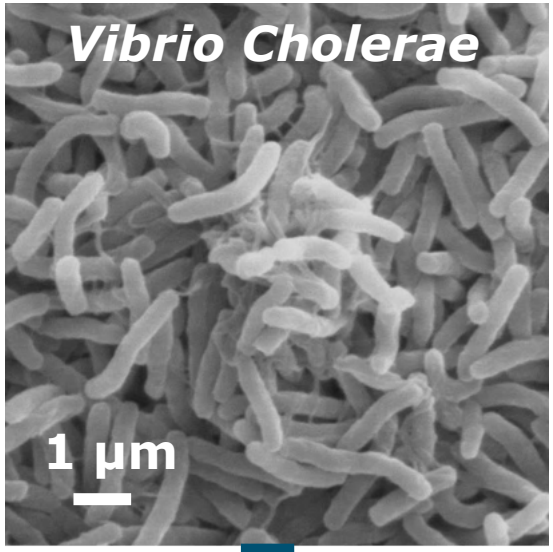
suikercodes localiseren infecties

suikercodes localiseren infecties

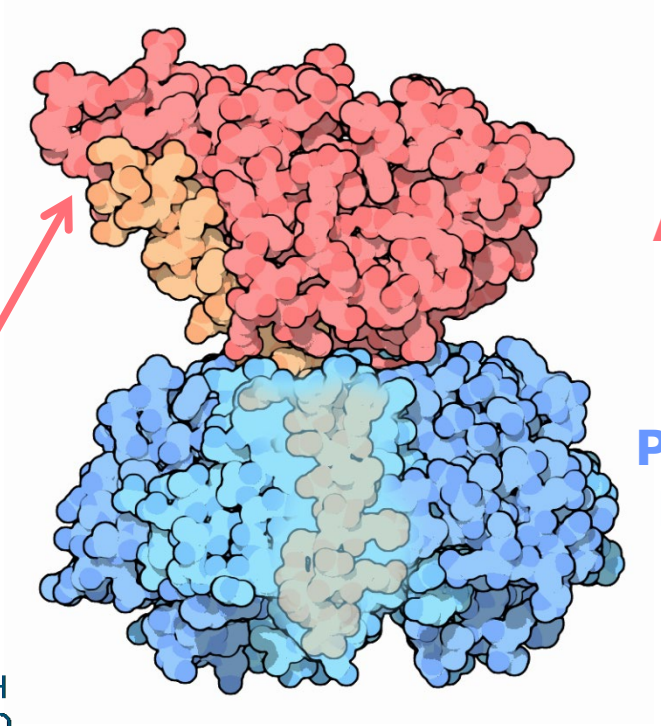


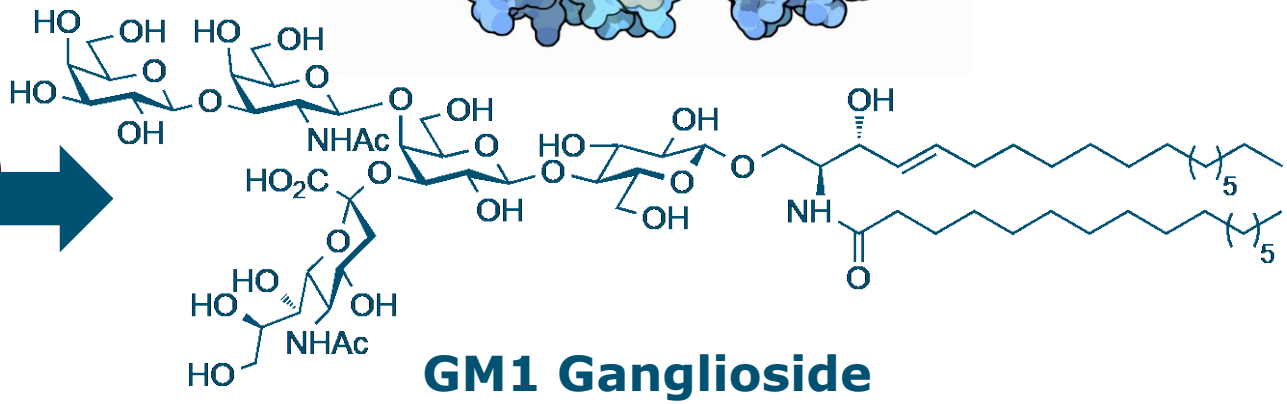
Een perfecte omhelzing met Cholera

Cholera: 3-5 miljoen infecties jaarlijks



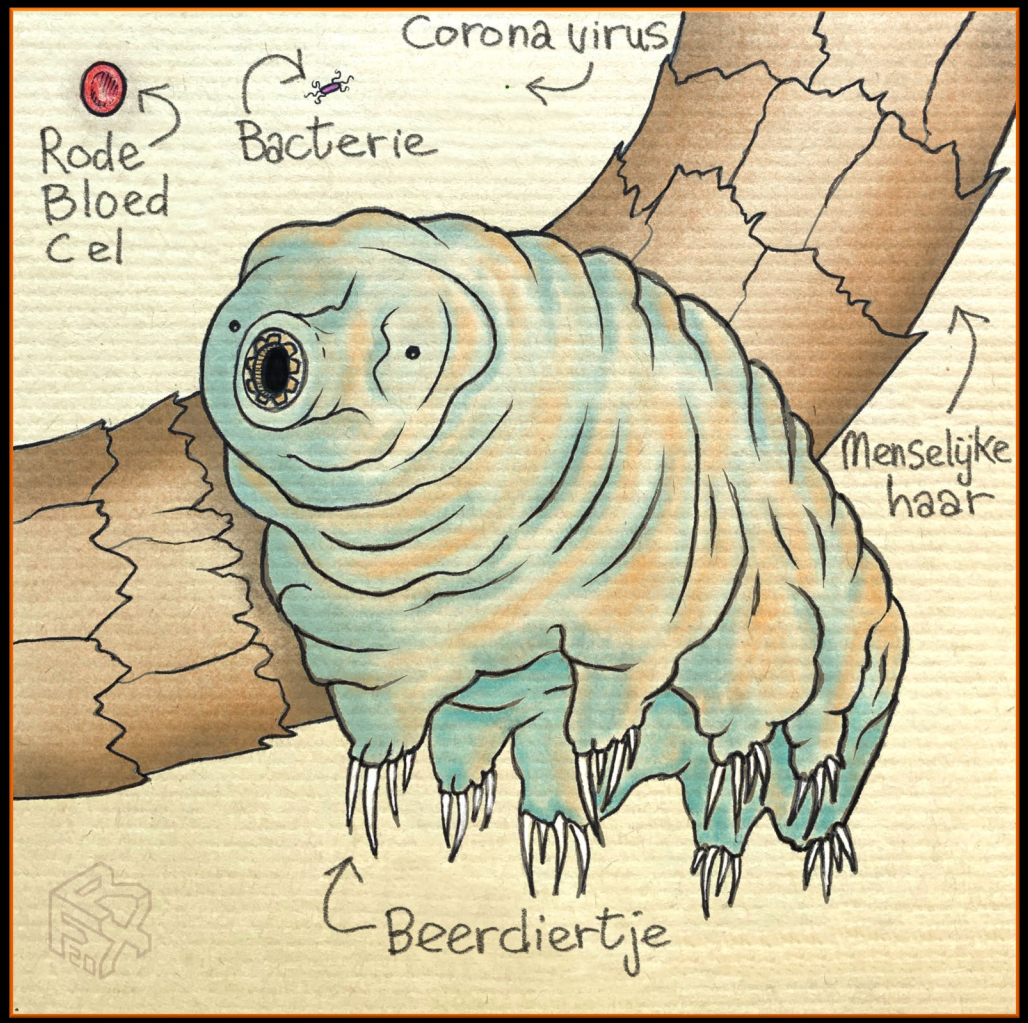
Cholera Toxine

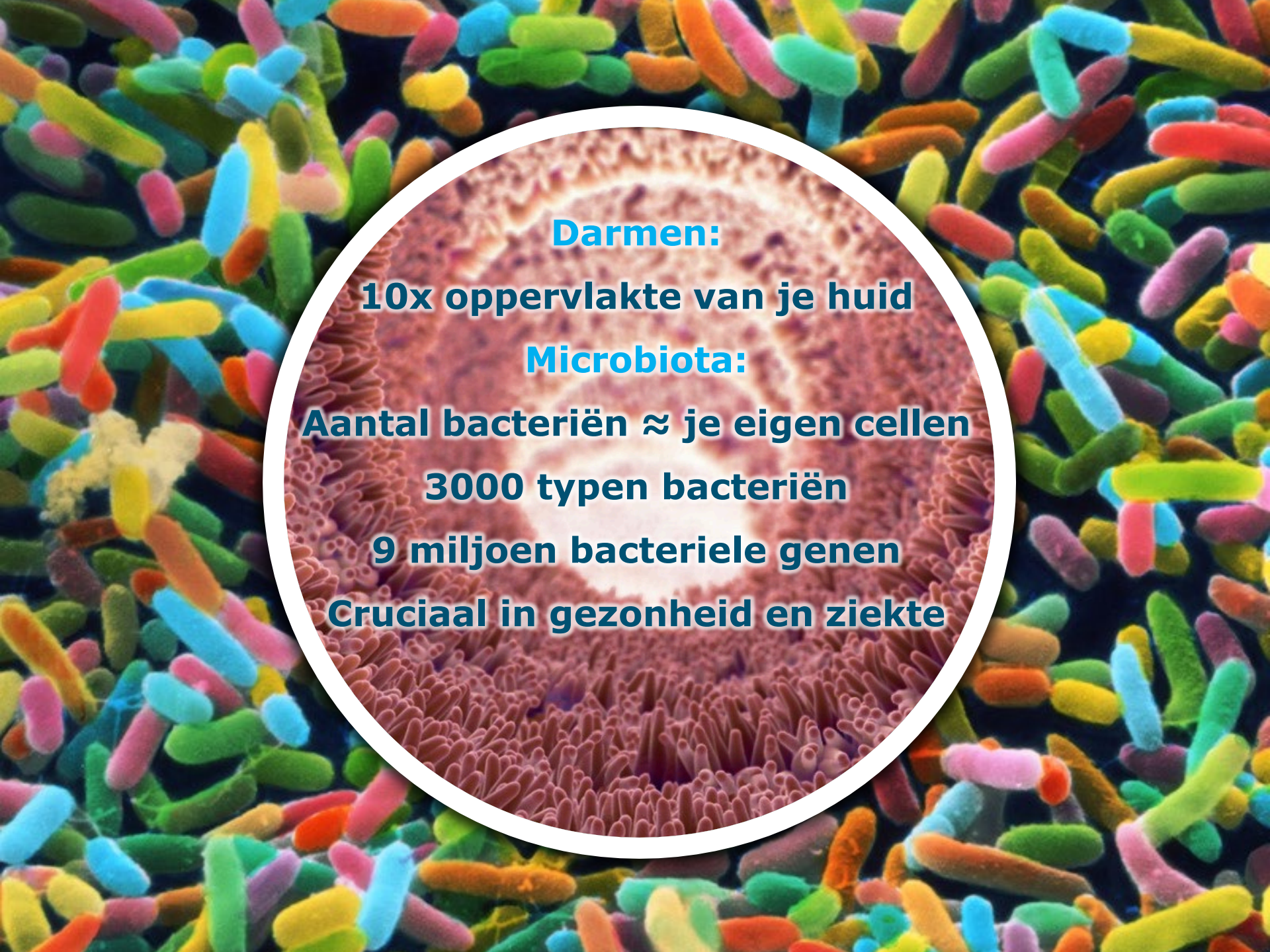




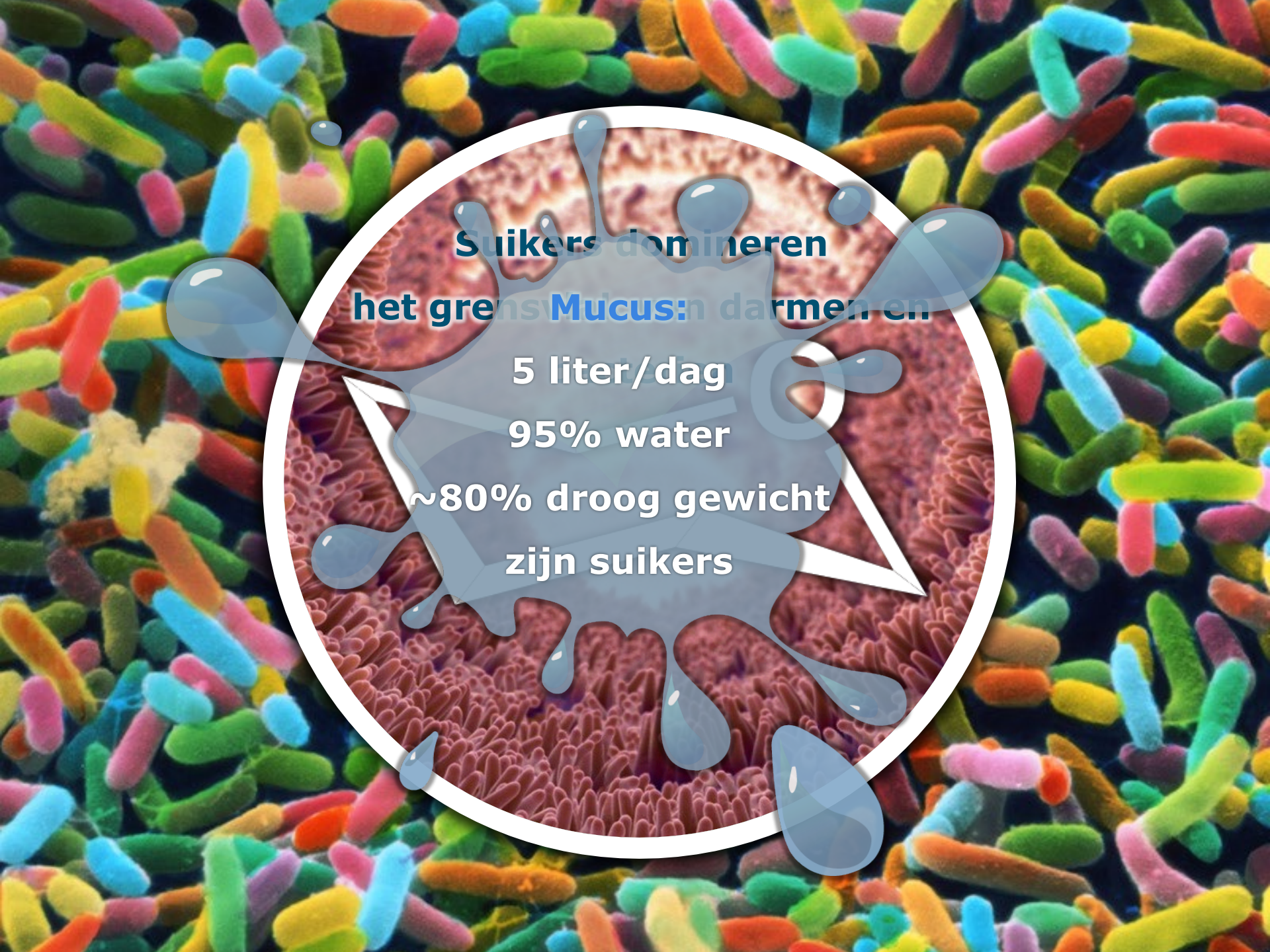
GM1 Ganglioside

Hoe groot is een bacterie?

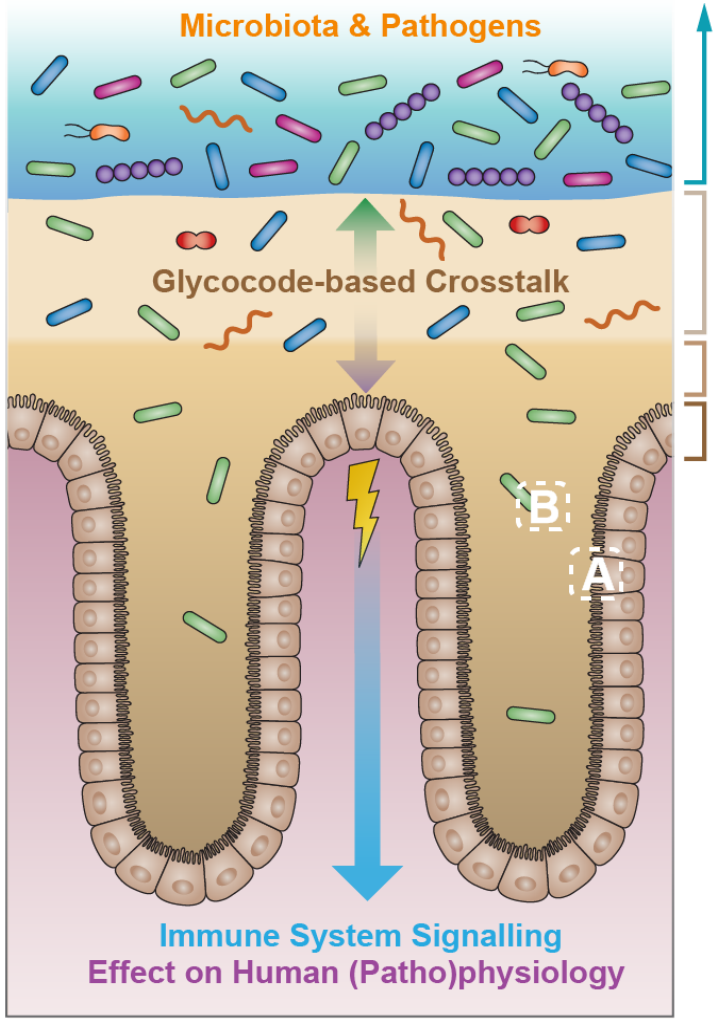


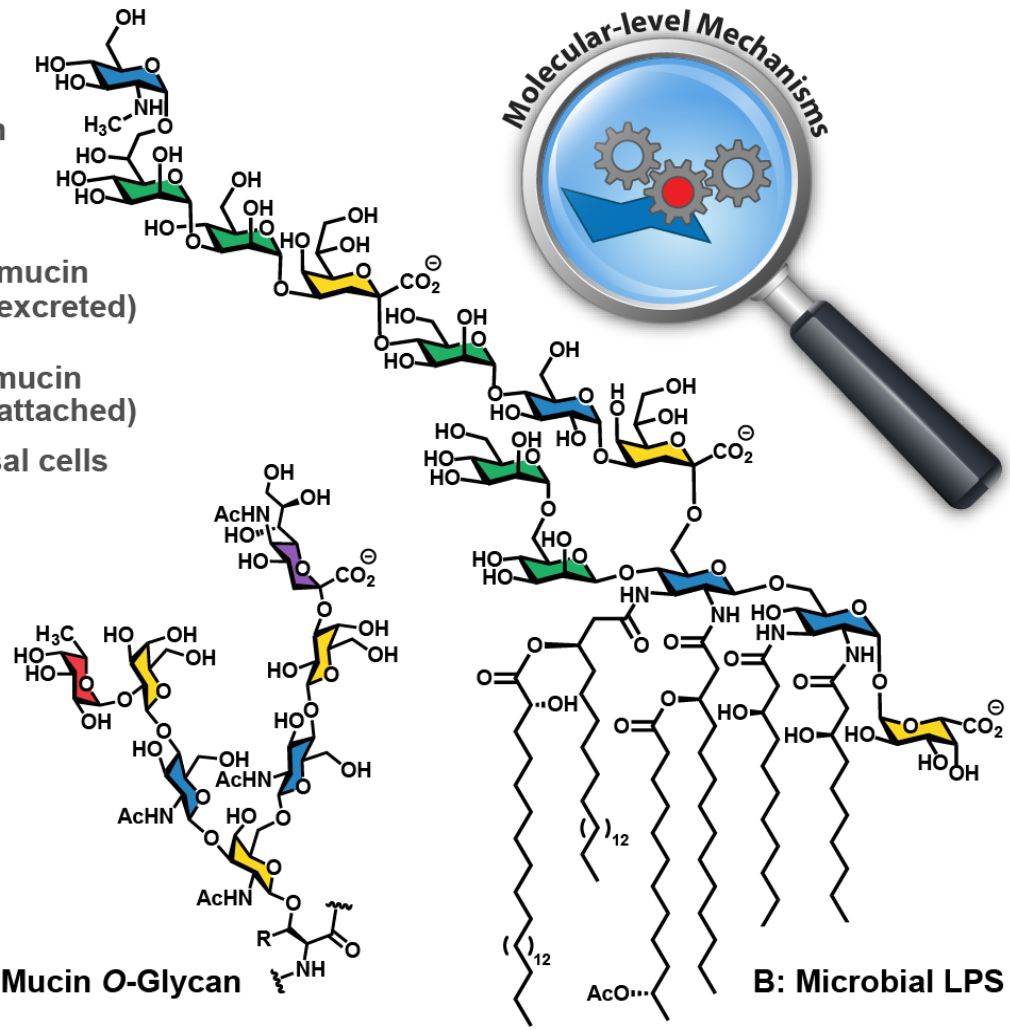

Darmen:
10x oppervlakte van je huid
Microbiota:
Aantal bacteriën ≈ je eigen cellen
3000 typen bacteriën
9 miljoen bacteriele genen
Cruciaal in gezonheid en ziekte

Suikers domineren
het grensvlak van darmen en
bacterien


Suikers dominieren
het grensvlak tussen darmen en
Mucus:
5 liter/dag
95% water
~80% droog gewicht
zijn suikers

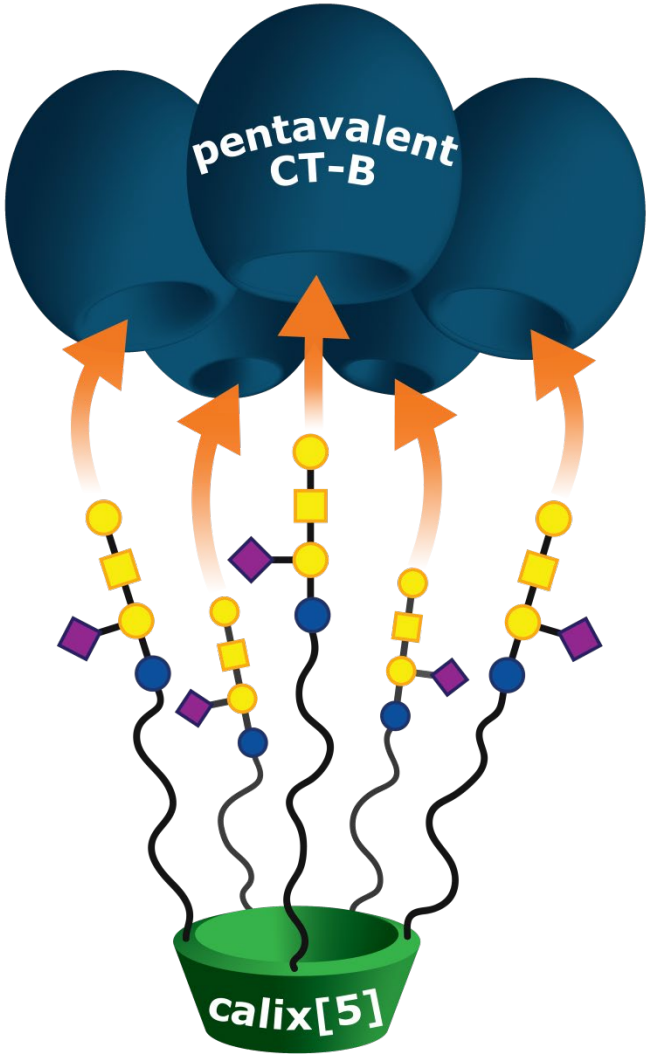
Suikers domineren het grensvlak van darmen en bacteriën

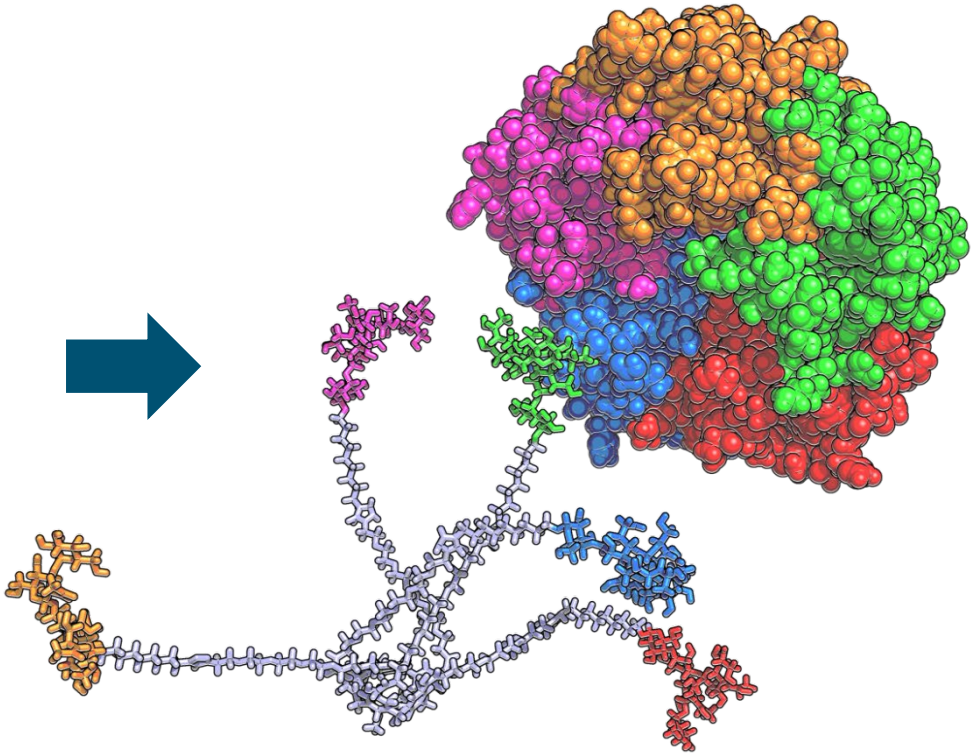




Bacteriën: the good 😃, the frenemy 🤔 and the ugly 😈

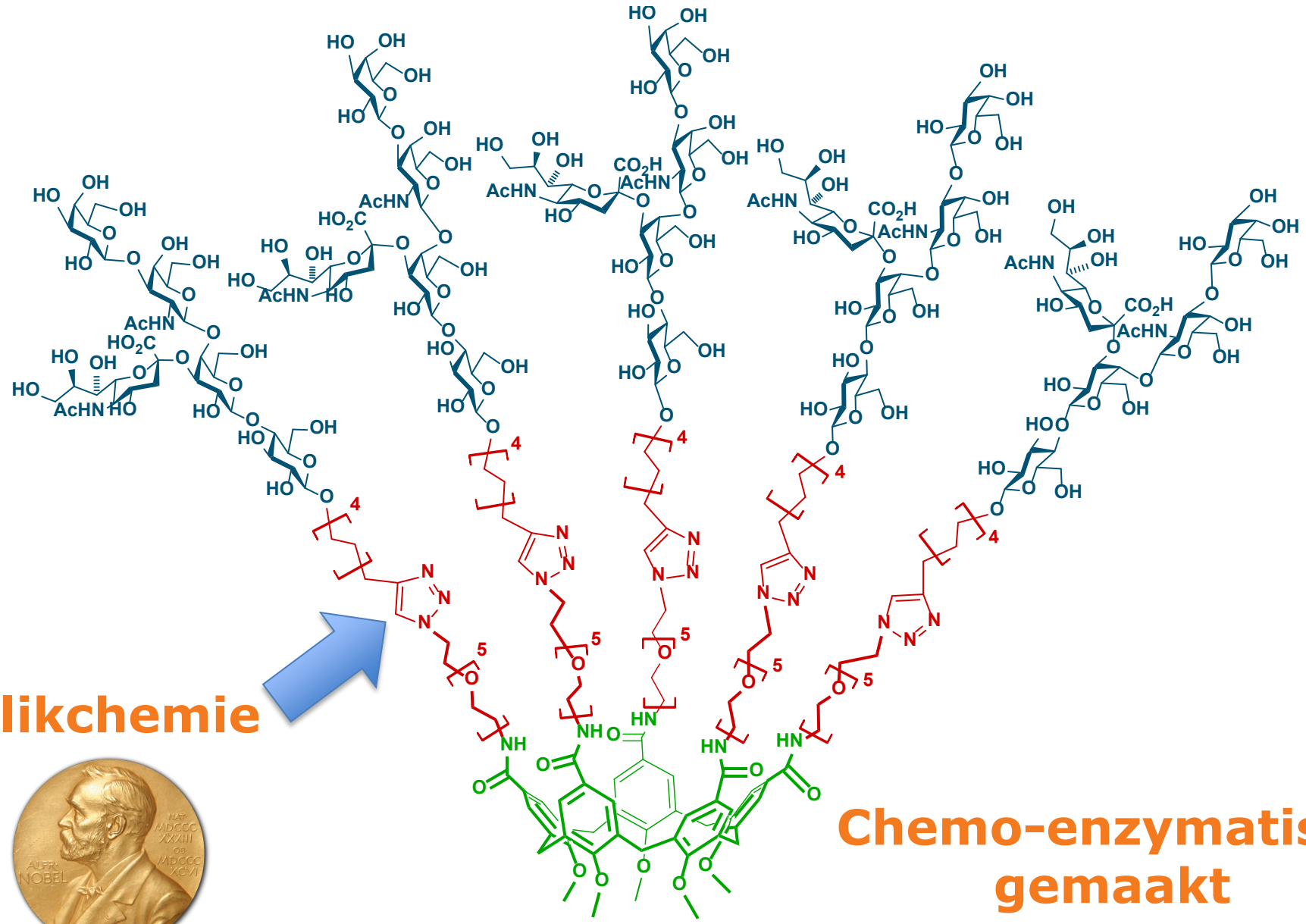
Een perfecte omhelzing met Cholera Toxine





pentavalent ligand voor CT-B

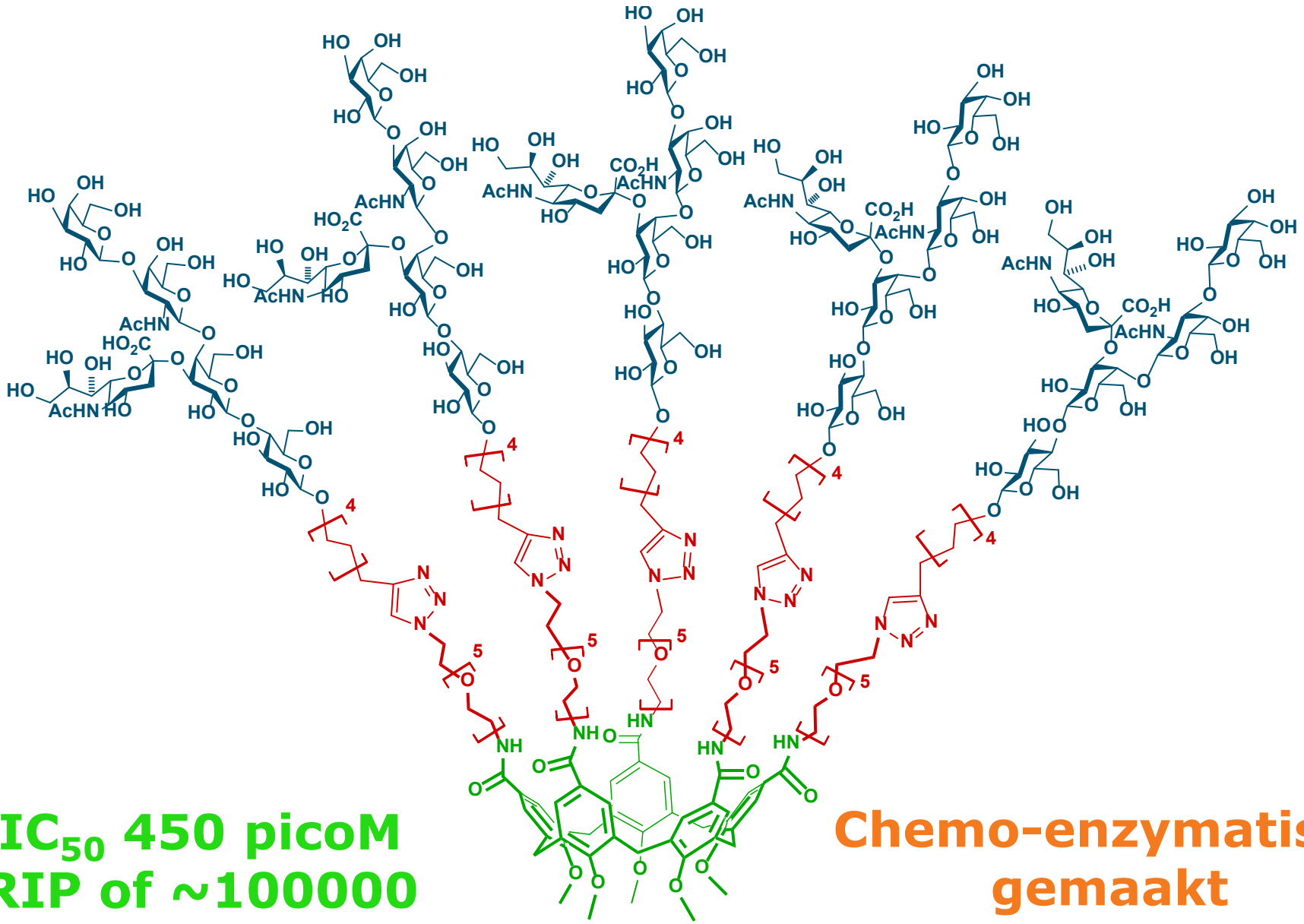
Pentavalente Glycocalix[5]arene



Klikchemie

Chemo-enzymatisch gemaakt

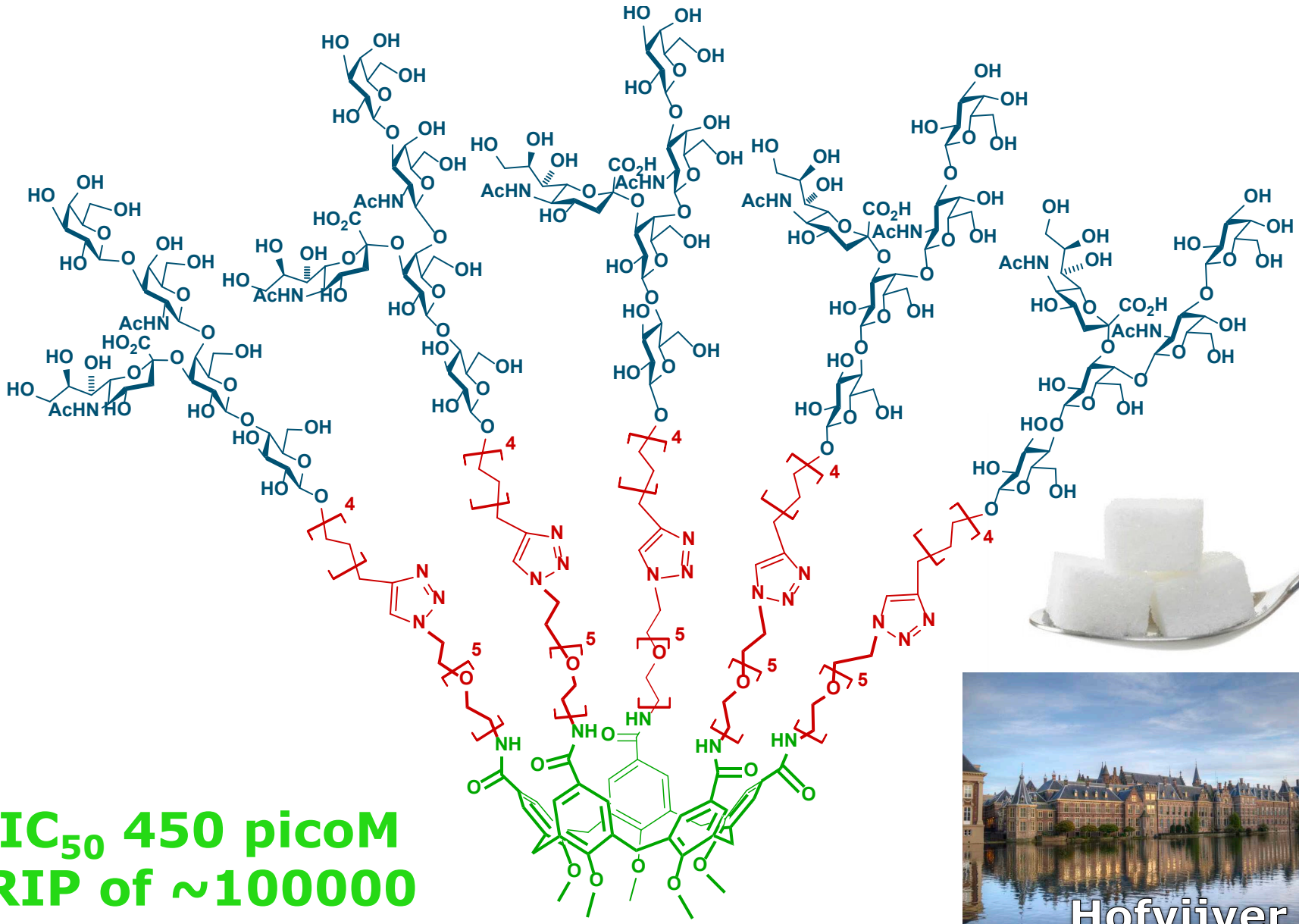
Pentavalente Glycocalix[5]arene



IC_{50} 450 picoM
RIP of ~100000

Chemo-enzymatisch gemaakt

Pentavalente Glycocalix[5]arene



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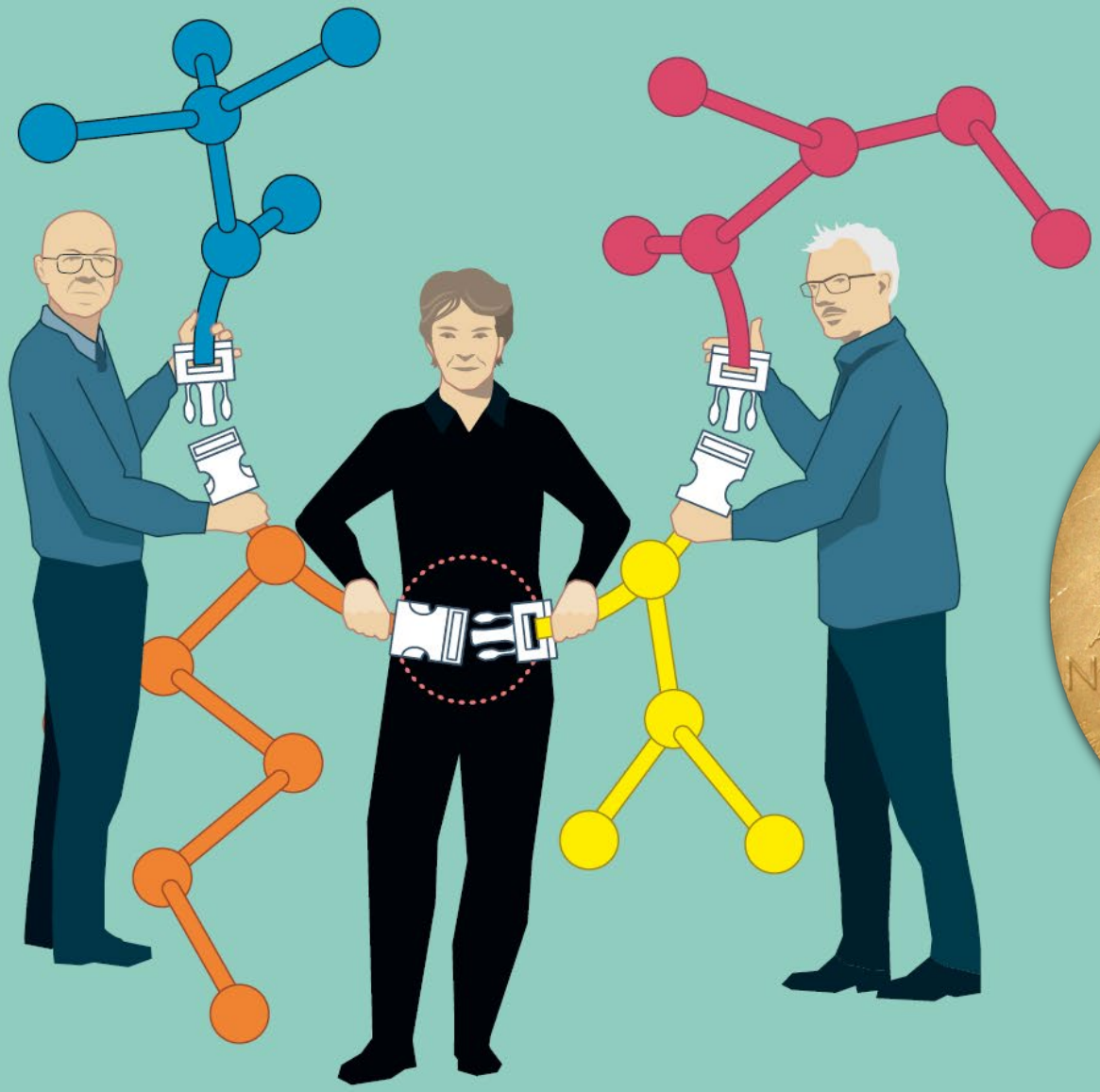
C3

Scheikunde Nobel prijs 2022: Klik chemie



©Johan Jarnestad/The Royal Swedish Academy of Sciences

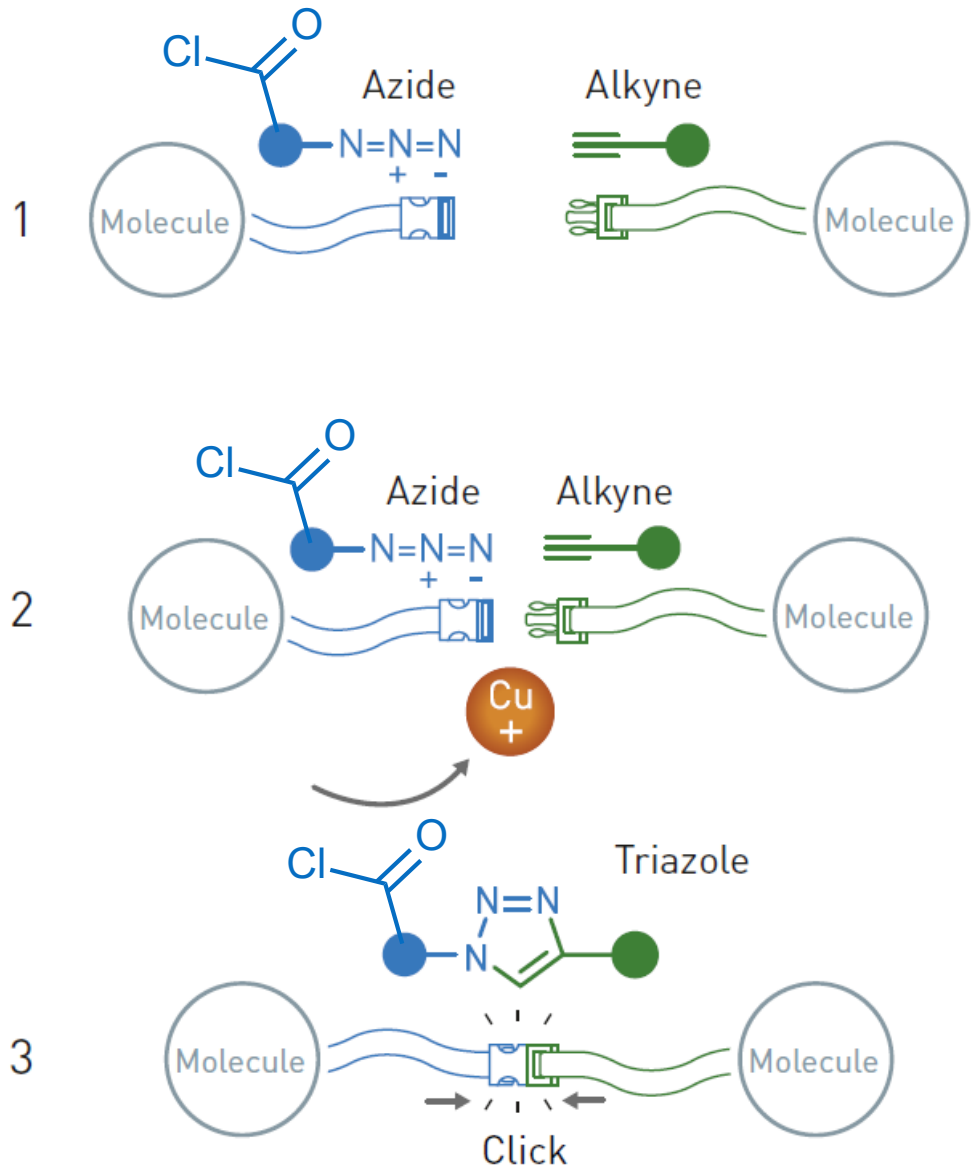
DS-65
18.6 mL H2O
1.6 mL
1.7.6
2.9
10.75
8 mL DCM

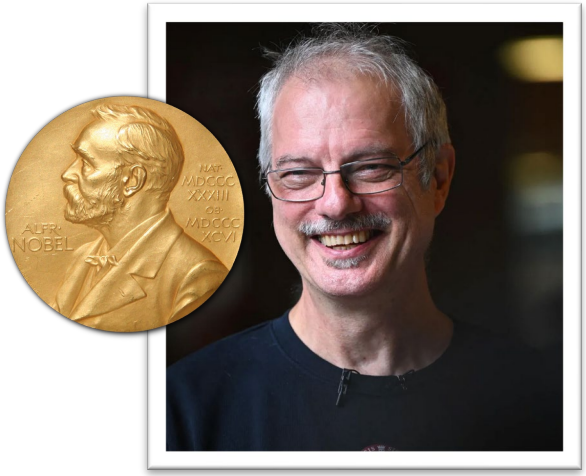
2001: Barry Sharpless introduceert Klik Chemie

Criteria voor een klik reactie:

- ✓ Hoge thermodynamische drijfkracht
- ✓ Modulair en breed toepassingsgebied
- ✓ Hoge opbrengst
- ✓ Atoom efficiënt
- ✓ Enkel ongevaarlijke nevenproducten
- ✓ Stereospecifiek
- ✓ Milde omstandigheden
- ✓ Zonder of onschadelijk oplosmiddel
- ✓ Simpele procedure
- ✓ Goedkope reagentia

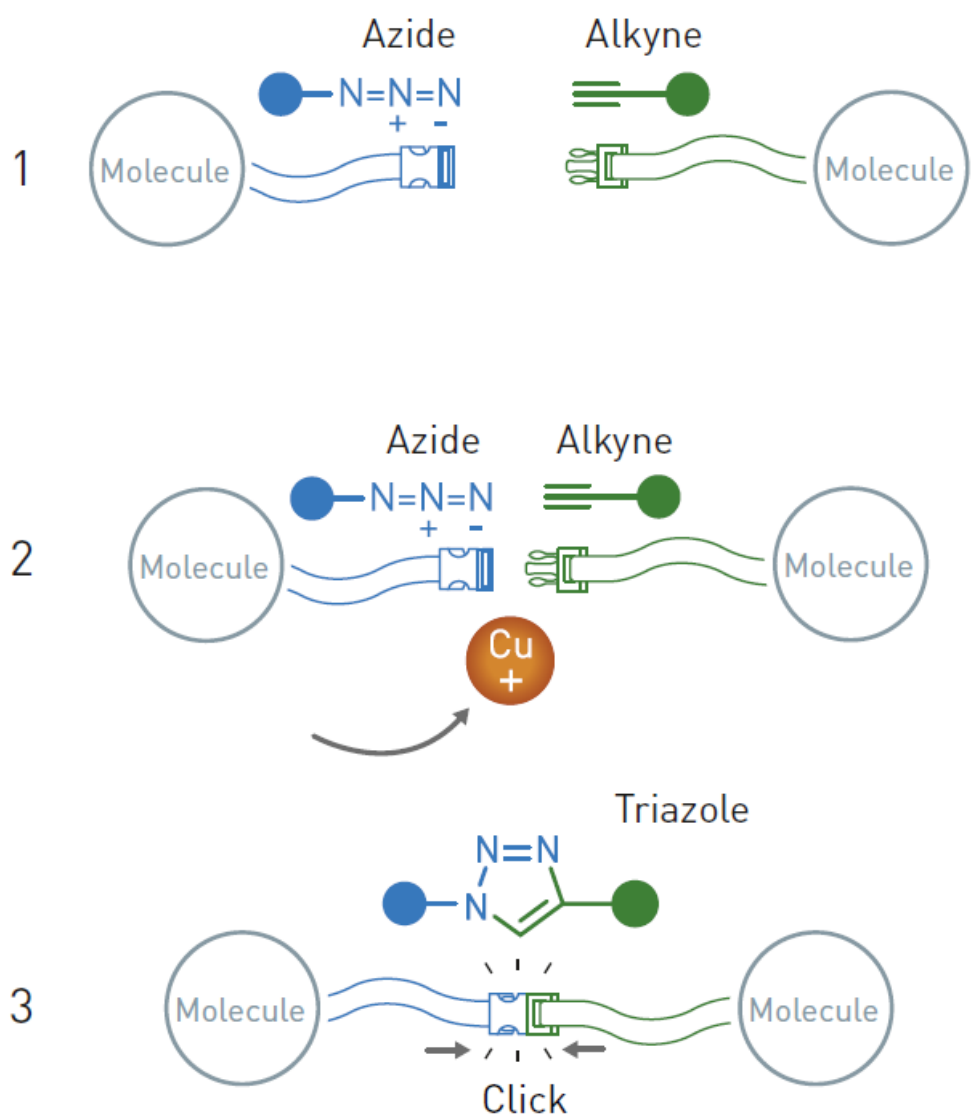
De ideale kandidaat: cycloadditie van azide en alkyn

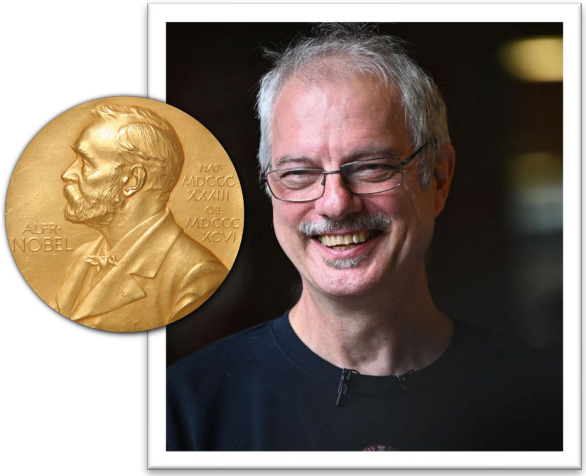




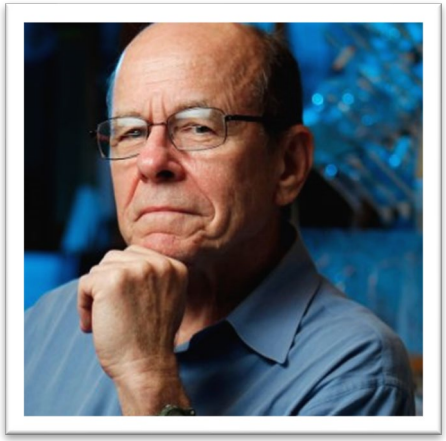
Morten Meldal
Serendipiteit

De ideale kandidaat: cycloadditie van azide en alkyn



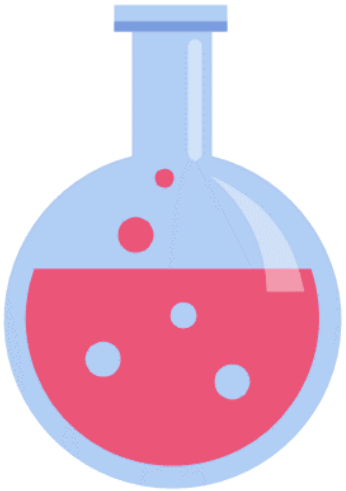


Morten Meldal
Serendipiteit

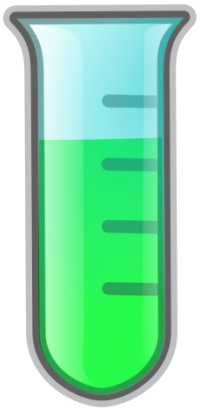


Barry Sharpless
Doelbewust

Volgende stap: waar vindt de klik reactie plaats?



vs



vs

in chemie lab **in vitro** **in vivo**

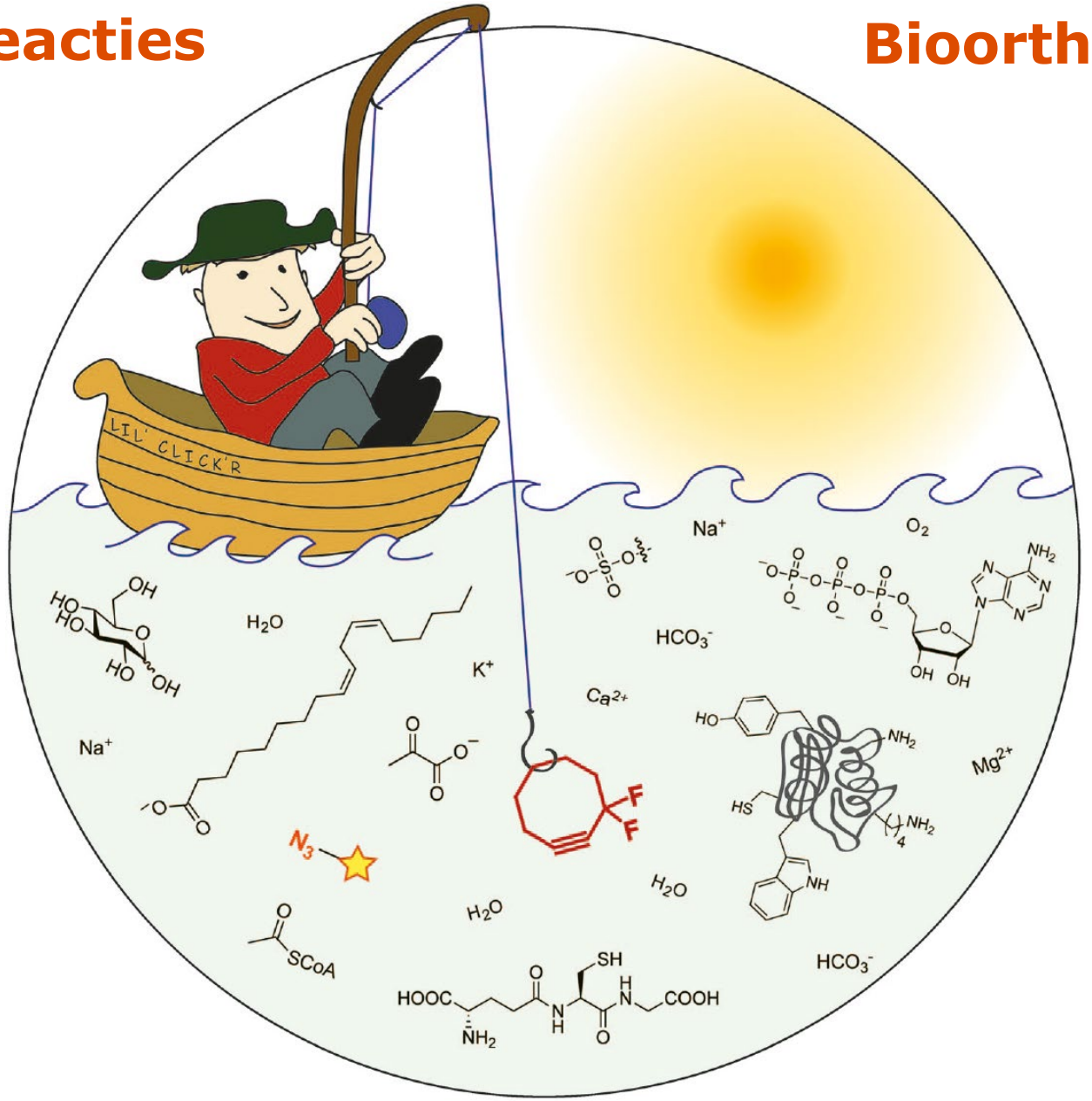
DS-65
18.6 mL H2O
1.6 mL
1.7.6
2.9
10.75
8 mL DCM

DS-65
18.6 mL H2O
1.6 mL
17.6
29

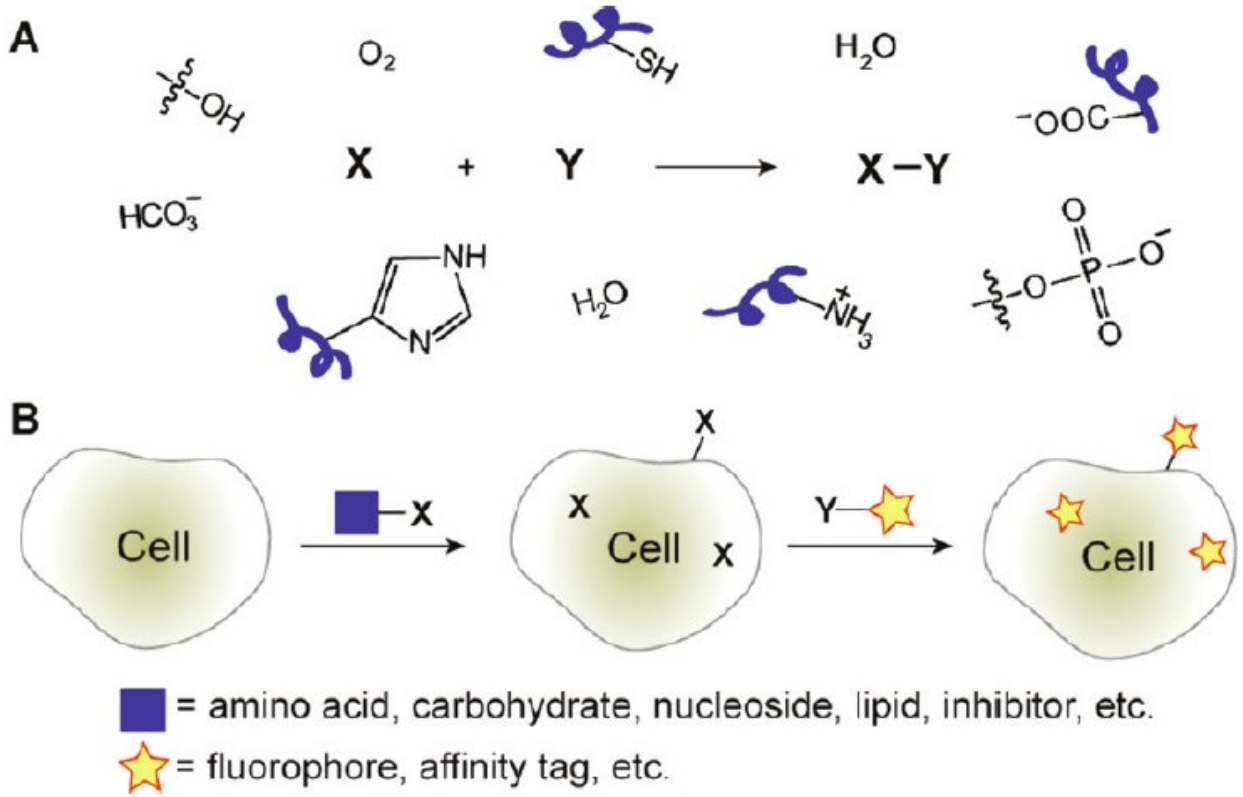
Vissen naar selectiviteit in een zee van functionaliteit

Klik Reacties

Bioorthogonale Chemie



‘Kunstmatige’ chemie in een levend organisme

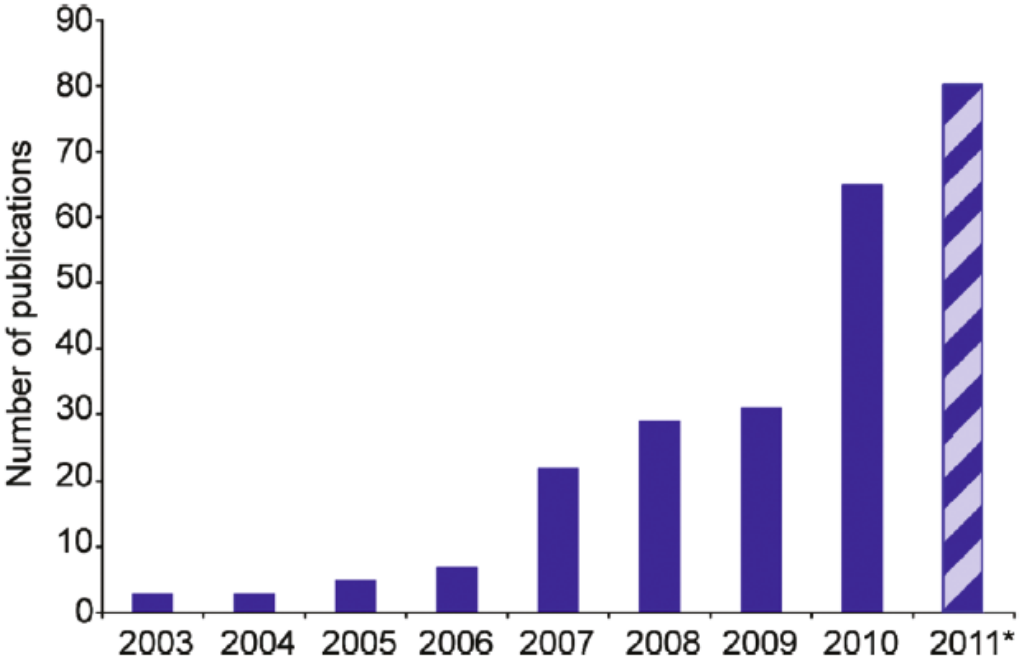


Selectiviteit: hoe controleer je de chemie?

Bioorthogonale chemie

Carolyn Bertozzi in 2003:

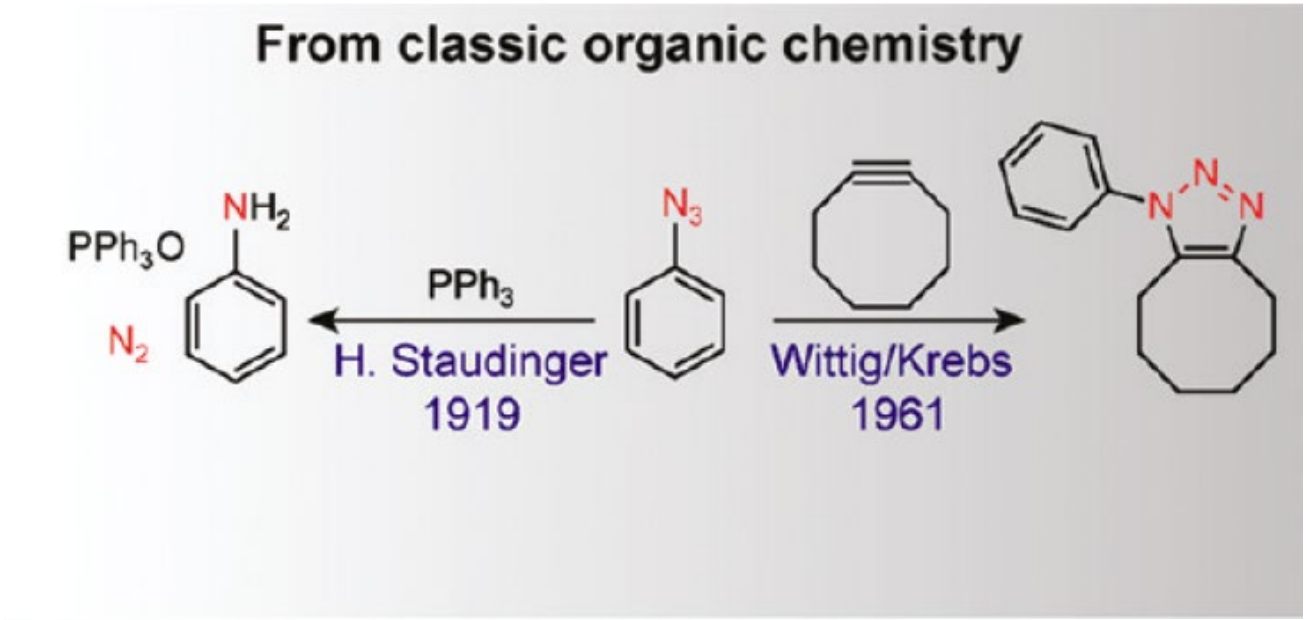
"Een chemische reactie die kan plaatsvinden in een levend system zonder de natuurlijke biochemische processen te verstoren"

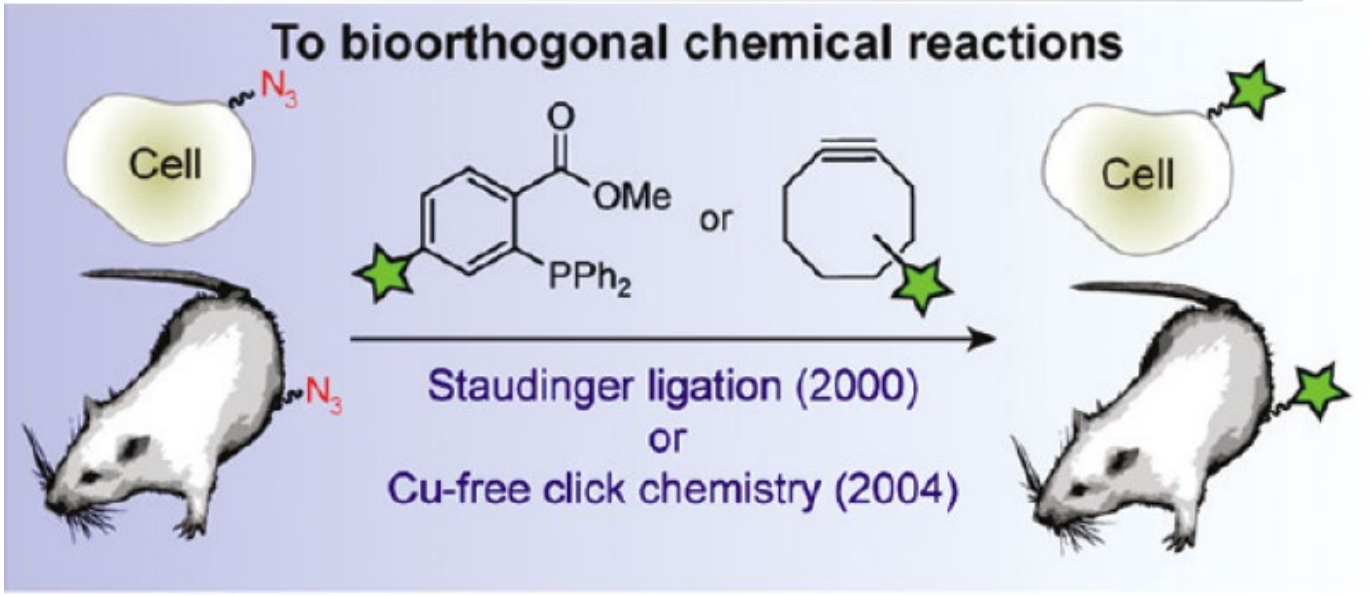


4 November 2022:

2015 wetenschappelijk publicaties

Bioorthogonale chemie

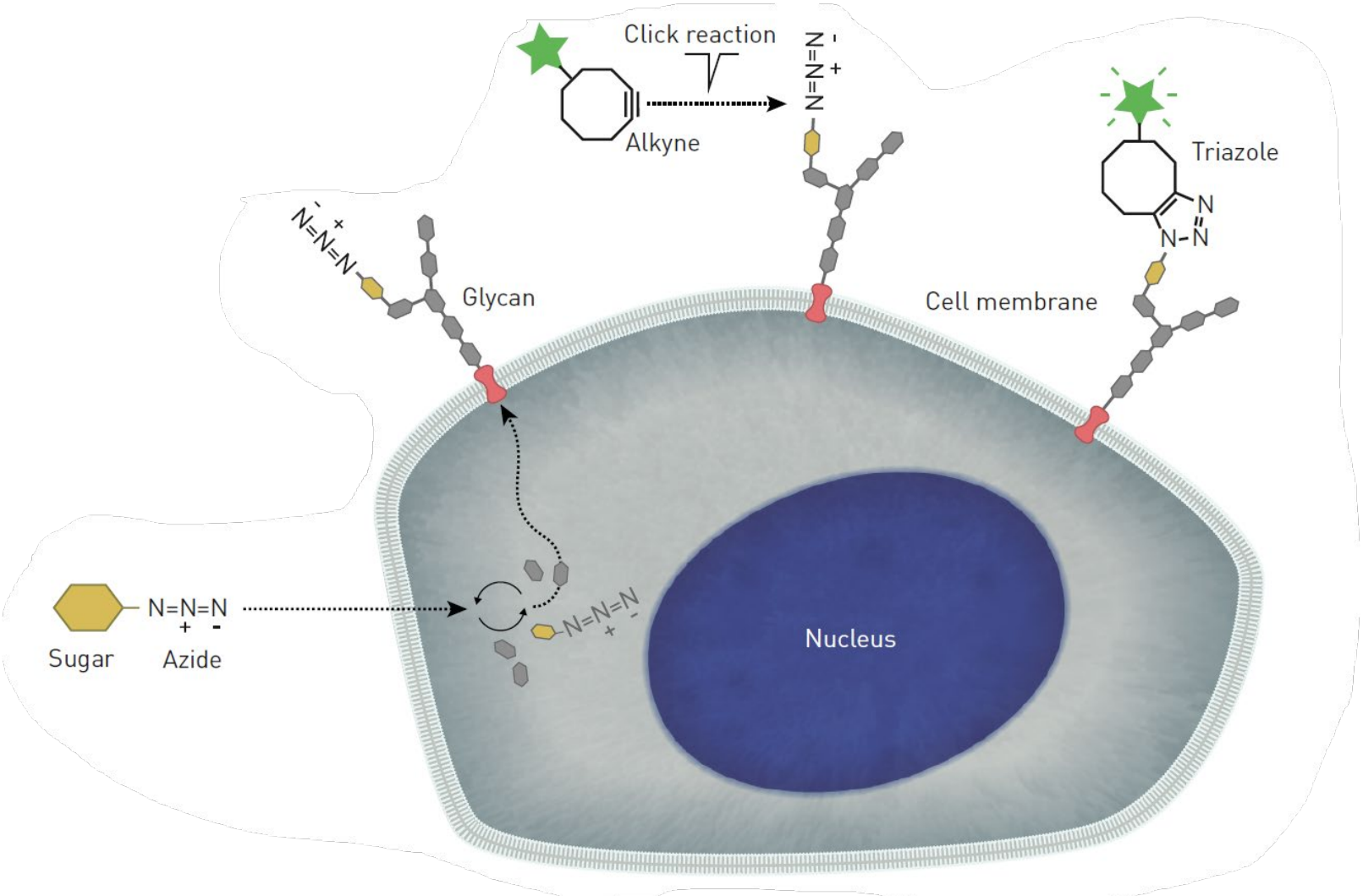




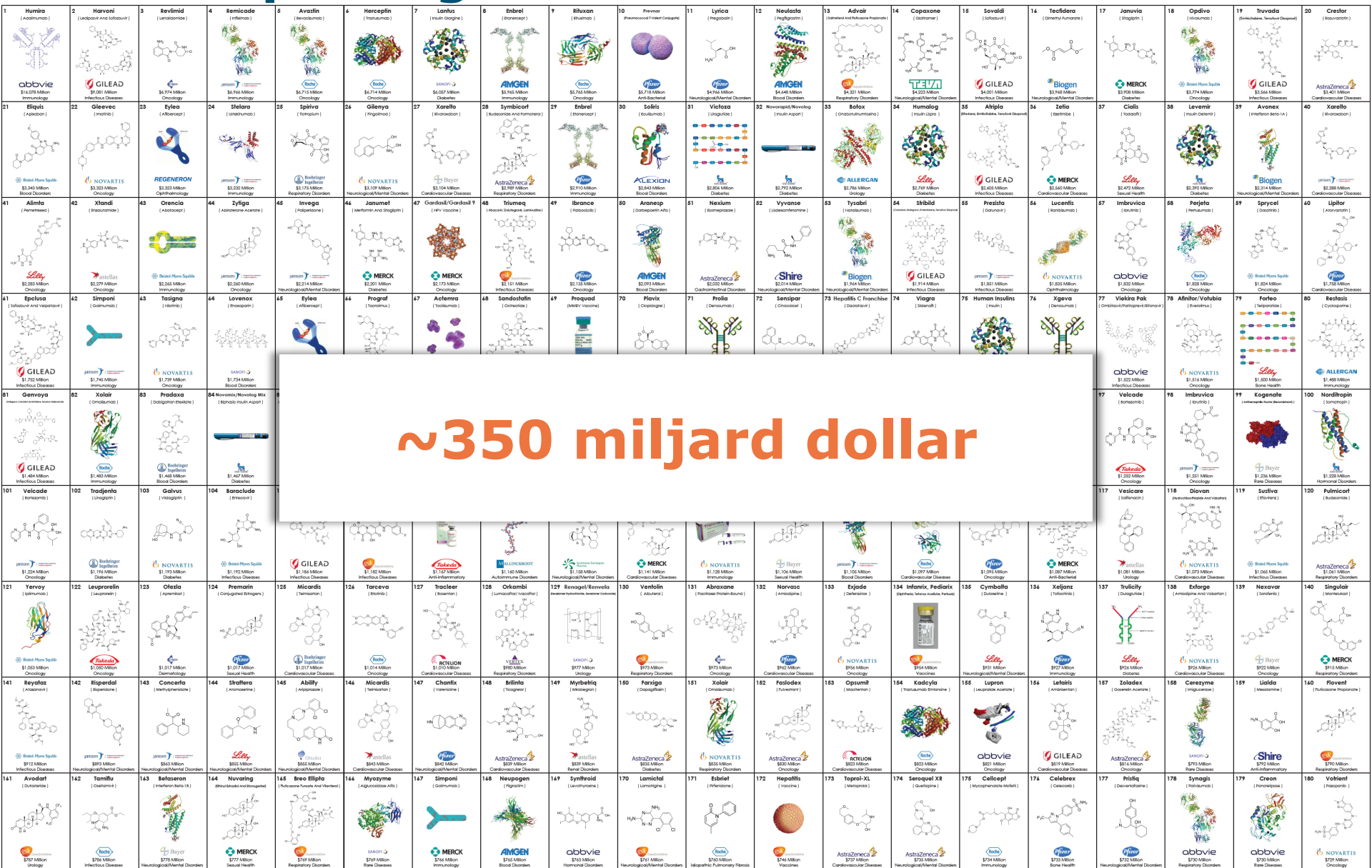
Bioorthogonale chemie

Carolyn Bertozzi in C2W magazine 2021:

Glycobiochemie wordt de nieuwe grote trend in biofarma



Top 200 geneesmiddelen USA 2016



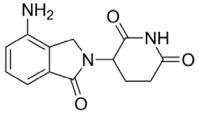
~350 miljard dollar

Top 200 geneesmiddelen USA 2016

1 Humira (Adalimumab) abbvie $16,078 Million Immunology	2 Harvoni (Ledipasvir And Sofosbuvir) GILEAD $9,081 Million Infectious Diseases	3 Revlimid (Lenalidomide) $6,974 Million Oncology	4 Remicade (Infliximab) janssen $6,966 Million Immunology	5 Avastin (Bevacizumab) Roche $6,715 Million Oncology	6 Herceptin (Trastuzumab) Roche $6,714 Million Oncology	7 Lantus (Insulin Glargine) SANOFI $6,057 Million Diabetes	8 Enbrel (Etanercept) AMGEN $5,965 Million Immunology	9 Rituxan (Rituximab) Roche $5,765 Million Oncology	10 Prevnar (Pneumococcal 7-Valent Conjugate) Pfizer $5,718 Million Anti-Bacterial	11 Lyrica (Pregabalin) Pfizer $4,966 Million Neurological/Mental Disorders	12 Neulasta (Pegfilgrastim) AMGEN $4,648 Million Blood Disorders	13 Advair (Salmeterol And Fluticasone Propionate) GSK $4,321 Million Respiratory Disorders	14 Copaxone (Glatiramer) TEVA $4,223 Million Neurological/Mental Disorders	15 Sovaldi (Sofosbuvir) GILEAD $4,001 Million Infectious Diseases	16 Tecfidera (Dimethyl Fumarate) Biogen $3,968 Million Neurological/Mental Disorders	17 Januvia (Sitagliptin) MERCK $3,908 Million Diabetes	18 Opdivo (Nivolumab) Bristol-Myers Squibb $3,774 Million Oncology	19 Truvada (Emtricitabine, Tenofovir Disoproxil) GILEAD $3,566 Million Infectious Diseases	20 Crestor (Rosuvastatin) AstraZeneca $3,401 Million Cardiovascular Diseases
21 Eliquis (Apixaban) Bristol-Myers Squibb $3,340 Million Blood Disorders	22 Gleevec (Imatinib) NOVARTIS $3,323 Million Oncology	23 Eylea (Aflibercept) REGENERON $3,323 Million Ophthalmology	24 Stelara (Ustekinumab) janssen $3,202 Million Immunology	25 Spiriva (Tiotropium) Boehringer Ingelheim $3,176 Million Respiratory Disorders	26 Gilenya (Fingolimod) NOVARTIS $3,109 Million Neurological/Mental Disorders	27 Xarelto (Rivaroxaban) Bayer $3,104 Million Cardiovascular Diseases	28 Symbicort (Budesonide And Formoterol) AstraZeneca $2,989 Million Respiratory Disorders	29 Enbrel (Etanercept) Pfizer $2,910 Million Immunology	30 Soliris (Eculizumab) ALEXION $2,843 Million Blood Disorders	31 Victoza (Liraglutide) Novo Nordisk $2,804 Million Diabetes	32 Novorapid/Novolog (Insulin Aspart) Novo Nordisk $2,792 Million Diabetes	33 Botox (Onabotulinumtoxina) ALLERGAN $2,786 Million Urology	34 Humalog (Insulin Lispro) Lilly $2,769 Million Diabetes	35 Atripla (Efavirenz, Emtricitabine, Tenofovir Disoproxil) GILEAD $2,605 Million Infectious Diseases	36 Zetia (Ezetimibe) MERCK $2,560 Million Cardiovascular Diseases	37 Cialis (Tadalafil) Lilly $2,472 Million Sexual Health	38 Levemir (Insulin Detemir) Novo Nordisk $2,392 Million Diabetes	39 Avonex (Interferon Beta-1A) Biogen $2,314 Million Neurological/Mental Disorders	40 Xarelto (Rivaroxaban) janssen $2,288 Million Cardiovascular Diseases
41 Alimta (Pemetrexed) Lilly $2,283 Million Oncology	42 Xtandi (Enzalutamide) Astellas $2,279 Million Oncology	43 Orencia (Abatacept) Bristol-Myers Squibb $2,265 Million Immunology	44 Zytiga (Abiraterone Acetate) janssen $2,260 Million Oncology	45 Invega (Paliperidone) janssen $2,214 Million Neurological/Mental Disorders	46 Janumet (Metformin And Sitagliptin) MERCK $2,201 Million Diabetes	47 Gardasil/Gardasil 9 (HPV Vaccine) MERCK $2,173 Million Oncology	48 Triumeq (Abacavir, Dolutegravir, Lamivudine) GSK $2,151 Million Infectious Diseases	49 Ibrance (Palbociclib) Pfizer $2,136 Million Oncology	50 Aranesp (Darbepoetin Alfa) AMGEN $2,093 Million Blood Disorders	51 Nexium (Esomeprazole) AstraZeneca $2,032 Million Gastrointestinal Disorders	52 Vyvanse (Lisdexamfetamine) Shire $2,014 Million Neurological/Mental Disorders	53 Tysabri (Natalizumab) Biogen $1,964 Million Neurological/Mental Disorders	54 Stribild (Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Disoproxil) GILEAD $1,914 Million Infectious Diseases	55 Prezista (Darunavir) janssen $1,851 Million Infectious Diseases	56 Lucentis (Ranibizumab) NOVARTIS $1,835 Million Ophthalmology	57 Imbruvica (Ibrutinib) abbvie $1,832 Million Oncology	58 Perjeta (Pertuzumab) Roche $1,828 Million Oncology	59 Sprycel (Dasatinib) Bristol-Myers Squibb $1,824 Million Oncology	60 Lipitor (Atorvastatin) Pfizer $1,768 Million Cardiovascular Diseases
61 Epclusa (Sofosbuvir And Velpatasvir) GILEAD $1,752 Million Infectious Diseases	62 Simponi (Golimumab) janssen $1,745 Million Immunology	63 Tasigna (Nilotinib) NOVARTIS $1,739 Million Oncology	64 Lovenox (Enoxaparin) SANOFI $1,734 Million Blood Disorders	65 Eylea (Aflibercept) Bayer $1,723 Million Ophthalmology	66 Prograf (Tacrolimus) Astellas $1,695 Million Immunology	67 Actemra (Tocilizumab) Roche $1,680 Million Immunology	68 Sandostatin (Octreotide) NOVARTIS $1,646 Million Oncology	69 Proquad (MMRV Vaccine)	70 Plavix (Clopidogrel)	71 Prolia (Denosumab)	72 Semsipar (Cinacalcet)	73 Hepatitis C Franchise	74 Viagra (Sildenafil)	75 Human Insulins (Insulin)	76 Xgeva (Denosumab)	77 Viekira Pak (Ombitasvir/Paritaprevir/Ritonavir)	78 Afinitor/Votubia (Everolimus)	79 Forteo (Teriparatide)	80 Restasis (Cyclosporine)
81 Genvoya (Emtricitabine, Cobicistat, Elvitegravir, Tenofovir Alafenamide) GILEAD $1,484 Million Infectious Diseases	82 Xolair (Omalizumab) Roche $1,483 Million Immunology	83 Pradaxa (Dabigatran Etexilate) Boehringer Ingelheim $1,468 Million Blood Disorders	84 Novomix/Novolog Mix (Biphasic Insulin Aspart) Novo Nordisk $1,467 Million Diabetes	85 Haemophilia (Recombinant Human Coagulation Factor VIII) Baxalta $1,466 Million Blood Disorders	86 Rituxan (Rituximab) Roche $1,462 Million Oncology	87 Complera (Rilpivirine, Emtricitabine, Tenofovir Disoproxil Fumarate) GILEAD $1,457 Million Infectious Diseases	88 Invokana (Canagliflozin/Canagliflozin, Metformin HCl) janssen $1,407 Million Diabetes	89											
101 Velcade (Bortezomib) janssen $1,224 Million Oncology	102 Tradjenta (Linagliptin) Boehringer Ingelheim $1,196 Million Diabetes	103 Galvus (Vildagliptin) NOVARTIS $1,193 Million Diabetes	104 Baraclude (Entecavir) Bristol-Myers Squibb $1,192 Million Infectious Diseases	105 Viread (Tenofovir Disoproxil) GILEAD $1,186 Million Infectious Diseases	106 Tivicay (Dolutegravir) GSK $1,182 Million Infectious Diseases	107 Entyvio (Vedolizumab) Takeda $1,167 Million Anti-Inflammatory	108 Actiar (Carfilzomib) AMGEN $1,160 Million Autoimmune Disorders	109											
121 Yervoy (Ipilimumab) Bristol-Myers Squibb $1,063 Million Oncology	122 Leuprorelin (Leuprorelin) Takeda $1,060 Million Oncology	123 Otezla (Apremilast) Celgene $1,017 Million Dermatology	124 Premarin (Conjugated Estrogens) Pfizer $1,012 Million Sexual Health	125 Micardis (Telmisartan) Boehringer Ingelheim $1,017 Million Cardiovascular Diseases	126 Tarceva (Erlotinib) Roche $1,014 Million Oncology	127 Tracleer (Bosentan) ACTELION $1,010 Million Cardiovascular Diseases	128 Orkambi (Lumacaftor/Ivacaftor) VERTEX $980 Million Respiratory Disorders	129 (Seroxat)											
141 Reyataz (Atazanavir) Bristol-Myers Squibb $912 Million Infectious Diseases	142 Risperdal (Risperidone) janssen $893 Million Neurological/Mental Disorders	143 Concerta (Methylphenidate) janssen $863 Million Neurological/Mental Disorders	144 Strattera (Atomoxetine) Lilly $855 Million Neurological/Mental Disorders	145 Abilify (Aripiprazole) Otsuka $855 Million Neurological/Mental Disorders	146 Micardis (Telmisartan) Astellas $843 Million Cardiovascular Disorders	147 Chantix (Varenicline) Pfizer $842 Million Neurological/Mental Disorders	148 Brilinta (Ticagrelor) AstraZeneca $839 Million Cardiovascular Disorders	149 Myrbetriq (Mirabegron) Astellas $839 Million Renal Disorders	150 Farxiga (Dapagliflozin) AstraZeneca $835 Million Diabetes	151 Xolair (Omalizumab) NOVARTIS $835 Million Respiratory Disorders	152 Faslodex (Fulvestrant) AstraZeneca $830 Million Oncology	153 Opsumit (Macitentan) ACTELION $823 Million Cardiovascular Disorders	154 Kadcyla (Trastuzumab Emtansine) Roche $823 Million Oncology	155 Lupron (Leuprolide Acetate) abbvie $821 Million Oncology	156 Letairis (Ambrisentan) GILEAD $819 Million Cardiovascular Disorders	157 Zoladex (Goserelin Acetate) AstraZeneca $816 Million Oncology	158 Cerezyme (Imiglucerase) SANOFI $793 Million Rare Diseases	159 Lialda (Mesalamine) Shire $792 Million Anti-Inflammatory	160 Flovent (Fluticasone Propionate) GSK $790 Million Respiratory Disorders
161 Avodart (Dutasteride) GSK $757 Million Urology	162 Tamiflu (Oseltamivir) Roche $756 Million Neurological/Mental Disorders	163 Betaseron (Interferon Beta-1B) Bayer $729 Million Neurological/Mental Disorders	164 Nuvaring (Ethinyl Estradiol And Etonogestrel) MERCK $727 Million Sexual Health	165 Breo Ellipta (Fluticasone Furoate And Vilanterol) GSK $709 Million Respiratory Disorders	166 Myozyme (Alglucosidase Alfa) SANOFI $709 Million Rare Diseases	167 Simponi (Golimumab) MERCK $766 Million Immunology	168 Neupogen (Filgrastim) AMGEN $760 Million Blood Disorders	169 Synthroid (Levothyroxine) abbvie $760 Million Hormonal Disorders	170 Lamictal (Lamotrigine) GSK $761 Million Neurological/Mental Disorders	171 Esbriet (Pirfenidone) Roche $760 Million Idiopathic Pulmonary Fibrosis	172 Hepatitis (Vaccine) GSK $746 Million Vaccines	173 Toprol-XL (Metoprolol) AstraZeneca $737 Million Cardiovascular Disorders	174 Seroquel XR (Quetiapine) AstraZeneca $735 Million Neurological/Mental Disorders	175 Celebrex (Celecoxib) Pfizer $733 Million Bone Health	176 Celebrex (Celecoxib) Pfizer $730 Million Cardiovascular Disorders	177 Pristiq (Desvenlafaxine) Pfizer $730 Million Neurological/Mental Disorders	178 Synagis (Palivizumab) abbvie $730 Million Respiratory Disorders	179 Creon (Pancrelipase) abbvie $730 Million Rare Diseases	180 Vytorin (Ezetimibe) NOVARTIS $729 Million Oncology
181 Zyprexa (Olanzapine) Lilly $725 Million Neurological/Mental Disorders	182 Aprovel (Irbesartan/Irbesartan, Hydrochlorothiazide) SANOFI $722 Million Cardiovascular Disorders	183 Kombiglyze (Saxagliptin/Saxagliptin, Metformin) AstraZeneca $720 Million Diabetes	184 Yasmin (Drospirenone And Ethinyl Estradiol) Bayer $719 Million Sexual Health	185 Fabrazyme (Agalsidase Beta) SANOFI $714 Million Rare Diseases	186 Benefix (Coagulation Factor IX) Pfizer $712 Million Rare Diseases	187 Pantoprazole (Pantoprazole) Takeda $709 Million Gastrointestinal Disorders	188 Epzicom (Abacavir And Lamivudine) GSK $704 Million Infectious Diseases	189 Kalydeco (Ivacaftor) VERTEX $703 Million Respiratory Disorders	190 Augmentin (Amoxicillin And Clavulanate) GSK $698 Million Anti-Bacterial	191 Kyprolis (Carfilzomib) AMGEN $692 Million Oncology	192 Lumigan (Bimatoprost) ALLERGAN $688 Million Ophthalmology	193 Toujeo (Insulin Glargine) SANOFI $688 Million Diabetes	194 Erbitux (Cetuximab) Lilly $687 Million Oncology	195 Zostavax (Zoster Vaccine Live) MERCK $685 Million Infectious Diseases	196 Cinryze (Complement C1 Esterase) Shire $680 Million Cardiovascular Disorders	197 Pulmozyme (Dornase Alfa) Roche $678 Million Rare Diseases	198 Synagis (Palivizumab) AstraZeneca $677 Million Respiratory Disorders	199 Ranexa (Ranolazine) GILEAD $677 Million Cardiovascular Disorders	200 Androgel (Testosterone) abbvie $675 Million Hormonal Disorders

3 Revlimid

(Lenalidomide)

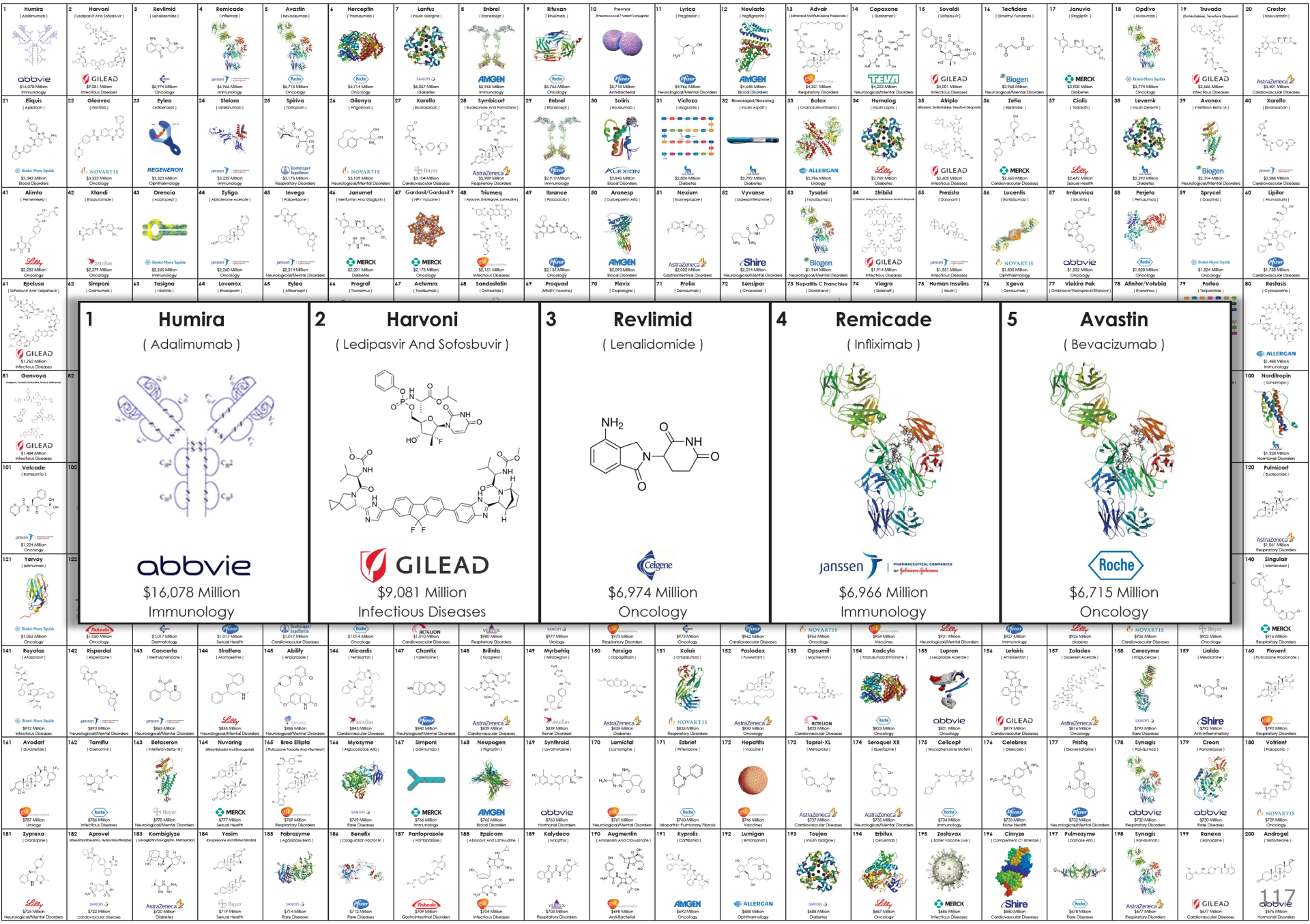


Celgene

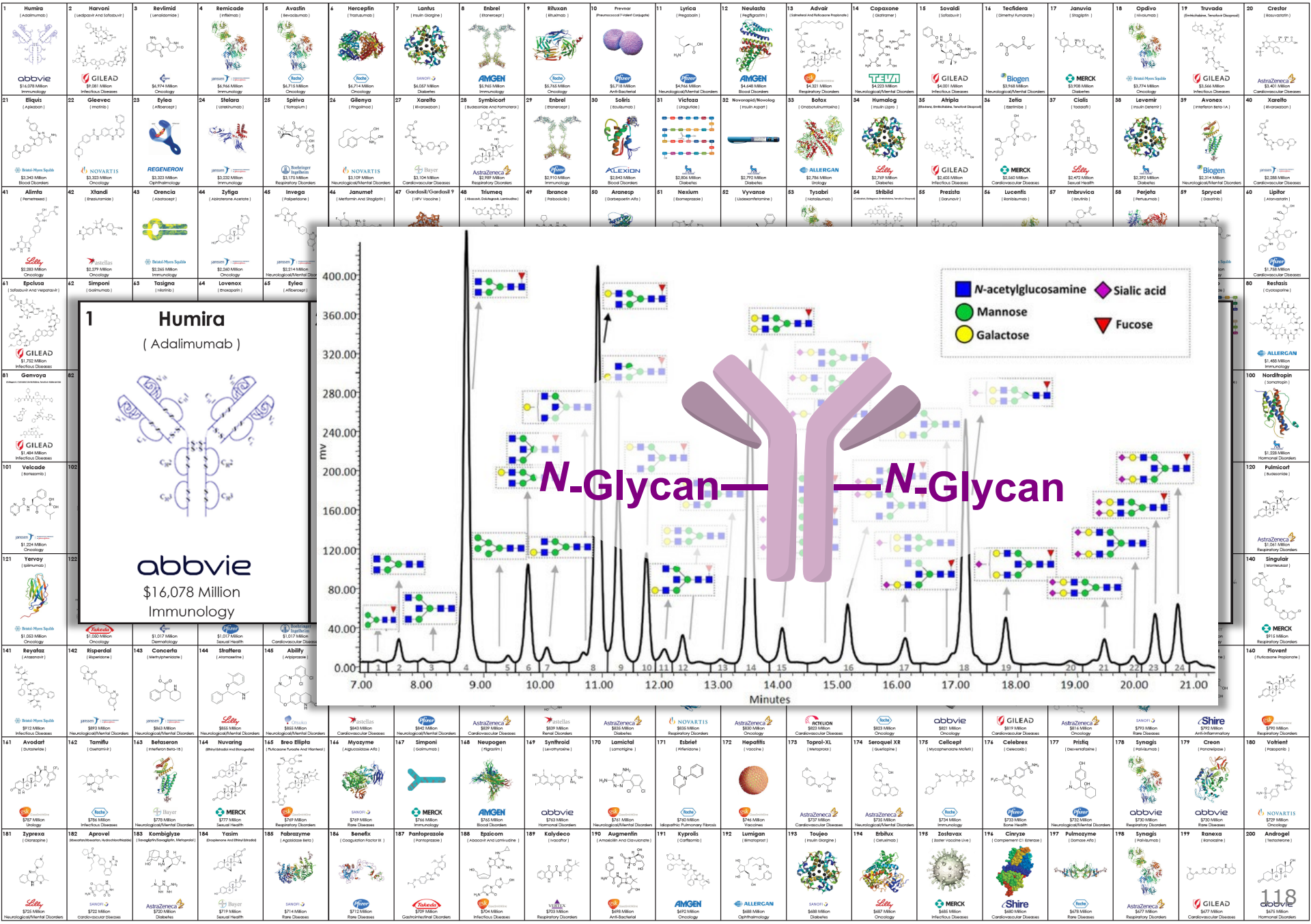
$6,974 Million

Oncology

Steeds meer: Biofarmaceutische geneesmiddelen/Biologicals

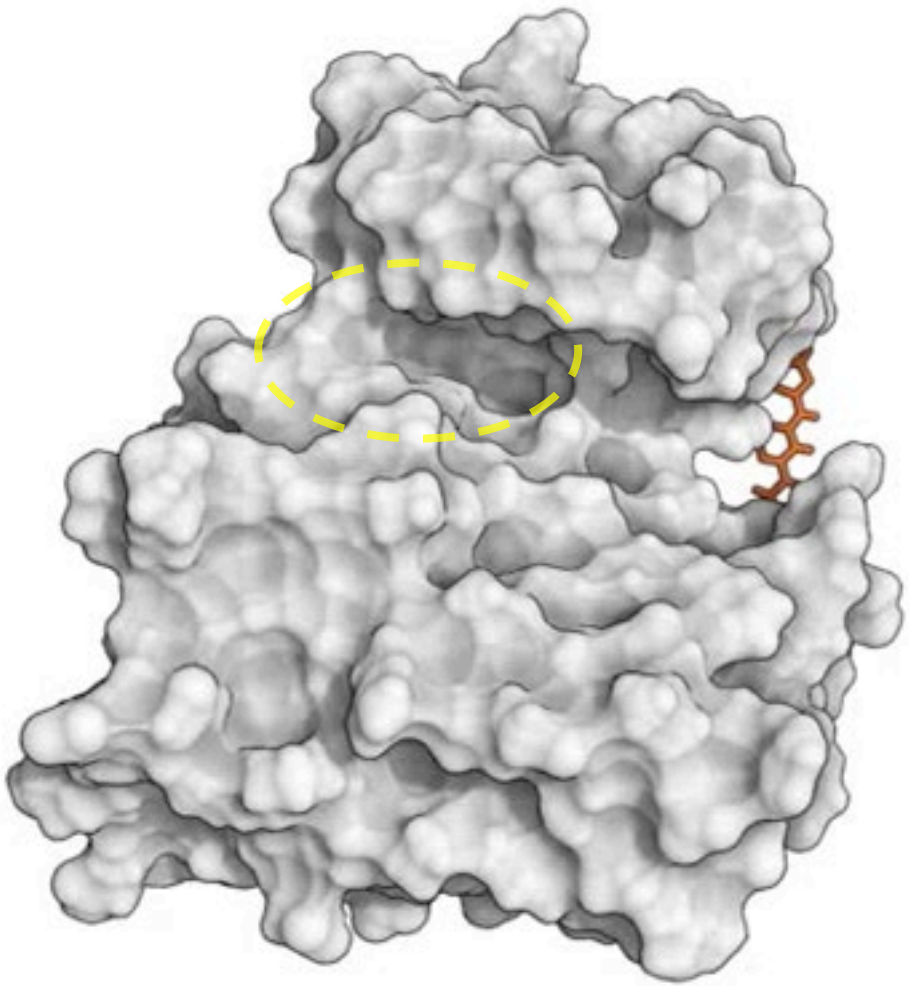


Steeds meer: Biofarmaceutische geneesmiddelen/Biologicals



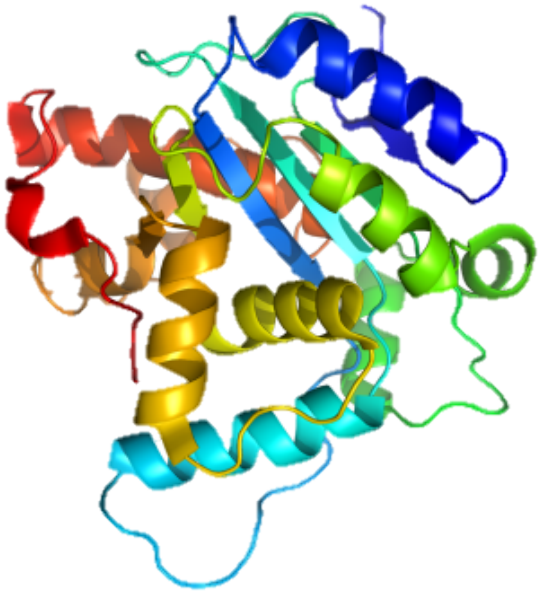
Geneesmiddel: één perfect passende sleutel?

Simulatie receptor ligand bindings "dans"

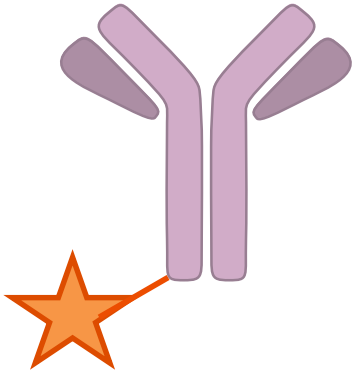


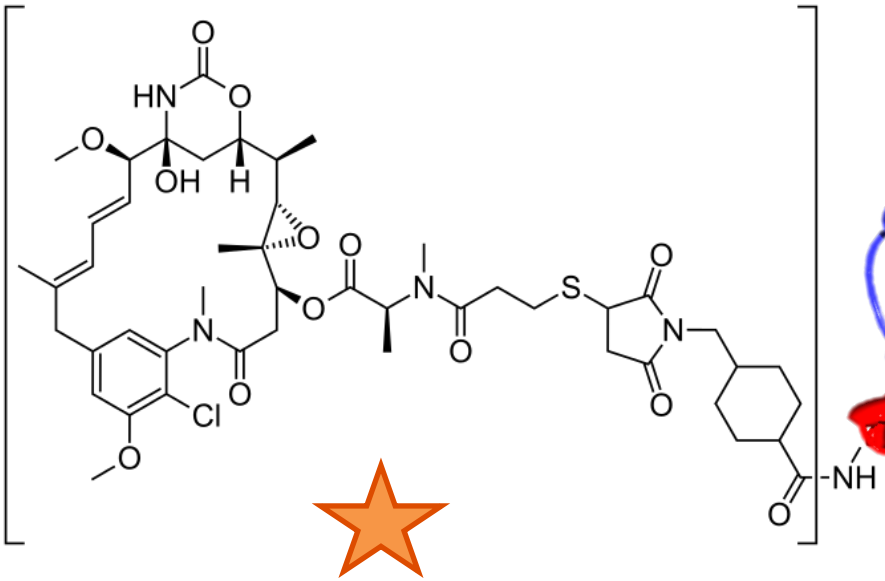
Receptor: Src kinase **Ligand:** antikanker medicijn dasatinib

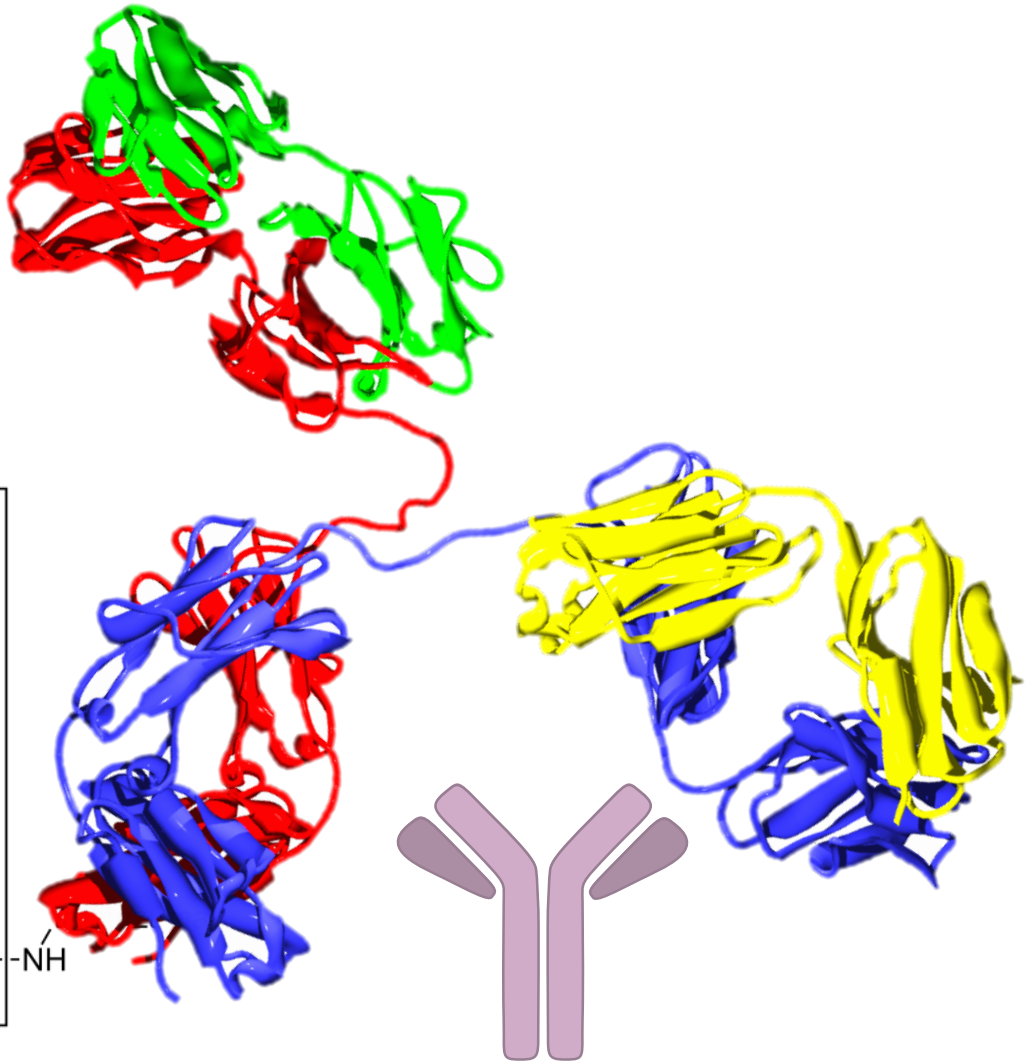
Waarom zou je iets aan een eiwit willen klikken



Biologics via bioorthogonal klik chemie



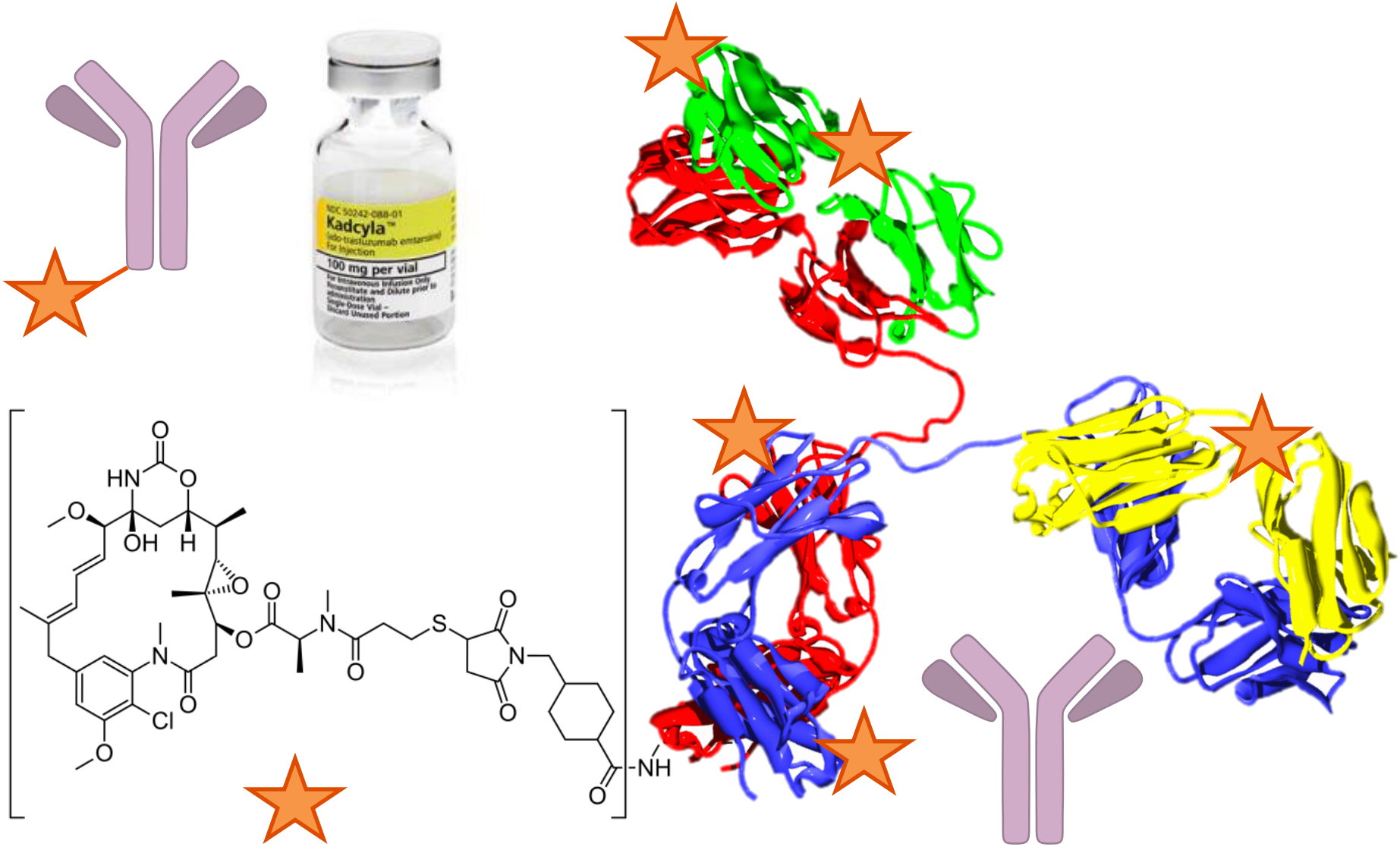




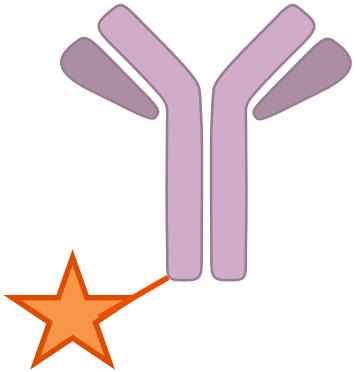
Mertansine cytotoxine

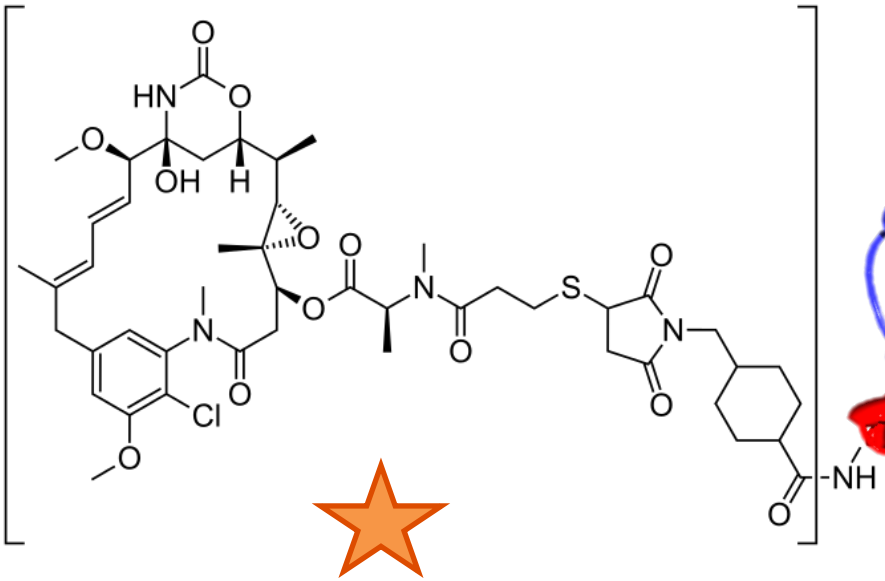
Anti-HER2 receptor monoclonaal antilichaam

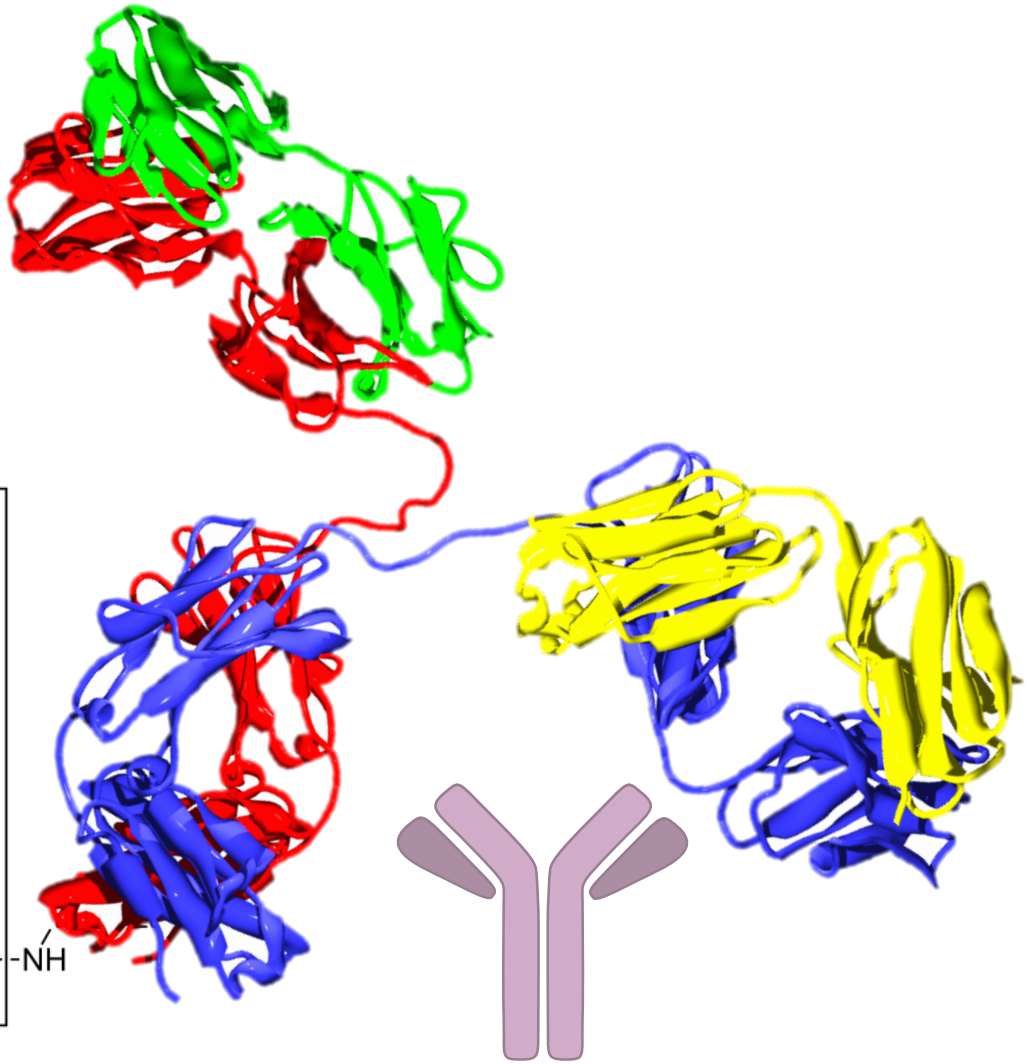
Biologics via bioorthogonal klik chemie



Biologics via bioorthogonal klik chemie



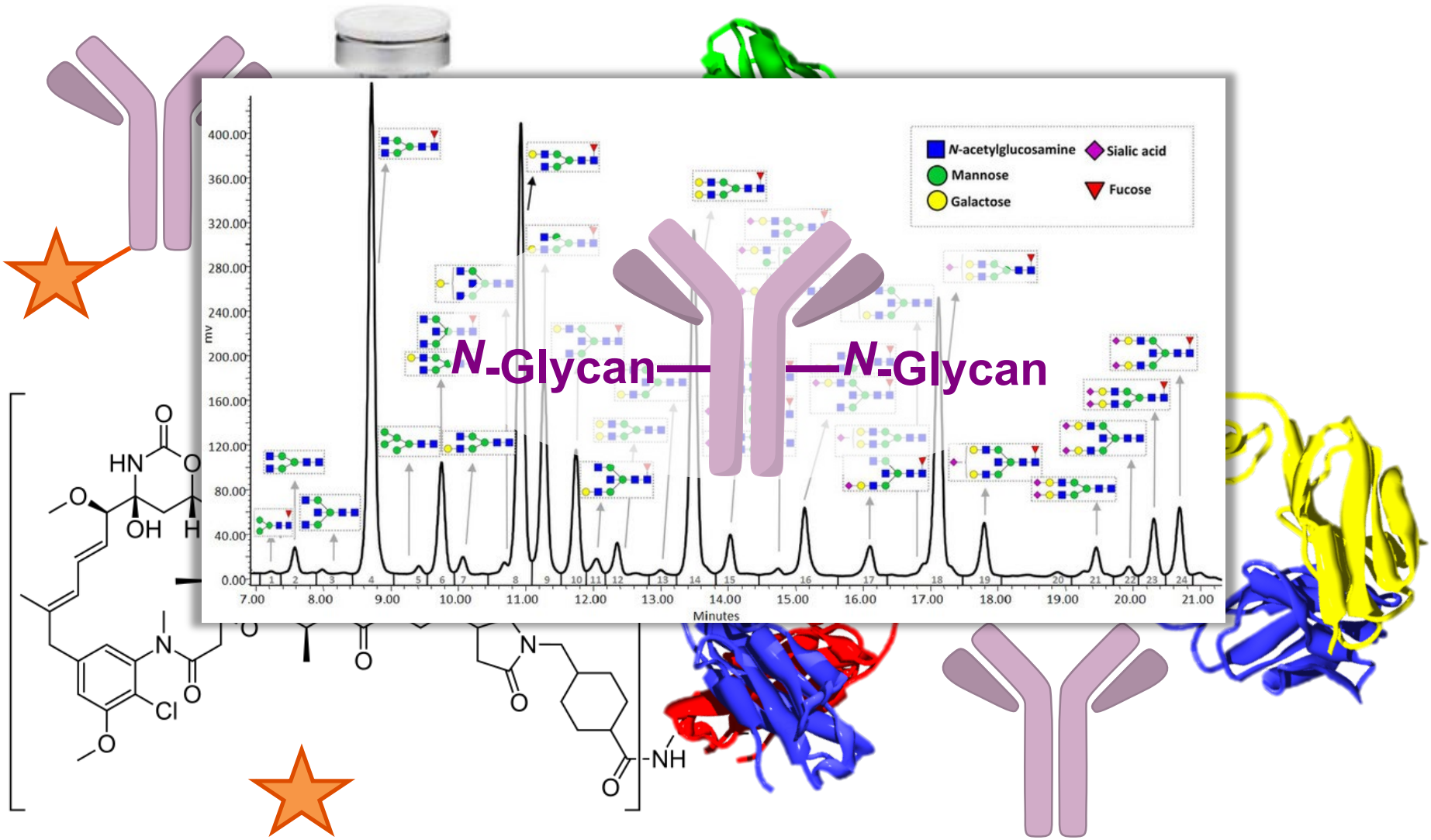




Mertansine cytotoxine

Anti-HER2 receptor monoclonaal antilichaam

Biologics via bioorthogonal klik chemie



Mertansine cytotoxine

Anti-HER2 receptor monoclonaal antilichaam

Is suiker altijd zoet?

Inhoud van mijn lezing:

- **Introducties:** chemische biologie → mij → suikers
- **Onderzoek:** slimmer zijn dan het griep virus
- **Onderzoek:** de perfecte omhelsing van Cholera
- **In het nieuws:** Klik chemie is gaaf!
- **Echt gebeurd:** Zoet biomoleculair moord mysterie
- Chemie op de basisschool?

Utrecht University

Tom Wennekes

Imagination at work

Woudschoten Chemie Conferentie 2022

C3

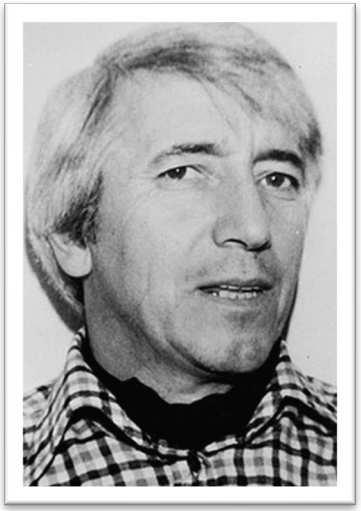
Zoet biomoleculair moord mysterie:

De dodelijke paraplu

Universiteit Utrecht

Tom Wennekes

Het mysterie begint op: 7 September 1978



Bulgaarse vluchteling
Georgi Markov

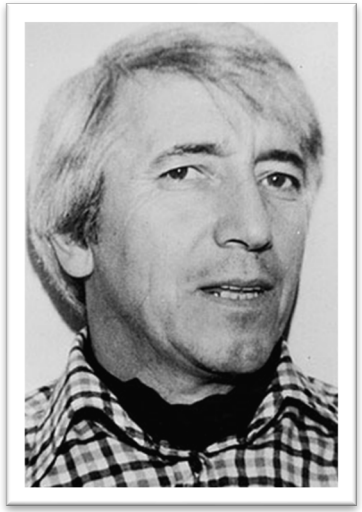
- Georgi werkt voor de BBC en staat op de bus te wachten bij Waterloo Bridge
- Een man met een paraplu loopt langs en Georgi voelt een kleine prik in zijn been
- Hij linkt het op dat moment niet aan de man en negeert het voorval
- Binnen enkele uren daarna heeft hij echter koorts en een dag later is hij dood

Wat gebeurde er?

Gedurende de autopsie vonden onderzoekers:

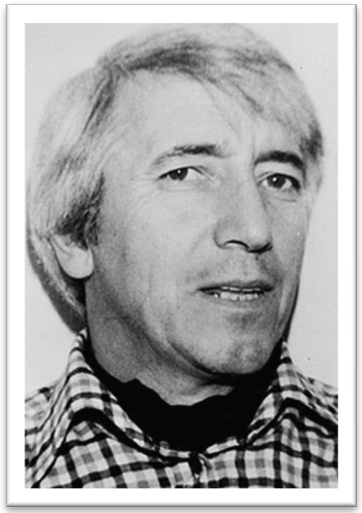
Een heel klein metalen kogeltje in een rode bult op zijn been

De dodelijke paraplu:



Bulgaarse vluchteling
Georgi Markov
(1929 –1978)

De dodelijke paraplu:



Bulgaarse vluchteling
Georgi Markov
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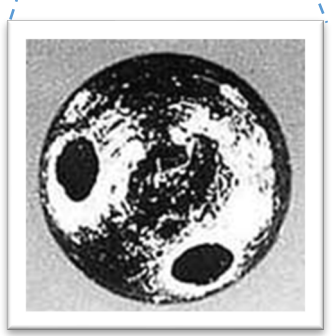


Metaal kogeltje
met twee holtes
0.2 mg Ricine

Biomoleculair moord mysterie:

De dodelijke paraplu

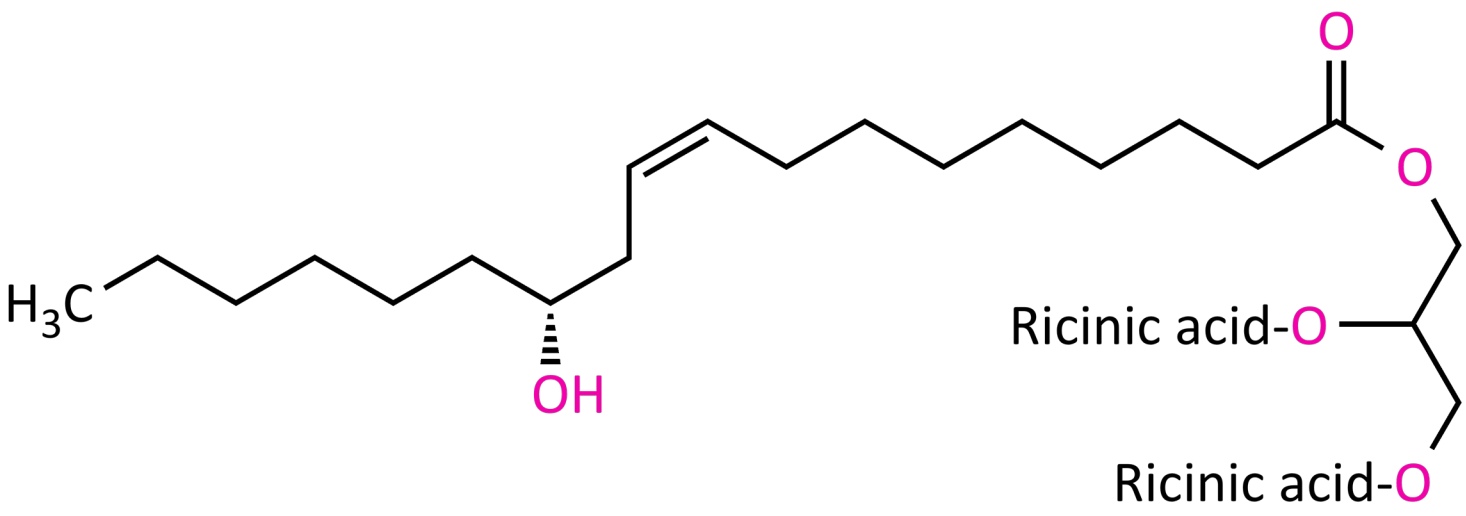
Ricine: een van de meest dodelijk natuurlijke gifstoffen

een paraplu

Hoe kan een eiwit een persoon doden?

Castor olie – Wonder olie

Castor olie – Wonder olie



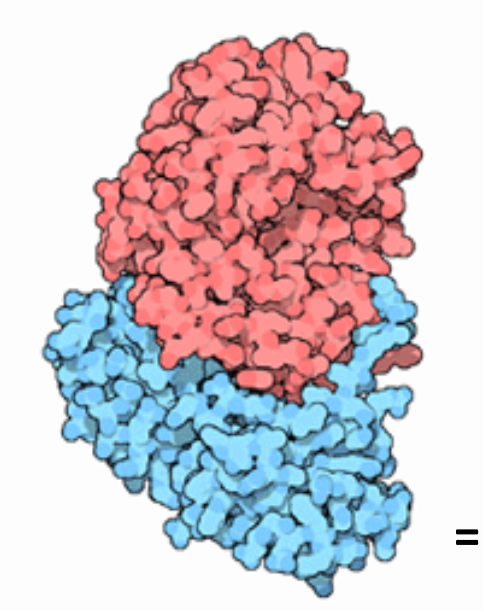
~95%

Castor olie plant, *Ricinus communis*

Wonderboom

Castor ‘bonen’ – Wonder ‘bonen’ van *Ricinus communis*

Eiwit: Ricine uit de wonderboon

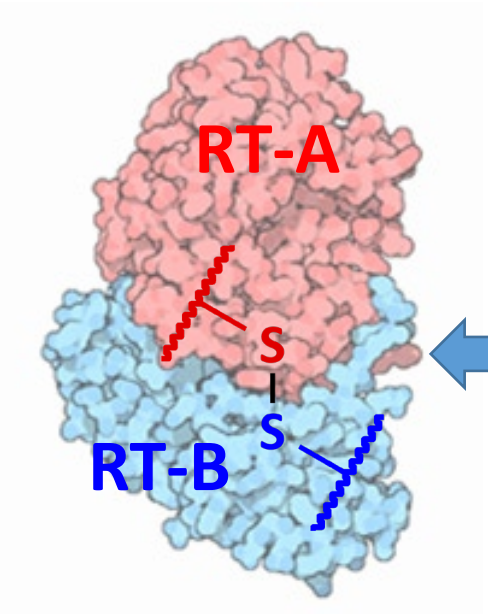


Ricin toxine-A

= dodelijk als het in de cel kan komen

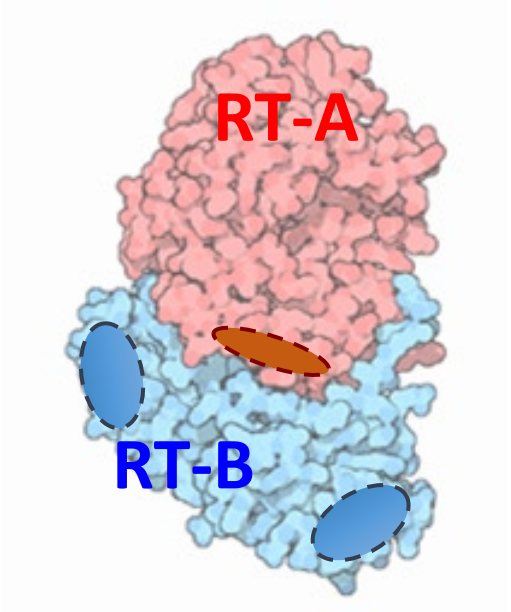
Ricin toxine-B

= helpt Ricin toxine A om in de cel te komen

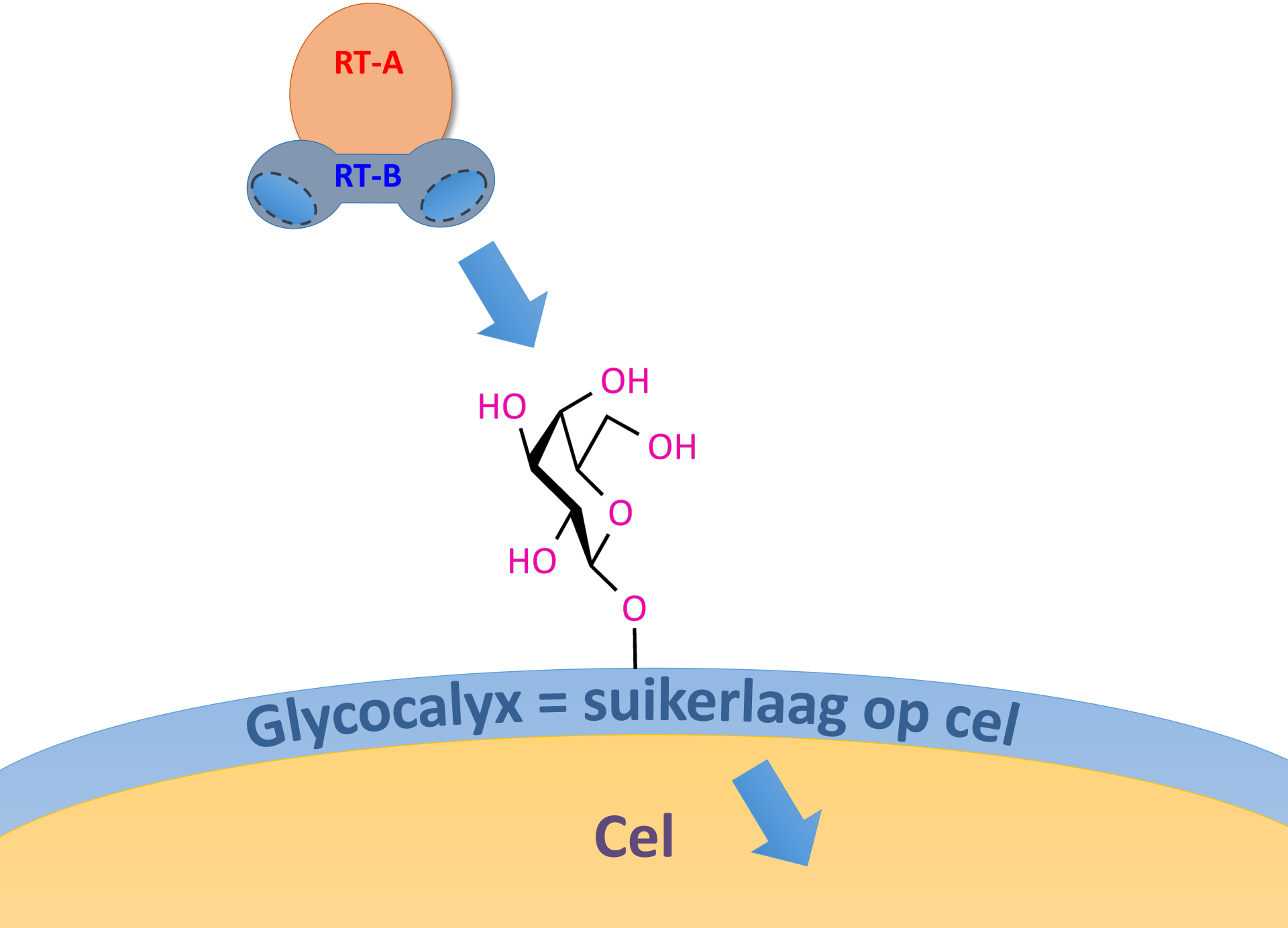


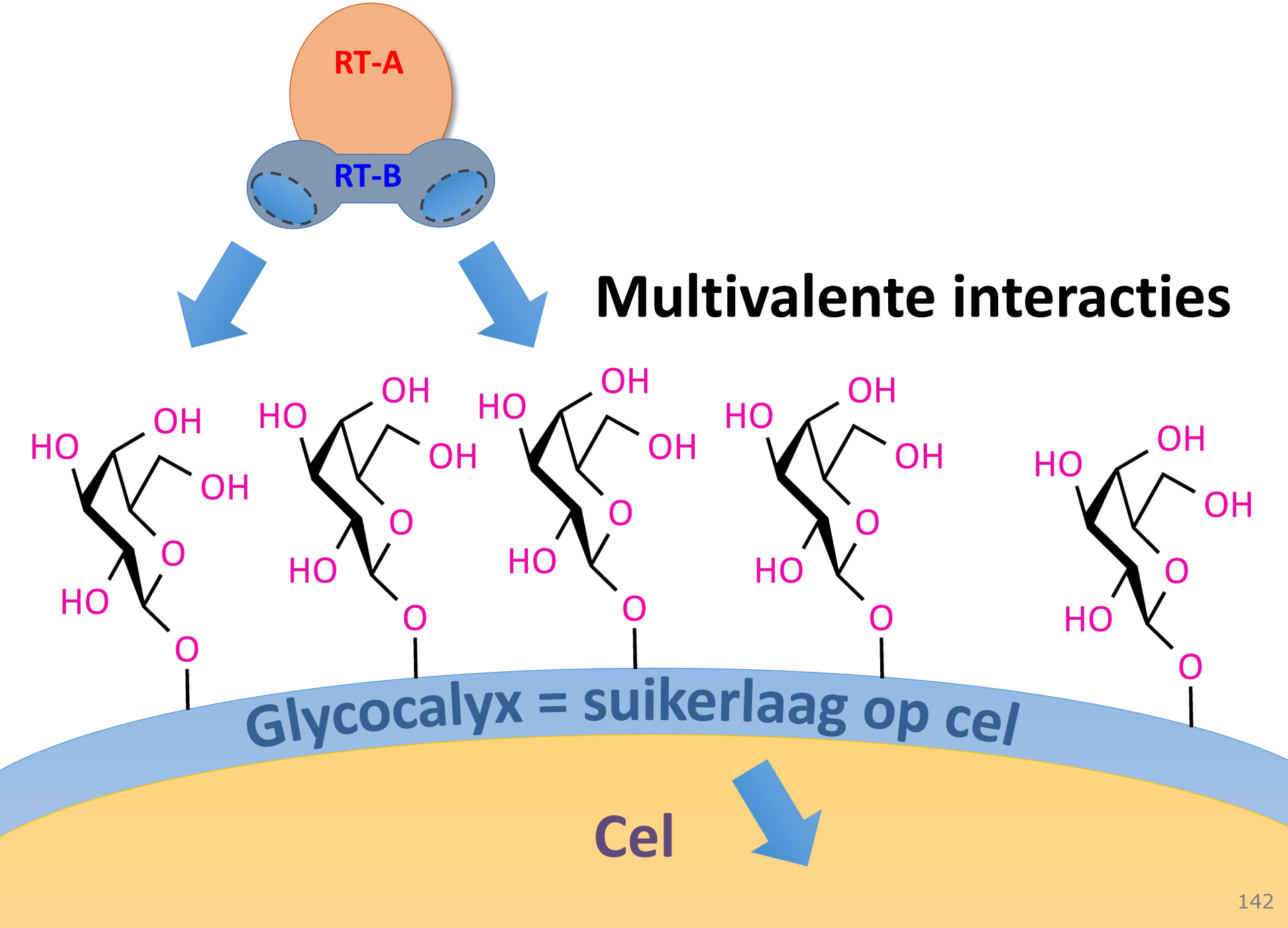
Galactose lectine

RT-A en RT-B zijn verbonden via disulfide brug



Twee galactose bindings sites


RT-A
RT-B
OH
HO
OH
O
HO
O
Glycocalyx = suikerlaag op cel
Cel


RT-A
RT-B
Multivalente interacties
HO
OH
OH
O
HO
O
HO
OH
OH
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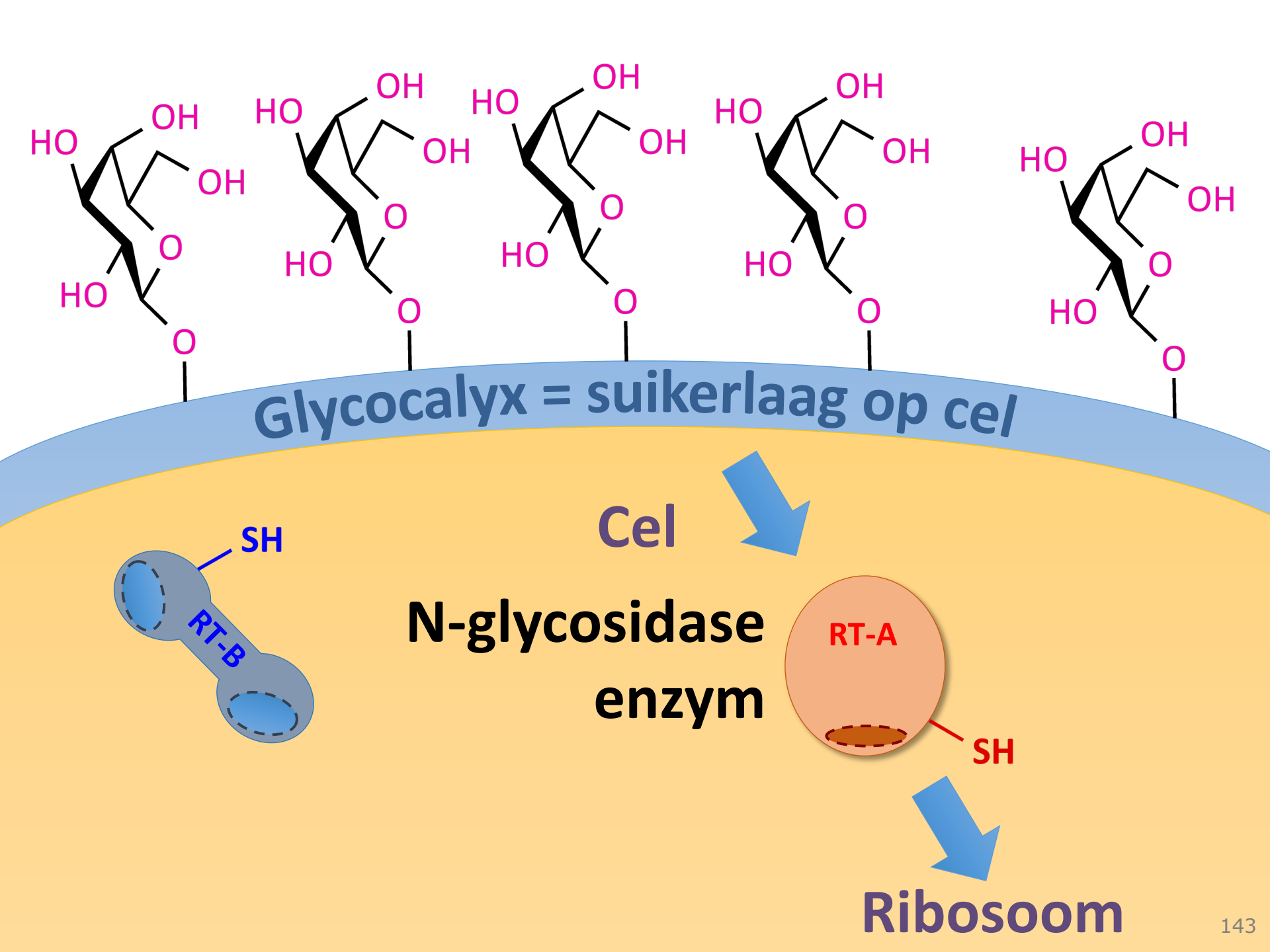
Glycocalyx = suikerlaag op cel
Cel


HO
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OH
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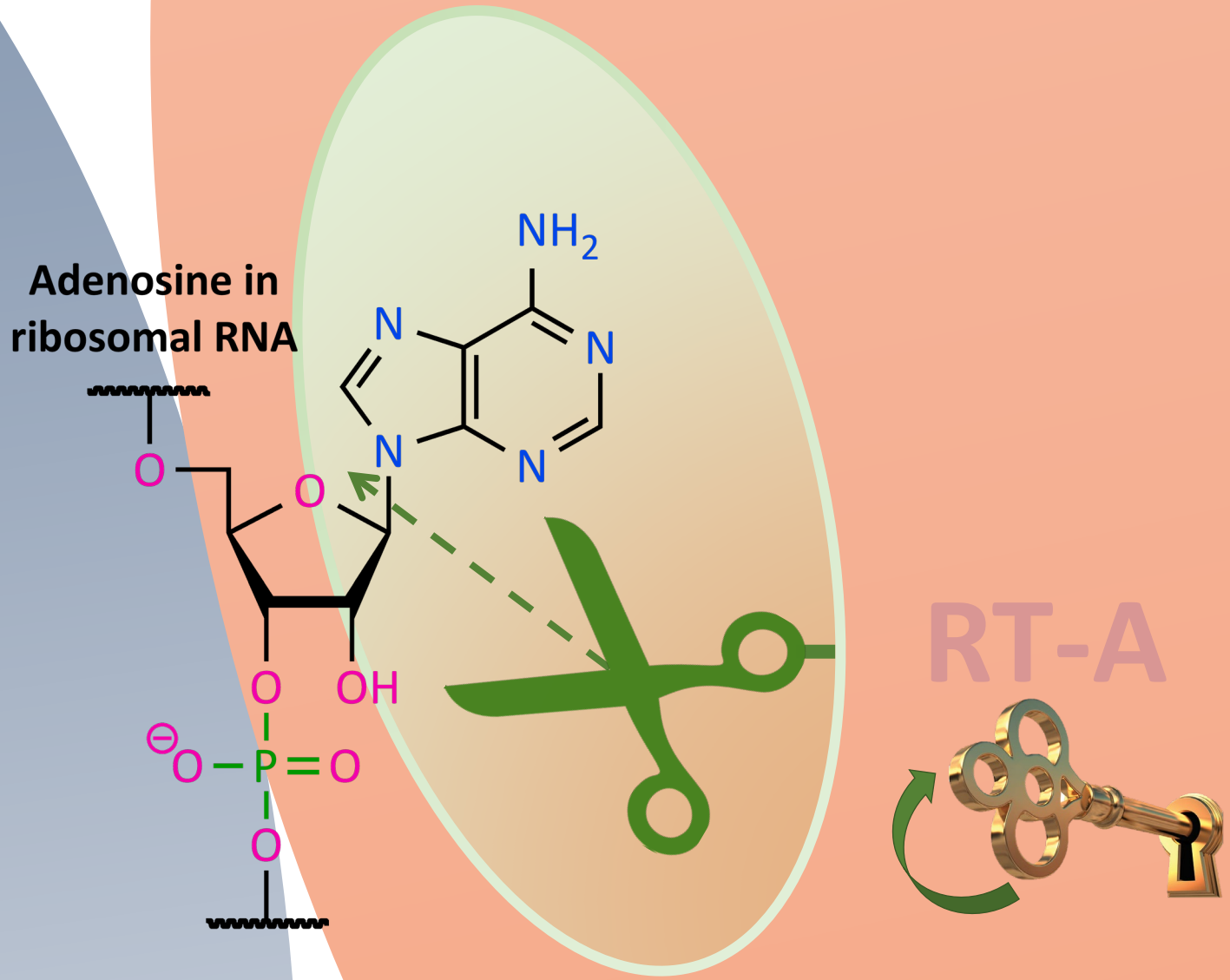
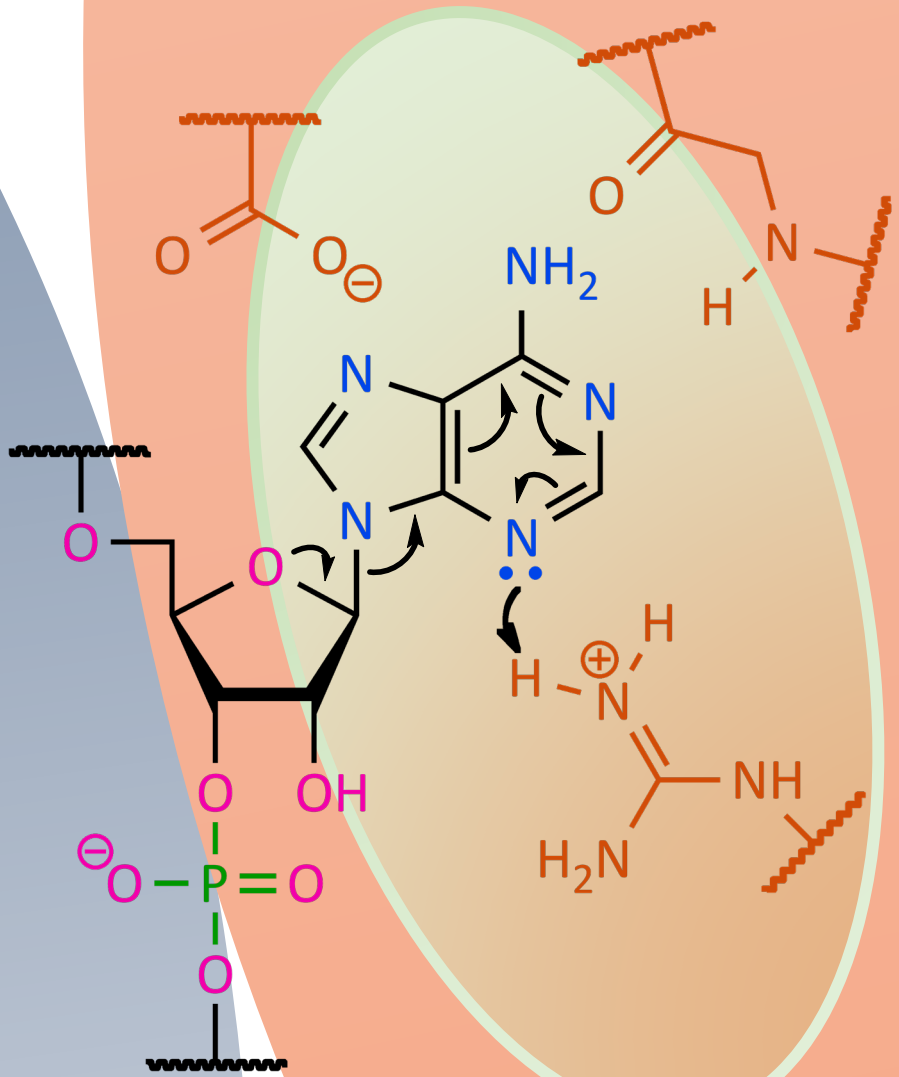
HO
O
Glycocalyx = suikerlaag op cel
Cel
SH
RT-B
N-glycosidase
enzym
RT-A
SH
Ribosoom

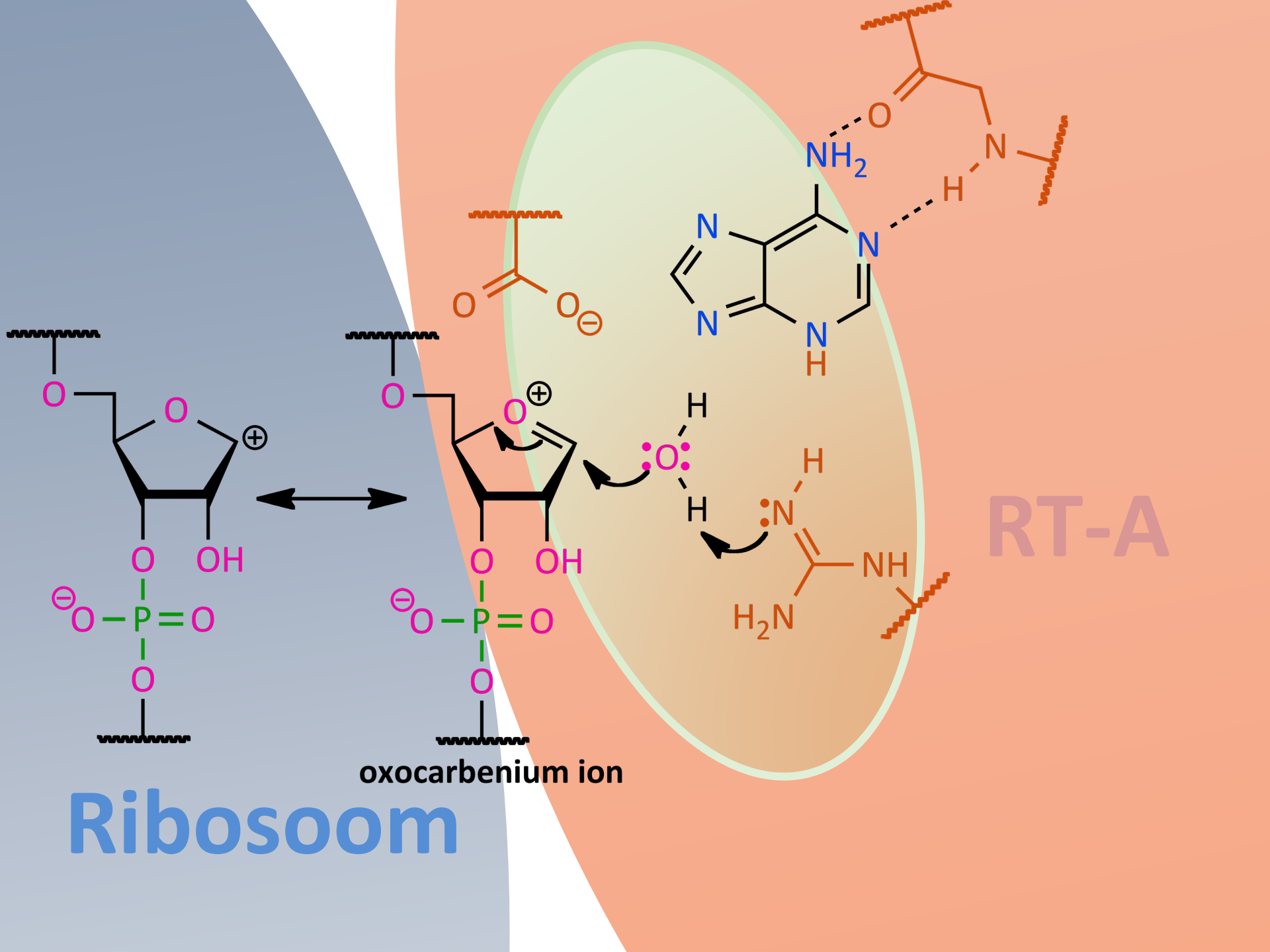


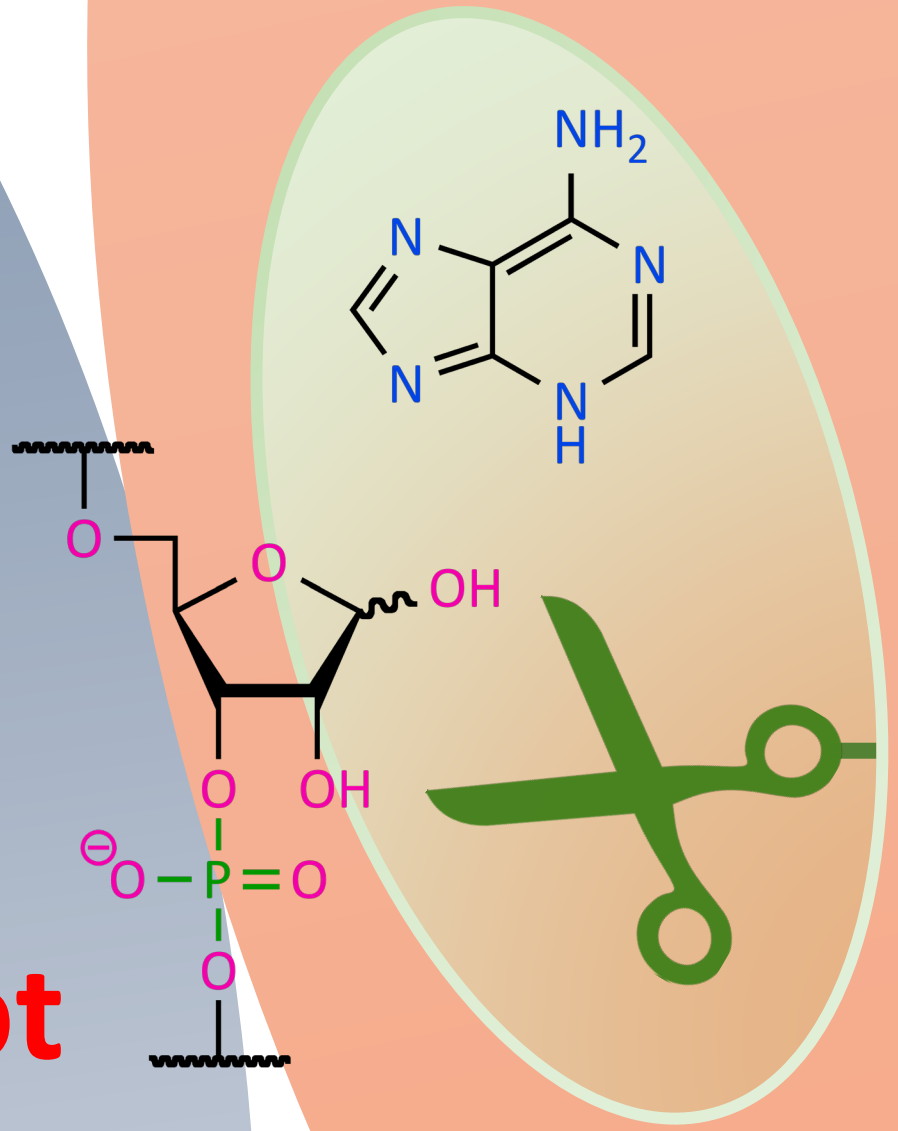
Ribosoom



RT-A

Ribosoom


oxocarbenium ion
Ribosoom
RT-A



RT-A

Kapot Ribosoom

Hoe kan zo’n kleine hoeveelheid Ricine een volwassen persoon doden?

1 ricine molecuul inactiveerd
~1500 ribosomen per minuut

Cell dood

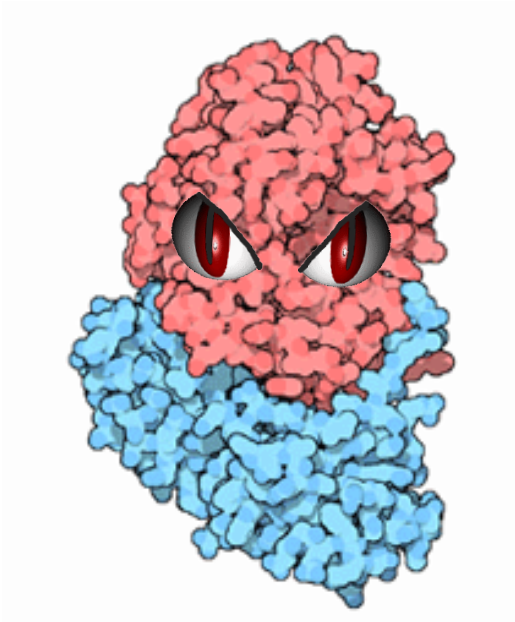
0.2 mg of Ricine

1 ricine molecuul inactiveerd
~1500 ribosomen per minuut

Cell dood

Menselijk lichaam = ~1 x 10^{14} cellen
0.2 mg ricine = 18 x 10^{14} moleculen

Pas op voor dit killer eiwit!



Is suiker altijd zoet?

Inhoud van mijn lezing:

- **Introducties:** chemische biologie → mij → suikers
- **Onderzoek:** slimmer zijn dan het griep virus
- **Onderzoek:** de perfecte omhelsing van Cholera
- **In het nieuws:** Klik chemie is gaaf!
- **Echt gebeurd:** Zoet biomoleculair moord mysterie
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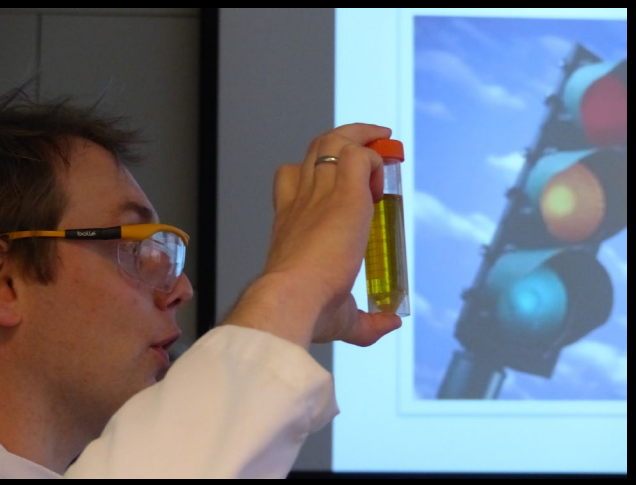
Kinderuniversiteit – Moleculen in Actie!



Ontwerp je eigen magische molecuul en de mooiste wint een prijs!

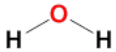
Je naam: **Hoe heet je molecuul?:**

Zes regels voor je molecuul ontwerp :

1 - Je mag zoveel waterstof (H), koolstof (C), zuurstof (O) of stikstof (N) atomen als je maar wilt gebruiken.
2 - H: heeft in totaal altijd maar 1 binding met een ander atoom
3 - C: heeft in totaal altijd 4 bindingen met andere atomen
4 - O: heeft in totaal altijd 2 bindingen met andere atomen
5 - N: heeft in totaal altijd 3 bindingen met andere atomen
6 - Tussen twee verbonden atomen kunnen maximaal drie bindingen zitten

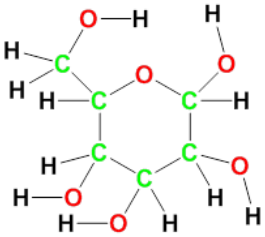
Vier voorbeelden:

Water:

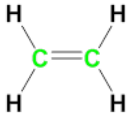


Stikstof gas:

Glucose suiker:



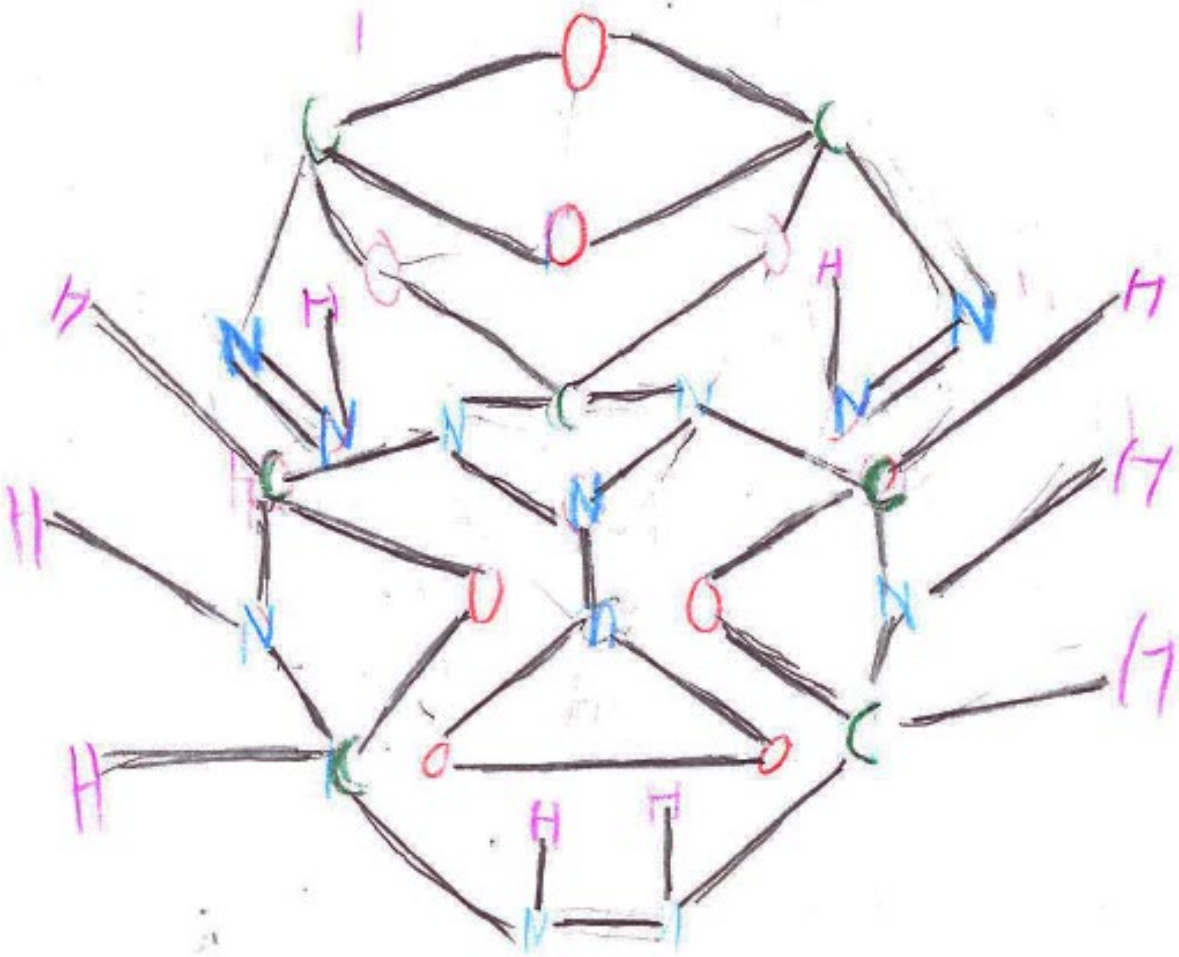
Etheen gas:



Mail een foto van je ontwerp formulier naar t.wennekes@uu.nl en misschien win je!

Je naam: Olaf

Hoe heet je molecuul?: lolocuul



Universiteits Museum Utrecht

Waar of niet waar?

Utrechtse basisscholieren worden wetenschapper voor één uur

Thema 2019:
Je kunt leven zonder suiker

Tot op heden:
~75 basisscholen bereikt en ongeveer ~2000 kinderen

Waar of niet waar?

Utrechtse basisscholieren worden wetenschapper voor één uur

Universiteits Museum Utrecht

WAAR OF ~~NIET~~ ~~WAAR?~~

Thema 2019:
Je kunt leven zonder suiker

Tot op heden:
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Waar of niet waar? Je kunt leven zonder suiker

Groep 5 Martin Luther King Basischool in Maartensdijk

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Wetenschap is teamwork en kost geld

Wennekes lab:

Yvette Luijkx
Pieter de Saint Aulaire
Tim Leenders
Xianke Meng
Lemeng Chao
Jun Yang Ong
Erianna Alvarado
Krishna Desai
Helena Ehren
Hanna de Jong
Tim Hogervorst

Infectie Biologie:

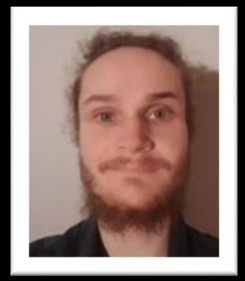
Karin Strijbis
Marc Wösten
Jos van Putten

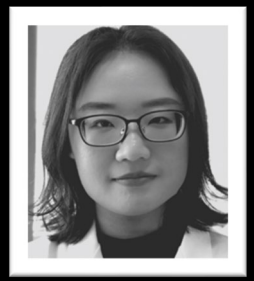
Financiering:

VENI
VIDI
BBOL

SweetCrosstalk
814102-H2020
MSCA-ITN-2018

@wennekeslab + @sweetcrosstalk





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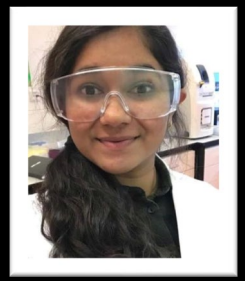

Chemische Biologie, Suikers & Geneesmiddelen

Typ “glycoscience” in Youtube voor onze video