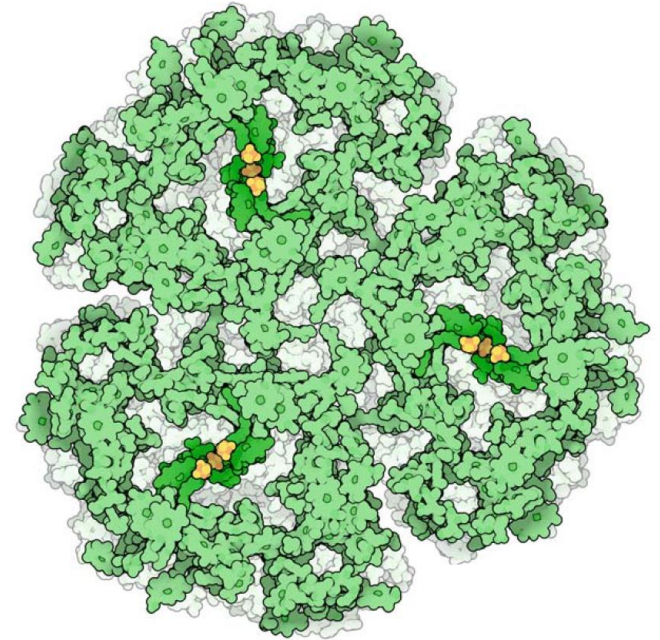
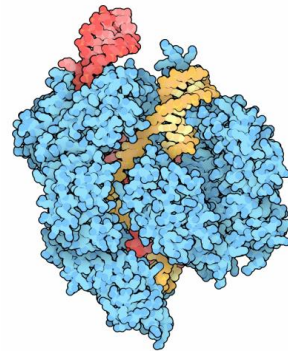
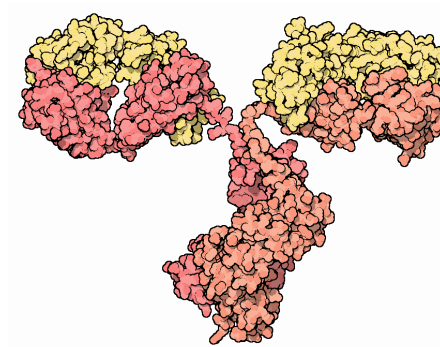


# Proteine:

## Molekulare Wundermaschinen, Biotechnologie und Zukunftsmusik

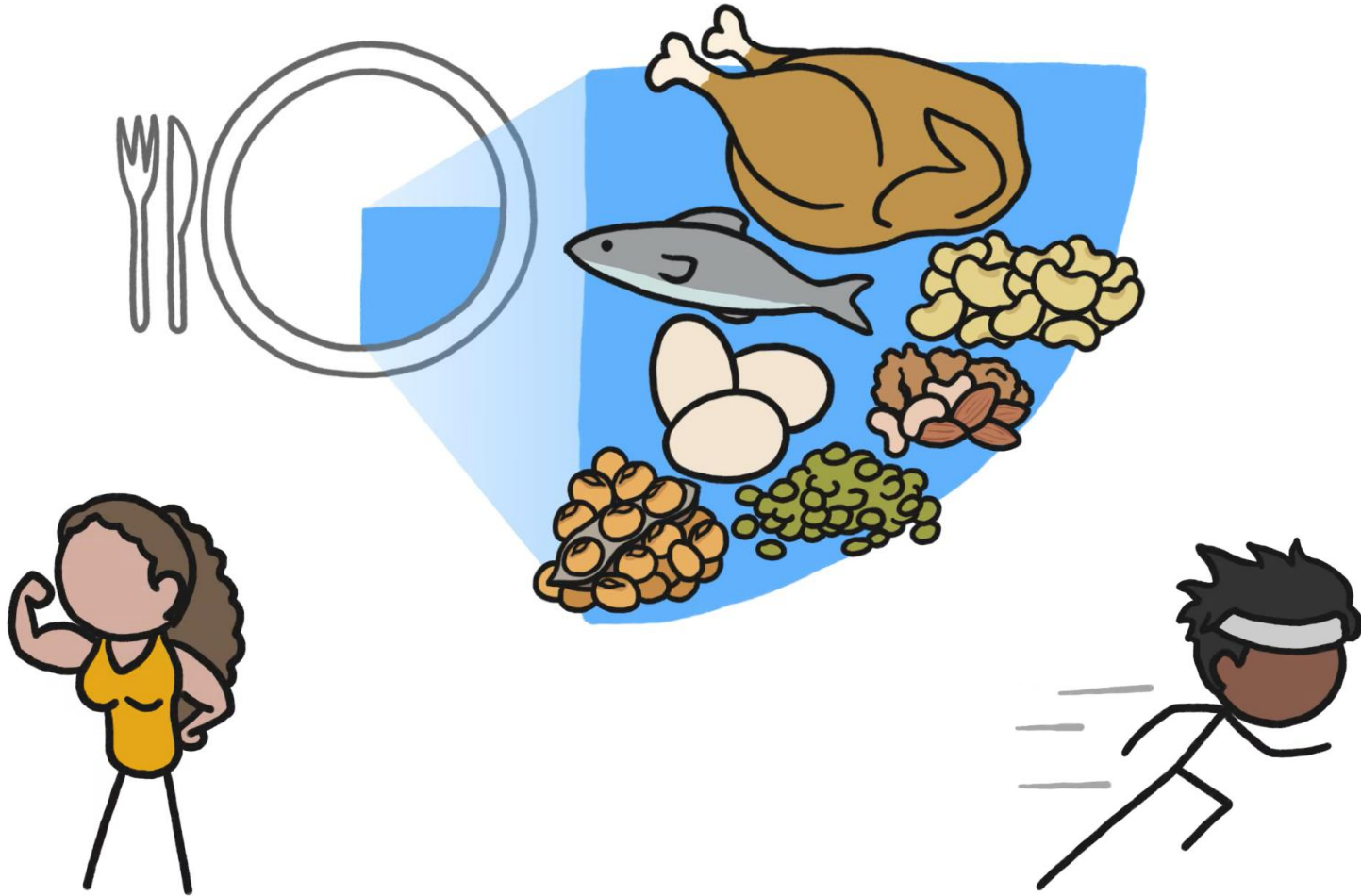
Matthias Lenz (M.Sc., M.Sc.)

10. November 2024



Bilder: David Goodsell/PDB-101

## Warum sprechen wir über Essen?



Proteine sind omnipräsent in unserem Alltag

Insulin

Hämoglobin

Keratin

Antikörper

Kollagen

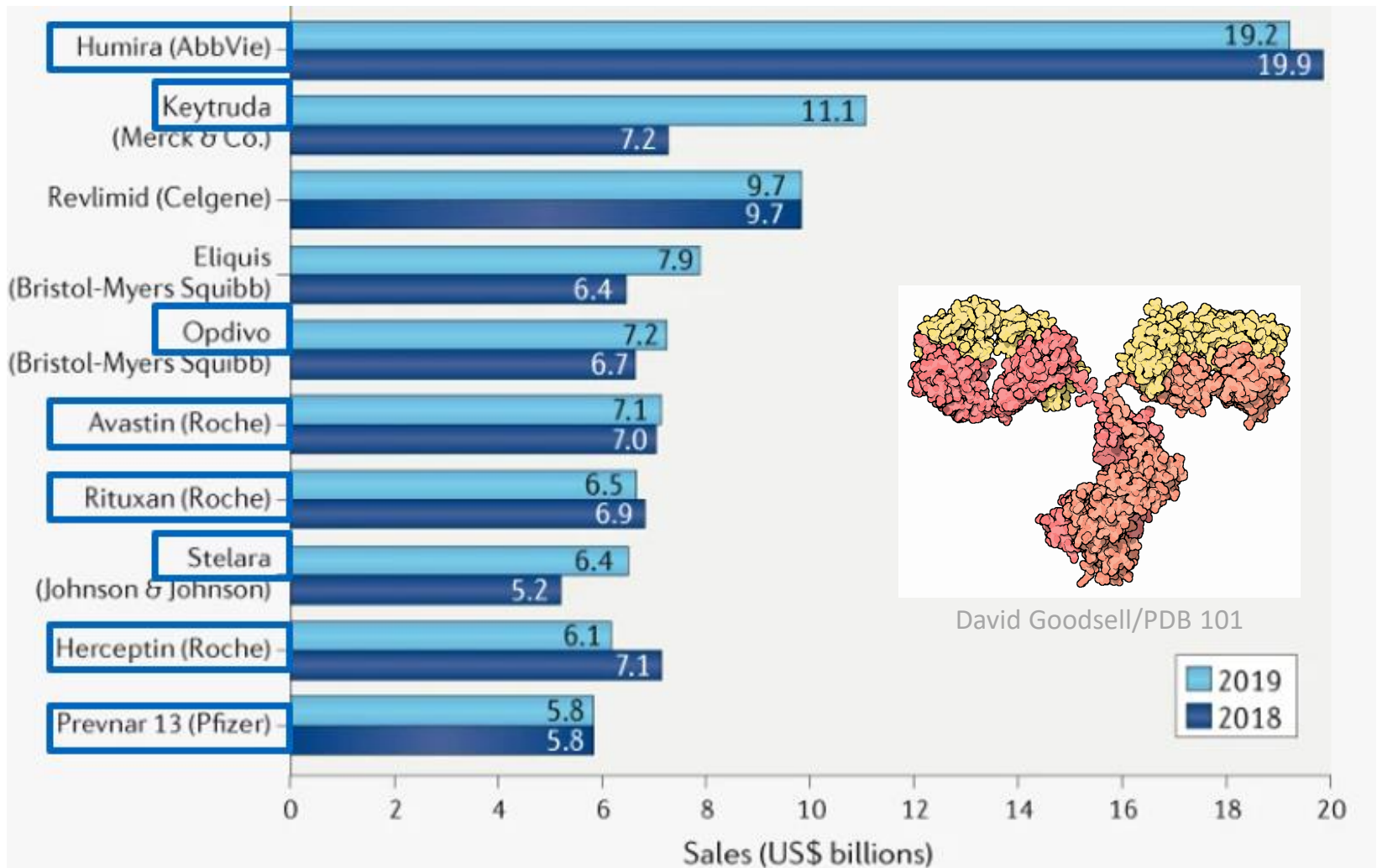
Wachstumshormon

CRISPR/Cas

Enzyme

Melanin

## Proteine sind die Blockbuster der modernen Medizin

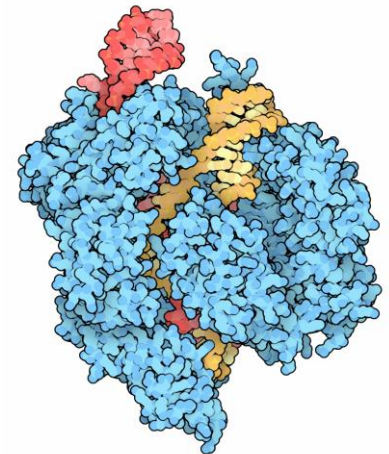


# Proteine sind an der Front der Forschung

 NOBELPRISET I KEMI 2024  
THE NOBEL PRIZE IN CHEMISTRY 2024

 KUNGL.  
VETENSKAPS-  
AKADEMIEN  
THE ROYAL SWEDISH ACADEMY OF SCIENCES

 <small>Photo: University of Washington</small>	 <small>Photo: The Royal Society</small>	 <small>Photo: BBVA Foundation</small>
<b>David Baker</b> University of Washington USA	<b>Demis Hassabis</b> Google DeepMind United Kingdom	<b>John M. Jumper</b> Google DeepMind United Kingdom
<i>"för datorbaserad proteindesign"</i> <i>"for computational protein design"</i>	<i>"för proteinstrukturprediktion"</i> <i>"for protein structure prediction"</i>	



David Goodsell/PDB-101

1. Die molekularen Maschinen des Lebens
2. Biotechnologie: Proteine als Stars in Medizin, Chemie & Co.
3. Aktuelle Proteinforschung und ihr Zukunftspotenzial

**1. Die molekularen Maschinen des Lebens**

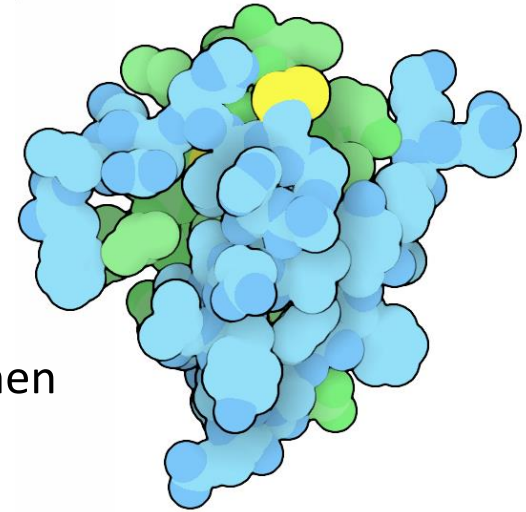
2. Biotechnologie: Proteine als Stars in Medizin, Chemie & Co.

3. Aktuelle Proteinforschung und ihr Zukunftspotenzial



## Proteine

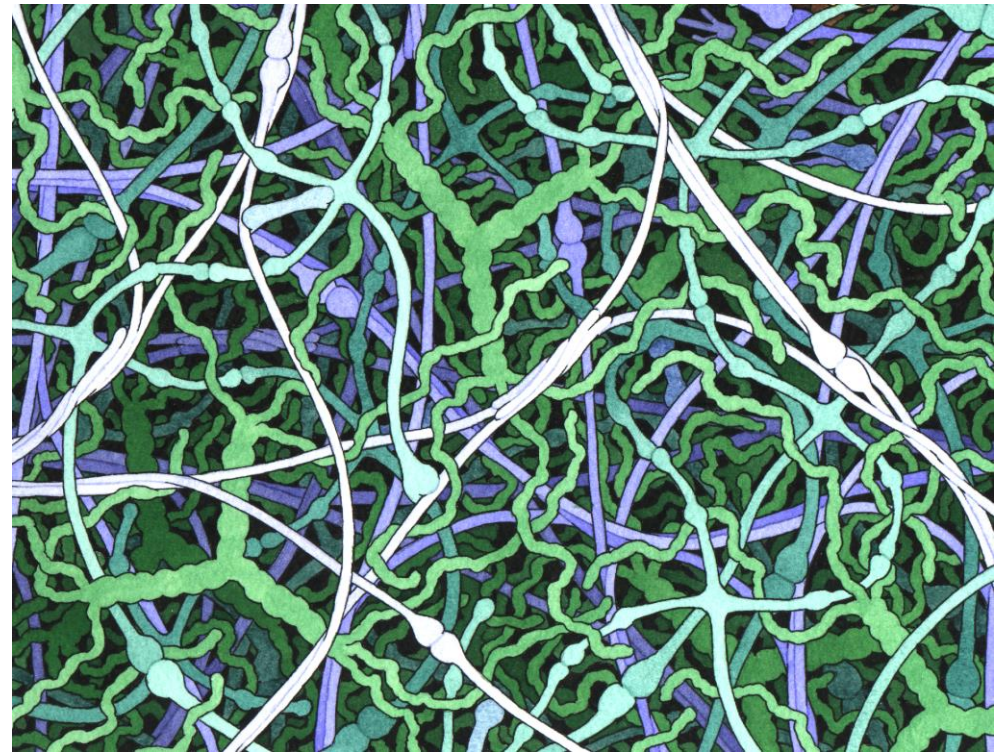
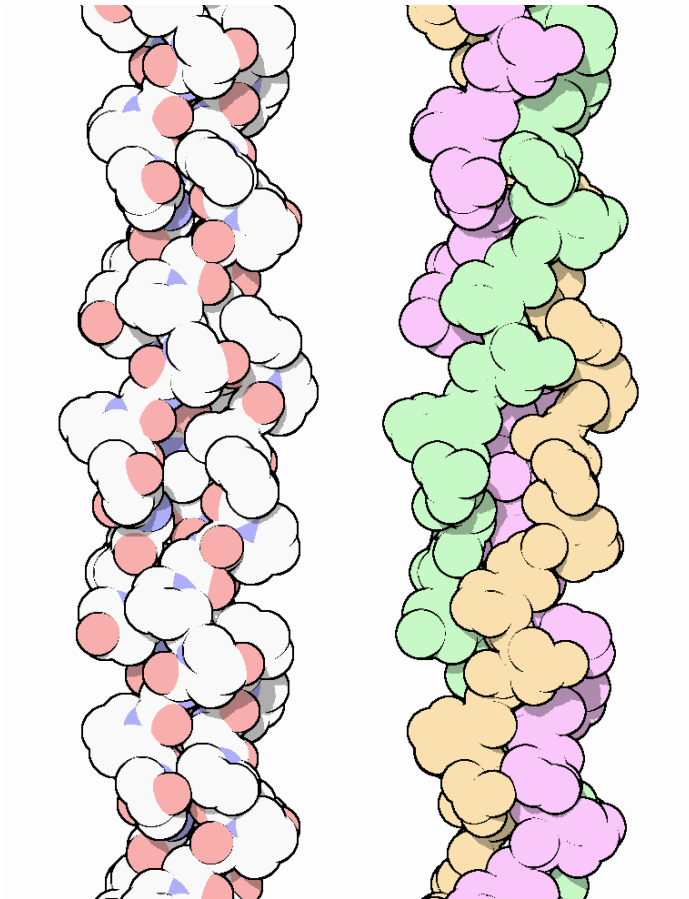
- Molekulare Maschinen; Arbeitstiere des Lebens
- Stemmen praktisch jede Aufgabe in biologischen Systemen
- Und das in sämtlichen Lebewesen
- Aber: So klein, dass man sie selbst mit einem (Licht-)Mikroskop nicht sehen kann! (typische Größe: 5 nM)
- Wenn wir sie so vergrößern würden, dass wir sie sehen könnten, sähen wir einzelne Atome!
- Viele Ähnlichkeiten zu “Markomaschinen”:  
Teile passen zusammen, wechselwirken, bewegen sich, ähnliche Aufgaben...



David Goodsell/PDB-101

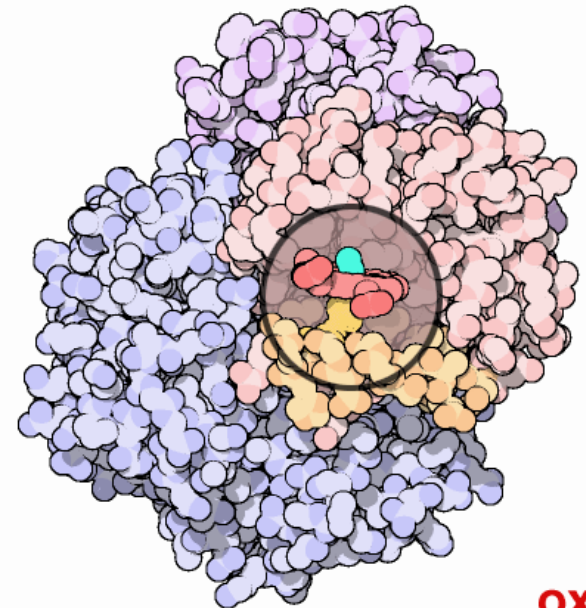
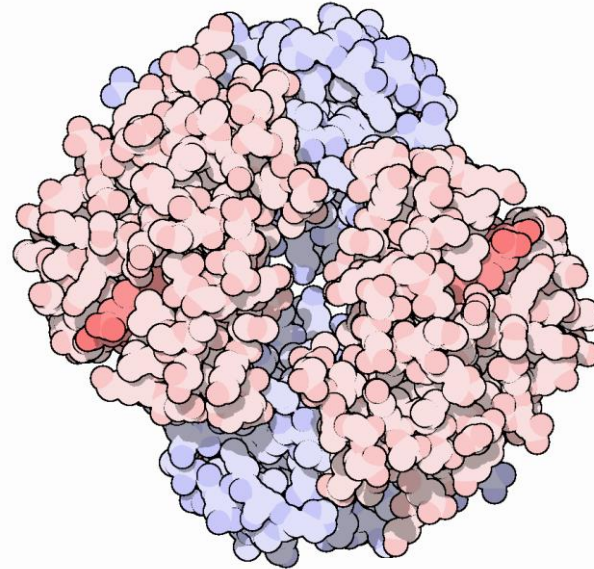
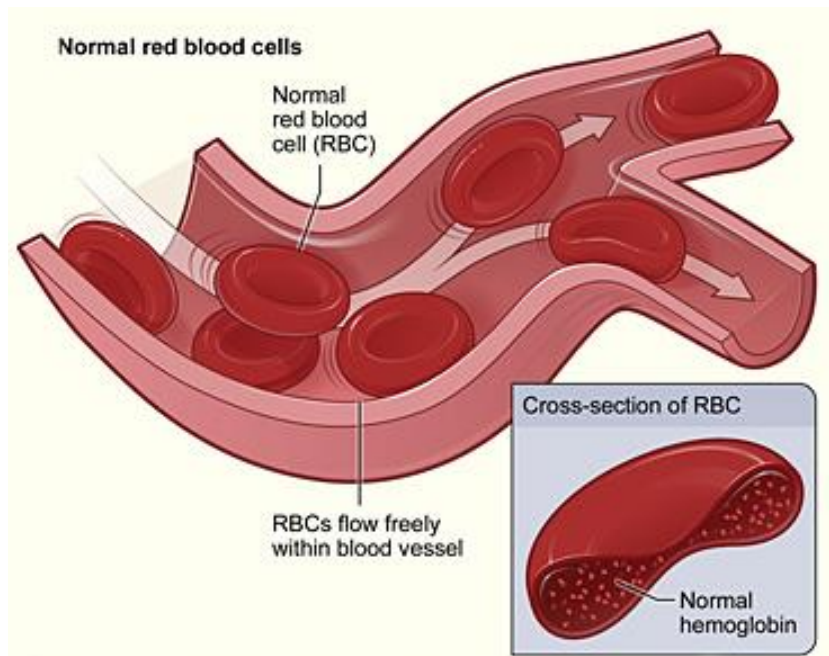


## Struktur und Stabilität (Kollagen)



Bilder: David Goodsell/PDB-101

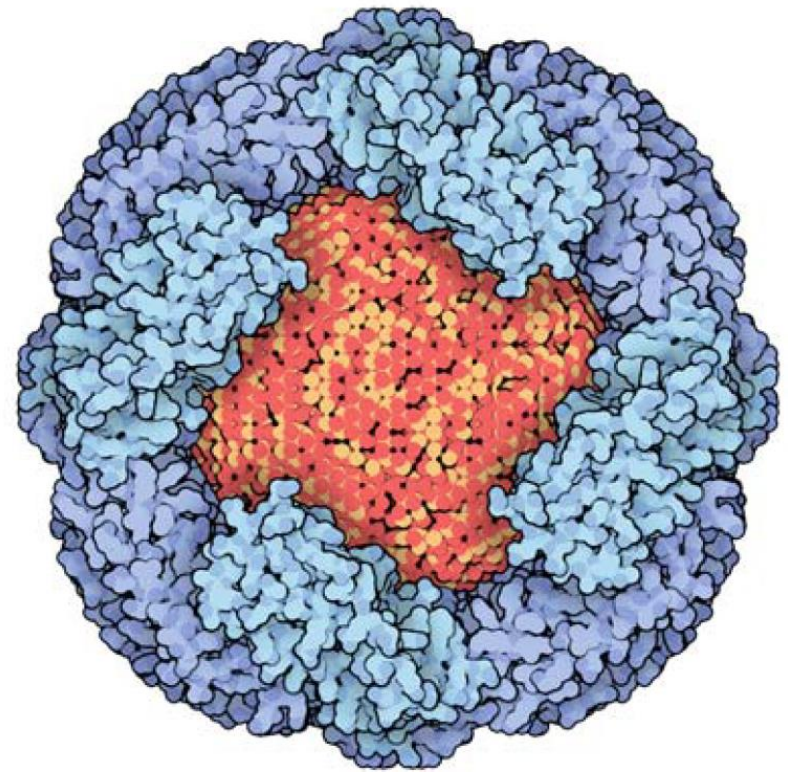
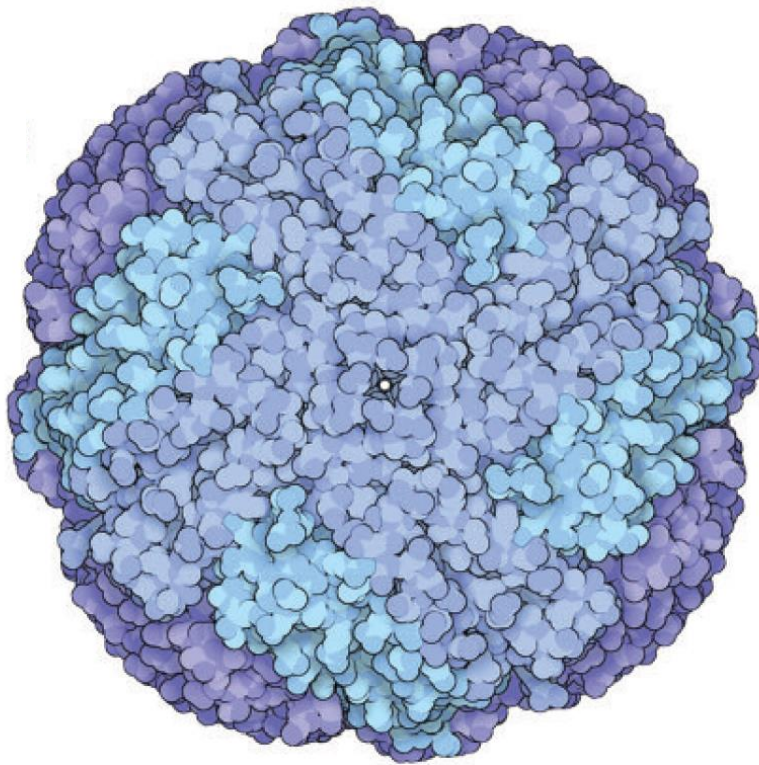
## Transport (Hämoglobin)



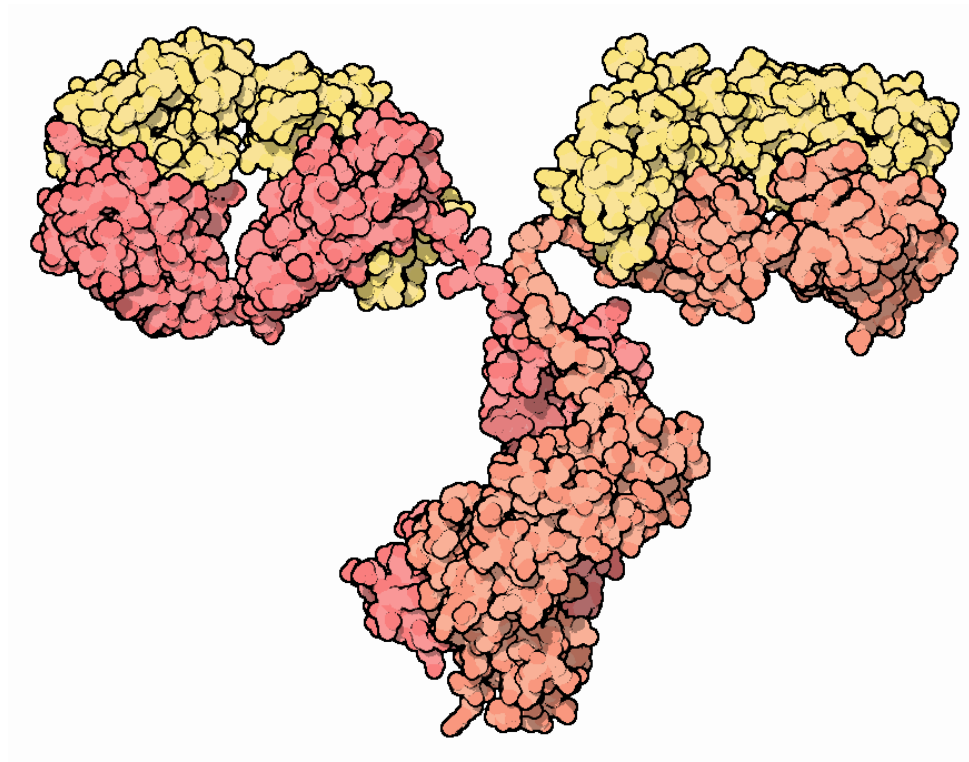
oxy



## Speicher (Ferritin)



## Verteidigung (Antikörper)



David Goodsell/PDB-101

## Verteidigung (Antikörper)



PROTEIN

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## Signale (Insulin)

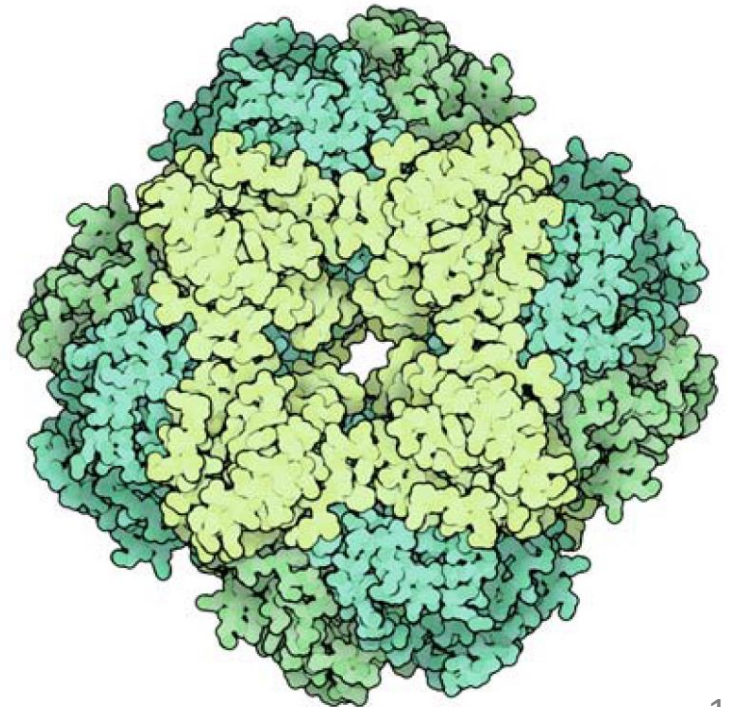
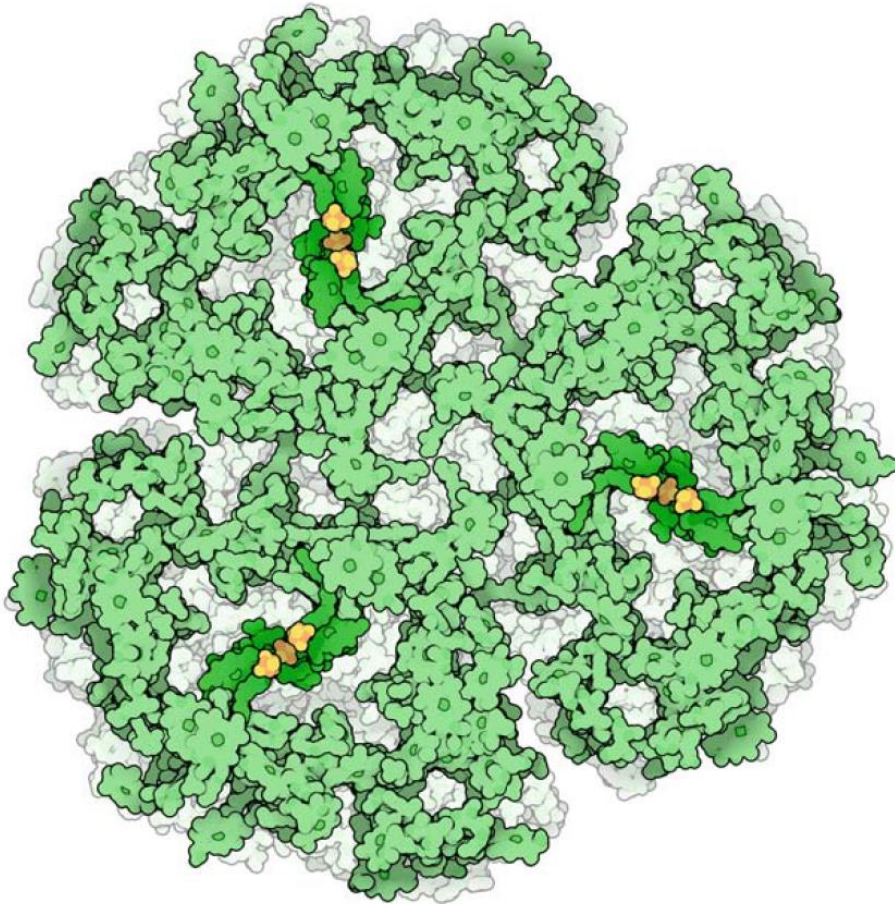


PROTEIN

RCSB PDB-101



## Energieumwandlung & Carbon Capture (Photosystem & RuBisCo)





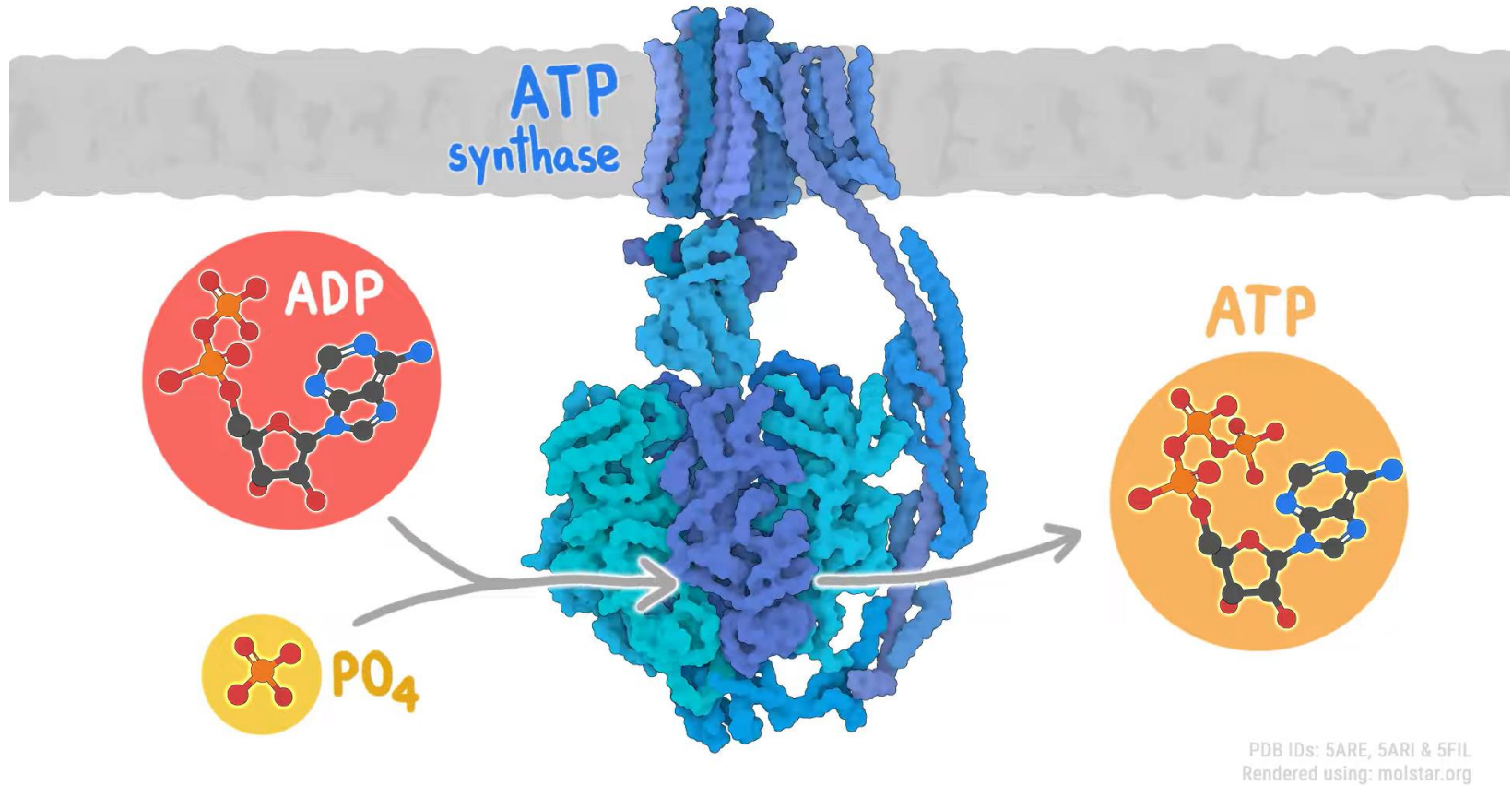
## Stoffabbau (Amylase)



PROTEIN

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## Stoffaufbau (ATP synthase)



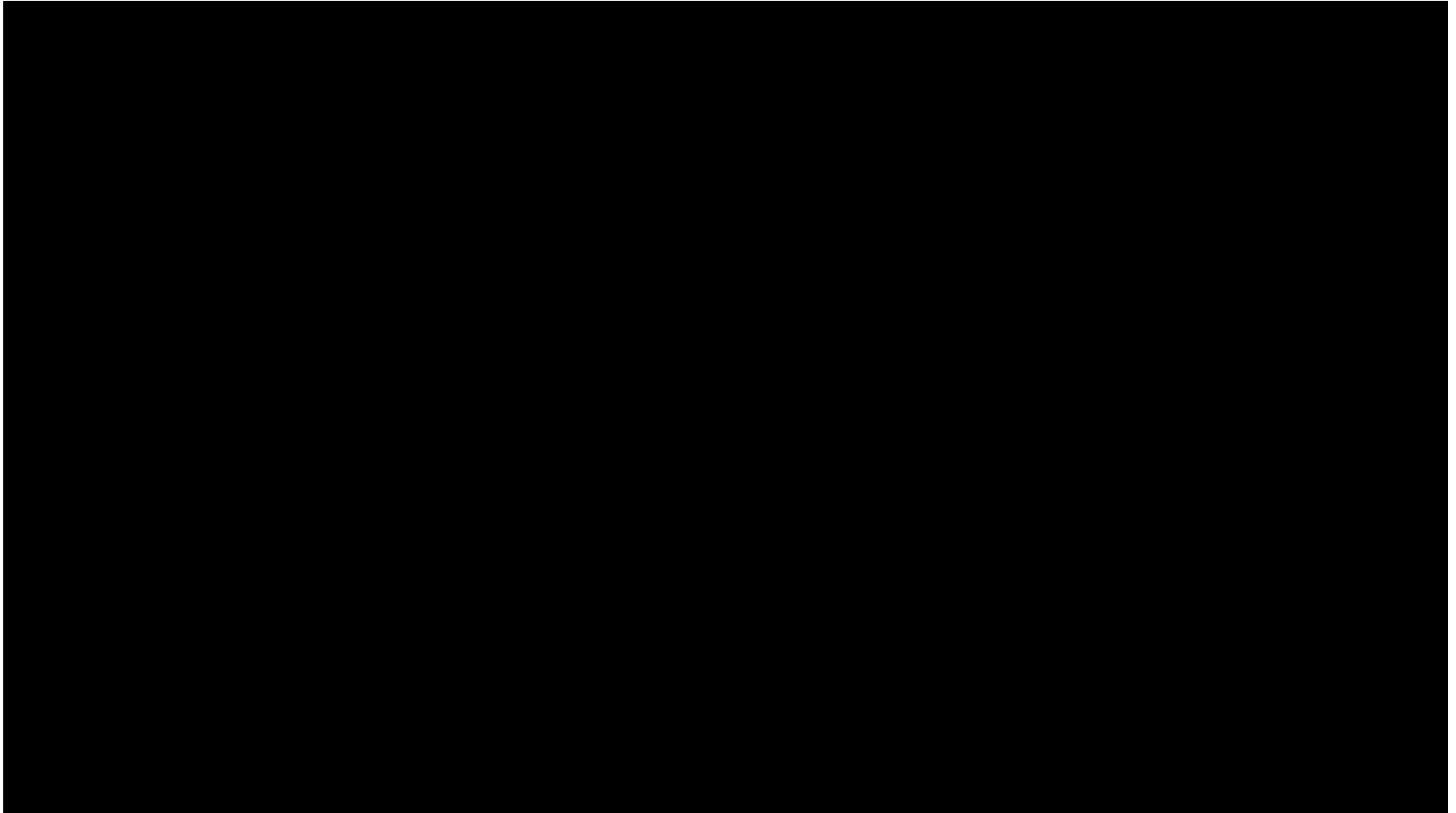
## Transport (Calcium-Pumpe)



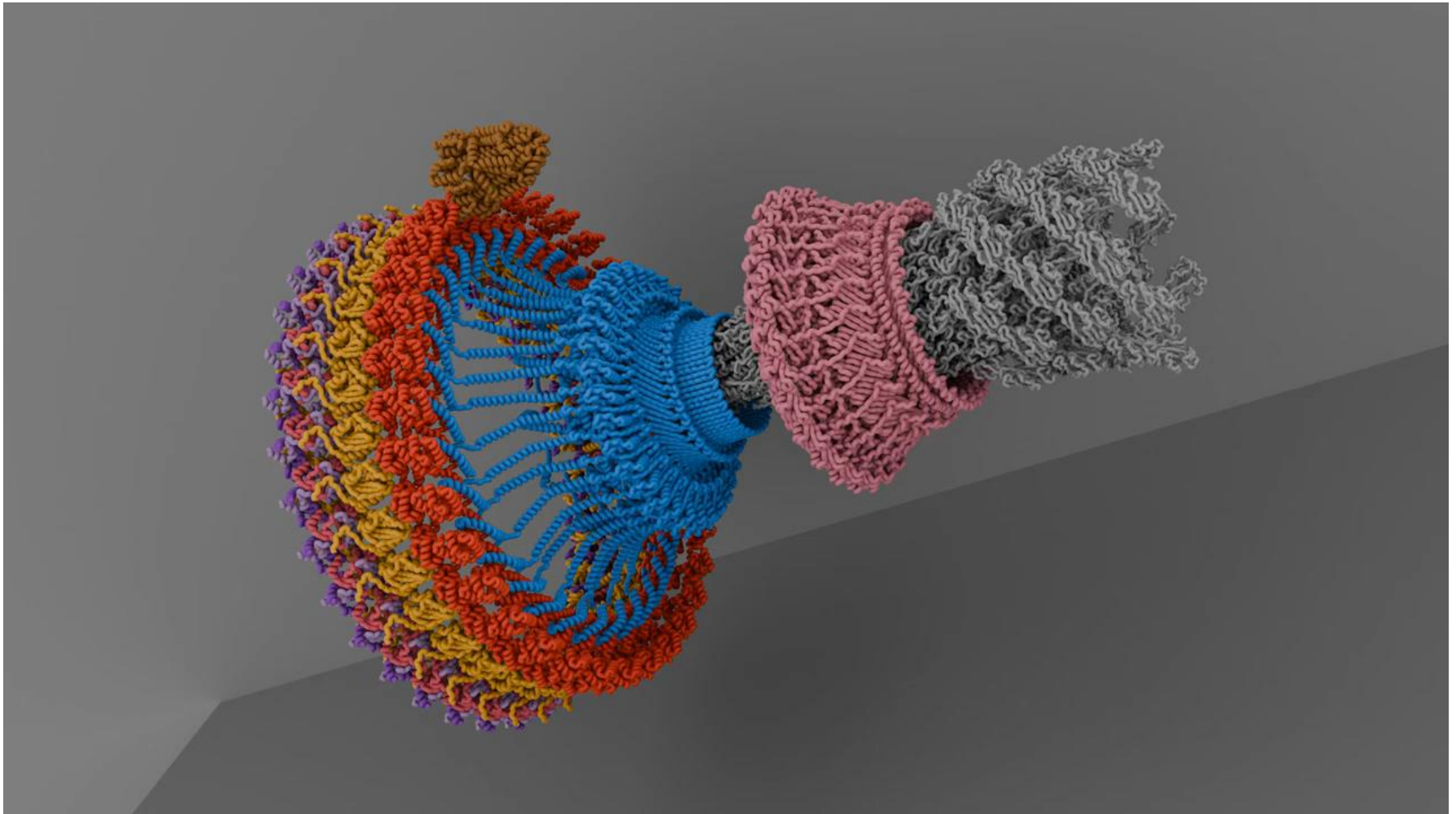
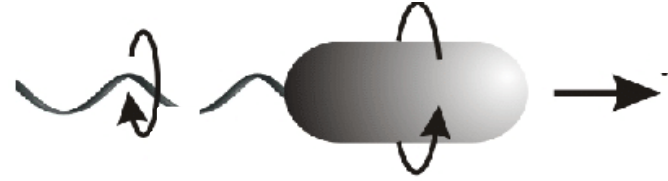
PROTEIN

RC3A PDB-101

## Infrastruktur (Mikrotubuli und Kinesin)



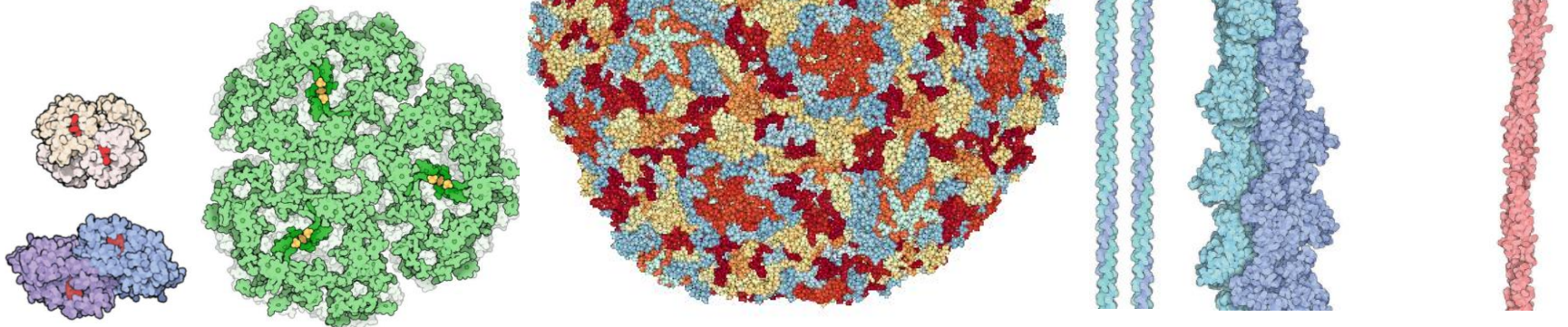
## Motilität (Flagellarkomplex)



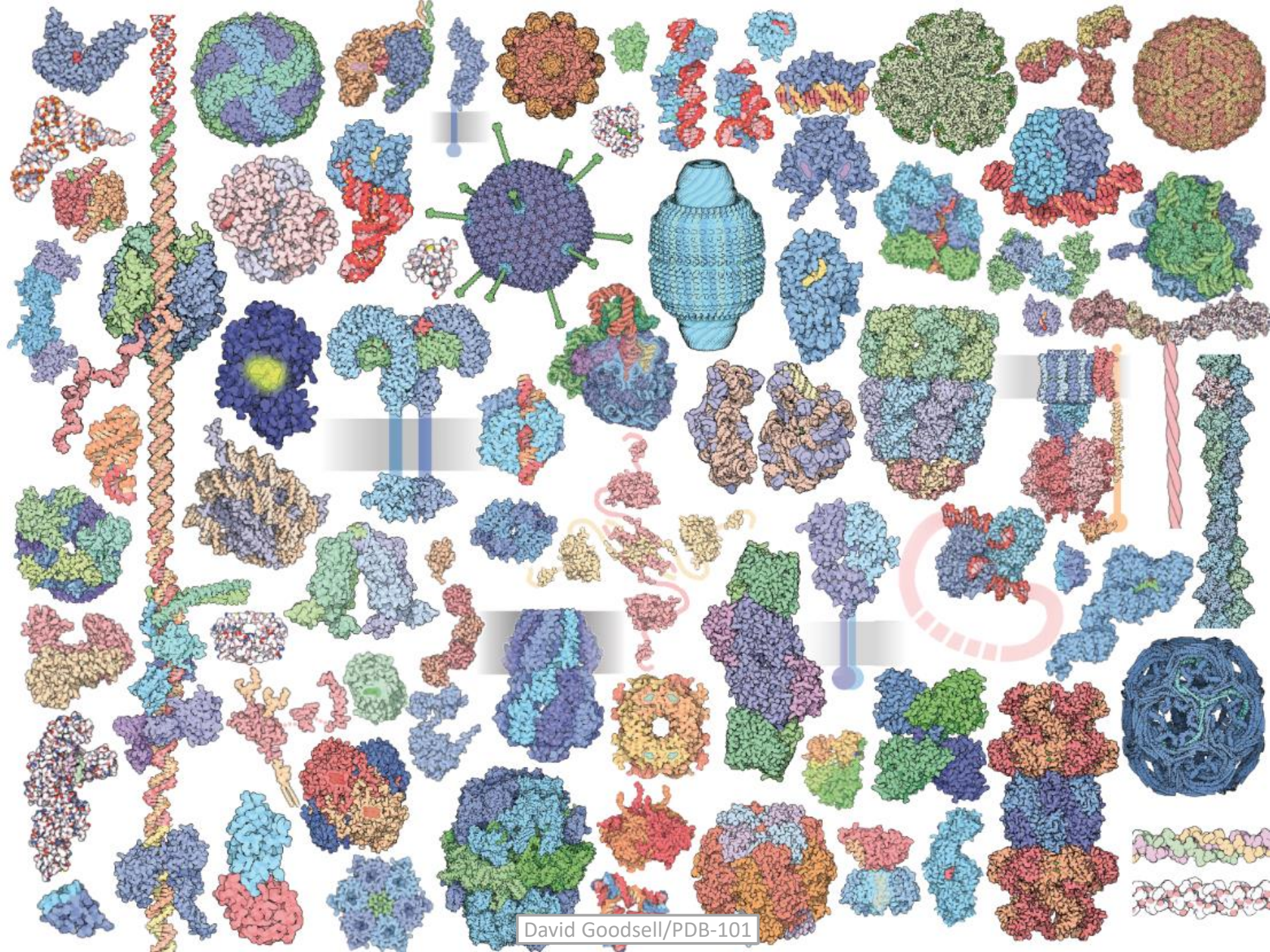


## Proteinfunktionen

- Struktur
- Transport und Speicher
- Stoffauf- und -abbau (Enzyme)
- Verteidigung
- Energieumwandlung
- Signalfunktion
- Wahrnehmung
- Motorik
- ...

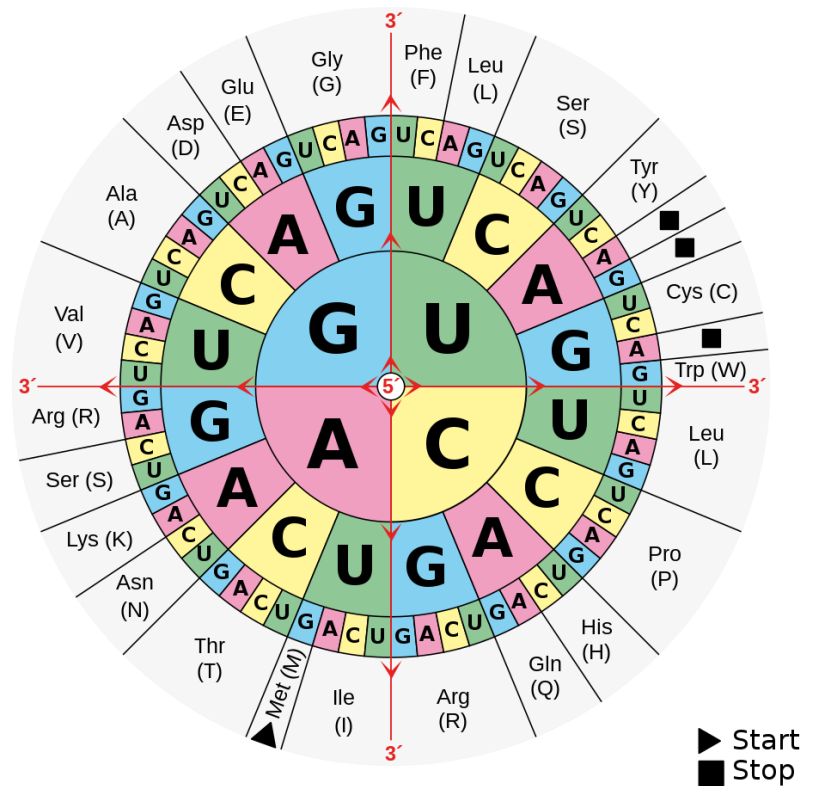
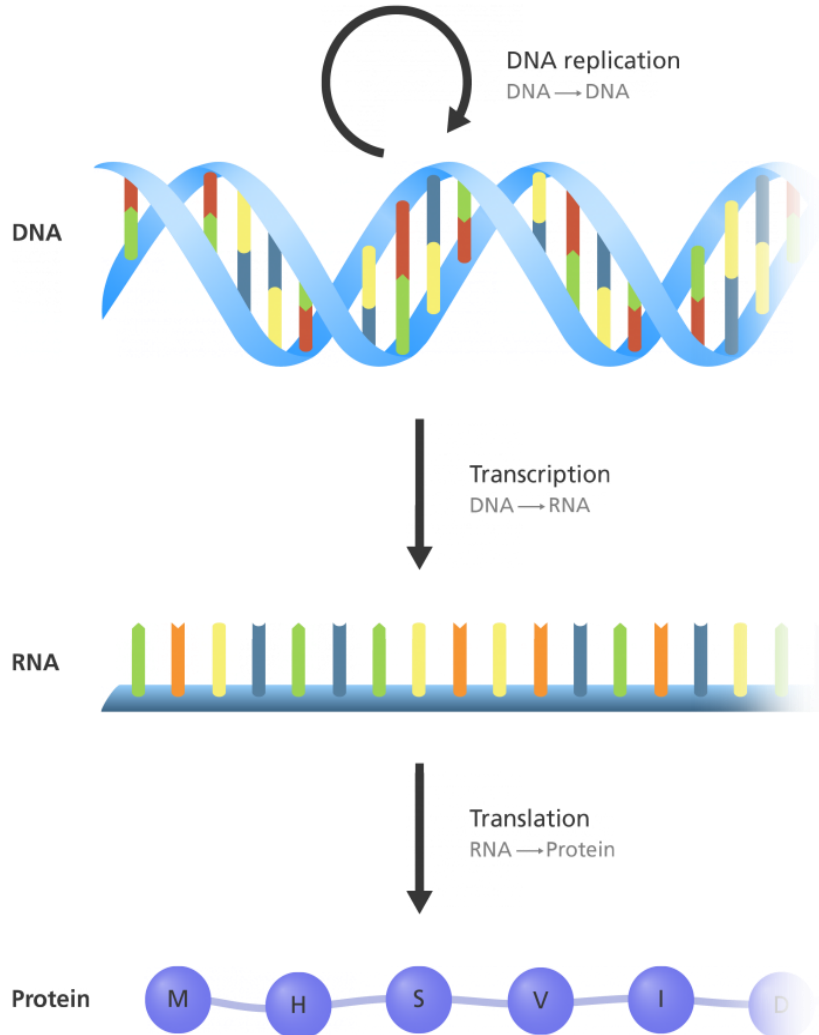






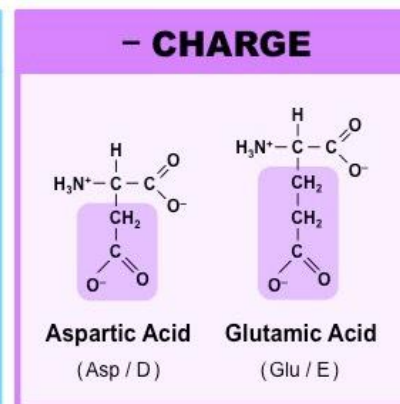
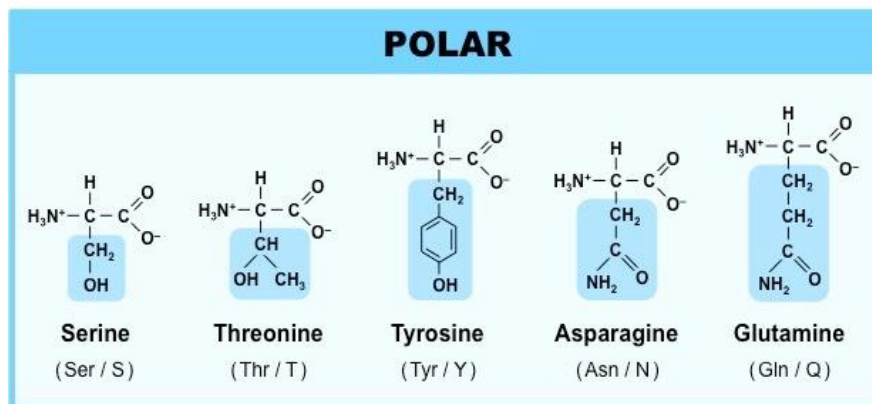
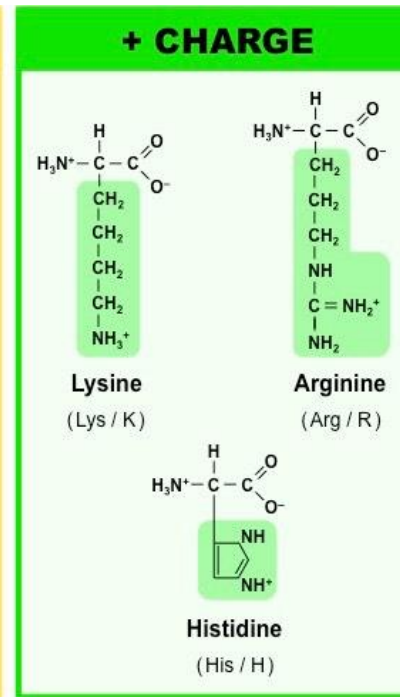
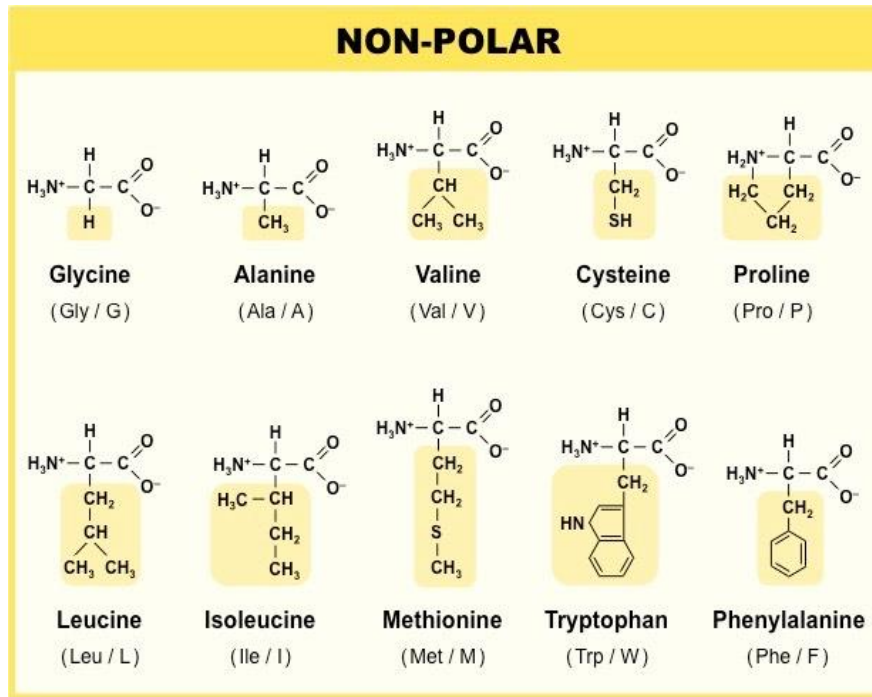


# Vom Bauplan zum Protein: Der genetische Code



Wikimedia Commons

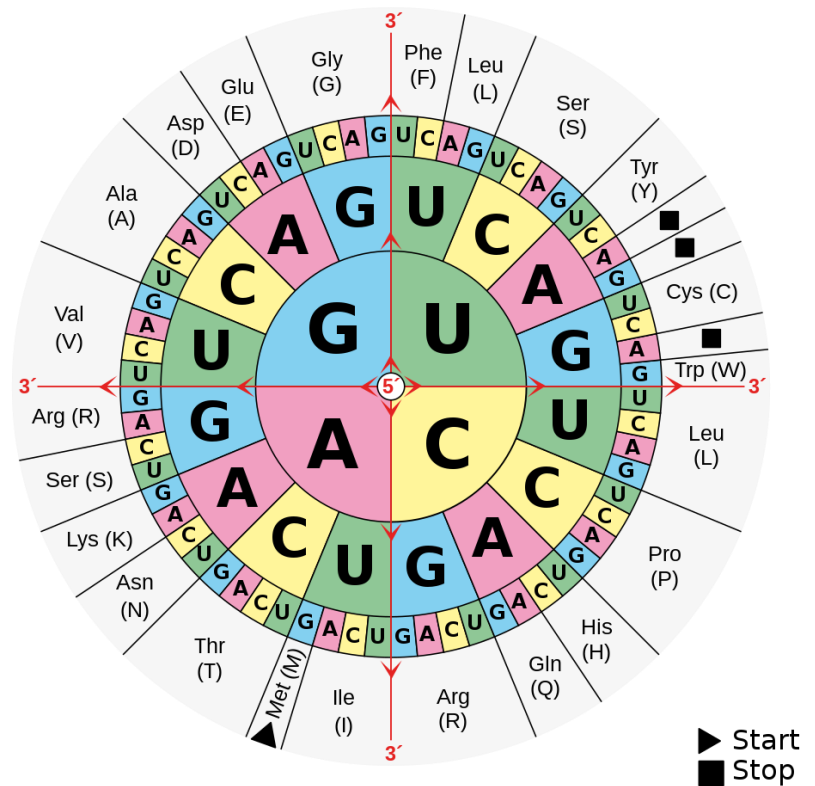
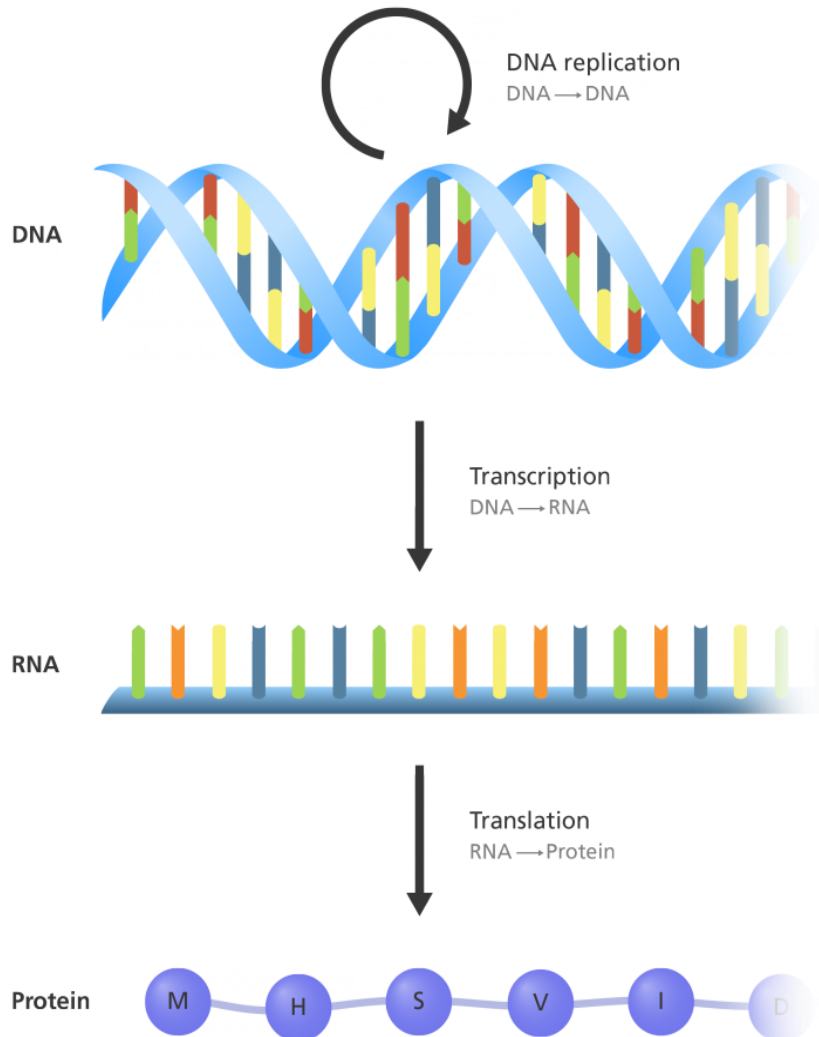
# Aminosäuren: Die 20 Bausteine aller Proteine



## Eigenschaften:

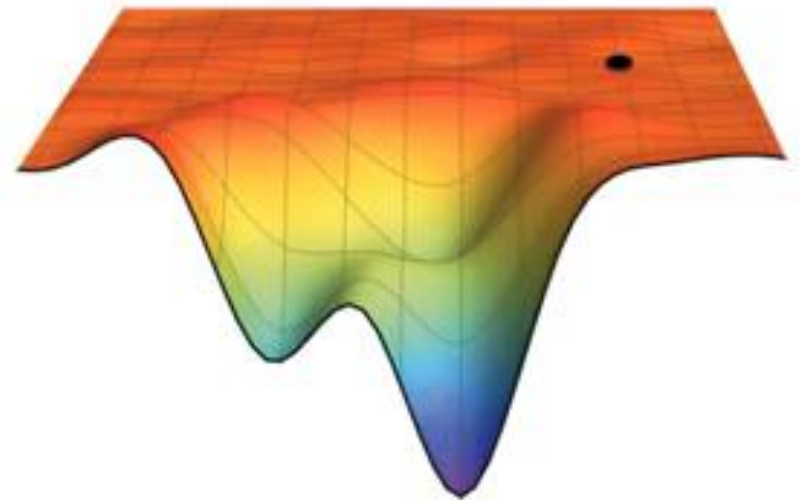
- Groß vs. klein
- Rigide vs. flexibel
- Hydrophil vs. hydrophob
- Neutral vs. sauer vs. basisch
- Chemisch inert vs. reaktiv

# Vom Bauplan zum Protein: Der genetische Code

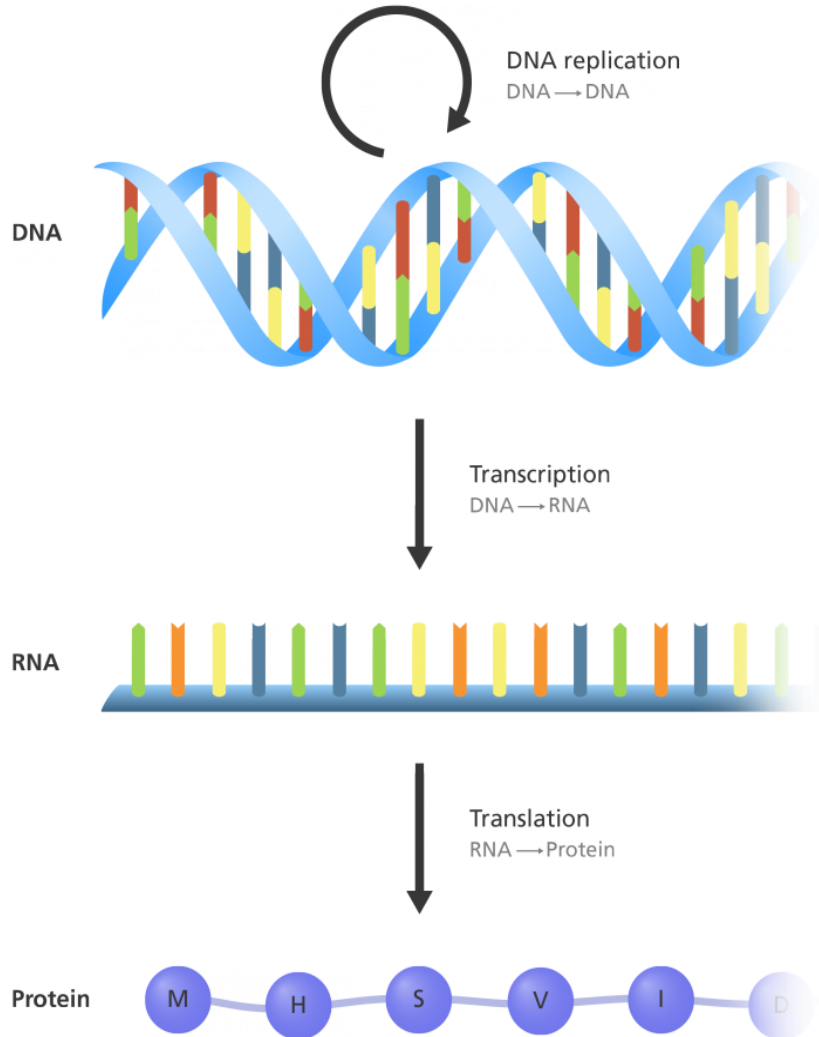


Wikimedia Commons

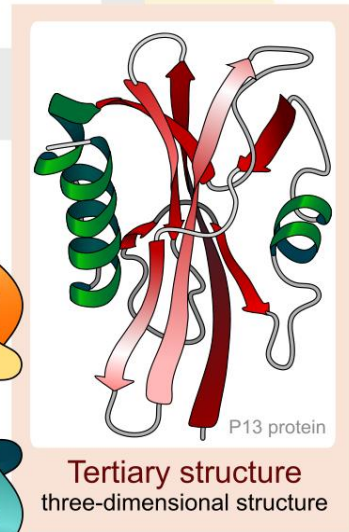
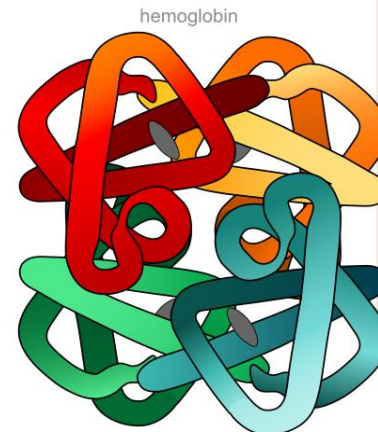
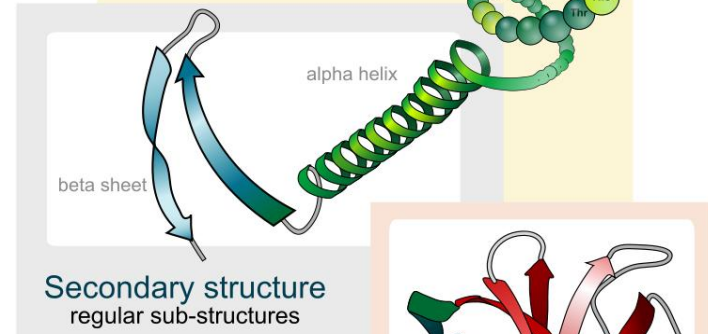
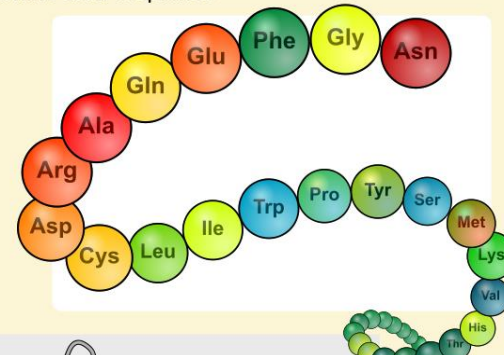
## Vom Bauplan zum Protein: Proteinfaltung



# Vom Bauplan zum Protein

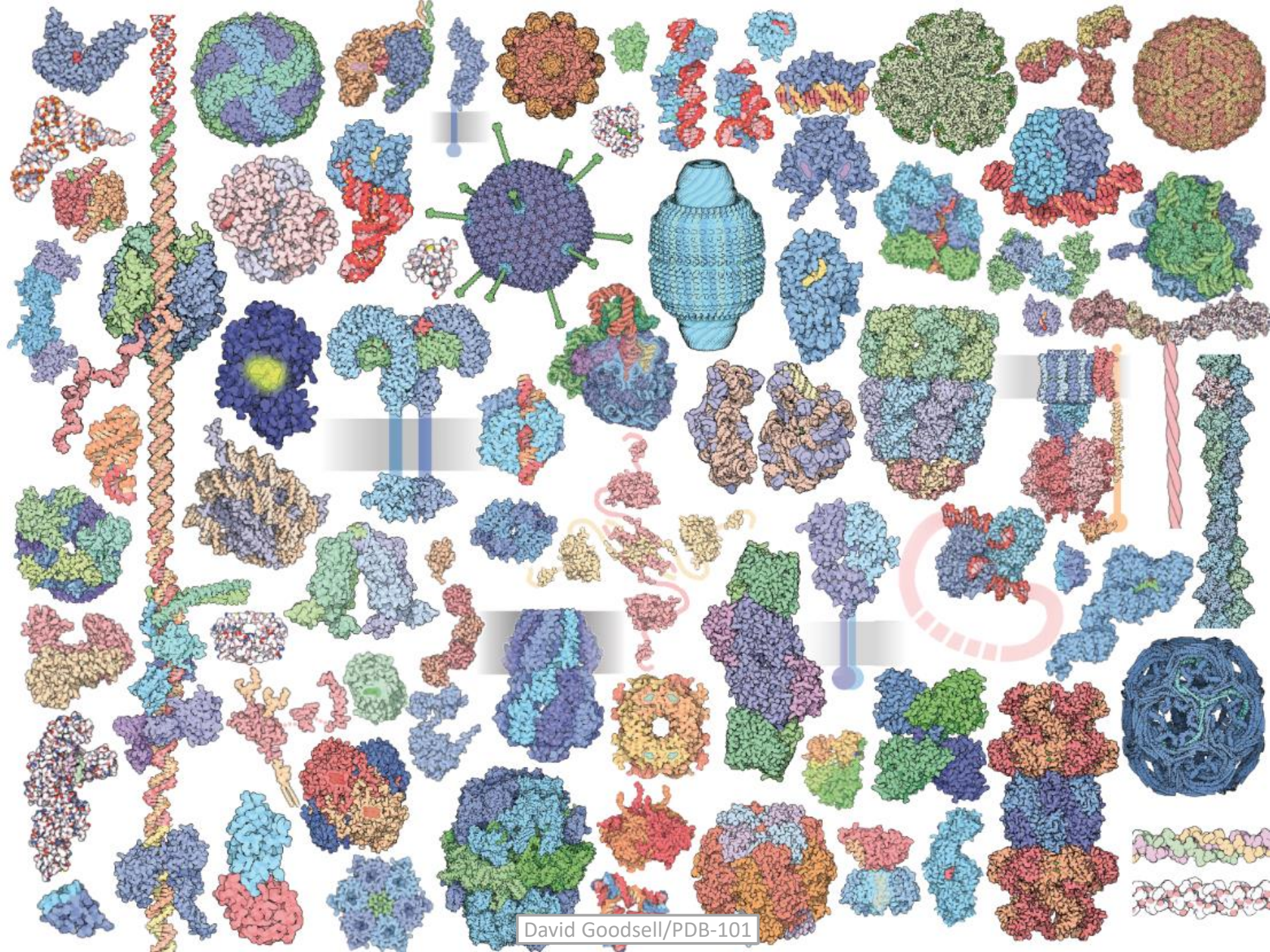


Primary structure  
amino acid sequence



Wikimedia Commons

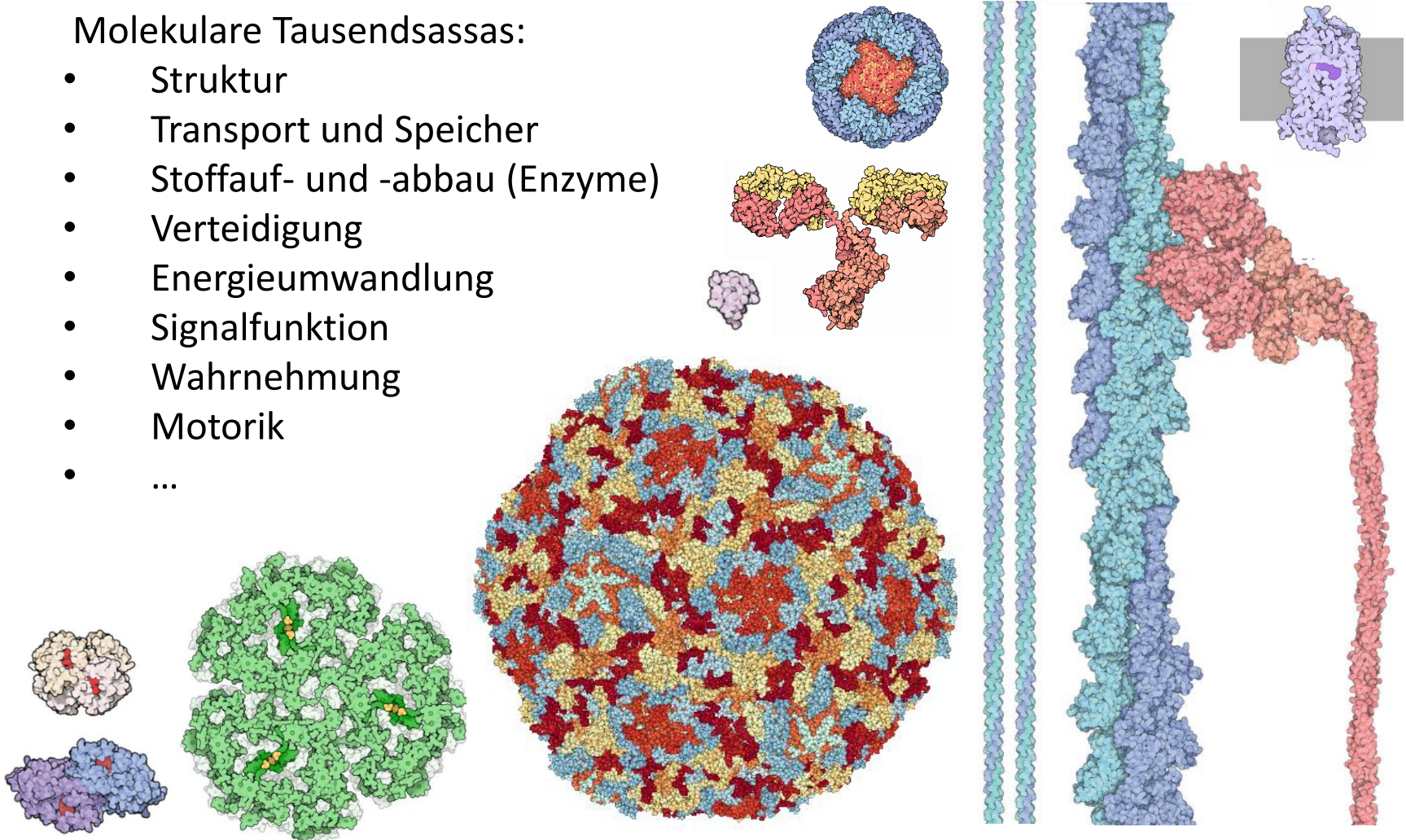






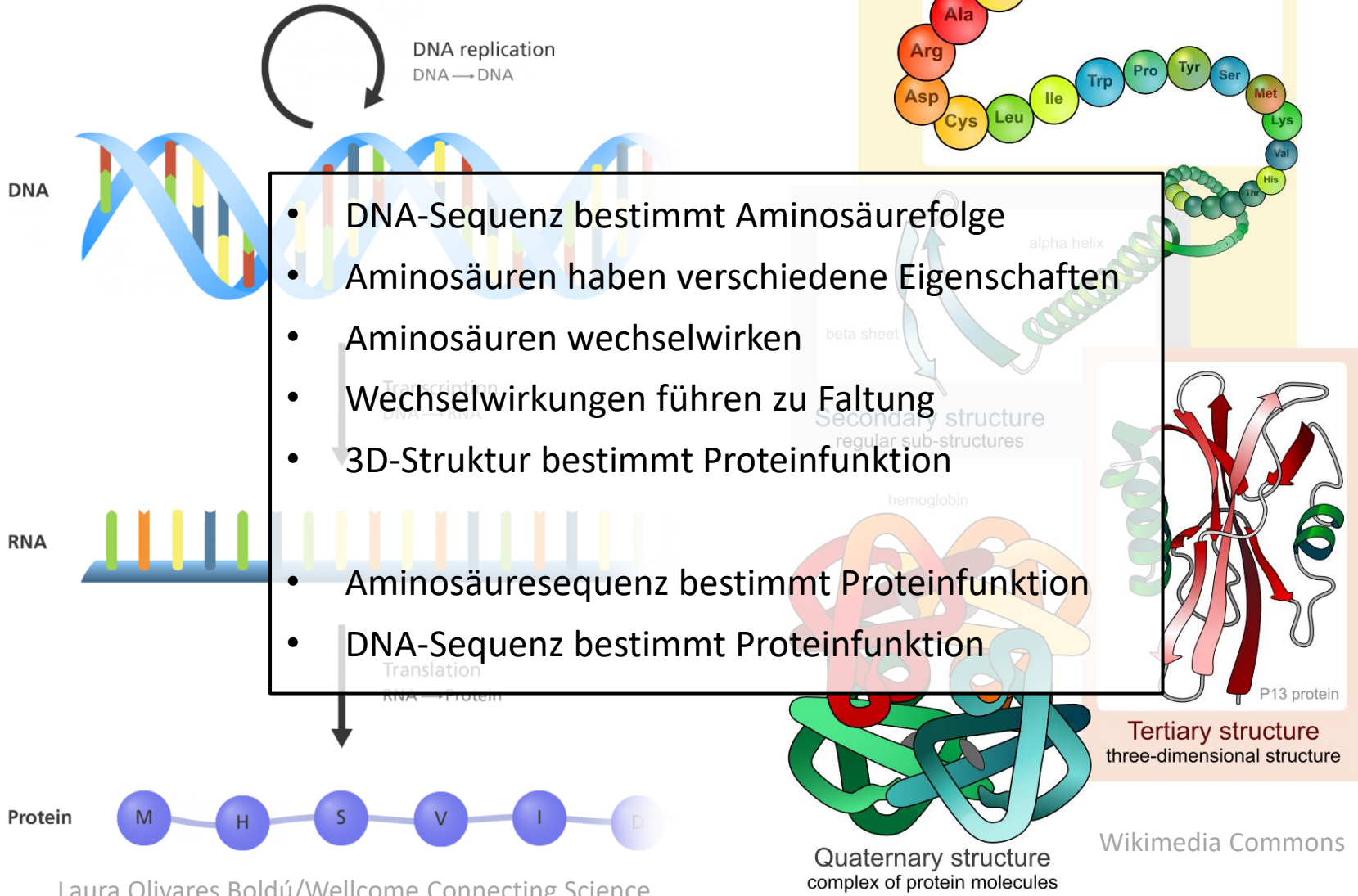
## Zusammenfassung

- Molekulare Tausendsassas:
  - Struktur
  - Transport und Speicher
  - Stoffauf- und -abbau (Enzyme)
  - Verteidigung
  - Energieumwandlung
  - Signalfunktion
  - Wahrnehmung
  - Motorik
  - ...



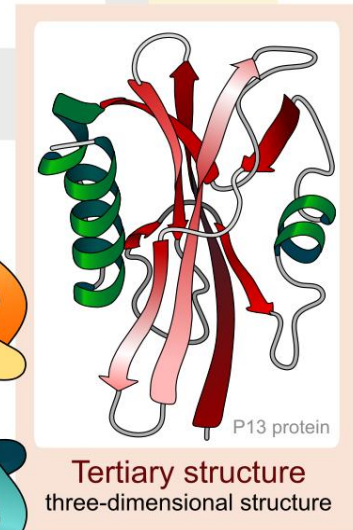
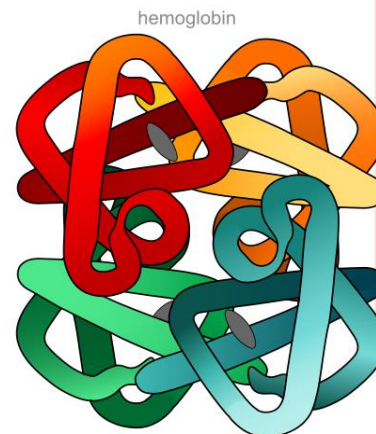
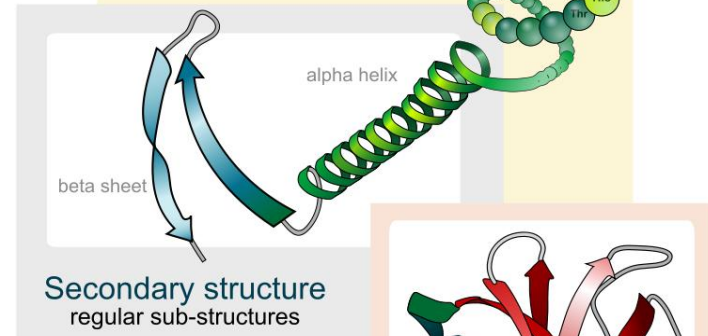
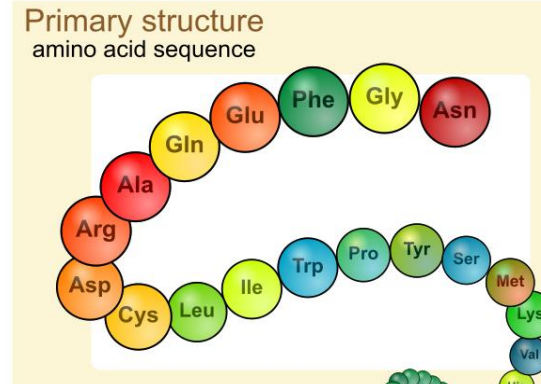
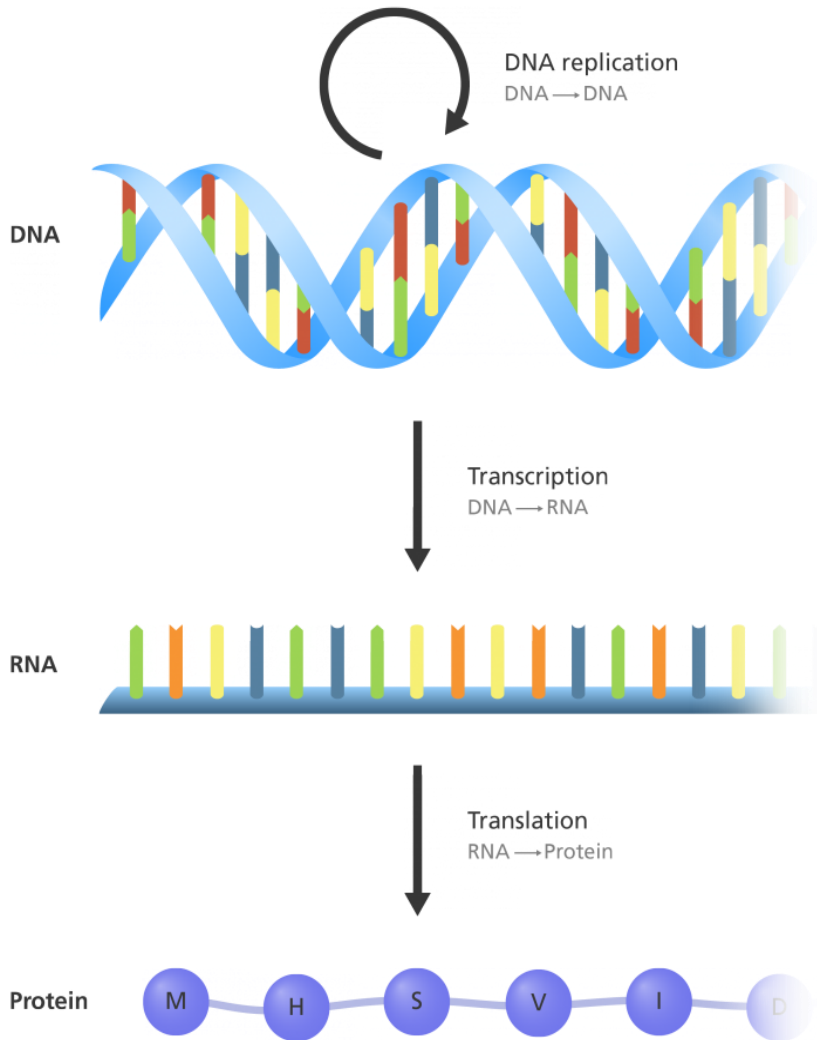


# Zusammenfassung



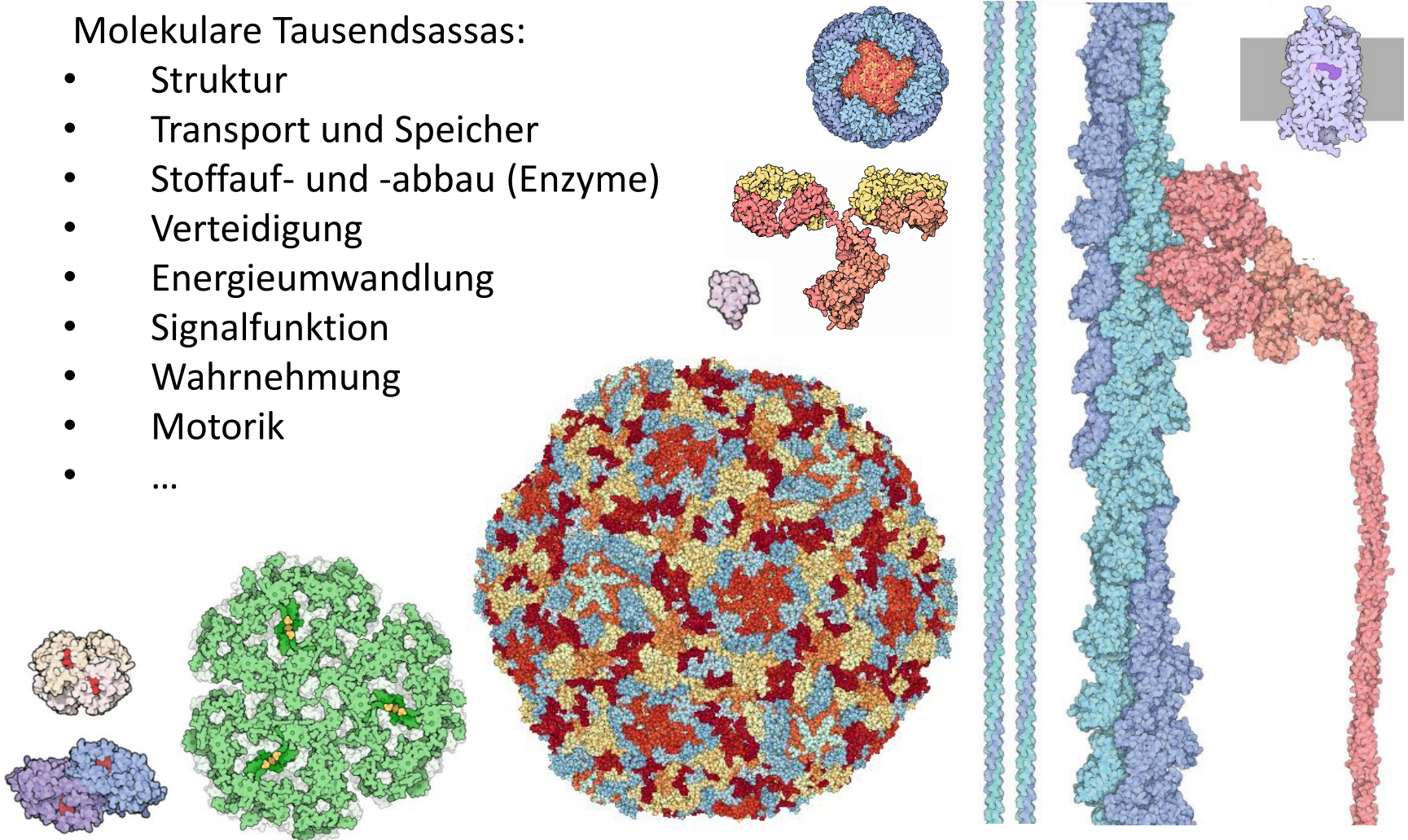
1. Die molekularen Maschinen des Lebens
- 2. Biotechnologie: Proteine als Stars in Medizin, Chemie & Co.**
3. Aktuelle Proteinforschung und ihr Zukunftspotenzial

# Recap Teil 1



## Recap Teil 1

- Molekulare Tausendsassas:
  - Struktur
  - Transport und Speicher
  - Stoffauf- und -abbau (Enzyme)
  - Verteidigung
  - Energieumwandlung
  - Signalfunktion
  - Wahrnehmung
  - Motorik
  - ...



## Biotechnologie

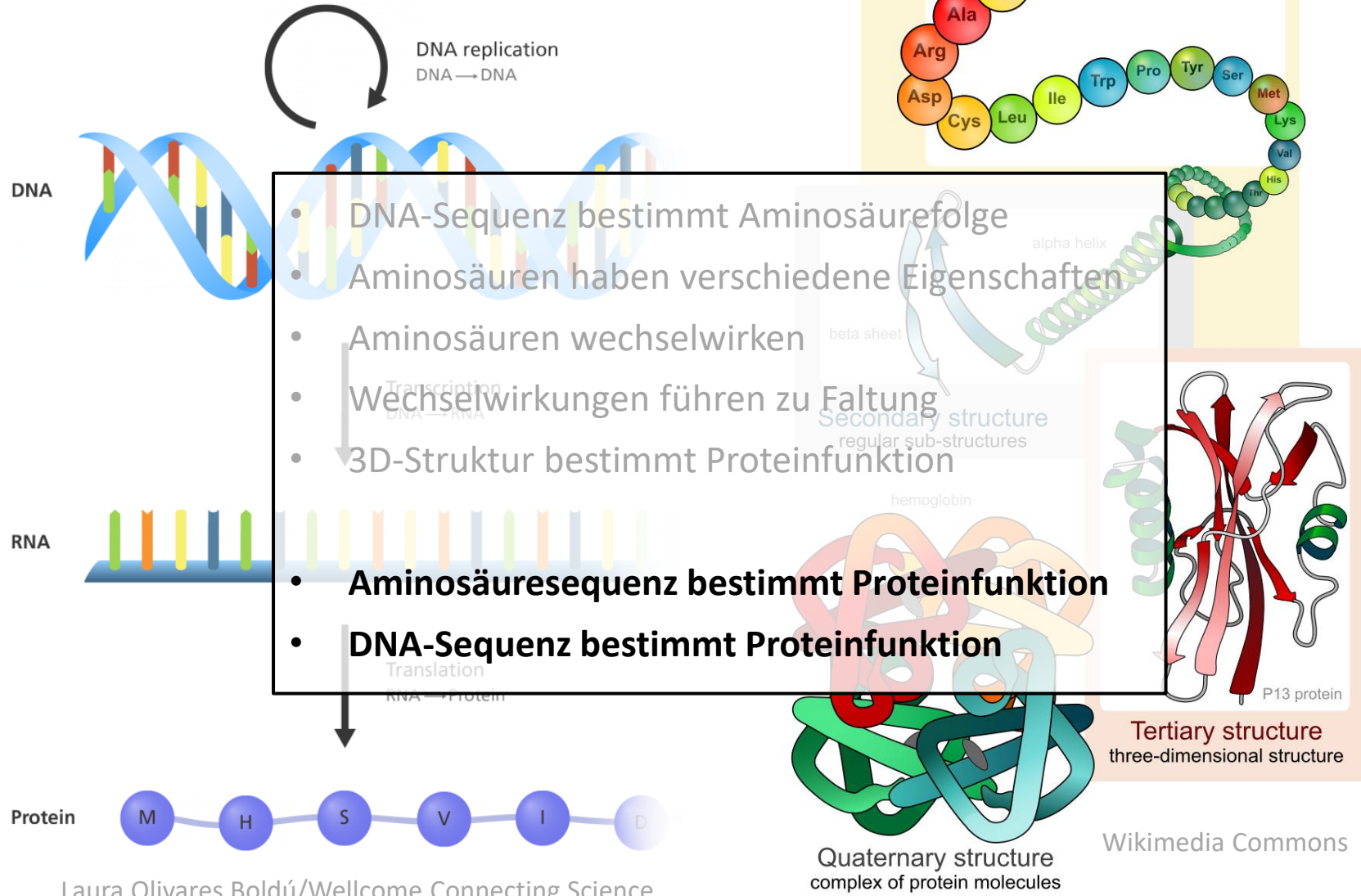
Technische Nutzung/Nutzbarmachung biologischer Prozesse



## Recap Teil 1

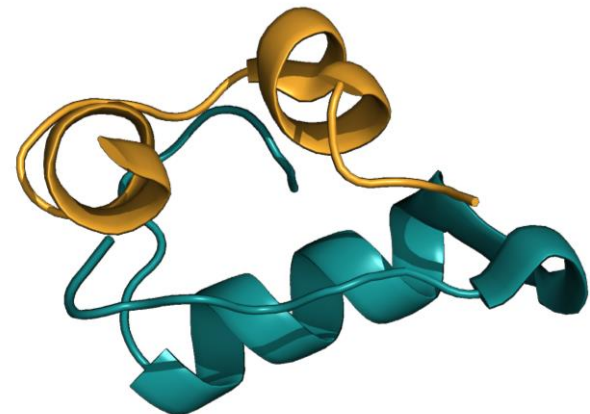
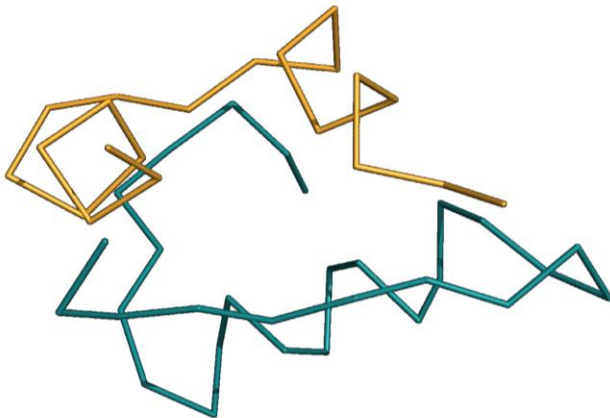
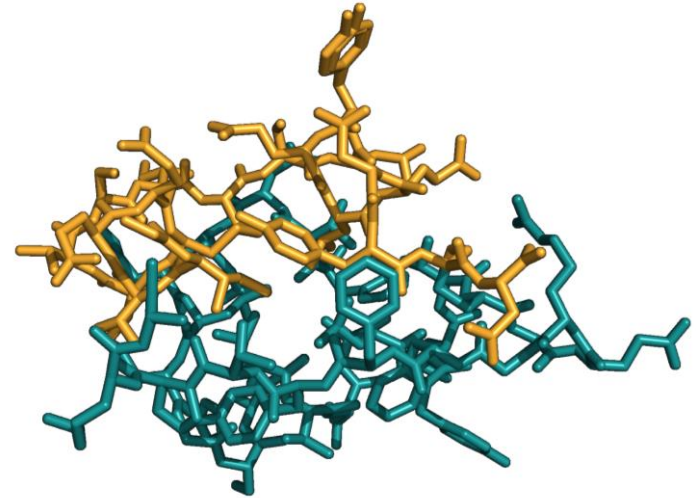
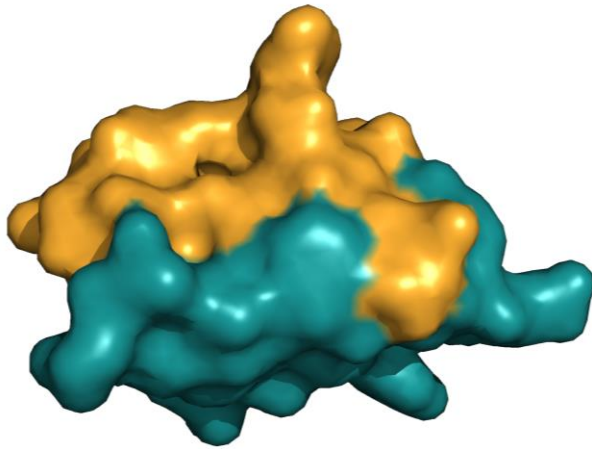


# Recap Teil 1





## Verschiedene Darstellungsformen von Proteinstrukturen



## Biotechnologie

Technische Nutzung/Nutzbarmachung biologischer Prozesse

„Urzeitliche“ Biotechnologie:



## Wiederholung: Insulin

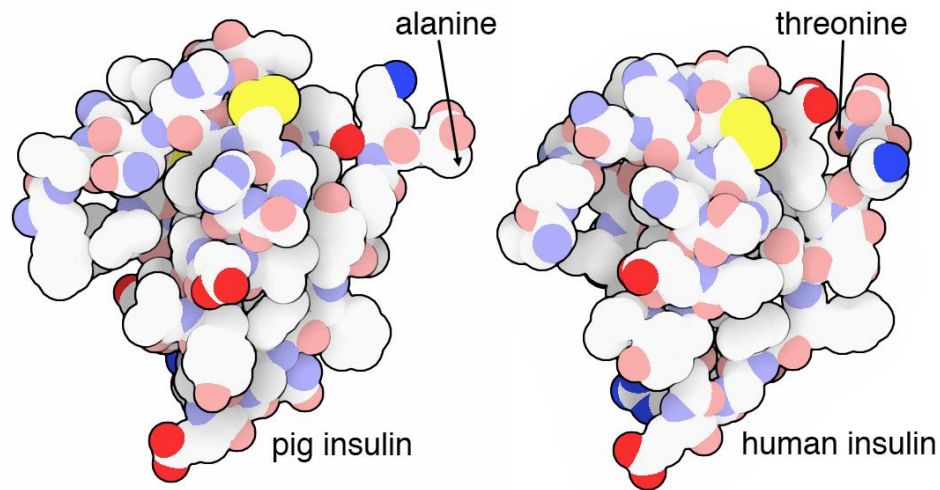


PROTEIN

CC-BY PDB-101

## Diabetes

- (funktioneller) Insulinmangel → Diabetes
- ~ 500 Mio Patienten; stark steigend → Therapie: Insulin
- Insulin ursprünglich aus Schwein und Rind isoliert (70 p.p.a.)



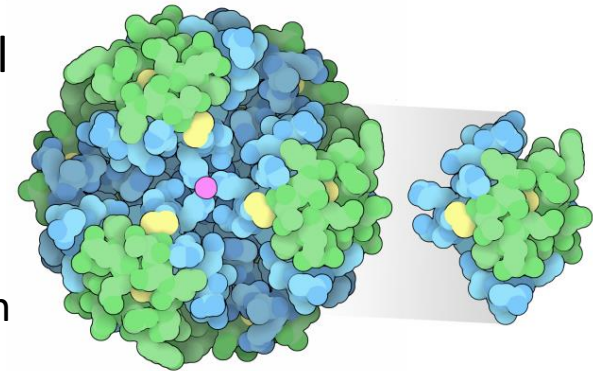
David Goodsell/PDB-101

- ABER:
  - Unzureichende Verfügbarkeit
  - Infektionsrisiko (insb. BSE)
  - Immunreaktionen

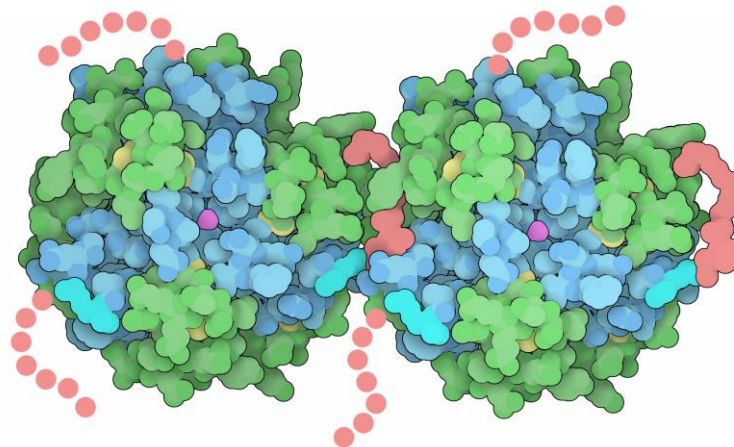


## Biotechnologische Insulinproduktion

- Seit 1982 Produktion *menschlichen* Insulins in *E. coli*
- Seit 1996: Varianten mit optimiertem Wirkprofil
  - *Insulin aspart*: Monomer begünstigt (B: P28D)  
→ beschleunigte Wirkung
  - *Insulin degludec*: KW-Brücken zwischen Hexameren  
→ verlangsamte Wirkung



Bilder: David Goodsell/PDB-101



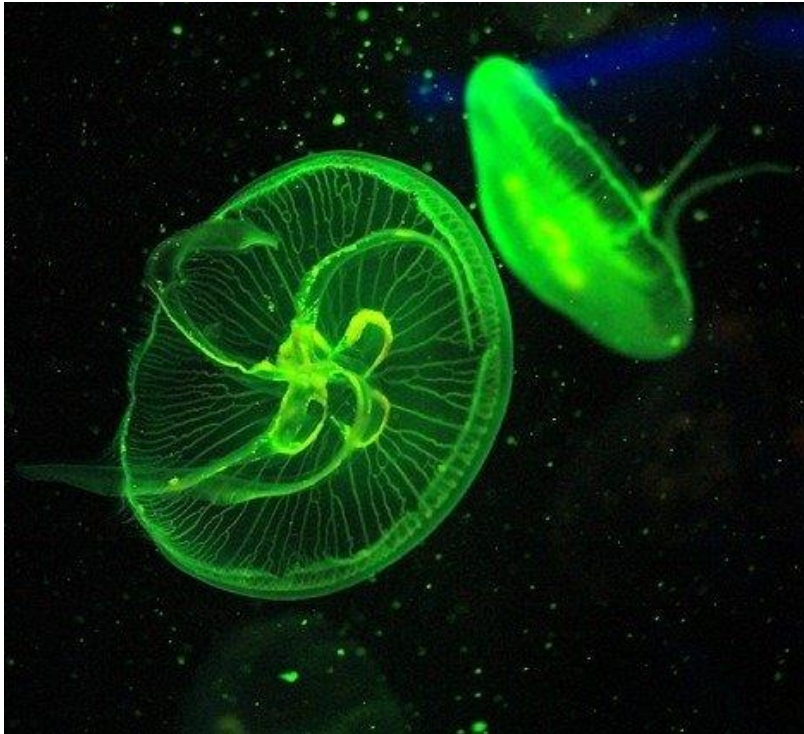
## Protein Engineering

Gezielte Veränderung (oder Gestaltung) von Proteinen zur Verbesserung ihrer Eigenschaften bzw. zum Generieren neuer Eigenschaften

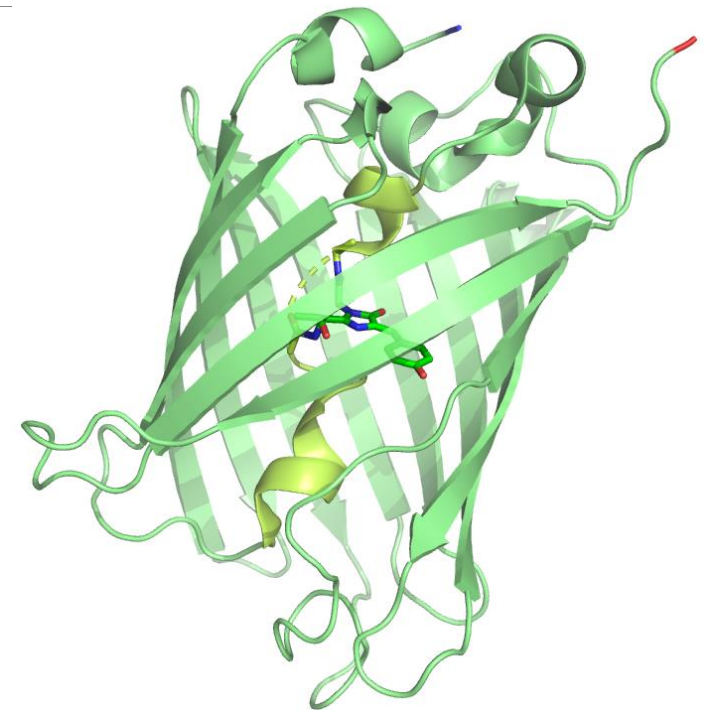
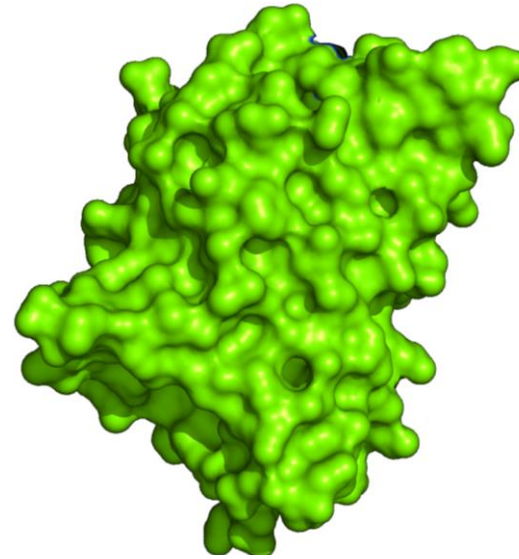
### Rationales Engineering:

- Start mit natürlichem Protein
- Wissen um Struktur genutzt
- Gezielte Veränderungen eingefügt

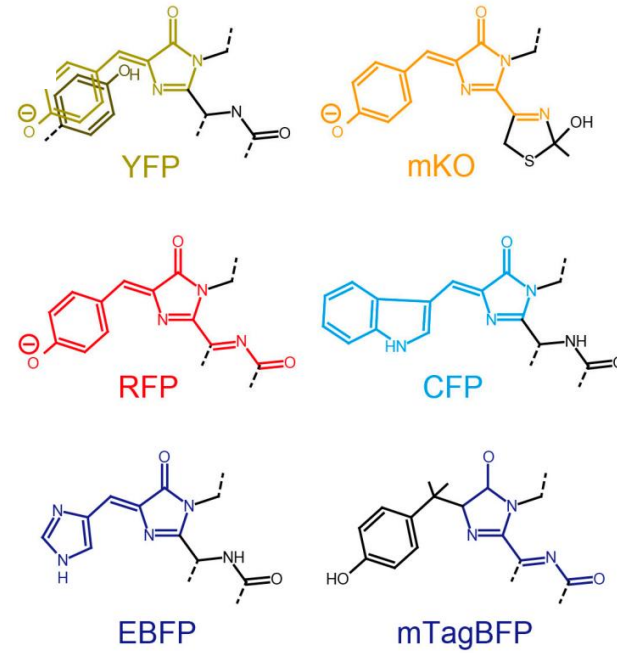
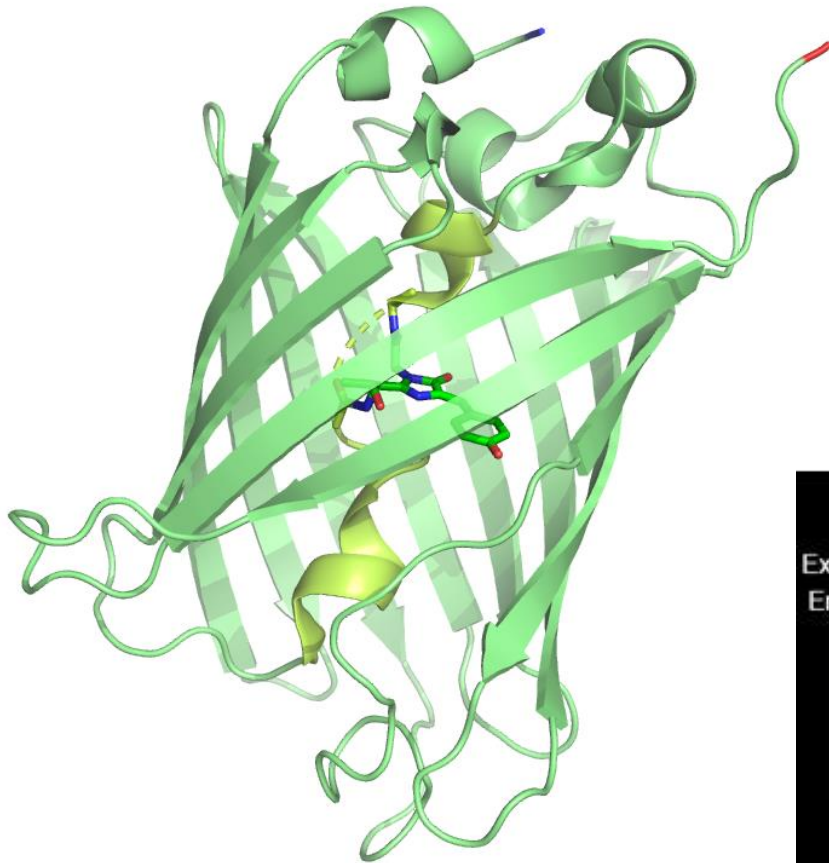
## Rationales Engineering



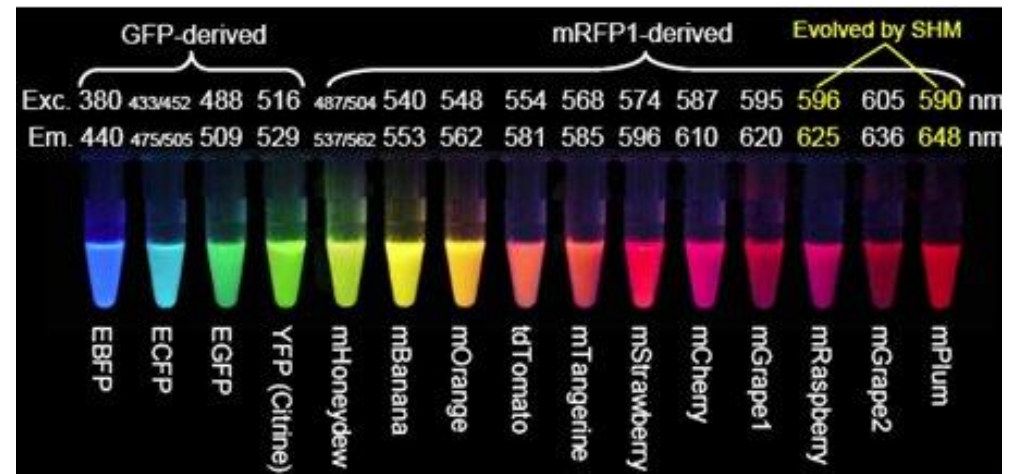
Pixabay (CC0)



# Rationales Engineering



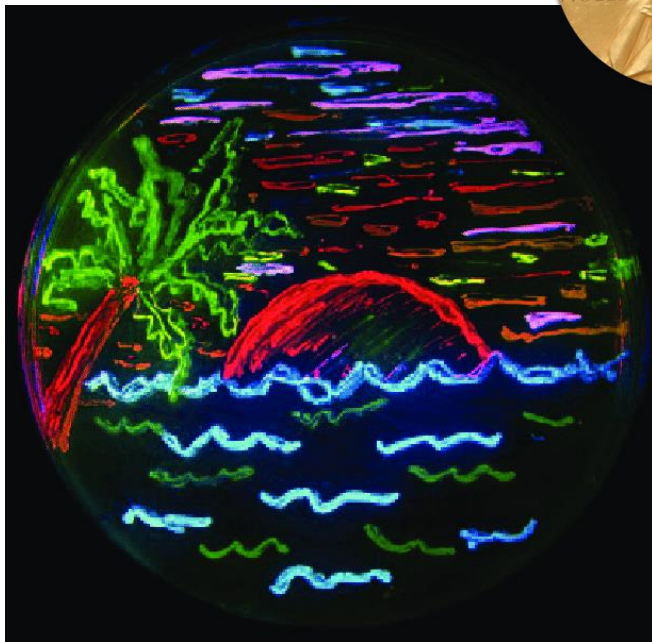
Shinoda et al. 2018, Int. J. Mol. Sci



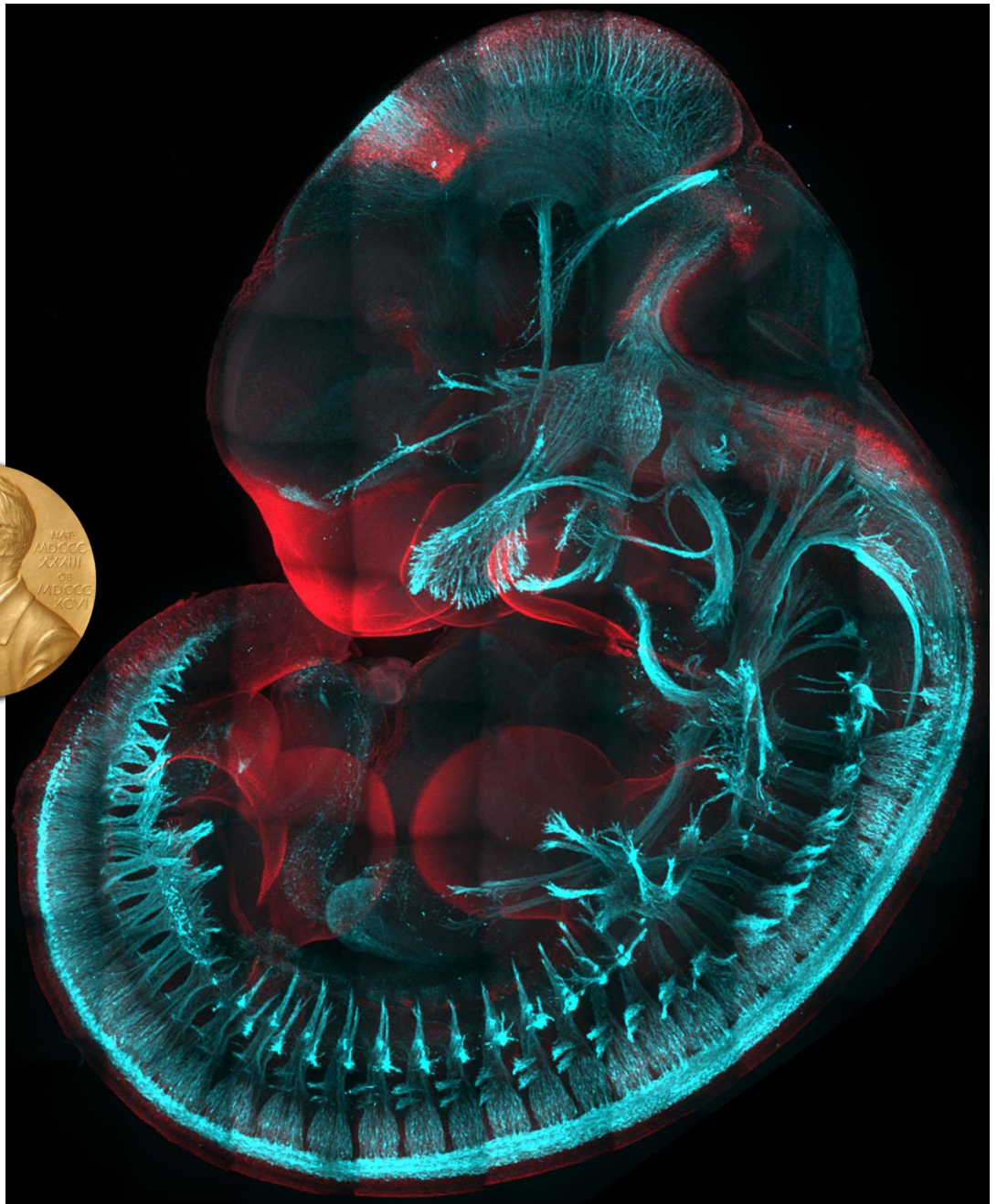




Wikimedia Commons



Karuso 2009, Chemistry in Australia



V. Pragathi Masamsetti, Children's Medical Research Institute

## Protein Engineering

Gezielte Veränderung (oder Gestaltung) von Proteinen zur Verbesserung ihrer Eigenschaften bzw. zum Generieren neuer Eigenschaften

### Rationales Engineering:

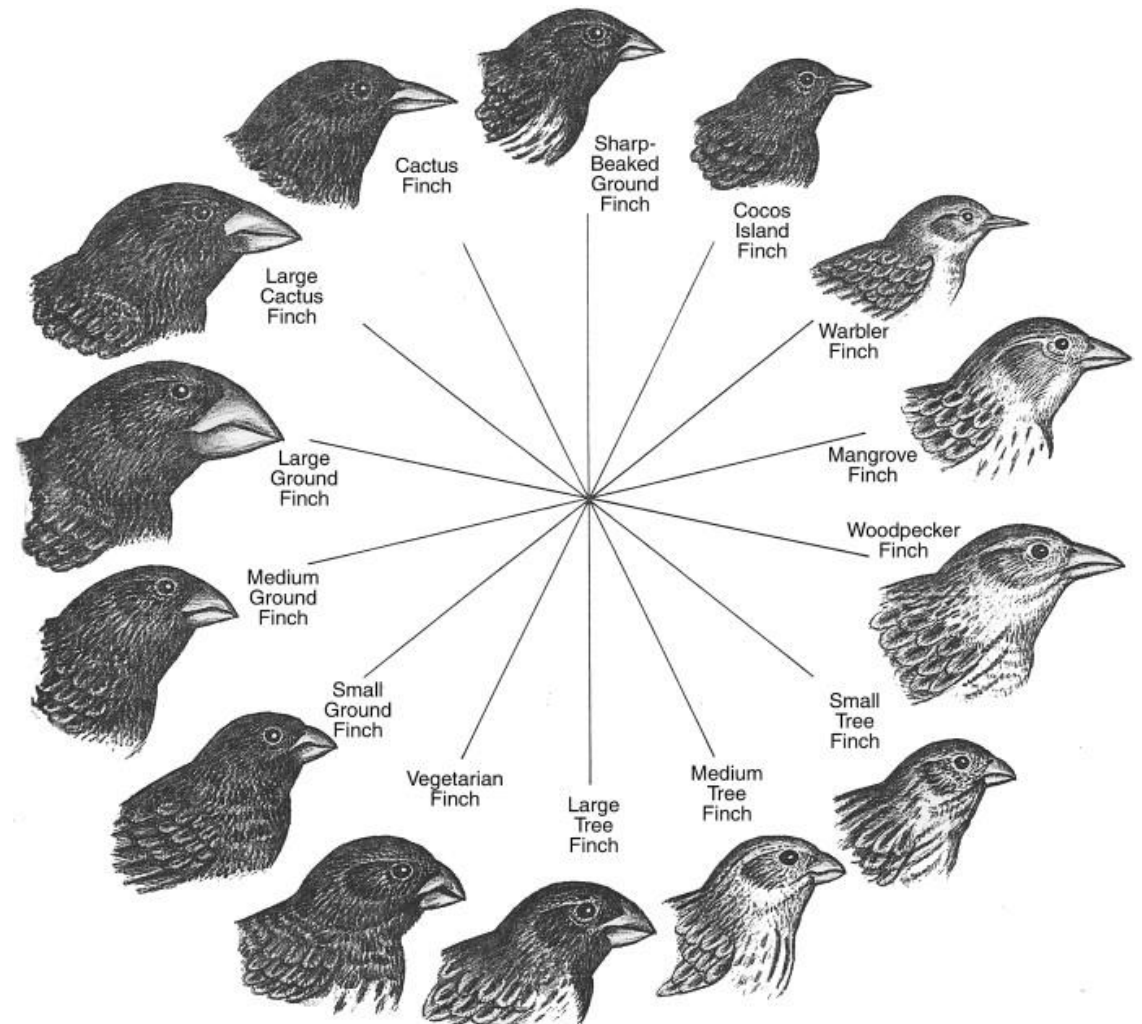
- Start mit natürlichem Protein
- Wissen um Struktur genutzt
- Gezielte Veränderungen eingefügt

... aber die großen Wunder der Natur sind nicht durch rationale Veränderungen entstanden...

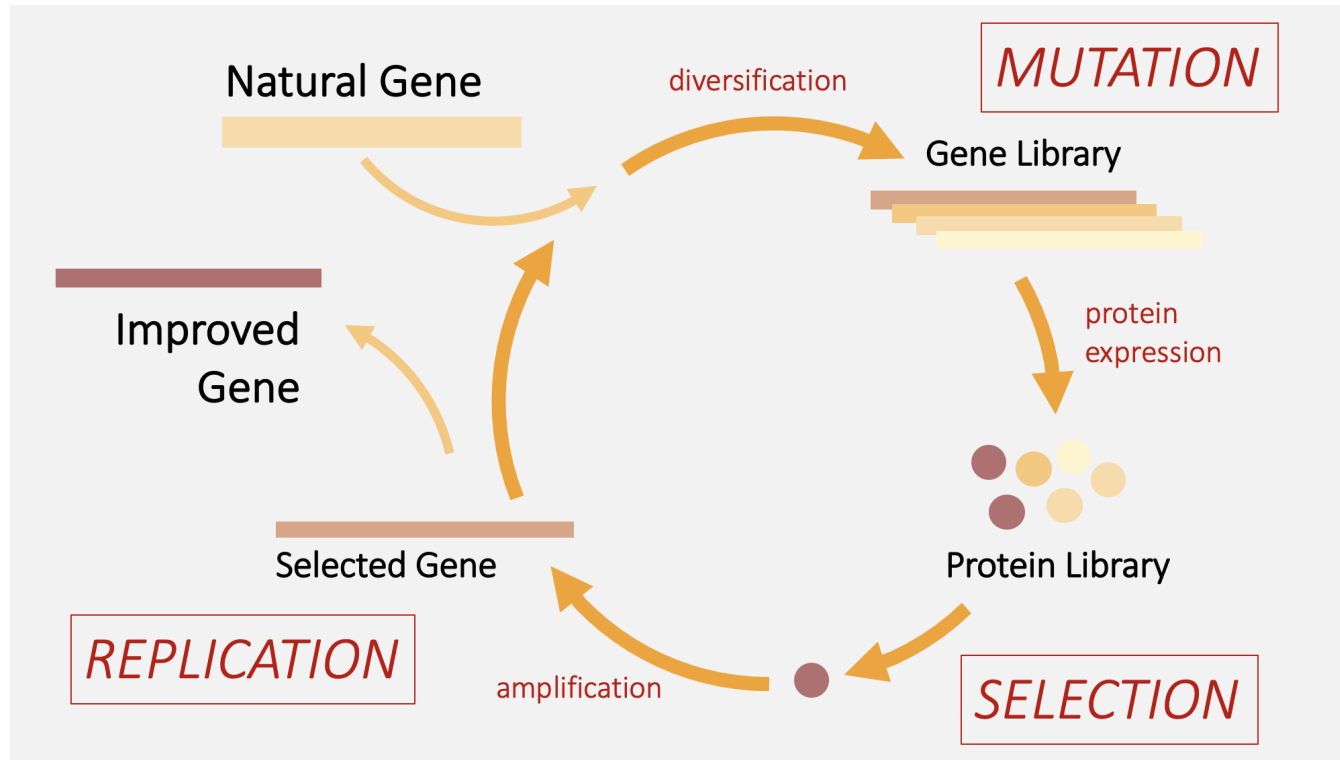
...sondern durch Evolution:

- Zufällige Mutationen
- Unterschiedliche Fitness
- Unterschiedlicher Erfolg in der Fortpflanzung

→ Survival of the fittest



## Gerichtete Evolution

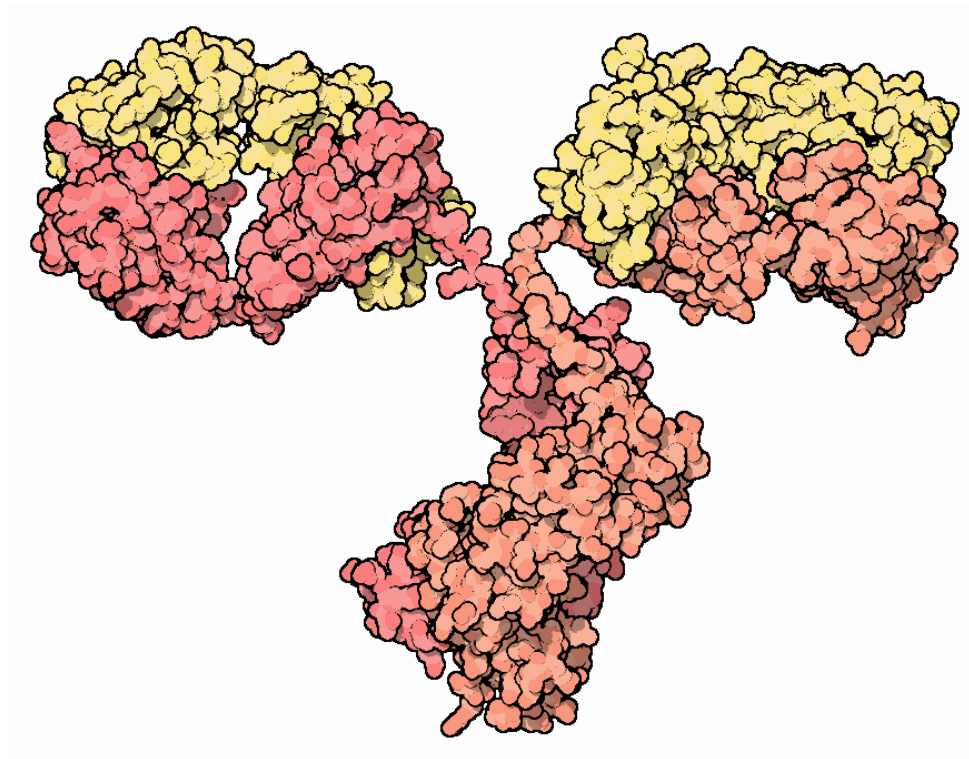


iGEM Team Stanford 2019

- Steuerbare und immens beschleunigte Evolution gewünschter Eigenschaften
- Erlaubt Exploration von Milliarden bis Billionen von Varianten eines Proteins!



## Wiederholung: Antikörper



David Goodsell/PDB-101

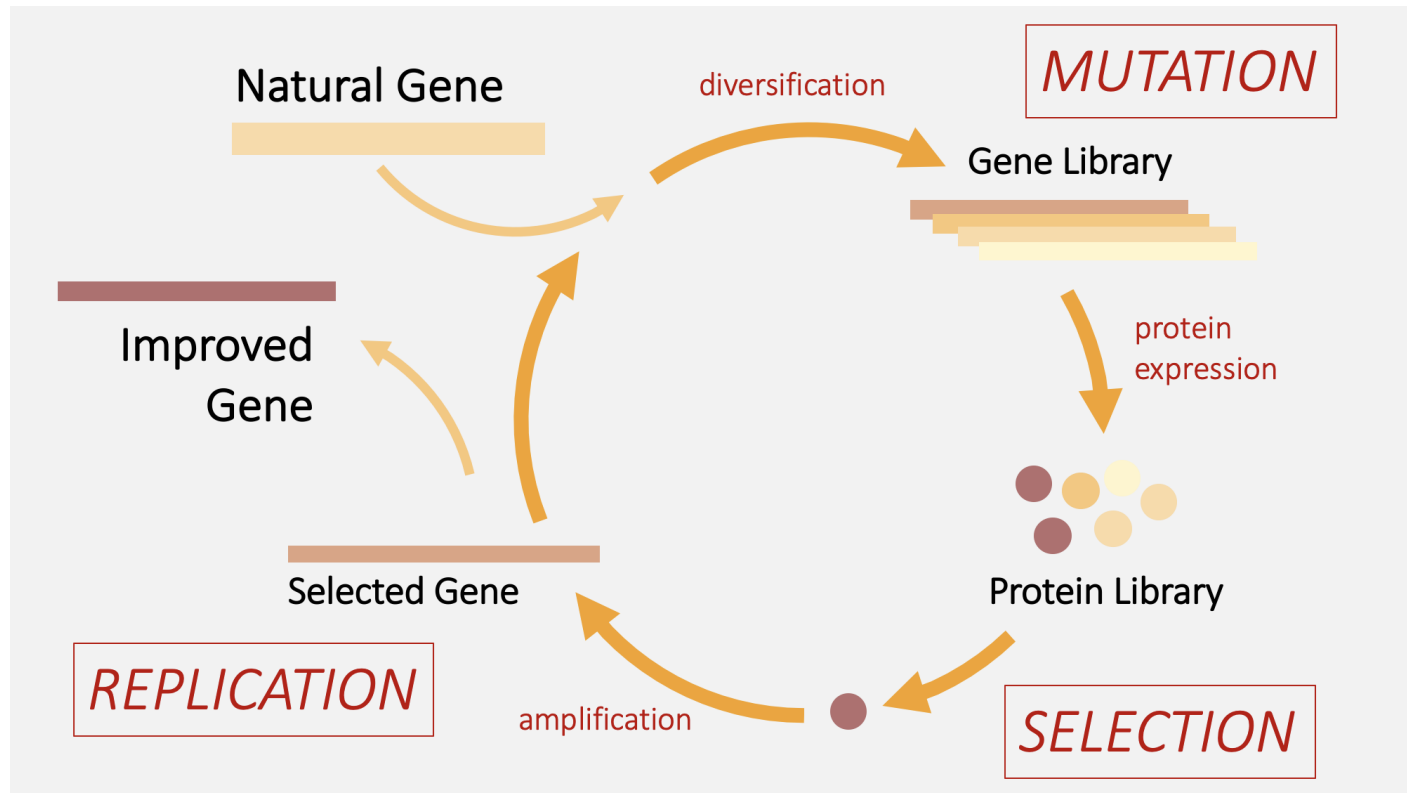
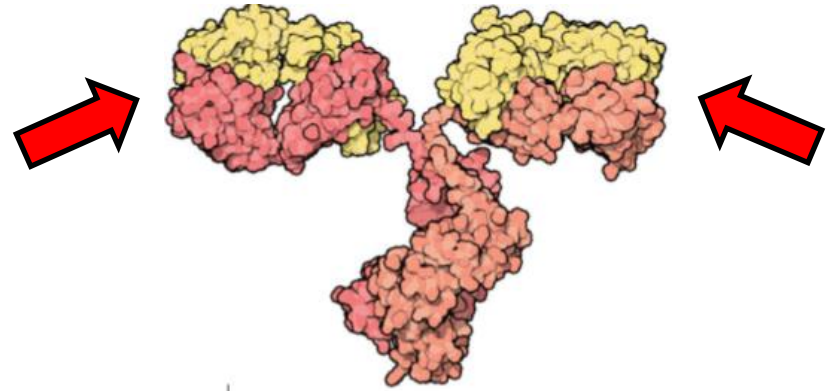
## Wiederholung: Antikörper



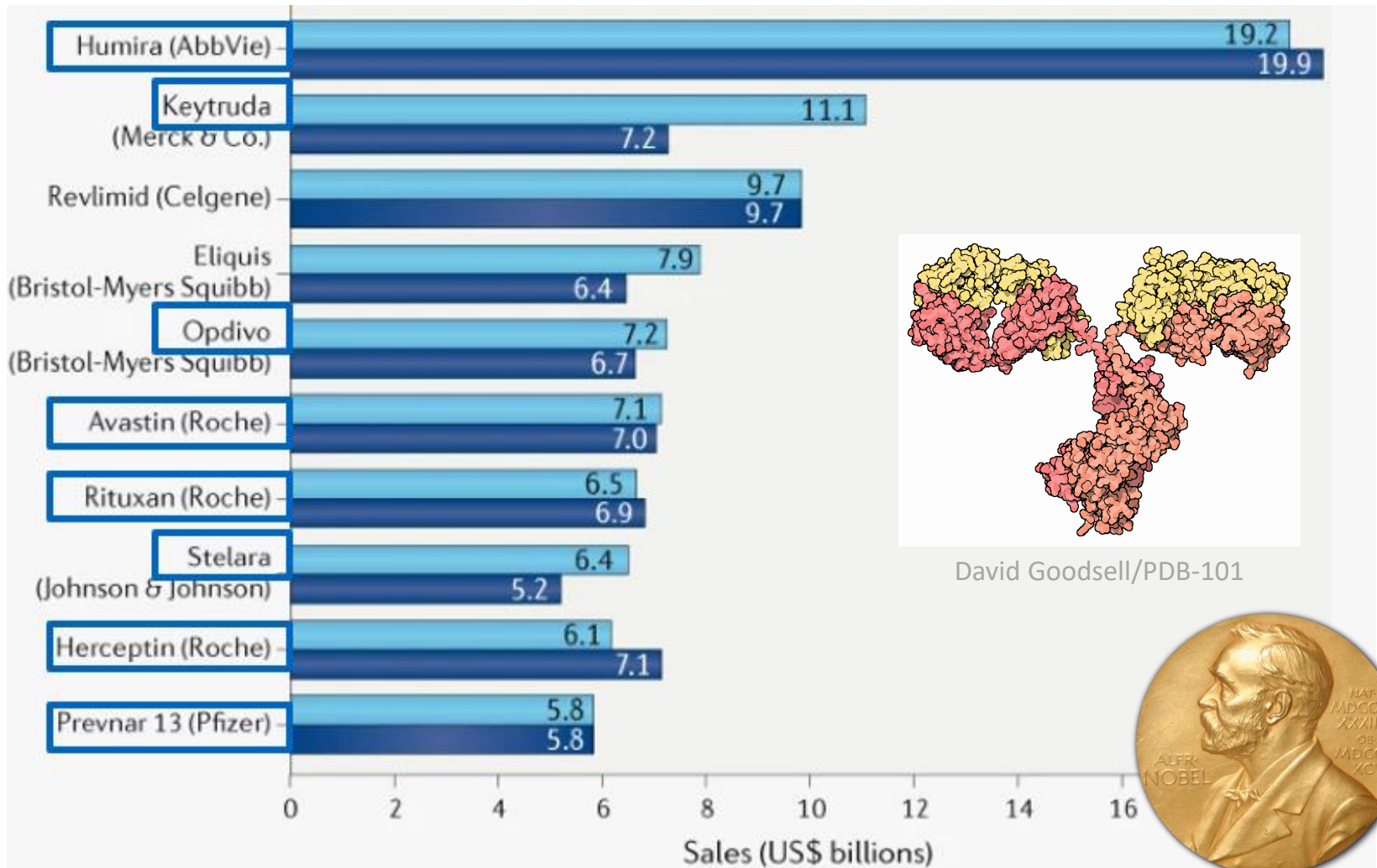
PROTEIN

CC-BY PDB-101

## Gerichtete Evolution



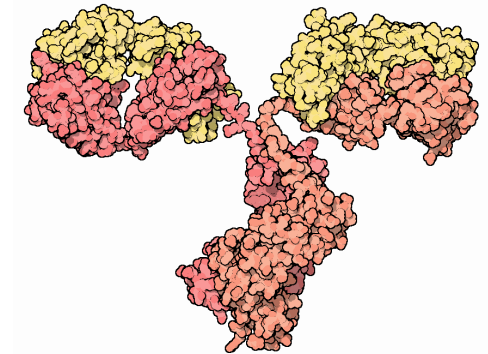
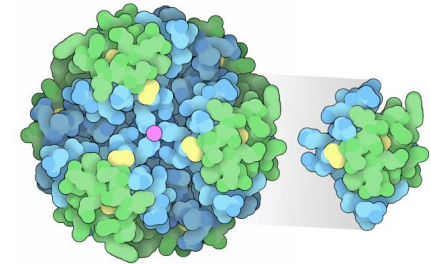
## Proteine sind die Blockbuster der modernen Medizin



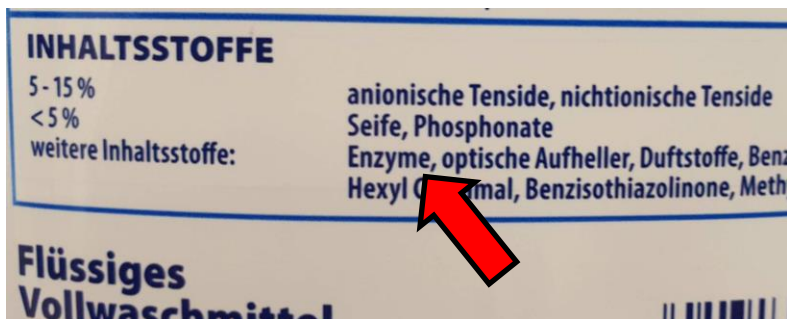


## Zusammenfassung

- Rationales Engineering:
  - Auf Basis von Strukturinformationen
  - Kleinteilige, genau geplante Veränderungen
  - Wenige Varianten untersucht
- Gerichtete Evolution:
  - Rapide künstliche Evolution in cleverem Experiment
  - Zahllose Varianten konkurrieren, beste bleiben
  - Nutzt i.d.R. Strukturinformation, allerdings flächiger
- In der Praxis werden beide Ansätze oft kombiniert



Bilder: David Goodsell/PDB-101



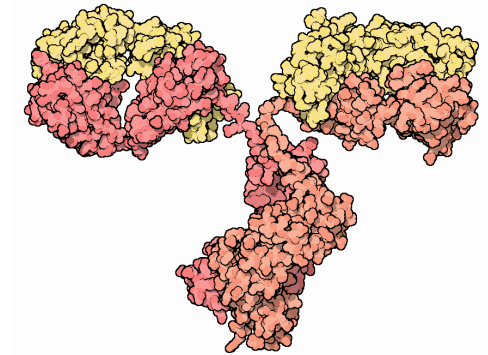
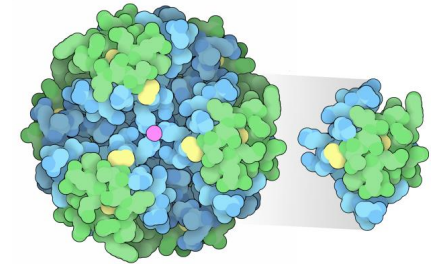
### Waschmittel:

- Proteasen, Lipasen, Cellulasen
- Erhöhte Stabilität und Aktivität
- Funktion bei niedrigen Temperaturen

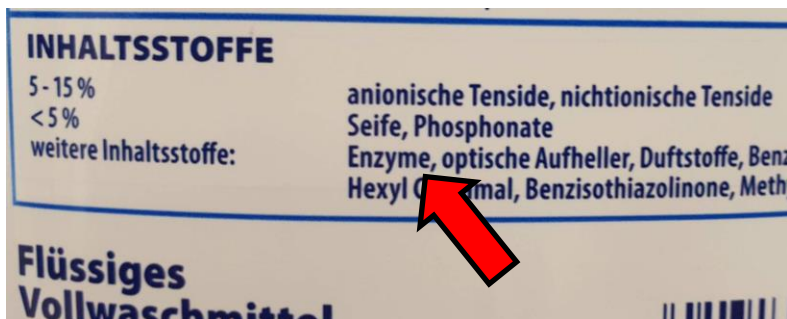
1. Die molekularen Maschinen des Lebens
2. Biotechnologie: Proteine als Stars in Medizin, Chemie & Co.
- 3. Aktuelle Proteinforschung und ihr Zukunftspotenzial**

## Recap Teil 2

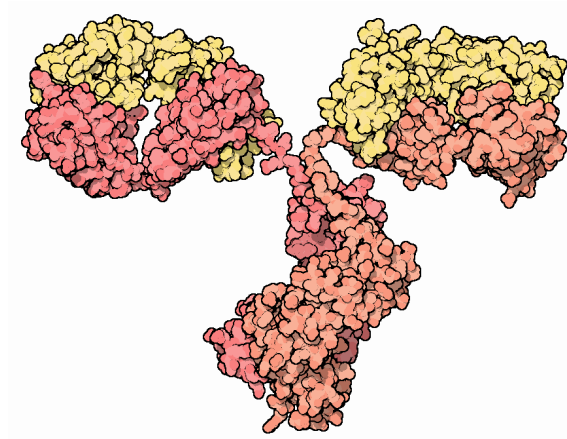
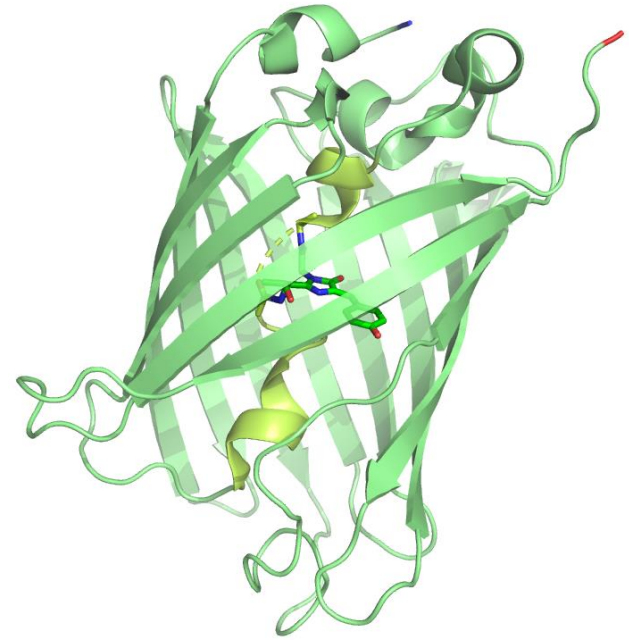
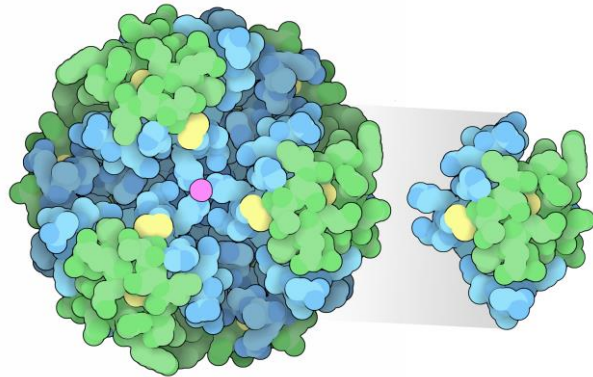
- Rationales Engineering:
  - Auf Basis von Strukturinformationen
  - Kleinteilige, genau geplante Veränderungen
  - Wenige Varianten untersucht
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  - Rapide künstliche Evolution in cleverem Experiment
  - Zahllose Varianten konkurrieren, beste bleiben
  - Nutzt i.d.R. Strukturinformation, allerdings flächiger
- In der Praxis werden beide Ansätze oft kombiniert



Bilder: David Goodsell/PDB-101



## Recap: Rationales engineering und gerichtete Evolution

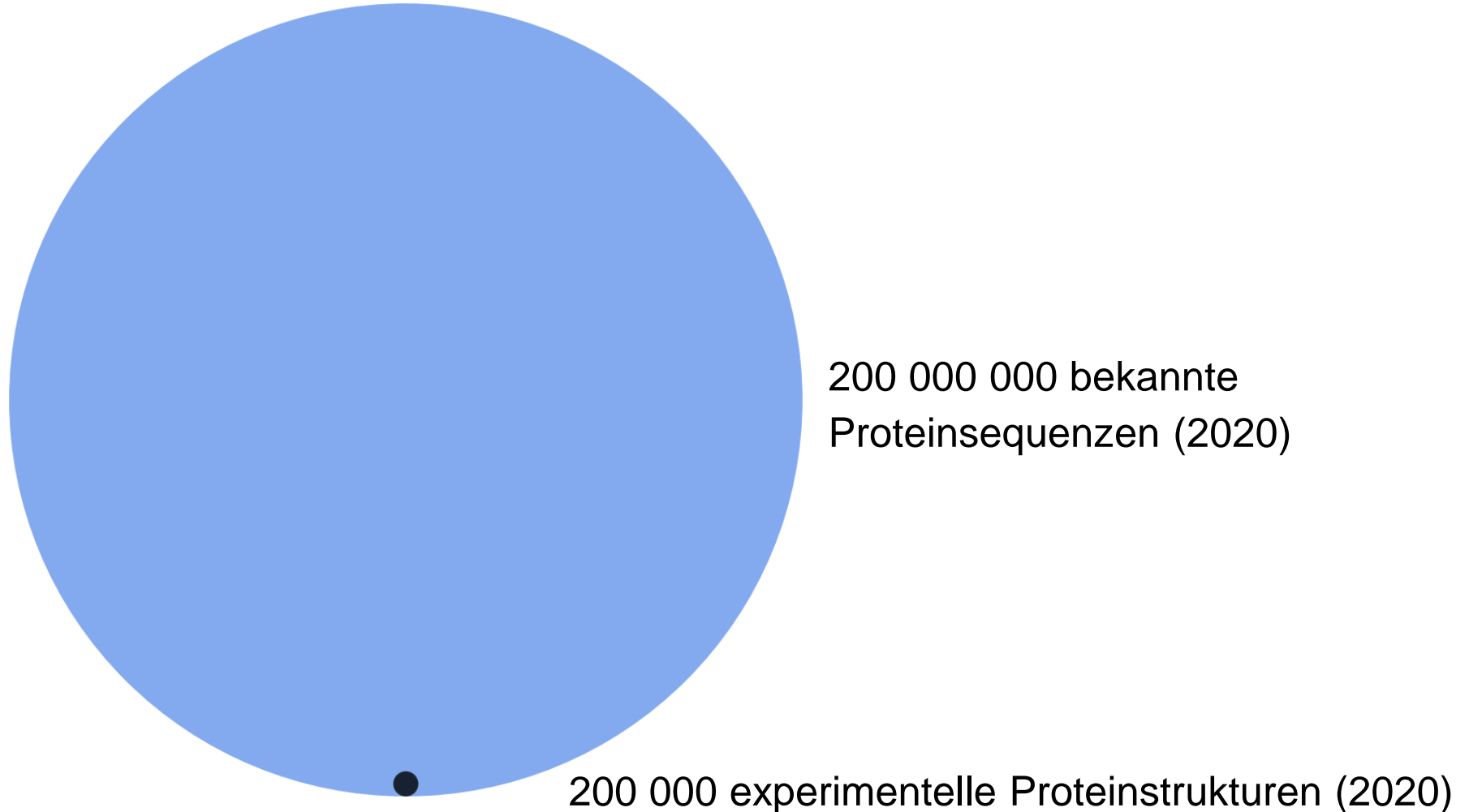


Bilder (li.): David Goodsell/PDB-101

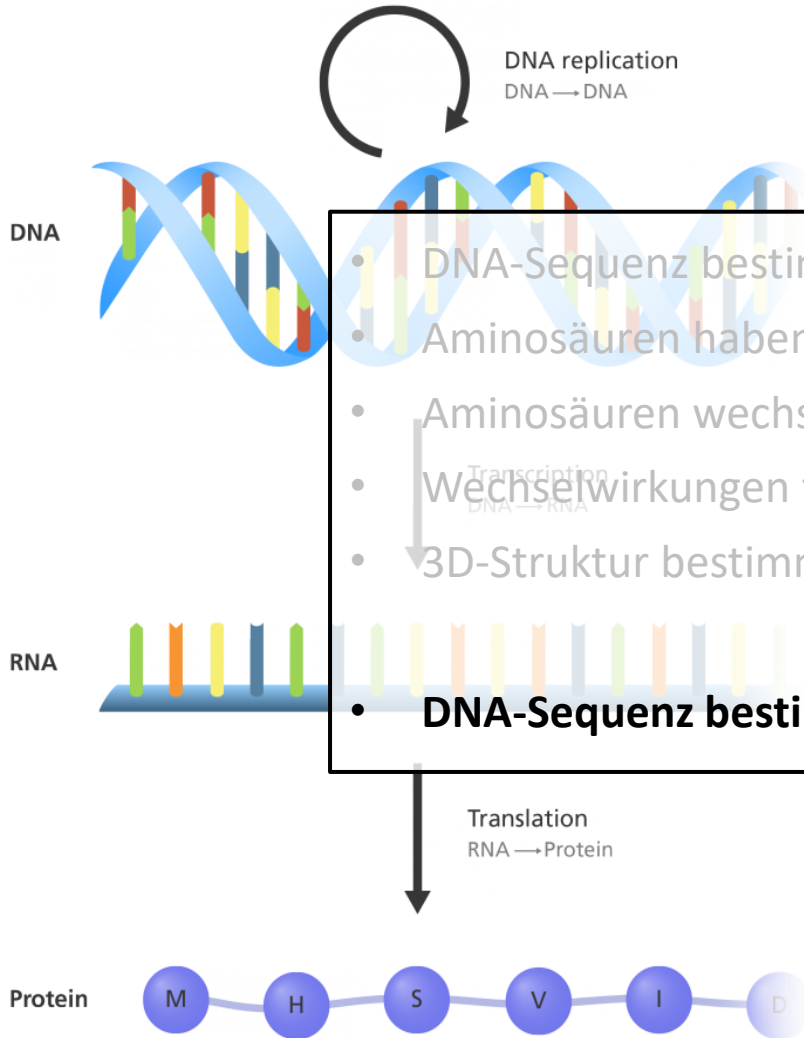
→ Protein Engineering benötigt in der Regel Strukturinformationen!



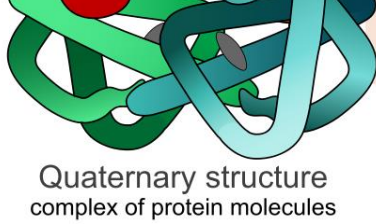
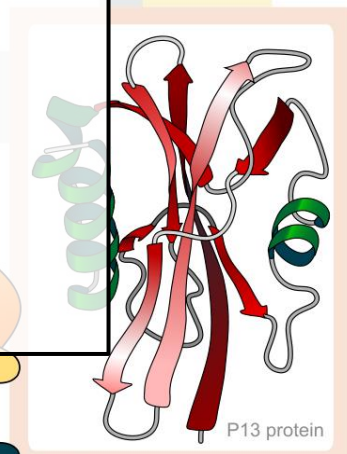
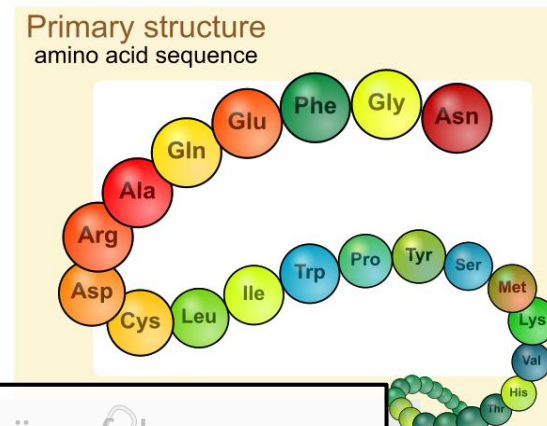
## Strukturverfügbarkeit limitiert Protein Engineering



# Lassen sich Strukturen vorhersagen?

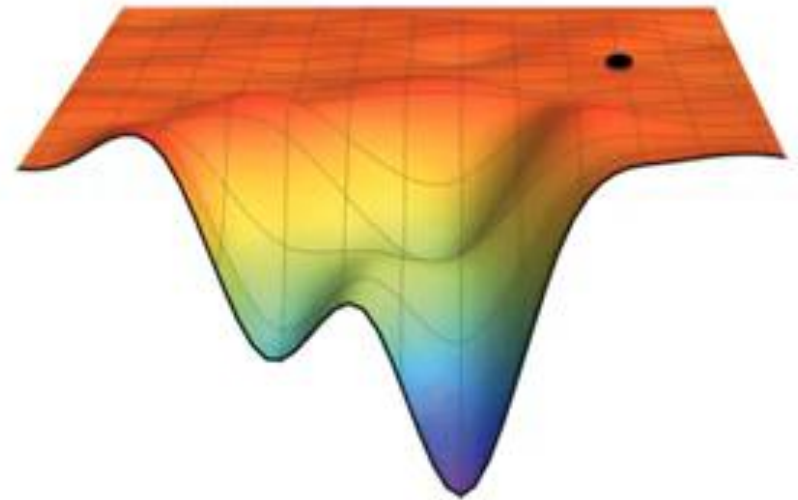


- DNA-Sequenz bestimmt Aminosäurefolge
- Aminosäuren haben verschiedene Eigenschaften
- Aminosäuren wechselwirken
- Wechselwirkungen führen zu Faltung
- 3D-Struktur bestimmt Proteinfunktion
- **DNA-Sequenz bestimmt Proteinfunktion**

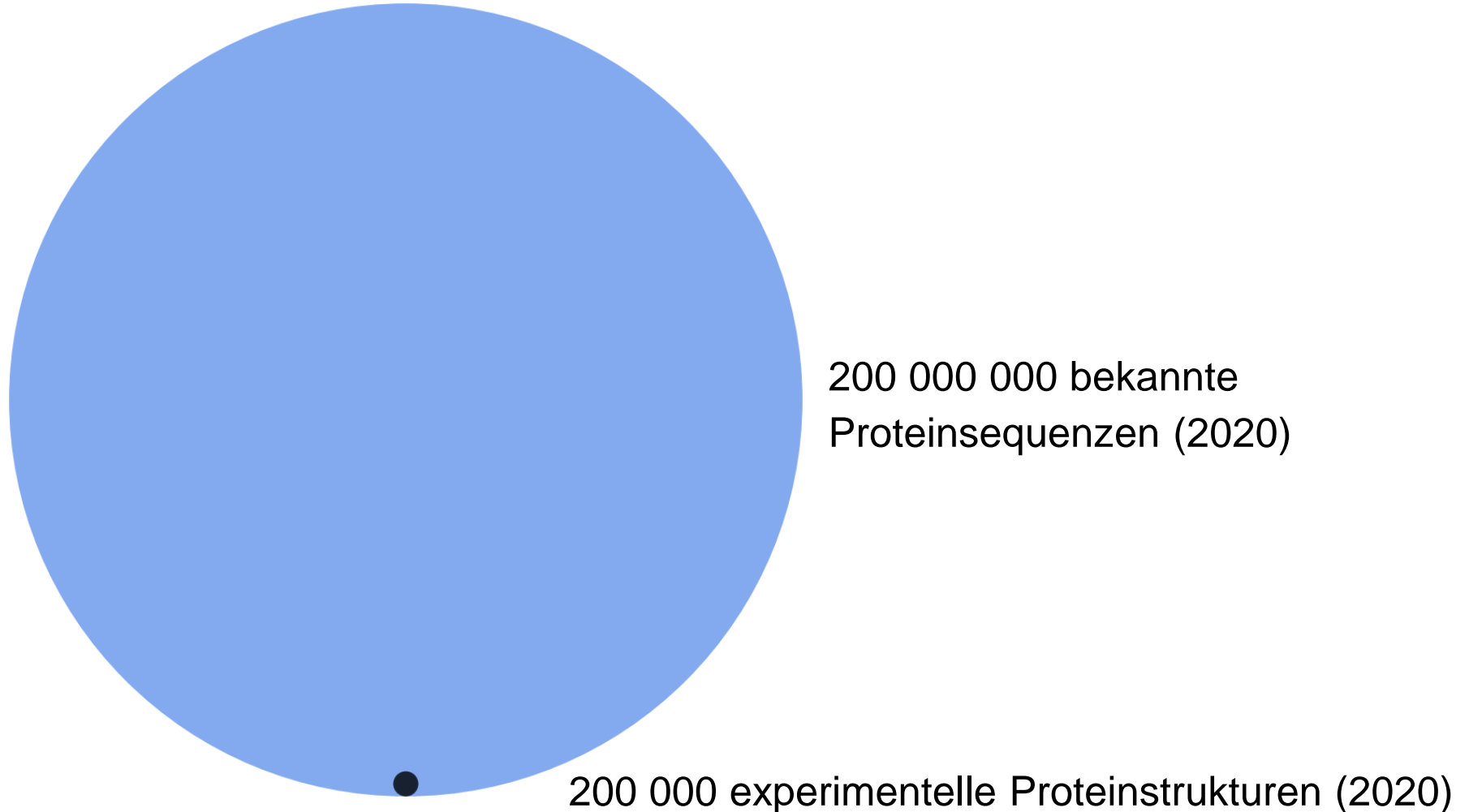


Wikimedia Commons

## Vom Bauplan zum Protein: Proteinfaltung

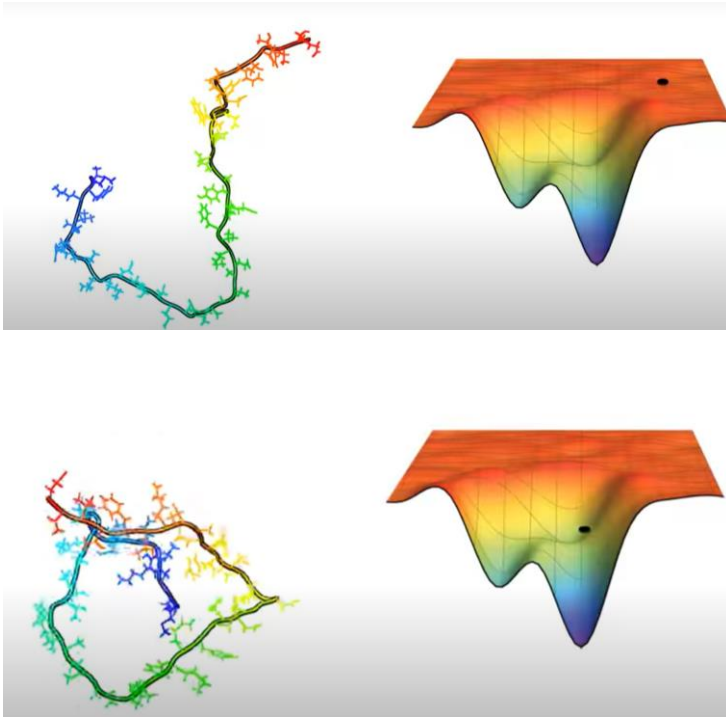


## Strukturverfügbarkeit limitiert Protein Engineering





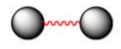
# Das Faltungsproblem



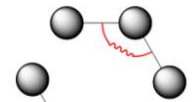
C. Fennell

$$\begin{aligned}
 U(R) = & \sum_{\text{bonds}} k_r (r - r_{eq})^2 \\
 & + \sum_{\text{angles}} k_\theta (\theta - \theta_{eq})^2 \\
 & + \sum_{\text{dihedrals}} k_\phi (1 + \cos[n\phi - \gamma]) \\
 & + \sum_{\text{impropers}} k_\omega (\omega - \omega_{eq})^2 \\
 & + \sum_{i < j}^{\text{atoms}} \epsilon_{ij} \left[ \left( \frac{r_m}{r_{ij}} \right)^{12} - 2 \left( \frac{r_m}{r_{ij}} \right)^6 \right] \\
 & + \sum_{i < j}^{\text{atoms}} \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}
 \end{aligned}$$

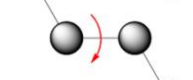
*bond*



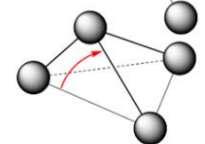
*angle*



*dihedral*



*improper*



*van der Waals*

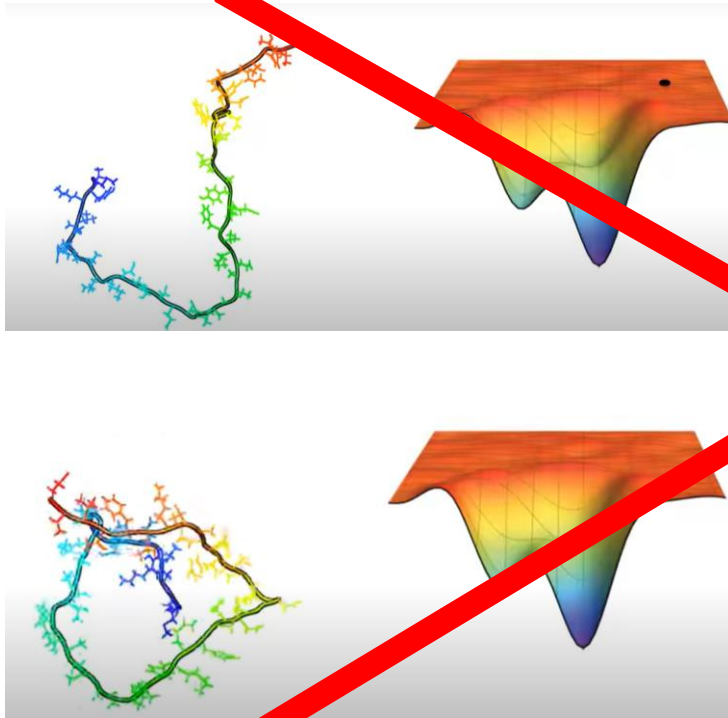


*electrostatic*



Chang et al. (2016), Catalysts

# Das Faltungsproblem



C. Fennell

$$\begin{aligned}
 U(R) = & \sum_{\text{bonds}} k_r (r - r_{eq})^2 \\
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 \end{aligned}$$

*bond*

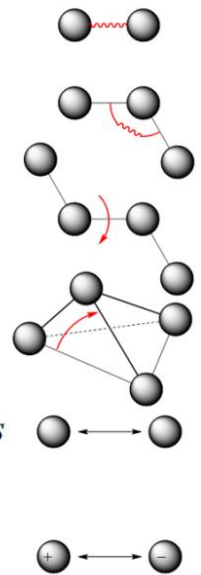
*angle*

*dihedral*

*improper*

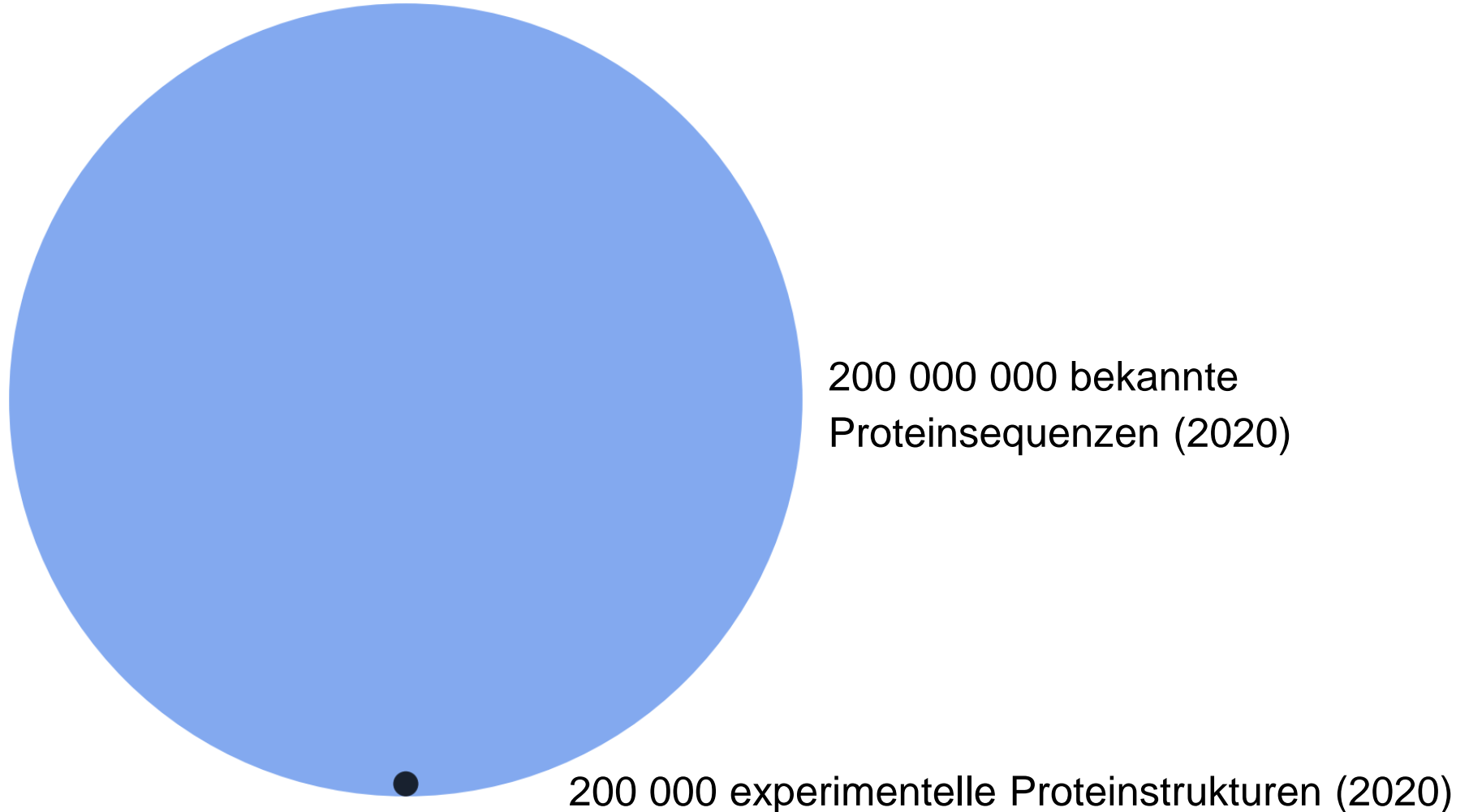
*van der Waals*

*electrostatic*

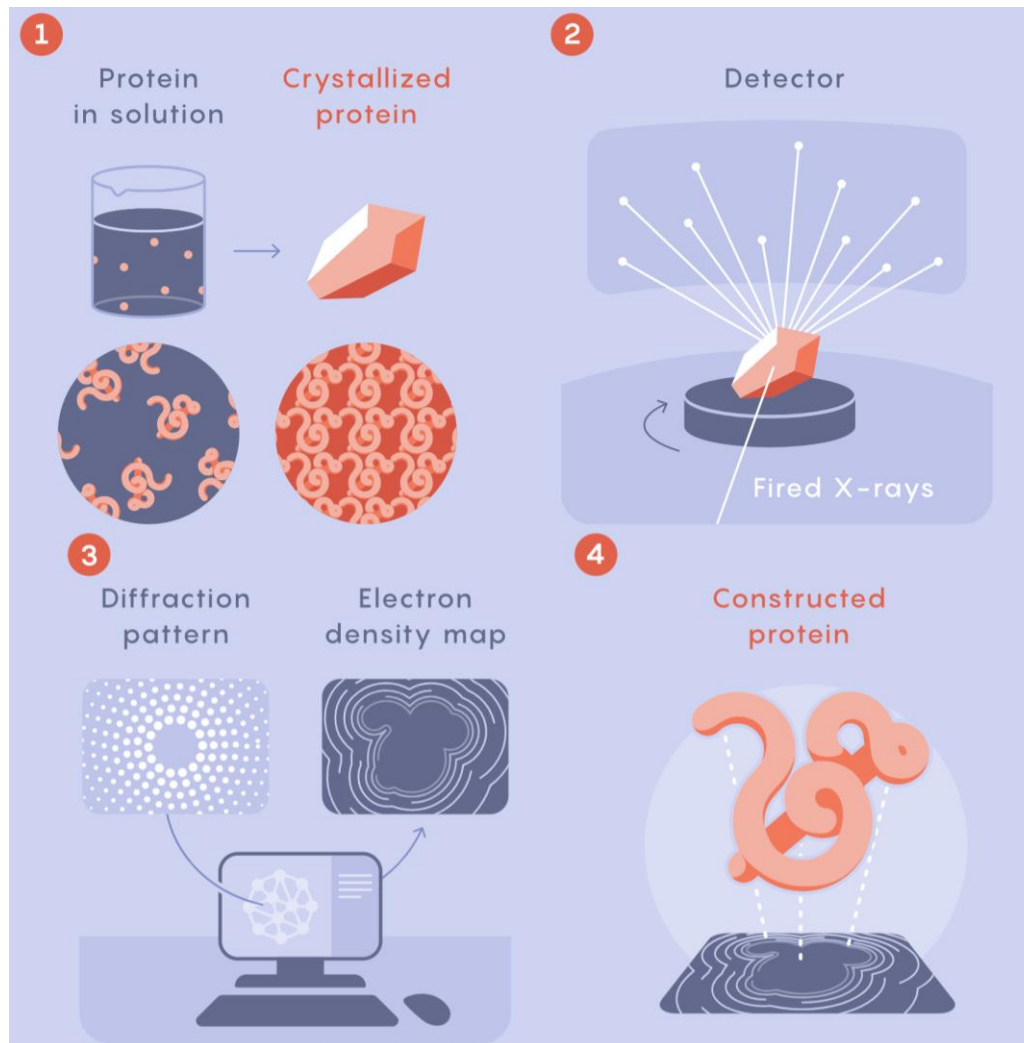


Chang et al. (2016), Catalysts

## Strukturverfügbarkeit limitiert Protein Engineering

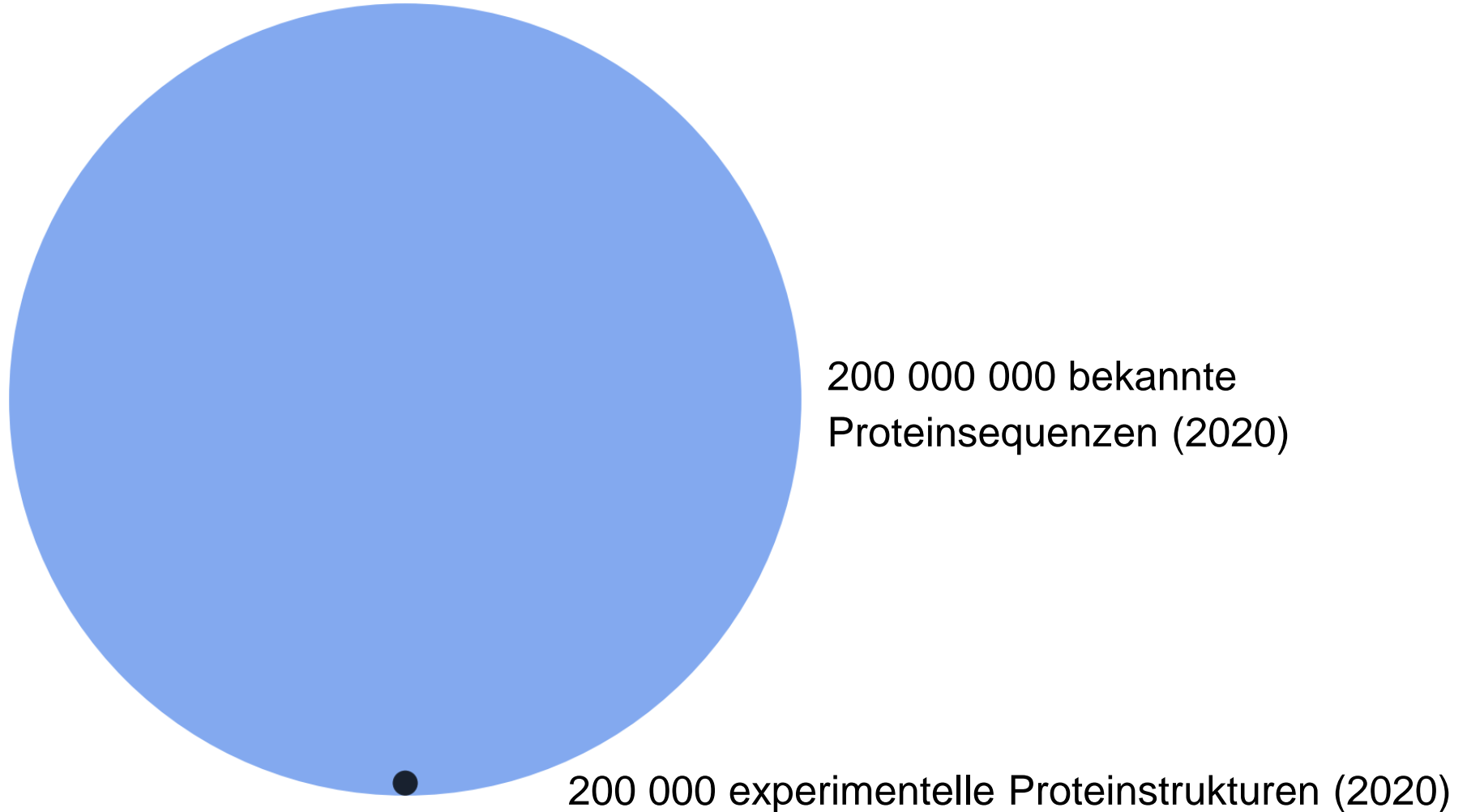


# Aufklären von Proteinstrukturen durch Röntgenkristallographie





## 70 Jahre Röntgenkristallographie



# AlphaFold



The image is a blue banner for the Nobel Prize in Chemistry 2024. At the top left is a gold Nobel medal. To its right, the text reads "NOBELPRISET I KEMI 2024" and "THE NOBEL PRIZE IN CHEMISTRY 2024". On the top right is the logo of the Royal Swedish Academy of Sciences, with the text "KUNGL. VETENSKAPS-AKADEMIEN" and "THE ROYAL SWEDISH ACADEMY OF SCIENCES". Below this, three portraits of the laureates are shown. Each portrait has a small vertical credit line to its left: "Photo: University of Washington" for David Baker, "Photo: The Royal Society" for Demis Hassabis, and "Photo: BBVA Foundation" for John M. Jumper. Below each portrait is the laureate's name and affiliation. At the bottom, the award reasons are listed in Swedish and English. The English text for Demis Hassabis is enclosed in a red rectangular box.

**David Baker**  
University of Washington  
USA

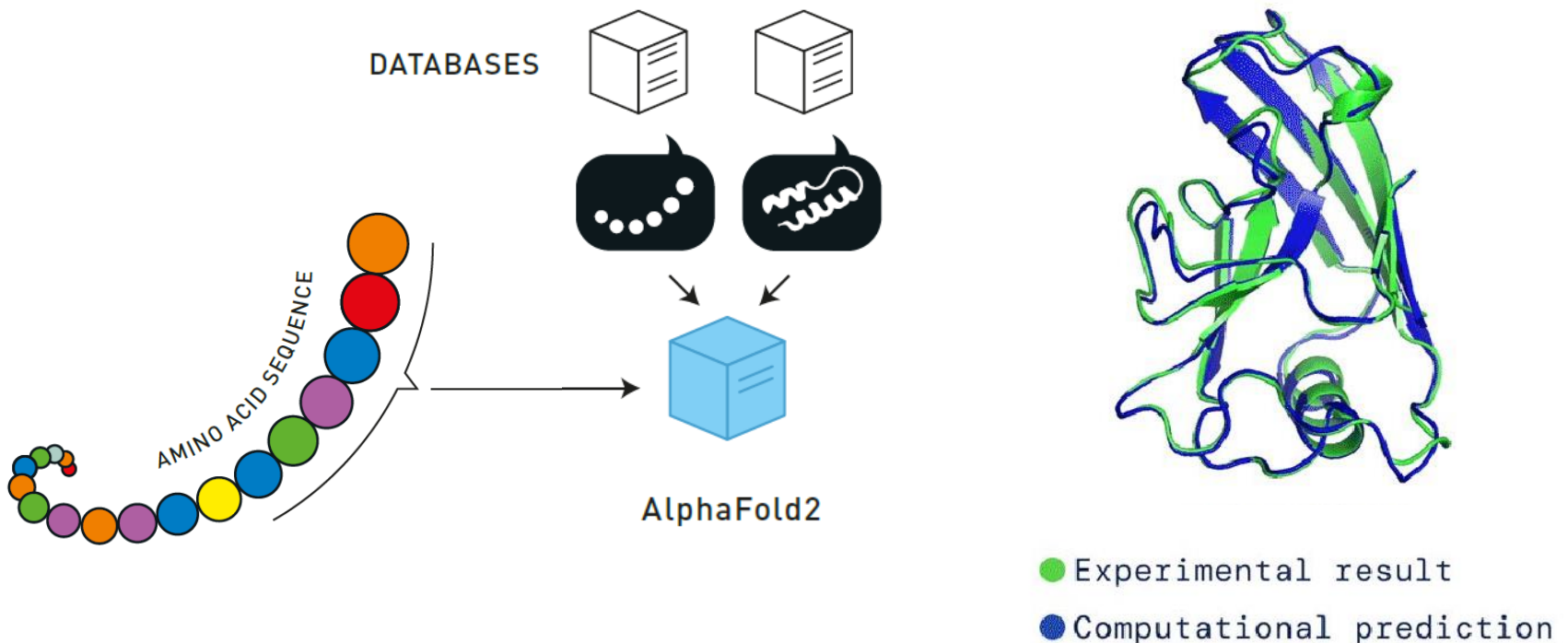
**Demis Hassabis**  
Google DeepMind  
United Kingdom

**John M. Jumper**  
Google DeepMind  
United Kingdom

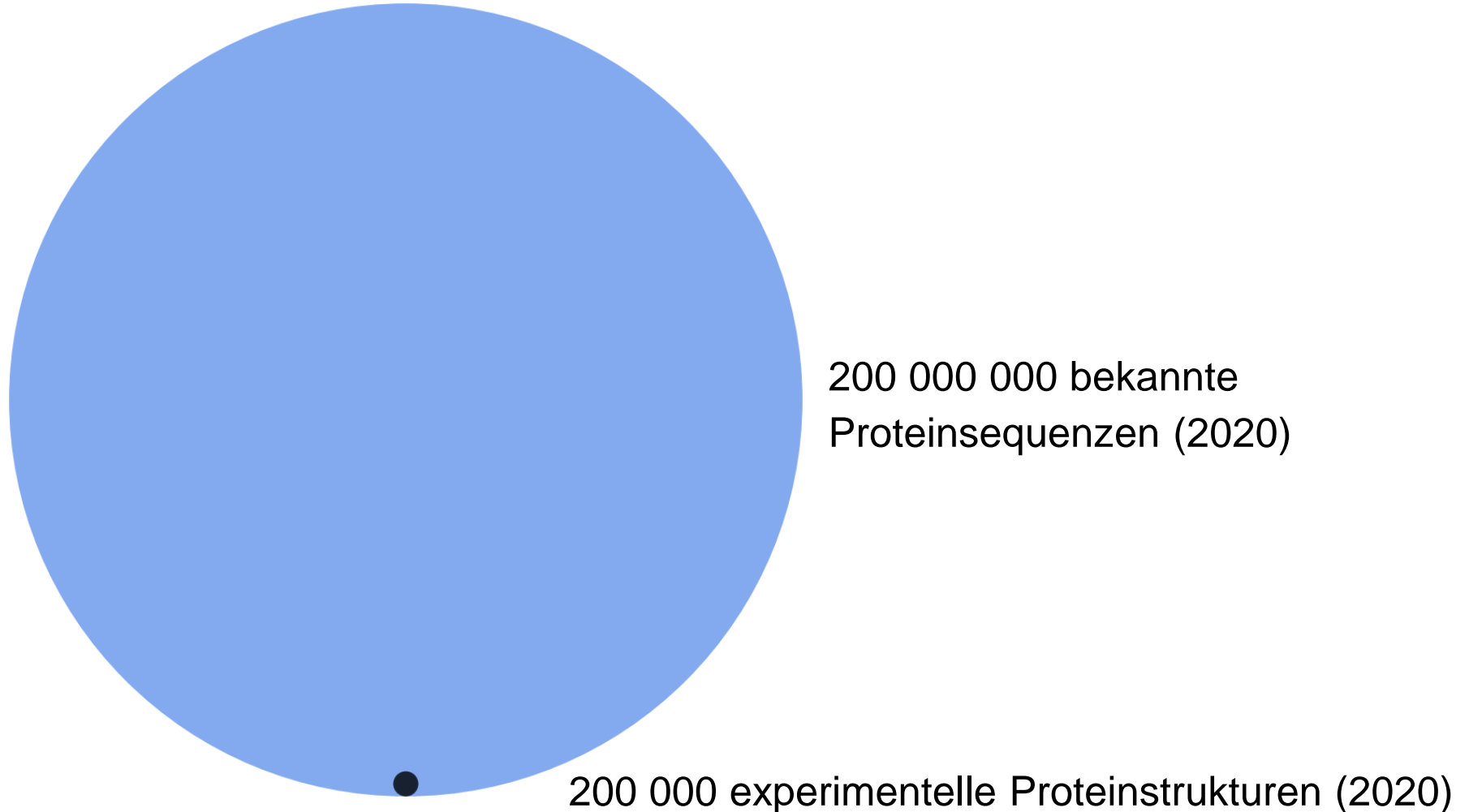
*"för datorbaserad proteindesign"*  
*"for computational protein design"*

*"för proteinstrukturprediktion"*  
*"for protein structure prediction"*

# Highly accurate protein structure prediction with AlphaFold

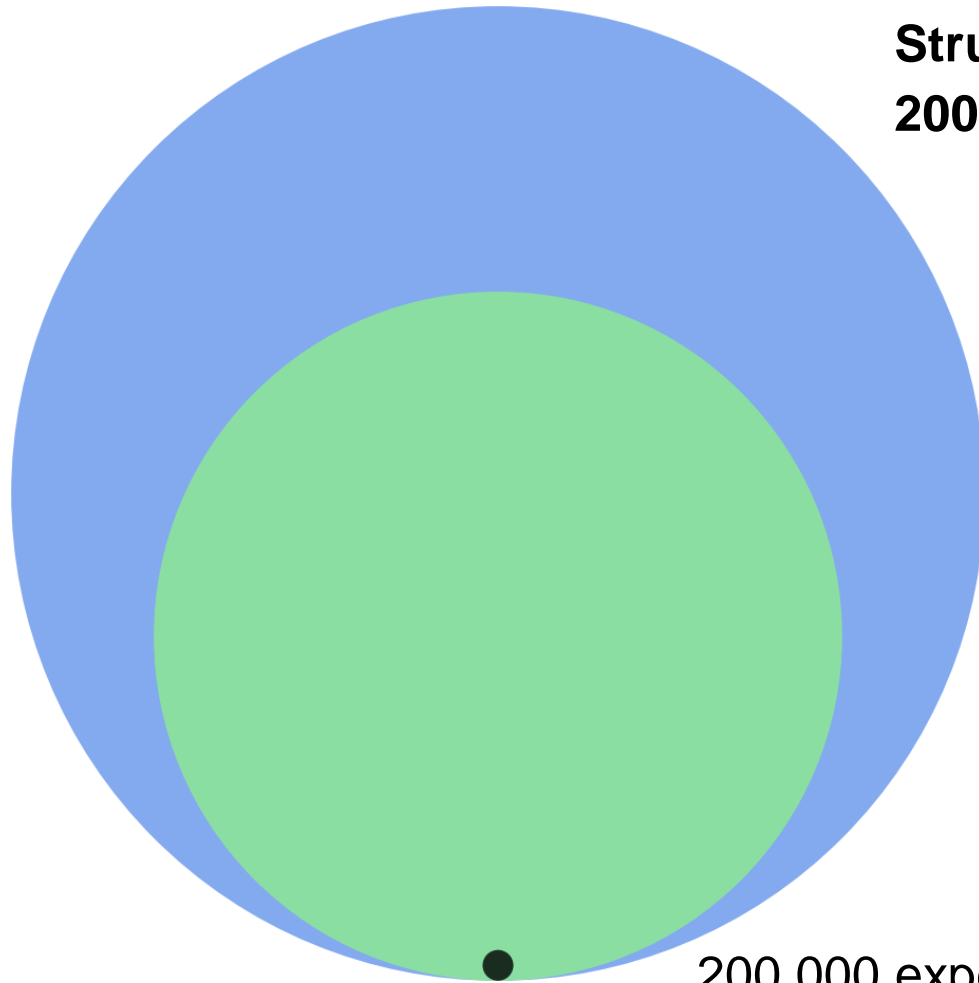


## Röntgenkristallographie (seit 1958)





## AlphaFold (2021)



**Strukturvorhersagen für alle  
200 000 000 bekannten Sequenzen**

**Ca. 50% mit ausreichender  
Qualität für meiste Engineering-  
Anwendungen**

200 000 experimentelle Kristallstrukturen (2020)

## De novo protein design



The image is a blue banner for the Nobel Prize in Chemistry 2024. At the top left is a gold Nobel medal. To its right, the text reads "NOBELPRISET I KEMI 2024" and "THE NOBEL PRIZE IN CHEMISTRY 2024". At the top right is the logo of the Royal Swedish Academy of Sciences, with the text "KUNGL. VETENSKAPS- AKADEMIEN" and "THE ROYAL SWEDISH ACADEMY OF SCIENCES". Below this, three portraits of the laureates are shown. Each portrait has a small vertical photo credit on its left side. Below each portrait is the laureate's name and affiliation. At the bottom, the award reasons are listed in italics. The first reason, "for computational protein design", is enclosed in a red rectangular box.

**NOBELPRISET I KEMI 2024**  
**THE NOBEL PRIZE IN CHEMISTRY 2024**

**KUNGL. VETENSKAPS- AKADEMIEN**  
THE ROYAL SWEDISH ACADEMY OF SCIENCES

Photo: University of Washington  
**David Baker**  
University of Washington  
USA

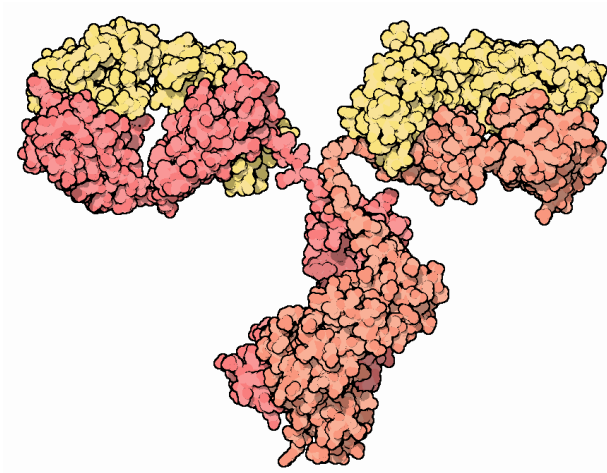
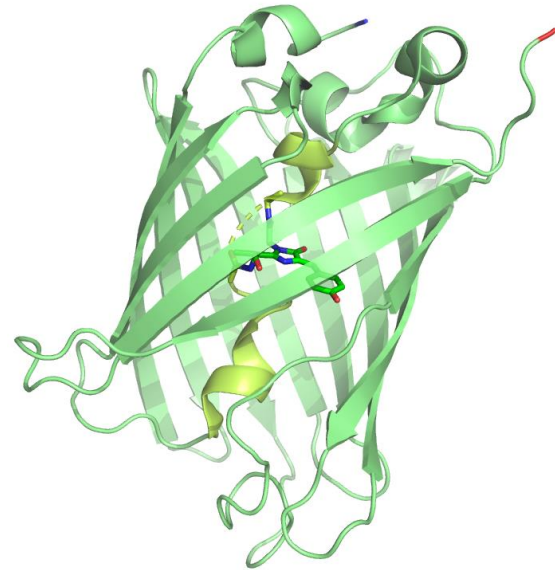
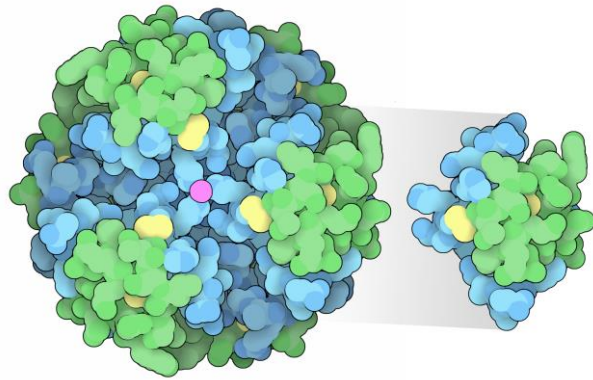
Photo: The Royal Society  
**Demis Hassabis**  
Google DeepMind  
United Kingdom

Photo: BBVA Foundation  
**John M. Jumper**  
Google DeepMind  
United Kingdom

*"för datorbaserad proteindesign"*  
**"for computational protein design"**

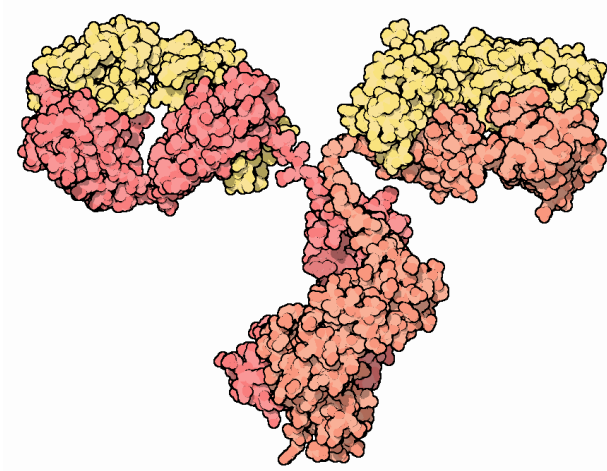
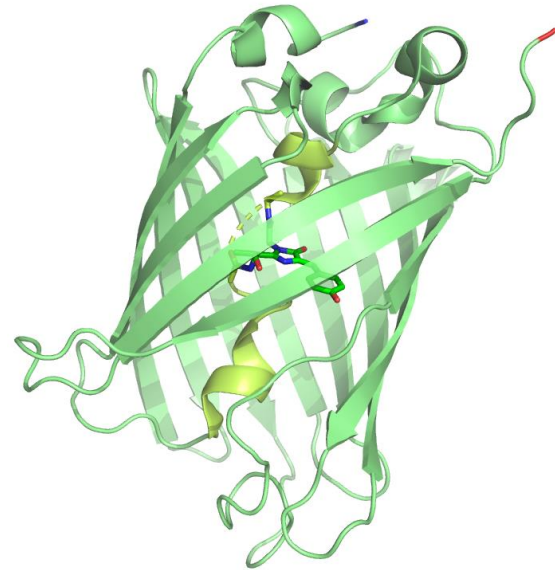
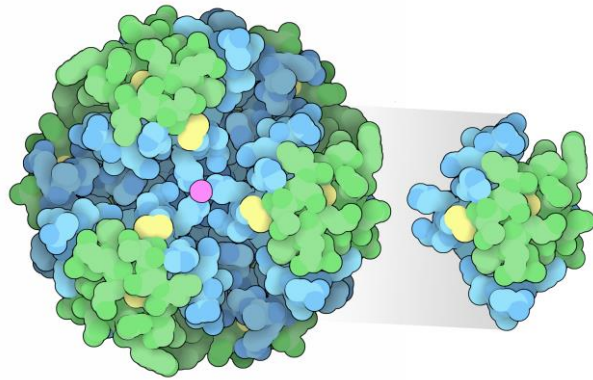
*"för proteinstrukturprediktion"*  
*"for protein structure prediction"*

## Protein Engineering basiert idR auf Strukturinformationen



Bilder (li.): David Goodsell/PDB-101

## Klassisches Protein Engineering basiert auf Strukturinformationen



Bilder (li.): David Goodsell/PDB-101



## De novo protein design



**David Baker**  
University of Washington  
USA

*"för datorbaserad proteindesign"*

*"for computational protein design"*

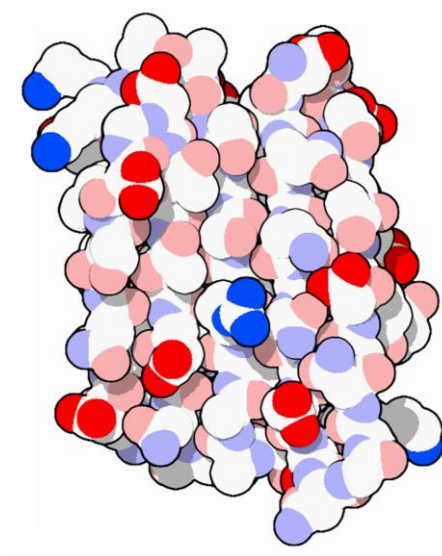
"If you want to build an airplane, you don't start by modifying a bird; instead, you first understand the principles of aerodynamics and build flying machines from those principles."

## *De novo* protein design: neue Faltungen und Reaktionen

Top7: an artificial protein fold not known to nature



Kuhlman et al. 2003, Science

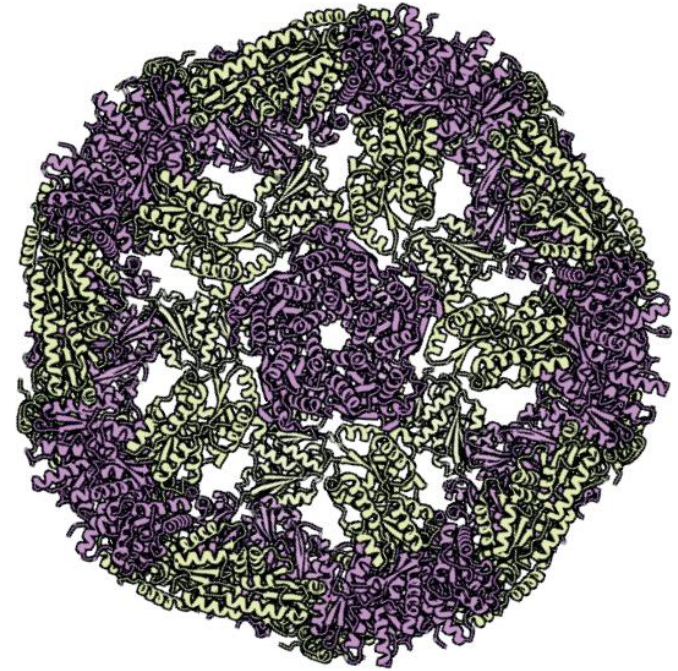
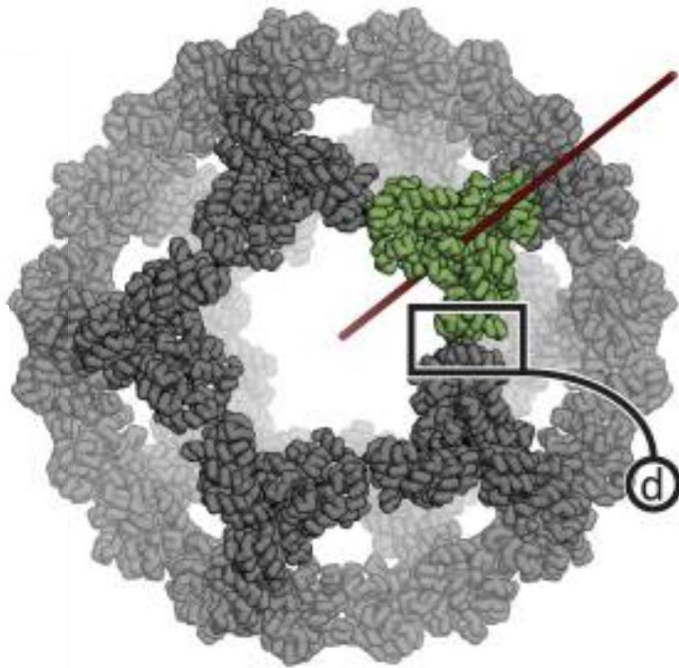


First de novo designed enzyme to catalyze a reaction new to nature



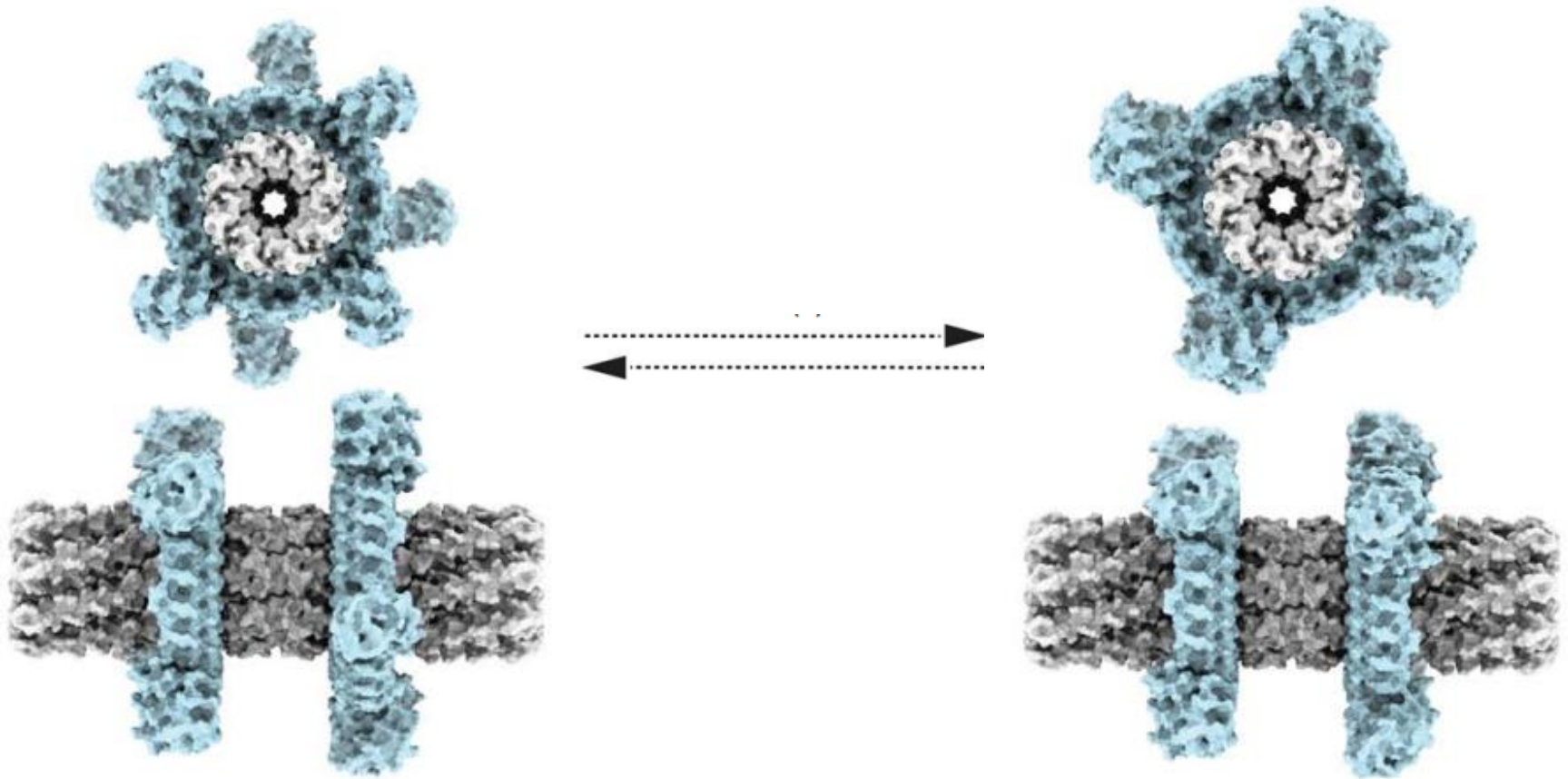
Röthlisberger et al. 2008, Nature

## *De novo* protein design: Nanomaterialien



Bilder: Hsia et al., 2016, Nature (li.); T. Kovalova/Royal Swedish Academy of Sciences (re.)

## *De novo* protein design: Achse/Rotor



Courbet et al. 2022, Science

## Methodischer Fortschritt

### Bis ca. 2010:

- Rationales Engineering und gerichtete Evolution
- limitierte Verfügbarkeit von Strukturen und Sequenzen

### Seit ca. 2010:

- De novo design wird langsam nützlich
- DNA-/Proteinsequenzen immer leichter zugänglich  
( $10^6$ -mal mehr Sequenzen als noch 2010)

### Seit ca. 2020:

- $10^3$ -mal mehr Proteinstrukturen (AlphaFold)
- De novo design wird robust

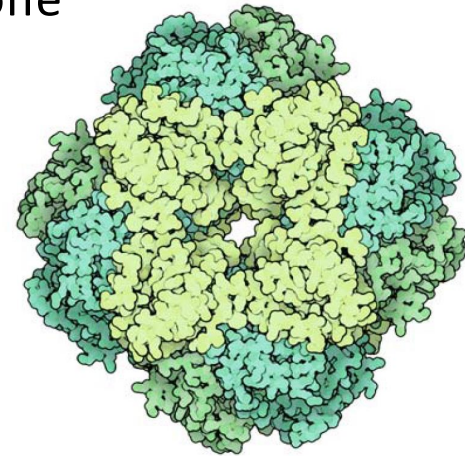
→ Feld erfährt aktuell massiven Schub

**Fast alle marktreifen Anwendungen noch aus Ära von vor 2010!**



## Protein Engineering im Krisenzeitalter

- Umweltschutz (z.B. Kunststoff- und Ölteppich-essende Proteine)
- Zirkuläre Biökonomie
  - Recycling durch abbauende Enzyme
  - Erneuerbare Kunst- und Werkstoffe
- Klimaschutz
  - Grüner Wasserstoff, Biodiesel
  - Green Chemistries
  - Carbon Capture
- Abfedern von Klimafolgen (Crop science)
- (Medikamente, personalisierte Medizin, Materialwissenschaften...)

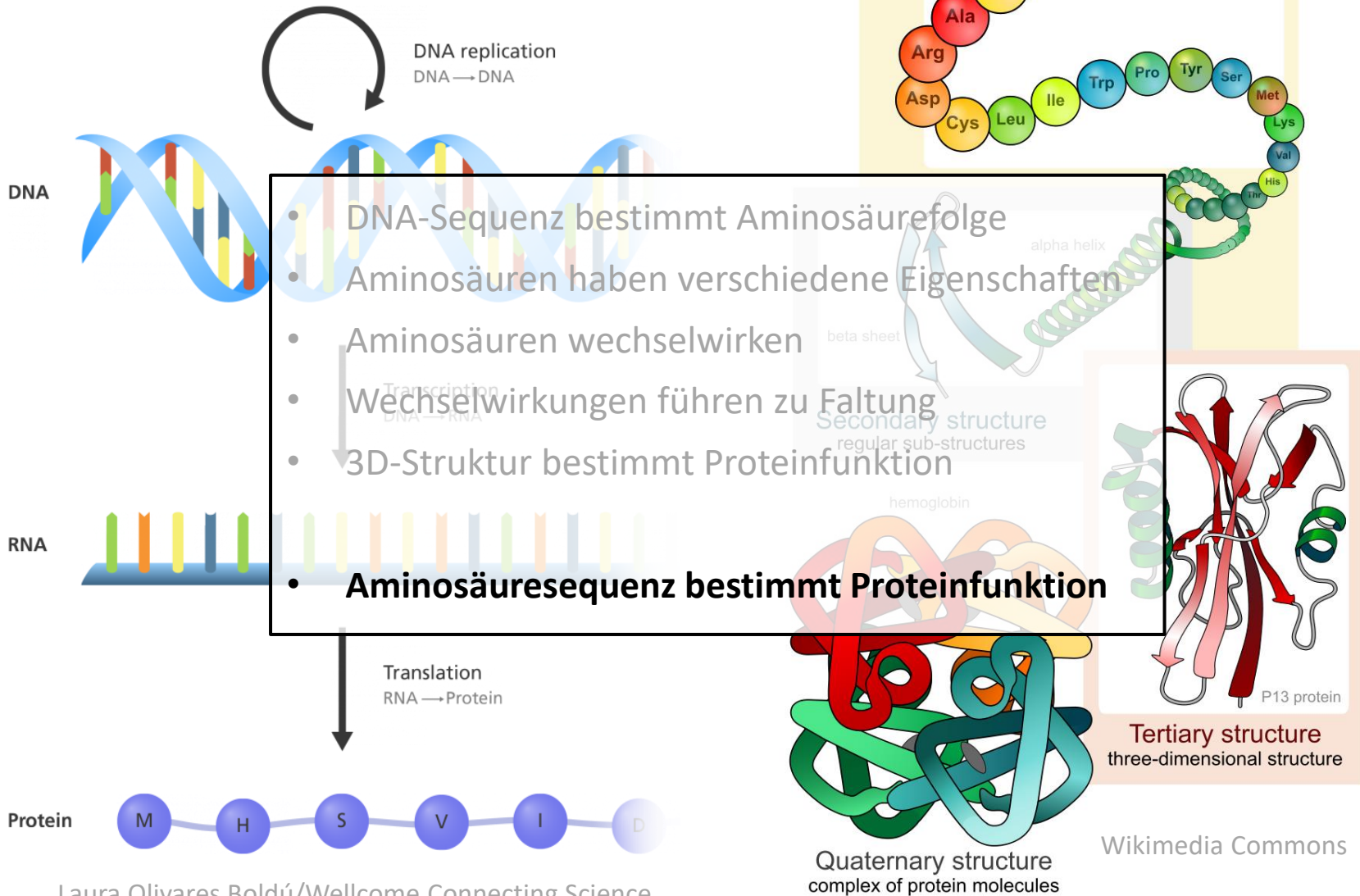


David Goodsell/PDB-101

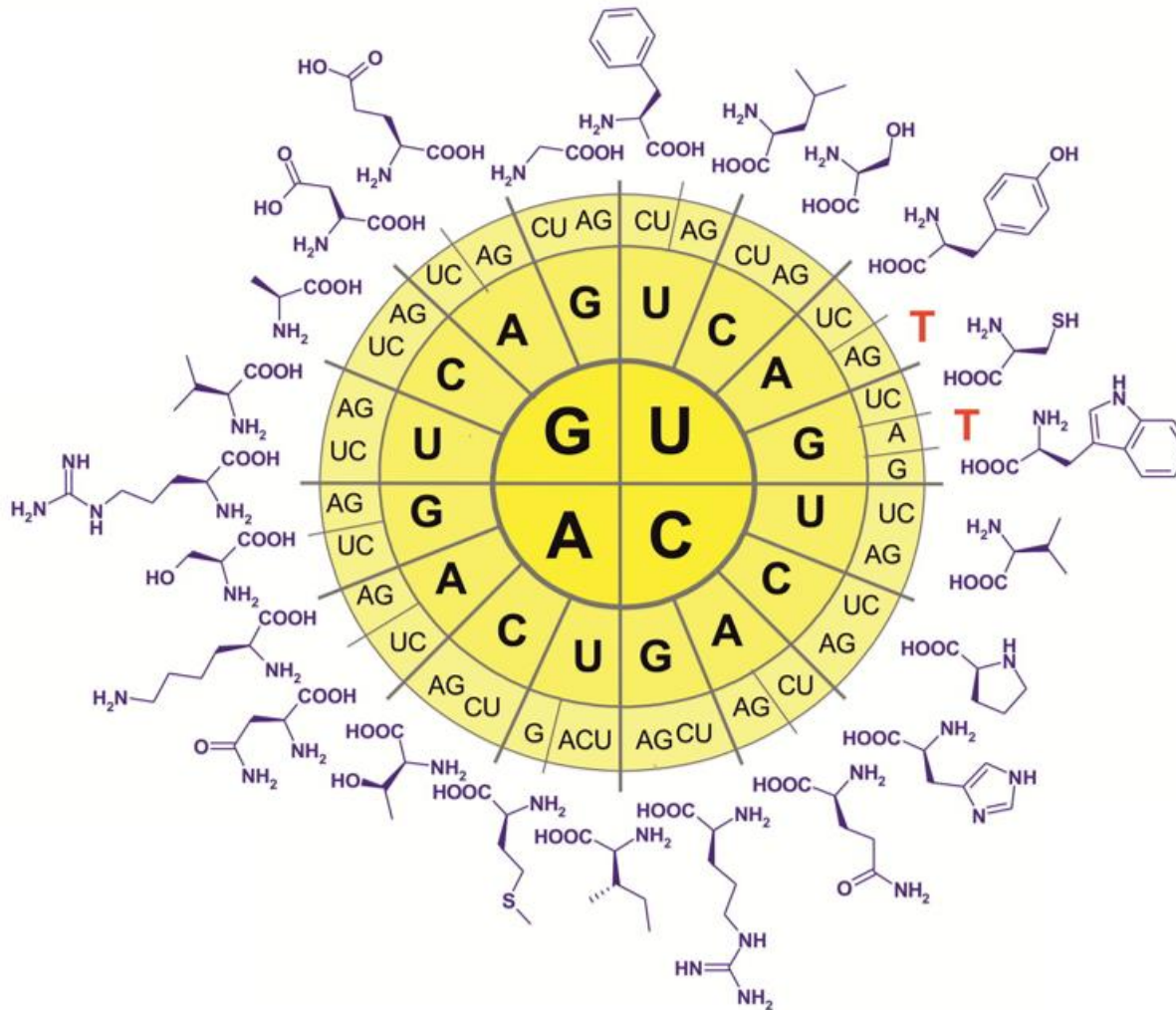
1. Die molekularen Maschinen des Lebens
2. Biotechnologie: Proteine als Stars in Medizin, Chemie & Co.
3. Aktuelle Proteinforschung und ihr Zukunftspotenzial

## Anhang: Genetic Code Reprogramming

# Genetic code reprogramming

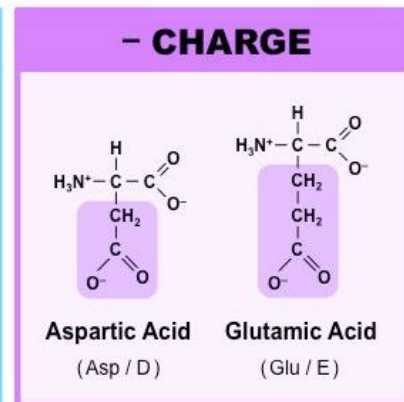
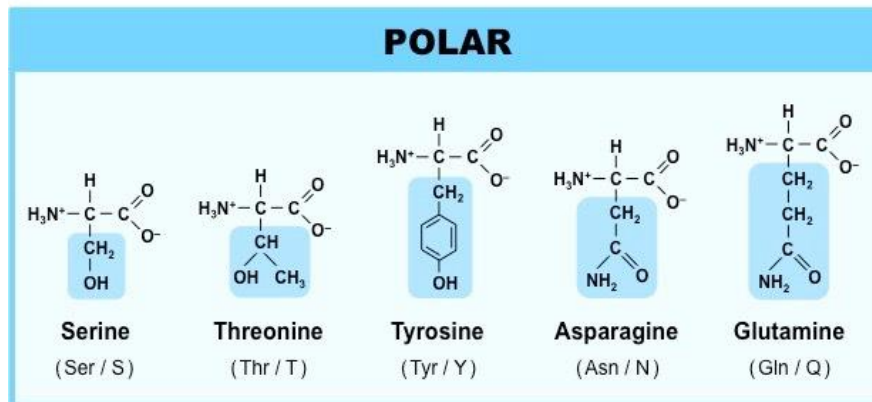
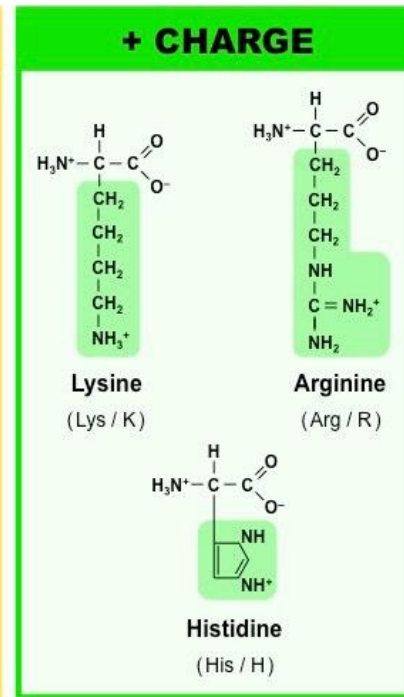
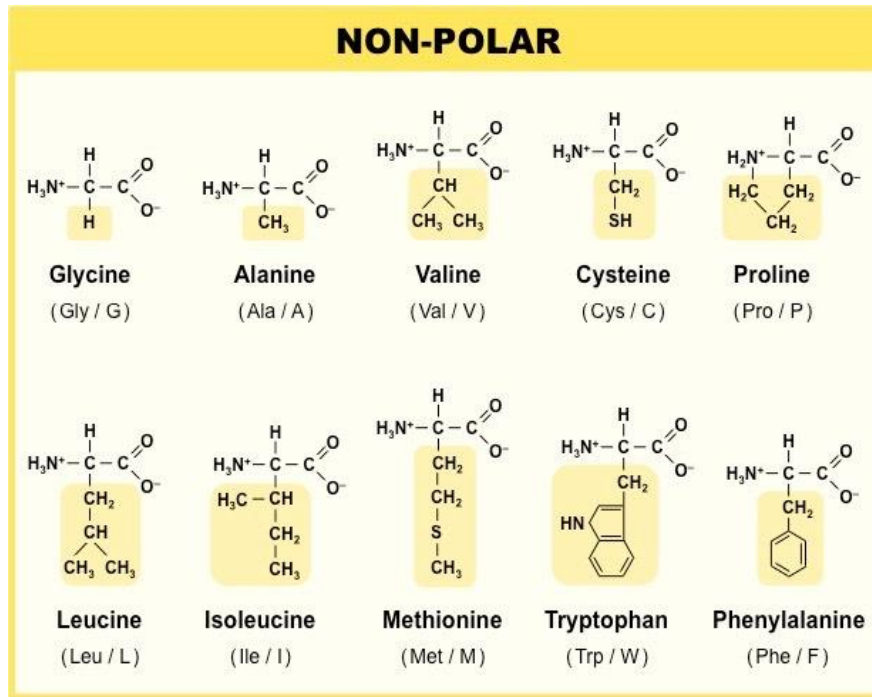


# Genetic code reprogramming





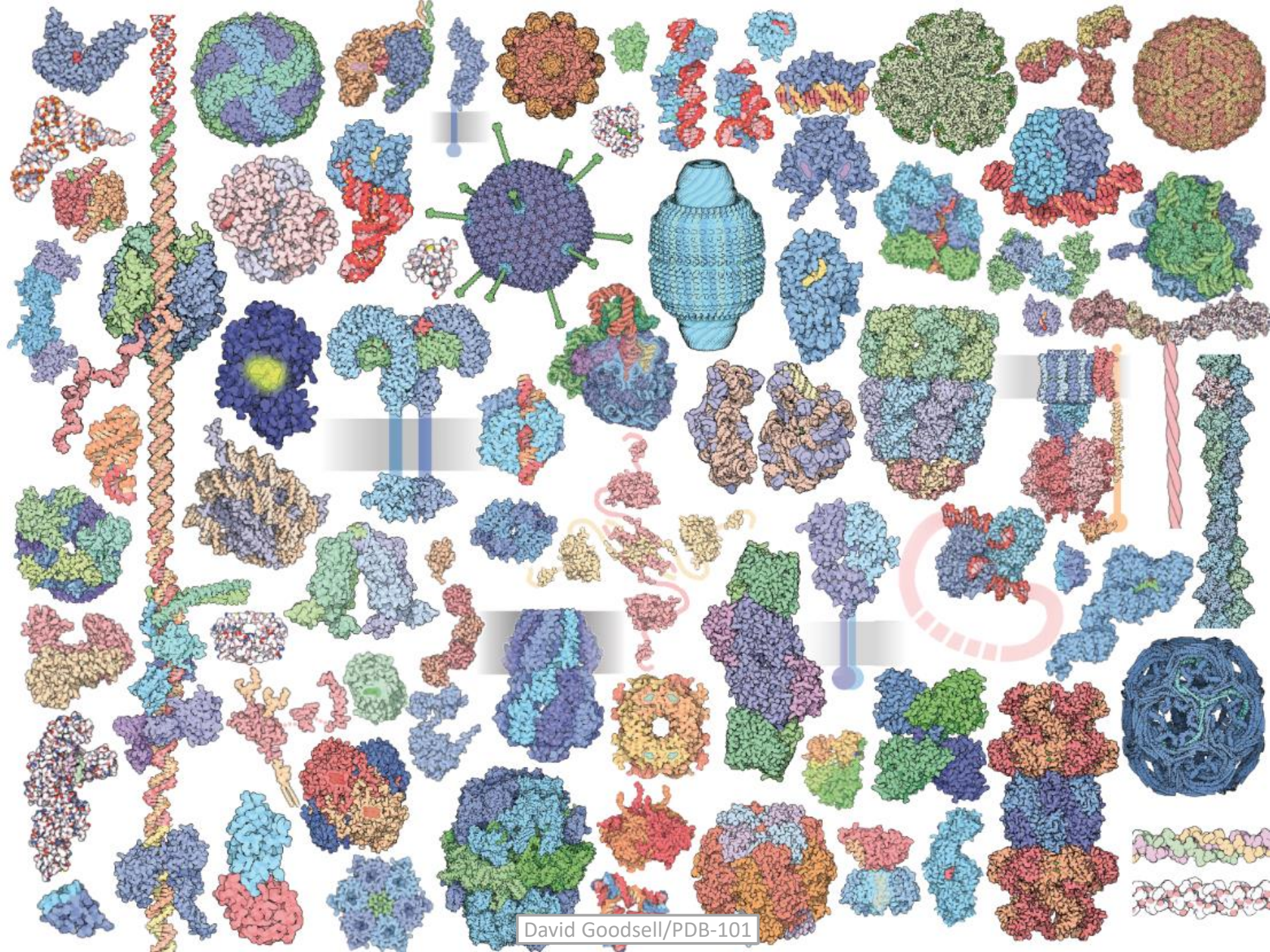
# Genetic code reprogramming



## Eigenschaften:

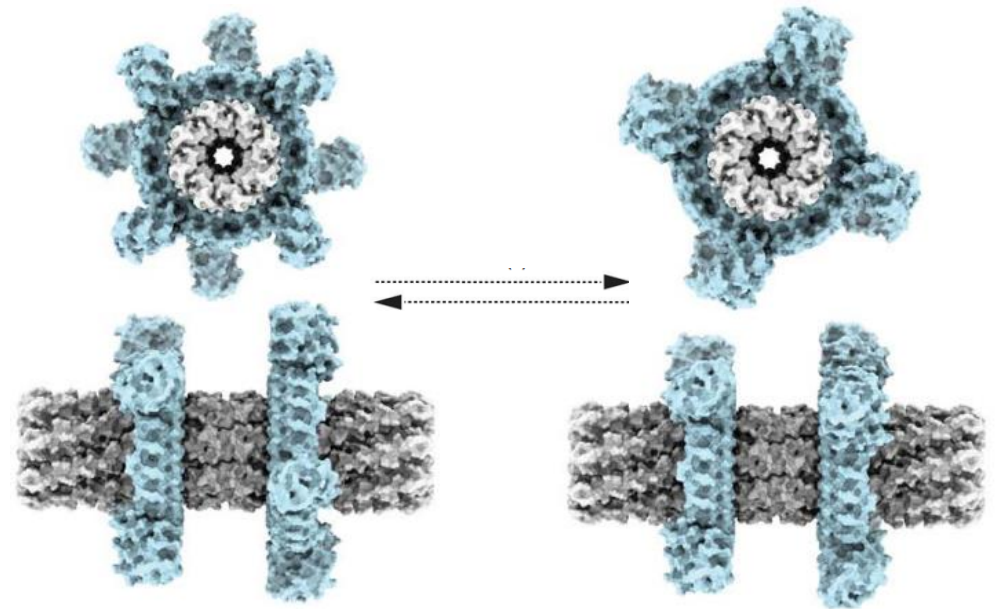
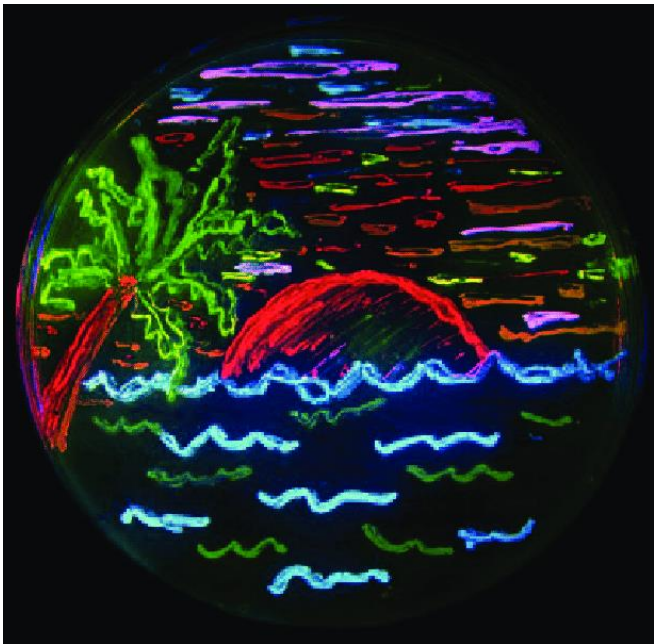
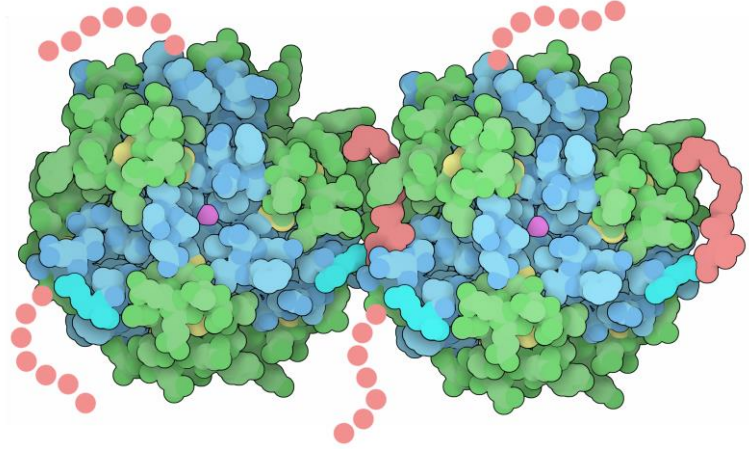
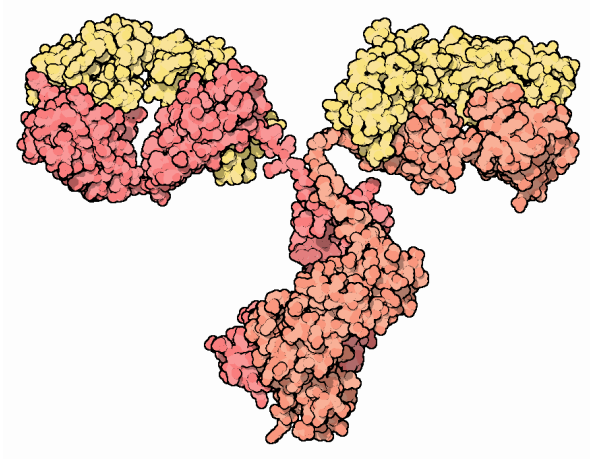
- Groß vs. klein
- Rigide vs. flexibel
- Hydrophil vs. hydrophob
- Neutral vs. sauer vs. basisch
- Chemisch inert vs. reaktiv



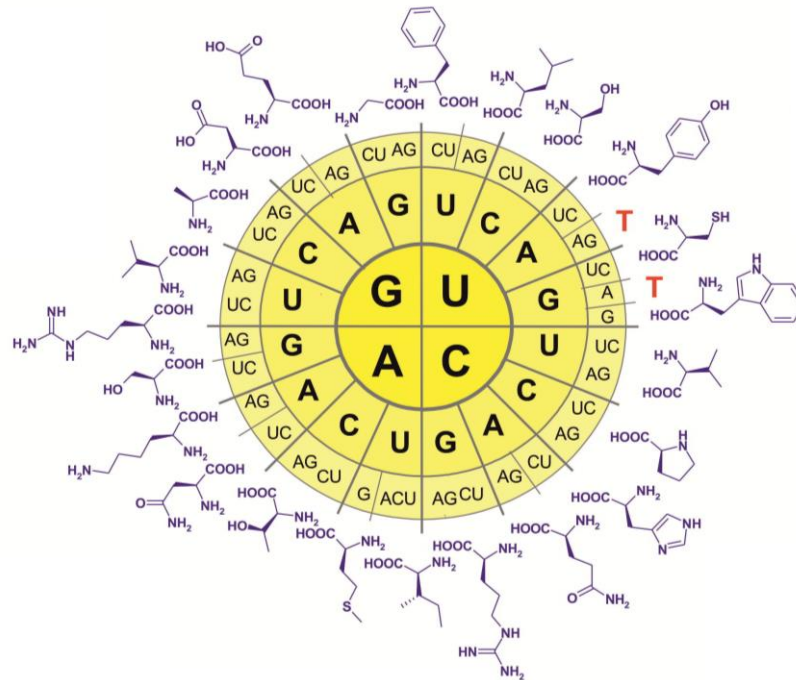




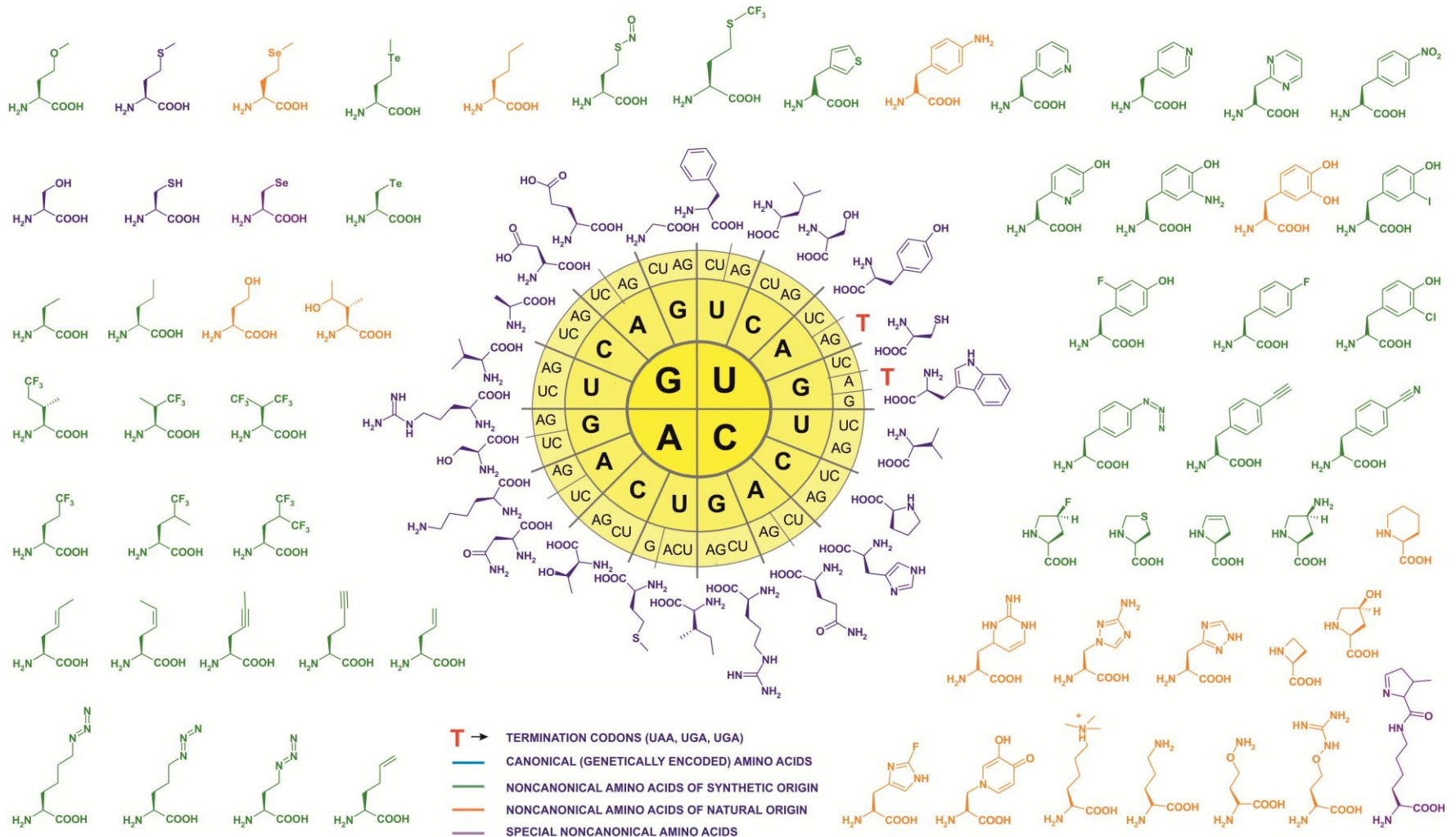
# Proteine: Molekulare Wundermaschinen, Biotechnologie und Zukunftsmusik



# Reprogrammieren des genetischen Codes



# Reprogrammieren des genetischen Codes





## Take-home messages

- Proteine sind molekulare Maschinen mit vielfältigsten Funktionen
- Grundlage des Lebens (sämtliche Organismen)
- Biotechnologie modifiziert Proteineigenschaften und -funktionen:  
(rationales engineering, gerichtete Evolution, *de novo* design)
- Proteine dominieren Medizin bereits; in Chemie immer wichtiger
- Proteinforschung entwickelt sich aktuell rasant
- Immenses Potenzial für zahlreiche Anwendungen; u.A.:
  - Umwelt- und Klimaschutz, Bioökonomie
  - Abfedern von Klimafolgen
  - Medizin, Materialwissenschaften, ...

**Vielen Dank für Ihre Aufmerksamkeit!**

