

PROTEINS AND DRUG DESIGN

Bojos per la Supercomputació

13 Abril 2024

Isaac Filella Mercè
Júlia Vilalta Mor

isaac.filella1@bsc.es, julia.vilalta@bsc.es

Dr Isaac Filella Merce

- BSc: Mathematics and Physics (UB)
- MSc: Bioinformatics (UPF)
- PhD: Bioinformatics (Sorbonne Université & Institut Pasteur)
- PostDoc: Drug Design + AI (BSC)



ifiell1@bsc.es



<https://www.linkedin.com/in/isaacfilella/>

Júlia Vilalta Mor

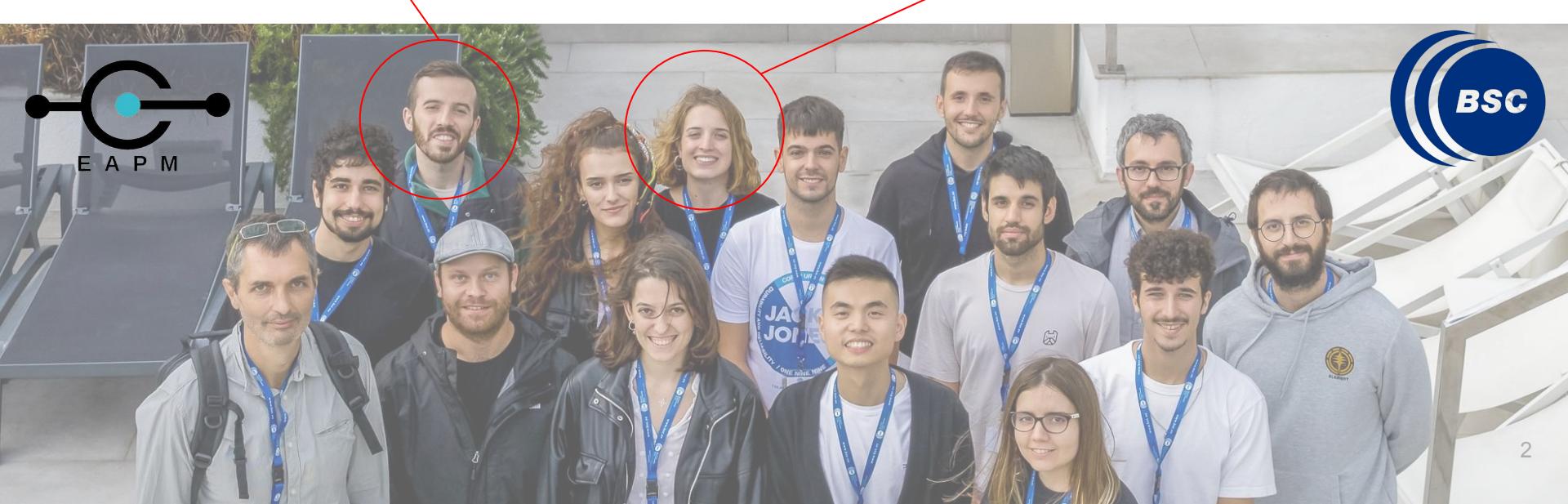
- BSc: Biotechnology (URV)
- MSc: Bioinformatics (UPF)
- PhD (now): EAPM (BSC)



jvilalta@bsc.es



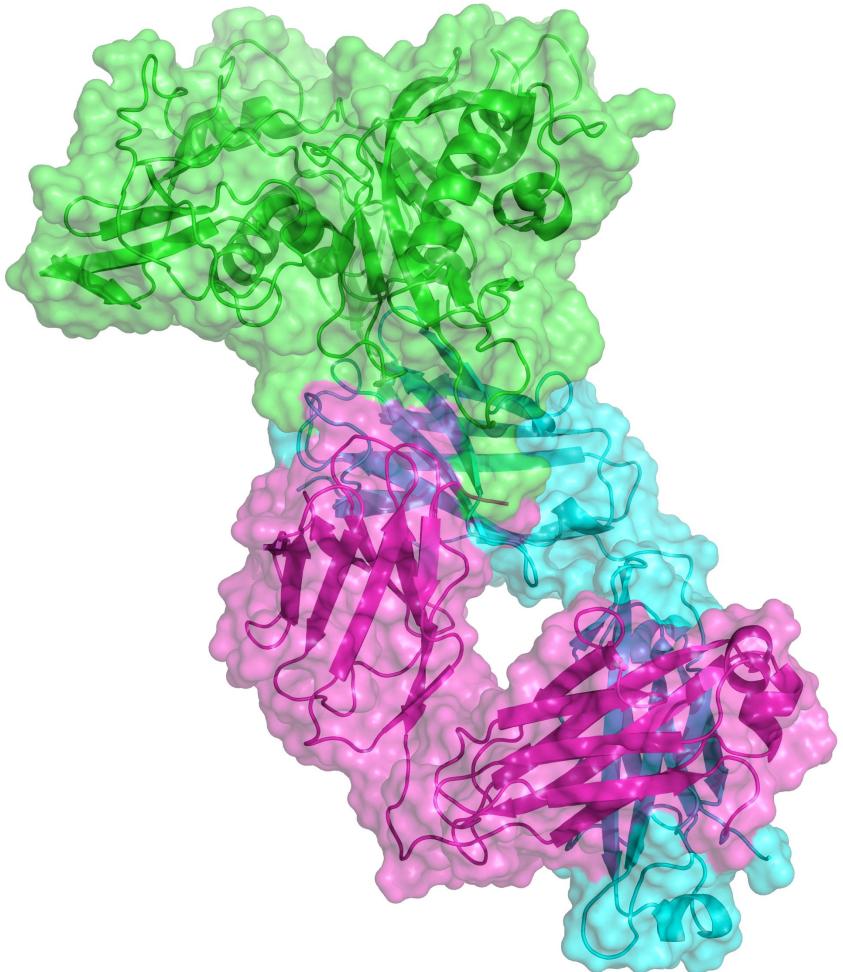
www.linkedin.com/in/julia-vilalta-mor



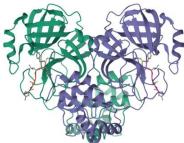
HORA	ACTIVITAT
9:30	Presentació
9:45	PART TEÒRICA: Les Proteïnes
10:45	QUIZ: Proteïnes
11:15	20 min break (esmorzar)
11:35	PART TEÒRICA: Drug Design
12:35	QUIZ: Drug Design
12:45	10 min break
13:00	PART PRÀCTICA I: Test MRTX1133 ligand docking

OUTLINE

1. Proteins
2. Enzymes
3. Enzyme engineering
4. Drug design

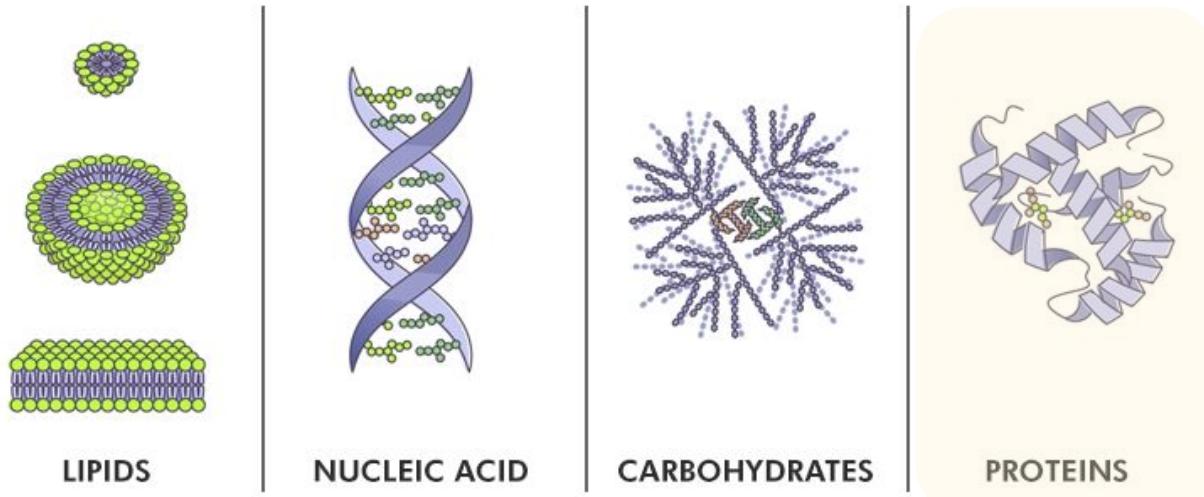


PROTEINS

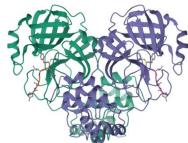


PROTEINS | What are proteins?

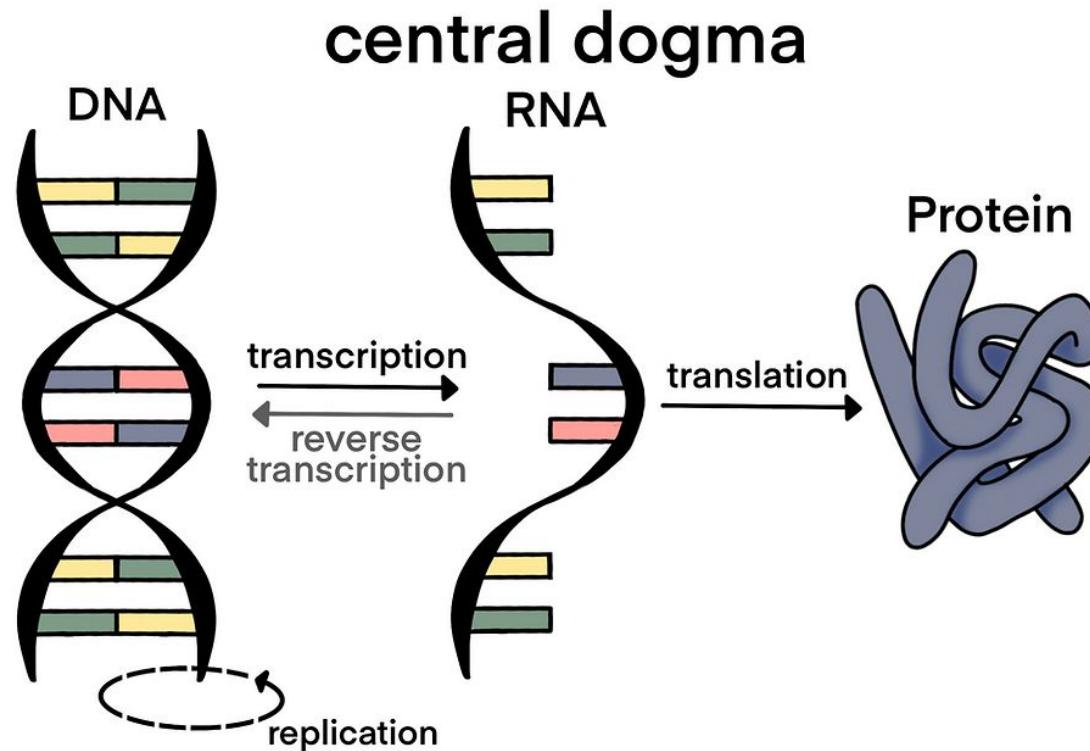
Biomolecules are all biological materials exclusive of cells. Biomolecules include proteins, lipids, etc. and can serve various functions like providing structural integrity to the tissue-engineered constructs.

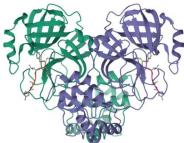


Proteins are large biomolecules present in all living organisms made up of chemical 'building blocks' called amino acids. They are important to the structure, function, and regulation of the body.



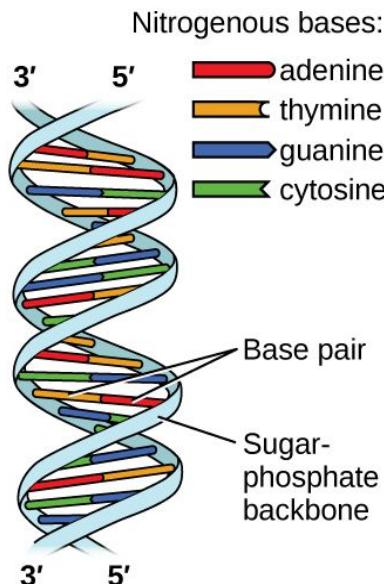
PROTEINS | How are they made?



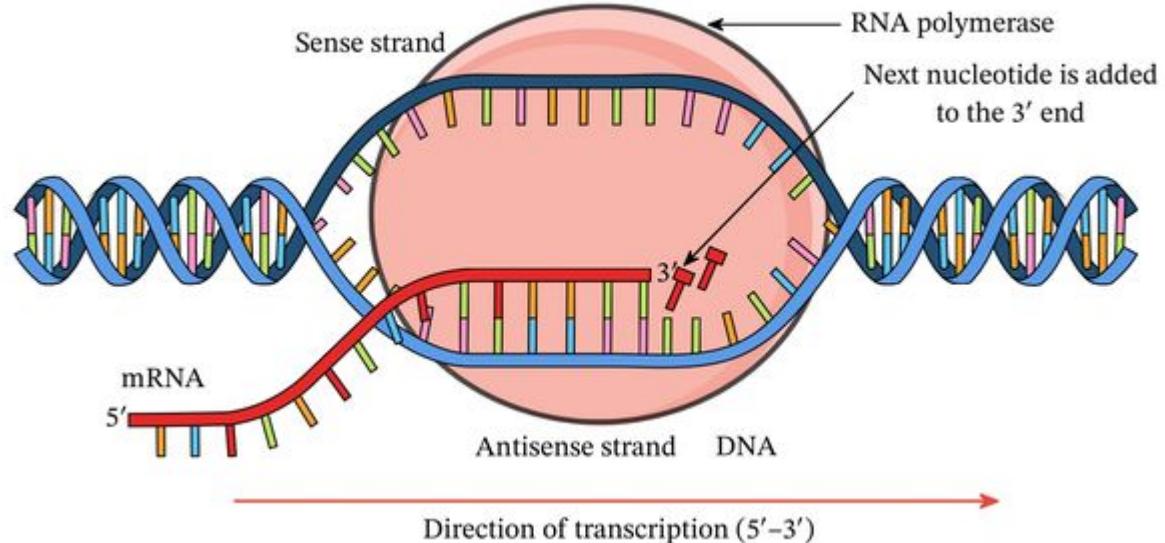


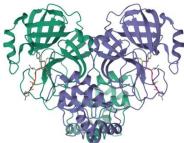
PROTEINS | How are they made?

TRANSCRIPTION: From DNA to RNA



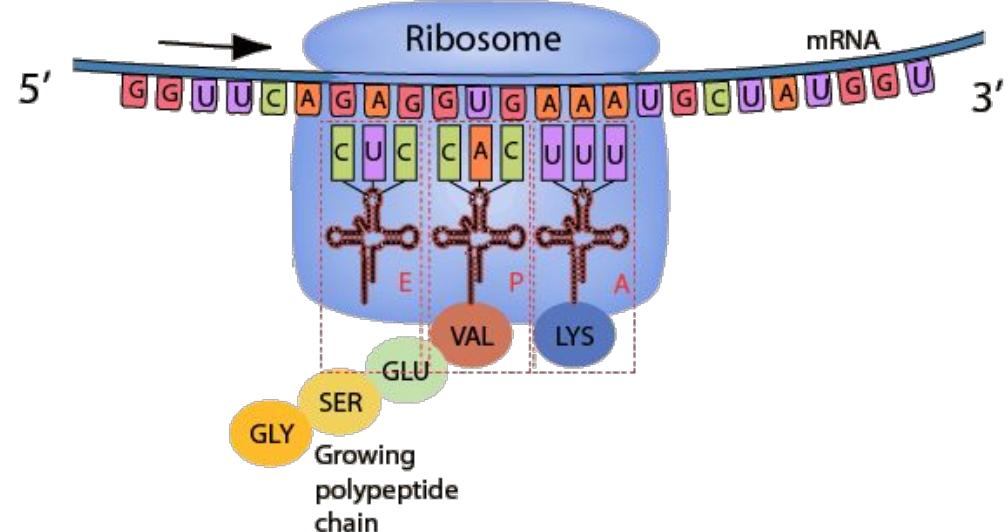
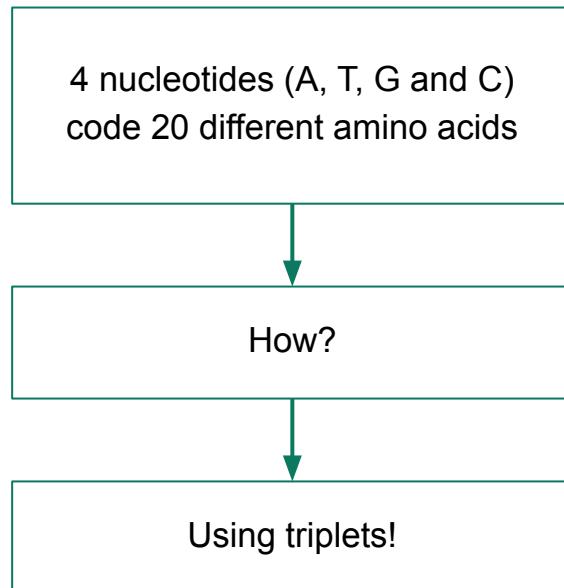
DNA
The Recipe Book of Life

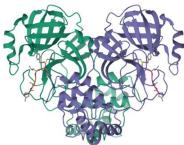




PROTEINS | How are they made?

TRANSLATION: From RNA to PROTEINS!

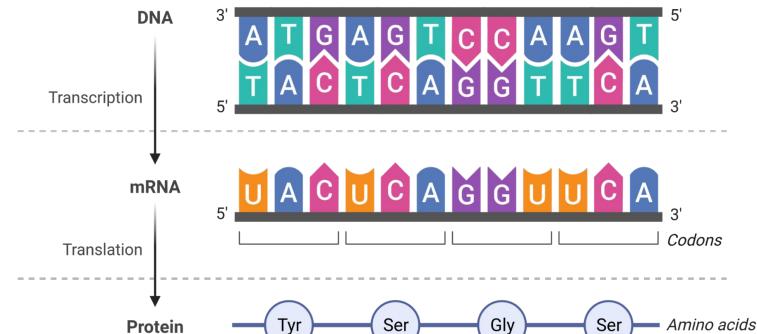


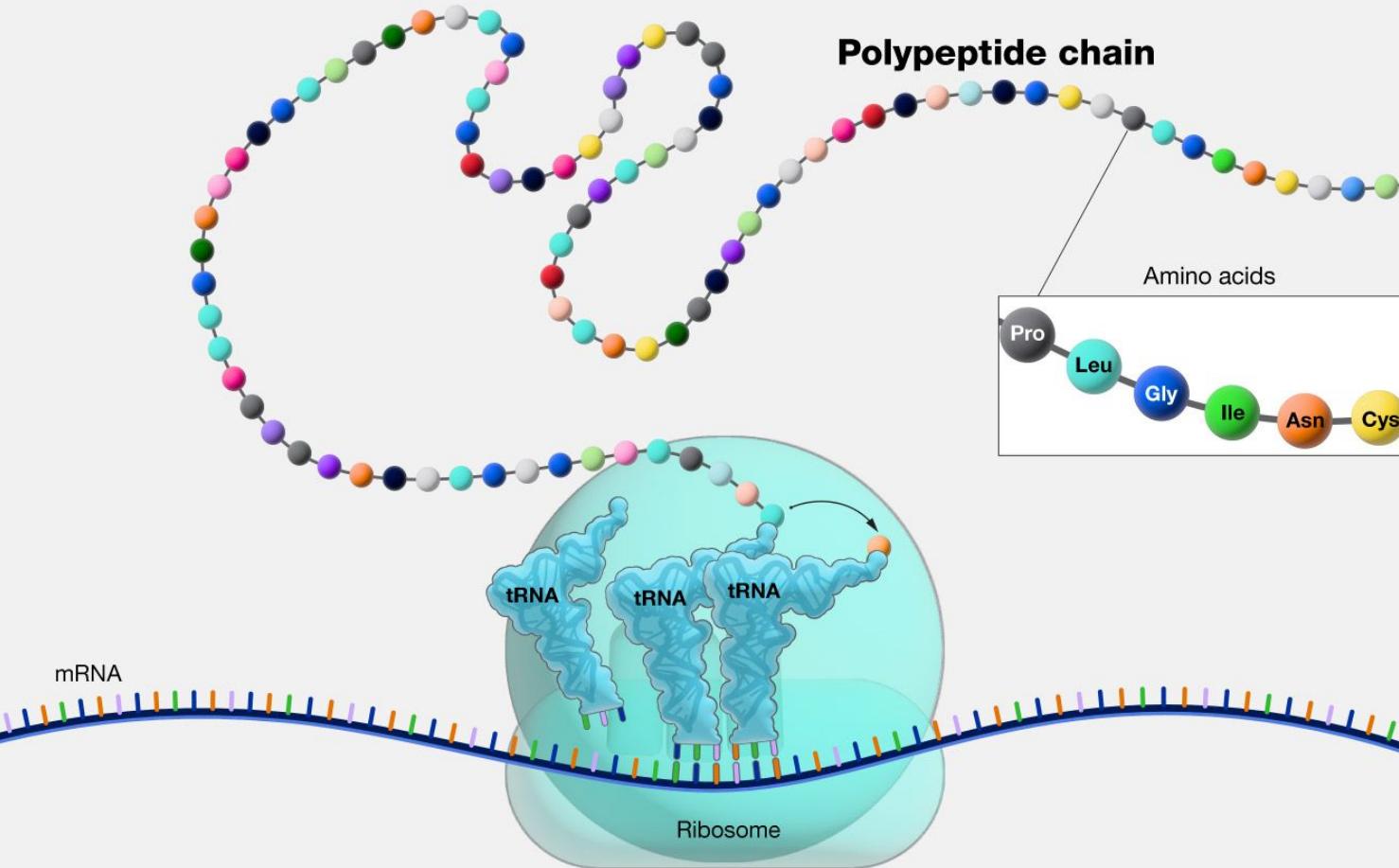


PROTEINS | How are they made?

From triplets of nucleotides to amino acids

Second base in codon				Last base in codon	
U	C	A	G		
U	UUU Phe UUC UUA Leu UUG	UCU UCC Ser UCA UCG	UAU Tyr UAC UAA STOP UAG	UGU Cys UGC UGA STOP UGG Trp	U C A G
C	CUU CUC Leu CUA CUG	CCU CCC Pro CCA CCG	CAU His CAC CAA Gln CAG	CGU CGC Arg CGA CGG	U C A G
A	AUU AUC Ile AUA AUG Met (start)	ACU ACC Thr ACA ACG	AAU Asn AAC AAA Lys AAG	AGU Ser AGC AGA Arg AGG	U C A G
G	GUU GUC Val GUA GUG	GCU GCC Ala GCA GCG	GAU Asp GAC GAA Glu GAG	GGU GGC Gly GGA GGG	U C A G

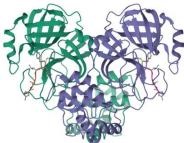




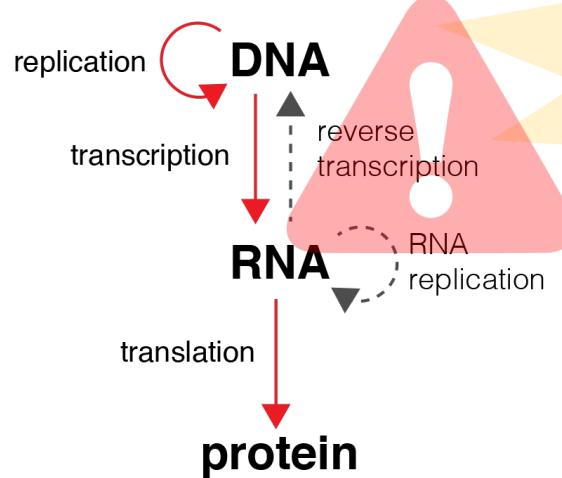
Polypeptide chain

Amino acids

Ala	Alanine
Arg	Arginine
Asn	Asparagine
Asp	Aspartic acid
Cys	Cysteine
Gln	Glutamine
Glu	Glutamic acid
Gly	Glycine
His	Histidine
Ile	Isoleucine
Leu	Leucine
Lys	Lysine
Met	Methionine
Phe	Phenylalanine
Pro	Proline
Ser	Serine
Thr	Threonine
Trp	Tryptophan
Tyr	Tyrosine
Val	Valine

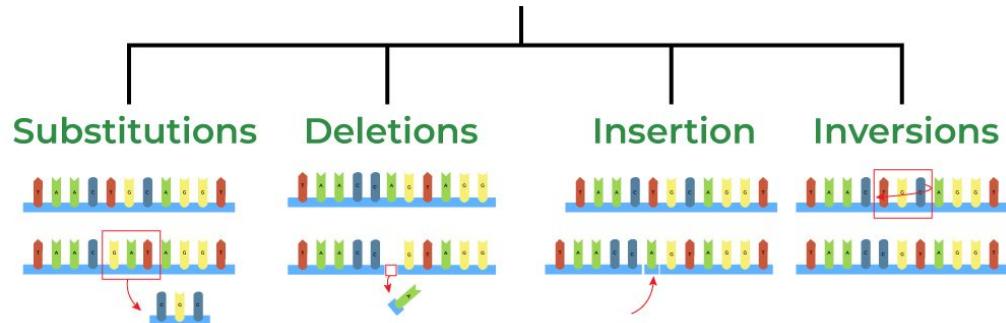


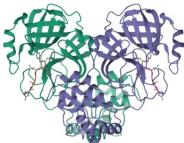
PROTEINS | What happens if there is an error during this process?



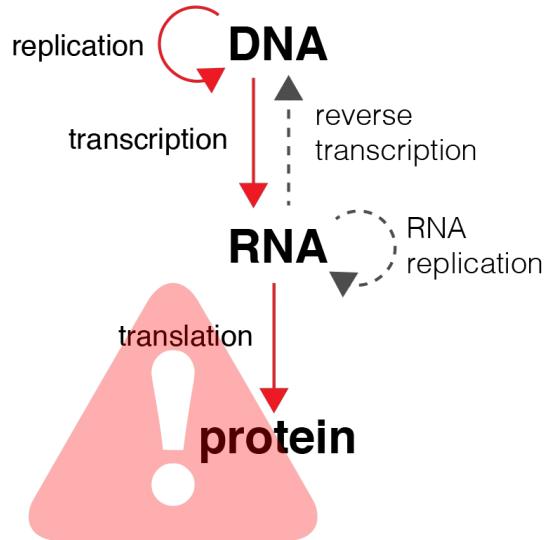
MUTATIONS!

Types of Mutations (At the DNA level)

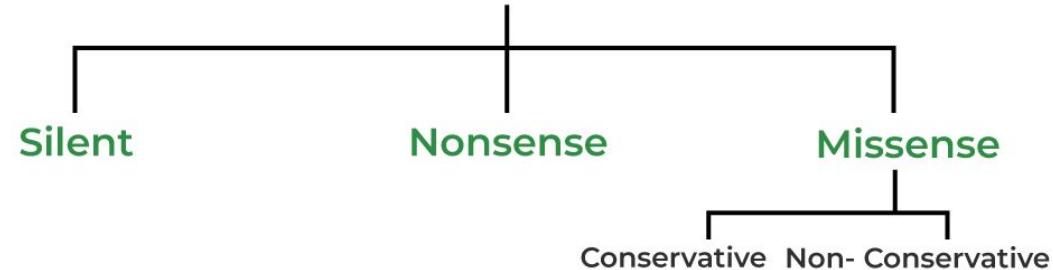




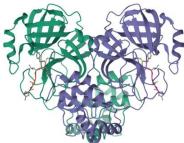
PROTEINS | What happens if there is an error during this process?



Types of Mutations (At the Protein level)



	No Mutation	Silent	Nonsense	Conservative	Non-Conservative
DNA Level					
mRNA Level					
Protein Level					
	Lys	Lys	STOP	Arg	Thr



PROTEINS | Why are MUTATIONS so important?



EVOLUTION: Mutations are necessary to warranty survival

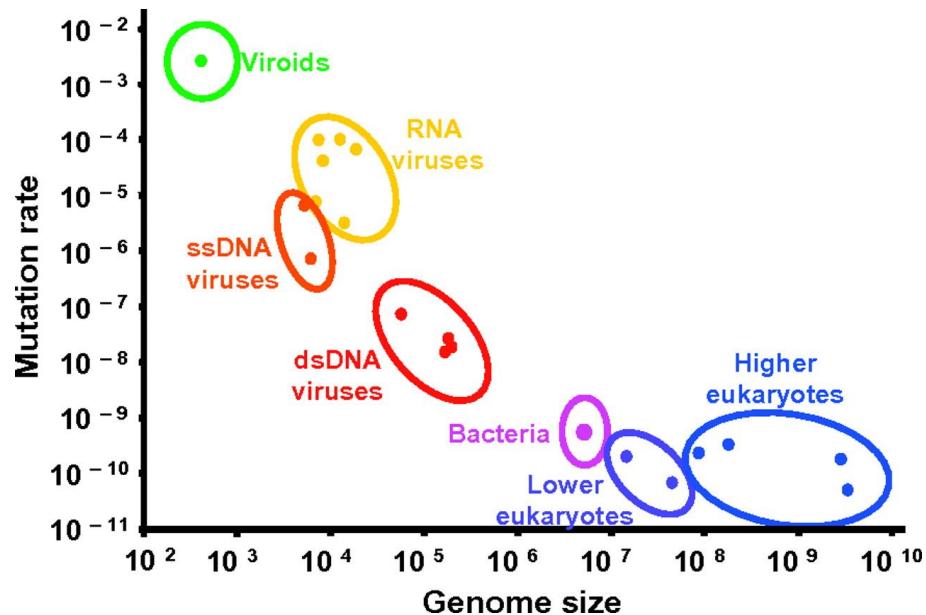
Having a high mutation rate

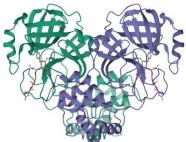


Better adaptation to environment changes



Difficult to be killed!





PROTEINS | Why are MUTATIONS so important?



Can originate DISEASES

Cancer

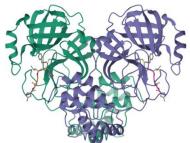
Cystic fibrosis

Death

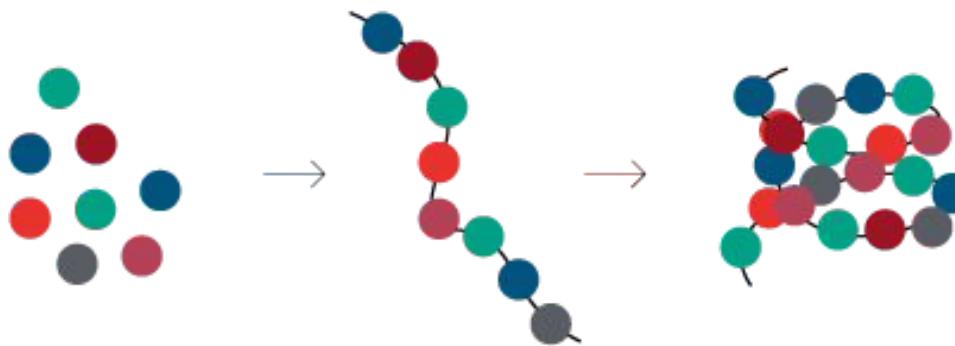
Sickle-Cell
Anemia

A type of β
thalassemias

Duchenne muscular
dystrophy



PROTEINS | Structure



Amino acids:

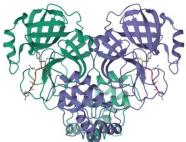
- Small molecules
- 20 different in nature
- Amino and acid group

Peptides:

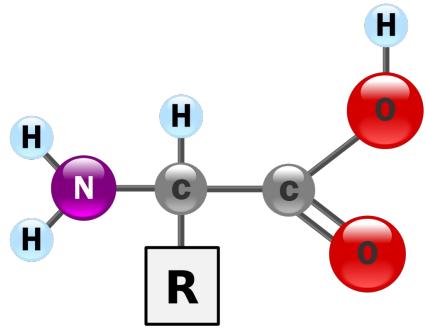
- A short chain of amino acids

Proteins:

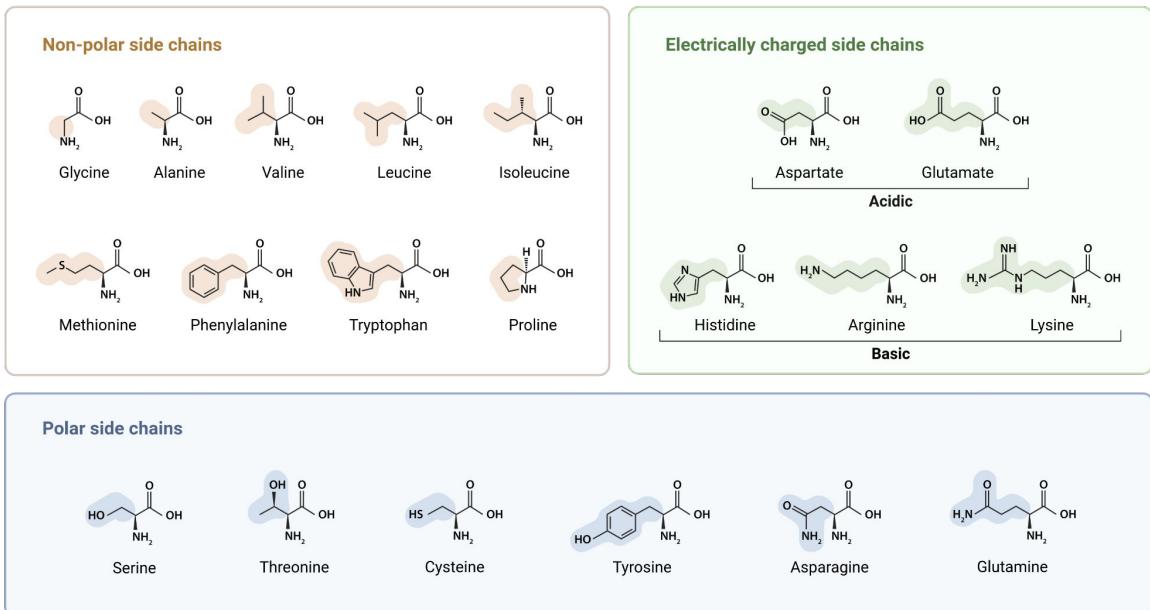
- A long peptide
- Has a particular folding
- Important for a function

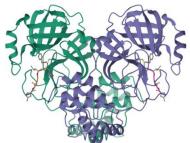


PROTEINS | Amino acids: the building blocks

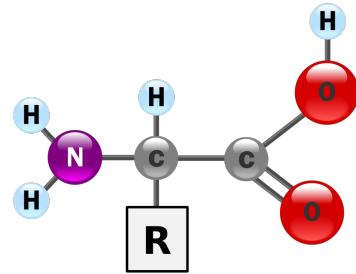


Amino acids share a common backbone





PROTEINS | Amino acid properties

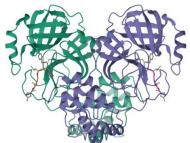


The only difference
between them is here!

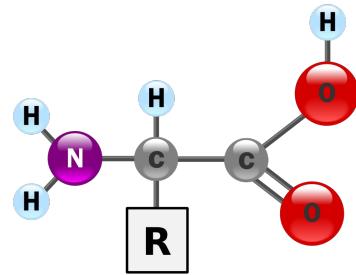
LARGE

Charged Polar
Hydrophobic small

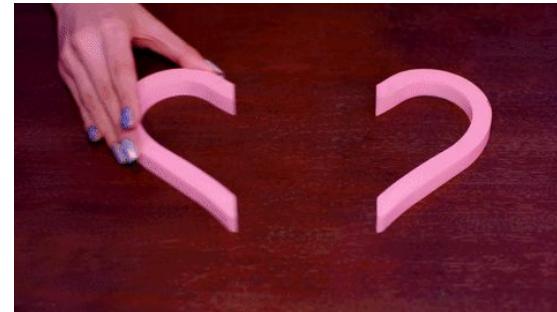
Positive Negative
Uncharged



PROTEINS | Amino acid properties



The only difference
between them is here!



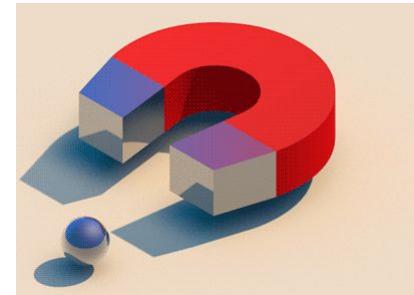
Charged



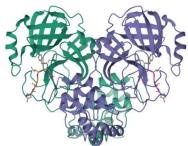
Size



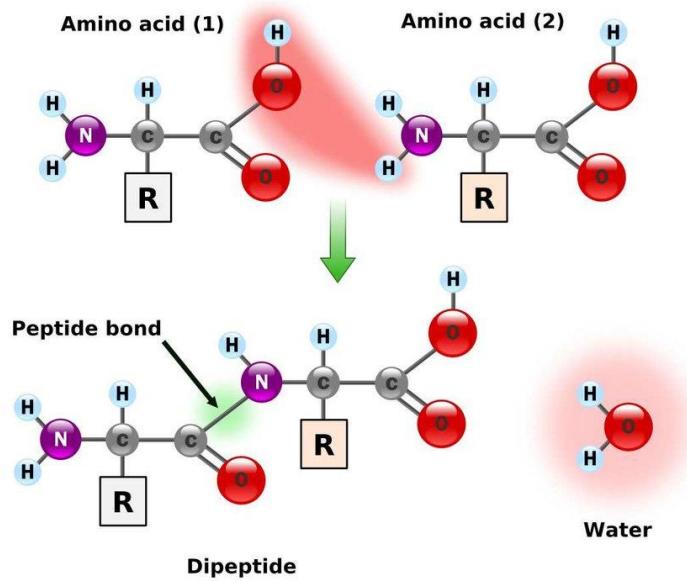
Hydrophobicity



Polarity



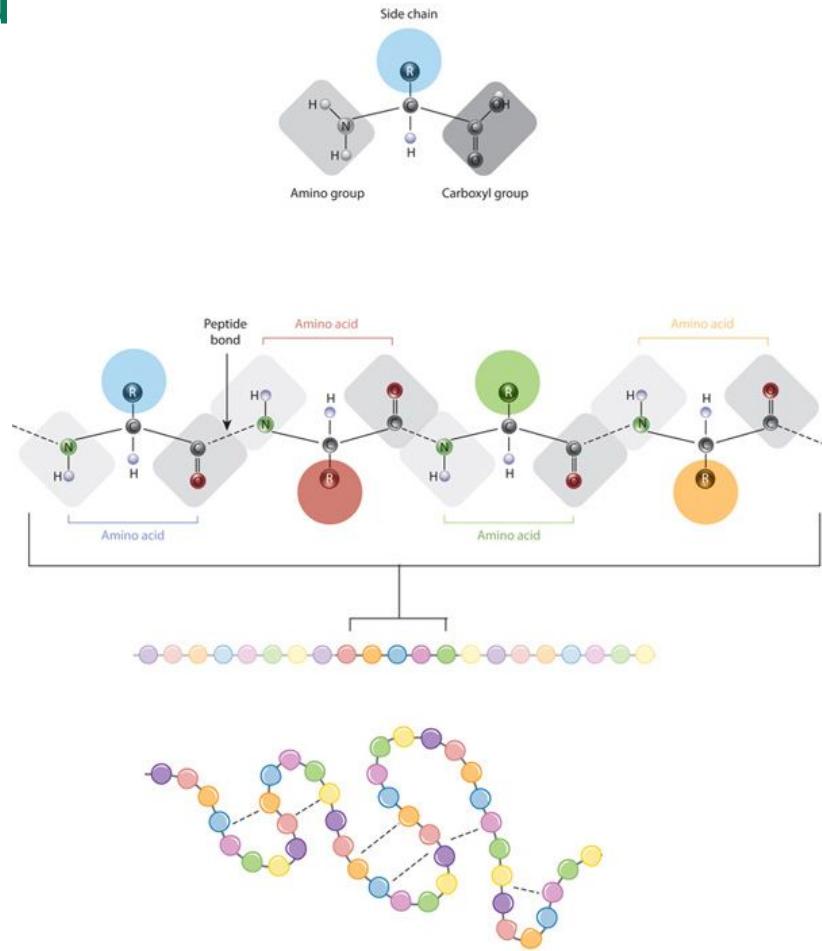
PROTEINS | Peptide bond

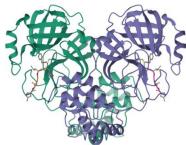


Amino acid (1) Amino acid (2)

Dipeptide

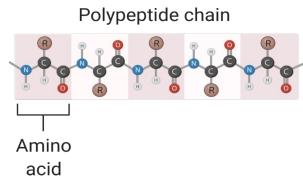
Water



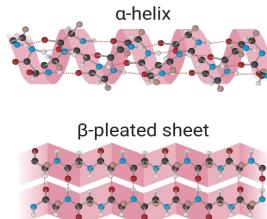


PROTEINS | Protein structure: FOLDING

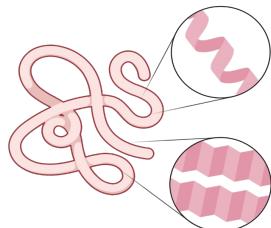
Primary structure



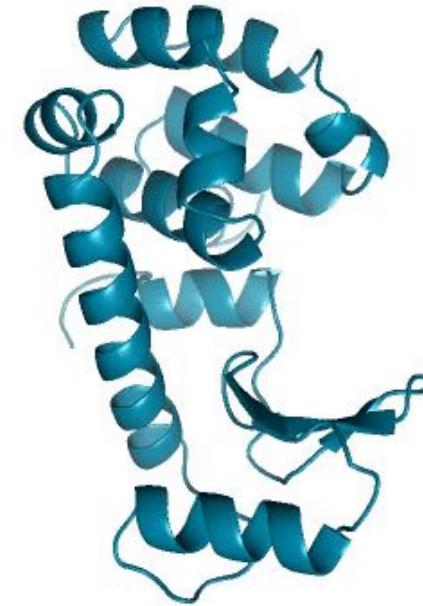
Secondary structure

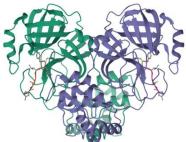


Tertiary structure



Quaternary structure

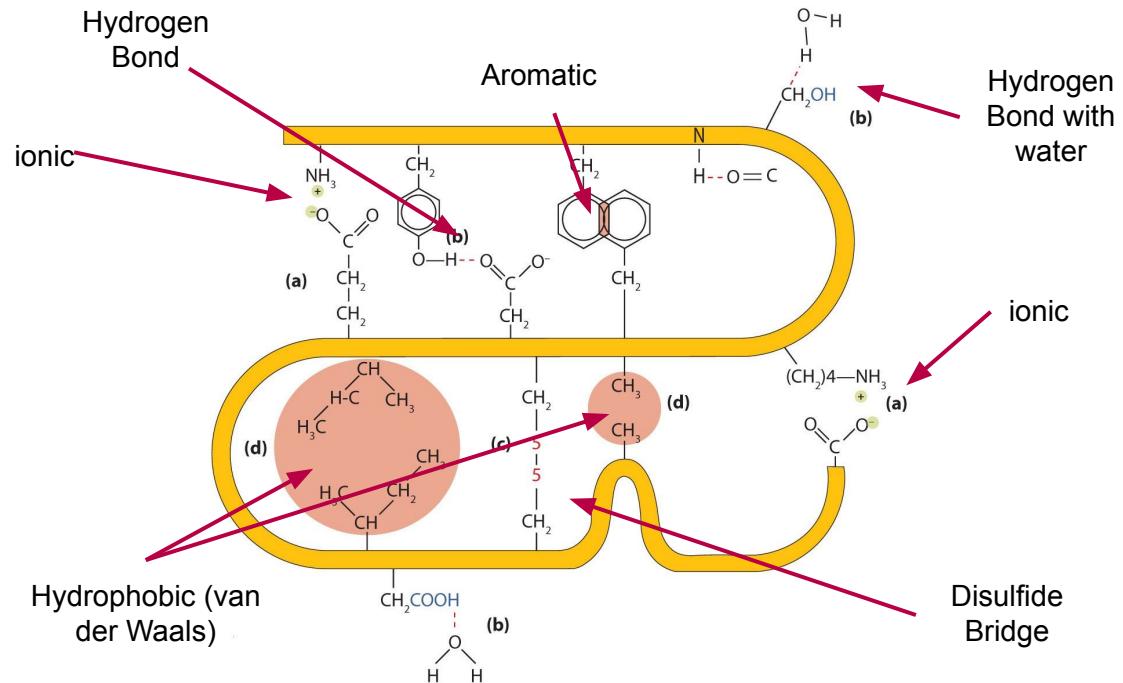


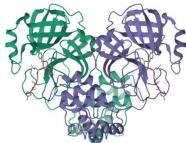


PROTEINS | Protein structure: FOLDING

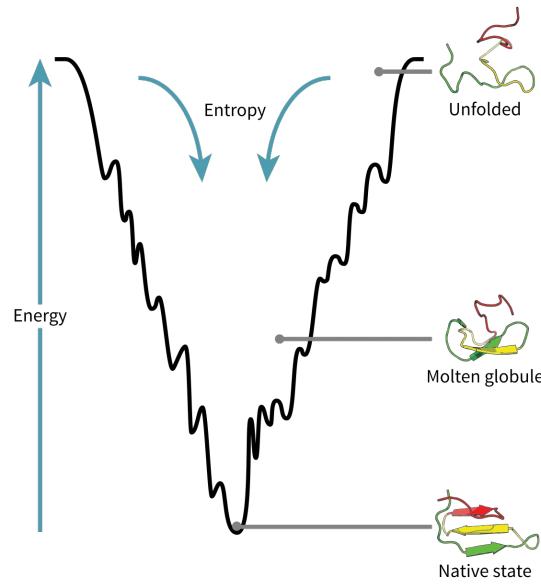
The folded structure of a protein is directly determined by its primary structure (amino acid sequence).

Competition between self-interactions and interactions with the environment (water or lipids) drives protein folding.

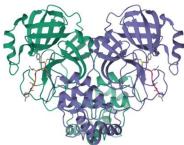




PROTEINS | Protein structure: FOLDING

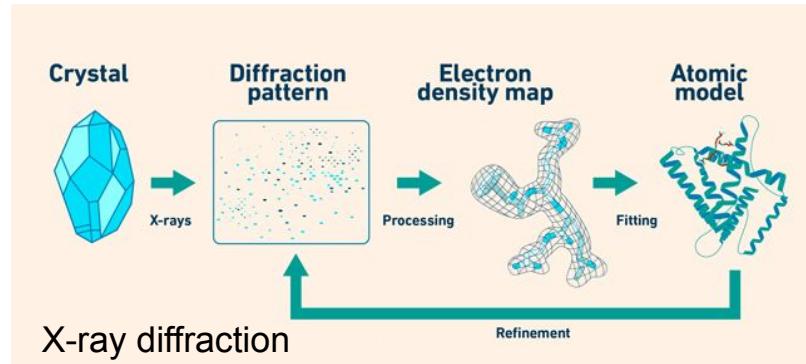


It has been hypothesized that during protein folding several conformational intermediate states are visited, tending to a low level of energy, the native state (folded) being the lowest energy (global minimum)

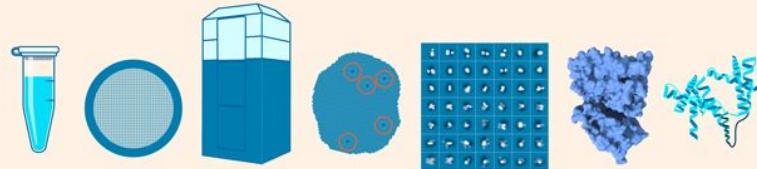


PROTEINS | How can we obtain the protein structure?

There are different methods to obtain the 3D structure of proteins. Each one of them uses different techniques and technologies

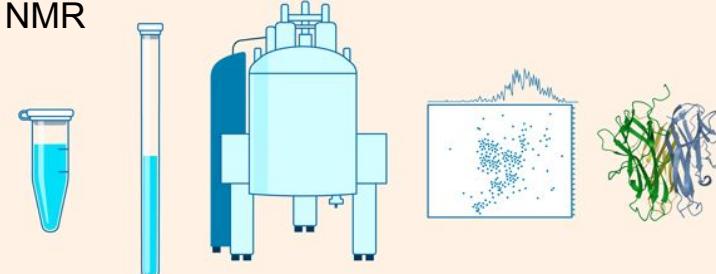


Cryo Electron Microscopy

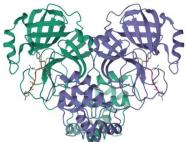


Purified protein Freezing / Negative staining EM data collection Particle picking Particle alignment and classification 3D model reconstruction Model refinement

NMR



Purified protein NMR sample preparation Data acquisition Spectral processing and assignment Structural analysis



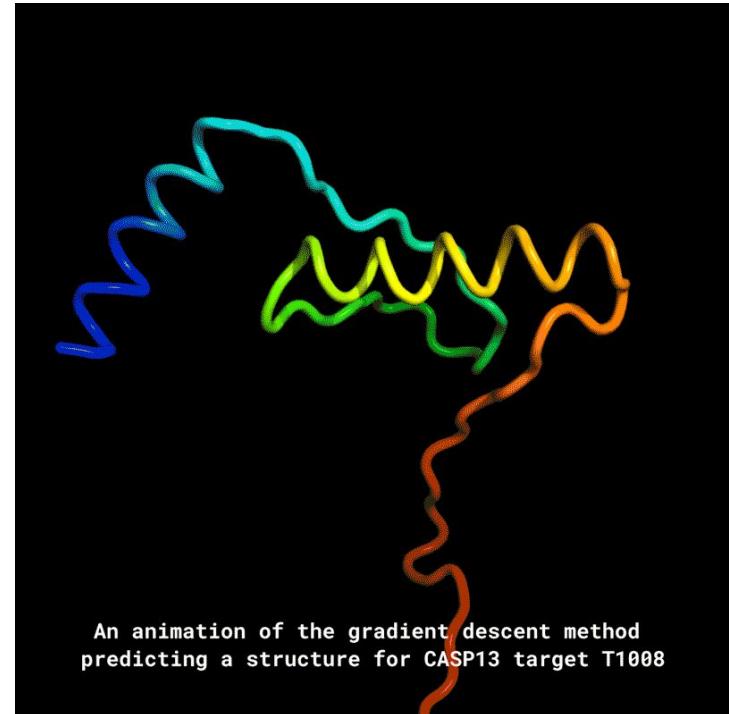
PROTEINS | From sequence to structure

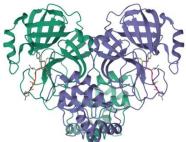
>Protein T1008

MKWVTFISLLFLFSSAYSRGVFRRDAHKSEVAHRFKD
LGEENFKALVIAFAQYLQQCPFEDHVKLVNEVTEFA
KTCVADESAENCDKSLHTLFGDKLCTVATLRETYGE
MADCCAKQEPPERNECFL...



<https://deepmind.com/blog/article/AlphaFold-Using-AI-for-scientific-discovery>





PROTEINS | Protein Folding solved by Machine Learning

AlphaFold Protein Structure Database

Home About FAQs Downloads

AlphaFold Protein Structure Database

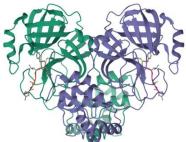
Developed by DeepMind and EMBL-EBI

Search for protein, gene, UniProt accession or organism BETA Search

Examples: Free fatty acid receptor 2 At1g58602 Q5VSL9 E. coli Help: AlphaFold DB search help

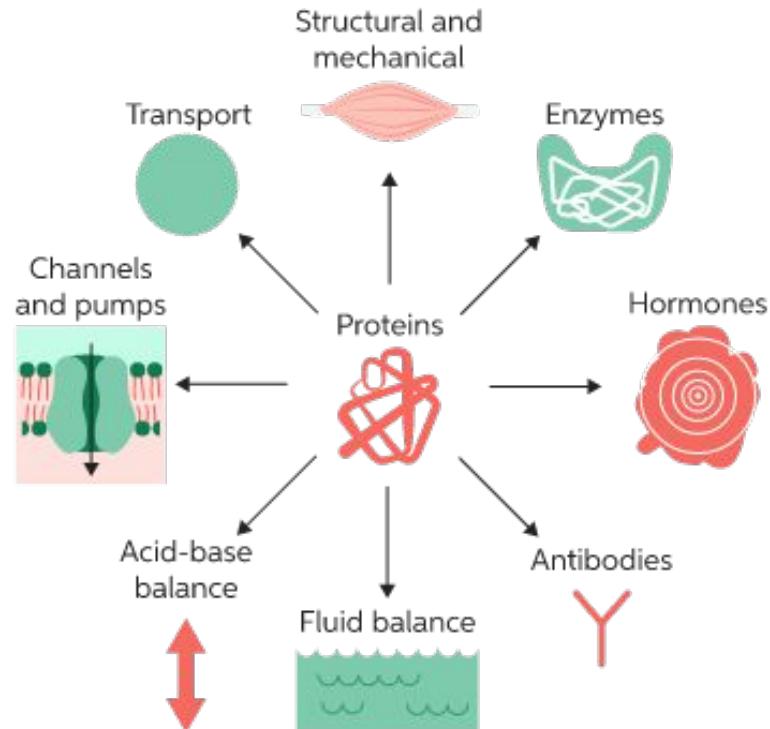
Feedback on structure: Contact DeepMind

<https://alphafold.ebi.ac.uk/>



PROTEINS | Functions

Proteins are involved in all biological processes

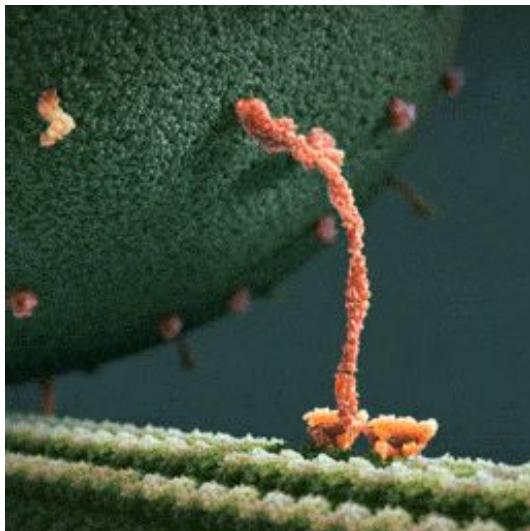


*But also cellular signaling, energy...



PROTEINS | Functions: some examples

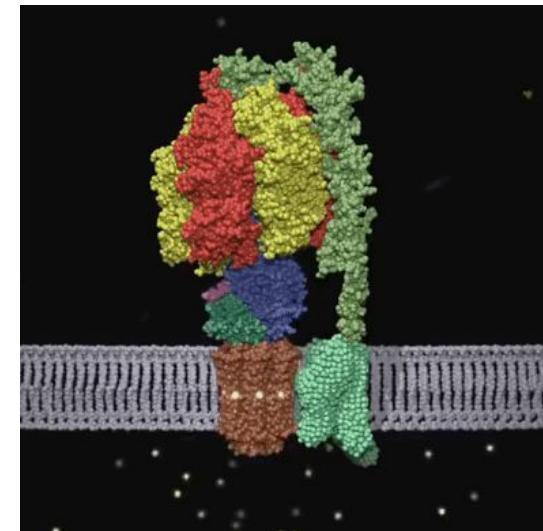
Proteins do everything!



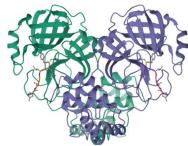
Kinesin



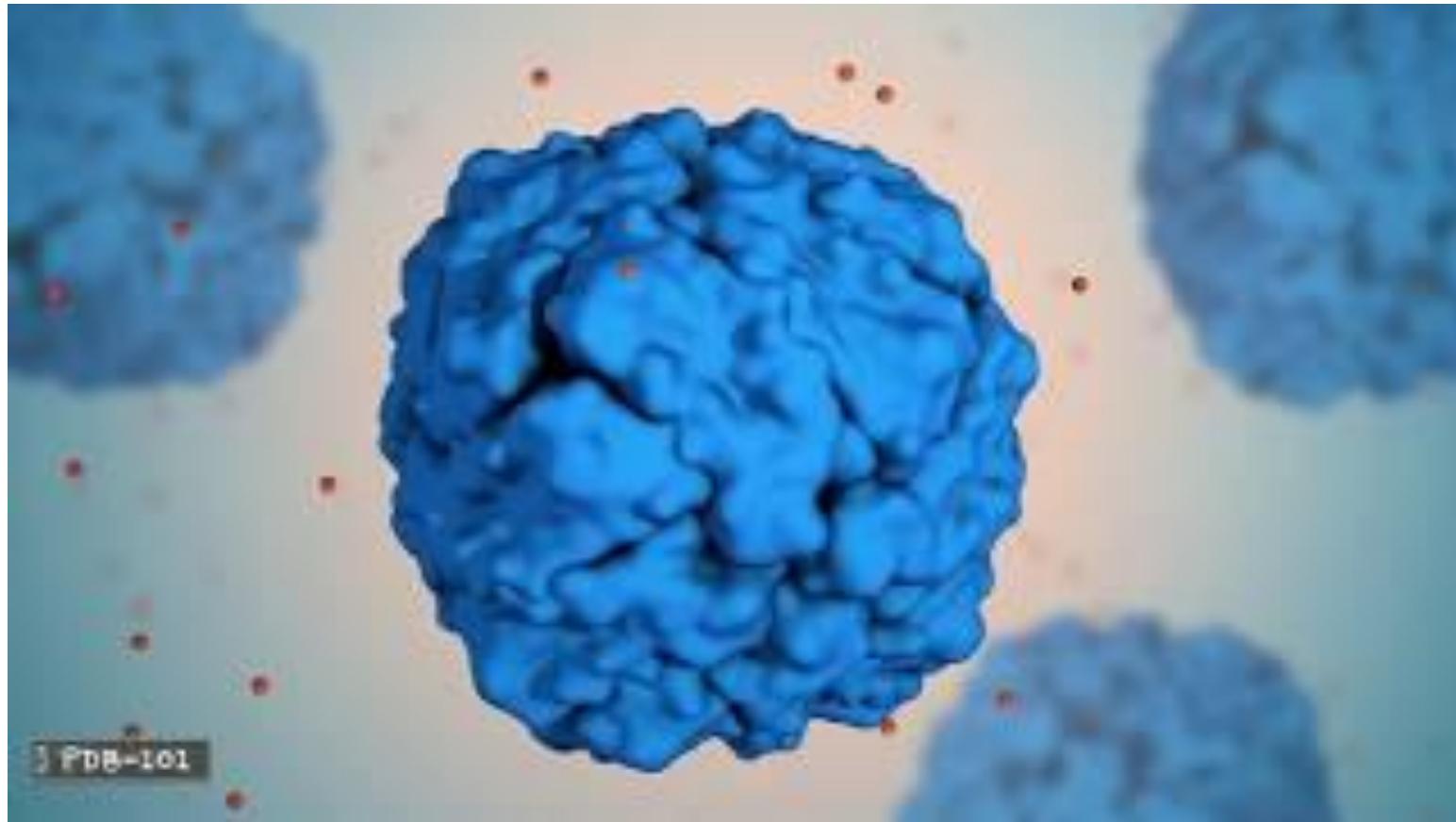
DNA Polymerase

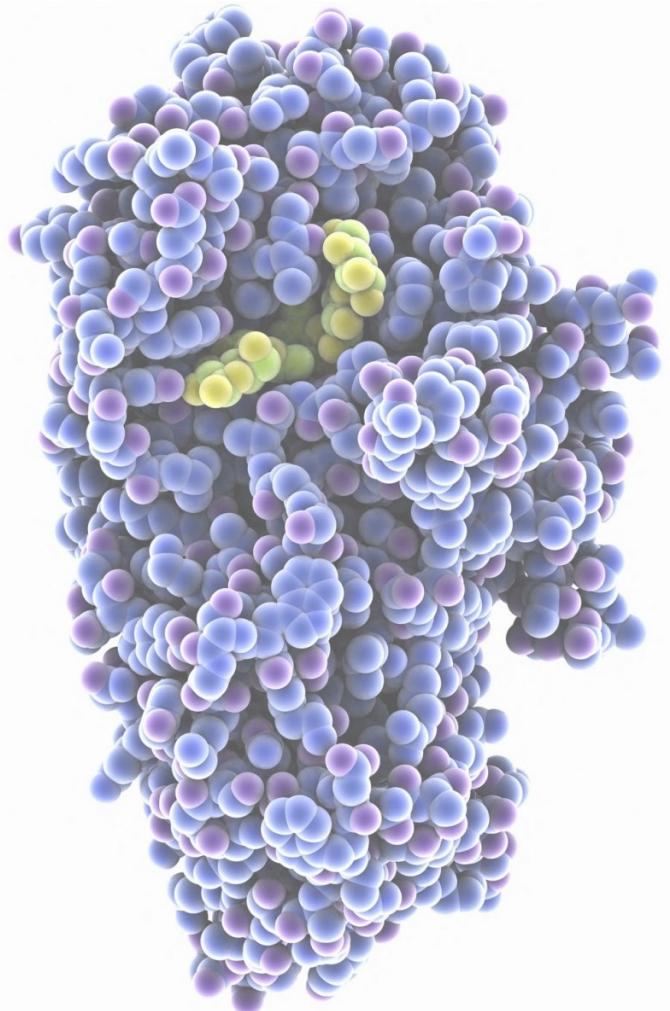


ATP Synthase



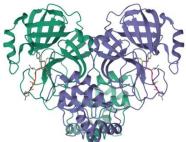
PROTEINS | Protein structure: SUMMARY





ENZYMES

5 MIN BREAK???

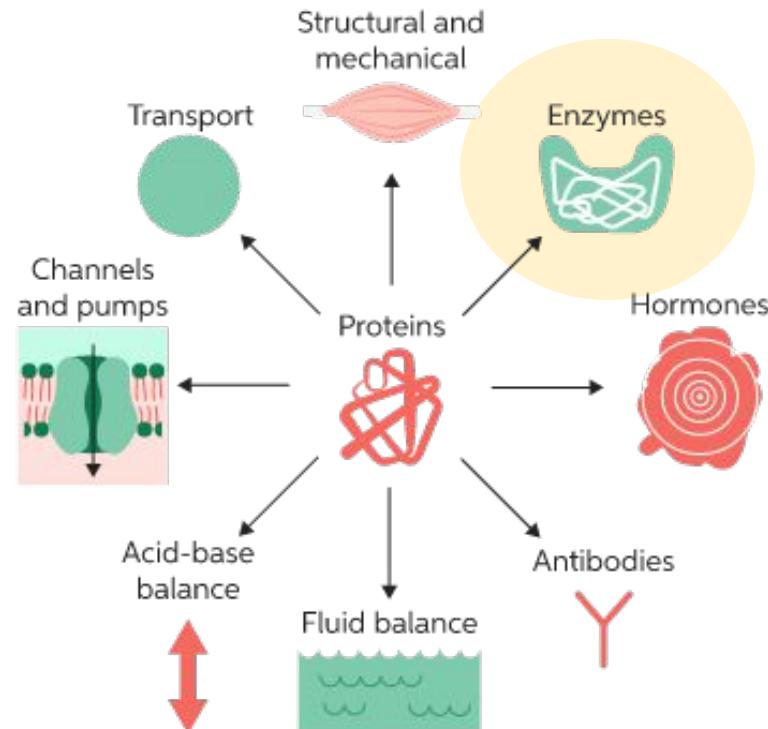


PROTEINS | Functions

What are enzymes?

Enzymes are proteins that catalyze chemical reactions

*So all enzymes are proteins but not all proteins are enzymes!



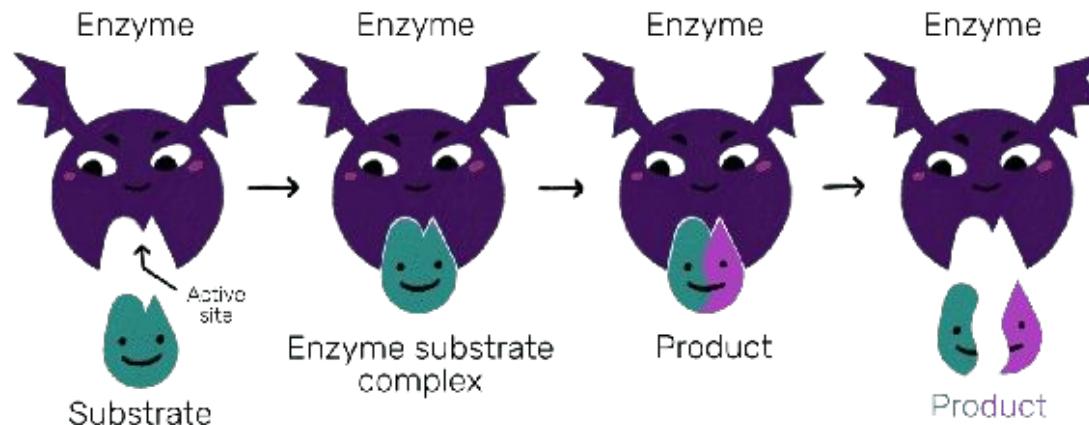
**But also cellular signaling, energy...*

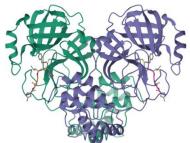


ENZYMES | What are enzymes?

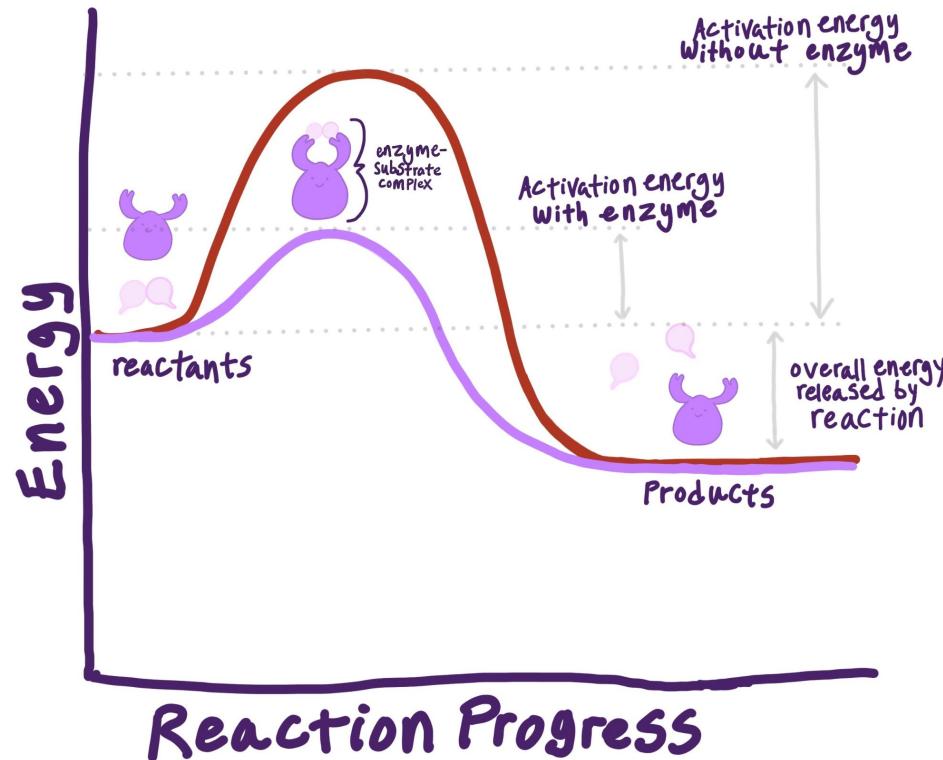
Enzymes are catalytic proteins that speed-up chemical reactions (from hundreds to nanoseconds)

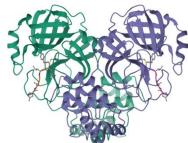
How Enzymes Work



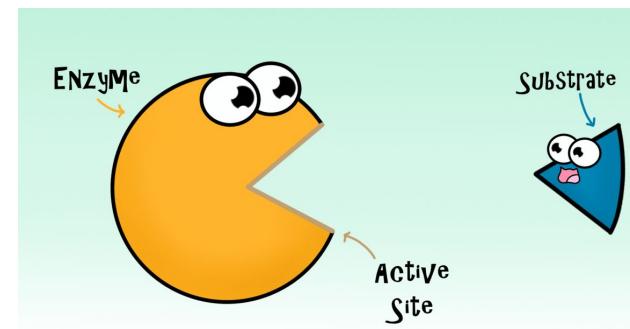
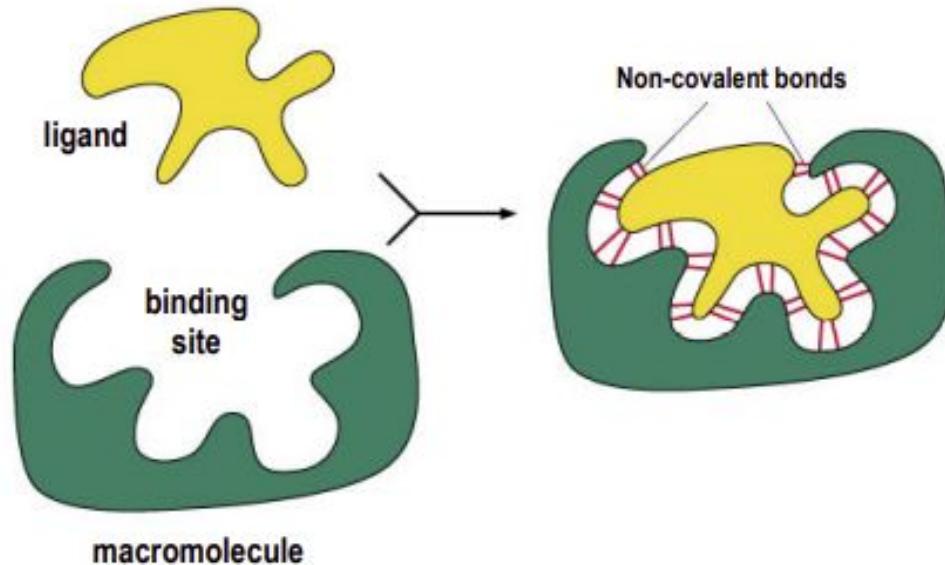


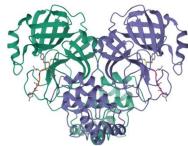
ENZYMES | Why are they necessary?



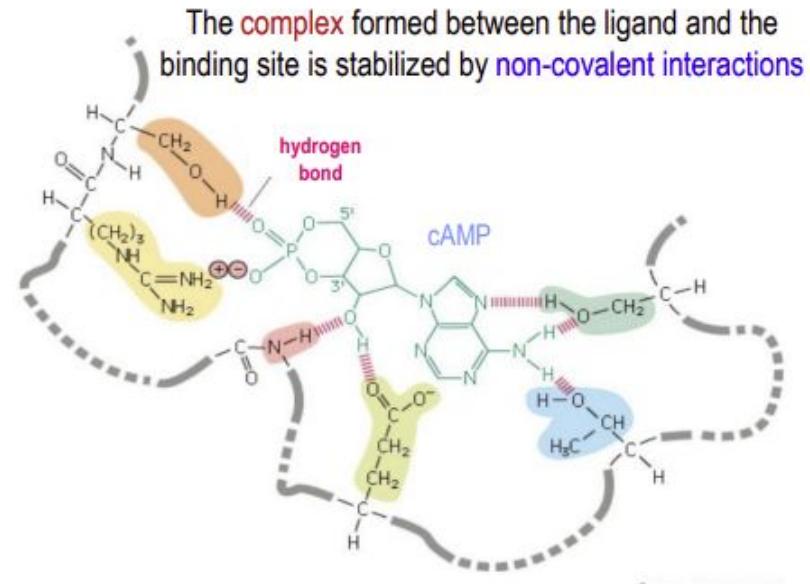
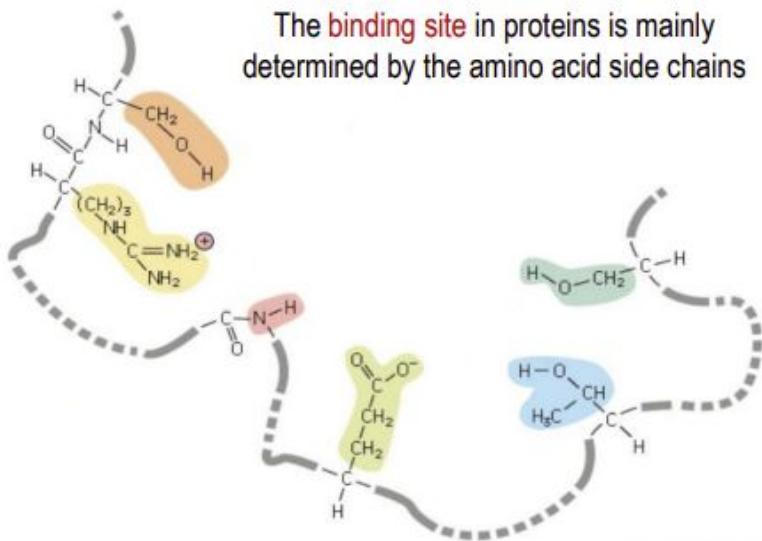


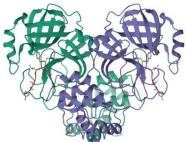
ENZYMES | The ligand-protein complex





ENZYMES | The ligand-protein complex





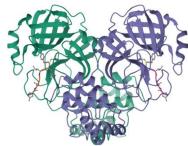
ENZYMES | Examples

There are a lot of types!!

Classification of Enzymes (IUMB System)

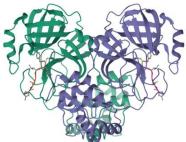
1. OXIDOREDUCTASES
2. TRANSFERASES
3. HYDROLASES
4. LYASES
5. ISOMERASES
6. LIGASES
7. TRANSLOCASES





ENZYMES | How do they work?





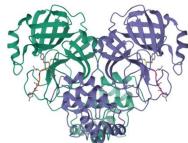
ENZYMES | Enzyme engineering

Mutations may change the efficiency of the enzyme

We can take advantage of this and customize enzymes.

This is enzyme engineering.





ENZYMES | Enzyme engineering: UTILITIES



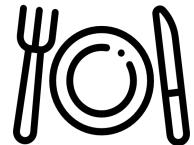
Pharmaceutics



Detergents



Textile



Food



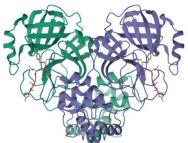
Cosmetics



Paper

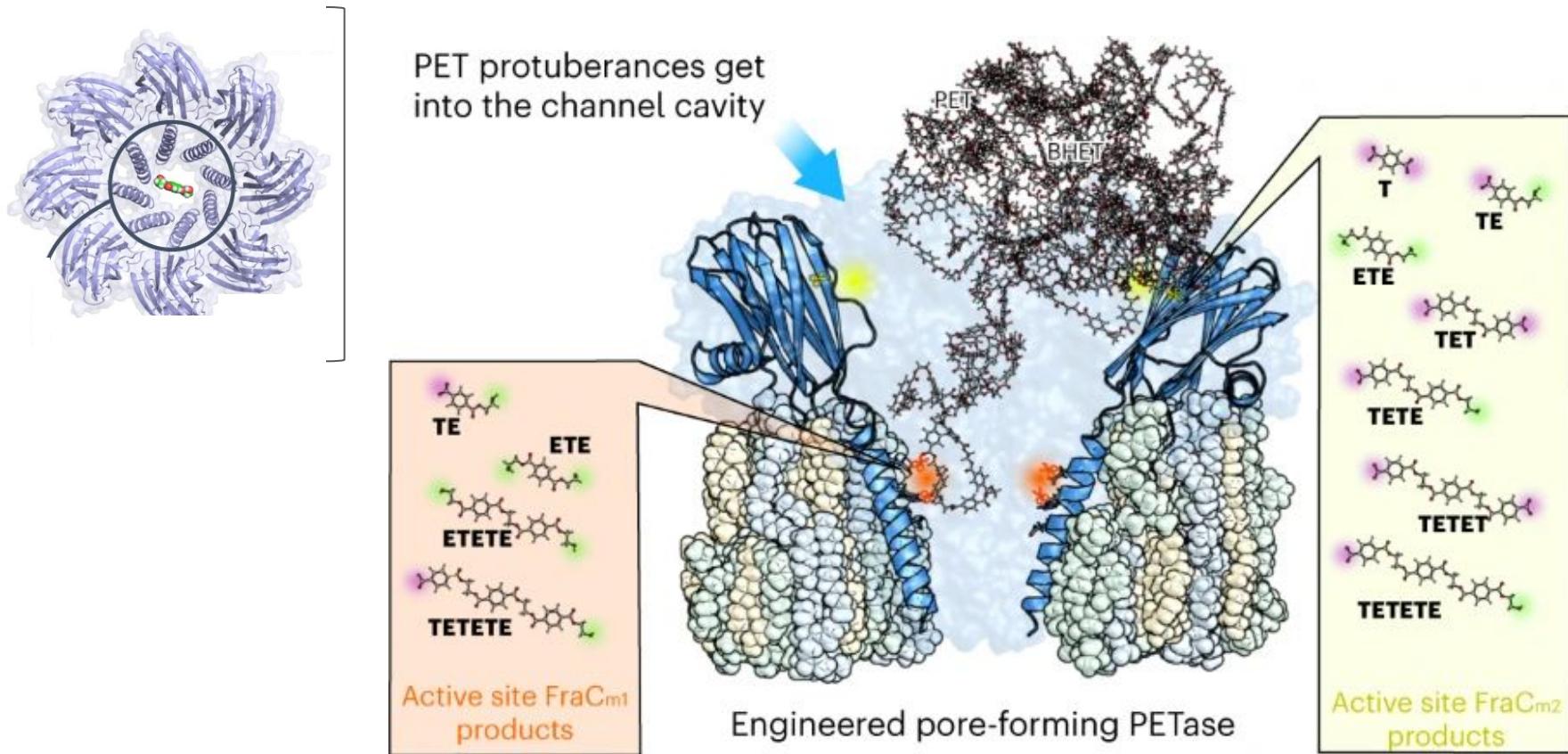
Proteins in industry

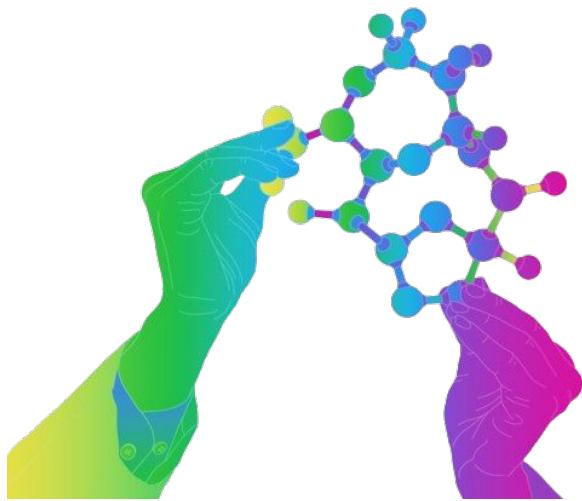




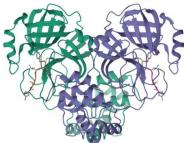
ENZYMES | Enzyme engineering: EXAMPLE

Plastic Degradation!





DRUG DESIGN

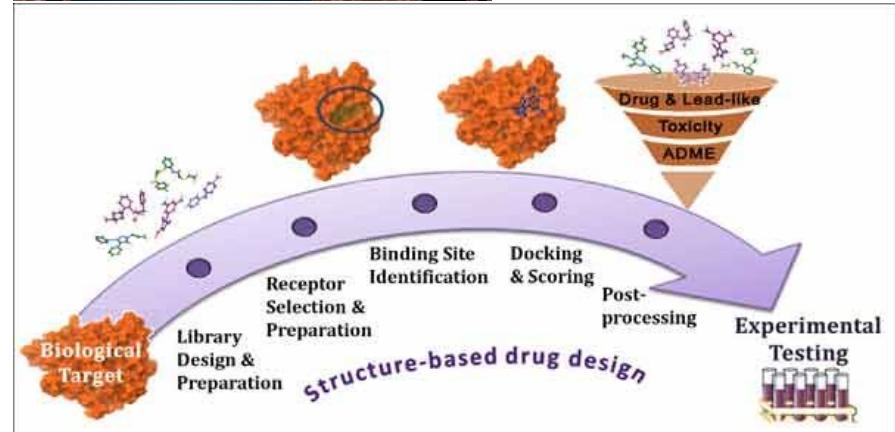
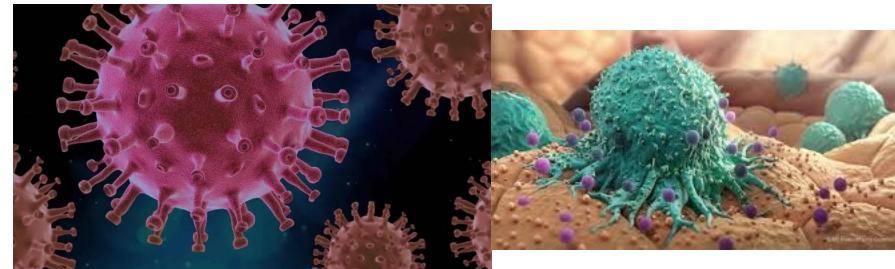


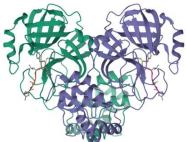
DRUG DESIGN | How to obtain a drug?

Past



Present





DRUG DESIGN | How do drugs work?

Antibiotics & Antivirals

1 2

Antibiotics and antiviral drugs are specific poisons. They need to kill pathogenic organisms like bacteria and viruses without poisoning the patient at the same time. Often, these drugs attack proteins that are only found in the targeted bacterium or virus and which are crucial for their survival or multiplication. For instance, **penicillin** attacks the enzyme that builds bacterial cell walls, and HIV protease inhibitors like **sauquinavir** attack an enzyme that is needed for HIV maturation.

1. D-alanyl-D-alanine carboxypeptidase with penicillin (1pwv)
2. HIV protease with saquinavir (1xb)

Anticancer Chemotherapy

3 4

Cancer cells grow and multiply without control. Since these cells are still similar to normal cells, it is difficult to kill them selectively with drugs that can't distinguish between the two. Many drugs currently used for cancer chemotherapy attack all growing cells, including cancer cells and normal cells. This causes the severe side effects of cancer chemotherapy, because the drugs attack rapidly-growing cells in hair follicles and the stomach. Two examples are shown here. **Bleomycin** attacks DNA in actively growing cells, often cleaving the DNA chain and killing the cell. **Paclitaxel (Taxol)** binds to tubulin, preventing the action of microtubules during cell division.

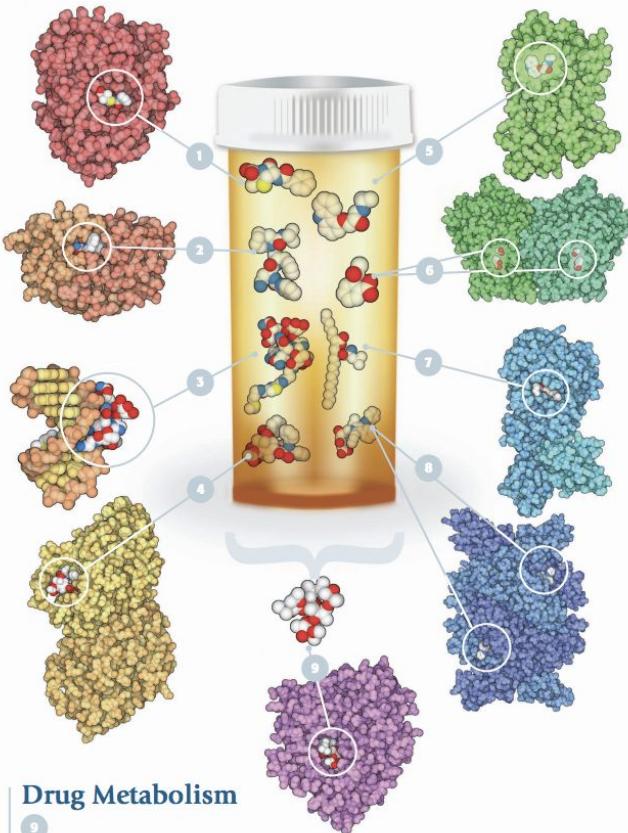
3. DNA with bleomycin (1mxk)
4. Tubulin with taxol (1ff)

Drug Metabolism

9

You have probably noticed that when you take drugs, the effects gradually wear off in a few hours. Enzymes like cytochrome P450 continually search for drugs and destroy them. This is important because it protects us from poisonous molecules in our diet and in the environment, but it means that we have to take multiple doses of drugs when being treated for a disease.

9. Cytochrome P450 3A4 with erythromycin (2j0d)



Drugs of Signaling Proteins

5 6

Many drugs are designed to keep bodily processes at normal healthy levels. Much of the body's regulation is done through elaborate communications between cells, so some of the most widely prescribed drugs function by blocking the signaling proteins that allow cells to communicate. G protein-coupled receptors, which transmit signals across cell membranes, are targets for many drugs. For instance, the drug loratadine (**Claritin**) is used to treat allergies because it blocks the histamine receptor; losartan (**Cozart**) is used to treat high blood pressure because it blocks the angiotensin II receptor; and **carazolol** is one of a large class of beta-blockers that bind to the adrenergic receptor, making it useful for treating heart disease. Signals can also be stopped by blocking the enzymes that create a signaling molecule. **Aspirin** blocks pain at the source by inhibiting the enzyme cyclooxygenase, which makes pain-signaling prostaglandin molecules.

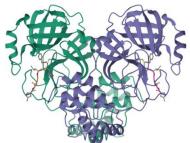
5. Adrenergic receptor with carazolol (2rh)
6. Prostaglandin H₂ synthase with aspirin (1pfb). The drug breaks into two pieces when it binds to the enzyme, and a smaller piece (an acetyl group) is attached to the enzyme with a covalent bond. The closeup shows the drug in one piece.

Lifestyle Drugs

7 8

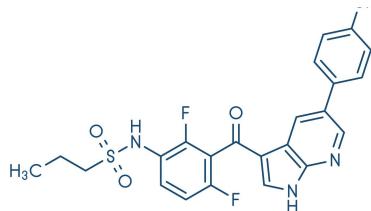
Pharmaceutical scientists have developed a number of drugs that help people modify their own health and bodily function. The drug orlistat (**Xenical** or **all**) blocks the action of pancreatic lipase, and thereby reduces the amount of fat that is absorbed from food. Atorvastatin (**Lipitor**) and simvastatin (**Zocor**) lower cholesterol by blocking the action of HMG-CoA reductase, an enzyme involved in the synthesis of cholesterol. These drugs can be used, along with changes in diet and exercise, to help lose weight, regulate cholesterol levels, and control heart disease.

7. Pancreatic lipase with an alkyl phosphonate inhibitor (1pb). The drug orlistat shown on the right is similar to the inhibitor found in the crystal structure.
8. HMG-CoA reductase with atorvastatin (1hwk)

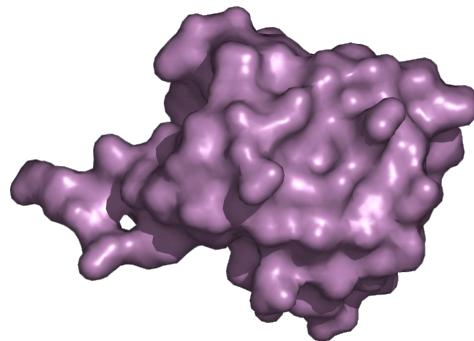


DRUG DESIGN | What can be a drug?

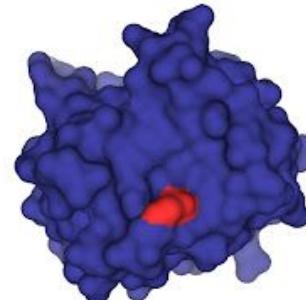
Small molecules



Proteins



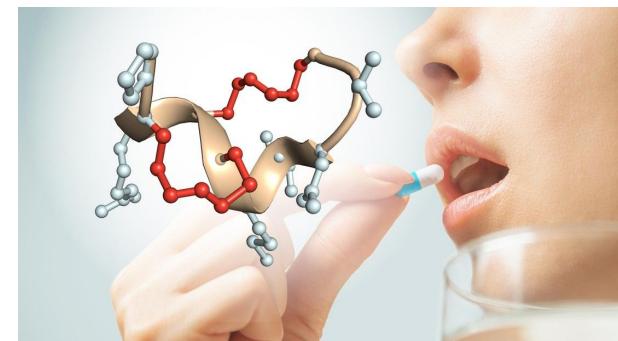
Recombinant proteins

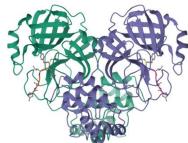


Antibodies

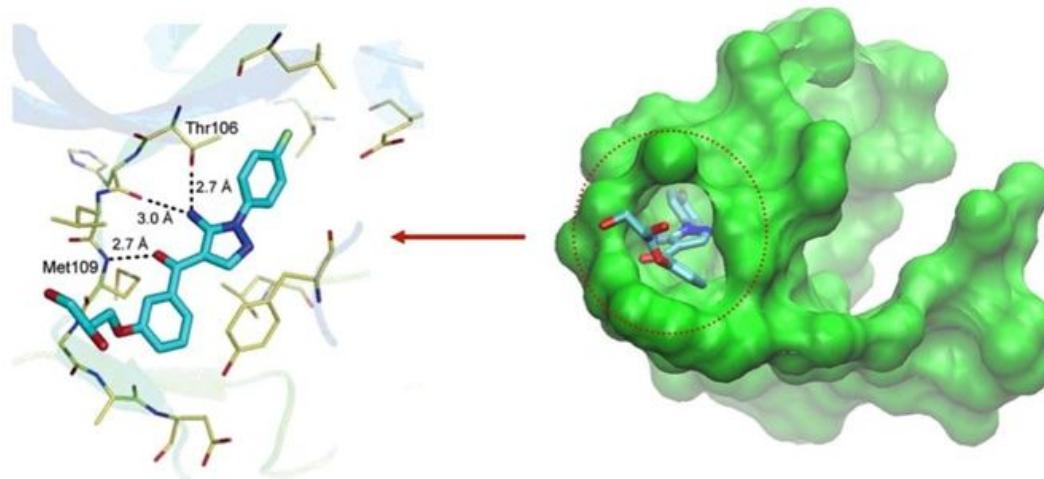
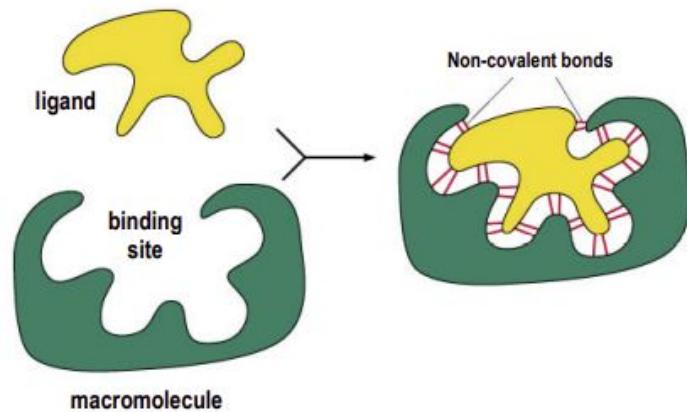


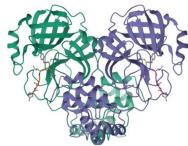
Peptides



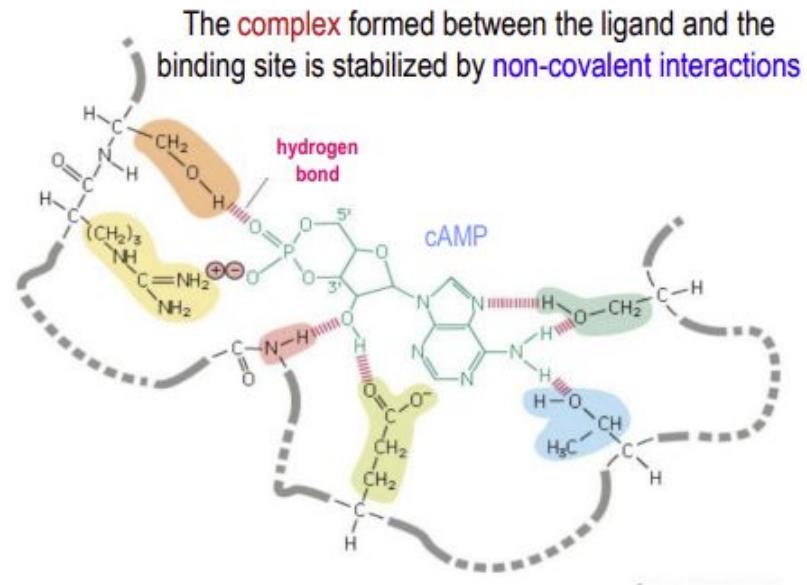
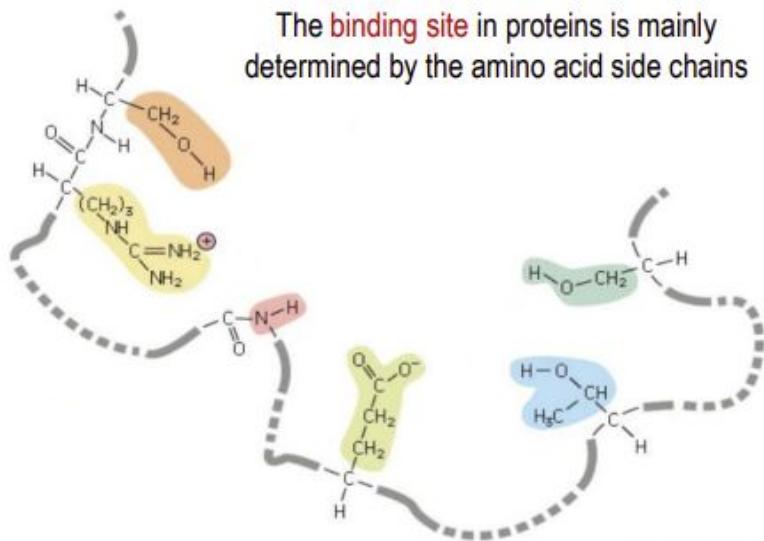


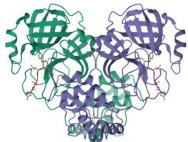
DRUG DESIGN | The ligand-protein complex



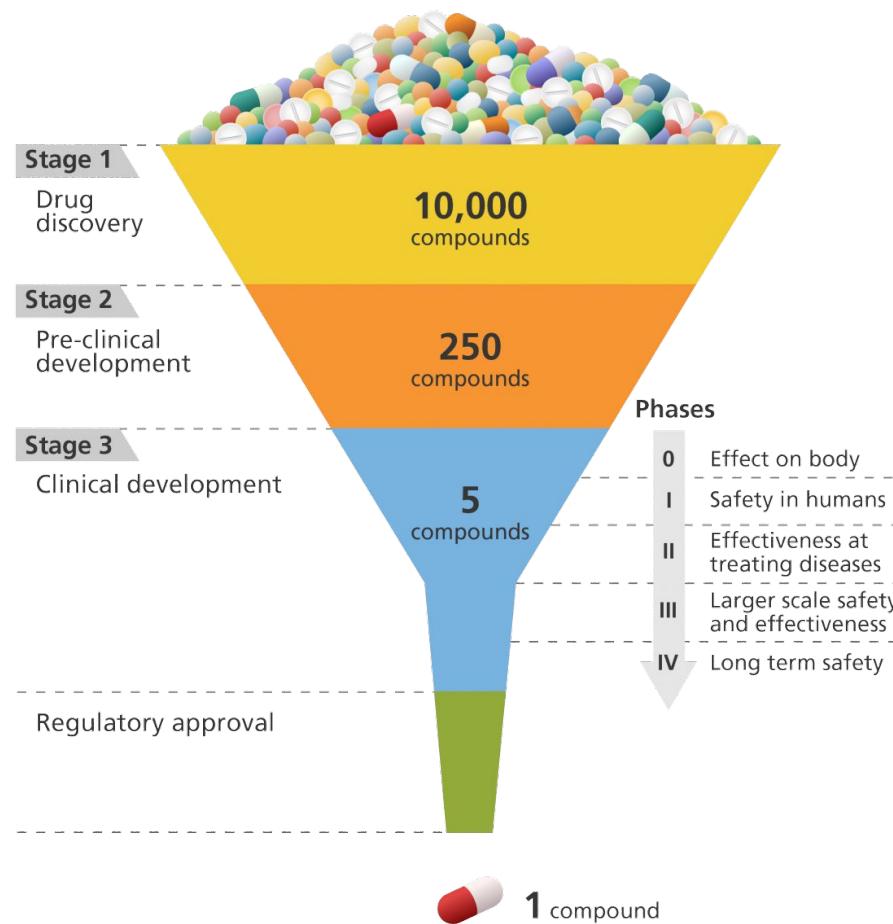


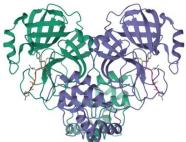
DRUG DESIGN | The ligand-protein complex





DRUG DESIGN | Stages

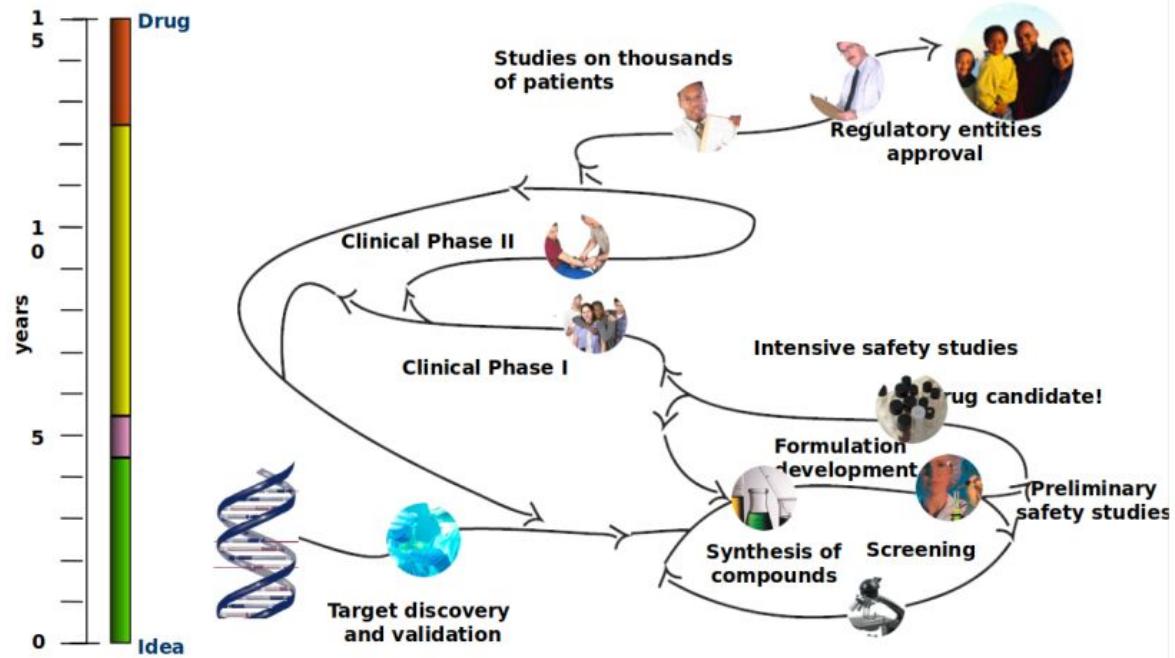




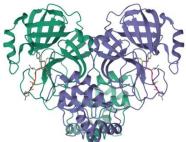
DRUG DESIGN | Stages

But the reality can be so...

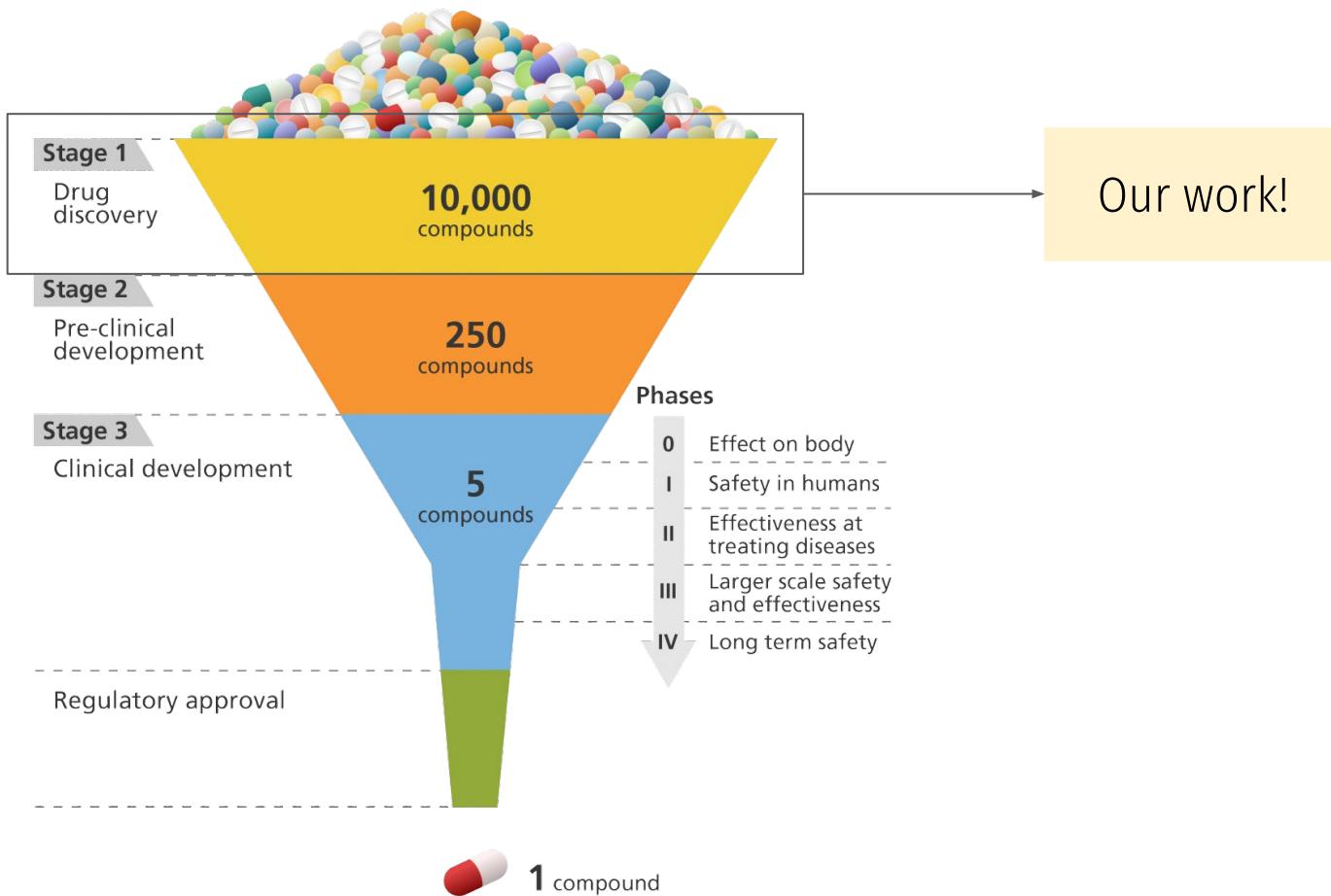
- Long
- No linear
- Unpredictable



This is why **computational techniques** are so important!!

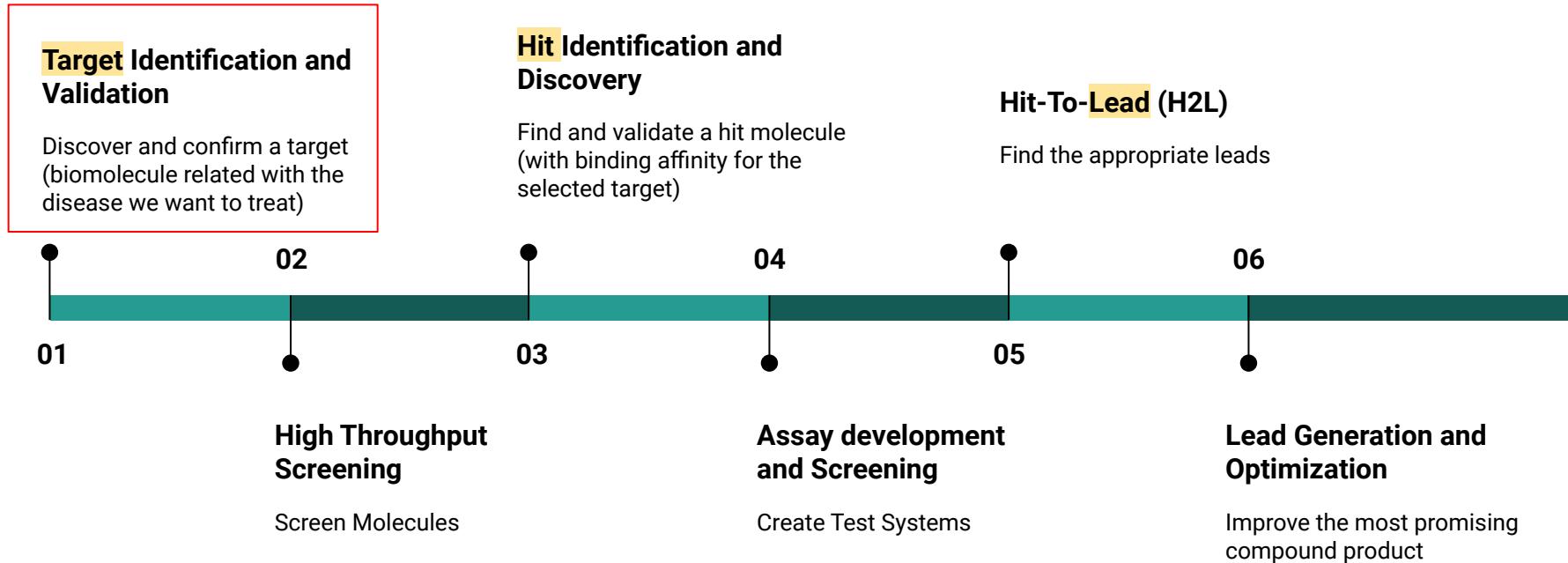


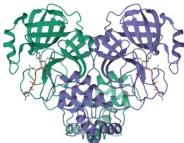
DRUG DESIGN | Stages





DRUG DESIGN | The early stage of Drug Discovery

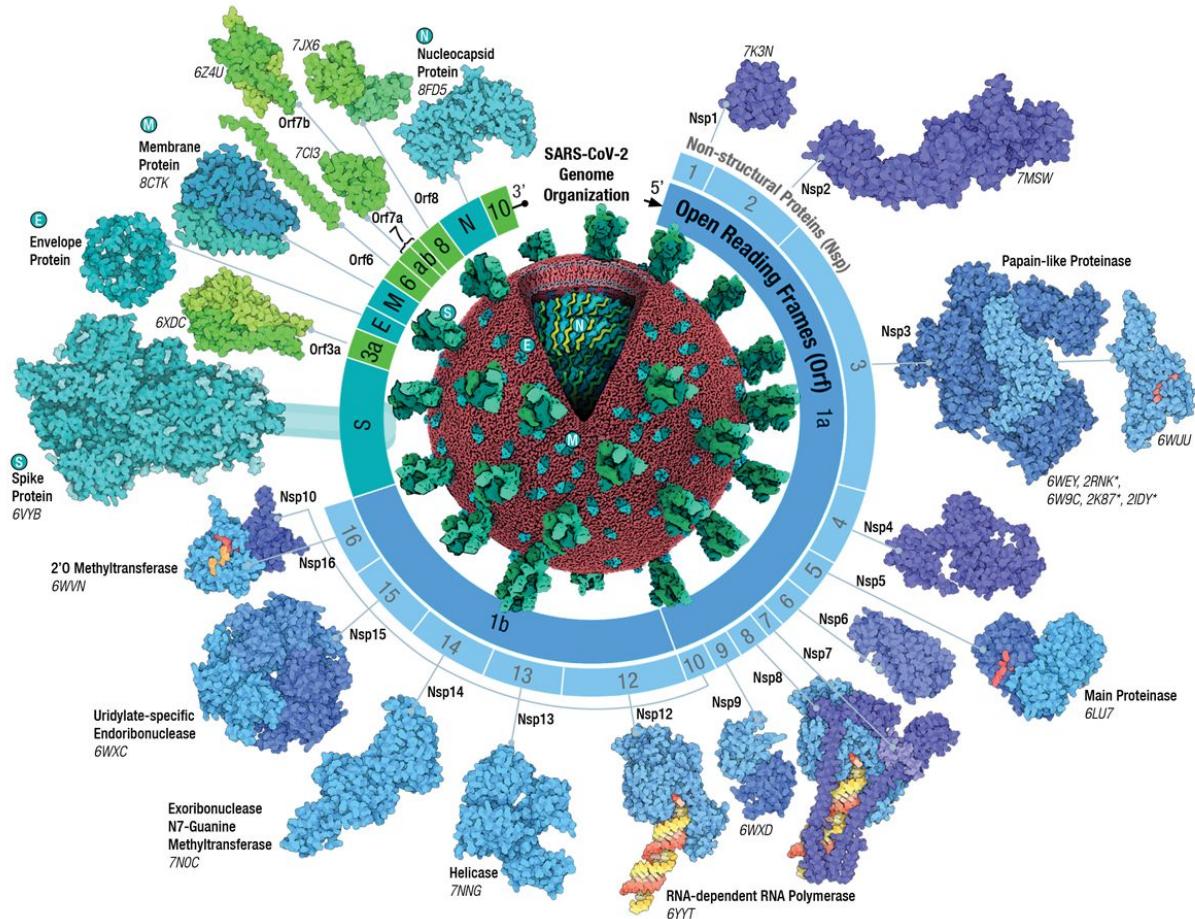


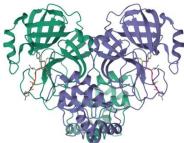


DRUG DESIGN | Target Identification and Validation

Example: Antiviral Drug for COVID-19 disease

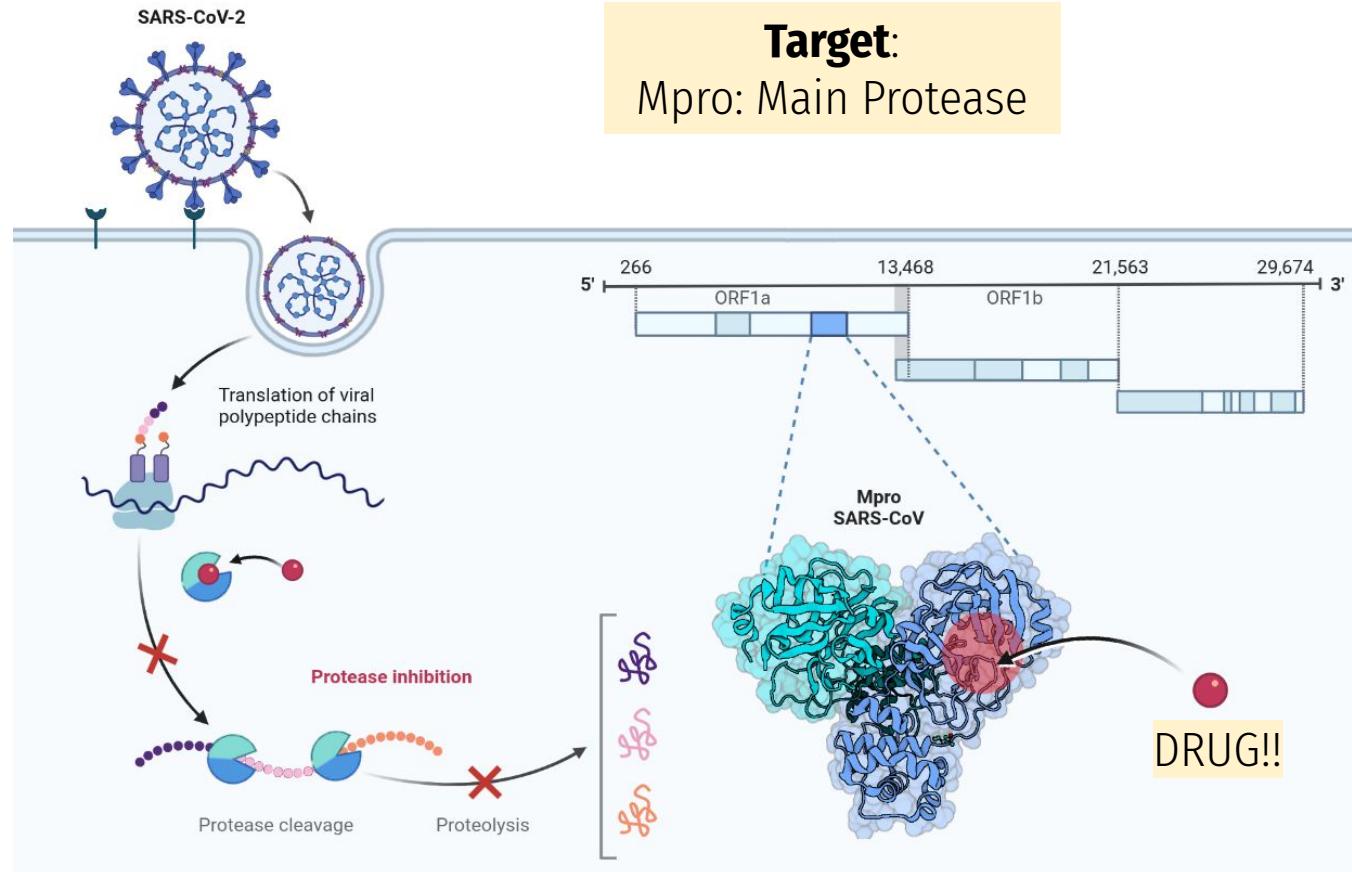
There are a lot
of candidates!!





DRUG DESIGN | Target Identification and Validation

Example: Antiviral Drug for COVID-19 disease





DRUG DESIGN | The early stage of Drug Discovery

Target Identification and Validation

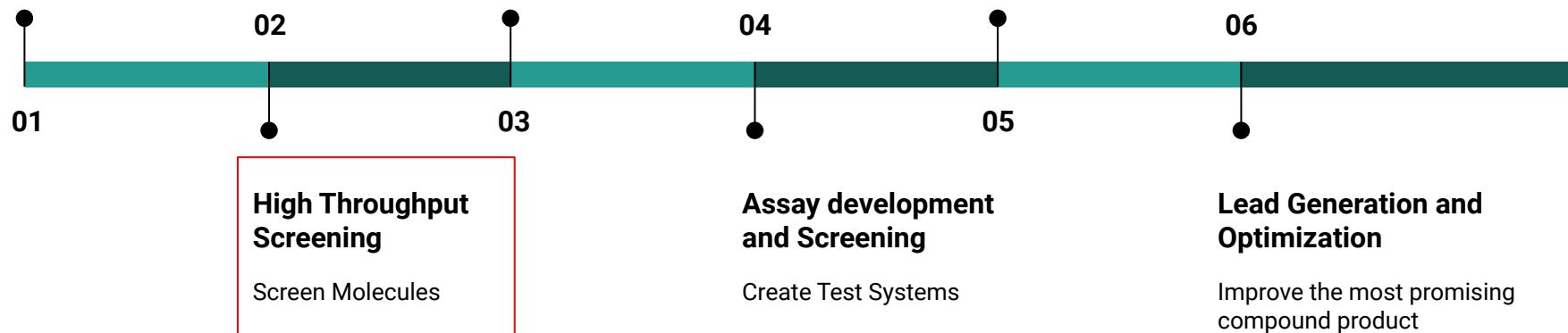
Discover and confirm a target (biomolecule related with the disease we want to treat)

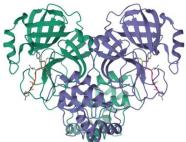
Hit Identification and Discovery

Find and validate a hit molecule (with binding affinity for the selected target)

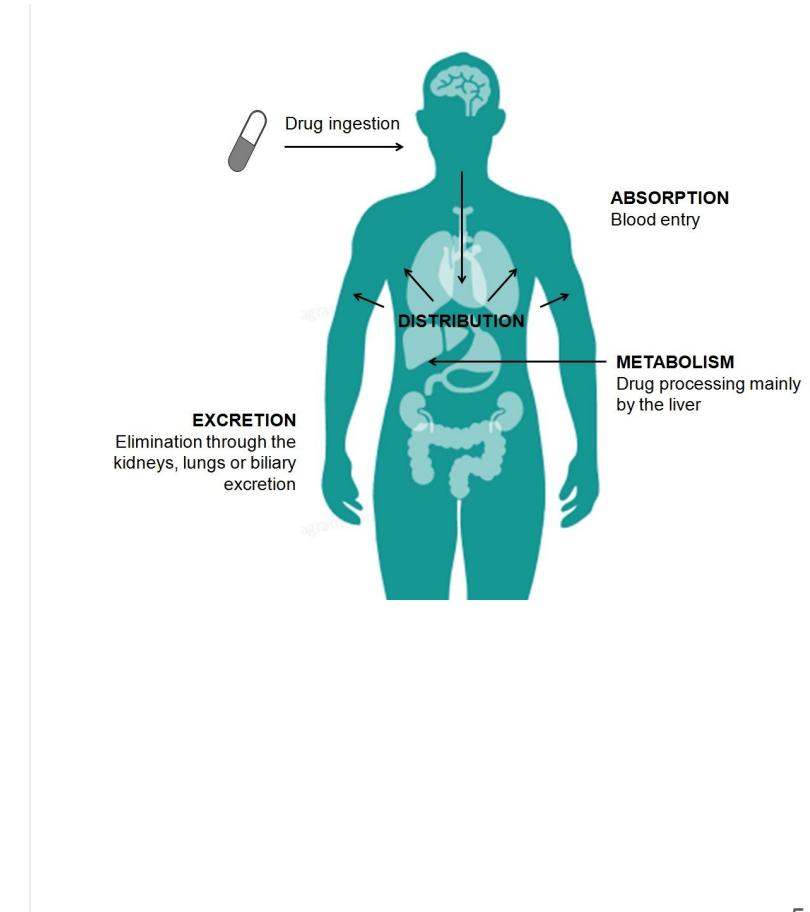
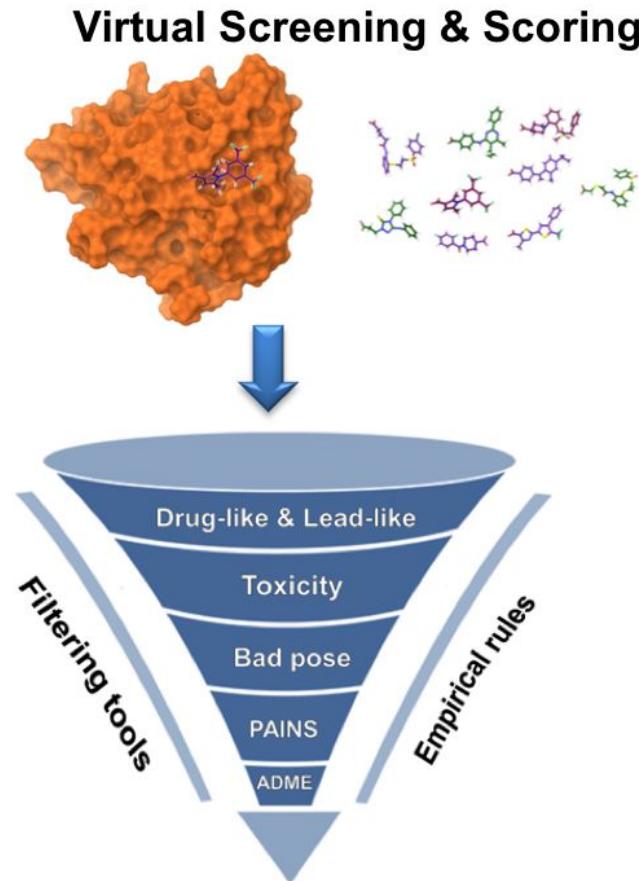
Hit-To-Lead (H2L)

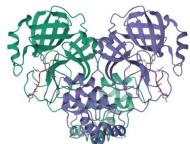
Find the appropriate leads



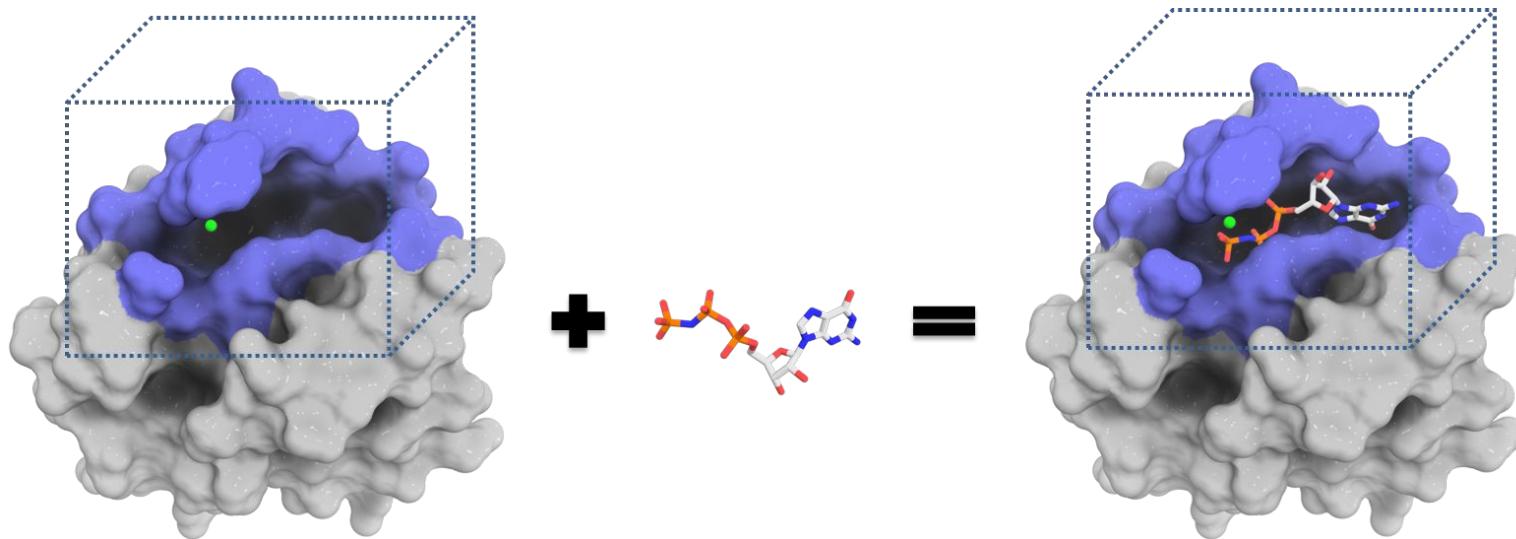


DRUG DESIGN | Virtual screening

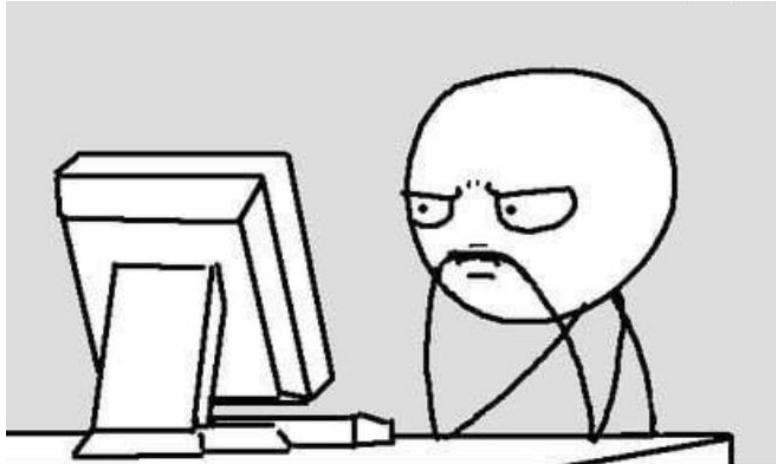




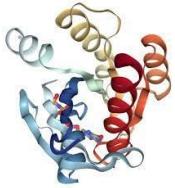
DRUG DESIGN | Ligand Docking



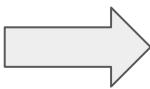
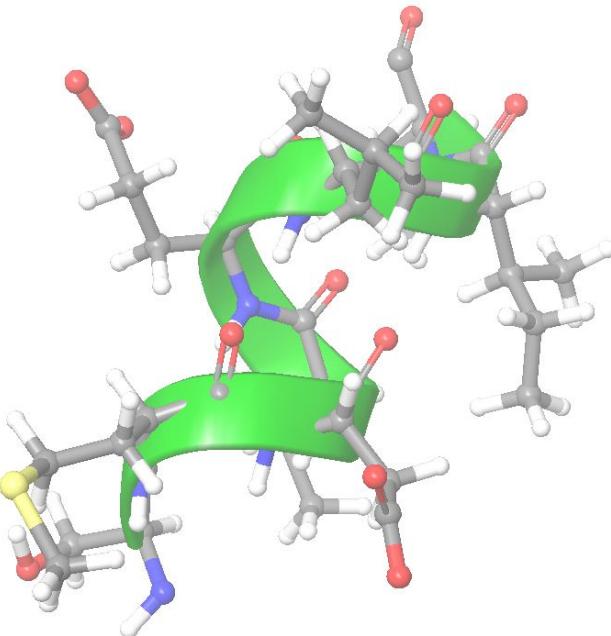
Spoiler: Let's get dirty!



PRACTICAL SESSION

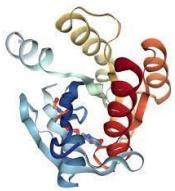


BACKGROUND | How is represented the structure of a protein?



PDB

ATOM	440	N	MET	A	35	-11.973	-17.218	-24.320	1.00	25.25	AA	N
ATOM	441	CA	MET	A	35	-12.452	-16.941	-22.967	1.00	27.09	AA	C
ATOM	442	C	MET	A	35	-13.127	-15.557	-22.885	1.00	25.70	AA	C
ATOM	443	O	MET	A	35	-14.073	-15.384	-22.118	1.00	22.59	AA	O
ATOM	444	CB	MET	A	35	-11.257	-16.970	-22.000	1.00	32.31	AA	C
ATOM	445	CG	MET	A	35	-10.576	-18.341	-21.882	1.00	38.75	AA	C
ATOM	446	SD	MET	A	35	-9.239	-18.407	-20.656	1.00	47.75	AA	S
ATOM	447	CE	MET	A	35	-7.989	-17.369	-21.466	1.00	45.85	AA	C
ATOM	448	H	MET	A	35	-10.989	-17.096	-24.516	1.00	0.00	H	
ATOM	449	HA	MET	A	35	-13.180	-17.699	-22.669	1.00	0.00	H	
ATOM	450	HB3	MET	A	35	-11.606	-16.685	-21.000	1.00	0.00	H	
ATOM	451	HB2	MET	A	35	-10.525	-16.221	-22.299	1.00	0.00	H	
ATOM	452	HG3	MET	A	35	-10.172	-18.654	-22.846	1.00	0.00	H	
ATOM	453	HG2	MET	A	35	-11.318	-19.088	-21.601	1.00	0.00	H	
ATOM	454	HE1	MET	A	35	-7.068	-17.366	-20.883	1.00	0.00	H	
ATOM	455	HE2	MET	A	35	-7.760	-17.746	-22.463	1.00	0.00	H	
ATOM	456	HE3	MET	A	35	-8.334	-16.340	-21.555	1.00	0.00	H	
ATOM	457	N	ASP	A	36	-12.698	-14.588	-23.712	1.00	24.96	AA	N
ATOM	458	CA	ASP	A	36	-13.361	-13.288	-23.836	1.00	25.58	AA	C
ATOM	459	C	ASP	A	36	-14.639	-13.439	-24.670	1.00	24.45	AA	C
ATOM	460	O	ASP	A	36	-15.669	-12.905	-24.274	1.00	25.82	AA	O
ATOM	461	CB	ASP	A	36	-12.444	-12.233	-24.501	1.00	25.98	AA	C
ATOM	462	CG	ASP	A	36	-11.205	-11.857	-23.690	1.00	26.05	AA	C
ATOM	463	OD1	ASP	A	36	-11.255	-11.923	-22.443	1.00	27.86	AA	O
ATOM	464	OD2	ASP	A	36	-10.181	-11.520	-24.320	1.00	29.62	AA	O1-
ATOM	465	H	ASP	A	36	-11.996	-14.820	-24.404	1.00	0.00	H	
ATOM	466	HA	ASP	A	36	-13.652	-12.934	-22.844	1.00	0.00	H	
ATOM	467	HB3	ASP	A	36	-13.009	-11.315	-24.661	1.00	0.00	H	
ATOM	468	HB2	ASP	A	36	-12.133	-12.565	-25.492	1.00	0.00	H	
ATOM	469	N	VAL	A	37	-14.604	-14.217	-25.766	1.00	25.05	AA	N
ATOM	470	CA	VAL	A	37	-15.760	-14.595	-26.598	1.00	24.00	AA	C
ATOM	471	C	VAL	A	37	-16.924	-15.160	-25.755	1.00	24.98	AA	C
ATOM	472	O	VAL	A	37	-18.068	-14.714	-25.890	1.00	24.53	AA	O
ATOM	473	CB	VAL	A	37	-15.298	-15.562	-27.727	1.00	25.68	AA	C
ATOM	474	CG1	VAL	A	37	-16.441	-16.189	-28.554	1.00	27.56	AA	C
ATOM	475	CG2	VAL	A	37	-14.251	-14.903	-28.645	1.00	25.94	AA	C



PRACTICAL | How to use Google Colab

practica.ipynb

File Edit View Insert Runtime Tools Help All changes saved

Files

sample_data vina condacolab_install.log

Here you have the virtual folder

+ Code + Text

```
 wget -q https://github.com/ccsb-scripts/AUTODOCK-VINA/releases/download/v1.2.5/vina_split_1.2.5_linux_x86_64
 [ ] chmod +x /content/vina/vina_split_1.2.5_linux_x86_64

 [ ] #Set up an alias for vina to be treated as a native binary
 %alias vina /content/vina/vina_1.2.5_linux_x86_64
 %alias vina_split /content/vina/vina_1.2.5_linux_x86_64
```

2. Test: MRTX1133 ligand docking into KRAS^{G12D} target protein

First we will upload the file containing the target protein (KRAS^{G12D}) with the ligand (MRTX1133) on its **true** experimentally known pose:

2.1 Uploading experimental

```
#@title 2.1 Uploading experimental
import os
from pathlib import Path
from google.colab import files

experimental_path = Path("/content/experimental/")

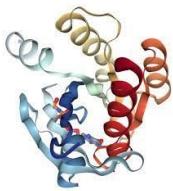
if os.path.exists(experimental_path):
    print("exp. path already exists")
if not os.path.exists(experimental_path):
    os.mkdir(experimental_path)
    print("exp. path was successfully created")

fl = files.upload();
```

Click here to execute the cell

Cells with text

Cells with code



PRACTICAL | Instructions

1. Open this Google Colab:
<https://tinyurl.com/bojospractica>
2. Read it carefully
3. Let's try it!

practica.ipynb ☆

File Edit View Insert Runtime Tools Help Last saved at March 20

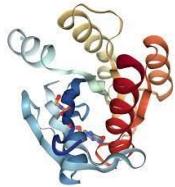
+ Code + Text

0.1. Molecular Docking

Molecular docking simulations are computational techniques that play a crucial role in drug design by emulating interactions between small molecules (ligands) and macromolecular targets (proteins). These methods computationally predict the binding mode (pose) and binding affinity of ligands within the binding sites of target proteins, thereby providing critical insights into the molecular mechanisms underlying ligand-receptor interactions.

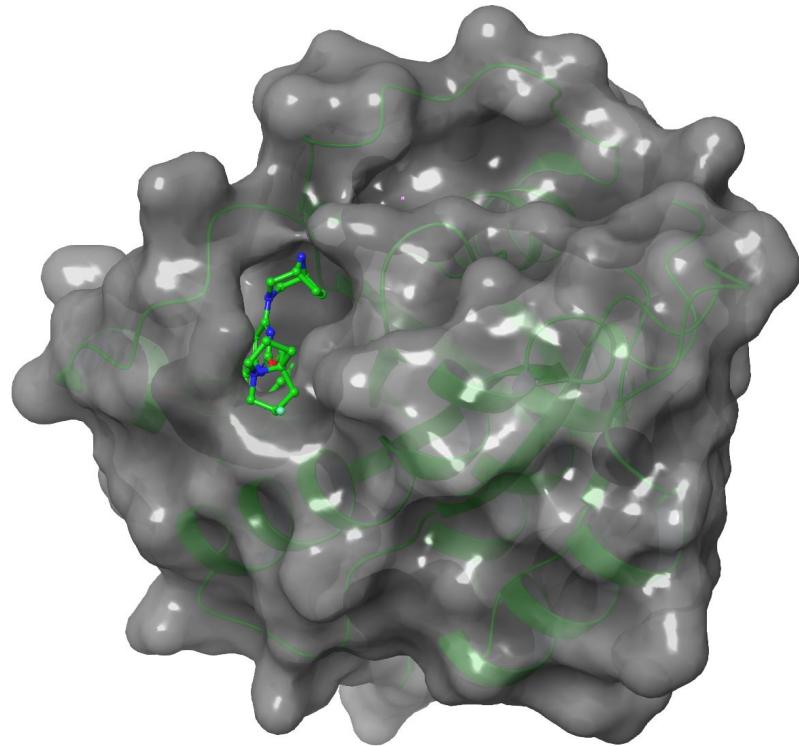
The diagram illustrates the molecular docking process:

- A protein (grey surface) with a binding site (blue surface) is shown.
- A small molecule (represented by red and white sticks) is shown separately.
- The resulting complex is shown, where the molecule is now bound within the protein's binding site.

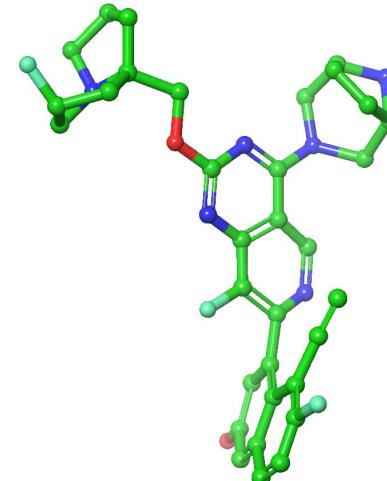


PRACTICAL | Biological Context

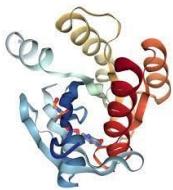
KRAS^{G12D} + MRTX1133



MRTX1133



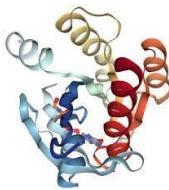
<https://tinyurl.com/krasmrtx1>
<https://tinyurl.com/ligandsdf>



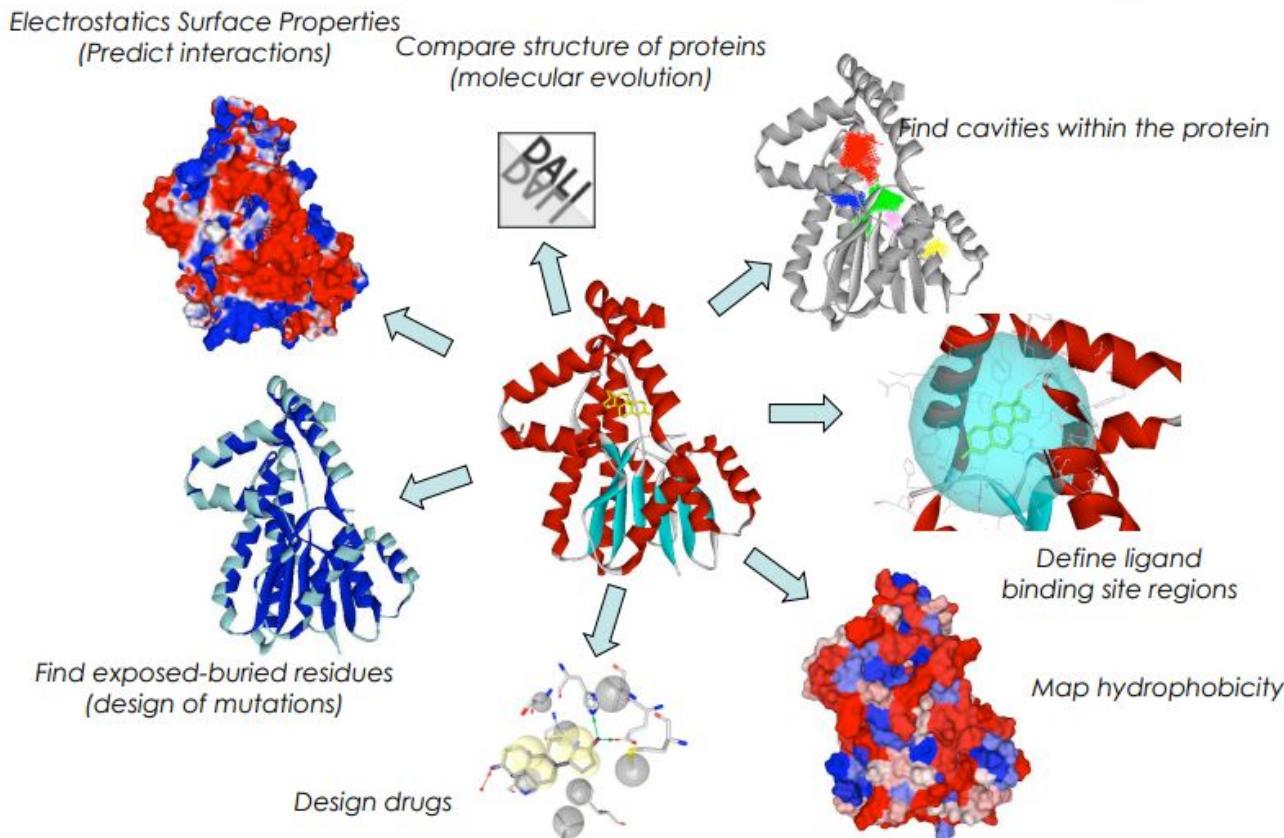
PRACTICAL | Docking

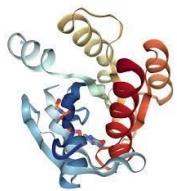
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receptor: "experimental/krasg12d_prep.pdbqt"
ligand: "experimental/mrtx1133_prep.pdbqt"
center_x: "-0.362"
center_y: "3.360"
center_z: "-24.427"
size_x: "20"
size_y: "20"
size_z: "20"

Mostrar código
```



BACKGROUND | What can we do with the structural knowledge?

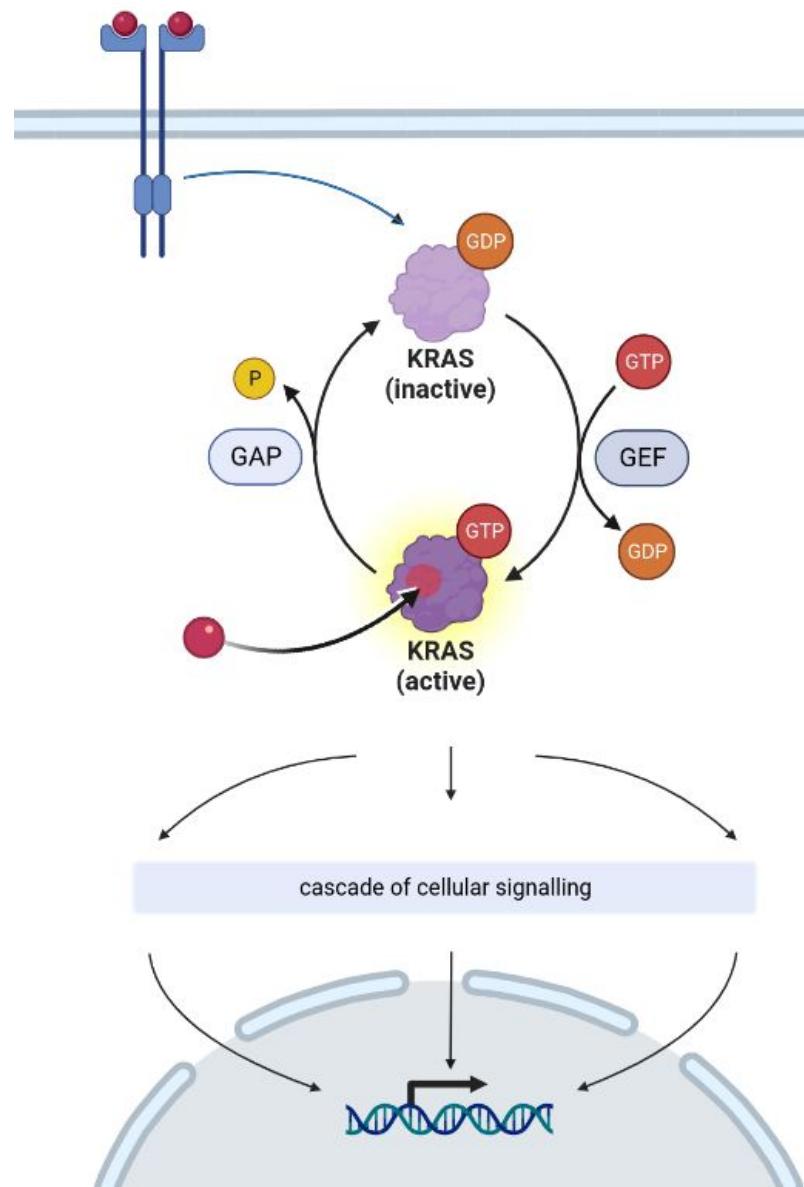


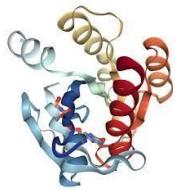


PRACTICAL | Target

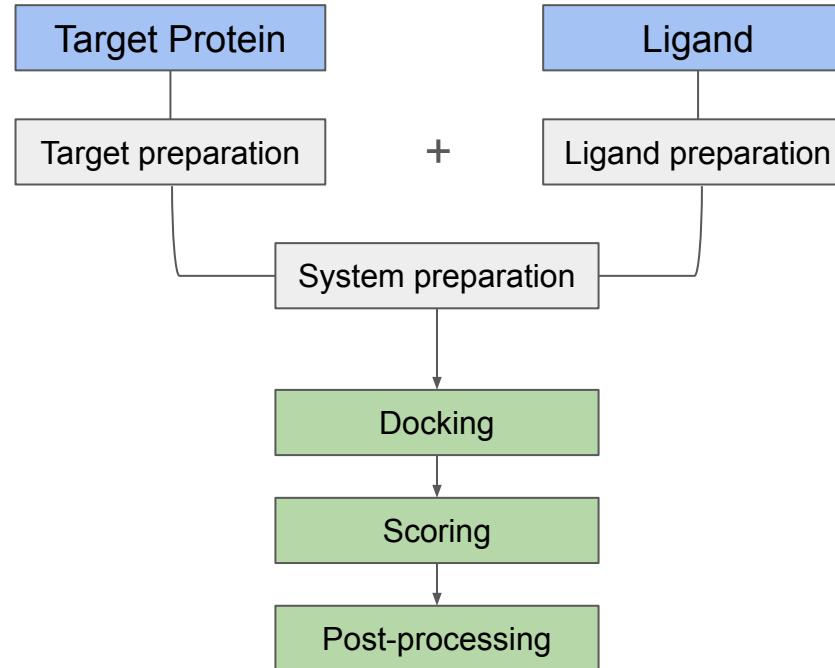
KRAS

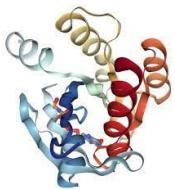
Mutation: G12D





PRACTICAL | Workflow





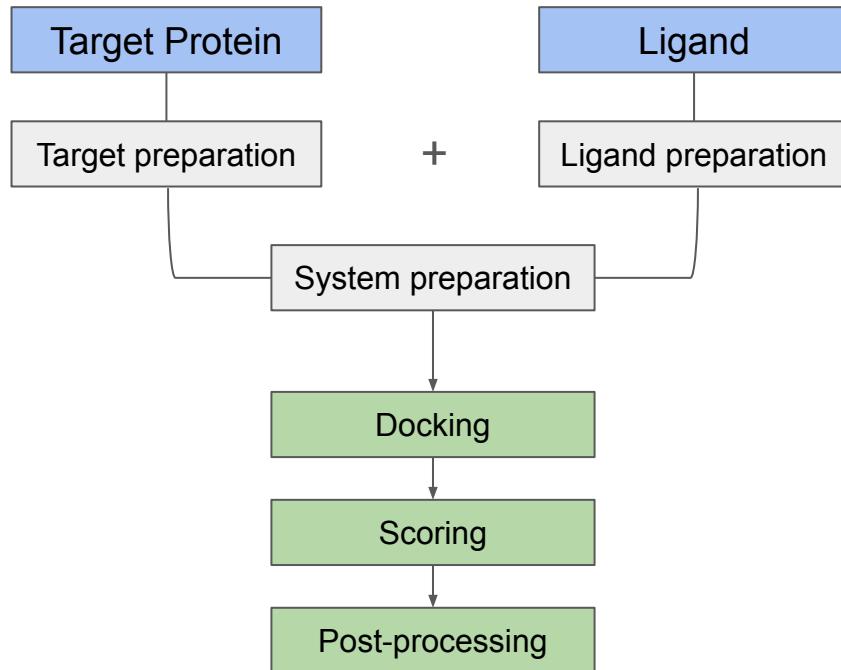
PRACTICAL | Workflow

1. Download and install the required programs (be patient!!)
2. Test: MRTX1133 ligand docking into KRAS G12D target protein
3. Virtual screening against KRAS G12D
4. Setting up and Performing Molecular Docking with AutoDOCK
5. Analysis

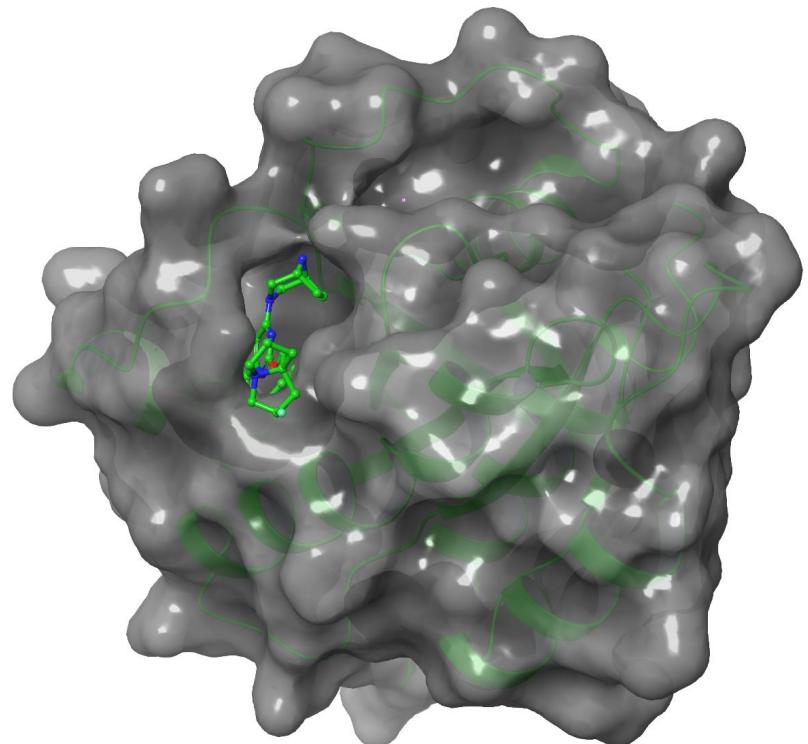
ACABAR

- Practica:

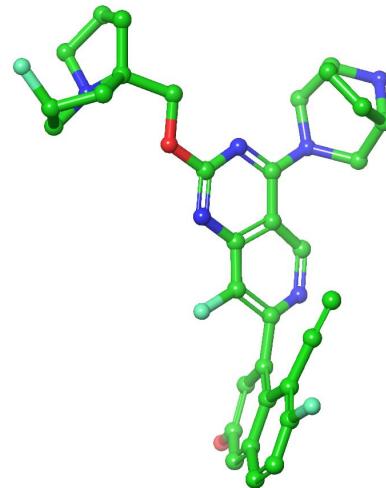
- Target: CDK2, KRAS G12D (mutacions), MPRO,
- Compostos
- /home/bubbles/ifilella/KRAS_test



KRAS^{G12D} + MRTX1133



MRTX1133



```
receptor: "experimental/krasg12d_prep.pdbqt
```

```
ligand: "experimental/mrtx1133_prep.pdbqt
```

```
center_x: "-0.362
```

```
center_y: "3.360
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center_z: "-24.427
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```
size_x: "20
```

```
size_y: "20
```

```
size_z: "20
```