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# Protein structure

Color index :

Main text

IMPORTANT

*Extra Info*

Drs Notes

Foundation Block - Biochemistry Team

Revised & Approved by:
Shayma Abdullah Alghanoum
Faisal Alotaibi

MED439
KING SAUD UNIVERSITY

# Objectives:

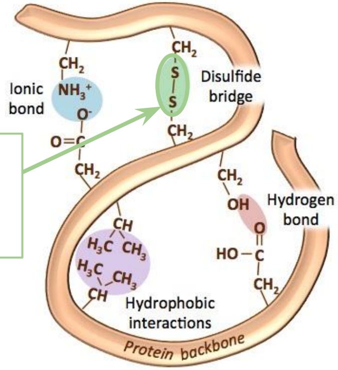
- Understand the peptide bonding between amino acids.
- Explain the different levels of protein structure and the forces stabilizing these structures and what happens when the protein is denatured.
- Define the a-helix and β-sheet as the most commonly encountered secondary structures in a protein molecule.
- Correlate the protein structure with function with hemoglobin as an example.
- Understand how the misfolding of proteins may lead to diseases like Alzheimer’s or prion disease.

# What are proteins ?

- Definition: Proteins are large, complex molecules that play many critical roles in the body.
- Proteins are made up of : hundreds or thousands of smaller units called amino acids, (protein building blocks) which are attached to one another in long chains.
- There are mainly 20 different types of amino acids that can be combined to make a protein.
- The sequence of amino acids determines each protein's unique three - dimensional (3D) structure and its specific function.
- The importance of proteins ?
  - They do most of the work in cells .
  - structure, function, and regulation of the body's tissues and organs.
- Proteins can be described according to their large range of functions in the body e.g :
  - antibody , enzyme , messenger , structural component and transport/storage.

A helpful video

# Primary structure



s.s bond = Disulfide bond
When this bond occurs ? If the cysteines are close to each other
Why ? There [SH] in their R group

- It is the linear sequence of amino acids.
- How to determine the primary structure sequence ?
  - DNA sequencing "indicate way"
  - Direct amino acids sequencing "direct way by analysing the amino acids "

covalent bond in the primary structure of protein

Peptide bond

They can be break by prolonged exposure to a strong acid or base at elevated temperature to hydrolyze (break) these bond or by using enzymes
- **Note that** : They are not broken by conditions that denature proteins such as heat -

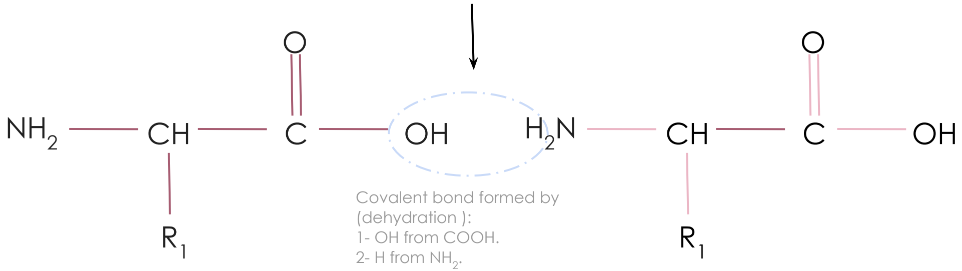
Disulfide bond (if any)

helps with ? Stimulating folding

# Peptide bonds (amide bond)

formed between a-carboxyl group of an amino acid and a-amino group of the other amino acid.

Two amino acids condense to form



$NH_2-CH(R_1)-C(=O)-OH \quad H_2N-CH(R_1)-C(=O)-OH$

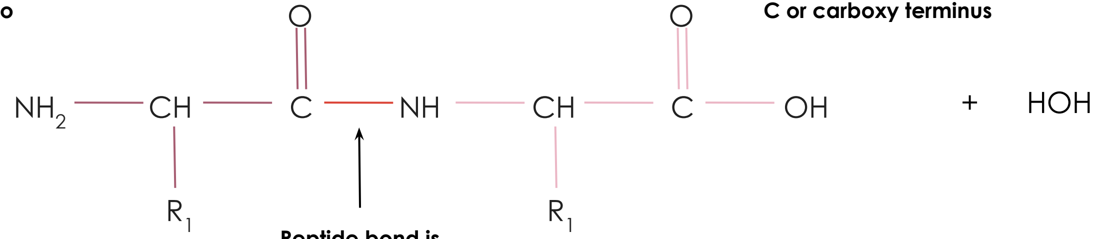
**Water is eliminated**

Covalent bond formed by (dehydration ):
1- OH from COOH.
2- H from $NH_2$.
"removal of water".

a dipeptide . If there are more it becomes a polypeptide. Short polypeptide chains are usually called peptides while longer ones are called proteins

**N or amino terminus**

We always read from **N- terminus** to **C-terminus**



$NH_2-CH(R_1)-C(=O)-NH-CH(R_1)-C(=O)-OH \quad + \quad HOH$

**C or carboxy terminus**

**Peptide bond is formed**

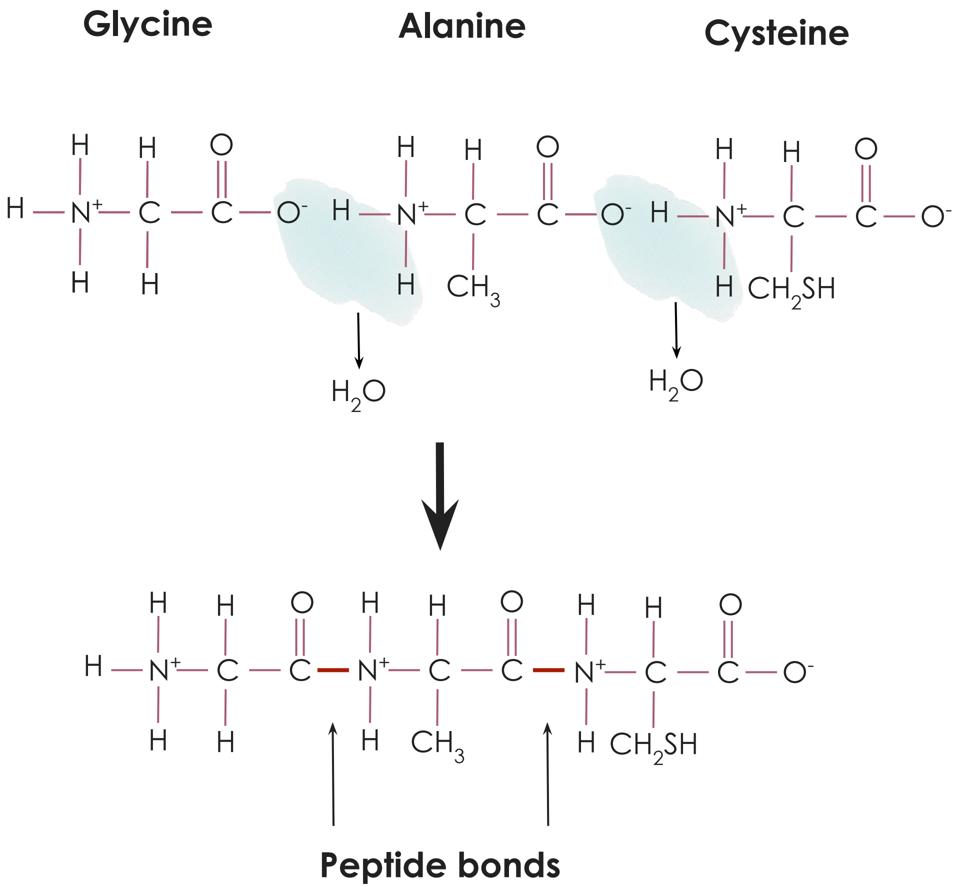
Residue 1

Residue 2

amino acid after bonding = residue , In other word Residue : amino acid in a peptide chain

# Peptide bonds (amide bond) , contd..

- Each amino acid in a chain makes two peptide bonds.
- The amino acids at the two ends of a chain make only one peptide bond.
- The amino acid with a free amino group is called amino terminus or $NH_2$-terminus.
- The amino acid with a free carboxylic group is called carboxyl terminus or COOH-terminus.



# Peptides

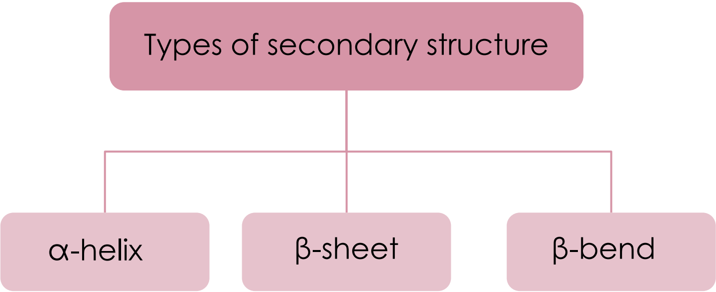
- Amino acids can be polymerized to form chains:

  - if you have **two amino acids** they will form **dipeptide** that has **one peptide bond.**
  - if you have **three amino acids** they will form **tripeptide** that has **two peptide bond.**
  - if you have **four amino acids** they will form **tetrapeptide** that has **three peptide bond.**
  - if you have **Few** ( 2-20 amino acids ) they will form **oligopeptide.**
  - If you have **more** ( more than 20 amino acids ) they will form **polypeptide.**

Number of peptide bonds = number of amino acids -1

# Secondary structure

- It is regular arrangements of amino acids that are located near to each other in the linear sequence ( **Excluding** the side chain ).
- Excluding the conformations (3D arrangements) of its side chains.
- for the secondary structure , we do not look at the **R side chains** nor do we look at the **hydrophobic interactions** that give it its 3D structure so we exclude that.. We **only** look at the hydrogen bonds.



Types of secondary structure

- α-helix
- β-sheet
- β-bend

**2dry structure**
1- α-helix

2dry structure
2 - β-sheet

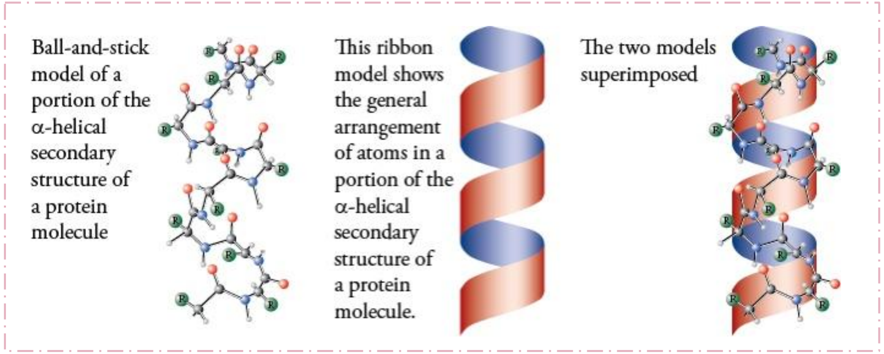
2dry structure
3 - β-bends

2dry structure
4 - other examples

# α-helix

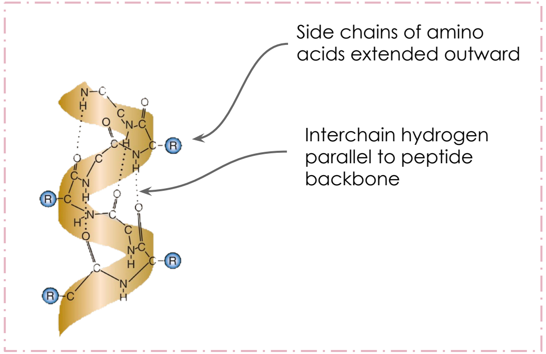
A helpful video

- It is a right-handed spiral, in which side chains of amino acids extended outward.(Anti-clockwise).
- Hydrogen bonds: Stabilize the a-helix. (form between the peptide bond carbonyl oxygen and amide hydrogen).
- Amino acids per turn: Each turn contains 3.6 amino acids.
- a-helix forms between amino acids in the same strand.
- acids per turn: Each turn contains 3.6 amino acids. بمعنى اللفة الوحدة بتسوي رابطه مع ثلاث احماض امينية والرابعه بتسوي رابطه هيدروجينية مع الأولى فكل لفه فيها ٣ ونص تقريبا
- Amino acids that disrupt an a-helix:
  - Proline → imino group,interferes with the smooth helical structure. proline has a ring structure that disrupts the helical structure
  - Glutamate, aspartate, histidine, lysine or arginine → form ionic bonds. The side chains are charged " Polar amino acids "
  - Bulky " big " side chain such as tryptophan , benzene.
  - Branched amino acids at the β-carbon, such as valine or isoleucine.


Ball-and-stick model of a portion of the α-helical secondary structure of a protein molecule

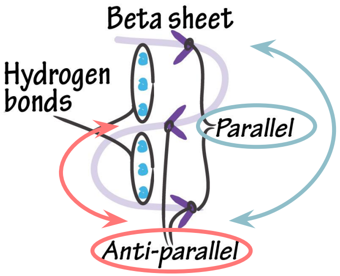
This ribbon model shows the general arrangement of atoms in a portion of the α-helical secondary structure of a protein molecule.

The two models superimposed

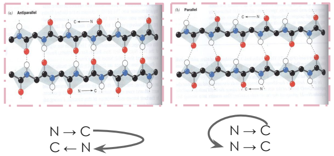

Side chains of amino acids extended outward

Interchain hydrogen parallel to peptide backbone

# β-sheet (Composition of αβ-sheet)



- Two or more polypeptide chains make hydrogen bonding with each other.
  - "beta sheet could be a long polypeptide while the alpha helix is just one polypeptide chain".
- Also called pleated sheets because they appear as folded structures with edges.
- Hydrogen bonds: Stabilize the β-sheet".
- Antiparallel : has beta turn & in the dotted lines picture the lines are straight because the H bonds are stable نقدر نقول لها لفة مرتبه وعشان هاللفة مرتبة بنلقى الروابط الهيدروجينية فيها مستقرة ومستقيمة يعني مرتبه بعد
- Parallel : in the dotted lines picture the lines are not straight because the H bonds are less stable نقدر نقول ان الـلفة مو مرتبه وبالتالي الروابط الهيدروجينية اقل استقراراً واقل ترتيباً

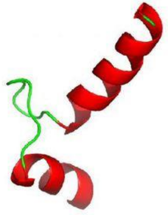


# β-bends ( reverse turns )

- Reverse the direction of a polypeptide chain.
- Usually found on the surface of the molecule and often include charged residues.
- The name comes because they often connect successive strands of antiparallel β-sheets.
- β-bends are generally composed of four amino acid residues, proline or glycine are frequently found in β-bends.
- glycine : smallest amino acid which makes it easier to bend.
- Proline: due to bending and bending due to lack of hydrogen bonds.

# Other secondary structure examples

## A) Nonrepetitive secondary structure :



- A significant portion of globular protein’s structure may be irregular or unique

(بمعنى فيها اجزاء ما نلقاها باحماض امينيه ثانيه) اجزاء ماتتكرر

- e.g : loop or coil conformation.

# Other secondary structure examples

## B) Supersecondary structures ( motifs ) :

A helpful video

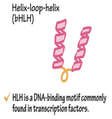
- A combination of secondary structural elements.

“that is, a-helices, β-sheets, and coils and These form primarily the core ( interior ) region of the molecule. They are connected by loop regions”

Example of Supersecondary structures ( motifs )

α-helix motifs

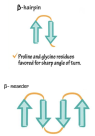
α α -motif: two α helices together



✓ HLH is a DNA-binding motif commonly found in transcription factors.

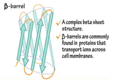
β-motifs

β hairpin: reverse turns connect antiparallel β sheets



✓ Proline and glycine residues favored for sharp angle of turn.

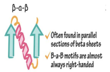
β barrels: rolls of β sheets



✓ A complex beta sheet structure.
✓ β-barrels are commonly found in proteins that transport ions across cell membranes.

α + β-motifs

β α β motif: a helix connects two β sheets



✓ Often found in parallel sections of beta sheets
✓ B-a-B motifs are almost always right-handed

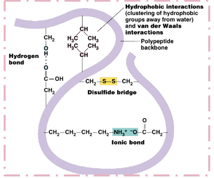
# Tertiary structure

- What is it ?

  - It is the three-dimensional (3D) structure of an entire polypeptide chain including side chains.
- Domain :

  - is the fundamental functional and 3D structural units of a polypeptide .
  - Polypeptide chains that are greater than 200 amino acids in length generally consist of two or more domains.
  - The core of a domain is built from combinations of supersecondary structural elements (motifs) and their side chains.
  - Domains can be combined to form tertiary structure.

Supersecondary structural elements (motifs) → The core of a domain → domain → Tertiary structure.



Interactions stabilizing tertiary structure

**Disulfide bonds**

a covalent linkage formed from the sulfhydryl group (-SH) of each of two cysteine residues to produce a cysteine residue

**Hydrophobic interaction**

Amino acids with nonpolar side chains tend to be located in the interior of the polypeptide molecule , where they associate with other hydrophobic amino acid

**Hydrogen bonds**

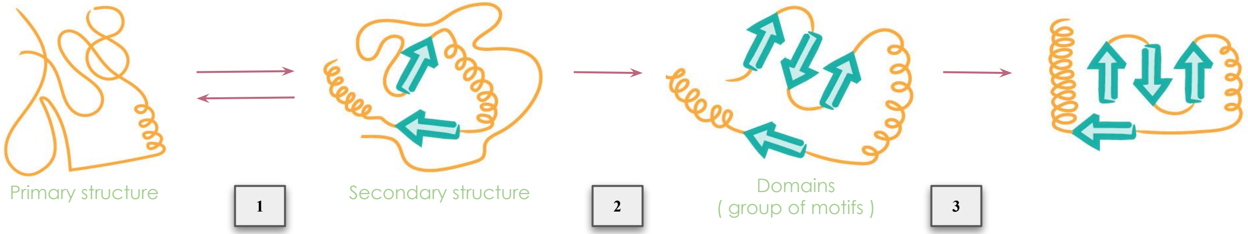
Amino acid side chains containing oxygen - or nitrogen- bound hydrogen

**Ionic interactions**

Negatively charged groups can interact with positively charged groups such as : carboxylate group (– COO–) in the side chain of aspartate and amino group (– $NH_3^+$)

# Tertiary structure, contd..

- Interactions between the side chains of amino acids determine how a long polypeptide chain folds into the intricate three-dimensional shape of the functional protein.



Primary structure

Formation of secondary structure

Secondary structure

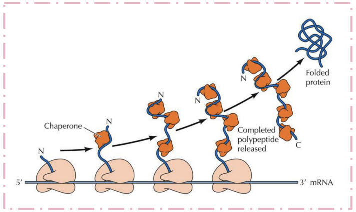
Formation of domains

Domains
( group of motifs )

Formation of final protein monomer

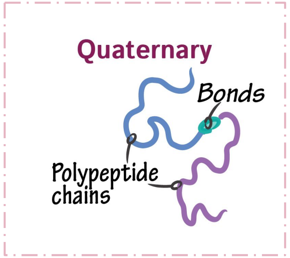
- Role of chaperons in protein folding:
  - Chaperons are a specialized group of proteins, required for the proper folding of many species of proteins. بمعنى اخر يتأكد بأن البروتين قاعد يتكوّن بالطريقه الصحيحه
  - They also known as "heat chock" proteins. عرضوا البروتين للحرارة ولقوا انه يزيد عند وجود الحراره
  - The interact with polypeptide at various stages during the folding process.

  Cuz they facilitate the folding process & make sure that there's not any mistakes during the process



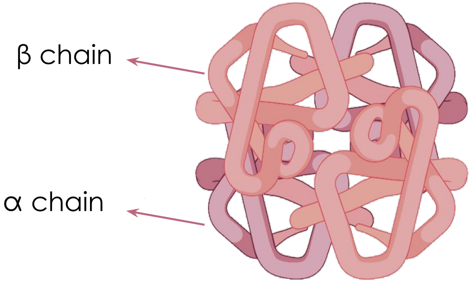
How Chaperons helps folding the protein:

# Quaternary structure



- Some proteins contain two or more polypeptide chains that may be structurally identical (homomeric) or totally unrelated (heteromeric).
- Each chain forms a 3D structure called subunit.
- According to the number of subunits : dimeric, trimeric, ... or multimeric.
- Subunits may either function independently of each other, or work cooperatively e.g. hemoglobin .

## Hemoglobin



- Hemoglobin: a globular protein.

  Spherical ( globe-like ) كرويه الشكل
- A multisubunit protein is called oligomer

  ( An oligomer usually refers to a macromolecular complex )
- Composed of $a_2 \beta_2$ subunits (4 subunits).
- Two same subunits are called protomers.

  ( a protomer is the structural unit of an oligomeric protein )

# Denaturation of proteins

- It results in the unfolding and disorganization of the protein’s secondary and tertiary structures.
- Most proteins, once denatured, remain permanently disordered.
- Denatured proteins are often insoluble and, therefore, precipitate from solution.

e.g the protein in the egg “ albumin “ once we put in in hoat it will be denatured and become insoluble

**Denaturation agents**

- Heat
- organic solvents
- Mechanical mixing
- Detergents
- strong acids or bases
- Ions of heavy metals ( e.g. lead and mercury )

# Proteins misfolding

- Every protein must fold to achieve its normal conformation and function.
- Abnormal folding of proteins leads to a number of diseases in humans.
- To wrap it up:
  - Misfolding in protein leads to disorders,
  - Amyloid protein when misfolded leads alzheimer’s
  - Prion disease occurs when prion protein is misfolded

| | Alzheimer’s disease | Creutzfeldt-Jacob or prion disease |
|---|---|---|
| Type of protein | β amyloid protein is a misfolded protein .<br>Amyloid is aggregates of misfolded proteins outside neurons, it interfere with neuron's ability of sending messages | Prion protein is present in normal brain tissue , in diseased brains, the same protein is misfolded. |
| The effect of the protein | It forms fibrous deposits or plaques in the brains of Alzheimer’s patients | It forms insoluble fibrous aggregates that damage brain cell |

# Take home messages

- Native conformation of the protein is the functional, fully folded protein structure
- The unique 3D structure of the native conformation is determined by its primary structure, i.e. the amino acid sequence
- Interactions of between the amino acid side chains guide the folding of the polypeptide chain to form secondary, tertiary and sometimes quaternary structures that cooperate in stabilizing the native conformation of the protein.
- Protein denaturation results in unfolding and disorganization of of the protein’s structure, which are not accompanied by hydrolysis of peptide bonds.
- Disease can occur when an apparently normal protein assumes a conformation that is cytotoxic, as in the case of Alzheimer disease and Prion disease.

# Quiz

| | | | |
|---|---|---|---|
| Q1 : Are a specialized group of proteins, required for the proper folding | | | |
| A ) Beta amyloid | B ) Prion | C ) Hemoglobin | D ) Chaperons |
| Q2 : Subunits are the building blocks of : | | | |
| A ) Primary Protein | B ) Secondary Protein | C ) Tertiary Protein | D ) Quaternary Protein |
| Q3 : Following the previous question, each subunit works …. | | | |
| A ) Independently | B ) Cooperatively | C ) both A&B | D ) Not specified |
| Q4 : The name of the bond between the two cysteine **proteins** is called : | | | |
| A ) Peptide bond | B ) Disulfide bond | C ) Hydrogen bond | D ) Both A and B |
| Q5 : the linear sequence of amino acids in protein is: | | | |
| A ) Primary Protein | B ) Secondary Protein | C ) Tertiary Protein | D ) quaternary Protein |
| Q6 : A tripeptide has : | | | |
| A ) 1 peptide bond | B ) 2 peptide bond | C ) 3 peptide bond | D) 4 peptide bond |

## SAQs :

Q1: What causes alzheimer's disease ?

Q2: What is the structural unit of an oligomeric protein?

Q3: Compare the stability in hydrogen bonds between parallel direction and anti-parallel direction?

Q3: A disulfide bond links two residues near to each other. What are these residues?

★ **MCQs Answer key:**

1) D 2) D 3) C 4) B 5) A 6)B

★ **SAQs Answer key:**

1) A misfolding in Beta Amyloid protein which forms fibrous walls in the brains of alzheimer's patients
2) protomer
3) H bonds are more stable in anti-parallel direction (or the parallel direction is less stable).
4) 2 Cysteine

## Girls team:

Alia Zawawi
Nada Babilli
Rania Aqil
Reem alamri
Reema Alomar
Reem Alqahtani
Renad Alhumaidi
Shaden Alobaid
Noura Alsalem
Lama Alahmadi
Sadem Alhazmi
Somow Abdulrahman
Budoor Almubarak
Samar Almohammedi
Nuha Alkudsi
Norah Alsheikh
Muneerah Alssdhan
Mayasem Alhazmi
Noura alshathri
Duaa Alhumoudi

## Boys team:

Mansour albawardi
Hassan alshuraf
Abdulrahman almbki
Mohammed alsayari
Abdullaziz alomar
Abdulaziz alrabiah
Saud alrasheed
Abdullah almazro
Hamad almousa
Ahmad alkhayat

> “ You can’t have a better tomorrow, if you’re still thinking about yesterday “

Made by

Shatha Aldhohair

Mishal Althunayan

Biochemistry439@gmail.com

@Biochemistry439