INTERNATIONAL COLLEGE OF PHARMACEUTICAL INNOVATION
国际创新药学院

Class	Pharm, BioPharm
Course	Fundamentals of Medicinal & Pharmaceutical Chemistry
Code	FUNCHEM.1
Title	Chemistry in Medicine and the Health Sciences: An introductory lecture
Lecturer	Prof. Xinchen Teng
Date	2024-10-09

Why Study Chemistry

The principles of chemistry are fundamentally embedded in health and biological sciences.

To the untrained eye it may be not obvious that chemistry is at the heart of invention and understanding in medical and biological systems.

Chemistry can provide the answers to the *how and why* questions constantly encountered in medical and biological disciplines.

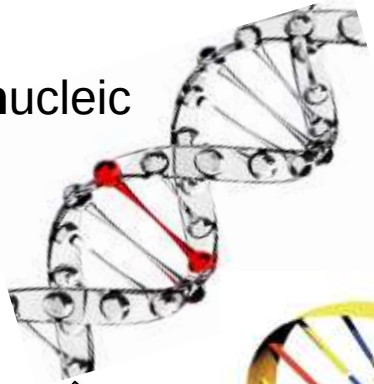
Our goal is to show you how to move confidently between the chemical, biological and medical scientific worlds.

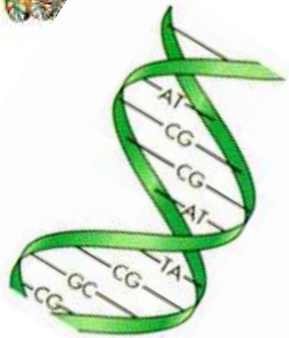
Note:
this lecture is an introduction; all topics will be covered in this years courses

Molecule of Life: From Letters to Structure

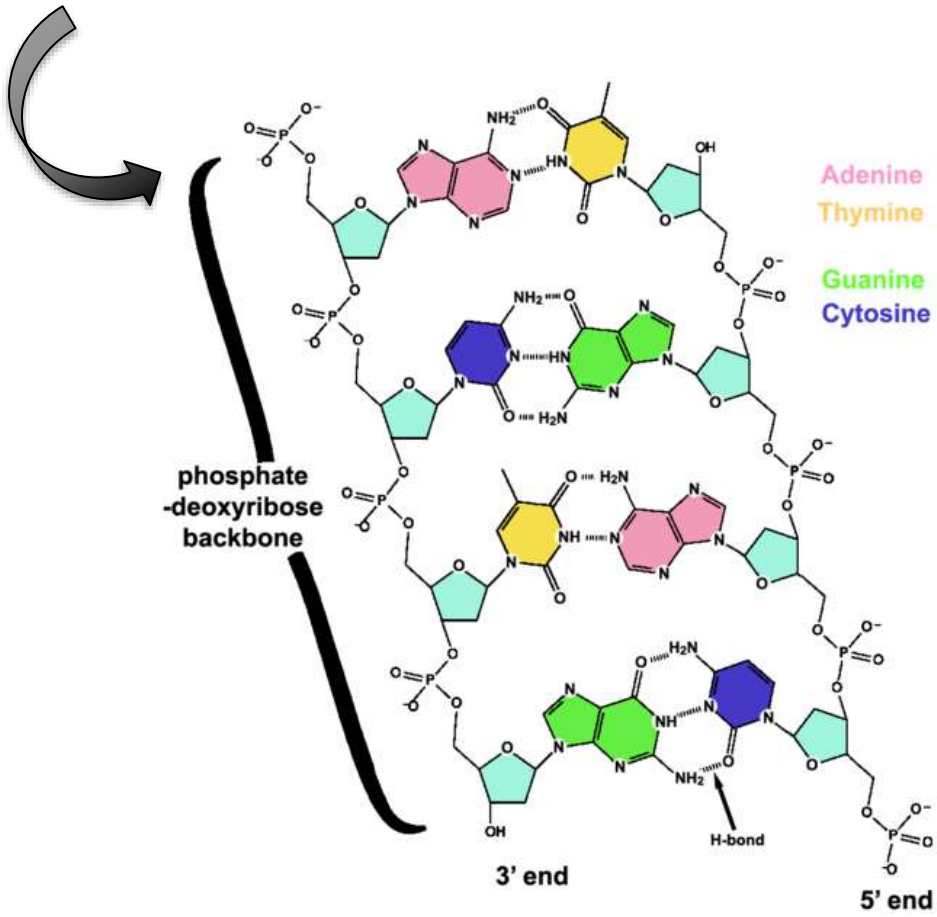
DNA

Deoxyribo**n**ucleic **a**cid





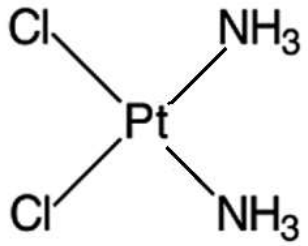
Molecule of Life: From Letters to Structure



It is at the level of chemical structure that fundamental understanding can be found

Discovery and Understanding of Cisplatin

The invention of the anticancer drug cisplatin is a story of chemistry hidden in the science of biology.

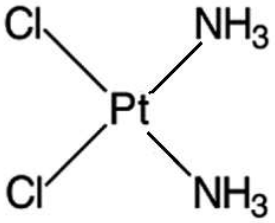


Cisplatin has broad spectrum anticancer activity and is particularly effective against testicular and ovarian tumours, head, neck and bladder cancers.

Cisplatin is often used in combination with other drugs such as vinblastin or bleomycin.

With the use of cisplatin in combination chemotherapy testicular cancer has gone from being 80% incurable to 95% curable.

Dr Barnett Rosenberg and Cisplatin



Why chose Pt ?

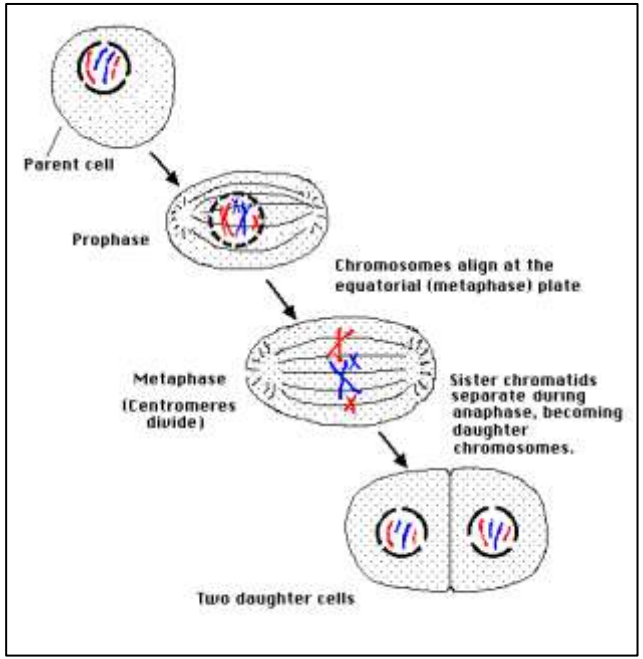
Discovered cisplatin by serendipity

	1 IA												13 IIIA	14 IVA	15 VA	16 VIA	17 VIIA	18 VIIIA	
1	1 H	2 IIA																2 He	1
2	3 Li	4 Be											5 B	6 C	7 N	8 O	9 F	10 Ne	2
3	11 Na	12 Mg	3 IIIV	4 IVB	5 VB	6 VIB	7 VIIB	8	9 VII	10	11 IB	12 IIB	13 Al	14 Si	15 P	16 S	17 Cl	18 Ar	3
4	19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr	4
5	37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe	5
6	55 Cs	56 Ba	57-71	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn	6
7	87 Fr	88 Ra	89-103	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rg	112 Cn	113 Uut	114 Fl	115 Uup	116 Lv	117 Uus	118 Uuo	7

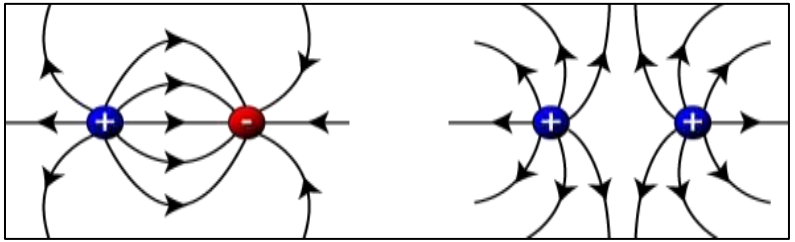
Experimental Observations Sparks Curiosity

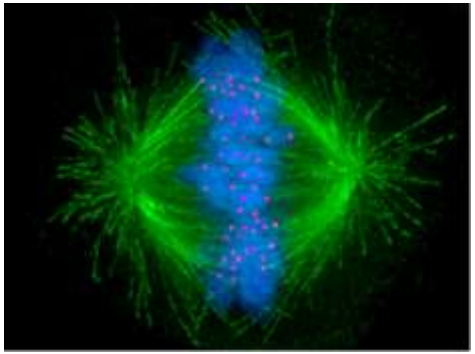
Similarity between mitotic spindles during cell division and force lines of electric fields ?

Cell division



Electric field





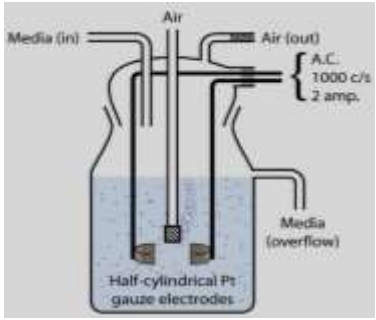
Fluorescence image of metaphase

Rosenberg's Experiment

E. coli bacteria cultured at 37°C in aerated medium containing -

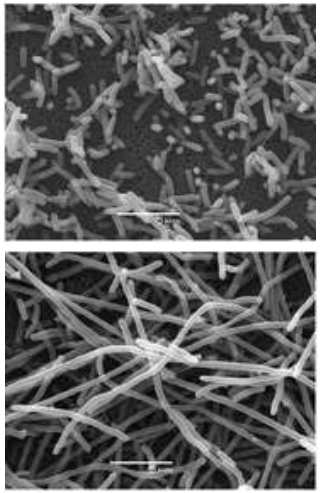
NH_4Cl, NaCl, $MgCl_2$, Na_2SO_4, glucose,
Na_2HPO_4/NaH_2PO_4 (pH 7 buffer)

Pt electrodes used in order to subject bacteria to electric fields.



Rosenberg's Results

- Inhibition of normal cell division.
- The bacteria grew into rod like long filaments.
- Cell division inhibited but no effect on growth of cells.



Rosenberg's Control Experiment

Control experiments showed that electrolysis of the media alone (without *E. coli*) and then growing *E. coli* in the media (without further electrolysis) afterwards also gave rise to the inhibition of normal cell division.

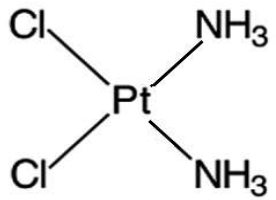
Rosenberg's Conclusions

Inhibition of cell division was shown to have nothing to do with electrical fields.

Explained by the unexpected formation of Pt compounds due to a reaction of the electrode with components of the cell media.

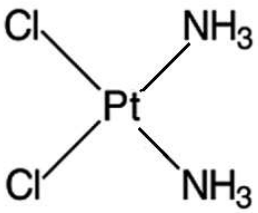
Further investigation of the Pt compounds being formed lead to the specific discovery of cisplatin.

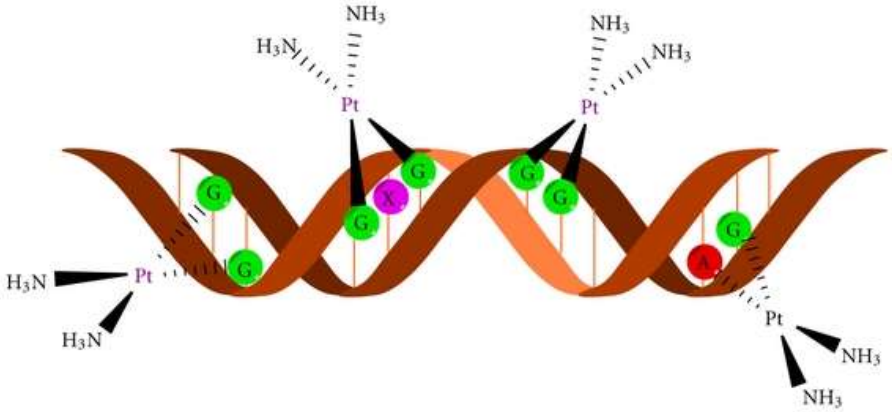
These results lead to its testing as an anticancer agent



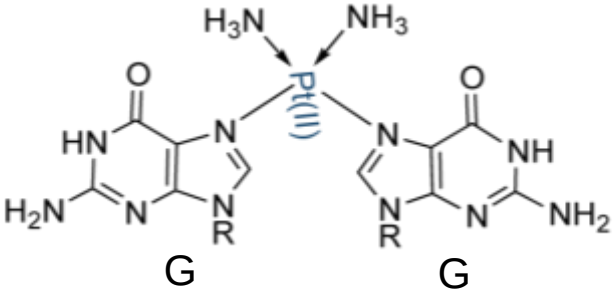
Cisplatin: How Does it Work

Cisplatin reacts with a nitrogen atom on two guanine base pairs forming two nitrogen to Pt bonds which inhibits cell replication.





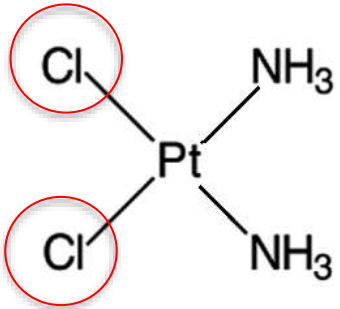
Structural View



*Cis*platin versus *Trans*platin

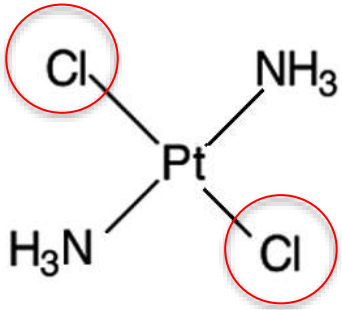
Note: cis means on the same side; trans means on opposite sides

Cisplatin



~95% cure rate for testicular cancer

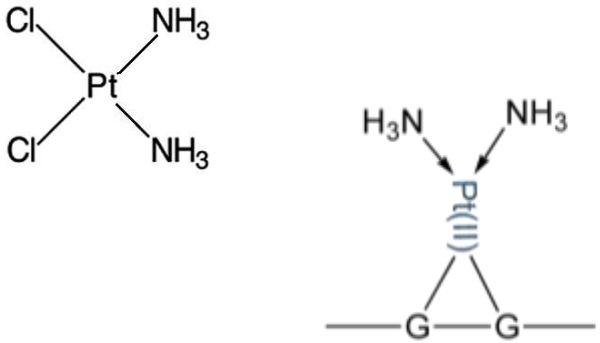
Transplatin



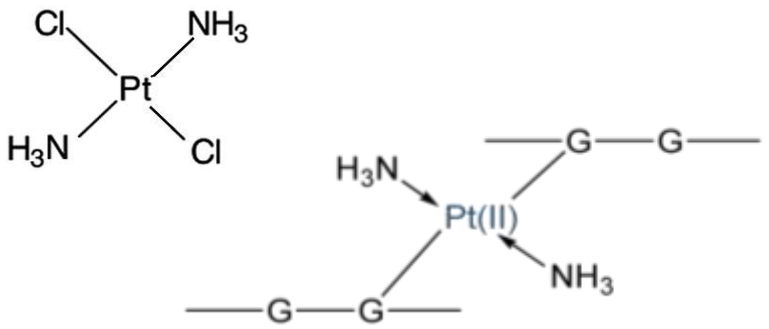
trans form is inactive !

but why when
it looks so similar to cisplatin ?

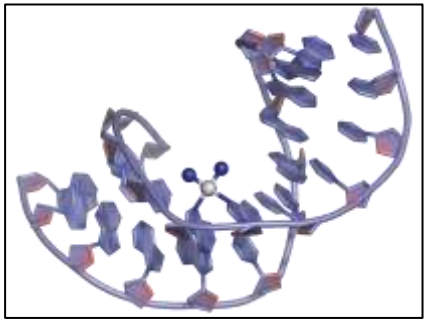
Answers are in the Chemistry and Cell Biology



cisplatin forms intra-strand crosslinks:
poorly repaired



trans-platin forms inter-strand crosslinks:
repaired more efficiently



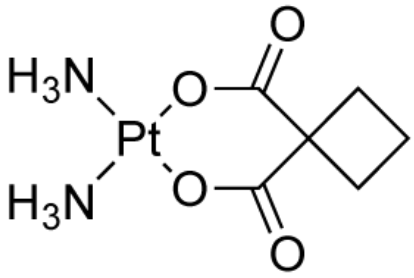
⇨ cancer therapeutic

more chemically reactive than cisplatin leading to its breakdown *in vivo* too quickly

⇩

inactive

From Understanding Comes Improvements



carboplatin

Lower chemical reactivity than cisplatin

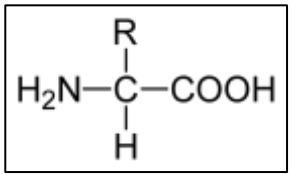
gives rise to improved therapeutic efficacy, less toxicity with less severe side effects

and

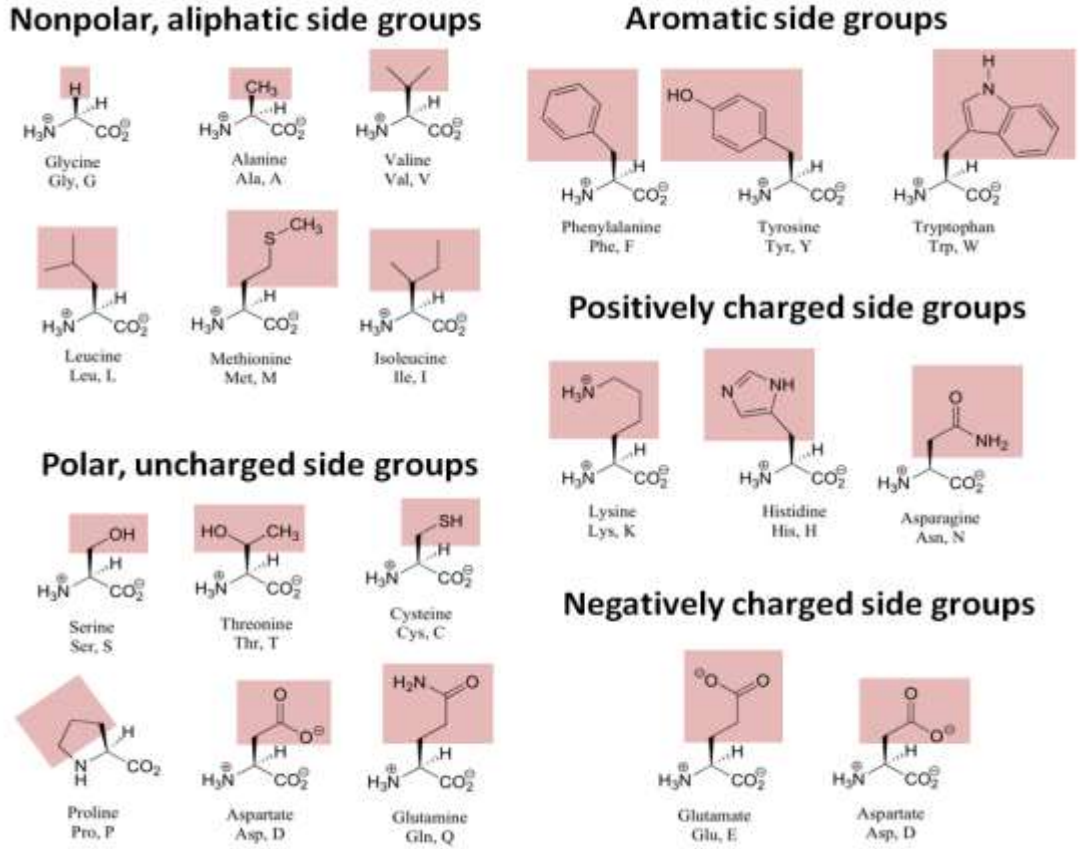
the story continues today with much research still on-going.

Amino Acids: Building Blocks of Proteins

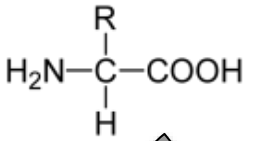
Proteins are large biomolecules consisting of long chains of amino acid residues



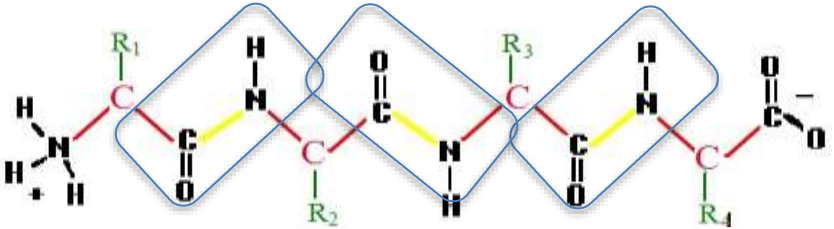
20 naturally occurring amino acids give rise to all proteins, enzymes, hormones, antibodies, all encoded for by the DNA



Covalent Joining the Amino Acid Building Blocks

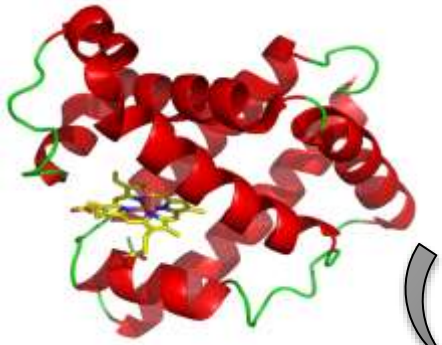


Amino acid:
average molecular mass ~110 Daltons (Da)



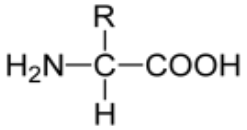
amide bond formation
polypeptide

Myoglobin
molecular mass
~ 17,000 Da

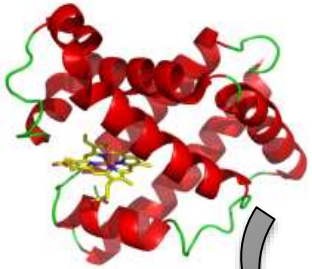


Haemoglobin
molecule mass
of ~ 65,000 Da

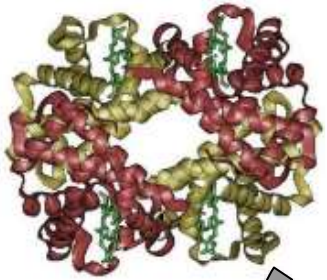
Counting How Many Amide Bonds ?



153 amino acid residues in myoglobin



4 myoglobins in haemoglobin



~280 million haemoglobins in a red blood cell

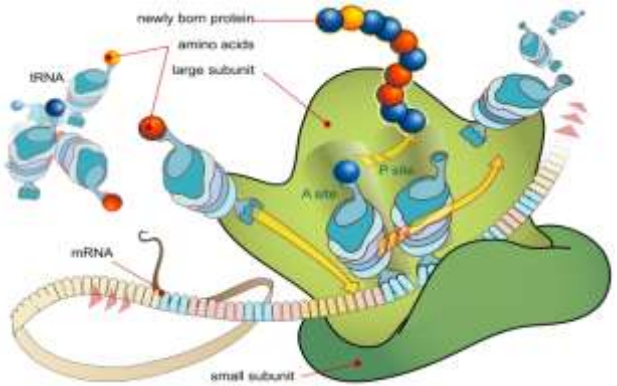
~ 2-3 x10^{13} (20 – 30 trillion) in a human

Sickle cell anemia

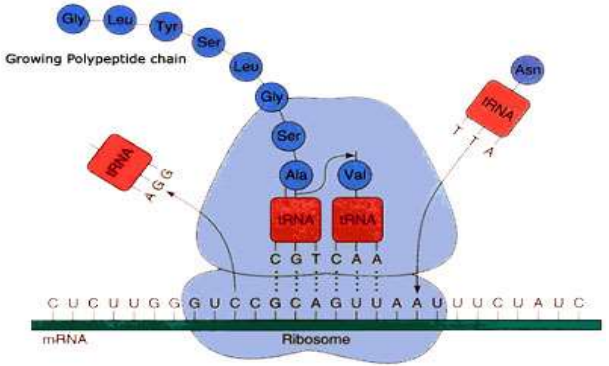
Caused by the mutation of a single nucleotide (Adenine to Thymine) of the β-globin gene, which results in one glutamate amino acid being substituted by a valine

Differing Views of Protein Bio-synthesis

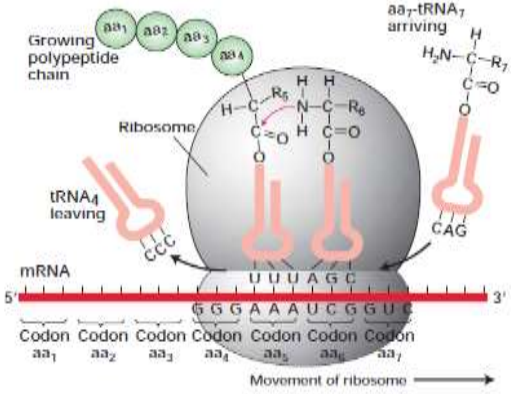
Cellular view



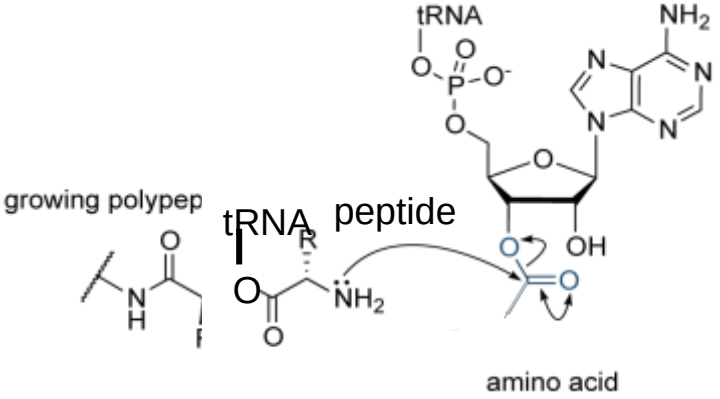
Pictorial view



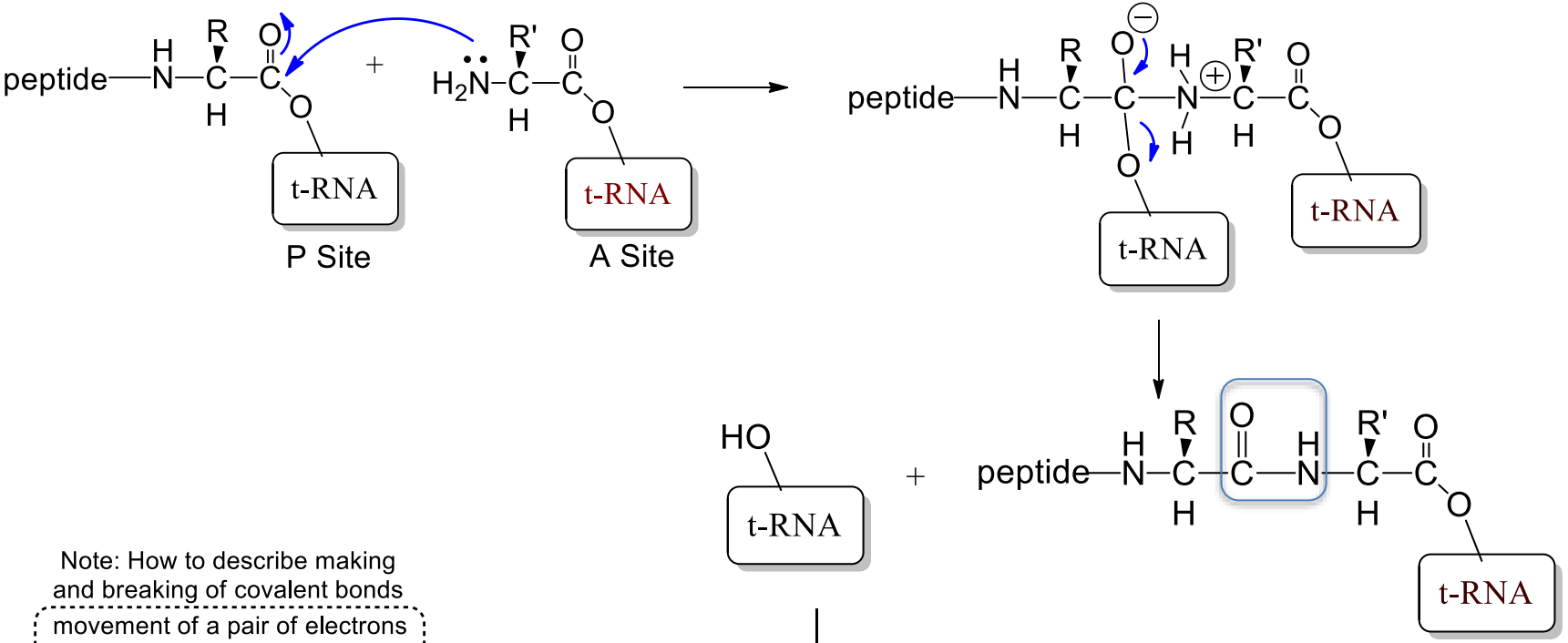
Semi-structural view



Amide bond forming view

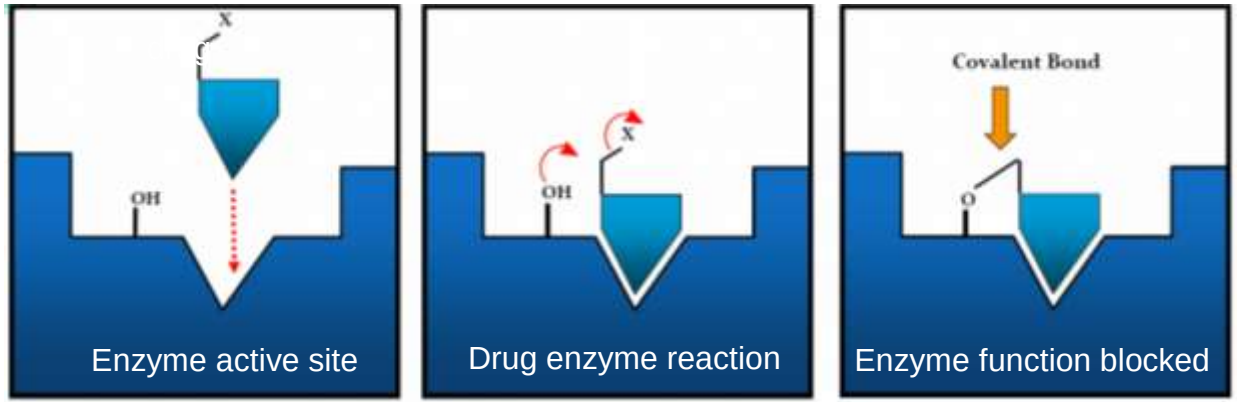


Chemical Mechanism of Amide Bond Formation in Protein Biosynthesis



Enzyme Inhibition for Therapeutic Effect

From Schematics to Chemical Reaction Mechanisms



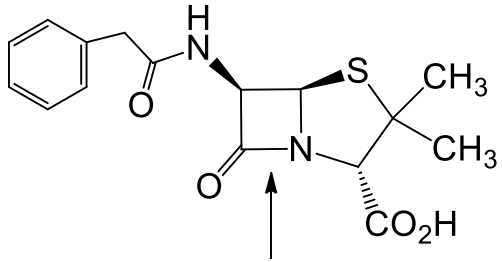
To inhibit an enzyme from functioning, the chemist can design adrug which binds irreversibly to the active site and block itpermanently.

These types of drugs typically react with an amino acid at the activesite of the enzyme to form a covalent bond.

Amino acids such a serine which has a reactive OH group is commonly present in enzyme active sites.

What is the Chemistry Behind Penicillin ?

Alexander Fleming



Penicillin G

β-lactam (cyclic amide)

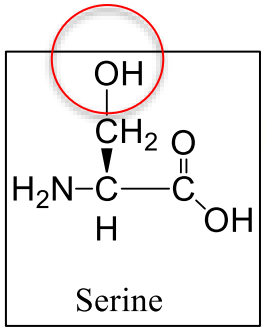
The β-lactam ring is central to its mode of action

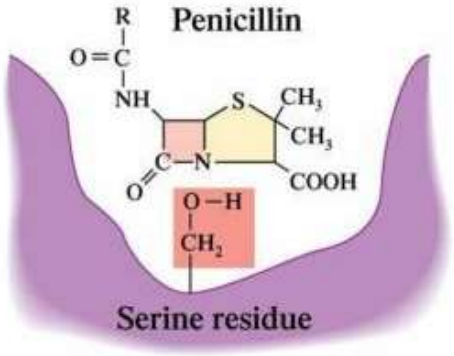
Bacterial cell wall is made up of long chains of sugars joined together by short peptide links which make the wall rigid.

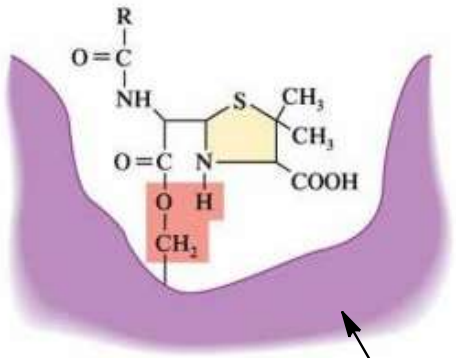
The bacterial enzyme transpeptidase catalyses the peptide cross linking step of cell wall construction making it rigid and strong.

Inhibition of transpeptidase enzyme prevents the formation of the bacterial cell wall and leads to bacterial cell death (antibiotic).

Penicillin Reacts with Serine Amino Acid Residue in Transpeptidase Enzyme

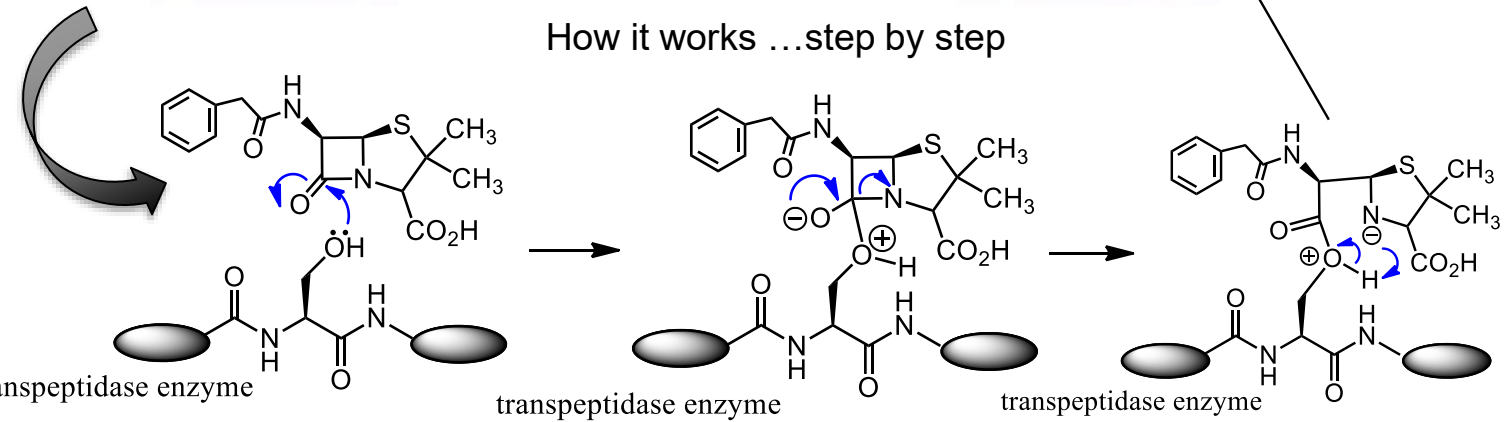






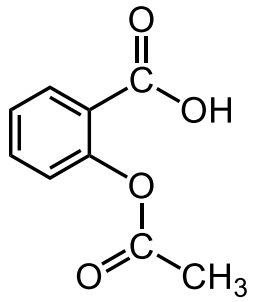
bacterial death

How it works …step by step



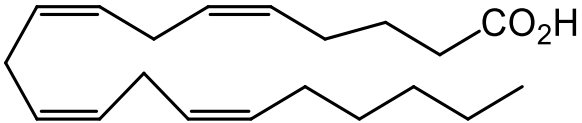
What Chemistry Does Aspirin Do To Relieve Pain

Prostaglandins are hormones which in very low concentrations in the body control production of pain, fever and inflammatory responses.



Acetylsalicylic Acid

Prostaglandins are made from arachidonic acid with the enzyme PGH_2 synthase being the catalyst for the reaction

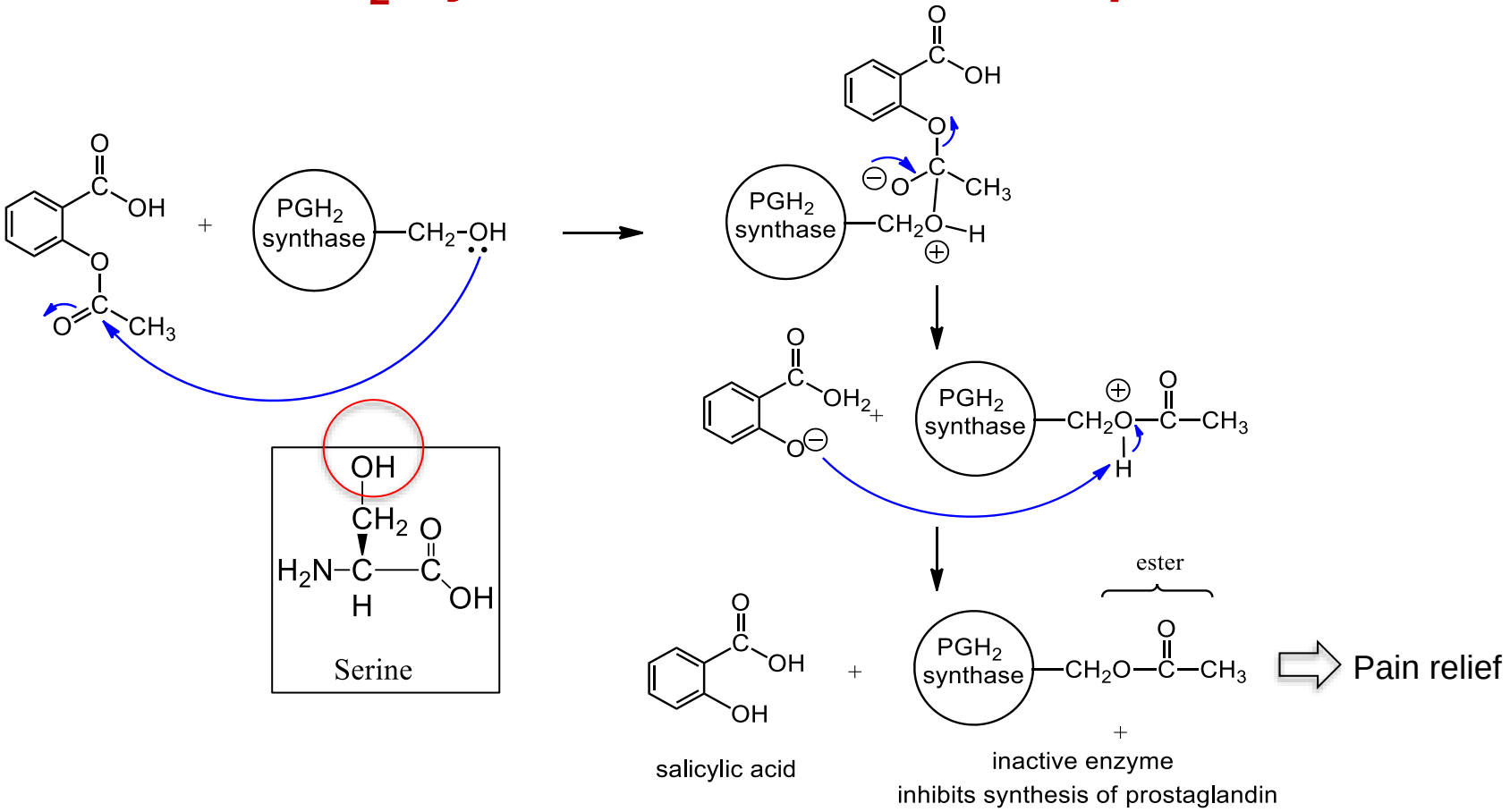


aspirin inhibits here → PGH_2 synthase

PGH_2 → $PGF_{2\alpha}$

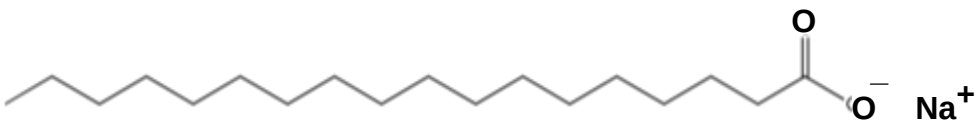
The acetyl (CH_3CO) group of aspirin is transferred to an alcohol group of the enzyme in a nucleophilic addition reaction, leaving the enzyme inactive

Reaction of OH from Serine Amino Acid Residue in PGH_2 Synthase with Ester of Aspirin

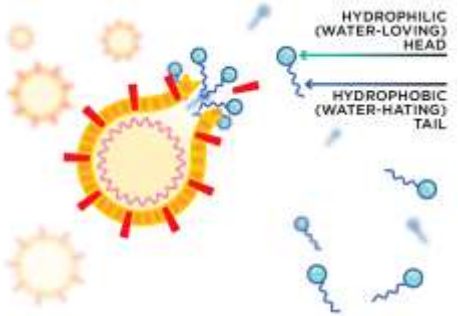


Covid-19 Related Chemistry

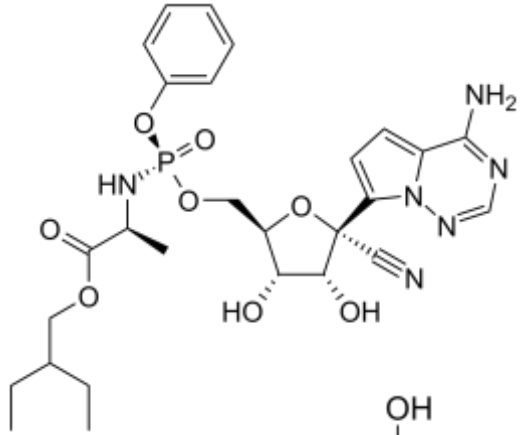
Soap



Surfactant



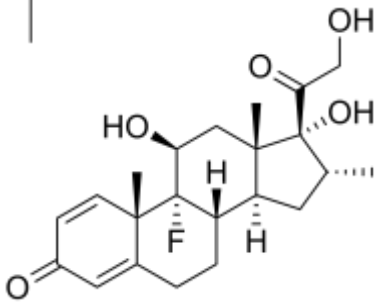
Remdesivir



Anti-viral

Prevents virus replicating

Dexamethasone



Anti-inflammatory

Calms immune system response

Good Luck with Your Chemistry Studies !

Come to your lectures / tutorials / labs and all will be explained !