Increasing population, increasing risk of communicable diseases (TB, Flu…)….
Increasing number of automobiles, decreasing air quality……..

….. Aap ka kya hoga janabe ali….

Every problem has a solution.What is it?

Let us rephrase the question. What do we want?
Woman does not live by bread alone! She needs butter, jam and wifi.
Optional (?): Clean air, enough food, clean energy & a disease free world..

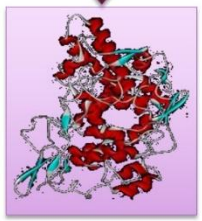
Find new (biomolecular) drug targets, develop new drugs ..keep some in store!
And don't tell microbes you got them!

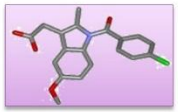
Kusuma School of Biological Sciences

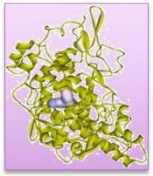
SBL-100: Towards a healthy tomorrow

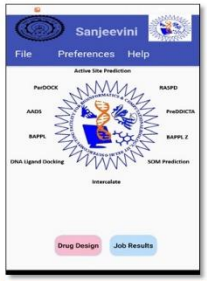
atggccctgtggatgcgcctcctgccccctgctggcgctgctggccctctggggacctgac.....

M A L W M R L L P L L A L L A L W G P D.....



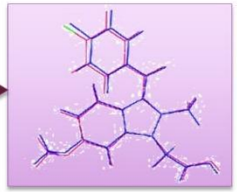


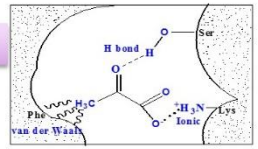




Sanjeevini App on mobile

Docking on a Supercomputer





Best Docked Structure

Send the lead molecule to xyz Pharmaceuticals for synthesis, clinical trials, approvals and recommendations on dosage etc. by a panel of doctors, all online

10 AM: Disease reported on a smart phone along with genome card and other reports/ symptoms.

5 PM: Drug delivered at door step what ever the disease!

Medicine taken by patient

Turns him/her into a healthy person

Goal: Personalized medicine:

Tools: Genomics + Proteomics + Metabolomics + Information Technology + Chemistry

The Nobel Prize in Physiology or Medicine 1988

"for their discoveries of important principles for drug treatment"

While drug development had earlier mainly been built on chemical modifications of natural products, the laureates introduced **a more rational approach** based on the understanding of basic biochemical and physiological processes

James W Black
London U., UK
b. 1924 (Scotland)

Gertrude B Elion
WRL USA
b. 1918 (USA)

George H Hitchings
WRL, USA
b. 1905 (USA)

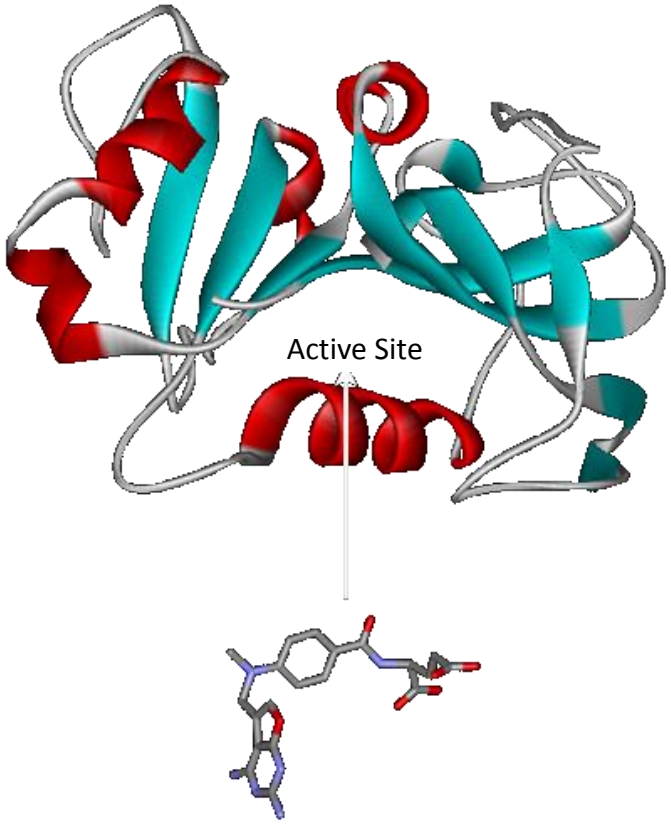
JB: Pharmacotherapeutic potential of receptor blocking drugs: betablocking drug-propanolol, characterized histamine receptors, H2 receptor antagonist-cimetidine
GE & GH: Thiogaunanine, 6-mercaptopurine for leukemia, pyrimethamine for malaria, azathioprine for preventing organ rejection, allopurinol for gout etc…

Rational Drug Design

Structure Based Drug Discovery

Drug molecule is like a duplicate key to jam (inhibitor) the lock (a biomolecular target) or open (activator) the lock.

Thus structure of the biomolecular target – the shape of the lock and the key hole – become important in designing the keys – the drugs. These are molecules. They are dynamic and they are surrounded by solvent, salt and other biomolecules in a cellular milieu..

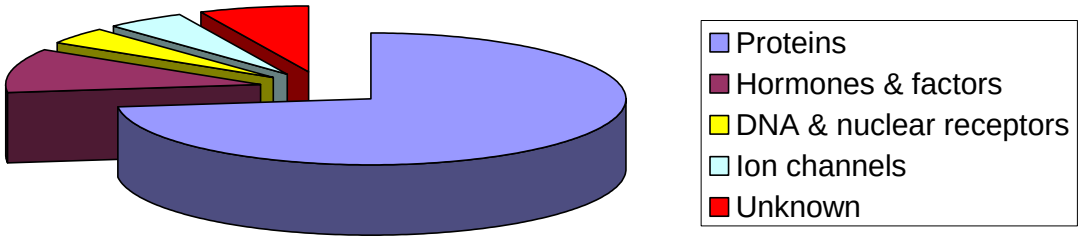


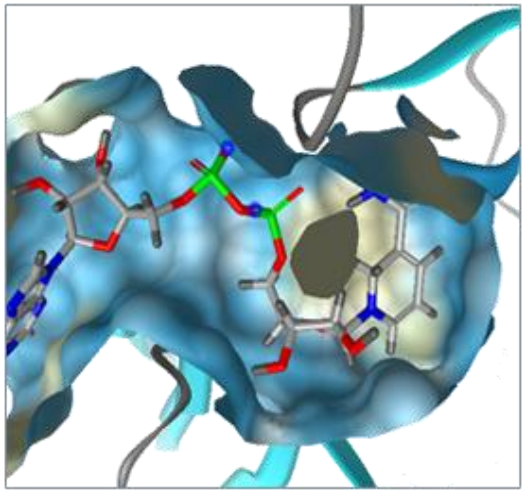
In a simplified view, a disease or a disorder can be traced to a protein going aberrant, lazy or overactive. Need activators for the former and inhibitors for the latter to cure disease / disorder. Most drugs are inhibitors.

If an essential protein is missing, it needs to be supplemented…gene therapy..insulin injections…

Proteins thus far have been the most attractive choice for drug discovery. However, with advances in nano biotechnology and drug delivery systems, DNA too could become a popular drug target.

Majority of Drug Targets are Proteins



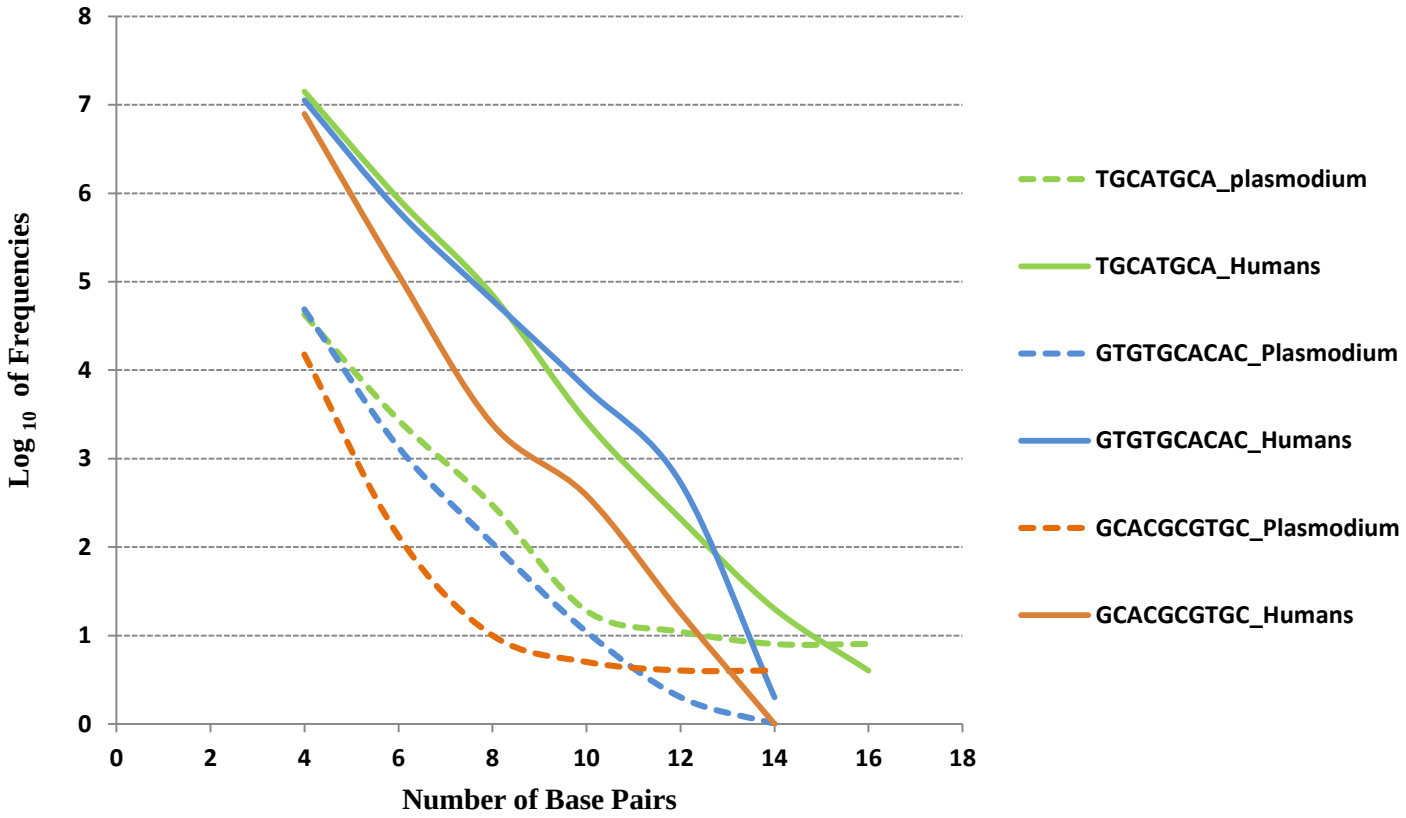


Protein structures are necessary for

- Structure-based drug-design
- Mapping the functions of proteins in metabolic pathways

	Experimental Approaches		**Computational approaches**	
	X-ray crystallography	**NMR spectroscopy**	**Comparative methods**	***De Novo* methods**
Time	at least 6 months	at least 6 months	Minutes to Hours	Hours to Days
Accuracy	very high	very high	Depends on similarity of template.	Moderate
Limitation	Prone to failure as crystallizing a protein is still an art and many proteins (e.g. membrane) cannot be crystallized.	Prone to failure, and is only applicable to small proteins (<150 amino acids).	Require a homologous template with at least 30% similarity. The accuracy is significantly reduced when the similarity is low.	Sampling and scoring limitations

DNA targeted drug discovery: Key issues- making big molecules and delivering them to the site



Logarithm of the frequencies of the occurrence of base sequences of lengths 4 to 18 base pairs in *Plasmodium falciparum* and in humans embedding a regulatory sequence TGCATGCA (shown in green), GTGTGCACAC (blue) and GCACGCGTGC (orange) or parts thereof, of the plasmodium. The solid lines and the dashed lines correspond to humans and plasmodium, respectively. Curves lying between 0 and 1 on the log scale indicate occurrences in single digits => Base sequence to constitute a unique target (occurs only once) must be 18 to 20 bp long.

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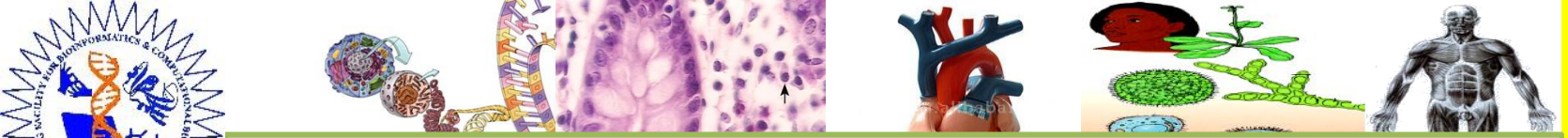
2012 WHO Report (Number of deaths in thousands)

	All Causes	**55,859**	**100**
Infectious and parasitic diseases		**6,431**	**11.5**
1.	**Tuberculosis**	935	1.7
2.	**STDs excluding HIV**	84	0.2
	a. Syphilis	79	0.1
	b. Chlamydia	1	0.0
	c. Gonorrhoea	1	0.0
	d. Trichomoniasis	0	0.0
	e. Other STDs	3	0.0
3.	**HIV/AIDS**	1,534	2.7
4.	**Diarrhoeal diseases**	1,498	2.7
5.	**Childhood-cluster diseases**	266	0.5
	a. Whooping cough	67	0.1
	b. Diphtheria	3	0.0
	c. Measles	130	0.2
	d. Tetanus	66	0.1
6.	**Meningitis**	395	0.7
7.	**Encephalitis**	78	0.1
8.	**Acute hepatitis B**	149	0.3
9.	**Acute hepatitis C**	39	0.1
10.	**Parasitic and vector diseases**	786	1.4
	a. Malaria	618	1.1
	b. Trypanosomiasis	18	0.0
	c. Chagas disease	8	0.0
	d. Schistosomiasis	22	0.0
	e. Leishmaniasis	48	0.1
	f. Lymphatic filariasis	0	0.0
	g. Onchocerciasis	0	0.0
	h. Leprosy	8	0.0
	i. Dengue	29	0.1
	j. Trachoma	0	0.0
	k. Rabies	35	0.1
11.	**Intestinal nematode infections**	3	0.0
	a. Ascariasis	3	0.0
	b. Trichuriasis	0	0.0
	c. Hookworm disease	0	0.0
12.	Other infectious diseases	664	1.2

About 11.5% of deaths (global averages) are due to microbial infections

These percentages may be more in third world countries!



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Microbial Infections: bacterial, viral, fungal & other parasitic infections

Bacterial infections: Pneumonia, Meningitis, Tuberculosis, Leprosy, Tetanus, Diphtheria, Cholera, Ecoli, Helicobacter Pylori, Salmonella, Shigella, Staphylococcus….

Mechanisms:

(1) Nutrients…Iron required by humans is selectively taken away by bacteria.
(2) Pathogens multiply in the host cells causing them to rupture.
(3) Toxins (endotoxins – lipid portions of lipopolysaccharides that are part of outer membrane of the cell wall of gram negative bacteria and exotoxins – proteins required for bacterial growth and metabolism of gram positive bacteria) destroy parts of host cell or inhibit metabolic functions of the host cell.

Preventive measures:

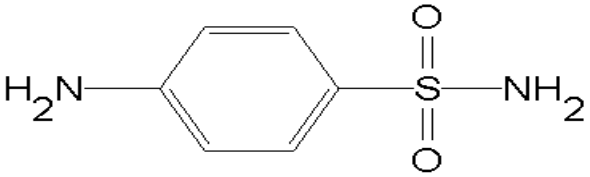
(1) Antiseptic measures (sterilization etc.),
(2) Usage of disinfectants (bleach etc.),
(3) cooking at temperatures above 73^{o}C etc..

Current strategies in antibacterial /drug discovery:

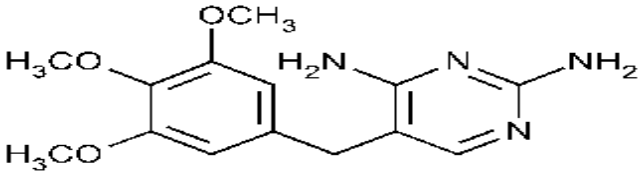
(1) Stop bacterial DNA synthesis
(2) Stop bacterial protein synthesis
(3) Stop bacterial cell wall synthesis

Antibiotics

Targeting DNA synthesis/replication



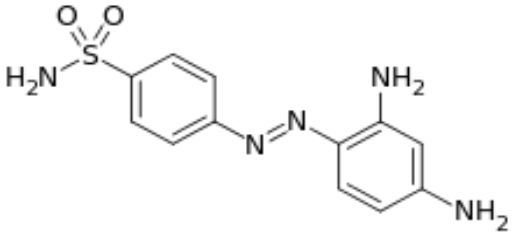
Sulfanilamide (a synthetic antibacterial compound, stops synthesis of folic acid in bacteria). Folic acid pathway is responsible for synthesis of certain amino acids and nucleic acid bases.



Trimethoprim inhibits DHFR enzyme involved in the synthesis of folic acid

The Nobel Prize in Physiology or Medicine 1939

"for the discovery of the antibacterial effects of prontosil“



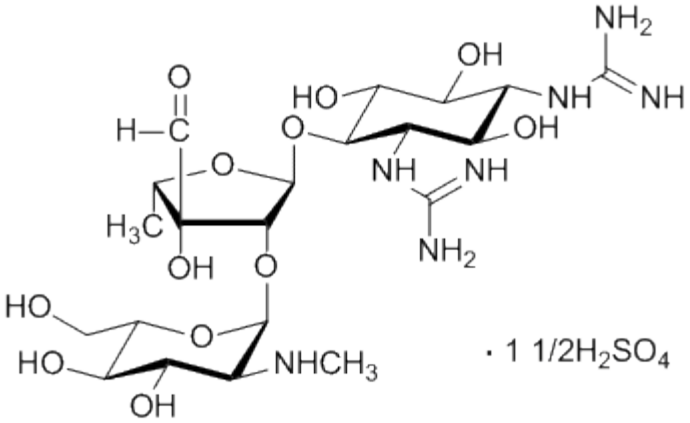
Prontosil – a synthetic antibacterial compound

Gerhard Domagk
Munster U, Germany
b. 1895 (Germany)

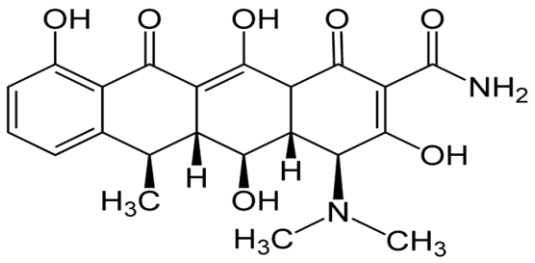
Prontosil is a derivative of sulfanilamide (*p*-aminobenzenesulphonamide). Some thousands of derivatives of sulphanilamide have been produced and tested for their antibacterial properties. Domagk's work has thus given to medicine, and also to surgery, a whole new series of weapons that are effective against many infectious diseases. Later, he attacked the problem of the chemotherapy of tuberculosis, developing for this the thiosemicarbazones (Conteben) and isonicotinic acid hydrazide (Neoteben). The supreme aim of chemotherapy is, in Domagk's opinion, the cure and control of carcinoma and he was convinced that this will be, in the future, achieved.

Antibiotics

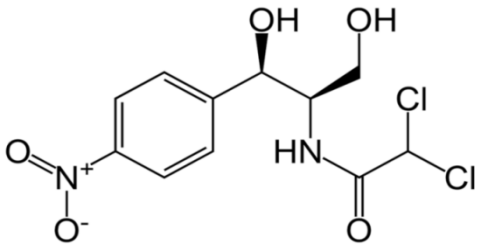
Targeting Protein synthesis



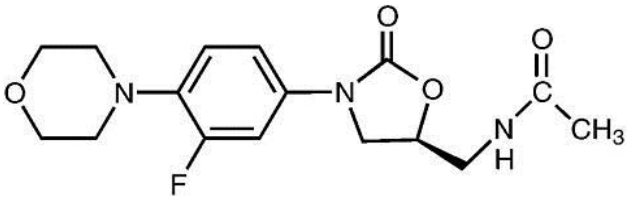
Streptomycin (aminoglycoside) causes mRNA to be misread by the ribosome.



Doxycycline (a tetracycline) inhibits protein synthesis (by binding to ribosomes ..at a different biochemical site than do the aminoglycosides)..eukaryotic ribosomes are structurally different and hence humans are safe. Tetracyclines are actively transported into bacterial and not mammalian cells.



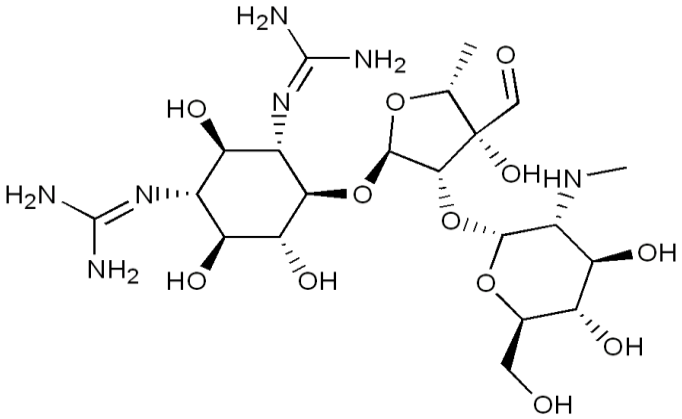
Chloramphenicol, a broad spectrum antibiotic, binds reversibly to 50 S subunit of ribosome, at sites near to or overlapping with those for lincomycin and erythromycin. Aminoacyl tRNA is thus prevented from binding its amino acid to the ribosomal binding site.



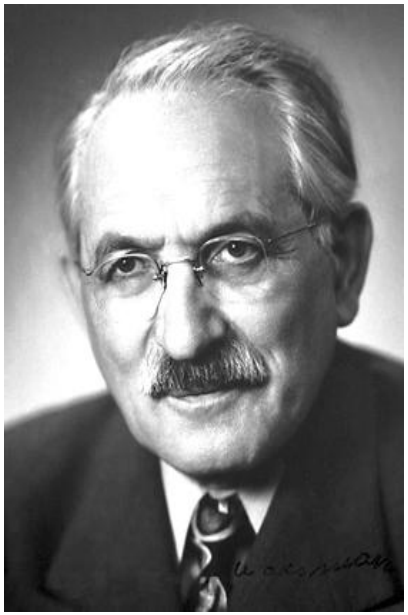
Linezolid – a quinolone – binds to bacterial ribosomes. Also implicated in inhibition of bacterial topoisomerase preventing DNA replication.

The Nobel Prize in Physiology or Medicine 1952

"for his discovery of streptomycin, the first antibiotic effective against tuberculosis"



Streptomycin – an antibacterial compound – the first of a class of drugs called aminoglycosides – the first effective treatment against tuberculosis



Selman A. Waksman
Rutgers U, USA
b. 1888 (Ukraine)

He has isolated, together with his students and associates, a number of new antibiotics, including actinomycin (1940), clavacin, streptothricin (1942), streptomycin (1943), grisein (1946), neomycin (1948), fradicin, candicidin, candidin, and others. Two of these, streptomycin and neomycin, have found extensive application in the treatment of numerous infectious diseases of men, animals and plants. They have been covered by patents, that on streptomycin having been recently listed as one of the ten patents that shaped the world.

The Nobel Prize in Chemistry 2009

"for studies of the structure and function of the ribosome"

The ribosomes (30S & 50S) in bacteria are different from their counterparts in animals / humans (40S & 60S) and hence constitute a good target for antibiotics

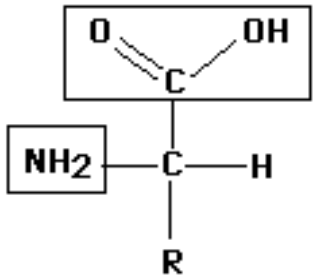
Venkatraman Ramakrishnan
Cambridge, UK
b. 1952 (India)

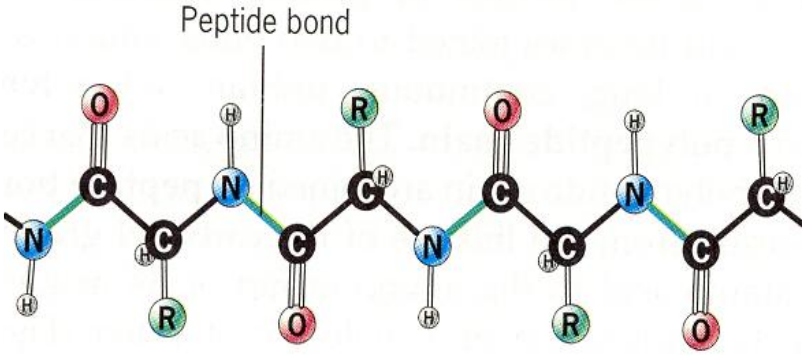
Thomas A. Steitz
Yale University , USA
b. 1940 (USA)

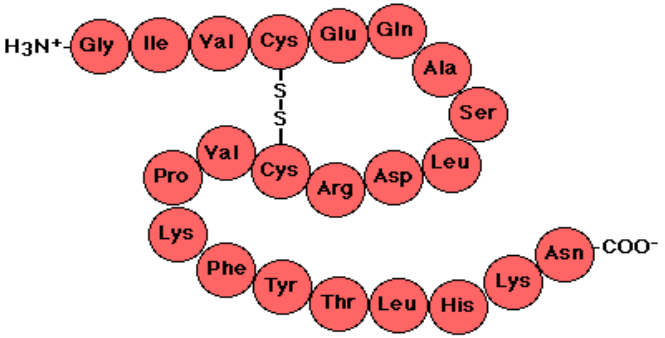
Ada E. Yonath
Weizmann Institute, Israel
b. 1939 (Israel)

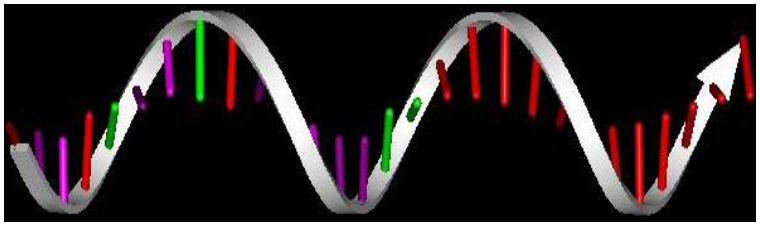
All the three laureates published their work almost simultaneously in 2000. First, Steitz published the 50S (large bacteria) subunit from the archaea, *Haloarcula marismortui* consisting of 2833 nucleotides and 27 proteins and soon after Yonath revealed the structure of the 30S subunit from *Thermus thermophilus*. Very soon after that, Ramakrishnan published a more detailed structure. In May 2001, other researchers began to build on those structures and reconstructed the entire *T. thermophilus* 70S particle at 5.5 angstrom resolution.

Protein synthesis – a closer look









mRNA

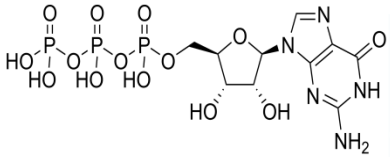
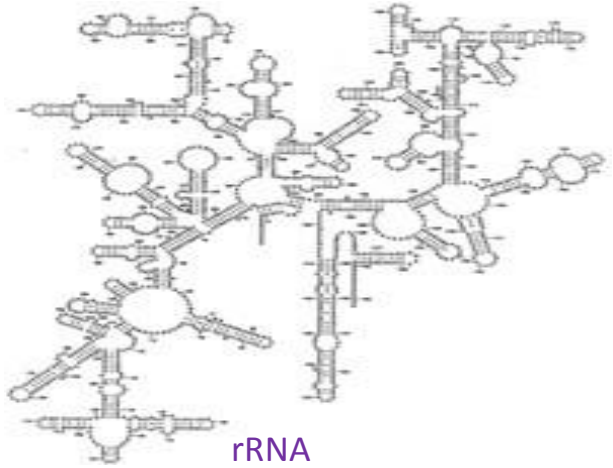
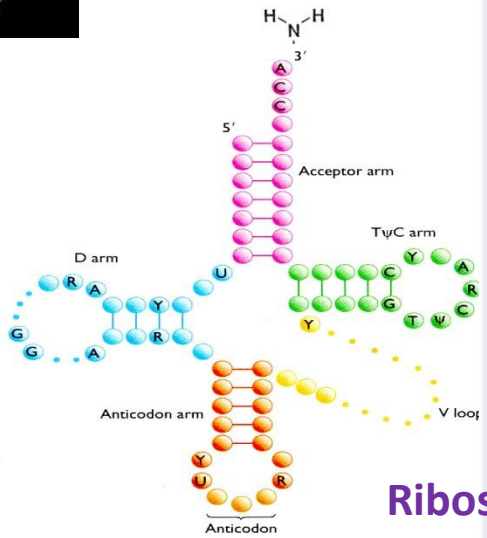


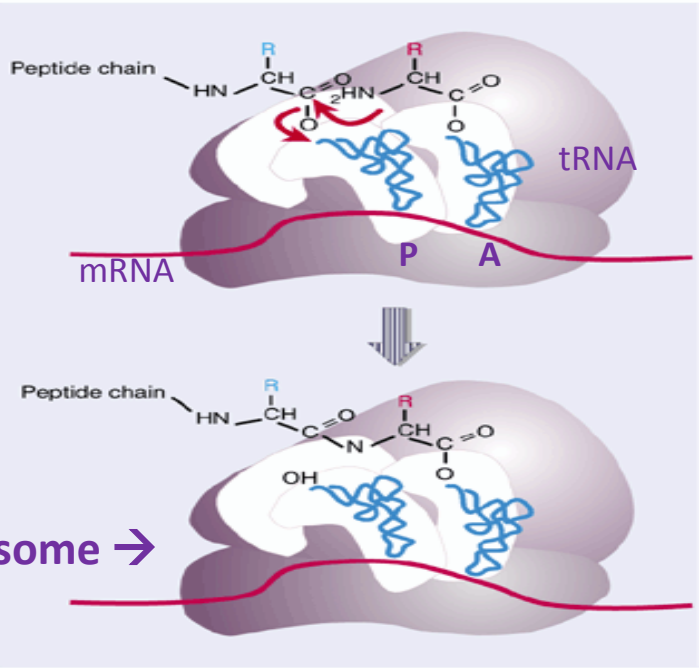
Figure Peptide bond formation takes place by reaction between the polypeptide of peptidyl-tRNA in the P site and the amino acid of aminoacyl-tRNA in the A site.



rRNA

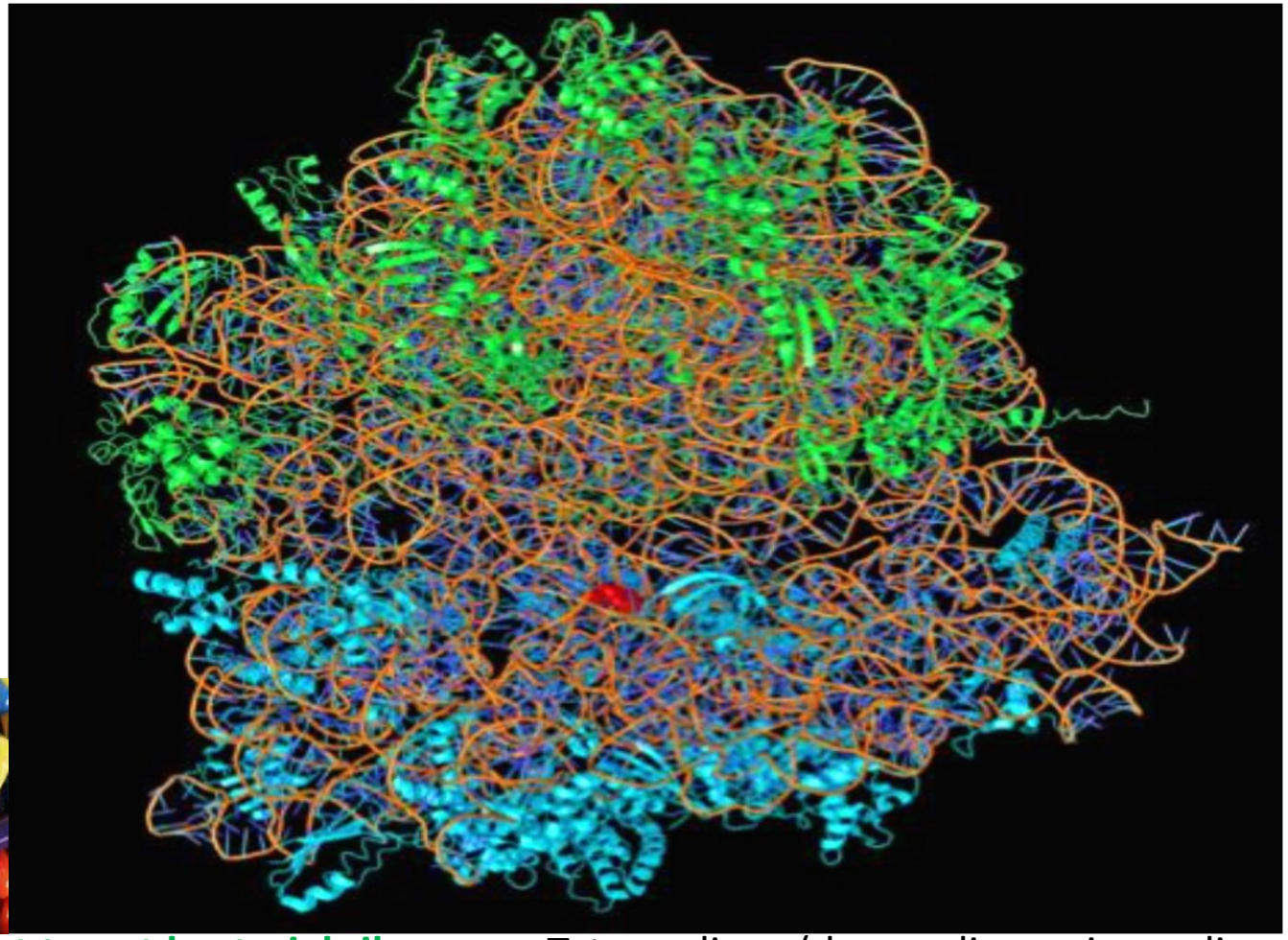


tRNA



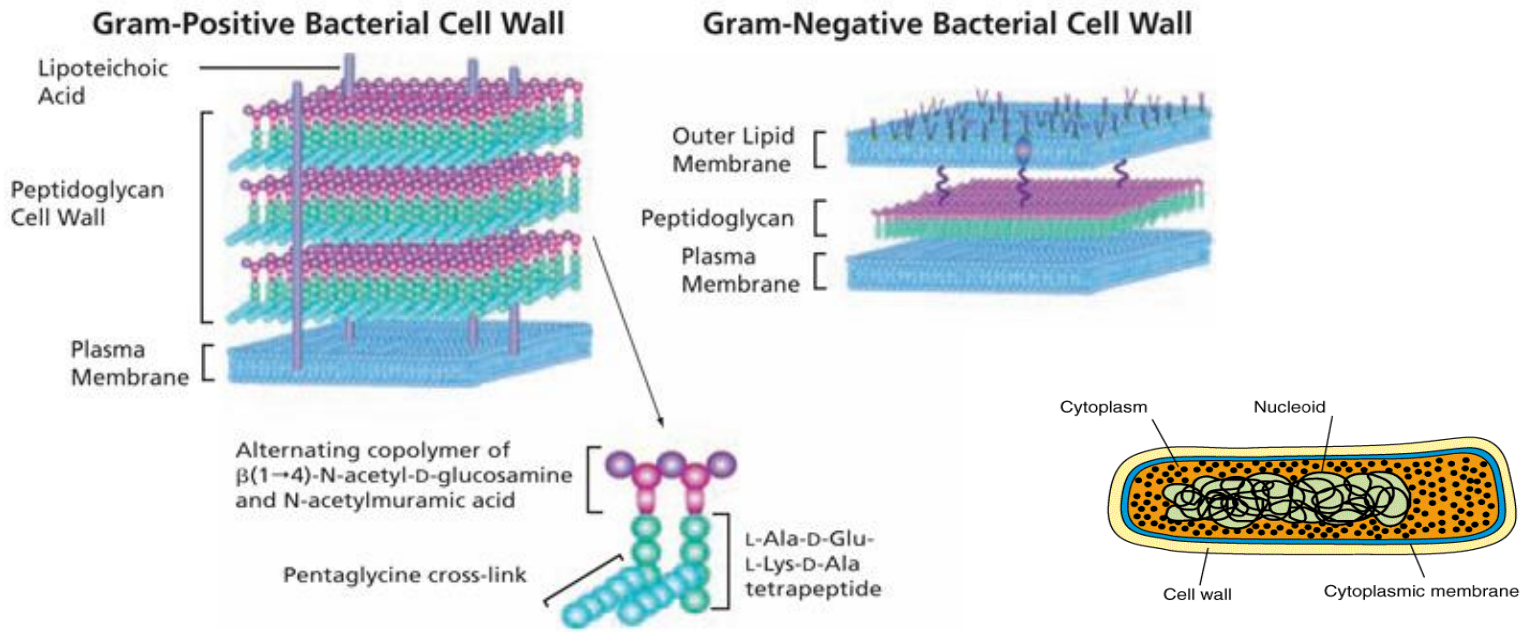
Ribosome →

What Ribosomes Look Like At Atomic Level
(~ 100,000 atoms – a technological / chemical challenge !)



Availability of the structures of bacterial ribosomes enables discovery of new antibiotics

Antibiotics that target bacterial ribosome. Tetracyclines (doxycycline, minocycline, tetracycline); Pleuromutilins [Altabax, (tiamulin and valnemulin -veterinary use)]; Macrolides (erythromycin, clarithromycin); Lincosamides (lincomycin -veterinary use, clindamycin); Everninomycins, Oxazolidinones (linezolid); Aminoglycosides (gentamicin, tobramycin, amikacin, kanamycin) Telithromycin (Ketek); Tylosin (veterinary use); Spectinomycin etc..

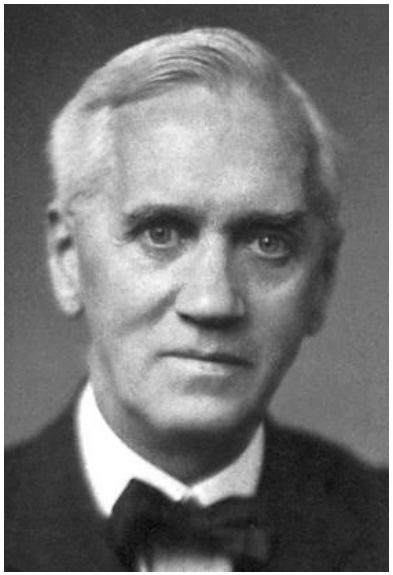


Bacterial Cell wall disruption.

- The function of the microbial cell wall is as a protective external support to the cell. Its rigid polymeric material functions as a continuous envelope to preserve the protoplast's integrity, something the delicate protoplasmic membrane cannot adequately do in the hypotonic environment in which the cell functions. Gram-positive bacteria attain internal osmotic pressures approaching 20 atmospheres, where as Gm-negative organisms exhibit pressures of 5-6 atmospheres, which although less, is still quite high. Such pressures in the absence of a cell wall lead to rupture (lysis) of the membrane and hence cell death. The cell wall effectively prevents this. As the cell grows, more cell wall must be synthesized to accommodate the additional protoplasmic material. Drugs that can prevent this synthesis in actively growing cells invariably cause rupture, since the membrane alone cannot contain the cellular contents. Both Gm+ and Gm- bacterial cell walls share the fundamental backbone of the peptidoglycan or murien. It consists of parallel polysaccharide chains cross-linked by short peptide chains.
- Stage-I: Formation of UDPNAM pentapeptide (Fosfomycin, D-cycloserine, alafosfolin inhibit this).
- Stage-II: Formation of disaccharide decapeptide monomeric unit (peptidoglycan chain). (Bacitracin, Vancomycin inhibit this)
- Stage-III: Cross-linkage of peptidoglycan chains (transpeptidation). (Conversion of water soluble polymeric substances with mobility into tough insoluble inflexible material. (**Penicillins** inhibit this).

The Nobel Prize in Physiology or Medicine 1945

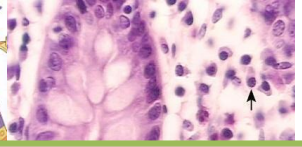
"for the discovery of penicillin and its curative effect in various infectious diseases”



Sir Alexander Fleming
London U., UK
b. 1881 (Scotland)

Ernst B Chain
U Oxford UK
b. 1906 (Germany)

Sir Howard Florey
U Oxford UK
b. 1898 (Australia)


Kusuma School of Biological Sciences

Serendipity

Alexander Fleming was looking for ways to destroy bacteria. In 1928, he was growing lots of bacteria known as staphylococci on agar plates. Before going on holiday in 1928 Alexander made two mistakes. He didn't put all of his plates in bleach to sterilise them, and he left the lab windows open. When he came back from a holiday, Alexander noticed that lots of his culture plates were mouldy. A common mould that might have grown happily on a slice of bread had landed on Alexander Fleming's plates – a stroke of luck which has saved millions of lives. Just before he put all the plates in the washing up to get clean, Fleming noticed something. Although lots of bacteria were growing on his plates, there was a clear ring in the jelly around some of the spots of mould – no bacteria were growing . Something had killed the bacteria that was covering the jelly. Straight away Fleming saw that this might be important. He labelled and saved the plates. Fleming worked hard on his mould, *Penicillium notatum*. He squeezed out some 'mould juice' which he called penicillin. But he couldn't get much penicillin from the mould. It wouldn't keep - even in the fridge - and he couldn't prove it would actually kill bacteria and make people better. By 1934 Fleming gave up on penicillin and went on to do different work!

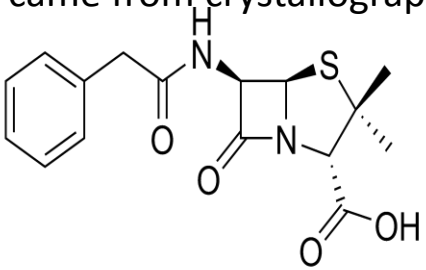
In 1938 Howard Florey and Ernst Chain at Oxford University decided to do some work on penicillin. They infected eight mice with bacteria which would normally kill them. Four were given penicillin. The four treated mice stayed healthy – but the other four died. They went on to treat Albert Alexander, a 43 year old policeman dying of a blood infection. Florey and Chain gave him penicillin for five days, and Albert was well on the way to health again when the penicillin ran out. Florey and Chain tried everything – they even collected spare penicillin from Albert's urine - but the infection came back and Albert died. Florey and Chain didn't give up. They collected more penicillin and used it on a 15 year old boy who had an infection after an operation. He was completely cured. They showed the value of penicillin in destroying bacteria.

The next problem was making enough of it to supply the demand of the soldiers in World War 2. In Britain all the big laboratories and factories were busy with the war effort. But Howard Florey knew lots of people in America, so the scientists took their mould to the United States where some of the big chemical companies helped them make penicillin on a large scale. Although Florey and Chain developed it as a medicine, Fleming and his mouldy plates will always be remembered. Penicillin became available to everyone and the history of infectious diseases changed for ever.

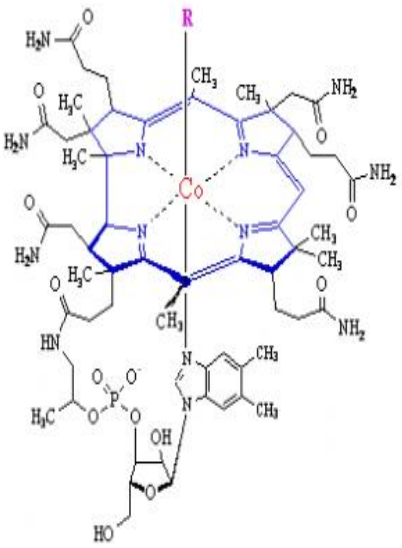
The Nobel Prize in Chemistry 1964

"for her determinations by X-ray techniques of the structures of important biochemical substances“

Chemists knew that penicillin consisted of 27 atoms: 11 hydrogen, 9 carbon, 4 oxygen, 2 nitrogen atoms and 1 sulphur atom. The trouble was that this combination of atoms could form two very different structures, and chemists couldn't decide which structure was more likely. Some chemists were convinced the structure contained two five-membered rings connected by a single bond, known as a thiazolidine-oxazolone. Others were equally sure it was a four-membered ring fused to a five-membered ring, known as a beta lactam. "The final solution of the problem of the structure of penicillin came from crystallographic X-ray studies."



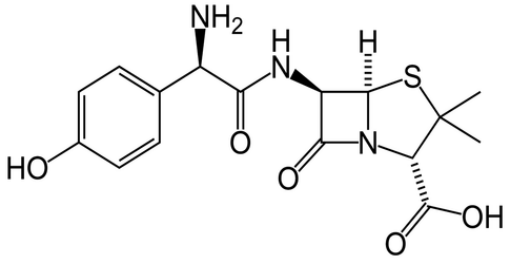
The enchanting β– lactam



She also solved the structure of Vitamin-B12, in addition to penicillin.

Dorothy Crowfoot Hodgkin
U Oxford UK
b. 1910 (Egypt)

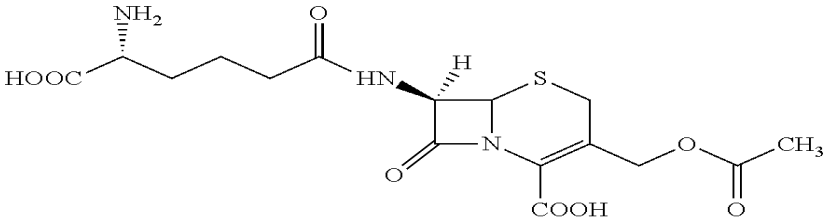
Knowledge of the penicillin structure finally opened new avenues for creating and developing semi-synthetic derivatives of penicillin – such as the cephalosporines – that sparked the creation of antibiotic treatments.



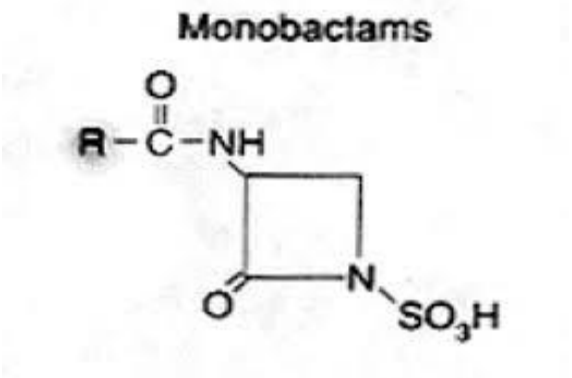
Amoxicillin (developed with novel side chains to 6-aminopencillanic acid).

Bacteria have started producing β-lactamase enzyme which destroys the 4-membered lactam ring making penicillin ineffective

I



Cephalosporin c is resistant to β–lactamase.

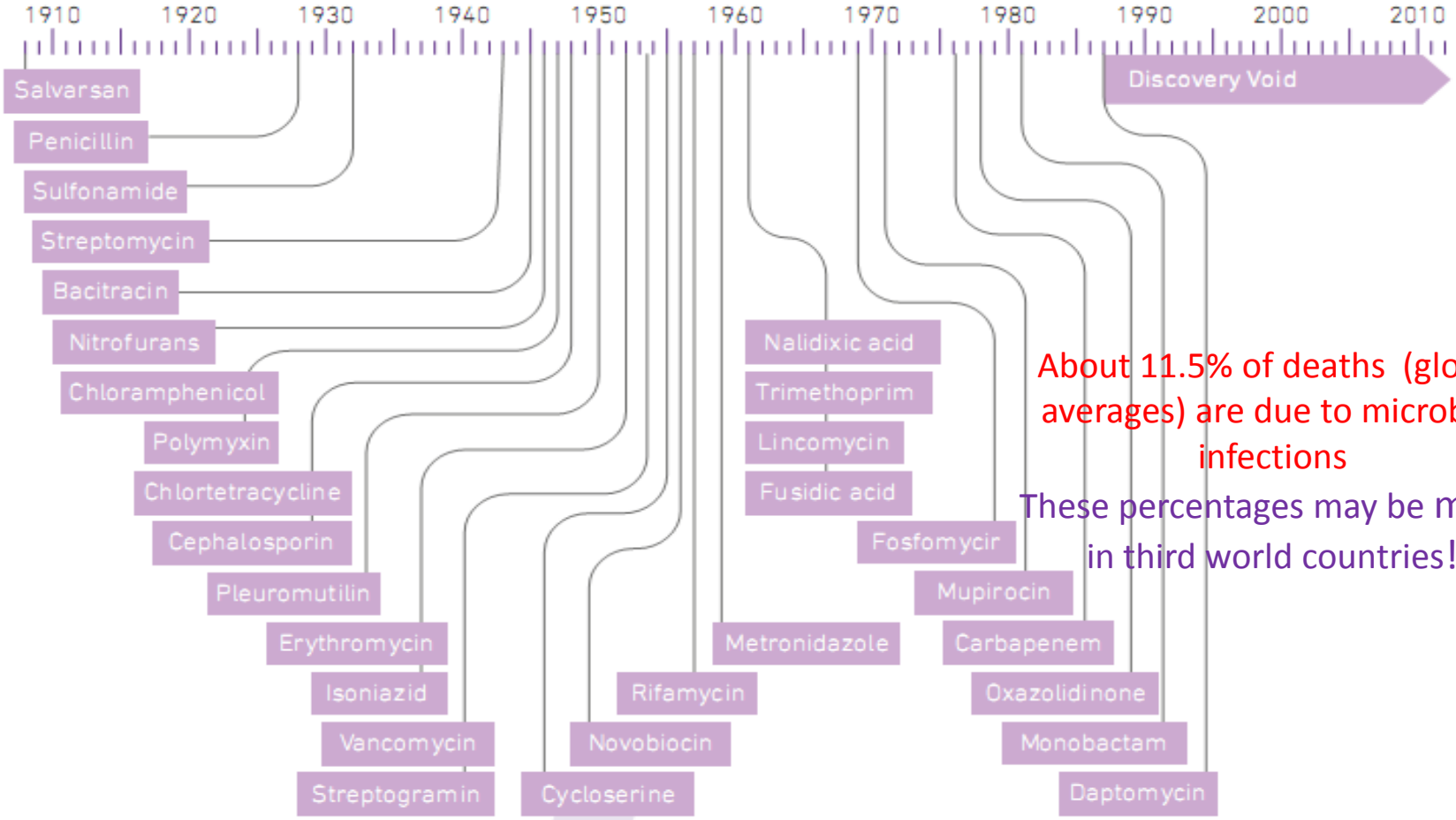


Monobactams are resistant to β-lactamases

What is the urgency for drug discovery now?

Figure 1 Dates of discovery of distinct classes of antibacterial drugs

Illustration of the "discovery void." Dates indicated are those of reported initial discovery or patent.



Adapted from Silver 2011 (1) with permission of the American Society of Microbiology Journals Department.

About 11.5% of deaths (global averages) are due to microbial infections

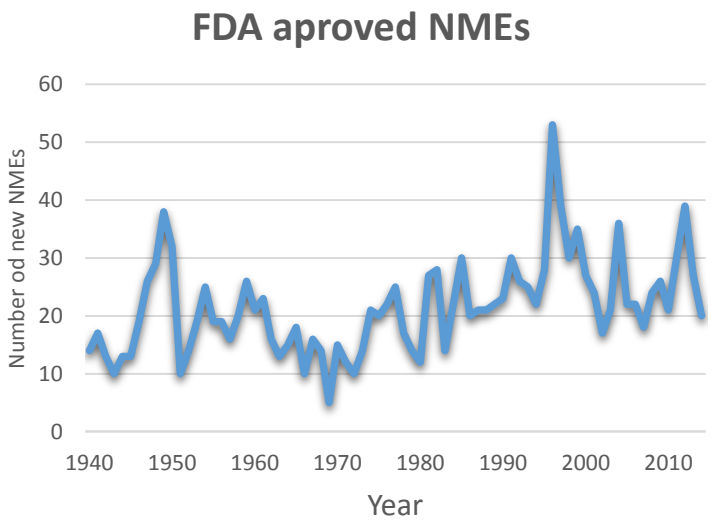
These percentages may be more in third world countries!

WHO-AMR Report 2014

Pharmaceutical R&D is Expensive

New Chemical Entities (NCEs) need to be continuously developed since income from older drugs gets gradually reduced on account of increasing competition from other products, generics as well drug resistance.

Total number of new molecular entities approved over the last 75 years: 2040!



Drug Development is an Uphill Task

Of the new drugs approved by FDA

Only 35% were New Molecular Entities (NME).

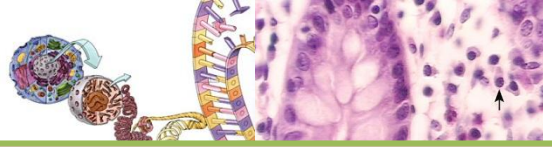
Only 15% were deemed to provide significant improvement over existing medicines.

Drug discovery pipe-line is drying up despite massive increase in genomic / proteomic data.

Millions of molecules are available in databases and so many more are getting synthesized every day in organic chemistry laboratories all over the world.

Only 2040 drugs in 75 years?

http://www.seniors.gov/articles/0502/medicine-study.htm

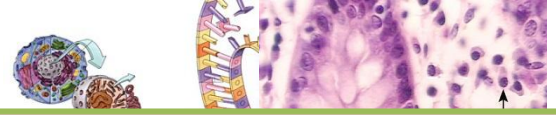


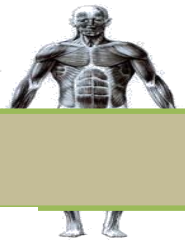
Kusuma School of Biological Sciences

20 Leading Causes of Death – World (WHO Report)

2015				2030			
Rank	Cause	Deaths (000s)	% deaths	Rank	Cause	Deaths (000s)	% deaths
1	Ischaemic heart disease	7594	13.2	1	Ischaemic heart disease	9245	13.2
2	Stroke	6700	11.7	2	Stroke	8578	12.2
3	Lower respiratory infections	3223	5.6	3	Chronic obstructive pulmonary disease	4568	6.5
4	Chronic obstructive pulmonary disease	3217	5.6	4	Lower respiratory infections	3535	5.0
5	Diarrhoeal diseases	1808	3.2	5	Diabetes mellitus	2464	3.5
6	HIV/AIDS	1667	2.9	6	Trachea, bronchus, lung cancers	2413	3.4
7	Trachea, bronchus, lung cancers	1636	2.9	7	Road injury	1854	2.6
8	Diabetes mellitus	1556	2.7	8	HIV/AIDS	1793	2.6
9	Road injury	1423	2.5	9	Diarrhoeal diseases	1617	2.3
10	Hypertensive heart disease	1137	2.0	10	Hypertensive heart disease	1457	2.1
11	Preterm birth complications	1133	2.0	11	Cirrhosis of the liver	1201	1.7
12	Cirrhosis of the liver	1028	1.8	12	Liver cancer	1186	1.7
13	Tuberculosis	887	1.5	13	Kidney diseases	1152	1.6
14	Kidney diseases	871	1.5	14	Stomach cancer	1143	1.6
15	Self-harm	836	1.5	15	Colon and rectum cancers	1075	1.5
16	Liver cancer	825	1.4	16	Self-harm	1007	1.4
17	Stomach cancer	797	1.4	17	Falls	976	1.4
18	Birth asphyxia and birth trauma	768	1.3	18	Alzheimer's disease and other dementias	966	1.4
19	Colon and rectum cancers	751	1.3	19	Preterm birth complications	917	1.3
20	Falls	714	1.2	20	Breast cancer	805	1.1

Good News! Bacterial infections are not the leading cause of deaths even in 2030! Drug resistance is not factored in.





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Bacteria commonly causing infections in hospitals and in the community

Name of bacterium/ resistance	Examples of typical diseases	No. out of 194 Member States providing data
Escherichia coli/	Urinary tract infections, blood stream infections	
- vs 3rd gen. cephalosporins		86
- vs fluoroquinolones		92
Klebsiella pneumoniae/	Pneumonia, blood stream infections, urinary tract infections	
- vs 3rd gen. cephalosporins		87
- vs 3rd carbapenems		71
Staphylococcus aureus/	Wound infections, blood stream infections	

Bacteria mainly causing infections in the community

Name of bacterium/ resistance	Examples of typical diseases	No. out of 194 Member States providing data
Streptococcus pneumoniae/ - non-susceptible or resistant to penicillin	Pneumonia, meningitis, otitis	67
Nontyphoidal Salmonella/ - vs fluoroquinolones	Foodborne diarrhoea, blood stream infections	68
Shigella species/ - vs fluoroquinolones	Diarrhoea ("bacillary dysenteria")	35
Neisseria gonorrhoea/ - vs 3rd gen. cephalosporins	Gonorrhoea	42

Bacteria are becoming resistant to existing drugs!

WHO 2014 report on antimicrobial resistance

Kusuma School of Biological Sciences

WHO -2014 report on AMR

Antimicrobial resistance (AMR) within a wide range of infectious agents is a growing public health of broad concern, increasingly…the problem is so serious that it threatens the achievements of modern medicine . A post antibiotic era – in which common infections and minor injuries can kill – far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century.

The fall from the bicycle did not kill but the scratch on the hand killed! That is what AMR can do!

For more than 60 years, antibacterial drugs have been regarded as the panacea to cure infections, whether or not their use is appropriate. Already in his Nobel Prize speech in 1945, Alexander Fleming warned that bacteria could become resistant to these remarkable drugs. Indeed, the development of each new antibacterial drug has been followed by the detection of resistance to it. The development of resistance is a normal evolutionary process for microorganisms, but it is accelerated by the selective pressure exerted by widespread use of antibacterial drugs. Resistant strains are able to propagate and spread where there is non-compliance with infection prevention and control measures.

Any solution: Find new (biomolecular) drug targets, develop new drugs ..keep some in store!

And don't tell microbes you got them!

Viruses do not have cell walls. They do not have distinct ribosomes….
Antibiotics don't work for viral infections!

It takes seven days(!) to get rid of common cold without medicine, but if you take medicine, it just takes one week for it to disappear!!

Viral infections

- Viruses are capsules with genetic material inside. Viruses are very tiny, much smaller than bacteria.

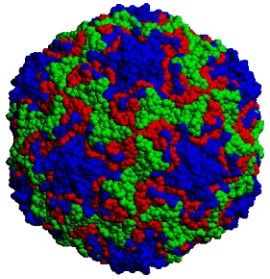
- Viruses are like hijackers. They invade living, normal cells and use those cells to multiply and produce other viruses like themselves. This eventually kills the cells, which makes the hosts sick.

- Viral infections are hard to treat because viruses live inside host body's cells. They are "protected" from medicines, which usually move through host's bloodstream. There are a few antiviral medicines available. Vaccines can help prevent viral diseases provided the viral genomes are not changing rapidly.

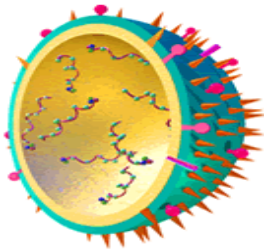
- Viruses have a protein coat and a core of genetic material, either RNA or DNA. Unlike bacteria, viruses can't survive without a host. They can only reproduce by attaching themselves to host cells. In most cases, they reprogram the host cells to make new viruses until the host cells burst and die. In other cases, they turn normal host cells into malignant or cancerous cells.

- Also unlike bacteria, most viruses do cause disease, and they're quite specific about the cells they attack. For example, certain viruses attack cells in the liver, respiratory system, or blood. In some cases, viruses target bacteria.

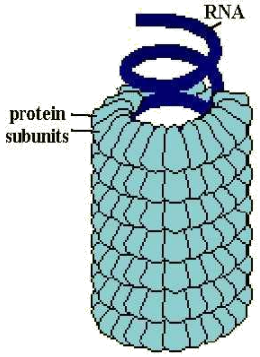
There are many kinds of viruses. The genetic material could be either DNA or RNA. A virus may infect an animal cell (eg. rhinovirus or influenza virus), a plant cell (Tobacco Mosaic Virus), or a bacterial cell (T4 bacteriophage). Those infecting humans include polio, influenza, herpes, smallpox, chickenpox, and human immunodeficiency virus (HIV) causing AIDS.



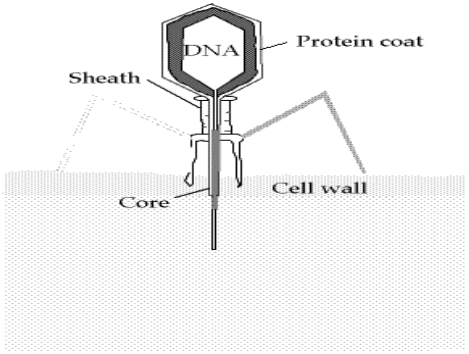
(i) Human Rhinovirus



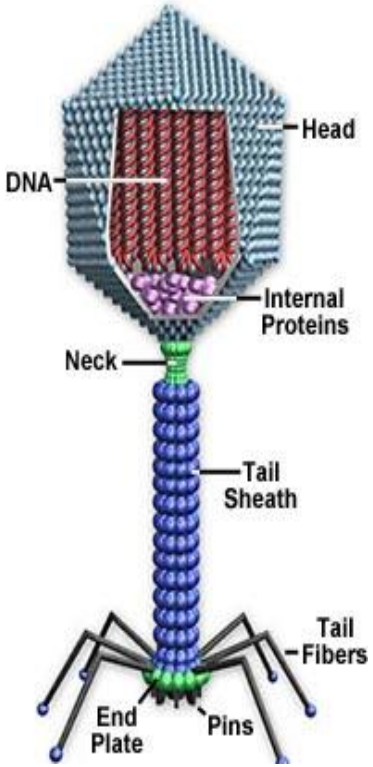
(ii) Influenza Virus



(iii) Plant Virus (TMV)



(iv) T4 bacteriophage and its method of injecting DNA into a bacteria cell



Structure of a virus

Some viral infections & phases of infection

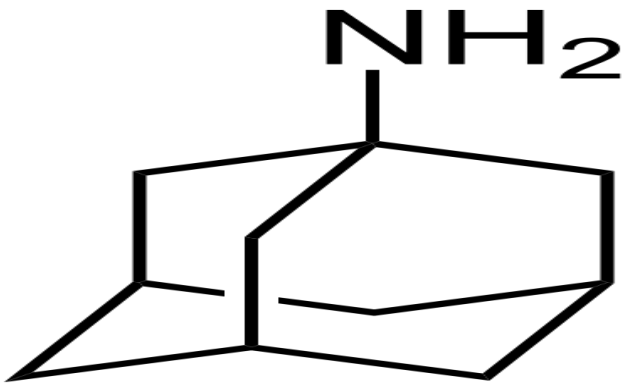
- Polio; Measles; Chikenpox; Influenza; Yellow fever; chikungunya
- HIV-AIDS
- HAV, HBV, HCV
- Human papilloma virus

Phase I: Initiation of infection: **Entry of virus into the host**

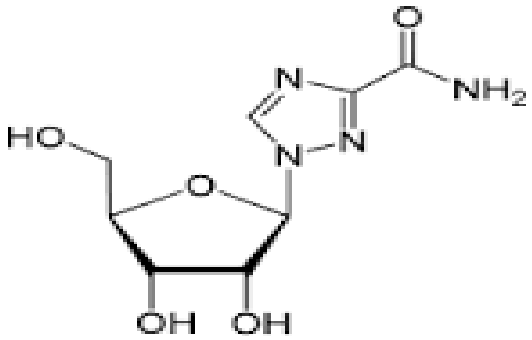
- First step is the adsorption of the virion onto the cell surface. Physical contact, collision frequency, contact area size, ionic conditions and several other factors are responsible. No drugs are available at this stage.
- Second step is penetration. Most common method is pinicytosis which leads to gradual engulfment of virion. Direct penetration can occur. Once inside, the virion moves in the host cells to sites where replicative steps can occur. (amantadine appears to prevent viral penetration/uncoating).
- Third step is uncoating, shedding of the protective protein coat, carried out by virus specific enzymes, synthesized by viral mRNA. No drugs available against uncoating.

- Phase II: **Viral DNA/RNA Synthesis** (Most available drugs work here)

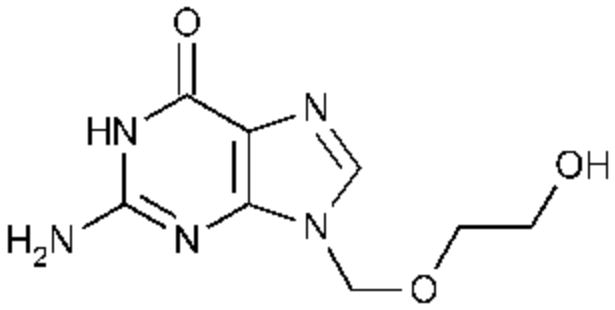
- Phase III: Coating and **release of viral particles** for propagating infection.



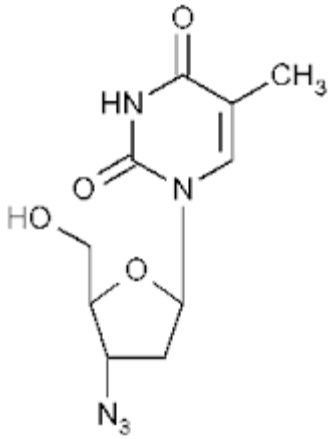
Early efforts: **Amantadine**, used to treat influenza A. Mechanism of action involves inhibition of viral uncoating step.



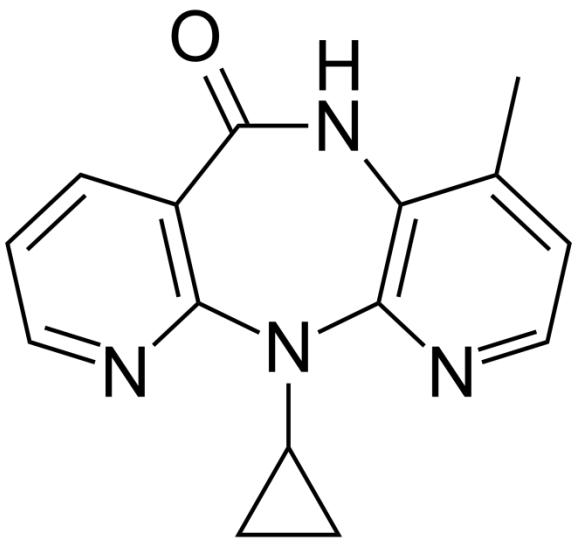
Ribavarin – a ring modified nucleoside – is used to treat syncitial viral infections, a rare disease in infants and hepatitis C when combined with interferon. Incorporation in DNA/RNA may be the mechanism.



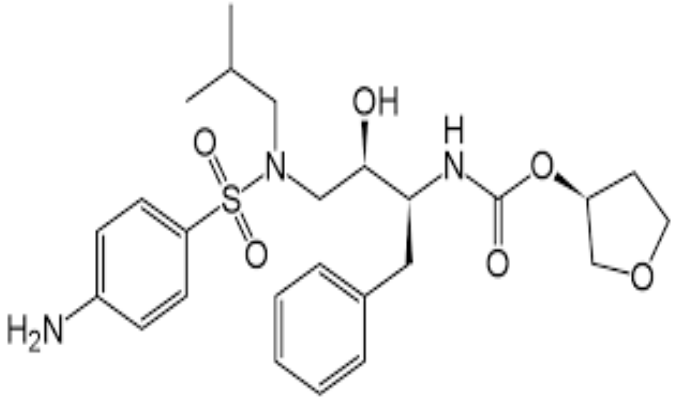
Acyclovir is active against a range of herpes viruses and cold sores, shingles, chicken pox (varicella virus) etc..The open chain analogs, like the normal nucleosides, are not active per se. They must be first converted to their triphosphate derivatives in the body by step wise addition of phosphates. The resulting triphosphates are then mistaken by the virus infected cell for GTP required for building DNA and incorporated into the growing chain. This causes premature chain termination and failure of new virion synthesis.



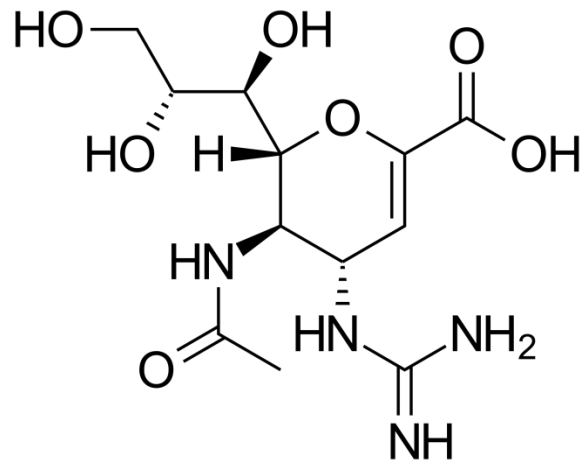
Zidovudine (AZT) or azathymidine is incorporated into growing DNA by reverse transcriptase which proves lethal to the infected cell.



Nevirapine, a non-nucleoside transcriptase inhibitor (NNRTI)works with the same mechanism. RNA viruses carry reverse transcriptase enzyme (RT) to convert their RNA into DNA in the host cell, followed by integration of viral DNA into host DNA. Humans don't carry RTs. Thus RTIs have been successful in treating infections of RNA viruses such as HIV. Resistance due to mutations in RTs is a problem!

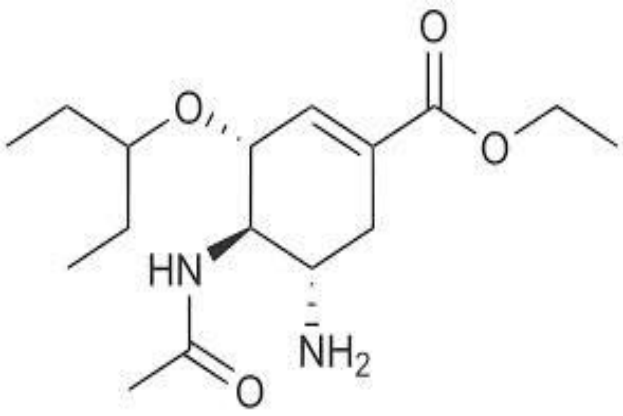


Amprenavir is a small molecule HIV protease inhibitor. The protein that makes up the coat of the virus is first elaborated as a much larger molecule. A protease cleaves this protein into fragments which are used to build the coat. Atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritinovir, saquinavir, tiprinavir etc. belong to this class of drugs. They all resemble a protein fragment but lack a cleavable peptide bond. This stops the virion-coating process.



Formation of new influenza virions, after the DNA has been replicated, starts with the formation of a bud on the surface of the cell. The bud at this point is covered and held in place by a complex polysaccharide called sialic acid. In the normal course, the enzyme neuraminidase is called into action to break open the sialic acid cover so as to complete the bud formation and release.

Zanamivir is the first neuraminidase inhibitor.



Tamiflu proved effective against bird flu. Tamiflu is a neuraminidase inhibitor.

Other classes of diseases/disorders & drugs

Antimalarials: Other parasitic infections: Artemisinin won the Nobel-2015

Analgetics & Nonsteroidal Antiinflammatory Agents (**NSAIDS**)
(Aspirin, Ibuprofen, diclofenac, morphine, thebain etc.)

Anticancer Drugs (Methotrexate, doxorubicin, bleomycin, vinca alkaloids, taxol)

Adrenergic drugs: effect peripheral nervous system mimicking or blocking neurotransmitters, acetyl choline, norepinephrine, dopamine etc.

Drugs for cardiovasular diseases: (for hypertension, heart diseases etc…captopril etc.)

Drugs for other metabolic disorders: Antidiabetics (Metformin etc.)

Psychoactive drugs: (barbiturates, valium etc.)

Histamine antagonists & local anesthetics (for allergies, asthma etc.. phenergan, procaine etc.)

Steroids

The Nobel Prize in Physiology or Medicine 2015

for their discoveries concerning a novel therapy against infections caused by roundworm parasites and malaria

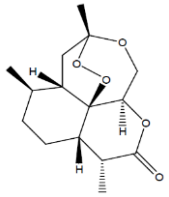
William C. Campbell
Drew U., NJ, USA
b. 1930, (Ireland)

Satoshi Omura
Kitasato U, Japan
b. 1935 (Japan)

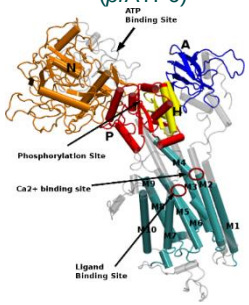
Youyou Tu
China Academy, China
b. 1930 (China)

Avermectin for river blindness and lymphatic filariasis & Artemisinin for malaria

Artemisinin is a great antimalarial ! But how does it work?



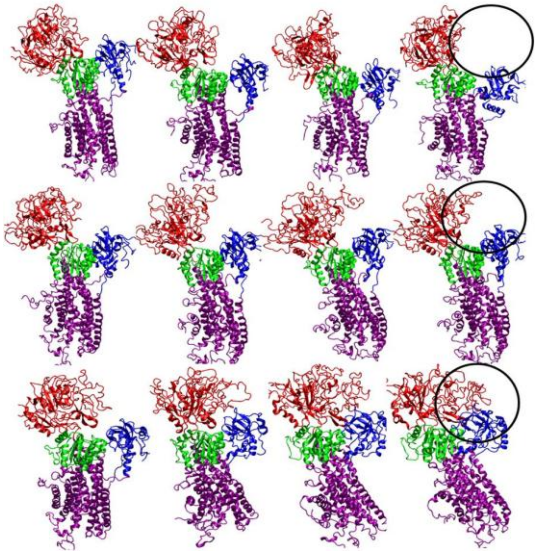
Artemisinin



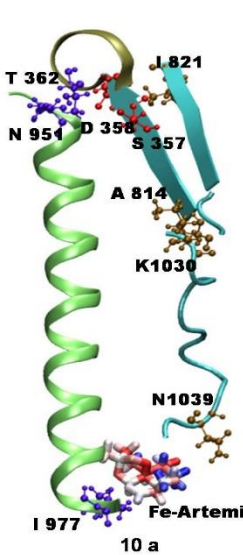
Unbound *pf*ATP6

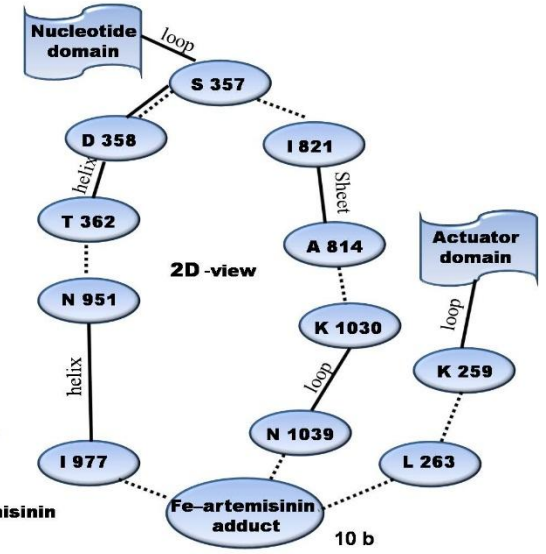
Artemisinin bound *pf*ATP6

Fe-artemisinin bound *pf*ATP6



MD snapshots of complexes on the interval of 25 ns



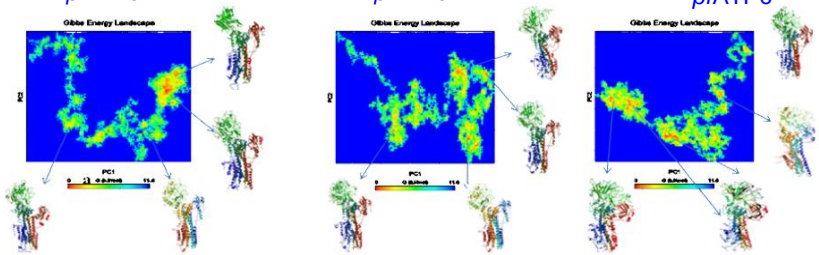


Interaction network of ligand and N-domain of PfATP6

Ca^{2+}bound *pf*ATP6

Artemisinin bound *pf*ATP6

Fe – Artemisinin bound *pf*ATP6

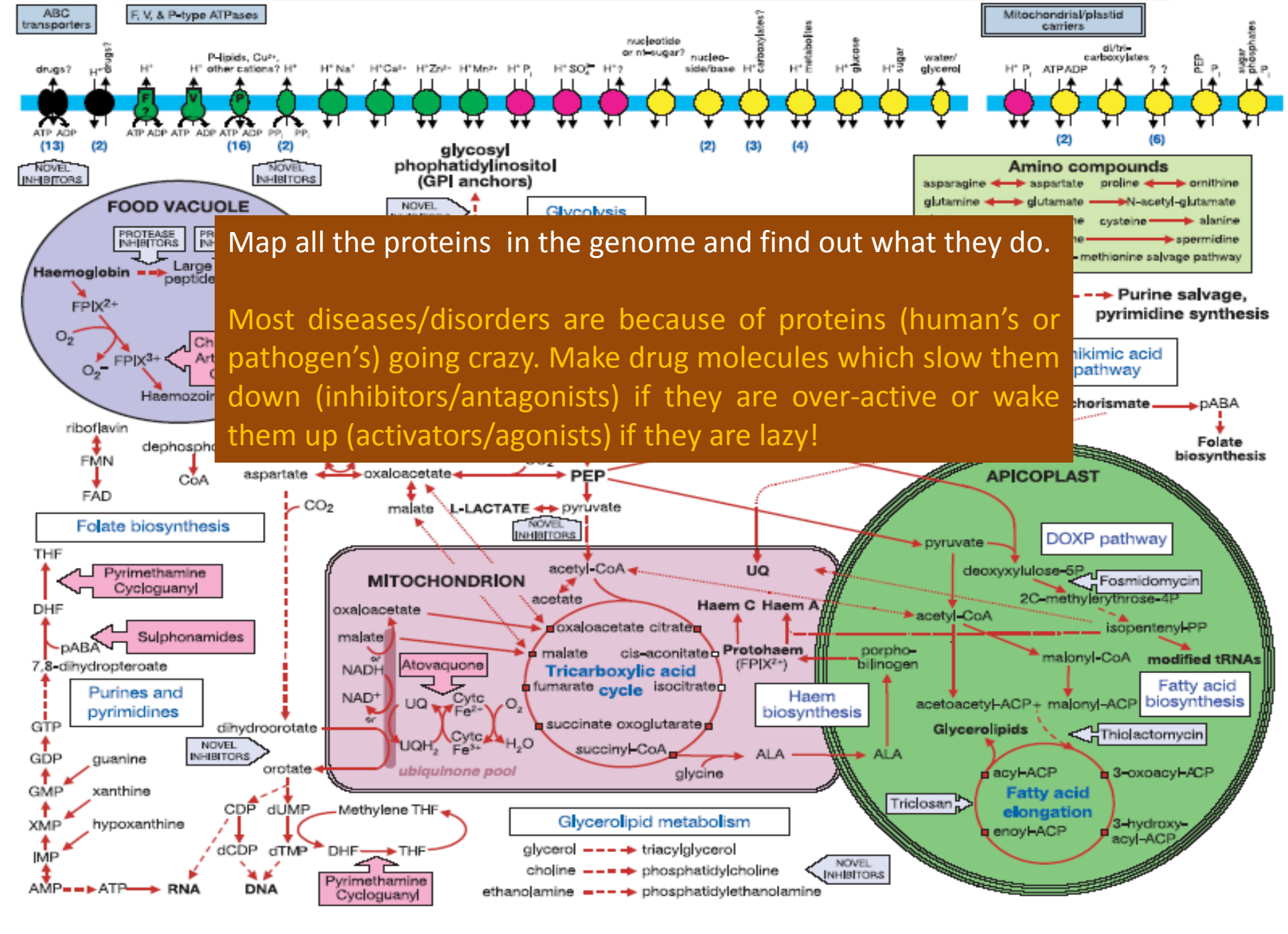


Iron in the blood electronically activates artemisinin and the activated complex then binds to an enzyme pfATPase of the parasite and induces a conformational change in the enzyme which closes the calcium pump in the parasite thus killing the parasite.

"F = ma" on a supercomputer (Molecular dynamics simulation) provides *an* answer

Ashutosh Shandilya, B. Jayaram, Sajeev Chacko, Indira Ghosh, "A Plausible mechanism for the antimalarial activity of artemisinin", 2013, *Scientific Reports 3, Article number: 2513*

OVERVIEW OF METABOLISM AND TRANSPORT IN *P.falciparum (malarial parasite)*



COST & TIME INVOLVED IN DRUG DISCOVERY

Target Discovery

2.5yrs ↓ *4%*

Lead Generation

Lead Optimization

3.0yrs ↓ *15%*

Preclinical Development

1.0yrs ↓ *10%*

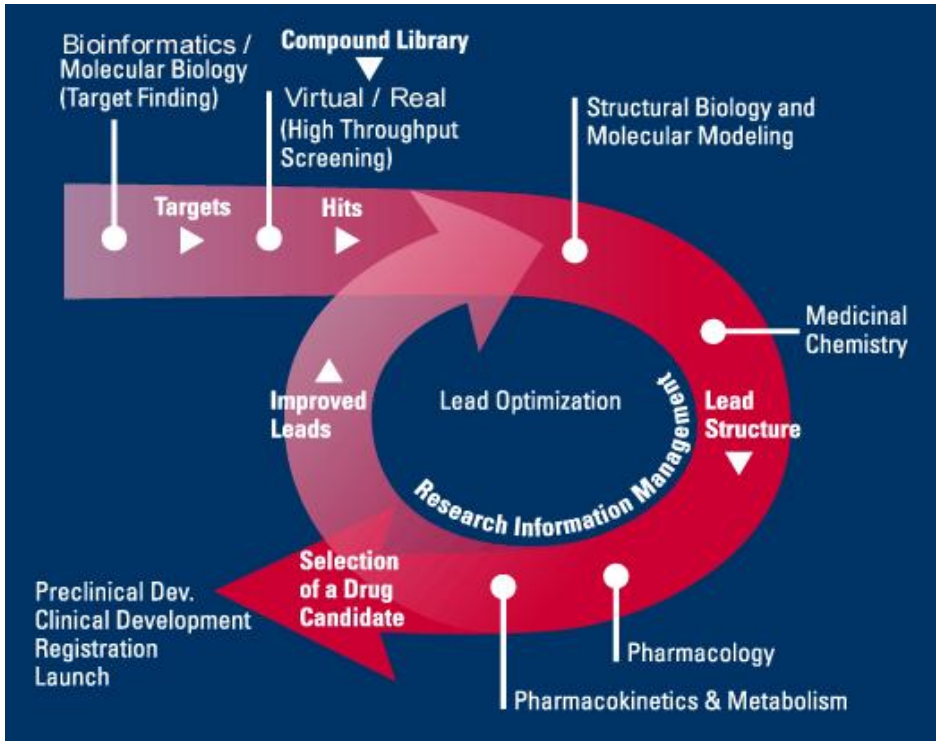
Phase I, II & III Clinical Trials

6.0yrs ↓ *68%*

FDA Review & Approval

1.5yrs ↓ *3%*

Drug to the Market

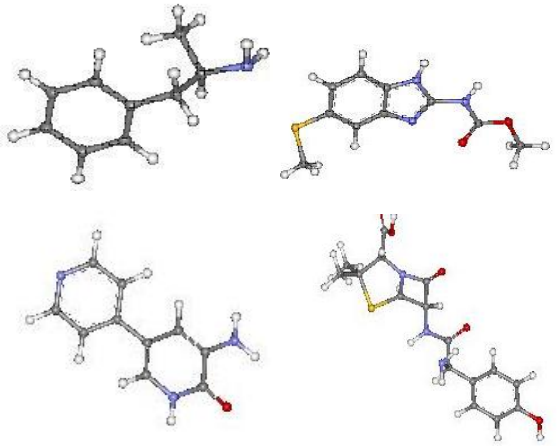


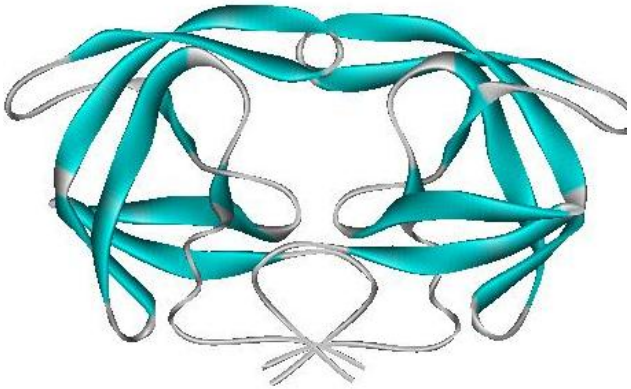
In silico interventions are poised to cut down the cost and time in drug discovery

14 yr $1.4 billion (revised to $2.6 billion in 2016)

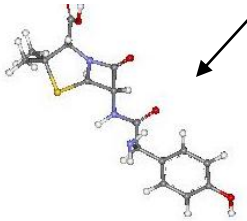
Source: PAREXEL's Pharmaceutical R&D Statistical Sourcebook, 2001, p96.; Hileman, Chemical Engg. News, 2006, 84, 50-1.

Target Directed Lead Molecule Design





Computer Aided Drug Design



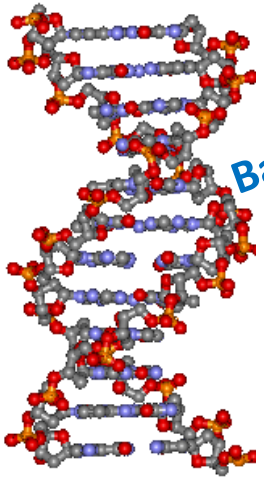
DRUG

NON-DRUG

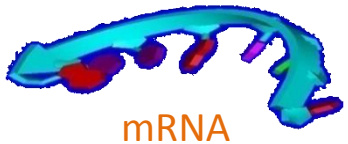
Genome

ChemGenome

A novel method to interpret the language of DNA and to identify protein coding genes and other functional units on genomic DNA



DNA



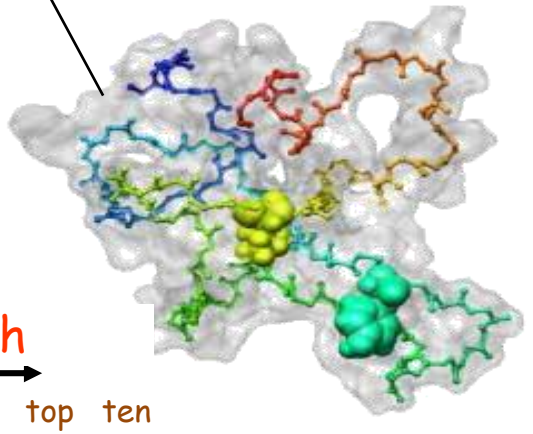
mRNA

...SEEARTINSCIENCE.....

Polypeptide Sequence

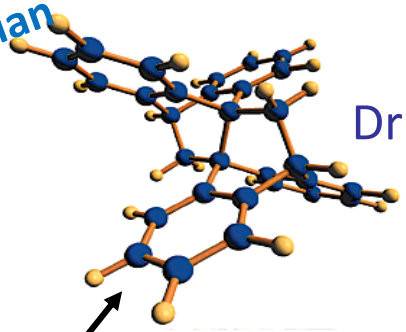
Bhageerath

Ranked among the top ten servers globally, Bhageerath predicts tertiary structures of proteins, tackling a grand challenge problem



Protein

Back to the dream plan



Drug

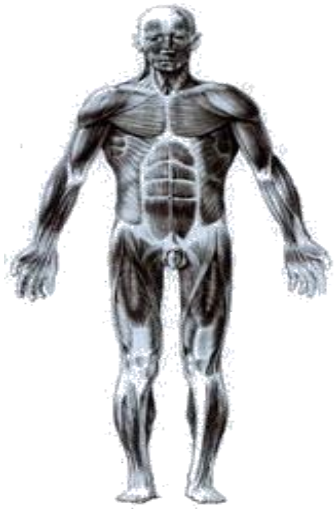
Sanjeevini

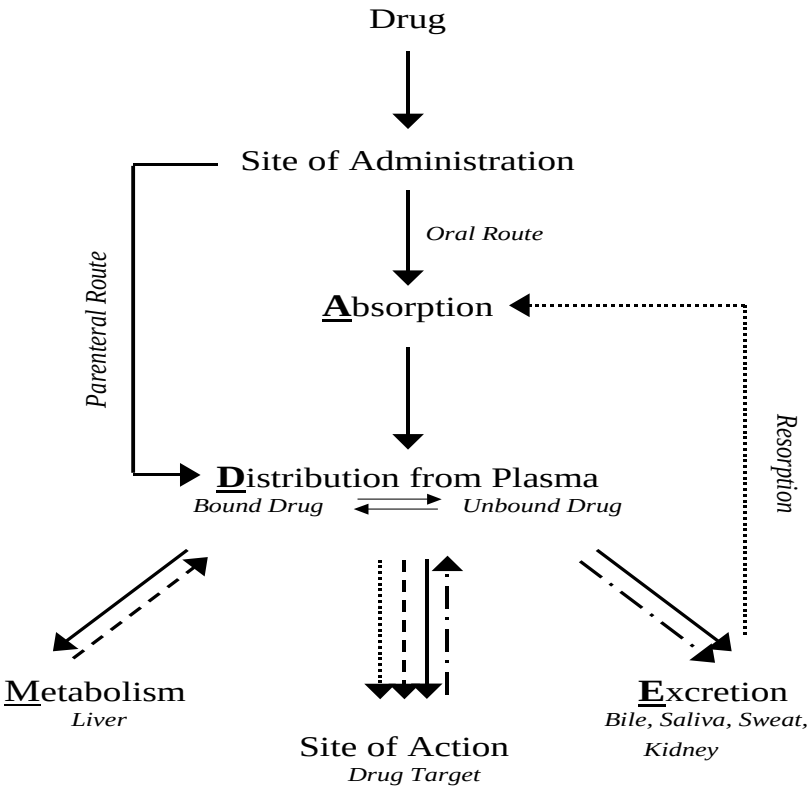
A freely accessible state of the art software suite for structure based drug discovery

Snapshot of the Supercomputer @IITD used for the deployment of *Dhanvantari* Suite

"GENOME TO DRUG" (*DHANVANTARI*) THE IITD PATHWAY ENVISAGES DELIVERING NOVEL DRUG MOLECULES/PERSONALIZED MEDICINE TO SOCIETY FROM GENOMIC / PROTEOMIC INFORMATION

Future of Drug Discovery: Towards a Molecular View of ADMET





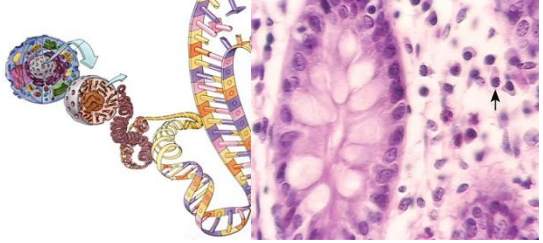
What are the five rules of toxicity?

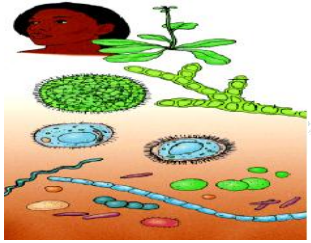
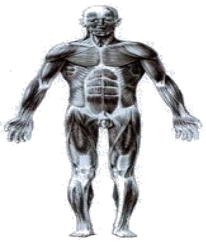
Can we make drugs which are least toxic to humans?

Can we automate this process?

The distribution path of an orally administered drug molecule inside the body is depicted. Black solid arrows: Complete path of drug starting from absorption at site of administration to distribution to the various compartments in the body, like sites of metabolism, drug action and excretion. Dashed arrows: Path of the drug after metabolism. Dash-dot arrows: Path of drug after eliciting its required action on the target. Dot arrows: Path of the drug after being reabsorbed into circulation from the site of excretion.

Affinity/specificity are under control but toxicity is yet to be conquered.


Now that

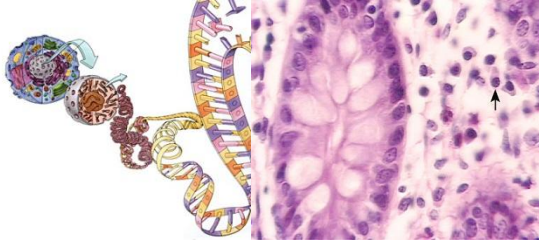
1. We understand the language of genomic DNA and can write our own genomic stories,

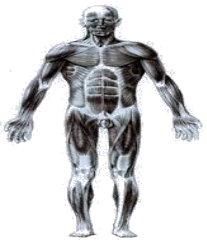
2. We solved the protein folding and inverse protein folding problem..and can create biocatalysts at will..,

3. We have algorithms and softwares for accurate ΔG, k, IC_{50}, LD_{50} predictions, &

4. We can create drugs for any person / any disease or disorder & have eradicated disease from the planet,

Let us move on ….





No need to ban Diwali fire crackers !

Clean up air pollutants…(CO/NO2/SO2 …) & Green house gases (CO2/CH4/N2O..)..using plants carrying synthetic genomes..and plant them on road side or decorate your room with them for clean air.

Use ideas from photosynthesis, nitrogen fixation, synthetic genomes (synthia)/Gene therapy/GM Crops to convert oxides of carbon and nitrogen to carbohydrates & proteins of your choice in a plant !!

Step 1: Write down the reactions ..Compute the total ΔG. If it is not spontaneous couple them to sun light or ATP hydrolysis..
Step 2: Design biocatalysts (inverse protein folding..given the shape, what is the sequence)..on the analogy of enzymes to catalyze the reactions to work in real time…
Step 3: Test the plan in a petri dish.
Step 4: Assemble a genome to execute the plan and insert it (viruses do) into a decorative plant.

Some of the carbohydrates generated could be used to produce ATP required for the reactions. Some of the proteins could be the biocatalysts you want to drive the reactions faster.

Assignment due in: 2020.