PENGANTAR ANTIMIKROBA

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Terminologi

- **Antimikroba:** bahan kimia *alami atau sintetik* yang digunakan untuk membasmi atau menghambat pertumbuhan mikroorganisme.

  Yang termasuk Antimikroba : Antibakteri, antivirus, antifungi

- **Menurut asalnya, ada 3 gol antimikroba :**

  Antimikroba alami

  Antimikroba Sintetik

  Antimikroba Semisintetik

Saat ini istilah Antibiotik tms Antibiotik alami, semisintetik & sintetik

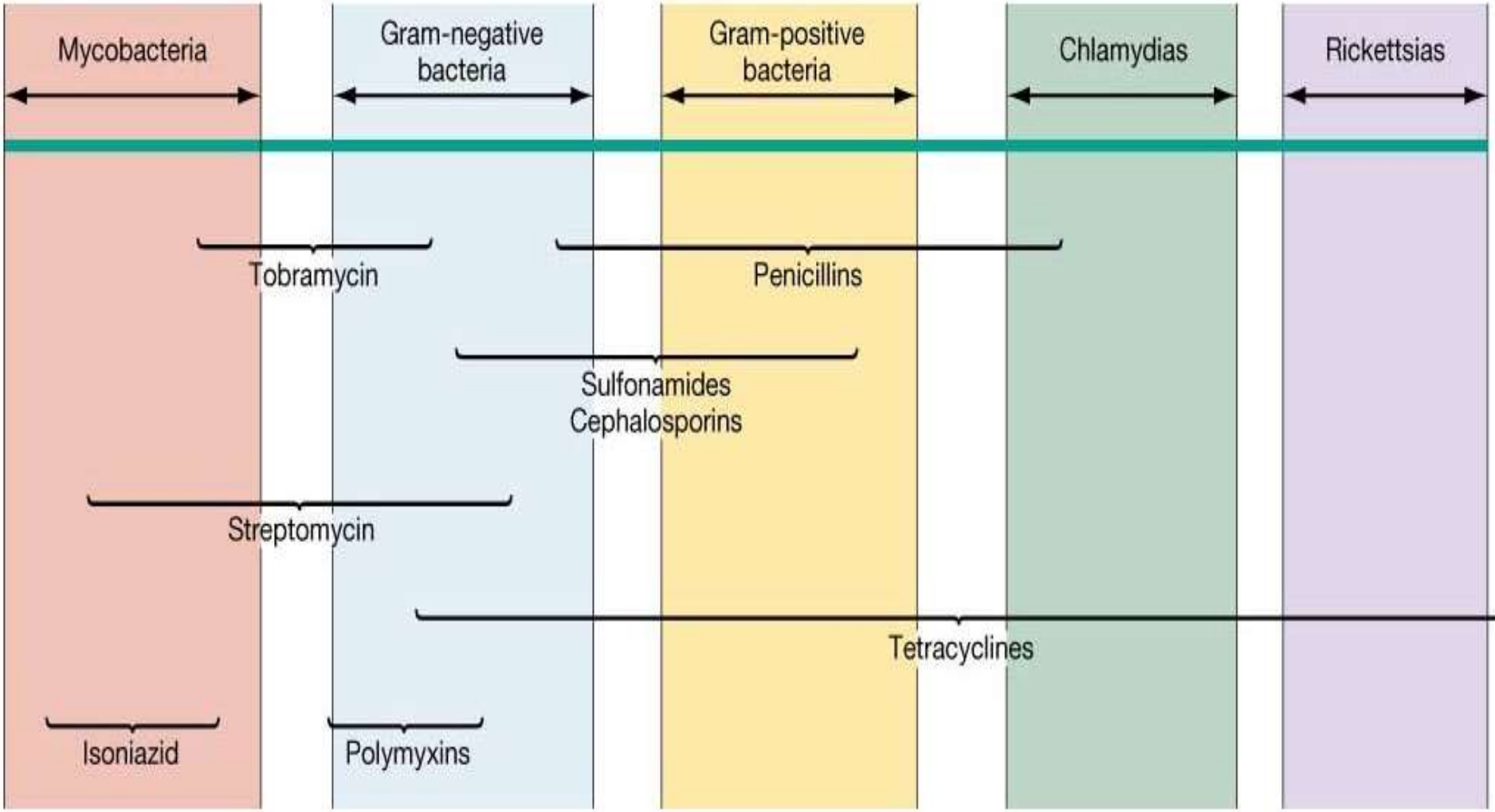
Karakteristik Antimikroba

- **Bds toksisitas selektif** (toksik thd sel mikroba tp tdk toksik thd sel hospes) : **tinggi** (antibakteri), **rendah** (antijamur, antiparasit, antivirus)

- **Bdsr kemampuan thd mikroba**:
  - ★ **sidal** (killing)
  - ★ **statik** (inhibitory)

- **Bds Spektrum** (rentang bakteri / mikroorganisme yang dipengaruhi oleh antibiotik tertentu) :
  - ☺ **Spektrum luas**
  - ☺ **Spektrum sempit**
  - ☺ **Spektrum terbatas**

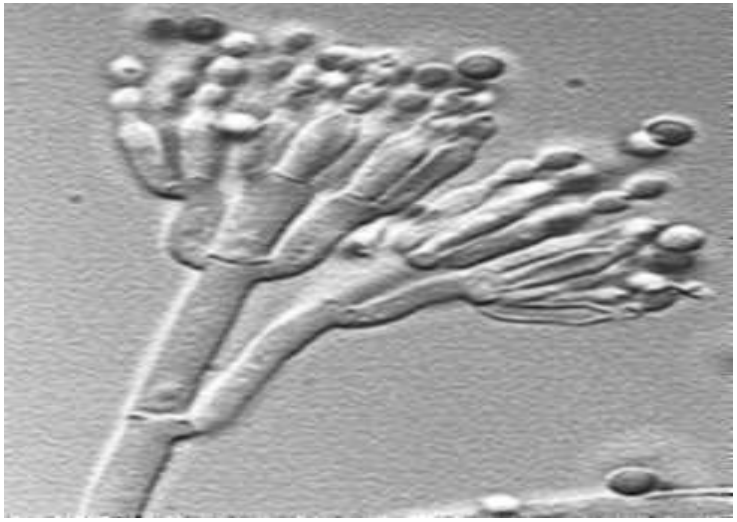
Spektrum antibakteri



SIFAT ANTIBIOTIKA yang BAIK

- Spektrum luas (??)
- Toksisitas selektif yang tinggi
- Nonalergen pada host.
- Bersifat bakterisidal bukan bakteriostatik
- Tidak merusak flora normal host.
- Mampu mencapai tempat infeksi.
- Murah dan mudah diproduksi.
- Stabil (have a long half-life).
- Resistensi jarang dan tidak mudah terjadi
- Tidak menyebabkan resistensi pada kuman

Sir Alexander Fleming



- 1910, Paul Ehrlich, German chemist, idea of selective toxicity : that certain chemicals that would be toxic to some organisms, e.g., infectious bacteria, would be harmless to other organisms, e.g., humans.
- 1928, Sir Alexander Fleming, a Scottish biologist, observed that *Penicillium notatum,* a common mold, had destroyed staphylococcus bacteria in culture.

- 1941 : Penggunaan Penicillin di klinik
- Paska PD II: Identifikasi streptomycin, chloramphenicol, chlor tetracyline
- 30% pasien MRS mendapat terapi Antimikroba
- Misused : 50% pasien yang didiagnosa viral resp.tract infection diberi AB
- The problem: AB-resistant pathogens

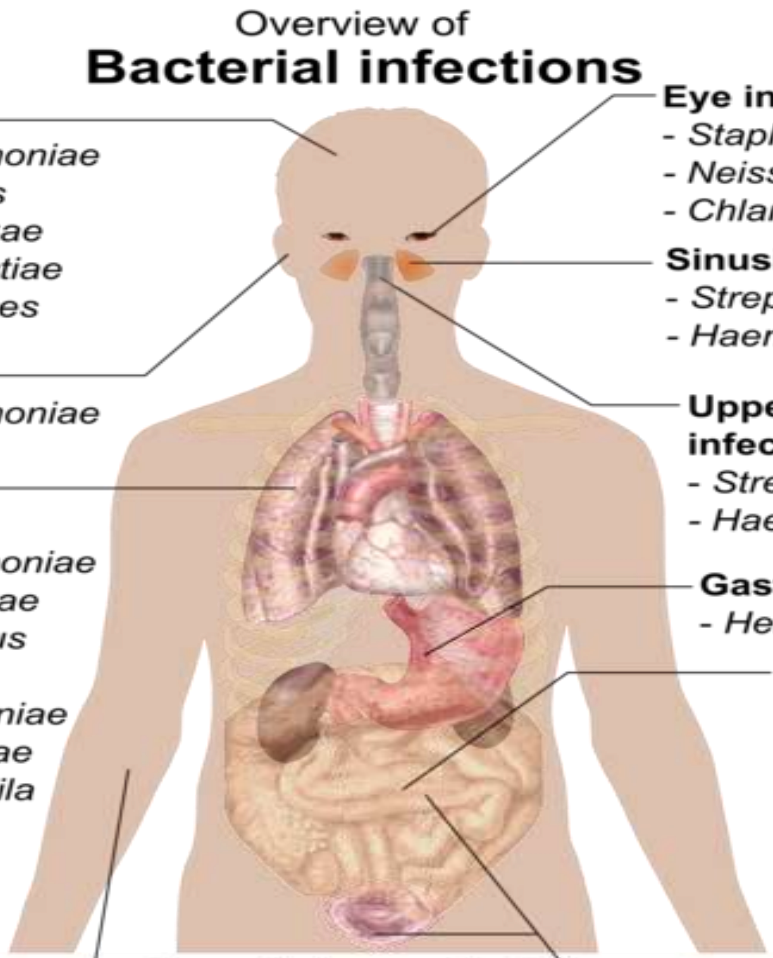
  → dokter harus bijaksana dan selektif dlm penggunaan AB


ANTIBAKTERI &
MEKANISME KERJANYA

Bakteri dan Tempat infeksi

- Bakteri tertentu mempunyai kecenderungan untuk menyebabkan infeksi pada tempat tertentu
- Pemilihan antibiotik sebelum tersedia kultur: (Terapi empiris)
  - » Tempat infeksi dan kemungkinan organisme penyebab
  - » Pengecatan Gram

Bakteri dan tempat infeksinya



Bacterial meningitis
- *Streptococcus pneumoniae*
- *Neisseria meningitidis*
- *Haemophilus influenzae*
- *Streptococcus agalactiae*
- *Listeria monocytogenes*

Otitis media
- *Streptococcus pneumoniae*

Pneumonia
Community-acquired:
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Staphylococcus aureus*

Atypical:
- *Mycoplasma pneumoniae*
- *Chlamydia pneumoniae*
- *Legionella pneumophila*

Tuberculosis
- *Mycobacterium tuberculosis*

Skin infections
- *Staphylococcus aureus*
- *Streptococcus pyogenes*
- *Pseudomonas aeruginosa*

Sexually transmitted diseases
- *Chlamydia trachomatis*
- *Neisseria gonorrhoeae*
- *Treponema pallidum*
- *Ureaplasma urealyticum*
- *Haemophilus ducreyi*

Eye infections
- *Staphylococcus aureus*
- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*

Sinusitis
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*

Upper respiratory tract infection
- *Streptococcus pyogenes*
- *Haemophilus influenzae*

Gastritis
- *Helicobacter pylori*

Food poisoning
- *Campylobacter jejuni*
- *Salmonella*
- *Shigella*
- *Clostridium*
- *Staphylococcus aureus*
- *Escherichia coli*

Urinary tract infections
- *Escherichia coli*
- Other Enterobacteriaceae
- *Staphylococcus saprophyticus*
- *Pseudomonas aeruginosa*

The molecular basis of antibacterial chemotherapy

- Chemotherapeutic drugs should be toxic to invading organisms and innocuous to the host. Such selective toxicity depends on the identification of biochemical differences between the pathogen and the host that can be appropriately exploited.
- Three general classes of biochemical reaction are potential targets for chemotherapy of bacteria:
  - *class I*: biochemical reactions that utilise glucose and other carbon sources to produce ATP and simple carbon compounds
  - *class II*: metabolic pathways utilising energy and class I compounds to make small molecules (e.g. amino acids and nucleotides)
  - *class III*: anabolic pathways that convert small molecules into macromolecules such as proteins, nucleic acids and peptidoglycan

Biochemical reactions as potential targets for chemotherapy

- Class I reactions are poor targets.
- Class II reactions are better targets:
  - *folate synthesis* in bacteria is inhibited by sulphonamides;
  - *folate utilisation* is inhibited by folate antagonists, for example **trimethoprim** (bacteria), **pyrimethamine** (malarial parasite).
- Class III reactions are important targets:
  - *peptidoglycan synthesis* in bacteria can be selectively inhibited by β-lactam antibiotics (e.g. **penicillin**);
  - *bacterial protein synthesis* can be selectively inhibited by antibiotics that prevent binding of tRNA (e.g. tetracyclines), promote misreading of mRNA (e.g. aminoglycosides), inhibit transpeptidation (e.g. **chloramphenicol**) or inhibit translocation of tRNA (e.g. **erythromycin**);
  - *nucleic acid synthesis* can be inhibited by altering base pairing of DNA template (e.g. the antiviral **vidarabine**), by inhibiting DNA polymerase (e.g. the antivirals **aciclovir** and **foscarnet**) or by inhibiting DNA gyrase (e.g. the antibacterial **ciprofloxacin**).

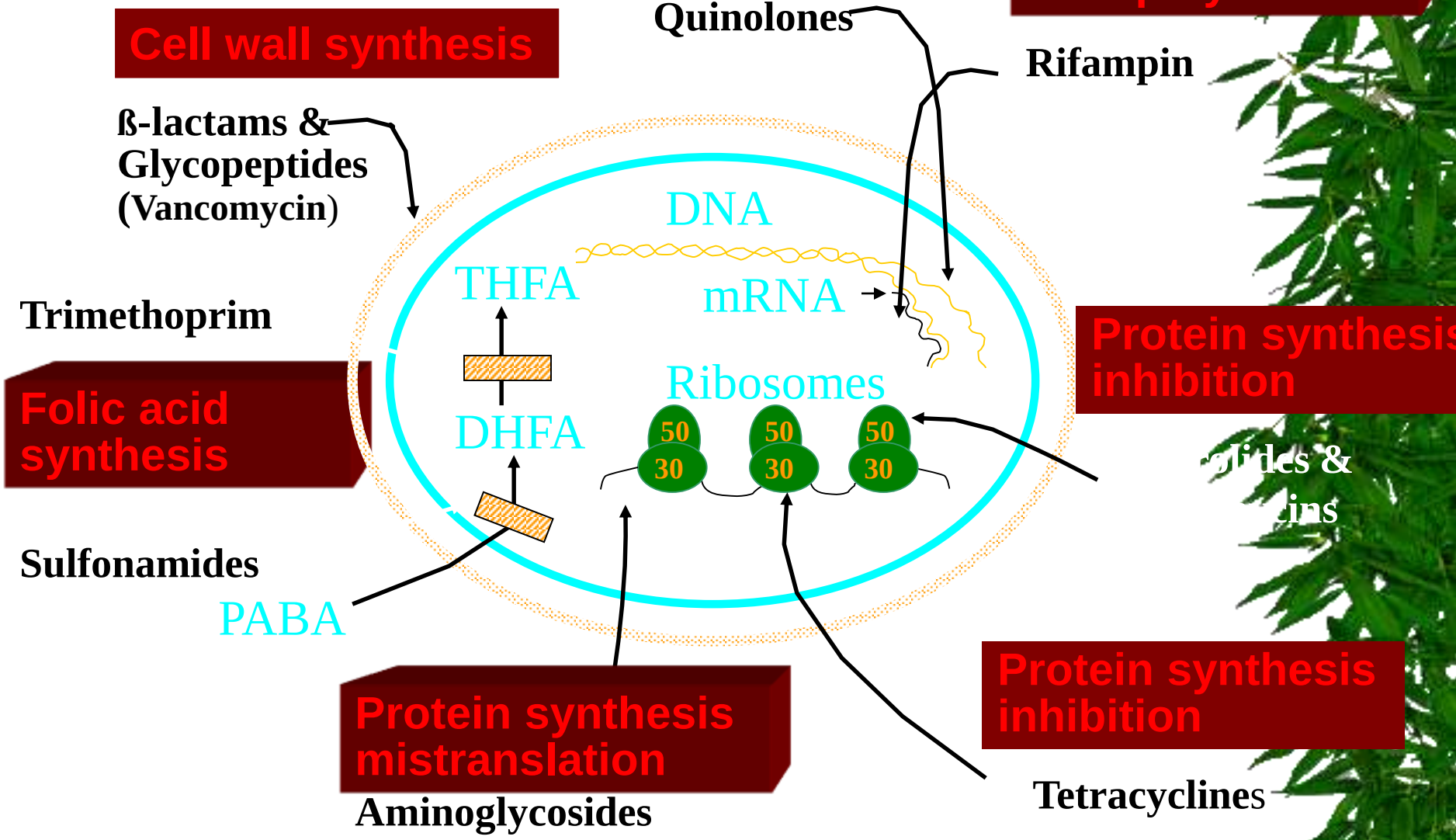
Penggolongan Antimikroba berdasar Mekanisme Kerja

A. Menghambat sintesa dinding sel
B. Merusak membran plasma
C. Menghambat sintesa protein
D. Menghambat sintesa asam nukleat
E. Menghambat sintesa metabolit essential

Formed structures of the cell that are targets for chemotherapy

- The bacterial cell wall may be affected by several classes of antibiotics, such as the β-lactams.
- The plasma membrane is affected by:
  - **amphotericin**, which acts as an ionophore in fungal cells
  - azoles, which inhibit fungal membrane ergosterol synthesis
- Microtubule function is disrupted by:
  - benzimidazoles (antihelminthics)
- Muscle fibres are affected by:
  - avermectins (antihelminthics), which increase Cl^- permeability
  - **pyrantel** (antihelminthic), which stimulates nematode nicotinic receptors, eventually causing muscle paralysis by depolarising neuromuscular block

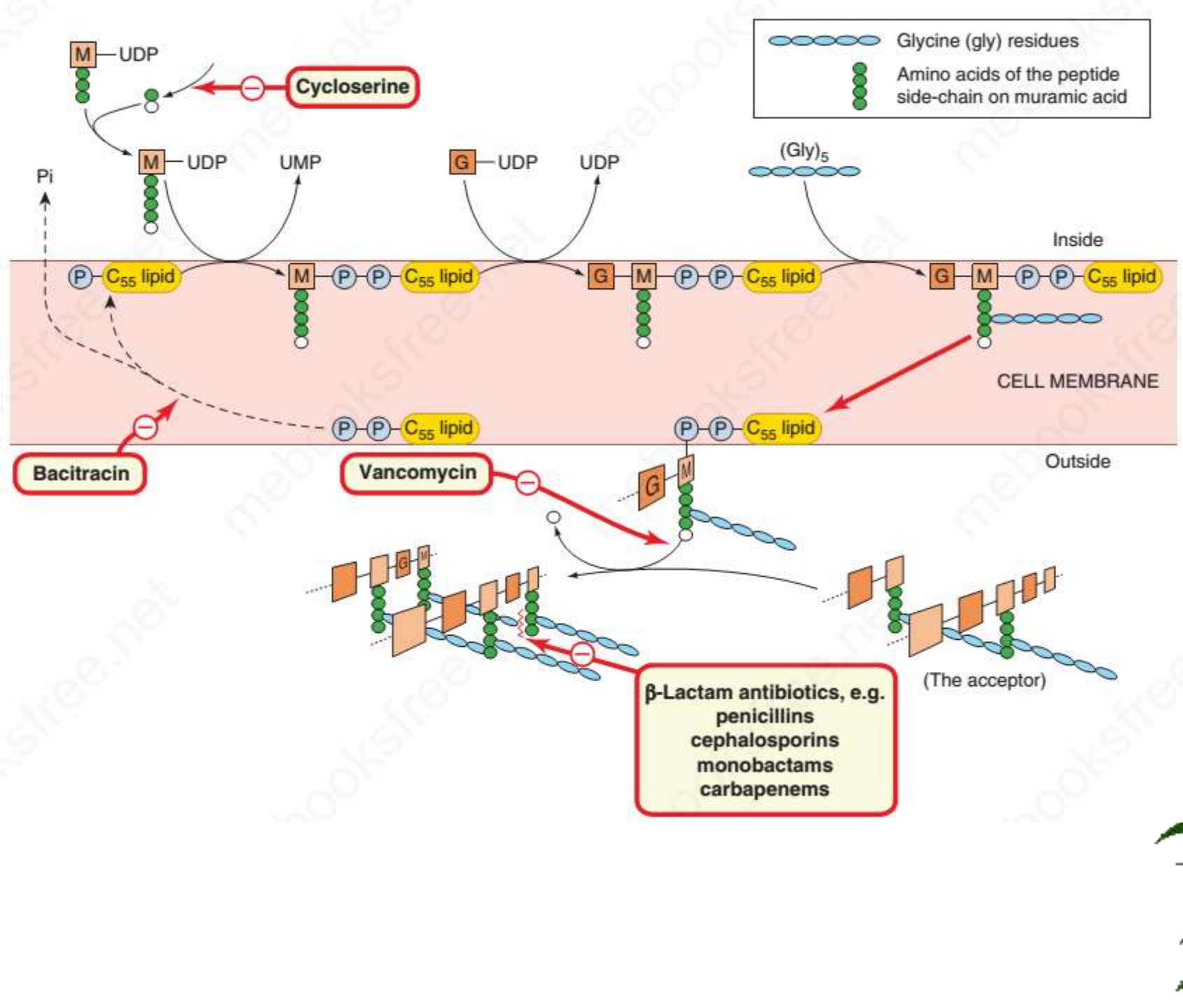
Antimikroba dan tempat kerja utama



Cohen. Science 1992; 257:1064

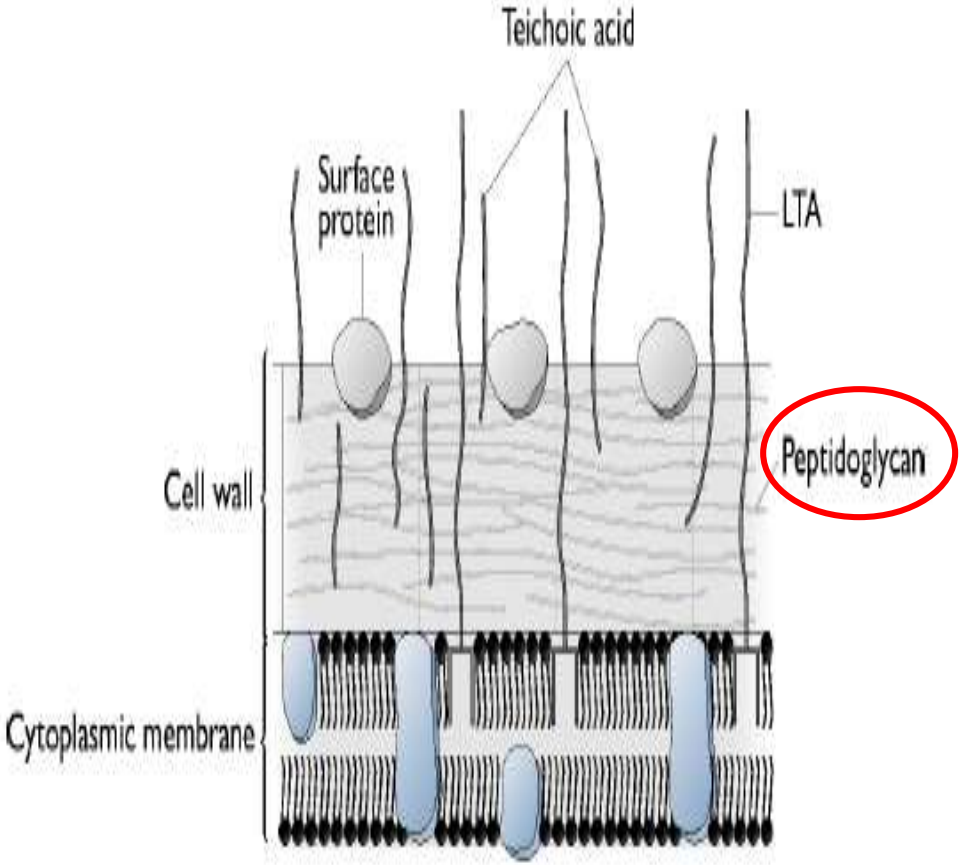
A. Menghambat Sintesa Dinding Sel

- Dasar Toksisitas selektif : perbedaan sel dinding bakteri (prokariot) {➔memp peptidoglikan} dg hospes (eukariot)
- Tiga tahap sintesa dinding sel yg dihambat antibiotik :
  - ✓ Sintesa monomer murein (Basitrasin, Sikloserin, Fosfomisin)
  - ✓ Polimerisasi (Vankomisin)
  - ✓ Transpeptidasi (thp akhir) : hambat cross-linking rantai peptida utk mmbentuk seny peptidoglikan → aktivasi enz otolitik dlm dinding sel → sel lisis (AB beta laktam : Penisilin, Sefalosporin, Karbapenem)
- Efektif saat bakteri sedang aktif membelah

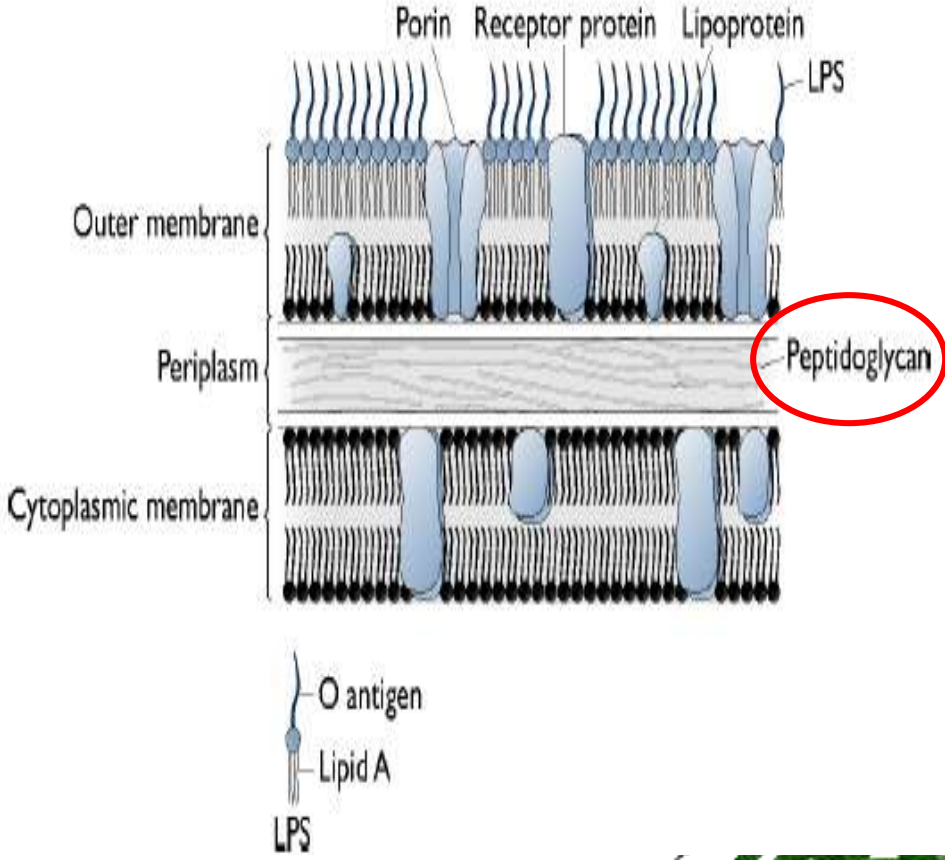

Glycine (gly) residues
Amino acids of the peptide side-chain on muramic acid
M
UDP
Cycloserine
M
UDP
UMP
G
UDP
UDP
(Gly)5
Pi
Inside
P
C55 lipid
M
P
P
C55 lipid
G
M
P
P
C55 lipid
G
M
P
P
C55 lipid
CELL MEMBRANE
P
P
C55 lipid
P
P
C55 lipid
Outside
Bacitracin
Vancomycin
G
M
G
M
β-Lactam antibiotics, e.g.
penicillins
cephalosporins
monobactams
carbapenems
(The acceptor)

Struktur Dinding Sel Bakteri

Gram positive



Gram negative



Peptidoglycan: berfungsi mempertahankan tekanan osmotik, Bentuk dan integritas struktural sel bakteri

B. Merusak Membran Plasma

- Berikatan pada membran, merubah permeabilitas, dan menyebabkan kebocoran (metabolit penting keluar)
- Contoh:
  - ☺ Polimiksin-B (mengikat fosfolipid membr bakteri)
  - ☺ Amphotericin B (mengikat ergosterol membr fungi)
  - ☺ Gol Azol :klotrimazol, ketokonazol, itrakonazol (hamb metilasi pd biosintesa ergosterol)

Perbedaan Struktur Bakteri dan Jamur

	Bacteria	Fungi
Nukleus	tidak	ya
Ukuran sel	1-5 m^3	20-50 m^3
Ribosom	70S	80S
Dinding sel	Peptidoglikan	Chitin
Membran	Tanpa sterol	Ergosterol

c. Menghambat Sintesa Protein

- Sebagian besar **bakteriostatik**
- Toksisitas Selektif krn **perbedaan strukt ribosom** prokariotik (bakteri) dan eukariotik (hospes)
  - Sel eukariotik mempunyai ribosom 80S (60S + 40S subunits).
  - Sel prokariotik mempunyai ribosom 70S (50S + 30S subunits).

C. Menghambat Sintesa Protein

- **Translasi (RNA → sintesa protein)**

  - mRNA ditranslasi oleh rRNA (70S)
  - 2 subunit ribosom : 30S, 50S

  ⇨ **30S : Aminoglikosida, Streptomisin, Tetrasiklin**

  50S : Makrolid, Kloramfenikol, Linkomisin, Streptogamin, Oksazolidinon

  - 3 tahap yg dipengaruhi :
    - Inisiasi : Aminoglikosida, Spektinomisin
    - Elongasi : Tetrasiklin, Kloramfenikol, Makrolid, Fusidic acid
    - Terminasi / Translokasi :

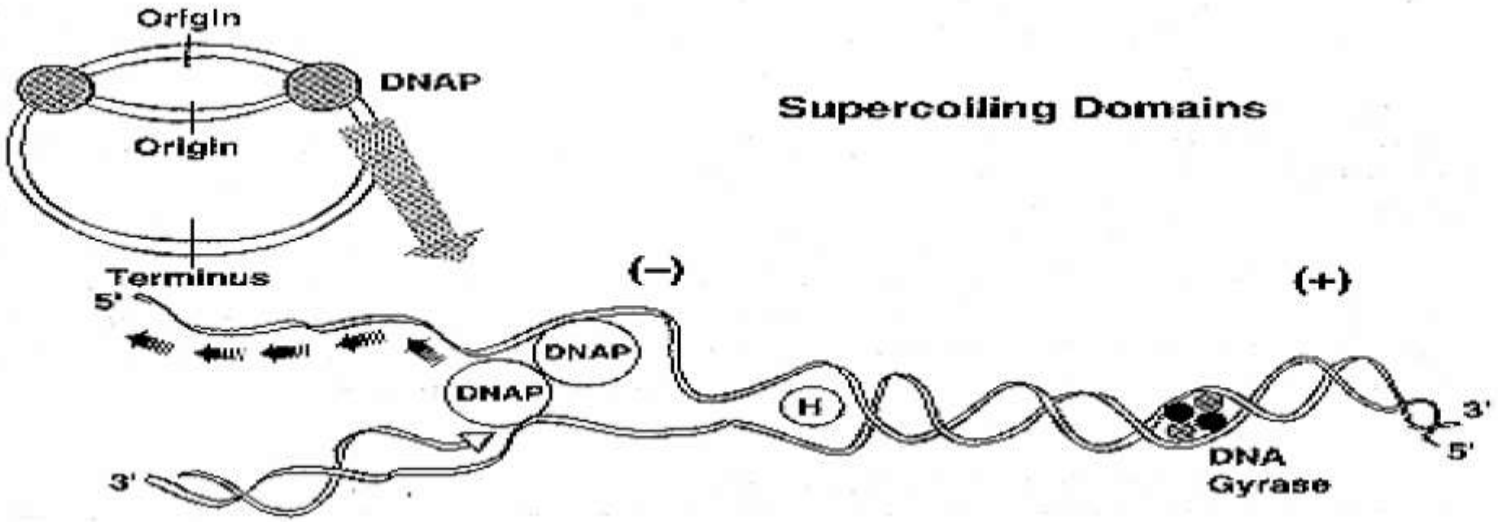
- **Aminoglikosida (streptomycin, kanamycin, gentamicin, tobramycin, amikacin, netilmicin, neomycin (topical)**
  - ✓ secara irreversibel mengikat 16S rRNA & membekukan kompleks inisiasi 30S (30S-mRNA-tRNA) shg inisiasi tidak terjadi.
  - ✓ Memperlambat sintesa protein yang telah berlangsung
  - ✓ Mengubah bentuk ribosom shg bentuk kodon juga berubah dan selanjutnya menyebabkan *misreading* oleh antikodon pada tRNA.

- **Spektinomisin :** secara reversibel mempengaruhi interaksi m-RNA dg 30S ribosom. Secara struktur mirip Aminoglikosida tapi tidak menyebabkan misreading mRNA

- **Tetrasiklin** : secara reversibel mengikat 30S ribosom dan menghambat ikatan aminoacyl-t-RNA pada *acceptor site* 70S ribosom mRNA
- **Kloramfenikol, Klindamisin & Linkomisin** : mengikat 50S ribosom dan menghambat aktivitas peptidyl transferase shg terjadi hamb perpnjangan rantai polipeptida
- **Makrolid (erythromycin, clarithromycin, azithromycin, spiramycin)** : menghambat *translocation* dg mencegah perjalanan ribosom di sepanjang mRNA
- **Fusidic acid** : mengikat *elongation factor G* (EF-G) dan menghambat *release* EF-G dari kompleks EF-G/GDP.

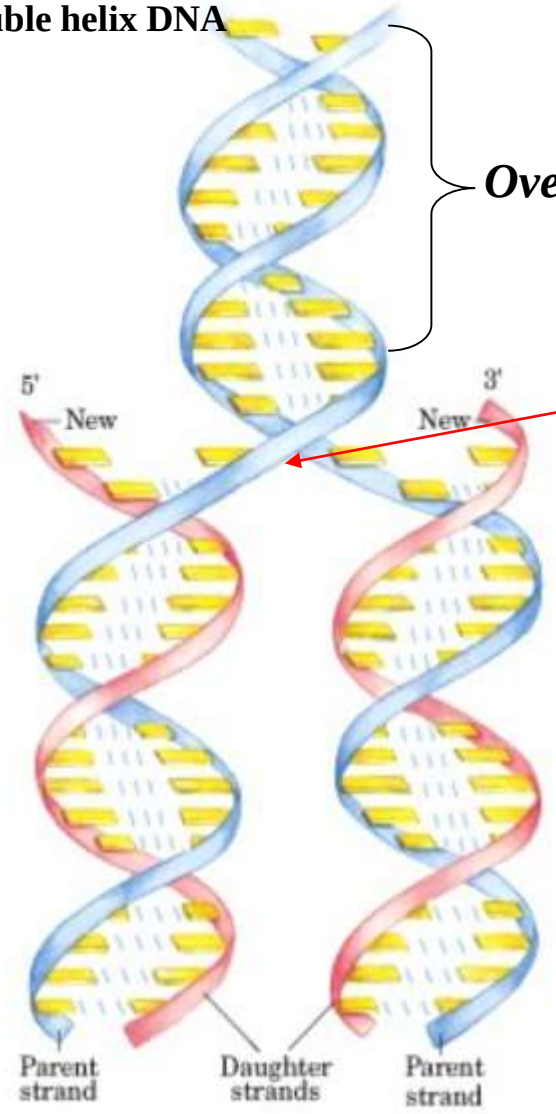
D. Menghambat sintesa asam nukleat

- Hambat sintesa DNA
  - **Contoh : Quinolon (<u>nalidixic acid</u>, <u>ciprofloxacin</u>**, ofloxacin, norfloxacin, levofloxacin, lomefloxacin, sparfloxacin)
  - mengikat sub unit A DNA gyrase (topoisomerase) dan mencegah supercoiling DNA, sehingga menghambat sintesa DNA
- Hambat sintesis RNA
  - **Contoh: rifampin**
  - Mengikat DNA-dependent RNA polymerase dan menghambat inisiasi sintesa mRNA



DNA Replications

Double helix DNA



Overwinding **(puntiran berlebihan)**

Titik pemisahan
(Replikasi & transkripsi)

Diatasi dengan:
Enzim DNA *gyrase*
(Topoisomerase)
↓
Negative supercoiling

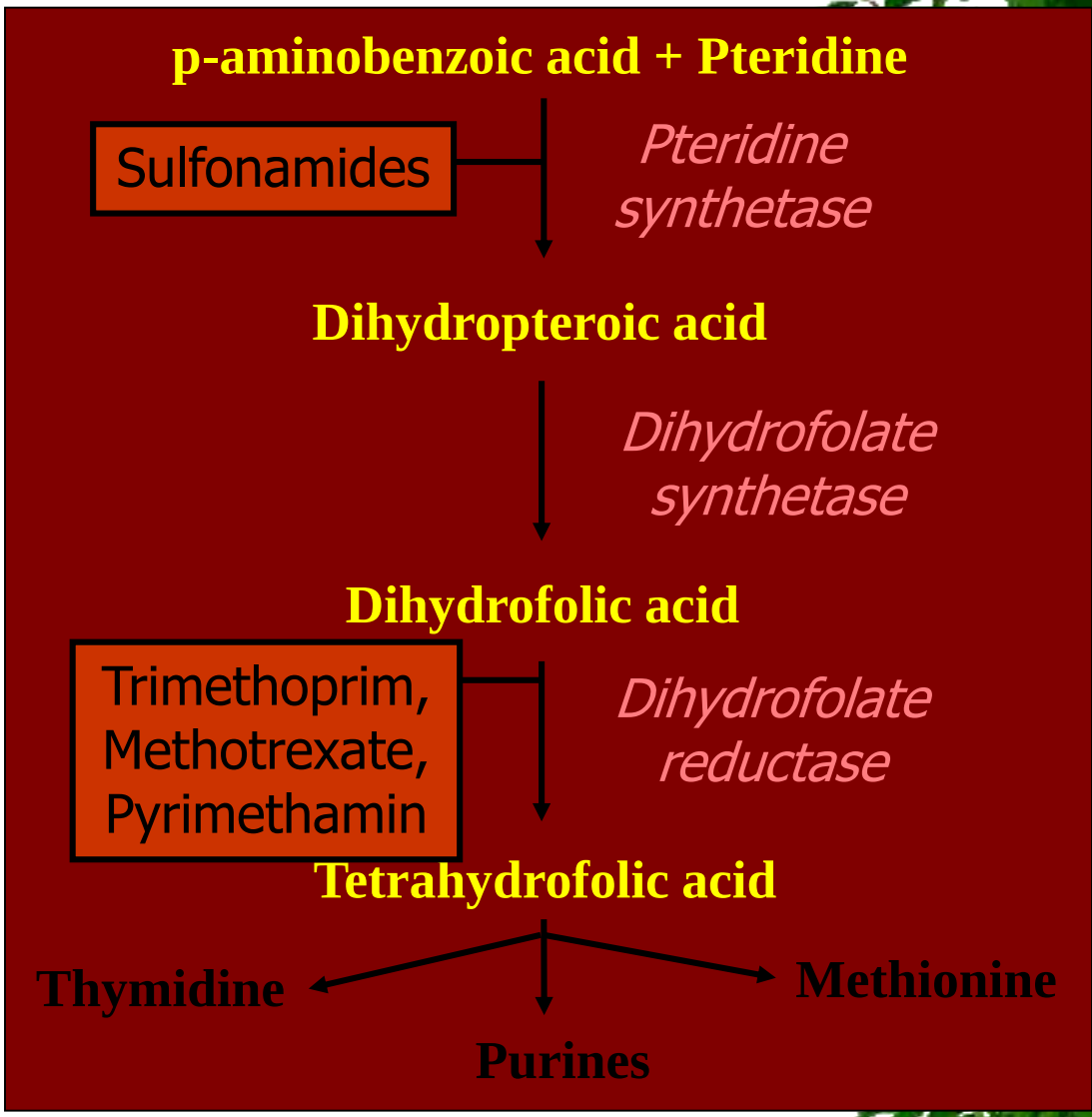
↑ ✗

Quinolone

E. Menghambat sintesa metabolit

- Sulfonamid analog thd PABA & secara kompetitif menghambat pembentukan dihydropteroic acid.

- Trimethoprim, MTX mengikat enzim dihydrofolate reductase dan menghambat pembentukan tetrahydrofolic acid




RESISTENSI
ANTIMIROBA

- Resistensi =kemampuan bakteri utk menetralisir & melemahkan daya kerja antibiotik.
- Resisten >< sensitif
- Satuan resistensi =KHM (Kadar Hambat Minimal) */Minimum Inhibitory Concentration (MIC) =kadar terendah AB(µg/mL) yg mampu menghambat tumbuh & berkembangnya bakteri. Peningkatan nilai KHM → tahap awal menuju resisten.*

Susceptibilitas vs. Resistensi

- Dosis obat harus cukup untuk bisa menimbulkan efek menghambat atau membunuh mikroorganisme
- Tapi besarnya dosis tersebut harus di bawah dosis yang bisa menimbulkan efek toksik pada sel manusia.

- Jk hal tsb dpt dicapai – mikroorganisme susceptibel / sensitif thd antimikroba
- Jk dosis efektif lebih tinggi daripada dosis toksik- mikroorganisme resisten thd antimikroba

- Beberapa kuman resisten antibiotik sdh banyak ditemukan di seluruh dunia,yaitu
  - *Methicillin-Resistant Staphylococcus Aureus (MRSA),*
  - *Vancomycin-Resistant Enterococci(VRE),*
  - *Penicillin-Resistant Pneumococci,*
  - *Klebsiella pneumoniae yang menghasilkan Extended-Spectrum Beta-Lactamase(ESBL),*
  - *Carbapenem-Resistant Acinetobacter baumannii*
  - *Multiresistant Mycobacterium tuberculosis*
- Terjadi akibat penggunaan antibiotik yang tidak bijak & penerapan kewaspadaan standar(*standard precaution) yg tdk benar di fasilitas pelayanan kesehatan.*

Asal Terjadinya Resistensi

- Resistensi non genetik
  - Bakteri tdk sedang aktif membelah
  - Bakteri menginfeksi organ yg tidak dpt dicapai obat
- Resistensi Genetik
  - merup sebagian besar kasus resistensi
  - dapat dipindahkan ke spesies bakteri lain
  - Dpt terj secara : kromosomal (mutasi spontan) & ekstrakromosomal (materi genetik lain mis. Plasmid)

- Antibiotic resistance is a naturally occurring phenomenon which plays a role in the normal bacterial ecology.
- In many bacterial species, resistance genes (r genes) are of ancient origin and are expressed in the presence of the antibiotic.
- R genes may be moved around between genetic elements within individual bacteria. There are several mechanisms:
  - Plasmids are extrachromosomal genetic elements that can replicate independently and can carry genes coding for resistance to antibiotics (r genes).
  - Transposons are stretches of DNA that can be transposed from one plasmid to another, from a plasmid to a chromosome or vice versa. A plasmid containing an r gene-bearing transposon may code for enzymes that cause the plasmid to be integrated with another. Following their separation, this transposon replicates so that both plasmids then contain the r gene.

- R genes, including *multicassette arrays* of drug resistance genes can also be transferred to other bacteria of the same, or different, species. There are several mechanisms:
  - The main method of transfer of r genes from one bacterium to another is by conjugative plasmids. The bacterium forms a connecting tube with other bacteria through which the plasmids pass.
  - A less common method of transfer is by transduction, i.e. the transmission by a bacterial virus (phage) of a plasmid bearing an r gene into another bacterium.

Mekanisme Resistensi

- **Obat diinaktivasi** (Mikroba memproduksi enzim yg merusak obat : β-lactamase; Chloramphenicol acetyl transferase; aminoglikosida adenilase, asetilase)
- **Obat gagal mencapai target** (mikroba mengubah permeabilitas membr sel)
- **Strukt target obat diubah** : mikroba mengubah RNA polymerase (rifampin), 30S ribosome (streptomycin), Penicillin binding proteins (penicillin, cephalosphorin), dll
- **Mikroba mengembangkan jln metab baru** : bakteri yg resisten thd sulfonamd mampu mengambil as. folat dari luar sel

Mekanisme Resistensi (lanj..)

- **Mikroba mengembangkan enz yg tetap dpt berfungsi utk metab nya tp tdk dpt dipengaruhi obat** : bakteri yg resisten thd trimethoprim
- **Mikroba memperbesar produksi metabolitnya :** bakteri yg resisten thd sulfonamd mampu menghasilkan PABA dlm jml besar

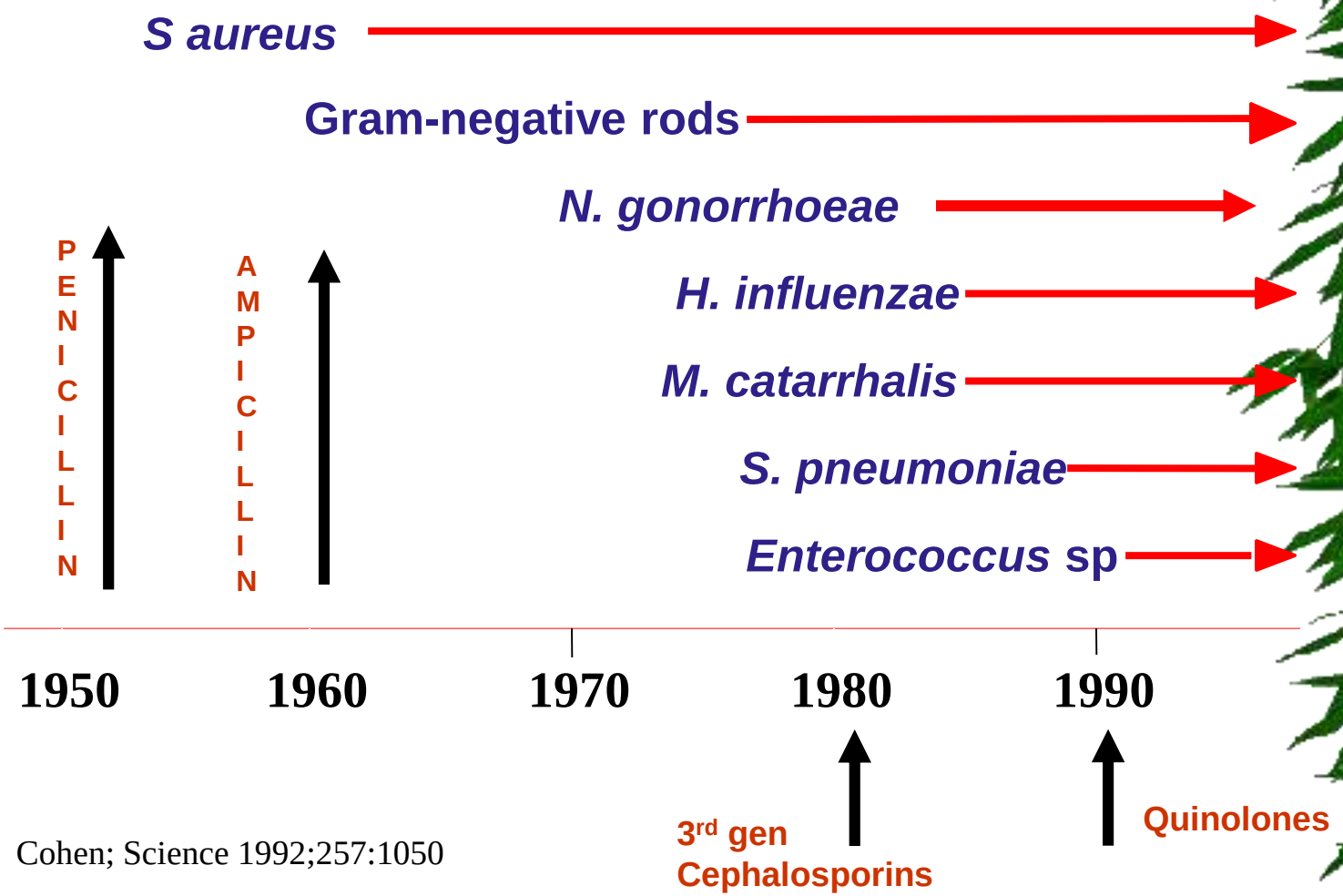
Agent	Mode of Antibacterial Action	Microbial Resistance Mechanism
Sulfonamides	Block synthesis of tetrahydrofolic acid and cell-linked metabolic pathways	R plasmid–coded, sulfonamide-resistant dihydrofolic acid synthetase
Trimethoprim	Competitive inhibition of dihydrofolic acid reductase; blocks synthesis of tetrahydrofolic acid	R plasmid–coded, trimethoprim-resistant dihydrofolic acid reductase
Penicillins and cephalosporins	Interfere with cell wall biosynthesis by interacting with penicillin-binding proteins	Hydrolysis of the antibiotic's β-lactam ring by β-lactamase enzyme
Tetracyclines	Inhibit protein synthesis by interaction with 30S and 50S ribosomal subunits	Interference with transport of drug into cell; cell unable to maintain drug
Aminoglycosides	Bind to 30S (and 50S) ribosomal subunit, cause translational misreading, inhibit peptide elongation	Enzymatic modification of drug by R plasmid–coded enzyme; drug has reduced affinity for ribosome; reduced drug transport into cell
Erythromycin and lincomycin	Bind to 50S ribosomal subunit; inhibit protein synthesis at chain elongation step	Enzymatic modification of ribosomal DNA of sensitive cells renders ribosome drug-resistant
Chloramphenicol	Inhibits protein synthesis by interacting with 50S ribosomal subunit	Drug inactivated by acetylation of –OH groups by chloramphenicol transacetylase; interference with drug transport into cell
Rifampin	Binds to bacterial RNA polymerase and blocks RNA synthesis (transcription)	Resistance arises by spontaneous mutation (no plasmid-coded mechanism known)

- Peningkatan kejadian resistensi bakteri terhadap AB bisa terjadi dg 2 cara,yaitu
  - Mekanisme *Selection Pressure. Jika bakteri resisten tersebut berbiak sec duplikasi setiap 20-30menit (untuk bakteri y*g berbiak cepat) → dlm 1-2 hari, seseorg tsb dipenuhi o/bakteri resisten. Jika seseorang terinfeksi oleh bakteri yang resisten maka upaya penanganan infeksi dg AB makin sulit .

    ⇒ penggunaan AB sec bijak
  - Penyebaran resistensi ke bakteri yg non-resisten melalui plasmid. Hal ini dpt disebarkan antar kuman sekelompok maupun dari satu org ke org lain.

    ⇒ me↑ ketaatan thd prinsip-kewaspadaan standar*(universal precaution).*

Emergence of Antibiotic-Resistant Bacteria



Cohen; Science 1992;257:1050


Prinsip
Penggunaan
ANTIMIKROBA

Faktor yg perlu dipertimbangkan

1. Resistensi mikroorganisme thd AB
2. Farmakokinetik dan Farmakodinamik AB
3. Interaksi AB dengan obat lain / makanan
4. Biaya

Farmakokinetik AB

a. *Time dependent killing.* Lamanya AB pd kdr ttt dlm darah hrs di atas KHM minimal selama 50% interval dosis. Mis.*penisilin,sefalosporin,& makrolida.*

b. *Concentration dependent.* Mkn ↑kadar AB dlm darah melampaui KHM→ mkn tinggi daya bunuhnya thd bakteri. Rasio kadar AB/KHM sekitar 10, artinya rejimen dosis yg dipilih harus mampu membuat kadar AB dlm serum / jaringan 10x > KHM. Jika tdk tercapai → gagal Tx (resistensi).

Variabel yg Mempengaruhi Farmakokinetik Antimikroba

Variable	Mechanism of Effect	Example
Age	Decreased renal function early in life and late in life	Need to decrease dose of aminoglycosides in neonates and elderly
Renal function	Important for drugs dependent on renal excretion	Need to decrease dose of aminoglycosides in patients with compromised renal function
Liver function	Important for drugs biotransformed in the liver	Need to decrease dose of chloramphenicol in patients with compromised liver function (e.g., premature newborns)
Fever/burns	Increased excretion or increased V_D of some drugs	Need to increase dose of aminoglycosides
Acetylation status	Important for drugs being acetylated	Need to increase dose of isoniazid in rapid acetylators on regimen of once- or twice-weekly dosage
Diabetes mellitus	Reduced absorption of certain drugs after intramuscular dosing	Need to increase dose of intramuscular penicillins in diabetics
Cystic fibrosis	Increased clearance and V_D of some drugs Altered absorption of some drugs	Need to increase dose of aminoglycosides in these patients Chloramphenicol palmitate malabsorbed because of lipase deficiency
GI surgery	Altered absorption of drugs in patients with short bowel (e.g., ileal bypass)	Ampicillin bioavailability is 15% of normal after small bowel bypass

V_D = volume of distribution.

Pola Aktivitas	Antibiotik	Tujuan Terapi	Parameter PK/PD
Tipe I Bakterisidal *concentration-dependence* dan	Aminoglikosid Fluorokuinolon Ketolid	Memaksimalkan kadar	- rasio *AUC-24* jam/KHM - rasio kadar puncak/KHM
Efek persisten yang lama			
Tipe II Bakterisidal *time-dependence* dan Efek persisten minimal	Karbapenem Sefalosporin Eritromisin Linezolid Penicillin	Memaksimalkan durasi paparan	waktu>KHM
Tipe III Bakterisidal *time-dependence* dan Efek persisten sedang sampai lama	Azitromisin Klindamisin Oksazolidinon Tetrasiklin Vankomisin	Memaksimalkan jumlah obat yang masuk sirkulasi sistemik	rasio *AUC-24* jam/KHM

AB Tipe I → rejimen dosis yg ideal =memaksimalkan kadar, makin ↑kadar, makin ekstensif & cepat tingkat bakterisidalnya→ prediktor efikasi AB =rasio AUC24jam/KHM,& rasio kadar puncak/KHM.

Mis.Aminoglikosid,efek optimal dicapai bila rasio kadar puncak/KHM minimal8-10 untuk mencegah resistensi. Fluorokuinolon vs bakteriGram (-), rasioAUC24jam/KHM optimal=125.

Prinsip Penggunaan AB Bijak

1. Spektrum sempit, indikasi ketat, dosis adekuat, interval & lama pemberian tepat.
2. Pembatasan penggunaan AB, diutamakan penggunaan AB lini pertama.
3. Indikasi ketat dimulai dg menegakkan Dx peny infeksi,menggunakan informasi klinis & hsl pemr lab spt mikrobiologi, serologi, dll. AB tdk utk peny infeksi krn virus / yang *self-limited*.
5. Pemilihan jenis AB harus berdasar pada:
   a. Informasi ttg spektrum kuman penyebab inf & pola kepekaan kuman thd AB.
   b. Hasil pemr mikrobiologi atau perkiraan kuman penyebab infeksi.
   c. Profil farmakokinetik dan farmakodinamik AB.
   d. mempertimbangkan hasil mikrobiologi & keadaan klinis pasien serta ketersediaan obat.
   e. *Cost effective:* paling cost-effective & aman.

Terapi Antimikroba

A. Terapi Empirical – awal – organisme penyebab infeksi belum diketahui – *single broad spectrum agent / combination*

- Tujuan : eradikasi / hambatan pertumbuhan bakteri yg diduga menj penyebab infeksi,sebelum ada hasil pemeriksaan mikrobiologi.
- Pemilihan AB bds dugaan bakteri apa yg paling sering menjadi penyebab infeksi tsb / pemr Gram
- Lama pemberian AB : 48-72jam, selanjutnya hrs dievaluasi klinis-mikrobiologis-data penunjang yg lain

B. Terapi Definitif – mikroorganisme teridentifikasi – *a narrow – spectrum low toxicity regiment to complete the course of treatment*

Penggunaan AB Profilaksis

- Tujuan AB profilaksis pada kasus pembedahan:

  a.Mencegah kejadian Infeksi Luka Operasi (ILO).

  b.Me↓ morbiditas & mortalitas pasca operasi.

  c.Menghamb munculnya flora normal resisten.

  d.Meminimalkan biaya.

- Indikasi : operasi bersih & op bersih kontaminasi.

- Pemilihan jenis AB:

  a.~ sensitivitas & pola bakteri patogen terbanyak pada kasus bersangkutan.

  Gunakan sefalosporin generasi I–II. Jk dicurigai melibatkan bakt anaerob dpt di(+) metronidazol. (KI memakai Sefalosporin gen III &IV, karbapenem, kuinolon)

  b.Spektrum sempit →me↓ risiko resistensi bakteri.

  c.Toksisitasrendah.

  d.Tidak ada interaksi merugikan dg obat anestesi.

  e.Bersifat bakterisidal, Harga terjangkau.

Penggunaan AB Profilaksis

- Rute pemberian : i.v, t.u i.v drip
- AB profilaksis diberikan ≤30menit sblm insisi kulit. Idealnya diberikan pada saat induksi anestesi.
- Dosis pemberian cukup tinggi → menjamin kadar puncak yg tinggi & dpt berdifusi dlm jar dg baik, kdr mencapai KHM s.d 2x kdr Tx
- Durasi pemberian adalah dosis tunggal. Dosis ulangan dapat diberikan jk ada perdarahan >1500ml atau operasi berlangsung > 3jam.

Kelas Operasi	Definisi	Penggunaan Antibiotik
Operasi Bersih	Operasi yang dilakukan pada daerah dengan kondisi pra bedah tanpa infeksi, tanpa membuka traktus (respiratorius, gastro intestinal, urinarius, bilier), operasi terencana, atau penutupan kulit primer dengan atau tanpa digunakan drain tertutup.	Kelas operasi bersih terencana umumnya tidak memerlukan antibiotik profilaksis kecuali pada beberapa jenis operasi, misalnya mata, jantung, dan sendi.
Operasi Bersih – Kontaminasi	Operasi yang dilakukan pada traktus (digestivus, bilier, urinarius, respiratorius, reproduksi kecuali ovarium) atau operasi tanpa disertai kontaminasi yang nyata.	Pemberian antibiotika profilaksis pada kelas operasi bersih kontaminasi perlu dipertimbangkan manfaat dan risikonya karena bukti ilmiah mengenai efektivitas antibiotik profilaksis belum ditemukan.
Operasi Kontaminasi	Operasi yang membuka saluran cerna, saluran empedu, saluran kemih, saluran napas sampai orofaring, saluran reproduksi kecuali ovarium atau operasi yang tanpa pencemaran nyata (*Gross Spillage*).	Kelas operasi kontaminasi memerlukan antibiotik terapi (bukan profilaksis).
Operasi Kotor	Adalah operasi pada perforasi saluran cerna, saluran urogenital atau saluran napas yang terinfeksi ataupun operasi yang melibatkan daerah yang purulen (inflamasi bakterial). Dapat pula operasi pada luka terbuka lebih dari 4 jam setelah kejadian atau terdapat jaringan nonvital yang luas atau nyata kotor.	Kelas operasi kotor memerlukan antibiotik terapi.

AB kombinasi

- AB kombinasi = pemberian AB > satu jenis utk mengatasi infeksi.
- Tujuan:

  a.Me↑ aktivitas AB pada infeksi spesifik (efek sinergis).

  b.Memperlambat & m(-) risiko bakteri resisten.
- Indikasi :(Bruntonet.Al,2008;Archer,GL.,2008):

  a.Infeksi oleh >satu bakteri (polibakteri).

  b.Abses intraabdominal, hepatik, otak & sal genital (inf campuran aerob & anaerob).

  c.Terapi empiris pada infeksi berat.
- Kombinasi AB dg tempat kerja beda →me↑ atau me↓aktivitas AB
- Kombinasi AB →antibiotik toksisitas aditif atau superaditif. Mis Vankomisin –nefrotoksik minimal, Vanko + Aminoglikosida →toksisitas ↑
- Perlu pengetahuan jenis infeksi, data mikrobiologi & AB →kombinasi rasional & efektif. Hindari u/ Tx empiris jangka lama, Biaya ↑↑

OBAT ANTIFUNGI

ANTIFUNGAL DRUGS
bds struktur

- **POLYENES**
  Amphotericin B, nystatin
- **AZOLES**
  Imidazoles:Ketoconazole..
  Triazoles: Fluconazole, itraconazole,voriconazole, posaconazole, ravuconazole
- **ALLYLAMINES**
  Terbinafine, butenafine
- **MORPHOLINE**
  Amorolfine
- **FLUORINATED PYRIMIDINE**
  Flucytosine
- **ECHINOCANDINS**
  Caspofungin, anidulafungin, micafungin
- **PEPTIDE-NUCLEOSIDE**
  Nikkomycin Z
- **TETRAHYDROFURAN DERIVATIVES**
  Sordarins, azasordarins
- **OTHER**
  Griseofulvin

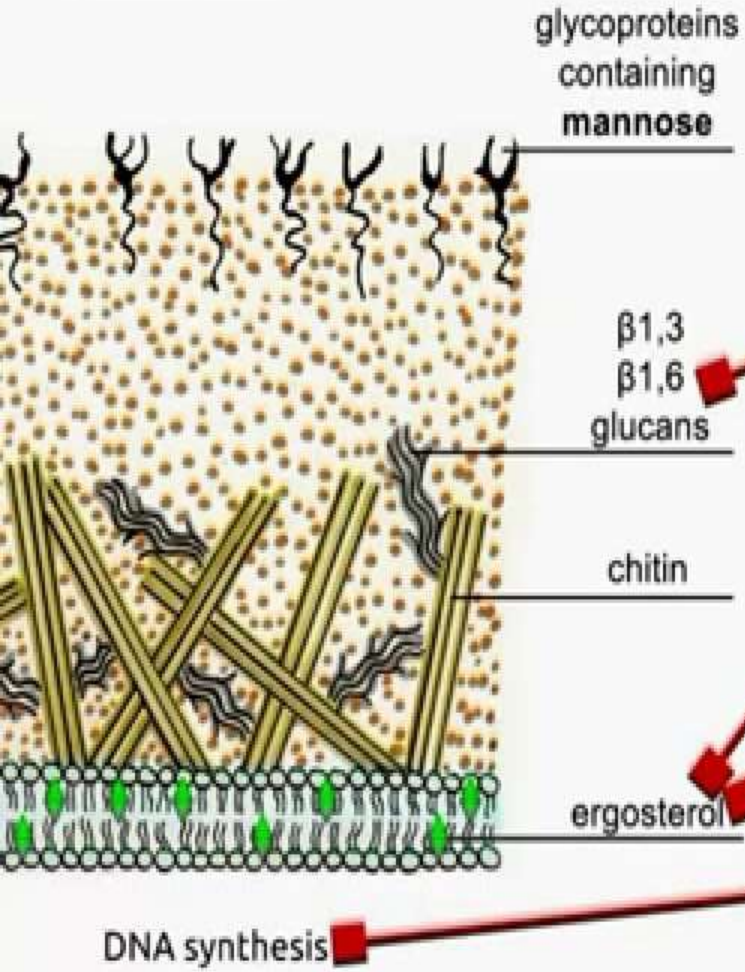
ANTIFUNGAL DRUGS --by mode of action

- **Membrane disrupting agents**
  Amphotericin B, Nystatin
- **Ergosterol synthesis inhibitors**
  Azoles, Allylamines, Morpholine
- **Nucleic acid inhibitor**
  Flucytosine
- **Anti-mitotic (spindle disruption)**
  Griseofulvin
- **Glucan synthesis inhibitors**
  Echinocandins
- **Chitin synthesis inhibitor**
  Nikkomycin
- **Protein synthesis inhibitors**
  Sordarins, azasordarins

TARGETS for antifungal activity

- **Ergosterol** (Cell membrane)
  - ✓ Drug-ergosterol interaction
  - ✓ Inhibition of ergosterol synthesis
- **RNA/EF3** (Nucleic acid/protein synthesis)
  - ✓ Incorporation of 5-FU in RNA
  - ✓ Inhibition of EF3
- **Glucan/Chitin (**Cell wall)
  - ✓ Inhibition of glucan/chitin synthesis

Fungi and Antifungal Agents



Antifungal Agents

Echinocandins (such as caspofungin, anidulafungin, micafungin) inhibit the enzyme that synthesizes β-glucans, called the "penicillin of antifungals"

Polyenes (such as amphotericin B) bind ergosterol, weaken the membrane, cause pore formation, leakage of K+ and Na+, fungal cell death; also confers mammalian toxicity.

Azoles (such as fluconazole, ketoconazole, itraconazole) inhibit the enzyme that synthesizes ergosterol

5-flucytosine (5-FC) is converted to 5-FU to inhibit DNA synthesis as a pyrimidine analog; side effect is myelosuppression

Antifungal Drugs

Imidazoles (COMET-K)

Clotrimazole
Oxiconazole
Miconazole
Econazole
Tioconazole
Ketoconazole

Azole antifungals inhibit lanosterol 14-α demethylase — the enzyme required to convert lanosterol into ergosterol.

Triazoles (FIT VIP)

Fluconazole
Itraconazole
Terconazole
Voriconazole
Isavuconazole
Posaconazole

Allylamines (ANT)

Amorolfin— Naftifine — Terbinafine

Inhibits squalene epoxidase!

Griseofulvin

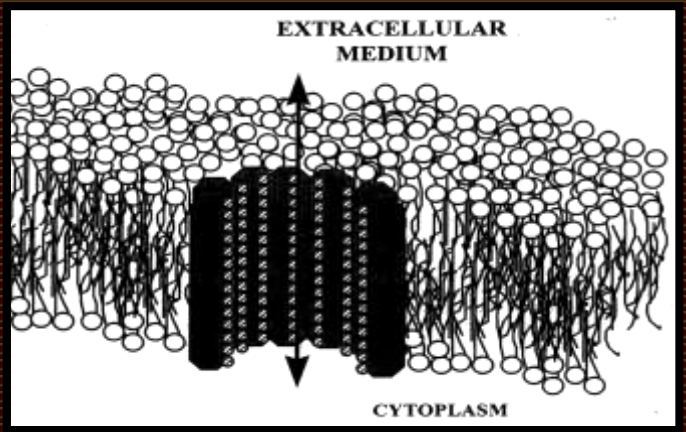
Binds to tubulin, inhibiting mitosis!

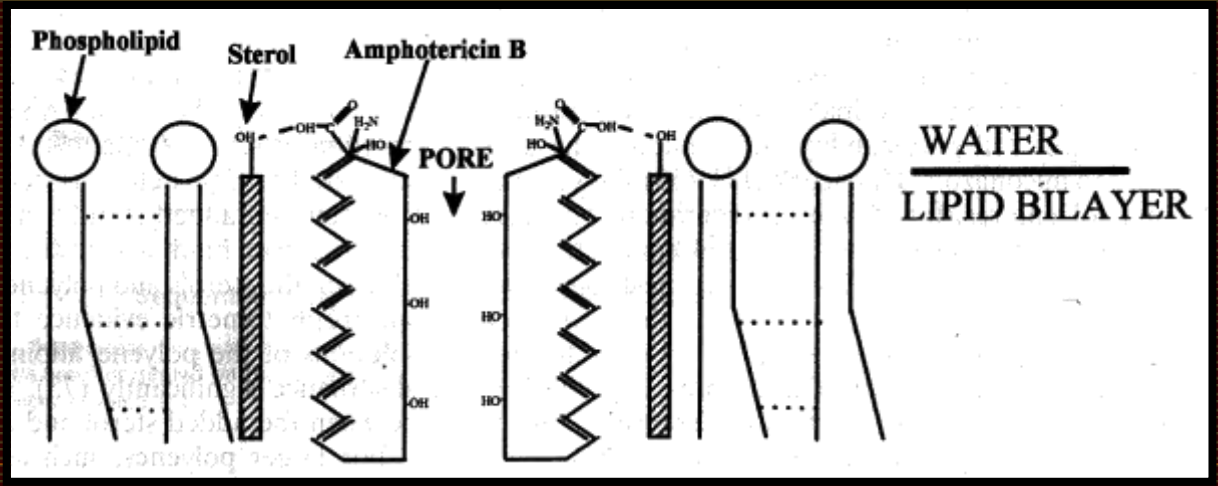
Echinocandins (MAC)

Micafungin — Anidulafungin — Caspofungin

Inhibits synthesis of glucan in cell wall via the enzyme 1,3-β-glucan synthase.

AMPHOTERICIN B generates pores in the membrane



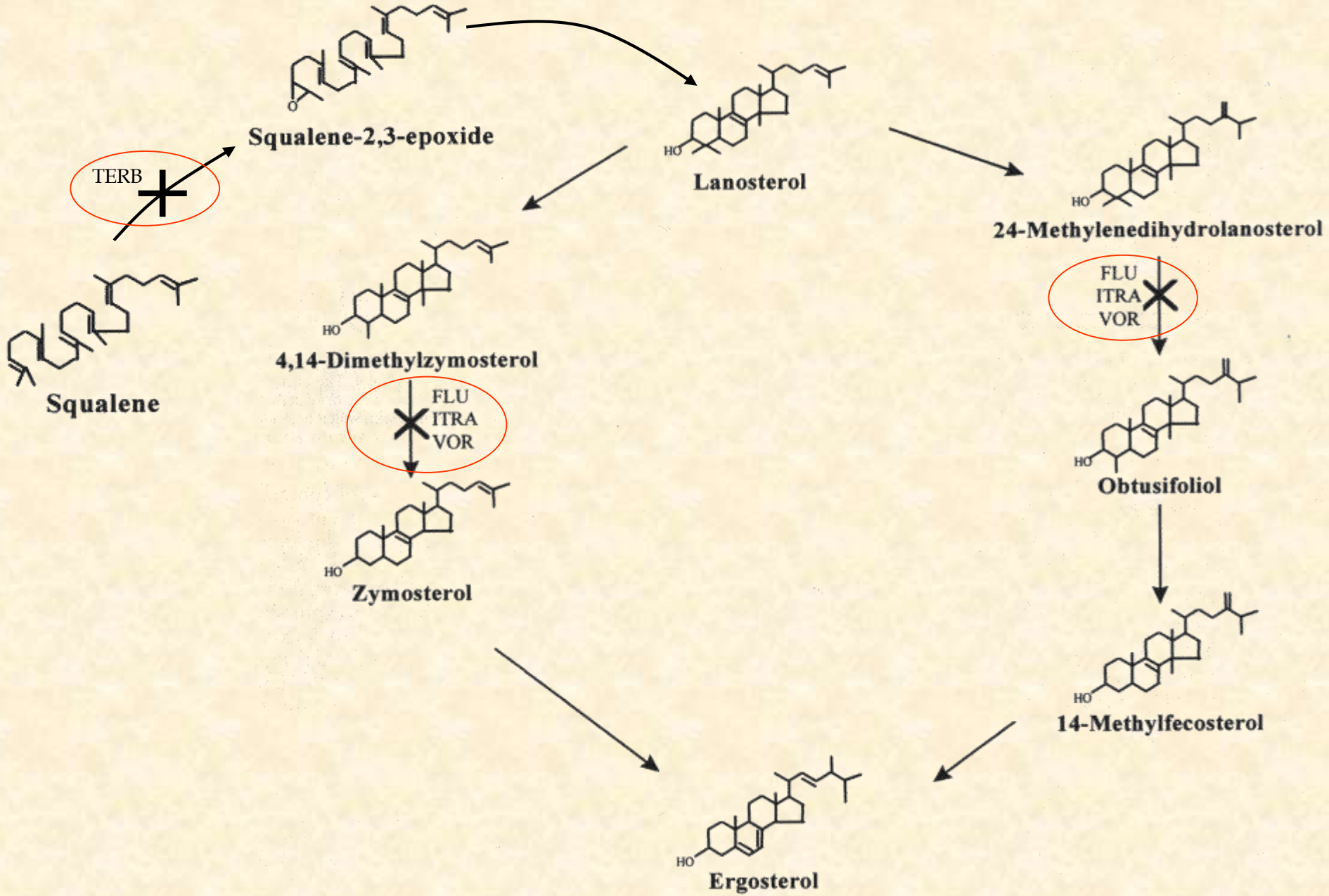


Clin Microbiol Rev 1999; 12: 501

Amphoterisin-B

- Mekanisme kerja : mengikat *fungal membrane sterols* (ergosterol) dan mengubah permeabilitas selektifnya thd K^{+} & Mg^{2+}.
- Bersifat fungisidal.
- Spektrum : most systemic fungi

Ergosterol synthesis



Azoles, allylamines & morpholines inhibit specific ENZYMES for ergosterol synthesis

Gene Name	Enzyme	Sterol Intermediate	Inhibitor
		Squalene	
ERG1	Squalene epoxidase	↓	Allylamines Thiocarbamates
		2,3-Oxidosqualene	
ERG7	Lanosterol Synthase	↓	
		Lanosterol	
ERG11	Lanosterol (C-14) Demethylase	↓	Azoles
ERG24	C-14 Sterol Reductase	↓	Morpholines
ERG25 ERGX ERGY	C-4 Sterol Demethylase Enzymes	↓	
		Zymosterol	
ERG6	C-24 Sterol Methyltransferase	↓	
		Fecosterol	
ERG2	C-8 Sterol Isomerase	↓	Morpholines
		Episterol	
ERG3	C-5 Sterol Desaturase	↓	
ERG5	C-22 Sterol Desaturase	↓	Azoles (?)
ERG4	C-24 Sterol Reductase	↓	
		Ergosterol	

Clin Microbiol Rev 1998; 11: 382

FLUCYTOSINE (5-fluorocytosine)
Incorporation of 5-FU into RNA

- Mekanisme kerja :
  - Masuk ke dlm sel fungi dg bantuan *permease*
  - Dikonversi menjadi 5-fluorouracil (5-FU) oleh *cytosine deaminase*
  - 5-FU menghambat *thymidylate synthetase*
  - disintesa menjadi 5-FUTP
  - bergabung dlm RNA.
- Penggunaan :
  - systemic fungi, mainly candida, and cryptococcus.
  - fungistatic.
  - used with amphotericin B (cryptococcal meningitis) and with itraconazole (chromoblastomyosis).

SORDARINS, AZASORDARINS
Inhibition of EF3

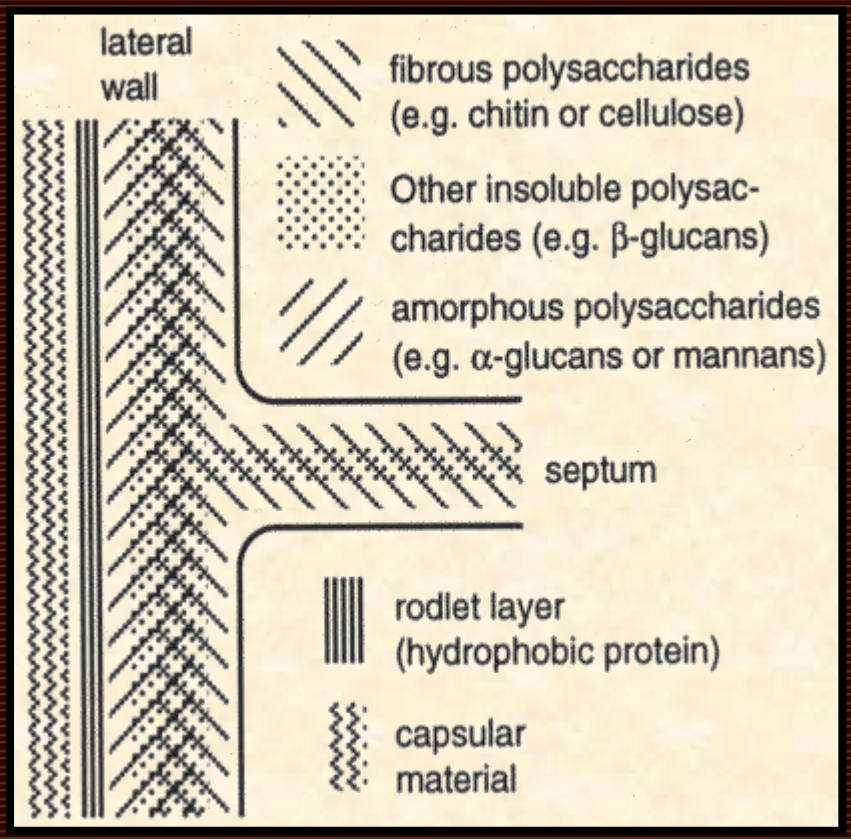
- EF3: A target in protein synthesis machinery unique to FUNGI

- GM 237354... (sordarins)
  GW 471558... (azasordarins)

- Yet investigational

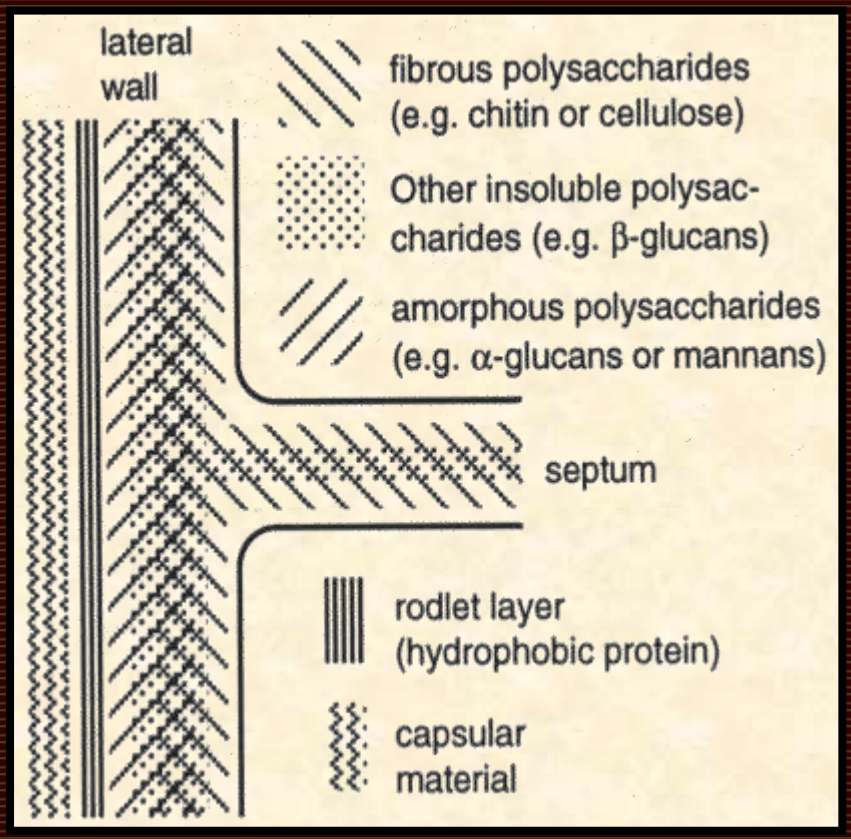
ECHINOCANDINS : Caspofungin is licensed

Inhibition of glucan synthesis



- Inhibition of β-(1-3) glucan synthesis (of glucan synthase ??)
- Secondary reduction in ergosterol & lanosterol
- Increase in chitin
- Kills hyphae at their growth tips and branching points
- Buds fail to seperate from the mother cell
- Yields osmotically sensitive fungal cells

NIKKOMYCIN
Inhibition of chitin synthesis



- Competitive inhibition of chitin synthase
- Yet investigational

OBAT ANTIVIRUS

Fathiyah Safithri

Obat untuk Infeksi Virus

- Virucidal (secara langsung menginaktivasi virus intak)
- Antiviral (menghambat replikasi virus dlm sel)
- Immunomodulator(meningkatkan / memodulasi respon host terhadap infeksi)

Target Terapi Virus

- Tempat infeksi virus dapat dicapai
- Reproduksi virus dapat ditekan

Dengan efek minimal pada sel hospes

Anti-Viral Ideal

- Water soluble
- Chemically and metabolically stable
- Easily absorbed (apolar)

NOT

- Toxic
- Carcinogenic
- Allergenic
- Mutagenic
- Teratogenic

Anti-Viral Ideal

Bekerja dg cara mempengaruhi :

- **Fungsi spesifik virus, mis enzyme penting dlm siklus hidup virus**
- **Fungsi selular yg dibutuhkan virus utk replikasi**

Jika mempengaruhi fungsi selular :

➔ pengaruhnya terutama pd sel virus yg mnginfeksi, bukan pd sel host *atau*

➔Hanya sel virus yg menginfeksi yang dibunuh.

Viral enzymes

Nucleic acid polymerases

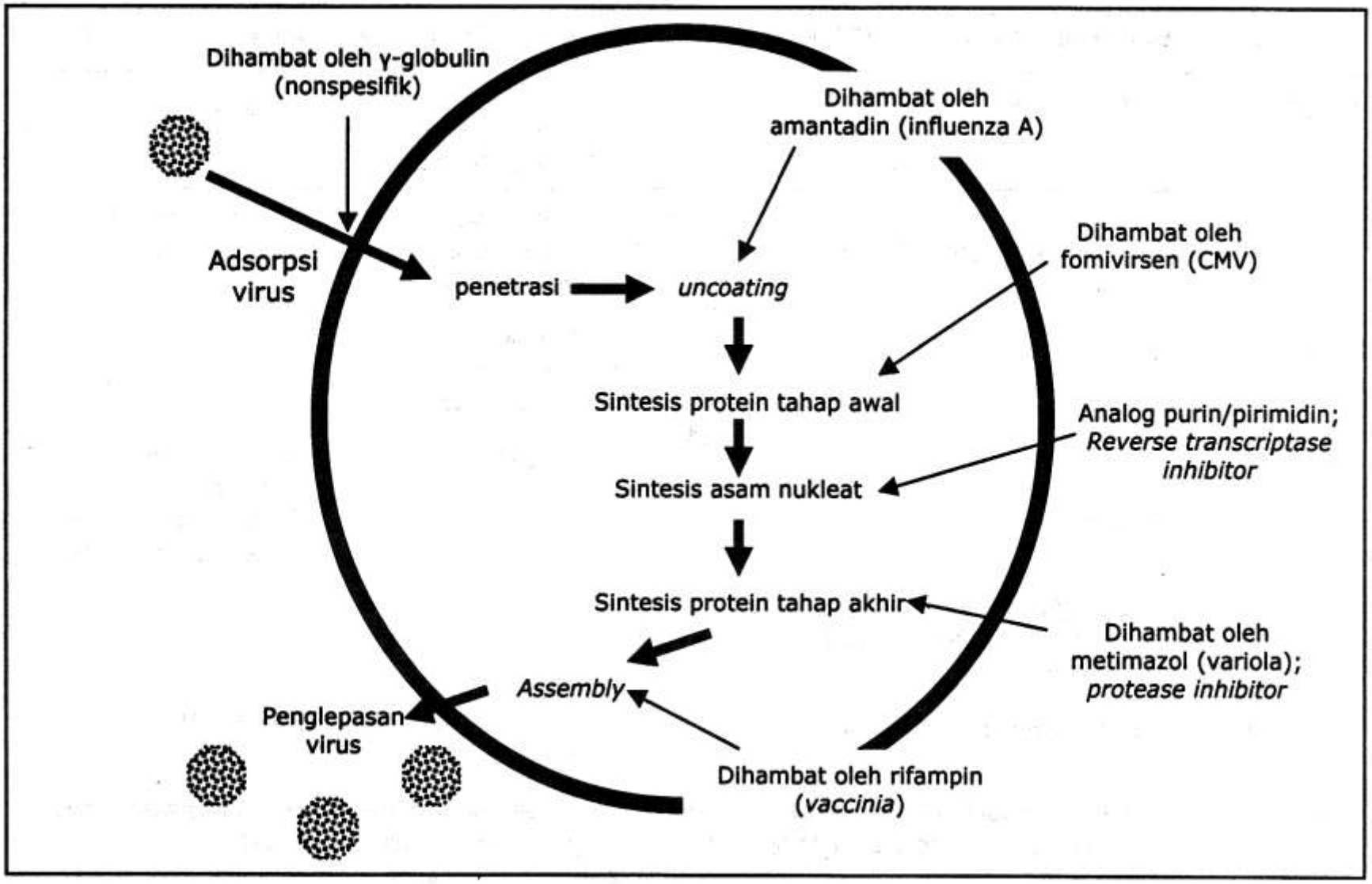
- DNA-dependent DNA polymerase - DNA viruses
- RNA-dependent RNA polymerase - RNA viruses
- RNA dependent DNA polymerase (RT) - Retroviruses

Protease (retrovirus)

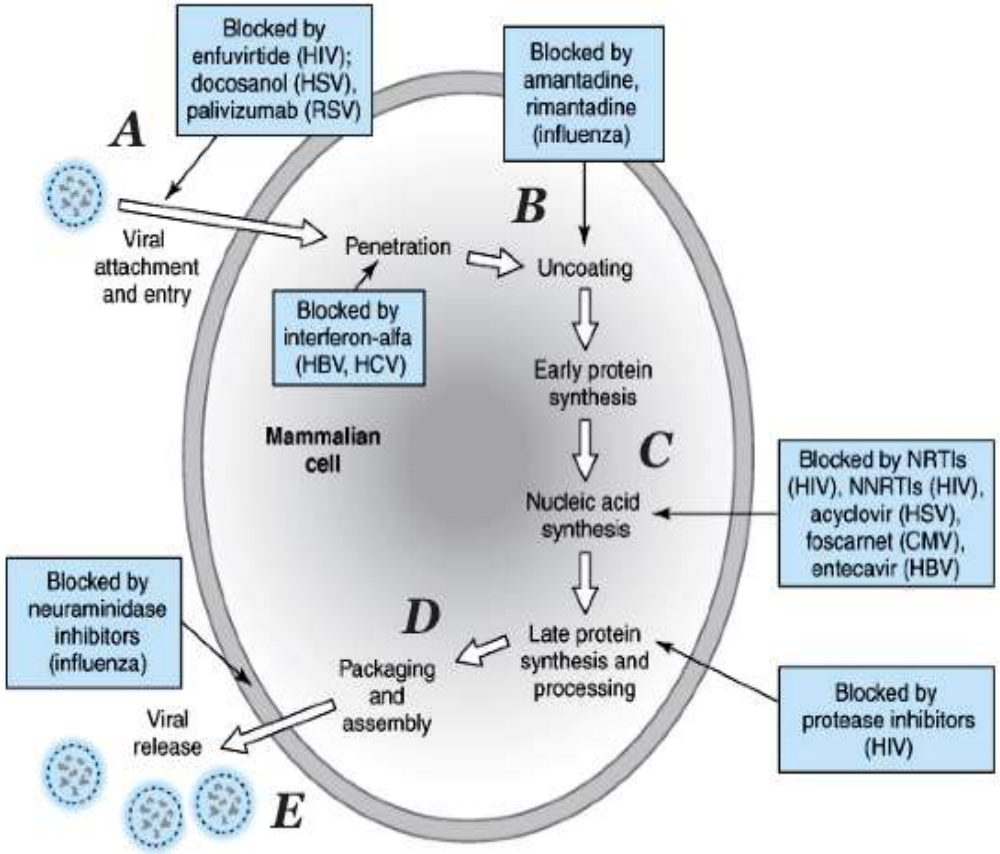
Integrase (retrovirus)

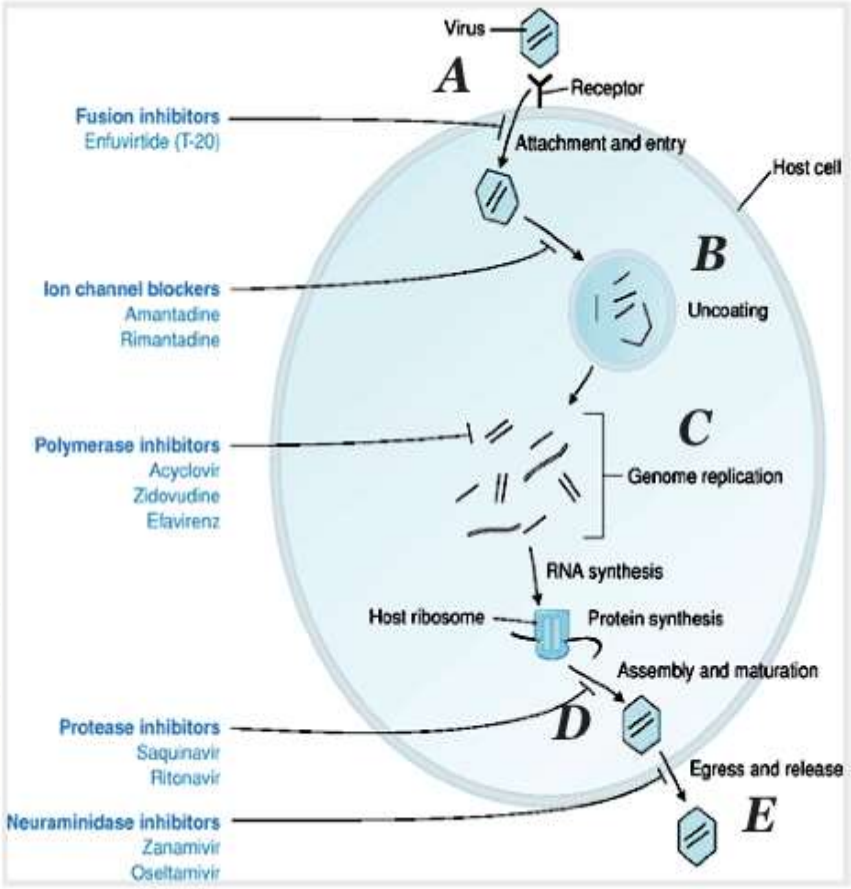
Neuraminidase (orthomyxovirus)

Titik Tangkap Anti VIRUS

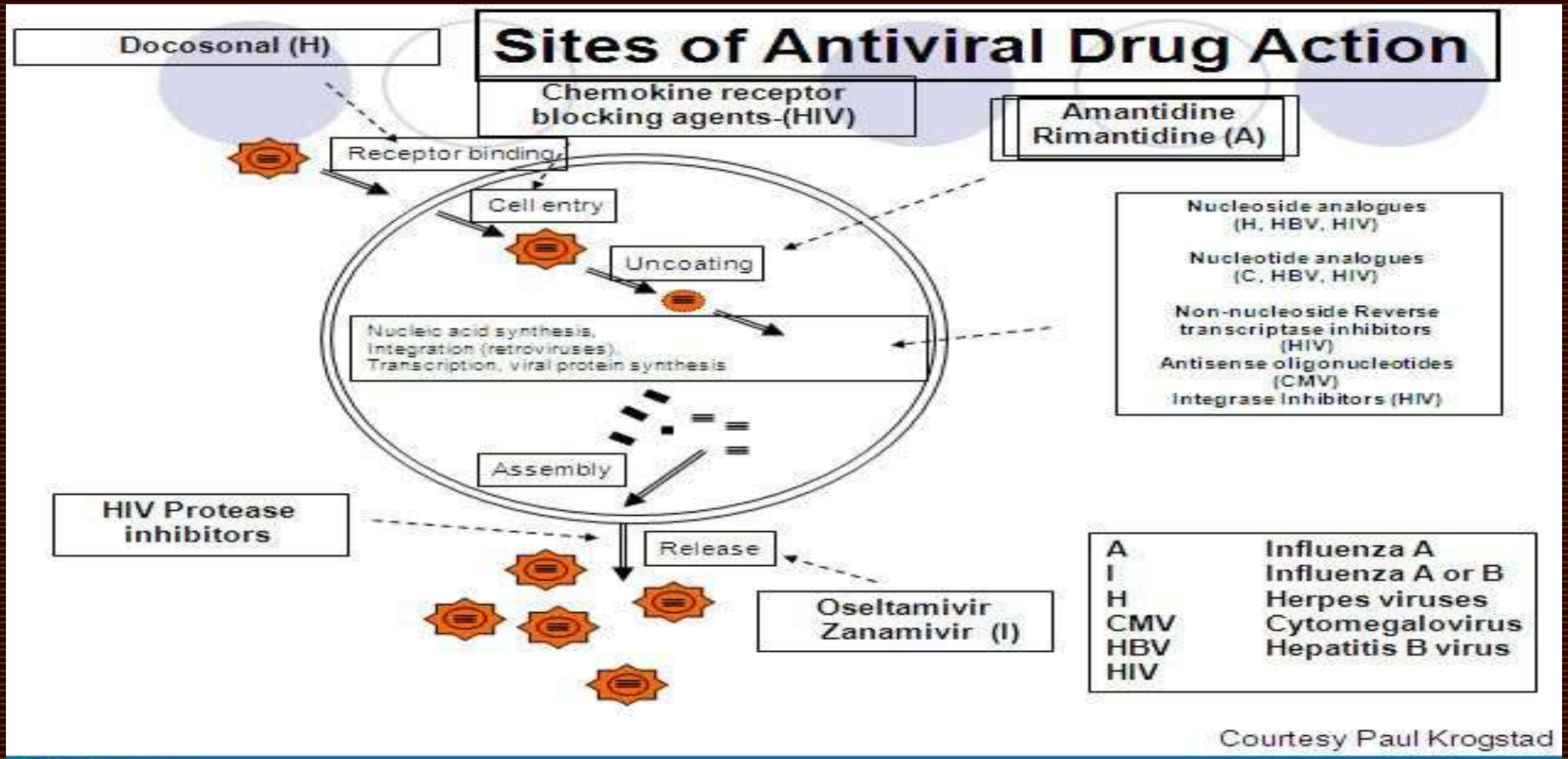


Gambar 41-1. Tempat kerja utama obat pada replikasi virus.


Blocked by enfuvirtide (HIV); docosanol (HSV), palivizumab (RSV)
Blocked by amantadine, rimantadine (influenza)
A
B
Viral attachment and entry
Penetration
Uncoating
Blocked by interferon-alfa (HBV, HCV)
Early protein synthesis
Mammalian cell
C
Nucleic acid synthesis
Blocked by NRTIs (HIV), NNRTIs (HIV), acyclovir (HSV), foscarnet (CMV), entecavir (HBV)
Blocked by neuraminidase inhibitors (influenza)
D
Late protein synthesis and processing
Packaging and assembly
Blocked by protease inhibitors (HIV)
Viral release
E

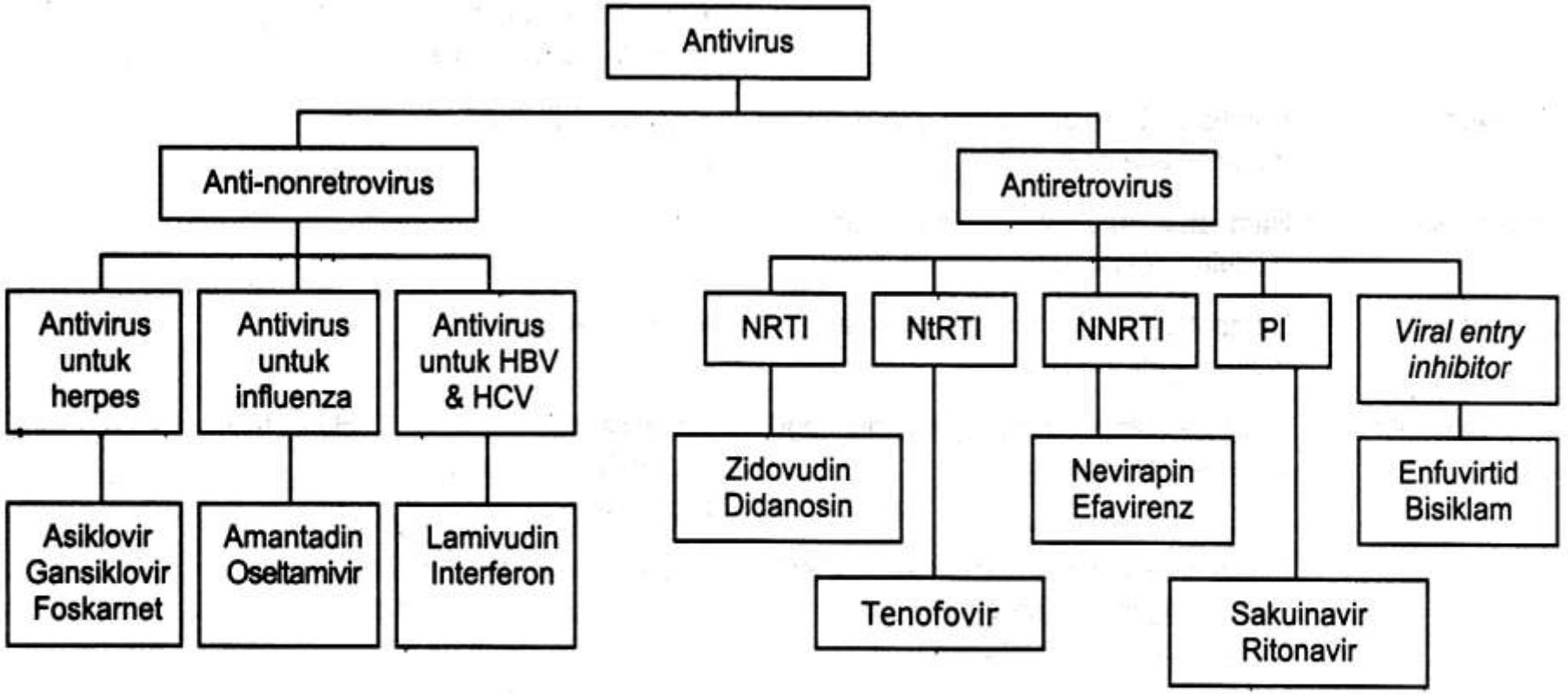

Virus
A
Receptor
Fusion inhibitors
Enfuvirtide (T-20)
Attachment and entry
Host cell
B
Ion channel blockers
Amantadine
Rimantadine
Uncoating
C
Polymerase inhibitors
Acyclovir
Zidovudine
Efavirenz
Genome replication
RNA synthesis
Host ribosome
Protein synthesis
Assembly and maturation
D
Protease inhibitors
Saquinavir
Ritonavir
Egress and release
Neuraminidase inhibitors
Zanamivir
Oseltamivir
E

Sites of Antiviral Drug Action



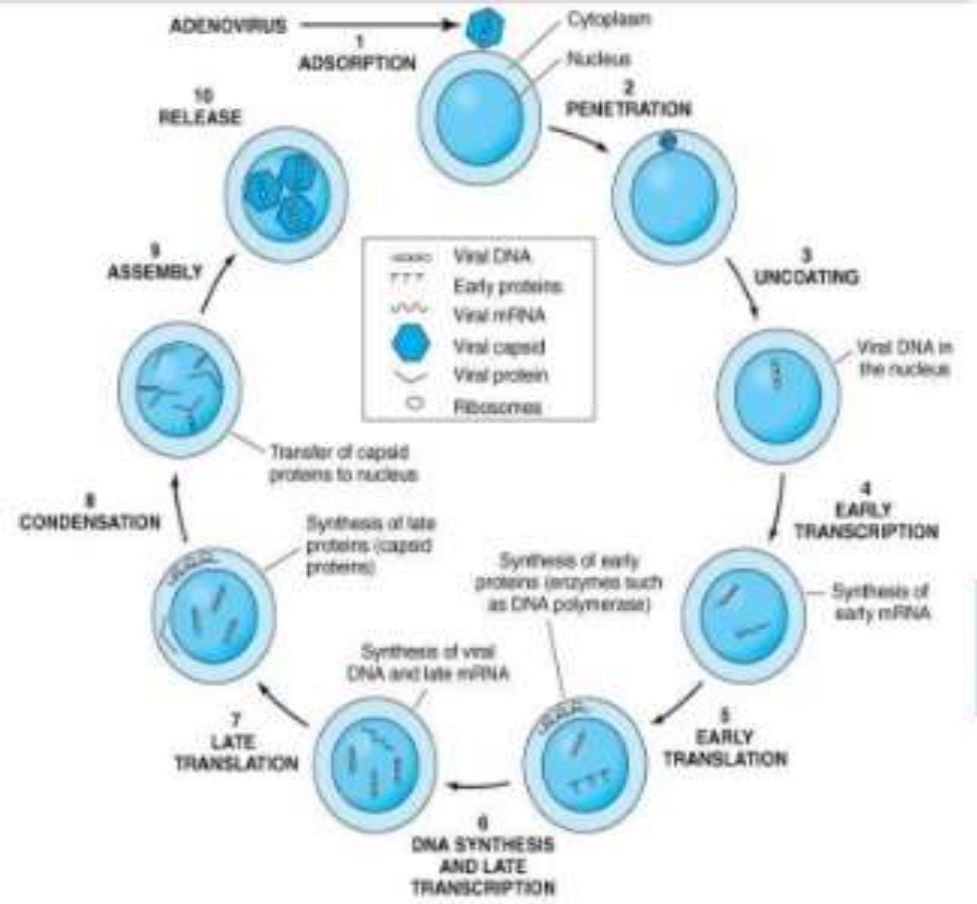
Courtesy Paul Krogstad

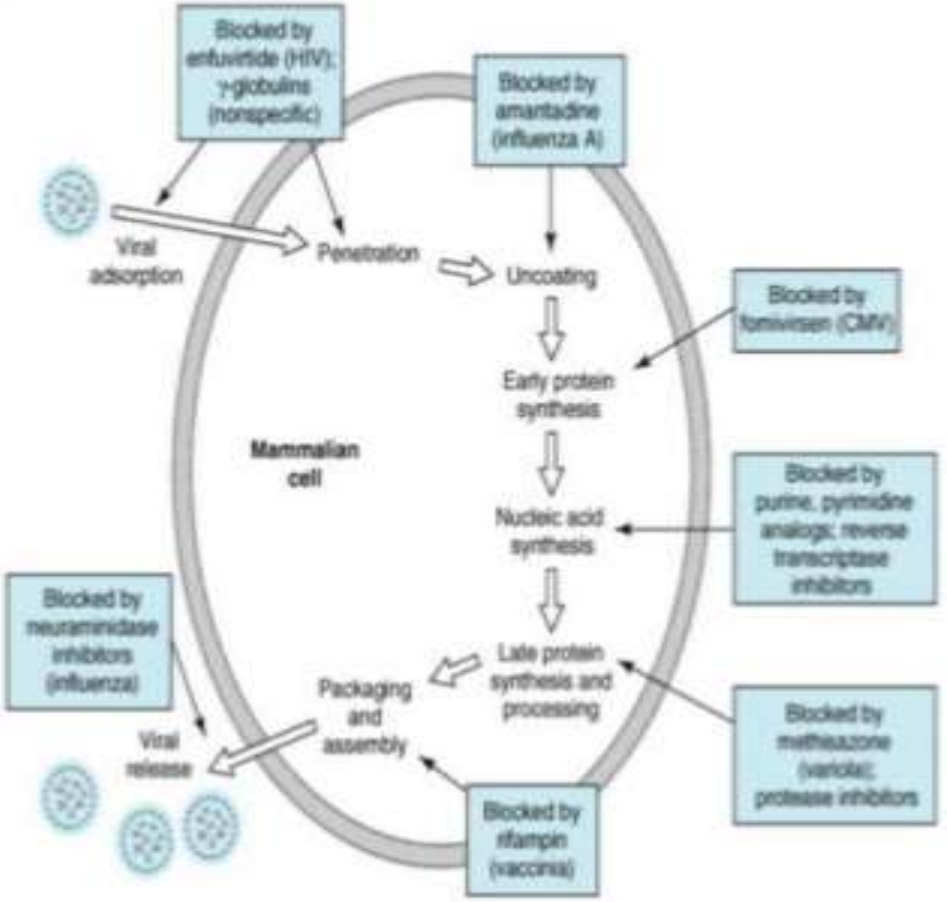
Penggolongan Anti Virus

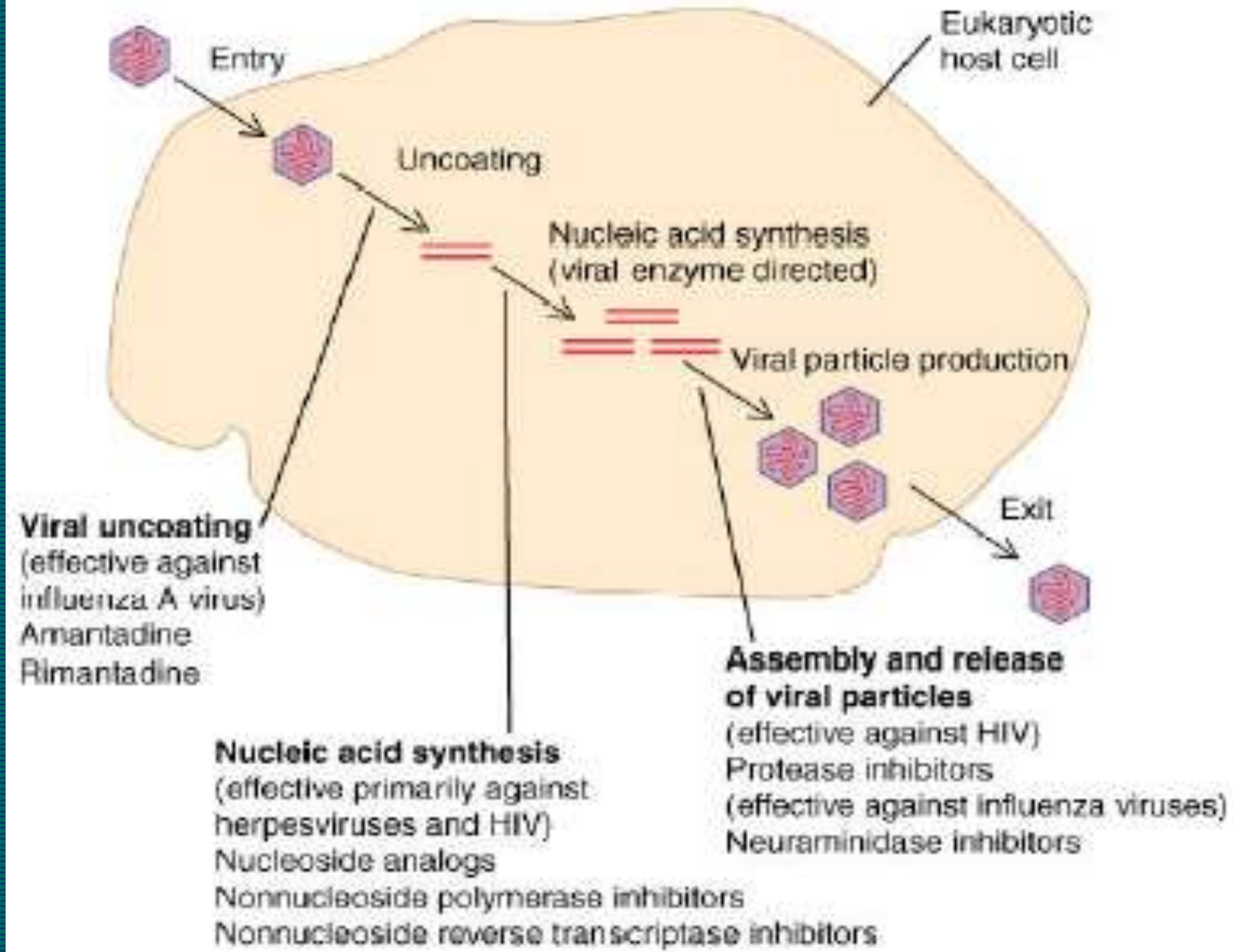


NRTI : *Nucleoside reverse transcriptase inhibitor*
NtRTI : *Nucleotide reverse transcriptase inhibitor*
NNRTI : *Non-nucleoside reverse transcriptase inhibitor*
PI : *Protease inhibitor*

Viral replication and sites of antiviral drug action





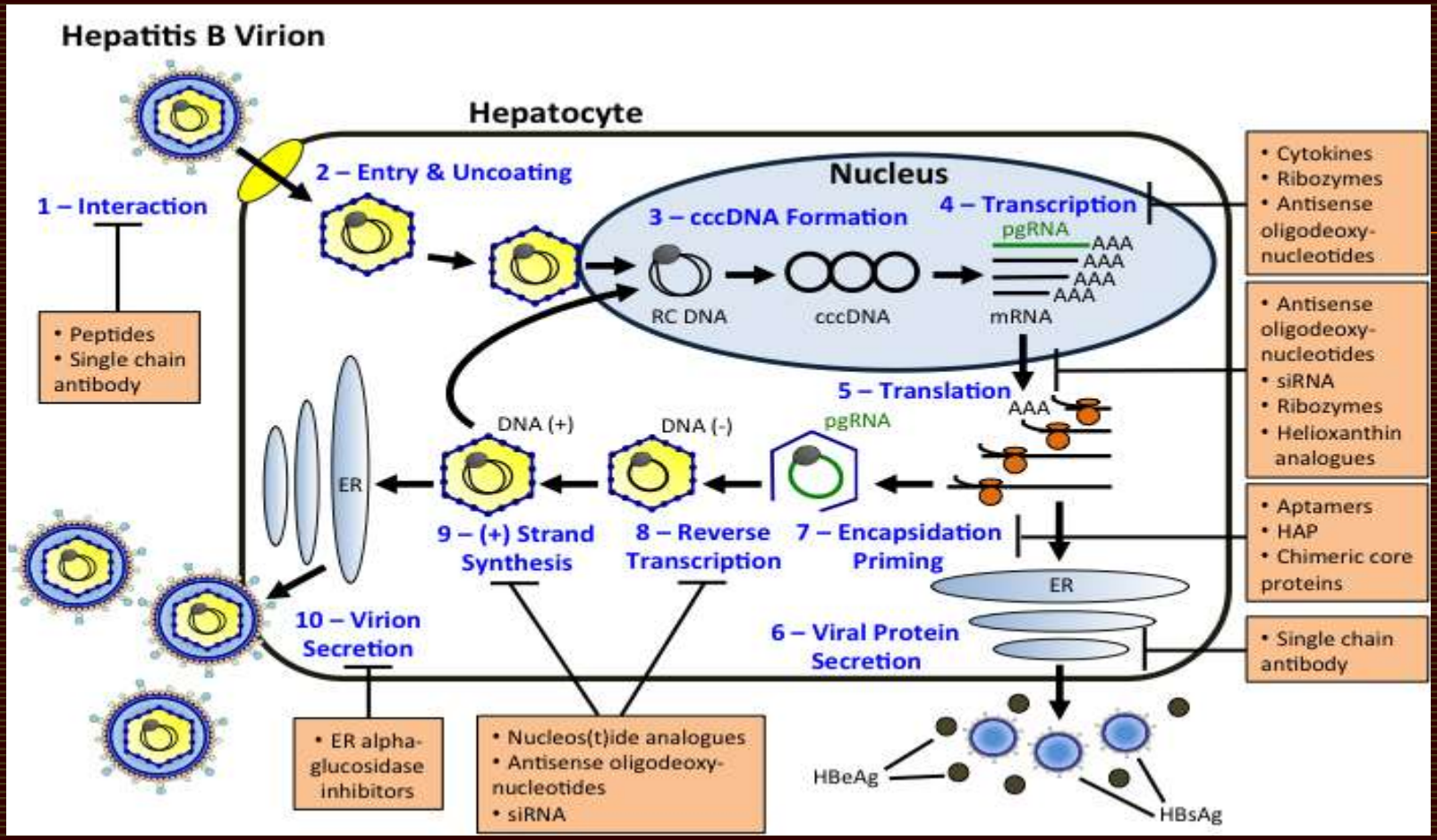

Entry
Eukaryotic host cell
Uncoating
Nucleic acid synthesis (viral enzyme directed)
Viral particle production
Exit
Viral uncoating
(effective against influenza A virus)
Amantadine
Rimantadine
Nucleic acid synthesis
(effective primarily against herpesviruses and HIV)
Nucleoside analogs
Nonnucleoside polymerase inhibitors
Nonnucleoside reverse transcriptase inhibitors
Assembly and release of viral particles
(effective against HIV)
Protease inhibitors
(effective against influenza viruses)
Neuraminidase inhibitors

VIRAL UNCOATING

- Mis : Amantadine, Rimantadine
- Mek. Kerja : mengikat bag dalam kanal ion yg dibentuk oleh protein transmembran M2, shg menghambat fungsi kanal sbg transpor H^+ ➔ suasana interior virus tidak asam ➔ uncoating (release RNA genom dari komplek nukleoprotein) tdk terjadi

INHIBITOR TRANSKRIPSI

- Interferon : famili sitokin yg membangkitkan komplek antiviral intraseluler, antiproliferasi, dan efek immunomodulasi
- Secara cepat disintesa & disekresi oleh sel yg terinfeksi virus
- Bukan antivirus, tp menstimuli daya tahan sel yg tidak terinfeksi thd virus

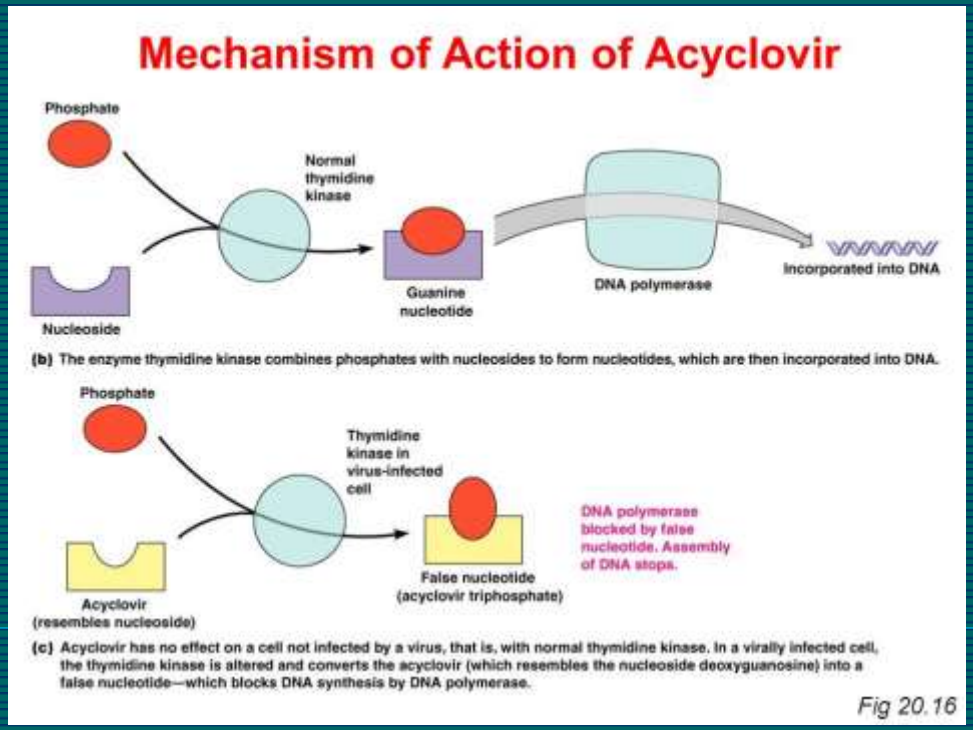

Hepatitis B Virion
Hepatocyte
Nucleus
1 – Interaction
• Peptides
• Single chain antibody
2 – Entry & Uncoating
3 – cccDNA Formation
4 – Transcription
pgRNA
AAA
AAA
AAA
AAA
RC DNA
cccDNA
mRNA
• Cytokines
• Ribozymes
• Antisense oligodeoxy-nucleotides
• Antisense oligodeoxy-nucleotides
• siRNA
• Ribozymes
• Helioxanthin analogues
5 – Translation
AAA
pgRNA
DNA (+)
DNA (-)
ER
9 – (+) Strand Synthesis
8 – Reverse Transcription
7 – Encapsidation Priming
• Aptamers
• HAP
• Chimeric core proteins
ER
6 – Viral Protein Secretion
• Single chain antibody
10 – Virion Secretion
• ER alpha-glucosidase inhibitors
• Nucleos(t)ide analogues
• Antisense oligodeoxy-nucleotides
• siRNA
HBeAg
HBsAg

INHIBITOR VIRAL TRANSLASI

- Fomivirsen
- Penggunaan: infeksi mata oleh CMV yg resisten thd pengobatan dg gansiklovir, sidovir
- Mek kerja : menghambat replikasi CMV dg cara mengeblok translasi.

INHIBITOR REPLIKASI RNA ATAU DNA

- Asiklovir, Adenin arabinose, Famsiklovir, Pensiklovir, Gansiklovir, idoxuridin, Ribavirin, Valasiklovir

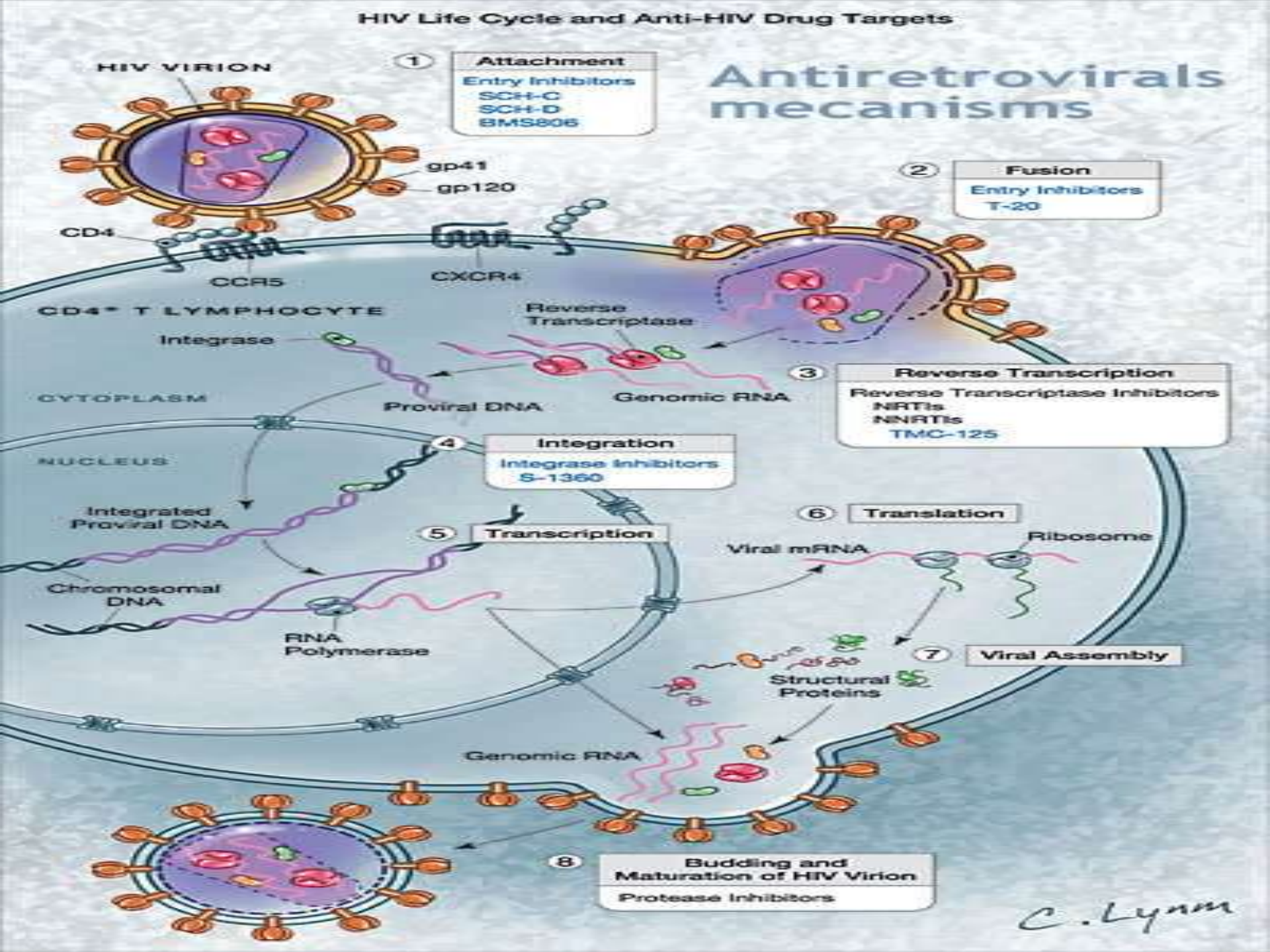


INHIBITOR VIRUS RELEASE

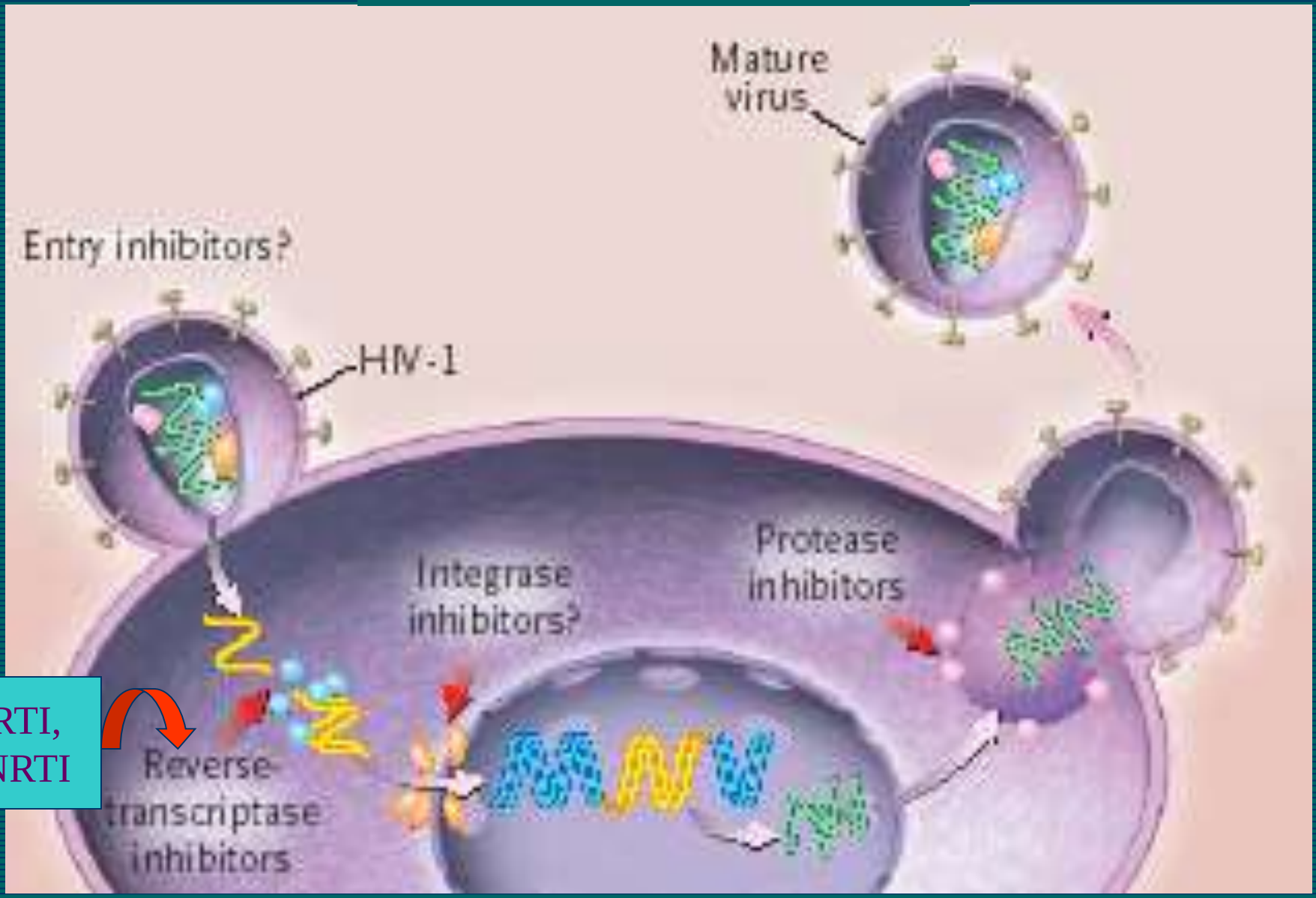
- Zanamivir, Oseltamivir

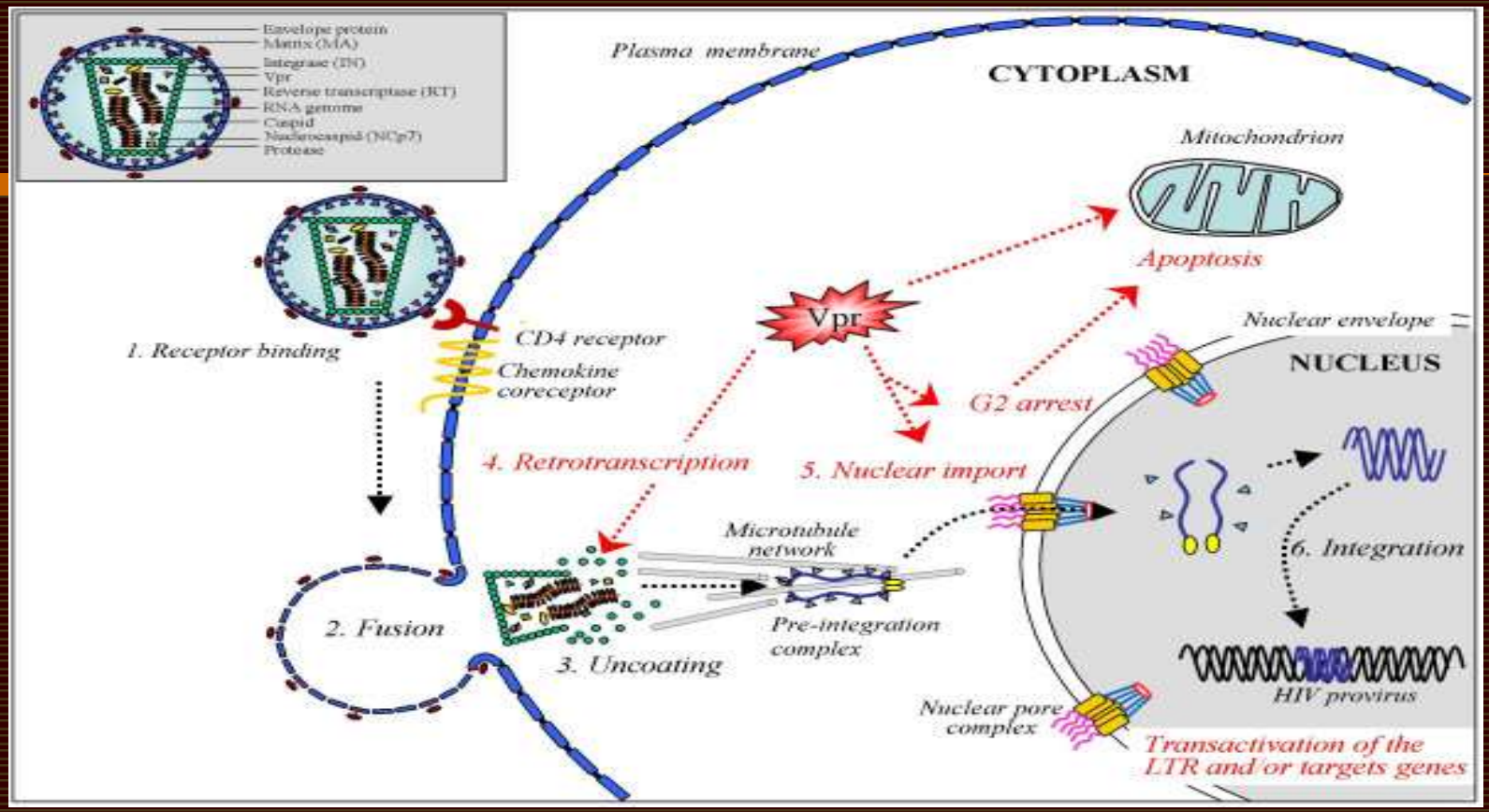
INHIBITOR REPLIKASI HIV

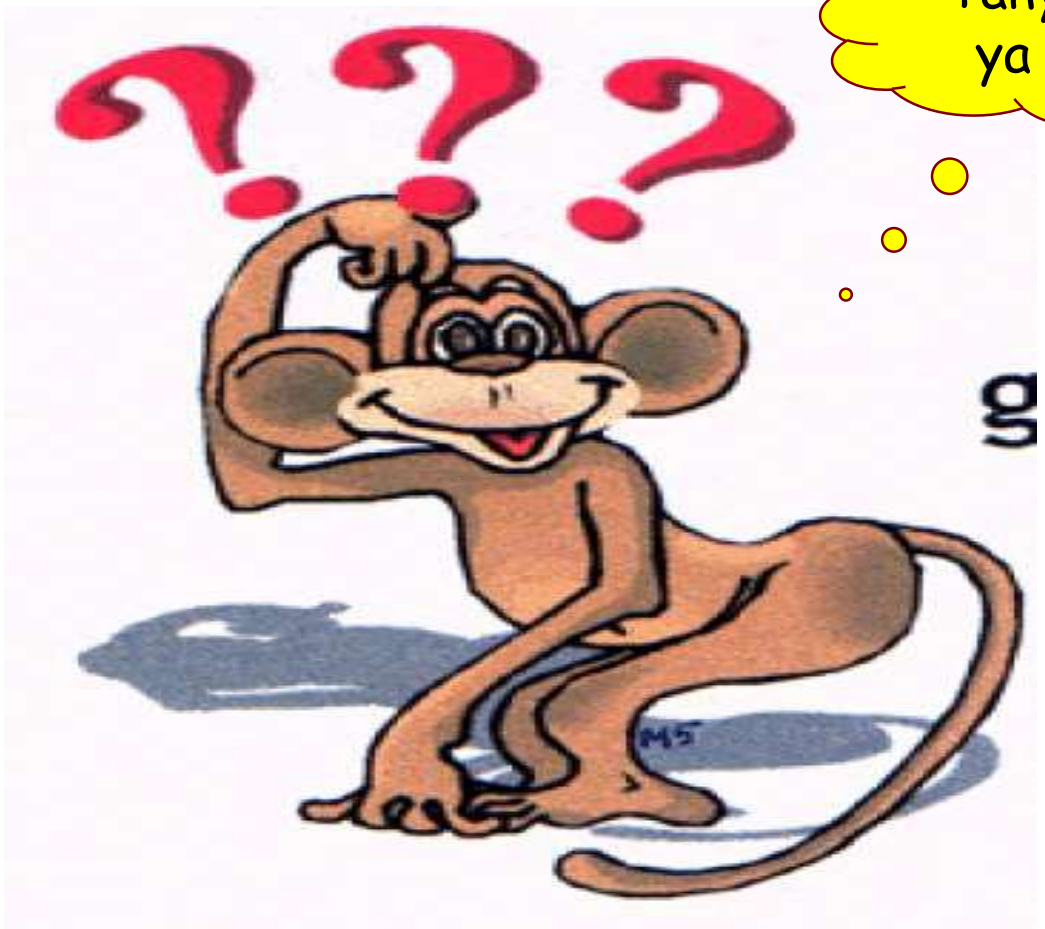
- Protease Inhibitors (PI)
  - Indinavir, nelfinavir, ritonavir, saquinovir
- Nucleoside reverse transcriptase inhibitors (NRTI)
  - Didanosine, lamivudine, stavudine, zalcitabine, zidovudine, Abacavir (new)
- Non-nucleosides reverse transcriptase inhibitors (NNRTI)
  - Delavirdine, nevirapine, Efavirenz (new)


HIV Life Cycle and Anti-HIV Drug Targets
Antiretrovirals mecanisms
HIV VIRION
gp41
gp120
CD4
CCR5
CXCR4
CD4+ T LYMPHOCYTE
CYTOPLASM
NUCLEUS
Integrase
Reverse Transcriptase
Proviral DNA
Genomic RNA
Integrated Proviral DNA
Chromosomal DNA
RNA Polymerase
Viral mRNA
Ribosome
Structural Proteins
Genomic RNA
1 Attachment
Entry Inhibitors
SCH-C
SCH-D
BMS806
2 Fusion
Entry Inhibitors
T-20
3 Reverse Transcription
Reverse Transcriptase Inhibitors
NRTIs
NNRTIs
TMC-125
4 Integration
Integrase Inhibitors
S-1360
5 Transcription
6 Translation
7 Viral Assembly
8 Budding and Maturation of HIV Virion
Protease Inhibitors
C. Lynn

Mekanisme Kerja




Envelope protein
Matrix (MA)
Integrase (IN)
Vpr
Reverse transcriptase (RT)
RNA genome
Capsid
Nucleocapsid (NCp7)
Protease
Plasma membrane
CYTOPLASM
Mitochondrion
Apoptosis
Vpr
Nuclear envelope
NUCLEUS
1. Receptor binding
CD4 receptor
Chemokine coreceptor
G2 arrest
4. Retrotranscription
5. Nuclear import
Microtubule network
6. Integration
2. Fusion
3. Uncoating
Pre-integration complex
HIV provirus
Nuclear pore complex
Transactivation of the LTR and/or targets genes


Tanya apa
ya ???..

terima kasih