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EC PHARMACOLOGY AND TOXICOLOGY
Mini Review

Bacteria Cell Wall Polypeptides as Targets for the Selectivity in Antimicrobial Peptides as Antibiotic compounds

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Abstract

There is an urgent need for new antibiotics which are effective against drug-resistant bacteria without contributing to resistance development [1]. Antimicrobial peptides (AMPs) are promising novel antibiotics, because they exhibit broad antimicrobial spectra and do not easily induce resistance. For clinical applications, it is important to develop potent AMPs with less toxicity against host cells. We have designed short cationic peptide mimics composed of two functional domains (KAAAK) embedded in a peptide surrogate composition. Due to their mechanism of action [2], Anti-Microbial Peptides (AMPs) have shown very low bacterial, fungal and viral Resistance [3]. We have designed and developed antimicrobial [4] short peptide surrogates that include β-turn (hairpin) [5-9] mimics as "homing [10]" moiety and two flanking lysine [11] rests in their sequences and with cationic amphipathic structures based on the mimicry [12] of naturally occurring antimicrobial peptides at very low concentrations, less than 10 μM. These short peptide surrogates exhibit this potent antimicrobial activity against a broad spectrum of bacteria including *E. coli* and methicillin-resistant *Staphylococcus aureus* with no adverse hemolytic activity and agglutination of erythrocytes [13]. Notably, these short peptide surrogates also did not result in any measurable resistance development in *E. coli*. MIC (minimum inhibitory concentrations) [14] experiments indicate that D- and L Freidinger type-β-turn based Cationic Anti-Microbial Peptides (CAMP) surrogates are almost identical both in the eradication of both Gram+ and Gram- bacteria. These results suggest similar behavior of "artificial" D- and "natural" L- peptide surrogates when binding to bacterial membranes There is, however, chiral sensitivity in human red blood cells (hRBC) hemolysis [15] and therefore a window of opportunity to reduce toxicity (hemolysis) by choosing the suitable chirality in the peptide surrogate. The peptide-mimetic design principle offers significant flexibility and diversity in the creation of new antimicrobial materials and their potential biomedical applications [16]. The potential of β-turn based short AMPs for selectivity studies to avoid eradication of "friendly" microorganism is discussed based on outer membrane bacterial proteins [17].

Our studies may contribute to further understanding of how CAMPs sense bacteria membrane [18] as well as provide a new direction to develop novel membrane disrupting agents [19,20]. A surrogate structure has been identified which may connect to outer membrane proteins of gram-negative bacteria [21], and alters the biological activity of antimicrobial peptide mimics [7,9,10,22-24,80,90,95].

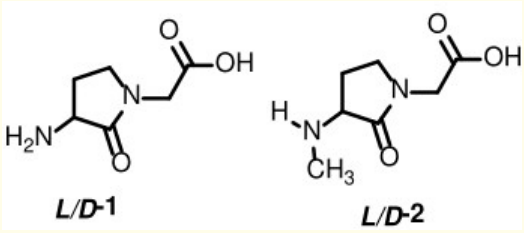
The different architecture of the cell wall [25] of Gram-positive and Gram-negative bacteria may present a tool for selective choice of targets regarding the eradication by antimicrobial peptides and their surrogates. B-turns and N-methylation may present a toolbox for the designers and synthetic people to design and synthesize the urgently needed for the rapidly emerging bacterial pandemics, the selective novel antibacterial agents.

Unfortunately, GS displays poor selectivity between microbial and mammalian cells, a fact that restricts its use to topical applications [5]. In recent years, considerable effort has been devoted to developing GS analogs with improved therapeutically index where the antimicrobial and cytotoxic (e.g., hemolytic) activities are dissociated. In this quest, both the β-strand and the β-turn regions have been extensively modified in SAR studies that have shed light on factors governing GS bioactivity, such as cationic nature, amphipathic character, β-sheet structure, ring size and global hydrophobicity [26].

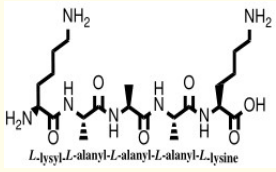
The penetration of AMPs into the membrane was computer simulated. High-Resolution Structures and Orientations of Antimicrobial Peptides Piscidin 1 and Piscidin 3 in Fluid Bilayers Reveal Tilting, Kinking, and Bilayer Immersion [27].

Moreover, Bacterial Outer Membrane Lipoprotein Lpp Is Gram-negative Bacterial Cell Surface Receptor for Cationic Antimicrobial Peptides [28]. Outer membrane protein Lpp of Gram-negative bacteria acts as a receptor for antimicrobial peptide. Scientists identify and characterize the Lpp, which is responsible for the recognition of cationic antimicrobial peptide. Lpp is a new target of antimicrobial peptide. Lpp may be used as a ligand to develop antimicrobial materials.

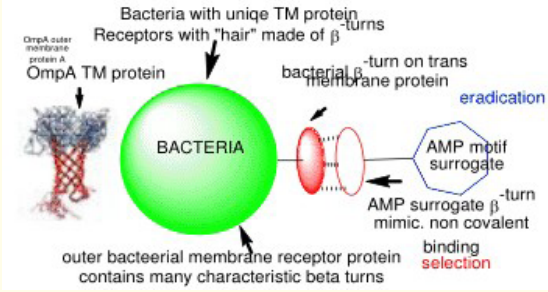
Keywords: *Bacteria; Cell-Wall Proteins; Selectivity; Beta-Turn; Selectivity; Peptide-Surrogates*



Hydrophobic Surrogate Tripeptide



Most Active Pentapeptide (KAAAK) Moiety From Dermaseptin



Recognition of Outer Membrane Domain by -Turn Mimic

(Figure 1)

Introduction

Healthcare-associated infections (HAIs)-infections patients can get while receiving medical treatment in a healthcare facility-are a major, yet often preventable, threat to patient safety. Together with health care and public health partners, CDC is working to bring increased attention to HAIs and prevention.

The advantage of antimicrobial peptides is the generality of their mechanism of action, which involves either compromising the bacterial membrane integrity or disrupting essential components inside the cells. This differs from the specific receptors targeted by conventional antibiotics which allow the pathogenic bacteria to develop resistance more rapidly. Furthermore, antimicrobial peptides are fast-acting and biodegradable, which alleviates the current concern over residual antibiotics in the environment. In addition to their direct microbicidal activities, these host defense peptides are particularly attractive because of the multiple activities that are associated with many members of this family. These include the regulation of the innate and adaptive immune systems, inflammation and wound healing, and additional anti-infective activities such as being antifungal, antiviral, antiparasitic or anti-cancerous.

However, this perception of the bioactivity of Amp and presumably their surrogates mat be too over estimated. The case with Gramicidin may contradict it.

Potential applications of β-turn Mimic in antibacterial combat

One of the approaches is to learn about the potential application of short peptide mimics like β-turn mimics, on the recognition with perspective to apply this if future drug design. The appearance of b-turns in protein interaction is by far more common than that of other, like β-turns. Non-covalent [29,30] interactions between the b-turn-mimics and some receptors on the cell wall of bacteria may supply enough energy differences that may allow differentiation between various bacterial transmembrane cell wall receptors [31] due to the receptor and β-turn mimic interactions. The interactions of some β-turn mimics with many classes of proteins which vary in their secondary structure (β-sheets, globular) have been found to rely on the interaction between β-turn mimics and the proteins.

Bacteria Cell Wall and Proteins [32]

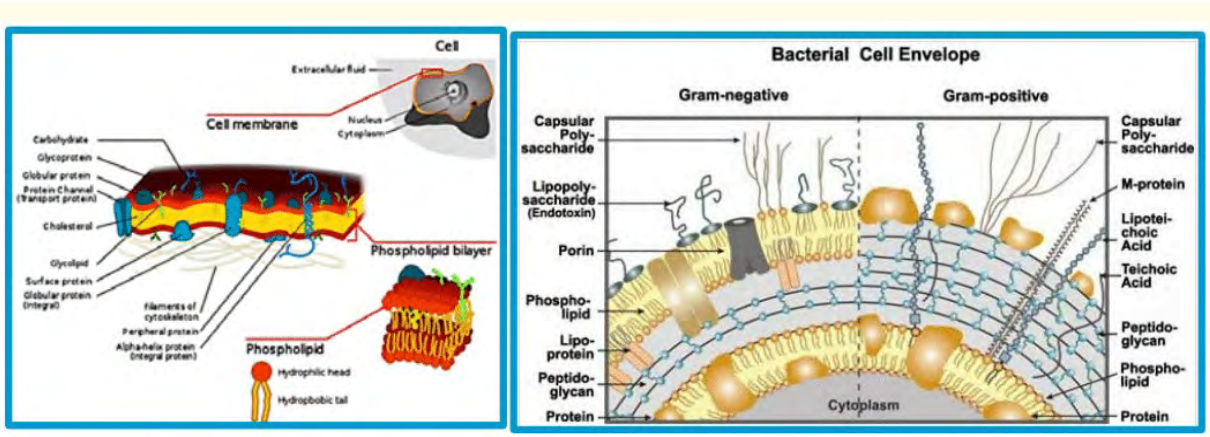


Figure 2

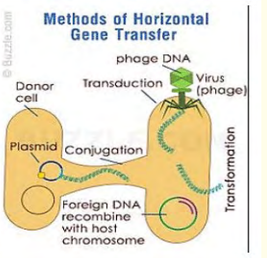
Many variants of β-turn mimic, one count nine β-turn types [33], have been applied so far in this area of research. It has been reported that Surrogate at the β-turn domain of Gramicidin S increase the biological activity [26]. One can read about benzodiazepines, β -turn mimic Hot=Tap for example [34].

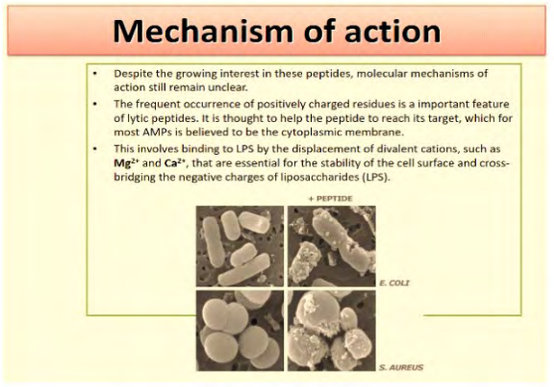
The lack of production and introduction of the newer and effective antibiotic/antibacterial drugs in clinical practice in the post-antibiotic golden age [35] has seen an increase in the emergence of the resistant pathogenic bacterial infections creating a significant problem in the global health of humankind. The situation today is that In 2011, an estimated 722,000 [36] patients contracted an infection during a stay in an acute care hospital in the US; 205 Americans die from hospital acquired infections (hospital acquired infections HAI, nosocomial infections [37]) every day.

Compounding the problem of antimicrobial-drug resistance is the immediate threat of a reduction in the discovery and development of new antibiotics [38,39].

It is now known that many different Gram-positive and Gram-negative pathogens communicate via the production and sensing of small, diffusible signal molecules, to coordinate virulence determinant production [40]. Horizontal genes transfer enables the transfer of resistance from one sort of bacteria to another either by Transformation, involves uptake of short fragments of naked DNA by naturally transformable bacteria. Transduction, involves transfer of DNA from one bacterium into another via bacteriophages. Conjugation which involves transfer of DNA via sexual pilus and requires cell -to-cell contact [41] (see cartoon below). Hunting the nightmare bacteria [42], therefore, this event, now termed quorum sensing, represents a novel therapeutic target offering the opportunity to attenuate virulence, and thus control infection, by blocking cell-to-cell communication.

HAI Estimates Occurring in US Acute Care Hospitals, 2011	
Major Site of Infection	Estimated No.
Pneumonia	157,500
Gastrointestinal Illness	123,100
Urinary Tract Infections	93,300
Primary Bloodstream Infections	71,900
Surgical site infections from any inpatient surgery	157,500
Other types of infections	118,500
Estimated total number of infections in hospitals	**721,800**





Frequency of aerobic bacteria from postoperative wound infection at Ayder Teaching and Referral Hospital, Mekelle, Ethiopia (January to June 2012)

No.	Gram	Microorganism	Frequency N (%
1	G+	*S. aureus*	40 (34.2)
2	G-	*Klebsiella* spp.	29 (24.8)
3	G+	CoNS[a]	18 (15.4)
4	G-	*Proteus spp.*	15 (12.8)
5	G-	*P. aeruginosa*	11 (9.4)
6	G-	*E. coli*	6 (5.1)
7		*Citrobacter* spp.	4 (3.4)
		Total	123 (100)

Figure 3: *Frequency of aerobic bacteria from postoperative wound infection at Ayder Teaching and Referral Hospital, Mekelle, Ethiopia (January to June 2012) [43].*

Wall [44] teichoic acids are found only in certain Gram-positive bacteria (such as staphylococci, streptococci, lactobacilli, and Bacillus spp); so far, they have not been found in gram- negative organisms. Teichoic acids are polyol phosphate polymers, with either ribitol or glycerol linked by phosphodiester bonds; their structures are illustrated in figure 2-9. Substituent groups on the polyol chains can include D-alanine (ester linked), N-acetylglucosamine, N-acetylglucosamine, and glucose; the substituent is characteristic for the teichoic acid from a bacterial species and can act as a specific antigenic determinant. Teichoic acids are covalently linked to the peptidoglycan. These highly negatively charged polymers of the bacterial wall can serve as a cation-sequestering [45].

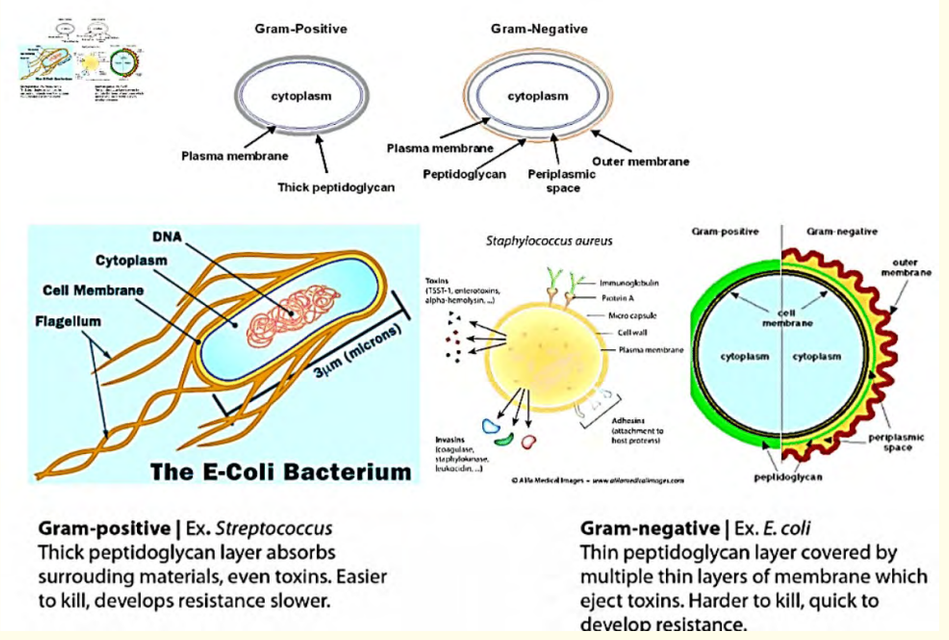


Figure 4

Current infection pandemic

Patients are infected annually, and Institute for Healthcare Improvement (IHI) estimates that more than 5,000 patients die each year as a result. While most patients are treated successfully, particularly if the infection is identified early, hospital stays are often extended by an average 9.1 days, accounting for excess costs of about $20,000 per patient. The total cost burden to the US health care system from MRSA infections is estimated at more than $2.5 billion annually.

Gram-positive and Gram-negative bacteria exist everywhere (a typical post-surgery infection in blue table above) [46], but pose unique threats to hospitalized patients with weak immune systems. Gram-positive bacteria cause tremendous problems and are the focus of many eradication efforts, but meanwhile, Gram-negative bacteria have been developing dangerous resistance and are therefore classified by the American Centers for Disease Control and Prevention (CDC) as a more serious threat. For this reason, the need for modern technologies that kill bacteria, both Gram-positive and Gram-negative, are essential to make hospitals safer for everyone. Both kinds of bacteria may cause fatal infection and should be eradicated one in the presence of the other.

The treatment of those serious bacterial infections in clinical practice is often complicated by antibiotic resistance. Therefore, there is an urgent need for innovative ideas in design and application of antimicrobial agents since bacteria gram-negative bacteria [21,47], develop strains that are intrinsically resistant to many antibiotics (persister) [48] strains, that are practically indifferent to all known antibiotic drugs. Furthermore, in the last decades, only two antibiotic classes with a novel mechanism of action (example is Teixobactin [49,50], a new cell wall inhibitor) have been marketed, and none of them are effective against persister Gram-negative bacteria. (The Top Ten Most Dangerous Bacteria on Earth [51]).

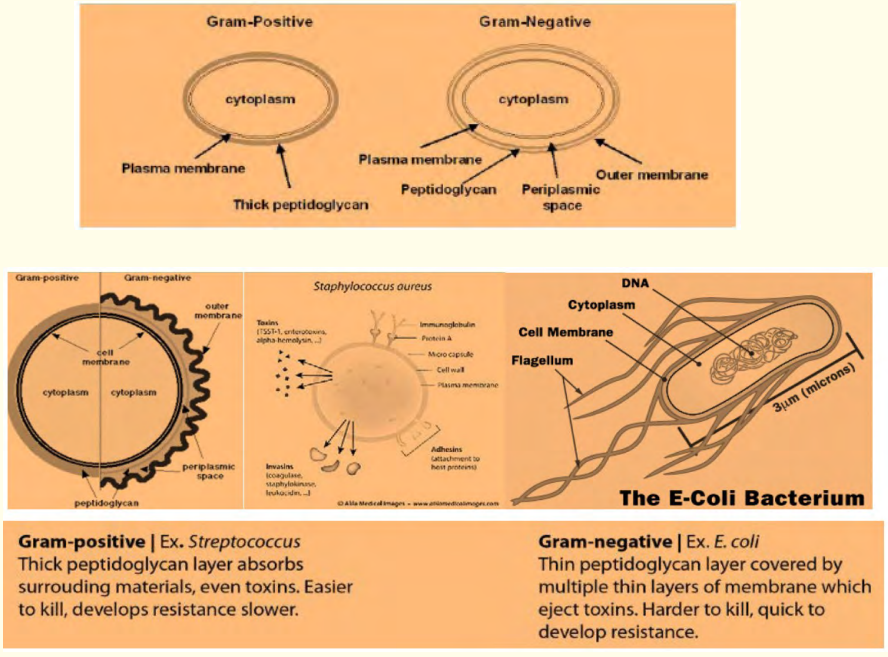
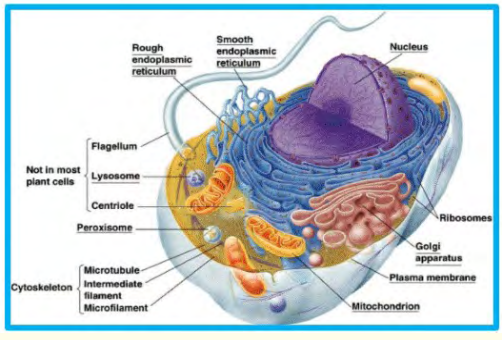
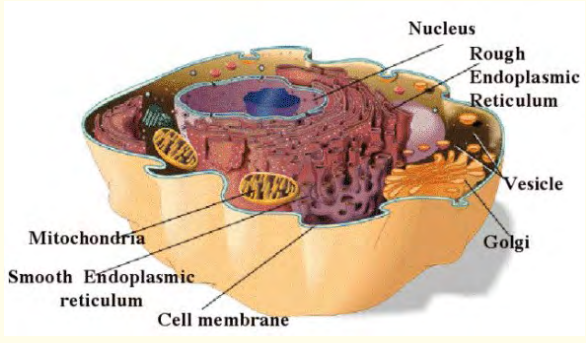
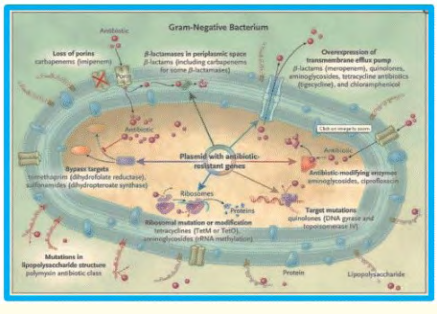


Figure 5





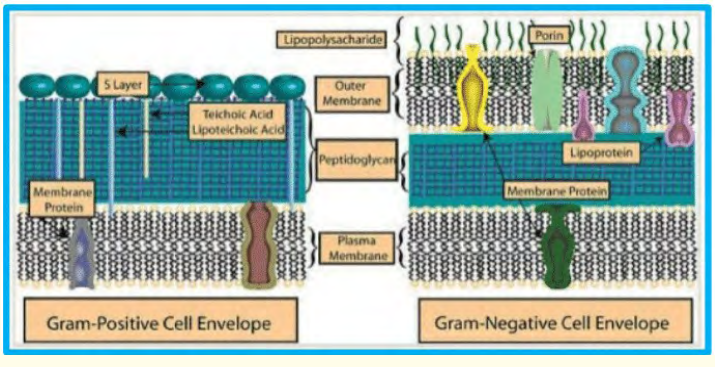
Bacteria Cell Diagram

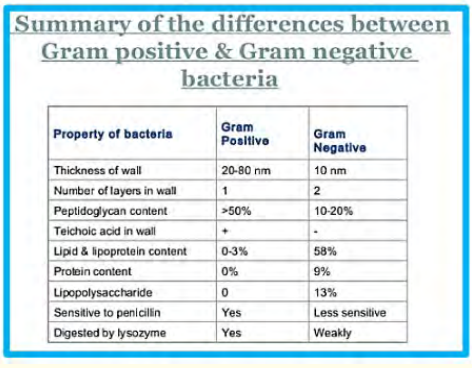


Mechanisms of Resistance in Gram-Negative Bacteria, and the Antibiotics Affected.

http://dlids.org/bacterial-cell-diagram.html

Seven mechanisms of resistance are shown in the gram-negative bacterium, with some being mediated by a mobile plasmid. These mechanisms include the loss of porins [52], which reduces the movement of drug through the cell membrane; the presence of β-lactamases in the periplasmic space, which degrades the β-lactam; increased expression of the transmembrane efflux pump, which expels the drug from the bacterium before it can have an effect; the presence of antibiotic-modifying enzymes, which make the antibiotic incapable of interacting with its target; target site mutations, which prevent the antibiotic from binding to its site of action; ribosomal mutations or modifications, which prevent the antibiotic from binding and inhibiting protein synthesis; metabolic bypass mechanisms [53], which use an alternative resistant enzyme to bypass the inhibitory effect of the antibiotic; and a mutation in the lipopolysaccharide, which renders the polymyxin class of antibiotics unable to bind this target. Red spheres indicate antibiotics.





Summary of the differences between Gram positive & Gram negative bacteria

Property of bacteria	Gram Positive	Gram Negative
Thickness of wall	20-80 nm	10 nm
Number of layers in wall	1	2
Peptidoglycan content	>50%	10-20%
Teichoic acid in wall	+	-
Lipid & lipoprotein content	0-3%	58%
Protein content	0%	9%
Lipopolysaccharide	0	13%
Sensitive to penicillin	Yes	Less sensitive
Digested by lysozyme	Yes	Weakly

Figure 6

To date, most antibiotics are targeted at intracellular processes and must be able to penetrate the bacterial cell envelope [54]. The outer membrane [55] of Gram-negative bacteria, crowded with sorts of proteins, provides a formidable barrier [56] (see cartoon sketch above) that must be overcome [20]. In Gram-positive bacteria the S layer (surface layer) is a part of the cell envelope found in almost all archaea, as well as in many types of bacteria. It consists of a monomolecular layer composed of identical proteins or glycoproteins and therefore easier to cross than the outer membrane, and serve as targets for many agents [57] in introduction of drugs and nutrients into the cell. Here are essentially two pathways that antibiotics can take through the outer membrane:

1. A lipid-mediated pathway for hydrophobic antibiotics, and
2. General diffusion porins for hydrophilic antibiotics.

The lipid [58] and protein compositions of the outer membrane have a strong impact on the sensitivity of bacteria to many types of antibiotics, and drug resistance involving modifications of these macromolecules is common [59]. Whereas the lipid bilayer determines the basic structure [60] of biological membranes, proteins are responsible for most membrane functions, serving as specific receptors, enzymes and transport [61-63] proteins [64]. As presented in the cartoon above, crossing (see you tube animations [65]) of the outer layers of bacteria cell wall [66] may include different energy. It seems that the Gram-negative is harder to cross. This may project on the speed of reaching of saturation in the respective cell membranes, needed for the eradication.

Pathways for protein transport

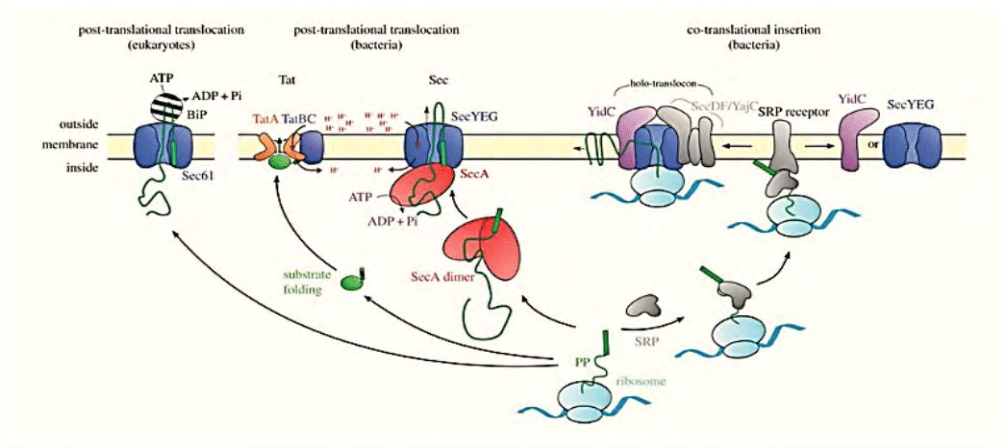


Figure 7: *Pathways for protein transport. From left to right: BiP (Binding Immunoglobulin Protein)-mediated post-translational translocation in eukaryotes; BiP is a HSP70 molecular chaperone located in the lumen of the endoplasmic reticulum (ER) that binds newly synthesized proteins as they are translocated into the ER, post-translational translocation of folded (Tat system) and unfolded (Sec system) proteins in bacteria; co-translational insertion in bacteria through the HTL complex or its individual components. Note that SecYEG has been shown here as a monomer for clarity [67]. The translocon (commonly known as a translocator or translocation channel) is a complex of proteins associated with the translocation of polypeptides across membranes. In eukaryotes, the term translocon most commonly refers to the complex that transports nascent polypeptides with a targeting signal sequence into the interior (cisternal or lumenal) space of the endoplasmic reticulum (ER) from the cytosol. This translocation process requires the protein to cross a hydrophobic lipid bilayer. The same complex is also used to integrate nascent proteins into the membrane itself (membrane proteins). In prokaryotes, a similar protein complex transports polypeptides across the plasma membrane or integrates membrane proteins. Bacterial pathogens can also assemble other translocons in their host membranes, allowing them to export virulence factors into their target cells. The bacterial translocation channel is formed by a heterotrimeric protein complex called SecYEG (Sec: secretory). It consists of the subunits SecY, SecE, and SecG.*

A drug that would specifically inhibit Tat transport could act in several ways, for example to affect the mechanism of energy transduction (which is currently unknown, but may be related to that used by the mitochondrial ATPase, the mechanism of twin-arginine signal peptide recognition, or perhaps the mechanism of disengaging signal peptides or transmembrane helices from the TatA channel. Since these latter two key activities involve peptide recognition, a peptide antimicrobial could be the answer to providing specific inhibition of the bacterial Tat pathway. They enable the use other substance needed for the cell's metabolism. In the membrane, not all β-barrel proteins are transport proteins [68]. In Most Transmembrane proteins, the polypeptide chain crosses the Lipid Bilayer in a α-Helical conformation [69].

Figure 8: *Only the α-carbon backbone of the polypeptide chain is shown, with the hydrophobic amino acids in green and yellow. The polypeptide segment shown is part of the bacterial photosynthetic reaction center illustrated in Figure 10-38, the structure of which was determined by X-ray diffraction. (Credit ref. [72]). The transport through the channel can be rationalized by single group rotation (SGR) mechanism [71].*

Some form smaller barrels that are filled with amino acid side chains that project into the center of the barrel. These proteins function as receptors or enzymes, here the barrel is used primarily as a rigid anchor that holds the protein in the membrane and orients the cytosolic loop regions that form binding sites for specific intracellular molecules.

Many investigations assume, based on early work of Merrifield [72,73] on the influence of the chirality of Cecropin on the ability to eradicate bacteria. synthetic D-enantiomers exhibit the same permeabilizing and biological activity as their natural L counterparts., The fact that both All D and all L do the same eradication of the bacteria, suggested the absence of a chiral transition in the eradication process [74]. This does not imply necessarily that no interaction between Antimicrobial peptides and outer membrane protein moieties does not influence processes essential to the survival of the microbes. This is to say that Experiments have shown that D-and L-amino acid versions of antimicrobial peptides exhibit similar binding [75] affinities to targets cells, suggesting that stereospecific receptors are not involved in targeting pathogenic cells [76]. In fact, many mechanisms other than electrostatic attraction gave been explored and formulated in recent years.

Outer membrane-active peptides play a key role in cellular processes, such as membrane fusion, which is a ubiquitous process and represents a key stage in protein trafficking [77], ex and endocytosis [78], viral entry and exit [79,80]. The target of many of these sequences is the lipid bilayer itself, but some (such as peptide hormones [81-84] and bacterial toxins [82,84-86]) likely act on proteins located in be the membranes. Although the basic structure of biological membranes is provided by the lipid layers [87] the membrane proteins (A typical plasma membrane is somewhere in between, with protein accounting for about 50 - 60% of its mass [88]).

The Protein-Protein Recognition, very often observed in interactions of antibodies with proteins in living organisms, is one of the main phenomena's still to be fully understood and exploited by pharmaceutical researchers. The exchange, called 3-D domain swapping, has now been observed in several proteins and apparently is a reasonably common evolutionary mechanism for the generation of dimeric and higher oligomeric forms of ancestor monomers Peptides and proteins are essential to many biological processes [89]. Complementarity, as dictated by interface topology, appears to contribute to interface specificity.

Recent papers report of the interaction of synthetic AMPs to the protein serum Albumin [90]. The research in areas like Tuberculosis is Targeting *Mycobacterium tuberculosis* and Other Microbial Pathogens.

Eradication of Bacteria

The following are basic Mechanisms of Antibiotics - Action and Resistance (see schematic presentation below):

1. Inhibition of Cell Wall Synthesis (most common mechanism)
2. Inhibition of Protein Synthesis (Translation) (second largest class)
3. Alteration of Cell Membranes
4. Inhibition of Nucleic Acid Synthesis
5. Antimetabolite Activity

The first barrier that an antimicrobial agent must overcome when interacting with its target is the microbial cell wall [91].

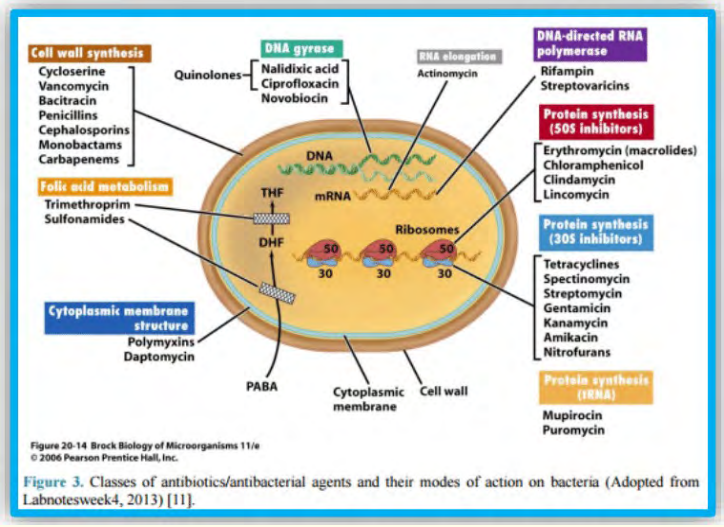


Figure 3. Classes of antibiotics/antibacterial agents and their modes of action on bacteria (Adopted from Labnotesweek4, 2013) [11].

Figure 9

Sites of action for antimicrobial agents [39]: All must cross the cell walls the antibacterial agents have to penetrate and in many instances cross the cell membranes. In most cases, is energy dependent [40,92]. This refers to many polypeptides that could provide a clue to one of the major problems in the antibacterial campaign: the selection of the harming microorganism as the only target for the potent antimicrobial peptides and their surrogates and eradicating them, leaving the contributing bacteria intact [93]. We assume that our antimicrobial peptides penetrate directly the cell wall [2] and do not undergo e3ndocytrosys or assistance of transportan [94].

In this paper, we would like to show that cell wall penetration [95] ability might lead the way for selective eradication of bacteria [96].

By using Improved Synthetic Antibacterial Peptides, it was found that some Lysine and Arginine-rich 9 - 14 amino acids peptide sequences show very efficient eradication of many strains of bacteria in sub-micro molar concentrations [97] (Table 1).

	MIC (μM)a								
Sequence	*M. tuberculosis*	*M. smegmatis*	*P. aeruginosa*	*E. coil*	*S. enterica serovar Typhimurium*	*C. albicans*	*S. epidermidis*	*S. aureus*	*E. faecalis*
WKWLKKWIK	1.1	1.9	2.9	5.8	11.5	5.8	0.7 - 0.3	0.7	11.5
ILRWKWRWWRWRR	2.4	2.4	5.7	1.4	2.9	5.7	0.7	0.7	2.9
ILPWKWRWWKWRR	2.6	2.2	5.7	1.4	5.7	2.9	0.7	0.7	2.9
RWRRICWWWW	2.8	5.7	11.2	1.4	2.8	5.6	0.7	0.7	2.8
WRKFWKYLK	3.0	1.5	6.0	0.8	6.0	3.0	0.8	0.8	6.0

Table 1: *Antimicrobial activity of selected peptides (library PL-D).*

The cell membrane-acting peptides (In our case Antimicrobial peptides for example) have common physicochemical properties; they are highly basic (cationic) due to the presence of multiple Lys and/or Arg residues and form amphipathic secondary structures (α-helix and β-sheet), which can be accommodated into membranes.

The bacteria cell membrane contains about one-third of the proteins in a cell and is the site for crucial processes, such as active transport [98] of nutrients and wastes, bacterial respiration, the establishment of the proton motive force in association with respiratory enzymes, ATP generation, and cell-cell communication in biofilms [99]. Antimicrobial peptides made by the host and several bioactive molecules that act on the membrane, validate its significance as an antibacterial target site. Cell wall proteins are a unique environment for the bacteria and therefore can be applied for selecting one sort of prokaryote from another, and bind to an agent that is able to eradicate the strain are chosen [100].

Usually, the membrane proteins are associated with Amphipols [101]. These detergent agents serve as molecular adapters to immobilize membrane proteins onto solid supports [2] (Figure 10).

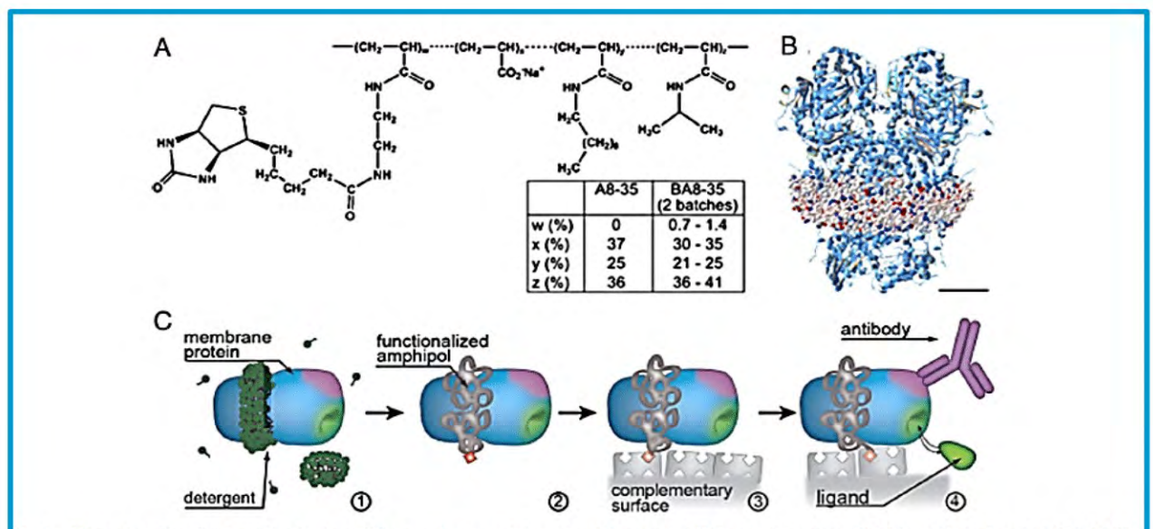


Fig. 1. Using a functionalized amphipol to immobilize membrane proteins onto solid supports. (*A*) Chemical structure of A8-35 and biotinylated A8-35 (BA8-35). *w*, *x*, *y*, and *z* are the percentages of each type of monomer: biotinylated, free, grafted with an octyl chain, and grafted with an isopropyl chain, respectively. Their distribution is random. On average, 1 molecule of A8-35 contains ~70 acrylate units, carrying ~18 octyl chains, for a molecular mass of 9–10 kDa. In the case of BA8-35, 2 batches were synthesized following different protocols (see *SI Text*). The structure shown is that of BA8-35-2. (*B*) Model of bovine cytochrome bc_1 (PDB ID code 1BGY) trapped in A8-35 [Reproduced with permission from ref. 18 (Copyright 2003, *Cellular and Molecular Life Sciences*).]. (Scale bar: 4 nm.) (C) Experimental principle of APol-mediated immobilization of MPs. A MP solubilized in detergent ① is transferred to a functionalized APol. The complex thus formed, ②, is applied to a support that exposes a functional group with which the APol can associate ③. Putative ligands of the protein are then flushed over the support ④ and their interaction with the immobilized protein detected by any convenient method.

Figure 10

The interaction between the peptide ligands and their receptor targets commonly involves β-turn structures. Yet, poor bioavailability and unfavorable pharmacokinetics, significantly compromise the use of peptides as drugs. For these reasons peptide surrogates are designed and synthesized to substitute the peptide in its functionality, avoiding the drawbacks and implanting new features that the original bioactive peptide did not acquire.

Protein–protein interactions (PPIs) regulate a wide array of cellular processes and are attractive targets for drug design. Turns are important targets for mimicry, both because they serve as recognition sites in peptides and proteins and because they allow a protein chain to fold back upon it to form a compact structure. β-turn mimics can interact and bring about recognition and association of proteins. It was also noted that some of the abilities of AMPs to combine with cell walls of microbes are due to short peptide motifs PXXXP [102]. This might contribute to Catherin [103] endocytosis. Regarding endocytosis, the structural and chemical requirement were investigated and Sequence YXRF Implicates a tight turn as the structural recognition motif for endocytosis [104].

Some natural and synthetic antimicrobial peptides were analyzed by NMR studies. This showed that in contrast to magazines reports, tachypneic I form a cyclic antiparallel β-sheet connected by a type II β-turn even in aqueous solution [105]. Therefore, investigators examined the use of β-turn mimics in the protein -protein interactions involving transmembrane receptors in nerve cells in protein interactions that involve β-turns [106].

Potential applications of b-turn Mimic in antibacterial combat

One of the approaches is to learn about the potential application of short peptide mimics like β-turn mimics, on the recognition with perspective to apply this if future drug design. The appearance of β-turns in protein interaction is by far more common than that of other, like β-turns. Non-covalent [29,30] interactions between the β-turn-mimics and some receptors on the cell wall of bacteria may supply enough energy differences that may allow differentiation between various bacterial transmembrane cell wall receptors [31] due to the receptor and β-turn mimic interactions. The interactions of some β-turn mimics with many classes of proteins which vary in their secondary structure (β-sheets, globular) have been found to rely on the interaction between β-turn mimics and the proteins.

Bacteria Cell Wall and Proteins [32]

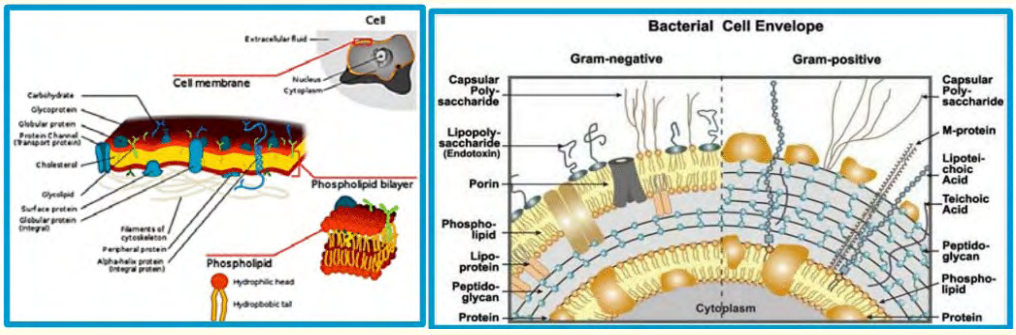
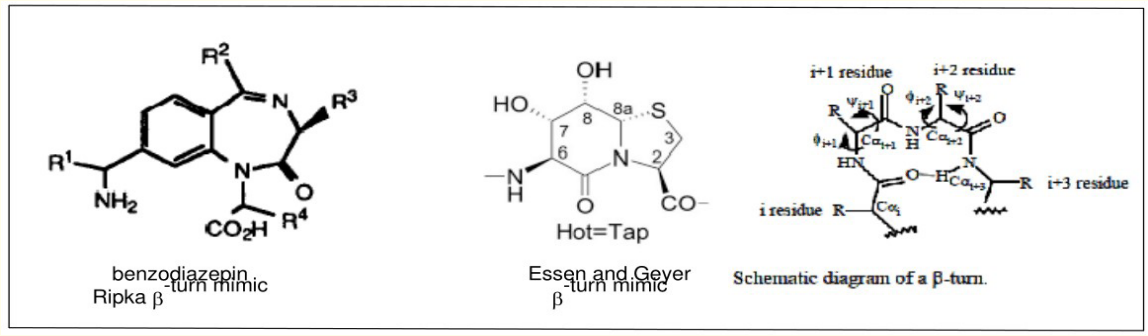


Figure 11

Many variants of β-turn mimic, one count nine β-turn types [33], have been applied so far in this area of research. It has been reported that Surrogate at the β-turn domain of Gramicidin S increase the biological activity [26]. One can read about benzodiazepines, β-turn mimic Hot=Tap for example [107].



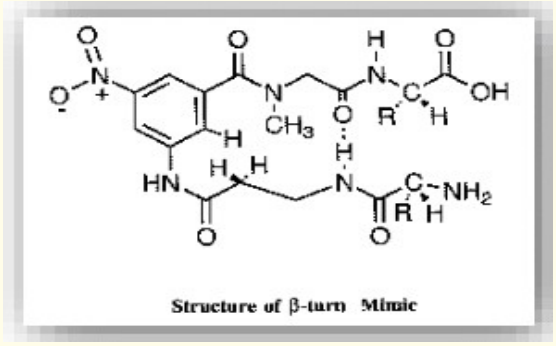


Figure 12

There is a growing demand for novel antimicrobial agents [108] for therapy but also for Hygiene and Agriculture, Soil Sterilization, for example. The class of compounds in the focus is the growing group of polypeptides isolates as part of the host defense systems of all organisms on earth (Antimicrobial peptides). Strains of the bacteria that harm are becoming more resistant to drugs but also live in the vicinity, in the same organism, as other useful and needed fauna of microorganism exist in the human gut, the "good" various strands of *Firmicutes, Bacteroidetes, Actinobacteria*, and *Proteobacteria* for example. We would like to selectively eradicate the "bad" (*Pseudomonas aeruginosa, Escherichia coli* (*E. coli*), *Clostridium difficult, Burkholderia cepacia, Klebsiella pneumonia, Staphylococcus aureus, Streptococcus pyrogens, Mycobacterium tuberculosis, Acinetobacter baumannii*, micro-organisms and leave the "useful" ones intact.

Now it is established that simple small molecules based on simple motifs [109] can be prepared and eradicate Gram+ as well as Gram- bacteria [110]. The next step is the differentiation stage (to attack only the unwanted bacteria). The selectivity mode we had in mind is to base the eradicating peptide surrogate on β-term mimics that are known to interact with cell wall proteins. In bacteria, mainly the outer part of transmembrane receptors [111-113]. after the surrogates settle in the inner part of the outer membrane, the ε-amine of lysine unit can "snorkel" [114].

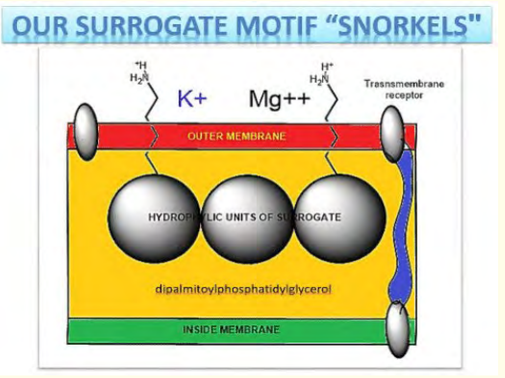


Figure 13

out and disintegrate the membranes of both Gram-positive and Gram-negative bacteria [115]. The interactions of an AMP with the membrane can¬not be explained by a sequential amino-acid pattern or motif; rather, they originate from a combina¬tion of physico-chemical and structural features including size, residue composition, overall charge, secondary structure, hydrophobicity and amphiphilic character. Pore formation by interaction with cell wall lipids and the changes in permeability and with it the ease of penetration of the AMPs through the forming pores is determining the effect on the eradication difference which is a result of disruption of the plasma membrane of the bacteria [24]. Moreover, interactions with the many components that furnish the architecture of the membranes are crucial for antibacterial activity.

Conclusion

From our study we conclude that the venerability of bacteria may depend on small structural variation in the composition of the biocide.

The architecture of the Gram-negative and that of the Gram-positive bacteria is quite different and could be drawn as follows.

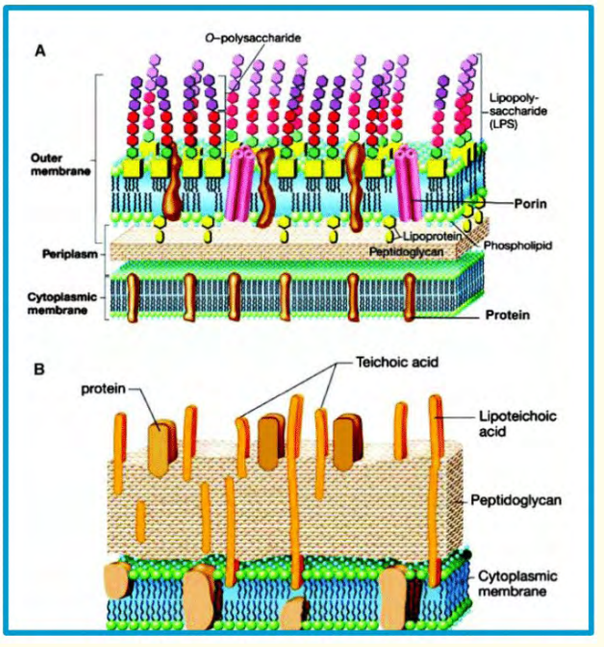


Figure 14: *A cartoon view of the membranes of (A) Gram-negative bacteria and (B) Gram-positive bacteria. The membranes of Gram-negative bacteria are composed of two layers: the outer membrane rich in LPS and the inner membrane rich in anionic PG. Gram-positive bacteria have a cell wall consisting of lipoteichoic acid and peptidoglycan and a cytoplasmic membrane.*

Outer membrane proteins, found in the outer membranes of bacteria

Cationic peptides have been found to bind to negatively charged lipopolysaccharides (LPS), a major component of the outer membrane of Gram-negative bacteria [116]. Disruptions are thought to appear in the (LPS) layer. We are therefore focusing on positively charged SMAMPs (contain Lysine rests) in our investigation.

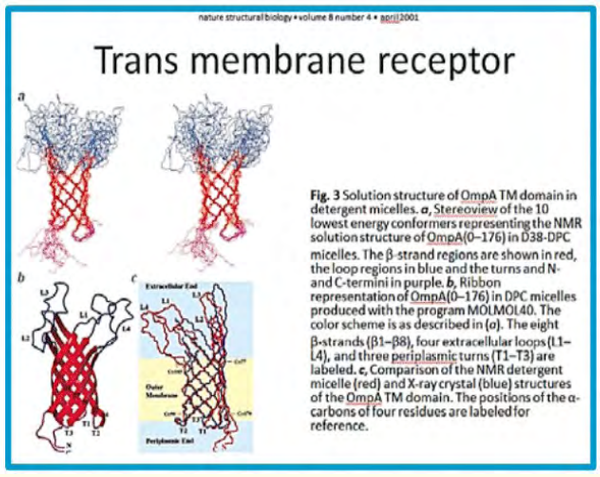


Figure 15

The cell wall of bacteria contains proteins. Mainly those that build the cell wall Toll, TLRn (n=1-13) transmembrane [39], signalling [117], Receptors [118-120] for instance. Current research reveals that short (as little as 4-5 amino acid sequences, PXXP that was mentioned above, for instance), polypeptide chains are the once forming a non-covalent attachment to the receptor on the outer membranes [121]. This region of the protein [122].

Some transmembrane receptors. Bonding short helix in non-covalent bond [123] from which the receptor is made is rich in β-turn [124] motifs and could provide a ground for non-covalent connections. It may become feasible that antibacterial peptide surrogates, based on mimics of such short peptide sequences, may attach to the proteomic part of the outer domain that the transmembrane receptor (LTR4 and LTR5 in particular). This may in this way selectively in the choice of bacteria to eradicate. Eradication will then be done by the usual membrane disassembling mechanism [2] the bacterial cell.

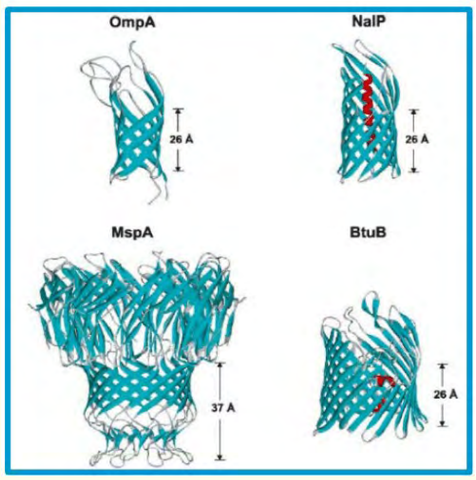


Figure 16: *Representative structures of h-barrel membrane proteins. OmpA, the transmembrane domain of OmpA of E. coli (PDB entry 1G90; NalP, translocator domain of autotransporter of N. meningitides (1UYN); MspA, porin of M. smegma 'tis (1UUN); BtuB, cobalamin transporter of E. coli (1NQE). The approximate location of the lipid bilayer is indicated in each structure. Note the much wider hydrophobic thickness of MspA.*

Protein-Protein Interfaces [54,125] interactions can be satisfied by adding a second copy of the interface domain to the monomeric polypeptide in such a fashion to allow it to interact with the original interface. (The latter strategy was employed by Mossing and Sauer [126] when they connected via a β- turn, a partial copy of the β-ribbon interface of λ-crop - DNA protecting protein - to the end of an intact copy. This allowed the second copy to loop back and interact with the remainder of the protein to form a stable monomer).

The different architecture of the cell wall of Gram-positive and Gram-negative bacteria may present a tool for selective choice of targets regarding the eradication by antimicrobial peptides and their surrogates. B-turns and N-methylation may present a toolbox for the designers and synthetic people to design and synthesize the urgently needed for the rapidly emerging bacterial pandemics, the selective novel antibacterial agents.

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