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Antibacterial Peptide Surrogates A Brief Review

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The Challenge Today

The world is confronted these days with a nosocomial pandemic. People die from infections they contracted in the healthcare facilities, hospitals and clinics due to the development of resistant strands of microbes. There is no remedy to those infected. One of every 25 persons entering the hospital get infected. Each of 9 of those dies from the nosocomial infection and there is practical no way for cure. Many look for the clue. Here is one approach.

Abstract

The herein described technology is based on nature's own defense mechanisms. The membranes of microbial cells are destroyed. This unique technology is a new class of antimicrobial treatment that activates the microbes own life processes for its eradication. It is based on the natural products, the antimicrobial peptides, that are the basis for the innate immune systems of all living organisms on earth.

These compounds have been considered as potential therapeutics because of their broad-spectrum activities and proven ability to avoid antimicrobial resistance, but their clinical and commercial developments have some limitations, such as susceptibility to proteases and a high cost of peptide production. To overcome these problems, many researchers have tried to develop short active peptides, their modifications and mimics with better properties while retaining their basic features of natural AMPs such as cationic charge and the amphipathic structure. Bioactive moieties which are identified in the sequences of the natural AMPs may serve as backbones to Synthetic surrogates of these host defense peptides. It is established that in many instances only small sequences of the AMPs are the active moiety, this can serve as a backbone to a design of synthetic mimics of antimicrobial peptides (SMAMPs) with superior qualities.

Keywords: *Antimicrobial Peptides; Peptide Surrogates; Eradication; Implants Coating*

Introduction

The antibiotics have represented a great revolution for humankind, the development of the times after the World War II [1,2] a golden age of antibiotics, the age of a "magic bullet" (the antibiotic molecule), as imagined by Paul Ehrlich [3], the pioneer of chemotherapy, with the property to kill or inhibit the growth of microorganisms by hitting the microbial structures with low toxicity for host cells and tissues, has determined a new era in the treatment and prophylaxis is of infectious disease and in the quality of human life. Those were the days we thought will never end. Unfortunately, This source fountain is drying out, one of the novel promising routes is to follow and develop the AM world, in part by way of synthetics peptide surrogates [4,5].

The Antimicrobial Peptides (AMP) Route

Nature has developed a defense strategy imbedded in the innate immune system in the form of thousands of compounds based on a polypeptide framework: the class of antimicrobial peptides. This system enabled organisms to survive for eons in the hostile environment

of billions of microbes, very ancient and robust living simple creatures that poses features like dormancy, and persistence unknown in other kingdoms of biology.

However, Antimicrobial peptides are very sensitive compounds and suffer from many drawbacks when intended to be applied by humans in their struggle against the microbes [6]:
Development of Antimicrobial Peptides as Anti-Infective Drugs

Advantages	Disadvantages
Broad-spectrum activity (antibacterial, antiviral, antifungal)	Discovery costs of synthesis and screening
Rapid onset of killing	Patent exclusivity for economic viability
Cidal activity	Systemic and local toxicity
Potentially low levels of induced resistance	Reduced activity based on salt, serum, and pH sensitivity
Concomitant broad anti-inflammatory activities	Susceptibility to proteolysis
	Pharmacokinetic (PK) and pharmacodynamic (PD) issues
	Sensitization and allergy after repeated application
	Natural resistance (e.g., Serratia marcescens)
	Confounding biological functions (e.g., angiogenesis)

Among the many advantages, there are also drawbacks [7] in which the hardest are instability in biologic environments (decomposition by enzymes) size of the molecule and difficulties to apply in high scale.

Although AMPs have some intrinsic drawbacks, such as susceptibility to enzymatic degradation, toxicity, and high production cost, currently, a new class of AMPs surrogates termed "peptidomimetics" have been developed [8]. This can mimic the bactericidal mechanism of AMPs, while being stable to enzymatic degradation and displaying potent activity against multidrug-resistant bacteria.

We have adopted the approach that involved the uncovering of the antibacterial motif [9,10] of an antimicrobial peptide and design and synthesis of surrogates of that motif.

It is agreed however, that the interactions of an AMP with the membrane cannot be explained by a particular sequential amino-acid pattern or motif; rather, they originate from a combination of physicochemical and structural features [11] including size, residue composition, overall charge, secondary structure, hydrophobicity and amphiphilic character [12,13].

From the Skin of the Frog to Selectivity Gram-Positive/Gram-Negative-Bacteria Eradication

The natural products, antimicrobial peptides, on the molecular level are only in part embracing the antimicrobial harpoon [14]. This includes motifs which are flanked by structural moieties that are attached or not removed from the "heart" of the killing units during evolution. There may be a lot of unneeded "structure" regarding the eradication of microbes. When such "overweight" is removed, it turns to become a quite low molecular weight peptide that is as efficient as the natural peptide does a "good job" in the eradication [15].

The passive transport through the phospholipid bilayer by direct penetration became the dogma in the field. 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 [16,17].

Antibacterial peptides have multiple roles in immune defense [18]. The case with Gramicidin (GS) may contradict the dogma. Although the mechanism of action of GS is not completely understood, it is generally accepted that the peptide kills bacterial cells through destabi-

lization and permeabilization of their cytoplasmic membranes. Synge [19] in the early years of the area, explored the cyclic antimicrobial peptide Gramicidin-S [4,5], which is applied today only for topical antibacterial therapy.

Katchalski (Katzir) prepared poly-lysine's and explored their biocidal quality [20,21] as bacteria killers. Notably, these short peptide surrogates [22] and did not result in any measurable resistance development in *E. coli*. MIC (minimum inhibitory concentrations) [23,24] Antibacterial peptides have multiple roles in immune defense [18].

The case with Gramicidin (GS) may contradict it. Although the mechanism of action of GS is not completely understood, it is generally accepted that the peptide kills bacterial cells through destabilization and permeabilization of their cytoplasmic membranes.

However, this perception of the bioactivity of the amphipathic AMPs and presumably their surrogates may be too over estimated, although cationic AMPs possess diverse secondary structures, their surfaces are uniformly amphipathic with both hydrophobic and hydrophilic residues. The architecture and micro-Structural determinants of antimicrobial activity in Synthetic antimicrobial peptide surrogates (SMAMPs), which mimic host defense peptides include charge, amphipathicity, hydrophobicity, flexibility and H-bonding capacity [25] are key factors which are considered.

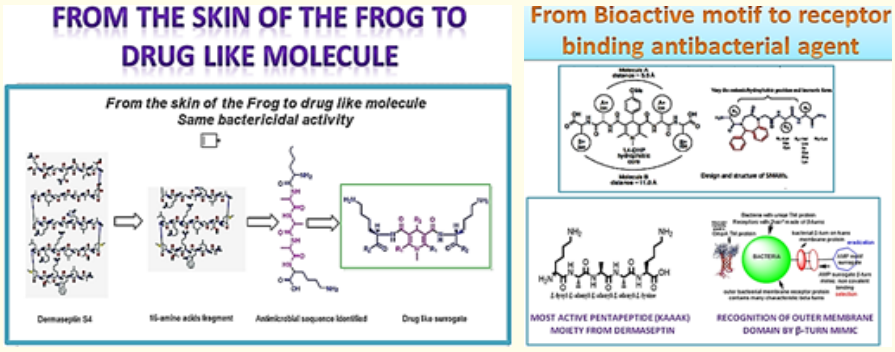
The roll of Lys in Cecropin-Mellitin is remarkable: Felix reported that in lysine-enriched peptides retain strong antimicrobial activity and, most importantly, have markedly reduced toxicity toward eukaryotic cells [26]. Despite very diverse peptide sequences and structures, most host defense peptides appear to act by a direct lysis of the pathogenic cell membrane. They are defined as membrane-active molecules by Takahashi, Feix and Sato [27-29]. While their lytic activity is generally not mediated by a chiral center [30], the exact mechanism [31] behind this activity is not fully understood [32,33].

The harnessing of the cell wall outer membrane receptor for a better activity of SMAMPs is attractive, particularly to combat Gram-negative microbes. Svendsen and his collaborators reported that SMAMP combines with serum albumin. Ting-Wei Chang [34] reported on the Outer Membrane Lipoprotein Lpp In Gram-negative Bacterial Cell Surface Receptor for Cationic Antimicrobial Peptides. Since architecture of such receptors openings are rich in β -turn moieties, conferring β- turn mimics [13,35-38] might strengthen such interactions with the outer membrane.

		5000 µg/ml	500 µg/ml	50 µg/ml	5 µg/ml	0.5 µg/ml
Tb-1	E.coli	not active	active	active	active	active
	S.Areus	not active	not active	not active	not active	not active
Tb-2	E.coli	not active	not active	active	active	not active
	S.Areus	not active	not active	not active	not active	not active
Tb-3	E.coli	not active	not active	not active	active	not active
	S.Areus	not active	not active	not active	not active	not active
Tb-4	E.coli	active	active	active	active	active
	S.Areus	not active	not active	active	active	active
Tb-5	E.coli	not active	not active	not active	not active	active
	S.Areus	not active	not active	not active	not active	not active
Tb-6	E.coli	not active	not active	not active	not active	not active
	S.Areus	not active	not active	not active	not active	not active
Tb-7	E.coli	not active	active	active	active	active
	S.Areus	not active	not active	not active	not active	not active
Tb-8	E.coli	active	active	active	active	not active
	S.Areus	not active	active	active	active	not active
Tb-9	E.coli	active	active	active	active	active
	S.Areus	not active	not active	not active	active	active
Tb-10	E.coli	not active	not active	not active	not active	not active
	S.Areus	not active	not active	not active	not active	not active
Tb-11	E.coli	not active	not active	not active	not active	not active
	S.Areus	not active	not active	not active	not active	not active
Tb-12	E.coli	Not active	active	active	active	active
	S.Areus	Not active	Not active	active	active	active

Results of biological(eradication) activity (hRBC <3% in all cases)

Peptides that were synthesized and evaluated



Cartoon that describes a way for minimizing a natural product antimicrobial peptide to "small molecules" with comparable antibacterial activity.

For example, Shatzmiller and coworkers [39,40] has identified in Dermaseptin-S4 a broad band antibacterial motif where 3 alanine residues are flanked by two lysine and prepared drug like antibacterial peptide surrogates.

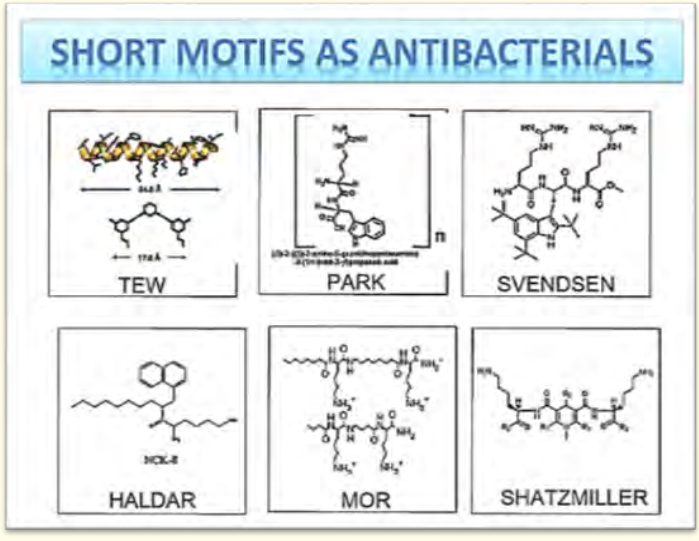
Adopting the peptidomimetic approach, Svendsen [41-43] and the company LYTIX have developed the topical anti-infective drug candidate LTX-109 [44].

In order to exploit the antibacterial potency in antimicrobial peptide, a bacteria-eradicating motif is to be discovered in many peptides [45] that have been taken for the design and synthesis of peptide surrogates in which many drawbacks of the natural peptides can be eliminated.

The general strategy is applied by many to the point where such motifs are identified [46]. Then the mimics designed, synthesize and check for antibacterial activity and toxicity. A usual procedure uses MIC determination an human erythrocytes hemolysis.

An example is the identification of an antibacterial motif in *Lactoferricin* [46,47] as follows. This was translated to a drug candidate by the company LTX 109:

Now, one can summarize some of such antibacterial as in the next chart:



Tew has taken this approach to the point where he expressed the idea in showing that the amphipathic motif of Magainin 2 [48] is in fact translated to a hydrocarbon scaffold, carrying the tow ω- amino groups providing a hydrophobic scaffold with two flanking positively charged amino units.

Mechanism of Eradication

The unique position of this research is based on the knowledge that AMPs eradicate microbes in a novel mechanism.

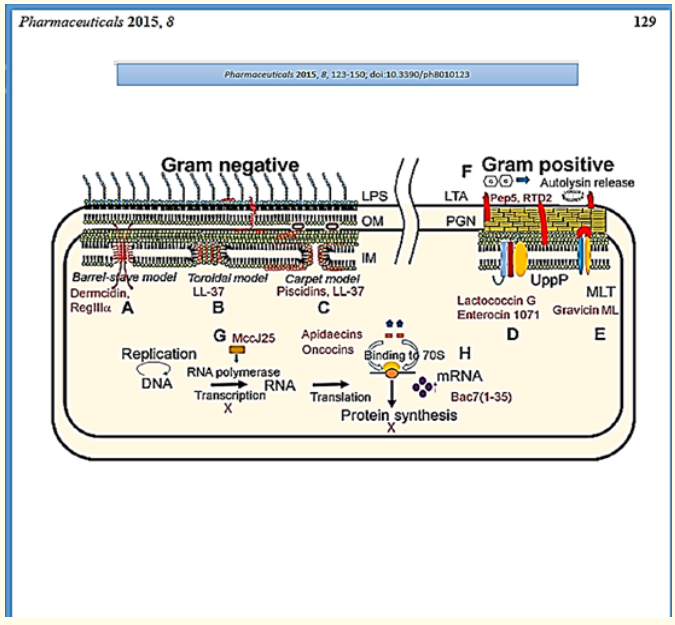
Historically, Professor KATCHALKI (KAZIR) at the 1940's investigated the effect of poly α-Lysine on bacteria and established the findings that the polymer is antibacterial. However, it cannot be applied to humans since it has toxic effects on blood [20,21].

Later, Compounds from amphibians were isolated and one peptide in particulate Magainin 2 was investigated by Zassloff as broad spectrum antibacterial, the synthesis and application of the analogue Pexiganan [49] brought this field forward.

Shai, Mitsuzaki and Huan [50,51] suggested the Carpet Mechanism for the eradication on the basis of outer membrane destruction, carpet and pore forming mechanism based on the electrostatic attraction of the positively charged N units in the peptides attracted to the PO3 negative units in the membrane's phospholipids.

About 40 diverse ways of mechanism in the literature to account for the biological activities of antimicrobial peptides. Since the predicted mode of action of our AMP surrogates relies on cell wall disruption, it is reasonable to speculate that such a non-enzymatic mechanism [52] would alleviate some of the drawbacks presented by natural antimicrobial peptides. 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.

Meanwhile, this was proven to be only a part of the whole picture. Today, there exists knowledge of many mechanisms [33,52] in which many AMP exercise their eradications. Some act in many ways, from cell membrane destruction to nucleic acid.



Mechanisms for eradication by AMPs [41].

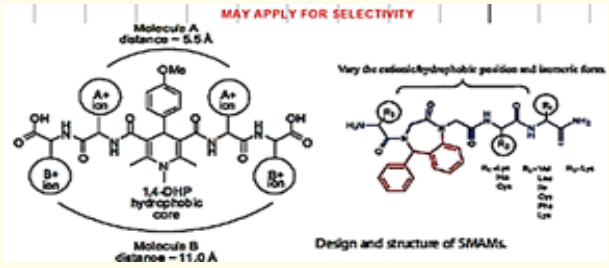
This may be due to the many physiological effects such peptides embrace [53]. One part acts in mechanism a and another part in mechanism b for instance.

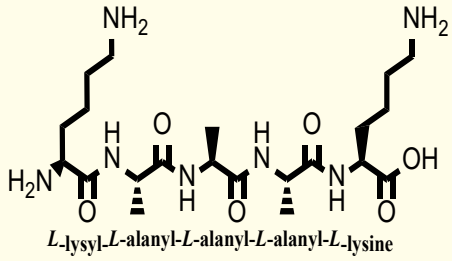
The question in what mechanism or mechanisms do the surrogates eradicate the bacteria are to be studied and reasonable pathways should be discovered. Today there is great controversy, also due to the fact that chirality [54] is not a factor in the interaction that determines the killing of the bacteria, applies to both Gram negative as well as Gram positive. Research today binds the eradication of the two types of bacteria in one pathway. There is only little difference in the eradication of G+ and G- bacteria [55].

There is a growing demand for novel antimicrobial agents 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 isolate as part of the host defense systems of all organisms on earth (Antimicrobial peptides) [56].

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 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 difficile, Burkholderia cepacia, Klebsiella pneumonia, Staphylococcus aureus, Streptococcus pyogenes, Mycobacterium tuberculosis, Acinetobacter baumannii*, micro-organisms and leave the "useful" ones intact.

We have published the surrogates of the antibacterial motif *L-lysyl-L-alanyl-L-Alanyl-L-alanyl-L-Lysine* isolated from Dermaseptin S4 in which privileged scaffolds entered in the hydrophobic moiety (1,4-Dihydropyridine (DHP) and Benzodiazepine, (BDZ). The BDZ unit can be regarded as a β -turn mimic [4], trying to mimic the existing β -hairpin identified in natural antimicrobial peptides [15].





The approach to the bacteria via an Outer Membrane Protein receptor cannot be excluded although there is no effect of chirality in applying the above-mentioned surrogates of the natural motif. In this view, we have prepared pair of enantiomer surrogates based on Freidinger's lactam and its NH2 -methylated analog [57].

We further extended our peptide-mimetic approach to utilize the "snorkeling" [58-60] effect well.

Characterized in peptides to control the interaction the bioactive structure with cell membranes [61]. The "snorkeling" [20,21] model is one in which peptides have long spacer "arms" in the cationic residues (lysine and arginine), which can reach to the lipid-water interface.

Thus, we have focused on the 4-5 amino acid amphipathic motif where three (or two) hydrophobic amino acids or their surrogate which are flanked by two cationic amino acids lysine (K) or arginine (R) (K-AA-K, K-AAA-K), [30] as examples. They are present in frog skins, (see above) [62-64], in human lactoferrin [65].

Lactoferricin and human saliva which are among the most studied AMP derived from the milk protein [66]. The complete sequence of lactoferricin corresponds to lactoferrin fragment 17-41 (FKCRRWQWRMKKLGAPSITCVRRAF) and sequences from within this fragment are also antimicrobial. Svendsen and Vogel and their groups shed light on the 3D structure of Lactoferricin [46,47,65].

The 16 amino acids fragment of Dermaseptins S4 was dissected systematically to 5 amino acids sequences (Scheme 1) and the penta-peptides synthesized and evaluated for eradication of both Gram negative (*E. coli*) and gram positive (MRSA Staph. Aur.) Results e in the figure below:

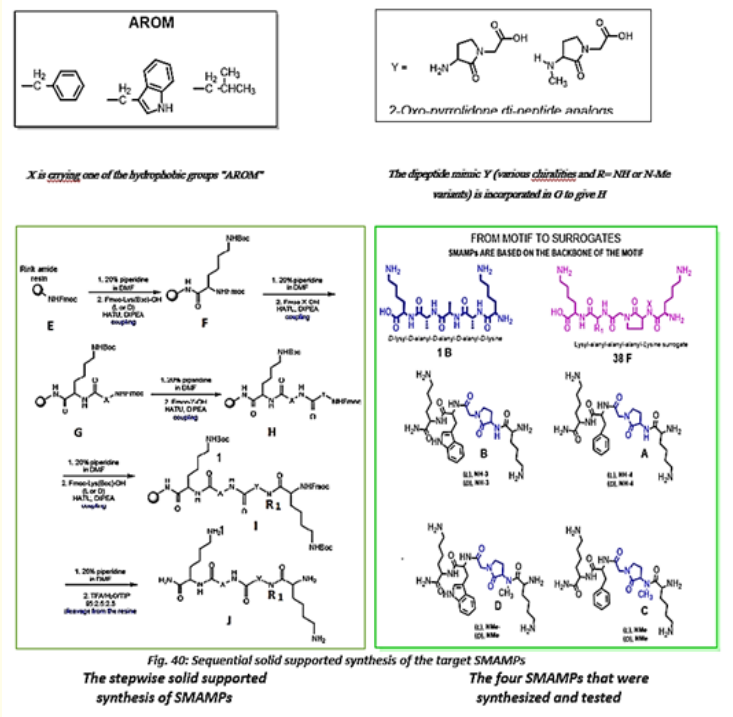


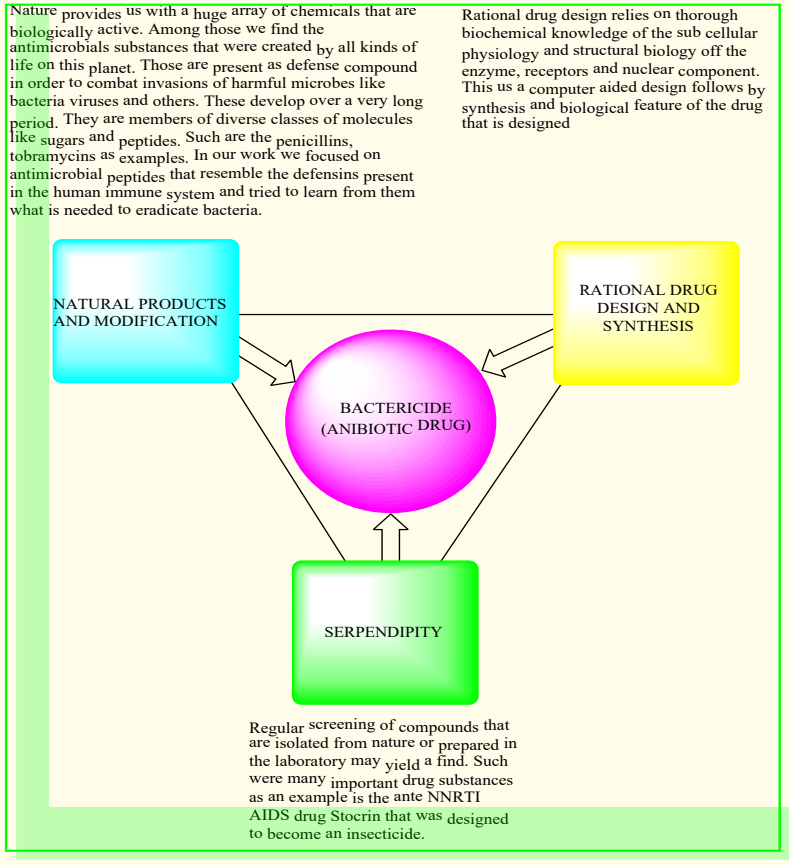
Fig. 40: Sequential solid supported synthesis of the target SMAMPs

The only parameter changed id NH vs NMe, compare Figure A and Figure B for example.

AMPs have been 'believed' to exhibit cell selectivity. That is, they selectively kill microorganisms without being significantly toxic to host cells. This concept, which coincides with roles of AMPs in innate immunity, comes from an affluence of observations that AMPs are nonhemolytic at concentrations well above their minimal inhibitory concentrations (MICs) against various microorganisms. However, it should be stressed that AMPs are potentially toxic to mammalian cells in the absence of microorganisms. The peptide-mimetic design principle offers significant flexibility [67,68] and diversity in the creation of new antimicrobial materials and their potential biomedical applications [70,71].

The tendency irrespective to the photolytic amino acids constructing the surrogate hydrophobic part is that N-methylation directs to higher hydrophobicity and stiffening of the agent, compared to the non-methylated one. This might influence the penetration into the outer membrane to enable cation capture by snorkeling. This may implies that the TEW description of entering the inner part of the outer membrane (Dipalmitoyl phosphatidyl glycerol (DPPG)) is determining the selection G+ vs. G- membranes [72].

Prevention and control of microbial-resistant organisms is one of the most complex management issues that health care professionals face. The clinical and financial burden to patients and health care providers is staggering. Antimicrobial agents are urgently desired. There is great hopes focusing on antimicrobial peptides and their surrogates regarding the nosocomial pandemic which approaches the medical world. Here are a few directions in which these new agent may help.



Apparent uses of SMAMPs in many areas.

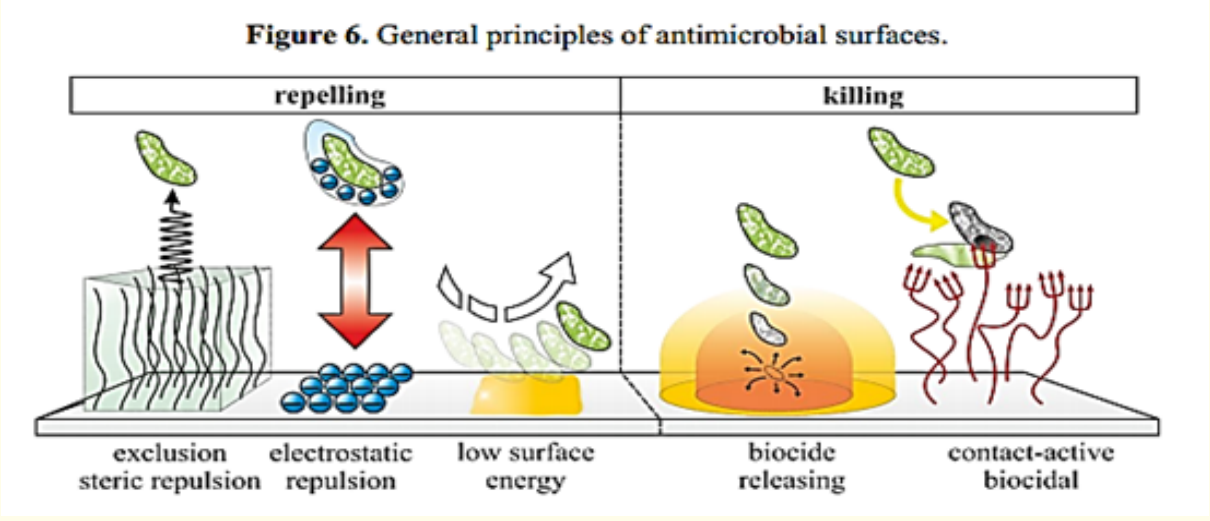
Protection of implants from bacterial infections

Modern medicine, in Orthopedy, Cardiology, Dentistry are some a read in which implants made of metals or alloys are applied. Implantable biomaterials are designed to replace a part of the body and/or its associated functions. In general, only the surface of an implant is in direct contact with the host tissue, and thus this portion of the biomaterial plays a critical role in determining biocompatibility. The surface of any material can change with time, and it is often distinctly different from the bulk material, predominantly because of oxidation and contamination. Therefore, attention must be given to the stability of the biomaterial surface because composition and structure generally affect the host response after implantation.

Biofilms on materials are extremely hard to remove and show great resistance to all kinds of biocides. Thus, the prevention of biofilm formation by antimicrobial surfaces is the best way to avoid spreading of diseases and material deterioration. In order to do this, the material must avoid the primary adhesion of living planktonic microbial cells from the surroundings. The focus of attention is to prevent biofilms from developing on these surfaces, Today, implants like cardiac pace makers, stents are coated with a polymer, Parylene as major coating technology today, that is inactive in respect of combating microbes. The interaction between devices and the surrounding tissue at the implant interface is essential for success or failure of implants. In that respect, coatings can be applied to facilitate the process of healing and obtain a continuous transition from living tissue to the synthetic implant [72]. A polymer [73] that will have antimicrobial ability may improve the defense against microbial infarctions cause by the implants, as unnatural unit placed in the living tissue of the body [74].

In general, this can be achieved by either repelling or killing the approaching cells (see Figure 8):

Figure 6. General principles of antimicrobial surfaces.

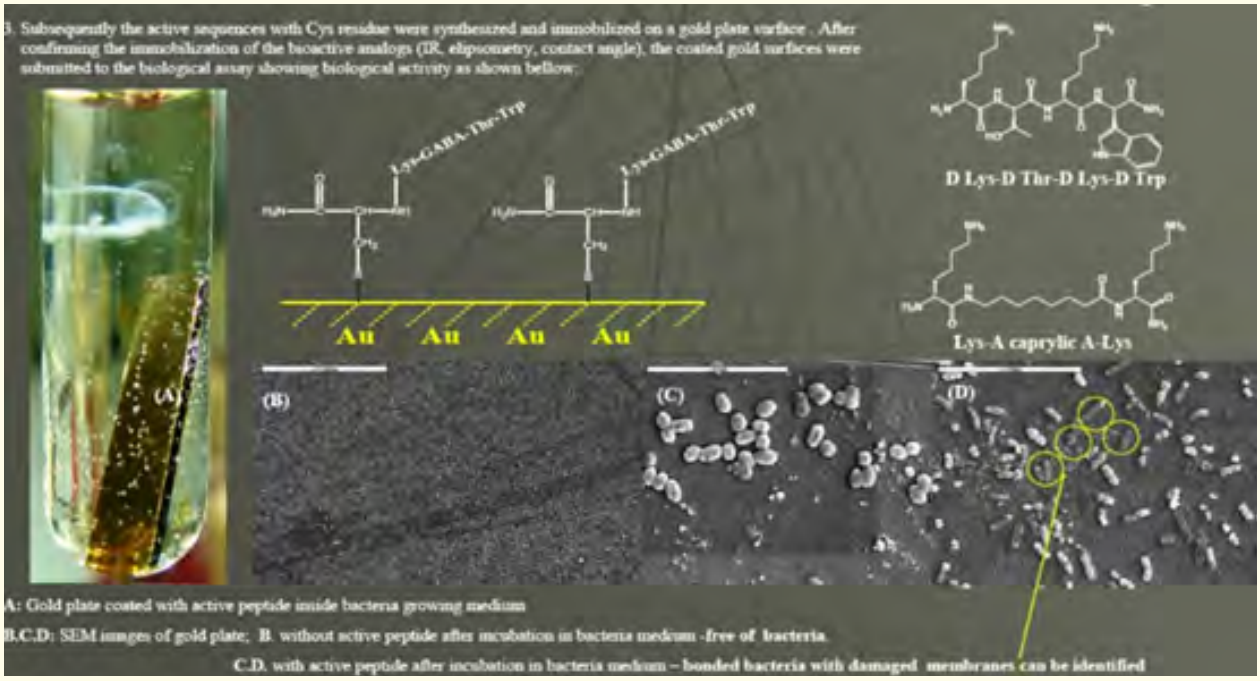


Great hopes and efforts are put into exploring the perspective of antimicrobial polymers [75-82].

The old polylysine [83] (α- and ε- variants) is in the focus of research. Although toxic and hemolytic.

ε-Poly-L-lysine (ε-PL) is a homo-poly-amino acid characterized by the peptide bond between the carboxyl and ε-amino groups of L-lysine. ε-PL shows a wide range of antimicrobial activity and is stable at elevated temperatures and under both acidic and alkaline conditions.

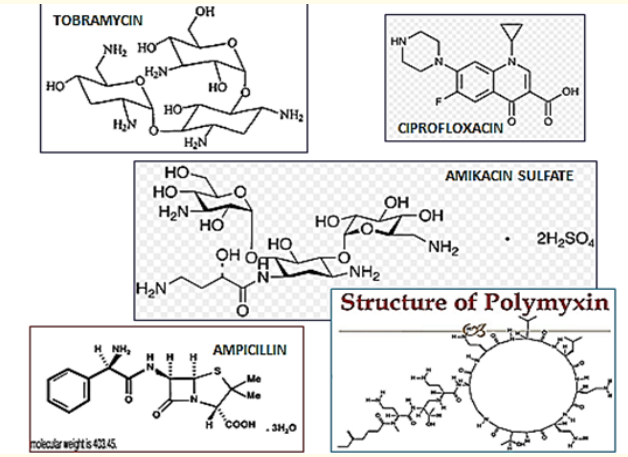
The coating of metal surfaces [84], focusing on prevention of periodontal infection after implantation [85]. We have attached SMAMPs to gold coated surface and observed the eradication of *E. Coli* [86].



SEM experiment coating of gold plated glass with SMAMPs based on the unit KAAAK inserting cysteine as SH vehicle.

The ability of penetration of the hydrophobic section of the AMP surrogate into the outer membrane of the bacteria is determining the eradication of the microorganism. The shallow hydrophobic sector may be unable to insert sufficiently into biological membranes to kill microorganisms. N-methylation stiffens the framework [87] and increases hydrophobicity enabling better penetration to the G+ membrane as compared to the protein rich outer membrane of the G-bacteria. This is translated to more efficient eradication of G+ bacteria in the N-CH_3 surrogates over the NH compounds.

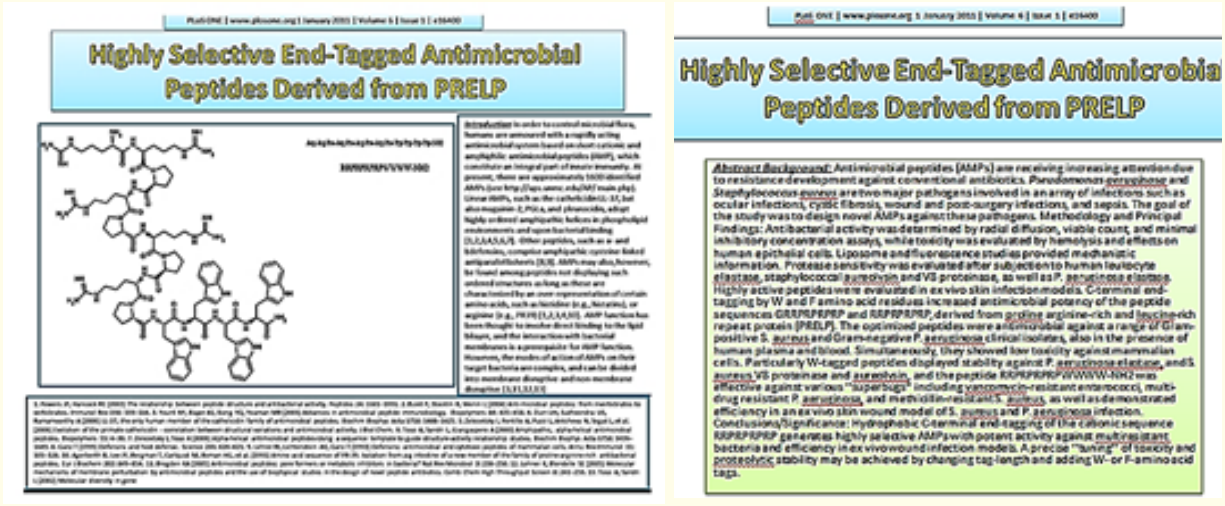
Gram-negative bacteria are more intrinsically resistant to antibiotics - they don't absorb the toxin into their insides. A cell wall disassembling strategy may be advantageous. Their ability to resist traditional antibiotics make them more dangerous in hospital settings, where patients are weaker and bacteria are stronger. New and very expensive antibiotics have been developed to combat these resistant species, but there remain some superbugs, multi-drug Resistant Organism (MDROs), that nothing can kill. Not only do the Gram-negative bacteria's natural defenses keep out these antibiotics, some even have an acquired resistance to antibiotics that make it to their inner cell bodies. In such cases, our results with the compound Figure C, D may pave a way towards a more efficient battle against the Gram-negative bacteria (see table above), pointing on the preferential killing of Gram negative of Gram-variable microbes [88,89]. The different behavior of Gram-negative and gram-positive bacteria to peptidomimetic was observed recently by researchers that investigated the effectivity of eradication with the mimics of protegrin-1 [90-95] induces membrane disruption by forming a pore/channel that leads to cell death. Gram-negative bacteria are almost not sensitive to structural changes whereas in gram-positive bacteria up to one order of magnitude difference in MIC values for different peptide moieties were reported . It has been reported [96,97] that Backbone N-methylation is common among peptide natural products and has a significant impact on both the physical properties and the conformational states of cyclic peptides. However, the specific impact of N-methylation on passive membrane diffusion in cyclic peptides has not been investigated systematically. Here we report a method for the selective, on-resin N-methylation of cyclic peptides to generate compounds with drug-like membrane permeability and oral bioavailability. Our example extends this finding to Antimicrobial peptide surrogates.



Seeking the Clue for Selective [98] Eradication

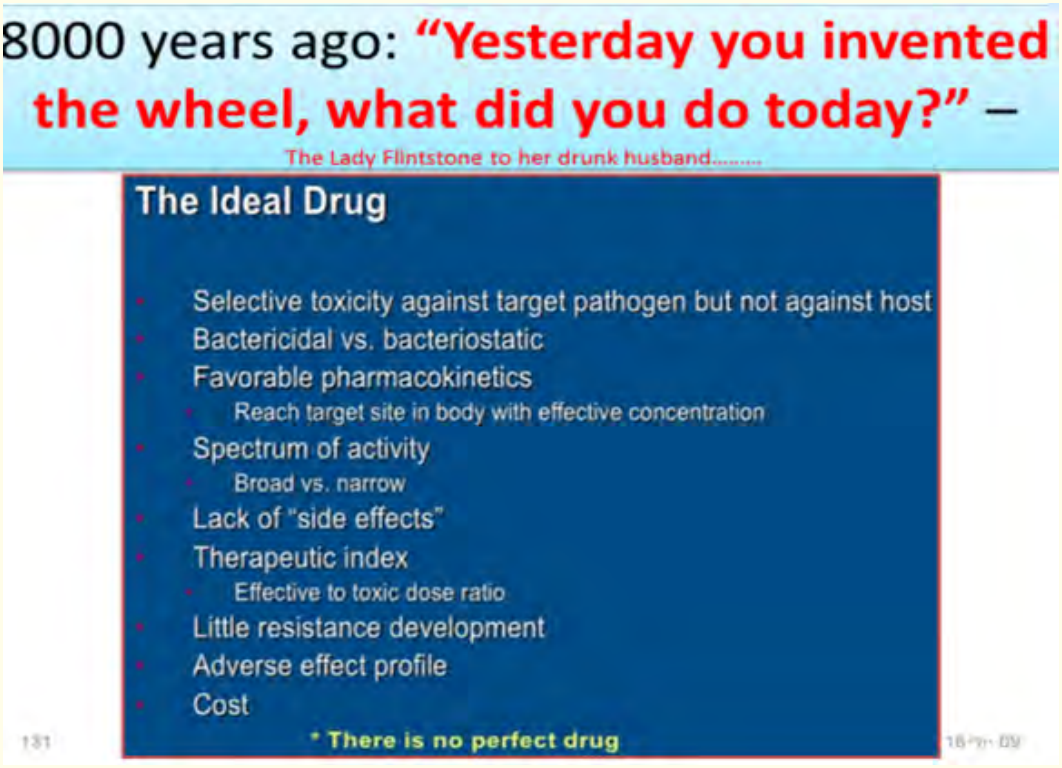
The effort against Nosocomial in regard to AMPs as measure against infections continues mainly in the peptide surrogates, including polymers, section.

However, the quest for naturally occurring bacteria's selective agents goes on. REALP is a short peptide that selectively eradicates Gram positive bacteria.



Mimics of natural peptides are rising as a possible solution for the application of mimics of AMP in the nosocomial battle. Degrado, Mor, and others are busy in research in the bioactive polymers area [99].

As times go by, commercialization of the efforts is starting to appear as startup companies.



Epilogue: What is it All About

The danger posed by growing resistance to antibiotics should be ranked along with terrorism on a list of threats to the nation.
Stop the Spread of Superbugs.
Help Fight Drug-Resistant Bacteria [100]

The citation says it: (Professor Dame Sally Davies, Government's chief medical officer for England, March 2013)

Superbug Infections

Today, the spread of antibiotic-resistant bacteria is alarming in the hospital environment where "superbugs" such as MRSA (methicillin-resistant *Staphylococcus aureus*), are the leading causes of mortality. Hospital-acquired infections can directly cost over $30,000 per incident and account for $4.5 billion annually in total extended care and treatment in the USA (U.S. Centre for Disease Control (CDC)). The emergence of aggressive types of resistant bacteria such as MRSA in the community is considered particularly worrisome.

In this work, we confirmed Huang [101] and associates Concluding Remark:

(There is) cell type selectivities of antimicrobial peptides.

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