REVIEW

Membrane-active peptides as anti-infectious agents

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Summary
The lipid components of pathogen cell membranes have been considered as a poor pharmacological target, due to their universal distribution and apparent homogeneity throughout living organisms. Among the rare exceptions to this view one could mention polyene antibiotics such as amphotericin, or peptide antibiotics such as the polymyxins and the gramicidins. In the last two decades, however, the above notion has been challenged by two main lines of discovery; first, natural antimicrobial peptides (AMPs) that kill pathogens by interaction with phospholipids and membrane permeabilization, and secondly, cell-penetrating peptides (CPPs), capable of introducing into cells a variety of cargoes in the absence of specific receptors, again by interaction at some point with membrane phospholipids. For both AMPs and CPPs, the pharmacological proof-of-concept has been successfully demonstrated, and promising applications as nanobiotechnological tools have been envisaged though not hitherto materialized in clinical settings. In this review we briefly examine the pros and cons of these two classes of therapeutic agents, as well as strategies aimed at rationalizing and expanding their potentiality.

Key words: membrane; cell-penetrating peptide; antimicrobial peptide; antibiotic resistance; infectious disease

“"All the people shall shout with a great shout; and the wall of the city will fall down flat, and the people will go up every man straight ahead."”
(Joshua 6:5)

Abbreviations

AMP, antimicrobial peptide
CPP, cell-penetrating peptide
DC, dendritic cell
HβD, human β defensin
HNP, human neutrophil peptide (human α-defensin)

IM, inner membrane
OM, outer membrane
PG, phosphatidyglycerol
PL, phospholipid
PM, plasma membrane

INTRODUCTION

The plasma membrane (PM), made up of phospholipids (PLs) and other PL-embedded components, constitutes the ultimate barrier isolating the intracellular milieu from the external environment, and as such, the arena where the
pathogen, on one side, and the host immune defences and antimicrobial drugs on the other side, draw their battle lines. Aside from a minority of free-diffusing molecules, drug entry is controlled by transporters and pores imposing rather stringent structural requirements for internalization. Though protective of cell integrity, strict PM crossing requirements become an Achilles’ heel for drugs, particularly antimicrobials, as even minor mutations in proteins involved in PM passage may partially or fully block drug uptake and subsequent activity (Hopkins et al. 2005).

A somewhat different antimicrobial paradigm, relying on the lethal hit of an antimicrobial peptide (AMP) on the PLs of the pathogen PM (Zhang and Falla 2009), is currently under scrutiny at pharma companies. Membrane-active AMPs of bacterial origin, such as gramicidins and polymyxins, previously ignored due to their toxicity, are undergoing a reappraisal as the repository of classical antibiotics without reported resistance problems is increasingly exhausted (Mogi and Kita 2009); daptomycin, another membrane-targeting peptide active against Gram-positive infections, has recently received clinical approval. This review will focus on various aspects of PM-antimicrobial interactions, with an emphasis on eukaryotic-derived AMPs and their man-made surrogates, as well as on the more recently discovered cell-penetrating peptides (CPPs).

ANTIMICROBIAL PEPTIDES FROM EUKARYOTIC SOURCES

Description and natural occurrence

Eukaryotic AMPs play a major role as a first chemical barrier against invading pathogens. As key components of innate immunity, AMPs are characterized by (i) activity on a broad variety of pathogens; (ii) constitutive expression or fast induction after contact with the pathogen; (iii) absence of immunological memory. These features are in contrast with acquired immune responses based on exquisite, highly specific antigen recognition but penalized by a fairly long onset, during which time host defence largely depends on the innate response of which AMPs are an essential part. Such immediacy in the face of infection is one reason why AMPs may have been preserved through evolution and are now pervasively found throughout eukaryotes, from unicellular amoebae to such simple pluricellular organisms as Hydra, and on to higher organisms including primates and man, in a display of universal efficacy associated to a rather tight gene economy.

For a given eukaryotic organism, an armamentarium based on a variety of AMPs is typical; e.g., for Drosophila, there are 20 inducible AMPs grouped in 7 families (Lemaitre and Hoffmann 2007). Partial target specificity can be found within a given antimicrobial peptidome, e.g., the much higher antifungal than antibacterial activities observed for drosomycin in Drosophila (Lemaitre and Hoffmann 2007) or histatin in humans.

As expected from their invasion-preventing role, AMPs are most abundant in anatomical locations where first contact with pathogens is likely: skin, mucosal tissues, biological fluids and professional phagocytes (Metz-Boutigue et al. 2009). Some have rather precise locations, e.g., dermicidin in sweat glands or histatins in higher primate saliva, while others are more generally distributed, e.g., human LL-37. In addition, the AMP repertoire of a given organism can be further increased through proteolysis, e.g., by trimming of a pre-existing AMP, as in histatin (Sun et al. 2009) and defensin isoforms, or by protease-mediated unmasking or enhancement of the antimicrobial activity of a large precursor, such as lactoferricin (from lactoferrin), haemocidins (from hemoglobin), or bufirin (from histones). Also, microbicidal activities have been postulated for proteins or peptides classified otherwise, e.g., hepcidin, a Fe²⁺ transporter, RNAses or various chemokines (Zasloff 2009), with the caveat of whether their physiological concentration is high enough for pathogen killing.

Natural AMPs epitomize biodiversity. The almost boundless variety of natural AMP leads, the increasing number of available genomes, as well as the development of peptidomics and of algorithms for AMP identification, have raised exponentially the number of putative or real AMPs. Exhaustive compilations of AMP sequences appear in free-access databases, either for peptides in general (http://pepbank.mgh.harvard.edu/) or solely for AMPs, such as AMSD (http://www.bbcm.units.it/~tossi/amisd.html), APD (http://aps.unmc.edu/AP/main.php), CAMP (http://www.bicnirrh.res.in/antimicrobial/), RAPD for recombinant AMPs (http://faculty.ist.unomaha.edu/chen/rapid/index.php), PhytAMP for plant AMPs (http://phytamp.pfba-lab-tun.org/main.php), or specific for certain AMPs such as defensins (http://defensins.bii.a-star.edu.sg/) or shrimp peneicidins (http://penbase.immunauqua.com/).

The structure-based AMP classification originally proposed by Boman remains largely in effect, with the inclusion of some new groups (Table 1). In general, AMP structural plasticity is inversely related...
<table>
<thead>
<tr>
<th>Peptide group</th>
<th>Representative peptide</th>
<th>Sequence</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear helical peptides without Cys</td>
<td>LL-37, <em>Homo sapiens</em></td>
<td>LLGDFRSSKEKIGKEFKRIVQRIKDLRNLVPRTES</td>
<td>[Image]</td>
</tr>
<tr>
<td>Linear peptides without Cys but enriched in a given amino acid except Arg or Lys</td>
<td>Indolicidin, <em>Bos taurus</em></td>
<td>ILPKWPWWPRR-NH₂⁺</td>
<td>[Image]</td>
</tr>
<tr>
<td>Peptides with a single internal disulfide bond</td>
<td>Lactoferricin, <em>Bos taurus</em></td>
<td>PKCRRWQWRMKGAPSTCVRAF</td>
<td>[Image]</td>
</tr>
<tr>
<td>Peptides with two or more internal disulfide bonds</td>
<td>HβD-1, <em>Homo sapiens</em></td>
<td>DHYNCVSSGQCLYSACPIFICTKQGTYRGGKKCCK=H</td>
<td>[Image]</td>
</tr>
<tr>
<td>Cyclic peptides</td>
<td>θ defensin, <em>Maccacus rhesus</em></td>
<td></td>
<td>[Image]</td>
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* Amidation of the C-terminal group.
to the number of disulfide bonds; thus, most α-helical peptides are unstructured in aqueous media, and only become structured upon contact with PLs or membrane-mimicking solvents such as trifluoethanol.

Although most AMPs have been described in monomeric form, a few examples of covalent heterodimeric AMPs linked by a disulfide bond are known, such as the amphibian distinctin, or halocyanin from the tunicate Halocynthia auratum. Hetero- and homodimer formation has also been reported for murine intestinal cryptdins, leading to diversified antimicrobial performance with respect to the original monomeric repertoire (Hornef et al. 2004).

Only one cyclic AMP, rhesus ω-defensin, has been so far isolated in vertebrates, as the result of head-to-tail ligation of two nonapeptides from truncated defensins. Retrocytin, its pseudogene-encoded human ortholog, appears to be unexpressed but its chemically synthesized version showed anti-HIV and lectin activities (Selsted 2004).

A high cationic character and some type of amphipathic higher structure appear to be the only common structural motifs shared by the vast majority of AMPs hitherto described. A few exceptional cases of anionic AMPs originating from prozymogen processing are known (Brogden et al. 1998).

Mechanism of action

Ever since the initial discovery of AMPs, disruption of cellular membranes in the targeted organism has been consistently observed (Lehrer et al. 1989) and reproduced on artificial membranes (Christensen et al. 1988). Furthermore, AMP enantiomers were equipotent with their all-L counterparts (Wade et al. 1990), ruling out chirality as a requirement for activity. Altogether, the PM permeabilization caused by AMP interaction with PLs is now unanimously regarded as an essential hallmark of AMP lethal action.

Several models have been postulated to account for AMP permeabilization of the PM, mostly deduced from model membrane studies. A brief description of the most prevailing models is outlined below. The reader is referred to recent and specialized reviews about this subject (e.g., Melo et al. 2009). The following events can be arbitrarily defined as sequential steps of the mechanism:

1. The AMP accumulates massively at the PM outer leaflet, with its axis parallel to the membrane plane. To minimize the free-energy of the system, the polar surface of the (amphipathic) AMP remains exposed to the external medium, and in interaction with PL polar head groups, while the hydrophobic surface contacts the fatty acid aliphatic chains of PLs.
2. Next, massive peptide insertion into the PM leads to an expansion of the outer leaflet and to mechanical stress by imbalance with the internal leaflet. Once a threshold value for this stress is reached, the system reacts by either “micellization” of the membrane by formation of supramolecular aggregates (“carpet-like” model), or by re-orienting a fraction of the membrane-bound AMP in a transversal mode, leading to the formation of mixed PL-AMP pores (“worm-hole”, toroidal, or two-state model), and promoting PL interchange between leaflets and membrane curvature.
3. In a final step, the mixed pore disintegrates, sending peptide randomly to both sides of the membrane. If the average lifetime of the pore is long enough, this will itself suffice for an irreversible loss of the pathogen’s internal homeostasis. Alternatively, a brief enough pore will give rise to a transitory, usually reversible disruption, which appears to be the typical course for those few AMPs known to act not primarily by PM disruption but upon intracellular targets.
4. As an alternative to step 2 above, the “barrel stave” model postulates an exclusively peptide-based pore formed at much lower AMP-PL stoichiometry than the carpet model, and driven by AMP self-affinity stronger than AMP-PL affinity.
5. Finally, formation of $H_{\text{II}}$, non-lamellar inverted hexagonal PL phases, defining an inverted micelle inside the membrane, has also been invoked as a mechanism of action for membranes made up of PLs promoting negative curvature, with the polycationic AMP acting as nucleating core for the micelle (Powers et al. 2005). This model accounts for AMP translocation without membrane permeabilization. In this and the above models, AMP aggregation in solution prior to membrane insertion would result in local AMP concentrations capable of inducing permeabilization at much lower concentrations than the isolated monomer, along with decreased membrane specificity.

Target specificity

The mainstay of AMP specificity for bacteria and fungi over higher eukaryotes is that the former show a higher percentage of anionic PLs that favour electrostatic interaction with polycationic AMPs. In addition, in higher eukaryotes the anionic PLs are confined to the cytosolic leaflet of the membrane, initially inaccessible to the AMP. This recognized fact, however, cannot by itself explain the marked variations in antibiotic activity observed for different AMPs. Among other factors having a modulating role on activity, several refer to the PL composition of the membrane, including (i) type and shape of the anionic PLs. Thus, for PLs with a bulky polar head (e.g., PS),
AMP insertion induces a positive (convex) curvature of the PM that favours formation of toroidal pores. For anionic PLs with an area of polar head region smaller than that of the hydrophobic tail, resulting in an inverted cone shape (e.g., PG), thus promoting a negative curvature a higher peptide stoichiometry is required for pore formation (Matsuzaki 2009); (ii) length and degree of unsaturation of the acyl chain, not only as a key factor for membrane fluidity, but also influencing AMP insertion ability. As a rule of thumb, the longer the chain, the higher the perturbation caused by the AMP; in addition, membranes with a high percentage of unsaturated fatty acids, and thus of higher fluidity, are leakier than more saturated ones (Matsuzaki 2009); (iii) sterols cause membrane rigidification and may thus impair AMP insertion. Prokaryotes, with the exception of Mollicutes (e.g., mycoplasmas), lack sterol in their PM, which explains the superior permeabilization by AMPs in comparison with eukaryote, sterol-rich PMs. The presence of ergosterol in fungi, yeasts and some parasitic Protozoa, is less protective against AMPs than the cholesterol of higher eukaryotes.

Other non-lipidic factors also affect the outcome of an AMP-microbe encounter include (i) external barriers such as the outer membrane (OM) of Gram-negative bacteria, with anionic lipopolysaccharide (LPS) as the major component of its external leaflet. In order to reach its PM target, an AMP traverses the OM by a mechanism called “self-promoting uptake” (Rosenfeld and Shai 2006) whereby it interacts first with anionic (lipid A) sites of LPS, displacing Mg\(^{2+}\) ions that crosslink LPS molecules, thereby disrupting the OM and allowing access of other AMP molecules to the periplasm and interaction with the PM. A further consequence of AMP-LPS binding is neutralization of endotoxic activity, preventing the shock caused by LPS release after massive killing of bacteria by other antibiotics (Jerala and Porro 2004); (ii) in Gram-positives, the peptidoglycan layer is also a serious hurdle for AMP translocation. Again, AMP interaction with (anionic) teichoic and lipoteichoic acid units abrogates their endotoxic character, avoiding an exalted inflammatory response; (iii) other anionic exopolysaccharides such as alginate or poly-\(\gamma\)-DL-glutamic acid, produced by fungal and bacterial biofilms, compete for AMP binding with anionic PLs of the PM, reducing AMP efficacy (Otto 2006). Encapsulated forms of fungi and bacteria are also more resistant to AMPs (Rodriguez-Hernández et al. 2006); (iv) the potential across the PM, negative at the cytoplasmic side, promotes AMP insertion; hence, AMP activity increases in polarized cells (Matsuzaki 2009). Finally (v) proteases specifically secreted by each type of pathogen degrade AMP molecules to various extents, thus contributing to the heterogeneity of AMP activity observed for different pathogens (Peschel 2002).

Intracellular targets
An increasing number of reports show that permeation of pathogen membranes cannot exclusively account for the lethal action of some AMPs, and thus point to intracellular targets (Otvs 2005). In mechanistic terms, either the toroidal pore or the inverted micelle models can satisfactorily explain AMP translocation through a PL bilayer. For AMPs acting in this way, the fact that the all-\(\alpha\) enantiomer is inactive – in contrast to AMPs acting purely through a PM-disruption mechanism – is usually taken as solid evidence in this direction. In most cases, the nature of the intracellular targets remains unknown. For those few that have been identified, targets are evolutionarily conserved housekeeping systems essential for viability, such as the DnaK chaperone for proline-rich AMPs pyrrochorycin and A3-APO, or DNA for the amphibian buforin (Otvs 2005). Mitochondria is the target for histatin 5, an AMP from human saliva (Luque-Ortega et al. 2008).

Alternative activities
Increasing evidence of AMP activities other than pathogen killing and often differing in important aspects from microbicidal action has been accumulating over the last decades. Most though not all of such activities can be said to follow a canonical pattern of peptide-receptor recognition, usually at concentrations one log below microbicidal ones, or in environments where antimicrobial activity is in some way blunted. These activities, in addition, tend to be strictly specific for a given peptide, in contrast with the broad antibiotic specificity of many AMPs. The structural constraints of these additional activities do not necessarily overlap with those of antimicrobial action (Wu et al. 2003); for instance, chiral discrimination tends to exist, in contrast with membrane permeabilization, where the all-\(\alpha\) enantiomer is usually equipotent with the natural version.

Most of these additional features are beneficial and synergistic vis-à-vis tissue repair and pathogen elimination. Thus, AMPs are known to promote proliferation of skin and mucosal cells, either directly or through mobilization of growth factors bound to the anionic sites of the glyocalyx (Otte et al. 2009). For other AMPs such as LL-37 or PR-39, angiogenic activity has been reported (Schittek et al. 2008). Also,
AMP cooperation with the antigen-specific immune response has been described as taking place through various mechanisms, including (i) induction of vascular permeability by mast cell degranulation; (ii) stimulation of chemokyme and chemotactic-like activities on different types of immune cells; (iii) maturation of antigen-processing cells; (iv) activation of professional phagocytes, or (v) modulation of cytokine maturation and release (Niyonsaba et al. 2009, Steinstraesser et al. 2009, Yang et al. 2009).

PHARMACOLOGICAL EXPLOITATION OF AMPs

AMPs have drawn the attention of the pharmaceutical industry by (i) the potential of their unique killing mechanism, different from the highly specific but resistance-prone mechanisms of other antimicrobials; (ii) their broad spectra of activity on a wide variety of pathogens; (iii) their extremely low – though not nil (Otto 2009) – levels of resistance induction; (iv) their fast killing rates. On the downside of an AMP-based therapy are high manufacturing costs (about 10× those of typical antibiotics), poor bioavailability due to protease degradation and sequestration by serum components, and low tissue penetration.

Despite these caveats, AMPs remain an attractive option for exogenous antibiotic chemotherapy. The low levels of posttranslational modification found in animal or plant AMPs as compared with fungal and bacterial counterparts make their chemical synthesis and structural manipulation both feasible and attractive. The goals of such modifications tend to be, first, improved activity and, second, size reduction in search of minimally active sequences that can diminish immunogenicity and synthesis costs. Several strategies along these lines are outlined in Table 2.

AMPs have also been proposed as candidate drugs against novel or multiresistant pathogens, or reagents against biological warfare (Dawson and Liu 2008), excluding manner, appear to be more diverse and complex than those of conventional AMPs (Alves et al. 2010).

Other potential uses for AMPs include infection imaging, by means of AMP-99mTc conjugates which allow discrimination between infectious and sterile inflammation processes by scintigraphic methods (Lupetti et al. 2003), and coating of medical devices (bone and dental cements, surgical sutures) to prevent biofilm or any other formation of infectious foci. Encapsulation in biodegradable vehicles would allow AMP sustained delivery for treating or preventing infections difficult to reach by systemic antibiotic administration, e.g., osteomyelitis. AMP inclusion in chewing gum to prevent caries formation has also been proposed.

The fact that AMPs are gene-encoded opens the possibility of expression either in the original or in an alien organism; expression can be transitory, e.g., encoded on adenoviral vectors, or permanent, e.g., in transgenic plants or cattle. For instance, artificial skin engineered to express AMPs can be grafted on severely burned patients (Carretero et al. 2004), or applied to stimulate re-epithelisation of chronic wounds. Also, pups fed with lactoferrin-expressing transgenic milk show improved survival and lower infection rates, and protegrin 1-expressing transgenic mice double their survival rate when infected with Actinobacillus suis. Also highly promising is the transgenic expression of AMPs in plants to prevent phytopathogen infection (Marcos et al. 2008).

CELL-PENETRATING PEPTIDES AS ANTI-INFECTIOUS AGENTS?

The main plus of CPPs is their ability to transport across the PM of cells a broad range of cargoes including small drugs, metal ions, peptides and proteins, nucleic acids or quantum dots (Torchilin 2008). The repertoire of CPPs has been constantly growing, from the early Antennapedia and Tat sequences to oligoarginines, proline-rich motifs or Pep-1, which can deliver non-covalently-bound cargoes (Vives et al. 2008). CPPs share structural traits with AMPs, such as cationic character and amphipathicity (to a degree). Their ability to translocate across membranes has parallels with the accepted mechanisms of action of AMPs (see 2.2 above); indeed, AMPs with intracellular targets (see 2.2 above); indeed, AMPs with intracellular targets (see 2.2 above) behave de facto as CPPs. Nevertheless, CPP internalization mechanisms, involving macropinocytosis, endocytosis by clathrin or caveolae and possibly other processes in a non-mutually excluding manner, appear to be more diverse and complex than those of conventional AMPs (Alves et al. 2010).

Some potential applications of CPPs in anti-infectious therapy have hitherto been envisaged, including i) uptake of drugs bypassing the absence or defective function of a dedicated receptor (Koczak et al. 2002); ii) uptake of otherwise PM-impermeable cargo molecules such as “pepducins”, peptide inhibitors interfering with signal transduction pathways, successfully assayed on cancer cells (Watkins et al. 2009); iii) drug delivery and accumulation into otherwise inaccessible compartments (Rao et al. 2009), or organelle-specific targeting by CPPs fitted with distinctive import motifs.
Table 2. Some strategies of AMP modification.

<table>
<thead>
<tr>
<th>Modification</th>
<th>Example</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimization at a given residue/position</td>
<td>Cryptdin 4</td>
<td>Role of conservative R → K substitution in antimicrobial activity</td>
</tr>
<tr>
<td>Replacement of specific residue(s)</td>
<td>Bactenecin 2</td>
<td>Optimization of antimicrobial activity</td>
</tr>
<tr>
<td>Non-natural amino acid surrogates</td>
<td>Ampetoids</td>
<td>Improvement of biological stability</td>
</tr>
<tr>
<td>Domain swapping</td>
<td>Magainin 2</td>
<td>Modification of antimicrobial and haemolytic activity</td>
</tr>
<tr>
<td>Delineation of minimal active sequence</td>
<td>Cecropin-melittin hybrids</td>
<td>Size reduction from 26 to 11 amino acids</td>
</tr>
<tr>
<td>Increasing cationic character</td>
<td>Short artificial peptides</td>
<td>Improvement of antifungal activity</td>
</tr>
<tr>
<td>Dimerization by interchain disulfide</td>
<td>Murine β defensin</td>
<td>Improvement of antimicrobial activity</td>
</tr>
<tr>
<td>Sequence hybridation</td>
<td>Cecropin A-melittin</td>
<td>Improved antimicrobial activity, lower toxicity</td>
</tr>
<tr>
<td>Juxtaposition of sequences with different mechanisms</td>
<td>Dermaseptin-RNAIII inhibiting peptide</td>
<td>Synergic antimicrobial activity</td>
</tr>
<tr>
<td>Heterodimerization</td>
<td>Distincin</td>
<td>Improved membrane interaction and protease stability</td>
</tr>
<tr>
<td>Linearization (disulfide reduction)</td>
<td>Plant defensin IB-Amp1</td>
<td>Improved antimicrobial activity</td>
</tr>
<tr>
<td>Cyclization (head-to-tail disulfide)</td>
<td>Histatin 3</td>
<td>3-log improvement of re-epithelization activity</td>
</tr>
<tr>
<td>Disulfide engineering</td>
<td>Minimal defensin template</td>
<td>Modification of antimicrobial and chemotactic profiles</td>
</tr>
<tr>
<td>Dimerization; intrachain disulfide formation</td>
<td>Bactenecin 5</td>
<td>Improved antimicrobial activity even at high ionic strength</td>
</tr>
<tr>
<td>Retro-enantio version</td>
<td>Cecropin-melittin hybrids</td>
<td>Improved stability and antimicrobial activity</td>
</tr>
<tr>
<td>Diastereomer formation</td>
<td>α-helical linear peptides</td>
<td>Reduced toxicity and protease susceptibility</td>
</tr>
<tr>
<td>Acylation</td>
<td>Cecropin A-melittin hybrids</td>
<td>Improved antimicrobial activity</td>
</tr>
</tbody>
</table>

(Santra et al. 2005); iv) real-time monitoring of infections by delivery of nuclease-resistant fluorescent tags targeting specific regions of a pathogen’s genome; v) RNA anti-pathogen therapy by means of antisense phosphorodiamidate morpholino oligomers (PMO) directed to the RNA of pathogens such as Ebola virus or Salmonella (Mitev et al. 2009), and vi) boosting the immune response, by immunogen coupling to a CPP and improved uptake by antigen-processing cells.

CONCLUSIONS AND OUTLOOK

Membrane active agents, particularly peptides, are currently at the threshold of a renewed lease of life. Formerly disregarded by their poor selectivity, they are undergoing a positive reappraisal that includes old antibiotics such as polymyxin or gramicidin, as well as AMPs and CPPs. Despite their many promising features, no AMP has yet reached the status of a clinically approved drug, and some authorized
opinions would limit AMP use to topical or colutory formulations, given the high cost and therapeutic uncertainty (partly due to lack of adequate trials) associated with systemic administration. The more recent arrival of CPPs, and the possibility of using them in proof-of-concept trials for an increasing number of drugs, will however face strong competition from other nanopharmacological approaches. Even so, it seems reasonable to foresee a continued expansion of the membrane-active peptide field, an area where biophysics, biochemistry, cell biology and pharmacology meet together.

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