membrane. These results suggest that D1-7 eliminates the lytic activity but retains the strong lipid membrane binding. For further confirmation, we measured liposome sizes and zeta potentials with and without D1-7 loading. Consistently, D1-7 did not affect the size of the liposome, but shifted the zeta potential (or surface charge) of the liposome towards the positive voltage range, because D1-7 is a positively charged peptide. Among numerous existing nanosystems for drug delivery, liposomes are approved by FDA for anti-cancer and gene therapy. Accordingly, this linker and/or its refinements could enhance the therapeutic potential of approved liposomal drugs by enabling flexible incorporation and cargo multiplexing through post-formulation surface editing.

1449-Pos

Cationic, Helical Antimicrobial Peptoids with Biomimetic Antimicrobial Activity

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Increasingly prevalent resistance of pathogenic bacteria to conventional small-molecule antibiotic drugs is creating an urgent need for the discovery of new classes of antibiotics that are active against biofilms. Bacteria that are multidrug resistant (MDR) are of increasing concern for infectious disease. Current treatment of these infections that involve resistant organisms may require 6-12 months of antibiotic treatment, creating difficulties with compliance.

We are continuing to develop oligo-N-substituted glycine (peptoid) mimics of cationic, helical antimicrobial peptides (AMPs), and some of our recently acquired data indicate that peptoids could address the problem of growing resistance. Peptoids have been shown to have extremely broad-spectrum activity, and certain peptoids function well in the presence of serum proteins. Their biophysical mechanism of action makes it difficult for bacteria to evolve resistance to them. We have tested our most promising peptoids, peptides and commercial antibiotics in vitro against bacterial biofilms of a variety of important bacterial organisms. We show that certain peptoids can be as active as the preferred conventional antibiotics against bacterial infections, even at low micromolar doses. Small, structured biomimetic oligomers such as our antimicrobial peptoids may offer a new class of drugs that are useful in treating persistent bacterial infections.

1450-Pos

Investigation of a Sequence-Modified Antimicrobial Peptide

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Antimicrobial peptides serve as one of the first lines of defense in the immune systems of higher organisms. These peptides specifically target and neutralize infecting bacteria in the host organism while exhibiting little or no toxic effect on host cells. The peptide C18G is a highly cationic, amphiphilic peptide derived from the C-terminal sequence of the human protein platelet factor 4 (involved in blood coagulation and wound repair) exhibited antibacterial activity against both gram positive and gram negative bacteria. Using a modified C18G sequence that did not significantly affect antimicrobial efficacy (Tyr3 changed to Trp and all Lys changed to Arg (C18G Y3W K R)). The binding affinity was measured with fluorescence spectroscopy using the W in the peptide sequence as a probe of peptide environment. Small unilamellar lipid vesicles were used to investigate the binding affinity of the peptide to bilayers composed of variable amounts of DOPC, POPG, and POPE. DOPC and POPE have a zwitterionic head group, whereas POPG has an anionic charged head group. These studies showed binding affinity had a dramatic dependence on lipid composition. The effect of pH on peptide binding and behavior was also examined and, as expected, also impacted binding affinity. Quenching of the Trp fluorescence by acrylamide was performed to confirm that the Trp was located in the membrane. Likewise circular dichroism (CD) spectroscopy was used to determine the structure of the peptide upon interaction with the lipid vesicles. Additionally, in an assay monitoring membrane permeabilization of *E. coli* the C18G Y3W K R peptide was shown to permealize bacterial membranes in a concentration dependent manner.

1451-Pos

Structural Aspects of the Interaction of Nk-2 Derived Peptides with Cancer Cells

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Antimicrobial peptides have gained interest as potential anti-cancer agents, e.g. inhibition of tumour growth in human prostate xenografts was shown by host defense like lytic peptides (1). We showed by Annexin V binding that, in prostate tumour cells, negatively charged phosphatidylserine (PS) accumulates in the outer plasma membrane leaflet, which normally resides in the inner leaflet. Thus, surface exposure of PS may make these cells susceptible to killing by these cationic peptides.

The aim of this study is to develop short peptide sequences derived from NK-2, which was shown to have anti-tumour activity (2). NKCS (Cys of NK-2 exchanged by Ser) is composed of two α-helices connected with a hinge region. Initially we studied the interaction of the parent peptide and its N- and C-terminal part with membrane mimetic systems. Vesicle leakage experiments revealed that the N-terminal fragment exhibits similar affinity towards PS as NKCS. Thermodynamic experiments indicate that the N-terminal helix resembles the properties of NKCS. Furthermore, calorimetric studies revealed that NKCS and its fragments have no significant effect on the thermotropic behaviour of PC liposomes mimicking healthy mammalian cell membranes. Both circular dichroism and Monte-Carlo simulation using the bilayer parameters derived from our structural characterization of the lipid model systems showed that the selectivity for PS correlated with the alpha-helical content of the peptides. The C-terminal part was less structured showing lower affinity to PS containing membranes. Thus, the shorter N-terminal peptide can be used as a template for further optimization, as in vitro tests on a human prostate carcinoma cell line showed significant cell damage.

(1) Papo N. et al., Cancer Res. 66 (2006) 5371-8.
(2) Schröder-Borm H. et al., FEBS Lett. 579 (2005) 6128-61.

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1452-Pos

Antimicrobial Peptide Mimics as Potential Anticancer Agents:Interactions of Acyl-Lysine Oligomer C12K-7Alpha8 with Ganglioside/DPPC Mixtures

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Recently, antimicrobial peptides (AMPs) have emerged as a promising anticancer remedy. Negative charge of the bacterial membranes gives some measure for selectivity of cationic AMPs, since mammalian cell membranes are largely zwitterionic. Accumulating evidence indicates that lipid composition of the cancer cell membranes is different from a healthy cell, displaying net membrane surface negative charge. Understanding the nature of the negatively charged membrane domains could provide a new basis for anticancer therapy drug design using antimicrobial peptides or their synthetic mimics. Here, we examine the effect of membrane glycosylation, which is shown to be increased in cancer cells, on activity of AMP analogs. In this work we probe interactions of antimicrobial peptide mimic, based on acyl-lysine architecture (OAK), C_{12} K-7α_8, with Langmuir monolayers containing monosialoganglioside GM_3 and disialoganglioside GD_3. Langmuir isotherms and fluorescence microscopy imaging results of pure GM_3 and GD_3 monolayers indicate a single liquid-extended (LE) phase. Constant pressure insertion assays show significant insertion of C_{12} K-7α_8 in both GM_3 and GD_3 monolayers at 30mN/m. AMP analogue insertion was also observed for GM_3: DPPC (30:70) and GD_3: DPPC (30:70) mixed monolayers, however at smaller extent as expected. Synchrotron grazing Incidence X-Ray diffraction (GIXD) data show a disordered phase for GD_3 and a weak ordering for GM_3, which disappears immediately after introduction of the AMP. X-ray Reflectivity data indicate the thinning of the lipid layer upon peptide insertion.

1453-Pos

Cancer Cell Proliferation is Inhibited by Phlip Mediated Delivery of Membrane Impermeable Toxin Phalloidin

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We wish to use the pH-(Low)-Insertion-Peptide (pHLIP) to transport therapeutic agents to acidic tumors, with the ultimate goal of improving the treatment of cancer. pHLIP inserts into a lipid bilayer under slightly acidic conditions (pH 6-6.5), forming a transmembrane helix. We demonstrate here that pHLIP-mediated translocation of a cell-impermeable, polar toxin phalloidin can inhibit the proliferation of cancer cells. The delivery constructs, pHLIP-K(rho)C(aph) and pHLIP-C(aph), both carry the phalloidin toxin at the inserting C-terminus, via a disulfide linkage that could be cleaved in cells. The constructs differ in that a lipophilic rhodamine moiety is also attached to the inserting end, near the phalloidin cargo, in pHLIP-K(rho)C(aph). After a brief incubation with 2-4 μM of pHLIP-K(rho)C(aph) at pH 6.1-6.2 (for 1-3 h), proliferation of HeLa, JC, and M4A4 cancer cells were severely disrupted (> 90% inhibitions). Cells