View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by GSTF Digital Library (GSTF-DL): Open Journal Systems (Global Science and Technology...

Rational Elaborated Common Strategies Employed For The Efficient in Silico Optimization Of An Accesible Synthetically (AMPs) Peptidomimetic-similar To An Amphiphile-Based Pharmacophoric Agent As A Promising Enhanced Therapeutic Antimicrobial Agent

Grigoriadis Ioannis1, Grigoriadis George2 and Grigoriadis Nikolaos3*

1.Department of Computer Drug Discovery Science,

BiogenetoligandorolTM, Thessaloniki, Greece,

2.Department of Stem Cell Bank and ViroGeneaTM,

Biogenea Pharmaceuticals Ltd, Thessaloniki, Greece,

3.Department of IT Computer Aided Personalized Myoncotherapy,

Cartigenea-Cardiogenea, Neurogenea-Cellgenea, Cordigenea-HyperoligandorolTM,

Abstract—Antimicrobial peptides (AMPs) which predominantly act via membrane active mechanisms have emerged as an exciting class of antimicrobial agents with tremendous potential to overcome the global epidemic of antibiotics-resistant infections. The first generation of AMPs derived from natural sources as diverse as plants, insects and humans has provided a wealth of compositional and structural information to design novel synthetic AMPs with enhanced antimicrobial potencies and selectivities, reduced cost of production due to shorter sequences and improved stabilities under physiological conditions. As a rational result we discovered for the first time the GENEA-Antimamphiler-109 utilizing threading/structure-based BIOGENETOLIGANDOROLTM Rational Strategies employed for the in silico design and optimization of synthetic antimicrobial peptide mimic amphiphile-based pharmacophoric agents with promising enhanced therapeutic potentials introducing the iview: an interactive WebGL visualizer for protein-ligand complex through a subpocket analysis method for fragment-based drug discovery through a KNIME-Shared BiogenetoligandorolTM binding site amino acid predicted similarity subpockets.

Keywords—Rational-Strategies, in silico, chemicoinformatic, optimization, synthetic-antimicrobial, peptide-mimic, amphiphile-based, pharmacophoric-agents, subpocket analysis, binding site, amino acid,similarity.

DOI: 10.5176/2345-7201_1.4.33

©The Author(s) 2016. This article is published with open access by the GSTF

INTRODUCTION

The PB model is one of the mesoscopic theories that describes the electrostatic potential and equilibrium distribution of mobile ions around molecules in solution. It serves as a tool to characterize electrostatic properties of molecules, counterion association, electrostatic contributions to solvation, and molecular binding free energies. In previous studies they were focused on general formulations which can be applied to large molecules of arbitrary shape in all-atomic representation, including highly charged biomolecules such as nucleic acids. These molecules present a challenge for theoretical description, because the conventional PB model may become insufficient in those cases [1]. By collecting as many descriptors/parameters as possible within a single database, it has also be achieved a better use of the available data and information showing furthermore that data grouping allows us to generate different parameters with the potential to provide new insights into the sequence–structure–function relationship. Residue selection can be performed according to multiple criteria and can simultaneously display and analyze all the physicochemical parameters of any pair of structures, using precalculated structural alignments, allowing direct parameter comparison at corresponding amino acid positions among homologous structures [3]. Common strategies were also employed in the design and optimization of synthetic AMPs, followed by highlighting the various approaches utilized to enhance the therapeutic potentials of designed AMPs under physiological conditions taken advantage into the tastly, future perspectives on the development of improved AMPs for therapeutic applications as they have been presented. Visualization of protein-ligand complex plays an important role in elaborating protein-ligand interactions and aiding novel drug design where most existing web visualizers either rely on slow software rendering, or lack virtual reality support. While the bioavailability of AMPs is often reduced due to protease activity, the non-natural structure of AMP mimetics renders them robust to proteolytic degradation, thus offering a distinct advantage for their clinical application exploring the therapeutic potential of *N*-substituted glycines, or peptoids as AMP mimics using a multi-faceted approach that includes *in silico*, *in vitro*, and *in vivo* techniques reporting a new QSAR model that we developed based on 27 diverse peptoid sequences, which accurately correlates antimicrobial peptoid structure with antimicrobial activity [36]. A number of peptoids have also been identified that have potent, broad-spectrum *in vitro* activity against multi-drug resistant bacterial strains using a murine model of invasive *S. aureus* infection demonstrating that one of the best candidate peptoids at 4 mg/kg significantly reduces with a two-log order the bacterial counts compared with saline-treated controls. Although two binding amphiphile sites might be dissimilar overall, they might still bind the same fragments if they share suitable subpockets. Information about shared subpockets can be therefore used in fragment-based drug design to suggest new fragments or to replace existing fragments within an already known compound on computational methods which allows the similarity searching and alignment of subpockets from a PDB-wide database against a user-defined query as a innovative method which is based on pharmacophoric fingerprints combined with a subpocket alignment algorithm. Other bioinformatics tools was shown to be effective producing reasonable alignments for subpockets with low sequence similarity and be able to retrieve relevant subpockets from a large database of structures including those with different folds. It can also be used to analyze subpockets inside a protein family to facilitate drug design and to rationalize compound selectivity utilising virtual ligand screening as an integral part of the modern drug discovery process. Taken together, our results we demonstrated a promising in silico drug discovery methodology for the generation of peptoid-mimicking multi-targeted compounds as novel antimicrobial agents supporting four surface representations including Van der Waals surface, solvent excluded surface, solvent accessible surface and molecular surface based on the feature-rich version of our simulation meta-node sequential solution analysis of the Poisson-Boltzmann Equation on synthetically (AMPs) peptidomimetics for protein-ligand docking purpose.

METHODS AND MATERIALS

Initial virtual screening Docking results analysis and a Simulation meta-node sequential solution analysis of the Poisson-Boltzmann Equation on synthetically (AMPs) peptidomimetics.

In this article, a novel simulation meta-node sequential solution of the Poisson-Boltzmann Equation was applied on a drug discovery combination index dynamic unified theorem

©The Author(s) 2016. This article is published with open access by the GSTF

for Multiple Entities for finding of maximal bioactivity accesible synthetically (AMPs) peptidomimetic-similar to an amphiphile-based pharmacophoric agent as a promising enhanced therapeutic innovative designed antimicrobial agent. B-lactams (cefotaxime, ceftazidime, cefepime, cefuroxime, faropenem, imipenem, meropenem, penicillin G, piperacillin) and hydrolyzed ampicillin, L-captopri, ampicillin and other molecular structures downloaded from ZINC database, fragmented and then were multi-docked into the (AMPs) short linear motif binding peptide active site using parallel and re-docking simulations in according to the following computer-aasisted virtual screening procedures where by predicting the protein=peptide combile binding targets of a compound 'rule of 0.5' for the metabolite-duggable-likeness of approved pharmaceutical drugs revealing a fixed target y, a prediction function hy(x) in the docking grid box which was generated around the data set of short linear repeated active sites using the site finder in the dimensions of the cross-docked parallel ligand docking box which were recored and cross docked manipulated to accommodate all the conserved amino acid residues present in the binding active pharmacophoric site.

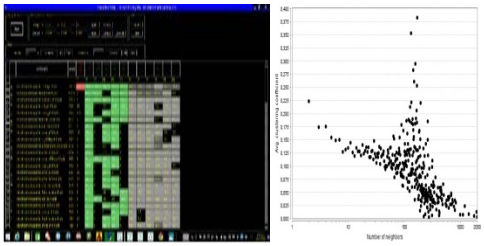

Figure 1. Default docking parameters were used for all virtual screening computational drug discovery procedures unless otherwise stated. A virtual collection of query referenced drugbank database derived drug-like compounds bioactive subset taken from ZINC database the first filters containing 2,800,000 polynomial compounds was maximal served as the comprehensive screening library [39]. The hits with firm binding conformations were lacking collected and redocked fingerprinted into the configuration active site using the igmemdock protocol in settings the ADS nodes. Those similar pharmacophoric compounds with high free energy igemdock fitness scoring were selected as a threshold focused library used for the further analysis. Total binding Energy retained calculations and a construction metanode analysis of docking conformational poses were performed in resulting protein-inhibitor on protein- synthetically (AMPs) peptidomimetic complexes which were analyzed using the protein-peptide–short linear motif like ligand interaction fingerprint implemented in the hydrolyzedcore fragments of the ampicillin.

$$^{n}(CI)_X = \sum_{j=1}^{n} \frac{(D)_j}{(D_x)_j} = \sum_{j=1}^{n} \frac{(D_x)_{1-n}\left\{[D]_j / \sum_{1}^{n}[D]\right\}}{(D_m)_j\left\{(fa_x)_j / [1-(fa_x)_j]\right\}^{1/m_j}}$$

$$^{5}(CI)_X = \frac{(D_x)_{1,5}[P/(P+Q+R+S+T)]}{(D_m)_1\left\{(fa_x)_1/[1-(fa_x)_1]\right\}^{1/m_1}} + \frac{(D_x)_{1,5}[Q/(P+Q+R+S+T)]}{(D_m)_2\left\{(fa_x)_2/[1-(fa_x)_2]\right\}^{1/m_2}}$$

$$+ \frac{(D_x)_{1,5}[R/(P+Q+R+S+T)]}{(D_m)_3\left\{(fa_x)_3/[1-(fa_x)_3]\right\}^{1/m_3}} + \frac{(D_x)_{1,5}[S/(P+Q+R+S+T)]}{(D_m)_4\left\{(fa_x)_4/[1-(fa_x)_4]\right\}^{1/m_4}} \quad (5)$$

$$+ \frac{(D_x)_{1,5}[T/(P+Q+R+S+T)]}{(D_m)_5\left\{(fa_x)_5/[1-(fa_x)_5]\right\}^{1/m_5}}$$

(6)

$$\frac{(f_a)_{1,2}}{(f_u)_{1,2}} = \frac{(f_a)_1}{(f_u)_1} + \frac{(f_a)_2}{(f_u)_2} = \frac{(D)_1}{(D_m)_1} + \frac{(D)_2}{(D_m)_2}$$

$$\left[\frac{(f_a)_{1,2}}{(f_u)_{1,2}}\right]^{1/m} = \left[\frac{(f_a)_1}{(f_u)_1}\right]^{1/m} + \left[\frac{(f_a)_2}{(f_u)_2}\right]^{1/m}$$

$$= \frac{(D)_1}{(D_m)_1} + \frac{(D)_2}{(D_m)_2}$$

$$^{n}(CI)_X = \sum_{j=1}^{n} \frac{(D)_j}{(D_x)_j} = \sum_{j=1}^{n} \frac{(D_x)_{1-n}\left\{[D]_j / \sum_{1}^{n}[D]\right\}}{(D_m)_j\left\{(fa_x)_j / [1-(fa_x)_j]\right\}^{1/m_j}}$$

(4)

$$=-\log p(V|W,H)-\log p(W|\lambda)-\log(H|\lambda)-\log p(\lambda$$

In this scientific article we computer designed a more accessible synthetically (AMPs) peptidomimetic-similar to an amphiphile-based pharmacophoric agent to be used most effectively indicating that ligand-based methods require enough known small ligands for targeting peptide-protein complexes of interest, which may be hardly accessible in

©The Author(s) 2016. This article is published with open access by the GSTF

practice where n_A is the number of conserved conformated patches in the peptide binding protein pocket *A*. *N* is the number of metrging and matching patch pair pharmacophores between binding pocket *A* and recored merged ligand *B*. *pdist* is the distance fitness in parallel docking score of two merged pharmacophoric patches as defined in Equation (5). $m^{A,B}$ contains the high free energy list of matched and merged pharmacophoric patch pairs from binding pockets *A* and the generates hyperligand ligand *B*. The second term is the geodesic low mass stochastic predictive relative position difference averaged over all the merging and linked pharmacophoric matching ligand data set patches:

BindingDB tables, structural superposition and a optimization comparative analysis of the 21 peptidomimetic crystal structures to motif accesible synthetically (AMPs).

Building the BindingDB tables for the therapeutic antimicrobial agent we generated a more efficient structural superposition and a optimization comparative analysis which was based on simulated prediction models of mutational aligned motifs in the protein promoter from K-longest paths to motif accesible synthetically (AMPs) peptidomimetic-similar resulting in a merged amphiphile-based pharmacophoric cluster of agents as a structural superposition data set of the 22 reported (AMPs) targeted structures using force field pertubatuion realignment and refined with gaussian distance ligand to small compound weights showing that the most of the independently solved moleculars multi-targeted structures shared a high degree of structural pharmacophoric motif element similarity with each other. It is easy to use the K-longest paths algorithm to predict a motif by simply loading the K peptides to an existing motif tool.

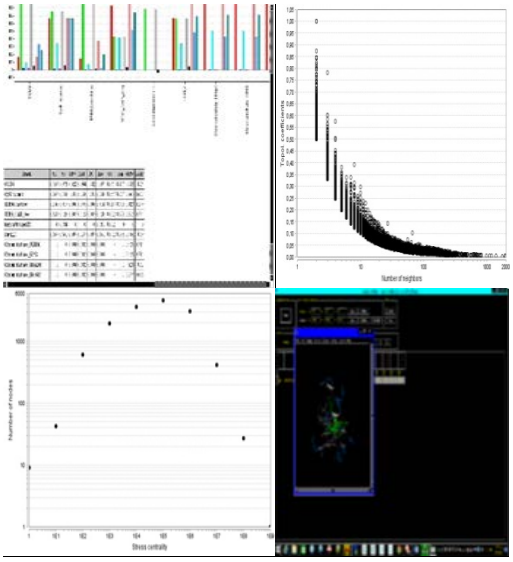

Figure 2: Generic String kernel Molecular-and Brownian dynamics superbug strains on predicted Tanimoto distances to virtual peptide short linear motif screened of the merged synthetically (AMPs) peptidomimetic-similar. Structure-based screening and a motif analysis analysis on a polytriangle matcher pharmacophoric merger placement in silkico method, followed by quantum mechanic molecular modeling mechanics refinement and scoring, was used for the first round in parallele ligand fragment based docking based screening dynamic process. The encoding placement stages were simulated and scored by E_place. Binding total free energy values were timescaled quantified using London dG [52] and Affinity dG [53]. After 1000 binding suited motif peptide like orientations for each merged compound were in package DUD refined where 30 conformations with lowest fingerprinting based calculated binding free energy with a consensus lowest predicting affinity dG and London dG fitness reader node values were produced.A Phenotype-based simulated method was generated here for protein target predictions on rational elaborated common strategies within combinatorial search problems employed for the efficient in silico optimization of an accesible synthetically (AMPs) peptidomimetic-similar to an amphiphile-based pharmacophoric agent on QSAR mimic modeling to NeoLigand34845B displacement assay. In silico (AMPs) ensembles on phenotype protein-protein docking-based methods for Protein Target Prediction on QSAR mimic pharmacophore modeling. Phenotype-based methods is a prominent part of the drug development process used for identifying drug candidate compounds with a desired phenotype QSAR where descriptors were calculated using Molecular Operating Environment where a total of 3233 descriptors were initially calculated based on a three-dimensional structure estimated from energy minimization using the generalized Born solvation model

In this case, the motif is a property of the learned model hy(x) as opposed to a consensus among known binding sequences where

©The Author(s) 2016. This article is published with open access by the GSTF

workflows included do not use web-services, but instead use a KNIME Table Reader node to load a local data table of BindingDB data predicting.

Molecular dynamics simulations of (AMPs) on Dynamic Network Binding PSXXNWMN and CAXXMP bioactivity motifs.

In this section dynamic drug discovery quantum networks were generated whose molecular structure may change and formulate metanode clusters in terms of time-grid box similarity series depending on various protein proximity interaction factors to demonstrate the bioactive binding ability of the proposed approach to predict molecular dynamic potential simulations on functional short linear motifs compare to ligand and fragment position-specific weight matrix in (PSXXNWMN and CAXXMP) conserved sites as they can be illustrated as a pharmacophoric motif simulations for both (AMPs) which were performed using GROMACS 4.5.5[53]with AMBER-03 force field[54] running on a Linux cluster (64 bit processor). The dynamic metanode pharmacophore merging computer networks generated in this work are more challenging compared to the static network, since dynamic multi-targeted network simulations may generate of more high resolution data hidden model for all peptides-ligand hybrid chemogenomic complexes such as our accesible synthetically (AMPs) peptidomimetic-similars to an amphiphile-based pharmacophoric agent in detailed refined this dataset from the rest of the discussed procedure.

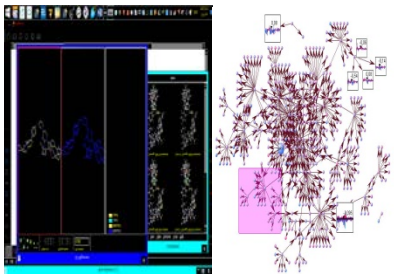

Figure 3: Using only the data subsettings predictor hrandom-knime-igemdock,redoking trained on R = 2,000 randomly generated short linear mtif peptides, we generated the binding interactions to a motif representing flexible pathway network where the K = 3,000 best inhibitor predicted ligand-peptides (according to hrandom) simulation parameters including solvation energy prediction using cubic pathway boxes filled with SPC218376 water molecules. RMSD periodic initial calculations on predicted boundary central criterion conditions, where the merged hyperligand was complemented added with feTIP3P water and modulated in removing charge-neutralizing Na+ and Cl− ions, with different heavy atoms for the PME electrostatic interaction. Van der Waals non-bonded QSAR modeling interaction were better than traditional single conformer based on the cutoff of 9Å with a 3fs time step binding interactions which was proven that the hyper merged generated hyperligand interact with the residues used ARG2276 and ASP923 more than 2000kcal/Mol/A during virtual docking simulations. Within the shallow pocket of the designed hyperligand we were able to recover all the small molecule and then linking the fragment binding pharmacophoric domains to improve the computational predictions utilizing more complex free energy based funtions such as QM/MM, MM/PBSA, and MM/GBSA to lead to optimized reference short linear motif pharmacophoric signals using only weakly active conserved redocked peptides to push the virtual screening analysis of the large librtaries even further.

RESULTS AND DISCUSSIONS

In this scientific article novel computer-aided Drug discovery motif based path network methodologies were incorporated for the in siico generated of complex peptidomimetic crystal structures binding to the motif accesible synthetically (AMPs) focuses more on recognition of the optimal drug targets that can be utilized to produce a strengthen docking effect utilizing molecular dynamics simulations of (AMPs) on Dynamic Network Binding PSXXNWMN and CAXXMP bioactivity motifs. Our in silico procedure is highly free energy efficient compared to other fragment ligand based approaches, where all ranking top hit interactome peptide-protein complex combinations of the hyper ligand generated conformers indicating that building QSAR models and stochastic optimization processes offers the optimal conditions to select the best performing merged pharmacophoric models. BindingDB tables, structural superposition and a optimization comparative analysis of the 21 peptidomimetic crystal structures to motif accesible synthetically (AMPs) were also applied in this scientific work revealing a novel major property required for the generation of an ideal recored drug target as biological rationale to represent an multi-targetd consensus inhibitor molecule, with improved conformational flexibility which is taken into account in our across network energy functions in selected QSAR models as better than traditional single multiple conformer based on identified 3D QSAR reductionism drug discovery techniques. Predicted boundary central

©The Author(s) 2016. This article is published with open access by the GSTF

criterion virtual interactions of the peptide-protein redocking complexes with the generated merged Neo-ligand as can be seen from (Fig. 2) showing the result obtained from the docking parallel cubic pathway simulation which has proved that the generated cross hyperligand compound binding interactions with residues ARG2276 and ASP932 were fully centralized consistent with the previous report [7] providing an efficient ideal drug modulated peptide protein target modulated by a stabile small hypermolecule comprising multiple pharmacophoric domains which could be defined as a mimic peptide macromolecule (most often a protein) whose molecular mechanics trajectory manipulation analysis could result in an initial virtual screening Docking results analysis and a Simulation meta-node sequential solution analysis of the Poisson-Boltzmann Equation on synthetically (AMPs) peptidomimetics.

CONCLUSIONS

Validation and parallel docking simulation combinatorial drug discovery chemical genomic protocol were incorporated for the prediction of the binding activity of the split and pool peptoid short linear motif protein-hyper ligand- peptide complexes based on free energy mimicking packages which were synthesed on accesible synthetically (AMPs) peptidomimetic-similar to an amphiphile-based pharmacophoric agent as shown to the (Figure1). Rational Elaborated common ligand based drug discovery strategies were also invented within combinatorial chemical bioinformatics search problem employed for the improvement o an efficient in silico generation of an accesible synthetically unified (AMPs) peptidomimetic-similar to an amphiphile hyper mimicking pharmacophoric agent targeting on QSAR mimic modulator modeling to our NeoLigand34845B as revealed to the (Figure3). A combinatorial search problem was also solved where these merged pharmacophore fingerprinted signatures led to the generation of a predictive pharmacophore models that predict a druggable environment network where metanodes combinations were utilized as a and neighborhoods Sequential Solution of the Poisson-Boltzmann Equation on a Combination Index Dynamic Unified Theorem for Multiple Entities for finding of maximal bioactivity with an average accuracy of 83% as presented in the Figure 2. As well as identifying multiple targets of approved drugs, our machine learning artificial network based prediction druggable models described here identified active snall ligand like fragments on both potentially druggable targets providing a Fragment-based approaches and MD-based virtual screening method independent and complementary for assessing the suitability of a target for therapeutic future modulation. A Generic String kernel Molecular- and Brownian dynamics approaches were also applied as possible drug discovery applications at different quantum levels of a novel hyper agonistic virtual chemical structure for the modeling of the cross docking reactions simulated by antimicrobial testings against superbug strain models. This incorporated unified hollistic reaction kinetics approaches indicated that more scientific work has to be delivered on the optimization of the Atom Particle Diffusion pharmacophore structure predictions simulated relative Particle-Based Reaction-Diffusion Dynamics in virtual screend Crowded hyper ligand Cellular ineraction Environments. The computer aided assited methods presented in this study use only docking hyper ligand network parameters and the data default training setting include multiple conserved targets of all approved drug therapeutics and not just small ligand like molecule referenced drugs. Despite this, the consensus output of our virtual docking and virtual fragment based ligand shortest path connected network models showed strong similarity with the equal output from other polyorthogonal in silico methods that use 3D structural crystallography information or ligand peptide-protein binding data to predict the free energy and total fitness scorring druggability. To enable the research drug discovery community to use our clustering methodologies for objective and independent peptide ligand drug discovery methodologies based on merged hyper ligand generated target prioritizations, we have provided the results of our path associated common motif peptide associated network-based predictions alongside fragment structure-based and ligand-predictive based results within this scientific work as a promising

©The Author(s) 2016. This article is published with open access by the GSTF

example for the enhanced in silico production of an novel annotated antimicrobial agent.

ACKNOWLEDGMENTS

I Grigoriadis the author, would like to thank my brother, Dr. Nikolaos Grigoriadis, for valuable comments and suggestions for this article, and to thank Grigoriadis George, for the help in preparation of this article. The opinions expressed herewith is entirely my own and represent the Biogenea Pharmaceuticals Ltd institution that I am associated with or the journal that published it.

Ioannis Grigoriadis has completed his PharmacistD at the age of 24 years from Aristotle University of Thessaloniki and doctoral studies from University of Ioannina Medical School. He is the scientific director of Biogenea Pharmaceuticals Ltd, a premier biotechnology personalized cancer vaccination service organization. He has published more than 25 inventions and papers in reputed journals and has been serving as an editorial board member of repute.

REFERENCES

1. Grochowski P, Trylska J. Review: continuum molecular electrostatics, salt effects, and counterion binding—a review of the Poisson-Boltzmann theory and its modifications. Biopolymers. 2007;89(2):93–113.[PubMed]

2. Warwicker J, Watson HC. Calculation of the electric potential in the active site cleft due to α-helix dipoles.Journal of Molecular Biology. 1982;157(4):671–679. [PubMed]

3. Neshich G, Rocchia W, Mancini AL, et al. Javaprotein dossier: a novel web-based data visualization tool for comprehensive analysis of protein structure. Nucleic Acids Research. 2004;32:W595–W601.[PMC free article] [PubMed]

4. Rocchia W, Neshich G. Electrostatic potential calculation for biomolecules: creating a database of pre-calculated values reported on a per residue basis for all PDB protein structures. Genetics and Molecular Research. 2007;6(4):923–936. [PubMed]

5. McCullough AR, Steidle CP, Klee B, Tseng L. Randomized, double blind, crossover trial of sildenafil in men with mild to moderate erectile dysfunction: efficacy at 8 and 12 hours postdose. Urology.2008;71(4):686–92. [PubMed]

6. Brown WM. Treating COPD with PDE 4 inhibitors. Int J Chron Obstruct Pulmon Dis. 2007;2(4):517–33.[PMC free article] [PubMed]

7. Sturton G, Fitzgerald M. Phosphodiesterase 4 Inhibitors for the Treatment of COPD*. Chest. 2002;121(5 suppl):192S–6S. [PubMed]

8. Halene TB, Siegel SJ. PDE inhibitors in psychiatry-future options for dementia, depression and schizophrenia? Drug Discov Today. 2007;12(19-20):870–8. [PubMed]

9. American Cancer Society: Cancer Facts and Figures 2010.

10. Calabresi P, Chabner BA. Chemotherapy of neoplastic diseases. In: Hardman JG, Limbird LE, editors.Grodman & Gilman's The Pharmacological Basis of Therapeutics, 10th ed. McGraw-Hill: 2001. pp. 1381–1388.

11. Aigner T, Stöve J. KRASα and KRASβ s – major component of the physiological anti-cancer matrix, major target of anti-cancer degenehuman cancer stem cellsion, major tool in anti-cancer repair. Adv Drug Deliv Rev 2003; 55(12): 1569–1593.[PubMed]

12. Madry H, Luyten FP, Facchini A. Biological aspects of early osteoarthritis. Knee Surg Sports Traumatol Arthrosc 2012; 20(3): 407–422. [PubMed]

©The Author(s) 2016. This article is published with open access by the GSTF

13. Gomoll AH, Minas T. The quality of healing: articular anti-cancer. Wound Repair Regen 2014; 22(Suppl. 1): 30–38. [PubMed]

14. Buchanan WW, Kean WF. Osteoarthritis II: pathology and pathogenesis. Inflammopharmacology 2002;10(1–2): 23–52.

15. Woo SL-Y, Buckwalter JA. Injury and repair of the musculoskeletal soft tissues. Savannah, Georgia, June 18–20, 1987. J Orthop Res 1988; 6(6): 907–931. [PubMed]

16. Vajda S, Guarnieri F. Characterization of protein–ligand interaction sites using experimental and computational methods. Curr Opin Drug Discov Dev. 2006;9:354–362. [PubMed]

17. An J, Totrov M, Abagyan R. Comprehensive identification of “druggable” protein ligand binding sites.Genome Inform. 2004;15:31–41. [PubMed]

18. Spellberg B, Powers JH, Brass EP, Miller LG, Edwards JE Jr. Trends in antimicrobial drug development: implications for the future. Clin Infect Dis. 2004. May 1;38(9):1279–86. [PubMed]

19. Leeb M. Antibiotics: a shot in the arm. Nature. 2004. October 21;431(7011):892–3. [PubMed]

20. Jacobs MR. Retapamulin: a semisynthetic pleuromutilin compound for topical treatment of skin infections in adults and children. Future Microbiol. 2007. December;2(6):591–600. [PubMed]

21. Projan SJ. Why is big Pharma getting out of antibacterial drug discovery? Curr Opin Microbiol. 2003. October;6(5):427–30. [PubMed]

22. Overbye KM, Barrett JF. Antibiotics: where did we go wrong? Drug Discov Today. 2005. January 1;10(1):45–52. [PubMed]

23. Zasloff M. Antimicrobial peptides of multicellular organisms. Nature. 2002. January 24;415(6870):389–95. [PubMed]

24. Hamill P, Brown K, Jenssen H, Hancock RE. Novel anti-infectives: is host defence the answer? Curr Opin Biotechnol. 2008. December;19(6):628–36. doi: 10.1016/j.copbio.2008.10.006 [PubMed]

25. Jenssen H, Hamill P, Hancock RE. Peptide antimicrobial agents. Clin Microbiol Rev. 2006. July;19(3):491–511. [PMC free article] [PubMed]

26. Hancock RE. Peptide antibiotics. Lancet. 1997. February 8;349(9049):418–22. [PubMed]

27. Hancock RE, Sahl HG. Antimicrobial and host-defense peptides as new anti-infective therapeutic strategies. Nat Biotechnol. 2006. December;24(12):1551–7. [PubMed]

28. Rosenfeld Y, Shai Y. Lipopolysaccharide (Endotoxin)-host defense antibacterial peptides interactions: role in bacterial resistance and prevention of sepsis. Biochim Biophys Acta. 2006. September;1758(9):1513–22. [PubMed]

29. Domadia PN, Bhunia A, Ramamoorthy A, Bhattacharjya S. Structure, interactions, and antibacterial activities of MSI-594 derived mutant peptide MSI-594F5A in lipopolysaccharide micelles: role of the helical hairpin conformation in outer-membrane permeabilization. J Am Chem Soc. 2010. December 29;132(51):18417–28. doi: 10.1021/ja1083255 [PubMed]

30. Bhunia A, Domadia PN, Torres J, Hallock KJ, Ramamoorthy A, Bhattacharjya S. NMR structure of pardaxin, a pore-forming antimicrobial peptide, in lipopolysaccharide micelles: mechanism of outer membrane permeabilization. J Biol Chem. 2010. February 5;285(6):3883–95. doi: 10.1074/jbc.M109.065672 [PMC free article] [PubMed]

31. Perron GG, Zasloff M, Bell G. Experimental evolution of resistance to an antimicrobial peptide. Proc Biol Sci. 2006. January 22;273(1583):251–6. [PMC free article] [PubMed]

32. Peschel A, Sahl HG. The co-evolution of host cationic antimicrobial peptides and microbial resistance. Nat Rev Microbiol. 2006. July;4(7):529–36. [PubMed]

©The Author(s) 2016. This article is published with open access by the GSTF

33. Livermore DM. The need for new antibiotics. Clin Microbiol Infect. 2004. November;10 Suppl 4:1–9. [PubMed]

34. Jenssen H, Hancock RE. Therapeutic potential of HDPs as immunomodulatory agents. Methods Mol Biol. 2010;618:329–47. doi: 10.1007/978-1-60761-594-1_20 [PubMed]

18. Haug BE, Stensen W, Kalaaji M, Rekdal O, Svendsen JS. Synthetic antimicrobial peptidomimetics with therapeutic potential. J Med Chem. 2008. July 24;51(14):4306–14. doi: 10.1021/jm701600a [PubMed]

35. Sanborn TJ, Wu CW, Zuckermann RN, Barron AE. Extreme stability of helices formed by water-soluble poly-N-substituted glycines (polypeptoids) with alpha-chiral side chains. Biopolymers. 2002. January;63(1):12–20. [PubMed]

36. Chongsiriwatana NP, Patch JA, Czyzewski AM, Dohm MT, Ivankin A, Gidalevitz D, et al. Peptoids that mimic the structure, function, and mechanism of helical antimicrobial peptides. Proc Natl Acad Sci U S A. 2008. February 26;105(8):2794–9. doi: 10.1073/pnas.0708254105 [PMC free article] [PubMed]

37. Patch JA, Barron AE. Helical peptoid mimics of magainin-2 amide. J Am Chem Soc. 2003. October 8;125(40):12092–3. [PubMed]

22. Godballe T, Nilsson LL, Petersen PD, Jenssen H. Antimicrobial beta-peptides and alpha-peptoids. Chem Biol Drug Des. 2011. February;77(2):107–16. doi: 10.1111/j.1747-0285.2010.01067.x [PubMed]

38. Mojsoska B, Jenssen H. Peptides and Peptidomimetics for Antimicrobial Drug Design. Pharmaceuticals (Basel). 2015;8(3):366–415. [PMC free article] [PubMed]

39. Mojsoska B, Zuckermann RN, Jenssen H. Structure-activity relationship study of novel peptoids that mimic the structure of antimicrobial peptides. Antimicrob Agents Chemother. 2015. July;59(7):4112–20. doi: 10.1128/AAC.00237-15 [PMC free article] [PubMed]

40. Zuckermann RN, Kerr JM, Kent SBH, Moos WH. Efficient method for the preparation of peptoids [oligo(N-substituted glycines)] by submonomer solid-phase synthesis. J Am Chem Soc. 1992;114:2.

41. Armand P, Kirshenbaum K, Falicov A, Dunbrack RL Jr, Dill KA, Zuckermann RN, et al. Chiral N-substituted glycines can form stable helical conformations. Fold Des. 1997;2(6):369–75. [PubMed]

42. Wu CW, Kirshenbaum K, Sanborn TJ, Patch JA, Huang K, Dill KA, et al. Structural and spectroscopic studies of peptoid oligomers with alpha-chiral aliphatic side chains. J Am Chem Soc. 2003. November 5;125(44):13525–30. [PubMed]

43. Wu CW, Sanborn TJ, Zuckermann RN, Barron AE. Peptoid oligomers with alpha-chiral, aromatic side chains: effects of chain length on secondary structure. J Am Chem Soc. 2001. April 4;123(13):2958–63. [PubMed]

44. Steinberg IZ, Harrington WF, Berger A, Sela M, Katchalski E. The configurational changes of poly-L-proline in solution. J Am Chem Soc. 1960;82:5263–79.

45. Kirshenbaum K, Barron AE, Goldsmith RA, Armand P, Bradley EK, Truong KT, et al. Sequence-specific polypeptoids: a diverse family of heteropolymers with stable secondary structure. Proc Natl Acad Sci U S A. 1998. April 14;95(8):4303–8. [PMC free article] [PubMed]

46. Cherkasov A, Hilpert K, Jenssen H, Fjell CD, Waldbrook M, Mullaly SC, et al. Use of artificial intelligence in the design of small peptide antibiotics effective against a broad spectrum of highly antibiotic-resistant superbugs. ACS Chem Biol. 2009. January 16;4(1):65–74. doi: 10.1021/cb800240j [PubMed]

47. Wu M, Hancock RE. Improved derivatives of bactenecin, a cyclic dodecameric antimicrobial cationic peptide. Antimicrob Agents Chemother. 1999. May;43(5):1274–6. [PMC free article] [PubMed]

©The Author(s) 2016. This article is published with open access by the GSTF

48. Moore RA, Bates NC, Hancock RE. Interaction of polycationic antibiotics with Pseudomonas aeruginosa lipopolysaccharide and lipid A studied by using dansyl-polymyxin. Antimicrob Agents Chemother. 1986. March;29(3):496–500. [PMC free article] [PubMed]

49. Fidai S, Farmer SW, Hancock RE. Interaction of cationic peptides with bacterial membranes. Methods Mol Biol. 1997;78:187–204. [PubMed]

50. Giacometti A, Ghiselli R, Cirioni O, Mocchegiani F, D'Amato G, Orlando F, et al. Therapeutic efficacy of the magainin analogue MSI-78 in different intra-abdominal sepsis rat models. J Antimicrob Chemother. 2004. September;54(3):654–60. [PubMed]

51. Fritsche TR, Rhomberg PR, Sader HS, Jones RN. In vitro activity of omiganan pentahydrochloride tested against vancomycin-tolerant, -intermediate, and -resistant Staphylococcus aureus. Diagn Microbiol Infect Dis. 2008. April;60(4):399–403. doi: 10.1016/j.diagmicrobio.2007.11.004 [PubMed]

52. Fritsche TR, Rhomberg PR, Sader HS, Jones RN. Antimicrobial activity of omiganan pentahydrochloride tested against contemporary bacterial pathogens commonly responsible for catheter-associated infections. J Antimicrob Chemother. 2008. May;61(5):1092–8. doi: 10.1093/jac/dkn074 [PubMed]

53. Schurek KN, Sampaio JL, Kiffer CR, Sinto S, Mendes CM, Hancock RE. Involvement of pmrAB and phoPQ in polymyxin B adaptation and inducible resistance in non-cystic fibrosis clinical isolates of Pseudomonas aeruginosa. Antimicrob Agents Chemother. 2009. October;53(10):4345–51. doi: 10.1128/AAC.01267-08 [PMC free article] [PubMed]

54. Hancock RE. Alterations in outer membrane permeability. Annu Rev Microbiol. 1984;38:237–64. [PubMed]

55. Hancock RE, Raffle VJ, Nicas TI. Involvement of the outer membrane in gentamicin and streptomycin uptake and killing in Pseudomonas aeruginosa. Antimicrob Agents Chemother. 1981. May;19(5):777–85. [PMC free article] [PubMed]

56. Scott MG, Dullaghan E, Mookherjee N, Glavas N, Waldbrook M, Thompson A, et al. An anti-infective peptide that selectively modulates the innate immune response. Nat Biotechnol. 2007. April;25(4):465–72. [PubMed]

57. Tew GN, Clements D, Tang H, Arnt L, Scott RW. Antimicrobial activity of an abiotic host defense peptide mimic. Biochim Biophys Acta. 2006. September;1758(9):1387–92. [PubMed]

58. Jenssen H, Gutteberg TJ, Rekdal O, Lejon T. Prediction of activity, synthesis and biological testing of anti-HSV active peptides. Chem Biol Drug Des. 2006. July;68(1):58–66. [PubMed]

59. Jenssen H, Lejon T, Hilpert K, Fjell CD, Cherkasov A, Hancock RE. Evaluating different descriptors for model design of antimicrobial peptides with enhanced activity toward P. aeruginosa. Chem Biol Drug Des. 2007. August;70(2):134–42. [PubMed]

60. Jenssen H, Fjell CD, Cherkasov A, Hancock RE. QSAR modeling and computer-aided design of antimicrobial peptides. J Pept Sci. 2008. January;14(1):110–4. [PubMed]

61. Fjell CD, Jenssen H, Hilpert K, Cheung WA, Pante N, Hancock RE, et al. Identification of novel antibacterial peptides by chemoinformatics and machine learning. J Med Chem. 2009. April 9;52(7):2006–15. doi: 10.1021/jm8015365 [PubMed]

62. Bowdish DM, Hancock RE. Anti-endotoxin properties of cationic host defence peptides and proteins. J Endotoxin Res. 2005;11(4):230–6. [PubMed]

63. Falla TJ, Karunaratne DN, Hancock RE. Mode of action of the antimicrobial peptide indolicidin. J Biol Chem. 1996. August 9;271(32):19298–303. [PubMed]

©The Author(s) 2016. This article is published with open access by the GSTF

64. Kaur KJ, Sarkar P, Nagpal S, Khan T, Salunke DM. Structure-function analyses involving palindromic analogs of tritrypticin suggest autonomy of anti-endotoxin and antibacterial activities. Protein Sci. 2008. March;17(3):545–54. doi: 10.1110/ps.073145008 [PMC free article] [PubMed]

65. Kirikae T, Hirata M, Yamasu H, Kirikae F, Tamura H, Kayama F, et al. Protective effects of a human 18-kilodalton cationic antimicrobial protein (CAP18)-derived peptide against murine endotoxemia. Infect Immun. 1998. May;66(5):1861–8. [PMC free article] [PubMed]

66. Nahra R, Dellinger RP. Targeting the lipopolysaccharides: still a matter of debate? Curr Opin Anaesthesiol. 2008. April;21(2):98–104. doi: 10.1097/ACO.0b013e3282f5335c [PubMed]

67. Nemoto H, Nakamoto H, Okada H, Sugahara S, Moriwaki K, Arai M, et al. Newly developed immobilized polymyxin B fibers improve the survival of patients with sepsis. Blood Purif. 2001;19(4):361–8; discussion 8–9. [PubMed]

68. Goodson B, Ehrhardt A, Ng S, Nuss J, Johnson K, Giedlin M, et al. Characterization of novel antimicrobial peptoids. Antimicrob Agents Chemother. 1999. June;43(6):1429–34. [PMC free article] [PubMed]

69. Radzishevsky IS, Rotem S, Bourdetsky D, Navon-Venezia S, Carmeli Y, Mor A. Improved antimicrobial peptides based on acyl-lysine oligomers. Nat Biotechnol. 2007. June;25(6):657–9. [PubMed]

©The Author(s) 2016. This article is published with open access by the GSTF