**Editorial: Highlights from selected articles in the journal involving host-defense peptides**

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During the period 2019-20, PEPTIDES received a large number of submissions that involved studies with host-defense peptides indicative of considerable interest in this area of research within the scientific community. This is illustrated by the fact that, at the time of writing, the Antimicrobial Peptide Database compiled by G. Wang and his colleagues at the University of Nebraska Medical Center (<http://aps.unmc.edu/AP/main.php>) lists 3250 such peptides with demonstrable biological activity. The widespread emergence of bacteria, fungi, and protozoa with varying degrees of resistance to commonly used antibiotics necessitates a search for new types of potent and effective, non-toxic antimicrobial agents. Peptides constitute a component of the system of innate immunity of eukaryotes and a select number, by virtue of their broad-spectrum activity and destructive mechanism of action, show therapeutic promise as anti-infective agents. In addition, it is well established that many peptides that were first identified on the basis of their antimicrobial activity are in fact multifunctional and, among other activities, possess cytokine-mediated immunomodulatory properties. This editorial draws attention to selected recent articles in the journal that have addressed the development peptide-based drugs that are active against drug-resistant microorganisms that represent a serious threat to public health or show therapeutic potential as anti-inflammatory agents.

 Of particular concern to the medical profession is the emergence of strains of *Mycobacterium tuberculosis*, a causative agent of tuberculosis, that have developed resistance to hitherto effective antibiotics. Abraham *et al* [1] report that B1CTcu5, a peptide belonging to the brevinin-1 family from skin secretions of the frog *Clinotarsus curtipes*, displays potent *in vitro* inhibitory activity against *M. tuberculosis* and eliminated intracellular mycobacteria without cytotoxic effects on human macrophages. Cryptococcal meningitis is a serious infection of the brain and spinal column caused by the fungus *Cryptococcus neoformans* that is prevalent in people with a compromised immune system. An article by Ma et al. [2] indicates that the antifungal peptide MSI-1 (GIWKFLKKAKKFWK-NH2) demonstrates promising activity against C.*neoformans in vitro* and in a *C. neoformans*-infected mouse model of cryptococcal meningoencephalitis. The peptide acts by increasing cell membrane permeability and decreasing production of pro-inflammatory cytokines and so represents candidate for use in infections caused by azole-resistant *Cryptococcus*. The common sexually transmitted disease trichomoniasis is caused by infection with the protozoan parasite *Trichomonas vaginalis.* Huang *et al.* [3] showed that the extensively studied fish antimicrobial peptide epinecidin-1 was active against metronidazole-resistant *T. vaginalis* and treatment with the peptide decreased content of the pathogen in mice infected vaginally with the pathogen.

 The emergence in malaria endemic regions of strains of *Plasmodium falciparum* with resistance to nearly all currently available antimalarial drugs constitutes a serious public health challenge. Chaianantakul *et al*. [4] report that peptide rR8-JR21 designed from a domain in the bifunctional enzyme dihydrofolate reductase-thymidylate synthase of *P. falciparum* showed growth inhibitory effects on *P. falciparum* NF54 parasites cultured *in vitro* while displaying low hemolytic activity against human erythrocytes. Treatment with the peptide delayed parasite development with an accumulation of ring stage parasites that did not develop to trophozoites. A study by Popov *et al*. [5] showed that peptide AC12 (ACFLTRLGTYVC), first isolated from skin secretions of the tree frog *Hypsiboas raniceps*, while lacking direct antimicrobial activity was effective in inhibiting synthesis of NO and the proinflammatory cytokines TNF-α and Il-12 when incubated with RAW 264.7 macrophage-like cells. The peptide displayed no cytotoxic effects in mammalian cells and consequently shows therapeutic potential for the treatment of inflammatory diseases.

 The disadvantages of antimicrobial peptides compared with conventional antibiotics include relatively low potency, cytotoxicity to human cells and for, systemic application, rapid clearance from the circulation. Recent articles involving structure-activity studies have addressed these problems leading to the design of analogs of naturally occurring peptides with potentially improved therapeutic properties. A comprehensive study involving evaluation of 45 analogs by Smirnova et al. [6] demonstrated that derivatives of the established broad-spectrum antimicrobial peptide, indolicin (ILPWKWPWWPWRR-NH2) in which tryptophan residues in the peptide were substituted either by 2-methyl-L-phenylalanine or D-phenylalanine and contained an N-terminal (CH2)10 hydrocarbon extension exhibited up to 3-fold greater activity against both Gram-negative and Gram-positive bacteria than the native peptide and were significantly less hemolytic.

 Citropin 1.1 (GLFDVIKKVASVIGGL-NH2), first isolated from skin secretions of the Australian tree frog *Litoria citropa*, has excited interest by virtue of its wide-spectrum antibacterial properties. A structure-activity study by Rodrigues de Almeida *et al*. [7] involving synthesis of 20 analogs demonstrated that the [W3F] and [W3F, D4R, K7R] derivatives showed appreciably increased activity against MRSA and a range of clinically-relevant Gram-negative pathogens while maintaining low cytotoxicity against mammalian cells. NMR studies indicated that citropin 1.1 forms a head-to-tail helical dimer in a membrane-mimetic environment The more active analogs displayed a greater tendency to adopt a stable α-helical conformation and to dimerize when in contact with a negatively-charged membrane.

**References**

[1] P. Abraham, L. Jose, T.T. Maliekal, R.A. Kumar, K.S Kumar, B1CTcu5: A frog-derived brevinin-1 peptide with anti-tuberculosis activity, Peptides 132 (2020) 170373. doi: 10.1016/j.peptides.2020.170373

[2] L. Ma, S. Wei, X. Ye, P. Xu, H. Chen, Z. Liu, et al., Antifungal activity of peptide MSI-1 against *Cryptococcus neoformans* infection in vitro and in murine cryptococcal meningoencephalitis, Peptides 130 (2020) 170334. doi: 10.1016/j.peptides.2020.170334

[3] H.N. Huang, C.M. Chuang, J.Y. Chen, P. Chieh-Yu, Epinecidin-1: A marine fish antimicrobial peptide with therapeutic potential against *Trichomonas vaginalis* infection in mice, Peptides 112 (2019) 139-148. doi: 10.1016/j.peptides.2018.12.004

[4] N. Chaianantakul, T. Sungkapong, J. Supatip, P. Kingsang, S. Kamlaithong, N. Suwanakitti, Antimalarial effect of cell penetrating peptides derived from the junctional region of *Plasmodium falciparum* dihydrofolate reductase-thymidylate synthase, Peptides 131 (2020) 170372. doi: 10.1016/j.peptides.2020.170372

[5] CSFC Popov, BS Magalhães, BJ Goodfellow, AL Bocca, DM Pereira, PB Andrade et al., Host-defense peptides AC12, DK16 and RC11 with immunomodulatory activity isolated from *Hypsiboas raniceps* skin secretion. Peptides113 (2019) 11-21. doi: 10.1016/j.peptides.2018.12.007

### [6] M.P. Smirnova, N.I. Kolodkin, A.A Kolobov, V.G. Afonin, I.V. Afonina, L.I. Stefanenko, et al., Indolicidin analogs with broad-spectrum antimicrobial activity and low hemolytic activity, Peptides 132 (2020) 170356. doi: 10.1016/j.peptides.2020.170356

[7] N. Rodrigues de Almeida, J. Catazaro, M. Krishnaiah, Y. Singh Chhonker, D.J. Murry, R. Powers, et al., Understanding interactions of Citropin 1.1 analogues with model membranes and their influence on biological activity. Peptides 119 (2019) 170119. doi: 10.1016/j.peptides.2019.170119