endemic countries, to co-ordinate these efforts, provide technical guidance and enlist support wherever needed. The PATTEC initiative might seem ambitious, but it is based on the principle of one step at a time, dealing progressively with what is technically feasible within the constraints of available resources and political commitment, against a background of Africa's declared unwillingness to accept the consequences of continued tsetse infestation.

References

1 Moore, D.A.J. *et al.* (2002) African trypanosomiasis in travelers returning to the United Kingdom. *Emerg. Infect. Dis.* 8, 74–76
2 Vreysen, M.J.B. *et al.* (2000) *Glossina austeni* (Diptera: Glossinidae) eradicated on the island of Unguja, Zanzibar, using the sterile insect technique. *J. Econ. Entomol.* 93, 123–135
3 Schofield, C.J. and Dias, J.C.P. (1999) The Southern Cone Initiative against Chagas disease. *Adv. Parasitol.* 42, 1–27
4 Muzari, M.O. (1999) Odour-baited targets as invasion barriers for tsetse flies (Diptera: Glossinidae): a field trial in Zimbabwe. *Bull. Entomol. Res.* 89, 73–77
5 Hargrove, J.W. (1993) Target barriers for tsetse flies (*Glossina* spp.) (Diptera: Glossinidae): quick estimates of optimal target densities and barrier widths. *Bull. Entomol. Res.* 83, 197–200
6 Hargrove, J.W. *et al.* (2000) Insecticide-treated cattle for tsetse control: the power and the problems. *Med. Vet. Entomol.* 14, 123–130

John P. Kabayo
PATTEC Co-ordination Office, Organisation of African Unity, PO Box 200032, Addis Ababa, Ethiopia.
e-mail: jpk.pattec@telecom.net.et

Antimicrobial peptides versus parasitic infections?

Jacopo Vizioli and Michel Salzet

Reports of antimicrobial peptides generally have evaluations of their antibacterial and antifungal activities. By contrast, little is known of their activities against protozoan and metazoan parasites. *In vitro* antiparasitic assays suggest that antimicrobial peptides could represent a powerful tool for the development of novel drugs to fight the parasite in the vertebrate host, or to complement current therapeutic strategies.

Published online: 24 September 2002

Multicellular organisms have developed an immediate immune response against infectious microorganisms [1,2]. During the past few years, studies on the components of this innate immune system have established the contribution of antimicrobial peptides (generally, small, cationic molecules of 2–8 kDa) to the defense response of the invertebrate host [3].

Peptides from the same families of antimicrobial peptides have been isolated from vertebrates, invertebrates and plants [4]. Similarities among natural antibiotics of distant evolutionary species have provided the basis for simple models to understand the innate immune system of more complex animals such as mammals. Many of these antimicrobial peptides present a strong activity *in vitro* against microorganisms that are resistant to conventional antibiotics, and they could provide design templates for anti-infectious agents in humans [3,5].

Development of antiparasitic drugs

Human parasite infections cause millions of deaths around the world every year. New antiparasitic drugs are needed that can be used alone or to complement existing products, and to overcome problems such as chloroquine resistance of *Plasmodium*.

Antimicrobial activity of cationic peptides mainly is exerted against bacteria and fungi, but some antiviral and anticancer effects have been described [6]. In contrast to the huge amount of literature on antibacterial and antifungal activities, few reports describe activities against protozoan and metazoan parasites. Invertebrate antimicrobial compounds are generally ineffective against eukaryotic cells as a result of their mode of action, and due to the different compositions of the cell membranes between eukaryotic and prokaryotic cells [6].

Reports of antiparasitic activities of natural antimicrobial compounds are mainly related to *Plasmodium* and *Leishmania*, two of the most widely distributed parasites, worldwide (see http://www.who.int).

Antimalarials

Antimalarial activities have been described for two classes of cationic natural antibiotics: (1) the linear amphipatic peptides; and (2) the cysteine-rich open-ended peptides. Cecropin and magainin, two linear α-helical molecules isolated from the hemolymph of the giant silk moth *Hyalophora cecropia* and the skin of the African frog *Xenopus laevis*, respectively, significantly reduced oocyst development in various *Plasmodium* spp., when injected into different anopheline mosquito species [7]. A stronger effect against *Plasmodium* was observed when using synthetic hybrids of cecropin and melittin (a linear peptide isolated from bee venom) [8].

Another cecropin-like synthetic peptide, Shiva-3, blocked *Plasmodium berghei* ookinetes development *in vitro*, and was effective against the early sporogonic stages in the mosquito midgut [9]. Recent work demonstrated that a series of derivatives of dermaseptin, a peptide isolated from the skin of a frog, selectively lysed *Plasmodium*-infected erythrocytes [10].

The first cysteine-rich cationic peptides reported as active against *Plasmodium* were the defensins, a family of 4-kDa molecules widely distributed in plants and animals. Two insect defensins interfered with the development of *Plasmodium gallinaceum* oocysts, when injected into mosquitoes, and were highly toxic to isolated sporozoites *in vitro* [11]. Activities against *P. berghei* developmental stages were recently described for two novel cysteine-rich antimicrobial peptides: (1) gambicin (8 kDa) from *Anopheles gambiae*, which showed a slight *in vitro* effect against ookinetes [12]; and (2) scorpine (isolated from venom of the scorpion *Pandinus imperator*), which has an amino acid sequence similar to a cecropin–defensin hybrid, and inhibits gametes and ookinetes development more efficiently than Shiva-3 [13].

Antileishmanials

Leishmania represent one of the most used models for *in vitro* antiparasitic assays. Several linear amphipatic antibiotics, effective against different *Leishmania* stages, represent potential candidates to help design novel drugs for topical treatment of this disease [6]. Cecropins isolated from different insects showed a lytic effect on promastigotes [14],

 1471-4922/02/$ – see front matter PII: S1471-4922(02)02389-9

and a modulation on leishmanicidal activity was observed using a variety of cecropin–melittin hybrids [15]. As demonstrated for dermaseptin [16], these peptides kill the parasite by altering the permeability of the plasma membrane. A further leishmanicidal activity has been reported for the cysteine-rich peptide gomesin, isolated from the hemocytes of the spider *Acanthoscurria gomesiana* [17].

Some natural antibiotics and their synthetic derivatives display lytic activity against other protozoan parasites, such as *Trypanosoma*, *Trichomonas* or *Cryptosporidium* [6]. Cecropin is the only antimicrobial peptide so far reported as active against a metazoan parasite, reducing *Brugia pahangi* microfilariae motility *in vitro*, and interfering with worm development when injected into mosquito hosts [18].

Transgenic expression

Invertebrate antimicrobial peptides could be expressed as antiparasitic agents in transgenic organisms to block the transmission of vector-borne diseases, as demonstrated by cecropin expression in symbiotic bacteria to fight *Trypanosoma* development in hemipteran hosts [19]. These antimicrobial peptides generally present a low toxicity for vertebrate cells, and few cases of pathogen resistance or *in vivo* degradation have been observed [6]. In addition, results have showed that natural antibiotics (e.g. mammalian defensins) are involved in modulating the immune response, not only by their antimicrobial activities, but also as important signaling molecules, implicated in different metabolic pathways [20]. These features make the antimicrobial peptides good candidates for the development of novel antiparasitic drugs and also as potential modulators of the immune response, which might be used in the future as immune-stimulating factors.

Conclusion

Biotechnology companies worldwide are developing novel antimicrobial drugs, based on natural peptides, which are directed mainly against bacterial and fungal infections. The reported *in vitro* activities of some antimicrobial peptides against parasites make them a powerful source of antiparasitic compounds. Their use for the development of a new generation of drugs for topic or systemic treatment of important parasitic diseases is a promising hope for the new century.

Acknowledgements

We thank Carl Lowenberger for his critical revision of this article. This work was supported in part by the Ministère Nationale de l'Enseignement, de la Recherche et des Technologies (MNERT), the Centre National de la Recherche Scientifique (CNRS) and the Agence Nationale de la Valorisation Regionale (ANVAR) Nord-Pas de Calais.

References

1 Borregaard, N. *et al.* (2000) Innate immunity: from plants to humans. *Immunol. Today* 21, 68–70
2 Salzet, M. (2001) Vertebrate innate immunity resembles a mosaic of invertebrate immune responses. *Trends Immunol.* 22, 285–288
3 Zasloff, M. (2002) Antimicrobial peptides of multicellular organisms. *Nature* 415, 389–395
4 Lehrer, R.I. and Ganz, T. (1999) Antimicrobial peptides in mammalian and insect host defense. *Curr. Opin. Immunol.* 11, 23–27
5 Hancock, R.E. (2000) Cationic antimicrobial peptides: towards clinical applications. *Expert. Opin. Investig. Drugs* 9, 1723–1729
6 Rivas, L. and Andreu, D. Cecropins and their hybrid peptides as versatile templates in the development of membrane-active antibiotic agents. In: *Pore-forming Peptides and Protein Toxins. Cellular and Molecular Mechanisms of Toxin Action.* (Menestrina, G. and Lazzarovici, P. eds) Harwood Academic (in press)
7 Gwadz, R.W. *et al.* (1989) Effects of magainins and cecropin on the sporogonic development of malaria parasites in mosquitoes. *Infect. Immun.* 57, 2628–2633
8 Boman, H.G. *et al.* (1989) Antibacterial and antimalarial properties of peptides that are cecropin-melittin hybrids. *FEBS Lett.* 259, 103–106
9 Rodriguez, M.C. *et al.* (1995) Effect of a cecropin-like synthetic peptide (Shiva-3) on the sporogonic development of *Plasmodium berghei*. *Exp. Parasitol.* 80, 596-604
10 Krugliak, M. *et al.* (2000) Antimalarial activities of dermaseptin S4 derivatives. *Antimicrob. Agents Chemother.* 44, 2442–2251
11 Shahabuddin, M. *et al.* (1998) *Plasmodium gallinaceum*: differential killing of some mosquito stages of the parasite by insect defensin. *Exp. Parasitol.* 89, 103–112
12 Vizioli, J. *et al.* (2001) Gambicin: a novel immune responsive antimicrobial peptide from the malaria vector *Anopheles gambiae*. *Proc. Natl. Acad. Sci. U. S. A.* 98,12630–12635
13 Conde, R. *et al.* (2000) Scorpine, an anti-malaria and anti-bacterial agent purified from scorpion venom. *FEBS Lett.* 471, 165–168
14 Akuffo, H. *et al.* (1998) *Drosophila* antibacterial protein, cecropin A, differentially affects non-bacterial organisms such as *Leishmania* in a manner different from other amphipathic peptides. *Int. J. Mol. Med.* 1, 77–82
15 Chicharro, C. *et al.* (2001) N-terminal fatty acid substitution increases the leishmanicidal activity of CA(1-7)M(2-9), a cecropin-melittin hybrid peptide. *Antimicrob. Agents Chemother.* 45, 2441–2449
16 Hernandez, C. *et al.* (1992) Functional and structural damage in *Leishmania mexicana* exposed to the cationic peptide dermaseptin. *Eur. J. Cell. Biol.* 59, 414–424
17 Silva, P.I. *et al.* (2000) Isolation and characterization of gomesin, an 18-residue cysteine-rich defense peptide from the spider *Acanthoscurria gomesiana* hemocytes with sequence similarities to horseshoe crab antimicrobial peptides of the tachyplesin family. *J. Biol. Chem.* 275, 33464–33470
18 Chalk, R. *et al.* (1995) *Brugia pahangi*: the effects of cecropins on microfilariae *in vitro* and in *Aedes aegypti*. *Exp. Parasitol.* 80, 401–406
19 Beard, C.B. *et al.* (2001) Bacterial symbiosis and paratransgenic control of vector-borne Chagas disease. *Int. J. Parasitol.* 31, 620–626
20 Salzet, M (2002) Antimicrobial peptides are signaling molecules. *Trends Immunol.* 23, 283–284

Jacopo Vizioli
Michel Salzet*
Laboratoire de Neuroimmunologie des Annélides, UMR CNRS 8017, SN3, IFR 118, Université des Sciences et Technologies de Lille, 59655 Villeneuve d'Ascq, France.
*e-mail: michel.salzet@univ-lille1.fr