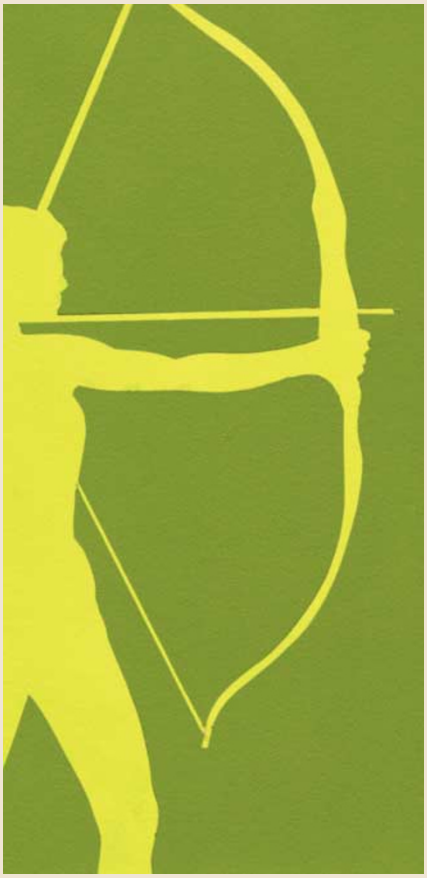
ANTI-INFECTIVES

Targeting SARS



A new study published in the *Proceedings of the National Academy of Sciences* (*USA*) has identified 15 compounds that are potent against the severe acute respiratory syndrome virus (SARS-CoV) in cell-based assays, including two drugs that are currently in use and several that are already in the clinical development pipeline.

The only available therapy for SARS-CoV is a combination of ribavirin and corticosteroids, which is effective — but only at concentrations that produce severe side effects. Since SARS was first isolated in 2002, it has caused more than 700 deaths worldwide, so finding effective antivirals for SARS is a priority.

High-throughput screening requires a simple and reliable assay system. Wu *et al.* used a cell-based assay to screen more than 10,000 compounds, all administered at 10 μM, for inhibition of virus cytopathic effects. From this primary screen, 50 compounds were selected for further analysis, first to determine if the compounds were cytotoxic and second to measure the concentration of the compound required to inhibit virus replication by 50% (EC_{50}).

The most potent inhibitor was valinomycin, a peptide insecticide with an EC_{50} of 0.85 μM. Aescin and reserpine, already in use in Europe and the United States, respectively, were also active against SARS-CoV, but neither drug is currently prescribed as an antiviral. Compounds that are structurally similar to reserpine and aescin were also screened, resulting in 10 new anti-SARS active compounds. Finally, a potent inhibitor of the HIV protease, TL-3, which is being developed as a treatment for AIDS in cats, was also effective against the SARS protease. These studies offer new hope for rapidly available SARS therapeutics.

Susan Jones

References and links

ORIGINAL RESEARCH PAPER Wu, C.-Y. *et al.* Small molecules targeting severe acute respiratory syndrome human coronavirus. *Proc. Natl Acad. Sci. USA* **101**, 10012–10017 (2004)

FURTHER READING Stadler, K. *et al.* SARS — beginning to understand a new virus. *Nature Rev. Microbiol.* **1**, 209–218 (2003)

WEB SITE

Wong laboratory: http://wong.scripps.edu/

INNATE IMMUNITY

Diverse defence

A report published in *Nature Immunology* presents the first detailed characterization of a new family of antimicrobial peptides in the mouse intestine.

Antimicrobial peptides are small, endogenous peptides containing <100 residues and are an important component of innate immunity.

So far, many different classes of antimicrobial peptides have been identified in mammals, including α-, β- and θ-defensins and cathelicidins. For more information on defensins in primates, see the review by Robert Lehrer on page 727 of this issue.

Hornef *et al.* were interested in a family of mouse-intestine-specific CRS (cryptdin-related sequence) peptides. CRS mRNAs have been characterized previously but the peptide products have never been characterized before. Using mRNA from intestinal tissue of healthy mice, Hornef *et al.* identified 15 new cDNAs encoding CRS peptides, bringing the total number of CRS peptide coding sequences to 23, comparable to the number of mouse α-defensin genes. Each CRS gene encodes a peptide containing a pro-region that is cleaved off during processing, leaving a mature cationic peptide containing nine conserved cysteines. Of the 15 new sequences identified, most of the sequence variation observed was in the pro-region, and so a total of 7 mature peptides were predicted by the coding sequences.

To screen for mature CRS peptides *in vivo*, whole mouse intestinal tissue was fractionated by reverse-phase HPLC. Analysis of the mass of fractions in the presence and absence of a reducing agent indicated the presence of dimers. To exclude the possibility that dimer formation was an experimental artefact, the extraction process was repeated in the presence of an alkylating agent that inhibits the formation of disulphide bonds. This confirmed that CRS peptides form covalent dimers *in vivo*. Six mature peptides were identified in a variety of homo- and heterodimers and, additionally, four peptides were also found in truncated form. Examination of the antibacterial activity of synthetic CRS dimers showed these agents had potent activity against bacterial species including *Salmonella enterica* serovar Typhimurium and *Streptococcus pyogenes*, with no cytotoxicity.

The complement of antimicrobial peptides varies from species to species. This study has revealed that in mice, the complement of CRS peptides matches that of the α-defensins in number, and perhaps also in potency. The ability to form hetero- and homodimers is a neat trick to expand the repertoire of intestinal peptide diversity and strengthen antimicrobial defence.

Sheilagh Clarkson

References and links

ORIGINAL RESEARCH PAPER Hornef, M. W. *et al.* Increased diversity of intestinal antimicrobial peptides by covalent dimer formation. *Nature Immunol.* **5**, 836–843 (2004)