

catalytic protease. This scheme also shows how protein degradation must be stringently balanced against unregulated hydrolysis.

Brötz-Oesterhelt *et al.* began with a 1985 US patent for a complex mixture of compounds with antibacterial activity against *staphylococci* and *streptococci*, as noted in the patent<sup>3</sup>. The authors purified the major component (ADEP 1) and determined its structure. They then developed a synthetic method to produce the compound, and tested it against drug-sensitive and drug-resistant Gram-positive bacterial strains.

One modified form of ADEP 1, ADEP 4, was 20–40 times more effective than ADEP 1 at killing bacteria *in vitro*. ADEP 4 also effectively killed bacteria in several rodent sepsis models of infection with *S. aureus* and *E. faecalis*; in these models, ADEP 4 worked just as well or better than linezolid.

The authors next tracked down how ADEP 1 operates. They isolated an ADEP 1-resistant strain of *Escherichia coli*. Using classical genetic methods, they found that resistance mapped to a single gene, the *clpP* gene, which encodes the ClpP protease. This finding suggested that ClpP was the ‘target’ of ADEP 1. In line with that idea, they showed that ADEP interacts directly with recombinant ClpP.

After ADEP binds ClpP, mayhem ensues. This interaction frees ClpP to operate with-

out being controlled by ClpA or ClpX, and to degrade intact, folded proteins. This is probably how ADEP kills the bacteria.

The identification of the bacterial proteasome as a ‘target’ for antibacterial compounds broadens our perspective of how to kill bacteria. Virtually all clinically useful antibacterial compounds inhibit essential bacterial functions—but ADEP hyperactivates an essential function, inducing widespread protein degradation.

The work also provides a lesson for the global pharmaceutical industry. In the 1960s and 1970s, antibiotic discovery was a productive area. Structurally unique compounds emerged that targeted bacterial protein synthesis (tetracyclines, aminoglycosides, macrolides and such), cell-wall biosynthesis ( $\beta$ -lactams and vancomycin) and DNA and RNA synthesis (fluoroquinolones and rifampicin). But resistance is inevitable, and many of these drugs are teetering on the abyss of ineffectiveness. The pharmaceutical industry seems to have lost its interest in antibacterial discovery<sup>8</sup>.

Chemical warfare has been waged for almost 1.5 billion years on planet Earth, as numerous microbes have competed for valuable resources in their ecological niches. In order to gain the upper hand, they have experimented with the synthesis of natural

products whose structural complexity is currently unknown—but which certainly dwarf any chemical collection in any storeroom on the planet.

In the glory days of antibiotic discovery, hundreds and perhaps thousands of bacteria were identified that secreted powerful antibacterial compounds into their environment. As more antibiotics were discovered and shown to be clinically useful, the desirability, or necessity, of discovering even more decreased. That is no longer the case.

Perhaps it is time to go ‘back to the future,’ and thoroughly reexamine the patent literature for compounds with demonstrated antibacterial activity. It may not be the compounds themselves that we seek, but new, unanticipated targets that can be explored for novel mechanisms of action.

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## Frog skin yields antiviral peptides

The tree frog *Litoria genimaculata* (pictured in its habitat in the Australian rainforest) is not an obvious choice of laboratory animal. But skin secretions of such amphibians could be a rich source of antimicrobial peptides with activity against HIV (*J. Virol.* **79**, 11598–11606).

Antimicrobial peptides are natural antibiotics, providing a first line of attack against microorganisms invading body fluids and skin. 880 such peptides have been isolated from species as diverse as spiders, scorpions, fruitflies and fish—and more than 20% are produced by the skin glands of frogs and toads.

Certain peptides such as human defensins are already known to have anti-HIV activity, but Scott VanCompernelle *et al.* explored whether any amphibian peptides would also block HIV infection. Screening a panel of 14 frog peptides, they found two that blocked HIV-1 infection of T cells, apparently by disrupting the viral envelope and preventing fusion with the target cell.

The peptides also had an unusual effect on infected dendritic cells. Dendritic cells are thought to capture and internalize HIV particles at mucosal surfaces, and then transfer the virus particles to T cells—the primary target of HIV infection. The frog peptides blocked this transfer—even when applied transiently to dendritic cells eight hours after HIV infection. How the peptides do this remains to be seen, but the study illustrates the largely untapped wealth of natural antimicrobial resources that could be explored for activity against human pathogens.



Courtesy of Douglas C. Woodhams

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