This MS technique is scalable but works on single molecules, meaning that it is suitable for detecting “scarce molecules—even in the presence of an abundant, interfering species,” Hanay continues. “It can be used both in a diagnostic setting and for basic research. In diagnostic settings, libraries for large bacterial proteins and single viruses will be compiled first, and these libraries will later be used to identify pathogens detected in a sample.”

“The work represents a considerable advance over previous NEMS-based mass spectrometry and offers a way forward to very sensitive biological assays,” says chemist Michael A. Morris of the University College Cork and the Centre for Research on Adaptive Nanostructures and Nanodevices at Trinity College; both are in Ireland. “The real excitement is generated by its ability to ‘sense’ and discriminate molecules of high molecular weight. This is a piece of work that might herald considerable advances in medical science and bring about dramatic changes in personal health care.”

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**RESEARCH ADVANCES**

**Promising Antimicrobials: Synthetic Molecules Based on Defensin Peptides**

Shannon Weiman

Nonpeptide defensin mimetics that act through host innate immune mechanisms are part of a novel strategy for combating drug-resistant microbes, according to Richard Scott, founder and Vice President of Research at PolyMedix of Radnor, Pa. Synthetic mimetics in this group target bacteria, fungi, and parasites with high selectivity, minimal cytotoxicity, and little risk of resistance, he says. Further, some of these mimetics are also effective against microorganisms in biofilms. He spoke during the symposium “Host Defense (Antimicrobial) Peptides: Major Players in Health and Novel Thera-

**MINITOPIC**

**Odds and Ends: Foods, Microbes, Guts Crossing Paths**

Here are some recent developments involving microorganisms, food products, digestive systems, and the like:

- The leaves of carob trees, whose pods are the source of a chocolate substitute, contain compounds with activity against *Listeria monocytogenes*, a foodborne pathogen, according to Nadhem Aissani of the University of Cagliari in Cagliari, Italy, and collaborators. Details appear in the September 14, 2012 *Journal of Agricultural and Food Chemistry* (doi: 10.1021/jf3029623).

- A “cocktail” containing six defined types of bacteria from the gastrointestinal tracts of mice can suppress *Clostridium difficile* and restore the microbial balance in such animals, according to Harry Flint, from the University of Aberdeen in Aberdeen, United Kingdom, and collaborators from several U.K. institutions. Details appear in the October 25, 2012 *PLOS Pathogens* (doi: ppat.1002995).

- Lactic acid bacteria programmed to make the protein elafin, which blocks proteases, can help to protect mice against colitis and symptoms associated with inflammatory bowel disease, according to Nathalie Vergnolle at INSERM in Toulouse, France, and her collaborators. Details appear in the October 31, 2012 *Science Translational Medicine* (doi: 10.1126/scitranslmed.3004212).

- A probiotic given in two doses daily and containing *Lactobacillus reuteri* NCIMB 30242 can lower levels of cholesterol-carrying molecules that circulate in the blood, according to Mitchell L. Jones of the Faculty of Medicine at McGill University in Montreal, Quebec, Canada, and a principal at nearby Micropharma, which funded the study. Jones presented his findings during the 2012 scientific sessions of the American Heart Association, convened in Los Angeles, Calif., in November.
peutics,” during the 2012 ICAAC, held in San Francisco last September.

Defensins are cysteine-containing peptides that are components of the innate immune system in both vertebrates and invertebrates. In humans, they are produced by skin, mucosal surfaces, and neutrophils as a first line of defense against microbes. As therapeutic products, however, they can be cytotoxic for mammalian cells. To counteract such effects, PolyMedix followed medicinal chemistry principles, building nonpeptide scaffolds with rigid cores and modifying side chains to improve microbial selectivity.

These efforts yield both narrow- and broad-spectrum antimicrobial agents that are bactericidal against both gram-positive and gram-negative bacteria, according to Scott. “Preclinical studies show that our defensin-mimetic compounds have activity against a number of biowarfare pathogens, including those that cause anthrax, plague, tularemia, listeriosis, and others,” he says. These agents are also effective against clinically important conventional pathogens, many of which are drug resistant, such as methicillin-resistant *Staphylococcus aureus* (MRSA).

The most advanced candidate drug, brilacidin, is under development as a systemic antibiotic and has successfully completed a phase II clinical trial in acute bacterial skin and skin structure infections caused by staphylococci. It is also being developed for topical use as a rinse for oral mucositis, a debilitating side effect of chemotherapy for which there is no specific treatment.

Other compounds in this set have potent antifungal activity, Scott says. For instance, PMX1502 is fungicidal against *Candida albicans* in animal infection models, unlike fluconazole, which is fungistatic. When treated with PMX1502, mice with systemic fungal infections show 100% survival compared to 40% when treated with fluconazole. Moreover, PMX1502 and another defensin mimetic compound, PMX519, are significantly more effective than the polyene antifungal drug Nystatin in treating oral candidiasis in mice.

Yet others among these nonpeptide candidates target tuberculosis and malaria, Scott says. The PolyMedix antimalaria candidate, for example, selectively disrupts the digestive vacuole of the parasite, improving mouse survival substantially.

Each of these selective antimicrobial candidate products is expected to be well tolerated in humans, based on findings from phase II clinical testing of brilacidin. Remarkably, microbes do not develop resistance to these agents when tested in serial passage assays, according to Scott. The compounds target and disrupt the microbial cell membranes, a process that seems less likely to lead to resistance mutations than targeting specific microbial proteins. Moreover, unlike conventional antibiotics, microbes have not developed resistance to defensins themselves despite their presence in innate immunity for hundreds of millions of years.