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Breast milk protein complex helps reverse antibiotic resistance

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A protein complex found in human breast milk can help reverse the antibiotic resistance of bacterial species that cause dangerous pneumonia and staph infections, according to new University at Buffalo research.

In petri dish and animal experiments, the protein complex—called Human Alpha-lactalbumin Made Lethal to Tumor Cells (HAMLET)—increased bacteria's sensitivity to multiple classes of antibiotics, such as penicillin and erythromycin.

The effect was so pronounced that bacteria including penicillin-resistant *Streptococcus pneumoniae* and methicillin-resistant *Staphylococcus aureus* (MRSA) regained sensitivity to the antibiotics they were previously able to beat, said researchers Anders Hakansson, PhD, Laura Marks, and Hazeline Hakansson, PhD, all in UB's Department of Microbiology and Immunology.

HAMLET's effects against *S. pneumoniae* were published in the journal *PLOS ONE* in August 2012 with Marks, Anders Hakansson and UB PhD student Emily Clementi as authors. HAMLET's effects on *S. aureus* will appear in *PLOS ONE* on May 1 at 5 p.m., and this press release is embargoed until that time. A graphic to illustrate this story is available at http://ubnews.smugmug.com/2013/hamlet-protein/.

"HAMLET has the potential minimize the concentrations of antibiotics we need to use to fight infections, and enable us to use well-established antibiotics against resistant strains again," said Anders Hakansson, lead

researcher and a UB assistant professor of microbiology and immunology who has long been interested in the protective effect of breast-feeding against infections.

The findings hold great promise in an era when hospitals are struggling to contain drug-resistant "superbugs" like MRSA, the culprit behind lethal hospital-acquired staph infections.

Bacteria seem to have difficulty developing resistance to HAMLET, dying in huge numbers even after being exposed to HAMLET for many generations.

Marks, an MD/PhD student in the UB School of Medicine and Biomedical Sciences' Medical Scientist Training Program, described another of HAMLET's benefits: "Unlike synthetic drugs, HAMLET is a naturally occurring human milk protein-lipid complex, and so is not associated with the types of toxic side effects that we so frequently see with the high-powered antibiotics needed to kill drug-resistant organisms."

The idea to test HAMLET in combination with other antibiotics was inspired, in part, by a presentation Marks saw on using drug cocktails to treat HIV.

"What really hit home for me in this lecture was the idea of using drug combinations where each drug had a different mechanism that could enhance the action of the other drug as an appealing way to optimize therapy for resistant organisms," she said. "I was immediately curious to see if using HAMLET together with existing therapies could result in synergistic interactions."

Findings of note:

- In lab experiments, HAMLET lowered the dose of antibiotics needed to fight *S. pneumoniae* and *S. aureus* by as much as a factor of eight or more.
- The effect was so pronounced that drug-resistant superbugs—including a strain of *S. aureus* insensitive to vancomycin, the "antibiotic of last resort"—regained sensitivity to antibiotics.
- Used together, HAMLET and antibiotics eradicated streptococcal and staphylococcal biofilms in petri dishes and deep in the noses of mice. This held true for strains previously resistant to antibiotics.

About HAMLET:

- Discovered during Hakansson's time in Catharina Svanborg's laboratory in Lund, Sweden, HAMLET has shown the ability to selectively kill both tumor cells and bacteria.
- In certain bacteria (including *S. pneumoniae* and *S. aureus*), HAMLET binds to and halts the activity of biological pumps and transporters that help regulate the flow of ions in and out of a cell. HAMLET also binds to and blocks the activity of two enzymes needed for glycolysis, a process bacteria use to obtain energy.
- In the bacteria it kills, HAMLET appears to spark a chain of chemical reactions that mirrors what happens in nature when bacterial cells self-destruct for the greater good of a bacterial community (a "biofilm"). This deadly process includes an influx of calcium and the activation of a serine/threonine kinase, and ends with cells rupturing.

What's next:

UB's Office of Science, Technology Transfer and Economic Outreach (STOR) has filed a provisional patent application detailing HAMLET's antibiotic capabilities, and Anders and Hazeline Hakansson have founded a company called Evincor to further develop HAMLET.

"The pharmaceutical industry is currently reluctant to develop antibiotics because they are only used for a short time and they will be used infrequently initially and only when nothing else works," Hazeline Hakansson said. "HAMLET, on the other hand, is more of an adjuvant and can be used widely in combination with common antibiotics; it already has a huge potential market that is only going to increase the next couple of years as antibiotic resistance increases.

"Some people estimate that it's only a question of time before we run out of antibiotics to combat bacteria," she continues.

"HAMLET is promising because we haven't been able to make bacteria resistant to it and it kills bacteria via a mechanism that is clearly different from that of commonly prescribed antibiotics."

The Hakanssons, a husband-and-wife team, say the next step is to test HAMLET on additional strains of *S. pneumoniae* and *S. aureus*—including those currently infecting patients—and to expand the in-vivo infection models used for testing to provide a proof of principle.

Provided by University at Buffalo