

## Old dogma, new tricks—21st Century phage therapy

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### Low hanging fruit—agricultural applications

Getting a phage-based human therapeutic to market means navigating some untested waters at FDA, but an easier commercial path exists for phage products. Bacterial contamination of foodstuffs is a multi-billion dollar problem affecting an estimated 76 million people annually in the US alone, according to the CDC. Bacteriophages could form the basis of products used to decontaminate food-processing plants, livestock and even farmers' fields. Getting such products to market generally means navigating the US Department of Agriculture (USDA; Washington, DC, USA) or the Environmental Protection Agency (EPA; Washington, DC, USA), which have lower regulatory hurdles to product approval. The FDA would not regulate such phage products unless they are used directly on foodstuffs.

Several phage companies are hoping some of these agricultural and environmental applications will turn out to be low-hanging fruit that will create a revenue stream to fund research into human therapeutics. At GangaGen, Janakiraman Ramachandran says his company hopes to have its first product, a phage that kills *Escherichia coli* 0157:H7 in manure, on the market in about 18 months. Manure, used as fertilizer, can contaminate groundwater if the manure comes from infected cattle. In May 2000, for instance, over 2,000 people in the farming community of Walkerton, Ontario (Canada) were made ill and seven died as a result of *E. coli* infection ultimately linked to a contaminated well.

Manure used as fertilizer is typically collected and liquefied before use; GangaGen is hoping to include an extra step in which phages that kill *E. coli* are added to the mix. The exponential reproduction of phage particles will make it possible to treat large vats of manure with relatively modest amounts of phage. The company has a subsidiary in Ottawa, Ontario, dedicated to agricultural and environmental phage R&D.

Biophage Pharma (Montreal, Quebec, Canada) is likewise working on phage products to combat *E. coli* as well as *Salmonella typhimurium*, says CEO Elie Farah. The company intends its products to be used in live animals and, in the case of *E. coli*, on carcasses before meat processing. That's particularly important for the processing of ground beef, since meat trimmings from different carcasses are combined as beef is ground, and *E. coli* from one contaminated carcass can be spread to a large amount of meat.

Intralytix, meanwhile, is concentrating on products that could be used to decontaminate food-processing facilities. In June 2002, the company received an experimental use permit from the EPA to test a phage preparation called LMP-102, active against *Listeria monocytogenes*, on nonfood contact surfaces. There are about 2,500 cases of listeriosis in the United States each year, 20% of which are fatal. Because of the seriousness of the illness, the USDA has a strict zero-tolerance policy on the bacterium in ready-to-eat foods; the detection of *L. monocytogenes* in deli meat in October 2002 was responsible for the biggest meat recall in US history.

LMP-102 has been used successfully in pilot tests in a few facilities, according to Alexander Sulakvelidze. The company, however, does not have a firm time line for commercialization. Intralytix has also asked FDA for permission to experimentally use the same preparation directly on foodstuffs, he adds. **Even Exponential Biotherapies, furthest ahead in developing human therapeutics, has a food safety R&D program, with a particular focus on *L. monocytogenes* and *Campylobacter jejuni*, a microbe commonly found in chicken. Though not considered deadly, *C. jejuni* is the leading cause of bacterial diarrhea in the United States.**

"One advantage of this approach is that the same phage can be used in cattle, swine, manure and even humans," says GangaGen's David Martin. "The issue is formulation and dose, but the active agent is the same."