

MINISTRING THEORY IN PRACTICE

BY MICHAEL LEVITEN, SENIOR WRITER

Mediphage Bioceuticals Inc.'s ministrings have safety, manufacturing and other advantages that could give conventional plasmids and related vectors a run for their money in the gene therapy space.

The newco's ministrings are linear DNAs with covalently closed ends. Like conventional plasmids, they can deliver 15-20kb of DNA -- up to five times the payload of viral vectors -- and are easily manufactured in bacteria. But ministrings lack prokaryotic sequences that silence therapeutic cargo, so they express the therapeutic gene longer and require less frequent dosing, said founder and CSO Roderick Slavcev, an associate professor of pharmacy at the University of Waterloo who invented the technology.

Ministring manufacturing uses a bacterial strain with an inducible bacteriophage telomerase that cuts the ministring from the plasmid and modifies the DNA ends, yielding a covalently closed molecule devoid of prokaryotic DNA. The one-day process was **disclosed** in 2016 in the *Journal of Visualized Experiments*; the newco has licensed the IP from Waterloo.

Slavcev's lab has also shown ministrings result in higher target gene expression *in vitro* and transfect 90-95% of cells vs. 40-70% for plasmids and minicircles.

While his team originally selected closed molecules for their higher activity, it found the closed ends also suppressed chromosomal insertions. A 2014 *Molecular Therapy - Nucleic Acids* from Slavcev's lab showed ministrings integrate into chromosomes with very low frequencies; but when they do, they break chromosomes to induce apoptosis.

This built-in suicide switch makes ministrings safer than plasmids, which should be a boon to young gene therapy patients who need repeated dosing as they grow, Slavcev said. Mediphage will conduct repeat-dose studies in undisclosed animal models in the next two months.

The newco is collaborating with Precision Nanosystems Inc. to develop nanoparticles for ministring delivery. Mediphage is also developing a pipeline of iPHAGEs, which are ministring-encoded therapies delivered with a bacteriophage. Its first iPHAGEs are in development for colorectal cancer and Alzheimer's disease, with IND submission expected in about two years.

At least two other companies, Generation Bio Co. and Mologen AG, have closed linear delivery systems for gene therapies and other genetic medicines

Generation Bio uses an episomal closed-ended DNA (ceDNA) vector (see "**Going Non-Viral**"). Slavcev said ceDNA contains inverted terminal repeats (ITRs) that permit insertional mutagenesis and so lack the kill switch ministrings have.

Generation Bio President and CEO Geoff McDonough told Biocentury ceDNA is likely to lead to less integration than adeno-associated viral (AAV) vectors, but the company hasn't directly compared AAV and ceDNA integration.

Slavcev also said ministrings are cheaper and easier to manufacture than Mologen's Midge (minimalistic immunogenically defined gene expression) vectors, which are closed linear molecules like ministrings but made *in vitro*. "You make a plasmid and cut it, then ligate oligos. There are a lot of enzymes and it's expensive."

Mologen spokesperson Claudia Nickolaus said "the Midge GMP process is a generic, high-standard, safe, fast and easily scalable procedure and does not involve any living cell, any microorganisms or viruses."

Mediphage has signed material transfer agreements (MTAs) with at least 10 companies to validate the platform, after which it aims to partner the tech with companies developing genetic medicines, including enzyme replacement (ERT) gene therapies.

In April, Mediphage joined Illumina Inc.'s Illumina Accelerator. In addition to space, equipment and access to capital, Illumina will match investments if the newco raises \$1-\$5 million during the six-month agreement.

COMPANY PROFILE

Mediphage Bioceuticals Inc., Toronto, Ontario

Technology: Ministring delivery vectors for gene therapies

Disease focus: Cancer, neurology

Clinical status: Preclinical

Founded: 2016 by Roderick Slavcev

University collaborators: University of Waterloo

Corporate partners: Illumina Inc., Precision Nanosystems Inc.

Number of employees: 3

Funds raised: C\$1.1 million (\$837,000)

Investors: Wing VCs, MITACS, NRC, University of Waterloo, undisclosed private individuals

CEO: Roderick Slavcev

Patents: 1 issued covering ministring DNA and rapid *in vivo* production system

COMPANIES AND INSTITUTIONS MENTIONED

Generation Bio Co., Cambridge, Mass.

Illumina Inc. (NASDAQ:ILMN), San Diego, Calif.

Mediphage Bioceuticals Inc., Toronto, Ontario

Mologen AG (Xetra:MGN), Berlin, Germany

Precision NanoSystems Inc., Vancouver, B.C.

University of Waterloo, Waterloo, Ontario

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