Thinking small to stop superbugs

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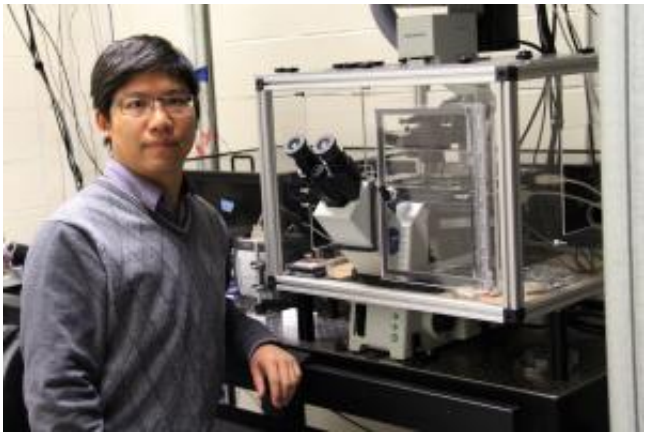

With the help of cutting edge microscopy, new research at U of T Mississauga could help stop "superbugs" in their tracks.

The Milstein Lab is taking a very close look at bacterial cells in hopes of figuring out how to stop the spread of antibiotic-resistant bacteria known as CRE or carbapenem-resistant Enterobacteriaceae. Dubbed the "nightmare bacteria," CRE infections are immune to even the strongest antibiotics and have the ability to transfer that drug resistance to other bacteria.

There are thousands of documented cases of superbugs in North America every year, and that number is rising. The infections, which can lead to pneumonia, sepsis, meningitis and more, have a 50 per cent

mortality rate. "That's worse than Ebola," says assistant physics professor Joshua Milstein. "We have to start investing in new approaches beyond antibiotics."

That's where the research of post-doctoral fellow Yong Wang comes in. Wang joined the Milstein Lab in July 2014 after winning a coveted three-year fellowship from the Human Frontier Science Program, which supports international collaborations in interdisciplinary research.

Wang is studying the behaviour of plasmids—circular strands of DNA containing foreign genes absorbed from other bacteria and viruses or from the environment—throughout the life cycle of the cell. To prevent harm to itself, bacterium can shut the genes off through a process called "xenogeneic silencing" that acts like a basic immune system, however, the genes may turn on again in the future. According to Wang, this process can result in strains of infection that are both more resistant and more virulent, turning the bacterium into a dangerous "superbug."

"We're studying that pathenogenisis—how the bacteria get this foreign DNA and how it eventually gets turned on," Milstein says. "If we can figure out how these things propagate, maybe we could figure out how to stop these things from propagating."

At the forefront of this research is a new technique called super-resolution imagery, At the forefront of this research is a new technique called super-resolution microscopy. Pioneered by the 2014 Nobel Prize winners in physics, this powerful microscopy is key to the lab's research. "It's an important technique that's driving a lot of the field at the moment," Milstein says.

With previous technology, researchers were unable to see fine details within small bacterial cells, however super-resolution microscopy lets researchers see very fine details, making it possible to watch the

complex behaviour of plasmids.

The technology doesn't come cheap—commercial versions run about $1-million—however the Milstein lab built its own microscope in 2012, using parts sourced on e-Bay, to create a DIY microscope for one-tenth that amount.

"With super-resolution imaging, you can image inside a bacteria and see things you could never see in the past," says Milstein. "Now we start to get these spectacular images."

The technology allows researchers to see an amazing level of detail within the cell, which will give researchers a boost when it comes to understanding how the bacteria replicate. The new microscope also lets Wang observe living cells, an important component of understanding plasmid activity. "We want to be able to track these plasmids as they move in a cell, says Wang. "We can watch a cell divide and see what it does next."

Wang hopes his research will lead to a quantitative understanding of how bacterial cells distribute plasmids during cell division. "If we understand that correctly, we hope to develop therapies or strategies to interfere with its propagation."

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