'Failed' experiment yields a biocontrol agent that doesn't trigger antibiotic resistance

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A failed experiment turned out to be anything but for bacteriologist Marcin Filutowicz. As he was puzzling out why what should have been a routine procedure wouldn't work, he made a discovery that led to the creation of a new biological tool for destroying bacterial pathogens - one that doesn't appear to trigger antibiotic resistance.

The discovery also led to the startup of a promising new biotechnology firm that has already brought Wisconsin a dozen new, high-paying, highly skilled jobs. Filutowicz is a professor of bacteriology in the University of Wisconsin-Madison College of Agricultural and Life Sciences.

His inspiration came one morning in 1999 when he was puzzling over a failed experiment. A researcher in his lab had been trying to insert two different mutations into an ordinary bacterial plasmid - a routine task for the experienced scientist - but every attempt failed to produce a live bacterium.

Plasmids are circular DNA molecules that are different from chromosomal DNA, the genetic material that encodes the instructions for life in all cells. Plasmids are small, non-chromosomal DNA molecules. They are common in bacteria. The genes in plasmids often encode information that confers some selective advantage to their hosts - such as the ability to resist antibiotics.

Plasmids are useful tools for genetic engineering. It is relatively easy for a scientist to alter a plasmid's genetic makeup and then transfer the plasmid into a bacterium. The host bacterium then replicates the recombinant plasmid and transfers copies of it to other bacteria in a process called conjugation.

As he investigated the failed experiment, Filutowicz - who has spent two decades studying how plasmid replication is regulated - made a critical observation. A plasmid with one or the other of the benign mutations persisted, although it replicated a little more frequently than a mutation-free plasmid. How could it be, he wondered, that a bacteria with both mutations could not survive? The professor surmised that when the two mutations were brought together, the plasmid carrying them became harmful by over-replicating within the bacterium, ultimately destroying it.

"And I thought, this is very cool!" recalls Filutowicz. "I didn't observe any survival or further resistance to over-replication, even though typically when bacteria are exposed to harmful agents like antibiotics, resistant strains emerge. Nothing with the killer plasmid survived."

The next step was to engineer a strain of bacteria that could suppress over-replication of the key plasmid. This so-called "Trojan horse" could then be used to spread the killer plasmid via conjugation to targeted bacterial pathogens that lacked the ability to resist over-replication.

"We harnessed this plasmid," thought Filutowicz. "Now, how can we use it?" The answer came in 1999, when he filed a disclosure through the Wisconsin Alumni Research Foundation, which patents the discoveries of UW-Madison researchers and licenses technology to industry. Filutowicz believed so strongly in the potential of the basic work done in his lab that he, along with professor of oncology Richard Burgess, started a company called ConjuGon - "because you conjugate and it's gone!" -- to develop the technology and ultimately bring it to human trials, which are currently planned for 2007 or 2008. A patent for his discovery has just been issued.

"We see a broad application for this work," he explains. "We can build things that don't exist in nature. It's a versatile concept that doesn't apply to just one antimicrobial agent."

Filutowicz and Burgess, wine enthusiasts who are as comfortable fermenting grapes as they are transforming bacterial plasmids, partnered with students from the Weinert Applied Ventures Program at the UW-Madison School of Business to develop a plan for ConjuGon. One of the students, Sal Braico, ultimately became Chief Operating Officer of the company. "Sal learned about biology and got experience with a start-up, and Dick and I got business expertise. It was a great partnership," Filutowicz says.

In addition to federal funding from the National Science Foundation and the Department of Defense, the company has also attracted so-called angel funding from outside investors. Filutowicz and Burgess are not on the payroll of the research park company themselves, but they are proud that ConjuGon employs other people and has created 12 high-paying and highly skilled jobs for the Madison area.

Because of that, says Filutowicz, ConjuGon is helping to ensure the future of microbial sciences at the UW-Madison.

"We have one of the largest and most prominent communities of microbiologists in the country on the UW-Madison campus," he says. "It's important to provide jobs and opportunities in Madison for people who train here."

And beyond helping to expand Wisconsin's booming biotechnology sector, success at ConjuGon will ultimately help nurture future scientific innovations from the university.

"Because WARF is the licensor of my patent, and the company is a licensee, ConjGon, if successful, will ultimately support more UW research," Filutowicz explains.

A powerful, long-reaching impact - all from an idea that originated in a failed experiment.

Source: University of Wisconsin-Madison

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