WHEN REPLICATION RUNS AWRY

Tuberculosis kills more than a million people each year. The World Health Organization says it's the leading cause of death from a single infectious agent — more deadly than HIV/AIDS.

One reason TB is so dangerous is that, out of the 10 million or so infections that arise each year, roughly 500,000 are from drug-resistant *Mycobacterium tuberculosis* – bacteria immune to physicians' first, and sometimes second, choice of antibiotics.

M. tuberculosis' ability to mutate and evolve drug resistance is poorly understood. It's a problem that naturally interests Dr. Eric Josephs, whose research centers on mutation.

Most organisms use an ancient molecular proofreading mechanism called DNA mismatch repair. As strands of DNA are replicated in the process of cell generation, mismatch repair reads each new string and, if it finds mistakes, fixes them.

"Almost every organism on the planet has the same proofreading mechanism, except for bacteria related to tuberculosis," says Josephs, an assistant professor at the Joint School of Nanoscience and Nanoengineering. "They appear to have a weird, independently-evolved proofreading mechanism suggestive of mismatch repair. But people don't know what proteins are involved or how it works."

Understanding that mechanism, and what turns it off and allows drug resistance to evolve, could one day unlock new treatments for TB and other diseases.

As a postdoc, Josephs used nanoscale techniques to study mismatch repair and mutation. A year after arriving at UNCG, he received a $291,000 grant from the National Institute of Allergy and Infectious Diseases to apply those same techniques to TB bacteria.

The R21 grant supports early stage research with potential to create transformative breakthroughs. Josephs' mutation research has implications not only for drug-resistant TB, but also for other diseases.

"Proteins involved in mismatch repair can malfunction and cause cancers," Josephs says. "They can also influence the onset of Huntington's disease and a number of neuromuscular diseases."

This year, Josephs also won a $1.7 million NIH R35 Maximizing Investigators' Research Award, a grant designed to support outstanding researchers early in their careers.

The funding will support a wide-ranging exploration of the mechanisms of mutation and mutation avoidance. Josephs hopes his work will shed further light on how diseases work and point the way to new potential treatments.

"New understanding about genetic mutation can be applied broadly to a number of different disease systems," he says.

The work could also have other applications in biotechnology and agriculture, where the ability to engineer changes in an organism's genetic makeup is critical.

By Mark Tosczak • Learn more at go.uncg.edu/josephs

Josephs' work on strategies to prevent accidental CRISPR mutations in the wrong genes was recently published in leading international journal "Nature Biotechnology." CRISPR is a molecular tool that enables scientists to introduce "targeted" mutations into specific genes in living organisms; many researchers think it holds the key to new disease treatments. "Preventing unwanted mutations," he explains, "is critical for future therapeutic applications."