Researchers discover new way to attack some forms of leukemia

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Each year, some 29,000 adults and 2,000 children are diagnosed with leukemia, a form of cancer that is caused by the abnormal production of white blood cells in the bone marrow. Current treatments rely primarily on killing the cancer cells, which also destroys normal cells. But what if a way could be found to reprogram cancerous cells back into normal cells? A team of Syracuse University researchers believes it may have found a way to do just that.

Led by Michael Cosgrove, assistant professor of biology in SU's College of Arts and Sciences, the team discovered a way to disrupt the protein switch that is a critical component in the process to create white blood cells. Its discoveries could lead to a more effective way to treat some forms of leukemia and revolutionize the approach to treating other forms of cancer. The research was recently published online in the prestigious *Journal of Biological Chemistry* of the American Society for Biochemistry and Molecular Biology, and is forthcoming in the print edition.

"We believe our discovery is just the tip of the iceberg," Cosgrove says. "Our hope is that from the knowledge we have gained in understanding how these proteins work in normal cells, we will be able to find new ways to treat all types of leukemia. We also think the discoveries will have broad implications in treating other types of cancer."

To understand how white blood cells are produced, one must begin by looking at the genetic code, the DNA, which provides the blueprint for

all the life processes that are carried out in cells throughout the body. All of the cells in the body begin as stem cells with the same DNA. If stretched out in one continuous strand, this genetic blueprint would be about two meters long (about six feet), yet cells somehow manage to compact this rather long DNA strand into its nucleus without tangling or disrupting the exact DNA sequence. "It's sort of like stuffing 10,000 miles of spaghetti into a basketball without it tangling or breaking," Cosgrove says. What differentiates a liver cell from a blood cell is how that DNA is compacted or packaged in the cell nuclei, which results in different genes being expressed and leads to the production of specialized cells (white blood cells, liver cells, pancreatic cells, etc.). Proteins control this DNA packaging process.

Cosgrove's research team has spent the past three years studying one of the proteins that regulate the way DNA is packaged when white blood cells are formed. The protein is called the Mixed Lineage Leukemia (MLL) protein. In normal cells, the MLL protein, which contains 3,969 amino acids, combines with three other proteins to create a molecular switch that controls the DNA packaging events required for the formation of white blood cells. In some types of leukemia, the MLL switch is broken, which prevents white blood cells from maturing properly, resulting in a dangerous proliferation of immature white blood cells.

Cosgrove's team identified a tiny component of the MLL protein—a peptide sequence that contains just six amino acids—that is responsible for assembling the MLL molecular switch in normal cells. The team members called this peptide sequence the "Win" motif. They discovered that a synthetic version of this peptide acts like a drug that breaks apart the MLL molecular switch, interrupting a critical enzymatic process that is required to produce white blood cells. When used against an MLL molecular switch that is broken—working too fast—the peptide drug attacks the protein switch and breaks it apart, which may slow or stop

the production of the abnormal white blood cells. This drug may help to reprogram the way DNA is packaged in leukemia cells and help convert the abnormal cells back into normal cells.

"Reprogramming the way DNA is packaged in cancerous cells is a new idea that has the potential to lead to better treatments with fewer side effects," Cosgrove says. "This last year has been fantastic. We have been learning something new about these proteins almost on a daily basis. Our hope is that as we continue to understand how these DNA packaging proteins work, we will find new ways to treat all types of leukemia as well as other diseases."

Source: Syracuse University