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Daisies lead scientists down path to new leukemia drug

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A new, easily ingested form of a compound that has already shown it can attack the roots of leukemia in laboratory studies is moving into human clinical trials, according to a new article by University of Rochester investigators in the journal, *Blood*.

The Rochester team has been leading the investigation of this promising therapy on the deadly blood cancer for nearly five years. And to bring it from a laboratory concept to patient studies in that time is very fast progress in the drug development world, said Craig T. Jordan, Ph.D., senior author of the Blood article and director of Translational Research for Hematologic Malignancies at the James P. Wilmot Cancer Center, at the University of Rochester Medical Center.

Clinical trials are expected to begin in England by the end of 2007. Investigators expect to initially enroll about a dozen adult volunteers who've been diagnosed with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) or other types of blood or lymph cancers, Jordan said.

Under development is dimethylamino-parthenolide (DMAPT), a form of parthenolide (PTL) that is derived from a daisy-like plant known as feverfew or bachelor's button. DMAPT is a water-soluble agent that scientists believe will selectively target leukemia at the stem-cell level, where the malignancy is born. This is significant because standard chemotherapy does not strike deep enough to kill cancer at the roots, thus resulting in relapses. Even the most progressive new therapies, such

as Gleevec, are effective only to a degree because they do not reach the root of the cancer.

DMAPT appears to be unique. It's mechanism of action is to boost the cancer cell's reactive oxygen species – which is like pushing the stress level of the cell over the edge – to the point where the cell can no long protect itself and dies, said Monica L. Guzman, Ph.D., the lead researcher on the DMAPT project and a senior instructor at the University of Rochester Medical Center.

Leukemia is different from most cancers and particularly hard to eradicate because leukemia stem cells lie dormant. Standard cancer treatments are designed to seek out actively dividing cells. But in studies so far, DMAPT can kill both dormant cells and cells that are busy dividing, Guzman said

Rochester investigators looked at whether DMAPT could eliminate leukemia in donated human cells, and in mice and dogs. In all cases, DMAPT induced rapid death of AML stem and progenitor cells, without harming healthy blood cells.

DMAPT also has shown potential as a treatment for breast and prostate cancer, melanoma, and multiple myeloma, Guzman said, although those studies have only been conducted in cell cultures to date.

"Once we begin seeing evidence from the clinical trials, it will give us more insight into the pharmacological properties of DMAPT and it will be easier to figure out its potential for other cancers," Guzman said.

In addition to the studies of DMAPT, Guzman and Jordan also reported in the same issue of Blood on another new type of leukemia drug known as TDZD-8. Although this agent is at a much earlier stage of development, it also shows the ability to kill leukemia stem cells and

may some day lead to better forms of treatment.

Source: University of Rochester Medical Center