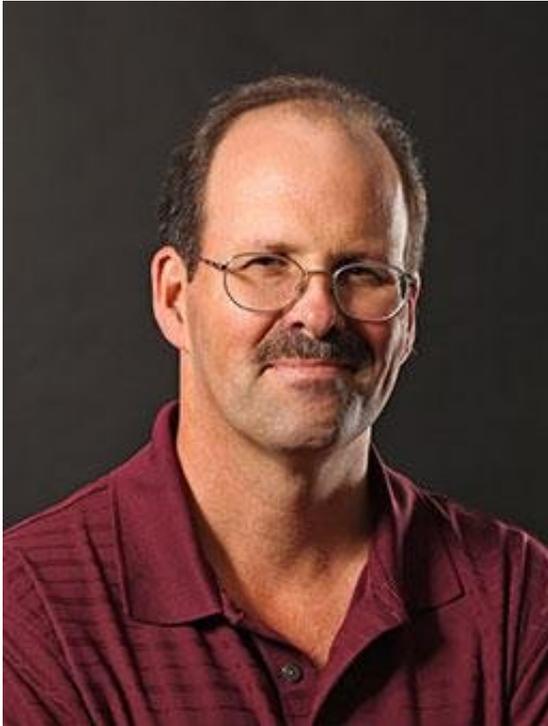


New combination treatment targets pre-leukemia stem cells

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Craig T. Jordan and colleagues characterize and target pre-leukemia stem cells. Credit: University of Colorado Cancer Center

Your body's blood cells are manufactured by hematopoietic stem cells in bone marrow. But just as regular, mature cells can become cancerous, so too can stem cells. When hematopoietic stem cells mutate in specific ways, the result can be damaged stem cells that create a type of pre-leukemic condition known as myelodysplastic syndrome, or MDS. On its own, MDS is a chronic condition that results in symptoms like anemia. In early stages, MDS can usually be managed with supportive care. However, as the disease progresses, about one in three cases of high-risk MDS will evolve into acute myeloid leukemia (AML), an extremely dangerous form of blood cancer that can be lethal.

There is no perfect treatment for MDS—current

strategies include chemotherapy, which tends to be ineffective against cancer [stem cells](#), and bone marrow transplant, which requires lengthy hospitalization, can include significant and lasting side effects, and is not appropriate for most MDS patients who tend to be older or more frail. A University of Colorado Cancer Center study published today in *Nature Communications* takes aim at the stem [cells](#) that create MDS and, eventually, AML. The study shows that MDS stem cells dramatically increase their energy use and production of proteins. And it shows that drugs that target these processes result in the death of MDS stem cells, while leaving healthy [blood stem cells](#) unharmed.

"Current treatments for MDS are not designed to specifically target the malignant stem cells. This makes treatment much like mowing over weeds without killing the root. Patients can achieve some benefit from chemotherapy, but eventually the MDS stem cells drive progression of the disease," says Craig T. Jordan, Ph.D., investigator at CU Cancer Center, Chief of the Division of Hematology and the Nancy Carroll Allen Professor of Hematology at the CU School of Medicine.

The story starts with a [protein](#) called CD123. Previous work has shown that AML stem cells tend to be coated with CD123. The study's lead investigator and first author Brett Stevens, Ph.D., proposed that CD123 might also be detectable in patients with MDS, and therefore act as way to distinguish MDS stem cells from normal stem cells. In a series of laboratory studies, Stevens also showed that stem cells with CD123 have unique properties.

Genes rarely function alone and instead are members of "pathways" that have certain larger functions. To zoom out from the level of genes to the level of pathways, Stevens, Jordan and colleagues used a technique called gene set enrichment analysis to cluster the genetic changes

they saw in CD123+ cells by their function.

"This let us explore not just what is turned on and off, but what these adjustments do, functionally, for the cell," Stevens says.

The major pathway magnified in CD123+ cells was one driving the action of ribosomes. Ribosomes make proteins, and the genetic changes in CD123+ cells meant that ribosomes in these cells were making far more proteins than they should. Interestingly, these pre-[leukemia stem cells](#) were making many more proteins without making many more cells. This is important because chemotherapy is designed to kill rapidly-dividing cells. These CD123+ pre-leukemia stem cells are not rapidly-dividing, and so they resist chemotherapy.

Another significantly magnified pathway in CD123+ cells had to do with energy. In cells, mitochondria use a process called oxidative phosphorylation to make ATP, which is the major unit of cellular energy. The more oxidative phosphorylation, the more ATP. And in CD123+ stem cells, there was much more oxidative phosphorylation.

Here is the important part: While CD123 is not directly druggable, the pathways of increased protein production and oxidative phosphorylation are.

Omacetaxine mepesuccinate is a protein synthesis inhibitor, FDA approved to treat chronic myeloid leukemia. When the group treated CD123+ stem cells with omacetaxine, it blocked protein production in these cells and the cells died.

"We have seen the usefulness of omacetaxine in CML and even hints of its activity in AML, and now we may see why this drug works. It looks like omacetaxine stops the protein synthesis that CD123+ stem cells need to live," Jordan says.

Secondly, the group targeted oxidative phosphorylation, the process that CD123+ stem cells were using to boost ATP production. As with protein synthesis, drugs exist to block oxidative phosphorylation. One of these drugs is venetoclax. Venetoclax blocked oxidative phosphorylation and

killed most but not all patient samples of CD123+ stem cells.

When the group added omacetaxine (to block protein synthesis) to venetoclax (to block oxidative phosphorylation), the combination was highly effective against CD123+ leukemia stem cells. Importantly, because it is only these pre-leukemic stem cells and not healthy stem cells that rely on protein synthesis and [oxidative phosphorylation](#), it is only these cancerous cells and not healthy cells that are killed. Both drugs are already FDA-approved for use in human patients, raising the possibility of immediate use.

"We see not only that this combination works, but why it works. We hope that omacetaxine and venetoclax will be a potent combination against advanced MDS," Jordan says.

More information: Brett M. Stevens et al, Characterization and targeting of malignant stem cells in patients with advanced myelodysplastic syndromes, *Nature Communications* (2018). [DOI: 10.1038/s41467-018-05984-x](https://doi.org/10.1038/s41467-018-05984-x)

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