

## NIH Grants Support Reformulation of Chemotherapy Drug that May Treat Blood and Solid Cancers, as well as Other Diseases such as Sickle Cell Anemia and Related Disorders



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Cleveland Clinic has received two grants from the National Institutes of Health to develop a new formulation of the chemotherapy drug decitabine (DACOGEN®) that in vitro research shows can kill cancer cells without harming normal cells.

Leading this drug development research project is Yogen Sauntharajah, MD, Cleveland Clinic Taussig Cancer Center, Hematologic Oncology and Blood Disorders. In 2003, he was the principal investigator of a clinical study at the University of Illinois in Chicago that found decitabine might be an effective alternative medication to treat sickle cell anemia patients who do not respond to hydroxyurea, the standard drug treatment.

For years, decitabine has been used as a chemotherapy drug and is classified as a demethylation and antimetabolite agent. In the early 1980s, other researchers found decitabine had the ability to deplete the enzyme, (cytosine-5-)methyltransferase 1, also known as DNMT1.

“DNMT1 has a context-specific function in the DNA of the cell,” says Dr. Sauntharajah. “It has a role in normal cells but the opposite role in cancer cells. When we deplete DNMT1, the normal cells proliferate. In cancer cells, however, the depletion of DNMT 1 will terminate a cancer cell after one or two cell divisions.”

Because in vitro research also shows normal cells are not adversely impacted by the depletion of DNMT1, this means decitabine has the potential of not triggering the debilitating side effects that come with traditional chemotherapy treatment.



Nevertheless, when decitabine is medically administered in high dosages, it can produce side effects in patients. Currently, the drug is given in high doses intravenously to patients with myelodysplastic syndrome (MDS).

The NIH grants, valued at about \$2.6 million, will support research to develop a new formulation of decitabine that will not be toxic to normal cells, which will eliminate the debilitating side effects for patients.

“We envision that we will be able to administer the new formulated decitabine in a lower dose pill format that would be taken orally by the patient two to three times a week,” Dr. Sauntharajah explains. “Our research also will include the pharmacogenomics factors to address the influence of genetic variation of decitabine’s response in patients, the drug’s safety and efficacy and the mechanisms by which cancer cells may become resistant to decitabine.”

Additionally, the NIH grants will support collaborative research with Joseph DeSimone, PhD, of the University of Illinois, to advance molecular research of decitabine for sickle cell anemia and blood disorders related to this disease.

“We’re very excited and optimistic that decitabine may become the next breakthrough treatment for sickle cell anemia, and related diseases like thalassemia,” says Dr. Sauntharajah. “We also think it is going to be a very important drug for blood and solid cancers. Our initial work will focus on blood cancer, but in collaborating with Brian Rini, MD, Cleveland Clinic Taussig Cancer Institute Solid Tumor Oncology, we are going to demonstrate decitabine’s role in solid cancer.”

The drug development research and subsequent clinic trials are expected to take about three to five years to complete.