Quinacrine, an old antimalaria drug given to millions of soldiers during World War II, is garnering new interest as a chemotherapeutic agent that targets two major cancer-promoting pathways—apparently with minimal toxicity to normal cells. Interest in the drug’s mechanism of action has also spawned a search for structural analogues culminating in a new class of compounds, dubbed curaxins, which appear to mimic how quinacrine works.

Recent studies in Wafik El-Deiry’s lab at the University of Pennsylvania with human colorectal and hepatocellular carcinoma show that quinacrine works synergistically with stalwarts of the chemotherapy arsenal as well as the newer targeted therapy sorafenib to delay tumor growth.

In particular, El-Deiry noted a set of experiments he and his colleagues published in The Aug. 1, 2011 issue of the Aug. 1, 2011, issue of Experiments. The group screened for small molecules that were also discovered to have medicinal properties a century ago. Quinacrine was used as an antibacterial agent until the advent of penicillin, and quinacrine is still used in the U.S. to treat intestinal parasites such as Giardia. Its widespread use by soldiers in the 1940s as a malaria prophylactic allowed for extensive follow-up testing for toxicity. Once its safety was confirmed as well as its anti-inflammatory properties, quinacrine was used experimentally to treat autoimmune disorders such as systemic lupus erythematosus.

Within the last decade, researchers have studied quinacrine’s mechanism of action in cancer cells at the molecular level and in animal studies. In 2005, a group from the Cleveland Clinic Foundation demonstrated that the aminoacridines, and in particular quinacrine, can restore the activity of the master tumor suppressor p53 in renal carcinoma cells through a mechanism that simultaneously suppressed activation of the cancer-promoting growth regulator NF-κB.

In 2007, a group led by Carter Van Waes, M.D., Ph.D., chief of the Head and Neck Surgery Branch at the National Cancer Institute, published results of a study showing that quinacrinerestored p53 activity and cisplatin sensitivity in a panel of nine well-characterized, p53-deficient head and neck squamous cell carcinoma lines in vitro.

Further study in animals failed to replicate the results of the laboratory work, but Van Waes attributes that result in part to quinacrine’s tendency to concentrate in the intestine, liver, and skin.

“The evidence that quinacrine synergizes with cisplatin provides some evidence that the effects of quinacrine in blocking NF-κB activation and reactivating p53 may synergize with these agents that we have had available to us and make them more effective,” said Van Waes. “Combinations of quinacrine as a prototype drug with other DNA-damaging therapies have combinatorial activity, and on that basis, it merits further study.”

Quinacrine as a Prototype Drug

Further study is just what Katarina Gurova, M.D., Ph.D., and her colleagues at Roswell Park Cancer Institute and Cleveland BioLabs Inc., in Buffalo, N.Y., did. The group screened for small molecules that would mimic quinacrine’s actions but possess a better bioavailability profile, structural stability, and a therapeutic range in the nanomolar scale instead of the micromolar scale, in which quinacrine is bioactive. They chose to further study three compounds, the curaxins, which had these qualities and potently activated p53 while inhibiting NF-κB.

The results of that study, published in the Aug. 10, 2011 issue of the journal Science Translational Medicine, demonstrate that curaxins potently inhibit an array of human tumor xenografts, including colon, renal cell carcinoma, and melanoma cell lines. Further investigation revealed that the compounds bind to the minor groove of DNA, inducing a twisting or kinking that then traps a key nuclear binding protein complex to the chromatin. The protein complex, called FACT for “facilitates chromatin transcription,”

The cells don’t die a ‘classic’ apoptotic cell death. Instead, it appears they die through a series of steps that may be complex to sort out.
rapidly moved from the soluble protein fraction of cells and bound tightly to DNA. This binding recruited other proteins, such as CK2, a protein kinase that regulates cell survival through NF-κB and is dysregulated in cancer. In the presence of curaxins, FACT-bound CK2 played a pivotal role in activating p53, as well as inhibiting NF-κB. Crucially for their potential antitumor activity, the curaxin compounds tested did not induce DNA breaks, which underlie the anticancer mechanism of DNA-binding chemotherapy agents such as cisplatin, nor were they toxic to normal cells. Moreover, they killed cancer cells without relying on p53-induced programmed cell death.

“The cells don’t die a ‘classic’ apoptotic cell death,” Gurova said. Instead, it appears they die through a series of steps that may be complex to sort out.

“This really provides a new model for thinking about how the class of drugs may work,” said Van Waes, who along with NCI colleagues, were the first to suggest CK2 as a new target in cancer.

In a commentary accompanying the Science Translational Medicine article, physician-scientists Giulio Draetta, M.D., professor of genomic medicine at the University of Texas M. D. Anderson Cancer Center in Houston, and Ronald DePinho, M.D., president of the Cancer Center, stated that the researchers’ use of a unique cell-based screening mechanism that excluded compounds inducing DNA damage “and their ability to affect multiple pathways fully justify a continued effort in evaluating them as anticancer agents that could possibly hit the clinic.”

“There is some intriguing new science here,” Draetta said in a phone interview. “This has been the paradigm: Unless you see DNA damage, the drug is not going to work. Here we are talking about a mechanism that’s completely different, and that’s why I am excited about it.”

However, Draetta tempered his enthusiasm, pointing out that the drugs have not shown activity against spontaneous tumors in animal models. He said he would like to see extensive medicinal chemistry on the compounds and more information about their ability to stay in blood plasma and migrate to tumor sites. He pointed out that the report presents some initial evidence, but more work needs to be done.

Gurova and her colleagues Andrei Purmal, Ph.D., Catherine Burkhart, and Andrei Gudkov, Ph.D., are co-inventors on a patent covering composition of matter and use of curaxins, which Cleveland BioLabs held and recently transferred to Incuron LLC in Moscow. Incuron will conduct the first safety study of its lead compound, CBLC137, via oral administration to patients with solid tumors in Russia beginning in the first quarter of 2012. Gurova said that an intravenous formulation of CBLC137 is now being prepared to maximize bioavailability, with plans to initiate a phase I safety trial in the U.S. as soon as preclinical toxicology studies are completed.

“Quinacrine is not forgotten,” Gurova said, noting that Cleveland BioLabs and Incuron are running a clinical trial with quinacrine for liver cancer, including primary hepatocellular carcinoma and metastases of other cancers to the liver.

The multi-center open-label, phase Ib safety and tolerability study in Russia began in January 2011 and has progressed through several dose escalations, Gurova said. The hope is that quinacrine’s tendency to concentrate in the liver will work to its advantage in treating these solid tumors.

Meanwhile, work continues on the curaxins and the new cancer target FACT.

“We are finding more and more evidence that FACT may be in principle a very good target for cancer,” Gurova said. “It is overexpressed in many types of cancer, and most normal adult tissues do not express FACT at all. If we inactivate FACT, tumor cells die, but normal cells do not. So it’s a very promising target.”

Gurova has no financial stake in the company but has accepted grant funding from Incuron to continue mechanistic studies of curaxins.