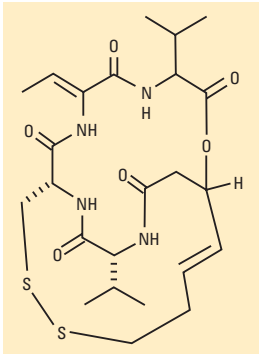
Enlisting apoptosis

Histone deacetylase inhibitors that trigger cell death are the subjects of several cancer clinical trials.

Cancer researchers are trying to develop drugs that trigger or enhance apoptosis, or programmed cell death, in tumor cells in which this process is suppressed. Some of the promising candidates now in clinical trials are histone deacetylase (HDAC) inhibitors such as depsipeptide FR901228, a cyclic peptide-like molecule with both ester and amide linkages.

Normally, the mammalian body contains natural protections against the development of cancer. In some cases, however, malignant cells manage to circumvent these natural defenses.



Depsipeptide FR901228.

A primary method by which malignant cells continue to survive is through transcriptional repression. This prevents the activation of tumor suppressor or apoptotic pathway genes that might otherwise lead to the destruction of the abnormal growth. HDAC inhibitors have been shown to trigger differentiation and decrease cell proliferation, as well as induce apoptosis.

FR901228 was first isolated from *Chromobacterium violaceum* by the Fujisawa Co. In preclinical testing, the molecule reduced tumor growth in murine models of human tumor xenografts and proved to have an acceptable toxicity profile. According to work published by researchers at Ohio State University and The Burnham Institute (*Blood* **2003,** *102,* 652–658), depsipeptide-induced apoptosis is associated with the down-regulation of cellular FLICE inhibitory protein (c-FLIP). Furthermore, their results showed a relationship between target enzyme inhibition of histone deacetylase, histone H3 and H4 acetylation, and apoptosis involving the tumor necrosis factor-receptor pathway of apoptosis—a pathway not used by other therapeutic agents.

The researchers suggest using histone H3 and H4 acetylation, inhibition of histone deacetylase, and down-regulation of FLIP as pharmacodynamic end points in clinical evaluations of this drug.

Currently, HDAC inhibitors such as FR901228 are being tested clinically, largely in conjunction with other anticancer drugs. For example, the National Cancer Institute (NCI) is recruiting patients for a lung cancer clinical trial in which the drug decitabine (DAC), a DNA-demethylating agent, will be combined with depsipeptide treatment. According to the NCI researchers in their trial description, DAC "enhances the immune response to tumors and may enable the *p16* gene, called the 'suppressor gene', to function normally." They also believe they have demonstrated that DAC-mediated target gene expression and apoptosis can be significantly enhanced in cancer cells by subsequent exposure to FR901228.

Clinical study is under way to investigate the cancer treatment potential of Aton Pharma's SAHA (suberoylanilide hydroxamic acid) and of Titan Pharmaceuticals' Pivanex, other HDAC inhibitors that induce tumor differentiation and/or apoptosis. Pivanex, for example, has been well tolerated in clinical trials and has shown preliminary evidence of efficacy in patients with non-small-cell lung cancer.

Preclinical studies indicate that the combination of Pivanex and docetaxel, an approved drug for second-line treatment of non-small-cell lung cancer, is synergistic. A current Phase I trial is designed to evaluate whether combination therapy with Pivanex and docetaxel provides clinical benefit over docetaxel alone in patients with chemotherapy-resistant non-small-cell lung cancer. A Phase II trial of Pivanex monotherapy of non-small-cell carcinoma is also ongoing; and a Phase I/II trial is planned for examining the efficacy of Pivanex against metastatic hepatic tumors.

Another HDAC inhibitor entering clinical trials is the investigational benzamide derivative drug MS-275. This compound has demonstrated potent and unique activity in vitro and in vivo. Researchers are recruiting patients for an MS-275 Phase I trial.

Mark S. Lesney is a senior associate editor of *Today's Chemist at Work.* ■

clinicaltrialsweb

Depsipeptide to treat thyroid and other advanced cancers (Phase I):
www.clinicaltrials.gov/ct/show/NCT00048334?order=1

Decitabine/depsipeptide infusion in patients with pulmonary and pleural malignancies (Phase I):
www.clinicaltrials.gov/ct/show/NCT00037817?order=5

Depsipeptide in pediatric patients with refractory solid tumors (Phase I):
www.clinicaltrials.gov/ct/show/NCT00069771?order=4

HDAC inhibitor, MS-275, in refractory solid tumors and lymphomas (Phase I):
www.clinicaltrials.gov/ct/show/NCT00012571?order=1

Depsipeptide in treating T-cell lymphoma (Phase II):
www.clinicaltrials.gov/ct/show/NCT00020436?order=5

Pivanex and docetaxel in advanced non-small-cell lung cancer (Phase II):
www.clinicaltrials.gov/ct/show/NCT00073385?order=2