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www.roswellpark.org/commercialization**Method for Increasing Efficacy of Anti-Folates**

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Keywords: Antifolate, 5-amino-4-imidazolecarboxamide riboside (Z), Methotrexate (MTX), MTX polyglutamate (MTXGn), Reduced Folate Carrier (RFC), and leukemia.

Collaboration Research Opportunity: Roswell Park Cancer Institute is seeking partners to help co-develop the use of exogenous 5-amino-4-imidazolecarboxamide riboside (Z) as a method for enhancing the uptake and efficacy of antifolates which act via inhibition of dihydrofolate reductase.

Summary: Anti-folates are antagonists of the action of the folate family of essential human vitamins, all of which are derived from the folic acid structure. The most commonly used antifolate in humans is currently methotrexate (MTX). MTX is used to treat a number of pathological conditions, including cancer, rheumatoid arthritis, psoriasis, and graft-versus-host disease following bone marrow transplantation. Newer anti-folates are currently only approved to treat specific cancers (colon and mesothelioma). Anti-folates that closely resemble the folates structurally and which include single glutamate (Glu) moiety that occurs in folates are termed "classical" anti-folates. Classical antifolates are primarily transported into human cells by the equilibrative reduced folate carrier (RFC). Transport by tumors can be limiting to the therapeutic effect of antifolates. It has been found that conditions that selectively increase antifolate uptake and/or metabolism into target cells should increase the therapeutic index of the antifolate.

There are currently no known compounds that potentiate the uptake and metabolism of antifolates via increased activity of the RFC. Likewise, there are no compounds that increase synthesis of antifolate polyglutamates.

Technology: Researchers at Roswell Park Cancer Institute have shown that exogenous 5-amino-4-imidazolecarboxamide riboside (Z) or its nucleobase would affect mammalian folate metabolism. Z also enhances the growth inhibitory potency of MTX against leukemia cells when given concurrently in short-term exposure. Researchers have also shown that Z does not decrease MTX efflux and that administration of Z with an antifolate could lead to increased therapeutic efficacy. Although this potentiating effect has been tested only in tumor cells, it may also occur in the target cells in other pathological conditions such as rheumatoid arthritis and psoriasis.

Potential Commercial Applications:

- Z enhances the growth inhibitory potency of MTX against leukemia cells when given concurrently in short term exposure, which raises the possibility that administration of Z with an antifolate could lead to increased therapeutic efficacy.
- Discovery of mechanisms by which antifolate transport could be increased in tumor cells might lead to greater therapeutic benefit from clinical use of current and future antifolates.
- Could be especially critical in childhood acute lymphoblastic leukemia (ALL) where clinical correlations have shown that median difference in MTX polyglutamate (MTXGn) accumulation between patients who respond to MTX-containing therapy and those who do not is only about three-fold. Increasing uptake of MTX even three-fold could increase MTXGn synthesis and might thus increase long term survival.



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Competitive Advantages:

- Current use of antifolates alone or with other cytotoxics has limited tumor range and narrow selectivity.
- Inclusion of Z potentiation should increase the therapeutic index and may increase the tumor range.
- Z has already been tested in clinical trials as a treatment for cardiac ischemia and it was found to be nontoxic.

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