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## Diarylacetylenes as inhibitors of Methionine S Adenosyltransferase-2 for hepatocellular and colorectal cancer treatment

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Colorectal cancer (CRC) is the third leading cause of cancer-related mortality worldwide. CRC is initiated by mutations of the tumor suppressor gene, adenomatous polyposis coli (APC), or $\beta$-catenin gene. These mutations stabilize $\beta$-catenin and constitutively activate Wnt/$\beta$ -catenin target genes, such as c-Myc and cyclin D1, ultimately leading to cancer. We developed a family of fluorinated diarylacetylene agents, called FIDAS agents, that inhibit the proliferation of CRC cells *in vitro* at nanomolar levels and *in vivo* at a dosage of 20 mg/kg. Using a biotinylated FIDAS analogue, we identified the catalytic subunit (MAT2A) of MAT2 as the direct and exclusive binding target of these diarylacetylene-based FIDAS agents. Structure-activity relationships defined the nature of aryl and heteroaryl rings as well as the substituents on these rings associated with potency as MAT2 inhibitors. MAT2 is up-regulated in many cancers, including liver cancers and colorectal cancers (CRC) and is a potentially important drug target. FIDAS agents inhibited MAT2 selectively without affecting MAT1 that supplies SAM for most cellular needs. Validation of MAT2 as a cancer target relied on the observation that shRNAs also inhibited CRC cell growth. A diarylacetylene-based FIDAS agent delivered orally repressed CRC and hepatocellular cancer xenografts in athymic nude mice. These findings suggest that diarylacetylene-based FIDAS analogs function as epigenetic regulators by targeting MAT2 and represent a family of novel and potentially useful agents for cancer treatment.

### Biography

Liliia M Kril is a Senior Research Technician in the Department of Molecular and Cellular Biochemistry at the University of Kentucky (USA) in Professor D.S. Watt's laboratory. She contributes to several, on-going drug development projects and her scientific contribution led to the development of novel MAT2A and tubulin inhibitors as promising anticancer agents as well as to the discovery of (N-amidinohydrazones) and N-(amidino)-N′-aryl-bishydrazones as new classes of antibacterial/antifungal agents. She is co-author of numerous papers published in peer-reviewed journals.

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