

Treating Cancer and Autoinflammatory Disease for over Six Decades: Structural Basis for Folate and Antifolate Trafficking via Human Folate Receptors

Charles E. Dann III, Assistant Professor
Department of Chemistry, Indiana University, Bloomington, Indiana
<http://www.indiana.edu/~dannlab/>

Human folate receptors (hFRs) are high affinity, glycosylphosphatidylinositol-anchored membrane surface proteins responsible for the uptake of both natural folate metabolites and therapeutic antifolate drugs. Antifolates have been approved by the FDA for treatment of patients with cancer and autoinflammatory disease since the late 1940s. While cytotoxicity is problematic at higher doses, classic and newer generation antifolates – most often methotrexate and pemetrexed, respectively – are still widely used to treat cancers derived from epithelial cell lineages (*e.g.* leukemia, choriocarcinoma, ovarian and breast cancers) and autoinflammatory diseases (*e.g.* rheumatoid arthritis, psoriasis, Crohn's disease). Humans possess at least three distinct transport pathways for the uptake of antifolates. As much of the antifolate toxicity could be ameliorated by designing therapeutics specifically taken up via the hFRs, we have set out to determine structures of hFR α and hFR β both alone and in ligand complexes at pH values indicative of key physiological transport states. Our data, representing the first structures of folate receptors, include six novel structural models illustrating the molecular determinants for folate and antifolate binding as well as the conformational changes at key stages of ligand transport. These structures will be the basis for the development of the next generation of antifolate therapeutics with the desired limited cytotoxicity profile in normal tissues.

