ASPARAGINE BIOSYNTHESIS AND ASPARAGINASE-RESISTANT ACUTE LYMPHOBLASTIC LEUKEMIA: STRUCTURE-BASED METHODS FOR INHIBITOR DISCOVERY. Nigel Richards, Department of Chemistry, University of Florida, Gainesville, FL 32611, USA

Clinical studies have identified an intriguing inverse correlation between asparagine concentration in the blood and the susceptibility of leukemia cells to chemotherapy. The therapeutic exploitation of this observation in treating acute lymphoblastic leukemia (ALL) is hampered by the appearance of drug-resistant tumor cells, which appear to up-regulate asparagine synthetase (ASNS) expression. This enzyme catalyzes the ATP-dependent synthesis of asparagine from aspartic acid, and compounds that inhibit ASNS therefore represent potential drugs for treating ALL and related leukemias. Our group has identified the first, potent inhibitor of human AS and has constructed a working model of how the inhibitor is bound within human ASNS. Progress in delineating the structural features that mediate inhibitor recognition and binding will be discussed in this lecture, together with theoretical and computational experiments that seek to validate hypotheses arising from this model of the inhibitor/ASNS complex.