Human P450 enzymes can be classified on the basis of their substrate classes, with some overlap. Most of the 57 human P450s have some catalytic function associated with them, at least with some xenobiotic chemicals. However, there are several “orphans” that are yet without substrates. We have been working with some of the orphans for more than a decade and used metabolomic approaches with some success. Current interest among the orphans are P450s 2S1, 4X1, and 20A1. We also use transgenic animal models to help guide our studies.