

Title– Metabolism of 5-fluorooxindole by Human Liver Cytochrome P450 Enzymes

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Abstract: The compound that is being explored as part of this research project is 5-fluorooxindole (5F2O) and is a common chemical compound found in several recently developed drugs, including the anti-cancer drug Famitinib. It is a derivative of the amino acid tryptophan, and its structure is useful for drug targeting due to its ability to donate and accept hydrogen bonds. While metabolism of fluorooxindole-containing products can involve a variety of chemical reactions, of particular interest from a hepatotoxicology standpoint is the oxidative defluorination reaction. This reaction involves the removal of the fluorine group attached to the benzene ring and its replacement with a hydroxyl (-OH) group. In this research project, the oxidative defluorination reaction is catalyzed by a family of enzymes called cytochrome P450s. Initial data collected on the reaction of 5F2O with two different cytochrome P450 enzymes (P450_{1A1} and P450_{2A6}) indicate that 5F2O is modified to form an intermediate product which is hypothesized to be a reactive quinoneamine similar to the quinoneamine metabolite indicated in Tylenol toxicity.

This research project has confirmed that the reaction between 5F2O and purified human P450_{2A6} enzyme is producing the expected oxidative defluorination reaction product 5-hydroxyoxindole via high-performance liquid chromatography (HPLC). Due to its high reactivity, the proposed quinoneamine intermediate is not able to be observed directly. However,

reactions performed using a trapping agent called glutathione showed the formation of a unique stable product that was observed via HPLC. Evidence suggests that this stable product is an adduct of the proposed quinoneamine intermediate. Future research work will include additional analysis of this stable product in hopes of confirming its identity as well as testing whether treatment with various chemical agents are able to mediate or prevent the formation of the proposed reactive quinoneamine intermediate (and thereby prevent formation of the glutathione-dependent stable product previously observed).

Christian worldview integration:

Inherent to a faithful Christian worldview is a theology of illness and suffering. The historical account of Genesis indicates that God's initial creation was "very good," meaning that it was without flaw and perfect, like God Himself (Genesis 1:31). However, the sin of humans in Genesis 3 marked a transition from a perfect creation to an imperfect world as a result of Adam and Eve's sin against God. The world we now know, which is capable of causing illness and suffering, is a direct result of sin. 1 Corinthians 15:21-22 states that death (both physical and spiritual) is a direct result of Adam's sinfulness, and provides the basis for Christian theology of illness. In this view, illnesses such as cancer are a direct result of sinfulness and are evidence of humanity's need for Christ.

However, the example of Christ reveals the importance of showing compassion to those who are experiencing physical suffering. Throughout the gospels, Jesus takes action to relieve the suffering of those with physical infirmities— healing the blind, lame, and leprous (Matthew 14:13-14, Matthew 20:30-34, among many others). Thus as Christians, it is extremely important to seek to help those who are experiencing physical suffering. Medication is a key element of care for those afflicted with various illnesses, with chemotherapy drugs representing a significant

component of care for those afflicted by cancer. In seeking to compassionately provide care, it is important to ensure that medications given to those who are ill do not worsen their condition or cause other negative side effects. This research project explores potential liver toxicity as a result of administration of 5-fluorooxindole containing-medications (such as the anti-cancer drug Famitinib). The results of this project will help to inform further research and development of anti-cancer drugs, and help to ensure that patients are not unwittingly injured by medications administered to them. To perform research of this kind is to show the compassion exemplified by Jesus by seeking to protect and bring healing to those who are ill.