Non-Confidential Description - PSU No. 3649
“The UGT2B10D67Y Gene Polymorphism as a Marker for Response to Olanzapine Treatment and Prevention of Side Effects”

**Keywords:**
Olanzapine, metabolism, glucuronidation, pharmacogenetics, UGT, atypical antipsychotic, diabetes, schizophrenia

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**Background**
The widely prescribed atypical antipsychotic Olanzapine (OLZ) is recommended as a first-line treatment for psychotic conditions such as schizophrenia and bipolar disorder. Olanzapine induces weight gain, hyperglycemia and dyslipidemia more than any other atypical antipsychotics, increasing long-term risk for diabetes mellitus, cardiovascular disease, and mortality. These adverse effects are seen only in a subset of patients, suggesting a genetic component to patient risk.

UDP-glucuronosyltransferase enzymes (UGTs) are phase II metabolic enzymes responsible for nearly 50% of OLZ metabolism and excretion, with the OLZ-10-N-glucuronide the major metabolite observed in the urine of subjects taking OLZ. Many known UGT polymorphisms can alter an individual's ability to metabolize a drug, leading to decreased plasma clearance levels and adverse drug reactions. While some of the UGTs have been examined for activity against OLZ, all of the known UGTs have not been tested, nor have the effects of UGT polymorphisms on OLZ metabolism. Investigating these effects could give doctors the ability to predict such side-effects before treatment begins and respond accordingly.

**Invention Description**
We have discovered the enzymes responsible for OLZ glucuronidation. Since glucuronidation is a major mode of OLZ elimination from the body, a polymorphism in the genes responsible for glucuronidation could significantly impact OLZ excretion. As a major determining factor of total circulating OLZ in a patient’s serum, it is equally significant in determining a patient’s overall response. These findings are extremely important in terms of developing individualized approaches to treating patients with schizophrenia, bipolar disorder, or other diseases for which OLZ has or will be found to be useful as a treatment modality in the future, as it could help instruct us in terms of both OLZ dosing regimens, or, more likely, changing the drugs to be used for treating each individual patient.

**Advantages/Applications**
- Allows for pre-treatment screening for adverse reactions and the possibility of individualized treatment regimes

**Patent Status**
Patent Pending