**ASSOCIATE PROGRAM DIRECTOR and PRINCIPAL INVESTIGATOR**

**Seth Ablordeppey, Ph.D.**

Associate MBRS Program Director  
College of Pharmacy and Pharmaceutical Sciences  
1520 South Martin Luther King Jr. Blvd.  
Dyson Building, Suite 201  
Florida A&M University  
Tallahassee, FL 32307  
Telephone: 850-599-3834  
E-mail: seth.ablordeppey@famu.edu

**Research:** Synthesis and Evaluation of Agents with Clozapine-like Dompaminergic Binding Profile - (Regular Score Project)

Atypical Antipsychotic Agents (AAAs) or Second Generation Antipsychotics (SGAs), typified by clozapine, are rapidly replacing the old typical antipsychotic agents (TAAs). While the AAAs have different binding profiles from the TAAs, it is still unsettled as to which receptor interactions are important for the more favorable therapeutic properties of the AAAs. Thus, the long-term goal of this research proposal is two-fold: to identify receptor interactions that may be primarily responsible for the superior clozapine-like therapeutic characteristics; and to identify new and novel antipsychotics. This study is based on the central hypothesis that the binding profile of clozapine at dopamine receptors is a primary contributor to its preferred therapeutic value as an atypical antipsychotic agent. The proposal, therefore, is designed to achieve the following specific objectives: to resynthesize at least a gram each of SYA 09, SYA 10 and SYA 11; to separate the enantiomers and obtain the binding profiles at D2, and D4 receptors; to identify the eutomer of each and evaluate their in-vivo behavioral profiles; to evaluate dopamine antagonists with $10 < D2Ki < 150$, and $D2/D4$ binding constant ratio in the range, $D2Ki/D4Ki \leq 1$, $1 < D2Ki/D4Ki < 3$ and $3 < D2Ki/D4Ki < 10$ in behavioral tests that correspond to antipsychotic efficacy in animal models; to conduct 3-D QSAR studies on published D-2 and D-4 ligands and suggest a pharmacophore model for D-2 and D-4 ligand binding; to design new analogs by incorporating D-4 pharmacophore elements into modified haloperidol templates; to synthesize the newly designed analogs and characterize them; to evaluate the binding profile of the synthesized compounds at the D-2 and D4 receptors and; to evaluate the behavioral profiles of selected analogs. Twenty-four analogs will be the primary focus of this research proposal. However, additional compounds will be proposed and synthesized based on initial SAR data generated in the proposal.

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