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Title of the Research Project	Development of GPCRX allosteric modulators for Van Houten syndrome and other neurological disorders
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List of collaborators and/or other partners in the project. Identify support and funding available for the project.	Selma Muntz, Ph.D. (Medicinal Chemist); Nelson Burns, Ph.D. (Molecular Pharmacologist); Manjula Leonard, M.D., Ph.D. (Drug Metabolism Scientist); Andrew McClure, Ph.D. (In vivo and Translational Pharmacology). Project is currently funded by an NIH R01.
A1. Project Name or Drug Target	GPCRx
A2. Therapeutic Areas for Project	Neurological disorders, Rare disease
A3. Therapeutic Area Detail	Van Houten syndrome (VHS, primary), Szyslak syndrome, epilepsy, intellectual disability, schizophrenia, Parkinson's disease
A4. Therapeutic Hypothesis	Primary loss-of-function mutations in the GPCRX gene lead to symptoms that mimic the single-gene disorder VHS, including seizures, intellectual disability, speech difficulties, and gait abnormalities. GPCRx protein levels are also low in autopsy samples of people with VHS and tool compounds that potentiate GPCRx activity can correct abnormal phenotypes in a VHS mouse model. Based on expression of the receptor and its ability to regulate neurotransmitter release, there may also be therapeutic potential in other neurological disorders; these indications are currently being explored in animal models using selective tool ligands.
A5. Genetic evidence for target relevance	Emerging genetic evidence suggests that primary mutations in the GPCRX gene lead to symptoms consistent with VHS.
A6. Pharmacological MOA for target regulation	A GPCRx positive allosteric modulator (PAM) corrects deficits in a VHS mouse model, and we also have evidence for therapeutic potential of GPCRX

	potentiation in mouse models of other rare diseases, such as Szyslak syndrome, as well as multigene disorders, like schizophrenia.
A7. Identify your project type, technology or asset	Novel assay/technology Novel target Small molecule program in Hit to Lead Stage
A8. Structural information available for target (e.g. crystal structure)	Yes
A9. If yes to question A8, describe the structural information available	Insert structural information or reference to structure (e.g., pdb file).
B1. What makes the project novel?	There are no allosteric modulators of GCPRx that have reached the stage of clinical testing.
B2. Risks and potential benefits	Administration of a PAM for one month did not induce overt toxicity in a mouse model of VHS syndrome. As no other compounds have reached clinical development, there is potential to be first-in-class.
B3. Importance of project	No modulators in clinical testing. Genetic evidence suggests a primary link to abnormal phenotypes, but patients are rare. VHS provides an opportunity to test the GPCRx hypothesis in patients with a defined, monogenic disorder. There are no FDA-approved treatments for VHS.
B4. Indicate target population, if known	VHS patients. There are adults with the disorder-propose to start with this population versus pediatric individuals.
B5. Indicate existence of known biomarkers (target engagement assays), if known	We have data with EEG recordings showing an abnormal signature in VHS animals that is corrected with compound. We are also exploring sleep/wake architecture based on signatures seen in Gpcrx KO mice as well as VHS model animals.
B6. Indicate clinical endpoints, if known	Seizures, cognitive endpoints, EEG
C1. Current stage of the project	Hit-2-Lead
C2. Validation of mechanism of action	Early selectivity data showing compounds are selective for target, knockout mice for target available to validate compound activity, knockout mice mimic symptoms of disease
C3. Aim of overall project	Development of GCPRx positive allosteric modulators for Van Houten syndrome
C4. Main approaches to achieve next milestone	Chemical optimization campaign for small molecules
C5. Strengths and experience of team	The Simpson Drug Discovery Center has a well-integrated process for compound development that integrates chemistry, molecular pharmacology, drug metabolism, in vivo studies, and translational biomarker work. For this project, we have completed a high-throughput screen and are currently in hit-to-lead activities. All in vitro and in vivo assays are in place and Springfield University is an ideal environment for VHS research due to the integration of VHS programs within the Simpson Center, the Springfield Taft Center for Intellectual Disability led by clinical VHS expert Dr. Ralph Waylon, and the Springfield Brain Institute led by VHS researcher, Dr. Lisa Bouvier. The Simpson

	Center has now advanced two compounds for other targets/indications into the clinic and is well poised to advance this program into eventual clinical testing.
C6. Short description of the research plan	We have begun a chemical optimization campaign stemming from a successful high throughput screen. We have all of the in vitro pharmacology, drug metabolism, and in vivo pharmacology assays in place to test optimized leads and perform pharmacokinetic/pharmacodynamic associations and are actively working on biomarker strategies.
C7. Plan for clinical/technology development, if known/applicable	While this project is in hit-to-lead, we are actively engaged in translational biomarker studies and have found that EEG may have value as a biomarker to assess target engagement and disease modification. We are also working to develop a positron emission tomography ligand for GPCRX to assess receptor occupancy.
D1. Existing treatments or drugs for this target or related targets; related technologies	Several companies have been reported to be working in this space, but no compounds have been reported to be in trials. Company Y has reported the development of a GPCRx agonist, but the current program would focus on PAMs, which is a different mode of pharmacology.
D2. Ongoing clinical trials involving this target/disease	-There is a natural history study of VHS ongoing (clinicaltrials.gov ######) -A trial with ketamine in VHS is enrolling (clinicalitrials.gov #####)
E1. Please list patent numbers, inventors and titles related to this work, if published	No patents issued, confidential provisional patent application available under NDA
E2. Is the proposed work related to an existing license, industry agreement or other relationship?	No; NIH funded
F. Publications Related to the Research	Insert DOI or Pubmed references here
G. Keywords	Van Houten syndrome, epilepsy, schizophrenia, Szyslak syndrome, GPCRX, allosteric modulator, high throughput screening, medicinal chemistry, Simpson Center for Drug Discovery, EEG, biomarker