WORKING TOGETHER TO DEVELOP NEW, RAPID-ACTING TREATMENTS FOR DEPRESSION

In the United States, 1 in 6 people will experience clinical depression. Unfortunately, about 30 percent of patients don't respond to any of the available treatments and they all take weeks to become effective. It is these patients who will benefit most from work of **Scott Thompson, PhD,** Professor and Chair of the Department of Physiology, and **Todd Gould, MD,** Associate Professor, Department of Psychiatry. These scientists in the University of Maryland School of Medicine (UMSOM) are leading research projects individually and collaboratively that are identifying new strategies for treating patients. Both researchers use mouse models and genetic engineering to identify molecular drug targets and new medications for treating depression. Combined, they now have multiple different candidate drugs that show promise as fast-acting antidepressants at various stages of preclinical and clinical development.

Dr. Thompson studies depression at the level of the neurons and neuronal circuits. Dr. Gould studies depression and mood disorders from the standpoint of behavioral outcomes and is an expert in using rodent behavior models to study these complex psychiatric disorders. The labs' expertise and efforts are complementary.

Patients with depression suffer not only from a depressed mood, but also anhedonia. That is, they feel no pleasure from normally rewarding experiences. Studying the brain circuits underlying reward behavior in mice has allowed the two labs to gain insights into potentially new ways to treat depressed patients. Of particular relevance are excitatory synapses that are activated by pleasurable experiences as part of reward pathways. These excitatory synapses are weakened when mice display anhedonia and are strengthened by the anesthetic drug ketamine, which is known to have fast-acting antidepressant activity, often within hours, in a majority of depressed patients. However, the use of ketamine as a fast-acting antidepressant is limited, because it causes memory and sensory disturbances and has the potential for abuse. Indeed, ketamine is used illegally as the recreational drug "Special K." The finding that ketamine has fast-acting antidepressant activity inspired both Dr. Gould and Dr. Thompson to see if they could "make a better ketamine."

Dr. Gould discovered that ketamine is metabolized into a molecule 2R,6R-HNK that has rapid antidepressant action in animals. He determined that this metabolite lacks the undesirable side effects of ketamine in mice. Together with Dr. Thompson, the molecule was discovered to directly strengthen excitatory synapses in reward circuits. He received a 2017 Harrington Scholar-Innovator award to continue the study of 2R,6R-HNK with the goal of translating his findings into clinical trials. By collaborating with the intramural program of the National Institutes of Health (NIH), Dr. Gould will be involved in the first-in-man (phase I) clinical trial for 2R,6R-HNK and the planned phase II trials in 2019. His team has taken an approach, which does not involve the pharmaceutical industry. So far, this approach has proceeded at a fraction of the cost that it typically takes industry to develop a new drug.

Dr. Thompson took a different approach to identify fast-acting antidepressants. He reasoned that drugs that reduced an inhibitory input into the reward pathways might be effective antidepressants. By looking through the literature, he re-purposed a set of compounds that could be used specifically to increase the activity only within the brain's reward circuits. Dr. Thompson's lab determined that these compounds effectively alleviated stress-induced depression behaviors in mice within 24 hours and strengthened the same neuronal connection that is strengthened by a single administration of ketamine or 2R,6R-HNK. In collaboration with Dr. Gould, they could show that these compounds produced none of the adverse effects of ketamine. Unfortunately, none of the available compounds used in the laboratory are clinically viable for development as treatments for patients. To bring this concept to clinical testing, Dr. Thompson worked with chemists at intramural program at the NIH to develop a compound with similar properties that could be patented. They then started a company, Asulon Therapeutics, to generate the capital needed to proceed toward clinical trials.

Whereas Gould's compound 2R,6R-HNK targets this synapse directly, Thompson's GABA-A-NAM strengthens this connection indirectly. Best of all, these compounds achieve this strengthening of the circuit after a single treatment without adverse effects. Although both researchers study the same disease, they are not competitors. The university encourages collaborative projects between researchers and supports diverse approaches to translating basic scientific findings into clinical practice. As Dr. Thompson states, *"Whether Dr. Gould's drug turns out to be the silver bullet or whether mine does, or whether both are, doesn't matter. What matters most is that our research leads to improved treatment options for patients with depression."*

Dr. Thompson and Dr. Gould

TREATMENTS FOR DEPRESSION

PSYCHOTHERAPY MEDICATIONS

- SSRIs, selective serotonin reuptake inhibitors (Prozac, Zoloft, Paxil, Celexa, Lexapro)
- SNRIs, serotonin and norepinephrine reuptake inhibitors (Effexor, Pristiq, Cymbalta)
- NDRIs, norepinephrine and dopamine reuptake inhibitors (Wellbutrin)
- Serotonin and norepinephrine receptor agonist (Remeron)
- Second-generation antipsychotics (Abilify, Seroquel)
- Tricyclic antidepressants (Elavil, Norpramin, Sinequan, Tofranil, Pamelor, Avantyl, Vivactil)
- Monoamine oxidase inhibitors (Nardil, Marplan, Parnate, Emsam)
- Experimental therapy: Ketamine, 4-chlorokynurenine, 2R,6R-HNK, GABA-A-NAM

BRAIN STIMULATION THERAPY

- Electroconvulsive therapy
- Repetitive transcranial magnetic stimulation
- Vagus nerve stimulation
- Experimental therapy: deep brain stimulation