syndromic ASD by generating hiPSC lines from eight non-syndromic ASD males (diagnosed via behavior consistent with DSM-IV criteria) along with five healthy male control individuals (Marchetto *et al*, 2017). Known syndromic forms of ASD were ruled out in all individuals involved with this study via exome sequencing and copy-number variant analysis. On the basis of MRI scans conducted between 2–4 years of age, all ASD individuals were found to possess mild to severe macrocephaly, defined as larger than average total brain volume compared with typically developing individuals. We hypothesized that ASD individuals sharing a co-morbidity would also share disruptions in common cellular phenotypes and signaling pathways, thereby increasing our ability to detect disruptions in these processes.

Initial observations indicated that both ASD hiPSCs and neural progenitor cells (NPCs) derived from hiPSCs proliferated at a higher rate than control cells and displayed decreased Wnt signaling. Pharmacological enhancement of the Wnt pathway rescued this proliferative phenotype. Interestingly, we have also found that disrupted Wnt signaling during mouse embryonic development leads to transient brain overgrowth and behaviors analogous to human symptoms of ASD, such as aberrant social and repetitive behaviors (Belinson *et al*, 2016). This remarkable pathway conservation between species suggests that aberrant Wnt signaling might have a critical role in ASD development.

In addition to NPCs, neurons were differentiated from ASD iPSC lines and displayed decreases in synapse number, which lead to defective network properties in ASD neuronal cultures. RNA sequencing was also performed in iPSCs, NPCs, and neurons, revealing both previously described and novel misregulated genes and pathways in ASD cells, including enrichment of genes linked with brain development in NPCs, likely reflecting the previously observed brain overgrowth phenotypes. A number of genes were also found to be misregulated during differentiation of NPCs to neurons in ASD cell lines, including various cation channels that might be responsible for aberrant network connectivity.

Our study illustrates that novel pathways and physiological processes in human cells can be identified in a non-syndromic neurological disorder if classified by endophenotypes. Further exploration of the genes/pathways identified in this study and the identification of new pathways associated with neurological disease in human cells promises to aid the development of more effective clinical targets.

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Innovative Therapeutic Intervention For Opioid Use Disorder

The United States is in the grip of an opioid misuse and overdose crisis. Progression from misuse to opioid use disorder (OUD) is marked by compulsive drug-taking and clinically significant impairment. Behavioral interventions along with treatment with OUD pharmacotherapeutics, such as buprenorphine, mitigates withdrawal, reduces mortality, opioid intake, and opioid-seeking behaviors, as well as improves psychosocial functioning (Volkow *et al*, 2014). Medication-assisted treatment is an important adjunct to the proper management of OUD patients, yet additional opportunities exist to enhance the probability of extended abstinence and recovery from OUD.

Dysregulation of the limbic-corticostriatal circuitry that subserves reward and adaptive behaviors contributes to OUD development as well as the vulnerability to relapse during abstinence. Serotonin (5-HT) neurotransmission confers modulatory control over this circuitry, particularly through the 5-HT_{2C} receptor (5-HT_{2C}R) (for review) (Cunningham and Anastasio, 2014). Selective 5-HT_{2C}R agonists, which lack intrinsic abuse liability, curb self-administration of psychostimulants (eg, cocaine, nicotine) as well as associated sensitivity to drug-associated cues and impulsivity in preclinical studies (for review) (Cunningham and Anastasio, 2014). These data sparked a clinical trial that demonstrated that the FDA-approved anti-obesity medication and first-in-class 5-HT_{2C}R agonist lorcaserin (Belviq) increased abstinence from smoking (Shanahan *et al*, 2016). Furthermore, the efficacy and safety of lorcaserin for cocaine use disorder is presently under study (https://clinicaltrials.gov/ct2/show/NCT03007394). We have recently demonstrated the efficacy of lorcaserin to suppress intake of the semisynthetic opioid oxycodone as well as associated cue reactivity in both abstinence and extinction-reinstatement paradigms, effects which were blocked by the selective 5-HT_{2C}R antagonist SB242084 (Neelakantan *et al*, 2017). Lorcaserin pretreatment also decreases opioid-induced behavioral sensitization and the physical signs of naloxone-

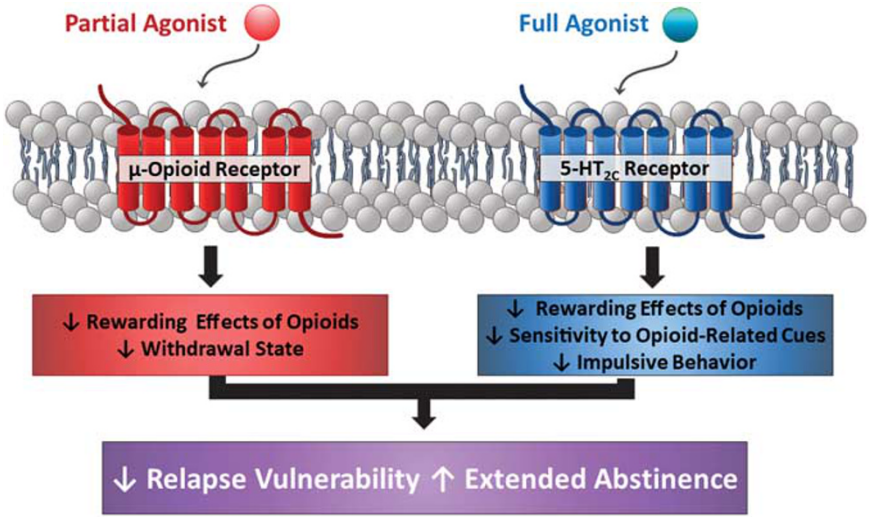

Figure 1. Either a μ-opioid receptor partial agonist, a full 5-HT_{2C} receptor (5-HT_{2C}R) agonist, or a combination may afford gains in reducing relapse vulnerability and extending abstinence in opioid use disorder (OUD). Partial agonist actions at the μ-opioid receptor reduce the rewarding effects of opioids and withdrawal. The selective 5-HT_{2C}R full agonist lorcaserin suppresses oxycodone intake and associated cue reactivity as well as impulsivity. Low-dose combinations of a μ-opioid receptor partial agonist plus the non-opioid lorcaserin may provide an additional new avenue to support recovery in OUD patients. While the brain locus for a potential receptor–receptor interaction is unknown, both the μ-opioid receptor and 5-HT_{2C}R are co-expressed in nodes of the limbic-corticostriatal circuitry engaged in drug reward and relapse vulnerability. The FDA-approved OUD medication buprenorphine is a μ-opioid receptor partial agonist, but is not selective given its complex actions at δ-, κ-, and nociceptin/opioid receptor-like receptors (NOP or ORL-1) (Lutfy and Cowan, 2004). Thus, other μ-opioid partial agonists may be needed to test the hypothesis that low-dose combinations with lorcaserin may add value in OUD medication-assisted therapy.

precipitated withdrawal following chronic opioid exposure in mice (Wu *et al*, 2015). Thus, the non-opioid medication lorcaserin acts as a 5-HT_{2C}R agonist to influence aspects of opioid-evoked behaviors, suggesting that the 5-HT_{2C}R system may play a key role in the shared mechanisms for addiction and relapse vulnerability across psychostimulant and opioid drug classes.

The development of pain medications with analgesic efficacy, but reduced abuse liability, remains a high priority. Of equally high priority is the identification of therapeutic interventions that increase the maintenance of abstinence after cessation of opioid intake, even in high drug cue environments. A selective 5-HT_{2C}R agonist, such as lorcaserin, may provide a new avenue to add value to the outcomes of medication-assisted treatment in OUD (Figure 1). The next step is to expand the present data set to definitively test the hypotheses that lorcaserin inhibits opioid withdrawal and countermands stress- and/or opioid-triggered relapse events, for example. It is also possible that low doses of lorcaserin administered in combination with a partial μ-opioid agonist, with limited abuse liability but efficacy to suppress opioid-induced euphoria and withdrawal may reduce relapse risk via regulation of two signaling pathways. The neurochemical mechanisms and sites of action for 5-HT_{2C}R systems to control opioid-related behaviors are also of interest. Finally, preclinical studies to evaluate low-dose combinations of a partial μ-opioid agonist plus lorcaserin will provide insight into the potential for translational value in clinical trials geared to reduce the devastation of opioid overdose and OUD.

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The Ketamine Metabolite 2R,6R-Hydroxynorketamine Blocks NMDA Receptors and Impacts Downstream Signaling Linked to Antidepressant Effects

Clinical studies have demonstrated a reproducible rapid antidepressant effect of low-dose ketamine in patients