Category

Best Startup

Product/Solution Name

Delix Psychoplastogens (such as DLX-001 and DLX-007)

Date of Approval

2023-05-09

Indications

The aperture for indications for psychoplastogens is broad, and even broader for Delix's non-hallucinogenic compounds in this class. Psychoplastogens are medications that produce rapid and enduring neuroplastic and therapeutic effects especially in indications where cortical dendritic or synaptic atrophy plays a role in the pathology.

Our first program in the clinic, DLX-001, is being developed for neuropsychiatric disorders where neuronal and circuit dysregulation has been found to be a core construct of the disorder. For example, Major Depressive Disorder (MDD) is a patient population where this cortical neuronal atrophy is marked, and the reversal of which maps on symptomatic improvement, thus this is where we are taking DLX-001 first.

Importantly, several additional mood and anxiety indications could benefit from DLX-001 or another Delix neuroplastogen, such as our second clinical program, DLX-007. DLX-007 has been partnered with NIH and NIDA for development as a treatment for substance use disorders (SUD). Importantly, because the therapeutic hypothesis underlying psychoplastogens is the growth of neurons in key circuits, our DLX-007 program is not substance specific and has demonstrated efficacy in a variety of substance-use models including heroine, alcohol, and polysubstance use.

As our platform of psychoplastogens continues to evolve and expand, the data generated to support widening of the indications to pursue has also grown. To date we have demonstrated preclinical utility across a range of neuropsychiatric disorders, including depression, fear, anxiety, SUD, and even psychosis, neurological indications such as cognitive flexibility, dendritic, spine, and synapse loss, as well multiple models of neurodegeneration such as Parkinson's and Alzheimer's disease. Delix aims to bring multiple novel CNS treatments forward from our platform, and at only 3 years old, we are well on our way.

Therapeutic Categories

CNS
Antidementia Agents
Antidepressants
Anti-inflammatory Agents
Antipsychotics
Anxiolytics
Bipolar Agents

Central Nervous System Agents

Attached Files:

- Delix_NIDA_December_2021.pdf
- Delix Therapeutics Initiates Phase I Trial for Novel Compound DLX001.pdf

Background information and need for solution/product

Psychoplastogens: A Long-Awaited Revolution in Neuropsychiatric Drug Treatment

In the US and EU alone there are over 300 million people who suffer from depression and PTSD, another 264 million patients with anxiety, and 162 million survivors of substance use disorder. Worldwide, there are more than 1 billion people suffering from a mental health disorder. As friends and family members, as care providers, or as patients ourselves, let alone as biotech leaders who have dedicated ourselves to the pursuit of CNS therapeutics, we all understand unmet need for safe, effective, and accessible mental health treatments. The drive to find new treatments is not lacking and the population in need is only growing but over the last few decades, psychiatric drug development has seen a dearth of innovation, driven by a lack in understanding of the underlying biology of the disorders.

Historically, the “Monoamine Imbalance” hypothesis of depression and other neuropsychiatric disorders played a dominant role in psychiatry and drug development. However, while the elevated norepinephrine, serotonin, or dopamine elicited by traditional antidepressants is manifested quickly, there is a significant delay in symptom reduction, clinical efficacy, and often inadequate treatment response. This discordance left scientists searching for other biological substrates of the etiology of depression.

As neuroscientists pursued this avenue of research, clinical and preclinical data across multiple modalities began to converge on pathways involved in neuroplasticity being dysregulated and a key component in the development of the pathology. Neuroplasticity involves a variety of biological processes that capacitate the brain to “rewire” itself in response to internal or external stimuli. These changes include structural modifications such as synaptic plasticity wherein individual synapses are strengthened or weakened, spinogenesis, synaptogenesis, and neurite outgrowth including axonal sprouting, axon regeneration, and dendritic growth or formation. It can be captured functionally in the form of evoked potentials and functional connectivity and synchrony of neural circuits. In clinical studies, grey matter volume obtained from MRI provides an indirect indicator of neuronal density.

Neuroplasticity is this function that underlies our ability to adapt, learn, remember, and plan and in depression this biological function is impaired. Postmortem studies have shown that depression leads to shortening and reduced complexity of dendritic arbors, across the brain and especially in the Prefrontal Cortex (PFC). Novel PET ligands have allowed us to measure synapses in vivo in patients. A particularly impactful study targeted synaptic vesicle glycoprotein 2A (SV2A), a presynaptic protein, to quantify nerve terminals and calculate synaptic density. They found a strong inverse relationship with the number of synapses and severity of depression symptoms. Notably, this was also associated with aberrant network function, as measured by magnetic resonance imaging (MRI) functional connectivity. Others have found similar markers of depression using FDG-PET, EEG, and TMS. These results have been replicated in several animal models of depression and chronic stress where further biological understanding can be explored, and hypotheses and new treatments tested.

Armed with this biological understanding, the search for fast acting antidepressants met success in explorations of Ketamine, a well-known anesthetic agent, that was found to have potent anti-depressant effects after a single infusion. Ketamine is a dissociative that binds the NMDA receptor. Its antidepressant effects are conserved at sub-anesthetic doses and preclinical studies show that ketamine rapidly induces synaptogenesis and reverses the synaptic deficits caused by chronic stress and other models of depressive phenotypes. Ketamine rapidly increases the number of dendritic spines and to restore aspects of functional connectivity. The ketamine studies stimulated a new generation of basic antidepressant research that identified new neural signaling mechanisms in antidepressant response and provided a conceptual framework linking a group of novel antidepressant mechanisms.

While studying ketamine's activities, traditional antidepressants were included as comparative controls. It was found that they, too, improved neuroplasticity but with a significantly protracted time course and to a lesser degree, mirroring the clinical effects. Indeed, antidepressant effects on neuroplasticity are shown to correlate with behavioral improvement, both in humans and in animal models, suggesting increased neuroplasticity as the substrate of most depression treatments. This work has been extended in other depression treatment modalities, as well, including ECT, TMS, and exercise.

When ketamine entered the arena, Professor David Olson, Delix co-Founder and Chief Innovation Officer, was inspired to identify other rapid-acting neuroplasticity promoting compounds. He found that serotonergic psychedelics, such as psilocybin, LSD, and DMT, were potent psychoplastogens, a term he coined for these compounds' transformative effects on neurons, brain circuits, and behaviors. Contemporaneously, clinicians were using the psychedelic assisted therapy to treat addiction, depression, anxiety, and other brain health disorders to tremendous effect.

And here is where Delix's origins begin; Dr. Olson is unique in that he is not only a neuroscientist but also a brilliant chemist. He understood that as transformative as these treatments were, the dissociations, the hallucinations, the in-clinic administration were going to make them the therapies for a select few and not the many, many patients who needed them. For the scale needed to ebb the mental health tsunami, he would need to build off of these learnings, and disaggregate the therapeutic, beneficial, neuroplastic effects from the intoxicating, cardiotoxic activities of these first generation psychoplastogens. After successfully achieving this at the lab-level, Delix's team of experienced neuroscience drug developers and commercializers built off this base, and are now crafting a range of third-generation psychoplastogens. Each are non-hallucinogenic, non-cardiotoxic, orally-bioavailable, brain penetrant small molecules that promote rapid (within 24 hours) and enduring (at least 7 days) neuroplasticity, inspired by psychedelic compounds made to be safe and scalable, take-at-home medications.

The company recently announced regulatory approval and initial recruitment for our phase I trial of our first clinical candidate, DLX-001. We are assessing safety, pharmacokinetics, psychometric functions, and markers of brain activity and, importantly, synaptic plasticity. Delix will serve this significant, unmet need by helping heal brain and psychiatric disorders at their core in a more accessible, convenient way than current mental health drugs and costly, time-intensive psychedelic therapies allow

Attached Files:

- 2021_Frontiers_Psychedelics and Other Psychoplastogens for Treating Mental Illness.pdf

History of the development of the solution/product

David E. Olson, Delix's Chief Innovation Officer and Co-Founder, discovered that psychedelics are potent promoters of neuroplasticity. In his lab at UC Davis, David and his team discovered that by tuning out the hallucinogenic liability and other potentially harmful side effects, self-administered compounds can be produced that are safer than that of first-generation psychedelics. Delix is building on this initial discovery, bringing these compounds into the clinic and working toward a future where a more cost-efficient, equitable and accessible approach to neuropsychiatric therapies is available to all, with the ultimate goal of providing patients medicines that are safe enough to be prescribed and taken at home.

Attached Files:

- 2018_Psychoplastogens A Promising Class of PlasticityPromoting Neurotherapeutics_Jnl Experimental Neuroscience.pdf
- 2021_Cell Press_Psychedelicinspired drug discovery using an engineered biosensor.pdf
- Delix_Key Publications_Summaries.pdf
- 2020_Nature_A nonhallucinogenic psychedelic analogue with therapeutic potential.pdf
- 2018_Cell Press_Psychedelics Promote Structural and Functional Neural Plasticity.pdf

Why this solution/product is innovative, the broad implications for future research, and/or how it will improve the human condition

Until recently, innovation in the development of novel neuropsychiatric medicines has been minimal and with one in five adults in the US currently suffer from a psychiatric disorder, according to The National Alliance on Mental Illness, there is a clear and unmet need for better solutions. On the near horizon, psychedelic-assisted therapies have shown great promise. However, these treatment paradigms require in-clinic administration and medical observation due to the hallucinatory effects, the invasive routes of administration, and risk for cardiac events. Not only does this lead to high treatment costs but also requires time, travel, and other life disruptions making access challenging. Even if access was not a hurdle, the contraindications such as neuropsychiatric or cardiac comorbidities make the addressable patient population to these transformative therapies estimated at <5% of the patients in need. Delix's mission is to bring the healing power of neuroplasticity-promoting psychoplastogens to the other 95% of patients who could benefit. By democratizing access to a new type of therapeutics while working within the structure of the existing medical system, we can fundamentally change the way the broader mental illness and other brain health disorders are treated.

Attached Files:

- 2023_Science_Psychedelics promote neuroplasticity through activation of intracellular 5HT2A receptors.pdf
- 2021_Frontiers_Psychedelics and Other Psychoplastogens for Treating Mental Illness.pdf

Please provide appropriate references (ie Pubmed links)

Publications and Webinars

1. Nature Webinar: Psychoplastogens: Evolution of the Psychedelic Revolution (https://vimeo.com/manage/videos/715628211)
2. Psychedelics promote neuroplasticity through the activation of intracellular 5-HT2A receptors https://www.science.org/doi/10.1126/science.adf0435

3. Psychedelic-Inspired Drug Discovery Using an Engineered Biosensor https://www.cell.com/cell/fulltext/S0092-8674(21)00374-3
4. An Analog of Psychedelics Restores Functional Neural Circuits Disrupted by Unpredictable Stress https://www.nature.com/articles/s41380-021-01159-1
5. A Non-Hallucinogenic Psychedelic Analog with Therapeutic Potentia https://www.nature.com/articles/s41586-020-3008-z
6. Psychedelics Promote Structural and Functional Plasticity https://www.cell.com/cell-reports/fulltext/S2211-1247(18)30755-1
7. Psychedelics and Other Psychoplastogens for Treating Mental Illness https://www.frontiersin.org/articles/10.3389/fpsyt.2021.727117/full
8. The Promise of Psychedelic Science https://pubs.acs.org/doi/10.1021/acsptsci.1c00071
9. The Subjective Effects of Psychedelics May Not Be Necessary for Their Enduring Therapeutic Effects https://pubs.acs.org/doi/10.1021/acsptsci.0c00192
10. Transient Stimulation with Psychoplastogens Is Sufficient to Initiate Neuronal Growth https://pubs.acs.org/doi/10.1021/acsptsci.0c00065
11. Identification of Psychoplastogenic N,N-Dimethylaminoisotryptamine (isoDMT) Analogues through Structure–Activity Relationship Studies https://pubs.acs.org/doi/10.1021/acs.jmedchem.9b01404
12. Chronic, Intermittent Microdoses of the Psychedelic N,N-Dimethyltryptamine (DMT) Produce Positive Effects on Mood and Anxiety in Rodents https://pubs.acs.org/doi/10.1021/acschemneuro.8b00692
13. Psychoplastogens: A Promising Class of Plasticity-Promoting Neurotherapeutics https://journals.sagepub.com/doi/10.1177/1179069518800508

Press Releases and Notable Media

1. https://www.delixtherapeutics.com/news/delix-therapeutics-initiates-phase-i-trial-for-novel-compound-dlx-001/
2. https://www.prnewswire.com/news-releases/pioneering-delix-therapeutics-study-published-in-science-elucidates-the-mechanism-of-psychedelic-induced-neuroplasticity-301749295.html?tc=eml_cleartime
3. https://www.prnewswire.com/news-releases/delix-therapeutics-partners-with-cellectricon-expressive-neuroscience-and-expands-science-team-to-accelerate-drug-discovery-and-translatability-301745288.html
4. https://www.nature.com/articles/d41586-022-02869-4
5. https://www.delixtherapeutics.com/news/news--delix-therapeutics-and-pfizer-uk-recognized-as-gender-equity-champions-for-women-in-the-workplace-by-healthcare-businesswomens-association/
6. https://www.delixtherapeutics.com/news/experienced-cns-industry-executive-eliseo-salinas
7. https://www.delixtherapeutics.com/news/experienced-cns-industry-executive-eliseo-salinas
8. https://www.delixtherapeutics.com/news/news---nature-biotechnology-selects-delix-therapeutics/
9. https://www.delixtherapeutics.com/news/nature-biotechnologysannual-survey-highlights-academic/
10. https://www.delixtherapeutics.com/news/get-ready-for-the-magic-mushroom-pill/
11. https://www.delixtherapeutics.com/news/taking-the-magic-out-of-magic-mushrooms/
12. https://www.delixtherapeutics.com/news/accessibility-is-key-for-the-psychedelic-revolution/
13. https://www.delixtherapeutics.com/news/news---drug-companies-are-investing-big-in-psychedelics/
14. https://www.delixtherapeutics.com/news/news---the-future-of-psychedelic-medicine-will-be-drugs-youve-never-heard-of/

15. https://www.delixtherapeutics.com/news/news---financing-announcement/
16. https://www.delixtherapeutics.com/news/news---nida-partnership/
17. https://www.delixtherapeutics.com/news/news---dr-krystal/
18. https://www.delixtherapeutics.com/news/news---fierce-biotech/
19. https://www.delixtherapeutics.com/news/news-series-a-announcement/