



HOPE FOR DEPRESSION
RESEARCH FOUNDATION

FUNDING THE BEST MINDS, TO HEAL MINDS.™

Leading Research Achievements, 2024

The state of global mental health is in crisis. While mental health disorders have long been on the rise, the drastic increase in depression and anxiety since the COVID-19 pandemic must be viewed as a second pandemic. The urgency to find new approaches to treatment beyond what is currently available has never been greater.

In the past year, HDRF's Depression Task Force of top brain scientists announced that—out of the 20,000 genes that make up the human body—they have identified 20 new gene targets in the brain that can lead to novel treatments for the illness. Through a series of collaborative research projects, they have found that these genes produce proteins whose levels get out of balance in stress-related disorders like depression.

“These top twenty gene targets have been tagged in a wide range of mouse models to demonstrate how the change in proteins is unhealthy and linked to depression and then validated in brain tissue from humans who died with depression,” said Dr. Eric Nestler, Head of the Depression Task Force and Chair of Psychiatry at Mount Sinai School of Medicine.

The list of new targets emerging from this research is below. The research is complex, but what's clear is that depression must be studied on multiple levels to understand how pathways of risk develop: genetic, epigenetic, molecular, cellular, and entire circuit networks.

Thank you for your valuable support in this effort.

1. Targets Involving Nerve Cells

Hyperpolarization-Activated Cyclic Nucleotide-Gate Channels (HCNs)

HCN channels were shown by HDRF laboratories to control the activity of the brain's dopamine neurons, which play an integral role in reward and motivation. HDRF research demonstrated further that abnormal activation of these channels drives susceptibility to chronic stress, while inhibitors of the channels exert antidepressant-like actions. Several HCN inhibitors have been developed by the pharmaceutical industry for other purposes and should now be studied in depression trials.

Sodium-Dependent Neutral Amino Acid Transporter (SLC6A15)

SLC6A15 was identified as a depression-associated gene by an HDRF laboratory via the review of large studies of patients with depression. The protein is found in abnormally high levels in hippocampus in depressed patients, and more recently associated with insomnia in several other clinical studies. Regulation of SLC6A15 as an antidepressant has been validated in several rodent models by HDRF investigators. In the next few years, development of small molecule inhibitors of SLC6A15 would be a straightforward endeavor.

5-HT4 Receptor (HTR4)

HDRF's preclinical work identified HTR4 as a target for the rapid reduction of anxiety- and depression-like behaviors in several rodent models. More recently, our pilot clinical studies have shown that prucalopride, an HTR4 activator, approved by the FDA for the treatment of constipation, has rapid antidepressant and anxiolytic activities. These findings provide the rationale for a clinical evaluation of this mechanism in humans with depression or anxiety.

2. Targets Involving Immune Cells in Circuit Networks

Interleukins

Work by several HDRF investigators has implicated certain pro-inflammatory cytokines, subtypes of interleukins, in subtypes of depression. This conclusion is based on concordant studies in both humans and animal models. Examples include the pro-inflammatory Interleukin 7 and Interleukin 34. Antibodies directed against these proinflammatory interleukins treat stress-induced neural and behavioral abnormalities in animal models, and HDRF-funded studies are under way to assess their antidepressant utility in humans.

FK506 Binding Protein 5 (FKBP5)

A growing body of evidence supports the importance of this protein in depression- and anxiety-related abnormalities in rodent models. The first available small molecule antagonists (inhibitor) of FKBP5, developed in HDRF-funded labs, are termed Safit 1 and Safit 2. These antagonists reduce anxiety-related behavior and increase positive coping with chronic stress in rodents. Clinical studies are being planned to start in the next few years.

Complement Subunits

Complement C1q A (C1QA), Complement C1q C (C1QC), Complement C3, and Integrin alpha M (ITGAM) are proteins in the brain involved in neuroinflammation, for which we have convergent evidence for their role in depression. They are positive hits in several of our genome-wide assays. We also see consistent differences in selectively bred rat lines with genetic differences in temperament (anxious versus more docile). Minocycline, which alters microglia activity and expression of these genes, reverses depression-like behaviors in animals with anxious temperament.

3. Targets Involving Growth Factors and Related Proteins

Fibroblast Growth Factor 9 (FGF9)

FGF9 a pro-depressant and pro-anxiety molecule which is the physiological antagonist (inhibitor) for FGF2. An HDRF laboratory discovered FGF2 earlier as a natural antidepressant and anxiolytic. We have shown that FGF9 does exactly the opposite in a range of measures. Evidence includes human postmortem studies, animal studies, mechanistic studies using viral

vectors. These data support the goal of creating antagonists of FGF9 as novel therapeutic agents.

Protocadherin 8 (PCDH8)

PCDH8 is a cell surface protein that is involved in neuroplasticity and whose expression is regulated by genes associated with depression risk. PCDH8 also shows altered expression in several HDRF datasets, and we have demonstrated its direct involvement in mediating depression- and anxiety-like behavior in rodent models.

Activin Receptor 1 (ACVR1)

Preclinical work in HDRF laboratories has shown that activin signaling in the hippocampus dentate gyrus is necessary and sufficient for an antidepressant-like response, with genome-wide data specifically implicating ACVR1. We are currently exploring the effects of specific ACVR1 agonists in reversing depression-related behavioral abnormalities in rodent models.

GPR56 (also known as ADGRG1)

GPR56 is a protein in the cell membrane that enhances connectivity among specific brain circuits. HDRF research has uncovered several convergent lines of evidence for the contribution of GPR56 to depression, based on both human and animal data. Molecules targeting GPR56 are being developed, which can be studied as potential therapeutic agents for human stress disorders.

4. Targets involving Genes and Gene Expression

Histone Deacetylases (HDAC1 and HDAC3)

Histone acetylation is highly regulated in brain in chronic stress models and in response to antidepressant treatments in these models. Administration of several available inhibitors of class I HDACs (specifically inhibitors of HDAC1 and HDAC3) exert robust antidepressant-like effects in chronic stress models. Several such HDAC inhibitors are in clinical development for cancer and could be studied readily in human depression.

Sirtuin 1 (SIRT1)

Sirtuins are called class III HDACs and serve to deacetylate not only histone proteins but several other classes of proteins as well. Resveratrol is a non-selective SIRT1 inhibitor which boosts reward function in animal models, while molecular manipulation of SIRT1 in these models directly implicates the protein in stress responses. Resveratrol has been studied in humans, where it is proposed to produce anti-aging effects, but its non-selectivity and side effects require the development of more specific agents.

Estrogen Receptor Alpha (ESR1)

Work in several HDRF laboratories has demonstrated that ESR1 is highly associated with stress resilience across several brain regions in several chronic stress models in rodents. This deduction is confirmed by direct experimental manipulation of ESR1 in animal models: ESR1 overexpression increases behavioral resilience in the face of chronic stress. Interestingly, this pro-resilience effect holds for both males and females.

Histone Methyltransferase 4 (KMT4; also known as DOT1L)

Research funded by HDRF has demonstrated that KMT4, which controls a specific type of histone methylation, exerts pro-depression-like effects in several chronic stress procedures in rodents, whereas the associated demethylating enzyme KDM2B exerts antidepressant-like effects. A KMT4 inhibitor, pinometostat, in clinical development for certain cancers, was found to produce pro-resilient and antidepressant-like effects in rodent models, thus, defining a way to test this novel mechanism in depressed humans.

ΔFOSB

HDRF investigators have shown that this FOS family transcription factor is induced by chronic stress exposure in specific neuronal cell types in the brain. Our genome-wide datasets further implicate ΔFOSB across several animal models. Blockade of ΔFOSB induction in these specific circuits produces antidepressant- and anxiolytic-like effects in these models. Small molecule inhibitors of ΔFOSB are being developed by an NIH-funded project associated with HDRF efforts.

5. Targets Related to Circuits Involved in Pain Regulation

Mu Opioid Receptor (MOR)

HDRF research has demonstrated that the antidepressant-like effects of the small molecule tianeptine are mediated through signaling actions at MOR. Evidence suggests that tianeptine affects MORs differently compared to traditional opioid drugs, and efforts are under way to synthesize tianeptine analogs that mimic these specific signaling mechanisms. Moreover, an HDRF-funded clinical study is using a novel behavioral method to identify a subtype of depressed humans who respond most positively to tianeptine.

Delta Opiate Receptor (DOR)

HDRF's research in animal models has shown that DOR is also involved in stress responses. For example, our work has demonstrated that DOR activity is necessary for the antidepressant-like effects of SSRIs. We are currently exploring the effects of specific compounds that activate DOR, several of which have been developed as analgesic compounds.

Enkephalinase (MME-Membrane Metalloendopeptidase)

Levels of MME and its substrate, enkephalin, are highly regulated across several HDRF animal models. As just one example, we have shown that SSRIs increase enkephalin levels in the hippocampal dentate gyrus, but only in the subgroup of rodents that respond behaviorally to these antidepressants. Moreover, our preliminary studies show that the enkephalinase inhibitor, RB101, has antidepressant-like effects in these models.

Thank You

The field of psychiatry is in great need of new neuroscience-based cures that can be individualized for each patient. HDRF is deeply proud of the Depression Task Force and its leadership in the field. We are grateful for your participation in this remarkable scientific initiative.