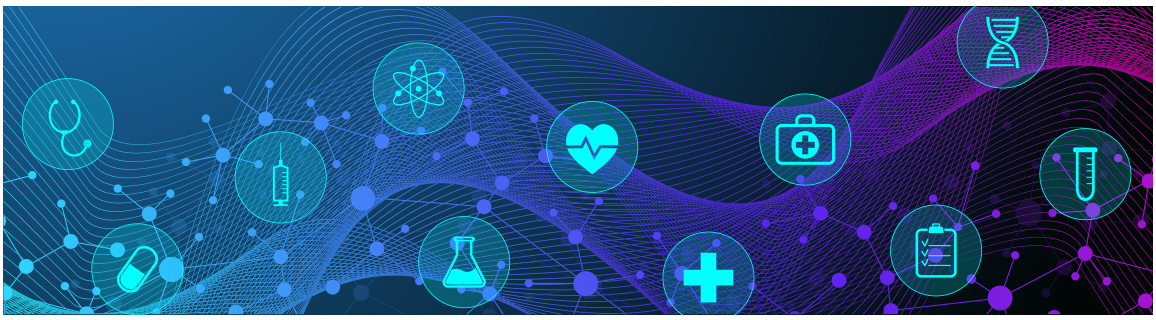
News & Impact 2019
PRECHTERPROGRAM.ORG

HEINZ C. PRECHTER BIPOLAR RESEARCH PROGRAM
MICHIGAN MEDICINE

CONTENTS

WORKING TO IMPROVE CARE

U-M PRECISION HEALTH + PRECHTER BIPOLAR RESEARCH are fueled by $10 MILLION in gifts



Support from the Richard Tam Foundation will accelerate U-M's translational bipolar disorder research in an effort to tailor care to individuals for improved results.

A new gift to the University of Michigan (U-M) aims to bring more precision to the care of people with bipolar disorder. It will expand and harness the power of massive data from U-M bipolar research, and allow researchers to mine that trove of information in combination with other data, using advanced tools created for Precision Health at U-M.

This new $5.8 million gift from the Richard Tam Foundation brings the foundation's total giving to U-M for bipolar research to $10 million, and will allow more scientists and clinicians to translate new knowledge into improved care.

Judith Tam, president of the Richard Tam Foundation, says the combination of the university's strength in studying bipolar disorder and related conditions, and the university's investment in precision health, inspired the gift.

The Richard Tam Foundation has given to U-M's bipolar work since 2014, helping fuel the growth of the **Heinz C. Prechter Bipolar Research Program** that has collected genetic samples and other data from people with and without bipolar illness for more than 13 years.

Melvin McInnis, M.D., director of the Prechter Program, says, "This new gift will allow us to build upon the infrastructure already in place at the university, to integrate clinical data and our research data, and ultimately to **build models of illness trajectories that will inform care**."

Sachin Kheterpal, M.D., MBA, a co-director of U-M Precision Health, praises the Richard Tam Foundation's position as a pioneer in giving to the new U-M initiative.

He says, "It's a very generous gift that is hopefully a model for future gifts, where we're able to demonstrate the value of researching individual diseases, marrying that research data with the Precision Health platforms we're building, and

"Precision health could help doctors figure out the right medicine to give to a particular patient, much more quickly, and could expand their toolbox through new discoveries. We've got brilliant people here, and I've seen the passion in their eyes when they talk about their research. They're not just doing their work and going home. They are on fire." —JUDITH TAM

CONTINUED ON PAGE 2

THANK YOU for rising to the challenge and helping us raise indispensable funds! **Read more** about the matching gift challenge on page 15.

$10 MILLION

CONTINUED FROM COVER

thereby increasing the potential for hundreds of researchers to benefit from the overall impact." The gift will create the **Tam Precision Health & Bipolar Collaboration Fund within Precision Health**.

"We absolutely need to **leverage our Precision Health platform to advance and support the pace of discovery research**. We are highly committed to collecting more robust bipolar research data, as well as information on other therapeutic treatments that would benefit from a very personalized approach," said Marschall S. Runge, M.D., Ph.D, U-M executive vice president for medical affairs.

In addition to **supporting Precision Health-related work**, the new gift **will continue support for bipolar disorder research projects at U-M**. It will also create a professorship in the Department of Psychiatry, with the proposed name of the **Richard Tam Professorship in Translational Bipolar Research**, pending approval by the U-M Board of Regents. This will allow the recruitment of another top bipolar researcher to U-M.

The Richard Tam Foundation **issued a challenge** to others interested in moving bipolar research forward, offering to **match bequest dollars to the Prechter Program documented in 2019**. Judith Tam hopes that the new gift will inspire even more giving by those who have seen the impact of bipolar disorder on those they love.

Says McInnis, **"The work that the Prechter Program is doing with Precision Health is absolutely fundamental and transformational in terms of the future of medicine, the future of mental health research and the future of our understanding of various different human illnesses."**

Melvin G. McInnis, M.D., FRCPsych
Thomas B. and Nancy Upjohn Woodworth Professor of Bipolar Disorder and Depression
Associate Director, U-M Depression Center
Professor of Psychiatry
Principal Investigator, Heinz C. Prechter Bipolar Research Program

Judith Tam
President of the Richard Tam Foundation

Collaborations

throughout

THE UNIVERSITY OF MICHIGAN

- Depression Center
- Department of Cell & Developmental Biology
- Department of Psychiatry
- Department of Pharmacy
- Department of Psychology
- Department of Pharmacology
- School of Kinesiology
- Computer Science and Engineering
- College of Engineering
- School of Public Health
- School of Social Work
- Department of Mathematics
- Cardiology
- Rackham Graduate School

Impact by the Numbers

1331 **Research participants** are enrolled in the Prechter Longitudinal Study of Bipolar Disorder – now in its **13**th year

50 **Collaborators** from **14** states and **5** countries

40 **Research staff** focused on running the different projects

11 Current **undergraduate, graduate, and medical students** who gain expertise and training in the course of doing the research

562 **Gifts donated** in FY19 by 460 donors, for a total of **$2,909,217**. **Thank you!**

21 Research associates accepted to **doctoral programs** over the past decade

18 Studies are contributing to our **knowledge about bipolar disorder**

21 Scientific publications in 2018

153 Scientific publications to date

PRECHTER FACULTY RETREAT BRINGS NEW ENERGY

ATTENDEES OF THE FACULTY RETREAT

Pictured left to right, back row: **Celeste Liebrecht, Holli Bertram, Ivy Tso, Sue O'Shea, Steve Taylor, Roman Giger, Melvin McInnis, Geoff Murphy, Neera Ghaziuddin, Paul Jenkins, Will Meurer, David Marshall, Srijan Sen**

Front row: **Helen Burgess, Cynthia Burton, Patty Deldin, Sagar Parikh, Emily Mower Provost**

In April 2019, Prechter Bipolar Research Program faculty and their collaborators held the first Prechter Bipolar Research faculty retreat. The retreat theme, ***Bipolar and Beyond***, reflects the conviction that bipolar disorder research has broad implications and will yield information directly relevant to other psychiatric and medical disorders.

Attendees were from multiple departments across the University of Michigan, **a reflection of the Prechter Program's dedication to engaging researchers from different disciplines**. These scientists bring new perspectives and techniques as well as physical samples and data to the study of bipolar disorder. For example, we were recently granted permission to engage with the approximately **2,000 bipolar individuals in the Michigan Genomics Initiative**, which will add substantially to the data from the over 1,300 individuals currently in the Longitudinal Study of Bipolar Disorder data set.

The retreat provided an exciting forum for new ideas, new collaborations and the development of a path forward. **A high priority goal is increased accessibility to our data by researchers**. This coming year will also see the formation of several organizing structures: an executive steering committee, a data task force and a scientific advisory committee. These committees will guide the continued growth of the Prechter Program. We are excited by the **energy, creativity and enthusiasm of our faculty and collaborators** and are convinced that working together will speed our path to discovery.

DATA LAB UPDATES

The Prechter Data Lab is responsible for the storage, retrieval and organization of our **diverse and growing datasets**. The data lab's primary aim is to assist our researchers with the data they need to gain knowledge into the causes and treatment for bipolar disorder. Our data includes **phenotypic, demographic, genetic, molecular and medical information** as well **as clinical, cognitive, behavioral and speech assessments**.

Our Longitudinal Study of Bipolar Disorder now includes 13 years of data from more than 1330 research participants. We have collaborated with the **University of Michigan Central Biorepository** to obtain and store biological specimens (blood/plasma/saliva) from our participants. We are also working with the **Precision Health Initiative** to integrate the ever-growing data resources at the University of Michigan, which includes the electronic-health record and geographical information systems, with our data. This treasure trove of data will provide insight and answers to questions about bipolar disorder.

We're excited to test new algorithms for analyzing our diverse data in novel ways and to collaborate with researchers throughout the University and world-wide.

To help achieve this goal, we've added a **new senior staff member, Anastasia Yocum, Ph.D.**, who recently joined the Prechter Data Lab as a Research Program Manager. With the help of our talented data programmers, Kritika Versha and Steve Anderau, **Dr. Yocum is charged with the design and development of a data management system which will allow researchers greater access to this great lake of data and increase progress in treating bipolar disorder**.

INTERVENTIONAL PSYCHIATRY TREATMENTS

Many treatments in psychiatry, while well supported by research, work only for some people. Most treatments for depression or bipolar disorder **take weeks to have a noticeable effect, and months to provide major relief** — an understandable yet sometimes frustrating "wait and see" approach. **Interventional psychiatry** leads us to a tipping point towards a new model of care in psychiatry. Through research, **novel treatments and approaches are emerging**, involving primarily intravenous medications and brain stimulation techniques. Below are several interventional psychiatry initiatives underway within the University of Michigan Department of Psychiatry.

ELECTROCONVULSIVE THERAPY (ECT)

ECT is one of the oldest forms of interventional psychiatry. After a patient is unconscious with general anesthesia and has been given a muscle relaxant, ECT is administered as a low dose electrical stimulation to the head, which produces seizure activity seen on brainwave monitoring (EEG monitor). **ECT is highly effective in severe bipolar depression**, and even is used in rare cases of mania where usual anti-manic medication is not working. Though ECT has been stigmatized in the media for years, **its effectiveness cannot be ignored**.

THE BIO-K (KETAMINE) STUDY

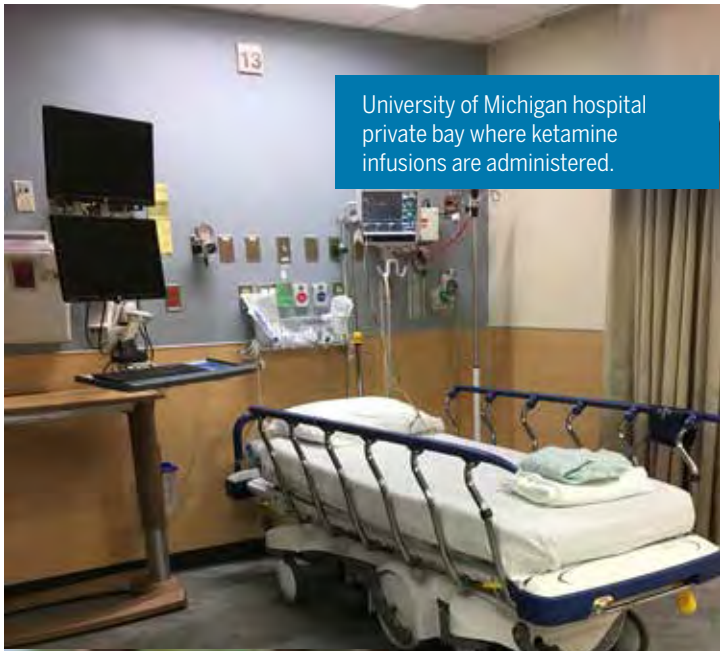
led by Sagar Parikh, M.D., FRCPC

Ketamine, typically used as a sedative in operating rooms, has been lauded as a **potential breakthrough medication for the treatment of depression**. Researchers from the University of Michigan Department of Psychiatry and Depression Center are part of a national team trying to find out if this medicine can help the symptoms of depression through the **Bio-K Study**. More specifically, we want to learn if some people have better response to ketamine treatments than others and if we can predict that response (biomarkers).

The Bio-K Study will enroll 100 individuals between 18–65 years of age with a diagnosis of major depressive disorder, bipolar disorder I or II, and who have treatment-resistant depression. Those who consent, and who pass a comprehensive screening process, receive three 40–100 minutes intravenous (IV) ketamine infusions over the course of eight to 11 days, at the University of Michigan hospital. Participants also complete blood draws before and after the infusions **so we can develop the biomarkers and, hopefully, enhance treatment for individuals dealing with these disorders**.

TRANSCRANIAL MAGNETIC STIMULATION (TMS)

In 2018, the FDA approved a new form of Transcranial Magnetic Stimulation (TMS), known as **Theta-Burst TMS**. TMS is a neuromodulatory technique which **applies magnetic pulses to the brain and stimulates nerve cells** in the region of the brain involved in mood control and depression. TMS can activate regions of the brain that have decreased activity in depression. The new version of TMS involves just a three-minute stimulation applied daily for either clinical depression or obsessive-compulsive disorder. Traditional TMS has long been FDA-approved but is not routinely administered by most practicing psychiatrists because it requires special equipment and training, and treatment usually involves 45 minutes daily for many weeks. **This new three-minute system has the potential to transform care for our patients by getting them to feel better in minutes**.



University of Michigan hospital private bay where ketamine infusions are administered.

Sagar V. Parikh, M.D., FRCPC
Professor of Psychiatry and John F. Greden Professor of Depression and Clinical Neuroscience

Learn more about Dr. Parikh on our website: myumi.ch/LB7gl

The complex world of **bipolar research** in the Prechter team

Our team recently presented several research posters at the **Albert J. Silverman Research Conference**, an annual event hosted by the University of Michigan's Department of Psychiatry.

Elena Lamping, BA

Data-derived Subsyndromal Classes of Bipolar Disorder Show Sparse Evidence of Neuropsychological Differences

"Using the Prechter Longitudinal Study of Bipolar Disorder cohort, classifications were created that divide those diagnosed with bipolar disorder based on their mood over long periods of time (depressed, stable, or rapid cycling). ***Through analyzing cognitive measures*** *administered during participants' first visits with the study, we found that these classifications do not differentiate based on neuropsychological performance, and only apply to select clinical measures."*

The Influence of Functional Remediation Intervention of Neuropsychological Performance in Bipolar Disorder

"A 21-week intervention tailored for improving daily functioning in bipolar disorder, called ***Functional Remediation****, was tested with the Prechter longitudinal cohort last year. After completing analyses, there were no significant cognitive improvements found, however, our sample was small, our participants were not remarkably cognitively impaired to begin with, and consistent attendance proved difficult for participants. We suggest adapting the intervention to better fit an American sample."*

Madison Kirby, BS

Relationship Between Burden of Psychotropic Medications and Cognitive Performance in a Large Sample of Individuals With Bipolar Illness

"When we looked at the medication variable and cognition scores, we found that there were significant relationships suggesting ***medications may negatively influence certain areas of cognition****. We no longer saw these relationships when we accounted for depression symptoms, so these effects may be better accounted for by depression symptoms, rather than psychotropic medications."*

Ariana Tart-Zelvin, PhD, & Bethany Navis, BS

Performance Validity Testing Among Individuals With Various Affective Disorders

"Previous research has provided mixed findings regarding whether or not ***cognitive impairments in individuals with various affective disorders*** *should be attributed to poor effort during cognitive testing. We compared measures of effort between individuals with various affective disorders to individuals with no history of mental health disorders and found no significant differences. Those with affective disorders put forth commensurate effort on testing, and as such, the cognitive impairments associated with such individuals should serve as a focus for research and clinical interventions."*

Daniela Lopez, MS

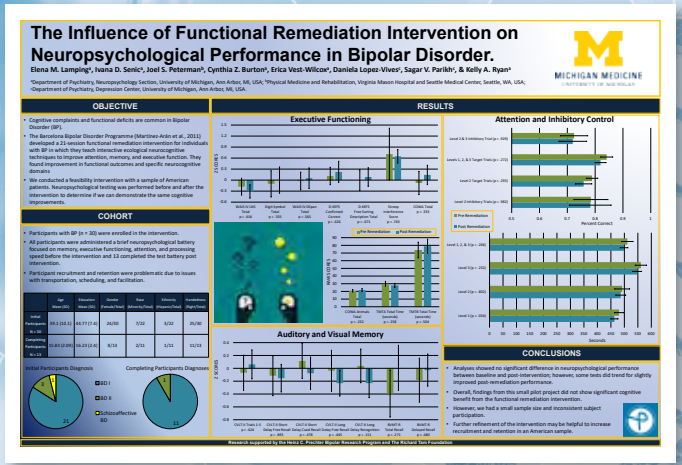
Using IV Ketamine More Effectively: Safety and Efficacy of 100-minute Versus 40-minute Intravenous Infusions for Refractory Unipolar or Bipolar Depression

"The ***Bio-K study*** *is trying to learn more about how the medication known as ketamine can help people living with depression. My poster showed some of the information we have collected from 10 participants at the University of Michigan site and some of the common side effects they've experienced."*

Andrew Nelson, PhD candidate

A Loss-of-Function Variant in *ANK3* from a Family With Bipolar Disorder Causes Altered Forebrain Circuitry

"ANK3 is one of the top genes linked to bipolar disorder. We found that a ***loss-of-function mutation in ANK3****, found in a family with bipolar disorder, leads to abnormalities in inhibitory and excitatory brain circuits and altered network synchronization. This work provides insight into how mutations in ANK3 may contribute to the underlying causes of bipolar disorder."*


The Influence of Functional Remediation Intervention on Neuropsychological Performance in Bipolar Disorder.

Elena M. Lamping[a], Ivana D. Senic[a], Joel S. Peterman[b], Cynthia Z. Burton[b], Erica Vest-Wilcox[a], Daniela Lopez-Vives[a], Sagar V. Parikh[a], & Kelly A. Ryan[a]

[a]Department of Psychiatry, Neuropsychology Section, University of Michigan, Ann Arbor, MI, USA; [b]Physical Medicine and Rehabilitation, Virginia Mason Hospital and Seattle Medical Center, Seattle, WA, USA; [a]Department of Psychiatry, Depression Center, University of Michigan, Ann Arbor, MI, USA.

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

OBJECTIVE

- Cognitive complaints and functional deficits are common in Bipolar Disorder (BP).
- The Barcelona Bipolar Disorder Programme (Martinez-Aran et al., 2011) developed a 21-session functional remediation intervention for individuals with BP in which they teach interactive ecological neurocognitive techniques to improve attention, memory, and executive function. They found improvement in functional outcomes and specific neurocognitive domains.
- We conducted a feasibility intervention with a sample of American patients. Neuropsychological testing was performed before and after the intervention to determine if we can demonstrate the same cognitive improvements.

COHORT

- Participants with BP (n = 30) were enrolled in the intervention.
- All participants were administered a brief neuropsychological battery focused on memory, executive functioning, attention, and processing speed before the intervention and 13 completed the test battery post intervention.
- Participant recruitment and retention were problematic due to issues with transportation, scheduling, and facilitation.

	Age Mean (SD)	Education Mean (SD)	Gender (Female/Male)	Race (White/Eq.Mixed)	Ethnicity (Hispanic/Non)	Handedness (Right/Total)
Initial Participants (n = 30)	39.5 (10.1)	16.77 (2.4)	24/30	7/22	3/22	26/30
Completing Participants (n = 13)	41.85 (7.09)	16.23 (2.4)	8/13	2/11	1/11	11/13

Initial Participants Diagnosis: BD I 1, BD II 8, Unspecified 22

Completing Participants Diagnosis: 3, 10

RESULTS

Executive Functioning

Attention and Inhibitory Control

Auditory and Visual Memory

CONCLUSIONS

- Analyses showed no significant difference in neuropsychological performance between baseline and post-intervention; however, some tests did trend for slightly improved post-remediation performance.
- Overall, findings from this small pilot project did not show significant cognitive benefit from the functional remediation intervention.
- However, we had a small sample size and inconsistent subject participation.
- Further refinement of the intervention may be helpful to increase recruitment and retention in an American sample.

Research supported by the Heinz C. Prechter Bipolar Research Program and The Richard Tam Foundation

Here is a snapshot of the breadth of research our team is engaged in — including a short summary of each poster that was presented.

Kate Campbell, PhD

Human Induced Pluripotent Stem Cell (hiPSC) Derived GABAergic and Glutamatergic Neuron Development and Function in Bipolar Disorder

*"Differences in the development and function of several types of brain cells likely contribute to bipolar disorder. We are **comparing brain cells** from bipolar patients to those from undiagnosed individuals to better understand these differences."*

Kaela Van Til, BA

Modeling Mood Course to Detect Markers of Effective Adaptive Interventions

*"The study team examined engagement strategies, adherence rates, and preferences of participants with bipolar disorder to **utilize mobile and wearable health technology.**"*

Kasia Glanowska, PhD & Cindy De Long, PhD

Alpha-Tocopherol and Polyunsaturated Fatty Acids Treatment Effects on Quality and Maturation of Cultured Neurons Derived from Induced Pluripotent Stem Cells

*"Neurons generated from patient-derived stem cells and grown in culture provide us with an unlimited supply of cells to investigate the biochemical and genetic properties of neuropsychiatric disorders, however, there is still **a need to optimize growth conditions** to obtain healthy, mature neurons to study. Adding omega-3 fatty acid and antioxidant to the media improved the maturation and electrical properties of neurons in culture, which will allow us to better compare these cells from control and bipolar disorder patients."*

Dan Schill, PhD

Characterization of Exosomes Isolated from Bipolar Patient Plasma and iPSC: Role in Neuronal Plasticity

*"Support cells in the brain release **tiny particles that can impact neurons** that take them up. We are investigating the differences in these particles in bipolar patients."*

Elise Trim, MSW candidate

Chronicity of Mood Symptoms in Bipolar Disorder and the Relationship to Neuropsychological Performance

*"We looked at what **different life factors** influence how chronic a person's bipolar disorder may be, and how this impacts their ability to remember, think, and solve problems."*

John Gideon, MS

Emotion Recognition From Natural Phone Conversations in Individuals With and Without Recent Suicidal Ideation

*"Our work demonstrates that **emotions can be automatically detected** from speech in natural phone conversations. Furthermore, individuals with suicidal thoughts have significantly lower variability in these estimates of negative emotion, when compared with healthy controls."*

René N. Caballero-Floran, PhD

Lithium Partially Reverses Presynaptic GABAergic Signaling Deficits in the *ANK3* W1989R Mouse Model

*"The lithium treatment allows **restoring the imbalance of neuronal circuitry** caused by mutations that alter neuronal excitability, a phenomenon involved in the pathology of bipolar disorder."*

Brontë Munson

Are Deficiencies in Emotion Perception Related to Health-Related Quality of Life in Bipolar Disorder?

*"Having difficulty correctly identifying emotions in others is a symptom of bipolar disorder. Our research was interested in how, if at all, **emotional perception deficits** affected the physical and mental health of our participants."*

Spotlight

on the **Jenkins Lab** in the U-M Department of Pharmacology

Paul Jenkins, Ph.D.,
Director, Jenkins Lab

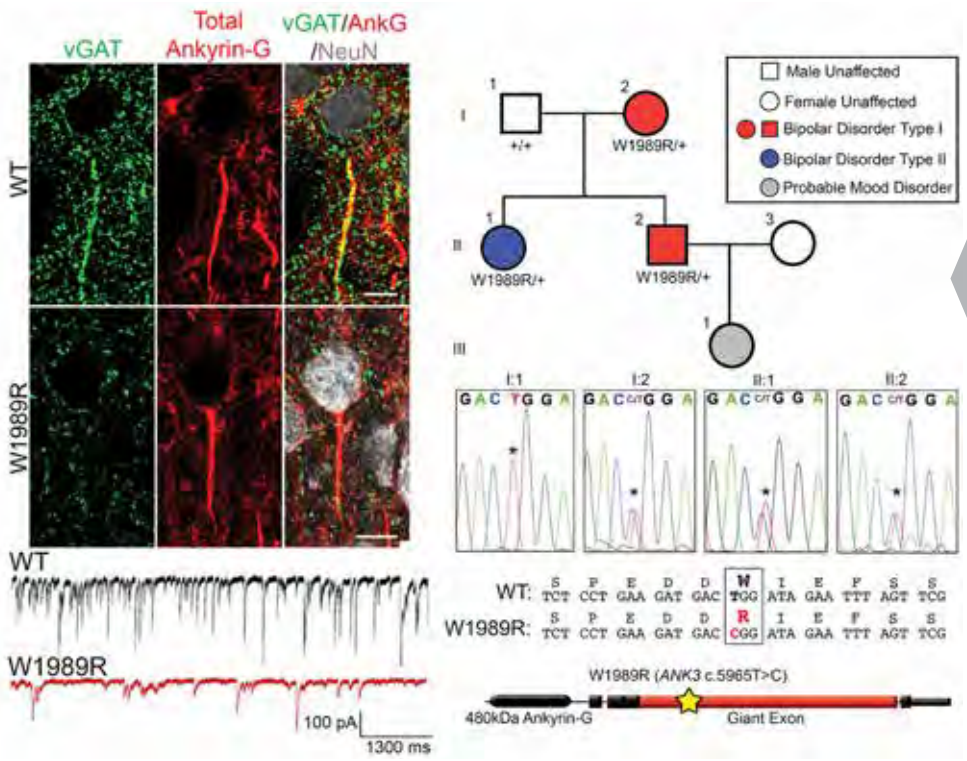
Learn more about Dr. Jenkins on our website: myumi.ch/LqGEv

Work in the Jenkins laboratory is focused on **understanding the cellular and molecular mechanisms underlying psychiatric disorders**, like bipolar disorder. Recent work from the laboratory gives important insight into the effects of **ankyrin-G *(ANK3)*** dysfunction on inhibitory signaling in the forebrain. **Inhibitory GABAergic** circuits are critical for the synchronization and higher order function of brain networks, and **defects in this circuitry are linked to neuropsychiatric diseases**, including bipolar disorder, schizophrenia, and autism.

Work in cultured neurons has shown that ankyrin-G plays a key role in the regulation of inhibitory synapses by interacting with the GABAA receptor associated protein (GABARAP). Recently, the Jenkins laboratory generated a knock-in mouse model in collaboration with Dr. Vann Bennett at Duke University that expresses a mutation that abolishes the ankyrin-G/GABARAP interaction *(Ank3* W1989R**). *Ank3* W1989R mice exhibit a striking reduction in forebrain GABAergic synapses resulting in neural cell hyper-excitability and disruptions in network synchronization.**

In collaboration with the Heinz C. Prechter Bipolar Research Program, the Jenkins lab **identified the *ANK3* W1989R variant in a family with bipolar disorde**r, suggesting a potential role of this variant in disease.

Our results highlight the **importance of ankyrin-G** in regulating forebrain circuitry and provide **novel insights into how *ANK3* loss-of-function variants may contribute to human disease**. Current work is focused on how commonly-used therapeutics affect inhibitory signaling in the *ANK3* loss-of-function mouse model, in an effort to **identify novel therapeutic targets for the treatment of bipolar disorder**. In addition, the lab is expanding its studies to include the **examination of neurons generated from patient-derived stem cells** to determine the effects of these variants in the exact genetic background of our patients.



The *ANK3* W1989R mutation causes loss of inhibitory synapses (left, green) on forebrain pyramidal neurons in mice. This causes decreases in inhibitory currents, the downward deflections in the electrophysiological recordings shown in this image. These currents are critical for normal forebrain synchronization and defects in these neurons have been implicated in a number of neuropsychiatric conditions, **including bipolar disorder**. The ***ANK3* W1989R variant is a rare variant present in 1 in 10,000 people of European American descent.** This allele was found in a family participating in the Prechter Program. Four family members carry the *ANK3* W1989R allele, all of which are affected by mood disorders.

Spotlight

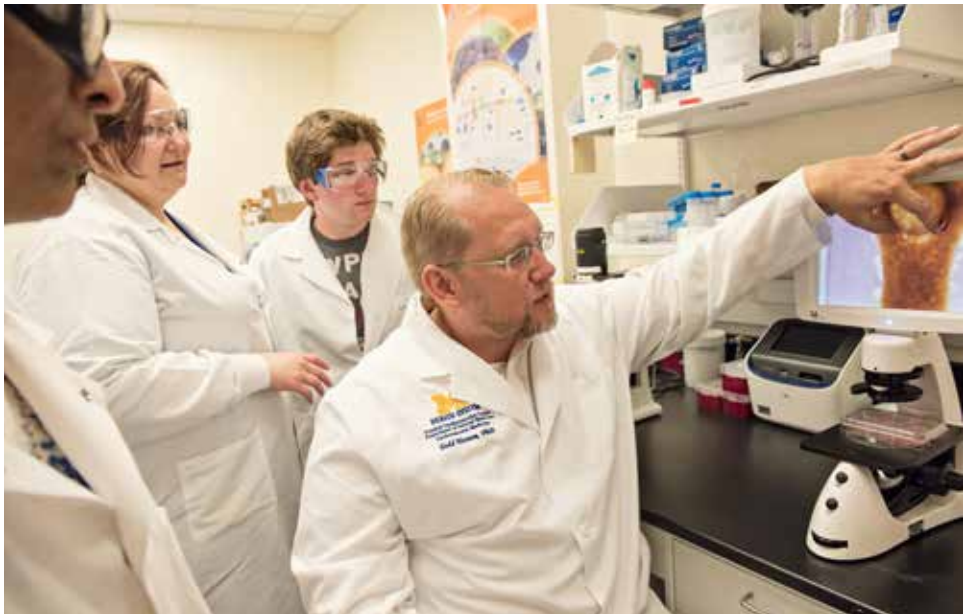
on the **Herron Lab** in the U-M Frankel Cardiovascular Center

A large number of patients with bipolar disorder **have been diagnosed with cardiac arrhythmias, suggesting a mechanistic link between these two diseases**. **Dr. Todd Herron** is the director of the Frankel Cardiovascular Regeneration Core Laboratory. His laboratory is working to determine **the links between cardiovascular health and bipolar disorder**.

Dr. Herron's research relies on the use of bipolar patient-specific induced pluripotent stem cell-derived cardiomyocytes (heart muscle cells). His lab has worked closely with Dr. Sue O'Shea and Dr. Melvin McInnis to **generate patient-specific cardiomyocytes using bipolar patient stem cells that have been cryobanked (collected and stored) as part of ongoing research in the Prechter study**.

Relying on stem cell-based approaches, we are able to generate patient-specific "heart in a dish" assays for **in-vitro testing of the links between bipolar depression and cardiac arrhythmias**. We have found a **genetic defect in the calcium channel gene** that is a risk factor for bipolar depression and cardiac arrhythmias. New research funded by the Depression Center's Berman Research Fund is focused on determining the role of the primary source of cellular energy — the mitochondria in cardiovascular health of bipolar disorder patients. Future application of **Dr. Herron's patient-specific "heart in a dish" approach may be used for bipolar patient-specific medication screening to determine patient-specific risk for drug-induced adverse cardiac events.**

The use of patient-specific stem cells, neurons and cardiomyocytes for in-vitro diagnostics is a novel aspect of personalized medicine for understanding and potentially treating patients.



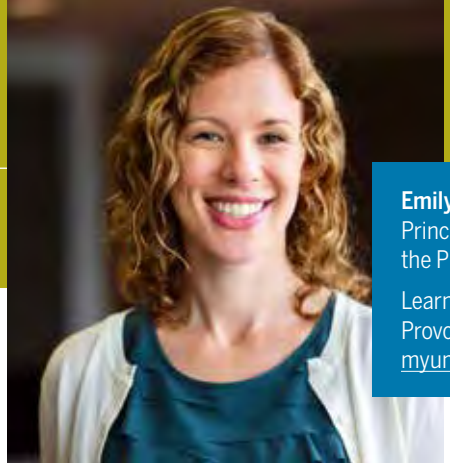
Frankel Cardiovascular Regeneration Core Laboratory staff with director **Todd J. Herron, Ph.D.** *(In the center of photo above and in the photo to the left pointing to monitor).*

Learn more about Dr. Herron on our website: myumi.ch/6QVmY

THE PRIORI STUDY ››››

PREDICTING **I**NDIVIDUAL **O**UTCOMES FOR **R**APID **I**NTERVENTION

LONGITUDINAL VOICE PATTERNS in Bipolar Disorder



Emily Mower Provost, Ph.D., Principal Investigator of the PRIORI study

Learn more about Dr. Mower Provost on our website: myumi.ch/6j5EV

The PRIORI project is inspired by the power of artificial intelligence and personal technology to monitor the human condition and augment health. Health changes do not occur in a vacuum. Time is a critical factor. In advance of experiencing episodes of ill health, individuals' behaviors change. When these changes are visible to the individual or to friends, family, and caregivers, **there is an opportunity for intervention.** But often, these changes occur outside of familiar observers or lack external evidence. **Our team is developing methods to observe and quantify critical personal and social changes.**

In our preliminary work, supported by NIMH R34, NSF CAREER, and foundation grants and awards, we developed a **smartphone mental health monitoring system** consisting of:

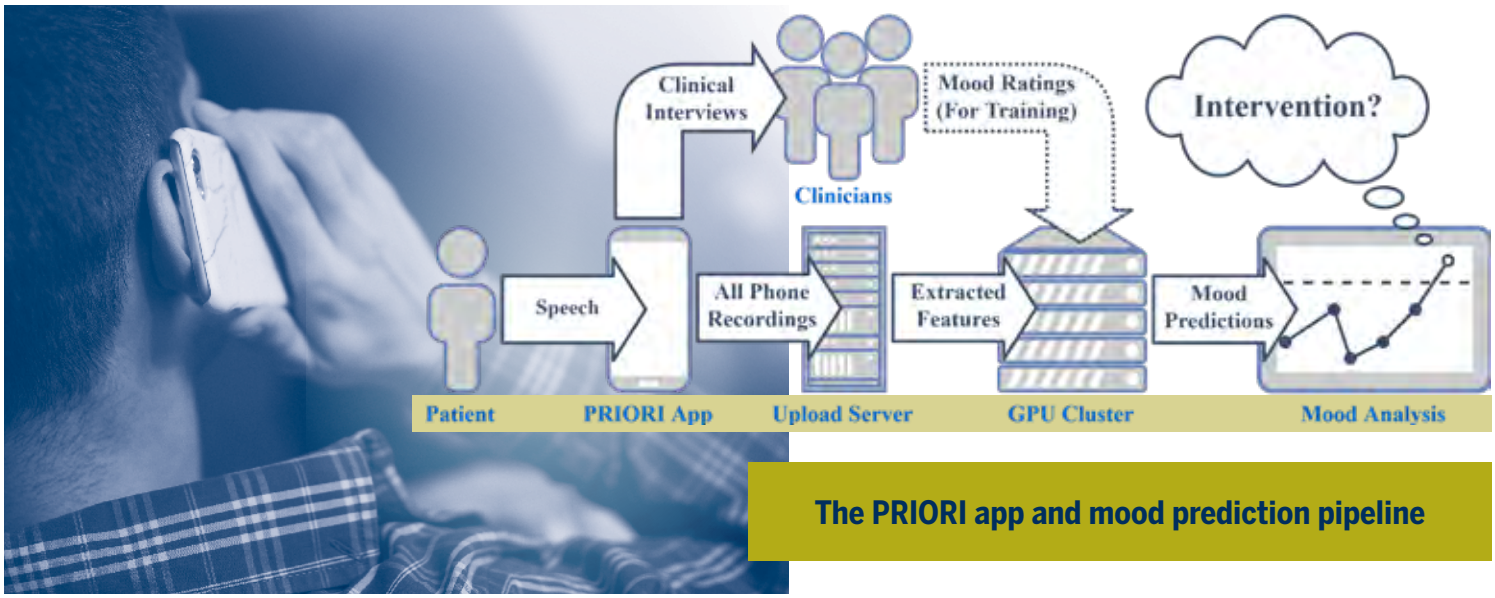
1. A deployable **smartphone app** that captures audio from telephone conversations and securely stores and transmits the data and
2. **Computational strategies to detect mood.**

The initial data set included 51 individuals with bipolar disorder and nine healthy controls who used the phone as their primary device for up to one year (avg. 26 weeks). **The PRIORI app recorded their side of every phone call that they made or received.** We obtained **measures of mood through weekly structured telephone interviews ('assessment calls')** with study clinicians using the Hamilton Depression Scale and the Young Mania Rating Scale. We refer to all calls made or received outside of these structured interviews as **'personal calls.'**

Our researchers in the Electrical Engineering and Computer Science department analyzed the initial dataset and found that **although we could predict the mood state of the participant when the person was talking to a clinician, the methods were not effective on personal calls.** We realized that we needed to change how we were thinking about the problem.

We needed something to bridge the divide between speech acoustics, which vary at the millisecond timescale, and mood, which varies over days to weeks to months! **Emotion was our bridge**. We conducted an emotion recognition proof-of-concept study on the initial dataset. Our team annotated 13,611 segments of speech (6-8 seconds each) from 12 participants and **developed accurate emotion recognition algorithms using these data.** We used the algorithms' predictions to differentiate between individuals at risk for suicide and healthy controls and to determine when interventions may be necessary to help the patient. We also transcribed the 13,611 segments and used the transcriptions to verify the accuracy of an automatic speech recognition (ASR) system. **Finally, we used the ASR output to measure how changes in the patterns of language are associated with changes in mood.**

Great progress has been made on the PRIORI project over the past year. **We have shown that speech collected in clinical environments *and* in natural personal interactions can be measured to detect changes in mood symptom severity**. We remain excited to continue to improve our approaches, partnering with our research participants and donors, to achieve our goal of improving care and quality of life for individuals with bipolar disorder.



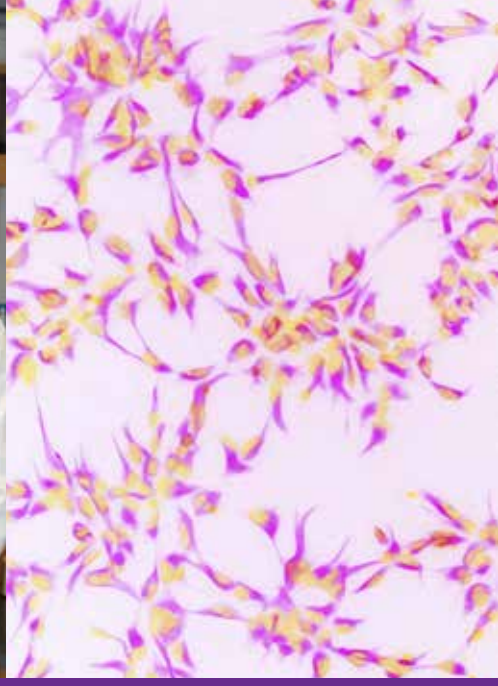
The PRIORI app and mood prediction pipeline

Interview
with K. Sue O'Shea, Ph.D.

Director of the University of Michigan
Center for Pluripotent Stem Cell Research

The O'Shea lab team, from left to right: **Cindy De Long, Eric Cousineau, Guihua Jiang, Kate Campbell, Sue O'Shea, Dan Schill, Durga Attili** (Missing: **Henry Tran, Sophie Mosher**).

Learn more about Dr. O'Shea and her work on our website: myumi.ch/JlwEQ

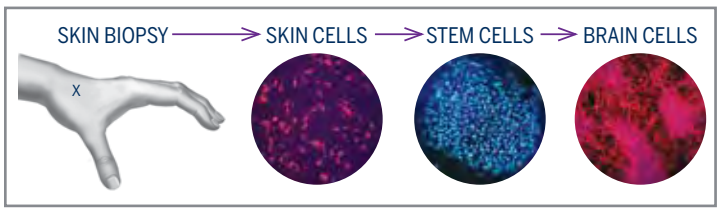


This photo illustrates the appearance of immature neurons derived from skin cells of an individual with bipolar disorder. Pink = the cell body of the neurons, yellow = the nucleus.

What work does your lab focus on?

The field of cell biology studies **the different structures and functions within and between cells.** For several years, we have used this approach to study neurons and glial cells from individuals with bipolar disorder. Our lab is currently comprised of nine researchers — post-docs, students and staff. In our lab, **we are interested in understanding how the human brain develops and how errors in that process can result in conditions such as bipolar disorder.**

To begin to do that, we have used a ground-breaking new method in which we take cells, such as skin cells, and cause them to behave as though they came from a very early-stage embryo. These cells are capable of forming all the cells of the body, and are called stem cells. **We take these stem cells and coax them to form neurons and glia of the developing brain and compare cells from control individuals with those from patients with bipolar disorder.**



We are currently **focusing our work on individuals carrying a change in a gene that lets calcium into cells, and is associated with bipolar disorder.** It is important to have a viable source of cells to study, as previously scientists needed to use postmortem brain samples to try to determine how bipolar brains might be altered.

We have shown that **neuronal cells derived from people with bipolar disorder signal to each other more frequently and more strongly.** We now have more than 30 cell lines in the lab that we can examine and test. Since we can't take a biopsy of human brains, this gives us a way to look at individual brain cells and find differences and whether normal function can be restored through pharmacological or other treatments.

Tell us about exosomes – What are they? Why is it important to study them?

All cells have ways of communicating with each other. One of those ways is by secreting chemical signals back and forth. Sometimes the chemical is released directly into the brain as neurotransmitters, other times, it is secreted in a membrane-bound packet that binds to the surface of target cells and then releases its contents directly into the cells. **These packets are called exosomes and they are released from supporting cells to give information to neurons in the brain**. We are very excited about exploring exosomes and their contents — what chemicals they carry and how the numbers, size and uptake is different between control and bipolar brain cells. We are looking at neurons and astrocytes, the star-shaped cells that help support neurons, and **exploring how lithium and ECT (electroshocks), two effective bipolar treatments, change the content or behavior of exosomes.**

Where do you see your work heading in the future?

Scientists always think first about **publishing** their work—we have one paper in press about this project and plan to submit a second very soon. If we find differences in the exosomes that could suggest ways to clear them from cells (to rid the brain of toxic proteins), or to identify over- or under-production of particular signaling molecules and proteins in the bipolar compared with control cells, we would then **think about ways to target those pathways directly**. We are extending this work to look at exosomes in peripheral blood—which could give us an idea about exosomes in the brain—and we are also culturing control neurons with exosomes derived from bipolar glia to determine whether they harm the control neurons. **We believe that understanding the cellular underpinnings of bipolar disorder will suggest new approaches to its treatment.**

How to Hold Up Your End of the Relationship When Living with Bipolar Depression

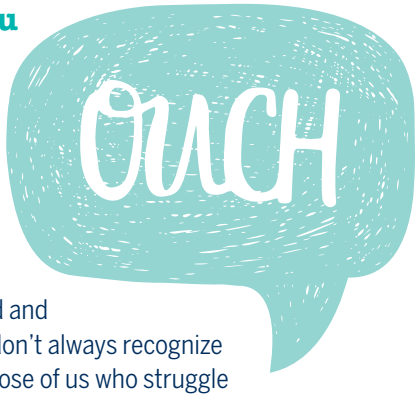
By Mitzi B., a Prechter Program research participant

I have struggled with bipolar depression for my whole life. 54 years. For a long time, I didn't have a name for why I always felt so hopeless and full of despair.

And then I got married. And he had to live with it too.

Knowing how to hold up your end of the relationship when living with bipolar depression can be very difficult but I am here to tell you that relationships don't have to self-destruct because of it. So, what are the best ways to have a healthy, happy relationship when you are struggling?

Recognize when you are depressed.



For those of us who struggle with bipolar depression, we often can tell when it hits. Simple tasks that just the day before were easy to do become difficult. Sleep is elusive. We are short tempered and crabby. Some of us, however, don't always recognize when we are depressed. For those of us who struggle with this, it is important to have a person who watches out for it for you.

Keeping in touch with your depression and sharing its presence with your partner is very important. Don't just expect your partner to guess that you are depressed. They might not recognize the signs and might not respond to your new mood and that could lead to some big problems between the two of you.

So, when depression hits, be clear about it. You and your partner you have a bit of a battle ahead. Together.

Talk to your partner about your depression.

Even the most sympathetic of partners doesn't really understand what depression is like unless they suffer from it themselves. Because of this, it's important to try to teach them what depression looks like for you.

After my bipolar diagnosis, my husband and I discussed what life was like for me when I was depressed. My message for him was 1) you haven't caused this and 2) you can't fix it and 3) I can't just suck it up and feel better.

Next, I explained to him what my depression looked like. That when I was depressed I felt like I had a 100 lb. gorilla on my back. Moving around, getting things done, communicating effectively, all required such a Herculean effort that I could barely manage. When I was depressed I was exhausted, easily angered, prone to long bouts of crying. Going to work, taking care of myself, all filled me with such an overwhelming sense of dread that I couldn't bear it.

Once he understood what my depression felt like and what my behavior was like when I was depressed, it made it much easier for him to empathize and not take personally my actions and instability.

So, when you ARE NOT depressed, take some time and share your experience with your partner. The better understanding they have of your depression, the better they will be able to deal with and cope with it.

Not only will this make your relationship stronger but you will also not feel so alone when the depression hits.

PRECHTER PROGRAM REPRESENTED AT NAMI CONVENTION 2019*

The National Alliance on Mental Illness National Convention took place in Seattle, WA, from June 19 to 22, 2019. This convention is the nation's largest gathering of mental health advocates that come together to share, learn and network around important mental health issues.

This year was the third year that the Prechter Program has participated in this convention. We had a booth in the exhibit hall where we talked to attendees about our research studies and focus areas, and our vision to accelerate discoveries to help people with bipolar disorder lead more fulfilling lives.

Our research director, Melvin McInnis, M.D., who was one of the two winners of the **2018 NAMI Research Award**, gave a bipolar research update presentation. The title of his well-attended talk was **"Bipolar Disorder: A Lifetime of Passion, an Unpredictable Journey."**

Cynthia Burton, Ph.D., who is a faculty member at the Prechter Program and current **NAMI Unger Research Fellow** at the University of Michigan, also spoke at the convention on **"Combining Cognitive Training and Brain Stimulation: A Feasibility Study."**

Read more about NAMI on page 15

Plan ahead for what to do when depression hits.

A key part of dealing with depression for me, and for my husband, was that I was able to, when I wasn't depressed, make a plan for what I needed when I was depressed. I knew from experience what I needed to get through my depression. Sharing it with my partner was key.

For me, when I get depressed I need five things: to get outside, to sleep, Pad Thai, The Walking Dead and my partner's patience and forbearance. I knew that those things would not cure my depression but that they made living with it easier.

So, when I WAS NOT depressed, my husband and I made a plan for what to do when I was. We would let me sleep in, go for a hike, get Pad Thai, watch some zombie TV and then we would send me back to sleep. We would do that, or some variation of that, to stay connected while I was depressed and help me get through it.

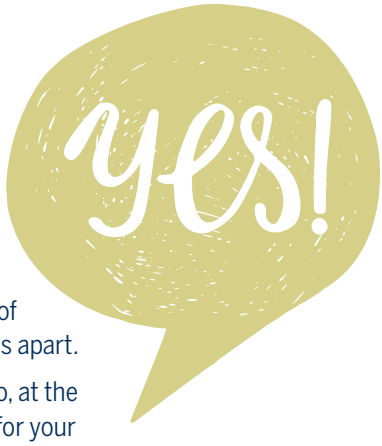
Don't make your partner suffer.

So, you have talked to your partner about your depression and made a plan for what you need when you are in it. Both of those things are great. Proactive.

Sometimes, however, those things just don't work and you are miserable. You are short tempered and difficult and not fun to be with.

At times like that, if you are stable and know that you are safe, let your partner go. Let them go about their day, guilt free. Encourage your partner to go do something they love instead of hang around being miserable with you. If you let them do this, they will come home refreshed and better able to support you. And they might even bring you some Pad Thai.

Agree to seek help.



One of the hardest things for someone who loves someone with depression is their sense of helplessness. They know that there is nothing that they can do to help their partner get out of this dark place. And that sense of helplessness can tear relationships apart.

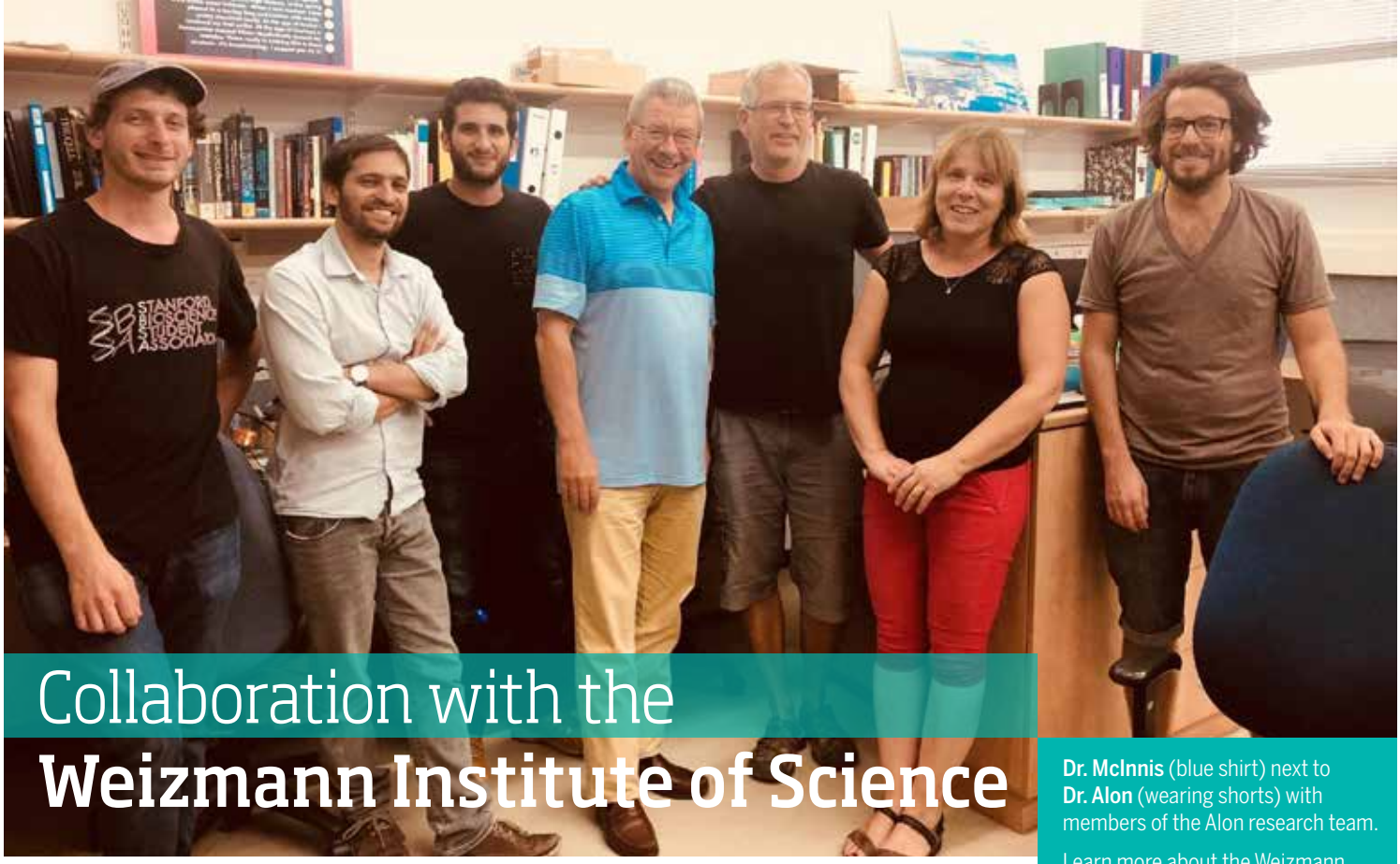
What can you do? You can agree to, at the very least, seek professional help for your bipolar depression: medication, yoga, and/or therapy. Whatever works for you and makes your partner feel supported.

It is important, for both of you in the relationship, to know that the depression isn't something that will be ignored but that will be addressed head on. That it is something that you can both learn to deal with and take on together. As a couple.

Read more articles on Mitzi's blog:
letyourdreamsbegin.com/blog


Our exhibit booth at the NAMI convention


A full house for Dr. McInnis' talk



Collaboration with the Weizmann Institute of Science

Dr. McInnis (blue shirt) next to **Dr. Alon** (wearing shorts) with members of the Alon research team.

Learn more about the Weizmann Institute: www.weizmann.ac.il

One of the many strengths of the Prechter Program is the network of connections that we have locally at the University of Michigan as well as in the international world of science. ***Working together*** **is the key to finding solutions for those living with bipolar disorder.**

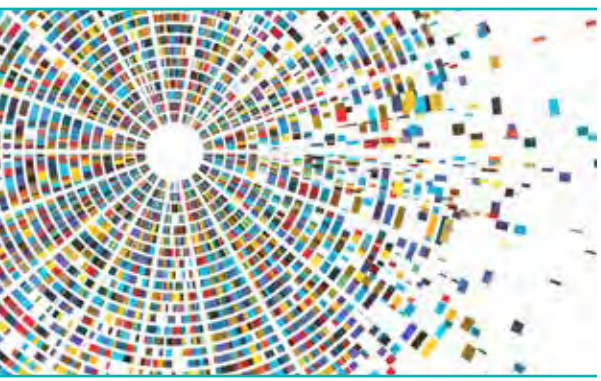
Describing moods and mood changes in bipolar disorder has always been difficult, both for individuals with the disorder and their treatment providers. In April 2019, our research director, Melvin McInnis, M.D., met with Professor Uri Alon and his team at the Weizmann Institute of Science in Rehovot, Israel to develop a joint strategy to tackle this problem.

The Weizmann Institute is an innovative, world-renowned institution focused on advancing science to improve the lives of humans. The collaboration with Dr. Alon was sparked by the publication in December 2017 of a Prechter Program paper outlining our Longitudinal Study of Bipolar Disorder. **Dr. Alon, a systems biologist and physicist, is interested in the longer-term patterns of human disease and is exploring changes in systems involving stress and stress hormones.** The Alon team is comprised of an eclectic group of scientists, ranging from mathematicians and biologists to psychologists, **all centered around outcomes and modeling of human disease.**

Together, our two labs are dedicated to **making sense of the course of bipolar disorder and developing computational models to describe the patterns of this disease.** The methods we plan to apply are similar to those used to analyze patterns in the stock market. Is the stock stable and rising? Or is it unstable and falling? There are many trajectories in the market, as there are **many patterns of illness that a person with bipolar disorder experiences.** This approach is an exciting new way to study and model mood changes in bipolar disorder.

The Prechter Program is now working with the Weizmann Institute to expand our research on the long-term variation in human experience and biology. We plan to **collect samples of hair** from our study participants with bipolar disorder. **Data on an individual's exposure to stress over time is reflected in the varying amounts of cortisol along a hair strand.** This offers the opportunity to discover how changes in stress relate to the course of bipolar. Can we describe the course of illness in the context of markers of stress and other measures?

The data gathered from our 13-year long Longitudinal Study of Bipolar Disorder may be key to unlocking the patterns of variation in this disorder. Scientists from the Prechter Program and the Alon lab are excited to begin research collaborations. Together, we plan to meet our goal to improve the lives of those with bipolar disorder.



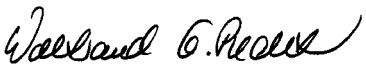
DEAR FRIENDS:

In January of 2017, the World Heritage Foundation-Prechter Family Fund committed to a $5,000,000 gift agreement to the University of Michigan Prechter Program Endowed Fund to ensure that the Prechter Longitudinal Study and the Prechter Bipolar Genetics Repository will always be available for future research. This gift agreement was a matching challenge to inspire others to donate to the Prechter Program.

As of this writing, 1,834 gifts have been made by all of you! Sometime this month, we expect to reach the matching gift goal of $5,000,000!

Thank you to our many devoted donors who have been contributing to the Prechter Program since its inception in 2004. We are so grateful for your consistent giving to our research. A heartfelt thank you goes out to the many donations made in memory of loved ones who struggled with bipolar illness, many of whom have lost their lives to suicide or other complications. You, like our family, have successfully transformed your grief into something positive.

I hope you will continue to partner with us. Again, my sincere thank you for your commitment to bipolar research.



Waltraud "Wally" Prechter
Founder, Heinz C. Prechter Bipolar Research Program

Dr. Gregory Dalack, Chair, Department of Psychiatry; **Dr. Melvin McInnis**, Research Director, Prechter Program; **Wally Prechter**, Founder, Prechter Program; **Dr. Marschall Runge**, Dean, University of Michigan Medical School, and Executive Vice President for Medical Affairs, Michigan Medicine; **Dr. John Greden**, Executive Director, University of Michigan Depression Center

WALLY PRECHTER Receives **Taubman Inspirational Philanthropist Award**

On November 1, 2018, during the *Victors for Michigan* campaign celebration, **our founder Waltraud "Wally" Prechter** received the University of Michigan's **A. Alfred Taubman Inspirational Philanthropist Award**. This award is given to special donors who have demonstrated an exceptional commitment to Michigan Medicine through their financial support, set an inspirational example for others — as Mr. Taubman did — to join them in changing the landscape of the causes they care about most, and have a longstanding relationship with the University of Michigan.

Wally, a University of Michigan alumna, founded the Heinz C. Prechter Bipolar Research Fund in 2001, following the death of her husband, Heinz C. Prechter, who had lived with bipolar disorder. In 2004, Wally transferred the Fund to the University of Michigan. To date, the Longitudinal Study of Bipolar Disorder has engaged over 1,300 research participants. **Today, the Heinz C. Prechter Bipolar Research Program is known world-wide as a leader in scientific investigation of this illness which affects more than 5.7 million adults in the United States each year.**

Wally has supported many areas at the University of Michigan, but her primary determination has been to apply scientific research with the goal of finding more effective treatment options for those living with bipolar disorder.

"I think that if you can – if you truly believe in something – you owe it to yourself to help, to give, and to make a difference. Because ultimately that is all you leave behind." **– Wally Prechter**

The Taubman Inspirational Philanthropist Award is named after philanthropist A. Alfred Taubman, a real estate developer who died in 2015 and who was one of America's most successful entrepreneurs and a dedicated supporter of the University of Michigan.

WALLY PRECHTER Recognized by **NAMI Michigan**

Wally Prechter was also recognized as a **Special Honoree at the 2019 NAMI Michigan Honors Gala**, which took place in March 2019 in Detroit. This annual black-tie event **celebrates heroes of mental health**.

NAMI is the **National Alliance on Mental Illness**, the nation's largest grassroots mental health organization dedicated to improving the lives of persons living with serious mental illness and their families. Founded in 1979, NAMI has become the nation's voice on mental illness, a nationwide organization with affiliates in every state who work in your community to raise awareness and provide support and education. **The Prechter Program collaborates nationally** via participation at the national conference, **and locally** in Michigan with local NAMI affiliates through our Bright Nights educational events and cross-promotion.

NAMI Michigan
National Alliance on Mental Illness

13TH Annual Prechter LECTURE

Tuesday, October 15, 2019, 6–9 p.m.

JOIN US

FEATURING: **Pete Earley**

AUTHOR OF: ***CRAZY*** *— A Father's Search Through America's Mental Health Madness*

- FREE EVENT: **RSVP at PrechterProgram.org/lecture**
- LIVE WEBCAST for those living outside of Ann Arbor: michmed.org/eZWlo
- PANEL DISCUSSION:
  - Mental health care in the justice system
  - The present & future of research in bipolar disorder
- RECEPTION
- BOOK SIGNING: Books available for purchase
- LOCATION:
  - University of Michigan
    A. Alfred Taubman Biomedical Science Research Bldg
    Kahn Auditorium
    109 Zina Pitcher Place, Ann Arbor, MI, 48109

"Parents of the mentally ill should find solace and food for thought in [this book's] pages."
— PUBLISHERS WEEKLY

"Explores the mind-boggling mess that America's mental health system has become and champions the case for reform."
— ROCKY MOUNTAIN NEWS

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- A gift in memory of James Munro Leaf
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HEINZ C. PRECHTER BIPOLAR RESEARCH PROGRAM
MICHIGAN MEDICINE

Rachel Upjohn Building • 4250 Plymouth Rd. • Ann Arbor, MI 48109

**OUR MISSION ›› ** The mission of the Heinz C. Prechter Bipolar Research Program is to discover the mechanisms that contribute to bipolar disorder, predict and improve outcomes, and develop effective, innovative treatments.

**OUR VISION ›› ** We are building a future where personalized and evidence-based treatments for bipolar disorder will enable every individual with the illness to lead a healthy and productive life.

SAVE-THE-DATE
May 2020

Metropolitan Museum of Design Detroit, in collaboration with the Heinz C. Prechter Bipolar Research Program, presents **'ENERGY' — Brain Health and the Power of Creative Expression — with an emphasis on the bipolar diagnosis.**

This month-long exhibit, showcasing artists and designers, will take place at **Collected Detroit gallery** and feature educational programming around brain health. Check our website for details as 2020 approaches.

To sign up to receive our yearly printed newsletter or our quarterly E-newsletter, please contact Kat at kbergman@umich.edu or 734-232-0456.

1-877-UM-GENES **PrechterProgram.org** **PRECHTERBIPOLARRESEARCH**