



DEPRESSION CENTER

HEINZ C. PRECHTER BIPOLAR RESEARCH FUND
UNIVERSITY OF MICHIGAN

What does the Prechter logo mean?

The blue ribbon "P" is surrounded by a white circle. It represents the cycle of the illness. Always in search for balance and wellness in life, patients with bipolar disorder alternate between the poles of "mania" and "depression." The blue ribbon breaking through the circle signifies the Prechter Fund's goal to advance breakthrough medical research to develop cures for the illness.



Collaborative research drives success

Scientific research has evolved over the decades from comprising primarily simple, well-controlled studies to complex, multi-faceted ones. Partnering with other experts is an integral part of our research mission; we do the best work when dedicated people with a shared vision come together. "I learn so much from all our collaborations — it is an opportunity to see the problem from a very different perspective, which provides new insights and offers novel approaches," states Melvin McInnis, M.D., the Prechter Bipolar Research Fund's principal investigator.

Here is a selection of our PARTNERSHIPS & COLLABORATIONS

COLLABORATIONS ACROSS THE UNIVERSITY OF MICHIGAN

Our large team consists of researchers from different departments and disciplines across the university.

Department of Cell and Developmental Biology: K. Sue O'Shea, Ph.D.

Dr. O'Shea's lab is working to derive induced pluripotent stem cells (iPSC) from skin biopsies from patients diagnosed with bipolar disorder and control individuals. This project involves sampling skin tissue and transforming those cells into stem cells and ultimately into nerve cells that look and behave like brain cells.

College of Engineering: Emily Mower Provost, Ph.D.

Dr. Mower Provost leads the development of computational methods of predicting mood swings in bipolar disorder. Her work focuses on understanding the specific patterns that accompany transitions from healthy euthymic states to either mania or depression. Her investigations suggest that manic and depressive mood states can be recognized from speech data collected via a smart phone app.

Department of Psychology: Ethan Kross, Ph.D.

The study "Facebook Use and Psychology" seeks to understand the relationship between Facebook use, emotions, and various everyday life behaviors in people with and without bipolar disorder. Participants grant us access to their Facebook walls, which we

anonymize and analyze in conjunction with their diagnostic information. The findings from this study have the potential to shed light on how people can effectively use personal websites in ways that buffer against psychological distress and facilitate mental health.

NATIONAL AND INTERNATIONAL COLLABORATIONS

Our research team is collaborating with several national and international institutions. Cornell, Johns Hopkins, Penn State, Stanford and Weill Cornell have all contributed samples to the Heinz C. Prechter Bipolar Genetics Repository. Several other institutions have requested samples from the repository for their own research studies.

The Prechter team is engaged in national and international research projects. One such project is the "Pharmacogenomics of Mood Stabilizer Response in Bipolar Disorder" study. The goal is to identify the genes that influence whether a patient will have a good response to two medications — lithium or valproate. For this study, we collaborate nationally with several universities and internationally with the University of Bergen in Norway and Dalhousie University in Canada.



"My group seeks to improve the understanding of the interaction between biological systems, clinical presentation, and physiological processes in bipolar disorder, and

implications for improving treatments. Our recent work has focused on improving the characterizing of the polyunsaturated fatty acid system and inflammatory markers of disease and relationship to mood and sleep."

Erika F. H. Saunders, M.D.

Chair of the Department of Psychiatry at Penn State College of Medicine and Milton S. Hershey Medical Center



A MESSAGE FROM OUR PRINCIPAL INVESTIGATOR

The study of bipolar disorder is the study of humanity; the throes of mania deliver an intense – almost unimaginable – euphoria, while the depths of depression draw people into a despair that has been compared to Dante’s inferno. The distance between these states defines infinity; when depression sets in, happiness seems light years away and in the manic state one conquers the universe with little to no reserve. The consequences of both mood states may be devastating for the person, family and community.

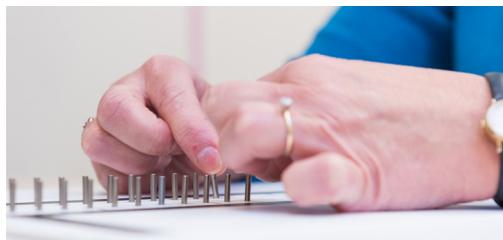
One cannot know bipolar disorder without knowing uncertainty. And knowing bipolar disorder drives many questions, but there is one fundamental question: how can this happen? And, the “how?” is naturally followed by “what can we do?”

As researchers, we focus on improving the lives of individuals living with bipolar disorder. In our field, collaborations and partnerships are vital for success. It is only when different research teams come together that we can hope to find individualized solutions for our patients. The strengths and passions of our team are vast, because each team member has expertise in a specific field – and when we come together, we maximize the potential to help those with the illness.

I am proud to lead such a passionate, multi-disciplinary team.

Melvin G. McInnis MD

Melvin G. McInnis, M.D., FRCPsych
Thomas B. and Nancy Upjohn
Woodworth Professor of Bipolar
Disorder and Depression
Professor of Psychiatry
Principal Investigator,
Heinz C. Prechter
Bipolar Research Fund



All research participants complete a series of neuropsychological tasks as part of their involvement with the longitudinal study.

Long-term collaboration with our research participants: 1,200th participant enrolled in our flagship study

On July 18, 2016, our research team enrolled the 1,200th participant in the **Prechter Longitudinal Study of Bipolar Disorder**.

The Longitudinal Study is our **flagship study** with the goal of identifying potential illness patterns in bipolar disorder. It is the **largest long-term research study for this illness in the nation** and has been ongoing for **ten years**. The study is designed to gather detailed clinical and biological data for research on the course of bipolar disorder and its outcomes by following and monitoring participants over their lifetime. We track patterns of disease, responses, and outcomes to interventions, and keep participants engaged in both their ongoing care and research of the illness.

Bipolar disorder is known to run in families, but most genes involved have not yet been identified. Additionally, every individual’s response to the illness, life circumstances, and treatment can vary widely.

Studying many individuals over time will allow scientists to better understand how to treat and, eventually, prevent bipolar disorder. It is out of this comprehensive study that we recruit participants for multiple other research studies ranging from genes and stem cell models, nutrition, neurodegeneration, to mobile health and clinical outcomes.

We would like to thank all research participants for their involvement with the longitudinal study. Many of our participants tell us that they feel a sense of satisfaction knowing that they have contributed to the understanding of bipolar disorder and to our search for more effective treatments for this debilitating disease. Without their involvement and dedication, this important research would not be possible.

“What makes our research program so unique is that it is ‘longitudinal,’ meaning it follows patients over time to learn how to predict the outcome of the illness, identify personalized treatments that prevent episodes, and provide the opportunity for health and success.”

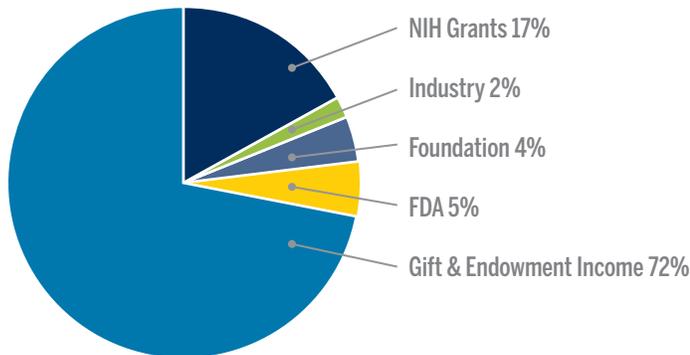
— Melvin G. McInnis, M.D.

FUNDING SOURCES

Our funding comes from **federal grants, corporate and foundation grants, FDA funding, and individual gifts and endowment income.**

With each year that our flagship Longitudinal Study of Bipolar Disorder grows, our research operation expands and we couldn't continue without the help of our supporters. The majority of the research infrastructure is funded by gifts and endowment income. This has been especially important this year as we've ended several federally-funded grants. Private support allows continuity of our research despite changing federal budgets.

Our research enterprise has an annual operating budget of approximately \$1,100,000. This supports research operations such as the longitudinal study and the Heinz C. Prechter Bipolar Genetics Repository, as well as projects across a wide spectrum of research domains including electrophysiology, metabolomics, phenomenology, environmental, computer technology, psychology, imaging, genetics, neuropsychology, and cell biology.



This year, philanthropy has supported 72 percent of the total resources allocated to bipolar research.

The University of Michigan also offers several avenues for **institutional support**. One such funding mechanism is a program called **MCubed**, the University of Michigan's revolutionary way of funding collaborative research.

MCubed stimulates innovative research by distributing real-time seed funding to multi-unit, faculty-led teams. Through this first-of-its-kind research funding program, faculty from at least two different campus units can form a collaborative trio, or "cube," and request funding to advance their idea right away.

OUR TEAM HAS HAD 2 "CUBED" PROJECTS FUNDED:

1 Cellular Models of Bipolar Disorder: Induced Pluripotent Stem Cells — Cube between medicine and the Life Sciences Institute

Bipolar disorder is a severe disorder characterized by variation in moods ranging from uncontrolled mania to disabling depression. There are several genes and molecular pathways implicated in the biology of the disorder, but currently there are few cellular models for molecular, biochemical, and cellular experimentation. Induced pluripotent stem cells (iPSC) lineages with neuronal derivatives have been developed by our team from four individuals with bipolar disorder and fibroblast lines established from a further six individuals to establish iPSC lines. Initial characterization of the iPSC and neurons include gene expression studies and dynamic calcium assays.

This project aimed to further characterize the iPSC and neuronal lines using genetic and biochemical methods focused on the molecular and biochemistry of the cell and behavior in relationship to other cells. This includes inter-cellular connectivity and features of the inter-neuronal synapse. The data analyses integrated clinical data with cellular and molecular models.

2 Integration of Comprehensive Clinical and Computational Data (iC3D) — Cube between medicine, engineering and nursing

This project integrates clinical and research data from our longitudinal study of bipolar disorder. The study includes 1,200 participants; data types include medical record, genetic, physiological, psychological, cellular modeling, metabolomic, circadian patterns, and mHealth data from mobile devices (acoustic and data use patterns).

This project will explore effective and efficient methods of integration, storage and retrieval of multiple data types for combined analysis aimed towards identification of mechanism and predictive models of bipolar disorder. There are a wide range of physical and mental health comorbid conditions that influence the manifestation of the illness, as well as an effect of environment. The goal is to develop computational algorithms to anticipate and predict health needs of individuals with unstable moods such as are found in bipolar disorder.

OUR RESEARCH BY THE NUMBERS



1,200

research participants are now enrolled in our flagship Longitudinal Study of Bipolar Disorder, which is in **year 10** of follow-up



40

collaborators from 14 states and 4 countries



39

research staff focused on running the different projects



16

research studies are contributing to a repository of biological materials and clinical data

Q&A with our TechStart interns

The University of Michigan Office of Technology Transfer's TechStart program provides internships to graduate students from various programs across the university. Students work in small, multi-disciplinary teams on U-M technology transfer projects, with input from the Tech Transfer staff, faculty inventors and industry mentors.

This summer, three interns worked for the Prechter team in defining the commercialization of **PRIORI (Predicting Individual Outcomes for Rapid Intervention) – our smart phone app that detects changes in the vocal patterns of patients diagnosed with bipolar disorder in order to identify early-warning signs associated with mood variation.** One of the symptoms of bipolar disorder is changes in speech. During mania, speech increases in rate, rhythm, and volume. During depression, the opposite occurs. The purpose of the PRIORI study is to design new computational approaches to detect these meaningful changes before a mood episode occurs. The hope is that predicting mood changes with significant time to intervene will go a long way toward **preventing prolonged episodes of mania and depression and even suicide.**

Tell us about your proposed workflow for PRIORI.



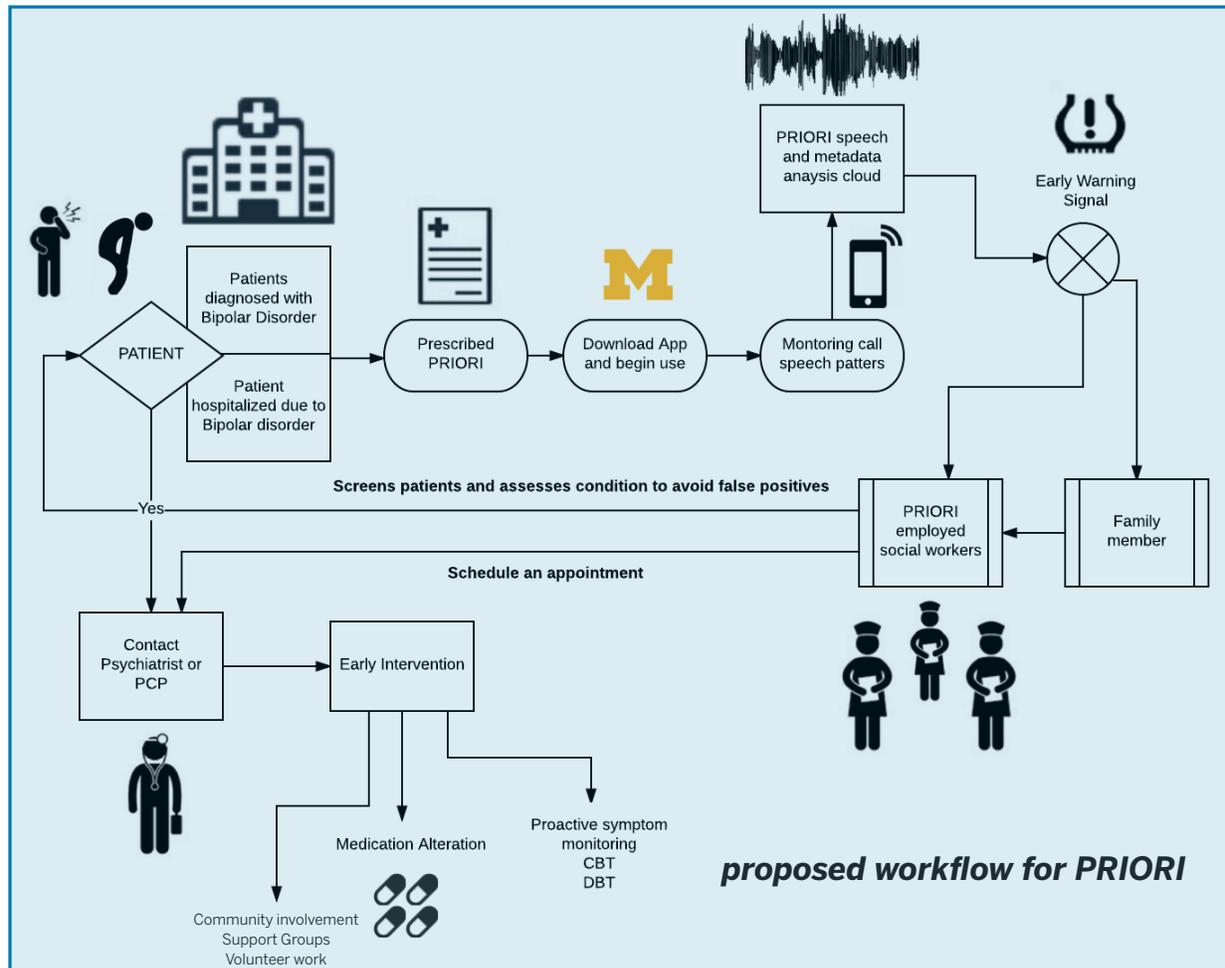
The PRIORI workflow was designed keeping in mind the key concerns of the three parties it is meant to serve: the patients, the psychiatrists and the insurance companies. The proposed workflow allows patients to connect with their psychiatrist through PRIORI appointed social workers (care managers) and get care when they most need it. Psychiatrists are shielded against any false positives by allowing social workers to respond to the generated alert first and screen the patients before getting them a therapist appointment. Lastly, the insurance companies benefit from lower costs of care due to proactive intervention and subsequent hospitalization stay reduction."

– **Tasha Mangaldas** is a recent Master's graduate in Materials Science and Engineering from the College of Engineering. She has previous experience working in medical start-ups and is interested in exploring the intersection of engineering and business operations in taking a product from conception to production.

PARTNERSHIPS & COLLABORATIONS



Sam Edandison, Tasha Mangaldas, and Mark Bolinger



What have you found would be the strength of PRIORI as a business?



The strength of PRIORI as a potential business venture is in its clinical advantage and its Michigan brand. In terms of clinical advantage, PRIORI is led by a medical researcher and is focused on detecting both mania *and* depression. Many of the competitors are focused solely on depression. From a business perspective, the Michigan brand is important; many of the potential payers we talked to were reassured that PRIORI was coming out of the University of Michigan. Funders may be more willing to align with research generated under the aegis and credibility of the University of Michigan.

— **Sam Edandison** is an J.D./M.B.A. student at the U-M Law School and Ross School of Business. His broad background includes experiences in consulting, operations, and law. Sam is inspired by the thought of taking an idea from an abstraction to a product.

What has this internship taught you about mental illness and bipolar disorder?

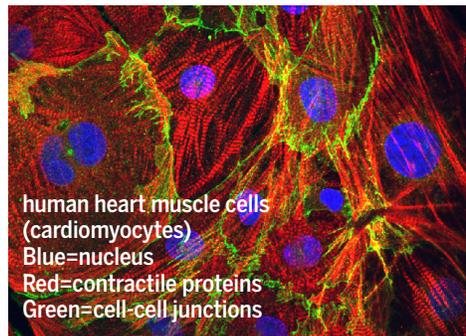
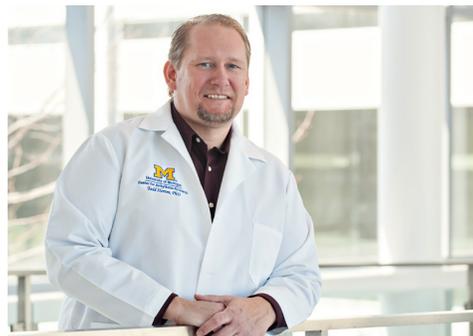


I'd had previous exposure to mental illness through some of my course work, but I'd never seen the human toll these diseases take on patients and families like I did in this internship. It's heartbreaking. The difficulty of treating these illnesses both from the perspective of available treatments and assessment of treatment efficacy was eye opening for me. It really emphasizes the need for the type of tool that the PRIORI team is developing."

— **Mark Bolinger** is a recent Ph.D. graduate of the Department of Molecular and Integrative Physiology. Mark is currently exploring future job opportunities with an eye toward intellectual property/patent law, and is fulfilling the internship at the Technology Transfer Office as an introduction to biotechnology and commercialization.

SPOTLIGHT ON

Todd Herron, Ph.D.
Assistant Research Professor,
Center for Arrhythmia Research,
Frankel Cardiovascular Center



Dr. Herron's project is titled "Cardiovascular disease in bipolar disorder patients: Patient specific disease modeling and medication testing" and its goal is to **study cardiovascular cells and neurons derived from the same bipolar patient.**

Bipolar patients experience elevated cardiovascular mortality rate, yet the connection between this psychiatric disorder and cardiovascular health is unclear. New experimental and clinical evidence suggests that genetic abnormalities of the calcium channel gene may contribute to neuronal dysfunction observed in patients with bipolar disorder. Interestingly, the same calcium channel gene is also expressed in the heart of bipolar patients. This suggests a common genetic link between bipolar patient neuronal function and cardiovascular health.

The calcium channel gene is crucial for proper cardiac function and genetic abnormalities can lead to cardiovascular disease. Expression of a mutated calcium channel gene in the hearts of bipolar patients may also have consequences on the safety and effectiveness of

psychoactive medications, which could include harmful side effects such as cardiac arrhythmias. An *in vitro* source of bipolar patient-specific neurons and cardiovascular cells is required to better understand the molecular basis of bipolar disorder and to personalize medication selection and prescription.

In this project, Dr. Herron is studying calcium channel gene expression and function in neurons and cardiomyocytes (heart muscle cells) derived from the same bipolar patient. Investigators in Dr. Herron's laboratory are generating **bipolar patient cardiomyocytes** and investigators in Dr. Sue O'Shea's laboratory are generating **bipolar patient neurons** for *in vitro* studies.

This collaborative project offers an unprecedented opportunity to study patient-specific neuronal and cardiac function. Furthermore, the investigators will test a panel of anti-psychotic medications in these *in vitro* neurons and cardiomyocytes to create an ***in vitro* diagnostic tool** that will provide a mechanistic and personalized basis for drug therapy decisions.



Waltraud E. Prechter
Founder,
Heinz C. Prechter Bipolar
Research Fund

PARTNERSHIPS & COLLABORATIONS

Dear Friends:

As Dr. McInnis states on the cover page, collaborations in research provide new insights and offer novel approaches. They are vitally important! Collaborations actually make the Prechter Fund stronger; they foster “out-of-the box” thinking and help us use our resources more wisely. We depend not only on scientific collaborations but also on philanthropic partnerships. It is our donors and their support that gives our scientists the tools necessary to advance their work.

Below, we are featuring our partnership with local artist Dominic Pangborn who designed beautiful silk neck ties and scarves for us. They are still for sale and make excellent accessories and gifts. On page 7, we are highlighting the Richard Tam Foundation’s commitment to our research enterprise.

Every gift, no matter its size, makes a difference in our mission — to achieve personalized treatments for the patient. Your contributions are a valuable asset in our efforts to combat bipolar disorder. Thank you so very much.

Very Sincerely,

Waltraud E. Prechter

Fashion design meets research in wearable human stem cell images

Dominic Pangborn designed scarves and ties that draw attention to Prechter team’s research advances

Dominic Pangborn’s artwork is always changing and he’s fearless in his approach. The designer’s signature ties are ubiquitous in the Detroit business community. Not for the wallflower, his ties, like all his designs, combine bold patterns and beautiful colors that serve as statement pieces that make the wearer stand out.

In May 2016 — national mental health month — Pangborn made a statement about research on mental health in collaborating with the Prechter Fund. He designed a new scarf and tie based on images generated by our scientists. “One of my greatest joys is to ‘pay it forward’ and give back to the community,” said Pangborn.

Pangborn’s silk neckties and scarves bear images of neural stem cells generated in Prechter-funded research, together with the hopeful shapes of butterflies. “To me, butterflies signify metamorphosis,” said Pangborn. **“Our society is finally at a point where mental illness is openly talked about and research is taking a turn for the better.”**

The Prechter bipolar research program includes research into the basic mechanisms underlying bipolar disorder. Our scientists generate stem cells from skin cells donated by people with the illness, and those without, and then grow the kinds of neural cells found in the brain. This process allows scientists to understand — in the laboratory — what’s different between the two kinds of cells, at the genetic and molecular level. Scientists can manipulate these ‘brain cells in a dish’ to test different medications.

“My team here at the University of Michigan Center for Pluripotent Stem Cell Research monitors the cells daily and we have learned that cells taken from bipolar patients fire more intensively and in a way that is significantly different than cells from an individual who doesn’t have bipolar disorder,” said K. Sue O’Shea, Ph.D., who heads the stem cell center. “By understanding the causes of bipolar disorder, we will be able to develop new treatments for the illness and most importantly, we’ll be able to prevent destructive mood episodes. Our ultimate goal is to allow people to live happy, normal lives.”

On May 5, 2016, the Prechter Fund and the Pangborn Collection store in downtown Ann Arbor, Michigan, hosted a reception to celebrate this unique collaboration and unveil Dominic Pangborn’s new neckties and scarves. The evening drew out many of our past supporters and lovers of art and design.

Our collaboration with Dominic Pangborn is ongoing — the ties and scarves are still for sale at the Pangborn Collection store at 335 S. Main Street in Ann Arbor, and at the web store: pangborncollection.com. They are priced at \$95.00. All proceeds will directly support our bipolar research projects.



Clockwise: Dominic Pangborn and our research director Dr. McInnis wearing the ties; Department of Psychiatry Chair Dr. Dalack with Dr. Conroy; the beautiful silk scarf.

Richard Tam Foundation provides continued support

A Richard Tam Foundation gift of \$906,000 to our research program will accelerate scientists' efforts to combat bipolar disorder and provide hope to the many people whose lives are affected by it. This gift will provide crucial funding to support the research team's efforts to turn scientific advances in the lab into personalized treatments for those who suffer from bipolar disorder.

Since 2014, the Richard Tam Foundation has given \$2.2 million to bipolar research at U-M. Richard Tam's daughter, Judith, says:

"I have seen how bipolar illness impacts those who suffer and those who love them. I believe that we are now on the cusp of important new discoveries. I am thrilled to support the effort to conquer this cruel disease that harms the lives of so many people in the U.S. and around the world."

In collaboration with the Heinz C. Prechter Bipolar Research Fund, the Foundation is supporting researchers in using creative new approaches, including induced pluripotent stem cell lines. "The goal is to develop a cellular model to identify differences between neuronal and glial cells from bipolar patients and controls. The long term goal of this work is to develop personalized treatments for patients," says K. Sue O'Shea, Ph.D., the Crosby-Kahn Collegiate Professor of Cell and Developmental Biology, and director of the University of Michigan Center for Pluripotent Stem Cell Research.

The Tam Foundation is also supporting research for those with developmental disabilities, bipolar disorder and catatonia. Dr. McInnis has tapped the insights of Neera Ghaziuddin, M.D., in the catatonia project, to identify families that have individuals with bipolar disorder, developmental disabilities and autism. "The Richard Tam Foundation

PARTNERSHIPS & COLLABORATIONS



The pluripotent stem cell core team pictured with Judith Tam (front row center).

support enables us to study and better understand the neurochemical mechanisms underlying catatonia. Catatonia, a diagnosis which is often overlooked, occurs in approximately 1 in 6 individuals with autism and may go unrecognized for months or years. This often results in treatment which is ineffective or even harmful in its long-term consequences. Understanding the neurochemical basis of this disorder will help us to develop more effective management of this disorder and consequently to improve the lives of the individuals who suffer from these illnesses," says Dr. Ghaziuddin.

Prechter Fund partnership with the UMMS Central Biorepository

As of January 2016, the Prechter Fund has partnered with the University of Michigan Medical School Central Biorepository (U-M CBR) to house and organize all of the Heinz C. Prechter Bipolar Genetics Repository biological samples. This collaboration saves time and money by reducing individual infrastructure expenses.

There are multiple benefits of using a centralized university resource. The CBR is a world-class, CAP accredited institutional resource with national standards and has safe, secure, and automated equipment that is too expensive to purchase and maintain in any one department. "We enhance our customers' research portfolio by providing a comprehensive biospecimen management system including a governance framework, sample processing, and storage expertise in a world-class, accredited, safe and monitored environment," says Zachary Klug, M.H.S.A., CBR Business Operations Manager.



A portable cryoport is used to temporarily store biological samples on-site at less than -140°C before weekly transfers to the CBR.



One of six cryofreezers maintained by the CBR. Each freezer holds more than 65,000 samples in liquid nitrogen vapor at -190°C.

PLEASE
JOIN US

10th ANNUAL
PRECHTER LECTURE



Wednesday, October 19, 2016, 6–9 p.m.

UNIVERSITY OF MICHIGAN | KAHN AUDITORIUM
A. ALFRED TAUBMAN BIOMEDICAL SCIENCE RESEARCH BUILDING
109 ZINA PITCHER PLACE | ANN ARBOR, MI 48109

FEATURING: **Mimi Baird**

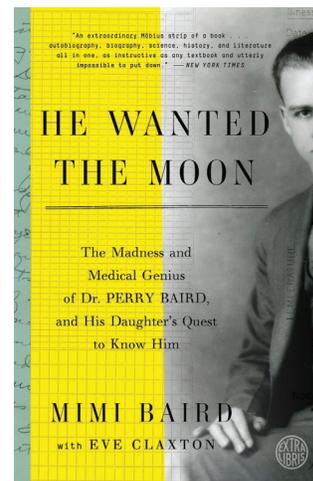
AUTHOR OF: **He Wanted the Moon**

**The Madness and Medical Genius of Dr. Perry Baird
and His Daughter's Quest to Know Him**

- › Mimi Baird's book talk will be followed by a panel discussion about the present and future of research in bipolar disorder, and a reception.
- › This event is free and open to the public. Please RSVP at www.prechterfund.org/lecture
- › If you are unable to attend, join via webcast: myumi.ch/LzGkQ (case sensitive)
- › The book will be available for purchase at the event.

"Baird's lonely, angry, grief-stricken, and occasionally grandiose account of his illness and its shattering costs is the reason we can't put [this book] down. His sharply detailed recollections are sometimes sane and sometimes not, but his writing is lucid even when his thinking isn't. His manuscript is a plea to understand his experience and, by extension, others."

— *THE BOSTON GLOBE*



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DEPRESSION CENTER

HEINZ C. PRECHTER BIPOLAR RESEARCH FUND
UNIVERSITY OF MICHIGAN

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

MISSION › › The mission of the Heinz C. Prechter Bipolar Research Fund is to provide a repository of longitudinal clinical, genetic, and biological data to investigators worldwide for collaborative research on the causes, prevention, and treatment of bipolar disorder.

VISION › › To personalize treatment of bipolar disorder and prevent recurrences to enable those with bipolar disorder to lead healthy and productive lives.

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.

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PRECHTERFUND.ORG

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