BD² Breakthrough Discoveries for thriving with Bipolar Disorder

Brain Omics Program Request for Applications (RFA)

September 2022

Executive Summary

We invite you to apply for the BD²: Breakthrough Discoveries for thriving with Bipolar Disorder Brain Omics Program. This program seeks to produce a strong research foundation that assesses the transcriptomic, epigenetic, and proteomic characteristics of brain tissue derived from people with bipolar disorder. We will fund an institution or consortium of partners who has access to a large and diverse collection of human brain tissue from people with bipolar disorder and carefully matched control subjects and can perform a variety of molecular, subcellular, cellular, and structural analyses, which may include morphological analyses, on these tissues. The funded partner will share all resulting data with the research community. Applicants who are selected for funding also will be able to use funds to significantly enlarge existing brain tissue collections in parallel. BD² intends to fund one applicant, which may be from one organization or a consortium of organizations, for up to $5 million to support the Brain Omics Program for up to three years. We welcome applications from multiple organizations that propose a coordinated effort.

Background

Bipolar disorder is a highly complex and heterogeneous disorder that is often debilitating. Even though it is prevalent in about 3% of individuals worldwide, little is known about its underlying biology. The molecular mechanisms involved in bipolar disorder etiology are not fully understood, and progress is hampered by the lack of sufficient samples and sequencing on samples from individuals with bipolar disorder. Advancements in our understanding and treatment of bipolar disorder to date remain far from ensuring that everyone living with it can manage their condition and lead independent, fulfilling lives.

BD² is a collective force to transform what we know about and how we treat bipolar disorder. It is a commitment to the 40 million people living with bipolar disorder, those not yet diagnosed, and their loved ones.

The Baszucki, Brin, and Dauten families united with the Milken Institute to create BD² to advance discoveries for families like theirs. For too long, there have been limited advances in the study and treatment of bipolar disorder due to lack of collaboration and funding. It's time for a new approach.

The BD^2 Brain Omics Program seeks to analyze a variety of epigenetic, transcriptomic, proteomic, and other omic characteristics of human brain tissue from people with bipolar disorder. We intend to support a partner who not only has access to a large number of diverse human brain tissue samples from people with bipolar disorder and is committed to growing that collection further, but also has infrastructure and experience in a range of omic analyses and other assays used in human postmortem brain studies. The partner should also be dedicated to open and collaborative science.

The Opportunity

Throughout the decades of bipolar disorder research, it has become clear that research strategies must shift drastically to ensure faster and more significant discoveries. Philanthropic support has presented a once-in-a-generation opportunity to develop a unique mechanism to bring the most capable and innovative minds together to explore one of the most complex mental disorders.

The field has the opportunity to build a robust program to examine the transcriptome, epigenome, proteome, and other molecular, subcellular, cellular, metabolic, morphological, and structural characteristics associated with bipolar disorder. The funded applicant may receive up to $5 million across all funded sites for up to three years to analyze and collect a large number of brain tissue samples, assess the various molecular and structural features, and share results of the analyses with the research community. Some funding can support infrastructure of the program, which may help the research community increase access to readily available human brain tissue, as well as strategies to increase the number of brain tissue samples from people with bipolar disorder. The funded partner(s) will be directed by a Scientific Steering Committee (SSC) and BD^2 program staff to ensure that teams are able to share resources, data, successes, and challenges throughout the funding period.

Ideally, applicant organizations will already have access to a large number of ethnically and racially diverse brain tissue samples of people with bipolar disorder. The selected organization should have deep expertise in brain banking, molecular omic techniques, and robust equipment and personnel infrastructure ready to perform a variety of assays in large volumes. Selected organization(s) will provide the data back to the research community to expedite data analysis and scientific advancements, and will be able to connect with partnering organizations and entities who will help with this process. The selected organization(s) should have a strong reputation within the research community and be connected to current brain banks and omics efforts in adjacent fields.

Commitment to Open Science

Open science is a key governing philosophy of BD^2, as it will allow for rapid and efficient sharing of new knowledge, catalyzing novel hypotheses to test. Funded investigators will be expected to adhere to BD^2's open science policies, including pre-print submissions, and sharing protocols and datasets to pre-approved repositories. Teams and their affiliated institutions should review our Open Science Policy prior to submission.

Important Dates

- September 12, 2022: RFA released
- November 11, 2022: Applications due
- November 2022 – February 2023: Application reviews and potential site visits and interviews
- March 2023: Awards announced

Eligibility

Organizational Eligibility

Application will only be considered from teams who meet all eligibility criteria below:

- Applications can feature multiple organizations that form a consortia of existing brain banks, research organizations, or non-profit organizations that collaborate to meet the goals of this RFA.
- Each applicant organization must be a non-profit academic or research organization, including domestic and non-U.S. non-profit organizations, domestic and non-U.S. public/private academic universities or institutions of higher learning (including colleges, universities, medical schools, and other related academic research organizations). Certain qualified governmental agencies with active biomedical research programs may also apply.
- The selected organization must have access to an existing cache of brain tissue samples from a diverse group of people with bipolar disorder via the organization's own efforts or through partnerships with other organizations. The number and diversity of samples will be part of the assessment process.
- The existing cache of brain tissue samples to which the selected organization will have access must be available for use in research based on consents from the individuals whose tissues are within the cache or a waiver of or exception to the requirement for such consents.
- The selected organization must provide the sample tissues in de-identified form, adhering to the standards for de-identification set forth in the Health Insurance Portability and Accountability Act (HIPAA) privacy regulations, 45 C.F.R. § 514(b).
- The selected organization must have an understanding of and proven ability to comply with applicable data protection regulations, including the privacy and security regulations implementing the HIPAA.
- The selected organization must make the resulting de-identified omics datasets readily available for the research field as soon as possible.
- If more than one organization will be involved in the project, one shall be proposed as the lead applicant organization, and the others included as sub-grantees. A Lead Principal Investigator (PI) who is affiliated with the lead applicant organization submitting the application must be identified.
- If an application contains more than one organization, each organization must identify a co-PI to lead efforts at their respective organization.
- The selected organization(s) may not subgrant any funding awarded to those organizations outside of those named in the application without approval, in writing, from the scientific leadership and program staff of the BD^2 Omics Program.

Leadership Eligibility

- A Lead PI must be identified for each application. The Lead PI is responsible for the scientific and technical direction, oversight, and management of the program. This includes contractual and financial obligations, and other organizational assurances and certifications. It is highly encouraged that the Lead PI have demonstrated experience in brain banking and molecular omics, cellular, or structural biology. The Lead PI will submit the application and be the primary point of contact between their team and the BD^2 program staff during the submission and selection process as well as throughout the grant for progress reporting and other matters.

- Lead PIs and co-PIs must hold a doctorate (e.g., Ph.D., M.D.) or related research doctorate degree.

Ineligibility

- Organizations that have no expertise in psychiatric genetics, access to samples, or sufficient expertise and infrastructure to perform any omics assays within the allotted three-year timeframe and allotted budget should not apply.
- This grant will not solely fund infrastructure or the expansion of brain tissue collection. Applicants must be able to share significant amounts of new data and results with the research community as a result of grant funding.

The Application

Applications should include a detailed scientific rationale and operational aspects of the proposed project. Required supplemental materials include letters of organizational commitment, a detailed budget, and the PI's Biosketch. All applications will be submitted via the Submittable online grant portal. All Lead PIs must create an account to access the portal and submit applications. The application is due **November 11, 2022**.

Application Details

A five (5) page application shall be submitted by the Lead PI. An application with multiple organizations must identify a lead organization. The Lead PI must be from the lead organization and submit the application. The application should discuss the organization(s) and leadership's brain banking expertise, molecular, cellular, and structural biology expertise, the organization(s) infrastructure, access to samples, commitment to open science, and a milestone-based timeline. Each section does not have a specified length; the only length requirement is that the application shall not exceed five (5) pages. See below for required sections within the application.

Overarching Strategy
Describe the overarching strategy that your team intends to implement in this proposed research. This strategy should include:

- A description of the potential brain regions and/or cell types or organelles you will analyze;
- The types of molecular, cellular, or structural experiments you intend to perform;
- Data analysis strategy;
- If applicable, strategy to enlarge the collection of brain tissue samples;
- How these data from the chosen brain regions and subsequent results will meet the goals of improving our understanding of the biology of bipolar disorder;
- Data sharing strategy that will be used to communicate data and findings to the field; and
- If applicable, how you intend to communicate and work with potential organizations in your grant.

Molecular, Cellular, and Structural Biology, and Brain Banking Expertise
Describe the molecular, cellular, and structural biology expertise of the lead PI and the organization that will be required to perform a robust omics exploration on a large number of human brain tissue samples from people with bipolar disorder. Include specific papers, affiliations, partnerships, results, or any other evidence of your expertise. Also discuss expertise in brain banking, which includes the collection, storage,

sharing, and analysis of high-quality human brain tissue. Outline the number of current staff available to work on the program, and the number of potential hires required to staff and operationalize the program. Applicants will be expected to share detailed protocols and standard operating procedures in the final stages of application review.

Infrastructure and Personnel
Outline the organization's current infrastructure that will allow for performing a variety of assays and analyses on a large number of brain tissue samples. This includes infrastructure to:

- Access and store high quality human brain tissue;
- Extract RNA, chromatin, DNA, protein, etc. from specific brain areas;
- Utilize state-of-the-art omic platforms that might include RNAseq, ChIPseq, HiCseq, CUT&RUNseq, WGBS, proteomics, metabolomics, etc.;
- Perform other relevant subcellular, cellular, and structural analyses as outlined in your overarching strategy; and
- Store, analyze, and share data.

This section should also:

- Outline the applicant's proven understanding of and ability to comply with the HIPAA privacy and security regulations and all other data protection requirements applicable to the research to be conducted; and
- Specifically outline the equipment and staff currently available at the organization(s) and the outstanding equipment needed to be purchased and additional personnel needed to be hired to operationalize the program. If the application has more than one organization, specify the organizational affiliation of the relevant equipment and personnel.

Sample Description
Provide a narrative description of samples that are available. Note that a template to disclose the full inventory and list of characteristics and demographics will be required in the application. This can be found in the grant portal. A full description includes:

- Human brain tissue sample number.
- Sample demographic features (racial, ethnic, gender, geographic, BMI, etc.). Please use the provided template to report demographic features of the samples.
    - Robust inclusion of individuals from non-European ancestries is a high priority. Brain banks that currently lack a diverse collection of brain tissue should describe their plans to diversify their collections if they are planning to increase their existing collection.
- Sample diagnostic information, if available (BD I, BD II, schizophrenia, etc.).
- Any other accompanying information that would be attached to the individual from whom the sample was acquired. This includes health records, actigraphic data, biosample readouts, or clinical data.
- Additional biosamples such as blood, CSF, or urine samples that might accompany human brain tissue samples.
- Control sample size and demographic information.
- Level of access to the samples (whether your organization has sole access, or whether it must be shipped from a partner, etc.).

Strategy to Increase Brain Tissue Samples, If Applicable
If applicable, describe plans to increase the number of samples in your organization's brain collection. A full description includes:

- The strategy that will be implemented to increase sample size from a diversity of individuals.
- An estimated number of human brains from individuals with bipolar disorder and matched controls that may be collected over the course of the grant along with estimates on demographic and diagnostic information.
- A strategy to make such brain samples available to the research community.

Commitment to Open Science
Describe your organization's current policies and actions that speak to encouraging an open scientific enterprise. This includes sharing data with other organizations and with the research community, participation in current psychiatric genetic efforts such as the Psychiatric Genetics Consortium, and any open science publication practices such as membership in cOAlition S. This also includes comingling or connecting these datasets with datasets from sequencing efforts in relevant disease areas such as depression, schizophrenia, autism, and neurodegeneration.

Projected Timelines and Milestones
Provide a detailed milestone-based timeline for the three-year award period, starting with receipt of funds, estimated for Spring 2023. Milestones include:

- Access to human brain tissue;
- Initiation of assays;
- Point of optimal performance;
- Initiation and completion of data analysis;
- Release of sequencing data to outside researchers; and
- If applicable, timeline for recruitment and collection of new brain tissue.

Letters of Commitment

- **Organizational commitment:** Each application must include a letter of commitment that demonstrates the organization's commitment to administering the grant according to a written grant agreement to be entered into between the selected organization and BD^2. The letter shall be signed by a department chair or a relevant authorized organizational representative, such as the Dean of Sponsored Research. Applications with multiple organizations must include a signature from a relevant authorized organizational representative from each organization.
- **Principal Investigator commitment:** An additional letter must state that each PI represented in the application is willing and able to commit to leading this project, to communicate regularly with program staff and the SSC as needed, and to adhere to open science principles. The letter shall be signed by the Lead PI and all co-PIs.

Detailed Budget

A detailed budget in USD, using the provided template: Acceptable expenditures shall include salary, fringe benefits, equipment, software, storage, reagents, project-related travel, and up to 15% indirect costs to support organizational infrastructure. Note that publication costs to open access journals will be covered by BD^2 and do not need to be budgeted in your proposal. Funding can also cover costs to expand phenotypic information of current brain tissue or allow for collecting robust phenotypic information of new brain tissue. The Lead PI's organization shall be proposed as the applicant organization and the other organization(s) shall be included as a sub-grantee(s), managed by the applicant organization. Each collaborating site must outline their subaward budget to clarify needs for all parties.

- The maximum allowable budget is inclusive of 15% indirect expenses. For applications including a sub-grantee, the maximum allowable indirect rate across both grantee and sub-grantee organizations remains 15% of the total award budget.
- For international applicants: Please note grants will be made in USD, and BD^2 is not responsible for changes in conversion rates.
- Grants selected for funding will be made payable to the applicant's organization. Under no circumstances will funding be paid to an individual. Please note that funds will be disbursed on an annual basis to the Lead PI's organization.

PI Biosketch

A biosketch of the lead PI and co-PIs, utilizing the NIH template, is required and shall not exceed five (5) pages per PI. If the lead PI or co-PI does not have a biosketch in an NIH template, a CV is sufficient.

Review Process

The written applications will be reviewed by the scientific leadership and program staff of the BD^2 Omics Program.

Application Review

Our review criteria will be based on the characteristics outlined below:

- **Brain banking and molecular, subcellular, cellular, or structural biology expertise:** The Lead PI, relevant staff associated with the application, and the organization(s) have robust molecular and relevant biology and brain banking expertise. Expertise in biology underlying bipolar disorder is also recommended.
- **Infrastructure:** There is ample existing infrastructure necessary to perform the required tasks and activities needed. There is little required in hiring new staff or purchasing additional equipment to handle the volume of samples.
- **Access to samples:** The organization has easy access to many samples of human brain tissue from people with bipolar disorder. The samples should be from a diverse group of individuals, including diversity as to sex and ancestral origin. No minimum number is required, but the samples should provide sufficient statistical power to advance our understanding of the molecular or structural biology of bipolar disorder. Collections that focus on groups traditionally under-examined in bipolar disorder genetics will also be considered.
- **Commitment to open science:** Open science and substantial collaboration by the applicant organization has been evidenced in previous and current partnerships, publications, and actions. The commitment to open science as described in the application is thoughtfully written and operationally feasible.

- **Projected milestones:** The milestone-based timeline highlights the ability to complete the molecular or structural analyses within three years. Milestones are realistic, affordable, and clear.
- **Cost realism:** A realistic budget that adequately supports personnel, equipment, overhead, and other needs to carry out the project.

Potential Site Visits and Virtual Interview

As needed, finalists may be asked to host a site visit or be interviewed virtually by members of the review committee. Details for site visit or virtual interview requirements will be provided to finalists.

Final Selection

Following the site visit, the SSC of BD^2 will reconvene to provide recommendations of the final partner to support the BD^2 Omics Program. Final decisions will be confirmed by the Program Board. Once notified, the awardee will work with the program team to implement the program.

Grant Terms and Policies

Each application will be applying for a grant that would provide up to $5 million over three years. The funded organization will be required to co-sign and agree in writing to BD^2's grant terms within thirty (30) days from receipt of notice of the award and prior to funds being released. BD^2's grant terms include, but are not limited to, the following items.

Use of Funds

Each team will be applying for a grant that would provide up to $5 million over three years. Because applications may be partially funded, teams will receive the amount that is sufficient to carry out the aims that are selected for funding.

- **Use of funds:** Funds may be used for scientific and technical personnel, supplies, and standard equipment needs directly related to the successful execution of the proposed scope or work. This also includes travel to relevant conferences and events. However, funds may not be used for laboratory or facility renovation.
- **Carryover funding:** Unused research funds may be carried over to the following year, with approval, and requests for no-cost extensions will be considered.
- **Indirect costs:** Indirect costs are included in the $5 million award over three years. Up to 15% of the entire grant budget may be slated for indirect costs. Note that awards may be lower than the maximum $5 million over three years. In such a case, only up to 15% of that specified grant budget may be allocated to indirect costs.
- **Unexpended funds:** Any funds not expended or committed for the purposes of the grant by the conclusion of the grant term must be returned to BD^2 unless otherwise agreed to by BD_2 in writing.
- **No cost extensions:** No cost extensions can be requested by teams within the last year of the award period.
- **Supplemental funding:** If a funded organization proposes to supplement any funds provided by BD2 with funds provided by a third party, the organization must first provide notice to BD2 and must ensure that the funding terms associated with any such third-party funds do not preclude sharing of data or publication or project results as outlined in this RFA.

Data Sharing Protocols

Open and responsible data sharing is a key tenet to avoiding roadblocks and delays in research findings. Therefore, data sharing and open science are key pillars of the BD^2 Brain Omics Program. Teams and their affiliated institutions should review and confirm that they can comply with our Open Science Policy prior to submission.

- **Open access:** All data resulting from any omics assay of this effort will be available to the scientific community at large at the earliest opportunity on preprint servers, online protocol platforms, and in an open access journal format.
    - **Publications:** All publications related to this funded work must be submitted to a preprint server, such as bioRxiv, before or concurrent with the first submission to a journal. An open access journal format is a requirement of this funding opportunity. Experimental protocols should be made publicly available through a protocol sharing service, such as bio-protocol or protocols.io. In addition, early sharing of null and incremental results, within the network and publicly, is encouraged. Scientific publications, preprints, and presentations that result from BD^2 awards are required to acknowledge support from BD^2.
    - **Data and Code Sharing:** All datasets and code, either curated or generated through the project, must be made publicly available and easily accessible online, as early as possible when feasible. This includes metadata, documentation, and intended computational use cases, as appropriate. BD^2 scientific leadership will work with grantees to identify appropriate data platforms.
- **Reporting Requirements:** Progress reports with financial report-outs are due annually or at other times as deemed necessary by the scientific leadership for project evaluation. Progress report forms will be provided by the BD 2 program staff.
    - Quarterly progress discussions will be held between program staff and the PIs of each team. Where necessary or helpful, follow-up could be expected.

Intellectual Property

Intellectual property resulting from, created, developed, conceived, or reduced to practice in whole or in part with funding from BD^2, including all patent, copyright, trademark, trade secret, and other rights therein (Grant IP) would be subject to obligations on the recipient organization to:

- Commercialize any Grant IP that has the potential to benefit patients who have bipolar disorder;
- Allow BD^2 or its sublicensee to commercialize any such Grant IP that the grantee is unwilling or unable to commercialize;
- Widely disseminate through publication the results of research funded with grants from BD^2; and
- Grant a research license to BD^2, the founding funders of BD^2, and all of their respective non-profit grantees to use and to practice Grant IP in the field of bipolar disorder.

Funding Awarded in BD²'s Discretion

Responding to this RFA and/or submitting an application does not entitle any individual or organization to receive funding from BD². Funding, if any, would be provided in BD²'s sole discretion pursuant to the terms of a written grant agreement executed by BD² and the selected grantee organization, the terms of which BD² may require to be acknowledged by the PI.

Contact Information

An automated email confirmation is generated upon application submission. If you do not receive confirmation within 24 hours of submitting your application, please check spam filters, then contact DiscoveryGrants@BipolarDiscoveries.org.

For inquiries about scientific priorities, eligibility requirements, application submission, as well as general and media inquiries, please contact: DiscoveryGrants@BipolarDiscoveries.org.