1st Annual Report

January 2008
EXECUTIVE SUMMARY

This annual report covers the period from February 1, 2007 to December 21, 2007, the first year of the Stanley Center for Psychiatric Research at the Broad Institute. In addition to the summary, the report includes five sections and appendices with more details. Sections include: Genetics, Chemical Biology, Chemistry, Neurobiology, and Animal Behavior. The appendices contain CVs of hires in 2007, organizational charts current in February 2007 and the present, intellectual property filings, animal space capability, an international collaborator list, a list of publications and presentations, and budgets for 2007 and 2008. The room for conducting animal behavioral studies will soon be finished and thus there is no data included from that project. Budgets for what has been spent in 2007 and projections for 2008 are included as a table and a pie chart showing the same data in a different format.

The Stanley Center (SC) is off to an excellent start. The most critical need going forward is to find funding to enlarge the patient sample collection for patients with bipolar disorder.

INFRASTRUCTURE AND NEW PERSONNEL

Since the inception of the SC in February 2007, we have hired several excellent scientists with doctoral-level degrees. Their CVs are included in Appendix B. They include:

CHEMISTRY: Dr. Mikel Moyer, Head of our Chemistry effort. Dr. Moyer has 20 years of experience at Pfizer. He has hired Dr. Pearlman, a computational chemist, Dr. Holson, a medicinal chemist, and he has tendered an offer to a young chemist finishing his training at MIT. All three of their CVs are included in Appendix B. With the help of Dr. Robert Gould in the Broad Therapeutic Platform, we have been able to use the services of Medicilon in China as a cost-effective way to make chemical structures needed by SC scientists. Thus we have two internal medicinal chemists, an outside source to supplement their efforts, access to hoods in the Broad Institute, and processes in place to promote interactions between chemists and biologists. We plan to set up a chemical biological database that will be accessible to chemistry project team members. This database will be used also by the Novel Therapeutics Platform at the Broad Institute. There is chemical support for exploratory biology projects and one project has been chosen as a bona fide drug discovery effort in collaboration with the Broad Therapeutic Platform.

CHEMICAL BIOLOGY: Two doctoral-level scientists have been hired: Dr. Jon Madison, a well-trained and accomplished scientist in neurobiology and molecular biology, and Dr. Jen Pan, a very accomplished neurobiologist with drug discovery experience. Their CVs are included in Appendix B. Additional expertise is now available with Dr. Thomas Nieland of the Broad shRNA platform. Dr. Nieland will devote at least 50% of his time to SC projects. Various technologies and tools have been added to the chemical biology effort.

GENETICS: Dr. Sklar has hired additional scientists with computational skills to her group and one additional postdoctoral scientist. A project manager, Dr. Jennifer Moran, has been hired by the Broad Genomics Platform who can guide the psychiatric genetics projects in that platform.
NEUROBIOLOGY: Superb collaborations now exist with Dr. Li-Huei Tsai of the Picower Institute. In addition, mission-relevant collaborations have been established with Dr. Hazel Sive of the Whitehead Institute, Dr. Morgan Sheng, Dr. Matthew Wilson, Dr. Martha Constantine-Paton and Dr. Elly Nedivi of the Picower Center, Dr. Frank Gertler of Biology, and recently with Dr. Ann Graybiel of the McGovern Institute. Aspects of these collaborations will be detailed in the project reviews below. As suggested by the Operating Committee in July 2007, each collaborator understands that their support is time-limited for two years unless their projects become mission critical to the SC. It is already clear that some of the projects will develop in a mission-critical direction.

ADMINISTRATIVE STRUCTURE: Dr. Janice Kranz (CV in Appendix B) was hired as the Administrative Head of the SC. She has been just superb in setting up a budget process, helping negotiate material transfer agreements through MIT, and dealing with a myriad of forms and regulations needed to acquire patient samples from the global collaborations we have implemented. We have established project team meetings on a rotating regular basis and a vibrant seminar series. The project team meetings are attended also by our collaborators in the various platforms at the Broad Institute.

OTHER FINANCIAL SUPPORT: To supplement our SC funding, the program has been modestly successful in obtaining other grant support from NIH with preliminary data obtained and funded by Dr. Scolnick and the SC. Importantly, seven million dollars was awarded by NIH to our collaborators to collect 7,500 patient samples and 7,500 controls in Sweden to increase the numbers of samples available for genetics of patients with schizophrenia. In the end, the NIMH funded enough only for 5,500 of each. Salary support for Dr. Matt Ogdie in Dr. Sklar’s group and a few NARSAD grants were obtained. With data now available on the DISC1 gene project, we are optimistic NIH grant support can be obtained to add dollars to this project. We also believe we can fashion agreements with 1-2 companies in the next year to aid and expedite the conduct of 1-2 of our programs, given their progress.

PROJECT SUMMARIES
The following are the most important findings in five different projects. More details are given below under each project.

1. Clear findings in the genetics of bipolar disorder and schizophrenia
2. The emergence of HDAC2 as a drug target to improve learning and memory
3. Several chemical hits in the various Lithium Project screens
4. The insight that a transcription factor, EGR1, plays an integral role in the cell’s response to lithium
5. Novel and creative insights into the mechanism of action of the gene product of DISC1 and the establishment of a system in zebrafish for studying the function of DISC1 gene, DISC1 gene variants, and a screen for chemicals that can reverse DISC1 deficiency

GENETICS
BIPOLAR DISORDER: In attempts to define the genetic architecture of bipolar disorder, Dr. Sklar, Dr. Purcell, and their collaborators have identified several genes in their primary genome scan which have subsequently been confirmed in both their own
extension samples and in a just completed meta-analysis of data from 4,435 cases and 6,225 controls. In particular, the most consistent associations with risk for bipolar disorder are observed in two genes:

1. **CACNA1C**: the pore-forming subunit (alpha 1c) of L-type voltage gated calcium channels. The strongest association signals in this gene in the meta-analysis are approximately $5 \times 10^{-8}$, values that approach robust statistical significance. Consistent results are observed in all three separate case samples. The relative risk to patients is modest, about 1.18. It is important to note that modest risk does not mean unimportance even for potential drug discovery. An example of this is found in studies done this year by Dr. Altshuler and his collaborators. They found genetic variations in HMG CoA reductase are associated with minor changes in cholesterol levels in humans. Yet the statins, drugs acting on this enzyme, lower cholesterol 30-50%. In the past, calcium channel blockers have been used to treat bipolar disorder with mixed results.

2. **ANK3**: brain-specific ankyrin a protein found at axon initial segments. The p-value here is approximately $5 \times 10^{-7}$. Like CACNA1C, the results are consistently observed in three separate case samples and confer a relative risk of bipolar disorder of 1.33. The biology seems to be more than a chance observation. ANK3 regulates currents that flow through sodium channels in the brain. It is of clear interest that this channel is the target of the drug Lamictal (Lamotrigine), which is used as a mood stabilizer in bipolar disorder based upon strong clinical studies.

The only way we can extend and confirm these findings is to obtain larger samples from patients with bipolar disorder. New data will become available through the FNIH-sponsored GAIN study in the next several months. We will be able to genotype about 1,000 additional samples in the same time frame and we have initiated an additional sample collection with our collaborator Dr. Craddock in the UK. However, we do not have sufficient funding to enlarge the collection to 20,000 samples in the next two years. Recognizing that the p-values we have on 4,435 samples are not unambiguous, it seems more than chance to us that the two highest hits are in genes known to regulate important ion channels in the brain. ANK3 interacts with a known drug target and CACNA1C has had some evidence in past clinical studies to suggest that drugs acting at it are efficacious. We plan to pursue molecular studies on each gene to further clarify their potential roles in bipolar disorder. In addition, pharmacogenetic studies are underway to identify alleles predictive of response or lack of response to drugs used to treat this disorder. Please see further details in the Genetics progress report.

**SCHIZOPHRENIA:** These studies involve an international collaboration; collaborators are listed in the Appendix C. SC funding for genotyping has facilitated Dr. Sklar’s efforts to fashion this international effort. Thus far 3,600 patient samples and 4,200 controls have been scanned and the association analyses are underway. A salient finding thus far is a validated deletion in **DISC1** in a single patient with schizophrenia with none in controls. This is the first clear human genetic evidence of the involvement of this gene in any patient since the original findings in the Scottish family. Nine cases of deletion in the region of chromosome 22 associated with Velocardiofacial syndrome have been detected. Additional deletions are being validated. One of these is on chromosome 15 in a region that codes for the alpha 7 nicotinic receptor. A large deletion is apparent in this region and it is detected in seven patients and not in controls. Its boundaries have not been fully defined or validated yet by RT PCR. Additional samples will be scanned by the FNIH GAIN program and we will have about 2,000+ samples from our Swedish project by the end of 2008. We believe the collections in schizophrenia will be about
20,000 in late 2008-2009. Thus, at the moment we do not plan additional sample collection for schizophrenia even though 30,000 samples would be ideal.

*It is clear that our effort is the largest and most comprehensive ever made to define the genetic architecture of these two disorders.* We plan to investigate common allele variants, rare variants, small and large deletions, and large copy number variants. The samples we plan to muster will be critical to fully define the genetic architecture of these diseases. Accomplishing this goal is a must for the field. We have fashioned international collaborations, leveraging the SC funding, and brought together many groups now willing to do meta-analyses of large sample numbers. In most cases, these investigators themselves are paying for collection of their samples. It is imperative that we continue these efforts and convince the NIMH to assign more funding to this effort.

**CHEMICAL BIOLOGY & CHEMISTRY**

Two of the three projects have already made significant progress.

**LITHIUM SCREENS:** Lithium is used to treat mania and to stabilize mood in patients with bipolar disorder. Lithium has been shown to ameliorate behaviors induced by amphetamine in animals and, in fact, by amphetamine *in humans*. A pathway in which lithium acts is regulated by an enzyme, GSK-3beta, although details of what is important to the effects of lithium after it inhibits this enzyme remain to be elucidated. Elevated catenin levels accompany the inhibition. We began an effort to:

1. Define the effects of lithium on messenger RNA expression patterns to understand more about how lithium works and to use a putative mRNA signature to screen for lithium mimetic drugs;

2. Screen for compounds in cell-based assays that could mimic lithium or potentiate lithium. The goal is to find such molecules, define their targets, and then optimize the structure of such chemicals to test in the animal amphetamine behavior model as a prelude to eventual clinical studies;

3. Attempt to define a molecular pharmacodynamic marker of lithium action to test its utility for predicting response in clinical trials.

   Studies on the mRNA signature have progressed well in both cell culture and in mice brains. A signature that overlaps the signature of known GSK-3beta inhibitors has been defined by Dr. Matt Ogdie. From his work, the role of Egr1, a transcription factor, has been discovered. Lithium leads to decreases in Egr1 protein levels and to proteins known to have promoters regulated by Egr1. In collaboration with Dr. Tsai, additional studies using an Egr1 GFP reporter strain of mice are planned. These studies are planned to determine if Egr1 can be measured in peripheral blood cells and used as a marker for lithium response in vivo. Egr1 protein levels do decrease in mice brains from mice treated with lithium.

   Two different reporter assays have been used in cultured cells in assays responsive to lithium. Details are given in the Chemical Biology progress report. Several different chemical structures have been found that either mimic lithium, potentiate lithium, or potentiate Wnt, a hormone that activates the pathway in which lithium acts.