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II. Appendix

Note: This ‘Executive Summary version’ is intended for a wide audience and thus does not contain the detailed scientific progress reports or the supplementary administrative appendices, which are referenced in the Operations section. Anyone interested in further information is encouraged to contact Liz Morris (see below)

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EXECUTIVE SUMMARY
Director: Ed Scolnick, M.D.

Overview

In this executive summary, I will review the highlights of this past year, 2009, from the Stanley Center for Psychiatric Research (abbreviated as ‘SC’ hereafter) and key findings in the field independent of the SC, provide rationale for the core projects we are pursuing, and provide our strategic plans for the next 1-2 years. First, however, I must mention a timely editorial in the journal *Nature* that was just published a few days ago (January 7, 2010 *Nature*, p. 9; also attached at the end of this document). I think it sets a perfect tone of hope and focus for this Annual Report, with its title, “A Decade for Psychiatric Disorders: There are many ways in which the understanding and treatment of conditions such as schizophrenia are ripe for a revolution.”

The third full year of the Stanley Center for Psychiatric Research has been another exciting and highly productive year. Novel and clinically relevant discoveries in the Genetics program continue to point a clear (albeit long) path towards an eventual full understanding of the genetic causes of schizophrenia and bipolar illness. The most striking finding of our and others’ recent genetics research on psychiatric diseases is that autism, schizophrenia and bipolar illness clearly share some risk genes. This is an important insight that has evolved from a general idea over the last 5-10 years to a solidified fact based on genetics studies in just the past 2-3 years. We anticipate the results of the Genetics Analyses will drive the future focus of all our research programs. A key milestone for the coming year –for the entire field--is to link a particular genetic variant to a biochemical function to the disease biology. Much of our effort in our Emerging Genes work is focused on this objective, and is significantly enhanced by our relationship with MIT’s Brain and Cognitive Sciences Department and multiple departments and Centers at MGH, Harvard and McLean Hospital. In addition, the neurobiology, behavioral biology and medicinal chemistry programs have advanced the progress on two targets (HDACs and GSK3) such that the HDAC program has a serious chance of leading to a clinical trial for potential new treatments. The GSK program is at a large-scale chemical screening stage looking for a suitable lead for a medicinal chemistry effort. We are continuing our discussions with both established pharma companies and venture groups on how to accelerate progress in these focused drug discovery projects.

Genetics

Rare Copy Number Variants (CNVs)

There are now data from whole genome association studies on thousands of samples from patients with schizophrenia and bipolar illness. Independent of the SC, data are also available from genomic studies of autism. In 2008, the SC and its International Schizophrenia Consortium (ISC) collaborators discovered rare highly penetrant CNVs on 3 chromosomes (1q21.1, 15q13.3 and 22q11.2) associated with risk of schizophrenia (SCZ). A 4th copy number variant (15q11.2) was described by Decode Genetics. These CNVs are deletions of blocks of genes, flanked on their respective chromosomes by repeat sequences which predispose to non-allelic homologous recombination. Recently, a duplication of a region on chromosome 9p24.1 has been discovered by an independent group (at Cold Spring Harbor and McLean Hospital) as
a risk locus for bipolar illness (BP). Reciprocal copy number variants have been noted on chromosome 16p11 which predispose to either autism or bipolar illness--deletions in autism and duplications in BP. The role of deletions in BP is not yet clear, but may play a role in early-onset bipolar illness. Some of these CNVs occur de novo during the development of a new fetus and some are inherited. These data are reminiscent of the finding by Jim Lupski (Chance et al., (1994) *Hum Mol Genet* 3: 223) in 1994 that reciprocal deletions and duplications on chromosome 17 lead to different demyelinating neuropathies with differing clinical presentation.

Our SC Genetics group has begun DNA sequencing of the genes delineated by these CNVs to determine if other more subtle mutations (such as point mutations or smaller insertions or deletions) also occur in any of the genes in these regions. Such mutations--independent of CNVs--might confer high risk for schizophrenia or bipolar illness.

The findings of these copy number variants indicate that autism, schizophrenia and bipolar illness share risk genes. This is an important insight that has emerged from the genetics just in the past 2-3 years. Details of what accounts for the differing clinical syndromes will require significant additional work including DNA sequencing. Pleiotropic phenotypes arising from different mutations in the same gene have been observed in many human genetic illnesses. It is a tenable hypothesis that various clinical psychiatric manifestations could be related to different mutations in the same genes, as well as in different genes (i.e., ‘disease-specific’ genes). Only with extensive additional sequencing data in each illness, and in controls, can we decipher this puzzle. There is an emerging awareness in the molecular psychiatry and neuroscience community that a large brain disease sequencing project is now needed to rapidly make progress in this important but complex field. In fact, in early December 2009, a brainstorming session to discuss this was held at Cold Spring Harbor, organized by Jim Watson and Dr Scolnick and attended by leading researchers (including Pamela Sklar, Mark Daly, and Stacey Gabriel of the broad Institute), non-profit groups focusing on psychiatric disease, and lobbyists.

**Common Single Nucleotide Polymorphisms (SNPs)**

From the various sample collections analyzed separately and in meta-analyses, common gene variants have also been discovered which confer risk for schizophrenia and bipolar illness. These variants are less penetrant, but still important in conferring disease risk. For bipolar illness, two genes in particular now stand out. Evidence has strengthened in the past year that ankyrin G, a brain-specific ankyrin gene, discovered as a risk gene in 2008, is a clear risk gene for bipolar illness. The protein is involved in the structure and function of the axon initial segment, a region that gates axon firing. Ankyrin is also needed for the proper arrangement of various ion channels in neurons.

A second gene has emerged from the meta-analyses in the past year, *SYNE1*. This is a huge gene (> 500 kb), which harbors within it a smaller gene (splice variant) expressed via an alternate start site. This smaller gene was dubbed ‘CPG2’ (for ‘Candidate Plasticity Gene’) by Dr. Elly Nedivi of the Picower Institute, who discovered it in a screen for activity-regulated neuronal genes. CPG2 is located selectively at excitatory-excitatory (‘E-E’) synapses and is involved in regulating the recycling of glutamate receptors on the surface of neuronal cells. The SNPs that associate with bipolar illness map within this CPG2 gene and extensive work is ongoing in collaboration with the Nedivi lab to determine if the DNA variants alter the biochemical function of CPG2.

In schizophrenia, unambiguous associations have also emerged in common variants. The two most compelling are the MHC locus on chromosome 6 and a gene called TCF4, an
important transcription factor involved in brain development, especially the pontine nucleus. Other associations are detailed in the Genetics section of the report.

Polygene Signature

In addition, work in 2009, involving larger samples than were available in 2008, has confirmed that a sizeable number of alleles comprise a signature that is more common in patients with schizophrenia and that also can detect a population of patients with bipolar illness. Strikingly, as described in our July 2009 Progress Report and in the July ’09 Nature paper attached to that report, this signature does not detect populations with 7 other non-psychiatric illnesses (Purcell et al., (2009) Nature 460: 748). Ongoing meta-analyses are refining the signature. The allelic signature may account for 35-40% of the heritable risk for these two illnesses. Our hypothesis is that with more data from larger samples a signature can be defined that may have predictive utility for these illnesses and also possibly distinguish each illness. This work is consistent with much work in flies and mice suggesting that various behavioral traits have a polygenic underpinning (Kendler et al.,(2006) Am J Psychiatry 163: 1683).

Pediatric Clinic

A new program has been initiated with the MGH Department of Psychiatry to obtain samples from children with various behavioral and cognitive problems seen in the clinic. This study, called ‘LOGIC’ (for Longitudinal Study of Genetic Influences on Cognition) and led by Dr. Alysa Doyle, is just getting started and is described in Section II’s Report on our Patient Sample Collection Effort). I am highlighting it here because I believe it is a unique effort with fantastic long-term potential for psychiatric research, perhaps akin to the Framingham Heart Study’s contribution to understanding heart disease. As genetic markers become more precise, a chip will be constructed to determine its utility in aiding diagnosis and eventually predicting natural history of such children’s behavioral problems. Eventually such data could guide treatment choices.

Going Forward

It is clear that rare copy number variants, involving many genes and which are highly penetrant, are risk loci for psychotic illness. Single nucleotide polymorphisms have pointed to more subtle variation in other genes which confer less penetrant risk. The key challenge going forward is to define the exact role of variants in single genes and the biochemical consequence of such variants in the function of such genes and the role in the pathogenesis of bipolar illness and schizophrenia.

In 2010, we will collaborate with the Medical and Population Genetics group at the Broad Institute to perform DNA sequencing on genes encompassed in the CNVs as well as the genes at the top of the association studies to begin to determine the role of rare variants in these same genes in disease risk. Some genotyping is being completed in 2009 which will yield more data. However, we plan to defer until 2011 more genotyping since a more sensitive gene chip (Illumina 5M) will be available by then, based upon data emerging from the “1000 Genomes” human genome sequencing project. Given how much the field has discovered in the last 2-3 years, we believe that in the next 1-2 years, new biochemical targets and pathways for treatment will begin to emerge from the genetic analyses, as more genotyping and sequencing data become available..

Please note that the majority of this sequencing effort (an expensive endeavor)—and, actually, the majority of the entire Genetics program to date-- is supported by non-SMRI funds,
consisting of several other private foundation grants and NIMH grants awarded to Pamela Sklar (such as the recent Grand Opportunity (GO) grant described in the Genetics report. This has allowed us to simultaneously develop our chemical biology and medicinal chemistry and animal behavioral programs while awaiting clarity on new drug targets from the emerging genetics. The SMRI funds, however, allowed the genetics to begin, and the genetics group has successfully leveraged these dollars to obtain other funding as noted

**Histone Deacetylase (‘HDAC’) Project**

**HDAC2 as Target for Cognition: Best Short-Term Chance for a New Therapy**

It had been clear from the inception of the Stanley Center that deciphering the genetic bases for schizophrenia and bipolar illness would be a difficult project, taking years of work, and yet critical to real progress in the field. We undertook this work in 2007 and have made significant progress. We also began, in parallel, to search for targets that might lead to new therapeutic approaches before the genetics could lead us to new targets for psychiatric disease.

One such target came from the work of Dr. Li-Huei Tsai, Director of the Picower Institute. In a different kind of genetically determined human brain disease called Rubinstein-Taybi Syndrome (RTS), patients have major impairment in cognitive functions regulated by the hippocampus. The Mendelian gene affected in this syndrome codes for a histone acetyltransferase, an enzyme required for an open chromatin state allowing transcription of various genes. A mouse model of this illness was described (Alarcon et al., 2004; Korzus et al., 2004; Wood et al., 2005) and a crude non-selective histone deacetylase (HDAC) inhibitor improved the cognitive dysfunction in the mice (Kandel Alarcon et al., 2004). The Tsai group showed more recently that a specific histone deacetylase--HDAC2--is the key HDAC involved in memory carried out via the hippocampus (Guan et al., 2009). Strikingly, as detailed in the Neurobiology report, the Tsai group has also recently found that a selective HDAC inhibitor can improve cognitive function in the RTS mouse model.

Based upon the human RTS and the HDAC2 work of Dr. Tsai, two years ago we initiated a project to find a selective class I HDAC inhibitor with as much specificity for HDAC2 as practically possible to test the hypothesis that inhibiting HDAC2 could be useful in improving learning and memory in various human brain diseases such as Alzheimer’s disease, schizophrenia, and post-traumatic stress disorder (PTSD)-like syndromes.

We have identified a compound, SC-027 (previously synthesized and described by a pharmaceutical company), that is an HDAC inhibitor with sufficient selectivity to test this hypothesis in animals. Additionally, the SC Medicinal Chemistry group effort is focused on discovering a small molecule unique to the SC (to allow patenting novel composition of matter), which would be similarly useful for in vivo tests. A recent patent from Takeda included a high-resolution crystal structure of HDAC2 and this structure is helping guide our medicinal chemistry efforts. Because the chemical patent on SC-027 by the pharmaceutical company will expire in 2010, we have filed strong use patents on the compound and are preparing unique crystal forms which will afford chemical composition patents. We also have filed use patents on the utility of inhibiting HDAC2.

The reason we have filed patents is that the behavioral studies in mice with this compound have shown remarkable results. Dr. Tsai, along with the SC Medicinal Chemistry and Chemical Biology groups, has shown that this compound can produce robust improvement
in associative memory tests and in improving extinction training in models of fear conditioning (which are models for human phobias and PTSD). The compound can be dosed systemically at 1mg/kg, has a good half-life, excellent oral bioavailability, and attains good brain levels. At this dose, it rapidly improves memory in a severe mouse model of Alzheimer’s, and restores a key synaptic protein in the same model. The beneficial effect is seen after only 10 days of dosing. Increases in specific histone acetylation marks in brain correlate with improved cognition after dosing. With just 2 doses, the compound greatly improves extinction training.

Based upon the literature on this compound in human trials for cancer at very high (>10X greater) doses--where it failed and was toxic, published animal safety data, and preliminary bone marrow safety studies that we have carried out, we believe that we can safely conduct a human trial to test the safety at these low doses and the efficacy in Alzheimer's, the memory problems in schizophrenia, or PTSD habituation. We are beginning to pursue multiple paths to raise the money to proceed to human trials. It is my strong opinion that this approach will have major clinical utility, and that when pharmaceutical companies learn of the data generated, there will be a major effort placed upon this target. Clearly, this is a hypothesis at this point in time. Our goal for 2010 is to position the project (and its support) to start a Phase I clinical trial by early 2011, to be followed by a Phase II efficacy trial in the disease deemed most relevant.

**HDAC Inhibitors as Mood Stabilizers**

Valproic acid (Depakote®) is used as a treatment for bipolar illness. Valproate has a number of different pharmacologic activities including histone deacetylase inhibition and increasing the concentration of gamma-aminobutyric acid (GABA) in the brain. It is not known which activity accounts for its efficacy in bipolar illness. One of its clear activities is the inhibition of several histone deacetylases. At doses used in patients, valproate yields high levels (> 100 micromolar) of drug. At these levels, clear evidence shows an increase in a number of histone acetylations in peripheral tissues.

As part of our HDAC program we have assessed whether valproate ameliorates amphetamine-induced hyperactivity, a model commonly used to assess efficacy of mood stabilizers and antipsychotics in regulating dopamine-mediated behavior. While valproate has no effect in our animal tests, one of the SC histone deacetylase inhibitors does ameliorate this hyperactivity similarly to lithium. In addition, this inhibitor appears to be effective in reducing depressive-like behavior similarly to lithium. Importantly, in contrast to lithium, the effect requires multiple doses of the HDAC inhibitor and the amelioration effect persists after the last dose, a timeframe consistent with a mechanism of chromatin modification. We believe identifying and validating this compound is an important milestone in our effort to discover a better mood stabilizer. However, we do not yet understand through which histone deacetylase(s) the efficacy is mediated.

In 2010, by assessing newer, more selective compounds from our HDAC chemistry effort, we hope to discover through which HDAC the effect is mediated. If we can do so, we would increase our effort to find an HDAC inhibitor suitable for clinical trials. We do not believe HDAC2 is the target for amelioration of amphetamine-induced hyperactivity.

**Lithium and DISC1 Projects**

Similar to our decision to pursue HDAC inhibitors before solid target and functional data emerged from the genetics, we decided in 2007 at the outset of the SC to form two other project
teams. Initially, these projects were viewed as distinct and had different rationales: (1) The ‘Lithium Project’ had the main goal of finding small molecules that either mimic or enhance the therapeutic efficacy of lithium (without the side effects); to meet this aim, significant effort was invested into cell, molecular, and chemical biological approaches to understand the elusive mechanism of lithium’s therapeutic action; (2) the ‘DISC1 project’ which sought to investigate in mouse neurodevelopment what the function of this apparent psychiatric risk gene, identified from a single Scottish family almost 10 years ago. These once independent projects continue to converge, highlighting the importance of the Wnt signaling pathway mediated by GSK3β.

Lithium has been known as a treatment for bipolar illness for close to 60 years. Many investigators have tried to define its biochemical mechanism of action, and relate the data to how it is effective in treating bipolar illness. Two major mechanisms have been proposed over decades of work:

1.) Lithium inhibits Inositol monophosphatase  
2.) Lithium inhibits GSK3β

Because no new compounds (based upon either hypothesis) are suitable for in vivo behavioral work despite a great deal of medicinal chemistry, no data exist that can clarify lithium’s mode of action. Data have been reported that suggest lithium’s inhibition of GSK3β is important in its clinical activity. The major caveat to these studies is the limitation in animal models of mania and whether they do or do not adequately phenocopy human bipolar mania. The major model used is a dopamine excess-mediated hyperactivity state. The most common way of inducing this state in animals is with amphetamine (i.e. amphetamine-induced hyperactivity). In this model it has been demonstrated that lithium leads to inhibition of GSK3β both by directly inhibiting the enzyme, and indirectly, by activating AKT which in turn phosphorylates GSK3β and further inactivates it.

In 2008, SC scientists showed that the DISC1 protein also inhibits GSK3β (Mao et al., 2009). Although the genome-wide association approach has not to date identified DISC1 as a risk locus (of statistical significance) for psychiatric disease, it seems indisputable that DISC1 and/ or the pathway(s) in which it is involved play some role: Disruption of DISC1 seems to be a major pathogenic event for severe mental illness in an extended Scottish family, and recent reports describe duplication or deletion of DISC1 in patients with autism (Crepel et al.,(2009) Clin Genet ; Williams et al.,(2009) Am J Med Genet A 149A: 1758). We have therefore focused our efforts on further understanding how lithium works and trying to find a safe, selective inhibitor of GSK3β. Based upon the binding of DISC1 to GSK3β we have developed a screening assay to detect compounds that would mimic DISC1’s effect on GSK3β. In 2009, we have conducted a novel high throughput screen to detect non-ATP-competitive allosteric inhibitors of this enzyme, funded by an NIH R03 grant that supported screening by the Broad’s MLPCN Center. The first screen of 300,000 compounds has been completed and follow-up work on the hits is beginning. If we can find a suitable lead, we will attempt to improve it with medicinal chemistry.

Finally, we have conducted cell-based RNAi screens to discover targets downstream from GSK3β for potential future chemistry efforts. Table 1 in the Chemical Neurobiology report delineates some of what we have found so far. We will assess these potential targets in the coming year to determine which might be most useful for a chemical screen to look for lead compounds.
Neurobiology & Chemical Biology Arising from Emerging Genetics

As the large scale genomics studies in schizophrenia and bipolar illness have begun to detect genes involved in these illnesses, we have initiated several exploratory parallel approaches to increase our understanding of the biological effects of gain or loss of function of these genes. We are now focusing our supported collaborations primarily on this goal. One of these entails an exploratory project in Drosophila by Dr. Mary Packard at U. Mass. Med. School. Despite the relative newness of this work, I have highlighted it here in some detail: the study began in July '09 but has rapidly progressed to be a very exciting approach for gaining insights into the emerging risk genes.

Drosophila Models of Functions of Risk Genes

Because many of the risk genes have conserved orthologues in Drosophila, one approach is to manipulate these genes in Drosophila to determine phenotypes caused by loss of function changes. In studies of Fragile X syndrome in the past decade this has been a productive approach and has helped lead to a potential new treatment for Fragile X, currently being tested in patients.

The primary goal of Dr. Packard’s Drosophila project is to identify the exact functional pathways in which GWAS-predicted bipolar disorder (BPD) and schizophrenia (SCZ) susceptibility genes may function. Applying a statistical approach called Gene Relationships Among Implicated Loci (GRAIL), the Sklar, Purcell, and Daly labs identified an intriguing list of thirty genes from the GWAS and Copy Number Variation studies that share key biological relationships (Raychaudhuri et al., 2009 PLoS Genet 5: e1000534). Indeed, all of the highly significant genes detected in the GRAIL analyses have been identified as players at neural synapses, implicating synaptic function as a common process in which these candidate disease genes may be required. Towards this goal, Dr. Packard is using a powerful system, the fruit fly Drosophila, and a highly tractable glutamatergic synapse: the larval neuromuscular junction (NMJ), to screen genes being prioritized for immediate follow-up for critical roles at synapses.

To test these genes for roles in synaptic function, Dr. Packard designs and generates powerful RNAi constructs that allow reliable targeted knockdown in vivo. This method allows any identified candidate gene to be knocked down specifically at synapses, and even allows targeting knockdown to either pre- or post-synaptic compartments. Dr. Packard has identified well-conserved Drosophila orthologs for 26 of the 30 genes on the GRAIL list and created RNAi transgenics for 19 of the 26 Drosophila orthologs. She has demonstrated dramatic knockdown in both pre- and post-synaptic cells using this RNAi method. As part of the pilot testing to optimize the choice of expression constructs for the RNAi screen, eight of the GRAIL-gene RNAi lines have been tested and already, five of these gene knockdowns resulted in striking synaptic defects. GRAIL-highlighted genes are being organized into categories based on RNAi phenotypes in order to identify to what extent the GRAIL list is likely to represent a set of genes that may share a common functional pathway that could provide great insights into the cellular etiology of SCZ and BPD.

A major goal of the Stanley Center’s mission is to identify genetic variations that will be confirmed as true associations in these illnesses, and to identify the precise role these variations may play in these disorders. As detailed in the Genetics section, we are working to identify the exact human genetic variants of GWAS-predicted BPD and SCZ susceptibility genes that may give rise to specific structural and physiological abnormalities that contribute to the SCZ and/or BPD phenotype. The fruitfly system will be used to test non-risk and risk genetic
variants as transgenic rescue constructs. If a variant is unable to rescue defects in synaptic function in a loss-of-function genetic background, the variant’s precise influence on synapses may be elucidated. Using this approach, we hope the work will create an experimental framework in which to identify how specific variations in GWAS-uncovered genes can confer susceptibility to SCZ and BPD, and thus to streamline the more difficult genetic strategies that are possible in mammalian systems.

**Mouse Models of Psychotic Illnesses**

Because the underlying genetics of psychotic illnesses has been elusive, until the last 2-3 years, no mouse models of the human illnesses exist based upon known human risk genes. It is worth noting that a mouse model of a human autism copy number variant has recently been successfully created (Meechan et al., (2009) *Proc Natl Acad Sci U S A* 106: 16434). Several groups including the SC are working to make such models for psychotic illnesses—and, importantly, communicating about their plans to minimize competition and maximize resources. Groups independent of the SC (CSH and others) are working on 16p11 deletions and duplications in mice in relevant mouse chromosomal locations. Dr. Tsai of the SC is working on the 1q21.1 and 15q13.3 models. In 2010 we will provide seed funding for a group at Mclean (led by Uwe Rudolph) to pursue the 9p24.1 duplication and triplication as a model for BP illness. When completed, these models will represent a resource in the field for testing new mechanism drugs. In addition, ankyrin G is being manipulated in mice to assess the effect of decreased function of the gene in various behaviors. Preliminary data are presented in the Behavioral Neurogenetics section. The data are suggestive that decreased function of ankyrin G may phenocopy some symptoms of BP illness. However, many more studies are needed to be sure this is true.

**Chemical Biology Approaches**

Screens are being run to look for small molecules that bind to different domains of ankyrin G, to access tool compounds useful for probing the function of ankyrin G. RNAi studies have been run to search for targets downstream of GSK3β to identify a target for a chemical screen downstream of this step in the catenin transcription pathway. An ideal goal would be to focus on one such target for a large chemical screen in 2010.

**Induced Pluripotent Stem (iPS) Cells**

The SC has established the capability of making iPS cells from human skin fibroblasts in collaboration with the Regenerative Medicine group at the MGH. The technology has progressed to being able to also make neural progenitor cells from the iPS cells. In collaboration with clinicians at the MGH and McLean hospital, we are collecting fibroblasts from 300 patients with schizophrenia, 300 with bipolar illness and 300 controls. These cells will be genotyped in order to identify which SNPs each cell /patient carries that are risk alleles for illness. Initial work will focus on cells from patients with deletions associated with schizophrenia.

As the technology progresses, we believe we will be able to define mRNA signatures for each illness vs. controls, and be able to recapitulate some aspects of the developmental abnormalities that lead to these illnesses. Meticulous cell culture methods are being employed, recognizing that variability in culture conditions will need to be tightly controlled and understood to interpret data that emerges.
Stanley Center Operations Overview

Productive focused research is made possible by good organizational structure, procedures, and management. This section highlights some of these key aspects and a few challenges.

The organizational chart for the Stanley Center in Appendix A shows the members within each disciplinary Program, Broad Platform, and SC-supported collaborators. We made several key hires in 2009. Dr. Yan-Ling Zhang is an experienced and talented enzymologist who joined us in Q1 ’09 from Merck Research Labs Boston. As Manager of Assay Development within the CB/NT Platform, she focuses on supporting the SC Medicinal Chemistry effort on the HDAC project; her elegant kinetics studies of the HDAC inhibitors has helped guide the SAR (Structure-Activity Relationship) designs. Two other critical hires are Dr. Doug Barker, Manager of Informatics, and Liz Morris, Sr. Administrative Assistant, both joining in Q3 ’09. Doug’s breadth of genetics and drug discovery research experience (in academia and industry), combined with informatics aptitude and management experience, makes him uniquely able to help all the groups and project teams to recognize, adapt and use existing Broad informatics resources (such as the computational cluster, efficiently organized storage space, medicinal chemistry analysis tools, animal behavior database and analysis). Liz Morris is providing us the continuity, professionalism, and organization to handle all our growing efforts, and she is very much appreciated.

As mentioned in previous reports, the core functional units of the Stanley Center are our cross-discipline Project Teams (progress of which was described above). Each SC Project Team focuses on all relevant aspects of each key research topic—currently, Genetics, DISC1, HDACs, Lithium, and Emerging Genes (which encompasses iPS studies). The Project Teams are constantly evolving—for example, ‘HDACs’ may evolve into ‘Epigenetics’, especially given the number of risk loci related to chromatin modification; ‘Lithium’ and ‘DISC1’ may merge into a project on the Wnt signaling pathway or GSK3β; any gene with an established causal variant might clearly ‘emerge’ from the Emerging Genes project team as its own focused project. The scientific results and needs drive our decision on how best to organize the research. We rotate weekly meetings, so that each Project Team meets at least once every two months. These Project Team meetings are the primary means of summarizing and communicating progress, fostering critical analysis, discussing and evaluating results, and establishing focus and key goals for each Project. A designated Group Leader is responsible for the ongoing progress and presentation of the work. Discussion and ideas for future direction are encouraged from all, though one challenge as we grow is to both involve and engage everyone (who are at different career stages—some academic, some professional), but also provide key guidance from the SC Management.

Another important part of our operations comes from our governance committees. Our SC Executive, Operating and Scientific Advisory Committees each provide regular critical feedback oversight and advice. Recently we have added two new members, Corey Goodman, a neuroscientist whose experience in academia, Big Pharma and biotech will add a valuable perspective; and Ken Kendler, a researcher who has worked and thought deeply about psychiatric genetics for 30 years. Our goal, especially for our Scientific Advisory Committee, is to have as many diverse perspectives with experience in our broad programs to constantly challenge us and keep our approaches and science sharp. The full list of governing committee members is in Appendix B.
Logistically, we report on our progress twice a year—typically in July/Aug and Dec/Jan. Because our funding year runs from Feb. 1 to Jan. 31, we have provided this detailed Annual Report, which includes the next funding year’s budget and summary of expenses, for review and approval by the Operating and Executive Committees. From ’07 to ’09, we scheduled a combined annual Advisory and Operating Committee meeting in July or August for a full-day (~8 am to 5 pm) review and discussion. We also invite all SC scientists and key collaborators to this event, which allows our scientists a chance to see, and to learn from, the critical thinking and strategic discussions applied to their projects. We feel it is important for all researchers to understand how their work fits into the bigger picture of the goals of the Stanley Center. We recently (Dec. ’09) found the consensus was to switch this main meeting to January. The next scheduled meeting is January 20, 2011. If this is successful (and is not too adversely affected by winter travel issues), then we plan to keep on this annual January timing.

To stay informed and responsive to the rapid pace of research, we use our Stanley Center Seminar Series to explore new ideas, technologies and fields, potential collaborations, and alternative perspectives, all immediately relevant to our Stanley Center mission. We aim for biweekly seminars (for a total of 20-25 each year), though we keep scheduling flexible to accommodate speakers’ availability. The seminar schedules from last year (Appendix C1) and the current ’09-’10 academic year (Appendix C2) reflect the breadth and quality of topic.

Collaborations continue to be a vital means to explore pilot projects in new areas and to pursue discoveries identified by the genetics or neurobiology programs and accelerate our overall research progress. The Genetics Program (as described in its report) has well-established multiple global collaborations that are ever expanding (in part due to a successful track record). We especially need to establish and use wise, effective collaborations to help us understand the growing list of genetic risk loci for schizophrenia and bipolar illness (including CNVs covering many genes and SNPs likely affecting single genes. By virtue of both being at the Broad Institute and having our Directors affiliated with MGH and MIT, we have many collaborative opportunities. Appendix D summarizes both our collaborations supported by the SC (Appendix D1) and our broader SC Collaborator Community (Appendix D2). Many of these are purely research collaborations (not supported by SC) that advance our and the collaborators’ complementary research interests. For funded collaborations, we continue to use the ‘2-year model’: provide initial “seed funding” (over a maximum of two years—typically support for 1 post-doc or researcher) to allow the projects to obtain sufficient preliminary data either to qualify for other grants, or to determine if they are critical to Stanley Center goals.

In closing, we should also discuss the impact of the Broad Institute establishing itself as a permanent, non-profit organization, transitioning from an administrative unit within MIT. This change became effective July 1, 2009. As anticipated, this conversion had no significant effects on our research. All the facilities and staff that currently comprise the Stanley Center have remained exactly the same. The capacity to undertake our scientific goals of this program have not changed. There have been some administrative bumps, such as needing MIT appointments in order to access our animal facility, and needing to issue subcontracts for our MIT collaborators. But these issues are not substantive. A few operational areas, particularly financial tracking and reporting, are still being worked out to fit our needs. However, improvements in some administrative functions are already noticeable, such as HR (policies, job ladders and titles are not limited by MIT’s purely academic philosophy), and Business Development (communication with members of this department is excellent, and turnaround time on several MTAs and licenses has been reduced). Overall, we strongly believe that this new structure will provide us even better opportunities to reach our research goals over the next ‘revolutionary decade’—modified quotation borrowed from the January 7 2010 Nature Editorial referred to earlier—and included, in closing, on the next page.
A decade for psychiatric disorders

There are many ways in which the understanding and treatment of conditions such as schizophrenia are ripe for a revolution.

A media circus surrounded President Bill Clinton’s visit to a New York medical centre in 2004 for a quadruple heart bypass. Yet barely a whisper was heard about other high-profile individuals’ visits there for the treatment of psychiatric disorders.

In Britain, the public donates £500 million (US$800 million) each year to charities for cancer research. For mental-health research, the figure is a few million, and most of that is for work on neurodegenerative diseases such as Alzheimer’s, rather than for earlier-onset conditions that can undermine people’s entire lives, such as depressive disorders.

It is time for such disparities to be addressed in a more coherent and aggressive way than in the past. The stigma of psychiatric disorders is misplaced; their burdens on society are significantly greater than those of more publicized diseases in developed and developing nations alike, and biomedical science is poised to make significant strides. The timescales are daunting and the challenges great – human neurons are less accessible than tumour cells, separating genetic and environmental influences is tough, and the diagnosis of the conditions is highly problematic. There is much to be done, and a decade is the timescale over which enhanced commitment is required.

The problem of stigma persists. In some countries, progress in this regard has been made with depression: a few high-profile and brave sufferers in some Western countries have stood up and identified themselves. By contrast, schizophrenia, when covered by the media at all, is mostly associated with murders carried out by a tiny minority of sufferers who have an acute form of the condition.

Research challenges

Schizophrenia – a combination of delusions, reduced motivation and diminished cognitive function – exemplifies many of the research challenges posed by psychiatric disorders as a whole. The extreme behaviours covered by the media are far from typical. Population studies indicate that the lifetime prevalence of all psychotic disorders (whose sufferers experience some sort of misperception of reality) is as much as 3%. Schizophrenia is controllable by medication and cognitive therapy, with a significant chance (a few tens of percent) of beneficial positive outcomes.

Frustratingly, the effectiveness of medications has stalled. Nobody understands the links between the symptoms of schizophrenia and the crude physiological pathologies that have so far been documented: a decrease in white brain matter, for example, and altered function of the neurotransmitter dopamine. The medications, which are often aimed at the dopamine systems associated with delusions, have advanced over the decades not in their efficacy but in a reduction of their debilitating side effects.

Both diagnosis and drugs primarily address a late stage in the development of schizophrenia – the presentation of delusions. The earlier stages are much less well defined and are ambiguous in that, as currently characterized, they could lead to a number of alternative conditions. Here, above all, is where progress is needed in the form of reliable biomarkers to identify those at risk and to allow biomedical or cognitive interventions to prevent or mitigate the development of the disorders. Early intervention would lead to better outcomes. A deeper understanding of the underlying biology is essential to improve diagnoses and therapies. New techniques – genome-wide association studies, imaging and the optical manipulation of neural circuits – are ushering in a new era in which the neural circuitry underlying cognitive dysfunctions, for example, will be delineated. tantalizingly, work in genetics is indicating how non-specific some genes are for schizophrenia, having associations in common with bipolar disorder and with autism. This suggests that the earlier stages of psychiatric disorders are multivalent, reinforcing the hope that early detection, coupled with a clearer understanding of the environmental factors, may allow prevention.

Environmental influence

Too little fundamental research is devoted to environmental factors. About 80% of the pattern of schizophrenia in populations seems to be determined by genetics, but part of that genetic influence lies in susceptibility to environmental influences. The remaining 20% of direct environmental influence is also ripe for more extensive investigation – epidemiological studies point to social stress (associated, for example, with migration or urbanization) as a significant influence, albeit in a minority of schizophrenia sufferers. As stated in a recent review of schizophrenia, a “worldwide challenge is to bring together the various disciplines that are needed to examine models of disease causation based on various aspects of gene–environment interplay” (J. van Os and S. Kapur, Lancet 374, 635–645; 2009).

Of course it won’t be just the basic biology of molecules and their networks that will be essential in understanding the mechanisms of schizophrenia. There is a higher level of explanation required to understand, for example, delusions and their persistence.

Whether for schizophrenia, depression, autism or any other psychiatric disorders, it is clear as Tom Insel, head of the US National Institute of Mental Health has emphasized (T. R. Insel J. Clin. Invest. 119, 706–705; 2009), that understanding these conditions is entering a scientific phase more penetratingly insightful than has hitherto been possible. But Insel also highlights the disruptive impact of the science on the practices of clinical psychiatrists – as biological insights develop, the crudity of current psychiatric diagnoses will become all too clear. Yet the exposure of many psychiatrists to contemporary biology is shallow at best. That, too, will need to change over the next decade.