2013 Update

from the Stanley Center for Psychiatric Research

The Mission of the Stanley Center is to reduce the burden of serious mental illness through research. The Center focuses on schizophrenia, bipolar disorder, and autism, both because these illnesses exact a severe toll on affected individuals, families, and society, and because recent advances in genomics and technologies have made them scientifically tractable in ways that we could not have imagined even a few years ago. We are committed to employing modern scientific approaches toward understanding the pathogenesis of these disorders at the molecular level, and to apply that information toward designing a new generation of much needed treatments.

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The last four years have been a time of wrenching paradox in translational research in psychiatry. The scientific possibilities have never been greater, but there has been a rapid and progressive de-emphasis on psychiatry by industry despite the high prevalence of psychiatric disorders and vast unmet medical need. We at the Stanley Center fervently believe that unless one wants to rely solely on luck, the history of successful treatment development in medicine begins with molecular understandings of disease mechanisms in humans.

Unfortunately, luck has run out on psychiatry. All of today's pharmacologic therapies, where they exist at all, are iterations on prototype compounds discovered serendipitously in the 1950s. For the highly impairing cognitive and deficit symptoms of schizophrenia, and the core social deficits of autism, pharmacologic treatments simply do not exist. Industry's decision to de-emphasize or exit psychiatry has occurred as companies have reflected on the field's ignorance of disease mechanisms, on the long-standing reliance on "black box" rodent behavior-based drug screens that have a 100% failure rate of detecting novel therapeutic mechanisms, and on a complete lack of treatment biomarkers for clinical trials. To underscore the upshot of this situation, a half-century has passed in which

no fundamentally new treatment mechanisms or drugs with greater efficacy than our ancient touchstones — lithium, imipramine, or clozapine — have achieved regulatory approval. Our central focus is the science and abnormal pathophysiology of the human diseases that we believe will ultimately lead to effective new

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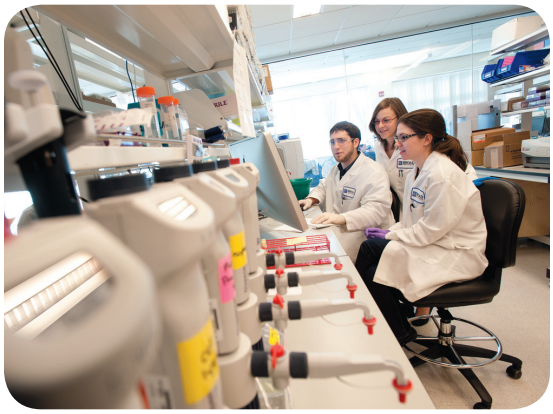

treatments. However, as an important corollary, in furtherance of our mission, the Stanley Center has been engaging industry, the National Institutes of Health, foundations, and a wide network of collaborators, with the goal of ensuring continued interest in treatment development based on the unprecedented scientific opportunity.

The opportunity to effectively investigate psychiatric disorders is truly historic, based, above all, on astonishing advances in technology. For example, the costs of genotyping and of sequencing DNA have dropped substantially — and continue to drop — while quality and speed continue to increase. As the Human Genome Project began, the cost of DNA sequencing was approximately $1.00 per nucleotide base. Currently, it can cost as little as $0.07 to sequence 1 million base pairs at the Broad Institute. Secondly, just as recognition was dawning that mouse models — still central to the identification of basic molecular mechanisms and of the relationship of brain circuits to behavior — had significant limitations as models of human disease, stem cell technology began to mature and provide important tools. These include the discovery of how to make induced pluripotent cells (iPS cells), the ability to convert both human embryonic stem cells (hESC) and iPS cells into neurons, and the ability to engineer disease-risk-associated DNA sequences into these cells (or out of cells derived from patients). The Stanley Center is fortunate to be an integral part of the Broad Institute of MIT and Harvard where superb technological platforms continue to evolve and where a culture of collaboration facilitates our ability to interact fruitfully with other disease programs in the service of speeding discovery.

The scientific approach: a bit more detail

The scientific key to our approach is based on the observation that risk of developing schizophrenia, bipolar disorder, or autism is more highly influenced by genes than most other mental or chronic medical disorders. A significant role for genes does not exclude environmental factors, but it does mean that

differences in the sequence of bases — the "alphabet" of the DNA that comprises our genomes — contains important information about how these disorders come about. Until now, the primary obstacle has been our inability to access this information because risk for these disorders is not contained in one or a few genetic variants, but is partitioned across hundreds of genes, each of which contributes a small increment of risk. The technologies that resulted from the human genome project have made it possible for us to identify changes in DNA sequence associated with risk of schizophrenia, bipolar disorder, and autism by enabling us to study populations so large that we can separate the "signal" we are interested in from the background "noise" created by normal variation among individuals. One astonishing result of this technology is that the cost of sequencing DNA has declined about *1 million-fold* over the past decade, and it has become possible to design relatively inexpensive DNA microarrays (gene chips) that will contain all known variation associated with psychiatric disorders.

The declining cost, and increasing speed and accuracy of DNA sequencing and genotyping with DNA microarrays (i.e. detection of disease-associated variants across the genome), has made it both feasible and affordable to study large numbers of patients and comparison subjects. We have thus engaged in continuing the expansion of global collaborations in order to achieve the numbers that we need. For the study of schizophrenia, the resulting Psychiatric Genomics Consortium has combined genotyping data sets for more than 35,000 patients and 47,000 healthy comparison subjects, and we and others have determined the sequence of genomic regions that encode the protein building blocks of cells for over 14,000 patients and comparison subjects. Work is following right behind on bipolar disorder and autism as we work with collaborators to expand access to patient populations worldwide. We are proud that the Stanley Center and Broad Institute have contributed the lion's share of genotyping and sequencing data and have taken the lead in much of the analysis.

This approach has permitted us confidently to identify more than 100 regions of the genome that are associated with schizophrenia. Even more exciting, is that the genes identified so far are not random hits on the genome, but identify important protein networks within the nervous system as playing a role in pathogenesis. A similar, indeed partly overlapping picture is emerging in bipolar disorder and autism. To reach the crux of the matter, the identification of DNA sequence variation associated with disease, no matter how small the individual contribution

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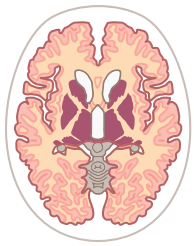

of any particular genomic region, has pointed us to particular molecules and cells in the brain that are involved in pathogenesis.

Of course we could not possibly be content with gene lists. Members of the Stanley Center are hard at work engineering risk-associated sequences into human stem cells and learning how to turn those cells into specific kinds of nerve cells (neurons) that have been implicated in the disorders under study. Since many of the genetic discoveries have pointed us toward synapses, the connections across which neurons communicate, we are working with bioengineers to develop "circuits on a chip" in which neurons make defined synaptic connections. Ultimately the goal is to see how disease processes alter the structure and function of synapses and to determine how we might correct abnormalities with drugs. Other members of the Stanley Center are using a diversity of animal models to study aspects of the nervous system that are too complex to recreate in a dish or on a chip. In all cases we are collaborating across multiple academic institutions and with industry because, despite our excitement, the road ahead is long and difficult, and our goal is to speed progress toward treatment.

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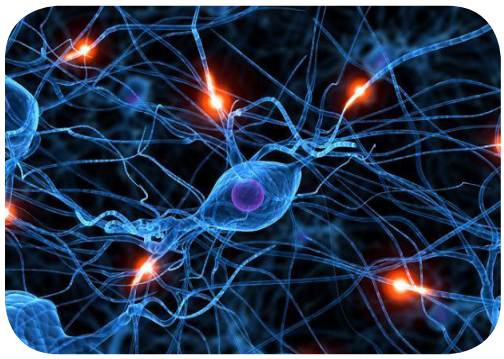

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