



Report of the NIMH Board of Scientific
Counselors Workgroup on Schizophrenia
Research in the DIRP

March 2013

Executive Summary

The arrival of a new Scientific Director (SD) of the NIMH Division of Intramural Research Programs (DIRP), Dr. Susan Amara, and the departure of two long-standing DIRP principal investigators (PIs) within the Clinical Brain Disorders Branch (CBDB), provide an opportunity for strategic planning and consideration of schizophrenia research in the DIRP. The purpose of this report is to provide guidance to the NIMH on future directions for schizophrenia research in the DIRP, specifically related to important directions for the field and to important areas/strategies for insuring high quality programmatic development. This document is a product of a workgroup created by the NIMH Board of Scientific Counselors (BSC) to discuss and make recommendations around this topic. The charge to the workgroup was:

Based on public health needs, current NIMH extramural investments and the changing ecology of the DIRP, are there compelling scientific opportunities in the area of schizophrenia research that can be uniquely and effectively conducted within the DIRP?

In the course of its deliberations, the workgroup explored the opportunities and needs within the field of schizophrenia research and, to the degree possible, within the DIRP environment. Notably, the workgroup recommended that the DIRP not design a future research program to investigate the Diagnostic and Statistical Manual (DSM)-defined disorder of schizophrenia, but instead to focus a future research program on psychoses, leading the field forward in the new conceptualization of mental health research that is consistent with the NIMH Research Domain Criteria (RDoC) initiative. The subsequent recommendations identify scientific strategies and organizational steps to ensure high impact research related to psychosis and its prevention, suggestions related to the analysis and use of existing resources within the DIRP that could be enlarged through a strategic planning effort led by the new Scientific Director (SD).

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Introduction and Workgroup Process

The NIMH Mission is “to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure. “ The NIMH Division of Intramural Research Programs (DIRP) offers outstanding resources, unique funding mechanisms, and an exceptional environment for research that will contribute to the NIMH Mission.

The arrival of a new NIMH DIRP Scientific Director (SD), Dr. Susan Amara, and the departure of a number of long-standing DIRP Principal Investigators (PIs) in the Clinical Brain Disorders Branch (CBDB) provides an opportunity for strategic planning and consideration of the future of schizophrenia research in the DIRP. The NIMH Board of Scientific Counselors (BSC) established this Workgroup on Schizophrenia Research in the DIRP to gather extramural experts in the field of schizophrenia and other brain disorders to discuss the unique contributions that could be made through schizophrenia research in the DIRP, and to make recommendations to the BSC and the SD regarding ways in which DIRP leadership might best proceed to ensure high impact scientific progress now and in the future.

Charge to the Workgroup

Based on public health needs, current NIMH extramural investments and the changing ecology of the DIRP, are there compelling scientific opportunities in the area of schizophrenia research that can be uniquely and effectively conducted within the DIRP?

Workgroup Process and Guiding Questions

This workgroup was created by the BSC to make recommendations on future research within the DIRP related to schizophrenia. The workgroup’s members are listed in Appendix B; their areas of expertise include research in schizophrenia and other brain disorders, and span from genetic and molecular studies to clinical therapeutic research; each member is a well-established investigator with extramural research funding from NIH. The workgroup met three times via phone and one time in person in January and February 2013.

The workgroup was guided by the following three questions regarding research opportunities in schizophrenia research:

- Is schizophrenia an important and timely area of research?
- Are components of schizophrenia research insufficiently represented in NIMH extramural investments?
- Can this type of research be uniquely and effectively conducted within the DIRP?

Opportunities and Needs

- The workgroup identified the need to understand and define the neurobiology of schizophrenia, but the DSM-defined disorder “schizophrenia” is likely a collection of different illnesses; therefore a focus on psychoses and the cognitive deficits often

observed in schizophrenia and related disorders will allow for more traction and will be consistent with the extramural NIMH Research Domain Criteria (RDoC) initiative that emphasizes a dimensional approach to different domains of brain function instead of DSM-defined diagnoses. The current situation provides an opportunity for the DIRP to lead the way forward in the conceptualization of mental illness research, not bound by DSM-defined diagnoses.

- The workgroup identified the need to explore recruitment of a new leader for a DIRP psychosis program. This individual must be at the forefront of the science, have a clear vision for the future of the field, be collaborative and facile with translational thinking, and be able to integrate across areas of science toward a unifying goal.
- The workgroup identified the need to consider a collaborative, center-like program organization dedicated to the study of psychosis, either by *de novo* creation or through strategic integration with existing units, and to increase communication among PIs and laboratories within the DIRP.
- The DIRP environment offers the unique resources for research with rare but informative patient populations that can be studied intensively in a manner that is interactive with extramural community. For example, extramural investigators and/or clinicians could serve as the referral base for individuals who have certain rare genetic lesions of interest, associated with high risk for psychosis.
 - This broad recruitment and focused research strategy is exemplified by Dr. Karen Berman's work with Williams syndrome individuals and Dr. Judith Rapoport's work with childhood onset schizophrenia.
 - Genetically identified populations at high risk for psychosis offer an opportunity for the identification and study of individuals at all stages of illness (including before the onset of psychosis, during the first episode of psychosis, and across treatment).
 - In depth knowledge from these populations could inform the development of model systems and a translational research program to gain a better understanding of the mechanisms responsible for psychosis.
- The development of unique model systems, that are difficult to develop in the extramural community (e.g. multiple allelic series analysis, noncoding variation transgenics), can drive discovery and fuel both forward and backward translational research, playing to the intrinsic strengths of the DIRP. In particular, the workgroup recommends the development of clinically relevant, construct-valid animal model systems and the integration of existing model system approaches into a programmatic vision, moving to non-human primates where significant investments are needed to catalyze the field (for example, transgenic marmosets).
- The DIRP environment offers the opportunity for longitudinal studies, as has been successfully demonstrated by many investigators including Dr. Jay Giedd. The workgroup identified the need for longitudinal brain imaging studies (structural and functional magnetic resonance imaging (MRI) as well as positron emission tomography (PET)) at the time of the first episode of psychosis and across the subsequent 5 - 10 years.

- The DIRP environment offers the opportunity for off-medication studies requiring an outstanding inpatient psychiatric setting. This capacity could be used for various types of patient research related to psychosis, including deep phenotyping during first episode psychosis and early stage treatment testing.
- The workgroup identified the need to define biomarkers of psychosis, especially those that index the pathophysiology of affected neural circuits. The DIRP has capacity for multiple neuroimaging modalities including PET and fMRI, and as the DIRP has done in the past, the collaborative development of new measures of brain function that offer promise as informative biomarkers.
- While technology development is essential to provide the tools needed to test compelling hypotheses in psychosis research, many of these goals may be most effectively achieved through an extramural request for applications (RFA) where many research groups can respond. However, the NIMH DIRP does have a history of successful PET ligand development. The workgroup identified the need to develop new PET ligands that target synaptic proteins involved in plasticity. The development of such ligands would be very valuable to researchers investigating psychosis and relevant treatments, and to the larger neuroscience community.
- The workgroup identified the need to more effectively utilize and share the existing resources within the DIRP, such as the NIMH Brain Bank and the research subject registry and data collected through the longstanding schizophrenia sibling study.
- The workgroup identified the need to develop a stronger computational, analytic, and informatics resource for use by DIRP investigators.
- The DIRP should consider whether opportunities exist to integrate existing programs with efforts of the BRAIN initiative to evaluate molecular, cellular and systems networks not practical in the extramural community.

Tactical Recommendations

- The workgroup recommends the DIRP build on existing strengths and consider establishing a psychosis research program, identifying and recruiting a new leader for this effort. As noted above, this individual must be at the forefront of the science, have a clear vision for the future of the field, be collaborative and facile with translational thinking, and be able to integrate across areas of science toward a unifying goal. This leader must also be able to foster a center-like environment in which investigators collaborate within a horizontal organizational structure. Given her experience and tenure in the DIRP, Dr. Karen Berman will be very valuable in discussions related to the qualities of the optimal leader. Such a leader should be considered in the goals and strategies articulated by a Strategic Planning Group charged to review existing programmatic structures, laboratories and sections and to make recommendations on best practices for aligning structures for the future with likely resource commitments and high impact science. This group could include senior members of the Board of Scientific Counselors, but also scientists with experience in administrative coordination of multi-scale programs and initiatives.

- The workgroup recommends the Scientific Director consider pursuing the intensive investigation of defined populations at high risk for psychosis toward the goal of identifying prevention strategies in these vulnerable populations as one of the DIRP strategic priorities. The DIRP offers the unique ability to recruit subjects across the country (via a distributed referral network) and bring them to one location for in-depth study, ensuring quality controls and consistency across all subjects. It is likely that an informative population or populations could be defined by specific genetic lesion(s), but the specific selection of populations should be determined by the lead investigator(s). Factors other than genetic liability might also be informative in selecting populations for study (e.g., psychosis associated with anti-NMDA receptor paraneoplastic syndromes or ketamine abuse). Within the study of rare, informative populations, the workgroup recommends pursuing the development of informative biomarkers that index some aspect of pathophysiology or therapeutic response. Such biomarkers could include neuroimaging or electroencephalogram (EEG) patterns of brain activity, cerebrospinal fluid (CSF) proteins, or induced pluripotent stem (iPS) cell characteristics. Examination of multiple high-risk populations could identify convergence and generalizability of the neurobiological basis of psychosis.
- The workgroup recommends that the DIRP consider pursuing scientifically justifiable, longitudinal studies, paced as resources and other priorities permit. Careful consideration should be given to which longitudinal studies would most benefit the field; a longitudinal study may be most beneficial when used in the investigation of individuals with rare genetic lesions that convey high risk for psychosis.
- The workgroup recommends that the DIRP make an effort to maintain the capacity for long term in-patient psychiatric studies as resources and other priorities permit. Careful consideration should be given to possible off-medication studies requiring an inpatient setting, potentially including deep phenotyping of subjects experiencing first-episode psychosis or early stage treatment testing.
- The workgroup recommends that any psychosis-focused program in the DIRP include the development of model systems (based on the biological knowledge gained through the study of the identified high risk populations) to further investigate the neurobiological mechanisms of psychosis. Examination of multiple model systems could detect convergence and increase evidence to support the identified pathophysiology. These models could also serve as important translational research tools, helping to identify potential therapeutic targets and interventions.
- The workgroup recommends that emphasis be placed on integrating clinical and basic research to ensure effective translation of research findings (forward and backward) within the proposed psychosis program.
- The workgroup recommends that the NIMH DIRP consider developing a core to provide computational, analytic, and informatics resources for use by the proposed psychosis program and across the NIMH DIRP.
- The extramural community has a number of programs investigating the prodrome and conversion to psychosis. The DIRP is not well-suited to examine the prodrome,

which benefits from distributed research sites where subjects do not have to travel long distances to participate in the studies. Therefore, the workgroup recommends that prodromal studies related to idiopathic psychoses not be pursued within the DIRP.

- The NIMH, in collaboration with other Institutes, is constructing a new National Neurobiobank for the centralized acquisition, receipt, storage and dissemination of human brains, related biospecimens, and associated clinical data. Research efforts within the DIRP should utilize this national resource, and if appropriate, contribute to it. Unfortunately, the data available to the workgroup regarding the existing NIMH DIRP Brain Bank data was not sufficient to determine how, and whether, integration with the National Neurobiobank might occur. The workgroup recommends that the DIRP arrange for a complete assessment of the NIMH Brain Bank to catalogue all of the material in the bank and all associated data (e.g., psychiatric autopsy, measures of agonal factors and tissue quality, etc). Until a complete and accurate inventory of this publically-funded resource is accomplished, the workgroup recommends that no sample withdrawals be made and no additional accruals occur. The DIRP is encouraged to maintain relationships with medical examiners' offices, if possible.
- The workgroup recommends that the DIRP arrange for an independent examination of the data collected as part of the clinical protocol "A Neurobiological Investigation of Patients with Schizophrenia Spectrum Disorders and Their Siblings" (95-M-0150). This examination should include subject information, as well as any data, deep phenotyping, and/or samples collected and stored. Until a complete inventory and assessment of this publically-funded resource is accomplished, the workgroup recommends that no future studies using these subjects be conducted and additional recruitment of subjects not occur. The DIRP is encouraged to maintain contact with subjects so they might be re-contacted for participation in future studies.
- Typically, the departure of a DIRP PI results in the sun-setting of that PI's research programs, however some research projects of departed CBDB PIs have continued under reassigned leadership, with non-DIRP researchers utilizing DIRP resources (such as space and imaging time), and without a clearly defined review structure. The workgroup recommends that these relationships be evaluated and structured to conform to DIRP standards for resource use by non-DIRP researchers and to ensure appropriate review mechanisms are in place.
- The DIRP and its faculty should maintain the highest standards of data and resource sharing, setting an example for the extramural research community.

Conclusions

The charge to this workgroup was both overarching and specific, asking the members to consider the current state of the science and the specific resources and environment of the DIRP. As described in this report, a number of promising avenues for research in psychoses

have been identified and specific recommendations regarding existing NIMH DIRP resources have been made. This workgroup was asked to make recommendations at a time of transition, with a new SD and recently departed DIRP PIs. This time of transition is a unique opportunity for the NIMH DIRP to move forward in developing a new and innovative program in psychosis research, with the mission of transforming the understanding of mental illness and paving the way for prevention, recovery, and cure.

Appendix A

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Appendix B

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