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Frontiers of Biomolecular Exploration in Brain Disorders

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Five volumes of the *Neuropsychopharmacology: The Next Generation of Progress* were published in print by the American College of Neuropsychopharmacology between the years 1968 and 2002. These volumes historically defined the scientific arena of neuropsychopharmacology and served for 40+ years as major references, providing a foundation of the research and therapeutics knowledge in psychiatric and neurological disorders. With the increasingly fast-paced evolution of our field, the ACNP opted to continue the tradition in the more dynamic format of devoting the first issue of its flagship journal each year to *Neuropsychopharmacology Reviews: The Next Generation of Progress.* The first six issues have provided outstanding and timely overviews of neuroplasticity (Vol. 1), central nervous system (CNS) drug discovery and development (Vol. 2), neurocircuitry (Vol. 3), cognition (Vol. 4), neurotherapeutics (Vol. 5), and epigenetics (Vol. 6). The seventh issue of *Neuropsychopharmacology Reviews* is devoted to biomolecular discovery and the implications for mechanisms, therapeutics, and biomarker development. The articles in this issue focus on the recent advances in the detection, subtyping, and monitoring of complex neural disease progression, the definition of new molecular targets for therapeutic intervention and biomarkers, with an emphasis on the use of genome-wide analytical technologies.

A biomolecule is an organic molecule (eg, neurotransmitter and metabolite) or macromolecule (eg, nucleic acid, protein, and lipid) produced by a living organism. Biomolecular discovery efforts have escalated in tune with the mapping of the human genome. Recently, the first general translation of the human genome was published ('Encyclopedia of DNA Elements' or ENCODE project), demonstrating that over 80% of the human genome is predicted to be biologically active (The ENCODE Project Consortium, 2012). Of interest to the field of neural disorders, the ENCODE Project found that a majority of the single-nucleotide polymorphisms (SNPs) associated with a disease reside in or near ENCODE-defined regions outside of protein-coding genes (The ENCODE Project Consortium, 2012). This observation has profound implications in that the disease progression may be tied not only to modifications in coding regions of the gene, such as those that result in proteins, but also to the regulatory elements found in non-coding and other regions (previously termed 'junk' DNA). Thus, discovery science has uncovered an even greater necessity to garner a holistic view of the genome and its diverse biomolecular products in the quest to understand neural disorders and to customize effective therapeutics and biomarkers of disease progression, diagnosis, and prognosis. This task is dependent upon the engagement of scientists from the disciplines of chemistry, biochemistry, molecular and cellular biology, pharmacology, engineering, and material scientists as well as preclinical and clinical investigators. Such teams are changing the landscape of neuroscience.

The publication of the human genome was a defining moment in scientific history, made accessible to bioscience because of brilliant advances in technology and engineering such as Sanger DNA sequencing, polymerase chain reactions, and high-throughput genotyping-enabled systems biology research built on knowledge derived in global data sets. The large-scale study of transcriptional products (transcriptome), chemical changes to DNA and histones (epigenome), proteins (proteome), metabolic networks (metabolome), carbohydrate molecules (glycome), and cellular lipids (lipidome) in a given cell, tissue, or organism is now revealing important facets of disease processes and therapeutic responses. Although no single analytical platform can capture the rich diversity of endogenous biomolecules in a given biological compartment, the application of highly sensitive, large-scale mass spectrometric capabilities in 'Omics investigations' is having a profound impact on natural science. The first three papers of the volume are built upon this core technology, serving as primers on mass spectrometry and explaining its role in an integrated bioanalytical approach to the study of disease processes. The review by Emmett *et al* (2014) orients the reader to the use of mass spectrometry and integration with complementary tools, including innovative mathematical–computational algorithms, to build knowledge from these global data sets. Emmett *et al* (2014) draw examples drawn from studies of glioblastoma and glioma-derived cancer stem-like cells and emphasize known observations in neural systems and the future for systems biology research in psychiatry and neurological disorders. In the next review, Wood (2014) provides the reader with an overview of mass spectrometry as applied to metabolomics and relates the technical advances to psychiatry and neurology. Mass spectrometry imaging is a powerful tool used to investigate the spatial distribution and topographical organization of biomolecules (proteins, peptides, neurotransmitters,

metabolites, and drugs) in complex tissue; Shariatgorji *et al* (2014) demonstrate how mass spectrometry imaging can provide chemical insights into the biomolecular associations in neural tissues and how these associations can be affected by disease or drug. These three papers provide guidance through the complex field of large-scale bioanalytical technologies and computation, specifically aimed toward the neuropsychopharmacological investigator.

The understanding of the response of specific cells within the CNS (normal *vs* diseased, treated *vs* untreated, and so on) and the evidence that these cell populations are 'drivers' of disease underscore the importance of identifying detailed biology at the molecular level of cells and circuits. Such analyses demand the use of technologies that can precisely isolate small-volume samples (eg, single cells). Romanova *et al* (2014) review the cutting-edge technologies that aid direct measurement of cell-to-cell signaling molecules in the nervous system, highlight effective approaches for the collection, separation, and detection of such small-volume samples and present strategies for use in the targeted and discovery-oriented research. From a translational perspective, a sizeable barrier exists in the application of such elegant single cell analyses to human brain, particularly in postmortem samples. McCullumsmith *et al* (2014) review the challenges and limitations of illuminating pathophysiological pathways in human brain and emphasized the integration of technologies applied to date to questions of neural mechanisms underlying schizophrenia. These papers illustrate the power of modern bioanalytical technologies in cellular neuroscience.

Proteins are large biomolecules that catalyze metabolic reactions, form cellular structure, and receive, amplify, and transduce signals; proteins also oligomerize into protein:protein interactions that are essential for biological functions. The human genome includes ~21 000 protein-encoding genes, but the total number of protein isoforms (unique structures) in human cells is estimated to be in the millions when protein variants and posttranslational modifications (eg, phosphorylation, glycosylation, and so on) are considered (Jensen, 2004). The past decade has been marked by extraordinary advances in proteomic techniques that have demonstrably increased our understanding of the composition, regulation, and function of protein complexes and pathways underlying altered neurobiological conditions. The next two papers in the issue emphasize neuroproteomics as a means to enrich our understanding of the mechanisms through which exposure to psychoactive drugs affects protein function and interactions (Stockton and Devi, 2014; Gorini *et al*, 2014). Stockton and Devi (2014) discuss an elegant quantitative proteomic approach and graph theory-inspired network analysis to enable our comprehension of how morphine impacts isolated presynaptic and postsynaptic functions of the striatal synapse. This article emphasizes the coupling of key technologies to target synaptic sites of protein interactions and plasticity, which contribute to the enduring behavioral and physiological changes associated with opiate addiction. Gorini *et al* (2014) profile the impact of alcohol exposure across cells, animals, and humans with an emphasis on protein–protein interaction networks and a systems biology integration of data to best understand the pathogenesis of alcohol dependence. These biomolecular discovery reviews are followed by two papers that explore in more detail protein:protein interactions as mediators of complex behaviors. Fuxe *et al* (2014) delves further into the dynamics of receptor–receptor interactions for G-protein-coupled receptor (GPCR) complexes in the CNS in light of their key involvement in psychiatric and neurological disorders. Special attention is paid to the unique contribution of 'moonlighting' proteins, which perform multiple autonomous and often unrelated functions without partitioning these functions into different protein domains of the polypeptide chain. Perreault *et al* (2014) focus on the evolving story of how dopamine GPCRs participate in heteromers to control complex behaviors. A heteromeric complex formed between the D1 and D2 receptors is marked by a unique signaling signature, providing a novel view of the physiology and behavior associated with dopamine systems. The authors speculate on the future for contemporary drug discovery strategies to incorporate receptor heteromers in the discovery process to create 'designer drugs' that target dopamine receptor heteromers.

Neural disorders (eg, psychiatric disorders and addiction, neurodegeneration, chronic pain, and traumatic brain injury) encompass numerous chronic health challenges and are a source of a profound degree of anguish. Medications are proven components in modern treatment protocols for many of these health adversities, but there is tremendous opportunity to advance novel neurotherapeutics. The reviews in this issue focus on biomolecules and networks that may underlie brain diseases states and open new avenues for molecular therapeutics. A resource in this light is the fifth volume of *Neuropsychopharmacology Reviews* ('Neurotherapeutics'), which provides a superb overview of prevention strategies, symptomatic treatments, and neuroprotective treatments in mental health and neurodegenerative disorders. There are no examples, however, of therapies that can yet reverse or halt progressive neural impairment permanently. Tissue regeneration strategies, such as cell transplantation and stimulation of self-repair mechanisms, provide hope for promoting recovery; however, clinical translation has been hampered by significant challenges. Tam *et al* (2014) provide an innovative biomaterials' approach to promote survival and integration of implanted cells and sustained delivery of biologics to CNS injury sites. Biomaterials can be used as cell or drug delivery vehicles and can provide physical support for damaged cells; as noted in Tam *et al* (2014), for example, water-swollen materials known as hydrogels exhibit mechanical properties similar to soft tissue that can serve as delivery vehicles for therapeutic molecules (eg, growth factors, proteins, and small molecules) to provide sustained and tunable drug release. Thus, Tam *et al* (2014) present a vision of the future development of

neurotherapeutics through a combined strategy of biomaterial, cell, and/or biomolecule in circumstances of degenerative or injury damage.

The imperative to uncover mechanisms and develop neurotherapeutics for specific neural diseases is matched by the need to extend biomolecular discovery to pinpoint biomarkers of neural status. A biomarker is any quantifiable biomolecule or process that is an indicator of a disease state or biological function. Although postmortem brain is a viable source for research investigations *ex vivo* (see McCullumsmith *et al*, 2014), accessing the status of brain function temporally *in vivo* is very challenging. Objective biomarkers accessible in a biofluid compartment (eg, blood, saliva, and cerebral spinal fluid) via functional imaging or other physiological measurements that accurately reflect pathophysiology and treatment response would serve to refine diagnostic and prognostic accuracy and reduce dependence on the patient's self-report. The final two reviews reflect the status of biomarker development in Alzheimer's disease and cocaine addiction, disorders that epitomize the challenges associated with the discovery of clinical biomarkers in neuropsychopharmacological disease. Blennow *et al* (2014) reviews biomarker availability and predictive utility for Alzheimer's disease, emphasizing the importance of effective biomarkers in clinical trials and verification of target engagement of new drug candidates in humans. Biomarker development for Alzheimer's disease has arguably progressed further compared with that for other neural diseases; however, this field is not without controversy and failed trials. The review by Bough *et al* (2014) encapsulates the state of biomarker discovery in addiction, using cocaine addiction as the example (see Gorini *et al* (2014), for discussion of biomarkers in alcoholism). Attention is drawn to cardiovascular physiology and neuroimaging measures as proximal opportunities to provide insight into addiction progression and treatment response. Peripheral biomolecules that inherently indicate susceptibility to addiction and/or the status of disease progression and recovery are lacking at present, but proteomics studies are uncovering adaptive changes in brains of animals and humans; it is possible that peripheral biomarkers could prove to be surrogate measures of neurobiological status, although it is too early to tell. Nevertheless, these papers provide a neurological and psychiatric example, respectively, of research directed to stratify patients with neural disorders with the promise to tailor treatment toward maximally precise defined outcomes. These results are encouraging for the entire field.

The previous articles provide a snapshot of our greatly enhanced understanding of brain function, plasticity, and circuitry that has arisen through novel technologies coupled with contemporary neuroscience; however, this information has not appreciably transformed treatment for brain disorders, and many hurdles hamper the trajectory toward optimized and personalized therapy for neural disorders. The topics of the final two papers provide perspectives for the future. Hyman (2014) argues that substantial opportunity exists to revitalize psychiatric therapeutics, while Colvis and Austin (2014) describe the role that the new National Center for Advancing Translational Sciences (NCATS) will have in generating innovative technologies and implementing diagnostics and therapeutics needed in a wide range of diseases.

The process of editing this issue has been a journey through the world of multiple disciplines and has provided an inspirational glimpse of the future. The following brief recognition of thanks to all of those who shepherded this issue from beginning to end seems minimal in the face of the efforts of many colleagues to see this project to fruition. Peter Kalivas and Gwenn Smith provided exemplary guidance and support throughout the process. John Neumaier is credited with curating an outstanding Hot Topics collection intended to stimulate thought in late-breaking scientific news in our field. The NPPR Managing Editor Natalie Marler went the distance to assure that all editorial details were in line, always with a great deal of expertise and a smile. Bill Carlezon served as our mentor and guide to editorial savvy. The Nature Publishing Group support team (Erin Dewalt, Vibert Gale, Katie Ris-Vicari, Elizabeth Yepez) was an invaluable contributor to the graphics and layout of the issue. We thank Dr Ekaterina Mostovenko and Norelle C Wildburger for contributing unpublished images for the front cover art. Most of all, we are extremely grateful to the authors who provided their words and perspectives, and the reviewers who shared the burden of evaluating these peer-reviewed manuscripts.

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