EDITORIAL

Molecular Genetic Advances in Neurological Disease: Special Review Issue

Diseases of the central nervous system remain among the most compelling maladies known to humankind. This is because neurological disorders are typically devastating to affected patients and their families, often robbing individuals of the qualities that we most strongly associate with being human, and because the vast majority of neurological and neurodegenerative disorders lack effective therapies. In the 1980s and 1990s, the advent of molecular genetics approaches to map and identify disease genes laid the foundation for a prodigious advance in our understanding of the pathogenic basis of numerous important neurological disorders. Some of this work focused on disorders that are strictly inherited, such as Huntington’s disease (HD), while other work took advantage of rare inherited forms of neurodegenerative diseases, such as Alzheimer’s disease (AD), Parkinson’s disease (PD), and amyotrophic lateral sclerosis (ALS), that occur sporadically and frequently in human populations. One fascinating aspect of this research has been the emergence of key themes that link even the rarest of these disorders with the most common, yielding a limited set of fundamental pathways and processes that appear to consistently be impinged upon in neuron dysfunction and neuronal loss. Given this paradigm, understanding why different neurons degenerate in distinct clinico-pathological entities has been an important question to address, with obvious importance for therapy development.

In this special review issue, we consider the state of basic and translational research on a broad range of neurological and neurodegenerative diseases, with reviews that span developments in genetics, molecular biology, cell biology, neurobiology, pharmacology, and regenerative medicine. This breadth of coverage reflects a key truism in our field, namely, that progress in the neurological and neurodegenerative disease field has required (and will continue to require) an interdisciplinary approach. Hence, we expect that this special review issue will offer a little something for everyone from a technical perspective, while providing in-depth coverage of some the key lines of investigation promoting research advances on the various diseases reviewed herein. Indeed, we both feel fortunate to be able to present the readers of Human Molecular Genetics with a line-up of investigators who are renowned in their fields and well recognized as leaders on the respective diseases upon which their reviews are based.

In the first piece from Christine van Broeckhoven and colleagues at the VIP and University of Antwerp in Belgium, we are provided with an overview of the status of AD research. We are reminded of the key genetic factors and pathways that have been unequivocally linked to AD pathogenesis, before we are presented a comprehensive summary of the genomics approaches that have most recently been taken to define genetic risk factors involved in predisposition to this disorder. A vision for what the future of AD research might hold serves as a useful guide on how our thinking is changing, as technical advances in genomics strategies will permit even more powerful ways to interrogate the genomes of AD patient populations.

As complement to AD genetics, we commissioned a second review on AD from Eliezer Masliah, of the University of California, San Diego, to address emerging views of pathogenesis from a molecular neuroscience perspective. In this review, which is co-authored by Dr Masliah and Dr Leslie Crews, molecular pathways believed to be responsible for the synaptic loss that produces the cognitive dysfunction in this disorder are outlined. Particular focus is placed upon a set of signaling pathways involving Fyn kinase, GSK-3-β kinase, and cyclin-dependent kinase-5 (CDK5), now believed to be important contributors to the synaptic dysfunction in AD. These authors also tackle the role of amyloid-β misfolding in AD, and discuss the importance of oligomerization in disease pathogenesis, presenting different explanations for how amyloid-β oligomers could produce toxicity.

In the first of two reviews on Parkinson’s disease (PD), Mark Cookson, of the National Institutes of Health, and Oliver Bandmann, of the University of Sheffield, provide a comprehensive overview of the different genes found to cause both recessive and dominant forms of this disorder. They begin by discussing the major genes responsible for recessive PD, and explain how their heretofore unrelated gene products may all actually be impinging upon the same pathways, and thus be related to one another. LRRK2 and α-synuclein are the major genes known to produce dominantly inherited PD, and thus deserve careful consideration, especially since α-synuclein is believed to be central to PD pathogenesis, linking familial PD with sporadic PD. After providing us with the current view of α-synuclein genetics and molecular pathology, we are introduced to LRRK2 and the extensive literature now available on its normal function and pathological role in PD. The review closes by stressing the importance of defining the various substrates for PD genes with kinase activity or ubiquitin ligase activity. This line of investigation remains among the hottest in the PD field, as validated substrates implicated in PD pathogenesis would be valuable targets for therapy development.

PD is of course one of the most common diseases of human-kind, and continues to dramatically increase in prevalence in the developed world, as our population ages. PD, of all the neurological diseases in this field, represents a disorder where the injection of genetic thought into the study of the disease clearly revolutionized the field and yielded a molecular pathway that linked historical neuropathology findings with pathogenic mechanisms. As we learn in this second
review of PD, a further understanding of the mechanistic basis of this disorder is being driven by advances in our understanding of genes whose products appear to be playing important roles in the regulation of mitochondrial quality control. This exciting and dynamic work is nicely chronicled by Charleen Chu, of the University of Pittsburgh, who provides an assessment of the key findings, and highlights the challenges that remain to address how PTEN-induced kinase 1 (PINK1) dysfunction leads to dopaminergic neuron loss in PD.

The maintenance of protein quality control is one of the major challenges in neurons, and proteotoxic stress is a prominent feature of all major neurodegenerative disorders. For this reason, much attention has been focused upon the processes that promote protein quality control and protein turnover, including especially the ubiquitin proteasome system (UPS) and the (macro)autophagy pathway. In our next review from Conrad Weihl of Washington University School of Medicine, we are introduced to a rare and fascinating disorder known as Inclusion Body Myopathy, Paget’s Disease of the Bone, and Frontotemporal Dementia (IBMPFD), an autosomal dominant disease that is caused by mutations in the gene for valosin-containing protein (VCP), also known as p97. Work on VCP/p97 has suggested that this protein is involved in the function of both the UPS and the autophagy pathway, making it a prime candidate for regulating the degradation fate of numerous proteins, including proteins now believed to be central to neurological diseases. For these reasons, the study of VCP/p97 mutations in IBMPFD may provide a powerful opportunity to delineate how protein quality control pathways operate in the CNS, underscoring why considerable effort is now being devoted to understanding this rather arcane disorder.

The next review switches the focus to amyotrophic lateral sclerosis (ALS), one of the most aggressive of the major adult-onset neurodegenerative disorders. Despite significant progress in the understanding of ALS pathogenesis, there is still no effective therapy, and patients with this disease typically die within only three to five years after onset of the first symptoms. The last few years have witnessed a series of entirely unexpected developments that have refocused the field upon a new paradigm for disease pathogenesis. This emerging view emphasizes the importance of altered RNA processing in motor neuron disease, and is insightfully and comprehensively presented by Don Cleveland and colleagues from the Ludwig Institute at the University of California, San Diego.

In the next two reviews, we shift our focus away from a specific disease processes to new opportunities made possible through technical advances. First, Shoji Tsuji, from the University of Tokyo brings the discussion back to gene discovery and genetic approaches, and informs us of new opportunities based on high-throughput sequencing technology. Dr Tsuji begins by reflecting on the significant scientific contributions that gene discoveries have made to our understanding of the molecular etiology of neurological disease, and he stresses the importance of continuing these efforts. He reviews contributions made through positional cloning efforts and then discusses disease-relevant alleles found by genome wide association studies (GWAS). In general GWAS studies, designed to find genes for common diseases based on the “common disease-common variant hypothesis” have yielded susceptibility genes accounting for only a small portion of the estimated heritability. Dr Tsuji goes on to make a strong case that rare variants with large effect sizes play a significant role in sporadic diseases and that next generation resequencing strategies will play a key role in identifying novel rare genes with large effects sizes for common disorders and that these new discoveries will continue to inform our molecular understanding of neurodegenerative disorders.

In the next review, we turn to Fred Gage and colleagues at the Salk Institute, so that we can take stock of the induced pluripotent stem cell (iPSC) field as it relates to the study of neurological disease. Dr Gage, whose laboratory has played a pivotal role in advancing this technology, reminds us of its potential utility and how it has been applied to model a variety of neurodevelopmental and neurodegenerative disorders. While there have been numerous successes that have buoyed the field, successful production of cellular phenotypes equating with the disease state, especially for neurodegenerative diseases, remains a crucial goal yet to be achieved. Dr Gage and colleagues also point out some likely useful applications of the iPSC approach in the realm of therapy development.

The next series of articles switch the focus to microsatellite expansion disorders. The first article in this series addresses an exciting topic that underscores the complexity of genetic pathology possible in the central nervous system. Maurice Swanson and colleagues, from the University of Florida, discuss bidirectional transcription and microsatellite expansion disorders. The initial discovery of these expansion mutations led to a flurry of investigations focused on protein loss, protein gain, or RNA gain of function mechanisms, depending on the position of the expansion mutation in the corresponding gene. These authors describe how these lines have been blurred in recent years with the realization that much of the genome and most of the expansion mutations are transcribed on both strands, and that antisense transcripts and non-coding transcripts can regulate gene expression on multiple levels. The authors review molecular evidence that toxic RNA and/or proteins, expressed from both strands, play roles for several of these disorders – spinocerebellar ataxia type 8, Fragile X tremor ataxia syndrome (FXTAS) and Huntington Disease Like 2, and then highlight a number of important future questions that will need to be addressed to understand both the normal function(s) of these transcripts and their potential contributions to disease.

In the next article, FXTAS is reviewed in greater detail. Paul Hagerman and Delores Garcia-Arocena, from the University of California, Davis, review the clinical features of this tremor-ataxia syndrome, a disorder found in older men carrying pre-mutation length CGG expansion alleles in the FMR1 gene. This transcription-dependent disorder is characterized by proteinaceous inclusions that accumulate in the brain and other tissues. The authors discuss a series of experiments done in model systems, which point to an RNA gain of function sequestration mechanism – similar to that found in myotonic dystrophy, but indirect models of RNA toxicity have also been proposed. The authors conclude by discussing an emerging view of FXTAS as the end-stage of a series of pathogenic processes that begins early in development.
Wansink and colleagues from Radboud University in The Netherlands continue the discussion on RNA gain-of-function with a review on myotonic dystrophy. Their article on therapeutic approaches to reverse RNA gain of function effects in this disorder is the first in a series of articles in this issue to focus on promising molecular therapies. The myotonic dystrophies are the best characterized examples of RNA-mediated expansion disorders with multiple lines of evidence supporting a model in which CUG or CCUG expansion transcripts sequester and dysregulate alternative splicing factors. The resulting dysregulation of hundreds of downstream genes is thought to underlie the multisystemic features of these disorders. These authors review a series of exciting recent papers that provide proof of concept data for reversing RNA gain of function effects by degrading the C/CUG expansion transcripts using antisense oligonucleotides, by preventing protein sequestration, or with CUG repeat hairpins using CAG-morpholino or small-molecule strategies.

Next, Carl Johnson, of the Hereditary Disease Foundation, and Beverly Davidson, from the University of Iowa, provide an update on efforts to develop treatments for Huntington’s disease. The authors review the molecular and clinical features of this devastating polyglutamine expansion disease and summarize three areas of ongoing effort to develop effective therapies for this disorder. First, they discuss recent progress made with antisense and siRNA strategies, and delineate future challenges of reducing mutant huntingtin expression gene without completely blocking expression of this essential protein. A second promising approach actively being pursued is to identify compounds that reduce levels of mutant huntingtin protein by enhancing its clearance/degradation. Finally, a third strategy is aimed at blocking mutant huntingtin-induced toxicity.

Helen Puccio and Stephane Schmucker from the Universite Louis Pasteur in Strasbourg France review recent developments in Friedreich’s ataxia, an autosomal recessive disorder caused by reduced expression of the mitochondrial protein frataxin. Frataxin deficiency leads to a loss of iron sulfur cluster (ISC) biosynthesis, mitochondrial iron overload, and oxidative stress. Most patients carry two GAA expansion alleles located in intron 1 of the frataxin gene. Several therapeutic strategies, designed to increase frataxin gene expression or reduce iron overload and oxidative stress, are being vigorously pursued, including the use of HDAC inhibitors which up-regulate frataxin expression.

Our final piece in this special issue is written by Christian Lorson and colleagues at the University of Missouri. These authors review molecular mechanisms and therapeutic approaches for spinal muscular atrophy (SMA), a devastating neurodegenerative disorder that is a leading cause of infant mortality. SMA is caused by loss of function of the survival motor neuron 1 (SMN1) gene. These authors provide an update on exciting pre-clinical therapeutic efforts, which have focused upon up-regulating a second nearly identical copy gene (SMN2) by shifting its alternative splicing pattern using therapeutic RNA and drug strategies. These strategies are likely to have a broad impact for genetic disease, because even rare genetic diseases can be corrected through this approach. Additionally, the possibility of replacing lost motor neurons by neural stem cells is discussed.

And so ends the special review issue on advances in the molecular genetics of neurological diseases. For an area of such breadth and depth, we recognize that a number of topics and subfields could not be covered, due to limitations of space, and we hope that our colleagues understand that these omissions were not intentional. Nonetheless, we hope that this collection of reviews will provide a comprehensive evaluation of many of the key issues and controversies driving research on neurological and neurodegenerative diseases, and will be as valuable to trainees entering the field, as it will be to investigators devoted to the study of one or more of these diseases. We indeed found it to be so, and look forward to many exciting developments in the next decade, awaiting especially the generation of effective therapies for these disorders, and the incorporation of these therapies into clinical practice.

**Albert La Spada**
Professor of Pediatrics and Cellular & Molecular Medicine
Division Head of Genetics, Department of Pediatrics & Rady Children’s Hospital – San Diego, Associate Director, Institute for Genomic Medicine, University of California, San Diego USA
E-mail: alaspada@ucsd.edu

**Laura P.W. Ranum**
Professor of Genetics, Cell Biology and Development Research Director, Paul and Sheila Wellstone Muscular Dystrophy Center Institute of Human Genetics, Institute For Translational Neuroscience, University of Minnesota Minneapolis USA
E-mail: ranum001@umn.edu