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Molecular medicine and neurodegenerative diseases

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Past advances in research and modern medicine have helped to produce cures for diseases that used to plague populations, and as a result, life expectancies have increased substantially throughout the years. For example, in East Asia, the average life expectancy has nearly doubled within the last sixty-four years (from 45 years old in 1950 to over 74 years old today). Such statistics often give promise and meaning to the medicinal opportunities offered through scientific research; however, the successes also present new challenges. Neurodegenerative diseases, often developed in the later stages of life, have become increasingly more prevalent, no doubt a direct result of increased longevity, as well as a serious medical and economical challenge

to today's society. For example, The World Health Organization projects that neurodegenerative diseases will surpass cancer to become the second leading cause of death by 2040. Therefore, the urgency to understand the fundamentals of neurodegenerative diseases as well as develop diagnostic and therapeutic agents is apparent.

In this themed issue of *Chemical Society Reviews* on molecular medicine and neurodegenerative diseases, several areas within the neurodegenerative field are explored, including mechanistic/structural studies of neurodegenerative processes, pathologically relevant biological pathways/factors, as well as the development of chemical tools, diagnostic/imaging agents, and potential therapeutic agents. By no means is this themed issue comprehensive on neurodegenerative diseases, but researchers new to the field, as well as others actively engaged in this field, will find broad insights into the multifactorial components of Alzheimer's disease (AD). Our hope is that the highlighted works from prominent scientists would stimulate scientists to target their current and future research toward answering some of the critical questions within the field that will be essential to uncovering the pathology of the disease so that possible treatments or therapeutics can be developed.

Neurodegenerative diseases are inherently complex and the disease etiology is not completely understood. Hallmarks of diseases have been identified, such

as aggregated misfolded proteins (*e.g.*, amyloid-β, Aβ; tau) in AD, yet the roles of these pathological features in disease onset and progression are still unclear. To develop an effective therapeutic, the fundamentals of the disease, such as the correlation of misfolded peptides to neuropathogenesis, need to first be fully revealed.

In the review of "Disordered amyloidogenic peptides may insert into the membrane and assemble into common cyclic structural motifs", Jang, Arce, Ramachandran, Kaga, Lal, and Nussinov (DOI: 10.1039/c3cs60459d) provide an overview of the interaction of Aβ with cell membranes contributing to cellular dysfunction. From this review, the readers will gain insights into aspects of the disease, such as a proposed mechanism of Aβ toxicity, through various conformational structures, particularly oligomers, of the Aβ peptide that could form amyloid channels within the membrane, ultimately leading to the loss of ionic homeostasis within the cell that directs cell death.

Moreover, Kotler, Walsh, Brender, and Ramamoorthy (DOI: 10.1039/c3cs60431d) offer an additional view on the interrelationship between Aβ peptides and cellular membranes as a potential underlying cause of toxicity. More interestingly, the authors present further perspective on the influence of gangliosides, molecules composed of a glycosphingolipid with one or more sialic

acids conjugated with the sugar chain, on Aβ aggregation pathway and Aβ-promoted membrane disruption.

Other components, such as cholesterol, are important to consider when evaluating the interaction between Aβ and cell membranes. Lee, Korshavn, Kochi, Derrick, and Lim (DOI: 10.1039/c4cs00005f), in their tutorial review, briefly describe the function of cholesterol in normal biological settings as well as its possible contribution to AD etiology. Furthermore, they also discuss an additional pathological factor to AD (*i.e.*, metals) with its possible interconnection to cholesterol in AD pathogenesis. Barnham and Bush (DOI: 10.1039/c4cs00138a) illustrate how the dyshomeostasis of essential biometals is associated with age-related neurodegenerative disorders (*i.e.*, AD, Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS)). This review also provides insight into therapeutic strategies that focus on targeting metal homeostasis.

Examination of the peptide itself and its processing pathways can prove to be

as important as investigating the relationship between amyloidogenic peptides and cell membranes. Posttranslational modification of both amyloid precursor protein (APP; forms Aβ after proteolytic cleavage by β-secretase (BACE1) and γ-secretase) and tau by addition of *O*-linked *N*-acetylglucosamine (*O*-GlcNAc) is illustrated in the review article by Yuzwa and Vocadlo (DOI: 10.1039/c4cs00038b). The authors summarize the biochemical role of *O*-GlcNAc and its link to tau/APP in AD. Potential protective effects have been demonstrated upon increased *O*-GlcNAc levels in the brain of AD mouse models, suggesting a new avenue of investigations to better understand the pathogenesis of this disorder.

As the mechanisms of the underlying factors that lead to neurodegeneration become more transparent, advancements in the construction of therapeutic agents must also be made in parallel to ultimately cure the diseases. Current treatments targeting acetylcholinesterase and *N*-methyl-D-aspartate (NMDA) receptor only alleviate symptoms, thus suggesting the need for

additional drug targets and drug discovery approaches. In "BACE1 (β-secretase) inhibitors for the treatment of Alzheimer's disease," Ghosh and Osswald (DOI: 10.1039/c3cs60460h) outline the evolution of the various chemotypes of BACE1 inhibitors, which have emerged in hopes of targeting BACE1 as an AD treatment due to BACE1's direct connection with Aβ generation. Early work on developing aspartyl protease transition state analog peptidomimetic inhibitors is covered as well as the more recent design of nonpeptide structural classes with heterocyclic scaffolds. In both cases, the review highlights examples where structure-based drug design plays a key role in inhibitor design. Several companies have advanced BACE inhibitors into clinical trials and the results are eagerly awaited.

In addition to the presence of aggregated misfolded proteins, an oxidative stress environment is often observed in AD-afflicted brains. As reviewed in "Development of nitric oxide synthase inhibitors for neurodegeneration and neuropathic pain" (DOI: 10.1039/c3cs60467e),
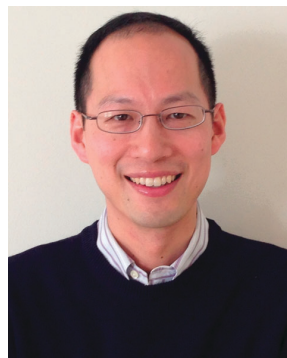
Christopher J. Chang

Chris Chang is the Class of 1942 Chair Professor in the Departments of Chemistry and Molecular and Cell Biology at UC Berkeley, as well as an Investigator with the Howard Hughes Medical Institute and Faculty Scientist in the Chemical Sciences Division of Lawrence Berkeley National Laboratory. Chris received his BS and MS degrees from Caltech in 1997, working with Prof. Harry Gray on electronic spectroscopy of metal–nitrido and metal–oxo complexes. After spending a year as a Fulbright scholar in Strasbourg, France with Dr Jean-Pierre Sauvage on molecular knots and molecular machines, Chris received his PhD from MIT in 2002 under the supervision of Prof. Dan Nocera, where his graduate work focused on fuel cell and oxygen catalysis. He stayed at MIT as a postdoctoral fellow with Prof. Steve Lippard, working on zinc biology and then began his independent career at UC Berkeley in Fall 2004. Research in the Chang lab is focused on chemical biology and inorganic chemistry, with particular interests in molecular imaging and catalysis applied to neuroscience, infectious diseases, and sustainable energy.

Benjamin F. Cravatt

Ben Cravatt is a Professor in the Skaggs Institute for Chemical Biology and Chair of the Department of Chemical Physiology at The Scripps Research Institute. He obtained his undergraduate education at Stanford University, receiving a BS in the Biological Sciences and a BA in History. He then trained with Profs Dale Boger and Richard Lerner and received a PhD in Macromolecular and Cellular Structure and Chemistry from The Scripps Research Institute (TSRI) in 1996. He joined the faculty at TSRI in 1997 as a member of the Skaggs Institute for Chemical Biology and the Department of Chemical Physiology. His research group is interested in developing and applying new technologies to elucidate the roles that enzymes play in physiological and pathological processes, especially as pertains to the nervous system and cancer.

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Mukherjee, Cinelli, Kang, and Silverman picture the role of nitric oxide (NO) in neuronal function as well as in neurodegeneration. Evidence links the dysregulation of nitrergic signaling, the overexpression of neuronal NO synthase (nNOS), and oxidative stress with neurodegeneration, implicating nNOS as a viable therapeutic target. The authors further discuss unique approaches for fashioning small molecules as nNOS inhibitors.

To date most researchers have taken a target-based approach in efforts to identify new therapies for neurodegenerative diseases. Pieper, McKnight, and Ready (DOI: 10.1039/c3cs60448a) provide a compelling example highlighting the potential power of phenotypic screening for neurodegenerative diseases. They present the discovery of a series of neuroprotective small molecules from an *in vivo* screen of hippocampal neurogenesis by monitoring the incorporation of bromodeoxyuridine (BrdU) into new synthesized DNA to label newly formed neurons within the dentate gyrus. This allowed them to find compounds that increased either proliferation or survival of hippocampal neural precursor cells. The P7C3 class of compounds (an aminopropyl carbazole, designated P7C3) was identified from this screen and the druglike properties were optimized through a series of medicinal chemistry efforts. These optimized compounds showed neuroprotective activity in animal models of PD, ALS, traumatic brain injury (TBI), retinal degeneration, and age-related cognitive decline, and efforts are underway to more fully understand the mechanism of action.

Manipulation of the endocannabinoid system could provide an alternative means to impact various neurodegenerative diseases. As reviewed by Konz and Nomura (DOI: 10.1039/c4cs00047a), the inhibition of monoacylglycerol lipase (MAGL), a 2-AG-degrading enzyme, has shown anti-inflammatory and neuroprotective effects in AD/PD mouse models. Furthermore, anti-amyloidogenic properties of MAGL inhibitors have been indicated, which implies another possible arsenal to combat neurodegenerative diseases.

In order to diagnose the status and progression of neurodegenerative disorders with and without treatment, single photon computed tomography (SPECT) or positron emission computed tomography (PET) has been the forerunner for molecular imaging. In ''PET/SPECT imaging agents for neurodegenerative diseases,'' Zhu, Ploessl, and Kung (DOI: 10.1039/c3cs60430f) describe a field of radiopharmaceuticals, examining the different isotopes for PET/SPECT imaging; focusing on imaging agents currently employed for AD and PD, as well as the future prospects for expanding imaging targets for these diseases. Hayne, Lim,

Douglas S. Johnson

Doug Johnson obtained his BS in chemistry from the University of Minnesota in 1991 where he did research in the laboratory of Prof. Thomas R. Hoye. He continued his studies at the Scripps Research Institute in La Jolla, CA where he obtained his PhD in organic chemistry under the guidance of Prof. Dale L. Boger in 1996. He then served as an NIH postdoctoral fellow in the laboratory of Prof. David A. Evans at Harvard University from 1997 to 1999. He joined Pfizer Worldwide Research and Development as a medicinal chemist in 1999 and is currently an Associate Research Fellow in the Neuroscience Medicinal Chemistry group located in Cambridge, MA. During his tenure at Pfizer, he has played significant roles on teams that have advanced 3 compounds into the clinic – PD 0332991, a CDK4/6 inhibitor in phase III clinical trials for breast cancer; PF-00217830, a D2 partial agonist, which advanced to phase II for schizophrenia; and PF-04457845, a FAAH inhibitor in clinical trials for the potential treatment of CNS disorders. In addition, his group is interested in applying chemical biology methods to enable drug discovery projects. Most recently, his group has used clickable photoaffinity probes to characterize the targets and the mechanism of action of γ-secretase inhibitors (GSIs) and modulators (GSMs) relevant to Alzheimer's disease.
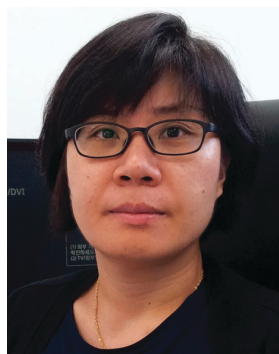
Mi Hee Lim

Mi Hee Lim is an Associate Professor of Chemistry at the Ulsan National Institute of Science and Technology (UNIST), Ulsan, Korea. She received an MSc under Prof. Wonwoo Nam at Ewha Womans University, Seoul, Korea, in 2001 and a PhD from MIT, USA in 2006 under the supervision of Prof. Stephen J. Lippard. After her PhD, she pursued her postdoctoral research as a TRDRP postdoctoral fellow in the laboratory of Prof. Jacqueline K. Barton at Caltech, USA. She was an Assistant Professor of Chemistry and Research Assistant Professor in the Life Sciences Institute at the University of Michigan, Ann Arbor, USA from 2008 to 2013 and moved to UNIST in the fall of 2013. Her research interests are in elucidating the roles of metals, proteins, and reactive oxygen species in human neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases.

and Donnelly (DOI: 10.1039/c4cs00026a) also examine radiopharmaceuticals, but in a slightly different manner. The authors present diagnostic imaging agents, composed of radioactive metal-based complexes of copper and technetium, to detect amyloid burden in the brain, as well as luminescent metal complexes for monitoring amyloid formation. They further discuss the use of metal complexes for inhibiting Aβ aggregation formation and toxicity. Based on this review, the potential development of metal complexes as theranostic (diagnostic and therapeutic) agents can be expected.

We would like to take this opportunity to thank all the authors who contributed to this issue.