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Animal models in autism research: The legacy of Paul H. Patterson

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More than 70 years have passed since the publication by Leo Kanner of his landmark paper describing the clinical profile of neurobehavioral abnormalities in children which later became the basis for the recognition of autism spectrum disorder (ASD) (Kanner, 1943). Although the clinical features and diagnostic criteria for autism have been subject of extensive discussion and controversy, we have now a better understanding of the spectrum of clinical, neurological and behavioral abnormalities associated with ASD. Progress in clinical evaluation has improved recognition and diagnosis, but has also unveiled the magnitude of the public health problem posed by ASD. Current estimates by the CDC are that 1 in 68 (14.6 per 1,000) school-aged children in the USA are diagnosed with ASD (Christensen et al., 2016). The challenge of this public health threat has accelerated an expanded search for genetic and environmental factors which may influence the high prevalence of ASD, and has

highlighted the need for research into the biological bases of autism. This effort has begun to reveal genetic and environmental influences which may interplay to determine the spectrum of neurobehavioral abnormalities that characterize ASD. Technological advances in molecular genetics have facilitated the identification of genes and polymorphisms associated with ASD, and epidemiological studies have identified potential environmental factors which may interact with genetic influences to underlie brain abnormalities that characterize ASD. Nonetheless, identification of genetic and environmental components represents only a first step. One of the major hurdles in autism research is establishing animal models of ASD to facilitate understanding of the neurobiological bases of the disorder, to rigorously test hypotheses regarding genetic and envorionmental interplay, and to assess therapeutic interventions aimed at modifying the dysfunctional neurobiological and neurobehavioral trajectories which characterize ASD. Complex neurobehavioral disorders, such as ASD, pose major challenges for modeling in animals. First, the complexity of human behavior and brain circuits strain the possibility of representing pathways of high neurobehavioral function in experimental animal systems. Second, variation in genetic and epigenetic backgrounds as well as the environmental mileu are difficult to capture and reproduce in experimental models. Despite these challenges, it is also clear that some environmental and genetic factors that influence neurobiological and behavioral disturbances associated with ASD can be dissected and analyzed in experimental settings and animal models. Further, experimental models, however imperfect, have often offered the only means to gain valuable mechanistic insights. Rapidly advancing knowledge about genes and pathways associated with ASD, as well as technological gains in genome engineering, can be expected to increase opportunities to study the etiology, pathogenesis, and potential treatments for ASD using molecularly-engineered animal models.

This special section of *Experimental Neurology*, focused on animal models of ASD, pays tribute and honors the groundbreaking contribution of Paul H. Patterson (1943–2014), a neuroscientist and Professor of Biological Sciences at California Institute of Technology. Paul was one of the first neurobiologists who took on the challenge of modeling the interplay of genetic and environmental risk factors in animal models for neurological disorders including ASD and schizophrenia. Paul's seminal work on the role of maternal infection and the identification of maternal-fetal immune system interactions as determinants of neurobehavioral trajectories opened up new routes for modeling complex human neurobehavioral disorders in animal models. His influential publications about maternal influenza virus infection (Shi et al., 2003), the role of IL-6 as mediator of changes in gene expression and behavior (Smith et al., 2007), and more recently the characterization of immunological disturbances in offspring of animals exposed to maternal infection (Hsiao et al., 2012) exemplify Paul's significant contributions and provided the strongest evidence supporting the role of environmental factors in the development of behavioral symptoms associated with ASD and schizophrenia. These studies provided a framework for modeling how the immune system can influence the maternal-fetal environment to produce neurobiological disturbances. Paul shared his bright scientific spirit with an enthusiasm for establishing collaborations. His research endeavors spread well outside the sphere of Caltech and involved many scientists in the USA and around the world.

The work presented in this special section is intended to represent this collaborative spirit and to exalt the innovative approaches that Paul introduced at the beginning of the 21th century to achieve a better understanding of the neurobiological basis of ASD. Current research in animal models to understand ASD now extends from C. elegans to zebrafish, from mouse models to non-human primates, from genes and environmental factors to cellular and immune mechanisms, to converge in a better picture of the neurobiology of ASD. The authors and research groups collected in this special section are leaders and pioneers of the efforts to understand ASD from the perspective of animal models.

Schmeisser and Parker address in their review the use of the non-parasitic nematode *Caenorhabditis elegans* and the opportunities it presents to examine the role of genes associated with synaptic function and their implications in the biology of ASD. The potential of the *C. elegans* model for examining critical questions in related with ASD are well described particularly in a model which appears to be simplistic but benefits from well understood genetics as well as neuroanatomical organization and connectivity.

The article by Meshalkina, Kaluef and colleagues provides a comprehensive review of the value of zebrafish (*Danio rerio*), a highly social and genetically well-characterized organism, as a promising model for studying complex brain disorders. The zebrafish model may have the versatility for accomplishing not only dissection of molecular pathways associated with synaptogenesis and brain connectivity but also behavioral, toxicological and therapeutic investigations and interventions. The authors describe features of the zebrafish model and their application to the evaluation of behavior, pharmacological intervention and genetic engineering to address the neurobiology of ASD.

The paper by Nicolini and Fahnestock describes the Valproic acid (VPA) prenatal exposure model as a valuable tool to investigate environmental and epigenetic influences in the development of neurobehavioral abnormalities which resemble features seen in ASD, and the possibility for further use of this model for investigating gene-environment interactions. The authors further discuss the possibility of using the VPA model for exploring potential interventions and therapeutics for ASD.

Wong and Hoeffer provide a comprehensive view of the function of interleukin 17A (IL-17A) and its role in the maternal infection model. Evidence linking T helper 17 (Th17) lymphocytes and the effector cytokine IL-17A to the development of MIA-associated ASD is explained. The authors describe the role of Th17 cells and Il-17A in processes of cortical development and mechanisms through which this cytokine pathway might influence core ASD-related cognitive and behavioral deficits in animal models of maternal inflammation.

Bilbo and colleagues provide an instructive review of maternal immune activation (MIA) in ASD. The interplay of environmental factors and inflammatory interactions with the developing brain to influence neurobehavioral correlates and risk of ASD is presented. The function of microglia and immune signaling pathways, such as Toll-like receptors, in the context of cortical development and synaptic modeling is discussed to facilitate an understanding of their association with disturbances that in the maternal models which produce ASD-like behavior.

The review by Bauman and Schumann discusses current research focused on the use of non-human primates as sophisticated animal models of ASD, with particular attention to the unique features of the models which provide the closest experimental paralells to human brain organization and behavior. The paper describes the modeling of the maternal infection in this non-human primate and summarizes potential treatment options which may be tested in the model.

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