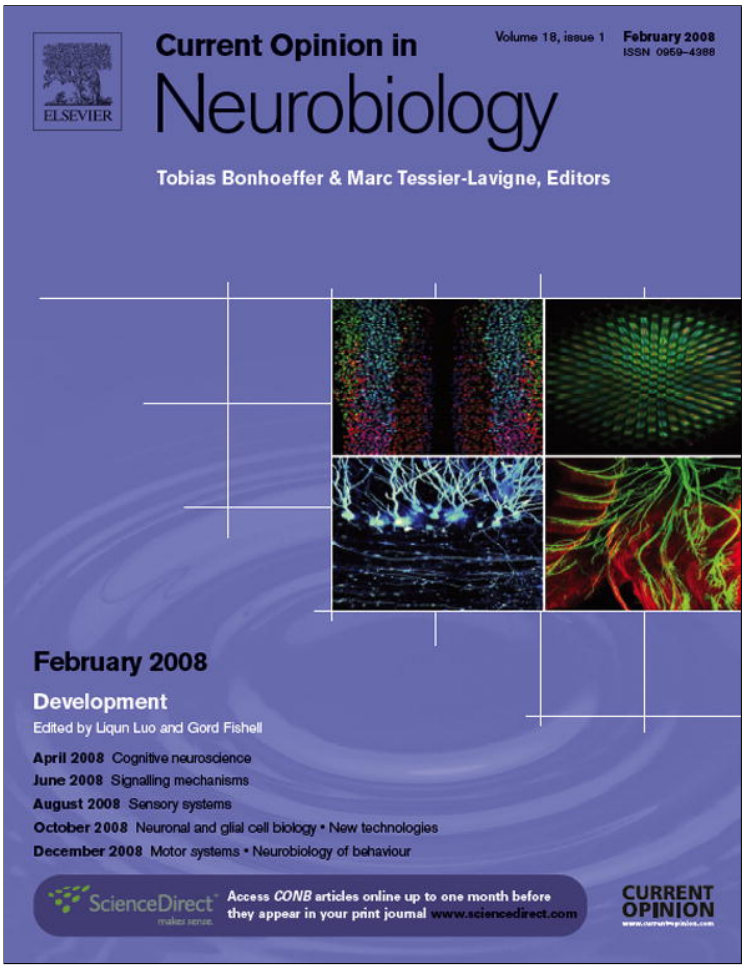

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Editorial overview

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Liqun Luo is a Professor of Biology at Stanford University, and an investigator of the Howard Hughes Medical Institute. His lab is developing and utilizing molecular genetic tools in fruit flies and mice to study the organization and assembly of neural circuits. One major focus in recent years has been to investigate the mechanisms by which wiring specificity is achieved during the assembly of the olfactory circuit in the fly brain.

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Gord Fishell is a Professor of Cell Biology at NYU School of Medicine and the coordinator of the Smilow Neuroscience Program. His laboratory is interested in using molecular genetic approaches to study how cortical interneuron diversity in mammals is generated and how specific subtypes of these neurons functionally integrate into the cerebral cortex during development. Present work in the laboratory is focused on examining how laminar and areal position within the cerebral cortex influences the connectivity of particular cortical interneuron subtypes.

How a functioning nervous system, capable of sensing, interpreting, and reacting to the world, derives from a single cell during development remains one of the most fascinating mysteries of modern biology. The solution involves an understanding of both general processes common to all developmental biology, such as tissue patterning, cell-fate specification, cell migration, and polarity, as well as events that are unique to the nervous system, including axon pathfinding, synaptic specificity between neurons, and the assembly of complex neural circuits. Both general and nervous-system-specific events must contend with the enormous diversity of the cell types in the nervous system, and the considerable logistics required for having the right number of cells in the right place for the assembly of neuronal circuitry. This annual issue on development brings another update on our collective ongoing efforts to tackle these mysteries.

We start this journey with the topics of neurogenesis and asymmetric cell division. Neural progenitors have the enormous task of generating large numbers of neurons with distinct properties and connection patterns, as well as their accompanying cohort of astrocytes and oligodendrocytes. The asymmetric segregation of fate determinants during neural progenitor cell divisions has been utilized widely as a mechanism to accomplish this goal. Zhong and Chia review the latest insights into the mechanisms of achieving asymmetric neural progenitor cell division, including the establishment and maintenance of cell polarity, mitotic spindle orientation, and cell-fate determinant localization. These mechanisms are highly conserved from flies to mammals, and set the stage for later developmental events such as fate diversification (Leone et al.; Dalla Torre di Sanguinetto et al.) and neuronal polarity (Barnes et al.).

Having examined the means by which discrete neural lineages produce diverse cell types, we turn our attention to the question of regional patterning and the way disease states inform us as to the underlying mechanisms through which neural structures are patterned. In their contribution, Millen and Gleeson provide us with a survey of the molecular and cellular events that give rise to the near crystalline cellular structure of the cerebellum. They then discuss how neurological disorders in humans that often result in widespread abnormalities impact the development of this structure.

Bringing together the examination of cell type and structure, Johnson and Desplan examine how in biology God does indeed play dice. They explore, among other stochastic events, how weighted probabilistic ratios determine a neuron's ability to detect light of different wavelengths or its sensitivity to a particular odorant from a repertoire numbering in the thousands. They discuss how these events utilize a developmentally encoded form of game theory to produce reliable outcomes. Why has evolution opted to take such

chances when the availability of more deterministic strategies could presumably provide more predictable results? They speculate that the vagaries of nature might prevent a more staid mechanism. Indeed, through playing the odds, biological organisms might ultimately eke out a competitive advantage.

Is a similar logic used to make more complex neuronal structures? In the cerebral cortex of mammals, McConnell and colleagues demonstrate that large numbers of neurons are produced in precise ratios through a transcriptional balancing act. Although work from numerous groups, most notably the McConnell laboratory, has revealed the developmental logic by which the neurons occupying different cortical layers are specified, the molecular mechanism underlying this process has until recently remained elusive. Since the pioneering work of Richard Sidman in the early 1960s, we have known that birthdate predicts the sequential inside–out production of cortical layers. In a spate of recent papers, the molecular determinants of corticofugal versus corticocortical projection neurons have at last begun to be revealed. One of the surprises emerging from this work is that negative regulation of transcription is turning out to be as crucial to this process as transcriptional activators. These findings provide a nice parallel to mechanisms that the Jessell laboratory and its progeny have shown to function in the spinal cord.

Two Jessell F1s, Jeremy Dasen and Sylvia Arber, as well as an F2 progeny, Dalla Torre di Sanguinetto, discuss in the next chapter of this series recent progress in our understanding of motor neuron specification. The motor neurons are vetted with the formidable task of providing the driving force for the entire swath of muscle groups in the body. The mutually repressive actions of class I and class II transcription factors (those being respectively repressed and induced by Sonic Hedgehog signaling) are well recognized to give rise to the progenitor domains that will produce the cardinal neuronal subtypes, including the MN progenitor domain. How does this miniscule subdivision produce the elaborate array of motor neuron columns and pools that are needed? A key to this process turns out to be the HOX genes. This review discusses the compelling finding that HOX genes are central to the formation of motor neuron subtypes by genetically interacting with other transcription factors. These include ETS and Runx genes, as well as homeobox genes such at Nkx6.1, Lim1, and Isl1 that are not HOX family members.

Once a newborn neuron has attained a particular fate, one of its first tasks is to generate two distinct kinds of neuronal processes: dendrites to receive information and axons to send information. This problem has been studied traditionally *in vitro*, such as dissociated hippocampal neurons in culture. Barnes, Solecki, and Polleux review recent studies that have identified key components, such as the LKB1 and SAD kinases, that function *in vivo* to regulate neuronal polarity. They also discuss the intriguing developmental, cell biological, and molecular connections between axon-dendrite polarity and polarity in migrating neurons or even neural progenitors (Zhong and Chia).

The next series of articles follow the journey of growth cones as they pioneer axonal pathfinding. Since the days of Ramon Y Cajal, we know that growth cones, which form at the distal tip of the axon and possess extensive filopodia and lamellipodia, have a special place in neuronal guidance. Drees and Gertler focus on a class of proteins called Ena/VASP, which are located at the growing tip of filopodia and lamellipodia. They help translating environmental signals through their regulation of cytoskeletal dynamics, and by ensuring the proper extension and turning of growth cones following preexisting axonal fasicules. In addition, these proteins, at least for a large number of cortical neurons, also appear essential for the formation of axons in the first place.

In order to help axons navigate complex environments, growth cones not only utilize proteins transported from the cell body, but also synthesize proteins locally from mRNAs resident in axons. Lin and Holt review recent findings demonstrating local axonal translation in a variety of systems, and discuss their regulation and potential functions. On the basis of the identity and activity of locally translated proteins, a 'differential translation' model is posited that suggests the asymmetric synthesis of 'attractive' or 'repulsive' proteins within the growth cone may help axons turn in response to extracellular cues.

After reaching their target, the next decision a developing axon makes is where and with whom to make synaptic connections. Margeta, Shen, and Grill review recent advances achieved through the study of the genetic model organism *C. elegans*, in which all the 7000 or so synapses between the 302 neurons in this organism can be scrutinized due to their previous description using serial section electron microscopy. Genetic analyses have identified a number of key molecules that specify where to make synapses, and how presynaptic apparatus is subsequently assembled. Remarkably, many of the molecules used to specify synapse formation are those used in axon pathfinding and even earlier during embryonic patterning.

The balance between excitation and inhibition is crucial to the proper function of neural networks. How the appropriate number of synapses are formed during development is a tightly regulated process that recent work has shown depends on both the neurotransmitter GABA, and the lock and key interactions between neuroligins

and neurexins. Huang and Scheiffele review the evidence in support of each of these mechanisms individually and speculate that the role of GABA signaling in mediating synapse formation may be partly due to postsynaptic interactions between GABAa receptors and neuroligins.

When group of neurons work together, as they do to accomplish sensory representations, they often exhibit interesting properties. Dendritic branches of individual neurons avoid each other so dendritic trees can maximally sample the sensory field (self-avoidance); while dendritic branches of neighboring neurons of the same type are also mutually repelled, such that the entire sensory field is represented by each type of neuron once and only once (tiling). Millard and Zipursky review recent evidence that different Dscams in insects, a family of Ig-superfamily cell surface recognition molecules with many alternatively spliced isoforms, play an essential role in intraneuronal self-avoidance as well as interneuronal tiling. Remarkably, mammalian Dscam may play analogous roles.

Early chapters discussed the evidence that the determination of neuronal character is clearly and strongly influenced by the expression of transcription factors but what of the specification of functional network properties? The neocortex of mammals provides an ideal context to explore this issue. Despite its uniform six-layer structure, it is functionally organized into 'areal' territories that subserve the different sensory modalities, including vision, hearing, and somatosensation, as well as higher motor function. While traditionally the specification of areal identity was thought to be controlled by afferent input, recent work, including significant contributions from the O'Leary laboratory, have demonstrated that the functional subdivisions of the cortex are intrinsically specified. O'Leary in his review describes recent work demonstrating the means by which a few key transcription factors, such as Emx2, Coup-TFII, and Sp8 bestow specific areal character within the distinct subdivisions of the neocortex.

In addition to genetic specification, the wiring pattern of the brain, especially those of higher vertebrates, can be profoundly influenced by experience. Nowhere has this been documented better than the ocular dominance of primary visual cortex; starting from the classic monocular deprivation experiments of Hubel and Wiesel. Morishita and Hensch provide a systematic comparison of ocular dominance plasticity during critical period versus in adults, from rodents to higher mammals. Recent investigations into the underlying cellular and molecular mechanisms, such as the involvement of excitation–inhibition balance, cell–cell signaling, and chromatin remodeling, could have important therapeutic implications in treating neurological and psychiatric diseases that result from defects in critical period plasticity.

Making a full circle, we return to neurogenesis in the last article. Traditionally, neurogenesis in the mammalian CNS was seen as solely a developmental phenomenon. The pioneering work of Nottenbolm, Alvarez-Buyalla, as well as Altman and Bayer has changed our view of this. It is now well established that in mammals neurogenesis persists in specialized niches in the adult brain. In the review by Song and colleagues, progress regarding the molecular underpinnings of the neurogenic niche is discussed with consideration to the extrinsic and intrinsic influences that shape adult neurogenesis. In addition, direct comparison of how adult neurogenesis differs from that seen in the embryo is explored. The authors leave us with the intriguing question as to what aspects of postnatal brain function are influenced by the integration of new neurons. Is adult neurogenesis a transitional phenomenon in the hippocampus and olfactory bulb during the so-called critical periods, or does it contribute to the function of these regions through adulthood? Whatever the answer, this review makes it clear that further surprises in this area will be forthcoming.