Introduction: stem cells and brain repair

This year’s Nobel Prize in Physiology or Medicine is given for discoveries that have enabled the development of organ and cell transplantation into a method for the treatment of human disease.

(Nobel Foundation 1990)

The current hoopla around stem cells can lead the casual observer to incorrectly conclude that regenerative medicine and stem cell science are emerging disciplines. Regenerative medicine is not new. Joseph Murray and Donnall Thomas received the 1990 Nobel Prize in Physiology or Medicine for their respective contributions to the first successful donor kidney and bone marrow transplants undertaken in 1954 and 1956—see above citation. Cell and organ transplantation are established treatments for a wide range of diseases. The current unrivalled spotlight on stem cells in general and embryonic stem cells in particular belie five decades of research in what was for many years considered a Cinderella area (Sotter 2006).

Regenerative neurology or brain repair also has a pedigree, indeed the first successful cell transplants (for Parkinson’s disease), the culmination of almost 20 years of experimental research, was reported in 1990 (Lindvall et al. 1990). So why the current excitement? Does this represent a passing fad or something more enduring? A series of related and unrelated findings explain why brain repair has captured the imagination: recognition of adult mammalian neurogenesis, availability of methods to isolate and propagate embryonic and adult neural stem cells, an ageing population and attendant increased societal burden of incurable neurodegenerative diseases. This concatenation of events catalysed by the recent widespread availability of human embryonic stem cell lines suggests that brain repair is indeed a realistic prospect and makes a theme issue on stem cells and neural repair timely and important.

Is repair of the damaged central nervous system (CNS) any different to repair of other organs? Clearly, there are fundamental differences, perhaps illustrated most simply by the observation that the ‘one size fits all’ approach—irrespective of aetiology of organ failure—adopted for visceral and haematopoietic replacement is inappropriate for neural repair. This highlights the need to design bespoke therapies tailored to the specific pathology of the target neurological disease. In addition, recovery of neural function, the goal of any therapy, does not necessarily follow macroscopic restoration of structure. The unprecedented challenge is to reconnect the circuitry of the damaged brain.

This issue attempts to emphasize and bridge the interdependency of developmental stem cell biology (inter-species) and clinical application. Although repair need not necessarily recapitulate development, insights rooted in an understanding of developmental principles and processes are central to the development of novel neural repair strategies. Consequently, this issue publishes accounts of epigenetic regulation of neurodevelopment plasticity, neural patterning and regional specification from flies to vertebrates. Such knowledge will inform on methods to direct and manipulate immature precursor/stem cell population(s) (endogenous or exogenous), as espoused in a series of papers on adult vertebrate neurogenesis and adult plasticity. The final three papers focus on major neurological syndromes (inflammation, neurodegeneration and tumours), and discuss how the study of disease can inform on stem cell biology. They conclude that targeted therapies manipulating endogenous stem cell behaviour are likely to emerge as the most rational treatment.

Magnus et al. (2007) open the issue with a cautionary polemic challenging conventional stem cell myths. Language matters. A strong case is made for precision when describing putative ‘stem cell’ properties of a given cell or population that reaches beyond semantics. Several examples are offered of the ‘casualization’ of language including a critique of ‘embryonic stem (ES)-like’ cells as a lazy inaccurate description of cells that do not contribute, inter alia, to the germ line and are better described as adult multipotent-like. A recurring theme is the need for care when drawing upon assumptions borrowed from the haematopoietic system. Disregarding inherent differences between organs where ongoing lifelong replacement is the norm with the constrained ability to regenerate around defined niches as in the neural system will, it is argued, lead inevitably to false promises.

The idea that stem cells have developmentally restricted competence to environmental signals is a theme that is developed by Allen (2007). Allen explores the role of intrinsic and extrinsic mechanisms in determining cell fate and adopts a developmental perspective on understanding how stem cells can be best exploited for therapeutic gain. The attachment of a ‘date and post-code’ identity to progenitor cells is reviewed. Fundamental to regional and temporal identity of progenitors is epigenetics, illustrated through an overview of neurogenesis and the temporal switch to gliogenesis. A conclusion of this analysis is that in vitro-derived neural precursors (NPCs) are a mixed bag with, for example, ES-derived NPCs (unlike foetal or adult NPCs) retaining a competence to developmental signals that allow controlled and
predictable cell subtype generation, an important asset for neural repair. Taking the argument full circle, Allen argues that improved understanding of epigenetic regulation of the hierarchical control of cell fate determination is ultimately likely to prove the most logical method to allow reprogramming of neural cells.

Additional model systems can shed light on generic principles of neural development, and the *Drosophila* neuroblast(s) has provided many insights into the molecular mechanisms underlying self-renewal and the generation of cellular diversity. Egger et al. (2007) showcase the utility of the ‘modular-Cartesian’ structure of the *Drosophila* CNS to study and follow the neuroblast through the developmental stages of induction, maintenance, temporal specification and post-embryonic reactivation. Relevance of the system to mammalian neurogenesis is evident at all stages including conservation of common signalling (Notch) and transcription factors (Sox) through to themes such as signal gradients, temporal loss of competence and a larval niche defined by glial cells reminiscent of the adult mammalian niche (see Riquelme et al. 2007).

The next two papers take a more parochial view of specification focusing on ventral spinal cord neurogenesis and gliogenesis. Both papers discuss in detail the influence of morphogens (extrinsic) on cellular (intrinsic) transcriptional circuits, which, acting in combinatorial codes through a language, often of double negatives, specify cell fate. Briscoe and Novitch (2007) discuss the remarkable insights gained over the last decade in respect to the exquisite spatial organization of the ventral spinal cord highlighting the role of graded inductive (Hedgehog) signals. Application of such developmental knowledge has enabled the generation of motor neuron derivatives from ES cells with retention of positional identity post transplantation, emphasizing the relevance of development to repair. This approach is likely to prove a template for *ex vivo*-directed differentiation of neuronal subtypes. Kessaris et al. (2007) discuss glial specification and speculate on the nature of glial heterogeneity. This is particularly pertinent in the area of astroglial biology, where the presence of a single protein (glial fibrillary acidic protein) remains the dominant means of ascribing cell identity; a hazardous practice given the range of regional specialization and variable expression of proteins dependent on the state of ‘reactivity’.

Zhang et al. (2007) discuss the implications of a series of studies examining the neural potential of human ES cells—several exploiting the conserved principles of neural development. Acknowledging the rapid advances in methods to control and direct neural derivation sufficient to generate putative neural subtypes relevant to common diseases, they advise caution and rigour in accepting the function or utility of a cell(s) in the absence of appropriate adult lesional studies. The need for ‘post-specification’ studies addressing the questions of cell survival (particularly in the adult environment), integration and pathfinding are highlighted.

Conceptually, promotion of endogenous processes is generally regarded as the most plausible strategy for brain repair. Kaslin et al. (2007), in a comparative analysis of adult vertebrate neurogenesis and regeneration, discuss phylogenetic differences in the ability to regenerate. Themes emerge: species that display significant post-embryonic growth have widespread adult neurogenesis and, in turn, the extent of regeneration in response to injury appears to correlate with the degree of adult neurogenesis. The ability to modulate constitutive regions of neurogenesis and the unexpected finding of experimental neurogenesis from non-neurogenic regions suggest that there is much to be learnt from the study of non-mammalian vertebrates in order to ‘unlock’ and harness the endogenous neurogenic potential of the injured adult mammalian brain. In a complementary article, Riquelme et al. (2007) discuss the two adult mammalian neurogenic niches: subventricular zone and hippocampal subgranular zone. In itself, this area of intense research activity illustrates once again the value of insights gained from phylogenetic comparisons, given the influence of earlier pioneering studies of the adult avian brain. The article introduces the cellular and extracellular players of the niche, highlighting the dynamic and inter-dependent nature of the niche with dialogue crossing cellular and regional boundaries. Once more the significance of astrocyte heterogeneity, both within and without the niche, is analysed—an important consideration if parenchymatous astrocytes are to have stem cell potential. The importance of conserved developmental canonical pathways (Wnt, BMP and Notch) is discussed with the rider that additional regulatory mechanisms distinct to adult neurogenesis have also been described.

The language, biology and study of neural stem cells, particularly adult neurogenesis, have led to conceptual advances in how brain tumours are considered and, by implication, how they may be treated. It is tempting to speculate on a correlation between adult proliferative zones and cancer cell initiation. Dirks (2007) reviews an emerging literature around the ‘cancer stem cell hypothesis’, illustrating once more the cross-over—of ideas at least—from blood to brain. Regardless of the source of the ‘initiating cancer stem cell’, experimental and pathological evidence suggesting that maintenance of a tumour is due to a cancer stem cell, with more relaxed criteria of ‘multipotency’, is discussed. Signalling pathways (albeit aberrant) and niches, both a focus of this issue, are reviewed with the role of Hedgehog signalling in medulloblastoma illustrative of the relevance of developmental insights to the understanding of brain tumours.

Two papers, by Ormerod et al. (2007) and Chandran et al. (2007), synthesize a wealth of developmental, experimental, pathological and clinical data to speculate on how actual stem cell-based therapies may emerge in two broad classes of neurological diseases: neurodegenerative and inflammatory. Taking a broad sweep but using Parkinson’s disease as the exemplar, Ormerod et al. (2007) discuss the conceptual and practical obstacles to be overcome before even focal, largely single cell-type loss diseases are to be repaired. The utility of stem cells beyond directed differentiation is discussed in both articles. For example, stem cells as a cellular reservoir of trophic factors may represent the first wave of stem cell-based treatment for several degenerative conditions. Chandran et al. (2007) consider the diverse challenges of repairing a
common disease, multiple sclerosis, that is multifocal, multifacified and appears to have two distinct, probably related, pathologies with a variable natural history. All is not lost: insights gained from the study of spontaneous repair or remyelination and reasons for its failure are reviewed and hold the promise for the development of novel therapeutic strategies that will supplement and enhance spontaneous repair. The challenge and opportunity that stem cells and their immunological consequences offer is considered. Ormerod et al. (2007) analyse the implications of non-matched cellular transplants and argue that the long-held view of the CNS as immune-privileged is an oversimplification. However, contingent on the disease, an immune response may indeed be welcome. This idea is extended in the context of demyelination where the combination of pathotropism and immune-modulatory potential of stem cells is discussed as a therapeutic option. Both articles conclude that a multifaceted approach, accepting the value of incremental clinical gains, is likely to prove effective for neural repair.

The concept of phenotypic potential beyond that of the tissue of origin has generated considerable heat and, of late, some light in the lay and scientific literature. The implications of somatic stem cell plasticity are immense and evaluated in two related articles. Fernandes et al. (2007) chronicle pioneering studies, much their own, in characterizing the origin and potential of adult skin precursor(s). The authors demonstrate how a developmental approach led to compelling evidence to support the contention that such precursors are neural crest derivatives. Leaving aside the relationship of the putative precursors to mesodermal derivatives, Ross & Verfaillie (2007) close the issue by evaluating adult stem cell plasticity with a focus on the potential of mesenchymal derivatives. Robust criteria centred on demonstration of function related precursors with therapeutic potential. 


