CHAPTER 12

Role of Endogenous Neural Stem Cells in Neurological Disease and Brain Repair

Jörg Dietrich and Gerd Kempermann

Introduction

There is abundant evidence that neural stem cells persist in the adult mammalian brain—including humans—throughout lifetime and support ongoing neurogenesis in restricted regions of the central nervous system (CNS). The potential role of neural stem cells not only in normal brain function, but also in neurological disease and repair now appears to be larger than anticipated only a few years ago. The question, however, remains whether the persistence of adult stem cells, their proliferation, and neurogenesis from these progenitors reflect the ability for self-repair in the mammalian brain. We here discuss recent advances in the understanding of the role of endogenous stem cells in normal brain function and under circumstances of neurological disease.

Neural Stem Cells in the Mammalian CNS

Neural stem cells (NSCs) are defined by their potential for theoretically unlimited self-renewal, and their ability to generate cells of both neuronal and glial lineages. During development, stem cells are found in the ventricular zone of the CNS.[1,2] In the adult brain, neural stem cells are primarily restricted to two brain regions, the subventricular zone of the lateral ventricles[3-8] and the subgranular zone of the dentate gyrus[9-11]—both regions in which neurogenesis persists throughout adulthood (Fig. 1). In low numbers, stem or progenitor cells have also been derived from many other brain regions, including septum, striatum,[12] cortex,[10] optic nerve,[12,13] spinal cord[14] and retina.[15,16] Apparently, these cells comprise a quiescent population of stem cells with as yet unknown functional relevance for the brain.

Stem cells of the adult brain have traditionally been classified as "multipotent". This term reflects their potential for differentiation into multiple neuroectodermal lineages, but not beyond this tissue-specificity. More recent evidence, however, suggests that cells with greater differentiation potential ("pluripotency") can be derived from the adult brain.[1,17-19] Moreover, stem cells from outside the brain can give rise to neurons in vivo (Fig. 2), at least under specific experimental conditions.[20-22]

The field of neural stem cell biology is currently undergoing dramatic changes in its concepts of "stemness", tissue-specificity, and developmental potential.[23,24] For the purpose of this review we adhere to the classical concepts of neural stem cell biology. However, much of what

Brain Repair, edited by Mathias Bähr. ©2006 Eurekah.com
and Kluwer Academic / Plenum Publishers.

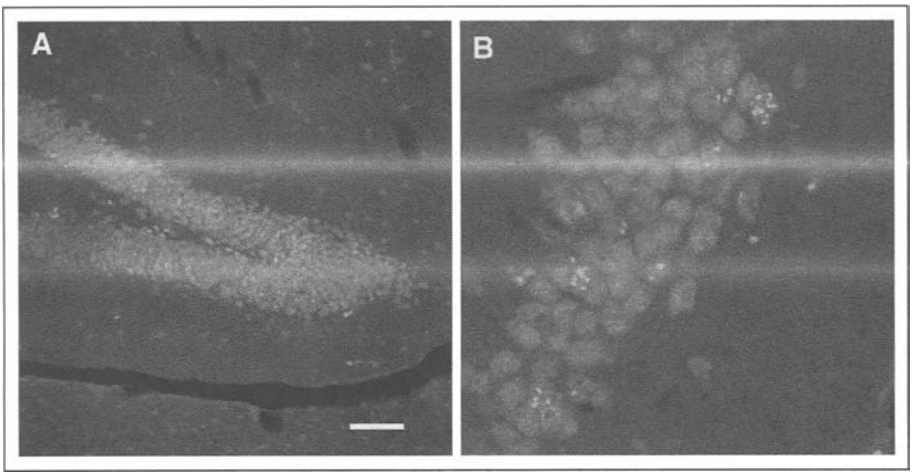

Figure 1. New neurons in the adult hippocampus. Confocal microscopic image of the hippocampus of an adult mouse, demonstrating neurogenesis in the granule cell layer of the dentate gyrus. A) Dividing cells in the subgranular zone (the border between granule cell layer and hilus) are labeled with proliferation marker bromodeoxyuridine (BrdU). B) Four to five weeks after cell division, newly generated neurons can be found throughout the granule cell layer. They are identified by their colocalization of immunoreactivity with antibodies against BrdU and neuronal marker NeuN. Astrocytes are identified by their expression of S100β. Scale bar (in A) equals 100μm for (A) and 20 μm for (B). Image from Kempermann, Bipolar Disorders 2002; 4:17-33, with kind permission of Munksgaard, Copenhagen, Denmark, ©2002.

will be discussed reflects a rather preliminary and probably simplifying view on the principles underlying stem cell biology in the adult brain.

Progeny from neural stem cells of the subventricular zone migrate along the rostral migratory stream to the olfactory bulb to differentiate into local interneurons.[25,26] In the hippocampus, neural stem cells give rise to new granule cells that extend their axons to area CA3 along the mossy fiber tract, as do all other granule cells of the dentate gyrus.[27-33] The new granule cells are electrophysiologically indistinguishable from older granule cells,[34] suggesting their functional integration.

Numerous factors that regulate adult hippocampal neurogenesis have been identified, but at present we are far from a unifying theory on which principles govern this regulation and which functional consequences it has (as reviewed in e.g., ref. 35).

Cells with stem-cell-like properties, dissected from diverse regions of the adult mammalian brain, can be induced to proliferate and differentiate in vitro in the presence of various growth factors, such as epidermal growth factor (EGF) or fibroblast growth factor (FGF-2).[2,11,36-38] Clonal analysis of these cells derived from the embryonic and adult brain has demonstrated their multipotency by giving rise to neurons, astrocytes and oligodendrocytes. This multipotency can also be detected in so-called neurospheres, a three-dimensional cell aggregates that are widely used to study neural stem cells in vitro.[37,39] With multiple neural stem cell populations loosely identified, questions arise where exactly these cells are located in the adult CNS and whether these stem cell populations are actually distinct cell types sharing similar potentials[40] or reflect different developmental stages that can be traced back to one unifying stem cell population. Interestingly, the isolation and characterization of neurospheres from different regions of the human embryonic CNS reveals a regionally specific pattern of growth and differentiation characteristics, suggesting the possible existence of distinct neural stem cell populations.[41] Consistent with these observations, there is evidence that stem cells

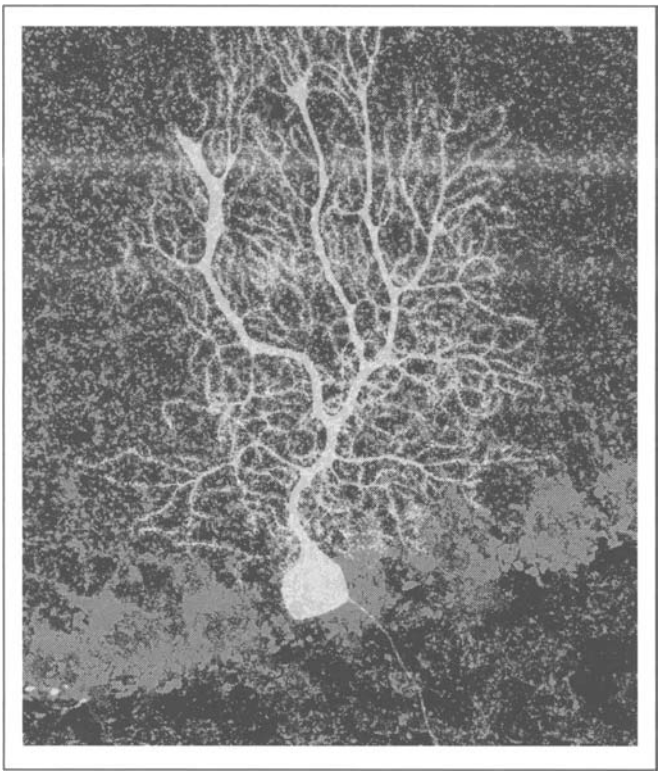

Figure 2. New neurons from bone marrow. Confocal microscopic image of bone marrow-derived Purkinje cells. One year after transplantation of bone marrow transduced with a retrovirus carrying green flourescent protein (GFP), donor-derived Purkinje cells were visualized by confocal microscopy. The surrounding staining is GAD (glutamate decarboxylase), identifying the neighboring GAD-expressing Purkinje cells (see Priller et al. J Cell Biol 2001; 155:733-738 for details. Image courtesy of Josef Priller, Berlin).

isolated from different brain regions maintain their regionally specific expression pattern of homeobox genes in vitro.[42] These results suggest that the identity of a particular stem or progenitor cell might be regionally and temporally specified depending on local environmental cues. However, in many respects, the behavior of the adult-derived stem and progenitor cells is indistinguishable from that of similar cells of the embryonic brain, suggesting some lineage continuity between the embryogenic and the adult CNS.[43]

Neural Stem Cells in Neurological Disease and Repair

The very existence of stem cells and neurogenesis in the adult brain throughout lifetime has shed new light on the potential of the brain for regeneration in the context of a variety of neurological diseases. In fact, several pathological conditions of the CNS have been associated with alterations in progenitor and stem cells – either as a consequence or as a cause of disease. In general, the following concepts for a stem cell-based therapy in the brain exist:

1. NSCs for direct replacement of lost cells from an identified neuronal population,
2. NSCs for replacement of glial or other cells with indirect effects on neurons (e.g., in spinal cord injury or multiple sclerosis),
3. NSCs for replacement of diffuse and complex cell losses (e.g., in stroke or trauma),

4. NSCs as vehicles for growth factor or gene delivery,
5. NSCs as basis of regeneration in situ, and
6. NSCs as target cells for other therapies based on the assumption that stem cells are involved in the pathology of a particular disease (e.g., depression, brain tumors).

In the following paragraphs we will discuss recent developments in which the concept of neural stem cells has been of special importance in changing the current understanding of neurological and psychiatric disease.

The Injured CNS

In contrast to other self-repairing tissues, such as the liver, skin or blood, the mammalian brain apparently lacks the regenerative potential to compensate adequately for neuronal and glial cell death, making this tissue particularly vulnerable to injury and disease.[44]

Repair strategies following CNS injury consist of different aspects of regeneration, including cellular replacement (by means of cell transplantation or endogenous stem cell activation), neurotrophic factor delivery, axon guidance and removal of growth inhibition, manipulation of intracellular signaling, bridging and artificial substrates, and modulation of the immune response (as reviewed in e.g., ref. 45).

For the purpose of this review we will specifically focus on recent findings in the contribution of endogenous neural stem cells to repair mechanisms.

Brain injury induced by traumatic lesions can cause a transient increase in proliferation of neural stem cells in the ventricle wall.[46-48] However, these studies could not clearly demonstrate any neuronal contribution of stem cells to the lesioned CNS.

As multipotent neural stem cells have been isolated from various regions of the adult mammalian brain, the failure of the normal brain to sufficiently regenerate under pathological conditions (e.g., traumatic brain injury) does not appear to be an intrinsic deficit of neural stem cells, but rather a characteristic feature of the damaged environment that does not sufficiently promote functional repair.

Nevertheless, the adult brain appears to be able to reorganize itself after *peripheral* injury and initial deficits in behavior, perception or cognition can be followed by a spontaneous recovery.[49-51] At least on a cortical level, this has been explained by the ability of the mammalian brain for cortical reorganization and plasticity.[52] From these studies, however, it cannot be concluded whether or to what extent adult neurogenesis contributes to such re-organizational processes.

In a more recent study Macklis and co-workers have demonstrated that neurogenesis can be induced in the lesioned neocortex of adult mice.[53] Endogenous precursor cells were stimulated by selective pyramidal cell apoptosis to generate cortical neurons that established appropriate corticothalamic connections. It has been speculated that either neural stem cells from the subventricular zone or resident cortical progenitors might have represented the source of these newborn neurons.[44] Thus, it seems possible that cells with stem-cell-like properties exist throughout the adult CNS. However, physiologically, these cells appear to give rise to neurons only in restricted neurogenic areas. Accordingly, it has also been suggested that adult neurogenesis represents the dormant capacity of the brain for a limited self-regeneration.[44] However, direct evidence is still missing that would clearly demonstrate the replacement of degenerated or dying neurons by newborn neurons. If this were the case, it would be important to know about the sequence of signals (e.g., released by apoptotic cell death) that are involved in the neurogenic response and that might direct newborn cells towards the lesioned area.

While the persistent neurogenesis in the brain with its apparent responsiveness to injury might reveal a possible endogenous repair program, the situation in the spinal cord seems to be somewhat different. A few studies report the existence of multipotent neural stem cells derived from adult spinal cord.[54-56] At present there is no convincing report on neurogenesis in the

adult mammalian spinal cord. Progenitor cells in the adult rodent spinal cord produce glial cells.[57] Although there is increased proliferation of parenchymal progenitor cells[56] and nestin-expressing ependymal cells in the spinal cord after traumatic injury,[58] neurogenesis as a response to injury has not been found. This suggests that in case of spinal cord injury mobilizing endogenous neural stem cells to initiate neuronal repair remains a relatively distant possibility. However, at present no study on spinal cord injury has used such a highly specific and local induction of cell death as in the described study by Macklis and co-workers.[53]

Spinal cord injury is usually followed by a combination of neuronal and axonal damage, inflammation and demyelination. Thus, mobilizing more restricted progenitor cell pools (e.g., oligodendrocyte precursors) after spinal cord injury might—under appropriate conditions—contribute to myelin repair, regeneration of conduction velocity, and functional improvement (see ref. 59). Functional recovery frequently observed after spinal cord trauma in rodents and humans appears to be a consequence rather of axonal plasticity than of neural stem cell activation. [60] Nevertheless, the stimulation of local progenitor pools[59] and the enhancement of axonal plasticity, e.g., by local application of growth factors[61] and neuroprotective factor,[62-65] or other compounds[66,67] might become a useful approach to promote recovery after adult spinal cord injury.

Thus far, cell transplantation strategies for the injured brain and spinal cord have been performed using a variety of cell types and tissues, such as neuronal cell lines,[68] embryonic neuroblasts,[69,70] neural precursors,[71] oligodendrocyte precursors[72] and spinal cord tissue.[73]

In many of these studies, the expression of appropriate neurotransmitters by the grafted cells, the receiving of synaptic inputs from host neurons, or the establishment of long-distance projections could be demonstrated. In addition, functional improvements have been observed. Thus, cellular replacement of the injured CNS via transplantation might be possible, however, it seems to be critically dependent on the molecular host environment and the functional integration of the grafted tissue into the neuronal synaptic circuitry.

Taken together, in the field of spinal cord injury, stem cell research and the potential recruitment of endogenous cellular repair mechanisms hold great promises, but at present only few data exist that substantiate this optimism. However, the existence of neural stem cells in the adult mammalian brain and the positive effects of physical activity or the exposure to a complex environment on adult hippocampal neurogenesis suggest a potential practical impact of this research for neurorehabilitation.[52]

Neurodegenerative Diseases

Neurodegenerative diseases are characterized by a continuous loss of neurons with specific patterns of neuronal cell death associated with distinct disturbances in the neuronal network. Examples are the loss of dopaminergic input to the striatum from the substantia nigra in Parkinson's disease or the degeneration of cortical neurons with a cholinergic deafferentation in Alzheimer's disease.

In the light of our current understanding of the limited regenerative capacity of the adult mammalian CNS, the hypothesis has emerged that neurodegenerative diseases might actually reflect a failure of endogenous neural stem cells to replace lost neurons.[74] This "malfunction" of neuro-regeneration could be due to a primary failure of stem cell proliferation, migration, appropriate differentiation or a combination of all three, resulting in a lack of neurons at critically important topographical locations. At present there is no experimental evidence that a generalized theory of this kind could hold true, because with extremely few well-documented exceptions adult neurogenesis is restricted to the olfactory system and the hippocampal dentate gyrus.

Neurogenesis within neurogenic regions can be stimulated in vivo after exogenous administration of various growth factors and cytokines, including erythropoietin,[75] brain derived

neurotrophic factor (BDNF),[76] Insulin-like growth factor I (IGF),[77] epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF).[78,79] Moreover, cytokine infusion has been shown to stimulate neurogenesis in animal models of neurological disease. For example, infusion of transforming growth factor alpha (TGFα) to the forebrain of 6-hydroxydopamine lesioned rats (a model for Parkinson's disease) resulted in increased cell proliferation, directed migration of newly generated cells toward the infusion site and increased numbers of neurons in the striatum. This increase of neurons was associated with improvements in apomorphine-induced rotations of the animals (indicative of motor improvement).[80] This result fits well with data from the first study using transplantation of embryonic stem cells into a model of Parkinson's disease.[81]

Although very little is known about what signals direct newborn cells towards a particular CNS lesion and what factors orchestrate the appropriate site-specific differentiation of neural progenitors, the activation of endogenous stem cells to induce neurogenesis might be a possible means to overcome neuronal cell loss that occurs during the course of neurodegenerative disease. Despite encouraging first findings, this strategy remains speculative at the present time.

Most experiences in using neural stem cells for treatment of neurological disease have been made in Parkinson's disease.[82] Fetal cells have already been transplanted to severely impaired patients in clinical trials[83-86] and demonstrate that fetal human mesencephalic cells containing dopaminergic neurons can survive after transplantation, restore striatal dopamine release, and ameliorate motor behavior impairments. However, clinical and experimental studies have shown that functional integration of the grafted neurons within the host brain is necessary to produce substantial recovery.[87-89]

In Huntington's disease, a genetic disease characterized by a progressive neurodegeneration in the striatum and cerebral cortex, transplantation of fetal neural tissue has also offered a therapeutic opportunity.[82,90] In animal models of Huntington's disease, transplantation of fetal striatal neuroblasts to the striatum have been shown to be functionally integrated into the host environment and to restore striatal connections.[91] Reconstruction of neuronal circuitry by grafted tissue into the striatum could also be demonstrated in primates.[92,93] Moreover, transplantation of fetal striatal tissue has also been applied in patients with Huntington's disease.[90,94] In a clinical study, five patients with Huntington's disease who received fetal grafts were assessed for therapeutic outcome one year after transplantation. Patients with presumed surviving grafts (demonstrated by positron-emission tomography) showed improvements in motor and cognitive functions, and functional benefits were seen in daily-life activities.[94]

Due to a number of limitations using fetal grafts (e.g., ethical problems, survival of grafted cells, and problems in standardization and quality control), future efforts will also focus on the in vitro expansion and differentiation of neural stem cells as alternative sources to primary fetal CNS tissue for replacement therapy in neurodegenerative diseases.[82,95,96]

A cell-mediated gene therapy of the diseased CNS offers an alternative approach for the treatment of neurodegenerative diseaes.[97-100] For example, specific neurotransmitter release (e.g., γ-aminobutyric acid or dopamine) by transplanted neurotransmitter-synthesizing cells into the affected regions of the CNS has been shown to improve disease-related symptoms.[101,102]

Taken together, neurodegenerative diseases in which a defined cell type is being lost or damaged, such as Parkinson's disease, might be good candidates for a targeted stem cell therapy. In contrast, owing to the diffuse nature of neuronal and glial cell death that is associated with other neurodegenerative diseases such as Alzheimer's disease, repair of such disorders represents a potentially different category of problem than the repair of focal degeneration. Assuming that there is no primary deficit in the neural stem cells themselves as a cause of disease, a direct stimulation of endogenous neural stem cells through pharmaceutical or behavioral manipulation might increase brain plasticity and repair. Regardless, the continued cell loss during the course of neurodegenerative diseases will be challenging to overcome. It seems substantial,

however, to define more clearly the cellular compartments affected in those disorders as a prelude to the analysis of cell protection or cell replacement strategies. It seems more likely that future therapies of neurodegenerative diseases will be advanced by general lessons on cellular development, survival and plasticity learned from stem cell biology than by the direct application of stem cells in these conditions.

Brain Tumors

Compelling theories are linking neural stem cell biology to neurological disease in the field of neuro-oncology. An increasing knowledge about neural stem and progenitor cells has started to shed light on the potential role of these cells in respect to tumorigenesis, brain tumor classification, and the treatment of brain tumors. Moreover, understanding the vulnerability of CNS precursor cells towards drug toxicity or irradiation might help to reveal the biological basis for brain damage frequently associated with cancer treatments.

Consistent with experiences in the treatment of tumors of the hematopoietic system, the diagnosis of brain tumors based on cell lineage appears to be of great potential value. In hemato-oncology, the normal cellular lineage to which a tumor is related seems to be closely correlated with treatment response and prognosis.[103-109]

At present, various precursor cell populations have been identified in the developing and/or mature CNS: EGF-dependent and FGF-dependent neuroepithelial stem cells (NSCs),[3,37,54,110-113] lineage-restricted precursor cells,[114-116] including neuron-restricted precursor (NRP) cells[114,117] and glial-restricted precursor (GRP) cells,[115] and oligodendrocyte-type-2 astrocyte (O2A) progenitor cells.[118,119] In addition, a number of astrocyte precursor cells [120-123] and a pre-O2A progenitor cell have been reported in the literature.[124] Both multipotent neural stem cells and lineage restricted precursor cells have also been identified in the adult mammalian brain, including humans.[11,125-131]

To make matters even more complex, there have been recent reports on stem cells with an overlapping developmental potential between the CNS and the hematopoetic system, which could give rise to both neural cells and blood cells.[23,132-136] Bartlett and colleages have isolated a more-than-multipotent stem cell from the adult mouse brain, whose developmental potential approached that of pluripotent embryonic stem cells.[1] Similar data exist for stem cells from bone marrow[137] and skin.[138] These data question the validity of the term "tissue specificity" of stem or progenitor cells and elucidate that we are far from a final systematic of stem cell biology in the adult.

All of the described cells could be potential targets of transformation events to initiate the development of a tumor in the CNS.[139] Thus, a lineage-based classification system for brain tumors might lead to the establishment of better prognostic criteria and might also help to define patient populations that would benefit from a particular treatment.[139-142]

Establishment of brain tumor models on the basis of CNS precursor cells will not only increase our understanding of potential genomic alterations during tumorigenesis, but will also provide helpful information on the relation between transformed precursor cells and the (heterogeneous) tumors they create in vivo.[140,143-145] In this regard, the cell lineage appears to be important in determining whether or not a particular genetic lesion will have functional consequence. For example, a specific genetic alteration could result in a different tumor-forming ability or tumor phenotype, depending on the precursor cell that was targeted.[146]

Several studies have described the expression of glial and neuronal markers in brain tumors, including astrocytomas, oligodendrogliomas, medulloblastomas and primitive neuroectodermal tumors (PNETS).[147-151] To date no markers are available that specifically and unambiguously label neural stem or precursor cells, only the development of antibodies to new cell type specific antigens, e.g., by gene expression analysis and microarray technology, might help to assign particular brain tumors to their lineages of origin. [152-154] For some tumor populations

such analysis has already been successfully applied in order to cluster tumors with a similar prognosis.[155-157]

Neural stem cells might become useful as possible means of brain tumor treatment. To achieve this it will be important to understand to what extend endogenous stem and precursor cells influence or modulate tumor cells in the CNS. The most straightforward approach is to use stem cells as vehicle cells in gene therapy, building on the readiness of these cells to develop tissue specificity and become functionally integrated in the host organism. For example, neural stem cells genetically modified to produce interleukin-4 promoted tumor regression and prolonged survival in mice injected intracranially with a mouse glioma cell line.[158] In another study, implantation of a neural stem cell line, engineered to produce cytosine deaminase (which converts 5-fluorocytosine to the oncolytic drug 5-fluorouracil), into the CNS of mice harboring a tumor resulted in a reduction of the tumor mass in vivo, when animals were treated with 5-fluorocytosine.[159] Interestingly, implanted neural stem cells were detected in the primary tumor mass when injected at a distance from the tumor and were also seen to co-cluster with tumor cells at distances remote from the tumor injection site. This result is exciting since one of the most important impediments to the treatment of malignant brain tumors has been the invasion of tumor cells into the surrounding normal brain tissue, which makes their treatment particularly challenging.[160,161] Many more experiments will be required and many questions will have to be answered before it is clear whether neural stem cells can be used for the treatment of brain tumors (as reviewed in refs. 162,163). For example, do neural stem cells really migrate towards dispersed tumor cells or are they simply using the same migratory substrates leading to an occasional juxtaposition? Do endogenous or transplanted neural stem cells change their biological properties (e.g., differentiation and proliferation) in case of a present tumor mass? What are potential adverse effects of transplanting neural stem cells into the human brain? And would it be possible to visualize and monitor transplanted stem cells in vivo to design controlled clinical studies? In this regard, there have already been promising results with labeling neural stem or progenitor cells in order to make them detectable by magnetic resonance imaging after transplantation.[164-166]

A different aspect relating neural stem cells to oncology has been raised in regard to the vulnerability of the CNS to conventional cancer treatment. In fact, traditional approaches to cancer therapy are often associated with severe neurotoxicity. For example, radiation-induced neurological complications include leukoencephalopathy, radionecrosis, myelopathy, cranial nerve damage and cognitive impairment.[167-169]

Moreover, it has been well known that many chemotherapeutic regimens may be associated with severe neurotoxicity. For example, multiple reports have confirmed cognitive impairment in children and adults after chemotherapy. Neurotoxicity of chemotherapy may be particularly hazardous when combined with radiotherapy.[169,170] For example, computed tomography (CT) studies of patients receiving both brain radiation and chemotherapy showed that all patients surviving a malignant glioma for more than 4 years developed leukencephalopathy and brain atrophy.[171]

Thus, improvements in survival for children with leukemias or brain tumors treated with radiotherapy and chemotherapy have led to increasing concerns on quality-of-life issues for long-term survivors, in which neuropsychological testing has revealed a high frequency of cognitive deficits.[168,172-175]

Potential clues to the biological basis of neurotoxicity, such as cognitive impairment, have come from studies on the effects of radiation on the brain. On a cellular basis, radiation appears to cause damage to both dividing and non-dividing CNS cells. Irradiation has been shown to cause apoptosis in the subgranular zone of the hippocampal dentate gyrus [176,177] and in the subependymal zone,[178] both of which are sites of continuing stem or progenitor cell proliferation in the adult CNS. Such damage also is associated with long-term impairment of

subependymal repopulation,[177] indicating that surviving stem cells are unable to regenerate the subependymal zone. This could in fact lead to a profound impairment of the overall cellular plasticity in the CNS.

Furthermore, non-dividing cells, such as oligodendrocytes, are also killed by irradiation,[179] which seems to be consistent with clinical evidence, where irradiation induces diffuse myelin and axonal loss, tissue necrosis and diffuse spongiosis of the white matter.[180] There is considerable discussion whether the damage caused by irradiation represents a direct or indirect effect on the brain. Although some damage in vivo might be secondary to vascular damage, radiation is also directly damaging important CNS populations, such as oligodendrocyte precursor cells.[181]

Recent studies have indicated that carmustine (BCNU), a lipophilic alkylating agent, is toxic for oligodendrocytes at doses that would be routinely achieved in patients. In contrast, astrocytes appear to be relatively resistant to BCNU, and O-2A cells showed intermediate levels of sensitivity.[182] The sensitivity of oligodendrocytes to BCNU raises the disturbing issue of whether the normal cells of the brain are damaged by exposure to chemotherapeutic agents. Preliminary results raise the concern that multiple types of neural precursor cells are at least as sensitive to death induced by chemotherapeutic agents as are cancer cells themselves (J. Dietrich and M. Noble, unpublished observations).

Taken together, in the field of neuro-oncology various intersections between neural stem cells and tumors of the CNS seem to emerge. An increasing knowledge about the lineage relationships and biological properties of different neural stem and precursor cells might help to better understand the process of tumorigenesis in the CNS and might also help to develop novel treatment options for future cancer therapies.

Demyelinating Diseases

Demyelination is a common feature of various neurological diseases with different underlying causes such as inflammation, automimmune reactions, degeneration, and trauma.[183-186] Multiple sclerosis (MS), as the most prominent example of a demyelinating disease, is characterized by chronic inflammatory focal demyelination associated with a variable degree of axonal loss.[187-189]

The appearance of demyelination and axonal loss very early in the course of the disease[190,191] suggests that strategies of myelin repair might be a possible means of protecting axons from further immunological insults.

In general, therapeutic strategies to promote myelin repair have focused on two major avenues: (1) cell transplantation to provide an exogenous source of cells which are competent to form myelin producing cells, and (2) recruitment of endogenous cell populations that are capable to produce myelin.[192]

Experimentally, the transplantation of certain types of cells, including oligodendrocyte precursor cells or multipotent stem cells, which are able to generate myelin-producing oligodendrocytes, can lead to remyelination of chronic demyelinated tissue.[193-197] Promising results in myelin repair and re-establishment of nerve conduction have come from the use of embryonic neural stem cells that were expanded in vitro and induced to the oligodendroglial lineage prior to transplantation.[192,193,198] However, regardless of the potential of transplanted cells to produce myelin, poor survival of grafted cells, lack of migration of these cells beyond the lesion site and therefore an unpredictable therapeutic outcome are current limitations to this approach.[199]

In demyelinated CNS regions a certain amount of remyelination occurs,[200-204] but remyelination in the adult damaged brain remains incomplete.[202,205-207]

The identity and origin of cells, that participate in endogenous remyelination has been unraveled to some degree. Multipotential stem cells, oligodendrocytes, or oligodendrocyte precursor cells are possible candidates involved in the remyelination process. Multipotent neural

stem cells have been implicated in myelin repair.[208] For example, in a lysolecithin-induced demyelination of the corpus callosum progenitors of the rostral subventricular zone (SVZ) expressing the polysialylated form of the neural cell adhesion molecule (PSA-NCAM) proliferate and seem to migrate towards the lesion site and differentiate into glia but not neurons.[209]

Whereas oligodendrocytes of the adult forebrain are primarily postmitotic,[210] persistent cycling oligodendrocyte precursor cells (OPCs) might represent the most likely population and source for myelin repair.[72,210-212]

OPCs are not only present in the developing but also in the adult mammalian brain.[118,213-215] Their specific function in the normal brain is largely unknown. It has been hypothesized that they play a role in influencing neuronal activity[216,217] and synaptic growth.[218,219]

In the injured brain or in case of demyelination, oligodendrocyte precursor cells might form a glial population that can be activated to proliferate and to become involved in repair mechanisms by giving rise to myelinating oligodendrocytes.[209,220] This exciting potential has initiated research on the exact meachnisms that induce oligodendrocyte precursor cells migration, proliferation and differentiation to promote myelin repair.

Several studies have also indicated the persistence of mitotic oligodendrocyte precursor cells in the *adult human* subcortical white matter.[221-224] However, only small numbers of oligodendrocytes are generated in the intact adult mammalian brain.[225] Thus, subcortical white matter progenitors appear to be a quiescent population, and oligodendrocyte differentiation from these cells to a myelinating stage is considered to be a rare event.[215]

In contrast, glial progenitor proliferation can be found after injury and in several animal studies of induced demyelination.[192,220,226] Moreover, oligodendrocyte precursor cells have also been identified in multiple sclerosis lesions.[227,228]

However, they apparently fail to proliferate and to differentiate during chronic stages of the disease.[203] Reasons for the incomplete repair might lie in a profound axonal loss, the lack of sufficient precursor migration towards a lesion, insufficient precursor pools that could be mobilized or the lack of permissive environmental cues (e.g., growth factors and cytokines) to activate precursor cells.

For example, immature cycling progenitor cells of the adult subcortical white matter can be recruited to give rise to myelin-producing oligodendrocytes in response to experimental focal demyelination by lysolecithin,[229] but do not migrate towards the lesioned area so that only cells present at the site of demyelination can participate in remyelination.[229] Consequently, severe demyelination might damage all resident progenitors at one particular lesion site—as it is to be assumed in chronic MS lesions—and thus profoundly reduce the capacity for myelin repair in that region.

Therefore it would be a useful approach to direct the migration of cycling precursor cells towards a demyelinated area that has suffered depletion of its own precursor population.

Since oligodendrocyte precursors fail to survive and migrate when transplanted into the *intact* mammalian brain,[230,231] multiple environmental factors might be important to trigger progenitor cells to proliferate and differentiate. In fact, the balance between cell proliferation and differentiation appears to be mediated by local environmental cues, such as growth factors locally synthesized by surrounding neurons and glia. For example, glial growth factor 2 (a neuroregulin isoform) or Insulin-Growth-Factor 1, have been shown to promote remyelination in animal models of inflammatory demyelination.[232]

The immune system itself is likely to influence myelin repair.[233-235] For example, there is evidence that circulating immunoglobulins bind to oligodendrocyte surface antigens to promote remyelination,[236] and that antigen-antibody binding may facilitate the opsonization of myelin debris allowing repair to proceed.[236]

Taken together, it remains to be determined to what extent cell types such as neural stem or progenitor cells can contribute to myelin repair. It is a substantial scientific challenge to determine the signals involved in the activation of oligodendrocyte precursor cells and in the induction of multipotent CNS precursor cells to proliferate and differentiate into migratory oligodendrocyte precursor cells to enhance remyelination and to improve neurological deficits.

Seizures

Epilepsy is a common neurological condition that is characterized by recurrent seizures due to hyperactivity and synchronization of activity within neuronal populations (as reviewed e.g., in refs. 237-240). Animal models of induced seizure activity attempt to mimic these characteristic features of epilepsy. For example, ***kindling*** is a widely used model, in which repeated electrical stimulation of limbic areas leads to a stimulus-induced stable seizure activity, that resembles the temporal lobe epilepsy in humans.[241,242] Other commonly used seizure models are based on the stimulation of glutamatergic or cholinergic receptors by drugs such as kainate and pilocarpine.[243-245] For review on other widely used seizure models, see e.g., ref. 245.

Epileptic activity has been reported to result in a number of long-term alterations, such as altered gene and growth factor expressions,[246-249] neuronal cell loss in the hippocampus,[250-253] Ammon's horn sclerosis,[254-258] dendritic abnormalities of pyramidal cells,[259] and synaptic reorganizations within the hippocampus,[260-262] all of which have a potential impact on the neuronal circuits. These effects might induce a cascade of consequences, including alterations of glutamate receptor expression, glial hypertrophy, axonal growth and formation of new synapses that might contribute to an increased susceptibility to further seizures.[263]

In patients with temporal lobe epilepsy, nests of ectopic granule cells have been described.[264,265] Similarly, Houser and co-workers found aberrant sprouting of mossy fibers, the axons of granule cells, in the brains of these subjects.[266] These findings were first interpreted as reflecting a deranged development and thus a cause of the seizures. Research on adult hippocampal neurogenesis has allowed the alternate hypothesis that these changes are a direct consequence of seizures.[267-271] Parent et al were the first to report that pilocarpine induced seizures in rats lead to a transient increase in cell proliferation in the dentate gyrus.[272] Others have extended on these findings with similar models and similar findings.[273-278] Such increased proliferation corresponds to the up-regulation of several cytokines and mitogens, as described elsewhere.[279-283] Interestingly, it appears that stimulation of neurogenesis following kainate-induced seizures requires endogenously synthesized FGF-2, since this result cannot be seen in FGF-2 knockout mice. [284] While the induction of cell proliferation has been convincingly documented in several studies, less attention has been given to the question, whether a greater number of mature, functionally relevant neurons develop from these dividing cells and what their ultimate fate is. Parent et al have initially speculated that it might be the new cells that produce aberrant connections considered to sustain seizure activity,[272] but later provided arguments that this might not be the case (see below).[285]

Activity-induced cell proliferation in the dentate gyrus—and in some cases neurogenesis—has been demonstrated in both electrical[286,287] and chemically induced seizures,[272,273,277,285,288] suggesting a fundamental response mechanism as a result of synchronized neuronal activity. However, it remains to be shown, whether altered neurogenesis is a cause or consequence of increased seizure activity.

Blümcke et al reported an increased proliferation index as assessed by Ki-67 immunoreactivity in the dentate gyrus of children with early-onset temporal lobe epilepsy who had undergone surgery to remove the epileptogenic focus in the hippocampus.[289] They found an increase in nestin-labeled cells as a putative marker of progenitor cells in the dentate gyrus. Although the further development of the proliferating cells remains unclear, these finding are suggestive that the response of the human hippocampus is similar to the rodent hippocampus. Scharfman

et al demonstrated that pilocarpine- and kainate-induced seizures in rats cause proliferation of hippocampal neural stem or progenitor cells whose progeny can migrate to the CA3 region of the hippocampus to give rise to ectopic $NeuN^+$ and $Calbindin^+$ granule cells.[277] This would be consistent with the observation by Houser et al in humans.[290] However, despite exhibiting granule cell specific intrinsic properties (e.g., membrane properties, firing behavior and morphology), these cells seem to be abnormally integrated into the CA3 network.[277]

Interestingly, conditions known to be able to induce neurogenesis, such as living in an enriched environment,[291] have not only been shown to be associated with reduced spontaneous apoptotic cell death in the rat hippocampus, but also to protect from kainate-induced seizure activity itself.[292] The relation between these two separate observations that is suggested by Young et al remains to be proven, but raises the question whether seizure-induced structural changes in the brain might be linked to altered stem cell activity.

It appears, however, that there are fundamental differences between the immature and the aged brain in regard to susceptibility to seizures and the functional consequences of seizures.[293-297] Despite the evidence that seizures result in a more profound cell death in aged animals compared to young animals,[295,298] seizures might have deleterious effects in the neonatal brain. For example, seizures in the developing brain can result in irreversible alterations in neuronal connectivity, as reviewed in 295. It has been reported that newborn animals receiving 10 daily electroconvulsive seizures have significantly smaller brains than controls.[298] Furthermore, seizures in the neonatal brain result in a reduced neurogenesis in the dentate gyrus, measured by BrdU incorporation and phenotypical characterization of newborn cells by the neuronal marker NeuN. In contrast, aged animals exposed to the same number of seizures show a significant increase in hippocampal neurogenesis.[299] While the underlying cause of the age-related differences is not exactly known, it has been speculated that increased glutamate release following seizures or a pronounced level of sensitivity to hypoxia in the neonatal brain might be partly responsible for altering the balance between cell death and birth.[299]

These observations are intriguing, because recurrent neonatal seizures could therefore—even in the absence of cell loss—have profound effects on brain development and might explain some of the late neurological impairments following recurrent seizure activity.[294,300-302]

In addition, recurrent seizures in the neonatal brain cause sprouting of mossy fibers into the inner molecular layer of the dentate gyrus and pyramidal layer of CA3 in rats. [303] While seizure-induced progenitor proliferation in the dentate gyrus can be inhibited by irradiation, synaptic remodeling of the mossy fiber pathway appears not to be altered.[285] Thus, it seems likely that mossy fiber synaptic reorganization is independent of neurogenesis, suggesting that sprouting arises from mature granule cells.[299]

A completely different question is whether the use of neural stem cells (either as transplanted cells or as recruitment of endogenous cells) might provide a possible means for the treatment of epilepsy.[82] For example, there have been several studies trying to circumvent the imbalance between excitatory and inhibitory neurotransmission in seizures by transplanting embryonic cells that release inhibitory neurotransmitters such as GABA. Although successful transplants resulted in seizure suppression, the underlying mechanisms of the graft action are mostly unclear and seizure suppression has so far only been transient.[304-307]

It remains to be established whether there is any potential therapeutic benefit to be derived from endogenous stem cell activity in response to seizures, and whether the seen effects are part of the epileptogenic pathology or attempts of endogenous regeneration.

In summary, repetitive seizures have been shown to lead to well-described neuropathological changes such as neuronal cell death, reactive gliosis, enhanced neurogenesis and axonal sprouting.[308] Most of these damages seen in animal models are similar to those seen in humans, e.g., in cases of intractable temporal lobe epilepsy. Many questions about the molecular mechanisms involved in these changes remain to be elucidated, as reviewed in e.g., ref. 309).

Better understanding the exact mechanisms that modulate proliferation and differentiation of neural stem and progenitor cells following seizure activity might offer potential targets for future therapies.

Ischemia

Cerebrovascular insults are a major cause for permanent neurological impairment. After cerebral infarction, necrotic tissue is usually not replaced and functional recovery of the patient is very limited. As in other areas, neural stem cell activity and neurogenesis in the adult brain might play a role in the clinical outcome of CNS disease such as cerebral infarction. Unfortunately, much of this general optimism is as yet backed by only limited experimental evidence. Nevertheless, the use of neural stem cells might offer future treatment options either as vehicle systems to deliver neurotrophic factors or as cell replacement therapy via transplantation. Recent studies have described a significant increase of cell proliferation in the subventricular zone and the dentate gyrus of the mammalian brain in response to vascular injury, such as global and focal ischemia in experimental models.[310-315]

Thus, transient ischemia could be a potent signal for inducing neural stem cell proliferation (as measured by BrdU-incorporation) and differentiation into neuronal and astroglial phenotypes (by co-labeling BrdU-positive cells with lineage specific markers). However, it is not known, what is actually reflected by the increase in the number of BrdU-labeled cells, which is interpreted as increased cell proliferation, because most conclusions are indirect. No specific positive markers for neural stem cells in vivo are known and most studies lack the examination of long survival periods in order to assess the net and long-term effects. Also, at least in the hippocampus, prolonged periods of global ischemia (> 2 minutes) seem to be necessary to significantly increase BrdU incorporation.[312] Despite several reports describing the proliferation and differentiation of hippocampal progenitors following global ischemia, further quantitative studies will be required to determine whether this also results in an sustained increase of granule neurons. Interestingly, BrdU incorporation in the subgranular zone of the dentate gyrus has been described to a more pronounced degree on the ipsilateral side, in case focal cerebral ischemia was applied,[310] suggesting that signals associated with cell death might locally stimulate cell proliferation.

Increased cell proliferation has also been described in the rat neocortex following transient global[316] and focal ischemia.[317] Newborn cells were distributed randomly in cortical layers II-VI with highest densities in the ischemic boundary zone.[316] Reactive neurogenesis in a photothrombotic stroke model has been reported,[317] which seems to fit well with cortical neurogenesis after phototoxic lesions [53] and the controversial report of spontaneous neurogenesis in cortical areas of the primate brain.[318] Photothrombotic stroke is an interesting model system that however lacks several features characterizing normal embolic or thrombotic ischemia. It remains generally conceivable that some ischemia-induced neurogenesis might also be present in the human brain in various brain areas and might even be a potential means for brain repair after stroke. However, the unequivocal demonstration of functional and lasting neurogenesis following ischemia has still to be made.

Mechanisms that have been shown to reduce vascular damage and ischemia-induced cell death, such as glutamate receptor blockade, have also been demonstrated to positively influence stem or progenitor cell proliferation.[319] Several mechanisms have been controversially discussed that might influence hippocampal neurogenesis after ischemia. Potential signals include changes of NMDA receptor signaling,[319-323] death of glutamatergic neurons that project into the granule cell layer,[322,324] dying hippocampal neurons,[272,273,325-329] growth factors or mitogenic factors such as FGF[330,331] and erythropoietin.[75]

In addition, age-related differences in stem or progenitor cell activity following ischemic insults appear to be important. While neurogenesis in the dentate gyrus following global

ischemia seems to be less accelerated in aged and more pronounced in young animals,[332] young animals seem also to be more vulnerable to ischemic insults. Neonatal rats exposed to cerebral ischemia show a severe and sustained damage of the subventricular zone (SVZ) with necrotic and apoptotic cell death.[333] More specifically, oligodendrocyte precursor cells and neural stem cells appear to be particularly vulnerable resulting in subcortical white matter demyelination and profound cell loss in the SVZ three weeks after the insult.[333] Moreover, there is evidence for a maturation-dependent vulnerability of oligodendrocyte precursors to hypoxia and ischemia, which might explain the selective vulnerability of the periventricular white matter to hypoxia and ischemia seen in the premature infant.[334]

Thus, neurological impairment (e.g., cognitive and motor dysfunction) caused by asphyxia of the newborn might be due to damage to progenitors and stem cells of the CNS.

It has been hypothesized that grafted neural tissue may be a possible means for therapy of brain ischemia by either direct cell replacement or by releasing neurotrophic factors to the damaged brain, as reviewed e.g., in refs. 82,335. A variety of grafted cell types have been studied in ischemic brain models, including fetal cells and tissues,[336] immortalized cells[337] and genetically modified cells, as reviewed in e.g., 338. Numerous reports have demonstrated that transplanted cells were able to survive, to migrate preferentially toward the lesioned area, to differentiate into neuronal cells, to re-establish functional connections within the host animal, and to restore functional deficits.[335-337,339] A first clinical study by Kondziolka et al is an initial indication that transplanting cultured neuronal cells into the brains of humans after stroke is safe and could have functional benefits.[340] In general, however, clinical application of this strategy appears premature, because risks and potential benefits cannot yet be reasonably judged.

The establishment of a functional neuronal circuitry between the host and the grafted tissue is dependent on many variables, including the availability of trophic factors. Neurotrophic factors are essential to maintain the physiological function of glia and neuronal cells.[341-344] Furthermore, proliferation and differentiation of endogenous stem and progenitor cells is also dependent on appropriate neurotrophic signals.[345,346]

In pathological situations, as in the ischemic brain, neurotrophic factors protect brain tissue from experimentally induced damage.[347-351] For example, gene delivery of the *glial cell line-derived neurotrophic factor* (GDNF) into the rat brain one day before a transient middle cerebral artery occlusion resulted in a significantly smaller infarct volume and was associated with a reduction of apoptosis. [352] Consistent with these reports, neurotrophin receptors are up-regulated in cholinergic striatal interneurons after global cerebral ischemia, suggesting that neurotrophin signaling might be important for the survival and function of these cells. [325]

In summary, recent findings have raised hopes for novel treatment approaches of ischemic brain damages, including activation of endogenous neural stem cells and transplantation of neural grafts. However, the use of neural transplants for the treatment of CNS ischemia has to be considered with caution and further pre-clinical studies are needed to validate the safety and efficacy of such an approach before neural stem cells could be applied to stroke patients. Alternatively, there is evidence that endogenous progenitors and stem cells are activated and might be involved in repair mechanisms following ischemic brain injury. As of yet, the plasticity of the adult human brain in acute and chronic ischemic conditions is poorly understood. For example, compensatory reactions and functional recovery (as it can be seen in stroke patients) that have been thus far explained by synaptic or functional plasticity might in fact include a limited neuronal replacement, potentially far from the injury site.

Mood Disorders

Adult hippocampal neurogenesis affects hippocampal function and is thus potentially involved in higher cognitive functions. Some of the known factors that are able to induce neuronal cell death and to potently suppress hippocampal neurogenesis are psychosocial stress[353,354] and glucocorticoid hormones.[355-357]

Major depression, although not a hippocampal disease in a strict sense, shows hippocampal impairment, for example with regard to symptoms of dementia and memory loss.[358,359] Recent studies have indicated that the pathogenesis and treatment of depression is likely to involve the impaired plasticity of neuronal circuits within the hippocampal formation. Thus, stress-induced impairment of dentate gyrus neurogenesis has been linked to the onset of clinical phases of depression [360]

In accordance with this hypothesis, studies using magnetic resonance imaging demonstrated selective atrophies in the *limbic-cortical-striatal-pallidal-thalamic tract*, which consistently includes a volume loss of the hippocampus in various psychiatric disorders, like in long-standing depression.[361] These findings were complemented by postmortem observations of hippocampal atrophy and cell loss in patients with mood disorders.[362-364] These structural changes correlate with deficits in declarative, spatial and contextual memory performance, supporting a link between hippocampal dysfunctions and the development and clinical appearance of certain psychiatric conditions.[365]

This hypothesis has led to the assumption that remodeling the hippocampal network, e.g., by increased neurogenesis, might be a possible means to influence the outcome of stress-related mood disorders.[355,366-368] Hence, circumstantial evidence to support this hypothesis has come from several studies showing that drugs used for treatment of depression, including tricyclic antidepressants and serotonin re-uptake inhibitors, as well as electroconvulsive therapy and physical activity stimulate adult hippocampal neurogenesis.[287,369-372]

It has been suggested that antidepressants might therefore exert their therapeutic effects by stimulating changes in neuronal systems, such as by an increase in neurogenesis – possibly by enhancing the expression of growth and survival promoting factors like neurotrophins.[373] Interestingly, in the case of serotonin re-uptake inhibitors, stimulation of neurogenesis requires long-term treatment,[374] which is consistent with the clinical experience of a long latency period before onset of an anti-depressive effect.

Furthermore, lithium (in clinical use for the treatment of bipolar disorders) has an effect on adult hippocampal neurogenesis, too.[375] This effect is possibly mediated through the upregulation of the anti-apoptotic protein bcl-2.[375]

Stimulation of neurogenesis (e.g., by antidepressants) might thus inhibit or reverse the effects of stress-induced downregulation of hippocampal neurogenesis and hippocampus atrophy.[370,374,376]

At present, however, it remains unknown, whether a disturbance in adult hippocampal neurogenesis is a consequence, cause or correlate of major depression and bipolar disorders.[35] Several recent reviews have speculated about this potential pathogenic link.[355,360,377] As of yet, this relation remains an interesting hypothesis that still has to be substantiated by empiric and experimental evidence. Intriguingly, major depression and schizophrenia share some characteristic features such as hippocampal involvement. Whether an impairment of cellular plasticity within the hippocampus is involved in schizophrenia has been suggested,[378-380] but at present, this hypothesis is even more speculative than in the case of major depression.

Summary

These examples show that stem-cell-based therapy of neuro-psychiatric disorders will not follow a single scheme, but rather include widely different approaches. This is in accordance with the notion that the impact of stem cell biology on neurology will be fundamental, providing a shift in perspective, rather than introducing just one novel therapeutic tool. Stem cell biology, much like genomics and proteomics, offers a "view from within" with an emphasis on a theoretical or real potential and thereby the inherent openness, which is central to the concept of stem cells. Thus, stem cell biology influences many other, more traditional therapeutic approaches, rather than introducing one distinct novel form of therapy.

Substantial advances have been made in neural stem cell research during the past few years. With the identification of stem and progenitor cells in the adult brain and the complex interaction of different stem cell compartments in the CNS—both, under physiological and pathological conditions—new questions arise: What is the lineage relationship between the different progenitor cells in the CNS and how much lineage plasticity exists? What are the signals controlling proliferation and differentiation of neural stem cells and can these be utilized to allow repair of the CNS? Insights in these questions will help to better understand the role of stem cells during development and aging and the possible relation of impaired or disrupted stem cell function and their impact on both the development and treatment of neurological disease. A number of studies have indicated a limited neuronal and glial regeneration in certain pathological conditions. These fundamental observations have already changed our view on understanding neurological disease and the brain's capacity for endogenous repair. The following years will have to show how we can influence and modulate endogenous repair mechanisms by increasing the cellular plasticity in the young and aged CNS.

References

1. Rietze RL, Valcanis H, Brooker GF et al. Purification of a pluripotent neural stem cell from the adult mouse brain. Nature 2001; 412(6848):736-9.
2. Temple S. The development of neural stem cells. Nature 2001; 414(6859):112-7.
3. Reynolds BA, Weiss S. Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. Science 1992; 255(5052):1707-10.
4. Alvarez-Buylla A, Garcia-Verdugo JM. Neurogenesis in adult subventricular zone. J Neurosci 2002; 22(3):629-34.
5. Alvarez-Buylla A, Herrera DG, Wichterle H. The subventricular zone: source of neuronal precursors for brain repair. Prog Brain Res 2000; 127:1-11.
6. Goldman SA, Nedergaard M, Crystal RG et al. Neural precursors and neuronal production in the adult mammalian forebrain. Ann N Y Acad Sci 1997; 835:30-55.
7. Martens DJ, Tropepe V, van Der Kooy D. Separate proliferation kinetics of fibroblast growth factor-responsive and epidermal growth factor-responsive neural stem cells within the embryonic forebrain germinal zone. J Neurosci 2000; 20(3):1085-95.
8. Chiasson BJ, Tropepe V, Morshead CM et al. Adult mammalian forebrain ependymal and subependymal cells demonstrate proliferative potential, but only subependymal cells have neural stem cell characteristics. J Neurosci 1999; 19(11):4462-71.
9. Ray J, Peterson DA, Schinstine M et al. Proliferation, differentiation, and long-term culture of primary hippocampal neurons. Proc Natl Acad Sci USA 1993; 90(8):3602-6.
10. Palmer TD, Markakis EA, Willhoite AR et al. Fibroblast growth factor-2 activates a latent neurogenic program in neural stem cells from diverse regions of the adult CNS. J Neurosci 1999; 19(19):8487-97.
11. Gage FH. Mammalian neural stem cells. Science 2000; 287(5457):1433-8.
12. Palmer TD, Ray J, Gage FH. FGF-2-responsive neuronal progenitors reside in proliferative and quiescent regions of the adult rodent brain. Mol Cell Neurosci 1995; 6(5):474-86.
13. Kondo T, Raff M. Oligodendrocyte precursor cells reprogrammed to become multipotential CNS stem cells. Science 2000; 289(5485):1754-7.
14. Shihabuddin LS, Horner PJ, Ray J et al. Adult spinal cord stem cells generate neurons after transplantation in the adult dentate gyrus. J Neurosci 2000; 20(23):8727-35.
15. Tropepe V, Coles BL, Chiasson BJ et al. Retinal stem cells in the adult mammalian eye. Science 2000; 287(5460):2032-6.
16. Reh TA, Levine EM. Multipotential stem cells and progenitors in the vertebrate retina. J Neurobiol 1998; 36(2):206-20.
17. Bjornson CR, Rietze RL, Reynolds BA et al. Turning brain into blood: a hematopoietic fate adopted by adult neural stem cells in vivo. Science 1999; 283(5401):534-7.
18. Johansson CB, Momma S, Clarke DL et al. Identification of a neural stem cell in the adult mammalian central nervous system. Cell 1999; 96(1):25-34.

19. Morshead CM, Benveniste P, Iscove NN et al. Hematopoietic competence is a rare property of neural stem cells that may depend on genetic and epigenetic alterations. Nat Med 2002; 8(3):268-73.
20. Mezey E, Chandross KJ, Harta G et al. Turning blood into brain: cells bearing neuronal antigens generated in vivo from bone marrow. Science 2000; 290(5497):1779-82.
21. Brazelton TR, Rossi FM, Keshet GI et al. From marrow to brain: expression of neuronal phenotypes in adult mice. Science 2000; 290(5497):1775-9.
22. Priller J, Persons DA, Klett FF et al. Neogenesis of cerebellar Purkinje neurons from gene-marked bone marrow cells in vivo. J Cell Biol 2001; 155(5):733-8.
23. Anderson DJ, Gage FH, Weissman IL. Can stem cells cross lineage boundaries? Nat Med 2001; 7(4):393-5.
24. Anderson DJ. Stem cells and pattern formation in the nervous system: the possible versus the actual. Neuron 2001; 30(1):19-35.
25. Lois C, Garcia-Verdugo JM, Alvarez-Buylla A. Chain migration of neuronal precursors. Science 1996; 271(5251):978-81.
26. Luskin MB. Restricted proliferation and migration of postnatally generated neurons derived from the forebrain subventricular zone. Neuron 1993; 11(1):173-89.
27. Altman J, Das GD. Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. J Comp Neurol 1965; 124(3):319-35.
28. Kaplan MS, Hinds JW. Neurogenesis in the adult rat: electron microscopic analysis of light radioautographs. Science 1977; 197(4308):1092-4.
29. Cameron HA, McKay RD. Adult neurogenesis produces a large pool of new granule cells in the dentate gyrus. J Comp Neurol 2001; 435(4):406-17.
30. Kuhn HG, Dickinson-Anson H, Gage FH. Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. J Neurosci 1996; 16(6):2027-33.
31. Stanfield BB, Trice JE. Evidence that granule cells generated in the dentate gyrus of adult rats extend axonal projections. Exp Brain Res 1988; 72(2):399-406.
32. Markakis EA, Gage FH. Adult-generated neurons in the dentate gyrus send axonal projections to field CA3 and are surrounded by synaptic vesicles. J Comp Neurol 1999; 406(4):449-60.
33. Hastings NB, Gould E. Rapid extension of axons into the CA3 region by adult-generated granule cells. J Comp Neurol 1999; 413(1):146-54.
34. van Praag H, Schinder AF, Christie BR et al. Functional neurogenesis in the adult hippocampus. Nature 2002; 415(6875):1030-4.
35. Kempermann G. Regulation of adult hippocampal neurogenesis – implications for novel theories of major depression. Bipolar disorders 2002; 4:17-33.
36. Palmer TD, Takahashi J, Gage FH. The adult rat hippocampus contains primordial neural stem cells. Mol Cell Neurosci 1997; 8(6):389-404.
37. Reynolds BA, Weiss S. Clonal and population analyses demonstrate that an EGF-responsive mammalian embryonic CNS precursor is a stem cell. Dev Biol 1996; 175(1):1-13.
38. Ciccolini F, Svendsen CN. Fibroblast growth factor 2 (FGF-2) promotes acquisition of epidermal growth factor (EGF) responsiveness in mouse striatal precursor cells: identification of neural precursors responding to both EGF and FGF-2. J Neurosci 1998; 18(19):7869-80.
39. Caldwell MA, He X, Wilkie N et al. Growth factors regulate the survival and fate of cells derived from human neurospheres. Nat Biotechnol 2001; 19(5):475-9.
40. Temple S. CNS development: The obscure origins of adult stem cells. Curr Biol 1999;9(11):R397-9.
41. Ostenfeld T, Joly E, Tai YT et al. Regional specification of rodent and human neurospheres. Brain Res Dev Brain Res 2002; 134(1-2):43-55.
42. Hitoshi S, Tropepe V, Ekker M et al. Neural stem cell lineages are regionally specified, but not committed, within distinct compartments of the developing brain. Development 2002; 129(1):233-44.
43. Johe KK, Hazel TG, Muller T et al. Single factors direct the differentiation of stem cells from the fetal and adult central nervous system. Genes Dev 1996; 10(24):3129-40.
44. Bjorklund A, Lindvall O. Self-repair in the brain. Nature 2000; 405(6789):892-3, 895.
45. Horner PJ, Gage FH. Regenerating the damaged central nervous system. Nature 2000; 407(6807):963-70.

46. Reznikov K. [Incorporation of 3H-thymidine into glial cells of the parietal region and cells of the subependymal zone of two-week and adult mice under normal conditions and following brain injury]. Ontogenez 1975; 6(2):169-76.
47. Szele FG, Chesselet MF. Cortical lesions induce an increase in cell number and PSA-NCAM expression in the subventricular zone of adult rats. J Comp Neurol 1996; 368(3):439-54.
48. Tzeng SF, Wu JP. Responses of microglia and neural progenitors to mechanical brain injury. Neuroreport 1999; 10(11):2287-92.
49. Merzenich MM, Nelson RJ, Stryker MP et al. Somatosensory cortical map changes following digit amputation in adult monkeys. J Comp Neurol 1984; 224(4):591-605.
50. Kaas JH, Merzenich MM, Killackey HP. The reorganization of somatosensory cortex following peripheral nerve damage in adult and developing mammals. Annu Rev Neurosci 1983; 6:325-56.
51. Wall PD, Egger MD. Formation of new connexions in adult rat brains after partial deafferentation. Nature 1971; 232(5312):542-5.
52. Taub E, Uswatte G, Elbert T. New treatments in neurorehabilitation founded on basic research. Nat Rev Neurosci 2002; 3:228-236.
53. Magavi SS, Leavitt BR, Macklis JD. Induction of neurogenesis in the neocortex of adult mice. Nature 2000; 405(6789):951-5.
54. Weiss S, Dunne C, Hewson J et al. Multipotent CNS stem cells are present in the adult mammalian spinal cord and ventricular neuroaxis. J Neurosci 1996; 16(23):7599-609.
55. Shihabuddin LS, Ray J, Gage FH. FGF-2 is sufficient to isolate progenitors found in the adult mammalian spinal cord. Exp Neurol 1997; 148(2):577-86.
56. Yamamoto S, Yamamoto N, Kitamura T et al. Proliferation of parenchymal neural progenitors in response to injury in the adult rat spinal cord. Exp Neurol 2001; 172(1):115-27.
57. Horner PJ, Power AE, Kempermann G et al. Proliferation and differentiation of progenitor cells throughout the intact adult rat spinal cord. J Neurosci 2000; 20(6):2218-28.
58. Namiki J, Tator CH. Cell proliferation and nestin expression in the ependyma of the adult rat spinal cord after injury. J Neuropathol Exp Neurol 1999; 58(5):489-98.
59. McTigue DM, Horner PJ, Stokes BT et al. Neurotrophin-3 and brain-derived neurotrophic factor induce oligodendrocyte proliferation and myelination of regenerating axons in the contused adult rat spinal cord. J Neurosci 1998; 18(14):5354-65.
60. Weidner N, Ner A, Salimi N et al. Spontaneous corticospinal axonal plasticity and functional recovery after adult central nervous system injury. Proc Natl Acad Sci USA 2001; 98(6):3513-8.
61. Rubio F, Kokaia Z, Arco A et al. BDNF gene transfer to the mammalian brain using CNS-derived neural precursors. Gene Ther 1999; 6(11):1851-66.
62. Grill R, Murai K, Blesch A et al. Cellular delivery of neurotrophin-3 promotes corticospinal axonal growth and partial functional recovery after spinal cord injury. J Neurosci 1997; 17(14):5560-72.
63. Liu Y, Kim D, Himes BT et al. Transplants of fibroblasts genetically modified to express BDNF promote regeneration of adult rat rubrospinal axons and recovery of forelimb function. J Neurosci 1999; 19(11):4370-87.
64. Himes BT, Liu Y, Solowska JM et al. Transplants of cells genetically modified to express neurotrophin-3 rescue axotomized Clarke's nucleus neurons after spinal cord hemisection in adult rats. J Neurosci Res 2001; 65(6):549-64.
65. Kim DH, Gutin PH, Noble LJ et al. Treatment with genetically engineered fibroblasts producing NGF or BDNF can accelerate recovery from traumatic spinal cord injury in the adult rat. Neuroreport 1996; 7(13):2221-5.
66. Teng YD, Lavik EB, Qu X et al. Functional recovery following traumatic spinal cord injury mediated by a unique polymer scaffold seeded with neural stem cells. Proc Natl Acad Sci USA 2002; 99(5):3024-3029.
67. Benowitz LI, Goldberg DE, Madsen JR et al. Inosine stimulates extensive axon collateral growth in the rat corticospinal tract after injury. Proc Natl Acad Sci USA 1999; 96(23):13486-90.
68. Whittemore SR. Neuronal replacement strategies for spinal cord injury. J Neurotrauma 1999; 16(8):667-73.
69. Shin JJ, Fricker-Gates RA, Perez FA et al. Transplanted neuroblasts differentiate appropriately into projection neurons with correct neurotransmitter and receptor phenotype in neocortex undergoing targeted projection neuron degeneration. J Neurosci 2000; 20(19):7404-16.

70. McDonald JW, Liu XZ, Qu Y et al. Transplanted embryonic stem cells survive, differentiate and promote recovery in injured rat spinal cord. Nat Med 1999; 5(12):1410-2.
71. Akiyama Y, Honmou O, Kato T et al. Transplantation of clonal neural precursor cells derived from adult human brain establishes functional peripheral myelin in the rat spinal cord. Exp Neurol 2001; 167(1):27-39.
72. Groves AK, Barnett SC, Franklin RJ et al. Repair of demyelinated lesions by transplantation of purified O-2A progenitor cells. Nature 1993; 362(6419):453-5.
73. Reier PJ. The Neurobiology of Central Nervous System Trauma. New York: Oxford University Press, 1994.
74. Armstrong RJ, Barker RA. Neurodegeneration: a failure of neuroregeneration? Lancet 2001; 358(9288):1174-6.
75. Shingo T, Sorokan ST, Shimazaki T et al. Erythropoietin regulates the in vitro and in vivo production of neuronal progenitors by mammalian forebrain neural stem cells. J Neurosci 2001; 21(24):9733-43.
76. Pencea V, Bingaman KD, Wiegand SJ et al. Infusion of brain-derived neurotrophic factor into the lateral ventricle of the adult rat leads to new neurons in the parenchyma of the striatum, septum, thalamus, and hypothalamus. J Neurosci 2001; 21(17):6706-17.
77. Aberg MA, Aberg ND, Hedbacker H et al. Peripheral infusion of IGF-I selectively induces neurogenesis in the adult rat hippocampus. J Neurosci 2000; 20(8):2896-903.
78. Wagner JP, Black IB, DiCicco-Bloom E. Stimulation of neonatal and adult brain neurogenesis by subcutaneous injection of basic fibroblast growth factor. J Neurosci 1999; 19(14):6006-16.
79. Kuhn HG, Winkler J, Kempermann G et al. Epidermal growth factor and fibroblast growth factor-2 have different effects on neural progenitors in the adult rat brain. J Neurosci 1997; 17(15):5820-9.
80. Fallon J, Reid S, Kinyamu R et al. In vivo induction of massive proliferation, directed migration, and differentiation of neural cells in the adult mammalian brain. Proc Natl Acad Sci USA 2000; 97(26):14686-91.
81. Bjorklund LM, Sanchez-Pernaute R, Chung S et al. Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model. Proc Natl Acad Sci USA 2002; 99(4):2344-9.
82. Bjorklund A, Lindvall O. Cell replacement therapies for central nervous system disorders. Nat Neurosci 2000; 3(6):537-44.
83. Freed CR, Greene PE, Breeze RE et al. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. N Engl J Med 2001; 344(10):710-9.
84. Wenning GK, Odin P, Morrish P et al. Short- and long-term survival and function of unilateral intrastriatal dopaminergic grafts in Parkinson's disease. Ann Neurol 1997; 42(1):95-107.
85. Lindvall O, Sawle G, Widner H et al. Evidence for long-term survival and function of dopaminergic grafts in progressive Parkinson's disease. Ann Neurol 1994; 35(2):172-80.
86. Lindvall O, Brundin P, Widner H et al. Grafts of fetal dopamine neurons survive and improve motor function in Parkinson's disease. Science 1990; 247(4942):574-7.
87. Dobrossy MD, Dunnett SB. The influence of environment and experience on neural grafts. Nat Rev Neurosci 2001; 2(12):871-9.
88. Piccini P, Lindvall O, Bjorklund A et al. Delayed recovery of movement-related cortical function in Parkinson's disease after striatal dopaminergic grafts. Ann Neurol 2000; 48(5):689-95.
89. Hagell P, Schrag A, Piccini P et al. Sequential bilateral transplantation in Parkinson's disease: effects of the second graft. Brain 1999; 122(Pt 6):1121-32.
90. Mazurova Y. New therapeutic approaches for the treatment of Huntington's disease. Acta Medica (Hradec Kralove) 2001; 44(4):119-23.
91. Dunnett SB, Nathwani F, Bjorklund A. The integration and function of striatal grafts. Prog Brain Res 2000; 127:345-80.
92. Kendall AL, Rayment FD, Torres EM et al. Functional integration of striatal allografts in a primate model of Huntington's disease. Nat Med 1998; 4(6):727-9.
93. Palfi S, Conde F, Riche D et al. Fetal striatal allografts reverse cognitive deficits in a primate model of Huntington disease. Nat Med 1998; 4(8):963-6.

94. Bachoud-Levi AC, Remy P, Nguyen JP et al. Motor and cognitive improvements in patients with Huntington's disease after neural transplantation. Lancet 2000; 356(9246):1975-9.
95. Svendsen CN, Smith AG. New prospects for human stem-cell therapy in the nervous system. Trends Neurosci 1999; 22(8):357-64.
96. Dietrich J, Easterday MC. Developing concepts in neural stem cells. Trends Neurosci 2002; 25(3):129-31.
97. Dumas TC, Sapolsky RM. Gene therapy against neurological insults: sparing neurons versus sparing function. Trends Neurosci 2001; 24(12):695-700.
98. Zurn AD, Widmer HR, Aebischer P. Sustained delivery of GDNF: towards a treatment for Parkinson's disease. Brain Res Brain Res Rev 2001; 36(2-3):222-9.
99. Hoffer B, Olson L. Treatment strategies for neurodegenerative diseases based on trophic factors and cell trasnplantation techniques. In: Mizuno Y YM, Calne DB, Horowski R et al, eds. Advances in Research on Neurodegeneration. Wien, New York: Springer Verlag, 1997:1-10.
100. Silani V, Braga M, Cardin V et al. The pathogenesis of ALS: implications for treatment strategies. Neurol Neurochir Pol 2001; 35(1 Suppl):25-39.
101. Martin JB. Gene therapy and pharmacological treatment of inherited neurological disorders. Trends Biotechnol 1995; 13(1):28-35.
102. Fisher LJ. Neural precursor cells: applications for the study and repair of the central nervous system. Neurobiol Dis 1997; 4(1):1-22.
103. Reya T, Morrison SJ, Clarke MF et al. Stem cells, cancer, and cancer stem cells. Nature 2001; 414(6859):105-11.
104. Moe PJ, Holen A. High-dose methotrexate in childhood all. Pediatr Hematol Oncol 2000; 17(8):615-22.
105. Rubnitz JE. Molecular diagnostics in the treatment of childhood acute lymphoblastic leukemia. J Biol Regul Homeost Agents 2000; 14(3):182-6.
106. Alizadeh AA, Staudt LM. Genomic-scale gene expression profiling of normal and malignant immune cells. Curr Opin Immunol 2000; 12(2):219-25.
107. Knuutila S, Teerenhovi L, Larramendy ML et al. Cell lineage involvement of recurrent chromosomal abnormalities in hematologic neoplasms. Genes Chromosomes Cancer 1994; 10(2):95-102.
108. Nilsson L, Astrand-Grundstrom I, Arvidsson I et al. Isolation and characterization of hematopoietic progenitor/stem cells in 5q-deleted myelodysplastic syndromes: evidence for involvement at the hematopoietic stem cell level. Blood 2000; 96(6):2012-21.
109. Russell NH. Biology of acute leukaemia. Lancet 1997; 349(9045):118-22.
110. McKay R. Stem cells in the central nervous system. Science 1997; 276:66-71.
111. Temple S, Qian X. Vertebrate neural progenitor cells: subtypes and regulation. Current Opinion in Neurobiology 1996; 6:11-17.
112. Reynolds BA, Tetzlaff W, Weiss S. A Mulitpotent EGF-Responsive Striatal Embryonic Progenitor Cell Produces Neurons and Astrocytes. J Neurosci 1992; 12(11):4565-4574.
113. Vescovi A, Gritti A, Galli R et al. Isolation and intracerebral grafting of nontransformed multipotential embryonic human CNS stem cells. J Neurotrauma 1999; 16:689-693.
114. Mayer-Proschel M, Kalyani AJ, Mujtaba T et al. Isolation of lineage-restricted neuronal precursors from multipotent neuroepithelial stem cells. Neuron 1997; 19(4):773-85.
115. Rao MS, Noble M, Mayer-Proschel M. A tripotential glial precursor cell is present in the developing spinal cord. Proc Natl Acad Sci USA 1998; 95(7):3996-4001.
116. Rao MS, Mayer-Proschel M. Glial-restricted precursors are derived from multipotent neuroepithelial stem cells. Dev Biol 1997; 188(1):48-63.
117. Kalyani A, Piper D, Mujitaba T et al. E-NCAM immunoreactive neuronal precursor cells differentiate into multiple neurotransmitter phenotypes. J Neurosci 1998; 18:7856-7868.
118. Raff MC, Miller RH, Noble M. A glial progenitor cell that develops in vitro into an astrocyte or an oligodendrocyte depending on culture medium. Nature 1983; 303(5916):390-6.
119. Noble M, Murray K. Purified astrocytes promote the in vitro division of a bipotential glial progenitor cell. Embo J 1984; 3(10):2243-7.
120. Fok-Seang J, Miller HR. Astrocyte precursors in neonatal rat spinal cord cultures. J Neurosci 1992; 12:2751-2764.

121. Fok-Seang J, Miller RH. Distribution and differentiation of A2B5+ glial precursors in the developing rat spinal cord. J Neurosci Res 1994; 37:219-235.
122. Seidman K, Teng A, Rosenkopf R et al. Isolation, cloning and characterization of a putative type-1 astrocyte cell line. Brain Res 1997; 753:18-26.
123. Mi H, Barres BA. Purification and characterization of astrocyte precursor cells in the developing rat optic nerve. J Neurosci 1999; 19:1049-1061.
124. Grinspan JB, Stern JL, Pustilnik SM et al. Cerebral white matter contains PDGF-responsive precursors to O-2A cells. J Neuroscience 1990; 10:1866-1873.
125. Palmer TD, Schwartz PH, Taupin P et al. Cell culture. Progenitor cells from human brain after death. Nature 2001; 411(6833):42-3.
126. Laywell ED, Rakic P, Kukekov VG et al. Identification of a multipotent astrocytic stem cell in the immature and adult mouse brain. Proc Natl Acad Sci USA 2000; 97(25):13883-8.
127. Roy NS, Wang S, Jiang L et al. In vitro neurogenesis by progenitor cells isolated from the adult human hippocampus. Nat Med 2000; 6(3):271-7.
128. Arsenijevic Y, Villemure JG, Brunet JF et al. Isolation of multipotent neural precursors residing in the cortex of the adult human brain. Exp Neurol 2001; 170(1):48-62.
129. Piper DR, Mujtaba T, Keyoung H et al. Identification and characterization of neuronal precursors and their progeny from human fetal tissue. J Neurosci Res 2001; 66(3):356-68.
130. Reubinoff BE, Itsykson P, Turetsky T et al. Neural progenitors from human embryonic stem cells. Nat Biotechnol 2001; 19(12):1134-40.
131. Zhang SC, Wernig M, Duncan ID et al. In vitro differentiation of transplantable neural precursors from human embryonic stem cells. Nat Biotechnol 2001; 19(12):1129-33.
132. Shih CC, Weng Y, Mamelak A et al. Identification of a candidate human neurohematopoietic stem-cell population. Blood 2001; 98(8):2412-22.
133. Scheffler B, Horn M, Blumcke I et al. Marrow-mindedness: a perspective on neuropoiesis. Trends Neurosci 1999; 22(8):348-57.
134. Parati EA, Bez A, Ponti D et al. Human neural stem cells express extra-neural markers. Brain Res 2002; 925(2):213-21.
135. Price J, Williams BP. Neural stem cells. Curr Opin Neurobiol 2001; 11(5):564-7.
136. Weissman IL, Anderson DJ, Gage F. Stem and progenitor cells: origins, phenotypes, lineage commitments, and transdifferentiations. Annu Rev Cell Dev Biol 2001; 17:387-403.
137. Krause DS, Theise ND, Collector MI et al. Multi-organ, multi-lineage engraftment by a single bone marrow-derived stem cell. Cell 2001; 105(3):369-77.
138. Toma JG, Akhavan M, Fernandes KJ et al. Isolation of multipotent adult stem cells from the dermis of mammalian skin. Nat Cell Biol 2001; 3(9):778-84.
139. Noble M, Dietrich J. Intersections between neurobiology and oncology: tumor origin, treatment and repair of treatment-associated damage. Trends Neurosci 2002; 25(2):103-7.
140. Noble M. The oligodendrocyte-type-2 astrocyte lineage: in vitro and in vivo studies on development, tissue repair and neoplasia. In: Gage FH, Christen Y., eds. Isolation, characterization and utilization of CNS stem cells. Berlin, Heidelberg: Springer, 1997: 101-128.
141. Linskey ME. Developmental glial biology: the key to understanding glial tumors. Clin Neurosurg 2000; 47:46-71.
142. Linskey ME. Glial ontogeny and glial neoplasia: the search for closure. J Neurooncol 1997; 34(1):5-22.
143. Barnett SC, Robertson L, Graham D et al. Oligodendrocyte-type-2 astrocyte (O-2A) progenitor cells transformed with c-myc and H-ras form high-grade glioma after stereotactic injection into the rat brain. Carcinogenesis 1998; 19(9):1529-37.
144. Holland EC, Celestino J, Dai C et al. Combined activation of Ras and Akt in neural progenitors induces glioblastoma formation in mice. Nat Genet 2000; 25(1):55-7.
145. Seyfried TN. Perspectives on brain tumor formation involving macrophages, glia, and neural stem cells. Perspect Biol Med 2001; 44(2):263-82.
146. Noble M, Gutowski N, Bevan K et al. From rodent glial precursor cell to human glial neoplasia in the oligodendrocyte-type-2 astrocyte lineage. Glia 1995; 15(3):222-30.
147. Kashima T, Tiu SN, Merrill JE et al. Expression of oligodendrocyte-associated genes in cell lines derived from human gliomas and neuroblastomas. Cancer Res 1993; 53(1):170-5.

148. Seyfried TN, Yu RK. Ganglioside GD3: structure, cellular distribution, and possible function. Mol Cell Biochem 1985; 68(1):3-10.
149. Tohyama T, Lee VM, Rorke LB et al. Nestin expression in embryonic human neuroepithelium and in human neuroepithelial tumor cells. Lab Invest 1992; 66(3):303-13.
150. Li J, Pearl DK, Pfeiffer SE et al. Patterns of reactivity with anti-glycolipid antibodies in human primary brain tumors. J Neurosci Res 1994; 39(2):148-58.
151. Yang HY, Lieska N, Shao D et al. Proteins of the intermediate filament cytoskeleton as markers for astrocytes and human astrocytomas. Mol Chem Neuropathol 1994; 21(2-3):155-76.
152. Shoshan Y, Nishiyama A, Chang A et al. Expression of oligodendrocyte progenitor cell antigens by gliomas: implications for the histogenesis of brain tumors. Proc Natl Acad Sci USA 1999; 96(18):10361-6.
153. Lu QR, Park JK, Noll E et al. Oligodendrocyte lineage genes (OLIG) as molecular markers for human glial brain tumors. Proc Natl Acad Sci USA 2001; 98(19):10851-6.
154. Marie Y, Sanson M, Mokhtari K et al. OLIG2 as a specific marker of oligodendroglial tumour cells. Lancet 2001; 358(9278):298-300.
155. Pomeroy SL, Tamayo P, Gaasenbeek M et al. Prediction of central nervous system embryonal tumour outcome based on gene expression. Nature 2002; 415(6870):436-42.
156. Van't Veer LJ, De Jong D. The microarray way to tailored cancer treatment. Nat Med 2002; 8(1):13-4.
157. Armstrong SA, Staunton JE, Silverman LB et al. MLL translocations specify a distinct gene expression profile that distinguishes a unique leukemia. Nat Genet 2002; 30(1):41-7.
158. Benedetti S, Pirola B, Pollo B et al. Gene therapy of experimental brain tumors using neural progenitor cells. Nat Med 2000; 6(4):447-50.
159. Aboody KS, Brown A, Rainov NG et al. From the cover: neural stem cells display extensive tropism for pathology in adult brain: evidence from intracranial gliomas. Proc Natl Acad Sci USA 2000; 97(23):12846-51.
160. Berens ME, Giese A. "...those left behind." Biology and oncology of invasive glioma cells. Neoplasia 1999; 1(3):208-19.
161. Prados MD, Levin V. Biology and treatment of malignant glioma. Semin Oncol 2000; 27(3 Suppl 6):1-10.
162. Noble M. Can neural stem cells be used to track down and destroy migratory brain tumor cells while also providing a means of repairing tumor-associated damage? Proc Natl Acad Sci USA 2000; 97(23):12393-5.
163. Noble M. Can neural stem cells be used as therapeutic vehicles in the treatment of brain tumors? Nat Med 2000; 6(4):369-70.
164. Lewin M, Carlesso N, Tung CH et al. Tat peptide-derivatized magnetic nanoparticles allow in vivo tracking and recovery of progenitor cells. Nat Biotechnol 2000; 18(4):410-4.
165. Franklin RJ, Blaschuk KL, Bearchell MC et al. Magnetic resonance imaging of transplanted oligodendrocyte precursors in the rat brain. Neuroreport 1999; 10(18):3961-5.
166. Bulte JW, Zhang S, van Gelderen P et al. Neurotransplantation of magnetically labeled oligodendrocyte progenitors: magnetic resonance tracking of cell migration and myelination. Proc Natl Acad Sci USA 1999; 96(26):15256-61.
167. Keime-Guibert F, Napolitano M, Delattre JY. Neurological complications of radiotherapy and chemotherapy. J Neurol. 1998; 245:695-708.
168. Grill J, Renaux VK, Bulteau C et al. Long-term intellectual outcome in children with posterior fossa tumors according to radiation doses and volumes. Int. J Radiat Oncol Biol Phys 1999; 45:137-145.
169. Schlegel U, Pels H, Oehring R et al. Neurologic sequelae of treatment of primary CNS lymphomas. J Neurooncol 1999; 43:277-286.
170. Cetingul N, Aydinok Y, Kantar M et al. Neuropsychologic sequelae in the long-term survivors of childhood acute lymphoblastic leukemia. Pediatr. Hematol. Oncol 1999; 16:213-220.
171. Stylopoulos LA, George AE, de Leon MJ et al. Longitudinal CT study of parenchymal brain changes in glioma survivors. AJNR Am J Neuroradiol 1988; 9(3):517-22.
172. Riva D, Giorgi C. The neurodevelopmental price of survival in children with malignant brain tumours. Childs Nerv Syst 2000; 16(10-11):751-4.

173. Waber DP, Tarbell NJ. Toxicity of CNS prophylaxis for childhood leukemia. Oncology (Huntingt) 1997; 11(2):259-64; discussion 264-5.
174. Glauser TA, Packer RJ. Cognitive deficits in long-term survivors of childhood brain tumors. Childs Nerv Syst 1991; 7(1):2-12.
175. Appleton RE, Farrell K, Zaide J et al. Decline in head growth and cognitive impairment in survivors of acute lymphoblastic leukaemia. Arch Dis Child 1990; 65(5):530-4.
176. Peissner W, Kocher M, Treuer H et al. Ionizing radiation-induced apoptosis of proliferating stem cells in the dentate gyrus of the adult rat hippocampus. Brain Res Mol. Brain Res 1999; 71:61-68.
177. Tada E, Parent JM, Lowenstein DH et al. X-irradiation causes a prolonged reduction in cell proliferation in the dentate gyrus of adult rats. Neuroscience 2000; 99(1):33-41.
178. Bellinzona M, Gobbel GT, Shinohara C et al. Apoptosis is induced in the subependyma of young adult rats by ionizing irradiation. Neurosci Lett 1996; 208:163-166.
179. Li YQ, Wong CS. Apoptosis and its relationship with cell proliferation in the irradiated rat spinal cord. Int. J Radiat Biol 1998; 74:405-417.
180. Vigliani MC, Duyckaerts C, Hauw JJ et al. Dementia following treatment of brain tumors with radiotherapy administered alone or in combination with nitrosourea-based chemotherapy: a clinical and pathological study. J Neurooncol 1999; 41:137-149.
181. Hopewell JW, van der Kogel AJ. Pathophysiological mechanisms leading to the development of late radiation-induced damage to the central nervous system. Front Radiat Ther Oncol 1999; 33:265-75.
182. Nutt CL, Noble M, Chambers AF et al. Differential expression of drug resistance genes and chemosensitivity in glial cell lineages correlate with differential response of oligodendrogliomas and astrocytomas to chemotherapy. Cancer Res 2000; 60(17):4812-8.
183. Lassmann H. Classification of demyelinating diseases at the interface between etiology and pathogenesis. Curr Opin Neurol 2001; 14(3):253-8.
184. McTigue DM, Popovich PG, Jakeman LB et al. Strategies for spinal cord injury repair. Prog Brain Res 2000; 128:3-8.
185. Beattie MS, Farooqui AA, Bresnahan JC. Review of current evidence for apoptosis after spinal cord injury. J Neurotrauma 2000; 17(10):915-25.
186. Kakulas BA. A review of the neuropathology of human spinal cord injury with emphasis on special features. J Spinal Cord Med 1999; 22(2):119-24.
187. Prineas JW, MacDonald WI. Demyelinating diseases. In: Graham DI, Lantos PL, eds. Greenfield's neuropathology. 6th ed. London: Arnold, 1997: 813-889.
188. Lassmann H, Bruck W, Lucchinetti C. Heterogeneity of multiple sclerosis pathogenesis: implications for diagnosis and therapy. Trends Mol Med 2001; 7(3):115-21.
189. Kornek B, Storch MK, Weissert R et al. Multiple sclerosis and chronic autoimmune encephalomyelitis: a comparative quantitative study of axonal injury in active, inactive, and remyelinated lesions. Am J Pathol 2000; 157(1):267-76.
190. Bitsch A, Schuchardt J, Bunkowski S et al. Acute axonal injury in multiple sclerosis. Correlation with demyelination and inflammation. Brain 2000; 123(Pt 6):1174-83.
191. Ferguson B, Matyszak MK, Esiri MM et al. Axonal damage in acute multiple sclerosis lesions. Brain 1997; 120(Pt 3):393-9.
192. Duncan ID, Grever WE, Zhang SC. Repair of myelin disease: strategies and progress in animal models. Mol Med Today 1997; 3(12):554-61.
193. Blakemore WF, Franklin RJ. Transplantation options for therapeutic central nervous system remyelination. Cell Transplant 2000; 9(2):289-94.
194. Blakemore WF, Olby NJ, Franklin RJ. The use of transplanted glial cells to reconstruct glial environments in the CNS. Brain Pathol 1995; 5(4):443-50.
195. Brustle O, McKay RD. Neuronal progenitors as tools for cell replacement in the nervous system. Curr Opin Neurobiol 1996; 6(5):688-95.
196. Cattaneo E, McKay R. Identifying and manipulating neuronal stem cells. Trends Neurosci 1991; 14(8):338-40.
197. Duncan ID. Glial cell transplantation and remyelination of the central nervous system. Neuropathol Appl Neurobiol 1996; 22(2):87-100.

198. Brustle O, Jones KN, Learish RD et al. Embryonic stem cell-derived glial precursors: a source of myelinating transplants. Science 1999; 285(5428):754-6.
199. Rao MS, Mayer-Proschel M. Precursor cells for transplantation. Prog Brain Res 2000; 128:273-92.
200. Prineas JW, Barnard RO, Kwon EE et al. Multiple sclerosis: remyelination of nascent lesions. Ann Neurol 1993; 33(2):137-51.
201. Prineas JW, Kwon EE, Goldenberg PZ et al. Multiple sclerosis. Oligodendrocyte proliferation and differentiation in fresh lesions. Lab Invest 1989; 61(5):489-503.
202. Ludwin SK. Remyelination in demyelinating diseases of the central nervous system. Crit Rev Neurobiol 1987; 3(1):1-28.
203. Wolswijk G. Chronic stage multiple sclerosis lesions contain a relatively quiescent population of oligodendrocyte precursor cells. J Neurosci 1998; 18(2):601-9.
204. Blakemore WF, Franklin, R.J.M., Noble, M. Glial cell transplantation and the repair of demyelinating lesions. In: Jessen KR, Richardson WD, eds. Glial cell development: Basic principles and relevance. Oxford: BIOS Scientific Publishers Ltd., 1996: 209-220.
205. Allen IV, Kirk, J. Demyelinating diseases. In: Adams JH, Duchen LW, eds. Greenfield's neuropathology. New York: Oxford University Press, 1992: 447-520.
206. Raine CS. Demyelinating Diseases. In: Davis RL, Robertson DM, eds. Textbook of Neuropathology. Baltimore: Williams and Wilkins, 1991: 535-620.
207. Nait-Oumesmar B, Lachapelle F, Decker L et al. Do central nervous system axons remyelinate? Pathol Biol (Paris) 2000; 48(1):70-9.
208. Decker L, Picard N, Lachapelle F et al. Neural precursors and demyelinating diseases. Prog Brain Res 2001; 132:175-84.
209. Nait-Oumesmar B, Decker L, Lachapelle F et al. Progenitor cells of the adult mouse subventricular zone proliferate, migrate and differentiate into oligodendrocytes after demyelination. Eur J Neurosci 1999; 11(12):4357-66.
210. Norton WT. Do oligodendrocytes divide? Neurochem Res 1996; 21(4):495-503.
211. Carroll WM, Jennings AR, Ironside LJ. Identification of the adult resting progenitor cell by autoradiographic tracking of oligodendrocyte precursors in experimental CNS demyelination. Brain 1998; 121(Pt 2):293-302.
212. Keirstead HS, Blakemore WF. Identification of post-mitotic oligodendrocytes incapable of remyelination within the demyelinated adult spinal cord. J Neuropathol Exp Neurol 1997; 56(11):1191-201.
213. Ffrench-Constant C, Raff MC. Proliferating bipotential glial progenitor cells in adult rat optic nerve. Nature 1986; 319(6053):499-502.
214. Wolswijk G, Noble M. Identification of an adult-specific glial progenitor cell. Development 1989; 105(2):387-400.
215. Gensert JM, Goldman JE. In vivo characterization of endogenous proliferating cells in adult rat subcortical white matter. Glia 1996; 17(1):39-51.
216. Bergles DE, Roberts JD, Somogyi P et al. Glutamatergic synapses on oligodendrocyte precursor cells in the hippocampus. Nature 2000; 405(6783):187-91.
217. Butt AM, Duncan A, Hornby MF et al. Cells expressing the NG2 antigen contact nodes of Ranvier in adult CNS white matter. Glia 1999; 26(1):84-91.
218. Levine JM, Reynolds R, Fawcett JW. The oligodendrocyte precursor cell in health and disease. Trends Neurosci 2001; 24(1):39-47.
219. Dou CL, Levine JM. Inhibition of neurite growth by the NG2 chondroitin sulfate proteoglycan. J Neurosci 1994; 14(12):7616-28.
220. Levine JM, Reynolds R. Activation and proliferation of endogenous oligodendrocyte precursor cells during ethidium bromide-induced demyelination. Exp Neurol 1999; 160(2):333-47.
221. Gogate N, Verma L, Zhou JM et al. Plasticity in the adult human oligodendrocyte lineage. J Neurosci 1994; 14(8):4571-87.
222. Armstrong RC, Dorn HH, Kufta CV et al. Pre-oligodendrocytes from adult human CNS. J Neurosci 1992; 12(4):1538-47.
223. Scolding NJ, Rayner PJ, Sussman J et al. A proliferative adult human oligodendrocyte progenitor. Neuroreport 1995; 6(3):441-5.

224. Roy NS, Wang S, Harrison-Restelli C et al. Identification, isolation, and promoter-defined separation of mitotic oligodendrocyte progenitor cells from the adult human subcortical white matter. J Neurosci 1999; 19(22):9986-95.
225. McCarthy GF, Leblond CP. Radioautographic evidence for slow astrocyte turnover and modest oligodendrocyte production in the corpus callosum of adult mice infused with 3H-thymidine. J Comp Neurol 1988; 271(4):589-603.
226. Redwine JM, Armstrong RC. In vivo proliferation of oligodendrocyte progenitors expressing PDGFalphaR during early remyelination. J Neurobiol 1998; 37(3):413-28.
227. Maeda Y, Solanky M, Menonna J et al. Platelet-derived growth factor-alpha receptor-positive oligodendroglia are frequent in multiple sclerosis lesions. Ann Neurol 2001; 49(6):776-85.
228. Scolding N, Franklin R, Stevens S et al. Oligodendrocyte progenitors are present in the normal adult human CNS and in the lesions of multiple sclerosis. Brain 1998; 121(Pt 12):2221-8.
229. Gensert JM, Goldman JE. Endogenous progenitors remyelinate demyelinated axons in the adult CNS. Neuron 1997; 19(1):197-203.
230. O'Leary MT, Blakemore WF. Oligodendrocyte precursors survive poorly and do not migrate following transplantation into the normal adult central nervous system. J Neurosci Res 1997; 48(2):159-67.
231. Franklin RJ, Bayley SA, Blakemore WF. Transplanted CG4 cells (an oligodendrocyte progenitor cell line) survive, migrate, and contribute to repair of areas of demyelination in X-irradiated and damaged spinal cord but not in normal spinal cord. Exp Neurol 1996; 137(2):263-76.
232. Dubois-Dalcq M, Murray K. Why are growth factors important in oligodendrocyte physiology? Pathol Biol (Paris) 2000; 48(1):80-6.
233. Hohlfeld R, Kerschensteiner M, Stadelmann C et al. The neuroprotective effect of inflammation: implications for the therapy of multiple sclerosis. J Neuroimmunol 2000; 107(2):161-6.
234. Molina-Holgado E, Vela JM, Arevalo-Martin A et al. LPS/IFN-gamma cytotoxicity in oligodendroglial cells: role of nitric oxide and protection by the anti-inflammatory cytokine IL-10. Eur J Neurosci 2001; 13(3):493-502.
235. Kil K, Zang YC, Yang D et al. T cell responses to myelin basic protein in patients with spinal cord injury and multiple sclerosis. J Neuroimmunol 1999; 98(2):201-7.
236. Warrington AE, Asakura K, Bieber AJ et al. Human monoclonal antibodies reactive to oligodendrocytes promote remyelination in a model of multiple sclerosis. Proc Natl Acad Sci USA 2000; 97(12):6820-5.
237. Browne TR, Holmes GL. Epilepsy. N Engl J Med 2001; 344(15):1145-51.
238. Stefan H. Pathophysiology of human epilepsy: imaging and physiologic studies. Curr Opin Neurol 2000; 13(2):177-81.
239. Hosford DA. Models of primary generalized epilepsy. Curr Opin Neurol 1995; 8(2):121-5.
240. Brodie MJ, French JA. Management of epilepsy in adolescents and adults. Lancet 2000; 356(9226):323-9.
241. Kalynchuk LE. Long-term amygdala kindling in rats as a model for the study of interictal emotionality in temporal lobe epilepsy. Neurosci Biobehav Rev 2000; 24(7):691-704.
242. Sutula TP. Experimental models of temporal lobe epilepsy: new insights from the study of kindling and synaptic reorganization. Epilepsia 1990; 31(Suppl 3):S45-54.
243. Meldrum BS, Akbar MT, Chapman AG. Glutamate receptors and transporters in genetic and acquired models of epilepsy. Epilepsy Res 1999; 36(2-3):189-204.
244. Kupferberg H. Animal models used in the screening of antiepileptic drugs. Epilepsia 2001; 42(Suppl 4):7-12.
245. Fisher RS. Animal models of the epilepsies. Brain Res Brain Res Rev 1989; 14(3):245-78.
246. Golarai G, Greenwood AC, Feeney DM et al. Physiological and structural evidence for hippocampal involvement in persistent seizure susceptibility after traumatic brain injury. J Neurosci 2001; 21(21):8523-37.
247. Whitaker WR, Faull RL, Dragunow M et al. Changes in the mRNAs encoding voltage-gated sodium channel types II and III in human epileptic hippocampus. Neuroscience 2001; 106(2):275-85.
248. Hendriksen H, Datson NA, Ghijsen WE et al. Altered hippocampal gene expression prior to the onset of spontaneous seizures in the rat post-status epilepticus model. Eur J Neurosci 2001; 14(9):1475-84.

249. Hughes PE, Alexi T, Walton M et al. Activity and injury-dependent expression of inducible transcription factors, growth factors and apoptosis-related genes within the central nervous system. Prog Neurobiol 1999; 57(4):421-50.
250. Osawa M, Uemura S, Kimura H et al. Amygdala kindling develops without mossy fiber sprouting and hippocampal neuronal degeneration in rats. Psychiatry Clin Neurosci 2001; 55(6):549-57.
251. Zhang LX, Smith MA, Li XL et al. Apoptosis of hippocampal neurons after amygdala kindled seizures. Brain Res Mol Brain Res 1998; 55(2):198-208.
252. Thompson K, Holm AM, Schousboe A et al. Hippocampal stimulation produces neuronal death in the immature brain. Neuroscience 1998; 82(2):337-48.
253. Sloviter RS, Dean E, Sollas AL et al. Apoptosis and necrosis induced in different hippocampal neuron populations by repetitive perforant path stimulation in the rat. J Comp Neurol 1996; 366(3):516-33.
254. Harding B, Thom M. Bilateral hippocampal granule cell dispersion: autopsy study of 3 infants. Neuropathol Appl Neurobiol 2001; 27(3):245-51.
255. Briellmann RS, Newton MR, Wellard RM et al. Hippocampal sclerosis following brief generalized seizures in adulthood. Neurology 2001; 57(2):315-7.
256. Fisher PD, Sperber EF, Moshe SL. Hippocampal sclerosis revisited. Brain Dev 1998; 20(8):563-73.
257. Liu Z, Mikati M, Holmes GL. Mesial temporal sclerosis: pathogenesis and significance. Pediatr Neurol 1995; 12(1):5-16.
258. Sloviter RS. The functional organization of the hippocampal dentate gyrus and its relevance to the pathogenesis of temporal lobe epilepsy. Ann Neurol 1994; 35(6):640-54.
259. Swann JW, Al-Noori S, Jiang M et al. Spine loss and other dendritic abnormalities in epilepsy. Hippocampus 2000; 10(5):617-25.
260. Schauwecker PE, Ramirez JJ, Steward O. Genetic dissection of the signals that induce synaptic reorganization. Exp Neurol 2000; 161(1):139-52.
261. Liu Z, Yang Y, Silveira DC et al. Consequences of recurrent seizures during early brain development. Neuroscience 1999; 92(4):1443-54.
262. Sloviter RS. Status epilepticus-induced neuronal injury and network reorganization. Epilepsia 1999; 40(Suppl 1):S34-9; discussion S40-1.
263. Ben-Ari Y. Cell death and synaptic reorganizations produced by seizures. Epilepsia 2001; 42(Suppl 3):5-7.
264. Houser CR. Granule cell dispersion in the dentate gyrus of humans with temporal lobe epilepsy. Brain Res 1990; 535(2):195-204.
265. Lurton D, El Bahh B, Sundstrom L et al. Granule cell dispersion is correlated with early epileptic events in human temporal lobe epilepsy. J Neurol Sci 1998; 154(2):133-6.
266. Houser CR. Morphological changes in the dentate gyrus in human temporal lobe epilepsy. Epilepsy Res Suppl 1992; 7:223-34.
267. Gorter JA, van Vliet EA, Aronica E et al. Progression of spontaneous seizures after status epilepticus is associated with mossy fibre sprouting and extensive bilateral loss of hilar parvalbumin and somatostatin-immunoreactive neurons. Eur J Neurosci 2001; 13(4):657-69.
268. Pierce JP, Milner TA. Parallel increases in the synaptic and surface areas of mossy fiber terminals following seizure induction. Synapse 2001; 39(3):249-56.
269. Pitkanen A, Nissinen J, Lukasiuk K et al. Association between the density of mossy fiber sprouting and seizure frequency in experimental and human temporal lobe epilepsy. Epilepsia 2000; 41(Suppl 6):S24-9.
270. Cantallops I, Routtenberg A. Kainic acid induction of mossy fiber sprouting: dependence on mouse strain. Hippocampus 2000; 10(3):269-73.
271. Wenzel HJ, Woolley CS, Robbins CA et al. Kainic acid-induced mossy fiber sprouting and synapse formation in the dentate gyrus of rats. Hippocampus 2000; 10(3):244-60.
272. Parent JM, Yu TW, Leibowitz RT et al. Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus. J Neurosci 1997; 17(10):3727-38.
273. Bengzon J, Kokaia Z, Elmer E et al. Apoptosis and proliferation of dentate gyrus neurons after single and intermittent limbic seizures. Proc Natl Acad Sci USA 1997; 94(19):10432-7.

274. Gray WP, Sundstrom LE. Kainic acid increases the proliferation of granule cell progenitors in the dentate gyrus of the adult rat. Brain Res 1998; 790(1-2):52-9.
275. Nakagawa E, Aimi Y, Yasuhara O et al. Enhancement of progenitor cell division in the dentate gyrus triggered by initial limbic seizures in rat models of epilepsy. Epilepsia 2000; 41(1):10-8.
276. Parent JM, Janumpalli S, McNamara JO et al. Increased dentate granule cell neurogenesis following amygdala kindling in the adult rat. Neurosci Lett 1998; 247(1):9-12.
277. Scharfman HE, Goodman JH, Sollas AL. Granule-like neurons at the hilar/CA3 border after status epilepticus and their synchrony with area CA3 pyramidal cells: functional implications of seizure-induced neurogenesis. J Neurosci 2000; 20(16):6144-58.
278. Scott BW, Wang S, Burnham WM et al. Kindling-induced neurogenesis in the dentate gyrus of the rat. Neurosci Lett 1998; 248(2):73-6.
279. Van Der Wal EA, Gomez-Pinilla F, Cotman CW. Seizure-associated induction of basic fibroblast growth factor and its receptor in the rat brain. Neuroscience 1994; 60(2):311-23.
280. Humpel C, Wetmore C, Olson L. Regulation of brain-derived neurotrophic factor messenger RNA and protein at the cellular level in pentylenetetrazol-induced epileptic seizures. Neuroscience 1993; 53(4):909-18.
281. Humpel C, Lippoldt A, Chadi G et al. Fast and widespread increase of basic fibroblast growth factor messenger RNA and protein in the forebrain after kainate-induced seizures. Neuroscience 1993; 57(4):913-22.
282. Bugra K, Pollard H, Charton G et al. aFGF, bFGF and flg mRNAs show distinct patterns of induction in the hippocampus following kainate-induced seizures. Eur J Neurosci 1994; 6(1):58-66.
283. Ballabriga J, Pozas E, Planas AM et al. bFGF and FGFR-3 immunoreactivity in the rat brain following systemic kainic acid administration at convulsant doses: localization of bFGF and FGFR-3 in reactive astrocytes, and FGFR-3 in reactive microglia. Brain Res 1997; 752(1-2):315-8.
284. Yoshimura S, Takagi Y, Harada J et al. FGF-2 regulation of neurogenesis in adult hippocampus after brain injury. Proc Natl Acad Sci USA 2001; 98(10):5874-9.
285. Parent JM, Tada E, Fike JR et al. Inhibition of dentate granule cell neurogenesis with brain irradiation does not prevent seizure-induced mossy fiber synaptic reorganization in the rat. J Neurosci 1999; 19(11):4508-19.
286. Scott BW, Wojtowicz JM, Burnham WM. Neurogenesis in the dentate gyrus of the rat following electroconvulsive shock seizures. Exp Neurol 2000; 165(2):231-6.
287. Madsen TM, Treschow A, Bengzon J et al. Increased neurogenesis in a model of electroconvulsive therapy. Biol Psychiatry 2000; 47(12):1043-9.
288. Sankar R, Shin D, Liu H et al. Granule cell neurogenesis after status epilepticus in the immature rat brain. Epilepsia 2000; 41(Suppl 6):S53-6.
289. Blumcke I, Schewe JC, Normann S et al. Increase of nestin-immunoreactive neural precursor cells in the dentate gyrus of pediatric patients with early-onset temporal lobe epilepsy. Hippocampus 2001; 11(3):311-21.
290. Houser CR. Neuronal loss and synaptic reorganization in temporal lobe epilepsy. Adv Neurol 1999; 79:743-61.
291. Kempermann G, Kuhn HG, Gage FH. More hippocampal neurons in adult mice living in an enriched environment. Nature 1997; 386(6624):493-5.
292. Young D, Lawlor PA, Leone P et al. Environmental enrichment inhibits spontaneous apoptosis, prevents seizures and is neuroprotective. Nat Med 1999; 5(4):448-53.
293. Kubova H, Moshe SL. Experimental models of epilepsy in young animals. J Child Neurol 1994; 9(Suppl 1):S3-11.
294. Wasterlain CG, Shirasaka Y. Seizures, brain damage and brain development. Brain Dev 1994; 16(4):279-95.
295. Holmes GL, Ben-Ari Y. The neurobiology and consequences of epilepsy in the developing brain. Pediatr Res 2001; 49(3):320-5.
296. Haas KZ, Sperber EF, Opanashuk LA et al. Resistance of immature hippocampus to morphologic and physiologic alterations following status epilepticus or kindling. Hippocampus 2001; 11(6):615-25.
297. Lado FA, Sankar R, Lowenstein D et al. Age-dependent consequences of seizures: relationship to seizure frequency, brain damage, and circuitry reorganization. Ment Retard Dev Disabil Res Rev 2000; 6(4):242-52.

298. Wasterlain CG, Plum F. Vulnerability of developing rat brain to electroconvulsive seizures. Arch Neurol 1973; 29(1):38-45.
299. McCabe BK, Silveira DC, Cilio MR et al. Reduced neurogenesis after neonatal seizures. J Neurosci 2001; 21(6):2094-103.
300. Hoch DB, Hill RA, Oas KH. Epilepsy and mental decline. Neurol Clin 1994; 12(1):101-13.
301. Battaglia D, Rando T, Deodato F et al. Epileptic disorders with onset in the first year of life: neurological and cognitive outcome. Europ J Paediatr Neurol 1999; 3(3):95-103.
302. Koh S, Storey TW, Santos TC et al. Early-life seizures in rats increase susceptibility to seizure-induced brain injury in adulthood. Neurology 1999; 53(5):915-21.
303. Holmes GL, Gairsa JL, Chevassus-Au-Louis N et al. Consequences of neonatal seizures in the rat: morphological and behavioral effects. Ann Neurol 1998; 44(6):845-57.
304. Loscher W, Ebert U, Lehmann H et al. Seizure suppression in kindling epilepsy by grafts of fetal GABAergic neurons in rat substantia nigra. J Neurosci Res 1998; 51(2):196-209.
305. Kokaia M, Cenci MA, Elmer E et al. Seizure development and noradrenaline release in kindling epilepsy after noradrenergic reinnervation of the subcortically deafferented hippocampus by superior cervical ganglion or fetal locus coeruleus grafts. Exp Neurol 1994; 130(2):351-61.
306. Kokaia M, Aebischer P, Elmer E et al. Seizure suppression in kindling epilepsy by intracerebral implants of GABA- but not by noradrenaline-releasing polymer matrices. Exp Brain Res 1994; 100(3):385-94.
307. Thompson K, Anantharam V, Behrstock S et al. Conditionally immortalized cell lines, engineered to produce and release GABA, modulate the development of behavioral seizures. Exp Neurol 2000; 161(2):481-9.
308. Cole AJ. Is epilepsy a progressive disease? The neurobiological consequences of epilepsy. Epilepsia 2000; 41(Suppl 2):S13-22.
309. Jankowsky JL, Patterson PH. The role of cytokines and growth factors in seizures and their sequelae. Prog Neurobiol 2001; 63(2):125-49.
310. Jin K, Minami M, Lan JQ et al. Neurogenesis in dentate subgranular zone and rostral subventricular zone after focal cerebral ischemia in the rat. Proc Natl Acad Sci USA 2001; 98(8):4710-5.
311. Kee NJ, Preston E, Wojtowicz JM. Enhanced neurogenesis after transient global ischemia in the dentate gyrus of the rat. Exp Brain Res 2001; 136(3):313-20.
312. Liu J, Solway K, Messing RO et al. Increased neurogenesis in the dentate gyrus after transient global ischemia in gerbils. J Neurosci 1998; 18(19):7768-78.
313. Iwai M, Hayashi T, Zhang WR et al. Induction of highly polysialylated neural cell adhesion molecule (PSA-NCAM) in postischemic gerbil hippocampus mainly dissociated with neural stem cell proliferation. Brain Res 2001; 902(2):288-93.
314. Takagi Y, Nozaki K, Takahashi J et al. Proliferation of neuronal precursor cells in the dentate gyrus is accelerated after transient forebrain ischemia in mice. Brain Res 1999; 831(1-2):283-7.
315. Kitagawa K, Matsumoto M, Hori M. Protective and regenerative response endogenously induced in the ischemic brain. Can J Physiol Pharmacol 2001; 79(3):262-5.
316. Jiang W, Gu W, Brannstrom T et al. Cortical neurogenesis in adult rats after transient middle cerebral artery occlusion. Stroke 2001; 32(5):1201-7.
317. Gu W, Brannstrom T, Wester P. Cortical neurogenesis in adult rats after reversible photothrombotic stroke. J Cereb Blood Flow Metab 2000; 20(8):1166-73.
318. Gould E, Reeves AJ, Graziano MS et al. Neurogenesis in the neocortex of adult primates. Science 1999; 286(5439):548-52.
319. Bernabeu R, Sharp FR. NMDA and AMPA/kainate glutamate receptors modulate dentate neurogenesis and CA3 synapsin-I in normal and ischemic hippocampus. J Cereb Blood Flow Metab 2000; 20(12):1669-80.
320. Arvidsson A, Kokaia Z, Lindvall O. N-methyl-D-aspartate receptor-mediated increase of neurogenesis in adult rat dentate gyrus following stroke. Eur J Neurosci 2001; 14(1):10-8.
321. Westerberg E, Monaghan DT, Kalimo H et al. Dynamic changes of excitatory amino acid receptors in the rat hippocampus following transient cerebral ischemia. J Neurosci 1989; 9(3):798-805.
322. Cameron HA, McEwen BS, Gould E. Regulation of adult neurogenesis by excitatory input and NMDA receptor activation in the dentate gyrus. J Neurosci 1995; 15(6):4687-92.

323. Gould E, Cameron HA, McEwen BS. Blockade of NMDA receptors increases cell death and birth in the developing rat dentate gyrus. J Comp Neurol 1994; 340(4):551-65.
324. Gould E, McEwen BS, Tanapat P et al. Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. J Neurosci 1997; 17(7):2492-8.
325. Larsson E, Lindvall O, Kokaia Z. Stereological assessment of vulnerability of immunocytochemically identified striatal and hippocampal neurons after global cerebral ischemia in rats. Brain Res 2001; 913(2):117-32.
326. Mody I, Otis TS, Bragin A et al. GABAergic inhibition of granule cells and hilar neuronal synchrony following ischemia-induced hilar neuronal loss. Neuroscience 1995; 69(1):139-50.
327. Sugimoto A, Shozuhara H, Kogure K et al. Exposure to sub-lethal ischemia failed to prevent subsequent ischemic death of dentate hilar neurons, as estimated by laminin immunohistochemistry. Brain Res 1993; 629(1):159-62.
328. Li Y, Chopp M, Powers C. Granule cell apoptosis and protein expression in hippocampal dentate gyrus after forebrain ischemia in the rat. J Neurol Sci 1997; 150(2):93-102.
329. Bering R, Draguhn A, Diemer NH et al. Ischemia changes the coexpression of somatostatin and neuropeptide Y in hippocampal interneurons. Exp Brain Res 1997; 115(3):423-9.
330. Kawamata T, Dietrich WD, Schallert T et al. Intracisternal basic fibroblast growth factor enhances functional recovery and up-regulates the expression of a molecular marker of neuronal sprouting following focal cerebral infarction. Proc Natl Acad Sci USA 1997; 94(15):8179-84.
331. Endoh M, Pulsinelli WA, Wagner JA. Transient global ischemia induces dynamic changes in the expression of bFGF and the FGF receptor. Brain Res Mol Brain Res 1994; 22(1-4):76-88.
332. Yagita Y, Kitagawa K, Ohtsuki T et al. Neurogenesis by progenitor cells in the ischemic adult rat hippocampus. Stroke 2001; 32(8):1890-6.
333. Levison SW, Rothstein RP, Romanko MJ et al. Hypoxia/ischemia depletes the rat perinatal subventricular zone of oligodendrocyte progenitors and neural stem cells. Dev Neurosci 2001; 23(3):234-47.
334. Back SA, Han BH, Luo NL et al. Selective vulnerability of late oligodendrocyte progenitors to hypoxia-ischemia. J Neurosci 2002; 22(2):455-63.
335. Park KI. Transplantation of neural stem cells: cellular & gene therapy for hypoxic-ischemic brain injury. Yonsei Med J 2000; 41(6):825-35.
336. Fukunaga A, Uchida K, Hara K et al. Differentiation and angiogenesis of central nervous system stem cells implanted with mesenchyme into ischemic rat brain. Cell Transplant 1999; 8(4):435-41.
337. Sinden JD, Stroemer P, Grigoryan G et al. Functional repair with neural stem cells. Novartis Found Symp 2000; 231:270-83; discussion 283-8, 302-6.
338. Nishino H, Borlongan CV. Restoration of function by neural transplantation in the ischemic brain. Prog Brain Res 2000; 127:461-76.
339. Hodges H, Nelson A, Virley D et al. Cognitive deficits induced by global cerebral ischaemia: prospects for transplant therapy. Pharmacol Biochem Behav 1997; 56(4):763-80.
340. Kondziolka D, Wechsler L, Goldstein S et al. Transplantation of cultured human neuronal cells for patients with stroke. Neurology 2000; 55(4):565-9.
341. Semkova I, Krieglstein J. Neuroprotection mediated via neurotrophic factors and induction of neurotrophic factors. Brain Res Brain Res Rev 1999; 30(2):176-88.
367. Manji HK, Moore GJ, Chen G. Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers: implications for the pathophysiology and treatment of manic-depressive illness. Biol Psychiatry 2000; 48(8):740-54.
368. Duman RS, Malberg J, Nakagawa S. Regulation of adult neurogenesis by psychotropic drugs and stress. J Pharmacol Exp Ther 2001; 299(2):401-7.
369. Blows WT. The neurobiology of antidepressants. J Neurosci Nurs 2000; 32(3):177-80.
370. Malberg JE, Eisch AJ, Nestler EJ et al. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 2000; 20(24):9104-10.
371. Kempermann G, van Praag H, Gage FH. Activity-dependent regulation of neuronal plasticity and self repair. Prog Brain Res 2000; 127:35-48.
372. van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat Neurosci 1999; 2(3):266-70.

373. Vaidya VA, Duman RS. Depresssion–emerging insights from neurobiology. Br Med Bull 2001; 57:61-79.
374. Duman RS, Nakagawa S, Malberg J. Regulation of adult neurogenesis by antidepressant treatment. Neuropsychopharmacology 2001; 25(6):836-44.
375. Chen G, Rajkowska G, Du F et al. Enhancement of hippocampal neurogenesis by lithium. J Neurochem 2000; 75(4):1729-34.
376. Czeh B, Michaelis T, Watanabe T et al. Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. Proc Natl Acad Sci USA 2001; 98(22):12796-801.
377. Duman RS, Malberg J, Thome J. Neural plasticity to stress and antidepressant treatment. Biol Psychiatry 1999; 46(9):1181-91.
378. Finamore TL, Seybold KS, Noble M et al. Contributions of hippocampal cellular damage and NMDA receptor dysfunction to behavioral markers of schizophrenia. Int J Neurosci 2001; 109(1-2):61-70.
379. Weinberger DR. Cell biology of the hippocampal formation in schizophrenia. Biol Psychiatry 1999; 45(4):395-402.
380. Port RL, Seybold KS. Hippocampal synaptic plasticity as a biological substrate underlying episodic psychosis. Biol Psychiatry 1995; 37(5):318-24.