

Neuro Stem Cell

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Abstract: The definition of stem cell is “an unspecialized cell that gives rise to a specific specialized cell, such as a blood cell”. Stem Cell is the original of life. All cells come from stem cells. Serving as a repair system for the living body, the stem cells can divide without limit to replenish other cells as long as the living body is still alive. When a stem cell divides, each new cell has the potential to either remain a stem cell situation or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, a bone cell, a nerve cell, or a brain cell. Stem cell research is a typical and important topic of life science. This material collects some literatures on neuro stem cell.

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Key words: stem cell; life; gene; DNA; protein; neuro

Literatures

Abramowsky, C. R., H. M. Katzenstein, et al. (2009). "Anaplastic large cell neuroblastoma." *Pediatr Dev Pathol* **12**(1): 1-5.

Anaplastic large cell neuroblastomas (ALCNB) are a subset of undifferentiated neuroblastomas with marked pleomorphic and anaplastic features that render them diagnostically challenging. We reviewed the records of all patients diagnosed with ALCNB at Children's Healthcare of Atlanta (Egleston Children's Hospital) for their clinical, biologic, and pathologic characteristics and their treatment outcomes. From 1998 to 2006, 7 patients were diagnosed with ALCNB. All patients presented with abdominal-pelvic masses, 3 of them of adrenal origin and 2 with thoracic extension, with clinical stages 3 or 4, and were considered to have high-risk disease. The N-MYC oncogene was amplified in 3 cases and catecholamines were elevated in 5 of 6 patients tested. All pretreatment tumors demonstrate pleomorphic, anaplastic morphology with bizarre mitoses admixed with undifferentiated but monomorphic cells with minimal if any neuroepithelial or neuro-ganglionic differentiation. Immunohistochemical markers for neuron specific enolase (NSE) and synaptophysin were strongly positive in all specimens and chromogranin in 4 of 5. Interestingly, all tumors showed strong Fli-1 nuclear positivity despite a negative CD-99 stain. However, reverse transcription polymerase chain reaction or fluorescent in-situ hybridization testing for Ewing sarcoma transcripts was negative in 4 available specimens. This same Fli-1 antibody had tested negative on 30 conventional neuroblastomas, indicating a peculiar cross reactivity with this subset of ALCNB. Posttreatment biopsies showed maturation changes to more conventional neuroblastoma histology in 5 of the 7 cases. Follow-up ranged from 9

months to 4 years from diagnosis (median: 25 months). Five patients are still alive after treatment, 1 died 9 months after diagnosis, and another patient refused high-risk therapy and progressed and died 9 months from diagnosis. Anaplastic large cell neuroblastomas are a subset of undifferentiated neuroblastomas characterized by the absence or marked paucity of histologic clues for the diagnosis of neuroblastoma. Although all these tumors are strongly positive for NSE and synaptophysin, they also show Fli-1 positivity. However, they are negative by molecular testing for EWS transcripts, and they are immunohistochemically negative for CD99. The true neuroblastic nature of these tumors is supported by the N-MYC oncogene amplification in some of them, catecholamine production, immunohistological reactivity, and their posttherapy maturation to a more recognizable neuroblastic morphology. Although follow-up is still somewhat limited, the response and survival of the patients in our institution is better than a previous European study that indicated an aggressive clinical behavior of these tumors, although treatment modalities were not described in that report. Further study of this variant of neuroblastoma with more patients is required to determine optimal therapy, more accurately predict outcome, and to ascertain if ALCNB are a distinct biologic group of neuroblastomas.

Alouani, S., S. Ketchum, et al. (1993). "Transcriptional activity of the neuron-specific enolase (NSE) promoter in murine embryonic stem (ES) cells and preimplantation embryos." *Eur J Cell Biol* **62**(2): 324-32.

Mouse embryonic stem (ES) cells were transfected with a plasmid composed of an E. coli lacZ gene fused to 1.8 kb of rat neuron-specific enolase (NSE) promoter sequences. While this

reporter construct had been shown previously to function exclusively in postmitotic neurons and neuroendocrine cells of transgenic mice, stably transfected ES cell clones unexpectedly displayed beta-galactosidase (beta-Gal) activity in the undifferentiated state. This transcriptional activity of the heterologous NSE promoter was confirmed by the identification of endogenous NSE mRNA in undifferentiated ES cells, mouse morulae and blastocysts. NSE protein, however, could not be found in undifferentiated ES cells. Interestingly, in ES cells which were cultured for 7 days under differentiation conditions *in vitro*, beta-Gal activity decreased to basal levels consistent with the parallel down-regulation of endogenous NSE mRNA. In contrast, prolonged culture of ES cells under differentiation conditions led to the reappearance of NSE mRNA and beta-Gal activity after 17 days. Significant increases in beta-Gal activity were also observed in ES cells which were cultured either on dishes coated with attachment factors such as laminin and gelatin or in the presence of nerve growth factor (NGF). These results suggest that i) transcriptional control mechanisms regulating neuronal gene expression are present at early developmental stages in the mouse and ii) ES cells provide a useful *in vitro* model system for the analysis of developmentally regulated cellular and molecular events coupled to neuron-specific enolase promoter activity.

Anderova, M., S. Kubinova, et al. (2006). "Transplantation of embryonic neuroectodermal progenitor cells into the site of a photochemical lesion: immunohistochemical and electrophysiological analysis." *J Neurobiol* **66**(10): 1084-100.

GFP labeled/NE-4C neural progenitor cells cloned from primary neuroectodermal cultures of p53-mouse embryos give rise to neurons when exposed to retinoic acid *in vitro*. To study their survival and differentiation *in vivo*, cells were transplanted into the cortex of 6-week-old rats, 1 week after the induction of a photochemical lesion or into noninjured cortex. The electrophysiological properties of GFP/NE-4C cells were studied *in vitro* (8-10 days after differentiation induction) and 4 weeks after transplantation using the whole-cell patch-clamp technique, and immunohistochemical analyses were carried out. After transplantation into a photochemical lesion, a large number of cells survived, some of which expressed the astrocytic marker GFAP. GFP/GFAP-positive cells, with an average resting membrane potential (V_{rest}) of -71.9 mV, displayed passive time- and voltage-independent K^+ currents and, additionally, voltage-dependent A-type K^+ currents (KA) and/or delayed outwardly rectifying K^+ currents (KDR). Numerous GFP-positive cells

expressed NeuN, betaIII-tubulin, or 68 kD neurofilaments. GFP/betaIII-tubulin-positive cells, with an average V_{rest} of -61.6 mV, were characterized by the expression of KA and KDR currents and tetrodotoxin-sensitive Na^+ currents. GFP/NE-4C cells also gave rise to oligodendrocytes, based on the detection of oligodendrocyte-specific markers. Our results indicate that GFP/NE-4C neural progenitors transplanted into the site of a photochemical lesion give rise to neurons and astrocytes with membrane properties comparable to those transplanted into noninjured cortex. Therefore, GFP/NE-4C cells provide a suitable model for studying neuro- and gliogenesis *in vivo*. Further, our results suggest that embryonic neuroectodermal progenitor cells may hold considerable promise for the repair of ischemic brain lesions.

Anderson, G. S., I. Tsujino, et al. (2003). "Preferential inactivation of paediatric solid tumour cells by sequential exposure to Merocyanine 540-mediated photodynamic therapy and Edelfosine: implications for the *ex vivo* purging of autologous haematopoietic stem cell grafts." *J Photochem Photobiol B* **69**(2): 87-95.

Paediatric solid tumours exhibit steep dose-response curves to alkylating agents and are therefore considered candidates for high-dose chemotherapy and autologous stem cell support. There is growing evidence that autologous stem cell grafts from patients with solid tumours are frequently contaminated with live tumour cells. The objective of this study was to perform, in a preclinical purging model, an initial assessment of the safety and efficacy of a two-step purging procedure that combined Merocyanine 540-mediated photodynamic therapy (MC540-PDT) with a brief exposure to the alkyl-lysophospholipid, Edelfosine. Human and murine bone marrow cells and Neuro-2a murine neuroblastoma, SK-N-SH human neuroblastoma, SK-ES-1 and U-2 OS human osteosarcoma, G-401 and SK-NEP-1 human Wilms' tumour, and A-204 human rhabdomyosarcoma cells were exposed to a fixed dose of MC540-PDT followed by a brief incubation with graded concentrations of Edelfosine. Survival was subsequently assessed by *in vitro* clonal assay or, in the case of CD34-positive haematopoietic stem cells, by an immunohistochemical method. Combination purging with MC540-PDT and Edelfosine depleted all tumour cells by >4 log while preserving at least 15% of murine granulocyte/macrophage progenitors (CFU-GM), 34% of human CFU-GM, and 31% of human CD34-positive cells. The data suggest that combination purging with MC540-PDT and Edelfosine may be useful for the *ex vivo* purging of

autologous stem cell grafts from patients with paediatric solid tumours.

Baehring, J. M. (2005). "An update on oligodendroglial neoplasms." *Curr Opin Neurol* **18**(6): 639-44.

PURPOSE OF REVIEW: The most widely accepted brain tumor classification system remains morphology-based but the increasing knowledge of the molecular pathogenesis of oligodendroglial tumors has spurred translational research yielding new diagnostic and therapeutic paradigms. These data have accumulated rapidly and, in combination with exciting new insights in the cellular origin of these tumors, necessitate a review. **RECENT FINDINGS:** 'Cancer stem cells' have been identified in gliomas. Further study of these cells will not only provide information on the cellular origin and pathogenesis of these tumors but may also give rise to new treatments that target a cell pool not amenable to current therapeutic strategies. Molecular tumor characteristics have been correlated with imaging findings, treatment response and prognosis. This has enabled neuro-oncologists to take a risk-stratified approach to patients with oligodendrogliomas that optimizes treatment efficacy and minimizes toxicity. Furthermore, more accurate epidemiological data have become available from population-based studies. **SUMMARY:** In spite of remarkable progress over the last 15 years, these tumors remain incurable. The search for a cure has to go on, while currently available multidisciplinary treatments are refined.

Bain, G., F. C. Mansergh, et al. (2000). "ES cell neural differentiation reveals a substantial number of novel ESTs." *Funct Integr Genomics* **1**(2): 127-39.

We have used a method for synchronously differentiating murine embryonic stem (ES) cells into functional neurons and glia in culture. Using subtractive hybridization we isolated approximately 1200 cDNA clones from ES cell cultures at the neural precursor stage of neural differentiation. Pilot studies indicated that this library is a good source of novel neuro-embryonic cDNA clones. We therefore screened the entire library by single-pass sequencing. Characterization of 604 non-redundant cDNA clones by BLAST revealed 96 novel expressed sequence tags (ESTs) and an additional 197 matching uncharacterized ESTs or genomic clones derived from genome sequencing projects. With the exception of a handful of genes, whose functions are still unclear, most of the 311 known genes identified in this screen are expressed in embryonic development and/or the nervous system. At least 80 of these genes are implicated in disorders of differentiation, neural development and/or neural function. This study

provides an initial snapshot of gene expression during early neural differentiation of ES cell cultures. Given the recent identification of human ES cells, further characterization of these novel and uncharacterized ESTs has the potential to identify genes that may be important in nervous system development, physiology and disease.

Bible, E., D. Y. Chau, et al. (2009). "Attachment of stem cells to scaffold particles for intra-cerebral transplantation." *Nat Protoc* **4**(10): 1440-53.

Cell-replacement therapy and tissue regeneration using stem cells are of great interest to recover histological damage caused by neuro-degenerative disease or traumatic insults to the brain. To date, the main intra-cerebral delivery for these cells has been as a suspension in media through a thin needle. However, this does not provide cells with a support system that would allow tissue regeneration. Scaffold particles are needed to provide structural support to cells to form de novo tissue. In this 16-d protocol, we describe the generation and functionalization of poly (D,L-lactic-co-glycolic) acid (PLGA) particles to enhance cell attachment, the attachment procedure to avoid clumping and aggregation of cells and particles, and their preparation for intra-cerebral injection through a thin needle. Although the stem cell-scaffold transplantation is more complicated and labor-intensive than cell suspensions, it affords de novo tissue generation inside the brain and hence provides a significant step forward in traumatic brain repair.

Bible, E., D. Y. Chau, et al. (2009). "The support of neural stem cells transplanted into stroke-induced brain cavities by PLGA particles." *Biomaterials* **30**(16): 2985-94.

Stroke causes extensive cellular loss that leads to a disintegration of the afflicted brain tissue. Although transplanted neural stem cells can recover some of the function lost after stroke, recovery is incomplete and restoration of lost tissue is minimal. The challenge therefore is to provide transplanted cells with matrix support in order to optimise their ability to engraft the damaged tissue. We here demonstrate that plasma polymerised allylamine (ppAAm)-treated poly(D,L-lactic acid-co-glycolic acid) (PLGA) scaffold particles can act as a structural support for neural stem cells injected directly through a needle into the lesion cavity using magnetic resonance imaging-derived co-ordinates. Upon implantation, the neuro-scaffolds integrate efficiently within host tissue forming a primitive neural tissue. These neuro-scaffolds could therefore be a more advanced method to enhance brain repair. This study provides a substantial step in the technology

development required for the translation of this approach.

Blondheim, N. R., Y. S. Levy, et al. (2006). "Human mesenchymal stem cells express neural genes, suggesting a neural predisposition." *Stem Cells Dev* **15**(2): 141-64.

Because of their unique attributes of plasticity and accessibility, bone marrow-derived mesenchymal stem cells (MSCs) may find use for therapy of neurodegenerative disorders. Our previous studies of adult human MSCs demonstrated that these cells express an extensive assortment of neural genes at a low but clearly detectable level. Here, we report expression of 12 neural genes, 8 genes related to the neuro-dopaminergic system, and 11 transcription factors with neural significance by human MSCs. Our results suggest that, as opposed to cells that do not express neural genes, human MSCs are predisposed to differentiate to neuronal and glial lineages, given the proper conditions. Our findings add a new dimension in which to view adult stem cell plasticity, and may explain the relative ease with which MSCs, transplanted into the central nervous system (CNS) differentiate to a variety of functional neural cell types. Our results further promote the possibility that adult human MSCs are promising candidates for cell-based therapy of neurodegenerative diseases.

Bodey, B., B. Bodey, Jr., et al. (1997). "Dendritic type, accessory cells within the mammalian thymic microenvironment. Antigen presentation in the dendritic neuro-endocrine-immune cellular network." *In Vivo* **11**(4): 351-70.

During mammalian ontogenesis, the thymic "pure" endodermal epithelial anlage develops and differentiates into a complex cellular microenvironment. Beginning the 7-8th week of intrauterine development, thymic epithelial cells chemotactically regulate (induce) numerous waves of migration of stem cells into the thymus, including the CD34+, yolk sac-derived, committed hematopoietic stem cells. In vitro experiments have established that CD34+ CD38dim human thymocytes differentiate into T lymphocytes when co-cultured with mouse fetal thymic organs. Hematopoietic stem cells for myeloid and thymic stromal dendritic cells (DCs) are present within the minute population of CD34+ progenitors within the mammalian thymus. The common myeloid, DC, natural killer (NK) and T lymphocyte progenitors have also been identified within the CD34+ stem cell population in the human thymus. Interactions between the endocrine and immune systems have been reported in various regions of the mammalian body including the anterior pituitary (AP), the skin, and the central (thymus) and peripheral lymphatic system. The

network of bone marrow derived DCs is a part of the reticuloendothelial system (RES) and DCs represent the cellular mediators of these regulatory endocrine-immune interactions. Folliculo-stellate cells (FSC) in the AP, Langerhans cells (LCs) in the skin and lymphatic system, "veiled" cells, lympho-dendritic and interdigitating cells (IDCs) in a number of tissues comprising the lymphatic system are the cell types of the DC meshwork of "professional" antigen presenting cells (APCs). Most of these cells express the immunocytochemical markers S-100, CD1, CD45, CD54, F418, MHC class I and II antigens, Fc and complement receptors. FSCs are non-hormone secreting cells which communicate directly with hormone producing cells, a form of neuro-endocrine-immune regulation. As a result, an attenuation of secretory responses follows stimulation of these cells. FSCs are also the cells in the AP producing interleukin-6 (IL-6), and they have also been identified as the interferon-gamma responsive elements. FSCs also express lymphatic DC markers, such as DC specific aminopeptidase, leucyl-beta-naphthylaminidase, non-specific esterase, MHC class I and II molecules and various other lymphatic immunological determinants [platelet derived growth factor-alpha chain (PDGF-alpha chain), CD13, CD14 and L25 antigen]. There is strong evidence that such DCs in the AP, and similar ones in the developing thymus and peripheral lymphatic tissue are the components of a powerful "professional" antigen presenting DC network. These APCs contain a specialized late endocytic compartment, MIIC (MHC class II-enriched compartment), that harbors newly synthesized MHC class II antigens en route to the cell membrane. The limiting membrane of MIIC can fuse directly with the cell membrane, resulting in release of newly secreted intracellular MHC class II antigen containing vesicles (exosomes). DCs possess the ability to present foreign peptides complexed with the MHC molecules expressed on their surfaces to naive and resting T cells. There are a number of "molecular couples" that influence DC and T lymphocyte interaction during antigen presentation: CD1/CD18 integrins, intercellular adhesion molecules (ICAMs), lymphocyte function associated antigen 3 (LFA-3), CD40, CD80/B7-1, CD86/B7-2, and heat-stable antigen. The "molecular couples" are involved in adhesive or co-stimulatory regulations, mediating an effective binding of DCs to T lymphocytes and the stimulation of specific intercellular communications. DCs also provide all of the known co-stimulatory signals required for activation of unprimed T lymphocytes. It has been shown that DCs initiate several immune responses, such as the sensitization of MHC-restricted T lymphocytes, resistance to infections and neoplasms, rejection of organ

transplants, and the formation of T-dependent antibodies. (ABSTRACT TRUNCATED)

Bogerts, B. (1981). "A brainstem atlas of catecholaminergic neurons in man, using melanin as a natural marker." *J Comp Neurol* **197**(1): 63-80.

The present paper provides an atlas showing the distribution of melanin-containing nerve cells in the human brainstem. It was found that neuro-melanin, which can be viewed as a waste product of catecholamine metabolism, is suitable as a natural marker for catecholaminergic neurons in the medulla oblongata, pons, and the mesencephalon of the adult human brain. Within these areas of the brain, there is a striking similarity between the location of melanin and the catecholamine cell bodies described in various animals and in human fetuses, whereas no melanin was found in the diencephalic dopaminergic cell groups. Cell counts from the center of each area showed that the mean density of melanin-containing perikarya varied considerably between the different areas.

Bokemeyer, C. (1998). "Current trends in chemotherapy for metastatic nonseminomatous testicular germ cell tumors." *Oncology* **55**(3): 177-88.

With the introduction of cisplatin-based chemotherapy, metastatic testicular cancer represents a model for a highly curable malignant disease. Approximately 70-80% of patients achieve a durable remission following chemotherapy +/- secondary surgery of residual tumors. With the development of prognostic classifications based on clinically available parameters, the aims of chemotherapy have been twofold: on the one hand, the reduction of toxicity in patients with 'low-risk' metastatic disease without a concomitant reduction in treatment efficacy and, on the other hand, the improvement of treatment results in patients with 'poor-prognosis' criteria who achieve a long-term cure rate of less than 50% with standard chemotherapy regimens. Despite a number of large randomized studies attempting either to avoid the toxicity of bleomycin or to reduce cisplatin-associated side-effects through the substitution with carboplatin, the combination of cisplatin, etoposide and bleomycin (PEB) given at 3-week intervals still remains the standard treatment for metastatic disease. The role of high-dose chemotherapy with autologous stem cell support is currently being investigated in order to improve the outcome of patients with relapse after previous chemotherapy and of patients initially exhibiting advanced metastatic disease. For patients with relapsed disease receiving high-dose chemotherapy, a prognostic score has recently been developed: cisplatin-refractory disease, beta human gonadotropin values > 1,000 U/l or primary

mediastinal germ cell tumors are factors characterizing patients which will profit less from high-dose chemotherapy treatment than patients with chemosensitive disease at relapse. Standard dose salvage regimens only result in a 20% long-term survival rate. In contrast, high-dose salvage chemotherapy may yield a cure rate of approximately 40%. However, the only randomized study comparing high-dose versus conventional-dose therapy in patients with relapsed disease is still ongoing. The investigation of dose-intensive approaches as first-line treatment is currently being studied by several institutions. Despite preliminary favorable results, this approach still cannot be considered standard treatment. A randomized study comparing high-dose chemotherapy with 4 cycles of standard PEB was initiated in the USA in 1996. The evaluation of new drugs in testicular cancer patients with absolute cisplatin-refractory disease has demonstrated that paclitaxel is one of the few agents with antitumor activity in these patients. Paclitaxel has therefore been included in combination regimens--such as cisplatin, ifosfamide and paclitaxel--for the treatment of patients with first and second relapse of testicular cancer. These combinations are used as induction therapy prior to high-dose salvage treatment. Due to the large group of patients with metastatic disease being cured nowadays, the long-term side effects of treatment have become even more important. One of the major risk factors for the development of late toxicities such as oto-, neuro-, nephro-, gonadal and cardiovascular toxicity is the cumulative dose of cisplatin applied during therapy. The development of new treatment strategies, such as the use of adjuvant chemotherapy for stage I disease, the widespread application of high-dose chemotherapy with peripheral stem cell rescue and the use of new cytotoxic agents, makes the evaluation of the late effects of treatment for testicular cancer within controlled clinical trials mandatory.

Bosman, F. T. (1997). "Neuroendocrine cells in non-endocrine tumors: what does it mean?" *Verh Dtsch Ges Pathol* **81**: 62-72.

In many human neoplasms histochemical techniques will demonstrate the presence of neuroendocrine cells. Their occurrence also in metastases indicates clearly that they form an integral part of the tumor cell population. As to their origin, for most tissues in which neuroendocrine cells normally occur, such as the digestive tract, the currently held view is that one stem cell population provides a repertoire of differentiation corresponding to all cell types which normally occur in that epithelium. Transformation of such a stem cell will give rise to a tumor stem cell in which the same repertoire of differentiation, including neuroendocrine

cells, can be found. The tumor neuroendocrine cells usually express neurohormonal peptides corresponding to their normal counterparts. These cells almost never lead to clinically manifest overproduction of neurohormonal peptides. In other tissues, such as the normal ovary, neuroendocrine cells do not occur and yet in tumors, e.g. ovarian mucinous cystadenomas and cystadenocarcinomas, they can be found. In the epithelial components of ovarian and testicular teratomas neuro-endocrine cells have also been detected. In spite of the biological interest of this phenomenon its clinical significance remains an open question. Several investigators have found that colorectal cancers with neuroendocrine differentiation behave more aggressively than tumors without these cells. Others dispute these observations. In the breast and in the prostate neuroendocrine differentiation has been very extensively investigated and there seems to be a reasonable consensus that their presence is associated with poorer prognosis.

Bossolasco, P., L. Cova, et al. (2005). "Neuro-glial differentiation of human bone marrow stem cells in vitro." *Exp Neurol* **193**(2): 312-25.

Bone marrow (BM) is a rich source of stem cells and may represent a valid alternative to neural or embryonic cells in replacing autologous damaged tissues for neurodegenerative diseases. The purpose of the present study is to identify human adult BM progenitor cells capable of neuro-glial differentiation and to develop effective protocols of trans-differentiation to surmount the hematopoietic commitment in vitro. Heterogeneous cell populations such as whole BM, low-density mononuclear and mesenchymal stem (MSCs), and several immunomagnetically separated cell populations were investigated. Among them, MSCs and CD90+ cells were demonstrated to express neuro-glial transcripts before any treatment. Several culture conditions with the addition of stem cell or astroblast conditioned media, different concentrations of serum, growth factors, and supplements, used alone or in combinations, were demonstrated to alter the cellular morphology in some cell subpopulations. In particular, MSCs and CD90+ cells acquired astrocytic and neuron-like morphologies in specific culture conditions. They expressed several neuro-glial specific markers by RT-PCR and glial fibrillary acid protein by immunocytochemistry after co-culture with astroblasts, both in the absence or presence of cell contact. In addition, floating neurosphere-like clones have been observed when CD90+ cells were grown in neural specific media. In conclusion, among the large variety of human adult BM cell populations analyzed, we demonstrated the in vitro neuro-glial potential of both the MSC and CD90+ subset of cells. Moreover,

unidentified soluble factors provided by the conditioned media and cellular contacts in co-culture systems were effective in inducing the neuro-glial phenotype, further supporting the adult BM neural differentiative capability.

Boutou, E., C. Hurel, et al. (2000). "Early expression of the BM88 antigen during neuronal differentiation of P19 embryonal carcinoma cells." *Int J Dev Neurosci* **18**(2-3): 321-8.

Previous studies have shown that the BM88 antigen, a neuron-specific molecule, promotes the differentiation of mouse neuroblastoma cells [23] (Mamalaki A., Boutou E., Hurel C., Patsavoudi E., Tzartos S. and Matsas R. (1995) The BM88 antigen, a novel neuron-specific molecule, enhances the differentiation of mouse neuroblastoma cells. *J. Biol. Chem.* **270**, 14201-14208). In particular, stably transfected with the BM88 cDNA, Neuro 2a cells over-expressing the BM88 antigen are morphologically distinct from their non-transfected counterparts; they exhibit enhanced process outgrowth and a slower rate of division. Moreover, they respond differentially to growth factors [10] (Gomez J., Boutou E., Hurel C., Mamalaki A., Kentroti S., Vernadakis A. and Matsas R. (1998) Overexpression of the neuron-specific molecule BM88 in mouse neuroblastoma cells: Altered responsiveness to growth factors. *J. Neurosci. Res.* **51**, 119-128). In order to further elucidate the role of the BM88 antigen in the differentiation of developing neurons we used the in vitro system of differentiating P19 cells which closely resembles early murine development in vivo. In this study, P19 cells were driven to the neuronal pathway with retinoic acid. We examined by immunofluorescence studies the expression of the BM88 antigen in these cells and we found that it correlates well with the expression of the polysialylated form of the neural cell adhesion molecule (PSA-NCAM) which characterizes early differentiating post-mitotic neurons. In contrast, very few of the BM88 antigen-positive/PSA-NCAM-positive cells expressed neurofilament protein, a marker of more mature neurons. Our findings, in accordance with previously reported data, strongly suggest that the BM88 antigen is involved in the early stages of differentiation of neuronal cells.

Buckwalter, M. S., M. Yamane, et al. (2006). "Chronically increased transforming growth factor-beta1 strongly inhibits hippocampal neurogenesis in aged mice." *Am J Pathol* **169**(1): 154-64.

There is increasing evidence that hippocampal learning correlates strongly with neurogenesis in the adult brain. Increases in neurogenesis after brain injury also correlate with

improved outcomes. With aging the capacity to generate new neurons decreases dramatically, both under normal conditions and after injury. How this decrease occurs is not fully understood, but we hypothesized that transforming growth factor (TGF)-beta1, a cell cycle regulator that rapidly increases after injury and with age, might play a role. We found that chronic overproduction of TGF-beta1 from astrocytes almost completely blocked the generation of new neurons in aged transgenic mice. Even young adult TGF-beta1 mice had 60% fewer immature, doublecortin-positive, hippocampal neurons than wild-type littermate controls. Bromodeoxyuridine labeling of dividing cells in 2-month-old TGF-beta1 mice confirmed this decrease in neuro-genesis and revealed a similar decrease in astrogenesis. Treatment of early neural progenitor cells with TGF-beta1 inhibited their proliferation. This strongly suggests that TGF-beta1 directly affects these cells before their differentiation into neurons and astrocytes. Together, these data show that TGF-beta1 is a potent inhibitor of hippocampal neural progenitor cell proliferation in adult mice and suggest that it plays a key role in limiting injury and age-related neurogenesis.

Burns, A. J., A. E. Lomax, et al. (1996). "Interstitial cells of Cajal mediate inhibitory neurotransmission in the stomach." *Proc Natl Acad Sci U S A* **93**(21): 12008-13.

The structural relationships between interstitial cells of Cajal (ICC), varicose nerve fibers, and smooth muscle cells in the gastrointestinal tract have led to the suggestion that ICC may be involved in or mediate enteric neurotransmission. We characterized the distribution of ICC in the murine stomach and found two distinct classes on the basis of morphology and immunoreactivity to antibodies against c-Kit receptors. ICC with multiple processes formed a network in the myenteric plexus region from corpus to pylorus. Spindle-shaped ICC were found within the circular and longitudinal muscle layers (IC-IM) throughout the stomach. The density of these cells was greatest in the proximal stomach. IC-IM ran along nerve fibers and were closely associated with nerve terminals and adjacent smooth muscle cells. IC-IM failed to develop in mice with mutations in c-kit. Therefore, we used W/W(V) mutants to test whether IC-IM mediate neural inputs in muscles of the gastric fundus. The distribution of inhibitory nerves in the stomachs of c-kit mutants was normal, but NO-dependent inhibitory neuro-regulation was greatly reduced. Smooth muscle tissues of W/W(V) mutants relaxed in response to exogenous sodium nitroprusside, but the membrane potential effects of sodium nitroprusside were attenuated. These data suggest that IC-IM play a critical serial role in NO-

dependent neurotransmission: the cellular mechanism(s) responsible for transducing NO into electrical responses may be expressed in IC-IM. Loss of these cells causes loss of electrical responsiveness and greatly reduces responses to nitric nerve stimulation.

Caldwell, M., M. O'Neill, et al. (1994). "NG-Nitro-L-arginine protects against ischaemia-induced increases in nitric oxide and hippocampal neuro-degeneration in the gerbil." *Eur J Pharmacol* **260**(2-3): 191-200.

To assess the effects of the nitric oxide synthase inhibitor NG-Nitro-L-arginine on behavioural, biochemical and histological changes following global ischaemia, the Mongolian gerbil was used. Ischaemia was induced by bilateral carotid occlusion for 5 min. NG-Nitro-L-arginine was administered i.p. at either 1 or 10 mg/kg 30 min, 6, 24, and 48 h after surgery. 5 min bilateral carotid occluded animals were hyperactive 24, 48 and 72 h after surgery. NG-Nitro-L-arginine caused some attenuation in this hyperactivity. The activity of nitric oxide synthase was increased in the cerebellum, brain stem, striatum, cerebral cortex and hippocampus of 5 min bilateral carotid occluded animals. NG-Nitro-L-arginine reversed the increase in nitric oxide synthase activity in all brain regions. Extensive neuronal death was observed in the CA1 layer of the hippocampus in 5 min bilateral carotid occluded animals 96 h after surgery. NG-Nitro-L-arginine significantly protected against the neuronal death of cells in the CA1 layer.

Capello, E., R. Saccardi, et al. (2005). "Intense immunosuppression followed by autologous stem cell transplantation in severe multiple sclerosis." *Neurol Sci* **26 Suppl 4**: S200-3.

Aggressive forms of multiple sclerosis (MS) represent a limited group of demyelinating diseases that rapidly progress to severe disability. Currently available therapies are poorly effective against these clinical entities. Recently, it has been demonstrated that intense immunosuppression followed by autologous haematopoietic stem cell transplantation (AHSCT) can affect the clinical course of individuals with severe MS and completely abrogate the inflammatory activity detected by MRI. We report the result of the Italian phase 2 GITMO study, a multicentre study in which 21 MS patients, who were rapidly deteriorating and not responding to the usual therapeutic strategies, were treated with this procedure. The clinical effect of the treatment is long lasting, with a striking abrogation of inflammation detected by MRI findings. These results support a role for intense immunosuppression followed by ASCT as treatment in rapidly evolving MS cases unresponsive to conventional therapies.

Carter, L. A., J. L. MacDonald, et al. (2004). "Olfactory horizontal basal cells demonstrate a conserved multipotent progenitor phenotype." *J Neurosci* **24**(25): 5670-83.

Stem cells of adult regenerative organs share a common goal but few established conserved mechanisms. Within the neural stem cell niche of the mouse olfactory epithelium, we identified a combination of extracellular matrix (ECM) receptors that regulate adhesion and mitosis in non-neural stem cells [intercellular adhesion molecule-1 (ICAM-1), beta1, beta4, and alpha-1, -3, and -6 integrins] and on horizontal basal cells (HBCs), candidate olfactory neuro-epithelial progenitors. Using ECM receptors as our guide, we recreated a defined microenvironment in vitro that mimics olfactory basal lamina and, when supplemented with epidermal growth factor, transforming growth factor alpha, and leukemia inhibitory factor, allows us to preferentially expand multiple clonal adherent colony phenotypes from individual ICAM-1+ and ICAM-1+/beta1 integrin+-selected HBCs. The most highly mitotic colony-forming HBCs demonstrate multipotency, spontaneously generating more ICAM-positive presumptive HBCs, a combination of olfactory neuroglial progenitors, and neurons of olfactory and potentially nonolfactory phenotypes. HBCs thus possess a conserved adhesion receptor expression profile similar to non-neural stem cells, preferential self-replication in an in vitro environment mimicking their in vivo niche, and contain subpopulations of cells that can produce multiple differentiated neuronal and glial progeny from within and beyond the olfactory system in vitro.

Chekenya, M. and G. J. Pilkington (2002). "NG2 precursor cells in neoplasia: functional, histogenesis and therapeutic implications for malignant brain tumours." *J Neurocytol* **31**(6-7): 507-21.

Diffusely infiltrating astrocytic tumours of the central nervous system (CNS) are the most frequent intracranial neoplasms and account for more than 60% of all primary brain tumours in man. Until recently, it was generally accepted that the glial component of the mature CNS, consisted of differentiated astrocytes, ependymal cells, oligodendrocytes and the non-neuro-ectodermal microglial cells. There exists a recently recognised population of glial cells that express the NG2 proteoglycan (NG2 cells). NG2 cells are dynamic and undergo rapid morphological changes in response to a variety of CNS pathologies. They are highly motile cells, which interact with various extracellular matrix (ECM) in association with the integrin receptors. During angiogenesis and response to tissue injury,

NG2 precursor cells are recruited to sites where vessel growth and repair are occurring. NG2 is over-expressed by both tumour cells and pericytes on the blood vessels of malignant brain tumours. The function of NG2 cells in the CNS, and the notion of them as a source of and/or lineage marker for some gliomas are discussed. In addition, their possible role in glioma angiogenesis, proliferation and invasion will be considered as will their value in provision of targets for clinical and pre-clinical therapeutic strategies in brain tumours.

Chen, Y., H. Chen, et al. (2006). "Adenovirus-mediated small-interference RNA for in vivo silencing of angiotensin AT1a receptors in mouse brain." *Hypertension* **47**(2): 230-7.

Because of the lack of pharmacological approaches, molecular genetic methods have been required to differentiate between angiotensin type 1(AT1) receptor subtypes AT1a and AT1b. RNA interference is a new tool for the study of gene function, producing specific downregulation of protein expression. In this study, we used the small hairpin RNA (shRNA) cassette method to screen target sites for selectively silencing AT1a or AT1b receptor subtypes in cultured Neuro-2a cells using real-time RT-PCR. For in vivo functional studies, we used C57BL mice with arterial telemetric probes and computerized licking monitors to test the effect of adenovirus carrying the DNA sequence coding AT1a shRNA (Ad-AT1a-shRNA). Ad-AT1a-shRNA was injected into the lateral ventricle (intracerebroventricular) or the brain stem nucleus tractus solitaries/dorsal vagal nucleus (NTS/DVN) with measurement of water intake, blood pressure (BP), and heart rate (HR) for up to 20 days after injection. Tissue culture studies verified the specificity and the efficiency of the constructs. In animal studies, beta-galactosidase staining and Ang receptor binding assays showed expression of shRNA and downregulation of Ang AT1 receptors in the subfornical organ and NTS/DVN by >70%. Intracerebroventricular injection of Ad-AT1a-shRNA increased water intake with no effect on BP or HR. In contrast, microinjection of Ad-AT1a-shRNA into NTS/DVN caused a decrease in BP with no effect on HR or water intake. Results demonstrate the use of the RNA interference method in site-directed silencing of gene expression and provide a method for the in vivo study of Ang AT1 receptor function.

Chen, Y., J. Z. Shao, et al. (2008). "Mesenchymal stem cells: a promising candidate in regenerative medicine." *Int J Biochem Cell Biol* **40**(5): 815-20.

Mesenchymal stem cells were initially characterized as plastic adherent, fibroblastoid cells.

In recent years, there has been an increasing focus on mesenchymal stem cells since they have great plasticity and are potential for therapeutic applications. Mesenchymal stem cells or mesenchymal stem cell-like cells have been shown to reside within the connective tissues of most organs. These cells can differentiate into osteogenic, adipogenic and chondrogenic lineages under appropriate conditions. A number of reports have also indicated that these cells possess the capacity to trans-differentiate into epithelial cells and lineages derived from the neuro-ectoderm, and in addition, mesenchymal stem cells can migrate to the sites of injury, inflammation, and to tumors. These properties of mesenchymal stem cells make them promising candidates for use in regenerative medicine and may also serve as efficient delivery vehicles in site-specific therapy.

Cheng, Z., Q. Zheng, et al. (2009). "Targeted induction of differentiation of human bone mesenchymal stem cells into neuron-like cells." *J Huazhong Univ Sci Technolog Med Sci* **29**(3): 296-9.

A systematic method of isolating and culturing human bone mesenchymal stem cells (hMSCs), and inducing them to differentiate into neuron-like cells in vitro was established. The hMSCs were isolated from bone marrow with the lymphocyte-separating medium, cultured and expanded in vitro, and induced after addition of compound neuro-revulsants. The morphological changes of hMSCs were observed, and the expression of surface markers in induced hMSCs was immunocytochemically identified during induction period. The hMSCs could be separated, cultured and expanded in vitro. After induction by compound neuro-revulsants for 48 h, the changes of neuron-like cells, such as cellular shrinkage and neurite growth, were observed in some cells. The immunochemical staining revealed nestin (+) or NF (+), and GFAP (-). It was concluded that hMSCs were successfully cultured and induced to differentiate into neuron-like cells.

Chopp, M. and Y. Li (2008). "Treatment of stroke and intracerebral hemorrhage with cellular and pharmacological restorative therapies." *Acta Neurochir Suppl* **105**: 79-83.

We describe some of our studies on use of neuro-restorative agents for treatment of neural injury. We focus on cell-based therapies and select from a variety of statins. In addition, we show that cell-based and pharmacological-based therapies enhance brain plasticity and promote recovery of function after stroke and intracerebral hemorrhage (ICH). Injured brain recapitulates ontogeny. Cerebral tissue around the infarction expresses developmental genes, many of

which are present only during embryonic or neonatal stages of development. Brain response to injury undergoes remodeling with induction of angiogenesis, neurogenesis, and synaptogenesis. The attempt at remodeling, although expressed as a partial improvement in patients with stroke and ICH, is clearly insufficient to promote substantial recovery in many patients. The goal of restorative therapies should be to activate and amplify this endogenous restorative brain plasticity process to potentiate functional recovery. The logic of restorative therapy is to treat intact or marginally compromised tissue and not injured or dying tissue. Thus, these treatments can be made available for all neurological injury. Once demonstrated to be effective for treatment of a large middle cerebral artery occlusion (MCAo), these restorative treatments can be applied to many types of injury, including ICH, traumatic brain injury, and neurodegenerative disease such as experimental autoimmune encephalomyelitis and multiple sclerosis.

Christophidis, L. J., T. Gorba, et al. (2009). "Growth hormone receptor immunoreactivity is increased in the subventricular zone of juvenile rat brain after focal ischemia: a potential role for growth hormone in injury-induced neurogenesis." *Growth Horm IGF Res* **19**(6): 497-506.

BACKGROUND: During recovery from an ischemic brain injury, a cerebral growth hormone (GH) axis is activated. Whilst GH has been demonstrated to be neuroprotective both in vitro and in vivo, a role for GH in neuro-restorative processes after brain injury has yet to be studied. **OBJECTIVE:** To explore a role for GH in injury-induced neurogenesis by examining GH receptor (GH-R) immunoreactivity within the subventricular zone (SVZ) of juvenile rats after brain injury and by testing the proliferative capacity of GH on embryonic mouse neural stem cells. **DESIGN:** Twenty-one day old rats were subjected to unilateral hypoxic-ischemia of the brain and sacrificed 1-15days later. Coronal brain sections from these animals and age-matched naive controls were immunostained for GH-R and cell markers of neurogenesis. The level of GH-R immunoreactivity in the ipsilateral and contralateral SVZ of each animal was semi-quantified both by independent blinded scoring by two examiners and blinded image analysis. To examine the effect of GH on proliferation of embryonic mouse neural stem cells, cells were treated with increasing concentrations of rat pituitary GH for 48h in the presence of 5'-bromo-2'-deoxyuridine. **RESULTS:** The level of GH-R immunoreactivity in the ipsilateral SVZ was significantly increased 5days after injury vs. the contralateral SVZ, coinciding both spatially and temporally with injury-induced neurogenesis. The

population of GH-R immunopositive cells in the ipsilateral SVZ at this time was found to include proliferating cells (Ki67 immunopositive), neural progenitor cells (nestin immunopositive) and post-proliferative migratory neuroblasts (doublecortin immunopositive). Stimulation of embryonic mouse NSCs with physiological concentrations of rat pituitary GH elicited a dose-dependent proliferative response. CONCLUSION: These results indicate a novel role for GH and its receptor in injury-induced neurogenesis, and suggest that GH treatment may potentiate endogenous neuro-restorative processes after brain injury.

Conigliaro, A., M. Colletti, et al. (2008). "Isolation and characterization of a murine resident liver stem cell." *Cell Death Differ* **15**(1): 123-33.

Increasing evidence provides support that mammalian liver contains stem/progenitor cells, but their molecular phenotype, embryological derivation, biology and their role in liver cell turnover and regeneration remain to be further clarified. In this study, we report the isolation, characterization and reproducible establishment in line of a resident liver stem cell (RLSC) with immunophenotype and differentiative potentiality distinct from other previously described liver precursor/stem cells. RLSCs, derived from fetal and neonatal murine livers as well as from immortalized hepatocytic MMH lines and established in lines, are Sca+, CD34-, CD45-, alpha-fetoprotein+ and albumin-. This molecular phenotype suggests a non-hematopoietic origin. RLSC transcriptional profile, defined by microArray technology, highlighted the expression of a broad spectrum of 'plasticity-related genes' and 'developmental genes' suggesting a multi-differentiative potentiality. Indeed, RLSCs spontaneously differentiate into hepatocytes and cholangiocytes and, when cultured in appropriate conditions, into mesenchymal and neuro-ectodermal cell lineages such as osteoblasts/osteocytes, chondrocytes, astrocytes and neural cells. RLSC capability to spontaneously differentiate into hepatocytes, the lack of albumin expression and the broad differentiative potentiality locate them in a pre-hepatoblast/liver precursor cells hierarchical position. In conclusion, RLSCs may provide a useful tool to improve liver stem cell knowledge and to assess new therapeutic approaches for liver diseases.

Corio, M., J. Peute, et al. (1991). "Distribution of serotonin- and dopamine-immunoreactivity in the brain of the teleost *Clarias gariepinus*." *J Chem Neuroanat* **4**(2): 79-95.

The distribution of serotonergic and dopaminergic cell bodies and varicose fibres in the

brain of the teleost *Clarias gariepinus* was studied immunohistochemically using antisera against formaldehyde-conjugated serotonin and dopamine. Many serotonergic and dopaminergic fibres innervated the areas dorsalis telencephali pars medialis and pars lateralis dorsalis, as well as the area ventralis telencephali pars ventralis. In the diencephalon, a large number of serotonergic and some dopaminergic fibres were found in the preoptic nucleus, innervating the cells of this nucleus. In addition, serotonergic and dopaminergic fibres were observed in the pituitary stalk and in all regions of the pituitary gland. Moreover, the diencephalon contained the highest number of serotonin- or dopamine-immunoreactive cell bodies. These cells were confined to the same periventricular nuclei as the nucleus ventromedialis thalami, the nucleus posterior periventricularis, the nucleus lateralis tuberculi, the nuclei recessus lateralis and recessus posterioris. Most cells of these nuclei were in contact with the cerebrospinal fluid of the third ventricle. The brainstem contained serotonergic cell bodies in the raphe nuclei and a few serotonergic and dopaminergic fibres. The torus semicircularis was densely innervated by serotonergic fibres and, to a lesser extent, dopaminergic fibres. In the midbrain of *Clarias gariepinus*, no dopaminergic homologue of the substantia nigra was observed. The results are discussed both in a comparative and a physiological context. In this regard, special attention has been paid to the contribution of hypothalamic monoamines in the regulation of gonadotropin secretion as an essential step in the neuro-endocrine control of reproduction.

Cosentino, M., R. Bombelli, et al. (2000). "HPLC-ED measurement of endogenous catecholamines in human immune cells and hematopoietic cell lines." *Life Sci* **68**(3): 283-95.

A rapid and simple HPLC-ED method is described to identify and measure catecholamines (CTs) and their major metabolites in immune cells. Using this method, intracellular CTs were quantified in human peripheral blood mononuclear cells (PBMCs), T and B lymphocytes, monocytes and granulocytes. Immune cell subsets were separated by density gradient centrifugation and immunomagnetic cell sorting. CTs were also found in the human hematopoietic cell lines NALM-6 (pre-B) and (in smaller amounts) in Jurkat (T lymphoblastoid) and U937 (promonocytic). In cultured PBMCs, intracellular CTs were reduced by both the tyrosine hydroxylase inhibitor alpha-methyl-p-tyrosine and the chromaffin granule depletant reserpine. In NALM-6 cells, both alpha-methyl-p-tyrosine and the dopamine-beta-hydroxylase inhibitor disulfiram reduced

intracellular CTs, supporting the presence of active synthetic pathways in these cells. Since sympathoadrenergic mechanisms play a key role in the interactions between the immune system and the nervous system, these findings may be relevant for a better understanding of the neuro-immune network.

Couldrey, C., M. B. Carlton, et al. (1999). "A retroviral gene trap insertion into the histone 3.3A gene causes partial neonatal lethality, stunted growth, neuromuscular deficits and male sub-fertility in transgenic mice." *Hum Mol Genet* **8**(13): 2489-95.

Spermatogenesis is a complex developmental process involving cell division and differentiation. Approximately half of all sterile males have defects in spermatogenesis or sperm function. An insight into the molecular control points regulating this process might help in treating male infertility. Gene trapping in embryonic stem cells and the generation of transgenic mice represents one route to identify genes expressed during spermatogenesis. The trapped gene is tagged with a lacZ reporter gene so that the expression pattern of the gene can be visualized by staining for beta-galactosidase activity. We have screened transgenic mouse lines for expression of trapped genes in the gonads. One such trap event was shown to be in the replacement histone 3.3A gene (H3.3A). This gene was expressed ubiquitously during embryonic development until 13.5 days post-coitum and in the adult heart, kidney, brain, testes and ovaries. This mutation resulted in postnatal death of 50% of homozygous mutants. Surviving mutants displayed reduced growth rates when competing with wild-type siblings for food. Mutant mice also had a neuromuscular deficit and males displayed reduced copulatory activity. When copulations did occur, these resulted in very few pregnancies, suggesting that mutations in the H3.3A gene may contribute to some cases of impaired fertility in man.

Crigler, L., R. C. Robey, et al. (2006). "Human mesenchymal stem cell subpopulations express a variety of neuro-regulatory molecules and promote neuronal cell survival and neuritogenesis." *Exp Neurol* **198**(1): 54-64.

Mesenchymal stem cells (MSCs) transplanted at sites of nerve injury are thought to promote functional recovery by producing trophic factors that induce survival and regeneration of host neurons. To evaluate this phenomenon further, we quantified in human MSCs neurotrophin expression levels and their effects on neuronal cell survival and neuritogenesis. Screening a human MSC cDNA library revealed expressed transcripts encoding BDNF and beta-NGF but not NT-3 and NT-4. Immunostaining demonstrated that BDNF and beta-

NGF proteins were restricted to specific MSC subpopulations, which was confirmed by ELISA analysis of 56 separate subclones. Using a co-culture assay, we also demonstrated that BDNF expression levels correlated with the ability of MSC populations or subclones to induce survival and neurite outgrowth in the SH-SY5Y neuroblastoma cell line. However, these MSC-induced effects were only partially inhibited by a neutralizing anti-BDNF antibody. MSCs were also shown to promote neurite outgrowth within dorsal root ganglion explants despite secreting 25-fold lower level of beta-NGF required exogenously to produce a similar effect. Interrogation of the human MSC transcriptome identified expressed mRNAs encoding various neurite-inducing factors, axon guidance and neural cell adhesion molecules. Moreover, a subset of these transcripts was shown to correlate with BDNF expression in MSC subclones. Collectively, these studies reveal the existence of MSC subpopulations that co-express neurotrophins and other potent neuro-regulatory molecules, which contribute to MSC-induced effects on neuronal cell survival and nerve regeneration. These subpopulations may represent more potent vectors for treating a variety of neurological disorders.

Daadi, M. M., S. Saporta, et al. (2001). "In vitro induction and in vivo expression of bcl-2 in the hNT neurons." *Brain Res Bull* **56**(2): 147-52.

Bcl-2 encodes membrane-associated proteins that suppress programmed cell death in cells of various origins. Compelling evidence suggests that bcl-2 is also involved in neuronal differentiation and axonal regeneration. The human Neuro-Teratocarcinoma (hNT) neurons constitute a terminally differentiated human neuronal cell line that is derived from the Ntera-2/clone D1 (NT2) precursors upon retinoic acid (RA) treatment. After transplantation into the central nervous system (CNS), the hNT neurons survive, engraft, maintain their neuronal identity, and extend long neurite outgrowth. We were particularly interested in the intracellular determinants that confer these post-transplant characteristics to the hNT neurons. Thus, we asked whether the hNT neurons express bcl-2 after transplantation into the rat striatum and if RA induction of the neuronal lineage is mediated by bcl-2. The grafted hNT neurons were first identified using three different antibodies that recognize human-specific epitopes, anti-hMit, anti-hNuc, and NuMA. After a 1-month post-transplant survival time, NuMA immunostaining revealed that 12% of the hNT neurons survived the transplantation. These neurons extended long neuritic processes within the striatum, as demonstrated using the human-specific antibody against the midsize neurofilament subunit HO14.

Importantly, we found that 85% of the implanted hNT neurons expressed bcl-2 and that the in vitro induction of the neuronal lineage from the NT2 precursors with RA resulted in an upregulation of bcl-2 expression. Together, these data suggest that the differentiation of the hNT neurons to a neuronal lineage could be mediated at least partially by bcl-2.

De Cata, A., D. Intiso, et al. (2007). "Prolonged remission of neuro-Behcet disease following autologous transplantation." *Int J Immunopathol Pharmacol* **20**(1): 91-6.

Two young male patients with severe progressive Behcet's disease with neurological involvement (N-BD) were treated by high-dose immunosuppressive chemotherapy (HIC) followed by autologous CD34+ selected peripheral blood stem cell transplantation (APBSCT). Neurological impairment and disability were quantified by means of Expanded Disability Status Scale (EDSS). Neuroimaging included spine and brain MRI and brain SPECT by radiolabeling technetium (Tc99m) Ethyl Cisteinate Dimer (ECD). Disease progression halted after treatment in both patients. At 48 months of follow-up they were therapy-free and one showed neurological status and disability improvement. Brain MRI findings were unchanged in both patients, but SPECT-ECD showed an increase of blood flow in the hypoperfused cerebral areas in the ameliorated patient. Immune ablation followed by APBSCT can modify the course of severe N-BD. Because of the high risk and the transplant-related mortality, these cases have to be carefully selected.

de Hemptinne, I., C. Boucherie, et al. (2006). "Unilateral induction of progenitors in the spinal cord of hSOD1(G93A) transgenic rats correlates with an asymmetrical hind limb paralysis." *Neurosci Lett* **401**(1-2): 25-9.

Transgenic rats expressing a mutated form of the human Cu/Zn superoxide dismutase (hSOD1(G93A)) develop an amyotrophic lateral sclerosis (ALS)-like phenotype, including motor neurone degeneration and reactive gliosis in the spinal cord. This study aimed at examining the presence of endogenous neural progenitors in the lumbar spinal cord of these rats at the end-stage of the disease. Immunohistochemical data clearly demonstrated the induced expression of the stem cell factor reported as a chemoattractant and survival factor for neural stem cells as well as nestin (neuro-epithelial stem cell intermediate filament) in the spinal cord sections. While the stem cell factor immunolabelling appeared diffuse throughout the gray matter, nestin labelling was restricted to clusters within the ventral horn. Interestingly, as paralysis regularly develops

asymmetrically, induction of nestin was only detected on the ipsilateral side of the predominant symptoms. Finally, immunohistochemical detection of the stem cell factor receptor (c-Kit) revealed its specific induction which coincided with nestin immunolabelling. Together, these results are indicative of endogenous recruitment of neural progenitors within lesioned tissues and could support the development of treatments involving endogenous or exogenous stem cells.

de Hemptinne, I., C. Vermeiren, et al. (2004). "Induction of glial glutamate transporters in adult mesenchymal stem cells." *J Neurochem* **91**(1): 155-66.

Adult bone marrow mesenchymal stem cells are multipotent cells that can differentiate into a variety of mesodermal tissues. Recent studies have reported on their ability to also evolve into non-mesodermal cells, especially neural cells. While most of these studies revealed that manipulating these cells triggers the expression of typical neurone markers, less is known about the induction of neuronal- or glial-related physiological properties. The present study focused on the characterisation of glutamate transporters expression and activity in rat mesenchymal stem cells grown in culture conditions favouring their differentiation into astroglial cells. Ten days exposure of the cells to the culture supplement G5 was found to increase the expression of nestin (neuro-epithelial stem cell intermediate filament), an intermediate filament protein expressed by neural stem cells. Simultaneously, a robust induction of the high-affinity glutamate transporter GLT-1 (and GLAST) expression was detected by RT-PCR and immunocytochemistry. This expression was correlated with a highly significant increase in the Na⁺-dependent [3H]D-aspartate uptake. Finally, while glial fibrillary acidic protein immunoreactivity could not be detected, the induced expression of the astrocytic enzyme glutamine synthetase was demonstrated. These results indicate that in vitro differentiation of adult mesenchymal stem cells in neural precursors coincides with the induction of functional glutamate transport systems. Although the astrocytic nature of these cells remains to be confirmed, this observation gives support to the study of mesenchymal stem cells as a promising tool for the treatment of neurological diseases involving glutamate excitotoxicity.

Deda, H., M. C. Inci, et al. (2009). "Treatment of amyotrophic lateral sclerosis patients by autologous bone marrow-derived hematopoietic stem cell transplantation: a 1-year follow-up." *Cytotherapy* **11**(1): 18-25.

BACKGROUND: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder

characterized by progressive loss of spinal cord and cortical motoneurons. Despite improved understanding of the mechanisms underlying ALS, in clinical practice the management of ALS remains essentially supportive and focused on symptom relief. However, over the past few years stem cell research has expanded greatly as a tool for developing potential new therapies for treating incurable neurodegenerative diseases. **METHODS:** Thirteen patients with sporadic amyotrophic lateral sclerosis (SALS) were included in this study, and bone marrow (BM)-derived hematopoietic progenitor stem cells were used. We selected patients with bulbar involvement and severe loss of movement. Our aim was to put the stem cells into the end of the brain stem and at the beginning of the spinal cord because the blood-brain barrier is intact in ALS and this region was the most affected part in our patients. Under general anesthesia, a total laminectomy was performed at the C1-C2 level. Stem cells were injected to the anterior part of the spinal cord. **RESULTS:** During the follow-up of 1 year after stem cell implantation, nine patients became much better compared with their pre-operative status, confirmed by electro neuro myography (ENMG). One patient was stable without any decline or improvement in his status. Three patients died 1.5, 2 and 9 months, respectively, after stem cell therapy as a result of lung infection and myocardial infarction (MI). **DISCUSSION:** These results show that stem cell therapy is a safe, effective and promising treatment for ALS patients.

Deng, Y. B., X. G. Liu, et al. (2006). "Implantation of BM mesenchymal stem cells into injured spinal cord elicits de novo neurogenesis and functional recovery: evidence from a study in rhesus monkeys." *Cytotherapy* **8**(3): 210-4.

BACKGROUND: Transplantation of mesenchymal stem cells (MSC) in rodent models has proved to be an effective therapeutic approach for spinal cord injury (SCI). However, further studies in primate models are still needed before clinical application of MSC to patients. **METHODS:** MSC were isolated from rhesus monkey BM and induced ex vivo to differentiate into neural lineage cells. Induced cells were labeled with Hoechst 33342 and injected into the injured sites of rhesus SCI models. Function of the injured spinal cord was assessed using Tarlov behavior assessment, sensory responses and electrophysiologic tests of cortical somatosensory-evoked potential (CSEP) and motor-evoked potential (MEP). In vivo differentiation of the implanted cells was demonstrated by the presence of neural cell markers in Hoechst 33342-labeled cells. The re-establishment of the axonal pathway was demonstrated using a true blue (TB) chloride

retrograde tracing study. **RESULTS:** Monkeys achieved Tarlov grades 2-3 and nearly normal sensory responses 3 months after cell transplantation. Both CSEP and MEP showed recovery features. The presence of the neural cell markers neurofilament (NF), neuro-specific enolase (NSE) and glial fibrillary acidic protein (GFAP) was observed in approximately 10% of Hoechst 33342-labeled cells. TB, originally injected at the caudal side of injured sites, was traceable in the rostral thoracic spinal cord, red nucleus and sensory motor cortex. **DISCUSSION:** Our results suggest that the implantation of MSC-derived cells elicits de novo neurogenesis and functional recovery in a non-human primate SCI model and should harness the clinical application of BM MSC in SCI patients.

Dezawa, M. (2006). "Insights into autotransplantation: the unexpected discovery of specific induction systems in bone marrow stromal cells." *Cell Mol Life Sci* **63**(23): 2764-72.

Many kinds of cells, including embryonic stem cells and tissue stem cells, have been considered candidates for transplantation therapy for neuro- and muscle-degenerative diseases. Bone marrow stromal cells (MSCs) also have great potential as therapeutic agents since they are easily isolated and can be expanded from patients without serious ethical or technical problems. Recently, new methods for the highly efficient and specific induction of functional neurons and skeletal muscle cells have been developed for MSCs. These induced cells were transplanted into animal models of stroke, Parkinson's disease and muscle degeneration, resulting in the successful integration of transplanted cells and improvement in the behavior of the transplanted animals. Here I describe the discovery of these induction systems and focus on the potential use of MSC-derived cells for 'auto-cell transplantation therapy' in neuro- and muscle-degenerative diseases.

Dezawa, M., H. Ishikawa, et al. (2005). "Potential of bone marrow stromal cells in applications for neuro-degenerative, neuro-traumatic and muscle degenerative diseases." *Curr Neuropharmacol* **3**(4): 257-66.

Cell transplantation is a promising strategy for the treatment of neurodegenerative and muscle degenerative diseases. Many kinds of cells, including embryonic stem cells and tissue stem cells, have been considered as candidates for transplantation therapy. Bone marrow stromal cells (MSCs) have great potential as therapeutic agents since they are easy to isolate and can be expanded from patients without serious ethical or technical problems. We discovered a new method for the highly efficient and specific

induction of functional Schwann cells, neurons and skeletal muscle lineage cells from both rat and human MSCs. These induced cells were transplanted into animal models of neurotraumatic injuries, Parkinson's disease, stroke and muscle dystrophies, resulting in the successful integration of transplanted cells and an improvement in behavior of the transplanted animals. Here we focus on the respective potentials of MSC-derived cells and discuss the possibility of clinical application in degenerative diseases.

Dietrich, J. and G. Kempermann (2006). "Role of endogenous neural stem cells in neurological disease and brain repair." *Adv Exp Med Biol* **557**: 191-220.

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 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 under 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.

Doolittle, N. D., C. P. Anderson, et al. (2001). "Importance of dose intensity in neuro-oncology

clinical trials: summary report of the Sixth Annual Meeting of the Blood-Brain Barrier Disruption Consortium." *Neuro Oncol* **3**(1): 46-54.

Therapeutic options for the treatment of malignant brain tumors have been limited, in part, because of the presence of the blood-brain barrier. For this reason, the Sixth Annual Meeting of the Blood-Brain Barrier Disruption Consortium, the focus of which was the "Importance of Dose Intensity in Neuro-Oncology Clinical Trials," was convened in April 2000, at Government Camp, Mount Hood, Oregon. This meeting, which was supported by the National Cancer Institute, the National Institute of Neurological Disorders and Stroke, and the National Institute of Deafness and Other Communication Disorders, brought together clinicians and basic scientists from across the U.S. to discuss the role of dose intensity and enhanced chemotherapy delivery in the treatment of malignant brain tumors and to design multicenter clinical trials. Optimizing chemotherapy delivery to the CNS is crucial, particularly in view of recent progress identifying certain brain tumors as chemosensitive. The discovery that specific constellations of genetic alterations can predict which tumors are chemoresponsive, and can therefore more accurately predict prognosis, has important implications for delivery of intensive, effective chemotherapy regimens with acceptable toxicities. This report summarizes the discussions, future directions, and key questions regarding dose-intensive treatment of primary CNS lymphoma, CNS relapse of systemic non-Hodgkin's lymphoma, anaplastic oligodendroglioma, high-grade glioma, and metastatic cancer of the brain. The promising role of cytoenhancers and chemoprotectants as part of dose-intensive regimens for chemosensitive brain tumors and development of improved gene therapies for malignant gliomas are discussed.

Dunn, I. F. and P. M. Black (2003). "The neurosurgeon as local oncologist: cellular and molecular neurosurgery in malignant glioma therapy." *Neurosurgery* **52**(6): 1411-22; discussion 1422-4.

Malignant gliomas are among the most challenging of all cancers to treat successfully, being characterized not only by aggressive proliferation and expansion but also by inexorable tumor invasion into distant brain tissue. Although considerable progress has been made in the treatment of these tumors with combinations of surgery, radiotherapy, and chemotherapy, these efforts have not been curative. Neurosurgeons as oncologists have increasingly turned their attention to therapies on a molecular scale. Of particular interest to neurosurgeons is the ability to deliver therapy locally to the tumor site or to take advantage of existing immunological mediators,

enhancing drug concentrations or therapeutic cell numbers while bypassing the blood-brain barrier to maximize efficacy and minimize systemic toxicity. Exciting local-therapy approaches have been proposed for these devastating tumors. In this review, we discuss the potential applications of bioreactors, neural stem cells, immunotherapies, biodegradable polymers, and convection-enhanced drug delivery in the treatment of malignant gliomas. These approaches are at different stages of readiness for application in clinical neurosurgery, and their eventual effects on the morbidity and mortality rates of gliomas among human patients are difficult to ascertain from successes in animal models. Nevertheless, we are entering an exciting era of "nanoneurosurgery," in which molecular therapies such as those discussed here may routinely complement existing surgical, radiological, and chemotherapeutic approaches to the treatment of neuro-oncological disease. The potential to deploy any of a number of eloquently devised molecular therapies may provide renewed hope for neurosurgeons treating malignant gliomas.

Ebadi, M., H. Brown-Borg, et al. (2005). "Metallothionein-mediated neuroprotection in genetically engineered mouse models of Parkinson's disease." *Brain Res Mol Brain Res* **134**(1): 67-75.

Parkinson's disease is characterized by a progressive loss of dopaminergic neurons in the substantia nigra zona compacta, and in other sub-cortical nuclei associated with a widespread occurrence of Lewy bodies. The cause of cell death in Parkinson's disease is still poorly understood, but a defect in mitochondrial oxidative phosphorylation and enhanced oxidative and nitrative stresses have been proposed. We have studied control(wt) (C57B1/6), metallothionein transgenic (MTtrans), metallothionein double gene knock (MTdko), alpha-synuclein knock out (alpha-syn(ko)), alpha-synuclein-metallothionein triple knock out (alpha-syn-MTtko), weaver mutant (wv/wv) mice, and Ames dwarf mice to examine the role of peroxynitrite in the etiopathogenesis of Parkinson's disease and aging. Although MTdko mice were genetically susceptible to 1, methyl, 4-phenyl, 1,2,3,6-tetrahydropyridine (MPTP) Parkinsonism, they did not exhibit any overt clinical symptoms of neurodegeneration and gross neuropathological changes as observed in wv/wv mice. Progressive neurodegenerative changes were associated with typical Parkinsonism in wv/wv mice. Neurodegenerative changes in wv/wv mice were observed primarily in the striatum, hippocampus and cerebellum. Various hallmarks of apoptosis including caspase-3, TNFalpha, NFkappaB, metallothioneins (MT-1, 2) and complex-1 nitration were increased; whereas glutathione, complex-1, ATP, and Ser(40)-

phosphorylation of tyrosine hydroxylase, and striatal 18F-DOPA uptake were reduced in wv/wv mice as compared to other experimental genotypes. Striatal neurons of wv/wv mice exhibited age-dependent increase in dense cored intra-neuronal inclusions, cellular aggregation, proto-oncogenes (c-fos, c-jun, caspase-3, and GAPDH) induction, inter-nucleosomal DNA fragmentation, and neuro-apoptosis. MTtrans and alpha-Syn(ko) mice were genetically resistant to MPTP-Parkinsonism and Ames dwarf mice possessed significantly higher concentrations of striatal coenzyme Q10 and metallothioneins (MT 1, 2) and lived almost 2.5 times longer as compared to control(wt) mice. A potent peroxynitrite ion generator, 3-morpholinolinosydnonimine (SIN-1)-induced apoptosis was significantly attenuated in MTtrans fetal stem cells. These data are interpreted to suggest that peroxynitrite ions are involved in the etiopathogenesis of Parkinson's disease, and metallothionein-mediated coenzyme Q10 synthesis may provide neuroprotection.

Eisch, A. J. and G. C. Harburg (2006). "Opiates, psychostimulants, and adult hippocampal neurogenesis: Insights for addiction and stem cell biology." *Hippocampus* **16**(3): 271-86.

Once thought to produce global, nonspecific brain injury, drugs of abuse are now known to produce selective neuro-adaptations in particular brain regions. These neuro-adaptations are being closely examined for clues to the development, maintenance, and treatment of addiction. The hippocampus is an area of particular interest, as it is central to many aspects of the addictive process, including relapse to drug taking. A recently appreciated hippocampal neuro-adaptation produced by drugs as diverse as opiates and psychostimulants is decreased neurogenesis in the sub-granular zone (SGZ). While the role of adult-generated neurons is not clear, their functional integration into hippocampal circuitry raises the possibility that decreased adult SGZ neurogenesis may alter hippocampal function in such a way as to maintain addictive behavior or contribute to relapse. Here, we review the impact of opiates and psychostimulants on the different stages of cell development in the adult brain, as well as the different stages of the addictive process. We discuss how examination of drug-induced alterations of adult neurogenesis advances our understanding of the complex mechanisms by which opiates and psychostimulants affect brain function while also opening avenues for novel ways of assessing the functional role of adult-generated neurons. In addition, we highlight key discrepancies in the field and underscore the necessity to move "beyond BrdU"--beyond merely counting new hippocampal cells

labeled with the S phase marker bromodeoxyuridine--so as to probe mechanistic questions about how drug-induced alterations in adult hippocampal neurogenesis occur and what the functional ramifications of alterations in neurogenesis are for addiction.

El Faza, S., N. Gharbi, et al. (2000). "Vasopressin and A1 noradrenaline turnover during food or water deprivation in the rat." Comp Biochem Physiol C Toxicol Pharmacol **126**(2): 129-37.

In the present study, we have examined in Wistar rats the effects of food or water deprivation of 3 days on the hypophyso-adrenal axis, vasopressinergic system and activity of A1 noradrenergic brain stem cell group, which is involved in the control of the hypothalamic neuro-endocrine activity. Levels of adrenocorticotrophic hormone (ACTH) and vasopressin (AVP) were determined by radio-immunoassay, and corticosterone level was determined by fluorimetric method. Plasma levels of ACTH and corticosterone were greatly increased in both groups of rats. In water-deprived rats, plasma AVP (13.83 +/- 1.63 vs. 3.03 +/- 0.23 pg/ml) and osmolality levels were significantly elevated with a marked decrease of AVP hypophysis content (272 +/- 65 vs. 1098 +/- 75 ng/mg protein), but not in food-deprived rats in which osmolality did not change and AVP remained stocked (2082 +/- 216 ng/mg protein) in the hypophysis without release in the plasma (1.11 +/- 0.23 pg/ml). These observations indicated that both food-deprivation and water-deprivation stimulated the pituitary adrenal axis thereby suggesting a stress state. AVP production is stimulated both by fluid and food restriction but is secreted with differential effects: during food restriction AVP secretion is limited to supporting the hypothalamic pituitary-adrenal system.

Finlay, J. L. (1999). "The role of high-dose chemotherapy and stem cell rescue in the treatment of malignant brain tumors: a reappraisal." Pediatr Transplant **3 Suppl 1**: 87-95.

The outcome for children with malignant brain tumors has improved modestly in recent years. Notable is the improved 5-yr disease-free survival for those children with 'standard-risk' medulloblastoma and other primitive neuro-ectodermal tumors (PNET) (i.e. tumors without neuraxis dissemination at presentation). For other children with newly diagnosed malignant brain tumors, especially in the absence of radical surgical resection, the outcome remains poor despite surgery, irradiation and conventional chemotherapy. Patients whose tumors recur despite initial therapy continue to experience a dismal outlook with these conventional strategies of treatment. In an attempt to improve the outlook for

such brain tumor patients with poor prognoses, strategies utilizing high-dose (potentially myeloablative) chemotherapy with autologous stem cell rescue have been developed. These studies, conducted initially in patients with recurrent tumors, were then extended to patients with newly diagnosed malignant gliomas and brain-stem tumors, as well as to young children with various malignant brain tumors at diagnosis in an attempt to avoid irradiation to the brain. The results of several of these studies are summarized, updating information reviewed in an earlier summary in 1996, demonstrating durable disease-free survival for a proportion of patients with recurrent malignant gliomas and medulloblastomas/PNET, as well as encouraging data in some of those patients with newly diagnosed brain tumors.

Fishbein, T. M., G. Novitskiy, et al. (2009). "Rejection reversibly alters enteroendocrine cell renewal in the transplanted small intestine." Am J Transplant **9**(7): 1620-8.

Acute small intestinal allograft rejection presents clinically as an abrupt increase in ileal fluid output in the absence of extensive inflammation. We questioned whether acute intestinal rejection might be accompanied by a disturbance of normal intestinal stem cell differentiation. We examined the intestinal epithelial secretory cell lineage among patients experiencing early rejection before and during rejection as well as following corrective therapy. Lineage-specific progenitors were identified by their expression of stage-specific transcription factors. Progenitors of the enteroendocrine cell (EEC) expressing neurogenin-3 (NEUROG3) were found to be disproportionately reduced in numbers, along with their more mature EEC derivatives expressing neuro D; the enteric hormone PYY was the most profoundly depleted of all the EEC products evaluated. No change in the numbers of goblet or Paneth cells was observed. Steroid treatment resulted in resolution of clinical symptoms, restoration of normal patterns of EEC differentiation and recovery of normal levels of enteric hormones. Acute intestinal rejection is associated with a loss of certain subtypes of EEC, most profoundly, those expressing PYY. Deficiency of the mature EECs appears to occur as a consequence of a mechanism that depletes NEUROG3 EEC progenitors. Our study highlights the dynamics of the EEC lineage during acute intestinal rejection.

Fujita, S. (2003). "The discovery of the matrix cell, the identification of the multipotent neural stem cell and the development of the central nervous system." Cell Struct Funct **28**(4): 205-28.

In the early 1960s I applied 3H-thymidine autoradiography to the study of the cells constituting the neural tube, and found that its wall was composed solely of one kind of single-layered epithelial cell, which perform an elevator movement between the mitotic and DNA-synthetic zones in the wall in accord with the cell cycle. They were identified as multipotent stem cells of the central nervous system (CNS) to which I gave the name of matrix cells. (3)H-thymidine autoradiography also revealed the chronology of development of these matrix cells: At first they proliferate only to expand the population (stage I), then switch to differentiate specific neuroblasts in given sequences (stage II), and finally change themselves into ependymoglioblasts, common progenitors of ependymal cells and neuroglia (stage III). Based on these findings, I proposed a monophyletic view of cytogenesis of the central nervous system. This matrix cell theory claiming the existence of multipotent stem cells has long been the target of severe criticism and not been accepted among neuro-embryologists for a long time. Recent findings by experimental and clinical neuroscientists on the importance of stem cells have renewed interest in the nature and biology of the multipotent neural stem cells. The present paper describes how the concept of the matrix cell (multipotent neural stem cells in vivo) emerged and what has come out from this view over the last 45 years, and how the basic concept of the matrix cell theory has recently been reconfirmed after a long period of controversy and neglect.

Fukunaga, A., T. Kawase, et al. (2003). "Functional recovery after simultaneous transplantation with neuro-epithelial stem cells and adjacent mesenchymal tissues into infarcted rat brain." *Acta Neurochir (Wien)* **145**(6): 473-80, discussion 480-1.

BACKGROUND: Cerebral infarction results in impairment of motor and cognitive functions. We performed intracranial transplantation of multipotential neuro-epithelial stem cells with mesenchyme into experimentally large ischemic lesions to study their potential to relieve deficits. **METHODS:** Wistar albino rats were subjected to transient middle cerebral artery occlusion for 60 minutes, producing an extensive ischemic lesion in the ipsilateral striatum and adjacent cerebral cortex. The rat mesencephalic neural plate at the early somite stage (embryonic day 10.5) together with adjacent ventral mesenchyme was used as donor material. We performed histological and immunohistochemical studies, with antibodies against tyrosine hydroxylase, and dopamine- and adenosine 3': 5'-monophosphate-regulated phosphoprotein 32 (DARPP-32; a striatal marker). Micro-angiograms were made by using

Microfil silicone rubber. Morris Water-maze learning and treadmill task were employed to evaluate motor and cognitive functions. **FINDINGS:** A viable non-tumoral mass was recognized in the rat striatum, up to as long as 156 days after transplantation. There were many cells positive for tyrosine hydroxylase or DARPP-32 in the graft. Some of the DARPP-32 positive cells within the graft had extended their dendrites into host tissues. In the micro-angiograms, many fine vessels were observed within the graft and dilated vessels meandered around the graft. Transplanted animals recovered significantly better in motor and cognitive functions than animals injected with only culture medium. **INTERPRETATION:** Neuro-epithelial stem cells may follow several lines of differentiation; along the naturally genetically programmed line of differentiation, or along other cell lines depending on different environments. Grafting of neuro-epithelial stem cells with mesenchyme may merit a further study as a treatment for cerebral infarction.

Georgopoulou, N., C. Hurel, et al. (2006). "BM88 is a dual function molecule inducing cell cycle exit and neuronal differentiation of neuroblastoma cells via cyclin D1 down-regulation and retinoblastoma protein hypophosphorylation." *J Biol Chem* **281**(44): 33606-20.

Control of cell cycle progression/exit and differentiation of neuronal precursors is of paramount importance during brain development. BM88 is a neuronal protein associated with terminal neuron-generating divisions in vivo and is implicated in mechanisms underlying neuronal differentiation. Here we have used mouse neuroblastoma Neuro 2a cells as an in vitro model of neuronal differentiation to dissect the functional properties of BM88 by implementing gain- and loss-of-function approaches. We demonstrate that stably transfected cells overexpressing BM88 acquire a neuronal phenotype in the absence of external stimuli, as judged by enhanced expression of neuronal markers and neurite outgrowth-inducing signaling molecules. In addition, cell cycle measurements involving cell growth assays, BrdUrd incorporation, and fluorescence-activated cell sorting analysis revealed that the BM88-transfected cells have a prolonged G(1) phase, most probably corresponding to cell cycle exit at the G(0) restriction point, as compared with controls. BM88 overexpression also results in increased levels of the cell cycle regulatory protein p53, and accumulation of the hypophosphorylated form of the retinoblastoma protein leading to cell cycle arrest, with concomitant decreased levels and, in many cells, cytoplasmic localization of cyclin D1. Conversely, BM88 gene silencing using RNA interference experiments

resulted in acceleration of cell proliferation accompanied by impairment of retinoic acid-induced neuronal differentiation of Neuro 2a cells. Taken together, our results suggest that BM88 plays an essential role in regulating cell cycle exit and differentiation of Neuro 2a cells toward a neuronal phenotype and further support its involvement in the proliferation/differentiation transition of neural stem/progenitor cells during embryonic development.

Gil-Loyzaga, P. (2005). "Neuroplasticity in the auditory system." Rev Laryngol Otol Rhinol (Bord) **126**(4): 203-7.

An increasing interest on neuroplasticity and nerve regeneration within the auditory receptor and pathway has developed in recent years. The receptor and the auditory pathway are controlled by highly complex circuits that appear during embryonic development. During this early maturation process of the auditory sensory elements, we observe the development of two types of nerve fibers: permanent fibers that will remain to reach full-term maturity and other transient fibers that will ultimately disappear. Both stable and transitory fibers however, as well as developing sensory cells, express, and probably release, their respective neuro-transmitters that could be involved in neuroplasticity. Cell culture experiments have added significant information; the in vitro administration of glutamate or GABA to isolated spiral ganglion neurons clearly modified neural development. Neuroplasticity has been also found in the adult. Nerve regeneration and neuroplasticity have been demonstrated in the adult auditory receptors as well as throughout the auditory pathway. Neuroplasticity studies could prove interesting in the elaboration of current or future therapy strategies (e.g.: cochlear implants or stem cells), but also to really understand the pathogenesis of auditory or language diseases (e.g.: deafness, tinnitus, dyslexia, etc.).

Greenfield, J. P., D. K. Jin, et al. (2009). "Surrogate markers predict angiogenic potential and survival in patients with glioblastoma multiforme." Neurosurgery **64**(5): 819-26; discussion 826-7.

OBJECTIVE: The neovascularization of malignant brain tumors is a poorly understood phenomenon. Radiographic and histological evidence of increased vascularity correlate with clinical grade of gliomas. However, a quantitative noninvasive assay to assess glioma vascularity and associated clinical aggressiveness has not been developed. Circulating endothelial progenitor cells are unique vascular precursors recruited from the bone marrow through the circulation to form new tumor blood vessels. These cells were measured in patients undergoing

surgery for glioblastoma multiforme (GBM). We hypothesized that this might reflect the extent of tumor vascularity, predict prognosis, or be useful as an assay to assess response to antiangiogenesis therapies. In addition, we report on a novel in vitro assay to assess the proangiogenic activity within the plasma samples obtained from glioma patients. **METHODS:** Fifty-six patients with various-grade gliomas had peripheral venous blood collected at the time of surgery and at subsequent visits during the follow-up period. The blood was separated into plasma and cellular fractions. The plasma was utilized in a human umbilical vein endothelial cell-based angiogenic assay. The cellular fraction containing endothelial progenitor cells was isolated, and specific cellular phenotypes were immunologically separated and counted using flow cytometry. Pathological samples were reviewed at the time of initial resection, and each patient's clinical course was monitored until the time of manuscript submission. **RESULTS:** Plasma derived from peripheral blood of patients with GBM scored significantly higher on the functional angiogenic scale compared with plasma derived from patients with low-grade gliomas and from controls. In addition, all patients with GBM had measurable numbers of bone marrow-derived endothelial precursor cells coexpressing CD133 and vascular endothelial growth factor receptor 2 in their peripheral circulation at the time of tumor resection. These cells range from less than 0.1% to 1.6% of the entire circulating mononuclear white blood cell population, or approximately 200,000 cells in some patients. A statistically significant relationship was observed between the percentage of endothelial progenitor cells in the peripheral blood at the time of initial GBM resection and survival. **CONCLUSION:** These studies suggest that plasma and circulating CD133+ vascular endothelial growth factor receptor 2+ proangiogenic cells are present in the peripheral blood of patients with glioma and can be used as a surrogate biomarker to measure tumor angiogenicity. These cells can be measured at the time of diagnosis and monitored in the postoperative period. These assays can be used to predict tumor aggressiveness. Also promising is their potential to identify patients with increased angiogenic activity who might respond maximally to antiangiogenesis therapies or to assess tumor response in patients using those therapies as the use of these adjuvant molecular modalities becomes more prevalent in neuro-oncology.

Grill, J. and R. Bhangoo (2007). "Recent development in chemotherapy of paediatric brain tumours." Curr Opin Oncol **19**(6): 612-5.

PURPOSE OF REVIEW: Chemotherapy has gained a larger importance in the management of brain

tumours, especially in children. RECENT FINDINGS: Converging results were presented in 2005 by the German, French and North-American cooperative groups indicating that a subgroup of young children with medulloblastoma (i.e. those with desmoplastic histology) could be cured with chemotherapy only strategies. The usefulness of high-dose chemotherapy followed by stem-cell transplant was shown not only as salvage strategy but also upfront in high-risk patients with medulloblastoma. Diffuse pontine glioma remains a devastating disease despite numerous attempts to improve on the standard radiotherapy. Targeted therapies have entered the paediatric neuro-oncology field as well. SUMMARY: In the most frequent paediatric brain tumors (medulloblastoma and low grade gliomas), the improvements have been impressive in recent years. These patients still await new targeted therapies to lower the burden of treatments and their related side-effects. Most of the brain tumours, however, are rare and the development of specific protocols too slow. Likely, they may have very specific biologic abnormalities that could be efficiently targeted in the near future.

Ha, Y., H. S. Park, et al. (2005). "Synthes Award for Resident Research on Spinal Cord and Spinal Column Injury: granulocyte macrophage colony stimulating factor (GM-CSF) prevents apoptosis and improves functional outcome in experimental spinal cord contusion injury." *Clin Neurosurg* **52**: 341-7.

OBJECTIVE: Granulocyte macrophage colony stimulating factor (GM-CSF) is a potent hematopoietic cytokine, which stimulates stem cell proliferation in the bone marrow and inhibits apoptotic cell death in leukocytes. However, the effects of GM-CSF in the central nervous system are still unclear. The present study was undertaken to determine if GM-CSF can rescue neuronal cells from apoptosis and improve neurologic function in a spinal cord injury (SCI) model. **METHODS:** To study the effect of GM-CSF on apoptotic neuronal death, we used a staurosporine-induced neuronal death model in a Neuro 2A (N2A) cell line (in vitro) and in a rat SCI model (in vivo). N2A cells were preincubated with GM-CSF for 60 minutes before being exposed to staurosporine for 24 hours. To inhibit GM-CSF, we pretreated N2A cells with antibodies of the GM-CSF receptor for 60 minutes. SCI was made by clip compression. Rats were treated with daily GM-CSF (20 microg/d) for 5 days. The number of apoptotic cells in the spinal cord and neurologic improvements were checked. **RESULTS:** GM-CSF pretreatment was found to significantly protect N2A cells from apoptosis, and neutralizing antibodies for the GM-CSF receptors inhibited the rescuing effect of GM-

CSF on apoptosis. In the rat SCI model, neurologic functions improved significantly in the GM-CSF-administered group versus the phosphate buffered saline (PBS)-treated control. TUNEL (terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeled) staining showed that GM-CSF administration reduced apoptosis in the injured spinal cord. **CONCLUSION:** Treatment of SCI with GM-CSF showed some beneficial effects. Neuronal protection against apoptosis is viewed as a likely mechanism underlying the therapeutic effect of GM-CSF in SCI.

Haeusler, G., I. Lues, et al. (1992). "Pharmacological basis for antihypertensive therapy with a novel dopamine agonist." *Eur Heart J* **13 Suppl D**: 129-35.

In the past, nearly all major mechanisms involved in the regulation of blood pressure have become targets of antihypertensive drugs. They include the brain stem with its neuronal circuits of central cardiovascular regulation, the sympathetic neuro-effector system, the kidney, the renin angiotensin aldosterone system and the vascular smooth muscle cell. There are various ways of influencing the function of the sympathetic nervous system, but the clinical potential of one mechanism of action has not yet been explored in detail. Drugs that inhibit noradrenaline release through stimulation of inhibitory receptors located at adrenergic nerve terminals in the cardiovascular system (inhibitory presynaptic receptors) are not available for the treatment of hypertension. Among the multiple presynaptic receptors, dopamine receptors which belong to the dopamine₂ subtype, are of particular interest. Carmoxirole is a novel indole derivative with a potent agonist action selective for dopamine₂-receptors of the periphery. Experimental evidence shows that carmoxirole lowers blood pressure in various models of hypertension mainly or exclusively through inhibition of noradrenaline release from sympathetic nerve endings. This effect of carmoxirole is mediated by presynaptic dopamine receptors with the characteristic that release inhibition is restricted to low rates of sympathetic nerve discharge.

Hamba, M. and H. Onimaru (1998). "Newborn rat brainstem preparation with the trigeminal nerve attached for pain study." *Brain Res Brain Res Protoc* **3**(1): 7-13.

Studies using a brainstem-spinal cord preparation isolated from newborn rats have provided substantial information on neuro-physiology, -pharmacology and -anatomy of the respiratory center, such as mechanisms of respiratory rhythm generation, development of a respiratory center or respiratory reflex [T. Murakoshi, T. Suzue, S. Tamai, A

pharmacological study on respiratory rhythm in the isolated brainstem-spinal cord preparation from newborn rat, *Br. J. Pharmac.* 86 (1985) 95-104 [5]; H. Onimaru, A. Arata, I. Homma, Primary respiratory rhythm generator in the medulla of brainstem-spinal cord preparations from newborn rats, *Brain Res.* 445 (1988) 314-324 [6]; H. Onimaru, I. Homma, Whole cell recordings from respiratory neurons in the medulla of brainstem-spinal cord preparations isolated from newborn rats, *Pflugers Arch.* 420 (1992) 399-406 [7]; J.C. Smith, K. Ballanyi, D.W. Richter, Whole-cell patch clamp recordings from respiratory neurons in neonatal rat brainstem in vitro, *Neurosci. Lett.* 314 (1992) 153-156 [10]; T. Suzue, Respiratory rhythm generation in the in vitro brainstem-spinal cord preparation of the neonatal rat, *J. Physiol. (London)* 354 (1984) 173-183 [11], reviewed in H. Onimaru, A. Arata, I. Homma, Neuronal mechanisms of respiratory rhythm generation: An approach using in vitro preparation, *Jpn. J. Physiol.* 47 (1997) 385-403 [8]. Recently, the dissecting method of the preparation was modified to introduce a brainstem preparation with the trigeminal primary afferents attached for pain studies [M. Hamba, Repetitive stimulation potentiated the stimulus-evoked firing in the trigeminal caudalis-in vitro study. *Neurosci. Res.* 20 (1996) s163 [2]; M. Hamba, Stimulation-induced responses of the trigeminal caudal neurons in the brainstem preparation isolated from newborn rats, *Brain Res.* 785 (1998) 66-74 [3]]. As reported previously [3], the activity-dependent change in the excitability of pain-processing neurons, wind-up phenomenon, was studied in the trigeminal caudalis by stimulating the mandibular nerve, using a modified brainstem preparation isolated from newborn rats. The caudalis, the medulla dorsal horn, is known as the center for processing pain and sensory information from the cranio-facial area. The results indicated that the brainstem preparation is applicable for studies on the neuroplasticity at the pain-processing synapses. Here, we describe the method for isolation of a brainstem preparation with the trigeminal mandibular nerve attached and for recording the synaptic response evoked in the caudal neurons, using a whole-cell patch clamp technique. In the present study, we demonstrated repetitive stimulation-induced responses of caudal neurons at postnatal day 1 as an example showing the feasibility of the preparation for pain studies.

Hartenstein, V., C. Nassif, et al. (1998). "Embryonic development of the *Drosophila* brain. II. Pattern of glial cells." *J Comp Neurol* 402(1): 32-47.

Glial cells in *Drosophila* and other insects are organized in an outer layer that envelops the surface of the central and peripheral nervous system

(subperineurial glia, peripheral glia), a middle layer associated with neuronal somata in the cortex (cell body glia), and an inner layer surrounding the neuropile (longitudinal glia, midline glia, nerve root glia). In the ventral nerve cord, most glial cells are formed by a relatively small number of neurogliaoblasts; subsequently, glial cell precursors migrate and spread out widely to reach their final destination. By using a glia-specific marker (antibody against the Repo protein) we have reconstructed the pattern of glial cell precursors at successive developmental stages, focusing on the glia of the supraesophageal ganglion and subesophageal ganglion which are not described in previous studies. Digitized images of consecutive optical sections were used to generate 3-D models that show the spatial pattern of glial cell precursors in relationship to the neuropile, brain surface, and peripheral nerves. Similar to their spatial organization in the ventral nerve cord, glial cells of the brain populate the brain nerves and outer surface, cortical cell body layer, and cortex-neuropile interface. Neuropile-associated glial cells arise from a cluster located at the base of the supraesophageal ganglion; from this position, they migrate dorsally along the developing axon tracts and by late embryonic stages form a sheath around all neuropile compartments, including the supraesophageal commissure. Surface and cell body glial cells derive from several discrete foci, notably two large clusters at the deutocerebrum/protocerebrum boundary and the posterior protocerebrum. From these foci, glial cells then fan out to envelop the surface of the supraesophageal ganglion.

Hayashi, H., S. Endo, et al. (2001). "JC virus large T protein transforms rodent cells but is not involved in human medulloblastoma." *Neuropathology* 21(2): 129-37.

JC virus (JCV) together with Simian virus 40 (SV40) and BK virus (BKV), belong to the polyomavirus group and these viruses are neuro-oncogenic to rodents by expression of large T antigen (LT), which binds to cellular p53 and pRB thus reducing the anticancer potential of the cell. The function of LT has not been clarified because small t antigen (st) is transcribed from the same start codon as the overlapping reading frame of LT, and is translated as a different protein with the same N-terminal residues (1-81 amino acids) by a splice-site variant of mRNA. To elucidate the function of LT without st, we constructed plasmids that express LT only by deleting the splicing region including the C-terminus of st, and consequently stable cell lines were established that express only JCLT, SV40LT and BKLT. The growth rates of these cells were examined in colonies on soft agar and it was found that LT alone has a transforming

capacity; the order of efficiency being SV40LT, BKLT and JCLT. In addition, to verify the involvement of JCV in human medulloblastoma, eight cases of medulloblastoma, six cases of frozen material and five cases of paraffin-embedded tissues which included three cases of frozen tissues, were examined. PCR assay, genomic Southern blotting, and in situ hybridization were applied to detect the JCV genome, and LT and st were examined by immunohistochemistry; the results were compared with JCV-infected tissues as a positive control. All methods failed to detect not only JCV genome but also LT protein in medulloblastoma and it was concluded that JCV LT has transforming activities in rodent cells, but is not related to human medulloblastoma.

He, J., D. H. Overstreet, et al. (2009). "Abstinence from moderate alcohol self-administration alters progenitor cell proliferation and differentiation in multiple brain regions of male and female P rats." *Alcohol Clin Exp Res* **33**(1): 129-38.

BACKGROUND: Acute and chronic ethanol exposure has been found to decrease hippocampal neurogenesis, reduce dendritic differentiation of new neurons, and increase cell death. Interestingly, abstinence from such treatment increases hippocampal neurogenesis and microglial genesis across several brain regions. The goal of the current investigation was to study cellular alterations on neuro- and cell-genesis during abstinence following alcohol self-administration using alcohol-preferring rats (P rats). **METHODS:** Male and female P rats were given the choice of drinking 10% alcohol in water or pure water for 7 weeks. Social interaction behavioral assessments were conducted at 5 hours upon removal of alcohol, followed by bromo-deoxyuridine (BrdU, 150 mg/kg x 1/d x 14 d) injections to label proliferating cells. Animals were then killed 4 weeks later to conduct immunohistochemical and confocal analyses using antibodies against BrdU and other phenotypic markers (NeuN for mature neurons; Iba-1 for microglia; GFAP for astrocytes; and NG(2) for oligodendrocyte progenitors). **RESULTS:** Mild alcohol withdrawal anxiety was detected by reduction in social interactions. The number of hippocampal BrdU(+) cells was increased approximately 50% during alcohol abstinence (26 +/- 2.8 in controls vs. 39 +/- 4 in alcohol group). BrdU(+) cells were also increased in the substantia nigra (SN) approximately 65% in the alcohol abstinent group (12 +/- 1 in controls vs. 19 +/- 1.5 in alcohol group). No gender differences were found. Confocal analyses indicated that approximately 75% of co-localization of BrdU(+) cells with NeuN in the hippocampal dentate gyrus (DG) resulting a net increase in neurogenesis in the alcohol abstinent group

compared to controls. In cingulum, greater proportion of BrdU(+) cells were co-localized with NG(2) in the alcohol abstinent group indicating increased differentiation toward oligodendrocyte progenitors in both genders. However, the phenotype of the BrdU(+) cells in SN and other brain regions were not identified by NeuN, Iba-1, GFAP, or NG(2) suggesting that these BrdU(+) cells probably remain in a nondifferentiated stage. **CONCLUSIONS:** These data indicate that abstinence from moderate alcohol drinking increases hippocampal neurogenesis, cingulate NG(2) differentiation, and SN undifferentiated cell proliferation in both males and females. Such cellular alteration during abstinence could contribute to the spontaneous partial restoration of cognitive deficits upon sobriety.

Heile, A. M., C. Wallrapp, et al. (2009). "Cerebral transplantation of encapsulated mesenchymal stem cells improves cellular pathology after experimental traumatic brain injury." *Neurosci Lett* **463**(3): 176-81.

PURPOSE: "Naked" human mesenchymal stem cells (MSC) are neuro-protective in experimental brain injury (TBI). In a controlled cortical impact (CCI) rat model, we investigated whether encapsulated MSC (eMSC) act similarly, and whether efficacy is augmented using cells transfected to produce the neuro-protective substance glucagon-like peptide-1 (GLP-1). **METHODS:** Thirty two Sprague-Dawley rats were randomized to five groups: controls (no CCI), CCI-only, CCI+eMSC, CCI+GLP-1 eMSC, and CCI+empty capsules. On day 14, cisternal cerebro-spinal fluid (CSF) was sampled for measurement of GLP-1 concentration. Brains were immuno-histochemically assessed using specific antibody staining for NeuN, MAP-2 and GFAP. In another nine healthy rats, in vitro. **RESULTS:** GLP-1 production rates were measured from cells explanted after 2, 7 and 14 days. GLP-1 production rate in transfected cells, before implantation, was 7.03 fmol/capsule/h. Cells were still secreting GLP-1 at a rate of 3.68 +/- 0.49, 2.85 +/- 0.45 and 3.53 +/- 0.55 after 2, 7 and 14 days, respectively. In both of the stem cell treated CCI groups, hippocampal cell loss was reduced, along with an attenuation of cortical neuronal and glial abnormalities, as measured by MAP-2 and GFAP expression. The effects were more pronounced in animals treated with GLP-1 secreting eMSC. This group displayed an increased CSF level of GLP-1 (17.3 +/- 3.4 pM). **CONCLUSIONS:** Hippocampal neuronal cell loss, and cortical glial and neuronal cyto-skeletal abnormalities, after CCI are reduced following transplantation of encapsulated eMSC. These effects were augmented by GLP-1 transfected eMSC.

Horton, S., A. Meredith, et al. (1999). "Correct coordination of neuronal differentiation events in ventral forebrain requires the bHLH factor MASH1." *Mol Cell Neurosci* **14**(4-5): 355-69.

MASH1 is a bHLH transcription factor specifically expressed in the developing nervous system that has an essential role in the formation of multiple neuronal lineages in the peripheral and central nervous systems. Here we demonstrate the requirement for MASH1 for normal development of ventral forebrain structures. MASH1 is expressed at high levels in the ventral telencephalon and specific regions within the ventral diencephalon. In the absence of MASH1, tissue morphology, proliferation, and gene expression within these forebrain regions is disrupted. The decreased incorporation of BrdU in the neuro-epithelium and the enlargement of the ventricles demonstrate a reduction in cell proliferation. A loss of anatomically distinct lateral and medial ganglionic eminences, and a disruption of axons traversing this region, indicate abnormalities in cell-type specification. The aberrant expression of Tuj-1, a marker of neuronal differentiation in the neuroepithelium, and *Dlx*, a marker of regional cell identity, in the ventricular zone in the MASH1 mutant brains suggest coordination of differentiation events is disrupted. In addition, the involvement of MASH1 in lateral inhibition processes that affect the development of these forebrain regions is implicated. Taken together, an essential role for MASH1 in the coordination of events required for correct cell-type specification and timing of differentiation during neural development in ventral forebrain regions is demonstrated.

Islam, O., X. Gong, et al. (2009). "Interleukin-6 and neural stem cells: more than gliogenesis." *Mol Biol Cell* **20**(1): 188-99.

Besides its wide range of action as a proinflammatory cytokine in the immune system, interleukin-6 (IL-6) has also attracted much attention due to its influence on the nervous system. In the present study we show that the designer fusion protein H-IL-6, consisting of IL-6 and its specific receptor IL-6R-alpha, but not IL-6 alone, mediates both neuro- as well as gliogenesis. Using immunocytochemistry, Western blot, and patch-clamp recording, we demonstrate that H-IL-6 induces the differentiation of neural stem cells (NSCs) specifically into glutamate-responsive neurons and two morphological distinctive astroglia cell types. H-IL-6-activated neurogenesis seems to be induced by the MAPK/CREB (mitogen-activated protein kinase/cAMP response element-binding protein) cascade, whereas gliogenesis is mediated via the STAT-3 (signal transducers and activators of transcription protein-3) signaling

pathway. Our finding that IL-6 mediates both processes depending on its specific soluble receptor sIL-6R-alpha has implications for the potential treatment of neurodegenerative diseases.

Jackson, G. H., B. Angus, et al. (2000). "High dose ifosfamide in combination with etoposide and epirubicin followed by autologous stem cell transplantation in the treatment of relapsed/refractory Hodgkin's disease: a report on toxicity and efficacy." *Leuk Lymphoma* **37**(5-6): 561-70.

Patients with Hodgkin's disease (HD) refractory to first line chemotherapy and those who have rapid or multiple relapses have a very poor prognosis. With the increasing use of hybrid chemotherapy these patients will have been exposed to many of the drugs active in HD so it is important to develop salvage regimens that are novel and demonstrate activity in this group of patients. We report the use of a continuous high dose infusion of ifosfamide at a dose of 9g/m² over 3 days in combination with etoposide and epirubicin followed by autologous stem cell transplant with either BEAM or Melphalan/VP16 conditioning in this difficult group. Forty six patients (28M:18F) with a median age of 28 years (range 13-45) were treated. Overall 39 out of 46 (85%) patients responded to treatment, with 17 achieving complete remission and 11 a good partial remission; 28 proceeded to autologous bone marrow/stem cell transplantation. In total, 23 patients are alive and in continuous remission with a follow up of between 12 and 61 months. Median overall survival for the whole group is 36 months. Haematological toxicity, particularly neutropenia (WHO grade IV), was observed in all cases but improved over the 3 courses of treatment in all patients. Non-haematological toxicity was not a major problem; no significant cardiac, hepatic, renal, pulmonary or neuro toxicity was observed and there were no deaths on treatment. This regime shows promise in patients with difficult Hodgkin's disease and warrants further study.

Jager, M., E. Queinnec, et al. (2008). "Insights into the early evolution of SOX genes from expression analyses in a ctenophore." *J Exp Zool B Mol Dev Evol* **310**(8): 650-67.

SOX genes encode transcription factors acting in various developmental processes in bilaterian animals, such as stem cell maintenance and the control of specification and differentiation of cell types in a variety of contexts, notably in the developing nervous system. To gain insights into the early evolution of this important family of developmental regulators, we investigated the expression of one subgroup B, two subgroup E, one subgroup F and two divergent SOX genes in the cydippid larva and in the adult of the

ctenophore *Pleurobrachia pileus*. Transcripts of the two unclassified SOX (PpiSOX2/12) were detected in the female germ line and in various populations of putative somatic stem cells/undifferentiated progenitors. The remaining genes had spatially restricted expression patterns in ciliated epithelial cells, notably within neuro-sensory territories. These data are compatible with an ancient involvement of SOX proteins in controlling aspects of stem cell maintenance, cellular differentiation and specification, notably within neuro-sensory epithelia. In addition, the results highlight the complexity of the ctenophore anatomy and suggest that the SOX played an important role in the elaboration of the unique ctenophore body plan during evolution, through multiple gene co-option.

Jin, G. Z., S. J. Cho, et al. (2008). "Rat mesenchymal stem cells increase tyrosine hydroxylase expression and dopamine content in ventral mesencephalic cells in vitro." *Cell Biol Int* **32**(11): 1433-8.

Mesenchymal stem cells (MSCs) are pluripotent adult stem cells. It has been shown that MSCs secrete neurotrophic factors involving nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF). Also, these neurotrophic factors can upregulate tyrosine hydroxylase (TH) gene expression in PC12 cells and neural stem cells. Here, we investigated the effect of co-culturing rat E13.5 ventral mesencephalic cells (VMCs) with MSCs from rat bone marrow on TH expression and dopamine (DA) content. The study consisted of 3 groups: MSC, VMC and a combined MSC+VMC group. All groups were cultured in serum-free neuro-basal medium for 3 days. Thereafter, each group was analyzed by RT-PCR, western blotting, and HPLC. The co-culture group showed a higher expression at TH and DA than the VMC group. However, TH and DA were not present in the MSC group. These observations suggest that MSCs could be an alternative source for treating neurodegenerative diseases such as Parkinson's disease (PD).

Jung, C. G., H. J. Kim, et al. (2005). "Homeotic factor ATBF1 induces the cell cycle arrest associated with neuronal differentiation." *Development* **132**(23): 5137-45.

The present study aimed to elucidate the function of AT motif-binding factor 1 (ATBF1) during neurogenesis in the developing brain and in primary cultures of neuroepithelial cells and cell lines (Neuro 2A and P19 cells). Here, we show that ATBF1 is expressed in the differentiating field in association with the neuronal differentiation markers beta-tubulin and MAP2 in the day E14.5 embryo rat brain, suggesting that it promotes neuronal differentiation. In

support of this, we show that ATBF1 suppresses nestin expression, a neural stem cell marker, and activates the promoter of *Neurod1* gene, a marker for neuronal differentiation. Furthermore, we show that in Neuro 2A cells, overexpressed ATBF1 localizes predominantly in the nucleus and causes cell cycle arrest. In P19 cells, which formed embryonic bodies in the floating condition, ATBF1 is mainly cytoplasmic and has no effect on the cell cycle. However, the cell cycle was arrested when ATBF1 became nuclear after transfer of P19 cells onto adhesive surfaces or in isolated single cells. The nuclear localization of ATBF1 was suppressed by treatment with caffeine, an inhibitor of PI(3)K-related kinase activity of ataxa-telangiectasia mutated (ATM) gene product. The cytoplasmic localization of ATBF1 in floating/nonadherent cells is due to CRM1-dependent nuclear export of ATBF1. Moreover, in the embryonic brain ATBF1 was expressed in the cytoplasm of proliferating stem cells on the ventricular zone, where cells are present at high density and interact through cell-to-cell contact. Conversely, in the differentiating field, where cell density is low and extracellular matrix is dense, the cell-to-matrix interaction triggered nuclear localization of ATBF1, resulting in the cell cycle arrest. We propose that ATBF1 plays an important role in the nucleus by organizing the neuronal differentiation associated with the cell cycle arrest.

Kageyama, K., H. Ikeda, et al. (2007). "Expression of adrenocorticotrophic hormone, prolactin and transcriptional factors in clinically nonfunctioning pituitary adenoma." *Endocr J* **54**(6): 961-8.

We describe here a case of a clinically nonfunctioning pituitary adenoma, but with expression of ACTH and PRL. A 42-year-old woman was referred to our department for further evaluation of pituitary tumor. She had no acromegaloid features, and no typical Cushingoid features. She had no galactorrhea, and had regular menses. GH, IGF-I, LH, FSH, TSH, ACTH and cortisol levels in blood were all within the normal ranges, while PRL levels were mildly elevated. Both ACTH and cortisol levels were adequately increased in response to CRH, and both were suppressed by a small dose of dexamethasone. Plasma ACTH and cortisol levels were decreased at night, suggesting the circadian rhythms for plasma ACTH levels were undisturbed. Based on these findings we did not clinically suspect ACTH-producing tumor, however immunohistochemistry revealed ACTH immunoreactivity in the pituitary adenoma. Therefore, the tumor was considered a silent corticotroph adenoma. PRL was co-expressed in a significant subpopulation of ACTH-immunoreactive tumor cells. Ptx1, Neuro D1, and T pit were densely

expressed and Pit-1 was sparsely expressed in the nuclei of adenoma cells. It is therefore possible that a tumor originating in an immature or uncommitted adenohypophysial stem cell may later differentiate into different cell types due to a combination of certain specific transcriptional factors.

Kalifa, C. and J. Grill (2005). "The therapy of infantile malignant brain tumors: current status?" *J Neurooncol* **75**(3): 279-85.

Malignant brain tumors are not uncommon in infants as their occurrence before the age of three represents 20-25% of all malignant brain tumors in childhood [1]. Genetic predisposition to infantile malignant brain tumors are known in Gorlin syndrome for example who present with desmoplastic medulloblastoma in about 5% of the affected patients. In addition, sequelae from tumor and its treatment are more severe at this age [2]. Thus, malignant brain tumors represent a true therapeutic challenge in neuro-oncology. Before the era of modern imaging and modern neurosurgery these malignant brain tumors were misdiagnosed or could not benefit of the surgical procedures as well as older children because of increased risks in this age group. Since the end of the 80s, noninvasive imaging procedures produce accurate diagnosis of brain tumors and improvement in neurosurgery, neuroanesthesia and perioperative intensive care permit safe tumor resections or at least biopsies. Consequently, the pediatric oncologists are more often confronted with very young children who need a complementary treatment. Before the development of specific approaches for this age group, these children received the same kind of treatment than the older children did, but their survival and quality of life were significantly worse. The reasons of these poor results were probably due in part to the fear of late effects induced by radiation therapy, leading to decrease the necessary doses of irradiation which increased treatment failures without avoiding treatment related complications [3]. At the end of the 80s, pilot studies were performed using postoperative chemotherapy in young medulloblastoma patients. Van Eys treated 12 selected children with medulloblastoma with MOPP regimen and without irradiation; 8 of them were reported to be long term survivors [4]. Subsequently, the pediatric oncology cooperative groups studies have designed therapeutic trials for very young children with malignant brain tumors. Different approaches have been explored: * Prolonged postoperative chemotherapy and delayed irradiation as designed in the POG (Pediatric Oncology Group). * Postoperative chemotherapy without irradiation in the SFOP (Societe Francaise d'Oncologie Pediatrique) and in the GPO (German Pediatric Oncology) studies. * The role of high-dose

chemotherapy with autologous stem cells transplantation was explored in different ways: High-dose chemotherapy given in all patients as proposed in the Head Start protocol. High-dose chemotherapy given in relapsing patients as salvage treatment in the French strategy. In the earliest trials, the same therapy was applied to all histological types of malignant brain tumors and whatever the initial extension of the disease. This attitude was justified by the complexity of the classification of all brain tumors that has evolved over the past few decades leading to discrepancy between the diagnosis of different pathologists for a same tumor specimen. Furthermore, it has become increasingly obvious that the biology of brain tumors in very young children is different from that seen in older children. However, in the analysis of these trials an effort was made to give the results for each histological groups, according to the WHO classification and after a central review of the tumor specimens. All these collected data have brought to an increased knowledge of infantile malignant brain tumors in terms of diagnosis, prognostic factors and response to chemotherapy. Furthermore a large effort was made to study long term side effects as endocrinopathies, cognitive deficits, cosmetic alterations and finally quality of life in long term survivors. Prospective study of sequelae can bring information on the impact of the different factors as hydrocephalus, location of the tumor, surgical complications, chemotherapy toxicity and irradiation modalities. With these informations it is now possible to design therapeutic trials devoted to each histological types, adapted to pronostic factors and more accurate treatment to decrease long term sequelae.

Kang, K. S., J. E. Park, et al. (2001). "Effects and neuro-toxic mechanisms of 2, 2', 4, 4', 5, 5'-hexachlorobiphenyl and endosulfan in neuronal stem cells." *J Vet Med Sci* **63**(11): 1183-90.

Endocrine disruptors are exogenous compounds thought to mimic the action of estrogen or other hormones and influence endocrine activity in the body (Juberg, 2000). These chemicals have adverse effects not only in the reproductive system but also in the central nervous system during development and throughout life. Polychlorinated biphenyls (PCBs) are a class of environmentally persistent and widespread halogenated hydrocarbons. It has been reported that PCBs are potential neurotoxicants. Endosulfan is an organochlorine insecticide that is extensively used to control pests in vegetables, cotton, and fruits. To determine the effect of 2, 2', 4, 4', 5, 5',-hexachlorobiphenyl(2, 4, 5-HCB) and endosulfan on embryo nervous system, we isolated neural stem cells from rat brain at embryonic day 17. Isolated neural

stem cells showed pluripotency. Stem cells could differentiate into neurons and glia. Neurite formation in endosulfan and 2, 4, 5-HCB treated cells. And it appeared to be decreased as compared with that in untreated cells. In order to know the neuro-toxic mechanisms of 2, 4, 5-HCB and endosulfan in neuronal stem cells, we investigated mitogen-activated protein kinase activity (MAPK) and gap junctional intercellular communication (GJIC). Endosulfan decreased the MAPK activity in dose dependent manner. Endosulfan and 2, 4, 5-HCB inhibited GJIC compared to the untreated cell by scrape loading dye transfer (SL/DT). 2, 4, 5-HCB and endosulfan decreased the expression of connexin 43 in dose dependent manner. These results indicated that 2, 4, 5-HCB and endosulfan may inhibit differentiation and proliferation of neural stem cells and gap junctional intercellular communication which play a crucial role in the maintenance of cellular homeostasis.

Kronenberg, G., L. P. Wang, et al. (2007). "Local origin and activity-dependent generation of nestin-expressing protoplasmic astrocytes in CA1." *Brain Struct Funct* **212**(1): 19-35.

Since reports that precursor cells in the adult subventricular zone (SVZ) contribute to regenerative neuro- and gliogenesis in CA1, we wondered whether a similar route of migration might also exist under physiological conditions. Permanent labeling of SVZ precursor cells with a lentiviral vector for green fluorescent protein did not reveal any migration from the SVZ into CA1 in the intact murine brain. However, in a nestin-GFP reporter mouse we found proliferating cells within the corpus callosum/alveus region expressing nestin and glial fibrillary acidic protein similar to precursor cells in the neighboring neurogenic region of the adult dentate gyrus. Within 3 weeks of BrdU administration, BrdU-positive nestin-GFP-expressing protoplasmic astrocytes emerged in CA1. Similar to precursor cells isolated from the dentate gyrus and the SVZ, nestin-GFP-expressing cells from corpus callosum/alveus were self-renewing and multipotent in vitro, whereas cells isolated from CA1 were not. Nestin-GFP-expressing cells in CA1 differentiated into postmitotic astrocytes characterized by S100beta expression. No new neurons were found in CA1. The number of nestin-GFP-expressing astrocytes in CA1 was increased by environmental enrichment. We conclude that astrogenesis in CA1 is influenced by environmental conditions. However, SVZ precursor cells do not contribute to physiological cellular plasticity in CA1.

Krouwer, H. G. and E. F. Wijdicks (2003). "Neurologic complications of bone marrow transplantation." *Neurol Clin* **21**(1): 319-52.

The various forms of HSCT are or will soon be accepted treatments for an ever-increasing number of hematologic and solid cancers. Attempts to reduce the mortality and morbidity of HSCT and at the same time preserve or increase its efficacy in tumor control include development of nonmyeloablative allogeneic stem-cell transplant strategies [208] and allogeneic laboratory research-enhancing graft acceptance [209,210]. Eventually, these efforts will reduce complication rates of HSCT, including neurologic complications. In the interim, the consultant neuro-oncologist or neurologist with a specific interest in this field is faced with complex clinical syndromes, neuroradiologic imaging studies and neurophysiologic tests, and generally poorly understood pathophysiologic mechanisms. Prospective studies of HSCT patients in large transplantation centers using clinical registries are needed.

Kuai, X. L., C. Gagliardi, et al. (2009). "Differentiation of nonhuman primate embryonic stem cells along neural lineages." *Differentiation* **77**(3): 229-38.

The differentiation of embryonic stem cells (ESCs) into neurons and glial cells represents a promising cell-based therapy for neurodegenerative diseases. Because the rhesus macaque is physiologically and phylogenetically similar to humans, it is a clinically relevant animal model for ESC research. In this study, the pluripotency and neural differentiation potential of a rhesus monkey ESC line (ORMES6) was investigated. ORMES6 was derived from an in vitro produced blastocyst, which is the same way human ESCs have been derived. ORMES6 stably expressed the embryonic transcription factors POU5F1 (Oct4), Sox2 and NANOG. Stage-specific embryonic antigen 4 (SSEA 4) and the glycoproteins TRA-1-60 and TRA-1-81 were also expressed. The embryoid bodies (EBs) formed from ORMES6 ESCs spontaneously gave rise to cells of three germ layers. After exposure to basic fibroblast growth factor (bFGF) for 14-16 days, columnar rosette cells formed in the EB outgrowths. Sox2, microtubule-associated protein (MAP2), beta-tubulinIII and glial fibrillary acidic protein (GFAP) genes and Nestin, FoxD3, Pax6 and beta-tubulinIII antigens were expressed in the rosette cells. Oct4 and NANOG expression were remarkably down-regulated in these cells. After removal of bFGF from the medium, the rosette cells differentiated along neural lineages. The differentiated cells expressed MAP2, beta-tubulinIII, Neuro D and GFAP genes. Most differentiated cells expressed early neuron-specific antigen beta-tubulinIII (73+/-4.7%) and some expressed intermediate neuron antigen MAP2 (18+/-7.2%). However, some differentiated cells expressed the glial

cell antigens A2B5 (7.17% \pm 1.2%), GFAP (4.93 \pm 1.9%), S100 (7 \pm 3.5%) and O4 (0.27 \pm 0.2%). The rosette cells were transplanted into the striatum of immune-deficient NIHIII mice. The cells persisted for approximately 2 weeks and expressed Ki67, NeuN, MAP2 and GFAP. These results demonstrate that the rhesus monkey ESC line ORMES6 retains the pluripotent characteristics of ESCs and can be efficiently induced to differentiate along neural lineages.

Lackie, P. M., C. Zuber, et al. (1994). "Polysialic acid of the neural cell adhesion molecule (N-CAM) is widely expressed during organogenesis in mesodermal and endodermal derivatives." *Differentiation* **57**(2): 119-31.

We have studied the expression of homopolymers of alpha 2,8-linked sialic acid (polySia) and the neural cell adhesion molecule (N-CAM) during the embryonic and fetal development of rat, chicken and man using immunocytochemistry and immunoblotting. During development, polySia and N-CAM were widely expressed in mesodermally and neuro-ectodermally derived elements. In specific developmental processes, cells of endodermal and ectodermal (non-neural) origin were also immunoreactive for these molecules. Loss of polySia and N-CAM immunoreactivity often accompanied differentiation of mesodermally derived cells. In cartilage formation for instance, cells in precartilaginous mesenchymal condensations stained for N-CAM and polySia until the first appearance of specific chondrocyte function, independent of the stage of development. Transient de novo expression of polySia, in newly induced ectodermal cells, paralleled the reciprocal inductive interactions of mesodermally derived cells with cells of ectodermal origin during hair follicle formation. All ectodermally derived hair follicle cells, except the putative stem cells, later ceased expression of these molecules. Ectodermal expression of polySia and N-CAM was otherwise rare. The endodermally derived epithelium of the digestive and respiratory tracts were polySia and N-CAM immunoreactive early in organogenesis (embryonic day 12 in mouse). Cells of this derivation later all became unreactive, although decrease in immunoreactivity during development was faster in derivatives of more cranial portions of the endoderm. In general, during organogenesis, epithelial elements showed polySia and N-CAM expression before and during epithelium formation, thereafter losing immunoreactivity, irrespective of the developmental origin of the epithelial cells. PolySia and N-CAM staining in the chicken respiratory tract epithelium was more wide-spread and lasted significantly longer than in either man or rat. Cells that expressed N-

CAM, but not polySia, were found during the development of both skin and pancreas, indicating independent control of polySia expression. Outside the nervous system no cells that expressed polySia but not N-CAM were observed.

Lafay-Cousin, L. and D. Strother (2009). "Current treatment approaches for infants with malignant central nervous system tumors." *Oncologist* **14**(4): 433-44.

The management of brain tumors in very young children remains a challenge for neuro-oncologists in large part because of the greater vulnerability of the developing brain to treatment-related toxicity. Nearly three decades of infant brain tumor clinical trials have led to significant progress in the delineation of prognostic factors and improvements in outcome. Innovative strategies that employ high-dose chemotherapy, intrathecal chemotherapy, modified focal irradiation, or combinations of these have been used to delay or avoid the use of conventional craniospinal irradiation in order to minimize the risk for deleterious neurocognitive impairment in survivors. However, it is difficult to evaluate the impact of such approaches on intellectual and functional outcome, and results to date are limited. This review covers the most recent therapeutic advances for the most common histological subtypes of malignant infant brain tumors: medulloblastoma, supratentorial primitive neuroectodermal tumor, ependymoma, atypical teratoid rhabdoid tumor, choroid plexus carcinoma, and high-grade glioma. Survival and neurocognitive outcome are emphasized.

Lehvaslaiho, H., L. Lehtola, et al. (1989). "A chimeric EGF-R-neu proto-oncogene allows EGF to regulate neu tyrosine kinase and cell transformation." *Embo J* **8**(1): 159-66.

The neu oncogene, characterized by Weinberg and colleagues, is a transforming gene found in ethylnitrosourea-induced rat neuro/glioblastomas; its human proto-oncogene homologue has been termed erbB2 or HER2 because of its close homology with the epidermal growth factor receptor (EGF-R) gene (c-erbB1). Expression of the rat neu oncogene is sufficient for transformation of mouse NIH 3T3 fibroblasts in culture and for the development of mammary carcinomas in transgenic mice, but the neu proto-oncogene has not been associated with cell transformation. We constructed a vector for expression of a chimeric cDNA and hybrid protein consisting of the EGF-R extracellular, transmembrane and protein kinase C-substrate domains linked to the intracellular tyrosine kinase and carboxyl terminal domain of the rat neu cDNA. Upon

transfection with the construct, NIH 3T3 cells gave rise to EGF-R antigen-positive cell clones with varying amounts of specific EGF binding. Immunofluorescence and immunoprecipitation using neu- and EGF-receptor specific antibodies demonstrated a correctly oriented and positioned chimeric EGF-R-neu protein of the expected apparent mol. wt on the surface of these cells. EGF or TGF alpha induced tyrosine phosphorylation of the chimeric receptor protein, stimulated DNA synthesis of EGF-R-neu expressing cells and led to a transformed cell morphology and growth in soft agar. In contrast, the neu proto-oncogene did not show kinase activity or transforming properties when expressed at similar levels in NIH 3T3 cells.(ABSTRACT TRUNCATED AT 250 WORDS)

Lei, Z., L. Yongda, et al. (2007). "Culture and neural differentiation of rat bone marrow mesenchymal stem cells in vitro." *Cell Biol Int* **31**(9): 916-23.

Adult bone marrow mesenchymal stem cells (MSCs) can differentiate into several types of mesenchymal cells, including osteocytes, chondrocytes, and adipocytes, but can also differentiate into non-mesenchymal cells, such as neural cells, under appropriate experimental conditions. Until now, many protocols for inducing neuro-differentiation in MSCs in vitro have been reported. But due to the differences in MSCs' isolation and culture conditions, the results of previous studies lacked consistency and comparability. In this study, we induced differentiation into neural phenotype in the same MSCs population by three different treatments: beta-mercaptoethanol, serum-free medium and co-cultivation with fetal mouse brain astrocytes. In all of the three treatments, MSCs could express neural markers such as NeuN or GFAP, associating with remarkable morphological modifications. But these treatments led to neural phenotype in a non-identical manner. In serum-free medium, MSCs mainly differentiated into neuron-like cells, expressing neuronal marker NeuN, and BME can promote this process. Differently, after co-culturing with astrocytes, MSCs leaned to differentiate into GFAP(+) cells. These data confirmed that MSCs can exhibit plastic neuro-differentiation potential in vitro, depending on the protocols of inducement.

Leung, K. K., P. M. Suen, et al. (2009). "PDZ-domain containing-2 (PDZD2) drives the maturity of human fetal pancreatic progenitor-derived islet-like cell clusters with functional responsiveness against membrane depolarization." *Stem Cells Dev* **18**(7): 979-90.

We recently reported the isolation and characterization of a population of pancreatic

progenitor cells (PPCs) from early trimester human fetal pancreata. The PPCs, being the forerunners of adult pancreatic cell lineages, were amenable to growth and differentiation into insulin-secreting islet-like cell clusters (ICCs) upon stimulation by adequate morphogens. Of note, a novel morphogenic factor, PDZ-domain containing-2 (PDZD2) and its secreted form (sPDZD2) were ubiquitously expressed in the PPCs. Our goals for this study were to evaluate the potential role of sPDZD2 in stimulating PPC differentiation and to establish the optimal concentration for such stimulation. We found that 10(-9)M sPDZD2 promoted PPC differentiation, as evidenced by the upregulation of the pancreatic endocrine markers (PDX-1, NGN3, NEURO-D, ISL-1, NKX 2.2, NKX 6.1) and INSULIN mRNA. Inhibited endogenous production of sPDZD2 suppressed expression of these factors. Secreted PDZD2 treatment significantly elevated the C-peptide content of the ICCs and increased the basal rate of insulin secretion. However, they remained unresponsive to glucose stimulation, reflected by a minimal increase in GLUT-2 and GLUCOKINASE mRNA expression. Interestingly, sPDZD2 treatment induced increased expression of the L-type voltage-gated calcium channel (Ca(v)1.2) in the ICCs, triggering calcium ion influx under KCl stimulation and conferring an ability to secrete insulin in response to KCl. Pancreatic progenitor cells from 10- and 13-week fetal pancreata showed peak expression of endogenous sPDZD2, implying that sPDZD2 has a specific role in islet development during the first trimester. In conclusion, our data suggest that sPDZD2 promotes functional maturation of human fetal PPC-derived ICCs, thus enhancing its transplanting potentials.

Lin, R. C., D. F. Matesic, et al. (1995). "Re-expression of the intermediate filament nestin in reactive astrocytes." *Neurobiol Dis* **2**(2): 79-85.

The intermediate filament nestin is highly expressed in multipotential stem cells of the developing central nervous system (CNS). During neuro- and gliogenesis, nestin is replaced by cell type-specific intermediate filaments, e.g. neurofilaments and glial fibrillary acidic protein (GFAP). In this study, we demonstrate that nestin expression is re-induced in reactive astrocytes in the lesioned adult brain. Following ischaemic and mechanical lesioning, a strong and sustained expression of nestin was noted in GFAP-positive cells surrounding the lesion site. Lesion experiments in transgenic mice carrying the lacZ gene under control of regulatory sequences from the nestin gene suggested that the upregulation of nestin in reactive astrocytes is mediated via the same sequences that control nestin expression during CNS

development. These observations and recent data on the co-expression of glial and neuronal marker antigens in reactive astrocytes point to a close relationship between proliferating astrocytes and neuroepithelial precursor cells.

Lucchini, G., D. Grioni, et al. (2008). "Encephalopathy syndrome in children with hematological disorders is not always posterior and reversible." *Pediatr Blood Cancer* **51**(5): 629-33.

BACKGROUND: Posterior reversible leukoencephalopathy (PRES) is a clinical-radiological event that can affect children undergoing chemotherapy regimen. Studies have shown that it is not always reversible, in spite of its original definition. We analyzed PRES cases which occurred during the last 10 years at our institute to focus on their clinical, radiological and EEG follow-up. **PROCEDURES:** We analyzed 12 cases of PRES in children who underwent intensive chemotherapy regimens, detailing the acute neurological presentation of the syndrome, their neuro-imaging characteristics (MRI) and EEG findings, in both an acute phase and during follow-up. **RESULTS:** All patients survived the acute event, showing a clinical recovery of the acute neurological signs in 1-3 days and normalization of the EEG pattern in a period ranging from 1 to 8 months. During long term follow-up, four patients developed either clinical impairment or EEG-MRI anomalies. **CONCLUSIONS:** We suggest that a long term follow-up is necessary to determine the reversibility of the neurological events. Clinical observation, as well as EEG and MRI should be included in follow-up evaluations.

MacDonald, J. L. and A. J. Roskams (2008). "Histone deacetylases 1 and 2 are expressed at distinct stages of neuro-glial development." *Dev Dyn* **237**(8): 2256-67.

The deacetylation of histone proteins, catalyzed by histone deacetylases (HDACs), is a common epigenetic modification of chromatin, associated with gene silencing. Although HDAC inhibitors are used clinically to treat nervous system disorders, such as epilepsy, very little is known about the expression pattern of the HDACs in the central nervous system. Identifying the cell types and developmental stages that express HDAC1 and HDAC2 within the brain is important for determining the therapeutic mode of action of HDAC inhibitors, and evaluating potential side effects. Here, we examined the expression of HDAC1 and HDAC2 in the murine brain at multiple developmental ages. HDAC1 is expressed in neural stem cells/progenitors and glia. In contrast, HDAC2 is initiated in neural progenitors and is up-regulated in post-mitotic neuroblasts and neurons, but not in fully differentiated

glia. These results identify key developmental stages of HDAC expression and suggest transitions of neural development that may utilize HDAC1 and/or HDAC2.

Mancardi, G. L., R. Saccardi, et al. (2001). "Autologous hematopoietic stem cell transplantation suppresses Gd-enhanced MRI activity in MS." *Neurology* **57**(1): 62-8.

BACKGROUND: Autologous hematopoietic stem cell transplantation (ASCT) has been recently utilized with encouraging results in patients with poorly controlled MS. **OBJECTIVE:** To determine in severe cases of MS the effect of ASCT on gadolinium (Gd)-enhanced MRI and to obtain information on clinical course and safety. **METHODS:** In a cooperative study, 10 patients with rapidly evolving secondary progressive MS were transplanted, after BEAM conditioning regimen (carmustine, etoposide, cytosine-arabioside, and melphalan), with unmanipulated autologous peripheral blood SC mobilized with high-dose cyclophosphamide (CY; 4 g/m²) and granulocyte-colony-stimulating factor. Triple-dose Gd-enhanced scans were performed monthly for a pretreatment period of 3 months and compared with serial monthly Gd-enhanced MRI for the following 6 months and then once every 3 months. **RESULTS:** The median follow-up is now 15 months (range 4 to 30 months). The number of Gd-enhancing lesions decreased immediately after mobilization with CY and finally dropped to zero in all cases after the conditioning regimen. The number of new T2-weighted positive lesions paralleled data obtained for Gd-enhanced MRI. Clinically, patients improved slightly or remained stable. **CONCLUSION:** These results demonstrate that the therapeutic sequence CY-BEAM-ASCT has the capacity to completely suppress MR-enhancing activity, an effect that is sustained with time. The final impact of this procedure on disease course remains to be established.

Mao, L. and J. Q. Wang (2003). "Adult neural stem/progenitor cells in neurodegenerative repair." *Sheng Li Xue Bao* **55**(3): 233-44.

Although the mammalian brain has long been thought to be entirely postmitotic, the recent discovery has confirmed an existence of neural stem or progenitor cells in various regions of the adult mammalian brain. Like embryonic stem cells, adult neural progenitor cells possess the capacity of self-renewal and differentiation potential for neurogenesis or gliogenesis. In addition to the subventricular zone and hippocampus where active cell division naturally occurs, adult neural progenitors with neurogenic potential exist in the striatum and the vicinity of dopaminergic neurons in the substantia nigra. Normally, progenitors in those regions proliferate at a

low level, and most proliferated cells remain uncommitted. In response to the selective lesion of nigrostriatal dopaminergic pathway by the neurotoxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or 6-hydroxydopamine, progenitors in the injured areas markedly increase their proliferation rate. Depending upon the magnitude and kinetics of the lesion, neurogenesis and gliogenesis were induced in the lesion sites at varying extents. A large number of growth and neurotrophic factors influence proliferation and/or differentiation of progenitor cells under normal and lesioned conditions. Some factors (epidermal and basic fibroblast growth factors and brain-derived neurotrophic factor) are facilitatory, while others (usually bone morphogenetic proteins) are inhibitory, for controlling division and fate of neuronal or glial progenitors. Expression of endogenous factors and their respective receptors in existing and newborn cells are also subject to be altered by the lesion. These genomic responses are considered to be important elements for the formation of a local molecular niche for a given phenotypic cell regeneration. Taken together, adult neural progenitor cells in the nigrostriatal dopaminergic system have the ability to respond to the lesion to repopulate missing cells. The regenerative neuro- or gliogenesis in situ can, at least in part, endogenously compensate injured neural elements, and achieve a self-repair of neurodegenerative disorders such as Parkinson's disease.

Marconi, A., M. Terracina, et al. (2003). "Expression and function of neurotrophins and their receptors in cultured human keratinocytes." *J Invest Dermatol* **121**(6): 1515-21.

Whereas nerve growth factor has been extensively studied in human keratinocytes, little is known on the role of other members of the neurotrophin family. We investigated the expression and function of neurotrophins and neurotrophin receptors in cultured human keratinocytes. We demonstrated by reverse transcription-polymerase chain reaction that keratinocytes synthesize neurotrophin-3, brain-derived neurotrophic factor, and neurotrophin-4/5. These cells also express tyrosinase kinase A and C, the nerve growth factor and neurotrophin-3 high-affinity receptors, respectively. On the other hand, only the truncated extracellular isoform of tyrosinase kinase B, the high-affinity brain-derived neurotrophic factor and neurotrophin-4/5 receptor, is detected in keratinocytes. Moreover, neurotrophin-3, brain-derived neurotrophic factor, and neurotrophin-4/5 proteins are secreted by human keratinocytes at low levels. Keratinocyte stem cells synthesize the highest amounts of nerve growth factor, while they secrete higher levels of nerve growth factor as

compared with transit amplifying cells. Neurotrophin-3 stimulates keratinocyte proliferation, where brain-derived neurotrophic factor or neurotrophin-4/5 does not exert any effect on keratinocyte proliferation. Addition of neurotrophin-3 slightly upregulates the secretion of nerve growth factor, whereas nerve growth factor strongly augments neurotrophin-3 release. Ultraviolet B irradiation downregulates nerve growth factor, whereas it augments neurotrophin-3 and neurotrophin-4/5 protein levels. Ultraviolet A irradiation increases the level of neurotrophin-3, whereas it does not exert any effect on the other neurotrophins. Finally, neurotrophins other than nerve growth factor fail to protect human keratinocytes from ultraviolet B-induced apoptosis. This work delineates a functional neurotrophin network, which may contribute to epidermal homeostasis.

Martinez-Contreras, A., M. Huerta, et al. (2002). "Astrocytic and microglia cells reactivity induced by neonatal administration of glutamate in cerebral cortex of the adult rats." *J Neurosci Res* **67**(2): 200-10.

Recent studies confirm that astrocytes and neurons are associated with the synaptic transmission, particularly with the regulation of glutamate (Glu) levels. Therefore, they have the capacity to modulate the Glu released from neurons into the extracellular space. It has also been demonstrated an intense astrocytic and microglia response to physical or chemical lesions of the central nervous system. However, the persistence of the response of the glial cells in adult brain had not been previously reported, after the excitotoxic damage caused by neonatal dosage of monosodium glutamate (MSG) to newborn rats. In this study, 4 mg/g body weight of MSG were administered to newborn rats at 1, 3, 5, and 7 days after birth, at the age of 60 days the astrocytes and the microglia cells were analyzed with immunohistochemical methods in the fronto-parietal cortex. Double labeling to glial fibrillary acidic protein (GFAP) and BrdU, or isolectin-B(4) and BrdU identified astrocytes or microglia cells that proliferated; immunoblotting and immunoreactivity to vimentin served for assess immaturity of astrocytic intermediate filaments. The results show that the neonatal administration of MSG-induced reactivity of astrocytes and microglia cells in the fronto-parietal cortex, which was characterized by hyperplasia; an increased number of astrocytes and microglia cells that proliferated, hypertrophy; increased complexity of the cytoplasm extension of both glial cells and expression of RNAm to vimentin, with the presence of vimentin-positive astrocytes. This glial response to neuroexcitotoxic stimulus of Glu on the immature brain, which persisted to adulthood, suggests that the

neurotransmitter Glu could trigger neuro-degenerative illnesses.

Martin-Fontecha, A., R. Broekhuizen, et al. (1993). "The neuro-endocrine component of the rat thymus: studies on cultured thymic fragments before and after transplantation in congenitally athymic and euthymic rats." *Brain Behav Immun* 7(1): 1-15.

An immunohistochemical study was done for the presence of tyrosine hydroxylase (noradrenergic innervation), neuron-specific protein PGP9.5, and anterior pituitary hormones (beta-subunit of follicle-stimulating hormone, growth hormone, beta-subunit of luteinizing hormone, prolactin, and beta-subunit of thyroid-stimulating hormone) in cultured thymic fragments before and after transplantation in congenitally athymic and euthymic rats. The cultured thymic fragments consisted of epithelial cells and were depleted of lymphocytes. After implantation in syngeneic and allogeneic athymic recipients and in syngeneic euthymic recipients, a recovery of the original architecture was found within 6 weeks; rejection occurred within 3 weeks for allogeneic transplantation in euthymic rats. During culture nerve-like profiles almost disappeared from the tissue, and reappeared simultaneously with the influx of host-derived cells and the restoration of the original thymic architecture. A high immunoreactivity for hormones and PGP9.5 was found in epithelial cells after culture and in the first phase after transplantation. These epithelial cells may represent precursor-epithelial cells, based on their unusual ultrastructure and combined expression of markers that in the normal thymus occur only on subcapsular/medullary epithelium or on cortex epithelium. These data indicate a potential role of the neuroendocrine function of the thymus during restoration of the thymus architecture starting from precursor-like epithelial cells.

Mobus, V., H. Wandt, et al. (2007). "Phase III trial of high-dose sequential chemotherapy with peripheral blood stem cell support compared with standard dose chemotherapy for first-line treatment of advanced ovarian cancer: intergroup trial of the AGO-Ovar/AIO and EBMT." *J Clin Oncol* 25(27): 4187-93.

PURPOSE: Although ovarian cancer is one of the most chemotherapy-sensitive solid tumors, cure after radical surgery and chemotherapy is uncommon. A randomized trial comparing high-dose sequential chemotherapy with peripheral blood stem cell (PBSC) support with platinum-based combination chemotherapy was conducted to investigate whether dose-intensification improves outcome. **PATIENTS AND METHODS:** One hundred forty-nine patients with untreated ovarian cancer were randomly assigned

after debulking surgery to receive standard combination chemotherapy or sequential high-dose (HD) treatment with two cycles of cyclophosphamide and paclitaxel followed by three cycles of HD carboplatin and paclitaxel with PBSC support. HD melphalan was added to the final cycle. The median age was 50 years (range, 20 to 65 years) and International Federation of Gynecology and Obstetrics stage was IIb/IIc in 4%, III in 78%, and IV in 17%. **RESULTS:** Seventy-six percent of patients received all five cycles in the HD arm and the main toxicities were neuro-/ototoxicity, gastrointestinal toxicity, and infection and one death from hemorrhagic shock. After a median follow-up of 38 months, the progression-free survival was 20.5 months in the standard arm and 29.6 months in the HD arm (hazard ratio [HR], 0.84; 95% CI, 0.56 to 1.26; P, .40). Median overall survival (OS) was 62.8 months in the standard arm and 54.4 months in the HD arm (HR, 1.17; 95% CI, 0.71 to 1.94; P, .54). **CONCLUSION:** This is the first randomized trial comparing sequential HD versus standard dose chemotherapy in first-line treatment of patients with advanced ovarian cancer. We observed no statistically significant difference in progression-free survival or OS and conclude that HD chemotherapy does not appear to be superior to conventional dose chemotherapy.

Mravec, B., L. Lackovicova, et al. (2009). "Brain response to induced peripheral cancer development in rats: dual fos-tyrosine hydroxylase and fos-oxytocin immunohistochemistry." *Endocr Regul* 43(1): 3-11.

OBJECTIVE: During last few decades a considerable number of data has emerged supporting the hypothesis that central nervous system might monitor and modulate tumor growth. This assumption is based on two facts: 1. immune system plays a crucial role in the development and progression of cancer; 2. immune and nervous systems communicate tightly and bidirectionally. The aim of present study was to elucidate whether tumor growth may induce detectable changes in brain structures that are involved in the response to immune challenges. **METHODS:** Using Fos immunohistochemistry, we investigated whether the advanced stage of cancer, induced by a single intraperitoneal injection of BP6-TU2 fibrosarcoma cells to male Wistar rats, could activate Fos expression in the nucleus of the solitary tract (NTS), amygdala and parabrachial nuclei (PBN) and also activate some of neuronal phenotypes including tyrosine hydroxylase (TH) neurons in the brainstem noradrenergic cell groups and hypothalamic oxytocinergic neurons. **RESULTS:** Twenty eight days after the initiation of tumor process we found increased Fos expression in NTS/A2, A1 noradrenergic cells, PBN as well as in the

hypothalamic paraventricular, supraoptic and accessory oxytocinergic neurons. These structures are involved in the transmission of signals related to immune challenges within the brain and consequent elaboration of neuro-endocrine responses. CONCLUSIONS: The data obtained are supporting the view that the information on peripheral tumor development might be transmitted to the brain. However, further studies are necessary to be performed to reveal whether our findings can be attributed to specific effect of cancer or whether observed changes in the activity of brainstem and hypothalamic neurons reflex processes that only accompany the cancer progression.

Mueller, M. M. and E. Seifried (2006). "Blood transfusion in Europe: basic principles for initial and continuous training in transfusion medicine: an approach to an European harmonisation." *Transfus Clin Biol* **13**(5): 282-5; quiz 286-9.

Over the past few decades, transfusion medicine and haemotherapy have evolved into complex medical disciplines comprising a broad field of subspecialties such as immunohaematology, blood component production, haemapheresis and haemostaseology. Transfusion medicine is thus an important qualification at the interfaces of analytical laboratory medicine, pharmaceutical production and clinical disciplines such as internal medicine, anaesthesiology or surgery. Physicians specialising in transfusion medicine are valuable and competent partners for these related disciplines when it comes to safe, effective and tailored haemotherapy. Why has transfusion medicine become so complex? On the one hand, one can discern problems such as infectious diseases like the HIV disaster in the past century, resulting in guidelines, directives and laws such as the transfusion law in Germany. Thereby, we now enjoy the highest level of blood product safety ever regarding viral transmission thanks to the broad implementation of PCR testing. On the other hand, there are numerous positive reasons for the increasing complexity of transfusion medicine: Modern medical therapies like stem cell transplantation, cellular therapy, transplantation of solid organs, regenerative medicine and surgery cannot exist without a safe supply of blood products and high quality standard as well as special blood products and laboratory services provided by blood banks and transfusion medicine specialists. Good laboratory practice (GLP), good manufacturing practice (GMP), quality management systems and quality control on the pharmaceutical manufacturer's level are only few examples of the standards in today's blood banking. European directives in the field of blood products, stem cell preparations and tissue have led to higher uniform

quality standards for biological preparations in a unified Europe, which is the desired outcome, but which also increases the complexity of this field. In contrast, directives 93/16/EEC and 2001/19/EC, the directives of the European Parliament and of the Council on the mutual recognition of professional qualifications of European doctors currently in force, as well as the impending directive 2005/36/EC, which has to be translated into national law until October 2007, do not include transfusion medicine, blood transfusion or immunohaematology at all. Other medical specialities, which like our field, are not common to all member states of the European Union, are listed in the above mentioned directives with the minimum length of training and minimal requirements for the qualifications. Examples include clinical biology, biological haematology, microbiology-bacteriology, biological chemistry, immunology, thoracic, paediatric or vascular surgery as well as physiotherapy, stomatology, neuro-psychiatry, dermato-venerology, occupational medicine, allergology, geriatrics, gastro-enterological surgery, community medicine, nuclear medicine, pharmacology, accident and emergency medicine or tropical medicine. Most of the above are medical specialities in some member states, but not in all. A concerted initiative inaugurated by the European Network of Transfusion Medicine Societies (EuroNet-TMS) and the European Blood Alliance (EBA) aims to compile the situation of the transfusion medicine speciality throughout Europe. A preliminary summary of the current situation in 15 European states was prepared in 2005 after a first set of questions, which was sent out by us via the EBA platform. The authors appreciate Clair Watts' compilation of the answers provided by the 15 European colleagues. A summary of these answers is depicted in Table 1. However, the initiative aims at a more complex analysis of the different requirements and constituent parts of the qualification in transfusion medicine in different countries. A long-term objective of this initiative might be to introduce the transfusion medicine specialisation into the above mentioned EC directives in order to facilitate mutual recognition of transfusion medicine qualifications throughout Europe.

Nakanishi, Y., M. Nakamura, et al. (2006). "Latanoprost rescues retinal neuro-glial cells from apoptosis by inhibiting caspase-3, which is mediated by p44/p42 mitogen-activated protein kinase." *Exp Eye Res* **83**(5): 1108-17.

The purpose of this study was to investigate whether latanoprost, a prostaglandin F₂alpha analogue, has a direct anti-apoptotic effect both in retinal neuro-glial cells in culture and in diabetic retina. R28 cells, immortalized retinal neuroglial

progenitor cells, were induced apoptosis by 24h serum deprivation. Serum withdrawal made up to 15% of R28 cells pyknotic and activated caspase-3 immunoreactive, and latanoprost acid suppressed apoptosis with dose dependency at an optimum concentration of 1.0 microM ($P < 0.001$). UO126, a mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase kinase (MEK) 1 and 2 inhibitor reversed this effect. Streptozotocin induced one- or three-month diabetic rats received balanced-salt-solution (BSS) in the left eye and latanoprost eye drops in the right for 5 days. Retinal wholemount was subjected to terminal dUTP nick end labeling (TUNEL) staining, whereas eyeballs were enucleated for cleaved caspase-3 immunofluorescence. Retinal homogenates were probed for phospho- or total p44/p42 MAPK and Akt. One- and three-month diabetic retina had 30.2 \pm 15.3 and 23.6 \pm 9.0 TUNEL positive cells per 0.5 cm², respectively, whereas control retina had few TUNEL positive cells. Latanoprost instillation significantly reduced these cells (10.0 \pm 3.1 and 11.3 \pm 3.1 cells per 0.5 cm²) for 1M and 3M, respectively, $P < 0.01$, whereas BSS did not. Latanoprost also significantly reduced cleaved caspase-3 immunoreactive cells in ganglion cell and inner nuclear layers ($P < 0.05$). Latanoprost increased phosphorylated to total protein ratio of p44/p42 MAPK ($P < 0.05$), but not of Akt. Taken together, the present findings suggest that latanoprost rescues retinal neurons and/or glial cells from apoptosis, which is probably mediated by p44/p42 MAPK through caspase-3 inhibition.

Nicolis, S. K. (2007). "Cancer stem cells and "stemness" genes in neuro-oncology." *Neurobiol Dis* 25(2): 217-29.

The main properties of stem cells include long-term self-renewal and the capacity to give rise to one or more types of differentiated progeny. Recently, much evidence was provided that leukemia and tumor maintenance and growth are sustained by a small proportion of cells exhibiting stem cell properties. In neural tumors, stem cells have been detected in glioblastoma, medulloblastoma and ependymoma. These observations imply that normal stem cells could be the origin of cancer stem cells; alternatively, a more differentiated progeny may revert to a "stem-like" status, and give rise to cancer stem cells. In adult brain residual stem cells are located in the hippocampus, the subventricular zone and possibly the cerebellum. However, evidence for the ability of more differentiated progeny (astroglia, oligodendroglia) to convert into "stem cells" in vitro has also been provided, thus greatly expanding the potential target of oncogenic mutations. In the framework of the cancer stem cell hypothesis, genes originally

identified as important for normal neural stem cells may be essential to support cancer stem cells as well. Stem cell genes act in several ways: they stimulate stem cell self-replication, inhibit differentiation, control excessive replication that might lead to "exhaustion" of the stem cell pool. Mutations in man and mouse, in spontaneous or experimental brain tumors, often target stem cell genes or genes lying in their functional pathway, the main examples being the Sonic hedgehog and the Wnt pathways. Interestingly, several stem cell genes are often overexpressed in brain tumors, even if they are not mutated. This suggests that these genes may be important for the generation of cancer stem cells from more differentiated precursors, or for cancer stem cell maintenance. Cancer stem cells partially differentiate in vivo, and in vitro they also give rise to seemingly normal differentiated progeny, like normal stem cells: thus, their main defect, leading to cancer, may lie in the unbalance between self-replication and terminal differentiation of this minority cell population. Knowledge of extrinsic diffusible factors affecting the activity of stem cell genes may help identifying tools for inducing cancer stem cell differentiation, which might be of use in therapy.

Ophof, T. (2007). "Embryological development of pacemaker hierarchy and membrane currents related to the function of the adult sinus node: implications for autonomic modulation of biopacemakers." *Med Biol Eng Comput* 45(2): 119-32.

The sinus node is an inhomogeneous structure. In the embryonic heart all myocytes have sinus node type pacemaker channels (I (f)) in their sarcolemma. Shortly before birth, these channels disappear from the ventricular myocytes. The response of the adult sinus node to changes in the interstitium, in particular to (neuro)transmitters, results from the interplay between the responses of all of its constituent cells. The response of the whole sinus node cannot be simply deduced from these cellular responses, because all cells have different responses to specific agonists. A biological pacemaker will be more homogeneous. Therefore it can be anticipated that tuning of cycle length may be problematic. It is discussed that efforts to create a biological pacemaker responsive to vagal stimulation, may be counterproductive, because it may have the potential risk of 'standstill' of the biological pacemaker. A normal sinus node remains spontaneously active at high concentrations of acetylcholine, because it has areas that are unresponsive to acetylcholine. The same is pertinent to other substances with a negative chronotropic effect. Such functional inhomogeneity is lacking in biological pacemakers.

Padma Srivastava, M. V. (2009). "Restorative therapy in stroke using stem cells." *Neurol India* **57**(4): 381-6.

The nonregenerative capability of the injured adult brain has been challenged in recent years and neural plasticity has been observed experimentally in both global and focal brain ischemia in animal models. Whether neuro-genesis increases in response to brain lesions or stem cells can be used for transplantation are the potential questions to be answered. Functional recovery may occur in a small or a localized brain injury using rehabilitation measures, but for large ischemic strokes, the restoration may require new synaptic connections within and away from the damaged tissue. In an infarcted area, the ischemic core may not respond to any pharmacological or rehabilitative intervention. For these reasons, the prospects of repairing the neuron system, using cell transplantation seems promising and may offer a unique approach for brain repair and restoration of function. On going animal and human trials have greatly helped us to burgeon our hopes on this method of restorative therapy after stroke. The ultimate aim of any therapeutic strategy is the maximum restoration possible and eventual complete normalcy of function.

Panagiotakos, G. and V. Tabar (2007). "Brain tumor stem cells." *Curr Neurol Neurosci Rep* **7**(3): 215-20.

The concept of brain tumor stem cells is gaining increased recognition in neuro-oncology. Until recently, the paradigm of a tumor-initiating stem cell was confined to hematopoietic malignancies where the hierarchical lineages of stem progenitor cells are well established. The demonstration of persistent stem cells and cycling progenitors in the adult brain, coupled with the expansion of the cancer stem cell concept to solid tumors, has led to the exploration of "stemness" within gliomas. Emerging data are highly suggestive of the subsistence of transformed multipotential cells within a glioma, with a subfraction of cells exhibiting increased efficiency at tumor initiation. However, data in support of true glioma stem cells are inconclusive to date, particularly with respect to functional characterization of these cells. Ongoing work aims at the identification of unique pathways governing self-renewal of these putative stem cells and at their validation as ultimate therapeutic targets.

Paus, R., P. Arck, et al. (2008). "(Neuro-)endocrinology of epithelial hair follicle stem cells." *Mol Cell Endocrinol* **288**(1-2): 38-51.

The hair follicle is a repository of different types of somatic stem cells. However, even though the hair follicle is both a prominent target organ and a

potent, non-classical site of production and/or metabolism of numerous polypeptide- and steroid hormones, neuropeptides, neurotransmitters and neurotrophins, the (neuro-)endocrine controls of hair follicle epithelial stem cell (HFeSC) biology remain to be systematically explored. Focussing on HFeSCs, we attempt here to offer a "roadmap through terra incognita" by listing key open questions, by exploring endocrinologically relevant HFeSC gene profiling and mouse genomics data, and by sketching several clinically relevant pathways via which systemic and/or locally generated (neuro-)endocrine signals might impact on HFeSC. Exemplarily, we discuss, e.g. the potential roles of glucocorticoid and vitamin D receptors, the hairless gene product, thymic hormones, bone morphogenic proteins (BMPs) and their antagonists, and Skg-3 in HFeSC biology. Furthermore, we elaborate on the potential role of nerve growth factor (NGF) and substance P-dependent neurogenic inflammation in HFeSC damage, and explore how neuroendocrine signals may influence the balance between maintenance and destruction of hair follicle immune privilege, which protects these stem cells and their progeny. These considerations call for a concerted research effort to dissect the (neuro-)endocrinology of HFeSCs much more systematically than before.

Perez, R. P., P. J. O'Dwyer, et al. (1991). "Comparative cytotoxicity of CI-973, cisplatin, carboplatin and tetraplatin in human ovarian carcinoma cell lines." *Int J Cancer* **48**(2): 265-9.

The clinical efficacy of cisplatin-based chemotherapy for ovarian cancer is frequently compromised by drug resistance or dose-limiting renal and neurologic toxicities. CI-973 (NK-121), a 2-methyl-1,4-butanediamine analogue of carboplatin, has shown little nephro- and neuro-toxicity in pre-clinical model systems and in phase-I trials. Its in vitro spectrum of activity against ovarian cancer cell lines has not been previously characterized. The in vitro activities of CI-973, cisplatin, carboplatin and tetraplatin were compared in several platinum-sensitive and -resistant human ovarian carcinoma cell lines. Cytotoxicity was assessed by inhibition of clonogenic survival in soft agar with continuous drug exposure. On a molar basis, cisplatin and tetraplatin were the most potent analogues, while carboplatin was consistently less potent. Cisplatin, carboplatin and CI-973 elicited a very similar response pattern by Spearman rank correlation, distinct from that seen with tetraplatin. The magnitude of resistance to CI-973 was comparable to cisplatin in 5 cell lines but was substantially lower in the highly cisplatin-resistant 2780-CP70 and OVCAR-10 cell lines. These results suggest that CI-973 and tetraplatin may have potential

utility in some cases of cisplatin-resistant ovarian cancer. In addition, our data are consistent with the existence of at least 2 platinum-resistance phenotypes—one with moderate levels of resistance to cisplatin, carboplatin and CI-973 but highly resistant to tetraplatin, the other highly resistant to cisplatin and carboplatin but only partially cross-resistant with tetraplatin and CI-973. The recognition of different resistance phenotypes may facilitate the study of cellular resistance mechanisms to cisplatin and newer platinum analogues.

Pillai, R., F. Scintu, et al. (2006). "Human astrocytes can be induced to differentiate into cells with neuronal phenotype." *Exp Cell Res* **312**(12): 2336-46.

Several recent studies have proposed that astrocytes may contribute to neurogenesis, not only as a source of trophic substances regulating it, but also as stem cells themselves. In order to better understand these mechanisms, primary astrocyte cultures were established from human fetal brain. After 3-4 weeks in culture, astrocytes (about 95% GFAP+; neurofilament, NF-; neuro-specific enolase, NSE-) were treated with a cocktail of protein kinase activators and FGF-1. After 5 h of treatment, most cells showed morphological changes that increased progressively up to 24-48 h, exhibiting a round cell body with long processes. Immunocytochemistry showed that treatment-induced NF and NSE expression in about 40% of cells. Nestin expression increased after treatment, whereas GFAP immunostaining was not significantly modified. Western blot and RT-PCR confirmed the results. No neuronal electrophysiological properties were observed after treatment, suggesting an incomplete maturation under these experimental conditions. Understanding the regenerative capability and neurogenic potential of astrocytes might be useful in devising therapeutic approaches for a variety of neurological disorders.

Poltavtseva, R. A., M. V. Marey, et al. (2002). "Evaluation of progenitor cell cultures from human embryos for neurotransplantation." *Brain Res Dev Brain Res* **134**(1-2): 149-54.

Human neural stem cells (HNSCs) are used in studies of neural development and differentiation, and are regarded as an alternative source of tissue for neural transplantation in degenerative diseases. Selection and standardization of HNSC samples is an important task in research and clinical approaches. We evaluated embryonal brain matter obtained from human 8-12-week-old fetuses by means of flow cytometry on a panel including: nestin; vimentin; NeuN; GFAP; beta-tubulin III; CD56; N-Cad; OB-Cad; HLA-ABC; HLA-DR; CD34, and annexin. Samples from embryos of even the same gestation

differ dramatically regarding neural cell development, their phenotype and viability. The samples containing the highest proportion of stem cells and multipotent progenitors of neural types, and the least of definitive cells and antigens of histocompatibility, were selected for further expansion in serum-free medium. Secondary phenotyping 14 days later revealed again a marked heterogeneity of the cultures. For the final culturing for 24 h in a serum-containing medium we selected only samples having following phenotype: nestin+, and vimentin+ no less than 25%; HLA-DR+ and CD34+ no more than 5%; GFAP+ no more than 10%; beta-tubulin+ no more than 20%; CD56+, N-Cad+, OB-Cad+, HLA-A,B,C+, and annexin+ no more than 15%; cell viability no less than 60%. Immunocytochemical study of selected samples proved that numerous neural stem cells, and neuro- and glioblasts necessary for transplantation were present. Our results demonstrate that the flow cytometry phenotyping allows the screening and standardization of HNSC samples for further expansion and transplantation.

Raidoo, D. M., P. K. Narotam, et al. (1998). "Cellular orientation of atrial natriuretic peptide in the human brain." *J Chem Neuroanat* **14**(3-4): 207-13.

Many peptide hormones and neurotransmitters have been detected in human neuronal tissue. The localisation of atrial natriuretic peptide (ANP) in the human brain was considered to be both interesting and relevant to the understanding of neurochemistry and brain water-electrolyte homeostasis. This vasoactive peptide hormone has been localised in rat and frog neuronal tissue. In the present study, we report the immunohistochemical localisation of ANP in autopsy samples of human brain tissue employing the avidin-biotin-peroxidase complex technique, using an antibody against a 28 amino acid fragment of human ANP. The most intense staining of immunoreactive ANP was detected in the neurones of preoptic, supraoptic and paraventricular nuclei of the hypothalamus, epithelial cells of the choroid plexus and ventricular ependymal lining cells. Immunoreactive neurones were also observed in the median eminence, lamina terminalis, infundibular and ventromedial nuclei of the hypothalamus, and in neurones of the brain stem, thalamic neurones and some neurones of the caudate nucleus. The network of ANP cells in numerous hypothalamic centres may regulate the salt and water balance in the body through a hypothalamic neuro-endocrine control system. ANP in the brain may also modulate cerebral fluid homeostasis by autocrine and paracrine mechanisms.

Rajasingh, J. and J. J. Bright (2006). "15-Deoxy-delta12,14-prostaglandin J2 regulates leukemia

inhibitory factor signaling through JAK-STAT pathway in mouse embryonic stem cells." Exp Cell Res **312**(13): 2538-46.

Embryonic stem (ES) cells are genetically normal, pluripotent cells, capable of self-renewal and differentiation into all cell lineages. While leukemia inhibitory factor (LIF) maintains pluripotency in mouse ES cells, retinoic acid and other nuclear hormones induce neuro-glial differentiation in mouse and human ES cells in culture. Peroxisome-proliferator-activated receptors (PPARs) are ligand-dependent nuclear receptor transcription factors that regulate cell growth and differentiation in many cell types. However, the role of PPARs in the regulation of ES cell growth and differentiation is not known. In this study, we show that LIF induces proliferation and self-renewal of mouse D3-ES cells in culture. However, treatment with 15-Deoxy-Delta(12,14)-Prostaglandin J(2) (15d-PGJ2), a natural ligand for PPARgamma, or all-trans retinoic acid (ATRA) results in a dose-dependent decrease in proliferation and self-renewal in D3-ES cells. Immunoprecipitation and Western blot analyses showed that LIF induces tyrosine phosphorylation of JAK1, TYK2 and STAT3 in 30 min and treatment with 15d-PGJ2 or ATRA results in a dose-dependent decrease in LIF-induced phosphorylation of JAK1 and STAT3 in D3-ES cells. However, treatment of D3-ES cells with Ciglitazone or 15d-PGJ2 for 48 h in culture resulted in a dose-dependent increase in PPARgamma protein expression. These results suggest that PPARgamma agonists regulate LIF signaling through JAK-STAT pathway leading to growth and self-renewal of ES cells.

Rich, J. N. (2008). "The Implications of the Cancer Stem Cell Hypothesis for Neuro-Oncology and Neurology." Future Neurol **3**(3): 265-273.

The cancer stem cell hypothesis posits that cancers contain a subset of neoplastic cells that propagate and maintain tumors through sustained self-renewal and potent tumorigenicity. Recent excitement has been generated by a number of reports that have demonstrated the existence of cancer stem cells in several types of brain tumors. Brain cancer stem cells - also called tumor initiating cells or tumor propagating cells - share features with normal neural stem cells but do not necessarily originate from stem cells. Although most cancers have only a small fraction of cancer stem cells, these tumor cells have been shown in laboratory studies to contribute to therapeutic resistance, formation of new blood vessels to supply the tumor, and tumor spread. As malignant brain tumors rank among the deadliest of all neurologic diseases, the identification of new cellular targets may have profound implications in neuro-

oncology. Novel drugs that target stem cell pathways active in brain tumors have been efficacious against cancer stem cells suggesting that anti-cancer stem cell therapies may advance brain tumor therapy. The cancer stem cell hypothesis may have several implications for other neurologic diseases as caution must be exercised in activating stem cell maintenance pathways in cellular therapies for neurodegenerative diseases. The ability for a small fraction of cells to determine the overall course of a disease may also inform new paradigms of disease that may translate into improved patient outcomes.

Richter, G. H., S. Plehm, et al. (2009). "EZH2 is a mediator of EWS/FLI1 driven tumor growth and metastasis blocking endothelial and neuro-ectodermal differentiation." Proc Natl Acad Sci U S A **106**(13): 5324-9.

Ewing tumors (ET) are highly malignant, localized in bone or soft tissue, and are molecularly defined by *ews/ets* translocations. DNA microarray analysis revealed a relationship of ET to both endothelium and fetal neural crest. We identified expression of histone methyltransferase enhancer of Zeste, *Drosophila*, Homolog 2 (EZH2) to be increased in ET. Suppressive activity of EZH2 maintains stemness in normal and malignant cells. Here, we found EWS/FLI1 bound to the EZH2 promoter *in vivo*, and induced EZH2 expression in ET and mesenchymal stem cells. Down-regulation of EZH2 by RNA interference in ET suppressed oncogenic transformation by inhibiting clonogenicity *in vitro*. Similarly, tumor development and metastasis was suppressed in immunodeficient Rag2(-/-)gamma(C)(-/-) mice. EZH2-mediated gene silencing was shown to be dependent on histone deacetylase (HDAC) activity. Subsequent microarray analysis of EZH2 knock down, HDAC-inhibitor treatment and confirmation in independent assays revealed an undifferentiated phenotype maintained by EZH2 in ET. EZH2 regulated stemness genes such as nerve growth factor receptor (NGFR), as well as genes involved in neuroectodermal and endothelial differentiation (EMP1, EPHB2, GFAP, and GAP43). These data suggest that EZH2 might have a central role in ET pathology by shaping the oncogenicity and stem cell phenotype of this tumor.

Ricotti, E., F. Fagioli, et al. (1998). "c-kit is expressed in soft tissue sarcoma of neuroectodermic origin and its ligand prevents apoptosis of neoplastic cells." Blood **91**(7): 2397-405.

During development, mice with mutations of stem cell factor (SCF) or its receptor c-kit exhibit defects in melanogenesis, as well as hematopoiesis and gonadogenesis. Consequently, accumulating

evidence suggests that the c-kit/SCF system plays a crucial role in all of these processes and in tumors which derive from them. Especially in neuroblastoma (infant tumors of neuroectoderm crest derivation such as melanocytes) it would appear that an autocrine loop exists between c-kit and SCF, and that the functional block of the c-kit receptors with monoclonal antibodies (MoAbs) results in a significant decrease in cellular proliferation. We studied the expression and role of c-kit and SCF in cell lines of soft tissue sarcoma of neuroectodermic origin, such as Ewing's sarcoma (ES) and peripheral neuro-ectodermal tumors (PNET). Using flow cytometry with MoAb CD117 PE, c-kit expression was highlighted in all six of the cell lines examined. This receptor was specifically and functionally activated by SCF, as shown by the binding experiments and the intracellular phosphotyrosine and immunoprecipitation studies that were performed. Using reverse transcriptase polymerase chain reaction analysis, five of the six cellular lines expressed the mRNA of SCF. In the medium measured by using an enzyme-linked immunosorbent assay, low concentrations of SCF were found: only the TC32 cellular line produced significantly higher levels (32 pg) than control. In serum-free culture the addition of SCF reduced the percentage of apoptotic cells from 25% to 90% in five out of the six cellular lines. This observation was confirmed by (1) the functional block of c-kit with MoAb: after 7 days of culture more than 30% of the cells were apoptotic (range 31.5% to 100%) in five out of six cell lines and there was also a decrease in the percentage of cells in phase S, and (2) c-kit antisense oligonucleotides: in the cellular lines treated with oligonucleotides (in relation to the untreated lines) there was a notable reduction ($P < .001$) both in the absolute number of cells and the 3H-thymidine uptake. These results indicate that ES and PNET express c-kit and its ligand SCF and that SCF is capable of protecting the tumor cells against apoptosis. Furthermore, the reverse transcriptase-polymerase chain reaction performed on the biopsies revealed the presence of mRNA both of SCF and c-kit in practically all of the samples studied. Our in vitro data lead us to assume that SCF may also inhibit tumor cell apoptosis in vivo.

Rieske, P., B. Krynska, et al. (2005). "Human fibroblast-derived cell lines have characteristics of embryonic stem cells and cells of neuro-ectodermal origin." *Differentiation* **73**(9-10): 474-83.

Fibroblasts are the most ubiquitous cells in complex organisms. They are the main cells of stromal tissue and play an important role in repair and healing of damaged organs. Here we report new data-initially serendipitous findings-that fibroblast-derived

cell line (human fetal lung derived cells, MRC-5) have the morphology, growth rate and gene expression pattern characteristic of embryonic stem cells and cells of neuro-ectodermal origin. We have developed a serum-free culture system to maintain these cells in proliferative state. We discovered that, at proliferative state, these cells express transcription factors of pluripotent cells, OCT-3/4 and REX-1, and embryonic cell surface antigens SSEA-1, SSEA-3, and SSEA-4, as well as TRA-1-60 and TRA-1-81. In addition to embryonic cell markers, the fibroblasts expressed neuroectodermal genes: Musashi-1, nestin, medium neurofilament, and beta-III tubulin. RT-PCR data revealed that mesencephalic transcription factors, Nurr-1 and PTX-3, were also expressed in MRC-5 cells, and that these cells could be induced to express tyrosine hydroxylase (TH). Expression of TH followed down-regulation of genes associated with cell proliferation, OCT-3/4, REX-1, and beta-catenin. These data indicate that the cells commonly known as fibroblasts have some of the characteristics of stem cells, and can be induced to become neuroectodermal cells and perhaps even mature neurons.

Rietze, R., P. Poulin, et al. (2000). "Mitotically active cells that generate neurons and astrocytes are present in multiple regions of the adult mouse hippocampus." *J Comp Neurol* **424**(3): 397-408.

Previous studies of the adult hippocampus of rodents and primates have reported neuro- and gliogenesis restricted to the region of the dentate gyrus. In the present study, by employing a prolonged bromodeoxyuridine (BrdU) labeling protocol that attempts to account for cytokinetic changes as an animal ages, we have identified mitotically active cells in multiple regions of the hippocampus, especially in Ammon's horn, of the adult mouse. Immediately following the labeling period, the BrdU-labeled cells did not express known markers for neurons and astrocytes. Subsequent analysis at 3-24 weeks after labeling demonstrated BrdU-labeled neurons and glia in these regions of the hippocampus. Although neuro- and gliogenesis in the adult mammalian hippocampus have been reported previously, these results demonstrate that the phenomenon is not limited to the region of the dentate gyrus, but rather extends into Ammon's horn. Furthermore, it suggests that ongoing cell production, albeit discrete and limited in nature, may be widespread in the adult mammalian central nervous system.

Rizvanov, A. A., A. P. Kiyasov, et al. (2008). "Human umbilical cord blood cells transfected with VEGF and L(1)CAM do not differentiate into neurons but transform into vascular endothelial cells and secrete neuro-trophic factors to support neuro-genesis-a novel

approach in stem cell therapy." *Neurochem Int* **53**(6-8): 389-94.

Genetically modified mono-nuclear cell fraction from human umbilical cord blood (HUCB) expressing human vascular endothelial growth factor (VEGF) and mouse neural L(1) cell adhesion molecule (L(1)CAM) were used for gene-stem cell therapy of transgenic (G)93(A) mice adopted as an animal amyotrophic lateral sclerosis (ALS) model. We generated non-viral plasmid constructs, expressing human VEGF(165) (pcDNA-VEGF) and mouse neural L(1) cell adhesion molecule (pcDNA-mL(1)CAM). Mono-nuclear fraction of HUCB cells were transiently transfected by electro-poration with a mixture of expression plasmids (pcDNA-VEGF+pcDNA-mL(1)CAM). Sixteen transgenic female and male mice were randomly assigned to three groups: (1) transplantation of genetically modified HUCB cells expressing L(1) and VEGF (n=6), (2) transplantation of un-transfected HUCB cells (n=5), and (3) control group (n=5). In first two experimental groups 1×10^6 cells were injected retro-orbitally in pre-symptomatic 22-25-week-old (G)93(A) mice. Our results demonstrate that HUCB cells successfully grafted into nervous tissue of ALS mice and survived for over 3 months. Therefore, genetically modified HUCB cells migrate in the spinal cord parenchyma, proliferate, but instead of transforming into nerve cells, they differentiate into endothelial cells forming new blood vessels. We propose that: (A) expression of mouse neural L(1)CAM is responsible for increased homing and subsequent proliferation of transplanted cells at the site of neuro-degeneration, (B) expression of human VEGF directs HUCB cell differentiation into endothelial cells, and (C) neuro-protective effect may stem from the delivery of various neuro-trophic factors from newly formed blood vessels.

Robb, S. M., E. Ross, et al. (2008). "SmedGD: the Schmidtea mediterranea genome database." *Nucleic Acids Res* **36**(Database issue): D599-606.

The planarian *Schmidtea mediterranea* is rapidly emerging as a model organism for the study of regeneration, tissue homeostasis and stem cell biology. The recent sequencing, assembly and annotation of its genome are expected to further buoy the biomedical importance of this organism. In order to make the extensive data associated with the genome sequence accessible to the biomedical and planarian communities, we have created the *Schmidtea mediterranea* Genome Database (SmedGD). SmedGD integrates in a single web-accessible portal all available data associated with the planarian genome, including predicted and annotated genes, ESTs, protein homologies, gene expression patterns and

RNAi phenotypes. Moreover, SmedGD was designed using tools provided by the Generic Model Organism Database (GMOD) project, thus making its data structure compatible with other model organism databases. Because of the unique phylogenetic position of planarians, SmedGD (<http://smedgd.neuro.utah.edu>) will prove useful not only to the planarian research community, but also to those engaged in developmental and evolutionary biology, comparative genomics, stem cell research and regeneration.

Roskams, T., R. V. Campos, et al. (1993). "Reactive human bile ductules express parathyroid hormone-related peptide." *Histopathology* **23**(1): 11-9.

Various cholestatic liver diseases as well as regeneration after submassive necrosis are accompanied by a striking increase in the number of bile ductules. These reactive bile ductules are thought to arise either from proliferation of pre-existing bile ductules or bile ductule-related facultative stem cells, or from ductular metaplasia of hepatocytes. Recently, we found that reactive bile ductules display neuro-endocrine features, and speculated that the substance(s), produced in the neuro-endocrine granules, might play a role in their growth and/or differentiation through an autocrine or paracrine pathway. Parathyroid hormone-related peptide has been shown to be encoded by a growth factor-regulated gene that may play a role in cell growth and differentiation. We studied the immunohistochemical expression of this peptide in human liver, including three normal biopsies, 11 cases of cholestatic liver disease, six cases of focal nodular hyperplasia and three cases of regenerating liver. In regenerating liver, primary biliary cirrhosis, primary sclerosing cholangitis and partial or intermittent obstruction, the majority of reactive ductular cells expressing neuro-endocrine markers also expressed parathyroid hormone-related peptide. In focal nodular hyperplasia, a smaller number of bile ductular cells expressed the peptide. These findings suggest that parathyroid hormone-related peptide is localized in bile ductular cells and may indicate a role for this hormone in the growth and/or differentiation of human reactive bile ductules.

Roskams, T., R. De Vos, et al. (1991). "Cells with neuroendocrine features in regenerating human liver." *APMIS Suppl* **23**: 32-9.

Regeneration of liver tissue in man after submassive necrosis is reflected by replicating features in hepatocytes, and by a remarkably increased number of bile duct structures that are thought to transdifferentiate into true functioning hepatocytes. Similar to the bile ductule-related "oval cells" in rats,

human bile ductular cells may therefore serve as "facultative stem cells" that become activated when hepatocyte regeneration is insufficient or inhibited. Our recent demonstration of neuroendocrine features in proliferating bile ductules in cholestatic liver disease prompted us to perform a similar immunohistochemical and electron microscopical study on regenerating human liver tissue after submassive liver necrosis. In the earliest stages of regeneration, bile ductular cells and small, singular cells in the periportal area expressed chromogranin-A and contained dense-cored, secretory granules. It is tempting to speculate that the scattered singular cells represent the human equivalent of the bipotential progenitor cells in the rat. In later stages of regeneration, these singular cells were no longer evident, suggesting their differentiation into other cell types. In these cases, neuro-endocrine cells corresponded to proliferating bile ductules and to scattered, typical hepatocytes, located near portal tracts and in regenerating nodules. In all cases, proliferating bile ductules displayed the neural cell adhesion molecule (NCAM). These data further support our hypothesis that the substance(s) produced in the dense cored secretory granules may play a role in the growth and/or differentiation of liver cells through an autocrine and or paracrine pathway.

Rubinstein, L. J. (1985). "Embryonal central neuroepithelial tumors and their differentiating potential. A cytogenetic view of a complex neuro-oncological problem." *J Neurosurg* **62**(6): 795-805.

The embryonal central nervous system (CNS) neoplasms are reviewed with special reference to their differentiating potential and in the light of current neuro-oncogenetic concepts partly derived from the experimental induction of neural tumors. The conceptual (and, occasionally, practical) distinction between adult-type and embryonal CNS tumors raises a complex problem, because neoplastic transformation essentially involves replicating stem cells in tissues of renewal and because in the human brain such cells are found mostly in the course of CNS development. A cytogenetic scheme is therefore needed to serve as a frame of reference for a classification of embryonal CNS tumors that will account for the different histological entities documented so far and for the range and the restrictions of their differentiating capabilities. Most embryonal CNS tumors can be fitted into such a scheme. The cerebral medulloepithelioma, the cerebral and cerebellar neuroblastomas, the primitive polar spongioblastoma, and the ependymoblastoma show characteristic morphological features and a correspondingly distinctive cellular differentiating potential. The differentiating capabilities of the cerebellar

medulloblastoma, the pineoblastoma, and the retinoblastoma are also distinctive, and are apparently determined by the cytogenesis of the area of the CNS in which the tumors originate. The indiscriminate application of a simplistic concept that would include all the so-called "primitive neuroectodermal tumors" into a single neuroepithelial tumor entity is unlikely to bring further understanding to the problem.

Rubinstein, L. J. (1987). "The correlation of neoplastic vulnerability with central neuroepithelial cytogeny and glioma differentiation." *J Neurooncol* **5**(1): 11-27.

The vulnerability of neuroepithelial cells in the central nervous system (CNS) to neoplastic transformation results from the interaction of several factors: the existence of a reserve population of stem cells, the capability of differentiated cells to reenter the kinetic cycle, the number of replicating cells at risk at a particular time, the length of time during which a particular cell population remains in the cycle, the state of differentiation and the further differentiation potential of that population, and the steps of differentiation that are achieved in successive cell generations. This concept explains many aspects of CNS tumor incidence and the relationship of central neuroepithelial embryonal tumors to tumors of adult cell type. The incidence of different types of central neuroepithelial tumors can be correlated with the width of the window of neoplastic vulnerability. Examples illustrating the existence of only a narrow window include such rare tumors as medulloepitheliomas, cerebral neuroblastomas, gangliogliomas and ependymoblastomas. By contrast, cerebellar medulloblastomas, astrocytomas, mixed astrocytomas and oligodendrogliomas, and glioblastomas exemplify instances in which a relatively wider window of vulnerability exists in the light of cellular neuro-ontogeny and of the capacity of glial cells for postnatal replication. The relationship that may occasionally be established between the development of a glioma and the production of cellular gliosis such as may follow brain injury or accompany multiple sclerosis can also be viewed in the light of that concept. Increasing awareness is needed concerning the development of postradiation gliomas, in particular after the apparently successful treatment of acute lymphocytic leukemia.

Rubio, F. J., Z. Kokaia, et al. (1999). "BDNF gene transfer to the mammalian brain using CNS-derived neural precursors." *Gene Ther* **6**(11): 1851-66.

Neural stem cell lines represent a homogeneous source of cells for genetic, developmental, and gene transfer and repair studies in the nervous system. Since both gene transfer of neurotrophic factors and cell replacement strategies

are of immediate interest for therapeutical purposes, we have generated BDNF-secreting neural stem cell lines and investigated to what extent different endogenous levels of BDNF expression affect in vitro survival, proliferation and differentiation of these cells. Also, we have investigated the in vivo effects of such BDNF gene transfer procedure in the rat neostriatum. Hippocampus- and cerebellum-derived cell lines reacted differently to manipulations aimed at varying their levels of BDNF production. Overexpression of BDNF enhanced survival of both cell types, in a serum-deprivation assay. Conversely, and ruling out unspecific effects, expression of an antisense version of BDNF resulted in compromised survival of cerebellum-derived cells, and in a lethal phenotype in hippocampal progenitors. These data indicate that endogenous BDNF level strongly influences the in vitro survival of these cells. These effects are more pronounced for hippocampus- than for cerebellum-derived progenitors. Hippocampus-derived BDNF overproducers showed no major change in their capacity to differentiate towards a neuronal phenotype in vitro. In contrast, cerebellar progenitors overproducing BDNF did not differentiate into neurons, whereas cells expressing the antisense BDNF construct generated cells with morphological features of neurons and expressing immunological neuronal markers. Taken together, these results provide evidence that BDNF controls both the in vitro survival and differentiation of neural stem cells. After in vivo transplantation of BDNF-overproducing cells to the rat neostriatum, these survived better than the control ones, and induced the expected neurotrophic effects on cholinergic neurons. However, long-term (3 months) administration of BDNF resulted in detrimental effects, at this location. These findings may be of importance for the understanding of brain development, for the design of therapeutic neuro-regenerative strategies, and for cell replacement and gene therapy studies.

Sanchez Alvarado, A., P. A. Newmark, et al. (2002). "The Schmidtea mediterranea database as a molecular resource for studying platyhelminthes, stem cells and regeneration." *Development* **129**(24): 5659-65.

Platyhelminthes are excellent models for the study of stem cell biology, regeneration and the regulation of scale and proportion. In addition, parasitic forms infect millions of people worldwide. Therefore, it is puzzling that they remain relatively unexplored at the molecular level. We present the characterization of approximately 3,000 non-redundant cDNAs from a clonal line of the planarian *Schmidtea mediterranea*. The obtained cDNA sequences, homology comparisons and high-throughput whole-mount in situ hybridization data

form part of the *S. mediterranea* database (SmedDb; <http://planaria.neuro.utah.edu>). Sixty-nine percent of the cDNAs analyzed share similarities with sequences deposited in GenBank and dbEST. The remaining gene transcripts failed to match sequences in other organisms, even though a large number of these (approximately 80%) contained putative open reading frames. Taken together, the molecular resources presented in this study, along with the ability of abrogating gene expression in planarians using RNA interference technology, pave the way for a systematic study of the remarkable biological properties displayed by Platyhelminthes.

Schmidt, K., A. S. Schulz, et al. (2008). "CNS complications in children receiving chemotherapy or hematopoietic stem cell transplantation: retrospective analysis and clinical study of survivors." *Pediatr Blood Cancer* **50**(2): 331-6.

BACKGROUND: Clinical studies analyzing CNS complications in pediatric oncology systematically are rare. **PROCEDURE:** In a single center retrospective analysis, CNS complications in 950 subsequent pediatric patients treated between 1992 and 2004 by chemotherapy or hematopoietic stem cell transplantation (HSCT) were studied. Forty-six patients had pre-existing CNS diseases and were excluded. Out of the 904 remaining, 76 (8.4%) had 82 CNS complications. **RESULTS:** The most common manifestations were seizures (in 50.6% of the CNS episodes), altered states of consciousness, and motor deficits (in 47.5% of the episodes each). CNS complications were caused by infections (26.8%), toxicity (25.6%), neoplasma (13.4%), vascular (10.9%), and metabolic disturbances (8.5%). In 14.6%, the mechanism remained unclear. Patients (23.7%) died from the CNS event. Neoplastic disorders had the worst (50%) while metabolic the best (0% mortality) prognosis. Imaging techniques were the most effective diagnostic measures, followed by laboratory analysis, clinical examination, and CSF analysis. A neuro-psychological (CBCL, CFT-1/-20-testing) examination could be done in 21 of 32 long-term survivors. Seven had a major, 3 minor neurological impairment, 11 were normal in all tests. **CONCLUSIONS:** These data show that there is not one typical CNS complication, but a wide variety. There is no close connection between either underlying disease or symptoms and cause of the complication. Prognosis is variable. About two thirds of the long-term survivors could lead a normal life.

Schmidt, N. O., D. Koeder, et al. (2009). "Vascular endothelial growth factor-stimulated cerebral microvascular endothelial cells mediate the

recruitment of neural stem cells to the neurovascular niche." *Brain Res* **1268**: 24-37.

Endogenous and transplanted neural stem cells (NSC) are highly migratory and display a unique tropism for areas of neuro-pathology. However, signals controlling NSC motility in health and disease are still ill-defined. NSC appear to be intimately associated with the cerebral vasculature and angiogenesis is a hallmark of many neurological disorders. This has led us to investigate the influence of quiescent and angiogenically active human endothelial cells on human NSC migration. In vivo we observed frequent perivascular accumulation of human NSC in the proximity of cerebral microvessels upon induction of angiogenesis by cerebral infusion of vascular endothelial growth factor (VEGF) into the murine brain. We analyzed the in vitro effects of conditioned media from human endothelial cells before and after angiogenic stimulation with VEGF on the migration of human NSC in vitro. Non-stimulated endothelial cells induced a moderate chemotactic migration that was significantly enhanced after angiogenic activation by VEGF. In order to identify cytokines that may function as stimulators of NSC chemotaxis, we screened endothelial cell-conditioned media for the expression of 120 different cytokines. We identified PDGF-BB, RANTES, I-TAC, NAP-2, GROalpha, Ang-2, and M-CSF as endothelial cell-released chemoattractants for human NSC in vitro. VEGF-stimulated cerebral microvascular endothelial cells secreted higher levels of Ang-2 and GROalpha, which in part were responsible for the enhanced chemoattraction of NSC. Our findings support the hypothesis that the angiogenically active microvasculature modulates the local guidance of NSC through endothelial cell-derived chemoattractants.

Schmidt-Choudhury, A., J. Meissner, et al. (1999). "Stem cell factor influences neuro-immune interactions: the response of mast cells to pituitary adenylate cyclase activating polypeptide is altered by stem cell factor." *Regul Pept* **83**(2-3): 73-80.

Mast cells degranulation can be elicited by a number of biologically important neuropeptides, but the mechanisms involved in mast cell-neuropeptide interactions have not been fully elucidated. Stem cell factor (SCF), also known as c-kit or kit ligand, induces multiple effects on mast cells, including proliferation, differentiation, maturation, and prevents apoptosis. We investigated the ability of SCF to affect mast cell responsiveness to the neuropeptides pituitary adenylate cyclase activating polypeptide (PACAP) and vasoactive intestinal peptide (VIP). PACAP 1-27, PACAP1-38, or VIP failed to induced preformed mediator release from mouse bone-marrow-cultured

mast cells (BMCMC) derived in concanavalin A-stimulated spleen conditioned medium (CM). By contrast, BMCMC grown in SCF-containing medium or freshly isolated peritoneal mast cells exhibited significant 3H-hydroxytryptamine (5-HT) release in response to PACAP peptides or VIP. Deoxyglucose and the mitochondrial inhibitor antimycin significantly inhibited PACAP-induced 5-HT release indicating that the central event induced by PACAP peptides was exocytosis. The G(alpha)i inhibitor, pertussis toxin, significantly diminished PACAP-induced 5-HT release from BMCMCs in SCF suggesting the involvement of heterotrimeric G-proteins. Western blot analysis using antibodies directed against the human VIP type I/PACAP type II receptor demonstrated a 70-72 kD immunoreactive protein expressed in greater amounts in BMCMC grown in SCF compared with BMCMC in CM. We conclude that SCF induces a mast cell population that is responsive to PACAPs and VIP involving a heterotrimeric G-protein-dependent mechanism.

Schweitzer, V. G. (1993). "Cisplatin-induced ototoxicity: the effect of pigmentation and inhibitory agents." *Laryngoscope* **103**(4 Pt 2): 1-52.

Cis-diamminedichloroplatinum II (cisplatin), a divalent platinum compound and potent cell-cycle nonspecific chemotherapeutic agent, produces a dose-limiting, permanent, high-frequency sensori-neural hearing loss and peripheral neuropathy, and a dose-related cumulative renal insufficiency with tubular necrosis and interstitial nephritis. The potential for dose-limiting and permanent cochlear (neuro) toxicity remains despite present methods of hypertonic saline, prehydration, and mannitol diuresis prior to drug administration. The exact mechanism(s) of ototoxicity and/or nephrotoxicity are still unknown. Continued aggressive high-dose cisplatin chemotherapy necessitates the investigation of ways to decrease the dose-limiting side effects that inhibit the administration of cisplatin at therapeutic and tumoricidal doses. This multifaceted project investigates two categories of potential inhibitors of cisplatin toxicity that, when coadministered with a known tumoricidal and ototoxic dose of cisplatin, will decrease or inhibit the ototoxicity: 1. phosphonic acid antibiotics (fosfomycin; 1,2 epoxypropylphosphonic acid); 2. nonglucocorticoid 21-aminosteroids, which are free oxygen radical scavengers (LAZAROIDS: U74006F and U78517F). This project also investigates the role of pigmentation as a variable affecting the evaluation of platinum-induced ototoxicity in the guinea pig animal model. Identification of an optimal animal model for future cisplatin toxicity research should be based on previously established species-specific differences in

total drug dose, systemic toxicity, and morphological and functional evidence of cochlear toxicity, as affected by differences in pigmentation and drug tolerance. Cytochrome c, brainstem auditory evoked response (BSER), scanning and transmission electron microscopy of organ of Corti and the stria vascularis, double-blind light microscopy of renal, small intestine, and peripheral nerve tissue, and gamma-emission analysis of ^{195m}platinum localization in inner ear neuroepithelium and the stria vascularis are used in the global evaluation of the ototoxic effects of cisplatin in both the adult albino and pigmented guinea pig.

Shahar, A., S. Reuveny, et al. (1992). "Differentiation of myoblasts and CNS cells grown either separately or as co-cultures on microcarriers." *Cytotechnology* **9**(1-3): 107-15.

Dispersed neuronal and muscular elements from fetal or neonatal origin, can organize and mature in culture when grown on positively charged cylindrical microcarriers (MCS), to a stage which simulate in vivo maturation. Cells arrange themselves on the MCS to form aggregates which remain floating in the nutrient medium. In such a tridimensional organization, the neuronal tissue is capable of regenerating a network of nerve fibers which establish synapse interconnections and undergo myelination. Oligodendrocytes organize on MCS in a tridimensional pattern and produce extensive myelin-like membranes. Myoblasts in MC-cultures fuse into polynucleated myotubes which become striated and contract spontaneously. Creatine kinase and acetylcholine receptor (AChR) are formed during myogenesis in similar quantities in MC-cultures and in monolayers. When both neuronal and muscle tissues are prepared from the same fetus (autologous nerve-muscle co-cultures) and are cultured on MCS, they interconnect to form neuro-muscular junctions. Cells from both tissues, exhibit better differentiation, for longer periods in MC-cultures than they do in monolayers. The floating functional entities are easy to sample and can be harvested for ultrastructural, immunocytochemical and biochemical analysis. In addition, MC-cultures can be used as a good tool for the study of acute and chronic exposures to toxicological agents, as well as for implantation into demyelinated, injured or dystrophic tissues. In this case the MCS in the implanted entities will serve as identifiable markers.

Shen, P. J., C. G. Yuan, et al. (2005). "Galanin in neuro(glio)genesis: expression of galanin and receptors by progenitor cells in vivo and in vitro and effects of galanin on neurosphere proliferation." *Neuropeptides* **39**(3): 201-5.

Considerable recent evidence suggests that in addition to its neuromodulatory role, galanin, like several other neuropeptides, also plays an important trophic role during development and after adult neural injury. Studies in our laboratory have identified high levels of galanin and galanin receptor expression in the subventricular zone, rostral migratory stream, subgranular zone of dentate gyrus and the medial corpus callosum--which include the main sites for continuing cell proliferation in both adult and developing rat brain. Galanin expression was also strongly and transiently induced in oligodendrocyte progenitor cells (OPCs) throughout the neocortex and corpus callosum by a benign physiological stimulus, cortical spreading depression (CSD). SD-like depolarization also occurs in peri-infarction areas following cerebral ischemia and is associated with proliferation of OPCs and transiently increased galanin expression. Together, these data suggest a putative role for galanin in regulating progenitor or 'stem cell' proliferation, migration and/or differentiation. Cultured adult and embryonic stem cells or 'neurospheres' express galanin and galanin receptor mRNA and preliminary studies suggest that sub-acute galanin treatment of cultured neurospheres decreases cell proliferation/survival, possibly by effects on the rate of apoptosis via GalR2 receptors.

Shuto, T., H. Fujino, et al. (2003). "Gamma knife radiosurgery for metastatic tumours in the brain stem." *Acta Neurochir (Wien)* **145**(9): 755-60.

BACKGROUND: Stereotactic radiosurgery has become important in the treatment of metastatic brain tumours and is often the first choice modality for eloquent or deep locations such as the brain stem. This study evaluated the efficacy of gamma knife radiosurgery (GKS) for the treatment of brain stem metastases. **METHODS:** The medical records of 25 patients with 31 tumours, 11 men and 14 women aged 42 to 78 years (mean 57.1 years), who underwent GKS for metastatic tumours in the brain stem were retrospectively reviewed. The results of GKS were evaluated according to the change in tumour size on neuro-imaging. **FINDINGS:** The most common location of the primary malignancy was the lung followed by the breast. Adenocarcinoma was found in 19 patients (24 lesions). No case of squamous cell carcinoma was found. The mean calculated tumour volume was 2.1 cm³ and the mean prescription dose to the tumour margin was 13.0 Gy. Mean duration of neuro-imaging follow up was 5.2 months and the overall tumour control rate was 77.4%. There was a significant correlation between the marginal dose delivered and the effect on neuro-imaging. New radiation-induced injury in the surrounding brain occurred in only 2 patients. **INTERPRETATION:**

GKS for brain stem metastases using a marginal dose of 15 Gy or less is effective and relatively safe. Accurate targeting of the tumour and safe dose planning are essential to obtain satisfactory results with GKS for brain stem metastases.

Smits, A. (2002). "Low-grade gliomas: clinical and pathobiological aspects." *Histol Histopathol* **17**(1): 253-60.

The optimal management of patients with low-grade gliomas remains a challenge for the treating physician. The natural history of the disease shows a large variety, and there is a substantial controversy about many of everyday treatment recommendations. However, new developments in clinical and basic research in neuro-oncology have occurred during the last years. In this review some of these new insights into clinical and biological aspects of low-grade gliomas are discussed, with focus on the translation of new knowledge from basic research into clinical practice. For example, molecular genetic profiling of tumour material has started to guide treatment recommendations and clinical management of some patients with oligodendrogliomas. Experimental studies of the different molecular pathways in tumour cells and in their normal counterparts involved in cell-cycle check-point control have elucidated some of the underlying mechanisms of resistance of gliomas to radiotherapy and chemotherapy. Finally, improved classification of the different subtypes of low-grade gliomas may be achieved in the near future by characterization of the genetic heterogeneity within the tumour and by identification of a putative stem cell as the origin of the tumour cells.

Sugaya, K. (2005). "Possible use of autologous stem cell therapies for Alzheimer's disease." *Curr Alzheimer Res* **2**(3): 367-76.

The statement, "neurodegenerative diseases are incurable because neurons do not regenerate during adulthood," has been challenged, and we have now found much evidence that the matured brain is capable of regenerating neurons. In our previous study, human neural stem cells (HNSCs) transplanted into aged rat brains differentiated into neural cells and significantly improved the cognitive functions of the animals, indicating that HNSCs may be a promising candidate for neuro-replacement therapy. However, because of ethical and practical issues associated with HNSCs, development of autologous stem cell strategies may be desired. We established new technologies to differentiate adult human mesenchymal stem cells into neural cells by modifying cell fate decisions. We also found a pyrimidine derivative that increases endogenous stem cell proliferation and neurogenesis after peripheral

administrations of this compound. Although these results may promise a bright future for clinical applications of stem cell strategies in Alzheimer's disease (AD) therapy, we must acknowledge the complexity of AD. For example, abnormal metabolism of the amyloid-beta precursor protein (APP) may affect stem cell biology, while the prevalence of amyloid-beta peptide (Abeta) toxicity theory in AD pathology tends to limit our focus on the physiological functions of APP. We found that excess APP in the environment causes glial differentiation of stem cells. Even though the glial activation may be useful to eliminate Abeta deposits, neuronal differentiation of stem cells is needed for replacement of degenerating neurons in the AD brain. Thus, further investigation of the influence of AD pathology on stem cell biology is required.

Tagliafico, E., S. Brunelli, et al. (2004). "TGFbeta/BMP activate the smooth muscle/bone differentiation programs in mesoangioblasts." *J Cell Sci* **117**(Pt 19): 4377-88.

Mesoangioblasts are vessel-derived stem cells that can be induced to differentiate into different cell types of the mesoderm such as muscle and bone. The gene expression profile of four clonal derived lines of mesoangioblasts was determined by DNA micro-array analysis: it was similar in the four lines but different from 10T1/2 embryonic fibroblasts, used as comparison. Many known genes expressed by mesoangioblasts belong to response pathways to developmental signalling molecules, such as Wnt or TGFbeta/BMP. Interestingly, mesoangioblasts express receptors of the TGFbeta/BMP family and several Smads and, accordingly, differentiate very efficiently into smooth muscle cells in response to TGFbeta and into osteoblasts in response to BMP. In addition, insulin signalling promotes adipogenic differentiation, possibly through the activation of IGF-R. Several Wnts and Frizzled, Dishevelled and Tcfs are expressed, suggesting the existence of an autocrine loop for proliferation and indeed, forced expression of Frzb-1 inhibits cell division. Mesoangioblasts also express many neuro-ectodermal genes and yet undergo only abortive neurogenesis, even after forced expression of neurogenin 1 or 2, MASH or NeuroD. Finally, mesoangioblasts express several pro-inflammatory genes, cytokines and cytokine receptors, which may explain their ability to be recruited by tissue inflammation. Our data define a unique phenotype for mesoangioblasts, explain several of their biological features and set the basis for future functional studies on the role of these cells in tissue histogenesis and repair.

Takahashi, T., R. Ueda, et al. (1986). "Two novel cell surface antigens on small cell lung carcinoma defined by mouse monoclonal antibodies NE-25 and PE-35." *Cancer Res* **46**(9): 4770-5.

Two mouse monoclonal antibodies, NE-25 and PE-35, defining novel cell surface antigens of small cell lung carcinoma (SCLC) were produced. The molecular weight of NE-25 and PE-35 antigens estimated by radioimmunoprecipitation was 25,000 and 35,000, respectively. NE-25 antigen was expressed on the majority of cell lines and tumor specimens of SCLC among lung carcinoma. These NE-25-positive cell lines showed typical growth morphology as SCLC classic lines and expressed high levels of neuroendocrine biomarkers, such as aromatic L-amino acid decarboxylase, while NE-25 antigen-negative lines lacked apparent neuroendocrine properties. This antigen was expressed also on a subset of neoplastic cells with (neuro)endocrine properties, including pulmonary carcinoid, and on various tumors of nervous tissues, such as neuroblastoma. Among the normal cells, Kulchitski cells of lung, thyroid gland, adrenal gland, Langerhans islet, and nervous tissues were positive. Thus, the expression of NE-25 antigen is closely associated with the neural and/or (neuro)endocrine differentiation state. On the contrary, PE-35 antigen was present on four major types of lung carcinomas as well as on squamous cell carcinoma and adenocarcinomas of various tissues, but it was absent from nervous tissue tumors. Thus, PE-35 antibody showed a "pan-epithelial" reactivity. Analysis by NE-25 and PE-35 antibodies provided evidence for the heterogeneities of SCLC by demonstrating four surface phenotypes, with the NE-25+/PE-35+ phenotype being most common. In addition, the results supported the current understanding that various histological types of lung carcinoma, including SCLC, are derived from a stem cell of the bronchial epithelium.

Teramoto, S., F. Kihara-Negishi, et al. (2005). "Classification of neural differentiation-associated genes in P19 embryonal carcinoma cells by their expression patterns induced after cell aggregation and/or retinoic acid treatment." *Oncol Rep* **14**(5): 1231-8.

Expression of neural differentiation-associated genes was examined by RT-PCR and macroarray analyses during neural differentiation of P19 embryonal carcinoma cells induced by cell aggregation and/or retinoic acid (RA) treatment. Results revealed that the neural genes examined could be classified into 4 groups based on their expression patterns. The 1st group included the Wnt-1, Id-1, Id-3 and cdc42 genes, expression of which was altered by cell aggregation alone, but not by RA treatment alone.

The 2nd group included the alphaN-catenin, Neuro D and GDNFRbeta genes, expression of which was altered by RA treatment alone, but not by cell aggregation. The 3rd group consisted of the Brn-2, TrkA, bcl-X, N-cadherin, E-cadherin and Otx-2 genes, expression of which was altered by either treatment. The 4th group included the ACTH, D4DR, NGC and Oct-3 genes, the expression of which changed only when both treatments were applied simultaneously. Expression of the Ets-1 and Fli-1 transcription factor genes was up-regulated by either treatment alone at initial stages of neural differentiation of P19 cells, although overexpression of these genes alone could not induce cell differentiation. Our results suggest that although both treatments are required for complete neural differentiation of P19 cells, cell aggregation or RA treatment alone drive differentiation to a certain extent at the gene expression level.

Theoharides, T. C., D. Kempuraj, et al. (2006). "Human umbilical cord blood-derived mast cells: a unique model for the study of neuro-immuno-endocrine interactions." *Stem Cell Rev* **2**(2): 143-54.

Findings obtained using animal models have often failed to reflect the processes involved in human disease. Moreover, human cultured cells do not necessarily function as their actual tissue counterparts. Therefore, there is great demand for sources of human progenitor cells that may be directed to acquire specific tissue characteristics and be available in sufficient quantities to carry out functional and pharmacological studies. A case in point is the mast cell, well known for its involvement in allergic reactions, but also implicated in inflammatory diseases. Mast cells can be activated by allergens, anaphylatoxins, immunoglobulin-free light chains, superantigens, neuropeptides, and cytokines, leading to selective release of mediators. These could be involved in many inflammatory diseases, such as asthma and atopic dermatitis, which worsen by stress, through activation by local release of corticotropin-releasing hormone or related peptides. Umbilical cord blood and cord matrix-derived mast cell progenitors can be separated magnetically and grown in the presence of stem cell factor, interleukin-6, interleukin-4, and other cytokines to yield distinct mast cell populations. The recent use of live cell array, with its ability to study such interactions rapidly at the single-cell level, provides unique new opportunities for fast output screening of mast cell triggers and inhibitors.

Ul Hassan, A., G. Hassan, et al. (2009). "Role of stem cells in treatment of neurological disorder." *Int J Health Sci (Qassim)* **3**(2): 227-33.

Stem cells or mother or queen of all cells are pleuripotent and have the remarkable potential to

develop into many different cell types in the body. Serving as a sort of repair system for the body, they can theoretically divide without limit to replenish other cells as long as the person or animal is alive. When a stem cell divides, each new cell has the potential to either remain a stem cell or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a brain cell. Stem cells differ from other kinds of cells in the body. All stem cells regardless of their source have three general properties: They are unspecialized; one of the fundamental properties of a stem cell is that it does not have any tissue-specific structures that allow it to perform specialized functions. They can give rise to specialized cell types. These unspecialized stem cells can give rise to specialized cells, including heart muscle cells, blood cells, or nerve cells. They are capable of dividing and renewing themselves for long periods. Unlike muscle cells, blood cells, or nerve cells -- which do not normally replicate themselves -- stem cells may replicate many times. A starting population of stem cells that proliferates for many months in the laboratory can yield millions of cells. Today, donated organs and tissues are often used to replace those that are diseased or destroyed. Unfortunately, the number of people needing a transplant far exceeds the number of organs available for transplantation. Pluripotent stem cells offer the possibility of a renewable source of replacement cells and tissues to treat a myriad of diseases, conditions, and disabilities including Parkinson's and Alzheimer's diseases, spinal cord injury, stroke, Cerebral palsy, Batten's disease, Amyotrophic lateral sclerosis, restoration of vision and other neuro degenerative diseases as well.

Uno, K., R. Minoda, et al. (1993). "Neuro-otologic abnormalities in myelopathy associated with human T-cell lymphotropic virus type 1." Ann Otol Rhinol Laryngol **102**(5): 359-62.

Auditory testing (pure tone audiometry, auditory brain stem response), and vestibular tests (eye tracking test, optokinetic pattern test, and caloric test) were performed to define neuro-otologic abnormalities in myelopathy associated with human T-cell lymphotropic virus type 1. Of the eight patients tested, seven showed sensorineural hearing loss and one showed mixed hearing loss on pure tone audiometry. The auditory brain stem responses of five patients showed increases of the I-III and I-V interpeak latencies. Two patients showed fast superimposed saccadic movements on the smooth pursuit test, and one other patient showed canal paresis on the caloric test. These findings suggest both the presence of neuro-otologic abnormality and involvement of the brain stem in myelopathy

associated with human T-cell lymphotropic virus type 1.

Urakawa, S., H. Hida, et al. (2007). "Environmental enrichment brings a beneficial effect on beam walking and enhances the migration of doublecortin-positive cells following striatal lesions in rats." Neuroscience **144**(3): 920-33.

Rats raised in an enriched environment (enriched rats) have been reported to show less motor dysfunction following brain lesions, but the neuronal correlates of this improvement have not been well clarified. The present study aimed to elucidate the effect of chemical brain lesions and environmental enrichment on motor function and lesion-induced neurogenesis. Three week-old, recently weaned rats were divided into two groups: one group was raised in an enriched environment and the other group was raised in a standard cage for 5 weeks. Striatal damage was induced at an age of 8 weeks by injection of the neuro-toxins 6-hydroxydopamine (6-OHDA) or quinolinic acid (QA) into the striatum, or by injection of 6-OHDA into the substantia nigra (SN), which depleted nigrostriatal dopaminergic innervation. Enriched rats showed better performance on beam walking compared with those raised in standard conditions, but both groups showed similar forelimb use asymmetry in a cylinder test. The number of bromodeoxyuridine-labeled proliferating cells in the subventricular zone was increased by a severe striatal lesion induced by QA injection 1 week after the lesion, but decreased by injection of 6-OHDA into the SN. Following induction of lesions by striatal injection of 6-OHDA or QA, the number of cells positive for doublecortin (DCX) was strongly increased in the striatum; however, there was no change in the number of DCX-positive cells following 6-OHDA injection into the SN. Environmental enrichment enhanced the increase of DCX-positive cells with migrating morphology in the dorsal striatum. In enriched rats, DCX-positive cells traversed the striatal parenchyma far from the corpus callosum and lateral ventricle. DCX-positive cells co-expressed an immature neuronal marker, polysialylated neural cell adhesion molecule, but were negative for a glial marker. These data suggest that environmental enrichment improves motor performance on beam walking and enhances neuronal migration toward a lesion area in the striatum.

von Wild, K. R. and G. Brunelli (2008). "Restoration of locomotion in posttraumatic paraplegics: the multidisciplinary approach and unexpected plasticity of single neurons--facts and fantasy." Acta Neurochir Suppl **101**: 47-53.

In Europe there are about 300,000 paraplegics and in every country approximately 1000 new cases per year. Treatment requires a multidisciplinary approach with scientific cooperation targeted to exchange personal knowledge and expertise. At present a completely disrupted spinal cord cannot heal for recovery of motor and/or sensory functioning, although some promising treatment modalities in laboratory animal experiments have been reported. No interventional stem cell procedure so far has shown evidence to restore impaired functioning in human paraplegics. However, functional electrical stimulation (FES) via an implanted neuroprosthesis (SUAW concept) and central nervous system-peripheral nervous system (CNS-PNS) connection have successfully been used for alternative compensatory strategies for voluntary locomotion. This report is to analyse the authors' experience from two European projects in paraplegic. Factors will be identified that might have caused the one or other pitfall since so far both surgical reconstructive procedures have not been adopted by rehabilitation physicians and/or restorative (neuro-)surgeons despite the promising functional results we have achieved. Unexpected plasticity of single neurons following CNS-PNS by-pass procedures is discussed. Future interventions, for example the present phase I prospective multiple centre study on the side effects, effectiveness, and reliability of intrathecal treatment of anti-Nogo-A antibodies, are presented and the Chinese stem cell implantation is critically reviewed.

Wackym, P. A., P. Popper, et al. (1990). "In situ hybridization for the study of gene expression in neuro-otologic research." *Otolaryngol Head Neck Surg* **103**(4): 519-26.

In situ hybridization histochemistry technology was developed for future application to neuro-otologic research. This method allowed the detection of cellular mRNA in tissue sections from the temporal bone or brainstem after cRNA/mRNA hybridization. To produce specific cRNA, single-stranded 35S-labeled cRNA (complimentary to target mRNA) is transcribed from commercially available plasmid vectors. These vectors contain promotor sequences for specific synthesis of RNA, and polylinker regions that will accept cloned DNA inserts for virtually any target nucleic acid sequence of interest. The protocol used in this research was optimized for studies that included concomitant immunohistochemical evaluation. The combination of in situ hybridization and immunohistochemistry provides the only method to correlate molecular information (gene expression) with biochemical or molecular markers, such as peptides or proteins (mRNA translation products) on individual cells in the

temporal bone or brainstem. Using these techniques, we examined the distribution of the neuropeptide calcitonin gene-related peptide in rat temporal bone and brainstem sections using calcitonin gene-related peptide (CGRP) antisera and CGRP cRNA probes. We used in situ hybridization histochemistry with a cRNA probe complementary to the 3'-end noncoding sequence of the alpha CGRP mRNA and immunohistochemistry with a polyclonal antibody to the (TYR)CGRP23-37 to study the distribution of CGRP mRNA and CGRP-like immunoreactivity in the central and peripheral facial nerve. Numerous motoneuron cell bodies in the facial nucleus and accessory seventh nucleus and cell bodies in the gustatory geniculate ganglion were found to contain CGRP mRNA and the CGRP peptide.(ABSTRACT TRUNCATED AT 250 WORDS)

Wang, N., M. Zeng, et al. (2002). "Protection of retinal ganglion cells against glaucomatous neuropathy by neurotrophin-producing, genetically modified neural progenitor cells in a rat model." *Chin Med J (Engl)* **115**(9): 1394-400.

OBJECTIVE: To investigate in vivo survival of retinal ganglion cells (RGCs) after partial blockage of optic nerve (ON) axoplasmic flow by sub-retinal space or vitreous cavity injection of brain-derived neural factor (BDNF) produced by genetically modified neural progenitor cells (NPCs). METHODS: Adult Sprague-Dawley (SD) rat RGCs were labeled with granular blue (GB) applied to their main targets in the brain. Seven days later, the left ON was intra-orbitally crushed with a 40 g power forceps to partially block ON axoplasmic flow. Animals were randomized to three groups. The left eye of each rat received a sham injection, NPCs injection or an injection of genetically modified neural progenitors producing BDNF (BDNF-NPCs). Seven, 15 and 30 days after ON crush, retinas were examined under a fluorescence microscope. By calculating and comparing the average RGCs densities and RGC apoptosis density, RGC survival was estimated and the neuro-protective effect of transplanted cells was evaluated. RESULTS: Seven, 15 and 30 days after crush, in the intra-vitreous injection group, mean RGC densities had decreased to 1885 +/- 68, 1562 +/- 20, 1380 +/- 7 and 1837 +/- 46, 1561 +/- 58, 1370 +/- 16, respectively with sham injection or neural progenitors injection. However, RGCs density in the groups treated with intra-vitreous injection of BDNF-NPC was 2101 +/- 15, 1809 +/- 19 and 1625 +/- 34. Similar results were found in groups after sub-retinal injection. Higher densities were observed in groups treated with BDNF-NPCs. There were statistically significant differences among groups through nonparametric tests followed by the Mann-Whitely test. RGC apoptosis density in BDNF-NPC at

each follow-up time was less than in other groups.
CONCLUSIONS: A continuous supply of neurotrophic factors by the injection of genetically modified neural progenitors presents a highly effective approach to counteract optic neuropathy and RGC degeneration after partial ON axoplasmic flow blockage.

Westfall, J. A., J. C. Kinnamon, et al. (1980). "Neuro-epitheliomuscular cell and neuro-neuronal gap junctions in Hydra." *J Neurocytol* **9**(6): 725-32.

Gap junctions have been described ultrastructurally between neurons and epitheliomuscular cells and between neurons and their processes in the hypostome, peduncle and basal disc of Hydra. All gap junctions examined in Hydra exhibit two apposed plasma membranes having a 2-4 nm gap continuous with the extracellular space. The gap junctions are variable in length from 0.1-1.6 micrometers and appear linear or V-shaped in section. Neuronal gap junctions in Hydra occur infrequently as compared to chemical synapses. Electron microscopy of serial sections has demonstrated the presence of adjacent electrical and chemical synapses (neuromuscular junctions) formed by the same neuron. In addition, multiple gap junctions were present between two neurons. This is the first ultrastructural demonstration of electrical synapses in the nervous system of Hydra. Such synapses occur in neurons previously characterized as sensory-motor-interneurons on the basis of their chemical synapses; these neurons appear to represent a type of stem cell characterized by having both electrical and chemical synapses.

Westphal, M. and K. Lamszus (2009). "Other experimental therapies for glioma." *Recent Results Cancer Res* **171**: 155-64.

Experimental therapies for glioma are mostly based on the insights into the cell biology of the tumors studied by modern methods including genomics and metabolomics. In surgery, intraoperative visualization of residual tumor by fluorescence has helped with the radicality of resection. Although temozolamide has become an important agent in the combined radiochemotherapy of newly diagnosed glioblastoma, understanding the underlying mechanisms of action and resistance has led to alterations in dosing schemes, which may be more beneficial than the introduction of new agents. Targeted therapies that have been highly promising in other solid tumors have been rather disappointing in gliomas, not for the lack of promising targets but most likely due to inefficacy of the reagents to reach their target. Direct delivery of reagents with interstitial infusion via convection-enhanced delivery has proven

to be safe and effective, but the potential of that technology has not been exploited because many technicalities are still to be worked out, and better, more selective reagents are needed. Gene therapy has been reactivated with direct adeno-viral application to transfer HSV-Tk into tumor cells by adenoviral vectors, still awaiting final analysis. Oncolytic viruses are also under long-term refinement and await definitive pivotal clinical trials. Immunotherapy is currently focusing on vaccination strategies using either specifically pulsed dendritic cells or immunization with a specific peptide, which is unique to the vIII variant of the epidermal growth factor receptor. An area attracting immense attention for basic research as well as translation into clinical use is the characterization of neural stem cells and their therapeutic potential when appropriately manipulated. In general, there is a wide spectrum of specific neuro-oncological therapy developments, which are not only extrapolated from general oncology but also based on translational research in the field of glioma biology.

Wohl, S. G., C. W. Schmeer, et al. (2009). "Optic nerve lesion increases cell proliferation and nestin expression in the adult mouse eye in vivo." *Exp Neurol* **219**(1): 175-86.

In the naive adult rodent eye cell proliferation does not occur. The aim of this in vivo study was to evaluate if quiescent putative progenitor-like cells within the adult mouse eye can be activated by optic nerve (ON) injury. For a comprehensive analysis, three areas were assessed: the ON, the neural retina, and the ciliary body (CB). Two lesion types were performed, i.e. intraorbital ON transection, or ON crush lesion, in order to analyse possible differences in cellular response after injury. This mouse study shows, for the first time that ON lesion up-regulates cell proliferation and nestin expression in the mouse eye as compared to naive controls. Numbers and distribution patterns of BrdU+ cells obtained were similar after both lesion types, suggesting analogous mechanisms of activation. Interestingly, a differential cell proliferative response was observed in the CB. After ON lesion, the absence of BrdU/TUNEL co-labelled cells confirmed that BrdU+ cells were indeed proliferating. Following ON lesion, in the retina approximately 18% of all BrdU+ cells were positive for the neural stem cell/progenitor cell (NSC/PC) marker nestin. The fraction of BrdU+/nestin+ cells in the CB was approximately 26%. Most of the BrdU+/nestin+ cells found in the neural retina were identified as reactive astrocytes and Muller cells. Since reactive glia cells can participate in adult neuro- and gliogenesis this may indicate a potential for regeneration after ON lesion in vivo.

Wrage, P. C., T. Tran, et al. (2008). "The neuro-glial properties of adipose-derived adult stromal (ADAS) cells are not regulated by Notch 1 and are not derived from neural crest lineage." *PLoS One* **3**(1): e1453.

We investigated whether adipose-derived adult stromal (ADAS) are of neural crest origin and the extent to which Notch 1 regulates their growth and differentiation. Mouse ADAS cells cultured in media formulated for neural stem cells (NSC) displayed limited capacity for self-renewal, clonogenicity, and neurosphere formation compared to NSC from the subventricular zone in the hippocampus. Although ADAS cells expressed Nestin, GFAP, NSE and Tuj1 in vitro, exposure to NSC differentiation supplements did not induce mature neuronal marker expression. In contrast, in mesenchymal stem cell (MSC) media, ADAS cells retained their ability to proliferate and differentiate beyond 20 passages and expressed high levels of Nestin. In neuritizing cocktails, ADAS cells extended processes, downregulated Nestin expression, and displayed depolarization-induced Ca(2+) transients but no spontaneous or evoked neural network activity on Multi-Electrode Arrays. Deletion of Notch 1 in ADAS cell cultures grown in NSC proliferation medium did not significantly alter their proliferative potential in vitro or the differentiation-induced downregulation of Nestin. Co-culture of ADAS cells with fibroblasts that stably expressed the Notch ligand Jagged 1 or overexpression of the Notch intracellular domain (NICD) did not alter ADAS cell growth, morphology, or cellular marker expression. ADAS cells did not display robust expression of neural crest transcription factors or genes (Sox, CRABP2, and TH); and lineage tracing analyses using Wnt1-Cre;Rosa26R-lacZ or -EYFP reporter mice confirmed that fewer than 2% of the ADAS cell population derived from a Wnt1-positive population during development. In summary, although media formulations optimized for MSCs or NSCs enable expansion of mouse ADAS cells in vitro, we find no evidence that these cells are of neural crest origin, that they can undergo robust terminal differentiation into functionally mature neurons, and that Notch 1 is likely to be a key regulator of their cellular and molecular characteristics.

Yachnis, A. T., L. B. Rorke, et al. (1992). "Desmoplastic primitive neuroectodermal tumor with divergent differentiation. Broadening the spectrum of desmoplastic infantile neuroepithelial tumors." *Am J Surg Pathol* **16**(10): 998-1006.

We report an unusual large, multicystic, posterior fossa neuroepithelial neoplasm involving the cerebellum, brain-stem, and quadrigeminal cistern of a 9-month-old girl. The neoplasm consisted of variably

sized, sharply demarcated nests of small cells with a high nuclear-cytoplasmic ratio and moderately basophilic nuclei, embedded in a desmoplastic, immature-appearing, mesenchymal stroma. The nests contained mitoses but none were seen in the stroma. Glial fibrillary acidic protein (GFAP), neurofilament protein, synaptophysin, and cytokeratin (AE-1) were expressed in the nests. Mesenchymal cells were negative for neural markers but positive for vimentin and desmin. The neoplasm was interpreted as a mixed mesenchymal and primitive neuroectodermal tumor (PNET) with histologic features reminiscent of a recently described intraabdominal desmoplastic small cell tumor. The tumor responded poorly to chemotherapy and a second operation was performed 1 year later. The second specimen bore no resemblance to the original and consisted of epithelial-like nests and clusters of neoplastic cells frequently interrupted by sinusoidal vessels. Tumor cells had medium-sized vesicular nuclei with small nucleoli, and a granular cytoplasm. Occasional less cellular islands of neuropil-like tissue contained larger cells having eccentric, vesicular nuclei with prominent nucleoli and abundant pink cytoplasm. Mitoses were not conspicuous. Many cells expressed synaptophysin, neurofilament protein, and GFAP. Neurofilament protein was strongly positive in the larger, neuron-like cells and synaptophysin stained the neuropil-like areas strongly but was less prominent in the neuronal perikarya. Unexpectedly, the neuropil-like areas expressed epithelial membrane antigen, whereas the neuronal cells were negative for chromogranin A. The peculiar histologic picture, combination of phenotypic markers, and remarkable biologic behavior of this unusual tumor defies classification according to existing nomenclature and exemplifies the broad range of phenotypes expressed by primitive neuro-epithelial neoplasms.

Yaghoobi, M. M., S. J. Mowla, et al. (2005). "Nucleostemin, a coordinator of self-renewal, is expressed in rat marrow stromal cells and turns off after induction of neural differentiation." *Neurosci Lett* **390**(2): 81-6.

Bone marrow stromal cells (BMSCs) are pluripotent stem cells with self-renewal property and potential to differentiate into a variety of cell types. Identification of the genes responsible for coordination of these processes and elucidation of the mechanisms underlying these events are of fundamental importance. Nucleostemin, a novel p53 binding protein localized in the nucleoli of ESCs, is not expressed in the differentiated cells of adult tissue, suggesting a role in maintaining stem cell self-renewal. In the present study, we have evaluated the expression profile of nucleostemin in rat BMSCs

before and after the induction of neural differentiation by RT-PCR and immunocytochemistry. The profile of nucleostemin expression is then compared to the key regulators of proliferation/differentiation such as: Oct-4, Nanog, Neuro D, and Cyclin D1. Our data reveal that there is no detectable expression of Oct-4 and Nanog in either non-differentiated or neurally differentiated BMSCs. In contrast, the expression of nucleostemin is relatively high in non-differentiated BMSCs, then sharply diminishes upon induction of differentiation and finally completely vanishes by 6h after initiation of differentiation. The disappearance of nucleostemin expression coincides with the appearance of Neurofilament-M and -H, MAP2, synaptophysin- and neuron-specific enolase as revealed by RT-PCR and/or immunocytochemistry. Expression of Neuro D and Cyclin D1 also diminish as differentiation proceeds but at much slower rates as compared to nucleostemin. In conclusion, our results suggest that nucleostemin, but not Oct-4 or Nanog, is expressed in BMSCs and it possibly regulates self-renewal proliferation in BMSCs.

Yalvac, M. E., A. A. Rizvanov, et al. (2009). "Potential role of dental stem cells in the cellular therapy of cerebral ischemia." *Curr Pharm Des* **15**(33): 3908-16.

Stem cell based therapies for cerebral ischemia (CI) utilize different cell sources including embryonic stem cells (ESCs), neural stem cells (NSCs), umbilical cord blood cells (UCBCs), mesenchymal stem cells (MSCs), and some immortalized cell lines. To date, experimental studies showed that all of these cell sources have been successful to some extent in attenuating the ischemic damage and improving functional recovery after brain injury. Bone marrow derived MSCs seem to be the most widely used and well characterized cell source, which can be also employed for autologous transplantation. Currently, there are two main theories behind the therapeutic effect of stem cell transplantation for treating CIs. The first concept is cell replacement theory in which transplanted stem cells differentiate into progenitor and specialized somatic cells to supersede dying cells. The other hypothesis is based on immuno-modulatory, neuro-protective and neuro-trophic abilities of stem cells which help reducing stroke size and increasing the recovery of behavioral functions. Recent studies focusing on alternative stem cell sources have revealed that dental stem cells (DSCs), including dental pulp stem cells (DPSCs) and dental follicle cells (DFCs) possess properties of MSCs and NSCs. They differentiate into neural lineage cells and some other cell types such as osteocytes, adipocytes, chondrocytes, muscle cells and hepatocytes. This

review is intended to examine stem cell therapy approaches for CI and emphasize potential use of DSCs as an alternative cell source for the treatment of brain ischemia.

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