OPENING PLENARY LECTURE 1

NEURAL STEM CELLS: FROM DEVELOPMENT TO REPAIR

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This lecture will focus upon the field of mammalian neural stem cells and precursors from two perspectives. The first part of the lecture will focus upon our work characterizing neural crest-like adult precursor cells from skin (Skin-derived Precursors or SKPs) both with regard to their basic biology and their potential therapeutic use for treatment of the damaged or degenerating nervous system. Keywords: stem cells, development, cortex, neural crest

OPENING PLENARY LECTURE 2

TRANSCRIPTIONAL REGULATORS THAT CONTROL SCHWANN CELL DEVELOPMENT, DEDIFFERENTIATION AND NERVE REPAIR

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The generation of myelinating and non-myelinating Schwann cells from the neural crest involves two intermediate cell types, Schwann cell precursors and immature Schwann cells. Schwann cell precursors differ from neural crest cells in molecular expression and their relationship with axons, while the switch from Schwann cell precursor to immature Schwann cell involves a coordinate change in molecular expression and response of the cells to survival signals and mitogens. This is accompanied by architectural reorganization that involves the appearance of blood vessels and connective tissue in the nerve and formation of an immature perineurium. Later in development Schwann cell myelination is triggered by signals from axons that set in train a sequence of phenotypic changes in immature Schwann cells, including upregulation of the key pro-myelin transcription factor Krox-20.

Recently we have used mice with Schwann cell selective knockout of the transcriptional regulators c-Jun, Notch and related genes to investigate the role of these signals in nerve development, in demyelination after injury and in nerve repair. We find that Notch signalling times the generation of Schwann cells from Schwann cell precursors, drives Schwann cell proliferation and negatively regulates the onset and maintenance of myelination (Woodhoo et al., Nature Neuroscience, in press, 2009). c-Jun is a potential inhibitor of myelination and shows a cross-inhibitory relationship with Krox-20. Crucially, it plays an essential role in the appropriate generation of denervated Schwann cells in injured nerves (Parkinson et al., J Cell Biol 181: 625-637, 2008) and plays a vital role in neuronal survival and nerve repair after injury. Our studies on c-Jun and Notch establish the existence of negative transcriptional regulation of myelin differentiation that may be particularly important in injured and regenerating nerves (Jessen and Mirsksy, Glia 56: 1592-1598, 2008).

PLENARY LECTURE 3

IMPACT OF SYSTEMIC INFLAMMATION ON THE BRAIN IN HEALTH AND DISEASE

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We have all at one time or another felt ill and experienced “sickness behaviour” as a consequence of a systemic infection. We know that inflammatory mediators generated at the site of a systemic infection communicate with the brain via both neural and humoral routes. Circulating cytokines or other inflammatory mediators communicate across the intact blood-brain barrier to resident macrophages within the brain, the perivascular macrophages and microglia, and these cells in turn communicate with neurons. This is part of our normal defence against injury and infection, a homeostatic mechanism. We suggested that these communication pathways from systemic inflammation to the brain would have very different consequences if the individual had an ongoing degenerative disease of the brain. Neurodegeneration is associated with an increase in the number of microglia that also adopt an activated morphology with increased expression of a number of surface or cytoplasmic molecules. We proposed that signalling from the peripheral inflammation to the diseased brain would lead to a switch in the microglia phenotype from a benign to aggressive phenotype with increased cytokine synthesis, exacerbation of acute symptoms and enhanced rate of progression of disease. Data will be presented from animal models and clinical studies demonstrating that systemic infections are indeed associated with accelerated disease progression. The resident microglia of the brain are long-lived cells that retain an ‘innate immune memory’ of tissue damage within the brain and become primed. Systemic infection or other environmental challenges may act on these primed cells in the ageing or diseased brain and in turn impact on behaviour and disease onset or progression.

PLENARY LECTURE 4

AXON GUIDANCE MOLECULES: FROM NEURON TO GLIA

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During development, growing axons are guided to their intermediate and final targets by a variety of secreted and membrane bound factors that can either enhance or inhibit their growth. Genetic and biochemical studies have led to the characterization of multiple families of evolutionarily conserved axon guidance molecules, such as netrins, semaphorins and slits. I will first discuss recent data obtained in our laboratory showing how the extensive knowledge of the molecular mechanisms controlling axon guidance can be used to perform targeted genetic manipulations of specific axonal tracts. This enables us to re-wire the brain and study the function of selected neuronal networks. The phenotypic analysis of mice deficient for axon guidance molecules or their receptors reveals that they control not only axon pathfinding but also neuronal migration and synaptogenesis. They have additional functions in non-neuronal cells, such as in blood vessels and in the immune system. Moreover, mounting evidence suggests that axon guidance molecules influence glial cells or their progenitors. For instance, netrin-1 and some secreted semaphorins were shown to modulate the migration of oligodendrocyte precursors in the spinal cord and optic nerve. We found that myelinating oligodendrocytes also express several transmembrane semaphorins such as SemA6A and Sema4D/CD100. Interestingly, myelination is delayed in mice lacking these proteins, and oligodendrocyte differentiation is halted in culture. Our data suggest both cell-autonomous and non-cell autonomous role for Sema6A in oligodendrocyte development. Furthermore, we are also investigating the ability of the SlitS and their receptors Robo to control the migration of adult neural stem cell derivatives and their possible use as a tool to enhance the colonization of demyelinating lesions by oligodendrocyte precursors.

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PLENARY LECTURE 5

IN VIVO IMAGING AND GENETIC ANALYSIS OF GLIAL CELL DEVELOPMENT

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During development, central and peripheral myelinating glial cells are produced by multipotent precursors, migrate long distances from their origins to their targets, divide to expand their numbers and, finally, recognize and wrap axons. These dynamic and diverse behaviors imply multiple layers of regulation that must depend on interactions of glial cells with their environments. Investigations of glial cell development have been mostly limited to analysis of fixed tissue and use of cell culture models, which cannot adequately model cell behaviors in vivo. To overcome these limitations, we created transgenic zebrafish that mark
PLENARY LECTURE 6
REGULATION OF BLOOD VESSEL PATTERNING AND GUIDANCE
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The formation of the vascular system during vertebrate embryonic development is crucial to ensure oxygen and nutrient delivery to all tissues in the organism. Blood vessels are formed by differentiation of primitive mesodermal cells into endothelial cells, which coalesce into primitive tubes that proliferate and migrate to colonize tissues. With the onset of the heart beat and blood flow, primitive vessels are rapidly remodelled into branched networks with a characteristic and reproducible anatomy. The major axial vessels such as the aorta and cardinal veins are common to developing mouse, chick and zebrafish embryos. Vessel branches penetrating different organs form at designated sites, and different organs each develop their specific, stereotyped vascular patterns. Formation of this stereotyped architecture ensures efficient oxygen and nutrient delivery and thus function of the vascular system. Vascular Endothelial Growth Factor (VEGF) is a key regulator of vascular development. VEGF is a secreted polypeptide that signals through high affinity receptors VEGFR1 and 2 expressed on the surface of endothelial cells. VEGF is expressed by hypoxic cells and attracts vessels towards hypoxic tissue areas. VEGF down-regulation upon appropriate oxygen supply targets cells for further endothelial growth and thereby ensures appropriate vessel coverage. Thus, differential sequestration of VEGF isoforms in the matrix is crucial for the balance between capillary branching and enlargement of vessel size. In addition to growth factor gradients, hemodynamic forces are important in the regulation of pattern formation. Thus, appropriate hemodynamics and growth factor gradients cooperate to shape the highly stereotyped vessel anatomy of vertebrate embryos. The stereotyped anatomy of vessels in the human body had already been observed several hundred years ago by some anatomists, such as Andreas Vesalius, who noted that blood vessels are often aligned with nerves and display similar branching patterns in peripheral tissues. The molecular mechanisms regulating common wiring of nerves and blood vessels have attracted considerable interest over the past few years. Developing axons navigate through the embryo by responding to a number of different signals in their immediate environment. Molecules such as Semaphorins, Slits and Netrins and their specific receptors provide key ligand–receptor interactions for this process during both neuronal and vascular development.

PLENARY LECTURE 7
GLIAL CELLS AS REGULATORS OF CNS PLASTICITY AND REGENERATION
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Growth of nerve fibres in the adult mammalian CNS is restricted to very short distances and spatial domains, thereby limiting the capacity of the CNS for plastic rearrangement of fibre connections and repair of large lesions. Both types of CNS glia contribute in important ways to neuronal growth restriction: astrocytes by synthesising growth inhibitory components, e.g. chondroitin sulfate proteoglycans, especially in regions of glial scars, and oligodendrocytes by the expression of a number of membrane proteina with specific growth inhibitory properties. Nogo-A, several ephrins, the semaphorins Sema4D and 6A, as well as the myelin proteins MAG and MOGp, have all been shown to induce growth cone collapse and arrest of neurite growth in vitro. Unequivocal in vivo evidence for a growth restricting function in the adult injured CNS exists mainly for Nogo-A so far. In intact animals, injection of function blocking antibodies against Nogo-A into the cerebellum or spinal cord led to transitory sprouting of collaterals and axonal arbors. Nogo-A KO mice exhibit higher levels of growth-associated and cytoskeletal proteins and their mRNAs in the intact spinal cord. DRG neurons dissected from these mice elaborate larger and more dynamic growth cones than wild type neurons. In a classical plasticity paradigm, monocular deprivation, visual cortex plasticity could be induced long after the end of the critical period in Nogo receptor (NgR) KO mice and in Nogo-A/B KO mice (McGeer et al., 2005). These results suggest that with the maturation of the CNS and the simultaneous oligodendrocyte differentiation and myelin formation, neurite growth inhibitors, in particular Nogo-A are expressed and function to limit growth and thereby stabilize the highly complex CNS during.

CROSS-TALK BETWEEN PARENCHYMA AND GLIAL CELLS:
PHYSIOLOGICAL AND PATHOLOGICAL RELEVANCE
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Glial cells can release signal molecules that mediate intercellular communication. In particular, ATP release from astrocytes is required for Ca2+ wave propagation among astrocytes and for feedback modulation of synaptic functions. We found that lysosomes in astrocytes contain abundant ATP and their partial exocytosis resulted in a low-level ATP release, whereas full exocytosis led to the release of a larger amount of ATP, together with lysosomal enzymes. Selective intracellular lysis of lysosomes abolished both ATP release and Ca2+ wave propagation among astrocytes. Furthermore, we found an impaired synaptic plasticity and decreased expression of excitatory synaptic activity in hippocampal CA1 neurons of mice with Niemann-Pick Type C1 disease (NPC1), a lysosome storage disease characterized by progressive neurodegeneration. Our results indicate that neural cells in NPC1 mutant mice may be deficient in lysosomal exocytosis of ATP, which may account for neurological symptoms in NPC1 disease, such as seizures, neurodegeneration, cognitive decline, and dementia. Together, these findings indicate that regulated lysosomal release from astrocytes contribute to intercellular signaling under physiological as well as pathological conditions.

CLOSING PLENARY LECTURE 9
CLOSING TALK BETWEEN PARENCHYMA AND GLIAL CELLS:
HIGHLIGHTS IN BRAIN TUMORS
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Glial-neuronal cells interactions are fundamental to the harmonious development of the brain. We mainly focus on those interactions mediated by extracellular matrix proteins and soluble factors. Further, we are looking to tunneling nanotubes (TNTs) which emerge from the cells to facilitate their contacts and exchange of elements. Since, these interactions mediate cell development, migration and differentiation we are currently investigating the role of the cerebral parenchyma in these events. We have analyzed how interactions between glial tumor and the cerebral parenchyma influence on expansion, migration and proliferation of tumor cells. By using natural drugs and cellular molecules such as the co-chaperone stress-inducible protein 1 (STI1), we have tried to manipulate migration and proliferation of glial cells tumor in vitro and in vivo. Our data might not only contribute to a better understanding of the cerebral cancer scenario but eventually contribute to design therapeutic approaches to this disease.