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Finding degrees of separation: Experimental approaches for astroglial and oligodendroglial cell isolation and genetic targeting

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Abstract

The study of CNS glial cell function requires experimental methods to detect, purify, and manipulate each cell population with fidelity and specificity. With the identification and cloning of cell- and stage-specific markers, glial cell analysis techniques have grown beyond physical methods of tissue dissociation and cell culture, and become highly specific with immunoselection of cell cultures *in vitro* and genetic targeting *in vivo*. The unique plasticity of glial cells offers the potential for cell replacement therapies in neurological disease that utilize neural cells derived from transplanted neural stem and progenitor cells. In this mini-review, we outline general physical and genetic approaches for macroglial cell generation. We summarize cell culture methods to obtain astrocytes and oligodendrocytes and their precursors, from developing and adult tissue, as well as approaches to obtain human neural progenitor cells through the establishment of stem cells. We discuss popular targeting rodent strains designed for cell-specific detection, selection and manipulation of neuroglial cell progenitors and their committed progeny. Based on shared markers between astrocytes and stem cells, we discuss genetically modified mouse strains with overlapping expression, and highlight SOX-expressing strains available for targeting of stem and progenitor cell populations. We also include recently established mouse strains for detection, and tag-assisted RNA and miRNA analysis. This discussion aims to provide a brief overview of the rapidly expanding collection of experimental approaches and genetic resources for the isolation and targeting of macroglial cells, their sources, progeny and gene products to facilitate our understanding of their properties and potential application in pathology.

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1. INTRODUCTION

Since their initial discovery, the perception of glia as being mere supportive “glue” for neurons has been transformed into an unexpectedly complex role as valuable partners in cell-cell communication and homeostasis. Diverse glial functions in neuronal conduction, synaptic development and repair have now overshadowed the previous concepts of glial cells as passive structural and, at best, trophic support for neurons. Aside from radial glia, ependymal cells, and cells of the neurovasculature, at least three major subtypes of glial cells: astrocytes, oligodendrocytes and microglia are present in the central nervous system (CNS). A fourth type, NG2 (nerve/glial antigen 2) cells or polydendrocytes, although widely recognized as oligodendrocyte progenitor cells (OPCs) in white matter (WM) structures, show expression patterns and electrical properties that defy conventional glial cell classification. Astrocytes are important regulators of neurotransmitter function, metabolic support, neuronal migration and development, synaptic processing, cell plasticity, excitotoxicity, immune function and blood-brain barrier integrity. Oligodendrocytes are myelin-producing cells of the CNS, and whose layers of compacted cell membranes ensheath axons with lipid-rich insulation that is critical for rapid salutatory conduction by axon fibers. In addition to myelination, oligodendroglia have been found to provide axons with direct metabolic support via lactate, a process that prevents axon degeneration and death (Lee et al., 2012). Both astrocytes and oligodendrocytes are described to develop from common progenitor populations. While many brain tumors consist predominantly of precursors of astrocytic nature, each of the individual glial cell types is now recognized as a viable therapeutic candidate in neurological disease, in addition to neurons. The growing importance of glial cells has led to the development of a variety of techniques for their purification and analysis. An important aspect of studying cellular function in the CNS lies in the ability to target individual cell populations, based on identity, developmental stage, and cellular lineage or fate. For their analysis *in vitro* and *in vivo*, specific glial populations may be collected by tissue isolation and culture methods, as well as through the use of genetic animal models. In separate sections of this paper, we will: A) review culture techniques for the production of astrocytes and oligodendrocyte progenitor cells primarily from rodent brain, and stem cell-based approaches to generate these cells, and B) describe driver mouse strains for glial-specific cell labeling and gene manipulation. In the second section, we will also highlight new reporter and effector mouse strains for driver-assisted gene ablation, cell identification and *in vivo* molecular capture that are now available for gene expression analysis.

2. Cell purification and primary glial cell culture

Glial cells may be acutely isolated from dissociated brain and spinal cord tissue either as a mixed population or with further purification via immunolabeling or reporter fluorescence in recombinant mouse strains. The first step of tissue dissociation consists of subjecting dissected tissue pieces to enzymatic digestion with papain and DNase I, followed by

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mechanical trituration using a series of needles of decreasing gauge size (e.g. 19, 21 then 23 G) (Belachew et al., 2002) and subsequent removal of aggregates by passing the suspension through a cell strainer (Belachew et al., 2002). For mature CNS white matter tissue with high myelin content, an additional purification step prior to cell selection is often beneficial to cell yield (Jiho Sohn, Univ California, Davis, personal communication) (Sohn et al., 2006). This involves layering the dissociated cell suspension onto a pre-formed density gradient of Percoll™, followed by high speed centrifugation, to separate neural cells from lipid-rich myelin, debris (Avellana-Adalid et al., 1996; Lubetzki et al., 1991) and blood cells. These purified cells, once cleared of Percoll™, may be maintained in culture (Zhang et al., 2004). Acutely isolated cells may also be selected by immunolabeling before collection by fluorescence-activated cell sorting (FACS) (Nielsen et al., 2006) (Figure 1). Alternatively, cells from fluorescent reporter mouse strains may be directly collected by single-channel FACS (Belachew et al., 2002) or doubly selected by a combination of immunolabeling and dual-channel FACS collection (Belachew et al., 2003).

Despite the limitation that primary cultured cells in isolation are not morphological and functional duplicates of their *in vivo* counterparts, cell cultures still hold an important and special place in current methodologies. Indeed it was in cultures developed by McCarthy and de Vellis (McCarthy and de Vellis, 1980) that astrocytes and oligodendrocyte progenitor cells (OPCs) were prepared from the neonatal rat and characterized in exhaustive detail, forming the foundation of current knowledge of glial cell characteristics, physiology and development. As summarized in Figure 1 and Table 1, astrocytes and oligodendrocytes are frequently obtained by the establishment of mixed glial cultures from dissociated CNS tissue of neonatal rodents, isolation of their common progenitor by shaking (Levine, 1989; Saneto and de Vellis, 1985) and positive immune-selection –‘panning’- with monoclonal antibody A2B5 against the surface antigen (Stallcup and Beasley, 1987). With the advantages of sensitivity, ease and cost (relative to whole animal models), applications such as high throughput pharmacological analysis (James et al., 2011) rely on cultures for reasons of volume and scalability. Importantly, the establishment of co-cultures between neurons and astrocytes or oligodendrocytes (Jones et al., 2012; Kunze et al., 2013; Pang et al., 2012; Yang et al., 2009), and between distinct glial cell types (Afshari and Fawcett, 2012; John, 2012; Schmitz et al., 2011), provides useful reconstructive evidence to corroborate tissue explant and whole animal observations.

2.1 Astrocytes

Astrocytes are responsible for the homeostasis of extracellular glutamate, therefore the expression of the glutamate transporters GLAST (EAAT1), GLT1 (EAAT2), and glutamine synthetase (GS) are unique identifying features (Bak et al., 2006). In addition, astrocyte differentiation is characterized by induction of intermediate filament proteins glial fibrillary acidic protein (GFAP) and vimentin (Desclaux et al., 2009; Menet et al., 2001), along with S100B and aldehyde dehydrogenase family 1 member L1 (ALDH1L1) (Brozzi et al., 2009; Yang et al., 2011) (Figure 1). In essence, the glial culture protocol is based on the inability of neurons to survive in cultures derived from newborn rats. The basic protocol consists of preparing dissociated cells from cerebral hemispheres, plating in flasks to obtain mixed glia in serum-containing medium, followed by mechanical separation of astrocytes,

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oligodendrocyte precursors and microglia, using physical properties of these cells (Figure 1). Purified astrocytes in serum-containing or defined media (Morrison and de Vellis, 1981; Morrison et al., 1985) are obtained through constant shaking to remove contaminating microglia and OPCs over the course of the 10-day procedure (Cole and de Vellis, 1997) (Table 1). These isolated neonatal cells lack processes and are highly plastic and proliferative, with a capacity to withstand multiple passages. Although widely used in many contexts including aging, these neonatal cells are known to possess distinct gene expression properties, and are considered more ‘activated’ than normal adult, mature astrocytes (Nakagawa and Schwartz, 2004), including gene changes in response to beta-amyloid exposure (Kurronen et al., 2012). Other differences, such as the differential expression of metabotropic glutamate receptors, have revealed underlying developmental changes in neuroglial communication (Sun et al., 2013). Recently, adult rat astrocytes obtained from postnatal day 90 rats, maintained over 5 weeks in serum-containing media, showed many characteristics of normal adult astrocytes (Souza et al., 2013), i.e. expression of GFAP, GS, ALDH1L1, and S100B, as well as the ability to metabolize glutamate and glucose. Based on the duration of the incubation, it is likely these astrocytes were derived from adult progenitor cells, and their susceptibility to oxidative stress (Lin et al., 2007; Pertusa et al., 2007) suggested an effect of aging in these cultures (Souza et al., 2013). However, clarification of adult characteristics await further direct comparison of these cells with neonatal astrocytes.

In addition to physical methods of cell enrichment, the versatile immunopanning procedure is widely used to select for specific glial populations. This technique uses antibody-based capture of cells via the cell- or stage-specific expression of cell surface antigens (Barres, 1993) (Figure 1, Table 1). Neonatal astrocytes and their precursors are purified using negative selection by passing cell suspensions from P1 rat optic nerves over sequential ‘panning’ dishes coated with antibodies – e.g. MRC-OX7 anti-Thy1.1 to deplete microglia and meningeal cells, followed by either an A2B5 or O4 dish to deplete OPCs (Mi and Barres, 1999). To meet the demand for directly isolated mature astrocytes, an immunopanning protocol was recently developed for tissue from rodents at the postnatal age of day 1 through 18 (P1-P18) (Foo et al., 2011), which until now had not been successful because of the lack of astrocyte-specific surface antigens for positive selection. These cells were obtained through a succession of panning plates for the sequential removal of endothelial cells and microglia, followed by microglia/macrophages (CD45), and O4+ OPCs before positively selecting for integrin beta 5, based on gene profiling data (Cahoy et al., 2008). This acute purification procedure yielded astrocytes which were dependent on trophic factors for survival, such as heparin-binding epidermal growth factor, and may thus be maintained in defined media without serum, as serum was found to irreversibly alter gene expression (Foo et al., 2011). Comparison with astrocytes obtained by the McCarthy and de Vellis protocol showed that the acutely isolated astrocytes showed more mature characteristics, namely slower cell division, and vascular dependence, as well as greater similarity in gene expression profile with cortical astrocytes (Foo et al., 2011). These would now be useful for studies of glial reactivity in degeneration and brain injury.

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2.2 Oligodendrocyte progenitor cells (OPCs)

Oligodendrocytes are the myelin-producing cells of the CNS which not only facilitate the conduction of action potentials but also support axonal integrity and metabolic activity (Funfschilling et al., 2012; Lee et al., 2012; Nave, 2010). Oligodendrocytes develop from oligodendrocyte progenitor cells (OPCs) which express cell surface antigens such as A2B5, platelet derived growth factor receptor alpha (PDGFRα), GD3 and NG2 (Figure 1). In addition, the lineage can be identified by the expression of transcription factors Sox10, Olig1 and Olig2. These transcription factors are not restricted to progenitors, and are also expressed in mature myelinating oligodendrocytes. Myelin proteins are widely used indicators of OPC maturation; these generally do not colocalize with OPC markers, and include: myelin basic protein (MBP), myelin-associated glycoprotein (MAG), myelin oligodendrocyte glycoprotein (MOG), myelin oligodendrocyte basic protein (MOBP), Connexin 47, proteolipid protein (PLP) and 2′,3′-cyclic nucleotide 3′ phosphodiesterase (CNP) (de Castro and Bribian, 2005).

OPC cultures from rat cortices or optic nerve had been the mainstay of *in vitro* methods to produce oligodendrocytes, because of the high yield of cells needed for histological and biochemical studies. Methods for the isolation of rat OPCs include the ‘shake-off’ method of McCarthy and de Vellis (McCarthy and de Vellis, 1980) (Table 1), exploiting differential adherence properties (Szuchet and Yim, 1984), immunopanning of dissociated neonatal rat cortices or adult optic nerve (Dugas and Emery, 2013; Gard et al., 1993; Gard et al., 1995; Mayer-Proschel, 2001; Shi et al., 1998), FACS with surface antigens (Behar et al., 1988), and density gradient centrifugation (e.g. Percoll™) (Colello and Sato-Bigbee, 2001; Vitry et al., 2001) (Figure 1), or combinations thereof. However, the demand for OPC cultures from mice has grown dramatically, largely due to the popularity of mouse genetic models and availability of sensitive assay technologies. Nevertheless, there are still major obstacles to overcome in obtaining mouse OPC cultures in adequate quantities using established rat techniques, because of innate species-specific differences in: antigen expression (Fanarraga et al., 1995), adhesion and cell proliferation/differentiation properties (Chen et al., 2007).

Typically, the shake-off method in combination with selective adhesion for astrocyte and microglial cell removal (Table 1) allows the economical enrichment of rat OPCs expressing A2B5 or NG2 antigens (Chen et al., 2007). The cells may be amplified and passaged post-shake with the addition of mitogens PDGF-AA and bFGF. The choice of medium affects cell survival, particularly under a mitogen-free differentiation paradigm, i.e. a N1-supplemented DMEM medium showed more cell death than B27/Neurobasal medium (Yang et al., 2005). This combination of B27 with Neurobasal medium also supported co-cultures of OPCs with hippocampal neurons (Yang et al., 2005). An alternative to the shake-off method involves enriching OPCs from dissociated E17 rat embryonic cortices by two sequential passages with trypsin, followed by culture in media containing PDGF-AA (Itoh, 2002). In addition to amplification of purified OPCs, the combination of PDGF and bFGF (Figure 1) may also be used to induce the formation of OPCs from neurosphere cultures from embryonic spinal cord (Fu et al., 2007). Yet another alternative for rat OPCs consists of pre-amplification in growth medium containing B104 neuroblastoma cell-conditioned medium which serves as an economical source of mitogens to amplify OPCs, followed by an

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isolation medium of DMEM/F12 containing EDTA, DNase I and insulin (Niu et al., 2012) to detach OPCs from the underlying bed of astrocytes with gentle aspiration.

Given the known differences in cell properties between rat and mouse OPCs, novel solutions for mouse OPC isolation have been developed to improve the efficiency and purity of isolation (Table 1). Approaches for mouse OPCs include: generation of oligospheres (Vitry et al., 1999) from neurospheres (Chen et al., 2007); serial passaging in mitogen-containing growth medium and selection and expansion of OP cell colonies from single cells (Lin et al., 2006), or enrichment through immuno-selection of NG2 cells by FACS (Horiuchi et al., 2010) or O4 antigen-based magnetic activated cell sorting (Dincman et al., 2012). An immunopanning procedure for mouse OPCs has also been developed which uses positive selection by PDGFRα instead of A2B5 (Emery and Dugas, 2013). These procedures primarily used embryonic or neonatal mouse cortices. Interestingly, a recent revival of the shake-off/selective adhesion method was described for mouse OPCs not only from neonatal but also adult cerebral cortex (Medina-Rodriguez et al., 2013) as well as human adult biopsies. This protocol uses papain to aid the removal of meninges and choroid plexus, and to facilitate mechanical dissociation. The papain concentration, incubation time and cell plating density are increased with age of the animal (up to P180). Unlike the McCarthy and deVellis protocol, PDGF-AA is included in the growth medium for plating of mixed glia of postnatal and adult mice, and the time in culture before shake-off varies from a minimum of 15 days for P15 cortices to 25 days for P180 (Medina-Rodriguez et al., 2013) (Table 1). When compared directly, the yield of cells with this method was reportedly an order of magnitude higher than with FACS (Medina-Rodriguez et al., 2013). Some minor modifications for human biopsy tissue, which require at least 30 days in culture, include reducing the size of the plating flask, increasing starting tissue mass and adjusting digestion conditions (Medina-Rodriguez et al., 2013). Continued improvements in the yield of OPCs are expected to enable investigators to conduct a wider range of cellular, molecular and biochemical assays with greater resolution.

2.3 Macroglial cells from pluripotent stem cells

The field of regenerative medicine has seen dramatic expansion and great promise with the discovery and generation of pluripotent stem cells. These not only provide a renewable source of genomically stable cells endowed with fate plasticity for transplantation therapies, but can also be used to help instruct investigators about the complexities of organ formation and cortical patterning (van den Ameele et al., 2014). Application of this technology to cell-based neurological repair strategies requires the conversion to functional cells over several stages, i.e. pluripotent to neural stem cell resembling neurogenic radial glia (Conti et al., 2005; Pollard et al., 2006), to neural precursor and then conversion to committed glia. Multi- or pluripotent stem cells include, and are not limited to, embryonic stem cells (ES), epiblast stem cells, and induced pluripotent stem cells (iPS) which do not have an embryonic origin (Figure 1). In addition to embryonic stem cells, neural stem cells can also be derived from fetal and adult mouse CNS (Conti et al., 2005; Pollard et al., 2006), or established from human fetal neural tissue (Sun et al., 2008). Conversely, neural stem cells (NSCs) can also serve as a source of pluripotent stem cells by reprogramming with factors (Kim et al., 2008).

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Pluripotent cells exist during different stages of embryonic development, offering a range of pluripotent states. Embryonic stem cells have been proposed as sources of neural precursor cells (NPCs) (Table 2) for transplantation and oligodendrocyte repair in demyelinating disease (Brustle et al., 1999) and as gene therapy vector in brain tumors (Benveniste et al., 2005; Uzzaman et al., 2005). Epiblast stem cells have also been used to generate NSCs (Jang et al., 2014). Several differences are notable between mouse EpiSCs and ES, in cell cycle characteristics, gene expression and signaling mechanisms for self-renewal and differentiation (Brons et al., 2007; Tesar et al., 2007). Both represent distinct pluripotent states (Jang et al., 2014), and these differences may underlie their differential abilities in chimera formation in the post-implantation embryo (Huang et al., 2012). Mouse epiblast stem cells have been isolated from early postimplantation rodent blastocysts (Brons et al., 2007; Tesar et al., 2007). However, recently, mouse epiblast stem cells isolated from preimplantation mouse embryos have been directed to produce NSCs under PDGF, FGF and Sonic Hedgehog (Najm et al., 2011b), which subsequently transition to expandable OPCs for the purposes of drug screening to promote myelinating oligodendrocytes (Najm et al., 2011b).

iPS cells are a major breakthrough in innovative clinical approaches (Inoue et al., 2014). These are generated by reprogramming differentiated somatic cells, such as fibroblasts, with a set of four transcription factors: Octamer-binding transcription factor 4 (Oct4), SRY-Box gene 2 (Sox2), Kruppel-like factor 4 (Klf4), and c-Myc (Takahashi et al., 2007b; Takahashi and Yamanaka, 2006). To minimize the risk of tumorigenicity from c-Myc reactivation, it was later found that c-Myc could be omitted (Nakagawa et al., 2008) or substituted with a non-transforming Myc family member (Nakagawa et al., 2010). As with epiblasts, iPS cells are not identical to ES cells, differing not only in origin, but also gene expression profile (Chin et al., 2009), and efficiency of oligodendrocyte generation (Tokumoto et al., 2010). Epiblast stem cells have also been derived from fibroblasts through reprogramming (Han et al., 2011). In addition to their potential for therapeutic cell replacement applications, iPS cell-derived astrocytes and neurons generated from patient somatic cells have been shown to offer novel approaches to studying the pathophysiology of neurological diseases such as Huntington’s and multiple sclerosis (Juopperi et al., 2012; Song et al., 2012).

Both mouse (Czepiel et al., 2011) and human (Ogawa et al., 2011b; Pouya et al., 2011; Wang et al., 2013) iPS cells have been successfully differentiated into precursors of oligodendrocytes (Table 2). The iPS-derived OPCs were transplanted into different demyelination models: a rat model of focal demyelination in the optic chiasm, (Pouya et al., 2011), as well as a cuprizone-induced paradigm (Czepiel et al., 2011). These were found to differentiate into MBP-expressing oligodendrocytes *in vivo* (Czepiel et al., 2011; Pouya et al., 2011). A recent study showed that iPS cells are not the only source of induced OPCs. The reprogramming of mouse embryonic fibroblasts with oligodendrocyte-specific genes, including Olig1, Olig2, Nkx2.2, Sox10, Myrf and Myt1, has resulted in the generation of induced OPCs which were capable of myelination following transplantation into slice cultures (Najm et al., 2013) (Figure 1) (Table 2). Because of the nature of multipotency, improvements in the directed differentiation of iPS-derived precursors are constantly being sought. It was found that the additional step of OPC purification or enrichment, by

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immunopanning from these iPS-derived cultures improved the efficiency of differentiation in vitro (Ogawa et al., 2011a), although transplant experiments using sorted and unsorted iPS-derived OPCs showed that terminal differentiation appeared more important than purity of cell stage for the prevention of teratoma formation *in vivo* (Czepiel et al., 2011). Despite losing the majority of the differentiated, transplanted OPCs to apoptosis, those that survived became mature and integrated functionally with axons (Czepiel et al., 2011). In contrast, transplantation of GFAP+ astrocytes for spinal cord injury has produced mixed results between glial-restricted precursors or iPS-derived cells (Hayashi et al., 2011), suggesting that for this type of injury, replacement of a single differentiated cell type may be less effective than NSCs or acutely isolated NPCs (Karimi-Abdolrezaee et al., 2010).

Recently, the reprogramming of astrocytes using hGFAP-driven Sox2 expression generated ectopic neuroblasts in the adult mouse striatum *in vivo*, which eventually produced mature neurons (Niu et al., 2013). Although glia have not been shown to be generated this way, it is possible that the cellular outcome of Sox2 overexpression is region-specific.

3. Genetic models for glial-specific targeting

The analysis and manipulation of glial cell function *in vivo* or *ex vivo* requires methods to detect and label the cells by lineage with consistency and fidelity. Many glial marker genes whose products have been identified previously as specific for a particular cell type or developmental stage have now become widely used as targeting tools, both as transgenic or knock-in mouse strains. These are listed in http://www.networkglia.eu/en/animal_models as well as under the GenSat project http://www.gensat.org/MMRC_report.jsp. For a comprehensive treatise on the background of glial markers and genetic targeting strains for macroglial, microglial and ependymal cells, the reader is directed to this recent review article (Pfrieger and Slezak, 2012). The following section instead aims to summarize, with the aid of Tables 3 and 4, the range of cell types found to be labeled and targeted by existing and new transgenic and knock-in mouse strains. New mouse lines developed for Cre-dependent or glial-specific molecular tagging are also described.

3.1 Astrocytes / Stem cells

In addition to the inherent heterogeneity of astrocytes, which can be classified into many subtypes, astrocytes express many of the same markers as NSCs, likely due to a shared astroglial lineage (Ihrie and Alvarez-Buylla, 2008). Therefore, the ability to selectively target the entire astrocyte population, or distinct subpopulations without also labeling or affecting neural stem and progenitor cells, remains an important and largely unresolved issue in the field.

For the experimental targeting of astroglial cells, an extensive collection of genetic mouse lines has been generated that drive transgene expression under a variety of astrocytic promoter elements, leading to strain-specific expression dynamics in populations of astrocytes and neural stem/progenitors, with varying levels of overlap between these and other cell types (Table 3).

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In spite of this, we make a cautionary note that specific expression patterns for all mouse lines outlined here, continue to lack thorough investigation and await more detailed analysis during development, adulthood, and aging. Transgene expression dynamics for every strain should be experimentally determined or validated by the researcher, whenever possible.

Among the available driver lines, the canonical and most-widely used astrocytic gene is GFAP. In particular, the 2.2 kb human GFAP promoter (gfa2), has been used to visualize and manipulate astrocytes with higher specificity and broader CNS expression compared to other GFAP promoter elements (Lee et al., 2008; Lee et al., 2006). Interestingly, using selective deletion of GFAP promoter regions, it has been determined that gfa2 expresses throughout the brain while expression from a 488 bp gfa28 promoter fragment is limited, thereby underlying regional astrocyte heterogeneity (Lee et al., 2006). Additionally, gfa28 also expresses in neurons as well as astrocytes, while gfa2 does not, indicating that a specific base-pair sequence is required for silencing neuronal expression, and suggests that expression in other cell types such as NSCs and neural progenitors is controlled by different GFAP promoter elements that may be silenced to narrow or expand expression in astrocytes and stem/progenitor cells (Lee et al., 2008).

In addition to being used to understand the behavior of astroglia *per se*, GFAP reporter transgenic mice have been developed for bioluminescence studies (Badr and Tannaus, 2011). Whereas luciferase activities have long been in use to define and quantify molecular interactions at promoter and enhancer regions *in vitro*, the imaging of luciferase activity in situ in transgenic mice offers a quantifiable measurement of gliosis *in vivo*, and can detect graded changes in astrocytic reactivity, for example after physiological stress, injury or neoplastic conditions (Burda and Sofroniew, 2014; Rivera-Zengotita and Yachnis, 2012). The first GFAP-luciferase transgenic mouse with about 12 kb of the mouse GFAP promoter has been used to monitor gliosis after kainate injury (Zhu et al., 2004), traumatic brain injury (Luo et al., 2014), experimentally induced inflammation (Luo et al., 2008), prion infection (Tamguney et al., 2009), and in a mouse model of Alzheimer's disease (Watts et al., 2011). A double transgenic strain was more recently generated which not only expresses firefly luciferase under 2.2kb of the human GFAP promoter but also the Renilla Luciferase driven by 0.5kb of the human GAPDH promoter (Cho et al., 2009). Determination of dual reporter ratios was reported to reduce variability between samples (Cho et al., 2010; Cho et al., 2009). These strains allow sensitive, non-invasive measurement of cellular response, a technique compatible with longitudinal studies of function and behavior (Luo et al., 2014).

While there is clear potential for the use of the human GFAP promoter to target astroglia, recent characterization of hGFAP-derived GFP expression suggests that it does not fully recapitulate endogenous GFAP activity in mice (Moon et al., 2011), perhaps indicating that upstream GFAP transcription-control mechanisms differ for (largely undefined) different subtypes of astrocytes. Further reflecting the functional diversity of astrocytes, endogenous GFAP activity is only detectable in a small proportion of protoplasmic (grey matter) astrocytes, compared to fibrous (white matter) astrocytes (Molofsky et al., 2012). Thus, the use of the GFAP promoter to label astrocytes in grey matter brain structures may be problematic.

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Probing how the heterogeneity of astroglia is defined at the molecular level is integral to increasing our understanding of the functional differences between astrocytes and other cell types. To this end, useful mouse lines for more effectively targeting CNS regions have been developed based on the different established astrocyte promoter genes (Table 3).

For example, a mouse line in which EGFP expression was driven by the astroglial promoter S100b (Vives et al., 2003) has been used in experiments to dissect the molecular underpinnings defining the identity of astrocytes and neural stem cells of the subventricular zone (SVZ). It was found that the expression of S100b defines a late developmental stage in astroglial cells, after which cells expressing GFAP lose their NSC multipotency and commit to mature into cortical astrocytes (Raponi et al., 2007). Furthermore, grafting experiments suggest that S100B expression is repressed in the adult SVZ microenvironment (Raponi et al., 2007).

One particular astroglial promoter, worth highlighting, that has received increased support as a pan-astrocytic marker is the folate metabolism enzyme, aldehyde dehydrogenase 1 family, member L1 (Aldh1L1) (Cahoy et al., 2008). The Aldh1L1-eGFP mouse line (Anthony and Heintz, 2007) was shown to label more astrocytes in the CNS than the glutamate transporter GLT1, which only co-localized with a subset of eGFP+ cells (Yang et al., 2011). Genetic fate mapping analysis using this line, along with newly generated Aldh1L1 BAC Cre animals, also revealed that adult-born neuroblasts in some areas of the brain are derived from Aldh1L1+ precursors, suggesting that these lines also target adult neural stem cells (Foo and Dougherty, 2013).

Although an inducible Cre mouse driven by the Aldh1L1 promoter has not yet been developed, recent inducible lines such as hGFAP-CreER^{T2} (Ganat et al., 2006), GLAST-CreER^{T2} (Mori et al., 2006), S100b-EGFP/CreER^{T2} (McMahon and Zhang, 2010) as well as Tet-On/Off systems, which are both inducible and reversible, have been successful in achieving relatively tight temporal control over astroglial gene expression (Table 3).

In an interesting study to determine whether subpopulations of astrocytes are actually committed to specific functions, or whether all astrocytes can take on many functions over time, the researchers crossed GLAST-CreER^{T2} (Mori et al., 2006) mice with an inducible EGFP reporter strain, and used the progeny (GLAST/eGFP) in comparison with Aldh1L1-eGFP (Anthony and Heintz, 2007) and other lines, to reveal significant heterogeneity in the reaction of astrocytes to injury (Bardehle et al., 2013). With live 2-photon imaging to visualize individual astrocytes, the authors found different astrocyte subtypes with unique injury responses, (either retaining their baseline morphology, directing their processes toward a lesion, or proliferating at juxtavascular sites), and concluded that astrocyte recruitment after injury relies on specific niche proliferation, which is markedly reduced after knock out of astrocytic RhoGTPase Cdc42 (Bardehle et al., 2013).

Another marker which is expressed in neural stem cells as well as differentiated neurons and astrocytes is the transcription factor Sox2. Sox2, a member of the SRY-related, high mobility group box family of transcription factors, is known to regulate self-renewal and multipotency (Avilion et al., 2003; Fong et al., 2008) while restricting differentiation (Boyer

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et al., 2005; Rodda et al., 2005), and is one of the four factors for establishing iPS cells (Takahashi et al., 2007a). However, although it is largely downregulated after fate commitment and maturation, Sox2 protein is still found in many differentiated astrocytes and some neurons in the neocortex, striatum and thalamus, indicating functions in these mature cells (Jinno, 2011; Komitova and Eriksson, 2004). Consistent with a role in astrogliogenesis, its overexpression promoted precursor differentiation into astroglia in favor of neurons (Bani-Yaghoub et al., 2006). The developmental relationship between Sox2 expression and the formation of astrocytes and even oligodendrocytes (Hoffmann et al., 2014), is being closely investigated.

The generation of a Sox2-EGFP knock-in mouse, which facilitates the isolation of these cells (Ellis et al., 2004) *in vivo* and *in vitro* demonstrated the reliability of Sox2 as a bona fide stem cell marker. Characterization of this knock-in strain has shown that Sox2 is expressed during embryonic development, and that its expression persists in neurogenic zones of adult tissues, such as brain, retina, tongue, testis, cervix lens epithelium and squamous epithelium of esophagus (Arnold et al., 2011). In the same study, lineage ablation with Sox2-Herpes Simplex Thymidine Kinase (HSTK) knock-in mice demonstrated a role in tissue replenishment and homeostasis (Arnold et al., 2011). A Sox2 transgenic mouse strain carrying 5.7 kb 5′ flanking sequences placed upstream of the (beta) geo G418 resistance gene facilitated the selection of cells for clonogenic assays (Zappone et al., 2000). A Sox2-Cre transgenic strain carrying 12.5 kb of upstream sequences (Hayashi et al., 2002; Vincent et al., 2003) has been demonstrated to be highly effective for epiblast-specific gene ablation. Interestingly, because of its early expression, an unexpected finding of maternal inheritance conferring transgene-independent recombination turned out to be a convenient advantage in complex breeding strategies (Hayashi et al., 2003; Vincent and Robertson, 2003). In order to target stem/progenitor cells temporally, however, a more recently established inducible Sox2-Cre BAC-based mouse strain (Kang and Hebert, 2012) should prove useful for modulating floxed genes in adult neural stem cells of neurogenic regions including the subventricular zone (SVZ) and dentate subgranular zone (SGZ). This study also showed Sox2-driven reporter expression in some adult astrocytes and neurons (Kang and Hebert, 2012).

3.2 Oligodendroglia

Many genes are specifically expressed by cells of the oligodendrocyte lineage, and these are widely used as reliable markers for different stages of the developing oligodendrocyte cell. For the majority of markers in this cell lineage, transgenic/knock-in reporter activity largely reflects the developmental expression of the endogenous protein. These genetic ‘driver’ strains may be loosely divided into three categories based on gene promoter activity: a) mature oligodendrocytes (MBP, MAG, MOBP, Cx47), b) progenitor cells (NG2, PDGFRa) and c) multiple developmental stages (CNP, PLP, Olig2, Olig1, Sox10) (Table 4).

With the exception of MBP, transgene expression driven by genes specific for mature myelinating oligodendrocytes, such as MAG, MOG, MOBP are largely germ-line. A Tamoxifen-inducible MBP line with 1.9kb of the mouse promoter (MCreER^{T2G}) was generated for the temporal manipulation of the unfolded protein response in mature

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myelinating oligodendrocytes (Gow, 2011), which reportedly did not suffer from leakiness or premature suppression as in previous constructs (Foran and Peterson, 1992; Turnley et al., 1991). In contrast, markers for OPCs are less restricted spatially and temporally, and their targeting strains are understandably designed with tamoxifen inducibility (ER-T2 or Tm), for use in studies of postnatal and adult progenitor cells. The chondroitin sulfate proteoglycan CSPG4, also known by its acronym NG2, is notably expressed in OPCs, but is also found in pericytes - perivascular cells immunopositive for PDGFRb, that regulate development and remodeling of blood vessels - and microglia (Gao et al., 2010; Zhu et al., 2012). Collectively, given their broad range of cell fates and function atypical of glia (Kukley et al., 2008; Sun and Dietrich, 2013), NG2+ polydendrocytes may be considered to constitute an independent category of cells (Butt et al., 2005; Nishiyama et al., 2009; Nishiyama et al., 2005). For this reason, labeling with NG2 to identify OPCs often involves the use of a second marker, like Olig2, to determine fate commitment (Ligon et al., 2006).

In addition to other OPC markers, like PDGFRα, and Ascl1/MASH1, the prominent oligodendrocyte and Schwann cell transcription factor of myelin, Sox10, is now beginning to be recognized as a viable option to label OPCs. Mouse lines have been generated to label Sox10-expressing cells of the neural crest and oligodendroglial lineage, and their progeny using fluorescent reporters (Shibata et al., 2010). Because Sox10 is expressed in both OPCs as well as in myelinating oligodendrocytes (Kuhlbrodt et al., 1998), as a driver of transgene and Cre expression, it may function in a manner akin to the CNP promoter, which is active over several stages of OPC lineage progression (see below). In lineage characterization studies with the Sox10-Cre or S4F:Cre transgenic mouse line that bears 28.5 kb upstream sequences placed in front of the mouse c-Fos promoter, the neural crest-derived cells and oligodendroglial populations were labeled, similar to endogenous expression of Sox10 (Stine et al., 2009). Tetracycline-inducible Sox10-directed transgene expression was attained with the establishment of Sox10-rtTA knockin (Ludwig et al., 2004). To enable temporal control of Sox10-mediated Cre expression, a Sox10-iCreER^{T2} BAC mouse strain was generated (Simon et al., 2012). Analysis of this strain using the floxed R26R reporter showed labeling of NG2+ OPCs and GSTpi oligodendrocytes, including an intermediate stage presumed to be GPR17+ (Simon et al., 2012).

Although both 2′,3′-cyclic nucleotide 3′-phosphodiesterase (CNP) and proteolipid protein (PLP) are recognized as protein indicators of mature cells capable of producing myelin, their transcripts and hence promoter activities are detected early in development (Kanfer et al., 1989; Lubetzki et al., 1991; Yuan et al., 2002), in OPCs (Mallon et al., 2002; Yuan et al., 2002) and beyond (Fuss et al., 2000a; Wight et al., 1993), allowing targeting of reporter or transgene expression in neural precursor cells and throughout the postnatal oligodendrocyte lineage – from OPCs through to myelinating oligodendrocyte (Ming et al., 2013; Yuan et al., 2002). Both are also active in the Schwann cell lineage (Mallon et al., 2002; Yuan et al., 2002). It is worth noting that both CNP- and PLP-promoter activities have been detected in neurons in gray matter structures of the medulla and hippocampus (Belachew et al., 2003; Miller et al., 2009) (Table 4). However, unlike the CNP promoter, the PLP promoter was recently found to be active in stem cells of the spinal cord (Harlow et al., 2014) (Table 4). The CNP-Cre knock-in (Lappe-Seifke et al., 2003) also shows early activity in Schwann cell precursors at E12 (Genoud et al., 2002), and has been used for gene ablation in OPCs

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(Genoud et al., 2002), myelinating oligodendrocytes (Brockschnieder et al., 2004; Kaga et al., 2006), Schwann cells (Grigoryan et al., 2013), and even enteric neurons and glia (Viader et al., 2011). The PLP-Cre is available as several tamoxifen-inducible strains (Doerflinger et al., 2003; Leone et al., 2003) for Cre targeting to oligodendroglia and Schwann cells. Interestingly, in addition to these lineages, fate-mapping of NG2+ cells using the PLP-Cre-ER^{T2} and Olig2-Cre-ER^{T2} lines have demonstrated multipotentiality of their targeted cells, with cerebellar Bergmann glia being labeled in addition to oligodendroglia and astrocytes (Chung et al., 2013).

3.3 Other reporter and effector mouse lines

BAC-based Prism transgenic animals are reporter lines which carry 3 transgenic alleles (Dougherty et al., 2012). Now available through Jackson Laboratories, these were generated to circumvent the combination of several alleles through extensive and costly breeding paradigms, and to determine the feasibility of producing a mouse line with multiple independently regulated transgenes at a single locus. The combination of three BACs – SNAP25, MOBP and Aldh1L1 - allows the simultaneous visualization of neurons, oligodendrocytes and astrocytes using 3 distinct fluorophores: mCherry, YFP and Cerulean respectively. In a second generation line, Prism 2.0, some toxicity issues were addressed by replacing mCherry with DsRedMax, and confining the YFP to the cytoplasm (Dougherty et al., 2012) (Table 3). These could be useful for FACS- cell isolation or immunodetection.

Recent developments in monitoring Cre-mediated recombination include the generation of dual fluorescent reporter Cre-dependent mouse strains. These fluorescent reporters express either red fluorescent protein or green fluorescent protein before recombination, and then either green fluorescent or red fluorescence respectively, after recombination (De Gasperi et al., 2008; Hasegawa et al., 2013). The interesting discovery of a pink mouse among colonies of another newly established strain expressing mCherry/EGFP dual reporters, further adds convenience during animal husbandry with the strong emission of mCherry that is visible to the naked eye (Hartwich et al., 2012). These dual fluorescent strains represent a departure from the previous dual reporters consisting of the combination of a fluorophore with an enzymatic reporter like beta-galactosidase or alkaline phosphatase (Lobe et al., 1999; Novak et al., 2000). Other dual fluorescent reporter strains, like the mT/mG, label fine projections by targeting reporter protein to membranes (Muzumdar et al., 2007). Another membrane-targeted reporter strain was recently described with mGFP that is uniquely expressed from the Tau locus (Hippenmeyer et al., 2005) as a knock-in, instead of the more commonly used chicken actin promoter. In this Tau-mGFP strain, the targeting cassette contains LoxP-STOP-LoxP-mGFP-IRES-NLS-LacZ (Hippenmeyer et al., 2005), allowing Cre-mediated control of mGFP expression from the Tau locus. Tau is expressed specifically in neurons and oligodendrocytes (Richter-Landsberg and Gorath, 1999). The Tau-mGFP strain was used with a PDGFRa-CreERT2 strain in a recent study to label the processes of newly generated oligodendrocytes in myelin internode analysis without occupying two fluorescent channels (Young et al., 2013).

While the isolation of targeted cells, either with transgene-reporter strains or using Cre/LoxP combinations enables transcriptome analysis, the process of cell isolation is laborious and

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notoriously low-yield, especially where low abundance RNA is being analyzed in rare cell populations such as adult progenitor cells. These types of studies have now been made more efficient and specific by removing the dependence on physical methods of cell isolation. Molecular tagging of polyribosome-bound RNA from the oligodendroglial lineage, the BAC-TRAP transgenic mice – Translating ribosome affinity purification (TRAP) – not only allows one to forego tissue dissociation and FACS, and disruption-associated artifacts, but also facilitates the isolation of RNA subpopulations that are actively translated (Doyle et al., 2008). A number of mouse strains expressing core ribosomal protein subunits have been developed for this purpose. For oligodendroglial analysis, L10a, a protein component of the 60S large ribosomal subunit, is expressed as a fusion gene with GFP under the control of the mouse CNP gene (Heiman et al., 2008). This allows subsequent GFP-mediated affinity purification of polysomal mRNAs from CNP-expressing oligodendroglial cells, as well as tracking oligodendrocytes from intact animals by fluorescence (Heiman et al., 2008; Lee et al., 2012). To overcome the limitation that different transgenic animals would be needed for different cell types, recently a conditional TRAP line (Rosa26fsTRAP) bearing GFP-RPL10a was established (Zhou et al., 2013), which is more widely accessible through the use of available Cre strains. Another Cre-dependent mouse line, called RiboTag, bears an RPL22 allele with a haemagglutinin epitope tag (Sanz et al., 2009). The RiboTag strain was elegantly designed with a duplicated exon 4 to ensure adequate expression of the wild type RPL22 allele prior to recombination (Sanz et al., 2009). Such polyribosome isolation systems are useful for analyzing oligodendroglial transcriptomes (Lee et al., 2012), ribosome binding of RNA populations and translational activity. A Rosa26-mCherry-RPL10a (mCherryTRAP) strain has also been generated (Hupe et al., 2014) for these applications.

Other RNA species, such as microRNA or miRNA, can now be immunoprecipitated through the expression of Argonaute (AGO) proteins. AGO proteins are central to the RNA-induced silencing complex (RISC) and bind miRNAs directly. AGO immunoprecipitation has been used to isolate miRNAs and their targets (Beitzinger et al., 2007; Easgow et al., 2007; Hendrickson et al., 2008; Karginov et al., 2007). In a recently developed AGO2 BAC strain, GFP and Myc are fused to the N-terminus of (tAGO2) of AGO2, and the transgene is knocked into the Rosa26 allele for Cre/LoxP-dependent recombination (R26-LSL-tAGO2) (He et al., 2012). tAGO2 may be immunoprecipitated with AGO2, Myc or GFP, allowing many options for studies of gene regulation involving miRNA.

4. Concluding remarks

This article provides a summary of *in vitro* and *in vivo* approaches to study astrocytes and oligodendrocytes by the selective isolation from, and cell-specific targeting within rodent brain. Because of their common origins (Zhu et al., 2008), strategies for generating cultures of these individual cell types from stem and progenitor cells are based on distinguishing physical properties, antigen or protein expression for cell selection, or directed maturation of stem cell populations. The advent of iPS cells has made human neural cells far more accessible, and although much work is still needed to implement the use of iPS cells for replacement therapy, these cells are useful to shed light on fundamental developmental processes and human disease mechanisms. With the ongoing characterization of more stem-

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and progenitor cell markers, a growing collection of glial-specific transgenic, Cre-based or inducible systems will continue to provide increasingly precise reporter-mediated detection and targeting of these cells and their gene products from brain tissue. These tools and the information gleaned from them may offer novel avenues vital for the diagnosis and treatment of brain disease.

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Abbreviations

GalC	galactocerebroside
FACS	Fluorescence-Activated Cell Sorting
BAC	bacterial artificial chromosome
PAC	P1 artificial chromosome
EGFP	enhanced green fluorescent protein
Aqp4	Aquoporin4
Apoe4	Apolipoprotein E4
Blbp	brain lipid binding protein
Cx	Connexin
FGFR	fibroblast growth factor receptor
GFAP	glial fibrillary acidic protein
GLAST	Glutamate-Aspartate transporter, also known as EAAT1
EAAT	Excitatory amino acid transporter
GLT1	glutamate transporter 1, also known as EAAT2
Kir	Inwardly-rectifying potassium channel
CNP	2′,3′-cyclic nucleotide 3′-phosphodiesterase
MBP	myelin basic protein
MOBP	myelin-associated oligodendrocyte basic protein
MAG	myelin-associated glycoprotein
MOG	myelin oligodendrocyte glycoprotein
PLP	proteolipid protein
NG2	neuron-glia antigen 2
PDGFRα	platelet derived growth factor receptor alpha

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PDGF	platelet derived growth factor
bFGF	basic fibroblast growth factor

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Highlights

- Astrocytes and oligodendrocytes express stage-specific, cell surface markers useful for cell identification and selection
- Astrocytes and oligodendrocytes can be acutely isolated from CNS tissue, cultured from progenitors or derived from stem cells
- Genetic models offer a variety of marker genes with which to target stem cells, astrocytes and oligodendrocytes *in vivo*, with overlapping expression across cell types
- Novel genetic models offer molecular tagging *in vivo* to facilitate gene expression analysis

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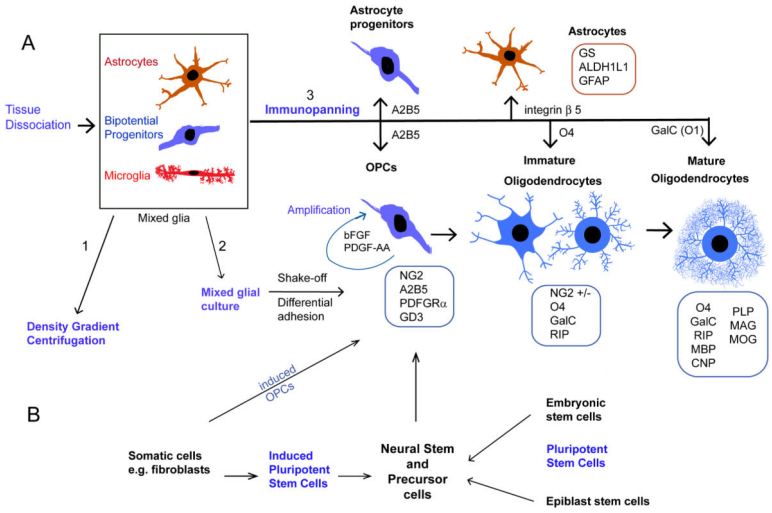

Figure 1.

Overview of strategies to produce astrocytes and oligodendrocytes from brain tissue or stem cells. A. CNS tissue-derived approach begins with tissue dissociation. The resulting cell suspension may be subjected to: 1. Density gradient centrifugation to remove myelin debris and blood cells, and cell fractions are isolated according to buoyant density. 2. Culture as mixed glia. At high plating density which promotes progenitor cell generation, when the bed monolayer of astrocytes reaches confluency and progenitor clusters loosely attached, bipotential progenitors and microglia are shaken off. OPC clusters are enriched after microglial removal by preferential adhesion to culture dishes, and may be subsequently amplified with mitogens PDGF-AA and bFGF. 3. Immunopanning sequentially on culture dishes coated with antibodies for positive and negative selection, depending on desired cell population. O4 and O1(GalC) have been used for the selection of committed oligodendroglial cells, while A2B5 has been used for selection of bipotential progenitor cells, namely from the optic nerve. GalC is a sphingolipid of myelin. A2B5 cells can generate both oligodendrocytes and type-2 astrocytes, which is believed to be an *in vitro* phenomenon (de Castro and Bribian, 2005). Boxes represent commonly used markers for the identification of the various glial cell stages over development. Immature oligodendrocytes which express the O4 antigen consist of NG2-expressing cells as well as those that have lost NG2 expression (NG2+/-).

B. Stem cell derived approach. Neural stem and precursor cells are obtained from pluripotent stem cells (iPS) which are cultured from embryonic or non-embryonic sources, including somatic cells such as adult or embryonic mouse fibroblasts. Both human and rodent iPS cells have been successfully differentiated into functional oligodendrocytes (Wang et al., 2013) through generating neural-restricted precursor cells. Mouse embryonic and lung fibroblasts have also produced induced OPCs by direct reprogramming with transcription factors (Najm et al., 2013).

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Table 1

Macroglial culture from CNS tissue

Method	Tissue source	Yield, Purity, culture conditions	Cellular characteristics General Remarks	References
ASTROCYTES				
Shaking and removal of contaminating cells	Neonatal rat cerebral hemisphere	Defined media with serum, 10 days in culture, withstands multiple passages	Proliferative, plastic cells lacking processes, differences in glutamate receptor expression, and more activated than *in-vivo* adult astrocytes	(Cole and de Vellis, 1997; Morrison and de Vellis, 1981; Morrison et al., 1985) (Nakagawa and Schwartz, 2004) (Sun and Dietrich, 2013)
Adult cells Mechanically dissociated and plated	P90 adult rat Cerebral Cortex	15×10^6 cells/cortex. With serum in DMEM/F12, Maintained for over 5 weeks	Reportedly more similar to adult astrocytes than prenatal counterparts	(Souza et al., 2013)
Immuno-panning, Sequential negative selection	E17 and P1 neonatal Rat Optic nerve	5000 purified astrocyte precursor cells per E17 rat, 4000 astrocytes per P1 optic nerve (90%)	E17: GFAP-, S100b-, A2B5+, Pax2+, Unlike P1 astrocytes, precursor survival requires bFGF and GGF, and differentiate with CNTF or LIF.	(Mi and Barres, 1999)
Immuno-panning, Negative selection	Adult human optic nerve heads	Based on neonatal rat method of Mi et al (Mi and Barres, 1999)	Further purification with cloning rings to eliminate smooth muscle and fibroblasts	(Yang and Hernandez, 2003)
Immuno-panning, Negative and Positive selection (Integrin beta5)	P1 – P18 rat cortex	98% GFAP+ astrocytes, Maintained with HB-EGFF or Wnt7a without serum	Slowly dividing, more similar to acutely isolated astrocytes *in vivo*	(Foo et al., 2011)
Rat OPCs				
Shake-off	Newborn rat cerebral hemispheres	Mixed glial cultures established in serum-containing media for 7–9 days, then shaken overnight. 95% oligodendroglia	Economical, high yield. Same mixed glial cultures used with different purification techniques after shake-off to generate astrocytes and oligodendroglia	(McCarthy and de Vellis, 1980)
A2B5-FACS or Shake-off and differential-adhesion	Newborn rat cerebral hemispheres	Up to 95% purity of OPCs. Utilized differential adhesion properties between microglia and oligodendroglia	Amplification of purified OPCs shown to occur by incubating with PDGF and insulin.	(Behar et al., 1988)
Dual passaging to eliminate astrocytes and neurons	E17 rat cortices	2 weekly passages with trypsin in serum media, then serum-free media with PDGF-AA for	Further differentiated with T3, T4 and NT3 without PDGF. OLs formed compact	(Itoh, 2002)

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Method	Tissue source	Yield, Purity, culture conditions	Cellular characteristics General Remarks	References
		2 days to expand OPCs.	myelin in neuron/ astrocyte co-culture	
Shake-off and differential adhesion removal of astrocytes and microglia	Neonatal rat cerebral cortices	Purification by differential adhesion: astrocytes and microglia attach to untreated plastic more efficiently than OPCs.	Economical and high yield. PDGF and bFGF used to amplify purified OPCs for 7–10 days.	(Chen et al., 2007)
Shake-off and differential adhesion	P2-P4 rat cerebral cortices	Mixed glia maintained for 10 days before shake-off.	OPCs amplified in N1/DMEM with PDGF Successful for OPC/ hippocampal neuron co-cultures	(Yang et al., 2005)
Immunopanni ng using negative and positive selection	Neonatal rat cortices and optic nerve; adult optic nerve	Ran-2 and GalC-based removal of astrocytes and OLs followed by positive selection with A2B5. >99.5% purity of OPCs.	Higher purity than shake-off, less damaging than FACS. Highly specific, has capacity to distinguish developmental stages.	(Dugas and Emery, 2013; Gard et al., 1993; Gard et al., 1995; Mayer-Proschel, 2001; Shi et al., 1998)
OPCs from NPCs	Embryonic rat spinal cord	NPCs in bFGF/EGF were gradually switched to PDGF and bFGF to generate oligospheres and then passaged at 7 days. Yields 95% pure OPCs	PDGF/bFGF more efficient than B104CM/bFGF, and preference for Accutase over trypsin to dissociate oligospheres	(Fu et al., 2007)
Preamplification before chemical modification of shake-off method	P1 rat cerebral cortices	15% B104 conditioned medium to expand mixed glia, isolation media with EDTA and DNase1 to detach OPCs by aspiration, further purified by gentle shaking. 85–95% OPC purity	Avoids costly purified growth factors; gentler than overnight shake-off. Reported higher yield of OPCs than shake-off method when compared directly.	(Niu et al., 2012)
Mouse OPCs				
Generation of Oligospheres	P0-3 mouse cortices	Percoll purification of dissociated cells and differential adhesion to deplete astrocytes. Plating in uncoated flasks generates floating spheres in N1/B104. Oligospheres obtained in 7 days.	Oligospheres expressed GAP43 and GD3. Spheres expandable for 2 months, myelinated shiverer mouse after transplantation.	(Vitry et al., 1999)
Generation of Oligospheres	E14.5-E17.5 multipotent progenitors	4 day-old embryonic neurospheres (10 days from neonate) in EGF/bFGF replaced by B104 medium to form oligospheres. Yields 95% OPCs	Circumvents difficulty with shake-off. Economical, high yield. Free floating oligospheres amenable to passaging.	(Chen et al., 2007)

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Method	Tissue source	Yield, Purity, culture conditions	Cellular characteristics General Remarks	References
Clonal expansion with B104 media, passaged repeatedly.	P5 mouse neocortex	Culture for 18 days, re-plated at low density in uncoated dish for 2–3 week to capture single cell-derived colonies, then passaged 50 generations to generate mOPCs. >99% NG2+, A2B5+	After capture, expanded clones are stored frozen. Aggregates removed during 2 weeks differentiation. Implantation into adult mouse brain produces OLs	(Lin et al., 2006)
FACS with NG2	Embryonic/Neonatal cortices	Mixed glia mildly trypsinized before FACS >95% OPCs Require cAMP for growth and survival	Unlike overlapping A2B5 and NG2 expression in rat OPCs, 25% NG2+ mouse OPCs expressed A2B5.	(Horiuchi et al., 2010)
Magnetic activated cell sorting with O4	P5-7 mouse cerebral cortex	Dissociated cells cleared with anti-mouse IgM magnetic beads before O4 antibody. Yields 3.68×10^5 OPCs per brain, >90% NG2+, A2B5+ after passage.	O4+ cells declined after passage. Bipotentiality reduced in DRG co-culture. In vitro OPC differentiation led to cell death; required CNTF for survival and maturation.	(Dincman et al., 2012)
Immunopanning Negative and Positive selection	P7 mouse cortex (OPCs); P12-16 (OLs)	Papain dissociation. PDGFRa (mouse CD140a), GalC or MOG selection, trypsinized and re-plated after panning. Yields 0.5×10^6 OPCs per brain	High purity and specificity. Consecutive positive panning for multiple stages possible. PDGF + NT3 or T3 for proliferation and maturation respectively	(Emery and Dugas, 2013)
Shake-off and differential adhesion	P0-P2 mouse cortices	Papain and mechanical dissociation, mixed glia supplemented with insulin, shake-off at 9 days. 50–60% OPCs	Technical considerations challenging, and lower OPC enrichment, but economical and avoids using mitogens. Convenient postnatal age for dorsal root ganglion co-cultures.	(O'Meara et al., 2011)
Shake-off and selective adhesion	Postnatal (P0, P15) and adult (P60, P180) cerebral cortex	Mechanical dissociation and various papain digestion conditions. Mixed glia cultured 10–25 days (postnatal) or 25–35 days (adult) before shake-off, enriched by 2 rounds of adhesion. PDGF-AA in growth medium.	Economical method with enhanced efficiency especially for adult OPCs, with 100,000 OPCs per gram weight adult CD1 tissue. OPC yield of 80,000 cells/animal higher than with FACS or optic nerve immunopanning and magnetic sorting. Reports mouse strain differences in numbers of adult OPCs isolated.	(Medina-Rodriguez et al., 2013)

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Method	Tissue source	Yield, Purity, culture conditions	Cellular characteristics General Remarks	References
Shake-off and selective adhesion	Human adult tumor margins and non-tumor biopsies	Same technique as above, except T25 flasks instead of T75. Confluency in 30–40 days before shake-off at lower speed than murine cells.	First reported protocol demonstrating OPCs isolation from biopsies. and use of PDGF-AA in growth medium	(Medina-Rodriguez et al., 2013)

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Table 2

Generation of macroglia cells from pluripotent stem cells

Origin	Method	Cell Products	Remarks & Application	References
Embryonic Stem cells (ESC)				
Mouse embryonic stem cell line previously established (Li et al., 1992)	ESC aggregated to embryoid bodies without LIF in 4 days, expanded in propagation media (ITSFn) for 5 days + 5 days in media with insulin, transferrin, selenium chloride, putrescine, progesterone, FGF2, and laminin. Glial precursor cell proliferation was induced in media with FGF2, EGF, and PDGF.	A2B5+ glial precursors were obtained. 4 days of growth factor withdrawal induces formation of 38% immature OLs (O4+) and 35% astrocytes (GFAP+)	Transplantation in myelin-deficient rat model	(Brustle et al., 1999)
Mouse embryonic stem cells previously established (Kyba et al., 2002)	Embryoid bodies formed without serum were transferred to media containing serum replacement (4 days), and then into serum replacement, EGF, FGF-2 and laminin (5 days), followed by serum replacement with FGF2 and PDGF.	Differentiation for 10 days: 98% astrocytes (GFAP+), further selected by FACS depletion of CD31.	ESC-derived astrocytes as gene therapy vector for transplantation into mice	(Benveniste et al., 2005; Uzzaman et al., 2005)
hESCs previously established (Thomson et al., 1998)	Retinoic acid and SHH agonist, purmorphamine, and T3 were used to induce oligodendroglial differentiation (110- 150 days in-vitro)	OPC production efficiency: 45% (OLIG2+/NKX2.2+ cell clusters) Generates: 83% OL lineage (OLIG2+) 37% OPCs (CD140α)	Generates OPCs but at lower efficiency than from hiPSCs (See iPS section for same study comparison.)	(Wang et al., 2013)
Epiblast stem cells				
Mouse epiblast stem cells with Oct-4 GFP transgene (**post-implantation**)	NSC induced by: 2 days in Activin A+ bFGF, then 2 days in neurosphere medium, then 3 days in expansion medium (EGF+bFGF) modified from: (Conti et al., 2005) (high bFGF)	3 weeks growth factor withdrawal induced: 50% astrocytes (GFAP+), 10% neurons (MAP2+), and 40% SOX-2, reportedly comparable with brain- derived NSCs.	Both epiblast and ESC-derived NSCs are multipotent but express different gene patterns. When transplanted into neonatal mouse brains both differentiated into neurons and astrocytes.	(Jang et al., 2014)
Mouse epiblast stem cells from **pre- and post-implantation** mouse embryos	Modulation of Activin and BMP signaling to NSC; then passaged in PDGF, FGF and SHH.	Neurons (not sustained) and primarily Olig2+/Nkx2.2+ OPCs. 64% OPCs subsequently expressed O4 and myelin proteins.	OPCs showed myelination *in-vitro*, *in-vivo* and in slice cultures. Useful for drug screening	(Najm et al., 2011a; Najm et al., 2011b)
		iPS		
Induced epiblast stem cells from adult and embryonic mouse fibroblasts	4 iPS factors used as reported (Takahashi and Yamanaka, 2006), but chemically defined media allowed development of induced epiblast stem cell without an embryonic stem cell intermediate.	Induced epiblast stem cells formed tetratomas, but not chimeras.	iEpiblast stem cells take longer to derive (3–5 week) than iPS cells (1–2 week). Overexpression of Klf4 allows for reversion to ESC.	(Han et al., 2011)
iPS cells derived from mouse embryonic fibroblast or adult tail tip fibroblasts	Retroviral transduction with Oct3/4, Sox2, Klf4 and c-Myc then cultured with ES media and feeder cells	Most iPS clones exhibited pluripotency and were genetically more similar to ES than fibroblasts. Differed from ESC in gene expression profile (Chin et al., 2009)	Low conversion efficiency to iPS cells. Teratoma formation decreased without c-Myc (Nakagawa et al., 2008; Nakagawa et al., 2010)	(Takahashi et al., 2007a; Takahashi and Yamanaka, 2006)

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Origin	Method	Cell Products	Remarks & Application	References
iPS cells derived from mouse embryonic fibroblast	Retroviral transduction with Oct3/4, Sox2, Klf4 and cMyc (Takahashi and Yamanaka, 2006); Produced **NSCs** with N2 medium, FGF, and EGF Produced **NPCs** with N2, PDGF, EGF, bFGF, then PDGF	OPCs differentiated in T3, and NT3. Astrocytes, a few neurons, and 18% MBP+ OL (80% OL purity after PDGFRα FACS)	OL myelinated neurons in culture and after transplantation in a cuprizone model without teratoma formation.	(Czepiel et al., 2011)
iPS cell line: MEF-Ng-20D-17 from embryonic mouse fibroblasts previously established (Okita et al., 2007)	Conversion of embryoid bodies to Nestin+ cells and then in N2, bFGF, bFGF +EGF and PDGF+bFGF OPCs differentiated with T3; modified from (Brustle et al., 1999)	14.1% A2B5+ OPCs were obtained from iPSCs compared to 12.6% from ESC. Differentiation to O4+ was lower in iPSC than ESCs. (Tokumoto et al., 2010) Immuno-panning increased efficiency of differentiation to O4+ from 2.3% to 43.5%. 62% of O4+ became MBP+ (21 days). (Ogawa et al., 2011a)	Similar efficiency of iPS and ESC to differentiation into A2B5+ OPCs. Lower efficiency of iPS to O4+ cells may be due to inhibitors of terminal differentiation of OPCs.	(Tokumoto et al., 2010)
iPS cells derived from mouse fibroblasts previously established (Moretti et al., 2010)	**NSC** induction with FGF and EGF are based on (Conti et al., 2005). **NPC** commitment involved decreasing bFGF and using valproic acid and BDNF (Spiliotopoulos et al., 2009). For Oligodendroglial commitment: 4 days with N2, forskolin, FGF-2, and PDGF and 4 days with T3 and ascorbic acid (Glaser et al., 2007) For astrocyte differentiation: 5 days with serum without EGF or FGF2	22 day neuronal protocol generated: 62% betaIII tubulin, 53% MAP2, 8% GFAP+ and some Nestin+/betaIIItubulin-. Oligodendroglial commitment protocol: All cells were NG2+ or O4+ and 25 % were committed through expressing NG2+/O4+. Astrocyte differentiation protocol: 100% GFAP+ cells	NSC from iPS have a reported similar differentiation efficiency to neurons as NSC derived from ESC.	(Onorati et al., 2010)
iPS cells derived from reprogramming adult mouse neural stem cells cultured from adult Oct-4-GFP mice	iPS cells produced with Oct-4 and Klf4 (2–3 weeks), or Oct-4 alone (4–5 weeks) if cells endogenously express Sox-2, Klf-4 and C-Myc	NSCs differentiate into neurons, astrocytes and oligodendrocytes after 20 passages and in-vivo and form teratomas. (Kim et al., 2009)	Two factors, depending on endogenous expression, may be sufficient for reprogramming NSCs into iPS cells.	(Kim et al., 2009; Kim et al., 2008)
iPS cells derived from mouse embryonic and lung fibroblasts	Doxycycline-inducible lentiviral vectors for Olig2, Nkx6.2, and Sox10 were used. OPCs produced with FGF2, PDGF-AA and SHH	Induced OPCs (iOPCs) produced in 14–21 days.	OPCs transplanted into slice cultures of Shiverer mice formed compact myelin.	(Najm et al., 2013)
hiPS from adult human dermal fibroblasts	Retroviral transduction of iPS factors: Oct3/4, Sox2, Klf4 and cMyc (Takahashi and Yamanaka, 2006)	iPS cells formed embryoid bodies *in vitro* and teratomas (made of ectoderm, mesoderm and endoderm) *in vivo* suggesting pluripotency.	hiPS could differentiate into neural cells.	(Takahashi et al., 2007b)
hiPS from adult human skin biopsy from a patient with Multiple Sclerosis	Dermal fibroblast expansion (14 days) (Park et al., 2008) followed by transduction with Oct3/4, Sox2, Klf4 and cMyc (Takahashi et al., 2007b). Cells were re-plated and cultured with feeder cells, hbFGF and butyrate and mechanically disrupted 18 days post-transduction	NSC were induced and differentiated into mixed culture containing astrocytes (50.5% GFAP+) and neurons (72.7% βIII-tubulin+ and 56.9% MAP2+) after 4 weeks in NS medium. Modified culture conditions enriched for immature and mature oligodendrocytes (47.2% O4+ and 88.9% MBP+)	Butyrate increased efficiency for derivation of iPS from expanded human dermal fibroblasts from 0.033–0.066% to 0.24–0.67%. iPS generated from a patient with MS has pluripotency.	(Song et al., 2012)
hiPS clones from adult human dermal fibroblasts	Feeder and serum free method using retroviral vectors for transfection with Oct3/4, Sox2, Klf4 and cMyc (Totonchi et al., 2010) A 9 week oligodendrocyte	Immunocytochemical analysis was used to determine 94% of cells at the final differentiation stage were of OL lineage (OLIG +). 95.7% A2B5+	OPCs transplanted into focal demyelinating optic nerve differentiated into myelinating OL (MBP+ and PLP +) and some astrocytes and neurons but not teratomas or tumors.	(Pouya et al., 2011)

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Origin	Method	Cell Products	Remarks & Application	References
	differentiation protocol included hESC medium/glial restriction medium, retinoic acid bFGF, and EGF at specified time points based on a method for hESC (Hatch et al., 2009).	19.5% of the cells were mature OL (MBP+). 73.7% of cells expressed GalC+ suggesting an immature OL phenotype. 52.4% of cells were NG2+ and 42.9% were α+ PDGFR suggesting an OPC phenotype. Non-oligodendrocyte cells included 1% astrocytes (GFAP +) and 5% neurons (MAP2+)		
hiPSC lines (fibroblast and keratinocyte origin) previously established (Chambers et al., 2009; Maherali et al., 2008)	Retinoic acid and SHH agonist, purmorphamine, and T3 were used to induce oligodendroglial differentiation. (110- 150 days in-vitro) GFAP + cells were found at 70 DIV. Withdrawal of growth factors for 2 weeks was used to induce maturation of OPCs (186–205 DIV)	OPC production efficiency: 73–80% (OLIG2+/NKX2.2+ cell clusters) Generates: 87–95% OL lineage (OLIG2+) 32–41% OPCs (CD140α) 40–50% astrocytes (GFAP+) 4–12% cells matured from OPCs to immature or mature OLs (O4+) FACS selection of O4+, CD140α, or A2B5 further purifies OPCs for transplant studies	Higher OPC derivation efficiency than from hESC (See ESC section for same study comparison.) Method favored OPC and immature OL differentiation for transplant. OLs myelinate neurons *in-vitro*; 4–10% of donor OPCs in Shiverer brains became MBP+ cells (78% OLIG2+ and the rest were GFAP+).	(Wang et al., 2013)

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Table 3

Mouse lines[a] for targeting Astroglia

Line	Construct	Cell Type	References
Aldh1L1-eGFP	BAC	Astrocytes, Neural Stem Cells, Muller Glia, Bergmann Glia, Radial Glia	GenSat* (Gong et al., 2003; Heintz, 2004) (Anthony and Heintz, 2007) (Bardehle et al., 2013; Cahoy et al., 2008; Doyle et al., 2008; Foo and Dougherty, 2013; Tsai et al., 2012; Yang et al., 2011)
Prism 1.0 and 2.0 (Aldh1L1-cerulean, SNAP25-mCherry, MOBP-YFP)	BAC	Astrocytes, Neurons, Oligodendrocytes	*(Dougherty et al., 2012)
Aldh1L1-Cre	BAC	Astrocytes, Radial Glia, Neural Stem Cells	*(Tien et al., 2012) (Foo and Dougherty, 2013)
Apoe4-EGFP	Knock-in	Astrocytes, Neuroepithelial Cells, Vascular Smooth Muscle Cells, Choroid Plexus Cells	*(Xu et al., 2006)
Apoe4-CreER^{T2}	BAC	Astrocytes	*(Slezak et al., 2007)
Aqp4- CreER^{T2}	BAC	Astrocytes	*(Slezak et al., 2007)
Blbp-GFP	Mouse 1.6 kb	Neural Stem Cells, Neural Progenitor Cells, Radial Glia	*(Anthony et al., 2004)
Blbp-EGFP	BAC	Astrocytes, Bergmann glia, radial glia, Neural Progenitor Cells	*(Schmid et al., 2006) (Howard et al., 2008; Mo et al., 2007)
Blbp-EYFP	BAC	Astrocytes, Neural Stem Cells, Radial Glia	*(Schmid et al., 2006)
Blbp-dsRed2	BAC	Astrocytes, Neural Stem Cells, Radial Glia	*(Schmid et al., 2006)
Blbp-Cre	Mouse 1.6 kb	Astrocytes, Radial Glial, Neural Stem Cells, Neural Progenitor Cells	*(Anthony et al., 2004) (Gibson et al., 2010; Hegedus et al., 2007)
Cx30-LacZ	Knock-in	Astrocytes, Ependymal Cells, Leptomeningeal Cells, Neurovascular Cells	*(Teubner et al., 2003) (Gosejacob et al., 2011)
Cx30-CreER^{T2}	BAC	Astrocytes, Neurovascular Cells	*(Slezak et al., 2007) (Barnabe-Heider et al., 2010; Gosejacob et al., 2011; Nomura et al., 2010)
Cx43-LacZ	Knock-in	Astrocytes, Neural Stem cells	*(Theis et al., 2001) (Contreras et al., 2002; Mori et al., 2006)
Cx43-CreER^{T}	Knock-in	Astrocytes, Neural Stem cells	*(Eckardt et al., 2004) (Gosejacob et al., 2011)
FGFR3-EGFP	BAC	Astrocytes	*(Heintz, 2004)
FGFR3-iCreER^{T2}	PAC	Astrocytes, Radial Glia, Neural Stem Cells	*(Bansal et al., 2003) (Cox et al., 2012; Rivers et al., 2008; Young et al., 2010; Zawadzka et al., 2010)
hGFAP-S65T-GFP	Human 2.2 kb	Astroyctes, Muller Glia, Radial Glia, Neural Stem Cells, Cortical Neurons	*(Zhuo et al., 2001) (Silbereis et al., 2010)
hGFAP-EGFP	Human 2.2 kb	Astrocytes, Radial Glia, Neural Stem Cells, Bergmann Glia	*(Nolte et al., 2001) (Benesova et al., 2009; Hirrlinger et al., 2005;

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Line	Construct	Cell Type	References
			Matthias et al., 2003; Wehner et al., 2003)
GFAP-GFP	Mouse 2.0 kb	Astrocytes, Neural Stem Cells, Radial Glia	*(Platel et al., 2009)
GFAP-EGFP	Mouse 2.6 kb	Astrocytes, Non-myelinating Schwann Cells	*(Suzuki et al., 2003) (Yamazaki et al., 2011)
GFAP-EGFP	Mouse 2.5 kb	Astrocytes, Muller Glia	*(Kuzmanovic et al., 2003)
hGFAP-AsRed2, -AmCyan1, -mRFP1	Human 2.2 kb	Astrocytes, Bergmann Glia	*(Hirrlinger et al., 2005)
hGFAP-dsRed	Human 2.2 kb	Astrocytes, Cerebellar Granule Neuron Precursors, Bergmann Glia, Radial Glia	*(Noraberg et al., 2007) (Silbereis et al., 2010)
hGFAP-LacZ	Human 2.2 kb	Astrocytes, Schwann Cells, Bergmann Glia, Muller Glia	*(Mucke et al., 1991) (Brenner et al., 1994; Johnson et al., 1995; Rio et al., 2002; Verderber et al., 1995)
hGFAP-LacZ	Human 1.8 kb	Astrocytes, Radial Glia, Neuroepithelial Precursor Cells	*(Andrae et al., 2001)
GFAP-LacZ	Mouse + 2.0 kb 5′	Astrocytes, Schwann Cells, Bergmann Glia	*(Mucke et al., 1991) (Campbell et al., 1993)
GFAP-LacZ	Mouse 2.0 kb	Radial Glia, Bergmann Glia, Tanycytes	*(Galou et al., 1994)
GFAP-LacZ	Mouse gene (ATG/TTG mutant)	Schwann Cells, Bergmann Glia	*(Johnson et al., 1995)
GFAP-Cre	Mouse gene (ATG/TTG mutant)	Neural Progenitor Cells, Ependymal Cells, Granule Neurons	*(Marino et al., 2000) (Garcia et al., 2004; Kwon et al., 2001)
GFAP-Cre	Mouse 2.0 kb	Astrocytes, Radial Glia	*(Casper and McCarthy, 2006)
hGFAP-Cre	Human 2.2 kb with insulators	Astrocytes, Radial Glia, Oligodendrocytes	*(Casper and McCarthy, 2006)
hGFAP-Cre	Human 2.2 kb	Astrocytes, Ependymal Cells, Radial Glia	*(Zhuo et al., 2001) (Bajenaru et al., 2002; McCarty et al., 2005; Peng et al., 2010)
hGFAP-CreER^{TM}	Human 2.2 kb	Astrocytes, Bergmann Glia	*(Chow et al., 2008)
hGFAP-CreER^{T2}	Human 2.2 kb	Astrocytes, Radial Glia, Bergmann Glia, Neural Stem Cells, Olfactory Bulb Neurons	*(Ganat et al., 2006) (Bruchas et al., 2011; Casper et al., 2007; Hirrlinger et al., 2006; Silbereis et al., 2010; Song et al., 2013)
GFAP-Luciferase	Mouse 12.0 kb	Astrocytes	*(Zhu et al., 2004) (Jany et al., 2013)
GFAP-Luciferase	Human 2.2 kb + 0.5 kb GAPDH with Renilla Luciferase	Astrocytes	*(Cho et al., 2009)
hGFAP-tTA	Human 2.2 kb	Astrocytes, Bergmann Glia	*(Lin et al., 2004; Wang et al., 2004) (Lopez et al., 2011)
hGFAP-tTA -mP1	Human 2kb, Gfa2	Astrocytes	*(Pascual et al., 2005)
hGFAP-tetO1-tTA *Transgenic rat*	Human 2.2 kb	Astrocytes	*(Barton et al., 2002)

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Line	Construct	Cell Type	References
GFAP-tet-ON	Mouse gene (ATG/TTG mutant)	Astrocytes, Muller Glia	*(Kim et al., 2003)
GLAST-EGFP	BAC	Astrocytes, Radial Glia	GenSat
GLAST-dsRed	BAC	Astrocytes, Radial Glia, Neural Stem Cells, Oligodendrocytes	*(Glowatzki et al., 2006) *(Regan et al., 2007)
GLAST-Cre-GFP	Knock-in	Astrocytes, Radial Glia, Muller glia, Bergmann glia	*(Mori et al., 2006)
GLAST-EMTB-GFP	BAC	Astrocytes, Radial Glia	*(Eom et al., 2011)
GLAST-Cre	BAC	Astrocytes, Radial Glia	*(Anthony and Heintz, 2008)
GLAST-CreER^{T2}	Knock-in	Astrocytes, Neural Progenitor Cells, Radial Glia, Tanycytes	*(Mori et al., 2006) (Bardehle et al., 2013; Bergami et al., 2008; Bonilla et al., 2008; Ninkovic et al., 2007; Robins et al., 2013; Snapyan et al., 2009)
GLAST-CreER^{T2}	BAC	Astrocytes, Bergmann Glia, Muller Glia, Neural Stem Cells, Radial Glia	*(Slezak et al., 2007) (Ehm et al., 2010; Fauquier et al., 2014; Sabelstrom et al., 2013)
Gli1-EGFP	Knock-in	Astrocytes, Radial Glia, Neural Stem Cells	(Garcia et al., 2010; Mesman et al., 2014)
Gli1-CreER^{T2}	Knock-in	Astrocytes, Radial Glia, Neural Stem Cells, Neural Progenitor Cells, OPCs	*(Ahn and Joyner, 2005)
Glt1-EGFP	BAC	Astrocytes, Radial Glia, Neural Stem Cells, Hippocampal and Somatosensory Cortical Neurons, Bergmann Glia	*(Regan et al., 2007) (de Vivo et al., 2010)
Glt1/EAAT2-tdTomato	8.3 kb transgenic	Astrocytes	*(Yang et al., 2011)
Kir4.1-EGFP	BAC	Astrocytes, NG2 Cells	*(Hibino et al., 2004) (Tang et al., 2009)
Nestin-eGFP	BAC	Astrocytes, Neural Stem Cells, Neural Progenitor Cells, Ependymal Cells	*(Roy et al., 2000) (Kawaguchi et al., 2001; Keyoung et al., 2001; Mignone et al., 2004)
Nestin-LacZ	Knock-in	Astrocytes, Neural Stem Cells, Neuroepithelial Cells	*(Zimmerman et al., 1994) (Frisen et al., 1995; Lin et al., 1995; Shan et al., 2006; Zhuo et al., 2001)
Nestin-rtTA	Knock-in	Astrocytes, Neural Stem Cells, Neural Progenitor Cells	*(Mitsuhashi et al., 2001) (Caviness et al., 2003; Farioli-Vecchioli et al., 2008; Suter et al., 2007)
Nestin-Cre	Rat 1.8 kb	Astrocytes, Neural Stem Cells, Neural Progenitor Cells	*(Zimmerman et al., 1994) (Betz et al., 1996; Hara et al., 2006; Imai et al., 2006)
Nestin-CreER^{TM}	BAC	Astrocytes, Neural Stem Cells, Neural Progenitor Cells, Ependymal Cells, Radial Glia	*(Kuo et al., 2006) (Pan et al., 2012)
Nestin-CreER^{T2}	Rat 5.3 kb	Astrocytes, Neural Stem Cells, Neural Progenitor Cells, Cerebellar Granule Neurons, Neurovascular Cells	*(Dranovsky et al., 2011) (Sahay et al., 2011; Sun et al., 2014)

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Line	Construct	Cell Type	References
Nestin-CreER^{T2}	Mouse 5.6 kb	Astrocytes, Radial Glia, Neural Stem Cells	*(Lagace et al., 2007) (Chen et al., 2009; DeCarolis et al., 2013)
Nestin-CreER^{T2}	Rat 5.8 kb	Astrocytes, Neural Stem Cells, Neural Progenitor Cells, Cerebellar Granule Neurons, Neurovascular Cells, Pericytes	*(Imayoshi et al., 2006) (Sun et al., 2014)
S100b-EGFP	Mouse 4.8 kb	Astrocytes, Oligodendrocytes, Ependymal Cells, Neurons, Enteric Glia, NG2 Cells	*(Vives et al., 2003) (Gulbransen and Sharkey, 2009; Hachem et al., 2005; Hachem et al., 2007; Raponi et al., 2007)
S100b-EGFP	Rat 9.0 kb	Astrocytes, Pituitary Folliculo-Stellate Cells	*(Itakura et al., 2007)
S100b-EGFP	Human 9.4 kb	Astrocytes, Schwann Cells	*(Zuo et al., 2004)
S100b-EYFP	Human 9.4 kb	Astrocytes, Schwann cells, Microglia, Bergmann Glia	*(Zuo et al., 2004) (Hayashi et al., 2007)
S100b-dsRed	Human 9.4 kb (9.6kb in the actual paper)	Astrocytes, Olfactory Ensheathing Cells	*(Windus et al., 2007; Windus et al., 2010)
S100b-YC 3.60 cameleon	Human 9.4 kb	Astrocytes, Schwann Cells, NG2 Cells, Mature Oligodendrocytes	*(Atkin et al., 2009)
S100b-Cre	Mouse 11.7 kb	Astrocytes, Bergmann Glia	*(Tanaka et al., 2008)
S100b-CreER^{T2}	BAC	Astrocytes, NG2 cells, Chondrocytes, Neural Dorsal Root Ganglion Cells,	*(McMahon and Zhang, 2010)
Sox2-EGFP	Knock-in	Embryonic, Trophoblasts, Neural Stem Cells	*(Ellis et al., 2004)
Sox2-Cre	Transgenic	Epiblast Cells, Neural Stem Cells	*(Hayashi et al., 2002)
Sox2-CreER^{TM}	BAC	Adult Neural Stem Cells, Some astrocytes and neurons	*(Kang and Hebert, 2012)
Sox2-iCreER^{T2}	Knock-in	Radial Glial Cells, Adult Neural Stem Cells, Neural Progenitor Cells, Neuroepithelial Cells, Ependymal Cells	*(Arnold et al., 2011)
Sox2-B geo G418	Transgenic	Neural Stem Cells	*(Zappone et al., 2000)
Sox2-HSTK	Knock-in	Neural Stem Cells	*(Arnold et al., 2011)

Note:

*denotes originator of the line. Findings in some cells are the result of fate-mapping analyses.

[a]Most lines listed are mouse except where otherwise indicated e.g. hGFAP-TetO1-tTA.

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Table 4

Mouse lines for targeting Oligodendroglia

Line	Construct	Cell Type	References
Cx47-EGFP	Knock-in	Mature Oligodendrocytes	*(Odermatt et al., 2003)
CNP-lacZ	Mouse 4.0 kb	OPCs and myelinating OLs	*(Gravel et al., 1998) *(Chandross et al., 1999)
CNP-lacZ neo			
CNP-EGFP	Mouse 4.0 kb	OPCs, myelinating OLs, Multipotent SVZ cells, Schwann cells, and neuronal precursors	*(Yuan et al., 2002) (Belachew et al., 2003) (Aguirre and Gallo, 2004; Belachew et al., 2001)
CNP-Cre	Knock-in	OPCs, myelinating OLs, PNS Neurons, and Schwann Cell Precursors	*(Lappe-Seifke et al., 2003) (Genoud et al., 2002)
MBP-lacZ	Mouse 1.3 kb Mouse 1.34 kb Mouse 1.9 kb Mouse 3.1 kb Mouse 9 kb	Mature Oligodendrocytes; Schwann cells (in 9 kb)	*(Turnley et al., 1991) *(Asipu et al., 2001) *(Gow et al., 1992) *(Foran and Peterson, 1992)
MBP-lacZ	Mouse 1.34–1.9 kb Mouse 6 kb	Mature oligodendrocytes, non- neural epithelial cells, astrocytic shaped oligodendrocytes, compact perivascular oligodendrocyte lineage cells; Schwann cells (in 6 kb)	*(Asipu et al., 2001) (Schiff et al., 2002) *(Forghani et al., 2001)
MBP-Cre	Mouse 1.3 kb Mouse 5.0 kb	Mature Oligodendrocytes	*(Niwa-Kawakita et al., 2000) *(Hisahara S et al., 2000)
MBP-CreER^{T2}	Mouse 1.9 kb	Mature Myelinating Oligodendrocytes	*(Gow, 2011)
MOBP-EGFP	BAC	Mature oligodendrocytes	* GENSAT, 2008
Prism 2.0: Snap25-DsRedMax/MOBP-YFP/Aldh1L1-Cerulean	BAC	Neurons, Oligodendrocytes, and Astrocytes	*(Dougherty et al., 2012)
MOG-iCre	Knock-in	Mature Oligodendrocytes	*(Hovelmeyer et al., 2005)
PLP-lacZ	Mouse 2.4 kb –exon 2	OPCs, myelinating OLs, and Schwann Cells	*(Wight et al., 1993)
PLP-sh ble-lacZ	Mouse 2.4 kb –exon 2	OPCs, myelinating OLs, and Schwann Cells	*(Spassky et al., 1998)
PLP-sh ble EGFP	Mouse 2.4 kb –exon 2	OPCs, myelinating OLs, and Schwann Cells	*(Sobottka et al., 2011)
PLP-EGFP	Mouse 2.4 kb –exon 2	OPCs, myelinating OLs, and Schwann Cells; OLs, spinal cord stem cells, neuronal progenitors, and non-myelinating satellite cells in sympathetic glia	*(Mallon et al., 2002) (Harlow et al., 2014)
PLP-GFP- S65T	Mouse 2.4 kb-intron 1	OPCs, myelinating OLs, and Schwann Cells	*(Fuss et al., 2000b)
PLP-dsRed	Mouse 2.4 kb-intron 1	OPCs, myelinating OLs, and Schwann Cells	*(Hirrlinger et al., 2005)
PLP-mtTA	Mouse 2.4 kb-intron 1	Myelinating OLs, Bergmann glia, Schwann cells in adult sciatic nerve	*(Inamura et al., 2012)

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Line	Construct	Cell Type	References
PLP-Cre	Mouse 3.7 kb Mouse 2.4 kb	OPCs, myelinating OLs, and Schwann Cells Embryonic Progenitors (neuroblasts and glioblasts) neuroepithelial and radial glial cells	*(Delaunay et al., 2008) *(Michalski et al., 2011) (Delaunay et al., 2009)
PLP-Cre ER^T	Mouse 2.4 kb	OPCs, myelinating OLs, Schwann Cells, Bergmann glia; Neurons and immature astrocytes in ventral forebrain, dorsal cerebral cortex, and hippocampus	*(Doerflinger et al., 2003) (Guo et al., 2009) (Chung et al., 2013) (Guo et al., 2010)
PLP-Cre ER^{T2}	Mouse 2.4 kb	OPCs, myelinating OLs and Schwann Cells	*(Leone et al., 2003)
Ascl1/Mash1-Cre ER^{TM}	BAC	OPCs, and Embryonic neuronal and oligodendrocyte-restricted precursors	*(Battiste et al., 2007)
Ascl1/Mash1-Cre ER^{T2}	Knock-in	OPCs, adult neural precursors; Hippocampal and olfactory bulb stem and progenitor cells	*(Kim et al., 2011)
NG2-dsRed	BAC	OPCs, pericytes, and microglia	*(Ziskin et al., 2007) *(Zhu et al., 2008) (Hall et al., 2014)
NG2-EYFP	Knock-in	OPCs, astrocytes	*(Karram et al., 2008)
NG2-Cre	BAC	OPCs, Astrocytes; neurons	*(Zhu et al., 2008) (Nishiyama et al., 2014)
NG2-Cre ER^{TM}	BAC	OPCs, pericytes, astrocytes	*(Zhu et al., 2011)
NG2-CreER ^{T2}	Knock-in	OPCs, gray matter astrocytes, and neurons	*(Huang et al., 2014)
Olig1-lacZ	Knock-in	OPCs	*(Zhou and Anderson, 2002)
Olig1-Cre	Knock-in	Motoneurons and OPCs	*(Lu et al., 2002)
Olig2-GFP	Knock-in	OPCs	*(Zhou and Anderson, 2002)
Olig2-Cre ER^{TM}	Knock-in	Motoneuron, OPCs and astrocytes	*(Takebayashi et al., 2002) (Dimou et al., 2008)
Olig2-tva-Cre	Knock-in	OPCs	*(Schuller et al., 2008)
PDGFRα-GFP	Knock-in	OPCs	*(Hamilton et al., 2003)
PDGFRα-CreER ^{T2}	PAC	OPCs, neurons, and astrocytes	*(Rivers et al., 2008) (Tripathi et al., 2010)
PDGFRα–$CreER^{TM}$	BAC	OPCs and some ventral neurons	*(Kang et al., 2010)
Sox10-Venus	BAC	OPCs, Schwann cells, and neural crest cells	*(Shibata et al., 2010)
Sox10-Cre	PAC	OPCs, Oligodendrocytes, Neural Crest Cells, Enteric Glia	*(Matsuoka et al., 2005) (Laranjeira et al., 2011; Potzner et al., 2007; Stolt et al., 2006)
Sox10-*fos*-Cre (S4F:Cre)	Transgenic	OPCs, myelinating OLs, and neural crest cells	*(Stine et al., 2009)

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Line	Construct	Cell Type	References
Sox10-rtTA	Knock-in	OPCs, myelinating OLs, and neural crest cells	*(Ludwig et al., 2004) (Kanaykina et al., 2010; Wahlbuhl et al., 2012)
Sox10-iCreER ^{T2}	BAC	OPCs, myelinating OLs, neural crest cells, and ependymal NG2 cells	*(Simon et al., 2012) (Ortega et al., 2013)

Note:

*denotes originator of the line. OPCs, oligodendrocyte progenitor cells; OLs, oligodendrocytes. mtTA, mammalian-optimized tetracycline-controlled transcriptional activator. Findings in some cells are the result of fate-mapping analyses.