G., and Caamaño, J.H. (2012). Immunity *37*, 721–734.

Brendolan, A., Rosado, M.M., Carsetti, R., Selleri, L., and Dear, T.N. (2007). Bioessays *29*, 166–177.

Castagnaro, L., Lenti, E., Maruzelli, S., Spinardi, L., Migliori, E., Farinello, D., Sitia, G., Harrelson, Z., Evans, S., Guidotti, L.G., et al. (2013). Immunity *38*, 782–791.

Kobayashi, Y., Kato, K., and Watanabe, T. (2011). Discov. Med. *12*, 351–362.

Koning, J.J., and Mebius, R.E. (2012). Trends Immunol. *33*, 264–270.

Koss, M., Bolze, A., Brendolan, A., Saggese, M., Capellini, T.D., Bojilova, E., Boisson, B., Prall, O.W.J., Elliott, D.A., Solloway, M., et al. (2012). Dev. Cell *22*, 913–926.

Landsman, L., Nijagal, A., Whitchurch, T.J., Vanderlaan, R.L., Zimmer, W.E., Mackenzie, T.C., and Hebrok, M. (2011). PLoS Biol. *9*, e1001143.

Mueller, S.N., and Germain, R.N. (2009). Nat. Rev. Immunol. *9*, 618–629.

Neyt, K., Perros, F., GeurtsvanKessel, C.H., Hammad, H., and Lambrecht, B.N. (2012). Trends Immunol. *33*, 297–305.

iOPs: A New Tool for Studying Myelin Pathologies?

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Generating patient-specific oligodendrocyte progenitors capable of repairing myelination defects observed in multiple neurological afflictions holds great therapeutic potential. Recently in *Nature Biotechnology*, Najm et al. (2013) and Yang et al. (2013) generated these progenitors by direct reprogramming, bringing us closer to their use in disease analysis and autologous transplantation strategies.

The progenitor cells that give rise to myelin-forming oligodendrocytes of the central nervous system (CNS), referred to as oligodendrocyte/type-2 astrocyte progenitor cells and oligodendrocyte precursor cells (and here abbreviated as O-2A/OPCs) have been of great interest in tissue repair for over 20 years. The initial demonstration, in 1993, that it was possible to purify O-2A/OPCs from the developing rat CNS, expand them extensively in vitro using specific combinations of mitogens, and then use these cells to repair demyelinating damage in the spinal cord (Groves et al., 1993) initiated a multilaboratory search for means of developing these approaches for therapeutic purposes. Achieving such a goal is particularly important due to the great range of neurological afflictions in which myelination abnormalities occur. Such afflictions include essentially all traumatic CNS injuries (including perinatal birth injuries, stroke, spinal cord injury, and traumatic brain injury), a wide range of genetic leukodystrophies, multiple chronic degenerative disorders (including multiple sclerosis, Alzheimer's disease, and Parkinson's disease), affective and neurocognitive disorders (including schizophrenia, depression, and autism), and consequences of systemic exposure to multiple chemotherapeutic agents and environmental toxicants.

The path to myelin repair has included notable successes in isolating multiple human cell populations able to generate oligodendrocytes in genetically hypomyelinated shiverer mice, which do not generate compact myelin due to a mutation in myelin basic protein. Such sources include human neuroepithelial stem cells, glial precursor cells isolated from human embryonic stem cells, and fetal glial precursor cells isolated from the embryonic CNS. However, cells derived from these sources will require coordinate use of immunosuppressive agents, thus leading to a need to use reprogramming strategies to enable generation of patient-specific precursor cells, either through the generation of induced pluripotent stem cells (Wang et al., 2013) or through direct reprogramming to the oligodendrocyte lineage.

Direct generation of oligodendrocyte precursors from autologous cells by direct reprogramming is a critical next step in the development of myelination repair strategies, and two papers in *Nature Biotechnology* (Najm et al., 2013; Yang et al., 2013) bring us much closer to achieving this goal. Two multilaboratory teams have used mouse and rat embryonic fibroblasts to directly generate precursor cells able to mature into oligodendrocytes using combinations of three transcription factors. In both cases, induced oligodendrocyte precursors (iOPs) expressed antigens that are also expressed by O-2A/OPCs, displayed similar morphologies and responded to appropriate mitogens, and showed appropriate global transcriptional remodeling indicative of oligodendrocyte precursors. The iOPs were induced to differentiate into oligodendrocytes by exposure to thyroid hormone or withdrawal of mitogens and exhibited appropriate morphologies and patterns of antigen expression in vitro. Moreover, iOPs were able to generate myelin-forming oligodendrocytes when transplanted into the shiverer mouse CNS.

While the studies converged on two of the three transcriptional regulators needed to generate iOPs, they differed in the cocktail's third component. Specifically, Olig2 and Sox10, both of which were previously known to be essential for oligodendrocyte generation (see Dugas et al., 2006 and references therein) were present in both transcription factor

mixtures, but one group identified Zfp536 as the third necessary member (Yang et al., 2013), while the other (Najm et al., 2013) identified Nkx6.2.

How far are we from accomplishing this type of direct reprogramming with human cells and will human iOPs be as effective at myelination as precursor cells obtained directly from the human fetal CNS? The fact that Olig2 and Sox10 are required in both cocktails suggests that these will form the basis for extending this work to human cells and hopefully will enable rapid generation of human iOPs. The key question will then be whether these cells can outperform progenitor cells isolated from the human embryonic CNS or generated from induced pluripotent human stem cells, which are able to myelinate the entire mouse CNS when transplanted in sufficient numbers and locations (Wang et al., 2013). While the promise of using autologous iOPs to eliminate the need for use of immunosuppression is important, if these cells are not as competent at myelinating large regions of the CNS then more work will be required to generate progenitor cells with improved functional properties. As O-2A/OPCs isolated from different regions of the developing rat CNS have markedly different capacities to undergo prolonged self-renewal (Power et al., 2002), attention to induction of the specific properties shown by subsets of these cells may be required to optimize iOP utility.

For all potential oligodendrocyte sources, it is essential that analysis moves beyond evaluation in shiverer mice, in which the CNS lacks the inflammation and glial scarring that characterizes all human pathological conditions with the possible exception of Pelizaeus-Merzbacher disease. O-2A/OPCs exposed to inflammatory cytokines cease division and differentiate into astrocytes (Tanner et al., 2011), and function of these progenitors is similarly suppressed by oxidative stress and by substances expressed in glial scar tissue (e.g., Franklin and Ffrench-Constant, 2008). Extrapolation from the benign shiverer environment to these more hostile circumstances remains too uncertain to offer unrestrained confidence in the broad clinical application of progenitor cell transplantation strategies for myelin replacement.

Two further questions, intimately connected to each other, are establishing the precise identity of the iOPs and determining their utility in analysis of genetic diseases characterized by myelination abnormalities. There are at least two distinct progenitor cell populations able to generate oligodendrocytes, these being O-2A/OPCs and the embryonically earlier glial-restricted precursor (GRP) cells. These cells share expression of several antigenic markers but differ in substrate and mitogen requirements and in the types of astrocytes they generate when exposed to bone morphogenetic proteins and interleukin-6 family members (Noble et al., 2004). Expression of the O4 antigen by dividing cells generated by forced expression of Olig2, Sox10, and Zfp536 (Yang et al., 2013) would place these cells firmly as classic O-2A/OPCs. In contrast, cells generated when Zfp536 is replaced by NKx6.2 were O4 negative (Najm et al., 2013) and could be an earlier stage of O-2A/OPC development or could even be GRP cells. Why might this distinction be important for using iOPs to study human disease? One example is provided by the analysis of Vanishing White Matter disease (VWMD), which is one of the most prevalent leukodystrophies and is characterized by progressive loss of myelination during early life. Analysis of glial precursor cells isolated from the brain of a child with VWMD and grown in GRP cell conditions showed that a major defect in these cells lies not in their ability to generate oligodendrocytes, but in their ability to generate astrocytes, suggesting that an important contribution to this disease of myelin pathology may be loss of astrocytes as a source of mitogens, survival factors, redox support, and the multiple other functions provided by these critical support cells (Dietrich et al., 2005). Regardless of these details, however, the availability of human iOPs will greatly accelerate our understanding of multiple devastating diseases.

REFERENCES

Dietrich, J., Lacagnina, M., Gass, D., Richfield, E., Mayer-Pröschel, M., Noble, M., Torres, C., and Pröschel, C. (2005). Nat. Med. *11*, 277–283.

Dugas, J.C., Tai, Y.C., Speed, T.P., Ngai, J., and Barres, B.A. (2006). J. Neurosci. *26*, 10967–10983.

Franklin, R.J., and Ffrench-Constant, C. (2008). Nat. Rev. Neurosci. *9*, 839–855.

Groves, A.K., Barnett, S.C., Franklin, R.J., Crang, A.J., Mayer, M., Blakemore, W.F., and Noble, M. (1993). Nature *362*, 453–455.

Najm, F.J., Lager, A.M., Zaremba, A., Wyatt, K., Caprariello, A.V., Factor, D.C., Karl, R.T., Maeda, T., Miller, R.H., and Tesar, P.J. (2013). Nat. Biotechnol. Published online April 14, 2013. http://dx.doi.org/10.1038/nbt.2561.

Noble, M., Pröschel, C., and Mayer-Pröschel, M. (2004). Dev. Biol. *265*, 33–52.

Power, J., Mayer-Pröschel, M., Smith, J., and Noble, M. (2002). Dev. Biol. *245*, 362–375.

Tanner, D.C., Cherry, J.D., and Mayer-Pröschel, M. (2011). J. Neurosci. *31*, 6235–6246.

Wang, S., Bates, J., Li, X., Schanz, S., Chandler-Militello, D., Levine, C., Maherali, N., Studer, L., Hochedlinger, K., Windrem, M., and Goldman, S.A. (2013). Cell Stem Cell *12*, 252–264.

Yang, N., Zuchero, J.B., Ahlenius, H., Marro, S., Ng, Y.H., Vierbuchen, T., Hawkins, J.S., Geissler, R., Barres, B.A., and Wernig, M. (2013). Nat. Biotechnol. Published online April 14, 2013. http://dx.doi.org/10.1038/nbt.2564.