them, however, screening of completely reconstituted ubiquitylation cascades may be necessary, as simple E1-E2 thioester assays would not have identified the CDC34 inhibitor found here. The identification of CC0651 is an exciting finding that sets the stage for the discovery of new E2 inhibitors, but only further work will reveal whether blocking ubiquitylation in the middle of the pathway will be better than blocking it at either end.

## REFERENCES

Bedford, L., Lowe, J., Dick, L.R., Mayer, R.J., and Brownell, J.E. (2011). Nat. Rev. Drug Discov. *10*, 29–46.

Ceccarelli, D.F., Tang, X., Pelletier, B., Orlicky, S., Xie, W., Plantevin, V., Neculai, D., Chou, Y.-C., Ogunjimi, A., Al-Hakim, A., et al. (2011). Cell *145*, this issue, 1075–1087.

Chou, T.F., Brown, S.J., Minond, D., Nordin, B.E., Li, K., Jones, A.C., Chase, P., Porubsky, P.R., Stoltz, B.M., Schoenen, F.J., et al. (2011). Proc. Natl. Acad. Sci. USA *108*, 4834–4839.

Deshaies, R.J., and Joazeiro, C.A. (2009). Annu. Rev. Biochem. *78*, 399–434.

Fiebiger, E., Hirsch, C., Vyas, J.M., Gordon, E., Ploegh, H.L., and Tortorella, D. (2004). Mol. Biol. Cell *15*, 1635–1646.

Kleiger, G., Saha, A., Lewis, S., Kuhlman, B., and Deshaies, R.J. (2009). Cell *139*, 957–968.

Orlicky, S., Tang, X., Neduva, V., Elowe, N., Brown, E.D., Sicheri, F., and Tyers, M. (2010). Nat. Biotechnol. *28*, 733–737.

Skaar, J.R., and Pagano, M. (2009). Curr. Opin. Cell Biol. *21*, 816–824.

Verma, R., Peters, N.R., D'Onofrio, M., Tochtrop, G.P., Sakamoto, K.M., Varadan, R., Zhang, M., Coffino, P., Fushman, D., Deshaies, R.J., and King, R.W. (2004). Science *306*, 117–120.

Zeng, X., Sigoillot, F., Gaur, S., Choi, S., Pfaff, K.L., Oh, D.C., Hathaway, N., Dimova, N., Cuny, G.D., and King, R.W. (2010). Cancer Cell *18*, 382–395.

# The Pessimist's and Optimist's Views of Adult Neurogenesis

**Gerd Kempermann**[1,2,*]
[1]CRTD, DFG Center for Regenerative Therapies Dresden
[2]DZNE, German Center for Neurodegenerative Diseases, Dresden
Tatzberg 47-49, 01307 Dresden, Germany
*Correspondence: gerd.kempermann@crt-dresden.de
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**The reports by Bonaguidi et al. (in this issue of *Cell*) and Encinas et al. (in *Cell Stem Cell*) come to differing conclusions about whether and how the proliferation of radial glia-like stem cells of the adult hippocampus impacts their long-term potential for neurogenesis.**

Adult neurogenesis had remained a footnote in neurobiology until the discovery of neural stem cells in the 1990s, which offered an explanation of where new neurons of the adult hippocampus and olfactory bulb might originate from. It was later discovered that the stem cells of the adult neurogenic regions have astrocytic properties and a morphology like radial glia. In the dentate gyrus of the hippocampus, these cells have a prominent process that branches out into the molecular layer. The question then arose of whether and how cells with such elaborate radial morphology would be capable of self-renewal—not only by asymmetric division (in which one morphologically distinct daughter cell would be generated), but also by symmetric division (which would produce not one but two new radial cells). Linked to this question is the important problem of how the type and rate of self-renewal would affect the population of stem cells over time. Now, two reports (in *Cell* [Bonaguidi et al., 2011] and *Cell Stem Cell* [Encinas et al., 2011]) come to substantially differing conclusions about the ability of radial glia-like stem cells in the hippocampus to self-renew and thus their capacity for maintaining neurogenic potential throughout life (Figure 1).

In a meticulous study based on various transgenic reporter models in mice, Encinas and colleagues show that the radial-glia like type-1 cells (quiescent neural progenitors [QNP] in their nomenclature; Mignone et al., 2004) divide asymmetrically to give rise to intermediate progenitor cells (amplifying neural progenitors [ANP], or type 2 in our nomenclature; Kempermann et al., 2004). The authors never observed symmetric division, and over time, the QNP cells disappear from the subgranular zone of the dentate gyrus by differentiating into astrocytes, thereby drying out the source for more new neurons (Encinas et al., 2011). In the study by Bonaguidi and colleagues, published in this issue, the authors use transgenic mice to induce sparse labeling of precursor cells (including the amazingly sophisticated two-color MADM reporter; Zong et al., 2005) to address a similar question

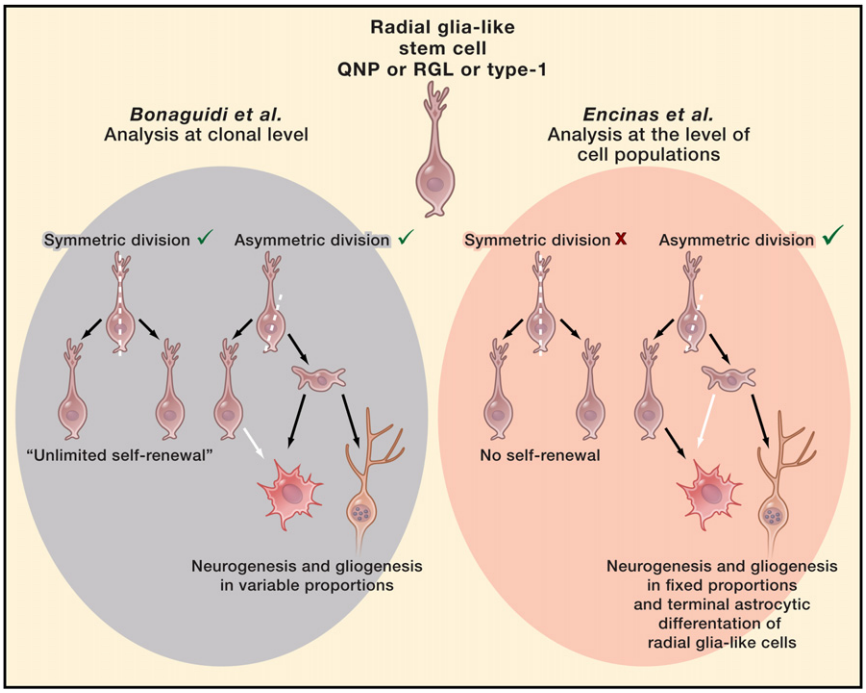


**Figure 1. Two Views of Adult Neurogenesis**

In principle, radial glia-like "stem" cells of the hippocampus might divide symmetrically or asymmetrically, which would have different consequences on the number of new neurons generated and for the maintenance of self-renewing stem cells, from which adult neurogenesis might originate at later times. Data by Bonaguidi et al. (2011) suggest that the stem cells of the hippocampus have a range of options in terms of self-renewal versus differentiation, whereas Encinas et al. (2011), examining precursor cells at the population level, do not find evidence for such flexibility. They instead propose that stem cells terminally differentiate into astrocytes.

at the level of individual clones originating from the radial glia-like stem cells (RGL cells in their terminology). They apply a clever computational approach to ascertain that a clone is, in fact, a clone and find all combinations of clonal compositions, including quiescent RGLs that are maintained at late time points (1 year) after undergoing symmetric division.

Thus, Encinas and colleagues present the notion that, in a predictable and deterministic way, stem cell proliferation consumes the population of stem cells, which are slowly but steadily "disposed" by being converted into neurons and astrocytes. In contrast, Bonaguidi et al. describe a relationship between self-renewal and multilineage differentiation that is more fluid and that permits the long-term maintenance of the stem cells. In the former view, type-1 cells are incapable of symmetric self-renewal, whereas the latter suggests this as possible.

If stem cells and their potential to generate new neurons are beneficial, and most readers will probably tend to believe so, the optimistic "maintenance" hypothesis may attract more sympathy than the more pessimistic "disposal" idea, but wishful thinking should not be our guide. What might explain the difference? Is it possible for both theories to be true at the same time?

First, there are potential caveats associated with the various tools (among which are both constitutive and inducible genetic reporters) regarding their sensitivity and specificity, which cannot be easily judged. Also, reporter constructs are genetic manipulations that might have unwanted repercussions in the cells and might show inexplicable preferences for subpopulations. The biology of reporter animals (which in the end carry a rather substantial mutation) is largely unexplored.

Second is the problem of scale. The results at the cellular or clonal scale apparently do not agree with results obtained with cell populations. This is also a methodological issue but more so a conceptual one. Similar problems are increasingly appearing throughout biology, when, for example, knockout mice have a different phenotype than predicted. This issue, however, does not resolve the qualitative discrepancy between the presence or absence of visible symmetric divisions of RGL/QNP cells in the two studies but could affect the more quantitative findings about the dynamics in the cohorts or populations of cells.

Finally, the question arising with the more rigid model proposed by Encinas et al. is whether it will prevail under conditions in which the animals are using their hippocampus in ethologically relevant ways. A few reports have suggested that the potential for neurogenesis can be maintained at a level corresponding to a much younger age (providing what I have termed a "neurogenic reserve" [Kempermann, 2008]). Encinas et al. state in their discussion that such effects would take place at the level of type-2 (ANP) progenitor cells and thus would be irrelevant here. Yet, very little is known about the regulation of the proliferation of type-1 cells. There are some initial studies indicating that the radial glia-like type-1 cells can be activated by seizure activity (Kunze et al., 2006; Steiner et al., 2008). How the radial glia-like population responds to long-term physiological stimuli has not yet been explored. And whether or not the glia-like intermediate precursor cells (type 2a), which still express several markers of radial glia (Steiner et al., 2006), can contribute to the population of cells with radial glial morphology has also not yet been fully resolved (Suh et al., 2007). Bonaguidi et al. do not answer this question either, but their results indicate that individual type-1 cells might have a range of options. At the cellular level, the system might be very dynamic or at least more dynamic than is apparent at the population level in the absence of regulation.

Bonaguidi et al. do touch on one potential underlying genetic mechanism that could control stem cell maintenance. In the tumor suppressor *Pten*, a phosphatase that inhibits proliferation, they present a plausible candidate gene for regulating the choice between these options. *Pten* is a known "stem cell"

gene that functions in the context of adult neurogenesis. Bonaguidi et al. show that conditional deletion of *Pten* in the stem cells leads to stem cell exhaustion after an initial boost in proliferation (although they only study relatively young mice).

But *Pten* would not act alone in regulating this process, and in the alternate scenario, the "disposal" of neural stem cells in adult neurogenesis would be a complex trait that is controlled by a network of regulators that are subject to behavioral modulation. If both Encinas et al. and Bonaguidi et al. are correct, neural stem cell fate will depend on such modulations. Could it be that, in the absence of appropriate stimuli, the stem cells are indeed predestined for disposal but that this fate can be overcome by unleashing the potential that exists in individual precursor cells? This is a testable hypothesis. How plastic is adult neurogenesis?

## REFERENCES


Bonaguidi, M.A., Wheeler, M.A., Shapiro, J.S., Stadel, R.P., Sun, G.J., Ming, G.-l., and Song, H. (2011). Cell *145*, this issue, 1142–1155.

Encinas, J.M., Michurina, T.V., Peunova, N., Park, J.H., Tordo, J., Peterson, D.A., Fishell, G., Koulakov, A., and Enikolopov, G. (2011). Cell Stem Cell *8*, 566–579.

Kempermann, G. (2008). Trends Neurosci. *31*, 163–169.

Kempermann, G., Jessberger, S., Steiner, B., and Kronenberg, G. (2004). Trends Neurosci. *27*, 447–452.

Kunze, A., Grass, S., Witte, O.W., Yamaguchi, M., Kempermann, G., and Redecker, C. (2006). Neurobiol. Dis. *21*, 324–332.

Mignone, J.L., Kukekov, V., Chiang, A.S., Steindler, D., and Enikolopov, G. (2004). J. Comp. Neurol. *469*, 311–324.

Steiner, B., Klempin, F., Wang, L., Kott, M., Kettenmann, H., and Kempermann, G. (2006). Glia *54*, 805–814.

Steiner, B., Zurborg, S., Hörster, H., Fabel, K., and Kempermann, G. (2008). Neuroscience *154*, 521–529.

Suh, H., Consiglio, A., Ray, J., Sawai, T., D'Amour, K.A., and Gage, F.H. (2007). Cell Stem Cell *1*, 515–528.

Zong, H., Espinosa, J.S., Su, H.H., Muzumdar, M.D., and Luo, L. (2005). Cell *121*, 479–492.