This discrepancy between normal and cancer stem cells in their dependence on PI(3)K–FoxO signalling is similar to that observed during aging. Normal lifespan is characterized by a paradox termed 'antagonistic pleiotropy' — gene function required in early life is often deleterious in later life. A similar phenomenon may occur in the conversion from a normal stem cell to a cancer stem cell. A cancer stem cell seemingly has to silence PTEN and probably also FoxO function, whereas a normal stem cell requires PTEN and FoxO for the maintenance of 'stemness'. Interestingly, this is also observed in *C. elegans*, where a germ-cell tumour — which could be considered a stem-cell originating tumour — regressed when DAF-16 was activated[14].

In the haematopoietic stem-cell compartment, FoxO transcription factors seem to regulate ROS levels. This is crucial for the maintenance of quiescence, preventing inappropriate cell division and subsequent HSC exhaustion. These observations could be representative of a common evolutionarily conserved pathway regulating adult stem-cell homeostasis. Indeed, *FoxO3a*$^{-/-}$ female mice display a distinctive ovarian phenotype, with global follicular activation leading to oocyte death and early depletion of functional ovarian follicles[15]. Foxo3a thus functions at the earliest stages of follicular growth as a suppressor of follicular activation, which has obvious parallels to its role as a suppressor of HSC activation.

Is it possible to manipulate this pathway for therapeutic use? Although it may be difficult to target FoxOs directly, current development of pharmacological inhibitors of PI(3)K–PKB may be beneficial for the activation of FoxO transcription factors, resulting in increased functionality of transplanted stem cells. This concept has recently been supported by the demonstration that the mTOR inhibitor, rapamycin, not only depleted leukaemia-initiating cells in PTEN-deficient mice, but also restored normal HSC function[7]. As long-term rapamycin treatment also inhibits PKB, it is plausible that rapamycin functions through restoration of FoxO activity. Therefore, these studies provide novel insights into malignant stem-cell development and suggest the intriguing possibility that agents used to eliminate cancer stem cells may actually be beneficial for maintenance of normal stem-cell function. □

COMPETING FINANCIAL INTERESTS
The authors declare that they have no competing financial interests.

1. Tothova, Z. *et al. Cell* **128,** 325–339 (2007).
2. Paik, J. H. *et al. Cell* **128,** 309–323 (2007).
3. Kops, G. J. *et al. Mol. Cell Biol.* **22,** 2025–2036 (2002).
4. Kops, G. J. *et al. Nature* **419,** 316–321 (2002).
5. Ito, K. *et al. Nature Med.* **12,** 446–451 (2006).
6. Ito, K. *et al. Nature* **431,** 997–1002 (2004).
7. Park, I. K. *et al. Nature* **423,** 302–305 (2003).
8. Yilmaz, O. H. *et al. Nature* **441,** 475–482 (2006).
9. Zhang, J. *et al. Nature* **441,** 518–522 (2006).
10. Reya, T. *et al. Nature* **423,** 409–414 (2003).
11. Murphy, M. J., Wilson, A. & Trumpp, A. *Trends Cell Biol.* **15,** 128–137 (2005).
12. Bouchard, C., Marquardt, J., Bras, A., Medema, R. H. & Eilers, M. *EMBO J.* **23,** 2830–2840 (2004).
13. Essers, M. A. *et al. Science* **308,** 1181–1184 (2005).
14. Pinkston, J. M., Garigan, D., Hansen, M. & Kenyon, C. *Science* **313,** 971–975 (2006).
15. Castrillon, D. H., Miao, L., Kollipara, R., Horner, J. W. & DePinho, R. A. *Science* **301,** 215–218 (2003).

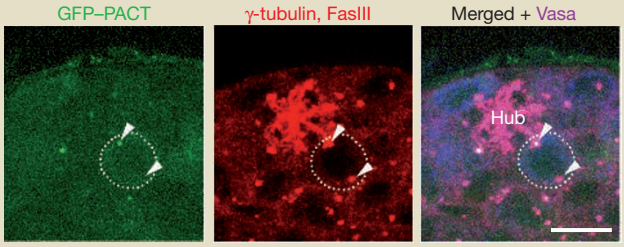
Daughter leaves mother

A defining characteristic of stem cells is their ability to divide asymmetrically into a self renewed mother cell and a differentiating daughter cell. Yamashita *et al.* (*Science* **315,** 518–521; 2007) have recently shown that in the *Drosophila* male germ line differential centrosome inheritance regulates this process.

Drosophila male germline stem cells (GSCs) are induced to self renew by signals from the stem cell niche composed of proximal somatic hub cells in the testes. Asymmetric GSCs division is governed by spindle orientation perpendicular to the hub cells, to produce a stem cell attached to the niche and a differentiating gonialblast. The positioning of centrosomes during interphase orientates the spindle: in G1, the single centrosome is located adjacent to the hub, and in G2 the duplicated centrosomes separate before spindle formation, so that one remains next to the hub and the other migrates to the opposite side of the cell.

Differential labelling of mother and daughter centrosomes by transient expression of the fluorescently labelled PACT domain of pericentrin like protein (which is only incorporated into centrioles during centrosome duplication) established that GSCs preferentially retain the mother centrosomes, whereas the daughter centrosome is inherited by the gonialblast destined to differentiate outside the niche microenvironment.

GSC centrosomes proximal to the hub maintain microtubules throughout the cell cycle, which in some cases extended towards the adherens junctions between GSC and hub cells. Thus, mother centrosomes may remain anchored to the GSC–hub interface via astral microtubules. In contrast, daughter centrosomes only had a few associated microtubules in interphase, which may allow them to move away from the stem-cell niche. Mutants in *centrosomin* (*cnn*), which is required for the anchoring of astral microtubules to centrosomes, show random mother and daughter centrosome separation.



The mother centrosome (labelled by embryonic expression of GFP–PACT) remains close to the hub-GSC interface, whereas the non-labelled daughter centrosome migrates toward the opposite side of the GSC. Green, GFP–PACT; Red, FasIII (hub) and γ-tubulin (centrosome); blue, Vasa (germ cells). The centrosomes are indicated by white arrows. The scale bar represents 10 μm.

These results indicate that the two centrosomes in dividing GSCs have different fates: the mother centrosome remains anchored to the hub in the self-renewed stem cell, whereas the newly formed daughter centrosome is free to move to the differentiating gonialblast, possibly because it is too immature to be hooked by the niche microtubules.

The anchoring of the mother centrosome may govern asymmetric division of the GSCs. The strategy of Yamashita *et al.* can now be used to determine whether differential centrosome inheritance is characteristic of other stem-cell types.

Sinéad Hayes