

## Cancer stem cells are everywhere

New findings call into question experimental anticancer approaches that target tumor stem cells—cells thought to seed tumor growth. These powerful cells were thought to be extremely rare on the basis of experiments showing that only a small fraction of cells in a tumor can seed a tumor in an immunocompromised mouse. But now, using even more severely immunocompromised mice, Elsa Quintana *et al.*<sup>1</sup> find that about 27% of melanoma cells from human subjects can seed a tumor. What's more, commonly used cancer stem cell markers, such as CD133, did not accurately identify the cells that initiate melanoma. Given that tumor stem cells might not be so rare after all, is it worth developing therapies to target them—and how will the findings change research on the origins of tumors? We asked three experts their views.

“We have to raise the bar in melanoma therapy.—Meenhard Herlyn

### Emmanuelle Passegué:

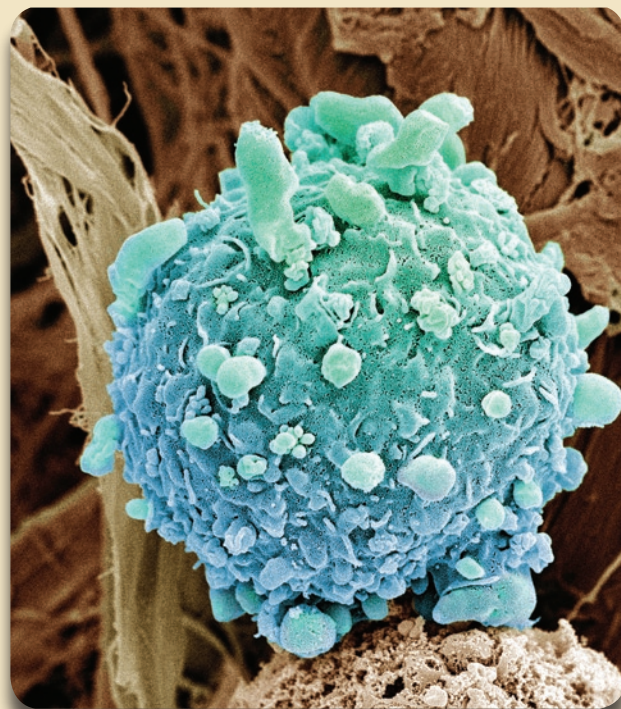
The findings will motivate the re-investigation of the frequency of tumor-initiating cells in a broad range of human cancers using this improved methodology. This effort will be particularly important for early-stage malignancies, in which such cells have been presumed to be quite rare. The open question is whether the numbers of tumor-initiating cells directly correlate with the stage of tumor development, being rare in benign nonmetastatic tumors and more abundant in advanced cancers such as the primary and metastatic melanoma used by Quintana *et al.*<sup>1</sup>. Addressing this issue will determine whether tumor stem cells are truly important in driving cancer progression and dissemination and whether they represent a key target for cancer treatment.

*Assistant Professor of Medicine, University of California, San Francisco, California, USA.*

### Shahin Rafii:

The findings highlight the need for more sensitive and reliable bioassays to define the true tumorigenic potential of individual human cancer-initiating cells. For instance, xenograft models do not account for the role of nonmalignant stromal cells in tumor progression or treatment resistance. Growth of stressed tumor xenograft cells, which are injured during harsh enzymatic preparation protocols, also demands rapid cellular adaptation to the poorly compatible stromal microenvironment of the mouse. This stromal incompatibility can greatly affect the proliferation of xenografted human cells, thereby resulting in underestimates of the number of cancer-initiating cells. Perhaps a large number of cancer cells would grow in a fully humanized microenvironment that closely mimics human organ-specific stromal cells. The answer may lie with the development of techniques to reproducibly isolate tumors along with their stroma, as well as more physiologically relevant *in vitro* clonal tumor explant models. Such systems might enable more accurate interrogation of the ability of primary human tumor cells to initiate cancer.

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Steve Geschmeissner / Photo Researchers, Inc.

A human melanoma cell. Where does it come from?

### Meenhard Herlyn:

Even though the study does not rule out the existence of cancer stem cells, the work clearly indicates that the goal for any therapy should be the elimination of all malignant cells, because each cell can expand to form a tumor and probably disseminate. The dismal progress in melanoma therapy in the last 30 years indicates that none of the previous strategies in chemotherapy or immunotherapy has succeeded in eliminating all malignant cells. We have to raise the bar in melanoma therapy.

*Program Leader, Molecular and Cellular Oncogenesis, Wistar Institute, Philadelphia, Pennsylvania, USA.*

1. Quintana, E., Shackleton, E., Sabel, M.S., Fullen, D.R., Johnson, T.M. & Morrison, S.M. Efficient tumor formation by single melanoma cells. *Nature* **456**, 593–599 (2008).