# Capturing cancer stem cells

Numerous studies have identified tumor-seeding cancer stem cells in a range of tumor types. To help define these cells, many researchers have relied on the expression of the cell surface molecule CD133, thought to be specific for such stem cells. Working with colon cancer, Sergey Shmelkov *et al.*[1] now call this premise into question. From their analyses in mice and in human tissues, the researchers conclude that CD133 is widely expressed and that it does not give a competitive edge to tumor cells. What do the findings mean for the quest to find and target cancer stem cells?

> "As attractive as the concept of a single marker is, it is now crucial to consider what such markers really mark.—*ZW*"

## Zena Werb:

Using a knock-in *LacZ* transgenic approach, Shmelkov *et al.*[1] show that CD133 is widely expressed in normal adult tissues as well as in colon cancer, and, indeed, both $CD133^+$ and $CD133^-$ cells initiate tumors in colon cancer. These $CD133^+$ and $CD133^-$ cells may actually mark cells of distinct behavioral subtypes within the tumor.

As attractive as the concept of a single marker is, it is now crucial to consider what such markers really mark. These molecules, which often lack tumor-specific function, may help tumor cells maintain their characteristics in a specific niche, or they may be expressed because of another gene turned on in the tumor or because of altered adhesion. So it is not hard to imagine that the markers may not be essential or constant, or that they may be expressed in normal tissues.

For understanding tumorigenesis and creating therapies, a spectrum of markers may be the answer.

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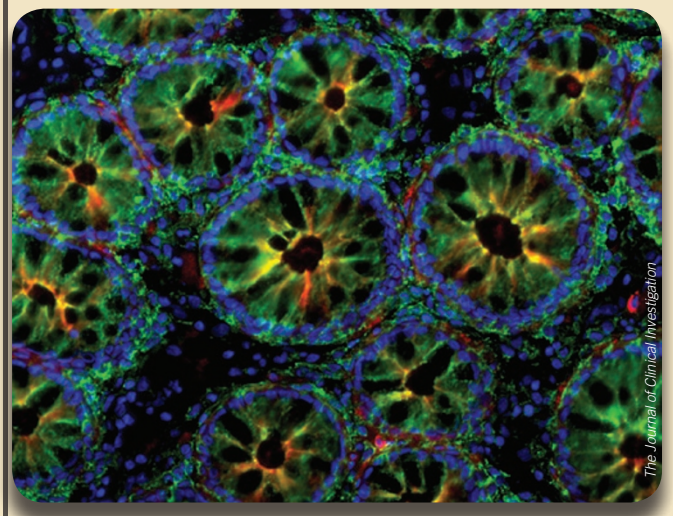


Shmelkov *et al.*[1] propose that CD133 is mainly a marker of mature epithelial cells. In human colons, they observed that expression of CD133 (red) overlapped with expression of an epithelial cell adhesion molecule (green).

## Jeremy Rich

Cancer stem cells are still defined through functional assays, but the prospective study of cancer stem cell–enriched tumor cell populations requires the identification of surface markers.

Unfortunately, no marker has proven perfect, and different groups have reported very different results with the same marker in the same tumor type. Similarly, interpretations of CD133 expression vary substantially depending on the analytic technique—which could partly explain why the findings of Shmelkov *et al.*[1] differ from those of other researchers.

Validation of cancer stem cell markers will require the adoption of consistent techniques in each tumor type, grade and stage and for each specific marker. No single marker is likely to be absolutely informative, but CD133 has proven repeatedly useful in brain tumor stem cell studies for many research groups.

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## Jeffrey Rosen:

The issue is not only whether CD133 is transcriptionally active in the colon cancer 'stem cells', but also which alternatively spliced and glycosylated epitopes of the protein can be recognized by specific monoclonal antibodies—a question also relevant for other types of cell surface molecules used to isolate cancer stem cells. So, although the techniques used by Shmelkov *et al.*[1] show that CD133 is not expressed specifically in cancer stem cells, the findings do not invalidate previous stem cell work using CD133 antibodies, which recognize a specific epitope that may not be conserved between mice and people.

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1. Shmelkov, S.V. *et al.* CD133 expression is not restricted to stem cells, and $CD133^+$ and $CD133^-$ metastatic colon cancer cells initiate tumors. *J. Clin. Invest.* **118,** 2111–2120 (2008).