

*“A recent study has shown that a complete, functioning breast can be grown out of a single breast stem cell in a mouse.”*

# From Curing Cancer to Growing Breasts

when small science turns big

By Sutheera Ratanasirintrawoot

At present, much effort has been put into enhancing our appearance. Strange as it may sound, one of the ways now considered promising in improving appearance is by an astounding discovery from stem cell research. Though cosmetic purposes are not the underlying reason for research on cancer stem cells, researchers' efforts to fight breast cancer have yielded a new discovery that could possibly lead to breast enhancement treatment.

A recent study has shown that a complete, functioning breast can be grown out of a single breast stem cell in a mouse. Although it will be a long time before we will be able to go to the clinic and ask for a customized breast through stem cell transplantation, it does seem that development in this field will advance at an amazing rate from now on and will benefit us by preventing and curing breast cancer more effectively. How a single stem cell, regardless of its small size, can go through such complicated transformations and provide such significant medical applications is truly intriguing.

## **Breast Cancer, a Ruthless Killer**

It is estimated that about 212,000 new cases of invasive breast cancer were diagnosed in the United States in 2005, along with 58,000 new cases of non-invasive breast cancer and as many as 40,000 deaths (1). It is no wonder, then, that breast cancer has been a focus of many researchers in the field (Figure 1). Stunning as this ground-breaking achievement is, it has not appeared out of thin air but rather is the culmination of years of intensive research into the basic biology of cancer.

It is worth considering why, despite researchers' painstaking attempts to develop an effective treatment for cancer, as well as the large amount of money spent each year on such research, we are still far away from winning this war. Could it be that so far we are taking the wrong approach? Is a new approach to this problem needed, or are we tracking down the wrong biological culprit while the real one is still “at large?”

## **Finding the Real Culprit: Cancer Stem Cells**

Prevailing clinical treatments typically

cause much suffering and fail to completely eradicate the disease, resulting in a high likelihood of relapse. Recently, however, the study of stem cells has shed light on the mechanisms possibly underlying cancer, and it is proposed that cancer may be a stem cell disease. As most current therapies indiscriminately target rapidly proliferating cells, they fail to affect cancer stem cells, a quiescent population with the ability to self-renew. The idea of cancer stem cells is intriguing as it explains the high rate of recurrence and promises alternative approaches to cancer treatment.

Cancer stem cells are the subject of a lot of controversy among leading scientists in the field. More rigorous evidence is required to confirm even the existence of the cells. The first data supporting the concept of cancer stem cells came from the study of leukemia and multiple myeloma, which demonstrated that only a small subset of the cancer cells possesses an extensive proliferative ability. This subset of cancer cells was later identified as leukemic stem cells and has since been proven to be able to recapitulate the disease when

transplanted into recipient mice. The success in identifying leukemic stem cells is largely due to the fact that the hematopoietic system is highly amenable to cell isolation and transplantation. In solid tumors, many cell types with different patterns of gene expression make it harder to target or isolate the cancer stem cells effectively. Indeed, the heterogeneity of tumors is one of the major glitches that hinder cancer treatments as cancerous cells can grow at different rates. Thus, a combination of treatments is required to eliminate the cancer completely.

As breast cancer is a solid tumor, the heterogeneity of cancer cells has to be taken into account when considering any treatment. Two general models of heterogeneity have been proposed, shown in Figure 1 (2). One of the models argues that cancer cells with distinct phenotypes are capable of proliferating extensively but any one cell has only a limited potential to form a new tumor. The other states that most cancer cells, in fact, possess only limited proliferative ability, with the exception of a subset of cells that are capable of both proliferating extensively and generating new tumors upon transplantation. The first model seems to be what current treatments are based on while the other offers a new way of viewing the nature of cancer and the tumorigenic (tumorigenic) ability of cancer cells.

### Caught Red-handed: Identification of the Breast Cancer Stem Cell

Many attempts have been made to isolate cancer stem cells from various types of tumors. However, to identify a very small subpopulation with distinct characteristics from a heterogeneous cell pool can be challenging. Muhammad Al-Hajj and his colleagues confirmed the cancer stem cell hypothesis, illustrated in the second model, by identifying tumorigenic breast cancer cells, the first cancer stem cells to be identified from solid tumors (3). The experiment was carried out by growing human breast

cancer cells in immuno-compromised mice. The result obtained shows that the subpopulation that has tumorigenic capability is very small.

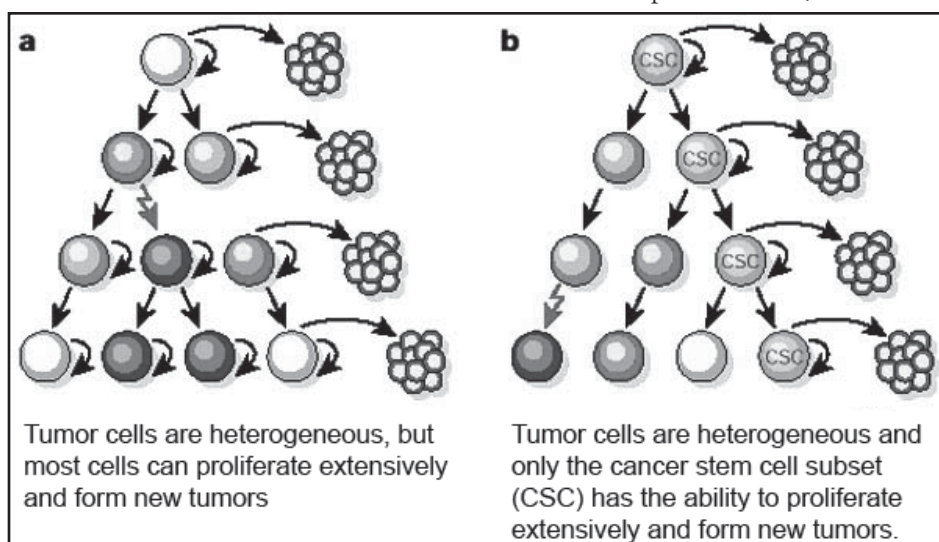
One of the factors behind this success is the ability to find markers, certain proteins on the cell surface that allow these subpopulations to be distinguished from one another. By using antibodies that recognize and bind to certain marker proteins, fluorescence activated cell sorting (FACS) can be used to sort out cells expressing these marker proteins with high accuracy, producing a pure population of cells. The combination of markers and antibodies chosen allows the sorting of cells into tumorigenic cells and non-tumorigenic ones depending on results from the cell engraftment. The tumorigenic sub-population is then isolated and allowed to grow through many rounds of cell division. The new tumor formed from such cells does, in fact, contain a diverse population of tumorigenic and non-tumorigenic cells as observed in the initial tumor. Such evidence points towards a major paradigm shift in the field of cancer biology. Armed with this new insight, scientists are seeking a cure by targeting the real culprit, the cancer stem cell.

This new approach to studying the progression of the disease promises newer cancer treatments with milder

side effects. Now that the real culprit has been identified, we can specifically eradicate the slow-cycling tumorigenic stem cells underlying the malignancy without affecting non-cancerous, rapidly proliferating cells. These proliferating cells, such as intestinal lining cells, immune cells, and hair follicle cells, are the most affected by current treatments. Chemotherapy, in particular, usually results in dramatic side effects, such as hair loss and compromised immunity. Furthermore, since breast stem cells are targets for malignant transformation, we might be able to provide preventive treatments for those at risk such as post-menopausal women or women with a family history of the disease (4). Once we have thoroughly characterized breast stem cells, it is highly likely that transformed breast cancer stem cells will still possess phenotypic characteristics shared with normal breast stem cells which would allow specific targeting.

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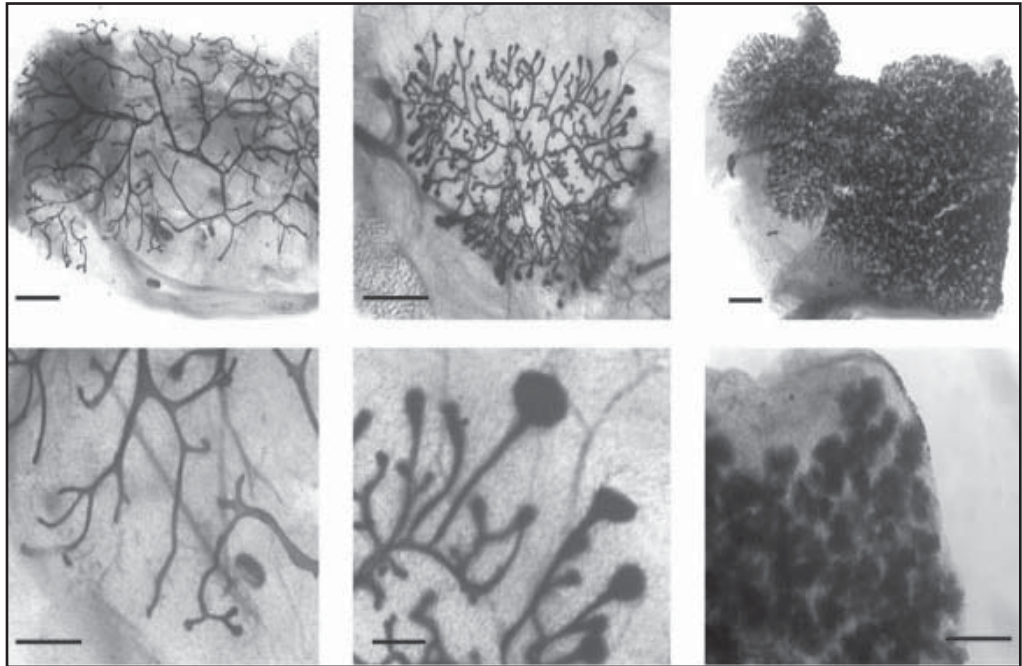
Given stem cell researchers' goal of recapitulating the natural differentiation of all stem cell types down their committed lineages, it is natural that the breast cancer stem cell will also be a target of such studies. A likely outcome is the development of new, less invasive



**Figure 1.** One theory suggests that cancer cells in general have the potential to proliferate extensively, but any one cell has a low probability of forming a new tumor (a). The other model states that most cancer cells have only limited proliferative potential, but a subset of cancer cells consistently proliferate extensively and can form new tumours on transplantation (b).

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therapies for breast cancer patients who undergo reconstructive surgery. This type of study – called directed differentiation of stem cells – has been done successfully in many types of stem cells. The notion is based on the ability of stem cells to differentiate into many cell types within their respective lineages. Skin stem cells, for example, are able to generate skin and hair follicles (5). To confirm the identity of the subpopulation isolated, Shackleton showed that a single cell from a discrete population of putative breast stem cells isolated from mouse mammary tissue can reconstitute the complete



**Figure 2.** The growth of the new epithelial cells came from the introduction of a single stem cell.

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mammary gland (6). After transplanting a single cell sorted by markers believed to be exclusive for mammary stem cells into the recipient mice, the authors recovered epithelial outgrowth from the transplanted mice after several weeks.

As seen in Figure 2, the dissected tissue shows the normal structure of the ductal regions. The figure shows not only newly grown mammary glands but also confirms that the tissue originated from the donor. Moreover, sections obtained from pregnant recipient mice were found to produce lipid droplets and milk proteins within alveoli (mammary tubes) and the ductal lumen (fluid-filled interior of the organ). Thus, in addition to forming a histologically normal mammary gland, a single, tiny, transplanted stem cell can reconstitute a complete and functional mammary gland. This striking finding has opened up a new arena for study and has been considered as a potential means of eventually growing new breasts for mastectomy patients.

### From Therapeutic to Cosmetic

Many might wonder whether such findings can lead to alternative breast enhancement treatment for cosmetic purposes. Theoretically, if we can find the markers specific for human breast

stem cells and conduct experiments similar to those done by Shackleton in mice, there is no reason why breast stem cell-based treatment should not be possible in humans in the future.

However, practically, there are still many barriers that need to be overcome. The breast stem cells have to be isolated from the recipients themselves to prevent immuno-rejection. This procedure is very difficult as we cannot randomly dissect a large tissue out of human patients and sort out the stem cell population as was done in mice. More research has to be conducted to first find the specific location where the relevant stem cells reside. In addition, directing stem cells to differentiate along a certain lineage can be more complicated than previously thought as the process requires specific factors and the precise functioning of tightly regulated pathways. Most importantly, the final step would be practically impossible because we would need human recipients to prove whether the single breast stem cell would be able to reconstitute an entire, functional breast. There is still the possibility that injecting stem cells into the body might disrupt several cellular mechanisms and cause aberrant overgrowth, or cancer, which would defeat

the purpose of the transplant.

Sadly, a stem cell treatment will not be regarded as an alternative cosmetic procedure for quite some time. Only after thorough research has been done to ensure the complete safety of the protocol will customized breasts be offered in the clinic. Even then, ethical concerns regarding the use of such a potent medical technology for cosmetic purposes will have to be confronted. Meanwhile, scientists will continue to focus on finding a cure for breast cancer, the number one killer of women among the various forms of cancer. Hopefully, stem cells, small in size yet large in the magnitude of the medical applications they offer, will fulfill their promise for a growing number of women threatened by breast cancer. **H**

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### References

1. Ahmedin J, et al. *CA Cancer J Clin* 55 (2005): 10-30.
2. Reya T, et al. *Nature* 414 (2001): 105-11.
3. Al-Hajj M, et al. *Proc Natl Acad Sci USA*. 100 (2003): 3983-8.
4. Smalley M and Ashworth A. *Nat Rev Cancer*. 3 (2003): 832-44.
5. Blanpain C, et al. *Cell* 118 (2004): 635-48.
6. Shackleton M, et al. *Nature*. 439 (2006): 84-8.