interconnects. The speed of charging and discharging depends on the amount of current that a transistor can provide, which is related to the width and length of the transistor. A well-designed silicon transistor can deliver roughly one milliampere of current per micrometre of width (1 mA μm^{-1}) (see go.nature.com/2z4wjda). By contrast, the typical nanotube transistors used by Hills *et al.* can provide only about 6 $\mu A\ \mu m^{-1}$. This is the main feature that will need improvement in future versions of the computer.

The first step for increasing the electric current is to reduce the transistor-channel length. It has already been demonstrated[2] that the channel lengths of nanotube transistors can be scaled down to 5 nm. The second step is to increase the density of nanotubes in each channel from as little as 10 nanotubes per micrometre to 500 nanotubes per micrometre. For these networks of randomly distributed nanotubes, there might be an upper limit on the achievable density, but a deposition technique has been shown[3] to boost the current in such networks to 1.7 mA μm^{-1}. The third step is to decrease the width of the transistors, and thereby the widths of the source and the drain, which would allow these electrodes to be charged and discharged more quickly[4]. These scaled-down transistors are essential for nanotube-based CMOS technology that operates at gigahertz frequencies[5].

Hills and colleagues' achievement is based on averaging the performances of several nanotubes in each transistor channel. In the large-scale nanotube computer of the distant future, the PMOS and NMOS transistors will contain only one nanotube. These nanotubes will need to be semiconducting: no design trick will provide a workaround if one of the two nanotubes in an inverter is metallic.

The authors' work is a great accomplishment that touches on many research topics — from materials science to processing technology, and from circuit design to electrical testing. However, more effort is required before the team will need a sales department. ■

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TUMOUR BIOLOGY

Cells tagged near an early spread of cancer

Cancer cells that travel to a distant site can prompt the normal neighbouring cells at that location to create a tumour-promoting microenvironment. A tool that identifies these normal cells offers a way to study this process. SEE ARTICLE P.603

MARIE-LIESSE ASSELIN-LABAT

Most types of cancer are lethal after tumour cells have left their primary site of growth and moved to colonize a distant organ through a process termed metastasis. Whether a cancer cell will metastasize is determined not only by the cell itself, but also by the microenvironment of that far-away site called the metastatic niche[1]. Only a small number of the cells that reach such a new location will successfully establish a presence there and proliferate[2]. The early processes that aid cancer-cell growth at secondary locations remain poorly understood, partly because of a scarcity of suitable tools with which to analyse these events. On page 603, Ombrato *et al.*[3] describe an innovative *in vivo* method for identifying and isolating the rare normal cells that are in close contact with cancer cells that have just migrated to a secondary site. This approach should help to clarify the early direct interactions between metastatic cells and neighbouring normal cells that help to shape the formation of a metastatic niche.

Ombrato and colleagues engineered mouse breast cancer cells to express a fluorescent protein containing a region of amino-acid residues that make it permeable to lipids (Fig. 1); this feature enabled the protein to be released from the cancer cell in a soluble form that could be taken up by neighbouring cells. The authors studied a model of metastasis in which mouse breast cancer cells that expressed this protein, plus a different fluorescent protein that could be used to specifically monitor cancer cells, were injected into the mouse tail vein and subsequently colonized the lung.

Analysis of lung tissue revealed that healthy cells located within a distance of five cell layers from cancer cells took up the protein, enabling the specific analysis of healthy cells in close contact with an emerging site of tumour growth. Ombrato *et al.* noted a direct correlation between the number of cancer cells in the lung and the number of neighbouring cells that took up the protein. These neighbouring cells included immune cells, which are known[4] to aid the colonization of the lung by breast cancer cells.

Previous studies have used other techniques to identify cells in the vicinity of malignant tumours, by, for example, tagging the cells that specifically receive vesicles released from tumour cells[5]. The advantage of Ombrato and colleagues' technique is that it offers a way to tag probably any type of cell present in the vicinity of a metastatic site.

The lipid-permeable fluorescent protein is

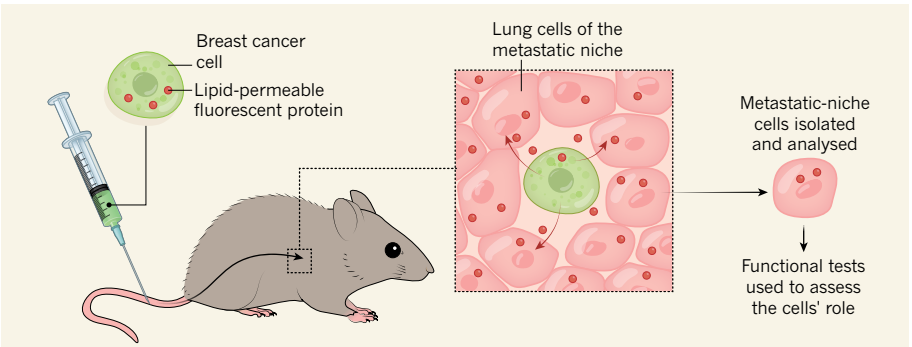

Figure 1 | A tool for identifying healthy cells in the vicinity of cancer cells. Ombrato *et al.*[3] engineered a fluorescent protein to contain amino-acid residues conferring lipid permeability, which enables the protein to enter cells. The authors engineered mouse breast cancer cells to express this protein, and injected the cells into the tail veins of mice. The cancer cells then colonized lung tissue at a site that is termed a metastatic niche. The fluorescent protein released there from tumour cells was taken up by the neighbouring healthy lung cells. The authors carried out direct *in situ* analysis, using approaches such as microscopy, to assess these healthy cells of the metastatic niche. The lung tissue was then removed, and the presence of the lipid-permeable fluorescent protein permitted the isolation and molecular characterization of these cells. This information allowed the authors to carry out functional tests *in vitro* to study how this type of healthy cell affects tumour growth.

stable in recipient cells for only approximately 48 hours. Thus, the authors' method allows an evaluation of the initial changes that occur at metastatic sites through time, but is not suitable for long-term tracking.

Cancer cells can alter their local environment to promote tumour growth through processes such as driving blood-vessel formation to increase nutrient supply, or causing changes that protect the tumour against immune attack[6]. The rare cancer cells that successfully thrive at a distant site usually alter the microenvironment there to promote their growth by, for example, starving normal cells of metabolite molecules to increase nutrient availability[7], or preparing a microenvironment that promotes tumour growth[8,9]. Ombrato and colleagues used their tool to identify and isolate healthy cells for molecular analysis by methods that included RNA sequencing, to track changes that might promote the formation of the metastatic niche.

The authors showed that normal lung cells (of a type called an epithelial cell) that surrounded invading breast cancer cells belonged to a cell lineage known as alveolar type 2 (AT2) cells. Metastasizing cells benefited from this type of microenvironment, as demonstrated by Ombrato and colleagues' observation that cancer cells grown with lung epithelial cells *in vitro* had a high proliferation rate.

The AT2 cells that the authors identified in the vicinity of the invading cancer cells also had characteristics of a comparatively undifferentiated sort of lung cell — a stem cell[10–14]. In the lung, most AT2 cells are fully differentiated, with only a small subset behaving like stem cells[15]. Do these cancer cells prefer to locate near lung stem cells, or do they drive the recruitment of such cells to their vicinity? Alternatively, might the cancer cells drive neighbouring differentiated AT2 cells to take on a stem-cell-like fate?

To investigate these possibilities, Ombrato and colleagues studied cancer cells grown *in vitro* with AT2 cells. This revealed that the presence of the cancer cells boosted the capacity of AT2 cells to act as stem cells and to give rise to various types of differentiated lung cell, compared with AT2 cells grown in the absence of cancer cells.

Future *in vivo* studies combining Ombrato and colleagues' labelling approach with other methods for tracing the lineage of lung stem cells will undoubtedly help to resolve how metastatic breast cancer cells create a microenvironment that nurtures tumour cells in the lung. The observation that breast cancer cells form a metastatic niche near lung stem cells is reminiscent of a previous observation: when prostate cancer cells metastasize to the bone, they settle near stem cells in the bone marrow, which helps to provide an environment that supports tumour growth[16].

Ombrato and colleagues' method holds great promise for addressing why a given type of cancer cell preferentially migrates to a particular initial secondary site, such as the bone marrow or lung. This key question has not been fully answered. Using the authors' technique to study breast cancer cell lines that have distinct organ preferences for their secondary sites[17] should provide insight about the mechanisms underlying such preferences.

It will be important to determine whether the authors' findings in mice are relevant for human cancer. In samples of human lung tissue containing metastatic breast cancer cells, Ombrato *et al.* found that lung epithelial cells neighbouring the tumour expressed a higher level of a protein associated with proliferation than did lung epithelial cells located farther away from the site of tumour invasion. Analyses to understand how this type of dividing cell supports breast cancer growth are essential areas for future studies.

If migrating tumour cells could be prevented from lodging in distant organs, this would have a major positive clinical impact. Because cancer cells often have a high level of genomic alteration, focusing instead on their neighbouring cells, which are genetically more stable, might be an effective strategy for targeting a metastatic niche. The complexity of the microenvironment at such sites, in which components such as immune and non-immune cells affect the settlement of cancer cells, will need to be characterized in depth to test whether manipulation of such regions is a potential therapeutic strategy. Ombrato and colleagues' method provides a crucial way forward for such endeavours. ■

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ARTHRITIS

An immune-cell barrier protects joints

Inflammation and the repair of damaged tissues are regulated by immune cells called macrophages. The finding that they form a layer that shields mouse joints from damage has implications for the treatment of arthritis. SEE LETTER P.670

CHRISTOPHER D. BUCKLEY

Immune cells called macrophages commonly function as scavenger-like (phagocytic) cells that ingest and remove damaged cells. Culemann *et al.*[1] report on page 670 that the macrophages present in joints also fulfil an unexpectedly different role.

Macrophages derive from two main cellular lineages[2]. One lineage arises from bone-marrow-derived immune cells called monocytes. The other lineage is monocyte independent, and is derived from cells that disperse into the tissues during embryonic development[2]. The tissue-resident macrophages in this lineage have distinctive gene-expression profiles[3,4] that depend on the particular tissue in which they reside.

Rheumatoid arthritis is an immune-mediated disease associated with inflammation and the destruction of the cartilage and bone in joints, and macrophages have a key role in the initiation of this condition. However, little is known about the relative contribution of the two lineages of macrophages to the development and function of joints in health and disease. To add to the complexity, macrophages exist as various subsets, some of which are pro-inflammatory, whereas others are anti-inflammatory and aid tissue repair[5].

To study macrophages, the authors began by focusing on a protein called CX3CR1, which is expressed on monocytes and macrophages. The authors engineered CX3CR1-expressing