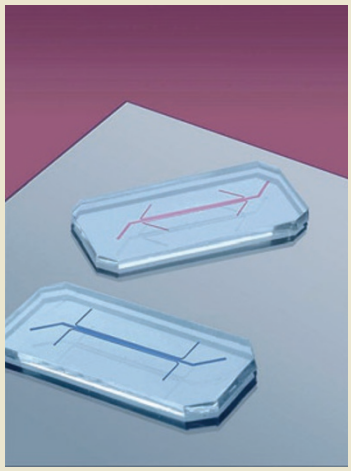
Lung on a chip



Efforts to mimic the alveolar-capillary interface—the fundamental functional unit of the lung—in cell culture have been frustrated primarily by the challenge of replicating the structural and functional properties of the system while simulating the mechanical changes associated with normal breathing. Huh *et al.* recreate the behavior of lung tissue in a microfluidic device by lining a thin (10 μm), porous and flexible membrane with human alveolar epithelial cells on one side and human pulmonary microvascular endothelial cells on the other. Application and release of a vacuum to two flanking chambers causes the membrane with its adherent tissue layers to stretch and then relax to its original size, thus recreating the dynamic mechanical distortion of the alveolar-capillary interface caused by breathing. The device reproduces organ-level responses to bacterial infection and inflammatory cytokines, and its use suggests that mechanical strain can promote nanoparticle-induced toxicity. These findings underscore the potential of the chip for evaluating the safety and efficacy of new drugs for lung disorders, or the effects of environmental toxins. (*Science* **328**, 1662–1668, 2010) *PH*

miRNAs, Dicer and metastasis

MicroRNAs (miRNAs) play a key role in the pathogenesis of cancer. Although the overexpression of individual miRNAs is important in numerous tumors, a global downregulation of miRNA levels is a hallmark of cancer. Martello *et al.* now show that members of the miR-103/107 family suppress the expression of Dicer, the enzyme responsible for the maturation of pre-miRNAs into miRNAs. Levels of miR-103/107 are inversely proportional to Dicer abundance in cancer cell lines and high miR-103/107 expression correlates with metastasis and poor prognosis in breast cancer. In mouse models of breast cancer, nonmetastatic cell lines can be converted to an invasive phenotype by miR-103/107 expression. Therapeutic targeting of the miRNAs with a specific antisense molecule reduces the number of lung metastases, making these miRNAs promising targets for antimetastatic drugs, although no effect on the growth of the primary tumor was observed. The miR-103/107 molecules promote an epithelial-to-mesenchymal transition, a developmental program associated with increased mobility and loss of cell adhesion that is frequently observed in metastatic cancer. (*Cell* **141**, 1195–1207, 2010) *ME*

Written by Kathy Aschheim, Laura DeFrancesco, Markus Elsner, Peter Hare & Craig Mak

Fungal histone acetylation inhibitors

Targeting fungal histone acetylation may provide a new source of drugs against *Candida albicans* infections, a particular problem for immunocompromised individuals, research by Wurtele *et al.* suggests. The authors set out to determine whether a fungal histone acetyltransferase enzyme (RTT109) not found in humans would make a good drug target. The particular modification that the enzyme makes—acetylation of lysine 56 on histone 3 (H3 Lys56)—is found on close to 30% of *C. albicans* histones, whereas only 1% of human histones bear the mark. Knocking out both copies of *RTT109* creates strains with greater sensitivity to certain antifungal agents; repressing the activity of the HST3 deacetylase enzyme led to fungal cell death. The effects were also mirrored by nicotinamide, an inhibitor of NAD-dependent deacetylases. A/J mice, a model particularly sensitive to *C. albicans* infection, which were injected with an HST3-repressed strain of the fungus or an *RTT109*-deleted strain failed to show signs of infection. Once again, nicotinamide treatment mirrored the effects of HST3 repression, but only in strains with wild-type RTT109, suggesting that nicotinamide, which acts as an anti-inflammatory, exerts its effects on infection through its interaction with the histone deacetylase pathway. Finally, the researchers showed that whereas some fungal pathogens are sensitive in various degrees to nicotinamide, all tested clinical isolates of *C. albicans*, the fungus with the greatest impact on human health, were sensitive. (*Nat. Med.* **16**, 774–780, 2010) *LD*

iPS cells from blood

As researchers contemplate clinical applications of induced pluripotent stem (iPS) cells, one practical consideration is the accessibility of the donor cells used for reprogramming. So far, most human iPS cells have been derived from fibroblasts collected through skin biopsies, a procedure that requires an incision and stitches. Following three 2009 papers on the reprogramming of human hematopoietic stem/progenitor cells from cord blood or from adults after mobilization by granulocyte colony stimulating factor, three new studies describe iPS cells from unmobilized adult blood cells. All three groups rely on the standard 'Yamanaka' reprogramming factors (*OCT4*, *SOX2*, *KLF4*, *C-MYC*), but Loh *et al.* and Staerk *et al.* deliver these with retroviruses, whereas Seki *et al.* use the nonintegrating Sendai virus. The latter method appears more efficient, allowing iPSCs to be generated from samples as small as 1 ml. Like keratinocytes from plucked hair (*Nat. Biotechnol.* **26**, 1276–1284, 2008), peripheral blood cells may provide a convenient source of iPS cells in a clinical context. (*Cell Stem Cell* **7**, 15–19; 20–24; 11–14, 2010) *KA*

Antibody therapy for thrombosis

Small-molecule therapeutics, such as aspirin and clopidogrel (Plavix), reduce the risk for heart attack and stroke by inhibiting platelets but at the cost of increased risk for excessive bleeding. Tucker *et al.* demonstrate an alternative strategy in baboons based on reducing platelet counts using neutralizing antibodies. This strategy was tested using a vascular graft model that mimics a damaged blood vessel at risk for thrombosis. Animals with fewer circulating platelets showed less potential for thrombosis in the graft model. Notably, the blood of these animals did not take longer to clot after cutting the animals' forearm, whereas aspirin treatment led to a statistically significant increase in bleeding time. Tucker *et al.* reduced platelet counts by treating animals with serum containing polyclonal neutralizing antibodies raised in baboons against thrombopoietin, a hormone essential for platelet production. Drugs that can be safely used to inhibit platelet production will be required before this strategy can be tested in humans. (*Sci. Transl. Med.* **2**, 37ra45, 2010) *CM*