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The creation of artificial lungs from decellularized tissue

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Lung failure is a major health problem, both in genetic disorders such as cystic fibrosis and following environmental insults in diseases such as emphysema and idiopathic pulmonary fibrosis. The restricted availability of histocompatible human lungs for transplantation is often a rate limiting factor for treatment. Transplanting both lungs increases patient long-term survival, but the shortage of lungs makes this controversial since it halves the number of recipients. This problem would be solved by being able to create two lungs for each patient. Lung transplantation is further complicated by chronic transplant rejection; after receiving a transplant a patient must be on immune-suppressing drugs for the rest of their lives even after tissue matching. This long-term immunosuppression has significant side effects and allows only <20% of recipients to survive more than 10 years after transplantation. We will avoid both immunological and availability problems by using a patient's own bronchial epithelial and endothelial cells to create two lungs. Previous approaches to populating decellularized lungs with bronchial epithelial and endothelial cells have met with only limited success. The introduced cells differentiated rapidly, producing only small foci of normal appearing alveolar or conducting airway histology, widely separated from other foci containing capillaries. We are overcoming these limitations by a variety of interventions to temporarily block differentiation and stimulate both proliferation and migration. Some of these approaches use chemical reagents, while others exploit oncogenes. A large number of oncogenes are known to block differentiation and stimulate both migration and proliferation. In preliminary experiments, we are introducing them and simply analyzing their effects on colonization of the decellularized lungs. In later experiments, these oncogenes will be under the control of inducible promoters or in Cre-lox excisable constructs. All constructs will contain herpes-virus TK suicide cassettes, so that any cells that escaped excision by Cre-lox could still be eliminated by treatment with ganciclovir if they began to proliferate excessively. Ultimately, we hope to be able to create transplantable lungs on demand for specific patients from their own stem cells, thus avoiding any need for ongoing immunosuppression.