生醫材料

導論

Tissue engineering technology on regenerative medicine”

"從生醫材料到組織工程"

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手寫生醫材料的定義是什麼（有3個、如

Definition of Biomaterials

Biomedical materials/ Bio-materials

- A biomaterial is a nonviable material used in a medical device, intended to interact with biological systems.

  Williams, 1987

- A material intended to interface with biological system to evaluate, treat, augment or replace any tissue, organ or function of the body*.

The major difference of biomaterials from other classes of materials is their ability to remain in a biological environment without damaging the surroundings and without getting damaged in that process.

* Williams, D.F. The Williams dictionary of Biomaterials. Liverpool: Liverpool University Press, 1999.

Definition of Biomaterials

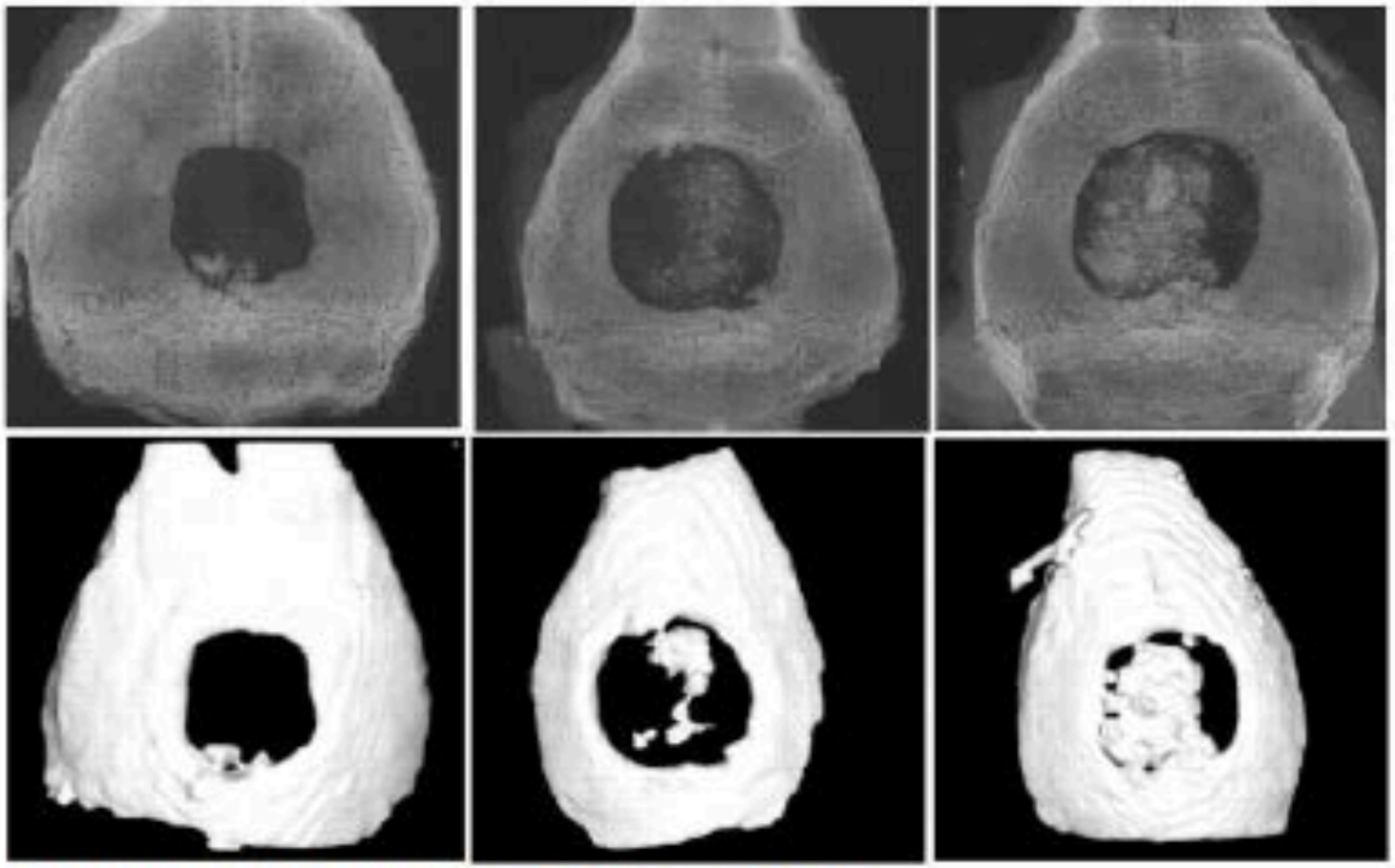
- Biomaterials

Can be defined as any material used to make devices to replace a part or a function of the body in a safe, reliable, economic, and physiologically acceptable manner.

Hill (1998). Copyright © 1998,Wiley Chap 1, INTRODUCTION

The compelling human side to biomaterials is that millions of lives are saved, and the quality of life is improved for millions more.

Bone regeneration



J of Biological Chemistry (2007), 282, 30938-48.

HAP **HAP +cells**

Biomaterial vs Tissue Engineering

History review

組織/器官交換

古埃及

獅身人面像/Sphinx

嵌合體

Chimera

骨移植

1265 Early Arabic Medicine - Used fish bone as spinal fusion

1668 Myth Meekeren - A piece of bone from a dog's skull bone was replaced in a cranial defect of nobleman

牙齒移植– **mid-1700s**

Transplanted tooth may carry tuberculosis

History review

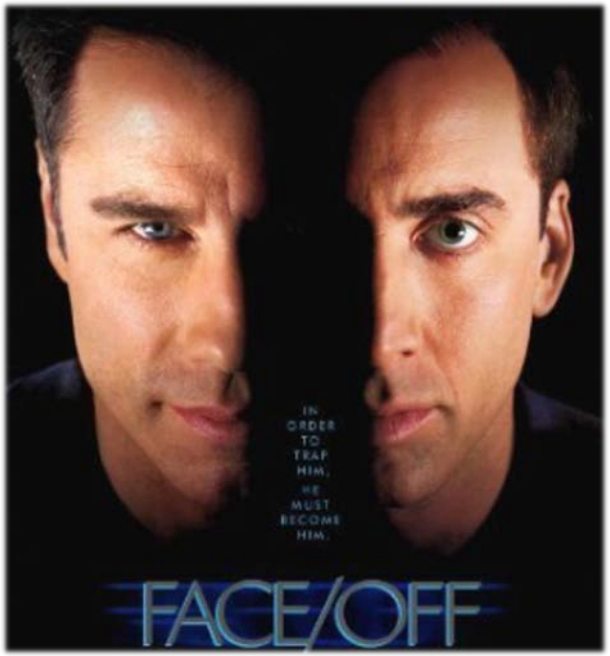
近年組織/器官交換移植

- **Kidney** - Attempted during 1940s and 1950s. Failed due to rejection.
  - Dr. Joseph Murray performed the first successful kidney transplantation between identical twin boys.
    Nobel Prize in 1990.
- **Liver**
  - First attempt in humans in 1963.
- **Lung**
  - First attempt in humans in 1963.
    Invention of the heart-lung machine
- **Bone marrow**, i.e., hematopoietic stem cell transplantation
- **Heart**

-First human-to-human heart transplantation was performed in 1967.

Face off

變臉



1997

https://www.youtube.com/watch?v=HORKG_I3-3Y

臉部移植

自由時報 Liberty Times Net
即時 政治 社會 生活 國際 地方 人物 蒐奇 影音 財經 娛樂 寵伴 NEW
汽車 時尚 體育 3C 評論 玩咖 食譜 健康 地產 專區 TAIPEI TIMES

臉部移植擁新人生 要先克服心理、身體排斥

讚 LINE

2019-01-09

〔記者方志賢、林惠琴／綜合報導〕高雄醫大附醫獲衛福部核可，將進行台灣第一例臉部移植手術。即將主刀的高醫外科部主任郭耀仁表示，變臉可望帶來新人生，但患者不僅心理需要調適，更要克服身體排斥問題。

高醫外科部主任郭耀仁（左一）帶著變臉團隊成員進行大體演練。（郭耀仁提供）

郭耀仁二○○八年擔任高雄長庚整形外科主任時，完成全球醫學文獻首例的迷你豬變臉手術，為小黑豬換上白臉、棕色豬換了黑臉；但迷你豬變臉後存活五、六週，也因排斥喪命。

郭耀仁說，臉部移植術後第一年發生急性排斥機會很高，但經高劑量免疫抑制治療，大都可控制。其他的併發症包含感染、代謝功能失調，還有五位接受移植手術的病患因癌症過世，包含淋巴癌、皮膚癌等。

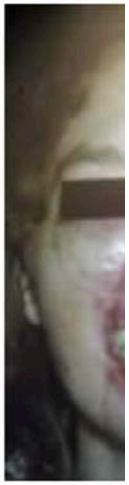
手術時間逾一天 最大挑戰

林口長庚醫院整形外傷科主任林承弘也表示，相較於一般器官移植是單一組織移植，臉部移植涉及皮膚、骨頭、神經、血管等，範圍較廣，尤其臉部又有口腔黏膜，免疫排斥性也會較高。

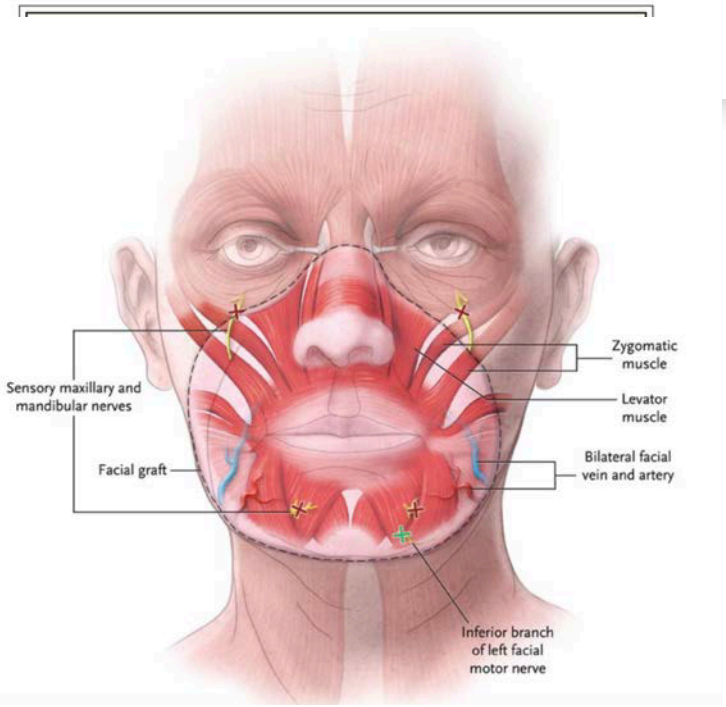
https://news.ltn.com.tw/news/life/paper/1259946

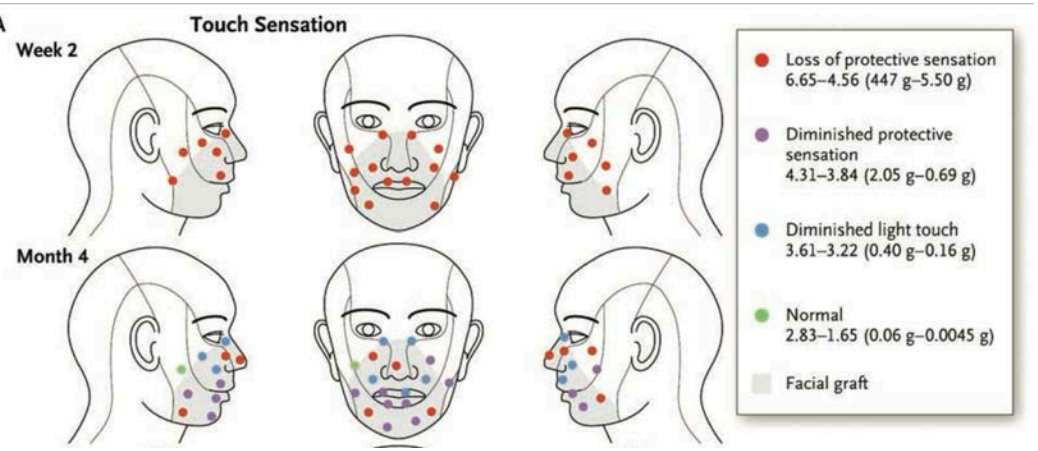
全球第一個接受臉部異體移植手術的人 (face allograft)

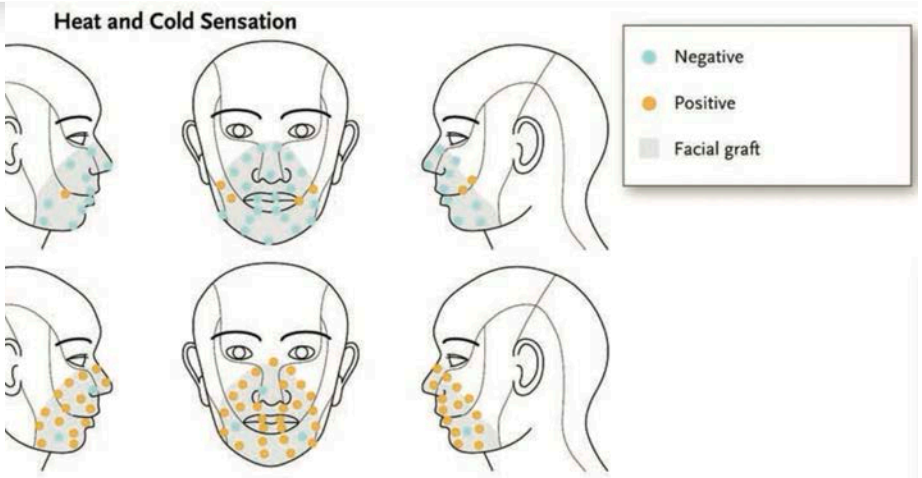
法國女子 Isabelle Dinoire

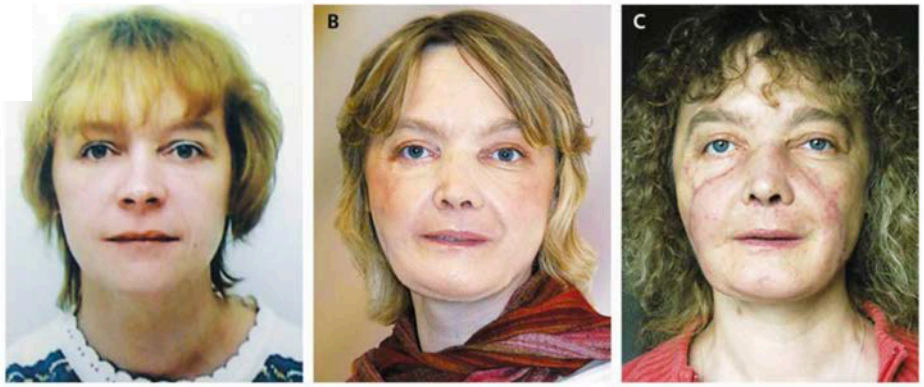


The NEW ENGLAND JOURNAL of MEDICINE









1 year

1.5 year

December 13, 2007
N Engl J Med 2007; 357:2451-2460
DOI: 10.1056/NEJMoa072828

From Hôpital Edouard Herriot, Université Lyon 1, Centaure Network, Lyon, France (J.-M.D., E.M., L.B., J.-L.B., J.K., A.E.J., P.P., N.L., A.S., D.B., P.G., G.B., O.H., M.M., X.M.); Catholic University of Louvain, Brussels (B.L.); University Hospital, Amiens, France (S.T., C.M., S.D., C.D., F.T.,

Organ shortage

- 自體移植（Autologous）

  - Patient's own tissue; immune acceptable

- 異體移植（Allogeneic）

  - Tissues from other human sources; may require engineering immune acceptance

- 異種移植（Xenogeneic）

  - Tissues from a different species; problematic immune acceptance and potential animal virus transmission.

Why need Tissue engineering/regeneration

- organ shortages
- Biomaterials has no biological function

為何需要發展組織工程

- 缺發可移植之組織器官，以人工方式產生可替代性之組織器官
- 生醫材料不具有生物功能

Tissue Engineering

1991

Cima/Vacanti/Langer:

Chondrocytes in a PGA scaffold;

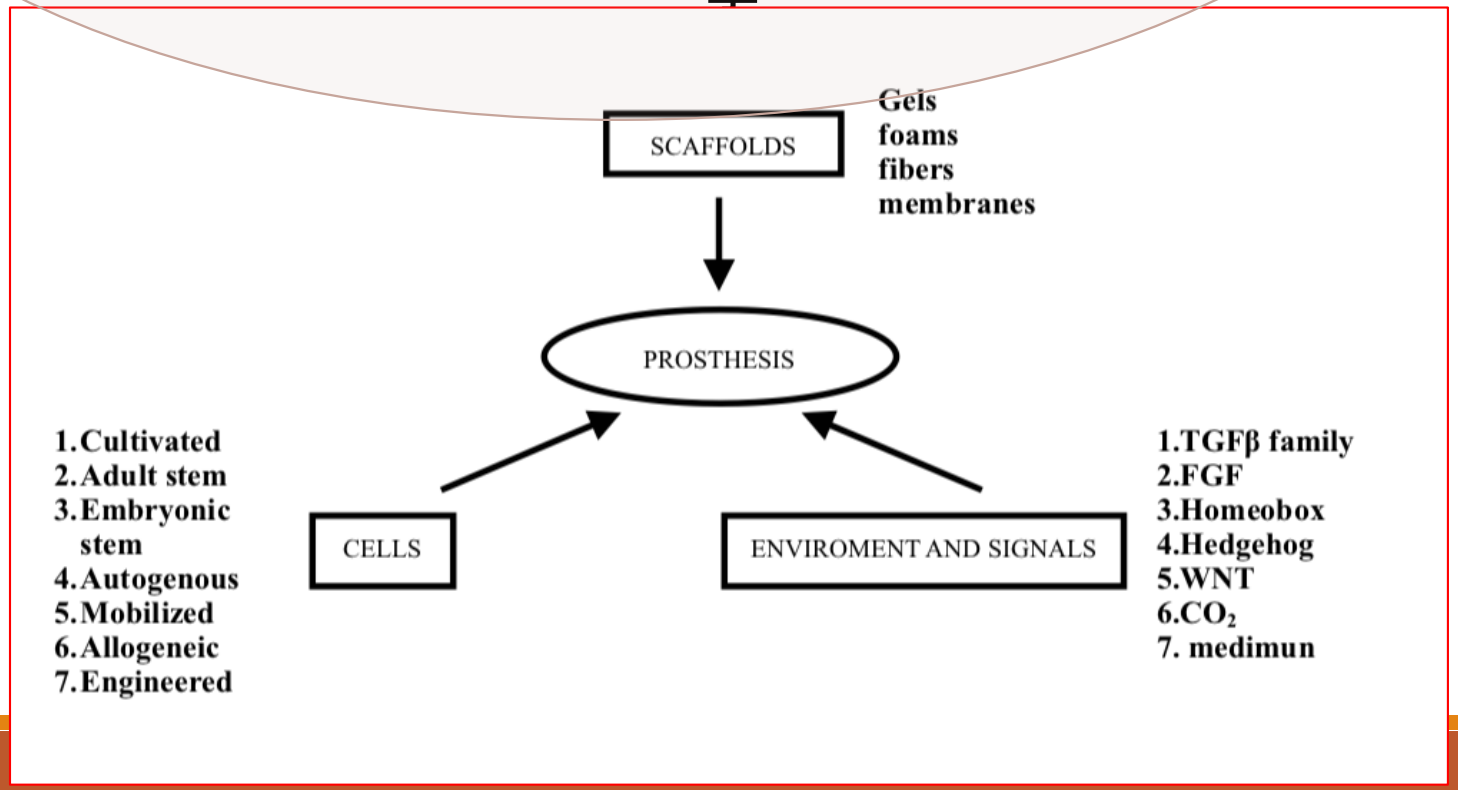
the ear on the nude mouse

組織工程三要素 (Tri-aids)

- Scaffolds or matrix (支架或基質)
- Cells (細胞)
- Signals (訊號)

生長因子/細胞激素/

物理性刺激:組織受力/壓力/流體力學



The Tissue Engineering Triad

The key process occurring during the *in vitro* and *in vivo* phases of tissue formation and maturation are:

1. Cell **proliferation**, sorting and differentiation
2. **Extracellular matrix production** and organization
3. **Degradation** of the scaffold.
4. **Remodeling** and potentially growth of the tissue

組織工程三要素 (Tri-aids)

The 1st phase

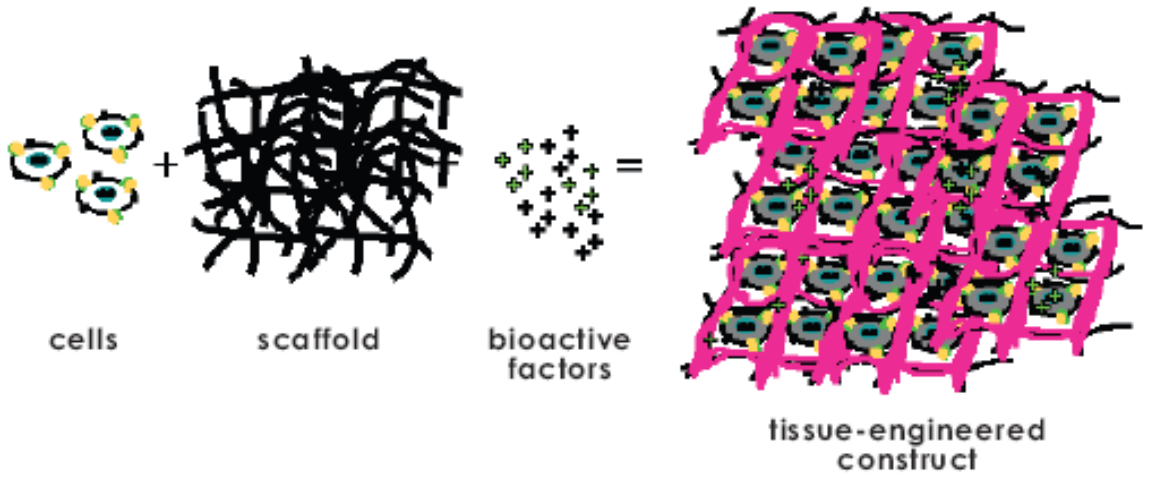
通過將選定的細胞和支架置於具有生長培養基的代謝和機械支持環境中，在體外形成組織結構，細胞在其中增殖並形成細胞外基質。

In vitro **formation of a tissue construct by placing the chosen cells and scaffold in a metabolically and mechanically supportive environment with growth media, in which the cells proliferate and elaborate extracellular matrix.**

The 2nd phase

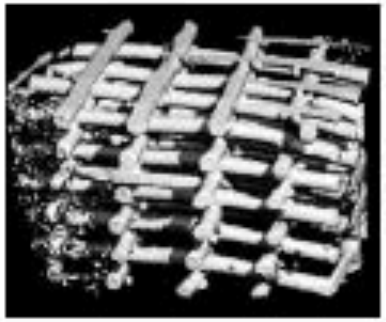
該構建體被植入適當的解剖位置，其中體內重塑旨在概括器官或組織的正常功能結構。

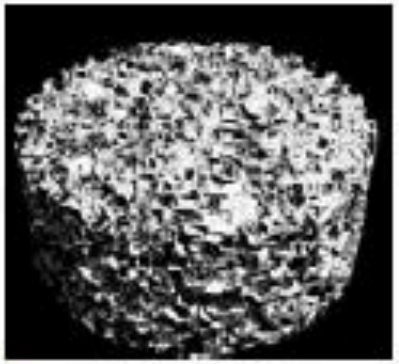
The construct is implanted in the appropriate anatomic location, where remodeling *in vivo* is intended to recapitulate the normal functional architecture of an organ or tissue .

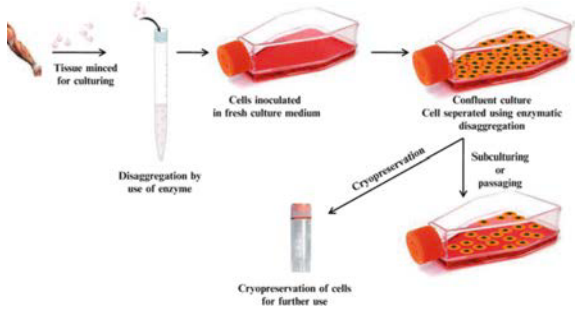


Scaffolds

- Biomaterial scaffolds materials:
  - **Polymeric**
    - *chitosan, alginate, etc.*
    - *foams, hydrogels, fibres, thin films*
  - **Natural**
    - *collagen, elastin, fibrin, etc.*
    - *hydrogels*
  - **Ceramic**
    - *calcium phosphate based for bone tissue engineering*
    - *porous structures*
- Permanent versus resorbable
  - *degradation typically by hydrolysis*
  - *must match degradation rate with tissue growth*





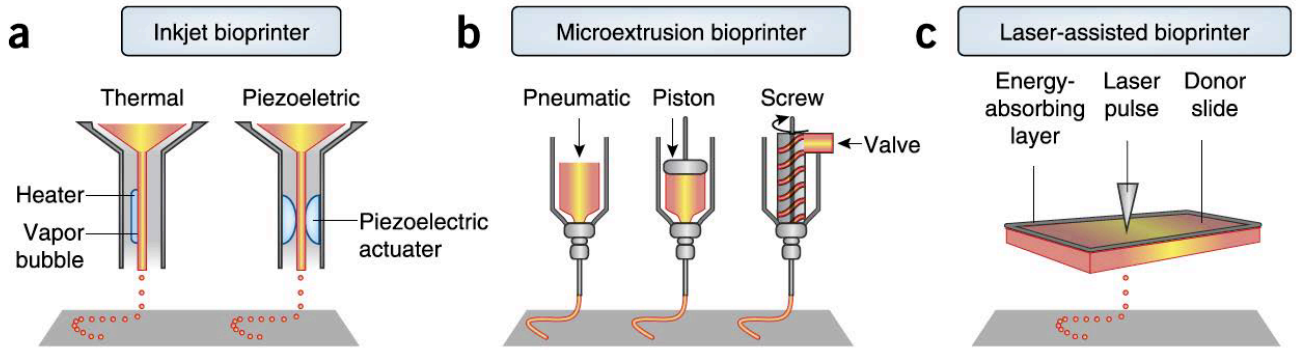


Nature Materials 4, 518 - 524 (2005)

Scaffolds

3D 列印支架與組織再生

- **3D Printing promises to produce complex biomedical devices according to computer design using patient-specific anatomical data.**

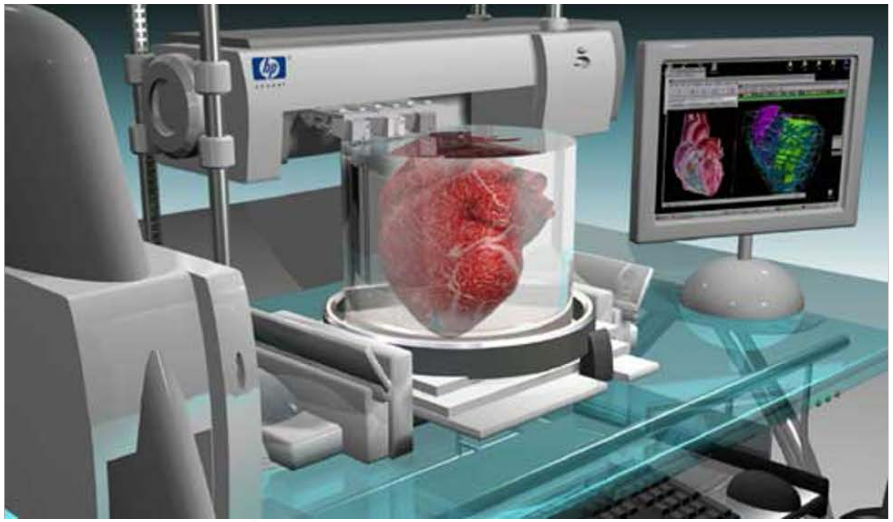


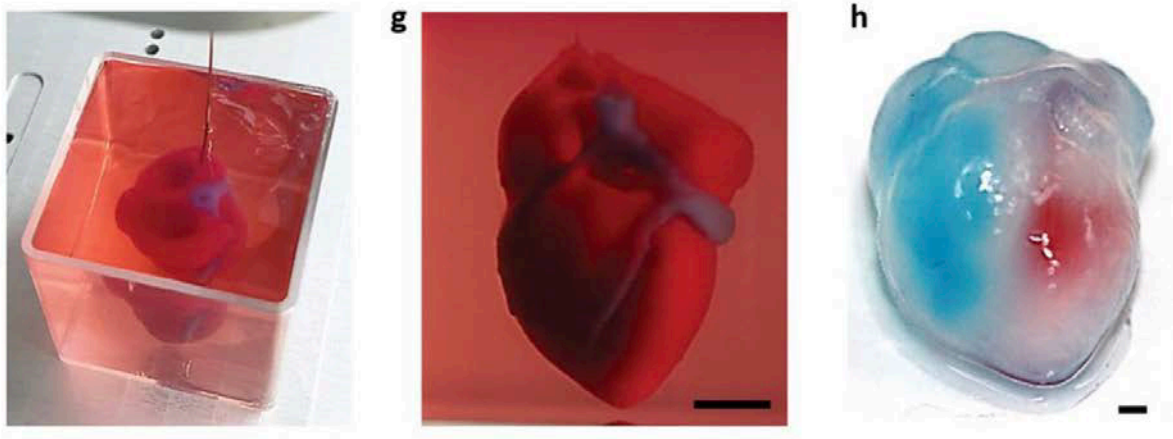
Journal of Biological Engineering (2015) 9:4

Scaffolds

3D 列印支架與組織再生

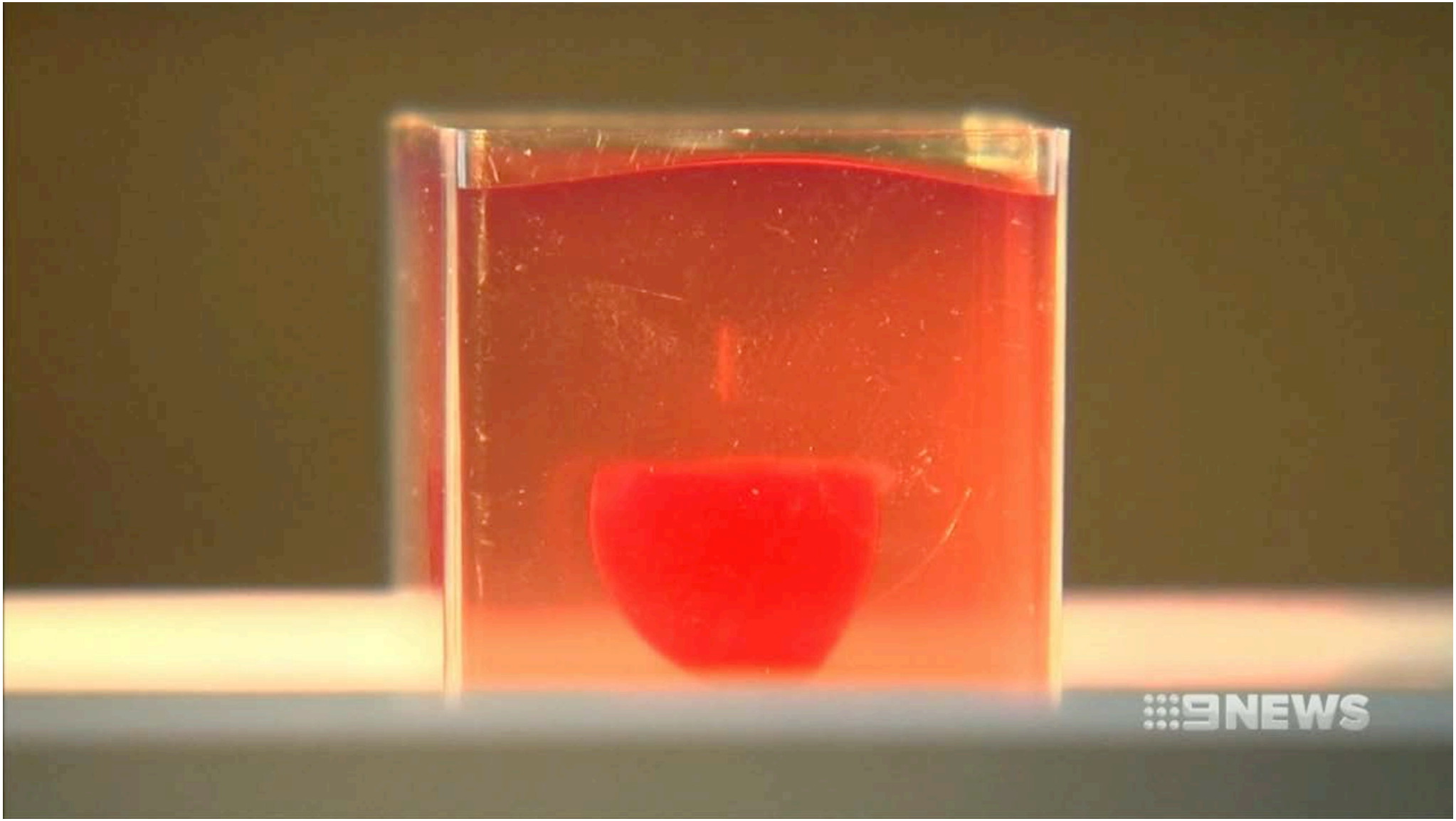
- Integrating biology and 3D printing technology
- A process where an artificial organ can be created using a 3D printer





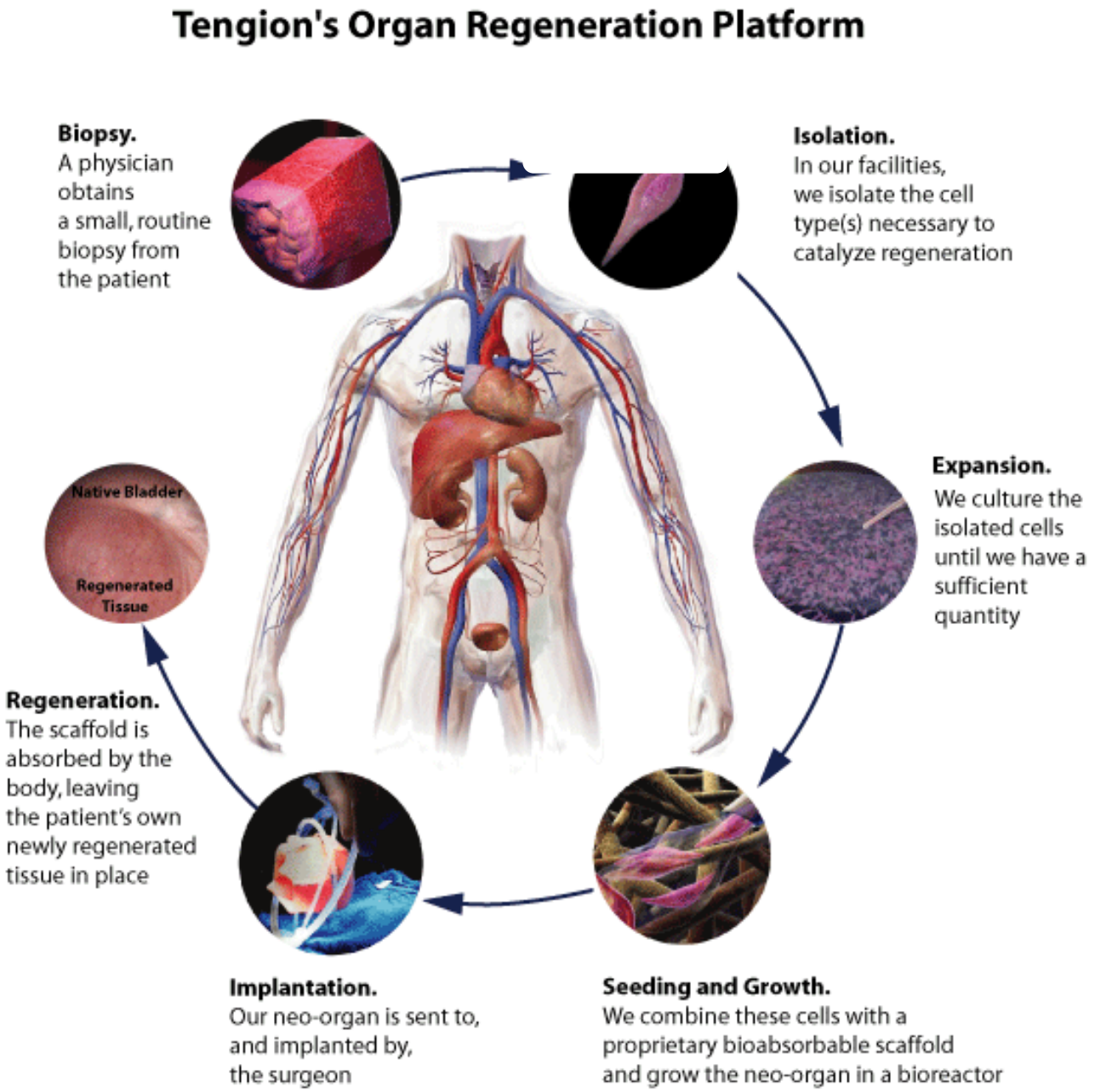
3D Printed Heart Using Human Tissue

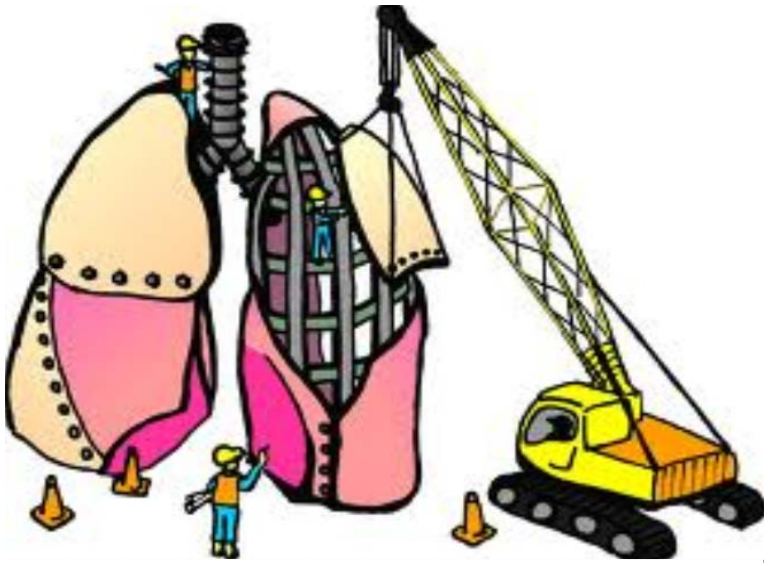
https://www.sciencealert.com/researchers-have-just-3d-printed-a-mini-heart-using-human-tissue


9NEWS

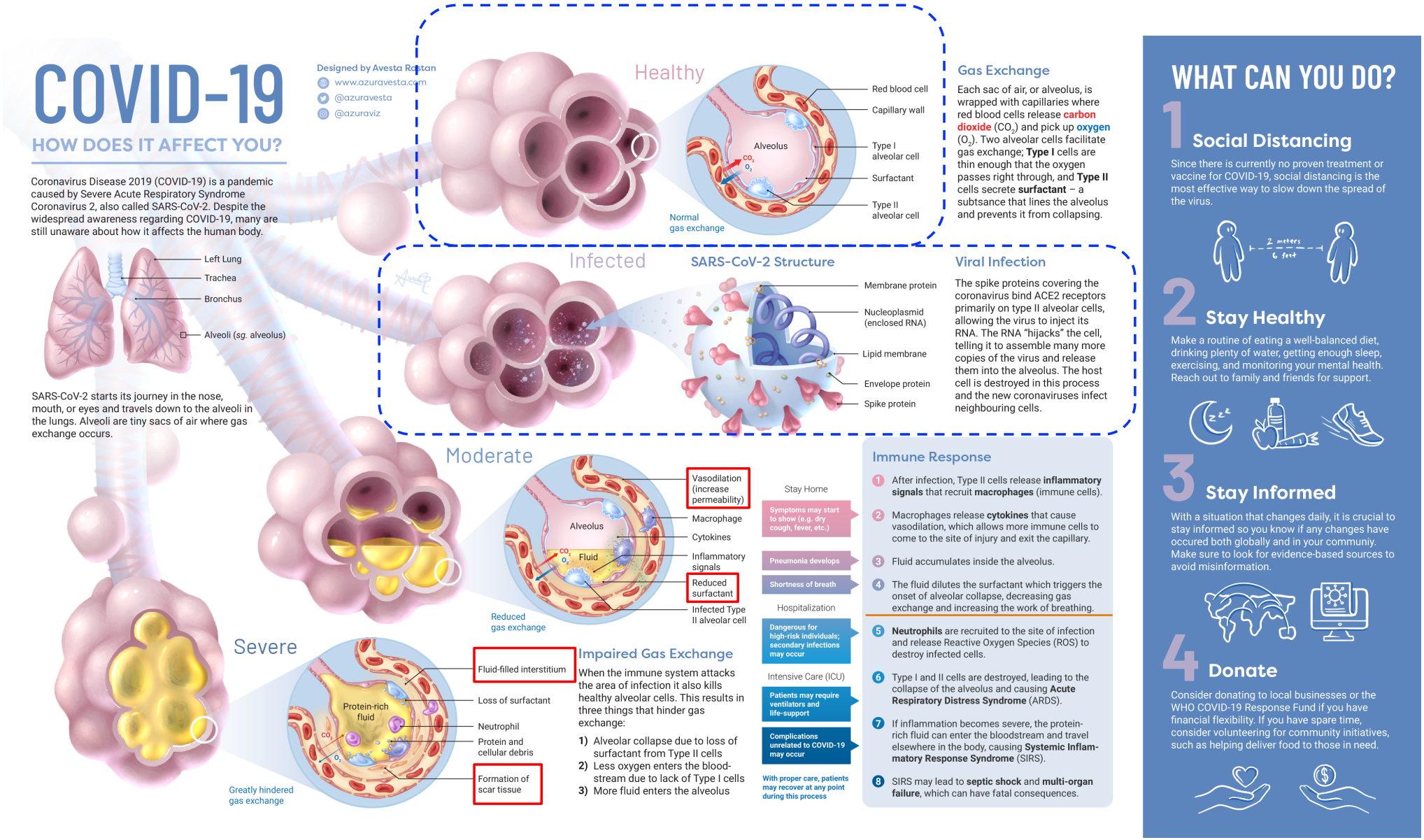
Regenerative medicine

http://www.tengion.com/technology/platform_large.html





Lung regeneration



Acute respiratory distress syndrome (ARDS) 急性呼吸窘迫症候群

High-altitude pulmonary edema (HAPE) 高山肺水腫

https://www.visualcapitalist.com/visualizing-what-covid-19-does-to-your-body/

Lung transplantation

- **Lung transplantation remains the only treatment option for many patients with end-stage lung disease.**

  - ***Chronic obstructive pulmonary disease (COPD)*** *慢性阻塞性肺病*
  - ***Congenital lung hypoplasia.*** *先天性肺發育不全*
  - ***Pneumoconiosis****肺塵症*, **emphysema** *肺氣腫*

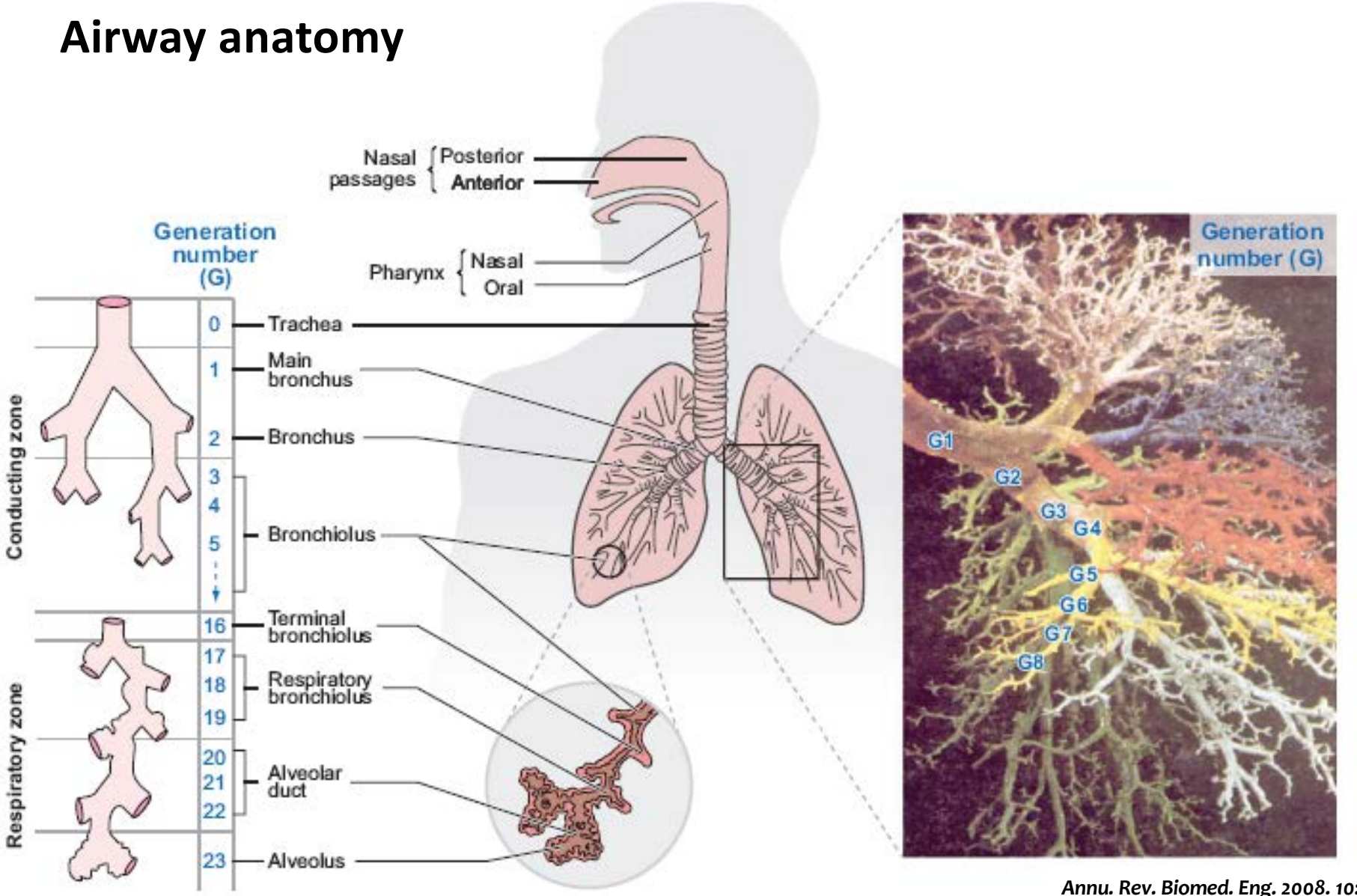
- **A shortage of available healthy donor lungs limits the reach of this treatment option and continues to leave numerous patients on the donor lung waitlist each year. (cadaveric donors)**

  More than 10% mortality of the waitlist

- **Chronic rejection of the allograft remains a secondary issue requiring long-term immunosuppression and the associated risks.**

Lung structure

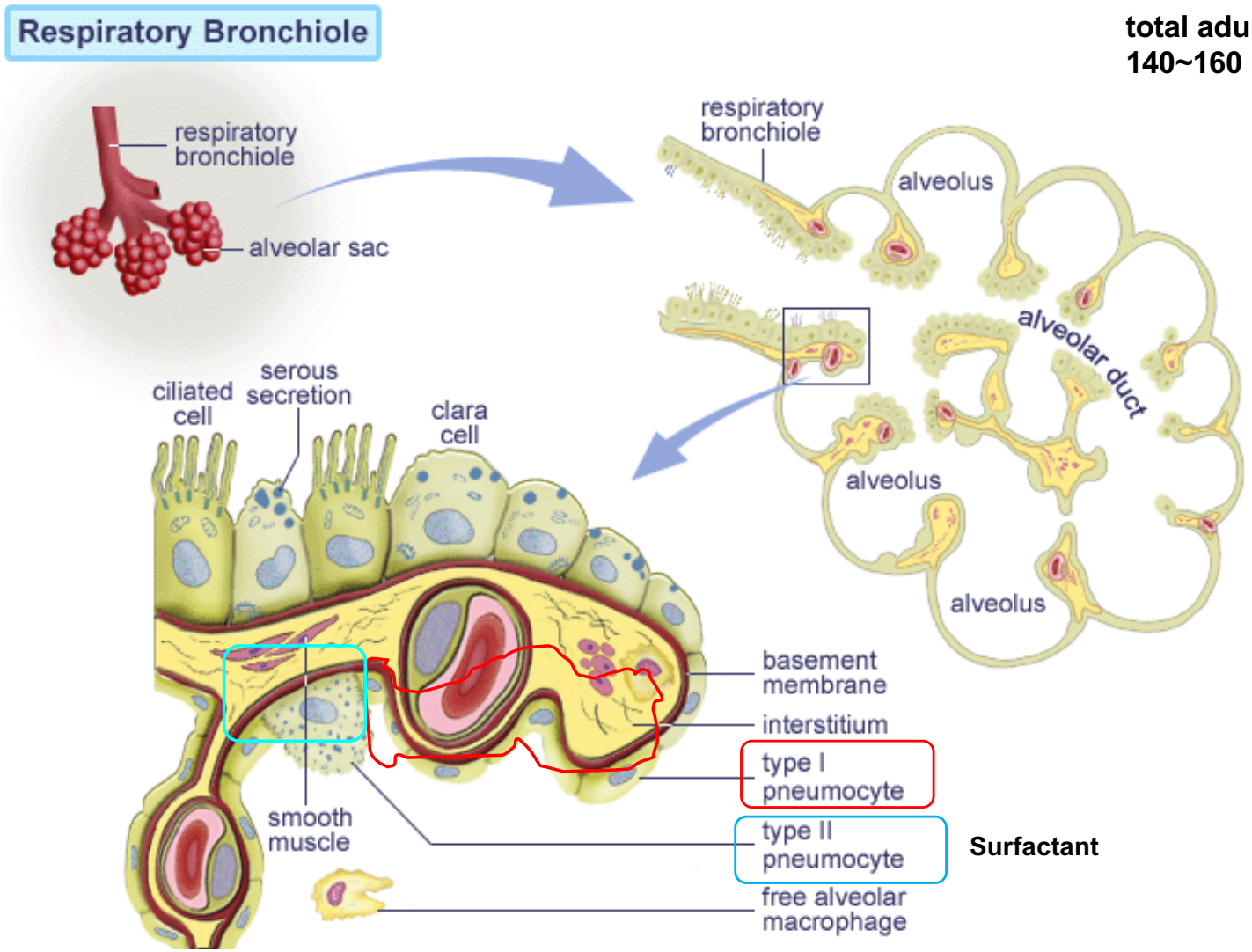
Airway anatomy



Annu. Rev. Biomed. Eng. 2008. 10:195–220
Targeted Drug-Aerosol Delivery

Lung structure

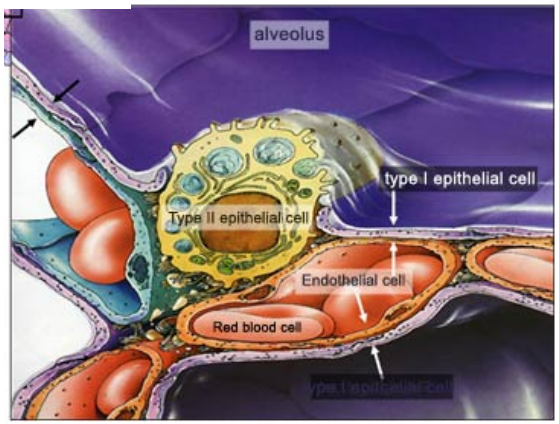
At the alveolar sac level, the total adult alveolar surface : 140~160 m^2



Surfactant

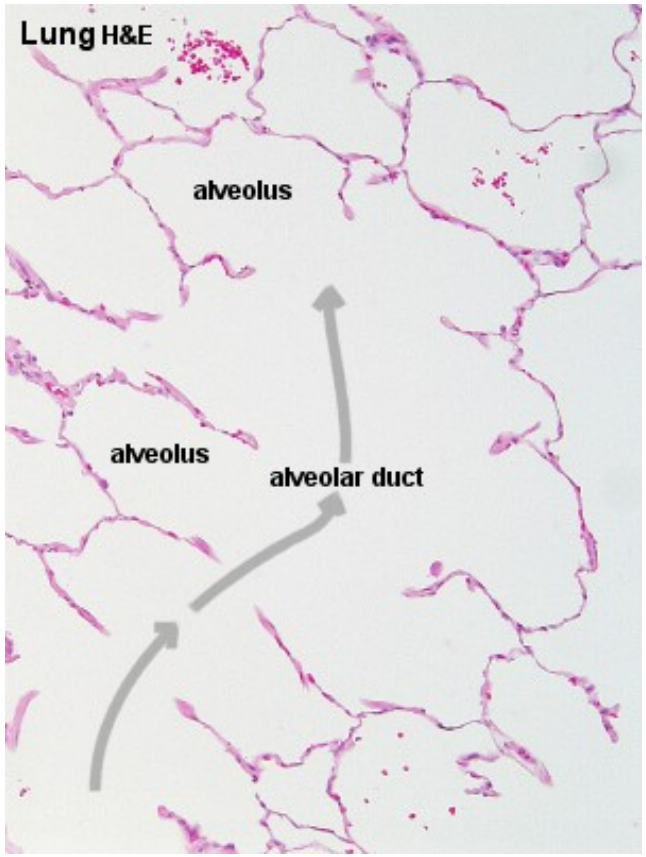
Towards the lower airways, the epithelium of the lung diminishes to a thickness of 0.1~0.4 μm in the alveoli

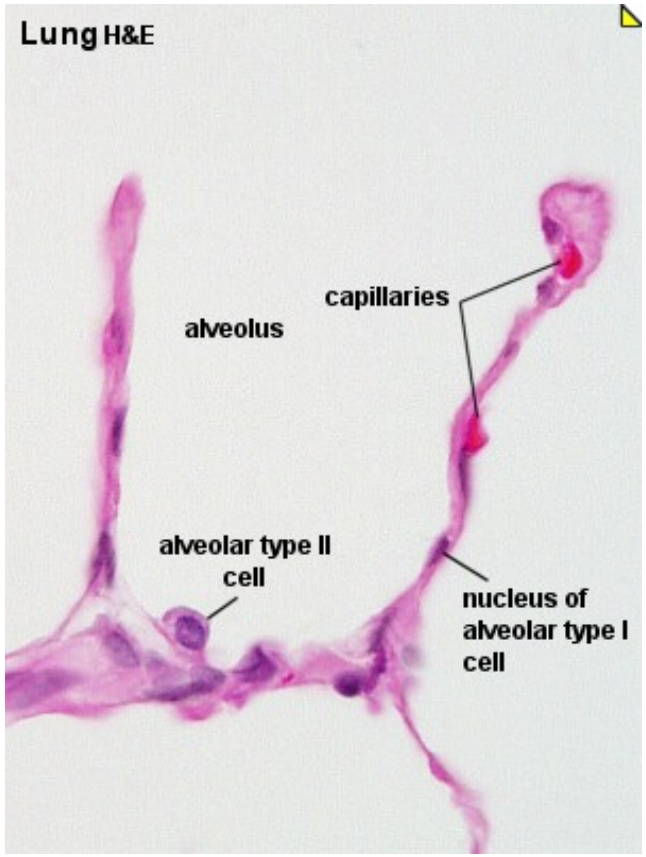
The air-blood barrier

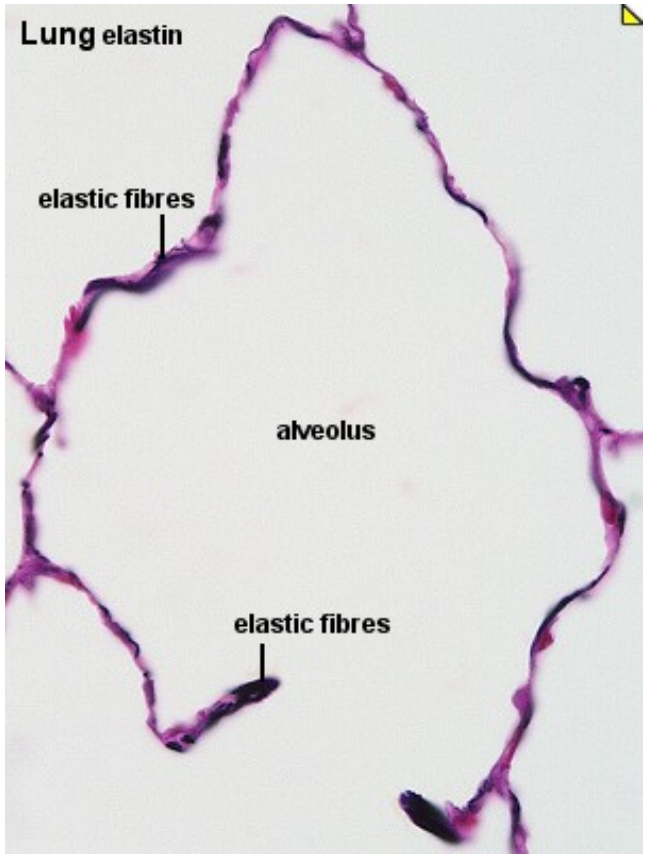


http://www.mmi.mcgill.ca/mmimediasampler2002/images/mckee-26no2.gif

Lung structure

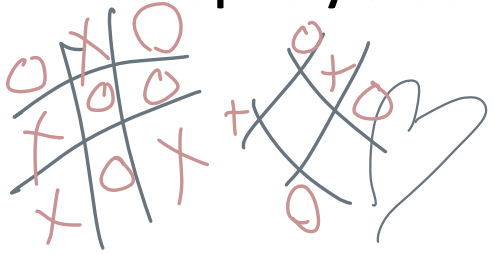






- **The alveolar wall consists of a narrow connective tissue core that contains:**
  - Fibroblasts
  - Myofibroblasts
  - Capillary endothelial cells
  - Extracellular matrix (ECM) components, such as elastin

- **The alveolar epithelium itself is made up of two cell types:**
  - **Type I pneumocytes: flattened cells, together with the capillary endothelium form the actual gas–blood exchange barrier.**
  - **Type II pneumocytes: cuboidal type II cells**

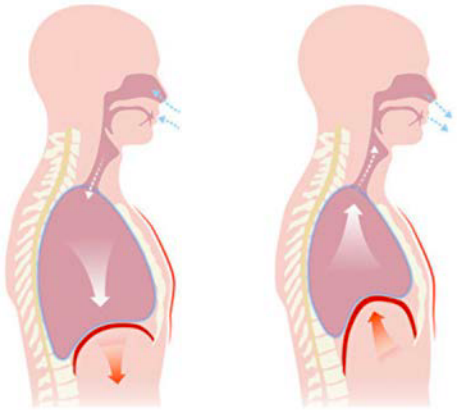


- **Alveolar type I cells comprise about 90% of the surface epithelial layer, with the rest of the surface (10%) made up of the more cuboidal type II cells.**

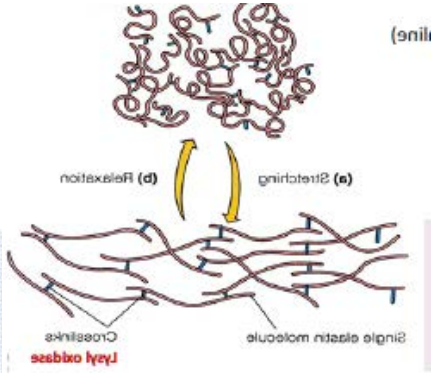
The definition of what is engineered lung can be

- **as simple as replication of the distal lung epithelia or**
- **as complex as the development of fully functional replacement tissues that include both distal lung and branching airways.**

Alveolar-capillary membrane



https://www.epochtimes.com/b5/20/12/2/n12591806.htm



alveolus

gas-liquid interface P_{O2}

alveolar epithelium

ECM scaffold

cyclic stretch

capillary endothelium

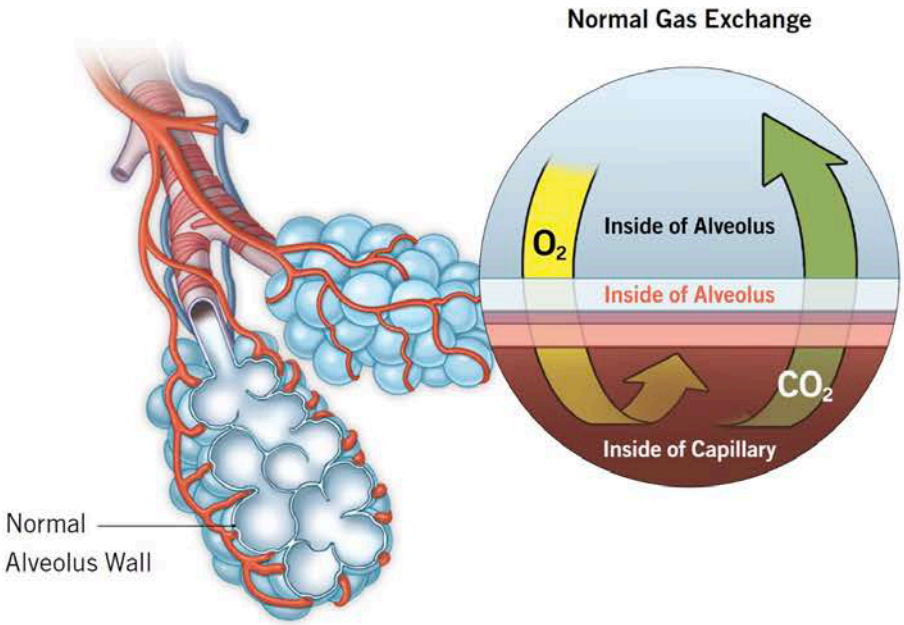
shear stress

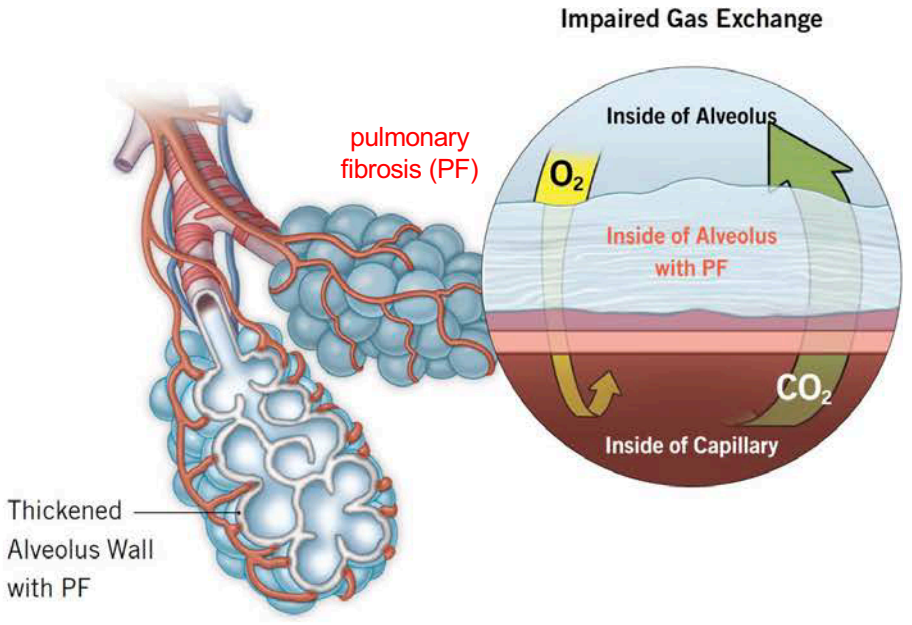
capillary

inspiration/ expiration

Lung fibrosis

Pulmonary fibrosis (PF) means scarring in the lungs





https://www.pulmonaryfibrosis.org/images/default-source/default-album/normal-and-impaired-gas-exchange.png?sfvrsn=c3b0918d_0

Normal lung

Scarring in the lung

Bioengineered Lung

The main components for the lung tissue engineering are:

(1) A suitable biological or synthetic three-dimensional (3D) scaffold

(2) Source cells (stem cells, proginetic cells)

(3) Growth factors required to drive cell differentiation and proliferation

(4) Bioreactor, a system that supports a 3D composite biologically active

Lung is a highly complex organ comprising diverse cell types derived from each of germ layers (ectoderm, mesoderm, or endoderm) of early embryo and geometric structure.

To be functional *in vivo*,

An engineered lung should

- Contain lung-specific cells
- Display the branching geometry of the airways and contain a perfusing microvasculature
- Provide barrier function to separate blood from air
- Have mechanical properties that allow ventilation at physiological pressures.

Difficulty to lung reparative or Regenerative

- **Highly complex structure**
- **Wide range of cellular diversity**
- **Pulmonary epithelium slow turnover rates**

In vitro

- **Pharmaceutical screening**
- **Models for lung development**
- **Characterization of mechanical injury**

Human lung epithelium model being tested as a platform for COVID-19 research

The developers of the lung epithelium model plan to investigate whether SARS-CoV-2 can infect and replicate in the model to assess whether it could be used in the fight against COVID-19.

https://www.drugtargetreview.com/news/59771/human-lung-epithelium-model-being-tested-as-a-platform-for-covid-19-research/

Cell source for development of engineered lung tissue

There are two approaches using progenitor cell populations to promote the growth of functional complex tissue that could be used to provide for this cellular diversity:

(1) The use of mixtures of unipotent somatic progenitor cells, each giving rise to an array of lung-specific single-cell lineages, fetal lung cells.

(2) The use of multipotent cells such embryonic stem cells or fetal lung tissue capable of differentiating into progeny with multiple differentiation phenotypes

Support scaffold for engineering lung

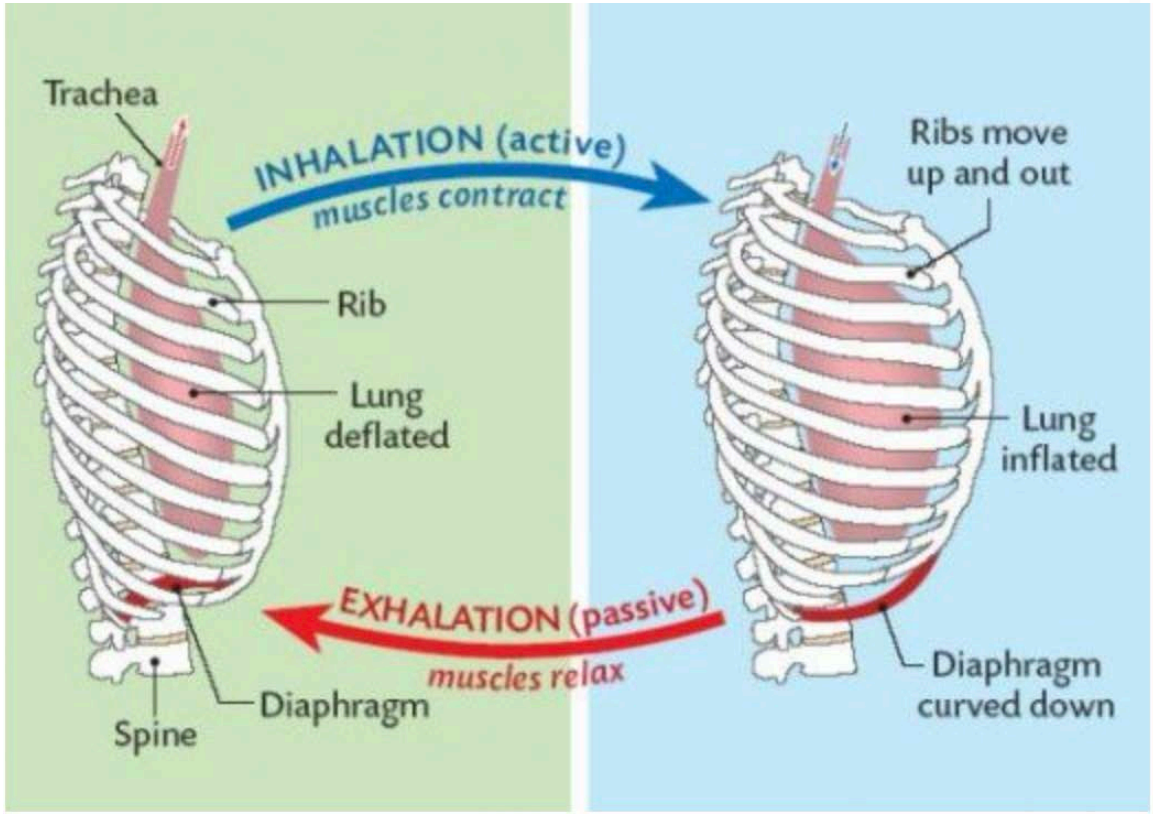
- Practices are biocompatibility of the material and ability to provide for 3D development of tissues
- Of critical importance in scaffold selection for development of lung tissue is the elasticity as well as the adsorption kinetics of the material used.
- For development of lung tissue, the scaffolding must remain long enough to provide the framework necessary to support cell growth and tissue development without impeding the elasticity or altering the elastic recoil of the engineered tissue
- If the biomaterial used is not as elastic as normal lung tissue, it will contribute to the restrictive condition similar to the disease process caused by the restrictive scar tissue formation seen in patients with idiopathic pulmonary fibrosis (特發性肺纖維化)or sarcoidosis (結節).

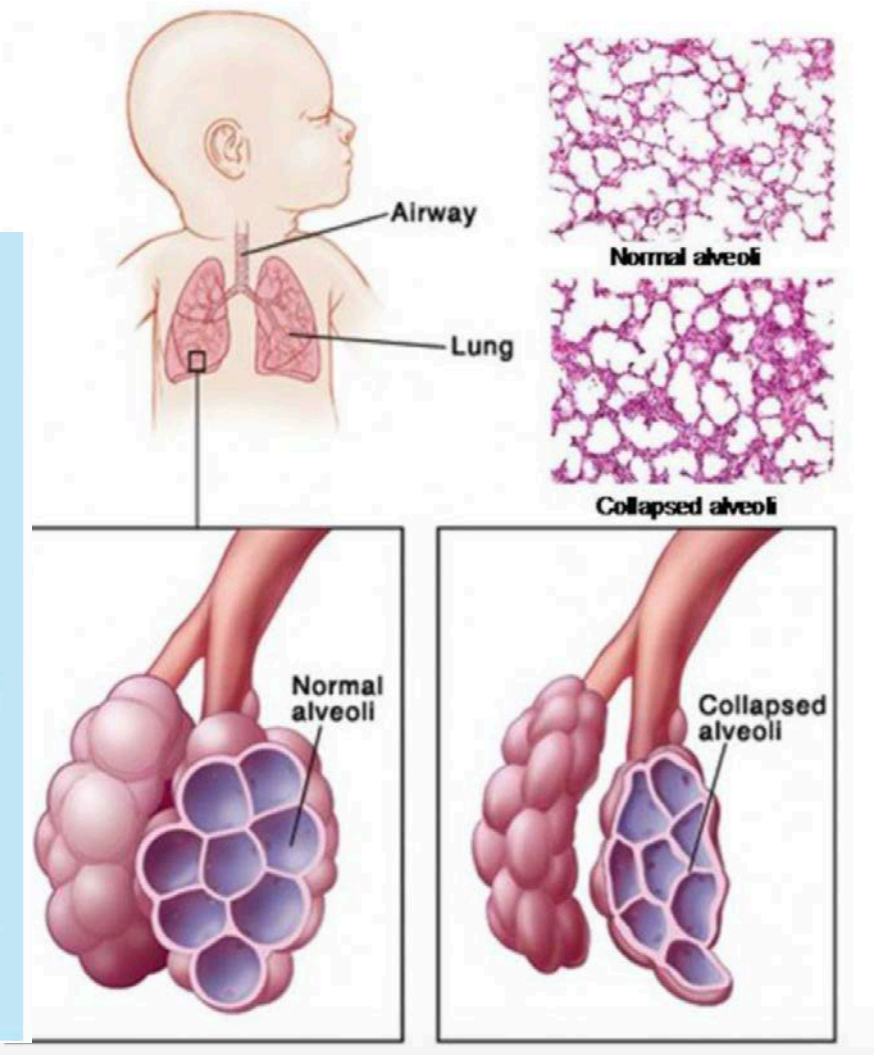
Support scaffold for engineering lung

- Porosity of the scaffold is also a consideration.
- Materials that contain interconnected micropores with geometry supporting movement of nutrients into the tissues and waste removal away from tissues are essential.
- The scaffold must also provide sufficient cell surface area to support cell seeding and movement of cells within the scaffold with subsequent cell attachment, while at the same time allowing for the interactions of cells in three dimensions that promote appropriate cell-to-cell signaling.
- The nature of complex organs such as the lung may eventually require the development of hybrid scaffolds formed from more than one material to provide all of the above scaffold requirements.

Compliance and Elastance

順從性　　彈性





https://owlcation.com/stem/Lung-Compliance-and-Elastance

Elastance = 1/Compliance = Pressure change / Volume change

Adipose Stromal Cells Improves Surgical Outcome for Pulmonary Emphysema（肺氣腫）

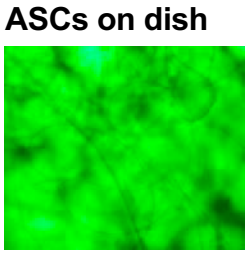
- Adipose tissue has been traditionally used in thoracic surgery settings as a reinforcing material for damaged lungs.
- Reported to contain an ample source of pluripotent cells, such as hematopoietic progenitors and spare mesodermal stem cells, which will differentiate into osteogenic, chondrogenic, myogenic, and neurogenic lineages.
- Adipose tissue–derived stromal cells (ASCs) were suggested to secrete multiple angiogenic growth factors, including hepatocyte growth factor (HGF)
- In lung, HGF is an important regenerative factor generated after a lung injury, it's an essential ligand to elicit lung repair and growth *in vitro* and *in vivo*.
- ASCs were seeded and cultured on a polyglycolic acid felt sheet (PGAF)

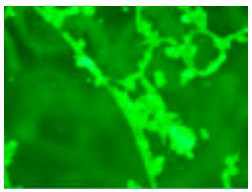
Adipose Stromal Cells Improves Surgical Outcome for Pulmonary Emphysema

Lung volume reduction surgery (LVRS)

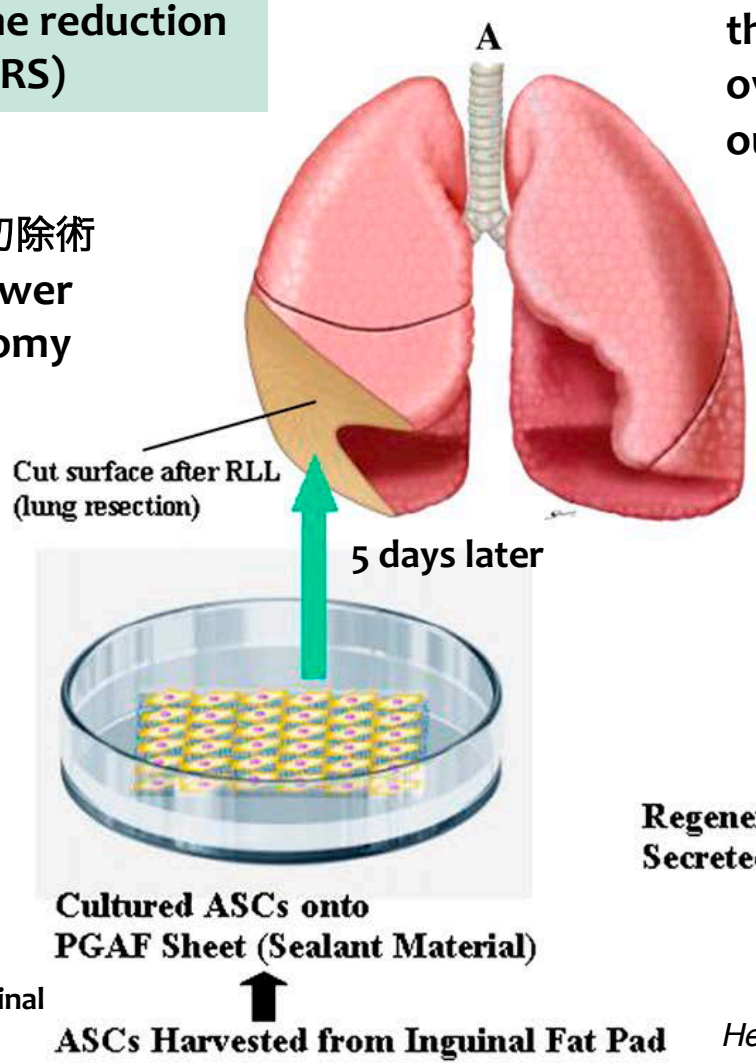
右下葉切除術
RLL: right lower lobectomy

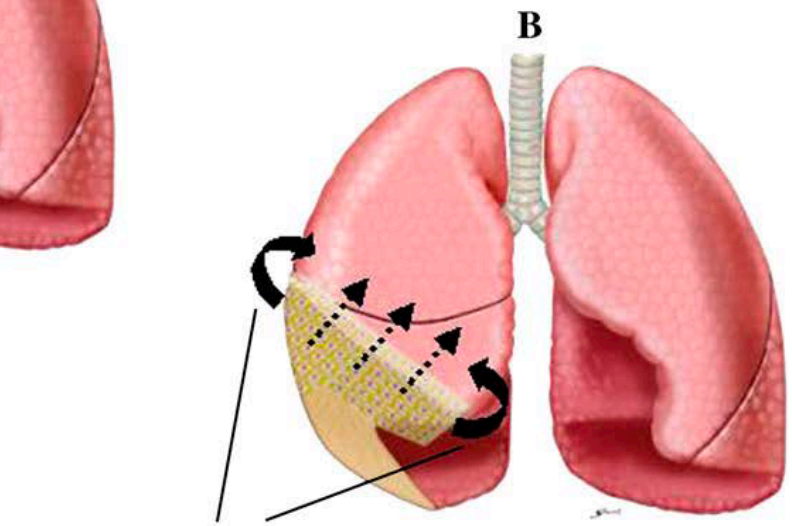
Tissue engineering techniques with cell-based therapy in the lung would contribute to overcoming the present limitations in the surgical outcome for pulmonary emphysema（肺氣腫）





Cells were isolated from Lewis rat inguinal adipose tissue





PGAF: 1 cm wide, 0.5 cm long 2 strips

Hepatocyte growth factor (HGF)

Autologous delivery of adipose tissue–derived stromal cells (ASCs) with polyglycolic acid felt sheet (PGAF)

Am J Respir Crit Care Med Vol 174. pp 1199–1205, 2006

Adipose Stromal Cells Improves Surgical Outcome for Pulmonary Emphysema

ASCs as a source of pulmotrophic factors

ASCs on PGAF

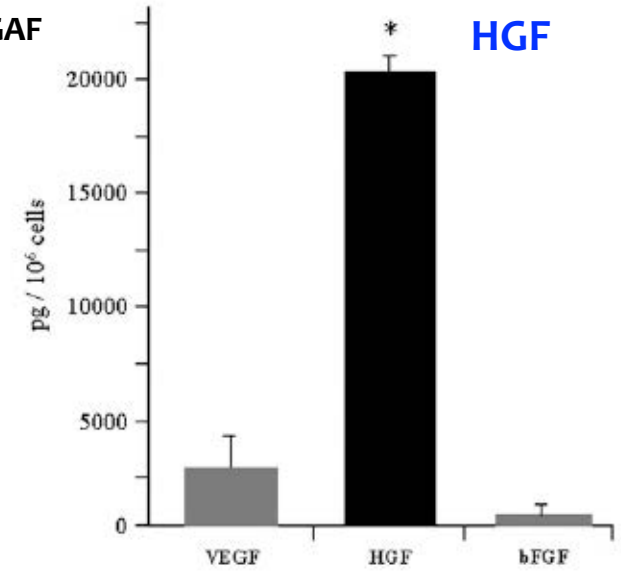


Figure 4. Secretion of vascular endothelial growth factor (VEGF), HGF, and basic fibroblast growth factor (bFGF) by ASCs cultured over 72 h on PGAF was measured by ELISA and is presented as mean ± SEM picograms of secreted factor normalized to 10^6 cells at time of harvest. Secretion of HGF was most significant. *$p < 0.01$.

- Vascular endothelial growth factor (VEGF)
- Hepatocyte growth factor (HGF)
- basic fibroblast growth factor (bFGF)

Lung tissue

Control: no cells

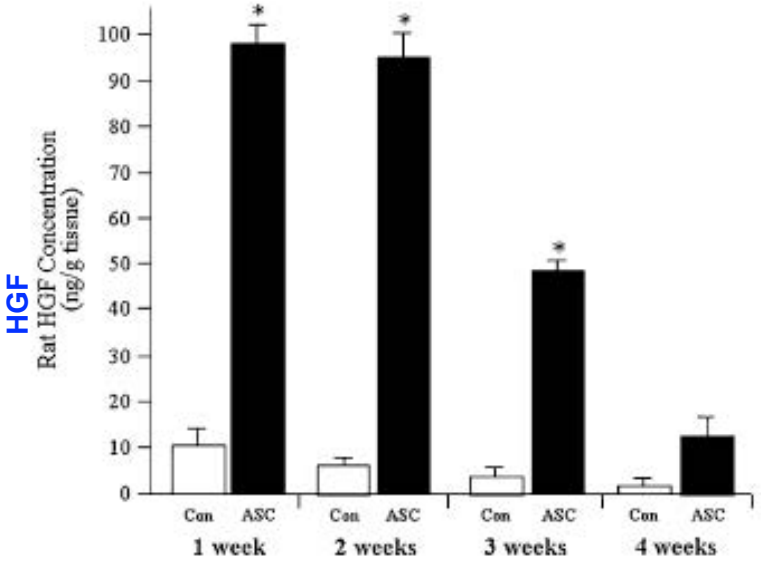
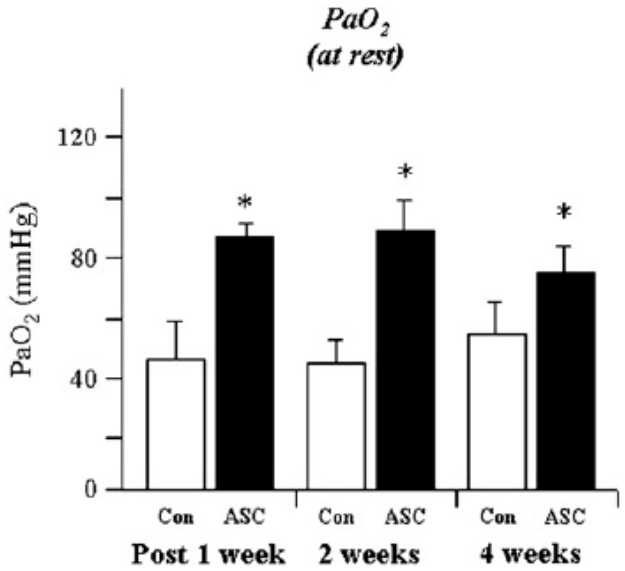
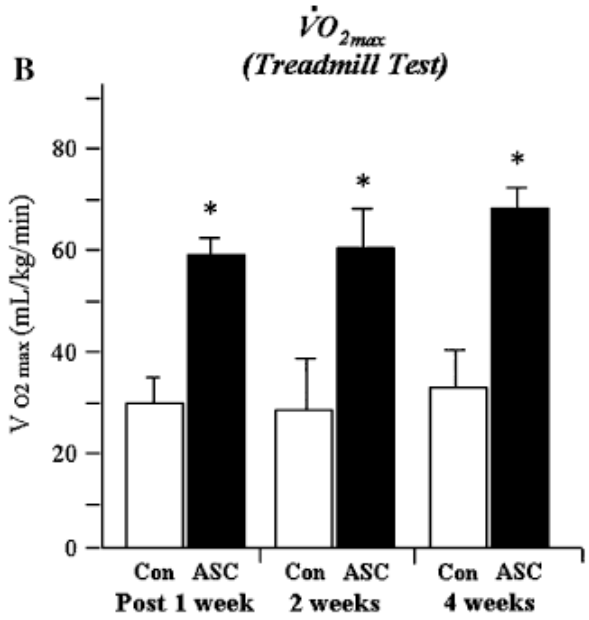


Figure 5. Expression of total HGF levels including both exogenous (ASC-derived) and endogenous (resident-produced) levels in lung tissue at 1, 2, 3, and 4 wk after the delivery of ASCs onto the remaining lung after surgical reduction. Control (Con) indicates rats that underwent surgical reduction alone without ASC transplantation. Each value represents the mean ± SEM of values obtained using five rats. *$p < 0.01$.

Am J Respir Crit Care Med Vol 174. pp 1199–1205, 2006

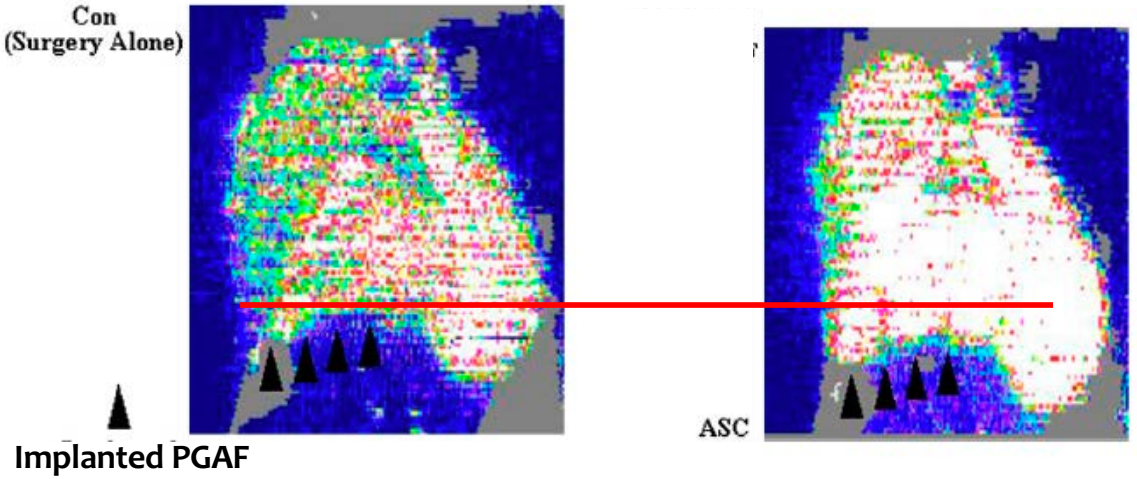
Adipose Stromal Cells Improves Surgical Outcome for Pulmonary Emphysema





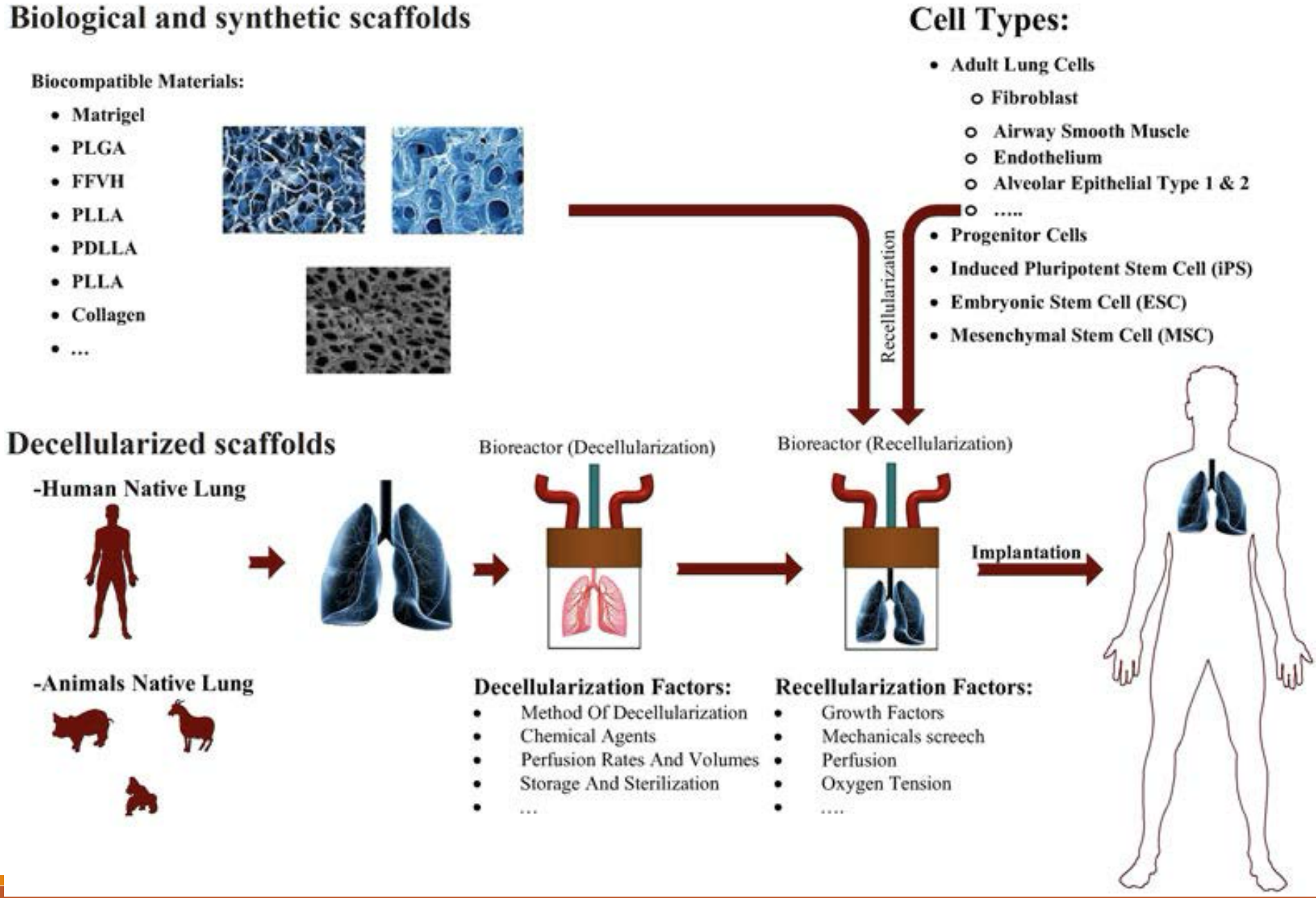
Therapeutic effects of ASCs trans-plantation with PGAF on local blood perfusion and pulmonary ventilation.

➢ *Laser Doppler analysis of lung blood perfusion*



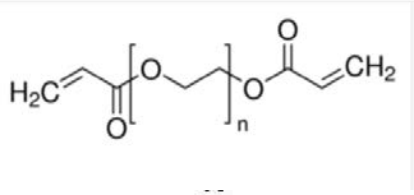
Am J Respir Crit Care Med Vol 174. pp 1199–1205, 2006

Lung tissue engineering

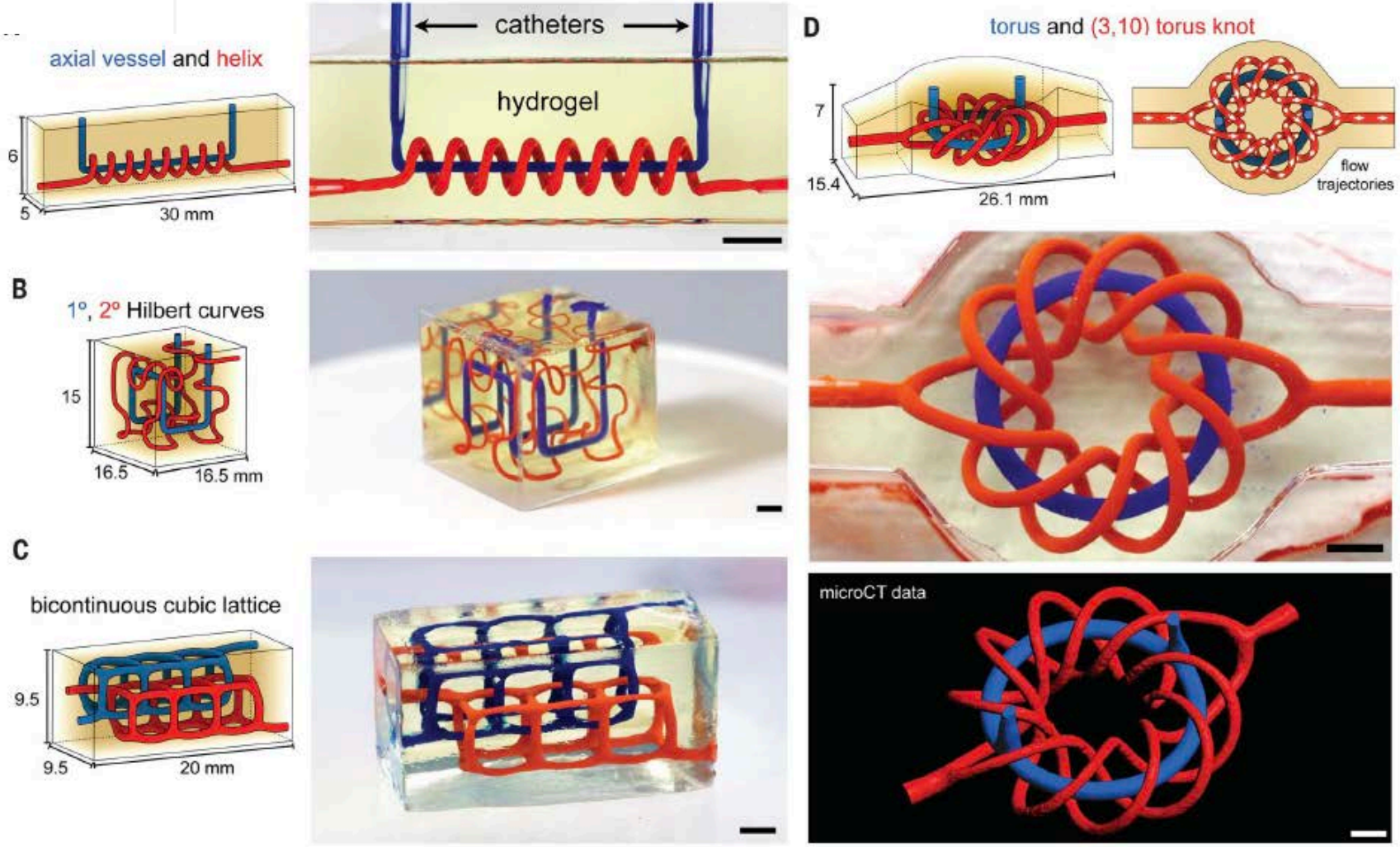


J Cell Physiol. 2019;1-15.

Tidal ventilation and oxygenation in hydrogels with vascularized alveolar model topologies.



20% Poly(ethylene glycol) diacrylate (PEGDA) hydrogel



Bagrat Grigoryan et al. Science 2019;364:458-464

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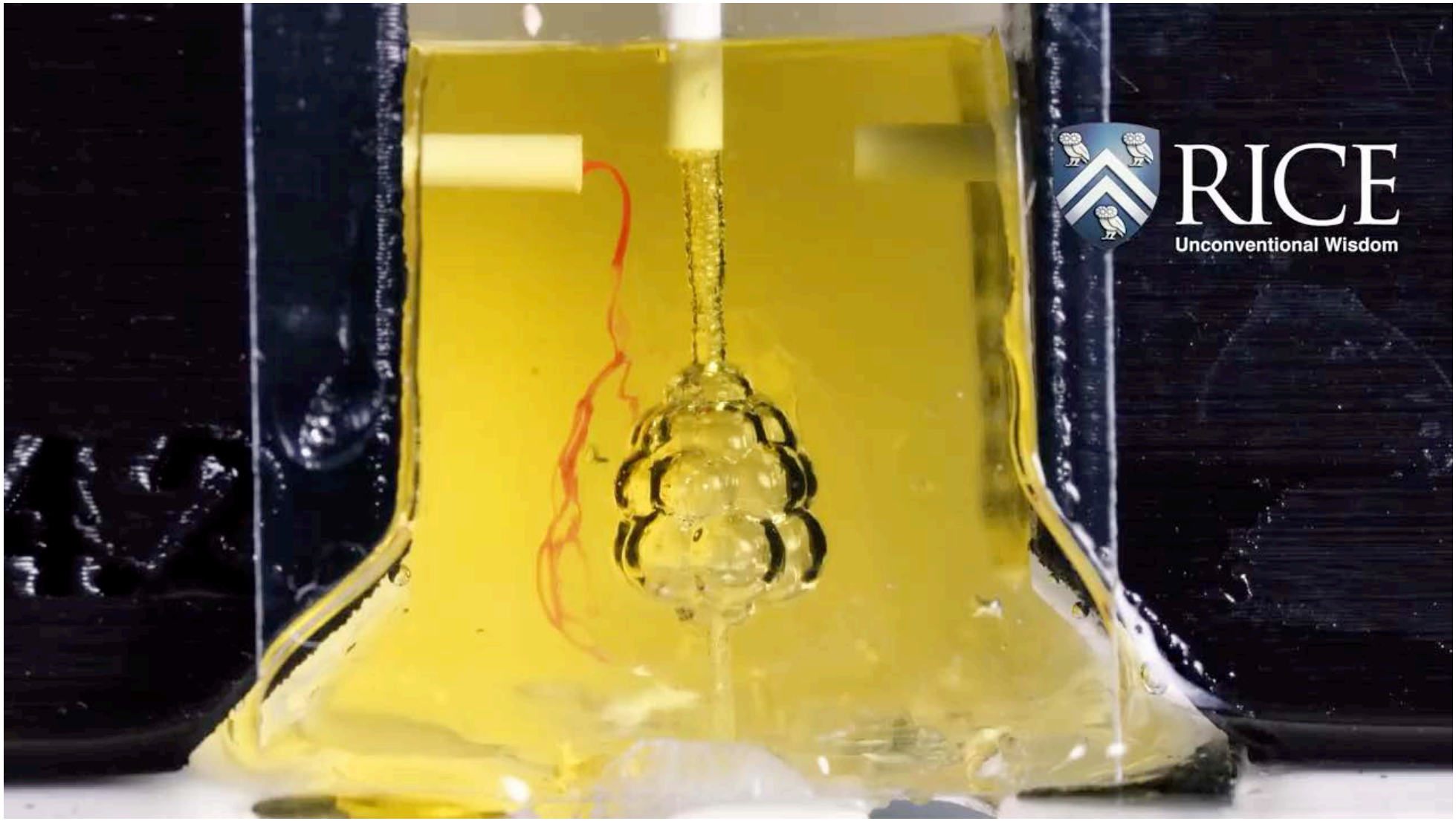
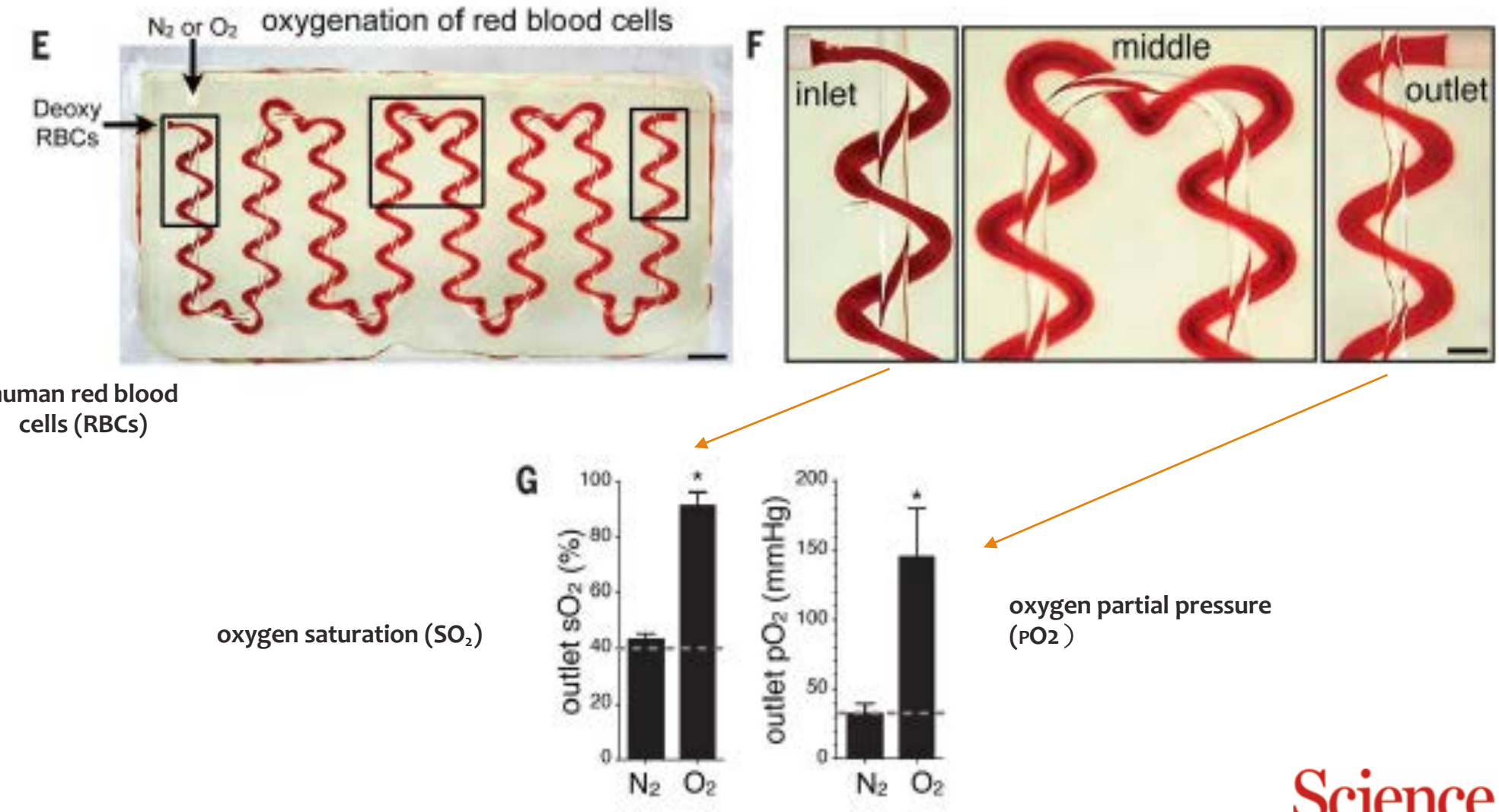
https://www.youtube.com/watch?v=GqJYMgAcc0Q



Tidal ventilation and oxygenation in hydrogels with vascularized alveolar model topologies.



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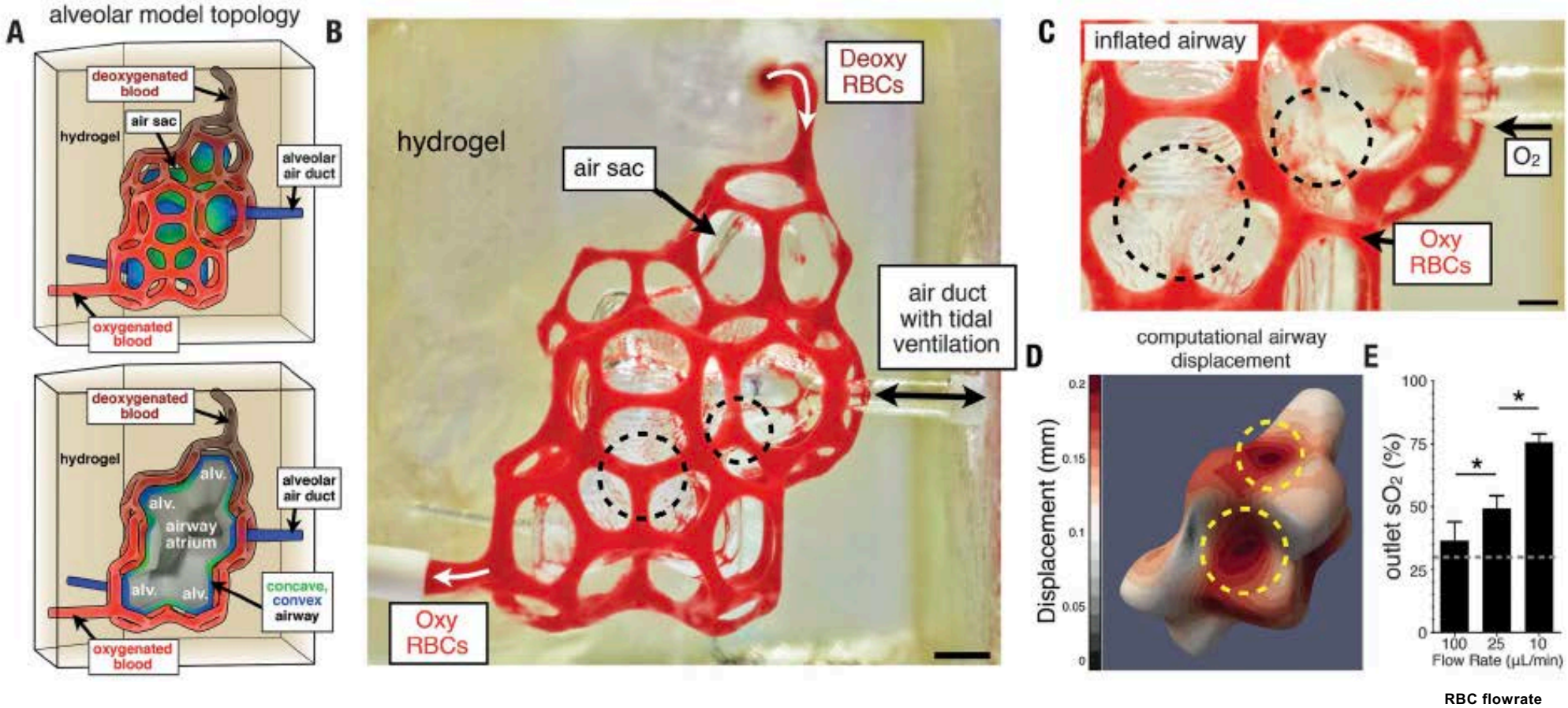

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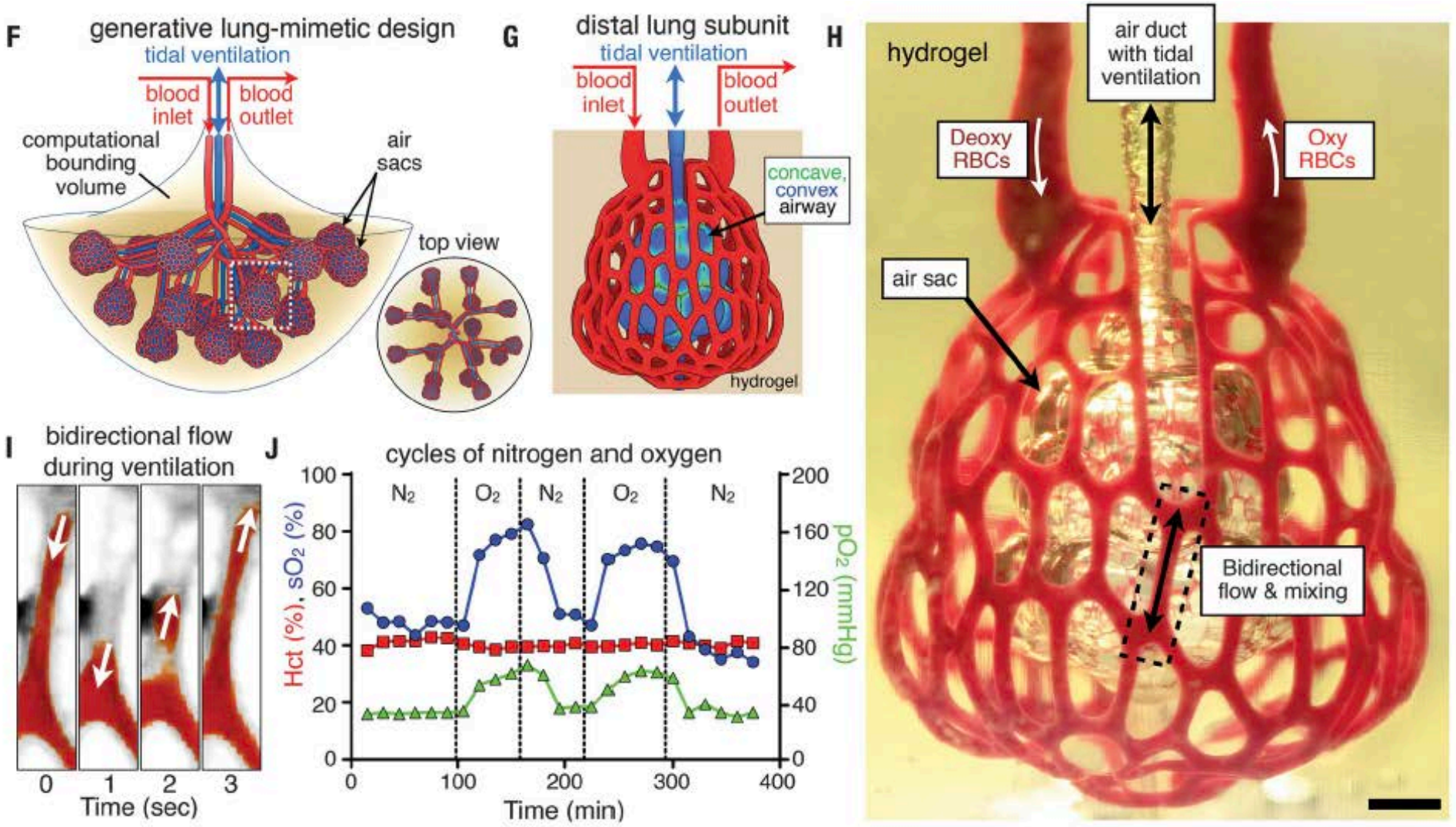
Tidal ventilation and oxygenation in hydrogels with vascularized alveolar model topologies.



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Thank you for your attention