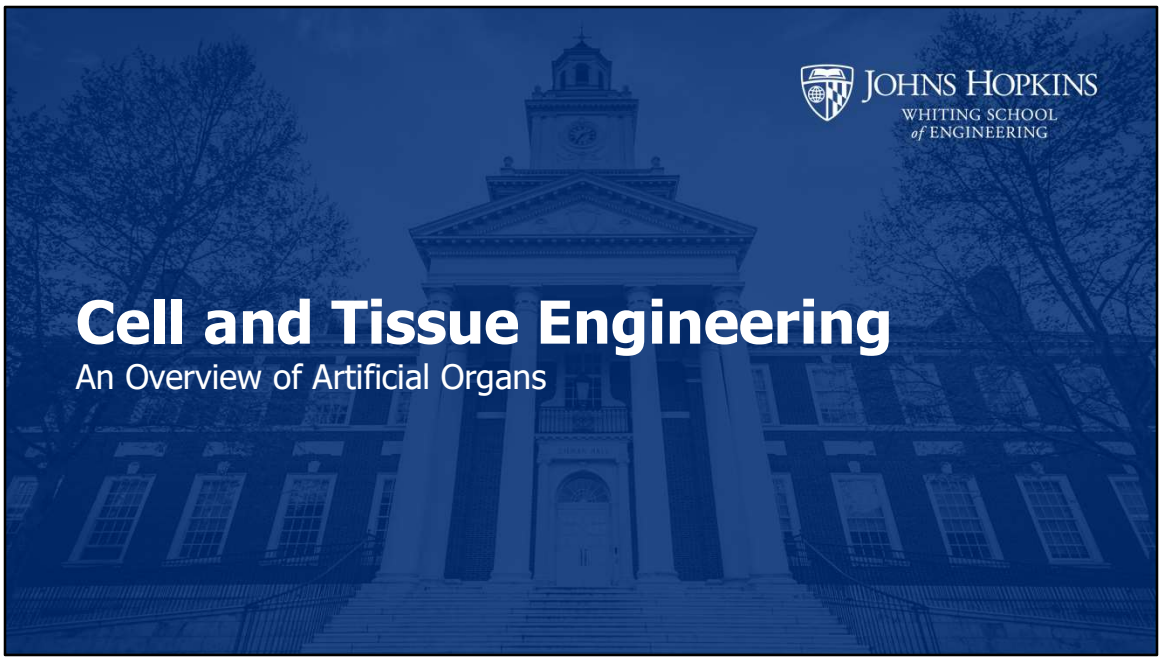
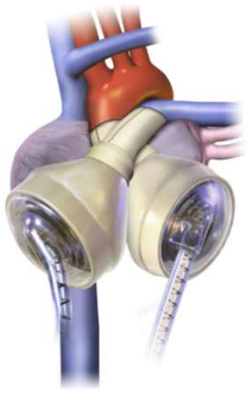
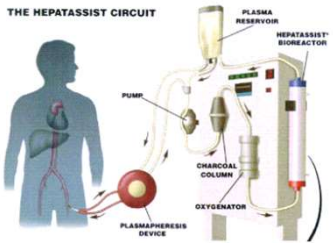


Welcome to cell and tissue engineering. This is Ethan Nyberg.

In this lecture, we're looking at artificial organs, the pathway for translating tissue engineered products to the market, including regulatory pathways.

Internal Artificial Organs





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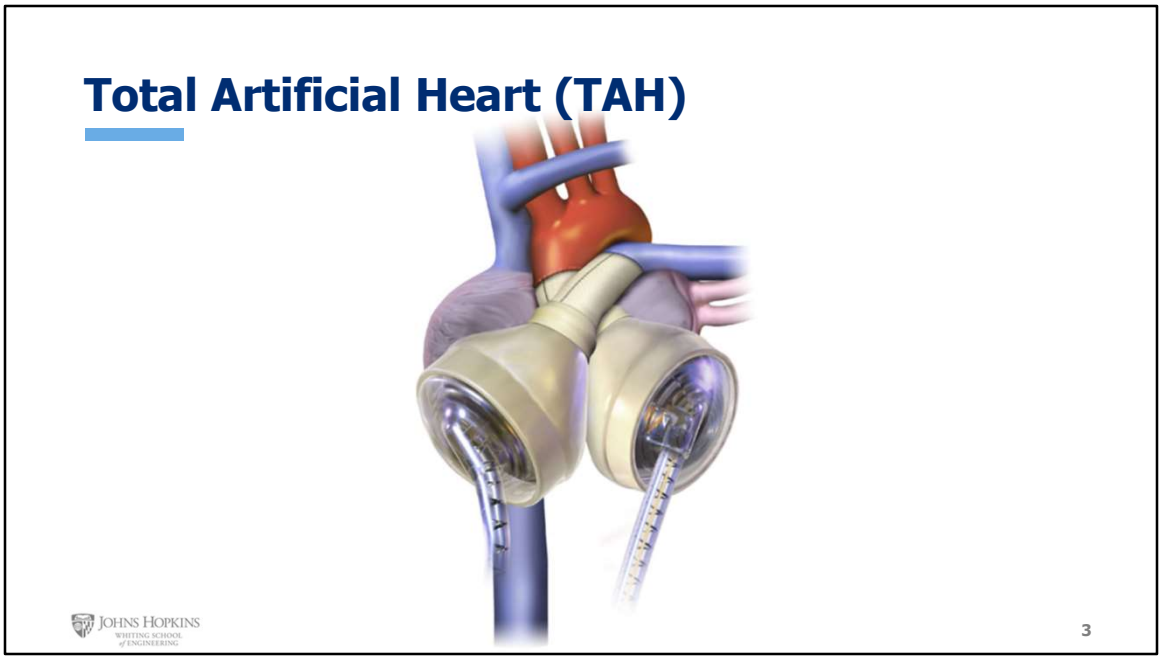
syncardia.com; .washington.edu; biomed.brown.edu/Courses/BI108/BI108_2002_Groups/liver/webpage/Circepg.htm

There have been many advances in the field of artificial organs for both internal and external artificial organs.

In this module, we will focus in on **internal** artificial organs, such as the heart, kidneys, and liver – devices that replace the function of a failing organ

First we will begin with products that are on the market or in the clinic. These are primarily **mechanical** devices. Later in the module, we will discuss tissue engineered solutions to organ failure.



Here is SynCardia system's total artificial heart. This was approved by the FDA in 2004 following a ten-year pivotal trial.

The TAH is commercially available and replaces the long-term mechanical function of the heart – critical to sustaining human life.

The heart is a major organ in the body. If it is not functioning properly, it will have a cascade of effects in other organs due to inadequate perfusion.

Let's quickly cover the design of the device:
- This TAH replaces the diseased right and left ventricles with artificial ventricles, connected with inflow cuffs to the atrium (beige cones)
- The outflow of the ventricles is connected via vascular grafts to the native pulmonary artery and aorta (wraps at the end of the conical).
- IN addition, the device is powered by an *external* drive system by the tubes hanging from the artificial ventricles.

Some of the device malfunctions that can occur include:
- Power failure

- Undesirable pumping action
- Part failure

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https://www.mayoclinic.org/tests-procedures/ventricular-assist-device/about/pac-20384529

Wearable Artificial Kidney

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End stage renal disease is another area where improved treatment options are needed. In 2011 over 100,000 patients started end stage renal disease treatment. These treatment options include

- Dialysis
- Kidney transplantation

Dialysis – a mechanical device takes over the function of the kidney and filters it to remove salts, toxins, and excess fluid from the blood.

- **Hemodialysis** can be conducted in the clinic, several times a week for several hours. You can imagine such a treatment burden total consumes a person's lifestyle, and has been associated with depression.
- **Peritoneal dialysis** is an at home option, performed during sleep. A permanent catheter is places in the abdomen to connect to the dialysis device.
    - Complications include infection due to the implanted catheter

More people await a kidney transplant than there are available kidneys. Coupled with the decreased quality of life associated with dialysis, we can understand the urgent need for other solutions for this patient population.

Clinical trials were approved for Blood Purification Technologies' Wearable Artificial Kidney

The hope for the device is an around the clock dialysis solution for patients.
Components include
- Harness
- Micropumps
- Bubble detectors
- Dialyzer
- Dialysate regenerating system
- Battery

Items to draw, filter, and return blood to the patient.

Similar to the TAH, there are malfunctions associated with the system.

Additionally, all treatments associated with blood must address the challenge of the body's clotting systems.

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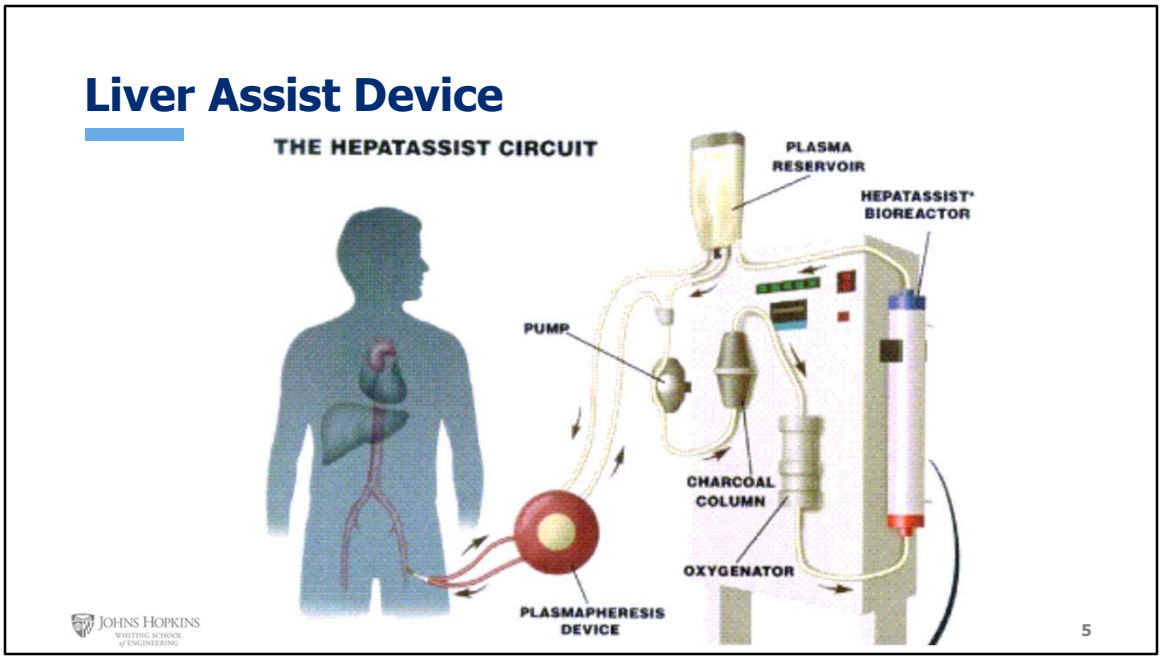
https://www.healio.com/news/nephrology/20210511/us-issues-patent-for-wearable-artificial-kidney



Finally, we'll look at liver assist devices for failing livers. According to the Organ Procurement and Transplantation Network (OPTN), there are over 11,000 Americans on the liver transplant waiting list.

Unlike the previously discussed solutions, the **HepatAssist** device is a solution that combines **living biochemical interactions** and mechanical function to treat the failing liver.

As you may recall from your physiology courses, the liver is a complex organ that has an ability to **regenerate** itself and perform a number of **metabolic**, **synthesizing**, and **regulatory** functions.

Liver failure is a life-threatening condition and rapid disease progression can prohibit recovery of the liver and result in multi-system organ failure

This device is hollow fiber **bioreactor** containing:
- **porcine hepatocytes**
- Charcoal column
- Membrane oxygenator

- Pump
- Heater
- Commercially available plasma separation machine
- Oxygen and temperature monitors

The device has passed through phase 1, 2 and 3 clinical trials with promising outcomes, but has been delayed by multiple acquisitions of the company

The use of porcine hepatocytes can cause an allergic reaction and rejection to the treatment and the different metabolic pathways between human and porcine cells are not well understood.

SO far, these solutions have been primarily mechanical in nature – BUT there has been progress in CTE solutions. These are still primarily benchtop and years from the clinic.

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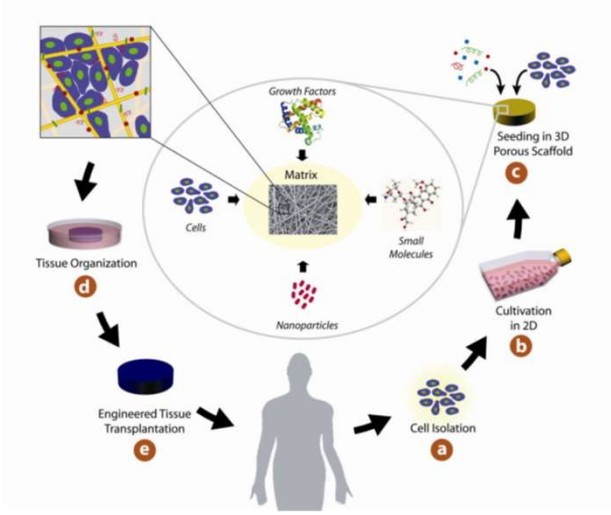
https://optn.transplant.hrsa.gov/

Towards Bioartificial Organs



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Dvir, T., Timko, B., Kohane, D. *et al.* Nanotechnological strategies for engineering complex tissues. *Nature Nanotech* **6**, 13–22 (2011).

Building on what we learned this semester about cell and tissue mechanics, biomaterials, stem cells, -- let's continue our discussion on CTE applications focused on internal organs.

Let's review quickly what we've covered (for specific tissue approaches) so far:

- Generally, start with a cell isolation procedure from the patient or donor
- Next cultivate in 2D or 3D culture to increase the number of cells and then harvest them from the culture
- Next, seed in a 3D porous scaffold with growth factors, small molecules, and nanoparticles as needed to direct cell behavior in the construct.
    - Engineers can take advantage of cell sheet engineering for applications that do not necessitate a 3D scaffold
    - Specific cells or combinations of specific cells make their own ECM to support 3D tissue formation and remodeling.
- Cells are further cultivated in a bioreactor under physiological conditions for organization into functional tissues
- These tissues are then transplanted to the patient to replace or restore tissues.

Form and functions of bioartificial organs are derived from the different types of cells

and tissues as needed for the application

Dvir, T., Timko, B., Kohane, D. *et al.* Nanotechnological strategies for engineering complex tissues. *Nature Nanotech* **6,** 13–22 (2011).

Design Considerations

Cell types
Cell numbers
Cell delivery techniques
Cell-cell interactions
Cell-matrix interactions
Tissue formation
Mature tissue function
Physiological sustainability
Surgical implementation

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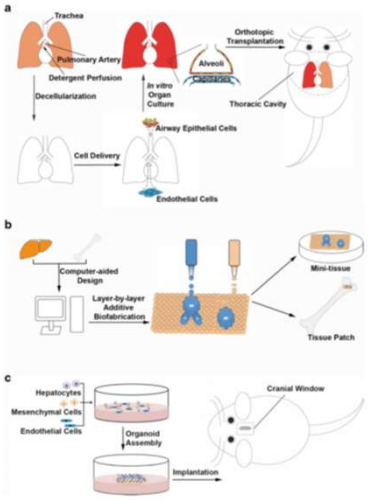
Let's review **design considerations** for bioartificial organs.

These should be similar in form and function to a **mammalian organ**, thus consider the following list:

Cell types – which cells, combinations of cells, ratios of cells are needed?
Cell numbers – how many needed? Can I grow that many?
Cell delivery techniques – how will this be done?
Cell-cell interactions – what are they
Cell-matrix interactions – what are they, how will the cells interact with scaffold,
Tissue formation - what growth factors and other physiological settings are needed for formation of tissue
Mature tissue function – Does it function effectively? Does it replace mechanical, metabolic function?
Physiological sustainability – how will it plug into interconnected body systems?
Surgical implementation – how will it be delivered to the patient?

On the Road to Bioartificial Organs



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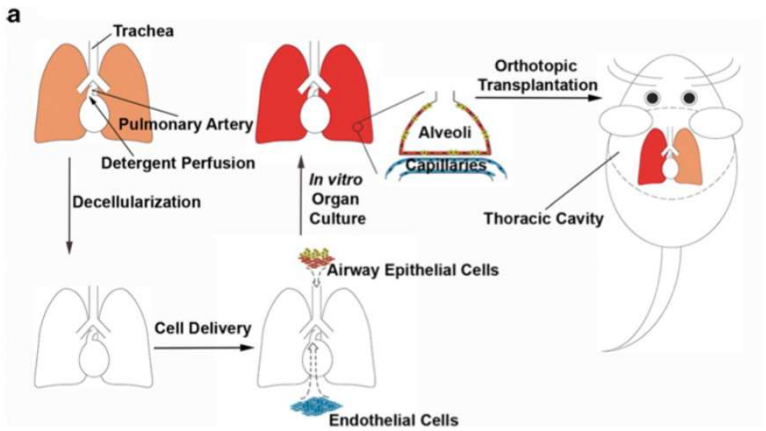
Ren & Ott, 2014

There are several strategies that have emerged over the years to address the fabrication of bioartificial organs. These include:

- Whole organ decellularization and recellularization
- 3D organ printing
- Organoid engineering.

Whole-Organ Decellularization & Recellularization



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Ren & Ott, 2014

To begin with, researchers have been successful with thin and less complicated organs such as bladders and cartilage – but solid, complex structures with dense vascularization (such as the heart and lungs) have proven to be a challenge.

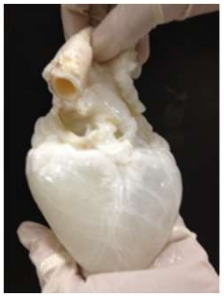
In this illustration, researchers use the native structure of an organ's ECM and structure to fabricate a transplant organ for patient use

First, a donor organ must be obtained. Next the organ is decellularized by removing all cellular components. This is achieved by the perfusion of detergents through the vascular structure of the organ. Vascular endothelial cells and organ specific cell types are the delivered to the organ – on the order of 100 to 1,500 billion cells – via media perfusion and cell injection methods

Generally, these are induced pluripotent stem cells

The cells mature under influence of growth factors and mechanical stimulation. After maturation, the organ can be transplanted to the patient.

Bioartificial Heart



Texas Heart Institute – Dr. Doris Taylor
Requirements:
• Perform the organ function
• Sterile
• Able to grow within patient
• Repair/compensate itself if injured

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Taylor, D. A., Hochman-Mendez, C., Elgalad, A., & Sampaio, L. C. (2019). Whole-heart scaffolds—how to build a heart. In *Handbook of Tissue Engineering Scaffolds: Volume One* (pp. 617-642). Woodhead Publishing.

A variety of organs have been fabricated using the decellularization platform, including heart, lung, liver, kidney.

Demonstrated a feasibility in heart transplants in animal models. The engineered hearts are able to begin to mimic the pumping action of the heart, but the platform has some remaining challenges:

- Sterility
- Growth with patient
- Self repair
- Homogenous cell distribution across the compartments of the organ
- Need for site specific delivery of cells

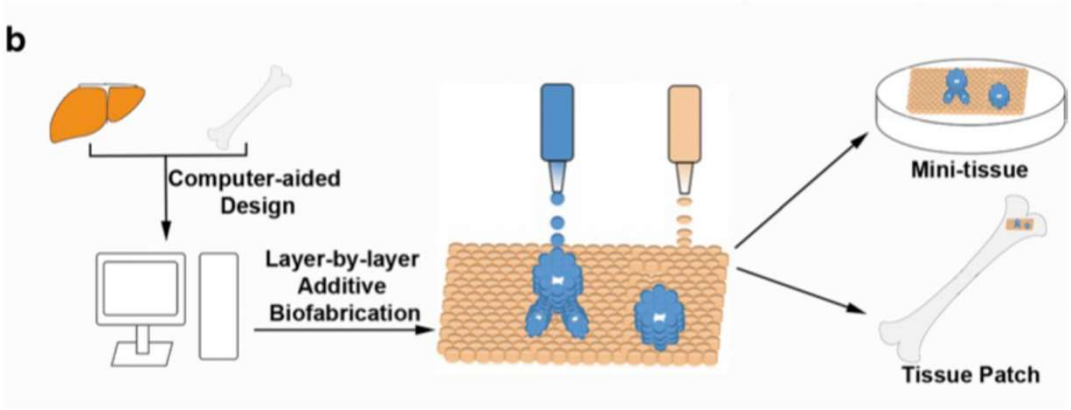
Ongoing studies for the quality of the repopulated vascular tree in the recellularized organs and the risk of fatal clotting.

Podcast - https://www.sciencefriday.com/segments/ghost-heart-engineering/

Taylor, D. A., Hochman-Mendez, C., Elgalad, A., & Sampaio, L. C. (2019).

Whole-heart scaffolds—how to build a heart. In *Handbook of Tissue Engineering Scaffolds: Volume One* (pp. 617-642). Woodhead Publishing.
Park, C., Fan, Y., Hager, G., Yuk, H., Singh, M., Rojas, A., ... & Roche, E. T. (2020). An organosynthetic dynamic heart model with enhanced biomimicry guided by cardiac diffusion tensor imaging. *Science robotics*, *5*(38).

3D-Organ Printing



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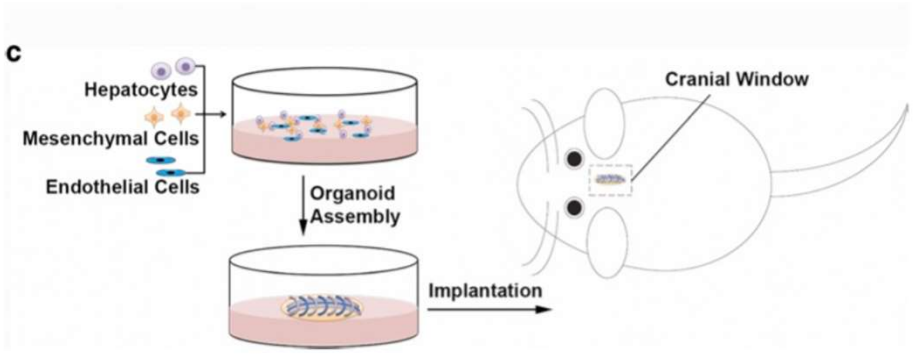
Ren & Ott, 2014

3D Organ printing
Instead of using a native organ as a scaffold, bioprinting can generate an organ de novo by layer by layer robotic additive manufacturing.
Similar to rapid prototype used by engineers.

Two main kinds of bioprinting
- Indirect – the scaffold is printed and then cells are implanted
- Direct – scaffold and cells at the same time

We'll hear about this in detain in a TED Talk by Dr. Tony Langer

Organoid Engineering



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Ren & Ott, 2014

In organoid engineering, mini organs are engineered from ESCs or IPSCS in 2D conditions.

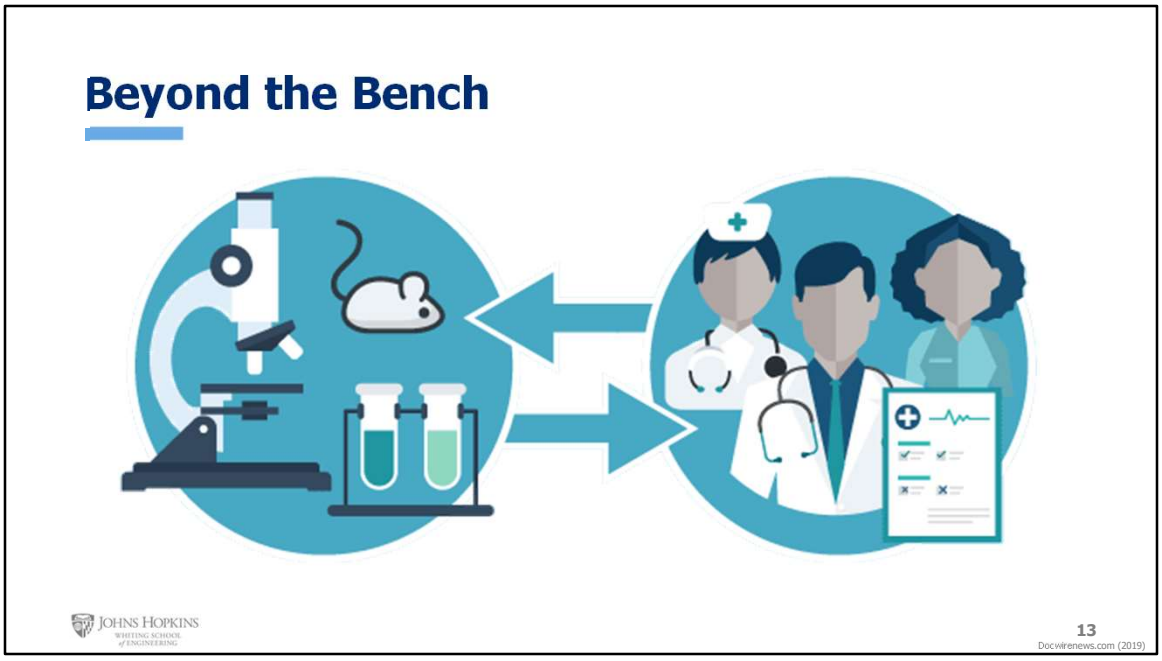
This has been done in the liver, with vascularized liver organoids that mimic the native liver anatomy and function. They cultured iPSCs--Hepatocytes, human mesenchymal stem cells, and endothelial cells.

The liver buds were transplanted into immunodeficient mice:
- A windowed cranial vault to assess vascular function
- Subcutaneous to evaluate function
- Mesentery to evaluate survival.

This example demonstrated the capability of dissociated cells to properly assemble in appropriate 2D culture conditions.

Generating transplantable organoids challenges include
- Scaling to clinically relevant sizes
- Complex scaffolds for complex organs

Proposed for functional building blocks – such as alveoli and glomeruli



Once bioartificial organs pass the design phases, they have several hurdles before arriving at the clinic:

- Securing funding to support development
- Preclinical testing
- Clinical testing
- Manufacturing
- FDA regulation
- Public perception of benefit
- Reimbursement from insurance providers

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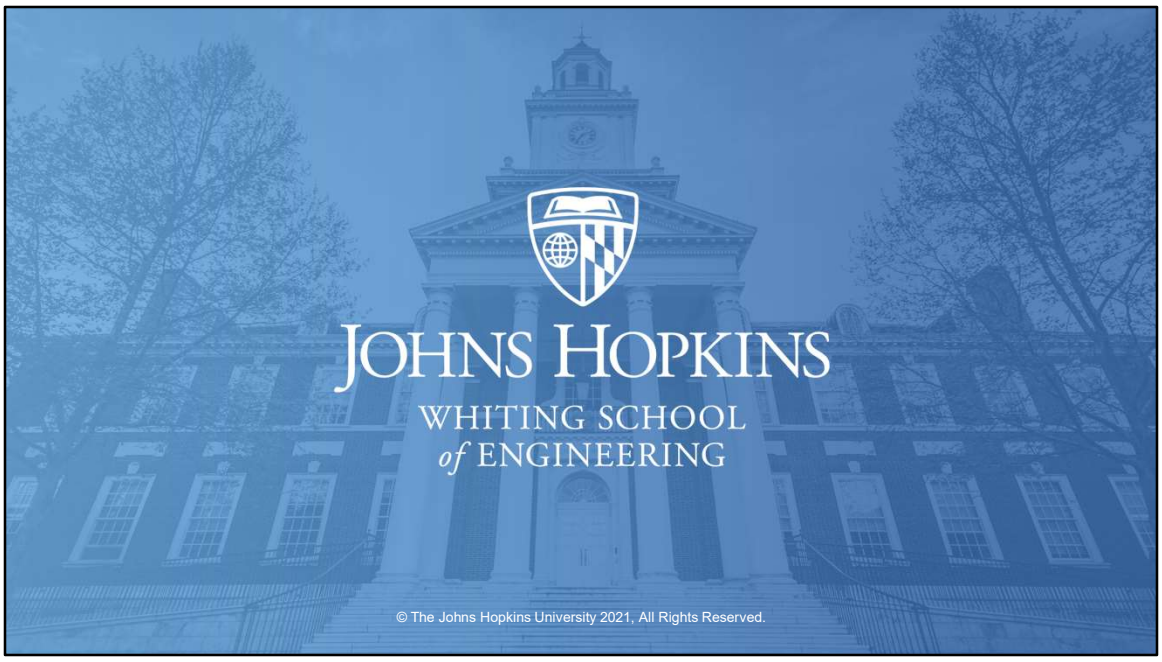
https://www.docwirenews.com/docwire-pick/bench-to-bedside-translating-science-from-the-lab-to-the-clinic/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