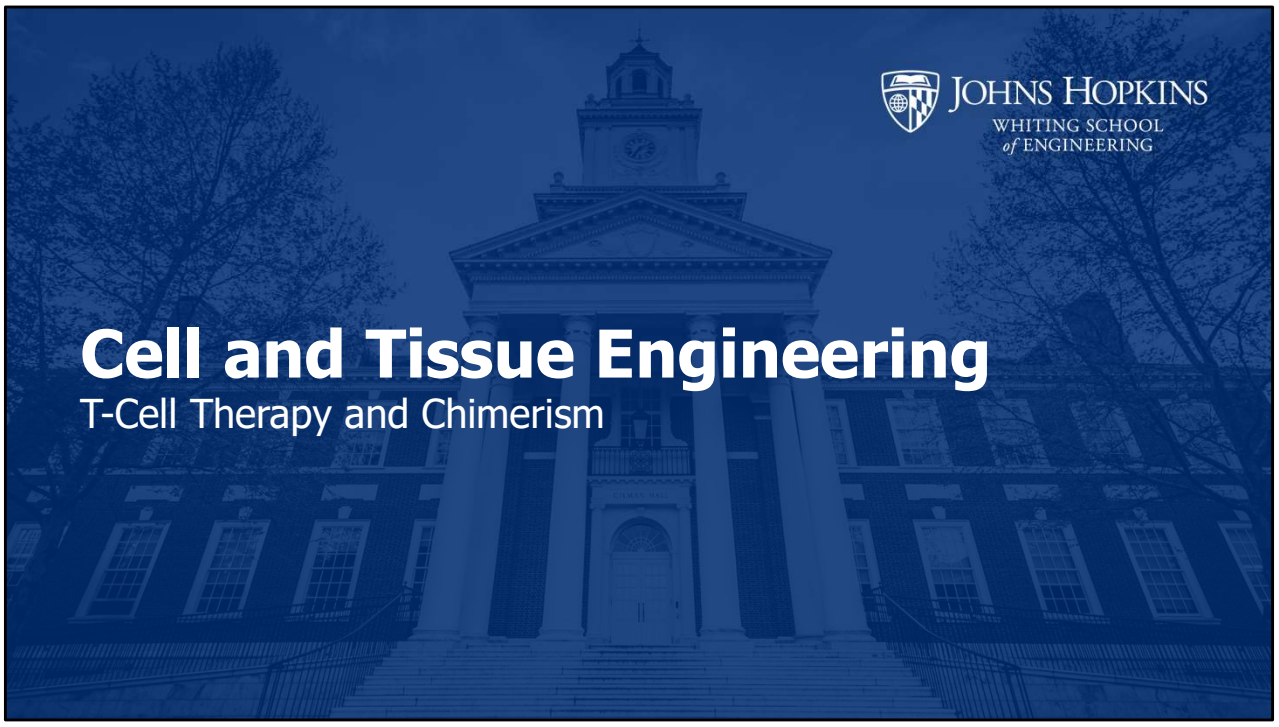
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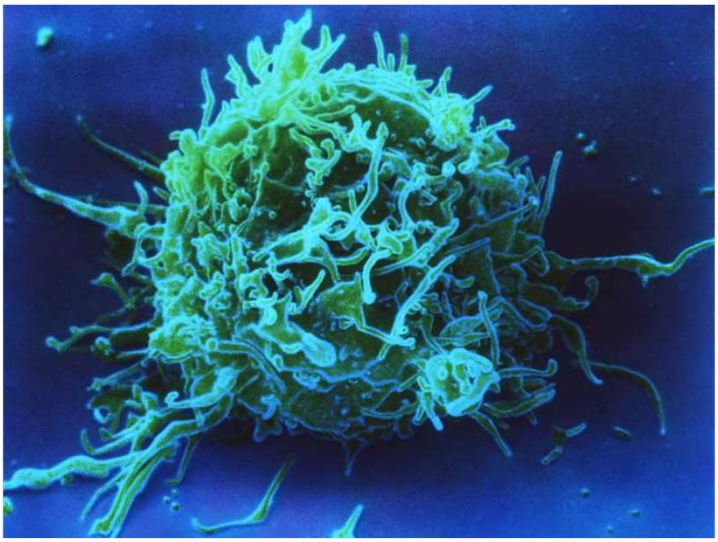
Cell and Tissue Engineering
T-Cell Therapy and Chimerism

## T-Cell Therapy



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Thinkmachineblog.net; Uphs.upenn.edu

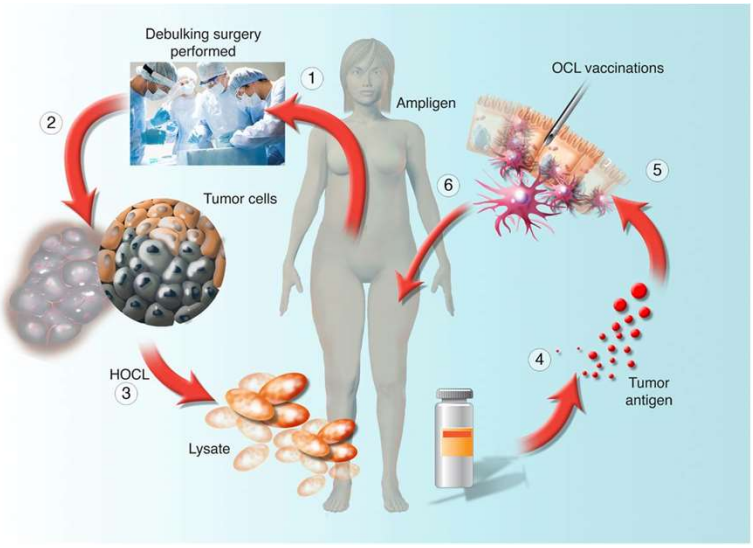
In the last video, I showed you the circulation path for lymphocytes because we are going to talk about them a bit more depth, but not just ordinary T-cells

Amazing progress has been made in T-cell therapies- specifically in **genetically engineered cells** and **adoptive transfer** methods.

These therapies are not only using your bodies circulatory system for delivery but also for **treatment**.

## T-Cell Therapy – Cancer Treatment Vaccine

**Whole Tumor Antigen Vaccine Study**

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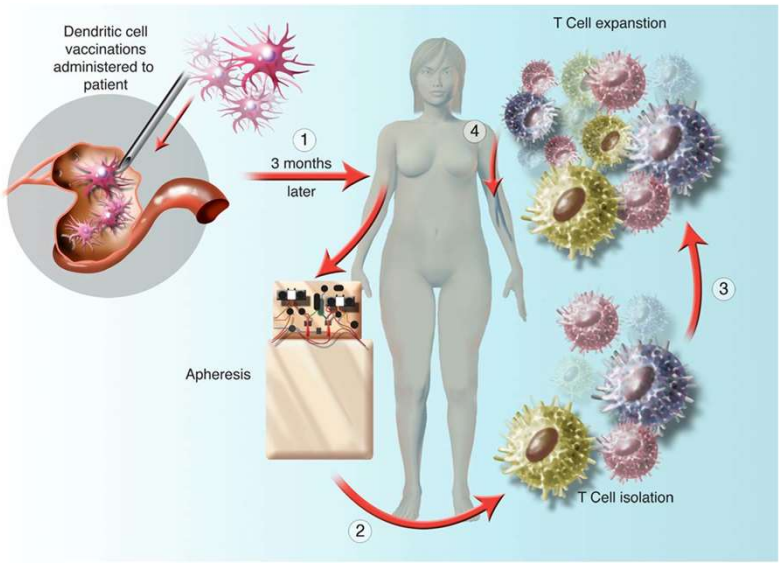
Upths.upenn.edu

Imagine that this is a patient suffering from cancer, say ovarian cancer. It has been shown for ovarian and other cancers that the tumor cells are **different** enough from the host that they can be **identified by the body's immune system**. Specifically dendritic cells can sense tumor specific antigens and present them to lymphocytes that will respond by destroying the tumor cells.

However this activation occurs **in too few** lymphocytes, **too late** in the game, and in the end your body's natural response is not enough.

In an effort to bolster the body's response scientist are working on a **tumor antigen vaccine.** In this process a vaccine is derived from a patients**' own tumor cells** without prior knowledge of what the tumor cell antigens are. **Lysate** from the tumor is used to **activate dendritic cells also harvested from the patient** or lysate can be injected directly back into the patient.

## T-Cell Therapy – Adoptive T-cell Therapy

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Uphs.upenn.edu

The early results with tumor antigen vaccines have been good but still researchers are looking for more potent methods of amplifying the vaccine response.

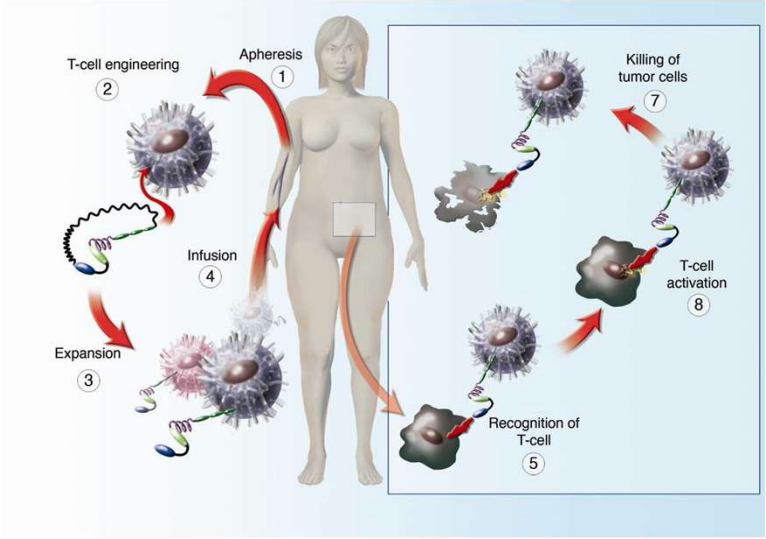
One method is called **adoptive t-cell therapy or adoptive transfer**. This approach is the most powerful technique to treat patients with advanced cancer malignancies.

In this method you harvest lymphocytes from the patients blood **post vaccine treatment** and further **activate them in culture** after a round of chemotherapy.

with adoptive transfer the T-cell you have are isolated, then activated, expanded, or engineered *ex vivo* and then put back in. This means that activation can be controlled and the T-cells can be tailored to improve the therapy.

## T-Cell Therapy – Genetically Engineered

**Antigen-specific artificial T-cell receptor → chimeric antigen receptor**

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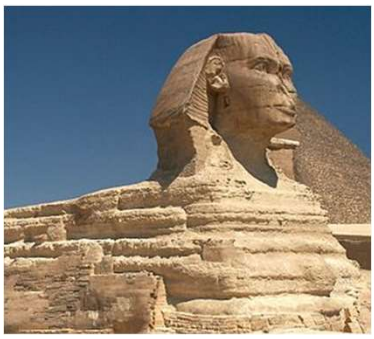
Upths.upenn.edu

Another way to engineer the T-cells is to genetically engineer the cells to express an artificial receptor for tumor antigen.

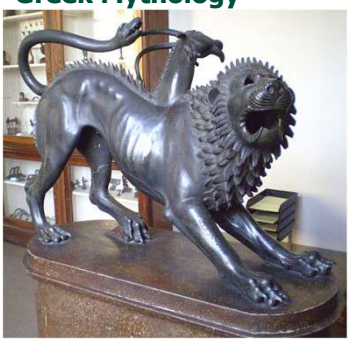
This chimeric antigen receptor (known as CAR-T therapy) is engineered to have high specificity for tumor cells and enhances the tumor cell killing ability of the immune system

## Chimerism: Tissue Transplant History

**Ancient Egypt**



**Greek Mythology**



**Modern Day**

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http://en.wikipedia.org/wiki/Sphinx; http://en.wikipedia.org/wiki/Chimera_(mythology); http://en.wikipedia.org/wiki/Chimera_(genetics

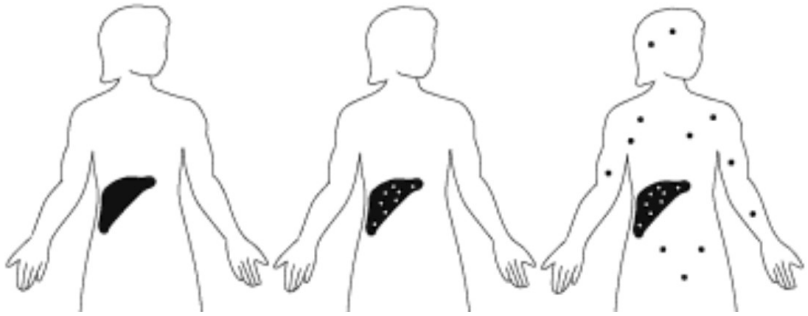
Let's step away from cancer and think more generally about treatments. Now what if the cells used in the treatments weren't from the donor – what if they were from another source?

Do you remember this slide from our very first lecture?

We began our journey talking about tissue transplantation – the creation of **chimera**. In Greek mythology you would associate this with a monster composed of a lion snake and goat, and in ancient Egypt a sphinx.

In tissue engineering it is simply joining of two genetically distinct cell populations.

## Microchimerism and Cell Trafficking



Transplantation of liver (black) into host (white)

Migration of host cells (white) into donor organ (black)

Migration of donor cells (black) into distant organ in the host(white)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Wordinfo.info; Tissue Engineering, Saltzman

So human chimeras aren't so imaginary after all..

When **creating** chimeras, and when **delivering** any cell for that matter, it doesn't have to be IV as we've discussed up to now. Cells can be introduced in a variety of ways – **directly** into a tissue for example.

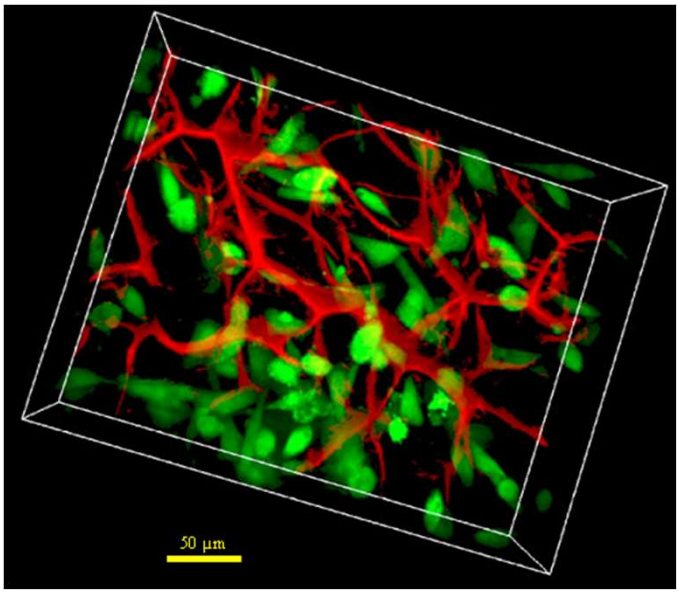
Regardless of delivery method we know that cells **transplanted** cells can **migrate**. They can migrate out of the blood stream, into the blood stream, and to distant tissue where they can live for reasonably long times.

Recipients of **liver transplants** display donor cells in their **skin, blood, heart** and other organs. Now If a tissue or organ is transplanted - then the opposite can happen as well – the host cells migrate **into the donor space**. As you can see from this image taken from your text – the end result is a mixed system – a **microchimera**.

It has been hypothesized that **microchimerism** is an important step in **the immune response to transplanted tissues (tolerance)**. Mixing the donor with the recipient may by tricking the immune system into seeing the donor cells as native. This hypothesis and the link between microchmerism and autoimmune disorders remains

controversial.

## Cell Penetration in 3D Tissues

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Nt.ntru.no; Gouma et al 2012

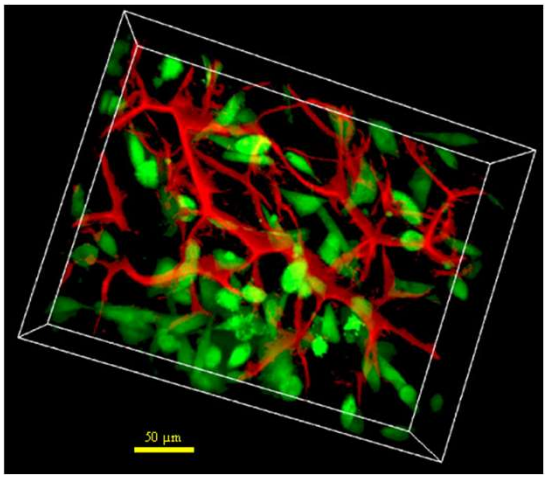
We know a lot about how cell move in the circulation and some about how cell migrate in and out of the vascular wall. But how do cells move through tissue?

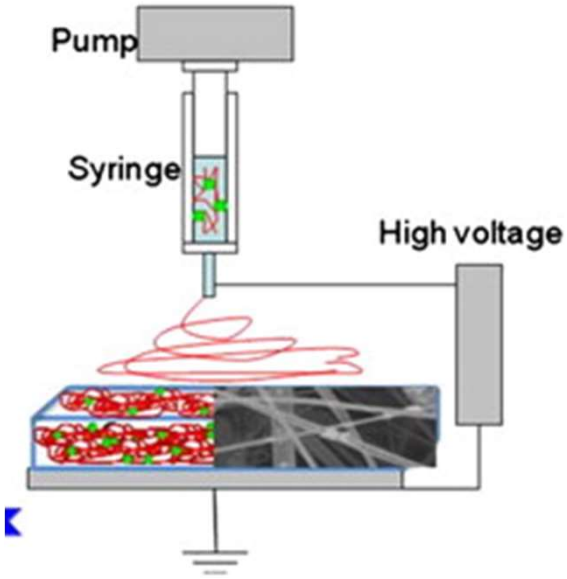
This image shows you **fibroblasts** in green and a **scaffold** in red, the **back** area is fluid, other matrix components.

We have already seen that there are **optimal ECM densities** – optimal **adhesivity** for migration speeds. Measuring these speeds in vivo holds many challenges, however data for the migration of pigmented retinal cells was found and is shown to be **several orders of magnitude slower** than 2D rates.

This tells us that we need to be careful in how we use 2D studies to design 3D studies and trials.

## Cell Penetration in 3D Tissues Cont.

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Nt.ntru.no; Gouma et al 2012

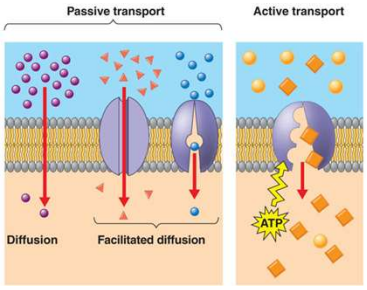
To overcome this speed discrepancy and facilitate cell seeding in 3D constructs engineers are employing methods **to seed cells while building up the tissue**.

Here I'm showing you an example of electrospinning **nano fibers** while **simultaneously** applying cells. This means that cell are incorporated **through** the entire thickness of the construct from the get it.

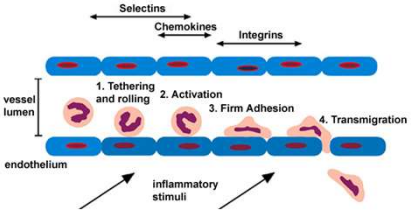
These techniques of course depend on the type of biomaterial being used and the method of forming that material – both this that we will be talking about in later modules.

## What have we learned?

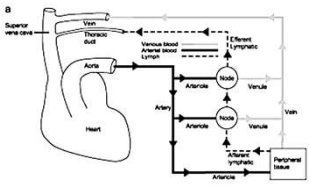
**Molecular transport across the cell membrane**




**Cell delivery across the vascular wall**




**Cell trafficking through the circulation**



**T-cell therapies**

**Microchimerism**

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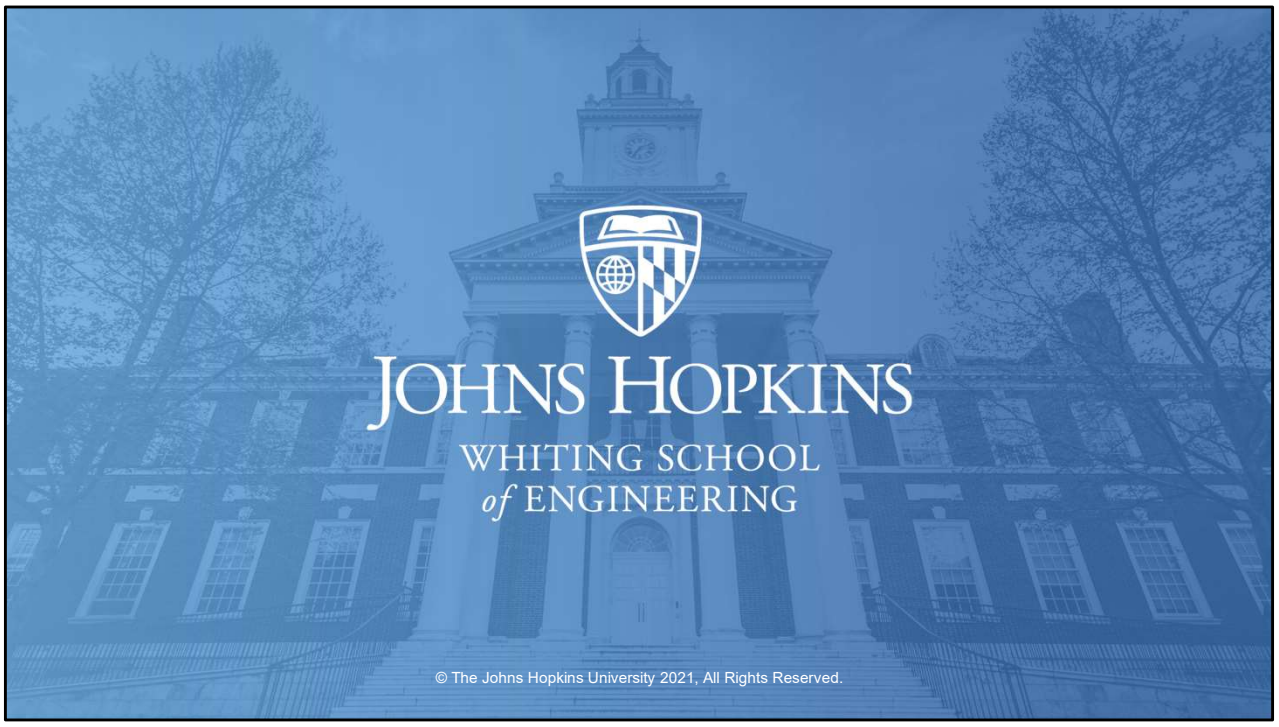
In this module we have covered

- Molecular transport, specifically across the cell membrane
- Cell delivery across vascular walls and other tissues
- Cell trafficking in the circulation
- T Cell therapies
- Microchimerism


The next lecture is from one of the biomedical engineering faculty here at JHU.

Dr. Warren Grayson runs the lab for craniofacial and orthopedic tissue engineering at Johns Hopkins in the Translational Tissue Engineering Center.

This lecture is a unique and wonderful opportunity for you to hear about tissue engineering directly from one of the field leaders.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