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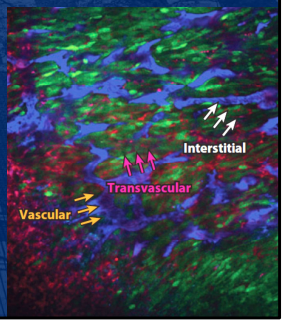
Cell and Tissue Engineering

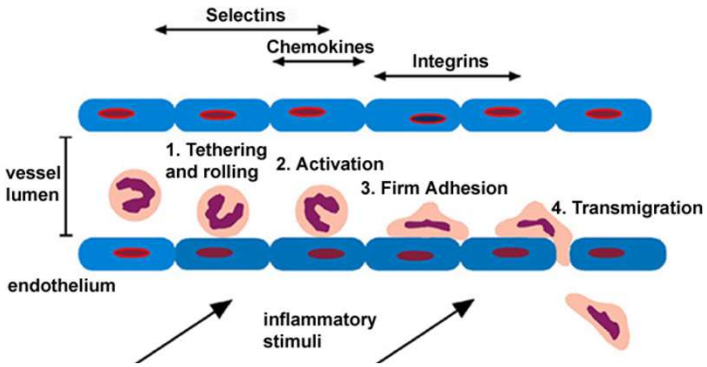
Cell Trafficking



Cell Delivery Through Layers of Cell (1)

Margination
Adhesion
Transmigration

The vascular wall is a barrier!



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Mpi-muenster.mpg.de; Kanoch et al 2011

Now we will transition from molecular transport to **cellular delivery**.

If a cell delivery system depends on cell **homing** to a target destination through the body, then the **basics of cell permeation through other cell layers** is necessary knowledge.

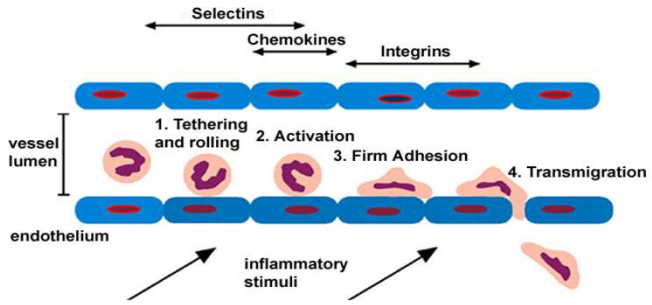
Earlier this semester we looked at how leukocytes use the **adhesion cascade** to adhere, roll and finally transmigrate across vascular endothelium.

Your book discusses these pathways in more detail for you in Chapter 10.

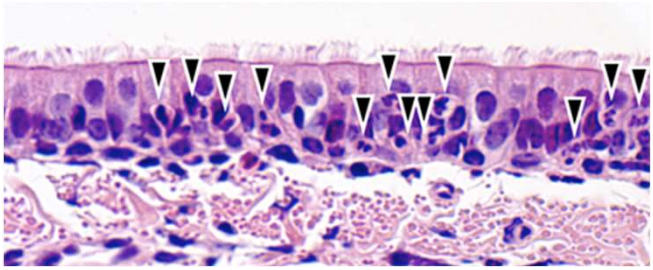
Cell Delivery Through Layers of Cell (2)

Margination
Adhesion
Transmigration

The vascular wall is a barrier!



Arrow heads indicate infiltrating neutrophils



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Mpi-muenster.mpg.de; Kanoch et al 2011

Immune cells like neutrophils also cross the epithelium of the airway – shown below - and also in the GI tract.

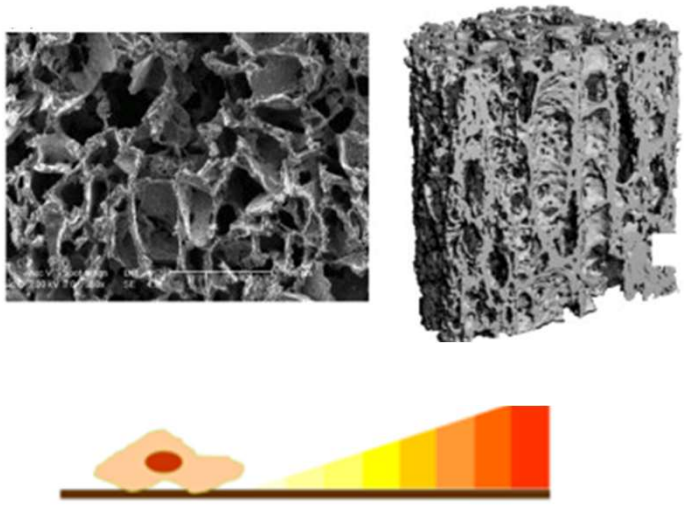
In **all** cases when **a cell crosses a tissue barrier**, it first must come close to the barrier – **margination** (recall attractive and repulsive forces),

adhere (weakly for rolling or strongly for firm adhesion)

and then **transmigrate**.

Seeding Cells in a 3D Scaffold

Margination
Adhesion
Transmigration



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Mpi-muenster.mpg.de; Kanoch et al 2011

You could imagine a similar scenario when **seeding cells** into a 3D scaffold.

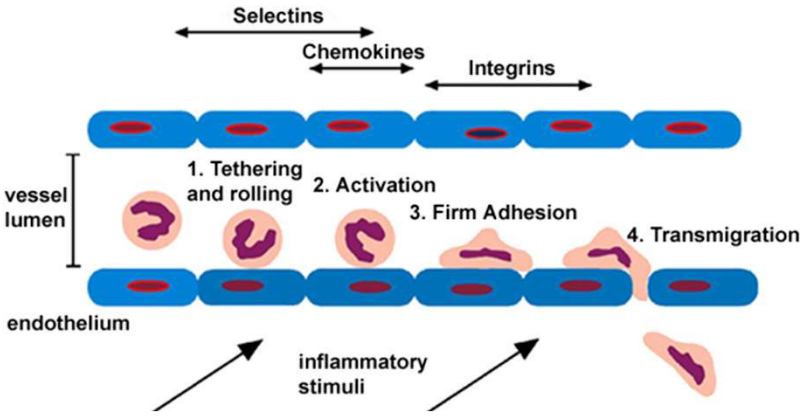
First the cells must be able to **approach** and **adhere** to the scaffold and then they must **migrate** around the construct to **penetrate to their destination**.

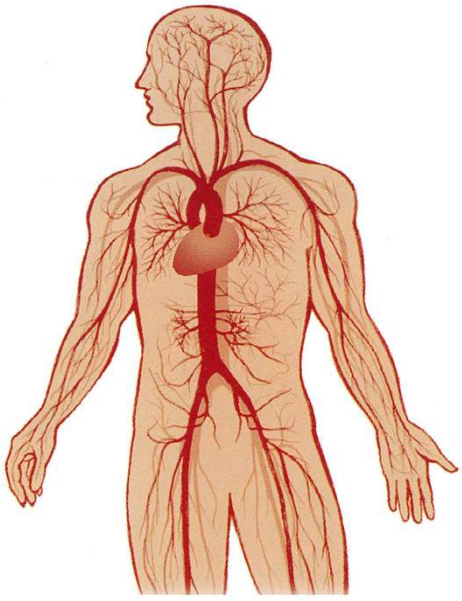
We know the movement of molecules is driven by concentration gradients or energy dependent transport

But a cell has its own power – its own energy to migrate. We learned about some mechanisms for directed migration already – including **chemotaxis**.

Cells can also move based on the cell density of the environment, that is being **over** or **under** crowded.

Using the Circulation for Cell Delivery





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wikipedia

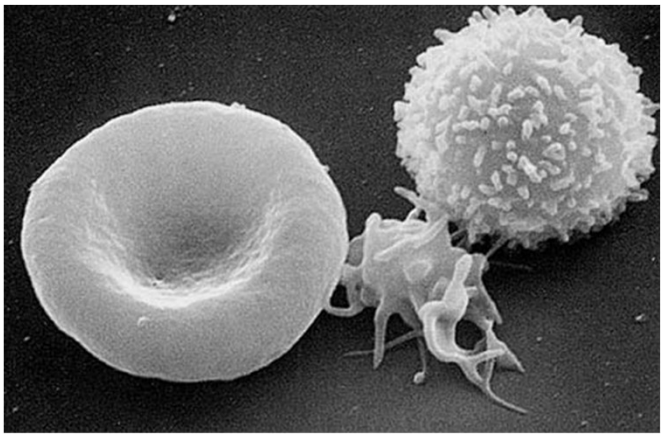
Let's go back to the body now. So we know a bit about how cells cross the vascular wall but we haven't talked about getting them **into the bloodstream**

At the beginning of this course we discussed ways to **engineer** cells. **Administering** these cells to the body is **the most basic form** of tissue engineering. The engineered cells may express a protein of interest, may behave in a desired way – **adhere** only in certain places, **migration** only on particular **substrates**.

Ideally we'd also like to engineer **homing mechanisms** so that our specialized cells can be delivered **generally**, perhaps to the blood stream, and find their way to the needed location.

During morphogenesis we saw complex direction of cell homing – the question is **can we learn** from these mechanisms and utilize them for homing in the adult organism?

Cell Delivery – Intravenous Administration



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wikipedia.org

IV or intravenous administration is an easy way to introduce cells into the body.

In this technique a needle is inserted into **vein** near the surface of the skin.

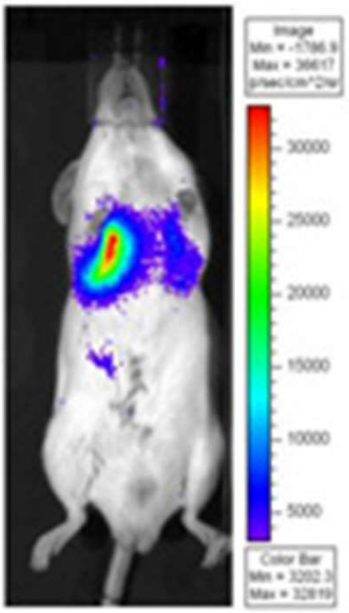
Arteries are typically not used for IV treatments, because, among other reasons, damage to an artery would sacrifice all downstream tissue, while damage to a vein would just result in fluid return through another vein.

IV administration is ideal for cells typically found in the blood stream like **RBC, WBC and platelets**. Transfusions have a fascinating history dating back to the 1600s. This history is detailed in your text but I'll give you the teaser that it involves both sheep and arsenic.

Cell Duration After IV Delivery

Circulating cells in the blood

Cell type	Lifespan in circulation
RBCs	110-120 days
Platelets	8 days
Neutrophils	0.3 days
Lymphocytes	30 days



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Adapted from Tissue Engineering, Saltzman; Uke.de; Imperial.ac.uk

The duration of circulation depends on the **cell type** and the **donor**.

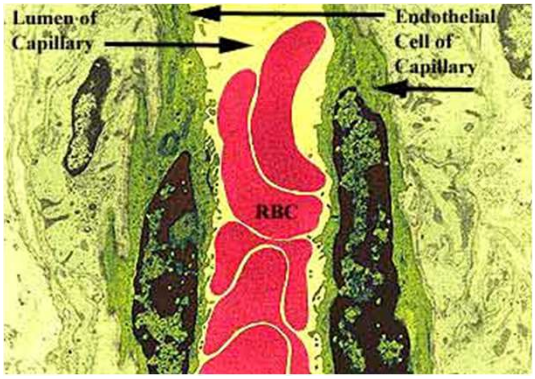
Transfused RBCs, for example, last approximately **110-120 days** in the circulation – this is about equal to the lifespan of a RBC and is determined by **donor related factors**.

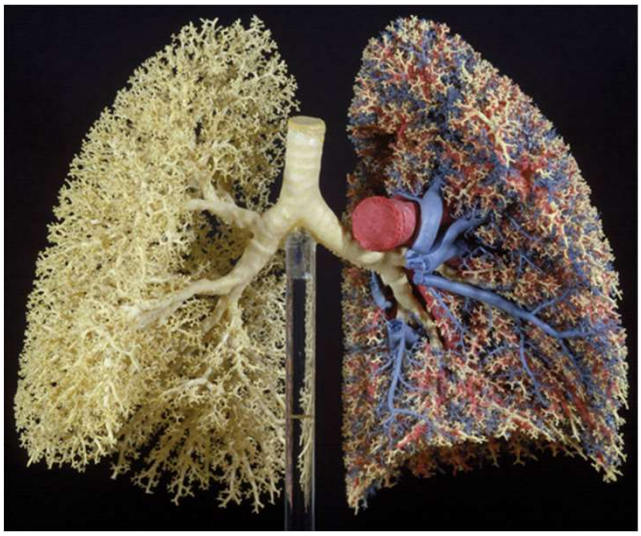
Cells that are **not** typically circulating and administered IV have a tendency to end up in a couple different locations.

The first is the **lungs**. As you can see in this image on the right, Infused **mesencymal stem cells** end up primarily in the lungs after just 5 minutes.

Mechanics of Lung Vasculature Trap Cells

Deforming RBCs in a capillary





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Faculty.une.edu; Imperial.ac.uk

The purpose of your lungs is to **maximize oxygen delivery** to your RBCs.

This is achieved through an intricate and extensive capillary network mirroring an equally intricate and extensive bronchi.

In this lung cast on the right, you can see the airways on the left in white and the arterial and venous vasculature.

Capillaries are on the order of 8-10microns in diameter, Which is **just about** the diameter of a neutrophil or RBC.

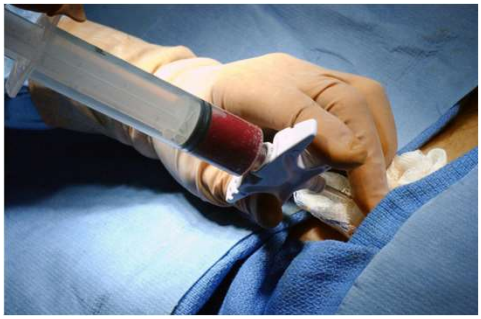
However RBCs move more quickly through the capillaries because they are **highly deformable**.

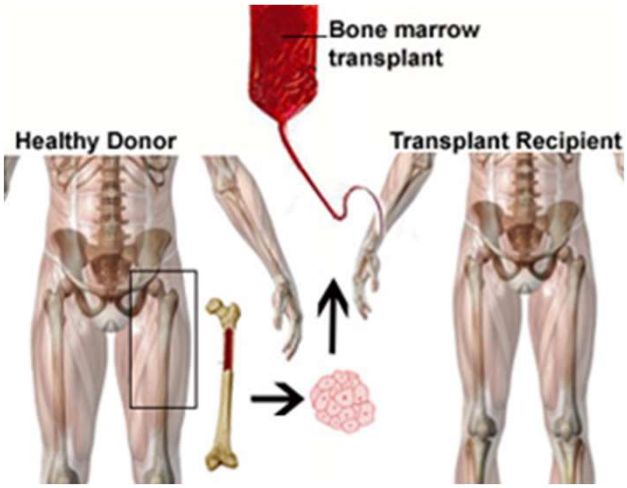
Neutrophils that are activated have a higher elastic modulus and decreasing deformability, which increases their transit time. This has benefits of course for the adhesion cascade, increasing contact with the endothelium. This is just another example of how mechanics play an integral role in cell and body functions.

You can see why larger cells (such as mesenchymal stem cells, sometimes over 30um after culture in vitro) would become trapped in this location – often one of the first capillary beds the transfused cells would encounter after injection into a vein.

Cell Homing of Transplanted Cells

Hematopoietic stem cells
know where to go
in transplants





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If cells don't get trapped in the lungs or elsewhere, tissue engineers would like to direct them to specific locations.

Targeting or homing is something that many cells in your body already do. Take bone marrow transplants for example.

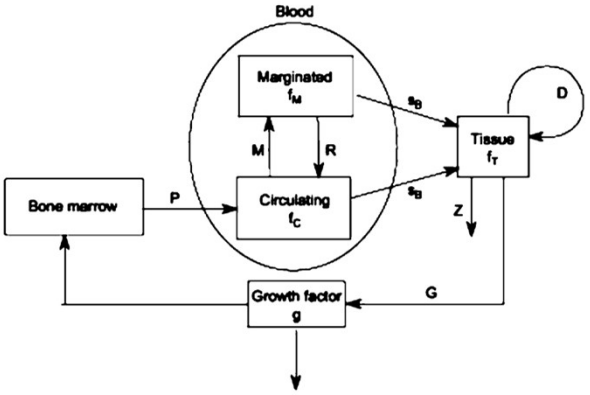
In these transplants bone marrow, or specifically **hematopoietic stem cells,** are harvested from a healthy donor – and then injected IV into an irradiated recipient.

These cells do need to be injected back into the **bone marrow space** – they simply **home** to that location and repopulate it. **They know where to go.**

Studies have also been done using isolated lymphocytes from the **blood** and from **lymph** tissue. Upon reinjection IV the cells from the blood tend **to stay in the blood compartment** while the cells form **lymph tissue** go back there.

Compartment Model of Cell Trafficking

M	margination
C	circulation
P	production in the bone marrow
Z	destruction
G	growth factor stimulation of production
D	proliferation in the tissue
R	Return



These studies and transplants tell us that homing, and targeting is **possible**.

As engineers we can use **computational** methods to **analyze** and **optimize** cell circulation and trafficking. In doing so we can try to predict the **ideal parameters** for our cell delivery strategies.

IN this diagram I'm showing you a **compartment** model of **monocytes** and neutrophils. Just as we did earlier this semester with receptor-ligand binding, ordinary differential equations can be written to describe this system.

This model includes two locations in the blood stream – **freely circulating and marginated**. These cells can travel to the **tissue** and **proliferate**, or be **destroyed**.

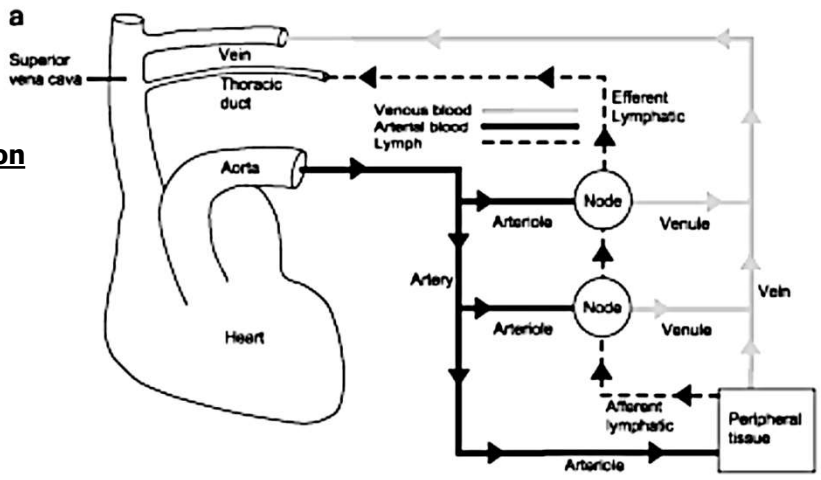
The tissue can also produce **growth factors** which stimulate production of more monocytes or neutrophils and sends them **into circulation**.

The researchers who developed this model and others run computer simulations to simultaneously solve the ODEs. The output of the simulations are predictions for **different immunotherapies**.

Circulatory System Paths

lymphocyte recirculation

Cell type	Lifespan in circulation
RBCs	110-120 days
Platelets	8 days
Neutrophils	0.3 days
Lymphocytes	**30 days**



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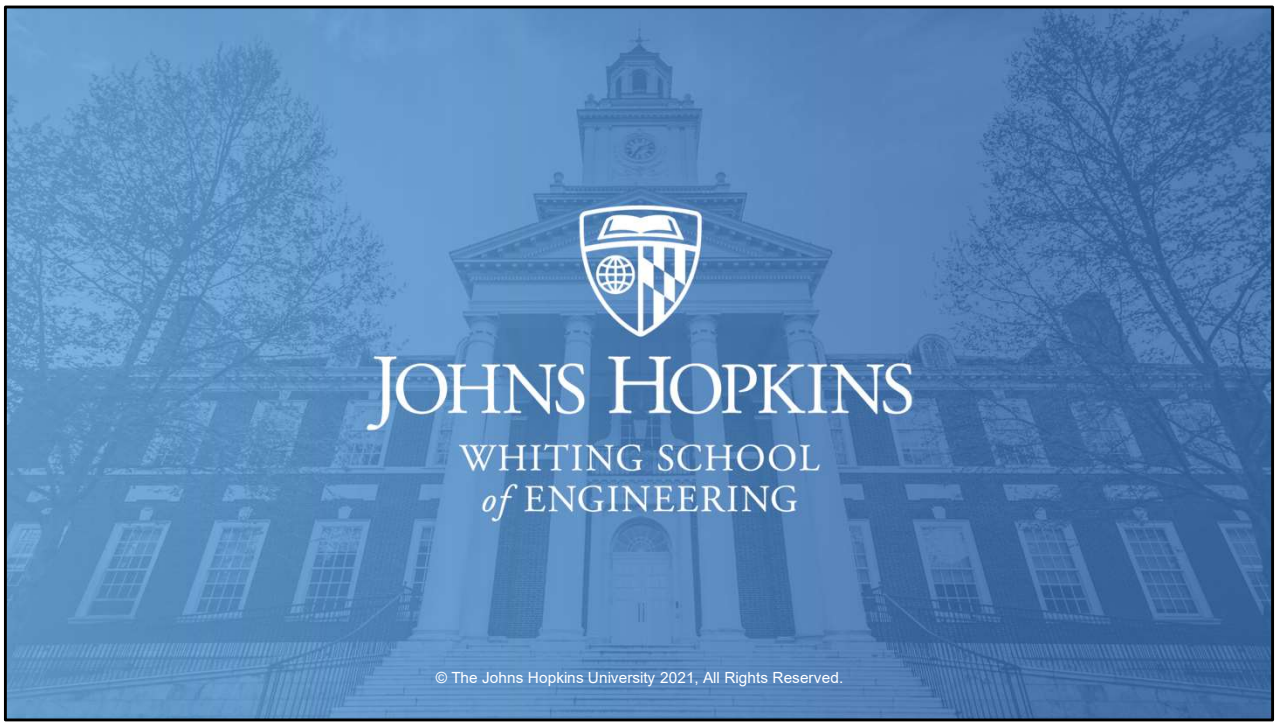
What that model didn't show are **the actual circulatory paths** in the body. Here I'm showing you a schematic of just that.

Lymphocytes or T-cells constantly **patrol** your circulatory system looking for foreign antigens. As you can see they **traverse** both the the **arterial** and **venous** side vasculature, moving in the direction of blood flow.

They also spend time in the **lymphatic tissues** – both the **nodes** and **flow.** If we follow from the **aorta** we see tracts to the major arteries – some cells splitting off in **arterioles** leading **to lymph nodes**, others taking **arteriolar** routes to **peripheral** tissues and organs.

They then return through **venules** leading to **collecting veins** and finally the **vena cava**. You can see the **lymphatic flow** leaving the tissue, going to the **lymph nodes** and back to the **thoracic duct**.

As we saw earlier healthy lymphocytes have a lifespan in the circulation of approximately 30 days.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