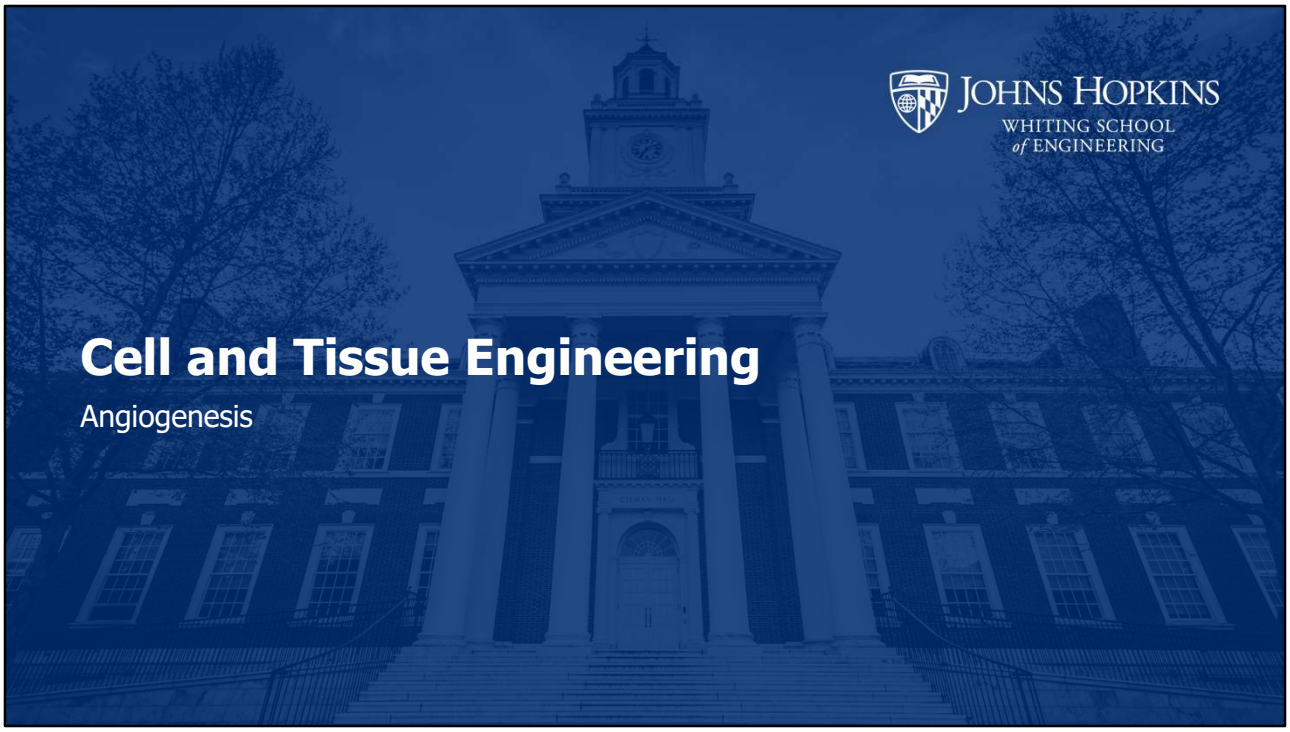
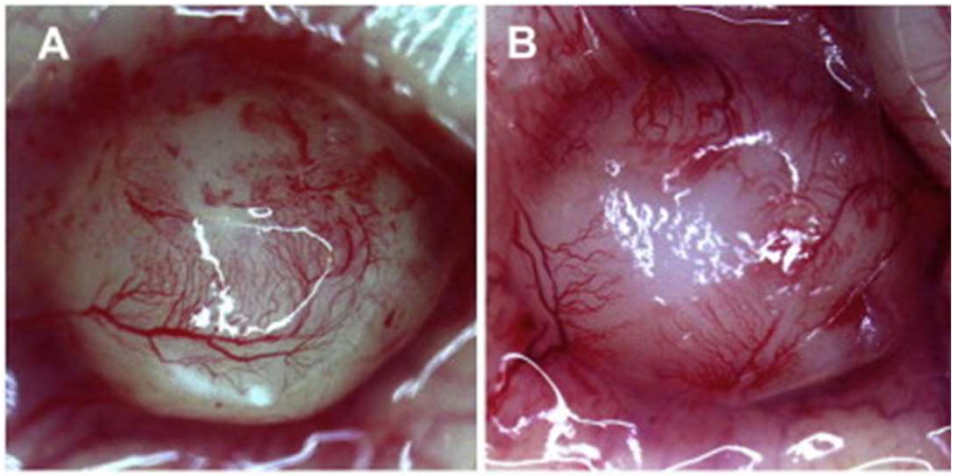


Cell and Tissue Engineering

Angiogenesis

Angiogenesis After Implantation

Host blood vessel growth into alginate beads



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Gong et al 2013

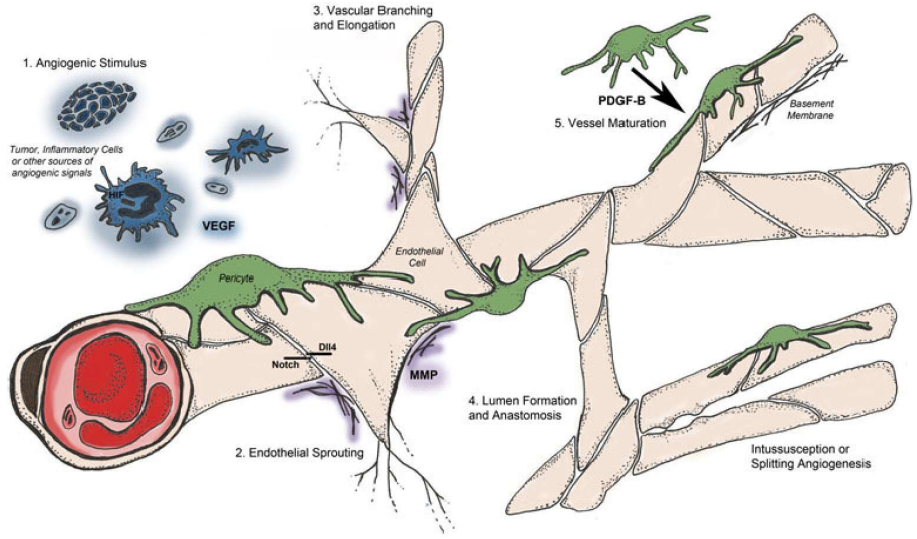
During wound healing new blood vessels grow into the injury site to replace those that have been damaged and to supply the tissue with necessary highways for trafficking repair cells.

New blood vessel growth is also critical to the survival of 3D tissue constructs that need the same highways for maintenance of the cell populations within them. Cells in the construct need **oxygen**, **nutrients**, and **waste removal** to function properly. So no matter what tissue you are engineering, you are always thinking about angiogenesis.

In this image, you are looking at blood vessels that have grown into alginate beads in a rodent model. You can easily see the **branched** structure of the vascular networks – extending from larger arterioles to smaller arterioles, and eventually capillaries.

ON the right you can clearly see the the growth is directed from the outside in – that is the vessels are growing towards the cell in the hypoxic center of the bead.

Angiogenesis Basics



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The process of angiogenesis is *generally* the same across all stimuli – including wound healing and implanted scaffolds.

This drawing breaks it down into 4 steps. We begin with a **stimulus** – **inflammatory** cells indicative of a wound, **tumor** cells trying to recruit a blood supply, or cells within the **construct** send out **distress** signals – these signals can also be directly supplied by the construct

One well known signal is **VEGF** or vascular endothelial growth factor – this and other signals call to the neighboring blood vessels to initiate **endothelial sprouting**. This is an important note – angiogenesis is the growth of **new blood vessels from preexisting** vessels not the **de novo** formation of blood vessels that occurs in early **morphogenesis**. In order to sprout towards the distress signal the surrounding ECM is broken down by **protease**

The vessel **elongates** and branches through **proliferation** and **migration** of endothelial cells. Current research shows that the **leading** or **tip** cell migrates while the **stalk** cells provide the necessary **proliferation**.

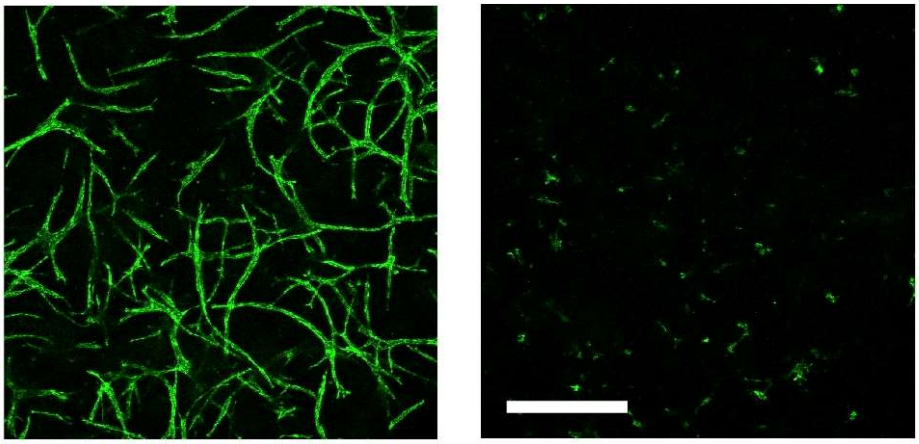
During this time the sprout is just a **chord** of endothelial cells – in step 4, lumens are constructed allow for blood flow in the new vessel.

Acquisition of supportive pericytes and basement membrane finally help the vessels mature and stabilize. Without these components the vessel will **prune** and **regress**.

This mechanism is for **sprouting** angiogenesis. We don't have time today to talk about **splitting** angiogenesis where one vessel divides longitudinally into two vessels. There is much less known about this mechanism.

Therapeutic Control of Angiogenesis

Induction **Suppression**



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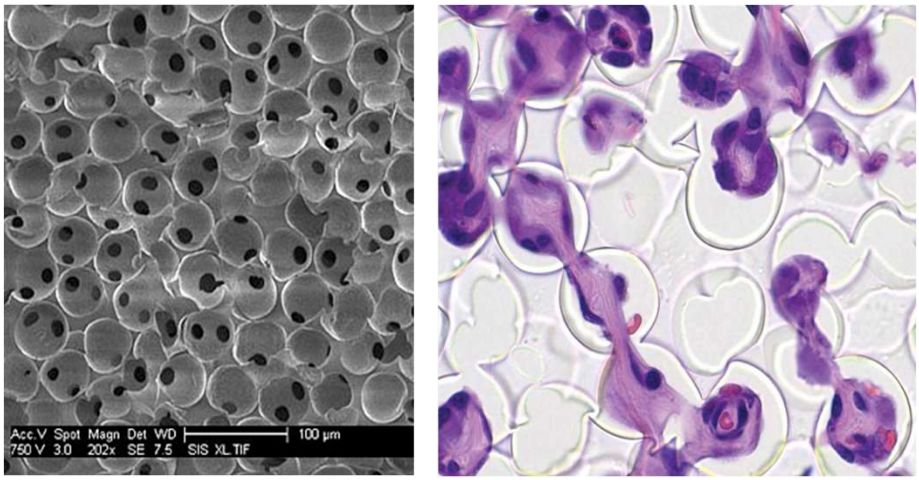
Hutton 2015

You body does a good job utilizing angiogenesis when needed. However, in tissue engineered settings we often need to help the process along through induction or stop the process if it is gone awry through suppression. Both of these modulatory actions fall under the umbrella of therapeutic control of angiogenesis.

Here you can see endothelial cells growing in a fibrin gel – these are exactly the same cells and construct, however the one on the left has the inducing factor VEGF and on the right suppressing levels of hypoxia.

Therapeutic Angiogenesis: Induction

Interconnected Hollow Spheres – 5μm pores



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No Vascularization in pores < 0.8 μm

5
Marshall, JA 2012

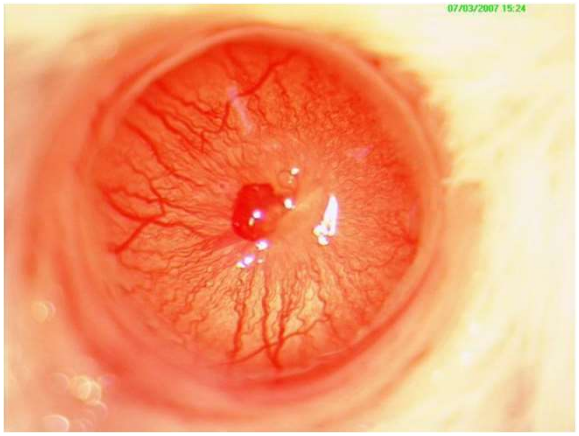
To achieve angiogenesis in a biomaterial you need **more than the signal** for growth – from encapsulated cells or seeded growth factor - you also need a suitable **pathway**.

Recent research has demonstrated that **pore size** regulates vascular growth and this idea is now explored at a commercial level with this product by the Healionics company.

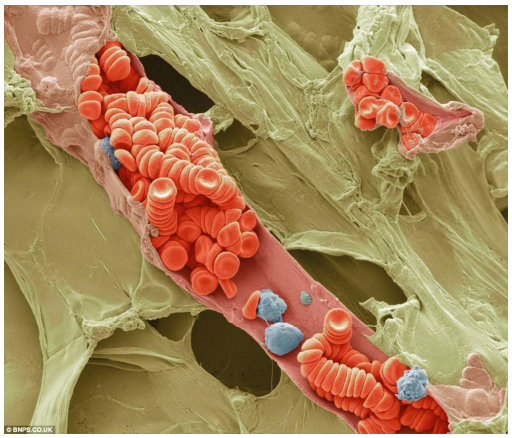
Their product features a unique structure of interconnected hollow spheres. IN this case the pores are roughly 5um. These create channels that allow for endothelial cell migration in angiogenesis. On the left you can see that after implantation blood vessels formed in this construct carry red blood cells.

Pores less than 0.8um were unable to support vascularization.

Therapeutic Angiogenesis: Suppression



Cornea – Naturally Avascular



Vascular network is an immune cell highway

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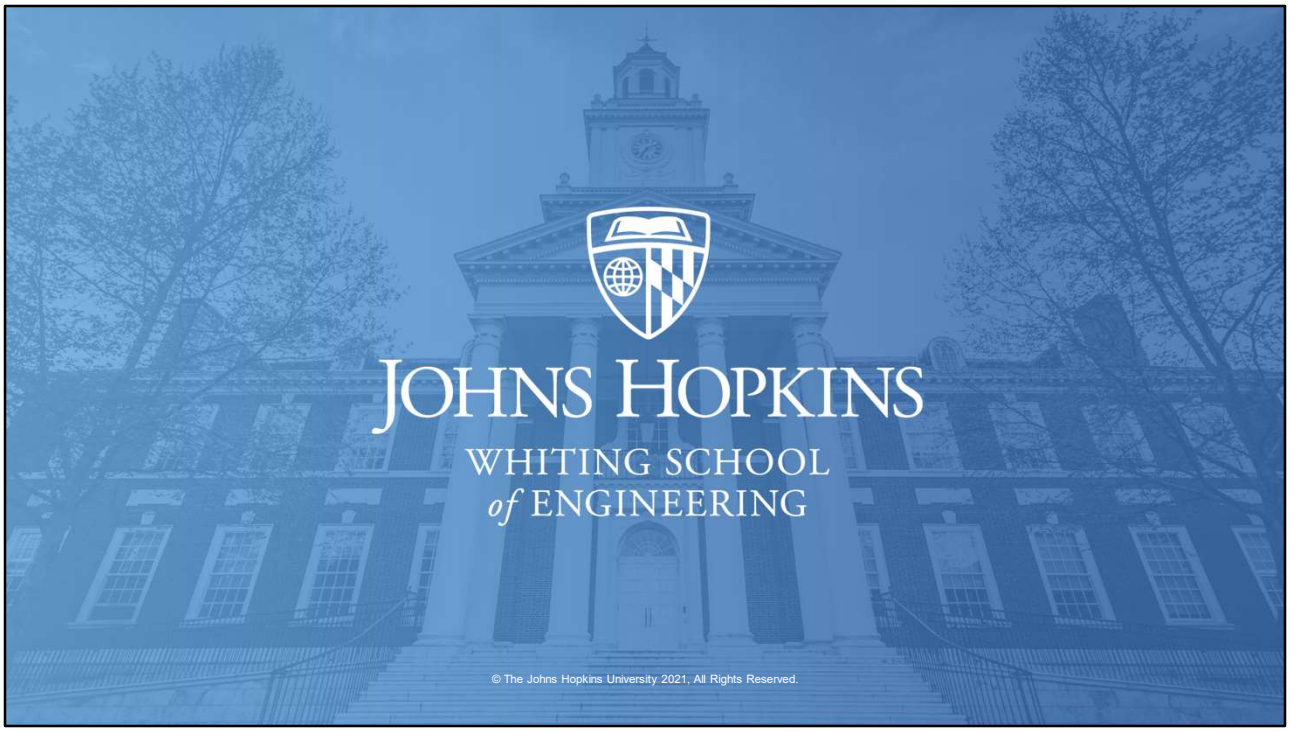
http://www.aiims.edu; Steve Gschmeissner

We need to decrease or block angiogenesis in tissues that are typically avascular – like the cornea and cartilage.

The cornea is actually a common tissue to perform pro-angiogenic assays since it is naturally devoid of vessels and is easily accessible for continuous monitoring.

Another reason to suppress angiogenesis is that in creating highways for needed oxygen delivery form red blood cells it also provides highways for immune cells.

Minimizing trauma during surgical implantation is one way to suppress angiogenesis and the inflammatory response in wound healing. This can reduce the chances of rejection.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