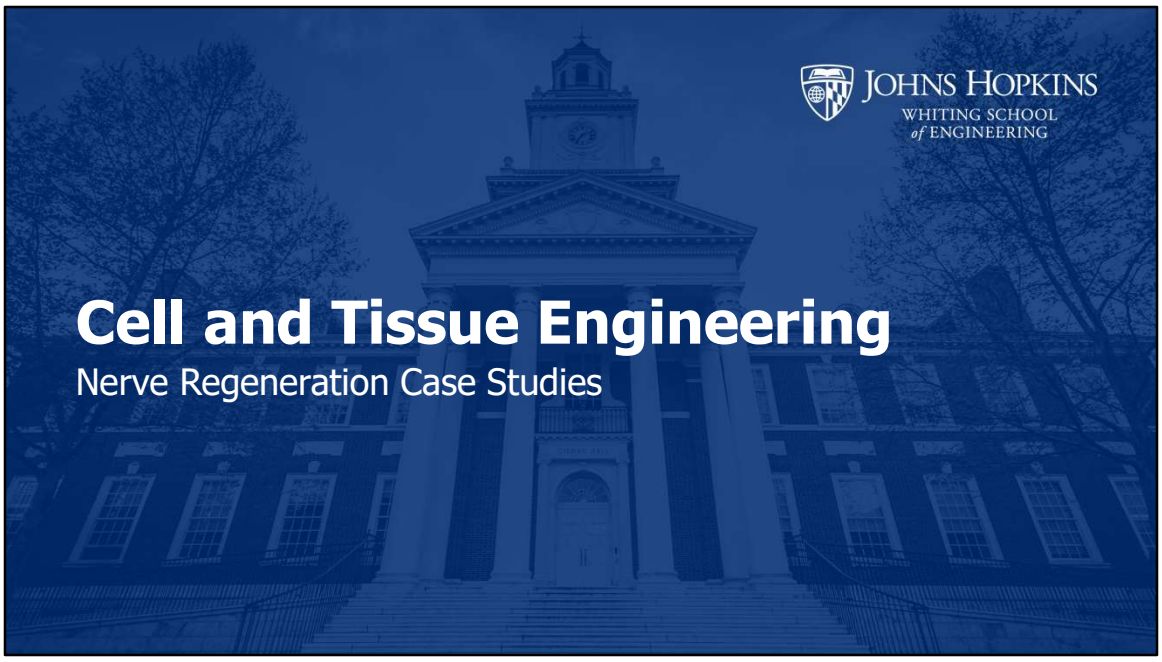
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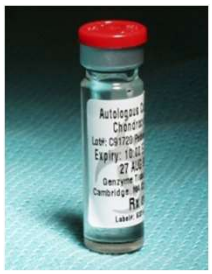
Cell and Tissue Engineering
Nerve Regeneration Case Studies

Case Studies in Tissue Engineering

Carticel (autologous cultured chondrocytes)



Epicel (cultured epidermal autografts)

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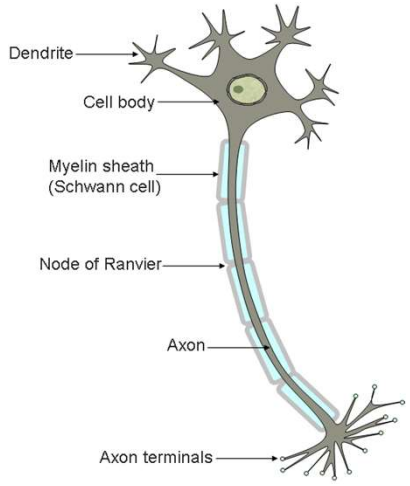
MACI, Smith & Nephew; GEM

The last tissue engineering challenge we'll talk about today is **nerve regeneration**. This is our third example of tissue engineered products, neurotube -- a Nerve guide made of absorbable woven polyglycolic acid mesh desiged for nerve repairs less than 3cm.

Nerve Regeneration – Small Gaps



Peripheral nerves *can* reconnect when distance < 1mm

Surgeons **reapproximate** nerve endings to close this distance

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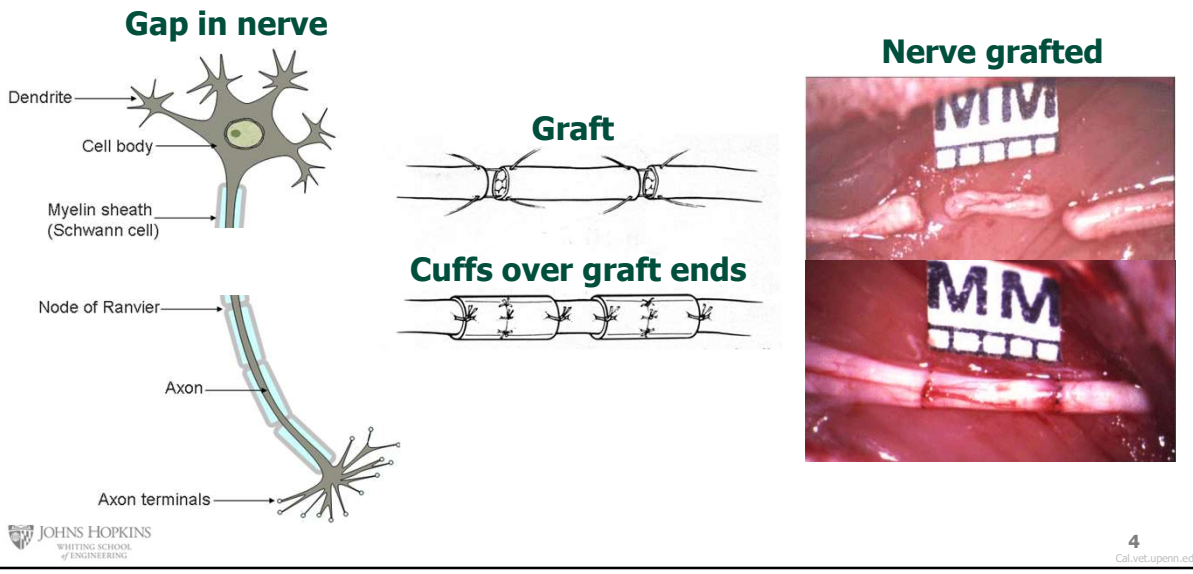
Scientopia.org

When a peripheral nerve is severed or injured the ends will only reconnect if the distance between the ends is small – by small I'm talking less than 1mm.

When the gap is this short, surgeons can actually go in and **reapproximate** the ends – they can bring the ends together.

Reapproximate - To bring (*separated parts*) back together, so as to close a wound or suture, etc.

Nerve Regeneration – Large Gaps



For larger gaps in peripheral nerves, the best strategy is to **fill** the gap site with an **autologous** or **allograft** nerve.

Here in the middle top schematic, you see the graft put between the proximal and distal ends of the gap. It is **sutured** in place, and then **cuffs** are placed around and sutured in place to protect the graft.

In the right panels, you see what this looks like for a 5mm gap. Here the sural nerve or short saphenous nerve has been **sacrificed** and is being used to repair another area.

Of course, these techniques are limited by **donor availability** and often show **fibrosis** at the suture sites, resulting in a **lack of function and failed repair**. For these reasons, alternatives (from the field of tissue engineering) are highly desired.

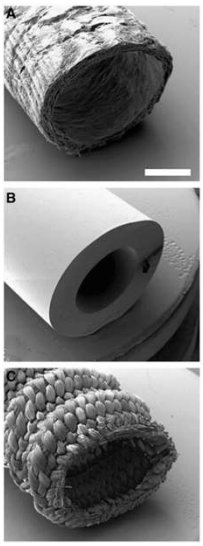
Nerve Guides / Conduits

Isolate the region for repair

Concentrates native growth/repair factors

Made from a variety of biomaterials

COLLAGEN	•NeuraGen® •Revolnerv® •Neuroflex™ •NeuroMatrix™
PGA	•Neurotube®
PCL	•Neurolac®
PVA*	•SaluTunnel™
SIS**	•AxoGuard™ Nerve Connector
CHITOSAN	•Reaxon® Nerve Guide



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Chrząszcz *Neurology and NeuroSurgery* 2018

One of the tissue engineered approaches to nerve regeneration is the use of a **nerve guide** or **conduit**. The idea is that you put the two ends of the severed nerve in the tube to **isolate** the region for repair – this isolation **concentrates** naturally produced **repair factors** from the nerve stumps, enhancing the body's regenerative potential

There are many FDA approved nerve conduits on the market– 3 examples are shown here on the right. **NeuroGen**, **Neurolac** and **Neurotube**, which we saw in the opening of this lecture. Most of the approved conduits are hollow structures made from collagen, polyglycolic acid, poly lactide caprolactone or alcohol-based hydrogels.

The middle column lists the many materials that have been used to make nerve conduits. You can see there are a number of collagen tubes, which have a range of degradation time from 8 months to 48 months.

Non-biodegradable materials have also been tested in humans including silicones, polytetrafluoroethylene and polyethylene.

Chrząszcz, Patrycja, et al. "Application of peripheral nerve conduits in clinical

practice: a literature review." *neurologia i neurochirurgia polska* 52.4 (2018): 427-435.

- https://core.ac.uk/download/pdf/268477169.pdf
- *Non degradable
- ** submucosa swine small intestine

FDA-Approved Nerve Conduits

Product name	Material	Structure	Company
NeuraGen®	Collagen Type I	Semipermeable, fibrillar structure of the collagen	Integra LifeSciences Co, Plainsboro, NJ, USA
NeuroFlex™	Collagen Type I	Flexible, semipermeable tubular collagen matrix	Collagen Matrix, Inc., Franklin Lakes, NJ, USA
NeuroMatrix™	Collagen Type I	Semipermeable tubular collagen matrix	Collagen Matrix, Inc.
NeuraWrap™	Collagen Type I	Longitudinal slit in the tubular wall structure	Integra LifeSciences Co
NeuroMend™	Collagen Type I	Semipermeable collagen wrap designed to unroll and self-curl	Collagen Matrix, Inc.
Neurotube®	Polyglycolic acid	Absorbable woven PGA Mesh Tube	Synovis Micro Companies Alliance, Birmingham, AL, USA
Neurolac™	Poly(D,L-lactide-co-ε-caprolactone)	Synthetic and transparent PLCL tubular structure	Polyganics BV, Groningen, Netherlands
Salutunnel™	Polyvinyl alcohol	Non-biodegradable PVA tubular structure	Salumedica LCC, Atlanta, GA, USA

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There are many FDA approved nerve conduits on the market– 3 examples are shown here on the right. NeuroGen, Neurolac and Neurotube which we saw in the opening of this lecture. Most of the approved conduits are hollow structures made from collagen, polyglycolic acid, poly lactide caprolactone or alcohol based hydrogels

Non-biodegradable materials have also been tested in humans including silicones, polytetrafluoroethylene and polyethylene.

Update 2016: Currently there are five commercially available FDA approved collagen type one nerve conduits: NeuraGen, NeuroMatrix, NeuroFlex, NeuraWrap, and NeuroMend (Table 3). Some collagen conduits have a degradation time as long as 48 months, while most have a short degradation time of four to eight months. https://www.hindawi.com/journals/bmri/2016/3856262/

https://www.dovepress.com/peripheral-nerve-conduits-technology-update-peer-reviewed-fulltext-article-MDER 2014

Improving Nerve Regeneration

Nerve Healing Process

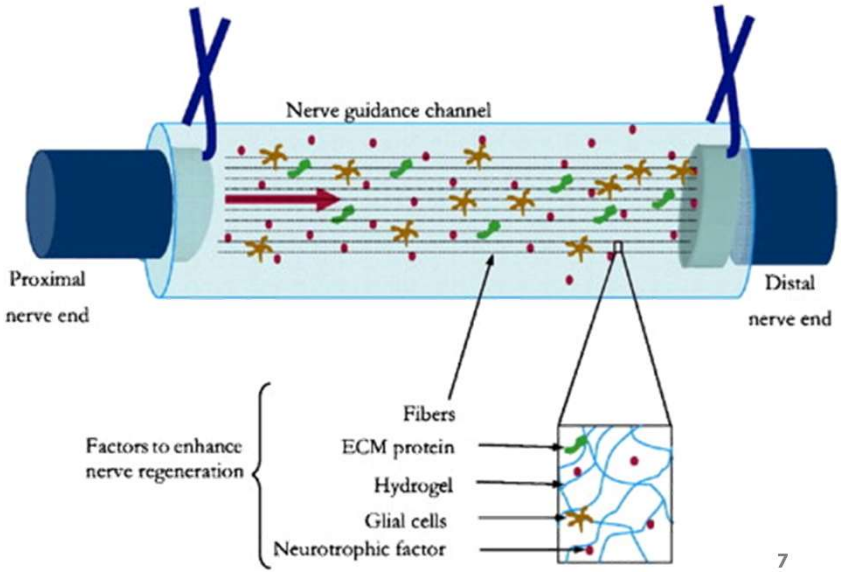
Fills with neurotrophic factors

Fibrin matrix develops

Matrix populated by Schwann cells etc.

Week 2 – Growth 1 mm/day

Finishes with myelin coat



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Studies have shown that in the first week following placement of a conduit the channel fills with **neurotrophic** factors (the pink dots here), then a **fibrin** matrix appears (blue here) which gets populated by **Schwann** cells, **fibroblasts** and **endothelial** cells.

By week 2, the axon is growing down the conduit at about **1mm/day** and finally the the new nerve tissue obtains a **myelin** coat.

To improve on the conduit, significant efforts have been made in **conduit scaffold material** – that is a material to fill the gap and introduce factors and support cells in this scaffold.

These modifications are attempts to **organize** and **accelerate** the naturally occurring process, speeding it along in hopes of superior regeneration.

Matrix components that are under investigation include: **collagen I, laminin, and Matrigel.** Although the concept of providing a **migratory path** is clear, the *experimental* results are not. In some cases, these matrices have **promoted** axon growth, while in others they've **stunted** it.

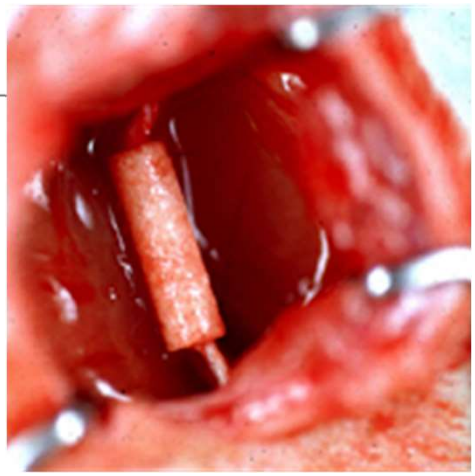
Recently experiments with **incorporated glial c**ells, which produce **neurotrophic** factors, have shown enhanced regeneration and myelination of the axon.

Tan, Aaron, Jayakumar Rajadas, and Alexander M. Seifalian. "Biochemical engineering nerve conduits using peptide amphiphiles." *Journal of controlled release* 163.3 (2012): 342-352.

- https://www.sciencedirect.com/science/article/pii/S0168365912006207
- Peripheral nerve injury is a debilitating condition. The gold standard for treatment is surgery, requiring an autologous nerve graft. Grafts are harvested from another part of the body (a secondary site) to treat the affected primary area. However, autologous nerve graft harvesting is not without risks, with associated problems including injury to the secondary site. Research into biomaterials has engendered the use of bioartificial nerve conduits as an alternative to autologous nerve grafts. These include synthetic and artificial materials, which can be manufactured into nerve conduits using techniques inspired by nanotechnology. Recent evidence indicates that peptide amphiphiles (PAs) are promising candidates for use as materials for bioengineering nerve conduits. PAs are biocompatible and biodegradable protein-based nanomaterials, capable of self-assembly in aqueous solutions. Their self-assembly system, coupled with their intrinsic capacity for carrying bioactive epitopes for tissue regeneration, form particularly novel attributes for biochemically-engineered materials. Furthermore, PAs can function as biomimetic materials and advanced drug delivery platforms for sustained and controlled release of a plethora of therapeutic agents.

Material Selection for Nerve Regeneration

Product name	Material	Structure
NeuraGen®	Collagen Type I	Semipermeable, fibrillar structure of the collagen
NeuroFlex™	Collagen Type I	Flexible, semipermeable tubular collagen matrix
NeuroMatrix™	Collagen Type I	Semipermeable tubular collagen matrix
NeuraWrap™	Collagen Type I	Longitudinal slit in the tubular wall structure
NeuroMend™	Collagen Type I	Semipermeable collagen wrap designed to unroll and self-curl
Neurotube®	Polyglycolic acid	Absorbable woven PGA Mesh Tube
Neurolac™	Poly(D,L-lactide-co-ε-caprolactone)	Synthetic and transparent PLCL tubular structure
Salutunnel™	Polyvinyl alcohol	Non-biodegradable PVA tubular structure



PLLA conduit in rat sciatic nerve model

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Biomed.brown.edu

Degradable conduits are designed to be eliminated by the time regeneration has occurred, while some non-degradable conduits need to be removed due to irritation. You can see that even for the same collagen material, there are many different structures that have been brought to market.

One things to note here is that the properties of the material selected can influence regeneration. In a study using the model on the right, with a rat sciatic nerve model, conduits with **smooth** surfaces resulted in attached nerve cables spanning the gap, while tests with **rough** surface polymer resulted in only **inflammatory** and **fibroblast** cell investment. From our prior lectures on surface properties, you understand how this happened.

Recap

Carticel (autologous cultured chondrocytes)

Epicel (cultured epidermal autografts)

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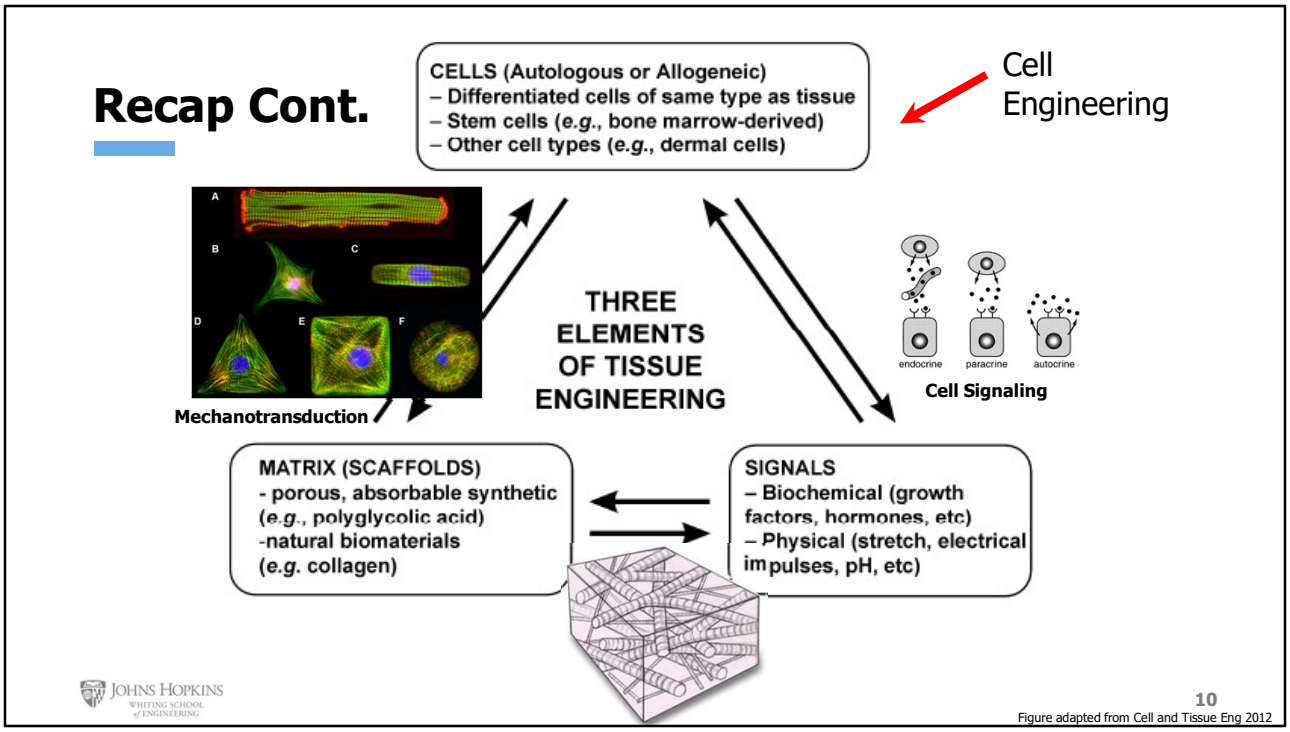
MACI, Smith & Nephew; GEM

Today we've covered a lot of material on tissue engineered products very quickly. To recap – we started with **cartilage** – looking cell free and cell containing solutions, their uses, limits and some FDA approval status. We next moved on to **skin** substitute and spoke about several of the commercially available products in this area. Last we examined the basics of **nerve regeneration strategies**.

What I want you to take away from this lecture is that these strategies, though **specific** to their tissue are not so **different** in their approaches.



Regardless of the tissue, we saw that approaches include the **three** elements of tissue engineering. The **tuning** of those pieces is what we spent the middle of the semester working on… how do we **select** and **tailor** a biomaterial – how do we **display** or **produce** a growth factor, how to do we select an appropriate **cell type**.

I hope that during and after this lecture you head is filled with those prior slides and texts, synthesizing the work you've put in over the semester, and you are starting to to see the complete picture of a tissue engineered product.

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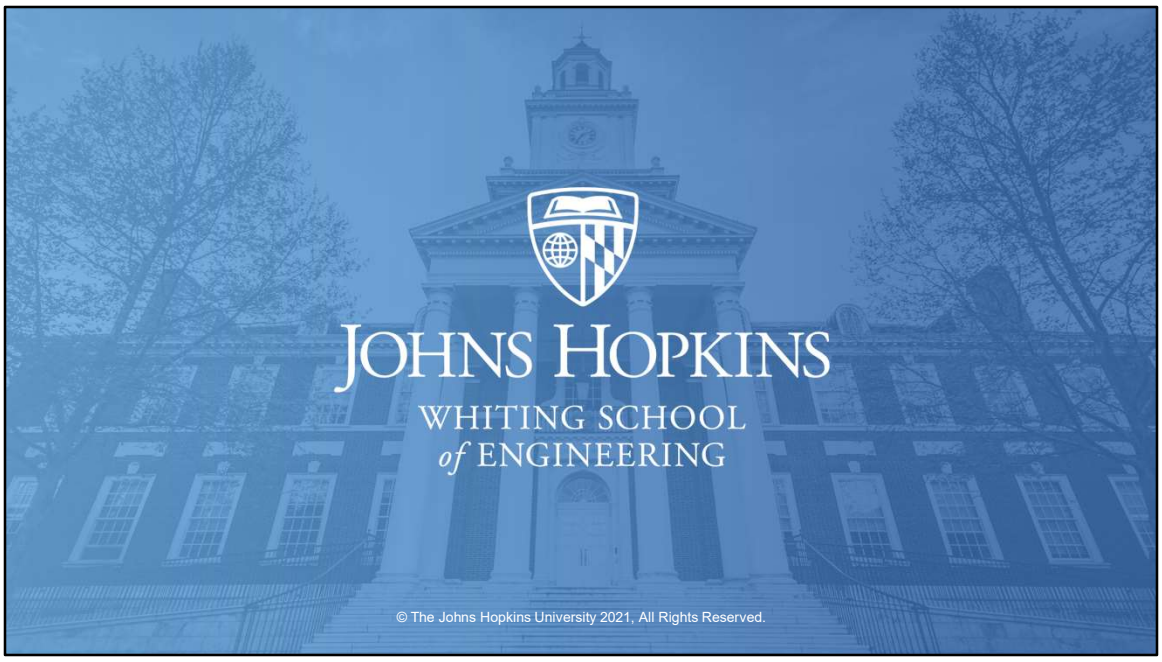
http://diseasebiophysics.seas.harvard.edu/research/mechanotransduction/
http://web1.johnshopkins.edu/JLAB/?page_id=8
http://alevelnotes.com/Cell-Signalling/131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