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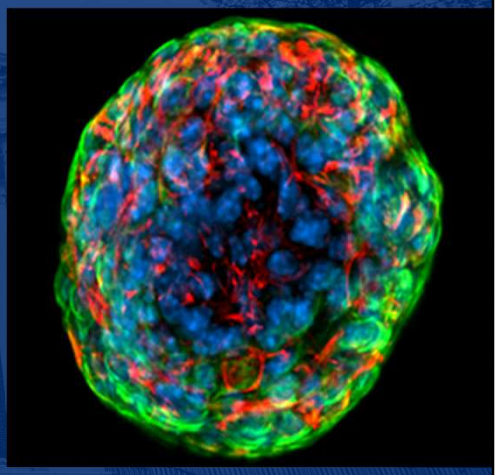
Cell and Tissue Engineering

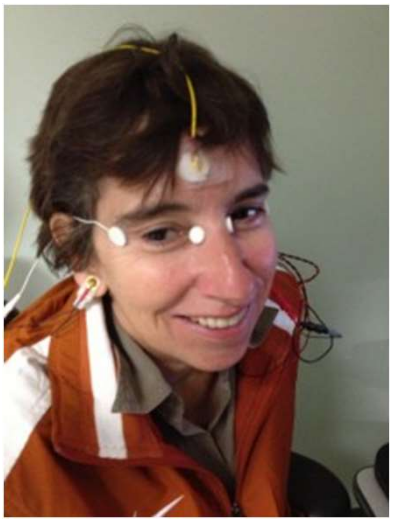
Using Stem Cells for Cell and Tissue Engineering



Stemcell.ny.gov

Stem Cell Rejection

- Embryonic stem cells
- Somatic or adult stem cells
  - Tissue resident (bone marrow, muscle, brain, skin teeth, heart, liver…)
- Induced pluripotent stem cells



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http://www.aisquared.com/blog/2013/08/looking-back-my-one-year-participation-in-a-stem-cell-clinical-trial/

Different types of stem cells have different interactions with the patient, especially the differences in **acceptance** by the patient's body.

The **rejection** status of embryonic stem cells is unknown. Two phase I clinical trials using these cells are testing for safety in treatments for Stargardt's Macular Dystrophy and age related macular degeneration.

Both are using embryonic stem cell-derived **retinal cells**. The first 4 patients have shown **no abnormal cell growth** or immune mediated transplant rejection. However researchers are uncertain as to whether this treatment has improved the **vision** of the patients.

The fourth patients from that trial is shown here – this patient received 100,000 cells at the Wills Eye Institute in Philadelphia.

A third clinical trial using oligodendrocyte progenitors derived from embryonic stem cells was **halted** in 2011 by the company Geron. This therapy was meant to treat spinal cord injuries, but the company canceled all stem cell programs to focus on only cancer therapeutics.

Somatic and induced pluripotent cells are autologous, however manipulation outside of the body, as we learned in the last module, can change that.

More recently, Japan's health ministry approved a a human clinical trial using iPS cell again to treat age related macular degeneration,

In 2014 the first patient in that study, 70 yo woman with age related macular degeneration, was treated with iPSCs in a 1.3x3mm sheet of differentiation retinal pigment epithelium cells. Importantly, this first patient was treated with autologous iPSCs, while future patients in the trial were treated with donor-matched cells – because the regulatory landscape in Japan changed.

In 2017, the company, RIKEN, reported a **severe adverse event** – the formation of a pre-retinal membrane which caused retinal edema, and the intervention surgically remove the membrane. The company thought it more likely that the cause of the membrane was the surgical procedure to implant the cells and not the cells themselves.

In Jan 2021, the same site began a broader trial with 50 patients with a variety of retinal pigment epithelium disorders.

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https://www.nature.com/articles/nature.2014.15915
https://www.nature.com/articles/nbt0915-890
https://www.nippon.com/en/news/yjj2021012000786/
https://ipscell.com/2018/01/adverse-event-in-ips-cell-trial-for-vision-loss-in-japan/

Blood and Tissue Matching Lowers Rejection Risk

- Allogenic
- Autogenic

- Bone Marrow
- Cord Blood
- Circulating Stem Cells

- Leukemia, lymphoma, sickle cell, ovarian cancers, neuroblastomas

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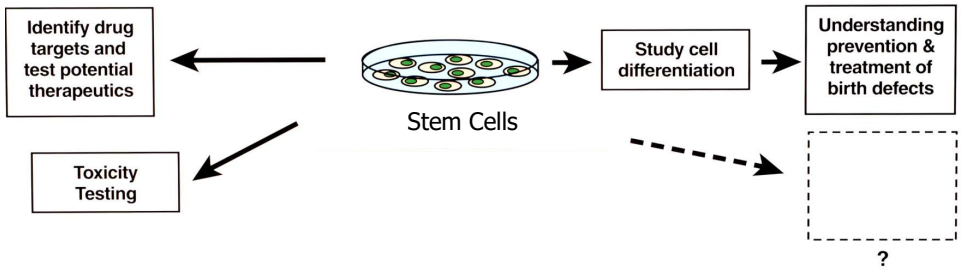
http://learn.genetics.utah.edu/content/tech/stemcells/sctoday/

Adult stem cells have been used in therapy for decades – think back to our talks on bone marrow transplants, cord blood, and circulating stem cells. Hematopoietic stem cells treat blood cancers such as leukemia and lymphoma, as well as sickle cell disease, ovarian cancers, and neuroblastomas.

These include both allogenic and autologous transplants which have low rejection risk when blood and tissue matched appropriately.

One advantage of banked, donor-matched cells, especially with iPSCs, is the ability to **observe genomic stability** before releasing cells to a patient. This advantage is one of the reasons for the change in Japan's regulatory landscape in the last slide.

Using Stem Cells to Advance Medicine



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http://www.youth-restored.com/types-of-stem-cells/

Ever since the discovery of stem cells, researchers have been excited about their potential use in tissue engineering.

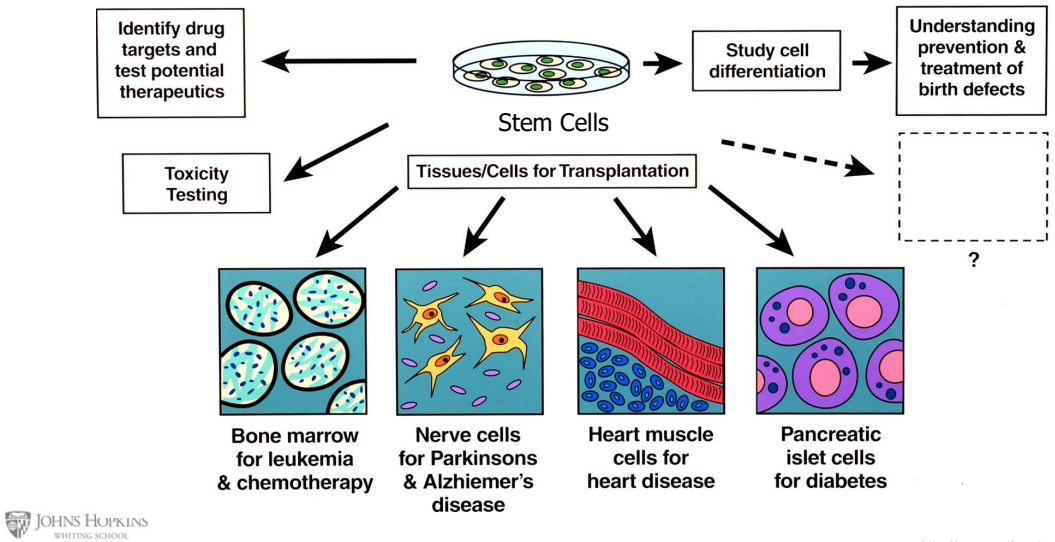
Starting here on the left, **models** can be built for **testing** drugs or finding potential **drug targets**.

And along the same grain, these models can be used for **toxicity** testing. You can imagine how **bioreactors** can be used in the same way.

On the right we see another avenue for tissue engineering research – that is simply **studying cell differentiation pathways**. This understanding is necessary not only for building cells and tissues, but also for controlling the cell phenotypes **in the long run**. This is further needed for understanding **birth defects** and associated **therapies**.

There is also an unknown box here – the mystery box which stands for the applications we don't yet know for these cells – perhaps something one of you will discover in your future work.

Using Stem Cells in Tissue Engineering



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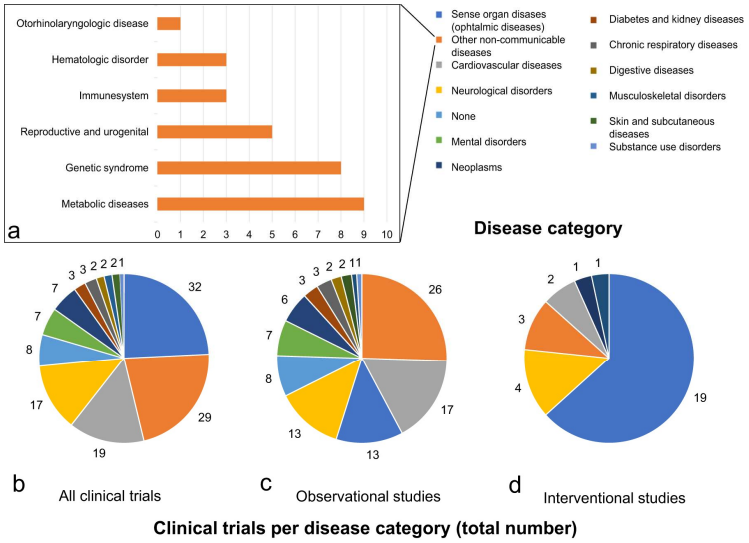
http://www.youth-restored.com/types-of-stem-cells/

Most of this course, we have been speaking of building cells and tissues – this is the most fundamental use of stem cells in tissue engineering

Here are some examples, we have talked about historic uses of bone marrow for cancer but there has also been success with **transplanted nerve cells** for treating Parkinson's and Alzheimer's diseases; Generating new **cardiac tissues** to replaced that which has been damaged by heart disease, or creating new **pancreatic islet cells** to cure diabetes.

Clinical Trials with Stem Cells

- iPSC, ESCs, Autologous
- Observational vs Interventional
- Ophthalmic disease
  - Contained implant site



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Deinsberger, Julia, David Reisinger, and Benedikt Weber. "Global trends in clinical trials involving pluripotent stem cells: A systematic multi-database analysis." *NPJ Regenerative medicine* 5.1 (2020)

Over the past two decades, there has been a growing amount of **stem cell clinical trials,** however very few **actual products** have been spun out to consumers.

One reason is because they are spread across a wide range of target diseases – although you can see there are 19 studies for ophthalmic diseases. Why ophthalmic? Well the eye is a relatively contained and immune privileged environment. You could also understand the benefit-risk to that patient population, most have already lost the majority of their eyesight and exhausted other medical treatment options, but otherwise have a good life expectancy.

Another reason we see very few translated studies is the **early state of the field**. We are continuing to rapidly discover the **how** of stem cells, and developing the tools to build, control, and engineer them. This it why you can see there is a massive share of observational studies for stem cells – trials where they are placed just to observe what happens (including safety data).

I want to quickly note that the use of stem cells is not sweet and rosy. Initial trials observed sometimes severe **immune** reactions and **dangerous cytokine storms**. Over the past decade, there's been a boom of '**stem cell clinics**' that are often unregulated and dangerous. They have not demonstrated effective treatments, but there is a record of adverse events: Many of the AEs identified involved serious bacterial infection, including at least two cases of septicemia, a life-threatening blood

infection. Others included serious and even lifelong disabilities such as partial or complete blindness (9); paraplegia (1); pulmonary embolism (6); cardiac arrest (5); tumors, lesions, or other growths (16); and organ damage or failure in several cases that resulted in death. Many of these AEs required hospitalization (104) and caused acute or worsening pain (55). The most common type of interventions linked to these AEs were autologous (that is, the stem cells were obtained from the patient's body) or donor stem cells administered by injection into the eye, spine, hip, shoulder, or knee.

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https://www.nature.com/articles/s41536-020-00100-4
https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/06/harms-linked-to-unapproved-stem-cell-interventions-highlight-need-for-greater-fda-enforcement

Stem Cells in Tissue Engineering for Replacement Tissues

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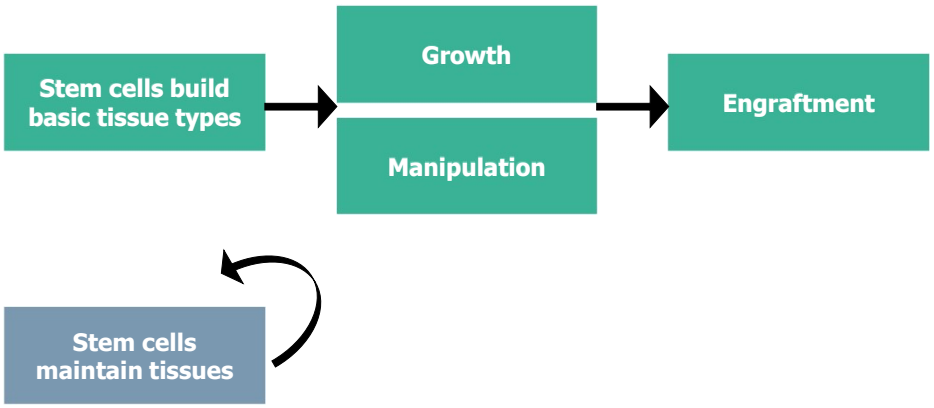
We have, at our fingertips, pluripotent and multipotent cells from which we can build the cells and tissues we want. The clinical trials we just saw at the start of this video used a single cell type derived from stem cells as a treatment.

To design a new tissue you need need to think about specific the stem cell **population** you want to start with – **growth** of that population to appropriate **numbers**, **manipulation** if needed into the various **lineages** – recall our prior discussion on the necessity of the blood supply – and then finally you need to think about **engrafting** this tissue.

Remember – Reservoir of Stem Cells for Homeostasis



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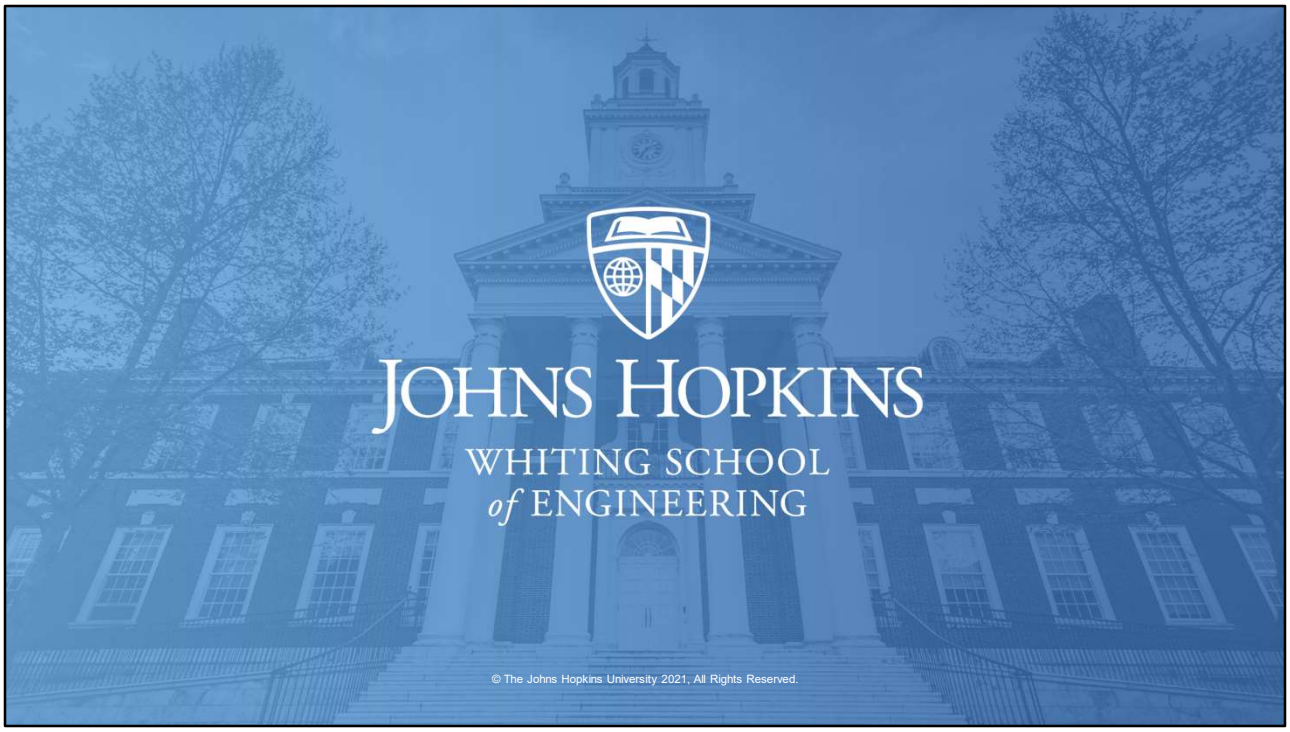
Beyond just building new tissues in the lab, tissue engineers need to remember the original purpose of the cell when designing the application.

Somatic stem cells are thought to reside in the tissue as a safety reservoir – there to repair the tissue when needed and return the body to homeostasis. It's important to think about how your application will survive over time – does it have it's own reservoir? Futher, it is thought that depleting this reservoir to create therapies may **diminish** the body's natural ability to repair.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