Cell Therapy in Hemophilia: What the Future Holds

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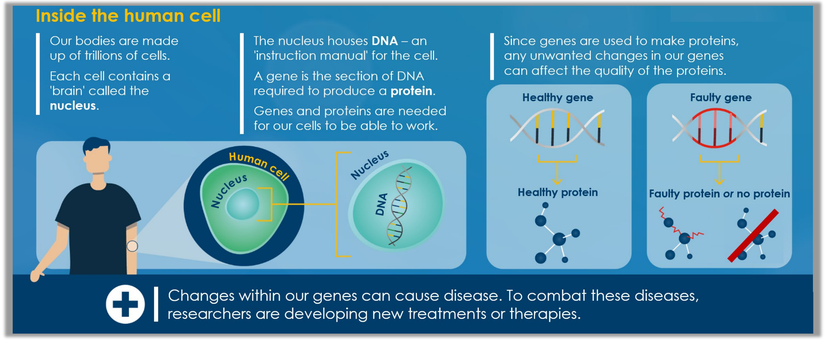
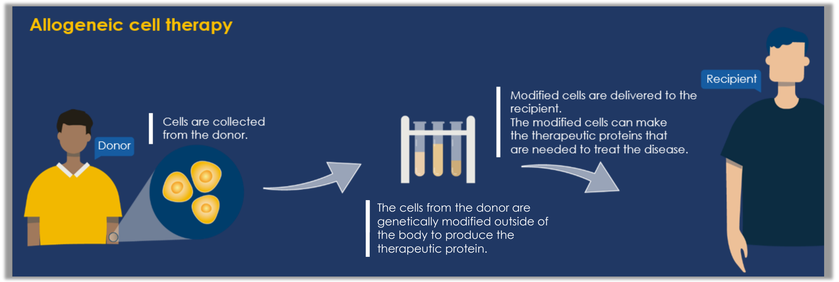
What is Allogeneic Cell Therapy?



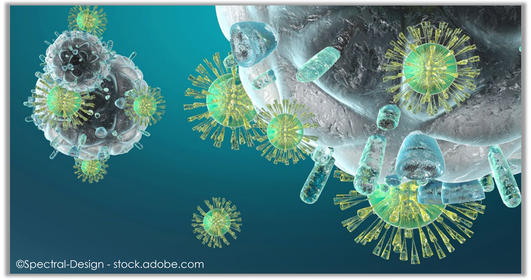
- **What is allogeneic cell therapy?**
  - Allogeneic cell therapy involves the transfer of whole cells into a person with a disease or condition to make up for the cells that are not working properly
  - The cells can be obtained from another person or from established human cell lines
    - The benefits of using established human cell lines is that there is ample supply, they are well characterized and they can be engineered more easily to produce therapeutic protein



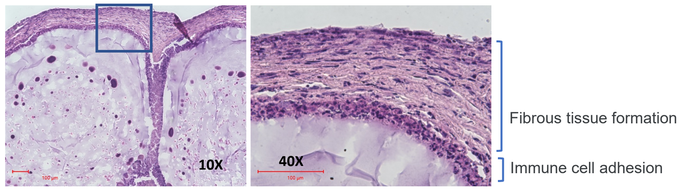
- Most proteins that are missing in **rare blood disorders** (e.g., factor VIII, factor VII, etc.) are **good candidates for cell therapy**:
  - ✓ their levels can vary widely without any toxicity (i.e. there is a minimal risk of overdose),
  - ✓ not much is needed for the patients to have a marked improvement in their symptoms
  - ✓ and their production is not regulated in response to bleeding

Key Challenge and Potential Solutions for Allogeneic Cell Therapy

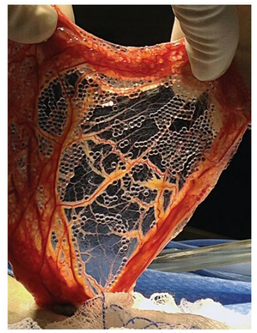
- One of the most significant **challenges** of allogeneic cell therapy is **immune rejection by the recipient** since the cells come from a different person
- Various biomaterials and/or devices can be used to protect the cells from the recipient's immune system



- However, they themselves can illicit a response called *foreign body response* which results in build-up of a thick layer of scar tissue called **pericapsular fibrotic overgrowth** or **PFO** (see microscope image below)



- PFO seals the encapsulated cells off from the recipient's body and **prevents nutrients from entering and therapeutic protein from getting released**
- As expected, **the longevity of cells encased in PFO is severely reduced**
- Thus – in order to provide a durable source of therapeutic protein, **there needs to be a technology which shields the cells from the recipient's immune system**
- Recently, scientists at Massachusetts Institute of Technology (MIT), identified **a group of molecules** that when combined with alginate (seaweed) **avoid the build-up of PFO** (see photo of clear alginate spheres on the right)
- This technology was applied to a **modular platform** which consists of **human cells that produce therapeutic protein (e.g. FVIII)** and that are **shielded by the two-compartment alginate sphere** which nurtures the cells and protects them from the recipient's immune system
- A **phase 1/2 clinical trial** of this investigational therapy in **hemophilia A** is expected to open in **2020**



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Context and Future Goals

How does allogeneic cell therapy for rare blood disorders fit in the context of new potential therapies like gene therapy?

- Both cell therapy and gene therapy have the potential to correct the faulty gene and thus **deal with the illness at its root cause**

Feature	Allogeneic Cell Therapy*	Gene Therapy*
Delivery of the corrected gene	• Uses cells from another person; the cells are genetically modified to produce therapeutic protein	• Viral construct (vector) used to introduce the genes to host cells
Placement in recipient's body	• Varies, but the cells remain within the protective material and/or device and do not mix with the recipient's cells	• The vector targets recipient's liver cells for delivery of the needed gene; there is potential for integration into the recipient's DNA
Eligibility	• Assuming a healthy person (despite their rare blood disorder), there are no limitations	• People with antibodies to AAV (common viral vector) and/or with liver disease are ineligible
Controlled dosing	• Yes – the amount of therapeutic protein produced increases with the amount of product (cells) placed in the body	• No – it is difficult to predict how much therapeutic protein will be produced in the recipient's body
Re-dosing	• Possible	• Currently not possible
Retrievability	• Potentially – devices can be removed, and shielded cells can also be removed if necessary	• No – once in the body, the viral vector is there permanently
Use in children	• Potential for use in children since the dose can be adjusted to the person's size and the product can be re-dosed.	• None for rare blood disorders; one approved gene therapy for ultra rare spinal muscular atrophy is available for children.
FDA approved	• No	• None in rare blood disorders yet

*Gene therapy has been, and is being studied, in a number of clinical trials. Cell therapy has not been studied in the clinic yet.

Additional reading:

- Cell Therapy in Hemophilia: Past, Present and Future, By Jelena Garafalo, Ph.D., Guillaume Carmona, Ph.D., and Devyn Smith, Ph.D. with Sigilon Therapeutics Inc., Cambridge, Mass. *Originally printed in Hemophilia Federation of America's 2019-20 Special Dateline Federation Magazine: Emerging Therapies*

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