

# Experimental Evidence Demonstrating “Homologous Use”

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# Definition

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**Ø Homologous use: repair, replacement or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic functions in the recipient as in the donor.**

**Ø Scientific evidence demonstrating that:**

**Ø HCT/P “inherently” have the property(ies) that lead to clinical efficacy**

**Ø HCT/P actually perform the same function in the donor**

# Example #1

**Homologous:** Hematopoietic stem cells for blood reconstitution

Ø Mechanism of action known: Direct cell proliferation and differentiation

## Scientific Evidence?

1. *In vitro* culture – progenitor cells can grow and differentiate
2. Animal models-lethal irradiation, rescue with bone marrow or even highly purified cells given I.V., blood cell counts eventually recover to “normal” levels.
3. Genetic marking to show new blood cells derived from donor stem cells.

## Example #2

**Non-Homologous:** *Stem cells for cardiac repair*

*Problem: mechanism(s) of action for efficacy unknown?*

- § *Direct differentiation*
- § *Fusion*
- § *Reduced inflammation*
- § *Stimulation of endogenous repair*
- § *Improved blood flow*

### **Scientific Evidence?**

**Problems:** *Efficacy may be multi-factorial, hard to determine mechanisms of action*

*HCT/P capabilities may only be seen during injury  
(not normally seen in donor)*

## Example #3

### **Non-Homologous:** Stem cells for autoimmune diseases

**Problem:** mechanism(s) of action for efficacy somewhat unknown?

- § Direct differentiation into hematopoietic blood cells, including lymphoid compartments – **already demonstrated**
- § New immune system is not “identical” to pre-high dose therapy
  - § Change in regulatory environment, shift in T-cell subsets
- § Other?

### **Efficacy is multi-factorial**

**Not all due to infused cell product**

**Hard to determine mechanism(s) of action**

**Different immune reconstitution only seen after injury  
(not normally seen in donor)**

**What scientific evidence needed for Homologous Use?**

## Example #4

***T<sub>reg</sub> for GVHD***

***Mechanism of Action – reduce allogeneic T-cell response***

- § *In vitro MLR testing*
  - § *Cytokine release*
  - § *Direct interaction*
- § *Small animal model data*
  - § *Reduce/eliminate GVHD*
  - § *Control autoimmune disease*

***Homologous or not?***

- § ***No GVHD or autoimmune disease in original donor***

## Next Steps?

Ø **Guidance from FDA?**

Ø **Working Group?**

**For Discussion**  
**Clarification of the Definition**

**21CFR1271.3**

***Homologous use: replacement or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic functions in the recipient as in the donor.***

***Proposal for consideration:***

***Homologous use: Intuitive or already clearly documented clinical evidence for efficacy in a specific clinical application.***

**It's not the product, it's the Clinical Application!**