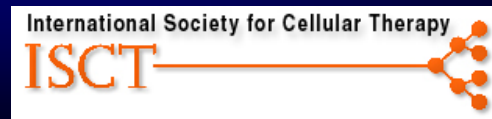


Experimental Evidence Demonstrating “Homologous Use”

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Definition

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➤ ***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.***

➤ **Scientific evidence demonstrating that:**

- **HCT/P “inherently” have the property(ies) that lead to clinical efficacy**
- **HCT/P actually perform the same function in the donor**

Example #1

Homologous: Hematopoietic stem cells for blood reconstitution

- *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_{reg} 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?

- **Guidance from FDA?**
- **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!