How the Alpha Stem Cell Clinics Network Delivers Stem Cell Treatment to Patients

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Presentation Outline

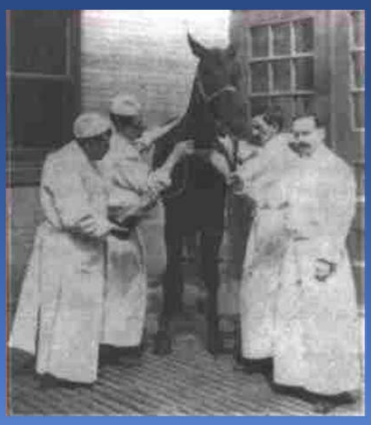
1. Historical Context for Cell Therapies
2. Current Regulatory and Best Practices for Stem Cell Treatments
3. Overview of the Alpha Stem Cell Clinics (ASCC) Network
4. How the ASCC Network Addresses these Consideration
5. Conclusion

The History

In 1901, diphtheria patients were routinely treated with antitoxin derived from the blood serum of horses. There were no central or uniform controls in place and the antitoxin was often manufactured in local plants.

In St. Louis, Missouri, that combination had tragic consequences. Thirteen children died of tetanus after being treated with diphtheria antitoxin made from the blood of a tetanus-infected retired, milk wagon horse named Jim.

The History: Jim the Milk Wagon Horse



Source: https://en.wikipedia.org/wiki/Jim_(horse)

The History: The Biologics Control Act

Soon after this and a similar tragedy in Camden, NJ, involving deaths and injuries related to a tainted biological product, Congress enacted the Biologics Control Act of 1902.

July 1, 2019 marked the 118th anniversary of the law, which gives the FDA's Center for Biologics Evaluation and Research (CBER) authority to regulate biological products and ensure their safety.

Definitions: Biologics

Biologics are medical products derived from living sources

- Includes vaccines, blood and blood derivatives, allergenic patch tests and extracts.
- Tests to detect HIV and hepatitis required
- Gene therapy / gene transfer products, cells and tissues for transplantation

Biologics may form the basis of novel treatments for a multitude of illnesses, including cancers, diseases of the immune system, and organs in need of repair or replacement

Definitions: HCT/Ps

HCT/Ps are human cell tissue products. The FDA "generally" considers an HCT/P to be for homologous use:

- Recipient cells or tissues that are identical (e.g., skin for skin) to the donor cells or tissues, and perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor; or
- Recipient cells or tissues that may not be identical to the donor's cells or tissues, but that perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor.

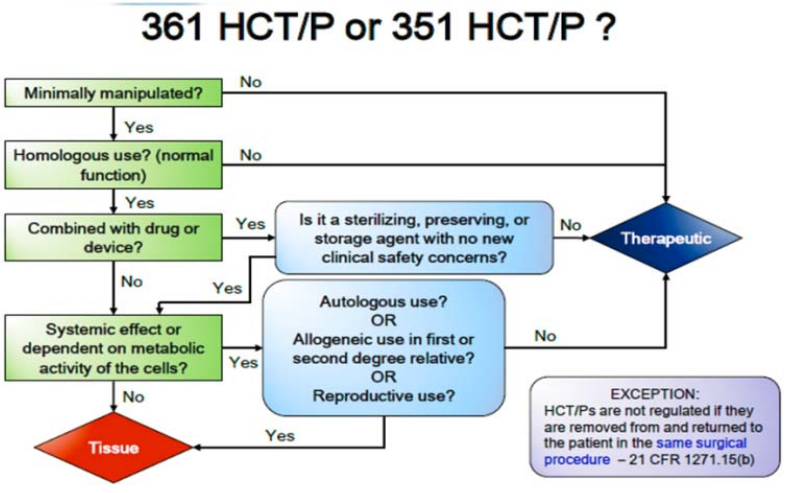
HCT/Ps: Two Regulatory Tiers

1. Tissue section 361 HCT/Ps are *lower risk* products
   - Premarket review not required
   - Product regulated solely under tissue regulations to control communicable disease (21 CFR 1271 & Subpart B)
   - Establishment registration and product listing required
2. Therapeutic section 351 HCT/Ps are *higher risk* products
   - Products regulated under tissue regulations and premarket review requirements (21 CFR Parts 1271)
   - Regulatory pathway can be Biologic or Device

HCT/P Under Section 351

Products under Section 351 require conducting clinical investigations under an ***investigational new drug (IND) application*** *and obtaining a* ***biologics license*** *through the FDA, whereas requirements under Section 361 focus only on the prevention of communicable diseases.*

HCT/P 361 or 351? Decision tree



QUINTILES

GMP: Good Manufacturing Practice

- A ***national*** standard for the production (manufacturing) of pharmaceuticals that assures safe and effective drugs (21 CFR 210, 211)
- Standard Operating Procedures (SOPs) govern every aspect of a GMP manufacturing process, including a GMP facility
- Strict environmental control to assure manufacturing of a sterile, potent and uncontaminated product for human administration.

GMP: The UC Davis Mantra

- ***It is not go***od enough to have a GMP facility, it is vitally important to run it at GMP level!
- SOPs for environmental cleaning, monitoring, presence of personnel 7 days a week

cGMP: Current Good Manufacturing Practice

- SOPs and documentation for everything
- Quality control (QC) and quality assurance (QA) personnel (different people) and procedures in place
- Product and reagents acceptance and release criteria defined and controlled (sterility and potency)
- Personnel training and testing for proficiency according to SOPs
- **DOCUMENT, DOCUMENT, DOCUMENT: WHAT ISN'T WRITTEN DOWN, DOESN'T EXIST!**

GTP: Good Tissue Practice

- Regulations that govern methods used in and facilities used for the manufacturing of human cellular and tissue-based products
- Includes:
  - Donor screening and testing
  - Product recovery, processing and storage
  - Labeling and distribution

GCP: Good Clinical Practice

- An international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials involving human subjects
- Assures that the rights, safety, and well being of trial subjects are protected, and that clinical trials are credible

Bringing a Product to the Clinic: Review and Oversight

Most Cases:

- FDA standards described previously
- Institutional review board and (IRB) and institutional biosafety committee (IBC)
- Data safety-monitoring (DSMB)

Some Cases

- Stem cell research oversight committee (ESCRO)
- Scientific peer review by expert panel

Shortcutting the Process is Risky

- Acute risks:
  - Immunological
  - Inflammatory Reactions
  - Infection
  - Physical injury
- Chronic risks – benign or even malignant neoplasms
- Many more potential long term outcomes: Systematic long term monitoring and tracking of patient outcomes (e.g. registries) advised

Real Harms Result

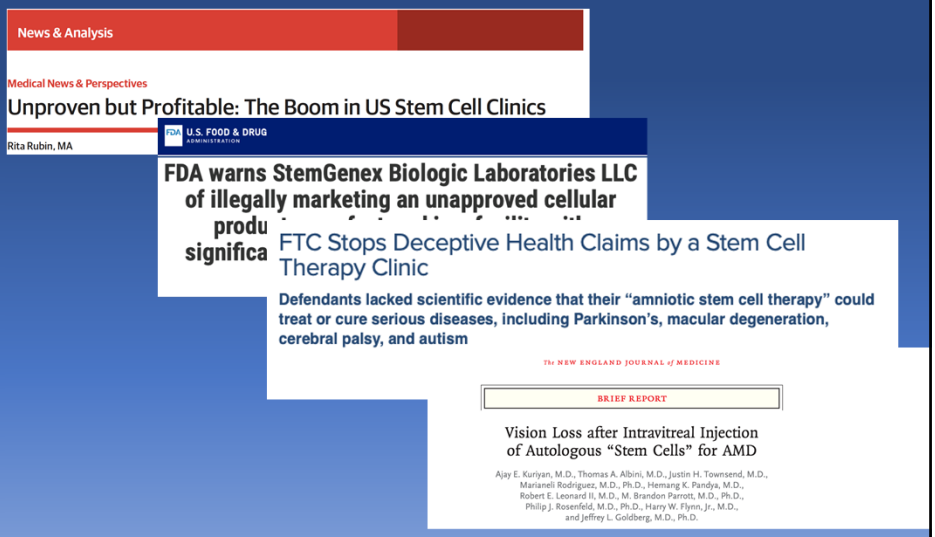


Table 1: Co-opted Tokens of Scientific Legitimacy[18]

Accreditations and awards	Asserting certification of products or practices by international standards organizations or claiming training certification
Boards and advisers	Convening scientific or medical advisory boards featuring prominent business leaders and academic faculty members
Clinical study registration	Registering trials whose apparent purpose is solely to attract patients willing to pay to participate in them
Ethics review	Using the imprimatur of "ethics review" to convey a sense of legitimacy to their products or procedures
Location	Renting of laboratory or business space within a legitimate scientific or government institution
Membership	Joining established academic or professional societies to suggest legitimacy by association
Outcome registries	Publication of open-ended voluntary monitoring data sets rather than undertaking controlled clinical trials
Patenting	Suggesting that patent applications or grants indicate clinical utility rather than initiation of an application process or recognition of novelty and inventiveness
Publication	Publishing research and commentary in journals with limited anonymous peer review
Rationales	Citing preclinical and other research findings to justify clinical application without sufficient efficacy testing in humans
Self-regulation	Forming organizations to self-regulate in ways that support premature commercialization
Technical Language	Using scientific-sounding words that imply academic rigor
Testimonials and Endorsements	Providing expert opinions or celebrity comments on unsupported clinical uses or standing of the provider

Federation of State Medical Boards

Stem Cell-based Treatments Are Unique

- How to mitigate risk
  - Process control / manufacturing per FDA guidance
  - Clinical protocols
  - Monitoring patient follow up
  - PI / Treatment team is certified in area practice
  - Knowledge / experience developed in ASCC Network is shared among teams

A Dedicate Stem Cell Treatment Network

- Located at leading medical centers
- Enabling access to stem cell and gene therapy treatments
- Teams of clinicians, nurses and technicians supporting patient-centered care

Providing Patients Access to Treatments

Since 2015:

- 95 + Clinical Trials
- 500 + Patients Treated
- 40 + Disease Indications
- Over $32 million in contracts with commercial sponsors

Selected ASCC Clinical Trials by Disease
Amyotrophic Lateral Sclerosis (ALS)
Brain Injury & Stroke
Cancer at Multiple Sites
Diabetes Type 1
Eye Disease / Blindness
Heart Failure
HIV / AIDS
Kidney Failure
Severe Combined Immunodeficiency (SCID)
Sickle Cell Anemia
Spinal Cord Injury

ASCC Standards for Clinical Trials

- FDA Investigational New Drug Application (IND)
- Scientific review
- Institutional Review Board (IRB) oversight
- Comprehensive informed consent
- Qualified teams handling products and delivering treatments to patients
- Patient follow up and monitoring including DSMB

Conclusions

- History demonstrates the need to protect patients from the harms of unproven treatments
- For HCT/Ps a robust system exists to ensure risk reduction and mitigation
- Good clinical practices ensure patient protections
- The know risks of stem cell products necessitates good manufacturing and clinical practices
- The Alpha Clinics Network are proof of concept