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.

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.
**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 good* 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
Delivering Patient Treatments

Shortcutting the Process is Risky

• Acute risks:
  o Immunological
  o Inflammatory Reactions
  o Infection
  o 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

Delivering Patient Treatments

Real Harms Result

News & Analysis
Medical News & Perspectives
Unproven but Profitable: The Boom in US Stem Cell Clinics

FDA warns StemGenex Biologic Laboratories LLC of illegally marketing an unapproved cellular product

FTC Stops Deceptive Health Claims by a Stem Cell Therapy Clinic

Defendants lacked scientific evidence that their “amniotic stem cell therapy” could treat or cure serious diseases, including Parkinson’s, macular degeneration, cerebral palsy, and autism

In New England Journal of Medicine

Brief Report

Vision Loss after Intravitreal Injection of Autologous “Stem Cells” for AMD

Katz, Shain W., Thomas A. Allen, MD, Justin S. Solomon, MD, William B. Greenlee, MD, Michael K. Rubenstein, MD, William J. Pendergraft, Jr., MD, Robert E. Green, MD, M. Brandon Myers, MD, PhD, Philip C. Hahn, MD, M. Michael Greenberg, MD, PhD, Philip C. Hahn, MD, M. Michael Greenberg, MD, PhD
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