Autologous Cellular Therapies

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Production Assistance for Cellular Therapy (PACT)
Autologous Cellular Therapies

- Definition
- Advantages & limitations
- Product types
- Regulatory issues
- Approved products
- Characteristics of products
- Issues & trends
The Ideal Commercial Cellular Therapy

Pre-prepared, third party, off-the-shelf, easy to store and deliver

Role for Autologous Cellular Therapy?
FDA Definition of Autologous Use

The implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered

21 CFR 1271.3
Advantages of Autologous Products

• The donor is immediately available
• No HLA matching is required
  – Reduced rejection
  – Reduced Graft-versus-Host disease but no Graft-versus-Disease effect (alloreactivity)
  – No immunosuppression required
Types of Autologous Products

- Hematopoietic progenitor cells
- Non-hematopoietic progenitor cells
- Cytotoxic cells - T lymphocytes
- Regenerative cells - Mesenchymal stromal cells
- Antigen-presenting cells - Dendritic cells
- Tumor vaccines – modified autol. tumor or Ag-loaded APC
- Etc.
Regulation of Autologous Products

- Determined by relative risk
  - "Unregulated"
  - Regulated by Section 361 of PHS Act
  - Regulated by Section 351 of PHS Act
Regulation of Autologous Products

• “Unregulated”

Minimally manipulated bone marrow for homologous use & not combined with another article

Processing that does not alter the relevant biological characteristics of cells or tissues

Repair reconstruction, replacement or supplementation of recipient’s cells or tissues with HCT/P that performs the same basic function or functions in the recipient as in the donor
Regulation of Autologous Products

• Regulated under Good Tissue Practices (GTP)

Other cells that are minimally manipulated and are for homologous use

Formal donor eligibility determination is not required for autologous donors but appropriate labeling of the product is still needed
Regulation of Autologous Products

• Regulated under Good Manufacturing Practices [GMP]
  – Cells that are more-than-minimally manipulated
  – Cells intended for non-homologous use
  – Cells combined with another article e.g. scaffold
Approved Products

Allogeneic

• HPC Cord Blood — NY Blood Center
• HPC Cord Blood — Ducord, Duke Univ.
• HPC Cord Blood — Clinimmune, Univ. CO
• Cultured Keratinocytes & Fibroblasts

  GINTUIT (oral mucogingivitis) - Organogenesis

Other

• BCG Live (Intravesical) — Thersys, Sanofi Pasteur
Approved Products

Autologous

• Carticell—Genzyme
• Provenge—Dendreon
• LaViv—Fibrocell
Carticell – Genzyme Biosurgery

- First approved product in 1997
- Autologous cultured chondrocytes
- Indication: Repair of symptomatic cartilage defects of the femoral condyle caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure
- Manufactured at company’s Cambridge facility
- Cost ~$10,360
Provenge - Dendreon

- Autologous APC stimulated with Prostatic acid phosphatase / GM-CSF
- Approved April 2010
- Indication: Asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer
- Manufactured at company’s centers
- Cost ~$93,000
LaViv - Fibrocell

- Autologous fibroblasts cultured for 11-22 weeks at the company
- Indication: decrease in frown/smile naso-labial folds
- Approved 2012
- Fibrocell has not announced a price, expected to be $1,000 to $2,000 to create the cell bank, and perhaps $300 to $500 for each of 3 treatment sessions.
Challenging the Model

Adipose-derived MSC used for regenerative medicine applications e.g. multiple sclerosis, macular degeneration
Challenging the Model

Celltex To Initiate New Clinical Program As It Responds To FDA Letter

Celltex makes identical copies of an individual's own stem cells and therefore should not be subject to FDA regulation as drugs.

However, the FDA said our process causes the cells to be considered biological drugs and thus is subject to those regulations.

We respectfully but firmly disagree with the FDA and intend to contest the agency's opinion within its administrative procedures. We are considering all options as we work with the agency toward a resolution.

David Eller, CEO and President of Celltex PR Newswire
Autologous Stem Cell and Non-Stem Cell Based Therapies

Autologous cell therapies are new therapeutic intervention where it introduces or uses cells or tissues from the individual, cultured, expanded and re-introduced at the site of the disease of the donor. They are widely promoted as next pillar or advancement in medical care.

Growth of the market is very rapid especially in regulatory approvals, applications areas and rapid improvements in efficacy of treatment; it has enormous advantages over allogenic stem cell therapies. Autologous transplants are relatively safe procedures, with less rates of complications and infections compared with allogenic transplants. In many instances, much of the procedure can be done on an outpatient basis. It helps in treating various dreadful diseases by transplanting their own body cells where it results in meager chances of transplant rejection.

We have also profiled leading players of this industry with their recent developments and other strategic industry activities. These include: Neostem (U.S.), Tengion (U.S.), Brainstorm Cell Therapeutics (U.S.), Dendreon Corporation (U.S.), Georgia Health Sciences University (U.S.), Regenexx (U.S.), Regeneus (Australia), Cytori Therapeutics (U.S.), Tigenix (Belgium).

Scope of the Report

This research report titled “Autologous Cell Therapy (2012-2017)” provides details about various ACT based treatments and their application areas. Every health regulatory bodies will be expecting companies and universities to develop therapy treatments, which are safer, affordable, robust, rapid, easy to use, effective and deliverable to the end user. ACT treatments for particular application areas it is safe, experiencing robust growth, minimal steps of procedure to follow and rapid in deriving the results. As for now the treatments prices are not affordable, but by the intrusion of government bodies, it will definitely experience a immense market growth.

The report gives a detailed analysis about state of the art of autologous cell therapies. It includes the current advances and applications of the technology and trends in terms of market size and growth of autologous cellular therapies in medical treatments globally. It also consists of funding details of the innovative therapy and recent activities in terms of mergers & acquisitions of the company, revenue forecasting. It includes latest therapy details and products which are available for licensing and approvals from various regulatory bodies. Using drivers, restraints and challenges it is forecasted for a period of five years i.e. 2012-2017. Opportunity strategy evaluation has been included which gives information for investors.

Autologous Cell Therapy technology is changing the medicinal treatments by introducing various new therapies. Its scope is vast and promising for the challenges.
Current Characteristics

• Harvest cells at center near patient
• Transportation to central processing center(s)
• Processing under cGMP conditions
• +/- Cryopreservation
• Transportation back to center near patient
• Possible storage at that center
• Administration at that center

[Image of a map with arrows indicating the flow of the process]

[Logos for Center for Cell & Gene Therapy (CAGT), Center for Advanced Therapies (CART), and Production Assurance for Cellular Therapies (PACT) at the bottom]
Autologous Therapeutic Cells

- Marrow/Apheresis mononuclear cells
- Marrow/Apheresis CD34, CD133 (other) cells
- NK cells
- Dendritic cells and other APC
- Mesenchymal stromal cells
- Antigen-specific T cells
- Etc.
Autologous to Allogeneic

• Mesenchymal Stromal Cells
  – Allogeneic used GvHD
  – Autologous used for regenerative applications
  – Now seeing allogeneic cells used in regenerative medicine
    • Based on minimal HLA expression

• Others?
Autologous Product Issues

• Cell Quality – often from heavily treated patients
  – May not grow or function as expected
• Uniform collection procedures
  – Training and competence, donor screening
• Transportation
  – Carrier/Packaging/Risk
• Processing
  – Regulated by FDA
• Cryopreservation
  – Effects?
• Administration
  – Practice of medicine?
Issues – collection, processing, delivery

- PROVENCE is intended solely for autologous use and is not routinely tested for transmissible infectious diseases
- Use of multiple lots – Variability?
- CARTICEL should not be used in patients with a known history of hypersensitivity to gentamicin, other amino-glycosides or materials of bovine origin
- Delivery: As per the CARTICEL labeling, please note that the FDA mandates that all CARTICEL surgeons must be trained in the surgical procedure.
Cryopreservation

Frozen or Fresh NK Products?

**Frozen**

One product for multiple infusions

**Post-thaw**

- Good viability right after thaw
- Recovery low after 24h
- Not cytotoxic right after thaw
- Did not expand well *in vivo*

**Fresh**

One product per infusion

- Good viability?
- Cytotoxic?
- Expand well *in vivo*?
- Continue to expand during shipment?
Fresh NK Potency is Retained After Shipping

24h after formulation

% Specific lysis

48h after formulation

% Specific lysis
Fresh Auto-NKs Expand in vivo

**Frozen NK**

**Fresh NK**
Fresh NK Continue to Expand During Shipping

<table>
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<th>24</th>
<th>48</th>
<th>0</th>
<th>24</th>
<th>48</th>
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<tbody>
<tr>
<td>Sample</td>
<td>Manual Count (M/ml)/Recovery (%)</td>
<td>Manual Count (M/ml)/Recovery (%)</td>
<td>Manual Count (M/ml)/Recovery (%)</td>
<td>Viability Trypan/7AAD (%)</td>
<td>Viability Trypan/7AAD (%)</td>
<td>Viability Trypan/7AAD (%)</td>
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<tr>
<td>Donor 1</td>
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<td>12.1/121%</td>
<td>13.7/137%</td>
<td>NA/85.8</td>
<td>81/97.8</td>
<td>87.8/98.3</td>
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<td>9.7/97%</td>
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<td>85/98.9</td>
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<td>Donor 3</td>
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<td>17.1/171%</td>
<td>NA/86.9</td>
<td>87/99.3</td>
<td>89.5/98.6</td>
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</table>
Issues

• Does cryopreservation alter cell function in ways not always detected by in vitro assays?
• If cells are shipped “fresh” are additional release tests required upon receipt?
• Are autologous therapies best suited to centralized commercial development or better practiced locally?
Localized Autologous Therapy

Two Models

**Traditional:** Processing/testing at in-house GMP Facility

**Emerging:** Processing/testing interoperatively
Localized Autologous Therapy

Two Models

- **Traditional**
  - Suitable for complex more-than-minimally manipulated products
  - Only option for long-term procedures
  - Multiple products from one collection
  - Existing regulatory framework

- **Emerging**
  - Suitable for shorter, automated GMP-compliant manipulation procedures
  - Requires rapid testing procedures
  - Safety considerations e.g. maximum out-of-body time
  - Potentially more complex regulatory issues
Can partially matched allogeneic T cells be used therapeutically without inducing serious GvHD?
Most Closely HLA Matched Allogeneic Virus-Specific Cytotoxic T-Lymphocytes (CTL) to Treat Persistent Reactivation or Infection with Adenovirus, CMV and EBV after Stem Cell Transplantation

CAGT
Helen Heslop
Ann Leen
Clio Rooney
Cath Bollard
Malcolm Brenner
Adrian Gee

Other Sites
MDACC | EJ Shpall
---|---
Harvard | Joe Antin, B Dey
Duke | Paul Szabolcs
CHLA | Neena Kapoor
Children's Boston | Sun Yun Pai
Miami | Gary Kleiner
Hackensack | Scott Rowley
Product

• Most closely HLA-matched multivirus specific CTLs (CHM-CTL)
  • CTL Lines already made for previous studies
  • New CTL lines made from donors with common alleles (PACT)

• 32 lines were available
Clinical Protocol

• Treatment of refractory EBV, CMV, or Adenovirus

• Patients receive $2 \times 10^7$ CHM-CTL/m$^2$ as a single infusion.

• If partial response may receive up to 4-5 additional doses at 2+ weekly intervals
Screening & Enrollment

• 77 patients screened
• Line identified for 68/77
  • Suitable line if matched at least one antigen with activity against infecting virus
• 9/77 no suitable line
• 45 patients enrolled
  • 21 with CMV
  • 9 with EBV
  • 15 with Adenovirus
Matching of CTL Line

<table>
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<tr>
<th>Matching</th>
<th>Recipient</th>
<th>Donor</th>
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</thead>
<tbody>
<tr>
<td>1/6 match</td>
<td>26%</td>
<td>24%</td>
</tr>
<tr>
<td>2/6 match</td>
<td>45%</td>
<td>45%</td>
</tr>
<tr>
<td>3/6 match</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>4/6 match</td>
<td>3%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Number of Infusions

- 33 patients  - 1 infusion
- 7 patients   - 2 infusions
- 4 patients   - 3 infusions
- 1 patient    - 5 infusions
Overall Response Rate

Cumulative incidence of CR/PR

First 40 pts based on viral load by day 42 post-infusion

N=40

82.4%
Improvements – Technical
More Rapid Manufacturing

Cytotoxic T Cells

- **Antigen source:** GMP EBV
- **APC:** Dendritic cells, LCL
- **Transduction of APC with vectors**
  - Antigens
- **Co-culture with lymphocytes**
- **Transduction with vectors**
  - CARs
- **Release testing** – minutes to weeks

6-12 Weeks for antiviral CTL
Improvements - Technical

Plasmids

PBMC + IL4/7

DC Generation + Nucleofection
7 days

Pepmix

PBMC

T cell stim/expansion
10 days

Bioreactor
Emerging Devices
Improvements - Scientific

Chimeric Antigen Receptor
T Cells

Better Targeting

Improved Immune Activation
Improvements - Scientific

Drug Inducible Suicide Genes

1. Viral transduction transfers the DNA from a vector into the target cell.

2. Vector-derived DNA directs expression of CID and accessory proteins.

3. The AP1903 drug key dimerizes the CID proteins, thus turning on the signal cascade.

Bellicum Pharmaceuticals

Provide a Safety Switch for Therapeutic Cells
Conclusions

• Autologous therapies are still active but may decline as limitations to use of allogeneic products are overcome.

• Autologous products may become of most use as in-house treatments as technologies improve.

• Technical improvements can facilitate this transition – inter-operative methods, rapid release testing etc.