Regulatory Challenges for the Development of Allogeneic Mesenchymal Stem Cell Products

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This presentation contains, and answers given to questions that may be asked today may constitute, forward-looking statements that are subject to a number of risks and uncertainties, many of which are outside our control. All statements regarding our strategy, future operations, financial position, estimated revenues or losses, projected costs, prospects, plans and objectives, other than statements of historical fact included in our prospectus, are forward-looking statements. When used in this presentation or in answers given to questions asked today, the words “may,” “will,” “could,” “would,” “expect,” “intend,” “plan,” “anticipate,” “believe,” “estimate,” “project,” “potential,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. You should not place undue reliance on forward-looking statements. While we believe that we have a reasonable basis for each forward-looking statement that we make, we caution you that these statements are based on a combination of facts and factors currently known by us and projections of future events or conditions, about which we cannot be certain. Important factors that could cause our actual results to differ materially from those expressed or implied by the forward-looking statements are included under “Risk Factors,” “Special Note Regarding Forward-Looking Statements” and elsewhere in our prospectus filed with the Securities and Exchange Commission on July 17, 2006. These cautionary statements qualify all of the forward-looking statements. In addition, market and industry statistics contained in this presentation are based on information available to us that we believe is accurate. This information is generally based on publications that are not produced for purposes of securities offerings or economic analysis.

All forward-looking statements speak only as of the date of this presentation. Except as required by law, we assume no obligation to update these forward-looking statements publicly or to update the factors that could cause actual results to differ materially, even if new information becomes available in the future.
Overview

• MSC Technology

• cGMP Production

• Preclinical Models “Proof of Principle”

• Pharm-Tox
Ex vivo cultured human MSCs derived from the bone marrow of healthy donors

- Bone Marrow Aspirate
- Adherence to surface of cell factory
- Expansion
- Passaged hMSCs
Differentiation Pathways
Classical Trilineage

Adipogenesis
Chondrogenesis
Osteogenesis

Lipid vacuoles
Type II collagen
Alkaline phosphatase
Mesenchymal Stem Cell Activity

- Tissue Protective
- Anti-inflammatory
- Trophic

- Anti-fibrotic
- Anti-apoptotic
- TNF Suppression
- IL-10 Production
- IL-4 Production
- Blocks T Cell Proliferation

Bone, Tendon, Cartilage, Muscle, Ligament, Fat, Stroma
Universal Compatibility

- MSCs express MHC Class I
- MSCs do not express MHC Class II
  - Do not express co-stimulatory molecules
- MSCs do not stimulate T-cell proliferation (MLR)
  - MSCs suppress T cell proliferation in vitro
- Survivability:
  - in vivo ~21 months as demonstrated in a baboon study (Devine et al)
  - MSC DNA detected in the human bone marrow at 1 month (Fouillard et al Leukemia 2007)
Mesenchymal stem cells are responsible for repairing damage to connective tissues and for controlling inflammation. **Young people have more and heal better.**
The Mesenchymal Stem Cell

As we age, the number declines.

Older people do not heal as well.
The Mesenchymal Stem Cell

Osiris puts these cells back in large numbers to assist with the healing of inflammatory and connective tissue disorders.
Manufacturing

Raw Materials
Donor Sourcing
Points to consider
Release testing
A Real World Therapeutic Model

Each donation produces up to 5000 units through a proprietary GMP manufacturing process.

Bone marrow from adult donors between the 18-30 years.

Mass Production

The product is stored at the point of care, ready to use when the patient needs it.

Ready to Use

...in anyone

The MSC can be used in patients unrelated to the donor without typing or matching, much like Type O blood.
Raw Materials

- **Fetal Bovine Serum**
  - US requirements: TSE free herd
  - EU requirements: non North American or EU derived

- **Heparin and Trypsin:**
  - TSE Guidelines (EMEA 410/01/rev2) for animal derived materials

- **Alternatives:**

- **Proposed alternatives: Human Sera and platelet lysates**
  - Difficult to meet cGMP requirements

- **Defined Media**
  - Recombinant factors
    - Quality, CoA
Stem Cell Donor Requirements

- Adult volunteer donors, ages 18-30
- Physical Exam
- Complete Medical/Social Questionnaire
  - Assessed for TSE and West Nile Virus risk
- Screened for the following pathogens:
  - HIV-2 antibody
  - Hepatitis B core antibody
  - Hepatitis C virus antibody
  - *Treponema pallidum*
  - EBV antibody viral capsid, (IgM)
  - Complete metabolic panel
  - Hepatitis B surface antigen
  - HIV-1 antibody
  - HTLV I and II antibody
  - CMV, antibody (IgG)
  - HLA typing
  - Complete blood count

- Dynamic: changing arena of pathogens
Points to Consider: Testing

In Process Intermediate Testing: *FDA PTC 1993*

Viral Testing:
HTLV I&II, HBV, CMV, HCV, HHV-8
HHV-6 A & B, HIV 1 & 2, HPV
Human Cell Line
Karyotyping
Morphology
Viral inclusion
Parvovirus B-19

*In Vitro* and *in vivo* tests
## Product Release Assays

<table>
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<tr>
<th>Test</th>
<th>Description</th>
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<tr>
<td>Phenotype/Identity</td>
<td>Cell surface markers, FACS</td>
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<td><strong>Potency</strong></td>
<td><strong>Biomarker, Biological activity:</strong></td>
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<td>Purity</td>
<td>Residuals from manufacturing</td>
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<tr>
<td>Strength</td>
<td>Cell viability</td>
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<td>Contaminants</td>
<td>Sterility / Endotoxin / Mycoplasma</td>
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Release Testing:
Product: Prochymal (GVHD, Crohn’s)

Testing
Sterility
Endotoxin
Mycoplasma
Viability
Phenotype
Potency
Residuals (BSA, Trypsin)
## Proof of Principle Studies

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<th>Indication</th>
<th>Clinical Phase</th>
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<td>Chondrogen</td>
<td>Meniscus repair</td>
<td>Phase I/II</td>
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<tr>
<td>Provacel</td>
<td>Cardiac</td>
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<td>Prochymal</td>
<td>GVHD</td>
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<td>Prochymal</td>
<td>Crohn’s Disease</td>
<td>Phase II</td>
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Preclinical Models: Issues

- Comparability of MSCs: Human to animal model
- Culture conditions for generation of MSCs not comparable
  - Base media differences
  - Passages, timing
- Final product characteristics:
  - Sterility
  - Endotoxin
  - Mycoplasma
  - Viability
  - Phenotype/identity (available reagents)
- Tri-lineage analysis
  - Different culture conditions
Rate limiting requirement:

- Proof of Principle established
- Ready for clinical trial
- **Hurdle before transition to clinical trials**
- Long term follow up of animals
  - Cardiac: pigs
  - Meniscus repair: goats
- Ectopic tissue formation
Prochymal:
GVHD
Crohn’s
Non-classical pathway

*In vitro* immunosuppressive activity
Preclinical models ?
Human trials
Animal Model

• Rat model for GVHD:
  — Challenging

• Mouse model for GVHD:
  — Mouse MSCs different

• No models available for translation
  — Dosing regimen and schema: Challenge
Human Experience

Endoscopic view of the colon in a patient with Grade IV GI GVHD

Supported:
- Treatment of aGVHD
- Crohn’s disease

Anti-Inflammatory

Trophic

Decrease in intestinal inflammation and ulceration at 9 days with corresponding crypt regeneration as depicted by the arrows.
Classical Pharm-Tox?

Trying to put cellular therapy in a box
Biological niche vs. drug distribution

- Homing
  - Adhesion, Migration, Invasion
- Immune recognition
- Immune response modulation
- Tissue repair
- Differentiation
  - Osteogenesis, Chondrogenesis, Adipogenesis, Epithelial, Endothelial
  - Survival
Preclinical studies

Rigorous evaluation to assess pharmacological and toxicological activities in comparison to the clinical agent

- Clinical observations
- Body weight
- Clinical pathology
- T-cell expression
- Immunogenicity
- Toxicokinetics
- Lymphoid organ histopathology
Pharmacokinetics challenges

No cell tracking method meets all of the following:

- Any donor and recipient
- No cell manipulation
- Signal is retained on proliferation
- Signal gone after cell death
- Histology
- Quantitative
Deep clinical pipeline

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