Novel Small Molecule Oxysterols for Regulation of Hedgehog Signaling, Bone Formation & Tumorigenesis

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MAX BioPharma’s Business Model

Licensed Technology from UCLA

- Collaborate with Strategic Partners (Biotech-Pharma)/Sublicense Technology
- Raise VC Funding and Continue Preclinical & Clinical Development
- Apply for Government Funding Support (SBIR; RO1)

Create Value for MAX BioPharma
Hedgehog Signaling: A Druggable Pathway
(Involved in tissue repair, stem cell maintenance, tumorigenesis)

Novel Regulatory Small Molecules

$
Problem: Localized Bone Formation - Spine Fusion

- Prevalent orthopedic and neurosurgical procedure to correct spinal instability
- Infuse (rhBMP2), by Medtronic, is the most commonly used bone growth factor
- Infuse may cause serious adverse effects especially in cervical spine; very costly
- Infuse revenue has plummeted from >$800M to <$400M
U.S. Bone Graft Substitute Market Projections ($ in billions)

Sources: Business Wire 2011; Life Science Intelligence 2013
MAX BioPharma’s Strategy for Stimulation of Bone Formation

- Proprietary Small Molecule Osteogenic Oxysterols
- Mesenchymal Stem Cells
- Mature Bone-Forming Osteoblasts
Robust bone forming activity when applied to progenitor cells that form bone cells (osteoblasts)

Small molecules with inexpensive synthesis route
Lead Osteogenic Oxysterol, Oxy133

Over 150 oxysterol analogues synthesized and screened in vitro for osteogenic activity

(Biological activity, ease & low cost of synthesis for scale up; safety profile)
Lead Osteogenic Oxysterol, Oxy133, Induces Osteogenesis of Human Mesenchymal Stem Cells

Bone mineral formation is stained black with von Kossa stain.
Lead Osteogenic Oxysterol, Oxy133, Induces Robust Spine Fusion in Rats and Rabbits

**Micro-CT Analysis**

- **Group I (Control)**
- **Group II (BMP2)**
- **Group III (Oxy133-20 mg)**
- **Group IV (Oxy133-2 mg)**

**Radiographic Analysis**

- **Group I (Control)**
- **Group II (BMP2)**
- **Group III (Oxy133-20 mg)**
- **Group IV (Oxy133-2 mg)**
Present Data:

1. Mechanism of action identified (transient induction of Hedgehog pathway activity through allosteric Smoothened activation)
2. Induction of robust spine fusion in rats
3. Healing of critical sized femoral defects in rats
4. Induction of robust spine fusion in rabbits
5. Healing of critical sized calvarial defects in rabbits

Planned Future IND-Enabling Studies:

1. Tox & PK
2. Primate spine fusion
**Problem**

*Additional Opportunities: Osteoporosis*

- Increasingly significant disease in the aging population (> 10 million men and women in the U.S.; >44 million with low bone mass)
- Characterized by brittle bones and increased risk of fractures (> 1.5 million fractures are treated per year in the U.S.)
- Caused by increased bone destruction (resorption) and decreased bone formation
- Medical cost of osteoporosis and fractures in older adults in 2008 was $22B in U.S.
- Current global osteoporosis drug market >$12 billion; increasing 10% annually
- Worldwide cost of osteoporosis forecasted to increase to $131.5 billion by 2050

Increased Bone Resorption by Osteoclasts

Reduced Bone Formation by Osteoblasts

Osteoporosis

Current Therapeutic Interventions

Future Therapeutic Interventions

X

Forteo

Oxy133-BTA

Identification of Bone-Targeted Osteogenic Oxysterols

Solution
Mesenchymal Stem Cells

Oxysterol Compounds

- Osteoblasts
  - Bone Formation
    - [osteoporosis; fracture healing; spinal fusion]

- Chondrocytes
  - Cartilage Formation
    - [osteoarthritis; wear & tear]

- Adipocytes
  - Fat Formation
    - [obesity; xanthoma]

- Myocytes
  - Muscle Formation
    - [muscular atrophy; muscular dystrophy]

- Fibroblasts
  - Connective Tissue
    - [tendon & ligament injury; aging]

- Hair Follicle
  - Hair Growth
    - [alopecia]

- Neurons
  - Neurogenesis
    - [nerve repair]

Additional Opportunities: Proprietary Small Molecule Oxysterols for Regenerative Medicine
Unregulated Activation of Hedgehog Signaling

Hedgehog Pathway Antagonists (GDC-0449; IPI-926; Cyclopamine)

Additional Opportunities: Blocking Hedgehog Signaling Inhibits Tumor Growth

Cancers associated with unregulated Hh signaling:
- Medulloblastoma (Brain Tumor)
- Gastrointestinal Cancers
- Basal Cell Carcinoma
- Prostate Cancer
- Ovarian Cancer
- Breast Cancer
- Colon Cancer
- Liver Cancer
- Small-Cell Lung Carcinoma
- Pancreatic Adenocarcinoma
- Rhabdomycosarcoma (in Muscle)

Genentech’s Vismodegib/Erivedge approved for metastatic basal cell carcinoma
Oncology Platform Technology: Tumor Microenvironment Targeting

MAX’s Preliminary Focus in Oncology: Inhibition of Hedgehog Signaling in Tumor Microenvironment

Inhibition of Tumor Growth and Metastasis

Diagram From: Hofmeister V, Schrama D, Becker JC Cancer Immunol Immunother; 2008

TUM = Tumor Cells
CAF = Cancer-Associated Fibroblasts/Myofibroblasts
TEC = Tumor Endothelial Cells
TAM = Tumor-Associated Macrophages
TAT = Tumor-Associated T Cells

Novel Small Molecule Oxysterols

MAXBioPharma
MAX BioPharma’s Accomplishments in Inhibiting Tumor Formation

- Demonstrated efficacy of using specific proprietary small molecule oxysterols for inhibition of autocrine & paracrine Hedgehog signaling \textit{in vitro};

- Demonstrated inhibition of tumor cell growth by proprietary small molecule Hedgehog pathway inhibitors \textit{in vitro} (myeloma, leukemia, osteosarcoma, pancreatic tumor cells); Elimination of tumor stem cells;

- Demonstrated efficacy of systemic delivery of small molecule oxysterol Hedgehog pathway antagonists & regulation of gene expression in target tissues \textit{in mice} (pancreatic tumor xenografts);
MAX BioPharma will file an IDE for its osteogenic lead compound to be examined in humans for spine fusion in 18-24 months.

### Development Plan for Bone Forming and Oncology Oxysterol Lead Compounds

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 6</th>
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<tr>
<td><strong>Localized bone formation in orthopedic procedures</strong>&lt;br&gt;(spine fusion, non-union fractures – Class III medical device)</td>
<td>Finish Preclinical Testing</td>
<td><strong>Clinical Trials</strong></td>
<td>→</td>
<td><strong>Commercialization</strong></td>
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<td><strong>Intervention with osteoporosis using bone-targeted osteogenic oxysterols</strong></td>
<td>R&amp;D - Preclinical Testing</td>
<td><strong>Clinical Trials</strong></td>
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<td><strong>Cancer targeting by inhibiting activity of Hedgehog (Hh) signaling pathway</strong></td>
<td>R&amp;D - Preclinical Testing</td>
<td><strong>Clinical Trials</strong></td>
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Funding & Milestones

Funding to Date:
- Approximately $4M of academic government grants
- $250K from Founders, friends, and family; $300K from 2 SBIR phase 1 grants

Funding Needed:

1. Bone Program (Localized): $8M
   - Milestones: - Preclinical studies with Oxy133 lead molecule (spine fusion in sheep followed by primates, Tox, PK)
                 - Payment of licensing fees and ongoing patent costs
                 - File IDE for spine fusion (class III medical device)
   - Timeline: 18-24 months

2. Bone Program (Systemic): $2M (with an additional $4M commitment)
   - Milestones: - Design and synthesis of bone targeted oxysterol lead
                 - Pre-clinical in vitro and in vivo efficacy studies
   - Timeline: 24-36 months
3. **Oncology Program**: $2M seed (with an additional $10M commitment)
   
   - **Milestones**:  - IND-enabling proof-of-concept in vivo studies  
       - Optimization and selection of lead molecule(s)
   
   - **Timeline**: 24-36 months
Since 2004, 8 patent applications have been filed by UCLA (1 granted, 5 PCT, and 2 Provisional)

Exclusive License Agreement for oxysterol IP between MAX BioPharma and UCLA

Significant trade secrets held by MAX BioPharma as a result of research on SAR of oxysterols
Founders & Directors

**Farhad Parhami, Ph.D., M.B.A. (Founder & President)**
Professor of Medicine, UCLA School of Medicine

**Michael E Jung, Ph.D. (Scientific Co-Founder)**
Professor of Chemistry and Biochemistry, UCLA Dept of Chemistry

**William Matsui, M.D. (Scientific Co-Founder)**
Associate Professor of Oncology, Johns Hopkins University School of Medicine

**Frank Stappenbeck, Ph.D. (Director of Medicinal Chemistry)**
MAX BioPharma, Inc.

**Jason Rifkin, J.D. (Director of Business Development)**
MAX BioPharma, Inc.

**Gonzalo Payan (Director of Corporate Finance)**
MAX BioPharma, Inc.
Key Takeaways

- Proprietary platform technology with the potential to target large unmet medical needs by providing novel therapeutic candidates

- A lead molecule identified and moving toward clinical trials for stimulation of localized bone formation in spine fusion, fracture healing, maxillofacial bone regeneration, etc…

- Viable additional opportunities in osteoporosis and cancer identified

- Patent protection and barriers to entry
Exit Strategy

- Acquisition in 5 to 7 years by a biotech/pharma company
  (ex. Genentech, Infinity, Teva, Takeda, Baxter, Eli Lilly, Amgen, Medtronic, J&J, …)

- IPO

MAX BioPharma
Molecules for Advanced Therapeutics

An exciting investment opportunity
Thank you