Cellular Therapies
Skin and Musculoskeletal Tissues
Challenges and Opportunities

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Application Opportunities Repair to Replacement

- Skin
  - Chronic wounds
  - Burns
  - Epidermolysis Bulosa

- Neuromuscular diseases

- Articular Cartilage
  - OA
  - Trauma/sports

- Bone
  - Craniofacial – trauma, tumor
  - Long bones – trauma, tumor, atrophy (OP)

- Tendon and Ligament
  - Sports, Foot and Ankle, Hand
  - Rotator cuff, ACL, Achilles

Cell-Based Products for Skin and Musculoskeletal Tissues

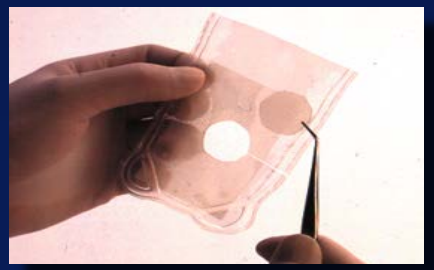
Carticel
Genzyme
1997

Transcyte
ATS/S&N
1997

Apligraf
Organogenesis
1999

Dermagraft
ATS/S&N
2001

Advanced Biohealing
2001



Orcel
Ortec
2001

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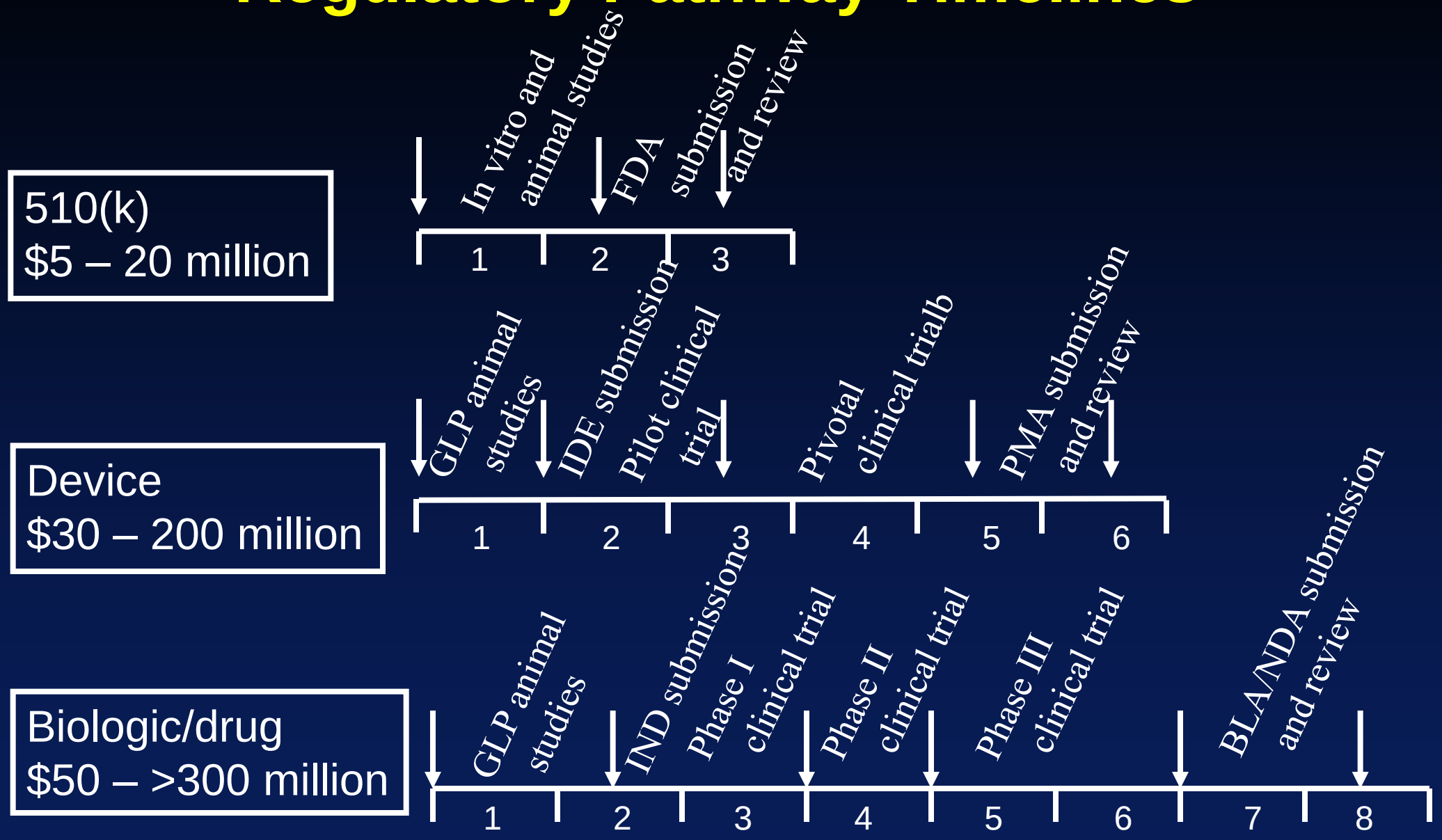
Regulatory Pathway Timelines



Ratcliffe A. In: Tissue Engineering in Musculoskeletal Clinical Practice, Sandell and Grodzinsky, Eds, AAOS. 2004

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Allografts

- **Cost: <$50,000**
- **Skin**
  - Skin substitutes for wound healing
  - Amniotic membrane for wound healing
- **Bone**
- **Articular cartilage**
- **Tendon and ligament**

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Return on Investment (ROI)

Development costs

- R&D Costs
- Time to market
- Risk

<

Income

- Price per unit
- # procedures/year
- Anticipated acceptance rate
- Reimbursement

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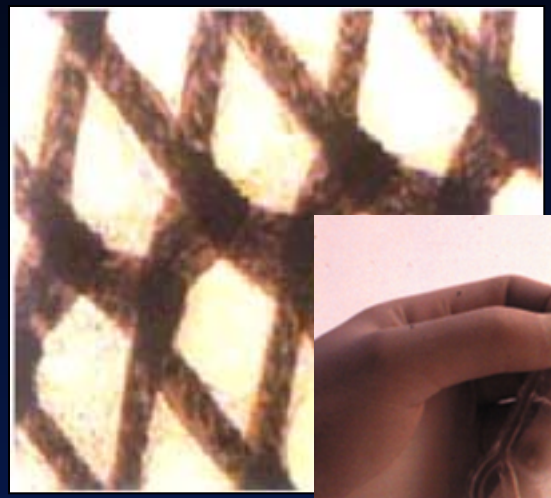
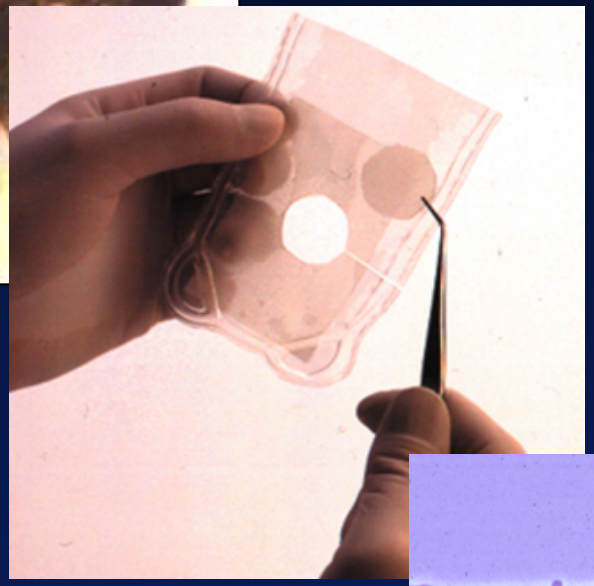
Cost to manufacture and sell

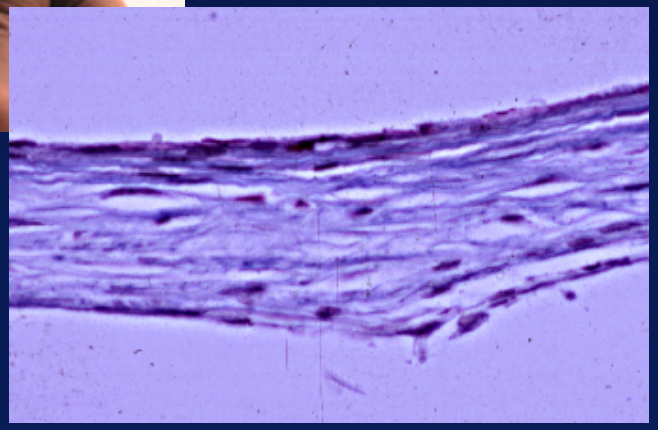
- Manufacturing costs
- Overhead
- Sales and marketing costs
- Licensing fees

Dermagraft®

A Living, Bioengineered, Human Dermal Replacement







Clinical need

- **Diabetic ulcers**
  - –800,000 / yr in the US
- **Venous ulcers**
  - –700,000 / yr in the US
- **Pressure sores**
  - – > 1,500,000 / yr

Healing Diabetic Foot Ulcers Using Dermagraft® as a Dermal Replacement

Week 0

Week 1

Week 3

Week 5

Week 8

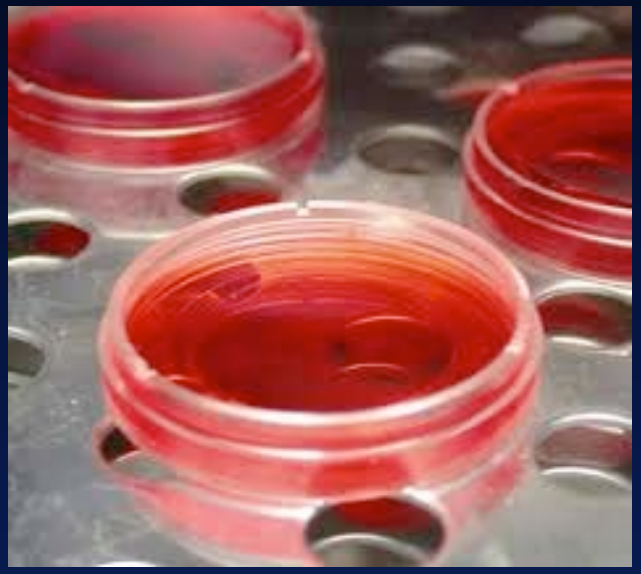
Week 10

Dermagraft implanted weekly for eight weeks

Balance Challenges with Opportunities

- Cost – *Increase efficiencies, Standards*
- Time – *Streamline studies required*
- Technical difficulty – *Cell source, Standards*
- Clinical uncertainty – *Improved clinical databases*
- Regulatory uncertainties – *Standards*
- Manufacturing – *Scalability, Standards*
- Predicted market opportunity – *Availability of data*
- International opportunities - *Harmonization*

Research and Cell Culture Scale-up

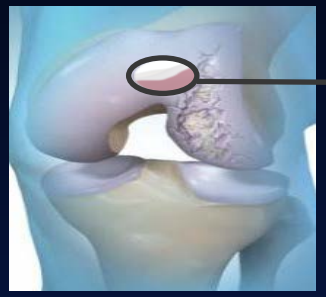


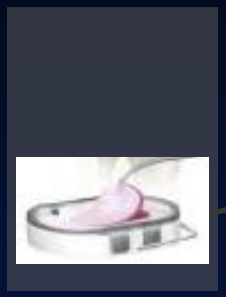
Innovative Manufacturing

- Automated manufacturing capabilities, efficient
- Supports high-volume production (bioreactor design), scaleable
- Provides product consistency, reproducible
- Economic
- Safe

AESCULAP
Biologics

NOVOCART® 3D Manufacturing Process





Patient biopsy

Automated cell growth & scaffold seeding

Final Product

Implant for lesion repair

+

+

=

Digest

Proliferation

Cell Collection + Scaffold Loading

Disposable Integrated Process

AESCULAP
Biologics

NOVOCART® 3D Commercial Scale-out

Cocoon™ Tree

Cocoon™ Orchard

Standard Model of Osteochondral Repair
NIH Funded, ASTM Standard

No Repair

Repair with osteochondral plug, 4 and 12 months

Autologous versus Allogeneic

- Very different business models
- Autologous
  - Minimally manipulated?
  - What are the minimum requirements for a cell preparation to be effective?
- Allogeneic
  - Cell expansion to make a cell bank and generate numbers of cells required (≥Passage 6?)
  - Exhaustive testing of cell bank to ensure cells are safe
  - What are the minimum requirements for a cell preparation to be effective?

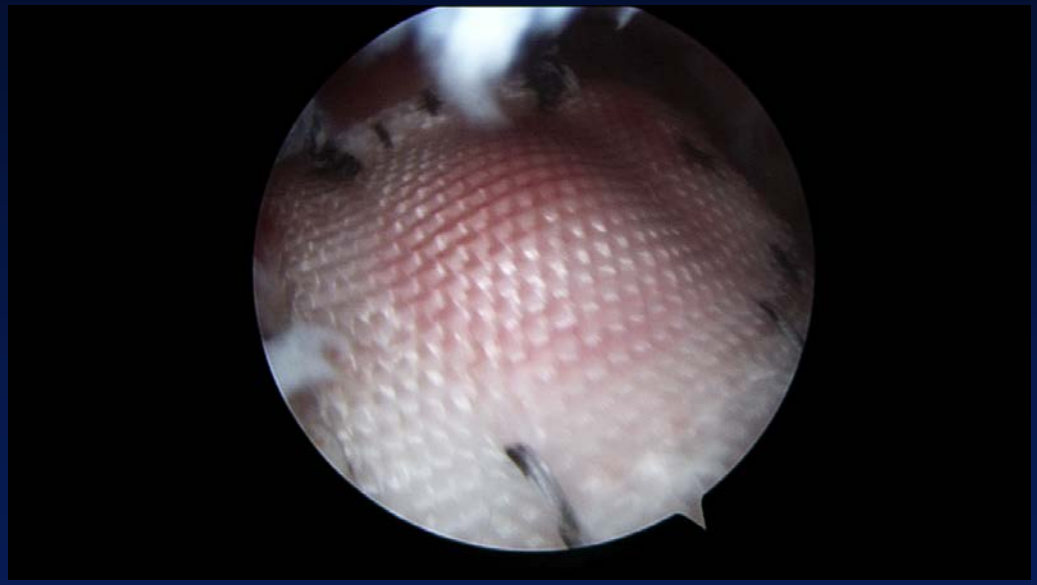
Biomimetics for Repair and Replacement

Present

- Biomaterials can be used to replicate mechanical properties of tissues
- Requires host to provide cells and active repair

Ideal

- Combine cells and ECM with biomaterial within single product



A challenge is to develop treatment that is therapeutically effective.

A challenge is to develop product that is commercially successful.

To have clinical impact, the challenge is to develop a product that is therapeutically effective and commercially successful.