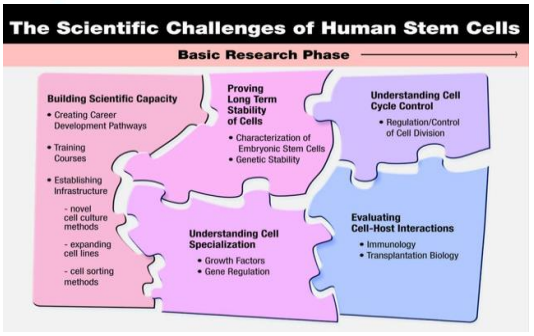
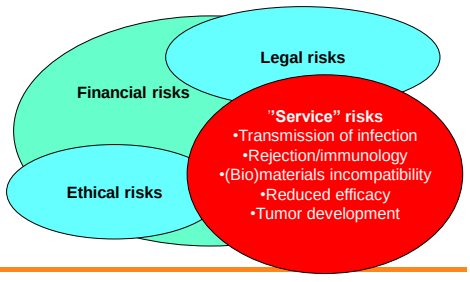
CHEM – E3225 Cell- and Tissue Engineering, 5 cr
Topic 8
Hypes and Hopes of tissue engineering

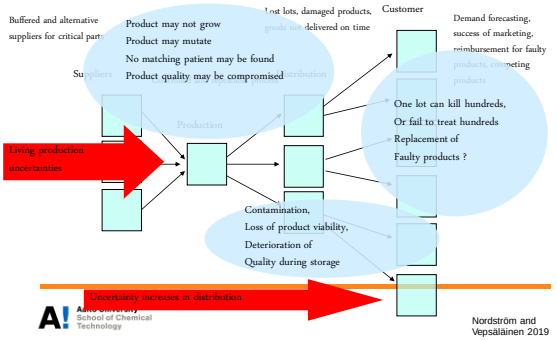


http://stemcells.nih.gov/info/media/challenges.htm

Risks involved with TE-products



Conventional vs. Living Production



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Differences of Chemical, Biologics and Cell-based (=living) Production

	Production typically	Variance (between units)	Shlef life	Quality/ sterility	Production control	Matching required
Chemical Production	Intence, continuous or batched	None to low	Years/ months	Sterile production, strict quality measures	Traditional	Never/ Allergy
Biologics production	Intense, bathed	Low to medium	Months	End product sterilized, strict quality measures	Traditional/ complex (sourcing mice etc)	Never/ Allergy
Living production	Non-intense, usually single unit	Medium to high	Days/ weeks	Never sterile, little or no reliable quality measures	Complex (cell inventories, patients, hospital environment)	Often / always

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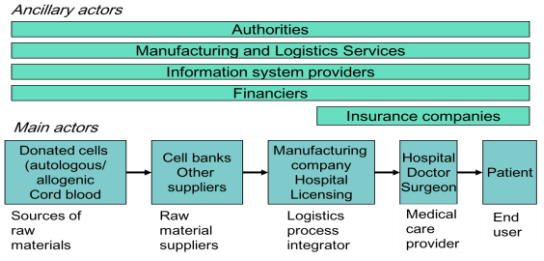
Supply chain for cells / tissues for regenerative medicine/tissue engineering



Nordström, K., Närhi, M. and Vepsäläinen A. (2009). Services for distribution of Tissue engineering products and therapies. *International Journal of Production and Productivity Management, vol 58, 1, 11-28.*

Regenenerative Medicine 1.0 (1990's – 2003): The "Good Times"

- 3300 full-time equivalents (FTEs), combined annual expenditure > $600 million; net capital value of 16 publicly traded startups > $2.5 billion (Lysaght et al. 2008, Mason et al. 2008)
- – Dermagraft® single-layered skin replacement for diabetic ulcers
- – Apligraf® bi-layered skin replacement for diabetic ulcers and severe burns
- – OrCel® bi-layered skin replacement for severe burns
- – Carticel® autologous cultured chondrocytes for treatment resistant cartilage damage in the knee-joint.
- Close to a dozen products were in FDA-level regulatory trials, including a bioartificial liver, an intracerebral pain implant and a second skin equivalent.
- • 2001-2003 majority of firms went bankrupt !

Then, "The worst of times" for TE

- The combined effect of the fall of the dot-com economy, the failed product launches, and the disappointing results from FDA clinical trails was devastating
  - Spending in the field, which had been growing at about 16% per year, declined by 20% between 2000 and 2002.
  - 19 firms out of 73 either filed for bankruptcy or closed doors; 27 others downsized significantly.
  - Overall 1800 workers out of 3100 were displaced
- The capital value of publicly traded tissue engineering companies fell by more than eightfold, from $2.5 billion to $300 million

Current Sales of RegenMed 2.0 Products* (2008) – just to give you an idea

- INFUSE Bone Graft products sales approaching $700 million
- Aggregate volume of private sector cord banking of adult stem cells $270 million
- Sales of biomaterials with a propensity for tissue regeneration > $240 million.
- Sales of living skin equivalents and cartilage approach $100 million per year
- No "heart-in-the box" products are available, rather the trend is towards acellular products
  - Products containing living cells are costly to manufacture, have expensive and extensive regulatory approval process, uncertainties in benefit vs. risk to the patient /investor -

* Lysaght et al. 2008

Products in the 2010 →

- The experiences in the 1990's had an impact on the kind of sopihistication that is targeted for
- More simple and less invasive products have been more succesfull in getting approval from regulatory agencies for entering the markets
- More advanced products still tend to be single – patient therapies performed in the hospital
- Mesenchymal stem cells and T-cells are the most commonly used cells; cancer is one of the most studied condition

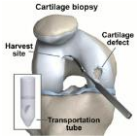
Product Name: INFUSE® Bone Graft

- **Applicant:** Wyeth Pharmaceuticals
  Address: P.O. Box 8299 Philadelphia, Pennsylvania 19101-8299
  Approval Date: April 30, 2004
- **What is it?** The INFUSE® Bone Graft device is used along with an intermedullary nail (IM nail) to help heal fractures of the lower leg bone (tibia).
- The INFUSE® device consists of two parts:
- a genetically-engineered human protein (rhBMP-2) to stimulate bone healing, and
- an absorbable collagen sponge made from cow (bovine) collagen that is soaked with the protein.
- **How does it work?**
- A metal rod, called an intermedullary nail or IM nail, is surgically implanted inside the tibia bone to stabilize the fracture.
- The INFUSE ® device is implanted at the fracture site to help the bone heal.
- **When is it used?** The INFUSE ® device is intended to be used along with internal stabilization (an IM nail) to help heal a fresh, open fracture of the tibia.
- **What will it accomplish?** In a clinical study, use of the INFUSE® device caused fractures to heal in a similar manner to bones not treated with the device. Patients who received INFUSE® required fewer interventions to promote healing compared to patients who did not receive the device. However, patients who received the device and required an intervention healed at a slower rate compared to patients who did not receive the device.

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm081154.htm

TE-Bone: Carticel®* an autologous cellular product

Step 1: Biopsy



A sample or "biopsy"
of healthy tissue is sent to manufacturer of Carticel®

Step 2: Implantation

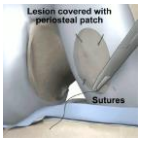
CARTICEL Manufacturing and Delivery

Biopsy can be stored for up to two years
For implantation cells are cultured at cell processing facility; in 3-5 weeks cells increase to approximately 12 million cells.
Strict quality and safety monitoring
Courier delivery of cultured cells (CARTICEL) hours before surgery.

*http:// www.carticel.com (Genzyme Corporation)

Step 3. Cartilage Injury Cleaned
During the second stage of CARTICEL implantation, the surgeon makes an incision to expose the knee and removes any dead or damaged tissue from the injury, leaving only healthy tissue.

Step 4. Periosteal Patch
Your surgeon takes a small piece of tissue from your shin bone and sews it securely over the injury. 1/2



Step 5. CARTICEL Implantation
Surgeon injects CARTICEL under the patch CARTICEL can grow and form new hyaline-like cartilage, with properties similar to those of the original cartilage.

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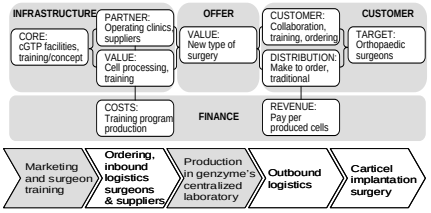
The Carticel® Business Model



Carticel business model elements (up) Carticel value chain (bottom) Genzyme functions coded grey

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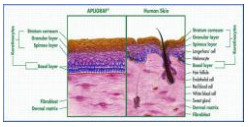
An illustrative example: Apligraf® Living Skin Equivalent



- FDA approval 1997 (Organogenesis); for treatment of severe burns and diabetic skin ulcers
- 1997-2002 sales $20 million/year, cost of producing and selling exceeded sales revenue
- Bankrupt in 2002; new start 2003
- 260 employees (2007)
- Operating at break-even
- More than 200,000 patients treated, sales of $60 milloin /year
- Largest enterprise selling a cell-based TE product

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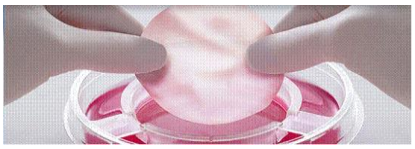
Example: Tissue engineered skin for wound healing – simple, but profitable

- http://www.organogenesis.com/news/media-materials/index.html
- http://www.apligraf.com/professional/what_is_apligraf/how_is_it_made/manufacturingVideo.html



(http://www.organogenesis.com)

Tissue engineered products on the market* from simple to complex: LAVIV

- LAVIV (azficel-T) by Fibrocell Science
- An autologous cellular product indicated for improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults
  - Also studies about improving acne scaring
- Patient's own fibroblasts are collected from patients, sampled, cultured and frozen to later inject them back to their own skin

* Commerical products, this does not inlcude products that are in use for single-patient treatment in hospitals under

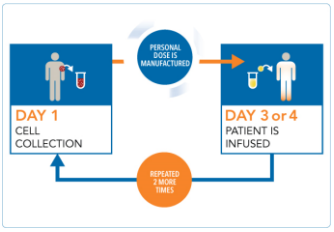
Tissue engineered products on the market: PROVENGE ®

- Provenge® (sipuleusel-T) by Dendreon
- First FDA-approved immunotherapy treatment for advanved prostate cancer
- an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone-refractory) prostate cancer
- Patient's own while blood cells are collected and activated with a recombinant antigen, and then infused back to the patient. The induced white blood cells have an improved recognition of prostate cancer cells and destroy them

PROVENGE ®

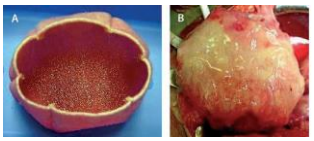
The recombinant antigen used to make PROVENGE is PAP-GM-CSF.

- prostatic acid phosphatase (PAP), an antigen expressed in more than 95% of prostate cancers,
- granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune-cell activator



Example: Engineering a tissue construct – getting more complicated, single patient applications in hospitals

- Urothelial and muscle cells were isolated from patients.
- Cells were seeded on a biodegradable bladder-shaped scaffold made of collagen and polyglycolic acid.
- The cell-scaffold construct was connected to the native bladder in the patient.

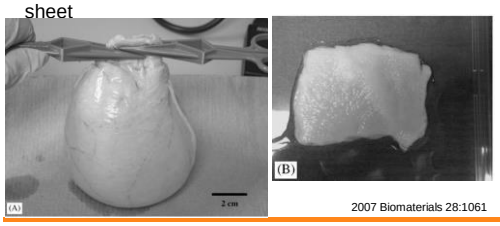


2006 The Lancet 367:1241

Acellular bladder matrix for tissue engineering

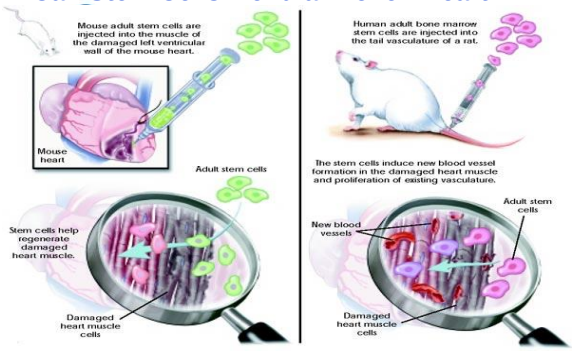
A. The intact porcine bladder

B. The final decellularized bladder matrix as a flattened sheet



2007 Biomaterials 28:1061

Can Stem Cells Mend a Broken Heart?



Strategies to repair heart muscle with adult stem cells.
http://stemcells.nih.gov/info/basics/basics6.asp

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Learning outcomes for E3225 Cell and Tissue Engineering 2019: Did we achieve these ??

1. describe major classes of human stem cells with potential for use for cell-based and tissue – engineering products
2. present culturing techniques, growth requirements in vitro and differentiation and generation of (induced) pluripotent stem cells
3. discuss the interactions of cells and implantable biomaterials
4. outline the relevance of Good manufacturing practices (GMP) with case examples
5. describe the meaning and implementation of validation, quality control, quality assurance, risk management, benefit vs. risk, bioethics
6. present the product development process of selected products and the key regulatory requirements from discovery to bringing products to the market

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