Business opportunities

HEALTH CARE
- Less hospitalisation
- Homecare
- Elderly population
- Health IT
- Telemedicine
- Early diagnosis
- Drugs on target
- Minimal invasive
- Body repair & beauty
- Nanobio fusion

ICT
- genotyping
- informatics
- smart homes
- biometric diagnosis
- assistive environment
- telesurgery
- wireless health sensors
- position & motion sensors
- hifu drug delivery
- hifu surgery
- μ-surgery
- μ-X-ray
- molecular imaging
- imaging via skin
- biocompatible
- nanofilters
- water/air/body fluids
- (wireless sensoric) implants
- bioswitch
- drug delivery
- prosthetic biomarkers
- chinese medicines
- artificial organs & blood
- regenerative medicine
- via skin medicine
- μ artificial cells

EQUIPMENT
- brain machine interface
- robotic surgery
- exo-skeletons
- in vitro cell imaging
- hifu tissue growth
- imaging
- nerve/muscle stimulation
- molecular medicine
- nutraceuticals
- molecular imaging

MATERIALS
- IT
- telecare
- tele monitoring
- smart textiles
- biofluidic lab-on-chip
- biosensor tags
- biocompatible
- nanofilters
- water/air/body fluids
- (wireless sensoric) implants
- artificial organs & blood
- regenerative medicine
- via skin medicine
- μ artificial cells

TECHNOLOGY RADAR
- biocompatible
Changing influence of Life science

Before 2015

- Basic research in drug development
- Regenerative medical science
- Technology for measuring biological substances
- Basic research for new medical technologies
- Understanding and treating brain conditions
- Environmental and ecological biology
- Controlling higher-order biological functions
- Higher-order brain functions
- Brain generation and growth
- Bioinfomatics
- Nanobiology

After 2015

- Socio-economic influence
- Index of knowledge increase
Expected time to realisation – Life sciences

Time of technology realisation

<table>
<thead>
<tr>
<th>Year</th>
<th>2005</th>
<th>2010</th>
<th>2015</th>
<th>2020</th>
<th>2025</th>
<th>2030</th>
<th>2035</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioinformatics</td>
<td>9.0 yrs.</td>
<td>9.0 yrs.</td>
<td>10.8 yrs.</td>
<td>10.6 yrs.</td>
<td>11.4 yrs.</td>
<td>10.8 yrs.</td>
<td>11.3 yrs.</td>
</tr>
<tr>
<td>Controlling higher-order biological functions</td>
<td>9.0 yrs.</td>
<td>9.0 yrs.</td>
<td>10.8 yrs.</td>
<td>10.6 yrs.</td>
<td>11.4 yrs.</td>
<td>10.8 yrs.</td>
<td>11.3 yrs.</td>
</tr>
<tr>
<td>Basic research in drug development</td>
<td>9.0 yrs.</td>
<td>9.0 yrs.</td>
<td>10.8 yrs.</td>
<td>10.6 yrs.</td>
<td>11.4 yrs.</td>
<td>10.8 yrs.</td>
<td>11.3 yrs.</td>
</tr>
<tr>
<td>Technology for measuring biological substances</td>
<td>9.0 yrs.</td>
<td>9.0 yrs.</td>
<td>10.8 yrs.</td>
<td>10.6 yrs.</td>
<td>11.4 yrs.</td>
<td>10.8 yrs.</td>
<td>11.3 yrs.</td>
</tr>
<tr>
<td>Environmental and ecological biology</td>
<td>9.0 yrs.</td>
<td>9.0 yrs.</td>
<td>10.8 yrs.</td>
<td>10.6 yrs.</td>
<td>11.4 yrs.</td>
<td>10.8 yrs.</td>
<td>11.3 yrs.</td>
</tr>
<tr>
<td>Nanobiology</td>
<td>9.0 yrs.</td>
<td>9.0 yrs.</td>
<td>10.8 yrs.</td>
<td>10.6 yrs.</td>
<td>11.4 yrs.</td>
<td>10.8 yrs.</td>
<td>11.3 yrs.</td>
</tr>
<tr>
<td>Regenerative medical science</td>
<td>9.0 yrs.</td>
<td>9.0 yrs.</td>
<td>10.8 yrs.</td>
<td>10.6 yrs.</td>
<td>11.4 yrs.</td>
<td>10.8 yrs.</td>
<td>11.3 yrs.</td>
</tr>
<tr>
<td>Understanding and treating brain conditions</td>
<td>9.0 yrs.</td>
<td>9.0 yrs.</td>
<td>10.8 yrs.</td>
<td>10.6 yrs.</td>
<td>11.4 yrs.</td>
<td>10.8 yrs.</td>
<td>11.3 yrs.</td>
</tr>
<tr>
<td>Basic research for new medical technologies</td>
<td>9.0 yrs.</td>
<td>9.0 yrs.</td>
<td>10.8 yrs.</td>
<td>10.6 yrs.</td>
<td>11.4 yrs.</td>
<td>10.8 yrs.</td>
<td>11.3 yrs.</td>
</tr>
</tbody>
</table>
Fundamental Ethical Principles at Stake.
“In the context of European pluralism, it is up to each Member State to forbid or authorise embryo research. In the latter case, respect for human dignity requires regulation of embryo research and the provision of guarantees against risks of arbitrary experimentation and instrumentalisation of human embryos.”
Legislation in individual countries incomplete, different.

The Oviedo Convention of the Council of Europe on human rights and biomedicine (1997)

Article 18: The creation of human embryos solely for research is prohibited.

About 30 states signed, 20 ratified


Second thoughts: have we overregulated?

Pressures of the science lobby, industry, patients..
### Regulations in EU Member States Regarding Human Embryonic Stem Cell Research (2003)

<table>
<thead>
<tr>
<th>Regulation</th>
<th>AT</th>
<th>BE</th>
<th>DK</th>
<th>DE</th>
<th>ES</th>
<th>FI</th>
<th>FR</th>
<th>GR</th>
<th>IE</th>
<th>IT</th>
<th>LU</th>
<th>NL</th>
<th>PT</th>
<th>SE</th>
<th>UK</th>
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</thead>
<tbody>
<tr>
<td>Allowing for the procurement of human embryonic stem cells from supernumerary embryos by law</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Prohibition of the procurement of embryonic stem cells from human embryos but allowing by law for the importation of human embryonic stem cell lines</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prohibition of the procurement of embryonic stem cells from human embryos</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No specific legislation regarding human embryo research</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Allowing for the creation of human embryos for stem cell procurement by law</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prohibition of the creation of human embryos for research purposes and for the procurement of stem cells by law or by ratification of the Convention of the Council of Europe on Human rights and Biomedicine signed in Oviedo on 4 April 1997</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Timescale for commercial opportunities

- Cell therapies
- Therapeutics
- Research applications
- Enabling technologies

Time (years)

- Value
- Training
- Cell banking
- Clinical trials
- Drug screening
- Toxicity testing
- Manufacturing
- Growth factors
Translation of stem cell research into commercial products

Stages:
- Basic Research
- Applied Development
- Clinical Therapies

Infrastructure:
- Universities, Research Institutes
- Biotech SMEs
- Pharma
- Clinicians

Stakeholders:
- Universities
- Research Institutes
- Biotech SMEs
- Pharma
- Clinicians
- Government / regulatory agencies

Financing:
- Research Councils
- Charities
- Commercial funding VC, pharma
- MIND THE GAP

Funding Gap
Bench to bed side – work flow

- Isolate individual stem cell populations
- Characterize & track stem cell populations
- Ensure that cells retain their functionality and potential to differentiate
- Ensure that cells are “transplant” ready
- Culture stem cell lines in a stable, multi- or pluripotent state, free from mutations & to sufficient quantity
- Enable Economical expansion to make cell-therapy a reality
- Control & activate stem cell differentiation to desired lineages
- Functionally active differentiated cells
Enabling technologies for Stem cell therapies

**Economic Production of Large Quantities of Cells**
- Process development
- Optimized media

**Isolation of Differentiated / Desired Cell Types**
- Dynabeads® ClinExVivo™

**Research tools**

**Batch Release Testing**
- Sterility/mycoplasma
- General safety
- Tumorogenicity
- Adventitious agents
- Novel cell-based test

**Cell Banking / Characterization**
Number of Stem Cell Firms Founded 1970-2006
Distribution of Firms by Country
Stem Cell Types Being Developed by Firms

- Adult Bone Marrow SCs (Incl Haematopoetic)
- Adult Muscle SCs (Myoblasts)
- Adult Neural SCs
- Adult Pancreatic & Liver SCs
- Adult Progenitor SCs
- Adult SCs (Unspecified)
- Adult Skin & Adipose Derived SCs
- Cord Blood SCs (Incl Placenta)
- Human Embryonic SCs (Incl Mesenchymal & Foetal)
- Mouse Embryonic SCs
- Unknown
Disease Focus of Stem Cell Firms

- Aesthetic/Cosmetic Applications
- Blood Disorders (Incl Leukemia & Sickle Cell Anaemia)
- Bone & Cartilage Disorders (Incl Osteoporosis, Osteoarthritis)
- Cancer
- Cardiovascular Diseases (Incl CMI)
- Diabetes
- Immunological Disorders
- Liver Disease
- Neurological & CNS Disorders (Incl Parkinson's, Alzheimer's, Huntington's & MS)
- Retinal Diseases
- Skin (Incl Burns & Wounds)
- Other
- Unknown
Organisation types of stem cell legal entities

**ORGANIZATION TYPE**

- Enabling Service (407)
- Enabling Technology (641)
- Therapeutic (264)
- Consultant (109)
- Academic / Research Center (342)
- Network (29)
- Society (49)
- Investor/Venture Capitalist (25)
- Regulatory Body (99)
- Publication (52)
### FIGURE 1
Top Ten Regenerative Medicine Products

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>Product Type</th>
<th>Therapeutic Area</th>
<th>Indication</th>
<th>Launch</th>
<th>2007 WW Revenue</th>
<th>'06-'07 Rev Growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medtronic</td>
<td>Infuse</td>
<td>Growth factor w/matrix</td>
<td>Bone</td>
<td>Spinal fractures, orofacial fractures, open tibial fractures</td>
<td>2002</td>
<td>~$700ME</td>
<td>18%</td>
</tr>
<tr>
<td>LifeCell</td>
<td>Allograft</td>
<td>Allogeneic acellular matrix</td>
<td>Skin</td>
<td>Skin replacement / hernia repair</td>
<td>1994</td>
<td>$167.1M</td>
<td>40%</td>
</tr>
<tr>
<td>Genzyme</td>
<td>Carticel</td>
<td>Autologous cell based</td>
<td>Cartilage</td>
<td>Knee repair</td>
<td>1995</td>
<td>~$88ME</td>
<td>~30%</td>
</tr>
<tr>
<td>Stryker</td>
<td>OP-1</td>
<td>Growth factor w/matrix</td>
<td>Bone</td>
<td>Humanitarian Device Exemption for spine fusion &amp; long bone fractures</td>
<td>2005</td>
<td>~$80ME</td>
<td>60%</td>
</tr>
<tr>
<td>RTI</td>
<td>Spinal Implants</td>
<td>Allogeneic Acellular matrix</td>
<td>Bone</td>
<td>Spinal fractures</td>
<td>1991</td>
<td>$41.1M</td>
<td>17%</td>
</tr>
<tr>
<td>Organogenesis</td>
<td>Apligraf</td>
<td>Allogeneic Neonatal cells w/matrix</td>
<td>Skin</td>
<td>Diabetic skin ulcers</td>
<td>1998</td>
<td>~$30ME</td>
<td>10%+</td>
</tr>
<tr>
<td>Advanced Biohealing</td>
<td>Dermgraft</td>
<td>Allogeneic Neonatal cells w/matrix</td>
<td>Skin</td>
<td>Diabetic skin ulcers</td>
<td>1997</td>
<td>~$20ME</td>
<td>10%+</td>
</tr>
<tr>
<td>Integra Lifesciences</td>
<td>Various</td>
<td>Allogeneic acellular matrix</td>
<td>Skin</td>
<td>Skin repair / replacement</td>
<td>2001</td>
<td>~$20ME each</td>
<td>25%</td>
</tr>
<tr>
<td>Osiris/ Nuvasive</td>
<td>Osteocell</td>
<td>Allogeneic cell based</td>
<td>Bone</td>
<td>Fracture repair</td>
<td>2005</td>
<td>$15.2M</td>
<td>83%</td>
</tr>
<tr>
<td>Cytori</td>
<td>Celution</td>
<td>Autologous cell based</td>
<td>Soft Tissue (adipose)</td>
<td>Reconstructive Breast Surgery</td>
<td>2008 (ex-US)</td>
<td>~$10-12M*</td>
<td>N/A</td>
</tr>
</tbody>
</table>

E=estimated from various sources  
*=company projections for 208  
Source: Company 10K Information, Frankel Group Analysis
## FIGURE 2
Cell Based Business Models

<table>
<thead>
<tr>
<th>Broad Product &amp; Large Patient Base</th>
<th>#1 Unachievable Model?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic benefit has to be extraordinary to compete with low cost therapies</td>
<td></td>
</tr>
<tr>
<td>Cost structure and manufacturing are not scalable</td>
<td></td>
</tr>
<tr>
<td>High risk of substitution &amp; relatively low barriers to competitive entry</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Niche Products &amp; Small Patient Base</th>
<th>#2 Current State Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Orphan” populations with no current efficacious therapy</td>
<td></td>
</tr>
<tr>
<td>Often “Salvage” therapies</td>
<td></td>
</tr>
<tr>
<td>Can be profitable but is not scalable</td>
<td></td>
</tr>
<tr>
<td>Creates strong relationships with caregivers and patients</td>
<td></td>
</tr>
<tr>
<td>E.g., Bone Marrow Transplant, Replicell, Carticel, Cytori</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>#3 Large Pharma Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low COGS: Cost structure is scalable</td>
</tr>
<tr>
<td>Easily delivered to patients</td>
</tr>
<tr>
<td>Lower cost therapy could compete against biologics &amp; possibly small molecules</td>
</tr>
<tr>
<td>High cost therapy that is “curative”</td>
</tr>
<tr>
<td>E.g., ESCs for diabetes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>#4 Specialty Biotech Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacious therapy that targets populations with high unmet needs</td>
</tr>
<tr>
<td>Moderate COGS for product (can include device component)</td>
</tr>
<tr>
<td>Cost structure can possibly be spread across multiple diseases (e.g., Osiris)</td>
</tr>
</tbody>
</table>

| Autologous | Allogeneic |

Source: Frankel Group Analysis
FIGURE 3
Today's Autologous Business Models

Service Based Model
- Source: End User
  - Replicell: End User outpatient collection facility
  - Carticel: End user harvest of cartilage
- Multiple Procedures: Off-Site Processing & Time Delay (up to 1 month)

Device Based Model
- Source: End User
  - Bone Marrow Transplant: End user collection of marrow / stem cells
  - Cytori: Harvest of adipose tissue from patient
- Single Procedure: No Off-Site Processing & Minimal Time Delay

End User Grafting
- Replicell: Bone graft
- Carticel: Cartilage graft

Off-Site Processing
- Replicell: Tissue Repair Cell production & expansion
- Carticel: Chondrocyte expansion

End User Grafting
- Bone Marrow Transplant: Processing of marrow/stem cells
- Cytori: Cells transplanted back into patient

On-Site Processing
- Bone Marrow Transplant: Cellution System used to separate / concentrate stem cells

Source: Company Information, Frankel Group Analysis
FIGURE 4
Today's Allogeneic Business Model – Speciality Pharma Model

Source: Allogeneic Donor
- Allograft: Tissue banks
- Bone Marrow Transplant: End user collection of marrow / stem cells
- Osteocell: Deceased donor

Product Can Be Used “On Demand”

End User Grafting
- Allograft: Complex hernia repair, other applications
- Bone Marrow Transplant: Transplant of marrow
- Osteocell: Bone defects

Processing
- Allograft: Cell removal
- Bone Marrow Transplant: Processing of marrow/stem cells
- Osteocell: Mesenchymal SC expansion

Off-Site Processing & No Time Delay

Source: Company Information, Frankel Group Analysis
Success is not final, failure is not fatal: it is the courage to continue that counts.

Winston Churchill